Diastereo- as well as Enantio-selective Lipase-catalysed Asymmetric Hydrolysis of Chlorofluoromethylated Alcohols

Takashi Yamazaki, Shinji Ichikawa, and Tomoya Kitazume*

Department of Bioengineering, Tokyo Institute of Technology, Ookayama, Meguro-ku, Tokyo 152, Japan

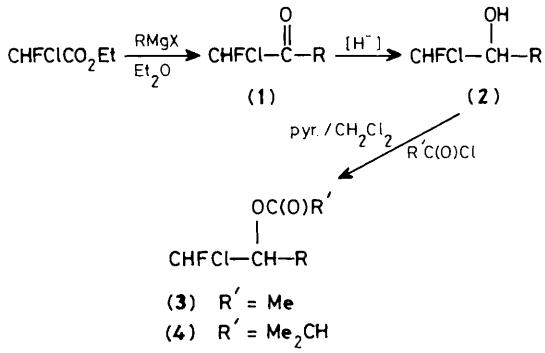
Lipase-catalysed hydrolysis of chlorofluoromethylated secondary esters proceeded effectively with excellent enantio- and diastereo-selectivity.

Lipase, a hydrolytic enzyme, has been employed for the preparation of chiral building blocks in a highly enantioselective manner.[1] However, when chiral compounds with more than two stereocentres were required, the principal approaches reported to date have required the separation of diastereoisomeric mixtures[2] or stereoselective preparation of the starting materials, both of which may be troublesome. The 'direct'† optical resolution of the diastereoisomeric mixture, an attractive and promising method, has only been demonstrated for the preparation of cyclic molecules.[3–5]

We describe the lipase-catalysed hydrolysis of chlorofluoromethylated secondary esters, not only an effective 'direct' optical resolution, but also the first example of such a resolution with acyclic molecules.[6]

The starting materials[7] were prepared as shown in Scheme 1. Two lipases, MY (*Candida cylindracea*, Meito Sangyo Co., Ltd., Japan) and P (*Pseudomonas sp.*, Amano Pharmaceutical Co., Ltd., Japan) were employed. This lipase-catalysed hydrolysis proceeded smoothly within 2—3 h except for the hydrolysis of (**4**) by lipasae P (around 10 h). Both the product (**2**) and the unreacted substrate (**3**) were recovered in 75—95% yield.

From the data in Table 1, the diastereoselective nature of this procedure is clear. However, generally, lipase P displayed



(**3**) R′ = Me
(**4**) R′ = Me_2CH

a; R = Ph
b; R = $PhCH_2$
c; R = $PhCH_2CH_2$

Scheme 1. Preparation of the starting materials.

R	(H⁻)	Diastereisomer ratio[a]
Ph	L-Selectride	97 : 3
	Bu^i_2AlH	49 : 51
$PhCH_2$	L-Selectride	85 : 15
	$NaBH_4$	42 : 58
$PhCH_2CH_2$	L-Selectride	77 : 23
	$NaBH_4$	44 : 56

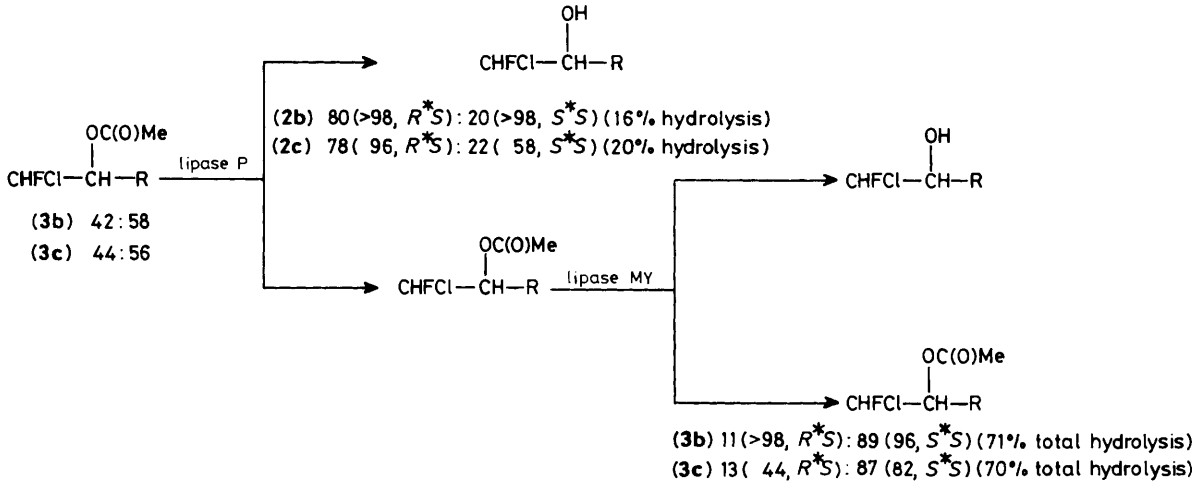
[a] Determined by capillary g.c.; the yields were 70—90% in each case.

† In this text, the term 'direct' implies the separation of stereoisomers during lipase-catalysed hydrolysis.

Table 1. Lipase-catalysed asymmetric hydrolysis of (**3**) and (**4**).

Run	Ester	Diastereoisomeric ratio[a]	Lipase	Hydrolysis ratio/%	Diastereoisomeric ratio [optical purity (% e.e.), configuration][b]	$[\alpha]_D$ (*c* in MeOH)[g]
1	(**3a**)	97 : 3	MY	28	>95 (63, *R*S*) : <5[c]	+17.03° (0.70)
2	(**4a**)	97 : 3	P	32	>99 (>98, *R*S*) : <1	+28.88° (0.82)
3	(**4a**)	49 : 51[f]	P	20	79 (>98, *R*S*) : 21 (>98, *S*S*)	+33.94° (0.87)
4	(**3b**)	85 : 15	MY	31	92 (52, *S*R*) : 8 (>98, *R*R*)	+15.45° (1.19)
5	(**3b**)	85 : 15	P	39	93 (>98, *R*S*) : 7 (>98, *S*S*)	−17.35° (1.01)
6	(**3b**)	42 : 58[e]	P	16	80 (>98, *R*S*) : 20 (>98, *S*S*)	−20.42° (0.96)
7	(**4b**)	85 : 15	MY	34	91 (19, *S*R*) : 9 (78, *R*R*)	+ 9.11° (0.98)
8	(**4b**)	85 : 15	P	23	96 (>98, *R*S*) : 4 (>98, *S*S*)	−19.31° (0.78)
9	(**4b**)	42 : 58[e]	P	10	69 (>98, *R*S*) : 31 (>98, *S*S*)	−18.88° (0.92)
10	(**3c**)	77 : 23	MY	39	84 (18, *S*R*) : 16 (>98, *R*R*)	+10.56° (0.94)
11	(**3c**)	44 : 56[e]	MY	74	17 (76, *R*S*) : 83 (88, *S*S*)[d]	−27.64° (0.98)
12	(**3c**)	77 : 23	P	31	93 (88, *R*S*) : 7 (28, *S*S*)	−22.43° (0.83)
13	(**3c**)	44 : 56[e]	P	20	78 (96, *R*S*) : 22 (58, *S*S*)	−20.52° (0.96)
14	(**4c**)	77 : 23	MY	42	87 (9, *S*R*) : 13 (41, *R*R*)	+ 7.72° (0.98)
15	(**4c**)	77 : 23	P	31	>99 (>98, *R*S*) : <1	−23.12° (0.97)
16	(**4c**)	44 : 56[e]	P	15	93 (>98, *R*S*) : 7 (>98, *S*S*)	−20.42° (0.60)

[a] Ratios for esters from alcohols reduced with L-Selectride. [b] Ratios for the hydrolysed alcohols. In parentheses are reported enantiomeric excess and configurations of major isomer. [c] These ratios were determined by ^{19}F n.m.r. [d] This alcohol was obtained by chemical transformation of the residual acetate after lipase-catalysed hydrolysis. [e] These esters were provided from alcohols reduced with $NaBH_4$. [f] This ester was synthesised from alcohol reduced with Bu^i_2AlH and the configuration of the minor diastereoisomer was assumed from the other examples. [g] Optical rotations were observed for the diastereoisomer mixture of alcohols.



Scheme 2. Diastereo- and enantio-selective preparation of chlorofluoromethylated alcohols *via* a two-step method.

a higher enantioselectivity than lipase MY.‡ Moreover, lipase MY afforded optically active alcohols (**2b**) with (*S**, *R*)-configuration§ in low to moderate optical purities (Runs 4, 7, 10, and 14), while lipase P provided the corresponding (*R**, *S*)-isomer§ with excellent selectivities (Runs 5, 8, 12, and 15). In particular, asymmetric hydrolysis of (**4c**) by lipase P (Run 15) demonstrated the high efficiency of 'direct' resolution. It formed the target molecule in a highly diastereo- and enantio-selective manner after 31% hydrolysis, while, in theory, this process should be stopped at 39% hydrolysis to obtain a single isomer in 100% enantiomeric excess (e.e.). The only exception in our experiments with lipase MY (Run 1) produced (**2a**) with the same stereochemistry as the product from lipase P catalysed hydrolysis.

In Run 10, lipase MY showed low enantioselectivity in reactions of the major diastereoisomer (18% e.e.), but with the minor diastereoisomer, almost complete discrimination was attained (>98% e.e.). Thus, the order of the ease of the hydrolysis should be (*S**, *R*) > (*R**, *S*) > (*R**, *R*) ≫ (*S**, *S*). These results suggest that the unchanged ester would be recovered with high diastereo- and enantio-selectivity under those conditions where hydrolysis was nearly complete. As expected, (*S**, *S*)-(**3c**) was obtained at 74% conversion with

‡ Determination of the isomeric ratio was carried out by 30 m × 0.3 mm capillary g.l.c. of the (MTPA) esters[8] from the hydrolysed alcohols. Silicone GE XE-60 column, N_2 carrier gas, 20 ml/min flow rate. The relative relationships of the alcohols (**2**) were still unknown,[9] although the absolute configuration of the hydroxylated carbon was determined by reductive elimination of chlorine by Bu^n_3SnH,[10,11] followed by the comparison of the optical rotation as in ref. 11.

§ G.l.c. of the MTP esters derived from (**2**) afforded four readily separable peaks from which we could distinguish that the first and the third peaks or the other sets are an enantiomeric pair, and the first and the second peaks are those from the compounds possessing (*R*)-configuration at the hydroxylated carbon. Then, we gave (*S**)-configuration at the fluorine-containing carbon atom for the first peak to distinguish these four components as (*S**, *R*), (*R**, *R*), (*R**, *S*), and (*S**, *S*) from the first to the fourth peaks.

good stereoselectivity (Run 11) and thus this approach constitutes a complementary method for the preparation of stereoisomers with (*R**, *S*)- and (*S**, *S*)-configuration. Considering that lipase P acted in an opposite manner to lipase MY, the combination of the two hydrolysis processes would give two isomers with high stereoselectivity (Scheme 2).

In conclusion, lipase was found to facilitate the diastereo- as well as enantio-selective preparation of chlorofluoromethylated alcohols. This is the first example of the 'direct' resolution in an acyclic system.

Received, 28th March 1988;¶ Com. 8/01219I

References

1 J. B. Jones, *Tetrahedron*, 1986, **42**, 3351; G. M. Whitesides and C. H. Wong, *Angew. Chem. Int. Ed. Engl.*, 1985, **24**, 617.
2 References discussing the enzymatic hydrolysis of both separated diastereoisomers. See, Z.-F. Xie, H. Suemune, I. Nakamura, and K. Sakai, *Chem. Pharm. Bull.*, 1987, **35**, 4454; H. Hemmerle and H. J. Gais, *Tetrahedron Lett.*, 1987, **30**, 3471; J. L. Pawlak and G. A. Berchtold, *J. Org. Chem.*, 1987, **52**, 1765; H. Akita, H. Matsukura, and T. Oishi, *Tetrahedron Lett.*, 1986, **27**, 5241.
3 M. Schneider, N. Engel, and H. Boensmann, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 64.
4 T. Sugai and K. Mori, *Synthesis*, 1988, 19.
5 T. Oritani and K. Yamashita, *Agric. Biol. Chem.*, 1973, **37**, 1691; 1973, **37**, 1695; 1974, **38**, 1965; 1975, **39**, 89.
6 For our related work, see: T. Yamazaki, M. Asai, T. Ohnogi, J. T. Lin, and T. J. Kitazume, *J. Fluorine Chem.*, 1987, **35**, 537; T. Kitazume, M. Asai, J. T. Lin, and T. Yamazaki, *ibid.*, 1987, **35**, 477; T. Kitazume, T. Sato, T. Kobayashi, and J. T. Lin, *J. Org. Chem.*, 1986, **51**, 1003; J. T. Lin, T. Yamazaki, and T. Kitazume, *ibid.*, 1987, **52**, 3211.
7 It is empirically known to us that the hydrolysis of isobutyrate by lipase P afforded better results in many cases. For some special system, see, J. T. Lin, M. Asai, T. Ohnogi, T. Yamazaki, and T. Kitazume, *Chemistry Express*, 1987, **2**, 293.
8 J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, 1969, **34**, 2543.
9 Considering the stability of hydrogen bonding between the fluorine and hydroxy group, this relative relationship may be assumed as *anti* for the major diastereoisomer produced by L-Selectride reduction (see B. Landmann and R. W. Hoffmann, *Chem. Ber.*, 1987, **120**, 331).
10 P. Bey, J. B. Ducep, and D. Schirlin, *Tetrahedron Lett.*, 1984, **25**, 5657.
11 T. Kitazume, N. Okamura, T. Ohnogi, M. Asai, and T. Yamazaki, *Chemistry Express*, 1988, **3**, 351.

¶ Received in revised form 26th September 1988.