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Stereodivergent Synthesis of Fluorinated Threonine Derivatives in High Optical Purity

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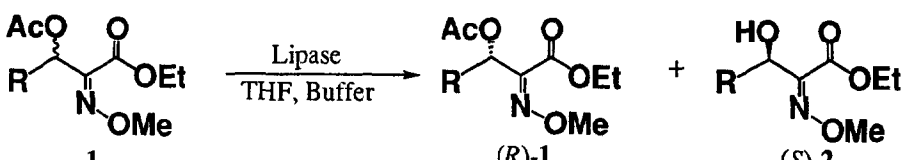
Abstract: Fluorinated 3-acetoxy-2-(methoxyimino)butyrates were resolved by lipase to give the corresponding alcohols and the acetates in high optical purity. The resolved alcohols were readily converted into mono-, di-, and trifluorothreonine and allo-threonine derivatives by hydrogenation of the methoxyimino group.

Intriguing biological properties of fluorine-containing amino acids coupled with difficulties associated with their preparation in optically active form have prompted us to explore straightforward approaches to them.[1] Fluorine-containing optically active threonines have been reported as highly promising amino acid derivatives due to the imparted antitumor activities.[2] However, the reported procedures based on the transformation of the chiral synthons suffer from the difficulties in the preparation of all four possible stereoisomers,[2b, d] whereas those utilizing an enzymatic resolution are promising but the substrate specificity encountered in such biological transformations often makes difficult the preparation of the desired materials in high optical purity.[2f, g] Our interest in the optical resolution of secondary alcohols possessing unsaturation in the neighbourhood has already led to an interesting discovery that racemic unsaturated alcohols were cleanly resolved into optically pure alcohols by the use of lipases.[3] With these phenomena in mind we screened the optical resolution of a variety of amino acid precursors containing a fluorine and an unsaturation at a suitable position for further functional group manipulations. Among them secondary alcohols possessing a methoxyimino functionality have been found to be excellent substrates for the optical resolution by lipases, and we wish to report herein a short synthesis of fluorinated threonine and allo-threonine derivatives in high optical purity.

The substrates for the optical resolution were prepared from mono-, di-, or tri-haloacetoacetates according to the procedure by Scolastico et al,[2b] and fluorinated 3-acetoxy-2-methoxyiminobutyrates were obtained in good yields.[4] The lipase mediated hydrolysis was carried out according to the following typical experimental procedure: to a solution of the acetate **1** (R = CH_2F) (240 mg, 1.43 mmol) in THF (3.6 mL) and phosphate



1 (*R*)-**1** (*S*)-**2**

R = CH_2F, CHF_2, CF_3, CH_2Cl

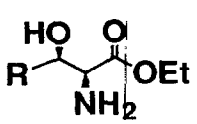
Table 1. Asymmetric Hydrolysis of 3-Acetoxy-2-methoxyiminobutyrate 1 with Lipase[a]

Entry	Lipase[b]	R	Temp (°C)	Time (h)	1/Yield[c] (%)	ee[d] (%)	2/Yield[c] (%)	ee[d] (%)	E[e]
1	PPL	CH_2F	40	144	66	8	30	66	5
2	AY	CH_2F	40	168	48	0	35	8	0
3	AK	CH_2F	rt	96	57	68	40	94	66
4	PS	CH_2F	55	13	35	>98	46	70	25
5	PS	CH_2F	rt	17.5	44	>98	45	>98	>458
6	PS	CH_2Cl	45	48	49	96	48	>98	>392
7	PS	CHF_2	rt	40	44	>98	50	>98	>458
8	PS	CF_3	40	48	47	90	43	82	48

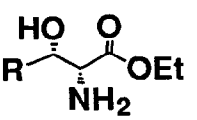
[a] The reaction was carried out according to the typical experimental procedure. [b] The following lipases were used: PPL (Tokyo Kasei); AY, AK, and PS (Amano). [c] Isolated yield by preparative TLC. [d] Determined by ^1H NMR, ^{19}F NMR, HPLC, and/ or capillary GLC analysis (SE-30, 50 m) of the corresponding (*R*)-MTPA esters. [e] See ref 10.

buffer (7.3 mL) was added lipase (Amano PS, 103 mg) at room temperature, and the mixture was stirred at room temperature for 17.5 hr. After filtration of the crude mixture through a pad of celite, the filtrate was concentrated in vacuo to give an oil, which was purified on preparative TLC to give the (*S*)-alcohol **2** (R = CH_2F) (51 mg, 45%) and the (*R*)-acetate **1** (R = CH_2F) (62 mg, 44%). The optical purity of the hydrolyzed alcohol was determined by transforming into the MTPA ester and analyzed by 270MHz ^1H NMR, ^{19}F NMR, GLC and / or HPLC, whereas the acetate was hydrolyzed with $KHCO_3$ in EtOH followed by a similar sequence to determine the enantiomeric excess. The results of the lipase mediated optical resolution of fluorine-containing methoxyimino alcohols are summarized in Table 1.

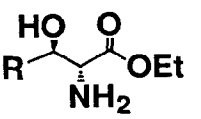
As to the biocatalyst, lipase AY was not effective at all (entry 2), and PPL and AK met with only moderate success (entries 1 and 3), whereas lipase PS recorded the best result in which the alcohol and the acetate were obtained in high optical purity (entry 4). In the case of monofluoro derivative the optical purity was enhanced by carrying out the hydrolysis at an ambient temperature, and almost complete resolution was attained when the reaction was conducted for 17.5 hr (entry 5). The difluoro and monochloro derivatives were also resolved in excellent optical purity (entries 6 and 7), whereas the trifluoro derivative gave the hydrolyzed alcohol in 90 %ee along with the acetate in 82 %ee (entry 8). These resolved alcohols and acetates were readily transformed into fluorine-containing threonine ethyl esters **3** by the selective reduction of methoxyimino functionality, and the results are shown in Table 2. Reduction of the mono-fluoro alcohol (*S*)-**2** (R = CH_2F) with $NaBH_4$-$ZrCl_4$[5] or BH_3-THF complex[6] gave the corresponding monofluoro threonine and allo-threonine ethyl esters in good to excellent optical purity. Difluoro derivatives were also reduced by the



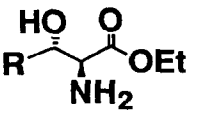
(2*S*,3*S*)-**3**



(2*R*,3*R*)-**3**



(2*R*,3*S*)-**4**



(2*S*,3*R*)-**4**

R = CH_2F, CHF_2, CF_3

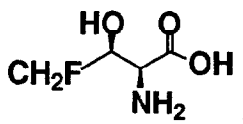
Table 2. Preparation of Fluorinated Threonine Ethyl Esters

Entry	Substrate	R	Method[a]	3/Yield[b] (%)	ee[c] (%)	Config[d]	4/Yield[b] (%)	ee[c] (%)	Config[d]
1	(*S*)-**2**	CH_2F	A	12	>98	(2*S*,3*S*)	39	>98	(2*R*,3*S*)
2	(*R*)-**2**	CH_2F	A	15	>98	(2*R*,3*R*)	41	40	(2*S*,3*R*)
3	(*S*)-**2**	CH_2F	B	15	>98	(2*S*,3*S*)	15	>98	(2*R*,3*S*)
4	(*R*)-**2**	CH_2F	B	26	>98	(2*R*,3*R*)	32	53	(2*S*,3*R*)
5	(*S*)-**2**	CHF_2	A	23	>98	(2*S*,3*S*)	46	61	(2*R*,3*S*)
6	(*R*)-**2**	CHF_2	A	44	>98	(2*R*,3*R*)	36	>98	(2*S*,3*R*)
7	(*S*)-**2**	CF_3	C	19	84	(2*S*,3*S*)	35	82	(2*R*,3*S*)
8	(*R*)-**2**	CF_3	C	41	>98	(2*R*,3*R*)	24	15	(2*S*,3*R*)

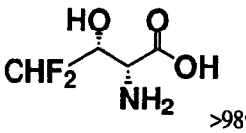
[a] Method A: BH_3•THF in THF at 0 °C~rt. Method B: $ZrCl_4$-$NaBH_4$ in THF at 0 °C~rt. Method C: 100 atm H_2/Pd-C in HCl-EtOH at 80 °C. [b] Isolated yield by silica gel column chromatography. [c] Determined by ^1H NMR, ^{19}F NMR, and / or HPLC analysis of the corresponding bis-(*R*)-MTPA derivatives. [d] Assignment of the absolute configuration, see text.

similar sequence in excellent optical purity, whereas the trifluroro derivatives were reduced under a hydrogen atmosphere in the presence of Pd/C.[7] Attempts to transform the acetates **1** directly into **3** and **4** under the reduction conditions resulted in the recovery of the starting materials. The optical purities of these alcohols were determined by converting into the corresponding bis-MTPA derivatives followed by analyses with ^1H NMR, ^{19}F NMR, and / or HPLC.

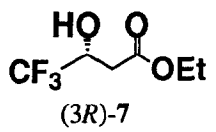
Determination of the absolute configuration was readily carried out by transforming the mono- and difluorothreonine esters (2*S*,3*S*)-**3** (R = CH_2F) and (2*R*,3*R*)-**3** (R = CHF_2) under the action of triethylamine in aqueous ethanol into mono- and difluorothreonines (2*S*,3*S*)-**5** and (2*R*,3*R*)-**6**, respectively followed by comparison of the sign of the optical rotations with those reported,[2a, f] indicating the hydrolyzed alcohols to be *S*-configurations. As to the trifluoro derivative, an authentic sample was prepared by the amination of the known ethyl (3*R*)-3-hydroxy-4,4,4-trifluorobutyrate (3*R*)-**7**[8] prepared by the bakers' yeast reduction of ethyl 4,4,4-trifluoroacetoacetate with di-*t*-butyl azodicarboxylate[2e] followed by reductive cleavage of the N-N



(2*S*,3*S*)-**5** >98% ee $[\alpha]_D^{23}$-20.0 (c 0.06, H_2O)



(2*R*,3*R*)-**6** >98% ee $[\alpha]_D^{23}$ +20.0 (c 0.02, H_2O)



(3*R*)-**7**
$[\alpha]_D^{23}$+7.67 (c 0.86, MeOH)

1) LDA, THF, (Boc) N=N (Boc)
2) CF_3COOH, CH_2Cl_2
3) H_2 / PtO_2, HCl, EtOH

(2*S*,3*R*)-**4** (R = CF_3)
$[\alpha]_D^{23}$ +4.4 (c 0.32, MeOH)

bond, and the comparison of the sign of the optical rotation unambiguously established the absolute configuration of the hydrolyzed alcohol to be *S*. Since the hydrolysis of the fluorine-containing threonine and

allo-threonine esters has already been carried out readily,[2] the present procedure provides a short access to those valuable substrates in high optical purity.

In summary, the present procedure for the optical resolution of fluorinated methoxyimino alcohols provides mono-, di-, and trifluorinated threonine esters in high optical purity, which in turn were converted into all four possible isomers. Since the methoxyimino alcohols are readily prepared via several reported procedures[9] the present methodology will be applicable to the synthesis of a variety of chiral amino acids in both natural and unnatural forms.

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4) **1**(R = CH_2F) was prepared in the following manner: hydroxyimination of ethyl 4-chloro-3-oxobutyrate with sodium nitrite in acetic acid to give ethyl 4-chloro-2-hydroxyimino-3-oxobutyrate, which was methylated with dimethyl sulfate and sodium carbonate in acetone to afford the corresponding methoxyimino derivative. Reduction of the ketone was carried out with sodium borohydride and cerium chloride in methanol to give **2** (R = CH_2Cl), which was fluorinated with potassium fluoride in diethylene glycol to give **2** (R = CH_2F). Acetylation with acetic anhydride and pyridine in the presence of a catalytic amount of DMAP in dichloromethane gave **1** (R = CH_2F). Difluoro and trifluoro derivatives **1** (R = CHF_2 and CF_3) were prepared in the same manner starting from 4,4-difluoro-3-oxobutyrate and 4,4,4-trifluoro-3-oxobutyrate, respectively.

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