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Enantioselective Synthesis of β,β-Difluoromalic Acid via Enzymic Resolution of Furyl Substituted Derivative

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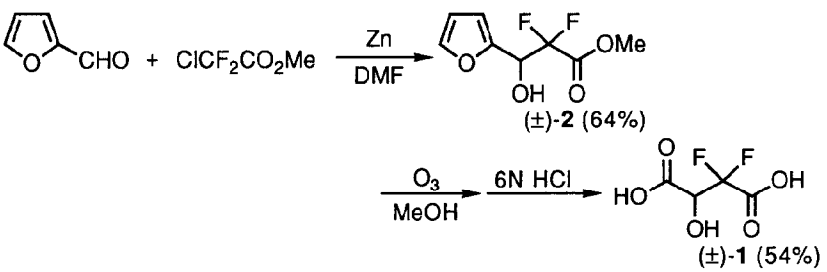
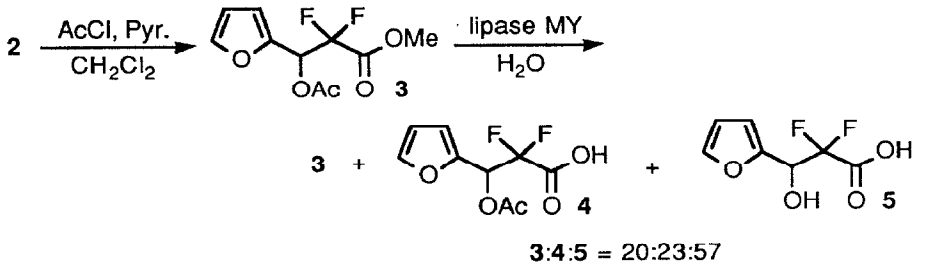
Abstract: (*R*)-and (*S*)-*N,N*-Diethyl 2,2-difluoro-3-(2-furyl)-3-hydroxypropionamide **7** have been obtained via enzymic resolution of the racemic acetate using lipase MY from *Candida cylindracea*. Ozonolysis of the (*S*)-**7** followed by hydrolysis afforded the (*S*)-β,β-difluoromalic acid **1**.

Malic acid is an important intermediate of the citric acid cycle and is found in a wide variety of organisms. Moreover, because of its commercial availability, chiral malic acid has been extensively used as chiral source for enantioselective synthesis of various complex molecules.[1] The incorporation of two fluorine atoms into the methylene group of this molecule would exert a pronounced influence on its chemical property with no significant effect on its geometry.[2] Such compound is potentially useful as probe for studies of the citric acid cycle and also as chiral building blocks for the synthesis of highly functionalized *gem*-difluorinated molecules. In this paper, as a part of our studies on biochemical preparation of optically active fluorine-containing compounds,[3] we report the facile synthesis of optically active β,β-difluoromalic acid **1** via enzymic resolution of the precursor bearing furan ring.

Our synthetic strategy involves kinetic resolution of α,α-difluoro-β-hydroxypropionic derivative bearing a furyl group on its β-position, which functions as latent carboxylic acid.[4] In fact, furyl substituted difluoromethylene compound **2**, which was easily obtained by Reformatsky reaction of methyl chlorodifluoroacetate with furfural,[5] was easily converted into racemic β,β–difluoromalic acid (±)-**1**[6] via ozonolysis followed by acid hydrolysis.



Thus, **2** was readily converted into the corresponding acetate **3** which was used as substrate for enzymic hydrolysis. However, kinetic resolution of **3** with lipase MY was unsuccessful giving the mixture of starting material **3**, β-acetoxyacid **4**, and β-hydroxyacid **5** due to non-regioselective hydrolysis of the substrate. Such an unexpected result has never been observed in the enzymic resolution for the similar



acylated derivatives of hydroxyesters bearing a furyl group[7] or fluorine atoms.[8] This difference indicates that the presence of two fluorine atoms on the carbon adjacent to the carbonyl enhances the electrophilicity of this ester towards water and facilitates hydrolysis of this function.

Therefore, we prepared *N,N*-diethyl amide **6**[9] which was found to be stable to the enzymic hydrolysis that cleaved the ester **3**, and kinetic resolution of various acylated derivatives of **6** with lipase MY and P were examined.[10] Results are shown in Table I.

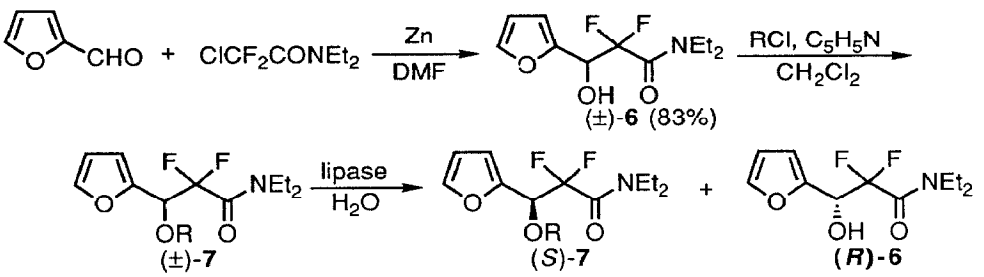
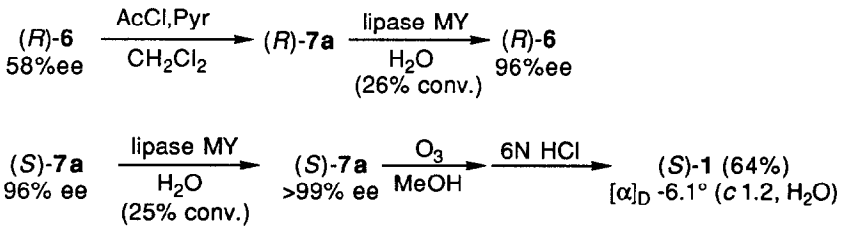


Table I.

substrate	R	lipase	time (h)	conv.[a] (%)	optical purity (% ee) (*S*)-**7**[b]	(*R*)-**6**[c]
7a	$COCH_3$	MY	5	61	96	58
7a	$COCH_3$	P	8	26	20	53
7b	$COCH_2CH_3$	MY	2	95	4	-[d]
7b	$COCH_2CH_3$	P	15	55	65	55
7c	$COCH(CH_3)_2$	MY	2	55	20	17
7c	$COCH(CH_3)_2$	P	24	0	-	-
7d	$CO(CH_2)_6CH_3$	MY	10	58	25	18
7d	$CO(CH_2)_6CH_3$	P	36	55	24	21
7e	COPh	MY	10	42	0	0
7e	COPh	P	24	0	-	-

[a]Determinated by ^{19}F NMR analysis of the crude mixture. [b]Confirmed by first transforming to the β-hydroxyamide **6** by chemical hydrolysis (K_2CO_3, MeOH) followed by convertion into the corresponding MTPA esters. [c]Checked by converting into the corresponding MTPA esters. [d]Not isolated

In all cases, cleavage of amide was not observed. For all substrates the reaction rates of lipase MY-catalyzed hydrolysis were higher than those of lipase P, and no reaction was observed when lipase P was employed for hydrolysis of **7c** and **7e**. Although hydrolysis of **7e** with lipase MY was non-enantioselective, in all other cases the *R* enantiomers were preferentially hydrolyzed to give (*S*)-enriched starting material and (*R*)-enriched hydrolyzed compound.[11] As seen in Table I, when the substrate (±)-**7a** was hydrolyzed with lipase MY, both (*S*)-**7a** and (*R*)-**6** were obtained in the highest optical purities, which were further enhanced by recycling procedures[12] as follows. Reacetylation of (*R*)-**6** provided (*R*)-**7a**, which was again treated with lipase MY (26% conv.) to give (*R*)-**6** in 96% ee, while additional enzymic hydrolysis (25% conv.) of (*S*)-**7a** afforded (*S*)-**7a** in >99% ee. Ozonolysis of (*S*)-**7a** followed by acid hydrolysis gave (*S*)-β,β-difluoromalic acid in 64% yield. The biological evaluation[13] and the synthetic application of this chiral material are now in progress.



Acknowledgement. We are grateful to Professor T. Taguchi, Tokyo College of Pharmacy, for providing valuable information which was helpful in establishment of the absolute stereochemistry of **6**.

References and Notes

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6. ^{1}H NMR (D_2O) δ 4.55 (dd, 1 H, J = 10.7, 15.1 Hz); ^{13}C NMR (D_2O) δ 173.9 (dd, J = 1.9, 5.0 Hz), 169.9 (t, J = 28.4 Hz), 117.1 (dd, J = 255, 257 Hz), 73.7 (t, J = 25.8 Hz); ^{19}F NMR (D_2O, TFA) δ -38.8 (dd, 1 F, J = 10.7, 258 Hz), -41.2 (dd, 1 F, J = 15.3, 258 Hz)
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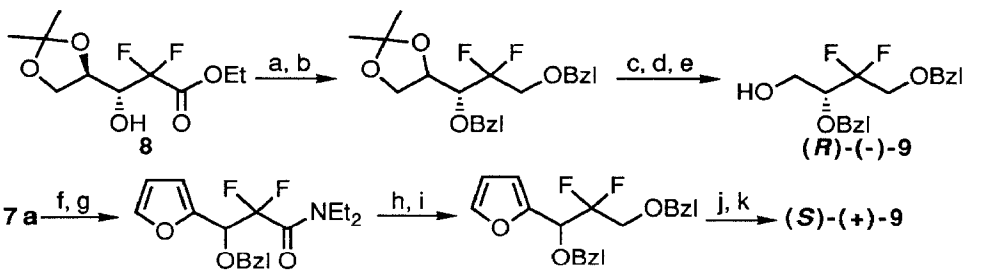
9. ^{1}H NMR ($CDCl_3$) δ 1.19 (t, 3 H, J = 7.1 Hz), 1.22 (t, 3 H, J = 7.1 Hz), 3.42 (q, 2 H, J = 7.1 Hz), 3.53 (q, 2 H, J =7.1 Hz), 4.1~4.5 (br, 1 H), 5.29 (dd, 1 H, J = 4.5, 18.7 Hz), 6.41 (dd, 1 H, J = 1.8, 3.3 Hz), 6.51 (dd, 1 H, J = 0.8, 3.3 Hz), 7.46 (dd, 1 H, J = 0.8, 1.8 Hz); ^{13}C NMR ($CDCl_3$) δ 163.4 (t, J = 28.4 Hz), 149.6 (t, J = 1.8 Hz), 143.3, 115.2 (dd, J = 260.9, 268.0 Hz), 110.9, 110.1, 69.3 (dd, J = 25.3, 30.4 Hz), 42.1 (dd, J = 5.4, 7.0 Hz), 41.8, 14.2, 12.2; ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ -105.4 (dd, 1 F, J = 5.3, 289 Hz), -115.9 (dd, 1 F, J = 18.3, 289 Hz)
10. To a suspension of the enzyme (150000 unit) in distilled water (300 mL) was added neat substrate (30.0 mmol) at 30 °C. The progress of hydrolysis was monitored by the decrease of the pH, which was maintained at initial value by continuous addition of 1N NaOH. After consumption of 1 mL of 1 N NaOH, the reaction mixture was diluted with ethyl acetate (300 mL) and filtered through a pad of celite. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (300 mL x 2). The combined organic extracts were washed with brine, dried over $MgSO_4$, and evaporated to give a crude mixture of **6** and **7**, which was separated by column chromatography on alumina (11:1 hexane/ethyl acetate).
11. The absolute stereochemistry of resolved compounds were determined as follows. The configurationally known compound **8** (Hertel, L. W.; Kroin, J. S.; Misner, J. W.; Tustin, J. M. *J. Org. Chem.* **1988**, *53*, 2406-2409.) was converted to triol dervative **9** which was found to be identical, except for signs of rotation, with that obtained from enzymatically unhydrolyzed substrate **7a**.



a: $NaBH_4$, EtOH. b: NaH, BzlBr, THF. c: 80% aq. AcOH. d: $Pb(OAc)_4$, CH_2Cl_2. e: $NaBH_4$, EtOH. f: K_2CO_3, MeOH. g: NaH, BzlBr, THF. h: LAH, THF, followed by $NaBH_4$ in THF-H_2O. i: NaH, BzlBr, THF. j: O_3, MeOH. k: LAH, THF.

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