Synthesis of (+)-(*R*)-1-Amino-2,2-difluorocyclopropane-1-carboxylic Acid through Lipase-Catalyzed Asymmetric Acetylation

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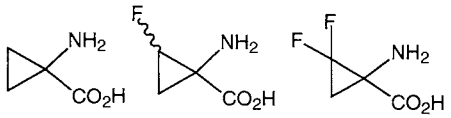
(Received February 5, 1999; CL-990075)

(+)-(*R*)-1-Amino-2,2-difluorocyclopropane-1-carboxylic acid was synthesized *via* the lipase-catalyzed asymmetric acetylation of a pro-chiral diol as the key step.

1-Aminocyclopropane-1-carboxylic acid (ACC) (**1**), which is found in many plants, has several biological activities.[1] In the field of medicinal chemistry, the introduction of a fluorine atom into biologically important compounds often has dramatic effects on their biological activity. In the case of ACC, Kirk reported that racemic mono-fluorinated ACC (**2**) [1-amino-2-fluoro-cyclopropane-1-carboxylic acid (FACC)] showed potencies comparable to the parent ACC at the NMDA receptor.[2]

gem-Difluorinated ACC [1-amino-2,2-difluorocyclopropane-1-carboxylic acid (DFACC)], which is an unknown compound in the literature, is also an attractive synthetic target, because some amino acids containing the *gem*-difluorocyclopropane moiety have interesting biological activities.[3] Peptides containing DFACC as their amino acid residue are also interesting compounds, since several peptides having the ACC residue show variegated biological activities.[1]

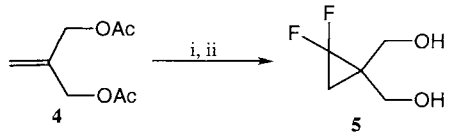


1 ACC **2** FACC **3** DFACC

Figure 1.

We now describe the first total synthesis of (+)-(*R*)-1-amino-2,2-difluorocyclopropane-1-carboxylic acid [(+)-(*R*)-DFACC] [(***R***)-**3**] through the lipase-catalyzed asymmetric acetylation of a pro-chiral diol as the key step.

The pro-chiral diol containing the *gem*-difluorocyclopropane moiety (**5**) was synthesized from the diacetate (**4**) as follows: Diacetate (**4**), easily prepared from 2-methylidene-1,3-propanediol, was subjected to difluorocyclopropanation using the difluorocarbene derived from sodium chlorodifluoroacetate in diglyme at 180 °C [4] followed by subsequent deacetylation to afford **5** (Scheme 1).

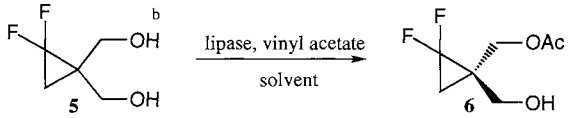


4 **5**

Scheme 1. Reagents and conditions: i) ClF_2CCO_2Na, diglyme, 180 °C (74%); ii) K_2CO_3, MeOH, H_2O (61%).

We then examined the lipase-catalysed asymmetric acetylation of **5**[5] to obtain the chiral monoacetate (**6**). Three commercially available lipases [porcine pancreatic lipase (PPL), Novozym 435 from *Candida antarctica*, and Amano PS from *Pseudomonas cepacia*] were tested for their selective acetylation ability toward **5** in organic solvents. As it is well known that the hydrophobicity of organic solvents can influence the enantioselectivity of lipase-catalyzed reactions,[6] a variety of organic solvents were used. These results are summarized in Table 1. The PPL-catalyzed reaction proceeded very slowly (Runs 1-5). Although several reactions proceeded at the appropriate reaction rate, PPL provided **6** in low enantiomeric excess (Runs 2, 4). The pro-chiral selectivity of Novozym 435 toward **5** was also very poor (Runs 6, 7). Excellent enantioselectivity (91.3% *ee*) with a high chemical yield was obtained when **5** was treated with lipase PS and vinyl acetate in benzene/di-*i*-propyl ether = 20:1 at 35 °C (Run 9). The selectivity was improved with an increase in the hydrophobicity of the solvent used (Runs 8-10).

Table 1. Lipase-catalyzed acetylation of the diol **5**



5 **6**

Run	Lipase[a] /mg	Solvent/ml	Vinyl acetate /eq	Reaction time/h	ee /%[c]	Yield/% **6**	Diacetate
1	PPL (10)	Pr^i_2O (2)	1	145	—	22.2	0.6
2	PPL (100)	PhH (2), Pr^i_2O (0.1)	1	146	23.5	91.0	6.1
3	PPL (100)	THF (2)	10	96	—	62.2	4.1
4	PPL (100)	AcOEt (2)	10	48	35.5	76.0	5.9
5	PPL (100)	CH_3CN (2)	10	96	—	68.1	8.3
6	Novozym435 (10)	PhH (1), Pr^i_2O (1)	1	1	45.8	90.8	2.6
7	Novozym435 (10)	Pr^i_2O (2)	1.5	1	37.5	89.6	10.1
8	PS (10)	PhH (1), Pr^i_2O (1)	10	1.5	88.6	95.1	1.7
9	PS (10)	PhH (2), Pr^i_2O (0.1)	10	1.5	**91.3**	96.5	1.2
10	PS (10)	CH_3CN (2)	10	0.5	—	73.9	3.7

[a]PPL: porcine pancreatic lipase (Amano), Novozym 435: *Candida antarctica* (Novo), PS: *Pseudomonas cepacia* (Amano). [b]10 mg of 5 was used. [c]Determined by HPLC analysis (DAICEL CHIRALCEL OB-H, hexane/*i*-PrOH = 20/1) of the corresponding benzoyl ester of 6.

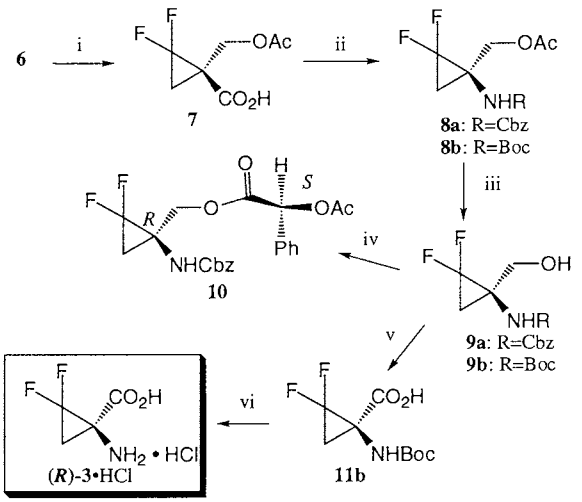
We next tried to synthesize the desired chiral amino acid [(***R***)-**3**] starting from the chiral mono-alcohol (**6**) (Scheme 2).

The oxidation of **6** with Jones reagent afforded the carboxylic acid **7**, and **7** was converted into carbamates (**8**)[7] using Shioiri's method [diphenylphosphoryl azide (DPPA), benzyl alcohol or *t*-butanol, and triethylamine in refluxing benzene].[8] The alkaline hydrolysis of **8** provided the *N*-protected aminoalcohols (**9**).[7,9]

At this stage, the ester **10** was prepared from **9a** and (*S*)-(+)-

O-acetylmandelic acid, and the absolute configuration of **10** was determined using an X-ray structural analysis. The ORTEP plot shows the X-ray structure of **10**[10] (Figure 2). This result means that **6** and **9** have the (*R*)-configuration.[11]

N-BocDFACC (**11b**) was obtained through the Jones oxidation of **9b**,[12] and the acid hydrolysis of **9b** provided the desired (+)-(*R*)-1-amino-2,2-difluorocyclopropane-1-carboxylic acid [(***R*)-3**][13] as a hydrochloride.



Scheme 2. Reagents and conditions: i) Jones oxid., rt; ii) for **8a**; DPPA, BnOH, Et_3N, C_6H_6, reflux, 50% in two steps, for **8b**; DPPA, *t*-BuOH, Et_3N, reflux, 51% in two steps; iii) K_2CO_3, MeOH, H_2O, rt, **9a**: 66%, **9b**: 93%; iv) (*S*)-(+)-*O*-acetylmandelic acid, DCC, DMAP, CH_2Cl_2, rt, 99%; v) Jones oxid., rt; vi) aq.HCl, AcOEt, rt, 99% in two steps.

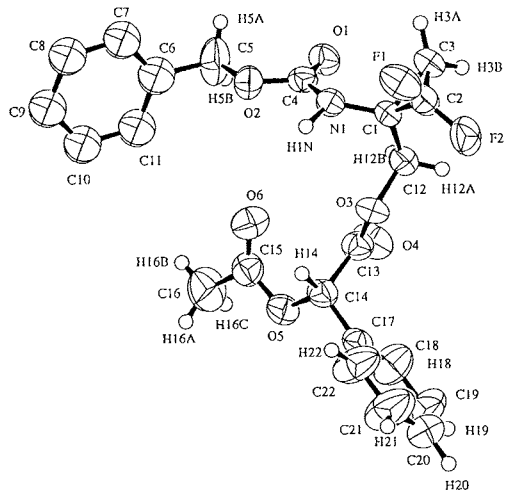


Figure 2. ORTEP diagram of **10** with 50% thermal ellipsoids. The minor disordered contribution of phenyl group of benzyloxycarbonyl group is omitted for clarity.

The asymmetric synthesis of (-)-(*S*)-1-amino-2,2-difluorocyclopropane-1-carboxylic acid [(*S*)-**3**, the enantiomer of (***R*)-3**] and a biological evaluation of (***R*)-3** are currently under investigation.

We thank Amano Pharmaceutical Co., Ltd., and Novo Nordisk Co., Ltd., for kindly providing the lipases.

References and Notes

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7 These compounds were purified by recrystallization from *n*-hexane (for **8b** and **9b**) or *n*-hexane / ethyl acetate (for **8a** and **9a**).

8 K. Ninomiya, T. Shioiri, and S. Yamada, *Tetrahedron*, **30**, 2151 (1974).

9 Based on HPLC analysis of the benzoyl esters of **9**. The optical purity of these compounds turned out to be almost 100%ee. Only one enantiomer was detected.

10 *Crystal data* for **10**: colorless prismatic crystals; mp 99-101 °C; recrystallized from *n*-hexane - ethyl acetate; $C_{22}H_{21}F_2NO_6$, M = 433.40, monoclinic, a = 10.129(3), b = 9.069(2), c = 12.606(2) Å, β = 109.500(14)°, U = 1091.5(4) Å^3, T = 296 K, space group $P2_1$ (no. 4), Z = 2, μ (Mo - Kα) = 0.107 mm^{-1}, 2801 reflections measured, 2657 reflections unique, $R1$ = 0.0572, $wR2$ = 0.1703.

11 The enantiopreference of the lipase-catalyzed asymmetric acetylation of **5** followed the empirical rule proposed by Kazlauskas *et al.*: A. N. E. Weissfloch and R. J. Kazlauskas, *J. Org. Chem.*, **60**, 6959 (1995).

12 Although the oxidation of **9a** with Jones reagent gave *N*-Cbz-DFACC (**11a**), all attempts (H_2-Pd/C-AcOEt, TMSI-CH_3CN or aq.KOH-MeOH) to deprotect the Cbz group from **11a** were unsuccessful.

13 (***R*)-3**•HCl: colorless crystals; mp 170 °C (decomp.); $[\alpha]_D^{27.2}$ +5.10° (c, 1.05, H_2O); IR (neat) cm^{-1}: 2899, 1722, 1472, 1186; ^{1}H-NMR (DMSO-d_6) δ: 2.54-2.59 (2H, m); ^{13}C-NMR (DMSO-d_6) δ: 20.53 (t, J_{CF}= 9.3 Hz), 79.05 (t, J_{CF}= 9.3 Hz), 109.26 (t, J_{CF}= 286.5 Hz), 164.62 (s); ^{19}F-NMR ($CDCl_3$) δ: -133.8 (1F, dt, J_{FF}= 157.2 Hz, J_{HF}= 11.6 Hz), -136.2 (1F, ddd, J_{FF}= 157.2 Hz, J_{HF}= 10.2, 6.5 Hz); FAB-HRMS Found 138.0363. Calcd for $C_4H_6F_2NO_2$ (M^++H) 138.0367.