Efficient Synthesis of Enantiopure 1,2-Bis(hydroxymethyl)-3,3-difluorocyclopropane Derivatives through Lipase-Catalyzed Reaction

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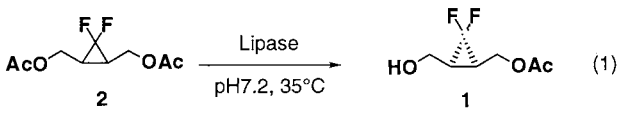
Efficient synthesis of chiral difluorocyclopropane building block has been accomplished; prochiral diacetate of 1,2-bis(hydroxymethyl)-3,3-difluorocyclopropane was converted to the corresponding monoacetate through *Alcaligenes* sp. lipase-catalyzed hydrolysis with >99% enantiomeric excess.

The difluoromethylene group is well known as an isoelectronic and isosteric substitute for oxygen in phosphate analogues [2] and geminal difluorinated compounds thus mimic the tetrahedral transition states related to the hydrolytic action of proteases and esterases; this caused enzyme inhibition to occur when the nucleophilic hydroxyl group is part of the active site of the enzyme.[2] The utility of cyclopropane derivatives in the construction of a variety of cyclic and acyclic organic compounds has been amply demonstrated.[3] Substitution of two fluorine atoms on the cyclopropane ring is expected to alter both chemical reactivity and biological activity due to the strong electron-withdrawing nature of fluorine.[4,5] These make efficient methods for the synthesis of a suitably functionalized building block for chiral difluorocyclopropane even more necessary. We describe here the first successful synthesis of an optically pure difluorocyclopropane building block **1** through lipase-catalyzed asymmetric hydrolysis of the corresponding prochiral diacetate **2**.[1]

For the strategy of this synthesis, we decided to use lipase-catalyzed hydrolysis protocol. The synthetic value of lipase has been well recognized because the reaction proceeds efficiently and selectively under mild conditions.[6,7]

Prochiral diacetate was prepared as follows; easily available diacetate of (*Z*)-2-butendiol was subjected to Taguchi's difluorocyclopropanation [8] using *cis*-addition of difluorocarbene [9] derived from sodium difluoroacetate in diglyme at 180 ℃ to afford diacetate **2** in more than 80% yield. The asymmetric hydrolysis of **2** was typically carried out as follows: to a phosphate buffer solution (10 ml, 0.1 M at pH 7.2) was added **2** (1.0 mmol) and lipase QL (50 wt% towards the substrate) and the mixture was stirred at 35 ℃ (Eq. 1). The alcohol **1** produced was extracted with ethyl acetate and purified by silica gel flash column chromatography (hexane / ethyl acetate = 5:1 to 2:1).



2 **1** (1)

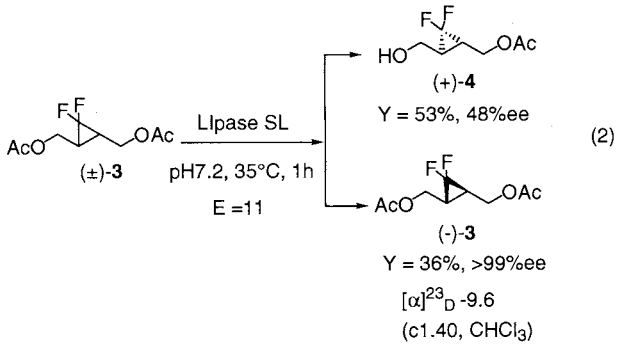
Twenty-eight commercially available lipases were screened for their activity but only five were found to have hydrolyzed acetate **2** to afford monoacetate **1** with more than 60% ee; lipase QL (Meito) from *Alcaligenes* sp. provided the corresponding monoacetate **1** in the highest enantiomeric excess (Table 1, Entry 1).[10] Lipase TL and PCL also gave **1** with good enantiomeric excess (Entries 2 and 3). In contrast, we obtained no reliable results when **2** was subjected to the reaction of PPL, though it once gave **1** with 96% ee (Entry 5). Because the PPL-catalyzed reaction proceeded very slowly, partial racemization of the product apparently occurred.

Table 1. Asymmetrization of prochiral diacetate **2** through lipase-catalyzed hydrolysis [a]

Entry	Lipase	Time (h)	%ee of **1** (Yield)	$[\alpha]^{23}_D$ of **1** (c in $CHCl_3$)
1	QL	5	>99 %ee (81%)	+15.5 (c1.2)
2	TL	6	90 %ee (58%)	+15.4 (c1.39)
3	PCL	8	85 %ee (97%)	+12.5 (c1.22)
4	AL	48	85 %ee (75%)	+12.5 (c1.20)
5	PPL	168	62 %ee (53%)	+10.0 (c1.00)

[a] The reaction was carried out in 0.1 M potassium phosphate buffer at pH 7.2 and enantiomeric excess was determined by capillary GC analysis using Chiraldex-GTa (ϕ 0.25 mm x 20 M, He, 70 ℃ or 100 ℃). [b] QL: *Alcaligenes* sp. TL: *Pseudomonas* sp. PCL: *Pseudomonas cepacia*. AL: *Achromobacter* sp. PPL: Porcine pancreatic lipase.

Diacetate of (*trans*)-1,2-bis(hydroxymethyl)-3,3-difluorocyclopropane **3** is not prochiral but racemic form, so that optical resolution of (±)-**3** was performed using lipase-catalyzed reaction (Eq. 2). In this reaction, the best result was recorded when (±)-**3** was reacted with lipase SL (*Pseudomonas cepacia* SL-25, Meito), and diacetate (-)-**3** remaining was obtained with >99% ee (E value [11] of the reaction was 11).[12]



(2)

In summary, we succeeded in synthesizing difluorocyclopropane building blocks **1** and **3** with extremely high optical purity through lipase-catalyzed reaction. Lipase-catalyzed reactions are particularly useful even for large-scale preparative organic synthesis. The present protocol will undoubtedly allow us to evolve a smarter and more convenient synthesis of chiral difluorocyclopropane derivatives. Further

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studies on the synthesis of difluoroanalogues of natural biologically active cyclopropane compounds are ongoing.

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References and notes

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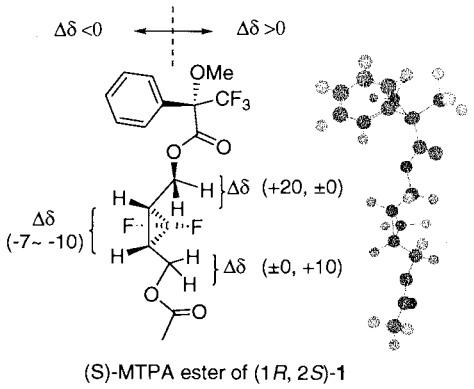
10 The absolute configuration of **1** produced was a tentative one. We assume it to be (1*R*, 2*S*) based on the results of Mosher's modified method by Kusumi et al.: I. Ohtani, T. Kusumi, Y. Kashman, and H. Kakisawa, *J. Am. Chem. Soc.*, **113**, 4092 (1991). (*R*)- and (*S*)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid (MTPA) demonstrated negative chemical shift differences ($\Delta\delta = \delta_S - \delta_R$) for protons on C-1 and C-2 shown below. The optimized structure by semiempirical (PM3) calculation of (*S*)-MTPA ester of (1*R*, 2*S*)-**1** agreed with these results (Fig. 1). We are now attempting to confirm this by X-ray crystallographic analysis of (*S*)-(+)-6-methoxy-α-methyl-2-naphthaleneacetate of **1**. However, single crystals suitable for X-ray diffraction have not yet been obtained.



(S)-MTPA ester of (1*R*, 2*S*)-**1**

Figure 1. $\Delta\delta=(\delta_S-\delta_R) \times 10^3$ for (*R*)- and (*S*)-MTPA esters of **1** by 500 MHz ^{1}H NMR analysis.

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12 The stereochemistry of (-)-**3** was tentatively assigned as (*R,R*), and (+)-**4** to be (*S,S*), based on the CD exciton chirality method using the 9-anthracenecarboxylate derivative. The CD spectrum of (-)-1,2-bis[(9-anthracene-carbonyl)methyl]-3,3-difluorocyclopropane converted from (-)-**3** exhibited the negative chirality on the Cotton effect [253.8 nm and 235.8 nm ($\Delta\varepsilon$ = 2.1), hexane]. For this method see: S. Egusa, M. Sisido, and Y. Imanishi, *Bull. Chem. Soc. Jpn.* **59**, 3175 (1985). For CD exciton theory see: N. Harada and K. Nakanishi, "Circular Dichroic Spectroscopy—Exciton Coupling in Organic Stereochemistry," University Science Books, Mill Valley, CA, and Oxford University Press: Oxford, (1983).