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Synthesis of optically active 2,2-difluorohomoallylalcohols by lipase-catalyzed transesterification

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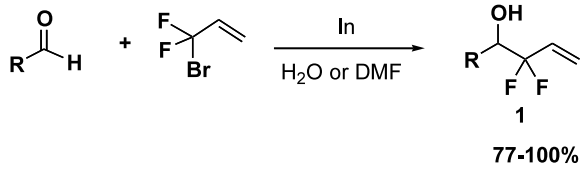
Abstract—Racemic 2,2-difluorohomoallylalcohols could be resolved into (*R*)-alcohols and (*S*)-acetates through *Pseudomonas fluorescens* lipase-catalyzed enantioselective transesterification. The utility of the resulting chiral, non-racemic 2,2-difluorohomoallylalcohols was demonstrated by conversion of one of the (*S*)-acetates into a synthetically important 2,2-difluoro-3-hydroxycarboxylate derivative. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

We have previously reported on the synthesis of 2,2-difluorohomoallylalcohols of the type **1** from the reaction of 3-bromo-3,3-difluoropropene and aldehydes in the presence of indium (Scheme 1). This method is easy and affords the desired products in high yields.[1]

Optically active 2,2-difluorohomoallylalcohols **1** can be considered very useful fluorine-containing chiral building blocks because they bear several different functional groups, which gives great scope for further transformations. For example, oxidation the alkene moiety of **1** can lead to either an aldehyde, or carboxylic acid derivatives. Using such a method, chiral, non-racemic 2,2-difluoro-3-hydroxycarboxylates,[2] which are versatile intermediates for the synthesis of several biologically important fluorinated peptides, might easily be obtained from the targeted optically active 2,2-difluorohomoallylalcohols **1**.



Scheme 1.

The hydroxyl moiety is also useful for further transformations of **1**: Percy and co-workers prepared 2,2-difluorohomoallylalcohols using our method and synthesized racemic difluorinated dihydropyrans from (±)-**1** by allylation of the hydroxyl moiety and subsequent ring closing metathesis.[3] Therefore, optically active difluorinated dihydropyrans, which are potential precursors of fluorinated sugar mimetics, can be obtained from the targeted optically active 2,2-difluorohomoallylalcohols **1** (Scheme 2).

The resolution of racemic alcohols through lipase-catalyzed transesterification in organic solvents is now a widely used methodology and has been successfully applied to a wide variety of substrates.[4] The lipase-catalyzed reaction proceeds under very mild conditions and many functional groups such as double bonds, triple bonds, carbonyl groups, cyano groups and halogen atoms are not affected by the reaction conditions. Optically active fluorinated alcohols have previously been obtained using this method of resolution.[5] As a result of their synthetic potential, we planned to resolve compounds **1** through lipase-catalyzed transesterification in

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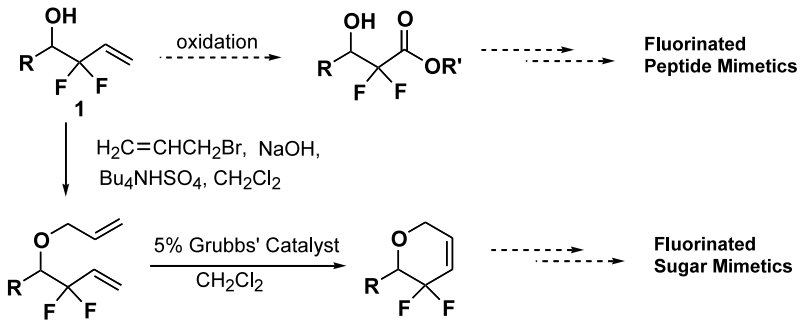


Scheme 2.

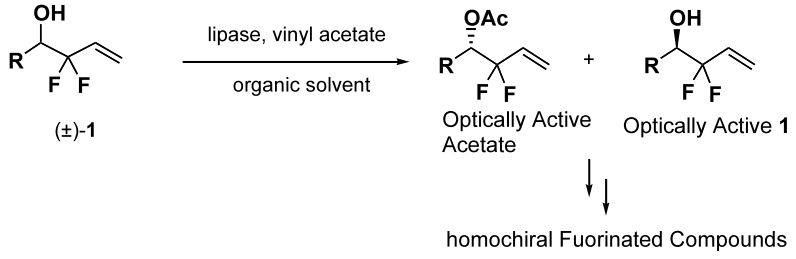
organic solvents and to utilize the optically active **1** as a chiral fluorinated building block (Scheme 3).

2. Results and discussion

2.1. Kinetic resolution of racemic fluorinated alcohols

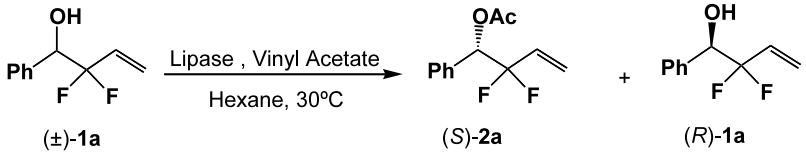
We first screened eight commercially available lipases (Amano AK, Amano AY, Amano PPL, Amano PS, Meito ALC, Meito PLC, Novozym 435 and Toyobo LIP) for their ability to mediate the transesterification of (±)-**1a** smoothly and with good enantioselectivity. In all reactions, vinyl acetate was used as the acylating agent in hexane solvent (Table 1). All of the lipases tested here show the same enantiopreference, which is expected to be for the *S*-configuration. The determination of the absolute configuration of the preferentially transesterified enantiomers will be discussed later. From this initial screening, lipase from *Pseudomonas fluorescens* (Amano AK) was selected and employed for further studies, because it demonstrated high enantioselectivity ($E^6=82$) and the best reactivity.

We next examined the effect of the organic solvents on the enantioselectivity and the reactivity of Amano AK lipase (Table 2). The lipase shows the highest enantioselectivity and reactivity in hexane. No correlation



Scheme 3.

Table 1.



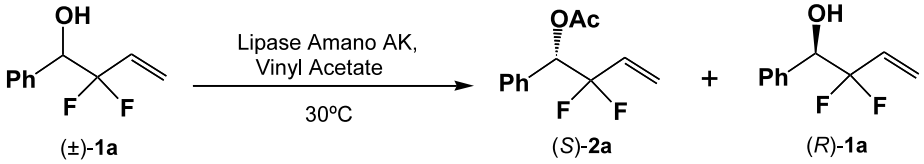
Lipase[a]	Time (h)	Conversion (%)	Ee **2a** (%)	Ee **1a** (%)	E^6
PCL[b]	1056	28	97	38	95
PFL	68	50	92	93	82
CAL	1061	23	90	27	25
AlsL[b]	981	35	75	41	10
PAL[b]	768	<9	–	–	–
AcsL[b]	114	<2	–	–	–
CRL	115	<0.6	–	–	–
PPL	114	0	–	–	–

Conditions: lipase (20 mg), **1a** (25 μmol), vinyl acetate (0.1 ml), hexane (1 ml).

[a] PCL: *Pseudomonas cepacia* (Amano PS), PFL: *P. fluorescens* (Amano AK), CAL: *Candida antarctica* (Novozym 435), AlsL: *Alcaligenes* sp. (Meito PLC), PAL: *Pseudomonas aeruginosa* (Toyobo LIP), AcsL: *Achromobacter* sp. (Meito ALC), CRL: *Candida rugosa* (Amano AY), PPL: *Porcine pancrea* (Amano PPL).

[b] Lipase (10 mg).

Table 2.



Solvent	Time (h)	Conversion (%)	Ee **2a** (%)	Ee **1a** (%)	E[6]
Hexane	68	50	92	93	82
Isooctane	94	55	76	92	24
Diisopropyl ether	361	43	90	67	38
Acetonitrile	967	40	70	46	9

between the hydrophobicity of the solvents and the E values was observed.[7]

We then investigated whether a combination of Amano AK and hexane as a reaction media could effectively resolve the analogous alcohols **1b**–**1f**. As shown in Table 3 **1a**–**1d** could be resolved with good enantioselectivity. It has been reported previously that many secondary alcohols in which the stereogenic carbons are attached to an aromatic group and an alkyl group could be resolved highly enantioselectively via lipase-catalyzed reactions.[8] In contrast, moderate enantioselectivity was observed for **1e** and **1f**, which have two aliphatic groups attached to the stereogenic carbons.

The lipase shows extremely high enantioselectivity (E> 100) toward all the *para*-substituted phenyl derivatives **1b**–**1d**. In this study, the effect of the substituents on the E values is not clear; it is meaningless to distinguish between E values greater than 100 when we are discussing the enantioselectivity of lipase-catalyzed reactions because the E values become increasingly sensitive to very small errors in the measurement of ee.[6]

2.2. Determination of the absolute configurations

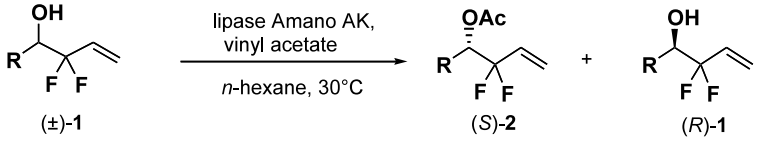
We synthesized ester **3** from optically active **1c** (obtained from the kinetic resolution of (±)-**1c**) and (*S*)-(+)-*O*-acetylmandelic acid. The absolute configuration of **3** was then determined by X-ray crystallographic analysis. The ORTEP plot (Scheme 4) shows the X-ray structure of **3**.

The absolute structure of **3** shows that optically active alcohol **1c** has *R*-configuration, (which means that the acetate product from the resolution reaction (compound **2c**) has *S*-configuration). Although the absolute configuration of alcohols **1a**, **1b** and **1d**–**1f** obtained from the kinetic resolution of the racemic alcohols were not determined, they were expected to have *R*-configuration based on the case of **1c** and the empirical rule for the enantiopreference of lipases.[9]

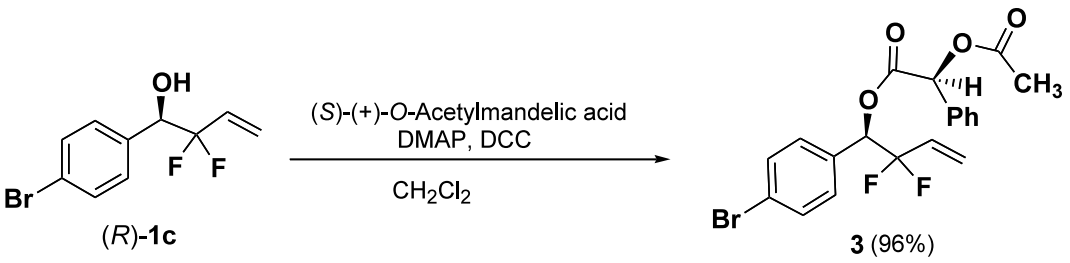
2.3. Synthesis of optically active 2,2-difluoro-3-hydroxycarboxylate derivatives

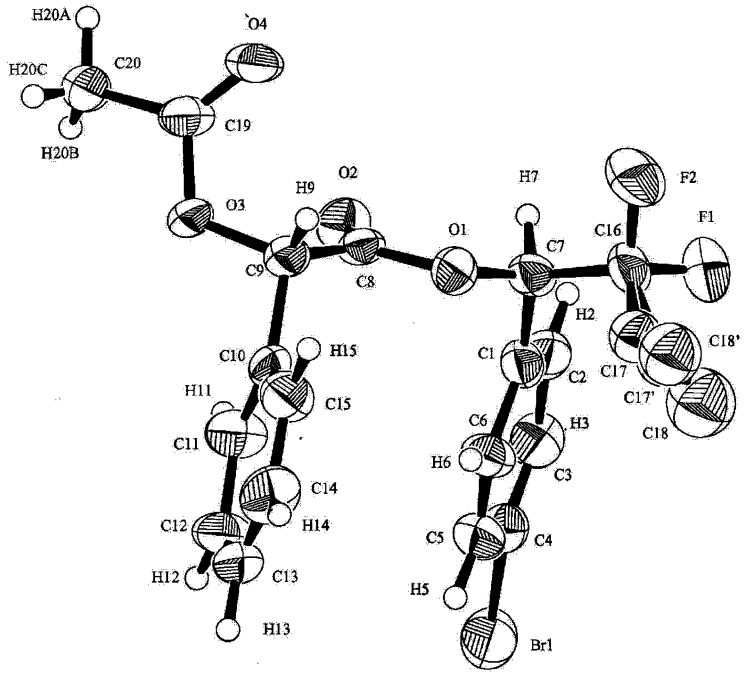
As was mentioned in the introduction to this paper, optically active 2,2-difluoro-3-hydroxycarboxylate derivatives are important compounds. As a demonstration of the synthetic potential of the compounds **2**, we planned to convert the obtained (*S*)-**2a** into the 2,2-difluoro-3-hydroxycarboxylate derivative **5**. In practice, this was effected in two steps: Ruthenium-catalyzed oxidation[10] of the alkene function of (*S*)-**2a** provided the carboxylic acid **4**. The reaction of trimethylsilyldiazomethane with **4** then afforded the desired methyl ester **5** in 41% overall yield (Scheme 5).

Table 3.

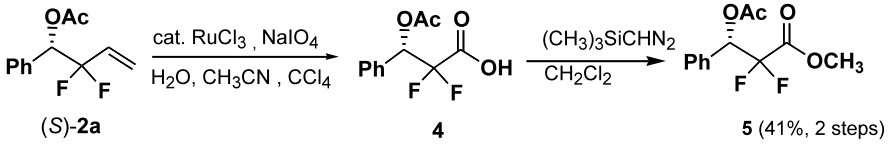


Substrate	Time (h)	Conversion (%)	Ee (*S*)-**2** (%)	Ee (*R*)-**1** (%)	E[6]
1a: R = C_6H_5	68	50	92	93	82
1b: R = *p*-CH_3O–C_6H_4	47	43	97	72	142
1c: R = *p*-Br-C_6H_4	48	43	97	74	146
1d: R = *p*-NC–C_6H_4	57	50	98	97	303
1e: R = cyclohexyl	47	49	88	86	43
1f: R = *n*-C_9H_{19}	48	46	76	65	14





Scheme 4.



Scheme 5.

3. Conclusion

The *P. fluorescens* lipase-catalyzed resolution of racemic 2,2-difluorohomoallylalcohols effectively afforded the (*R*)-alcohols **1** and (*S*)-acetates **2**. A 2,2-difluoro-3-hydroxycarboxylate derivative **5** could be obtained from the optically active **2**. The resulting optically active 2,2-difluorohomoallylalcohols and their derivatives are expected to be useful chiral fluorinated building blocks.

4. Experimental

4.1. General

2,2-Difluorohomoallylalcohols (**1a** and **1c**) were prepared according to the author's method.[1] Amano AK, Amano AY, Amano PPL and Amano PS were supplied by Amano Enzyme, Inc. Meito ALC and Meito PLC were supplied by Meito Sangyo Co., Ltd. Novozym 435 and Toyobo LIP were supplied by Novo Nordisk and Toyobo Co., Ltd., respectively. The infrared spectra (IR) were measured using a Jasco IR-8300 FT-IR spectrophotometer. The ^{1}H and ^{19}F NMR spectra were obtained using a JEOL JNM-400 instrument with tetramethylsilane (for ^{1}H) and chlorotrifluoromethane (for ^{19}F) as the internal standards. The mass spectra (MS) and high-resolution mass spectra (HR-MS) were measured with a JEOL JMS D-200 spectrometer. Melting points were measured with a Yanaco MP-S3 melting-point apparatus. Optical rotations were measured with a Perkin–Elmer 241 polarimeter. Gas chromatograms were recorded on a Shimadzu GC-14B with an OV 101 bonded capillary column (Gasukuro Industry), 17 m× 0.25 mm, or a CP Cyclodextrin-B-236-M-19 capillary

column (Chrompack), 25 m×0.25 mm, or a Gamma DEX 120 capillary column (Supelco), 30 m×0.25 mm. HPLC analyses were done on a Hitachi L-6250 intelligent pump with a Hitachi L-4000 UV detector using a chiral column CHIRALPAK AD-H (Daicel), 250 mm×4.6 mm. Column chromatography was performed on silica gel (Wakogel C300).

4.2. Representative procedure for the preparation of racemic 2,2-difluorohomoallylalcohols, 1b, 1d–f

A suspension containing *p*-anisaldehyde (340 mg, 2.50 mmol), 3-bromo-3,3-difluoropropene (0.38 ml, 3.57 mmol), powdered indium (430 mg, 3.57 mmol) and DMF (5 ml) was stirred for 3 h at rt. The reaction mixture was then quenched with 10% HCl and extracted with ether (3×20 ml). The combined organic extract was washed with brine, dried over anhydrous magnesium sulfate and the solvent was removed in vacuo. The residue was purified using chromatography on silica gel (*n*-hexane:ethyl acetate = 5:1) to give 512 mg (94%) of (±)-**1b**.

4.2.1. (±)-2,2-Difluoro-1-(*p*-methoxyphenyl)but-3-en-1-ol, 1b. Colorless oil. IR (neat) cm^{-1}: 3410; ^1H NMR δ: 2.55–2.63 (1H, br), 3.81 (3H, s), 4.85 (1H, t, $J=10$ Hz), 5.46 (1H, d, $J=10$ Hz), 5.59 (1H, d, $J=18$ Hz), 5.79 ~ 5.92 (1H, m), 6.89 (2H, d, $J=8$ Hz), 7.34 (2H, d, $J=8$ Hz); ^{19}F NMR δ: −108.72 (1F, dt, $J_{FF}=250$ Hz, $J_{FH}=10$ Hz), −110.05 (1F, dd, $J_{FF}=250$ Hz, $J_{FH}=10$ Hz); MS (*m*/*z*) 214 (M^+). HRMS calcd for $C_{11}H_{12}F_2O_2$ (M^+), 214.0805. Found: 214.0813.

4.3. (±)-1-(*p*-Cyanophenyl)-2,2-difluorobut-3-en-1-ol, 1d

Chemical yield, quant.: colorless crystals, mp 63–66°C (*n*-hexane). IR (neat) cm^{-1}: 3427, 2230; ^1H NMR δ: 2.83 (1H, s), 4.99 (1H, t, $J=9$ Hz), 5.48 ~ 5.60 (2H, m), 5.77 ~ 5.91 (1H, m), 7.56 (2H, d, $J=8$ Hz), 7.66 (2H, d, $J=8$ Hz); ^{19}F NMR δ: −106.79 (1F, d, $J_{FF}=250$ Hz), −110.05 (1F, d, $J_{FF}=250$ Hz); MS (*m*/*z*) 210 (M^++H). HRMS calcd for $C_{11}H_9F_2NO$ (M^+), 209.0652. Found: 209.0651.

4.3.1. (±)-1-Cyclohexyl-2,2-difluorobut-3-en-1-ol, 1e. Chemical yield, 58%: colorless oil. IR (neat) cm^{-1}: 3398; ^1H NMR δ: 1.10 ~ 1.25 (5H, m), 1.52 ~ 1.75 (4H, m), 1.85 ~ 1.98 (2H, m), 3.48 ~ 3.55 (1H, m), 5.52 (1H, d, $J=12$ Hz), 5.72 (1H, d, $J=12$ Hz), 5.94 ~ 6.01 (1H, m); ^{19}F NMR δ: −104.38 (1F, dt, $J_{FF}=250$ Hz, $J_{FH}=12$ Hz), −110.05 (1F, dd, $J_{FF}=250$ Hz, $J_{FH}=12$ Hz); MS (*m*/*z*) 191 (M^+). HRMS calcd for $C_{10}H_{11}F_2$ (M^+-H_5O), 169.0829. Found: 169.0831.

4.3.2. (±)-3,3-Difluorotridec-1-en-4-ol, 1f. Chemical yield, 70%, a colorless oil. IR (neat) cm^{-1}: 3398; ^1H NMR δ: 0.88 (3H, t, $J=7$ Hz), 1.15 ~ 1.46 (16H, m), 3.76 (1H, q, $J=9$ Hz), 5.54 (1H, d, $J=11$ Hz), 5.71 (1H, d, $J=18$ Hz), 5.91 ~ 6.04 (1H, m); ^{19}F NMR δ: −109.23 (1F, dt, $J_{FF}=244$ Hz, $J_{FH}=11$ Hz), −110.05 (1F, dt, $J_{FF}=244$ Hz, $J_{FH}=11$ Hz); MS (*m*/*z*) 233 (M^+−H). HRMS calcd for $C_{13}H_{24}FO$ (M^+−F), 215.1812. Found: 215.1812.

4.4. Lipase-catalyzed transesterification of alcohols, 1

A typical experimental procedure is as follows: The lipase (20 mg) was placed in a vial to which was added the alcohol (25 μmol), vinyl acetate (0.1 ml) and hexane (1 ml). The resulting suspension was then stirred at 30°C. The reaction was quenched by filtration and the filtrate was concentrated under reduced pressure. The residue was chromatographed on a silica gel column using hexane–ethyl acetate as the eluent to afford an acetate (*S*)-**2** and an unreacted alcohol (*R*)-**1**. An aliquot of the combined fractions containing the unreacted alcohol (*R*)-**1** was analyzed by HPLC or GC to determine the ee of the alcohol. The ee of the produced ester was also determined as mentioned above; **2e** and **2g** were hydrolyzed (1 M NaOH, MeOH) into the corresponding alcohols, the ees of which were determined as mentioned above. The *E* value and the conversion of the reaction were calculated from the ees of the unreacted alcohol and the produced ester.[6]

We also conducted preparative kinetic resolution of all the alcohols using a combination of Amano AK and hexane. From 1.5 to 11 mmol of the racemic fluorinated alcohols were resolved (Table 4). The experimental procedure of the preparative kinetic resolution is the same as that of the small scale resolution.

Table 4. Preparative kinetic resolution of (±)-**1**

Substrate	Produced esters (*S*)-**2**			Recovered alcohol (*R*)-**1**		
	Yield (%)	Ee (%)	$[\alpha]_D$ ($CHCl_3$)	Yield (%)	Ee (%)	$[\alpha]_D$ ($CHCl_3$)
(±)-**1a**	34	84	+52.2 (21°C, *c* 1.45)	39	79	−14.7 (23°C, *c* 1.13)
(±)-**1b**	34	90	+71.3 (23°C, *c* 1.14)	35	94	−20.2 (23°C, *c* 1.01)
(±)-**1c**	40	97	+53.8 (22°C, *c* 1.21)	38	96	−14.3 (24°C, *c* 1.13)
(±)-**1d**	50	97	+59.2 (30°C, *c* 1.09)	50	88	−7.5 (31°C, *c* 1.07)
(±)-**1e**	46	87	+5.3 (25°C, *c* 1.03)	36	95	+20.5 (23°C, *c* 1.09)
(±)-**1f**	49	67	−8.2 (25°C, *c* 1.05)	42	82	+19.7 (25°C, *c* 1.10)

4.4.1. (+)-(*S*)-4-Acetoxy-3,3-difluoro-4-phenylbut-1-ene, (*S*)-2a. Colorless oil. IR (neat) cm^{-1}: 1754; ^1H NMR δ: 2.15 (3H, s), 5.48 (1H, d, $J=11$ Hz), 5.62 (1H, d, $J=18$ Hz), 5.78∼5.91 (1H, m), 5.99 (1H, t, $J=9$ Hz), 7.34∼7.42 (5H, m); ^{19}F NMR δ: −107.07 (1F, dd, $J_{FF}=250$ Hz, $J_{FH}=12$ Hz), −110.05 (1F, dt, $J_{FF}=250$ Hz, $J_{FH}=12$ Hz); MS (m/z) 226 (M^+). HRMS calcd for $C_{12}H_{12}F_2O_2$ (M^+), 226.0805. Found: 226.0806.

4.4.2. (+)-(*S*)-4-Acetoxy-3,3-difluoro-4-(*p*-methoxyphenyl)but-1-ene, (*S*)-2b. Colorless oil. IR (neat) cm^{-1}: 1752; ^1H NMR δ: 2.14 (3H, s), 3.81 (3H, s), 5.48 (1H, d, $J=11$ Hz), 5.62 (1H, d, $J=17$ Hz), 5.77∼5.87 (1H, m), 5.94 (1H, t, $J=11$ Hz), 6.88 (2H, d, $J=9$ Hz), 7.33 (2H, d, $J=9$ Hz); ^{19}F NMR δ: −107.37 (1F, dd, $J_{FF}=256$ Hz, $J_{FH}=11$ Hz), −110.05 (1F, dt, $J_{FF}=256$ Hz, $J_{FH}=11$ Hz); MS (m/z) 256 (M^+). HRMS calcd for $C_{13}H_{14}F_2O_3$ (M^+), 256.0911. Found: 256.0910.

4.4.3. (+)-(*S*)-4-Acetoxy-4-(*p*-bromophenyl)-3,3-difluorobut-1-ene, (*S*)-2c. Colorless oil. IR (neat) cm^{-1}: 1749; ^1H NMR δ: 2.15 (3H, s), 5.50 (1H, d, $J=11$ Hz), 5.62 (1H, d, $J=17$ Hz), 5.76∼5.85 (1H, m), 5.90 (1H, t, $J=11$ Hz), 7.27 (2H, d, $J=10$ Hz), 7.49 (2H, d, $J=10$ Hz); ^{19}F NMR δ: −107.37 (1F, dd, $J_{FF}=250$ Hz, $J_{FH}=11$ Hz), −110.05 (1F, d, $J_{FF}=256$ Hz); MS (m/z) 306 (M^+ for ^{81}Br) 304 (M^+ for ^{79}Br). HRMS calcd for $C_{12}H_9{}^{79}BrF_2O_2$ (M^+ −2H), 303.9729. Found: 303.9736.

4.4.4. (+)-(*S*)-4-Acetoxy-4-(*p*-cyanophenyl)-3,3-difluorobut-1-ene, (*S*)-2d. Colorless oil. IR (neat) cm^{-1}: 2230, 1752; ^1H NMR δ: 2.18 (3H, s), 5.54 (1H, d, $J=11$ Hz), 5.64 (1H, d, $J=17$ Hz), 5.79∼5.92 (1H, m), 5.99 (1H, t, $J=9$ Hz), 7.52 (2H, d, $J=8$ Hz), 7.67 (2H, d, $J=8$ Hz); ^{19}F NMR δ: −105.77 (1F, dd, $J_{FF}=250$ Hz, $J_{FH}=12$ Hz), −110.45 (1F, tt, $J_{FF}=256$ Hz, $J_{FH}=12$ Hz); MS (m/z) 251 (M^+). HRMS calcd for $C_{13}H_{11}F_2NO_2$ (M^+), 251.0757. Found: 251.0757.

4.4.5. (+)-(*S*)-4-Acetoxy-4-cyclohexyl-3,3-difluorobut-1-ene, (*S*)-2e. Colorless oil. IR (neat) cm^{-1}: 1750; ^1H NMR δ: 1.04∼1.29 (6H, m), 1.71∼1.82 (5H, m), 2.11 (3H, s), 4.95∼5.02 (1H, m), 5.50 (1H, d, $J=11$ Hz), 5.70 (1H, d, $J=18$ Hz), 5.83∼5.96 (1H, m); ^{19}F NMR δ: −102.71 (1F, dd, $J_{FF}=250$ Hz, $J_{FH}=12$ Hz), −110.45 (1F, tt, $J_{FF}=250$ Hz, $J_{FH}=12$ Hz). Anal. calcd for $C_{12}H_{18}F_2O_2$: C, 62.05; H, 7.81. Found: C, 61.86; H, 7.67%.

4.4.6. (−)-(*S*)-4-Acetoxy-3,3-difluorotridec-1-ene, (*S*)-2f. Colorless oil. IR (neat) cm^{-1}: 1749; ^1H NMR δ: 0.88 (3H, t, $J=7$ Hz), 1.14∼1.39 (16H, m), 2.10 (3H, s), 5.11∼5.20 (1H, m), 5.52 (1H, d, $J=11$ Hz), 5.70 (1H, d, $J=18$ Hz), 5.81∼5.95 (1H, m); ^{19}F NMR δ: −107.21 (1F, dd, $J_{FF}=250$ Hz, $J_{FH}=12$ Hz), −112.51 (1F, dt, $J_{FF}=250$ Hz, $J_{FH}=12$ Hz); MS (m/z) 277 (M^++H). HRMS calcd for $C_{15}H_{23}F_2O$ (M^+-H_3O); 257.1717. Found: 257.1718.

4.5. (+)-[(*R*)-1-(*p*-Bromophenyl)-2,2-difluorobut-3-enyl] (*S*)-acetoxyphenylacetate, 3

To a stirred solution of **1c** (730 mg, 2.77 mmol), (*S*)-(+)-*O*-acetylmandelic acid (627 mg, 3.23 mmol) and *N*,*N*-dimethylaminopyridine (43 mg, 0.35 mmol) in dichloromethane (5 ml) was added dicyclohexylcarbodiimide (6.44 mg, 3.12 mmol) at room temperature under an inert atmosphere and stirred for 1.5 h. The reaction mixture was diluted with ethyl acetate (10 ml) and filtered with Celite. The filtrate was washed with water, dried over anhydrous magnesium sulfate and evaporated. The residue was purified using chromatography on silica gel (*n*-hexane:ethyl acetate = 10:1) to give **3** as colorless crystals (1163 mg, 96%). mp 91–92°C (*n*-hexane). $[\alpha]_D^{26}$ +29.0 (*c* 1.02, $CHCl_3$). IR (neat) cm^{-1}: 1751; ^1H NMR δ: 2.19 (3H, s), 5.51 (1H, d, $J=11$ Hz), 5.63 (1H, d, $J=18$ Hz), 5.74∼5.88 (2H, m), 6.04 (1H, s), 6.86 (2H, d, $J=8$ Hz), 7.31 (2H, d, $J=8$ Hz), 7.36∼7.43 (5H, m); ^{19}F NMR δ: −106.23 (1F, d, $J_{FF}=245$ Hz), −110.29 (1F, dd, $J_{FF}=245$ Hz, $J_{FH}=28$ Hz); MS (m/z) 441 (M^++H for ^{81}Br) 439 (M^++H for ^{79}Br). HRMS calcd for $C_{20}H_{18}{}^{81}BrF_2O_4$ (M^++H for ^{81}Br), 441.0339. Found: 441.0310.

4.6. X-Ray crystallographic data for 3

A colorless plate crystal of **3** was mounted on a glass fiber. All measurements were made on a Rigaku AFC7R diffractometer with graphite-monochromated Mo–Kα radiation ($\lambda=0.71073$ Å) and a rotating anode generator. The structure was solved by Patterson methods (PATTY[11]), and the non-hydrogen atoms were refined anisotropically except for those of the disordered olefinic group.

$C_{20}H_{17}BrF_2O_4$, $M=439.25$, monoclinic, space group $P12_11$, $a=10.223(4)$, $b=8.866(6)$, $c=11.220(4)$ Å, $\beta=101.82(3)°$, $V=995.5(8)$ Å^3, $Z=2$, $F(000)=444$, $\mu=2.110$ cm^{-1}, $D_{calcd}=1.465$ g cm^{-3}. Final goodness of fit = 1.095, $R_1=0.0402$, $wR_2=0.1174$.

Crystallographic data (excluding structure factors) for the structure of **3** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 193905. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.7. (+)-Methyl (*S*)-3-acetoxy-2,2-difluoro-3-phenylpropanoate, 5

To a stirred solution of **2a** (200 mg, 0.876 mmol) in acetonitrile (4 ml) and carbon tetrachloride (4 ml) was added an aqueous solution (4 ml) of sodium periodate (1.53 g, 7.19 mmol) and ruthenium trichloride trihydrate (9 mg, 0.03 mmol). The reaction mixture was stirred at rt for 2.5 h and extracted with dichloromethane (2×30 ml). The extract was washed with water and dried over anhydrous magnesium sulfate and the solvent evaporated. The residue was diluted with ether (50 ml) and extracted with saturated aqueous sodium bicarbonate (3×30 ml). The aqueous extract was acidified with hydrochloric acid to pH 1 and extracted with ether (3×30 ml). The combined

organic extract was washed with brine, dried over anhydrous magnesium sulfate and the solvent evaporated to afford crude **4**. The crude **4** was diluted with dichloromethane and trimethylsilyldiazomethane (10% in *n*-hexane, 0.4 ml) was added. The resulting mixture was evaporated and the residue was purified using chromatography on silica gel (*n*-hexane:ethyl acetate = 12:1) to give **5** as a colorless oil (93 mg, 41%). $[\alpha]_D^{28}$ +26.8 (*c* 1.09, $CHCl_3$). IR (neat) cm^{-1}: 1768; ^1H NMR δ: 2.08 (3H, s), 3.77 (3H, s), 6.16 (1H, q, $J = 19$ Hz), 7.31 ~ 7.37 (5H, m); ^{19}F NMR δ: −113.90 (1F, dd, $J_{FF} = 260$ Hz, $J_{FH} = 19$ Hz), −117.38 (1F, dd, $J_{FF} = 260$ Hz, $J_{FH} = 19$ Hz); MS (*m*/*z*) 258 (M^+). HRMS calcd for $C_{12}H_{12}F_2O_4$ (M^+), 258.0704. Found: 258.0697.

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