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# Synthesis of Enantiomerically Pure 4-Acetoxy-2-fluoro-2-cyclopenten-1-one

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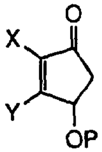
**Abstract:** Addition of molecular fluorine to *cis*-2-cyclopentene-1,4-diol gave the *cis-anti* adduct stereoselectively. This *meso* diol was dissymmetrized by means of acetylation under lipase catalysis to afford the monoacetate with a high enatiomeric purity. Oxidation of the monoacetate followed by elimination of hydrogen fluoride under basic conditions furnished the titled compound which is an attractive building block for chiral fluorinated molecules.

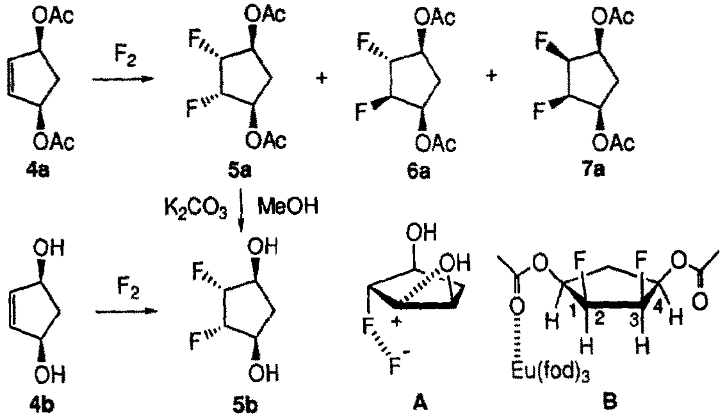
Modification of biological activity of organic molecules by introducing a fluorine substituent has attracted much interest in the field of medicinal chemistry.[1] However, general methods for the mild and selective introduction of a single fluorine substituent into the molecules are limited.[1,2] For this reason, there is considerable current interest in the development of fluorine-containing building blocks. As a continuation of our works on the synthesis of versatile building blocks for chiral fluorinated molecules,[3,4] we planned to synthesize an enantiomerically pure 4-acetoxy-2-fluoro-2-cyclopenten-1-one (1). This compound is expected to serve as a potential intermediate for fluorinated molecules, since the non-fluorinated analogue (2)[5] and the 3-fluoro analogue (3)[6] have been used for a variety of biologially active compounds.



1: X = F, Y = H, P = Ac
2: X = Y = P = H
3: X = H, Y = F, P = H

Scheme 1

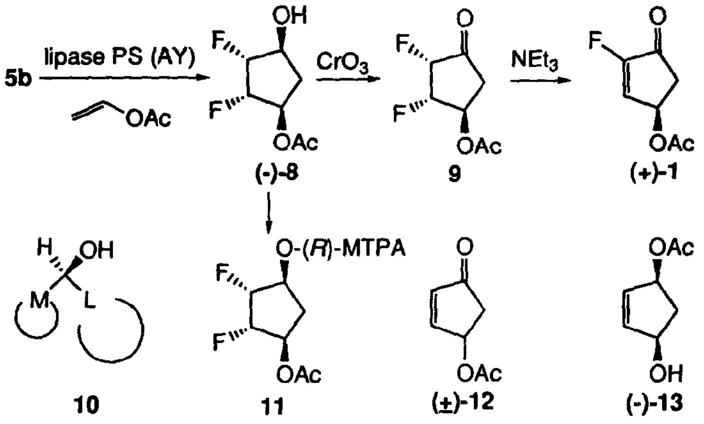
The addition of molecular fluorine to alkenes proceeds stereoselectively to give *cis* adducts and the method has now gained potential synthetic utility for the preparation of fluorinated compounds.[2,3,7,8] Thus, a solution of *cis*-2-cyclopentene-1,4-diol diacetate (**4a**)[9] was treated at a low temperature with molecular fluorine diluted with nitrogen to afford the *cis-anti* adduct (**5a**, 30%) together with the stereoisomers **6a** (15%) and **7a** (6%) after careful separation by column chromatography. The stereochemistry of these products was assigned by $^1$H-NMR spectroscopic study. Compound **6a** was readily assigned due to the unsymmetrical structure. The structures of compounds **5a** and **7a**, difficult to distinguish by the direct analysis, were determined by use of a shift reagent. Thus, on addition of Eu(fod)$_3$, the signal of C$_2$- and C$_3$-protons of **7a** was shifted to lower field than that of **5a** (see **B** in Scheme 2). Deprotection of **5a** with methanolic potassium carbonate gave the diol (**5b**). The fluorination of diol **4b** proceeded much more stereoselectively to give **5b** (24%) as the major product, as revealed by gas-liquid chromatography (GLC) analysis of the acetylated reaction mixture. This improvement of stereoselectivity is rationalized by assuming an intermediate **A** in which the carbocation is more stabilized by the adjacent hydroxyl group than by the acetoxyl group.



**Scheme 2**

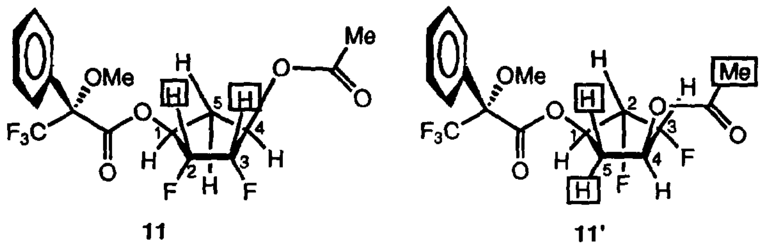
Based on our successful result obtained in the chemoenzymatic dissymmetrization of a *meso*-cyclopentane-1,3-diol derivative,[10] compound **5b** was subjected to the monoacetylation reaction under lipase catalysis. Thus, stirring a mixture of **5b** and lipase PS or AY in vinyl acetate afforded the monoacetate [(-)-**8**] in good yields. The enantiomeric excess (ee) with lipase PS was 91%, as determined by Mosher's method[11] [500 MHz $^1$H-NMR analysis of the *R*-MTPA ester (**11**)]. It has been reported that lipases PS and P better recognize secondary alcohols (or their acetates) depicted as **10** than the other enantiomers.[10,12] Indeed, the acetylation occurred selectively at the hydroxyl group with *R*-configuration, as evidenced by the $^1$H-NMR analysis of **11**. Namely, due to shielding effect of the phenyl ring, the $C_2$- and $C_3$-protons of **11** appeared at higher fields than those of the minor diastereomer (**11'**) derived from (+)-**8**, while the $C_5$- and acetyl-protons of **11'** appeared at higher fields than those of **11** (see Table I). This method for determination of the absolute configuration is quite reliable, since the similar differences of the chemical shifts were observed in the $^1$H-NMR spectrum of the *R*-MTPA ester derived from structurally related monoacetate [(-)-**13** (50% ee)] prepared from **4b** by the reported procedure.[13]

Enantiomerically pure (-)-**8**, obtained by recrystallization of the crude product, was oxidized by chromium (VI) oxide to give the ketone (**9**), which without isolation was treated with triethylamine to afford the desired compound (-)-**1** in 21% overall yield from (-)-**8**. It should be noted that when 4-acetoxy-2-cyclopenten-1-one [(±)-**12**] was treated with molecular fluorine (3-5 mole equivalents), none of the adduct (racemic **9**) was formed and the starting ketone was recovered quantitatively.



Scheme 3

**Table I. Selected Chemical Shifts of 11 and 11'**



| No. | Chemical shifts (ppm) | | | |
|---|---|---|---|---|
| | 2-H | 3-H | 5-H | Me |
| 11 | 4.988 | 4.934 | 1.740<br>3.016 | 2.049 |
| 11' | 5.1-5.3 | 5.1-5.3 | 1.608<br>2.721 | 1.993 |

In summary, we have succeeded in the synthesis of optically pure (+)-**1** using the *meso*-difluorodiol derivative **5b** as the key intermediate. This method should also be applicable to preparation of achiral 2-fluoro-2-cycloalken-1-ones[14] starting from 2-alken-1-ols. This application and the use of (+)-**1** as chiral dienophile in Diels-Alder reaction are currently underway and the result will be reported elsewhere.

## Experimental Section

All melting points were determined on a micro-hot stage (Yanagimoto) and are uncorrected. Optical rotaions were determined on a JASCO DIP-340 polarimeter. IR spectra were recorded on a JASCO A-102 spectrometer. $^1$H-NMR spectra were recorded on a JEOL JNM-GX 500 (500 MHz) spectrometer with tetramethylsilane as an internal standard. Mass spectra (MS) were taken with a JEOL JMS DX 303 spectrometer. Gas-liquid chromatography (GLC) analyses were performed on a JEOL JGC-20K gas chromatograph using a flame ionization detector and a 5% OV-17 column (on Chromosorb W, 2 m x 3 mm i. d. glass tube). Silca gel used for column chromatography was Wakogel C-200 and the ratio of solvent mixtures is shown as v/v. Preparative TLC were carried out on precoated Merck Kieselgel 60 $F_{254}$ plates. Fluorine, diluted to 5% with nitrogen, was gifted from Asahi Glass Co., Ltd., Tokyo, Japan. Lipases PS and AY were gifted from Amano Pharmaceutical Co., Ltd., Nagoya, Japan.

### (*1S**,*2R**,*3S**,*4R**)-, (*1S**,*2R**,*3R**,*4R**)-, and (*1S**,*2S**,*3R**,*4R**)-1,4-Diacetoxy-2,3-difluorocyclopentane (5a, 6a, and 7a)

Molecular fluorine diluted (15.0 mmol) to 5% with nitrogen was introduced to a solution of **4a** (920 mg, 5.0 mmol)$^9$ in fluorotrichloromethane (200 ml), chloroform (200 ml), and ethanol (10 ml) at -78 °C with vigorous stirring. The solution was purged with nitrogen for 20 min, and then washed succesively with 5% sodium bicarbonate solution and brine. The solution was dried over magnesium sulphate and evaporated *in vacuo*. The residue was chromatographed on a Lobar Column B (LiChroprep Si 60, Merck) with hexane-ethyl acetate (10:1) to give **6a** (61 mg, 6%) and then **5a** (164 mg, 15%) as oils. Further elution with hexane-ethyl acetate (3:1) gave **7a** (66 mg, 6%) as an oil.

**5a**: High-resolution MS *m/z*: Calcd for $C_9H_{12}F_2O_4$ ($M^+$): 222.0704. Found: 222.0693. IR ($CHCl_3$): 1745 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 1.588 (1H, dt, *J*=16.0, 4.5 Hz, $C_5$-H), 2.098 (6H, s, Ac x 2), 2.976 (1H, dt, *J*=16.0, 8.5 Hz, $C_5$-H), 4.977 (2H, ddd, *J*=48.0, 14.5, 3.5 Hz, $C_2$- and $C_3$-H), 5.196-5.263 (2H, m, $C_1$- and $C_4$-H).

**6a**: High-resolution MS *m/z*: Calcd for $C_9H_{12}F_2O_4$ ($M^+$): 222.0704. Found: 222.0708. IR ($CHCl_3$): 1745 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 1.894-1.954 (1H, m, $C_5$-H), 2.110 and 2.127 (each 3H, s, Ac), 2.690 (1H, m, $C_5$-H), 4.944-5.280 (4H, m, $C_1$-H--$C_4$-H).

**7a**: High-resolution MS *m/z*: Calcd for $C_9H_{12}F_2O_4$ ($M^+$): 222.0704. Found: 222.0690. IR ($CHCl_3$): 1745 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 1.590 (1H, dt, *J*=16.0, 4.5 Hz, $C_5$-H), 2.134 (6H, s, Ac x 2), 2.978 (1H, dt, *J* = 16.0, 8.0 Hz, $C_5$-H), 4.977 (2H, m, $C_1$- and $C_4$-H).

### (*1S**,*2R**,*3S**,*4R**)-2,3-Difluorocyclocyclopentane-1,4-diol (5b)

a) A mixture of **5a** (110 mg, 0.494 mmol), potassium carbonate (137 mg, 1.0 mmol), and methanol (10 ml) was stirred at room temperature for 12 h. The solvent was evaporated *in vacuo* and the residue was extracted with ethyl acetate. Purification of the extract by preparative TLC (5% MeOH-dichloromethane) gave **5b** (58.2 mg, 85%) as an oil. High-resolution MS *m/z*: Calcd for $C_5H_8F_2O_2$: 138.0492. Found: 138.0489. IR ($CHCl_3$): 3400, 3020, 2930 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 1.629 (1H, dt, *J*=15.5, 5.0 Hz, $C_5$-H), 2.042 (2H, br, OH x 2), 2.677 (1H, dt, $J$=15.5, 7.5 Hz, $C_5$-H), 4.380-4.446 (2H, m, $C_1$- and $C_4$-H), 4.820-4.952 (2H, m, $C_2$- and $C_3$-H).

b) Following the procedure given for fluorination of **4a**, **4b** (500 mg, 5.0 mmol)[9] was treated with molecular fluorine (15.0 mmol) at -78 °C. The solvent was evaporated *in vacuo*. The residue was passed through short column of silica gel with ethyl acetate. The solution was evaporated and chromatographed on a Lobar Column B (LiChroprep Si 60, Merck) with hexane-ethyl acetate (1:1). Fractions containing **5b** (analyzed by GLC) were evaporated to give **5b** (165 mg, 24%) as an oil.

### (1*S*,2R,3*S*,4*R*)-4-Acetoxy-2,3-diflurocyclopentan-1-ol [(-)-8]

a) A mixture of **5b** (97 mg, 0.7 mmol), lipase AY (97 mg), and vinyl acetate (10 ml) was stirred at 22 °C. The reaction progress was analyzed by GLC. After 9 h, the mixture was filtered through Celite, and the filtrate was evaporated *in vacuo*. Purification of the residue by column chromatography with hexane-ethyl acetate (3:1) gave (-)-**8** (89 mg, 70%) as a solid. $[\alpha]_D^{23}$ -47.3 ($c$=1.0, $CHCl_3$). The ee was 92% based on the $^1$H-NMR spectrum of the *R*-MTPA ester (*vide infra*). Recrystallization of this sample from ether-pentane gave enatiomerically pure (-)-**8** as prisms of mp 60-61 °C. High-resolution MS *m/z*: Calcd for $C_7H_{10}F_2O_3$ ($M^+$): 180.0598. Found: 180.0579. IR ($CHCl_3$): 3610, 1730 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 1.600 (1H, dt, $J$=15.0, 5.0 Hz, $C_5$-H), 2.099 (3H, s, Ac), 2.840 (1H, dt, $J$=15.0, 8.0 Hz, $C_5$-H), 4.408-4.475 (1H, m, $C_1$-H), 4.829 (1H, ddd, $J$=51.0, 12.0, 4.0 Hz, $C_3$-H), 5.042 (1H, ddd, $J$=50.0, 13.5, 4.0 Hz, $C_2$-H), 5.152-5.228 (1H, m, $C_4$-H). $[\alpha]_D^{24}$ -54.5 ($c$=1.0, $CHCl_3$).

b) A mixture of **5b** (58.5 mg, 0.424 mmol), lipase PS (230 mg), and vinyl acetate (10 ml) was stirred at 24 °C for 3 days. The mixture was filtered as in a) and subjected to preparative TLC with 5% methanol-dichloromethane to give (-)-**8** (49 mg, 64%) as a solid of $[\alpha]_D^{27}$ -45.7 ($c$=1.0, $CHCl_3$). The ee of this sample was 91% based on $^1$H-NMR analysis of the *R*-MTPA ester.

### Preparation of the *R*-MTPA Esters (11 and 11') from (-)-8

A mixture of crude (-)-**8** obtained by method a) was condensed with (*R*)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid (1.5 mol equiv.) by DCC method under DMAP catalysis. Purification by preparative TLC with hexane-ethyl acetate (5:1) gave a mixture of **11** and **11'** (yield, 80%) as an oil. The ee of crude (-)-**8** was estimated to be 92% based on the $^1$H-NMR analysis of this mixture.

### (*R*)-4-Acetoxy-2-fluoro-2-cyclopenten-1-one [(+)-1]

Recrystallized (-)-**8** (54 mg, 0.3 mmol) was added to a solution of $CrO_3$ (60 mg, 0.6 mmol) in acetic acid (2 ml) and the whole was stirred under ice-cooling for 4 h. The mixture was diluted with dichloromethane and washed successively with water, 5% sodium bicarbonate solution, and brine. Evaporation of the solvent gave **9** as an oil, which was stirred in ether (2 ml) and triethylamine (61 mg, 0.6 mmol) at room temperature for 2 h. The solvent was evaporated and the residue was purifitied by preparative TLC with hexane-ethyl acetate (2:1) to give (+)-**1** [7 mg, 21% from (-)-**8**] as an oil. High-resolution MS *m/z*: Calcd for $C_7H_7FO_3$ ($M^+$): 158.0379. Found: 158.0379. IR ($CHCl_3$): 1745, 1660 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 2.113 (3H, s, Ac), 2.455 (1H, dt, $J$=19.0, 1.0 Hz, $C_5$-H), 2.943 (1H, dd, $J$=19.0, 6.0 Hz, $C_5$-H), 5.750-5.785 (1H, m, $C_4$-H), 6.930 (1H, d, $J$=3.0 Hz, $C_3$-H). $[\alpha]_D^{24}$ +34.5 ($c$=0.89, $CHCl_3$).

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