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Effect of fluorine substitution of α- and β-hydrogen atoms in ethyl phenylacetate and phenylpropionate on their stereoselective hydrolysis by cultured cancer cells

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Abstract

(±)-Ethyl 2-fluoro-2-phenylacetate was stereoselectively hydrolyzed by cultured cells of several rat cancer cell lines to give the carboxylic acid rich in the *R* enantiomer. The stereoselectivity increased for (±)-ethyl 2-fluoro-2-phenylpropionate (**2b**) with all present cell lines and for (±)-ethyl 2-phenyl-3,3,3-trifluoropropionate (**3b**) with rat hepatoma McA-RH7777 cell line. The stereoselectivity was different for the different cell lines, as McA-RH7777 cells preferred (*R*)-**2b** in contrast with the preference towards (*S*)-**2b** by other cells such as *ras* oncogene-transformed rat liver Anr4 cells. These stereoselectivities were different from those for non-fluorinated (±)-ethyl 2-phenylpropionate. Thus fluorine atoms are recognized by ester hydrolases of cancer cells, and fluorine substitution on the acyl group will be useful for making ester-type anticancer prodrugs more specific to cancer cells.

Keywords: Cancer cells; Ethyl phenylacetate; Ethyl phenylpropionate; Fluorine substitution; Stereoselective hydrolysis

1. Introduction

Recently, we have found that several synthetic esters can be stereoselectively hydrolyzed by cultured cancer cells, and that the stereoselectivities are often different or even reversed between the cultured cells and the corresponding normal tissue [1–3]. Thus the chirality of acyl groups is important in preparing ester-type anticancer prodrugs which are specifically hydrolyzed in cancer cells for activation to the parent drugs. The stereoselectivities are dependent on the structure of the acyl group. Previous studies with *N*-acetyl- and *N*-trifluoroacetylphenylalanine esters have shown that the trifluoromethyl group causes a remarkable alteration in the stereoselectivity during enzymatic hydrolysis [2]. To obtain more information on the effect of fluorine atoms, we started the present study on the enzymatic hydrolysis of the α- and β-fluorinated acyl esters.

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2. Results and discussion

Three fluorinated esters, (±)-ethyl 2-fluoro-2-phenylacetate (**1b**), 2-fluoro-2-phenylpropionate (**2b**) and 2-phenyl-3,3,3-trifluoropropionate (**3b**) (Fig. 1), were used as substrates for enzymatic hydrolysis. The ester **1b** was prepared by treatment of the commercially available acid **1a** with diazoethane [4], **2b** by fluorine substitution of the hydroxyl group in (±)-ethyl atrolactate with diethylaminosulfur tri-

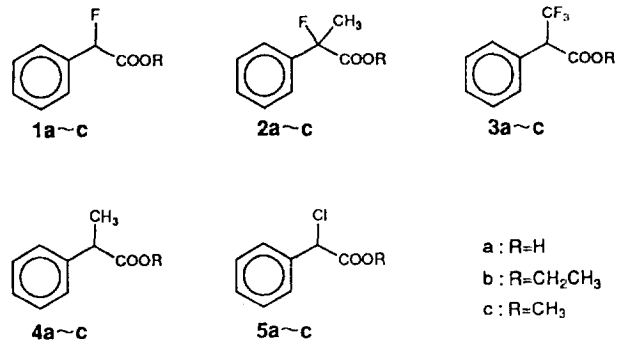

Fig. 1. Structures of compounds **1–5**.

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Table 1
Stereoselectivity in the enzymatic hydrolysis of racemic esters; the absolute configuration and optical purity (% e.e.) of the preferentially formed acid enantiomer and the conversion rate (%, in parentheses) are given; + and − for **3b** indicate that the major enantiomer moves faster and slower respectively than the counter enantiomer in chiral HPLC; nt, not tested

Cell/tissue	Substrate				
	1b	**2b**	**3b**	**4b**	**5b**
BRL 3A	*R* 55.4 (20)	nt	nt	*R* 82.0 (7)	nt
Anr4	*R* 37.0 (26)	*S* 69.3 (18)	(0)	*R* 93.2 (10)	*R* 86.5 (9)
Anr13-1	*R* 2.8 (18)	*S* 64.8 (9)	(0)	*R* 91.1 (11)	*R* 70.3 (4)
H4-II-E	*R* 8.1 (31)	*S* 33.1 (9)	−(1)	*R* 68.3 (9)	*R* 37.5 (4)
McA-RH7777	*R* 6.3 (57)	*R* 54.8 (40)	+60.8 (4)	*R* 20.3 (35)	*R* 54.4 (16)
XC	*R* 17.7 (13)	*S* 76.1 (10)	(0)	*R* 83.9 (7)	*R* 32.6 (4)
Liver	*R* 3.3 (27)	*R* 34.3 (26)	+31.3 (15)	*R* 19.1 (39)	*R* 19.3 (29)

fluoride (DAST) [5], and **3b** from 2,2,2-trifluoroacetophenone essentially according to Aaron et al. [6]. In addition, (±)-ethyl 2-phenylpropionate (**4b**) and 2-chloro-2-phenylacetate (**5b**) were prepared from the commercial precursors and were used as references.

Stereoselectivity in enzymatic hydrolysis was studied by high-performance liquid chromatography (HPLC) with a chiral column. The enzymatically formed acids were converted to methyl esters and all the methyl esters (**1c–5c**) were resolved by HPLC. Optically active methyl 2-fluoro-2-phenylacetate (**1c**), required for the configurational assignment, was prepared by fluorine substitution of methyl (*R*)- and (*S*)-mandelate (**6b**) with DAST. Although the optical yield was dependent on the reaction temperature (4 to −78 °C), (*R*)-**6b** gave the dextrorotatory ester **1c** and (*S*)-**6b** the levorotatory ester (Fig. 2). Hamman et al. [7] determined the configuration for (−)-**1c** to be *R* based on a circular dichroism study. The present results and Hamman's conclusions are consistent with the usual stereochemical course in the fluorination by DAST (i.e. inversion of configuration) [8–10]. The major enantiomer of (−)-**1c** moved faster than that of (+)-**1c** in the Chiralcel OJ column, indicating that the faster moving enantiomer had the *R* configuration. The specimen of (*R*)-**2c**, prepared from (*R*)-(−)-**2a** [11] kindly provided by Hamman, showed that this enantiomer also moved faster than the counter enantiomer in the above HPLC column. For the trifluoromethyl analog (**3**), the levorotatory acid appears in the literature [12], but its absolute configuration is not clear. Enantiomers of **3c** have not been assigned by HPLC. Enantiomeric assignment of the HPLC peaks of the non-halogenated ester (**4c**) and the chloroester (**5c**) was performed using authentic specimens.

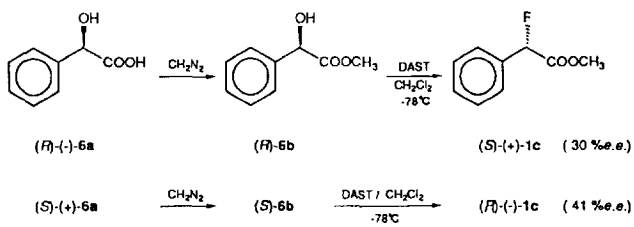

Fig. 2. Scheme showing the formation of (*S*)-(+)-**1c** from (*R*)-**6b** and (*R*)-(−)-**1c** from (*S*)-**6b**.

The results of the enzymatic hydrolysis are summarized in Table 1. Hydrolysis of the α-fluoroester (**1b**) by BRL 3A, Anr4 and XC cells was clearly stereoselective. Other cells and normal liver homogenate also stereoselectively hydrolyzed **1b**, although poorly. Thus ester hydrolases in the cultured cells can differentiate between the fluorine and α-hydrogen atoms. The high negative charge on the fluorine atom may contribute to the molecular recognition. Interestingly, the observed stereoselectivities were all for *R* enantiomer preference. BRL 3A is a non-cancerous cell line. Anr4 and Anr13-1 are *ras* oncogene-transformed rat liver cell lines, where Anr13-1 is more malignant than Anr4. H4-II-E and McA-RH7777 are true cancer (hepatoma)-derived cell lines and XC is a rat sarcoma cell line [3]. The optical purities of **1a** formed from **1b** (Table 1) seem to indicate that malignant cells are less stereoselective for this substrate than the non-cancerous or oncogene-transformed cells.

The stereoselectivity of the α-fluoroester **1b** was increased remarkably by the introduction of one methyl group at the α-position as shown by ester **2b** (Fig. 3). It is notable that the direction of stereoselectivity for **2b** was reversed between normal liver homogenate and several cultured cell lines, including H4-II-E hepatoma cell line. Thus the introduction of an α-methyl group caused not only an increase in the degree of stereoselectivity, but a change in its direction. On the other hand, comparison between the results for **2b** and the non-fluorinated ester (**4b**) shows that the introduction of an α-fluorine atom reduced the degree of stereoselectivity with Anr4, Anr13-1, H4-II-E and XC cell lines, but increased it with McA-RH7777 cell line and normal liver homogenate. If we consider that α-F and α-H atoms occupy spatially equivalent positions, it may be concluded that the preferred config-

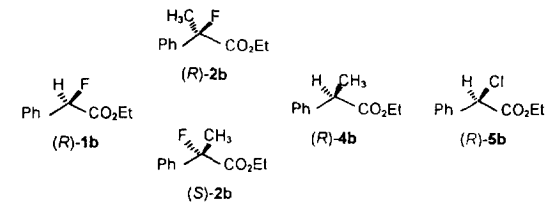

Fig. 3. Structures of compounds (*R*)-**1b**, (*R*)-**2b**, (*S*)-**2b**, (*R*)-**4b** and (*R*)-**5b**.

uration is the same for **2b** and **4b** in the former case (Anr4, Anr13-1, etc.), while it is reversed between the two esters in the latter case (McA-RH7777). The substrate specificity of the enzyme seems to be different between esterases in the former cells and those in McA-RH7777 cells and normal liver.

An effect of fluorine substitution on the stereoselectivity was also found with the trifluoromethyl derivative (**3b**). The stereoselectivity of McA-RH7777 cells increased for this substrate compared with that of the non-fluorinated substrate (**4b**), but the reaction rate was low. Other cultured cells were unable to hydrolyze **3b**. The presence of more than one fluorine atom leads to low water solubility of the ester, which may cause the poor reactivity of **3b** with esterases.

The stereoselectivity was hardly affected by chlorine substitution, as the stereoselectivity of the α-chloroester **5b** was almost parallel to that of **4b**.

Comparison between the data for **1b**, **4b** and **5b** indicates that the substituent size is more important than the electron density for high stereoselectivity in enzymatic hydrolysis. However, the direction of stereoselectivity with these three substrates was uniform for all of the present cell lines and normal liver homogenate. The result for **2b** was in contrast with this uniformity, implying that α-fluorine substitution plus α-methyl substitution makes stereoselectivity in enzymatic hydrolysis more diverse.

The chiral molecular recognition of the cellular esterases is clearly affected by the fluorine atom in the substrate. The fluorine effect should arise from the high electron density on this atom resulting in, for example, hydrogen bond formation [13] between it and the enzyme molecule. This polar interaction is further modified by steric interaction between the substrate and the enzyme by the α-methyl group. These combined effects may increase the chance that cancer and normal cells will be differentiated by the stereoselective hydrolysis of ester-type anticancer prodrugs containing a fluorinated acyl group.

3. Experimental details

3.1. Analytical instruments

Melting points were measured on a hot stage and are uncorrected. Optical rotations were measured with a Jasco DIP-140 digital polarimeter. ^{1}H-NMR and mass spectra were taken with a JEOL JNM-EX400 spectrometer (400 MHz) and a JEOL JMS-AX500 mass spectrometer (70 eV) respectively.

3.2. Chemicals

(±)-2-Fluoro-2-phenylacetic acid (**1a**), (*R*)-(−)- and (*S*)-(+)-mandelic acid (**6a**), (±)-2-chloro-2-phenylacetyl chloride and DAST were purchased from Aldrich Chemical Co., Milwaukee. (±)-Atrolactic acid hemihydrate and 2,2,2-trifluoroacetophenone were obtained from Tokyo Chemical Industries, Ltd., Tokyo. (±)-Ethyl 2-phenylpropionate (**4b**) was prepared in previous work [2].

3.3. Syntheses

3.3.1. (±)-Ethyl 2-fluoro-2-phenylacetate (1b)

(±)-**1a** was treated with diazoethane by the usual method [4]. The product was purified by silica gel column chromatography to give (±)-**1b** as an oil in better than 98% yield. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, t, J=6.8 Hz, CH_3), 4.25 (2H, m, CH_2), 5.77 (1H, d, J_{HF}=47.8 Hz, CHF), 7.38–7.46 (5H, m, Ph). MS m/z: 182 (M^+) and 109. High-resolution MS (HRMS) m/z: 182.0760 (M^+), calculated $C_{10}H_{11}FO_2$=182.073. IR (neat) ν: 3020, 2970, 1750, 1200, 1050, 740 and 700 cm^{-1}.

3.3.2. (±)-Methyl 2-fluoro-2-phenylacetate (1c)

(±)-**1a** was methylated with diazomethane to give the methyl ester in a quantitative yield as an oil. ^{1}H-NMR ($CDCl_3$) δ: 3.78 (3H, s, CH_3), 5.79 (1H, d, J_{HF}=47.3 Hz, CHF), 7.40–7.46 (m, 5H, Ph). MS m/z: 168 (M^+), 109 and 59. HRMS m/z: 168.0605 (M^+), calculated $C_9H_9FO_2$=168.0587. IR (neat) ν: 3050, 2940, 1760, 1220, 1050, 730 and 700 cm^{-1}.

3.3.3. (±)-2-Fluoro-2-phenylpropionic acid (2a)

(±)-Atrolactic acid (1.35 g) was treated with DAST (2.24 g) in 9 ml methylene chloride at 4 °C for 3 h [5]. The reaction mixture was poured into 10 ml ice-cold water and stirred at room temperature for 15 h. The product was extracted with methylene chloride (10 ml×3) and purified by preparative thin layer chromatography (TLC) to give **2a** as an oil (0.25 g, 19% yield). IR (neat) ν: 3800–2100, 1720, 1250, 1150, 780, 720, 700 and 650 cm^{-1}.

3.3.4. (±)-Ethyl 2-fluoro-2-phenylpropionate (2b)

(±)-Ethyl atrolactate, prepared from atrolactic acid with diazoethane, was treated with DAST as described above to give **2b** as an oil (75% yield). ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7.3 Hz, CH_3), 1.93 (3H, d, J_{HF}=22.4 Hz, $FCCH_3$), 4.24 (2H, q, J=7.3 Hz, CH_2), 7.32–7.40 (3H, m, Ph), 7.49–7.52 (2H, m, Ph). MS m/z: 196 (M^+), 123, 103 and 77. HRMS m/z: 196.0911 (M^+), calculated $C_{11}H_{13}FO_2$=196.0900. IR (neat) ν: 3040, 2980, 1750, 1220, 1050, 720 and 700 cm^{-1}.

3.3.5. (±)-Methyl 2-fluoro-2-phenylpropionate (2c)

(±)-Methyl atrolactate was converted to **2c** by DAST in 75% yield to give an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.93 (3H, d, J_{HF}=22.4 Hz, $FCCH_3$), 3.76 (3H, s, CH_3), 7.34–7.40 (3H, m, Ph), 7.49–7.51 (2H, m, Ph). MS m/z: 182 (M^+), 123, 77 and 59. HRMS m/z: 182.0741 (M^+), calculated $C_{10}H_{11}FO_2$=182.0743. IR (neat) ν: 3000, 2930, 2750, 1750, 1280, 1130 and 700 cm^{-1}.

3.3.6. (±)-2-Phenyl-3,3,3-trifluoropropionic acid (3a)

This acid was prepared from 2,2,2-trifluoroacetophenone (**7**) by the method of Aaron et al. [6], but *n*-butyl lithium was used instead of sodium ethoxide for Wittig condensation of **7** with (methoxymethyl)triphenylphosphonium chloride (**8**). To a suspension of **8** (10 g in 100 ml diethyl ether) was added an *n*-butyl lithium/hexane solution (20 ml, 33 mmol) at 0 °C under an argon atmosphere. After stirring for 45 min, ketone **7** (5 g) was poured into the mixture. This mixture was stirred at room temperature for 2 h, and the insoluble salt was removed by filtration. The concentrated filtrate was distilled at a reduced pressure to give an oil (4.6 g, b.p. 107–132 °C/18 mmHg) containing 1-methoxy-2-phenyl-3,3,3-trifluoropropene. Hydrolysis of the oil and $KMnO_4$ oxidation of the resulting aldehyde were carried out according to Aaron et al. [6]. The final product, **3a**, was crystallized from hexane as fine needles (1.04 g, 18% overall yield based on **7**, m.p. 76–79 °C). ^{1}H-NMR ($CDCl_3$) δ: 4.35 (1H, q, J_{HF} = 8.5 Hz, CF_3CH), 7.38–7.46 (5H, m, Ph). MS *m/z*: 204 (M^+), 159, 140, 109, 91, 69 and 45. HRMS *m/z*: 204.0432 (M^+), calculated $C_9H_7F_3O_2$ = 204.0398. IR (neat) ν: 3700–2200, 1730, 1170, 700 and 670 cm^{-1}.

3.3.7. (±)-Ethyl 2-phenyl-3,3,3-trifluoropropionate (3b)

Ethylation of (±)-**3a** with diazoethane gave an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J = 7.0 Hz, CH_3), 4.2–4.3 (3H, m, CH_2 and $CH(CF_3)$), 7.38–7.45 (5H, m, Ph). MS *m/z*: 232 (M^+), 159, 140 and 109. HRMS *m/z*: 232.0705 (M^+), calculated $C_{11}H_{11}F_3O_2$ = 232.0711. IR (neat) ν: 3030, 2980, 1750, 1100, 1020, 700 and 680 cm^{-1}.

3.3.8. (±)-Methyl 2-phenyl-3,3,3-trifluoropropionate (3c)

Methylation with diazomethane gave an oil. ^{1}H-NMR ($CDCl_3$) δ: 3.77 (3H, s, CH_3), 4.32 (1H, q, J_{HF} = 8.6 Hz, CF_3CH), 7.36–7.44 (5H, m, Ph). MS *m/z*: 218 (M^+), 159, 140, 109, 105, 59 and 40. HRMS *m/z*: 218.0514 (M^+), calculated $C_{10}H_9F_3O_2$ = 218.0555. IR (neat) ν: 3020, 2950, 1750, 1110, 1010, 700 and 680 cm^{-1}.

3.3.9. (±)-Ethyl 2-chloro-2-phenylacetate (5b)

(±)-Chloro-2-phenylacetyl chloride was added to an excess amount of ethanol with a 2–3 molar excess of pyridine. Usual workup and purification by preparative TLC gave the ethyl ester in 69% yield as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, t, J = 7.2 Hz, CH_3), 4.23 (2H, m, $OCHHCH_3$), 5.40 (1H, s, CHCl), 7.3–7.55 (5H, m, ph) MS *m/z*: 198 (M^+), 1163, 125 and 89. HRMS *m/z*: 198.0408 (M^+), calculated $C_{10}H_{11}ClO_2$ = 198.0448. IR (neat) ν: 3040, 2970, 1750, 1160, 1020, 730 and 690 cm^{-1}.

3.3.10. (±)-Methyl 2-chloro-2-phenylacetate (5c)

Similar treatment of the acid chloride with methanol gave the methyl ester **5c** as an oil (75% yield). ^{1}H-NMR ($CDCl_3$) δ: 3.76 (3H, s, CH_3), 5.36 (1H, s, CClH), 7.35–7.40 (3H, m, Ph), 7.46–7.50 (2H, m, Ph). MS *m/z*: 184 (M^+), 149, 125, 77 and 59. HRMS *m/z*: 184.0257 (M^+), calculated $C_9H_9ClO_2$ = 184.0292. IR (neat) ν: 3020, 2950, 1750, 1160, 1000, 730 and 700 cm^{-1}.

3.3.11. Enantiomerically enriched (R)- and (S)-1c

(*R*)-(−)-Mandelic acid (**6a**) was converted to the methyl ester, which was treated with DAST at −78 °C in the same way as described above to give (+)-**1c** (34% yield, oil, $[\alpha]_D^{23}$ = +23.7° (*c* = 0.94, $CHCl_3$), 30% e.e.; Ref. [14]: $[\alpha]_D^{25}$ = −116° (*c* = 0.94, $CHCl_3$) for (*R*)-**1c**, 95% e.e.), whose major enantiomer moved more slowly than the other enantiomer in HPLC with a Chiralcel OJ column (see below). Similarly, (*S*)-(+)-**6a** was converted to (−)-**1c** (11% yield, oil, $[\alpha]_D^{23}$ = −29.4° (*c* = 0.94, $CHCl_3$), 41% e.e.), whose major enantiomer moved more quickly than the counter enantiomer in the above HPLC system.

3.3.12. Enantiomerically enriched (R)-5c

(*S*)-(+)-Mandelic acid (520 mg) was mixed with 1.25 g PCl_5. After heating to 110 °C for 0.5 h, the reaction mixture was poured into 20 ml ice-cold water. The mixture was extracted three times with 20 ml methylene chloride. The combined organic phases were worked up in the usual way. The crude product was recrystallized from benzene to give (*R*)-(−)-2-chloro-2-phenylacetic acid (**5a**) as a crystalline solid (69 mg, 12% yield), m.p. 72–74 °C, $[\alpha]_D^{26}$ = −26.0° (*c* = 3.3, benzene), 19% e.e. (Refs. [15,16]: m.p. 56–58 °C, $[\alpha]_D$ = +132.13° (*c* = 3.33, benzene), for (*S*)-(+)-**5a**). A small portion of the acid was methylated with diazomethane to give the methyl ester (*R*)-**5c**, which was identical with (±)-**5c** by gas chromatography (GC).

3.4. Chromatographic analysis

GC analysis was carried out with a silica capillary column (OV-1 phase; 0.25 mm i.d. × 25 m; carrier gas flow rate, 2.0 cm^3 min^{-1}). The column temperature was 120 °C and the retention times in GC were 3.6, 2.6, 3.9, 2.9, 2.7, 2.0, 7.1 and 5.0 min for **1b**, **1c**, **2b**, **2c**, **3b**, **3c**, **5b** and **5c** respectively. HPLC analysis was performed with a Chiralcel OJ column (Daicel Chemical Industries Ltd., Tokyo; 4.6 mm i.d. × 250 mm) using 10% 2-propanol in hexane as the mobile phase at a flow rate of 0.75 cm^3 min^{-1}. Peaks were detected by UV absorption measurement (220 nm). The capacity factors were 3.95, 4.50, 2.76, 3.28, 5.58 and 5.09 for (*R*)-**1c**, (*S*)-**1c**, (*R*)-**2c**, (*S*)-**2c**, (*R*)-**5c** and (*S*)-**5c** respectively, and 3.34 and 3.71 for (±)-**3c**. Data for the other compounds have been described previously [2,3].

3.5. Cell culture and hydrolysis

The source of the cells and their culture conditions have been described previously [3]. A solution containing ethyl ester (**1c–5c**; 1 mg) in ethanol (10 μl) was added to a suspension of each cell line in phosphate buffer (90 μl containing 1×10^7 (BRL 3A, Anr4 and XC) or 6×10^6 (Anr13-1, H4-II-E and McA-RH7777) cells, or rat liver homogenate prepared from a section of 20 mg wet weight). The mixtures

were stirred at 30 °C for 12 h, acidified to pH ≤ 2 with 2 N HCl, saturated with NaCl and extracted with EtOAc (1 ml × 2). The combined organic layers were divided into two portions (0.3 and 1.7 ml). The smaller portion was methylated with diazomethane for GC determination of the acid and the remaining ethyl ester. The larger portion was concentrated in vacuo. The acid formed in the concentrate was isolated by preparative TLC (silica gel F_{254} aluminum sheets (0.2 mm thick, Merck) developed with benzene/EtOAc/formic acid (5:2:0.1)) and then methylated with diazomethane for HPLC for optical purity determination.

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References

[1] Y. Ogawa, Y. Yamazaki and H. Okuno, *Bioorg. Med. Chem. Lett., 4* (1994) 757.

[2] Y. Yamazaki, Y. Ogawa, A.S. Afify, Y. Kageyama, T. Okada, H. Okuno, Y. Yoshii and T. Nose, *Biochim. Biophys. Acta, 1243* (1995) 300.

[3] Y. Kageyama, Y. Yamazaki, A.S. Afify, Y. Ogawa, T. Okada and H. Okuno, *Chirality, 7* (1995) 297.

[4] J.A. Marshall and J.J. Partridge, *J. Org. Chem., 33* (1968) 4090.

[5] G.L. Cantrell and R. Filler, *J. Fluorine Chem., 27* (1985) 35.

[6] C. Aaron, D. Dull, J.L. Schmiegel, D. Jaeger, Y. Ohashi and H.S. Mosher, *J. Org. Chem., 32* (1967) 2797.

[7] S. Hamman, D.R. Michals, S.T. Pickard and H.E. Smith, *J. Fluorine Chem., 62* (1993) 131.

[8] M. Hudlicky, in A.S. Kende et al. (ed.), *Organic Reactions*, Vol. 35, Wiley, New York, 1988, p. 513.

[9] J. Leroy, E. Hebert and C. Wakselman, *J. Org. Chem., 44* (1979) 3406.

[10] T. Kusumoto, T. Hanamoto, K. Sato, T. Hiyama, S. Takehara, T. Shoji, M. Osawa, T. Kuriyama, K. Nakamura and T. Fujisawa, *Tetrahedron Lett., 31* (1990) 5343.

[11] S. Hamman, *J. Fluorine Chem., 60* (1993) 225.

[12] S. Watanabe, *Jpn. Kokai Tokkyo Koho, H4-63598* (1992) (C.A. 117: 110133n).

[13] A.W. Baker and A.T. Shulgin, *Nature, 206* (1965) 712.

[14] K. Miyamoto, S. Tsuchiya and H. Ohta, *J. Fluorine Chem., 59* (1992) 225.

[15] P. Walden, *Chem. Ber., 28* (1895) 1287.

[16] J.A. Mills and W. Klyne, in W. Klyne (ed.), *Progress in Stereochemistry*, Vol. 1, Butterworths, London, 1954, p. 177.