

Selective mono-fluorination of diols *via* a cyclic acetal of *N,N*-diethyl-4-methoxybenzamide

Mitsuhiro Suwada, Tsuyoshi Fukuhara, Shoji Hara *

Division of Chemical Process Engineering, Graduate School of Engineering, Hokkaido University, Sapporo 060-8628, Japan

Received 16 March 2007; received in revised form 8 April 2007; accepted 15 April 2007

Available online 19 April 2007

Abstract

Selective mono-fluorination of 1,2- and 1,3-diols was achieved using *N,N*-diethyl-4-methoxybenzamide diethyl acetal and Et₃N-3HF. The reaction proceeds through a cyclic acetal of the benzamide, and only one hydroxy group was fluorinated and another one was acylated.

© 2007 Elsevier B.V. All rights reserved.

Keywords: Mono-fluorination of diol; Benzamide acetal; Triethylamine trishydrogen fluoride

1. Introduction

Recently, we succeeded in the selective mono-fluorination of 1,2- and 1,3-diols using *N,N*-diethyl- α,α -difluoro-4-methylbenzylamine (DFMBA), and a cyclic acetal of the benzamide was expected to be formed as an intermediate from DFMBA and the diol [1]. In this paper, we prepared the cyclic amide acetals from amide diethyl acetals and diols, and converted them to the mono-fluorination products by Et₃N-3HF.

2. Result and discussion

The cyclic acetal of *N,N*-diethyl-3-methylbenzamide (**1a**), which is an expected intermediate in the reaction of ethylene glycol with DFMBA [1], was prepared by transacetalization from *N,N*-diethyl-3-methylbenzamide diethyl acetal and ethylene glycol [2], and was applied to the fluorination without isolation. When the reaction of **1a** with Et₃N-3HF was carried out at 140 °C for 30 min, 2-fluoroethyl 3-methylbenzoate (**2a**), which is the same product as in the reaction of ethylene glycol with DFMBA [1], was obtained in 66% yield. Similarly, the cyclic acetal of *N,N*-diethylbenzamide (**1b**), *N,N*-diethyl-4-chlorobenzamide (**1c**), and *N,N*-diethyl-4-methoxybenzamide (**1d**) were prepared from the corresponding benzamide diethyl acetal and ethylene glycol, and used for the fluorination reaction under the same

conditions. Among them, **1d** gave the best result and 2-fluoroethyl 4-methoxybenzoate (**2d**) was obtained in 80% yield (Table 1). From the cyclic acetals of DMF and DMA, the corresponding fluorination products could not be obtained under the same conditions.

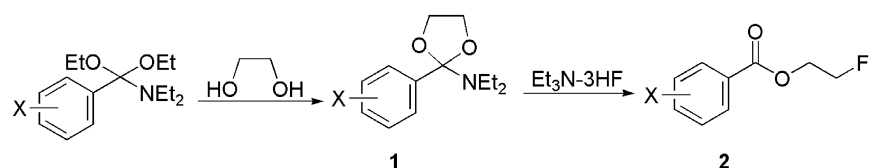
The cyclic acetal intermediate **1d** is isolable by distillation after the transacetalization, and from the isolated **1d**, **2d** could be obtained in 83% yield by the reaction with Et₃N-3HF at 140 °C for 30 min. These results showed that the reaction proceeds through the cyclic acetal intermediate **1** as expected. The reaction from **1** to **2** must be proceeding as follows: Elimination of diethylamine from **1** took place to give a dioxolenium intermediate [3], and subsequent fluoride attack, generated from DFMBA or Et₃N-3HF, on the dioxolenium intermediate gave the fluoroethyl benzoate **2** (Scheme 1).

In order to optimize the reaction conditions, the fluorination reaction of **1d** was carried out under various conditions. Lower temperature (120 °C) or shorter reaction time (10 min) caused the decrease of the yield. On the other hand, higher temperature (160 °C) or longer reaction time (1 h) could not improve the result. We also applied various fluoride sources such as KF, TBAF, Et₃N-2HF, and Et₃N-4HF, but the results could not be improved. The present method was applied to the reaction with various 1,2- and 1,3-diols (Table 2). From *cis*-1,2-cyclohexanediol, *trans*-2-fluorocyclohexyl 4-methoxybenzoate (**3**) was obtained in 75% yield (Entry 1). The reaction proceeded with inversion of the stereochemistry. On the other hand, from *trans*-1,2-cyclohexanediol, *trans*-2-fluorocyclohexanol was obtained in low yield and the expected methoxybenzoyl ester

* Corresponding author. Fax: +81 11 706 6556.

E-mail address: hara@org-mc.eng.hokudai.ac.jp (S. Hara).

Table 1
Fluorination of ethylene glycol using benzamide diethyl acetals^a



1 (X)	Product 2 (X)	Yield (%) ^b
1a (3-Me)	2a (3-Me)	66
1b (H)	2b (H)	54
1c (4-Cl)	2c (4-Cl)	57
1d (4-MeO)	2d (4-MeO)	80

^a Transacetalization was carried out using 1.1 eq of acetal under reduced pressure at 50 °C for 1 h. Fluorination was carried out at 140 °C for 30 min using 2 eq of Et₃N-3HF.

^b Isolated yield based on ethylene glycol.

of *cis*-2-fluorocyclohexanol was not formed. In this case, the formation of the cyclic acetal is slow due to the steric effect and a cyclohexene oxide must be initially formed by the reaction of the *trans*-cyclohexanediol with amide acetal [4]. The subsequent ring opening fluorination of the epoxide by Et₃N-3HF provided *trans*-2-fluorocyclohexanol [5]. In the reaction with 1,2-dodecanediol, the fluorination took place non-regioselectively to give a mixture of 1- and 2-fluorinated products (**4a**:**4b** = 71:29) (Entry 2). In the reaction of *cis*-1,2-cyclododecandiol, the resulting *trans*-2-fluorocyclododecyl 4-methoxybenzoate was subjected to the transesterification reaction without isolation [6] and *trans*-2-fluorocyclododecanol (**5**) was obtained in 56% overall yield from cyclododecandiol (Entry 3). As the reaction proceeds stereoselectively, the optically active fluorohydrin derivatives could be selectively prepared from optically active diols without losing their original enantiomeric purity. For instance, when (*R,R*)-hydrobenzoin was subjected to the reaction, (*1R,2S*)-2-fluoro-1,2-diphenylethyl 4-methoxybenzoate (**7**) was obtained in 77% yield (>95%de) (Entry 5). Its absolute stereochemistry was determined by comparison of its optical rotation with the product from DFMBFA after converting to the 3-methylbenzoic

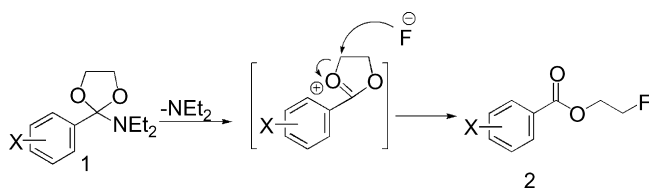
acid ester (Scheme 2). Similarly, from (*R,R*)-2,3-butanediol, (*2R,3S*)-3-fluoro-2-butyl 4-methoxybenzoate (**6**) was obtained in 79 % yield (>95%de) (Entry 4).

The reaction of 1,3-diols is sluggish and higher temperature (160 °C) was required to complete the reaction (Entries 6 and 7). Recently, we found that the reaction of β-amino alcohols with DFMBFA also proceeds through the similar cyclic intermediate to give fluoroalkylamides [7]. The reaction of *N*-phenyl-2-aminoethanol and *N*-phenyl-1-amino-2-octanol with the benzamide diethyl acetal and Et₃N-3HF proceeded as in the case of DFMBFA and *N*-acylated 2-fluoroethylamine (**10**) and 2-fluorooctylamine (**11**) were obtained, respectively (Entries 8 and 9).

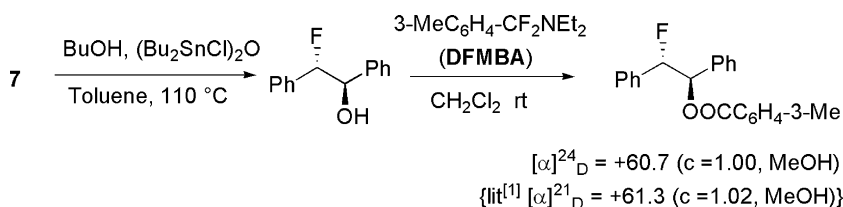
3. Experimental

3.1. General methods

The melting points were measured with a Yanagimoto micro melting-point apparatus and uncorrected. The IR spectra were recorded using a JASCO FT/IR-410. The ¹H NMR (400 MHz) spectra, ¹⁹F NMR (376 MHz) spectra and ¹³C NMR (100 MHz) spectra were recorded in CDCl₃ on a JEOL JNM-A400II FT NMR and the chemical shift, δ, are referred to TMS (¹H, ¹³C) and CFCl₃ (¹⁹F), respectively. The ¹H NMR (270 MHz) spectra and ¹³C NMR (68 MHz) spectra were recorded on a JEOL JNM-A270II FT NMR. The EI-high-resolution mass spectra were measured on a JEOL JMS-700TZ. Optical rotation was measured with a Horiba High Sensitive Polarimeter. *cis*-1,2-Cyclohexanediol, 1,2-dodecanediol, (*R,R*)-2,3-butanediol, 1,3-propanediol, 2,2-dimethyl-1,3-propanediol, *N*-phenyl-2-ethanolamine

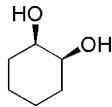
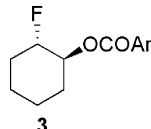
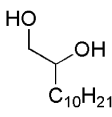
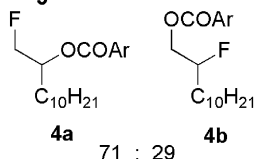
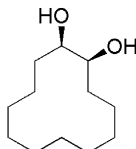
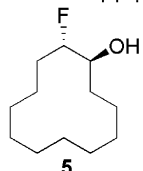
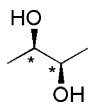
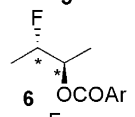
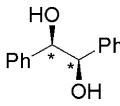
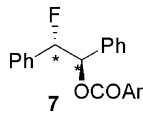
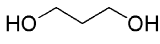
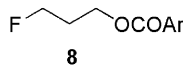
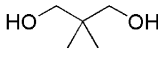
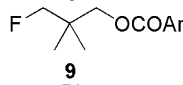
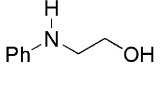
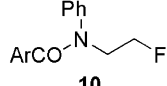
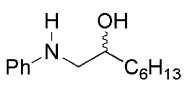
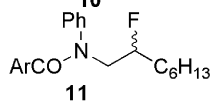


Scheme 1.



Scheme 2.

Table 2
Fluorination of diols and amino alcohol using *p*-methoxybenzamide diethyl acetal and Et₃N·3HF^a

Entry	Substrate	Product	Yield (%) ^b
1			75
2			83
		71 : 29	
3			56 ^c
4			79 (>95)
5			77 (>95)
6			60 ^d
7			66 ^d
8			72 ^e
9			72 ^e

^a If otherwise not mentioned, the reaction was carried out at 140 °C for 30 min. Ar = *p*-MeOC₆H₄.

^b Isolated yield based on diol or amino alcohol used and in parentheses, diastereomeric excess.

^c 1,2-Dichloroethane was used as solvent and the product was converted to fluorohydrin before isolation.

^d The reaction was carried out at 160 °C for 30 min.

^e The reaction was carried out at 100 °C for 30 min.

N,N-diethylbenzamide, *N,N*-diethyl-4-methoxybenzamide, *N,N*-diethyl-3-methylbenzamide, and *N,N*-diethyl-4-chlorobenzamide were purchased from Tokyo Chemical Industry Co., Ltd. *cis*-1,2-Cyclododecanediol was separated by column chromatography from a mixture of the stereoisomers obtained from Tokyo Chemical Industry Co., Ltd. (*R,R*)-Hydrobenzoin (99%ee) was obtained from Aldrich. Et₃N·3HF was prepared according to the literature [8]. Dichlorotetrabutylstannoxane was prepared according to the literature [9]. A 30 ml-Teflon FEP centrifuge tube with screw cup was obtained from Flon Industry and used as a reaction vessel in fluorination reaction.

3.2. Preparation of *N,N*-diethyl-4-methoxybenzamide diethyl acetal

To a 300 ml three-necked glass flask equipped with mechanical stirrer, a reflux condenser, and a dropping funnel were introduced *N,N*-diethyl-4-methoxybenzamide (20.73 g, 100 mmol) and CH₂Cl₂ (50 ml) under N₂ atmosphere. After addition of oxalyl chloride (12.95 g, 102 mmol) from the dropping funnel at room temperature, the reaction mixture was stirred under reflux for 90 min. The mixture was cooled to -40 °C, and a dry ethanol (27.64 g, 600 mmol) and Et₃N (20.60 g, 204 mmol) were added successively. Then, the temperature was allowed to rise up to room temperature and CH₂Cl₂ was carefully removed under reduced pressure. After the addition of hexane (100 ml), the precipitate was removed by filtration under N₂ atmosphere. The filtrate was concentrated under reduced pressure and the residue was distilled to give *N,N*-diethyl-4-methoxybenzamide diethyl acetal (14.08 g, 50 mmol) in 50% yield (bp 94 °C/0.42 mmHg). As it is moisture sensitive, it was kept and used as 1 M CH₂Cl₂ solution under N₂. IR: (neat) ν 2972, 1609, 1509, 1244, 1083 cm⁻¹. ¹H NMR (270 MHz) δ 0.97 (t, *J* = 7.1 Hz, 6H), 1.17 (t, *J* = 7.1 Hz, 6H), 2.60 (q, *J* = 7.1 Hz, 4H), 3.25–3.37 (m, 2H), 3.45–3.56 (m, 2H), 3.80 (s, 3H), 6.83 (d, *J* = 8.8 Hz, 2H), 7.41 (d, *J* = 8.8 Hz, 2H). ¹³C NMR (68 MHz) δ 15.05 (2C), 16.05 (2C), 42.37 (2C), 55.14, 56.37 (2C), 109.02, 112.59 (2C), 128.37 (2C), 132.71, 158.67. HRMS (EI): calc. for C₁₆H₂₇NO₃: 281.1991, found: 281.1990.

3.2.1. *N,N*-Diethyl 4-methoxybenzamide ethylene acetal (**1d**)

bp 85 °C/0.28 mmHg. IR (neat): 2968, 1509, 1246 cm⁻¹. ¹H NMR (270 MHz) δ 0.98 (t, *J* = 7.16, 6H), 2.71 (q, *J* = 7.11, 4H), 3.73–3.78 (m, 2H), 3.82 (s, 3H), 4.01–4.06 (m, 2H), 6.84–6.89 (m, 2H), 7.45–7.48 (m, 2H). ¹³C NMR δ 14.18 (2C), 40.34 (2C), 55.20, 63.85 (2C), 113.07 (2C), 119.75, 128.31 (2C), 133.13, 159.38. HRMS (EI): calc. for C₁₄H₂₀NO₃ (M⁺-H): 250.1443, found: 250.1447.

3.3. Fluorination of diols

3.3.1. 2-Fluoroethyl 4-methoxybenzoate (**2d**)

A mixture of ethylene glycol (62 mg, 1 mmol) and a CH₂Cl₂ solution of *N,N*-diethyl-4-methoxybenzamide diethyl acetal (1.2 ml of 1 M solution, 1.2 mmol) in a 30 ml-Teflon FEP tube was stirred at 50 °C under reduced pressure for 1 h to remove the generate ethanol and complete the transacetalization. To the crude **1d**, Et₃N·3HF (322 mg, 2 mmol) was added and the mixture was stirred at 140 °C for 30 min. The reaction mixture was cooled to room temperature and aq. NaHCO₃ (6 ml) was added. The product was extracted with ether, dried over MgSO₄, and concentrated under reduced pressure. Purification by column chromatography (silica gel/hexane-ether) gave **2d** (158 mg, 0.8 mmol) in 80% yield. IR: (neat) ν 2959, 1715, 1607, 1511, 1258, 1169 cm⁻¹. ¹H NMR (400 MHz) δ 3.87 (s, 3H), 4.59 (dt, *J* = 28.8, *J* = 4.2 Hz, 2H), 4.68 (dt, *J* = 47.4, *J* = 4.2 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 8.04 (d, *J* = 8.8 Hz,

2H). ^{13}C NMR (100 MHz) δ 55.42, 63.54 (d, $J = 19.9$ Hz), 81.55 (d, $J = 170.4$ Hz), 113.64 (2C), 122.03 (2C), 131.79, 163.55, 166.08. ^{19}F NMR (376 MHz) δ -225.01 (tt, $J = 47.6$, $J = 28.7$ Hz, 1F). HRMS (EI): calc. for $\text{C}_{10}\text{H}_{11}\text{FO}_3$: 198.0686, found: 198.0692.

3.3.2. 2-Fluoroethyl 3-methylbenzoate (2a)

IR: (neat) ν 2958, 1725, 1596, 1276 cm^{-1} . ^1H NMR (400 MHz) δ 2.40 (s, 3H), 4.52–4.80 (m, 4H) 7.31–7.38 (m, 2H), 7.87 (d, $J = 7.8$ Hz, 1H), 7.88 (s, 1H). ^{13}C NMR (100 MHz) δ 21.12, 63.70 (d, $J = 20.7$ Hz), 81.39 (d, $J = 171.0$ Hz), 126.80, 128.23, 129.50, 130.15, 133.91, 138.14, 166.43. ^{19}F NMR (376 MHz) δ -225.03 (tt, $J = 47.6$, $J = 28.7$ Hz, 1F). HRMS (EI): calc. for $\text{C}_{10}\text{H}_{11}\text{FO}_2$: 182.0743, found: 182.0743.

3.3.3. 2-Fluoroethyl benzoate (2b)

IR: (neat) ν 2958, 1724, 1276 cm^{-1} . ^1H NMR δ 4.53–4.81 (m, 4H), 7.26–7.48 (m, 2H), 7.56–7.60 (m, 1H), 8.07–8.10 (m, 2H). ^{13}C NMR (100 MHz) δ 63.83 (d, $J = 19.9$ Hz), 81.43 (d, $J = 170.9$ Hz), 128.42 (2C), 129.66, 129.75 (2C), 133.24, 166.37. ^{19}F NMR (376 MHz) δ -225.09 (tt, $J = 47.6$, $J = 28.6$ Hz, 1F). HRMS (EI): calc. for $\text{C}_9\text{H}_9\text{FO}_2$: 168.0586, found: 168.0589.

3.3.4. 2-Fluoroethyl 4-chlorobenzoate (2c)

IR: (neat) ν 2958, 1725, 1596, 1276 cm^{-1} . ^1H NMR (400 MHz) δ 4.52–4.80 (m, 4H), 7.42–7.45 (m, 2H), 8.00–8.03 (m, 2H). ^{13}C NMR (100 MHz) δ 64.03 (d, $J = 19.8$ Hz), 81.31 (d, $J = 170.9$ Hz), 128.06, 128.78 (2C), 131.13 (2C), 139.72, 165.49. ^{19}F NMR (376 MHz) δ -225.13 (tt, $J = 47.6$, $J = 28.7$ Hz, 1F). HRMS (EI): calc. for $\text{C}_9\text{H}_8\text{ClFO}_2$: 202.0197, found: 202.0181.

3.3.5. trans-2-Fluorocyclohexyl 4-methoxybenzoate (3)

IR: (neat) ν 2994, 1713, 1607, 1259, 1103 cm^{-1} . ^1H NMR (400 MHz) δ 1.34–1.81 (m, 6H), 2.12–2.20 (m, 2H), 3.86 (s, 3H), 4.59 (dm, $J = 50.3$ Hz, 1H), 5.05–5.13 (m, 1H), 6.91–6.94 (m, 2H), 8.00–8.03 (m, 2H). ^{13}C NMR (100 MHz) δ 22.76 (d, $J = 9.5$ Hz), 22.99, 29.38 (d, $J = 6.1$ Hz), 30.40 (d, $J = 18.3$ Hz), 55.43, 74.03 (d, $J = 19.5$ Hz), 91.93 (d, $J = 178.5$ Hz), 113.55 (2C), 122.73, 131.70 (2C), 163.37, 165.62. ^{19}F NMR (376 MHz) δ -182.11 (brd, $J = 45.2$ Hz, 1F). HRMS (EI): calc. for $\text{C}_{14}\text{H}_{17}\text{FO}_3$: 252.1162, found: 252.1162.

3.3.6. 1-Fluoro-2-dodecyl 4-methoxybenzoate (4a)

IR: (neat) ν 2926, 1714, 1607, 1257 cm^{-1} . ^1H NMR (400 MHz) δ 0.87 (t, $J = 6.9$ Hz, 3H), 1.24–1.43 (m, 16H), 1.67–1.83 (m, 2H), 3.36 (s, 3H), 4.56 (dm, $J = 45.0$ Hz, 2H), 5.26 (dm, $J = 19.2$ Hz, 1H), 6.93 (d, $J = 9.0$ Hz, 2H), 8.02 (d, $J = 8.9$ Hz, 2H). ^{13}C NMR (100 MHz) δ 14.10, 22.66, 25.19, 29.29, 29.40 (2C), 29.50, 29.55, 29.71 (d, $J = 5.5$ Hz), 31.87, 55.43, 72.56 (d, $J = 19.2$ Hz), 83.77 (d, $J = 173.9$ Hz), 113.59 (2C), 122.47, 131.74 (2C), 163.45, 165.83. ^{19}F NMR (376 MHz) δ -231.25 (dt, $J = 22.6$, $J = 47.7$ Hz, 1F). HRMS (EI): calc. for $\text{C}_{20}\text{H}_{31}\text{FO}_3$: 338.2257, found: 338.2256.

3.3.7. 2-Fluoro-1-dodecyl 4-methoxybenzoate (4b)

White solid. mp 36 °C. IR: (KBr) ν 2926, 1718, 1607, 1257 cm^{-1} . ^1H NMR (400 MHz) δ 0.88 (t, $J = 6.8$ Hz, 3H), 1.26–1.84 (m, 18H), 3.87 (s, 3H), 4.29–4.50 (m, 2H), 4.79 (dm, $J = 49.0$ Hz, 1H), 6.93 (d, $J = 9.0$ Hz, 2H), 8.03 (d, $J = 8.8$ Hz, 2H). ^{13}C NMR (100 MHz) δ 14.10, 22.67, 24.81 (d, $J = 4.3$ Hz), 29.31, 29.35, 29.42, 29.51, 29.57, 31.46 (d, $J = 20.6$ Hz), 31.88, 55.43, 66.01 (d, $J = 22.3$ Hz), 91.58 (d, $J = 172.1$ Hz), 113.64 (2C), 122.16, 131.77 (2C), 163.52, 166.06. ^{19}F NMR (376 MHz) δ -187.52–187.13 (m, 1F). HRMS (EI): calc. for $\text{C}_{20}\text{H}_{31}\text{FO}_3$: 338.2257, found: 338.2262.

3.3.8. trans-2-Fluorocyclododecanol (5)

A CH_2Cl_2 solution of *N,N*-diethyl-4-methoxybenzamide diethyl acetal (1.2 ml of 1 M solution, 1.2 mmol) and *cis*-1,2-cyclododecanediol (200 mg, 1 mmol) were introduced into a 30 ml-Teflon FEP tube, and a volatile part was removed under reduced pressure. Then 1 ml of 1,2-dichloroethane was added and the reaction mixture was stirred at 50 °C for 1 h under reduced pressure. To the reaction mixture, Et_3N -3HF (325 mg, 2.1 mmol) was added and the mixture was stirred at 140 °C for 30 min. The reaction mixture was cooled to room temperature and aq. NaHCO_3 (6 ml) was added. The product was extracted with ether, dried over MgSO_4 , and concentrated under reduced pressure. The crude product, butanol (10 ml), and dichlorotetrahydrodistannoxane (0.534 mg, 1 mmol), and toluene (5 ml) were introduced into a 25-ml glass flask equipped with a reflux condenser and the mixture was stirred under reflux. The transesterification reaction was monitored by GC and the disappearance of the 2-fluorocyclododecyl 4-methoxybenzoate was confirmed after 160 h. After removal of the volatile part under reduced pressure, 2-fluorocyclododecanol (112 mg, 0.56 mmol) was isolated by column chromatography (silica gel/hexane-ether) in 56% overall yield from the diol. White solid. mp 65 °C. IR: (KBr) ν 3366, 2933, 1470, 1022 cm^{-1} . ^1H NMR (400 MHz) δ 1.26–1.95 (m, 20H), 2.21 (t, $J = 3.3$ Hz, 1H), 3.84–3.96 (m, 1H), 4.56 (dm, $J = 49.5$ Hz, 1H). ^{13}C NMR (100 MHz) δ 20.35 (d, $J = 3.3$ Hz), 20.57, 22.55, 22.59, 23.72, 23.76, 23.98, 24.01, 27.83 (d, $J = 21.7$ Hz), 28.73 (d, $J = 5.6$ Hz), 70.44 (d, $J = 18.4$ Hz), 95.31 (d, $J = 166.1$ Hz). ^{19}F NMR (376 MHz) δ -194.02–194.32 (m, 1F). HRMS (EI): calc. for $\text{C}_{12}\text{H}_{23}\text{FO}$: 202.1733, found: 202.1726.

3.3.9. (2R,3S)-3-Fluoro-2-butyl 4-methoxybenzoate (6)

IR: (neat) ν 2988, 1713, 1258, 1168, 1101 cm^{-1} . ^1H NMR (400 MHz) δ 1.35–1.44 (m, 6H), 3.86 (s, 3H), 4.78 (dm, $J = 48.3$ Hz, 1H), 5.16 (dm, $J = 18.3$ Hz, 1H), 6.92 (d, $J = 9.0$ Hz, 2H), 8.01 (d, $J = 9.1$ Hz, 2H). ^{13}C NMR (100 MHz) δ 14.14 (d, $J = 6.3$ Hz), 16.40 (d, $J = 22.8$ Hz), 55.24, 71.94 (d, $J = 22.4$ Hz), 90.83 (d, $J = 172.3$ Hz), 113.49 (2C), 122.50, 131.55 (2C), 163.37, 165.37. ^{19}F NMR (376 MHz) δ -186.64 to -187.01 (m, 1F). (2R,3R)-isomer, -186.64 to -186.03 (m, 1F). HRMS (EI): calc. for $\text{C}_{12}\text{H}_{15}\text{FO}_3$: 226.1005, found: 226.1008. $[\alpha]_{\text{D}}^{22.4} = -10.0$ ($c = 1.00$, MeOH).

3.3.10. (1*R*,2*S*)-2-Fluoro-1,2-diphenylethyl 4-methoxybenzoate (**7**)

White solid. mp 100 °C. IR: (KBr) ν 1709, 1258, 706 cm^{-1} . ^1H NMR (400 MHz) δ 3.87 (s, 3H), 5.85 (dd, $J = 46.3$, $J = 4.1$ Hz, 1H), 6.26 (dd, $J = 18.1$, $J = 4.2$ Hz, 1H), 6.93 (d, $J = 8.9$ Hz, 2H), 7.18–7.32 (m, 10H), 8.02 (d, $J = 8.9$ Hz, 2H). ^{13}C NMR (100 MHz) δ 55.36, 77.35 (d, $J = 25.4$ Hz), 94.44 (d, $J = 181.1$ Hz), 113.65 (2C), 122.09, 126.37, 126.44, 127.75 (2C), 127.99 (2C), 128.04 (2C), 128.41, 128.61, 131.76 (2C), 134.97 (d, $J = 2.9$ Hz), 135.59 (d, $J = 20.6$ Hz), 163.57, 164.90. ^{19}F NMR (376 MHz) δ -188.91 (dd, $J = 46.3$, $J = 18.3$ Hz, 1F). HRMS (EI): calc. for $\text{C}_{22}\text{H}_{19}\text{FO}_3$: 350.1318, found: 350.1316. $[\alpha]_{\text{D}}^{20.4} = +96.0$ ($c = 1.00$, MeOH).

3.3.10.1. (1*R*,2*S*)-2-Fluoro-1,2-diphenylethanol. Butanol (13 ml), **7** (298 mg, 0.85 mmol), dichlorotetrahydroxydistanoxane (578 mg, 1.1 mmol), and toluene (5 ml) were introduced into a 25-ml glass flask equipped with a reflux condenser, and the mixture was stirred under reflux for 90 h. After removal of the volatile part under reduced pressure, (1*R*,2*S*)-2-fluoro-1,2-diphenylethanol (330 mg, 0.65 mmol) was isolated by column chromatography (silica gel/hexane-ether). White solid. mp 98 °C (lit. [10] 99 °C). IR: (KBr) 3578, 3033, 2880, 1452, 1050, 965, 706 cm^{-1} . ^1H NMR (400 MHz) δ 2.10 (d, $J = 3.9$ Hz, 1H), 4.98–5.03 (m, 1H), 5.52 (dd, $J = 45.8$, $J = 5.56$ Hz, 1H), 7.22–7.35 (m, 10H). ^{13}C NMR (100 MHz) δ 76.31 (d, $J = 27.2$ Hz), 96.21 ($J = 177.8$ Hz), 126.78 (d, $J = 7.2$ Hz), 126.98 (2C), 127.00 (2C), 128.19 (2C), 128.25 (2C), 128.79 (d, $J = 1.7$ Hz), 135.95 (d, $J = 19.9$ Hz), 138.82 (d, $J = 3.1$ Hz). ^{19}F NMR (376 MHz) δ -183.83 (dd, $J = 45.8$, $J = 12.2$ Hz, 1F). $[\alpha]_{\text{D}}^{22.1} = +19.7$ ($c = 1.00$, MeOH).

3.3.10.2. (1*R*,2*S*)-2-Fluoro-1,2-diphenylethyl 3-methylbenzoate. To a CH_2Cl_2 solution (3 ml) of 2-fluoro-1,2-diphenylethanol (66 mg, 0.3 mmol) in a 30 ml-Teflon FEP tube was added DFMB (70 mg, 0.33 mmol) at 0 °C, and the mixture was stirred at room temperature for 1 h. To the reaction mixture, 2 ml of water was added and the separated aqueous layer was extracted with ether three times. Organic layer was dried over MgSO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel/hexane-ether) to give 2-fluoro-1,3-diphenylethyl 3-methylbenzoate (87 mg, 0.26 mmol). $[\alpha]_{\text{D}}^{24} = +60.7$ ($c = 1.00$, MeOH) {lit [1] $[\alpha]_{\text{D}}^{21} = +61.3$ ($c = 1.02$, MeOH)}

3.3.11. 3-Fluoro-1-propyl 4-methoxybenzoate (**8**)

IR: (neat) ν 2970, 1710, 1607, 1511, 1257, 1103 cm^{-1} . ^1H NMR (400 MHz) δ 2.16 (dm, $J = 25.7$ Hz, 2H), 3.87 (s, 3H), 4.43 (t, $J = 6.2$ Hz, 2H), 4.62 (dt, $J = 46.9$, $J = 5.9$ Hz, 2H), 6.92 (d, $J = 9.0$ Hz, 2H), 7.99 (d, $J = 8.9$ Hz, 2H). ^{13}C NMR (100 MHz) δ 29.81 (d, $J = 19.8$ Hz), 55.26, 60.44 (d, $J = 5.7$ Hz), 80.61 (d, $J = 165.2$ Hz), 113.50 (2C), 122.37, 131.45 (2C), 163.31, 166.03. ^{19}F NMR (376 MHz) δ -222.57 (tt,

$J = 47.0$, $J = 25.7$ Hz, 1F). HRMS (EI): calc. for $\text{C}_{11}\text{H}_{13}\text{FO}_3$: 212.0849, found: 212.0841.

3.3.12. 3-Fluoro-2,2-dimethylpropyl 4-methoxybenzoate (**9**)

IR: (neat) ν 2968, 1714, 1607, 1258 cm^{-1} . ^1H NMR (400 MHz) δ 1.05 (d, $J = 1.8$ Hz, 6H), 3.84 (s, 3H), 4.14 (d, $J = 1.1$ Hz, 2H), 4.27 (d, $J = 47.9$ Hz, 2H), 6.92 (d, $J = 9.0$ Hz, 2H), 7.99 (d, $J = 8.9$ Hz, 2H). ^{13}C NMR (100 MHz) δ 20.63 (d, $J = 5.0$ Hz, 2C), 35.87 (d, $J = 17.4$ Hz), 55.26, 68.56 (d, $J = 4.1$ Hz), 88.10, 113.54 (2C), 122.44, 131.42 (2C), 163.32, 165.92. ^{19}F NMR (376 MHz) δ -226.89 (t, $J = 47.6$ Hz, 1F). HRMS (EI): calc. for $\text{C}_{13}\text{H}_{17}\text{FO}_3$: 240.1162, found: 240.1160.

3.3.13. *N*-(2-Fluoroethyl)-*N*-phenyl 4-methoxybenzamide (**10**)

IR: (neat) ν 2959, 2839, 1642, 1606, 1254 cm^{-1} . ^1H NMR (400 MHz) δ 3.74 (s, 3H), 4.19 (dt, $J = 25.6$, $J = 4.9$ Hz, 2H), 4.75 (dt, $J = 47.5$, $J = 4.9$ Hz, 2H), 6.66 (d, $J = 8.9$ Hz, 2H), 7.09–7.29 (m, 7H). ^{13}C NMR (100 MHz) δ 51.58 (d, $J = 21.4$ Hz), 55.10, 81.43 (d, $J = 169.0$ Hz), 112.91 (2C), 126.48, 127.47 (2C), 127.58, 129.14 (2C), 130.90 (2C), 144.46, 160.67, 170.12. ^{19}F NMR (376 MHz) δ -222.81–-222.43 (m, 1F). HRMS (EI): calc. for $\text{C}_{16}\text{H}_{16}\text{FNO}_2$: 273.1165, found: 273.1159.

3.3.14. *N*-(2-Fluorooctyl)-*N*-phenyl 4-methoxybenzamide (**11**)

White solid. mp 47 °C. IR: (KBr) ν 2931, 2857, 1644, 1606, 1254 cm^{-1} . ^1H NMR (400 MHz) δ 0.88 (t, $J = 6.8$ Hz, 3H), 1.29–1.72 (m, 10H), 3.70 (s, 3H), 3.71–3.78 (m, 1H), 4.30 (ddd, $J = 33.7$, $J = 14.4$, $J = 2.1$ Hz, 1H), 4.95 (dm, $J = 51.0$ Hz, 1H), 6.64 (d, $J = 8.9$ Hz, 2H), 7.09–7.29 (m, 7H). ^{13}C NMR (100 MHz) δ 13.93, 22.40, 24.69 (d, $J = 3.0$ Hz), 28.92, 31.52, 32.85 (d, $J = 19.9$ Hz), 54.99, 55.48 (d, $J = 21.4$ Hz), 92.13 (d, $J = 170.5$ Hz), 112.83 (2C), 126.26, 127.42 (2C), 127.72, 128.97 (2C), 130.82 (2C), 144.80, 160.56, 170.09. ^{19}F NMR (376 MHz) δ -184.97–-184.58 (m, 1F). HRMS (EI): calc. for $\text{C}_{22}\text{H}_{28}\text{NO}_2\text{F}$: 357.2104, found: 357.2103.

References

- [1] A. Yoneda, T. Fukuhara, S. Hara, Chem. Commun. (2005) 3589–3590.
- [2] R.A. McClelland, S. Gedge, J. Bohonek, J. Org. Chem. 46 (1982) 886–891.
- [3] R.A. McClelland, M. Ahmad, J. Org. Chem. 44 (1979) 1855–1860.
- [4] R.F. Abdulla, R.S. Brinkmeyer, Tetrahedron 35 (1979) 1675–1735.
- [5] T. Inagaki, T. Fukuhara, S. Hara, Synthesis (2003) 1157–1159.
- [6] J. Otera, N. Dan-oh, H. Nozaki, J. Org. Chem. 56 (1991) 5307–5311.
- [7] T. Nomoto, T. Fukuhara, S. Hara, Synlett (2006) 1744–1746.
- [8] S. Ayuba, N. Yoneda, T. Fukuhara, S. Hara, Bull. Chem. Soc. Jpn. 75 (2002) 1597–1603.
- [9] D.L. Tierney, P.J. Moehs, D.L. Hasha, J. Organometal. Chem. 620 (2001) 211–226.
- [10] S. Rozen, O. Lerman, J. Org. Chem. 45 (1980) 672–678.