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Electrochemical fluorination of *N*-containing carboxylic acids Part 5. Fluorination of the methyl esters of *cis*-2,6-dimethylmorpholino-group substituted carboxylic acids

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Abstract

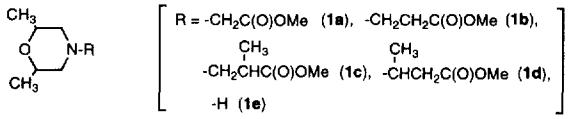
Cis-2,6-dimethylmorpholine and its derivatives having an ester group were subjected to electrochemical fluorination. The electrochemical fluorination of *cis*-2,6-dimethylmorpholine afforded only a small quantity of *F*-(*N*-fluoro-2,6-dimethyl-morpholine), whereas the *N*-(methoxycarbonylalkyl)-substituted *cis*-2,6-dimethyl-morpholines gave the corresponding *F*-acid fluorides in fair yields. *Cis*-and *trans*-isomerization on two methyl substituents of the morpholine ring occurred through electrochemical fluorination of pure *cis*-2,6-dimethylmorpholine to give a 1:0.25–0.5 mixture of *cis*- and *trans*-isomers having a *F*-2,6-dimethylmorpholino-moiety. The formation of a seven-membered ring expanded product was confirmed as a by-product in the fluorination of methyl *cis*-2,6-dimethylmorpholino-acetate. Spectroscopic data as well as physical properties of new nitrogen-containing *F*-carboxylic acids are presented. © 1998 Elsevier Science S.A.

Keywords: Electrochemical fluorination; Perfluoroacid fluorides; Perfluoro(*N*-fluoro-2,6-dimethylmorpholine); Ring-expansion

1. Introduction

The preparation of *F*-carboxylic acids is of great synthetic importance since these compounds can be converted into a variety of organofluorine compounds containing a *F*-alkyl group [1,2]. We have reported the preparation of various *N*-containing *F*-carboxylic acids by the electrochemical fluorination (ECF) of methyl esters of the corresponding carboxylic acids [3–6]. These studies revealed that the yield of the uncleaved fluorinated product was dependent heavily on the structure of the substrate used. The following two points were observed in our study on the yields of *F*-acid fluorides [4]; (1) the introduction of a cyclic amino group into the substrate dramatically improves the yield and (2) among the cyclic amino groups studied such as pyrrolidino, piperadino, and piperidino group, the morpholino group is most effective.

In order to obtain versatile synthetic building blocks for various organofluorine compounds of interest, we have extended our study to the preparation of *F*-carboxylic acids having a *F*-(2,6-dimethylmorpholino) group. We now present the results of the ECF of methyl esters of carboxylic acids having a *cis*-2,6-dimethylmorpholino group (**1a–d**), and *cis*-2,6-dimethylmorpholine (**1e**) (Scheme 1).



Scheme 1.

2. Results and discussion

It is known that an extensive cleavage of the C–N bond occurs in the ECF of secondary amines [7]. Nevertheless, the ECF has been used practically as the method for the preparation of the corresponding *F*-cyclic amines, which contain an N–F bond. For example, the ECF of morpholine [8] and piperidine [9,10] has been reported. Pyridines can be substituted for piperidines as the starting material for the preparation of *F*-(N-fluoropiperidines) [11–15]. In comparison with the ECF of morpholine which afforded the *F*-(*N*-

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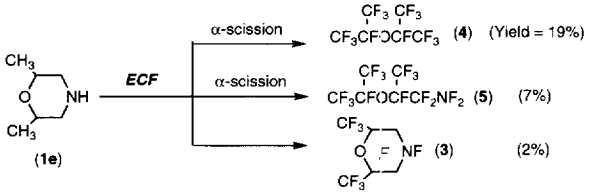
fluoromorpholine) in ca. 12% yield [8], the ECF of *cis*-2,6-dimethylmorpholine (**1e**) gave the desired product, *F*-(*N*-fluoro-2,6-dimethylmorpholine) (**3**), in rather low yield (2%) (Scheme 2). The main product of the above reaction was *F*-(di-*iso*-propylether) (**4**) which resulted from α-scission of **1e** during fluorination. A small quantity of *N,N*-difluoroamino-*F*-(2,4-dimethyl-3-oxa-pentane) (**5**) was obtained as an another cleaved product. These results were in contrast with those obtained by the fluorination of 2,6-dimethylmorpholine by Lin and Lagow [16], who reported a 95% yield of **3**. However, special fluorination technique involving a strict control on the reaction temperature using a diluted fluorine gas hampered the ready access to **3**.

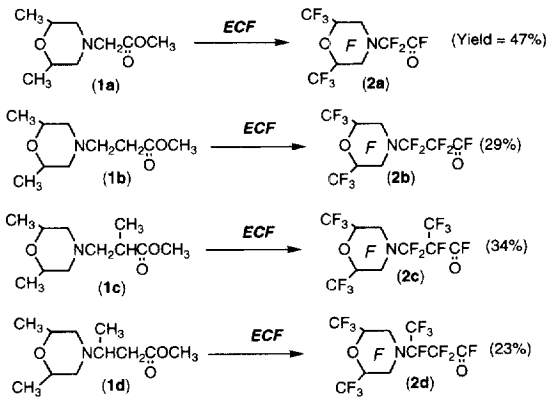
When *cis*-2,6-dimethylmorpholine derivatives was subjected to ECF in a form of tertiary amines which have a methoxycarbonyl-substituted alkyl group such as a $-CH_2CO-(O)CH_3$ group instead of the hydrogen of N–H of **1e**, the corresponding *F*-acid fluorides having a *F*-2,6-dimethylmorpholine group were obtained in fair to good yields (Scheme 3).

The results of the ECF of methyl *cis*-2,6-dimethylmorpholino-acetate (**1a**), methyl 3-(*cis*-2,6-dimethylmorpholino)-propionate (**1b**), methyl 3-(*cis*-2,6-dimethyl-morpholino)-*iso*-butyrate (**1c**), and methyl 3-(*cis*-2,6-dimethyl-morpholino)-*n*-butyrate (**1d**) are shown in Table 1.

The products having a *F*-2,6-dimethylmorpholino-group consisted of a mixture of *cis*- and *trans*-forms due to the isomerization of the two methyl ring substituents during ECF, which made the identification of the products rather complicated. The *cis*-form has two equatorial CF_3-groups at 2,6-

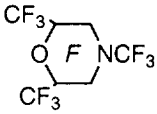
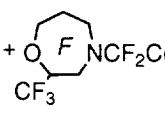
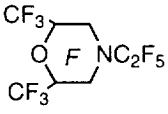
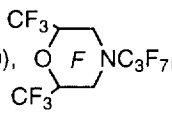


Scheme 2.

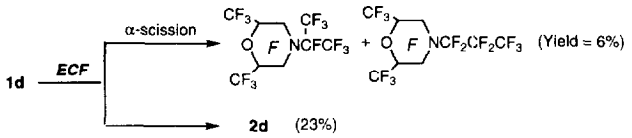


Scheme 3.

Table 1
Results of the fluorination of methyl esters of 2,6-dimethylmorpholino-substituted carboxylic acids

Run	Sample g (mol)	Current Passed (Ahr)	Fluorinated product (g)	Products obtained (Yield %)
1	**1a**, 39.5 (0.211)	220	16.9[a] (42.3)[b]	$C_2F_5OC_2F_5$ (3.9)[c], $C_2F_5OC_3F_7$ (**5**) (3.3), $C_3F_7OC_3F_7$ (**4**)(11.8),  (**6**)(2.3), **2a** +  (47.4)
2	**1b**, 40.6 (0.202)	226	5.3 (56.9)	**5** (1.3), **4** (2.8), **6** (6.9),  (**7**)(20.7), **2b** (29.3)
3	**1c**, 38.6 (0.180)	208	12.8 (47.1)	**5** (3.3), **4** (6.6), **6** (2.9), (**7**)(2.0),  (**8**)(6.5), **2c** (34.4)
4	**1d**, 40.4 (0.188)	199	1.8 (37.1)	**4** (0.8), **6** (trace), **7** (7.8), **8** (6.4), **2d** (22.8)

[a] Products obtained in a cold trap (−78°C).
[b] Products obtained as cell drainings.
[c] Arranged in order of the elution time on GC.



Scheme 4.

position of *F*-morpholino-group, whilst the *trans*-form has one axial and one equatorial CF_3-groups.

In the case of **1d**, an isomerization of the *N*-alkyl group also occurred during ECF. Though *F*-(*N-iso*-propyl-2,6-dimethylmorpholine) was expected to be formed as the cleaved product from **1d**, *F*-(*N-n*-propyl-2,6-dimethylmorpholine) (*n*-**8**) (31%) was obtained in addition to the *F*-(*N-iso*-propyl-2,6-dimethylmorhpoline) (*iso*-**8**) (69%) (Scheme 4).

In addition to the desired *F*-acid fluorides (**2a–d**), a small quantity of *cis*- and *trans*-forms of *F*-(*N*-alkyl-2,6-dimethylmorpholines) (**6**, **7** and **8**) was inevitably formed as cleaved products by the fluorination of **1a–d**. As the alkyl group at the 4-position of the *F*-(*N*-alkyl-2,6-dimethylmorpholine) becomes larger from CF_3 to C_2F_5, and *n*-C_3F_7, these stereo isomers became to be resolved into each of *cis*- and *trans*-forms on GC. In every case, the isomers which were major constituents had shorter retention times than those of other isomers on GC. The ratio of the stereoisomers found in **2a–c**, **6**, **7** and **8** was in the range of 1:0.25–0.5 by ^{19}F NMR, in which the former was assigned to the *cis*-form.

The assignment of the *cis*- and *trans*-isomers was conducted by studying the ^{19}F NMR data of methyl *F*-(2,6-dimethylmorpholino-acetate) (**10**) and *N*-difluoromethyl-*F*-(2,6-dimethylmorpholine) (**12**). In the ^{19}F NMR of **10**, for example, two sets of signals which belonged to each of *cis*- and *trans*-forms appeared in a ratio of 1:0.48 (Fig. 1).

The peak centered at −85.05 ppm (m, J = 10.16 Hz), and the peaks showed an AB system (−83.71 ppm, −87.32 ppm, J_{AB} = 226 Hz) were assigned to those of N–CF_2 group at 4 position respectively. The *cis*-form has a plane of symmetry and hence is a meso compound, while the *trans*-form does not. Therefore, the AB system of the latter peaks is considered to be caused by the asymmetry of the *trans*-*F*-2,6-dimethylmorpholino-group substituent. This proved to be a clue for distinguishing between *cis*- and *trans*-forms of **10**. In the case of the ^{19}F NMR spectrum of **12** having a –NCF_2H group, the peak due to –NCF_2H group showed similar splitting pattern to that of **10**. Thus, the isomer which shows AB pattern for the peaks due to –NCF_2H group was assigned to the trans-form of **12** similarly. Furthermore, the distinctive difference of the chemical shift of the peak due to –CF at the 2,6-position was observed between *cis*- and *trans*-forms of **10** and **12**. With respective to the –CF at the 2,6-position, the peaks (−127.94 ppm and −129.35 ppm) of *cis*-forms of **10** and **12** appeared at higher field than those (−123.3 ppm and −124.03 ppm) of *trans*-forms. The difference of this chemical shift between two isomers was observed in all *F*-(2,6-dimethylmorpholino) group substituted compounds, and was useful for the determination of the *cis*- to *trans*-mixing ratio. The peaks due to CF group at 2- and 6-position of **6–8**, and the methyl esters of **2a–c** (**10**, **14**, and **15**) were in a range of −127.9 to −128.9 ppm for the *cis*-forms and −123.3 to −124.0 ppm for the *trans*-forms.

It is interesting to note that the proposed assignment of *cis*- and *trans*-forms to them was consistent with the observation that an isomer, having a lower dipole moment, had a comparatively small retention time than that of another isomer on

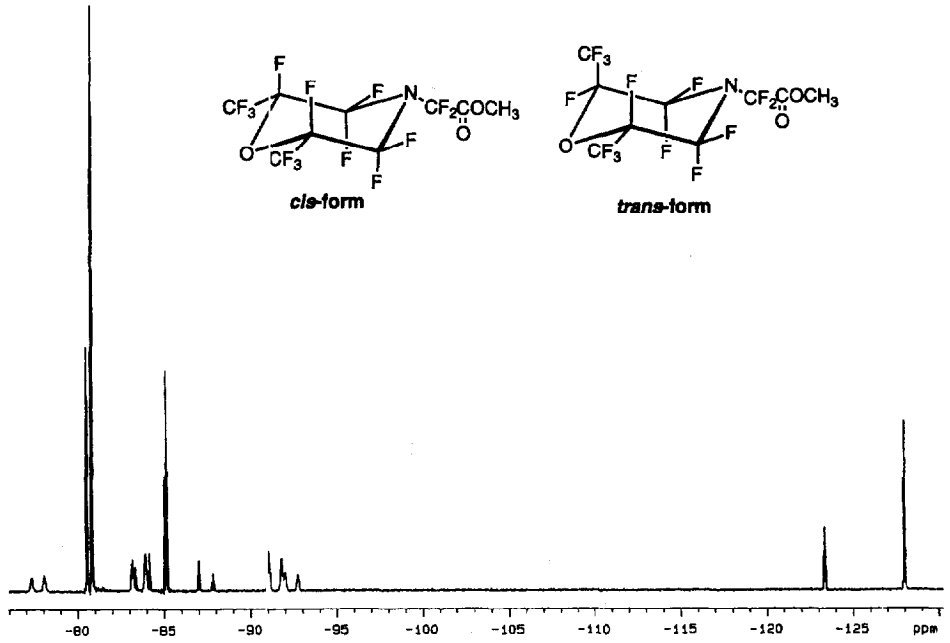
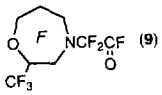


Fig. 1. ^{19}F NMR of methyl *F*-(2,6-dimethylmorpholino-acetate).

GC [17]. In order to check the conformity to this empirical rule for *F*-(*N*-alkyl-2,6-dimethylmorpholines), the heat of formation and the dipole moment of *cis*- and *trans*-isomers were calculated for **6** using a semi-empirical molecular orbital theory (Scheme 5).

The difference of the heat of formation between two isomers was very small (−796.999 kcal/mol for *cis*-form and −795.496 kcal/mol for *trans*-form, respectively), which suggests the isomerization of two methyl groups of *cis*-2,6-dimethylmorpholino-group occurs easily during ECF. While, the dipole moments of *cis*- and *trans*-forms of **6** were estimated as 0.062 Da [1] and 0.221 Da [1], respectively. According to the empirical rule, the *cis*-isomers of *F*-(*N*-alkyl-2,6-dimethyl-morpholines) including **6** is expected to be eluted faster than the *trans*-ones. The GC analysis of **6**, **7**, and **8** was found to follow this empirical rule, which showed the retention time of two isomers was in the order of a *cis*- < *trans*-form.

A seven-membered cyclic compound, *F*-[(2-methyl-1,4-oxazepan)-4-yl-acetyl fluoride] (**9**), was also formed as a by-product of *F*-(2,6-dimethylmorpholinoacetyl fluoride) (**2a**) in the fluorination of **1a**.



(9)

The formation of **9** was confirmed by studying the NMR and Mass data of the methyl esters (**10** and **11**) which were obtained by treating the crude fluorination product of **1a** with methanol (Scheme 6).

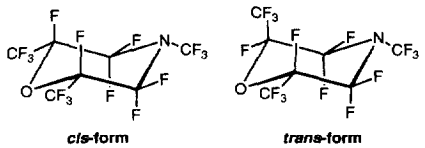
The identification of **9** was also deduced by studying the products obtained from the pyrolysis in ethylene glycol of a potassium salt of the crude fluorination product of **1a** [18] (Scheme 7).The NMR analysis of the decarboxylated product revealed that it is composed of *N*-difluoromethyl-*F*-(2,6-dimethylmorpholine) (**12**) (93%) and *N*-difluoromethyl-*F*-(2-methyl-1,4-oxazepine) (**13**) (7%). The latter compound (**13**) was derived from **9** according to the reaction shown in Scheme 7.

The ring expansion of **1a** which led to the formation of **9** occurred during ECF. It is not unprecedented that such a ring expansion occurs in ECF of cyclic compounds bearing a side chain. For example, the formation of *F*-oxepane has been found in ECF of 2-methyloxanes [19].

3. Experimental details

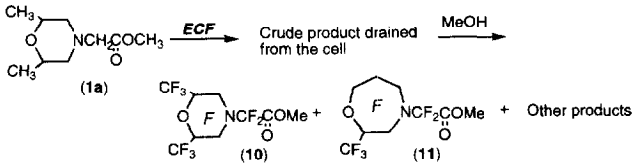
Boiling points are uncorrected. Methyl esters of carboxylic acids having a 2,6-dimethylmorpholino-group were prepared by the reaction of *cis*-2,6-dimethylmorpholine with methyl chloroacetate [20], methyl acrylate [21], methyl methacrylate [22] and methyl crotonate [23] by the methods similar to those described in the literature. The reaction between *cis*-2,6-dimethylmorpholine and methyl chloroacetate in ether

[1] ID = 3.33564×10^{-24} C·m.

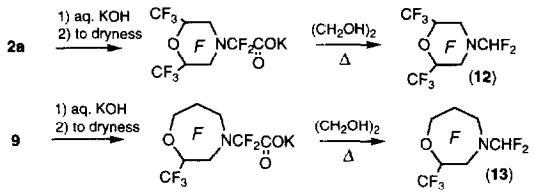


dipole moment:	0.062	0.221	(D)
Heat of formation:	-796.999	-795.496	(Kcal/mol)

Scheme 5.



Scheme 6.



Scheme 7.

was conducted in the presence of 1 equiv. of triethylamine, which serves as a hydrogen chloride scavenger. These substrates for fluorination had the following boiling points: methyl *cis*-2,6-dimethylmorpholino-acetate, bp 90°C/6 mm Hg, methyl *cis*-2,6-dimethylmorpholino-propionate, bp 99°C/5 mm Hg, methyl *cis*-2,6-dimethyl-morpholino-*iso*-butyrate, bp 97°C/4 mm Hg, methyl *cis*-2,6-dimethyl-morpholino-*n*-butyrate, bp 104°C/5 mm Hg. For electrochemical fluorination of *cis*-2,6-dimethylmorpholine itself, this compound was used as received. Anhydrous hydrogen fluoride (AHF) (Daikin Industries) was better than 99.8% pure. The electrolytic fluorination apparatus and operating procedures were similar to those described previously [1,2]. Analytical GLC work was carried out with a Shimadzu GC-14B gas chromatograph using stainless columns (3 mm diameter) packed with 25% Fomblin YR on Chromosorb PAW (6.4 m). For a semi-preparative work, a GASUKURO LL-75 modified gas chromatograph employing stainless columns (10 mm diameter) packed with 30% KelF wax on Chromosorb PAW (4.9 m), and a Varian model 920 GC employing an aluminum column (3/8 in. diameter) packed with 20% KF-96 on Chromosorb PAW (20 ft) were used. The carrier gas was helium in all cases. Infrared spectra were measured on a Shimadzu FTIR-8000PC spectrometer using a 6 cm gas cell with KBr windows. ^{19}F NMR spectra were measured on Varian Unity Inova 300 spectrometer (282.238 MHz for ^{19}F and 299.95 MHz for ^{1}H, respectively). Chemical shifts for ^{19}F and ^{1}H NMR spectra were reported with respective to $CFCl_3$ and TMS, respectively. Positive shifts are downfield from the reference. Mass spectra were measured on a Shimadzu GC/MS-QP5000 instrument fitted with a capillary

column (Neutra Bond-1, 30 m long, 0.25 ID, 1.5 μm thick) at 70 eV. Elemental analyses were performed by Beller Laboratories in Göttingen, Germany. Molecular orbital calculations were conducted by a MOPAC program [24], and a CAChe system (Sony Tektronix) was also used. The dipole moment and the heat of formation were calculated using PM3 Hamiltonian.

3.1. Fluorination of methyl cis-2,6-dimethylmorpholino-acetate (1a)

The sample **1a** (39.5 g, 0.211 mol) was charged into the cell which contained 450 ml electrically purified AHF, and the solution was subjected to fluorination with an anodic current density of 3.0 A/dm^2, a cell voltage of 5.9–6.1 V and a cell temperature of 7–8°C over a period of 482 min (220 A h). At the final stage of the fluorination, the voltage reached 6.7 V.

The effluent gases from the cell were passed over NaF pellets and then condensed in a trap cooled at −78°C. The gaseous products which did not condense in the −78°C trap were then bubbled through a fluoropolymer bottle containing water and a gas washing bottle containing an aqueous solution of a mixture of K_2CO_3, KOH and KI. All products except new ones were identified by comparison of their infrared spectra and GLC retention times with those of authentic samples. New compounds were separated from the other products by use of semi-preparative GLC, and their structures were determined on the basis of their IR, ^{19}F NMR and Mass spectra.

The products (16.9 g) condensed in the −78°C trap consisted of *F*-diethylether (2.1 g), *F*-(ethylpropylether) (**5**) (2.1 g), *F*-di-*iso*-propylether (**4**) (6.4 g), *F*-(*N*-methyl-2,6-dimethylmorpholine) (**6**) (1.2 g), *F*-(2,6-dimethylmorpholinoacetyl fluoride) (**2a**) (3.9 g), and unidentified (1.2 g). Cell drainings (42.3 g) consisted of **5** (2.4 g), **6** (0.7 g), 2a (38.8 g) and unidentified (0.4 g). The yield of **2a** was 47.4% based on the sample fed.

F-(di-*iso*-propylether) (**4**) had bp 55 ~ 56°C. IR (gas): 1306 (ms), 1263 (vs), 1204 (ms), 1159 (s), 1140 (ms), 1121 (w), 988 (w), 812 (w), 727 (m), 702 (w), 536 (w). ^{19}F NMR: −80.92 (m, 12F), −142.11 (m, 2F). Mass: 335 $[M–F]^+$ (0.1), 285 $[M–CF_3]^+$ (3.9), 169 $C_3F_7^+$ (31.6), 150 $C_3F_6^+$ (0.5), 147 $C_3F_5O^+$ (8.8), 131 $C_3F_5^+$ (0.4), 119 $C_2F_5^+$ (6.6), 100 $C_2F_4^+$ (6.0), 69 CF_3^+ (100).

F-(*N*-methyl-2,6-dimethylmorpholine) (**6**) (nc) had bp 88°C. Ir(gas): 1357 (s), 1259 (vs), 1223 (m), 1177 (ms), 1153 (ms), 1128 (w), 1105 (w), 849 (w), 694 (w). Mass: 380 $[M–F]^+$ (2.6), 330 $[M–CF_3]^+$ (0.5), 292 $C_6F_{10}NO^+$ (5.1), 264 $C_5F_{10}N^+$ (1.3), 214 $C_4F_8N^+$ (2.1), 164 $C_3F_6N^+$ (3.6), 150 $C_3F_6^+$ (53.2), 119 $C_2F_5^+$ (3.1), 114 $C_2F_4N^+$ (6.3), 100 $C_2F_4^+$ (20.6), 69 CF_3^+ (100). The *cis*- to *trans*-ratio of **6** was 1:0.35 by the integration of the peak due to CF at 2,6-position of the morpholino-group. ^{19}F NMR data of *cis*- and *trans*-form of **6** are shown in Table 2.

F-(2,6-dimethylmorpholinoacetyl fluoride) (**2a**) (nc) showed the following IR spectra. IR(gas): 1894 ν(C=O)(ms), 1344 (s), 1317 (w), 1256 (vs), 1211 (w), 1163 (s), 1130 (ms), 1103 (m), 1092 (m), 1038 (w), 872 (w), 849 (m), 802 (w), 745 (w), 687 (w). Further analysis of **2a** was done as its methyl ester. Methyl *F*-(2,6-dimethylmorpholino-acetate) (**10**) was prepared by mixing about 2 g of cell drainings with 1 ml of methanol. The reaction was complete within a few minutes. Then the lower layer of the reaction mixture was separated and subjected to semi-preparative GLC to give pure **10** as the major product and small quantities of methyl *F*-[(2-methyl-1,4-oxazepan)-4-yl-acetate] (**11**).

Methyl *F*-(2,6-dimethylmorpholino-acetate) (**10**) (nc) had bp 175–178°C, n_D^{20}1.3239. IR (capillary film): 1797.5 ν(C=O). The compound **10** could be measured for each of *cis*- and *trans*-forms by means of GC-MS. Mass data of *cis*-**10**: 380 $[M–CO_2Me]^+$ (2.3), 169 $C_3F_7^+$ (6.2), 164 $C_3F_6N^+$ (4.0), 150 $C_3F_6^+$ (4.1), 114 $C_2F_4N^+$ (7.8), 109 $CF_2CO_2Me^+$ (13.6), 100 $C_2F_4^+$ (5.3), 69 CF_3^+ (26.2), 59 CO_2Me^+ (100). Mass data of *trans*-**10** were the same as that of *trans*-form. Analysis: $C_9F_{14}NO_3H_3$ requires: C, 24.60; F, 60.59%. Found: C, 24.46; F, 60.59%. ^{19}F and ^{1}H NMR data of **10** are shown in Table 2.

Methyl *F*-[(2-methyl-1,4-oxazepan)-4-yl-acetate] (**11**). Mass: 380 $[M–CO_2Me]^+$ (3.2), 214 $C_4F_8N^+$ (2.7), 169 $C_3F_7^+$ (8.0), 150 $C_3F_6^+$ (3.7), 114 $C_2F_4N^+$ (15.2), 109 $CF_2CO_2Me^+$ (14.0), 100 $C_2F_4^+$ (15.1), 81 $C_3F_5^+$ (8.6), 69 CF_3^+ (26.2), 59 CO_2Me^+ (100). $[M–F]^+$ (2.6), 330 $[M–CF_3]^+$ (0.5), 292 $C_6F_{10}NO^+$ (5.1), 264 $C_5F_{10}N^+$ (1.3), 214 $C_4F_8N^+$ (2.1), 164 $C_3F_6N^+$ (3.6), 150 $C_3F_6^+$ (53.2), 119 $C_2F_5^+$ (3.1), 114 $C_2F_4N^+$ (6.3), 100 $C_2F_4^+$ (20.6), 69 CF_3^+ (100). ^{19}F NMR: −74.55 and −84.35 ppm (m, J_{AB} = 259.3 Hz, 2F), −79.92 (d–d, 17.2 Hz, 11.9 Hz, 3F), −81.70 and −84.58 ppm (m, J_{AB} = 167.1 Hz, 2F), −83.1 and −88.2 ppm (m, J_{AB} = 222.1 Hz, 2F, −83.2 and −95.3 ppm (m, J_{AB} = 234.0 Hz, 2F), −121.1 and −123.9 ppm (m, J_{AB} = 273.8 Hz, 2F), −133.4 ppm (s, 1F).

3.2. Fluorination of methyl cis-2,6-dimethylmorpholino-propionate (1b)

The sample **1b** (40.6 g, 0.202 mol) was fluorinated similarly under the following conditions; 3.3 A/dm^2, 6.0–6.2 V, 7–8°C, 553 min (226 A h). Work-up gave product in the −78°C trap (5.3 g): **5** (0.8 g), **4** (1.8 g), **6** (0.6 g), *F*-(*N*-ethyl-2,6-dimethylmorpholine) (**7**) (0.9 g), unidentified (1.2 g). Cell drainings (56.9 g): 7 (17.9 g), *F*-(2,6-dimethylmorpholino-propionyl fluoride) (**2b**) (28.2 g), unidentified (10.8 g). The yield of **2b** was 29.3%.

F-(*N*-ethyl-2,6-dimethylmorpholine) (**7**) (nc) had bp 105–106°C. The compound **7** could be resolved into *cis*- and *trans*-form by means of GC fitted with either packed and capillary columns, and their IR and Mass data were measured for each of *cis*- and *trans*-isomers. *Cis*-*F*-(*N*-ethyl-2,6-dimethylmorpholine) (**7**). IR (gas): 1360 (ms), 1337 (ms),

Table 2
NMR data of **6**, **7**, **8**, **10**, **14** and **15**

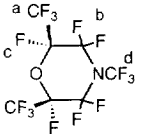
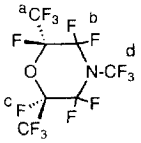
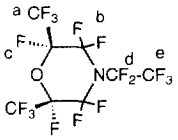
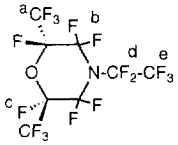
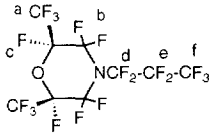
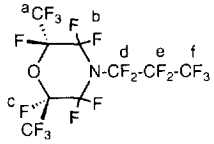
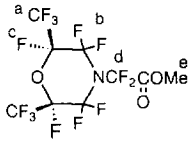
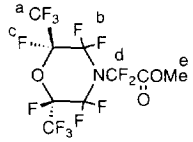
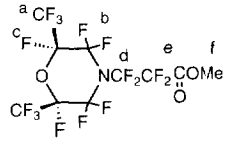
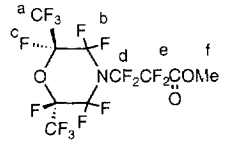
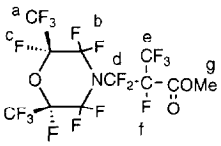
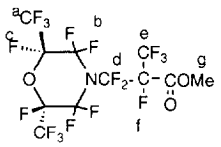
Compd No	Formula	Chemical shifts (ppm) [a,b]		J (Hz)
Cis-**6**		a	−80.81	d,d (J = 5.4, 14.1)
		b	−86.23, −92.34	J_{AB} = 203
		c	−128.1	m
		d	−51.45	t,t (J = 18.9, 10.4)
Trans-**6**		a	−80.52	d,d (J = 14.1, 8.8)
		b	−79.18, −94.26	J_{AB} = 199
		c	−123.3	t,d (J = 17.2, 8.5)
		d	−52.10	t,t (J = 20.6, 5.1)
Cis-**7**		a	−80.6	d,d (J = 14.11, 8.5)
		b	−79.49, −96.76	J_{AB} = 214
		c	−128.67	m
		d	−95.76	t,t (J = 34.4, 7.1)
		e	−86.75	t (J = 13.83)
Trans-**7**		a	−80.36	d,d (J = 11.28, 8.75)
		b	−76.06, −92.76	J_{AB} = 202
		c	−123.38	t,d (J = 19.75, 8.75)
		d	−89.35 | J_{AB} = 239	t,t (J = 36.1, 8.7)
			−98.51 | J_{AB} = 239	t,t (J = 27.4, 10.2)
		e	−84.94	t,t (J = 12.1, 5.4)
Cis-**n-8**		a	−80.54	d,d (J = 29.4, 7.1)
		b	−78.65, −96.98	J_{AB} = 215
		c	−128.66	m
		d	−90.95	m
		e	−128.1	t (J = 22.4)
		f	−81.23	t (J = 10.4)
Trans-**n-8**		a	−80.28	d,d (J = 13.8, 8.5)
		b	−75.25, −92.71	J_{AB} = 203
		c	−123.45	t,d (J = 17.5, 8.5)
		d	−83.90, −94.87	J_{AB} = 242
		e	−127.0	m
		f	−81.16	t (J = 10.2)
Cis-**10**		a	−80.8	d,d (J = 14.11, 7.05)
		b	−83.47, −91.34	J_{AB} = 212
		c	−127.94	m
		d	−85.05	m (J = 10.16)
		e	δ 3.995	s
Trans-**10**		a	−80.50	d,d (J = 13.8, 8.7)
		b	−77.62, −92.31	J_{AB} = 206
		c	−123.3	t,d (J = 17.2, 8.47)
		d	−83.71, −87.32	J_{AB} = 226 (J_{AX} = 10.44)
		e	δ 4.006	s
Cis-**14**		a	−80.62	m
		b	−78.55, −97.05	J_{AB} = 205
		c	−128.59	m
		d	−91.99	t (J = 31.9)
		e	−120.51	t (J = 18.9)
		f	δ 3.980	s
Trans-**14**		a	−80.35	m
		b	−75.17, −97.05	J_{AB} = 209
		c	−123.44	t,d (J = 17.2, 7.1)
		d	−84.7, −94.48	J_{AB} = 246
		e	−117.9 | J_{AB} = 270	t,t (J = 17.2, 3.7)
			−119.4 | J_{AB} = 270	m
		f	δ 3.999	s

Table 2 (*continued*)

Compd No	Formula	Chemical shifts (ppm) [a,b]		*J* (Hz)
Cis-**15**		a	−80.67	t,d (*J* = 13.5, 8.4)
		b	−77.62, −78.53	d,m (*J* = 87.5)
			−97.80, −98.65	m
		c	−128.6, −128.9	t,d (*J* = 21.5, 11.2)
		d	−83.33, −84.52	J_{AB} = 238
			−83.52, −84.72	m
		e	−73.56	m
		f	−178.40, −178.56	m
		g	δ 3.980	s
Trans-**15**		a	−80.38	m
		b	−74.51, −92.59	m
			−75.62, −93.36	m
		c	−123.7, −124.0	t,d (*J* = 19.2,6.8)
		d		
		e	−73.44	m
		f	−178.03, −179.0	m
		g	δ 3.972	s

[a] ^{19}F Chemical shifts in ppm relative to internal CCl_3F.
[b] Only obvious chemical shifts and coupling constans are given.

1310 (w), 1281 (s), 1258 (vs), 1244 (s), 1225 (m), 1188 (ms), 1169 (ms), 1151 (ms), 1130 (w), 1109 (m), 1199 (m), 1036 (w), 843 (m), 802 (w), 768 (w), 733 (w), 689 (m), 589 (w), 532 (w). Mass: 430 $[M–F]^+$ (1.2), 380 $[M–CF_3]^+$ (7.2), 292 $C_6F_{10}NO^+$ (8.9), 264 $C_5F_{10}N^+$ (2.3), 214 $C_4F_8N^+$ (4.3), 192 $C_4F_6NO^+$ (2.8), 169 $C_3F_7^+$ (16.6), 164 $C_3F_6N^+$ (10.4), 150 $C_3F_6^+$ (65.8), 131 $C_3F_5^+$ (2.9), 119 $C_2F_5^+$ (100), 114 $C_2F_4N^+$ (15.2), 100 $C_2F_4^+$ (32.2), 97 $C_2F_3O^+$ (3.6), 69 CF_3^+ (94.8). *Trans-F-*(*N*-ethyl-2,6-dimethylmorpholine) (**7**). IR (gas cell): 1137 (ms), 1310 (m), 1279 (m), 1254 (vs), 1219 (ms), 1173 (s), 1130 (ms), 1094 (w), 847 (m), 710 (m), 696 (w). The Mass data of *trans*-7 were almost the same as that of *cis*-form. ^{19}F and ^1H NMR data of *cis*- and *trans*-7 are shown in Table 2.

The characterization of **2b** was conducted in a form of the methyl ester which was prepared by the same method as that explained for **2a**. Methyl *F*-[3-(2,6-dimethylmorpholino)-propionate] (**14**) had bp 156–159°C, n_D^{20}1.3187. IR (capillary film): 1789.8 ν(C=O). The compound **14** could be measured for each of *cis*- and *trans*-forms by GC-MS in a similar way that explained for **10** and **11**. Mass data of *cis*-**14**: 380 $[M–CF_2CO_2Me]^-$ (4.8), 214 $C_4F_8N^+$ (2.1),169 $C_3F_7^+$ (6.2), 164 $C_3F_6N^+$ (4.9), 150 $C_3F_6^+$ (4.1), 114 $C_2F_4N^+$ (8.8), 109 $CF_2CO_2Me^+$ (13.9), 100 $C_2F_4^+$ (5.1), 81 $C_2F_3^+$ (5.6), 69 CF_3^+ (26.5), 59 CO_2Me^+ (100). Mass data of *trans*-**14** was the same as that of *cis*-**14**. The *cis*- to *trans*-ratio of **14** was 1:0.31 by the integration of the peak due to CF at 2,6-position of the morpholino-group. Analysis: $C_{10}F_{16}NO_3H_3$ requires: C, 24.54; F, 62.17%. Found: C, 24.60; F, 62.19%. ^{19}F NMR of *cis*- and *trans*-12 are shown in Table 2.

*3.3. Fluorination of methyl 3-(cis-2,6-dimethylmorpholino)-iso-butyrate (**1c**)*

The sample **1c** (38.6 g, 0.180 mol) was fluorinated similarly under the following conditions; 3.0 A/dm^2, 6.2–6.4 V, 7–8°C, 603 min (208 A h). Work-up gave product in the −78°C, (12.8 g): 5 (1.7 g), 4 (4.2 g), 6 (2.0 g), 7 (1.5 g), *F*-(*N*-propyl-2,6-dimethylmorpholine) (**8**) (0.3 g) and unidentified (3.1 g). Cell drainings (47.1 g): 8 (5.5 g), *F*-[3-(2,6-dimethylmorpholino)-*iso*-butyryl fluoride] (**2c**) (32.5 g) and unidentified (9.1 g). The yield of **2c** was 34.4%. The compound **8** was found to be almost pure *F*-(*N*-*n*-propyl-2,6-dimethylmorpholine) (*n*-**8**) by its ^{19}F NMR.

F-(*N*-*n*-propyl-2,6-dimethylmorpholine) (*n*-**8**) (nc) had bp 128°C. The IR and Mass data of *n*-**8** were measured for each of *cis*- and *trans*-forms in a similar way as that for **7**. *Cis*-perfluoro(*N*-*n*-propyl-2,6-dimethylmorpholine) (*n*-**8**). IR (gas): 1350 (m), 1339 (ms), 1312 (m), 1279 (s), 1258 (vs), 1234 (s), 1188 (ms), 1161 (s), 1151 (s), 1107 (ms), 1076 (ms), 1061 (w), 880 (w), 957 (m), 843 (m), 716 (w), 692 (m), 685 (m), 540 (w). Mass: 380 $[M–C_2F_5]^+$ (10.9), 292 $C_6F_{10}NO^+$ (4.4), 214 $C_4F_8N^+$ (4.7), 169 $C_3F_7^+$ (68.5), 164 $C_3F_6N^+$ (9.4), 150 $C_3F_6^+$ (34.0), 131 $C_3F_5^+$ (2.7), 119 $C_2F_5^+$ (6.5), 114 $C_2F_4N^+$ (11.7), 100 $C_2F_4^+$ (23.8), 97 $C_2F_3O^+$ (2.6), 69 CF_3^+ (100). *Trans-F-*(*N*-*n*-propyl-2,6-dimethylmorpholine) (*n*-**8**). IR (gas): 1339 (s), 1313 (w), 1279 (s), 1254 (vs), 1234 (s), 1215 (w), 1169 (s), 1148 (ms), 1126 (ms), 1074 (m), 847 (w), 721 (w), 708 (w), 681 (w). Mass data of *trans*-*n*-**8** were the same as that of *cis*-*n*-**8**. ^{19}F and ^1H NMR of *cis*- and *trans*-*n*-**8** are shown in Table 2.

F-[3-(2,6-dimethylmorpholino)-*iso*-butyryl fluoride] (**2c**) (nc). IR (gas): 1890, 1875 ν(C=O) (ms), 1358 (ms), 1339 (s), 1308 (m), 1279 (s), 1259 (vs), 1188 (ms), 1153 (s), 1107 (m), 1072 (m), 1011 (w), 843 (w), 694 (w). Further characterization of **2c** was conducted in a form of the methyl ester which was obtained by the same method as that explained for **2a**. Methyl *F*-[3-(2,6-dimethylmorpholino)-*iso*-butyrate] (**15**) had bp 175–178°C, n_D^{20}1.3178. IR (capillary film): 1794 ν(C=O). The compound **15** could be measured for each of *cis*- and *trans*-forms by GC-MS. Mass data of *cis*-**15**: 380 $[M-C_2F_4CO_2Me]^+$ (2.6), 209 $C_3F_6CO_2Me^+$ (3.4), 169 $C_3F_7^+$ (4.5), 150 $C_3F_6^+$ (12.0), 131 $C_3F_5^+$ (3.4), 114 $C_2F_4N^+$ (2.1), 100 $C_2F_4^+$ (7.7), 81 $C_2F_3^+$ (8.1), 69 CF_3^+ (19.6), 59 CO_2Me^+ (100). Mass data of *trans*-**15** were the same as that of *trans*-**15**. The *cis*- to *trans*-ratio of **15** was 1:0.38 by the integration of the peak due to CF at 2,6-position of the morpholino-group. Analysis: $C_{11}F_{18}NO_3H_3$ requires: C, 24.49; F, 63.45%. Found: C, 24.41; F, 63.20%. ^{19}F and ^{1}H NMR of *cis*- and *trans*-**15** are shown in Table 2.

3.4. Fluorination of methyl 3-(cis-2,6-dimethylmorpholino)-n-butyrate (1d)

The sample **1d** (40.4 g, 0.188 mol) was fluorinated similarly under the following conditions; 3.0 A/dm^2, 6.0–6.3 V, 7–8°C, 568 min (199 A h). Work-up gave product in the −78°C, (1.8 g): **4** (0.6 g), **6** (trace), **7** (0.3 g), unidentified (0.8 g). Cell drainings (37.1 g): **7** (6.5 g), **8** (5.7 g), *F*-[3-(2,6-dimethylmorpholino)-*iso*-butyryl fluoride] (**2d**) (22.5 g) and identified (2.4 g). The yield of **2d** was 22.8%. The compound **8** was found to be a mixture of *F*-(*N*-*iso*-propyl-2,6-dimethylmorpholine) (*iso*-**8**) (69%) and *F*-(*N*-*n*-propyl-2,6-dimethyl-morpholine) (*n*-**8**) (31%) by the integration of the peaks due to CF_3 of N-C_3F_7 group [−75.23 ppm (m, 3F), −76.52 ppm (m, 6F)]. The *cis*- to *trans*-ratio of **8** was 1: 0.47 by the integration of the peaks due to CF group [−126.04 ppm (m, 2F), −122.54 ppm (m, 2F)].

Methyl *F*-[3-(2,6-dimethylmorpholino)-*n*-butyrate] (**16**) (nc) had bp 175–178°C, n_D^{20}1.3239. IR (gas): 1792 ν(C=O)(s). Mass: 480 $[M-CO_2Me]^+$ (0.5), 430 $[M-CF_2CO_2Me]^+$ (4.7), 209 $C_3F_6CO_2Me^+$ (7.1), 169 $C_3F_7^+$ (10.6), 150 $C_3F_6^+$ (13.8), 131 $C_3F_5^+$ (4.5), 119 $C_2F_5^+$ (4.2), 114 $C_2F_4N^+$ (3.2), 100 $C_2F_4^+$ (9.7), 69 CF_3^+ (32.6), 59 CO_2Me^+ (100). Analysis: $C_{11}F_{18}NO_3H_3$ requires: C, 24.49; F, 63.45%. Found: C, 24.64; F, 63.44%. The ^{19}F NMR of **16** was very complicated. Only several peaks were determined. NMR: −74.58 (m, 3F), −80.68 (m, 6F), −156.76 (d, 1F), 3.978 (s, 3H).

3.5. Fluorination of cis-2,6-dimethylmorpholine (1e)

The sample **1e** (35.8 g, 0.311 mol) was fluorinated similarly under the following conditions; 2.7 A/dm^2, 6.1–6.3 V, 7–8°C, 513 min (226 A h). Work-up gave product in the −78°C, (24.4 g): **5** (2.7 g), **4** (15.4 g), *F*-(*N*-fluoro-2,6-dimethylmorpholine) (**3**) (0.7 g), *N*,*N*-difluoroamino-*F*-(2,4-dimethyl-3-oxa-pentane) (**5**) (2.9 g), unidentified (2.7 g). Cell drainings (13.5 g): **4** (5.1 g), **3** (1.6 g), **5** (5.0 g), unidentified (1.8 g). The yield of **3** was 2.1%.

F-(*N*-fluoro-2,6-dimethylmorpholine) (**3**) [16] showed the following ^{19}F NMR and Mass spectra. ^{19}F NMR: −128.68 (m, 2F), −113.97 (m, 1F), −107.56 and −104.40 (J_{AB} = 188.2 Hz, 4F), −80.33 (m, 6F). Mass: 330 $[M-F]^+$ (8.0), 280 $C_5F_{10}NO^+$ (8.8), 214 $C_4F_8N^+$ (3.9), 169 $C_3F_7^+$ (17.4), 150 $C_3F_6^+$ (64.7), 119 $C_2F_5^+$ (4.9), 114 $C_2F_4N^+$ (36.8), 100 $C_2F_4^+$ (33.2), 97 $C_2F_3O^+$ (5.1), 69 CF_3^+ (100).

N,*N*-difluoroamino-*F*-(2,4-dimethyl-3-oxa-pentane) (**5**) (nc) had bp 69–70°C. IR (capillary film): 1249 (broad, vs), 1199 (s), 1165 (s), 1149 (s), 1131 (s), 1089 (w), 989 (s), 955 (m), 947 (m), 923 (m), 876 (m), 761 (w), 745 (m), 744 (m), 729 (m), 710 (w), 698 m (w), 688 (w). ^{19}F NMR: −141.63 (m, 1F), −138.59 (m, 1F), −116.32 and −114.95 (J_{AB} = 204.6 Hz, 2F), −80.89 (s, 3F), −80.31 (s, 3F), −79.70 (m, 3F), 17.96 (m, 1F), 18.67 (m, 1F). Mass: 335 $[M-NF_2]^+$ (0.6), 318 $[M-CF_3]^+$ (0.8), 285 $[M-CF_2NF_2]^+$ (1.2), 169 $C_3F_7^+$ (36.2), 150 $C_3F_6^+$ (5.9), 147 $C_3F_5O^+$ (6.6), 119 $C_2F_5^+$ (14.9), 100 $C_2F_4^+$ (9.5), 97 $C_2F_3O^+$ (6.1), 69 CF_3^+ (100).

3.6. Preparation of 12 and 13

3.6.1. Preparation of F-(2,6-dimethylmorpholino-acetic acid) (17) and its K salt

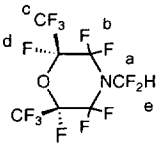
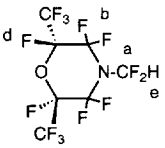
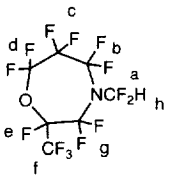
In a 100 ml 3-necked flask which contained 39.1 g of cell drained product obtained in the fluorination of **1a** and 20 ml of ethylene glycol, total of 1.5 ml water was added by 0.5 ml each within 5 min intervals under vigorous agitation at room temperature. The temperature rose to 43°C. After the removal of the ether, the residue was distilled under reduced pressure and gave 26.2 g of *F*-(2,6-dimethylmorpholino-acetic acid) (**17**) (Yield 67%); bp 73–85°C/8 mm Hg. IR: 1778 ν(C=O)(s). The K salt of **17** was made by neutralizing the acid with 10% aq. KOH by using a phenolphthalein as an indicator and dried for further reaction.

3.6.2. Pyrolysis of K salt of 17

The 75 ml Hoke cylinder which contained 6.9 g of K salt of **17** and 2.6 g ethyleneglycol was evacuated at −78°C, and the reaction mixture was held at 175°C for 5.5 h. After removing the volatile gas (CO_2) at −78°C, the products were transferred to the collection trap by using a vacuum line. The products (5.0 g) obtained had a vapor pressure of 11 mm Hg at room temperature. It consisted of *N*-difluoromethyl-*F*-(2,6-dimethylmorpholine) (**12**) (93%) and *N*-difluoromethyl-*F*-(2-methyl-1,4-oxazepan) (**13**) (7%) which were identified by a combined use of IR, NMR and Mass spectral data.

N-difluoromethyl-*F*-(2,6-dimethylmorpholine) (**12**) (nc) had bp 82.0–83.0°C. IR (gas): 1444 (m), 1374 (ms), 1332 (ms), 1284 (vs), 1258 (vs), 1228 (ms), 1282 (s),

Table 3
NMR data of **12** and **13**

Compd No	Formula	Chemical shifts (ppm) [a,b]	*J* (Hz)
Cis-**12**		a −96.95	d,q (*J* = 55.31, 10.2)
		b −81.7, −100.5	J_{AB} = 206.6
		c −80.8	d,d (*J* = 13.8, 6.8))
		d −129.35	m
		e δ 6.989	t (*J* = 55.79)
Trans-**12**		a −91.15, −103.37	(ABXY, J_{AB} = 218.7, J_{AX} = 60.4, J_{AY} = 6.7, J_{BX} = 53.3, J_{BY} = 8.5)
		b −76.06, −95.99	J_{AB} = 203.2
		c −80.55	d,d (*J* = 11.28, 8.5)
		d −124.03	
		e δ 6.989	t (*J* = 55.79)
13		a −92.29, −97.4	(ABX, J_{AB} = 216, J_{AX} = 58, J_{BX} = 55)
		b −83.37, −93.64	J_{AB} = 214.36
		c −120.78, −123.34	(ABXY, J_{AB} = 272.1, J_{AX} = 42.9, J_{AY} = 13.8)
		d −83.54	*J* = 5.36
		e −134.61	
		f −80.20	*J* = 13.83
		g −80.18, −96.30	J_{AB} = 232.6
		h δ 6.725	t (*J* = 55.5)

[a] ^{19}F Chemical shifts in ppm relative to internal CCl_3F.
[b] Only obvious chemical shifts and coupling constans are given.

1147 (vs), 1131 (vs), 1105 (m), 952 (w), 845 (ms), 708 (w), 693 (ms). Mass: 362 $[M-F]^+$ (9.9), 292 $C_6F_{10}NO^+$ (5.7), 264 $C_5F_{10}N^+$ (4.4), 150 $C_3F_6^+$ (61.7), 119 $C_2F_5^+$ (4.5), 114 $C_2F_5N^+$ (5.7), 100 $C_2F_4^+$ (15.1), 69 CF_3^+ (26.3), 51 CF_2H^+ (100). Analysis: $C_7F_{14}NOH$ requires: C, 22.05; F, 69.82%. Found: C, 22.15; F, 69.63%. The *cis*- to *trans*-ratio of **12** was 1:0.39 by the integration of the peak due to CF at 2,6-position of the morpholino-group. ^{19}F and ^1H NMR data of **12** are shown in Table 3 together with those of **13**.

N-difluoromethyl-*F*-(2-methyl-1,4-oxazepan) (**13**) (nc). IR (gas): 1449 (w), 1354 (m), 1321 (ms), 1293 (s), 1255 (vs), 1212 (s), 1238 (ms), 1153 (s), 1101 (m), 1080 (w), 1062 (W), 998 (w), 882 (w), 692 (w). Mass: 362 $[M-F]^+$ (4.1), 312 $[M-CF_3]^+$ (6.8), 292 $C_6F_{10}NO^+$ (11.7), 264 $C_5F_{10}N^+$ (18.3), 195 $C_4F_7M^+$ (30.8), 150 $C_3F_6^+$ (29.1), 131 $C_3F_5^+$ (7.2), 114 $C_2F_5N^+$ (28.9), 100 $C_2F_4^+$ (92.1), 69 CF_3^+ (64.9), 51 CF_2H^+ (100). Analysis: $C_7F_{14}NOH$ requires: C, 22.05; F, 69.82%. Found: C, 22.14; F, 69.50%.

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