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NEW OPTICALLY RESOLVED PERFLUORO(2-DIMETHYLAMINO-PROPIONIC ACID) AND PERFLUORO(3-DIALKYLAMINO-ISO-BUTYRIC ACIDS)

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SUMMARY

Racemic perfluoro(2-dimethylamino-propionic acid), and several kinds of perfluoro(3-dialkylamino-iso-butyric acids) [di-alkyl amino-group: dimethylamino, pyrrolidino or morpholino-group] were separated successfully on a gram scale into their enantiomers via diastereomeric amides with (-)-1-phenylethylamine by means of preparative silica gel HPLC. Subsequent hydrolysis afforded the optically resolved new perfluorocarboxylic acids.

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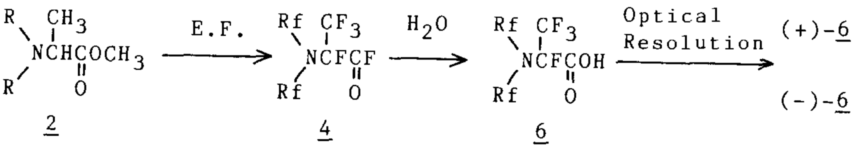
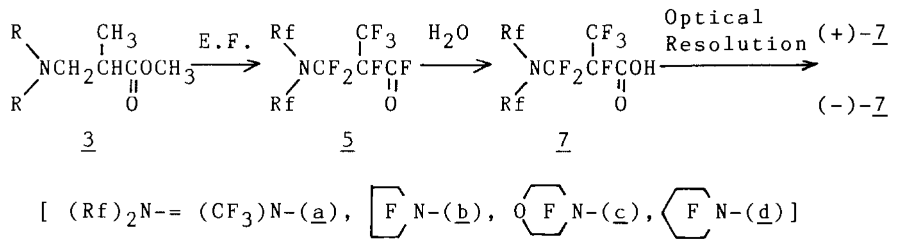
INTRODUCTION

Perfluorinated compounds containing both a chiral carbon and a functional group are considered to be prospective new building blocks for optically active compounds, because there are many possibilities for the development of new applicability with them which is difficult to attain by use of hydrocarbon-type ones [1] (+)- and (-)-perfluoro-2-propoxyproinic acid (1) have been prepared for the first time as an example of perfluorinated optically active agents for the purpose of chiral derivatizing agents by Ishikawa *et al* [2]. In addition to this, optically active perfluorocarboxylic acids have attracted much attention as suitable materials for ferroelectric liquid crystals in order to improve the durability and the response time recently [3]. Therefore, more convenient and efficient methods for the preparation of optically active new perfluoro-compounds are still desired.

We have recently synthesized various perfluoro(2-dialkylamino-propionyl fluorides (4) [4] and perfluoro-(3-dialkylamino-iso-butyryl fluorides (5) [5] by the electrochemical fluorination of the corresponding methyl 2-dialkylamino-propionates(2) and methyl 3-dialkylamino-iso-butyrates(3), respectively. By the the hydrolysis of 4 and 5, corresponding perfluoro(2-dialkylamino-propionic acids)(6) and perfluoro(3-dialkylamino-iso-butyric acids)(7) were easily obtained. Already we have performed the optical resolution of some kinds of perfluoro(2-dialkylamino-propionic acids), *i.e.*, 7b-7d, from corresponding diastereomeric amides by silica gel column chromatography [6].

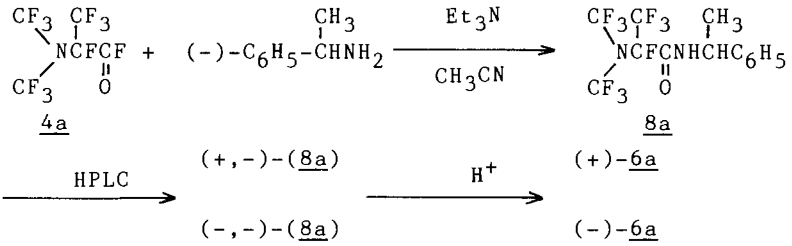




In this paper, we wish to report the results of the optical resolution via diastereomeric amides of perfluoro(2-dimethylamino-propionic acid) with (-)-1-phenylethylamine which could not be resolved in the previous work and those of diastereomeric amides of some perfluoro(3-dialkyamino-iso-butyric acids) by means of preparative silica gel high performance liquid chromatography (HPLC).

RESULTS AND DISCUSSION

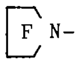
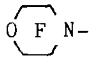
Optical Resolution of Perfluoro(2-dimethylamino-propionic acid) via (-)-1-Phenylethylamine Amide



Although some kinds of diastereomeric amides from perfluoro(2-dialkylamino-propionyl fluorides)(4), [dialkyl amino-group: pyrrolidino, morpholino or piperidino group, i.e., 4b-4d] with (-)-1-phenylethylamine have been completely separated from each other by means of silica gel column

TABLE 1

HPLC Separation of Diastereomeric Amides Derived from 4 and (-)-1-Phenylethylamine[a]

$(Rf)_2N$-	k' [b]		α [c]
	(+,-)	(-,-)	
$(CF_3)_2N$- 8a	1.20	1.05	1.14
 8b	1.51	1.02	1.48
 8c	1.46	1.02	1.43
 8d	1.61	1.01	1.59

[a] Operating conditions: silica gel(Shim Pak CLC SIL,6.0 mm i.d. X 150 mm);eluent, 0.5% i-PrOH/ hexane, 1.0 ml/min, 25°C. [b] Capacity factors (retention volume of diastereomer-void volume of column)/(void volume of column). [c] Separation factor=$k'_{(+,-)}/k'_{(-,-)}$.

chromatography, satisfactory separation of the amides obtained from perfluoro(2-dimethylamino-propionyl fluoride)(4a) could not be performed by a similar way. So, in order to achieve complete separation of the diastereomers,6a, HPLC was applied. On the basis of preliminary results of the analytical HPLC separation of 6a, good separation was also expected in a preparative scale with a silica gel column using hexane containing small amount of i-PrOH as an eluent. The results of an analytical HPLC separation of diastereomers (8a-8d) with a silica gel column are listed in Table 1. Among all diastereomeric pairs, (-,-)-isomers eluted faster than (+,-)-isomers. The value of separation factor for diastereomers, 8a,(1.14) was rather smaller than those for the other diastereomers,8b,8c,8d,(1.43-1.48) but the peaks of 8a were well designed, which suggested the possibility of the separation even for 8a (Fig. 1).

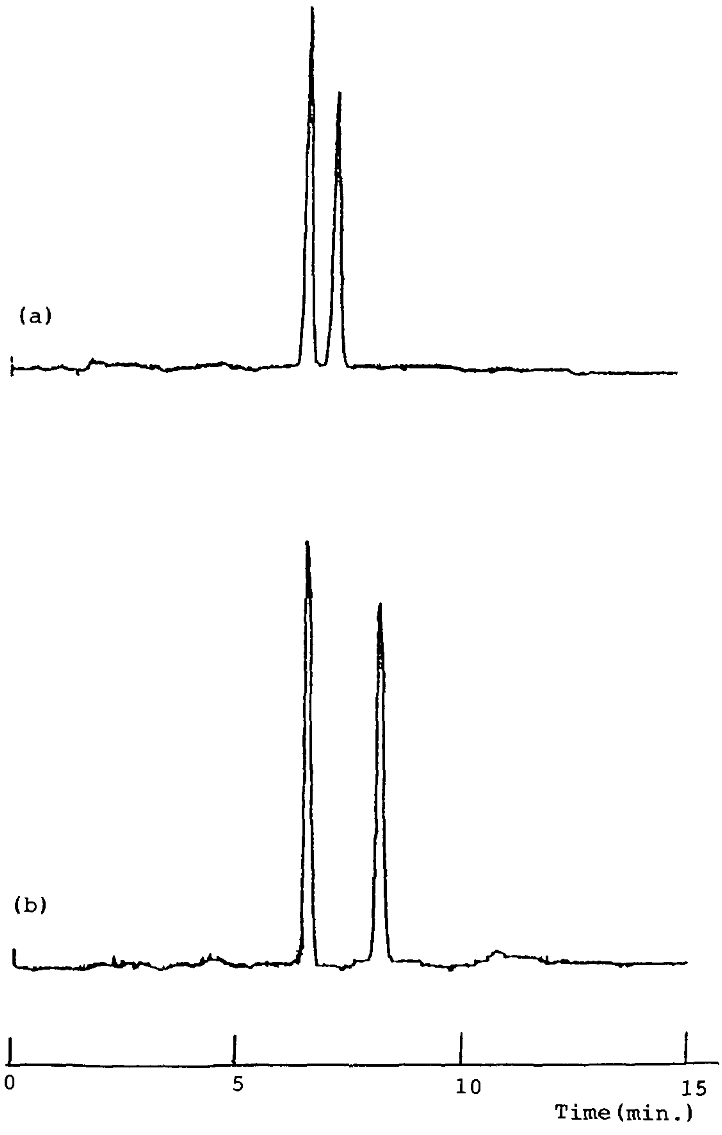
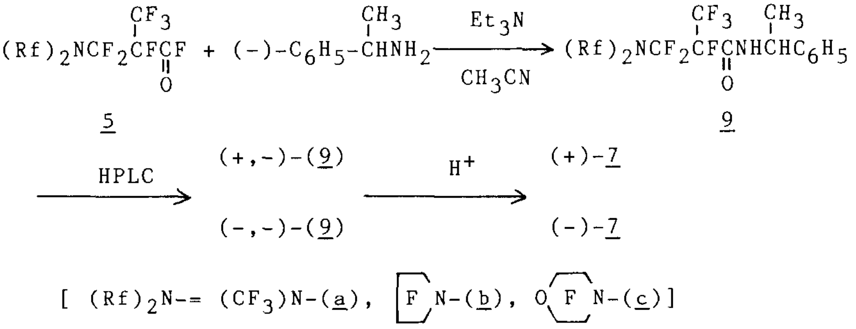


Fig. 1. Analytical HPLC Chromatograms of the Amides 8.
(a) 8a, (b) 8b.
Analytical conditions were the same as described in Table 1.

Thus, semi-gram samples of 8a were completely separated into each (+,-)-isomer and (-,-)-isomer by preparative HPLC using a silica gel column with the aid of recycle procedure.

Both of the separated amides were hydrolyzed by a similar procedure to the case of the preparation of optically active perfluoro(2-iso-propoxypropionc acids) [7], and corresponding free carboxylic acids were obtained.

Optical Resolution of Perfluoro(3-dialkylamino-iso-butyric acids) via (-)-1-Phenylethylamine Amide



$$(Rf)_2NCF_2\overset{CF_3}{\overset{|}{C}}F\underset{\underset{O}{\|}}{C}F + (-)\text{-}C_6H_5\text{-}\overset{CH_3}{\overset{|}{C}}HNH_2 \xrightarrow[CH_3CN]{Et_3N} (Rf)_2NCF_2\overset{CF_3}{\overset{|}{C}}F\underset{\underset{O}{\|}}{C}NH\overset{CH_3}{\overset{|}{C}}HC_6H_5$$

5 9

$$\xrightarrow{HPLC} \begin{matrix}(+,-)\text{-}(9)\\(-,-)\text{-}(9)\end{matrix} \xrightarrow{H^+} \begin{matrix}(+)\text{-}7\\(-)\text{-}7\end{matrix}$$

[$(Rf)_2N$-= $(CF_3)N$-(a), F N-(b), O F N-(c)]

As the example of title compounds, the optical resolution of perfluoro(3-dimethylamino-iso-butyric acid)(9a), perfluoro-(3-pyrrolidino-iso-butyric acid)(9b) and perfluoro(3-morpholino-iso-butyric acid)(9c) were conducted and optically resolved corresponding carboxylic acids were successfully obtained.

It was found that values of the separation factor for title diastereomers were larger than those of diastereomers from perfluoro-2-dialkylamino-propionic acids having the same perfluorodialkyl-amino groups by analytical silica gel HPLC. For instance, values of separation factor of 8a, 8b and 8c were 1.14, 1.48 and 1.43 (Table 1), respectively; while those of 9a, 9b and 9c were 1.54, 1.74 and 1.56 (Table 2) respectively with the same analytical conditions. In all cases, (-,-)-isomers eluted also faster than (+,-)-isomers.

TABLE 2
HPLC Separation of Diastereomeric
Amides Derived from 5 and (-)-1-Phenylethylamine[a]

Diastereomeric Amides	k'[b]		α[c]
	(+,-)	(-,-)	
9a	1.62	1.05	1.54
9b	1.83	1.05	1.74
9c	1.64	1.05	1.56

[a] Operating conditions were identical with those described in Table 1. [b] and [c] Definitions were identical with those of [b] and [c] in Table 1, respectively.

Thus, the separation of the diastereomeric amides of 9 by HPLC was performed easily and about a gram sample of diastereomeric sample was completely separated into (+,-)-isomers and (-,-)-isomers without a recycle procedure.

Base line separation of all the diastereomeric amides were also conducted by analytical GLC with the similar conditions applied in the previous work (see the Experimental section and the reference [6]). These separated amides gave similar absorption patterns in their IR spectra for both diastereomers.

These diastereomerically pure amides were hydrolyzed by treatment with conc. H_2SO_4 and subsequent that with aq. NaOH to give free corresponding carboxylic acids.

In the case of chiral fluorinated compounds, especially for chiral perfluorinated ones, ^{19}F NMR technique can also be applicable for the determination of optical purity when appropriate chemical shift difference among each diastereomers on its spectra appears [2,8,9]. For example, in the case of diastereomers from 1 the difference of absorption peaks due to α-CF_3 [2] and in the case of 4d that due to methine fluorine attached to the chiral carbon [6], which are large enough to calculate the mixture ratio of the diastereomers, are available for the determination of their optical purity. Though such occurrence of the difference of their chemical shifts on their ^{19}F NMR spectra were expected in the case of 9 similarly, neither of these absorption peaks showed distinguishable differences between each diastereomers.

However, 9 showed enough separation between the diastereomers to calculate the mixture ratio by HPLC and GLC analysis. Thus, there is a possibility for the use of chiral derivatizing for these optically resolved perfluorocarboxylic acids by means of HPLC and GLC.

Applications of these optically resolved perfluorocarboxylic acids for the determination of the purity of other kind of chiral compounds, for example chiral alcohols, are under way.

EXPERIMENTAL

Apparatus

Optical rotations were measured with a JASCO DIP-370 spectrometer using a quartz cell (3mm X 100mm). IR spectra were recorded on a Hitachi EPI-G3 spectrometer. ^{1}H NMR spectra were measured on 5% solutions in $CDCl_3$ using $SiMe_4$ as an internal standard and were recorded on a Hitachi R-90H(90.01MHz) spectrometer. ^{19}F NMR spectra were measured on 5% solutions in $CDCl_3$ using CCl_3F as an internal standard on a Hitachi R-90F(84.68MHz) spectrometer.

HPLC measurements were carried out on a Shimadzu LC-6A with UV detection at 254 nm using stainless column packed with Shim-pak CLC SIL(6.0 mm i.d. X 150 mm). The column was kept at 25 °C.

Preparative HPLC were carried out on a Shimadzu LC-8A with UV detection at 254 nm using stainless column packed with

DEVELO SIL 60(50 mm i.d. X 0.5 m) at room temperature.

GLC analysis was carried out on a Shimadzu GC-6A using a stainless column (3 mm i.d. X 3.0 m) packed with 10% Thermol III on Uniport B (60-80 mesh). The carrier was helium. The column was kept at 160°C.

Reagents

Perfluoro(2-dimethylamino-propionyl fluoride) [4a] and perfluoro(3-dialkylamino-iso-butyryl fluorides) [5] were all made by the electrochemical fluorination of the corresponding methyl esters of 2-dimethylamino-propionate and 3-dialkylamino-iso-butyrates, respectively.

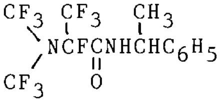
(-)-1-Phenylethylamine(Wako Chemical Ltd.) was used as received.

Optical Resolution of Perfluoro(2-dimethylamino-propionic acid) via (-)-1-Phenylethylamine Amide

To a solution of (-)-1-phenylethylamine (4.30 g, 35.5 mmol) and triethylamine (3.60 g, 35.6 mmol) in 20 ml of acetonitrile, perfluoro(2-dimethylamino-propionyl fluoride) (4a)(10.0 g, 33.4 mmol) was added at room temperature. After 2 hr. standing, the solvent was evaporated under reduced pressure. The residue was dissolved in 2N HCl (150 ml) and extracted with ether (50 ml X 2). The ether solution was washed with 2N $NaHCO_3$ and water, and dried over $MgSO_4$. After evaporation of the solvent, pure 1:1 mixture of the diastereomeric amides(11.96 g, 29.9 mmol, 90% yield) was obtained.

The diastereomeric mixture (0.3 g) was separated by means of HPLC on a silica gel column (DEVELO SIL 60, 50mm i.d X 500mm) using 0.5% i-PrOH/hexane as an eluent(40 ml/min.) and a solvent. Similar work up was carried out several times and the following diastereomerically pure samples were obtained.

(+,-)-8a(nc):

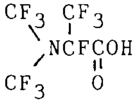


$(CF_3)_2NCF(CF_3)C(=O)NHCH(CH_3)C_6H_5$

$[\alpha]_D^{20}$(c=1.0,$CHCl_3$),-59.0;m.p.,89.0-89.5°C. IR(KBr); 3346(NH),1696(C=O). ^1H NMR(δ);1.56(CH_3),5.56(CH),6.63(NH), 7.32(C_6H_5). ^{19}F NMR(δ);-52.0(CF_3-N),-73.4(CF_3),-136.0(CF). (-,-)-8a(nc):$[\alpha]_D^{20}$(c=1.0,$CHCl_3$),-66.9: m.p.,98.5-99.0°C. IR, ^1H NMR and ^{19}F NMR spectra were similar to those of the (+,-)-isomer.

Conc. H_2SO_4(2.5 ml) was added to 2.0 g of (+,-)-8a and the mixture was stirred for 1hr. at room temperature. The reaction mixture was dissolved with 30 ml of water containing ice. Separated oily layer was extracted with ether(5ml X 3). After the ether was evaporated, 6N NaOH(5.0 ml) was added to the residue. The solution was refluxed for 3 hr. The reaction mixture was acidified with 6N HCl and the separated oily layer was extracted with ether (5 ml X 3). The ether solution was dried over $MgSO_4$. After the ether was evaporated, 1.0 ml of conc. H_2SO_4 was added to the residue. By evaporating it at reduced pressure, 1.2 g of the carboxylic acid,(+)-4a, was obtained.

(+)-Perfluoro(2-dimethylamino-propionic acid)(+)-4a(nc):



$(CF_3)_2NCF(CF_3)C(=O)OH$

$[\alpha]_D^{20}$(c=1.0,$CHCl_3$),10.5; b.p.,85.0-86.0°C/45torr . IR(KBr);1776(C=O). ^1H NMR(δ);10.2. ^{19}F NMR(δ);-52.0(CF_3-N), -73.2(CF_3),-140.2(CF). Found:C,20.18%. Calculated for $C_5F_{10}NO_2H$:C,20.22%.

By a similar way, 1.3 g of (-)-4a was also obtained from 2.0 g (-,-)-8a.

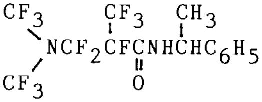
(-)-Perfluoro(2-dimethylamino-propionic acid)(-)-4a (nc):

$[\alpha]_D^{20}$(c=1.0,$CHCl_3$),-10.5; b.p.,85.0-86.0°C/45torr. IR, ^1H NMR and ^{19}F NMR spectra were identical with (+)-isomer. Found:C,20.19%. Calculated for $C_5F_{10}NO_2H$:C,20.22%.

Optical Resolution of Perfluoro(2-dimethylamino-iso-butyric acid) via (-)-1-Phenylethylamine Amide

The following diastereomerically pure samples were also obtained from perfluoro(2-dimethylamino-iso-butyryl fluoride) by a similar treatment to that described above.

(+,-)-9a(nc):



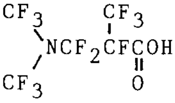
$(CF_3)_2NCF_2CF(CF_3)C(=O)NHCH(CH_3)C_6H_5$

$[\alpha]_D^{20}$(c=1.0,$CHCl_3$),-49.1. IR(KBr);3335(NH),1701(C=O). ^1H NMR(δ);1.56(CH_3),5.56(CH),6.63(NH),7.32(C_6H_5). ^{19}F NMR(δ); -52.8(CF_3-N),-73.8(CF_3),-84.7(CF_2),-177.0(CF).

(-,-)-9a(nc):$[\alpha]_D^{20}$(c=1.0,$CHCl_3$),-62.1:m.p.,98.5-99.0°C. IR and ^1H NMR spectra were similar to those of the (+,-)-isomer. ^{19}F NMR(δ);-52.8(CF_3-N),-73.9(CF_3),-84.7(CF_2), -177.2(CF).

(+)- And (-)- Perfluoro(2-dimethylamino-iso-butyric acid) were also prepared from the diastereomerically pure amides by a similar procedure as the case of (+)- and (-)-perfluoro(2-dimethylamino propionic acid).

(+)-Perfluoro(2-dimethylamino-iso-butyric acid)(+)-7a(nc):



$(CF_3)_2NCF_2CF(CF_3)C(=O)OH$

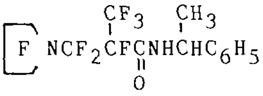
$[\alpha]_D^{20}$(c=1.0,$CHCl_3$),9.4; b.p.,72.0-73.0°C/35torr. IR(KBr);1772(C=O). ^1H NMR(δ);10.2. ^{19}F NMR(δ);-52.0(CF_3-N), -73.2(CF_3),-84.5(CF_2),-176.2(CF). Found:C,20.73%. Calculated for $C_6F_{12}NO_2H$:C,20.76%.

(-)-Perfluoro(2-dimethylamino-iso-butyric acid)(-)-7a(nc): $[\alpha]_D^{20}$(c=1.0,$CHCl_3$),-9.4; b.p.,72.0-73.0°C/35torr. IR, ^1H NMR and ^{19}F NMR spectra were identical with (+)-isomer. Found:C,20.74%. Calculated for $C_6F_{12}NO_2H$:C,20.76%.

Optical Resolution of Perfluoro(2-pyrrolidino-iso-butyric acid) via (-)-1-Phenylethylamine Amide

The following diastereomerically pure samples were also obtained from perfluoro(2-pyrrolidino-iso-butyryl fluoride) by a similar treatment to that described above.

(+,-)-9b(nc):



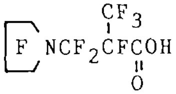
$\boxed{F}NCF_2\overset{CF_3}{C}F\underset{\overset{\|}{O}}{C}NH\overset{CH_3}{C}HC_6H_5$

$[\alpha]_D^{20}$(c=1.0,$CHCl_3$),-47.9. IR(KBr);3335(NH),1701(C=O). ^1H NMR(δ);1.56(CH_3),5.56(CH),6.63(NH),7.32(C_6H_5). ^{19}F NMR(δ); -73.6(CF_3),-73.8(CF_3),-87.2 and -89.9(CF_2,J_{AB}=134Hz),-90.8(CF_2) -133.0(CF_2),-180.5(CF).

(-,-)-9b(nc):$[\alpha]_D^{20}$(c=1.0,$CHCl_3$),-62.5:m.p.,74.5-75.5°C. IR, ^1H NMR and ^{19}F NMR spectra were similar to those of the (+,-)-isomer.

(+)- And (-)- Perfluoro(2-pyrrolidino-iso-butyric acid) were also prepared from the diastereomerically pure amides by a similar procedure as the case of (+)- and (-)-perfluoro(2-dimethylamino propionic acid).

(+)-Perfluoro(2-pyrrolidino-iso-butyric acid)(+)-7b(nc):



$\boxed{F}NCF_2\overset{CF_3}{C}F\underset{\overset{\|}{O}}{C}OH$

$[\alpha]_D^{20}$(c=1.0,$CHCl_3$),11.1; b.p.,87.0-88.0°C/35torr. IR(KBr);1772(C=O). ^1H NMR(δ);10.2. ^{19}F NMR(δ);-52.0(CF_3-N), -73.2(CF_3),-84.5(CF_2),-176.2(CF). Found:C,23.46%. Calculated for $C_8F_{14}NO_2H$:C,23.49%.

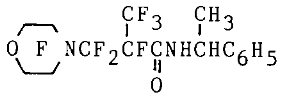
(-)-Perfluoro(2-pyrrolidino-iso-butyric acid)(-)-7b(nc):

$[\alpha]_D^{20}$(c=1.0,$CHCl_3$),-11.1; b.p.,87.0-88.0°C/35torr. IR, ^1H NMR and ^{19}F NMR spectra were identical with (+)-isomer. Found:C,23.46%. Calculated for $C_8F_{14}NO_2H$:C,23.49%.

Optical Resolution of Perfluoro(2-morpholino-iso-butyric acid) via (-)-1-Phenylethylamine Amide

The following diastereomerically pure samples were also obtained from perfluoro(2-morpholino-iso-butyryl fluoride) by a similar treatment to that described above.

(+,-)-9c(nc):

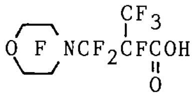


$[\alpha]_D^{20}$(c=1.0,$CHCl_3$),-47.5. IR(KBr);3375(NH),1699(C=O). ^1H NMR(δ);1.56(CH_3),5.56(CH),6.63(NH),7.32(C_6H_5). ^{19}F NMR(δ); -73.6(CF_3),-84.1(CF_2),-87.7(CF_2),-93.0(CF_2),-178.7(CF).

(-,-)-9c(nc):$[\alpha]_D^{20}$(c=1.0,$CHCl_3$),-62.5:m.p.,74.5-75.5. IR,^1H NMR and ^{19}F NMR spectra were similar to those of the (+,-)-isomer.

(+)- And (-)- perfluoro(2-morpholino-iso-butyric acid) were also prepared from the diastereomerically pure amides by a similar procedure as the case of (+)- and (-)-perfluoro(2-dimethylamino propionic acid).

(+)-Perfluoro(2-morpholino-iso-butyric acid)(+)-7c (nc):



$[\alpha]_D^{20}$(c=1.0,$CHCl_3$),12.0; b.p.,89.0-91.0°C/35torr. IR(KBr);1772(C=O). ^1H NMR(δ);10.2. ^{19}F NMR(δ);-73.6(CF_3), -84.0(CF_2),-87.5(CF_2),-93.0(CF_2),-176.2(CF). Found:C,22.58%. Calculated for $C_8F_{14}NO_3H$:C,22.60%.

(-)-Perfluoro(2-pyrrolidino-iso-butyric acid)(-)-7c(nc):

$[\alpha]_D^{20}$(c=1.0,$CHCl_3$),-12.1; b.p.,89.0-91.0°C/35torr. IR, ^1H NMR and ^{19}F NMR spectra were identical with (+)-isomer. Found:C,22.57%. Calculated for $C_8F_{14}NO_3H$:C,22.60%.

REFERENCES

1 N. Ishikawa, J. Fluorine Chem., 25 (1984) 17.

2 H. Kawa, F. Yamaguchi and N. Ishikawa, J. Fluorine Chem., 20 (1982) 475.

3 a) S. Sugawara, Jap. Pat. 1-294652 (1989); b) ibid., Jap. Pat. 2-5644 (1990); c) Y. Suzuki, Jap. Pat. 2-28127 (1990).

4 a)T. Abe, E. Hayashi, H. Baba and H. Fukaya, J. Fluorine Chem., 48 (1990) 257; b)T. Abe, E. Hayashi, H. Fukaya and H. Baba, J. Fluorine Chem., 50 (1990) 173.

5 T. Abe, E. Hayashi, H. Fukaya and H. Baba, 14th Fluorine Chemistry Symposium, Kyoto, Japan ; Abstract P-18 (1989).

6 a)E. Hayashi, H. Fukaya, T. Abe and K, Omori, Chem. Lett. (1990) 737; b) E. Hayashi, H. Fukaya, T. Abe and K. Omori, J. Fluorine Chem., 52 (1991) 133.

7 H. Kawa, F. Yamaguchi and N. Ishikawa, Chem. Lett., (1982) 745.

8 J. A. Dale, D. L. Dull and S. Mosher, J. Org. Chem., 34 (1969) 2543.

9 Y. Takeuchi, H. Ogura, Y. Ishii and T. Koizumi, J. Chem. Soc. Perkin I, (1989) 1721.