Preparation of the Isoflurane Enantiomers[1]

Chialang G. Huang,* Leonid A. Rozov, Donald F. Halpern, and Gerald G. Vernice

Anaquest, Inc., a Subsidiary of BOC Health Care, Inc., 100 Mountain Avenue, Murray Hill, New Jersey 07974

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The enantiomers of the inhalation anesthetic agent, isoflurane (1-chloro-2,2,2-trifluoroethyl difluoromethyl ether), are prepared by a synthesis starting from 2,2,2-trifluoroethanol. (*R*)-(+)-Dehydroabietylamine is used as the resolving agent for the racemic acid intermediate 1. The optical purities of both (*S*)-(+)- and (R)-(−)-isofluranes are determined to be >99% ee (enantiomeric excess) by chiral capillary gas chromatography.

Introduction

Today all of the clinically used volatile anesthetics, halothane,[2] enflurane,[3] isoflurane,[4] sevoflurane,[5] and desflurane,[6] which provide unconsciousness, amnesia, analgesia, and muscle relaxation, are highly fluorinated compounds. The anesthetic action of these agents has puzzled scientists for many years. Recent studies[7-10] have shown that the inhalation agents may stereospecifically bind to the sensitive protein targets in the central nervous system. The preparation of enantiomerically pure volatile agents were proposed to further evaluate the stereoselective dependency of a protein-based theory.

Four of the medicinally useful volatile anesthetic agents of today possess an asymmetric center: halothane, enflurane, isoflurane, and desflurane. Until now, the preparation of the pure enantiomers of these anesthetics eluded researchers.[11] In addition to the synthetic challenge these compounds posed, the lack of a direct analytical method to determine the optical purity of these enantiomers was also a major issue. Recently, Meinwald et al. reported[12] that the optical purity of halothane, enflurane, or isoflurane can be measured by GC (gas chromatography) using chiral capillary columns. This success has permitted the complete separation of the pure enantiomers on a microscale.

Meinwald's group synthesized the halothane and enflurane enantiomers in high enantiomeric purities.[13] At the same time and parallel to their work, we proposed synthesis of the isoflurane enantiomers. Previous syntheses[4,14,15] of isoflurane produced only racemic mixtures. Most recently, Young and Brandt[16] disclosed an enzymatic approach to the enantiomers of isoflurane and desflurane. Unfortunately, no experimental work was described, and there was no indication of how the desired optical purity of these enantiomers was achieved or determined. On the contrary, we have devised a synthesis to prepare both enantiomers of isoflurane with an optical purity of >99% ee (enantiomeric excess).

Results and Discussion

Philosophically, we recognized that using chiral auxiliaries to guide the formation of the chiral carbon would be quite elegant, but difficult, in this case. We, therefore, opted for the introduction of an achiral synthon which could be formed prior to the generation of the stereogenic center, used for resolution, and be a suitable latent hydrogen (H). A carboxyl group was chosen because simple diastereomeric salt separation by recrystallization, followed by decarboxylation, would lead to the isoflurane enantiomers.

Placement of the carboxylic acid moiety in the methyl fragment of the carbon skeleton (1, as outlined in Scheme I) or in the ethyl fragment (2, as outlined in Scheme II)

Scheme I
(retrosynthesis)

$$CF_3CHClOCF_2H \rightarrow \underset{\mathbf{1}}{CF_3CHClOCF_2COOH} \rightarrow \underset{\mathbf{3}}{CF_3CH_2OCF_2COOH} \rightarrow CF_3CH_2OH + XCF_2COOH$$

Scheme II
(retrosynthesis)

$$CF_3CHClOCF_2H \rightarrow \underset{\mathbf{2}}{HOOCCF_2CHClOCF_2H} \rightarrow HOOCCF_2CH_2OCF_2H \rightarrow EtOOCCF_2CH_2OH + :CF_2$$

becomes a point of consideration; in the end both routes were evaluated synthetically. The use of nucleophilic displacement reaction (S_N2) to generate the prochiral backbone (3 in Scheme I) from an abundant supply of haloacetic acids or esters, coupled with our experience in photochemical chlorination to introduce the stereogenic center, made this route more attractive than the other route (Scheme II). However, the placement of the chiral auxiliary at greater than three carbons from the existing chiral center raised questions about the effectiveness of the diastereomeric resolution process. And lastly, recent

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(1) Huang, C. G. Presented at the 203rd National Meeting of the American Chemical Society, San Francisco, April 1992; paper FLUO 18.
(2) Suckling, C. W.; Raventos, J. Br. Patent 767 779, 1957.
(3) Terrell, R. C. U.S. Patent 3 469 011, 1969.
(4) Terrell, R. C. U.S. Patent 3 535 388, 1970.
(5) Regan, B. M.; Longstreet, J. C. U.S. Patent 3 689 571, 1972.
(6) Terrell, R. C. U.S. Patent 4 762 856, 1988.
(7) Franks, N. P.; Lieb, W. R. *Trans Pharmacol. Sci.* **1987**, *8*, 169.
(8) Evers, A. S.; Berkowitz, B. A.; d'Avignon, D. A. *Nature* **1987**, *328*, 157.
(9) Franks, N. P.; Lieb, W. R. *Nature* **1984**, *310*, 599.
(10) Franks, N. P.; Lieb, W. R. *Nature* **1985**, *316*, 349.
(11) Edamura, F. Y.; Larsen, E. R.; Peters, H. M. Presented at the 159th National Meeting of the American Chemical Society, 1970; paper ORGN 84.
(12) Meinwald, J.; Thompson, W. R.; Pearson, D. L.; König, W. A.; Runge, T.; Francke, W. *Science* **1991**, *251*, 560.
(13) Pearson, D. L. Ph.D. Dissertation, Cornell University, 1990; *Diss. Abstr. Int. B* **1992**, *52*, 6400-1.
(14) Croix, L. S. U.S. Patent 3 637 477, 1972.
(15) Siegemund, G. Br. Patent 1 475 387, 1977.
(16) Young, J. W.; Brandt S. U.S. Patents 5 114 714 and 5 114 715, 1992.

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literature[17,18] reaffirmed the usefulness of the carboxylic acid group as a suitable latent hydrogen for this type of substrate.

The synthetic task now becomes managable through a three-stage program: (1) the preparation of the racemic acid 1; (2) resolution of 1; and (3) the decarboxylation of the enantiomers of 1 to yield the desired enantiomers of isoflurane.

The preparation of the prochiral acid 3 by S_N2 displacement by 2,2,2-trifluoroethoxy anion (Scheme III)

Scheme III

$$CF_3CH_2OH + XCF_2COOR \xrightarrow[(2)\ H_3O^+]{(1)\ KOH,\ H_2O} \quad X = Cl, Br;\ R = H, Et$$

$$CF_3CH_2OCF_2COOH \xrightarrow[C_6H_4(COCl)_2]{C_6H_5COCl\ or} CF_3CH_2OCF_2COCl$$

3 4

proceeded as expected from model compound[17] studies in about 40% yield. Similar results could be obtained using ethyl bromodifluoroacetate. Unexpectedly, the yield of acid 3 was higher (55–65%) when chlorodifluoroacetic acid was used in place of its ester.

Acyl chloride 4 was obtained in high purity and good yield (60–65%) when benzoyl chloride or phthaloyl dichloride were used.

The free-radical chlorination of the acyl chloride 4 resulted in a mixture of the monochlorinated acyl chloride $CF_3CHClOCF_2COCl$ (5) and the dichlorinated acyl chloride $CF_3CCl_2OCF_2COCl$ (6) in a 2:1 ratio. Because the overall yield of the monochloro acyl chloride 5 was low, another approach was needed to produce 5 or a derivative. Paleta[19,20] and Dedek et al.[21] found that an α-chloro halogenated ester, CFYZCClMCOOR′ (Y, Z, M = Cl, F; R′ = 2-propyl, methyl, *n*-butyl), can be reduced photochemically using 2-propanol as the hydrogen source.

The stereogenic center was introduced by photochemical reduction of the dichloro isopropyl ester 7 in 40% chemical yield (Scheme IV).

Scheme IV

$$CF_3CCl_2OCF_2COCl \xrightarrow{(CH_3)_2CHOH}$$

6

$$CF_3CCl_2OCF_2COOCH(CH_3)_2 \xrightarrow[(CH_3)_2CHOH]{UV}$$

7

$$CF_3CHClOCF_2COOCH(CH_3)_2 \xrightarrow{H_3O^+}$$

8

$$(\pm)\text{-}CF_3CHClOCF_2COOH$$

Improvements of this process were realized when perhalogenation of 4 followed by chemoselective dehalogenation, without isolation, afforded an increased yield over the stepwise process. This process approached 75% yield.

Bellucci et al.[22] reported the resolution of chlorofluoroacetic acid using (*R*)-(+)-dehydroabietylamine. Ishikawa and Kawa[23] utilized (*S*)-(−)-α-methylbenzylamine to resolve perfluoro-2-propoxypropionic acid, $CF_3CF(OC_3F_7)COOH$. We have also found that (*R*)-(+)-dehydroabietylamine and the racemic acid 1 successfully form a pair of diasteromeric salts that can be separated and purified by recrystallization in ethyl acetate or chloroform. The diastereomeric salt that exhibited a negative optical rotation, 10 [(−)-(+)-$CF_3CHClOCF_2COO^-H_3N^+C_{20}H_{29}$], precipitated, while the salt with a positive optical rotation, 9 [(+)-(+)-$CF_3CHClOCF_2COO^-H_3N^+C_{20}H_{29}$], remained in solution. Pure 10 was obtained by recrystallization from ethyl acetate five to seven times to give a product with an optical rotation of $[\alpha]^{25}_D = -14°$ (c = 1.0, MeOH). The diastereomeric salt 9 was recrystallized from chloroform to a constant optical rotation. The concentrated mother liquors afforded additional positive diastereomeric salt. Pure 9 exhibited an optical rotation of $[\alpha]^{25}_D = +55°$ (c = 1.0, CH_3OH). The yield of the "negative" diastereomeric salt 10, 25.3%, was much greater than the yield of the "positive" diastereomeric salt 9, 9.4%, because 10 required fewer recrystallizations to produce optically pure material.

The desired enantiomers of 1, 11 [(+)-$CF_3CHClOCF_2COOH$], and 12 [(−)-$CF_3CHClOCF_2COOH$], were isolated by the hydrolysis of the diastereomeric ammonium salts, 9 and 10, by refluxing them in dilute ammonium hydroxide. Yields were 80–85%.

Control of the optical purity of these chiral acids was pivotal to the synthetic plan. The optical purities of the enantiomeric acids 11 and 12 were determined by first converting them to their diastereomeric amide derivatives with (*S*)-(−)-α-methylbenzylamine and by analyzing the amide's [$CF_3CHClOCF_2CONHCH(CH_3)C_6H_5$] proton NMR spectroscopy. The methyl protons of the diastereomers exhibited the expected difference in chemical shifts; the addition of a shift reagent, $Eu(hfc)_3$, enhanced this difference and provided two sets of doublets for the methyl groups (Figure 1). The enantiomeric purity of 11 and 12 was inferred from the measured ratio of the methyl groups of the diastereomers.

Finally, decarboxylation raised the possibility of racemizing the substrate. Careful use of only 1 equiv of potassium hydroxide resulted in retention of the configuration.

The isolated enantiomers of isoflurane were analyzed for optical purity (Figure 2) using a Lipodex A chiral capillary GC column (Machery-Nagel, Dueren, Germany).[12] For >99% ee of the (+)-isoflurane, 13, and (−)-isoflurane, 14, the optical rotations $[\alpha]^{25}_D = +107.8°$ and $[\alpha]^{25}_D = -107.2°$ (neat) are obtained, respectively. The lack of racemization during the decarboxylation reaction places the stereogenic control of the synthesis at the resolution step as planned.

Although direct decarboxylation of the pure positive and negative diastereomeric salts, 9 and 10, affords lower yields than those from the two-step process, the optical purities of the isoflurane enantiomers from either process were equivalent.

Our initial efforts to determine the absolute configurations of 13 and 14 via X-ray crystallography were not successful. However, using a vibrational circular dichroism

(17) Beecham Research Labs., Ltd. Br. Patent 873 244, 1960.
(18) Halpern, D. F.; Robin, M. L. U.S. Patent 4 996 371, 1991.
(19) Paleta, O.; Dadak, V.; Dedek, V. *J. Fluorine Chem.* 1988, *39*, 397.
(20) Sendrik, V. P.; Paleta, O.; Dedek, V. *Collect. Czech. Chem. Commun.* 1976, *41*, 874.
(21) Liska, F.; Dedek, V.; Holik, M. *Collect. Czech. Chem. Commun.* 1971, *36*, 2846.
(22) Bellucci, G.; Berti, G.; Borraccini, A.; Macchia, F. *Tetrahedron* 1969, *25*, 2979.
(23) Kawa, H.; Ishikawa, N. *Chem. Lett.* 1980, 843.

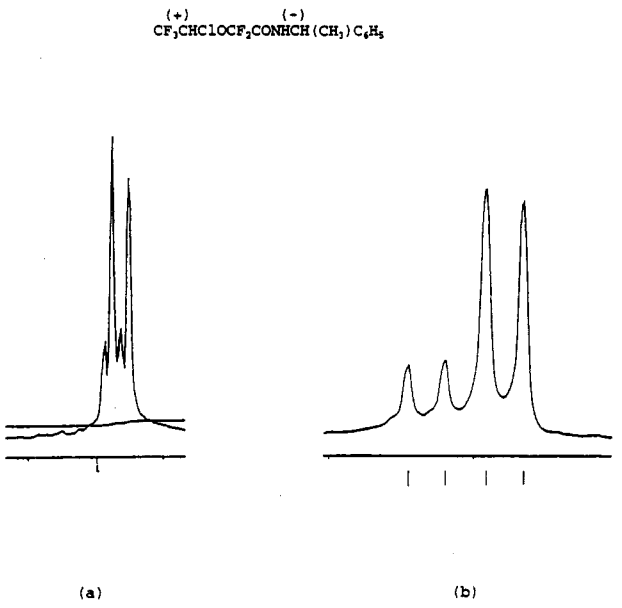

Figure 1. ^1H NMR spectra (C_6D_6) of 80% ee of the (+) (−)-diastereomer, (+) (−)-$CF_3CHClOCF_2CONHCH(CH_3)C_6H_5$: (a) without the shift reagent and (b) with a shift reagent, europium-(III)[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]$_3$.

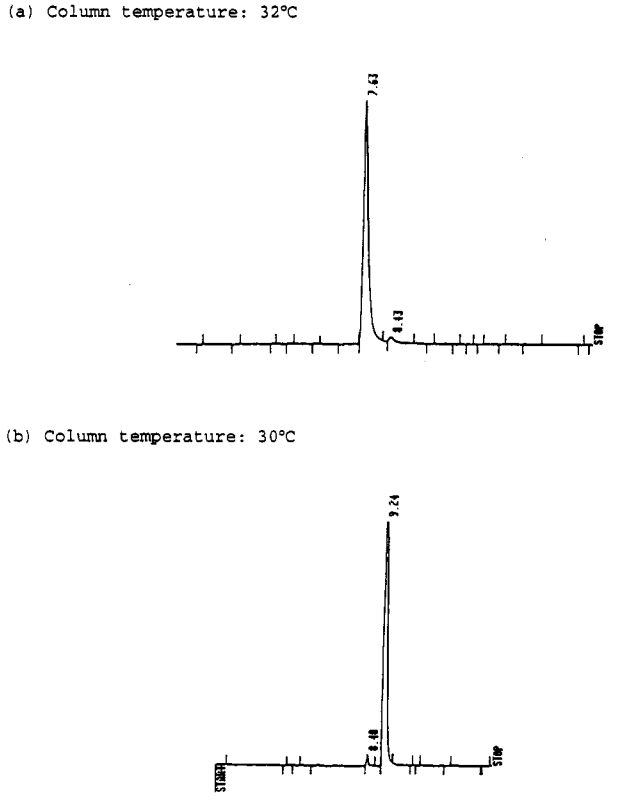

Figure 2. Gas chromatograms of (a) 97.8% ee of (*S*)-(+)-isoflurane and (b) 95.6% ee of (*R*)-(−)-isoflurane on a Lipodex A capillary column.

(VCD) technique, it was determined that (+)-isoflurane has the "*S*" configuration and (−)-isoflurane has the "*R*" configuration. The detailed results of these studies have been published by Polavarapu et al.[24]

Conclusion

We have made enantiomerically pure (+)- and (−)-isoflurane, **13** and **14**, in overall yields of 1.0% and 2.5%, respectively. Both compounds were subjected to *in vitro* and *in vivo* pharmacological screening. The *in vitro* work[25] has identified two possible binding sites in proteins for isoflurane: the potassium ion channels and the central nicotinic acetylcholine receptors. These results have provided support for the protein-based theory of inhalation anesthesia. Sigificant cardiovascular changes in rats[26] and potency differences in mice[27] between the enantiomers and the racemate have also been observed. With the availability of the pure enantiomers of isoflurane, halothane and enflurane, researchers may have additional opportunities to gain a better understanding of the molecular mechanism of anesthesia.

Experimental Section

General. All reagents, except (*R*)-(+)-dehydroabietylamine, were used without further purification. (*R*)-(+)-Dehydroabietylamine was purified to 99% ee according to the literature procedure.[28]

Elemental analyses were performed either by Robertson Laboratories, Madison, NJ, or by Schwartzpkof Laboratories, Woodside, NY.

Melting points were recorded on a Thomas Hoover capillary melting point apparatus without correction.

High-resolution NMR spectra were obtained on an IBM AF 270 Fourier transform spectrometer. ^1H (270.13 MHz) NMR chemical shifts were recorded relative to tetramethylsilane. ^{19}F (254.17 MHz) NMR chemical shifts were recorded relative to fluorotrichloromethane with negative values assigned to signals at higher field and positive values assigned to signals at lower field. Some ^1H (60 MHz) NMR spectra were also obtained on a Varian EM 360 NMR spectrometer or on a Joel GSX 270 NMR spectrometer.

Infrared spectra were obtained on a Shimadzu IR-460 infrared spectrophotometer or on a Digilab FTS-60 spectrometer.

Optical rotations were measured on a Perkin Elmer 241 polarimeter connected to a Brinkmann RM 6 constant temperature water bath.

Gas chromatograms were obtained using the following equipment and conditions: for chemical purity (a) for volatile samples, an HP 5790A gas chromatograph with a thermal conductivity detector at 250 °C; 130 °C injection, and a helium carrier gas flow of 18 mL/min through a 1/8-in. × 8-ft stainless steel column packed with 1% SP-1000 on 60/80 mesh Carbopack B; a 30-min run with the temperature programming from 90 to 150 °C was used; (b) for carboxylic acids, an HP 5780 gas chromatograph with a flame-ionization detector at 275 °C, injection temperature of 135 °C and a helium gas flow of 4 mL/min through a 0.25-mm × 30-mm glass DB-1701 capillary column using temperature programming from 100 to 200 °C over 20 min; for optical purity: a Gow-Mac 750P gas chromatograph, with a 50-m Lipodex A glass capillary column at room temperature, a flame-ionization detector at 200 °C, an injection temperature of 150 °C and the splitter set at 60 mL/min. The pressure for the carrier gas helium flow was set at 0.9 atm.

(2,2,2-Trifluoroethoxy)difluoroacetic Acid, 3. (a) Ethyl Chlorodifluoroacetate Method. To a 1-L three-neck round-bottom flask equipped with a magnetic stirring bar, a 250-mL pressure-equalizing additional funnel, a thermometer, and a reflux condenser were added 69.0 g (0.69 mol) of 2,2,2-trifluoroethanol, 100.0 g (0.69 mol) of ethyl chlorodifluoroacetate, and 86.0 g of water. A solution of 107.0 g (1.62 mol) of 85% potassium hydroxide in 220 mL of water was added over 30 min with vigorous stirring. The reaction temperature rose to 65 °C. The reaction mixture was then heated to reflux for 40 h and then distilled. A

(24) Pollavarapu, P.; Cholli, A. L.; Vernice G. G. *J. Am. Chem. Soc.* **1992**, *114*, 10953.
(25) Franks, N. P.; Lieb, W. R. *Science* **1991**, *254*, 427.
(26) Lysko, G.; Robinson, J.; Ferrone, R. Anaquest, Inc., unpublished results.
(27) Harris, B.; Moody, E.; Skolnick, P. *European J. Pharmacol.* **1992**, *217*, 215.
(28) Gottstein, W.; Cheney, L. C. *J. Org. Chem.* **1965**, *30*, 2072.

low-boiling fraction, up to a head temperature of 95 °C, was removed, and the residual material was cooled to room temperature. Two hundred mL of 18% HCl solution was gradually added, and the mixture was stirred for 30 min. Then the lower organic layer was removed, and the upper aqueous layer was extracted with 4 × 75-mL portions of ether. The combined organic layer and the ether extracts was washed with 100 mL of water and dried overnight over anhydrous sodium sulfate. The ether was distilled at atmospheric pressure. The crude product was redistilled twice using a distillation apparatus with a 20-cm Vigreux column to give 53.5 g (40%) of the title compound, bp 78–82 °C/20 mmHg. ^{1}H NMR ($CDCl_3$): δ 4.3 (q, J_{FCCH} = 7.3 Hz, CH_2), δ 9.2 (s, COOH). ^{19}F NMR ($CDCl_3$): δ −74.5 (t, J_{FCCH} = 7.3 Hz, CF_3), δ −81.2 (s, CF_2). Anal. Calcd for $C_4H_3F_5O_3$: C, 24.77; H, 1.56; F, 48.95. Found: C, 24.55; H, 1.56; F, 48.83.

(b) Chlorodifluoroacetic Acid Method. A solution of 10.0 kg (76.9 mol) of chlorodifluoroacetic acid, 8.6 kg (86.0 mol) of 2,2,2-trifluoroethanol, and a solution of 10.8 kg (163.9 mol) of 85% potassium hydroxide in 6.5 L of water were added simultaneously to a 50-L flask at 90 °C over 4 h. Good stirring and an alkaline pH were maintained throughout the addition. The reaction mixture was then heated at reflux for 48 h and then cooled to room temperature. Twelve L of concentrated hydrochloric acid was added gradually. An organic layer was separated, and the aqueous layer was extracted with 10 × 5-L portions of ether. The combined ethereal solutions were added to the organic portion. The combined organic phase was dried over anhydrous magnesium sulfate and filtered. Ether and excess 2,2,2-trifluoroethanol were removed by distillation at atmospheric pressure to 100 °C, and the remaining crude product was fractionally distilled through a 830-mm-long column packed with 0.375-cm Berl Saddles. The desired product was collected at 75–80 °C/20 mmHg to yield 8.9 kg (60%).

(2,2,2-Trifluoroethoxy)difluoroacetyl Chloride, 4. (a) Benzoyl Chloride Method. Benzoyl chloride, 46.2 g (0.33 mol), and 43.0 g (0.22 mol) of the nonchlorinated acid **3** were mixed in a 250-mL flask connected to a distillation assembly having a 10-cm Vigreux column, a receiver connected to a dry ice trap, and a gas bubbler. The mixture was gradually heated to 220 °C and the temperature was maintained until the gas evolution stopped. During this period the reaction mixture darkened. The liquid that distilled from 50 to 85 °C was collected. Fractional distillation of this liquid gave 27.3 g (58%) of the acyl chloride **4**, bp 82–83 °C. ^{1}H NMR ($CDCl_3$): δ 4.3 (q, J_{FCCH} = 7.9 Hz, CH_2). ^{19}F NMR ($CDCl_3$): δ - 75.0 (t, J_{FCCH} = 7.9 Hz, CF_3), δ - 80.0 (s, CF_2). Anal. Calcd for $C_4H_2ClF_5O_2$: C, 22.61; H, 0.95; F, 44.70; Cl, 16.68. Found: C, 22.90; H, 1.05; F, 44.99; Cl, 16.59%.

(b) Phthaloyl Dichloride Method. A 12-L flask, equipped with a mechanical stirrer, a thermometer, a condenser which was connected to a fraction collector, and a 10% sodium hydroxide solution scrubber, was charged with 5.25 kg (24.6 mol) of phthaloyl dichloride. The acid **3**, 4.7 kg (24.0 mol), was added gradually over 2 h, and the mixture was heated slowly at the same time to 100 °C. After the addition was completed, the resulting solution was heated to reflux. The precipitated solids and the fractions collected below 80 °C were discarded. The fractions from 81 to 85 °C and from 85 to 95 °C were collected. Each fraction was separately redistilled. The two redistilled fractions boiling from 80 to 87 °C were combined to give 3.2 kg (63%) of **4**.

(±)-(1-Chloro-2,2,2-trifluoroethoxy)difluoroacetyl Chloride, 5. The chlorination reaction was carried out in a cylindrical glass reactor equipped with a magnetic stirring bar, a thermometer, a gas dispersion tube, and a reflux condenser topped with a dry ice condenser which was connected to an empty flask followed by a series of two dilute sodium hydroxide solution scrubbers. The reactor was charged with 190.0 g (0.89 mol) of the nonchlorinated acyl chloride **4**. Chlorine gas, 76.0 g (1.07 mol), was slowly bubbled into the liquid acyl chloride while the reactor was being irradiated with a 250-W incandescent light at 50 °C. At 3-h intervals, a small portion of the reaction mixture was converted to its methyl ester and analyzed by GC. After 50 h the chlorination was terminated. The mixture contained 3% of **4** and 61% of **5**, and the reminder was primarily the dichloroacyl chloride **6**. Multiple fractional distillations of the product mixture gave several fractions, bp 92–93 °C, with chemical purities between 95% and 99%. The calculated yield based on the GC data was 48%. The fraction having a purity of 99% was used for the characterization. ^{1}H NMR ($CDCl_3$): δ 6.2 (q, J_{FCCH} = 4.1 Hz, CHCl). ^{19}F NMR ($CDCl_3$, proton decoupled): δ −79.9 and −80.5 (AB quartet, J_{FCF} = 134.5 Hz, nonequivalent CF_2), δ −80.4 (s, CF_3). Anal. Calcd for $C_4HCl_2F_5O_2$: C, 19.45; H, 0.41; F, 38.47; Cl, 28.71. Found: C, 19.58; H, 0.40; F, 38.45; Cl, 28.87%.

(1,1-Dichloro-2,2,2-trifluoroethoxy)difluoroacetyl Chloride, 6. The title compound was obtained from distillation of the chlorination product mixture at bp 108–110 °C after removal of **5** as described above. ^{19}F NMR ($CDCl_3$): δ −78.1 (s, CF_2), δ −79.2 (s, CF_3). Anal. Calcd for $C_4Cl_3F_5O_2$: C, 17.07; F, 33.76; Cl, 37.79. Found: C, 17.23; F, 33.79; Cl, 37.64%.

(±)-(1-Chloro-2,2,2-trifluoroethoxy)difluoroacetic Acid, 1. To a vigorously stirred solution of 125 mL of water and 125 mL of acetone was added 78.7 g (97%, 0.31 mol) of the monochloroacyl chloride **5**. The reaction mixture was maintained at reflux for 2.25 h, and then cooled to room temperature. The mixture was extracted four times with ether, and the combined ethereal solution was washed with 10% HCl and dried over anhydrous sodium sulfate overnight. After evaporation of the ether, the remaining liquid was distilled twice from an equal volume of concentrated sulfuric acid to give 66.0 g (93.3%) of **1**, bp 56–59 °C/5 mmHg. An analytically pure sample was prepared by an additional fractional distillation. ^{1}H NMR ($CDCl_3$): δ 3.9 (q, J_{FCCH} = 3.9 Hz, CHCl), δ 7.8 (s, COOH). ^{19}F NMR ($CDCl_3$, proton decoupled): δ −80.5 (s, CF_3), δ −81.5 and −81.9 (AB quartet, J_{FCF} = 142.1 Hz, nonequivalent CF_2). IR (neat): 1770 cm^{-1} (C=O). Anal. Calcd for $C_4H_2ClF_5O_3$: C, 21.02; H, 0.88; F, 41.57; Cl, 15.51. Found: C, 21.09; H, 0.91; F, 41.42; Cl, 15.45.

2-Propyl (1,1-Dichloro-2,2,2-trifluoroethoxy)difluoroacetate, 7. To 200 mL of absolute 2-propanol at room temperature was added 51.3 g (0.18 mol) of the dichloroacyl chloride **6**. The reaction mixture was maintained at reflux for 2 h and then cooled to room temperature. It was diluted with water. The organic layer was removed, and the aqueous layer was extracted with 3 × 100-mL portions of ether. The ether extracts were combined with the organic phase. The resulting solution was washed with water and dried over anhydrous calcium chloride overnight. Evaporation of ether followed by distillation of the remaining liquid afforded 44.5 g (80%) of the ester **7**, bp 57–58 °C/10 mmHg. ^{1}H NMR ($CDCl_3$): δ 1.4 (d, J_{HCCH} = 6.3 Hz, CH_3), δ 5.2 (septet, J_{HCCH} = 6.3 Hz, CH). ^{19}F NMR ($CDCl_3$): δ −79.3 (s, CF_2), δ −84.2 (s, CF_3). Anal. Calcd for $C_7H_7Cl_2F_5O_3$: C, 27.56; H, 2.31; F, 31.15; Cl, 23.25. Found C, 27.84; H, 2.33; F, 31.15; Cl, 23.19.

(±)-2-Propyl (1-Chloro-2,2,2-trifluoroethoxy)difluoroacetate, 8, by Reduction of the Dichloro Ester 7. A mixture of 14.1 g (46.0 mmol) of **7** and 41.0 g (0.69 mol) of 2-propanol was irradiated in a glass vessel with a 450-W (a higher wattage lamp may reduce the reduction time) medium-pressure mercury UV immersion lamp (Ace Glass) at 10-cm distance at room temperature for 3 h. During irradiation a low flow of nitrogen was passed through the reaction vessel to purge the HCl generated. The reaction mixture was poured into water, the organic layer was collected, and the aqueous layer was extracted with 3 × 50-mL portions of ether. The organic layers were combined, washed with water, and dried over anhydrous calcium chloride overnight. The ether was evaporated, and the residue was distilled at 53–55 °C/25 mmHg to yield 7.7 g (62%) of **8**. ^{1}H NMR ($CDCl_3$): δ 1.5 (d, J_{HCCH} = 6.3 Hz, CH_3), δ 5.2 (septet, J_{HCCH} = 6.3 Hz, CH), δ 6.2 (q, J_{FCCH} = 4.0 Hz, CHCl). ^{19}F NMR ($CDCl_3$): δ −80.5 (s, CF_2), δ −81.9 (q, J_{FCCH} = 4.0 Hz, CF_3). Anal. Calcd for $C_7H_8ClF_5O_3$: C, 31.01; H, 2.98; F, 35.10; Cl, 13.10. Found: C, 31.22; H, 2.93; F, 34.88; Cl, 13.31.

The Racemic Acid 1 by Hydrolysis of the Monochloro Ester 8. A mixture of 38.0 g (0.14 mol) of **8**, 300 mL of acetone, and 300 mL of a dilute HCl solution (concd HCl:water = 1:1) was heated at reflux for 3 h. The two-phase yellow green reaction mixture became homogeneous. The reaction mixture was cooled to ambient temperature, and 200 mL of water was added. The organic layer was removed, and the aqueous layer was extracted with 3 × 50-mL portions of ether. The organic layer was combined with the ether extracts, washed with water, and dried over anhydrous calcium chloride overnight. The ether was evaporated, and the residual liquid was distilled from concentrated sulfuric acid to afford 25.8 g (80%) of the racemic acid **1**.

The Racemic Acid 1 by a One-Pot Process from a Mixture

of the Monochloroacyl Chloride 5 and the Dichloroacyl Chloride 6. To 120.0 g (2.0 mol) of 2-propanol was added 49.0 g of the crude product comprising 47% of **5** and 51% of **6** from the chlorination of the acyl chloride **4** dropwise at room temperature. After the addition was completed the mixture was heated at reflux for 3 h. GC analysis of a sample from the mixture indicated the presence of 47% and 51% of the 2-propyl esters, **8** and **7**, respectively. The reaction mixture was cooled to ambient temperature and irradiated with a UV light as previously described in the preparation of **8** from the dichloro ester **7**. The mixture was then poured into a separatory funnel and washed five times each with 200-mL portions of water. The organic layers collected after each washing were combined to afford 46.9 g of the crude **8** which was mixed with 400 mL of acetone and 200 mL of dilute HCl solution (HCl:water = 1:1). The mixture was heated at reflux for 3 h. The resulting brown-red colored solution was cooled to room temperature and diluted with 300 mL of water. The organic layer was separated, and the aqueous layer was extracted with 3 × 100-mL portions of ether. The ether extracts were combined with the organic layer. This solution was washed with water and dried over anhydrous calcium chloride overnight. The ether was evaporated, and the remaining liquid was distilled from 50 mL of concentrated sulfuric acid to give 33.2 g (80% from the mixture of **5** and **6**) of **1**.

(−)-(1-Chloro-2,2,2-trifluoroethoxy)difluoroacetic Acid (*R*)-(+)-Dehydroabietylammonium Salt, 10. A solution of 375.0 g (1.3 mol) of purified (*R*)-(+)-dehydroabietylamine in 2.5 L of ethyl acetate was added to a solution of 300.0 g (1.3 mol) of the racemic acid **1** in 500 mL of ethyl acetate at room temperature. A mild exotherm was observed. The reaction mixture was stirred for another 2 h. The resulting solid was filtered and washed with 6 × 1-L portions of ethyl acetate. The white solid was recrystallized six times from 3-L portions of ethyl acetate to afford, after drying, 169.0 g (25.3% from the racemic acid **1**) of a snow white salt **10**, mp (sealed tube) 185–189.5 °C (brown liquid). Optical rotation: $[\alpha]^{25}_{D}$ = −14.0°, $[\alpha]^{25}_{365}$ = −38.0°, *c* = 1.0, MeOH. ^{19}F NMR (CD_3OD, proton decoupled): δ −79.9 (s, CF_2), δ −80.2 (s, CF_3). Anal. Calcd for $C_{24}H_{33}ClF_5NO_3$: C, 56.08; H, 6.47; F, 18.48; Cl, 6.90; N, 2.73. Found: C, 56.44; H, 6.30; F, 18.43; Cl, 7.04; N, 2.73.

(+)-(1-Chloro-2,2,2-trifluoroethoxy)difluoroacetic Acid (*R*)-(+)-Dehydroabietylammonium Salt, 9. The mother liquor from the filtrations of the negative diastereomeric salt **10** was combined with the six wash solutions. After evaporation of the solvent, the residue was recrystallized twice from chloroform. The solid has an optical rotation of $[\alpha]^{25}_{D}$ = +50° (*c* = 1, MeOH). The mother liquor from the first recrystallization of the negative salt was taken through the same process of solvent removal and solid recrystallizations from chloroform, until an optical rotation of $[\alpha]^{25}_{D}$ = +49° (*c* = 1, MeOH) was obtained. The two solids with positive rotations were combined and recrystallized three more times from chloroform. During this process all of the mother liquors were combined, stripped of solvent, and recrystallized to recover the positive salt. A white salt, 63.6 g (9.4% from the racemic acid **1**), was obtained after drying, mp (sealed tube) 161–168.5 °C. Optical rotation: $[\alpha]^{25}_{D}$ = +55.0°, $[\alpha]^{25}_{365}$ = +176.9°, *c* = 1.0, MeOH. ^{19}F NMR (CD_3OD, proton decoupled): δ −78.4 (s, CF_2), δ −78.8 (s, CF_3). Anal. Calcd for $C_{24}H_{33}ClF_5NO_3$: C, 56.08; H, 6.47; F, 18.48; Cl, 6.90; N, 2.73. Found: C, 56.03; H, 6.20; F, 18.31; Cl, 6.92; N, 2.68.

(−)-(1-Chloro-2,2,2-trifluoroethoxy)difluoroacetic Acid, 12. A mixture of 3225 g of 2% ammonium hydroxide solution and 70.0 g (0.14 mol) of the negative diastereomeric salt **10** ($[\alpha]^{25}_{D}$ = −14.0°, *c* = 1.0, MeOH) was heated at reflux for 6 h. The solid dissolved completely, and a heavy oil (dehydroabietylamine) collected at the bottom of the reaction flask. After the flask was cooled to room temperature, the aqueous solution was decanted and extracted with ether three times to remove the dissolved amine. The remaining aqueous phase was acidified with 200 mL of concentrated HCl. The acidic solution was extracted with ether four times. The ethereal solutions were combined and dried over anhydrous sodium sulfate overnight. The ether was evaporated, and the residue was distilled twice from concentrated sulfuric acid to yield 24.9 g (77.8%) of **12**, bp 56.5–60 °C/4 mmHg. Optical rotation: $[\alpha]^{25}_{D}$ = −70.2°, $[\alpha]^{25}_{365}$ = −215.6°, *c* = 1.0, $CHCl_3$. This corresponds to >99% ee. ^{1}H and ^{19}F NMR spectra ($CDCl_3$) were the same as those of the racemic acid **1**.

(+)-(1-Chloro-2,2,2-trifluoroethoxy)difluoroacetic Acid, 11. A mixture of 325.5 g (0.63 mol) of the positive diastereomeric salt **9** ($[\alpha]^{25}_{D}$ = +55.0°, *c* = 1.0, MeOH) and 7388 g of 3% ammonium hydroxide was heated at reflux for 6.5 h. Following the same workup procedure for the enantiomer **12**, 117.2 g (81.2%) of **11** was distilled at 44–46 °C/2.5 mmHg. Optical rotation: $[\alpha]^{25}_{D}$ = +70.8°, $[\alpha]^{25}_{365}$ = +220.4°, *c* = 1.0, $CHCl_3$. This corresponds to >99% ee. ^{1}H and ^{19}F NMR spectra ($CDCl_3$) were the same as the racemic acid **1**.

General Procedure for the Preparation of the Chiral Amides $CF_3CHClOCF_2CONHCH(CH_3)C_6H_5$. Following the procedure for the acyl chloride preparation, a mixture of 3.1 g (13.6 mmol) of the (−)-acid **12** (90% ee) and 2.9 g (20.0 mmol) of benzoyl chloride gave 0.9 g (26.8%) of (−)-(1-chloro-2,2,2-trifluoroethoxy)difluoroacetyl chloride, bp 89–92 °C. At room temperature, 0.81 g (3.3 mmol) of this (−)-acyl chloride, in 20 mL of toluene, was added to 0.80 g (6.6 mmol) of (*S*)-(−)-α-methylbenzylamine in 20 mL of toluene with good stirring. The reaction mixture was left at ambient temperature for 2 h. The solid α-methylbenzylammonium chloride salt formed was removed by filteration and discarded. The liquid filtrate was washed twice with water and dried over anhydrous sodium sulfate. After evaporation of the toluene, the yellowish solid was redissolved in toluene. The solution was washed with dilute HCl solution (HCl:water = 1:1) and dried over anhydrous sodium sulfate. The evaporation of toluene left 0.95 g (86.8%) of the chiral amide. ^{1}H NMR revealed the optical purity to be 90% ee.

(*R*)-(−)-1-Chloro-2,2,2-trifluoroethyl Difluoromethyl Ether (Isoflurane), 14. (a) By Decarboxylation of the (−)-Acid, 12. To 553.2 g (2.42 mol, >99% ee) of **12** was added 156.2 g (88%, 2.45 mol) of potassium hydroxide pellets dissolved in 655.6 g of water. The mixture was neutral to pH paper. Then 514.6 g of diethylene glycol (4.85 mol) was added, and the reaction mixture was heated to 210 °C (oil temperature) in a flask equipped with a distillation apparatus attached to two dry ice traps and a gas bubbler. Water distilled first. Then a mixture of water and an organic liquid codistilled at 70–110 °C while CO_2 gas was evolved. The water layer in the receiver was discarded, and the organic layer was combined with the liquids from the dry ice traps. This combined organic liquid was washed with dilute sodium bicarbonate solution and dried overnight over anhydrous calcium chloride and then combined with solid potassium carbonate at −16 °C overnight. After removal of the potassium carbonate by filtration, the liquid was distilled from 42 to 46 °C to afford 168.8 g (37.8%) of neutral **14**. The chemical purity of this material was >99.5% (GC), and the optical purity was >99% ee (chiral GC). Optical rotation: $[\alpha]^{25}_{D}$ = −107.2°, $[\alpha]^{25}_{365}$ = −328.9°, neat. ^{1}H NMR ($CDCl_3$): δ 6.0 (q, J_{FCCH} = 3.9 Hz, CHCl), δ 6.4 (t, J_{FCH} = 71.6 Hz, CF_2H). ^{19}F NMR ($CDCl_3$, proton decoupled): δ −80.6 (s, CF_3), δ −87.6 and −88.3 (AB quartet, J_{FCF} = 161.0 Hz, nonequivalent CF_2).

(b) By Decarboxylation of the Negative Diastereomeric Salt 10. A mixture of 51.4 g (0.10 mol) of the diastereomeric ammonium salt **10** ($[\alpha]^{25}_{D}$ = −14.0°, *c* = 1.0, MeOH), 106.1 g (1.00 mol) of diethylene glycol, 6.7 g (88%, 0.10 mol) of potassium hydroxide pellets, and 100.0 g (5.55 mol) of water was heated in a reaction flask equipped with a distillation head connected to a dry ice trap and a bubbler. Gas evolution (CO_2) started after water was distilled. The majority of the crude product was collected in the dry ice trap. It was slowly warmed to room temperature and was dried over anhydrous calcium chloride overnight. Distillation of the dried crude product gave 3.8 g (20.6%) of (*R*)-(−)-isoflurane **14** with a chemical purity of 98.5% (GC) and an optical purity of 99% ee (chiral GC).

(*S*)-(+)-1-Chloro-2,2,2-trifluoroethyl Difluoromethyl Ether (Isoflurane), 13. (a) Using the acid decarboxylation procedure previously described, a mixture of 117.2 g (0.51 mol, >99% ee) of the (+)-acid **11**, 33.6 g (88%, 0.53 mol) of potassium pellets, 92.4 g of water, and 109.5 g (1.0 mol) of diethylene glycol was heated to 230 °C (oil). The product was collected by distillation from 95 to 130 °C. After neutralization and purification, 37.7 g (40.0%) of **13**, >99.6% chemical purity (GC) and >99% ee optical purity (chiral GC), was obtained. Optical rotation: $[\alpha]^{25}_{D}$ =

+107.8°, $[\alpha]^{25}_{365}$ = +330.9°, neat. ^1H and ^{19}F NMR spectra were the same as those from (*R*)-(−)-isoflurane (14).

(b) By Decarboxylation of the Positive Diastereomeric Salt 9. In a similar manner, a mixture of 47.0 g (0.09 mol) of the positive diastereomeric salt, **9** ($[\alpha]^{25}_D$ = +55.0°, *c* = 1.0, MeOH), 6.1 g (88%, 0.09 mol) of potassium hydroxide pellets, 91.0 g (5.05 mol) of water, and 97.0 g (0.91 mol) of diethylene glycol gave 3.7 g (22.0%) of (*S*)-(+)-isoflurane (13) with a chemical purity of 99.0% (GC) and an optical purity of >99% ee (chiral GC).

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