Asymmetric Synthesis of the Volatile Anesthetic 1,2,2,2-Tetrafluoroethyl Chlorofluoromethyl Ether Using a Stereospecific Decarboxylation of Unusual Stereochemical Outcome†

Leonid A. Rozov,‡ Patrice W. Rafalko,[1,§] Suzanne M. Evans,‡ Linda Brockunier,‡ and Keith Ramig*,‡

Ohmeda Inc., Pharmaceutical Products Division, and BOC Group Technical Center, 100 Mountain Avenue, Murray Hill, New Jersey 07974

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Acid **1** is optically resolved by diastereomeric amide formation/chromatography/hydrolysis. Decarboxylation of the enantiomers of acid **1** gives the enantiomers of ether **2** with a very high degree of stereospecificity. The absolute configurations of both the starting acid and the ether product are determined to be (*R*)-(+) and (*S*)-(−). The data indicate that decarboxylation occurs with clean inversion of configuration. A mechanism is proposed to rationalize this unusual result. The enantiomers of ether **2** are converted to diastereomers of the volatile anesthetic **3** by a route consisting of trichlorination of the methyl group to give **9**, monofluorination to yield **10**, and monoreduction to afford the target anesthetic.

Four of the volatile anesthetics currently in clinical use, halothane,[2] enflurane,[3] isoflurane,[4] and desflurane,[5] contain a chiral carbon atom and are used in their racemic form. Recently, there has been interest in obtaining these compounds enantiomerically pure[6] because, in common with many other chiral pharmaceuticals, the optical antipodes in some cases differ in pharmacological profile from each other. For example, the enantiomers of isoflurane exhibit significant potency differences in mice;[7] cardiovascular differences in rats have also been noted.[8] The availability of individual enantiomers of volatile anesthetics may also make it possible to elucidate the molecular mechanism of anesthesia.[9]

The present study details the first asymmetric preparation of 1,2,2,2-tetrafluoroethyl chlorofluoromethyl ether (**3**),[10] a volatile anesthetic which contains two chiral carbon atoms and therefore is a mixture of four stereoisomers. Our task was not the preparation of each enantiomer separately, which may have been exceedingly laborious considering the high degree of difficulty associated with the asymmetric syntheses of the aforementioned small molecules containing only one chiral carbon atom. We were content with achieving the more modest goal of synthesizing diastereomeric pairs of ether **3**. It was anticipated that the diastereomeric pairs may have different pharmacological properties when compared to each other or to the racemates.

Results and Discussion

The key steps of our synthetic strategy are outlined in Scheme 1. The first challenge is resolution of 1-methoxytetrafluoropropionic acid (**1**), which is easily prepared[11] from commercially available hexafluoropropylene oxide. The individual enantiomers would then be decarboxylated to afford the enantiomers of 1,2,2,2-tetrafluoroethyl methyl ether (**2**).[12] The decarboxylation of acid (±)-**1** is known to give ether (±)-**2**,[13] but the stereochemical course of the reaction has until recently remained unclear.[14] We will demonstrate that the reaction proceeds with a very high degree of stereospecificity. Ether (±)-**2** has previously been converted to racemic ether **3** in low yield.[10] A route will be disclosed which not only gives a better yield, but also causes no racemization when applied to ethers (+)- and (−)-**2**.

Resolution of Acid 1. For the resolution of acid (±)-**1**, a diastereomeric amide formation/chromatographic separation/hydrolysis sequence proved effective (Scheme 2). Kawa et al. have resolved a closely related fluorinated acid by this route.[15]

Acid chloride (±)-**4**[16] is formed in good yield by treatment of acid (±)-**1** with phthaloyl dichloride. When acid chloride (±)-**4** is treated with (*S*)-(−)-1-phenethylamine, secondary amide (1*R*,*S*)-**5** is formed in high yield. The diastereomers of secondary amide (1*R*,*S*)-**5** are easily separated by medium-pressure liquid chromatography on a 100 g scale. After recrystallization, the diastereomeric excess (de) of secondary amide (1*R*)-**5** is >99.9% (HPLC

† This paper is dedicated with warmest regards to Dr. Yuri V. Zeifman on the occasion of his 60th birthday.

‡ Ohmeda, Inc.

§ BOC Group Technical Center.

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(1) Inquiries regarding the X-ray crystal structure should be directed to this author.

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(3) Terrell, R. C. US Patent 3 469 011, 1969.

(4) Terrell, R. C. US Patent 3 535 388, 1970.

(5) Terrell, R. C. US Patent 4 762 856, 1988.

(6) (a) Pearson, D. L. Ph.D. Dissertation, Cornell University, **1990**; *Diss. Abstr. Int. B* **1992**, *52*, 6400. (b) Schurig, V.; Grosenick, H. *J. Chromatogr. A* **1994**, *666*, 617. (c) Staerk, D. U.; Shitangkoon, A.; Vigh, G. *Ibid.* **1994**, *663*, 79. (d) Huang, C. G.; Rozov, L. A.; Halpern, D. F.; Vernice, G. G. *J. Org. Chem.* **1993**, *58*, 7382. (e) Rozov, L. A.; Huang, C. G.; Halpern, D. F.; Vernice, G. G. US Patent 5 283 372, 1994.

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(16) Muffler, H.; Siegemund, G.; Schwertfeger, W. *J. Fluorine Chem.* **1982**, *21*, 107.

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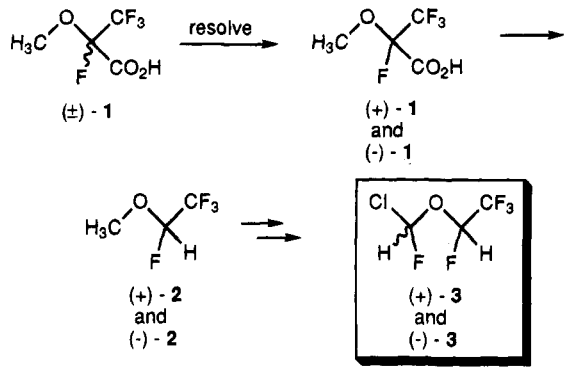
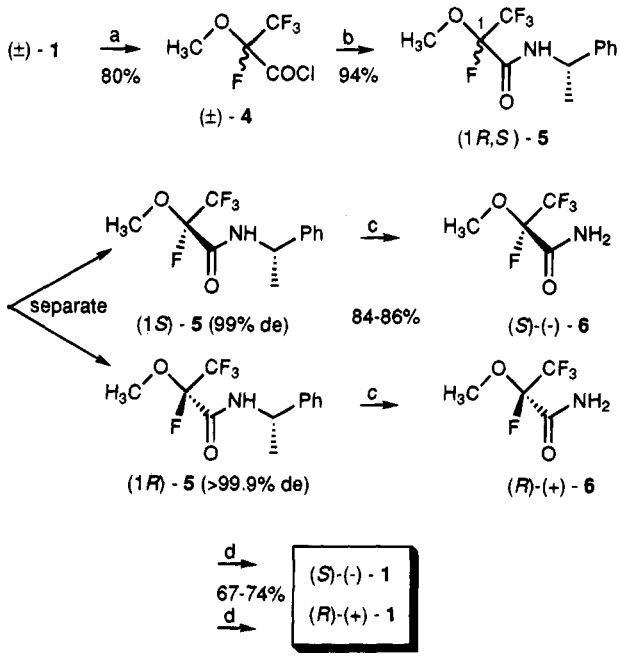
Scheme 1



Scheme 2



reagents: (a) phthaloyl dichloride; (b) (*S*)-(-)-1-phenethylamine; (c) H_2SO_4; (d) NaOH/H_2O

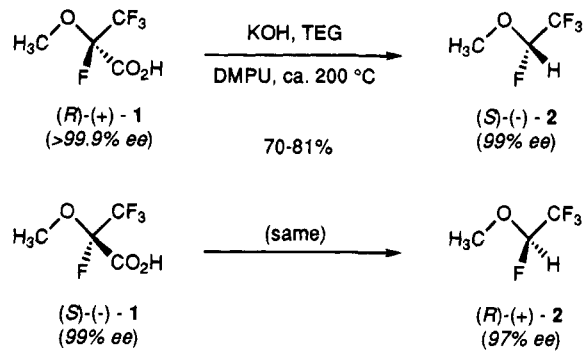
analysis), while the de of secondary amide (1*S*)-**5** is 99%. (See below for determination of absolute configuration.) Use of (−)-ephedrine in place of (*S*)-(−)-1-phenethylamine, or diastereomeric salt formation with (*S*)-(−)-1-phenethylamine, gives diastereomers which are not separable.

Secondary amides (1*R*)- and (1*S*)-**5** prove resistant to acidic and basic hydrolysis. Recourse is made to debenzylation with concentrated sulfuric acid,[15] which furnishes primary amides (*R*)-(+)- and (*S*)-(−)-**6**[17] in high yield. The resolution is completed by basic hydrolysis, yielding acids (*R*)-(+)- and (*S*)-(−)-**1**. Although the ee of each acid is not determined directly, it is reasonable to assume that no racemization occurs during the conversion of secondary amide **5**; thus, it is highly probable that the ee of acid (*R*)-(+)-**1** is >99.9%, while that of acid (*S*)-(−)-**1** is 99%.

Decarboxylation of Acid 1 To Give Ether 2. Decarboxylation of highly fluorinated carboxylic acids has been effected previously by thermolysis of their metal salts.[6d,18] Indeed, acid (±)-**1** has been converted to ether

(17) Racemate: Pasetti, A.; Tarli, F.; Sianesi, D. *Gazz. Chim. Ital.* **1968**, *98*, 277.

Scheme 3



(±)-**2** in 24% yield by this procedure.[13] We now demonstrate that acid **1** can be decarboxylated in high yield and give evidence of nearly exclusive inversion of configuration.

Treatment of acid (*R*)-(+)-**1** with potassium hydroxide in 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU)/triethylene glycol (TEG) followed by thermolysis at 180−210 °C gives ether (*S*)-(−)-**2** in 70−81% yield (Scheme 3); these same conditions when applied to acid (*S*)-(−)-**1** give ether (*R*)-(+)-**2**. (See below for assignment of absolute configuration to ether **2**.) The ee of the product is determined by chiral capillary GC using a cyclodextrin-derived stationary phase (see Experimental Section).

Significance of the Observed Inversion of Configuration. Examples of decarboxylations which proceed with a high degree of stereospecificity in acyclic systems are rare. Doyle and Vogl[19] have partially resolved and decarboxylated the strychnine salt of bromochlorofluoroacetic acid under conditions similar to those used for acid **1**. The bromochlorofluoromethane they produced maintained a high degree of optical activity, but it was not determined whether retention or inversion of configuration was the dominant pathway. Also, the inherent stereochemical preference of the acid remains to be demonstrated, because it is possible that the "strychnonium" cation of the salt is acting as a chiral proton source.

Cram[20] has studied decarboxylation of chiral carboxylic acids and has concluded that the degree and direction of stereospecificity depends primarily on the polarity of the solvent and the nature of the substituents on the α carbon atom. These same trends have been noted in such closely related reactions as cleavage of tertiary alcohols[21] and the Haller−Bauer cleavage of phenyl ketones.[22] Regarding the solvent-dependent stereospecificity, it was found in general that nonpolar solvents caused retention of configuration in the products, while use of polar solvents led to either partial inversion or complete racemization. While high levels of retention could be attained in these types of reactions, the highest level of inversion seen was ca. 70%.

In the present case, the very high level of inversion of configuration is probably due to a combination of inver-

(18) LaZerte, J. D.; Hals, L. J.; Reid, T. S.; Smith, G. H. *J. Am. Chem. Soc.* **1953**, *75*, 4525. Hudlicky, T.; Fan, R.; Reed, J. W.; Carver, D. R.; Hudlicky, M. *J. Fluorine Chem.* **1992**, *59*, 9.

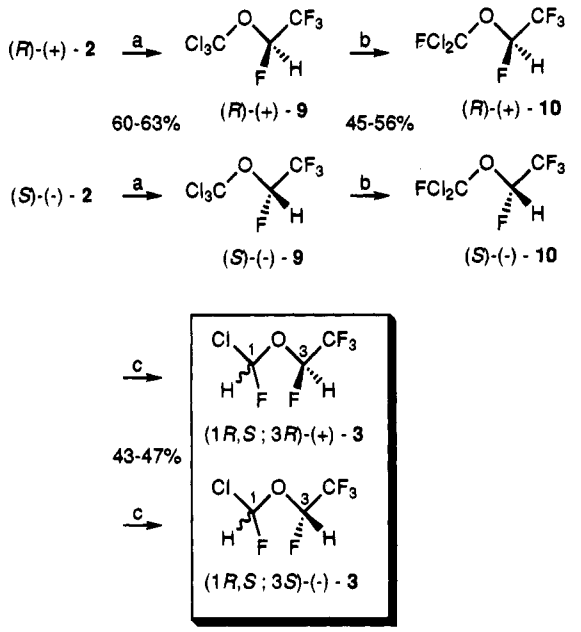
(19) Doyle, T. R.; Vogl, O. *J. Am. Chem. Soc.* **1989**, *111*, 8510.

(20) Cram, D. J.; Wingrove, A. S. *J. Am. Chem. Soc.* **1963**, *85*, 1100. Cram, D. J.; Haberfield, P. *J. Am. Chem. Soc.* **1961**, *83*, 2363. Cram, D. J.; Haberfield, P. *J. Am. Chem. Soc.* **1961**, *83*, 2354.

(21) Hoffmann, T. D.; Cram, D. J. *J. Am. Chem. Soc.* **1969**, *91*, 1009 and earlier papers in this series. D. J. Cram *Fundamentals of Carbanion Chemistry*; Academic Press: New York, 1965; Chapter 4.

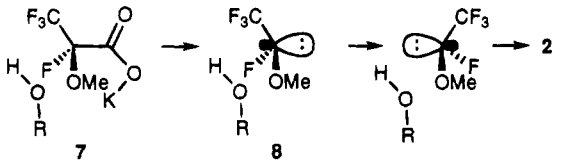
(22) Gilday, J. P.; Paquette, L. A. *Org. Prep. Proc. Int.* **1990**, *22*, 169 and references therein.

Scheme 4



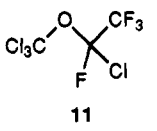
reagents: (a) Cl_2, hv; (b) SbF_3/Br_2; (c) 2-propanol, hv

sion-promoting polar solvents and substituent effects. One possibility involves positioning of the proton of triethylene glycol opposite the carboxyl leaving group, as in **7**. This could be due to complexation of the potassium ion with the oxygen atom of triethylene glycol and/or hydrogen bonding with the highly electronegative substituents. After decarboxylation, rapid inversion of the presumed intermediate **8** occurs, followed by proton capture to give ether **2**. The paucity of experimental data does not allow more definite conclusions to be made regarding the mechanism.



Conversion of Ether 2 to the Product Ether 3. The remaining part of the synthesis features new and improved conditions for the conversion of ethers (*R*)-(+)- and (*S*)-(−)-**2** to the target ethers (1*R*,*S*;3*R*)-(+)- and (1*R*,*S*;3*S*)-(−)-**3** (Scheme 4). We first used ether (±)-**2** as a model compound to test the new conditions. Treatment of this compound with chlorine while irradiating with incandescent light gives in 74% yield a 19:1 mixture of trichloromethyl ether (±)-**9** and tetrachloro ether **11**. The mixture is subjected to fluorination with antimony trifluoride/bromine,[23] giving dichlorofluoromethyl ether (±)-**10** in 51% yield. Also isolated in 21% yield is chlorodifluoromethyl ether (±)-**12**. Irradiation of dichlorofluoromethyl ether (±)-**10** with UV light in 2-propanol[24] affords racemic ether **3** in 49% yield.

Application of the above conditions to ethers (*R*)-(+)- and (*S*)-(−)-**2** gives the target ethers (1*R*,*S*;3*R*)-(+)- and (1*R*,*S*;3*S*)-(−)-**3**,[25] respectively, with little if any erosion of the ee. Ether (*R*)-(+)-**2** (97% ee) furnishes ether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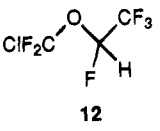

12

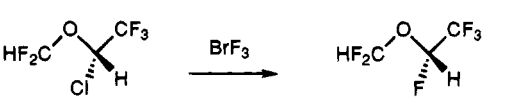
(1*R*,*S*;3*R*)-(+)-**3** (≥95% ee), while ether (*S*)-(−)-**2** (99% ee) furnishes (1*R*,*S*;3*S*)-(−)-**3** (≥95% ee). The ee of both target ethers **3** is determined by chiral capillary GC (see Figure 1) using the same conditions as those used for ether **2**. The ee of ethers **9**, **10**, and **12** is not determined because the enantiomers are not resolved by GC; apparently at least one proton is needed on the methoxy group of these ethers for resolution using this particular stationary phase. Enantiomer separation using the A, C, D, and E versions of the Lipodex series of cyclodextrin capillary GC columns (Machery–Nagel, Germany) is also unsuccessful for these substrates.

Stereochemical Proofs of Acid 1 and Ether 2. The absolute configurations of secondary amides (1*R*)- and (1*S*)-**5**, and thus of acids (*R*)-(+)- and (*S*)-(−)-**1**, are proven by an X-ray crystal structure of a derivative of secondary amide (1*R*)-**5**. Suitable crystals of secondary amide (1*R*)-**5** could not be grown, so the carbonyl group is reduced to methylene with borane[26] (Scheme 5). After hydrochloride salt formation, suitable crystals of salt (2*R*)-**13** are grown from acetone/water. The X-ray crystal structure[27] unequivocally proves that the absolute configuration of the fluorine-bearing carbon atom of salt (2*R*)-**13** and, by inference, the acids (+)- and (−)-**1** are as shown.

Proof of the absolute configurations of ethers (+)- and (−)-**2** comes from sodium/methanol reduction of the byproduct chloro ether (−)-**12**. Isolated is the anesthetic (−)-desflurane, the identity of which is established by chiral capillary GC. (See Experimental Section.) It has been previously established that the absolute configurations of desflurane are (*R*)-(+) and (*S*)-(−);[28] therefore,

(23) Ishihara, T.; Kuroboshi, M. *Chem. Lett.* **1987**, 1145.
(24) Paleta, O.; Dadak, V.; Dedek, V. *J. Fluorine Chem.* **1988**, *39*, 397.
(25) Also seen along the way were ethers **11** and **12**.

(26) Brown, H. C.; Heim, P. *J. Org. Chem.* **1973**, *38*, 912.
(27) For details of the X-ray crystal structure determination, see ref 14b.
(28) Polavarapu, P. L.; Cholli, A. L.; Vernice, G. G. *J. Pharm. Sci.* **1993**, *82*, 791. The method used by Polavarapu et al., comparison of theoretical and actual vibrational circular dichroism (VCD) spectra of the enantiomers, has in all instances provided the correct absolute configuration when the results are compared against X-ray crystal structure determinations. However, there have been several suspicious findings since the absolute configuration of desflurane was established by this VCD technique. First, it has been reported that, during a synthesis of optically enriched desflurane from optically enriched isoflurane, nucleophilic substitution of chloride by fluoride proceeded with an extremely high degree of *retention* of configuration,[30] which is unusual if one assumes an S_N2 or S_N1 type of mechanism to be operative. The evidence for the absolute configurations of both isoflurane[31] and desflurane was based on the same type of VCD technique. The behavior of the enantiomers of isoflurane vs those of desflurane on chiral GC stationary phases is also unusual. Using the results of the VCD studies, it has been reported that while (*R*)-(+)-desflurane elutes first on a capillary GC column using Chiraldex G-TA stationary phase,[29] (*S*)-(+)-isoflurane elutes first under identical conditions.[6d] We have since corroborated this trend using several members of the Lipodex series of stationary phases. It seems odd that such a subtle change in structure would cause a reversal of GC elution order. The above evidence, when viewed with the present unprecedented result of essentially complete *inversion* of configuration during a C–C bond cleavage in an acyclic system, warrants independent proofs of the absolute configurations of both isoflurane and desflurane. We are currently working toward this end.



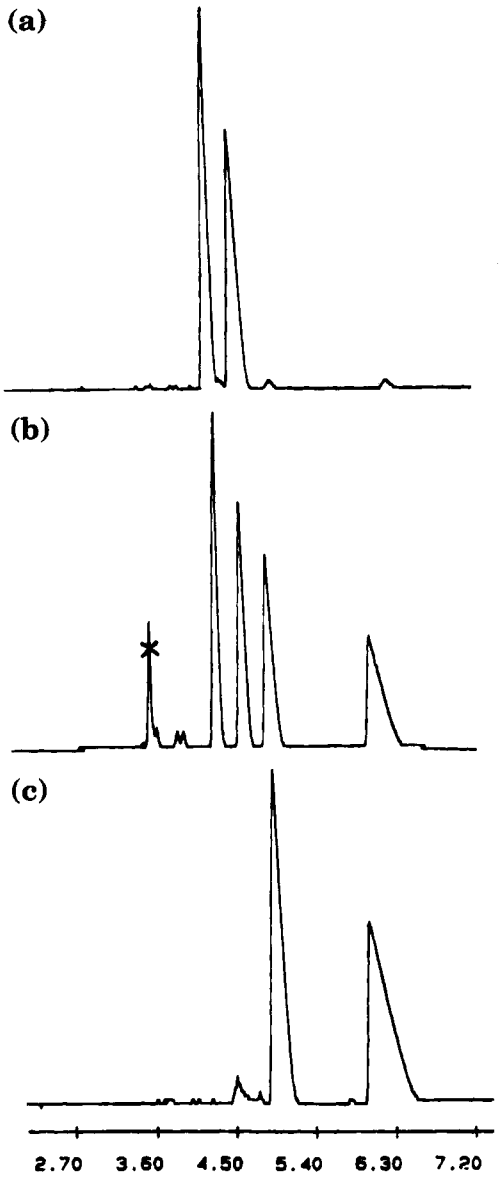


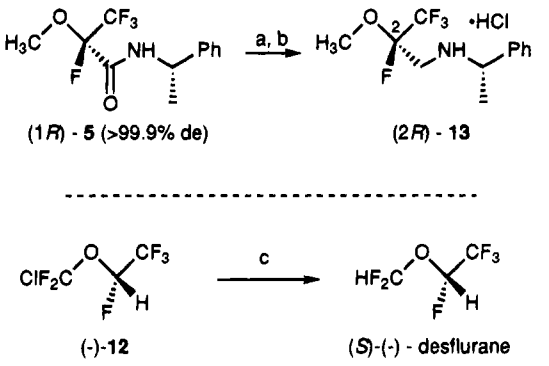
Figure 1. (a) Chiral GC trace of (1*R*,*S*;3*R*)-(+)-**3** (≥95% ee); (b) chiral GC trace of *rac*-**3** (peak marked with "X" is an unknown impurity); (c) chiral GC trace of (1*R*,*S*;3*S*)-(−)-**3** (≥95% ee).

by inference, the absolute configurations of ether **2**, as well as ethers **9**, **10**, **12**, and **3** (C-3), are the same.

Conclusion

We have synthesized diastereomeric pairs of the volatile anesthetic 1,2,2,2-tetrafluoroethyl chlorofluoromethyl ether, (1*R*,*S*;3*R*)-(+)-**3** and (1*R*,*S*;3*S*)-(−)-**3**, by controlling the stereochemistry at one of the chiral carbon atoms. Noteworthy in the synthesis is the stereospecific decarboxylation of acid **1**, which proceeds with nearly complete inversion of configuration. This is the only case of which we are aware in which carbon−carbon bond cleavage in an acyclic system results in a synthetically useful level of inversion of configuration. Although stereospecific C-C bond creation is in general a more useful process, in specific cases where stereospecific defunctionalization of a molecule is needed, this type of reaction could become useful.

Scheme 5



reagents: (a) BH_3/THF; (b) HCl; (c) Na, MeOH, NH_4Cl

Experimental Section

General. All reagents were used without further purification. Elemental analyses were performed either by Robertson Laboratories, Madison, NJ, or by Schwartzkopf Laboratories, Woodside, NY. Melting points were recorded on a Thomas Hoover capillary melting point apparatus without correction. Optical rotations were obtained on a Perkin Elmer 241 polarimeter.

High resolution NMR spectra were obtained on a Bruker AC-300 Fourier transform spectrometer. ^1H (300 MHz) NMR chemical shifts were recorded relative to tetramethylsilane. ^{19}F (282 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. All spectra were taken in $CDCl_3$ unless otherwise noted. Infrared spectra were obtained on a Bio-Rad FTS-60 FT-IR spectrometer. Mass spectra were taken on HP-5995B GC/MS instrument with direct ionization probe with electron impact ionization.

Gas chromatograms were obtained using the following equipment and conditions: For chemical purity (i.e. area %) of volatile samples, an HP 5790A gas chromatograph with a thermal conductivity detector at 250 °C; 130 °C injection temp, 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 90−150 °C was used. For optical purity: HP-5880 gas chromatograph, with a 40 m Chiraldex G-TA capillary column (Advanced Separation Technologies (ASTEC), Whippany, NJ) at 35 °C, a flame-ionization detector at 250 °C, an injection temperature of 150 °C, and the split ratio set at 100:1. The helium flow rate was set at 1 mL/min. Preparative GC was performed on a Varex PSGC-10−40 instrument with a thermal conductivity detector at 125 °C, injector temperature 150 °C, and a helium flow rate of 85 mL/min through a 1 cm × 2 m stainless steel column packed with 10% SP-1000 on Carbopack B.

Medium pressure liquid chromatography was performed using a Biotage Kiloprep 100 pump. Loading: 100 g/4 kg of 230−400 mesh silica gel; flow rate: 250 mL/min; eluent: 10−50% ethyl acetate/hexane. Analytical HPLC analysis was performed on a Waters Model 840 instrument: Column: Alltech Lichrosorb SI 50 51, 250 × 4.6 mm; UV detector at 254 nm; flow rate: 1.0 mL/min; mobile phase: 15:85 ethyl acetate/hexane.

1-Methoxytetrafluoropropionyl Chloride ((±)-4). Phthaloyl dichloride (372.0 g, 1.83 mol) and 278.0 g (1.58 mol) of the acid (±)-**1** were mixed in a 1 L 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 ca. 200 °C. The liquid that distilled from 75 to 80 °C was collected. Fractional distillation of this liquid gave 245.4 g (80%) of the acid chloride (±)-**4**, bp 78−80 °C (lit.[16] bp 79−80 °C): ^1H NMR: δ 3.66 (s, CH_3). ^{19}F NMR: δ −80.1 (d, J = 3.0 Hz, 3F, CF_3), −129.0 (q, J = 3.0 Hz, 1F, CF).

(*R,S*)-1-Methoxy-1,2,2,2-tetrafluoropropionic Acid (*S*)-(−)-1-Phenethylamide ((1*R,S*)-5). To a stirred solution of 22.6 g (0.187 mol) of (*S*)-(−)-1-phenethylamine and 15.0 g (0.19 mol) of pyridine in 250 mL of absolute ether was added dropwise a solution of 36.3 g (0.187 mol) of acid chloride (±)-**4** in 25 mL of ether. A solid started to form and the temperature of the reaction mixture reached 36 °C. After the addition was finished, the reaction mixture was maintained at reflux for 4 h and then cooled to room temperature. An equal volume of water (ca. 300 mL) was added, the ether layer was collected, and the aqueous layer was extracted with 3 × 100 mL portions of ether. The organic layers were combined, washed with 10% hydrochloric acid and water, and dried over anhydrous calcium chloride overnight. After evaporation of the ether the crude product solidified. Isolated was 49.2 g (94%) of a crude diastereomeric mixture (1*R,S*)-**5**. ^{1}H NMR: δ 1.57 (d, J = 6.9 Hz, 3H, CH_3CH), 1.58 (d, J = 6.9 Hz, 3H, CH_3CH), 3.52 (d, J = 1.2 Hz, 3H, OCH_3), 3.61 (d, J = 1.2 Hz, 3H, OCH_3) 5.17−5.22 (m, 2H, CHCH$_3$), 6.72 (br s, 2H, NH), 7.25−7.39 (m, 10H, Ph). ^{19}F NMR: δ −81.7 (d, J = 3.5 Hz, 3F, CF_3CF), −81.8 (d, J = 3.5 Hz, 3F, CF_3CF), −136.3 (q, J = 3.5 Hz, 1F, CF$_3$CF), −136.6 (q, J = 3.5 Hz, 1F, CF$_3$CF).

(*R*)-(+)-1-Methoxy-1,2,2,2-tetrafluoropropionic Acid (*S*)-(−)-1-Phenethylamide ((1*R*)-5) and (*S*)-(−)-1-Methoxy-1,2,2,2-tetrafluoropropionic Acid (*S*)-(−)-1-Phenethylamide ((1*S*)-5). Diastereomers (1*R*)-**5** and (1*S*)-**5** were separated preparatively by medium-pressure liquid chromatography on 230−400 mesh silica gel eluting with 10−50% ethyl acetate/hexane. The diastereomers were given a final recrystallyzation from 9% ethyl acetate/hexane. The de of secondary amide (1*R*)-**5** was >99.9% by HPLC analysis, while the de of secondary amide (1*S*)-**5** was 99%. (1*R*)-**5**: R_f in 20% ethyl acetate/hexane = 0.41; mp 63−64 °C; $[\alpha]^{25}_D$ = −83° (c = 1, CHCl$_3$). ^{1}H NMR: δ 1.57 (d, J = 6.9 Hz, 3H, CH_3CH), 3.52 (d, J = 1.2 Hz, CH$_3$OCF), 5.20 (qd, J = 6.9, 6.9 Hz, 1H, HNCHCH$_3$), 6.78 (br s, 1H, NH), 7.29 - 7.40 (m, 5H, Ph). ^{19}F NMR (proton decoupled): δ −81.8 (d, J = 3.5 Hz, 3F, CF_3CF), −136.3 (q, J = 3.5 Hz, 1F, CF$_3$CF); IR (KBr) (cm^{-1}): 3312 (NH), 1681 (C=O); MS (*m/e*, (relative intensity)): 279 (M$^+$) (25), 264 (5), 244 (5), 216 (13), 105 (100). Anal. Calcd for $C_{12}H_{13}F_4NO_2$: C, 51.62; H, 4.69; N, 5.02; F 27.21. Found: C, 51.70; H, 4.62; N, 4.97; F 27.14%. (1*S*)-**5**: R_f in 20% ethyl acetate/hexane = 0.29; mp 71−2 °C; $[\alpha]^{25}_D$ = −112° (c = 1, CHCl$_3$). ^{1}H NMR: δ 1.58 (d, J 6.9 Hz, 3H, CH_3CH), 3.61 (d, J = 1.2 Hz, CH$_3$OCF), 5.20 (qd , J = 6.9, 6.9 Hz, 1H, HNCHCH$_3$), 6.78 (br s, 1H, NH), 7.29−7.40 (m, 5H, Ph). ^{19}F NMR (proton decoupled): δ −81.7 (d, J = 3.5 Hz, 3F, CF_3CF), −136.6 (q, J = 3.5 Hz, 1F, CF$_3$CF). IR (KBr) (cm^{-1}): 3346 (NH), 1681 (C=O). MS (*m/e*, (relative intensity)): 279 (M$^+$) (25), 264 (5), 244 (5), 216 (13), 105 (100). Anal. Calcd for $C_{12}H_{13}F_4NO_2$: C, 51.62; H, 4.69; N, 5.02; F 27.21. Found: C, 51.60; H 4.68; N, 4.96; F 26.89%.

(*R*)-(+)-1-Methoxy-1,2,2,2-tetrafluoropropionamide ((*R*)-(+)-6). Concentrated H_2SO_4 (337 mL) was added dropwise with stirring to 150.0 g (0.537 mol) of secondary amide (1*R*)-**5**. The resulting dark brown slurry was stirred for 1 h. The reaction mixture was poured with vigorous stirring into 2.5 L of ice−water and extracted with 5 × 500 mL portions of ether. The ether extracts were combined, washed with water, and dried over anhydrous calcium chloride overnight. After evaporation of ether, the remaining solid was recrystallized from methylene chloride. Two crops of the title compound with a total weight of 78.1 g (84%) were collected and combined, mp 114 °C (lit.[17] for racemate, mp 109 °C (from benzene)), $[\alpha]^{25}_D$ = +33° (c = 1, MeOH). ^{1}H NMR (DMSO-d_6): δ 3.63 (d, J = 1.2 Hz, 3H, OCH_3), 8.35 (br s, 1H, NH$_2$), 8.45 (br s, 1H, NH$_2$). ^{19}F NMR (DMSO-d_6, proton decoupled): δ −81.9 (d, J = 3.2 Hz, 3F, CF_3CF), −135.6 (q, J = 3.2 Hz, 1F, CF$_3$CF).

(*S*)-(−)-1-Methoxy-1,2,2,2-tetrafluoropropionamide ((*S*)-(−)-6). Using the procedure previously described, from 50.0 g (0.18 mol) of secondary amide (1*S*)-**5** and 120 mL of concentrated H_2SO_4 were obtained four crops of the title compound with a total weight of 26.9 g (86%), mp 114 °C, $[\alpha]^{25}_D$ = -30° (c = 1, MeOH). ^{1}H and ^{19}F NMR spectra were the same as those of primary amide (*R*)-(+)-**6**.

(*R*)-(+)-1-Methoxytetrafluoropropionic Acid ((*R*)-(+)-1). A mixture of 59.4 g (0.34 mol) of primary amide (*R*)-(+)-**6** and 600 mL of 5 M sodium hydroxide solution was heated at reflux for 2 h. After the flask was cooled to room temperature, the reaction mixture was acidified with 600 mL of 1:1 solution of concd hydrochloric acid/water. The acidic solution was extracted with 3 × 200 mL portions of ether. The ethereal solutions were combined and dried over anhydrous magnesium sulfate overnight. The ether was evaporated, and distillation of the residue afforded 40.2 g (67%) of acid (*R*)-(+)-**1**, bp 60−61 °C/8 mmHg (lit.,[11] for racemate, bp 67−68 °C/12 mmHg), $[\alpha]^{25}_D$ = +24° (neat). NMR ^{1}H: δ 3.65 (s, 3H, CH$_3$), 10.8 (s, 1H, OH). ^{19}F NMR (proton decoupled): δ −81.6 (d, J = 3.3 Hz, 3F, CF_3CF), −136.0 (q, J = 3.3 Hz, 1F, CF$_3$CF).

(*S*)-(−)-1-Methoxytetrafluoropropionic Acid ((*S*)-(−)-1). Using the amide hydrolysis procedure previously described, from 10.4 g (0.06 mol) of primary amide (*S*)-(−)-**6** and 100 mL of 5 M NaOH was obtained 7.9 g (74%) of acid (*S*)-(−)-**1**, bp 60−61 °C/8 mmHg, $[\alpha]^{25}_D$ = −22° (neat). ^{1}H and ^{19}F NMR spectra were the same as those of acid (*R*)-(+)-**1**.

(*S*)-(−)-1,2,2,2-Tetrafluoroethyl Methyl Ether ((*S*)-(−)-2). A mixture of 19.2 g (0.11 mol) of acid (*R*)-(+)-**1**, 16 mL of TEG, 55 mL of DMPU, and 7.0 g (88%, 0.11 mol) of potassium hydroxide pellets was heated in a 250 mL reaction flask equipped with a distillation head attached to an oil bubbler. After the water produced in the reaction was distilled off and discarded, two dry ice traps were put between the distillation set up and the bubbler. The evolution of CO_2 started at 155 °C; at 180−190 °C the product started to condense in the distillation receiver and the dry ice traps. The reaction mixture was held at 200 °C for 1 h and at 210 °C for 1 h. The product which collected in the cold traps was warmed to room temperature under a dry ice condenser until the evolution of low boiling materials stopped and then was combined with the product which collected in the distillation receiver. Washing with cold water and drying over calcium chloride gave 10.1 g (70%) of ether (*S*)-(−)-**2**, bp 38−39 °C (lit.,[12] for racemate, bp 36−38 °C). The chemical purity of this material was >98% (GC), and the optical purity was 99% ee (chiral GC, retention time 5.6 min), $[\alpha]^{25}_D$ = −68° (neat). ^{1}H NMR: δ 3.68 (d, J = 1.5 Hz, 3H, CH$_3$OCF), 5.27 (dq, J = 62.3, 3.0 Hz, 1H, CF$_3$CHF). ^{19}F NMR (proton decoupled): δ −84.4 (d, J = 6 Hz, 3F, CF_3CF), −146.3 (q, J = 6 Hz, 1F, CF$_3$CF).

(*R*)-(+)-1,2,2,2-Tetrafluoroethyl Methyl Ether ((*R*)-(+)-2). Using the acid decarboxylation procedure previously described, from 44.5 g (0.248 mol) of acid (*S*)-(−)-**1**, 16.0 g (88%, 0.250 mol) of KOH, 35.5 mL of TEG and 122 mL of DMPU was obtained 26.6 g (81%) of ether (*R*)-(+)-**2**, bp 38−39 °C. The chemical purity of this material was >99% (GC) and optical purity was 97% ee (chiral GC, retention time 4.0 min), $[\alpha]^{25}_D$ = +67° (neat). ^{1}H and ^{19}F NMR spectra were the same as those of ether (*S*)-(−)-**2**.

(*R,S*)-1,2,2,2-Tetrafluoroethyl Trichloromethyl Ether ((±)-9) and (*R,S*)-1-Chloro-1,2,2,2-tetrafluoroethyl Trichloromethyl Ether ((±)-11). The chlorination was carried out in a 500 mL three neck round bottom flask equipped with a magnetic stirring bar, a thermometer, a gas dispersion tube, and a 1 meter long reflux condenser kept at −10 °C. This condenser was connected to an empty flask followed by a series of two water scrubbers. The reactor was charged with 355.0 g (2.7 mol) of ether (±)-**2**. Chlorine gas was slowly bubbled into ether (±)-**2** while the reaction mixture was being irradiated with a 250 W incandescent light. Toward the end of the reaction, the temperature of the mixture reached 75 °C. At 3 h intervals, the composition of the reaction mixture was analyzed by ^{19}F NMR. After 30 h the chlorination was terminated, and the crude product was washed with water and dried over anhydrous calcium chloride overnight. Distillation produced 490.0 g of a fraction bp 44−47 °C/145 mmHg containing 95% of trichloro ether (±)-**9** (lit.[13] bp 96−97 °C), and 5% of tetrachloroether (±)-**11**. Yield of (±)-**9**: 74% (^{19}F NMR). ^{1}H NMR: δ 6.0 (dq, J = 54.3, 2.8 Hz). ^{19}F NMR (proton decoupled): δ −83.3 (d, J = 6.1 Hz, 3F, CF_3CF), −148.1 (q, J = 6.1 Hz, 1F, CF$_3$CF). Tetrachloro ether (±)-**11**: ^{19}F NMR: δ −82.6 (q, J = 3.0 Hz, 1F, CF$_3$CF), −85.9 (d, J = 3.0 Hz, 3F, CF_3CF). MS (from GC-MS analysis) (*m/e* (relative intensity)): 233, 235, 237, 239 (10) (M$^+$ − Cl), 135, 137, (100)

(CF_3CFCl); 117, 119, 121, 123 (30) (CCl_3), 85, 87, 63, 65 (60) (COCl).

(*S*)-(−)-1,2,2,2-Tetrafluoroethyl Trichloromethyl Ether ((*S*)-(−)-9). Using the chlorination procedure described previously for ether (±)-**2**, the chlorination of 105.3 g (0.8 mol) of ether (*S*)-(−)-**2** (99% ee, 98% pure) afforded 125.4 g of a mixture, containing (by ^{19}F NMR) 90% of ether (*S*)-(−)-**9** (yield 60%, $[\alpha]^{25}_D = -37°$ ($c = 1$, $CHCl_3$)) and 10% of tetrachloro ether **11** (absolute configuration unknown). ^1H NMR and ^{19}F NMR spectra for ether (*S*)-(−)-**9** were the same as those of ether (±)-**9**.

(*R*)-(+)-1,2,2,2-Tetrafluoroethyl Trichloromethyl Ether ((*R*)-(+)-9). Using the chlorination procedure described previously for ether (±)-**2**, the chlorination of 105.7 g (0.8 mol, 97% ee, 99% pure) of ether (*R*)-(+)-**2** afforded 132.0 g of a mixture containing (by ^{19}F NMR) 90% of ether (*R*)-(+)-**9** (yield 63%, $[\alpha]^{25}_D = +36°$ ($c = 1$, $CHCl_3$)) and 10% of tetrachloro ether **11**. ^1H NMR and ^{19}F NMR spectra for ether (*R*)-(+)-**9** were the same as those of ether (±)-**9**.

(*R,S*)-1,2,2,2-Tetrafluoroethyl Dichlorofluoromethyl Ether ((±)-10) and (*R,S*)-1,2,2,2-Tetrafluoroethyl Chlorodifluoromethyl Ether ((±)-12). The fluorination was carried out in a 250 mL three neck round bottom flask equipped with a magnetic stirring bar, a thermometer, an addition funnel, and a distillation assembly having a 10 cm Vigreux column, a receiver connected to a trap, and a gas bubbler. Both receiver and trap were cooled with ice−water. The reactor was charged with 60.0 g (0.254 mol) of trichloro ether (±)-**9** containing 5% of tetrachloro ether **11**, and 30.4 g (0.17 mol) of antimony trifluoride. This mixture was gradually heated to 55 °C with rapid stirring, and bromine 27.2 g (0.17 mol) was added dropwise. After the first 2 mL of bromine was added, a vigorous reaction started. The temperature of the distilling head did not exceed 60 °C. The product mixed with bromine was collected in the chilled receiver. The heating was stopped when the temperature of the distilling head dropped to 25 °C. The contents of the receiver was transfered to a 250 mL flask equipped with a stir bar, a reflux condenser, and an addition funnel. It was treated dropwise at 0−5 °C with cold 10% solution of sodium hydroxide until the red color disappeared. The lower organic layer was washed with water and dried over anhydrous calcium chloride overnight. Distillation, using a 50 cm column packed with 3 mm glass beads and equipped with a Dewar-type distilling head, afforded two fractions: Monochloro ether (±)-**12**: 11.2 g (21%), bp 22−24 °C. ^1H NMR: δ 5.96 (dq, $J = 53.0$, 2.8 Hz). ^{19}F NMR (proton decoupled): δ −29.5 (dd, $J = 5.5$, 9.9 Hz, 1F), −30.6 (dd, $J = 4.1$, 9.9 Hz, 1F), −84.0 (d, $J = 5.5$ Hz, 3F), −147.4 (qdd, $J = 5.5$, 5.5, 4.1 Hz, 1F). Anal. Calcd for C_3HClF_6O: C, 17.79; H, 0.49; Cl, 17.51; F, 56.30. Found: C, 17.88; H, 0.47; Cl 17.20; F, 56.19%. Dichloro ether (±)-**10**: 28.3 g (51%), bp 55−58 °C. ^1H NMR: δ 6.0 (dq, $J = 53.0$, 2.9 Hz). ^{19}F NMR (proton decoupled): δ −13.3 (d, $J = 5.9$ Hz, 1F), −84.0 (d, $J = 5.9$ Hz, 3F), −147.8 (dq, $J = 5.9$, 5.9 Hz, 1F). Anal. Calcd for $C_3HCl_2F_5O$: C, 16.46; H, 0.46; Cl, 32.37; F, 43.39. Found: C, 16.64; H, 0.43; Cl, 32.08; F, 43.09%.

(*S*)-(−)-1,2,2,2-Tetrafluoroethyl Dichlorofluoromethyl Ether ((*S*)-(−)-10) and (*S*)-(−)-1,2,2,2-Tetrafluoroethyl Chlorodifluoromethyl Ether ((*S*)-(−)-12). Using the fluorination procedure previously described, from 122.6 g (0.52 mol) of trichloro ether (*S*)-(−)-**9** containing 10% of ether **11**, 62.3 g (0.35 mol) of antimony trifluoride and 55.4 g (0.35 mol) of bromine was obtained 11.2 g (11%) of monochloro ether (*S*)-(−)-**12**, bp 22−24 °C, $[\alpha]^{25}_D = -33°$ ($c = 1$, $CHCl_3$), and 51.6 g (45%) of dichloro ether (*S*)-(−)-**10**, bp 55−58 °C, $[\alpha]^{25}_D = -38°$ ($c = 1$, $CHCl_3$). ^1H and ^{19}F NMR spectra of ethers (*S*)-(−)-**12** and (*S*)-(−)-**10** were the same as those of the racemic compounds **12** and **10**, respectively.

(*R*)-(+)-1,2,2,2-Tetrafluoroethyl Dichlorofluoromethyl Ether ((*R*)-(+)-10) and (*R*)-(+)-1,2,2,2-Tetrafluoroethyl Chlorodifluoromethyl Ether ((*R*)-(+)-12). Using the fluorination procedure previously described, from 130.0 g (0.55 mol) of trichloro ether (*R*)-(+)-**9** containing 10% of tetrachloro ether **11**, 66.0 g (0.37 mol) of antimony trifluoride, and 59.2 g (0.37 mol) of bromine was obtained 16.2 g (14%) of monochloroether (*R*)-(+)-**12**, bp 22−24 °C, $[\alpha]^{25}_D = +34°$ ($c = 1$, $CHCl_3$), and 67.9 g (56%) of dichloro ether (*R*)-(+)-**10**, bp 57−58 °C, $[\alpha]^{25}_D = +39°$ ($c = 1$, $CHCl_3$). ^1H and ^{19}F NMR spectra of ethers (*R*)-(+)-**10** and (*R*)-(+)-**12** were the same as those for the racemic compounds **10** and **12**, respectively.

***rac*-1,2,2,2,-Tetrafluoroethyl Chlorofluoromethyl Ether (*rac*-3).** A mixture of 30.8 g (0.14 mol) of dichloro ether (±)-**10** and 150 mL of 2-propanol was irradiated in a quartz flask with a 450 W medium pressure mercury UV immersion lamp at 10 cm distance at room temperature for 6 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 lower organic layer was washed several times with water to remove the traces of 2-propanol and acetone and dried over anhydrous calcium chloride overnight. Distillation afforded 14.0 g of 92% pure *rac*-**3**, bp 50−51 °C, (lit.[10] bp 51 °C), yield (GC) 49%. An analytically pure sample was prepared by prep GC. Analytical GC analysis showed the presence of two peaks with equal areas, each peak corresponding to two diastereomers of *rac*-**3**. Chiral GC analysis showed the presence of four peaks with equal areas corresponding to four enantiomers (Figure 1b; retention times 4.4, 4.7, 5.0, 6.2 min) of *rac*-**3**. ^1H NMR: δ 5.95 (dq, $J = 21.0$, 2.9 Hz, 1H), 6.14 (dq, $J = 21.0$, 2.9 Hz, 1H), 7.00 (d, $J = 19$ Hz, 1H), 7.19 (d, $J = 19$ Hz). ^{19}F NMR (proton decoupled): δ −79.4 (d, $J = 10$ Hz, 1F), −80.3 (dq, $J = 6.1$, 2.0 Hz, 1F), −84.0 (d, $J = 6.0$ Hz, 3F) −84.1 (dd, $J = 6.2$, 2.0 Hz, 3F), −147.2 (dq, $J = 10.0$, 6.0 Hz, 1F), −147.8 (dq, $J = 6.1$, 6.2 Hz, 1F). ^{19}F NMR (proton coupled): δ −79.4 (dd, $J = 57.0$, 10 Hz, 1F), −80.3 (ddq, $J = 57.0$, 6.1, 2.0 Hz, 1F), −84.0 (dd, $J = 6.0$, 3.0 Hz, 3F), −84.1 (ddd, $J = 6.2$, 2.8, 2.0 Hz, 3F), −147.2 (ddq, $J = 55.0$, 10.0, 6.0 Hz, 1F), −147.8 (ddq, $J = 54.0$, 6.1, 6.2 Hz, 1F). Anal. Calcd for $C_3H_2ClF_5O$: C, 19.52; H, 1.09; Cl, 19.21; F, 51.49. Found: C, 19.55; H, 1.14; Cl, 19.49; F, 52.16%.

(*S*)-(−)-1,2,2,2-Tetrafluoroethyl (*R,S*)-Chlorofluoromethyl Ether ((1*R,S*;3*S*)-(−)-3). Using the reduction procedure previously described, from 51.0 g (0.23 mol) of dichloro ether (*S*)-(−)-**10** and 220 mL of 2-propanol after 4 h of irradiation was obtained 20.3 g (47%) of monochloro ether (1*R,S*;3*S*)-(−)-**3**, bp 49−50 °C. In this case, preparative GC was not needed to purify the product. Chiral GC showed the presence of two peaks (Figure 1c; retention times 5.0 and 6.2 min) with equal areas; optical purity (by GC) ≥95% ee, $[\alpha]^{25}_D = -49°$ (neat). ^1H NMR and ^{19}F NMR spectra of the product ether were the same as those for ether *rac*-**3**. Anal. Calcd for $C_3H_2ClF_5O$: C, 19.52; H, 1.09; Cl, 19.21; F, 51.49. Found: C,-19.71; H, 1.17; Cl, 18.99; F, 51.36%.

(*R*)-(+)-1,2,2,2-Tetrafluoroethyl (*R,S*)-Chlorofluoromethyl Ether ((1*R,S*;3*R*)-(+)-3). Using the reduction procedure previously described, from 59.0 g (0.27 mol) of dichloro ether (*R*)-(+)-**10** and 250 mL of 2-propanol after 4 h of irradiation was obtained 21.2 g (43%) of ether (1*R,S*;3*R*)-(+)-**3**, bp 49−50 °C. In this case, preparative GC was not needed to purify the product. Chiral GC showed the presence of two peaks (Figure 1a; retention times 4.4 and 4.7 min) with equal area; optical purity (by GC) ≥95% ee, $[\alpha]^{25}_D = +47°$ (neat). ^1H NMR and ^{19}F NMR spectra of ether (1*R,S*;3*R*)-(+)-**3** were the same as those for the ether *rac*-**3**. Anal. Calcd for $C_3H_2ClF_5O$: C, 19.52; H, 1.09; Cl, 19.21; F, 51.49. Found: C, 19.65; H, 1.03; Cl, 18.95; F, 51.32%.

***N*-(*S*)-1-Phenethyl-(*R*)-2,3,3,3-tetrafluoro-2-methoxypropylamine ((2*R*)-13).** A solution of secondary amide (1*R*)-**5** (1.01 g, 3.62 mmol) in 3.0 mL tetrahydrofuran was added to borane/tetrahydrofuran (8.0 mL, 1.0 M in tetrahydrofuran, 8.0 mmol) at room temperature under argon. The solution was heated at reflux for 19.5 h. After cooling to room temperature, 1 mL of a 1:1 v:v mixture of concd hydrochloric acid and water was carefully added. The resulting white mass was held at room temperature for 1 h, and then most of the tetrahydrofuran was distilled at atmospheric pressure. To the white solid was added 10 mL of a 1:1 v:v mixture of 50% sodium hydroxide and water with rapid stirring. After all the solid had dissolved/reacted, 10 mL water was added and extraction with 3 × 20 mL methylene chloride was performed. The combined extracts were washed with 20 mL brine and dried over magnesium sulfate. Removal of the solvent in vacuo gave crude product

which was purified by radial chromatography (4 mm rotor, 20% ethyl acetate/hexane). Isolated was 616 mg (64%) of free base of salt (2*R*)-**13** as a colorless liquid, TLC $R_f = 0.57$ in 20% ethyl acetate/hexane.

Ethereal hydrogen chloride (2.6 mL, 1.0 M in ether, 2.6 mmoL) was added to a solution of the free base (608 mg, 2.29 mmol) dissolved in 10 mL of anhydrous ether. During the addition, 20 mL additional ether was added to aid in stirring. The mixture was suction filtered, washing with 2 × 10 mL ether. Isolated was 640 mg (93%) salt (2*R*)-**13** as a white powder. This substance (626 mg) was recrystallized from a boiling solution of 35 mL of 2-propanol/10 mL of hexane. After holding at room temperature for 1 h, the mixture was suction filtered, washing with 2 × 10 mL hexane. Isolated was 503 mg of (2*R*)-**13** as white needles, mp = 225 °C (sublimes), $[\alpha]^{25}_D = +19°$ (c = 1, MeOH). ^{1}H NMR (CD_3OD): δ 1.74 (d, J = 6.9 Hz, 3H), 3.12 (dd, J = 27, 14 Hz, 1H), 3.66 (dd, J = 14, 6.9 Hz, 1H), 3.70–3.72 (m, 3H), 4.52 (q, J = 6.9 Hz, 1H), 7.48–7.52 (m, 5H). ^{19}F NMR (CD_3OD, proton decoupled): −77.0 (br s, 3F), −133.7 (br s, 1F). Anal. Calcd for $C_{12}H_{16}F_4ClNO$: C, 47.77; H, 5.35; N, 4.64. Found: C, 47.81; H, 5.39; N, 4.59%.

Single crystals of amine (2*R*)-**13** suitable for X-ray crystallographic structure determination[27] were grown by slow evaporation from a 12% v:v water in acetone solution. Tables of coordinates and equivalent isotropic temperature factors, anisotropic thermal parameters, bond distances, bond angles, intermolecular contacts, and structure factors have been deposited with the Crystallographic Data Centre, 12 Union Road, Cambridge, CB2, 1EW, England.

Conversion of Monochloro Ether (−)-12 to (*S*)-(−)-Desflurane. In a flask fitted with a dry ice/acetone condenser, sodium (1.05 g, 45.7 mmol; cut into small pieces) was added to a slurry of chloro ether (−)-**12** (2.10 g, 10.4 mmol) and ammonium chloride (0.666 g, 12.5 mmol) in 10 mL methanol under argon at 0 °C with rapid stirring. During the 0.5 h addition time, the reaction temperature never rose above 24 °C. After addition, the mixture was held at 10–20 °C for 1 h, after which time no sodium remained. After cooling to 0 °C, 2 mL of acetic acid was slowly added, keeping the temperature below 27 °C. The thick white mixture was partitioned between 10 mL of carbon tetrachloride and 90 mL of water. The lower organic layer was washed with 30 mL water and dried over calcium chloride. ^{1}H and ^{19}F NMR analysis showed a 1.5:1 mixture of chloro ether **12** and the anesthetic desflurane. Chiral capillary GC analysis at 35 °C on a Chiraldex G-TA column showed that the anesthetic was the (*S*)-(−) form, based on its longer retention time.[29]

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