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Chiral Interactions of the Fluoroether Anesthetics Desflurane, Isoflurane, Enflurane, and Analogues with Modified Cyclodextrins Studied by Capillary Gas Chromatography and Nuclear Magnetic Resonance Spectroscopy: A Simple Method for Column-Suitability Screening

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Abstract: Eighteen chiral analogues of the chiral fluoroether anesthetics desflurane, isoflurane, and enflurane are synthesized and studied by capillary GC on four cyclodextrin-derived stationary phases. Trends in separability and elution order of enantiomers are related to structure and absolute configuration. In particular, a very large separation factor is found for the commercial anesthetic desflurane using Lipodex® E stationary phase, suggesting that a preparative enantiomer separation is possible. One of the stationary phases, Cyclodex® G-TA, is found to be a chiral shift reagent for several of the fluoroethers. A rough correspondence is found relating the enantiomeric separation factor of a fluoroether and the chemical shift differences between its ^{1}H and ^{19}F nuclei in the NMR spectrum. Based on this data, it is proposed that a simple NMR experiment can screen chiral stationary phases prior to a desired gas chromatographic enantiomer separation of a given chiral compound.

INTRODUCTION

Three of the commercial fluoroether anesthetics,[2] desflurane (**1a**), isoflurane (**2a**), and enflurane (**3a**) (Table 1), are chiral but are clinically administered in their racemic form. For chiral pharmaceuticals and biologically active compounds in general, it is common for one enantiomer to exhibit the desired activity while the other enantiomer may be less active, inactive, or poisonous. This realization has prompted asymmetric syntheses of these volatile anesthetics.[3] Meinwald and Pearson[4] reported the synthesis of individual enantiomers of **3a**. Reports from our laboratories have documented the preparation of single enantiomers of **1a**[5] and **2a**.[6] We have also synthesized the desflurane analogues **1b**[7] and **1f**[8a] in high optical purity; the racemates of these compounds have been shown to have anesthetic properties.[9] Preliminary pharmacological data suggest there is little potency difference between the enantiomers of both **1a** and **3a**. However, the enantiomers of anesthetic **2a** exhibit a twofold difference in potency,[10a-c] as well as a marked difference in odor:[10d] The less potent (*R*)-(−)-enantiomer has a typical ethereal odor, while the more potent (*S*)-(+)-enantiomer has no odor at all. Aside from the search for differential potency in the enantiomers of these molecules, another reason for their synthesis is to study the very complex biological mechanism of anesthesia.

Table 1. Structures of Fluoroethers

	1	2	3
a	$CF_3CHFOCF_2H$*	$CF_3CHClOCF_2H$*	$CHFClCF_2OCF_2H$‡
b	$CF_3CHFOCH_3$*	$CF_3CHClOCH_3$‡	$CHFClCF_2OCH_3$‡
c	$CF_3CHFOCF_2Cl$*	$CF_3CHClOCF_2Cl$†	$CHFClCF_2OCF_2Cl$‡
d	$CF_3CHFOCFCl_2$*	$CF_3CHClOCFCl_2$†	$CHFClCF_2OCFCl_2$‡
e	$CF_3CHFOCCl_3$*	$CF_3CHClOCCl_3$‡	$CHFClCF_2OCCl_3$‡
f	$CF_3CHFOCHClF$*	$CF_3CHClOCHClF$§	$CHFClCF_2OCHClF$‡
g			$CHFClCF_2OCH_2F$‡
h			$CHFClCF_2OCH_2Cl$‡
i			$CHFClCF_2OCHCl_2$‡

*Available to us in both racemic and optically active form. ‡Available to us in racemic form only. †Optically active form synthesized for this study. §Racemate synthesized for this study.

The fact that the enantiomers of **2a** differ in potency makes a receptor-based theory[10a,11] more plausible.

Critical to the synthetic endeavors described above was application of capillary GC using modified cyclodextrin stationary phases,[12] which is the best way to accurately determine the enantiomeric purity of these types of molecules. There have been reports of both analytical[13] and preparative[14] GC separations of fluoroether enantiomers using various cyclodextrin stationary phases. In a study closely related to our work, Vigh et al.[13a] have reported the analytical enantiomeric separation of **1a**, **2a**, and **3a** on several Cyclodex® chiral GC stationary phases. Derivatized cyclodextrin stationary phases are broadly applicable because the chiral analyte is not required to be functionalized for effective enantiomeric discrimination. Of current interest is the mechanism by which this discrimination occurs.[12c,15] It has been noted that for mechanistic studies, analyte/stationary phase combinations are needed in which chiral discriminatory forces are very strong, i.e. combinations which give a high separation factor (α).[12c] While the preponderance of analytes give low α values, halogenated enantiomers in many cases are separated unusually well. We have undertaken a systematic study of the gas chromatographic behavior of these fluoroether anesthetics and analogues (**1a-f**, **2a-f**, **3a-i**) using four cyclodextrin stationary phases in order to delineate the structural requirements for enantiomer separation. Two γ-cyclodextrin derivatives, 2,5-di-O-pentyl-3-O-trifluoroacetyl-γ-cyclodextrin (Cyclodex G-TA) and 2,5-di-O-pentyl-3-O-butanoyl-γ-cyclodextrin (Lipodex® E), were chosen to probe the influence of substitution at the 3-position of γ-cyclodextrin; to assess the role of cyclodextrin cavity size, two other stationary phases, 2,3,5-tri-O-penytl-β-cyclodextrin (Lipodex® C) and 2,3,5-tri-O-penytl-α-cyclodextrin (Lipodex® A), were selected. In several cases, exceptionally high α values are observed, making these particular fluoroether/stationary phase combinations good candidates for mechanistic studies or preparative separations.

Currently, there is no good method for predicting whether a column lined with a particular cyclodextrin stationary phase will separate the enantiomers of a chiral compound. We will give preliminary indications that

the stationary phases can be used as chiral shift reagents[15d,16] in ^1H and ^{19}F NMR spectroscopy of these compounds. It will be demonstrated that the GC α values obtained using one of the stationary phases can be related to the magnitude of the NMR chemical shift differences between nuclei of the two enantiomers in the presence of that phase in a non-polar solvent at room temperature; thus, it is suggested that a simple and inexpensive NMR experiment can indicate whether a column will separate the enantiomers of a chiral analyte.

RESULTS AND DISCUSSION

Fluoroether Synthesis

Anesthetics **1a**, **2a**, and **3a** were obtained from Ohmeda Inc. The syntheses of enantiomers of **1a**[5] and **2a**[6] have been described. The absolute configuration of **1a** has been found to be (*R*)-(+)/(*S*)-(−),[17a] while that of **2a** is (*R*)-(−)/(*S*)-(+).[17b] The preparations of racemic and optically active **1b-f** have been reported;[7-9] their absolute configurations are also (*R*)-(+)/(*S*)-(−).[8a,18] Compound **2b** has been prepared previously.[19] Compounds **2c**, **2e**, **3b**, **3e**, **3h**, **3i**,[20] and **2d**, **3c**, **3d**, **3f**, **3g**[21] are known.

The missing member of the isoflurane analogue series, **2f**, is prepared by photoreduction[22] of **2d** with 2-propanol (eq 1). This necessitated an improved synthesis of **2d**, because we were unable to reproduce the conditions of Terrell et al.[20,21] properly. Modification of this procedure by use of SbF_3/Br_2[22] allows production of both **2c** and **2d**, which are easily separated by fractional distillation. In the same fashion, **3c** and **3d** are synthesized from **3e**.

$$\underset{\mathbf{2e}}{CF_3CHClOCCl_3} \xrightarrow{SbF_3/Br_2} \underset{\mathbf{2c}}{CF_3CHClOCF_2Cl} + \underset{\mathbf{2d}}{CF_3CHClOCFCl_2} \xrightarrow{\text{2-propanol/h}\nu} \underset{\mathbf{2f}}{CF_3CHClOCHClF} \qquad (1)$$

In the case of **3g**, we found insufficient experimental detail published[21] to successfully reproduce the synthesis. Treatment of **3h** with KF in ethylene glycol[24] gives **3g** uneventfully.

Optical resolution of **2c** and **2d** is accomplished by enantioselective complex formation with brucine. Meinwald et al.[4] have resolved related fluoroethers by this method. The enantiomers of **2c** are each isolated in ≥92% ee. In the case of **2d** however, only the (+)-isomer could be obtained with a high (85% ee) degree of enantiomeric purity.

GC Studies

Tables 2, 3, and 4 show the results of our GC studies. The column temperatures reported are the minimum which are consistent with acceptable peak shape, thus the α values are probably maximized. Considering fluoroether structure first, it can be seen that for the desflurane and isoflurane series, separability is strongly related to the amount and nature of substitution at the methoxy group, while for the enflurane series, this relation does not hold. The most striking trend can be seen in Tables 2 and 3. Comparison of entries 1, 2, and 6 with entries 3, 4, and 5 shows that a proton on the methoxy group of desflurane and isoflurane derivatives is required for effective separation. However, the enflurane derivatives (Table 4) do not mirror this trend. The origin of this effect is unclear, but it may be due to a subtle alteration of the dipole moment of the molecule as hydrogens are substituted by chlorines. For the compounds which show enantiomeric separation,

Table 2. Enantiomeric Separations of Desflurane and Analogues on Cyclodextrin Stationary Phases

entry	Fluoroether (bp, °C)	α*	k`1†	column T (°C)	phase
1	$CF_3CHFOCF_2H$‡ (24) (desflurane)	1.14	0.12	30	Cyclodex G-TA
		1.85	0.46	25	Lipodex E
		1.20	0.16	25	Lipodex C
		1.29	0.16	25	Lipodex A
2	$CF_3CHFOCH_3$‡ (38)	1.67	0.10	45	Cyclodex G-TA
		2.38	0.23	55	Lipodex E
		1.00	0.11	25	Lipodex C
		1.15	0.10	25	Lipodex A
3	$CF_3CHFOCF_2Cl$ (24)	1.00	0.05	25	Cyclodex G-TA
		1.00	0.10	25	Lipodex E
		1.00	0.07	25	Lipodex C
		1.00	0.05	25	Lipodex A
4	$CF_3CHFOCFCl_2$ (58)	1.00	0.14	45	Cyclodex G-TA
		1.00	0.26	40	Lipodex E
		1.00	0.18	40	Lipodex C
		1.00	0.27	25	Lipodex A
5	$CF_3CHFOCCl_3$ (97)	1.00	0.21	75	Cyclodex G-TA
		1.00	0.21	85	Lipodex E
		1.00	0.27	75	Lipodex C
		1.00	0.91	35	Lipodex A
6	$CF_3CHFOCHFCl$‡,§,25 (50)	1.10, 1.26 (1:1:1:1)¶	0.33, 0.38	40	Cyclodex G-TA
		1.09, 1.42 (1:2:1)¶	0.47, 0.53	50	Lipodex E
		1.03, 1.23 (1:1:1:1)¶	0.79, 0.97	25	Lipodex C
		1.04, 1.16 (1:1:1:1)¶	0.93, 1.21	25	Lipodex A

*separation factor ($k`_2/k`_1$) †capacity factor of first-eluting peak ‡(*R*)-(+)-enantiomer elutes first §α and k` values are reported in the following manner: $\alpha_{1,2}$, $\alpha_{2,3}$ (or $\alpha_{3,4}$) $k`_1$, $k`_2$ (or $k`_3$) ¶indicates number and area ratio of peaks

it appears that the CF_3CHXO group allows more effective discrimination between enantiomers than the $CHFClCF_2O$ group. When the two favorable strucural characteristics are combined, i.e. a non-chlorinated methoxy group on the CF_3CHXO backbone, unusually high α values can be obtained, as in entries 1 and 2 of Table 2. In particular, the combination of desflurane and Lipodex E gives a high enough α value to attempt a preparative separation. Another trend is the regularity of elution order within a series. For desflurane and two derivatives (Table 2; entries 1, 2, and 6[25]), the (*R*)-(+)-isomers elute first. For isoflurane and two derivatives (Table 3; entries 1, 3, and 4) however, the (*S*)-(+)-isomers[26] elute first.

Turning to structure of the stationary phase, we find that the γ-cyclodextrin derivatives are more effective than the β or α derivatives. This may be due to the greater ability of the larger and less rigid γ-cyclodextrin to accomodate the fluoroether in an orientation for effective chiral recognition. There is no clear choice between Cyclodex G-TA and Lipodex E as to which performs better. While Lipodex E gives the two highest α values

Table 3. Enantiomeric Separations of Isoflurane and Analogues on Cyclodextrin Stationary Phases

entry	Fluoroether (bp, °C)	α*	k'1†	column T (°C)	phase
1	$CF_3CHClOCF_2H$‡ (48) (isoflurane)	1.31	0.30	40	Cyclodex G-TA
		1.19	0.34	60	Lipodex E
		1.08	0.54	30	Lipodex C
		1.17	0.62	25	Lipodex A
2	$CF_3CHClOCH_3$ (68)	1.00	0.76	35	Cyclodex G-TA
		1.00	1.88	40	Lipodex E
		1.06	0.28	45	Lipodex C
		1.08	0.54	25	Lipodex A
3	$CF_3CHClOCF_2Cl$‡ (54)	1.09	0.19	35	Cyclodex G-TA
		1.00	0.12	60	Lipodex E
		1.00	0.10	60	Lipodex C
		1.00	0.23	25	Lipodex A
4	$CF_3CHClOCFCl_2$‡ (87)	1.06	0.41	60	Cyclodex G-TA
		1.00	0.51	60	Lipodex E
		1.00	0.66	40	Lipodex C
		1.00	0.76	35	Lipodex A
5	$CF_3CHClOCCl_3$ (130)	1.00	0.42	90	Cyclodex G-TA
		1.00	0.52	90	Lipodex E
		1.01	0.86	75	Lipodex C
		1.00	1.37	60	Lipodex A
6	$CF_3CHClOCHFCl$§ (80)	1.15, 1.22 (1:1:1:1)¶	0.43, 0.54	60	Cyclodex G-TA
		1.12, 1.25 (1:2:1)¶	0.52, 0.59	75	Lipodex E
		1.03, 1.06 (1:1:1:1)¶	0.63, 0.68	60	Lipodex C
		1.06, 1.07 (2:1:1)¶	1.26, 1.34	45	Lipodex A

*separation factor (k'_2/k'_1) †capacity factor of first-eluting peak ‡(*S*)-(+)-enantiomer elutes first §α and k' values are reported in the following manner: $\alpha_{1,2}$, $\alpha_{2,3}$ (or $\alpha_{3,4}$) k'_1, k'_2 (or k'_3) ¶indicates number and area ratio of peaks

(Table 2, entries 1 and 2), Cyclodex G-TA separates the enantiomers of two of the isoflurane derivatives (Table 3, entries 3 and 4) which none of the other three phases can. Comparison of the ability of the two tri-O-pentylated cyclodextrins (Lipodex C and A) shows that cavity size has little effect on separability. This is not surprising in view of the evidence that the analyte may not have to enter the cavity of the cyclodextrin at all for enantiomeric discrimination to take place.[15c]

^1H and ^{19}F NMR Studies

Tables 5 and 6 show the effect of Cyclodex G-TA stationary phase on the chemical shifts of ^1H and ^{19}F nuclei of several compounds from the isoflurane and desflurane series. In all cases, the Cyclodex G-TA causes significant deshielding in both enantiomers (Table 5), although no detectable changes in coupling constants are found.

Table 4. Enantiomeric Separations of Enflurane and Analogues on Cyclodextrin Stationary Phases

entry	Fluoroether (bp, °C)	α*	k'1†	column T (°C)	phase
1	$CHFClCF_2OCF_2H$ (56) (enflurane)	1.18	0.34	45	Cyclodex G-TA
		1.00	1.57	40	Lipodex E
		1.04	0.41	40	Lipodex C
		1.00	1.08	25	Lipodex A
2	$CHFClCF_2OCH_3$ (70)	1.00	0.55	45	Cyclodex G-TA
		1.05	1.33	40	Lipodex E
		1.04	0.54	40	Lipodex C
		1.09	0.91	25	Lipodex A
3	$CHFClCF_2OCF_2Cl$ (64)	1.11	0.16	60	Cyclodex G-TA
		1.25	0.49	40	Lipodex E
		1.00	0.44	40	Lipodex C
		1.03	0.63	25	Lipodex A
4	$CHFClCF_2OCFCl_2$ (100)	1.06	0.42	75	Cyclodex G-TA
		1.05	0.41	85	Lipodex E
		1.00	0.58	75	Lipodex C
		1.01	1.05	55	Lipodex A
5	$CHFClCF_2OCCl_3$ (140)	1.03	0.90	90	Cyclodex G-TA
		1.03	1.22	90	Lipodex E
		1.03	2.68	75	Lipodex C
		1.00	1.16	85	Lipodex A
6	$CHFClCF_2OCHFCl$§ (87)	1.07, 1.05 (1:2:1)¶	0.47, 0.50	65	Cyclodex G-TA
		1.21, 1.27 (1:1:1:1)¶	0.67, 0.84	75	Lipodex E
		1.05 (1:3)¶	0.73	60	Lipodex C
		1.09, 1.33 (1:1:2)¶	1.76, 1.91	35	Lipodex A
7	$CHFClCF_2OCH_2F$ (80)	1.05	0.46	60	Cyclodex G-TA
		1.18	0.61	75	Lipodex E
		1.04	1.46	40	Lipodex C
		1.05	1.18	35	Lipodex A
8	$CHFClCF_2OCH_2Cl$ (110)	1.04	0.71	80	Cyclodex G-TA
		1.15	1.23	85	Lipodex E
		1.03	0.99	75	Lipodex C
		1.06	2.08	55	Lipodex A
9	$CHFClCF_2OCHCl_2$ (120)	1.04	0.64	90	Cyclodex G-TA
		1.21	1.60	85	Lipodex E
		1.02	1.33	75	Lipodex C
		1.03	2.22	55	Lipodex A

*separation factor (k'_2/k'_1) †capacity factor of first-eluting peak §for stationary phases which give >2 peaks, α and k' values are reported in the following manner: $\alpha_{1,2}$, $\alpha_{2,3}$ (or $\alpha_{3,4}$) k'_1, k'_2 (or k'_3) ¶indicates number and area ratio of peaks

Table 5. ^1H and ^{19}F (Proton Decoupled) Chemical Shifts in c-C_6D_{12}, With and Without Cyclodex G-TA*,†

entry	compound	a	b	c	d	e
1	$CF_3CHClOCF_2H$	5.90, q	6.24, dd	-76.01, d	-82.49, d; -83.53, br d	
	c a d b	6.00 (*S*)	6.38 (*S*)	-75.77 (*S*)	-82.15 (*S*); -83.06 (*S*)	
		6.04 (*R*)	6.42 (*R*)	-75.70 (*R*)	-82.14 (*R*); -83.14 (*R*)	
2	$CF_3CHClOCF_2Cl$	5.93, q	-75.61, d		-25.37, d; -25.90, br d	
	b a d	6.00 (*S*)	-75.48 (*S*)		-25.25 (*S*); -25.75 (*S*)	
		6.00 (*R*)	-75.48 (*R*)		-25.24 (*R*); -25.77 (*R*)	
3	$CF_3CHClOCFCl_2$	6.00, q	-75.15, d	-8.15, br s		
	b a c	6.05 (*S*)	-75.10 (*S*)	-8.08 (*S*)		
		6.05 (*R*)	-75.09 (*R*)	-8.10 (*R*)		
4	$CF_3CHFOCF_2H$	5.77, dq	6.25, dd	-80.01, d	-80.44, dd; -81.75, dd	-141.60, qdd
	c a e d b	5.92 (*S*)	6.46 (*S*)	-79.54 (*S*)	-80.03 (*S*); -81.08 (*S*)	-140.99 (*S*)
		5.89 (*R*)	6.45 (*R*)	-79.60 (*R*)	-80.10 (*R*); -81.15 (*R*)	-140.99 (*R*)
5	$CF_3CHFOCH_3$	5.10, dq	3.55, d	-79.49, d	-141.63, q	
	c a d b	5.34 (*S*)	3.69 (*S*)	-79.03 (*S*)	-141.03 (*S*)	
		5.21 (*R*)	3.63 (*R*)	-79.21 (*R*)	-141.18 (*R*)	
6	$CF_3CHFOCFCl_2$	5.79, dq	-79.16, d	-8.04, d	-142.47, qd	
	b a d c	5.93 (*S*)	-79.01 (*S*)	-7.89 (*S*)	-142.40 (*S*)	
		5.93 (*R*)	-79.01 (*R*)	-7.89 (*R*)	-142.40 (*R*)	

*Experimental conditions: 50-60 mg of G-TA and the appropriate amount of racemic fluoroether to make a 1:1 molar ratio in 0.5-0.8 mL cyclohexane-d_{12} at r. t. †Data recorded in the following manner: chemical shift in ppm without G-TA, multiplicity chemical shift in ppm with G-TA (enantiomer)

Table 6. Comparison of GC α Values from Tables 2 and 3 with NMR Chemical Shift Differences Between Enantiomers ($\Delta\partial_{R,S}$) Calculated from Table 5

				$\Delta\partial_{R,S}$ (Hz)				
entry	compound	α	elution order	CF_3CH	OCH	CF_3	$OCF_{(2)}$	CF_3CF
1	$CF_3CHClOCF_2H$	1.31	*S*,*R*	12*	12*	20*	3*, 23†	
2	$CF_3CHClOCF_2Cl$	1.09	*S*,*R*	0		0	3*, 6†	
3	$CF_3CHClOCFCl_2$	1.06	*S*,*R*	0		3*	6†	
4	$CF_3CHFOCF_2H$	1.14	*R*,*S*	9†	3†	17†	20†, 20†	0
5	$CF_3CHFOCH_3$	1.67	*R*,*S*	39†	18†	51†		42†
6	$CF_3CHFOCFCl_2$	1.00	*R*,*S*	0		0	0	0

*Nuclei from the (*S*)-enantiomer are more shielded. †Nuclei from the (*R*)-enantiomer are more shielded.

Table 6 indicates that there is some regularity within a fluoroether analogue series. For the isoflurane series (entries 1, 2, and 3), the nuclei of the first-eluting (*S*)-enantiomers are the most shielded, except for fluorines which give rise to broadened signals,[27] which are less shielded. In the desflurane series (entries 4, 5, and 6), the nuclei of the first-eluting (*R*)-enantiomers are the most shielded. A similar trend has been noted by König in a related study.[15d] Our data add to the growing evidence that cyclodextrins are useful as NMR shift reagents,[15d,16] although their usefulness in proton spectroscopy is limited by interference of the numerous signals from the cyclodextrin. Derivatized cyclodextrins in particular may emerge as the reagents of choice for chiral molecules which contain no highly polar functionality, because such funtionality is not always required for chiral discrimination.

The NMR data of Table 6 also show a rough correspondence between the magnitudes of α and chemical shift differences between nuclei of enantiomers ($\Delta\partial_{R,S}$). Compound **1b**, which has the highest separation factor, also has the greatest $\Delta\partial_{R,S}$ for both nuclei. On the other hand, **1d**, which shows no enantiomeric separation, has a $\Delta\partial_{R,S}$ of zero for all nuclei. While this relation is not unexpected, as both α and $\Delta\partial_{R,S}$ are related to differences in binding free energy, the practical value of the information is that it suggests a method for screening of capillary GC columns. With an inexpensive amount of stationary phase, one can perform a simple NMR experiment to determine whether a desired enantiomeric separation is feasible before buying an expensive capillary column. The 7.5 Tesla field strength of the NMR spectrometer used in this study is relatively low by today's standards. It is likely that an instrument of higher field strength would be useful in seeing cyclodextrin-induced chemical shift differences in compounds which have typical α values of less than 1.1.

EXPERIMENTAL

General

The 80 m X 0.25 mm I.D. fused silica Cyclodex G-TA capillary GC column was obtained from ASTEC (Whippany, NJ, USA). The 50 m X 0.25 mm I.D. fused silica Lipodex A, C,and E columns were obtained from Macherey-Nagel (Düren, Germany). The Cyclodex G-TA stationary phase used in the NMR experiments was obtained from ASTEC (Whippany, NJ, USA). Cyclohexane-d_{12} was obtained from Wilmad (Buena, NJ, USA). All other reagents were obtained from Aldrich Chemical Company (Milwaukee, WI, USA) and used as provided.

Methods

A Gow-Mac 750P gas chromatograph equipped with a flame ionization detector was used for all chiral separations. Approximately 20 nL of fluoroether was injected with a split ratio of 1/100. The injection port temperature was 150 °C and the detector temperature was 175 °C. Helium at 1.0 bar was used as the carrier gas. Methane was used to calculate the dead volumes of each column. All analyses were performed isothermally. For chemical purity (i.e. area %), an HP 5790A gas chromatograph fitted with a 12' X 1/8" SS-316 column packed with 20% SE-30 on 60/80 mesh Chromasorb PAW was used. A thermal conductivity detector at 200 °C and an injection port temperature of 175 °C were used.

NMR spectra were obtained on a Bruker AC-300 Fourier transform spectrometer. ^1H NMR chemical shifts at 300 MHz were recorded relative to tetramethylsilane. ^{19}F NMR chemical shifts at 282 MHz were recorded relative to fluorotrichloromethane.

1-Chloro-2,2,2-trifluoroethyl Chlorodifluoromethyl Ether (2c) and 1-Chloro-2,2,2-trifluoroethyl Dichlorofluoromethyl Ether (2d)

The fluorination was carried out in a 200 mL three-neck round bottom flask equipped with a magnetic stir bar, an addition funnel, and a distillation assembly having a 10 cm Vigreux column and an ice water-cooled receiver connected to a gas bubbler. The reactor was charged with **2e** (30 g, 0.12 mol) and SbF_3 (14.3 g, 0.08 mol). This mixture was gradually heated with an oil bath to 55 °C with rapid stirring, and Br_2 (20.5 g, 0.128 mol) was added dropwise. After the first two mL, a vigorous reaction started. The temperature of the distilling head did not exeed 65 °C. The product mixed with bromine was collected in the 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 200 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% NaOH solution until the red color disappeared. The lower organic layer was washed with water and dried over $CaCl_2$ overnight. Distillation using a 50 cm vacuum-jacketed column packed with 3 mm glass beads afforded 7.6 g (29%) of **2c** (bp 55 °C) and 3.6 g (13%) of **2d** (bp 87 °C), both of which were >99% pure by GC. Spectral characteristics were as expected.[21]

Optical Resolution of 2c and 2d

Adapting the procedure of Meinwald and Pearson,[4] a 3:1 molar ratio of **2c** and brucine was heated at reflux for 1 h. The mixture was cooled to -78 °C and a vacuum of 10^{-2} mmHg was applied. A fraction boiling below r.t. was enriched in the (*R*)-(−)-enantiomer.[26] A fraction boiling between r. t. and 150 °C was enriched in the other enantiomer. The two fractions were separately subjected to three more cycles, giving (*R*)-(−)-**2c** ($[\alpha]_D^{25}$ = −96.4° (c = 1 in $CHCl_3$)) in 93.6 % ee and (*S*)-(+)-**2c** ($[\alpha]_D^{25}$ = +95.8° (c = 1 in $CHCl_3$)) in 92.2% ee, as judged by GC analysis on Cyclodex G-TA stationary phase. In a similar fashion, (*S*)-(+)-**2d** ($[\alpha]_D^{25}$ = +95.6° (c = 1 in $CHCl_3$)) was isolated in 85% ee.

1-Chloro-2,2,2-trifluoroethyl Chlorofluoromethyl Ether (2f)

A mixture of **2d** (158 g, 0.67 mol) and 2-propanol (1000 mL) was irradiated with a 450 W medium pressure Hg UV lamp for 8 h while sweeping the solution with N_2. The mixture was poured into water, and the lower organic layer was washed several times to remove traces of 2-propanol and acetone. After drying with $CaCl_2$, distillation using a 50 cm vacuum-jacketed column packed with 3 mm glass beads furnished 44 g (33%) of **2f** (bp 80 °C), >99% pure by GC. ^1H NMR ($CDCl_3$): ∂ 7.1 (d, J = 59 Hz, 1H), 6.9 (d, J = 56 Hz, 1H), 6.1 (q, J = 4.0 Hz, 1H), 6.0 (q, J = 4.0 Hz, 1H); ^{19}F NMR ($CDCl_3$): ∂ -80.1 (dd, J = 4.0, 2.7 Hz, 3F), -80.2 (d, J = 4.0 Hz, 3F), -82.4 (d, J = 59 Hz, 1F), -82.8 (dq, J = 56, 2.7 Hz, 1F). Anal. calcd. for $C_3H_2Cl_2F_4O$: C, 17.93; H, 1.0; Cl, 35.29; F, 37.82%. Found: C, 17.88; H, 0.99; Cl, 35.08; F, 37.45%

2-Chloro-1,1,2-trifluoroethyl Chlorodifluoromethyl Ether (3c) and 2-Chloro-1,1,2-trifluoroethyl Dichlorofluoromethyl Ether (3d)

The fluorination was carried out in a 250 mL three-neck round bottom flask equipped with a mechanical stirrer, an addition funnel, and a distillation assembly having a 10 cm Vigreux column and an ice water-cooled receiver connected to a gas bubbler. The reactor was charged with **3e** (50.0 g, 0.198 mol) and SbF_3 (23.7 g, 0.132 mol). This mixture was gradually heated with an oil bath to 100 °C with rapid stirring, and Br_2 (31.7 g, 0.198 mol) was added dropwise. After the first few drops, a vigorous reaction with evolution of substantial amounts of low boiling materials started. At this time, some product mixed with the starting ether was ejected into the receiver. After this, the vigorous reaction moderated and products mixed with bromine continued to be collected in the receiver. The temperature of the distilling head did not exeed 80 °C. The heating was stopped when this temperature dropped to 30 °C. The contents of the receiver was transfered to a 1 L flask equipped with a stir bar, a reflux condenser, and an addition funnel. It was treated dropwise at 0 - 5 °C with cold 10% NaOH solution until the red color disappeared. The lower organic layer (24.9 g) was washed with water and dried over $CaCl_2$ overnight. This reaction was repeated four more times on the same scale. Crude mixtures from the five runs were combined (108.3 g) and distilled using a 50 cm vacuum-jacketed column packed with 3 mm glass beads, affording 42.0 g of **3c** (bp 65 °C) and 40.0 g of **3d** (101 °C), both of which were >99% pure by GC. Spectral characteristics were as expected.[21]

2-Chloro-1,1,2-trifluoroethyl Fluoromethyl Ether (3g)

The fluorination was carried out in a 1 L three neck round bottom flask equipped with a mechanical stirrer, a thermometer, an addition funnel, and a distillation assembly having a reciever connected to a gas bubbler. The reactor was charged with spray-dried KF (63.3 g, 1.09 mol) and diethylene glycol (300 mL). This mixture was gradually heated to 170 °C with rapid stirring and **3h** (100 g, 0.546 mol) was added dropwise. After the first 2 mL was added, reaction started and the product began to distill. During the 2 h addition time, the temperature of the distilling head did not exceed 90 °C and the temperature of the pot did not exceed 200 °C. The crude product (62.0 g) was washed with water and dried over $CaCl_2$ overnight. Distillation using a 50 cm column packed with 3 mm glass beads and a distilling head afforded 44.6 g (49%) **3g** (bp 84 °C), >99% pure by GC. Spectral characteristics were as expected.[21]

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25. The asymmetric synthesis of this compound was stereocontrolled at only the CF_3-bearing chiral carbon atom.[8a] Thus, the two non-racemic samples we analyzed were mixtures of diastereomers, i.e. (*R*,*S*)/(*R*,*R*) and (*S*,*S*)/(*S*,*R*). It was found that the components of the former mixture, which have the *R* configuration at the CF_3-bearing chiral carbon atom, eluted before the components of the latter.
26. The absolute configurations of **2c** and **2d** are assumed to be the same as the closely-related isoflurane,[17b] i.e. if isoflurane is (*S*)-(+)/(*R*)-(−), so are **2c** and **2d**. In support of this, it is noted that constancy of optical rotation sign as methoxy group substitution is changed holds for all compounds in the desflurane series.[8a]
27. Significant broadening, possibly due to long-range interactions, of one of the signals of the two diastereotopic fluorines of **2a** and **2c** and the signal of the lone methoxy-group fluorine of **2d** is seen. Why these fluorines do not follow the trend seen for the other nuclei remains unclear.

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