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Preparation of (+)-chlorofluoroiodomethane, determination of its enantiomeric excess and of its absolute configuration

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Abstract—Chlorofluoroiodoacetic acid ($FClICCO_2H$) has been synthesized in four steps from chlorotrifluoroethylene. Enantioenriched (+)-chlorofluoroiodomethane **1** [(+)-CHFClI] with 63.3% ee was obtained by stereoselective decarboxylation in triethyleneglycol at 110 °C and 110 mmHg of the diastereomeric salt {(+)-$FClICCO_2H$, (−)-strychnine} having 67% de. The enantiomeric excess of (+)-CHFClI was determined by gas chromatography on a chiral modified cyclodextrin stationary phase. The (*S*)-(+)-/(*R*)-(−)-configurations were assigned by quantum mechanical calculations of the specific rotation using density functional theory.

1. Introduction

The preparation of very simple chiral molecules in their enantiomerically enriched form is important for many fundamental aspects of chirality. Recently, novel chiral bridge-head polyhalogenated adamantane derivatives have been prepared in enantioenriched forms by Schreiner et al.[1a] Chiral 1-bromo-1-fluoro-1-iodoalditols have also been syntheized by Suarez et al.[1b,c] and fluoroiodoacetic acid resolved by Myers et al.[1d] Pentaatomic chiral halogenomethanes are currently being studied in our laboratory and are of interest for parity violation (PV) measurements. Although it is generally accepted that enantiomeric pairs have the same energy, this is not true if taking into account the weak interaction, responsible for PV effects.[2,3] The possibility of measuring such small effects at a molecular level still remains a challenge. In this context, chiral halogenomethanes such as chlorofluoroiodomethane **1** (CHFClI) are thought to be the compounds of choice for measuring PV effects.[4] In the last 20 years, much attention has been focused on bromochlorofluoromethane **2** (CHFClBr), one of the simplest chiral molecules.[5] Recently, very accurate ultra-high infra-red (IR) spectra were measured on (+)- and (−)-CHFClBr in order to attempt to measure the absorption differences between the two enantiomers. Although parity violation was not observed, an upper limit of 10^{-13} was obtained for the relative energy difference $\Delta E_{PV}/E$.[5,6] Parallel to experiments, relativistic ab initio calculations on several chiral halogenomethanes have shown that the PV effects were several orders of magnitude higher for iodinated halogenomethanes, like CHFBrI and CHFClI.[4,7]

Racemic chlorofluoroiodomethane was originally synthesized by Haszeldine in 1952 by a Hunsdiecker reaction on chlorofluoroacetic acid.[8] More recently, it has been obtained by reaction of chlorodiiodomethane with HgF_2 by Novak et al., who investigated the electronic structure of CHFClI and CHFBrI.[9] As we were interested in synthesizing CHFClI in a way that would allow us to obtain it in an optically active form, we investigated the synthesis of nonracemic chlorofluoroiodoacetic acid **3** ($FClICCO_2H$) and its decarboxylation into **1**. This strategy has already been found to be efficient in the case of CHFClBr whose enantiomers could be obtained by highly stereoselective decarboxylation of optically active bromochlorofluoroacetic acid **4** ($FClBrCCO_2H$)[5,10] and in the synthesis of chiral anesthetic desflurane[11] subject to subsequent reappraisal of its absolute configuration.[12]

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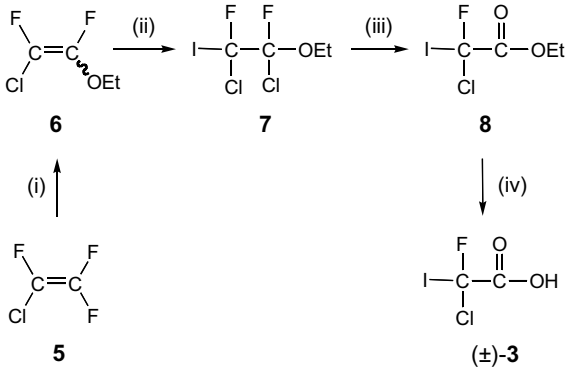
2. Results and discussion

2.1. Synthesis of (±)-chlorofluoroiodoacetic acid

Chlorofluoroiodoacetic acid (±)-**3** was prepared in four steps from chlorotrifluoroethene **5** (Scheme 1). The first step involved a regioselective nucleophilic substitution of the fluoride by an ethoxide moiety at the CF_2 group.[13] This was accomplished according to the literature[14] and gave 2-chloro-1,2-difluoro-1-ethoxyethene **6** as a mixture of *Z* and *E*-isomers. In the second step, iodine monochloride was added to chloro-1,2-difluoro-1-ethoxyethene in dry dichloromethane and gave 1,2-dichloro-1,2-difluoro-2-iodo-1-ethoxyethane **7** in 45% yield as a mixture of two *R*R**, *R*S** diastereomers. According to Markovnikov's rule, this chloroiodination is regioselective and allows the fixing of three different halogen atoms (F, Cl and I) at the same carbon atom.[15] 1,2-Dichloro-1,2-difluoro-2-iodo-1-ethoxyethane **7** was subsequently hydrolyzed in 78% yield with concentrated sulfuric acid to ethyl chlorofluoroiodoacetate **8**,[15] following the classical transformation of a $-CF_2-OR$ group into a –CO–OR moiety.[13] Finally, ester **8** was saponified by aqueous sodium hydroxide to give the acid (±)-**3**. Chlorofluoroiodoacetic acid was found to be relatively unstable and difficult to characterize.[16] In general, all the iodinated compounds had a lower stability when in a pure state and had to be stored in the dark at low temperature (−30 °C). However, it was observed that the iodinated compounds were much more stable in diethyl ether solutions. Therefore, while the reaction yields drastically decreased in the purification of the compounds, the reactions were found to be almost quantitative when the compounds were not purified and kept in diethyl ether (see Scheme 1). In this way, up to 40 g of (±)-**3** can be prepared in four steps.



Scheme 1. Synthesis of (±)-chlorofluoroiodoacetic acid **3**. Reagents and conditions: (i) EtONa, Et_2O;[14] (ii) ICl, CH_2Cl_2, 45% (99% in ethereal solution); (iii) concd H_2SO_4, 78% (89% in ethereal solution); (iv) aq NaOH then H_2SO_4, 30% (100% in ethereal solution).

2.2. Synthesis of (+)-chlorofluoroiodomethane

The resolution of (±)-$FClICCO_2H$ was investigated by crystallization of the diastereomeric salts with chiral amines.[17] Among several attempts, the most successful trial was the use of (−)-strychnine as the resolving agent. As depicted in Scheme 2, the strychninium salt was prepared and could be crystallized by stirring in chloroform, to yield the less soluble *n* salt {(+)-$FClICCO_2H$, (−)-strychnine} with 72% diastereomeric excess (de); the more soluble *p* salt {(−)-$FClICCO_2H$, (−)-strychnine} was found to be ca 20% de. The use of methanol as the solvent of crystallization enabled us to obtain mother liquors containing the more soluble *p* salt with a de of ca 50%; unfortunately this contained many impurities.

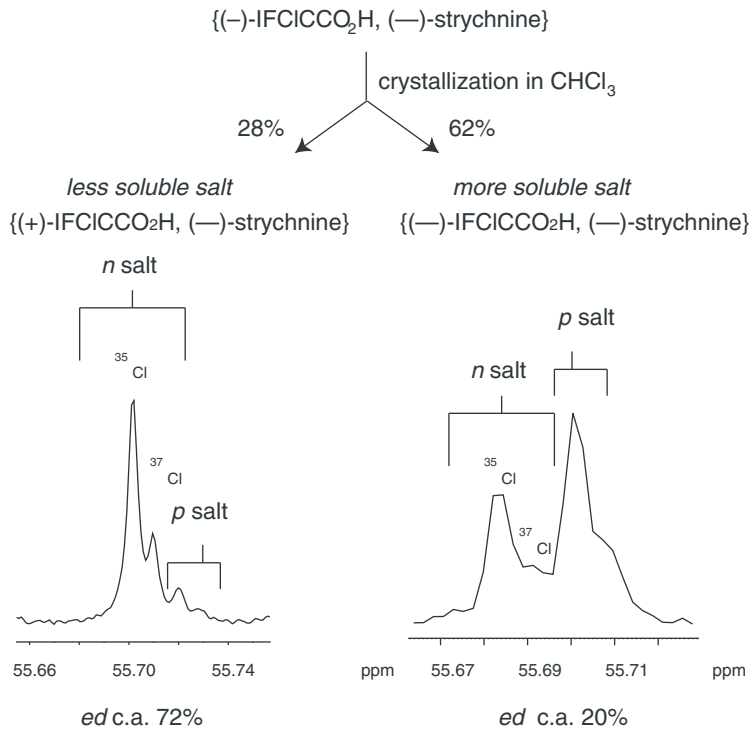
The de was directly determined by ^{19}F NMR of the salt in $CDCl_3$ at 200 MHz (Scheme 2). The high sensitivity of ^{19}F NMR enabled us to observe isotopic effects for certain classes of chlorofluoro molecules.[18] This was also the case for $FClICCO_2H$ and its derivatives (i.e. esters and salts). Scheme 2 shows two sets of peaks corresponding to the two diastereomeric salts *n* {(+)-$FClICCO_2H$, (−)-strychnine} and *p* {(−)-$FClICCO_2H$, (−)-strychnine}, each consisting of the two ^{35}Cl and ^{37}Cl isotopic species. The isotopic effect on the chemical shift (IECS) in this particular case was found to be ca 8 ppb.

An enantioenriched sample of (+)-CHFClI with 63.3% ee was subsequently obtained by decarboxylation of the strychninium *n* salt with 67% de in triethyleneglycol at 110 °C and 100 mmHg with 30% yield (Scheme 3).[19] Reducing the pressure made it easier to recover the compound in a cold trap. The moderate yield obtained once again can be explained by the low stability of the compound at high temperature. For comparison, Novak and co-workers obtained (±)-**1** from $CHClI_2$ with 24% yield.[9] Such decarboxylation reactions conserve the enantiomeric enrichment and for this reason are already proven to be important in the synthesis of optically active fluorinated anesthetics.[20] This occurs with retention of configuration, as shown by Schurig et al. in the case of desflurane.[12a] This was also shown in the case of CHFClBr.[5a] From this work, it can be seen that even compounds containing iodine efficiently conserve their enantiomeric integrity under decarboxylation. However, the unavailability of a suitable salt enriched in (−)-$FClICO_2H$ prevents access to pure (clean) enantioenriched (−)-**1**. In fact, decarboxylation under the same conditions of the *p* salt having 50% de gave (−)-CHFClI but contaminated with other impurities. Consequently, additional efforts will be made to prepare chemically pure (−)-CHFClI in the future.

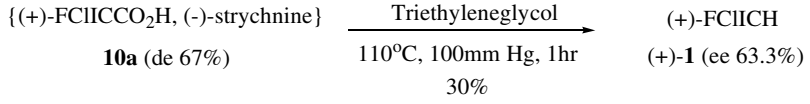
2.3. Enantiomeric excess of (+)-CHFClI

Due to the lack of a suitable functionality, the determination of the ee of such small molecules such as CHFClI is not straightforward. Thus far, the only successful method is enantioselective gas chromatography utilizing chiral stationary phases at cryogenic temperature[21] and the enantioselective recognition by chiral hosts such as nonracemic cryptophanes.[22]

Racemic CHFClI was separated into enantiomers in 13 min on a 40 m × 0.25 mm (id) fused silica capillary



Scheme 2. Reagents and conditions: crystallization of diastereomeric *n* and *p* salts, respectively, {(+)-FClICCO$_2$H, (−)-strychnine} **10a** and {(−)-FClICCO$_2$H, (−)-strychnine} **10b**, in chloroform at room temperature and under stirring. Diastereomeric excesses (de) of **10a** and **10b**, visualized by ^{19}F NMR in CDCl$_3$.



Scheme 3. Synthesis of (+)-chlorofluoroiodomethane (+)-**1** by decarboxylation of strychninium *n* salt **10a**.

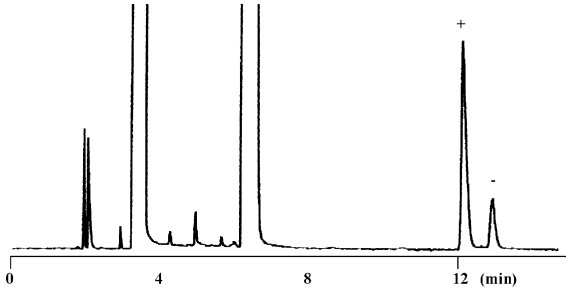


Figure 1. Chiral gas chromatography of (+)-CHFClI sample on a 40 m 2,6-dipentyl-3-butanoyl-γ-CD (bonded) phase at 15 °C and 100 Kpa.

column coated with 0.25–40 m Chirasil-γ-Dex (octakis(3-O-butanoyl-2,6-di-*n*-pentyl)-γ-cyclodextrin linked via an octamethylene spacer to polydimethylsiloxane,[23] at 15 °C and 100 KPa dihydrogen. An ee of 63.3% was determined for (+)-CHFClI (cf. Fig. 1).

2.4. Absolute configuration of CHFClI

The absolute configuration of CHFClI was established using quantum mechanical predictions of specific rotations using a Gaussian 03 program.[24] Three different systems, namely CHFClI, FClBrCCOOH and FClICCOOH, were investigated for this purpose. Since the decarboxylation occurs via retention of configuration,[5a,12a] the absolute configuration of CHFClI can also be established from that of FClICCOOH. Due to the low stability of acid **3**, it was not possible to obtain confident specific rotations of resolved **3**. Since the experimental specific rotation of FClICCOOH is not available, the reliability of the predictions for FClICCOOH can be established via corresponding calculations on FClBrCCOOH by comparing the predicted specific rotation for FClBrCCOOH with its experimental specific rotation.

2.4.1. Specific rotation of (*S*)-CHFClI. Calculations were performed using B3LYP density functional and three different basis sets, namely 3-21G**, MidiX and DGDZVP. In each calculation, the geometry was fully optimized and the specific rotation computed at the optimized geometry. All calculations predicted positive specific rotation for (*S*)-CHFClI. Of these three calculations, the B3LYP/DGDZVP basis set predicted specific rotations are believed to be the more accurate. These specific rotations are 5.8, 6.2, 7.5 and 19.3, respectively, at 589, 577, 546 and 435 nm. Based on these

results, the absolute configuration of CHFClI is suggested as being (*S*)-(+) and (*R*)-(−). The magnitudes of the calculated specific rotations are approximately two times larger than those of the corresponding experimental rotations (see Table 1). This discrepancy in magnitude may partly be attributed to the basis set and/or solvent influence.

Table 1. Experimental specific rotations of (+)-CHFClI (*c* 2.15, cyclohexane) and calculated ones by using DFT and the B3LYP/DGDZVP basis set

λ (nm)	589	577	546	435
$[\alpha]^{26}$ (ee 63.3%)	1.6	1.7	2.0	5.6
$[\alpha]^{26}_{max}$	2.5	2.7	3.1	8.8
Calcd $[\alpha]_{max}$ for (*S*)-enantiomer	5.8	6.2	7.5	19.2

2.4.2. Specific rotation of (*S*)-FClBrCCOOH. Since the acids can exist in both monomeric and dimeric forms in solution, it is necessary to investigate both forms. The conformations of FClBrCCOOH in monomeric and dimeric forms were fully optimized and the specific rotations were calculated at the optimized geometries. The monomeric acid exists in two conformations (see Fig. 2), namely *trans*-FClBrCCOOH and *cis*-FClBrCCOOH, where *trans*/*cis* refers to the F atom being *trans*/*cis* to the OH group. The populations of the *trans* and *cis* conformers obtained from Gibbs energies evaluated at B3LYP/aug-cc-pVDZ are 70% and 30%, respectively. The population weighted specific rotations for the monomeric acid with an (*S*)-configuration obtained at the B3LYP/6-31G* level are: 8.5, 9.0, 10.5 and 21.5, respectively, at 589, 577, 546 and 435 nm, while those obtained at the B3LYP/aug-cc-pVDZ level are 11.9, 12.6, 14.5 and 28.2, respectively, at 589, 577, 546 and 435 nm. The dimeric acid existed in three conformations (see Fig. 2), namely *trans–trans*, *cis–trans* and *cis–cis*, where *trans*/*cis* refers to the F atom being *trans*/*cis* to the OH group in the same monomeric part. The populations of these three conformers obtained from Gibbs energies evaluated at B3LYP/aug-cc-pVDZ are 52%, 28% and 20%, respectively. The population weighted specific rotations obtained at the B3LYP/6-31G* level for the (*S*)-configuration of dimeric acid are: 10.1, 10.7, 12.4 and 24.2, respectively, at 589, 577, 546 and 435 nm while those obtained at the B3LYP/aug-cc-pVDZ level are 13.4, 14.0, 15.9 and 26.1, respectively, at 589, 577, 546 and 435 nm. The specific rotations for the monomeric and dimeric acids are approximately the same at 589 nm. Thus one would expect a specific rotation of around ~+10 at 589 nm for (*S*)-FClBrCCOOH, regardless of the monomer–dimer equilibrium in solution. The absolute configuration of FClBrCCOOH was established by Costante et al.[25] as (*S*)-(+), with an observed maximum specific rotation of +15.5. The absolute configuration of CHFClBr was also established as (*S*)-(+) in the literature.[26] Thus the present calculations on FClBrCCOOH are in agreement with the literature conclusions and support the use of calculations on FClICCOOH to establish the absolute configuration of CHFClI.

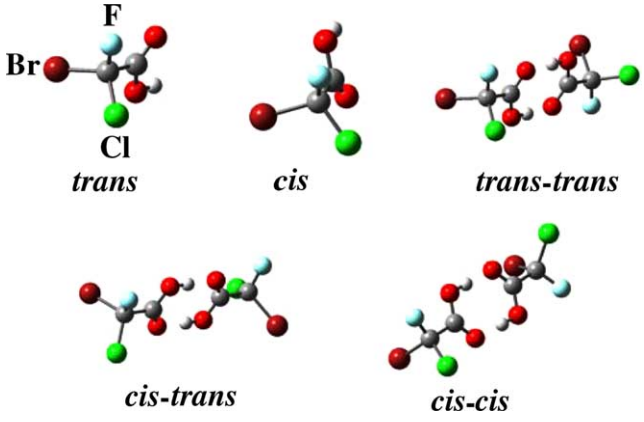


Figure 2. Conformations of (*S*)-FClBrCCOOH in monomeric and dimeric forms.

2.4.3. Specific rotation of (*S*)-FClICCOOH. The conformations for monomeric and dimeric FClICCOOH are same as those for FClBrCCOOH (Fig. 2). The population weighted specific rotations of monomeric (*S*)-FClICCOOH obtained at B3LYP/DGDZVP level are, 28.0, 29.3, 33.2 and 48.4, respectively, at 589, 577, 546 and 435 nm. The population weighted specific rotations of dimeric (*S*)-FClICCOOH obtained at B3LYP/DGDZVP level are, 25.7, 26.5, 28.4 and 16.0, respectively, at 589 nm, 577, 546 and 435 nm. Here again, the specific rotation of the monomer and dimer are approximately the same at 589 nm, hence the specific rotation of (*S*)-FClICCOOH at 589 nm is expected to be around ~+25 and independent of the monomer–dimer equilibrium, as for FClBrCCOOH. The (*S*)-(+)-configuration predicted for FClICCOOH is consistent with (*S*)-(+)-configuration suggested in the above discussion for CHFClI, CHFClBr and FClBrCCOOH.

3. Conclusion

Multigram-scale quantities of racemic $FClICCO_2H$ have been prepared from chlorotrifluoroethene. (+)-CHFClI was then synthesized for the first time from the partially resolved diastereomeric *n* salt {(+)-$FClICCO_2H$, (−)-strychnine} by decarboxylation proceeding with retention of configuration. The enantiomeric excess of (+)-CHFClI was determined by enantioselective gas chromatography and found to be 63.3% ee. The absolute configuration was determined as (*S*)-(+) and (*R*)-(−). The spectroscopic properties of CHFClI are now under investigation to establish its propensity as a favourable probe for a novel parity violation test at the molecular level by ultra-high IR spectroscopy.

4. Experimental

4.1. General

^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker DPX 200 spectrometer (at 200 MHz for ^{1}H,

50.4 MHz for ^{13}C and 188.6 MHz for ^{19}F). Melting or decomposition temperatures were measured using a Perkin–Elmer DSC7 microcalorimeter. Mass spectra were recorded by the Centre de Spectrométrie de Masse, Université de Lyon, France. Optical rotations (in deg cm^2 g^{-1}) were measured in a 1 dm thermostated quartz cell on a Jasco-P1010 polarimeter. Elemental analyses were carried out by the Service Central d'Analyses, CNRS. Enantioselective gas chromatography was carried out with a Carlo Erba instrument (HRGC 5300, Mega Series) equipped with a flame ionization detector operated at 250 °C and a split injector (split ratio: 1:100) operated at 200 °C.

Compounds **6**–**8** in their pure form were prepared according to the literature.[14,15] The procedures for the compounds kept in solution are described herein. Diethyl ether was distilled over sodium. Ethanol was distilled over Mg and I_2.

4.2. (*R*S**)- and (*R*R**)-1,2-dichloro-1,2-difluoro-2-iodo-1-ethoxyethane 7

4.2.1. Compound in solution. A solution of iodine monochloride (53.8 g, 0.33 mol) in 200 mL of dry Et_2O was added dropwise to a stirred solution of **6** (34.27 g, 0.24 mol) in 50 mL of dry Et_2O at −78 °C. After stirring at room temperature for 2 h, the mixture was washed with 10% NaOH and then with water. After drying over Na_2SO_4 and partial evaporation of the solvent, 73 g (99%) of a solution of **7** in Et_2O was obtained as a mixture of (*R*R**)- and (*R*S**)-diastereomers [titrated by ^1H NMR ($CDCl_3$) with the use of CH_2Cl_2 as the internal reference].

4.2.2. Pure compound. A solution of iodine monochloride (28.4 g, 175 mmol) in 65 mL of dry CH_2Cl_2 was added dropwise to a stirred solution of **6** (18 g, 126 mmol) in 50 mL of dry CH_2Cl_2 at −78 °C. After stirring at room temperature for 2 h, the mixture was washed with 10% NaOH and then with water. After drying over Na_2SO_4 and evaporation of the solvent, the remaining liquid was purified by distillation under vacuum (bp 59 °C/5 mmHg) to give 13 g (34%) of **7** as a mixture of (*R*R**)- and (*R*S**)-diastereomers. ^1H NMR ($CDCl_3$) δ 1.38 (t, 3H, CH_3) 4.15 (m, 2H, CH_2). ^{19}F NMR ($CDCl_3$, $CFCl_3$ as internal reference) δ −69.28 (d, $^3J_{FF}$ = 18.2 Hz, CFClOEt), −69.06 (d, $^3J_{FF}$ = 16.4 Hz, CFClOEt), −67.46 (d, $^3J_{FF}$ = 18.2 Hz, CFClI), −62.40 (d, $^3J_{FF}$ = 16.4 Hz, CFClI) (two diastereomers) in agreement with literature data.[15]

4.3. (±)-Ethyl chlorofluoroiodoacetate (±)-8[27]

4.3.1. Compound in solution. The above solution of **7** (73 g, 0.24 mol) in Et_2O was added dropwise with stirring to 45 mL of concentrated sulfuric acid at 0 °C. The resulting mixture was stirred at 10 °C for 4 h and then poured into 100 g of ice and extracted with Et_2O. The organic layer was washed with brine, water, dried over Na_2SO_4 and the solvent partially stripped off to give a solution of 56.7 g (89%) of ester **8** [titrated by ^{19}F NMR ($CDCl_3$) with the use of CF_3CO_2H as the internal reference].

4.3.2. Pure compound. The above **7** (2.2 g, 8.5 mmol) was added dropwise with stirring to 1 mL of concentrated sulfuric acid at 0 °C. The resulting mixture was stirred at 10 °C for 4 h, then poured into 20 g of ice and extracted with Et_2O. The organic layer was washed with water, dried over Na_2SO_4 and the solvent stripped off to give 1.5 g (78%) of ester **8**. ^1H NMR ($CDCl_3$) δ 1.36 (t, $^3J_{HH}$ = 2.6 Hz, 3H, CH_3), 4.36 (q, $^3J_{HH}$ = 2.6 Hz, 2H, CH_2). ^{13}C NMR ($CDCl_3$) δ 13.26 (s, CH_3), 64.19 (s, OCH_2), 63.60 (d, J^1_{CF} = 318.4 Hz, CFClI), 162.16 (d, J^2_{CF} = 26.2 Hz, CO). ^{19}F NMR ($CDCl_3$; $CFCl_3$ as internal reference) δ −66.59. HRCIMS (+): $[M+H]^+$ 266.90850 (calcd for $C_4H_6O_2FICl$ 266.43905).

4.4. (±)-Chlorofluoroiodoacetic acid (±)-3

4.4.1. Compound in solution. The above solution of ester **8** (45.2 g, 0.17 mol) in Et_2O was added dropwise at 0 °C to 45 mL of aqueous 25% NaOH (0.28 mol). This solution was stirred at 0 °C for 40 min and acidified at this temperature by the addition of a solution of 3.5 M H_2SO_4 until acidic. The aqueous phase was then extracted with Et_2O and gave a solution of 40.5 g (100%) of (±)-**3** [titrated by ^{19}F NMR ($CDCl_3$) with the use of CF_3CO_2H as internal reference].

4.4.2. Pure compound. The above ester **8** (5.2 g, 19.5 mmol) was added dropwise at 0 °C to 20 mL of aqueous 10% NaOH (50 mmol). This solution was stirred at 0 °C for 40 min and acidified at this temperature by the addition of a solution of 3.5 M H_2SO_4 until acidic. The aqueous phase was then extracted with Et_2O and the organic layer concentrated to give 1.4 g (30%) of (±)-**3** as a white solid, which was very unstable under normal *P*, *T* conditions and at sunlight, giving a purple liquid (which can be partially purified by drying under vacuum). ^1H NMR ($CDCl_3$) δ 7.84 (OH). ^{13}C NMR ($CDCl_3$) δ 62.25 (d, J^1_{CF} = 317.52 Hz, CFClI), 166.04 (d, J^2_{CF} = 27.16 Hz, CO). ^{19}F NMR ($CDCl_3$; $CFCl_3$ as internal reference) δ −68.03.[15]

4.5. Strychninium chlorofluoroiodoacetate *n* and *p* salts 10a and 10b

An ethereal solution of (±)-**3** (45 g, 189 mmol) was added to a stirring solution of (−)-strychnine (62.7 g, 187.5 mmol) in $CHCl_3$ (200 mL) at 0 °C. After stirring for 2 h at room temperature, the solution was concentrated, washed with methanol and dried under very high vacuum, to yield (*n*,*p*) salts **10a** and **10b** (106.5 g, 99%) as a yellow solid. ^{19}F NMR (C_6D_6, $CFCl_3$ as internal reference): δ 55.72. ^1H NMR (MeOD) δ 1.43–1.51 (1H), 1.68–1.76 (1H), 2.09–2.22 (2H), 2.55–2.63 (1H), 2.69–2.78 (1H), 3.01–3.14 (1H), 3.28–3.54 (1H), 3.77–3.83

(1H), 4.15–4.24 (1H), 4.27–4.43 (1H), 4.50 (1H), 6.39 (1H), 7.15–7.43 (3H), 8.01 (1H). ^{13}C NMR ($CDCl_3$) δ 16.29, 17.72, 25.36, 30.62, 41.02, 42.08, 47.09, 50.25, 51.91, 52.12, 59.02, 60.86, 63.99, 99.43, 116.39, 122.45, 124.87, 128.48, 129.85, 133.30, 134.88, 141.73, 160.82, 168.011, 168.59. Mp (decomp), 122 °C. Anal. Calcd for $C_{23}H_{22}O_4N_2ClFI$: C, 48.23. H, 4.05. Found: C, 48.88; H, 4.34.

4.6. Crystallization of salts 10a and 10b

4.6.1. Experiment 1. A solution of 9.58 g of (±)-strychninium chlorofluoroiodoacetate in 25 mL of $CHCl_3$ was allowed to crystallize at 15 °C for one day without stirring. After filtration, 2.75 g (29%) of {(+)-$FClICCO_2H$, (−)-strychnine} **10a** were obtained as a yellow precipitate, de 67% (determined by ^{19}F NMR in $CDCl_3$ at 200 MHz). From the mother liquors, after evaporation of the solvent, 6.7 g (70%) of {(−)-$FClICCO_2H$, (−)-strychnine} **10a** were obtained, de 5% (determined by ^{19}F NMR in $CDCl_3$ at 200 MHz).

4.6.2. Experiment 2. A solution of 10.36 g of (±)-strychninium chlorofluoroiodoacetate in 25 mL of $CHCl_3$ was allowed to crystallize at room temperature for one day under stirring. After filtration, 2.68 g (28%) of {(+)-$FClICCO_2H$, (−)-strychnine} **10a** were obtained as a yellow precipitate, de 72% (determined by ^{19}F NMR in $CDCl_3$ at 200 MHz). From the mother liquors, after evaporation of the solvent, 6.45 g (62%) of {(−)-$FClICCO_2H$, (−)-strychnine} **10b** were obtained, de 20% (determined by ^{19}F NMR in $CDCl_3$ at 200 MHz).

4.6.3. Experiment 3. A solution of 1 g of (±)-strychninium chlorofluoroiodoacetate in 5 mL of MeOH was allowed to crystallize at room temperature for one day under stirring. After filtration, 0.449 g (45%) of {(+)-$FClICCO_2$ H, (−)-strychnine} **10a** was obtained as a yellow precipitate, de 67% (determined by ^{19}F NMR in $CDCl_3$ at 200 MHz). From the mother liquors, after evaporation of the solvent, 0.378 g (38%) of {(−)-$FClICCO_2H$, (−)-strychnine} **10b** was obtained, de 51% (determined by ^{19}F NMR in $CDCl_3$ at 200 MHz).

4.7. (+)-Chlorofluoroiodomethane (+)-1

The strychninium salt **10a** was thoroughly dried under high vacuum before decarboxylation. Then, 2.4 g (4.2 mmol) of **10a** in triethyleneglycol TEG (9 mL) was decarboxylated, by heating at 110 °C, under 110 mmHg, and under stirring for 1 h. 0.24 g (30%) of (+)-**1** was collected in a liquid nitrogen trap. ^1H NMR ($CDCl_3$) δ 7.62 (d, $^2J_{HF} = 50.2$ Hz). ^{13}C NMR ($CDCl_3$) δ 55.04 (d, $^1J_{CF} = 308.4$ Hz). ^{19}F NMR ($CDCl_3$; $CFCl_3$ as internal reference) δ 86.99 (d, $^2J_{HF} = 50.2$ Hz). ^{19}F NMR ($CDCl_3$; CF_3CO_2H as internal reference) δ −11.03 (d, $^2J_{HF} = 50.3$ Hz) in agreement with literature data.[9] See Table 1 for experimental specific rotation values.

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