Preparation of Chlorofluoroacetic Acid Derivatives for the Analysis of Chiral Alcohols

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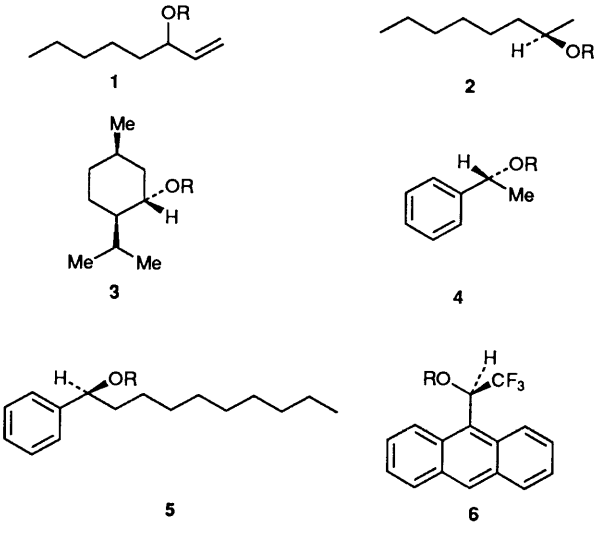
(*R*)- and (*S*)-Chlorofluoroacetic acid (CFA) esters of several chiral secondary alcohols have been prepared and compared with the corresponding esters of Mosher's acid. CFA itself is a readily accessible and optically stable acid which gives the expected diastereoisomeric products with chiral alcohols without epimerization. The resulting diastereoisomers are more volatile than those derived from Mosher's acid, and are well resolved by both GC and HPLC. Both ^{1}H and ^{19}F NMR spectra of CFA esters show characteristic signals in regions rarely overlapped by other signals. Since CFA is a strong organic acid, it reacts with alcohols spontaneously to give esters without any additional catalysis.

Determining the optical purity of biologically active compounds and of the products of any asymmetric synthesis is important in much contemporary research. One approach used frequently for this purpose is the preparation of derivatives of chiral alcohols and amines using 3,3,3-trifluoro-2-methoxy-2-phenylpropionic acid (Mosher's acid, MTPA), which gives rise to diastereoisomers which may be separable by GC or HPLC, or detected by NMR techniques.[1,2] This approach has been widely applied, and has proven extremely useful. However, there are examples where this method failed.[3,4] New agents for the preparation of derivatives are, therefore, of potential interest, and some new examples have been described recently.[5–9] Among these α-aryl-α-fluoroacetates seem to be good candidates.[4] The presence of a fluorine atom at the chiral centre of the acetic acid moiety results in the separation of characteristic peaks in both ^{1}H and ^{19}F NMR spectra. Moreover, the peaks of interest are usually found at chemical shifts which are not overlapped by other signals. The separation of diastereoisomeric signals can be enhanced by additional functional groups attached to the chiral C–F centre.[4] This substitution leads, however, to decreased volatility, making the compounds less suitable for GC analysis. We report here the results of our study of an alternative derivatizing agent, chlorofluoroacetic acid (CFA). CFA is one of the simplest optically active compounds appropriate for this application.[10] We anticipated that diastereoisomeric CFA esters might permit easy GC and/or HPLC separation, as well as NMR spectral differentiation.

CFA is readily accessible,[11] easily resolved[10,12] and the absolute configuration of its enantiomers has already been established.[13] For esterification of CFA we chose the 1,3-dicyclohexylcarbodiimide (DCC) method, which gives high yields even with sterically hindered alcohols.[14,15] In order to obtain a quantitative reaction with respect to the starting alcohol, we used a 3 mol excess of the reagents.[16] Since it is known that various chiral alcohols can be esterified spontaneously by CF_3CO_2H,[17] or by other halogen-containing acetic acids,[18] we have also directly esterified CFA with 1-phenylethanol **4a** using CFA as the solvent. Neither racemization nor kinetic resolution during these esterifications was observed. A variety of secondary alcohols **1a–6a** were converted into CFA esters **1b–6b** (Table 1). The same alcohols were converted into MTPA esters **1c–6c** (Table 2) using commercially available (*R*)- and (*S*)-MTPA chlorides following a standard procedure.[1,2] We have examined the GC and HPLC



a R = H
b R = OCCHClF
c R = OC(CF$_3$)(OMe)(Ph)

behaviour of both CFA and MTPA esters of alcohols **1a–6a**, as well as the ^{1}H and ^{19}F NMR spectra of these compounds. The results are summarised in Table 3, in which we record the chemical shift non-equivalence ($\Delta\delta_{H,F}$) of diastereoisomers in both ^{1}H and ^{19}F NMR spectra and also differences in retention times (Δt_r, GC, HPLC). In general, esters derived from MTPA show larger $\Delta\delta$ values than do CFA esters. This is not unexpected, in view of the increased non-bonded steric and electronic interactions resulting from the presence of an aromatic ring attached to the chiral carbon atom of the MTPA esters.[1,4]

However, the CHFCl proton resonance of diastereoisomeric CFA esters typically appears as a characteristic doublet ($J_{H,F}$ 50 Hz) in a region not often disturbed by other signals ($\delta \cong 6.30$, see Table 1). This, along with the sharpness of these peaks, greatly facilitates the analysis of the chiral alcohols.[4] The same favourable feature is also seen in the ^{19}F NMR spectra ($\delta \cong -68$, $J_{F,H}$ 50 Hz). The chromatographic behaviour of CFA diastereoisomers appears to be superior to that of MTPA esters. This is important because using a chromatographic

Table 1 Spectroscopic data for CFA esters **1b–6b** of alcohols **1a–6a** prepared using racemic CFA

Alcohol	Spectroscopic data for CFA ester
(*R,S*)-**1a**	δ_H 0.88 (t, 3 H, *J* 6, CH_3), 1.61–1.75 (m, 8 H, CH_2), 5.21–5.38 (m, 3 H, C=CH_2, OCH); 5.71–5.88 (m, 1 H, –CH=), 6.27 (d, $J_{H,F}$ 50, 1 H, CHF); δ_F −67.79 (d, $J_{F,H}$ 50, CHF), −67.86 (d, $J_{F,H}$ 50, CHF); ν_{max}/cm^{-1} 3096, 2941, 2874, 1767, 1253, 1107, 964, 822; *m/z* 167, 151, 137, 110, 95, 81, 69 (BP), 41
(*R*)-**2a**	δ_H 0.87 (t, 3 H, *J* 6, CH_3), 1.15–1.63 (m, 13 H, CH_2, CH), 5.00–5.10 (m, 1 H, HCO), 6.24 (d, 1 H, $J_{H,F}$ 50, CHClF); δ_F −67.75 [d, $J_{F,H}$ 50, CHClF (*R,R*)], −67.86 [d, $J_{F,H}$ 50, CHClF (*R,S*)]; ν_{max}/cm^{-1} 2938, 2871, 1765, 1463, 1289, 1191, 1116, 959, 826; *m/z* 157, 139, 112, 83, 70, 57, 41 (BP)
(*S*)-**3a**	δ_H 0.89–0.98 (m, 9 H, 3 × CH_3), 1.20–1.91 (m, 9 H, CH_2, CH), 5.18 (m, 1 H, OCH), 6.24 [d, $J_{H,F}$ 50, CHClF, (*S,R*)]; 6.25 [d, $J_{H,F}$ 50, CHClF, (*S,S*)]; δ_F −67.65 [d, $J_{F,H}$ 50, CHClF, (*S,S*)], −67.68 [d, $J_{F,H}$ 50, CHClF, (*S,R*)]; ν_{max}/cm^{-1} 2966, 2852, 1766, 1289, 1191, 1113, 822; *m/z* 207, 138, 109, 95 (BP), 67, 41
(*R*)-**4a**	δ_H 1.64 (d, 3 H, *J* 6.6, CH_3), 6.06 (q, 1 H, *J* 6.6, HCO), 6.32 [d, $J_{H,F}$ 50, CHClF, (*R,S*)], 6.35 [d, $J_{H,F}$ 50, CHClF, (*R,R*)], 7.42 (m, 5 H, ArH); δ_F −68.48 [d, $J_{F,H}$ 50, CHClF, (*R,S*)], −68.51 [d, $J_{F,H}$ 50, CHClF, (*R,R*)]; ν_{max}/cm^{-1} 3074, 2993, 1780, 1202, 1107, 1063, 953, 822; *m/z* 216, 201, 173, 146, 105 (BP), 77, 51
(*S*)-**5a**	δ_H 0.87 (t, 3 H, *J* 6, CH_3), 1.21–1.99 (m, 14 H, CH_2), 5.76–5.87 (m, 1 H, HCO), 6.26 [d, $J_{H,F}$ 50, CHClF, (*R,R*)], 6.29 [d $J_{H,F}$ 50, CHClF, (*R,S*)]; δ_F −67.52 [d, $J_{F,H}$ 50, CHClF, (*R,R*)], −67.73 [d, $J_{F,H}$ 50, CHClF, (*R,S*)]; ν_{max}/cm^{-1} 3073, 2994, 2866, 1781, 1458, 1282, 1185, 1113, 964, 822; *m/z* 328, 261, 233, 201, 173, 117, 104 (BP), 41
(*R*)-**6a**	δ_H 6.40 (d, 1 H, $J_{H,F}$ 49, CHClF), 6.46 (d, $J_{H,F}$ 49, CHClF), 7.45–8.61 (m, 10 H, ArH), CF_3CH); δ_F −69.13 (d, $J_{F,H}$ 49, CHClF), −69.18 (d, $J_{F,H}$ 49, CHClF), 5.81 (d, 1 H, *J* 7.8, $HCCF_3$); ν_{max}/cm^{-1} 3061, 1785, 1354, 1271, 1192, 1137, 886, 784; *m/z* 370 (BP), 301, 259, 238, 178, 151, 119, 67

Table 2 Spectroscopic data for MTPA esters **1c–6c** of alcohols **1a–6a**

Alcohol	Spectroscopic data for MTPA ester
(*R,S*)-**1a**	δ_H 0.84 (t, *J* 6.4, CH_3), 0.87 (t, *J* 6.4, CH_3), 1.17–1.36 (m, 6 H, CH_2), 1.52–1.73 (m, 2 H, CH_2CO), 3.54, 3.55 (2 × s, 3 H, OCH_3), 5.16–5.38 (m, 2 H, C=CH_2), 7.36–7.49 (m, 5 H, ArH); δ_F 6.13 (s, CF_3); ν_{max}/cm^{-1} 2950, 1758, 1215, 1181, 1123 and 1013; *m/z* 189 (BP), 139, 128, 119, 111, 105, 77, 69
(*R*)-**2a**	δ_H 0.85 [t, *J* 6.6, CH_3, (*R,S*)]; 0.87 [t, *J* 6.6, CH_3(*R,R*)] 1.11–1.37 (m, 11 H, CH_2, CH_3), 1.32 (d, 3 H, *J* 6.4, $CHCH_3$), 1.52–1.72 (m, 2 H, $OCCH_2$), 3.49 [s, 3 H, OCH_3, (*R,R*)]; 3.56 [s, 3 H, OCH_3. (*R,S*)], 5.10–5.19 (m, 1 H, OCH), 7.34–7.54 (m, 5 H, ArH); δ_F 6.14 [s, CF_3, (*R,R*)], 6.61 [s, CF_3, (*R,S*)]; ν_{max}/cm^{-1} 2940, 2868, 1758, 1455, 1383, 1244, 1181, 1122, 1016, 846; *m/z* 189 (BP), 158, 119, 105, 89, 77, 57
(*S*)-**3a**	δ_H 0.81 [d, *J* 6.6, 2 × CH_3, (*S,R*)], 0.88 [d, *J* 6.6, 2 × CH_3, (*S,S*)], 0.94 [d, 3 H, *J* 7, CH_3, (*S,R*)]; 0.96 [d, 3 H, *J* 6.6, CH_3, (*S,S*)]; 1.01–1.81 (m, 9 H, CH, CH_2), 3.54 [s, 3 H, OCH_3, (*S,S*)], 3.56 [s, 3 H, OCH_3, (*S,R*)]; 5.25–5.33 (m, 1 H, OCH), 7.36–7.52 (m, 5 H, ArH); δ_F 6.18 [s, CF_3, (*S,S*)], 6.59 [s, CF_3, (*R,S*)]; ν_{max}/cm^{-1} 3069, 2962, 2882, 1754, 1456, 1382, 1017, 972; *m/z* 189, 158, 139, 127, 105, 83 (BP), 77, 69, 55
(*R*)-**4a**	δ_H 1.57 [d, *J* 6.6, CH_3, (*R,R*)], 1.68 [d, *J* 6.6, CH_3, (*R,S*)], 3.45 [s, 3 H, OCH_3, (*R,S*)], 3.47 [s, 3 H, OCH_3, (*R,R*)], 6.08 [q, *J* 6.6, $CHCH_3$, (*R, S*)], 6.13 [q, *J* 6.6, $CHCH_3$, (*R,R*)], 7.21–7.42 (m, 10 H, ArH); δ_F 6.68 [s, CF_3, (*R,S*)], 6.89 [s, CF_3, (*R,R*)]; ν_{max}/cm^{-1} 3072, 2992, 1760, 1453, 1232, 1182, 1123, 1014, 860; *m/z* 189, 158, 119, 105, 77 (BP)
(*S*)-**5a**	δ_H 0.87 (t, 3 H, *J* 6.8, CH_3), 1.09–1.40 (m, 14 H, CH_2), 1.57–1.99 (m, 2 H, $OCCH_2$), 3.43 [s, 3 H, OCH_3, (*S,S*)], 3.53 [s, 3 H, OCH_3, (*S,R*)], 5.85 [d, *J* 6.6, OCH, (*S,R*)], 5.92 [d, *J* 6.6, OCH, (*S,S*)], 7.27–7.43 (m, 10 H, ArH); δ_F 6.69 [s, CF_3, (*S,R*)], 6.91 [s, CF_3, (*S,S*)]; ν_{max}/cm^{-1} 2934, 2564, 1757, 1455, 1183, 1123, 1014; *m/z* 217, 89, 174, 158, 139, 123, 119, 91 (BP), 77
(*R*)-**6a**	δ_H 3.28 [s, 3 H, OCH_3, (*R,S*)], 3.67 [s, 3 H, OCH_3, (*R,R*)], 7.18–8.60 (m, 10 H, ArH, CF_3CH); δ_F 6.32 [d, $^3J_{F,H}$ 7.7, CF_3CH, (*R,S*)], 6.37 [s, CF_3, (*R,R*)], 6.64 [s, CF_3, (*R,S*)], 6.88 [d, $^3J_{F,H}$ 7.7, $HCCF_3$, (*R,R*)]; ν_{max}/cm^{-1} [a] 3095, 3059, 3009, 2850, 1627, 1528, 1498, 1452, 1398, 1277, 1268, 1239, 1225; *m/z* 259 (BP), 239, 209, 190, 189, 174, 119, 105, 77

[a] IR spectrum was recorded on Bruker ISS FTIR spectrometer (in CCl_4).

method as an analytical tool permits actual separation as well as analysis, and can be more precise than NMR spectroscopy.[19] It is known that halogen-containing acetates are well resolved on non-polar GC phases, where the retention times are related to the atomic weight and the number of halogen atoms in the molecule. Fluorine is exceptional, its introduction resulting in significant shortening of retention times.[20] The relatively low column temperatures required for good resolutions of CFA diastereoisomers can be attributed to (*i*) their lower molecular weight, (*ii*) the presence of fluorine in the molecule, and perhaps also (*iii*) little hydrogen bonding with the liquid phase.[21] Good separations were also obtained using HPLC on silica gel; CFA esters **2a** and **4a** can even be resolved by TLC on silica gel plates, where two fully separated spots of diastereoisomers appeared (none of the MTPA esters studied in this paper showed such a separation).

In order to obtain reliable results in chiral alcohol analysis, the derivative preparation must not favour one alcohol enantiomer over the other, and must be free of racemization. Chiral acetic acids having an enolizable α-hydrogen atom are certainly capable of racemizing. Nevertheless, CFA is sufficiently optically stable to be used for preparing derivatives of chiral secondary alcohols. CFA is the least reactive of the halogenated acetic acids towards nucleophilic substitution.[22] Optically pure CFA does not show any change in specific rotation in aqueous solution and can be converted into its acid chloride or methyl ester and reduced to the corresponding alcohol without any racemization.[10,12] Based on all of these considerations, CFA seems to be an attractive choice for the stereochemical analysis of chiral alcohols.

Experimental

^1H (200 MHz) and ^{19}F (188 MHz) NMR spectra were recorded on a Varian XL-200 spectrometer. Chemical shifts (in $CDCl_3$) are expressed on the δ scale measured from residual $CHCl_3$ (7.25) and internal CF_3CO_2H (0.0) for ^{19}F. *J* Values are given in Hz. Mass spectra were obtained using a Hewlett-Packard 5890 gas chromatograph (column DB-5, 30 m × 0.25 mm i.d.) coupled to an HP 5970 mass selective detector. IR spectra were recorded in the gas phase using a Hewlett-Packard 5890 II gas chromatograph (column: Carbowax, 30 m × 0.25 mm i.d.) coupled to an HP-5965 infrared detector. For GC analyses, a Hewlett-Packard gas chromatograph was used (columns: DB-5, 30 m × 0.25 mm i.d., Carbowax, 30 m × 0.25 mm i.d.) with helium as the carrier gas. HPLC analyses were performed using a Hewlett-Packard HP 1090 apparatus equipped with silica columns [3 × (450 mm × 3 i.d.), Tessek, Czech Republic, silica 5 μm, 3% diethyl ether in hexane, flow rate: 0.4 cm^3 min^{-1}, DAD UV detector (220 nm) controlled by an HP-85B computer]. $[\alpha]_D$ Values are given in units of 10^{-1} deg cm^2 g^{-1}.

For the preparation of diastereoisomeric esters, the following secondary alcohols were purchased and used without further purification: (*R,S*)-oct-1-en-3-ol **1a** (Aldrich 0-528-4), (*R*)-(−)-octan-2-ol **2a** (Aldrich, 14,799-0), (+)-isomenthol **3a** (Aldrich 24,219-5), (*R*)-(+)-1-phenylethanol **4a**, (Aldrich 23,742-6), (*S*)-

Table 3 Chromatographic and spectroscopic differences between diastereoisomers of esters of alcohols **1a–6a** with CFA and MTPA

Ester		GC				Δδ (Hz)		HPLC		
Acid	Alcohol[a]	t_r/min of diast.[b]		T/°C[c]	Δt_r	^{1}H	^{19}F	t_r/min of diast.		R_s[d]
CFA	(*R,S*)-**1a**	32.19	33.08	95	0.89	—	12	23.36	24.16	1.6
	(*R*)-**2a**[e]	30.45 (*R,S*)	32.17 (*R,R*)	95	1.72	—	21	21.03 (*R,S*)	22.29 (*R,R*)	2.6
	(*S*)-**3a**	30.47 (*S,R*)	31.80 (*S,S*)	115	1.33	0.8	62	18.59 (*S, S*)	20.02 (*S,R*)	1.9
	(*R*)-**4a**[f]	62.90 (*R,S*)	64.17 (*R,R*)	115	1.27	6	6	18.32 (*R,R*)	21.57 (*R,S*)	4.6
	(*S*)-**5a**	33.97 (*S,S*)	34.58 (*S,R*)	190	0.61	6	38	16.97 (*S,R*)	17.20 (*S,S*)	0.6
	(*R*)-**6a**[g]	24.88	25.02	200	0.14	12	9		30.66	—
MTPA	(*R,S*)-**1a**	27.51	28.46	155	0.95	2	—	20.99	21.29	0.6
	(*R*)-**2a**	32.32 (*R,S*)	32.86 (*R,R*)	155	0.54	13	88		22.86	—
	(*S*)-**3a**		32.75	170	—	4	86		20.49	—
	(*R*)-**4a**	22.77 (*R,S*)	23.38 (*R*)*R*)	170	0.61	4	39	17.58 (*R,S*)	18.51 (*R,R*)	2.3
	(*S*)-**5a**	31.70 (*S,S*)	32.13 (*S,R*)	225	0.43	20	39		20.34	—
	(*R*)-**6a**	26.71 (*R,R*)	29.84 (*R,S*)	235	3.13	78	50	31.86 (*R,R*)	36.16 (*R,S*)	0.6

[a] See Experimental. [b] Optimal resolution obtained on Carbowax and DB-5 columns for CFA and MPTA esters, respectively. [c] GC column temperature. [d] Resolution, $R_s = 1.18^* (t_r^1 - t_r^2) \Big/ \left(\frac{w^1 + w^2}{2}\right)$ Compounds **6b** and **2c**, **3c** and **5c** were not resolved at all. [e] TLC separation: silica gel plates, 20% diethyl ether in light petroleum, R_f 0.28 (*R,R*), 0.31 (*R,S*). [f] R_f 0.62 (*R,R*), 0.68 (*R,S*). [g] The configuration was not determined.

(−)-1-phenyldecan-1-ol **5a** (Aldrich 33,161-9) and (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol **6a** (Aldrich 21,135-4). Since obtaining both $\Delta\delta$ and Δt_r was the main objective of this paper, the CFA esters were prepared as mixtures of diastereoisomers, using racemic chlorofluoroacetic acid. To identify particular diastereoisomers in a mixture, esters of optically active alcohols with either (*R*)- or (*S*)-chlorofluoroacetic acid were also prepared. The syntheses were accomplished *via* DCC esterification[14,15] using a 3 mol excess of reagents. The reaction was worked up as soon as the starting alcohol had disappeared from the reaction mixture (TLC, typically 0.5–24 h, yield: 91–97%). For GC analyses of CFA and MTPA esters, two different columns were used, giving the best resolution of particular sets of diastereoisomers (see Table 3). The NMR and mass spectra of the resultant esters are given in the Tables 1 and 2, while the spectral and chromatographic comparisons are summarized in Table 3.

Resolution of Chlorofluoroacetic Acid.[12]—To a solution of racemic chlorofluoroacetic acid (16.8 g, 150 mmol) in ethyl acetate (125 cm^3) at 0 °C was added a 0 °C solution of (*S*)-(−)-α-methylbenzylamine (18.2 g, 150 mmol) in ethyl acetate (125 cm^3). After mixing thoroughly, the resulting solution was set aside at 0 °C for 2 h and then at room temperature for 3 h during which time the two diastereoisomeric salts were deposited as a white solid (33 g), m.p. 115–126 °C (decomp.). Fractional recrystallization from acetone afforded the (*S,R*)-diastereoisomeric salt (8.1 g, 35 mmol, 46%) (about five recrystallizations), m.p. 143–145 °C (decomp.); $[\alpha]_D^{25}$ −11.5 (*c* 3.80 in MeOH). Determination of the diastereoisomeric excess of the resolved salts was carried out by GC of the corresponding ethyl chlorofluoroacetate enantiomers on Lipodex A [a sample of the ethyl ester was prepared by mixing (*S*)-(−)-α-methylbenzylammonium salt (10 mg) with Dowex 50W-X8 exchange resin (50 mg) in absolute ethanol (0.5 cm^3); the mixture was set aside for 48 h prior to GC analysis]. In a similar manner, (*R*)-(+)-α-methylbenzylamine afforded the pure (*R,S*)-diastereoisomeric salt, m.p. 143–145 °C (decomp.); $[\alpha]_D^{25}$ 11.2 (*c* 3.80 in MeOH).

The CFA was released from its α-methylbenzylammonium salt by means of acid. Thus, the (*R,S*)-diastereoisomeric salt (0.85 g, 3.64 mmol) was covered by methylene dichloride (2 cm^3) and concentrated hydrochloric acid (0.37 cm^3, 3.74 mmol) was added to it. After being stirred for 1 h at room temp., the solution was dried over magnesium sulfate and then concentrated under reduced pressure. Distillation of the residue afforded (*S*)-chlorofluoroacetic acid (0.36 g, 91%), b.p. 86–94 °C/40 mmHg; δ_H 6.30 (d, $J_{H,F}$ 50, 1 H, CClFH) and 6.88–7.25 (br s, 1 H, CO_2H); δ_F −68.09 (d, $J_{F,H}$ 50).

(R,R)-*Octan-2-yl Chlorofluoroacetate* **2b** (*Prepared in an Excess of CFA*).—(*R*)-Chlorofluoroacetic acid (59 mg, 0.52 mmol), (*R*)-octan-2-ol (13.7 mg, 0.105 mmol) and Drierite (38 mg) were placed in a 1 cm^3 conical vial. The mixture was set aside at room temperature and the reaction mixture was monitored either by GC or TLC. As soon as the starting alcohol had disappeared from the reaction mixture (about 3 days), the reaction mixture was diluted with light petroleum (1 cm^3, containing 5% of diethyl ether), transferred onto a Pasteur pipette silica column, and chromatographed using the same solvent mixture to give the product (22.8 mg, 97%). When the column was eluted with pure diethyl ether (*R*)-chlorofluoroacetic acid (36 mg, 77%) was recovered. The spectral data were identical with those for (*R,R*)-**2b** given in Table 1.

Acknowledgements

This work was supported in part by the Program in Science and Technology Cooperation, U.S. Agency for International Development, under Grant DHR-5600-G-00-1051-00 (L. S.), and by the Czech Grant Agency (L. S., A. S., J. V., Grant 203/93/0102), and in part by a grant to J. M. (GM 48088) from the National Institutes of Health.

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Paper 4/02810D
Received 12*th May* 1994
Accepted 2*nd August* 1994