Reactions involving hexafluoropropylene oxide: novel ring opening reactions and resolution of a racemic mixture of a bromofluoro ester, ultrasound mediated Reformatsky reactions and stereoselectivity

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A novel ring opening reaction of hexafluoropropylene oxide (HFPO) 1 with lithium bromide/zinc bromide and subsequent reaction of the resulting acyl fluoride with primary and secondary alcohols gave bromofluoro esters 2, 3, 4 and 7. Reaction of the corresponding acyl fluoride with water leads to acid 9 which on treatment with dehydroabietylamine 10 gave the diastereomeric salt 11. Resolution of 11 and subsequent hydrolysis and esterification reactions led to enantiomerically pure ester 12. Reformatsky reactions with 2 were studied which gave the alcohols 6 and 5. A Reformatsky reaction of 12 with formaldehyde afforded an alcohol 13 which is indicated by NMR spectroscopy in the presence of a chemical shift reagent to have proceeded stereoselectively.

Introduction

There is much interest in the preparation of fluorinated compounds as potential intermediates for the pharmaceutical and agricultural chemical industries. To date there are relatively few reports of the preparation and reactions of chiral fluoro compounds and their use in synthesis. We now report a new method for the formation, resolution and Reformatsky reactions of some bromopolyfluoro esters alone and in the presence of a chiral auxiliary which appear to take place with a high level of stereoselectivity. This study addressed two problems: firstly, the development of a reliable method for the preparation of the desired bromo esters from readily available starting materials, and secondly, to see if the Reformatsky reaction of chiral bromofluoro esters proceeds stereoselectively or with racemisation.

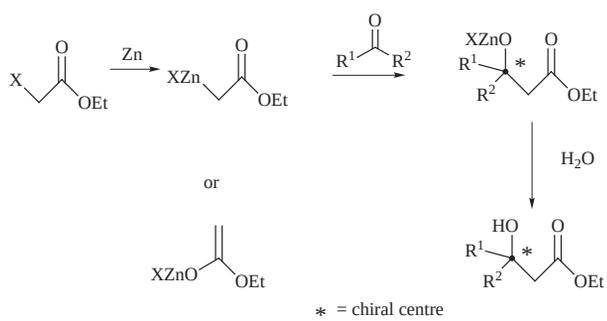
Fluorocarbon epoxides are important intermediates in organofluorine chemistry, especially hexafluoropropylene oxide **1** (HFPO), which is the most versatile representative.[1–3] There have been some reports[4,5] of the use of **1** in the synthesis of bromofluoro esters but the yields are either poor or the reaction involves the use of pressure tubes. Thus, an improvement to the existing methods or a new method was required which gave consistently good yields under mild conditions. Having developed such a method we then needed to address the problem of resolution of the resulting esters or acids derived therefrom.

The Reformatsky reaction, in its classical form, consists of the zinc induced formation of β-hydroxy alkanoates from ethyl haloacetates and aldehydes or ketones. It was first described a century ago by Reformatsky[6] and is still one of the best methods available for preparing β-hydroxy acids from the corresponding esters, as shown in Scheme 1.

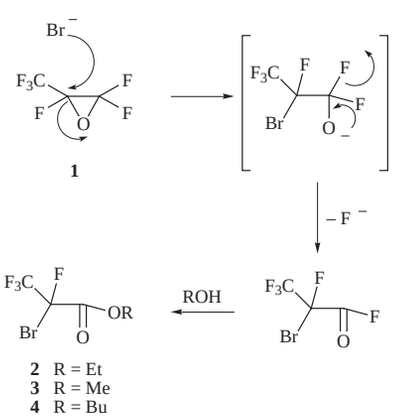
The structure of the Reformatsky reagent has been the subject of considerable debate as to whether it largely exists as a carbon or oxygen metallated reagent or whether it is monomeric or dimeric in solution. The structure clearly has a large bearing on its reactivity and, importantly, from our study, stereoselectivity. These issues are discussed below. The role of the activation of the zinc and in particular the use of ultrasound in such reactions[7] was also part of our study.

Results and discussion

Reaction of bromide ion as nucleophile for the ring opening of hexafluoropropylene oxide and subsequent reaction of the first formed acyl fluoride in an alcoholic medium has been shown by Tarrant[5] and by Knunyants[4] to yield bromofluoro esters. The synthesis of the bromofluoro esters from hexafluoropropylene oxide **1** and an appropriate source of bromide ion is shown in Scheme 2. The ring opening reaction proceeds at the central



Scheme 1



Scheme 2

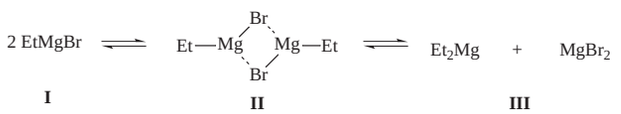
carbon atom of the epoxide **1** leading to the acyl fluoride, which was then transformed into the corresponding esters by the work up in an alcoholic medium; work up using water leads to the corresponding acid **9**.

In order to obtain reference samples and to gain experience of the reaction we first tried to repeat the reported literature methods. Knunyants[4] and co-workers reported that heating of

1 at 140 °C in a sealed glass tube with 45% aqueous hydrobromic acid as the bromide ion source afforded **2** in moderate yield. Instead of using a sealed glass tube we repeated the reaction in a metal autoclave with a Teflon liner. The Teflon liner should have avoided a reaction between the hydrobromic acid and the metallic autoclave material: however, only green coloured inorganic salts were isolated, generated from a reaction between acidic vapours and the lid of the metal autoclave.

A second method due to Tarrant,[5] which involved the reaction of **1** with ethylmagnesium bromide, gave the bromo ester **2** in 16% yield and not in the 61% as claimed in the literature.[5] We were unable to increase the yield of **1** by any of a number of variations of reaction conditions we tried.

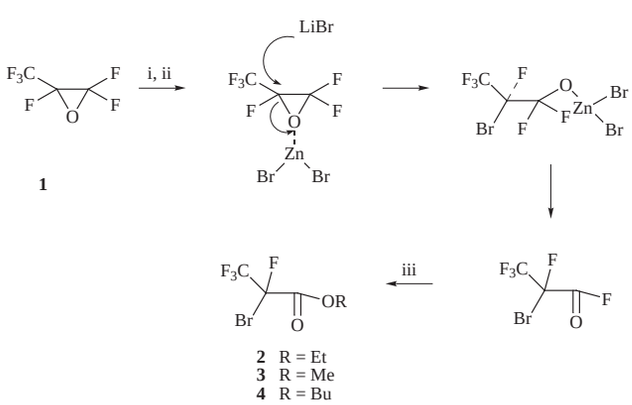
In a similar reaction, using $MgBr_2 \cdot OEt_2$ in a THF solution[8] as the bromide ion source, we were able to increase the yield of **2** to 33%. This would imply that in the Grignard reaction the ring opening is in fact solely due to the magnesium bromide present. In the case of the Grignard reagent the amount of magnesium bromide present in the solution is dependent on the solvent system. In a solution of THF, for example, the Schlenk equilibrium[8] lies predominantly in favour of the aggregate **II** (see Scheme 3), whereas in a diethyl ether solution, the original



Scheme 3

form **I** of the Grignard reagent is dominant, and form **III** is the major component in triethylamine as solvent.

Since these methods gave, at least in our hands, only relatively poor yields of the desired ester we sought to find an alternative route to ester **2**. In the light of the reaction with $MgBr_2 \cdot OEt_2$ we felt that a more reactive source of bromide ion or some activation of the epoxide was needed. We first tried lithium bromide alone as the soluble bromide source without success. Thus, we decided that a mixture of lithium bromide and zinc bromide might be sufficiently active for the ring opening reaction of epoxide **1**. This proved to be the most efficient method for the synthesis of bromofluoro esters. The first formed acyl fluoride (Scheme 4) was converted to the corresponding ester by the



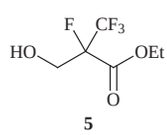
Scheme 4 *Reagents*: i, LiBr; ii, $ZnBr_2$; iii, ROH

addition of the appropriate alcohol. Thus, the addition of ethanol afforded the ester **2** in 61% yield. Clearly the increase in yield and decrease in reaction times are due to the addition of the zinc bromide. In the same way the corresponding methyl and butyl esters **3** and **4** were synthesized. The successful synthesis of a variety of esters by this novel approach shows its general applicability. Indeed, this methodology could be applicable to a whole range of fluorinated epoxides, work beyond the scope of the present study. Recently, a different route to compounds containing the CF_3CF group has been reported.[9]

We wished to see if it was possible to obtain the corresponding and potentially very useful iodo ester by the same route. Unfortunately, the ring opening reaction of hexafluoropropylene oxide **1** with lithium iodide and $BF_3 \cdot OEt_2$ or zinc iodide as Lewis acids did not lead to the corresponding ethyl 2-iodotetrafluoropropionate. It was found during attempts to isolate the esters that thermal decomposition, even at moderate temperatures, was a rapid reaction giving copious quantities of iodine. This is in agreement with previous observations.[5] Having now succeeded in developing a reliable route to the desired bromo esters we were able to investigate their abilities to enter into the Reformatsky reaction.

The Reformatsky reactions were carried out under standard conditions and under the influence of ultrasound, firstly to activate the zinc metal and secondly to accelerate the process, possibly inducing stereoselectivity since it has been reported that sonication appeared to diminish racemisation.[10]

We first investigated the reaction of ester **2** with formaldehyde since the product of the reaction should be a mixture of enantiomers only whereas any other aldehyde would yield a diastereomeric mixture and make analysis of the reaction much more difficult. Thus, formaldehyde gas in a stream of nitrogen was passed into a solution of **2** in THF containing zinc powder. In the first experiment the mixture was reacted under classical Reformatsky reaction conditions of heating and stirring at 60 °C until reaction started and then stirring at 40 °C for 1 h. In the second experiment the mixture was sonicated at room temperature for 1 h; an exotherm was observed, in this case, after a few minutes of irradiation. The reactions afforded an oil in each case in yields of 37 and 54%, respectively. The structure of the product was readily confirmed by physical methods (see Experimental section for details of this and other structural assignments) to be a racemic mixture of ethyl 2-fluoro-2-trifluoromethyl-3-hydroxypropanoate **5**. Thus, we were able to



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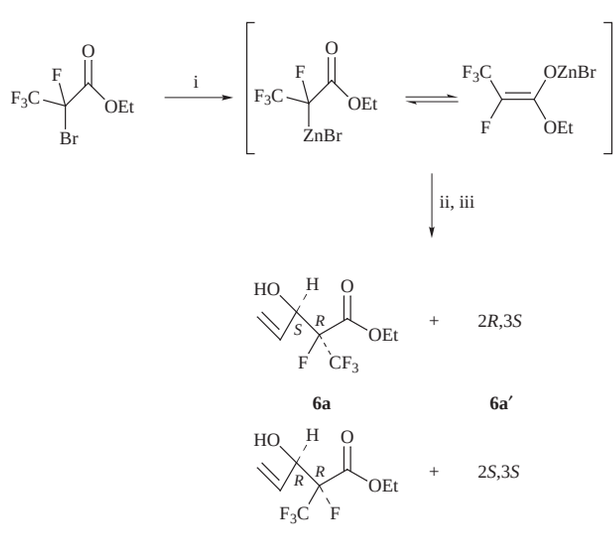
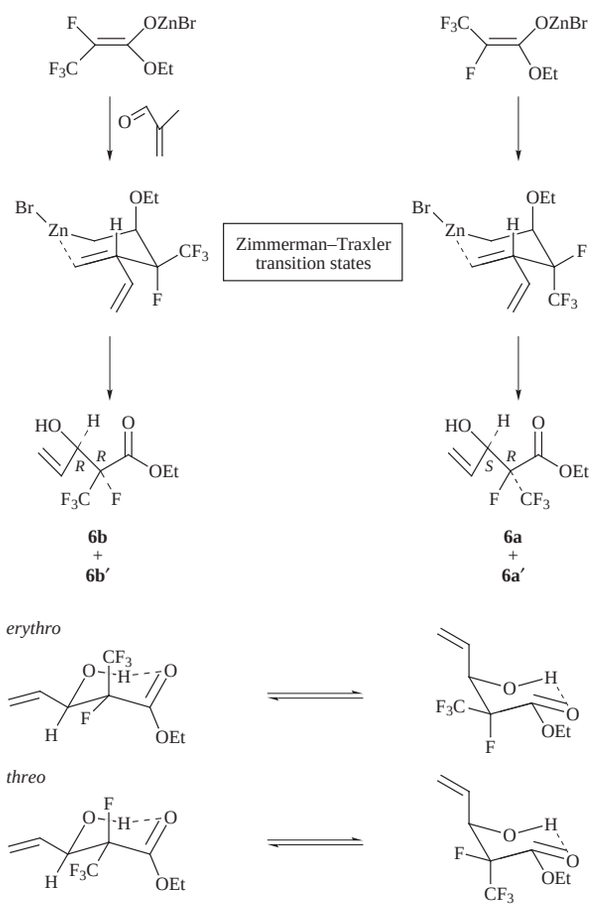
establish that our bromo ester was able to participate in the Reformatsky reaction.

We next studied the reaction of ethyl 2-bromotetrafluoropropanoate **2** and acrolein under sonication conditions (Scheme 5). The product, ethyl 2-fluoro-3-hydroxy-2-trifluoromethylpent-4-enoate **6**, was obtained as a diastereomeric mixture of **6a**/**6a**′ and **6b**/**6b**′ in the ratio of 2 : 3.



Scheme 5 *Reagents*: i, Zn/ultrasound; ii, acrolein; iii, 2% HCl

The assignment of the *relative* configuration of the diastereoisomers obtained from similar aldol forming reactions has been discussed.[11] Both correlations between *anti* and *gauche* H–H couplings and the ^{13}C chemical shifts in *erythro* and *threo* isomers have been used in the prediction of structure. In the case of proton coupling the argument is rehearsed that there is hydrogen bonding between the hydroxy group and the carbonyl group holding the molecule in a chair-like conformation, as shown in Scheme 6.



Scheme 6

This has the effect of placing the protons on C2 and C3 in the *gauche* or *anti* arrangements; such arrangements have different coupling constants, which enables structural assignments to be made. Heathcock has also reported that it is possible to assign *erythro* and *threo* configurations of appropriate aldols using ^{13}C chemical shifts; generally he reported that the *erythro* isomers showed an upfield shift for methine and *C*OH carbon atoms. It seemed to us not an unreasonable assumption that the *gauche* and *anti* H–F couplings can be used in the same way. As shown in the ^{19}F NMR spectrum of ethyl 2-fluoro-3-hydroxy-2-trifluoromethylpent-4-enoate **6** (see Fig. 1) the two diastereoisomers are clearly distinguishable by the different chemical shifts and coupling constants: the CF_3 groups of the two diastereoisomers appear as two separated doublets with almost the same values for the $^3J_{FF}$ couplings (*ca.* 7 Hz). The CF group of the (2*R*,3*R*)-diastereoisomer **6b** [and the CF group of its corresponding (2*S*,3*S*)-enantiomer **6b**′] appears as a doublet of quartets with 21.6 Hz for the $^3J_{HF}$ *gauche* coupling and 7.6 Hz for the $^3J_{FF}$ coupling. The CF group of the (2*S*,3*R*)-diastereoisomer **6a** [and the (2*R*,3*S*)-diastereoisomer **6a**] appears at a chemical shift of −189.3 ppm as another doublet of quartets, but with a bigger $^3J_{HF}$ coupling constant of 22.9 Hz for the *anti* relationship of the hydrogen and the fluorine atoms. Although the coupling constant differences are small they are sufficiently large to be of value. We therefore make tentative assignments of structure for the diastereoisomers **6a**,**a**′,**b**,**b**′ as above.

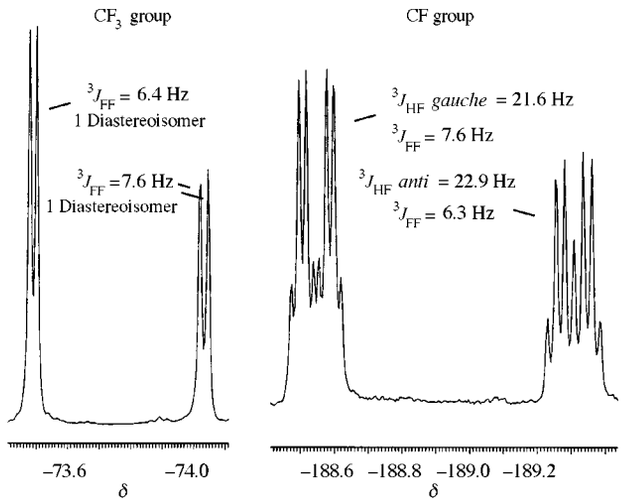
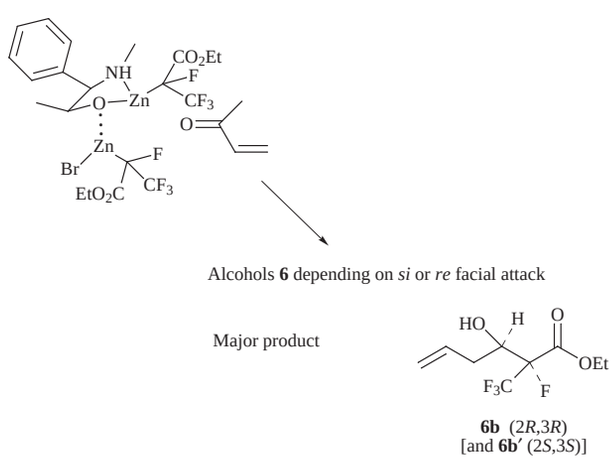


Fig. 1 ^{19}F NMR Spectrum of the two diastereoisomers of ethyl 2-fluoro-3-hydroxy-2-trifluoromethylpent-4-enoate **6**

Pedrosa[12] has reported the synthesis of chiral α,α-difluoro-β-hydroxy esters *via* an enantioselective Reformatsky reaction. The addition of the Reformatsky reagent, generated from ethyl bromo-2,2-difluoroacetate, to aldehydes in the presence of chiral alcohols such as (1*S*,2*R*)-*N*-methylephedrine yielded the β-hydroxy esters with good enantiomeric excess (ee). The enantiomeric excesses were good for aromatic aldehydes and modest for aliphatic ones. We repeated the Reformatsky reaction with ethyl 2-bromotetrafluoropropanoate **2** and acrolein in the presence of (1*S*,2*R*)-*N*-methylephedrine to investigate whether the addition of the chiral auxiliary would lead to a higher diastereomeric excess (de) than the diastereomeric excess of 20% obtained for the uncatalysed reaction. Apart from the addition of the chiral amino alcohol, the reaction was run under the same conditions (4 h sonication). The diastereomeric excess (de) was determined by integration of the signals in both ^1H and ^{19}F NMR spectra. The assignment of the relative configuration at C2 and C3 was possible due to the different values for the $^3J_{HF}$ *gauche* and *anti* coupling constants. The de for the Reformatsky reaction in the presence of (1*S*,2*R*)-*N*-methylephedrine was calculated to be 80% in favour of the diastereoisomers **6b** and **6b**′. The asymmetric induction of this aldehyde with the less crowded face is shown in Scheme 7.

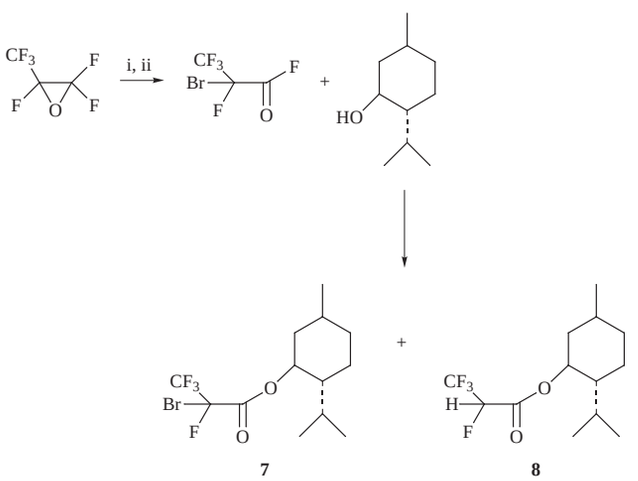


Scheme 7

The structure of the Reformatsky reagent has for some time been the subject of much debate, with the choice of either the traditional *O*-enolates or the *C*-metallated species. Recent studies have shown that the latter, particularly with fluoro derivatives, is the more likely structure. The earliest study by Orsini,[13] subsequently updated,[14] indicated by ^{13}C NMR

spectroscopy that the structure of the reagent in solution is *C*-metallated. This was further substantiated by Dekker *et al.*[15] who were able to crystallise the reagent and show by X-ray analysis that in the solid state the reagent was an eight-membered ring dimer with *C*-metallation and coordination between the zinc atom of one molecule with the carbonyl oxygen of the second molecule. Perhaps more relevant to our studies is the work of Burton and Easdon[16] who have shown, in an elegant study using ^{13}C NMR spectroscopy to compare the spectra of the zinc reagent and the corresponding trimethylsilyl reagent from ethyl bromodifluoroacetate, that the former is completely in the *C*-metallated form, whereas the silyl derivative is a mixture of the *C*- and *O*-silylated species. These three groups thus conclude that reactions of the Reformatsky reagent should be treated from a mechanistic point of view as *C*-metallated species and that reactions with carbonyl compounds should be considered in terms of either the Cram or Felkin–Anh models.

Thus, although it is possible to readily explain the formation of the products we obtained in terms of the traditional Zimmermann–Traxler transition state argument (Scheme 6), we feel in the light of the convincing arguments for the Reformatsky reagent to be largely a *C*-metallated species that we should apply the Cram or Felkin–Anh approach to our results. Thus, we can readily see (Scheme 7) that the relatively low diastereo-



Scheme 8 *Reagents*: i, LiBr; ii, $ZnBr_2$

meric excess we see in the reaction in the absence of the ephedrine derivative can be accounted for by the relatively small steric demand of the vinyl group, so that the degree of attack at either the *re* or *si* faces is comparable. However, in the case of the ephedrine complexed reagent there is now considerable steric constraint and interaction with the vinyl group now comes into play, leading to the observed stereoselectivity (Scheme 7).

These results now lead to an intriguing possibility, *i.e.* if the reaction is carbanionic in character and if we were able to obtain the Reformatsky reagent from a chiral bromofluoro ester, will the anion have sufficient lifetime to allow us to trap it before it inverts or adopts a configuration which would lead to racemisation? There is some evidence that in the anion, like fluorinated radicals, there is some degree of pyramidal character due to interaction of the fluorine lone pairs with the negative charge. Molecular orbital calculations[17] suggest that this hypothesis has a degree of validity. If these ideas are correct then reaction of either of the enantiomers of **2** with formaldehyde in a reaction similar to that described above should lead to a single chiral product.

Thus, we investigated methods for the resolution of **2**. The first attempt we made was to react **2** with enantiomerically pure (*S*)-(−)-1-phenylethylamine; the reaction proceeded

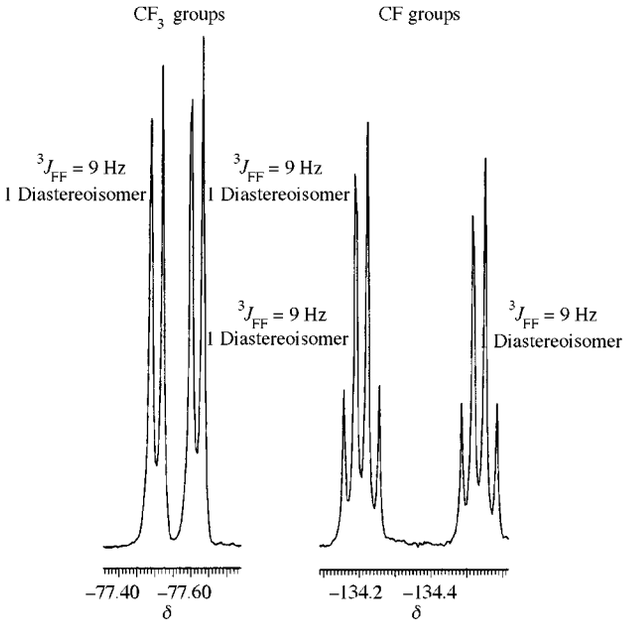


Fig. 2 ^{19}F NMR spectrum of menthyl 2-bromotetrafluoropropanoate

smoothly to produce a mixture of the expected amides, and the two diastereoisomers could clearly be distinguished by NMR spectroscopy. Unfortunately we were unable to separate the isomers, either by column chromatography or by repeated crystallisation. We next tried resolution of the acids *via* the formation of esters of chiral alcohols. When we reacted the acid **2** with (1*R*,2*S*,5*R*)-(−)-menthol as described above for the formation of the ethyl ester, we obtained a mixture of unreacted menthol (30%), the desired mixture of diastereoisomers of menthyl 2-bromotetrafluoropropanoate **7** (62%) and, slightly surprisingly, menthyl 2,3,3,3-tetrafluoropropanoate **8** (8%) (Scheme 8).

The desired menthyl esters were readily separated from the mixture by column chromatography, but again we were unable, despite using a variety of conditions, to separate the diastereoisomers. The ^{19}F NMR spectrum of the purified menthyl ester **7** clearly showed two sets of diastereoisomers with two doublets for the CF_3 groups at −77.5 and −77.7 ppm and two quartets for the CF groups at −134.2 and 134.5 ppm, as shown in Fig. 2. The use of dehydroabietylamine **10** has been reported to be successful in the resolution of a racemic mixture of a phenoxyacetic acid[18] and also in the resolution of 2-(2,2,2-trifluoroethoxy)-2,2-difluoroacetic acid, a precursor in the preparation of the enantiomers of the anaesthetic desfluorane.[19] Pure dehydroabiethylamine is not commercially available and had to be purified from its acetate salt, which is obtained from so-called technical dehydroabiethylamine. The pure amine **10** was reacted with racemic 2-bromotetrafluoropropionic acid *rac*-**9**, itself obtained from reaction of the acyl fluoride obtained by ring opening of **1** with lithium bromide and zinc bromide with water (Scheme 9).

This reaction afforded the salt **11** which was characterised by optical rotation measurements and, more importantly, by X-ray analysis (see Fig. 3). It is known that the amine has the (*R*)-configuration and it was thus possible to deduce that the bromo acid was in the (*S*)-configuration. The amine salt was readily converted to the sodium salt by reaction with sodium hydrogen carbonate, and this salt was finally converted to the desired ethyl (*S*)-2-bromopropanoate **12** by standard esterification. The ester had an optical rotation of −3.5.

The Reformatsky reaction with the resolved ethyl (*S*)-2-bromotetrafluoropropanoate **12** and formaldehyde was carried out as above for the racemic ester to yield an alcohol **13** in 56% yield and with an optical rotation of −0.03 (Scheme 10).

Table 1 ^{1}H NMR data for **5** and **13** with Eu(hfphmc)$_3$ shift reagent[a]

Proton	δ_H (pattern, J/Hz)	
	5	**13**
Ester methylene	4.7 (br s)	4.57 (q, $^3J_{HH}$ 7)
Alcohol methylene Ha	5.3 (br m)	4.86 (dd, $^2J_{HH}$ 15.8, $^3J_{HF_{anti}}$ 28)
Alcohol methylene Hb	5.3 (br m)	4.73 (dd, $^2J_{HH}$ 15.8, $^3J_{HF_{gauche}}$ 29)
Methyl	1.5 (br)	1.42 (t, $^3J_{HH}$ 7)

[a] With 72 mg of shift reagent.

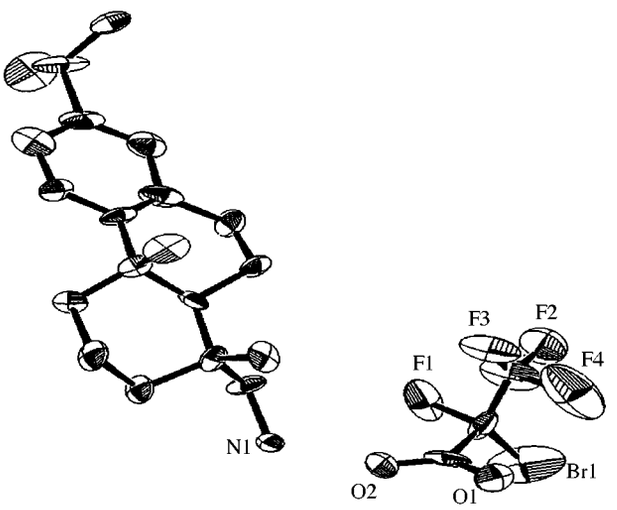
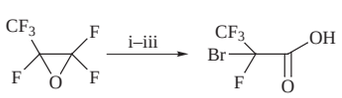
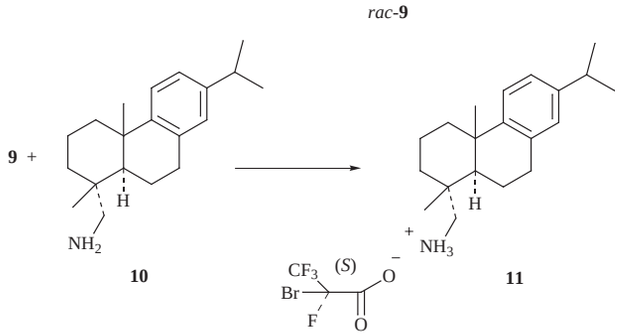


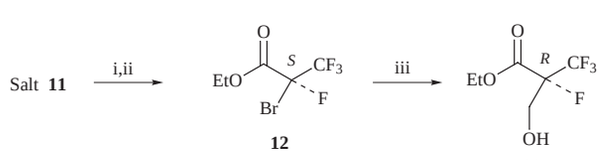
Fig. 3 X-Ray structure of **11**



rac-**9**



Scheme 9 *Reagents*: i, LiBr; ii, $ZnBr_2$; iii, H_2O



Scheme 10 *Reagents*: i, $NaHCO_3$; ii, EtOH–H_2SO_4; iii, Zn, CH_2O

The ^{1}H NMR spectrum of **13** in the presence of Eu(hfphmc)$_3$ was most informative when compared to that of the racemic mixture. The data, shown in Table 1, clearly shows patterns, especially for the CH_2OH group, which indicate that **13** is largely a single isomer, leading to the conclusion that the reaction has proceeded with some degree of stereoselectivity. At present we have been unable to obtain a suitable crystalline derivative of **13** for X-ray analysis to confirm if there has been total retention or inversion of configuration in the reaction. This and further results of experiments with added chiral auxiliaries and other aldehydes will be reported in due course.

Experimental

The ^{1}H NMR (300 MHz) and the ^{13}C NMR spectra (75 MHz) were measured on a Bruker AC 300 NMR spectrometer unless stated otherwise. The ^{1}H NMR spectra (400 MHz) were measured on a Bruker AMX 400 NMR spectrometer. The ^{19}F NMR spectra were carried out either on a JEOL NMR spectrometer, type FX 90 Q (84.26 MHz), or on a Bruker AC 300 NMR spectrometer (282.4 MHz); tetramethylsilane and fluorotrichloromethane were used as internal references. For the characterization of the signals the following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sext = sextet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, quin = pseudo quintet *etc.* *J* Values are given in Hz. In the case of diastereoisomeric mixtures some peaks are common to both sets of isomers. The mass spectra (CI-MS/EI-MS) were measured on a VG-Prospec-triple focusing mass spectrometer. For GC–MS analysis, a Carlo Erba 8000 series GC was used with a 50 m BPX 4 column (helium carrier gas, 70 eV, electron impact). The optical rotations were measured on a Perkin-Elmer 241 polarimeter (Na line), at 25 °C. For medium-pressure column chromatography, silica gel 60 (mesh 230–400) from Merck with a particle size of 60 Å, grade 9385 was used. Thin layer chromatography was performed on TLC plastic sheet silica gel 60 F_{254}, pre-coated with a layer thickness of 0.2 mm from Merck, Art. 5735. Gas chromatographic analysis was carried out using a Philips PYE Unicam Series 304 chromatograph with a 50 m CD-SIL-CB 19 column. The data were registered by a JCL 600 chromatography data system. High performance liquid chromatography (HPLC) was carried out using a Gilson HPLC apparatus (Pump Module 303, UV Det Model 111, Pulse Damper Model 802 C) with a UV_{254} detector and a Techspere 5 silica column (25 cm × 4.6 mm i.d.). The sonication reactions were carried out in a Camlab (Transonic T 460/H, highfield frequency: 35 kHz) ultrasound bath. Ether refers to diethyl ether.

Synthesis of ethyl 2-bromotetrafluoropropanoate 2

With ethylmagnesium bromide. To magnesium turnings (3.04 g, 0.125 mol) and dried tetrahydrofuran (12 cm^3), ethyl bromide (0.5 cm^3, 6.6 mmol) was added until the initiation of the Grignard reaction was visible. The remaining ethyl bromide (8.9 cm^3, 0.12 mol) in tetrahydrofuran (30 cm^3) was added dropwise over a period of 30 min. The Grignard reagent was used without further purification in the synthesis of **2**. Ethylmagnesium bromide (0.125 ml in tetrahydrofuran) in a flask equipped with an inner thermometer, a Drikold condenser and a gas inlet tube was cooled to 0 °C. Compound **1** (20.7 g, 0.125 mol) was bubbled through the solution during a period of 1.5 h. Tetrahydrofuran (70 cm^3) was added to the reaction mixture to reduce the viscosity of the medium. After stirring overnight at room temperature the solution was cooled to −10 °C and ethanol (12.5 cm^3) was added. Evaporation of the solvents followed by distillation afforded **2** (5 g, 16%), bp 119–122 °C (lit.,[4] 122–123 °C); δ_F([$^2H_6$]acetone, 282.4 MHz) −77.8 (s, CF_3), −135.2 (s; CFBr); δ_H([$^2H_6$]acetone) 4.5 (q, $^3J_{HH}$ 7.5, 2H; OCH_2), 1.39 (t, $^3J_{HH}$ 7.5, 3H; CH_3); δ_C([$^2H_6$]acetone) 161.2 (d, $^2J_{CF}$ 34.8; COF), 120.4 (qd, $^1J_{CF}$ 278.9, $^2J_{CF}$ 34.8; CF$_3$), 89.2 (dq, $^1J_{CF}$ 278.8, $^2J_{CF}$ 34.8; CFBr), 65.3 (s; OCH$_2$), 13.5 (s; CH$_3$); EI-MS: *m*/*z* 253/251 (M^+, $C_5H_5BrF_4O_2^+$, 2 Br isotopes, 3%), 227/225 ($M^+ - CO$, 2 Br isotopes, 3%), 209/207 ($M^+ - CO_2$, 2 Br isotopes, 45%), 181/179 ($[M + H]^+ - C_3H_5O_2$ 2 Br isotopes, 100%), 162/160 ($C_2H_1F_3Br^+$, 2 Br isotopes, 83%), 109 ($C_4H_5FO_2^+$, 87%), 69 (CF_3^+, 97%), 44 (CO_2^+, 92%).

With MgBr·OEt$_2$ in THF. To magnesium turnings (3.47 g, 0.144 mol) and ether (300 cm^3) in a flask equipped with a nitrogen inlet, a water condenser with drying tube and a septum, 1,2-dibromoethane (10.3 cm^3, 0.123 mol) was added over a period of 30 min. Stirring for 1 h led to a two phase system, with $MgBr_2$·OEt_2 as the lower layer. The ether complex was

immiscible in the excess of ether solution and its amount was estimated by transferring into a flask of known weight.

To $MgBr{\cdot}OEt_2$ (12.91 g, 0.05 mol) in a flask equipped with a gas inlet tube, a Drikold condenser, a septum and an inner thermometer at a temperature of 0 °C (ice water bath), tetrahydrofuran (100 cm^3) was added and **1** (8.4 g, 0.05 mol) was condensed into the mixture over a period of 45 min. The white salt which had been formed from the magnesium complex upon addition of tetrahydrofuran disappeared gradually with the addition of the epoxide to give a yellow solution. After stirring overnight at room temperature the mixture was cooled to −10 °C and ethanol (5.27 cm^3, 0.09 mol) was added. The solution was allowed to stir for 2 h at room temperature and was then acidified with 5% aqueous hydrochloric acid. The organic layer was separated and the aqueous layer was extracted with ether (2 × 50 cm^3). The organic layers were combined, dried (Na_2SO_4) and evaporated. The bromo ester was purified by distillation to give **2** (4.2 g, 32.8%, bp 118–119 °C).

With lithium bromide/zinc bromide. Compound **1** (8.3 g, 0.05 mol) was bubbled through a solution of lithium bromide (4.35 g, 0.05 mol) and zinc bromide (2.25 g, 0.01 mol) in tetrahydrofuran (75 cm^3) in a flask fitted with a Drikold condenser, a gas inlet tube, a nitrogen inlet and an inner thermometer and cooled to −78 °C, over a period of 1 h. The reaction mixture was allowed to stir at room temperature for 20 h. The solution was then cooled to −10 °C and absolute ethanol (6 cm^3) was added. Stirring at room temperature was continued for a further 48 h. The reaction was quenched by the addition of 10% aqueous hydrochloric acid (40 cm^3). The resulting layers were separated and the aqueous layer was extracted with ether (3 × 50 cm^3). The organic layers were combined, dried ($MgSO_4$) and the solvents were distilled off *via* a K-piece at normal pressure. Purification was carried out by fractional distillation (20 mmHg, 37–40 °C) to give **2** (7.4 g, 61%).

Synthesis of methyl 2-bromotetrafluoropropanoate 3

Compound **1** (40 g, 0.24 mol) was condensed over a period of 30 min into a solution of lithium bromide (22 g, 0.25 mol) and zinc bromide (11.25 g, 0.05 mol) in tetrahydrofuran (300 cm^3) in a flask fitted with a Drikold condenser, an inner thermometer, a gas inlet tube and a nitrogen inlet and cooled to −78 °C. The reaction mixture was allowed to warm to room temperature and stirring was continued for 15 h. The solution was then cooled to −10 °C and absolute methanol (30 cm^3) was added dropwise over a period of 30 min. After stirring at room temperature for 10 h the reaction mixture was quenched with 10% aqueous hydrochloric acid (50 cm^3). The organic layer was separated and the aqueous layer was extracted with ether (3 × 40 cm^3). The organic layers were combined and dried ($MgSO_4$). Ether and tetrahydrofuran were distilled off at normal pressure with a K-piece. Purification was carried out *via* fractional distillation (60 mmHg, 40 °C) to give **3** (27.6 g, 46%) as a single component by both GC and HPLC; δ_F(282.4 MHz, $CDCl_3$) −77.9 (d, $^3J_{FF}$ 10.2; CF_3), −135.2 (q, $^3J_{FF}$ 10.2; CF); δ_H($CDCl_3$) 3.99 (s; OCH_3); δ_C($CDCl_3$) 161.2 (d, $^2J_{CF}$ 26.3; *C*O), 119.5 (qd, $^1J_{CF}$ 283.9, $^2J_{CF}$ 29.1; *C*F_3), 89 (qd, $^1J_{CF}$ 272.1, $^2J_{CF}$ 38; *C*F), 54.7 (s; OCH$_3$); CI-MS: *m*/*z* 258/256 ($[M + NH_4]^+$, $C_4H_7BrF_4NO_2^+$, 2 Br isotopes, 0.5%), 241/239 (M^+, $C_4H_3BrF_4O_2^+$, 2 Br isotopes, 1%), 158 (M^+ − Br, 65%), 109 ($C_3F_3O^+$, 100%), 69 (CF_3^+, 29%).

Synthesis of n-butyl 2-bromotetrafluoropropanoate 4

Compound **1** (83 g, 0.5 mol) was condensed over a period of 4 h into a solution of lithium bromide (44 g, 0.5 mol) and zinc bromide (22.5 g, 0.1 mol) in tetrahydrofuran (600 cm^3) in a flask fitted with a Drikold condenser, an inner thermometer, a nitrogen inlet and a gas inlet tube and cooled to −78 °C. The reaction mixture was then allowed to stir at room temperature for 22 h. The solution was cooled to −20 °C and dried n-butanol (68.6 cm^3, 0.75 mol) was added dropwise over a period of 30 min. After stirring at room temperature for 3 days the reaction mixture was quenched with 10% aqueous hydrochloric acid (500 cm^3). Ether (200 cm^3) was added to allow an easier separation of the two layers. The organic layer was separated and the aqueous layer was extracted with ether (3 × 150 cm^3). The organic layers were combined, dried ($MgSO_4$) and evaporated to afford a yellow liquid. The solution contained n-butyl 2-bromotetrafluoropropanoate **4** (57.2 g, 41%) and n-butanol and was used without further purification; δ_F(282.4 MHz, $CDCl_3$) −78 (d, $^3J_{FF}$ 8.9; CF_3), −134.2 (q, $^3J_{FF}$ 8.9; CF); δ_H($CDCl_3$) 4.3 (t, $^3J_{HH}$ 7, 2H; OCH_2), 1.63 (quin, $^3J_{HH}$ 7, 2H; $CH_2CH_2CH_2$), 1.35 (sext, $^3J_{HH}$ 7, 2H; CH_2CH_3), 0.9 (t, $^3J_{HH}$ 7, 3H; CH_3); δ_C($CDCl_3$) 160.6 (d, $^2J_{CF}$ 26.3; *C*O), 120.5 (qd, $^1J_{CF}$ 284.2, $^2J_{CF}$ 29.6; *C*F_3), 88.2 (dq, $^1J_{CF}$ 271.4, $^2J_{CF}$ 38.1; *C*F), 68.2 (s; OCH_2), 30.0 (s; $CH_2CH_2CH_2$), 18.6 (s; CH_2CH_3), 13.2 (s; CH_3); EI-MS: *m*/*z* 300/298 ($[M + NH_4]^+$, $C_7H_{13}BrF_4NO_2^+$, 2 Br isotopes, 1%), 200 (M^+ − Br, 45%), 109 ($C_3F_3O^+$, 50%), 58 ($C_4H_{10}^+$, 100%).

Synthesis of ethyl 2-fluoro-3-hydroxy-2-trifluoromethylpent-4-enoate 6

Method A. A mixture of acrolein (0.87 cm^3, 0.013 mol), zinc powder (2.61 g, 0.04 mol), ethyl 2-bromotetrafluoropropanoate **2** (5.06 g, 0.02 mol) and tetrahydrofuran (20 cm^3) in a flask fitted with a Drikold condenser and an inner thermometer was sonicated for 4 h with a maximum temperature of 60 °C. On addition of 2% aqueous hydrochloric acid (20 cm^3) a yellow oil was formed which was extracted with ether (3 × 50 cm^3). The organic layer was dried ($MgSO_4$) and evaporated. Distillation *in vacuo* (7 mmHg, 60–63 °C, colourless liquid) afforded **6** (1.2 g, 40%) as a diastereomeric mixture which was resolved by HPLC and shown to contain no other material; δ_F($CDCl_3$, 282.4 MHz) −73.3 (d, $^3J_{FF}$ 6.4, **6a**/**6a′**; CF_3), −73.9 (d, $^3J_{FF}$ 7.6, **6b**/**6b′**; CF_3), −188.5 (dq, $^3J_{HF_{gauche}}$ 21.6, $^3J_{FF}$ 7.6, **6b**/**6b′**; CF), −189.3 (dq, $^3J_{HF_{anti}}$ 22.9, $^3J_{FF}$ 6.3, **6a**/**6a′**; CF); δ_H($CDCl_3$) 5.78 (ddd, $^3J_{HH_{trans}}$ 15.75, $^3J_{HH_{cis}}$ 11.25, $^3J_{HH}$ 7.5; CH=CH_2), 5.4/5.33 (d, $^3J_{HH_{trans}}$ 15.75; CH_2=CH), 5.28/5.23 (d, $^3J_{HH_{cis}}$ 11.25, CH_2=CH), 4.52 (dd, $^3J_{HF_{anti}}$ 22.1, $^3J_{HH}$ 7.3, **6a**/**6a′**; CHOH), 4.5 (dd, $^3J_{HF_{gauche}}$ 20.6, $^3J_{HH}$ 6.6, **6b**/**6b′**; CHOH), 4.25/4.21 (q, $^3J_{HH}$ 7.5, OCH_2), 1.25/1.2 (t, $^3J_{HH}$ 7.5; CH_3); δ_C($CDCl_3$) 163.9 (d, 1C, $^2J_{CF}$ 25), 163 (d, 1C, $^2J_{CF}$ 24.2), 131.1 (s, *C*H=CH_2), 121.1 (qd, 1C, $^1J_{CF}$ 286, $^2J_{CF}$ 21.0, *C*F_3), 120.7 (dq, $^1J_{CF}$ 285.9, $^2J_{CF}$ 19.3, *C*F_3), 120.6/120.5 (s; *C*H_2=CH), 94/93.8 (dq, $^1J_{CF}$ 236, $^2J_{CF}$ 30; CF), 72.5 (d, $^2J_{CF}$ 20.3; 1 HO*C*H), 72.2 (d, $^2J_{CF}$ 20.9; HO*C*H), 63.2/63.3 (s; O*C*H_2), 13.2 (s, *C*H_3); GC–MS (t_R = 7.5 min for **6b**/**6b′** and 8 min for **6a**/**6a′**): *m*/*z* 231 ($[M^+ + 1]^+$, $C_8H_{11}F_4O_3^+$, 10%), 202 ($[M + 1]^+ - C_2H_5$, 12%), 182 ($C_5H_4F_3O_2^+$, 29%), 174 ($[M + 1] - C_3H_5O$, 17%), 162 ($[M + 1]^+ - CF_3$, 7%), 57 ($C_3H_5O^+$, 100%).

Method B. A mixture of acrolein (0.73 g, 0.87 cm^3, 0.013 mmol), zinc (2.61 g, 0.04 mol), ethyl 2-bromotetrafluoropropanoate **2** (5.06 g, 0.02 mol), *N*-methylephedrine (2.3 g, 0.013 mol) and tetrahydrofuran (50 cm^3) in a flask fitted with a Drikold condenser, a septum (with a nitrogen inlet) and an inner thermometer was sonicated for 8 h with a maximum temperature of 50 °C. The reaction was then quenched with 10% aqueous hydrochloric acid (40 cm^3). The organic layer was separated and the aqueous layer was extracted with ether (3 × 20 cm^3). The organic layers were combined, dried ($MgSO_4$) and evaporated. Purification by Kugelrohr distillation (10 mmHg, 70 °C) gave **6** (1.2 g, 40.2%) in the diastereoisomeric ratio 1:9 (**6a**/**6a′**:**6b**/**6b′**) as indicated by HPLC and integration of ^{1}H and ^{19}F NMR signals. For analytical data see Method A.

Synthesis of ethyl 2-fluoro-3-hydroxy-2-trifluoromethylpropanoate 5

Method A. Gaseous formaldehyde generated from paraformaldehyde (0.2 g) was condensed over a period of 1 h into a suspension of zinc (0.65 g, 0.01 mol) in anhydrous tetrahydrofuran (5 cm^3) in a flask equipped with a Drikold condenser, an

Anschutz adapter, an inner thermometer, a septum and a PTFE gas inlet tube and cooled to 0 °C. Ethyl 2-bromotetrafluoropropanoate **2** (2 g, 0.008 mol) was added and the reaction mixture was sonicated for 1 h. At the beginning of the sonication an exothermic reaction (with a maximum temperature of 60 °C) was observed. After 5 min the reaction temperature dropped to 40 °C and stayed constant for the rest of the sonication. The reaction was then quenched with 10% aqueous hydrochloric acid (10 cm^3) and the organic material was extracted with ether (3 × 10 cm^3). The organic layers were combined, dried ($MgSO_4$) and evaporated. Purification by Kugelrohr distillation (10 mmHg, 50 °C) gave **5** (0.4 g, 54%) as a colourless liquid as a single component by GC and HPLC analysis; δ_F(282.4 MHz, $CDCl_3$) −76 (d, $^3J_{FF}$ 7.6; CF_3), −182.9 (ddq, $^3J_{HF_{anti}}$ 27.9, $^3J_{HF_{gauche}}$ 15.2, $^3J_{FF}$ 7.6; C*F*); δ_H($CDCl_3$) 4.36 (qd, $^3J_{HH}$ 7, $^5J_{HF}$ 1.5; OCH_2), 4.17 (ddq, $^2J_{HH}$ 12.9, $^3J_{HbF_{anti}}$ 29, $^4J_{HF}$ 1.1; C*Hb*F), 4.07 (ddq, $^2J_{HH}$ 12.9, $^3J_{HaF_{gauche}}$ 15, $^4J_{HF}$ 1.1; C*Ha*F), 2.7 (s, br; O*H*), 1.3 (t, $^3J_{HH}$ 7; CH_3); δ_C($CDCl_3$) 162.9 (d, $^2J_{CF}$ 25.3; *C*O), 120 (qd, $^1J_{CF}$ 285.6, $^2J_{CF}$ 27.9; CF_3), 93 (dq, $^1J_{CF}$ 231.8, $^2J_{CF}$ 30.6; *C*F), 67.9 (s; OCH_2), 61.6 (d, $^2J_{CF}$ 21.1; *C*H_2), 13.8 (s; *C*H_3); CI-MS: *m*/*z* 222 ([M + NH_4]$^+$, $C_6H_{12}F_4NO_3^+$, 100%), 204 (M^+, $C_6H_8F_4O_3^+$, 1%), 186 ($M^+ - H_2O$, 15%) [Found: 222.075451 ($C_6H_{12}NO_3F_4$). Required: 222.075331 ($C_6H_{12}NO_3F_4$)].

Method B. Gaseous formaldehyde generated from paraformaldehyde (0.4 g) was swept in stream of nitrogen into a suspension of zinc (1.3 g, 0.02 mol) in anhydrous tetrahydrofuran (10 cm^3) in a flask equipped with a Drikold condenser, an Anschutz adapter and inner thermometer, a septum and cooled to 0 °C. Ethyl 2-bromotetrafluoropropanoate **2** (4 g, 0.016 mol) was added and the reaction mixture was stirred at 60 °C for 5 min and then cooled to 40 °C. Stirring at this temperature was continued for 55 min. The reaction was then quenched with 10% aqueous hydrochloric acid (25 cm^3) and the organic material was extracted with ether (3 × 20 cm^3). The organic layers were combined, dried ($MgSO_4$) and evaporated. Purification was carried out by distillation (10 mmHg, 52 °C) to give **5** (1 g, 37%).

Synthesis of (±)-2-bromotetrafluoro-*N*-(1-phenylethyl)propanamide

(*S*)-(−)-1-Phenylethylamine (0.96 cm^3, 7.5 mmol) was added dropwise over a period of 10 min to ethyl 2-bromotetrafluoropropanoate **2** (1.9 g, 7.5 mmol) and ether (10 cm^3) cooled to 0 °C. After 20 min the ice bath was removed and the mixture was allowed to stir at room temperature for 2 days. After this time the reaction mixture was heated under reflux for 3.5 h. Extraction with hexane (2 × 20 cm^3) and evaporation of the solvent gave a diastereomeric mixture of 2-bromotetrafluoro-*N*-(1-phenylethyl)propanamide (0.9 g, 37%, mp 69–71 °C, yellow crystals); δ_F($CDCl_3$, 282.4 MHz) −77.3 (s; CF_3) −134.9 (s; C*F*); δ_H($CDCl_3$) 7.41–7.25 (m, 10H; ring protons), 6.52 (s, 2H; N*H*), 5.16 (quin, $^3J_{HH}$ 7.5, 2H; C*H*), 1.61/1.6 (d, $^3J_{HH}$ 7.5, 6H; CH_3); δ_C($CDCl_3$) 159.5 (d, $^2J_{CF}$ 34.8; *C*O), 128.9 (s; ring carbon), 127.9 (s; ring carbon, *C-ortho*), 126.1 (s; ring carbon, *C-meta*), 125.3 (s; ring carbon, *C-para*), 120 (qd, $^1J_{CF}$ 278.4, $^2J_{CF}$ 34.8; CF_3), 92 (dq, $^1J_{CF}$ 278.4, $^2J_{CF}$ 34.8; *C*F), 49.9 (s; *C*H), 21.1 (s; *C*H_3), 20.9 (s; *C*H_3); GC–MS (2 diastereoisomers with t_R = 14.81 and 14.96 min): *m*/*z* 329/327 (M^+, $C_{11}H_{10}F_4NO^+$, 2 Br isotopes, 1%), 314/312 ($M^+ - CH_3$, 2 Br isotopes, 6%), 248 (M^+ − Br, 100%), 105 ($C_7H_7N^+$, 28%). The crude material was purified by column chromatography (R_f 0.43, ethyl acetate–hexane, 2:8), though this technique was not appropriate to resolve the two diastereoisomers. After the addition of D_2O to the sample, the ^{1}H NMR spectrum showed two doublets for the methyl groups of each isomer. The quintet at δ 5.1 changed into a quartet, indicating the loss of the coupling between the nitrogen proton and the proton at the adjacent carbon atom.

Synthesis of menthyl 2-bromotetrafluoropropanoate 7

Compound **1** (83 g, 0.5 mol) was condensed over a period of 1 h into a solution, cooled to −78 °C, of lithium bromide (44 g, 0.5 mol) and zinc bromide (22.5 g, 0.1 mol) in tetrahydrofuran (600 cm^3) in a flask fitted with a Drikold condenser, an inner thermometer, a nitrogen inlet and a gas inlet tube. After stirring overnight at room temperature the mixture was cooled to −10 °C and a solution of (1*R*,2*S*,5*R*)-(−)-menthol (78.1 g, 0.5 mol) in tetrahydrofuran (150 cm^3) was added dropwise over a period of 45 min. The reaction mixture was allowed to stir at room temperature for three days and was then acidified with 10% aqueous hydrochloric acid (400 cm^3). The organic layer was separated and the aqueous layer was extracted with ether (3 × 300 cm^3). The organic layers were combined and washed with 10% aqueous potassium hydroxide (1 × 500 cm^3), 10% aqueous hydrochloric acid (1 × 500 cm^3) and brine (1 × 500 cm^3). The organic layer was separated, dried ($MgSO_4$) and evaporated. The remaining tetrahydrofuran was distilled off with a K-piece at normal pressure. NMR analysis of the crude material (119.5 g) indicated diastereomeric mixtures of the target molecule **7** (62%) and of menthyl 2,3,3,3-tetrafluoropropanoate **8** (8%), and also the presence of unreacted menthol (30%). Menthyl 2-bromotetrafluoropropanoate **7** together with menthyl 2,3,3,3-tetrafluoropropanoate **8** was separated from the menthol by column chromatography (230–400 mesh silica) on elution with hexane–ether (95:5). The resolution of the two diastereoisomers of menthyl 2-bromotetrafluoropropanoate **7** *via* column chromatography was not successful although it was possible to obtain pure samples of **7** (74 g, 44%) and **8** (3 g) as diastereomeric mixtures; R_f (**7**) (hexane–dichloromethane, 9:1) = 0.55, colourless oil; R_f (**8**) (hexane–dichloromethane, 9:1) = 0.29, colourless liquid.

The ^{19}F NMR spectrum of the pure sample shows two sets of signals for menthyl 2-bromotetrafluoropropanoate **7**, indicating the existence of two diastereoisomers in a ratio of 53:47; δ_F(282.4 MHz, $CDCl_3$) −77.5 (d, $^3J_{FF}$ 9; CF_3), −77.7 (d, $^3J_{FF}$ 9; CF_3), −134.2 (q, $^3J_{FF}$ 9; C*F*), −134.5 (q, $^3J_{FF}$ 9; C*F*); δ_H($CDCl_3$) 4.87 (ddd, $^3J_{H_{ax}H_{ax}}$ 11, $^3J_{H_{ax}H_{ax}}$ 11, $^3J_{H_{ax}H_{eq}}$ 4.4, 1H at C_5; C*H*O), 4.86 (ddd, $^3J_{H_{ax}H_{ax}}$ 11.1, $^3J_{H_{ax}H_{ax}}$ 11, $^3J_{H_{ax}H_{eq}}$ 4.4, 1H at C_5; C*H*O), 2.1 (m, 2H, C*H* at C_4), 1.89 (m, 2H, C*H* at C_7), 1.7 (m, 4H, CH_2 at C_6), 1.5 (m, 4H, CH_2 at C_9), 1.1 (m, 4H, CH_2 at C_8), 0.93 (d, $^3J_{HH}$ 7, 6H, protons at C_1/C_3), 0.9 (d, $^3J_{HH}$ 7, 6H, protons at C_1/C_3), 0.85 (m, 2H, protons at C_2), 0.77 (d, $^3J_{HH}$ 7, 3H, protons at C_{10}), 0.75 (d, $^3J_{HH}$ 7, 3H, protons at C_{10}); δ_C($CDCl_3$) 160.2 (d, $^2J_{CF}$ 26.1, *C*O), 121.5 (qd, $^1J_{CF}$ 283.6, $^2J_{CF}$ 29.6, *C*F_3), 89 (dq, $^1J_{CF}$ 271.8, $^2J_{CF}$ 29.6, *C*F), 79.6 (s, C_5; *C*HO), 46.8 (s, C_4, *C*H), 46.7 (s, C_4, *C*H), 39.8 (s, C_7, *C*H), 39.7 (s, C_7, *C*H), 33.9 (s, C_6, *C*H_2), 31.4 (s, C_9, *C*H_2), 26.1 (s, C_8, *C*H_2), 25.8 (s, C_8, *C*H_2), 23.2 (s, C_2, *C*H), 23.0 (s, C_2, *C*H), 21.8 (s, C_3, *C*H_3), 20.6 (s, C_1, *C*H_3), 20.5 (s, C_1, *C*H_3), 15.9 (s, C_{10}, *C*H_3), 15.7 (s, C_{10}, *C*H_3); EI-MS: *m*/*z* 363/361 (M^+, $C_{13}H_{19}BrF_4O_2^+$, 2 Br isotopes, 1%), 321/319 ($M^+ - CO_2$, 2 Br isotopes, 2%), 239 ($C_{12}H_{19}F_4^+$, 3%), 181/179 ($C_2BrF_4^+$, 2 Br isotopes, 32%), 138 ($C_{10}H_{18}^+$, 90%), 123 ($C_9H_{15}^+$, 65%), 95 ($C_7H_9^+$, 100%).

The ^{19}F NMR spectrum of menthyl 2,3,3,3-tetrafluoropropanoate **8** shows also two sets of signals indicating the existence of two diastereoisomers in a ratio of about 1:1; δ_F(282.4 MHz, $CDCl_3$) −75.9 (dd, $^3J_{FF}$ 12.7, $^3J_{HF}$ 6.3, CF_3), −75.8 (dd, $^3J_{FF}$ 11.5, $^3J_{HF}$ 6.3, CF_3), −167.5 (dq, $^2J_{HF}$ 44, $^3J_{FF}$ 11.4, 1 C*F*), −167.7 (dq, $^2J_{HF}$ 47, $^3J_{FF}$ 12.7, C*F*); δ_H($CDCl_3$) 5.03 (dq, $^2J_{HF}$ 46.3, $^3J_{HF}$ 6.6, CF*H*), 5.0 (dq, $^2J_{HF}$ 46.3, $^3J_{HF}$ 6.2, CF*H*), 4.87 (ddd, $^3J_{H_{ax}H_{ax}}$ 11, $^3J_{H_{ax}H_{ax}}$ 11, $^3J_{H_{ax}H_{eq}}$ 4, proton at C_5), 4.84 (ddd, $^3J_{H_{ax}H_{ax}}$ 11, $^3J_{H_{ax}H_{ax}}$ 11, $^3J_{H_{ax}H_{eq}}$ 4, proton at C_5), 2 (m, 2H, protons at C_4), 1.85 (m, 2H, protons at C_7), 1.7 (m, 4H, protons at C_6), 1.45 (m, 4H, protons at C_9), 1.05 (m, 4H, protons at C_8), 0.91 (m, 2H, protons at C_2), 0.89 (d, $^3J_{HH}$ 6, 6H, methyl protons at C_1/C_3), 0.87 (d, $^3J_{HH}$ 6, 6H, methyl protons at C_1/C_3), 0.75 (d, 3H, methyl protons at C_{10}), 0.71 (d, 3H, methyl protons at C_{10}); δ_C($CDCl_3$) 161.4 (d, $^2J_{CF}$ 23.4; CO), 119.5 (qd, $^1J_{CF}$ 282.4, $^2J_{CF}$ 25.9; CF_3), 84.5 (dq, $^1J_{CF}$ 199.8, $^2J_{CF}$ 35.3; C*F*), 84.3 (dq, $^1J_{CF}$ 200.4, $^2J_{CF}$ 35.4; *C*F), 78.1 (s, C_5; *C*OH), 77.9 (s,

C_5; *C*OH), 46.7 (s, C_4; *C*H), 40.3 (s, C_7, *C*H), 40.1 (s, C_7; *C*H), 33.9 (s, C_6; *C*H_2), 31.3 (s, C_9; *C*H_2), 26.1 (s, C_8; *C*H_2), 25.6 (s, C_8; *C*H_2), 23.2 (s, C_2, *C*H), 22.9 (s, C_2; *C*H), 21.7 (s, C_3; *C*H_3), 20.5 (s, C_1; *C*H_3), 20.4 (s, C_1; *C*H_3), 15.9 (s, C_{10}; *C*H_3), 15.5 (s, C_{10}; *C*H_3); EI-MS: *m*/*z* 283 ([M − H]$^+$, $C_{13}H_{19}F_4O_2^+$, 10%), 173 ($C_{10}H_{18}FO^+$, 100%), 139 ($C_{10}H_{19}^+$, 80%), 124 ($C_9H_{16}^+$, 70%), 96 ($C_7H_{12}^+$, 93%), 81 ($C_6H_9^+$, 93%) [Found: 302.175375 ($C_{13}H_{24}NO_2F_4$). Required: 302.174317 ($C_{13}H_{24}NO_2F_4$)].

Synthesis of 2-bromotetrafluoropropanoic acid 9

Compound **1** (83 g, 0.5 mol) was bubbled through a solution of lithium bromide (44 g, 0.5 mol) and zinc bromide (22.5 g, 0.1 mol) in tetrahydrofuran (600 cm^3) in a flask fitted with a Drikold condenser, a gas inlet tube, a nitrogen inlet and an inner thermometer and cooled to −78 °C. The reaction mixture was allowed to warm to room temperature and stirred for 24 h. The solution was cooled to −20 °C and water (13.5 cm^3, 0.75 mol) was added. Stirring at room temperature was then continued for 5 h. The organic material was then extracted with ether (3 × 250 cm^3). The organic layers were combined, dried ($MgSO_4$) and evaporated. Fractional distillation (12 mmHg, 68–72 °C) afforded **9** (80.6 g, 72%) as a single component by HPLC; δ_F(282.4 MHz, $CDCl_3$) −78 (s; CF_3), −134.5 (s; C*F*); δ_H($CDCl_3$) 12.2 (s; COO*H*); δ_C($CDCl_3$) 162.1 (d, $^2J_{CF}$ 26.2; *C*OOH), 120 (qd, $^1J_{CF}$ 283.7, $^2J_{CF}$ 29.7; *C*F_3), 88.5 (dq, $^1J_{CF}$ 270.8, $^2J_{CF}$ 38; *C*F); EI-MS: *m*/*z* 228/226 ([M + H]$^+$, 2 Br isotopes, $C_3H_2BrF_4O_2^+$, 2%), 180/182 (M$^+$ − CO_2H, 2 Br isotopes, 27%), 69 (CF_3^+, 32%), 49 ([M + H]$^+$ − C_2BrF_3O, 100%).

Synthesis of dehydroabietylamine acetate

Technical dehydroabietylamine (90 g, 32 mol = 61 g, 0.19 mol of 100% pure amine), toluene (150 cm^3) and acetic acid (20 g, 0.45 mol) were heated to 65–70 °C. The solution was allowed to stir at this temperature for 1 h. After cooling down the reaction mixture the crude dehydroabietylamine acetate was obtained in three crops. The salt was purified by recrystallization from boiling toluene (300 cm^3). The colourless crystals were collected and washed with *n*-pentane (3 × 100 cm^3) and air dried to give dehydroabietylamine acetate (40 g, 56%) as white needles (mp 137–139 °C, lit.,[18] 140–143 °C).

Synthesis of dehydroabietylamine 10

Dehydroabietylamine acetate (25 g, 0.07 mol), water (93 cm^3) and 10% aqueous sodium hydroxide (30 cm^3) were mixed together at room temperature. A white solid precipitated from a yellow oil. The mixture was cooled in an ice-water bath to complete the precipitation. The amine **10** was extracted with ether (3 × 50 cm^3). Evaporation of the dried extract gave **10** as a viscous oil which crystallized very slowly (13 g, 63%, lit.,[18] 98%; mp 46 °C, lit.,[18] 43–45 °C); δ_H($CDCl_3$, 400 MHz) 7.12 (d, $^3J_{HH}$ 7.5, 1H; aromatic proton at C_6), 6.95 (d, $^3J_{HH}$ 7.5, 1H; aromatic proton at C_5), 6.34 (s, 1H; aromatic proton at C_9), 2.95–2.78 (m, 3H; 2 protons at C_{10}, 1 proton at C_3), 2.53 (d, $^2J_{HH}$ 14.25, 1H; $C_{20}HNH_2$), 2.34 (d, $^2J_{HH}$ 14.25, 1H; $C_{20}HNH_2$), 2.25 (dt, $^2J_{HH}$ 14.25, $^3J_{HH}$ 4, 1 axial proton at C_{14}), 1.9–1.63 (m, 4H; proton at C_{11} and C_{15}), 1.48 (dd, $^3J_{HH_{ax}}$ 15, $^3J_{HH_{eq}}$ 4.5, 1H; proton at C_{12}), 1.39–1.24 (m, 3H; 2 protons at C_{16}, 1 equatorial proton at C_{14}), 1.23 (d, $^3J_{HH}$ 7.5, 6H; methyl groups of isopropyl group), 1.22 (s, 3H; CH_3 at C_{17}), 0.9 (s, 3H; CH_3 at C_{13}); δ_C($CDCl_3$, 75 MHz) 147.6 (s, aromatic carbon; C_4), 145.6 (s, aromatic carbon; $C_{7/8}$), 134.8 (s, aromatic carbon; $C_{7/8}$), 126.9 (s, aromatic carbon; C_5), 124.4 (s, aromatic carbon; C_6), 123.9 (s, aromatic carbon; C_9), 56.3 (s; CH, C_2), 53.9 (s; *C*H_2, C_{20}), 44.9 (s; *C*H, C_{12}), 38.7 (s; *C*H_2, C_{10}), 37.5 (s, quaternary C; C_{17}), 37.3 (s; quaternary C, C_{13}), 35.3 (s; *C*H_2, C_{14}), 30.3 (s; *C*H_2, $C_{15/16}$), 23.9 (s; *C*H_2, C_{11}), 18.7 (s; *C*H_2, $C_{15/16}$); EI-MS: *m*/*z* 285 (M$^+$, $C_{20}H_{31}N^+$, 24%), 254 ($C_{19}H_{26}^+$, 16%), 239 ($C_{18}H_{23}^+$, 100%).

Synthesis of 2-bromotetrafluoropropanoic acid dehydroabietylamine salt 11

Dehydroabietylamine **10** (31 g, 0.11 mol) in ethyl acetate (200 cm^3) was added to a solution of 2-bromotetrafluoropropanoic acid **9** (24.8 g, 0.11 mol) in ethyl acetate (100 cm^3). During addition an exothermic reaction was observed up to 42 °C. Stirring was continued for 2 h. The resultant white precipitate was filtered off and washed with ethyl acetate (5 × 100 cm^3) and dried in a desiccator over phosphorus pentoxide. The solid was purified by recrystallization from ethyl acetate (5 times) to give **11** (9 g, 16.2%) as white needles (mp 198 °C). The optical rotation was measured to be $[\alpha]_D^{25}$ +21.7 (*c* 1, MeOH); δ_F(282.4 MHz, $CDCl_3$) −76.8 (d, $^3J_{FF}$ 9; CF_3), −124.1 (q, $^3J_{FF}$ 9; C*F*). The mother liquor from the first recrystallization and the solution from the six washings were combined and evaporated. The light yellow solid was recrystallized three times from ethyl acetate to give a further crop of **11** (7.8 g, 14%) as white needles. The optical rotation was measured to be $[\alpha]_D^{25}$ +20.7 (*c* 1, MeOH). A third crop was obtained by combining all the mother liquors from the remaining recrystallizations. Evaporation and recrystallization from ethyl acetate (three times) gave **11** (2.2 g, 4%) with an optical rotation of $[\alpha]_D^{25}$ +18.1 (*c* 1, MeOH). In total, **11** was obtained enantiomerically pure in an overall yield of 34%. The absolute configuration of 2-bromotetrafluoropropanoic acid **9** was determined by X-ray crystallography of a single crystal of the amine salt **11** with its known stereochemistry for the amine moiety (see Fig. 3). According to the X-ray structure the isolated bromofluoro acid has the (*S*) configuration.

Synthesis of ethyl (*S*)-2-bromotetrafluoropropanoate 12

A solution of sodium hydrogen carbonate (4.5 g, 0.053 mol) in water (250 cm^3) was added to 2-bromotetrafluoropropanoic acid dehydroabietylamine salt **11** {$[\alpha]_D^{25}$ +21.7 (*c* 1, MeOH), 24 g, 0.048 mol} and heated under reflux for 6 h. The reaction mixture was allowed to cool to room temperature overnight. The solution was filtered and extracted with ether (2 × 100 cm^3) to remove any remaining dehydroabietylamine **10**. The aqueous solution was evaporated to dryness to give the sodium salt of 2-bromotetrafluoropropanoate (9.6 g, 82%) as a white solid. The optical rotation of the sodium salt was measured to be $[\alpha]_D^{25}$ −3.7 (*c* 1, H_2O); δ_F(282.4 MHz, D_2O) −75.7 (d, $^3J_{FF}$ 9; CF_3), −124.5 (q, $^3J_{FF}$ 9, C*F*).

Absolute ethanol (10 cm^3, 0.17 mol) and concentrated sulfuric acid (15 cm^3) were mixed together and cooled to 3 °C in an ice bath. This solution was added to the sodium salt of (*S*)-2-bromotetrafluoropropanoic acid (6 g, 0.024 mol) and the mixture stirred for three days at room temperature. The white emulsion which formed was poured onto ice water (20 cm^3) and the organic layer was separated and dried over molecular sieves. Ethyl 2-bromotetrafluoropropanoate **12** (4.5 g, 73.5%) was obtained as a colourless liquid. Gas chromatographic analysis indicated the ester **12** was formed in a clean esterification reaction with a purity of 100%. The optical rotation of the resolved ester **12** was measured to be $[\alpha]_D^{25}$ −3.5 (*c* 1, MeOH); δ_F(282.4 MHz, $CDCl_3$) −77.7 (d, $^3J_{FF}$ 10.2; CF_3), −135 (q, $^3J_{FF}$ 8.9; C*F*).

Reformatsky reaction of 12 with formaldehyde

As above for the reaction of **2** with formaldehyde, ester **12** (2 g) afforded ethyl (*R*)-2-fluoro-3-hydroxy-2-trifluoromethylpropanoate (0.68 g); $[\alpha]_D^{25}$ −0.03; δ_H[Eu(hfphmc)$_3$] (72 mg) 4.86 (dd, $^2J_{HaHb}$ 15.5, $^3J_{HaF}$ 28; C*Ha*F), 4.73 (dd, $^2J_{HaHb}$ 15.8; C*Hb*F), 4.57 (q, $^3J_{HH}$ 7; OCH_2), 1.42 (t, $^3J_{HH}$ 7; CH_3). The ^{19}F NMR spectrum, apart from line broadening, was essentially the same as for ester **2**.

References

1 W. Mahler and P. R. Resnick, *J. Fluorine Chem.*, 1973, **3**, 451.
2 H.-G. Elias, *An Introduction to Plastics*, VCH, Weinheim, 1993, 249.

3 (*a*) L. A. Rozov and K. Ramig, *Tetrahedron Lett.*, 1994, **35**, 4501; (*b*) K. Ramig, L. Brockunier, P. W. Rafalko and L. A. Rozov, *Angew. Chem., Int. Ed. Engl.*, 1985, **24**, 161.
4 I. L. Knunyants, V. V. Shokina and I. V. Galakhov, *Khim. Geterosikl. Soedin*, 1966, 873.
5 P. Tarrant, R. O'B. Watts, C. J. Allison and K. P. Barhold, *J. Fluorine Chem.*, 1973, **3**, 7.
6 S. N. Reformatsky, *Ber. Dtsch. Chem. Ges.*, 1887, **20**, 1210.
7 B. H. Han and P. J. Boudjouk, *J. Org. Chem.*, 1982, **47**, 5030.
8 L. M. Harwood, A. C. Manage, S. Robin, S. F. G. Hopes, D. J. Watkin and C. E. Williams, *Synlett*, 1993, 777.
9 K. Ogi, M. Akazone and K. Ogura, *Tetrahedron Lett.*, 1998, **39**, 30.
10 A. M. Doherty, I. Sircar, B. E. Kornberg, J. Quin, R. T. Winters, J. S. Koltenborn, M. D. Taylor, B. L. Batley, S. R. Rupundalo, M. T. Ryanand and C. A. Painchard, *J. Med. Chem.*, 1992, **35**, 2.
11 C. H. Heathcock, M. C. Pirring and J. E. Sohn, *J. Org. Chem.*, 1979, **44**, 4294.
12 J. M. Andrés, M. A. Martínez, R. Pedrosa and A. Pérez-Encabo, *Synthesis*, 1996, 1070.
13 F. Orsini, F. Pelizzoni and G. Ricca, *Tetrahedron Lett.*, 1982, **23**, 3945.
14 F. Orsini, F. Pelizzoni and G. Ricca, *Tetrahedron*, 1984, **40**, 278.
15 J. Dekker, J. Boersma and G. J. M. van der Kerk, *J. Chem. Soc., Chem. Commun.*, 1983, 553.
16 D. J. Burton and J. Easdon, *J. Fluorine Chem.*, 1988, **38**, 125.
17 R. L. Powell, personal communication.
18 I. Auerbach, F. H. Verhoek and A. L. Heune, *J. Am. Chem. Soc.*, 1950, **72**, 299.
19 C. H. Huang, L. A. Rozov, D. F. Halpern and G. G. Vernice, *J. Org. Chem.*, 1993, **58**, 7382.

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