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TETRAHEDRON: *ASYMMETRY*

Resolution and absolute configuration of bromofluoroacetic acid

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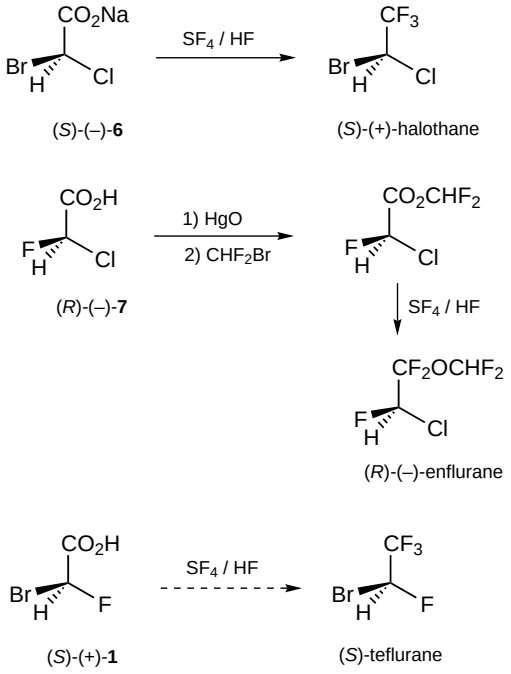
Abstract—The resolution of racemic bromofluoroacetic acid ($BrFHCCO_2H$) **1** was effected by crystallisation of its diastereoisomeric α-methylbenzylamine salts. The crystal structure of the *p* salt (+)-**3a** {(+)-$BrFHCCO_2H$·(*R*)-(+)-α-methylbenzylamine} was solved by X-ray crystallography and the (*S*)-(+)/(*R*)-(−) absolute configuration was established for **1**. Diastereoisomeric esters **5a** and **5b**, obtained by addition of bromofluoroacetic acid to enantiomerically pure epoxychroman **4**, were used to determine the enantiomeric excess of **1** by ^{19}F NMR. Moreover, the diastereoisomerically pure ester **5a**, resulting from addition of enantiomerically pure (+)-**1** to **4**, gave single crystals and its X-ray crystal structure corroborated the (*S*)-(+)/(*R*)-(−) absolute configuration of **1**.

1. Introduction

Bromofluoroacetic acid ($FBrHCCO_2H$) **1** belongs to the family of chiral fluorinated carboxylic acids, some of which are commonly used in the NMR determination of enantiomeric excesses[1] (e.e.'s) and in the synthesis of enantioenriched anaesthetics.[2] Indeed, next to the well-known 2-methoxy-3,3,3-trifluoro-2-phenylpropionic acid (Mosher's acid MTPA),[3] a growing range of fluorinated carboxylic acids are being used for NMR determination of the e.e.'s of alcohols and amines, such as α-cyano-α-fluorophenylacetic acid ($CNFPhCCO_2H$)[4] or chlorofluoroacetic acid ($ClFHCCO_2H$).[5] Their use in ^{19}F NMR offers essentially the following advantages: the differences in chemical shifts between the diastereoisomers are in the range of several ppm and additionally, the fluorine signals are only due to one or two fluorinated groups and therefore give NMR spectra which are simple to analyse.[1]

Chiral fluorinated carboxylic acids are key intermediates in the synthesis of optically active anaesthetics.[2] For example, Pearson has demonstrated that 96% e.e. samples of (*S*)-(+) and (*R*)-(−) halothane could be prepared by reaction of SF_4/HF with the sodium salt of the resolved bromochloroacetic acid **6** (Scheme 1).[6,7] Similarly, he prepared optically active enflurane from the resolved chlorofluoroacetic acid **7** by forming its mercury salt and by combining it with bromodifluoromethane, followed by treatment with SF_4/HF.[6]



Scheme 1. Synthesis of some optically active anaesthetics.

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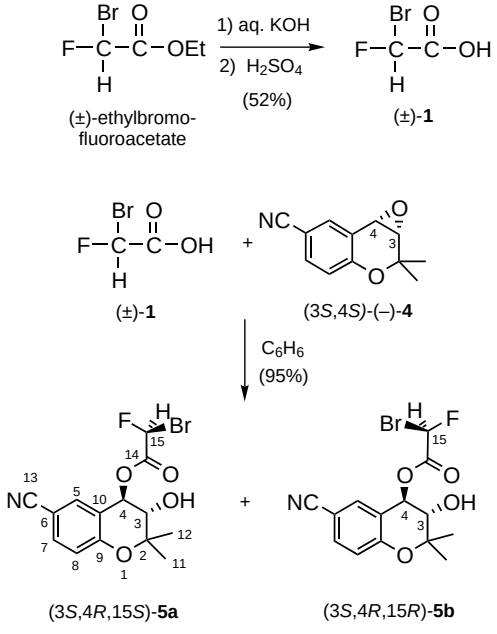
Racemic chlorofluoroacetic acid **7** was resolved by crystallisation of its α-methylbenzylamine salts and the (*S*)-(+)/(*R*)-(−) absolute configuration of **7** was obtained from the X-ray crystal structure analysis of the less soluble salt. Isoflurane was also synthesised from 1-chloro-2,2,2-trifluoroethoxidifluoroethanoic acid by using a highly stereospecific decarboxylation reaction.[8] Very recently, racemic fluoroiodoacetic acid was resolved by crystallisation of its ephedrine salts and proved to be an important synthon in the asymmetric synthesis of fluorinated HIV protease inhibitors.[9]

It is also notable that bromochlorofluoromethane (CHFClBr),[10] one of the simplest chiral molecules, was synthesised from bromochlorofluoroacetic acid[11] by a decarboxylation reaction which has been shown to proceed with retention of configuration.[12–14] The deuterated analogue CDFClBr[12] was also obtained by conducting the decarboxylation reaction in deuterated water.[15]

Most of the fluorinated acids mentioned above were resolved by crystallisation of their diastereoisomeric salts formed with chiral amines, which seems to be the easiest way to resolve such compounds.[16,17] However, the resolution of bromofluoroacetic acid **1** has not been accomplished so far, although it could probably find use in the preparation of the two enantiomers of teflurane by reaction with SF_4/HF (see Scheme 1).[18]

2. Results and discussion

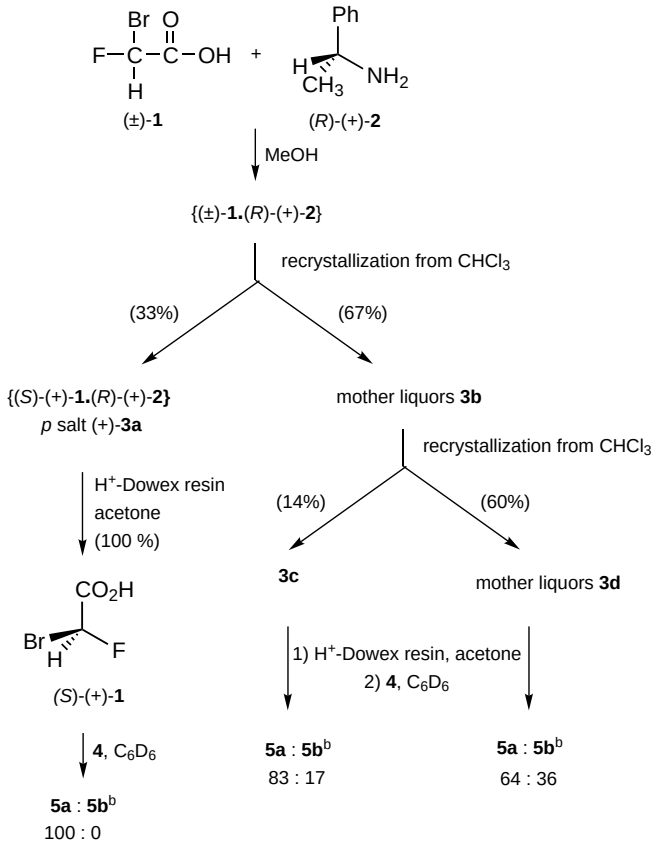
Racemic bromofluoroacetic acid (±)-**1** was prepared by saponification of the commercially available (±)-ethylbromofluoroacetate in 52% yield after distillation (Scheme 2).[19] A general method to determine the e.e. of chiral carboxylic acids is to measure the proportions of their diastereoisomeric covalent esters by NMR.[20] For this purpose, enantiopure (−)-(3*S*,4*S*)-6-cyano-2,2-dimethyl-3,4-epoxychroman **4** was advantageously used to measure the e.e. of the resolved acid **1**, via the formation of the diastereoisomeric esters **5a** and **5b** (Scheme 2). This method was inspired by Belluci et al. who used enantiopure 1,2-epoxy-1-phenylcyclohexane to determine the e.e. of chlorofluoroacetic acid **7** by ^{19}F NMR.[21] The advantage of epoxychroman **4** is that it can be synthesised in enantioenriched form by Jacobsen asymmetric epoxidation reaction and can be obtained in enantiomerically pure form by recrystallisation from toluene.[22] Preliminary studies have been performed with the racemic acid (±)-**1** to check that no kinetic resolution occurred during the opening reaction of the epoxide. Moreover, the 188.2 MHz ^{19}F NMR spectrum in C_6D_6 of the diastereoisomeric mixture gave two 1:1 doublets at −150.03 and −150.13 ppm ($CFCl_3$ as internal reference). This reaction is very convenient as it can be conducted on NMR tube scale, and has been applied to other α-fluorinated carboxylic acids such as chlorofluoroacetic acid.[23] The regioselectivity of the opening reaction of **4** and the *trans* stereochemistry of the 3,4-bond were first assumed according to published results.[24] The benzylic position is still preferred for the attack of the nucleophile and the *trans* stereochemistry is consistent with the 7.1 Hz coupling constant measured between C(3)H and C(4)H. These assumptions were further corroborated by X-ray crystal structure analysis of the pure diastereoisomer **5a** (see Fig. 2 below).



Scheme 2. Synthesis of (±)-**1** and formation of covalent diastereoisomeric esters **5a** and **5b**.

The resolution of **1** was investigated by crystallisation of the diastereoisomeric salts formed with chiral amines.[16,17] Among the seven commercially available optically active amines tested,[25] α-methylbenzylamine **2** gave the best results. Therefore, one recrystallisation of the diastereoisomeric salt {(±)-$BrFHCCO_2H$·(*R*)-(+)-α-methylbenzylamine} from chloroform gave the pure diastereoisomer (+)-**3a** {(+)-$BrFHCCO_2H$·(*R*)-(+)-α-methylbenzylamine} (*p* salt)[26] in 33% yield ($[\alpha]_{436}^{25}$ +23.6 (*c* 1, MeOH)) (Scheme 3). Following the same procedure, one recrystallisation of the diastereoisomeric salt {(±)-$BrFHCCO_2H$·(*S*)-(−)-α-methylbenzylamine} in chloroform gave the diastereoisomer (−)-**3a** {(−)-$BrFHCCO_2H$·(*S*)-(−)-α-methylbenzylamine} (*p* salt)[26] in 33% yield ($[\alpha]_{436}^{25}$ −22.3 (*c* 1, MeOH)).

(+)-Bromofluoroacetic acid (+)-**1** ($[\alpha]_D^{25}$ +28.0 (*c* 1.1, acetone)) and (−)-bromofluoroacetic acid (−)-**1** ($[\alpha]_D^{25}$ −31.1 (*c* 1, acetone)) were subsequently recovered in quantitative yield by hydrolysis of the *p* salts (+)-**3a** and (−)-**3a**, respectively, using strongly acidic Dowex resin in acetone.[27] They were then subjected to reaction with the (−)-(3*S*,4*S*)-6-cyano-2,2-dimethyl-3,4-epoxychroman **4**. From (+)-**1**, the resulting ^{19}F NMR spectrum displayed only one doublet at −150.13 ppm corresponding to **5a**, suggesting that the (+)-acid was enantiopure within the NMR measurement error (3–4%). For (−)-**1**, an e.e. of 84% ((+)-**1**/(−)-**1** 8:92) was obtained by following the same procedure.[28]



Scheme 3. Resolution of (±)-**1** into (+)-**1** by recrystallisation in chloroform of its (*R*)-(+)-α-methylbenzylammonium salts and determination of the diastereoisomeric purity of the salts via the formation of esters **5a** and **5b**. [a] Specific rotations $[\alpha]_{436}^{25}$ (*c* 1, MeOH). [b] Proportions of **5a** and **5b** obtained from ^{19}F NMR in C_6D_6.

One can notice on Scheme 3 that the *p* salt is the major compound recovered, even in the mother liquors, and exceeds the expected 50% theoretical percentage. Indeed, the acids recovered after hydrolysis of the salts, always led to diastereoisomeric esters enriched in **5a**. In fact, preparation of the (*n*,*p*) salt from racemic (±)-**1** in methanol with either (*R*)- or (*S*)-α-methylbenzylamine, always led, after crystallisation, to a mixture of *n* and *p* salts with an *n*:*p* ratio different from 1:1 in favour of the *p* salt. This was attributed to interconversion between the *S* and *R* acids during the preparation of the salt in methanol, and to the preferential crystallisation of the *p* salt.[29]

Single crystals suitable for X-ray analysis were grown within one night from a methanol solution of (+)-**3a**. The asymmetric unit (Fig. 1) corresponds to an acid–base pair, where the NH_3^+ group of the α-methylbenzylammonium residue shares three hydrogen bonds with the carboxylate group. The carbonyl C(2)–O(2) bond (1.227 Å) of the carboxylate interacts with the α-methylbenzylammonium residue through one H bond, whereas the hydroxylate C(2)–O(1) bond (1.268 Å) interacts with the ammonium residue through two H bonds. The (*S*)-(+)/(*R*)-(−) absolute configuration of the bromofluoroacetic acid could be established from the crystal structure, according to the value of 0.012 found for the Flack parameter. Moreover, the *S* configuration could be deduced by comparison with the known *R* configuration of the α-methylbenzylammonium fragment in (+)-**3a**. This result is not in accordance with that predicted using Brewster's rule. This semi-empirical rule, based on atomic polarisabilities, has been used for the determination of the absolute configurations of several classes of chiral compounds.[30] It was thus interesting to test the validity of Brewster's rule by considering the absolute configuration of the small α-halogenocarboxylic acids already established. Brewster observed for a wide range of chiral substances, that the molecule drawn in Scheme 4 displayed a positive optical rotation in the Fischer projection shown, considering the polarisability order A>B>C>D. In this context, the (*S*)-(+) assignment for $BrFHCCO_2H$ is not consistent with the polarisability order Br>Cl>CO_2H>H>F used by Brewster. The same conclusion can be drawn in the case of chlorofluoroacetic acid[21] and bromochloroacetic acid.[6] In fact, polarisability orders can be reversed in certain cases when particular interactions, e.g. hydrogen bonds, play an important role.[31]

Single crystals of pure diastereoisomer **5a** were grown from C_6D_6 solution in NMR tubes, after several weeks. The X-ray structure was solved (monoclinic, $P2_1$) and the asymmetric unit corresponds to the ester **5a** together with one molecule of benzene. The solvent was disordered and localised in two equipopulated positions, as depicted in Fig. 2. With a Flack parameter of 0.022, the absolute configuration for **5a** corresponds to the (3*S*,4*R*,15*S*) diastereoisomer, confirming the *trans* stereochemistry.

3. Conclusion

Racemic bromofluoroacetic acid **1** was resolved for the first time by crystallisation of its α-methylbenzylammonium salts. Its absolute configuration ((*S*)-(+) and (*R*)-(−)) could be determined from the X-ray crystal structure of the less soluble salt (+)-**3a**. After Dowex resin hydrolysis of the diastereomeric salts, the e.e. of the resolved (+) and (−) acids were determined by ^{19}F NMR of the covalent diastereoisomeric esters **5a** and **5b**, the structures of which were confirmed by X-ray crystallography.

4. Experimental

4.1. General

^1H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker DPX 200 spectrometer (at 200.13 MHz for ^1H, 50.4 MHz for ^{13}C and 188.2 MHz for ^{19}F). Melting or decomposition temperatures were measured on a Perkin–Elmer DSC7 microcalorimeter. Rotations (in deg cm^2 g^{-1}) were measured in a 1 dm thermostatically controlled quartz cell (25°C) on a Perkin–Elmer 241 micropolarimeter. Elemental analyses were carried out

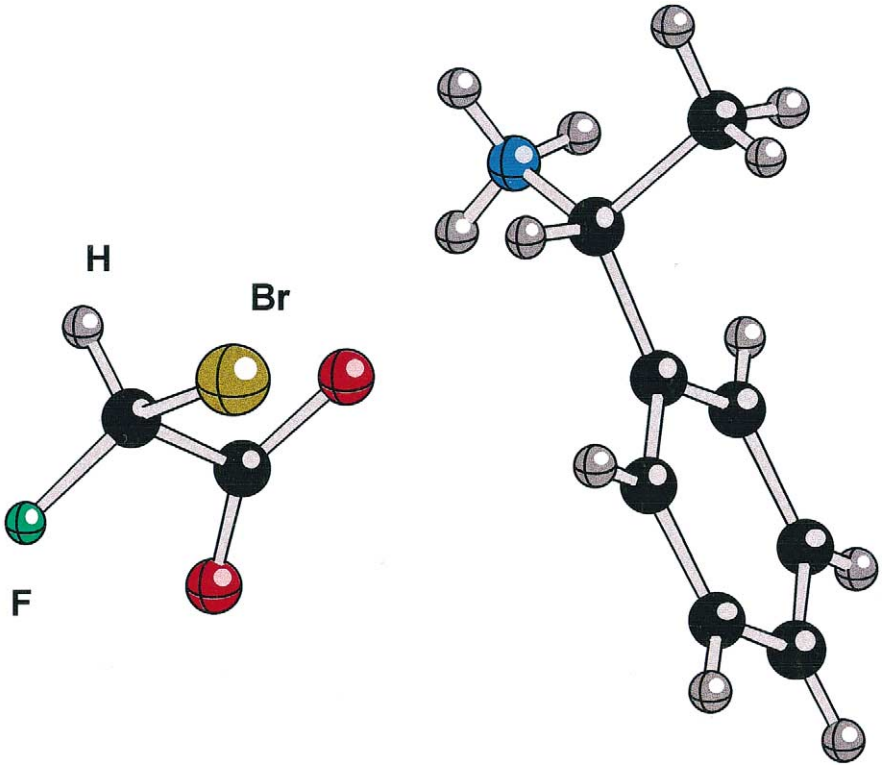


Figure 1. X-Ray crystal structure of *p* salt (+)-**3a** {(*S*)-(+)-**1**·(*R*)-(+)-**2**}.

by the Service Central d'Analyses, CNRS. Mass spectra were recorded by the Centre de Spectrométrie de Masse, Université de Lyon1, France. Ethyl bromofluoroacetate was purchased from Acros. (+)- and (−)-α-Methylbenzylamine were purchased from Acros or Aldrich and were 99 and 98% e.e., respectively. The Dowex 50x8-100 resin was purchased from Janssen Chimica.

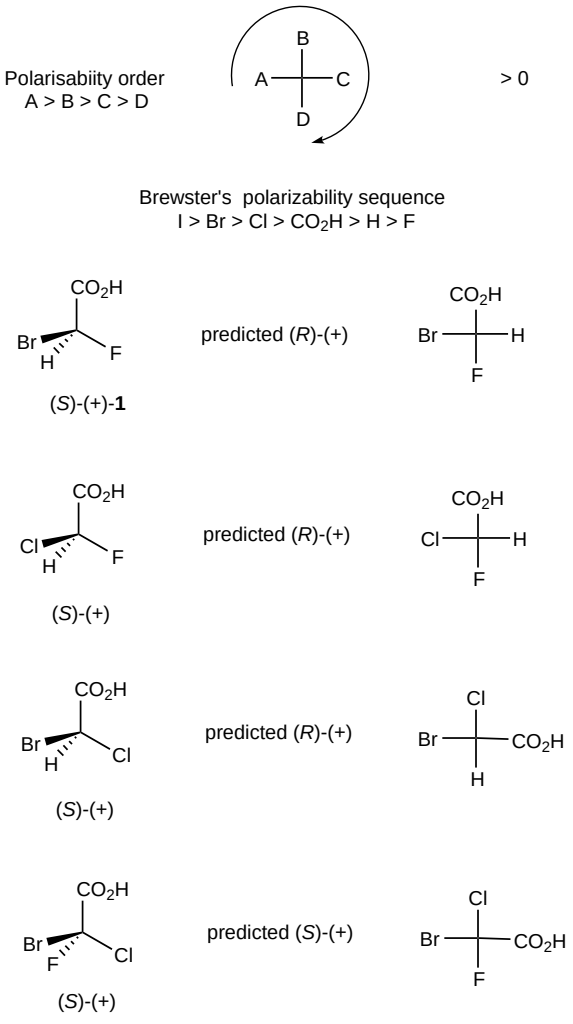
4.2. (±)-Bromofluoroacetic acid 1

Ethyl bromofluoroacetate (5 g, 27 mmol) was added dropwise at 0°C to aqueous KOH (1.25 M, 33 mL, 41 mmol). The solution was stirred at 0°C for 90 min and acidified at this temperature by addition of aqueous H_2SO_4 (4.3 M, 10 mL, 43 mmol). The aqueous phase was then continuously extracted with diethyl ether for 4 h. The organic layer was concentrated and distilled under reduced pressure to give (±)-**1** as a hygroscopic white solid (2.2 g, 52%) (T_{eb} 75–80°C/17 torr). ^{1}H NMR ($CDCl_3$) δ 6.64 (1H, d, $J=50.6$ Hz, CHF), 5–7.5 (broad, OH). ^{13}C NMR ($CDCl_3$) δ 79.61 (d, $^1J_{CF}=$ 263.5 Hz, CFHBr), 170.43 (d, $^2J_{CF}=26.4$ Hz, C=O). ^{19}F NMR ($CDCl_3$, $CFCl_3$ as internal reference) δ from −150.7 to −152.7 (d, $J=50.6$ Hz). Due to its highly hygroscopic character, elemental analysis and melting point were not determined.

4.3. (3*S*,4*R*)-4-[(*R*,*S*)-Bromofluoroacetoxy]-3,4-dihydro-6-cyano-2*H*-1-benzopyran-3-ol 5a and 5b

A solution of (−)-(3*S*,4*S*)-6-cyano-2,2-dimethyl-3,4-epoxychroman **4** (122.45 mg, 60.8 mmol) in dry benzene (5 mL) was added dropwise at 0°C under argon to a solution of bromofluoroacetic acid (±)-**1** (95.4 mg, 60.8 mmol) in dry benzene (10 mL) containing 4 Å molecular sieves. After stirring under argon at room temperature for 24 hours, the mixture was filtered, dried over sodium sulfate and concentrated to give **5a** and **5b** as a white paste (218 mg, 95%). ^{1}H NMR (C_6D_6) δ 0.99 (s, 3H, CH_3, **5b**), 1.00 (s, 3H, CH_3, **5a**), 1.09 (s, 3H, CH_3, **5b**), 1.13 (s, 3H, CH_3, **5a**), 2.07 (s, OH), 3.38 (d, 2H, $J=7.1$ Hz, H_3), 5.75 (d, 2H, $J=7.1$ Hz, H_4), 5.94 (d, 1H, $J=50.2$ Hz, H_{15}, **5b**), 6.03 (d, 1H, $J=50.2$ Hz, H_{15}, **5a**), 6.44 (d, 1H, $J=8.6$ Hz, H_8, **5b**), 6.45 (d, 1H, $J=8.6$ Hz, H_8, **5a**), 6.84 (m, 2H, H_7), 7.23 (d, 1H, $J=1.2$ Hz, H_5, **5b**), 7.31 (d, 1H, $J=1.1$ Hz, H_5, **5a**). NMR ^{19}F (C_6D_6, $CFCl_3$ as internal reference) δ −150.13 (d, $J=50.4$ Hz, **5a**), −150.03 (d, $J=50.4$ Hz, **5b**). ^{13}C NMR (C_6D_6, 50.4 MHz) δ 19.80 (CH_3, **5a**), 20.33 (CH_3, **5b**), 25.22 (CH_3, **5b**), 25.53 (CH_3, **5a**), 72.09, 72.42, 72.64, 73.05, 79.55, 79.78, 80.94 (d, $^1J_{CF}=$ 264.5 Hz, CFHBr), 104.77, 118.56, 118.64, 118.81, 119.50, 119.75, 133.34, 133.61, 134.06, 156.63, 165.06 (d, $^2J_{CF}=26.5$ Hz, C=O, **5a**), 165.34 (d, $^2J_{CF}=27.1$ Hz, C=O, **5b**). HR-LSIMS(+): $[M+H]^+$ 358.00952 (calcd for $C_{14}H_{14}BrFNO_4$ 358.0090).

The opening of epoxychroman **4** with resolved samples of acid **1** (see below) was also conducted on NMR tube scale. A typical procedure is as follows: To a solution of epoxychroman **4** (28.1 mg, 0.14 mmol) in benzene-d_6 (0.1 mL) containing 4 Å molecular sieves, was added acid **1** (2.8 mg, 14 mmol) in benzene-d_6 (0.4 mL). The NMR spectrum was recorded after 1 day.



Scheme 4. Brewster's rule.

4.4. Resolution of (±)-1 by crystallisation of its (*R*)-(+) and (*S*)-(−)-α-methylbenzylammonium salts

To a solution of (*R*)-(+)-α-methylbenzylamine (1.73 g, 14.3 mmol) in methanol (5 mL) cooled to 0°C was added acid **1** (2.24 g, 14.3 mmol) in methanol (5 mL). After stirring for one night and evaporation of the solvent, the recovered solid was recrystallised from chloroform (20 mL). After filtration, the *p* salt (+)-**3a** was obtained as a white solid (1.3 g, 33%), mp (decomp.) ca. 110°C, $[\alpha]_{436}^{25}$ +23.6 (*c* 1, MeOH). Anal. calcd. for $C_{10}H_{13}BrFNO_2$: C, 43.18; H, 4.71. Found: C, 42.51; H, 4.70. Evaporation of the mother liquors furnished 2.62 g (67%) of **3b** as a beige paste [NB: the specific rotation could not be measured because of the presence of coloured impurities] which was recrystallised from chloroform (2 mL) to give after filtration **3c** as a white solid (365 mg, 14%). $[\alpha]_{436}^{25}$ +35.3 (*c* 1, MeOH). Evaporation of the mother liquors furnished **3d** as a beige paste (1.55 g, 60%). [NB: the specific rotation could not be measured because of the presence of coloured impurities]. Salts **3a** to **3d** were subsequently hydrolysed on acidic Dowex resin to afford the partially resolved acids as described below.

To a solution of (*S*)-(−)-methylbenzylamine (773 mg, 6.4 mmol) in methanol (2 mL) cooled to 0°C was added acid **1** (1 g, 6.4 mmol) in methanol (2 mL). After stirring for one night and evaporation of the solvent, the recovered solid was recrystallised from chloroform (10 mL). After filtration *p* salt (−)-**3a** was obtained as a white solid (569 mg, 33%), mp (decomp.) ca. 120°C, $[\alpha]_{436}^{25}$ −22.3 (*c* 1, MeOH).

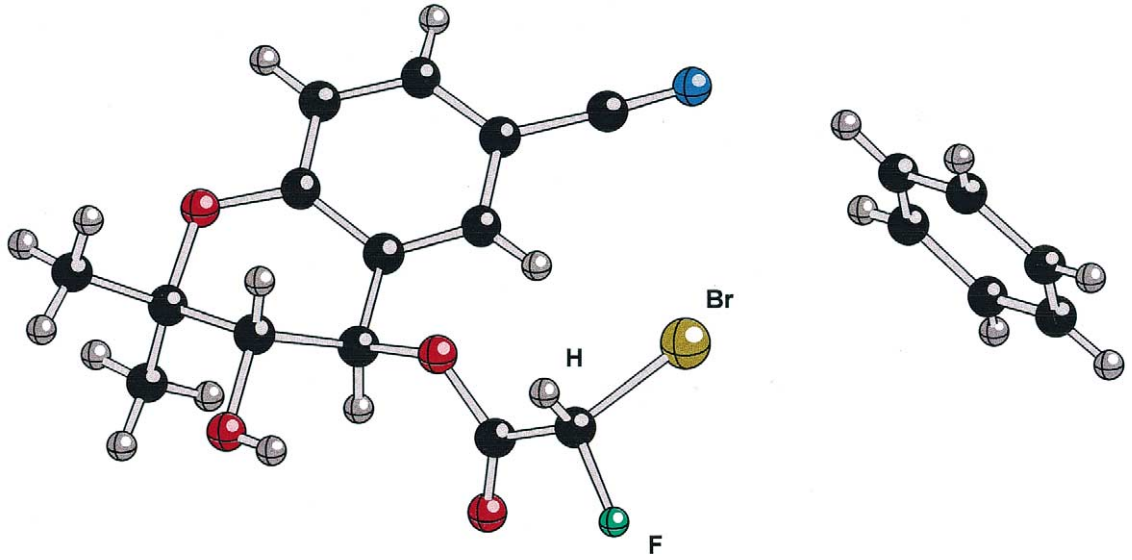


Figure 2. X-Ray crystal structure of diastereomerically pure ester **5a**.

4.5. Recovery of (+) and (−)-1 from the α-methylbenzylammonium salts

A typical procedure is as follows: Dowex 50x8 resin was first washed with water, acidified with HCl (1 N), washed again with water until neutrality and finally washed with acetone. Then, to a solution of salt **3a** (50.3 mg) in acetone (0.5 mL) Dowex resin (250 mg) were added. After stirring for 3 hours at room temperature, the solution was filtrated, and the resin washed with acetone. After drying over $MgSO_4$ and evaporation of the solvent, the (+)-acid (41.7 mg) was obtained. $[\alpha]_D^{25}$ +28.0 (*c* 1.1, acetone). Within the experimental error of NMR, an e.e. of 100% was measured after reaction of (+)-**1** with **4** in the NMR tube in C_6D_6 (only **5a** was observed). To a solution of salt (−)-**3a** (100 mg) in acetone (1 mL), Dowex resin (250 mg) was added. After stirring for 3 hours at room temperature, the solution was filtered and the resin washed with acetone. After drying over $MgSO_4$ and evaporation of the solvent, the (−)-acid (79 mg) was obtained. $[\alpha]_D^{25}$ −31.1 (*c* 1, acetone). Within the NMR error, an e.e. of 84% (which corresponds to a ratio (+)-**1**/(−)-**1** of 8/92) was measured after reaction of (−)-**1** with **4** in the NMR tube in C_6D_6 solution.

4.6. Crystal structure of the *p* salt {(+)-1·(*R*)-(+)-α-methylbenzylamine} (+)-3a

$C_{10}H_{13}BrFNO_2$, $M=278.11$, orthorhombic, space group $P2_12_12_1$, $a=6.9539(14)$, $b=8.6913(17)$, $c=18.312(4)$ Å, $V=1106.8(4)$ Å^3, $Z=4$, $F(000)=560$, $\mu=37.08$ cm^{-1}, $D_{calcd}=1.669$ g cm^{-3}, graphite-monochromated Mo–Kα radiation ($\lambda=0.71073$ Å). Data sets were collected on a Nonius Kappa CCD diffractometer. The structure was solved by direct methods and the non-hydrogen atoms were refined anisotropically using full-matrix least-squares based on F^2 to give $R_1=0.0512$, $wR_2=0.1067$ for all data (2430 independent reflections) and 146 parameters. Flack parameter $x=0.01(2)$.

4.7. Crystal structure of (3*S*,4*R*)-4-[(*S*)-bromofluoroacetoxy]-3,4-dihydro-6-cyano-2*H*-1-benzopyran-3-ol 5a

$C_{14}H_{13}BrFNO_4{\cdot}C_6H_6$, $M=436.27$, monoclinic, space group $P2_1$, $a=10.768(2)$, $b=7.0174(14)$, $c=13.789(3)$ Å, $\beta=107.65(3)°$, $V=992.9(3)$ Å^3, $Z=2$, $F(000)=444$, $\mu=21.04$ cm^{-1}, $D_{calcd}=1.459$ g cm^{-3}, graphite-monochromated Mo–Kα radiation ($\lambda=0.71073$ Å). Data sets were collected on a Nonius Kappa CCD diffractometer. The structure was solved by direct methods and the non-hydrogen atoms were refined anisotropically using full-matrix least-squares based on F^2 to give $R_1=0.0649$, $wR_2=0.1497$ for all data (2438 independent reflections) and 217 parameters. Flack parameter $x=0.02(2)$.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 181950 and 181951 for (+)-**3a** and **5a**, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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25. (*S*)-(−) and (*R*)-(+)-α-Methylbenzylamine, (1*R*,2*S*)-(−)-ephedrine, (1*R*,2*R*)-(−)-2-amino-1-(4-nitrophenyl)-1,3-propanediol, (1*R*,2*R*)-(−)-2-dimethylamino-1-(4-nitrophenyl)-1,3-propanediol, (−)-brucine, (−)-quinine and (−)-strychnine.
26. According to the definition given in Ref. 17, the *p* salt designates the diastereoisomers {(+)-**1**·(+)-**2**} and/or {(−)-**1**·(−)-**2**}; the *n* salt designates {(+)-**1**·(−)-**2**} and/or {(−)-**1**·(+)-**2**}.
27. Classical acidic hydrolysis of the salt in an aqueous solution followed by extraction with an organic solvent failed due to the solubility of **1** both in water and in common organic solvents. The acidic hydrolysis in non-aqueous media followed by distillation caused racemisation of the acid.
28. The specific rotation values and enantiomeric purities do not correlate exactly because the acid is highly hygroscopic and therefore always contains water.
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