Anomalous fluorinations of 3-aryl-2-hydroxypropanoic esters by diethylaminosulfur trifluoride (DAST)

David Haigh,*[a,b] Lee J. Jefcott,[a] Katherine Magee[c] and Hamish McNab*[c]

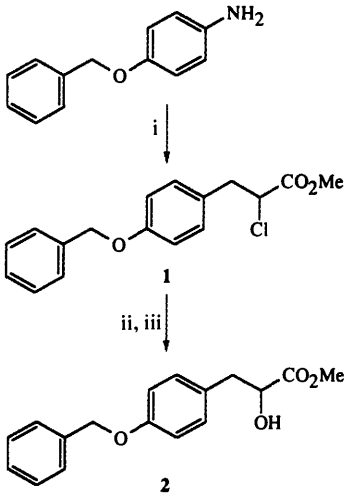
[a] *Department of Medicinal Chemistry, SmithKline Beecham Pharmaceuticals, Great Burgh, Yew Tree Bottom Road, Epsom KT18 5XQ, UK*
[b] *New address: Department of Medicinal Chemistry, SmithKline Beecham Pharmaceuticals, New Frontiers Science Park, Cold Harbour Road, The Pinnacles, Harlow, Essex CM19 5AD, UK*
[c] *Department of Chemistry, The University of Edinburgh, West Mains Road, Edinburgh EH9 3JJ, UK*

Treatment of 3-aryl-2-hydroxypropanoic esters 8 with diethylaminosulfur trifluoride (DAST) gives considerable amounts of rearranged 2-aryl-3-fluoropropanoic esters 12 together with the expected products 11. The extent of rearrangement is dependent on solvent and on the substitution pattern of the aryl ring; the mechanism of rearrangement probably involves anchimeric assistance by the aryl group in the S_N1 component of the reaction pathway. Reaction of the isomeric 3-hydroxy-2-phenylpropanoic ester 13 shows much less rearrangement under similar conditions, and an elimination product 21 is also obtained.

In the last decade there has been a growth of interest in biologically active fluorinated compounds, particularly 2-fluorocarbonyl compounds,[1] as enzyme inhibitors and biological probes.[2] The reaction of alcohols with diethylaminosulfur trifluoride (DAST) has proved to be an exceptionally versatile route to such aliphatic fluoro compounds.[3] In view of our own interest in 2-fluoro esters as antidiabetic agents[4] we have studied the reactions of DAST with a series of methyl 2-hydroxy-3-phenylpropanoates (methyl phenyllactates) and show that the reactions unexpectedly give a mixture of 2-fluoro-3-phenylpropanoates and 3-fluoro-2-phenylpropanoates. The ratio of these products is both dependent on the solvent and on the nature of a 4-substituent in the aryl ring.

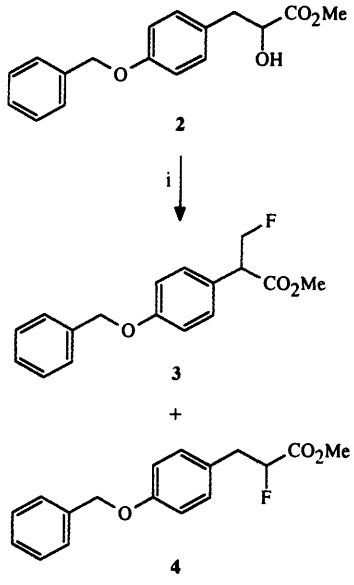
Results and discussion

Methyl 3-(*p*-benzyloxyphenyl)-2-hydroxypropanoate **2**, the starting material for our initial studies, was prepared according to Scheme 1.[5] Meerwein alkylation of *p*-benzyloxyaniline by a modification of the reported method[6] gave chloro ester **1**.† Exposure of **1** to refluxing sodium hydroxide, followed by re-esterification of the resulting hydroxy acid afforded the hydroxy ester **2**.



Scheme 1 *Reagents and conditions:* i, $NaNO_2$, *conc.* HCl, acetone, 5 °C, then methyl acrylate, CuI, 35 °C, 63%; ii, NaOH, $CaCO_3$, aq. dioxane, reflux; iii, MeOH, *conc.* HCl, reflux, 75% (two steps)

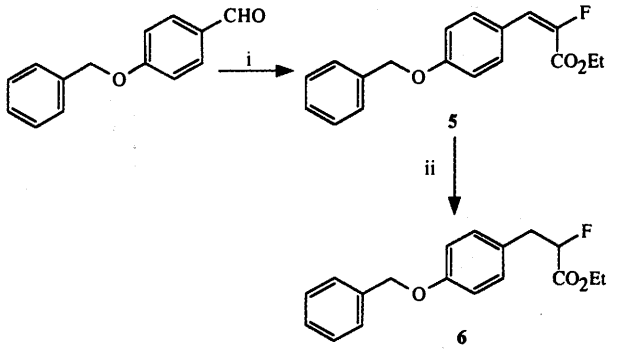
Reaction of **2** with DAST in dichloromethane at 0 °C to room temperature gave complete consumption of starting material after 1 h, and work-up by the standard method gave a good yield of product (66%). However, analysis of this product by ^1H NMR spectroscopy showed that the product was predominantly the 3-fluoro-2-(*p*-benzyloxyphenyl)propanoate **3** (89 mol%) and that the expected product **4** was present only to the extent of 11 mol% (Scheme 2). The assignment of the direct



Scheme 2 *Reagents and conditions:* i, DAST, CH_2Cl_2, 0 °C–room temp.

substitution product **4** followed from a comparison of the coupling constants with authentic 2-fluoro-3-phenylpropanoates.[7] It was further substantiated by an independent synthesis of the corresponding ethyl ester **6** (Scheme 3) involving reaction of *p*-benzyloxybenzaldehyde with ethyl 2-fluoro-2-(diethoxy-

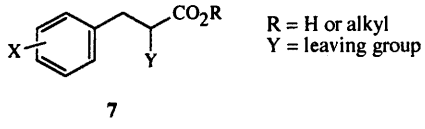
† Meerwein alkylation reactions of this type have been reported for the preparation of both 2-bromo and 2-chloro esters. To our knowledge, this reaction has not been examined as a means of preparation of the corresponding 2-fluoro esters.



Scheme 3 *Reagents and conditions:* i, $(EtO)_2P(O)CHFCO_2Et$, NaH, THF, 0 °C–room temp., 72%; ii, H_2, 10% Pd/C, EtOAc, 66%

phosphoryl)acetate[8] and hydrogenation[6,9] of the resultant 2-fluoropropenoate **5**. The assignment of the rearranged product **3** followed by comparison with published ^1H NMR data of closely related 3-fluoro-2-phenylcarboxylic acids and esters.[10] The presence in the spectrum of **3** of two one-proton multiplets showing $^2J_{HF}$ of *ca.* 47 Hz is particularly revealing.

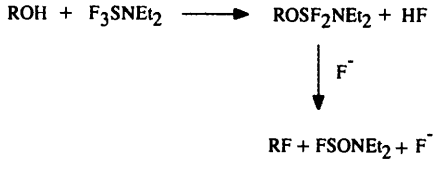
Such 1,2-aryl migrations are well known in the nucleophilic substitution chemistry of the 3-arylpropanoic acid derivatives **7**.[11,12] Indeed, similar results have been observed in the prepar-



7

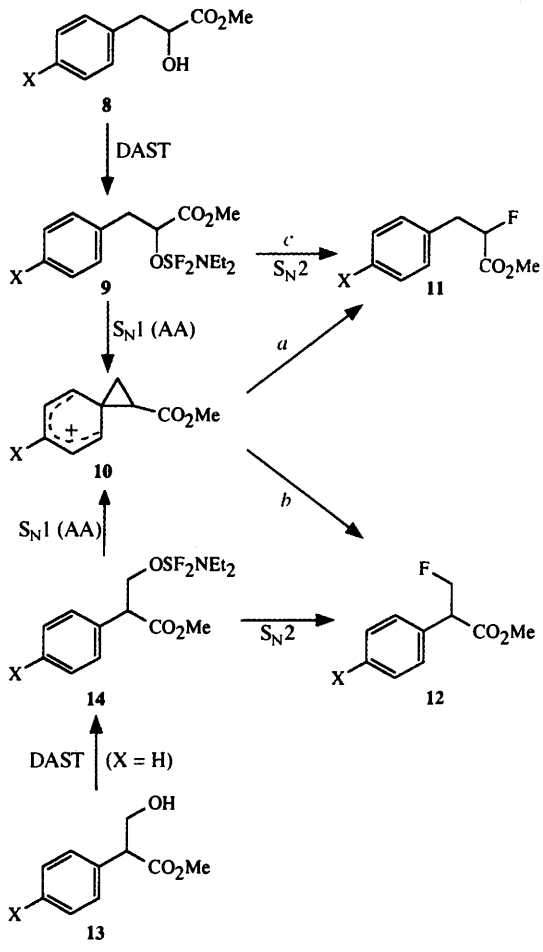
ation of fluoro-compounds by nitrosation reactions of substituted phenylalanines in the presence of hydrogen fluoride,[10,13] but we believe that this is the first example of a tropane-type skeletal rearrangement in DAST chemistry.[14]

The mechanism of DAST fluorination is thought to involve the formation of a covalent intermediate which can react with fluoride ion by mixed S_N1 and S_N2 processes to give the product (Scheme 4).[3] In some cases, rearrangement products character-

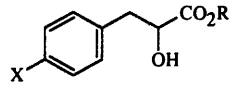


Scheme 4

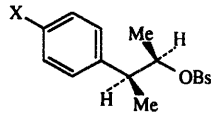
istic of carbocation intermediates are obtained, but in other examples the reaction can proceed with inversion (signifying S_N2) or retention (signifying neighbouring group participation) of configuration. In our example a possible mechanism, shown in Scheme 5, involves anchimeric assistance (AA) from the electron rich aryl group of the intermediate **9** derived from precursor **8** (X = OCH_2Ph) to give the spiro-intermediate **10** which can then give the two products **11** and **12** by reaction with fluoride ion (routes *a* and *b* respectively). Alternatively, it is possible that some or all of the direct products **11** arise by S_N2 reaction of the intermediate **9** (route *c*). We therefore decided to probe the mechanism in three ways. First, a range of 3-aryl-2-hydroxypropanoic esters with different *para* substituents was reacted with DAST; we anticipated that the amount of rearrangement product **12** should be dependent on the nucleophilicity of the aryl ring. Second, we varied the solvent polarity in an attempt to affect the S_N1 and S_N2 components of the mechanism. Finally, the complementary precursor **13** (X = H) was reacted with DAST to establish whether the key intermediate **10** can be accessed, *via* **14**, from an alternative starting material.



Scheme 5



15 X = H, R = Me
16 X = Cl, R = H
17 X = Cl, R = Me
18 X = NO_2, R = H
19 X = NO_2, R = Me



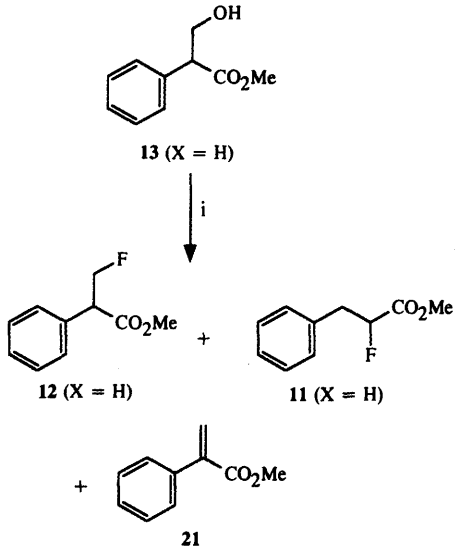
20 Bs = *p*-$BrC_6H_4SO_2$

The propanoic esters **15**, **17** and **19** were made by methylation of the corresponding carboxylic acid using iodomethane in dimethylformamide in the presence of anhydrous potassium carbonate. 3-(*p*-Chlorophenyl)-2-hydroxypropanoic acid **16** was made by standard hydrolysis of the diazonium salt derived from commercially available *p*-chlorophenylalanine; the corresponding *p*-nitro compound **18** was made in similar fashion after nitration of phenylalanine following literature procedures.[15]

When methyl 2-hydroxy-3-phenylpropanoate **8** (X = H) was treated with DAST in dichloromethane under identical conditions to those described above, a 53:47 ratio of rearranged (**12**, X = H) to unrearranged (**11**, X = H) products was obtained. This confirms that the reduced nucleophilicity of the aromatic ring also reduces the component of the anchimerically assisted pathway and leads to more of the direct substitution product. The results of the *p*-chloro and *p*-nitro analogues **17** and **19** also follow this trend (Table 1). Because the direct substitution products **11** can arise by either S_N1 or S_N2 routes (Scheme 5) it is not possible in the absence of chirality data to delineate the relative importance of the two routes, though it is possible to estimate limiting values if certain reasonable assumptions are made. Thus, if it is assumed that **2** (*i.e.* **8**; X = OCH_2Ph) reacts totally *via* the anchimerically assisted S_N1 pathway, then 11% of the fluoride attack on the intermediate **10** takes place at the

Table 1 Comparison of the degree of rearrangement in products formed by treatment of **8** with DAST and from acetolysis of **20**

Substituent	Ratio of **11**:**12** from reaction of **8** with DAST	Maximum (%) rearrangement from reaction of **8** with DAST	Rearrangement (%) from acetolysis of **20** (ref. 16)
p-OR	11:89 (R = CH_2Ph)	100 (R = CH_2Ph)	100 (R = Me)
H	47:53	60	59
p-Cl	71:29	33	39
p-NO_2	100:0	0	1



Scheme 6 *Reagents and conditions:* i, DAST, CH_2Cl_2, 0 °C–room temp., 2 h

carbon atom bearing the ester group and the remaining 89% at the methylene carbon atom. If it is also assumed that attack of fluoride on **10** to give **11** or **12** is independent of the *para*-substituent, then the *maximum* anchimerically assisted S_N1 component of the reaction pathway can be calculated (Table 1). The figures which arise are coincidentally remarkably similar to those for rearrangement in the solvolysis of *threo*-3-phenyl-2-butyl *p*-bromobenzenesulfonates **20** for which an anchimerically assisted mechanism has been proved by Brown *et al.* using a combination of kinetic and product analysis.[16]

Because the unsubstituted methyl 2-hydroxy-3-phenylpropanoate **8** (X = H) gave almost equal amounts of rearranged **12** and unrearranged **11** products when treated with DAST in dichloromethane (**11**:**12** ratio 47:53), this compound was used for initial experiments on the effect of solvent on the course of the reaction. Our anticipation that less polar solvents should favour the S_N2 pathway and therefore lead to a reduction in the rearranged product **12** were borne out when hexane (**11**:**12** ratio 87:13) or toluene (**11**:**12** ratio 61:39) were used. Surprisingly the greatest effect was found with ether solvents; *none* of the rearranged product **12** could be detected by ^1H NMR spectroscopy when either diethyl ether or tetrahydrofuran were employed. This effect is apparently general, since treatment of the *p*-benzyloxy compound **2** with DAST in diethyl ether resulted in a reduction of the **11**:**12** ratio from 11:89 observed in dichloromethane to 43:57 in diethyl ether. Although incomplete, these studies have demonstrated that the mechanistic spectrum of such DAST reactions is highly sensitive to solvent effects, and that considerable optimisation may be possible from a preparative point of view.

Finally, we examined the reaction of the complementary precursor methyl 3-hydroxy-2-phenylpropanoate (methyl tropate) **13** (X = H) with DAST in dichloromethane for 2 h at room temperature. Following standard work-up, ^1H NMR analysis of the crude product mixture indicated the presence of the expected direct product methyl 3-fluoro-2-phenylpropanoate **12** (X = H) (67 mol%) and rearranged product methyl 2-fluoro-3-phenylpropanoate **11** (X = H) (5 mol%) (Scheme 6). In addition, a third major component was identified as methyl 2-phenylpropenoate **21** (28 mol%) by comparison with published ^1H NMR spectroscopic data.[17] It is noteworthy that the ratio of products **11**:**12** (7:93) in this case differs dramatically from that observed in the reaction of methyl 2-hydroxy-3-phenylpropanoate **8** (R = H) with DAST which gave approximately equimolar amounts of the same two products under similar conditions. This suggests that the balance between the anchimerically assisted S_N1 reaction and the direct S_N2 process in the intermediate sulfonium species **14** (X = H) relatively favours the S_N2 reaction compared with the case of the isomeric intermediate **9** (Scheme 5).

The presence of substantial amounts of the elimination product **21** in this case was unexpected, but is consistent with the presence of a more acidic proton on the carbon atom next to the good leaving group in the intermediate **14** compared with the isomeric species **9**. The possibility that **21** arose by elimination of hydrogen fluoride during basic work-up was discounted by an experiment in which a dichloromethane solution of the product mixture from the reaction of **13** (X = H) with DAST was re-exposed to aqueous sodium hydrogen carbonate. The ratio of alkene **21** to fluorinated products **11** and **12** (X = H) did not change, hence elimination of hydrogen fluoride during work-up is unlikely.

Conclusions

We have shown that DAST-mediated fluorinations are subject to rearrangement when appropriate groups are present to participate in anchimeric assistance. The partition of the reaction mechanism between S_N1 and S_N2 components is sensitive to substitution pattern and to solvent, and these factors must be considered when designing a synthetic route involving fluorination with this reagent.

Experimental

General experimental details

Mass spectrometry was carried out using electron impact (EI) or chemical ionisation (CI) with ammonia as the reagent gas. Compounds characterised by high resolution mass measurement were homogeneous by TLC. ^1H NMR spectra were recorded at 200, 270 or 400 MHz and ^{13}C NMR spectra at 50, 68 or 100 MHz for solutions in $CDCl_3$. Chemical shifts are given in δ (ppm) relative to tetramethylsilane and coupling constants, *J*, are quoted in Hz. Reagents and solvents were normally used without purification.

Methyl 3-(*p*-benzyloxyphenyl)-2-chloropropanoate 1

A solution of sodium nitrite (16.5 g, 0.24 mol) in water (50 cm^3) was slowly added to a mechanically stirred, acetone–dry ice cooled suspension of *p*-benzyloxyaniline (51.4 g, 0.22 mol), acetone (250 cm^3) and concentrated hydrochloric acid (50 cm^3) such that the temperature of the reaction did not exceed 5 °C. The mixture was stirred at 5 °C for 1 h prior to the addition of methyl acrylate (100 cm^3) and the suspension was then warmed

to 30 °C. Copper(I) iodide (1.0 g, 0.005 mol) was added portionwise over 30 min such that the temperature of the reaction mixture did not exceed 35 °C and the stirring was continued for an additional 30 min at this temperature. The solvent was evaporated under reduced pressure, the residue was diluted with water (500 cm^3) and extracted with dichloromethane (3 × 400 cm^3). The combined organic solutions were washed with water (4 × 500 cm^3) and brine (500 cm^3), dried ($MgSO_4$) and the solvent was evaporated. The resulting solid was chromatographed on silica gel using dichloromethane–hexane (70:30 v/v) to afford the *title compound* **1** (41.6 g, 63%) as a pale yellow solid, mp 74–75 °C (from dichloromethane–isohexane) [Found: C, 66.85; H, 5.65%; M^+ (EI), 304.0867. $C_{17}H_{17}ClO_3$ requires C, 67.0; H, 5.6%; *M*, 304.0866]; ν_{max}(KBr)/cm^{-1} 1745 (CO); δ_H(270 MHz) 3.11 (1 H, dd, *J* 14.0 and 7.4, ArC*H*HCH), 3.30 (1 H, dd, *J* 14.0 and 7.4, ArCH*H*CH), 3.72 (3 H, s, OMe), 4.40 (1 H, t, *J* 7.4, $ArCH_2CH$), 5.04 (2 H, s, $PhCH_2$), 6.91 (2 H, d, *J* 8.7, aryl 3-H and 5-H), 7.12 (2 H, d, *J* 8.7, aryl 2-H and 6-H) and 7.35 (5 H, m, Ph); δ_C(100 MHz) 40.3 ($ArCH_2$), 52.3 (OMe), 57.4 ($ArCH_2CH$), 70.0 ($PhCH_2O$), 114.9 (2 C, s, aryl 3-C and 5-C), 127.5 (2 C, s, phenyl 3-C and 5-C), 127.9 (phenyl 4-C), 128.2 (phenyl 1-C), 128.6 (2 C, s, phenyl 2-C and 6-C), 130.4 (2 C, s, aryl 2-C and 6-C), 136.9 (aryl 1-C), 158.1 (aryl 4-C) and 169.7 (CO); *m/z* (EI) 304 (M^+, 43%), 268 (7), 197 (4), 177 (6), 149 (4), 119 (6) and 91 (100).

Methyl 3-(*p*-benzyloxyphenyl)-2-hydroxypropanoate 2

A mechanically stirred suspension of chloro ester **1** (18.27 g, 60 mmol), calcium carbonate (6.0 g, 60 mmol), sodium hydroxide (2.54 g, 63.5 mmol), dioxane (105 cm^3) and water (165 cm^3) was heated at reflux for 16 h (**CARE:** frothing) then allowed to cool to room temperature. Aqueous hydrochloric acid (2 mol dm^{-3}; 500 cm^3) was added and the mixture was extracted with ethyl acetate (3 × 300 cm^3). The combined ethyl acetate solutions were washed with water (2 × 700 cm^3) and brine (700 cm^3), dried ($MgSO_4$) and the solvent was evaporated to afford the crude hydroxy acid (15.51 g). The acid was dissolved in methanol (375 cm^3) containing concentrated hydrochloric acid (0.4 cm^3) and the solution was heated at reflux for 21 h, cooled and concentrated under reduced pressure. The residue was suspended in water (500 cm^3) and extracted with dichloromethane (3 × 400 cm^3). The combined dichloromethane solutions were washed with water (2 × 1000 cm^3) and brine (1000 cm^3), dried ($MgSO_4$) and the solvent was evaporated. The resulting solid was chromatographed on silica gel using dichloromethane–methanol (98.5:1.5 v/v) as eluent to afford the *title compound* **2** (12.83 g, 75%) as a white solid, mp 68–70 °C (from dichloromethane–isohexane) [Found: C, 71.2; H, 6.3%; M^+ (EI), 286.1204. $C_{17}H_{18}O_4$ requires C, 71.3; H, 6.3%; *M*, 286.1205]; ν_{max}(KBr)/cm^{-1} 3500 (OH) and 1735 (CO); δ_H(270 MHz) 2.68 (1 H, br, exchanges with D_2O, OH), 2.91 (1 H, dd, *J* 14.0 and 6.6, ArC*H*HCH), 3.06 (1 H, dd, *J* 14.0 and 4.4, ArCH*H*CH), 3.77 (3 H, s, OMe), 4.45 (1 H, m, $PhCH_2CH$), 5.03 (2 H, s, $PhCH_2O$), 6.90 (2 H, d, *J* 8.8, aryl 3-H and 5-H), 7.12 (2 H, d, *J* 8.8, aryl 2-H and 6-H) and 7.30–7.50 (5 H, m, Ph); δ_C(67.8 MHz) 39.7 ($ArCH_2$), 52.5 (OCH_3), 70.0 ($PhCH_2O$), 71.3 ($ArCH_2CH$), 114.8 (2 C, s, aryl 3-C and 5-C), 127.5 (2 C, s, phenyl 3-C and 5-C), 127.9 (phenyl 4-C), 128.4 (aryl 1-C), 128.6 (2 C, s, phenyl 2-C and 6-C), 130.5 (2 C, s, aryl 2-C and 6-C), 137.0 (phenyl 1-C), 157.8 (aryl 4-C) and 174.6 (CO); *m/z* (EI) 286 (M^+, 43%), 227 (6), 197 (100), 177 (3), 149 (4), 136 (4) and 107 (33).

Reaction of methyl 3-(*p*-benzyloxyphenyl)-2-hydroxypropanoate 2 with DAST

A solution of **2** (0.572 g, 2.0 mmol) in dichloromethane (20 cm^3) was added over *ca.* 2 min to an ice-cooled solution of DAST (0.26 cm^3, 2.0 mmol) in dichloromethane (20 cm^3) under argon. The cooling bath was removed and the solution was stirred at room temperature for 1 h, by which time TLC showed complete consumption of starting material. Water (40 cm^3) was added to the reaction mixture, the layers were separated and the dichloromethane solution was washed with aqueous sodium hydrogen carbonate (40 cm^3) and brine (40 cm^3), dried ($MgSO_4$) and concentrated to give a yellow gum (0.570 g). The gum was chromatographed on silica gel using dichloromethane–ethyl acetate (98:2 v/v) as eluent to afford a colourless gum (0.380 g, 66%), comprising an inseparable mixture of the rearranged fluoro compound **3** (89 mol%) together with the desired fluoropropanoate **4** (11 mol%) which was not characterised further. The ^1H NMR spectrum of the latter compound was consistent with that of authentic *ethyl* fluoropropanoate **6**, see below.

Methyl 2-(*p*-benzyloxyphenyl)-3-fluoropropanoate 3. δ_H(270 MHz) 3.71 (3 H, s, OMe), 3.97 (1 H, ddd, $^3J_{HF}$ 13.2, $^3J_{HH}$ 9.1 and $^3J_{HH}$ 5.5, PhC*H*), 4.54 (1 H, ddd, $^2J_{HF}$ 46.4, $^2J_{HH}$ 9.1 and $^3J_{HH}$ 5.5, C*H*HF), 4.92 (1 H, dt, $^2J_{HF}$ 46.8, $^2J_{HH}$ 9.1 and $^3J_{HH}$ 9.1, CH*H*F), 5.04 (2 H, s, $PhCH_2$), 6.95 (2 H, d, *J* 8.6, aryl 3-H and 5-H), 7.21 (2 H, d, *J* 8.6, aryl 2-H and 6-H) and 7.40 (5 H, m, Ph).

Methyl 3-(*p*-benzyloxyphenyl)-2-fluoropropanoate 4. δ_H(270 MHz) 3.12 (2 H, m, $ArCH_2CHF$), 3.76 (3 H, s, OMe), 5.04 (2 H, s, $PhCH_2$), 5.07 (1 H, ddd, $^2J_{HF}$ 48.9, $^3J_{HH}$ 7.6 and $^3J_{HH}$ 4.2, $ArCH_2CHF$), 6.95 (2 H, d, *J* 8.6, aryl 3-H and 5-H), 7.18 (2 H, d, *J* 8.6, aryl 2-H and 6-H) and 7.40 (5 H, m, Ph).

Ethyl (*E*)-3-(*p*-benzyloxyphenyl)-2-fluoropropenoate 5

A solution of butyllithium (1.6 mol dm^3 in hexane; 9.84 cm^3, 15.7 mmol) was added over *ca.* 5 min to a solution of ethyl 2-fluoro-2-(diethoxyphosphoryl)acetate (3.63 g, 15 mmol) in dry tetrahydrofuran (20 cm^3) under argon at −78 °C, such that the reaction temperature did not exceed −70 °C. The mixture was stirred at −78 °C for 1 h then added, over 5 min, to a solution of *p*-benzyloxybenzaldehyde (3.18 g, 15 mmol) in tetrahydrofuran (20 cm^3) at −78 °C. The solution was allowed to warm to room temperature and stirred for an additional 20 h before being diluted with water (300 cm^3) and extracted with ethyl acetate (2 × 250 cm^3). The combined ethyl acetate solutions were washed with water (500 cm^3) and brine (500 cm^3), dried ($MgSO_4$) and concentrated to afford a gum. The gum was chromatographed on silica gel using dichloromethane–isohexane (60:40 v/v) as eluent to afford the (E)-*fluoroalkene* **5** (3.23 g, 72%) as a colourless wax [Found: M^+ (EI), 300.1162. $C_{18}H_{17}FO_3$ requires *M*, 300.1162]; ν_{max}(film)/cm^{-1} 1728 (CO) and 1605 (C=C); δ_H(270 MHz) 1.28 (3 H, t, *J* 7.2, OCH_2CH_3), 4.27 (2 H, q, *J* 7.2, OCH_2CH_3), 5.08 (2 H, s, CH_2Ph), 6.84 (1 H, d, $^3J_{HF}$ 23.6, olefinic H), 6.95 (2 H, d, *J* 8.8, aryl 3-H and 5-H) and 7.25–7.60 (7 H, m, aromatic H); δ_C(100 MHz) 14.0 (OCH_2CH_3), 61.5 (OCH_2CH_3), 70.0 (OCH_2Ph), 114.5 (2 C, s, aryl 3-C and 5-C), 121.8 (1 C, d, $^2J_{CF}$ 26.9, olefinic CH), 123.4 (1 C, d, $^3J_{CF}$ 9.3, aryl 1-C), 127.5 (2 C, s, phenyl 2-C and 6-C), 128.1 (phenyl 4-C), 128.6 (2 C, s, phenyl 3-C and 5-C), 131.7 (2 C, d, $^4J_{CF}$ 2.6, aryl 2-C and 6-C), 136.7 (phenyl 1-C), 145.9 (1 C, d, $^1J_{CF}$ 252.5, olefinic CF), 159.3 (aryl 4-C) and 160.8 (1 C, d, $^2J_{CF}$ 35.7, CO); *m/z* (EI) 300 (M^+, 100%), 255 (6), 181 (8), 107 (8) and 91 (100).

Ethyl 3-(*p*-benzyloxyphenyl)-2-fluoropropanoate 6

A solution of alkene **5** (1.03 g, 3.4 mmol) in ethyl acetate (50 cm^3) was hydrogenated over 10% palladium on charcoal (50% water; 0.1 g) at room temperature and pressure for 80 min. The mixture was filtered through Celite, concentrated and the residual oil chromatographed on silica gel using dichloromethane–isohexane (1:1 v/v) as eluent to afford the *title compound* **6** as a colourless oil (0.67 g, 66%) [Found: C, 71.4; H, 6.4%. M^+ (EI), 302.1319. $C_{18}H_{19}FO_3$ requires C, 71.5; H, 6.3%. *M*, 302.1318]; ν_{max}(film)/cm^{-1} 1745 (CO); δ_H(400 MHz) 1.23 (3 H, t, *J* 7.2, OCH_2CH_3), 3.09 (1 H, ddd, $^3J_{HF}$ 24.4, $^2J_{HH}$ 14.8 and $^3J_{HH}$ 7.4, ArC*H*HCHF), 3.14 (1 H, ddd, $^3J_{HF}$ 27.6, $^2J_{HH}$ 14.8 and $^3J_{HH}$ 4.2, ArCH*H*CHF), 4.21 (2 H, q, *J* 7.2, OCH_2CH_3), 5.02 (1 H, ddd, $^2J_{HF}$ 48.9, $^3J_{HH}$ 7.4 and $^3J_{HH}$ 4.2, $ArCH_2CHF$), 5.03 (2 H, s, $PhCH_2O$), 6.91 (2 H, d, *J* 8.6, aryl

3-H and 5-H), 7.15 (2 H, d, J 8.6, aryl 2-H and 6-H) and 7.27–7.45 (5 H, m, Ph); δ_C(100 MHz) 14.1 (OCH_2CH_3), 37.9 (1 C, d, $^2J_{CF}$ 21.2, $ArCH_2CH$), 61.5 (OCH_2CH_3), 70.0 ($PhCH_2O$), 89.4 (1 C, d, $^1J_{CF}$ 186.9, $ArCH_2CHF$), 114.9 (2 C, s, aryl 3-C and 5-C), 127.4 (2 C, s, phenyl 2-C and 6-C), 127.9 (phenyl 4-C), 128.6 (2 C, s, phenyl 3-C and 5-C), 129.3 (aryl 1-C), 130.5 (2 C, s, aryl 2-C and 6-C), 137.1 (phenyl 1-C), 158.1 (aryl 4-C) and 169.2 (1 C, d, $^2J_{CF}$ 23.6, CO); *m/z* (EI) 302 (M^+, 100%), 282 (10), 257 (3), 229 (3), 197 (4), 163 (4) and 109 (8).

Methyl 3-aryl-2-hydroxypropanoates 15, 17 and 19

A solution of iodomethane (2.13 g, 15 mmol) and the appropriate propanoic acid (15 mmol) in dimethylformamide (50 cm^3) was treated with anhydrous potassium carbonate (2.07 g, 15 mmol), and the mixture was stirred overnight at room temperature. The resulting suspension was added to water (70 cm^3), extracted with diethyl ether (3 × 50 cm^3) and the combined organic extracts were washed with water (3 × 50 cm^3) and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave the crude propanoic esters.

The following compounds were made in this way.

Methyl 2-hydroxy-3-phenylpropanoate 15. Yield 75%, mp 47–48 °C (lit.,[18] mp 48.5 °C); δ_H(200 MHz) 2.74 (1 H, s), 2.96 (1 H, dd, ^2J 13.9 and ^3J 6.8), 3.12 (1 H, dd, ^2J 13.9 and ^3J 4.5), 3.76 (3 H, s), 4.45 (1 H, dd, ^3J 4.5 and 6.8) and 7.18–7.33 (5 H, m).

Methyl 3-(*p*-chlorophenyl)-2-hydroxypropanoate 17. Yield 8%, mp 61–63 °C after dry flash column chromatography on silica [lit.,[19] mp of (−)-enantiomer 61–63 °C]; δ_H(200 MHz) 2.89 (1 H, dd, ^2J 14.0 and ^3J 6.8), 2.9 (1 H, br s), 3.06 (1 H, dd, ^2J 14.0 and ^3J 4.3), 3.75 (3 H, s), 4.40 (1 H, dd, ^3J 4.3 and 6.8), 7.12 (2 H, d, ^3J 8.4) and 7.23 (2 H, d, ^3J 8.4), *m/z* 216 (M^+, 1.3%), 214 (M^+, 4.5), 198 (9), 196 (28), 155 (7), 127 (32) and 125 (100).

Methyl 2-hydroxy-3-(*p*-nitrophenyl)propanoate 19. Yield 57%, mp 58–60 °C (compound reported previously in a patent[20]); δ_H(200 MHz) 2.8 (1 H, br s), 3.03 (1 H, dd, ^2J 14.0 and ^3J 7.0), 3.22 (1 H, dd, ^2J 14.0 and ^3J 4.2), 3.77 (3 H, s), 4.47 (1 H, dd, ^3J 4.2 and 7.0), 7.38 (2 H, d, ^3J 8.6) and 8.13 (2 H, d, ^3J 8.6); *m/z* 207 [$(M - 18)^+$, 25%], 176 (11), 166 (15), 137 (17) and 91 (33).

Small-scale reactions of 3-aryl-2-hydroxypropanoic esters with DAST

A solution of the propanoic ester (0.4 mmol) in dichloromethane (5 cm^3) was added dropwise over 2 min to a solution of DAST (140 μl, 1.1 mmol) in dichloromethane (5 cm^3) at 0 °C. The ice bath was removed and the mixture was stirred at room temperature for 1 h. Water (20 cm^3) was added to the mixture, and the organic layer was separated, washed with dilute aqueous sodium hydrogen carbonate (2 × 20 cm^3) and with brine (2 × 20 cm^3) and dried over magnesium sulfate. Removal of the solvent under reduced pressure gave the crude mixture of products which was analysed by ^1H NMR spectroscopy without further purification. Assignments were made by comparison of the coupling patterns of the multiplets in the range δ_H 3.9–5.5 with those rigorously identified (see above), and ratios were determined by careful integration of the expanded multiplets.

Minor alterations in the method were required when other solvents were used, as follows. For solubility reasons, an increased quantity of hexane (50 cm^3) was employed. Because of the solubility of tetrahydrofuran in water, the mixture obtained after aqueous quenching was saturated with salt and the organic products were extracted into dichloromethane before work-up in the usual way.

Methyl 3-hydroxy-2-phenylpropanoate 13 (X = H)

A solution of 3-hydroxy-2-phenylpropanoic acid (5.00 g, 30 mmol) in methanol (100 cm^3) containing toluene-*p*-sulfonic acid hydrate (0.15 g, 0.8 mmol) was heated at reflux for 18 h, cooled and concentrated. The residue was chromatographed on silica gel using dichloromethane–methanol (98.5:1.5 v/v) as eluent to afford the ester **13** (X = H) (4.45 g, 82%) as a colourless oil [Found: M^+ (EI), 180.0787. $C_{10}H_{12}O_3$ requires M, 180.0787]; ν_{max}(film)/cm^{-1} 3420 (OH) and 1740 (CO); δ_H(270 MHz) 2.52 (1 H, br, exchanges with D_2O, OH), 3.70 (3 H, s, OMe), 3.81 (2 H, m, CH_2OH), 4.11 (1 H, dd, J 10.1 and 7.9, PhC*H*) and 7.30 (5 H, m, Ph); δ_C(100 MHz) 52.2 (OMe), 53.9 (PhCH), 64.6 (CH_2OH), 127.8 (phenyl 4-C), 128.2 (2 C, s, phenyl 3-C and 5-C), 128.9 (2 C, s, phenyl 2-C and 6-C), 135.6 (phenyl 1-C) and 173.6 (CO); *m/z* (CI, ammonia) 198 (MNH_4^+, 100%) and 181 (MH^+, 4).

Reaction of methyl 3-hydroxy-2-phenylpropanoate 13 (X = H) with DAST

A solution of **13** (X = H) (1.80 g, 10 mmol) in dichloromethane (50 cm^3) was added over 5 min to an ice cooled, stirred solution of DAST (3.63 cm^3, 27.5 mmol) in dichloromethane (50 cm^3) under argon. The cooling bath was removed and the mixture was stirred at room temperature for 2 h before being diluted with water (100 cm^3) and the pH adjusted to 7 by the addition of aqueous sodium hydrogen carbonate. The layers were separated and the aqueous phase was extracted with dichloromethane (150 cm^3). The combined dichloromethane solutions were washed with brine (200 cm^3) and dried ($MgSO_4$). Evaporation of the solvent afforded the crude reaction product as a gum (1.99 g). ^1H NMR analysis of this material showed the presence of **12** (X = H), **11** (X = H) and **21** in the ratio 67, 5 and 28 mol% respectively, which could not be separated by silica gel chromatography [Found: M^+ (EI), 182.0743 and 162.0680. $C_{10}H_{11}FO_2$ and $C_{10}H_{10}O_2$ require M, 180.0743 and 162.0681 respectively].

Methyl 3-fluoro-2-phenylpropanoate 12 (X = H). δ_H(270 MHz) 3.72 (3 H, s, OMe), 4.02 (1 H, ddd, $^3J_{HF}$ 13.2, $^3J_{HH}$ 9.1 and $^3J_{HH}$ 5.5, PhC*H*), 4.58 (1 H, ddd, $^2J_{HF}$ 46.2, $^2J_{HH}$ 9.1 and $^3J_{HH}$ 5.5, C*H*HF), 4.97 (1 H, dt, $^2J_{HF}$ 47.1, $^2J_{HH}$ 9.1 and $^3J_{HH}$ 9.1, CH*H*F) and 7.33 (5 H, m, Ph).

Methyl 2-fluoro-3-phenylpropanoate 11 (X = H). δ_H(270 MHz) 3.16 (1 H, ddd, $^3J_{HF}$ 24.2, $^2J_{HH}$ 14.6 and $^3J_{HH}$ 7.7, PhC*H*-HCHF), 3.22 (1 H, ddd, $^3J_{HF}$ 28.9, $^2J_{HH}$ 14.6 and $^3J_{HH}$ 4.1, PhCH*H*CHF), 3.77 (3 H, s, OMe), 5.11 (1 H, ddd, $^2J_{HF}$ 49.0, $^3J_{HH}$ 7.7 and $^3J_{HH}$ 4.1, $PhCH_2CHF$) and 7.30 (5 H, m, Ph).

Methyl 2-phenylpropenoate 21. δ_H(270 MHz) 3.82 (3 H, s, OMe), 5.89 (1 H, d, J 1.2, olefinic H), 6.37 (1 H, d, J 1.2, olefinic H) and 7.33 (5 H, m, Ph).

Acknowledgements

We are grateful to SmithKline Beecham Pharmaceuticals for the award of a vacation studentship (to K. M.)

References

1 (*a*) S. Rozen and R. Filler, *Tetrahedron*, 1985, **41**, 1111; (*b*) D. J. Burton, A. Thenappan and Z.-Y. Yang, *Selective Fluorination in Organic and Bioorganic Chemistry*, American Chemical Society, Washington, DC, 1991, p. 91.

2 J. T. Welch and S. Eswarakrishnan, *Fluorine in Bioorganic Chemistry*, Wiley, New York, 1991.

3 M. Hudlicky, *Org. React. (N. Y.)*, 1988, **35**, 513.

4 D. Haigh, *Int. Pat. Appl.*, WO 93/21166, 1993.

5 (*a*) R. M. Hindley, *Int. Pat. Appl.*, WO 92/02520, 1992; (*b*) B. C. C. Cantello, M. A. Cawthorne, G. P. Cottam, P. T. Duff, D. Haigh, R. M. Hindley, C. A. Lister, S. A. Smith and P. L. Thurlby, *J. Med. Chem.*, 1994, **37**, 3977.

6 Y. Kawamatsu, H. Asakawa, T. Saraie, E. Imamiya, K. Nishikawa and Y. Hamuro, *Arzneim.-Forsch.*, 1980, **30**, 585.

7 (*a*) Y. Takeuchi, K. Nagata and T. Koizumi, *J. Org. Chem.*, 1989, **54**, 5453; (*b*) A. Thenappan and D. J. Burton, *J. Org. Chem.*, 1990, **55**, 2311.

8 (*a*) H. Machleidt and R. Wessendorf, *Liebigs Ann. Chem.*, 1964, **674**, 1; (*b*) A. Thenappan and D. J. Burton, *J. Org. Chem.*, 1990, **55**, 4639.

9 Hydrogenolysis of 2-fluoropropenoates and analogous fluoroalkenylphosphonates is often accompanied by hydrogenolytic cleavage of the carbon-fluorine bond. See, for example (*a*) P. Martinet, R. Sauvetre and J.-F. Normant, *J. Fluorine Chem.*, 1991, **52**, 419; (*b*) G. M. Blackburn and M. J. Parratt, *J. Chem. Soc., Perkin Trans. 1*, 1986, 1417.

10 (*a*) F. Faustini, S. De Munari, A. Panzeri, V. Villa and C. A. Gandolfi, *Tetrahedron Lett.*, 1981, **22**, 4533; (*b*) R. Keck and J. Retey, *Helv. Chim. Acta*, 1980, **63**, 769.
11 (*a*) K. Koga, C. C. Wu and S. Yamada, *Tetrahedron Lett.*, 1971, 2283; (*b*) K. Koga, C. C. Wu and S. Yamada, *Tetrahedron Lett.*, 1971, 2287; (*c*) K. Koga, C. C. Wu and S. Yamada, *Chem. Pharm. Bull.*, 1972, **20**, 1272; (*d*) K. Koga, C. C. Wu and S. Yamada, *Chem. Pharm. Bull.*, 1972, **20**, 1282.
12 (*a*) S. Yamada, K. Koga, T. M. Juang and K. Achiwa, *Chem. Lett.*, 1976, 927; (*b*) T. M. Juang and S. Yamada, *Chem. Pharm. Bull.*, 1984, **32**, 4426.
13 (*a*) G. A. Olah, G. K. S. Prakash and Y. L. Chao, *Helv. Chim. Acta*, 1981, **64**, 2528; (*b*) J. Barber, R. Keck and J. Retey, *Tetrahedron Lett.*, 1982, **23**, 1549; (*c*) S. Hamman and C. G. Beguin, *Tetrahedron Lett.*, 1983, **24**, 57.
14 For a related reaction see H. Uneme and Y. Okada, *Bull. Chem. Soc. Jpn.*, 1992, **65**, 2401.
15 E. Brown, R. Joyeau, M. Paterne and P.-F. Casals, *C. R. Seances Acad. Sci., Ser. C*, 1978, **287**, 125.
16 H. C. Brown, C. J. Kim, C. J. Lancelot and P. von R. Schleyer, *J. Am. Chem. Soc.*, 1970, **92**, 5244.
17 E. I. Snyder, *J. Am. Chem. Soc.*, 1963, **85**, 2624.
18 A. McKenzie and G. Martin, *J. Chem. Soc.*, 1913, **103**, 112.
19 T. Schmidt, C. Fedtke and R. R. Schmidt, *Ger. Offen*, 2 426 651 (1975).
20 A. D. Robertson, G. R. Martin and J. S. Buckingham, *Eur. Pat. Appl.*, EP 313 397 (1987).

Paper 6/04186H
Received 14*th June* 1996
Accepted 6*th September* 1996