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Elemental fluorine. Part 19: Electrophilic fluorination of hexyl derivatives bearing electron withdrawing groups☆

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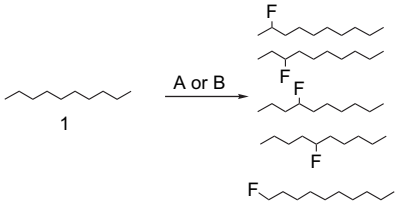
Abstract—Reaction of a series of model hexyl derivatives of the form C_6H_{13}–X (X=Cl, Br, I, CO_2Me, COMe, CHO) with both elemental fluorine and Selectfluor™ was studied in order to assess the impact of electron withdrawing functional groups upon fluorination of an alkyl chain. Fluorination generally occurs at secondary sites, with a slight preference for those that are furthest removed from the electron withdrawing group, consistent with an electrophilic substitution process, although mixtures of fluorinated products are obtained in most cases.

1. Introduction

Fluorination can confer unusual, and sometimes valuable, chemical and biological properties upon a molecular system and these effects have been exploited by the life science industries for the development of many fluorinated pharmaceuticals and agrochemicals.[2,3] Regio- and stereo-selective introduction of fluorine atoms at unactivated sites that are remote from a functional group in aliphatic systems by viable synthetic methodology that is also suitable for large scale synthesis, presents a formidable challenge to organofluorine chemistry.[4] Therefore, in this context, effective fluorination procedures that involve selective transformation of carbon–hydrogen to carbon–fluorine bonds at remote sites would be extremely valuable in order to expand the range of fluorinated systems that may be readily accessed from nonfluorinated precursors.

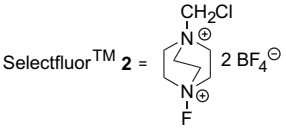
Electrophilic aliphatic substitution processes are not very common but Rozen[4] and, subsequently, the Durham group[5] have demonstrated that electrophilic fluorination of aliphatic sites by elemental fluorine and electrophilic fluorinating reagents of the N–F class[6] can be achieved. A broad parallel has been established between the products observed for reactions between open-chain hydrocarbons, such as *n*-decane **1** (Scheme 1) and with either elemental fluorine or Selectfluor™ **2**.[5] This is significant evidence for the role of fluorine as an electrophile, rather than a radical under the conditions used, because radical clock experiments conducted using Selectfluor™ showed no evidence of a radical process for fluorination of several unsaturated systems.[7,8] It is possible that acetonitrile performs a similar role of hydrogen bonding to the incipient fluoride ion in the transition state, similar to that suggested by Rozen for the role of chloroform (Scheme 2).



A (61% conv.) 63%, 2.4 : 1.3 : 1.1 : 1 : 0.5

B (84% conv.) 58%, 2.4 : 1.3 : 1 : 1.1

A, 10% F_2 in N_2 (*v/v*), CH_3CN, 0 °C; B, Selectfluor, CH_3CN, reflux 16 h.



Scheme 1.

☆ For Part 18 see Ref. 1.

Keywords: Fluorine; Selective fluorination; Fluorinating agents; Electrophilic aliphatic substitution.

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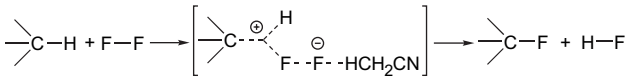
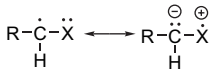


Scheme 2.

Selective electrophilic fluorination of aliphatic systems bearing functional groups could, in principle, offer methodology for the synthesis of a range of fluorinated systems where fluorine is attached to sites remote from the functional group itself, if the influence of individual functional groups on the approaching fluorinating agent can be established and eventually made sufficiently dominant.

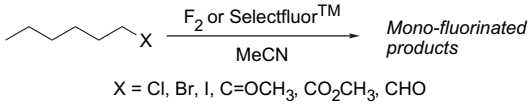
Chlorination and bromination of saturated aliphatic derivatives have been extensively studied[9–11] and the effect of a functional group upon the relative reactivities of the carbon–hydrogen bonds in an adjoining saturated aliphatic chain towards free radical chlorination has long been established. For example, it is well known that an inductively electron withdrawing substituent significantly deactivates the carbon–hydrogen bonds that are attached to the carbon atom bearing the functional group towards electrophilic chlorine atoms, although the effect rapidly falls off with distance.[9] Also, a competing mesomeric stabilising influence may render the 1-position active (Scheme 3).



Scheme 3.

To date, however, there is little related systematic assessment concerning reactions of fluorine with substituted alkanes.[12,13] Of the very few studies of this type, in research involving fluorination of various steroid derivatives, Rozen[4] demonstrated that electron withdrawing groups such as acetyl, chlorine and trifluoromethyl-acetyl favoured fluorination at the furthest removed tertiary carbon–hydrogen bonds, consistent with an electrophilic aliphatic substitution process.

In this series, we are developing the use of elemental fluorine as a viable reagent for organic synthesis[14] and, here, we describe the fluorination of a range of model hexyl systems, each bearing an electron withdrawing group (Scheme 4), in order to establish the effect of each functionality upon the conversion of unactivated carbon–hydrogen bonds to carbon–fluorine bonds, at sites within an alkyl chain.



Scheme 4.

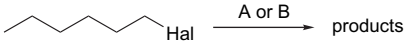
We set out to establish the relative selectivities at each carbon site in the aliphatic chain towards electrophilic fluorination. For comparison purposes, we also describe the fluorination of the same substrates by Selectfluor™. Fluorination of many unsaturated systems by Selectfluor™ have been reported,[6] but reactions at saturated sites remain largely limited to our previous work.

2. Results and discussion

Fluorination of 1-halohexanes with fluorine and Selectfluor™ were carried out using solutions in acetonitrile at 0 °C and reflux temperature, respectively, and the results are contained in Table 1.

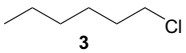
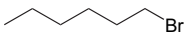
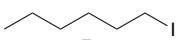
1-Chlorohexane **3** gave a mixture of three major products **4b–d** in the ratio 1:1.8:1.9, arising from substitution of hydrogen located at the 3-, 4- and 5-positions, respectively, and a large number of other components each in very small quantities. Fluorination by Selectfluor™ was slightly more selective with the 3-, 4- and 5-fluoro derivatives **4a–d** being formed in the ratio 1:2.7:5.2:10.1 in slightly higher overall yield. Preparative scale GC was used to isolate an analytically pure sample of an isomeric mixture of the two main products **4c** and **4d**. Identification of 1-chloro-5-fluorohexane **4d** could be made on the basis of the $^{2}J_{CF}$ coupling constant observed for the resonance attributed to the methyl group, readily identified by ^{13}C DEPT, whilst the methyl resonance for 1-chloro-4-fluorohexane **4c** showed only $^{3}J_{CF}$ coupling. In both cases, fluorination of the 1- and 2-positions was minor, indicating the deactivating effect of the chlorine atom at the adjacent sites. Moreover, these results demonstrate more selectivity than those observed for radical chlorination and, this is, of course, consistent with electrophilic fluorination at saturated carbon, where we would anticipate polar influences to be more important than for radical processes.

Table 1. Fluorination of haloalkanes



Hal = Cl, Br, I

A, 10% F_2 in N_2 (*v/v*), CH_3CN, 0 °C; B, Selectfluor, CH_3CN, reflux 16 h.

Substrate	Conditions A or B (conv. %)	Product(s) (yield %)
 **3**	A (72)	22%, **4a**:**4b**:**4c**:**4d**, trace:1:1.8:1.9+many unidentified products
	B (53)	56%, **4a**:**4b**:**4c**:**4d**, trace:1:2.7:5.2:10.1
 **5**	A (100)	Many unidentified products
	B (30)	75%, **6a**:**6b**:**6c**, 1:1.9:3.8
 **7**	A (100)	Many unidentified products
	B (100)	Many unidentified products

Direct fluorination of 1-bromohexane **5** by fluorine gave a very complex mixture from which no products could be identified. It is likely that the brominated substrate is oxidised by fluorine to either a BrF_2 or BrF_4 derivative followed by elimination, in processes analogous to those reported by Adcock et al. in perfluorination reactions of similar substrates.[15] In contrast, Selectfluor™ led to reasonable yields of products **6a–c** fluorinated at the 3-, 4- and 5-positions in a ratio 1:1.9:3.8, which is similar to those obtained upon fluorination of chlorohexane. The 5-fluoro-bromohexane **6c** and 4-fluoro-bromohexane **6b** products were isolated by preparative GC as a mixture of isomers and identified by the techniques described above.

1-Iodohexane **7** gave intractable tars upon reaction with either fluorine or Selectfluor™, probably arising from oxidation processes in both cases.

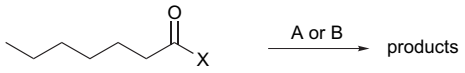
Results of fluorination reactions between model carbonyl containing hexyl systems and either fluorine or Selectfluor™ are collected in Table 2.

Fluorination of methyl enanthate **8** by fluorine gave four main products **9a–d** in the ratio 1:3.5:6.4:5.6 along with small quantities of numerous other products including trace quantities of other monofluorinated derivatives and some tar. The four major products were isolated as a mixture of isomers by preparative scale GC and this enabled their characterisation by NMR techniques indicated above. Similarly, Selectfluor™ gave the same four main products and traces of many other fluorinated systems.

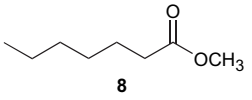
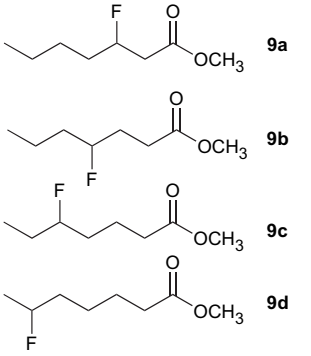
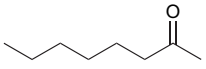
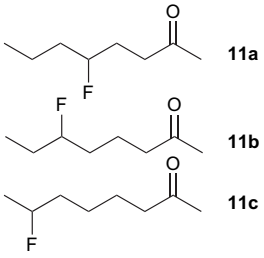
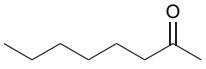
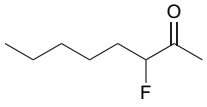
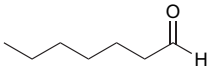
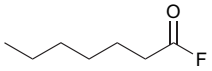
Fluorination of octan-2-one **10** with fluorine gave a mixture of three main monofluorinated products **11a–c** arising from substitution of carbon–hydrogen bonds at the 5-, 6- and 7-methylene sites in the ratio 1:1.7:1.3 along with other products and tar. In contrast, reaction of Selectfluor™ with octan-2-one was an efficient and selective process that gave 3-fluoro-heptan-2-one **11d** as the only product. Selectfluor™ makes the reaction medium more acidic in nature[5] and, therefore, promotes the formation of an enol form of the ketone, which allows selective fluorination of the enolic 3-position.

Fluorination of heptanal **12** with fluorine gave heptanoic acid fluoride **13** as a major product (Scheme 5), which could readily be identified by ^{19}F NMR (δ_F=+20 ppm) of the reaction mixture. Due to the instability of these systems towards hydrolysis, 2,4-dinitrobenzyl alcohol **14** was added to the reaction mixture and the corresponding ester **15** was isolated by column chromatography. A mechanism for the transformation of aldehydes to acid fluorides using fluorine is given

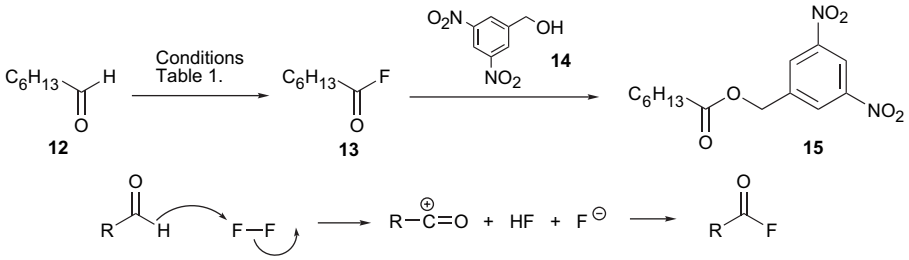
Table 2. Fluorination of carbonyl derivatives



A, 10% F_2 in N_2 (*v/v*), CH_3CN, 0 °C; B, Selectfluor, CH_3CN, reflux 16 h.

Substrate	Conditions A or B (conv. %)	Product(s) (yield %)
 **8**		 **9a**, **9b**, **9c**, **9d** + many other unidentified products in trace quantities
	A (64)	68%, **9a**:**9b**:**9c**:**9d**, 1:3.5:6.4:5.6
	B (57)	48%, **9a**:**9b**:**9c**:**9d**, 1:1.3:1.3:3.7
 **10**		 **11a**, **11b**, **11c**
	A (64%)	41%, **11a**:**11b**:**11c**, 1:1.7:1.3
 **10**		
	B (100)	**11d**, 65%
 **12**		
	A (100)	**13**, 66%[a]
	B (100)	Many unidentified products

[a] Isolated as an ester (see Scheme 5).



Scheme 5.

in Scheme 5. In contrast, Selectfluor™ gave a mixture of products, which could not be identified.

Fluorination reactions of benzaldehyde derivatives to acids, via acid fluorides, mediated by Selectfluor™ have been described by Banks et al.[16] and single electron transfer processes were suggested to account for this transformation.

3. Conclusions

In general, therefore, fluorination of model hexyl derivatives of the form C_6H_{13}–X (X=Cl, Br, I, CO_2Me, COMe, CHO) with either elemental fluorine or Selectfluor™ leads to a mixture of monofluorinated products that predominantly arise from fluorination of secondary, rather than primary, sites with slight selectivity for fluorination of methylene sites that are furthest removed from the electron withdrawing functionality. Fluorination does not, in general, occur at sites adjacent to the functional group with the exception being fluorination of ketones by Selectfluor™ and replacement of aldehydic hydrogens by fluorine using either reagent. Under the conditions used so far, the selectivity of the reactions, with the same exceptions, is not sufficient to be regarded as being synthetically useful, although the regioselectivity observed is generally consistent with an electrophilic aliphatic substitution process.

4. Experimental

4.1. General

All starting materials were obtained commercially (Aldrich) and all solvents were dried using literature procedures. NMR spectra were recorded in deuterochloroform, unless otherwise stated, on a Varian VXR 400S NMR spectrometer with tetramethylsilane and trichlorofluoromethane as internal standards. Spectral assignments were made with the aid of data collected by ^{1}H–^{1}H COSY and ^{1}H–^{13}C HETCOR experiments and coupling constants are given in hertz. In ^{19}F NMR spectra, upfield shifts are quoted as negative. Mass spectra were recorded on either a VG 7070E spectrometer or a Fisons VG Trio 1000 spectrometer coupled with a Hewlett Packard 5890 series II gas chromatograph. Accurate mass measurements were performed by the EPSRC National Mass Spectrometry service, Swansea, U.K. Elemental analyses were obtained on either a Perkin–Elmer 240 or a Carlo Erba Elemental Analyser. Melting points were recorded at atmospheric pressure and are uncorrected. Column chromatography was carried out on silica gel (Merck no. 1-09385, 230–400 mesh) and TLC analysis was performed on silica gel TLC plates using dichloromethane as an eluent.

4.2. Reactions with elemental fluorine

4.2.1. General procedure. Elemental fluorine, as a 10% (v/v) mixture with nitrogen, was passed at a rate of ca. 50 ml min^{-1} through a stirred, cooled (0 °C) mixture, which consisted of the substrate and acetonitrile. After addition of fluorine, the reaction mixture was poured into water (100 ml), neutralised ($NaHCO_3$) and extracted with dichloromethane (3×40 ml). The combined, dried ($MgSO_4$), organic extracts were evaporated to give a crude product. The composition of a weighed crude reaction mixture was determined by GC–MS analysis and the conversion of starting material was calculated from GC peak intensities. The amount of fluorinated product in the crude product was determined by adding a known amount of fluorobenzene to a weighed amount of the crude product mixture. Comparison of the relative intensities of the appropriate ^{19}F NMR resonances gave the yield of fluorinated derivative, based upon the conversion obtained above. Analytical samples of fluorinated products were obtained by either preparative scale GC or column chromatography. Yields of fluorinated products are based on the conversion of starting material.

4.2.1.1. 1-Chlorohexane 3. 1-Chlorohexane **3** (8.36 g, 69 mmol), elemental fluorine (208 mmol) and anhydrous acetonitrile (140 ml) gave a dark yellow crude mixture (9.02 g), which contained **4b**, **4c** and **4d** (1.51 g, 22%, 72% conv.) in the ratio 1.0:1.8:1.9, respectively, and a trace amount of 1-chloro-6-fluorohexane; δ_F −217.49 (m), a large number of other unidentified products (16%) and tar (10%). Purification of the crude product by preparative scale GC gave an analytically pure sample consisting of 1-chloro-4-fluorohexane **4c** and 1-chloro-5-fluorohexane **4d** as a mixture of isomers and as a colourless liquid; (Found: C, 51.8; H, 8.7. $C_6H_{12}ClF$ requires: C, 52.0; H, 8.7%); *1-chloro-4-fluorohexane* ***4c***: δ_H 0.98 (3H, t, $^3J_{HH}$ 7.6, CH_3), 1.4–2.0 (6H, m, CH_2), 3.60 (2H, m, CH_2Cl), 4.42 (1H, dm, $^2J_{HF}$ 49.5, CHF); δ_F −182.64 (m); δ_C 9.3 (d, $^3J_{CF}$ 6.4, C-6), 28.1 (d, $^2J_{CF}$ 21.0, C-5), 28.3 (d, $^3J_{CF}$ 3.8, C-2), 32.0 (d, $^2J_{CF}$ 21.3, C-3), 44.9 (s, CH_2Cl), 94.9 (d, $^1J_{CF}$ 168.3, CF); *m/z* (EI$^+$) 118 (M^+−HF, 5%), 91 (25), 82 (22), 73 (16), 55 (100); *1-chloro-5-fluorohexane* ***4d***: δ_H 1.35 (3H, dd, $^3J_{HF}$ 24.0, $^3J_{HH}$ 6.0, CH_3), 1.4–2.0 (6H, m, CH_2), 3.55 (2H, t, $^3J_{HH}$ 6.8, CH_2Cl), 4.68 (1H, dm, $^2J_{HF}$ 48.5, CHF); δ_F −173.29 (m); δ_C 21.0 (d, $^2J_{CF}$ 20.9, CH_3), 22.5 (d, $^3J_{CF}$ 5.0, C-3), 32.3 (s, C-2), 36.1 (d, $^2J_{CF}$ 21.0, C-4), 44.8 (s, CH_2Cl), 90.7 (d, $^1J_{CF}$ 164.4, CF).

4.2.1.2. 1-Bromohexane 5. 1-Bromohexane **5** (5.0 g, 30 mmol), elemental fluorine (60 mmol) and anhydrous acetonitrile (140 ml) gave an orange reaction mixture, which was decolourised using aqueous sodium metabisulfite and then worked up as above to give a yellow crude product mixture (6.2 g), which contained **5** (56%) and many unidentified products (>20). No further purification was attempted.

4.2.1.3. 1-Iodohexane 7. 1-Iodohexane **7** (8.0 g, 38 mmol), elemental fluorine (38 mmol) and anhydrous acetonitrile (ml) gave a red-purple reaction mixture, which was decolourised using aqueous sodium metabisulfite and then worked up as above to give a yellow crude product mixture (7.6 g), which contained many unidentified products (>20). No further purification was attempted.

4.2.1.4. Methyl enanthate 8. Methyl enanthate **8** (4.37 g, 30 mmol), elemental fluorine (91 mmol) and acetonitrile (140 ml) gave a brown crude product mixture (7.25 g), which contained **9a**, **9b**, **9c** and **9d** (2.14 g, 68%, 64% conv.) in the ratio 1.0:3.5:6.4:5.6, respectively, and a trace amount of methyl 7-fluoroenanthate; δ_F −217.23 (m) and several unidentified products (24%). Purification of the

crude product by preparative scale GC gave **9a–d** as a mixture of isomers and as a colourless liquid; (Found: C, 59.1; H, 9.3. $C_8H_{15}FO_2$ requires: C, 59.2; H, 9.3%); *methyl 3-fluoroenanthate* ***9a***: δ_F −183.62 (m); δ_C 92.4 (d, $^1J_{CF}$ 167.9, CHF), 173.9 (s, C═O); δ_H 0.80–1.00 (1H, m, CH_2 and/or CH_3), 1.27–1.65 (7H, m, CH_2 and/or CH_3), 2.30–2.38 (3H, m, CH_3), 3.67–6.68 (3H, m, OCH_3), 4.25–5.02 (1H, m, CHF); *methyl 4-fluoroenanthate* ***9b***: δ_F −180.08 (m); δ_C 90.6 (d, $^1J_{CF}$ 169.4, CHF), 174.6 (s, C═O); *methyl 5-fluoroenanthate* ***9c***: δ_F −182.8 (m); δ_C 95.4 (d, $^1J_{CF}$ 167.5, CHF), 174.1 (s, C═O); *methyl 6-fluoroenanthate* ***9d***: δ_F −173.14 (m); δ_C 21.2 (d, $^2J_{CF}$ 22.9, CH_3), 36.8 (d, $^2J_{CF}$ 20.6, CH_2CHF), 90.7 (d, $^1J_{CF}$ 164.5, CHF), 174.3 (s, C═O); other ^{13}C resonances that could not be assigned with certainty to each particular isomer, but are consistent with the structures of **9a–d** proposed, are as follows: δ_C 9.6 (d, J_{CF} 4.9, CH_3–B), 14.1 (s, CH_3–B), 14.2 (s, CH_3–B), 18.5 (s, CH_2), 18.6 (s, CH_2), 20.9 (d, J_{CF} 4.1, CH_2), 24.9 (d, J_{CF} 5.0, CH_2), 27.2 (d, J_{CF} 4.2, CH_2), 28.5 (d, $^2J_{CF}$ 22.6, CH_2CHF), 29.9 (d, J_{CF} 4.2, CH_2), 30.5 (d, $^2J_{CF}$ 21.4, CH_2CHF), 33.9 (s, CH_2), 34.2 (d, $^2J_{CF}$ 21.0, CH_2CHF), 34.8 (d, $^2J_{CF}$ 20.2, CH_2CHF), 37.4 (d, $^2J_{CF}$ 20.6, CH_2CHF), 40.5 (d, $^2J_{CF}$ 24.0, CH_2CHF), 51.7 (s, OCH_3), 51.8 (s, OCH_3), 51.8 (s, OCH_3), 51.9 (s, OCH_3); *m/z* (CI^+, NH_3) 180 (M^++18, 100%), all isomers gave similar results.

4.2.1.5. Octan-2-one 10. Elemental fluorine (120 mmol), octan-2-one (2.8 g, 24 mmol) and acetonitrile (140 ml) gave a brown oil (2.9 g, 64% conv.), which contained 7-fluoro-octan-2-one, 6-fluoro-octan-2-one and 5-fluoro-octan-2-one in the ratio 1.3:1.7:1. Purification of the crude product by column chromatography using hexane–ethyl acetate gave 7-fluoro-octan-2-one and 6-fluoro-octan-2-one as a yellow oil and as a mixture of isomers (1.0 g, 41%); *7-fluoro-octan-2-one*: δ_H 1.32 (dd, $^3J_{HF}$ 23.7, $^3J_{HH}$ 6.1, CH_3CFH), 1.35–1.6 (m), 2.10 (s, C═OCH_3), 4.25 (dm, $^2J_{HF}$ 45.4, C*H*F); δ_F 173.1 (dm, $^2J_{HF}$ 46.2); δ_C 21.1 (d, $^2J_{CF}$ 22.7, C-8), 23.7 (s, C-1), 24.8 (d, $^3J_{CF}$ 4.7, C-5), 30.0 (s, C-4), 36.8 (d, $^2J_{CF}$ 20.6, C-6), 43.7 (s, C-3), 90.6 (d, $^1J_{CF}$ 165.2, C-7), 208.8 (s, C-2); *m/z* (EI^+) 147.1 (M^++H, 3%), 146.0 (2), 126 (42), 41 (100); *6-fluoro-octan-2-one*: δ_H 0.9 (t, $^3J_{HH}$ 7.73, CH_3), 1.21–1.60 (m, CH_2), 2.11 (s, C═OCH_3), 2.43 (t, $^3J_{HH}$ 6.8, CH_2C═O), 4.44 (dm $^2J_{HF}$ 44.7, C*H*F); δ_F 182.3 (dtt, $^2J_{HF}$ 47.2, $^3J_{HF}$ 26.5, 20.5); δ_C 9.4 (d, $^3J_{CF}$ 5.8, C-8), 19.6 (d, $^3J_{CF}$ 4.0, C-4), 23.7 (s, C-1), 28.2 (d, $^2J_{CF}$ 21.8, C-7), 34.1 (d, $^2J_{HF}$ 21.0, C-5), 43.4 (s, C-3), 94.5 (d, $^1J_{HF}$ 165.5, C-6), 209.0 (s, C-1); *m/z* (EI^+) 146.1 (M^++H, 1%), 126.1 (12), 42 (100); *5-fluoro-octan-2-one*: δ_F 183.3 (dm, $^2J_{HF}$ 46.2); *m/z* (EI^+) 146.1 (M^++H, 1%), 126.1 (12), 42 (100).

4.2.1.6. Heptanal 12. Elemental fluorine (234 mmol) as a 10% (v/v) mixture with nitrogen was passed through a cooled (0 °C) and stirred mixture of heptanal (6.61 g, 58 mmol) and acetonitrile (140 ml). After all the fluorine has been added, 3,5-dinitrobenzyl alcohol **14** (5.0 g, 25 mmol) was added to the reaction mixture, which was then heated for 24 h at reflux temperature. After the usual work up and drying, a brown crude product was obtained and purification by column chromatography using dichloromethane as eluent gave *(3,5-dinitrophenyl)methyl heptanoate* **15** (2.57 g, 39%) as a pale yellow solid; mp 38–40 °C; (Found: C, 53.9; H, 5.8; N, 8.9. $C_{14}H_{18}N_2O_6$ requires C, 54.2; H, 5.9; N, 9.0%); δ_H 0.87 (3H, t, $^3J_{HH}$ 7.2, CH_3), 1.29 (6H, m, CH_2), 1.66 (2H, m, CH_2), 2.44 (2H, t, $^3J_{HH}$ 7.6, H-6), 5.29 (2H, s, H-8), 8.54 (2H, m, ArH), 8.99 (1H, m, ArH); δ_C 13.9 (s, CH_3), 22.4 (s, C-2), 24.7 (s, C-3), 28.7 (s, C-4), 31.3 (s, C-5), 33.9 (s, C-6), 63.5 (s, CH_2O), 118.4 (s, ArH), 127.7 (s, ArH), 140.8 (s, Ar), 148.6 (s, $ArNO_2$), 173.1 (s, C═O); *m/z* (EI^+) 223 (54), 181 (48), 129 (13), 43 (100).

4.3. Fluorinations using Selectfluor™ 2

4.3.1. General procedure. A solution consisting of **2**, substrate and acetonitrile (130 ml) was stirred and heated (65 °C). After 24 h, the reaction mixture was poured into water, neutralised ($NaHCO_3$) and extracted with dichloromethane (3×50 ml). The combined, dried ($MgSO_4$), organic extracts were evaporated to give a crude product, which was analysed by GC–MS and ^{19}F NMR as described above and purified by column chromatography.

4.3.1.1. 1-Chlorohexane 3. 1-Chlorohexane **3** (8.00 g, 67 mmol), **2** (25.96 g, 73 mmol) and acetonitrile (260 ml) gave a dark yellow product (8.24 g). Purification of the crude product by preparative scale GC gave an analytically pure sample of 1-chloro-2-fluorohexane, 1-chloro-3-fluorohexane, 1-chloro-4-fluorohexane and 1-chloro-5-fluorohexane (2.75 g, 56%, 53% conv.) as a mixture of isomers, in the ratio 1.0:2.7:5.2:10.1, respectively, as a yellow oil; spectral data as above.

4.3.1.2. 1-Bromohexane 5. 1-Bromohexane **5** (5.00 g, 30 mmol), **2** (11.80 g, 33 mmol) and acetonitrile (120 ml) gave a dark yellow product (7.93 g), which contained **6a**, **6b** and **6c** (1.10 g, 75%, 30% conv.) in the ratio 1.0:1.9:3.8, respectively, and a large number of other unidentified products (10%). Purification by preparative scale GC gave an analytically pure sample of 1-bromo-4-fluorohexane **6b** and 1-bromo-5-fluorohexane **6c** as a mixture of isomers and as a colourless oil; (Found: C, 39.6; H, 6.7. $C_6H_{12}BrF$ requires: C, 39.3; H, 6.6%); *1-bromo-4-fluorohexane* ***6b***: δ_H 0.98 (3H, t, $^3J_{HH}$ 7.6, CH_3), 1.2–2.0 (6H, m, CH_2), 3.40 (2H, m, CH_2Br), 4.43 (1H, dm, $^2J_{HF}$ 48.8, CHF); δ_F −181.18 (m); δ_C 9.3 (d, $^3J_{CF}$ 5.7, CH_3), 28.1 (d, $^2J_{CF}$ 21.0, C-5), 28.4 (d, $^3J_{CF}$ 3.8, C-2), 33.2 (d, $^2J_{CF}$ 20.9, C-3), 33.6 (s, C-1), 94.8 (d, $^1J_{CF}$ 168.3, CF); *m/z* (EI^+) 102 (M^+−HBr, 10%), 83 (31), 74 (52), 55 (100); *1-bromo-5-fluorohexane* ***6c***: δ_H 1.32 (3H, dd, $^3J_{HF}$ 23.0, $^3J_{HH}$ 6.0, CH_3), 1.2–2.0 (6H, m, CH_2), 3.40 (2H, m, CH_2Br), 4.66 (1H, dm, $^2J_{HF}$ 48.8, CHF); δ_F −171.83 (m); δ_C 21.0 (d, $^2J_{CF}$ 22.8, CH_3), 23.8 (d, $^3J_{CF}$ 4.6, C-3), 32.5 (s, C-2), 33.5 (s, CH_2Br), 35.9 (d, $^2J_{CF}$ 20.6, C-4), 90.7 (d, $^1J_{CF}$ 164.9, CHF).

4.3.1.3. 1-Iodohexane 7. 1-Iodohexane **7** (5.0 g, 24 mmol), **2** (9.2 g, 26 mmol) and acetonitrile (90 ml) gave, after 16 h of stirring, a red-purple reaction mixture, which was decolourised using aqueous sodium metabisulfite and then worked up as above to give a yellow crude product mixture (7.3 g), which contained >30 unidentified products by GC–MS. No further purification was attempted.

4.3.1.4. Methyl enanthate 8. Methyl enanthate **8** (4.00 g, 28 mmol), **2** (13.66 g, 31 mmol) and acetonitrile (140 ml)

gave a yellow product (4.68 g), which contained **9a**, **9b**, **9c** and **9d** (1.24 g, 48%, 57% conv.) as a mixture of isomers in the ratio 1.0:1.3:1.3:3.7, respectively, and as a colourless liquid; spectral data as above.

4.3.1.5. Octan-2-one 10. Octan-2-one **10** (5.00 g, 39 mmol), **2** (15.25 g, 43 mmol) and acetonitrile (150 ml) gave a yellow crude mixture (17.13 g), which contained **11e** (65%). Preparative GC gave an analytical sample of 3-fluoro-octan-2-one **11e** as a colourless liquid; (Found: C, 65.4; H, 10.4. $C_7H_{13}F$ requires C, 65.7; H, 10.3%); ν_{max}/cm^{-1} 1726 (C=O), 1081 (C–F); δ_H 0.89 (3H, m, CH_3), 1.31 (4H, m, H-6, H-7), 1.39 (2H, m, H-5), 1.8 (2H, m, H-4), 2.25 (3H, m, C=OCH_3), 4.65 (1H, m, CHF); δ_C 13.9 (s, C-8), 22.4 (s, C-7), 24.1 (d, $^3J_{CF}$ 3, C-5), 25.9 (s, C-1), 31.3 (s, C-6), 31.8 (d, $^2J_{CF}$ 21, C-4), 96.0 (d, $^1J_{CF}$ 185, C-3), 208.8 (d, $^2J_{CF}$ 25, C-2); δ_F −189.94 (m); *m*/*z* (EI$^+$) 146 (M$^+$, 4%), 111 (0.2), 99 (0.9), 76 (31), 55 (8).

4.3.1.6. Heptanal 12. Heptanal **12** (5.00 g, 44 mmol), **2** (17.04 g, 48 mmol) and acetonitrile (150 ml) gave a dark brown crude mixture (4.66 g), which contained many unidentified components by GC–MS and ^{19}F NMR analysis. No further purification was attempted.

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