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Addition of perfluoroalkyl iodides to 4-pentenol and its derivatives: one-pot preparation of 2-[(*F*-alkyl)methyl]-tetrahydrofurans

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Abstract

Depending on the nature of the alkaline medium, the radical addition of perfluoroalkyl iodides to 4-pentenol gives a mixture of 5-(*F*-alkyl)-4-pentenol and 2-[(*F*-alkyl)-methyl]tetrahydrofuran, or the latter alone.

Introduction

During the course of our research related to the preparation of perfluoroalkylated surfactants for biomedical uses, and in particular for emulsifying fluorocarbons to serve as *in vivo* O_2 carriers [1–3], perfluoroalkylated alcohols of the type $C_nF_{2n+1}CH{=}CH(CH_2)_pOH$ (**1**) and $C_nF_{2n+1}(CH_2)_qOH$ (**2**), with various lengths of perfluoroalkyl and polymethylene groups, were needed. These building blocks were necessary to synthesize surfactants with modular molecular structures in order to study the respective influence of the perfluoroalkyl tail and hydrocarbon spacer lengths on their physical and biological behaviour, and to permit the stepwise adjustment of the emulsion characteristics.

Experimental

Perfluoroalkyl iodides (a gift from Atochem) were purified by washing with an aqueous solution of sodium thiosulphate, followed by light-free distillation and storage under argon in the dark. Other solvents and reagents were purchased from Aldrich and used without further purification. Gas chromatography was performed on a Delsi instrument (FID detector) fitted with a 3 m × 1/4 in. column packed with 30% SE30 on Chromosorb. All GLC analyses were performed as follows: 80 °C for 3 min, then heating 10 °C

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min^{-1} up to 200 °C with an 8 ml min^{-1} nitrogen flow rate (T_R in min). Infrared spectra were obtained on a Bruker IFS spectrometer as films. ^{1}H, ^{13}C (internal reference Me_4Si) and ^{19}F (internal reference $CFCl_3$, negative for upfield shifts) NMR spectra, all samples in $CDCl_3$ solution, were recorded on Bruker WH90 or AC200 spectrometers (protons and carbons are numbered according to IUPAC nomenclature). Combined gas–liquid chromatography/mass spectrometry was performed with a Delsi–Nermag R10-10B instrument equipped with a dual EI/CI source.

Radical addition with the AIBN initiator

With long reaction time: preparation of 4 and 5

4-Pentenol (2.16 g; 25.1 mmol) (T_R, 5.5 min) and 16.8 g (37.6 mmol, T_R, 3.5 min) of *F*-hexyl iodide with 132 mg (0.8 mmol) of AIBN were heated at 100–110 °C for 22 h until total disappearance (GLC monitoring) of 4-pentenol and 5-(*F*-hexyl)-4-iodopentanol (T_R, 16 min) (**3**) had occurred. The excess recyclable *F*-hexyl iodide having been removed, the mixture was diluted in ether and washed successively with water, aqueous sodium bicarbonate, aqueous sodium thiosulphate and water again. After drying over sodium sulphate and evaporation of the ether, distillation gave 3.70 g of 2-[(*F*-hexyl)methyl]tetrahydrofuran (**4**) (36%; T_R, 10 min) and 4.23 g of 5-(*F*-hexyl)-1,4-diiodopentane (**5**) (26%; T_R, 19 min). An analytical grade sample of **5** was further purified by chromatography over silica gel (eluant: heptane).

2-[(*F*-Hexyl)methyl]tetrahydrofuran (**4**): b.p., 32 °C/0.04 mmHg. IR (cm^{-1}): 2950; 2870 (CH); 1240–1140 (CF). ^{19}F NMR δ: -80.7 (CF_3); -112.8 ($CF_2\alpha$); -121.6 (2F); -122.7 (2F); -123.4 (2F); -125.9 ($CF_2\omega$) ppm. ^{1}H NMR δ: 1.55–2.51 (m, CH_2CH_2CH, $C_6F_{13}CH_2CH$, 6H); 3.81 and 3.93 (ABdd, $J_{5a,5b} = 8.35$ Hz, $J_{4a,5a} = J_{4b,5a} = 7.0$ Hz, $J_{4a,5b} = 7.35$ Hz, $J_{4b,5b} = 6.30$ Hz, H-5a,5b, 2H); 4.21 (quintuplet, $J_{2,3} = J_{2,6} = 6$ Hz, H-4, 1H) ppm. ^{13}C NMR δ: 72.2 (t, $^3J_{C,F} = 2.6$ Hz, C-2); 67.9 (C-5); 36.8 (t, $^2J_{C,F} = 21$ Hz, $C_6F_{13}CH_2$); 32.5 (C-3); 25.6 (C-4) ppm. Mass spectrometry (EI): $M^{\cdot+}$ 404 (1); *m/e* 73 (11); 72 (64); 71 (97); 69 (20); 57 (10); 56 (22); 46 (23); 45 (83); 44 (100); 43 (59). Analysis: Calcd. for $C_{11}H_9F_{13}O$ (404.2): C, 32.69; H, 2.25; F, 61.11%. Found: C, 32.98; H, 2.19; F, 61.52%.

5-(*F*-Hexyl)-1,4-diiodopentane (**5**): b.p., 97 °C/0.04 mmHg. ^{19}F NMR δ: -81.5 (CF_3); -111.3 (Fa) and -116.0 (Fb) ($CF_2\alpha$, $^2J_{Fa,Fb} = 268$ Hz); -122.3 (2F); -122.4 (2F); -123.6 (2F); -126.8 ($CF_2\omega$) ppm. ^{1}H NMR δ: 2.02 (m, $CH_2CH_2CH_2I$, 4H); 2.87 (m, $C_6F_{13}CH_2$, 2H); 3.24 (broad t, $^3J_{H,H} = 6$ Hz, CH_2I, 2H); 4.34 (quintuplet, $^3J_{H,H} = 6.4$ Hz, CHI, 1H) ppm. ^{13}C NMR δ: 41.8 (t, $^2J_{C,F} = 20.8$ Hz, C-5); 40.9 (t, $^2J_{C,F} = 2.2$ Hz, C-4); 33.4 (C-2); 18.5 (C-3); 4.2 (C-1) ppm. Mass spectrometry (EI): $(M+1)^+$ 643 (2); $M^{\cdot+}$ 642 (2); *m/e* 516 (28); 515 (29); 388 (9); 387 (9); 156 (14); 155 (32); 119 (10); 77 (19); 74 (34); 73 (87); 70 (18); 56 (23); 53 (13); 44 (30); 43 (100). Mass spectrometry (CI, isobutane): $(M+1)^+$ 643 (56); $M^{\cdot+}$ 642 (6); *m/e* 518 (8); 517 (37); 516 (100); 515 (76); 388 (6). Analysis: Calcd. for $C_{11}H_9F_{13}I_2$ (641.98): C, 20.58; H, 1.41; F, 38.47; I, 39.54%. Found: C, 20.80; H, 1.40; F, 38.00; I, 39.98%.

*With short reaction time: preparation of **3***

The same amount of reactants having been heated for 1 h, unreacted 4-pentenol and excess of *F*-hexyl iodide were removed rapidly (0.03 mmHg, 25–30 °C). The remaining mixture was then treated as above. The crude product (8 g) contained **3**, **4** and **5** in a 70:22:8 ratio. Chromatography on silica gel (eluant: heptane then methylene chloride) afforded 6.12 g (46%) of **3**.

5-(*F*-Hexyl)-4-iodopentanol (***3***): ^{19}F NMR δ: -81.4 (CF_3); -111.6 (Fa) and -116.1 (Fb) ($CF_2\alpha$, $^2J_{\mathrm{Fa,Fb}}=270$ Hz); -122.4 (2F); -123.5 (2F); -124.3 (2F); -126.8 ($CF_2\omega$) ppm. ^{1}H NMR δ: 1.88 (broad s, $\mathrm{C}H_2\mathrm{C}H_2\mathrm{CH_2O}H$, 5H); 2.87 (m, $C_6F_{13}CH_2$, 2H); 3.70 (t, $^3J_{\mathrm{H,H}}=6$ Hz, $\mathrm{C}H_2\mathrm{OH}$, 2H); 4.42 (quintuplet, $^3J_{\mathrm{H,H}}=6.5$ Hz, CHI, 1H) ppm. ^{13}C NMR δ: 61.6 (C-1); 41.8 (t, $^2J_{\mathrm{C,F}}=21.1$ Hz, C-5); 37.0 (C-4); 32.7 (C-2); 20.3 (C-3) ppm. Analysis: Calcd. for $C_{11}H_{10}F_{13}IO$ (532.08): C, 24.83; H, 1.89; F, 46.42; I, 23.85%. Found: C, 25.20; H, 2.10; F, 45.59; I, 23.77%.

*In alkaline medium: preparation of **4** and **8***

2-[(*F*-Hexyl)methyl]tetrahydrofuran (**4**) was prepared by heating 2.16 g of 4-pentenol, 16.8 g of *F*-hexyl iodide and 132 mg of AIBN in the presence of 3.5 ml (1.2 equiv.) of 2,6-lutidine for 5 h. The crude product, diluted in ether, was washed with water, 0.1N aq. HCl, and again with water. Compound **4** was obtained in 79% yield (8.07 g) by distillation. The same procedure, but with pyridine instead of lutidine, gave 65% of **4**.

2-[(*F*-Octyl)methyl]tetrahydrofuran [**8**] was prepared by heating 2.16 g of 4-pentenol, 20 g (36.6 mmol) of *F*-octyl iodide, 132 mg of AIBN and 1.2 equiv. of 2,6-lutidine for 5 h. After treatment and distillation, this afforded 8.59 g of **8** (69%; T_R, 12 min).

2-[(*F*-Octyl)methyl]tetrahydrofuran (**8**): b.p., 42 °C/0.01 mmHg. IR (cm^{-1}): 2950; 2860 (CH); 1250–1130 (CF). ^{19}F NMR δ: -81.4 (CF_3); -113.5 ($CF_2\alpha$); -122.4 (6F); -123.2 (2F); -124.1 (2F); -126.7 ($CF_2\omega$) ppm. ^{1}H NMR δ: 1.51–2.54 (m, $\mathrm{C}H_2\mathrm{C}H_2\mathrm{CH}$, $\mathrm{C_6F_{13}C}H_2\mathrm{CH}$, 6H); 3.79 and 3.91 (ABdd, $J_{5a,5b}=8.35$ Hz, $J_{4a,5a}=J_{4b,5a}=7.0$ Hz, $J_{4a,5b}=7.35$ Hz, $J_{4b,5b}=6.30$ Hz, H-5a,5b, 2H); 4.20 (quintuplet, $J_{2,3}=J_{2,6}=6$ Hz, H-4, 1H) ppm. ^{13}C NMR δ: 72.1 (t, $^3J_{\mathrm{C,F}}=2.8$ Hz, C-2); 67.8 (C-5); 36.5 (t, $^2J_{\mathrm{C,F}}=21$ Hz, $C_6F_{13}CH_2$); 32.3 (C-3); 25.4 (C-4) ppm. Analysis: Calcd. for $C_{13}H_9F_{17}O$ (504.19): C, 30.97; H, 1.80; F, 64.06%. Found: C, 31.00; H, 1.71; F, 64.35%.

Radical addition using a modified Burton procedure

*On 4-pentenol: preparation of **1** and **4***

A mixture of 8.3 g (97 mmol) of 4-pentenol, 72.7 g (163 mmol) of *F*-hexyl iodide, 3 g (30 mmol) of $\mathrm{Cu^ICl}$ and 18 ml (299 mmol) of ethanolamine in 100 ml t-butanol were refluxed until the disappearance of the alkenol. The crude mixture was poured into ether, washed, dried over sodium sulphate and purified by distillation, affording 6.8 g (17%) of **4** and 23.1 g (59%) of 5-(*F*-hexyl)-4-pentenol (**1**).

5-(*F*-Hexyl)-4-pentenol (**1**): b.p., 58–59 °C/0.01 mmHg. IR(cm^{-1}): 3335 (OH); 2945; 2880 (CH); 1680 (C=C); 1240–1150 (CF) ppm. ^{19}F NMR δ: −81.8 (CF$_3$); −107.4 (*Z*) and −112.0 (*E*) (CF$_2\alpha$, *Z*/*E* = 10:90); −122.3 (2F); −123.7 (2F); −124.1 (2F); −126.9 (CF$_2\omega$) ppm. ^{1}H NMR δ: 1.73 (quintuplet, $^3J_{\mathrm{H,H}}$ = 6.1 and 7.1 Hz, $\mathrm{CH_2C}\mathit{H}_2\mathrm{CH_2}$, 2H); 2.31 (broad s, $\mathrm{C}\mathit{H}_2\mathrm{CH}$=, O*H*, 3H); 3.69 (t, $^3J_{\mathrm{H,H}}$ = 6.1 Hz, $\mathrm{C}\mathit{H}_2\mathrm{OH}$, 2H); 5.63 (m, $\mathrm{C_6F_{13}C}\mathit{H}$=, 1H); 6.43 (m, $\mathrm{C_6F_{13}CH{=}C}\mathit{H}$, 1H) ppm. Mass spectrometry (EI): $(\mathrm{M-H_2O})^{\cdot+}$ 386 (3); *m*/*e* 118 (25); 117 (63); 97 (16); 77 (15); 69 (14); 60 (16); 58 (35); 47 (57); 46 (100). Analysis: Calcd. for $C_{11}H_9F_{13}O$ (404.2): C, 32.69; H, 2.25; F, 61.11%. Found: C, 32.76; H, 2.38; F, 61.14%.

On 5-[2′-(Tetrahydropyranyloxy)]-1-pentene: preparation of 1

5-[2′-(Tetrahydropyranyloxy)]-1-pentene was prepared by stirring 49.8 g (578 mmol) of 4-pentenol, 74.4 g (873 mmol) of dihydropyran and 14.6 g (58 mmol) of pyridinium *p*-toluenesulphonate [6] in 125 ml of anhydrous methylene chloride for 27 h (GLC monitoring) at room temperature. Conventional treatment and distillation gave 91.1 g of the ether (93%); b.p., 32 °C/0.01 mmHg. IR(cm^{-1}): 2940; 2870 (CH); 1640 (C=C). ^{1}H NMR δ: 1.60 (m, CH$_2$, 8H); 2.10 (m, $\mathrm{C}\mathit{H}_2\mathrm{CH}$=, 1H); 3.56 (m, CH$_2$O, 4H); 4.52 (broad, s, O−CH−O, 1H); 4.95 (m, $\mathrm{CH{=}C}\mathit{H}_2$, 2H); 5.78 (m, $\mathrm{C}\mathit{H}\mathrm{{=}CH_2}$, 1H) ppm. Analysis: Calcd. for $C_{10}H_{18}O_2$ (170.25): C, 70.55; H, 10.66%. Found: C, 70.32; H, 10.78%.

1-(*F*-Hexyl)-5-[2′-(tetrahydropyranyloxy)]-1-pentene (**7**) was prepared according to the modified Burton procedure [4, 5] by reacting 59.6 g (350 mmol) of 5-[2′-(tetrahydropyranyloxy)]-1-pentene with 265.3 g (595 mmol) of *F*-hexyl iodide to give 150 g (88%) of **7**; b.p., 77 °C/0.01 mmHg. IR (cm^{-1}): 2950; 2870 (CH); 1680 (C=C); 1240–1140 (CF). ^{19}F NMR δ: −81.5 (CF$_3$); −107.3 (*Z*) and −111.9 (*E*) (CF$_2\alpha$, *Z*/*E* = 10:90); −122.2 (2F); −123.6 (2F); −124.0 (2F); −126.9 (CF$_2\omega$) ppm. ^{1}H NMR δ: 1.67 (m, CH$_2$, 8H); 2.37 (m, $\mathrm{C}\mathit{H}_2\mathrm{CH}$=, 2H); 3.67 (m, CH$_2$O, 4H); 4.61 (broad s, O−CH−O, 1H); 5.68 (m, $\mathrm{C_6F_{13}CH}$=, 1H) 6.47 (m, $\mathrm{C_6F_{13}CH{=}C}\mathit{H}$, 1H) ppm. Analysis: Calcd. for $C_{16}H_{17}F_{13}O_2$ (488.3): C, 39.36; H, 3.51; F, 50.58%. Found: C, 39.64; H, 3.70; F, 50.59%.

5-(*F*-Hexyl)-4-pentenol (**1**) was obtained by heating the tetrahydropyranyl ether **7** (144.4 g, 295.7 mmol) at 55 °C in ethanol with 7.4 g (29.6 mmol) of pyridinium *p*-toluenesulphonate [6]. After the usual treatment and distillation, this afforded 104.2 g (87%) of compound **1** (71% overall yield).

Preparation of 5-(F-hexyl)pentanol (2)

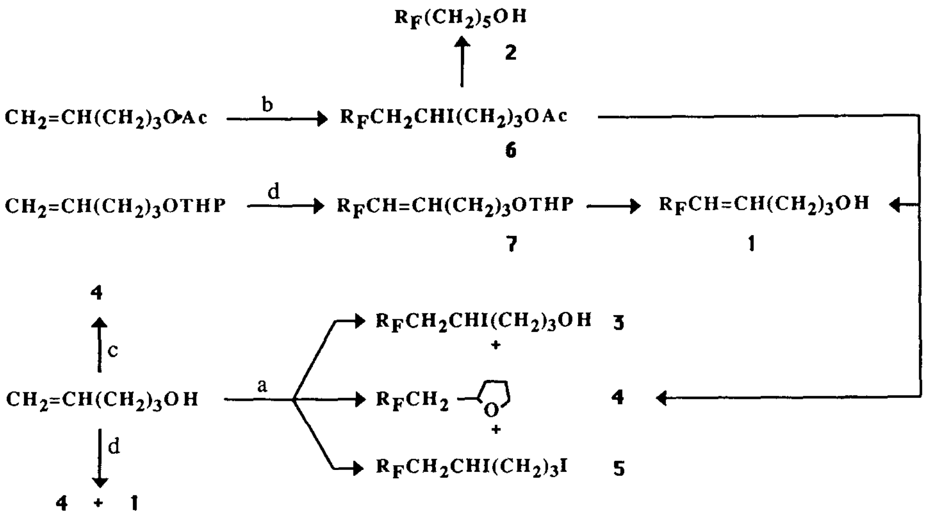
5-(*F*-Hexyl)-4-iodopentyl acetate (**6**) was prepared by heating 26.1 g (204 mmol) of 4-pentenyl acetate, obtained by the acetylation of 4-pentenol via a standard method, with 150 g (336 mmol) of *F*-hexyl iodide and 560 mg (3.4 mmol) of AIBN overnight at 95 °C. Distillation of the crude product gave 94.9 g (82%) of **6**; b.p., 82 °C/0.01 mmHg. ^{19}F NMR δ: −81.4 (CF$_3$); −110.0 (Fa) and −117.3 (Fb) (CF$_2\alpha$, $J_{\mathrm{Fa,Fb}}$ = 268 Hz); −122.4 (2F); −123.5 (2F); −124.1 (2F); −126.8 (CF$_2\omega$) ppm. ^{1}H NMR δ: 1.92 (m, CH$_2$, 4H); 2.05 (s, CH_3, 3H); 2.88 (m, $C_6F_{13}CH_2$, 2H); 4.11 (t, $^3J_{H,H}=7$ Hz, CH_2O, 2H); 4.37 (quintuplet, $^3J_{H,H}=6.1$ Hz, CHI, 1H) ppm. ^{13}C NMR δ: 171.0 (C=O); 63.0 (C-1); 41.7 (t, $^2J_{C,F}=20.9$ Hz, C-5); 36.8 (CHI or C-4); 28.9 (C-2); 20.7 (C-3); 19.4 (CH_3C=O) ppm. Analysis: Calcd. for $C_{13}H_{12}F_{13}IO_2$ (574.12): C, 27.20; H, 2.11; F, 43.02; I, 22.10%. Found: C, 27.69; H, 1.95; F, 41.78; I, 22.11%.

5-(*F*-Hexyl)pentanol (**2**) was obtained by bubbling HCl gas through 20.1 g (307.4 mmol) of Zn powder (<325 mesh) suspended in a solution of 59 g (102.8 mmol) of 5-(*F*-hexyl)-4-iodopentyl acetate (**6**) in 150 ml of ethanol until the Zn was totally consumed. The mixture was then refluxed until no 5-(*F*-hexyl)pentyl acetate remained (GLC monitoring). Ethanol having been removed, the crude product was dissolved in diethyl ether, washed and evaporated under vacuum. After distillation, 32.9 g (79%) of **2** were obtained; b.p., 75–76 °C/0.3 mmHg. IR(cm^{-1}): 3345 (OH); 2950; 2880 (CH); 1240–1150 (CF). ^{19}F NMR δ: −81.3 (CF_3); −114.7 ($CF_2\alpha$); −122.1 (2F); −123.0 (2F); −123.8 (2F); −126.5 ($CF_2\omega$) ppm. ^1H NMR δ: 1.25 and 1.35 (m, $CH_2CH_2CH_2CH_2OH$, 6H); 1.82 (m, $C_6F_{13}CH_2$, 2H); 2.30 (s, OH, 1H); 3.41 (t, $^3J_{H,H}=6$ Hz, CH_2OH, 2H) ppm. ^{13}C NMR δ: 62.3 (C-1); 32.2 (C-2); 30.8 (t, $^2J_{C,F}=22.4$ Hz, C-5); 25.7 (C-3); 20.0 (t, $^3J_{C,F}=3.5$ Hz, C-4) ppm. Analysis: Calcd. for $C_{11}H_{11}F_{13}O$ (406.19): C, 32.53; H, 2.73; F, 60.80%. Found: C, 32.39; H, 2.63; F, 60.09%.

Results and discussion

The linear perfluoroalkylated alcohols **1** and **2** are described in the literature for $p=1$, 2 and 9 and for $q=1$–5, 9 and 11 [3, 7–12], and some of these have achieved commercial importance ($p=1$ and $q=1,2$). However, the unsaturated alcohols **1** with $p=3$ have not yet been reported, and the synthesis described for the saturated alcohols **2** with $q=5$ involves the addition of an *F*-alkylsulphonyl chloride on to 4-pentenoic acid followed by consecutive hydrogenolysis and hydrogenation [10] hence the use of toxic, corrosive and expensive reagents. It therefore appeared attractive and convenient to prepare 5-(*F*-alkyl)-4-iodopentanols (**3**) which could then give **1** by dehydroiodination or **2** by hydrogenolysis, depending on the reaction conditions. Numerous methods are described for synthesizing such intermediates, all of which involve the addition of a perfluoroalkyl iodide to a terminal double bond promoted by heat, photolysis, free-radical initiators, metals, transition metal complexes, electrolysis, enzymes or phase-transfer conditions [13].

However, when *F*-hexyl iodide was heated with 4-pentenol in the presence of α,α′-azoisobutyronitrile (AIBN) as a radical initiator, an unexpected behaviour was observed: GLC monitoring showed the normal consumption of 4-pentenol in *c*. 3 h, but two main new products (**4** and **5**) were detected along with the expected iodo adduct **3** (Scheme 1). On increasing the reaction time, **3** decreased rapidly and disappeared almost totally after about 24 h,



a) R_FI, AIBN, Δ1h.; b) R_FI, AIBN, Δ24h.; c) R_FI, AIBN, 2,6-lutidine; d) R_FI, CuCl(I), ethanolamine.
$R_F = C_6F_{13}$; THP = tetrahydropyran.

Scheme 1. Addition of *F*-hexyl iodide to 4-pentenol and its derivatives.

to the benefit of **4** and **5** plus some other by-products in low yield (5–10%). Typically, after 24 h at 100–110 °C, **4** and **5** were obtained in 36% and 26% yields, respectively, after treatment and distillation, and were characterized by mass spectrometry, and ^1H and ^{13}C NMR spectroscopy as consisting of 2-[(*F*-hexyl)methyl]tetrahydrofuran and 5-(*F*-hexyl)-1,4-diiodopentane. Compounds **4** and **5** no longer exhibit any ν(OH) vibrations in their IR spectra; their mass spectra display the molecular peak $M^{+\cdot}$ which is in agreement with the proposed structures, and present the characteristic ether cleavages for **4** and the consecutive losses of (I· then HI) and (HI then I·) from the molecular peak for **5**. The ^{19}F NMR spectra confirmed the presence and integrity of the perfluoroalkyl chain; compound **5** exhibits an AB system for the CF_2 group linked to CH_2CHI, a feature already noted for this particular segment [3]. Characterization of **5** was further achieved by comparing its ^1H and ^{13}C NMR spectra with those of **3**, which are very similar. The only differences concern the terminal methylene group whose protons are shifted from 3.70 ppm in **3** to 3.22 ppm in **5** and the carbon from 61.2 ppm to 4.2 ppm; this reflects the replacement of the hydroxy group by an iodine atom [14]. Product **4** exhibits a very informative non-fluorine-decoupled ^{13}C spectrum: the assignments of C-α ($^2J_{C,F} = 21$ Hz) and C-β ($^3J_{C,F} = 2.6$ Hz) to the perfluoroalkyl chain were made on the basis of C,F coupling constants. The highly deshielded C-β (72.2 ppm) is in accordance with a C−O shift, consequent to an intramolecular cyclization; moreover the ^{13}C NMR spectrum is similar to those of 2-alkyltetrahydrofuran [15] and 2-[2′-(*F*-alkyl)ethyl]-tetrahydrofuran [16], except for small chemical shift differences due to the proximity of the perfluoroalkyl group.

When the reaction was stopped after heating for 1 h at 100–110 °C and then treated, the three major products **3**, **4** and **5** were obtained in a 70:20:10 ratio (GLC). Compound **3**, which could not be purified by distillation, was isolated in 46% yield by liquid chromatography and characterized as the 'normal' expected addition product; **3** is heat-sensitive. When heated, pure **3** gave a mixture of **3**, **4** and **5** once more.

The formation of the side-products **4** and **5** could, however, be anticipated. Indeed, **3** under heat, and the radical intermediate $R_FCH_2\dot{C}H(CH_2)_3OH$, could both give the most favourable five-membered cyclization compound **4** [see eqn. (1)]. A radical intramolecular cyclization, such as the one observed here, has already been reported when perfluoroalkyl iodide was allowed to react on diallyl ether [17].

$$\mathbf{3} \xrightarrow{-HI} \mathbf{4} \underset{-HI}{\overset{+HI}{\rightleftharpoons}} \mathbf{3}+\mathbf{3'} \xrightarrow{+HI} \mathbf{5} \qquad (1)$$

As is well documented, the HI evolved was capable of cleaving the ether **4** [18] to give **3** + **3′** [1-(*F*-hexyl)-5-iodo-2-pentanol, presumably present in the mixture] and then, via a nucleophilic substitution, the HI converted these alcohols **3** and **3′** into the diiodide **5**, the reaction terminating on total consumption of HI; the water produced in this last stage was observed during the experimental work. This sequence was confirmed by the introduction of an acid scavenger into the reaction medium, thus preventing the formation of the diiodo compound **5**. Indeed, when the reaction was performed with 1.2 equiv. of triethylamine, the absence of **5** was ascertained by GLC, and, in addition to **4**, the competing dehydroiodated product **1** was also detected (**4**/**1** in *c.* 75:25 ratio).

By adding a weaker base, it was expected that the *F*-alkylated tetrahydrofuranyl derivatives **4** ($R_F = C_6F_{13}$) and **8** ($R_F = C_8F_{17}$) could be obtained exclusively in a one-pot reaction. Indeed, when the reaction was performed in the presence of pyridine or 2,6-lutidine, the 2-[(*F*-alkyl)methyl]tetrahydrofurans **4** and **8** were obtained in 65–80% yield. While the 2-(*F*-alkyl)-tetrahydrofurans [19] and 2-[2′-(*F*-alkyl)ethyl]tetrahydrofurans [16, 20] are well known, this is the first reported preparation of the 2-[(*F*-alkyl)methyl]-tetrahydrofurans.

As the desired intermediate iodo-alcohol **3** could not be obtained readily and in good yield, we chose to synthesize the 5-perfluorohexyl-4-pentenols (**1**) by a modified Burton procedure [4, 5] using the one-pot, two-step reaction devised in this laboratory. This improved method, which proved effective for $p = 9$ [3], was less attractive for $p = 3$. Indeed, the two reactants *F*-hexyl iodide and 4-pentenol, when refluxed in t-butanol with Cu^ICl and ethanolamine, again gave a mixture of the expected 5-(*F*-hexyl)-4-pentenol (**1**) and of the tetrahydrofuranyl derivative **4** in *c.* 7:3 ratio (GLC); distillation afforded **1** and **4** in 59% and 17% yields, respectively. Hence, whatever the procedure used (two-pot, two-step or one-pot, two-step), the presence of an alkaline reaction medium prevented the formation of the diiodo compound **5**, but the formation of the cyclized product **4** always occurred. This side-reaction, being due to the nucleophilic attack of the hydroxy group of compound **3**, was suppressed by using a protected hydroxy group. In this way the intermediate **6**, obtained in 82% yield by radical addition of perfluoroalkyl iodide on to 4-pentenyl acetate, afforded, after hydrogenolysis, the saturated alcohol **2** in 79% yield. But **6** not only provided the unsaturated alcohol **1**: when heated with potassium hydroxide in ethanol, it also gave a mixture of **4** and **1** in a 75:25 ratio.

Finally, 5-(*F*-hexyl)-4-pentenol (**1**) was prepared in three steps from 4-pentenol: perfluorohexyl iodide was added to the protected alkenol, 5-[2′-(tetrahydropyranyloxy)]-1-pentene, using the modified Burton procedure [4, 5], then the tetrahydropyranyl was removed [6] affording **1** in the *Z*/*E* form (10:90) in 71% overall yield.

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References

1 (a) J. G. Riess, *J. Chim. Phys.*, *84* (1987) 1119; (b) J. G. Riess and M. Le Blanc, in K. C. Lowe (ed.), *Blood Substitutes: Preparation, Physiology and Medical Applications*, Ellis Horwood, Chichester, 1988, Chap. 5, p. 94.
2 J. G. Riess, J. Greiner, M. Le Blanc, Y. S. Lin, A. Manfredi, S. Pace, C. Varescon and L. Zarif, *Actual. Chim. Therap.*, *15* (1988) 247.
3 A. Milius, J. Greiner and J. G. Riess, *New J. Chem.*, *15* (1991) 337.
4 D. J. Burton and L. Kehoe, *Tetrahedron Lett.*, (1966) 5163.
5 L. Zarif, J. Greiner, S. Pace and J. G. Riess, *J. Med. Chem.*, *33* (1990) 1262.
6 M. Miyashita, A. Yoshikoshi and P. A. Grieco, *J. Org. Chem.*, *42* (1977) 3772.
7 N. O. Brace, *J. Org. Chem.*, *20* (1982) 313, and references cited therein.
8 S. K. De and S. R. Palit, *Adv. Fluorine Chem.*, *6* (1970) 69.
9 H. Blancou, S. Benefice and A. Commeyras, *J. Fluorine Chem.*, *23* (1983) 57.
10 A. H. Ahlbrecht, *US Pat.*, *3285975*(1966) [*Chem. Abst.*, *66* (1967) 46013].
11 T. Umemoto, Y. Kuriu and O. Miyano, *Tetrahedron Lett.*, *23* (1982) 3579.
12 P. L. Coe, N. E. Milner and J. A. Smith, *J. Chem. Soc.*, *Perkin Trans. 1*, (1975) 654.
13 (a) R. N. Haszeldine and B. R. Steele, *J. Chem. Soc.*, (1953) 1199; (b) R. N. Haszeldine, D. W. Keen and A. E. Tipping, *J. Chem. Soc.*, (1970) 414; (c) N. O. Brace, *J. Org. Chem.*, *28* (1963) 3093; (d) P. L. Coe and N. E. Milner, *J. Organomet. Chem.*, *39* (1972) 395; (e) A. E. Feiring, *J. Org. Chem.*, *50* (1985) 3269; (f) K. V. Werner, *J. Fluorine Chem.*, *28* (1985) 229; (g) P. Calas and A. Commeyras, *J. Fluorine Chem.*, *16* (1980) 553; (h) T. Kitazume and T. Ikeya, *J. Org. Chem.*, *53* (1988) 2350; (i) G. B. Rong and R. Keese, *Tetrahedron Lett.*, *31* (1990) 5615.
14 E. Breitmaier and W. Voelter, in H. F. Ebel (ed.), *^{13}C NMR-Spectroscopy*, Verlag Chemie, Weinheim, 1974.
15 E. L. Eliel, V. S. Rao and K. M. Pietrusiewicz, *Org. Magn. Reson.*, *12* (1979) 461.

16 D. E. Bergstrom, M. W. Ng and J. J. Wong, *J. Chem. Soc., Perkin Trans. 1*, (1983) 741.

17 X. Y. Lu, S. M. Ma and J. G. Zhu, *Tetrahedron Lett.*, *29* (1988) 5129.

18 (a) H. Kropf, J. Thiem and H. Nimz, in *Houben Weyl, Methoden der Organischen Chemie*, 4th edn., G. Thiem Verlag, Stuttgart, 1979, vol. 6(1a part 1), pp. 446–544; (b) M. V. Bhatt and S. U. Kulkarni, *Synthesis*, (1983) 249.

19 (a) R. N. Haszeldine and R. Rowland, *US Pat. 3816286*(1972) [*Chem. Abstr.*, *81* (1974) 49245]; (b) T. N. Abroskina, A. D. Sorokin, R. V. Kudryavtsev and Y. A. Cheburkov, *Izv Akad. Nauk SSSR, Ser. Khim.*, *74* (1972) 1823 [*Chem. Abstr.*, *81* (1974) 169373]; (c) J. Courtieu, J. Julien, T. L. Nguyen and S. K. Kan, *Tetrahedron*, *32* (1972) 669; (d) R. D. Chambers and B. Grievson, *J. Chem. Soc., Perkin Trans. 1*, (1985) 2215.

20 A. Chauvin, J. Greiner, R. Pastor and A. Cambon, *J. Fluorine Chem.*, *27* (1985) 385.