ELSEVIER

Journal of Fluorine Chemistry 113 (2002) 195–200

JOURNAL OF FLUORINE CHEMISTRY

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Synthesis of fluorinated amphiphiles by the reaction of protected hydroxy carbaldehyde with perfluorinated organomagnesium compounds

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Received 24 August 2001; accepted 27 September 2001

Abstract

Fluorinated amphiphilic compounds with enhanced chemical stability were synthesized by the reaction of 5-(2,2,5-trimethyl-1, 3-dioxane)carbaldehyde (**1**) with perfluoroalkylmagnesium bromides (**2**), followed by deprotection. The key aldehyde **1** was prepared by Swern oxidation of 5-(2,2,5-trimethyl-1,3-dioxane)methanol (**3**). © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Fluorophilic; Amphiphilic; Polyfluorinated polyol; Grignard reaction; Perfluoroalkylmagnesium iodide; Polyfluoroorganometallic; Nucleophilic addition

1. Introduction

Amphiphilic compounds possessing a perfluoroalkyl moiety display, among other properties, high surface activity. They can generally be applied as surfactants. Fluorinated surfactants are significantly more surface active than their hydrocarbon analogs and display higher tendency to self-assembly, thus forming stable supramolecular assemblies such as vesicles, tubules, etc. [1]. Fluorosurfactants generally do not extract membrane proteins [2]. Those with good hemocompatibility and low toxicity can be applied for various medical uses, e.g. oxygen carriers, intravenous transport of drugs and oxygen transporting gels for surgery [1–5].

Fluorinated surfactants usually contain a non-fluorinated spacer connecting the hydrophilic and perfluorinated (hydrophobic and fluorophilic) parts with a CH_2–CF_2-(perfluoroalkyl) grouping, from which hydrogen fluoride can easily be eliminated [6,7]. Moreover, some fluorinated amphiphilic compounds contain hydrolyzable moieties [4], e.g. ester groups, that can also cause chemical instability in potential in vivo applications. We hence directed our research to the preparation of amphiphilic compounds of higher (bio)chemical stability. We have designed the structures as follows: firstly, the reactive ester groups that combine hydrophilic and hydrophobic parts were excluded; secondly, the possibility of HF elimination in the –CH_2–CF_2 grouping has been reduced by making the hydrogen in the vicinal position to the perfluorinated chain less accessible by steric hindrance.

In this paper, amphiphilic compounds with a perfluorinated hydrophobic part were constructed by the coupling of perfluoroalkylated organomagnesiums with a protected dihydroxyaldehyde. Fluorinated organometallic compounds are of lower stability than their non-fluorinated counterparts [8], and therefore, have not found such an extensive application in organic chemistry. Nevertheless, two general methods can be employed for the attachment of a perfluorinated chain to substrate, viz. the addition reaction of in situ generated perfluoroalkylzinc reagent [9], or perfluoroalkylmagnesium reagent [10]. As the latter method appeared to be more convenient for our purposes, we have applied it for the preparation of the title amphiphilic compounds.

2. Results and discussion

2.1. Preparation of 5-(2,2,5-trimethyl-1,3-dioxane)carbaldehyde (*1*)

5-(2,2,5-Trimethyl-1,3-dioxane)carbaldehyde (**1**) was prepared in two steps from commercially available 2-(hydroxymethyl)-2-methylpropan-1,3-diol by protection of two hydroxy groups in the form of acetale with acetone [11], followed by Swern oxidation with Me_2SO–$(COCl)_2$ reagent [12] (see Scheme 1).

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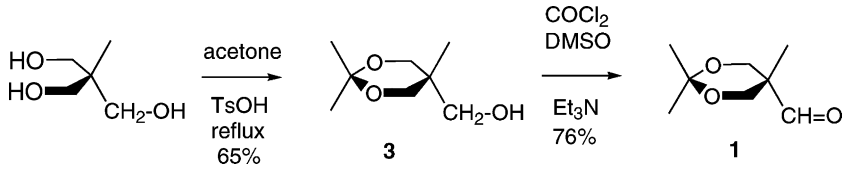
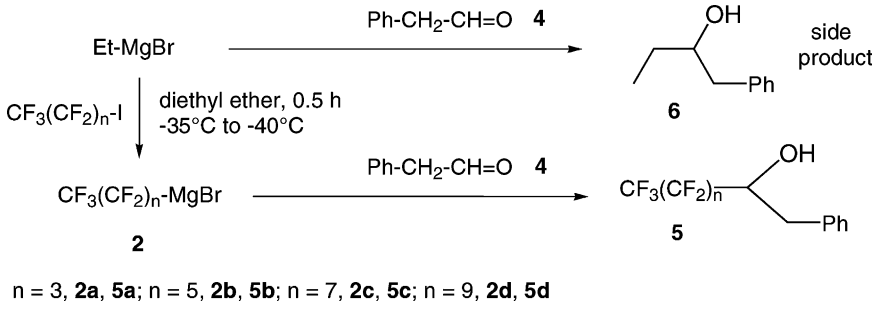
0022-1139/02/$ – see front matter
PII: S0022-1139(01)00544-9



Scheme 1.



Scheme 2.

2.2. Model reaction and optimisation of the reaction conditions

Before starting nucleophilic additions with the protected aldehyde **1** we optimised the reactions conditions by carrying out the reactions with easily available phenylacetaldehyde (**4**) as a model substrate. Four perfluoroalkylmagnesium bromides **2a–d** were prepared by transmetallation of the corresponding perfluoroalkyl iodides with ethylmagnesium bromide in diethyl ether at −40 to −35 °C. First we followed the procedure according to [10] using molar equivalents of perfluorinated alkyl iodide and EtMgBr, short reaction time for transmetallation (procedure A) and subsequent addition of aldehyde **4** to the reaction mixture. Surprisingly, along with the target products, polyfluorinated 1-phenylalkan-2-ols **5a–d**, large amounts of side 2-phenylbutan-2-ol (**6**), formed by the reaction of ethylmagnesium bromide with the substrate **4** were obtained (Scheme 2).

We, therefore, employed a larger excess of perfluoroalkyl iodide (up to 150%) and extended the transmetallation time to 3 h (procedure B). As shown in Table 1, the amounts of the side product **6** were decreased, but its formation not completely suppressed, thus indicating that the metal–halogen exchange reactions with the perfluoroalkyl iodides have still not been completed.

2.3. Nucleophilic additions to 5-(2,2,5-trimethyl-1,3-dioxane)carbaldehyde (*1*)

To improve the transmetallation in the reaction of perfluoroalkylmagnesium compounds **2** with protected aldehyde **1**, we increased the excess of both starting perfluoroalkyl iodide (200%), and ethylmagnesium bromide (150%) relative to **1** (as procedure C, Table 1). After this change of the reactant ratios, transmetallations proceeded with nearly complete conversion and the products, protected polyfluorinated triols **7a–d**, were formed in acceptable yields (Scheme 3, Table 1).

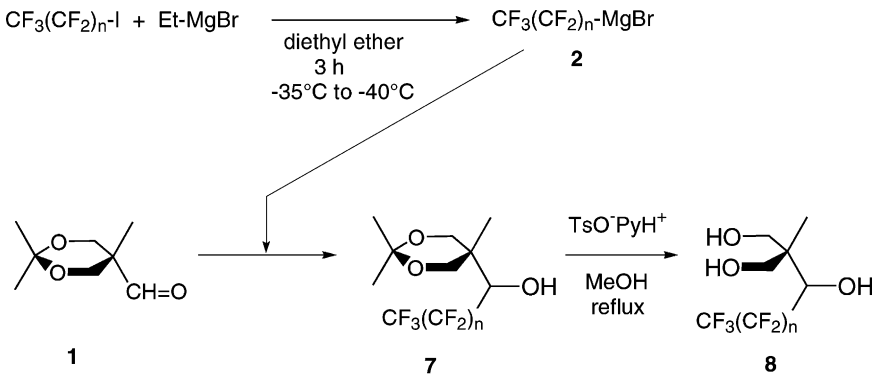
2.4. Deprotections

Among a number of methods for the removal of isopropylidene protecting group, we chose reacetalisation by refluxing methanol in the presence of a catalytic amount of pyridinium 4-toluenesulfonate [13] (Scheme 3). In this way, the isolation of amphiphilic polyfluorinated triols **8** by the extraction from an aqueous medium has been avoided. On the other hand, it has been surprising that the yields of the deprotections substantially decreased with the length of the perfluorinated chain, which has been a subject of our further study.

Table 1
Results of reactions of aldehydes **1**, **4** with perfluoroalkylmagnesium bromides **2**

Aldehyde	Alkyl-MgBr	Procedure	Product	Yield[a] (%)	Side product[b] (%)
4	**2a**	A	**5a**	31	46
4	**2a**	B	**5a**	51	17
4	**2b**	A	**5b**	44	33
4	**2b**	B	**5b**	55	22
4	**2c**	A	**5c**	58	21
4	**2d**	B	**5d**	44	17
1	**2a**	C	**7a**	48	
1	**2b**	C	**7b**	49	
1	**2c**	C	**7c**	72	
1	**2d**	C	**7d**	61	

[a] Preparative yields.
[b] Relative yield.



n = 3, **2a**, **7a**: 48%, **8a**: 77%; n = 5, **2b**, 7**b**: 49%, **8b**: 62%; n = 7, **2c**, **7c**: 72%, **8c**: 58%; n = 9, **2d**, **7d**: 61%, **8b**: 37%.

Scheme 3.

3. Conclusions

We succeeded in the preparation of amphiphilic polyfluorinated triols by the reactions of protected dihydroxyaldehyde **1** with perfluoroalkylmagnesium bromides **2**, formed by in situ reaction of perfluoroalkyl iodides with ethylmagnesium bromide. Transmetallations did not proceed as smoothly as reported [10], therefore, a higher excess of perfluoroalkyl iodides and longer reaction time had to be employed to avoid the side reaction of non-transmetallated ethylmagnesium bromide with aldehyde **1**. Amphiphilic polyfluorinated triols **8** prepared display enhanced stability against bases, since elimination of HF is suppressed due to lower accessibility of hydrogen atoms by the base.

4. Experimental details

4.1. General comments

Temperature data were not corrected. ^{1}H NMR spectra were recorded with a Varian Gemini 300 HC spectrometer at 300.1 MHz using TMS as internal standard, ^{13}C NMR spectra (at 100.6 MHz using TMS as internal standard) and ^{19}F NMR (at 376.5 MHz using $CFCl_3$ as internal standard with upfield values designed negative) were measured with a Bruker AM 400 spectrometer. FT-IR spectra were recorded with a Nicolet 740 instrument in KBr. Elementary analyses were carried out by the Laboratory of Elementary Analyses of ICT Prague.

2-(Hydroxymethyl)-2-methylpropane-1,2-diol, phenylacetaldehyde (**4**), ethyl bromide, oxalyl chloride and pyridinium 4-toluenesulfonate (Aldrich) were used without further purification. Perfluoroalkyl iodides were kindly gifted by Elf Atochem. Ethylmagnesium bromide was prepared and its concentration estimated according to [14]. Diethyl ether, dichloromethane, methanol and DMSO were dried according to [15]. Silica (60–200 μm, Merck) was used for column chromatography. 5-(2,2,5-Trimethyl-1,3-dioxane)methanol (**3**) was prepared according to [10] in a 64% yield.

4.2. 5-(2,2,5-Trimethyl-1,3-dioxane)carbaldehyde (*1*)

A solution of Me_2SO (5.0 ml, 75 mmol) in dichloromethane (30 ml) was slowly added to a solution of oxalyl chloride (4.5 ml, 50 mmol) in dichloromethane (150 ml) at −78 °C. After stirring for 15 min, the solution of 5-(2,2,5-trimethyl-1,3-dioxane)methanol (**3**, 3.6 g, 22 mmol) in dichloromethane (10 ml) was added dropwise. The mixture was stirred for 10 min at −78 °C and 60 min at −45 °C. Triethylamine (30 ml, 0.21 mol) was added and temperature was left to rise slowly to 0 °C. After 20 min at 0 °C, 200 ml of a saturated aqueous solution of NH_4Cl was added, the organic layer was separated and the aqueous layer was extracted twice with dichloromethane (200 ml). Combined organic layers were dried with $MgSO_4$, solvents were evaporated and the aldehyde **3** was obtained by distillation under nitrogen as colourless liquid (2.72 g, 76.2%, bp = 60−90 °C/80–660 Pa). ^{1}H NMR ($CDCl_3$) δ: 9.75 (s, 1H), 4.05 (d, 2H, $^2J_{HH}$ = 12.0 Hz); 3.72 (d, 2H, $^2J_{HH}$ = 12.0 Hz); 1.42 (s, 3H); 1.32 (s, 3H); 0.84 (s, 3H); ^{13}C NMR ($CDCl_3$) δ: 97.6 (s); 64.6 (s); 44.8 (s); 27.4 (s); 19.1 (s); 14.3 (s); IR ($CHCl_3$): 832 (m), 1087 (s), 1208 (s), 1718 (m), 2992 (s). Anal. Calcd. for $C_8H_{14}O_3$: C, 60.8; H, 8.9. Found: C, 59.8%; H, 8.5%.

4.3. Reactions of perfluoroalkylmagnesium bromides *2* with aldehydes *1* and *4*

4.3.1. General procedure A

To a solution of perfluoroalkyl iodide (120%) in diethyl ether (3 ml/mmol) cooled to −45 °C and protected from light, ethylmagnesium bromide (120%) was added dropwise. The reaction mixture was stirred at −35 to −40 °C for 0.5 h. The aldehyde (100%) was dissolved in diethyl ether (2 ml/mmol) and dropwise added to the reaction mixture at −35 to −40 °C. The temperature of the reaction mixture was left to rise slowly to −10 °C in 2 h. Then the reaction mixture was washed with saturated solution of NH_4Cl (2 × 20 ml), and the aqueous layer was extracted twice with

diethyl ether (20 ml). The combined organic layers were dried with $MgSO_4$ and solvent was evaporated. Products were isolated by column chromatography.

4.3.2. General procedure B

This procedure followed general procedure A, but larger excess of perfluoroalkyl iodide (150%) and larger transmetallation time (3 h) were used.

4.3.3. General procedure C

This procedure also followed general procedure A, but even larger excess of perfluoroalkyl iodide (200%) and ethylmagnesium bromide (150%) were used. Instead of purification of the crude reaction mixture by column chromatography, the side product **6** was removed from the crude reaction mixture by heating in vacuo (80 °C/200 Pa, 3 h).

4.3.4. 3,3,4,4,5,5,6,6,6-Nonafluoro-1-phenylhexan-2-ol (*5a*)

Reaction of phenylacetaldehyde (**4**, 0.28 g, 2.3 mmol), perfluorobutyl iodide (1.4 g, 4.0 mmol) and EtMgBr (2.4 ml, 1.44 M, 3.5 mmol) after general procedure B afforded a 83:17 mixture of polyfluorohexanol **5a** and the side product **6**. Pure polyfluorohexanol **5a** (0.42 g, 51%) was obtained as crystals. ^{1}H NMR ($CDCl_3$) δ: 7.20–7.40 (m, 5H); 4.33 (m, 1H); 3.13 (d, 1H, $^2J_{HH} = 13.7$ Hz); 2.89 (dd, 1H, $^2J_{HH} = 13.7$ Hz, $^3J_{HH} = 10.4$ Hz); 2.00 (bs, 1H); ^{19}F NMR ($CDCl_3$) δ: −81.4 (t, 3F, $J_{FF} = 10$ Hz); −120.6 (dm, 1F, $^2J_{FF} = 285$ Hz); −122.5 (dm, 1F, $^2J_{FF} = 299$ Hz); −123.4 (m, 1F, $^2J_{FF} = 299$ Hz); −126.0 (dm, 1F, $^2J_{FF} = 300$ Hz); −127.4 (dm, 1F, $^2J_{FF} = 300$ Hz); −127.5 (dm, 1F, $^2J_{FF} = 285$ Hz); ^{13}C NMR ($CDCl_3$) δ: 135.6 (s); 129.5 (s); 128.9 (s); 127.3 (s); 108–119 (m); 71.1 (dd, $^2J_{CF} = 28$Hz, $^2J_{CF} = 23$ Hz); 35.6 (s); IR ($CHCl_3$): 712 (m), 1136 (s), 1236 (s), 3473 (m). Anal. Calcd. for $C_{12}H_9F_9O$: C, 42.4; H, 2.7. Found: C, 42.6%; H, 3.1%.

4.3.5. 3,3,4,4,5,5,6,6,7,7,8,8,8-Tridecafluoro-1-phenyloctan-2-ol (*5b*)

Reaction of phenylacetaldehyde (**4**, 0.31 g, 2.6 mmol), perfluorohexyl iodide (1.8 g, 4.0 mmol) and EtMgBr (2.0 ml, 1.44 M, 2.9 mmol) after procedure B afforded a 78:22 mixture of polyfluorooctanol **5b** and side product **6**. Pure polyfluorooctanol **5b** (0.63 g, 55%) was obtained as crystals. ^{1}H NMR ($CDCl_3$) δ: 7.20–7.40 (m, 5H); 4.33 (m, 1H); 3.13 (d, 1H, $^2J_{HH} = 13.7$ Hz); 2.89 (dd, 1H, $^2J_{HH} = 13.7$ Hz, $^3J_{HH} = 10.1$ Hz); 2.00 (bs, 1H); ^{19}F NMR ($CDCl_3$) δ: −81.3 (t, 3F, $J_{FF} = 10$ Hz); −120.7 (dm, 1F, $^2J_{FF} = 283$ Hz); −122.0 (m, 2F); −122.2 (dm, 1F, $^2J_{FF} = 295$ Hz); −122.9 (dm, 1F, $^2J_{FF} = 295$ Hz); −122.9 (dm, 1F, $^2J_{FF} = 295$ Hz); −123.6 (dm, 1F, $^2J_{FF} = 295$ Hz); −126.2 (dm, 1F, $^2J_{FF} = 294$ Hz); −127.1 (dm, 1F, $^2J_{FF} = 294$ Hz); −127.2 (dm, 1F, $^2J_{FF} = 283$ Hz); ^{13}C NMR ($CDCl_3$) δ: 135.7 (s); 129.5 (s); 128.8 (s); 127.3 (s); 107–120 (m); 71.1 (dd, $^2J_{CF} = 27$ Hz, $^2J_{CF} = 24$ Hz); 35.6 (s); IR ($CHCl_3$) 699 (w), 1207 (s), 1239 (s), 2922 (w), 3466 (w). Anal. Calcd. for $C_{14}H_9F_{13}O$: C, 38.2; H, 2.1. Found: C, 38.7%; H, 2.5%.

4.3.6. 3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluoro-1-phenyldecan-2-ol (*5c*)

Reaction of phenylacetaldehyde (0.87 g, 7.4 mmol), perfluorooctyl iodide (4.7 g, 8.7 mmol) and EtMgBr (5.9 ml, 1.44 M, 8.5 mmol) after procedure A was carried out with a transmetallation time increased to 1 h and afforded a 79:21 mixture of polyfluorodecanol **5c** and side product **6**. Pure polyfluorodecanol **5c** (2.32 g, 57.9%) was obtained as crystals. ^{1}H NMR ($CDCl_3$) δ: 7.20–7.40 (m, 5H); 4.33 (m, 1H); 3.13 (d, 1H, $^2J_{HH} = 14.3$ Hz); 2.86 (dd, 1H, $^2J_{HH} = 14.3$ Hz, $^3J_{HH} = 10.4$ Hz); 2.00 (d, 1H, $^3J_{HH} = 6.6$ Hz); ^{19}F NMR ($CDCl_3$) δ: −81.2 (t, 3F, $J_{FF} = 10$ Hz); −120.7 (dm, 1F, $^2J_{FF} = 285$ Hz); −121.9 (m, 2F); −122.3 (m, 4F); −122.5 (m, 2F); −123.0 (dm, 1F, $^2J_{FF} = 298$ Hz); −123.4 (dm, 1F, $^2J_{FF} = 298$ Hz); −126.4 (dm, 1F, $^2J_{FF} = 299$ Hz); −126.9 (dm, 1F, $^2J_{FF} = 299$ Hz); −127.2 (dm, 1F, $^2J_{FF} = 285$ Hz); ^{13}C NMR ($CDCl_3$) δ: 135.6 (s); 129.5 (s); 128.9 (s); 127.3 (s); 107–120 (m); 71.0 (dd, $^2J_F = 28$ Hz, $^2J_{CF} = 24$ Hz); 35.6 (s); IR (KBr) 660 (w), 1151 (s), 1202 (s), 1230 (s), 3463 (w). Anal. Calcd. for $C_{16}H_9F_{17}O$: C, 35.6; H, 1.7. Found: C, 35.0%; H, 1.8%.

4.3.7. 3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12,12-Henicosafluoro-1-phenyldodecan-2-ol (*5d*)

Reaction of phenylacetaldehyde (**4**, 0.59 g, 5.1 mmol), perfluorodecyl iodide (4.6 g, 7.1 mmol) and EtMgBr (4.0 ml, 1.44 M, 5.8 mmol) after general procedure B afforded a 82:18 mixture of polyfluorododecanol **5d** and side product **6**. Pure polyfluorododecanol **5d** was obtained (1.44 g, 44.0%) as crystals. ^{1}H NMR ($CDCl_3$) δ: 7.20–7.40 (m, 5H); 4.33 (m, 1H); 3.13 (d, 1H, $^2J_{HH} = 13.7$ Hz); 2.88 (dd, 1H, $^2J_{HH} = 14.1$ Hz $^3J_{HH} = 10.4$ Hz); 2.00 (d, 1H, $^3J_{HH} = 6.0$ Hz); ^{19}F NMR ($CDCl_3$) δ: −81.2 (t, 3F, $J_{FF} = 10$ Hz); −120.7 (dm, 1F, $^2J_{FF} = 284$ Hz); −121.9 (m, 2F); −122.2 (m, 8F); −122.4 (m, 2F); −123.2 (m, 2F); −126.6 (m, 2F); −127.2 (dm, 1F, $^2J_{FF} = 284$ Hz); ^{13}C NMR ($CDCl_3$) δ: 135.6 (s); 129.5 (s); 128.9 (s); 127.3 (s); 107–120 (m); 71.1 (dd, $^2J_{CF} = 27$ Hz, $^2J_{CF} = 24$ Hz); 35.6 (s); IR (KBr) 649 (w), 1151 (s), 1206 (s), 3467 (s). Anal. Calcd. for $C_{16}H_9F_{21}O$: C, 33.8, H, 1.4, Found: C, 33.7%; H, 1.7%.

4.3.8. 2,2,3,3,4,4,5,5,5-Nonafluoro-1-[5-(2,2,5-trimethyl-1,3-dioxane)]pentan-1-ol (*7a*)

Reaction of protected hydroxyaldehyde **1** (0.40 g, 2.5 mmol), perfluorobutyl iodide (1.7 g, 4.9 mmol) and EtMgBr (1.9 ml, 1.94 M, 3.8 mmol) afforded after general procedure C a 73:27 mixture of polyfluoropentanol **7a** and starting aldehyde **1**. Pure polyfluoropentanol **7a** was obtained (0.46 g, 48%) as a wax. ^{1}H NMR ($CDCl_3$) δ: 4.65 (dd, 1H, $^3J_{HF} = 25.2$ Hz, $^3J_{HH} = 6.6$ Hz); 4.00 (dd, 1H, $^2J_{HH} = 12.1$ Hz, $^4J_{HH} = 2.7$ Hz); 3.91 (dt, 1H, $^2J_{HH} = 12.6$ Hz, $J = 1.8$ Hz); 3.68 (dd, 1H, $^2J_{HH} = 12.1$ Hz, $^4J_{HH} = 2.7$ Hz); 3.52 (d, 1H, $^2J_{HH} = 12.1$ Hz); 3.50

(d, 1H, $^3J_{HH}$ = 7.6 Hz); 1.46 (s, 3H); 1.40 (s, 3H); 0.94 (s, 3H); ^{19}F NMR ($CDCl_3$) δ: −81.4 (t, 3F, J_{FF} = 10 Hz); −116.8 (dm, 1F, $^2J_{FF}$ = 284 Hz); −122.4 (dm, 1F, $^2J_{FF}$ = 295 Hz); −123.5 (dm, 1F, $^2J_{FF}$ = 295 Hz); −124.3 (dm, 1F, $^2J_{FF}$ = 284 Hz); −125.6 (dtt, 1F, $^2J_{FF}$ = 293 Hz, J_{FF} = 15 Hz, J_{FF} = 6 Hz); −127.5 (ddt, 1F, $^2J_{FF}$ = 284 Hz, J_{FF} = 15 Hz, J_{FF} = 10 Hz); ^{13}C NMR ($CDCl_3$) δ: 108–120 (m); 98.7 (s); 68.1 (dd, $^2J_{CF}$ = 26 Hz, $^2J_{CF}$ = 21 Hz); 67.1 (s); 38.2 (s); 27.1 (s); 20.0 (s); 14.7 (s); IR ($CHCl_3$) 1082 (m), 1134 (s), 1204 (s), 1235 (s), 2995 (m), 3429 (m). Anal. Calcd. for $C_{12}H_{15}F_9O_3$: C, 38.0; H, 4.0. Found: C, 42.0%; H, 4.8%.

*4.3.9. 2,2,3,3,4,4,5,5,6,6,7,7,7-Tridecafluoro-1-[5-(2,2,5-trimethyl-1,3-dioxane)]heptan-1-ol (**7b**)*

Reaction of aldehyde **1** (0.30 g, 1.9 mmol), perfluorohexyl iodide (1.7 g, 4.0 mmol) and EtMgBr (1.5 ml, 1.94 M, 2.8 mmol) afforded after general procedure C a 90:10 mixture of polyfluoroheptanol **7b** and starting aldehyde **1**. Pure polyfluoroheptanol **7b** was obtained (0.45 g, 49%) as a wax. ^{1}H NMR ($CDCl_3$) δ: 4.68 (dd, 1H, $^3J_{HF}$ = 25.0 Hz, $^3J_{HH}$ = 6.9 Hz); 4.02 (dd, 1H, $^2J_{HH}$ = 12.1 Hz, $^4J_{HH}$ = 2.7 Hz); 3.92 (dm, 1H, $^2J_{HH}$ = 12.6 Hz); 3.69 (dd, 1H, $^2J_{HH}$ = 12.6 Hz, $^4J_{HH}$ = 2.7 Hz); 3.52 (d, 1H, $^2J_{HH}$ = 12.1 Hz); 3.17 (d, 1H, $^3J_{HH}$ = 7.7 Hz); 1.45 (s, 3H); 1.40 (s, 3H); 0.96 (s, 3H); ^{19}F NMR ($CDCl_3$) δ: −81.3 (t, 3F, J_{FF} = 10 Hz); −116.7 (dm, 1F, $^2J_{FF}$ = 282 Hz); −121.8 (dm, 1F, $^2J_{FF}$ = 296 Hz); −121.8 (dm, 1F, $^2J_{FF}$ = 296 Hz); −122.2 (dm, 1F, $^2J_{FF}$ = 296 Hz); −122.8 (dm, 1F, $^2J_{FF}$ = 274 Hz); −123.0 (dm, 1F, $^2J_{FF}$ = 296 Hz); −123.7 (dm, 1F, $^2J_{FF}$ = 274 Hz); −123.9 (dm, 1F, $^2J_{FF}$ = 282 Hz); −126.1 (dm, 1F, $^2J_{FF}$ = 297 Hz); −127.2 (dm, 1F, $^2J_{FF}$ = 297 Hz); ^{13}C NMR ($CDCl_3$) δ: 107–122 (m); 98.8 (s); 68.2 (dd, $^2J_{CF}$ = 26 Hz, $^2J_{CF}$ = 22 Hz); 67.1 (s); 38.2 (s); 27.1 (s); 20.0 (s); 14.7 (s); IR (KBr) 828 (w), 1146 (s), 1205 (s), 1240 (s), 1380 (m), 3002 (w), 3424 (w). Anal. Calcd. for $C_{14}H_{15}F_{13}O_3$: C, 35.1; H, 3.2. Found: C, 35.4%; H, 3.2%.

*4.3.10. 2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,9-Heptadecafluoro-1-[5-(2,2,5-trimethyl-1,3-dioxane)]-nonan 1-ol (**7c**)*

Reaction of protected hydroxyaldehyde **1** (0.50 g, 3.2 mmol), perfluorooctyl iodide (3.5 g, 6.3 mmol) and EtMgBr (2.4 ml, 1.94 M, 4.6 mmol) afforded after general procedure C polyfluorononanol **7c** (1.25 g, 71.8%) as crystals. ^{1}H NMR ($CDCl_3$) δ: 4.67 (d, 1H, $^3J_{HF}$ = 24.7 Hz); 4.01 (dd, 1H, $^2J_{HH}$ = 12.1 Hz, $^4J_{HH}$ = 2.2 Hz); 3.92 (d, 1H, $^2J_{HH}$ = 12.6 Hz); 3.68 (dd, 1H, $^2J_{HH}$ = 12.6 Hz, $^4J_{HH}$ = 2.7 Hz); 3.59 (d, 1H, $^2J_{HH}$ = 12.1 Hz); 3.26 (d, 1H, $^3J_{HH}$ = 6.0 Hz); 1.45 (s, 3H); 1.43 (s, 3H); 0.97 (s, 3H); ^{19}F NMR ($CDCl_3$) δ: −81.3 (t, 3F, $^3J_{FF}$ = 10 Hz); −116.8 (dm, 1F, $^2J_{FF}$ = 282 Hz); −122.0 (m, 2F); −122.4 (m, 4F); −122.5 (m, 2F); −123.0 (dm, 1F, $^2J_{FF}$ = 316 Hz); −123.5 (dm, 1F, $^2J_{FF}$ = 316 Hz); −126.4 (dm, 1F, $^2J_{FF}$ = 286 Hz); −127.1 (dm, 1F, $^2J_{FF}$ = 286 Hz); ^{13}C NMR ($CDCl_3$) δ: 105–120 (m); 98.8 (s); 68.4 (dd, $^2J_{CF}$ = 26 Hz, $^2J_{CF}$ = 21 Hz); 67.1 (s); 38.2 (s); 27.1 (s); 20.1 (s); 14.7 (s); IR (KBr) 653 (w), 1151 (s), 1208 (s), 1375 (w), 3381 (w). Anal. Calcd. for $C_{16}H_{15}F_{17}O_3$: C, 33.2; H, 2.6. Found: C, 32.4%; H, 2.6%.

*4.3.11. 2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-Henicosafluoro-1-[5-(2,2,5-trimethyl-1,3-dioxane)]undecan-1-ol (**7d**)*

Reaction of aldehyde **1** (0.40 g, 2.5 mmol), perfluorodecyl iodide (3.25 g, 5.0 mmol) and EtMgBr (1.9 ml, 1.94 M, 3.8 mmol) afforded after general procedure C a 97:3 mixture of polyfluoroundecanol **7d** and starting aldehyde **1**. Pure polyfluoroundecanol **9d** was obtained (1.03 g, 60.8%) as crystals. ^{1}H NMR ($CDCl_3$) δ: 4.67 (dd, 1H, $^3J_{HF}$ = 25.0 Hz, $^3J_{HH}$ = 5.2 Hz); 4.03 (dd, 1H, $^2J_{HH}$ = 12.1 Hz, $^4J_{HH}$ = 2.2 Hz); 3.92 (dm, 1H, $^2J_{HH}$ = 12.6 Hz); 3.69 (dd, 1H, $^2J_{HH}$ = 12.1 Hz, $^4J_{HH}$ = 2.4 Hz); 3.53 (d, 1H, $^2J_{HH}$ = 11.5 Hz); 2.88 (d, 1H, $^3J_{HH}$ = 5.0 Hz); 1.45 (s, 3H); 1.43 (s, 3H); 0.97 (s, 3H); 0.90 (bs, 1H); ^{19}F NMR ($CDCl_3$) δ: −81.3 (t, 3F, J_{FF} = 10 Hz); −116.8 (dm, 1F, $^2J_{FF}$ = 286 Hz); −122.0 (m, 2F); −122.3 (m, 10F); −123.2 (m, 2F); −123.9 (dm, 1F, $^2J_{FF}$ = 286 Hz); −126.6 (dm, 1F, $^2J_{FF}$ = 289 Hz); −126.7 (dm, 1F, $^2J_{FF}$ = 289 Hz); ^{13}C NMR ($CDCl_3$) δ: 107–119 (m); 98.8 (s); 68.5 (dd, $^2J_{CF}$ = 26 Hz, $^2J_{CF}$ = 21 Hz); 67.1 (s); 38.2 (s); 27.1 (s); 20.1 (s); 14.8 (s); IR (KBr) 642 (w), 1154 (s), 1208 (s), 1631 (w), 3390 (w). Anal. Calcd. for $C_{18}H_{15}F_{21}O_3$: C, 31.8%; H, 2.2. Found: C, 30.8%; H, 2.2%.

*4.4. Deprotection of cyclic alkanols **7** to polyfluoroalkylated triols **8***

4.4.1. General procedure

Protected polyfluoralkanols **7** were dissolved in methanol (10 ml) and pyridinium 4-toluenesulfonate (0.1 g) was added. The mixture was stirred and heated to reflux for 24 h. Solvent was removed and product, polyfluoroalkylated triol **8**, was isolated by column chromatography (eluent: dichloromethane/ethyl acetate 1/1).

*4.4.2. 4,4,5,5,6,6,7,7,7-Nonafluoro-2-(hydroxymethyl)-2-methylheptan-1,3-diol (**8a**)*

Reaction of polyfluoropentanol **7a** (512 mg, 1.35 mmol) afforded after general procedure polyfluoroalkanetriol **8a** (353 mg, 77.0%) as a wax. ^{1}H NMR (DMSO-d_6) δ: 5.95 (d, 1H, J = 8.2 Hz); 4.69 (t, 1H, J = 5.0 Hz); 4.60 (t, 1H, J = 5.0 Hz); 4.27 (dd, 1H, J = 29.7 Hz, J = 8.8 Hz); 3.3–3.6 (m, 4H); 0.88 (s, 3H); ^{19}F NMR (DMSO-d_6) δ: −80.0 (t, 3F, J_{FF} = 10 Hz); −113.3 (dm, 1F, $^2J_{FF}$ = 277 Hz); −119.5 (dm, 1F, $^2J_{FF}$ = 295 Hz); −122.2 (dm, 1F, $^2J_{FF}$ = 277 Hz); −122.5 (dm, 1F, $^2J_{FF}$ = 295 Hz); −123.8 (dm, 1F, $^2J_{FF}$ = 291 Hz); −126.4 (dm, 1F, $^2J_{FF}$ = 291 Hz); ^{13}C NMR (DMSO-d_6) δ: 107–122 (m); 68.0 (dd, J = 26 Hz, J = 21 Hz); 63.5 (s); 63.0 (s); 44.3 (s); 15.0 (s); IR (KBr) 726 (w), 1031 (m), 1048 (m), 1133 (s), 1238 (s), 3336 (m), 3460 (m). Anal. Calcd. for $C_9H_{11}F_9O_3$: C, 32.0, H; 3.2. Found: C, 33.6%; H, 3.8%.

*4.4.3. 4,4,5,5,6,6,7,7,8,8,9,9,9-Tridecafluoro-2-(hydroxymethyl)-2-methylnonane-1,3-diol (**8b**)*

Reaction of polyfluoroheptanol **7b** (789 mg, 1.65 mmol) afforded after general procedure fluorinated triol **8b** (450 mg, 61.8%). ^{1}H NMR (DMSO-d_6) δ: 5.97(d, 1H, $J = 8.0$ Hz); 4.69 (t, 1H, $J = 5.0$ Hz); 4.60 (t, 1H, $J = 5.0$ Hz); 4.27 (dd, 1H, $J = 29$ Hz); 3.3–3.6 (m, 4H); 0.86 (s, 3H); ^{19}F NMR (DMSO-d_6) δ: −79.7 (t, 3F, $J = 10$ Hz); −112.9 (d, 1F, $^2J_{FF} = 271$ Hz); −119.0 (d, 1F, $^2J_{FF} = 297$ Hz); −120.1 (dm, 1F, $^2J_{FF} = 303$ Hz); −120.8 (dm, 1F, $^2J_{FF} = 300$ Hz); −120.9 (dm, 1F, $^2J_{FF} = 297$ Hz); −121.6 (dm, 1F, $^2J_{FF} = 303$ Hz); −121.7 (dm, 1F, $^2J_{FF} = 271$ Hz); −122.0 (dm, 1F, $^2J_{FF} = 300$ Hz); −124.5 (dm, 1F, $^2J_{FF} = 291$ Hz); −125.6 (dm, 1F, $^2J_{FF} = 291$ Hz); ^{13}C NMR (DMSO-d_6) δ: 107–122 (m); 68.0 (dd, $J = 26$ Hz, $J = 20$ Hz); 63.4 (s); 63.0 (s); 44.3 (s); 15.0 (s); IR (KBr) 1022 (m), 1146 (s), 1208 (s), 1240 (s), 1632 (w), 2962 (w), 3422 (m). Anal. Calcd. for $C_{11}H_{11}F_{13}O_3$: C, 30.2; H, 2.5. Found: C, 32.5%; H, 3.2%.

*4.4.4. 4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-Heptadecafluoro-2-(hydroxymethyl)-2-methylundecane-1,3-diol (**8c**)*

Reaction of polyfluorononanol **7c** (1.50 g, 2.60 mmol) afforded after general procedure polyfluoroalkanetriol **8c** (0.81 g, 58.1%) as crystals. ^{1}H NMR (DMSO-d_6) δ: 5.89 (d, 1H, $J = 8.2$ Hz); 4.68 (t, 1H, $J = 4.4$ Hz); 4.58 (t, 1H, $J = 4.4$ Hz); 4.25 (dd, 1H, $J = 29.1$ Hz, $J = 8.0$ Hz); 3.3–3.6 (m, 4H); 0.86 (s, 3H); ^{19}F NMR (DMSO-d_6) δ: −80.3 (t, 3F, $J = 10$ Hz); −113.4 (d, 1F, $^2J_{FF} = 273$ Hz); −119.3 (d, 1F, $^2J_{FF} = 297$ Hz); −120.5 (dm, 1F, $^2J_{FF} = 300$ Hz); −120.9 (dm, 1F, $^2J_{FF} = 300$ Hz); −121.2 (dm, 1F, $^2J_{FF} = 297$ Hz); −121.6 (m, 2F); −121.7 (dm, 1F, $^2J_{FF} = 300$ Hz); −121.8 (dm, 1F, $^2J_{FF} = 300$ Hz); −122.0 (dm, 1F, $^2J_{FF} = 311$ Hz); −122.8 (dm, 1F, $^2J_{FF} = 311$ Hz); −125.3 (dm, 1F, $^2J_{FF} = 291$ Hz); −126.2 (dm, 1F, $^2J_{FF} = 291$ Hz); ^{13}C NMR (DMSO-d_6) δ: 107–122 (m); 68.1 (dd, $J = 25$ Hz, $J = 21$ Hz); 63.4 (s); 63.0 (s); 44.2 (s); 14.9 (s); IR (KBr) 660 (w), 1023 (m), 1151 (s), 1205 (s), 1243 (s), 3416 (m). Anal. Calcd. for $C_{13}H_{11}F_{17}O_3$: C, 29.0; H, 2.1. Found: C, 30.4%; H, 2.4%.

*4.4.5. 4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12,13,13,13-Henicosafluoro-2-(hydroxymethyl)-2-methyltridecan-1,3-diol (**8d**)*

Reaction of polyfluoroundecanol **7d** (938 mg, 1.38 mmol) afforded after general procedure polyfluoroalkanetriol **8d** (323 mg, 36.9%) as crystals. ^{1}H NMR (DMSO-d_6) δ: 5.79 (d, 1H, $J = 8.2$ Hz); 4.69 (broad s, 1H); 4.55 (broad s, 1H); 4.20 (dd, 1H, $J = 29.1$ Hz, $J = 8.2$ Hz); 3.3–3.6 (m, 4H); 0.84 (s, 3H); ^{19}F NMR (DMSO-d_6) δ: -81.0 (t, 3F, $J_{FF} = 10$ Hz); −113.5 (dm, 1F, $^2J_{FF} = 278$ Hz); −119.4 (dm, 1F, $^2J_{FF} = 300$ Hz); −120.6 (dm, 1F, $^2J_{FF} = 303$ Hz); −121.3 (dm, 1F, $^2J_{FF} = 300$ Hz); −121.6 (m, 9F); −122.6 (m, 3F); −125.9 (dm, 1F, $^2J_{FF} = 286$ Hz); −126.3 (dm, 1F, $^2J_{FF} = 286$ Hz); ^{13}C NMR (DMSO-d_6) δ: 107–120 (m); 68.3 (dd, $J = 24$ Hz, $J = 20$ Hz); 63.5 (s); 63.2 (s); 44.1 (s); 14.8 (s); IR (KBr) 555 (w), 647 (w), 1153 (s), 1210 (s), 3401 (m). Anal. Calcd. for $C_{15}H_{11}F_{21}O_3$: C, 28.2; H, 1.7. Found: C, 29.1%; H, 2.6%.

Acknowledgements

The research has been supported by the Grant Agency of the Czech Republic (Grant nos. 203/98/1174 and 203/01/1311). We are indebted to Elf Atochem for a kind gift of perfluoroalkyl iodides. We thank heartily Dr. Vladimír Církva for the preparation of 5-(2,2,5-trimethyl-1,3-dioxane)-methanol (**3**).

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