Journal of Fluorine Chemistry 130 (2009) 308–316

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

journal homepage: www.elsevier.com/locate/fluor

Novel perfluoroalkylated oligo(oxyethylene) methyl ethers with high hemocompatibility and excellent co-emulsifying properties for potential biomedical uses

Robert Kaplánek [a], Oldřich Paleta [a,*], Ivana Ferjentsiková [b], Milan Kodíček [b]

[a] Department of Organic Chemistry, Prague Institute of Chemical Technology, Technická 5, 16628 Prague 6, Czech Republic
[b] Department of Biochemistry and Microbiology, Prague Institute of Chemical Technology, Technická 5, 16628 Prague 6, Czech Republic

ARTICLE INFO

Article history:
Received 7 October 2008
Received in revised form 28 November 2008
Accepted 1 December 2008
Available online 9 December 2008

Keywords:
Perfluoroalkylated oligo(oxyethylene) ethers
Perfluoroalkylated oxiranes
Radical addition
Reduction of C–I bond
1-*O*-Fluoroalkyl-D-xylitol
Hemocompatibility
Microemulsion stability

ABSTRACT

Two series of novel perfluoroalkylated amphiphilic compounds were synthesized from monomethyl ethers of mono-, di- and tri-(oxyethylene) glycols. The first series $CH_3(OCH_2CH_2)_nOCH_2CH(OH)CH_2–CF_2(CF_2CF_2)_nCF_3$ ($n = 1–3$) bearing the hydroxy group at the spacer between hydrophilic and hydrophobic parts was prepared by the reactions of the monomethyl ethers with 2-(perfluoroalkylmethyl)oxiranes in 76–97% yields. The second series $CH_3(OCH_2CH_2)_nOCH_2CH_2CH_2–CF_2(CF_2CF_2)_nCF_3$ ($n = 1–3$) possessing the non-hydroxylated spacer was synthesized from allyl methyl ethers of oligo(oxyethylene) glycols using radical additions of perfluoroalkyl iodides and subsequent selective reductions of the C–I bond in the adducts in overall yields of 23–69%. Some of the novel amphiphilic compounds displayed very low hemolytic activity to erythrocytes and excellent co-emulsifying properties on testing on perfluorodecalin/Pluronic F-68 microemulsions. 1-*O*-(2-Hydroxy-4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyl)-D-xylitol was prepared by a novelized synthesis and employed as a standard compound in the testing.

1. Introduction

Some classes of highly fluorinated or perfluorinated compounds (PFCs), including perfluorocarbons, perfluorinated trialkylamines or nitrogen heterocycles have ability to dissolve large amount of gases, namely oxygen and carbon dioxide, even more than water or blood [1,2]. Another outstanding property of these compounds is their biological inertness. This property and ability to dissolve large volumes of respiratory gases have made them attractive for (potential) biomedical uses [3–7].

Water colloidal systems prepared from perfluorinated components, as various types of emulsions, fluorinated vesicles (liposomes), and other highly fluorinated self-assemblies, have significant potential in the biomedical field. Emulsions for injectable oxygen carriers (blood substitutes) useful in cardiopulmonary bypass surgery, liquid ventilation, perfusion of isolated organs or cell-cultivation, contrast agents for diagnosis by ultrasound imaging, vesicles in drug delivery systems, and gels with dispersed PFC phase for skin and wound protection are main areas of applied research for these colloidal systems [8–13]. As perfluorocarbons are highly hydrophobic molecules, their water emulsions can be prepared on using an appropriate biocompatible amphiphilic surfactant [14].

Pluronic F-68 (the poly[oxyethylene]-poly[oxypropylene] block copolymer) is one of the most biocompatible synthetic surfactants known. It has found numerous applications in the biomedical field, including the treatment of hemorrhagic shock or as a dispersant for drugs. Lecithins are used as emulsifiers, especially in fat emulsions for parenteral nutrition and for the preparation of liposomes for drug targeting. However, neither Pluronic F-68 nor lecithins are particularly fluorophilic, and the stability of the emulsions they form with PFCs is usually poor. It has been shown that a strong stabilization of PCFs emulsions can be achieved by combining the properties of PF-68 with amphiphilic perfluoroalkylated surfactants. A perfluoroalkylated tail improves the adhesion of a co-surfactant to the fluorocarbon phase. Thus, fluorinated co-surfactants play key role by allowing stabilization of such emulsions. Some of them appeared to be low hemolytic [15–18].

Up to the present, a range of emulsifiers bearing perfluorinated moiety have been studied. As the hydrophilic part, polyhydroxy-

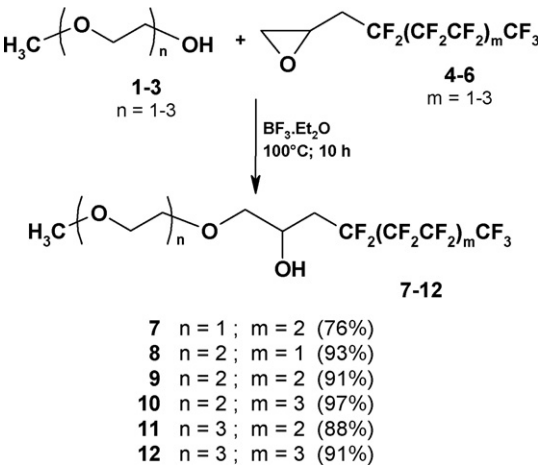
* Corresponding author.
E-mail address: oldrich.paleta@vscht.cz (O. Paleta).

0022-1139/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.jfluchem.2008.12.001

lated groups or saccharides [8,9,19–23], poly(oxyethylene) chain or 2-hydroxyethyl groups [4,14,24–29], sulfinyl or sulfone group [20,21,29–31], and organic salts [19,31–33] were employed.

Herein, we describe the synthesis of perfluoroalkylated amphiphiles consisting of oligo(oxyethylene) hydrophilic part and trimethylene spacer. Similar amphiphilic compounds bearing polyethylene glycol moiety as hydrophilic part have been reported [4,14,24,27,34,35].

Their ability to stabilize perfluorodecalin–water emulsions [4] and hemolytic effect on a suspension of red blood cells were studied [24,34]. In this paper we present results of testing of the novel compounds for hemocompatibility, microemulsion stability and co-emulsifying properties for two series of co-emulsifiers, which differ in the corresponding pairs by hydroxy group attached to the hydrocarbon spacer. In contrast to the former reports [8,16], we have found that the properties tested are not simply dependent on the chain length of the poly(oxyethylene) and/or perfluoroalkyl moieties.



Scheme 1. Preparation of amphiphiles **7–12**.

2. Chemistry

Both two series of the novel perfluoroalkylated amphiphilic compounds **7–12** and **24–28** were synthesized by transformations of the industrially available monomethyl ethers of mono-, di- and tri-(oxyethylene) glycols **1–3**.

2.1.1. Preparation of amphiphiles 7–12

For the connection of the oligo(oxyethylene) moiety with the hydroxylated spacer and perfluoroalkyls, we employed the epoxide ring opening reaction of 2-(perfluoroalkyl)methyl oxiranes **4–6** (Scheme 1) [23,36–38]. The reaction was catalyzed efficiently by boron trifluoride diethyl etherate, a strong Lewis acid, to activate the epoxide cycle to the *O*-nucleophile ring opening in the perfluoroalkylated epoxides **4–6**. The epoxide ring opening proceeded with the complete regioselectivity at the less substituted carbon atom [23,36–38].

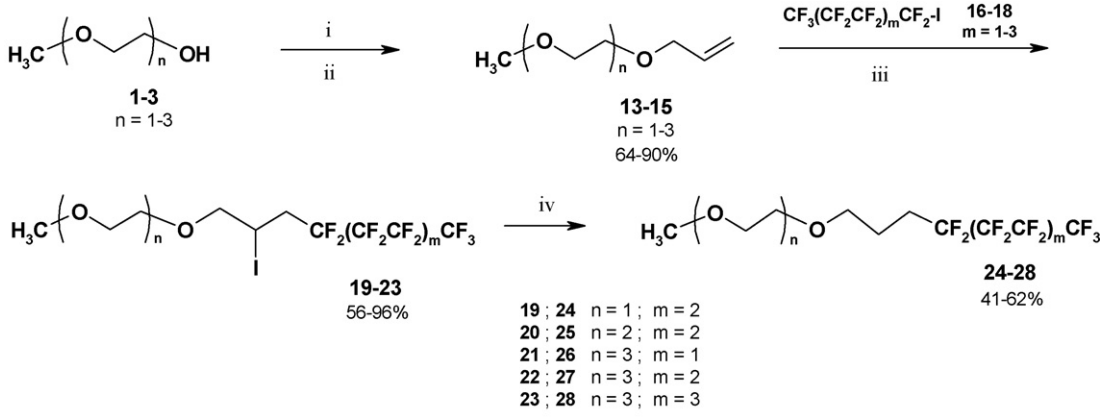
The reactions were carried out without any solvent at 100 °C for 10 h (Scheme 1) to afford perfluoroalkylated amphiphiles **7–12** in 76–97% isolated yields. The preparation of the **7** and **12** we already reported as intermediates in the synthesis of perfluoroalkylated amphiphilic methacrylates [38].

2.1.2. Preparation of amphiphiles 24–28

Amphiphilic compounds with propane-1,3-diyl spacer between a perfluoroalkyl chain and hydrophilic oligo(oxyethylene) moiety were prepared by a three-step synthesis (Scheme 2). In the first step, the starting monomethyl ethers **1–3** were converted into the corresponding allyl methyl ethers **13–15**. In the second step, perfluorinated alkyls were introduced into the ethers **13–15** by the radical addition of perfluoroalkyl iodides **16–18** initiated by *N*,*N*′-azobis(isobutyronitrile) (AIBN) or sodium dithionite. In the third step, the C–I bonds in the adducts **19–23** were reduced to obtain the desired amphiphiles **24–28** (Scheme 2).

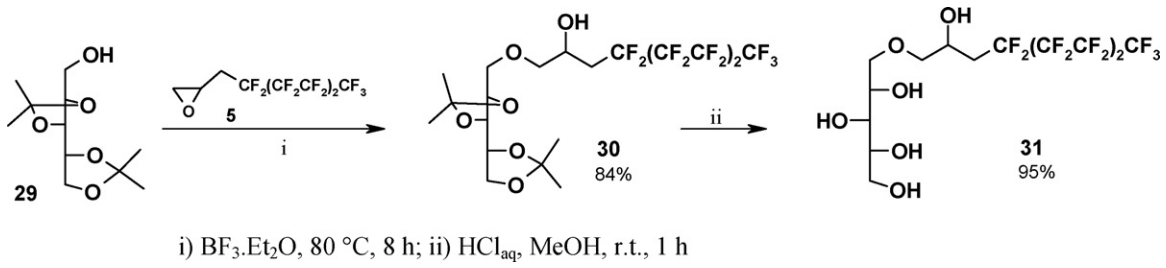
For the preparation of the allyl ethers **13–15**, modified reaction conditions of those published [39,40] were applied in that manner that the monomethyl ethers **1–3** were metallated with sodium hydride in diethyl ether and subsequently reacted with excess allyl bromide (Scheme 2) to obtain **13–15** in 64–90% yields. Several initiation systems have been reported for the radical additions of perfluoroalkyl iodides **16–18**, e.g. azo compounds, metals and their salts, organic peroxides or sodium dithionite [41]. In our radical additions, AIBN as the initiator without any solvent [41,42] afforded generally higher yields of additions in comparison with sodium dithionite in the acetonitrile–water system [42–46]. The yields of the additions are summarized in Table 1. In the case of perfluorooctyl iodide (**18**), the difference in yields is high probably due to a low solubility of the iodide **18** in the acetonitrile–water solvent.

Several methods have been reported for the reduction of C–I bonds in addition products of perfluoroalkyl iodides. The reagents include Bu_3SnH/AIBN [47–51], H_2/Pd/C [42,44,46],



i) NaH, Et_2O, reflux, 2 h; ii) AllylBr, Et_2O, reflux, 4 h; iii) AIBN, 100°C, 3 h, or $Na_2S_2O_4$/$NaHCO_3$, MeCN/H_2O, r.t., 2 h; iv) Zn, $NiCl_2.6H_2O$, THF/ H_2O, r.t., 4 h

Scheme 2. Preparation of amphiphiles **24–28**.



i) $BF_3.Et_2O$, 80 °C, 8 h; ii) HCl_{aq}, MeOH, r.t., 1 h

Scheme 3. Preparation of xylitol derivative **31**.

Table 1
The results of the radical additions of perfluoroalkyl iodides onto allyl (oligo)ethers **13–15**.

Alkene	Iodide	Initiator	Yield[a] (%)
$CH_3OCH_2CH_2OCH_2CH{=}CH_2$ (**13**)	$C_6F_{13}I$ (**17**)	AIBN	91
$CH_3OCH_2CH_2OCH_2CH{=}CH_2$ (**13**)	$C_6F_{13}I$ (**17**)	$Na_2S_2O_4$	91
$CH_3(OCH_2CH_2)_2OCH_2CH{=}CH_2$ (**14**)	$C_6F_{13}I$ (**17**)	AIBN	96
$CH_3(OCH_2CH_2)_2OCH_2CH{=}CH_2$ (**14**)	$C_6F_{13}I$ (**17**)	$Na_2S_2O_4$	81
$CH_3(OCH_2CH_2)_3OCH_2CH{=}CH_2$ (**15**)	C_4F_9I (**16**)	AIBN	87
$CH_3(OCH_2CH_2)_3OCH_2CH{=}CH_2$ (**15**)	C_4F_9I (**16**)	$Na_2S_2O_4$	86
$CH_3(OCH_2CH_2)_3OCH_2CH{=}CH_2$ (**15**)	$C_6F_{13}I$ (**17**)	AIBN	95
$CH_3(OCH_2CH_2)_3OCH_2CH{=}CH_2$ (**15**)	$C_6F_{13}I$ (**17**)	$Na_2S_2O_4$	85
$CH_3(OCH_2CH_2)_3OCH_2CH{=}CH_2$ (**15**)	$C_8F_{17}I$ (**18**)	AIBN	95
$CH_3(OCH_2CH_2)_3OCH_2CH{=}CH_2$ (**15**)	$C_8F_{17}I$ (**18**)	$Na_2S_2O_4$	56

[a] Isolated yield.

$Zn/HCl_{(g)}$ [52–54], Zn/AcOH [55–57], $Zn/NiCl_2$ [58,59] or $LiAlH_4$ [60,61]. Unfortunately, the reductions do not run with the complete conversion of the starting iodo derivatives in particular cases or the separation and purification of the products from a reaction mixture can be problematic causing a decrease of yields. The reduction of the iodo intermediates **19–23** using $Zn/NiCl_2$ in THF–water mixture at room temperature for 24 h was our method of choice to afford the amphiphiles **24–28** in yields of 41–62% (Scheme 2).

2.1.3. Preparation of xylitol derivative 31

Xylitol derivative **31** has been employed as a standard in testing emulsion stability and hemocompatibility in recent papers [37]. Herein we report an improved method of the preparation of this compound as follows (Scheme 3): protected xylitol **29** was reacted with 2-(perfluorohexyl)methyl oxirane (**5**) without solvent in the presence of $BF_3{\cdot}Et_2O$ as a catalyst to afford the xylitol derivative **30** in the yield of 84% (Lit. 76% [37]). Deprotection of hydroxy groups was carried out using hydrochloric acid in methanol in the yield of 95% of the end-product **31** (Lit. 82% [37]).

3. Testing of co-emulsifying properties and hemocompatibility

The novel amphiphiles **7–12** and **24–28** were tested as co-surfactants for oxygen carriers and other biomedical uses as specified in literature [7–13]. Perfluoroalkylated co-surfactants for microemulsions are usually used in amounts up to 10% relatively to the main emulsifier, e.g. Pluronic F-68, and can stabilize microemulsions in positive cases [7,9,15–17]. For an assessment of co-emulsion stability and hemolytic activity of the new amphiphilic compounds, we applied methods that have been used in our recent reports (the methods are briefly described in Section 5) [22,23,37]. Microemulsions were prepared by sonication. In testing, a reference microemulsion of Pluronic F-68 with perfluorodecalin was used, in which Pluronic was gradually substituted with the amphiphile tested and the effect of this substitution observed (Tables 2–5). The xylitol amphiphile **31** has been included in testing as a standard compound to verify reliability of testing results with respect to the quality of hemoglobin used [37].

3.1. Co-emulsifying properties and microemulsion stability

The testing of co-emulsifying properties was based on visual evaluation of the state of an emulsion (see Section 5). The first, a very efficient test, was stability of emulsions during 5 min centrifugation (Table 2). It was surprising that the amphiphiles

Table 2
Stability[a,b] of emulsions during centrifugation (400 × *g* for 5 min).

Emulsifier	Substitution of Pluronic F-68 by tested emulsifiers (% w/w PF-68)				
	20%	40%	60%	80%	100%
	Emulsion stability				
$MeO(CH_2CH_2O)$–$CH_2CH(OH)CH_2$–C_6F_{13} (**7**)	+	+	+	+	+
$MeO(CH_2CH_2O)_2$–$CH_2CH(OH)CH_2$–C_4F_9 (**8**)	–	–	–	–	–
$MeO(CH_2CH_2O)_2$–$CH_2CH(OH)CH_2$–C_6F_{13} (**9**)	+	+	+	–	–
$MeO(CH_2CH_2O)_2$–$CH_2CH(OH)CH_2$–C_8F_{17} (**10**)	–	–	–	–	–
$MeO(CH_2CH_2O)_3$–$CH_2CH(OH)CH_2$–C_6F_{13} (**11**)	Emulsions were not formed[a]				
$MeO(CH_2CH_2O)_3$–$CH_2CH(OH)CH_2$–C_8F_{17} (**12**)	Emulsions were not formed[a]				
$MeO(CH_2CH_2O)$–$CH_2CH_2CH_2$–C_6F_{13} (**24**)	+	+	+	+	–
$MeO(CH_2CH_2O)_2$–$CH_2CH_2CH_2$–C_6F_{13} (**25**)	+	+	+	+	–
$MeO(CH_2CH_2O)_3$–$CH_2CH_2CH_2$–C_4F_9 (**26**)	–	–	–	–	–
$MeO(CH_2CH_2O)_3$–$CH_2CH_2CH_2$–C_6F_{13} (**27**)	+	+	+	–	–
$MeO(CH_2CH_2O)_3$–$CH_2CH_2CH_2$–C_8F_{17} (**28**)	+	–	–	–	–
[Xylitol-1-yl]-$CH_2CH(OH)CH_2$–C_6F_{13} (**31**)[c]	+	+	+	+	–

[a] For the compounds **11** and **12**, the emulsions were not formed by initial sonication.
[b] Plus (+) means no apparent change of the emulsion; minus (–) means colaps of the emulsion.
[c] Ref. [37].

Table 3
Stability of emulsions during standing at r.t. for 8 weeks[a,b].

Emulsifier	Substitution of Pluronic F-68 by tested emulsifiers (% w/w PF-68)				
	20%	40%	60%	80%	100%
	Emulsion stability				
$MeO(CH_2CH_2O)$–$CH_2CH(OH)CH_2$–C_6F_{13} (**7**)	+	+	+	+	+
$MeO(CH_2CH_2O)_2$–$CH_2CH(OH)CH_2$–C_4F_9 (**8**)	–	–	–	–	–
$MeO(CH_2CH_2O)_2$–$CH_2CH(OH)CH_2$–C_6F_{13} (**9**)	+	+	+	–	–
$MeO(CH_2CH_2O)_2$–$CH_2CH(OH)CH_2$–C_8F_{17} (**10**)	–	–	–	–	–
$MeO(CH_2CH_2O)$–$CH_2CH_2CH_2$–C_6F_{13} (**24**)	+	+	+	+	–
$MeO(CH_2CH_2O)_2$–$CH_2CH_2CH_2$–C_6F_{13} (**25**)	+	+	+	+	–
$MeO(CH_2CH_2O)_3$–$CH_2CH_2CH_2$–C_4F_9 (**26**)	–	–	–	–	–
$MeO(CH_2CH_2O)_3$–$CH_2CH_2CH_2$–C_6F_{13} (**27**)	+	+	+	+	–
$MeO(CH_2CH_2O)_3$–$CH_2CH_2CH_2$–C_8F_{17} (**28**)	–	–	–	–	–
[Xylitol-1-yl]-$CH_2CH(OH)CH_2$–C_6F_{13} (**31**)[c]	+	+	–	–	–

[a] For the compounds **11** and **12**, the emulsions were not formed by initial sonication.
[b] Plus (+) means no apparent change of the emulsion; minus (–) means colaps of the emulsion.
[c] Ref. [37].

Table 4
Stability of emulsions at 37 °C for 6 h after mixing with erythrocytes[a,b].

Emulsifier	Substitution of Pluronic F-68 by tested emulsifiers (% w/w PF-68)				
	20%	40%	60%	80%	100%
	Emulsion stability				
$MeO(CH_2CH_2O)$–$CH_2CH(OH)CH_2$–C_6F_{13} (**7**)	+	+	+	+	+
$MeO(CH_2CH_2O)_2$–$CH_2CH(OH)CH_2$–C_4F_9 (**8**)	–	–	–	–	–
$MeO(CH_2CH_2O)_2$–$CH_2CH(OH)CH_2$–C_6F_{13} (**9**)	+	+	+	–	–
$MeO(CH_2CH_2O)_2$–$CH_2CH(OH)CH_2$–C_8F_{17} (**10**)	+	–	–	–	–
$MeO(CH_2CH_2O)$–$CH_2CH_2CH_2$–C_6F_{13} (**24**)	+	+	+	+	–
$MeO(CH_2CH_2O)_2$–$CH_2CH_2CH_2$–C_6F_{13} (**25**)	+	+	+	+	–
$MeO(CH_2CH_2O)_3$–$CH_2CH_2CH_2$–C_4F_9 (**26**)	–	–	–	–	–
$MeO(CH_2CH_2O)_3$–$CH_2CH_2CH_2$–C_6F_{13} (**27**)	+	+	+	–	–
$MeO(CH_2CH_2O)_3$–$CH_2CH_2CH_2$–C_8F_{17} (**28**)	–	–	–	–	–
[Xylitol-1-yl]-$CH_2CH(OH)CH_2$–C_6F_{13} (**31**)[c]	+	+	+	+	–

[a] For the compounds **11** and **12**, the emulsions were not formed by initial sonication.
[b] Plus (+) means no apparent change of the emulsion; minus (–) means colaps of the emulsion.
[c] Ref. [37].

11 and **12**, possessing tri(oxyethylene) hydrophilic part and hydroxylated spacer, did not form microemulsions by initial sonication even at only 20% substitution of Pluronic. In contrast, their counterparts **27** and **28** possessing non-hydroxylated spacer formed stable microemulsions at 20–60% and 20% substitution of Pluronic, respectively (Table 2). In addition, also the amphiphile **25** with non-hydroxylated spacer formed more stable emulsions than its counterpart **9**. When comparing the effect of the perfluoroalkyl length, it can be seen that perfluorobutyl causes instability of emulsions at all concentrations (amphiphiles **8** and **26**). Stable emulsions at high concentrations of co-emulsifier are those bearing perfluorohexyl: substitution of Pluronic up to 60% (**9**, **27**), 80% (**24**, **25**) or 100% (**7**) was found. On the other hand, perfluorooctyl also caused almost complete instability of emulsions (compounds **10** and **28**). The number of oxyethylene units in the amphiphiles also influenced stability of emulsions. The effect is

Table 5
Range of hemolysis[a,b].

Emulsifier	Substitution of Pluronic F-68 by tested emulsifiers (% w/w PF-68)				
	20%	40%	60%	80%	100%
	Range of hemolysis[a,b]				
$MeO(CH_2CH_2O)$–$CH_2CH(OH)CH_2$–C_6F_{13} (**7**)	0[c]	0	0	0.5	0.5
$MeO(CH_2CH_2O)_2$–$CH_2CH(OH)CH_2$–C_4F_9 (**8**)	1.4	1.5	3.0	5.3	5.6
$MeO(CH_2CH_2O)_2$–$CH_2CH(OH)CH_2$–C_6F_{13} (**9**)	0	0	0	1.0	0.8
$MeO(CH_2CH_2O)_2$–$CH_2CH(OH)CH_2$–C_8F_{17} (**10**)	0	0	0	0.3	0.5
$MeO(CH_2CH_2O)$–$CH_2CH_2CH_2$–C_6F_{13} (**24**)	0	0.5	0.8	1.1	NT[d]
$MeO(CH_2CH_2O)_2$–$CH_2CH_2CH_2$–C_6F_{13} (**25**)	3.1	5.2	10.6	23	98.6
$MeO(CH_2CH_2O)_3$–$CH_2CH_2CH_2$–C_4F_9 (**26**)	1.7	2.7	7.5	10.9	63.6
$MeO(CH_2CH_2O)_3$–$CH_2CH_2CH_2$–C_6F_{13} (**27**)	1.3	2.5	9.0	52.5	79.7
$MeO(CH_2CH_2O)_3$–$CH_2CH_2CH_2$–C_8F_{17} (**28**)	0	0	0	0	0
[Xylitol-1-yl]-$CH_2CH(OH)CH_2$–C_6F_{13} (**31**)	0	0	0	0.6	0.8

[a] For the compounds **11** and **12**, the emulsions were not formed by initial sonication.
[b] Hemolysis up to 1% is irrelevant.
[c] Zero value means hemolysis below 0.5%.
[d] Not tested.

apparent in the series of amphiphiles having hydroxylated spacer: compound **7** with one oxyethylene unit afforded emulsions stable up to 100% substitution of Pluronic (Table 2); the emulsions containing **9** bearing two oxyethylene units were stable up to 60% substitution of Pluronic, while **11** with three oxyethylene units did not form microemulsions at all.

The second test of microemulsions was a long-term stability on standing at room temperature for 8 weeks mimicking a long-term storage. The results (Table 3) have revealed that the stabilities of the emulsions were the same as those on centrifugation (Table 2) with a slight divergence to a lower value for the amphiphile **28**. The third test was for stability of the microemulsions in the presence of erythrocytes at 37 °C mimicking human blood. As shown in Table 4, also this test revealed almost the same stabilities of the microemulsions as those on centrifugation (Table 2) with a slight divergence to a higher value (20% substitution of Pluronic) for the amphiphile **10** and to a lower value for the amphiphile **28**.

It can be summarized that very good co-emulsifying properties enabling up to 60% of Pluronic substitution displayed amphiphiles **9** or **27** and excellent properties displayed amphiphiles **7**, **24** and **25** (100, 80 and 80% substitution of Pluronic).

3.2. Hemocompatibility

Hemolytic activity of perfluoroalkylated amphiphiles **7–12** and **24–28** on human erythrocytes was tested using a reference perfluorodecalin/Pluronic F-68 microemulsion mixed with erythrocytes (heterogeneous mixture). Pluronic F-68 was gradually substituted with the amphiphile tested and the amount of extracellular hemoglobin was determined spectrophotometrically as per cent degree of hemolysis. The results of the testing are summarized in Table 5 and reveal that the dominant effect on hemolytic activity is the structure of the spacer: the set of amphiphiles **7–10** bearing hydroxylated spacer displayed generally lower hemolytic activity (i.e. better hemocompatibility) than the amphiphiles in the set **24–28**. It has also been apparent that the hemocompatibility increases with longer perfluoroalkyl-chain length causing the complete hemocompatibility up to 100% of Pluronic substitution for the amphiphiles **10** and **28**.

3.3. Effects of perfluoroalkyl chain length on amphiphiles properties

It can generally be concluded that the effects are more or less combined with the hydrophilic moiety and a spacer in the molecule of a perfluoroalkylated amphiphile. In addition, the effects on emulsion stability and hemolytic activity are usually not parallel as observed recently [23,37]. For example, in the case of perfluoroalkylated aliphatic triols [23], hemocompatibility was increasing with perfluoroalkyl chain length, while microemulsion stability was better for perfluorohexyl than perfluorooctyl in particular cases. Similar effects were observed for perfluoroalkylated D-galactopyranose and D,L-xylitol possessing 2-hydroxypropane-1,3-diyl spacer [37]. In this paper, it can be observed that the best emulsion stability revealed amphiphiles **7**, **9**, **24**, **25**, **27** bearing perfluorohexyl (Tables 2-4), while hemocompatibility was the best for compounds **10** and **28** bearing perfluorooctyl (Table 5).

4. Conclusions

Two series of novel perfluoroalkylated amphiphilic compounds consisting of oligo(oxyethylene) hydrophilic part and 2-hydroxypropane-1,3-diyl (**7–12**) or propane-1,3-diyl spacer (**24–28**) were synthesized in overall yields of 73-97% and 23–69%, respectively, for testing of co-emulsifier properties and hemocompatibility. Some of the amphiphilic compounds prepared (**7**, **9**, **24**, **28**) displayed a zero level hemolytic activity to erythrocytes and excellent co-emulsifying properties (**7**, **9**, **24**, **25**, **27**) on testing on perfluorodecalin/Pluronic F-68 microemulsions. Thus, some of the compounds synthesized are suitable for further biochemical and pharmacological testing. These easily accessible surfactants could find application in biomedical and also technical areas.

5. Experimental

5.1. General comments and chemicals

NMR spectra were recorded on a Varian Gemini 300 MHz (FT, ^{1}H at 300 MHz, ^{13}C at 75 MHz, ^{19}F at 281 MHz) instrument using TMS and $CFCl_3$ as the internal standards. Chemical shifts are quoted in ppm (δ-scale; s: singlet; bs: broad singlet; d: doublet; t: triplet; m: multiplet), coupling constants *J* in Hz, solvents: $CDCl_3$, CD_3OD.

The chemicals used were as follows: perfluoroalkyl iodides were obtained from Atofina S.A.; activated charcoal, AIBN, sodium dithionite, sodium hydride (60% suspension in mineral oil; oil was removed by washing with dry diethyl ether before use), 2-(methoxy)ethanol, 3,6-dioxaheptan-1-ol, perfluorodecalin, trifluoroacetic acid, 3,6,9-trioxadecan-1-ol, zinc (all Aldrich); allyl bromide, nickel (II) chloride hexahydrate, $BF_3{\cdot}Et_2O$, sodium hydrocarbonate (Lachema Brno, Czech Rep.); silica gel (60–100 μm, Merck). All solvents were purchased from Penta and dried according to standard procedures. All reactions requiring anhydrous conditions were performed using dried solvents and under inert atmosphere.

2-(Perfluoroalkyl)methyl oxiranes were prepared according the reported procedure [62]. 1,2:3,4-Di-*O*-isopropylidene-D-xylitol was prepared according literature [63].

5.2. Chemistry

5.2.1. General procedure for preparation of 7–12

2-(Perfluoroalkyl)methyl oxirane **4–6**, ethylene glycol monomethyl ether **1–3** (molar ratio 1:8–10) and $BF_3{\cdot}Et_2O$ were heated while stirring at 100 °C for 10 h. After cooling down, excess of ethylene glycol monomethyl ether and $BF_3{\cdot}Et_2O$ were removed under reduced pressure. Crude product was purified by using column chromatography on silica gel (eluent:petroleum ether/acetone 4:1, v/v).

5.2.1.1. 9,9,10,10,11,11,12,12,13,13,14,14,14-Tridecafluoro-2,5-dioxatetradecan-7-ol (7). l,2-Epoxy-4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononane (**5**; 1.505 g; 4 mmol), 2-methoxyethanol (**1**; 3.10 g; 40 mmol), $BF_3{\cdot}Et_2O$ (0.20 mL). Product **7** was obtained as yellowish liquid (1.330 g; 76%).

^{1}H NMR ($CDCl_3$): δ = 2.05–2.55 (m, 2H, CH_2–R_F), 3.35 (s, 3H, CH_3), 3.40–3.90 (m, 7H, 3× CH_2–O and CH–O), 4.23 (s, 1H, OH). ^{13}C NMR ($CDCl_3$): δ = 34.5 (t, 1C, CH_2–R_F, *J* = 21 Hz), 58.8 (s, 1C, CH_3), 64.2 (s, 1C, CH); 70.6, 71.9 (2× s, 2× 1C, 2× CH_2–O); 74.9 (s, 1C, *CH_2*–CH), 103.0–124.0 (m, 6C, 5× CF_2 and CF_3). ^{19}F NMR ($CDCl_3$): δ = −81.4 (t, 3F, CF_3, *J* = 10 Hz), −113.2 (m, 2F, CH_2–CF_2); −122.3, −123.3, −124.1 (3× m, 3× 2F, 3× CF_2); −126.6 (m, 2F, *CF_2*–CF_3).

Anal. Calcd. for $C_{12}H_{13}F_{13}O_3$: C, 31.87; H, 2.90. Found: C, 32.03; H, 3.07%.

5.2.1.2. 12,12,13,13,14,14,15,15,15-Nonafluoro-2,5,8-trioxapentadecan-10-ol (8). l,2-Epoxy-4,4,5,5,6,6,7,7,7-nonafluoroheptane (**4**; 0.579 g; 2.1 mmol), 3,6-dioxaheptan-1-ol (**2**; 2.40 g; 20 mmol), $BF_3{\cdot}Et_2O$ (0.20 mL). Product **8** was obtained as yellowish liquid (0.772 g; 93%).

^{1}H NMR ($CDCl_3$): δ = 2.05–2.45 (m, 2H, CH_2–R_F), 3.32 (s, 3H, CH_3), 3.40–4.00 (m, 11H, 5× CH_2–O and CH–O), 4.25 (bs, 1H, OH). ^{13}C NMR ($CDCl_3$): δ = 34.3 (t, 1C, CH_2–R_F, *J* = 21 Hz), 58.8 (s, 1C,

CH_3), 64.1 (s, 1C, CH), 70.4 (s, 2C, 2× CH_2–O), 70.7 (s, 1C, CH_2–O), 71.7 (s, 1C, CH_2–O), 74.8 (s, 1C, *CH_2*–CH), 105.0–120.0 (m, 4C, 3× CF_2 and CF_3). ^{19}F NMR ($CDCl_3$): δ = −81.7 (tt, 3F, CF_3, *J* = 10.3/3.2 Hz), −113.0 (m, 2F, CH_2–CF_2), −124.7 (m, 2F, CF_2), −126.5 (m, 2F, *CF_2*–CF_3).

Anal. Calcd. for $C_{12}H_{17}F_9O_4$: C, 36.37; H, 4.32. Found: C, 36.32; H, 4.37%.

5.2.1.3. 12,12,13,13,14,14,15,15,16,16,17,17,17-Tridecafluoro-2,5,8-trioxaheptadecan-10-ol (9). l,2-Epoxy-4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononane (**5**; 1.880 g; 5 mmol), 3,6-dioxaheptan-1-ol (**2**; 6.00 g; 50 mmol), BF_3·Et_2O (0.20 mL). Product **9** was obtained as colourless liquid (2.280 g; 91%).

^{1}H NMR ($CDCl_3$): δ = 2.07–2.40 (m, 2H, CH_2–R_F), 3.32 (s, 3H, CH_3), 3.38-3.70 (m, 11H, 5× CH_2–O and CH–O), 4.21 (s, 1H, OH). ^{13}C NMR ($CDCl_3$): δ = 34.5 (t, 1C, CH_2–R_F, *J* = 21 Hz), 58.8 (s, 1C, CH_3), 64.1 (s, 1C, CH); 70.4, 70.5, 70.7, 71.8 (4× s, 4× 1C, 4× CH_2–O); 74.8 (s, 1C, *CH_2*–CH), 104.0–124.0 (m, 6C, 5× CF_2 and CF_3). ^{19}F NMR ($CDCl_3$): δ = −81.4 (t, 3F, CF_3, *J* = 10.1 Hz), −113.2 (m, 2F, CH_2–CF_2); −122.3, −123.3, −124.1 (3× m, 3× 2F, 3× CF_2); −126.6 (m, 2F, *CF_2*–CF_3).

Anal. Calcd. for $C_{14}H_{17}F_{13}O_4$: C, 33.88; H, 3.45. Found: C, 34.12; H, 3.57%.

5.2.1.4. 12,12,13,13,14,14,15,15,16,16,17,17,18,18,19,19,19-Heptadecafluoro-2,5,8-trioxanonadecan-10-ol (10). 1,2-Epoxy-4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluoroundecane (**6**; 0.710 g; 1.50 mmol), 3,6-dioxaheptan-1-ol (**2**; 1.80 g; 15 mmol), BF_3·Et_2O (0.20 mL). Product **10** was obtained as yellowish liquid (0.863 g; 97%).

^{1}H NMR ($CDCl_3$): δ = 2.10–2.45 (m, 2H, CH_2–R_F), 3.33 (s, 3H, CH_3), 3.40–4.00 (m, 11H, 5× CH_2–O and CH–O), 4.28 (bs, 1H, OH). ^{13}C NMR ($CDCl_3$): δ = 34.4 (t, 1C, CH_2–R_F, *J* = 21 Hz), 58.7 (s, 1C, CH_3), 64.1 (s, 1C, CH); 70.4, 70.4, 70.6, 71.7 (4× s, 4× 1C, 4× CH_2–O); 74.8 (s, 1C, *CH_2*–CH), 102.0–124.0 (m, 8C, 7× CF_2 and CF_3). ^{19}F NMR ($CDCl_3$): δ = −81.5 (t, 3F, CF_3, *J* = 10.9 Hz), −112.8 (m, 2F, CH_2–CF_2); −122.1, −122.3, −123.2, −123.7 (4× m, 4× 2F, 4× CF_2); −126.7 (m, 2F, *CF_2*–CF_3).

Anal. Calcd. for $C_{16}H_{17}F_{17}O_4$: C, 32.23; H, 2.87. Found: C, 32.15; H, 2.89%.

5.2.1.5. 15,15,16,16,17,17,18,18,19,19,20,20,20-Tridecafluoro-2,5,8,11-tetraoxaicosan-13-ol (11). l,2-Epoxy-4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononane (**5**; 0.621 g; 1.66 mmol), 3,6,9-trioxadecan-1-ol (**3**; 1.65 g; 10 mmol), BF_3·Et_2O (0.20 mL). Product **11** was obtained as yellowish liquid (0.785 g; 88%).

^{1}H NMR ($CDCl_3$): δ = 2.10–2.44 (m, 2H, CH_2–R_F), 3.33 (s, 3H, CH_3), 3.40–3.78 (m, 15H, 6× CH_2–O and CH–O), 4.23 (bs, 1H, OH). ^{13}C NMR ($CDCl_3$): δ = 34.4 (t, 1C, CH_2–R_F, *J* = 21 Hz), 58.8 (s, 1C, CH_3), 64.1 (s, 1C, CH), 70.4 (s, 1C, CH_2–O), 70.5 (s, 3C, 3× CH_2–O); 70.7, 71.8 (2× s, 2× 1C, 2× CH_2–O); 74.9 (s, 1C, *CH_2*–CH), 105.0–125.0 (m, 6C, 5× CF_2 and CF_3). ^{19}F NMR ($CDCl_3$): δ = −81.3 (t, 3F, CF_3, *J* = 10.0 Hz), −113.2 (m, 2F, CH_2–CF_2); −122.3, −123.3, −124.1 (3× m, 3× 2F, 3× CF_2); −126.6 (m, 2F, *CF_2*–CF_3).

Anal. Calcd. for $C_{16}H_{21}F_{13}O_5$: C, 35.57; H, 3.92. Found: C, 35.33; H, 4.09%.

5.2.1.6. 15,15,16,16,17,17,18,18,19,19,20,20,21,21,22,22,22-Heptadecafluoro-2,5,8,11-tetraoxadocosan-13-ol (12). 1,2-Epoxy-4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluoroundecane (**6**; 0.619 g; 1.30 mmol), 3,6,9-trioxadecan-1-ol (**3**; 2.13 g; 13 mmol), BF_3·Et_2O Et_2O (0.20 mL). Product **12** was obtained as yellowish liquid (0.763 g; 91%).

^{1}H NMR ($CDCl_3$): δ = 2.05–2.40 (m, 2H, CH_2–R_F), 3.29 (s, 3H, CH_3), 3.32–3.78 (m, 15H, 6× CH_2–O and CH–O), 4.19 (bs, 1H, OH). ^{13}C NMR ($CDCl_3$): δ = 34.3 (t, 1C, CH_2–R_F, *J* = 21 Hz), 58.6 (s, 1C, CH_3), 64.0 (s, 1C, CH), 70:3 (s, 1C, CH_2–O), 70.4 (s, 3C, 3× CH_2–O); 70.6, 71.7 (2× s, 2× 1C, 2× CH_2–O); 74.8 (s, 1C, *CH_2*–CH), 105.0–124.0 (m, 8C, 7× CF_2 and CF_3). ^{19}F NMR ($CDCl_3$): δ = −81.4 (t, 3F, CF_3, *J* = 9.3 Hz), −112.8 (m, 2F, CH_2–CF_2); −122.2, −122.4, −122.4, −123.2, −123.8 (5× m, 5× 2F, 5× CF_2); −126.7 (m, 2F, *CF_2*–CF_3).

Anal. Calcd. for $C_{18}H_{21}F_{17}O_5$: C, 33.76; H, 3.31. Found: C, 33.68; H, 3.32%.

5.2.2. General procedure for preparation of ethylene glycol allyl methyl ethers **13–15**

The solution of ethylene glycol monomethyl ethers **1–3** in diethyl ether were added dropwise to stirred suspension of NaH in anhydrous diethyl ether. Mixture was refluxed for 2 h while stirring. A solution of allyl bromide (2 molar equivalent per alkanol) was then added dropwise and reaction mixture was refluxed for 4 h. After cooling down, water was carefully added to hydrolyze the excess of NaH. Volatile compounds were removed under reduced pressure and crude product **13–15** was distilled.

5.2.2.1. 4,7-Dioxaoct-1-ene (13). Sodium hydride (60% suspension in oil; 4.70 g; 117.5 mmol) in Et_2O (100 mL), 2-methoxyethanol (**1**; 7.20 g; 95 mmol) in Et_2O (20 mL), allyl bromide (24.20 g; 200 mmol). Product **13** was obtained as colourless liquid (7.073 g; 64%; b.p. 127–128 °C).

^{1}H NMR ($CDCl_3$): δ = 3.34 (s, 3H, CH_3), 3.47–3.60 (m, 4H, 2× CH_2–O), 3.97 (ddd, 2H, CH_2-allyl, *J* = 5.5/2.7/1.1 Hz), 5.15 (dd, 1H, =CH_2, *J* = 8.8/1.1 Hz), 5.26 (dd, 1H, = CH_2, *J* = 17.0/1.1 Hz), 5.88 (ddt, 1H,=CH–, *J* = 17.0/8.8/5.5 Hz). ^{13}C NMR ($CDCl_3$): δ = 58.9 (s, 1C, CH_3), 69.1 (s, 1C, CH_2–OMe), 71.8 (s, 1C, *CH_2*–CH_2–OMe), 72.1 (s, 1C, CH_2-allyl), 117.0 (s, 1C, =CH_2), 134.6 (s, 1C, –CH=).

Anal. Calcd. for $C_6H_{12}O_2$: C, 62.04; H, 10.41. Found: C, 61.77; H, 10.56%.

5.2.2.2. 4,7,10-Trioxaundec-1-ene (14). Sodium hydride (60% suspension in oil; 5.00 g; 150 mmol) in Et_2O (120 mL), 3,6-dioxaheptan-1-ol (**2**; 12.02 g; 100 mmol) in Et_2O (20 mL), allyl bromide (24.20 g; 200 mmol). Product **14** was obtained as colourless liquid (11.640 g; 73%; b.p. 86 °C/15 mm Hg.

^{1}H NMR ($CDCl_3$): δ = 3.31 (s, 3H, CH_3), 3.46–3.68 (m, 8H, 4× CH_2–O), 3.96 (dd, 2H, CH_2-allyl, *J* = 5.5/1.1 Hz), 5.12 (dd, 1H, =CH_2, *J* = 8.8/1.7 Hz), 5.23 (dd, 1H, =CH_2, *J* = 17.0/1.7 Hz), 5.83 (ddt, 1H, = CH–, *J* = 17.0/8.8/5.5 Hz). ^{13}C NMR ($CDCl_3$): δ = 58.8 (s, 1C, CH_3); 69.2, 70.3, 70.4, 71.7, 72.0 (5× s, 5× 1C, 5× CH_2–O); 116.8 (s, 1C, =CH_2), 134.6 (s, 1C, –CH=).

Anal. Calcd. for $C_8H_{16}O_3$: C, 59.98; H, 10.07. Found: C, 59.90; H, 10.02%.

5.2.2.3. 4,7,10,13-Tetraoxatetradec-1-ene (15). Sodium hydride (60% suspension in oil; 2.40 g; 100 mmol) in Et_2O (80 mL), 3,6,9-trioxadecan-1-ol (**3**; 12.06 g; 73 mmol) in Et_2O (20 mL), allyl bromide (15.71 g; 130 mmol). Product **15** was obtained as colourless liquid (13.497 g; 90%; b.p. 117–119 °C/5 mm Hg).

^{1}H NMR ($CDCl_3$): δ = 3.28 (s, 3H, CH_3), 3.42–3.63 (m, 12H, 6× CH_2–O), 3.93 (d, 2H, CH_2-allyl, *J* = 5.5 Hz), 5.09 (d, 1H, =CH_2, *J* = 9.9 Hz), 5.20 (dd, 1H, =CH_2, *J* = 17.0/1.1 Hz), 5.82 (ddt, 1H, =CH–, *J* = 17.0/9.9/5.5 Hz). ^{13}C NMR ($CDCl_3$): δ = 58.7 (s, 1C, CH_3); 69.1, 70.2 (2× s, 2× 1C, 2× CH_2–O); 70.3 (3× s, 3C, 3× CH_2–O); 71.7, 71.9 (2× s, 2× 1C, 2× CH_2–O); 116.7 (s, 1C, =CH_2), 134.5 (s, 1C, –CH=).

Anal. Calcd. for $C_{10}H_{20}O_4$: C, 58.80; H, 9.87. Found: C, 58.79; H, 9.93%.

5.2.3. General procedure for radical additions of perfluoroalkyl iodides to allyl ethers **13–15**

via AIBN: Allyl derivative **13–15**, perfluoroalkyl iodide **16–18** (molar ratio 1:2) and AIBN (50 mg; two portions (2 mg × 50 mg) were added in a hour interval) were heated under nitrogen

atmosphere at 100 °C for 3 h. Volatile compounds were removed under reduced pressure. The crude product **19–23** was purified by column chromatography on silica gel (eluent:petroleum ether/acetone 4:1, v/v).

via sodium dithionite: Allyl derivative **13–15** and perfluoroalkyl iodide **16–18** (molar ratio 1:2) were dissolved in acetonitrile. Water was added followed by a mixture of $Na_2S_2O_4$ and $NaHCO_3$. Reaction mixture was vigorously stirred at room temperature for 2 h. Water (150 mL) was then added and the mixture was extracted with diethyl ether (5 mL × 50 mL). The organic fraction was washed with brine (3 mL × 50 mL) and dried over $MgSO_4$. Diethyl ether and excess of perfluoroalkyl iodide were removed under reduced pressure. The crude product **19–23** was purified by column chromatography on silica gel (eluent:petroleum ether/acetone 4:1, v/v).

*5.2.3.1. 9,9,10,10,11,11,12,12,13,13,14,14,14-Tridecafluoro-7-iodo-2,5-dioxatetradecane (**19**). Via AIBN*: 4,7-Dioxaoct-1-ene (**13**; 1.162 g; 10 mmol), perfluorohexyl iodide (**17**; 8.910 g; 20 mmol), AIBN (150 mg). Product **19** was obtained as yellowish liquid (5.112 g; 91%).

Via sodium dithionite: 4,7-Dioxaoct-1-ene (**13**; 0.750 g; 6.45 mmol), perfluorohexyl iodide (**17**; 5.354 g; 12.0 mmol), acetonitrile (180 mL), water (45 mL), $Na_2S_2O_4$ (85%, 6.750 g; 30.0 mmol), $NaHCO_3$ (2.522 g; 30.0 mmol). Product **19** was obtained as yellowish liquid (3.306 g; 91%).

^{1}H NMR ($CDCl_3$): δ = 2.52–2.80 and 2.98–3.24 (2× m, 2H, CH_2–R_F), 3.36 (s, 3H, CH_3), 3.50–3.85 (m, 6H, 3× CH_2–O), 4.29–4.41 (m, 1H, CH–I). ^{13}C NMR ($CDCl_3$): δ = 14.2 (s, 1C, CH–I), 37.3 (t, 1C, CH_2–R_F, *J* = 21 Hz), 58.9 (s, 1C, CH_3); 70.4, 71.8, 76.2 (3× s, 3× 1C, 3× CH_2–O); 104.0–127.0 (m, 6C, 5× CF_2 and CF_3). ^{19}F NMR ($CDCl_3$): δ = −81.4 (t, 3F, CF_3, *J* = 10 Hz), −114.1 (m, 2F, CF_2–CH_2); −122.2, −123.3, −124.1, −126.6 (4× m, 4× 2F, 4× CF_2).

Anal. Calcd. for $C_{12}H_{12}F_{13}IO_2$: C, 25.64; H, 2.15. Found: C, 25.55; H, 2.20%.

*5.2.3.2. 12,12,13,13,14,14,15,15,16,16,17,17,17-Tridecafluoro-10–iodo-2,5,8-trioxaheptadecane (**20**). Via AIBN*: 4,7,10-Trioxaundec-1-ene (**14**; 1.602 g; 10 mmol), perfluorohexyl iodide (**17**; 8.910 g; 20 mmol), AIBN (150 mg). Product **20** was obtained as yellowish liquid (5.820 g; 96%).

Via sodium dithionite: 4,7,10-Trioxaundec-1-ene (**14**; 0.620 g; 3.78 mmol), perfluorohexyl iodide (**17**; 4.460 g; 10.0 mmol), acetonitrile (100 mL), water (25 mL), $Na_2S_2O_4$ (85%, 5.000 g; 25.0 mmol), $NaHCO_3$ (2.131 g; 25.0 mmol). Product **20** was obtained as yellowish liquid (1.907 g; 81%).

^{1}H NMR ($CDCl_3$): δ = 2.50–2.76 and 2.94–3.18 (2× m, 2H, CH_2–R_F), 3.34 (s, 3H, CH_3), 3.46–3.81 (m, 10H, 5× CH_2–O), 4.26–4.40 (m, 1H, CH–I). ^{13}C NMR ($CDCl_3$): δ = 14.3 (s, 1C, CH–I), 37.4 (t, 1C, CH_2–R_F, *J* = 21 Hz), 58.8 (s, 1C, CH_3); 70.4, 70.5, 70.6, 71.9 (4× s, 4× 1C, 4× CH_2–O); 76.2 (s, 1C, *CH_2*–CHI), 102.0–125.0 (m, 6C, 5× CF_2 and CF_3). ^{19}F NMR ($CDCl_3$): δ = −81.5 (t, 3F, CF_3, *J* = 10.4 Hz), −114.2 (m, 2F, CF_2–CH_2); −122, −123.4, −124.2, −126.7 (4× m, 4× 2F, 4× CF_2).

Anal. Calcd. for $C_{14}H_{16}F_{13}IO_3$: C, 27.74; H, 2.66. Found: C, 27.69; H, 2.74%.

*5.2.3.3. 15,15,16,16,17,17,18,18,18-Nonafluoro-13–iodo-2,5,8,11-tetraoxaoctadecane (**21**). Via AIBN*: 4,7,10,13-Tetraoxatetradec-1-ene (**15**; 2.249 g; 11 mmol), perfluorobutyl iodide (**16**; 5.193 g; 15 mmol), AIBN (150 mg). Product **21** was obtained as yellowish liquid (5.282 g; 87%).

Via sodium dithionite: 4,7,10,13-Tetraoxatetradec-1-ene (**15**; 0.510 g; 2.5 mmol), perfluorobutyl iodide (**16**; 1.386 g; 4.0 mmol), acetonitrile (50 mL), water (13 mL), $Na_2S_2O_4$ (85%, 2.250 g; 10.0 mmol), $NaHCO_3$ (0.840 g; 10.0 mmol). Product **21** was obtained as yellowish liquid (1.182 g; 86%).

^{1}H NMR ($CDCl_3$): δ = 2.46–2.76 and 2.90–3.20 (2× m, 2H, CH_2–R_F), 3.32 (s, 3H, CH_3), 3.45–3.90 (m, 14H, 7× CH_2–O), 4.21–4.38 (m, 1H, CH–I). ^{13}C NMR ($CDCl_3$): δ = 14.2 (s, 1C, CH–I), 37.1 (t, 1C, CH_2–R_F, *J* = 21 Hz), 58.8 (s, 1C, CH_3); 70.3, 70.4, 70.4, 70.5, 70.5, 71.8 (6× s, 6× 1C, 6× CH_2–O); 75.9 (s, 1C, *CH_2*–CHI), 105.0–125.0 (m, 4C, 3× CF_2 and CF_3). ^{19}F NMR ($CDCl_3$): δ = −81.7 (tt, 3F, CF_3, *J* = 3.0/10.5 Hz), −113.0 (m, 2F, CH_2–CF_2), −124.6 (m, 2F, CF_2), −126.4 (m, 2F, *CF_2*–CF_3).

Anal. Calcd. for $C_{14}H_{20}F_9IO_4$: C, 30.56; H, 3.66. Found: C, 30.56; H, 3.76%.

*5.2.3.4. 15,15,16,16,17,17,18,18,19,19,20,20,20-Tridecafluoro-13–iodo-2,5,8,11-tetraoxaicosane (**22**). Via AIBN*: 4,7,10,13-Tetraoxatetradec-1-ene (**15**; 2.040 g; 10 mmol), perfluorohexyl iodide (**17**; 8.910 g; 20 mmol), AIBN (150 mg). Product **22** was obtained as yellowish liquid (6.177 g; 95%).

Via sodium dithionite: 4,7,10,13-Tetraoxatetradec-1-ene (**15**; 0.530 g; 2.6 mmol), perfluorohexyl iodide (**17**; 1.800 g; 4.0 mmol), acetonitrile (48 mL), water (12 mL), $Na_2S_2O_4$ (85%, 2.250 g; 10.0 mmol), $NaHCO_3$ (0.840 g; 10.0 mmol). Product **22** was obtained as yellowish liquid (1.420 g; 85%).

^{1}H NMR ($CDCl_3$): δ = 2.46–2.72 and 2.90–3.16 (2× m, 2H, CH_2–R_F), 3.31 (s, 3H, CH_3), 3.42–3.80 (m, 14H, 7× CH_2-O), 4.27–4.35 (m, 1H, CH–I). ^{13}C NMR ($CDCl_3$): δ = 14.2 (s, 1C, CH–I), 37.2 (t, 1C, CH_2–R_F, *J* = 21 Hz), 58.7 (s, 1C, CH_3); 70.3, 70.4, 70.4, 70.5, 71.7 (5× s, 5× 1C, 5× CH_2–O); 75.9 (s, 1C, *CH_2*–CHI), 104.0–126.0 (m, 6C, 5× CF_2 and CF_3). ^{19}F NMR ($CDCl_3$): δ = −81.3 (t, 3F, CF_3, *J* = 9.9 Hz), −114.1 (m, 2F, CF_2–CH_2); −122.3, −123.3, −124.1, −126.6 (4× m, 4× 2F, 4× CF_2).

Anal. Calcd. for $C_{16}H_{20}F_{13}IO_4$: C, 29.56; H, 3.10. Found: C, 29.67; H, 3.22%.

*5.2.3.5. 15,15,16,16,17,17,18,18,19,19,20,20,21,21,22,22,22-Heptadecafluoro-13–iodo-2,5,8,11-tetraoxadocosane (**23**). Via AIBN*: 4,7,10,13-Tetraoxatetradec-1-ene (**15**; 1.630 g; 8 mmol), perfluorooctyl iodide (**18**; 4.570 g; 15 mmol), AIBN (150 mg). Product **23** was obtained as yellowish liquid (5.670 g; 95%).

Via sodium dithionite: 4,7,10,13-Tetraoxatetradec-1-ene (**15**; 0.510 g; 2.5 mmol), perfluorooctyl iodide (**18**; 2.185 g; 4.0 mmol), acetonitrile (50 mL), water (14 mL), $Na_2S_2O_4$ (85%, 2.250 g; 10.0 mmol), $NaHCO_3$ (0.840 g; 10.0 mmol). Product **23** was obtained as yellowish liquid (1.050 g; 56%).

^{1}H NMR ($CDCl_3$): δ = 2.42–2.76 and 2.84–3.18 (2× m, 2H, CH_2–R_F), 3.29 (s, 3H, CH_3), 3.40–3.84 (m, 14H, 7× CH_2–O), 4.20–4.40 (m, 1H, CH–I). ^{13}C NMR ($CDCl_3$): δ = 14.2 (s, 1C, CH–I), 37.2 (t, 1C, CH_2–R_F, *J* = 22 Hz), 58.7 (s, 1C, CH_3), 70.3 (s, 1C, CH_2–O), 70.4 (s, 3C, 3× CH_2–O); 70.5, 71.7 (2× s, 2× 1C, 2× CH_2–O); 76.0 (s, 1C, *CH_2*–CHI), 105.0–125.0 (m, 8C, 7× CF_2 and CF_3). ^{19}F NMR ($CDCl_3$): δ = −81.6 (t, 3F, CF_3, *J* = 10.3 Hz), −112.8 (m, 2F, CH_2–CF_2); −122.1, −122.3 (2× m, 2× 2F, 2× CF_2); −123.2 (m, 4F, 2× CF_2), −123.7 (m, 2F, CF_2), −126.7 (m, 2F, *CF_2*–CF_3).

Anal. Calcd. for $C_{18}H_{20}F_{17}IO_4$: C, 28.82; H, 2.69. Found: C, 28.67; H, 2.77%.

*5.2.4. General procedure for reduction of C–I bond in adducts **19–23***

Zinc and $NiCl_2{\cdot}6H_2O$ (molar ratio 10:1) were suspended in THF and one drop of water was added. Suspension was stirred under nitrogen atmosphere at r.t. for 30 min, then a solution of iodo derivative **19–23** (1 equivalent per $NiCl_2$) in THF was added. Reaction mixture was stirred for 24 h, then filtered and insoluble material was washed with THF. Volatile compounds were removed under reduced pressure. Crude product **24–28** was purified by column chromatography on silica gel (eluent:diethyl ether).

*5.2.4.1. 9,9,10,10,11,11,12,12,13,13,14,14,14-Tridecafluoro-2,5-dioxatetradecane (**24**).* Zinc (1.300 g; 20 mmol), $NiCl_2{\cdot}6H_2O$ (0.483 g;

2.0 mmol), THF (10 mL), water (one drop), 2,5-dioxa-9,9,10,10,11,11,12,12,13,13,14,14,14-tridecafluoro-7-iodotetradecane (**19**; 1.124 g; 2.0 mmol). Product **24** was obtained as yellowish liquid (0.450 g; 52%).

^{1}H NMR ($CDCl_3$): δ = 1.77–2.00 (m, 2H, *CH*$_2$–CH_2–R_F), 2.02–2.35 (m, 2H, CH_2–R_F), 3.35 (s, 3H, CH_3), 3.44–3.74 (m, 6H, 3× CH_2–O). ^{13}C NMR ($CDCl_3$): δ = 20.7 (s, 1C, *CH*$_2$–CH_2–R_F), 27.9 (t, 1C, CH_2–R_F, *J* = 22.2 Hz), 58.9 (s, 1C, CH_3); 69.7, 70.1, 71.9 (3× s, 3× 1C, 3× CH_2); 105.0–125.0 (m, 6C, 5× CF_2 and CF_3). ^{19}F NMR ($CDCl_3$): δ = −81.4 (tt, 3F, CF_3, *J* = 2.3/10.5 Hz), −113.2 (m, 2F, CF_2–CH_2); −122.3, −123.3, −124.1, −126.6 (4× m, 4× 2F, 4× CF_2).

Anal. Calcd. for $C_{12}H_{13}F_{13}O_2$: C, 33.04; H, 3.00. Found: C, 33.17; H, 2.99%.

*5.2.4.2. 12,12,13,13,14,14,15,15,16,16,17,17,17-Tridecafluoro-2,5,8-trioxaheptadecane (**25**).* Zinc (1.300 g; 20 mmol), $NiCl_2{\cdot}6H_2O$ (0.483 g; 2.0 mmol), THF (10 mL), water (one drop), 12,12,13,13,14,14,15,15,16,16,17,17,17-tridecafluoro-10-iodo-2,5,8-trioxaheptadecane (**20**; 1.204 g; 2.0 mmol). Product **25** was obtained as yellowish liquid (0.390 g; 41%).

^{1}H NMR ($CDCl_3$): δ = 1.77–1.94 (m, 2H, *CH*$_2$–CH_2–R_F), 2.05–2.30 (m, 2H, CH_2–R_F), 3.36 (s, 3H, CH_3), 3.44–3.70 (m, 10H, 5× CH_2–O). ^{13}C NMR ($CDCl_3$): δ = 28.5 (s, 1C, *CH*$_2$–CH_2–R_F), 29.7 (t, 1C, CH_2–R_F, *J* = 22 Hz), 58.9 (s, 1C, CH_3); 70.5, 70.7, 71.8, 74.9 (4× s, 4× 1C, 4× CH_2); 105.0–125.0 (m, 6C, 5× CF_2 and CF_3). ^{19}F NMR ($CDCl_3$): δ = −81.4 (t, 3F, CF_3, *J* = 9.9 Hz), −113.3 (m, 2F, CF_2–CH_2); −122.3, −123.3, −124.1, −126.6 (4× m, 4× 2F, 4× CF_2).

Anal. Calcd. for $C_{14}H_{17}F_{13}O_3$: C, 35.01; H, 3.57. Found: C, 35.24; H, 3.68%.

*5.2.4.3. 15,15,16,16,17,17,18,18,18-Nonafluoro-2,5,8,11-tetraoxaoctadecane (**26**).* Zinc (0.790 g; 12 mmol), $NiCl_2{\cdot}6H_2O$ (0.281 g; 1.2 mmol), THF (10 mL), water (one drop), 15,15,16,16,17,17,18,18,18-nonafluoro-13-iodo-2,5,8,11-tetraoxaoctadecane (**21**; 0.833 g; 1.5 mmol). Product **26** was obtained as yellowish liquid (0.390 g; 61%).

^{1}H NMR ($CDCl_3$): δ = 1.70–1.90 (m, 2H, *CH*$_2$–CH_2–R_F), 2.00–2.30 (m, 2H, CH_2–R_F), 3.30 (s, 3H, CH_3), 3.40–3.80 (m, 14H, 7× CH_2–O). ^{13}C NMR ($CDCl_3$): δ = 20.5 (s, 1C, *CH*$_2$–CH_2–R_F), 27.6 (t, 1C, CH_2–R_F, *J* = 22.7 Hz), 58.7 (s, 1C, CH_3); 69.4, 70.0, 70.3 (3× s, 3× 1C, 3× CH_2); 70.4 (s, 3C, 3× CH_2), 71.7 (s, 1C, CH_2), 105.0–125.0 (m, 4C, 3× CF_2 and CF_3). ^{19}F NMR ($CDCl_3$): δ = −81.7 (tt, 3F, CF_3, *J* = 3.0/9.4 Hz), −113.0 (m, 2F, CH_2–CF_2), −124.7 (m, 2F, CF_2), −126.4 (m, 2F, *CF*$_2$–CF_3).

Anal. Calcd. for $C_{14}H_{21}F_9O_4$: C, 39.63; H, 4.99. Found: C, 39.67; H, 5.10%.

*5.2.4.4. 15,15,16,16,17,17,18,18,19,19,20,20,20-Tridecafluoro-2,5,8,11-tetraoxaicosane (**27**).* Zinc (1.300 g; 20 mmol), $NiCl_2{\cdot}6H_2O$ (0.483 g; 2.0 mmol), THF (10 mL), water (one drop), 15,15,16,16,17,17,18,18,19,19,20,20,20-tridecafluoro-13-iodo-2,5,8,11-tetraoxaicosane (**22**; 1.133 g; 2.0 mmol). Product **27** was obtained as yellowish liquid (0.650 g; 62%).

^{1}H NMR ($CDCl_3$): δ = 1.74–1.94 (m, 2H, *CH*$_2$–CH_2–R_F), 1.98–2.30 (m, 2H, CH_2–R_F), 3.34 (s, 3H, CH_3), 3.45–3.80 (m, 14H, 7× CH_2–O). ^{13}C NMR ($CDCl_3$): δ = 22.5 (s, 1C, *CH*$_2$–CH_2–R_F), 27.4 (t, 1C, CH_2–R_F, *J* = 19.4 Hz), 58.9 (s, 1C, CH_3); 60.1, 62.0, 69.3, 69.7, 69.8, 70.0, 70.2 (7× s, 7× 1C, 7× CH_2); 102.0–125.0 (m, 6C, 5× CF_2 and CF_3). ^{19}F NMR ($CDCl_3$): δ = −81.3 (tt, 3F, CF_3 *J* = 2.4/10.8 Hz), −113.2 (m, 2F, CF_2–CH_2); −122.3, −123.3, −124.1, −126.6 (4× m, 4× 2F, 4× CF_2).

Anal. Calcd. for $C_{16}H_{21}F_{13}O_4$: C, 36.65; H, 4.04. Found: C, 36.89; H, 3.92%.

*5.2.4.5. 15,15,16,16,17,17,18,18,19,19,20,20,21,21,22,22,22-Heptadecafluoro-2,5,8,11-tetraoxadocosane (**28**).* Zinc (0.520 g; 8 mmol), $NiCl_2{\cdot}6H_2O$ (0.190 g; 0.8 mmol), THF (8 mL), water (one drop), 15,15,16,16,17,17,18,18,19,19,20,20,21,21,22,22,22-heptadecafluoro-13-iodo-2,5,8,11-tetraoxadocosane (**23**; 0.750 g; 1.0 mmol). Product **28** was obtained as yellowish liquid (0.407 g; 64%).

^{1}H NMR ($CDCl_3$): δ = 1.75–1.90 (m, 2H, *CH*$_2$–CH_2–R_F), 2.00–2.28 (m, 2H, CH_2–R_F), 3.31 (s, 3H, CH_3), 3.40–3.80 (m, 14H, 7× CH_2–O). ^{13}C NMR ($CDCl_3$): δ = 20.6 (s, 1C, *CH*$_2$–CH_2–R_F), 27.8 (t, 1C, CH_2–R_F, *J* = 22.8 Hz), 58.7 (s, 1C, CH_3); 69.5, 70.1, 70.4 (3× s, 3× 1C, 3× CH_2); 70.5 (s, 3C, 3× CH_2), 71.8 (s, 1C, CH_2), 102.0–125.0 (m, 8C, 7× CF_2 and CF_3). ^{19}F NMR ($CDCl_3$): δ = −81.6 (t, 3F, CF_3, *J* = 10.3 Hz), −112.9 (m, 2F, CH_2–CF_2), −122.1 (m, 2F, CF_2), −122.3 (m, 4F, 2× CF_2); −123.2, −123.7 (2× m, 2× 2F, 2× CF_2); −126.7 (m, 2F, *CF*$_2$–CF_3).

Anal. Calcd. for $C_{18}H_{21}F_{17}O_4$: C, 34.63; H, 3.39. Found: C, 34.75; H, 3.44%.

5.2.5. Preparation of standard for testing – xylitol derivative **31**

*5.2.5.1. 5-O-(4,4,5,5,6,6,7,7,8,8,9,9,9,-Tridecafluoro-2-hydroxynonyl)-1,2;3,4-di-O-isopropylidene-DL-xylitol (**30**).* 1,2:3,4-Di-*O*-isopropylidene-DL-xylitol (**29**; 2.320 g; 10 mmol), 1,2-epoxy-4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononane (**5**; 3.761 g; 10 mmol) and $BF_3{\cdot}Et_2O$ (0.20 mL) were heated at 80 °C for 8 h while stirring. After cooling down, volatile compounds were removed under reduced pressure. Crude product was purified by column chromatography on silica gel (eluent:petroleum ether/acetone 4:1, v/v). Product **30** was obtained as yellowish viscous liquid (5.122 g; 84%).

^{1}H NMR ($CDCl_3$): δ = 1.16, 1.18, 1.37 and 1.43 (4× s, 12H, 4× CH_3), 1.95–2.48 (m, 2H, CH_2–R_F), 2.72 (s, 1H, OH), 3.30–4.60 (m, 10H, 7× xylitol protons, CH–OH, $CH_2^{1'}$–O). ^{13}C NMR ($CDCl_3$): 21.7 and 21.8 (2× s, 4C, 4× CH_3), 34.7 (t, 1C, C-3′, *J* = 21 Hz), 64.4 (s, 1C, C-2′), 66.7 and 68.2 (2× s, 1C, C-1), 69.0 (s, 1C, C-2), 69.2 (s, 1C, C-5), 71.4 (s, 1C, C-1′), 72.4 (s, 2C, C-3, C-4), 109.4 (s, 2C, 2× quart. C), 105.0–125.0 (m, 6C, 5× CF_2 and CF_3). ^{19}F NMR ($CDCl_3$): δ = −81.4 (t, 3F, CF_3, *J* = 8.7 Hz), −114.1 (m, 2F, CF_2–CH_2); −122.2, −123.3, −124.1, −126.6 (4× m, 4× 2F, 4× CF_2).

Anal. Calcd. for $C_{20}H_{25}F_{13}O_6$: C, 39.48; H, 4.14. Found: C, 39.40; H, 4.34%.

*5.2.5.2. 5-O-(4,4,5,5,6,6,7,7,8,8,9,9,9-Tridecafluoro-2-hydroxynonyl)-DL-xylitol (**31**).* 5-*O*-(2-Hydroxy-4,4,5,5,6,6,7,7,8,8,9,9,9,-tridecafluorononyl)-1,2:3,4-di-*O*-isopropylidene-DL-xylitol (**30**; 5.120 g; 8.42 mmol) was dissolved in methanol (40 mL) and hydrochloric acid (36%; 2 mL) was added. Reaction mixture was stirred at room temperature for 1 h. Volatile compounds were then removed under reduced pressure. Crude product **31** was purified using activated charcoal. Product **31** was obtained as yellowish semi-solid mass (4.223 g; 95%).

^{1}H NMR (CD_3OD): δ = 2.10–2.60 (m, 2H, CH_2CF_2), 3.40–4.35 (m, 10H, 4× *CH*–OH, *CH*$_2$OH, 2× CH_2–O), 4.86 (m, 5H, 5× OH). ^{13}C NMR (CD_3OD): δ = 35.6 (t, 1C, *CH*$_2$$CF_2$, *J* = 20 Hz), 64.3 (s, 1C, C-1), 65.1 (s, 1C, C-2′), 72.0 (s, 1C, C-2), 72.2 and 72.3 (2× s, 1C, C-3), 73 and 73.9 (2× s, 1C, C-4), 74.0 (s, 1C, C-5), 76.2 (s, 1C, C-1′), 105.0–125.0 (m, 6C, 5× CF_2 and CF_3). ^{19}F NMR (CD_3OD): δ = −81.0 (t, 3F, CF_3, *J* = 9.8 Hz), −112.4 (m, 2F, CF_2–CH_2); −121.5, −122.6, −123.3, −126.0 (4× m, 4× 2F, 4× CF_2).

Anal. Calcd. for $C_{14}H_{17}F_{13}O_6$: C, 31.83; H, 3.24. Found: C, 31.55; H, 3.33%.

5.3. Co-emulsifying properties of the novel amphiphiles

5.3.1. Preparation of the emulsions

Perfluorodecalin (0.125 mL) was mixed with isotonic Tris–HCl buffer of pH 7.4 and Pluronic F-68 (block co-polymer of polyoxypropylene and polyoxyethylene, 5%, w/v) as a standard

emulsifier and the mixture was sonicated for 15 s to afford 0.5 mL of an emulsion.

5.3.2. Testing of co-emulsifying properties

In the preparation of an emulsion (see above), Pluronic F-68 was partially or completely substituted by the tested co-emulsifier; if any apparent phase separation of water and perfluorodecalin phases did not appear immediately after finishing the test, the emulsion was considered to be stable. Stable emulsions in the test are indicated as "+", unstable emulsion are denoted marked by the sign "−". Stabilities of the mixtures were tested under three different conditions: (1) stability during centrifugation: the emulsion was centrifuged for 5 min at 400 g; (2) long-term stability at room temperature: the emulsion was gently stirred (magnetic spinbar) for 6 weeks; (3) stability of the emulsion in the presence of erythrocytes: the emulsion was mixed with erythrocytes and gently stirred (magnetic spinbar) at 37 °C for 6 h.

5.4. Hemocompatibility of the novel amphiphiles

Human erythrocytes (from a healthy donor, stored in a refrigerator not longer than 1 week) were washed by isotonic Tris–HCl buffer. Packed erythrocytes (0.5 mL) were added to the emulsion of perfluorodecalin (see above), the mixture was then gently stirred at 37 °C for 6 h and after that shortly centrifuged. The amount of the extracellular hemoglobin in the water phase was determined spectrophotometrically and used as a measure of hemolytic activity of the co-emulsifier tested.

Acknowledgements

The authors thank the Atofina S.A. for the gift of perfluoroalkyl iodides. The research was supported by the Grant Agency of the Czech Republic (Project 203/01/1131) and of the Ministry of Education of the Czech Republic (Project MSM 6046137301).

References

[1] T.M. Reed, in: J.H. Simons (Ed.), Fluorine Chemistry, vol. 2, Academic Press, New York, 1954 (Chapter 2).
[2] R. Battino, H.I. Clever, Chem. Rev. 66 (1966) 395–463.
[3] J.G. Riess, M. LeBlanc, Angew. Chem. Int. Ed. Engl. 17 (1978) 621–634.
[4] G. Mathis, P. Leempoel, J.-C. Ravey, C. Selve, J.-J. Delpuech, J. Am. Chem. Soc. 106 (1984) 6162–6171.
[5] M.P. Krafft, Biomaterials 19 (1998) 1529–1539.
[6] J.G. Riess, P. Vierling, C. Santaella, J. Greiner, J. Fluorine Chem. 107 (2001) 337–354.
[7] J.G. Riess, Tetrahedron 58 (2002) 4113–4131.
[8] J.G. Riess, M.P. Krafft, Biomaterials 19 (1998) 1529–1539.
[9] J.G. Riess, J. Greiner, Carbohydr. Res. 327 (2000) 147–168.
[10] K.C. Lowe, J. Fluorine Chem. 109 (2001) 59–65.
[11] M.P. Krafft, Adv. Drug Deliv. Rev. 47 (2001) 209–228.
[12] J.G. Riess, J. Fluorine Chem. 114 (2002) 119–126.
[13] J.G. Riess, J. Fluorine Chem. 118 (2002) 19–26.
[14] C. Selve, B. Castro, P. Leempoel, G. Mathis, T. Gartiser, J.-J. Delpuech, Tetrahedron 39 (1983) 1313–1316.
[15] L. Zarif, A. Manfredi, C. Varescon, M. Le Blanc, J.G. Riess, J. Am. Oil Chem. Soc. 66 (1989) 1515–1523.
[16] J.G. Riess, S. Pace, L. Zarif, Adv. Mater. 3 (1991) 249–251.
[17] J. Greiner, J.G. Riess, P. Vierling, in: R. Filler, Y. Kobayashi, L.M. Yagupolskii (Eds.), Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications, Elsevier, Amsterdam, 1993, pp. 339–380.
[18] E. Kissa (Ed.), Fluorinated Surfactants, Synthesis, Properties, Applications, M. Dekker, New York, 1994, p. 469.
[19] M.P. Krafft, J.G. Riess, Biochimie 80 (1998) 489–514.
[20] P. Barthelemy, J.C. Maurizis, J.M. Lacombe, B. Pucci, Bioorg. Med. Chem. Lett. 8 (1998) 1559–1562.
[21] P. Barthelemy, N. Cuvillier, Y. Chaudier, J.J. Benattar, B. Pucci, J. Fluorine Chem. 105 (2000) 95–102.
[22] O. Paleta, I. Dlouhá, R. Kaplánek, K. Kefurt, M. Kodíček, Carbohydr. Res. 337 (2002) 2411–2418.
[23] V. Církva, R. Kaplánek, O. Paleta, M. Kodíček, Collect. Czech Chem. Commun. 67 (2002) 1436–1448.
[24] C. Selve, S. Achilefu, J. Chem. Soc. Chem. Commun. 13 (1990) 911–912.
[25] F. Szönyi, A. Cambon, J. Fluorine Chem. 36 (1987) 195–209.
[26] J. Afzal, B.M. Fung, E.A. O'Rear, J. Fluorine Chem. 34 (1987) 385–394.
[27] H. Meinert, U. Geister, J. Fluorine Chem. 68 (1994) 221–226.
[28] S. Achilefu, L. Mansuy, C. Selve, S. Thiebaut, J. Fluorine Chem. 70 (1995) 19–26.
[29] N.G. Jaoued, R. Oueslati, A. Hedhli, Synth. Commun. 35 (2005) 543–556.
[30] S. Dieng, B. Bertaina, A. Cambon, J. Fluorine Chem. 28 (1985) 425–440.
[31] R. Kaplánek, O. Paleta, J. Fluorine Chem. 128 (2007) 789–796.
[32] P. Vierling, C. Santaella, J. Greiner, J. Fluorine Chem. 107 (2001) 337–354.
[33] M. Gaysinski, J.P. Le Forestier, A. Cambon, J.M. Devoiselle, H. Maillols, P. Chang, J. Fluorine Chem. 83 (1997) 175–182.
[34] H. Meinert, P. Reuter, J. Mader, L. Haidmann, H. Northoff, Biomater. Artif. Cells Immobilization Biotechnol. 20 (1992) 115–124.
[35] C. Gentilini, M. Boccalon, L. Pasquato, Eur. J. Org. Chem. (2008) 3308–3313.
[36] V. Církva, B. Ameduri, B. Boutevin, O. Paleta, J. Fluorine Chem. 84 (1997) 53–62.
[37] V. Církva, R. Polák, O. Paleta, K. Kefurt, J. Moravcová, M. Kodíček, S. Forman, Carbohydr. Res. 339 (2004) 2177–2186.
[38] R. Kaplánek, O. Paleta, J. Michálek, M. Přádný, J. Fluorine Chem. 126 (2005) 595–600.
[39] K. Oka, N. Fujiue, S. Nakanishi, T. Takata, R. West, T. Dohmaru, J. Organomet. Chem. 611 (2000) 45–51.
[40] Z. Zhang, D. Sherlock, R. West, R. West, K. Amine, L.J. Lyons, Macromolecules 36 (2003) 9176–9180.
[41] N.O. Brace, J. Fluorine Chem. 93 (1999) 1–25.
[42] R. Kaplánek, T. Bříza, M. Havlík, P. Martásek, V. Král, J. Fluorine Chem. 128 (2007) 179–183.
[43] W.Y. Huang, J. Fluorine Chem. 58 (1992) 1–8.
[44] Z.F. Wang, J.C. Xu, Tetrahedron 54 (1998) 12597–12608.
[45] M. Hein, R. Miethchen, Tetrahedron Lett. 39 (1998) 6679–6682.
[46] M. Hein, R. Miethchen, D.J. Schwaebisch, J. Fluorine Chem. 98 (1999) 55–60.
[47] J.O. Metzger, U. Linker, Liebigs Ann. Chem. 3 (1992) 209–216.
[48] C. Naud, P. Calas, H. Blancou, A. Commeyras, J. Fluorine Chem. 104 (2000) 173–184.
[49] S.V. Arehart, C. Pugh, J. Am. Chem. Soc. 119 (1997) 3027–3037.
[50] P. Hartmann, A. Collet, M. Viguier, J. Fluorine Chem. 95 (1999) 145–152.
[51] C. Amato, P. Calas, J. Fluorine Chem. 124 (2003) 169–176.
[52] N.O. Brace, J. Org. Chem. 27 (1962) 4491–4498.
[53] J. Greiner, A. Milius, J.G. Riess, J. Fluorine Chem. 56 (1992) 285–293.
[54] P.L. Nostro, S.H. Chen, J. Phys. Chem. 97 (1993) 6535–6540.
[55] N.O. Brace, J.E. Van Elswyk, J. Org. Chem. 41 (1976) 766–771.
[56] M. Graupe, T. Koini, V.Y. Wang, G.M. Nassif, R. Colorado, R.J. Villazana, H. Dong, Y.F. Miura, O.E. Shmakova, T.R. Lee, J. Fluorine Chem. 93 (1999) 107–116.
[57] C.J. Davis, D. Burton, Z.-Y. Yang, J. Fluorine Chem. 70 (1995) 135–140.
[58] K. Takai, T. Takagi, T. Baba, T. Kanamori, J. Fluorine Chem. 125 (2004) 1959–1964.
[59] M. Kotora, M. Hajek, B. Ameduri, B. Boutevin, J. Fluorine Chem. 68 (1994) 49–56.
[60] D. Bonafoux, Z. Hua, B. Wang, I. Ojima, J. Fluorine Chem. 112 (2001) 101–108.
[61] X.H.D. Cheng, K. Malay, S. Diele, C. Tschierske, Angew. Chem. Int. Ed. Engl. 41 (2002) 4031–4035.
[62] V. Církva, B. Ameduri, B. Boutevin, O. Paleta, J. Fluorine Chem. 83 (1997) 151–158.
[63] A. Holý, Collect. Czech. Chem. Commun. 47 (1982) 2786–2805.