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Three-fold polyfluoroalkylated amines and isocyanates based on tris(hydroxymethyl)aminomethane (TRIS)

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Abstract

Three-fold polyfluoroalkylated amines were prepared from tris(hydroxymethyl)aminomethane (TRIS) in five steps including perfluoroalkyl iodide addition to the corresponding allyl derivative, reduction of C–I bond and deprotection of the amino group. They can be easily converted to the corresponding isocyanates.
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1. Introduction

Fluorinated building blocks are widely used in organic syntheses in the field of highly fluorinated compounds (*fluorous* compounds) [1–3]. In most cases, the blocks are linear or of branched character; branched ones with several fluorinated chains are most attractive. They allow several fluorinated chains to be connected to the nonfluorinated organic skeleton and to achieve the desired properties of the molecule in separation techniques, in material chemistry or in biomedicinal applications.

Tris(hydroxymethyl)aminomethane (TRIS) can be used as a precursor for the construction of larger branched nonfluorinated molecules (dendrons and dendrimers) [4–9]. On the other hand, for the construction of fluorinated branched molecules, there is only one described synthesis using TRIS [10]. Therefore our aim was to find the way for utilization of TRIS as a basic building block for construction of branched polyfluorinated amines with three fluorinated chains, which could be serve as nucleophilic agents for introducing fluorinated units into molecules. The amines could be converted into corresponding isocyanates, which can be used as electrophilic polyfluoralkylating agents.

2. Results and discussion

TRIS was already used in one case for the construction of a tris(polyfluorinated)amide [10], which was investigated as an amphiphile. In this amphiphile the fluorinated chains are connected to the TRIS skeleton via acylation by means of the 3-(perfluoroalkyl)propanoyl chloride.

In our case, acylation is not suitable method for connection of fluorinated chains and preparation of the amines. A free amino group can attack a carbonyl group and form the corresponding oxazoline [11,12]. Moreover, the acyl derivatives can be relatively easily hydrolyzed. Therefore we decided to connect fluorinated chains via much more stable ether bond. In the first step, we converted suitably protected TRIS into a three-fold allylated derivative. In the second step, fluorinated chains were introduced by radical addition of perfluoroalkyl iodides initiated by sodium dithionite or *N*,*N*′-azobis(isobutyronitrile) (AIBN). In the third step, after reduction and deprotection, amines are obtained. The final step was the preparation of three-fold polyfluoroalkylated isocyanates as shown in the following reaction, Scheme 1.

At first, the amino group of the TRIS was protected by Boc. For the protection slightly modified conditions from published

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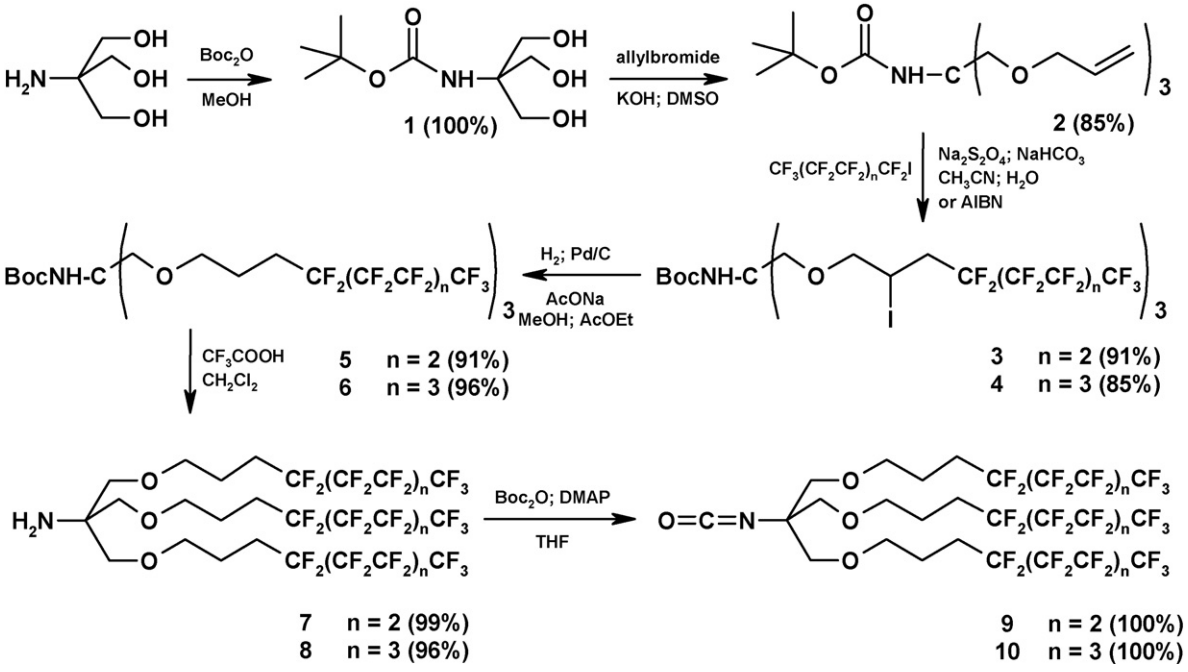

Scheme 1.

methods [13–15] were used. TRIS was reacted with di-*tert*-butyl dicarbonate in methanol. The reaction afforded protected aminotriole **1** in quantitative yield. In the next step, three allyl groups were connected to the protected triol **1** by alkylation with allybromide [15,16] in the presence of potassium hydroxyde in dimethyl sulfoxide and corresponding allylderivative **2** was obtained in 85% yield. For the connection of the fluorinated chains we used radical addition of perfluoroalkyl iodide to the double bond of the allyl group. There exist many aprroaches for the initiation [17]. We used two different initiators: sodium dithionite [18–21] and AIBN [17]. While using sodium dithionite in the acetonitrile–water system, yields of additions were lower in comparision with these using AIBN without any solvent. In the case of longer chain perfluorinated iodides, the difference is extreme, probably due to the low solubility of the perfluorooctyl iodide in the acetonitrile–water mixture. The results of the additions are summarized in the following Table 1.

For the reduction of the iodide from the adducts, tributylstannane is widely used, but the separation and purification of the product from the reaction mixture can be a problem. Therefore we chose for the reduction hydrogen on a palladium catalyst at atmospheric pressure [19–22]. The suspension of Pd/C in MeOH–ethyl acetate solution of iododerivative **3** and sodium acetate was stirred under hydrogen atmosphere overnight. The reduction afforded polyfluorinated products **5**, **6** in high yields. The great advantage of this method, as compared to reduction by tributylstannane, is the fact, that separation of the product can be easily accomplished by simple extraction from salts into petroleum ether and evaporation of the solvent. Next step, deprotection of the protective group was accomplished with trifluoroacetic acid in dichloromethane. Desired polyfluorinated amines **7**, **8** were obtained almost in quantitative yields 96–99%. In the final step the amino group was converted to isocynate by reaction with di-*tert*-butyl dicarbonate in the presence of 4-(*N*,*N*-dimethylamino)pyridine (DMAP) [8,9,23,24] in THF in 100% yield.

Table 1
The results of additions

Iodide	Initiator	Yield[a] (%)
$C_6F_{13}I$	$Na_2S_2O_4$	82
$C_6F_{13}I$	AIBN	91
$C_8F_{17}I$	$Na_2S_2O_4$	55
$C_8F_{17}I$	AIBN	85

[a] Isolated yield.

3. Conclusions

We prepared branched primary amines **7**, **8** and isocyanates **9**, **10** with three polyfluorinated chains by synthesis from commercialy available precursors using common synthetic and separation techniques. The overall isolated yields of the amines **7**, **8** are 70% and 67% respectively, isocyanates **9**, **10** were prepared from amines **7**, **8** in quantitative yields. The amines **7**, **8** and isocyanates **9**, **10** can be used as fluorinated tags or protecting groups in organic synthesis and fluorous separation techniques or as the building blocks in dendrimer chemistry.

4. Experimental

4.1. General

NMR spectra were recorded on a Varian Gemini 300 HC (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, q – quadruplet, m – multiplet), coupling constants J in Hz, solvents $CDCl_3$, D_2O.

The chemicals used were as follows: AIBN, allyl bromide, sodium dithionite, 4-(*N*,*N*-dimethylamino)pyridine, Pd/C (10%), perfluorohexyl iodide and perfluorooctyl iodide, trifluoroacetic acid (all Aldrich), silica gel (60–100 μm, Merck). Anhydrous DMSO and di-*tert*-butyl dicarbonate were purchased from Fluka. All chemicals were used without further purification. Other solvents were purchased from Penta and dried according to standard procedures.

*4.1.1. N-(tert-butyloxycarbonyl)-2-amino-2-(hydroxymethyl)propane-1,3-diol (BocTRIS; **1**)*

2-Amino-2-(hydroxymethyl)propane-1,3-diol (TRIS) (6.057 g; 50 mmol) was dissolved in MeOH (180 mL). Solution of di-*tert*-butyl dicarbonate (11.350 g; 52 mmol) in MeOH (40 mL) was added over 30 min. Reaction mixture was stirred at room temperature overnight. After evaporation to dryness, product **1** was obtained as a white solid (11.060 g; 100%).

^{1}H NMR (D_2O) δ 1.38 (s, 9H, 3 × CH_3), 3.46 (s, 1H, NH), 3.66 (s, 6H, CH_2O); ^{13}C NMR (D_2O) δ 28.2, 60.7, 61.0, 63.6, 154.7.

*4.1.2. N-(tert-butyloxycarbonyl)-tris[(allyloxy)methyl]aminomethane (**2**)*

BocTRIS (**1**) (851 mg; 3.85 mmol) and allylbromide (2.782 g ≡ 2 mL; 23 mmol) was dissolved in dry DMSO (35 mL). Powdered KOH (1290 g; 23 mmol) was added in several portions in 15 min. Reaction mixture was stirred at room temperature overnight. Water (100 mL) was added and the mixture was extracted with toluene (5 × 50 mL). The organic fraction was washed with brine (3 × 50 mL) and dried over Na_2SO_4. Toluene was removed under reduced pressure. The crude product was purified by column chromatography on silica gel (eluent:toluene/ethyl-acetate 9:1). Product **2** was obtained as a pale yellow oil (1.117 g; 85%).

^{1}H NMR ($CDCl_3$) δ 1.39 (s, 9H, 3 × CH_3), 3.67 (s, 6H, C–CH_2O), 3.91–3.98 (m, 6H, OCH_2C=), 4.94 (s, 1H, NH), 5.08–5.27 (m, 6H, =CH_2), 5.76–5.92 (m, 3H, =CH–); ^{13}C NMR ($CDCl_3$) δ 28.2, 58.4, 69.0, 70.8, 72.2, 116.6, 134.7, 154.7.

*4.1.3. N-(tert-butyloxycarbonyl)-tris[(2-iodo-4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyloxy)methyl]aminomethane (**3**)*

4.1.3.1. Via sodium dithionite. Allyl derivative **2** (373 mg; 1.09 mmol) and perfluorohexyl iodide (2190 mg; 4.91 mmol) were dissolved in MeCN (12 mL). Water (4 mL) was added, followed by $NaHCO_3$ (504 mg; 6 mmol) and $Na_2S_2O_4$ (80%; 1088 mg; 5 mmol). Reaction mixture was vigorously stirred at room temperature overnight. Water (75 mL) was added and the mixture was extracted with diethyl ether (4 × 50 mL). The organic fraction was washed with brine (3 × 50 mL) and dried over Na_2SO_4. Diethyl ether and excess of perfluorohexyl iodide were removed under reduced pressure. The crude product was purified by column chromatography on silica gel (eluent:toluene). Product **3** was obtained as a pale yellow honey (1504 mg; 82%).

4.1.3.2. Via AIBN. Allyl derivative **2** (442 mg; 1.29 mmol) and perfluorohexyl iodide (3465 mg; 7.77 mmol) and AIBN (50 mg; two next portions (2 × 50 mg) were added in hour sequence) were heated under argon atmosphere at 85 °C for 4 h. Then excess of perfluorohexyl iodide was removed under reduced pressure. The crude product was purified by column chromatography on silica gel (eluent:toluene). Product **3** was obtained as a colourless honey (1980 mg; 91%).

^{1}H NMR ($CDCl_3$) δ 1.42 (s, 9H, 3 × CH_3), 2.58–3.12 (m, 6H, CH_2R_F), 3.60–3.75 (m, 6H, CH_2O), 3.81 (s, 6H, C–CH_2O), 4.30–4.45 (m, 3H, CH), 4.94 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 14.5, 28.2, 37.9 (t, $^2J_{CF}$ = 21 Hz), 58.8, 69.5, 75.8, 79.5, 104.0–125.0 (m), 154.8; ^{19}F NMR ($CDCl_3$) δ −81.6 (t, 9F, $^3J_{FF}$ = 9.8 Hz), −115.5 to −112.5 (m, 6F), −122.5 (m, 6F), −123.6 (m, 6F), −124.3 (m, 6F), −126.9 (m, 6F).

Anal. calcd. for $C_{36}H_{31}F_{39}I_3NO_5$: C, 25.75; H, 1.86. Found: C, 25.63; H, 1.93.

*4.1.4. N-(tert-butyloxycarbonyl)-tris[(2-iodo-4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoroundecyloxy)methyl]aminomethane (**4**)*

4.1.4.1. Via sodium dithionite. Allyl derivative **2** (564 mg; 1.65 mmol) and perfluorooctyl iodide (4056 mg; 7.43 mmol) were dissolved in MeCN (35 mL). Water (13 mL) was added, followed by $NaHCO_3$ (756 mg; 9 mmol) and $Na_2S_2O_4$ (80%; 1632 mg; 7.5 mmol). Reaction mixture was vigorously stirred at room temperature overnight. Water (100 mL) was added and the mixture was extracted with diethyl ether (4 × 50 mL). The organic fraction was washed with brine (3 × 50 mL) and dried over Na_2SO_4. Diethyl ether and excess of perfluorooctyl iodide were removed under reduced pressure. The crude product was purified by column chromatography on silica gel (eluent:toluene). Product **4** was obtained as a pale yellow wax (1785 mg; 55%).

4.1.4.2. Via AIBN. Allyl derivative **2** (445 mg; 1.3 mmol) and perfluorooctyl iodide (4258 mg; 7.8 mmol) and AIBN (50 mg; two next portions (2 × 50 mg) were added in hour sequence) were heated under argon atmosphere at 85 °C for 4 h. Then excess of perfluorooctyl iodide was removed under reduced pressure. The crude product was purified by column chromatography on silica gel (eluent:toluene). Product **4** was obtained as a white wax (2191 mg; 85%).

^{1}H NMR ($CDCl_3$) δ 1.41 (s, 9H, 3 × CH_3), 2.56–3.10 (m, 6H, CH_2R_F), 3.60–3.75 (m, 6H, CH_2O), 3.81 (s, 6H, C–CH_2O), 4.27–4.44 (m, 3H, CH), 4.94 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 14.5, 28.2, 37.9 (t, $^2J_{CF}$ = 21 Hz), 58.9, 69.5, 75.8, 79.5, 102.0–126.0 (m), 154.8; ^{19}F NMR ($CDCl_3$) δ −81.6 (t, 9F, $^3J_{FF}$ = 10.4 Hz), −112.4 to −115.8 (m, 6F), −122.3 (m, 6F), −122.7 (m, 12F), −123.5 (m, 6F), −124.2 (m, 6F), −127.0 (m, 6F).

Anal. calcd. for $C_{42}H_{31}F_{51}I_3NO_5$: C, 25.49; H, 1.58. Found: C, 25.37; H, 1.59.

*4.1.5. N-(tert-butyloxycarbonyl)-tris[(4,4,5,5,6,6,7,7,8,8,9,9,9-tridekafluorononyloxy)methyl]aminomethane (**5**)*

Iododerivative **3** (1215 mg; 0.724 mmol) and sodium acetate (594 mg; 7.25 mmol) were dissolved in MeOH (20 mL) and ethyl acetate (20 mL). Pd/C (10%; 500 mg; previously suspended in MeOH (20 mL)) was added and black suspension was stirred under hydrogen atmosphere overnight. Reaction mixture was filtered, Pd/C was washed with methanol (40 mL) and ethyl acetate (40 mL). Solvents were removed under reduced pressure. Solid residue was suspended in petroleum ether (150 mL) and insoluble salts were filtered and washed with additional portions of petroleum ether (3 × 50 mL). Petroleum ether was removed under reduced pressure; product **5** was obtained as a yellowish honey (856 mg; 91%).

^{1}H NMR ($CDCl_3$) δ 1.39 (s, 9H, 3 × CH_3), 1.75–1.93 (m, 6H, $CH_2CH_2R_F$), 2.00–2.26 (m, 6H, CH_2R_F), 3.48 (t, 6H, CH_2O, $^3J_{HH}$ = 5.9 Hz), 3.64 (s, 6H, C–CH_2O), 4.82 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 20.7, 27.9 (t, $^2J_{CF}$ = 22 Hz), 28.1, 58.5, 69.7, 69.8, 79.3, 102.0–125.0 (m), 154.9; ^{19}F NMR ($CDCl_3$) δ −81.7 (t, 9F, $^3J_{FF}$ = 9.8 Hz), −115.1 (m, 6F), −122.6 (m, 6F), −123.6 (m, 6F), −124.2 (m, 6F), −126.9 (m, 6F).

Anal. calcd. for $C_{36}H_{34}F_{39}NO_5$: C, 33.22; H, 2.63. Found: C, 33,03; H, 2.78.

*4.1.6. N-(tert-butyloxycarbonyl)-tris[(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoroundecyloxy)methyl]aminomethane (**6**)*

Iododerivative **4** (1537 mg; 0.776 mmol) and sodium acetate (730 mg; 8.9 mmol) were dissolved in MeOH (20 mL) and ethyl acetate (20 mL). Pd/C (10%; 500 mg; previously suspended in ethyl acetate (20 mL)) was added and black suspension was stirred under hydrogen atmosphere overnight. Reaction mixture was filtered, Pd/C was washed with methanol (40 mL) and ethyl acetate (40 mL). Solvents were removed under reduced pressure. Solid residue was suspended in petroleum ether (150 mL) and insoluble salts were filtered and washed with additional portions of petroleum ether (3 × 50 mL). Petroleum ether was removed under reduced pressure; product **6** was obtained as a white wax (1198 mg; 96%).

^{1}H NMR ($CDCl_3$) δ 1.41 (s, 9H, 3 × CH_3), 1.76–1.93 (m, 6H, $CH_2CH_2R_F$), 2.02–2.28 (m, 6H, CH_2R_F), 3.49 (t, 6H, CH_2O, $^3J_{HH}$ = 5.9 Hz), 3.64 (s, 6H, C–CH_2O), 4.82 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 20.5, 27.6 (t, $^2J_{CF}$ = 22 Hz), 28.1, 58.3, 69.5, 69.6, 79.2, 102.0–125.0 (m), 154.7; ^{19}F NMR ($CDCl_3$) δ −81.4 (t, 9F, $^3J_{FF}$ = 9.8 Hz), −115.0 (m, 6F), −122.4 (m, 6F), −122.5 (m, 12F), −123.3 (m, 6F), −124.1 (m, 6F), −126.8 (m, 6F).

Anal. calcd. for $C_{42}H_{34}F_{51}NO_5$: C, 31.50; H, 2.14. Found: C, 31.50; H, 2.18.

*4.1.7. Tris[(4,4,5,5,6,6,7,7,8,8,9,9,9-tridekafluorononyloxy)methyl]aminomethane (**7**)*

Boc-derivative **5** (610 mg; 0.47 mmol) was dissolved in CH_2Cl_2 (40 mL) and trifluoroacetic acid (4 mL). Reaction mixture was stirred at r.t. for 3 h, then evaporated to dryness. Residue was alkalized with aqueous ammonia (50 mL) and extracted with diethyl ether (3 × 75 mL). The organic fraction was washed with water (2 × 50 mL) and brine (50 mL) and dried over Na_2SO_4. Diethyl ether was removed under reduced pressure; product **7** was obtained as a pale yellow honey (563 mg; 99%).

^{1}H NMR ($CDCl_3$) δ 1.66 (bs, 2H, NH_2), 1.75–1.96 (m, 6H, $CH_2CH_2R_F$), 2.00–2.26 (m, 6H, CH_2R_F), 3.31 (s, 6H, C–CH_2O), 3.46 (t, 6H, CH_2O, $^3J_{HH}$ = 5.9 Hz); ^{13}C NMR ($CDCl_3$) δ 20.6, 27.8 (t, $^2J_{CF}$ = 22 Hz), 55.9, 69.7, 72.7, 104.0–122.0 (m); ^{19}F NMR ($CDCl_3$) δ −81.6 (t, 9F, $^3J_{FF}$ = 9.1 Hz), −115.0 (m, 6F), −122.5 (m, 6F), −123.5 (m, 6F), −124.1 (m, 6F), −126.8 (m, 6F).

Anal. calcd. for $C_{31}H_{26}F_{39}NO_3$: C, 30.99; H, 2.18. Found: C, 31.10; H, 2.21.

*4.1.8. Tris[(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoroundecyloxy)methyl]aminomethane (**8**)*

Boc-derivative **6** (1195 mg; 0.75 mmol) was dissolved in CH_2Cl_2 (40 mL) and trifluoroacetic acid (3 mL). Reaction mixture was stirred at r.t. for 3 h, then evaporated to dryness. Residue was alkalized with aqueous ammonia (50 mL) and extracted with diethyl ether (3 × 75 mL). The organic fraction was washed with water (2 × 50 mL) and brine (50 mL) and dried over Na_2SO_4. Diethyl ether was removed under reduced pressure; product **8** was obtained as white wax (1072 mg; 96%).

^{1}H NMR ($CDCl_3$) δ 1.61 (bs, 2H, NH_2), 1.73–1.94 (m, 6H, $CH_2CH_2R_F$), 1.98–2.26 (m, 6H, CH_2R_F), 3.31 (s, 6H, C–CH_2O), 3.47 (t, 6H, CH_2O, $^3J_{HH}$ = 5.9 Hz); ^{13}C NMR ($CDCl_3$) δ 20.6, 27.8 (t, $^2J_{CF}$ = 22 Hz), 55.9, 69.7, 72.7, 104.0–122.0 (m); ^{19}F NMR ($CDCl_3$) δ −81.5 (t, 9F, $^3J_{FF}$ = 9.8 Hz), −115.0 (m, 6F), −122.4 (m, 6F), −122.6 (m, 12F), −123.4 (m, 6F), −124.1 (m, 6F), −126.8 (m, 6F).

Anal. calcd. for $C_{37}H_{26}F_{51}NO_3$: C, 29.60; H, 1.75. Found: C, 29.44; H, 1.81.

*4.1.9. Tris[(4,4,5,5,6,6,7,7,8,8,9,9,9-tridekafluorononyloxy)methyl]methyl isocyanate (**9**)*

Aminoderivative **7** (174 mg; 145 μmol) and DMAP (18 mg; 174 μmol) were dissolved in anhydrous THF (4 mL) at −15 °C. Solution of di-*tert*-butyl dicarbonate (44 mg; 203 μmol) in anhydrous THF (4 mL) was added drop-wise and reaction mixture was stirred at −15 °C for 1 h, then evaporated to dryness. The resulting residue was purified by column chromatography on silica gel (eluent:toluene). Product **9** was obtained as a pale yellow oil (177 mg; 100%).

^{1}H NMR ($CDCl_3$) δ 1.78–1.96 (m, 6H, $CH_2CH_2R_F$), 2.04–2.30 (m, 6H, CH_2R_F), 3.47 (s, 6H, C–CH_2O), 3.54 (t, 6H, CH_2O, $^3J_{HH}$ = 5.9 Hz); ^{13}C NMR ($CDCl_3$) δ 20.6, 27.7 (t, $^2J_{CF}$ = 22 Hz), 63.8, 70.0, 71.2, 105.0–125.0 (m), 127.8; ^{19}F NMR ($CDCl_3$) δ −81.5 (t, 9F, $^3J_{FF}$ = 9.8 Hz), −115.0 (m, 6F), −122.5 (m, 6F), −123.5 (m, 6F), −124.1 (m, 6F), −126.8 (m, 6F).

Anal. calcd. for $C_{32}H_{24}F_{39}NO_4$: C, 31.31; H, 1.97. Found: C, 31.24; H, 1.98.

*4.1.10. Tris[(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoroundecyloxy)methyl]methyl isocyanate (**10**)*

Aminoderivative **9** (264 mg; 176 μmol) and DMAP (26 mg; 212 μmol) were dissolved in anhydrous THF (6 mL) at −10 °C. Solution of di-*tert*-butyl dicarbonate (54 mg; 246 μmol) in anhydrous THF (6 mL) was added drop-wise and reaction mixture was stirred at −10 °C for 1 h, then evaporated to dryness. The resulting residue was purified by column chromatography on silica gel (eluent:toluene). Product **10** was obtained as a pale yellow oil (268 mg; 100%).

^{1}H NMR ($CDCl_3$) δ 1.78–1.96 (m, 6H, $CH_2CH_2R_F$), 2.10–2.28 (m, 6H, CH_2R_F), 3.47 (s, 6H, C–CH_2O), 3.54 (t, 6H, CH_2O, $^3J_{HH}$ = 5.9 Hz); ^{13}C NMR ($CDCl_3$) δ 20.6, 27.6 (t, $^2J_{CF}$ = 22 Hz), 63.8, 70.0, 71.2, 105.0–125.0 (m), 127.8; ^{19}F NMR ($CDCl_3$) δ −81.6 (t, 9F, $^3J_{FF}$ = 9.8 Hz), −115.1 (m, 6F), −122.4 (m, 6F), −122.6 (m, 12F), −123.4 (m, 6F), −124.2 (m, 6F), −126.8 (m, 6F).

Anal. calcd. for $C_{38}H_{24}F_{51}NO_4$: C, 29.88; H, 1.58. Found: C, 29.79; H, 1.64.

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