On the Structure of PHB (= Poly[(*R*)-3-hydroxybutanoic Acid]) in Phospholipid Bilayers: Preparation of Trifluoromethyl-Labeled Oligo[(*R*)-3-hydroxybutanoic Acid] Derivatives

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Oligomers of (*R*)-3-hydroxybutanoate (OHB) have previously been shown to transport cations through lipid bilayers. The ion-transport activity has been attributed to the formation of hydrophobic aggregates or pores, which have been identified by fluorescence-microscopy measurements of membrane-incorporated fluorescence-labeled OHBs. To obtain more information about these aggregates, we describe here the synthesis of the specifically F-labeled HB oligomers **II**–**IV** for structural investigation by means of solid-state ^{19}F-NMR spectroscopic techniques.

1. Introduction. – Poly[(*R*)-3-hydroxybutanoic acid] (PHB) is a linear homopolymer which occurs as a high-molecular-mass **s**torage material (**s**PHB) [1] and in a low-molecular-mass form, **c**omplexed to other macromolecules such as proteins [2], polynucleotides [3], and polyphosphates, and is then referred to as **c**PHB[2]). cPHB has been detected in eucaryotic and procaryotic cells, in human aorta tissue, and in blood plasma. In *E. coli*, cPHB and CaPPi form a complex that functions as an ion channel [5]. The existence of this ion channel has been established in patch-clamp experiments by comparing a complex from *E. coli* membranes with that formed from synthetic oligo(3-hydroxybutanoic acid) (OHB) and Ca^{2+} polyphosphate [6]. OHBs alone have been shown to transport cations across bulk membranes in U-tubes [7] and to form conductive, nonselective ion channels through lipid bilayers [8] (*Fig.*,*a*). Furthermore, OHBs of 32 or more residues cause concentration-driven Ca^{2+} transport when incorporated into liposomes [9]. From kinetic analysis, it was proposed that three 32mers aggregate to form an ionophoric pore (*Fig.*,*b*). The structures of the channels and pores consisting of or containing PHB are not known. Structures have been proposed [6][9] that are derived from modeling, or form the structure of PHB in stretched fibers [10], in lamellar crystallites [11], and in single crystals of cyclic oligomers [12]. Although the conformation of PHB and linear OHB in the solid state is known to be a 2_1 helix, the structure in solution has not yet been determined. While NMR- [13] and fluorescence-spectroscopic measurements support the fact that the polyester has a flexible conformation, CD spectroscopy provides hints regarding the presence of a secondary structure in solution and in lipid bilayers [14].

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[1]) Part of the Ph.D. theses of *M. R.* (Diss. ETH No. 14677, 2002) and *M. A.* (Diss. ETH No. 14869, 2002), ETH Zürich.

[2]) For review articles, see [4].

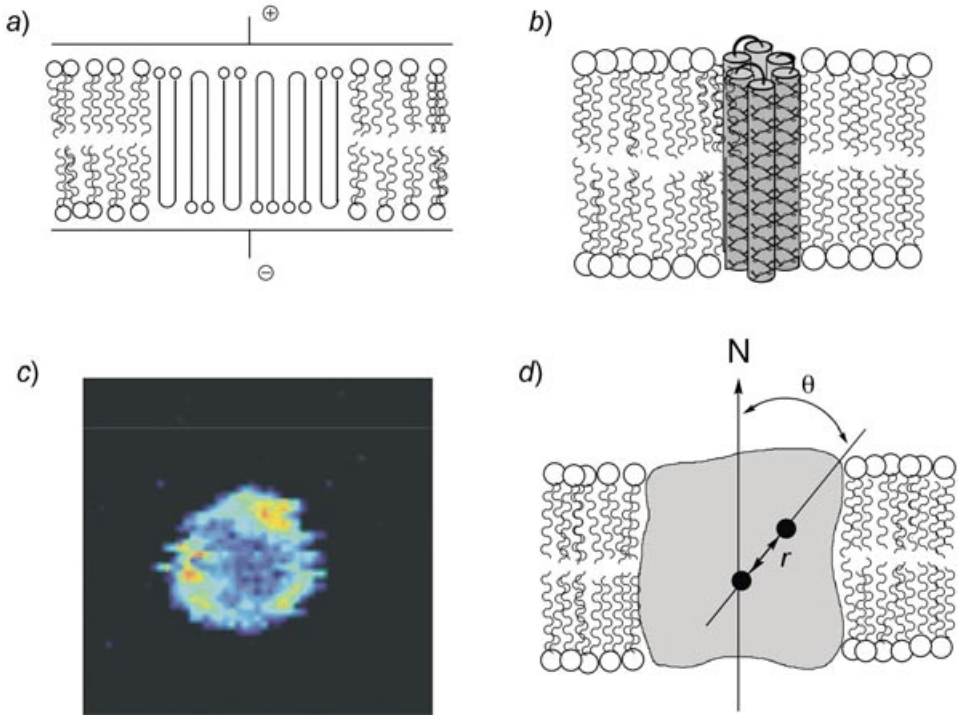
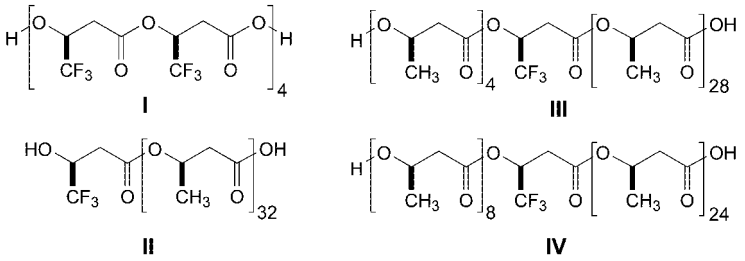


Figure. *Hairpins of OHB 32mers have been proposed to form aggregates for ion transport through lipid bilayers by* a) *a single channel or* b) *a pore mechanism*. c) *Scanning confocal fluorescence intensity image of a liposome containing fluorescence-labeled OHB 32mers showing formation of aggregates.* d) *F-Labeled OHB oligomers incorporated in the membrane should allow the determination of internuclear distances* r *and the orientation of the OHBs with respect to the membrane normal N*

Fluorescence-microscopic studies of liposomes containing fluorescence-labeled OHBs demonstrated that OHBs with 32 residues tend to form aggregates [14]. This is seen by bright spots in the membrane (*Fig.*, *c*), and it is compatible with the kinetic analysis of Ca^{2+} transport through the vesicle walls (*Fig.*, *b*) [9].

To obtain more-detailed information about the structure and conformation of the OHB aggregates or pores in lipid bilayers, we describe here the synthesis of trifluoro-labeled OHBs (*i.e.*, precursor **31**) and **II**–**IV** for structural investigation by means of solid-state ^{19}F-NMR techniques. From such measurements, we hope to deduce the orientation of the oligomers with respect to the membrane, as well as the internuclear distances and orientation between the labeled nuclei, which in turn may lead to information about the aggregates (pores), which mediate ion transport through membranes (*Fig.*, *d*).

2. Synthesis of the Trifluoromethyl-Labeled OHBs. – We are interested in monodisperse oligomers of 3-hydroxybutanoic acid (HB) for a variety of reasons. These include their use in obtaining more-detailed information about inter- and intracellular degradation by enzymes [15] and their study with regard to structural and



functional properties in solution, in lipid bilayers, and in the solid state. To this end, we have previously reported the synthesis and structural investigation of various linear and cyclic OHB derivatives [16], including OHBs with attached fluorescent dyes [14][17], with specific isotope labeling (^{13}C and ^{2}H) [13], and specific side chains (β-depsides with side chains of alanine, valine, and leucine) [18].

The synthesis of linear oligomers **C** of HB up to a chain length of 128 residues has been accomplished by a fragment-coupling procedure [16][3]). This method is based on the segment condensation, in which two orthogonal protecting groups at a fully protected oligomer can be selectively removed (*Scheme 1*) and the resulting fragments **A** and **B** be coupled ($(COCl)_2$ activation, then pyridine in CH_2Cl_2, with warming from $-78°$). Following this procedure, we prepared the building blocks **1**–**22**, required for the synthesis of the mono(trifluoromethyl)-labeled target molecules **II**–**IV**.

For the synthesis of the *all*-trifluorohydroxybutanoic acid oligomers of type **I** and the oligomers **II**–**IV** containing one 4,4,4-trifluoro-3-hydroxybutanoic acid unit at different positions in the OHB chains, orthogonally protected (*S*)-4,4,4-trifluoro-3-hyroxybutanoic acid derivatives **26** and **27** had to be prepared (*Scheme 2*). The synthesis of enantiomerically pure (*S*)-4,4,4-trifluoro-3-hydroxybutanoic acid (**25**) was accomplished following the procedure previously developed by us [20]. Starting from ethyl 4,4,4-trifluoro-3-oxobutanoate (**23**), the corresponding racemic trifluorohydroxy acid *rac*-**25** was obtained by reduction with $NaBH_4$ and hydrolysis of the ester **24**. Either enantiomer could be obtained by crystallization with one of the enantiomers of phenethylamine. The enantiomerically pure (*S*)-4,4,4-trifluoro-3-hydroxybutanoic acid (**25**) was transformed to the benzyl ester **26**, which was either used in the coupling reaction or protected by $^{t}BuMe_2Si$[4]) at its OH group (*O*-terminus), with subsequent debenzylation (H_2, Pd/C) to give the hydroxy-protected acid **27** (*Scheme 2*).

Thus the *O*-silyl-protected hydroxy acid **27** and the benzyl ester **26** were coupled to the dimer **28** in 40% yield (*Scheme 3*); *C*- or *O*-terminal deprotection resulted in **29** and **30**, respectively, and further coupling gave the tetramer **31**[5]) in 32% yield (*Scheme 3*). The lower yields in the coupling steps, as compared to the coupling of the nonfluorinated HB units, may be due to the sterically more demanding trifluoromethyl group (16.8 Å^3 *vs.* 42.6 Å^3), and the more-labile $^{t}BuMe_2Si$ protecting group.

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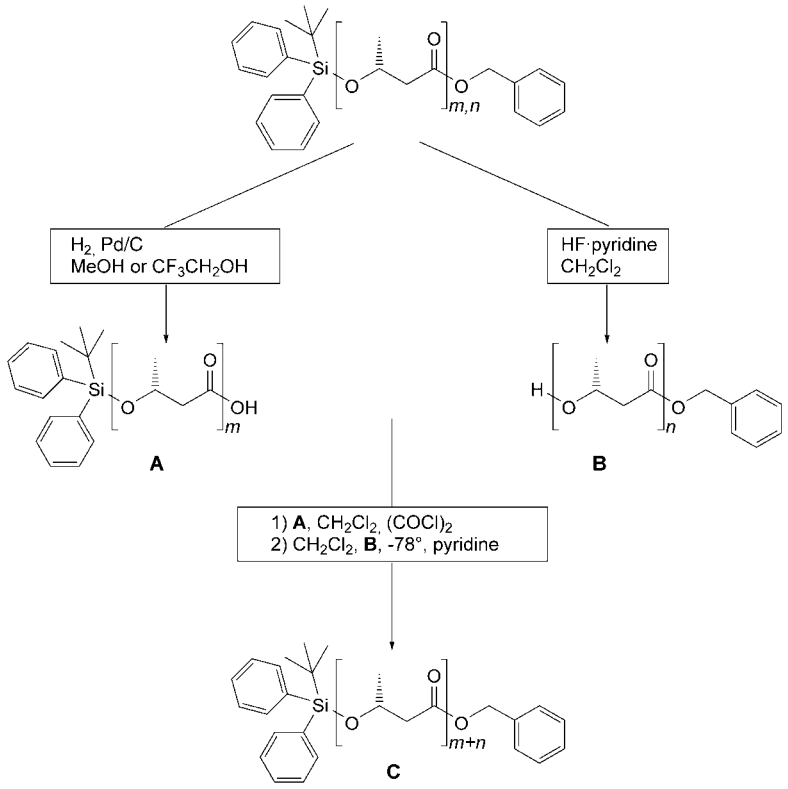
[3]) The syntheses started from (*R*)-3-hydroxybutanoic acid, as obtained from commercial PHB [19].

[4]) The protection with $^{t}BuPh_2Si$-Cl gave low yields, which might be due to steric hindrance.

[5]) The *all*-trifluoro tetramer **31** is a light oil, compared to the HB tetramer, which is a viscous oil.

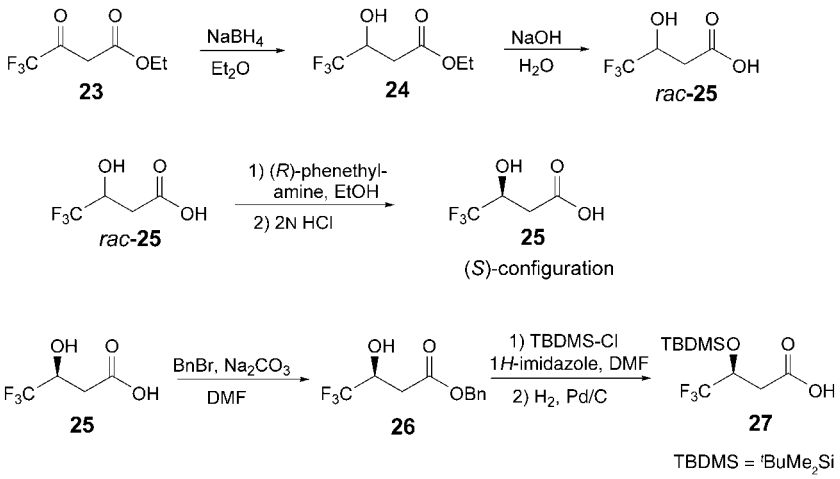
Scheme 1. *Synthesis of Oligo[(*R*)-3-hydroxybutanoates]* (OHB) *by a Fragment-Coupling Procedure* [16]. Preparation of OHB building blocks for the synthesis of specifically trifluoro-labeled OHB derivatives **II**–**IV**.



Acid **A**	*m*	Alcohol **B**	*n*	Oligomer **C**	*n* + *m*	Yield [%]
1	1	**2**	1	**3**	2	77
4	2	**5**	2	**6**	4	88
7	4	**8**	4	**9**	8	91
10	8	**11**	8	**12**	16	83
13	16	**14**	16	**15**	32	73
7	4	**14**	16	**16**	20	70
10	8	**14**	16	**17**	24	77
10	8	**18**	20	**19**	28	83
		20	24			
		21	28			
		22	32			

Therefore, no further attempts towards the synthesis of longer *all*-trifluoro-HB oligomers were carried out; instead, we turned our attention to the preparation of HB oligomers containing one (*S*)-4,4,4-trifluoro-3-hydroxybutanoic acid unit at different positions in the OHB chain **II**–**IV** (*Scheme 3*). Hence, the tetramer acid **7** and the

Scheme 2. *Preparation of Orthogonally Protected (*S*)-4,4,4-Trifluoro-3-hydroxybutanoic Acid Derivatives for the Fragment-Coupling Procedure*



octamer acid **10** were coupled with the benzyl trifluorohydroxybutanoate[6]) **26** under the segment-coupling conditions shown in *Scheme 1*, to obtain pentamer **32** and nonamer **33**, respectively, while the 32mer **22** was coupled with 3-*O*-protected trifluorobutanoic acid **27** to give **36** (*Scheme 4*). Compound **36** was fully deprotected (H_2, Pd/C; HF·pyridine) to give the target oligomer **II**, with the trifluorohydroxybutanoic acid unit in the terminal position.

For the assembly of the trifluoro-labeled oligomers **37** and **38**, the fully protected oligomers **32** and **33** were debenzylated to yield the corresponding acids **34** and **35**, which were used in the coupling with hydroxybutanoates **21** and **20**. Following desilylation of oligomers **37** and **38** (→ **39** and **40**, resp.) and debenzylation gave the desired oligomers **III** and **IV**, respectively, with one trifluorohydroxybutanoic acid unit in the 5 and 9 positions, respectively.

Conclusions. – In conclusion, the experiments described herein provide, for the first time, trifluorohydroxybutanoate oligomers up to the tetramer. The results suggest that use of a different hydroxy-protecting group should lead to better yields, which would in turn allow the synthesis of longer-chain trifluorohydroxy oligomers with yet unknown properties. Furthermore, using the segment-coupling procedure, we were able to

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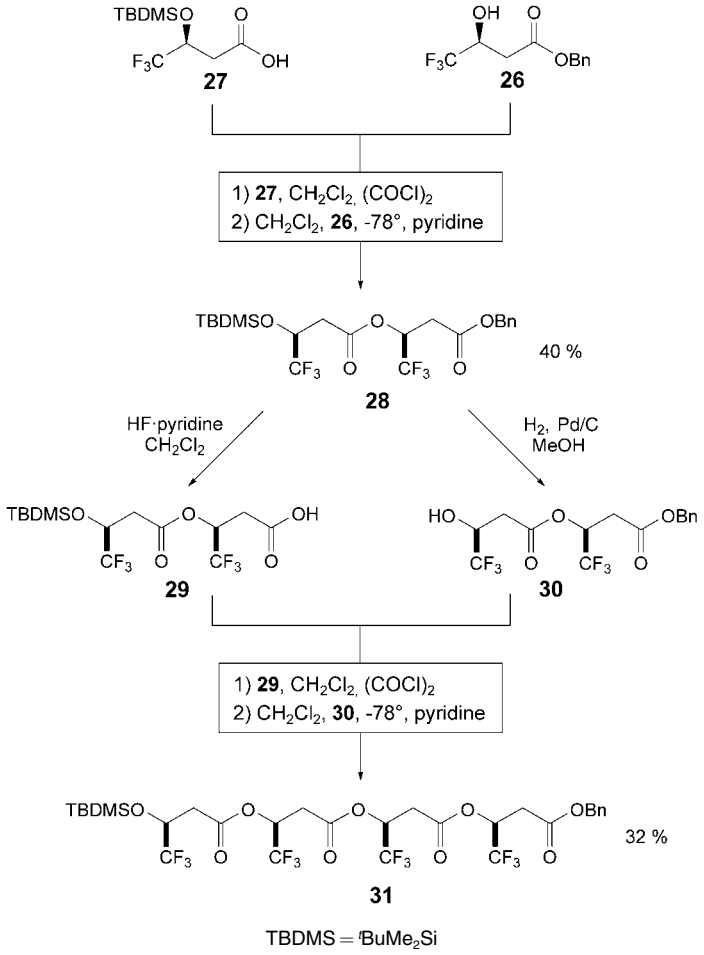
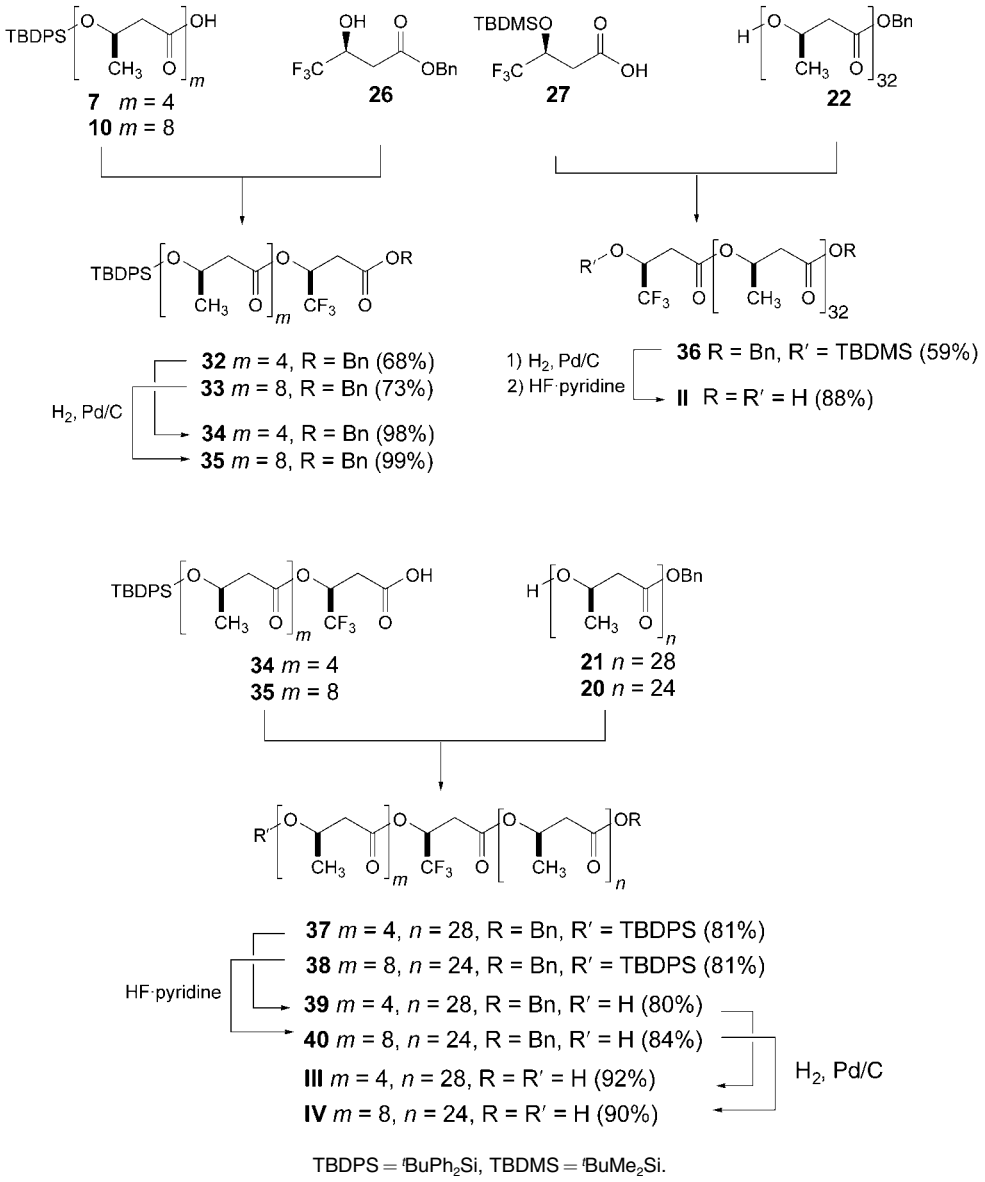
[6]) To circumvent potential problems with respect to the larger trifluoromethyl group, the coupling was first carried out at the *O*-terminus of these oligomers.

Scheme 3. *Preparation of* all-*Trifluorohydroxybutanoate Dimer* **28** *and Tetramer* **31**



synthesize three specifically labeled HB oligomers **II**–**IV** that contain one trifluorohydroxy acid unit in position 1, 5, or 9 of the oligomer chain. These oligomers will now enable us to investigate the OHB aggregates and pores (see *Fig.*) by using the trifluoro group as a magnetic label that will provide further information about the structure and function of OHB in lipid bilayers.

Scheme 4. *Synthesis of Specifically Labelled OHB Derivatives* **II**–**IV** *with One Trifluorohydroxybutanoate Residue at Position 1, 5, or 9 in the Oligomer Chain*



TBDPS = ^{t}BuPh$_2$Si, TBDMS = ^{t}BuMe$_2$Si.

Experimental Part

1. *General*. All solvents used were either *puriss p.a.* quality or distilled over appropriate drying reagents. CH_2Cl_2 and DMF were stored over 4Å-molecular sieves. All other reagents were used as received from *Fluka* or *Senn*. Compounds **1**–**15**, **17**, and **20** were synthesized as described [16]. For high vacuum $< 10^{-4}$ mbar, a turbomolecular pump *Balzers TSH065* was employed. TLC: *Merck* silica-gel *60* F_{254} anal. plates; detection

either by UV or by dipping into a soln. of I_2 (30 g) and KI (2 g) in EtOH/H_2O 1:1 (400 ml) and drying in the air. Flash chromatography (FC): *Merck* silica-gel *60* (40–63 μm). M.p.: *Buechi 510*. Optical rotation: 10-cm, 1-ml cell, at r.t.; *Perkin-Elmer 241* polarimeter. IR: *Perkin-Elmer 1600-FT* spectrophotometer. ^{1}H-NMR: *Bruker AMX-II-500* (5001 MHz), *AMX-400* (400 MHz), *ARX-300* (300 MHz), or *Varian Gem-200* (200 MHz) spectrometer. ^{13}C-NMR: *Bruker AMX-II-500* (125 MHz), *AMX-400* (100 MHz), *ARX-300* (75 MHz), or *Varian-Gem-200* (50 MHz) spectrometer; in $CDCl_3$ unless other specified. MS: *VG ZAB2-SEQ* for LSI (FAB) with 3-nitrobenzyl alcohol as matrix, *Bruker Reflex-MALDI-TOF* spectrometer for MALDI-TOF, and *IonSpec Ultima MALDI FT-MS* for high-resolution MS (HR-MS) in a 2,5-dihydroxybenzoic acid (DHB) matrix. Elemental analysis were conducted by the Microanalytical Laboratorium für Organische Chemie, ETH Zürich.

2. *Preparation of Acid Chlorides: General Procedure 1* (*GP 1*). Similar to the reported procedure [16], the carboxylic acid was dissolved in CH_2Cl_2, and oxalyl chloride (1.5 equiv.) and one drop of DMF were added. The mixture was stirred at r.t. until the gas evolution ceased (2–8 h). The solvent was evaporated and the oily residue dried under h.v.

3. *Coupling of Acid Chlorides with an Alcohol: General Procedure 2* (*GP 2*). Similar to the reported procedure [16], the well-dried acid chloride was dissolved under Ar in CH_2Cl_2 and cooled to $-78°$. After the addition of a soln. of the appropriate alcohol (1 equiv.) in CH_2Cl_2, a soln. of pyridine (1 equiv.) in CH_2Cl_2 was slowly injected. The mixture was allowed to warm to r.t. within 12 h and then stirred for another 10 h. Subsequent dilution with Et_2O was followed by thorough washing with 1M HCl (2×), sat. $NaHCO_3$, and sat. NaCl solns. The org. phase was dried ($MgSO_4$) and evaporated.

4. *Cleavage of Benzyl Ester: General Procedure 3* (*GP 3*). The benzyl ester protected oligoester was dissolved in MeOH or CF_3CH_2OH, and a catalytic amount of 10% Pd/C was added. The apparatus was evacuated and flushed three times with H_2. After the mixture was stirred under H_2 (balloon) for 18 h, filtration through *Celite* and evaporation yielded the crude carboxylic acid.

5. *(*tert*-Butyl)diphenylsilyl or (*tert*-Butyl)dimethylsilyl Ether Deprotection: General Procedure 4* (*GP 4*). The appropriate silyl ether was dissolved in CH_2Cl_2 in a plastic flask and cooled to 0°. A solution of 70% HF·pyridine was added, and the biphasic system was vigorously stirred for 20 min. After the emulsion was poured into H_2O, Et_2O was added and the org. phase separated. The org. phase was washed subsequently with H_2O (2×), sat. $NaHCO_3$ (3×), and sat. NaCl solns., dried ($MgSO_4$), and evaporated.

6. *Products. α-[(*tert*-Butyl)diphenylsilyl]-ω-(benzyloxy)leicosakis{oxy[(1*R*)-1-methyl-3-oxopropane-1,3-diyl]}* (**16**). According to *GP 1*, **7** (0.670 g, 1.109 mmol) in CH_2Cl_2 (5 ml) was transformed to the acid chloride. Subsequent coupling (*GP 2*) at $-78°$ with **14** (1.29 g, 0.739 mmol) and pyridine (2.0 equiv., in deviation from *GP 2*) in CH_2Cl_2 (5 ml) yielded, after FC (CH_2Cl_2/Et_2O 2:1), 1.06 g (70%) of **16**. White solid. M.p. 124.5–125.5°. $[\alpha]_D^{r.t.} = +0.37$ ($c = 1.15$, $CHCl_3$). IR ($CHCl_3$): 3620*w*, 2990*m*, 2936*w*, 1738*w*, 1458*w*, 1383*w*, 1305*s*, 1179*s*, 1136*s*, 1101*m*, 1060*s*, 979*m*. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.03 (*s*, ^{t}Bu); 1.11 (*d*, $J = 6.1$, Me); 1.21 (*d*, $J = 6.3$, Me); 1.24 (*d*, $J = 6.3$, Me); 1.25 (*d*, $J = 6.3$, Me); 1.25–1.28 (*m*, 16 Me); 2.34–2.62 (*m*, 39 H, CH_2); 2.67 (*dd*, $J = 15.6$, 7.7, 1 H, CH_2); 4.22–4.28 (*m*, CH); 5.11 (*s*, PhCH_2); 5.17–5.20 (*m*, CH); 5.21–5.33 (*m*, 18 CH); 7.31–7.43 (*m*, 11 arom. H); 7.66–7.68 (*m*, 4 arom. H). ^{13}C-NMR (125 MHz, $CDCl_3$): 19.1; 19.6; 19.7; 19.8; 19.8; 19.9; 23.4; 26.9; 40.7; 40.8; 40.9; 40.9; 41.0; 44.6; 66.5; 66.7; 67.2; 67.4; 67.5; 67.7; 67.8; 78.6; 127.5; 127.6; 128.3; 128.6; 129.6; 129.7; 133.9; 134.2; 135.7; 135.8; 135.8; 169.1; 169.2; 169.2; 169.4; 169.9; 170.3. MALDI-TOF-MS (pos.): 2093.91 (12, $[M + Na + 4\ H]^+$), 2092.9 (31, $[M + Na + 3\ H]^+$), 2091.9 (64, $[M + Na + 2\ H^+]$), 2090.9 (100, $[M + Na + 1\ H]^+$), 2098.9 (79, $[M + Na]^+$), 2004.9 (2), 1747.7 (3), 1661.7 (3), 1575.7 (3), 1489.6 (3), 1403.6 (3), 1317.5 (4), 1231.5 (5), 1145.5 (5), 1059.4 (4), 973.4 (4). Anal. calc. for $C_{103}H_{146}O_{41}Si$ (2068.37): C 59.81, H 7.11; found: C 60.02, H 7.12.

*α-Hydro-ω-(benzyloxy)eicosakis{oxy[(1*R*)-1-methyl-3-oxopropane-1,3-diyl]}* (**18**). According to *GP 4*, **16** (0.798 g, 386 μmol) in CH_2Cl_2 (5 ml) was deprotected with 70% HF·pyridine (0.15 ml, 5.78 mmol, 15 equiv.) at 0°. Workup and washings with pentane afforded 0.590 g (83%) of **18**. White solid. M.p. 135–136°. $[\alpha]_D^{r.t.} = -2.84$ ($c = 1.04$, $CHCl_3$). IR ($CHCl_3$): 3011*w*, 2986*m*, 2937*w*, 2878*w*, 1738*s*, 1458*w*, 1383*w*, 1306*s*, 1177*s*, 1135*s*, 1101*m*, 1059*s*, 979*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.22 (*d*, $J = 6.3$, Me); 1.24 (*d*, $J = 6.3$, Me); 1.26–1.29 (*m*, 17 Me); 1.30 (*d*, $J = 6.3$, Me); 2.36–2.63 (*m*, 39 H, CH_2); 2.68 (*dd*, $J = 15.6$, 7.6, 1 H, CH_2); 3.08 (*d*, $J = 3.9$, OH); 4.16–4.20 (*m*, CH); 5.12 (*s*, PhCH_2); 5.20–5.33 (*m*, 19 CH); 7.31–7.38 (*m*, 5 arom. H). ^{13}C-NMR (125 MHz, $CDCl_3$): 19.7; 19.8; 19.8; 19.9; 22.5; 40.7; 40.8; 43.3; 64.4; 66.5; 67.5; 67.6; 67.7; 67.8; 77.2; 128.3; 128.6; 135.7; 169.1; 169.2; 169.4; 169.9; 172.0. MALDI-TOF-MS (pos.): 1855.8 (7, $[M + Na + 4\ H]^+$), 1854.8 (25, $[M + Na + 3\ H]^+$), 1853.8 (60, $[M + Na + 2\ H]^+$), 1852.8 (100, $[M + Na + 1\ H]^+$), 1851.8 (97, $[M + Na]^+$), 1765.8 (3), 1661.7 (1), 1489.6 (1), 1403.6 (1), 1317.5 (2), 1231.5 (2), 1145.5 (2), 1059.4 (2). Anal. calc. for $C_{87}H_{128}O_{41}$ (1858.03): C 57.10, H 7.05; found: C 57.15, H 7.21.

*α-[(*tert*-Butyl)diphenylsilyl]-ω-(benzyloxy)octacosakis{oxy[(1*R*)-1-methyl-3-oxoane-1,3-diylprop]}* (**19**). According to *GP 1*, **10** (0.304 g, 322 μmol) in CH_2Cl_2 (3 ml) was transformed to the acid chloride, and subsequent coupling (*GP 2*) at −78° with **18** (0.3 g, 161 μmol) in CH_2Cl_2 (3 ml) yielded, after FC (CH_2Cl_2/Et_2O 3:1 → 2:1), 0.370 g (83%) of **19**. White solid. M.p. 144–145°. $[\alpha]_D^{r.t.} = +0.05$ ($c = 0.53$, $CHCl_3$). IR ($CHCl_3$): 3015*w*, 2987*m*, 2934*w*, 1739*w*, 1457*w*, 1384*w*, 1305*m*, 1179*m*, 1136*m*, 1101*m*, 1060*m*, 979*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.03 (*s*, ^{t}Bu); 1.11 (*d*, $J = 6.1$, Me); 1.21 (*d*, $J = 6.3$, Me); 1.24 (*d*, $J = 6.3$, Me); 1.25 (*d*, $J = 6.4$, Me); 1.25–1.29 (*m*, 24 Me); 2.37 (*dd*, $J = 14.6$, 7.7, 1 H, CH_2); 2.37–2.63 (*m*, 54 H, CH_2); 2.67 (*dd*, $J = 15.6$, 7.6, 1 H, CH_2); 4.23–4.28 (*m*, CH); 5.12 (*s*, PhCH_2); 5.15–5.29 (*m*, CH); 5.20–5.32 (*m*, 26 CH); 7.32–7.44 (*m*, 11 arom. H); 7.65–7.68 (*m*, 4 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 19.2; 19.6; 19.7; 19.8; 19.8; 20.0; 23.4; 26.9; 40.7; 40.8; 40.9; 41.1; 44.6; 66.5; 66.7; 67.2; 67.4; 67.5; 67.6; 67.7; 67.8; 77.2; 127.5; 127.6; 128.3; 128.6; 129.6; 129.7; 133.9; 134.3; 135.7; 135.8; 169.1; 169.2; 169.9; 170.3. MALDI-TOF-MS (pos.): 2784.1 (12, $[M + Na + 4\ H]^+$), 2783.3 (31, $[M + Na + 3\ H]^+$), 2782.1 (64, $[M + Na + 2\ H]^+$), 2781.2 (100, $[M + Na + 1\ H]^+$), 2780.1 (79, $[M + Na]^+$). Anal. calc. for $C_{135}H_{194}O_{57}Si$ (2757.07): C 58.81, H 7.09; found: C 58.87, H 7.09.

*α-Hydro-ω-(benzyloxy)octacosakis{oxy[(1*R*)-1-methyl-3-oxopropane-1,3-diyl]}* (**21**). According to *GP 4*, **19** (0.350 g, 126 μmol) in CH_2Cl_2 (5 ml) was deprotected with 70% HF · pyridine (42 μl, 1.65 mmol, 13 equiv.) at 0°. Workup and washings with pentane afforded 0.305 g (96%) of **21**. White solid. M.p. 149–150°. $[\alpha]_D^{r.t.} = -2.07$ ($c = 0.49$, $CHCl_3$). IR ($CHCl_3$): 3015*w*, 2983*m*, 2939*w*, 2875*w*, 1740*s*, 1457*w*, 1381*w*, 1310*m*, 1180*m*, 1136*m*, 1098*m*, 1059*m*, 985*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.22 (*d*, $J = 6.3$, Me); 1.24 (*d*, $J = 6.3$, Me); 1.26–1.29 (*m*, 25 Me); 1.30 (*d*, $J = 6.3$, Me); 2.38 (*dd*, $J = 15.9$, 8.3, 1 H, CH_2); 2.40 (*dd*, $J = 15.5$, 5.8, 1 H, CH_2); 2.42–2.63 (*m*, 53, 1 H, CH_2); 2.68 (*dd*, $J = 15.6$, 7.6, 1 H, CH_2); 3.09 (*d*, $J = 3.8$, OH); 4.16–4.20 (*m*, CH); 5.12 (*s*, PhCH_2); 5.20–5.33 (*m*, 27 CH); 7.32–7.37 (*m*, 5 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 19.6; 19.7; 19.8; 19.9; 22.5; 40.7; 40.8; 41.1; 43.3; 64.4; 66.5; 67.4; 67.5; 67.6; 67.7; 67.8; 77.2; 128.3; 128.6; 135.7; 169.1; 169.2; 169.4; 169.9; 172.0. MALDI-TOF-MS (pos.): 2544.1 (13, $[M + Na + 4\ H]^+$), 2543.1 (44, $[M + Na + 3\ H]^+$), 2542.1 (80, $[M + Na + 2\ H]^+$), 2541.1 (100, $[M + Na + 1\ H]^+$), 2540.1 (71, $[M + Na]^+$), 1747.7 (1), 1661.7 (2), 1575.7 (2), 1489.6 (1), 1403.6 (1), 1317.6 (1), 1231.5 (2), 1145.5 (1), 1059.4 (1), 973.4 (1). Anal. calc. for $C_{119}H_{176}O_{57}$ (2518.67): C 56.75, H 7.04; found: C 56.74, H 6.92.

rac-*4,4,4-Trifluoro-3-hydroxybutanoic Acid* (*rac*-**25**) [20]. A mixture of $NaBH_4$ (1.85 g, 49 mmol) in Et_2O (35 ml) was cooled to 0°. At 0°, 4,4,4-trifluoro-3-oxobutanoic acid ethyl ester (**23**; 30 g, 163 mmol) was added, and the soln. was stirred further for 3 h. The suspension was filtered over *Celite* and the filtrate acidified with 1M HCl, stirred further for 0.5 h, and again filtered over *Celite*. The org. phase was washed with sat. NaCl soln., dried ($MgSO_4$), and evaporated to give *rac*-4,4,4-trifluoro-3-hydroxybutanoic acid ethyl ester (**24**; 28.5 g, 95%) as a light yellow oil. The crude ester was dissolved in a soln. of 1N NaOH (100 ml) and stirred for 1 h under reflux. The soln. was extracted with Et_2O (2×), acidified to pH 1 with conc. HCl soln. and subsequently extracted with Et_2O (3×). The Et_2O phase was dried and evaporated: *rac*-**25** (91%). White solid. ^{1}H-NMR (300 MHz, (D_6)DMSO): 2.41–2.63 (*m*, CH_2); 4.25–4.36 (*m*, CH); 6.7 (br. *s*, OH); 12.5 (br. *s*, COOH). ^{19}F-NMR (282 MHz): −78 (*d*, $J = 7.5$, CF_3). All anal. data in agreement with those in [20].

*(3*S*)-4,4,4-Trifluoro-3-hydroxybutanoic Acid* (**25**) [20]. A soln. of (1*R*)-1-phenylethylamine (=(*αR*)-α-methylbenzenemethanamine; 19.14 g, 15.8 mmol) in EtOH (200 ml) was added to a soln. of *rac*-**25** (25 g, 15.8 mmol) in EtOH (50°). The mixture was cooled to r.t. and stirred for 12 h. The mixture was filtered and the obtained white solid recrystallized twice from EtOH. After drying, the (1*R*)-1-phenyl-ethylammonium (3*S*)-4,4,4-trifluoro-3-hydroxybutanoate was isolated as a white powder, which was subsequently dissolved in 2N HCl and extracted with Et_2O (5×). The combined org. phase was evaporated: 5.25 g (21%) of **25**. White oil, which was used in subsequent transformations without purification. All anal. data in agreement with those in [20].

*(3*S*)-4,4,4-Trifluoro-3-hydroxybutanoic Acid Benzyl Ester* (**26**). To a soln. of **25** (18.05 g, 114.2 mmol) in DMF were added benzyl bromide (13.6 ml, 1.2 equiv.) and Na_2CO_3 (70 g, 5.8 equiv. The soln. was stirred for 12 h and evaporated. FC (pentane/Et_2O 3:1) yielded **26** (22.5 g, 79%). Colorless oil. R_f (pentane/Et_2O 3:1) 0.3. $[\alpha]_D^{r.t.} = -23.8$ ($c = 1$, $CHCl_3$) IR ($CHCl_3$): 3465*w*, 1725*s*, 1608*w*, 1498*m*, 962*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 2.69–2.81 (*m*, CH_2); 3.34 (br. *s*, OH); 4.46–5.0 (*m*, CH); 5.15–5.22 (*dd*, $J = 12$, $J = 1$, PhCH_2); 7.35–7.41 (*m*, 5 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 170.4; 135.0; 128.7; 128.4; 125.7; 122.9; 67.3; 34.76. ^{19}F-NMR (282 MHz, $CDCl_3$): −80.12 (*d*, $J = 6.4$, CF_3). FAB-MS: 249.3 ($[M + H]^+$). Anal. calc. for $C_{11}H_{11}F_3O_3$ (248.20): C 53.23, H 4.47; found: C 52.97, H 4.50.

*(3*S*)-3-(*tert*-Butyl)dimethylsilyl]oxy}-4,4,4-trifluorobutanoic Acid* (**27**). A soln. of **26** (7.17 g, 29 mmol) in DMF was cooled to 0°. At 0°, 1*H*-imidazole (4.91 g, 72.5 mmol) and ^{t}BuMe$_2$SiCl (5.7 g, 37.7 mmol) were added, and the soln. was stirred further for 24 h. The solvent was evaporated and the residue diluted with CH_2Cl_2. The org. phase was washed subsequently with 1M HCl, sat. $NaHCO_3$, and sat. NaCl soln., dried ($MgSO_4$), and evaporated. The resulting crude product was subsequently transformed according to *GP 3* to give the crude

product, which was purified by distillation: **27** (81%). Colorless oil. IR ($CHCl_3$): 3646*m*, 3010*m*, 2953*w*, 1724*s*, 1607*w*, 1489*w*, 962*m*, 657*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.09 (*s*, Me); 0.13 (*s*, Me); 0.87 (*s*, ^{t}Bu); 2.64–2.77 (*m*, CH); 4.45–4.51 (*m*, CH). ^{13}C-NMR (100 MHz, $CDCl_3$): 175.7; 128.7; 125.8; 123.0; 120.2; 68.1; 25.5; 18.0. ^{19}F-NMR (282 MHz, $CDCl_3$): −79.52 (*d*, J = 6.5, CF_3). HR-FT-MALDI-MS: 273.0394 ($[M+H]^+$). Anal. calc. for $C_{10}H_{19}F_3O_3Si$ (272.34): C 44.10, H 7.03; found: C 44.21, H 6.89.

*(3*S*)-3-[[(*tert*-Butyl)dimethylsilyl]oxy]-4,4,4-trifluorobutanoic Acid (1*S*)-3-(Benzyloxy)-3-oxo-1-(trifluoromethyl)propyl Ester* (**28**). According to *GP 1*, **27** (8.5 g, 3.12 mmol) in CH_2Cl_2 (60 ml) was transformed to the acid chloride, and subsequent coupling (*GP 2*) at −78° with **26** (7.75 g, 31.2 mol) in CH_2Cl_2 (60 ml) yielded, after FC (CH_2Cl_2/pentane 3:1), 6.23 g (40%) of **28**. Colorless oil. R_f (pentane/Et_2O 3:1) 0.3. $[\alpha]_D^{r.t.} = -3.8$ (c = 1, $CHCl_3$). IR ($CHCl_3$): 2933*w*, 2859*w*, 1768*m*, 1742*m*, 1463*w*, 1376*w*, 1309*m*, 1280*m*, 1177*m*, 1140*s*, 1036*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.13 (*s*, Me); 0.16 (*s*, Me); 0.89 (*s*, ^{t}Bu); 2.62–2.86 (*m*, 2 CH_2); 4.48–4.52 (*m*, CH); 5.16 (*s*, PhCH_2); 5.82–5.86 (*m*, CF_3CH); 7.33–7.40 (*m*, 5 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 168.0; 135.4; 130.2; 128.9; 128.8; 128.7; 126.5; 125.2; 122.8; 121.4; 68.7; 67.3; 53.4; 33.4; 25.5. ^{19}F-NMR (282 MHz, $CDCl_3$): −77.17 (*d*, J = 6.5, CF_3); −78.89 (*d*, J = 6.5, CF_3). FAB-MS: 445 ($[M-{}^t\mathrm{Bu}]^+$). Anal. calc. for $C_{21}H_{28}F_6O_5Si$ (502.53): C 50.19, H 5.62; found: C 50.42, H 5.51.

*(3*S*)-3-[[(*tert*-Butyl)dimethylsilyl]oxy]-4,4,4trifluorobutanoic Acid (1*S*)-1-(Carboxymethyl)-2,2,2-trifluoroethyl Ester* (**29**). According to *GP 3*, **28** (1 g, 2 mmol) in CF_3CH_2OH (40 ml) was debenzylated: **29** (quant.). Colorless oil. IR ($CHCl_3$): 1763*w*, 1455*w*, 1376*w*, 1356*w*, 1281*m*, 1177*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.09 (*s*, Me); 0.15 (*s*, Me); 0.86 (*s*, ^{t}Bu); 2.64–2.89 (*m*, 2 CH_2); 4.47–4.53 (*m*, CH); 5.77–5.83 (*m*, CF_3CH); 11.44 (br., COOH). ^{13}C-NMR (100 MHz, $CDCl_3$); 174.8; 168.1; 128.4; 126.4; 125.1; 122.7; 121.3; 118.9; 68.8; 68.2; 66.7; 65.8; 36.4; 33.2; 25.5; 17.9. ^{19}F-NMR (282 MHz, $CDCl_3$): −77.34 (*d*, J = 6.5, CF_3); −78.96 (*d*, J = 6.5 CF_3). FAB-MS (435 ($[M+Na]^+$).

*(3*S*)-4,4,4-Trifluoro-3-hydroxybutanoic Acid (1*S*)-3-(Benzyloxy)-3-oxo-1-(trifluoromethyl)propyl Ester* (**30**). According to *GP 4*, **28** (2 g, 3.98 mmol) in CH_2Cl_2 (60 ml) was deprotected to give the crude product. FC (pentane/Et_2O 3:1) gave **30** in quant. yield. Colorless oil. R_f (pentane/Et_2O 3:1) 0.65. $[\alpha]_D^{r.t.} = 6.9$ (c = 1, $CHCl_3$). IR ($CHCl_3$): 3312*w*, 3015*w*, 1743*s*, 1451*w*, 1303*s*, 1276*s*, 1170*m*, 1133*m*, 1053*w*, 953*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 2.63–2.71 (*m*, CH_2); 2.72–2.81 (*m*, CH_2); 3.03 (br., OH); 4.39–4.47 (*m*, CH); 5.14 (*s*, PhCH_2); 5.80–5.88 (*m*, CF_3CH); 7.34–7.39 (*m*, 5 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 168.3; 168.1; 134.9; 128.7; 128.6; 128.3; 127.1; 125.5; 122.7; 121.4; 67.5; 67.4; 53.4; 34.9; 33.3. ^{19}F-NMR (282 MHz, $CDCl_3$): −77.83 (*d*, J = 6.3, CF_3); −80.22 (*d*, J = 6.4 CF_3). FAB-MS: 389.0 ($[M+H]^+$). Anal. calc. for $C_{15}H_{14}F_6O_5$ (388.26): C 46.40, H 3.63; found: C 46.56, H 3.75.

*(3*S*)-3-{(*S*)-3-[[(*tert*-Butyl)dimethylsilyl]oxy]-4,4,4-trifluoro-1-oxobutoxy}-4,4,4-trifluorobutanoic Acid (1*S*)-3-[(1*S*)-3-(Benzyloxy)-3-oxo-1-(trifluoromethyl)propoxy]-3-oxo-1-(trifluoromethyl)propyl Ester (=(5*S*,9*S*,13*S*,17*S*)-2,2,3,3-Tetramethyl-7,11,15-trioxo-5,9,13,17-tetrakis(trifluoromethyl)-4,8,12,16-tetraoxa-3-silanonadecan-19-oic Acid Benzyl Ester*; **31**). According to *GP 1*, **29** (0.825 g, 2 mmol) in CH_2Cl_2 (15 ml) was transformed to the acid chloride, and subsequent coupling (*GP 2*) at −78° with **30** (0.97 g, 2.5 mmol) in CH_2Cl_2 (25 ml) yielded, after FC (pentane/Et_2O 3:1), 0.5 g (32%) of 31. Colorless oil. R_f (pentane/Et_2O 3:1) 0.46. $[\alpha]_D^{r.t.} = 13.7$ (c = 1, $CHCl_3$). IR ($CHCl_3$): 1777*m*, 1743*m*, 1404*w*, 1360*w*, 1309*m*, 1280*m*, 1177*m*, 1140*s*, 1040*w*, 963*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.11 (*s*, Me); 0.13 (*s*, Me); 0.87 (*s*, ^{t}Bu); 2.67–2.95 (*m*, 4 CH_2); 4.46–4.52 (*m*, CH); 5.09..5.19 (*dd*, J = 12, J = 8, PhCH_2); 5.74–5.86 (*m*, 3 $CFCH_3$); 7.32–7.39 (*m*, 5 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 167.8; 167.6; 165.8; 134.9; 128.7; 128.4; 127.8; 126.3; 125.5; 124.0; 123.9; 123.3; 121.6; 121.7; 119.5; 68.1; 67.8; 67.3; 66.9; 66.5; 66.4; 66.2; 66.1; 65.9; 36.4; 32.9; 32.6; 25.4; 17.9. ^{19}F-NMR (282 MHz, $CDCl_3$): −77.70 (*d*, J = 6.5, CF_3); −77.84 (*d*, J = 6.3, CF_3); −79.63 (*d*, J = 6.4, CF_3). HR-FT-MALDI-MS: 805.1638 ($[M+Na]^+$). Anal. calc. for $C_{29}H_{34}F_{12}O_9Si$ (782.65): C 44.51, H 4.38; found: C 44.78, H 4.25.

*(5*R*,9*R*,13*R*,17*R*,21*S*)-2,2,5,9,13,17-Hexamethyl-7,11,15,19-tetraoxo-3,3-diphenyl-21-(trifluoromethyl)-4,8,12,16,20-pentaoxa-3-silatricosan-23-oic Acid Benzyl Ester* (**32**). According to *GP 3*, **6** (2,3 g, 3.4 mmol) was deprotected to yield **7**, which was transformed to the acid chloride (*GP 1*). Subsequent coupling (*GP 2*) at −78° with **26** (1.01 g, 4 mmol) in CH_2Cl_2 (25 ml) yielded, after FC (pentane/Et_2O 3:1), 1.92 g (68%) of **32**. Colorless oil. R_f (pentane/Et_2O 3:1) 0.31. IR ($CHCl_3$): 3010*w*, 2982*w*, 2933*w*, 2858*w*, 1737*s*, 1456*m*, 1381*m*, 1306*s*, 1177*w*, 1138*w*, 1102*w*, 1061*w*, 1005*w*, 969*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.02 (*s*, ^{t}Bu); 1.11 (*d*, J = 6.2, Me); 1.20–1.25 (*d*, J = 6.3, 3 Me); 2.34–2.64 (*m*, 4 CH_2); 2.78–2.86 (*m*, CH_2); 4.22–4.28 (*m*, CH); 5.10–5.27 (*m*, PhCH_2); 5.77–5.83 (*m*, CF_3CH); 7.31–7.46 (*m*, 11 arom. H); 7.52–7.68 (*m*, 4 arom. H). ^{13}C-NMR (125 MHz, $CDCl_3$): 170.3; 169.2; 169.0; 167.8; 167.8; 135.7; 135.1; 134.2; 133.8; 129.6; 129.5; 128.6; 128.5; 127.5; 127.4; 124.2; 121.9; 119.7; 108.0; 67.4; 67.2; 67.1; 67.0; 66.7; 66.6; 66.3; 66.0; 65.8; 64.2; 58.4; 44.5; 40.8; 40.6; 39.9; 33.4; 26.8; 23.4; 19.7; 19.6; 19.5; 19.1. ^{19}F-NMR (282 MHz, $CDCl_3$): −77.46 (*d*, J = 6.4, CF_3). ^{19}F-NMR (282 MHz, $CDCl_3$):

– 77.46 (*d*, *J* = 6.5, CF_3). HR-FT-MALDI-MS: 853.047 ([*M* + Na]$^+$). Anal. calc. for $C_{43}H_{53}F_3O_{11}Si$ (830.97): C 62.15, H 6.43; found: C 62.16, H 6.51.

*(5*R*,9*R*,13*R*,17*R*,21*R*,25*R*,29*R*,33*R*,37*S*)-2,2,5,9,13,17,21,25,29,33-Decamethyl-7,11,15,19,23,27,31,35-octaoxo-3,3-diphenyl-37-(trifluoromethyl)-4,8,12,16,20,24,28,32,36-nonaoxa-3-silanonatriacontanoic Acid Benzyl Ester* (**33**). According to *GP 3*, **9** (2,7 g, 2 mmol) was deprotected to give **10**, which was transformed to the acid chloride (*GP 1*). Subsequent coupling (*GP 2*) at – 78° with **26** (0.6 g, 2.4 mmol) in CH_2Cl_2 (40 ml) yielded, after FC (pentane/Et_2O 2 : 3), 1.71 g (73%) of **33**. Colorless oil. R_f (pentane/Et_2O 2 : 3) 0.5. IR ($CHCl_3$): 2984*w*, 1738*s*, 1382*m*, 1305*m*, 1260*s*, 1177*m*, 1102*w*, 1059*w*, 974*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.03 (*s*, ^{t}Bu); 1.11 (*d*, *J* = 6.1, Me); 1.20 – 1.26 (*m*, 7 Me); 2.34 – 2.66 (*m*, 8 CH_2); 2.77 – 2.87 (*m*, CH_2); 4.24 – 4.29 (*m*, CH); 5.10 – 5.39 (*m*, PhCH_2, 6 CH); 5.76 – 5.83 (*m*, CF_3CH); 7.30 – 7.45 (*m*, 11 arom. H); 7.57 – 7.67 (*m*, 4 arom. H). ^{13}C-NMR (125 MHz, $CDCl_3$): 170.3; 169.2; 169.1; 167.8; 167.7; 144.7; 135.8; 135.1; 134.2; 133.9; 129.6; 129.5; 128.6; 128.5; 128.3; 127.6; 127.5; 127.2; 126.5; 124.2; 122.0; 119.8; 110.9; 67.6; 67.5; 67.2; 67.1; 66.7; 66.4; 66.1; 65.8; 44.6; 40.9; 40.8; 40.6; 40.0; 33.4; 27.2; 26.9; 23.4; 19.7; 19.5; 19.1. ^{13}F-NMR (282 MHz, $CDCl_3$): – 77.81 (*d*, *J* = 6.3, CF_3). Anal. calc for $C_{59}H_{77}F_3O_{19}Si$ (1175.33): C 60.29, H 6.60; found: C 60.10, H 6.66.

*(5*R*,9*R*,13*R*,17*R*,21*S*)-2,2,5,9,13,17-Hexamethyl-7,11,15,19-tetraoxo-3,3-diphenyl-21-(trifluoromethyl)-4,8,12,16,20-pentaoxa-3-silatricosan-23-oic Acid* (**34**). According to *GP 3*, **32** (700 mg, 843 mmol) in MeOH (30 ml) was debenzylated to yield 612 mg (98%) of **34**. Viscous oil. IR ($CHCl_3$): 3560*w*, 3010*w*, 2986*m*, 2937*w*, 2879*w*, 1740*s*, 1458*m*, 1381*m*, 1307*m*, 1125*m*, 980*m*. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.03 (*s*, ^{t}Bu); 1.11 (*d*, *J* = 6.1, Me); 1.20 (*d*, *J* = 6.3, Me); 1.24 (*d*, *J* = 6.2, Me); 1.28 (*d*, *J* = 6.3, Me); 2.36 – 2.77 (*m*, 5 CH_2); 4.22 – 4.28 (*m*, CH); 4.83 (br. *s*, OH); 5.15 – 5.21 (*m*, 2 CH); 5.28 (br. *s*, CH); 5.81 (br. *s*, CH); 7.36 – 7.47 (*m*, 11 arom. H); 7.65 – 7.67 (*m*, 4 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 19.2; 19.6; 19.8; 19.8; 23.4; 26.9; 33.5; 40.0; 40.9; 41.1; 44.6; 58.5; 66.7; 67.4; 67.5; 68.3; 122.1; 124.3; 127.5; 127.6; 129.6; 129.7; 133.9; 134.2; 135.8; 135.8; 168.3; 169.2; 170.2; 170.7; 170.9. ^{19}F-NMR (282 MHz, $CDCl_3$): 77.38 (*d*, *J* = 6.4). MALDI-TOF-MS (pos.): 786.3 (14, [*M* + 2 Na – H + 1 H]$^+$), 785.3 (14, [*M* + 2 Na – H]$^+$), 765.3 (14, [*M* + Na + 2 H]$^+$), 764.3 (44, [*M* + Na + 1 H]$^+$), 763.3 (100, [*M* + Na]$^+$), 537.2 (15), 473.2 (20), 451.2 (22), 443.1 (20), 421.1 (14). Anal. calc. for $C_{36}H_{47}F_3O_{11}Si$ (740.84): C 58.37, H 6.39; found: C 58.27, H 6.14.

*(5*R*,9*R*,13*R*,17*R*,21*R*,25*R*,29*R*,33*R*,37*S*)-2,2,5,9,13,17,21,25,29,33-Decamethyl-7,11,15,19,23,27,31,35-octaoxo-3,3-diphenyl-37-(trifluoromethyl)-4,8,12,16,20,24,28,32,36-nonaoxa-3-silanonatriacontanoic Acid* (**35**). According to *GP 3*, **33** (650 mg, 553 mmol) in Et_2O (30 ml) was debenzylated to yield 615 mg (quant.) of **35**. Viscous oil. IR ($CHCl_3$): 3553*w* (br.), 3010*w*, 2986*m*, 2938*w*, 2879*w*, 1740*s*, 1457*m*, 1383*m*, 1308*m*, 1125*w*, 980*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.03 (*s*, ^{t}Bu); 1.11 (*d*, *J* = 6.1, Me); 1.21 (*d*, *J* = 6.4, Me); 1.24 (*d*, *J* = 6.3, Me); 1.26 (*d*, *J* = 6.6, Me); 1.26 (*d*, *J* = 6.5, Me); 1.27 (*d*, *J* = 6.3, Me); 1.28 (*d*, *J* = 6.4, Me); 1.29 (*d*, *J* = 6.2, Me); 2.39 (*A*), 2.50 (*B*) (*AB* of *ABX*, J_{AB} = 14.6, J_{AX} = 6.7, J_{BX} = 5.8, CH_2); 2.41 – 2.69 (*m*, 6 CH_2); 2.59 (*A*), 2.72 (*B*) (*AB* of *ABX*, J_{AB} = 16.2, J_{AX} = 8.8, J_{BX} = 4.4, CH_2); 2.77 (*A*), 2.83 (*B*) (*AB* of *ABX*, J_{AB} = 16.4, J_{AX} = 9.8, J_{BX} = 3.7, CH_2); 4.22 – 4.30 (*m*, CH); 5.21 – 5.34 (*m*, 7 CH); 5.78 – 5.84 (*m*, CH); 7.35 – 7.42 (*m*, 11 arom. H); 7.65 – 7.68 (*m*, 4 arom. H). ^{13}C-NMR (125 MHz, $CDCl_3$): 19.2; 19.6; 19.7; 19.8; 19.8; 23.4; 26.9; 33.2; 39.9; 40.8; 40.9; 41.0; 44.6; 66.3; 66.6; 66.7; 67.2; 67.3; 67.6; 67.7; 67.7; 67.8; 68.4; 76.7; 77.0; 77.2; 77.3; 127.5; 127.6; 129.6; 129.7; 133.9; 134.3; 135.8; 135.8; 168.1; 169.0; 169.3; 169.3; 169.4; 169.5; 169.6; 170.1; 170.4. ^{19}F-NMR (282 MHz, $CDCl_3$): 77.38 (*d*, *J* = 6.4). MALDI-TOF-MS (pos.): 1130.4 (10, [*M* + 2 Na – H + 1]$^+$), 1129.4 (15, [*M* + 2 Na – H]$^+$), 1109.4 (27, [*M* + Na + 2]$^+$), 1108.4 (64, [*M* + Na + 1]$^+$), 1107.4 (100, [*M* + Na]$^+$), 817.3 (7), 1765.3 (8), 731.3 (19), 709.3 (9), 679.2 (8), 645.2 (8), 593.2 (9), 559.2 (7), 529.1 (7), 507.1 (5), 473.2 (5). Anal. calc. for $C_{52}H_{71}F_3O_{19}Si$ (1085.20): C 57.55, H 6.59; found C 57.48, H 6.69.

*α-[(3*S*)-3-[[(*tert*-Butyl)dimethylsilyl]oxy}-4,4,4-trifluoro-1-oxobutyl]-ω-(benzyloxy)dotriacontakis{oxy-[(1*R*)-1-methyl-3-oxopropane-1,3-diyl]}* (**36**). According to *GP 1*, **27** (0.102 g, 0.375 mmol) was transformed to the acid chloride, and subsequent coupling (*GP 2*) at – 78° with desilylated **15** (0.535 g, 0.187 mmol) (→ **22**) in CH_2Cl_2 (15 ml) yielded, after FC (CH_2Cl_2/Et_2O 3 : 1), 0.34 g (59%) of **36**. White solid. R_f (CH_2Cl_2/Et_2O 3 : 1) 0.25. IR ($CHCl_3$): 3035*w*, 2984*w*, 2933*w*, 1737*s*, 1458*w*, 1382*m*, 1305*m*, 1177*m*, 1134*w*, 1100*w*, 1058*m*, 978*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.09 (*s*, Me); 0.13 (*s*, Me); 0.86 (*s*, ^{t}Bu); 1.24 – 1.34 (*m*, 32 Me); 2.40 – 2.65 (*m*, 33 CH_2); 4.46 – 4.49 (*m*, CH); 5.11 (*s*, PhCH_2); 5.19 – 5.32 (*m*, 32 CH); 7.31 – 7.36 (*m*, 5 arom. H). ^{19}F-NMR (282 MHz, $CDCl_3$): – 79.09 (*d*, *J* = 6.5, CF_3). MALDI-TOF-MS: 3140.3 ([*M* + Na]$^+$). HR-FT-MALDI-MS: 3140.234 ([*M* + Na]$^+$). Anal. calc. for $C_{145}H_{217}F_3O_{67}Si$ (3117.35): C 55.87, H 7.02; found: C 55.82, H 7.07.

*α-[(3*S*)-4,4,4-Trifluoro-3-hydroxy-1-oxobutyl]-ω-hydroxydotriacontakis{oxy[(1*R*)-1-methyl-3-oxopropane-1,3-diyl]}* (**II**). According to *GP 4* and *GP 3*, **36** (0.095 g, 0.035 mmol) was fully deprotected and the product precipitated from CH_2Cl_2/pentane: **II**. White solid. IR ($CHCl_3$): 3010*w*, 2986*w*, 2936*w*, 1737*s*, 1458*w*, 1382*m*, 1305*m*, 1263*m*, 1177*w*, 1134*w*, 1058*m*, 978*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.26 – 1.32 (*m*, 32 Me); 2.43 – 2.64 (*m*, 33 CH_2); 3.61 (br. *s*, OH); 4.06 – 4.13 (*m*, CH); 5.11 – 5.25 (*m*, 31 CH); 5.62 – 5.72 (*m*, CH). ^{19}F-NMR

(282 MHz, $CDCl_3$): −79.52 (*d*, *J* = 6.4, CF_3). MALDI-TOF-MS: 2934.6 ($[M+Na-H]^+$), 2951.1 ($[M+K]^+$). HR-FT-MALDI-MS (pos.): 2935.1290 ($C_{132}H_{198}F_3NaO_{67}^+$; calc. 2935.1858).

α-[(3S,7R,11R,15R,19R)-7,11,15,19,22,22-Hexamethyl-1,5,9,13,17-pentaoxo-21,21-diphenyl-3-(trifluoromethyl)-4,8,12,16,20-pentaoxa-21-silatricos-1-yl]-ω-(benzyloxy)octacosakis{oxy[(1R)-1-methyl-3-oxopropane-1,3-diyl]} (**37**). According to *GP 1*, **34** (240 mg, 221 μmol) was transformed to the acid chloride, and subsequent coupling (*GP 2*) at −78° with **21** (538 mg, 221 μmol) in CH_2Cl_2 (15 ml) yielded, after FC (CH_2Cl_2/Et_2O 5:1 → 3:1), 580 mg (81%) of **37**. White solid. M.p. 138–139°. IR ($CHCl_3$): 3010*w*, 2985*m*, 2936*w*, 1738*w*, 1457*w*, 1383*w*, 1306*m*, 1177*m*, 1136*m*, 1103*m*, 1059*m*, 984*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.03 (*s*, ^{t}Bu); 1.11 (*d*, *J* = 6.1, Me); 1.21 (*d*, *J* = 6.3, Me); 1.24 (*d*, *J* = 6.3, Me); 1.24 (*d*, *J* = 6.3, Me); 1.25–1.29 (*m*, 28 Me); 2.37 (*dd*, *J* = 14.6, 6,9, 1 H, CH_2); 2.40 (*dd*, *J* = 15.5, 9.0, 1 H, CH_2); 2.42–2.65 (*m*, 30 CH_2); 2.74 (*A*), 2.79 (*B*) (*AB* of *ABX*, J_{AB} = 16.6, J_{AX} = 9.1, J_{BX} = 4.3, CH_2); 4.23–4.29 (*m*, CH); 5.15–5.20 (*m*, CH); 5.21–5.32 (*m*, 30 CH); 5.75–5.81 (*m*, CH); 7.31–7.44 (*m*, 11 arom. H); 7.65–7.68 (*m*, 4 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 19.2; 19.6; 19.7; 19.7; 19.8; 19.8; 19.9; 23.4; 26.9; 33.5; 40.1; 40.6; 40.6; 40.7; 40.8; 40.9; 41.1; 41.0; 44.6; 66.1; 66.4; 66.5; 66.7;67.2; 67.5; 67.5; 67.6; 67.7; 67.7; 67.8; 68.6; 77.2; 127.5; 127.6; 128.3; 128.6; 129.6; 129.7; 134.0; 134.3; 135.7; 135.8; 135.8; 167.1; 167.8; 168.9; 169.0; 169.1; 169.2; 169.9; 170.3. ^{19}F-NMR (282 MHz, $CDCl_3$): 77.26 (*d*, *J* = 6.4). MALDI-TOF-MS (pos.): 3266.4 (37, $[M+Na+4H]^+$), 3265.4 (68, $[M+Na+3H]^+$), 3264.3 (98, $[M+Na+2H]^+$), 3263.3 (100, $[M+Na+1H]^+$), 3262.3 (54, $[M+Na]^+$), 3176.3 (2), 2571.3 (1), 2117.7 (1), 1661.7 (2), 1575.7 (2), 1535.6 (2), 1317.6 (1), 1115.3 (2). Anal. calc. for $C_{155}H_{221}F_3O_{67}Si$ (3241.49): C 57.43, H 6.87; found: C 57.55, H 6.85.

α-[(3S,7R,11R,15R,19R,23R,27R,31R,35R)-7,11,15,19,23,27,31,35,38,38-Decamethyl-1,5,9,13,17,21,25,29,33-nonaoxo-37,37-diphenyl-3-(trifluoromethyl)-4,8,12,16,20,24,28,32,36-nonaoxa-37-silanonatriacont-1-yl]-ω-(benzyloxy)tetracosakis{oxy[(1R)-1-methyl-3-oxopropane-1,3-diyl]} (**38**). According to *GP 1*, **35** (435 mg, 587 μmol) was transformed to the acid chloride, and subsequent coupling (*GP 2*) at −78° with **20** (227 mg, 88 μmol) in CH_2Cl_2 (5 ml) yielded, after FC (CH_2Cl_2/Et_2O 4:1 → 2:1), 230 mg (81%) of **38**. White solid. IR ($CHCl_3$: 3010*w*, 2986*m*, 2934*w*, 1738*w*, 1384*w*, 1305*m*, 1179*m*, 1136*m*, 1103*m*, 1059*m*, 979*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.03 (*s*, ^{t}Bu); 1.11 (*d*, *J* = 6.1, Me); 1.21 (*d*, *J* = 6.3, Me); 1.24 (*d*, *J* = 6.3, Me); 1.24 (*d*, *J* = 6.3, Me); 1.26–1.29 (*m*, 28 Me); 2.37 (*dd*, *J* = 14.6, 6.8, 1 H, CH_2); 2.40 (*dd*, *J* = 15.5, 5.7, 1 H, CH_2); 2.41 (*dd*, *J* = 15.3, 6.5, 1 H, CH_2); 2.44–2.62 (*m*, 59, 1 H, CH_2); 2.68 (*dd*, *J* = 15.6, 7.6, 1 H, CH_2); 2.71 (*dd*, *J* = 15.7, 7.5, 1 H, CH_2); 2.74 (*A*), 2.79 (*B*) (*AB* of *ABX*, J_{AB} = 16.6, J_{AX} = 9.5, J_{BX} = 4.4, CH_2); 4.23–4.29 (*m*, CH); 5.12 (*s*, PhCH_2); 5.15–5.21 (*m*, CH); 5.22–5.32 (*m*, 30 CH); 5.75–5.80 (*m*, CH); 7.30–7.47 (*m*, 11 arom. H); 7.66–7.69 (*m*, 4 arom. H). ^{13}C-NMR (125 MHz, $CDCl_3$): 19.2; 19.6; 19.7; 19.7; 19.8; 19.8; 19.9; 23.4; 26.9; 33.5; 40.0; 40.6; 40.6; 40.7; 40.7; 40.8; 40.9; 41.0; 44.6; 66.1; 66.4; 66.5; 66.7; 67.2; 67.5; 67.6; 67.7; 67.7; 67.8; 68.6; 77.2; 77.8; 78.0; 78.4; 78.8; 122.1; 127.5; 127.6; 128.4; 128.6; 129.6; 129.7; 134.0; 134.3; 135.7; 135.8; 135.8; 167.1; 167.8; 169.0; 169.1; 169.1; 169.2; 169.9; 170.3. ^{19}F-NMR (282 MHz, $CDCl_3$): 77.24 (*d*, *J* = 6.4). MALDI-TOF-MS (pos.): 3266.4 (37, $[M+Na+4H]^+$), 3265.4 (66, $[M+Na+3H]^+$) 3264.3 (97, $[M+Na+2H]^+$), 3263.3 (100, $[M+Na+1H]^+$), 3262.3 (53, $[M+Na]^+$), 3178.3 (3), 3129.4 (3), 3123.3 (3), 2768.5 (2), 2482.2 (2), 1661.7 (3), 1115 (3). Anal. calc. for $C_{155}H_{221}F_3O_{67}Si$ (3241.49): C 57.43, H 6.87; found: C 57.33, H 6.99.

α-[(3S,7R,11R,15R,19R)-19-Hydroxy-7,11,15-trimethyl-1,5,9,13,17-pentaoxo-3-(trifluoromethyl)-4,8,12,16-tetraoxalicos-1-yl]-ω-(benzyloxy)octacosakis{oxy[(1R)-1-methyl-3-oxopropane-1,3-diyl]} (**39**). According to *GP 4*, **37** (540 mg, 167 μmol) in CH_2Cl_2 (5 ml) was desilylated with HF·pyridine (56 μl, 2.16 mmol, 13 equiv.) at 0° for 9 h. Workup and washings with hot pentane yielded 419 mg (84%) of **39**. White solid. IR ($CHCl_3$): 3010*w*, 2986*m*, 2937*w*, 2879*w*, 1740*s*, 1458*w*, 1382*w*, 1305*m*, 1136*m*, 1101*m*, 1059*w*, 980*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.22 (*d*, *J* = 6.3, Me); 1.24 (*d*, *J* = 6.3, Me); 1.26–1.29 (*m*, 28 Me); 1.30 (*d*, *J* = 6.3, Me); 1.31 (*d*, *J* = 6.3, Me); 2.39 (*dd*, *J* = 16.0, 8.5, 1 H, CH_2); 2.40 (*dd*, *J* = 15.5, 5.8, 1 H, CH_2); 2.43–2.65 (*m*, 30 CH_2); 2.69 (*dd*, *J* = 15.6, 7.6, 1 H, CH_2); 2.72 (*dd*, *J* = 15.7, 7.5, 1 H, CH_2); 2.75 (*A*), 2.79 (*B*), (*AB* of *ABX*, J_{AB} = 16.5, J_{AX} = 9.1, J_{BX} = 4.3, CH_2); 3.07 (*d*, *J* = 3.9, OH); 4.15–4.21 (*m*, CH); 5.11 (*s*, PhCH_2); 5.15–5.34 (*m*, 31 CH); 5.76–5.80 (*m*, CH); 7.31–7.38 (*m*, 5 arom. H). ^{13}C-NMR (125 MHz, $CDCl_3$): 19.6; 19.7; 19.7; 19.8; 19.8; 19.9; 22.5; 33.5; 40.1; 40.6; 40.6; 40.7; 40.7; 40.8; 41.0; 43.3; 64.4; 66.1; 66.4; 66.5; 67.2; 67.5; 67.5; 67.6; 67.7; 67.7; 67.8; 68.6; 77.2; 128.3; 128.6; 135.7; 167.2; 167.8; 169.0; 169.1; 169.2; 169.2; 169.4; 169.9; 172.0. ^{19}F-NMR (282 MHz, $CDCl_3$): 77.26 (*d*, *J* = 6.4). MALDI-TOF-MS (pos.): 3028.2 (23, $[M+Na+4H]^+$), 3027.2 (51, $[M+Na+3H]^+$), 3026.2 (89, $[M+Na+2H]^+$), 3025.2 (100, $[M+Na+1H]^+$), 3024.2 (61, $[M+Na]^+$). 2882.6 (2), 2771.8 (3), 2059.2 (4), 1747.7 (2), 1661.7 (3), 1575.7 (3), 1489.6 (3), 1227.5 (3), 1115.3 (4). Anal. calc. for $C_{139}H_{203}F_3O_{67}$ (3003.09): C 55.59, H 6.82; found: C 55.67, H 6.87.

α-[(3S,7R,11R,15R,19R,23R,27R,31R,35R)-35-Hydroxy-7,11,15,19,23,27,31-heptamethyl-1,5,9,13,17,21,25,29,33-nonaoxo-3-(trifluoromethyl)-4,8,12,16,20,24,28,32-octaoxahexatriacont-1-yl]-ω-(benzyloxy)tetracosakis-{oxy[(1R)-1-methyl-3-oxopropane-1,3-diyl]} (**40**). According to *GP 4*, **38** (180 mg, 55 μmol) in CH_2Cl_2 (9 ml) was desilylated with HF·pyridine (18 μl, 720 mmol, 13 equiv.) for 7 h. Workup and washings with hot pentane

yielded 132 mg (80%) of **40**. White solid. IR ($CHCl_3$): 3010*w*, 2987*m*, 2937*w*, 2878*w*, 1740*s*, 1458*w*, 1382*w*, 1306*s*, 1179*m*, 1136*m*, 1103*m*, 1060*w*, 979*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.14 (*d*, *J* = 6.3, Me); 1.22 (*d*, *J* = 6.3, Me); 1.24 (*d*, *J* = 6.3, Me); 1.26–1.29 (*m*, 27 Me); 1.30 (*d*, *J* = 6.3, Me); 1.31 (*d*, *J* = 6.3, Me); 2.37–2.64 (*m*, 31 CH_2); 2.68 (*dd*, *J* = 15.6, 7.7, 1 H, CH_2); 2.72 (*dd*, *J* = 15.8, 7.6, 1 H, CH_2); 2.75 (*A*), 2.80 (*B*) (*AB* of *ABX*, J_{AB} = 16.6, J_{AX} = 8.8, J_{BX} = 4.5, CH_2); 3,07 (br. *s*, OH); 4.15–4.21 (*m*, CH); 5.12 (*s*, PhCH_2); 5.21–5.33 (*m*, 31 CH); 5.76–5.81 (*m*, CH); 7.31–7.38 (*m*, 5 arom. H). ^{13}C-NMR (125 MHz, $CDCl_3$): 19.6; 19.6; 19.7; 19.8; 19.8; 19.9; 22.5; 29.7; 33.5; 40.0; 40.6; 40.6; 40.7; 40.8; 41.0; 43.2; 58.5; 64.4; 66.1; 66.3; 66.5; 67.2; 67.4; 67.5; 67.6; 67.7; 67.7; 67.8; 68.6; 77.2; 128.3; 128.6; 135.7; 167.2; 167.8; 169.1; 169.2; 169.4; 169.9; 172.0. ^{19}F-NMR (282 MHz, $CDCl_3$): 77.26 (*d*, *J* = 6.4). MALDI-TOF-MS (pos.): 3028.2 (21, $[M + Na + 4\ H]^+$), 3027.2 (50, $[M + Na + 3\ H]^+$), 3026.2 (83, $[M + Na + 2\ H]^+$), 3025.2 (100, $[M + Na + 1\ H]^+$), 3024.2 (56, $[M + Na]^+$), 2882.5 (4), 2771.7 (5), 2669.0 (5), 2413.6 (3), 2314.9 (3), 1896.6 (4), 1716.0 (3), 1661.7 (3), 1575.7 (4), 1489.6 (3), 1227.5 (5), 115.3 (6). Anal. calc. for $C_{139}H_{203}O_{67}F_3$ (3003.09: C 55.59, H 6.81; found: C 55.74, H 6.87.

*α-[(3*S*,7*R*,11*R*,15*R*,19*R*)-19-Hydroxy-7,11,15-trimethyl-1,5,9,13,17-pentaoxo-3-(trifluoromethyl)-4,8,12,16-tetraoxaeicos-1-yl]-ω-hydrooctacosakis{oxy[(1*R*)-1-methyl-3-oxopropane-1,3-diyl* (**III**). According to *GP 3*, **39** (190 mg, 63 μmol) in Et_2O (25 ml) was treated with Pd/C (100 mg) under H_2 for 96 h. Workup resulted in 169 mg (92%) of **III**. White solid. IR ($CHCl_3$): 3610*m* (br.), 3010*m*, 2983*m*, 2941*m*, 2883*m*, 1740*s*, 1456*m*, 1384*m*, 1309*w*, 1179*m*, 1152*m*, 1055*m*, 983*m*. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.09 (*d*, *J* = 6.3, Me); 1.13 (*d*, *J* = 6.3, Me); 1.15–1.26 (*m*, 28 Me); 1.27 (*d*, *J* = 6.3, Me); 1.33 (*d*, *J* = 6.3, Me); 2.33–2.63 (*m*, 63, 1 H, CH_2); 2.66 (*dd*, *J* = 15.5, 7.5, 1 H, CH_2); 2.69 (*A*), 2.72 (*B*) (*AB* of *ABX*, J_{AB} = 16.4, J_{AX} = 9.0, J_{BX} = 4.5, CH_2); 3.71 (br. *s*, 2 OH); 4.08–4.15 (*m*, CH); 5.12–5.24 (*m*, 31 CH); 5.68–5.75 (*m*, CH). ^{13}C-NMR (125 MHz, $CDCl_3$): 19.2; 19.3; 19.4; 19.5; 19.5; 19.8; 22.2; 33.2; 39.7; 40.5; 40.6; 40.7; 42.9; 43.2; 64.1; 66.9; 67.2; 67.3; 67.4; 67.5; 67.6; 68.1; 69.4; 101.2; 156.2; 166.8; 167.4; 168.7; 168.8; 168.9; 169.0; 169.1; 169.2; 169.3; 170.1; 171.7; 213.9. ^{19}F-NMR (282 MHz, $CDCl_3$): 77.25 (*d*, *J* = 6.4). MALDI-TOF-MS (pos.): 2938.2 (13, $[M + Na + 4\ H]^+$), 2937.2 (40, $[M + Na + 3\ H]^+$), 2936.2 (77, $[M + Na + 2\ H]^+$), 2935.2 (100, $[M + Na + 1\ H]^+$), 2934.2 (65, $[M + Na]^+$). HR-FT-MALDI-MS (pos.): 2934.1903 ($C_{132}H_{197}F_3NaO_{67}^+$; calc. 2934.1858).

*α-[(3*S*,7*R*,11*R*,15*R*,19*R*,23*R*,27*R*,31*R*,35*R*)-35-Hydroxy-7,11,15,19,23,27,31-heptamethyl-1,5,9,13,17,21,25,29,33-nonaoxo-3-(trifluoromethyl)-4,8,12,16,20,24,28,32-octaoxahexatriacont-1-yl]-ω-hydrotetracosakis{oxy-[(1*R*)-1-methyl-3-oxopropane-1,3-diyl]}* (**IV**). According to *GP 3*, **40** (63 mg, 21 μmol) in Et_2O (10 ml) was treated with Pd/C (60 mg) under H_2 fo r96 h. Workup resulted in 58 mg (90%) of **IV**. White solid. IR ($CHCl_3$): 3574*m* (br.), 3007*m*, 2981*m*, 2891*m*, 1740*s*, 1455*m*, 1386*m*, 1311*w*, 1180*m*, 1055*m*, 945*m*. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.07 (*d*, *J* = 6.4, Me); 1.12 (*d*, *J* = 6.3, Me); 1.13–1.24 (*m*, 28 Me); 1.28 (*d*, *J* = 6.3, Me); 1.33 (*d*, *J* = 6.3, Me); 2.30–2.61 (*m*, 63, 1 H, CH_2); 2.65 (*dd*, *J* = 15.5, 7.5, 1 H, CH_2); 2.68 (*A*), 2.72 (*B*) (*AB* of *ABX*, J_{AB} = 16.5, J_{AX} = 9.1, J_{BX} = 4.5, CH_2); 3.61 (br. *s*, OH); 4.08–4.15 (*m*, CH); 5.15–5.25 (*m*, 31 CH); 5.68–5.74 (*m*, CH). ^{13}C-NMR (125 MHz, $CDCl_3$): 19.2; 19.3; 19.4; 19.5; 19.6; 19.8; 22.2; 33.2; 39.7; 40.3; 40.5; 40.7; 42.9; 43.2; 64.1; 66.9; 67.2; 67.3; 67.4; 67.5; 67.6; 68.2; 69.3; 101.2; 156.2; 166.8; 167.4; 168.7; 168.8; 168.9; 169.0; 169.1; 169.2; 169.3; 170.0; 171.7; 213.9. ^{19}F-NMR (282 MHz, $CDCl_3$): 77.25 (*d*, *J* = 6.4). MALDI-TOF-MS (pos.): 2938.2 (15, $[M + Na + 4\ H]^+$), 2937.2 (41, $[M + Na + 3\ H]^+$), 2936.2 (76, $[M + Na + 2\ H]^+$), 2935.2 (100, $[M + Na + 1\ H]^+$), 2934.2 (67, $[M + Na]^+$). HR-FT-MALDI-MS (pos.): 2934.1894 ($C_{132}H_{197}F_3NaO_{67}^+$; calc. 2934.1858).

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