Solid-phase synthesis of a library of linear oligoester ion-channels†‡

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A solid-phase synthesis protocol was used to prepare fifteen new linear tetra-, and penta-esters structurally related to an active lead compound. The structures were assembled from three types of hydroxyl protected building blocks: monoalkyl esters of hydroxyglutaric acid, ω-hydroxyacids, and α-hydroxymethylalkanoic acids. The standard methodology gave acceptable quantities of material free of small molecule impurities. Mass spectrometric analysis revealed the presence of deletions due to incomplete coupling, as well as additions and macrolactones due to partial acidic rearrangement on release from the solid-support. The amount of these impurities could be estimated from the ^{1}H NMR spectra, and their implications for subsequent activity analysis are discussed.

Introduction

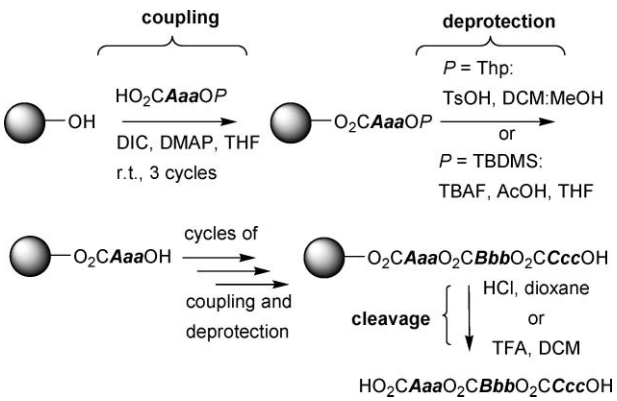
The synthesis and characterization of compounds and systems that mimic the functions of natural ion-channel proteins continues to capture the imagination and energy of many research teams.[1–3] In addition to the inherent challenge to produce macroscopically detectable events from a single supramolecular structure in a complex membrane environment, there are important practical examples of analytical and therapeutic applications of synthetic channels.[4–6] As in other catalytic systems the active structures are difficult to infer and mechanistic insights are often ambiguous and incomplete. As a result, much recent progress rests on the structure–activity optimization of a lead compound using assumed structures and mechanistic hypotheses.[7–10] This research strategy places particular emphasis on efficient syntheses of targeted libraries of related structures.

We recently reported a solid-phase methodology that is well-suited to the creation of targeted libraries of ion-channels based on linear oligoesters of long-chain ω-hydroxyacids.[11] Our initial study was designed to explore the synthetic methodology and to demonstrate the activity of compounds within the class of potential structures. The method uses a cycle of coupling of a protected hydroxyacid to a solid support followed by deprotection to open a new alcohol for subsequent cycles. The resulting linear oligoester is assembled from the carboxyl- to the hydroxyl-terminus. Trimers and tetramers were readily prepared; some types of pentamers undergo a side reaction during the final cleavage from the support. Even with the known limitations, a vast number of potential compounds can in principle be prepared.

This report discusses an extension of the pool of precursors and the preparation of a set of compounds selected to probe basic mechanistic questions. We were alert to the potential activity of shorter oligomers and the confounding effect such impurities would have on mechanistic investigations. The focus of this report is an examination of the impurities that arise in the production of a library of compounds using the established methodology. A concurrent paper examines the activity of the compounds prepared, and probes mechanistic aspects of the active members of this library.[12]

Results and discussion

The general method for the preparation of linear oligoesters is summarized in Scheme 1. Wang resin is initially loaded with an ω-hydroxyacid protected as either the tetrahydropyranyl or *tert*-butyldimethyl silyl ether. Following three cycles of loading the protecting group is removed to expose a new alcohol for subsequent coupling steps. The step-wise synthesis of coupling/deprotection is finally terminated by acidic cleavage of the product from the resin. The reaction steps are separated by washing steps to remove reaction byproducts.[11]



Scheme 1 Solid-phase synthesis methodology.

The synthesis of the required building blocks is given in Scheme 2. These are of three types. The most lipophilic are mono-esters of hydroxyglutaric acid, readily prepared from the commercially available protected glutaric anhydride. The dodecyl derivative (***G(12)***) was previously reported[11]; the decyl (***G(10)***), tetradecyl(***G(14)***) and hexadecyl (***G(16)***) derivatives were

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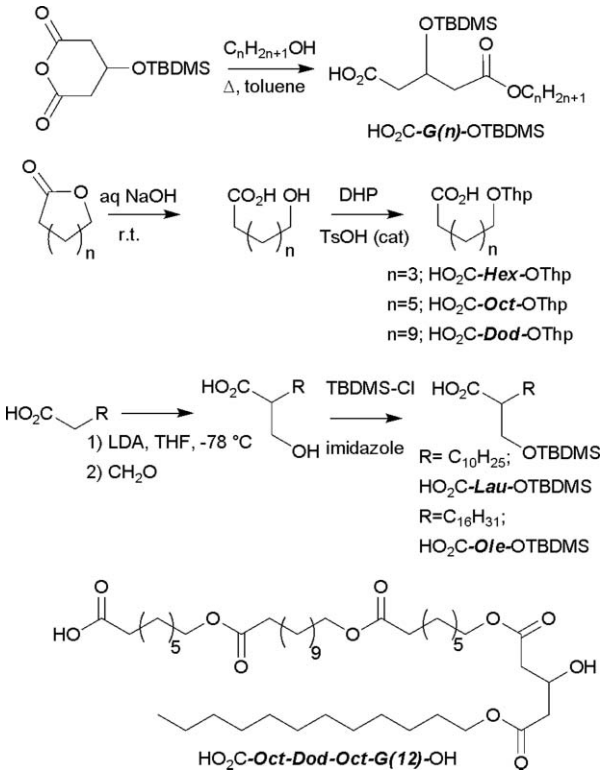

Scheme 2 Synthesis of protected hydroxyacids.

prepared in similarly good yields. A second series are the linear ω-hydroxyacid derivatives. The C_8 and C_{12} compounds (***Oct, Dod***) were reported previously.[11] The C_6 compound (***Hex***) was prepared by basic hydrolysis of caprolactone followed by protection as the tetrahydropyranyl ether. The building block HO_2C-***Hex***-OThp is unstable with respect to reversion to caprolactone and hydroxy valeraldehyde, which occurs slowly over a period of months.

A third series of β-hydroxyacid building blocks was prepared using the known reaction of a carboxylate α-anion with formaldehyde.[13] The primary alcohol was then protected as the *tert*-butyldimethyl silyl ether from the corresponding silyl chloride with imidazole catalysis. The overall yields of the protected acids were poor, but sufficient quantities could be prepared from oleic and lauric acids to explore the subsequent synthesis.

Scheme 2 also shows the type of linear oligoester that the synthesis can produce together with a mnemonic nomenclature that specifies structure. As used in preceding paragraphs, each building block is assigned a three-character code. Following the practice in peptide chemistry the names are written from the carboxyl- to the hydroxyl-terminus. The termini are specified to indicate the degree of protection and/or protonation, but the internal esters are assumed in the name.

The nine available building blocks have the potential to produce 6561 tetramers and a further 32805 possible pentamers given the limitation that the methodology cannot produce pentamers with the ***G(n)*** unit at the carboxyl terminus.[11] Of this diversity, we chose to target structures related to the known active tetramer HO_2C-***Oct-Dod-Oct-G(12)***-OH. The available building blocks offer a number of possible structural variations that might relate to activity. For example, tetramers with a common carboxy terminus HO_2C-***Oct-Dod-Oct-*** and the possible ***G(n)*** units and/or the ***Ole/Lau*** units as the hydroxyl terminus would provide compounds with a variation in lipophilicity. Similarly, constitutional isomers in which the ***Oct***, ***Dod***, and ***G(12)*** units were shuffled within the structure would provide compounds of constant lipophilicity but variable ester and alkyl location *e.g.* HO_2C-***Oct-Oct-Dod-G(12)***-OH or HO_2C-***G(12)-Oct-Dod-Oct***-OH.[11] Longer or shorter compounds are available through substitution of ***Oct*** and/or ***Dod*** units *e.g.* HO_2C-***Dod-Dod-Dod-G(12)***-OH or HO_2C-***Oct-Oct-Oct-G(12)***-OH. The role of the esters could be probed with a derivative such as HO_2C-***Hex-Oct-Hex-Oct-G(12)***-OH which has a very similar total length to the parent. We eventually settled on 15 new tetramers and pentamers as an initial target library that offered interesting structural variations for structure–activity evaluation.

The compounds were prepared using the loading, deprotection, coupling, washing, cleavage, and purification protocols previously established.[11] The new units HO_2C-***Ole***-OTBDMS and HO_2C-***Lau***-OTBDMS couple slowly to the Wang resin, so target compounds having either of these units in the carboxyl-terminal position were subject to reaction cycles of 8 + 16 + 16 hours in place of the usual 5 + 5 + 16 hour protocol. Although all compounds were finally characterized by NMR and MS, the purification did not use a spectroscopic technique to locate the compound in the fractions of the gel filtration column. Rather, a fixed cut (fractions 8–10) was processed. This mimics an automated library synthesis which runs the risk of missing the desired compound or of collecting related impurities, problems that a human might be able to identify and avoid.

The isolated products were apparently free of small-molecule impurities from the synthesis and showed all and only the expected signals in the NMR spectra. There is a great deal of spectral simplification due to the direct overlap of signals from repeated substructures in the oligomers. For example, all internal esters of ***Hex***, ***Oct***, and ***Dod*** show the signal for -CH_2CO_2R as a simple triplet at 2.2 ppm and the signal for RCO_2CH_2- as a simple triplet at 4.0 ppm in the ^{1}H NMR spectrum. Similarly carboxyl-terminal ***G(n)*** units show signals for the methine at 5.5 ppm as a quintet, and HO_2CCH_2- signals as a triplet at 2.7 ppm. Hydroxyl-terminal ***G(n)*** show signals for the methine at 4.4 ppm as a quintet, and RO_2CCH_2- signals as a triplet at 2.5 ppm. As a consequence of these overlaps, NMR spectroscopy cannot be used to detect the presence of impurity structures that arise through incomplete reaction during synthesis. As an example, the NMR spectrum of mixture of the desired tetramer HO_2C-***Oct-Dod-Oct-G(12)***-OH is directly superimposable on that of a "deletion" impurity such as HO_2C-***Dod-Oct-G(12)***-OH.§

Such potential deletion impurities can be detected by mass spectrometry. All compounds show the expected sodiated parent ion by +LSIMS from a matrix of *meta*-nitrobenzyl alcohol containing 0.1% sodium acetate (Table 1). This $(M + Na)^+$ ion is frequently the base peak and is usually accompanied by a relatively

§ Deletion impurities of this type are also very difficult to detect by elemental analysis: HO_2C-***Oct-Dod-Oct-G(12)***-OH Calculated for $C_{45}H_{82}O_{11}$: C 67.62; H 10.28; HO_2C-***Oct-Oct-G(12)***-OH $C_{33}H_{60}O_9$: C 65.97, H 10.07. At a standard precision of ±0.4%, the deletion impurity would have to exceed 25% of the mixture in order to be "detected" by elemental analysis for carbon; the hydrogen analysis would be acceptable at all mixture compositions. The compounds have no suitable chromophores for simple HPLC analysis, although minor colored impurities can be readily detected.

Table 1 Mass spectroscopic data of compounds prepared.[a]

Compound	Molecular ion	Deletions detected		Additions detected		Decompositions detected
	$(M + Na)^+$	$(M - \textbf{\textit{Oct}} + Na)^+$	$(M - \textbf{\textit{Xxx}} + Na)^+$	$(M + \textbf{\textit{Oct}} + Na)^+$	$(M + \textbf{\textit{Xxx}} + Na)^+$	$(Lactone + H)^+$
HO_2C-***Oct-Dod-Oct-G(10)***-OH	793 (100)	—	—	935 (4)	991 (6)[c]	341 (12)
HO_2C-***Oct-Dod-Oct-G(12)***-OH	821 (100)	679 (5)	—	963 (8)	—	341 (19)
HO_2C-***Oct-Dod-Oct-G(14)***-OH	849 (100)	707 (50)	651 (12)[c]	—	—	—
HO_2C-***Oct-Dod-Oct-G(16)***-OH	877 (100)	735 (20)	679 (7)[c]	1019 (4)	—	—
HO_2C-***G(12)-Oct-Dod-Oct***-OH	821 (40)	679 (100)	—	—	—	483 (12)
HO_2C-***Oct-Oct-Dod-G(12)***-OH	821 (100)	679 (23)	—	—	—	—
HO_2C-***Dod-Oct-Oct-G(12)***-OH	821 (100)	679 (28)	—	963 (8)	1019 (4)[c]	—
HO_2C-***Oct-Oct-Oct-G(12)***-OH	765 (100)	623 (13)	—	907 (11)	—	—
HO_2C-***Dod-Dod-Dod-G(12)***-OH	933 (100)	—	735 (60)[c]	—	1131 (11)[c]	—
HO_2C-***Dod-Dod-Oct-G(12)***-OH	877 (90)	735 (100)	679 (50)[c]	—	—	—
HO_2C-***Oct-Dod-Dod-G(12)***-OH	877 (50)	735 (100)	679 (47)[c]	—	933 (15)[c]	—
HO_2C-***Oct-Dod-Oct-Lau***-OH	735 (18)	—	—	877 (7)	—	—
HO_2C-***Oct-Dod-Oct-Oleate***[b]	787 (48)	—	—	929 (15)	—	341 (90)
HO_2C-***Hex-Oct-Hex-Oct-G(12)***-OH	851 (30)	709 (90)	737 (50)[d]	929 (5)	965 (8)[d]	—
HO_2C-***Lau-Oct-Dod-Oct-G(12)***-OH	1033 (100)	—	—	—	1245 (70)[f]	—
HO_2C-***Ole-Oct-Dod-Oct-G(12)***-OH	1115 (70)	973 (65)	831 (100)[e]	—	—	—
HO_2C-***Oct-G(12)-Oct-Dod-Oct***-OH	963 (100)	821 (50)	—	—	—	483 (41)

[a] (+) LSIMS *meta*-nitrobenzyl alcohol plus 0.1% sodium acetate matrix. Ion mass (intensity relative the bass peak as %). [b] Hydroxy terminus of HO_2C-***Oct-Dod-Oct***-OH esterified with oleic acid. [c] Deletion or addition of ***Dod***. [d] Deletion or addition of ***Hex***. [e] Deletion of ***Ole***. [f] Addition of ***Lau***.

weak $(M + H)^+$ and occasionally by an ion $(M + 2Na - H)^+$ which can be viewed as the sodiated sodium carboxylate ion of the parent compound. As expected, ions corresponding to deletions of one of the components can also be identified by ions of mass $(M - \textbf{\textit{Xxx}} + Na)^+$. These ions occur in virtually every sample examined and in some samples they are the base peak of the spectrum. Only ions where ***Xxx*** = ***Oct***, ***Dod***, or ***Hex*** were observed; the loss of the ***G(n)*** units was never found. This is an artifact of the purification by gel permeation in which the fraction selected is biased towards the highest masses. Despite the predominance of $(M - \textbf{\textit{Oct}} + Na)^+$ ions in Table 1, these are unlikely to be simple terminal fragmentation artifacts of the mass spectrometer as seen in the spectra of HO_2C-***Dod-Dod-Oct-G(12)***-OH, HO_2C-***Hex-Oct-Hex-Oct-G(12)***-OH, and other examples with internal ***Oct*** units. No quantitative inference can be drawn from the significant ion intensities observed for the deletion products as the technique emphasizes ions of lower masses relative to higher mass ions. Thus the deletions are apparently over-represented in the observed spectra.

In addition to ions at lower than expected mass, most samples also exhibited ions at *higher* mass than the expected molecular ion of the parent (Table 1). The ions observed have masses corresponding to $(M + \textbf{\textit{Xxx}} + Na)^+$. These ions do not appear to be artifacts of the mass spectrometric technique as additions of both terminal units and internal units can be observed in some cases (*e.g.* HO_2C-***Oct-Dod-Oct-G(10)***-OH). As noted above, the technique is biased towards detection of ions of lower mass, so the relatively low intensities observed for this type of addition impurity under-represent the condition within the sample.

Finally, some samples exhibited relatively significant ions corresponding to the macrocyclic lactones *cyclo*(-***Oct-Dod***) and *cyclo*-(-***Oct-Dod-Oct***). An alternate representation of the same mass would be a dehydration of a linear oligomer. It is possible that these ions arise from decomposition by transesterification during cleavage from the solid support. They are especially abundant in the LSIMS of products of simple dimers and trimers with terminal primary alcohols such as HO_2C-***Oct-Dod-OH*** and HO_2C-***Oct-Dod-Oct***-OH.[14]

Although Table 1 paints a bleak picture of the impurities present in the samples, many of the NMR spectra suggest that the samples are predominantly the expected compounds. As noted above, superposition of signals from the desired products and the detected impurities results no additional signals. Impurities will however perturb the expected relative integrations of signals associated with the sub-units within the structures. We selected a reference signal that is uniquely associated with one unit within the structure such as the methine signal from the ***G(n)*** units and compared the integration to that of a probe signal in which superposition was likely. Any increase or decrease relative to the expectation from the desired structure was then related to the amount of the "unseen" impurity. In a quantitative sense there is an additional correction for the difference in the numbers of protons contributing to the probe signal from the impurity relative to the desired compound. This required an assumption of the nature of predominant impurity which we took from the MS data in Table 1.

Table 2 summarizes the results. In roughly half the samples, the compound directly isolated by the protocols followed have acceptable purities for the proposed structure activity survey. However, the other samples show a variety of problems. In three samples there was contamination from trifluoroacetate esters of a linear species such as HO_2C-***Oct-Dod-Oct***-OH. In these cases direct integration of the impurity is possible since the trifluoroacetate esters gave a unique signal for $-CH_2O_2CCF_3$ slightly downfield of the main ester signals due to $-CH_2O_2C-$. This problem is easily remedied by use of the HCl in dioxane cleavage conditions. Although both +***Oct*** and −***Oct*** products were detected by MS in most samples, these are usually relatively minor as assessed by the NMR method. The +***Lau*** observed for

Table 2 NMR signals and assumptions used to estimate compound purity and recovery of compounds prepared[a]

Compound	Reference[c]	Probe[d]	Assumed impurity	Purity estimate (%)	Recovery[e] (%)
HO_2C-***Oct-Dod-Oct-G(10)***-OH	***G(n)*** *CH*	-CH_2O_2C-	+***Oct***	>95	13
HO_2C-***Oct-Dod-Oct-G(12)***-OH	***G(n)*** *CH*	-CH_2O_2C-	Lactone	84	49
HO_2C-***Oct-Dod-Oct-G(14)***-OH	***G(n)*** *CH*	-CH_2O_2C-	−***Oct***	>95	38
HO_2C-***Oct-Dod-Oct-G(16)***-OH	***G(n)*** *CH*	-CH_2O_2C-	+***Oct***	>95	34
HO_2C-***G(12)-Oct-Dod-Oct***-OH	***G(n)*** *CH*	-CH_2O_2C-	Lactone	92	37
HO_2C-***Oct-Oct-Dod-G(12)***-OH	***G(n)*** *CH*	-$CH_2O_2CCF_3$	TFA	76	<5
HO_2C-***Dod-Oct-Oct-G(12)***-OH	***G(n)*** *CH*	-$CH_2O_2CCF_3$	TFA	55	24
HO_2C-***Oct-Oct-Oct-G(12)***-OH	***G(n)*** *CH*	-$CH_2O_2CCF_3$	TFA	53	18
HO_2C-***Dod-Dod-Dod-G(12)***-OH	***G(n)*** *CH*	-CH_2O_2C-	−***Oct***	89	24
HO_2C-***Dod-Dod-Oct-G(12)***-OH	***G(n)*** *CH*	-CH_2O_2C-	−***Oct***	91	18
HO_2C-***Oct-Dod-Dod-G(12)***-OH	***G(n)*** *CH*	-CH_2O_2C-	−***Oct***	76	9
HO_2C-***Oct-Dod-Oct-Lau***-OH	***Lau*** *CH*	-CH_2O_2C-	+***Oct***	78	81
HO_2C-***Oct-Dod-Oct-Oleate***[b]	-*CH*=*CH*-	-CH_2O_2C-	+***Oct***	91	<5
HO_2C-***Hex-Oct-Hex-Oct-G(12)***-OH	***G(n)*** *CH*	-CH_2O_2C-	−***Oct***	>95	8
HO_2C-***Lau-Oct-Dod-Oct-G(12)***-OH	***G(n)*** *CH*	-CH_2O_2C-	+***Lau***	70	<5
HO_2C-***Ole-Oct-Dod-Oct-G(12)***-OH	***G(n)*** *CH*	-CH_2O_2C-	−***Oct***	>95	7
HO_2C-***Oct-G(12)-Oct-Dod-Oct***-OH	***G(n)****CH*	-CH_2O_2C-	lactone	>95	40

[a] 300 MHz ^{1}H NMR spectra in $CDCl_3$. Integration of the probe signal relative to the reference signal. See text for discussion of the purity estimate protocol. [b] Hydroxy terminus of HO_2C-***Oct-Dod-Oct***-OH esterified with oleic acid. [c] ***G(n)*** *CH* δ 4.55 (1H), ***Lau*** *CH* δ 2.55 (1H), -*CH*=*CH*- δ 5.33 (2H). [d] -CH_2O_2C- δ 4.05–3.9, -$CH_2O_2CCF_3$ δ 4.35. [e] Yield of isolated product as a percentage of the potential yield based on the starting resin capacity.

HO_2C-***Lau-Oct-Dod-Oct-G(12)***-OH is a more significant impurity in the isolated sample of this compound.

It is important to consider how the impurities arise and what, if anything, can be done to reduce or eliminate them from the isolated products. It is likely that deletions are the result of incomplete coupling during synthesis, although loss of a terminal unit during acidic cleavage is a potential contributor as well. No product due to "deletion" of ***G(n)*** units was observed by MS, but incomplete coupling of the terminal ***G(12)*** unit is a potential source of the trifluoroacetate esters directly detected in three cases (Table 2). These could also arise as decomposition products during the TFA cleavage step. The gel filtration process used to clean up the samples is capable of removing lower molecular weight impurities, and the yield of recovered products is moderate to low in all cases, so it is possible that acidic decomposition occurs in all cases and the gel filtration effectively removes the products in most cases. Our protocol of isolating a defined fraction has the potential to capture somewhat different "cuts" of mixtures that differ in the hydrodynamic radii of the components. The presence of macrocyclic lactones in some samples suggests a role for acid-catalyzed decomposition as well, and also indicates that the gel filtration protocol in at least these cases is recovering components that are significantly smaller than the targets.

The addition sequences are potentially due to impurity hydroxyacids in the building blocks used for coupling. Every effort was made to ensure high purity and all spectroscopic techniques indicated such impurities were very small or entirely absent. Even so, a few percent would be expected to propagate into the products with the potential to produce some detectable addition sequences. This source is very unlikely to reduce purity below 90%. An alternative is addition by transesterification during acidic cleavage. The addition products are larger than the expected target, so would not be expected to be removed by gel filtration.

What are the implications of the type and quantity of the impurities in the samples for the proposed survey of structure–activity relationships? Our previous study showed that linear oligomers lacking a ***G(12)*** unit were quite inactive, so impurities such as the TFA esters are probably inactive and would not contribute to an observed transport.[11] Similarly, it is unlikely that the lactone impurities are active transporters. Shorter sequences that do carry a terminal ***G(n)*** unit have potential act as detergents, so conclusions about significant activity from these samples will have to be tempered by this factor. In cases where the purity is significantly below 90%, some correction to the concentration will be required. The addition sequences pose the most serious problems as their activity cannot be ruled out, so significant activity from samples containing relatively large amounts of this type of impurity will require careful scrutiny.

Conclusions

The goal of this report is to examine the solid-phase synthesis of oligoester ion-channel candidates with a focus on whether or not the methodology developed constitutes a reliable protocol for the (semi-)automated preparation of a library of compounds. In all cases, the desired target was formed, usually as the predominant species. However, there are signs that the acidic cleavage used to remove the products from the resin gives rise to transesterification. In some cases the amounts of these materials is significant in the recovered products. Although these impurities may ultimately prove to be inactive, their repeated presence in the samples suggests that the methodology will require additional refinement before it can be reliably used to prepare a high quality library.

Experimental

General

All reagents were obtained from commercial sources and were used without further purification unless noted otherwise. Dry THF was dried over sodium and benzophenone and distilled. Thin layer chromatography was performed on Macherey-Nagel polygram sil/UV254 for TLC plate. Column chromatography was performed on silica gel (grade 60, 60–200 mesh). Standard

coupling, deprotection, and cleavage conditions on Wang resin were previously reported.[11] The coupling cycles for HO_2C-***Lau***-OTBDMS and HO_2C-***Ole***-OTBDMS onto Wang resin were 8, 16, and 16 hours.

6-(Tetrahydro-pyran-2-yloxy)-hexanoic acid (HO_2C-*Hex*-OThp). To a stirred solution of caprolactone (20 mL, 0.18 mol) in dioxane (80 mL) under an ice bath 30 mL NaOH (8 M) was added. Allow the solution to warm to room temperature over 2.5 hours and then quenched with 40 mL HCl (6 M). The aqueous solution was extracted with $CHCl_3$ (2 × 100 mL). The organic layer was washed with 100 mL water, dried with Na_2SO_4 and concentrated *in vacuo* to yield an oil (8.83 g) (partial ^{1}H NMR (300 MHz) consistent with HO_2C-***Hex***-OH: 3.61 t, J= 6.63 Hz; 2.32, t, J= 6.63 Hz). The crude product and *p*-TsOH (1.27 g, 7.4 mmol) was dissolved in THF (200 mL). While this solution was stirred under an ice bath, DHP (6.4 mL, 0.07 mol) was added. The resulting solution was stirred for four hours and allowed to warm to ambient temperature afterwhich ether (200 mL) was added. The organic solution was then washed with water (2 × 100 mL) and dried with $MgSO_4$. The crude product was purified on a silica gel column (810 g, 5 cm ID x 85 cm) with the eluent DCM:ether (3:1) to yield a clear, colorless oil identified as HO_2C-***Hex***-OThp (9.07 g, 22% yield from caprolactone).^{1}H NMR (500 MHz, $CDCl_3$): 1.38–1.83 (m, 14H), 2.34 (t, 2H, J= 7.4 Hz), 3.35–3.39 (m, 1H), 3.46–3.50 (m, 1H), 3.69–3.74 (m, 1H), 3.82–3.86 (m, 1H), 4.55–4.56 (m, 1H); ^{13}C NMR (125.75 MHz, $CDCl_3$): 19.8, 24.7, 25.7, 26.0, 29.6, 31.0, 34.1, 62.6, 67.5, 99.1, 179.5. HREI: Calcd for $C_{11}H_{19}O_4^+$ [M–H$^+$]: 215.1283 Found: 215.1278.

2-(*tert*-Butyldimethylsilanyloxymethyl)-dodecanoic acid (HO_2C-*Lau*-OTBDMS). To a stirred solution under a dry ice and ethanol bath of THF (180 mL) and diisopropylamine (8.2 mL) was added butyl lithium (39 mL, 1.6 M). The solution was stirred for 10 minutes at 0 °C. A THF solution (30 mL) of lauric acid (5.86 g, 29.2 mmol) was added dropwise such that the solution was below 0 °C. Upon the full addition the mixture was heated to 35 °C for 1.5 hours while formaldehyde was bubbled in (by a thermal decomposition of 13.6 g of paraformaldehyde). The mixture was then cooled below 10 °C and then 100 mL of 1 M HCl was added. To the mixture 500 mL of THF was added and the aqueous layer was removed. The organic layer was then washed with 300 mL water dried with Na_2SO_4 and concentrated *in vacuo.* The crude product was purified on a silica gel column (53 g, 3 cm ID x 30 cm) using petroleum ether: ethyl acetate (4:1) to yield a clear, colorless oil (0.617 g, 9%). The pure oil was dissolved in 50 mL DCM and imidazole (0.73 g, 4 eq.), *tert*-butylchlorodimethylsilane (0.81 g, 2 eq.) was added. The mixture was stirred for 18 hours. To the mixture, a 2 M K_2CO_3 solution (16 mL) was added with 16 mL THF and 64 mL MeOH and stirred for 5 hours. DCM (400 mL) was then added and washed with 100 mL HCl (1M) and water (100 mL). The organic layer was dried with $MgSO_4$ and *in vacuo.* The crude product was purified on a silica gel column (53 g, 3 cm ID x 30 cm) using petroleum ether: ethyl acetate (4:1) to yield HO_2C-***Lau***-OTBDMS as a clear, colorless oil (0.603 g, 6%). ^{1}H NMR (500 MHz, $CDCl_3$): 0.04 and 0.05 (2 singlets, 6H), 0.84–0.98 (m, 12H), 1.23–1.33 (m, 16H), 1.39–1.64 (m, 2H), 2.52–2.57 (m, 1H), 3.70–3.78 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): –5.34, –5.29, 14.3, 18.4, 22.9, 26.0, 27.4, 28.4, 29.5, 29.6, 29.76, 29.79, 29.8, 32.1, 48.3, 64.0, 179.7. IR: 1710 cm^{-1} (s). HRLSIMS: Calcd for $C_{19}H_{39}O_3Si^+$ [M–H + Na$^+$]: 366.2566 Found: 366.2545.

2-(*tert*-Butyldimethylsilanyloxymethyl)-octadec-9-enoic acid (HO_2C-*Ole*-OTBDMS). To a stirred solution under a dry ice and ethanol bath of THF (180 mL) and diisopropylamine (8.2 mL) was added butyl lithium (39 mL, 1.6 M). The solution was stirred for 10 minutes at 0 °C. A THF solution (30 mL) of lauric acid (8.26 g, 29.2 mmol) was added dropwise such that the solution was below 0 °C. Upon the full addition the mixture was heated to 35 °C for 1.5 hours while formaldehyde was bubbled in (by a thermal decomposition of 13.8 g of paraformaldehyde). The mixture was then cooled below 10 °C and then 100 mL of 1 M HCl was added. To the mixture 500 mL of THF was added and the aqueous layer was removed. The organic layer was then washed with 3 × 100 mL water dried with 100 mL brine and concentrated *in vacuo.* The crude product was purified on a silica gel column (323 g) using petroleum ether: ethyl acetate (4:1) to yield a clear, colorless oil (0.471 g, 5%). The pure oil was dissolved in 50 mL DCM and imidazole (0.41 g, 4 eq.), *tert*-butylchlorodimethylsilane (0.454 g, 2 eq.) was added. The mixture was stirred for 17 hours. To the mixture, a 2 M K_2CO_3 solution (8 mL) was added with 8 mL THF and 32 mL MeOH and stirred for 7 hours. DCM (450 mL) was then added and washed with 100 mL HCl (1M) and water (200 mL). The organic layer was dried with $MgSO_4$ and *in vacuo.* The crude product was purified on a silica gel column (53 g, 3 cm ID x 30 cm) using petroleum ether: ethyl acetate (4:1) to yield HO_2C-***Ole***-OTBDMS as a clear, colorless oil (0.901 g, 7%). ^{1}H NMR (500 MHz, $CDCl_3$): 0.035 and 0.039 (2 singlets, 6H), 0.73–0.98 (m, 12H), 1.21–1.41 (m, 18H), 1.43–1.49 (m, 1H), 1.57–1.62 (m, 1H), 2.00–2.03 (m, 4H), 2.52–2.57 (m, 1H), 3.70–3.78 (m, 2H), 5.29–5.36 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): -5.34, –5.29, 14.3, 18.4, 22.8, 22.9, 25.9, 26.0, 27.36, 27.38, 28.4, 29.3, 29.4, 29.6, 29.67, 29.7, 29.8, 29.9, 30.0, 31.8, 32.1, 48.3, 64.0, 129.9, 130.2, 179.8. IR: 1709 cm^{-1} (s). HRLSIMS: Calcd for $C_{25}H_{50}O_3SiNa^+$ [M + Na$^+$]: 449.3427 Found: 449.3435.

3-(*tert*-Butyldimethylsiloxy)-5-oxo-5-(decyloxy) pentanoic acid (G(10)). To a stirred toluene solution (20 mL) of 3-(*tert*-butyldimethylsilyloxy)glutaric anhydride (0.97 g, 3.96 mmol) was added 1-decanol (0.75 mL, 3.92 mmol). The solution was stirred at reflux overnight and the solvent was removed under reduced pressure to give a crude product. The crude product was dissolved in pentane (80 mL) and cooled in a dry ice/ethanol bath for 10 minutes before filtration. The filtrate was cooled again in a dry ice/ethanol bath for 10 minutes and then filtered. This crystallization was repeated until no more solids were produced. The filtrate was concentrated under reduced pressure to afford a colorless oil identified as **G(10)** (1.49 g, 93%). ^{1}H NMR (500 MHz, $CDCl_3$): 0.04–0.06 (m, 6H), 0.82–0.89 (m, 12H), 1.24 (br, 14H), 1.57–1.61 (m, 2H), 2.53–2.64 (m, 4H), 4.01–4.07 (m, 2H), 4.52 (quintet, 1H, J = 6 Hz); ^{13}C NMR (125.77 MHz, $CDCl_3$): –4.8, –4.7, 14.3, 18.1, 22.9, 25.8, 26.1, 28.8, 29.45, 29.50, 29.71, 29.73, 32.1, 42.4, 42.6, 65.1, 66.3, 171.2, 177.0. IR: 1736 cm^{-1} (s), 1711 cm^{-1} (s). HRLSIMS: Calcd for $C_{21}H_{42}O_5SiNa^+$ [M + Na$^+$]: 425.2699 Found: 425.2717.

3-(*tert*-Butyldimethylsiloxy)-5-oxo-5-(tetradecyloxy) pentanoic acid (G(14)). To a stirred toluene solution (20 mL) of 3-(*tert*-butyldimethylsilyloxy)glutaric anhydride (1.92 g, 7.86 mmol) was

added 1-tetradecanol (1.65 g, 7.68 mmol). The solution was stirred at reflux overnight and the solvent was removed under reduced pressure to give a crude product. The crude product was dissolved in pentane (80 mL) and cooled in a dry ice/ethanol bath for 10 minutes before filtration. The filtrate was cooled again in a dry ice/ethanol bath for 10 minutes and then filtered. This crystallization was repeated until no more solids were produced. The filtrate was concentrated under reduced pressure to afford a colorless oil identified as **G(14)** (2.514 g, 71%). ^{1}H NMR (500 MHz, $CDCl_3$): 0.04–0.08 (m, 6H), 0.82–0.89 (m, 12H), 1.23 (br, 22H), 1.57–1.62 (m, 2H), 2.53–2.64 (m, 4H), 4.01–4.08 (m, 2H), 4.52 (quintet, 1H, $J = 6$ Hz); ^{13}C NMR (125.77 MHz, $CDCl_3$): –4.8, –4.7, 14.3, 18.1, 22.9, 25.9, 26.1, 28.8, 29.5, 29.6, 29.72, 29.79, 29.86, 29.88, 29.9, 32.1, 42.4, 42.6, 65.1, 66.3, 171.2, 177.0. IR: 1738 cm^{-1} (s), 1713 cm^{-1} (s). HRLSIMS: Calcd for $C_{25}H_{50}O_5SiNa^+$ [M + Na$^+$]: 481.3325 Found: 481.3307.

3-(*tert*-Butyldimethylsiloxy)-5-oxo-5-(hexadecyloxy) pentanoic acid (G(16)). To a stirred toluene solution (20 mL) of 3-(*tert*-butyldimethylsilyloxy)glutaric anhydride (1.9 g, 7.9 mmol) was added 1-hexadecanol (1.48 g, 6.10 mmol). The solution was stirred at reflux overnight and the solvent was removed under reduced pressure to give a crude product. The crude product was dissolved in pentane (80 mL) and cooled in a dry ice/ethanol bath for 10 minutes before filtration. The filtrate was cooled again in a dry ice/ethanol bath for 10 minutes and then filtered. This crystallization was repeated until no more solids were produced. The filtrate was concentrated under reduced pressure to afford a colorless oil identified as **G(16)** (0.977 g, 33%). ^{1}H NMR (500 MHz, $CDCl_3$): 0.04–0.08 (m, 6H), 0.82–0.89 (m, 12H), 1.23–1.32 (m, 26H), 1.57–1.63 (m, 2H), 2.54–2.65 (m, 4H), 4.01–4.08 (m, 2H), 4.52 (quintet, 1H, $J = 6$ Hz); ^{13}C NMR (125.77 MHz, $CDCl_3$): –4.8, –4.7, 14.3, 18.1, 22.9, 25.9, 26.1, 28.8, 29.5, 29.6, 29.73, 29.80, 29.88, 29.89, 29.92, 32.2, 42.3, 42.5, 65.1, 66.4, 171.2, 176.2. IR: 1738 cm^{-1} (s), 1713 cm^{-1} (s). HRLSIMS: Calcd for $C_{27}H_{55}O_5SiNa^+$ [M + Na$^+$]: 487.3813 Found: 487.3813.

HO_2C-*Oct-Dod-Oct-G(10)*-OH. Prepared using the standard conditions on Wang resin (0.23 g, 0.17 mmol) to produce HO_2C-***Oct-Dod-Oct-G(10)*-OH**

(18 mg; 0.023 mmol, yield 13%). ^{1}H NMR (500 MHz, $CDCl_3$): 0.85 (t, J= 7.0 Hz, 3H), 1.20–1.70 (m, 56H), 2.26, 2.27, and 2.32 (overlapping t, J= 7.5 Hz, 6H), 2.50–2.53 (m, 4H), 4.03, 4.075 and 4.078 (overlapping t, J= 6.7 Hz, 8H), 4.40–4.46 (m, 1H). ^{13}C NMR (125.75 MHz, $CDCl_3$): 14.3, 22.9, 24.8, 25.1, 25.2, 25.9, 25.96, 26.08, 26.13, 28.68, 28.75, 28.8, 28.9, 29.05, 29.07, 29.1, 29.2, 29.36, 29.43, 29.45, 29.5, 29.6, 29.70, 29.72, 32.1, 34.0, 34.5, 34.6, 40.9, 64.5, 64.7, 65.0, 65.1, 65.2, 172.10, 172.13, 174.2, 174.2, 178.7. HRLSIMS: Calcd for $NaC_{43}H_{78}O_{11}^+$ [M + Na$^+$]: 793.5442 Found: 793.5451.

HO_2C-*Oct-Dod-Oct-G(14)*-OH. Prepared using the standard conditions on Wang resin (0.20 g, 0.20 mmol) to produce HO_2C-***Oct-Dod-Oct-G(14)*-OH** (63.1 mg; 0.076 mmol, yield 38%). ^{1}H NMR (500 MHz, $CDCl_3$): 0.85 (t, J= 7.0 Hz, 3H), 1.20–1.70 (m, 64H), 2.253, 2.26, and 2.31 (overlapping t, J= 7.5 Hz each, 6H), 2.50–2.53 (m, 4H), 4.02, 4.066, and 4.069 (overlapping t, J= 6.7 Hz each, J= 1.0 Hz, 8H), 4.40–4.46 (m, 1H). ^{13}C NMR (125.75 MHz, $CDCl_3$): 14.3, 22.9, 24.8, 25.0, 25.2, 25.86, 25.93, 26.06, 26.10, 28.65, 28.73, 28.77, 28.83, 29.02, 29.05, 29.11, 29.15, 29.3, 29.4, 29.5, 29.6, 29.67, 29.68, 29.75, 29.82, 29.84, 29.86, 32.1, 34.1, 34.5, 34.6, 40.9, 64.5, 64.7, 65.0, 65.1, 65.2, 172.08, 172.10, 174.1, 174.2, 179.1. HRLSIMS: Calcd for $NaC_{47}H_{86}O_{11}^+$ [M + Na$^+$]: 849.6068 Found: 849.6085.

HO_2C-*Oct-Dod-Oct-G(16)*-OH. Prepared using the standard conditions on Wang resin (0.20 g, 0.21 mmol) to produce HO_2C-***Oct-Dod-Oct-G(16)*-OH** (58.7 mg; 0.071 mmol, yield 34%). ^{1}H NMR (500 MHz, $CDCl_3$): 0.86 (t, J= 7.0 Hz, 3H), 1.18–1.70 (m, 76H), 2.26, 2.27, and 2.32 (overlapping t, J= 7.5 Hz, 6H), 2.51–2.53 (m, 4H), 4.03 (t, J= 6.7 Hz, 4H), 4.08 (t, J= 6.7 Hz, 4H), 4.40–4.46 (m, 1H). ^{13}C NMR (125.75 MHz, $CDCl_3$): 14.3, 22.9, 24.8, 25.1, 25.2, 25.9, 25.96, 26.09, 26.13, 28.69, 28.76, 28.80, 28.86, 29.06, 29.08, 29.14, 29.19, 29.23, 29.4, 29.5, 29.57, 29.63, 29.70, 29.72, 29.79, 29.88, 29.91, 32.1, 33.9, 34.5, 34.6, 40.9, 64.5, 64.7, 65.0, 65.1, 65.3, 172.11, 172.14, 174.17, 174.23, 178.1. HRLSIMS: Calcd for $NaC_{49}H_{90}O_{11}^+$ [M + Na$^+$]: 877.6381 Found: 877.6374.

HO_2C-*Oct-Oct-Dod-G(12)*-OH. Prepared using the standard conditions on Wang resin (0.23 g, 0.53 mmol) to produce HO_2C-***Oct-Oct-Dod-G(12)*-OH** (6 mg; 7.5 μmol, yield 1%). ^{1}H NMR (500 MHz, $CDCl_3$): 0.86 (t, J= 7.0 Hz, 3H), 1.22–1.72 (overlapping signals, 58H), 2.265 and 2.267 (overlapping t, J= 7.5 Hz each, 4H), 2.33 (t, J= 7.5 Hz, 2H), 2.50–2.57 (m, 4H), 4.030 and 4.032 (overlapping t, J= 6.7 Hz each, 4H), 4.08 (t, J= 6.8 Hz, 4H), 4.40–4.46 (m, 1H). ^{13}C NMR (125.75 MHz, $CDCl_3$): 14.3, 22.9, 24.8, 25.07, 25.10, 25.11, 25.9, 25.96, 26.09, 28.6, 28.69, 28.76, 28.79, 29.06, 29.09, 29.13, 29.18, 29.22, 29.44, 29.48, 29.6, 29.72, 29.78, 29.8, 29.9, 32.1, 33.9, 34.51, 34.54, 40.9, 64.5, 64.6, 65.0, 65.1, 65.3, 172.11, 172.14, 174.10, 174.17, 177.96. HRLSIMS: Calcd for $NaC_{45}H_{82}O_{11}^+$ [M + Na$^+$]: 821.5755 Found: 821.5753.

HO_2C-*Dod-Oct-Oct-G(12)*-OH. Prepared using the standard conditions on Wang resin (0.22 g, 0.50 mmol) to produce HO_2C-***Dod-Oct-Oct-G(12)*-OH** (3.7 mg;.015 mmol, yield 3%). ^{1}H NMR (500 MHz, $CDCl_3$): 0.86 (t, J= 7.0 Hz, 3H), 1.24–1.72 (overlapping signals, 60H), 2.25–2.69 (m, 8H), 4.03, 4.04, and 4.08 (overlapping t, J= 6.7 Hz each, 8H), 4.40–4.46 (m, 1H). ^{13}C NMR (125.75 MHz, $CDCl_3$): 14.3, 22.9, 24.9, 25.07, 25.12, 25.2, 25.91, 25.98, 26.10, 26.12, 28.70, 28.77, 28.81, 28.86, 29.06, 29.11, 29.20, 29.23, 29.38, 29.40, 29.45, 29.56, 29.63, 29.7, 29.8, 29.85, 29.93, 31.1, 32.1, 33.65, 33.67, 34.5, 34.6, 40.9, 64.6, 64.7, 65.0, 65.1, 65.3, 172.11, 172.15, 174.1. HRLSIMS: Calcd for $NaC_{45}H_{82}O_{11}^+$ [M + Na$^+$]: 821.5755 Found: 821.5766.

HO_2C-*Oct-Oct-Oct-G(12)*-OH. Prepared using the standard conditions on Wang resin (0.319 g, 0.24 mmol) to produce HO_2C-***Oct-Oct-Oct-G(12)*-OH** (12 mg; 0.019 mmol, yield 8%). ^{1}H NMR (500 MHz, $CDCl_3$): 0.86 (t, J= 7.0 Hz, 3H), 1.20–1.70 (m, 50H), 2.20–2.35 (overlapping signals, 10H), 2.5 (d, 4H), 4.04 and 4.08 (overlapping t, J= 6.5 Hz, 8H), 4.42–4.46 (m, 1H). ^{13}C NMR (125.75 MHz, $CDCl_3$): 14.3, 22.9, 24.8, 25.08, 25.13, 25.91, 25.97, 26.1, 28.69, 28.77, 28.79, 29.06, 29.09, 29.12, 29.2, 29.5, 29.6, 29.7, 29.79, 29.86, 29.94, 32.1, 33.6, 34.5, 34.6, 40.9, 64.5, 64.6, 65.0, 65.1, 65.3, 172.1, 174.1, 174.2. HRLSIMS: Calcd for $NaC_{41}H_{74}O_{11}^+$ [M + Na$^+$]: 765.5129 Found: 765.5121.

HO_2C-*Dod-Dod-Dod-G(12)*-OH. Prepared using the standard conditions on Wang resin (0.242 g, 0.55 mmol) to produce HO_2C-***Dod-Dod-Dod-G(12)*-OH** (39 mg; 0.13 mmol, yield 24%). ^{1}H NMR (500 MHz, $CDCl_3$): 0.85 (t, J= 7.0 Hz, 3H), 1.22–1.70

(m, 70H), 2.25 and 2.30 (overlapping t, J= 7.5 Hz each, 6H), 2.50–2.57 (m, 4H), 4.02 and 4.07 (overlapping t, J= 6.8 Hz, 8H), 4.40–4.45 (m, 1H). ^{13}C NMR (125.75 MHz, $CDCl_3$): 14.3, 22.9, 24.9, 25.2, 26.06, 26.11, 28.7, 28.8, 29.2, 29.3, 29.41, 29.43, 29.52, 29.57, 29.60, 29.65, 29.67, 29.68, 29.75, 29.80, 29.82, 32.1, 34.1, 34.6, 40.9, 64.6, 65.0, 65.20, 65.21, 172.1, 174.2, 179.2. HRLSIMS: Calcd for $NaC_{53}H_{98}O_{11}^+$ [M + Na^+]: 933.7007 Found: 933.7019.

HO_2C-*Dod-Dod-Oct-G(12)*-OH. Prepared using the standard conditions, on Wang resin (0.24 g, 0.54 mmol) to produce HO_2C-***Dod-Dod-Oct-G(12)***-OH (27 mg;.097 mmol, yield 18%). ^{1}H NMR (500 MHz, $CDCl_3$): 0.85 (t, J= 7.0 Hz, 3H), 1.23–1.70 (overlapping signals, 60H), 2.261, 2.264, and 2.32 (overlapping t, J = 7.5 Hz each, 6H), 2.51–2.58 (m, 4H), 4.03 and 4.08 (overlapping t, J = 6.7 Hz each, 8H), 4.40–4.46 (m, 1H). ^{13}C NMR (125.75 MHz, $CDCl_3$): 14.3, 22.9, 24.9, 25.1, 25.2, 25.9, 26.08, 26.13, 28.68, 28.75, 28.85, 29.05, 29.18, 29.26, 29.36, 29.43, 29.45, 29.54, 29.58, 29.63, 29.66, 29.70, 29.77, 29.82, 29.84, 32.1, 34.1, 34.5, 34.6, 40.9, 64.6, 64.7, 65.0, 65.1, 65.2, 172.09, 172.11, 174.14, 174.3, 179.0. HRLSIMS: Calcd for $NaC_{49}H_{90}O_{11}^+$ [M + Na^+]: 877.6381 Found: 877.6384.

HO_2C-*Oct-Dod-Dod-G(12)*-OH. Prepared using the standard conditions on Wang resin (0.305 g, 0.23 mmol) to produce HO_2C-***Oct-Dod-Dod-G(12)***-OH (17 mg; 0.020 mmol, yield 9%). ^{1}H NMR (500 MHz, $CDCl_3$): 0.85 (t, J= 6.8 Hz, 3H), 1.20–1.63 (m, 62H), 2.26 and 2.31 (overlapping t, J= 7.5 Hz each, 4H), 2.49–2.56 (m, 4H), 4.02 and 4.07 (overlapping t, J= 6.8 Hz, 8H), 4.40–4.46 (m, 1H). ^{13}C NMR (125.75 MHz, $CDCl_3$): 14.3, 22.9, 24.8, 24.9, 25.2, 25.9, 26.07, 26.12, 28.73, 28.78, 28.8, 29.06, 29.1, 29.21, 29.25, 29.34, 29.41, 29.44, 29.53, 29.58, 29.61, 29.66, 29.68, 29.69, 29.76, 29.81, 29.82, 32.1, 34.06, 34.13, 34.51, 34.58, 34.60, 40.9, 64.5, 64.6, 65.0, 65.21, 65.22, 172.2, 174.22, 174.3, 179.1, 179.2. HRLSIMS: Calcd for $NaC_{49}H_{90}O_{11}^+$ [M + Na^+]: 877.6381 Found: 877.6382.

HO_2C-*Oct-Dod-Oct-Lau*-OH. Prepared using the standard conditions on Wang resin (0.105 g, 0.11 mmol) to produce HO_2C-***Oct-Dod-Oct-Lau***-OH (64 mg, 89.8 μmol, yield 81%). ^{1}H NMR (500 MHz, $CDCl_3$): 0.86 (t, J= 7.0 Hz, 3H), 1.12–1.80 (overlapping signals, 51H), 2.25–2.45 (m, 8H), 2.52–2.58 (m, 1H), 3.71–3.90 (m, 2H), 4.01–4.2 (overlapping signals, 8H). ^{13}C NMR (125.75 MHz, $CDCl_3$): 13.9, 14.3, 20.0, 22.9, 24.2, 24.9, 25.0, 25.08, 25.12, 25.2, 25.8, 25.9, 26.0, 26.1, 26.6, 27.2, 27.5, 28.5, 28.75, 28.77, 28.8, 28.9, 29.0, 29.1, 29.17, 29.20, 29.24, 29.37, 29.47, 29.54, 29.65, 29.71, 29.75, 29.78, 29.80, 29.81, 29.92, 31.1, 32.1, 32.9, 33.9, 34.3, 34.5, 34.55, 34.6, 45.2, 47.8, 59.2, 63.4, 64.50, 64.53, 64.7, 64.9, 173.7, 174.18, 174.22, 175.86, 177.5. HRLSIMS: Calcd for $NaC_{41}H_{76}O_9^+$ [M + Na^+]: 735.5387 Found: 735.5374.

HO_2C-*Oct-Dod-Oct-Oleate*. Prepared using the standard conditions, on Wang resin (0.105 g, 1.1 mmol) to produce HO_2C-***Oct-Dod-Oct-Oleate*** (2 mg, 3 μmol, yield 0.2%). ^{1}H NMR (500 MHz, $CDCl_3$): 0.86 (t, J= 7.0 Hz, 3H), 1.12–1.80 (overlapping signals, 66H), 1.99 (q, 3H), 2.25–2.35 (overlapping signals, 8H), 4.02–4.05 (overlapping signals, 6H), 5.31-–5.33 (overlapping signals, 2H). ^{13}C NMR (125.75 MHz, $CDCl_3$): 14.3, 22.9, 24.8, 25.1, 25.2, 26.0, 26.1, 26.6, 27.4, 27.5, 28.8, 28.9, 29.08, 29.12, 29.24, 29.34, 29.37, 29.40, 29.46, 29.47, 29.55, 29.65, 29.71, 29.74, 29.92, 30.0, 31.1, 32.1, 33.7, 34.55, 34.61, 64.49, 64.54, 64.7, 64.9, 96.4, 130.0, 130.2, 174.18, 174.22, 174.3. HRLSIMS: Calcd for $NaC_{46}H_{84}O_8^+$ [M + Na^+]: 787.6064 Found: 787.6042.

HO_2C-*Hex-Oct-Hex-Oct-G(12)*-OH. Prepared using the standard conditions on Wang resin (0.214 g, 0.16 mmol) to produce HO_2C-***Hex-Oct-Hex-Oct-G(12)***-OH (11.3 mg; 13.3 μmol, yield 8%). ^{1}H NMR (500 MHz, $CDCl_3$): 0.86 (t, J= 7.0 Hz, 3H), 1.24–1.68 (overlapping signals, 52H), 2.25–2.37 (m, 8H), 2.52–2.53 (m, 4H), 4.01–4.11 (m, 10H), 4.40–4.46 (m, 1H). ^{13}C NMR (125.75 MHz, $CDCl_3$): 14.3, 22.9, 24.1, 24.4, 24.5, 24.6, 24.7, 24.8, 25.1, 25.5, 25.5, 25.6, 25.69, 25.72, 25.75, 25.82, 25.90, 25.94, 25.97, 26.1, 28.41, 28.45, 28.55, 28.68, 28.76, 28.96, 29.07, 29.1, 29.2, 29.4, 29.6, 29.7, 29.78, 29.84, 29.85, 32.1, 33.8, 33.9, 34.4, 34.5, 40.9, 41.0, 64.2, 64.3, 64.4, 64.6, 64.7, 64.8, 65.0, 65.1, 65.3, 172.05, 172.1, 172.2, 173.8, 173.8, 173.9, 174.1, 174.2, 177.8. HRLSIMS: Calcd for $NaC_{45}H_{80}O_{13}^+$ [M + Na^+]: 851.5497 Found: 851.5481.

HO_2C-*Lau-Oct-Dod-Oct-G(12)*-OH. Prepared using the standard conditions on Wang resin (0.222 g, 0.17 mmol) to produce HO_2C-***Lau-Oct-Dod-Oct-G(12)***-OH (6.7 mg; 6.6 μmol, yield 4%). ^{1}H NMR (500 MHz, $CDCl_3$): 0.86 (t, J= 7.0 Hz, 12H), 1.12–1.71 (overlapping signals, 153H), 2.25–2.34 (m, 10H), 2.52–2.54 (m, 4H), 2.67–2.80 (m, 2H), 4.01–4.3 (overlapping signals, 14H), 4.40–4.45 (m, 1H). ^{13}C NMR (125.75 MHz, $CDCl_3$): 14.3, 22.9, 24.8, 25.0, 25.09, 25.14, 25.21, 25.76, 25.85, 25.92, 26.0, 26.10, 26.14, 26.6, 27.2, 28.5, 28.70, 28.74, 28.77, 28.81, 28.87, 28.92, 28.98, 29.05, 29.07, 29.15, 29.20, 29.24, 29.30, 29.36, 29.46, 29.57, 29.60, 29.64, 29.67, 29.71, 29.73, 29.80, 29.85, 29.86, 31.1, 32.1, 32.8, 33.7, 34.27, 34.32, 34.5, 34.6, 34.7, 40.9, 44.6, 45.2, 63.2, 64.49, 64.53, 64.62, 64.7, 65.03, 65.13, 65.3, 172.1, 172.2, 173.7, 174.2, 174.6, 176.2. HRLSIMS: Calcd for $NaC_{45}H_{82}O_{11}^+$ [M + Na^+]: 1033.7531 Found: 1033.7584.

HO_2C-*Ole-Oct-Dod-Oct-G(12)*-OH. Prepared using the standard conditions on Wang resin (0.232 g, 0.17 mmol) to produce HO_2C-***Ole-Oct-Dod-Oct-G(12)***-OH (13.5 mg;.015 mmol, yield 7%). ^{1}H NMR (500 MHz, $CDCl_3$): 0.85 (t, J= 7.0 Hz, 6H), 1.22–1.71 (overlapping signals, 80H), 1.96–2.00 (overlapping signals, 4H), 2.25–2.34 (m, 7H), 2.52–2.54 (m, 4H), 2.6–2.8 (m, 1H), 4.01–4.09 (overlapping signals, 8H), 4.16–4.23 (m, 2H), 4.40–4.45 (m, 1H), 5.29–5.35 (m, 1H). ^{13}C NMR (125.75 MHz, $CDCl_3$): 14.3, 22.9, 24.8, 25.0, 25.1, 25.2, 25.9, 25.96, 26.09, 26.14, 26.56, 27.2, 27.4, 27.4, 28.5, 28.7, 28.76, 28.80, 28.86, 28.99, 29.06, 29.08, 29.15, 29.19, 29.23, 29.29, 29.36, 29.45, 29.47, 29.53, 29.55, 29.57, 29.64, 29.71, 29.78, 29.84, 29.85, 29.98, 31.1, 32.1, 34.0, 34.29, 34.37, 34.5, 34.60 34.2, 40.9, 44.8, 45.4, 64.4, 64.5, 64.6, 64.7, 65.0, 65.1, 65.3, 129.9b, 130.3, 172.11, 172.13, 173.8, 174.16, 174.23, 174.5, HRLSIMS: Calcd for $NaC_{64}H_{116}O_{13}^+$ [M + Na^+]: 1115.8314 Found: 1115.8287.

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