Synthesis and characterization of a series of novel phenol- and polyphenol-based glycerolipids[1]

Rolf Schmidt, Joseph G. Carrigan, and Christine E. DeWolf

Abstract: A building block approach was used to design a modular synthetic route for the preparation of novel glycerolipids with phenolic and polyphenolic headgroups. Based on this scheme, it is possible to vary the substitution pattern of the headgroup, the stereochemistry of the backbone, and the length of the sidechains. Five glycerolipids with different headgroups and identical backbone stereochemistry and chain length have been prepared.

Key words: glycerolipid, polyphenol, hydrogen bonding, lipid-protein interaction, self-adhering.

Résumé : On a développé une méthode modulaire de synthèse de nouveaux glycérolipides comportant des têtes phénoliques et polyphénoliques. En se basant sur ce schéma, il est possible de faire varier la nature du groupe de tête, la stéréochimie du squelette et la longueur des chaînes latérales. On a préparé cinq glycérolipides dont la stéréochimie du squelette et la longueur de la chaîne sont les mêmes, mais qui diffèrent par la nature de leur groupe de tête.

Mots clés : glycérolipide, polyphénol, liaison hydrogène, interaction lipide-protéine, autoadhérente.

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Introduction

It is well-known that polyphenols bind and precipitate proteins and (or) peptides and can act as antioxidants (Handique and Baruah (1) provide a comprehensive review of natural and synthetic polyphenols). Furthermore, poly(phenol) films have been used as protective coatings for proteins immobilized onto electrodes (2). A novel synthetic lipid, 1,2-dipalmitoylgalloylglycerol (DPGG), has been prepared (3) that incorporates a polyphenol as the headgroup. The authors suggest that this lipid has the potential to exhibit comparable protein-binding properties (4) so that Langmuir–Blodgett films of such lipids could prove useful as biocompatible coatings. Pollastri et al. (3) demonstrated the self-adhesive nature of DPGG bilayers and proposed both strong inter- and intra-bilayer hydrogen bonding between gallic acid headgroups. We have recently shown that DPGG monolayers exhibit strong lateral cohesion and high rigidity, which can also be attributed to lateral hydrogen bonding (5). The influence of hydrogen bonding on monolayer and bilayer phase behaviour has been previously documented for lipids such as phosphatidylethanolamines and cerebrosides (3, 6, 7). To probe and understand the lateral cohesion in monolayers due to a hydrogen bonding network requires systematic chemical modification with respect to hydrogen bonding sites. In contrast to phosphatidylethanolamines and cerebrosides, DPGG provides an ideal template for a library of analogous lipids. We have employed a building block approach to design a modular synthetic route for the preparation of this library of novel glycerolipids with phenolic and polyphenolic headgroups. We report here the preparation of DPGG analogues with headgroups varying in number and position of hydroxyl groups (Fig. 1).

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Results and discussion

The preparation of DPGG in two steps from tri-O-benzylgalloyl chloride and dipalmitoylglycerol has been described in the literature (3). The key features of this synthesis are the use of the benzyl protecting group and the introduction of a side chain bearing glycerol moiety. We report a more modular synthetic route to DPGG and some of its analogues, which allows for easy variation not only of the headgroup (number and position of hydroxyl groups) but also the stereochemistry of the backbone (R or S) and the chemical character of the side chains (chain length, units of unsaturation, functionalization, etc.) (Scheme 1). All of these parameters are known to influence monolayer phase behaviour and more generally, lipid self-assembly properties.

Compounds **3a**, **3c**, and **3e** are commercially available in gram quantities. Compounds **3b** and **3d** were prepared by well-known methods from 3-hydroxybenzoic acid methyl ester and 3,4-dihydroxybenzoic acid, respectively. Therefore, it is easy to alter the headgroup structure of the title compounds by varying the substitution pattern of the starting material. In the first step of the synthesis of the title compounds, phenol-bearing benzoic acids **3** are reacted with a racemic mixture of 2,2-dimethyl-1,3-dioxolane-4-methanol (solketal, a protected glycerol) to give compounds **4**. Importantly, the same procedure could be used to prepare the enantiomerically pure analogues starting from commercially

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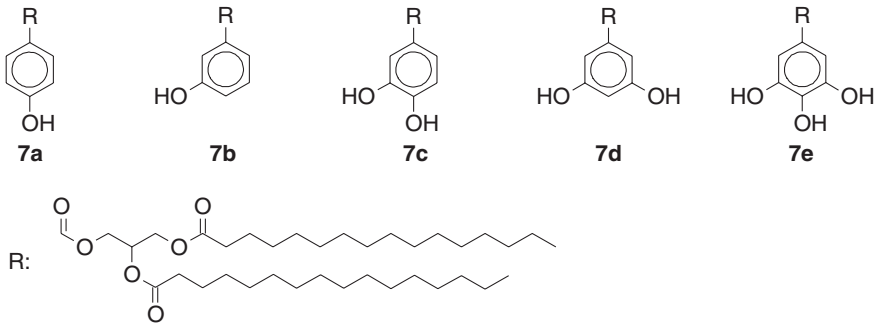
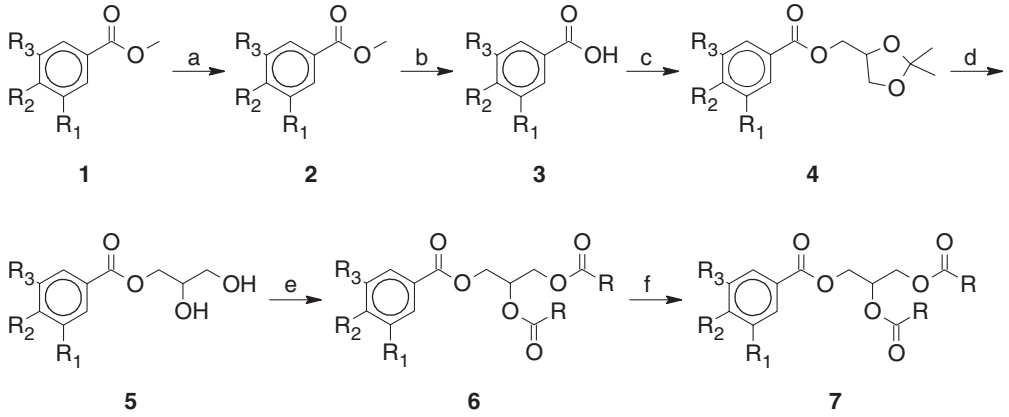
Fig. 1. Chemical structure of DPGG (**7e**) and prepared analogues.



Scheme 1. Reagents: (*a*) BnBr, K_2CO_3, CH_2Cl_2–MeOH, (*b*) KOH, THF–H_2O, (*c*) solketal, 1-methylimidazole, *p*-TsCl, MeCN, (*d*) Amberlyst® 15, MeOH–H_2O, (*e*) hexadecanoic acid, DMAP, EDCI, CH_2Cl_2, (*f*) H_2, 10% Pd–C.



1, 7	R_1	R_2	R_3
a	H	OH	H
b	OH	H	H
c	OH	H	OH
d	OH	OH	H
e	OH	OH	OH

2–6	R_1	R_2	R_3
a	H	OBn	H
b	OBn	H	H
c	OBn	H	OBn
d	OBn	OBn	H
e	OBn	OBn	OBn

available (*R*)-(-)- or (*S*)-(+)-2,2-dimethyl-1,3-dioxolane-4-methanol instead of the racemic mixture, provided that the pH is held between 7 to 8 to retain optical purity (8). The isopropylidene and benzyl protecting groups were chosen from orthogonal sets to provide selective deprotection of the isopropylidene in step d (Fig. 1). The protected benzoates **4** were not isolated, but the glycerol moiety was deprotected by treatment with wet Amberlyst® 15, a strongly acidic resin that allows for easy removal from the reaction mixture by gravity filtration. The advantage of Amberlyst® 15, aside from easy removal, is the fact that the sulfonic residues bound to the resin beads provide significant steric hindrance to prevent ester cleavage (9). Cleavage of the isopropylidene protecting group with I_2 in methanol (10) or under acidic conditions using aqueous acetic acid (11) was not successful. It has to be noted that a similar approach has previously been employed by Schmidt and Blank (12) for the preparation of compounds **4e** and **5e**. However, reaction times are generally much shorter and workup much simpler for our synthetic scheme with similar yields. In the next step, the palmitoyl side chains were introduced by coupling **5** with palmitic acid in the presence of *N*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide hydrochloride (EDCI) and 4-dimethylaminopyridine (DMAP) (13, 14). This acylation method was shown to be superior to the coupling of acid chlorides or anhydrides with the corresponding aliphatic acids (15). Furthermore, excess EDCI and the 1-(3-dimethylamino-propyl)-3-ethyl-urea formed during the reaction can easily be removed from the reaction mixture by liquid–liquid extraction because of their good solubility in water. The reaction has also been successfully carried out with the corresponding myristoyl and stearoyl side chains (data not shown). In addition, it is possible to selectively introduce two dissimilar side chains (e.g., palmitoyl and stearoyl) by successive coupling with the respective acids (15, 16).

Diacetylation in the first step as well as 1,2-acyl migration in the second step can be avoided by maintaining the reaction temperature between 0 and 20 °C (15). The benzyl protecting group is removed by catalytic hydrogenation under moderate pressure in the final step. The reaction time in-

creases with the number of benzyl groups to be removed. DPGG and its benzyl-protected precursor were also prepared by this method with comparable yields to the literature (3).

Conclusion

We have prepared a library of phenolic and polyphenolic glycerolipids according to a relatively simple modular reaction scheme. Moreover, the same scheme can be used to prepare glycerolipids that are enantiomerically pure and (or) have dissimilar side chains.

Experimental

All chemicals were purchased from commercial suppliers and used without further purification. 4-Benzyloxybenzoic acid, 3,5-di-benzyloxybenzoic acid, and 3,4,5-tris-benzyloxybenzoic acid were obtained from Tokyo Chemical Industry Co., Ltd. (TCI, Tokyo, Japan). ^{1}H spectra were obtained at 300 MHz and ^{13}C NMR spectra were obtained at 75 MHz in $CDCl_3$ unless otherwise noted using the NMR solvent as an internal reference. Abbreviations used in the descriptions of NMR spectra are singlet (s), doublet (d), triplet (t), multiplet (m), broad signal (br). The coupling constants (*J*) are given in Hertz. Mass spectrometry measurements were carried out on a MALDI mass spectrometer using dithranol as a matrix. IR measurements were carried out using a liquid cell equipped with KBr windows and in $CDCl_3$ unless otherwise noted. All melting points are uncorrected. Silica gel for flash chromatography was acquired from Life Force Inc. (Flushing, New York).

3,4-Dihydroxybenzoic acid methyl ester (1d)

3,4-Dihydroxybenzoic acid (1 g, 6.49 mmol) was dissolved in 40 mL of MeOH. After the addition of 2 drops of concd. H_2SO_4, the solution was refluxed for 7 days. The reaction was stopped by the addition of 300 mL of distilled H_2O. The mixture was extracted with ethyl acetate – hexanes (60:40). The organic layers were combined, dried over Na_2SO_4, and the solvent removed under reduced pressure to give 0.8 g of a light-brown solid in 73% yield.

3-Benzyloxybenzoic acid methyl ester (2b)

Compound **2b** was prepared according to the literature (17) with a reaction time of 6 h. The product was purified by flash chromatography on SiO_2 (hexanes – ethyl acetate, 80:20) to give 0.98 g of a white solid in 61% yield.

3,4-Bis-benzyloxybenzoic acid methyl ester (2d)

Compound **2d** was prepared in a manner analogous to **2b**. However, 2.3 equiv. of benzyl bromide were used and gave 1.19 g of a white solid in 77% yield.

3-Benzyloxybenzoic acid (3b)

Compound **2b** (0.75 g, 3.1 mmol) was dissolved in 35 mL of THF. A solution of KOH (1.04 g, 18.6 mmol, 6 equiv.) in 50 mL of distilled H_2O was added and the reaction was stirred for 24 h. The reaction mixture was added to 250 mL of distilled H_2O and acidified to pH 5 with 2N HCl. The mixture was extracted with diethylether. The organic layers were combined, dried over Na_2SO_4, and the solvent removed under reduced pressure to yield 0.67 g of a white solid in 95% yield.

3,4-Bis-benzyloxy-benzoic acid (3d)

Compound **3d** was prepared in a manner analogous to **3b** with a reaction time of 48 h. The reaction gave 0.67 g of a white solid in 70% yield.

Synthesis of the benzyloxybenzoic acid 2,3-dihydroxypropyl esters (5a–5d)

Typical procedure

Compound **3a** (1.0 g, 4.38 mmol), 1-methyl-imidazole (1.08 g, 13.14 mmol, 3 equiv.), and *p*-toluenesulfonyl chloride (1.17 g, 6.13 mmol, 1.4 equiv.) were dissolved in 45 mL of CH_3CN and stirred for 30 min. After the addition of racemic 2,2-dimethyl-1,3-dioxolane-4-methanol (0.58 g, 4.38 mmol, 1 equiv.), the solution was stirred under inert atmosphere for 3 h. The volume of the solution was reduced to approximately 4 mL under reduced pressure and the solution filtered through Al_2O_3 with 40 mL of CH_2Cl_2. The solvent was removed under reduced pressure to give 1.0 g of a white solid which was used without further purification. Compound **4a** (0.15 g, 0.438 mmol) was suspended in 40 mL of EtOH–H_2O (95:5). Wet Amberlyst® 15 (0.180 g, 1 equiv.) was added to the suspension and the suspension was refluxed for 24 h. The solution was allowed to cool to room temperature and 40 mL of CH_2Cl_2 and 300 mL of brine were added. The mixture was extracted with CH_2Cl_2 (2 × 20 mL). The organic layers were combined, dried over Na_2SO_4, and the solvent removed under reduced pressure. The crude was purified by flash chromatography on SiO_2 (ethyl acetate – hexanes, 70:30) to give 0.105 g of a white solid in 80% yield.

Data for 5a

Melting point 77–79 °C. IR (cm^{-1}) ν: 3614, 3036, 2952, 2886, 1713, 1606. ^{1}H NMR δ: 8.01 (m, 2H), 7.40 (m, 5H), 7.01 (m, 2H), 5.13 (s, 2H, Ar*CH*$_2$), 4.42 (m, 2H), 4.00 (m, 1H), 3.71 (m, 2H). ^{13}C NMR δ: 166.7, 162.8, 136.1, 131.8, 128.7, 128.2, 127.5, 122.1, 114.6, 70.45, 70.13, 65.5, 63.4. MS *m*/*z*: 325.3 $[M + Na]^+$

Data for 5b

Yield 80%, mp 76–78 °C. IR (cm^{-1}) ν: 3618, 3036, 2952, 2884, 1719, 1586. ^{1}H NMR δ: 7.68 (m, 2H), 7.40 (m, 6H), 7.19 (m, 1H), 5.11 (s, 2H, Ar*CH*$_2$), 4.42 (m, 2H), 4.06 (m, 1H), 3.72 (m, 2H). ^{13}C NMR δ: 166.8, 158.7, 136.4, 130.9, 129.6, 128.6, 128.1, 127.5, 122.4, 120.5, 115.4, 70.3, 70.2, 65.8, 63.4. MS *m*/*z*: 325.3 $[M + Na]^+$.

Data for 5c

Yield 85%, mp 94 to 95 °C. IR (cm^{-1}) ν: 3618, 3035, 2952, 2884, 1717, 1596. ^{1}H NMR δ: 7.38 (m,10H), 7.28 (d, 2H, *J* = 2.33 Hz), 6.82 (t, 1H, *J* = 2.34 Hz), 5.07 (s, 4H, Ar*CH*$_2$), 4.52 (m, 2H), 4.05 (m, 1H), 3.71 (m, 2H). ^{13}C NMR δ: 166.6, 159.8, 136.4, 131.4, 128.6, 128.2, 127.6, 108.6, 107.4, 70.4, 70.3, 65.9, 63.4. MS *m*/*z*: 431.4 $[M + Na]^+$.

Data for 5d

Yield 83%, mp 80 to 81 °C. IR (cm^{-1}) ν: 3613, 3034, 2951, 2885, 1712, 1601. ^{1}H NMR δ: 7.63 (m, 2H), 7.39 (m, 10H), 6.93 (m, 1H), 5.23 (s, 2H, ArCH_2), 5.20 (s, 2H, ArCH_2), 4.37 (m, 2H), 4.02 (m, 1H), 3.68 (m, 2H). ^{13}C NMR δ: 166.7, 153.3, 148.3, 136.7, 136.4, 128.6, 128.5, 128.0, 127.9, 127.4, 127.1, 124.3, 122.3, 115.7, 113.2, 71.3, 70.8, 70.4, 65.6, 63.3. MS *m/z*: 431.4 $[M + Na]^+$.

Data for 5e

Yield 57%.

Synthesis of benzyloxybenzoic acid 2,3-bis-hexadecanoyloxypropyl esters (6a–6e)

Typical procedure

Compound **5a** (0.38 g, 1.25 mmol) and hexadecanoic acid (0.73 g, 2.825 mmol, 2.26 equiv.) were dissolved in 20 mL of CH_2Cl_2. A suspension of DMAP (0.35 g, 2.825 mmol, 2.26 equiv.) and EDCI (0.58 g, 3 mmol, 2.4 equiv.) in 10 mL of CH_2Cl_2 was added to the reaction mixture and the mixture was stirred for 4 h. Brine (300 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (2 × 20 mL). The organic layers were combined, dried over Na_2SO_4, and the solvent removed under reduced pressure. The product was purified by flash chromatography on SiO_2 (hexanes – ethyl acetate, 80:20) to give 0.80 g of a white solid in 82% yield.

Data for 6a

Melting point 64–66 °C. IR (cm^{-1}) ν: 2927, 2855, 1736, 1606. ^{1}H NMR δ: 7.98 (m, 2H), 7.39 (m, 5H), 7.01 (m, 2H), 5.41 (m, 1H), 5.12 (s, 2H, ArCH_2), 4.41 (m, 3H), 4.24 (m, 1H), 2.33 (t, 2H, *J* = 7.5 Hz, CH_2COO), 2.32 (t, 2H, *J* = 7.6 Hz, CH_2COO), 1.61 (m, 4H, CH_2CH_2COO), 1.27 (m, 48H), 0.88 (t, 6H, *J* = 6.70 Hz, CH_3). ^{13}C NMR δ: 173.3, 172.9, 165.7, 162.8, 136.2, 131.8, 128.7, 128.2, 127.4, 122.1, 114.6, 70.1, 68.9, 62.6, 62.3, 34.3, 34.1, 31.9, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 24.9, 24.8, 22.7, 14.1. MS *m/z*: 802.1 $[M + Na]^+$.

Data for 6b

Reaction time 6 h, yield 44%, mp 51 to 52 °C. IR (cm^{-1}) ν: 2927, 2855, 1735, 1586. ^{1}H NMR δ: 7.64 (m, 2H), 7.39 (m, 6H), 7.18 (m, 1H), 5.42 (m, 1H), 5.11 (s, 2H, ArCH_2), 4.43 (m, 3H), 4.24 (m, 1H), 2.33 (t, 2H, *J* = 7.5 Hz, CH_2COO), 2.32 (t, 2H, *J* = 7.6 Hz, CH_2COO), 1.61 (m, 4H, CH_2CH_2COO), 1.27 (m, 48H), 0.88 (t, 6H, *J* = 6.7 Hz, CH_3). ^{13}C NMR δ: 173.3, 172.9, 165.8, 158.8, 136.5, 130.8, 129.5, 128.6, 128.1, 127.5, 122.3, 120.5, 115.3, 70.2, 68.9, 63.0, 62.2, 34.3, 34.1, 31.9, 29.8, 29.7, 29.5, 29.4, 29.3, 29.2, 29.1, 24.9, 24.8, 22.7, 14.1. MS *m/z*: 802.1 $[M + Na]^+$.

Data for 6c

Reaction time 12 h, yield 94%, mp 66–68 °C. IR (cm^{-1}) ν: 2927, 2855, 1736, 1596. ^{1}H NMR δ 7.38 (m, 10H), 7.26 (d, 2H, *J* = 2.3 Hz), 6.81 (t, 1H, *J* = 2.3 Hz), 5.41 (m, 1H), 5.07 (s, 4H, ArCH_2), 4.45 (m, 3H), 4.22 (m, 1H), 2.33 (t, 4H, *J* = 7.5 Hz, CH_2COO), 1.61 (m, 4H, CH_2CH_2COO), 1.27 (m, 48H), 0.88 (t, 6H, *J* = 6.7 Hz, CH_3). ^{13}C NMR δ 173.3, 172.9, 165.7, 159.8, 136.4, 131.4, 128.6, 128.1, 127.6, 108.5, 107.5, 70.3, 68.8, 63.0, 62.1, 34.3, 34.1, 31.9, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 24.9, 24.8, 22.7, 14.1. MS *m/z*: 908.3 $[M + Na]^+$.

Data for 6d

Reaction time 12 h, yield 63%, mp 45–47 °C. IR (cm^{-1}) ν: 2927, 2855, 1736, 1601. ^{1}H NMR δ: 7.62 (m, 1H), 7.58 (d, 1H, *J* = 2.1 Hz), 7.42 (m, 10H), 6.93 (d, 1H, *J* = 8.5 Hz), 5.41 (m, 1H), 5.23 (s, 2H, ArCH_2), 5.20 (s, 2H, ArCH_2), 4.40 (m, 3H), 4.17 (m, 1H), 2.33 (t, 4H, *J* = 7.5 Hz, CH_2COO), 1.61 (m, 4H, CH_2CH_2COO), 1.27 (m, 48H), 0.88 (t, 6H, *J* = 6.7 Hz, CH_3). ^{13}C NMR δ: 173.3, 172.9, 165.6, 153.2, 148.4, 136.8, 136.5, 128.6, 128.5, 128.0, 127.9, 127.4, 127.1, 124.1, 122.3, 115.5, 113.2, 71.6, 70.8, 68.9, 62.7, 62.2, 34.3, 34.1, 31.9, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 24.9, 24.8, 22.7, 14.1. MS *m/z*: 908.3 $[M + Na]^+$.

Data for 6e

Reaction time 15 h, yield 70%.

Synthesis of hydroxybenzoic acid 2,3-bis-hexadecanoyloxypropyl esters (7a–7e)

Typical procedure

Compound **6a** (0.2 g, 0.257 mmol) was dissolved in 20 mL of dry THF. 10% Pd–C (0.07 g, 30 wt%) was added and the reaction mixture was placed in a pressure reactor and stirred under 3.5 atm (1 atm = 101.325 kPa) of hydrogen gas for 4 h. The mixture was filtered through Celite 545 and the solvent removed under reduced pressure to give 0.14 g of a white solid in 80% yield.

Data for 7a

Melting point 69–71 °C. IR (cm^{-1}) ν: 3587, 2927, 2855, 1736, 1610. ^{1}H NMR δ: 7.94 (m, 2H), 6.86 (m, 2H), 5.42 (m, 1H), 5.33 (br, 1H, *OH*), 4.44 (m, 3H), 4.24 (m, 1H), 2.33 (t, 2H, *J* = 7.5 Hz, CH_2COO), 2.32 (t, 2H, *J* = 7.5 Hz, CH_2COO), 1.61 (m, 4H, CH_2CH_2COO), 1.27 (m, 48H), 0.88 (t, 6H, *J* = 6.7 Hz, CH_3). ^{13}C NMR δ: 173.5, 173.1, 165.7, 160.0, 132.1, 122.1, 115.3, 69.0, 62.7, 62.3, 34.3, 34.1, 31.9, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 24.9, 24.8, 22.7, 14.1. MS *m/z*: 712.0 $[M + Na]^+$.

Data for 7b

Reaction time 6 h, 61% yield, mp 64 to 65 °C. IR (cm^{-1}) ν: 3594, 2927, 2855, 1734, 1593. ^{1}H NMR δ: 7.61 (m, 1H), 7.48 (m, 1H), 7.32 (m, 1H), 7.06 (m, 1H), 5.43 (m, 1H), 5.20 (br, 1H, *OH*), 4.43 (m, 3H), 4.24 (m, 1H), 2.33 (t, 2H, *J* = 7.4 Hz, CH_2COO), 2.32 (t, 2H, *J* = 7.5 Hz, CH_2COO), 1.61 (m, 4H, CH_2CH_2COO), 1.27 (m, 48H), 0.88 (t, 6H, *J* = 6.7 Hz, CH_3). ^{13}C NMR δ: 173.4, 173.1, 165.7, 155.8, 130.1, 129.8, 122.1, 120.5, 116.3, 68.9, 63.0, 62.2, 34.3, 34.1, 31.9, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 24.9, 24.8, 22.7, 14.1. MS *m/z*: 712.0 $[M + Na]^+$.

Data for 7c

Reaction time 7 h, 53% yield, mp 78 to 79 °C. IR (cm^{-1}) ν: 3594, 2927, 2855, 1733, 1605. ^{1}H NMR δ: 7.07 (d, 2H, *J* = 2.2 Hz), 6.59 (t, 1H, *J* = 2.3 Hz), 5.45 (m, 3H), 4.41 (m, 3H), 4.24 (m, 1H), 2.33 (t, 6H, *J* = 7.6 Hz, CH_2COO), 1.61 (m, 4H, CH_2CH_2COO), 1.27 (m, 48H), 0.88 (t, 6H, *J* = 6.7 Hz, CH_3). ^{13}C NMR δ: 173.6, 173.3, 165.4, 157.1, 131.6, 109.2, 107.8, 68.5, 63.1, 62.2, 34.3, 34.1, 31.9, 29.7, 29.6,

29.5, 29.4, 29.3, 29.2, 29.1, 24.9, 24.8, 22.7, 14.1. MS *m*/*z*: 728.0 $[M + Na]^+$.

Data for 7d

Reaction time 7 h, 50% yield, mp 92 to 93 °C. IR (cm^{-1}) ν: 3566, 2927, 2855, 1734, 1616. ^1H NMR δ: 7.07 (d, 2H, *J* = 2.2 Hz), 6.59 (t, 1H, *J* = 2.3 Hz), 5.45 (m, 3H), 4.41 (m, 3H), 4.24 (m, 1H), 2.33 (t, 6H, *J* = 7.6 Hz, CH_2COO), 1.61 (m, 4H, CH_2CH_2COO), 1.27 (m, 48H), 0.88 (t, 6H, *J* = 6.7 Hz, CH_3). ^{13}C NMR δ: 173.7, 173.4, 166.3, 149.8, 146.8, 123.1, 120.9, 115.9, 114.6, 68.9, 62.5, 62.2, 34.3, 34.1, 31.9, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 24.9, 24.8, 22.7, 14.1. MS *m*/*z*: 728.0 $[M + Na]^+$.

Data for 7e

Reaction time 8 h. The product was then adsorbed to silica in the presence of 1 mL of acetic acid and purified by flash chromatography on SiO_2 using a solvent gradient of hexanes – ethyl acetate from 90:10 to 30:70. The product was then extracted from 200mL of brine with $CHCl_3$ (5 × 20 mL). The organic layers were combined, dried over Na_2SO_4, and the solvent removed under reduced pressure to give 0.050 g of a white solid in 70% yield.

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