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Epoxidizable Fatty Amide–Phenol Conjugates

Jonathan A. Zerkowski · Michael J. Haas

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Abstract This paper reports the synthesis of a series of novel compounds where carboxylic acids have been linked to a phenol through amidomethyl units. For instance, one, two, or three fatty acids have been selectively appended to the phenol in yields above 75%. The fatty acid used was oleic acid, which was subsequently epoxidized. Other functional groups, such as amino acids, can be incorporated in these compounds. Examples of monomers that are suitable for polymerization were also prepared: one acrylamide, one styrene derivative, and two types of AB_2 diamino acids, all of which contain oleic units that are sites for epoxidation and crosslinking. Fatty acid aryl ethers were prepared using hydroxy fatty acids. These molecules are intended to serve as augmented analogues of epoxidized vegetable oil. Their amide groups should lead to intermolecular aggregation through hydrogen bonding, and the option to covalently include other functional groups may permit tuning of the macroscopic materials properties of films, coatings, or solids constructed from them.

Keywords Co-products (Waste) < biobased products · Polymers/coatings < biobased products · Fats and oils · Oleochemistry

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J. A. Zerkowski (✉) · M. J. Haas
USDA, ARS, Eastern Regional Research Center,
600 E. Mermaid Lane, Wyndmoor, PA 19038, USA
e-mail: jonathan.zerkowski@ars.usda.gov

Introduction

Crosslinked materials produced from epoxidized vegetable oils (EVO) have been known and studied for decades [1], but it is only in recent years that copolymerization of EVO with other additives, with the goal of imparting new properties, has been studied. There are two basic approaches for crosslinking the EVO. First is self-polymerization, where a Lewis acid catalyst is used to activate epoxide units for reaction with themselves, forming a polyether network [2]. With this route, other epoxide monomers can be included, such as glycidol derivatives. The second route is to incorporate co-monomers such as amines that are reactive with the epoxide unit; the structure of this crosslinker can be varied to alter the final properties of the material [3]. Some very interesting heterogeneous blends (using natural fibers [4], clay [5], or ceramic nanoparticles [6]) that give nanocomposites have been formed, in particular by an offshoot of this technique: the epoxide ring is opened with a group that is itself polymerizable, such as an acrylic unit [7]. Alternatively, the epoxides can be hydrolyzed to polyols that react with isocyanates to give polyurethanes. Clearly, a need has been perceived for the ability to tune the properties of EVO, which by itself offers only a limited range of bulk mechanical properties, even though it is an abundant and cheap polymer building block. Since one benefit of EVO is its green character, it would be desirable if other structural units for incorporation into EVO could also be bio-derived.

Recent advances in the pyrolysis of lignocellulosic material suggest one such alternative for the preparation and modification of EVO analogues. One class of compounds that are present in "pyrolysis oil" is phenols [8]. While current pyrolysis methods do not yield high percentages or high purities of the phenolic fraction, work is underway that will permit greater control of the product distribution, so

that a specific class of chemical structure can be obtained [9]. Alternatively, it has been shown that phenol can be produced through biotech routes with microorganisms, using glucose and the shikimic acid pathway [10].

Our aim was to examine ways to combine this new biobased source of phenolics with agriculture-derived fatty acids (FA) to prepare new, and highly modifiable, versions of EVO. The thrust of this initial work is synthetic and exploratory, attempting to map out functional group patterns that are attainable; obviously the specific lab-scale procedures employed may require refinement before scaling up. Compounds combining phenolics with unsaturated alkyl chains are known in nature and synthetically. They have proven to be of interest for fundamental scientific behavior as well as for technological uses. Urushiol is the cross-linkable component of natural lacquer [11]. Cardanol is found in cashew nut oil, and has been shown to form fibrous aggregates [12]. Galià et al. [13] have prepared fatty acid esters with trihydroxybenzoates and used these to crosslink silica particles. The work reported here presents a new family of fatty acid/phenol amides that should function similarly to EVO, but with structurally distinct features that allow a wide range of derivatization (Scheme 1).

Experimental

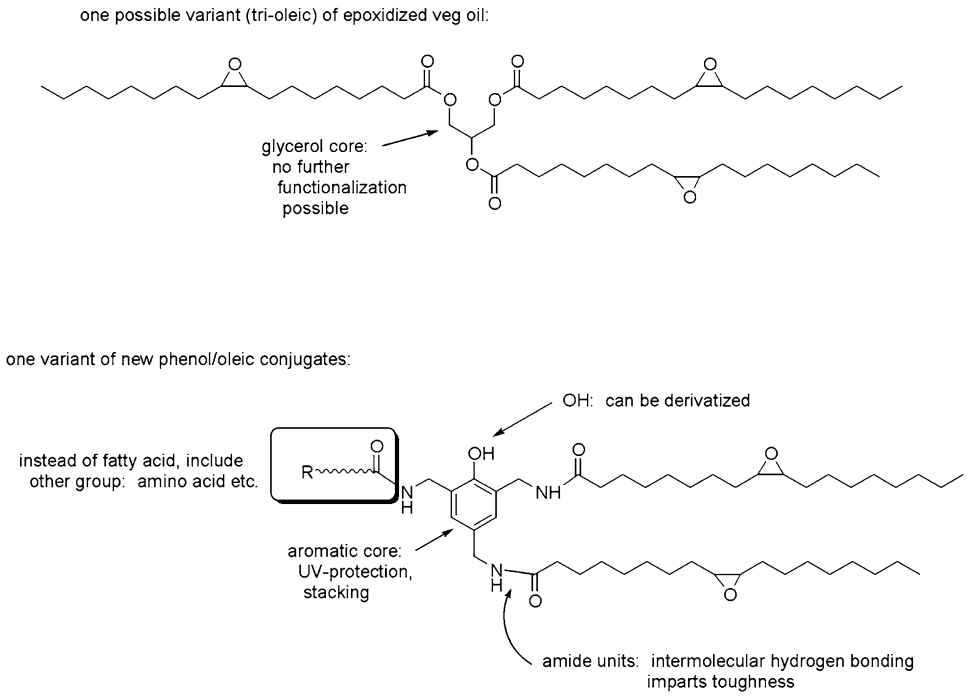
General

Chemicals and reagents were obtained commercially from Sigma-Aldrich (St. Louis, MO) and Lancaster Synthesis (Alfa Aesar, Ward Hill, MA). All solvents and reagents were used as received. Silica gel used for column chromatography (Grade 60 Å, mesh 230–400, particle size 40–63 μm), was obtained from Fisher Scientific (Fairlawn, NJ). NMR spectra were recorded at room temperature in $CDCl_3$ referenced to tetramethylsilane on either a Varian Associates (Walnut Creek, CA) Gemini 200 MHz or Inova 400 MHz instrument. LCMS data were recorded on a Waters/Micromass (Milford, MA) ZMD instrument with atmospheric pressure chemical ionization (APCI), using direct injection (no column) with 9:1 CH_3CN:0.5% HCO_2H in CH_3CN as eluant. Masses were determined as sodiated ionic adducts of the products, $[M + Na]^+$.

Amidomethylation of phenol (Tscherniac–Einhorn reaction) [14] (Fig. 1)

Phenol (0.45 g, 4.8 mmol) and hydroxymethylchloroacetamide (1.5 g, 12 mmol) were added in one portion to 9 mL acetic acid and 1 mL sulfuric acid. The mixture was stirred magnetically overnight, then poured onto approximately 150 mL crushed ice. The liquid was decanted from the gummy solid, partially neutralized with approx. 2 g $NaHCO_3$, and extracted with ethyl acetate (5 × 100 mL) and chloroform (2 × 100 mL). The organic fractions were combined with the gummy solid to dissolve it, dried over $MgSO_4$, and evaporated. The residue could then be used as is for further reactions, or could be purified by column chromatography on silica gel with ethyl acetate as eluant. Four major fractions were obtained, which were identified by MS and NMR to be, in order of elution, **1a**, **1b** together

Scheme 1



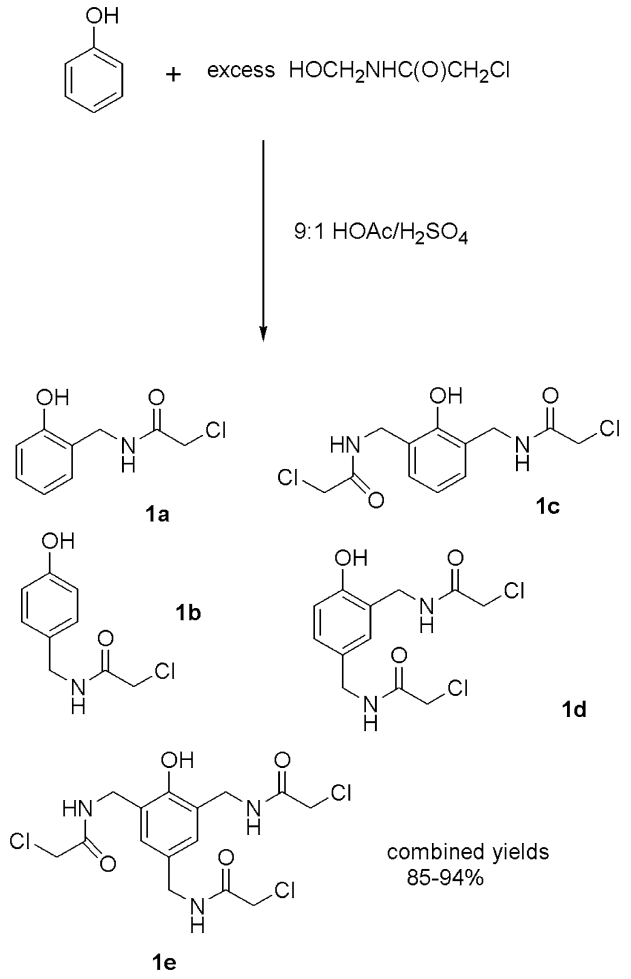


Fig. 1 Preparation of amidomethylated phenols

with **1c** (separable using a second column with 1:1 hexane/ethyl acetate or 5% MeOH/$CHCl_3$), **1d**, and **1e**. Combined yields of the products ranged from 85 to 94%, based on phenol. **1a**: ^{1}H NMR: 4.13 (s, 2H, CH_2Cl), 4.47 (d, 6.9 Hz, 2H, $ArCH_2$), 6.88 (t, 6.5 Hz, 1H, Ar), 6.97 (d, 6.6 Hz, 1H, Ar), 7.17 (d, 6.5 Hz, 1H, Ar), 7.26 (t, 6.4 Hz, 1H, Ar), 7.39 (br s, 1H, NH), 9.30 (s, 1H, OH). ^{13}C NMR: 40.7 CH_2Cl, 42.3 $ArCH_2$, 117.9 Ar C ortho to OH, 120.5, 130.0, 130.4, 131.0, 155.4 ArC-OH, 168.7 amide C=O (since these patterns recur in subsequent compounds, for brevity assignments are not repeated below). **1b**: 4.13 (s, 2H, CH_2Cl), 4.42 (d, 6.7 Hz, 2H, $ArCH_2$), 6.75–6.95 (br s, 1H, NH), 6.84 (d, 8.0 Hz, 2H, 2- and 6-ArH), 7.18 (d, 8.0 Hz, 2H, 3- and 5-ArH), 10.1 (s, 1H, OH). ^{13}C NMR: 42.5, 43.6, 115.9, 129.4, 128.7, 156.1, 166.3. **1c**: 4.13 (s, 4H, CH_2Cl), 4.48 (d, 6.9 Hz, 4H, $ArCH_2$), 6.85 (t, 7.2 Hz, 1H, 4-ArH), 7.20 (d, 7.3 Hz, 2H, 3- and 5-ArH), 7.46 (br s, 2H, NH), 9.42 (s, 1H, OH). ^{13}C NMR: 40.6, 42.6, 120.2, 124.9, 130.8, 154.3, 167.5. **1d**: 4.13 (s, 2H, CH_2Cl), 4.15 (s, 2H, CH_2Cl), 4.45 (m, 4H, $ArCH_2$), 6.85 (br s, 1H, para NH), 6.88 (d, 6.5 Hz, 1H, 6-ArH), 6.95 (s, 1H, 3-ArH), 7.09 (d, 6.6 Hz, 1H, 5-ArH), 7.32 (br s, 1H, ortho NH), 9.50 (s, 1H, OH). ^{13}C NMR: 40.6, 42.4, 42.7, 43.4, 118.2, 123.9, 129.0, 129.9, 130.8, 155.4, 166.3, 168.6. **1e**: 4.12 (s, 2H, para CH_2Cl), 4.15 (s, 4H, ortho CH_2Cl), 4.46 (m, 6H, $ArCH_2$), 6.82 (br s, 1H, para NH), 7.05 (s, 2H, 3- and 5-ArH), 7.36 (br s, 2H, ortho NH), 9.60 (s, 1H, OH). ^{13}C NMR: 40.4, 42.5, 42.7, 43.2, 125.3, 129.0, 130.5, 154.0, 166.1, 167.6.

Tri-oleic and mixed oleic/amino acid adducts (Figs. 2, 3)

Trisubstituted molecule **1e** (400 mg, 0.98 mmol) was heated to reflux in 7 mL EtOH and 3 mL conc. HCl for 2 h. The solvent was removed under a stream of nitrogen overnight, and the solid was triturated three times with Et_2O. The residue was then dissolved in 5 mL *N*,*N*-dimethylformamide (DMF), and 1,8-diazabicycloundecene (DBU, 0.46 g, 3 mmol) was added. To this mixture was added a solution of oleic acid (1.13 g, 4.0 mmol), hydroxybenzotriazole hydrate (HOBt, 0.63 g, 4.1 mmol), and diisopropyl carbodiimide (DIC, 0.40 g, 3.2 mmol) that had been pre-mixed for 10 min in 5 mL DMF. The reaction was stirred magnetically for 3 h, then solvent was removed on the rotary evaporator. The residue was purified by column chromatography to give **2a** (730 mg, 77%). ^{1}H NMR: 0.88 (t, 6.7 Hz, 9H, CH_3), 1.15–1.43 m, 1.51–1.71 m, 1.83–2.11 (m, 12H, =CH–CH_2), 2.20 (t, 7.2 Hz, 6H, $CH_2C(O)$), 4.25 (d, 6.9 Hz, 2H, para $ArCH_2$), 4.31 (d, 6.8 Hz, 4H, ortho $ArCH_2$), 5.23–5.44 (m, 6H, olefin H), 5.96 (m, 1H, para NH), 6.58 (m, 2H, ortho NH), 7.03 (s, 2H, Ar), 10.2 (br s, 1H, OH). ^{13}C NMR: 14.2, 22.8, 25.6, 25.8, 27.3, 29.2–29.8, 32.0, 36.6, 36.9, 40.3, 43.0, 126.0, 129.5, 129.8, 130.1, 153.9, 173.3, 174.7. APCI: $C_{63}H_{110}N_3O_4{\cdot}Na^+$ calc 997.8 Da, found 997.4 Da.

For the mixed adducts, **1e** (550 mg, 1.3 mmol) was deprotected similarly, then dissolved in 7 mL DMF with DBU (0.61 g, 4 mmol) and treated with a premixed solution of 1:1 oleic acid (0.56 g, 2 mmol) and 3-(*tert*-butoxycarbonylamino)-propanoic acid (Boc-β-alanine, 0.38 g, 2 mmol), DIC (0.52 g, 4.1 mmol), and HOBt (0.63 g, 4.1 mmol) in 5 mL DMF. Column chromatography with ethyl acetate provided three product groups: the trioleic adduct **2a** (19%), identical to the sample prepared above, the mixed products **3a–3d** (48%, Fig. 3), and the tris–Boc-β-alanine adduct **3e** (24%). Compounds **3a–3d** could be separated from each other by using 5% MeOH/$CHCl_3$ as eluant. **3a**: ^{1}H NMR: 0.90 (t, 6.6 Hz, 6H, CH_3), 1.11–1.42 m, 1.45 (s, 9H, Boc tBu), 1.52–1.79 m, 1.84–2.11 (m, 8H, =CH–CH_2), 2.21 (t, 7.2 Hz, 4H, oleic $C(O)CH_2$), 2.42 (t, 7.4 Hz, 2H, alanine $C(O)CH_2$), 3.44 (q, 6.8 Hz, 2H, alanine CH_2NH), 4.24–4.44 (m, 6H, $ArCH_2$), 5.25–5.47 (m, 6H, Boc-NH and olefin H), 6.29 (br, 1H,

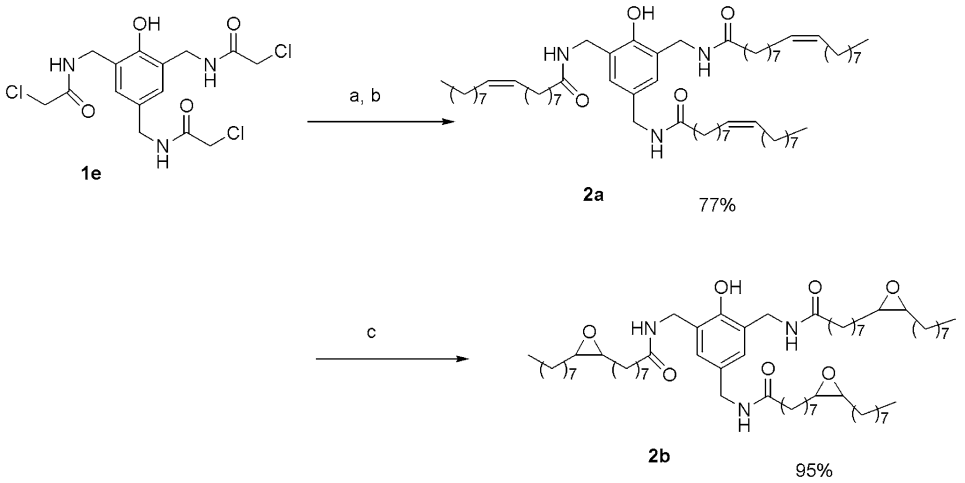


Fig. 2 Preparation of the tri-oleic adduct and its epoxidation. Reagents and conditions: *a* 7:3 EtOH/conc. HCl, reflux, 2 h, then evaporation. *b* DMF with DBU, then a premixed solution of oleic acid, DIC, and HOBt (see "Experimental" for abbreviations). *c* mCPBA, CH_2Cl_2, 16 h

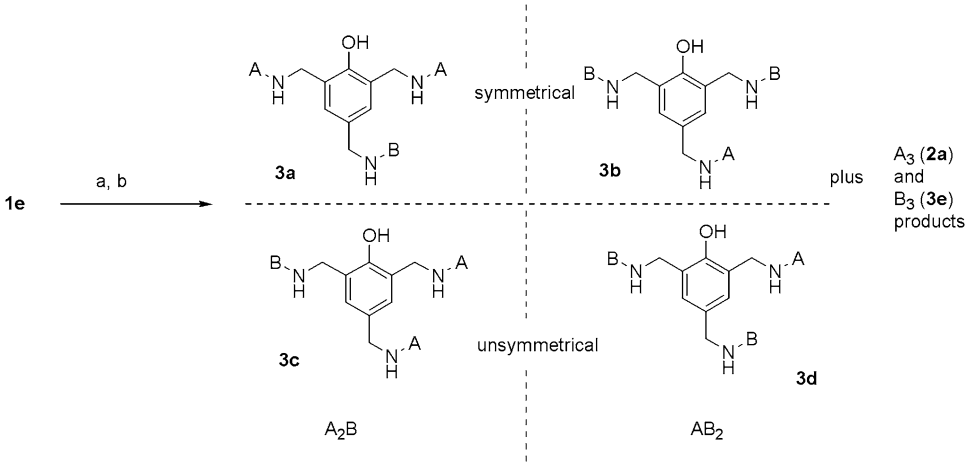


Fig. 3 Preparation of the mixed oleic/Boc-*β*-alanine adducts. Reagents and conditions: *a* 7:3 EtOH/conc. HCl, reflux, 2 h, then evaporation. *b* DMF with DBU, then a premixed solution of 1:1 oleic acid:Boc-*β*-alanine, DIC, and HOBt. *A* oleic, *B* Boc-*β*-alanine

amide), 6.58 (br, 2H, amide), 7.05 (br, 2H, Ar). ^{13}C NMR: 14.2, 22.8, 25.6, 27.3, 28.5, 29.2–29.9, 32.0, 36.5, 40.2, 79.6, 126.0, 129.8, 130.1, 153.8, 156.4 (carbamate C=O), 174.7. **3b**: ^{1}H NMR: 0.90 (t, 6.6 Hz, 3H, CH_3), 1.10–1.40 m, 1.44 (s, 18H, Boc tBu), 1.52–1.77 m, 1.91–2.09 (m, 4H, =CH–CH_2), 2.20 (t, 7.3 Hz, 2H, oleic C(O)CH_2), 2.41 (t, 7.2 Hz, 4H, alanine C(O)CH_2), 3.39 (q, 6.6 Hz, 4H, alanine CH_2NH), 4.23 (d, 6.8 Hz, 2H, ArCH_2), 4.37 (d, 6.9 Hz, 4H, ArCH_2), 5.24 (br, 2H, Boc NH), 5.31–5.42 (m, 2H, olefin H), 6.04 (br, 1H, amide), 6.95–7.13 (br, 2H, amide), 7.03 (s, 2H, Ar). ^{13}C NMR: 14.2, 22.8, 25.8, 27.3, 28.5, 29.2–29.9, 32.0, 36.3, 36.8, 40.1, 42.9, 79.7, 129.7, 129.8, 130.1, 153.7, 156.3 (carbamate C=O), 172.9, 173.3. **3c**: ^{1}H NMR: 0.90 (t, 6.7 Hz, 6H, CH_3), 1.06–1.38 m, 1.44 (s, 9H, Boc tBu), 1.52–1.77, 1.91–2.13 (m, 8H, =CH–CH_2), 2.15-2.28 (m, 4H, oleic C(O)CH_2), 2.40 (t, 7.3 Hz, 2H, alanine C(O)CH_2), 3.41 (q, 6.4 Hz, 2H, alanine CH_2NH), 4.24 (d, 7.9 Hz, 2H, ArCH_2), 4.29–4.41 (m, 4H, ArCH_2), 5.25 (br s, 1H, Boc NH), 5.28–5.44 (m, 4H, olefin H), 5.96, 6.63, and 6.92 (each br s, 1H, amides), 7.02 (s, 2H, Ar). ^{13}C NMR: 14.2, 22.8, 25.6, 25.8, 27.3, 28.5, 29.2–29.9, 32.0, 36.3, 36.4, 36.8, 40.2, 40.3, 43.0, 79.6, 129.6, 129.8, 130.1, 153.8, 156.2 (carbamate C=O), 172.5, 173.2, 175.1. **3d**: ^{1}H NMR: 0.90 (t, 6.8 Hz, 3H, CH_3), 1.09–1.39 m, 1.45 (s, 18H, Boc tBu), 1.52–1.79 m, 1.92–2.09 (m, 4H, =CH–CH_2), 2.20 (t, 7.2 Hz, 2H, oleic C(O)CH_2), 2.28–2.49 (m, 4H, alanine C(O)CH_2), 3.23–3.50 (m, 4H, alanine CH_2NH), 4.10–4.41 (m, 6H, ArCH_2), 5.26–5.58 (m, 6H, Boc NH and olefin H), 6.77 (br s, 1H, NH), 6.90–7.05 (m, 3H, NH and Ar), 7.20 (br s, 1H, amide). ^{13}C NMR: 14.2, 22.8, 25.7, 27.3, 28.5, 29.2–29.8, 32.0, 36.1, 36.4, 36.7, 40.2, 42.8, 79.5, 125.8, 126.0, 129.8, 130.1, 153.6, 156.3 and 156.4 (two distinct carbamate C=O), 171.7, 172.7, 175.2. **3a** and **3c**: calc $C_{53}H_{92}N_4O_6{\cdot}Na^+$ 904.3 Da, found 904.1 and 904.5 Da respectively. **3b** and **3d**: calc $C_{43}H_{73}N_5O_8{\cdot}Na^+$ 811.1 Da, found 811.1 and 811.4 Da, respectively.

Epoxidation (Fig. 2)

Tri-oleic adduct **2a** (100 mg, 0.1 mmol) was dissolved in 10 mL CH_2Cl_2, and to it was added *m*-chloroperbenzoic

acid (77% by weight, 112 mg, 0.5 mmol). The reaction was stirred at rt overnight, diluted with 40 mL CH_2Cl_2, then washed with a dilute solution of sodium bisulfite (2 × 50 mL) and sodium bicarbonate (2 × 50 mL). Solvent was removed to afford **2b** (96 mg, 95%). ^{1}H NMR: 0.88 (t, 6.7 Hz, 9H, CH_3), 1.15–1.48 m, 1.51–1.71 m, 2.20 (t, 7.3 Hz, 6H, $CH_2C(O)$), 2.80–2.99 (m, 6H, HC–O epoxide), 4.25 (d, 6.9 Hz, 2H, para $ArCH_2$), 4.31 (d, 6.8 Hz, 4H, ortho $ArCH_2$), 5.96 (m, 1H, para NH), 6.58 (m, 2H, ortho NH), 7.03 (s, 2H, Ar), 10.2 (br s, 1H, OH). ^{13}C NMR: 14.2, 22.8, 25.6, 25.7, 26.7, 27.9, 29.1–29.8, 31.9, 36.5, 36.8, 40.3, 43.0, 57.4 (epoxide C–O), 126.0, 129.5, 130.2, 153.9, 173.1, 174.6. $C_{63}H_{111}N_3O_7{\cdot}Na^+$ 1044.8 Da, found 1045.1 Da.

Oleic/Acryloyl Compound (Fig. 4)

Disubstituted molecule **1d** (0.80 g, 2.6 mmol) was dissolved in 15 mL EtOH, and a solution of thiourea (200 mg, 2.6 mmoL) in 5 mL EtOH was added. The mixture was heated to reflux for 2 h. Solvent was removed on the rotary evaporator, and the residue was taken up in 5 mL DMF with DBU (0.4 g, 2.6 mmol). A solution of oleic acid (0.8 g, 2.8 mmol), HOBt (460 mg, 3.0 mmol), and DIC (352 mg, 2.8 mmol) that had been premixed for 10 min in 3 mL DMF was added, and stirred for 2 h. Solvent was removed, and the residue was purified by column chromatography on silica gel with ethyl acetate. Four products were obtained: the dioleic adduct (318 mg, 18%), two isomers of monooleic/monochloroacetic product (310 and 342 mg, respectively, 51% total), and the unchanged starting material (dichloroacetic adduct **1d**, 160 mg, 20%). One of the mixed monosubstituted isomers (200 mg, 0.41 mmol) was selected and deprotected as above with thiourea in EtOH. After removal of solvent, it was dissolved in 3 mL DMF with DBU (61 μL, 0.41 mmol), and a premixed solution of acrylic acid (35 mg, 0.41 mmol), DIC (63 mg, 0.41 mmol), and HOBt (76 mg, 0.41 mmol) was added. After 2 h, solvent was removed, and the crude was chromatographed on silica gel with ethyl acetate to afford molecule **4** (167 mg, 87%). The isomer pattern, with the acrylic unit ortho to the phenol OH as shown in Fig. 4, was tentatively assigned using 2D NMR spectroscopy. Briefly, ^{3}J couplings were observed between one of the benzylic CH_2 groups and the phenol C as well as the acrylic carbonyl. ^{1}H NMR: 0.91 (t, 6.7 Hz, 3H, CH_3), 1.16–1.45 m, 1.56–1.78 m, 1.91–2.11 (m, 4H, =CH–CH_2), 2.17 (t, 7.3 Hz, 2H, CH_2–C(O)), 4.26 (d, 6.8 Hz, $ArCH_2$), 4.37 (d, 6.8 Hz, $ArCH_2$), 5.26–5.43 (m, 2H, oleic olefin H), 5.66–5.84 (m, 1H, acrylic), 5.90 br s (NH), 5.97–6.18 (m, 1H, acrylic), 6.27–6.42 (m, 1H, acrylic), 6.90 (d, 7.5 Hz, 1H, Ar-6H), 6.98 (s, Ar-3H), 7.09 (d, 7.6 Hz, 1H, Ar-5H), 7.16 br s (NH). ^{13}C NMR: 14.2, 22.8, 25.8, 27.3, 29.2-29.9, 32.0, 36.9, 40.5, 43.1, 118.2, 124.5, 128.0, 128.5, 129.5, 129.6, 129.8, 130.2, 130.7, 131.5, 155.5, 167.9, 173.3. $C_{29}H_{46}N_2O_3{\cdot}Na^+$ calc 493.3 Da, found 493.6 Da.

Conversion to a Styrene Derivative [15] (Fig. 5)

Molecule **5a** (0.23 g, 0.58 mmol), prepared from **1b** analogously to other oleic versions (see Fig. 2), was dissolved in 5 mL pyridine and trifluoromethanesulfonic anhydride (98 μL, 0.58 mmol) was added in an ice bath. After 2 h, tlc showed starting material still present, so another 10 μL of the anhydride was added. The solvent was removed, and the product isolated by column chromatography (280 mg, 93%). This triflate **5b** (0.20 g, 0.39 mmol) was then placed in a screw-cap pressure vial, and $PdCl_2$ (5 mg), PPh_3 (10 mg), potassium vinyltrifluoroborate ($KBF_3(CH{=}CH_2)$, 52 mg, 0.39 mmol) and Cs_2CO_3 (381 mg, 3 equiv., 1.2 mmol) were added, along with 3 mL of 9:1 THF/water. The vial was sealed and heated at 80 °C for 7 h, then stirred at rt overnight. Removal of solvent and chromatography afforded styrene derivative **5c** (108 mg, 70%). ^{1}H NMR **5c**: 0.90 (t, 6.6 Hz, 3H, CH_3), 1.15–1.43 m, 1.55–1.78 m, 1.82–2.12 (m, 4H, =CH–CH_2), 2.22 (t, 7.3 Hz, 2H, $CH_2C(O)$), 4.46 (d, 6.5 Hz, $ArCH_2$), 5.26 (d, 10.5 Hz, 1H, Ar–CH=C*H*(trans)), 5.32–5.45 (m, 2H, oleic olefin), 5.70 (br s, 1H, amide), 5.75 (d, 17.6 Hz, Ar–CH=C*H*(cis)), 6.72 (dd, 10.6 and 17.6 Hz, Ar–CH=), 7.25 (d, 8.0 Hz, 2H, Ar), 7.39 (d, 8.1 Hz, 2H, Ar). ^{13}C NMR: 14.2, 22.8, 25.9, 27.3, 29.3–29.9, 32.0, 36.9, 43.4, 114.1, 126.6, 128.1, 129.8, 130.1, 136.4, 137.0, 138.1, 173.0. $C_{27}H_{43}NO{\cdot}Na^+$ calc 420.3 Da, found 420.6 Da.

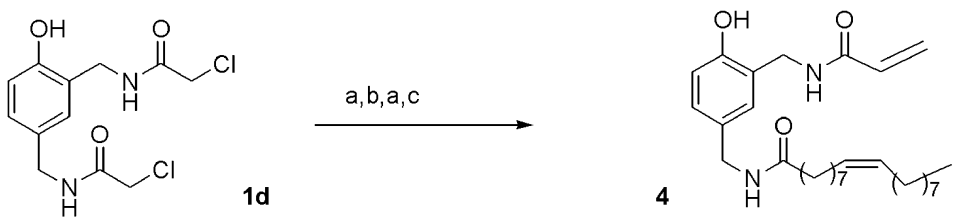


Fig. 4 Preparation of the oleic/acrylic adduct. Reagents and conditions: *a* one equiv thiourea, EtOH, reflux, then evaporation. *b* DMF with DBU, then a premixed solution of oleic acid, DIC, and HOBt. *c* DMF with DBU, then a premixed solution of acrylic acid, DIC, and HOBt

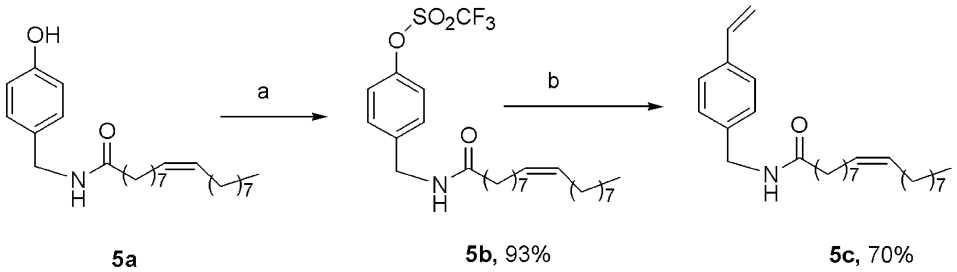


Fig. 5 Conversion of a phenol to a styrene. *a* $(CF_3SO_2)_2O$, pyridine. *b* $PdCl_2$, Cs_2CO_3, PPh_3, $KF_3BCH{=}CH_2$, 9:1 THF/water, 80 °C

Mitsunobu (Aryl Ether) Products [16] (Fig. 6)

Molecule **1b** (0.37 g, 1.9 mmol), PPh_3 (0.55 g, 2.1 mmol), and 17-hydroxy oleic acid methyl ester [17] (0.72 g, 2.3 mmol), were dissolved in 10 mL THF. To this mixture was added diisopropyl azodicarboxylate (DIAD, 0.42 g, 2.1 mmol) in 2 mL THF. The reaction was stirred overnight. Solvent was removed, and column chromatography on silica gel gave **6a** (805 mg, 86%). Reactions using molecules **1c** or **1d** afforded similarly **6c** (69%) or **6b** (73%), respectively.

Aryl ether **6a** (0.18 g, 0.37 mmol) was then treated with thiourea (50 mg, 0.66 mmol) in 10 mL EtOH for 2 h at reflux, and solvent was removed. DMF (3 mL) and DBU (56 μL, 0.37 mmol) were added, followed by a premixed solution of oleic acid (113 mg, 0.4 mmol), DIC (50 mg, 0.4 mmol), and HOBt (61 mg, 0.4 mmol). After 2 h, the solvent was removed, and column chromatography gave molecule **7** (204 mg, 81%). Molecule **6b** (350 mg, 0.6 mmol) was deprotected and coupled similarly with 2 equiv of 17-azido oleic acid (prepared as reported by us previously [17]). The DMF solvent was removed, and the crude taken up in THF with approximately 100 μL H_2O, then PPh_3 (393 mg, 1.5 mmol) was added. The reaction was stirred for 1 h, then Boc anhydride (436 mg, 2 mmol) was added. The reaction was stirred overnight, solvent was removed, and column chromatography gave molecule **8b** (489 mg, 65% from **6b**). **6c**: ^{1}H NMR: 1.15–1.52 m, 1.55–1.81 m, 1.93–2.12 (m, 4H, =CH–CH_2), 2.33 (t, 7.1 Hz, 2H, C(O)CH_2), 3.67 (s, 3H, Me ester), 4.01–4.19 (m, 1H, ArOC(17)H), 4.09 (s, 4H, CH_2Cl), 4.58 (d, 6.9 Hz, 4H, CH_2NH), 5.28–5.43 (m, 2H, olefin H), 7.07–7.20 (m, 3H, 2 × NH and Ar para H), 7.21–7.30 (m, 2H, Ar-3H and -5 H). ^{13}C NMR: 19.8, 25.0, 25.8, 27.3, 29.2–29.8, 34.2, 37.1, 40.0, 42.8, 51.6, 80.0 (C(17)-O), 124.6, 129.4, 129.9, 130.0, 131.3, 154.0, 165.9, 174.5. **7**: ^{1}H NMR: 0.91 (t, 6.8 Hz, 3H, CH_3), 1.18–1.43 m, 1.53–1.77 m, 1.94–2.12 (m, 8H, =CH–CH_2), 2.21 (t, 7.2 Hz, 2H, amide C(O)CH_2), 2.32 (t, 7.3 Hz, 2H, ester C(O)CH_2), 3.69 (s, 3H, Me ester), 4.26–4.37 (m, 1H, ArOC(17)H), 4.39 (d, 6.9 Hz, 2H, $ArCH_2$), 5.25–5.43 (m, 4H, olefin H), 5.64 (br s, NH), 6.86 (d, 8.0 Hz, 2H, Ar), 7.10 (d, 8.0 Hz, 2H, Ar). ^{13}C NMR: 14.2, 19.8, 22.8, 25.0, 25.6, 25.9, 27.3, 29.2–29.9, 34.2, 36.6, 37.0, 43.2, 51.6, 74.1 (C(17)-O), 116.1, 129.3, 129.9, 130.1, 130.3, 157.8, 172.9, 173.4. **8b**: ^{1}H NMR: 1.12 (d, 6.9 Hz, 6H, CH_3), 1.21–1.42 m, 1.45 (s, 18H, Boc tBu), 1.52–1.79 m, 1.94–2.09 (m, 12H, =CH–CH_2), 2.14–2.24 (m, 4H, amide C(O)CH_2), 2.32 (t, 7.3 Hz, 2H, ester C(O)CH_2), 3.52–3.62 (m, 2H, C(17)*H*–NH), 3.69 (s, 3H, Me ester), 4.27–4.50 (m, 5H, $ArCH_2$ and ArOC(17)H), 5.28–5.43 (m, 6H, olefin H), 5.80 (m, 3H, amide and Boc NH), 5.98 (m, 1H, amide), 6.82 (d, 6.6 Hz, 1H, Ar-3H), 7.11–7.22 (m, 2H, Ar-5H and -6H). ^{13}C NMR: 19.7 (C(18) next to O–Ar), 21.3 (C(18) next to NH-Boc), 22.8, 25.0, 25.6, 25.9, 26.1, 27.3, 28.5, 29.2-29.9, 32.0, 34.3, 36.6, 37.0, 37.5, 40.7, 43.3, 47.1 (C(17)H-NHBoc), 51.5 (Me ester), 79.0 (Boc quaternary C), 79.2 (C(17)-O), 117.9, 123.9, 129.1, 129.9, 130.1, 130.8, 155.4 (Boc carbamate C=O), 157.7 (ArC-OH), 173.0, 173.4. **6c**: $C_{31}H_{48}Cl_2N_2O_5{\cdot}Na^+$ calc 621.3 Da, found 621.6 Da. **7**: $C_{44}H_{75}NO_4{\cdot}Na^+$ calc 704.6 Da, found 704.4 Da. **8b**: $C_{73}H_{128}N_4O_9{\cdot}Na$ + 1228.8 Da, found 1228.5 Da.

Results and Discussion

Strategies for Linking Phenol to FA

We sought a synthetically flexible method for creating FA–phenol conjugates, that is, a method that would permit incorporation of other functional groups in a variety of spatial arrangements. Several methods were available. The most obvious would be just to prepare the phenyl ester, but then there would be no options for further derivatization using the FA carboxy unit, and further chemical modifications of the Ar ring might hydrolyze the ester. In fact this route has been reported in a patent for preparing anti-tumor compounds that are esters of phenols and fatty acids [18]. An alternative is to use acid-catalyzed addition of the electron-rich aromatic ring to the olefin. While this procedure is convenient on a large scale, it consumes the olefin, so epoxidation would not be possible. Instead, we took advantage of the electron-rich character in a different way, using the Tscherniac–Einhorn reaction. This long-known reaction [14] uses acid catalysis to substitute a hydroxymethyl amide onto the ring, affording amidomethylated

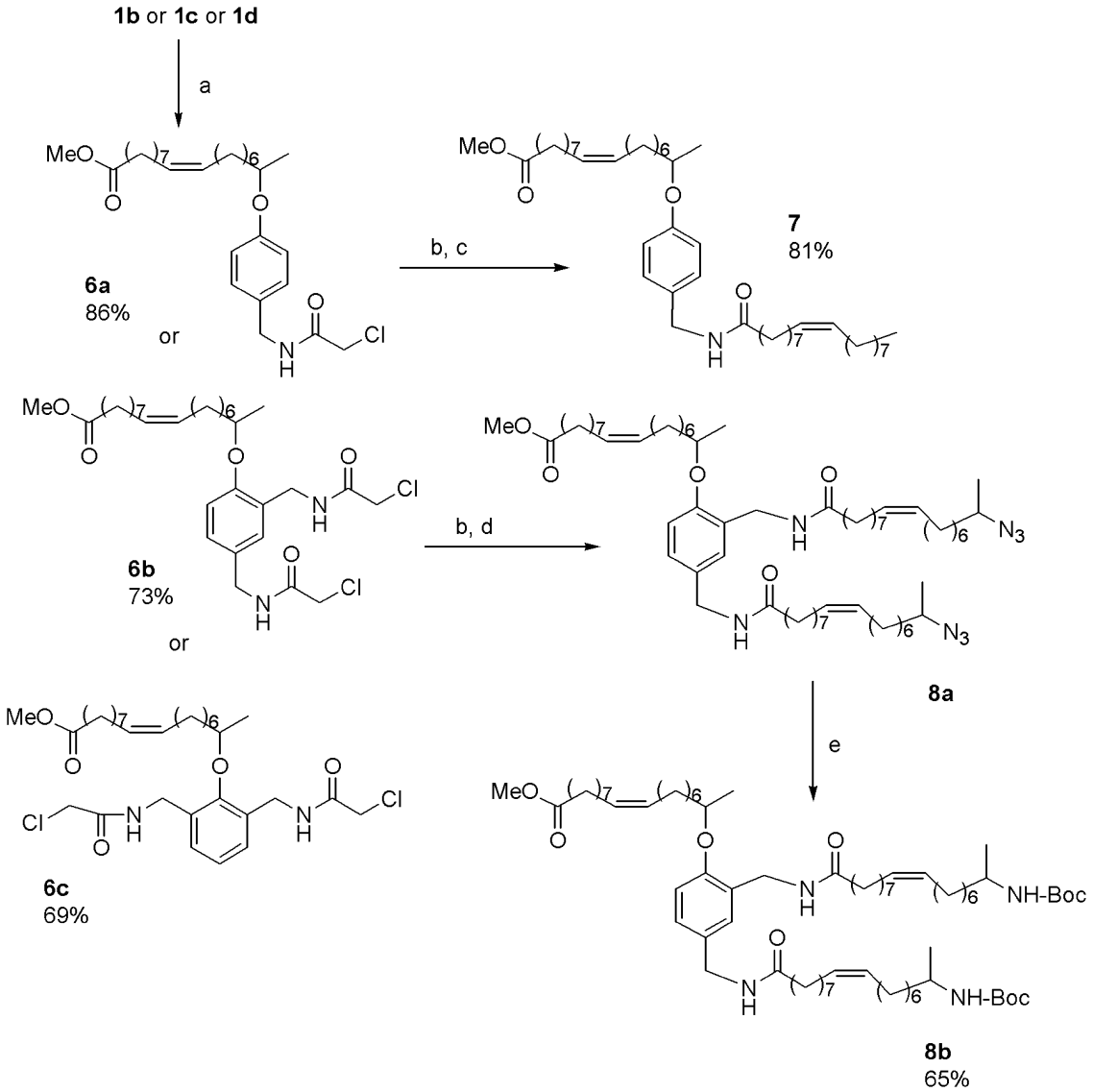


Fig. 6 Synthesis of oleic aryl ethers. *a* 17-OH oleic acid, DIAD, PPh_3. *b* Thiourea, EtOH, reflux, then evaporation. *c* DMF with DBU, premixed solution of oleic acid, DIC, and HOBt. *d* DMF with DBU, premixed solution of 17-azido oleic acid, DIC, and HOBt. *e* PPh_3, aq. THF, then Boc_2O

phenols. By controlling the stoichiometry of the reagents, the product distribution can be driven toward predominant addition of one, two, or three such units, although of course a mixture of products is obtained. This distribution is not a drawback in our intended use of these compounds for two reasons. First, all the compounds can be separated from each other via silica gel chromatography if a specific substitution pattern is desired. Alternatively, for use in materials blends with EVO, we propose that there is no need to separate the individual compounds, they can just be employed as a collected group. This grouping of a variety of molecules is analogous to the heterogeneous nature of EVO itself, since some of the fatty acid chains are saturated and unepoxidized (stearic), some mono or di-epoxidized (oleic or linoleic). One special benefit of the amidomethylphenol structure that our molecules possess is the presence of the hydrogen-bonding NH–CO units. Intermolecular hydrogen bonding between amides is known to impart toughness to polymers, such as nylons, that contain such groups. To the best of our knowledge, FA/phenol conjugates linked through an amidomethyl unit have not been previously reported.

The Tscherniac–Einhorn reaction between two or three equivalents of hydroxymethylchloroacetamide and phenol proceeds smoothly at room temperature, and isolation of the products is straightforward (Fig. 1). The chloroacetamide unit, which essentially serves as a protecting group, has the benefit of being removable with different classes of

reagent, either acid, base, or nucleophile. We found that the base method was cumbersome and gave unsatisfactory results (unidentified side products). The acid route is convenient, but after removal of the aqueous solvent, the chloroacetic acid is still present—if it is not removed, it will compete with the incoming acyl unit that is intended for ligation to the aminomethylphenol. Fortunately, the chloroacetic acid can be fully removed by evaporation or by trituration with diethyl ether. NMR of the material after this treatment showed that no chloroacetic units remained. Once the chloroacetyl group is removed, the free amine is coupled to oleic acid or some other acid using standard amide-forming protocols. We used carbodiimide couplings, but other reagents could be used. In principle, acylation could also occur at the phenol OH, but that group is a poor nucleophile, and we have not observed any such products. The deprotected aminomethyl phenols are obtained as their hydrochloride salts, so during couplings we include a stoichiometric amount of 1,8-diazabicycloundecene (DBU), a non-nucleophilic base.

Synthesis of FA/amidomethylphenol conjugates

The simplest example in this new family of molecules is the triply substituted oleyl phenol **2a** (Fig. 2). After removal of the chloroacetyl groups from **1e** with HCl, coupling with oleic acid gave **2a** in good yield. Since one ultimate use for these compounds is in crosslinking, we also examined its epoxidation. This reaction went smoothly to give the expected product **2b**. Neither the phenol group nor the amide interferes with the epoxidation.

A more complicated situation arises if different acylating partners are used (Fig. 3). We reacted the acid-deprotected tris aminomethylphenol with a mixture containing one equivalent of oleic acid and one equivalent of Boc-β-alanine. As expected, a mixture of products was observed: small amounts of trioleic (**2a**) and tri-Boc-β-alanine adducts, plus the mono oleic/di Boc-β-Ala and the di oleic/mono Boc-β-Ala adducts. There is a further complication in that the two 2:1 compounds can each be symmetric or non-symmetric. With careful chromatography, all four compounds can be isolated, however. Our motivation behind performing this separation was simply to identify the compounds, not to propose that it would be practical to do so. Instead, we would expect that employment of these compounds in a crosslinked matrix with EVO would simply keep all the relatives together, that is, A_3, B_3, and all isomers of A_2B and AB_2. It is true that the B_3 compound would not take part in epoxidation and crosslinking, but it could presumably be extracted out of the material after these steps.

One interesting manner in which the chloroacetamide protecting group can be taken advantage of is by partial deprotection. Since its removal by a nucleophile is on a stoichiometric basis, not catalytic, it is easier to control. We used one equivalent of thiourea [19] to partially deprotect the disubstituted molecule **1d**, then coupled the product to oleic acid (Fig. 4). The deprotection procedure can be repeated with another equivalent of thiourea, then the amine coupled to a different acyl group. To demonstrate the appending of a group that could be used for polymerization, the second acyl group we attached was an acryloyl unit. We propose that the acrylic unit can be polymerized first, then the pendant oleic chain epoxidized. Concerning the utility of thiourea as a stepwise deprotectant, results are mixed. Even though a single equivalent of it can be added, the species in solution are not selective, that is, once one of the chloroacetyl groups has been removed, even though there is only one equivalent total of thiourea, the second chloroacetyl group on the same molecule could also be removed. As a result, after the oleic acid coupling described for **1d**, we observed dioleic product as well as unreacted **1d** and the expected two isomers of monooleic/monochloroacetyl (one with FA ortho to OH and the other para). This product distribution of four molecules is similar to what would be expected if we had used HCl to remove both chloroacetyl groups in a single step, then coupled with an equimolar mixture of acrylic acid and oleic acid. We can only speculate, but it may be that separation of the ortho/para isomers may be easier when one of the groups is chloroacetyl, that is, since it is less hydrophobic than a longer alkyl group, it is "more different" from the oleic group, and polarity differences between the isomers may aid chromatographic separation.

A second way to introduce a polymerizable unit to this class of molecules is through the phenolic OH (Fig. 5). Recent synthetic advances have shown how this functional group can be readily converted to a vinyl unit [15]. These routes rely on the easy conversion of OH to a trifluoromethanesulfonate, which then reacts with a metal catalyst and a vinylating reagent in a Suzuki–Miyaura reaction. We found that this methodology worked well with our oleic phenol conjugate **5a**. The resulting styrene compound **5c** should be polymerizable to afford a polystyrene derivative with oleic amidomethyl units at the para position, following which the olefin groups of the pendant oleic chains would be epoxidized and crosslinked. As an aside, it might be worth noting the structural similarity of molecule **5a** to FA derivatives of *p*-coumaric acid. Since lipophilization of phenolics is an active area of research [20], these FA–amidomethyl phenols could find a role in such studies as well as in materials chemistry.

Another use for the OH group is by forming ethers with it, using Mitsunobu protocols [16]. This route requires an alcohol reacting partner, for which we chose a hydroxylated fatty acid, namely 17-hydroxy oleic acid. The preparation of

this hydroxy fatty acid from fermentation of fats or oils was described by us previously [17]. Isolation of the arylated hydroxy fatty acid was straightforward (Fig. 6). We also investigated whether substitution ortho to the OH by the chloroacetamidomethyl group would be too sterically hindering to allow ether formation at the OH. It was interesting to observe that both the 2,6-disubstituted and 2,4-disubstituted molecules **1c** and **1d** gave good yields of the aryl ethers **6c** and **6b**. This synthetic route has the advantage of incorporating another unit of epoxidizable fatty acid, but one that still possesses its carboxylic group for further derivatization. The COOH of the hydroxy fatty acid, in other words, was not used to make a connection to the phenol group, so it can be employed as a "carrier" for some other functional group of choice, either as an ester or an amide. In this way, the basic phenol/fatty acid structure can be converted to another kind of AB_2 monomer, as shown in the preparation of **8b** (Fig. 6). After Mitsunobu reaction with 17-hydroxy oleic acid to give the aryl ether with 2,4-di(chloroacetyl) amino methyl groups **6b**, the chloroacetyl groups were removed with thiourea. This is a case where HCl deprotection of chloroacetyl could well be unacceptable (hydrolyzing the methyl ester or perhaps adding across the C=C). The deprotected amine groups were then coupled to 17-azido oleic acid, a compound we recently reported [17]. The resulting di-azide **8a** could be used in click reactions, although, if the products were intended for later epoxidation and crosslinking, problems might arise with the 1,2,4-triazole that the click reaction produces: it could be oxygenated by an epoxidation agent. Instead, we used the Staudinger reaction to reduce the azide to NH_2, and prepared the Boc derivative in situ. This molecule **8b** is thus set to be used as an AB_2 monomer in the preparation of hyperbranched polymers that are epoxidizable and crosslinkable. In conjunction with acrylamide **4** and styrene derivative **5c**, it suggests some new directions in structural motifs for the preparation of bioderived, fatty acid-based polymers and materials.

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