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ORIGINAL PAPER

Omega-Functionalized Fatty Acids, Alcohols, and Ethers via Olefin Metathesis

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Abstract Methyl 17-hydroxy stearate was converted to methyl octadec-16-enoate using copper sulfate adsorbed on silica gel. This compound served as a useful substrate for the olefin metathesis reaction. As a result, several fatty acids with novel functional groups at the ω-end were prepared: a glyceryl ether attached at the 18-carbon, an aromatic fatty acid from eugenol, and a ferrocenyl fatty acid. By employing the unsaturated fatty alcohol, other groups were introduced, namely the terminal fluoride, bromide, and iodide were prepared, as was a thiol derivative. The penultimate and omega olefins reported here should serve as building blocks that allow fatty acids to make a greater contribution to a range of emerging technological areas.

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

Introduction

Chemical derivatization of fatty acids is almost exclusively performed toward the middle of the chain (not counting transformations of the carboxylic group) since that is where nature overwhelmingly provides the functionality, usually olefinic and more rarely an alcohol. From the standpoint of molecular design of lipidic materials, this limitation is regrettable, since there are fewer options for controlling the shapes of the chemical building blocks. While being able to tailor and make use of groups at the α and ω ends of a hydrophobic fatty acid chain would have an impact on more familiar materials such as polymers, films and coatings, and bilayers and micelles, there are also newer areas of technology where an expanded palette of fatty acid structures could be put to use, if it were available. These include matrices for protein crystallization [1], delivery vehicles for drugs or nucleic acids [2–4], and design of structures ranging from carbon nanotube arrays [5] to microfluidic reactors [6] to membrane-permeable prodrugs [7]. Fortunately, there are some readily available fatty acids that offer different substitution patterns. In particular, we have been exploring transformations of 17-OH or 18-OH oleic and stearic acid, which are readily obtained from glycolipids, namely sophorolipids. The sophorolipids in turn are obtained in good amounts by fermentation of low-value agricultural byproducts [8]. Our previous work involved replacing the OH with an azide or propargyl group and performing click reactions [9]. While this approach proved to be a useful way to link together disparate types of molecules, since the click reaction is widely tolerant of many functional groups, there may be situations where the resulting polar 1,2,3-triazole might not be desirable, e.g. in a predominantly hydrophobic environment. This paper reports the dehydration of 17-OH stearic acid and subsequent products containing enhanced functionality that are made using olefin metathesis and other reactions.

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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 an Inova 400 MHZ instrument. LCMS data were recorded on a Waters 3100 instrument with positive-mode Electrospray Ionization (ESI), using direct injection (no column) with 9:1 CH_3CN:0.5% HCO_2H in CH_3CN as eluent. Masses reported in Da, were determined as sodiated ionic adducts of the products $[M+Na]^+$ or protonated adducts $[M+H]^+$.

Preparation of ω-2 Fatty Acid **2** [10]

The copper sulfate/silica reagent was prepared by slowly adding 35 g of silica gel to a warm aqueous solution (approx. 50 °C) of copper sulfate pentahydrate (13.6 g brought up to 50 mL) with stirring in a crystallization dish. The slurry that formed remained fluid enough to be magnetically stirrable until the last few grams of silica were added, at which point it was mixed by hand. This method avoided the presence of a separate aqueous layer, which would lead to the appearance of discrete copper sulfate crystals. The wet silica was heated at 50 °C overnight, then in an oven at 200 °C for 2 h, following which, it was stored in a vacuum desiccator and used without any further changes.

To a solution of methyl 17-hydroxy stearate **1a** (1 g, 3.2 mmol) in 25 mL of toluene was added approximately 2 g of the copper sulfate/silica reagent. The toluene mixture was refluxed overnight, after which another portion of the reagent was added. Total reflux time was 24 h. The silica was filtered off, toluene removed under vacuo, and the product **2** was separated from unreacted starting material by passage through a short column of silica gel (Fig. 1). Three repetitions gave yields of 53, 57, and 66%. Carbon tetrachloride could be used as solvent instead of toluene with no apparent differences in yield. ^{1}H NMR 1.20–1.44 br s, 1.49–1.75 (m 5H, $C(O)CH_2CH_2$ and $=CHCH_3$), 1.90–2.11 (m, 2H, CH_2–CH=), 2.32 (t, 7.2 Hz, 2H, $CH_2C(O)$), 3.67 (s, 3H, Me ester), 5.30–5.45 (m, 2H, olefin). ^{13}C NMR 25.1, 27.1, 29.4–29.9, 32.8, 34.3, 51.7, 124.7, 132.0, 174.6. MS calc. for $C_{19}H_{36}O_2{\cdot}H^+$ 297.3 found 297.4.

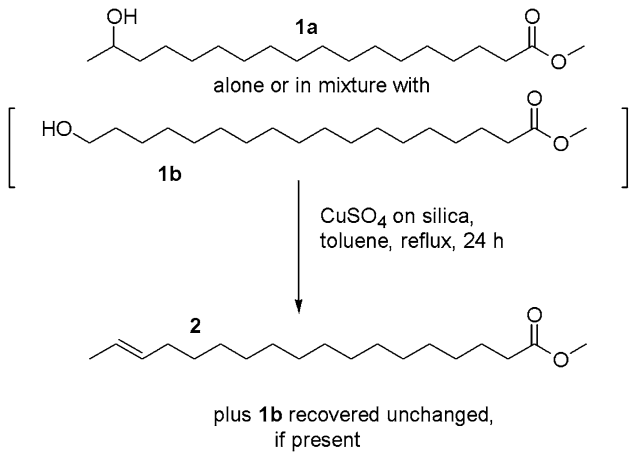

Fig. 1 Conversion of a hydroxy fatty acid to a monounsaturated fatty acid

General Conditions for Cross-Metathesis [11]

The reacting components were dissolved in 10 mL of methylene chloride in the ratios listed below, Grubbs' second-generation metathesis catalyst was added (5 mol % based on limiting metathesis partner) and the mixture was heated under nitrogen in a water bath at 40–45 °C overnight. After 18 h, another portion of catalyst was added and reaction continued for another 8 h. Solvent was removed and the crude mixture was applied to a silica gel column.

Compound **4**

2 (0.5 g, 1.8 mmol) and **3** (0.93 g, 5.4 mmol), yield = 0.32 g (45%). ^{1}H NMR 1.20–1.42 m, 1.38 and 1.44 (each s, 3H, acetonide methyls), 1.55–1.72 m, 1.98–2.12 (m, 2H, CH_2–CH=), 2.32 (t, 7.3 Hz, 2H, $CH_2C(O)$), 3.35–3.59 (m, 2H, CH_2OCH_2CH=), 3.68 (s, 3H, Me ester), 3.69–3.85 and 3.96–4.16 (dd, 6.4 and 8.2 Hz, 2H, acetonide ring CH_2), 3.83–3.94 (m, 2H, CH_2OCH_2CH=), 4.22–4.35 (m, 1H, glyceryl CH), 5.45–5.80 (m, 2H, olefin). ^{13}C NMR 25.2, 27.1, 29.4–29.9, 32.8, 34.3, 51.6, 67.2, 71.1, 72.5, 74.9, 109.6, 126.0, 135.5, 174.6. MS calc. for $C_{25}H_{46}O_5{\cdot}Na^+$ 449.3 found 449.3.

Compound **7**

6 (0.41 g, 1.3 mmol) and **3** (0.68 g, 3.9 mmol), yield = 0.28 g (51%). ^{1}H NMR 1.21–1.42 m, 1.38 and 1.44 (each s, 3H, acetonide methyls), 1.55–1.72 m, 1.98–2.11 (m, 2H, CH_2CH=), 2.06 (s, 3H, acetate CH_3), 3.35–3.59 (m, 2H, CH_2OCH_2CH=), 3.69–3.81 and 3.96–4.16 (dd, 6.5 and 8.2 Hz, 2H, acetonide ring CH_2), 3.81–3.94 (m, 2H, CH_2OCH_2CH=), 4.07 (t, 7.5 Hz, 2H, $CH_2OC(O)$), 4.22–4.37 (m, 1H, glyceryl CH), 5.45–5.80 (m, 2H, olefin). ^{13}C NMR 21.2, 25.6, 26.1, 27.0, 28.8, 29.3–29.8, 32.5,

64.9, 67.2, 71.0, 72.6, 75.0, 109.6, 126.1, 135.6, 171.5. MS calc. for $C_{26}H_{48}O_5 \cdot Na^+$ 463.3 found 463.3.

Compound **16**

2 (0.5 g, 1.8 mmol), eugenol (0.89 g, 5. 4 mmol), yield = 0.42 g (59%). ^{1}H NMR 1.16–1.41 br s, 1.50–1.71 m, 1.94–2.08 (m, 2H, CH_2CH=), 2.30 (t, 7.4 Hz, 2H, CH_2C(O)), 3.25 (d, 5.9 Hz, 2H, ArCH_2), 3.67 (s, 3H, Me ester), 3.86 (s, 3H, eugenol OMe), 5.46–5.57 (m, 2H, olefin), 6.63–6.73 (m, 2H, Ar), 6.84 (d, 6.2 Hz, 1H, Ar). ^{13}C NMR 25.1, 29.2–29.7, 32.6, 34.2, 38.8, 51.5, 55.9, 111.1, 114.2, 121.1, 129.1, 132.1, 133.2, 143.8, 146.5, 174.5. MS calc. for $C_{26}H_{42}O_4 \cdot Na^+$ 441.3 found 441.4.

Compound **17**

Allyl ethyl ferrocene ether (0.33 g, 1.2 mmol), **2** (0.15 g, 0.53 mmol), yield = 108 mg (41%). ^{1}H NMR 1.56 (d, 7.5 Hz, 3H, OCHCH_3), 1.58–1.73 m, 1.91–2.07 (m, 2H, CH_2CH=), 2.32 (t, 7.3 Hz, 2H, CH_2C(O)), 4.16 (br s, 9H, ferrocene), 4.11–4.20 (m, 2H, OCH_2), 4.20–4.30 (m, 1H, OCH), 5.33–5.43 (m, 2H, olefin). ^{13}C NMR: 20.1, 25.1, 27.3, 29.2–29.9, 32.8, 34.2, 51.5, 65.9, 67.9, 68.2, 68.8 (br), 75.0, 130.0, 130.5, 174.4. MS calc. for $C_{31}H_{47}FeO_3 \cdot H^+$ 524.3 found 524.6.

Compound **3** was prepared by dissolving commercially available 3-allyloxy-1,2-propane diol in CH_2Cl_2, adding 2,2-dimethoxy propane (3 equiv) and pyridinium *p*-toluenesulfonate (PPTS, 5 mol%), and stirring at room temperature overnight. The solvent was removed and the crude was passed through a short plug of silica gel to remove PPTS, affording **3**. The allyl ether of ferrocenyl ethanol was prepared by combining ferrocenyl ethanol with allyl bromide (3 equiv) in DMSO and adding powdered KOH (1.5 equiv), then pouring the mixture into water after 2 h and extracting with 1:1 hexane/ethyl ether.

Reduction of Methyl Ester to Give **6** [12]

Compound **2** (1.1 g, 3.9 mmol) and poly(methylhydrosiloxane) (0.58 g, 10 mmol Si–H equivalents) were placed in a flask, and then titanium tetraisopropoxide (1.1 g, 4.5 mmol) was added. The mixture was stirred magnetically under nitrogen and heated to 60 °C for 3 h. After cooling to room temperature, 30 mL THF was added, followed by cautious dropwise addition of 30 mL 4 M NaOH. This mixture was stirred overnight. To remove some of the THF, a stream of nitrogen was directed over it for a few hours, then it was poured into 300 mL H_2O and extracted with 1:1 hexane/ethyl ether. TLC indicated that the crude material was almost pure. After removing the solvent, the material was dissolved in 15 mL CH_2Cl_2 and acetic anhydride (0.48 mL, 5 mmol), pyridine (0.5 mL, 6 mmol), and 4-dimethylaminopyridine (DMAP, 20 mg) were added. The mixture was stirred overnight, extracted with water, and organic solvent was evaporated. The acetate **6** obtained (0.89 g, 77%) was subsequently used without further purification. ^{1}H NMR 1.20–1.42, 1.57–1.70 (m, 5H, –OCH_2CH_2 and =CHCH_3), 1.91–2.09 (m, 2H, CH_2–CH=), 2.07 (s, 3H, acetate CH_3), 4.07 (t, 7.4 Hz, 2H, CH_2–O) 5.38–5.48 (m, 2H, olefin). ^{13}C NMR 18.0, 22.7, 25.8, 26.9, 29.3–29.8, 32.7, 32.8, 63.5, 124.6, 131.9, 171.7. MS Calc. for $C_{20}H_{38}O_2 \cdot H^+$ 311.3 found 311.4.

Dihydroxylation to **5** and Epoxidation to **12**

Compound **4** (0.15 g, 0.35 mmol) was dissolved in 10 mL 1:1 *t*-BuOH/H_2O, and to the solution was added 0.7 g commercially available "AD-β" mix (Sharpless' reagent) along with 100 mg methanesulfonamide. The mixture was stirred overnight at room temperature, then sodium metabisulfite was added. The reaction was poured into 200 mL H_2O and 100 mL ethyl acetate and extracted. Removal of solvent followed by passage through a short plug of silica gel with 1:1 hexane/ethyl acetate gave analytically pure material, 94%. ^{1}H NMR 1.13–1.34 br s, 1.36 and 1.44 (each s, 3H, acetonide methyls), 1.50–1.70 m, 2.31 (t, 7.2 Hz, 2H, CH_2C(O)), 3.44–3.52 (m, 1H), 3.52–3.71 (m, 4H), 3.66 (s, 3H, methyl ester), 3.69–3.78 (m, 2H), 4.02–4.10 (dd, 6.5 and 8.1 Hz, 1H, one of the acetonide ring CH_2), 4.24–4.33 (m, 1H, glyceryl CH). ^{13}C NMR 25.2, 27.1, 29.4–29.9, 32.8, 34.3, 51.6, 63.3, 66.5, 72.4, 72.8, 74.6, 74.8, 109.7, 174.4. MS Calc. for $C_{25}H_{48}O_7 \cdot Na^+$ 483.3 found 483.7.

Compound **7** (0.15 g, 0.34 mmol) was dissolved in 10 mL CH_2Cl_2 and 100 mg meta-chloroperbenzoic acid was added. The reaction was stirred at room temperature overnight. Sodium metabisulfite and 10 mL H_2O were added and stirred for 30 min, then the mixture was extracted with saturated $NaHCO_3$ (3 × 20 mL). Solvent was removed and the material was passed through a short plug of silica gel with 3:1 hexane/ethyl acetate to obtain **12** (0.13 g, 85%). ^{1}H NMR 1.15–1.45 br s, 1.34 and 1.41 (each s, 3H, acetonide methyls), 1.50–1.65 m, 2.03 (s, 3H, acetate methyl), 2.76–2.82 and 2.87–2.94 (each m, 2H, epoxide ring), 3.39–3.61 (m, 4H, CH_2OCH_2), 3.67–3.78 (m, 1H, one of the CH_2 acetonide ring protons), 3.96–4.08 (m, 3H, CH_2OC(O) and one of the CH_2 acetonide ring protons), 4.21–4.32 (m, 1H, glyceryl CH). ^{13}C NMR 21.3, 25.6, 26.1, 26.9, 28.8, 29.4–29.9, 31.9, 56.2, 57.1, 64.9, 66.8, 72.1, 72.5, 74.9, 109.8, 171.6. MS calc. for $C_{26}H_{48}O_6 \cdot Na^+$ 479.3 found 479.6.

Eliminations to Give Terminal Alkenes [13] and Substitution with Thioacetate

Compound **7** (0.25 g, 0.6 mmol) was dissolved in 30 mL of MeOH and hydrogenated over 5% Pd/C for 4 h. The solid was filtered off, the solution was concentrated in vacuo to about 5 mL of methanol, and a solution of LiOH (84 mg, 2 mmol) in 2 mL of water was added. THF was added until the mixture was homogenous (approx. 3 mL), then it was heated at 45 °C for 3 h. Solvent was removed, citric acid was added to lower the pH to approximately 3, and the crude was extracted with 1:1 hexane/ethyl ether. The free alcohol thus obtained was dissolved in 5 mL of 1,2-dichloroethane, then to this solution were added NEt_3 (0.34 mL, 2.5 mmol), triphenylphosphine (0.34 g, 1.3 mmol), and 1,2-dibromotetrachloroethane (0.42 g, 1.3 mmol). The mixture was stirred at room temperature for 1 h, after which time tlc indicated complete conversion of the starting material to a less polar compound. Solvent was removed, the material was applied to a silica gel column, and the product 18-bromo compound was isolated. This compound was then dissolved in 20 mL of acetone to which NaI (0.9 g, 6 mmol) was added and heated at 45 °C overnight. Solvent was removed in vacuo, and the material was extracted with ether. The resulting iodide **8** (249 mg, 86% from **7**) was split into two portions. One portion (150 mg, 0.3 mmol) was dissolved in 3 mL DMSO and tetrabutylammonium fluoride hydrate (0.34 g, 0.8 mmol) was added. The mixture was stirred overnight, then poured into 300 mL of H_2O and extracted with ether (50 mL × 2). Column chromatography in 9:1 hexane/ether gave the terminal alkene **9** (70 mg, 63%) and the fluoride **10** (29 mg, 25%). The other portion (80 mg, 0.16 mmol) was dissolved in acetone along with potassium thioacetate (114 mg, 1 mmol) and heated to 45 °C overnight. Solvent was removed, the crude applied to silica gel, and eluted with 4:1 hexane/ether to give **11** (69 mg, 93%). ^{1}H NMR (only the chemically relevant new peaks differing from **7** are listed) **9**: 4.90–5.08 (m, 2H, $=CH_2$), 5.72–5.95 (m, 1H, =CH). ^{13}C NMR 114.2 and 139.5 (terminal olefin). MS Calc. for $C_{24}H_{46}O_3{\cdot}Na^+$ 405.3 found 405.6. **10**: ^{1}H NMR 4.34 and 4.57 (each t, 6.5 Hz, 2H, ^{1}J H/F = 47.3 Hz, CH_2–F). ^{13}C 83.6, 85.3 (CH_2–F). MS Calc. for $C_{24}H_{47}FO_3{\cdot}Na^+$ 425.3 found 425.5. **11**: 2.87 (t, 6.8 Hz, 2H, CH_2–S). ^{13}C NMR 30.8 (S–CH_2), 196.4 (S–C=O). MS Calc. for $C_{26}H_{50}O_4S{\cdot}Na^+$ 481.3 found 481.5.

Compound **1b** (0.27 g, 0.86 mmol) was treated similarly as **7** in the preceding paragraph to make the iodide, using NEt_3 (0.56 mL, 4 mmol), triphenylphosphine (0.45 g, 1.7 mmol), and 1,2-dibromotetrachloroethane (0.55 g, 1.7 mmol), then NaI (1.35 g, 9 mmol). The resulting iodide (0.32 g, 0.77 mmol) was dissolved in 5 mL DMSO, and tetrabutylammonium fluoride hydrate (0.84 g, 2 mmol) was added. The mixture was stirred overnight, then poured into 300 mL of H_2O and extracted with ether (50 mL × 2). Column chromatography in 9:1 hexane/diethyl ether afforded terminal alkene **13** (154 mg, 71%) and fluoride **14** (45 mg, 20%). **13**: ^{1}H NMR 1.20–1.45 br s, 1.53–1.71 m, 1.97–2.12 (m, 2H, CH_2CH=), 2.32 (t, 7.2 Hz, 2H, CH_2C(O)), 3.68 (s, 3H, Me ester), 4.90–5.08 (m, 2H, CH_2=), 5.72–5.95 (m, 1H, =CH). ^{13}C NMR 25.1, 29.0–29.7 br, 33.9, 34.2, 51.7, 114.2, 139.3, 174.5. MS calc. for $C_{19}H_{36}O_2{\cdot}H^+$ 297.3, found 297.2. **14**: ^{1}H NMR 1.20–1.49 br s, 1.54–1.73 m, 1.73–1.87 m, 2.32 (t, 7.3 Hz, 2H, CH_2C(O)), 3.68 (s, 3H, Me ester), 4.34 and 4.57 (two triplets, 6.6 Hz, ^{1}J H/F = 47.3 Hz, 2H, CH_2–F). ^{13}C NMR: 25.1, 27.0, 28.9–27.9, 30.3, 30.7, 32.8, 34.7, 51.5, 82.7, 85.9, 174.2. MS calc. for $C_{19}H_{37}FO_2{\cdot}Na^+$ 339.4 found 339.3.

Non-Metathesis Route to Glyceryl Ether

Acetate **6** (0.65 g, 2.1 mmol) was dissolved in 10 mL MeOH, then LiOH hydrate (0.13 g, 3 mmol) in 3 mL H_2O was added, followed by THF until the solution became homogeneous with only slight haziness, about 7 mL total THF. The reaction was heated at 45 °C in a waterbath for 3 h, then at RT overnight. Solvents were removed, saturated citric acid solution was added and the mixture was extracted with ether (2 × 50 mL). After removing the ether, the crude material was dissolved in methylene chloride, and pyridine (0.4 mL, 5 mmol) and methanesulfonyl chloride (0.35 g, 3 mmol) were added. The reaction was stirred at RT overnight, then solvent was removed and the crude was purified by passage through a short silica gel plug. This mesylate **6a** and solketal (0.66 g, 5 mmol) were dissolved in 2 mL of DMSO, then powdered KOH (0.17 g, 3 mmol) was added and stirred vigorously for 2 h, after which time the mixture was poured into 500 mL of H_2O and extracted with 100 mL of ether. Column chromatography afforded **15** in 67% yield (0.49 g) based on the starting acetate **6**. ^{1}H NMR 1.20–1.35 br s, 1.38 and 1.44 (each s, 3H, acetonide methyls), 1.50–1.72 (m 5H, OCH_2CH_2 and $=CHCH_3$), 1.89–2.11 (m, 2H, CH_2–CH=), 3.36–3.59 (m, 4H, –CH_2OCH_2–), 3.68–3.75 and 4.01–4.06 (dd, 6.4 and 8.2 Hz, 2H, acetonide ring CH_2), 4.19–4.35 (m, 1H, glyceryl CH), 5.32–5.48 (m, 2H, olefin). ^{13}C NMR 18.2, 25.6, 26.3, 27.0, 29.4–29.9, 32.8, 67.1, 72.1, 72.2, 75.0, 109.6, 123.8 (cis), 124.7, 131.1 (cis), 131.9. MS calc. for $C_{24}H_{46}O_3{\cdot}Na^+$ 405.3 found 405.6.

Alkylation of Phenolic Fatty Acid **16**

Compounds **16** (200 mg, 0.48 mmol), **1a** (220 mg, 0.7 mmol) and triphenylphosphine (158 mg, 0.6 mmol) were dissolved in 10 mL THF. To this solution was added a

solution of diisopropyl azodicarboxylate (121 mg, 0.6 mmol, in 3 mL THF) dropwise. The reaction was stirred magnetically under N_2 overnight, then solvent was removed at reduced pressure and the crude was applied to a silica gel column. Elution with 3:1 hexane/ethyl acetate afforded **16a** (235 mg, 69%). ^{1}H NMR 1.22 (d, 6.8 Hz, 3H, OCHCH_3), 1.25–1.53 br s, 1.53–1.75 m, 1.90–2.06 (m, 2H, =CHCH_2), 2.31 (t, 7.4 Hz, 4H, 2 × CH_2C(O)), 3.23 (d, 5.9 Hz, 2H, ArCH_2), 3.67 (s, 6H, 2 × methyl ester), 3.81 (s, 3H, Ar–OCH_3), 4.07–4.15 (m, 1H, ArOCH), 5.41–5.53 (m, 2H, olefin), 6.63–6.73 (m, 2H, Ar), 6.79 (d, 6.4 Hz, 1H, Ar). ^{13}C NMR: 19.3, 22.9, 25.2, 25.6, 29.3–29.9, 32.1, 32.8, 34.3, 38.9, 51.6, 56.1, 80.1, 112.7, 116.1, 120.4, 129.1, 132.2, 134.1, 146.5, 150.5, 174.6. MS calc. for $C_{45}H_{78}O_6 \cdot Na^+$ 737.8 found 737.8.

Results and Discussion

Preparation of ω-2 Alkene

The necessary first step is to perform dehydration of the penultimate alcohol to afford an alkene. Our standard starting material was methyl 17-hydroxystearate, produced by hydrogenation of the oleic hydroxy fatty acid that is the most abundant component in sophorolipids. In principle, there should be many methods to accomplish the dehydration, most of which involve converting the OH to a leaving group (halide, sulfonate ester) and elimination. Even the most straightforward of these routes, however, requires the cost and time of extra reagents which could furthermore complicate cleanup. While such routes can work well, and we have employed some in the past [14], we sought a more direct route that could be performed without an intermediate transformation. The direct elimination of alcohols to alkenes using copper sulfate adsorbed on silica gel has been reported [10]. It worked adequately in our hands; several repetitions gave yields in the 53–66% range after 24 h. While these yields are not high, the simplicity of the reaction and the ease of separation of product from unreacted starting material, which can then easily be recycled for another round, more than make up for moderate yields. A side benefit is that this dehydration works tolerably on secondary alcohols but not at all on primary ones, so that if the 18-OH stearate is present, it remains unchanged. This terminal alcohol is a minor component isolated from the sophorolipids, and normally we separated it away from the 17-hydroxy version using silica gel chromatography prior to the dehydration, but in one test reaction where we did not remove it, it was recovered intact, although there did appear to be a little of an unknown side product that was formed.

Cross-Metathesis Reactions

After installing the olefin at the C16–C17 position of the chain, we set out to demonstrate the variety of functional groups that could be added at this site of a fatty acid by employing olefin cross-metathesis with Grubbs' "second-generation" catalyst [11]. This reaction has been applied to mid-chain olefinic fatty acids before [15–18], but not, to our knowledge, closer to the hydrophobic terminus of the C18 chain. The obvious difference is that a larger proportion of the carbon chain is retained, up to the C16 point instead of C9 with oleates, which opens up a new range of longer lipidic building blocks. A quite different but fascinating reaction that affords long-chain α,ω-FA using a Pd catalyst has been dubbed "isomerizing carbonylation" [19]. Cross-metathesis is of course an inherently complicated proposition, since the system is at equilibrium, and a number of different products that can themselves participate in secondary equilibria are the result. Fortunately, when the olefins are terminal or near the end of a chain, as they are for all the examples here, low-molecular weight byproducts (here ethylene, propene, or 2-butene) are lost to evaporation, simplifying the resulting product mix. Another way to drive the reaction to the desired mixed product is to use one partner in excess [11]. In our work, we used 3 eq of the non-FA component.

The first, fairly obvious moiety to include was a modified glycerol unit, **3**. Cross-metathesis with this partner would, after removal of the acetonide protecting group and diesterification, give a structure analogous to a triacylglycerol, in particular an ether version that is "inverted" in the sense that one carboxyl group is at the opposite end from the glycerol (Fig. 2). Glycerol ethers are of interest for their biological activity, and have been identified as crucial for inducing adipogenesis [20]. We obtained **4** in 45% yield. Yields reported here are unoptimized; see [18] for an example of a thorough investigation of reaction parameters. Interestingly, that work found that phenol-derived Schiff base variants of the catalyst were particularly active, while use of the same second-generation catalyst as here gave 48% conversion of methyl oleate and 30% yield of desired cross-metathesis products even when the cross-metathesis partner was present in a fivefold excess. One modification that can be made to **4** is to use the olefin near the glycerol unit as the site of further attachment of fatty acids, namely by dihydroxylation to give **5**. This molecule possesses two distinct groups of hydroxy units, two tied up as the acetonide and two free, that could be used independently to attach different groups.

Glyceryl ether **4** also opens the door to novel chemistry that can be done at the carboxylic acid so that functional groups can be positioned at, for example, the interlayer region of a bilayer. Making esters would be a

straightforward way to proceed, but we chose to not retain the carboxylic unit and instead explored options for different kinds of chemistry. (Although it is important to note that molecule **4** is an AB_2 monomer which could be used to build hyperbranched or dendritic polyesters). Reduction of the methyl ester to an alcohol would be the starting point for several new lipidic structures. We were concerned, however, that reduction protocols might also adversely affect the acetonide protecting group, so instead we performed the reduction on **2** to give an ω-2 unsaturated alcohol first, prior to cross-metathesis. Reduction of the methyl ester using Buchwald's poly(methylhydrosiloxane)/$Ti(OiPr)_4$ method worked smoothly [12]. This protocol appears to be a good, general, mild method for transformation of FAs to fatty alcohols. The alcohol was protected as an acetate (see [21] for a related approach using oleyl alcohol), and yields of cross-metathesis with **6** were similar to those for the methyl ester.

We employed acetate **7** for three different sets of transformations. First was elimination to give a new terminal alkene. A mild, efficient procedure was recently reported for this conversion, using the terminal iodide and tetrabutylammonium fluoride hydrate [13]. Elimination was accomplished by the route shown in Fig. 3. The acetate was hydrolyzed, the OH converted to Br then to I, and fluoride ion was used as base. To our surprise, the fluoride by-product **10** was separable from the terminal alkene **9** using silica gel chromatography. Conveniently, this route also was the set-up for a second transformation of **7**, via **8**, namely substitution with thioacetate to give **11** (Fig. 4). Positioning a sulfur atom at the end of a hydrophobic chain will contribute to the longer-term goal of constructing triacylglycerol-like molecules that could be adhered to metal surfaces as self-assembled monolayers. Thirdly, by way of analogy to the transformation of **4** to **5**, we also used the olefin of **7** in an oxygenating reaction, this time epoxidation.

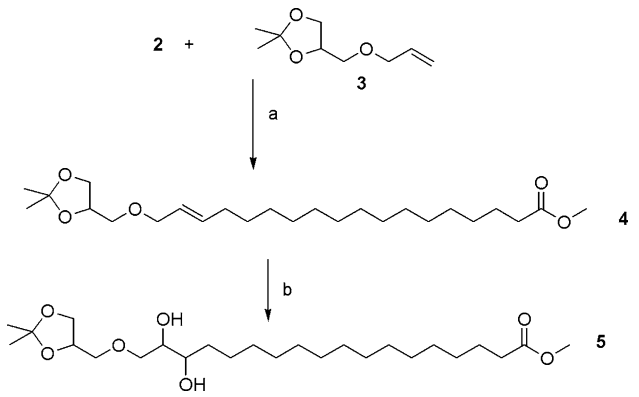

Fig. 2 Conditions **a** Grubbs' second-generation Ru olefin metathesis catalyst, CH_2Cl_2, 40 °C, 24 h. **b** Sharpless' asymmetric dihydroxylation reagent, *t*-BuOH/H_2O, 16 h

When the fluoride elimination conditions were applied to 18-OH stearic variant **1b**, subsequent to bromination and iodination, the terminal alkene/fluoride **13** and **14** mixture were again obtained and were separable. It is interesting to note that overall this reaction sequence, using either **7** or **1b**, affords three terminal halides, F, Br, and I; the fluoro and iodo versions could be useful as radiolabeled compounds. In our opinion, molecule **6** has the potential to be a powerful synthon for constructing new fatty acid/alcohol derivatives. Our aim was to use the acetate as a masked alkene precursor, through the OH to halide to terminal alkene sequence. In this way, iterative cross-metatheses for example between **9** and **6** could be used to build up very long chain molecules.

Utilizing the α,ω groups of **6** in a different sequence would form the basis of an alternate route to a close relative of **9** that did not rely on cross-metathesis. This alternative route consists of deprotecting the acetate, converting the OH to a mesylate or other leaving group, and then forming an ether linkage between this molecule and

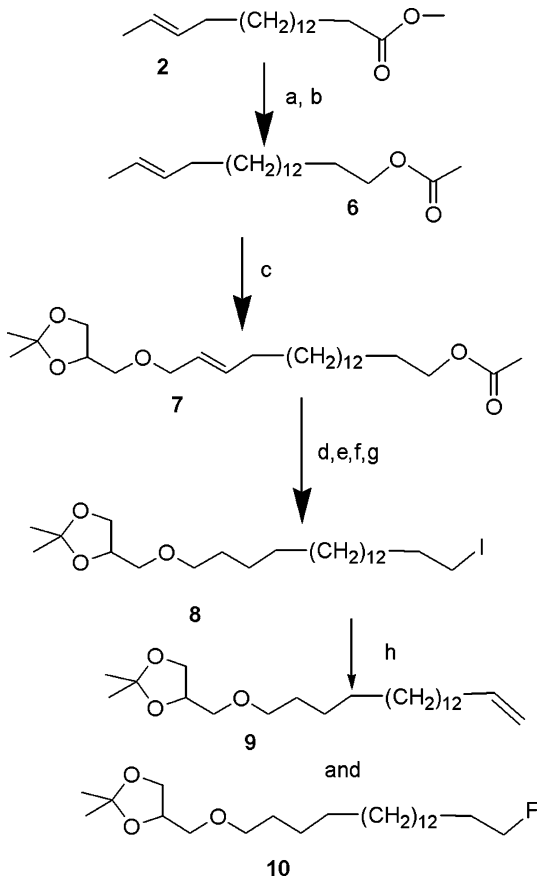

Fig. 3 Reagents and conditions **a** poly(methylhydrosiloxane), $Ti(OiPr)_4$, then NaOH; **b** acetic anhydride, pyridine, dmap; **c** Grubbs' second-generation metathesis catalyst, **3**; **d** H_2 over Pd/C; **e** LiOH in MeOH/water/THF; **f** Ph_3P, $BrCl_2CCCl_2Br$ in $ClCH_2CH_2Cl$; **g** NaI in acetone; **h** Bu_4NF hydrate, DMSO

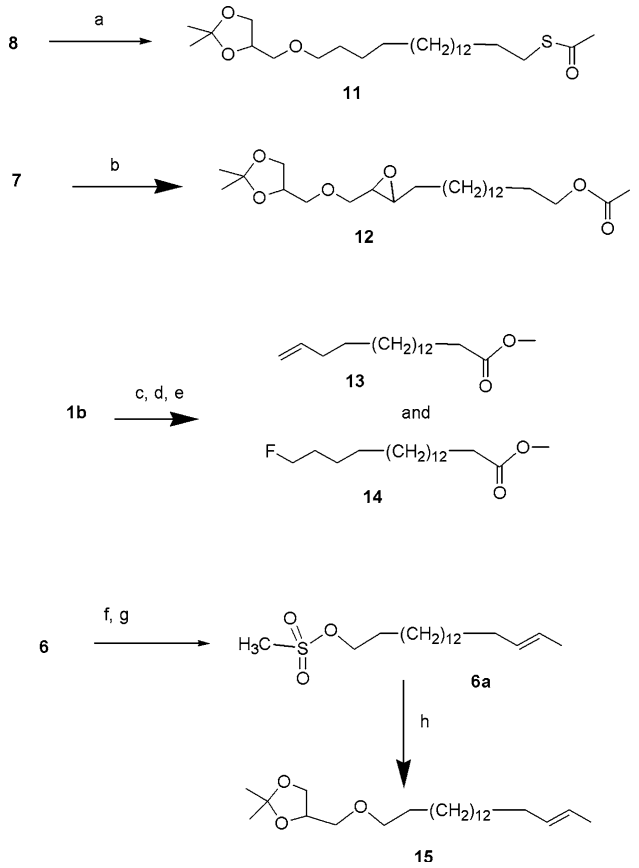

Fig. 4 Reagents and conditions **a** potassium thioacetate in acetone; **b** m-$ClC_6H_4CO_3H$ in CH_2Cl_2; **c** Ph_3P, $BrCl_2CCCl_2Br$ in $ClCH_2CH_2Cl$; **d** NaI in acetone; **e** Bu_4NF hydrate, DMSO; **f** LiOH in MeOH/water/THF; **g** methanesulfonyl chloride, pyridine, CH_2Cl_2; **h** solketal, DMSO, KOH

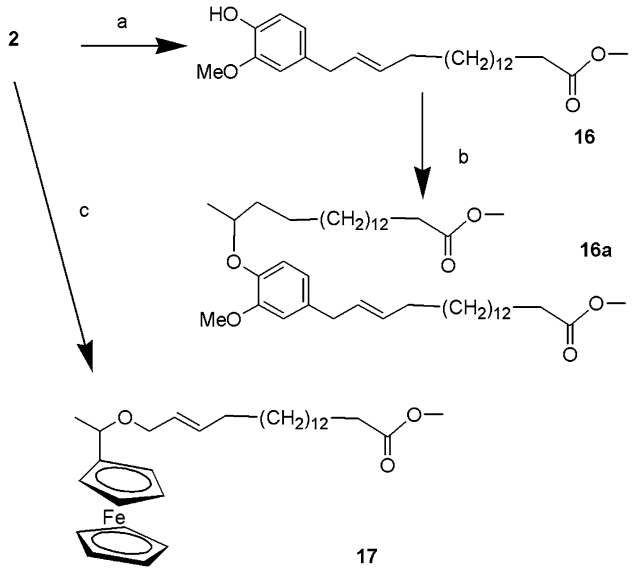

Fig. 5 Reagents and conditions **a** Grubbs' second-generation metathesis catalyst, eugenol; **b** **1a**, PPh_3, diisopropyl-azodicarboxylate; **c** Grubbs' second-generation metathesis catalyst, allyl ferrocenyl ethyl ether

solketal to give **15**. Molecules **9** and **15** represent starting points for experiments that would test subtle differences in the sizes of bilayer-spanning linkers, since self-metathesis of **15** would give a C32 chain connecting two glyceryl units and self-metathesis of **9** would give a C34 chain. If the small difference in carbon chain length were unimportant to a given application, molecule **15** would probably be a preferred building block, since it is prepared by a better synthetic route.

Other functional groups besides glycerol can of course be ω-appended to the fatty acid chain using metathesis. To limit the range of choices, we investigated only non-polar groups that would be of interest in a membrane or bilayer environment. (Although as an aside, since allylation of carbohydrates is readily performed, this method may prove to be a powerful way to append fatty acids to sugars through non-hydrolyzable linkages. Such structures would be alternatives to fatty acid esters of sugars, which are under investigation as bio-surfactants, and even to the native sophorolipid structure, where the glycosidic linkage to the fatty acid is also hydrolyzable.) There is interest in adding aromatic units to fatty acids, on the theory that improvement to properties such as lubrication or oxidation resistance may result [22]. Olefin cross-metathesis is an excellent way to install an aromatic unit. We used the bio-derived compound eugenol to obtain **16**. The phenolic OH is still available for further chemistry. We employed it in the Mitsunobu reaction with another unit of **1a** to give the pseudo-dimeric fatty acid ether **16a** (Fig. 5). This series of steps should be a potent way to create aromatic ethers of fatty acids. Finally, this methodology presents an opportunity to include redox-active units in lipid bilayers [23]. Ferrocenyl fatty acid **17** is the first example of an entirely new class of fatty acid derivative.

Conclusions

Using a cheap and easily prepared heterogeneous reagent, bio-derived hydroxy fatty acid **1a** is conveniently converted into an ω-2 monounsaturated fatty acid. This compound and its alcohol analogue that is simple to prepare are useful substrates for transition metal-catalyzed metathesis, which is a wide-ranging technique for introducing functional groups. Taken collectively, these ω-functionalized fatty acids should promote investigations into new advanced lipidic materials. The added functional groups provide a springboard to continued derivatization, e.g. through subsequent metathesis reactions for **9**, **13**, or **15**, disulfide formation for **11**, alkylation of the phenolic OH for **16**, and transition metal catalyzed couplings for **8**.

References

1. Li D, Lee J, Caffrey M (2011) Crystallizing membrane proteins in lipidic mesophases. A host lipid screen. Cryst Growth Des 11:530–537
2. Carmona-Ribeiro AM (2010) Biomimetic nanoparticles: preparation, characterization and biomedical applications. Int J Nanomed 5:249–259
3. Kusumoto K-I (2009) Structural features of glutamate-based lipidic materials for small interfering RNA delivery system. J Biomed Mater Res Part A 89:739–750
4. Belletti D, Riva G, Tosi G, Forni F, Barozzi P, Luppi M, Vandelli MA, Ruozi B (2011) Novel polymeric/lipidic hybrid systems (PLHs) for effective Cidofovir delivery: preparation, characterization and comparative in vitro study with polymeric particles and liposomes. Int J Pharm 413:220–228
5. Thauvin C, Perino A, Contal E, Morin E, Schultz P, Meunier S, Wagner A (2011) Programmed dispersions of MWNTs in aqueous media by coating with photopolymerizable synthetic amphiphiles. J Phys Chem C 115:7319–7322
6. Jesorka A, Stepanyants N, Zhang H, Ortmen B, Hakonen B, Orwar O (2011) Generation of phospholipid vesicle-nanotube networks and transport of molecules therein. Nat Protoc 6:791–805
7. Kaki SS, Adlercreutz P (2011) Lipase-catalyzed synthesis and characterization of 1-butanoyl-2-palmitoyl phosphatidylcholine, a potential lipidic prodrug of butyric acid. Chem Phys Lipids 164:246–250
8. Ashby RD, Solaiman DKY, Foglia TA (2008) Property control of sophorolipids: influence of fatty acid substrate and blending. Biotechnol Lett 30:1093–1100
9. Zerkowski JA, Nuñez A, Strahan GD, Solaiman DKY (2009) Clickable lipids: azido and alkynyl fatty acids and triacylglycerols. J Am Oil Chem Soc 86:1115–1121
10. Nishiguchi T, Machida N, Yamamoto E (1987) Dehydration of alcohols catalyzed by copper(II) sulfate adsorbed on silica gel. Tetrahedron Lett 28:4565–4568
11. Chatterjee AK, Choi T-L, Sanders DP, Grubbs RH (2003) A general model for selectivity in olefin cross metathesis. J Am Chem Soc 125:11360–11370
12. Reding MT, Buchwald SL (1995) An inexpensive air-stable titanium-based system for the conversion of esters to primary alcohols. J Org Chem 60:7884–7890
13. Bérubé M, Kamal F, Roy J, Poirier D (2006) A dehydrohalogenation methodology for synthesizing terminal olefins under mild conditions. Synthesis 2006:3085–3091
14. Zerkowski JA, Solaiman DKY (2007) Polyhydroxy fatty acids derived from sophorolipids. J Am Oil Chem Soc 84:463–471
15. Behr A, Krema S (2011) Metathesis applied to unsaturated lipid compounds. Lipid Technol 23:156–157
16. Behr A, Westfechtel A, Gomes JP (2008) Catalytic processes for the technical use of natural fats and oils. Chem Eng Technol 31:700–714
17. Miao X, Dixneuf PH, Fischmeister C, Bruneau C (2011) A green route to nitrogen-containing groups: the acrylonitrile cross-metathesis and applications to plant oil derivatives. Green Chem 13:2258–2271
18. Behr A, Gomes JP (2011) The cross-metathesis of methyl oleate with *cis*-2-butene-1,4-diyl diacetate and the influence of protecting groups. Beilstein J Org Chem 7:1–8
19. Stempfle F, Quinzler D, Heckler I, Mecking S (2011) Long-chain linear C19 and C23 monomers and polycondensates from unsaturated fatty acid esters. Macromolecules 44:4159–4166
20. Homan EA, Kim Y-G, Cardia JP, Saghatelian A (2011) Monoalkylglycerol ether lipids promote adipogenesis. J Am Chem Soc 133:5178–5181
21. Rybak A, Meier MAR (2008) Cross-metathesis of oleyl alcohol with methyl acrylate: optimization of reaction conditions and comparison of their environmental impact. Green Chem 10:1099–1104
22. Black KD, Gunstone FD (1996) The Friedel-Crafts adducts of methyl oleate with benzene and toluene. Chem Phys Lipids 79:87–94
23. Mertins O, Messina P, Labbé E, Vivier V, Arbault S, Lemaître F, Buriez O, Amatore C (2011) Electrochemical analysis of the interactions and reactivity of ferrocene-based drugs with a lipid environment: a qualitative overview. Inorg Chim Acta 374:59–68