JOC*Note*

Synthesis of Benzophenone-Containing Fatty Acids

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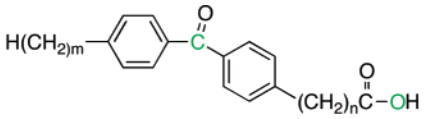

1, m = 10, n = 1; **2**, m = 7, m = 4; **3**, m = 4, n = 7; **4**, m = 1, n = 10; **5**, m = 1, n = 13; **6**, m = 1, n = 15

Distance from C to O range: 7.9Å for **1** to 25.0Å for **6**

Syntheses of new benzophenone-containing fatty acids (FABPs) **1**, **5**, and **6** and a new route to FABP **3** are described. Combined with the known **2** and **4**, these FABPs comprise a set of photoactivatable fatty acid analogues with the crosslinking site at defined distances from the carboxylic acid hydroxyl group oxygen atoms ranging from 7.9 to 25.0 Å.

Photoactivatable fatty acid analogues have a long history. Benzophenone-bearing carboxylic acid chains were first synthesized by Breslow for his studies of remote functionalization in steroids[1] and subsequently for use as photochemical probes of model membrane structures.[2] At approximately the same time, Khorana pioneered the use of photoactivatable phospholipids containing aryl azides or diazo ketone moieties.[3−5] More recently, several other groups have used fatty acids or phospholipids containing benzophenones for studies in model membranes[6−9] or for labeling membrane proteins.[10,11] Of particular note are the membrane-spanning dicarboxylic acids having a benzophenone[12−14] or a trifluoromethylaryldiazirine[15] in the center.

As part of a study of cellular cholesterol efflux and HDL formation, we have been preparing benzophenone-containing analogues of cholesterol[16−18] and phospholipids[19] as additional prospective photoaffinity labeling agents. For incorporation into the phospholipid analogues, fatty acids containing the benzophenone photophore at different defined positions along the entire hydrocarbon chain length were desired, to afford the possibility of photocrosslinking at a range of depths within cell membranes. This Note describes a series of six such fatty acid benzophenone analogues (FABPs), compounds **1**−**6** (Figure 1).

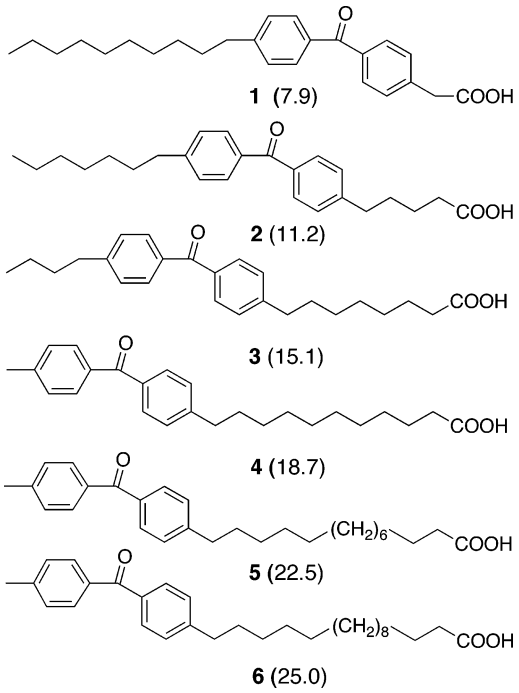

FIGURE 1. Structures of benzophenone-containing fatty acids **1**−**6** with the distance (in Å) from the hydroxyl group oxygen atom to the keto carbonyl group carbon atom, as measured in the fully extended conformation by the Spartan program, shown in parentheses for each compound.

Molecular modeling using the Spartan program indicates that in **1**−**6** the photocrosslinking carbonyl carbon atom will be at the respective distances shown in Figure 1 from the carboxylic

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(1) Breslow, R.; Baldwin, S.; Flechtner, T.; Kalicky, P.; Liu, S.; Washburn, W. *J. Am. Chem. Soc.* **1973**, *95*, 3251−3262.
(2) Czarniecki, M. F.; Breslow, R. *J. Am. Chem. Soc.* **1979**, *101*, 3675−3676.
(3) Chakrabarti, P.; Khorana, H. G. *Biochemistry* **1975**, *14*, 5021−5033.
(4) Gupta, C. M.; Radhakrishnan, R.; Gerber, G. E.; Olsen, W. L.; Quay, S. C.; Khorana, H. G. *Proc. Natl. Acad. Sci. U.S.A.* **1979**, *76*, 2595−2599.
(5) Gupta, C. M.; Costello, C. E.; Khorana, H. G. *Proc. Natl. Acad. Sci. U.S.A.* **1979**, *76*, 3139−3143.
(6) Gogoll, A.; Schäfer, H. J. *Liebigs Ann. Chem.* **1987**, 589−596. Gogoll, A.; Schäfer, H. J. *Liebigs Ann. Chem.* **1987**, 597−606.
(7) Markovic, D. Z.; Durand, T.; Patterson, L. K. *Photochem. Photobiol.* **1990**, *51*, 389−394.
(8) Markovic, D. Z.; Patterson, L. K. *Photochem. Photobiol.* **1993**, *58*, 329−334.
(9) Lala, A. K.; Kumar, E. R. *J. Am. Chem. Soc.* **1993**, *115*, 3982−3988.
(10) Page, M. G. P.; Rosenbusch, J. P. *Biochem. J.* **1986**, *235*, 651−661.
(11) Montecucco, C.; Schiavo, G. *Biochem. J.* **1986**, *237*, 309−312.
(12) Nakatani, Y.; Yamamoto, M.; Diyizou, Y.; Warnock, W.; Dollé, V.; Hahn, W.; Milon, A.; Ourisson, G. *Chem.−Eur. J.* **1996**, *2*, 129−138.
(13) Diyizou, Y. L.; Genevois, A.; Lazrak, T.; Wolff, G.; Nakatani, Y.; Ourisson, G. *Tetrahedron Lett.* **1987**, *28*, 5743−5746.
(14) Yamamoto, M.; Warnock, W. A.; Milon, A.; Nakatani, Y.; Ourisson, G. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 259−261.
(15) Delfino, J. M.; Schreiber, S. L.; Richards, F. M. *J. Am. Chem. Soc.* **1993**, *115*, 3458−3474.
(16) Spencer, T. A.; Wang, P.; Li, D.; Russel, J. S.; Blank, D. H.; Huuskonen, J.; Fielding, P. E.; Fielding, C. J. *J. Lipid Res.* **2004**, *45*, 1510−1518.
(17) Gan, Y.; Blank, D. H.; Ney, J. E.; Spencer, T. A. *J. Org. Chem.* **2006**, *71*, 5864−5869.
(18) Gan, Y.; Spencer, T. A. *J. Org. Chem.* **2006**, *71*, 5870−5875.
(19) Wang, P.; Blank, D. H.; Spencer, T. A. *J. Org. Chem.* **2004**, *69*, 2693−2702.

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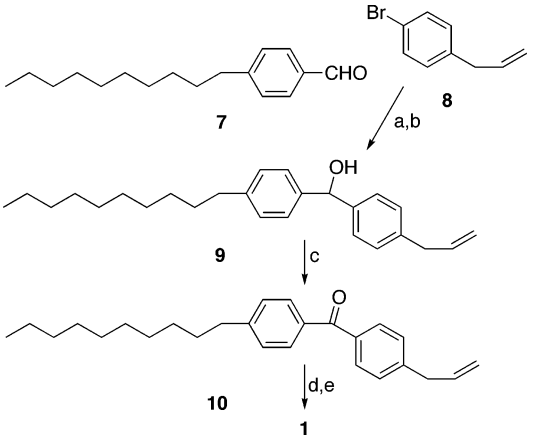
SCHEME 1. Synthesis of 1[a]



[a] Reagents and conditions: (a) Mg, Et_2O, Δ, 1 h; (b) **7**, Et_2O, rt, overnight; (c) PCC, CH_2Cl_2, rt, 7 h; (d) O_3, acetone, −50 °C, 15 min; (e) Jones reagent at 0 °C, then rt, overnight.

acid oxygen atom, which is assumed to be approximately at the membrane surface.

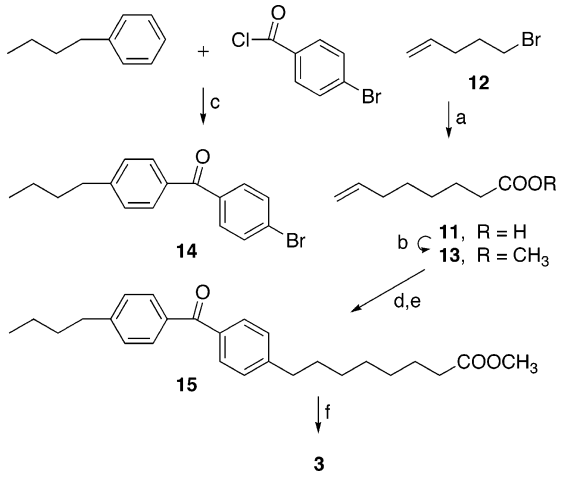
Among the series **1**−**6**, three have previously been described in the literature. Markovic et al.[7,8] have reported an efficient two-step synthesis of compound **2**, which we have not attempted to improve. Lala and Kumar[9] have reported the preparation of **3**, but we have developed the more efficient route described below. We have previously described in detail an improved synthesis of compound **4**.[19] Herein are described efficient syntheses of the new FABPs **1**, **5**, and **6**, as well as the improved route to **3**.

Synthesis of 1. When initial Friedel−Crafts approaches, such as reaction of 4-*n*-decyl benzoyl chloride with methyl phenylacetate, were unexpectedly disappointing, the route depicted in Scheme 1 was adopted. 4-*n*-Decylbenzaldehyde (**7**) was prepared from 1-phenyl-*n*-decane by the method of Osman[20] and treated with the Grignard reagent derived from 1-allyl-4-bromobenzene (**8**), prepared by the method of Parr et al.,[21] to afford benzhydrol **9** in 41% yield. Successive conversions of **9** with PCC to give **10** in 92% yield and of **10** by oxidative ozonolysis to give a 59% yield of **1** completed the synthesis.

Synthesis of 3. 7-Octenoic acid (**11**) was prepared by a new method from 5-bromo-1-pentene (**12**) and β-propiolactone in 92% yield by the procedure of Watson and Wagener[22] (Scheme 2), in a type of reaction also used in the syntheses of **5** and **6** described below. After esterification of **11** to methyl 7-octenoate (**13**) in 94% yield, Suzuki coupling[23] with 4-bromo-4′-*n*-butylbenzophenone (**14**), prepared by Friedel−Crafts reaction of *n*-butylbenzene and 4-bromobenzoyl chloride,[24] gave a 75% yield of keto ester **15**,[9] which was saponified in 82% yield to afford **3**.

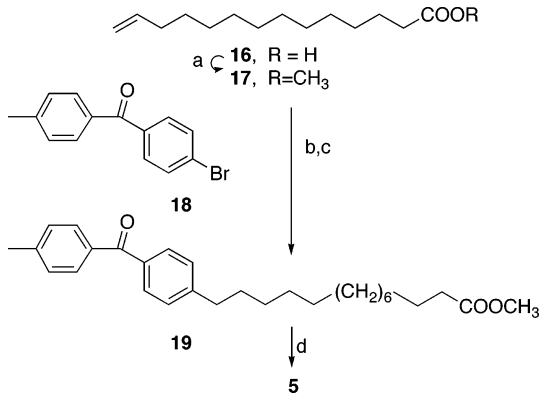
Synthesis of 5. 13-Tetradecenoic acid (**16**), prepared by the method of Watson and Wagener,[22] was esterified in 98% yield to give **17** which was coupled[23] with 4-bromo-4′-methylbenzophenone (**18**), prepared, as before,[19] by the method of

SCHEME 2. Synthesis of 3[a]



[a] Reagents and conditions: (a) Mg, THF, Δ, 2 h, β-propiolactone, CuCl, THF, 0 °C, rt, 1 h; (b) MeOH, H_2SO_4, Δ, overnight; (c) $AlCl_3$, −15 °C, rt, overnight; (d) 9-BBN, THF, 0 °C, rt, 4 h; (e) **14**, $Pd(dppf)Cl_2$, Cs_2CO_3, $AsPh_3$, DMF, H_2O, THF, Δ, overnight; (f) NaOH, EtOH, H_2O, rt, overnight.

SCHEME 3. Synthesis of 5[a]



[a] Reagents and conditions: (a) MeOH, H_2SO_4, Δ, overnight; (b) 9-BBN, THF, 0 °C, rt, 4 h; (c) **18**, $Pd(dppf)Cl_2$, Cs_2CO_3, $AsPh_3$, DMF, H_2O, THF, Δ, overnight; (d) NaOH, EtOH, H_2O, rt, overnight.

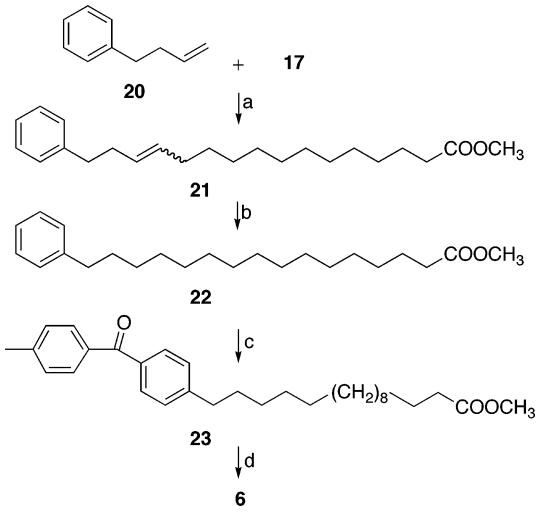
Nakatani et al.,[25] to give **19**. Crude **19** was saponified to afford **5** in 70% yield from **17** (Scheme 3).

Synthesis of 6. Methyl 13-tetradecenoate (**17**) was also used in the synthesis of **6** shown in Scheme 4. Olefin cross-metathesis of **17** with 4-phenyl-1-butene (**20**) using the Grubbs first-generation catalyst, by the procedure of Boyle et al.,[26] gave key intermediate **21** in 87% yield as a mixture judged to be ca. 8:1 trans/cis on the basis of precedent[27] and the ^{13}C NMR chemical shifts for the allylic carbon atoms.[28] Hydrogenation of **21** over 10% Pd/C gave 99% of **22**, which was condensed with *p*-toluyl chloride to give 99% of **23**. Saponification of **23** afforded a 95% yield of **6**.

Thus, the six FABPs with their photophores at the positions shown in Figure 1 are all now available for incorporation into

(20) Osman, M. A. *Helv. Chim. Acta* **1982**, *65*, 2448−2449.
(21) Parr, W.; Grohmann, K.; Hägele, K. *Liebigs Ann. Chem.* **1974**, 655−666.
(22) Watson, M. D.; Wagener, K. B. *Macromolecules* **2000**, *33*, 5411−5417.
(23) Johnson, C. R.; Braun, M. P. *J. Am. Chem. Soc.* **1993**, *115*, 11014−11015.
(24) Agzamova, K. D.; Yuldashev, Kh. Yu.; Nuriddinova, M. eds: Abdurasuleva, A. R. *Sint. Reakts. Sposobn. Org. Soedin.* **1983**, 22−27.
(25) Nakatani, K.; Dohno, C.; Nakamura, T.; Saito, I. *Tetrahedron Lett.* **1998**, *39*, 2779−2782.
(26) Boyle, T. P.; Bremner, J. B.; Coates, J. A.; Keller, P. A.; Pyne, S. G. *Tetrahedron* **2005**, *61*, 7271−7276.
(27) O'Leary, D. J.; Blackwell, H. E.; Washenfelder, R. A.; Grubbs, R. H. *Tetrahedron Lett.* **1998**, *39*, 7427−7430.
(28) Batchelor, J. G.; Cushley, R. J.; Prestegard, J. H. *J. Org. Chem.* **1974**, *39*, 1698−1705.

SCHEME 4. Synthesis of 6[a]



[a] Reagents and conditions: (a) $RuCl_2(=CHPh)(PCy_3)_2$, CH_2Cl_2, Δ, overnight; (b) 10% Pd/C, hexane, H_2, rt, overnight; (c) *p*-toluyl chloride, CH_2Cl_2, $AlCl_3$, rt, overnight; (d) NaOH, EtOH, H_2O, rt, overnight.

phospholipid analogues or for other biochemical applications. FABP **4** has already been incorporated into photoactivatable phosphatidylcholine analogues[19] for projected studies of reverse cholesterol transport and HDL formation, and similar analogues will be prepared from the other five FABPs.

Experimental Section

(4-Allylphenyl)-(4-decylphenyl)-methanol (9). To a mixture of 0.49 g (20.1 mmol) of magnesium in 10 mL of dry ether was added a solution of 2.64 g (13.4 mmol) of **8** in 10 mL of dry ether. After the mixture had been heated at reflux for 1 h, a solution of 1.1 g (4.46 mmol) of **7** in 10 mL of dry ether was added dropwise. The resulting mixture was stirred overnight at room temperature, diluted with 50 mL of saturated NH_4Cl, and extracted with ether. The organic layer was washed with brine, dried, filtered, and evaporated to give 2.9 g of residue which was purified by chromatography with 10:1 pentane/ether to give 0.66 g (41%) of **9** as a colorless oil: ^{1}H NMR δ 7.31 (m, 4H), 7.21 (m, 4H), 6.02 (m, 1H), 5.83 (s, 1H), 5.13 (m, 2H), 3.42 (d, J = 6.9 Hz, 2H), 2.63 (t, J = 7.8 Hz, 2H), 2.28 (brs, 1H), 1.64 (m, 2H), 1.34 (m, 14H), 0.94 (t, J = 6.6 Hz, 3H); ^{13}C NMR δ 142.6, 142.1, 141.5, 139.6, 137.6, 128.9, 128.8, 126.9, 126.8, 116.1, 76.2, 40.2, 35.9, 32.2, 31.8, 30.0, 29.9, 29.8, 29.7, 23.0, 14.4. Anal. Calcd for $C_{26}H_{36}O$: C, 85.66; H, 9.95. Found: C, 85.85; H, 9.91.

(4-Allylphenyl)-(4-decylphenyl)-methanone (10). To a solution of 580 mg (1.59 mmol) of **9** in 10 mL of CH_2Cl_2 was added 515 mg (2.39 mmol) of PCC. The mixture was stirred at room temperature for 7 h and then passed through a short pad of neutral alumina column with CH_2Cl_2. The solvent was evaporated to give 590 mg of residue which was purified by chromatography with 25:1 hexane/ethyl acetate to give 503 mg (92%) of colorless oily **10**: ^{1}H NMR δ 7.78 (m, 4H), 7.32 (m, 4H), 6.02 (m, 1H), 5.16 (m, 2H), 3.51 (d, J = 6.6 Hz, 2H), 2.72 (t, J = 7.8 Hz, 2H), 1.69 (m, 2H), 1.31 (m, 14H), 0.92 (t, J = 6.6 Hz, 3H); ^{13}C NMR δ 196.5, 148.3, 145.1, 136.7, 136.2, 135.5, 130.6, 130.5, 128.7, 128.6, 116.9, 40.4, 36.3, 32.2, 31.5, 29.9, 29.8, 29.7, 29.6, 29.57, 23.0, 14.4. Anal. Calcd for $C_{26}H_{34}O$: C, 86.13; H, 9.45. Found: C, 86.15; H, 9.56.

4-(4-Decylbenzoyl)phenyl Acetic Acid (1). Through a solution of 500 mg (1.38 mmol) of **10** in 20 mL of acetone was bubbled O_3 for 30 min at −50 °C, followed by N_2 for 15 min. A solution of Jones reagent (500 mg of CrO_3 in 1.5 mL of H_2O and 0.49 mL of concd H_2SO_4) was added at 0 °C, and the resulting mixture was stirred overnight at room temperature, quenched with 2-propanol, and filtered. Most of the solvent was removed under reduced pressure, and a solution of 2 N NaOH was added to the residue to adjust the pH to ca. 12. The aqueous layer was washed with ether, then reacidified and extracted with ethyl acetate. The organic layer was washed with brine, dried, filtered, and evaporated to give 1.1 g of residue which was purified by chromatography with 9:1 to 1:1 hexane/ethyl acetate to give 310 mg (59%) of **1** (mp 61−64.5 °C). Recrystallization from hexane gave **1**: mp 71.5−73.0 °C; ^{1}H NMR δ 7.82 (d, J = 8.1 Hz, 2H), 7.77 (d, J = 8.1 Hz, 2H), 7.45 (d, J = 8.1 Hz, 2H), 7.32 (d, J = 8.1 Hz, 2H), 3.79 (s, 2H), 2.72 (t, J = 7.8 Hz, 2H), 1.69 (m, 2H), 1.32 (m, 14H), 0.92 (t, J = 6.6 Hz, 3H); ^{13}C NMR δ 196.4, 177.2, 148.6, 137.9, 137.2, 135.2, 130.65, 130.61, 129.6, 128.6, 41.3, 36.3, 32.2, 31.4, 29.9, 29.9, 29.7, 29.6, 29.5, 22.9, 14.4. Anal. Calcd for $C_{25}H_{32}O_3$: C, 78.91; H, 8.48. Found: C, 78.65; H, 8.46.

8-[4-(4-*n*-Butylbenzoylphenyl)]octanoic Acid (3). To a solution of 432 mg (2.77 mmol) of **13** in 4 mL of THF was added 6.0 mL of 0.5 M 9-BBN dropwise at 0 °C. The mixture was stirred at room temperature for 4 h, then transferred via syringe to a mixture of 796 mg (2.51 mmol) of **14**,[24] 411 mg (0.50 mmol) of $Pd(dppf)Cl_2$, 2.46 g (7.56 mmol) of Cs_2CO_3, and 154 mg (0.50 mmol) of $AsPh_3$ in 6.5 mL of DMF, 1.5 mL of H_2O, and 6.5 mL of THF. The resulting mixture was heated at reflux overnight and then passed through a short pad of celite with 100 mL of ether. The organic layer was washed with brine, dried, filtered, and evaporated to give 2.1 g of brown oil which was purified by chromatography with 10:1 hexane/EtOAc to give 741 mg (75%) of methyl 8-[4-(4-*n*-butylbenzoylphenyl)]octanoate (**15**) as a colorless oil: ^{1}H NMR δ 7.75 (m, 4H), 7.29 (m, 4H), 3.69 (s, 3H), 2.70 (m, 4H), 2.33 (t, J = 7.5 Hz, 2H), 1.67 (m, 6H), 1.40 (m, 8H), 0.97 (t, J = 7.5 Hz, 3H); ^{13}C NMR δ 196.6, 174.5, 148.1, 148.0, 135.7, 135.6, 130.5, 130.5, 128.5, 128.5, 51.7, 36.2, 36.0, 34.3, 33.6, 31.3, 29.4, 29.3, 29.3, 25.2, 22.6, 14.2. To a solution of 313 mg (0.79 mmol) of **15** in 5 mL of ethanol was added a solution of 342 mg (8.6 mmol) of NaOH in 10 mL of H_2O. The mixture was stirred at room temperature overnight and evaporated, and the residue was acidified to pH = 1 with concd HCl and extracted with EtOAc. The organic layer was washed with brine, dried, filtered, and evaporated to give 480 mg of residue which was purified by chromatography with 4:1 hexane/EtOAc to give 246 mg (82%) of **3** as a white solid: mp 37.2−39.8 °C; ^{1}H NMR δ 7.76 (m, 4H), 7.32 (m, 4H), 2.71 (m, 4H), 2.39 (t, J = 7.5 Hz, 2H), 1.67 (m, 6H), 1.42 (m, 8H), 0.98 (t, J = 7.5 Hz, 3H); lit.[9] ^{1}H NMR δ 8.02 (d, 4H), 7.29 (d, 4H), 2.67 (t, J = 7.5 Hz, 4H), 2.37 (t, J = 7.5 Hz, 2H), 1.65 (m, 6H), 1.35 (m, 8H), 0.94 (t, J = 7.2 Hz, 3H); ^{13}C NMR δ 196.7, 180.3, 148.2, 148.0, 135.7, 135.6, 130.5, 130.5, 128.5, 128.5, 36.2, 36.0, 33.6, 31.3, 29.3, 29.3, 29.2, 24.9, 22.6, 14.2.

Methyl 14-(4-(4-Methylbenzoyl)phenyl)tetradecanoate (19). To a solution of 0.83 g (3.45 mmol) of **17** in 5 mL of THF was added 8.2 mL of 0.5 M 9-BBN at 0 °C. The mixture was stirred at room temperature for 4 h, then transferred via syringe to a mixture of 1.21 g (4.40 mmol) of **18**, prepared by the method of Nakatani et al.,[25] 412 mg (0.50 mmol) of $Pd(dppf)Cl_2$, 4.15 g (13 mmol) of Cs_2CO_3, and 153 mg (0.5 mmol) of $AsPh_3$ in a mixture of 8 mL of THF, 2 mL of H_2O, and 8 mL of DMF. The resulting mixture was heated at reflux overnight, passed through a short pad of Celite, and washed with 100 mL of hexane/ethyl acetate. The organic layer was washed with water and brine, dried, and evaporated to give 2.15 g of brown oily **19**. Crystallization of a small sample from hexane/ethyl acetate afforded colorless **19**: mp 51.9−52.8 °C; ^{1}H NMR δ 7.75 (m, 4H), 7.30 (m, 4H), 3.69 (s, 3H), 2.71 (t, J = 7.5 Hz, 2H), 2.47 (s, 3H), 2.33 (t, J = 7.5 Hz, 2H), 1.66 (m, 4H), 1.31 (m, 18H); ^{13}C NMR δ 196.6, 174.6, 148.2, 143.2, 135.6, 135.5, 130.5, 129.2, 128.5, 51.7, 36.3, 34.4, 31.5, 29.9, 29.9, 29.8, 29.8, 29.7, 29.7, 29.6, 29.5, 29.4, 25.2, 21.9. Anal. Calcd for $C_{29}H_{40}O_3$: C, 79.77; H, 9.23. Found: C, 79.52; H, 9.04.

14-(4-(4-Methylbenzoyl)phenyl)tetradecanoic Acid (5). The 2.15 g of crude **19** prepared as just described was dissolved in 10 mL of ethanol and diluted with a solution of 2.50 g (62 mmol) of NaOH in 20 mL of H_2O. The resulting mixture was stirred at room temperature overnight and evaporated, and the residue was acidified to pH = 1 with concd HCl and extracted with CH_2Cl_2. The organic layer was washed with brine, dried, filtered, and evaporated to give 1.87 g of white solid which was crystallized from hexane/ethyl acetate to give 1.02 g (70% over two steps) of colorless **5**: mp 77.2−78.2 °C; ^{1}H NMR δ 7.75 (m, 4H), 7.30 (m, 4H), 2.71 (t, J = 7.5 Hz, 2H), 2.47 (s, 3H), 2.38 (t, J = 7.5 Hz, 2H), 1.66 (m, 4H), 1.31 (m, 18H); ^{13}C NMR δ 196.6, 179.7, 148.2, 143.2, 135.6, 135.5, 130.5, 129.2, 128.5, 36.3, 34.2, 31.5, 29.9, 29.8, 29.7, 29.7, 29.6, 29.5, 29.3, 24.9, 21.9. Anal. Calcd for $C_{28}H_{38}O_3$: C, 79.58; H, 9.06. Found: C, 79.63; H, 8.98.

16-Phenylhexadec-13-enoic Acid Methyl ester (21). According to the procedure of Boyle et al.,[26] to a solution of 2.47 g (1.03 mmol) of **17** and 5.44 g (4.12 mmol) of **20** in 80 mL of CH_2Cl_2 was added 422 mg (0.52 mmol) of bis(tricyclohexylphosphonium)-benzylidene ruthenium(IV) dichloride (Grubbs catalyst I). The resulting mixture was heated at reflux overnight, cooled, and evaporated to give 7.83 g of residue which was purified by chromatography with 60:1 hexane/EtOAc to give 3.10 g (87%) of colorless oily **21** as a 8:1 trans/cis mixture according to ^{1}H NMR: ^{1}H NMR δ 7.29 (m, 2H), 7.22 (m, 3H), 5.48 (m, 1.76H), 5.44 (m, 0.24H), 3.70 (s, 3H), 2.71 (t, J = 7.5 Hz, 2H), 2.34 (t, J = 7.5 Hz, 4H), 2.02 (br, 2H), 1.66 (m, 2H), 1.31 (br, 16H); ^{13}C NMR δ 174.6, 142.5, 131.4, 131.0, 129.5, 128.9, 128.7, 128.5, 128.4, 126.0, 125.9, 51.7, 36.4, 36.3, 34.7, 34.4, 32.8, 29.9, 29.8, 29. 8, 29.7, 29.5, 29.4, 29.4, 27.5 (weak), 25.2. Anal. Calcd for $C_{23}H_{36}O_2$: C, 80.18; H, 10.53. Found: C, 79.98; H, 10.57.

16-Phenyl Hexadecanoic Acid Methyl Ester (22). To 1.32 g (3.84 mmol) of **21** in 15 mL of hexane was added 140 mg of 10% Pd/C. The mixture was stirred at room temperature under a balloon of H_2 overnight, then passed through a short pad of silica gel with ether. The filtrate was evaporated to give 1.32 g (99%) of **22**, which was crystallized from hexane/ethanol to give **22**: mp 40.5−41.8 °C; ^{1}H NMR δ 7.31 (m, 2H), 7.21 (m, 3H), 3.70 (s, 3H), 2.64 (t, J = 7.5 Hz, 2H), 2.34 (t, J = 7.5 Hz, 2H), 1.65 (m, 4H), 1.32 (br, 22H); ^{13}C NMR δ 174.6, 143.2, 128.7, 128.5, 125.8, 51.7, 36.3, 34.4, 31.8, 29.9, 29.9, 29.8, 29.7, 29.6, 29.5, 29.4, 25.2. Anal. Calcd for $C_{23}H_{38}O_2$: C, 79.71; H, 11.05. Found: C, 79.78; H, 11.11.

16-[4-(4-Methyl Benzoyl) Phenyl] Hexadecanoic Acid Methyl Ester (23). To a solution of 0.86 g (2.48 mmol) of **22** in 10 mL of CH_2Cl_2 was added 0.5 mL (3.72 mmol) of *p*-toluyl chloride at −5 °C, followed by 0.55 g (4.10 mmol) of $AlCl_3$ in two portions. The resulting mixture was stirred at room temperature overnight, quenched with 100 mL of saturated $NaHCO_3$ solution, and extracted with CH_2Cl_2. The organic layer was washed with brine, dried, and evaporated to give 1.4 g of residue which was purified by chromatography with 10:1 hexane/EtOAc to give 1.14 g (99%) of **23** as a white solid, which was recrystallized from hexane/ethanol to give **23**: mp 57.7−59.1 °C; ^{1}H NMR δ 7.76 (m, 4H), 7.30 (m, 4H), 3.70 (s, 3H), 2.69 (t, J = 7.5 Hz, 2H), 2.47 (s, 3H), 2.33 (t, J = 7.5 Hz, 2H), 1.65 (m, 4H), 1.31 (m, 22H); ^{13}C NMR δ 196.6, 174.6, 148.2, 143.2, 135.6, 135.5, 130.5, 129.2, 128.5, 51.7, 36.3, 34.4, 31.5, 29.9, 29.9, 29.8, 29.7, 29.7, 29.6, 29.5, 29.4, 25.2, 21.9. Anal. Calcd for $C_{31}H_{44}O_3$: C, 80.13; H, 9.54. Found: C, 79.99; H, 9.61.

16-[4-(4-Methyl Benzoyl) Phenyl] Hexadecanoic Acid (6). To a solution of 0.92 g (1.98 mmol) of **23** in 5 mL of ethanol was added a solution of 1.21 g (30 mmol) of NaOH in 10 mL of H_2O. The mixture was stirred at room temperature overnight and evaporated, and the residue was acidified to pH = 1 with concd HCl and extracted with EtOAc. The organic layer was washed with brine, dried, filtered, and evaporated to give 0.89 g of residue which was crystallized from hexane to give 0.85 g (95%) of colorless **6**: mp 80.1−81.8 °C; ^{1}H NMR δ 7.75 (m, 4H), 7.30 (m, 4H), 2.71 (t, J = 7.5 Hz, 2H), 2.47 (s, 3H), 2.38 (t, J = 7.5 Hz, 2H), 1.67 (m, 4H), 1.31 (m, 22H); ^{13}C NMR δ 196.6, 179.7, 148.2, 143.2, 135.6, 135.5, 130.5, 129.2, 128.5, 36.3, 34.2, 31.5, 29.9, 29.9, 29.8, 29.7, 29.7, 29. 6, 29.5, 29.3, 24.9, 21.9. Anal. Calcd for $C_{30}H_{42}O_3$: C, 79.96; H, 9.39. Found: C, 79.74; H, 9.59.

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Supporting Information Available: General experimental methods, preparations of known compounds **7**, **8**, **11**, **13**, **14**, and **16**−**18**, ^{1}H and ^{13}C NMR spectra of all compounds except **8**, and atom coordinates for molecular modeling of compounds **1**−**6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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