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Synthesis of 23-, 25-, 27-, and 29-Membered (*Z*)-Selective Unsaturated and Saturated Macrocyclic Lactones from 16- and 17-Membered Macrocyclic Lactones and Bromoalcohols by Wittig Reaction, Yamaguchi Macrolactonization, and Photoinduced Decarboxylative Radical Macrolactonization

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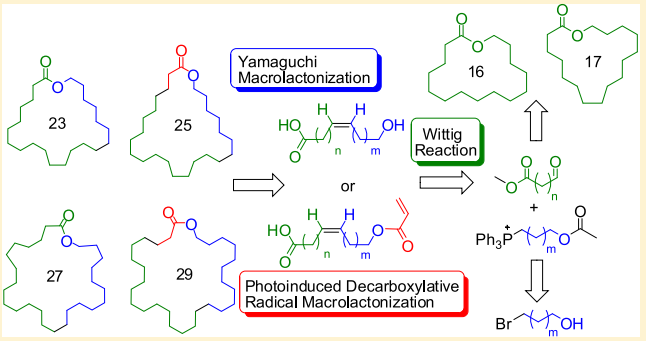
Supporting Information

ABSTRACT: A new strategy for the synthesis of 23-, 25-, 27-, and 29-membered (*Z*)-selective unsaturated and saturated macrocyclic lactones from commercially available 16- and 17-membered macrocyclic lactones and bromoalcohols by Wittig reaction, Yamaguchi macrolactonization, and photoinduced decarboxylative radical macrolactonization is described. The position of the unsaturated part in the macrocyclic lactones can be controlled by changing the number of carbons in the starting materials. This protocol can provide facile access to the desired large-ring (*Z*)-selective unsaturated and saturated macrocyclic lactones from simple starting materials.



INTRODUCTION

Macrocyclic lactones contain cyclic esters with a large-sized (more than 12-membered) ring. These lactones are found in a variety of natural products such as exaltolide **1** (16-membered macrocyclic lactone) and cyclohexadecanolide **2** (17-membered macrocyclic lactone), which are used in perfumes, and synthetic pharmaceuticals such as erythromycin and clarithromycin, which have strong antibacterial and antitumor activities (Scheme 1a).[1] Therefore, a number of efficient synthetic routes to macrocyclic lactones have been developed based on transition-metal-catalyzed ring-closing metathesis,[2] Horner−Wadsworth−Emmons reaction,[3] Yamaguchi macrolactonization,[4] Shiina macrolactonization,[5] and intramolecular radical cyclization using azobisisobutyronitrile and Bu_3SnH.[6] We recently reported a radical cyclization of carboxylic acids bearing electron-deficient alkenes via photoinduced decarboxylation[7] under mild photoredox catalyst conditions for the formation of macrocyclic lactones in high yields (Scheme 1b).[8] The radical cation of phenanthrene (Phen) photogenerated through photoinduced electron transfer between the excited state of Phen and 1,4-dicyanobenzene (DCB) can oxidize the carboxylate ion to produce the alkyl radical via decarboxylation. Cyclization of the resulting radical to an α,β-unsaturated carbonyl group leads to the formation of an α-carbonyl radical, which subsequently participates in back-electron transfer with the radical anion of DCB to yield macrocyclic lactones after protonation. This photoreaction has been proven to allow for a two-carbon ring expansion of macrocyclic lactones. Fortunately, the obtained macrocyclic lactones (18-, 20-, 22-, and 24-membered macrocyclic lactones) in the photoreaction have been identified as candidate pheromones involved in communicating reproductive dominance in the bee family Halictidae. To enable experimental bioassays testing the function of these putative pheromones, the synthesis of 23-, 25-, 27-, and 29-membered macrocyclic lactones **3**−**6** is desirable. This motivation encouraged us to design a new synthetic strategy for these macrocyclic lactones from commercially available 16- and 17-membered macrocyclic lactones **1**, **2** and bromoalcohols **9** by means of Wittig reaction, Yamaguchi macrolactonization, and photoinduced decarboxylative radical macrolactonization (Scheme 1c). Carboxylic acids containing a (*Z*)-alkene and a hydroxy group (**7**) or an acyloxy group (**8**) are key

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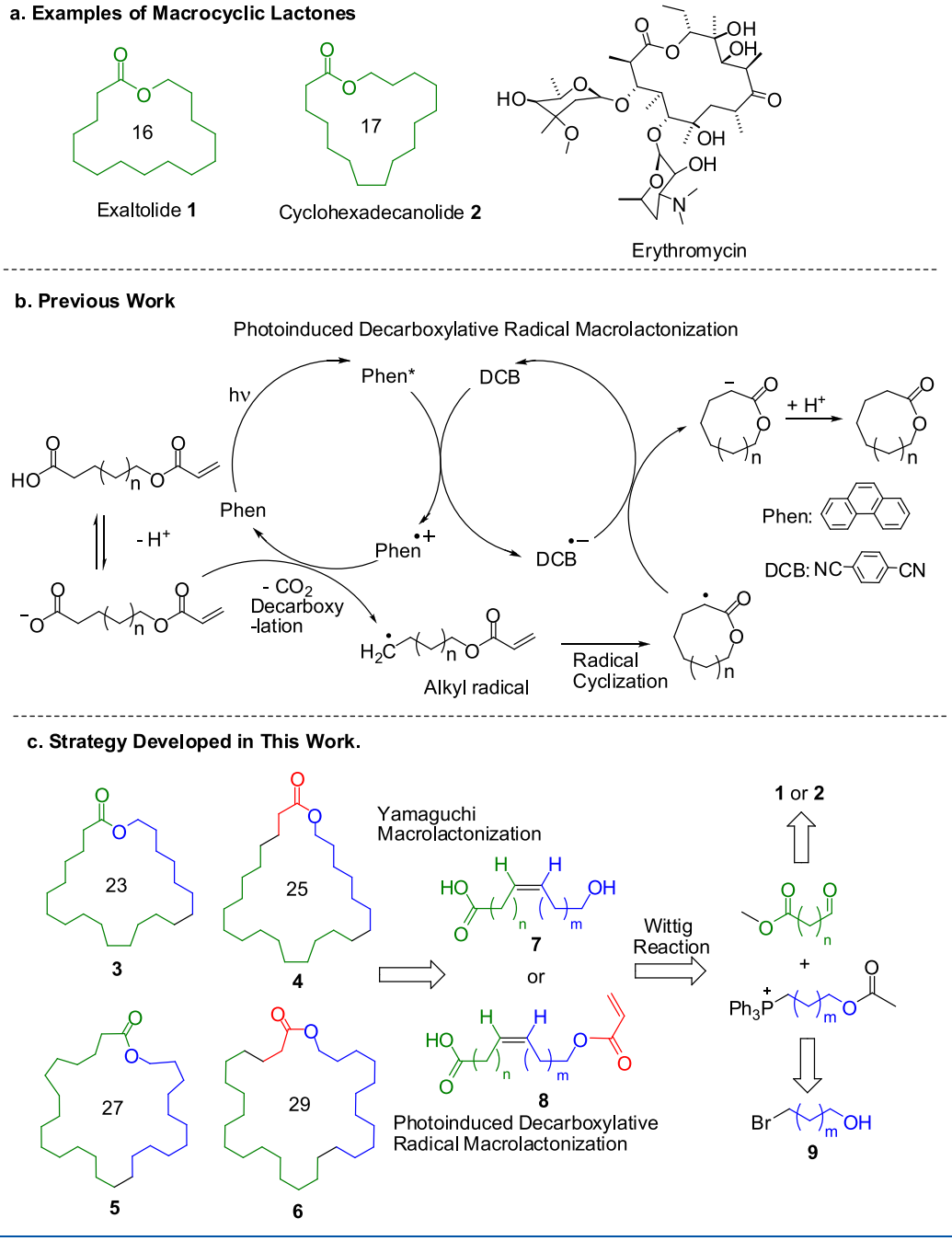
Scheme 1. (a) Examples of Macrocyclic Lactones, (b) Photoinduced Decarboxylative Radical Macrolactonization of Carboxylic Acid Bearing Electron-Deficient Alkene (Previous Work), and (c) Strategy Developed in This Work

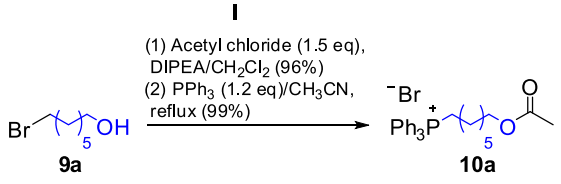


intermediates in our synthetic route, and they are prepared by the Wittig reaction of phosphonium bromide derived from **9** and aldehydes derived from **1** or **2**. The results of this effort, which led to the development of a new route to large-ring-saturated and (*Z*)-selective unsaturated macrocyclic lactones, are described below.

RESULTS AND DISCUSSION

Synthesis of 23-, 25-, 27-, and 29-Membered Macrocyclic Lactones 3−6 from 16-Membered Macrocyclic Lactone 1 and Bromoalcohols 9a and 9b. Initially, 23-membered macrocyclic lactone **3** (*C* = 22: carbon number in macrocyclic lactones, bromoalcohols, and acryloyl group) was synthesized by Wittig reaction and Yamaguchi macrolactonization from 16-membered macrocyclic lactone **1** (*C* = 15) and 7-bromoheptanol **9a** (*C* = 7). Protection of the hydroxy group of **9a** by acetylation and refluxing with PPh_3 yielded the corresponding phosphonium bromide **10a** as the Wittig reaction precursor (96 and 99%) (Scheme 2; these two steps

Scheme 2. Preparation of 10a from 9a



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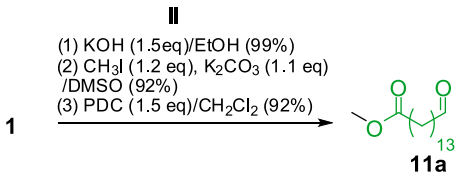
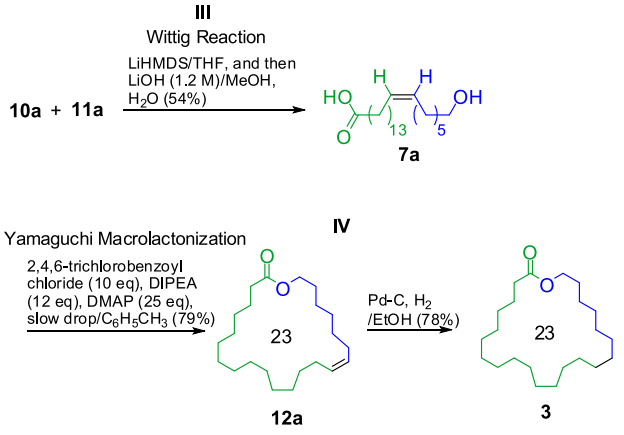
were illustrated by **I**). Hydrolysis of **1** with KOH, followed by esterification with CH_3I, afforded a methyl ester (92%), which was converted into the corresponding aldehyde **11a** (92%) by pyridinium dichromate (PDC) oxidation (Scheme 3; these

Scheme 3. Preparation of 11a from 1



three steps were illustrated by **II**). Sequential Wittig reaction of **10a** with **11a** and hydrolysis in one pot selectively afforded (*Z*)-alkene **7a** bearing carboxy and hydroxy groups in moderate yield (54%), which may be due to the low solubility of the corresponding (*E*)-alkene (Scheme 4; this sequential

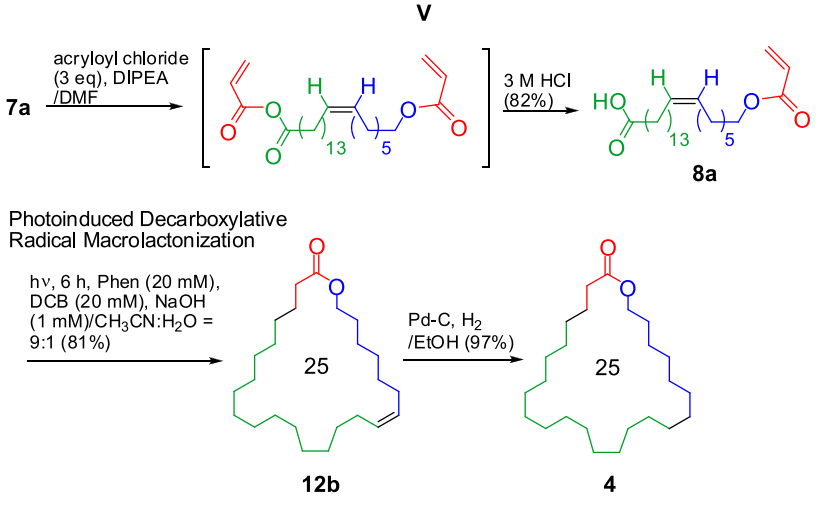
Scheme 4. Preparation of 3 from 10a and 11a by Wittig Reaction and Yamaguchi Macrolactonization



reaction was illustrated by **III**). Yamaguchi macrolactonization of **7a** proceeded smoothly to afford (*Z*)-selective unsaturated 23-membered macrocyclic lactone **12a** (79%), probably because the (*Z*)-alkene unit in **7a** assisted this macrocyclization. In general, the synthesis of unsaturated macrocyclic lactones was employed by transition-metal-catalyzed ring-closing metathesis,[2] leading to the formation of (E) and (*Z*) mixtures; however, (*Z*)-unsaturated macrocyclic lactone was exclusively obtained by this protocol. Reduction of **12a** by Pd–C and H_2 provided saturated 23-membered macrocyclic lactone **3** in a slightly lower yield (78%) because this saturated lactone was slightly volatile (Scheme 4; these two steps were illustrated by **IV**). On the other hand, a similar reduction of the larger-sized unsaturated macrocyclic lactones such as **12b–d** yielded almost quantitative yields of saturated macrocyclic lactones **4–6**. Before Yamaguchi macrolactonization, a similar reduction of unsaturated carboxylic acid **7a** by Pd–C and H_2 gave an insoluble saturated carboxylic acid, which was not used in further synthesis. These results indicated that the presence of the (*Z*)-alkene unit in **7a** is essential for promoting the macrolactonization and increasing the solubility of the carboxylic acid. Thus, (*Z*)-selective unsaturated and saturated 23-membered macrocyclic lactones **12a** and **3** (*C* = 22) were prepared by Wittig reaction and Yamaguchi macrolactonization from **1** and **9a** (*C* = 15 + 7).

Next, to synthesize 25-membered macrocyclic lactone **4** (*C* = 24), photoinduced decarboxylative radical macrolactonization was employed because this protocol can facilitate a two-carbon ring expansion (*C* = 3 (addition of acryloyl group) − 1 (decarboxylation) = 2) of macrocyclic lactones (Scheme 5). In our previous report,[8] we mentioned that the addition of an acryloyl group to carboxylic acids bearing a hydroxy group, such as **7a**, required three steps, leading to the loss of time and a decrease in the total yield. The improved one-pot method is shown in Scheme 5. Addition of 3 equiv of acryloyl chloride to **7a** led to the formation of an intermediate bearing both an acrylic ester and an acid anhydride, and subsequent hydrolysis with 3 M HCl in one pot exclusively yielded carboxylic acid **8a** bearing an acrylic ester. Photoreaction of an aqueous (aq) acetonitrile solution (CH_3CN/H_2O = 9:1, v/v) containing Phen (20 mM), DCB (20 mM), carboxylic acid **8a** (1 mM), and NaOH (1 mM) with irradiation by a 100 W high-pressure mercury lamp equipped with a Pyrex filter (>280 nm) under an argon atmosphere for 6 h at room temperature afforded (*Z*)-selective unsaturated 25-membered macrocyclic lactone **12b** in 81% yield. The (*Z*)-alkene unit in **8a** could promote radical macrocyclization via photoinduced decarboxylation. A similar reduction of **12b** by Pd–C and H_2 provided saturated

Scheme 5. Preparation of 4 from 7a by Photoinduced Decarboxylative Radical Macrolactonization



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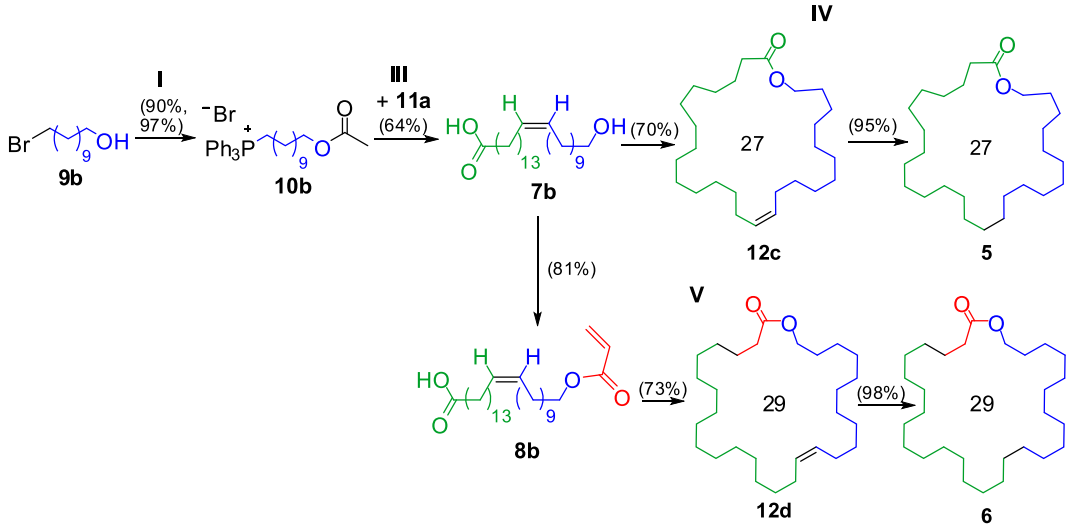
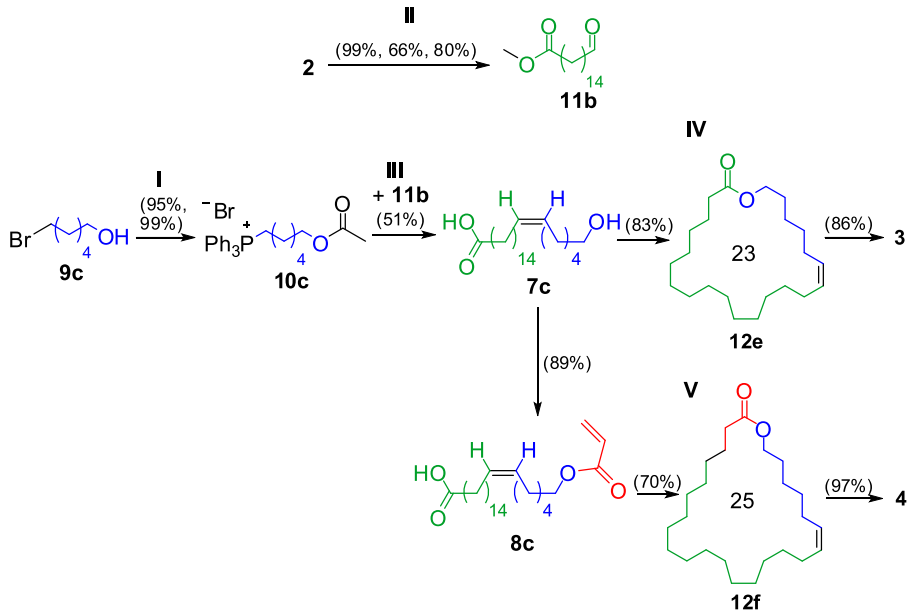
Scheme 6. Preparation of 5 and 6 from 1 and 9b



Scheme 7. Preparation of 3 and 4 from 2 and 9c



25-membered macrocyclic lactone **4** in high yield (97%, Scheme 5; these four steps including the photoreaction were illustrated by **V**). Thus, two-carbon elongated macrocyclic lactone **4** (C = 24) was also prepared from **7a** by photoinduced decarboxylative radical macrolactonization (C = 15 + 7 + 2).

To synthesize 27- and 29-membered macrocyclic lactones (C = 26 and 28) from **1** (C = 15), 11-bromoundecanol **9b** (C = 11) was used as a starting material (Scheme 6). Similar repetition of reaction sequences (**I** + **III**) between **9b** and **11a** (C = 15) yielded the corresponding carboxylic acid **7b**. Yamaguchi macrolactonization and reduction **IV** of **7b** led to the formation of (Z)-selective unsaturated and saturated 27-membered macrocyclic lactones **12c** and **5** (C = 15 + 11), while the addition of acryloyl group and photoreaction **V** of **7b** provided (Z)-selective unsaturated and saturated 29-membered macrocyclic lactones **12d** and **6** (C = 15 + 11 + 2). These results show that changing the number of carbons in the starting bromoalcohol **9** can help us control the size of the macrocyclic lactones.

Synthesis of 23- and 25-Membered Macrocyclic Lactones 3 and 4 from 17-Membered Macrocyclic Lactone 2 and 6-Bromohexanol 9c. Finally, we attempted to synthesize 23- and 25-membered macrocyclic lactones **3** and **4** from the 17-membered macrocyclic lactone **2** (C = 16) and 6-bromohexanol **9c** (C = 6) as starting materials (Scheme 7). The use of macrocyclic lactones and bromoalcohols with different carbon numbers helped us alter the position of the (Z)-alkene part in the unsaturated macrocyclic lactones. A similar repetition (**I** + **II** + **III**) sequence of **2** and **9c** through the formation of **10c** and **11b** produced the corresponding carboxylic acid **7c**, which had the unsaturated part at a different position. Moreover, subjecting carboxylic acids **7c** and **8c** to conditions **IV** or **V** provided the respective 23- and 25-membered (Z)-selective unsaturated macrocyclic lactones **12e** and **12f** having the (Z)-alkene part at different positions, and a similar reduction of **12e** and **12f** afforded saturated macrocyclic lactones **3** and **4** (C = 16 + 6 and 16 + 6 + 2). Thus, the use of macrocyclic lactones with different carbon numbers (C

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= 15 or 16) and bromoalcohols (C = 6 or 7) as the starting materials allowed us to prepare 23-membered macrocyclic lactone **3** (C = 15 + 7 or 16 + 6) and 25-membered macrocyclic lactone **4** (C = 15 + 7 + 2 or 16 + 6 + 2) via the formation of unsaturated macrocyclic lactones **12** with the (Z)-alkene unit at different positions.

CONCLUSIONS

We proposed a new strategy for the synthesis of 23-, 25-, 27-, and 29-membered (Z)-selective unsaturated and saturated macrocyclic lactones from 16- and 17-membered macrocyclic lactones and bromoalcohols. The (Z)-alkene unit in **7** and **8** promoted the macrolactonization and increased the solubility of the substrates. The use of macrocyclic lactones and bromoalcohols with different carbon numbers as the starting materials in our protocol helped in changing the ring size of the macrocyclic lactones and the (Z)-alkene position. The role of these macrocyclic lactones in the chemical communication systems of species in the Sweat Bee family Halictidae is currently being investigated.

EXPERIMENTAL SECTION

General Information. All reagents and solvents were used as received from commercial suppliers. IR spectra were recorded on a Fourier transform infrared spectrometer. ^{1}H NMR spectra were recorded in $CDCl_3$ containing tetramethylsilane as an internal standard and were acquired on either a 300 or 500 MHz spectrometer. $^{13}C\{^1H\}$ NMR spectra were acquired on a 125 MHz spectrometer. High-resolution mass spectra were obtained using a double-focusing magnetic sector mass spectrometer coupled with fast atom bombardment (FAB). The light source was a Riko UV-100HA high-pressure (100 W) mercury arc, and Pyrex vessels (18 mm × 180 mm) were directly attached to the light source (λ > 280 nm, Phen mainly absorbed at 313 nm light). Column chromatography was performed on Wakogel C-300, particle size 45−75 μm.

Procedure for Synthesis of 23-, 25-, 27-, and 29-Membered Macrocyclic Lactones 3−6 by Reaction of 1 or 2 with 9. *Preparation of Phosphonium Bromides **10a−c** from **9a−c** (**I**).* Acetyl chloride (1.5 equiv, 0.72 mL, 10.1 mmol) in anhydrous CH_2Cl_2 (1 mL) was added dropwise to a solution of 7-bromoheptanol **9a** (1.30 g, 6.66 mmol) and *N*,*N*-diisopropylethylamine (DIPEA) (3.3 mL) in anhydrous CH_2Cl_2 (33 mL) at 0 °C. The mixture was stirred overnight at room temperature, then quenched by 1 M HCl, and extracted with $CHCl_3$. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using hexane/EtOAc = 5:1 as the eluent to yield 7-bromoheptyl acetate as a colorless liquid (1.52 g, 6.39 mmol, 96%). A similar acetylation using **9b** (1.00 g, 3.98 mmol) and **9c** (1.23 g, 6.79 mmol) yielded 11-bromoundecanyl acetate (1.05 g, 3.58 mmol, 90%) and 6-bromohexyl acetate (1.44 g, 6.45 mmol, 95%), respectively.

7-Bromoheptyl Acetate. Colorless oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.06 (t, J = 6.7 Hz, 2H), 3.41 (t, J = 6.8 Hz, 2H), 2.05 (s, 3H), 1.91−1.82 (m, 2H), 1.68−1.59 (m, 2H), 1.50−1.35 (m, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 171.0, 64.3, 33.7, 32.5, 28.3, 28.2, 27.8, 25.5, 20.8.

11-Bromoundecanyl Acetate. (Using hexane/EtOAc = 10:1 as the eluent), colorless oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.05 (t, J = 6.7 Hz, 2H), 3.41 (t, J = 6.9 Hz, 2H), 2.04 (s, 3H), 1.90−1.80 (m, 2H), 1.65−1.57 (m, 2H), 1.45−1.28 (m, 14H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 171.2, 64.7, 34.1, 32.9, 29.5, 29.5, 29.4, 29.3, 28.8, 28.6, 28.2, 25.9, 21.1.

6-Bromohexyl Acetate. Colorless oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.07 (t, J = 6.6 Hz, 2H), 3.43 (t, J = 6.8 Hz, 2H), 2.06 (s, 3H), 1.93−1.84 (m, 2H), 1.71−1.61 (m, 2H), 1.54−1.36 (m, 4H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 171.1, 64.3, 33.7, 32.6, 28.4, 27.8, 25.1, 21.0.

7-Bromoheptyl acetate (1.52 g, 6.41 mmol) and PPh_3 (1.2 equiv, 2.03 g, 7.74 mmol) in anhydrous CH_3CN were refluxed for 48 h under an argon atmosphere. The mixture was evaporated, and then Et_2O was added to the residue and filtered. The filtrate was washed with Et_2O several times and dried in vacuo to afford 7-*O*-acetyl pentyltriphenylphosphonium bromide **10a** as a yellow oil in a quantitative yield (3.21 g, 6.41 mmol, quant.). A similar procedure using 11-bromoundecanyl acetate (0.100 g, 0.341 mmol) and 6-bromohexyl acetate (1.21 g, 5.42 mmol) gave the corresponding phosphonium bromides **10b** (0.183 g, 0.330 mmol, 97%) and **10c** (2.74 g, 5.42 mmol, quant.), respectively.

*7-O-Acetyl Pentyltriphenylphosphonium Bromide (**10a**).* Yellow oil; IR (neat, cm^{-1}) 2934, 2858, 1731, 1437, 1243, 1113; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90−7.69 (m, 15H), 3.99 (t, J = 6.7 Hz, 2H), 3.79−3.88 (br, 2H), 2.02 (s, 3H), 1.66−1.54 (m, 4H), 1.27 (m 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 171.5, 135.2, 133.9, 133.8, 130.7, 130.7, 118.9, 118.2, 64.6, 30.5, 30.4, 29.0, 28.6, 25.7, 23.1, 22.9, 22.8, 22.7, 21.3; high-resolution mass spectrometry (HRMS) (FAB) calcd for $(M - Br)^+$ $C_{27}H_{32}O_2P$: 419.2134, found: 419.2154.

*11-O-Acetyl Undecanyltriphenylphosphonium Bromide (**10b**).* Yellow oil; IR (neat, cm^{-1}) 2929, 2853, 1733, 1438, 1114; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87−7.73 (m, 15H), 4.04 (t, J = 6.6 Hz, 2H), 3.74 (br, 2H), 2.05 (s, 3H), 1.67−1.53 (m, 4H), 1.26 (m, 14H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 171.4, 135.1, 133.8, 133.7, 130.6, 130.5, 118.7, 118.1, 64.7, 30.6, 30.5, 29.5, 29.3, 29.2, 28.6, 25.9, 23.0, 22.7, 22.6, 21.1; HRMS (FAB) calcd for $(M - Br)^+$ $C_{31}H_{40}O_2P$: 475.2760, found: 475.2743.

*6-O-Acetyl Hexyltriphenylphosphonium Bromide (**10c**).* Yellow oil; IR (neat, cm^{-1}) 2934, 2862, 1731, 1437, 1114; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89−7.69 (m, 15H), 3.99 (t, J = 6.5 Hz, 2H), 3.82 (br, 2H), 2.02 (s, 3H), 1.72−1.55 (m, 4H), 1.36−1.32 (m, 4H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 171.2, 135.1, 135.0, 133.7, 133.6, 130.6, 130.5, 118.7, 118.0, 64.3, 30.1, 30.0, 28.2, 25.7, 22.9, 22.7, 22.6, 22.5, 21.1; HRMS (FAB) calcd for $(M - Br)^+$ $C_{26}H_{30}O_2P$: 405.1978, found: 405.1996.

*Preparation of Aldehydes **11a** and **11b** from **1** and **2** (**II**).* 16-Membered macrocyclic lactone **1** (4.81 g, 20 mmol) was added to a solution of KOH (1.68 g, 30 mmol) in EtOH (80 mL), and the mixture was refluxed for 2 h. The resulting mixture was evaporated, and then Et_2O was added to the residue and filtered. The filtrate was dried in vacuo to afford the ring-opened potassium carboxylate as a white solid in a quantitative yield (5.91 g, quant.), as reported by us previously.[8] Also, the similar hydrolysis of 17-membered macrocyclic lactone **2** (1.62 g, 6.37 mmol) gave the corresponding potassium carboxylate in a quantitative yield (2.03 g, quant.).

The potassium carboxylate derived from **1** (5.91 g, 20 mmol), CH_3I (1.2 equiv, 1.49 mL, 24 mmol), and K_2CO_3 (1 equiv, 5.91 g, 20 mmol) in anhydrous dimethyl sulfoxide (80 mL) was stirred overnight at 50 °C, and then water was added. The product was extracted with Et_2O, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by column chromatography on silica gel using hexane/EtOAc = 25:1−1:1 as the eluent gave methyl 15-hydroxypentadecanoate as a white solid in 92% yield (4.98 g, 18.4 mmol). Similar methylation of the potassium carboxylate derived from **2** (2.00 g, 6.44 mmol) yielded methyl 16-hydroxyhexadecanoate (1.22 g, 4.25 mmol, 66%).

Methyl 15-Hydroxypentadecanoate. White solid; m.p. 53−54 °C; IR (KBr, cm^{-1}) 3370, 2920, 2850, 1741; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.67−3.64 (m, 5H), 2.31 (t, J = 7.5 Hz, 2H), 1.63−1.55 (m, 4H), 1.26−1.21 (m, 20H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 174.5, 62.9, 51.5, 34.1, 32.8, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 25.8, 25.0; HRMS (FAB) calcd for $(M + H)^+$ $C_{16}H_{33}O_3$: 273.2424, found: 273.2427.

Methyl 16-Hydroxyhexadecanoate. White solid; m.p. 57−58 °C, IR (KBr, cm^{-1}) 3427, 2923, 2850, 1740; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.68−3.64 (m, 5H), 2.30 (t, J = 7.6 Hz, 2H), 1.62−1.54 (m, 4H), 1.26−1.21 (m, 22H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ

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174.5, 63.0, 51.5, 34.2, 32.8, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 25.8, 25.0; HRMS (FAB) calcd for $(M + H)^+$ $C_{17}H_{35}O_3$: 287.2581, found: 287.2570.

Methyl 15-hydroxypentadecanoate (0.600 g, 2.20 mmol) was added to a solution of PDC (1.5 equiv, 1.24 g, 3.30 mmol) in anhydrous CH_2Cl_2 (10 mL) under an argon atmosphere. The mixture was stirred overnight at room temperature, filtered through celite, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using hexane/EtOAc = 10:1 as the eluent to yield aldehyde **11a** as a white solid (0.547 g, 2.02 mmol, 92%). Similar PDC oxidation of methyl 16-hydroxyhexadecanoate (1.16 g, 4.05 mmol) gave aldehyde **11b** (0.916 g, 3.24 mmol, 80%).

*Methyl 15-Formylpentadecanoate **11a**.* White solid; m.p. 43−44 °C; IR (KBr, cm^{-1}) 2913, 2853, 1741; ^1H NMR (500 MHz, $CDCl_3$) δ 9.74 (s, 1H), 3.65 (s, 3H), 2.40 (t, J = 7.4 Hz, 2H), 2.28 (t, J = 7.4 Hz, 2H), 1.61−1.58 (m, 4H), 1.28−1.20 (m, 18H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 203.0, 174.4, 51.5, 43.9, 34.1, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 25.0, 22.1; HRMS (FAB) calcd for $(M + H)^+$ $C_{16}H_{31}O_3$: 271.2268, found: 271.2269.

*Methyl 16-Formylhexadecanoate **11b**.* White solid; m.p. 43−44 °C; IR (KBr, cm^{-1}) 2918, 2850, 1723; ^1H NMR (500 MHz, $CDCl_3$) δ 9.77 (s, 1H), 3.67 (s, 3H), 2.42 (t, J = 7.4 Hz, 2H), 2.30 (t, J = 7.7 Hz, 2H), 1.62−1.58 (m, 4H), 1.30−1.20 (m, 22H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 203.0, 174.4, 51.5, 43.9, 34.1, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 25.0, 22.1; HRMS (FAB) calcd for $(M + H)^+$ $C_{17}H_{33}O_3$: 285.2424, found: 285.2413.

*Wittig Reactions of **10a−c** with **11a** and **11b** for Preparation of **7a−c** (**III**).* Lithium hexamethyldisilazide (1.3 M, 1 equiv, 3.90 mL, 5.07 mmol) in tetrahydrofuran (THF) was slowly added to a solution of 7-*O*-acetyl pentyltriphenylphosphonium bromide **10a** (2.51 g, 5.03 mmol) in anhydrous THF (44 mL) under an argon atmosphere at −78 °C. Aldehyde **11a** (1 equiv, 1.36 g, 5.04 mmol) in anhydrous THF (44 mL) was also added dropwise to the mixture at −78 °C, stirred for 30 min at −78 °C, and further stirred for 2 h at room temperature. A solution of LiOH (7.59 g, 320 mmol) in H_2O (88 mL) and MeOH (88 mL) was added to the resulting mixture and stirred overnight at 50 °C. The aqueous layer was acidified (1 M HCl) to pH 2−3, extracted with Et_2O, and washed with brine. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using hexane/EtOAc = 4:1−3:1 as the eluent to yield carboxylic acid **7a** (0.968 g, 2.72 mmol, 54%) as a white solid. Similar Wittig reactions of **10b** (0.400 g, 0.720 mmol) with **11a** (0.198 g, 0.715 mmol) and **10c** (0.190 g, 0.391 mmol) with **11b** (0.110 g, 0.387 mmol) produced **7b** (0.186 g, 0.465 mmol, 65%) and **7c** (0.0706 g, 0.201 mmol, 52%), respectively.

*22-Hydroxy-15-(Z)-docosenoic Acid (**7a**).* White solid; m.p. 53−54 °C; IR (KBr, cm^{-1}) 3358, 2916, 2850, 1691; ^1H NMR (500 MHz, $CDCl_3$) δ 5.38−5.31 (m, 2H), 3.63 (t, J = 6.6 Hz, 2H), 2.33 (t, J = 7.4 Hz, 2H), 2.01 (m, 4H), 1.64−1.55 (m, 4H), 1.33−1.26 (m, 26H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 179.5, 130.1, 129.7, 62.9, 34.2, 32.5, 29.8, 29.7, 29.6, 29.5, 29.4, 29.3, 29.1, 27.3, 27.2, 25.7, 24.8; HRMS (FAB) calcd for $(M + H)^+$ $C_{22}H_{43}O_3$: 355.3207, found: 355.3201.

*26-Hydroxy-15-(Z)-hexacosenoic Acid (**7b**).* White solid; m.p. 63−64 °C; IR (KBr, cm^{-1}) 3387, 2917, 2848, 1698; ^1H NMR (500 MHz, $CDCl_3$) δ 5.32 (m, 2H), 3.65 (t, J = 6.6 Hz, 2H), 2.34 (t, J = 7.4 Hz, 2H), 2.01 (m, 4H), 1.66−1.54 (m, 4H), 1.33−1.26 (m, 34H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 179.3, 129.9, 129.8, 63.1, 34.0, 32.7, 32.6, 29.8, 29.7, 29.6, 29.59, 29.5, 29.4, 29.3, 29.2, 29.1, 27.2, 25.7, 24.7; HRMS (FAB) calcd for $(M + H)^+$ $C_{26}H_{51}O_3$: 411.3833, found: 411.3834.

*22-Hydroxy-16-(Z)-docosenoic Acid (**7c**).* White solid; m.p. 55−56 °C; IR (KBr, cm^{-1}) 3444, 2917, 2850, 1696; ^1H NMR (500 MHz, $CDCl_3$) δ 5.35 (m, 2H), 3.65 (t, J = 6.6 Hz, 2H), 2.34 (t, J = 7.4 Hz, 2H), 2.02 (m, 4H), 1.64−1.57 (m, 4H), 1.33−1.26 (m, 26H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 179.5, 130.3, 129.6, 63.1, 34.1, 32.7, 29.8, 29.7, 29.6, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 29.0, 27.3, 27.2, 25.5, 24.8; HRMS (FAB) calcd for $(M + H)^+$ $C_{22}H_{43}O_3$: 355.3207, found: 355.3201.

*Yamaguchi Macrolactonization of **7a−c** for Preparation of **12a, 12c, and 12e** and Reduction of **12a, 12c, and 12e** for Preparation of **3** and **5** (**IV**).* A solution of 22-hydroxy-15-(Z)-docosenoic acid **7a** (0.0200 g, 0.0564 mmol), 2,4,6-trichlorobenzoyl chloride (10 equiv, 0.138 g, 0.0882 mL, 0.564 mmol), and DIPEA (12 equiv, 0.115 mL, 0.660 mmol) in anhydrous toluene (22 mL) was added dropwise to a solution of 4-dimethylaminopyridine (25 equiv, 0.190 g, 1.39 mmol) in anhydrous toluene (177 mL) under an argon atmosphere. The mixture was stirred for 2 h at room temperature and quenched by saturated aq NH_4Cl. The aqueous layer was extracted with EtOAc and washed with brine. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using hexane/chloroform = 3:1 as the eluent to yield unsaturated 23-membered macrocyclic lactone **12a** as a colorless oil (0.0151 g, 0.0446 mmol, 79%). Similar Yamaguchi macrolactonization of **7b** (0.0600 g, 0.169 mmol) and **7c** (0.0233 g, 0.0629 mmol) yielded **12c** (0.0618 g, 0.150 mmol, 89%) and **12e** (0.0176 g, 0.0522 mmol, 83%), respectively.

*15-(Z)-Cyclodocosenolide **12a**.* Colorless oil; IR (neat, cm^{-1}) 2925, 2852, 1736; ^1H NMR (300 MHz, $CDCl_3$) δ 5.35 (m, 2H), 4.09 (t, J = 6.3 Hz, 2H), 2.32 (t, J = 6.9 Hz, 2H), 2.03 (m, 4H), 1.64−1.60 (m, 4H), 1.35−1.27 (m, 26H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 174.1, 130.2, 129.9, 64.4, 34.5, 29.7, 29.1, 29.0, 28.9, 28.8, 28.7, 28.6, 28.5, 28.4, 28.3, 28.2, 27.1, 26.6, 26.3, 26.2, 24.9; HRMS (FAB) calcd for $(M + H)^+$ $C_{22}H_{41}O_2$: 337.3101, found: 337.3100.

*15-(Z)-Cyclohexacosenolide **12c**.* White solid; m.p. 52−53 °C; IR (KBr, cm^{-1}) 2911, 2850, 1727; ^1H NMR (500 MHz, $CDCl_3$) δ 5.35−5.34 (m, 2H), 4.09 (t, J = 6.0 Hz, 2H), 2.31 (t, J = 6.9 Hz, 2H), 2.02 (m, 4H), 1.62 (t, J = 6.6 Hz, 4H), 1.35−1.26 (m, 34H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 174.2, 130.3, 129.7, 64.8, 34.6, 29.6, 29.0, 28.8, 28.7, 28.6, 28.5, 28.4, 28.3, 28.2, 26.6, 25.9, 25.0; HRMS (FAB) calcd for $(M + H)^+$ $C_{26}H_{49}O_2$: 393.3727, found: 393.3746.

*16-(Z)-Cyclodocosenolide **12e**.* Colorless oil; IR (neat, cm^{-1}) 2925, 2854, 1737; ^1H NMR (500 MHz, $CDCl_3$) δ 5.35 (m, 2H), 4.09 (t, J = 6.0 Hz, 2H), 2.31 (t, J = 6.9 Hz, 2H), 2.02 (t, J = 6.0 Hz, 4H), 1.63 (m, 4H), 1.26 (m, 26H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 174.1, 130.0, 129.9, 64.2, 34.5, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 29.0, 28.7, 28.5, 28.4, 26.9, 26.5, 26.0, 25.0; HRMS (FAB) calcd for $(M + H)^+$ $C_{22}H_{41}O_2$: 337.3101, found: 337.3132.

Unsaturated lactone **12a** (0.0271 g, 0.0803 mmol) was added to a solution of 10% Pd/C (0.00830 g) in MeOH (8.3 mL) and purged with H_2. The mixture was stirred overnight, filtered through celite, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using hexane/chloroform = 1:1 as the eluent to yield cyclodocosanolide **3** as a colorless oil (0.0212 g, 0.0626 mmol, 78%). Similar reduction of **12c** (0.0265 g, 0.0714 mmol) and **12e** (0.0146 g, 0.0371 mmol) yielded cyclohexacosanolide **5** (0.0259 g, 0.0692 mmol, 97%) and **3** (0.0126 g, 0.0319 mmol, 86%), respectively.

*Cyclodocosanolide **3**.* Colorless oil; IR (neat, cm^{-1}) 2925, 2854, 1738; ^1H NMR (500 MHz, $CDCl_3$) δ 3.83 (t, J = 6.0 Hz, 2H), 2.04 (t, J = 7.2 Hz, 2H), 1.38−1.34 (m, 4H), 1.02 (m, 34H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 174.2, 64.4, 34.7, 29.1, 29.0, 28.9, 28.8, 28.7, 28.6, 28.3, 28.2, 28.1, 28.0, 27.8, 27.7, 26.1, 25.2; HRMS (FAB) calcd for $(M + H)^+$ $C_{22}H_{43}O_2$: 339.3258, found: 339.3283.

*Cyclohexacosanolide **5**.* White solid; m.p. 29−30 °C; IR (KBr, cm^{-1}) 2925, 2853, 1739; ^1H NMR (300 MHz, $CDCl_3$) δ 4.09 (t, J = 6.2 Hz, 2H), 2.31 (t, J = 7.2 Hz, 2H), 1.64−1.60 (m, 4H), 1.28 (m, 42H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 173.9, 64.2, 34.4, 29.1, 29.0, 28.9, 28.8 28.7, 28.6, 28.5, 28.4, 28.3, 28.2, 25.8, 24.9; HRMS (FAB) calcd for $(M + H)^+$ $C_{26}H_{51}O_2$: 395.3884, found: 395.3881.

*Addition of Acryloyl Group to **7a−c** for Preparation of **8a−c** (**V**).* Acryloyl chloride (3 equiv, 0.823 mL, 1.02 mmol) was added dropwise to a solution of 22-hydroxy-15-(Z)-docosenoic acid **7a** (0.120 g, 0.338 mmol) and DIPEA (0.26 mL) in anhydrous dimethylformamide (2.6 mL) at 0 °C under an argon atmosphere. The mixture was stirred for 2 h at room temperature, followed by the addition of 3 M HCl at 0 °C, and stirred for 12 h at 50 °C. The mixture was extracted with hexane/EtOAc = 4:1, dried over Na_2SO_4,

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and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using chloroform/EtOAc = 8:1 as the eluent to yield **8a** as a colorless oil (0.114 g, 0.281 mmol, 83%). Similar addition of the acryloyl group to **7b** (0.139 g, 0.338 mmol) and **7c** (0.120 g, 0.338 mmol) gave **8b** (0.112 g, 0.338 mmol, 81%) and **8c** (0.101 g, 0.301 mmol, 89%), respectively.

*22-Acryloxy-15-(Z)-docosenoic Acid (**8a**).* Colorless oil; IR (neat, cm^{-1}) 2918, 2850, 1725, 1696; ^1H NMR (300 MHz, $CDCl_3$) δ 6.41 (dd, J = 17.2, 1.5 Hz, 1H), 6.12 (dd, J = 17.2, 10.4 Hz, 1H), 5.82 (dd, J = 10.4, 1.5 Hz, 1H), 5.37−5.33 (m, 2H), 4.15 (t, J = 6.7 Hz, 2H), 2.35 (t, J = 7.5 Hz, 2H), 2.01 (m, 4H), 1.67−1.61 (m, 4H), 1.35−1.26 (m, 26H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 179.2, 166.4, 130.5, 130.1, 129.6, 128.6, 64.7, 33.9, 29.8, 29.7, 29.6, 29.4, 29.3, 29.2, 29.1, 28.9, 28.6, 27.2, 27.1, 25.8, 24.7; HRMS (FAB) calcd for $(M + H)^+$ $C_{25}H_{45}O_4$: 409.3312, found: 409.3300.

*26-Acryloxy-15-(Z)-hexacosenoic Acid (**8b**).* Colorless oil; IR (neat, cm^{-1}) 2919, 2850, 1721, 1694; ^1H NMR (500 MHz, $CDCl_3$) δ 6.40 (dd, J = 17.2, 1.5 Hz, 1H), 6.12 (dd, J = 17.2, 10.3 Hz, 1H), 5.82 (dd, J = 10.3, 1.5 Hz, 1H), 5.35 (t, J = 4.6 Hz, 2H), 4.15 (t, J = 6.9 Hz, 2H), 2.35 (t, J = 7.4 Hz, 2H), 2.01 (m, 4H), 1.69−1.60 (m, 4H), 1.35−1.26 (m, 34H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 179.4, 166.4, 130.5, 129.9, 129.9, 128.6, 64.8, 33.9, 29.8, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 28.6, 27.2, 25.9, 24.7; HRMS (FAB) calcd for $(M + H)^+$ $C_{29}H_{53}O_4$: 465.3938, found: 465.3948.

*22-Acrolyoxy-16-(Z)-docosenoic Acid (**8c**).* Colorless oil; IR (neat, cm^{-1}) 2917, 2849, 1725, 1701; ^1H NMR (500 MHz, $CDCl_3$) δ 6.40 (dd, J = 17.2, 1.5 Hz, 1H), 6.12 (dd, J = 17.2, 10.3 Hz, 1H), 5.82 (dd, J = 10.3, 1.5 Hz, 1H), 5.36 (t, J = 7.2 Hz, 2H), 4.15 (t, J = 6.9 Hz, 2H), 2.35 (t, J = 7.4 Hz, 2H), 2.04−1.99 (m, 4H), 1.68−1.61 (m, 4H), 1.39−1.25 (m, 26H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 180.1, 166.5, 130.6, 130.4, 129.4, 128.7, 64.8, 34.2, 29.8, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 28.6, 27.3, 27.1, 26.0, 25.7, 24.8; HRMS (FAB) calcd for $(M + H)^+$ $C_{25}H_{45}O_4$: 409.3312, found: 409.3316.

*Photoinduced Decarboxylative Radical Macrolactonization of **8a−c** for Preparation of **12b**, **12d**, and **12f** and Reduction of **12b**, **12d**, and **12f** for Preparation of **4** and **6** (**V**).* An aqueous solution (CH_3CN 171 mL, H_2O 19 mL) of 22-acryloxy-15-(Z)-docosenoic acid **8a** (0.0792 g, 0.170 mmol, 1 mM), NaOH (0.0068 g, 0.170 mmol, 1 mM), Phen (0.610 g, 3.42 mmol, 20 mM), and DCB (0.440 g, 3.42 mmol, 20 mM) in Pyrex vessels (18 mm × 180 mm) was purged with argon for 10 min. The mixture was irradiated with a 100 W high-pressure mercury lamp for 6 h. Then, the solvent was concentrated under reduced pressure. The product was purified by silica gel column chromatography using hexane/EtOAc = 1:0−30:1 as the eluent to obtain unsaturated macrocyclic lactone **12b** as a colorless oil (0.0523 g, 0.124 mmol, 73%). Similar photoreactions of **8b** (0.0792 g, 0.170 mmol) and **8c** (0.0803 g, 0.197 mmol) yielded the corresponding unsaturated lactones **12d** (0.0523 g, 0.124 mmol, 73%) and **12f** (0.0503 g, 0.119 mmol, 60%), respectively.

*15-(Z)-Cyclotetracosanolide **12b**.* Colorless oil; IR (neat, cm^{-1}) 2925, 2853, 1731; ^1H NMR (300 MHz, $CDCl_3$) δ 5.36 (m, 2H), 4.08 (t, J = 6.4 Hz, 2H), 2.31 (t, J = 7.1 Hz, 2H), 2.05−1.99 (m, 4H), 1.63−1.57 (m, 4H), 1.34−1.27 (m, 30H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 174.2, 130.6, 130.5, 64.5, 34.6, 32.5, 32.1, 29.8, 29.6, 29.0, 28.9, 28.8, 28.7, 28.6, 27.8, 26.1, 25.0; HRMS (FAB) calcd for $(M + H)^+$ $C_{24}H_{45}O_2$: 365.3414, found: 365.3412.

*15-(Z)-Cyclooctacosanolide **12d**.* White solid; m.p. 39−40 °C; IR (KBr, cm^{-1}) 2919, 2852, 1738; ^1H NMR (300 MHz, $CDCl_3$) δ 5.35 (m, 2H), 4.09 (t, J = 6.2 Hz, 2H), 2.31 (t, J = 6.9 Hz, 2H), 2.03−1.98 (m, 4H), 1.64−1.58 (m, 4H), 1.34−1.27 (m, 38H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 174.2, 130.7, 130.6, 64.4, 34.6, 32.4, 32.2, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 29.0, 28.8, 28.76, 28.7, 28.2, 26.1, 25.2; HRMS (FAB) calcd for $(M + H)^+$ $C_{28}H_{53}O_2$: 421.4040, found: 421.4019.

*16-(Z)-Cyclotetracosanolide **12f**.* Colorless oil; IR (neat, cm^{-1}) 2924, 2853, 1737; ^1H NMR (301 MHz, $CDCl_3$) δ 5.37 (m, 2H), 4.08 (t, J = 6.4 Hz, 2H), 2.31 (t, J = 7.0 Hz, 2H), 2.05−1.98 (m, 4H), 1.64−1.62 (m, 4H), 1.39−1.27 (m, 30H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 174.2, 130.8, 130.3, 64.4, 34.5, 32.4, 32.1, 29.1, 29.0, 28.9, 28.8, 28.7, 28.6, 28.5, 28.4, 27.9, 25.4, 25.1; HRMS (FAB) calcd for $(M + H)^+$ $C_{24}H_{45}O_2$: 365.3414, found: 365.3401.

The abovementioned reduction of unsaturated lactones **12b** (0.0265 g, 0.0725 mmol), **12d** (0.0259 g, 0.0615 mmol), and **12f** (0.0146 g, 0.0400 mmol) with Pd−C and H_2 gave saturated lactones **4** (0.0251 g, 0.0703 mmol, 97% from **12b**) (0.0126 g, 0.0344 mmol, 86% from **12f**) and **6** (0.0255 g, 0.0602 mmol, 98%), respectively.

*Cyclotetracosanolide **4**.* Colorless oil; IR (neat, cm^{-1}) 2925, 2855, 1737; ^1H NMR (500 MHz, $CDCl_3$) δ 4.09 (t, J = 5.4 Hz, 2H), 2.31 (t, J = 8.0 Hz, 2H), 1.70−1.59 (m, 4H), 1.41−1.15 (m, 38H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 174.1, 64.4, 34.6, 29.3, 29.2, 29.1, 29.0, 28.9, 28.8, 28.7, 28.6, 28.4, 28.3, 28.2, 28.1, 26.1, 25.14; HRMS (FAB) calcd for $(M + H)^+$ $C_{24}H_{47}O_2$: 367.3571, found: 367.3557.

*Cyclooctacosanolide **6**.* White solid; m.p. 34−35 °C; IR (KBr, cm^{-1}) 2922, 2853, 1736; ^1H NMR (500 MHz, $CDCl_3$) δ 4.08 (t, J = 6.3 Hz, 2H), 2.31 (t, J = 7.4 Hz, 2H), 1.70−1.59 (m, 4H), 1.40−1.14 (m, 46H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 174.2, 64.5, 34.6, 29.4, 29.3, 29.2, 29.1, 29.0, 28.9, 28.8, 28.7, 26.1, 25.14; HRMS (FAB) calcd for $(M + H)^+$ $C_{28}H_{55}O_2$: 423.4197, found: 423.4178.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.9b00870.

^1H and ^{13}C NMR spectra of 7-bromoheptyl acetate; ^1H and ^{13}C NMR spectra of **10a**, **11a**, **7a**, **12a**, **3**, **8a**, **12b**, **4**, 11-bromoundecanyl acetate, **10b**, **7b**, **12c**, **5**, **8b**, **12d**, **6**, **11b**, 6-bromohexyl acetate, **10c**, **7c**, **12e**, **8c**, **12f** (PDF)

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Notes

The authors declare no competing financial interest.

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