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Synthesis of Mayolene-16 and Mayolene-18: Larval Defensive Lipids from the European Cabbage Butterfly

Douglas B. Weibel, Laura E. Shevy, Frank C. Schroeder, and Jerrold Meinwald*

Department of Chemistry and Chemical Biology, Cornell University, Ithaca, New York 14853

circe@cornell.edu

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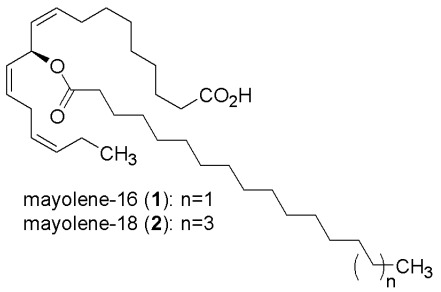
A tandem Wittig approach has been employed for the synthesis of both (11*S*,9*Z*,12*Z*,15*Z*)- and (11*R*,9*Z*,12*Z*,15*Z*)-hydroxyoctadeca-9,12,15-trienoic acid (11-hydroxylinolenic acid, 11-HLA) from (*R*)-glyceraldehyde acetonide. From (11*R*)-HLA we have prepared the corresponding palmitic acid and stearic acid esters, mayolene-16 (**1**) and mayolene-18 (**2**), insect defensive compounds recently identified from *Pieris rapae* larvae. In addition, we describe the synthesis of three macrocyclic oligomers (**24**−**26**) derived from (11*R*)-HLA.

Introduction

As part of our ongoing investigation of the chemical defenses of insect larvae and pupae, we have recently characterized a new family of biologically active lipids, the mayolenes, from the glandular hair secretion of larvae of the European Cabbage butterfly, *Pieris rapae*.[1] The mayolenes consist of (11*R*)-HLA[2] (11-HLA = 11-hydroxylinolenic acid) esterified with a series of homologous saturated fatty acids. The major components of this larval defensive secretion, mayolene-16 (**1**) and mayolene-18 (**2**), are (11*R*)-HLA esters of palmitic acid and stearic acid, respectively.



Following the structural characterization of the mayolenes, we were interested in synthesizing the individual enantiomers of 11-HLA, which we needed to determine the absolute configuration of these natural products, as well as to provide samples of the mayolenes for further study of their biological activity.[1] At an early stage in the course of characterizing the mayolenes, we considered candidate structures **24**−**26**, structural analogues of the polyazamacrolides recently indentified from ladybird beetle pupae.[3] To establish the presence or absence of these macrocyclic lactones in the insect secretion and to study their biological activity, we wished to prepare compounds **24**−**26** as well. We now report the synthesis of both enantiomers of 11-HLA, mayolene-16 (**1**) and mayolene-18 (**2**), and of the oligomeric macrolides **24**−**26**.

Results and Discussion

Because the bis-allylic hydroxyl group in 11-HLA is particularly prone to 1,4-elimination, we sought syntheses of (11*R*)- and (11*S*)-HLA compatible with the acid- and heat-sensitive nature of the intermediates and product. Our route utilizes two consecutive Wittig reactions to construct the $C_{9-}C_{10}$ and $C_{12-}C_{13}$ *cis* double bonds, and allows both enantiomers of 11-HLA to be prepared from (*R*)-glyceraldehyde acetonide (**9**) simply by varying the order in which the two Wittig reactions are carried out (Scheme 1).

To prepare (11*R*)-HLA, the ylide derived from (3*Z*)-3-hexyltriphenylphosphonium bromide (**6**)[4] was treated with **9**,[5] providing diene **10** with excellent diastereoselectivity (*Z*:*E* > 99:1, GC).[6] Deprotection of the acetonide using methanolic hydrochloric acid afforded diol **11** (Scheme 2).

Conversion of **11** to the corresponding di-*tert*-butyldimethylsilyl ether, followed by anticipated regioselective deprotection of the primary silyl ether using HF−pyr[7] surprisingly gave only the undesired product, arising from selective removal of the secondary, allylic silyl ether. To circumvent this problem, diol **11** was regioselectively protected as the primary *tert*-butyldimethylsilyl ether **12** using TBSCl and triethylamine in the presence of DBU.[8]

(1) Smedley, S. R.; Schroeder, F. C.; Weibel, D. B.; Meinwald, J.; Lafleur, K. A.; Renwick, J. A.; Rutowski, R.; Eisner, T. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 6822.

(2) We could locate only a single reference to 11-HLA in the literature: Hamberg, M. *J. Chem. Soc., Perkin Trans. 1* **1993**, 3065.

(3) Schroeder, F. C.; Smedley, S. R.; Gibbons, L. K.; Farmer, J. J.; Attygalle, A. B.: Eisner, T.; Meinwald, J. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 13387.

(4) Sandri, J.; Viala, J. *J. Org. Chem.* **1995**, *60*, 6627.

(5) Jackson, D. Y. *Synth. Commun.* **1998**, *18*, 337.

(6) For a review of the chemistry of optically active glyceraldehyde acetonide, see: Jurczak, J.; Pikul, S.; Bauer, T. *Tetrahedron* **1986**, *42*, 447.

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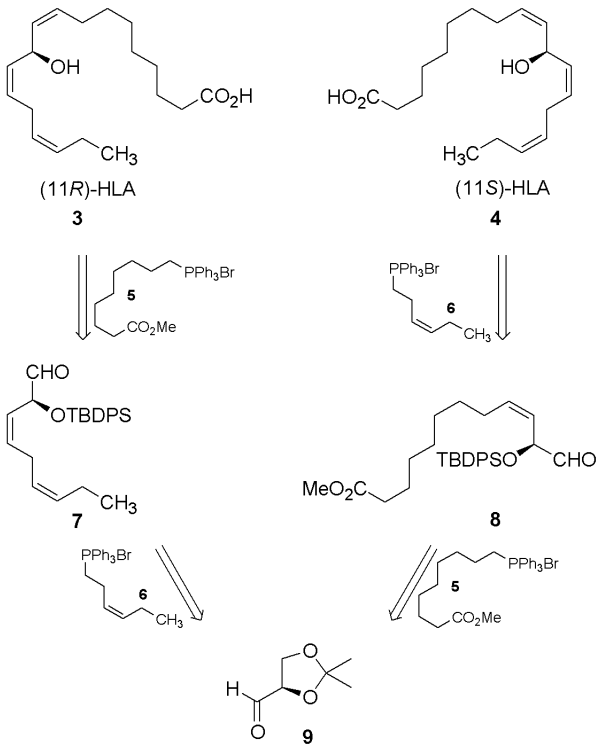
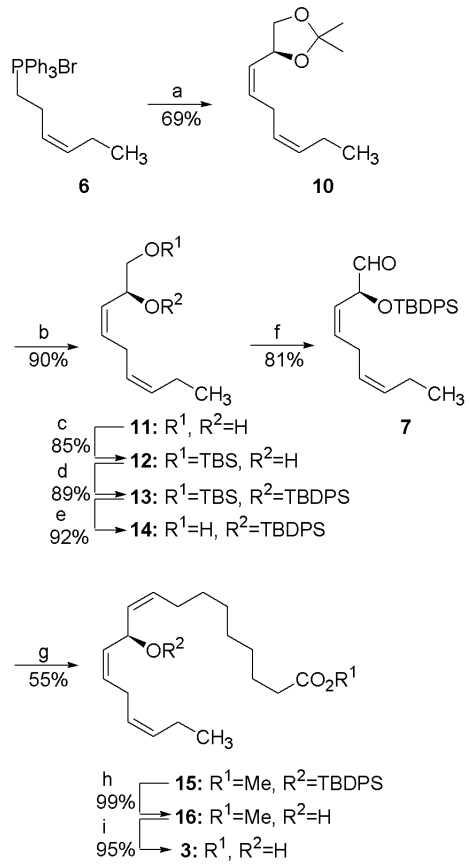
SCHEME 1



The secondary hydroxyl group in silyl ether **12** was protected as the *tert*-butyldiphenylsilyl ether to provide **13**, followed by selective deprotection of the primary silyl ether in the presence of PPTS, affording alcohol **14**. Interestingly, the *tert*-butyldiphenylsilyl group in **14** was found to migrate slowly to the primary hydroxyl group. Oxidation of freshly prepared **14** using tetrapropylammonium perruthenate/4-methylmorpholine *N*-oxide (TPAP/NMO)[9] afforded aldehyde **7**, which was subsequently treated with the ylide prepared from (8-carboxymethyloctyl)triphenylphosphonium bromide (**5**)[10] to yield trienoate **15**. Treatment of **15** with TBAF afforded alcohol **16**, which upon hydrolysis with aqueous lithium hydroxide followed by careful neutralization, provided (11*R*)-HLA (**3**).

To prepare (11*S*)-HLA, **9** was treated with the ylide derived from **5** to afford **17** with excellent diastereoselectivity (*Z*:*E* > 98:2, GC). Deprotection of **17** with methanolic hydrochloric acid afforded diol **18** (Scheme 3). Protection of the primary hydroxyl group as the *tert*-butyldimethylsilyl ether gave **19**. The free secondary hydroxyl group of **19** was protected as the *tert*-butyldiphenylsilyl ether to afford **20**, which was regioselectively deprotected at the primary hydroxyl group to yield alcohol **21**. Oxidation of **21** with PCC provided aldehyde **8**. A Wittig reaction between **8** and the ylide prepared from **6** afforded triene **22**, which was subsequently deprotected using TBAF, to yield alcohol **23**. Hydrolysis of **23** provided (11*S*)-HLA (**4**). With synthetic samples of optically pure (11*R*)- and (11*S*)-HLA in hand, we showed the absolute configuration of the mayolenes to be (11*R*).[1]

SCHEME 2[a]



[a] Reagents and conditions: (a) LiHMDS, −78 °C, THF, then **9**; (b) HCl, MeOH; (c) TBSCl, Et_3N, DBU, CH_2Cl_2; (d) TBDPSCl, DMAP, CH_2Cl_2; (e) PPTS, EtOH; (f) TPAP, NMO, CH_2Cl_2; (g) **5**, LiHMDS, −78 °C, THF, then **7**; (h) TBAF, THF; (i) LiOH, MeOH.

We next focused on a convenient esterification technique that would permit the preparation of mayolene-16 (**1**) and mayolene-18 (**2**). We found that the synthesis of these labile compounds could be carried out by preactivating palmitic or stearic acid with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI)[11] in the presence of DMAP, followed by the addition of **3** (Scheme 4). To avoid elimination, we carefully neutralized the reaction mixture using pH 5.75 buffer, followed by extraction and flash chromatography on wet silica gel, to afford pure **1** and **2**. The ^{1}H NMR, ^{13}C NMR, and ESI mass spectra of **1** and **2** were found to be indistinguishable from those determined for the natural materials,[1] confirming the structures assigned to the mayolenes on spectroscopic grounds.

In the early stages of characterizing the larval *Pieris* defensive secretion, spectroscopic evidence had suggested that macrocyclic lactones such as **24**−**26**, admixed with several fatty acids, might be important constituents. We therefore investigated conditions for the macrolactonization of (11*R*)-HLA to afford authentic samples of the corresponding mono- and oligomeric macrolides. While macrolactonization of (11*R*)-HLA using 2-chloro-1-methylpyridinium iodide,[12] 2,2′-dipyridyl disulfide,[13] and DCC/DMAP/DMAP−HCl[14] furnished only elimination prod-

(8) Kim, S.; Chang, H. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3669.

(9) (a) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *Chem. Commun.* **1987**, 1625. (b) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.

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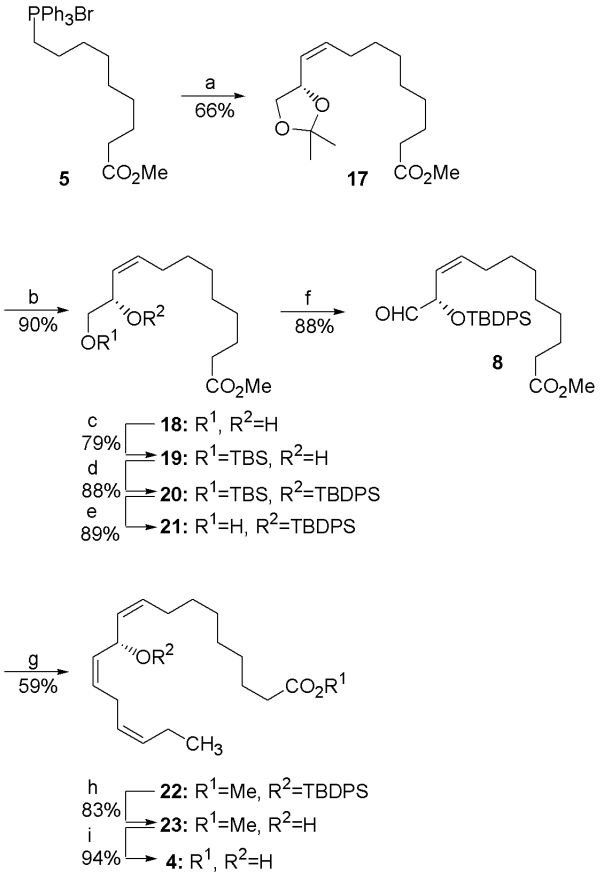
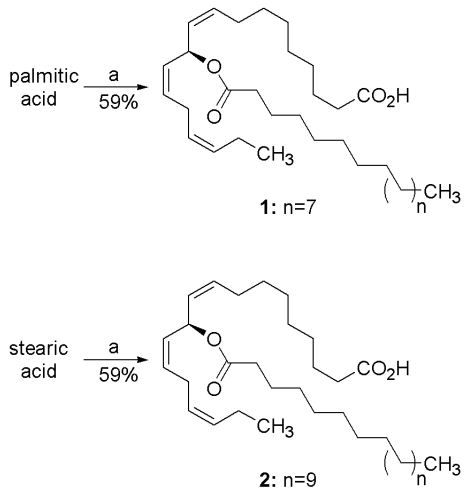
SCHEME 3[a]



[a] Reagents and conditions: (a) (a) LiHMDS, −78 °C, THF, then **9**; (b) HCl, MeOH; (c) TBSCl, Et_3N, DBU, CH_2Cl_2; (d) TBDPSCl, DMAP, CH_2Cl_2; (e) PPTS, EtOH; (f) PCC, NaOAc, CH_2Cl_2; (g) **6**, LiHMDS, −78 °C, THF, then **8**; (h) TBAF, THF; (i) LiOH, MeOH.

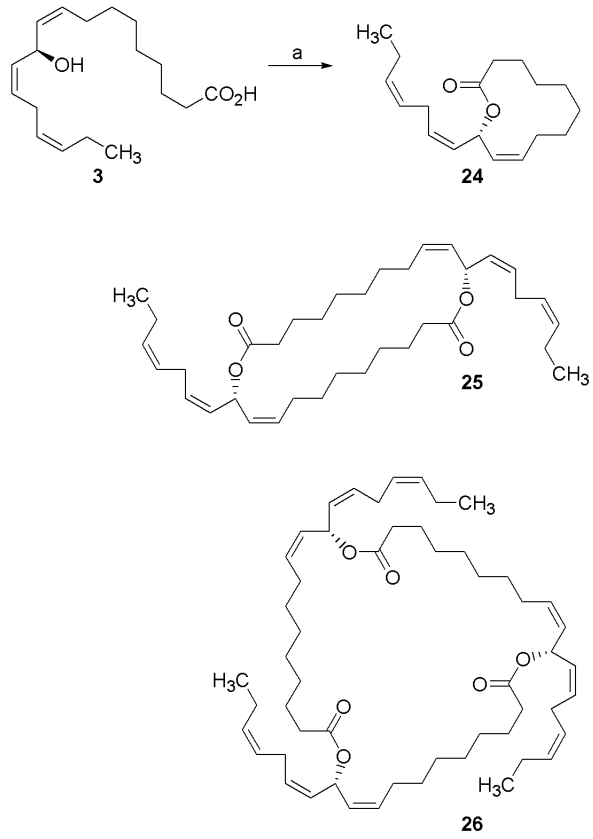
SCHEME 4[a]



[a] Reagents and conditions: (a) EDCI, DMAP, CH_2Cl_2, then **3**.

ucts, we found that 2,4,6-trichlorobenzoyl chloride/Et_3N/DMAP[15] yielded predominantly the desired macrolides **24**−**26** (Scheme 5), along with small amounts of tetrameric and pentameric macrolides. Similar experience during the total synthesis of mueggelone,[16] an allylic 10-membered macrolide independently isolated by two

SCHEME 5[a]



[a] Reagents and conditions: (a) iPr_2NEt, 2,4,6-trichlorobenzoyl chloride, benzene, then DMAP.

groups from cyanobacterial blooms, has been reported. Only by employment of 2,4,6-trichlorobenzoyl chloride/Et_3N/DMAP was successful macrolactonization of the appropriate precursor to mueggelone accomplished.[17]

Chromatography of the macrolactonization products formed from (11*R*)-HLA provided samples of pure **24**−**26**, along with the tetramer, and a sample of a pentamer admixed with small amounts of the tetramer and higher oligomers. The ^1H NMR spectra of macrolides **24**−**26** are readily distinguishable from each other and from the natural secretion. While the ^1H NMR spectra of the tetramer and pentamer are virtually indistinguishable, and resemble some relevant portions of the ^1H NMR spectra of *O*-acyl derivatives of the acyclic monomer (11*R*)-HLA, the C-11 proton chemical shift value in these macrolides is clearly upfield of the corresponding C-11 proton in *O*-acyl derivatives of (11*R*)-HLA, indicating that none of these macrolides are present in the glandular hair secretion.

In summary, we have described a concise route to both enantiomers of 11-HLA from (*R*)-glyceraldehyde ac-

(12) Mukaiyama, T.; Usui, M.; Saigo, K. *Chem. Lett.* **1976**, 49.
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(14) Boden, E. P.; Keck, G. E. *J. Org. Chem.* **1985**, *50*, 2394.
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(16) (a) Papendorf, O.; König, G. M.; Wright, A. D.; Chorus, I.; Oberemm, A. *J. Nat. Prod.* **1997**, *60*, 1298. (b) Stierle, D. B.; Stierle, A. A.; Bugni, T.; Loewen, G. *J. Nat. Prod.* **1998**, *61*, 251.
(17) (a) Ishigami, K.; Motoyoshi, H.; Kitahara, T. *Tetrahedron Lett.* **2000**, *41*, 8897. (b) Motoyoshi, H.; Ishigami, K.; Kitahara, T. *Tetrahedron* **2001**, *57*, 3899.

etonide (**9**) and the Wittig reagents prepared from phosphonium ylides **5** and **6**. From (11*R*)-HLA, we have prepared mayolene-16 (**1**) and mayolene-18 (**2**), both of which exhibit strong insect-deterrent activity in bioassays.[1] To facilitate chemical characterization of the *Pieris rapae* secretion, we also synthesized several macrolides derived from (11*R*)-HLA. These macrolides turned out not to be part of the larval armamentarium.

Experimental Section

General Information. All commercially available reagents were used without further purification. Solvents were either used as purchased or distilled using common practices where appropriate. All reactions were carried out under dry nitrogen. TLC was performed using 2.5 × 7.5 cm plates precoated with silica gel (200 μm), and spots were visualized by anisaldehyde. Silica gel (60 Å) was used for flash column chromatography. An aliquot of aqueous ammonium hydroxide was added to solutions of mayolene-16 (**1**) and mayolene-18 (**2**) prior to positive ion electrospray mass spectrometry.

(4*S*,1′*Z*,4′*Z*)-2,2-Dimethyl-4-hepta-1,4-dien-1-yl-1,3-dioxolane (10). A 1.0 M solution of lithium bis(trimethylsilyl)-amide (4.22 mL, 4.22 mmol) in THF was added dropwise over 30 min to a stirred solution of **6** (1.96 g, 4.61 mmol) in THF (8 mL) at 0 °C. After being stirred for 30 min at 0 °C, the deep orange solution was cooled to −78 °C, and to the solution was added dropwise a solution of **9** (500 mg, 3.84 mmol) in THF (3 mL). The solution was stirred for 3 h at 0 °C, at which time the reaction was quenched by slow addition of a saturated aqueous NH_4Cl solution (30 mL). After brief stirring, the yellow liquid was extracted with CH_2Cl_2 (45 mL). Combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under vacuum. Flash chromatography (30:1 hexane/ethyl acetate) of the residual orange oil provided **10** (520 mg, 69%) as a clear oil.

(2*S*,3*Z*,6*Z*)-3,6-Nonadiene-1,2-diol (11). Concentrated aqueous hydrochloric acid (3.3 mL) was added dropwise to a stirred solution of **10** (2.03 g, 10.3 mmol) in methanol (30 mL) at 0 °C. After the solution was stirred for 4 h at 0 °C, the pH was adjusted to 7 by slow addition of an aqueous NH_4OH solution (25%, v/v). After methanol was removed under vacuum, the solution was diluted with water (15 mL) and extracted with ether (110 mL). Combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under vacuum. Flash chromatography (1:1 hexane/ethyl acetate) of the residual yellow oil provided **11** (1.45 g, 90%) as a light yellow oil.

(2*S*,3*Z*,6*Z*)-1-[(*tert*-Butyldimethylsilyl)oxy]-3,6-nonadien-2-ol (12). Triethylamine (0.045 mL, 0.33 mmol), DBU (0.010 mL, 0.065 mmol), and *tert*-butyldimethylsilyl chloride (50 mg, 0.33 mmol) were added to a stirred solution of **11** (51 mg, 0.33 mmol) in CH_2Cl_2 (0.5 mL). After being stirred for 6 h at rt, the solution was washed with 10 mL of ice cold aqueous HCl (5%, v/v) and extracted with CH_2Cl_2 (40 mL). The combined organic layers were washed with a saturated aqueous $NaHCO_3$ solution (15 mL), dried ($MgSO_4$), filtered, and concentrated under vacuum. Flash chromatography (15:1 hexane/ethyl acetate) of the residual oil provided **12** (75 mg, 85%) as a clear oil.

(2*S*,3*Z*,6*Z*)-1-[(*tert*-Butyldimethylsilyl)oxy]-2-[(*tert*-butyldiphenylsilyl)oxy]-3,6-nonadiene (13). DMAP (440 mg, 3.60 mmol) and *tert*-butyldiphenylsilyl chloride (0.93 mL, 3.60 mmol) were added to a stirred solution of **12** (487 mg, 1.80 mmol) in CH_2Cl_2 (10 mL). After being stirred for 18 h at rt, the solution was diluted with brine (25 mL) and extracted with CH_2Cl_2 (75 mL). Organic extracts were combined, dried ($MgSO_4$), filtered, and concentrated under vacuum. Flash chromatography (60:1 hexane/ethyl acetate) of the residual oil provided **13** (816 mg, 89%) as a clear oil.

(2*S*,3*Z*,6*Z*)-2-[(*tert*-Butyldiphenylsilyl)oxy]-3,6-nonadien-1-ol (14). PPTS (196 mg, 0.78 mmol) was added to a stirred solution of **13** (795 mg, 1.56 mmol) in ethanol (20 mL). After being stirred for 6.5 h at 55 °C, the solution was cooled to rt, diluted with brine (40 mL), and extracted with CH_2Cl_2 (100 mL). Organic extracts were combined, dried ($MgSO_4$), filtered, and concentrated under vacuum. Flash chromatography (10:1 hexane/ethyl acetate) of the residual oil provided **14** (565 mg, 92%) as a clear oil.

(2*S*,3*Z*,6*Z*)-2-[(*tert*-Butyldiphenylsilyl)oxy]-3,6-nonadien-1-al (7). Powdered, activated 4 Å molecular sieves (375 mg), 4-methylmorpholine *N*-oxide (132 mg, 1.13 mmol), and tetrapropylammonium perruthenate (13 mg, 0.037 mmol) were added to a stirred solution of **14** (297 mg, 0.75 mmol) in CH_2Cl_2 (5 mL). After being stirred for 35 min at rt, the solution was filtered through a small pad of SiO_2, which was subsequently washed with CH_2Cl_2. The combined CH_2Cl_2 washes were concentrated under vacuum. Flash chromatography (50:1 hexane/ethyl acetate) of the residual oil provided **7** (240 mg, 81%) as a clear oil.

(11*R*,9*Z*,12*Z*,15*Z*)-11-[(*tert*-Butyldiphenylsilyl)oxy]octadeca-9,12,15-trienoic Acid Methyl Ester (15). A 1.0 M solution of lithium bis(trimethylsilyl)amide (0.76 mL, 1.07 mmol) in THF was added dropwise to a solution of **5** (584 mg, 1.15 mmol) in THF (8 mL) and HMPA (1 mL) at −78 °C. After the solution was stirred at −78 °C for 45 min, a solution of **7** (300 mg, 0.76 mmol) in THF (2 mL) was added dropwise. The solution was stirred for 1 h at −78 °C, subsequently stirred for 3 h at 0 °C, and then quenched by slow addition of a saturated aqueous solution of NH_4Cl (10 mL). THF was removed under vacuum and the resulting oil extracted with CH_2Cl_2 (50 mL). Combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under vacuum. Flash chromatography (30:1 hexane/ethyl acetate) of the residual oil provided **15** (229 mg, 55%) as a bright yellow oil.

(11*R*,9*Z*,12*Z*,15*Z*)-11-Hydroxyoctadeca-9,12,15-trienoic Acid Methyl Ester (16). A 1.0 M solution of tetrabutylammonium fluoride (0.32 mL, 0.32 mmol) in THF was added dropwise to a stirred solution of **15** (118 mg, 0.21 mmol) in THF (1.0 mL). The solution was stirred for 4.5 h at rt, then poured into brine (5 mL), and extracted with CH_2Cl_2 (20 mL). Combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under vacuum. Flash chromatography (4:1 hexane/ethyl acetate) of the residual oil provided **16** (65.8 mg, 99%) as a clear oil.

(11*R*,9*Z*,12*Z*,15*Z*)-11-Hydroxyoctadeca-9,12,15-trienoic acid (3). A solution of **16** (11.0 mg, 0.035 mmol) in CH_3OH (0.25 mL) was treated with an aqueous solution of LiOH (0.400 mL, 3 M) and stirred for 3.5 h at 50 °C. The cloudy solution was cooled to rt and carefully titrated to pH 6.0 with 0.25 M aqueous HCl. THF was removed under vacuum and the residue dissolved in ether (1.0 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum. Flash chromatography (2:1 hexane/ethyl acetate) of the residual oil provided **3** (10.0 mg, 95%) as a clear oil: $[\alpha]_D$ +6.4 (*c* 1.60, CH_3OH); R_f = 0.44 (1:1 hexane/ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.40−5.52 (m, 5 H), 5.27−5.34 (m, 2 H), 2.81−2.97 (m, 2 H), 2.34 (t, J = 7.4 Hz, 2 H), 2.02−2.21 (m, 4 H), 1.66 (app quintet, J = 7.2 Hz, 2 H), 1.28−1.42 (m, 8 H), 0.99 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.3, 132.7, 132.4, 131.5, 131.1, 130.4, 126.6, 64.0, 34.2, 29.7, 29.24, 29.22, 29.1, 27.9, 26.2, 24.8, 20.8, 14.4; IR (neat, cm^{-1}) 3886, 3658, 3012, 2962, 2930, 2856, 1710, 1462, 1412, 1248, 1070; MS (ESI+) *m*/*z* 294 (294 calcd for $C_{18}H_{30}O_3$); MS (ESI−) *m*/*z* 293; MS/MS (ESI−) daughter ions of *m*/*z* 293, *m*/*z* 275, 197, 95.

Mayolene-16 (1) [(11*S*,9*Z*,12*Z*,15*Z*)-11-Hexadecanoyloxyoctadeca-9,12,15-trienoic Acid]. A solution of palmitic acid (14.4 mg, 0.056 mmol) in CH_2Cl_2 (0.25 mL) was treated with DMAP (6.9 mg, 0.056 mmol) and EDCI (10.7 mg, 0.056). The resulting cloudy solution was stirred for 10 h at rt followed by the addition of a solution of **3** (15.0 mg, 0.051 mmol) in CH_2Cl_2 (0.10 mL). After the solution was stirred for 12 h, the solvent was removed under vacuum. The residue was dissolved in NaOAc buffer (10 mL, 0.4 M, pH 5.75) and extracted with

ether. Combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under vacuum. Flash chromatography (5:1 hexane/ethyl acetate) of the residual oil provided **1** (16.0 mg, 59%) as a white solid: $[\alpha]_D$ −1.5 (*c* 0.84, CH_2Cl_2); R_f = 0.47 (3:1 hexane/ethyl acetate); ^{1}H NMR (500 MHz, benzene-d_6) δ 6.74−6.80 (m, 1 H), 5.58−5.64 (m, 2 H), 5.48−5.54 (m, 2 H), 5.41−5.46 (m, 2 H), 3.12−3.20 (m, 1 H), 3.02−3.12 (m, 1 H), 2.28−2.36 (m, 1 H), 2.16−2.25 (m, 3 H), 2.04−2.12 (m, 4 H), 1.47−1.64 (m, 4 H), 1.12−1.37 (m, 32 H), 0.93 (m, 3 H), 0.92 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, benzene-d_6) δ 179.2, 172.3, 133.9, 132.9, 132.0, 128.0, 127.8, 126.7, 66.3, 34.5, 34.0, 32.3, 30.16, 30.15, 30.13, 30.12, 30.11, 30.10, 30.08, 30.00, 29.81, 29.80, 29.7, 29.5, 29.2, 28.3, 26.7, 25.3, 24.9, 23.1, 20.9, 14.4, 14.3; HRMS (ESI) *m*/*z* 550.4812 (550.4835 calcd for $C_{34}H_{64}NO_4$ (M + NH_4^+)).

Mayolene-18 (2) [(11*S*,9*Z*,12*Z*,15*Z*)-11-Octadecanoyloxyoctadeca-9,12,15-trienoic Acid]. A solution of stearic acid (21.2 mg, 0.074 mmol) in CH_2Cl_2 (0.30 mL) was treated with DMAP (9.1 mg, 0.074 mmol) and EDCI (14.3 mg, 0.074). The resulting cloudy solution was stirred for 12 h at rt followed by the addition of a solution of **3** (20.0 mg, 0.068 mmol) in CH_2Cl_2 (0.10 mL). After the solution was stirred for 15 h, the solvent was removed under vacuum. The residue was dissolved in NaOAc buffer (10 mL, 0.4 M, pH 5.75) and extracted with ether. Combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under vacuum. Flash chromatography (5:1 hexane/ethyl acetate) of the residual oil provided **2** (22.4 mg, 59%) as a white solid: $[\alpha]_D$ −1.4 (*c* 0.90, CH_2Cl_2); R_f = 0.51 (3:1 hexane/ethyl acetate); ^{1}H NMR (500 MHz, benzene-d_6) δ 6.74−6.80 (m, 1 H), 5.58−5.64 (m, 2 H), 5.48−5.54 (m, 2 H), 5.41−5.46 (m, 2 H), 3.12−3.20 (m, 1 H), 3.02−3.12 (m, 1 H), 2.28−2.36 (m, 1 H), 2.16−2.25 (m, 3 H), 2.04−2.12 (m, 4 H), 1.57−1.64 (m, 4 H), 1.12−1.37 (m, 36 H), 0.93 (m, 3 H), 0.92 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, benzene-d_6) δ 179.2, 172.3, 133.9, 132.9, 131.9, 128.0, 127.8, 126.7, 66.3, 34.5, 34.0, 32.3, 30.18, 30.16, 30.14, 30.11, 30.10, 30.09, 30.01, 29.82, 29.80, 29.59, 29.29, 28.2, 26.6, 25.3, 24.9, 23.1, 20.9, 14.4, 14.3; HRMS (ESI) *m*/*z* 578.5138 (578.5148 calcd for $C_{36}H_{68}NO_4$ (M + NH_4^+)).

Macrolides 24−26. A solution of **3** (28.5 mg, 0.097 mmol) in benzene (2.0 mL) was treated with ^{i}Pr$_2$NEt (86.0 uL, 0.48 mmol) and 2,4,6-trichlorobenzoyl chloride (75.0 uL, 0.48). The resulting solution was stirred for 3 h at rt and then rapidly cannulated into a solution of DMAP (177 mg, 1.45 mmol) in benzene (25 mL). After being stirred for 14 h, the solution was diluted with ether (25 mL), filtered through Celite, and concentrated under vacuum. Flash chromatography (CH_3CN) of the residual oil on C-18-modified silica gel provided **24** (11.8 mg, 44%), **25** (9.5 mg), and **26** (2.2 mg) as clear oils.

Data for (10*Z*)-12-[(1*Z*,4*Z*)-Hepta-1,4-dienyl]-1-oxacyclododec-10-en-2-one (24): ^{1}H NMR (500 MHz, benzene-d_6) δ 6.60 (m, $J_{12,11}$ = $J_{12,1'}$ = 8.2, 1 H, 12-H), 5.63 (m, $J_{10,11}$ = 10.8, $J_{11,12}$ = 8.2, 1 H, 11-H), 5.39−5.49 (m, 2 H, 4′-H and 5′-H), 5.49−5.57 (m, 2 H, 1′-H and 2′-H), 5.35 (m, $J_{10,11}$ = 10.8, $J_{10,9ax}$ = 12, $J_{10,9eq}$ = 4.5, 1 H, 10-H), 3.10−3.20 (m, 2 H, 3′-H), 2.39 (m, $J_{9eq,9ax}$ = 13, $J_{10,9ax}$ = 12, $J_{9ax,\ 8ax}$ = 11.7, $J_{9ax,8eq}$ = 3, 1 H, 9-H_{ax}), 2.15 (ddd, $J_{3ax,3eq}$ = 14, $J_{3eq,4ax}$ = 2.5, $J_{3eq,4eq}$ = 7.5, 1 H, 3-H_{eq}), 2.05 (m, $J_{6',7'}$ = 7.5, 2 H, 6′-H), 2.02 (ddd, $J_{3ax,3eq}$ = 14, $J_{3ax,4ax}$ = 11.5, $J_{3ax,4eq}$ = 2.5, 1 H, 3-H_{ax}), 1.80 (m, 1 H, 4-H_{ax}), 1.78 (m, $J_{9eq,9ax}$ = 13, $J_{10,9eq}$ = 4.5, 1 H, 9-H_{eq}), 1.20−1.52 (m, 7 H), 0.97−1.07 (m, 2 H), 0.90 (t, $J_{7',6'}$ = 7.5, 3 H, 7′-H); ^{13}C NMR (126 MHz, benzene-d_6) δ 173.1 (C-2), 136.7 (C-10), 132.6 (C-2′), 132.5 (C-5′), 128.7 (C-1′), 128.7 (C-11), 126.9 (C-4′), 64.9 (C-12), 36.2 (C-3), 29.8 (C-5), 27.0 (C-8), 26.5 (C-3′), 25.6 (C-9), 24.9 (C-6), 24.6 (C-7), 22.1 (C-4), 20.7 (C-6′), 14.3 (C-7′); MS (ESI) *m*/*z* 277 (277 calcd for $C_{18}H_{29}O_2$ (M + H^+)).

Data for (10*Z*,22*Z*)-12,24-Di[(1*Z*,4*Z*)-Hepta-1,4-dienyl]-1,13-dioxacyclotetraeicosa-10,22-diene-2,14-dione (25): ^{1}H NMR (500 MHz, benzene-d_6) δ 6.76 (m, $J_{12,11}$ = $J_{12,1'}$ = 8.7, 2 H, 12-H), 5.60 (m, $J_{1',2'}$ = 11, $J_{1',12}$ = 8.7, 2 H, 1′-H), 5.58 (m, $J_{10,11}$ = 10.8, $J_{11,12}$ = 8.7, 2 H, 11-H), 5.49 (m, $J_{1',2}$ = 11, $J_{2',3'}$ = 7.4, 2 H, 2′-H), 5.42 (m, $J_{10,11}$ = 10.8, $J_{10,9b}$ = 12, $J_{10,9a}$ = 5, 2 H, 10-H), 5.40−5.47 (m, 4 H, 4′-H and 5′-H), 3.02−3.15 (m, 4 H, 3′-H), 2.55 (m, $J_{9a,9b}$ = 13, $J_{10,9b}$ = 9, 2 H, 9-H_b), 2.18 (t, $J_{3,4}$ = 7.2, 4 H, 3-H), 1.95 (m, $J_{9a,9b}$ = 13, $J_{10,9a}$ = 5, 2 H, 9-H_a), 2.05 (m, $J_{6',7'}$ = 7.5, 4 H, 6′-H), 1.63−1.72 (m, 2 H, 4-H_b), 1.45−1.53 (m, 2 H, 1-H_a), 1.12−1.43 (m, 16 H), 0.91 (t, $J_{7',6'}$ = 7.5, 6 H, 7′-H); ^{13}C NMR (126 MHz, benzene-d_6) δ 172.1 (C-2), 134.6 (C-10), 132.8 (C-5′), 132.0 (C-2′), 128.5 (C-1′), 128.0 (C-11), 126.8 (C-4′), 65.9 (C-12), 34.6 (C-3), 29.35 (C-8), 29.3 (C-5), 28.8 (C-6), 28.8 (C-7), 27.9 (C-9), 26.7 (C-3′), 25.3 (C-4), 20.9 (C-6′), 14.4 (C-7′); MS (ESI) *m*/*z* 553 (553 calcd for $C_{36}H_{57}O_4$ (M + H^+)).

Data for (10*Z*,22*Z*,34*Z*)-12,24,36-Tri[(1*Z*,4*Z*)-hepta-1,4-dienyl]-1,13,25-trioxacyclohexatriaconta-10,22,34-triene-2,14,26-trione (26): ^{1}H NMR (500 MHz, benzene-d_6) δ 6.77 (m, $J_{12,11}$ = $J_{12,1'}$ = 8.8, 3 H, 12-H), 5.61 (m, $J_{1',2'}$ = 11, $J_{1',12}$ = 8.8, 3 H, 1′-H), 5.60 (m, $J_{10,11}$ = 10.8, $J_{11,12}$ = 8.8, 3 H, 11-H), 5.51 (m, $J_{1',2'}$ = 11, $J_{2',3'}$ = 7.4, 3 H, 2′-H), 5.48 (m, $J_{10,11}$ = 10.8, $J_{10,9b}$ = 9, $J_{10,9a}$ = 5, 3 H, 10-H), 5.40−5.48 (m, 6 H, 4′-H and 5′-H), 3.04−3.17 (m, 6 H, 3′-H), 2.42 (m, $J_{9a,9b}$ = 13, $J_{10,9b}$ = 12, 3 H, 9-H_b), 2.19 (t, $J_{3,4}$ = 7.2, 6 H, 3-H), 2.14 (m, $J_{9a,9b}$ = 13, $J_{10,9a}$ = 5, 3 H, 9-H_a), 2.07 (m, $J_{6',7'}$ = 7.5, 6 H, 6′-H), 1.53−1.64 (m, 6 H, 4-H), 1.14−1.38 (m, 24 H), 0.94 (t, $J_{7',6'}$ = 7.5, 9 H, 7′-H); ^{13}C NMR (126 MHz, benzene-d_6) δ 172.0 (C-2), 134.1 (C-10), 132.8 (C-5′), 131.9 (C-2′), 128.3 (C-1′), 127.8 (C-11), 126.7 (C-4′), 66.1 (C-12), 34.5 (C-3), 29.6 (C-8), 29.3 (C-6), 29.2 (C-5), 29.1 (C-7), 28.2 (C-9), 26.6 (C-3′), 25.2 (C-4), 20.8 (C-6′), 14.3 (C-7′); MS (ESI) *m*/*z* 830 (830 calcd for $C_{54}H_{85}O_6$ (M + H^+)).

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Supporting Information Available: Analytical data for compounds **7** and **10**−**16**, experimental procedures and analytical data for compounds **4**, **8**, and **17**−**23**, and spectroscopic data of the naturally occurring mixture of mayolenes. This material is available free of charge via the Internet at http://pubs.acs.org.

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