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Enzymatic Desaturation of Fatty Acids: Δ^{11} Desaturase Activity on Cyclopropane Acid Probes

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The formation of methylenecyclopropanes by enzymatic desaturation of 11-cyclopropylundecanoic acid (**1**) and its disubstituted derivatives *cis*- and *trans*-**3**−**5** has been investigated using the Δ^{11} desaturase of *Spodoptera littoralis* as model enzyme. Gas chromatography coupled to mass spectrometry analyses of methanolyzed lipidic extracts from tissues incubated with each probe revealed that all the cyclopropyl fatty acids were transformed into the corresponding 11-cyclopropylidene acids, except for compound *trans*-**5** (**5b**), which was not desaturated at C11. The formation of methylenecyclopropane **9** as the only reaction product from **1** indicates that a potential radical intermediate is too short-lived to allow rearrangement reactions. Information on the Δ^{11} desaturase substrate binding domain is provided considering the cyclopropyl probes **3**−**5** as conformationally restricted analogues of the straight-chain substrates.

Introduction

Unsaturated fatty acids are biosynthesized in nature from saturated fatty acids by the action of specific desaturases.[1] Besides the natural substrates, it has been reported that some enzymes act on non-natural fatty acids. Thus, *Saccharomyces cerevisiae* Δ^9 desaturase transforms both thia-[2a−c] and fluorofatty acids[3] into the corresponding unsaturated derivatives. Additionally, both thia-[2d] and odd numbered fatty acids[4,5] are desaturated by moth desaturases. The lack of information about the tridimensional structure of membrane-bound desaturases impairs the theoretical prediction of other non-natural possible desaturase substrates. However, experimental data obtained with moth Δ^{11} desaturases allow us to anticipate some potential substrates. Thus, the Δ^{11} desaturases from moths produce *E* and *Z* unsaturated fatty acids, either exclusively[6] or as a mixture of isomers.[7] The cloning and functional expression of the cDNA encoding the Δ^{11} desaturases from several insect species has provided the genetic evidence that formation of both isomers is catalyzed by a single enzyme.[8] Results from our laboratory[4] with the *Spodoptera littoralis* Δ^{11} desaturase as model showed that the geometry, *Z* or *E*, of the resulting C11-desaturated product depends on the substrate chain length. Thus, a single Δ^{11} desaturase transforms heptadecanoic, hexadecanoic, and pentadecanoic acids into the (*Z*)-11-monounsaturated products and tetradecanoic and tridecanoic acids into both the (*Z*)- and (*E*)-11-olefinic acids.[4,7b] In a previous paper,[9] we also showed that the Δ^{11} desaturase removes the pro-(*R*) hydrogen atom at C11 and either the *pro*-(*R*) or the *pro*-(*S*) hydrogen atoms at C12 to give the *Z* or the *E* isomer, respectively. Since desaturation reactions are *syn* dehydrogenation processes and the lifetime of the reaction intermediate is extremely short,[10] the dihedral angle between the two hydrogen atoms removed to afford each isomer should be close to 0° at the enzyme active site. In the case of the pentadecanoyl, hexadecanoyl, and heptadecanoyl derivatives, only their *eclipsed* conformers (dihedral angle C10−C11−C12−C13 ≈ 0°) would fit into the enzyme cavity, thus giving exclusively the (*Z*)-11

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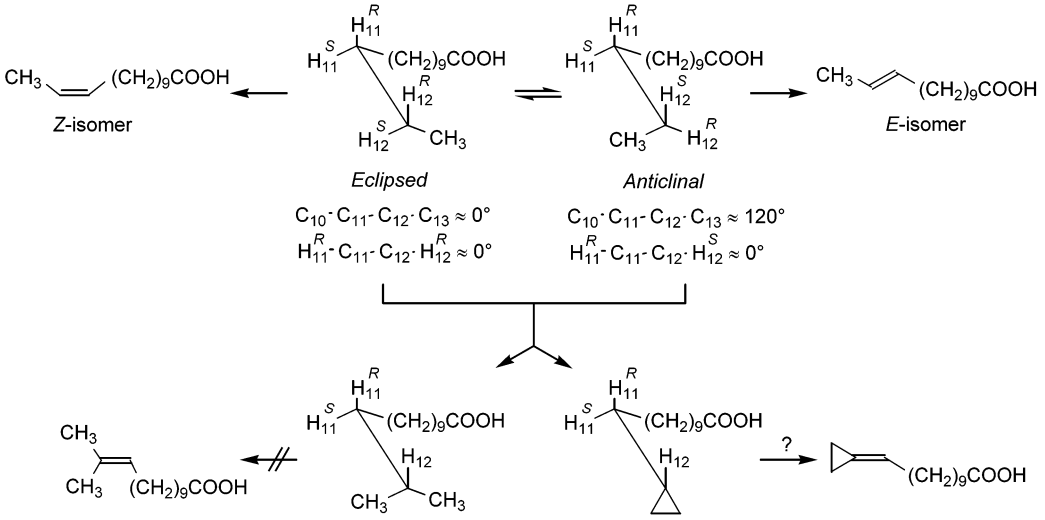


FIGURE 1. Formation of (*Z*)- and (*E*)-11 fatty acids by the Δ^{11} desaturase, as exemplified with tridecanoic acid, and potential substrates substituted at C12.

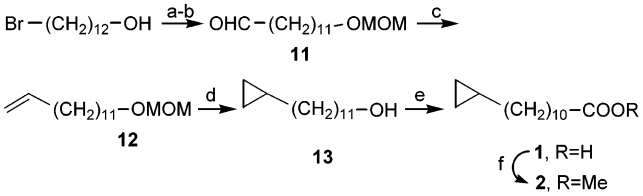
monounsaturated products. Conversely, in the shorter tridecanoyl and tetradecanoyl substrates, the enzyme binding pocket would accommodate both the *eclipsed* and *anticlinal* (dihedral angle C10−C11−C12−C13 ≈ 120°) conformers to give both the (*Z*)- and (*E*)-11 monounsaturated acids, respectively (Figure 1). This hypothesis suggested that short-chain fatty acids substituted at C12, which would formally arise from overlaying those *eclipsed* and *anticlinal* conformers of the straight-chain substrates, might be enzymatically transformed into the 11-monounsaturated products. However, preliminary experiments evidenced that 12-methyltridecanoic acid was not desaturated by this Δ^{11} desaturase,[11] indicating that 12-methyl substitution makes the substrate too bulky to fit into the enzyme substrate binding pocket or, alternatively, the presence of the additional methyl group impedes the correct positioning of C11 and/or C12 with respect to the enzyme iron oxidizing cluster. In this paper, we report on the results obtained with the less hindered cyclopropyl analogues **1** and **3**−**5**.

Results and Discussion

Synthesis of Probes. The synthesis of all the different probes was accomplished from the corresponding ω-bromo alcohol by way of well-established methodology (Schemes 1 and 2). The cyclopropane ring was formed by Simmons−Smith reaction of the suitable olefin with Et_2Zn and CH_2I_2.[12] Hydrolysis and further oxidation (pyridinium dichromate)[13] of the resulting cyclopropane derivative gave the final acid **1**.

The preparation of compounds **3**−**5** was carried out by a similar synthetic scheme, but cyclopropanation was performed on the ester intermediates **25**−**27**. This modification was introduced to avoid submitting the cyclopropane derivatives to the acidic conditions needed to hydrolyze the protective group, which resulted in the cleavage of the disubstituted cyclopropane ring.

SCHEME 1. Synthetic Route for the Cyclopropane Fatty Acids and Esters 1 and 2[a]



[a] Reagents and conditions: (a) $CH_2(OCH_3)_2$/LiBr/*p*-TsOH/25 °C/16 h;[14] (b) pyridine *N*-oxide/$NaHCO_3$/toluene/reflux/4 h;[15] (c) Ph_3PCH_3Br/*n*-BuLi/THF/−20 °C/1.5 h, then add **11** in THF at −40 °C, then −40 → +25 °C and 2 h/reflux; (d) Et_2Zn/CH_2Cl_2/−20 °C, then add CH_2I_2/−20 °C/1 h then −20 → +25 °C/48 h, then 10% HCl in MeOH/25 °C/14 h; (e) 0.2 M PDC/DMF/25 °C/6 h; (f) CH_2N_2/Et_2O.

Methylenecyclopropane **10** was also synthesized to have an authentic standard for the unambiguous identification of this compound in the biological extracts. This standard was prepared (Scheme 3) by Wittig reaction of the suitable aldehyde with cyclopropylidenetriphenylphosphorane.[16] Hydrolysis of the protective group and further oxidation[13] afforded 11-cyclopropylideneundecanoic acid **9**, which was transformed into the corresponding methyl ester **10** with diazomethane.

Desaturation of 1. Mechanistic Considerations. Probe **1** was incubated with *S. littoralis* pheromone glands, which contain the Δ^{11} desaturase,[7b] and fatty acid methyl esters were obtained by base methanolysis of pheromone gland lipidic extracts. Analyses by GC−MS were carried out as previously reported[17] using three capillary columns of different polarities. As shown in Figure 2, analyses of extracts from tissues incubated with **1** revealed the presence of two methyl esters that were absent in controls. The retention times of both compounds in the three different columns (Figure 2) and their mass

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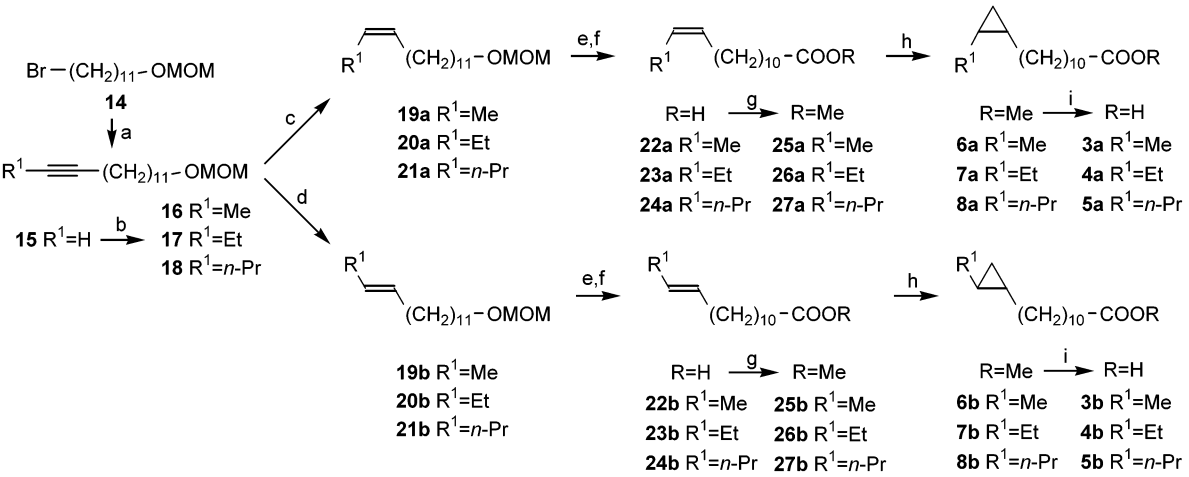
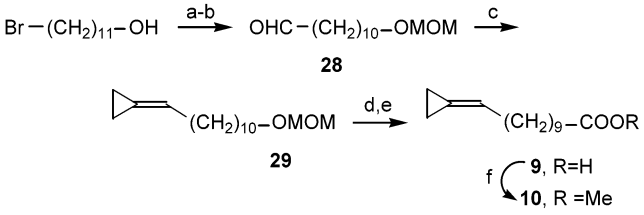
SCHEME 2. Synthetic Routes for the Cyclopropane Fatty Acids and Esters 3−8[a]



[a] Reagents and conditions: (a) NH_3(l)/−78 °C, then add acetylene for 1.5 h, then add Li and DMSO, −78 → +25 °C, then add **14** in DMSO/25 °C/1 h; (b) *n*-BuLi/0 °C/5 min, then add R^1I/0 °C/16 h; (c) H_2/Lindlar/25 °C/1 h; (d) Na/NH_3(l)/−78 °C/THF/10 min, then 8 h at −30 °C; (e) 10% HCl in MeOH/25 °C/16 h; (f) CrO_3/H_2O/H_2SO_4/acetone/25 °C/4 h; (g) BF_3·Et_2O/ MeOH/25 °C/1 h; (h) Et_2Zn/CH_2Cl_2/−20 °C, then add CH_2I_2/−20 °C/1 h then −20 → +25 °C/16 h; (i) 2.5N KOH/MeOH/H_2O/25 °C/16 h.

SCHEME 3. Synthetic Routes for the Methylenecyclopropane Fatty Acids and Esters 9 and 10[a]



[a] Reagents and conditions: (a) $CH_2(OCH_3)_2$/LiBr/*p*-TsOH/25 °C/16 h; (b) pyridine *N*-oxide/$NaHCO_3$/toluene/reflux/4 h; (c) Ph_3Pc-C_3H_5Br/*n*-BuLi/THF/−20 °C/1.5 h, then add **28** in THF at −40 °C, then −40 → +25 °C, then reflux/2 h; (d) 10% HCl in MeOH/25 °C/14 h; (e) 0.2 M PDC/DMF/25 °C/6 h; (f) CH_2N_2/Et_2O/25 °C/5 min.

spectra (Figure 3) were coincident with those of authentic samples of **2** and **10**.

In many reported examples,[4,18] desaturation reactions catalyzed by membrane-bound acyl CoA desaturases occur in two steps: initial rate-limiting abstraction of the hydrogen atom located nearest to the carboxyl moiety and further fast elimination of the neighboring hydrogen to give the olefinic bond. The nature of the reaction intermediate formed upon abstraction of the first hydrogen is still unclear, although the occurrence of a radical has been proposed.[10,18a] In light of the cryptoregiochemistry of the Δ^{11} desaturase studied here,[4] should a C11 substrate radical **i** be formed during the desaturation

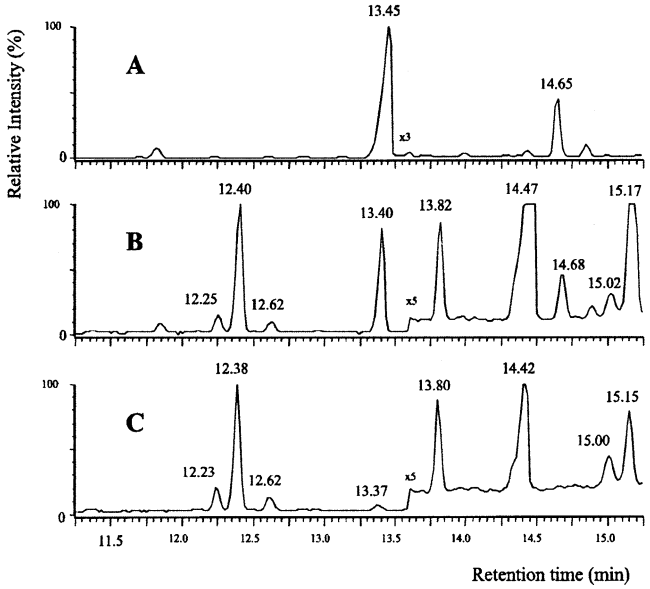


FIGURE 2. (A) GC−MS chromatograms (poly(biscyanopropyl)-siloxane column) of synthetic samples of **2** (13.45 min) and **10** (14.65 min), (B) methanolyzed lipidic extracts from tissues incubated with **1**, and (C) extracts from controls. All traces arise from monitoring the ion *m*/*z* 81, which is the most abundant fragment in the mass spectrum of **10**. In chromatogram B, products are methyl (*E*)-11-tetradecenoate (12.25 min), methyl (*Z*)-9-tetradecenoate (12.40 min), methyl (*Z*)-11-tetradecenoate (12.62 min), **2** (13.40 min), methyl hexadecanoate (14.47 min), **10** (14.68 min), and methyl (*Z*)-9-hexadecenoate (15.17 min).

reaction, compounds arising from this intermediate should be detected (Figure 4). However, neither (*Z*)- nor (*E*)-11,13-tetradecadienoic acid methyl esters were detected at the retention times of authentic synthetic samples, even by GC−MS with the sensitive selecting ion monitoring mode. Likewise, neither the cyclopropylcarbinol **iv** nor the rearranged alcohol **v** (Figure 4) were found at the expected retention times by GC−MS with selected ion monitoring after derivatization with bis-

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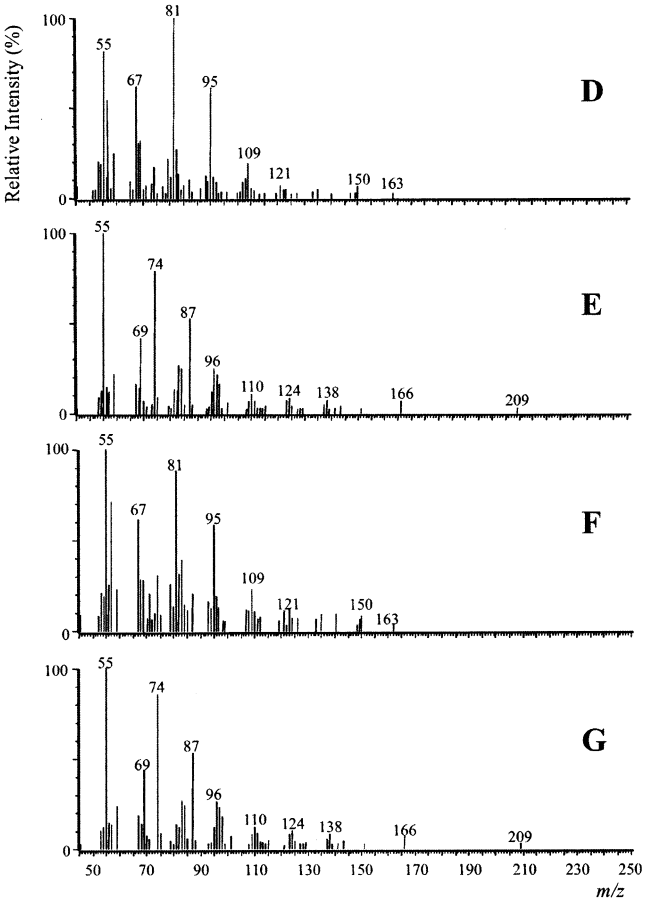

FIGURE 3. (D) and (E) Mass spectra of synthetic standards **10** and **2** (t_R = 14.65 and 13.45 min, respectively, in chromatogram A from Figure 2). (F) and (G) Mass spectra of compounds **10** and **2** obtained from tissues incubated with compound **1** (t_R = 14.68 and 13.40 min, respectively, in chromatogram B from Figure 2).

(trimethylsilyl)trifluoroacetamide.[19,20] The only distinctive compound encountered in tissues incubated with **1** as compared to controls was the methylenecyclopropane ester **10**. This result is against the occurrence of a long-lived radical intermediate in the Δ^{11} desaturase-catalyzed reaction; however, the formation of a radical with a rearrangement rate constant too low to compete with the elimination of C12−H cannot be disregarded.[21]

Desaturation of 3−5. Steric Considerations. After showing that **1** had been enzymatically transformed into **9**, the scope of this biotransformation was investigated with the disubstituted cyclopropanes **3**−**5**. These probes

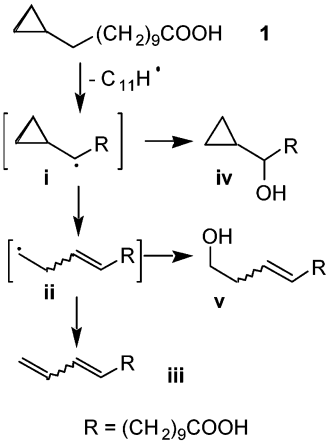

FIGURE 4. Theoretical products (**iii**−**v**) expected from the cyclopropylcarbinyl radical **i** derived from **1**.

were incubated with the Δ^{11} desaturase-containing glands, fatty acid methyl esters were then obtained and the extracts were analyzed by GC−MS using three capillary columns of different polarities. The analyses revealed that all the cyclopropane probes of *cis* stereochemistry were converted into the corresponding methylenecyclopropane products.[22] Although authentic synthetic samples were not available for these compounds, they were tentatively identified on the basis of their mass spectra (Figure 5), which were in complete accordance with that of **10**. The mass spectra of these compounds exhibited characteristic fragments, such as the molecular ion ($M^{\bullet+}$) at m/z = 252, 266 and 280 for the methyl, ethyl, and propyl derivatives, respectively, and ions arising from loss of either methoxy ($M^{\bullet+}$ − 31) or methanol ($M^{\bullet+}$ − 32) from $M^{\bullet+}$. Loss of the MacLafferty rearrangement fragment from $M^{\bullet+}$ ($M^{\bullet+}$ − 74) affords the ions at m/z = 178, 192, and 206, respectively, for the methyl-, ethyl-, and propylcyclopropylydene products. The more abundant fragments, also present in the mass spectrum of **10**, correspond to $C_5H_7^+$ (m/z = 67) and $C_6H_9^+$ (m/z = 81). However, these mass spectra could also correspond to the conjugated dienes that would arise from rearrangement of the corresponding radical intermediates **i** (Figure 4), whose formation was ruled out with probe **1**. Taking the ethyl derivative **4** as a representative example, the retention times of the four isomers of methyl 11,13-hexadecadienoate, which were available in our laboratories, were clearly different from that of the desaturation product of **4** in the poly(biscyanopropyl)siloxane column. This result demonstrated that the product formed upon desaturation of **4** was not an 11,13-hexadecadienoic acid, but probably a cyclopropylidene fatty acid. Although authentic synthetic samples of the conjugated 11,13-dienoates putatively derived from **3** and **5** were not available, their desaturation products were tentatively identified as cyclopropylidene fatty acids on the basis of their relative retention times with respect to the substrates under the different chromatographic conditions, which were in complete accordance with the different chromatographic behavior of **4** and its cyclopropylidene derivative.

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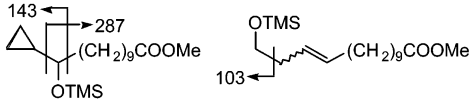
(20) The diagnostic ions recorded in the SIM−GC−MS analyses were: 328 (M), 313 (M − Me), 297 (M − MeO), 73 (TMS), 89 (OTMS), 103, 143, 287, (see the assignment below). Conversions above 0.5% should be detected with this technique.



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(22) Percent conversions (product/(product + substrate)100 ratios, as determined from the abundances of the M − 31 ($MeO^{\bullet}$) ions in the GC−MS chromatograms of extracts after each treatment), were between 5 and 10% in all cases.

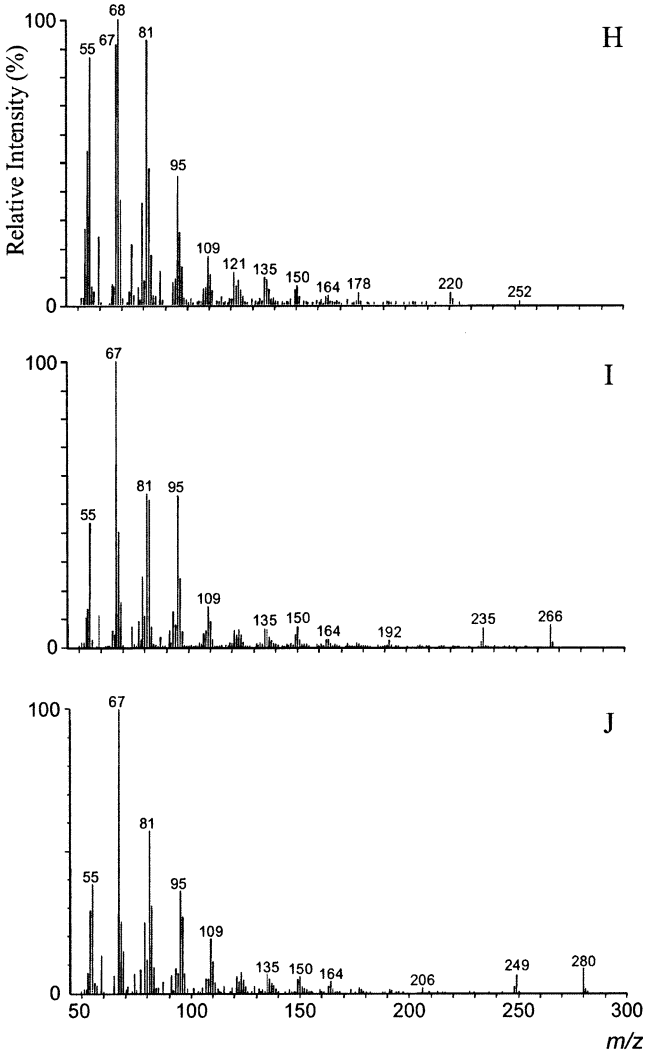

FIGURE 5. Mass spectra of the products obtained after incubation with pheromone gland tissues of **3a** (**H**), **4a** (**I**), and **5a** (**J**). Cyclopropanes **3b** and **4b** afforded the same compounds formed from **3a** and **4a**, respectively. Retention times (min, methyl esters) in the GC−MS chromatograms (nonpolar column, see conditions in the Experimental Procedures) are **6a**, 21.45; **6b**, 20.45; **7a**, 23.27; **7b**, 22.48; **8a** 25.15; **8b**, 24.39.

trans-Cyclopropanes **3b**−**4b** were also desaturated to the corresponding cyclopropylidene products, as concluded from the presence, in the GC−MS chromatograms, of the same products formed from the *cis*-cyclopropyl substrates.[23] Interestingly, no cyclopropylidene acid was detected after incubations with **5b**, thus showing that this probe is not a substrate of the Δ^{11} desaturase.

Cyclopropanes **3**−**5** can be regarded as conformationally restricted analogues of the straight chain Δ^{11} desaturase substrates. Conformational restrain is introduced either by binding C12 to C14 or by insertion of a methylene group between C12 and C13. Since the linear substrates of C15 to C17 lose the *pro*-(*R*) hydrogen atoms from both C11 and C12, it can be concluded that only

(23) The enantiomerically pure stereoisomers 12*S*,13*R* and 12*R*,13*R* of cyclopropanes **3b**−**4b** should afford the enantiomerically pure methylenecyclopropanes 13*R*, and the enantiomerically pure diastereomers 12*S*,13*S* and 12*R*,13*S* of probes **3b**−**4b** should give the enantiomerically pure methylenecyclopropanes 13*S*.

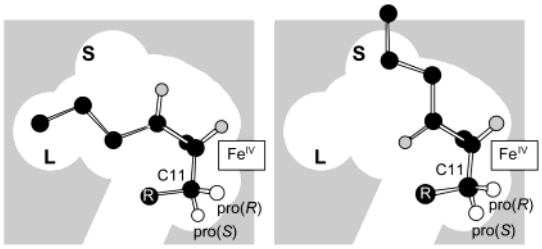

FIGURE 6. Models of (12*S*,13*S*)-**5a** (left) and (12*S*,13*R*)-**5b** (right) and the hypothetical end of the Δ^{11} desaturase substrate binding channel showing the large (L) and small (S) pockets. As depicted in the right side drawing, the size of the small pocket does not allow the accommodation of the terminal methyl group in **5b**. Black indicates C and light gray shows the cyclopropane hydrogen atoms at C12 and C13. The prochiral C11-H are shown in white. R indicates $(CH_2)_8COOH$ and Fe^{IV} stands for the oxidizing iron cluster. The models were obtained with the Hyperchem 6.0 program. The dihedral angle C10−C11−C12−C13 was set to 0°.

the (12*S*,13*S*) (*cis*) stereoisomer of **5** and both (12*S*,13*S*) (*cis*) and (12*S*,13*R*) (*trans*) stereoisomers of **4** are enzymatically desaturated at C11. The graphical analysis of these data (Figure 6) suggest that the end of the Δ^{11} desaturase substrate binding channel, which holds the substrate terminal alkyl chain beyond C12, has two different cavities: a large one (L, Figure 6), which accommodates *cis*-**3**−**5**, as well as the *eclipsed* conformation of the natural substrates, and a small pocket (S, Figure 6), which holds *trans*-**3**−**4**, but not **5b**, as well as the *anticlinal* conformer of the natural substrate that affords the *E* olefinic product. The use of other conformationally restricted fatty acids should provide additional information about the tridimensional structure of the Δ^{11} desaturase substrate binding domain. These studies are under way in our laboratories.

Experimental Procedures

Materials and Methods. Reactions sensitive to moisture were carried out under Ar atmosphere. Commercial grade reagents were used directly without further purification. Solvents were dried by standard methods and distilled before use. Reactions were monitored by TLC on precoated silica gel Merck 60 F_{254} (0.1 mm) sheets. Purification of products by column chromatography was performed on Merck silica gel 60. The probes were prepared as described in the following section. *S. littoralis* specimens were reared as reported elsewhere.[3b]

Instrumentation. Fourier transform infrared spectra (FT-IR) were recorded in chloroform solutions and are reported in cm^{-1}. ^1H NMR and ^{13}C NMR spectra were obtained in $CDCl_3$ solutions at 300 MHz for ^1H and 75 MHz for ^{13}C. Chemical shifts are expressed in delta (δ) units, parts per million (ppm) relative to the singlet at 7.26 ppm of $CDCl_3$ for ^1H and in ppm relative to the central line of a triplet at 77.0 ppm of $CDCl_3$ for ^{13}C. ^{13}C Multiplicities and $^{13}C-^1H$ connectivities were ascertained by DEPT and HETCOR experiments using standard pulse sequences. Gas chromatography-coupled to mass spectrometry (GC−MS) was performed on a quadrupole mass selective detector coupled to a gas chromatograph equipped with fused silica capillary columns (25 m × 0.25 μm × 0.22 mm i.d.) with different stationary phases: 5% phenyl/95% dimethylpolysiloxane (nonpolar), nitroterephthalic acid modified poly(ethylene glycol) (high polarity) and poly(biscyanopropyl)siloxane (very high polarity). Helium was used as carrier gas at a flow rate of 1 mL/min. Samples were injected in the splitless mode and the split valve was closed for 48 s.

Injector and interface were set at 250 °C. The mass spectrometer was operated by electron ionization (EI, 70 eV) and in the scan mode (working range 45−300 amu) unless otherwise indicated.

Synthesis of Probes. 12-Methoxymethoxy-1-bromododecane. To a solution of 12-bromo-1-dodecanol (3.7 g, 14.0 mmol) in dimethoxymethane (28 mL, 2.8 mol), was added LiBr (242 mg, 2.8 mmol), and *p*-toluensulfonic acid (239 mg, 1.3 mmol) and stirred at room temperature. The reaction was monitored by TLC (hexane/EtOAc, 8:2) until it was completed (16 h). After that, the crude was extracted with hexane (3 × 25 mL), dried over $MgSO_4$, and filtered. Solvents were evaporated under vacuum to yield 4.1 g (13.3 mmol, 95%) of an oil identified as 12-methoxymethoxy-1-bromododecane. IR (film): 2927, 2854, 1465, 1440, 1214, 1149, 1110, 1045. ^{1}H NMR: 4.59 (s, 2H), 3.49 (t, J = 6.5 Hz, 2H), 3.38 (t, J = 7.0 Hz, 2H), 3.34 (s, 3H), 1.83 (tt, J = 7.0 Hz, 2H), 1.56 (tt, J = 6.5 Hz, 2H), 1.25 (bs, 16H). ^{13}C NMR: 96.4, 67.8, 55.1, 34.1, 32.8, 29.7, 29.5, 29.4, 28.7, 28.2, 26.2. Anal. Calcd for $C_{14}H_{29}BrO_2$: C, 54.37; H, 9.45; Br, 25.84; O, 10.35. Found: C, 54.53; H, 9.35; Br, 26.02.

12-Methoxymethoxydodecanal (11). A solution of 12-methoxymethoxy-1-bromododecane (4.0 g, 13.6 mmol), pyridine *N*-oxide (2.6 g, 27.0 mmol), and sodium bicarbonate (2.3 g, 27.0 mmol) in toluene (17 mL) was stirred at reflux for 4 h (TLC, hexane/EtOAc, 8:2). The resulting yellowish solution was allowed to reach room temperature, and water (68 mL) was added. The mixture was extracted with hexane (4 × 50 mL), and the organic layer was washed with brine (25 mL), dried over $MgSO_4$, and filtered. Solvents were evaporated under vacuum giving 2.8 g (11.5 mmol, 85%) of a dark oil identified as 12-methoxymethoxydodecanal (**11**). IR (film): 2927, 2854, 1726, 1465, 1147, 1110, 1045. ^{1}H NMR: 9.73 (t, J = 2.0 Hz, 1H), 4.59 (s, 2H), 3.48 (t, J = 6.5 Hz, 2H), 3.33 (s, 3H), 2.39 (td, J = 7.0, 2.0 Hz, 2H), 1.56 (m, 4H), 1.24 (bs, 14H). ^{13}C NMR: 202.9, 96.3, 67.8, 55.0, 43.9, 29.7, 29.5, 29.4, 29.3, 29.1, 26.2, 22.0. Anal. Calcd for $C_{14}H_{28}O_3$: C, 68.81; H, 11.55; O, 19.64. Found: C, 69.03; H, 11.50.

13-Methoxymethoxy-1-tridecene (12). A solution of 8.8 g (24.6 mmol) of methyltriphenylphosphonium bromide (previously dried for 16 h at 90 °C and 10^{-1} Torr) in THF (55 mL) was cooled to −20 °C, and 17 mL of *n*-BuLi (1.48 M in hexane, 25.5 mmol) was dropwise added while the color was turning yellow and, eventually, red. After the mixture was kept at −20 °C for 1.5 h, it was cooled to −40 °C and a solution of 12-methoxymethoxydodecanal (**11**) (1.5 g, 6.1 mmol) in THF (4 mL) was slowly added. The solution was allowed to reach room temperature for 1 h, and then it was refluxed for 2 h (TLC, hexane/EtOAc, 8:2). After that time, the reaction was cooled to room temperature and quenched by dropwise addition of water (12 mL). The THF was evaporated under vacuum and the residue extracted with hexane (3 × 10 mL). The organic layer was washed with water until neutral pH and then with 1 N HCl aqueous solution (2 × 10 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum to yield 1.74 g of a mixture that was purified by flash chromatography using hexane and then 1% EtOAc/hexane as eluent to give 0.9 g (3.7 mmol, 61%) of 13-methoxymethoxy-1-tridecene (**12**). IR (film): 2925, 2854, 1641, 1463, 1456, 1440, 1149, 1112, 1045. ^{1}H NMR: 5.79 (tdd, J = 17.0, 10.0, 6.5 Hz, 1H), 4.96 (dtd, J = 17.0, 2.0, 2.0 Hz, 1H), 4.90 (dtd, J = 10.0, 2.0, 1.0 Hz, 1H), 4.59 (s, 2H), 3.49 (t, J = 6.5 Hz, 2H), 3.33 (s, 3H), 2.01 (m, 2H), 1.56 (m, 2H), 1.24 (bs, 16H). ^{13}C NMR: 139.2, 114.1, 96.4, 67.9, 55.0, 33.8, 29.7, 29.6, 29.5, 29.4, 29.1, 28.9, 26.2. Anal. Calcd for $C_{15}H_{30}O_2$: C, 74.32; H, 12.47; O, 13.20. Found: C, 74.50; H, 12.41.

11-Cycloproyl-1-undecanol (13). To a solution of 500 mg (2.2 mmol) of 13-methoxymethoxy-1-tridecene **12** in CH_2Cl_2 (30 mL) and cooled to −20 °C were dropwise added 6.6 mL (6.6 mmol) of Et_2Zn and then 795 μL (9.9 mmol) of CH_2I_2. Monitoring of the reaction was performed by GC (**12**, t_R = 17.83 min, MOM protected 11-cyclopropyl-1-undecanol, t_R = 20.71 min; 80 °C (2 min) then 5 °C/min up to 280 °C). When no evolution of the reaction was observed by GC, an additional 2 equiv (one at a time) of both Et_2Zn and CH_2I_2 was added until 13-methoxymethoxy-1-tridecene (**11**) was not present by GC. The reaction was then quenched by dropwise addition of 3 N NaOH (15 mL), the methylene chloride was removed under vacuum, and the resulting crude was extracted with hexane (4 × 20 mL). The combined organic layer was washed with brine (2 × 20 mL), dried over $MgSO_4$, filtered, and evaporated under vacuum to yield 543 mg of a colorless oil. This oil was treated by slowly addition of 10% hydrogen chloride in methanol solution (32 mL), stirred at room temperature for 16 h (TLC, hexane/EtOAc, 8:2), and extracted with Et_2O (100 mL). The organic layer was washed with 1 N HCl (4 × 25 mL), dried over $MgSO_4$, filtered, and evaporated under vacuum giving 466 mg of a yellow oil that was purified by flash chromatography using a hexanes−EtOAc gradient as eluent, yielding 11-cyclopropyl-1-undecanol (**13**) (310 mg, 1.6 mmol, 73%). IR (film): 3339, 3077, 3011, 2923, 2852, 1479, 1463, 1454, 1444, 1056, 1012. ^{1}H NMR: 3.62 (t, J = 6.5 Hz, 2H), 1.54 (m, 2H), 1.25 (bs, 16H), 1.16 (m, 2H), 0.62 (m, 1H), 0.36 (dd, J = 8.0, 8.0, 2.0 Hz, 2H), −0.04 (dd, J = 5.0, 5.0, 1.5 Hz, 2H). ^{13}C NMR: 63.1, 34.8, 32.8, 29.7, 29.6, 29.5, 29.4, 25.7, 10.9, 4.3. Anal. Calcd for $C_{14}H_{28}O$: C, 79.18; H, 13.29; O, 7.53. Found: C, 79.28; H, 13.20.

11-Cyclopropylundecanoic Acid (1). To 250 mg (1.3 mmol) of 11-cyclopropyl-1-undecanol (**13**) was added, at 0 °C, 44 mL (8.8 mmol) of a 0.2 M solution of PDC in DMF, and the resulting mixture was stirred for 6 h (TLC, hexane/EtOAc, 8:2) at room temperature. The reaction was quenched by placing the flask in an ice bath and addition of water (250 mL). The resulting mixture was extrated with Et_2O (5 × 50 mL), and the combined organic layer was washed with water (7 × 50 mL) and brine (4 × 50 mL), dried with $MgSO_4$, filtered, and evaporated at reduced pressure to give 245 mg of a yellowish oil that was purified by flash chromatography using deactivated (with 10% of water) silica gel and CH_2Cl_2−MeOH gradient as the eluent, yielding 200 mg (0.9 mmol, 69%) of 11-cyclopropylundecanoic acid (**1**). IR (film): 2400−3500, 2918, 2850, 1702, 1463, 1428, 1409, 1294, 1242, 1149, 1108, 1043. ^{1}H NMR: 10.79 (bs, 1H), 2.32 (t, J = 7.0 Hz, 2H), 1.61 (m, 2H), 1.25 (b, 14H), 1.16 (m, 2H), 0.62 (m, 1H), 0.35 (dd, J = 8.0, 8.0, 2.0 Hz, 2H), −0.04 (dd, J = 5.0, 5.0, 1.5 Hz, 2H). ^{13}C NMR: 180.3, 34.8, 34.09, 29.7, 29.6, 29.5, 29.4, 29.2, 29.0, 24.7, 10.9, 4.3. Anal. Calcd for $C_{14}H_{26}O_2$: C, 74.29; H, 11.58; O, 14.14. Found: C, 74.17; H, 11.65.

11-Cyclopropylundecanoic Acid Methyl Ester (2). An analytical sample of 11-cyclopropylundecanoic acid methyl ester (**2**) was obtained by treatment of 11-cyclopropylundecanoic acid (**1**) with an ethereal solution of diazomethane. This compound was characterized by GC−MS: m/z 209 (M^+ − 31, 5), 166 (10), 87 (66), 74 (100), 69 (52), 55 (97).

11-Methoxymethoxy-1-bromoundecane (14). Following the same synthetic procedure as for 12-methoxymethoxy-1-bromododecane, treatment of 10 g (39.8 mmol) of 11-bromoundecanol afforded 11.3 g (38.3 mmol, 96%) of 11-methoxymethoxy-1-bromoundecane (**14**) as a yellowish oil.[24] IR (film): 2927, 2854, 1465, 1440, 1149, 1110, 1045. ^{1}H NMR: 4.59 (s, 2H), 3.49 (t, J = 6.5 Hz, 2H), 3.38 (t, J = 7.0 Hz, 2H), 3.33 (s, 3H), 1.82 (tt, J = 7.0 Hz, 2H), 1.56 (m, 2H), 1.26 (bs, 14H). ^{13}C NMR: 96.3, 67.81, 55.0, 33.9, 32.8, 29.7, 29.5, 29.4, 28.7, 28.1, 26.2. Anal. Calcd for $C_{13}H_{27}BrO_2$: C, 52.88; H, 9.22; Br, 27.06; O, 10.84. Found: C, 52.78; H, 9.26; Br, 27.26.

13-Methoxymethoxy-1-tridecyne (15). In a flask at −78 °C were condensed about 233 mL of NH_3, and a stream of previously dried acetylene was bubbled for 1 h. Li metal was added (254 mg, 37.0 mmol), and once it was dissolved 26 mL of DMSO was added and the ammonia was evaporated by changing the coldfinger by a Dimroth coil condenser a leaving

(24) Xu, Z.; Byun, H.-S.; Bittman, R. *J. Org. Chem.* **1991**, *56*, 7183−7186.

the system to reach room temperature. To the resulting solution was added 6.0 g (20.0 mmol) of 11-methoxymethoxy-1-bromoundecane (**14**) in 3 mL of DMSO, and the mixture was allowed to stir at room temperature (the reaction was monitored by GC, from 120 to 280 °C at a 10 °C/min rate, t_R for **15** = 10.21 min, t_R for **14** = 11.94 min) for 1 h. The reaction was quenched by addition of 68 mL of water and extraction with hexane (4 × 20 mL). The combined organic layer was dried over $MgSO_4$ and concentrated to give 4.7 g (19.6 mmol, 98%) of 13-methoxymethoxy-1-tridecyne (**15**) as an oil. IR (film): 3312, 2928, 2855, 1466, 1147, 1112, 1044. ^{1}H NMR: 4.59 (s, 2H), 3.48 (t, J = 6.5 Hz, 2H), 3.33 (s, 3H), 2.15 (dt, J = 7.0, 3.0 Hz, 2H), 1.91(t, J = 3.0 Hz, 1H), 1.56 (m, 2H), 1.49 (m, 2H), 1.24 (bs, 14H). ^{13}C NMR: 96.3, 84.8, 68.0, 67.8, 55.0, 29.7, 29.5, 29.4, 29.1, 28.7, 28.5, 26.2, 18.4. Anal. Calcd for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74; O, 13.31. Found: C, 75.12; H, 11.57.

14-Methoxymethoxy-1-tetradecyne (16). *n*-BuLi (8 mL, 12.0 mmol, 1.4 M) was slowly added to a solution of 13-methoxymethoxy-1-tridecyne (**15**) (2.3 g, 9.6 mmol) in THF (11 mL) at 0 °C. After 5 min, 700 μL (11.2 mmol) of methyl iodide in 11 mL of HMPA was dropwise added at 0 °C. The resulting mixture was stirred at room temperature (the reaction was monitored by GC, from 120 °C to 280 °C at a 10 °C/min rate, t_R for **16** = 11.90 min, t_R for **15** = 10.21 min) for 16 h. The reaction was quenched by addition, at 0 °C, of 5 mL of saturated aqueous NH_4Cl solution and removal of solvent under vacuum and extraction with hexane (4 × 10 mL). The organic layer was washed with brine (2 × 200 mL), dried over $MgSO_4$, filtered, and concentrated giving 2.2 g of crude product that was purified by flash column chromatography using a hexanes−EtOAc gradient as the eluent. 14-Methoxymethoxy-1-tetradecyne (**16**) (1.5 g, 5.9 mmol, 61%) was obtained as an oil. IR (film): 2927, 2855, 1465,1148, 1112, 1046. ^{1}H NMR: 4.59 (s, 2H), 3.49 (t, J = 6.5 Hz, 2H), 3.33 (s, 3H), 2.08 (qt, J = 2.5, 2.0 Hz, 2H), 1.75 (t, J = 2.5 Hz, 3H), 1.56 (m, 2H), 1.44 (m, 2H), 1.24 (bs, 14H). ^{13}C NMR: 96.3, 79.4, 75.3, 67.8, 55.1, 29.7, 29.6, 29.5, 29.4. 29.2, 29.1, 28.9, 26.2, 18.7, 3.5. Anal. Calcd for $C_{16}H_{30}O_2$: C, 75.54; H, 11.89; O, 12.58. Found: C, 75.68; H, 11.78.

15-Methoxymethoxy-3-pentadecyne (17). Following the same procedure as for 14-methoxymethoxy-1-tetradecyne (**16**), the reaction of 2.0 g (8.3 mmol) of 13-methoxymethoxy-1-tridecyne (**15**), 8 mL of *n*-BuLi (10.7 mmol, 1.34 M), 9 mL of THF, 9 mL of HMPA, and 800 μL (10.0 mmol) of ethyl iodide produced 2.2 g (8.2 mmol, 99%) of 15-methoxymethoxy-3-pentadecyne (**17**). IR (film): 2928, 2855, 1465, 1148, 1112, 1046. ^{1}H NMR: 4.61 (s, 2H), 3.51 (t, J = 6.5 Hz, 2H), 3.35 (s, 3H), 2.13 (m, 4H), 1.56 (m, 2H), 1.46 (m, 2H), 1.27 (bs, 14H), 1.11 (t, J = 7.0 Hz, 3H). ^{13}C NMR: 96.3, 81.5, 79.5, 67.8, 55.0, 29.7, 29.5, 29.4. 29.1, 28.8, 26.2, 18.7, 14.4, 12.4. Anal. Calcd for $C_{17}H_{32}O_2$: C, 76.06; H, 12.02; O, 11.92. Found: C, 75.90; H, 12.12.

16-Methoxymethoxy-4-hexadecyne (18). Following the same procedure as for 14-methoxymethoxy-1-tetradecyne (**16**), the reaction of 2.0 g (7.8 mmol) of 13-methoxymethoxy-1-tridecyne (**15**), 8 mL of *n*-BuLi (10.7 mmol, 1.34 M), 9 mL of THF, 9 mL of HMPA, and 908 μL (9.3 mmol) of propyl iodide produced 2.2 g of a crude product that was purified by flash chromatography. 16-Methoxymethoxy-4-hexadecyne (**18**) (1.4 g, 5.0 mmol, 64%) was obtained. IR (film): 2928, 2855, 1465, 1149, 1112, 1046. ^{1}H NMR: 4.59 (s, 2H), 3.49 (t, J = 6.5 Hz, 2H), 3.33 (s, 3H), 2.10 (m, 4H), 1.56 (m, 2H), 1.45 (m, 2H), 1.25 (bs, 16H), 0.94 (t, J = 7.0 Hz, 3H). ^{13}C NMR: 96.4, 80.4, 80.0, 67.9, 55.1, 29.7, 29.6, 29.5, 29.4. 29.2, 29.1, 28.8, 26.2, 22.5, 20.8, 18.7, 13.4. Anal. Calcd for $C_{18}H_{34}O_2$: C, 76.54; H, 12.13; O, 11.33. Found: C, 76.41; H, 12.18.

14-Methoxymethoxy-(*Z*)-2-tetradecene (19a). To a flask containing 30 mg of Lindlar catalyst in 5 mL of hexane were added 507 mg (2.0 mmol) of 14-methoxymethoxy-1-tetradecyne (**16**) dissolved in 2 mL of hexane. The suspension was degassed by three cycles of vacuum/hydrogen filling and eventually kept under hydrogen atmosphere with vigorous stirring at room temperature (the reaction was monitored by GC, from 120 to 280 °C at a 10 °C/min rate, t_R for **19a** = 10.99 min, t_R for **16** = 11.90 min) for 1 h. The suspension was filtered through a Celite pad, and the solvent was evaporated under reduced pressure. 14-Methoxymethoxy-(*Z*)-2-tetradecene (**19a**) (497 mg, 1.9 mmol, 95%) was obtained. IR (film): 2925, 2854, 1463, 1150, 1112, 1046, 966, 920. ^{1}H NMR: 5.38 (m, 2H), 4.59 (s, 2H), 3.49 (t, J = 6.5 Hz, 2H), 3.33 (s, 3H), 1.96 (m, 2H), 1.58 (m, 5H), 1.24 (bs, 18H). ^{13}C NMR: 130.9, 123.6, 96.3, 67.8, 55.0, 32.6, 29.7, 29.6, 29.5, 29.4, 29.3, 26.8, 26.2, 12.7. Anal. Calcd for $C_{16}H_{32}O_2$: C, 74.94; H, 12.58; O, 12.48. Found: C, 74.78; H, 12.52.

15-Methoxymethoxy-(*Z*)-3-pentadecene (20a). Following the same procedure as for **19a**, treatment of 778 mg (3.0 mmol) of 15-methoxymethoxy-3-pentadecyne (**17**), 46 mg of Lindlar catalyst, and 10 mL of hexane yielded 770 mg (2.9 mmol, 97%) of 15-methoxymethoxy-(*Z*)-3-pentadecene (**20a**). IR (film): 2925, 2854, 1463, 1150, 1112, 1046, 966, 920. ^{1}H NMR: 5.31 (td, J = 15.0, 15.0, 5.0, 5.0 Hz, 2H), 4.59 (s, 2H), 3.49 (t, J = 6.5 Hz, 2H), 3.34 (s, 3H), 2.01 (m, 4H), 1.56 (m, 2H), 1.24 (bs, 16H), 0.93 (t, J = 7.5 Hz, 3H). ^{13}C NMR: 131.5, 129.3, 96.4, 67.9, 55.1, 29.8, 29.7, 29.6, 29.5, 29.4, 29.3, 27.1, 26.2, 20.5, 14.4. Anal. Calcd for $C_{17}H_{34}O_2$: C, 75.50; H, 12.67; O, 11.83. Found: C, 75.66; H, 12.60.

16-Methoxymethoxy-(*Z*)-4-hexadecene (21a). Following the same procedure as for **19a**, treatment of 527 mg (2.0 mmol) of 16-methoxymethoxy-4-hexadecyne (**18**), 31 mg of Lindlar catalyst, and 6 mL of hexane yielded 526 mg (1.9 mmol, 95%) of 16-methoxymethoxy-(*Z*)-4-hexadecene (**21a**). IR (film): 2925, 2855, 1465, 1149, 1112, 1046, 967, 920. ^{1}H NMR: 5.33 (m, 2H), 4.59 (s, 2H), 3.49 (t, J = 6.5 Hz, 2H), 3.34 (s, 3H), 1.99 (m, 4H), 1.56 (m, 2H), 1.24 (bs, 18H), 0.88 (t, J = 7.0 Hz, 3H). ^{13}C NMR: 130.1, 129.6, 96.4, 67.9, 55.1, 29.7, 29.6, 29.5, 29.4, 29.3, 27.2, 26.2, 22.9, 13.8. Anal. Calcd for $C_{18}H_{36}O_2$: C, 76.00; H, 12.76; O, 11.25. Found: C, 76.18; H, 12.66.

14-Methoxymethoxy-(*E*)-2-tetradecene (19b). In a flask at −78 °C were condensed about 60 mL of NH_3 and 500 mg (2.0 mmol) of 14-methoxymethoxy-1-tetradecyne (**16**), dissolved in 21 mL of THF, and 226 mg (9.8 mmol) of Na metal was added. Once the sodium was dissolved, the mixture was mantained at −33 °C for 8 h, the ammonia was evaporated, and 30 mL of MeOH was carefully added. The solvent was removed under vacuum, and the crude was treated with 50 mL of a saturated aqueous NH_4Cl solution, extracted with Et_2O (3 × 10 mL), and washed with brine (2 × 20 mL). The organic layer was dried over $MgSO_4$ and concentrated to give 401 mg (1.6 mmol, 80%) of 14-methoxymethoxy-(E)-2-tetradecene (**19b**) as an oil. IR (film): 2925, 2854, 1463, 1150, 1112, 1046, 966, 920. ^{1}H NMR: 5.39 (m, 2H), 4.59(s, 2H), 3.49 (t, J = 6.5 Hz, 2H), 3.33 (s, 3H), 1.94 (m, 4H), 1.56 (m, 2H), 1.24 (bs, 16H), 0.93 (t, J = 7.5 Hz, 3H). ^{13}C NMR: 131.8, 129.4, 96.4, 67.8, 55.0, 32.6, 29.7, 29.6, 29.5, 29.4, 29.2, 26.2, 25.6, 13.9. Anal. Calcd for $C_{16}H_{32}O_2$: C, 74.94; H, 12.58; O, 12.48. Found: C, 74.82; H, 12.68.

15-Methoxymethoxy-(*E*)-3-pentadecene (20b). Following the same procedure as for **19b**, treatment of 500 mg (1.9 mmol) of 15-methoxymethoxy-3-pentadecyne (**17**), 56 mL of NH_3, 215 mg (9.3 mmol) of Na, and 20 mL of THF yielded 401 mg (1.5 mmol, 79%) of 15-methoxymethoxy-(*E*)-3-pentadecene (**20b**). IR (film): 2925, 2854, 1463, 1150, 1112, 1046, 966, 920. ^{1}H NMR: 5.39 (m, 2H), 4.59(s, 2H), 3.49 (t, J = 6.5 Hz, 2H), 3.33 (s, 3H), 1.94 (m, 4H), 1.56 (m, 2H), 1.24 (bs, 16H), 0.93 (t, J = 7.5 Hz, 3H). ^{13}C NMR: 131.8, 129.4, 96.4, 67.9, 55.0, 32.6, 29.7, 29.6, 29.5, 29.4, 29.2, 26.2, 25.6, 13.9. Anal. Calcd for $C_{17}H_{34}O_2$: C, 75.50; H, 12.67; O, 11.83. Found: C, 75.58; H, 12.70.

16-Methoxymethoxy-(*E*)-4-hexadecene (21b). Following the same procedure as for **19b**, treatment of 500 mg (1.8 mmol) of 16-methoxymethoxy-4-hexadecyne (**18**), 59 mL of NH_3, 226 mg (9.8 mmol) of Na, and 21 mL of THF yielded 474 mg (1.7 mmol, 94%) of 16-methoxymethoxy-(*E*)-4-hexadecene (**21b**). IR

(film): 2926, 2855, 1465, 1149, 1112, 1046, 967, 920. ^{1}H NMR: 5.36 (m, 2H), 4.59 (s, 2H), 3.49 (t, J = 6.5 Hz, 2H), 3.33 (s, 3H), 1.94 (m, 4H), 1.56 (m, 2H), 1.23 (bs, 18H), 0.85 (t, J = 7.0 Hz, 3H). ^{13}C NMR: 130.6, 130.1, 96.3, 67.9, 55.0, 34.7, 32.6, 29.7, 29.6, 29.5, 29.4, 29.1, 26.2, 22.7, 13.6. Anal. Calcd for $C_{18}H_{36}O_2$: C, 76.00; H, 12.76; O, 11.25. Found: C, 75.82; H, 12.86.

(*Z*)-12-Tetradecenoic Acid (22a). To 167 mg (0.7 mmol) of 14-methoxymethoxy-(*Z*)-2-tetradecene (**19a**) placed in a flask was dropwise added 9 mL of a 10% hydrogen chloride methanolic solution. The mixture was stirred at room temperature for 16 h (TLC, hexane/EtOAc, 8:2), and then it was diluted with 30 mL of Et_2O and decanted. The organic layer was washed with 1 N HCl (4 × 20 mL), dried over $MgSO_4$, filtered, and evaporated at reduced pressure to give 138 mg of a crude product that was used without further purification. Thus, a solution of freshly prepared Jones reagent [prepared by adding 63 μL (1.2 mmol) of 98% H_2SO_4 at 0 °C to a solution of 66 mg (0.7 mmol) of CrO_3 in 0.5 mL of water] was slowly added at 0 °C to this crude dissolved in 4 mL of acetone. The mixture was stirred at room temperature for 4 h (TLC, CH_2Cl_2/MeOH, 9:1). The reaction was quenched by addition of 15 mL of water and extraction with Et_2O (4 × 10 mL). The organic layer was washed with brine (2 × 20 mL), dried over $MgSO_4$, filtered, and concentrated to yield 141 mg (0.6 mmol, 86%) of (*Z*)-12-tetradecenoic acid (**22a**).[25] IR (film): 2400−3500, 2925, 2854, 1708, 1465, 1411, 1284, 1226. ^{1}H NMR: 5.39 (m, 2H), 2.33 (t, J = 7.5 Hz, 2H), 1.99 (m, 2H), 1.61 (m, 5H), 1.24 (bs, 14H). ^{13}C NMR: 179.8, 131.7, 123.6, 33.9, 29.6, 29.5, 29.4, 29.3, 29.2, 29.0, 26.8, 24.6, 17.9. Anal. Calcd for $C_{14}H_{26}O_2$: C, 74.29; H, 11.58; O, 14.14. Found: C, 74.16; H, 11.52.

(*Z*)-12-Pentadecenoic Acid (23a). Following the same procedure as for **22a**, treatment of 658 mg (2.4 mmol) of 15-methoxymethoxy-(Z)-3-pentadecene (**20a**) with 35 mL of 10% hydrogen chloride methanolic solution produced 416 mg of a crude product that was dissolved in 10 mL of acetone and treated with Jones reagent (188 mg (1.9 mmol) of CrO_3, 1300 μL of water and 163 μL of H_2SO_4) to yield 411 mg (1.7 mmol, 71%) of (*Z*)-12-pentadecenoic acid (**23a**). IR (film): 2400−3500, 2927, 2855, 1711, 1464, 1413, 1283, 1234. ^{1}H NMR: 5.31 (m, 2H), 2.31 (t, J = 7.5 Hz, 2H), 1.99 (m, 4H), 1.59 (m, 2H), 1.24 (bs, 14H), 0.92 (t, J = 7.0 Hz, 3H). ^{13}C NMR: 180.4, 131.4, 129.2, 34.1, 29.7, 29.5, 29.4, 29.2, 29.0, 27.0, 24.6, 20.4, 14.3. Anal. Calcd for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74; O, 13.31. Found: C, 74.81; H, 11.67.

(*Z*)-12-Hexadecenoic Acid (24a). Following the same procedure as for **22a**, treatment of 184 mg (0.6 mmol) of 16-methoxymethoxy-(*Z*)-4-hexadecene (**21a**) with 9 mL of 10% hydrogen chloride methanolic solution produced 145 mg of a crude product that was dissolved in 4 mL of acetone and treated with Jones reagent (62 mg (0.6 mmol) of CrO_3, 428 μL of water and 54 μL of H_2SO_4) to yield 139 mg (0.5 mmol, 83%) of (*Z*)-12-hexadecenoic acid (**24a**). IR (film): 2400−3500, 2927, 2856, 1711, 1464, 1414, 1286, 1232. ^{1}H NMR: 5.33 (m, 2H), 2.31 (t, J = 7.5 Hz, 2H), 1.98 (m, 4H), 1.60 (m, 2H), 1.24 (bs, 16H), 0.87 (t, J = 7 Hz, 3H). ^{13}C NMR: 180.4, 130.0, 129.6, 34.1, 29.7, 29.5, 29.4, 29.2, 29.0, 27.2, 24.6, 22.9, 13.8. Anal. Calcd for $C_{16}H_{30}O_2$: C, 75.54; H, 11.89; O, 12.58. Found: C, 75.38; H, 11.78.

(*E*)-12-Tetradecenoic Acid (22b). Following the same procedure as for **22a**, treatment of 300 mg (1.2 mmol) of 14-methoxymethoxy-(*E*)-2-tetradecene (**19b**) with 18 mL of 10% hydrogen chloride methanolic solution produced 238 mg of a crude product that was dissolved in 6 mL of acetone and treated with Jones reagent (15 mg (0.2 mmol) of CrO_3, 0.8 mL of water and 100 μL of H_2SO_4) to yield 260 mg (1.2 mmol, 99%) of (*E*)-12-hexadecenoic acid (**22b**).[25] IR (film): 2400−3500, 2926, 2853, 1702, 1466, 1437, 1362, 1196, 1171, 966. ^{1}H NMR: 5.39 (m, 2H), 2.32 (t, J = 7.5 Hz, 2H), 1.94 (m, 2H), 1.61 (m, 5H), 1.24 (bs, 14H). ^{13}C NMR: 179.1, 131.6, 124.5, 33.9, 32.6, 29.6, 29.5, 29.4, 29.2, 29.1, 29.0, 24.7, 17.9. Anal. Calcd for $C_{14}H_{26}O_2$: C, 74.29; H, 11.58; O, 14.14. Found: C, 74.16; H, 11.62.

(*E*)-12-Pentadecenoic Acid (23b). Following the same procedure as for **22a**, treatment of 300 mg (1.1 mmol) of 15-methoxymethoxy-(*E*)-3-pentadecene (**20b**) with 17 mL of 10% hydrogen chloride methanolic solution produced 232 mg of a crude product that was dissolved in 6 mL of acetone and treated with Jones reagent (104 mg (1.0 mmol) of CrO_3, 730 μL of water and 91 μL of H_2SO_4) to yield 228 mg (1.0 mmol, 91%) of (*E*)-12-pentadecenoic acid (**23b**). IR (film): 2400−3500, 2929, 2855, 1704, 1461, 1436, 1197, 1170, 966. ^{1}H NMR: 5.39 (m, 2H), 2.33 (t, J = 7.5 Hz, 2H), 1.96 (m, 4H), 1.61 (m, 2H), 1.25 (bs, 14H), 0.94 (t, J = 7.0 Hz, 3H). ^{13}C NMR: 179.2, 131.9, 129.4, 33.9, 32.5, 29.6, 29.5, 29.4, 29.2, 29.1, 29.0, 25.6, 24.7, 13.9. Anal. Calcd for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74; O, 13.31. Found: C, 74.87; H, 11.71.

(*E*)-12-Hexadecenoic Acid (24b). Following the same procedure as for **22a**, treatment of 300 mg (1.1 mmol) of 16-methoxymethoxy-(*E*)-4-hexadecene (**21b**) with 16 mL of 10% hydrogen chloride methanolic solution produced 245 mg of a crude product that was dissolved in 6 mL of acetone and treated with Jones reagent (102 mg (1.0 mmol) of CrO_3, 700 μL of water and 90 μL of H_2SO_4) to yield 243 mg (1.0 mmol, 91%) of (*E*)-12-hexadecenoic acid (**24b**). IR (film): 2400−3500, 2926, 2854, 1704, 1465, 1439, 1197, 1170, 966. ^{1}H NMR: 5.37 (s, 2H), 2.33 (t, J = 7.5 Hz, 2H), 1.94 (m, 4H), 1.61 (m, 2H), 1.25 (bs, 16H), 0.86 (t, J = 7.0 Hz, 3H). ^{13}C NMR: 177.5, 130.5, 130.1, 34.7, 33.8, 32.6, 29.6, 29.5, 29.4, 29.2, 29.1, 29.0, 24.7, 22.7, 13.6. Anal. Calcd for $C_{16}H_{30}O_2$: C, 75.54; H, 11.89; O, 12.58. Found: C, 75.45; H, 11.96.

(*Z*)-12-Tetradecenoic Acid Methyl Ester (25a). To a solution of 141 mg (0.6 mmol) of (*Z*)-12-tetradecenoic acid (**22a**) in 2 mL of MeOH was added 160 μL of BF_3·OEt_2, and the mixture was stirred at room temperature for 1 h (TLC, hexane/Et_2O, 1:1). The reaction was quenched by addition of 5 mL of water, evaporation of solvent, and extraction with hexane (4 × 10 mL). The organic layer was washed with brine (2 × 20 mL), dried with $MgSO_4$, filtered, and evaporated under vacuum to give a crude product that was purified by flash chromatography using a hexanes−Et_2O gradient as the eluent. The yield was 73 mg (0.3 mmol, 50%) of (*Z*)-12-tetradecenoic acid methyl ester (**25a**). IR (film): 2926, 2855, 1743, 1463, 1436, 1196, 1171. ^{1}H NMR: 5.38 (m, 2H), 3.64 (s, 3H), 2.28 (t, J = 7.5 Hz, 2H), 1.99 (m, 2H), 1.60 (m, 5H), 1.23 (bs, 14H). ^{13}C NMR: 174.3, 130.9, 123.6, 51.4, 34.1, 29.5, 29.4, 29.3, 29.2, 29.1, 26.8, 24.9, 12.7. Anal. Calcd for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74; O, 13.31. Found: C, 74.82; H, 11.71.

(*Z*)-12-Pentadecenoic Acid Methyl Ester (26a). Following the same procedure as for **25a**, treatment of 411 mg (1.7 mmol) of (*Z*)-12-pentadecenoic acid (**23a**) with 434 μL of BF_3·OEt_2 (3.4 mmol) in 2 mL of MeOH provided a crude oil that was purified by flash chromatography using a hexanes−Et_2O gradient as the eluent to yield 167 mg (0.6 mmol, 39%) of (*Z*)-12-pentadecenoic acid methyl ester (**26a**). IR (film): 2927, 2855, 1744, 1463, 1436, 1196, 1171. ^{1}H NMR: 5.31 (m, 2H), 3.64 (s, 3H), 2.28 (t, J = 7.5 Hz, 2H), 2.0 (m, 4H), 1.61 (m, 2H), 1.24 (bs, 14H), 0.93 (t, J = 7.0 Hz, 3H). ^{13}C NMR: 174.3, 131.5, 129.3, 51.4, 34.1, 29.7, 29.5, 29.4, 29.2, 29.1, 27.1, 24.9, 20.5, 14.4. Anal. Calcd for $C_{16}H_{30}O_2$: C, 75.54; H, 11.89; O, 12.58. Found: C, 75.39; H, 11.93.

(*Z*)-12-Hexadecenoic Acid Methyl Ester (27a). Following the same procedure as for **25a**, treatment of 139 mg (0.5 mmol) of (*Z*)-12-hexadecenoic acid (**24a**) with 139 μL of BF_3·OEt_2 (1.1 mmol) in 1 mL of MeOH provided a crude oil that was purified by flash chromatography using a hexanes−Et_2O gradient as the eluent to yield 55 mg (0.2 mmol, 41%) of (*Z*)-12-hexadecenoic acid methyl ester (**27a**). IR (film): 2926, 2855, 1744, 1458, 1436, 1196, 1171. ^{1}H NMR: 5.33 (m, 2H), 3.64 (s, 3H), 2.28 (t, J = 7.5 Hz, 2H), 1.98 (m, 4H), 1.59 (m, 2H), 1.24 (bs, 16H), 0.88 (t, J = 7 Hz, 3H). ^{13}C NMR: 174.3, 130.1, 129.6,

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51.4, 34.1, 29.7, 29.5, 29.4, 29.3, 29.2, 29.1, 27.2, 24.9, 22.9, 13.8. Anal. Calcd for $C_{17}H_{32}O_2$: C, 76.06; H, 12.02; O, 11.92. Found: C, 75.78; H, 12.22.

(*E*)-12-Tetradecenoic Acid Methyl Ester (25b). Following the same procedure as for **25a**, treatment of 260 mg (1.1 mmol) of (*E*)-12-tetradecenoic acid (**22b**) with 296 μL of $BF_3{\cdot}OEt_2$ (2.3 mmol) in 1 mL of MeOH provided 147 mg (0.6 mmol, 55%) of (*E*)-12-tetradecenoic acid methyl ester (**25b**). IR (film): 2926, 2853, 1743, 1461, 1437, 1196, 1171, 966. ^{1}H NMR: 5.39 (m, 2H), 3.64 (s, 3H), 2.27 (t, J = 7.5 Hz, 2H), 1.93 (m, 2H) 1.60 (m, 5H), 1.23 (bs, 14H). ^{13}C NMR: 174.3, 131.6, 124.5, 51.4, 34.1, 32.6, 29.6, 29.5, 29.4 29.2, 29.1, 24.9, 17.9. Anal. Calcd for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74; O, 13.31. Found: C, 75.09; H, 11.57.

(*E*)-12-Pentadecenoic Acid Methyl Ester (26b). Following the same procedure as for **25a**, treatment of 228 mg (1.0 mmol) of (*E*)-12-pentadecenoic acid (**23b**) with 245 μL of $BF_3{\cdot}OEt_2$ (2 mmol) in 1 mL of MeOH provided 150 mg (0.6 mmol, 60%) of (*E*)-12-pentadecenoic acid methyl ester (**26b**). IR (film): 2929, 2855, 1743, 1461, 1436, 1197, 1170, 965. ^{1}H NMR: 5.39 (m, 2H), 3.64 (s, 3H), 2.28 (t, J = 7.5 Hz, 2H), 1.94 (m, 2H), 1.59 (m, 2H), 1.23 (bs, 14H), 0.93 (t, J = 7.5 Hz, 3H). ^{13}C NMR: 174.3, 131.8, 129.3, 51.4, 34.1, 32.5, 29.6, 29.5, 29.4, 29.2, 29.1, 25.6, 24.9, 13.9. Anal. Calcd for $C_{16}H_{30}O_2$: C, 75.54; H, 11.89; O, 12.58. Found: C, 75.74; H, 11.92.

(*E*)-12-Hexadecenoic Acid Methyl Ester (27b). Following the same procedure as for **25a**, treatment of 243 mg (1.0 mmol) of (*E*)-12-hexadecenoic acid (**24b**) with 245 μL of $BF_3{\cdot}OEt_2$ (2 mmol) in 1 mL of MeOH provided 162 mg (0.6 mmol, 60%) of (*E*)-12-hexadecenoic acid methyl ester (**27b**). IR (film): 2926, 2854, 1745, 1465, 1439, 1197, 1170, 967. ^{1}H NMR: 5.36 (m, 2H), 3.64 (s, 3H), 2.28 (t, J = 7.5 Hz, 2H), 1.93 (m, 4H), 1.59 (m, 2H), 1.23 (bs, 16H), 0.86 (t, J = 7.0 Hz, 3H). ^{13}C NMR: 174.3, 130.5, 130.1, 51.4, 34.7, 34.1, 32.6, 29.6, 29.5, 29.4, 29.2, 29.1, 24.9, 22.7, 16.6. Anal. Calcd for $C_{17}H_{32}O_2$: C, 76.06; H, 12.02; O, 11.92. Found: C, 76.18; H, 12.12.

11-(*cis*-2-Methylcyclopropyl)undecanoic Acid Methyl Ester (6a). (*Z*)-12-Tetradecenoic acid methyl ester (**25a**) (73 mg,0.3 mmol) was dissolved in 4 mL of CH_2Cl_2 and cooled to −20 °C. To this solution were added 910 μL (0.9 mmol) of Et_2Zn (1 M solution in hexane) and then, in dropwise fashion, 110 μL (1.4 mmol) of CH_2I_2. The reaction was monitored by GC (120 °C/1 min, then 10 °C/min up to 280 °C; **6a**, t_R = 10.84 min, **25a**, t_R = 9.72 min), and when no starting material was observed, it was quenched by dropwise addition of a 3 N NaOH aqueous solution (3 mL). Methylene chloride was evaporated to avoid the formation of emulsions, and the remaining mixture was extracted with hexane (4 × 10 mL). The combined organic layer was washed with brine (2 × 15 mL), dried over $MgSO_4$, filtered, and evaporated under vacuum yielding 76 mg (0.3 mmol, 99%) of **6a** as a clear oil. IR (film): 3061, 2925, 2854, 1743, 1463, 1435, 1197, 1170. ^{1}H NMR: 3.64 (s, 3H), 2.28 (t, J = 7.5 Hz, 2H), 1.58 (m, 2H), 1.23 (bs, 14H), 0.98 (d, J = 6.0 Hz, 3H), 0.51−0.81 (m, 3H), −0.37 (m, 1H). ^{13}C NMR: 174.3, 51.4, 34.2, 34.1, 29.6, 29.4, 29.2, 29.1, 24.9, 22.7, 15.7, 13.2, 9.3. GC−MS: 223 (M^+ − 31, 8), 180 (25), 138 (10), 96 (25), 87 (35), 74 (60), 69 (62), 55 (100). Anal. Calcd for $C_{16}H_{30}O_2$: C, 75.54; H, 11.89; O, 12.58. Found: C, 75.45; H, 11.84.

11-(*cis*-2-Ethylcyclopropyl)undecanoic Acid Methyl Ester (7a). Following the same procedure as for the synthesis of **6a**, treatment of 167 mg (0.7 mmol) of (*Z*)-12-pentadecenoic acid methyl ester (**26a**) with 2.0 mmol of Et_2Zn and 238 μL (3.0 mmol) of CH_2I_2 in 8 mL of CH_2I_2 provided 142 mg (0.5 mmol, 71%) of 11-(*cis*-2-ethylcyclopropyl)undecanoic acid methyl ester (**7a**). IR (film): 3060, 2925, 2854, 1744, 1463, 1436, 1196, 1171. ^{1}H NMR: 3.64 (s, 3H), 2.28 (t, J = 7.5 Hz, 2H), 1.59 (m, 2H), 1.24 (bs, 18H), 0.95 (t, J = 7.0 Hz, 3H), 0.49−0.65 (m, 3H), −0.35 (m, 1H). ^{13}C NMR: 174.3, 51.4, 34.1, 30.2, 29.7, 29.6, 29.4, 29.2, 29.1, 28.6, 24.9, 21.9, 17.7, 15.9, 14.5, 10.7. GC−MS: 237 (M^+ − 31, 5), 194 (8), 110 (10), 97 (15), 96 (16), 87 (40), 74 (60), 69 (62), 55 (100). Anal. Calcd for $C_{17}H_{32}O_2$: C, 76.06; H, 12.02; O, 11.92. Found: C, 75.91; H, 12.20.

11-(*cis*-2-Propylcyclopropyl)undecanoic Acid Methyl Ester (8a). Following the same procedure as for the synthesis of **6a**, treatment of 55 mg (0.2 mmol) of (*Z*)-12-hexadecenoic acid methyl ester (**27a**) with 0.6 mmol of Et_2Zn and 74 μL (0.9 mmol) of CH_2I_2 in 2.5 mL of CH_2Cl_2 provided 56 mg (0.2 mmol, 99%) of 11-(*cis*-2-propylcyclopropyl)undecanoic acid methyl ester (**8a**). IR (film): 3059, 2925, 2854, 1744, 1457, 1436, 1196, 1170. ^{1}H NMR: 3.64 (s, 3H), 2.28 (t, J = 7.5 Hz, 2H), 1.58 (m, 2H), 1.25 (bs, 20H), 0.89 (t, J = 7.0 Hz, 3H), 0.50−0.69 (m, 3H), −0.34 (m, 1H). ^{13}C NMR: 174.3, 51.4, 34.1, 30.9, 30.2, 29.7, 29.6, 29.4, 29.3, 29.2, 28.7, 24.9, 23.3, 15.7, 15.5, 14.1, 10.9. GC−MS: 251 (M^+ − 31, 10), 208 (10), 166 (14), 152(15), 97 (19), 87 (21), 74 (38), 69 (45), 55 (100). Anal. Calcd for $C_{18}H_{34}O_2$: C, 76.54; H, 12.13; O, 11.33. Found: C, 76.43; H, 12.10.

11-(*trans*-2-Methylcyclopropyl)undecanoic Acid Methyl Ester (6b). Following the same procedure as for the synthesis of **6a**, treatment of 125 mg (0.5 mmol) of (*E*)-12-tetradecenoic acid methyl ester (**25b**) with 1.6 mmol of Et_2Zn and 189 μL (2.3 mmol) of CH_2I_2 in 6.5 mL of CH_2Cl_2 provided 112 mg (0.4 mmol, 80%) of 11-(*trans*-2-methylcyclopropyl)-undecanoic acid methyl ester (**6b**). IR (film): 3061, 2925, 2854, 1744, 1462, 1437, 1197, 1170. ^{1}H NMR: 3.64 (s, 3H), 2.28 (t, J = 7.5 Hz, 2H), 1.59 (m, 2H), 1.24 (bs, 14H), 1.15 (m, 2H), 0.97 (d, J = 6 Hz, 3H), 0.34 (m, 2H), 0.11 (m, 2H). ^{13}C NMR: 174.4, 51.4, 34.2, 34.1, 29.7, 29.6, 29.5, 29.4, 29.2, 29.1, 24.9, 19.9, 19.1, 12.8, 12.6. GC−MS: 223 (M^+ − 31, 5), 180 (8), 138 (10), 96 (20), 87 (30), 74 (50), 69 (50), 55 (100). Anal. Calcd for $C_{16}H_{30}O_2$: C, 75.54; H, 11.89; O, 12.58. Found: C, 75.49; H, 11.82.

11-(*trans*-2-Ethylcyclopropyl)undecanoic Acid Methyl Ester (7b). Following the same procedure as for the synthesis of **6a**, treatment of 144 mg (0.6 mmol) of (*E*)-12-pentadecenoic acid methyl ester (**26b**) with 1.7 mmol of Et_2Zn and 205 μL (2.5 mmol) of CH_2I_2 in 7 mL of CH_2Cl_2 provided 137 mg (0.5 mmol, 83%) of 11-(*trans*-2-ethylcyclopropyl)undecanoic acid methyl ester (**7b**). IR (film): 3060, 2924, 2853, 1745, 1464, 1438, 1199, 1171. ^{1}H NMR: 3.64 (s, 3H), 2.28 (t, J = 7.5 Hz, 2H), 1.59 (m, 2H), 1.23 (bs, 14H), 1.11 (m, 4H), 0.91 (t, J = 7.0 Hz, 3H), 0.32 (m, 2H), 0.11 (m, 2H). ^{13}C NMR: 174.4, 51.4, 34.3, 34.1, 29.7, 29.6, 29.5, 29.4, 29.2, 29.1, 27.3, 24.9, 20.6, 18.6, 13.8, 11.5. GC−MS: 237 (M^+ − 31, 5), 194 (8), 110 (10), 97 (15), 96 (14), 87 (35), 74 (52), 69 (55), 55 (100). Anal. Calcd for $C_{17}H_{32}O_2$: C, 76.06; H, 12.02; O, 11.92. Found: C, 75.94; H, 12.13.

11-(*trans*-2-Propylcyclopropyl)undecanoic Acid Methyl Ester (8b). Following the same procedure as for the synthesis of **6a**, treatment of 152 mg (0.6 mmol) of (*E*)-12-hexadecenoic acid methyl ester (**27b**) with 1.8 mmol of Et_2Zn and 205 μL (2.5 mmol) of CH_2I_2 in 7 mL of CH_2Cl_2 provided 145 mg (0.5 mmol, 83%) of 11-(*trans*-2-propylcyclopropyl)-undecanoic acid methyl ester (**8b**). IR (film): 3060, 2925, 2854, 1745, 1457, 1436, 1196, 1170. ^{1}H NMR: 3.64 (s, 3H), 2.28 (t, J = 7.5 Hz, 2H), 1.61 (m, 2H), 1.24 (bs, 20H), 0.88 (t, J = 7.0 Hz, 3H), 0.35 (m, 2H), 0.12 (m, 2H). ^{13}C NMR: 174.4, 51.4, 36.5, 34.3, 33.9, 29.7, 29.6, 29.5, 29.4, 29.2, 29.1, 24.7, 22.8, 19.7, 18.5, 14.0, 11.7. GC−MS: 251 (M^+ − 31, 5), 208 (5), 166 (5), 152(5), 97 (21), 87 (25), 74 (38), 69 (45), 55 (100). Anal. Calcd for $C_{18}H_{34}O_2$: C, 76.54; H, 12.13; O, 11.33. Found: C, 76.83; H, 12.06.

11-(*cis*-2-Methylcyclopropyl)undecanoic Acid (3a). To a solution of 64 mg (0.3 mmol) of 11-(*cis*-2-methylcyclopropyl)-undecanoic acid methyl ester (**6a**) and 0.5 mL of a 2.5 N solution of KOH in methanol were added three drops of water. The mixture was stirred at room temperature for 16 h (TLC, CH_2Cl_2/MeOH, 9:1). The reaction was quenched by addition of 1 N HCl aqueous solution (10 mL), the solvent was removed at reduced pressure, and the remaining mixture was extracted with CH_2Cl_2 (4 × 5 mL). The organic layer was dried over

$MgSO_4$, filtered, and evaporated and the residue was purified by flash chromatography using a CH_2Cl_2/MeOH gradient as the eluent to yield 48 mg (0.2 mmol, 67%) of 11-(*cis*-2-methylcyclopropyl)undecanoic acid **(3a)**. IR (film): 2400−3500, 3061, 2925, 2854, 1708, 1463, 1361, 1197, 1170. ^{1}H NMR: 2.33 (t, J = 7.5 Hz, 2H), 1.61 (m, 2H), 1.23 (bs, 14H), 0.98 (d, J = 6.0 Hz, 3H), 0.51−078 (m, 3H), −0.37 (m, 1H). ^{13}C NMR: 179.9, 34.2, 34.0, 29.6, 29.4, 29.2, 29,1, 28.4, 24.7, 22.7, 15.7, 13.2, 9.3. Anal. Calcd for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74; O, 13.31. Found: C, 75.12; H, 11.78.

11-(*cis*-2-Ethylcyclopropyl)undecanoic Acid (4a). Following the same procedure as for the synthesis of **3a**, treatment of 142 mg (0.5 mmol) of 11-(*cis*-2-ethylcyclopropyl)-undecanoic acid methyl ester (**7a**) provided 125 mg (0.5 mmol, 99%) of 11-(*cis*-2-ethylcyclopropyl)undecanoic acid (**4a**). IR (film): 2400−3500, 3060, 2925, 2854, 1708, 1463, 1436, 1196, 1171. ^{1}H NMR: 2.33 (t, J = 7.5 Hz, 2H), 1.61 (m, 2H), 1.25 (bs, 18H), 0.96 (t, J = 7.0 Hz, 3H), 0.50−0.69 (m, 3H), −0.35 (m, 1H). ^{13}C NMR: 179.9, 34.0, 30.2, 29.7, 29.6, 29.4, 29.2, 29.0, 28.6, 24.7, 21.9, 17.7, 15.9, 14.5, 10.7. Anal. Calcd for $C_{16}H_{30}O_2$: C, 75.54; H, 11.89; O, 12.58. Found: C, 75.65; H, 11.80.

11-(*cis*-2-Propylcyclopropyl)undecanoic Acid (5a). Following the same procedure as for the synthesis of **3a**, treatment of 56 mg (0.2 mmol) of 11-(*cis*-2-propylcyclopropyl)-undecanoic acid methyl ester (**8a**) provided 48 mg (0.2 mmol, 99%) of 11-(*cis*-2-propylcyclopropyl)undecanoic acid (**5a**). IR (film): 2400−3500, 3059, 2925, 2854, 1704, 1457, 1436, 1196, 1170. ^{1}H NMR: 2.33 (t, J = 7.5 Hz, 2H), 1.58 (m, 2H), 1.25 (bs, 20H), 0.89 (t, J = 7.0 Hz, 3H), 0.50−0.69 (m, 3H), −0.34 (m, 1H). ^{13}C NMR: 179.5, 36.5, 34.3, 33.9, 29.7, 29.6, 29.4, 29.3, 29.2, 28.7, 24.9, 23.3, 15.7, 15.5, 14.1, 10.9. Anal. Calcd for $C_{17}H_{32}O_2$: C, 76.06; H, 12.02; O, 11.92. Found: C, 75.92; H, 12.12.

11-(*trans*-2-Methylcyclopropyl)undecanoic Acid (3b). Following the same procedure as for the synthesis of **3a**, treatment of 111 mg (0.4 mmol) of 11-(*trans*-2-methylcyclopropyl)undecanoic acid methyl ester (**6b**) provided 97 mg (0.4 mmol, 99%) of 11-(*trans*-2-methylcyclopropyl)undecanoic acid (**3b**). IR (film): 2400−3500, 3061, 2925, 2854, 1708, 1463, 1361, 1197, 1170. ^{1}H NMR: 2.33 (t, J = 7.5 Hz, 2H), 1.61 (m, 2H), 1.24 (bs, 14H), 0.98 (d, J = 6.0 Hz, 3H), 0.26−0.47 (m, 2H), 0.11 (m, 2H). ^{13}C NMR: 179.9, 34.2, 34.0, 29.7, 29.6, 29.5, 29.4, 29.2, 29.0, 24.7, 19.9, 19.1, 12.9, 12.6. Anal. Calcd for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74; O, 13.31. Found: C, 75.07; H, 11.81.

11-(*trans*-2-Ethylcyclopropyl)undecanoic Acid (4b). Following the same procedure as for the synthesis of **3a**, treatment of 137 mg (0.5 mmol) of 11-(*trans*-2-ethylcyclopropyl)undecanoic acid methyl ester (**7b**) provided 118 mg of a crude product that was purified by flash chromatography using a CH_2Cl_2/MeOH gradient as the eluent to yield 93 mg (0.4 mmol, 80%) of 11-(*trans*-2-ethylcyclopropyl)undecanoic acid (**4b**). IR (film): 2400−3500, 3060, 2853, 1705, 1464, 1438, 1199, 1171. ^{1}H NMR: 2.33 (t, J = 7.5 Hz, 2H), 1.61 (m, 2H), 1.25 (bs, 14H), 1.12 (m, 4H), 0.91 (t, J = 7.0 Hz, 3H), 0.27−0.38 (m, 2H), 0.11 (m, 2H,). ^{13}C NMR: 180.0, 34.3, 34.0, 29.7, 29.6, 29.5, 29.4, 29.2, 29.0, 27.3, 24.7, 20.6, 18.6, 13.8, 11.5. Anal. Calcd for $C_{16}H_{30}O_2$: C, 75.54; H, 11.89; O, 12.58. Found: C, 75.61; H, 11.85.

11-(*trans*-2-Propylcyclopropyl)undecanoic Acid (5b). Following the same procedure as for the synthesis of **3a**, treatment of 145 mg (0.5 mmol) of 11-(*trans*-2-propylcyclopropyl)undecanoic acid methyl ester (**8b**) provided 131 mg of a crude product that was purified by flash chromatography using a CH_2Cl_2/MeOH gradient as the eluent to yield 97 mg (0.4 mmol, 80%) of 11-(*trans*-2-propylcyclopropyl)undecanoic acid (**5b**). IR (film): 2400−3500, 3060, 2925, 2854, 1708, 1457, 1436, 1196, 1170. ^{1}H NMR: 2.33 (t, J = 7.5 Hz, 2H), 1.61 (m, 2H), 1.24 (bs, 20H), 0.88 (t, J = 7.0 Hz, 3H), 0.30−0.39 (m, 2H), 0.12 (m, 2H). ^{13}C NMR: 179.6, 36.5, 34.3, 33.9, 29.7, 29.6, 29.5, 29.4, 29.2, 29.1, 24.7, 22.8, 19.7, 18.5, 14.0, 11.7. Anal. Calcd for $C_{17}H_{32}O_2$: C, 76.06; H, 12.02; O, 11.92. Found: C, 75.98; H, 12.16.

11-Methoxymethoxyundecanal (28). Treatment of 4.0 g (13.6 mmol) of 11-methoxymethoxy-1-bromoundecane under the above conditions provides 2.2 g (9.6 mmol, 71%) of 11-methoxymethoxyundecanal (**28**) as dark oil. IR (film): 2927, 2856, 1726, 1465, 1457, 1147, 1110, 1045, 919. ^{1}H NMR: 9.73 (t, J = 2.0 Hz, 1H), 4.59 (s, 2H), 3.49 (t, J = 6.5 Hz, 2H), 3.33 (s, 3H), 2.39 (dt, J = 7.5 and 2.0 Hz, 2H), 1.56 (m, 4H), 1.26 (bs, 12H). ^{13}C NMR: 202.9, 96.3, 67.8, 55.1, 43.8, 29.7, 29.5, 29.4, 29.3, 29.1, 26.2, 22.0. Anal. Calcd for $C_{13}H_{26}O_3$: C, 67.79; H, 11.38; O, 20.84. Found: C, 67.90; H, 11.29.

(11-Methoxymethoxyundecylidene)cyclopropane (29). This product was prepared following the same procedure as for the synthesis of 13-methoxymethoxy-1-tridecene (**12**) by using 100 mg (0.4 mmol) of 11-methoxymethoxyundecanal (**28**), 684 mg (1.8 mmol) of cyclopropyltriphenylphosphonium bromide in 5 mL of THF, and 1.3 mL of *n*-BuLi (1.48 M, 1.8 mmol). The reaction provided 150 mg of a crude product that was purified by flash chromatography using as eluent hexane and then a hexanes−EtOAc gradient to yield 80 mg (0.3 mmol, 75%) of (11-methoxymethoxyundecylidene)cyclopropane (**29**). IR (film): 3055, 2925, 2854, 1465, 1436, 1147, 1116, 1068, 1045. ^{1}H NMR: 5.73 (ddt, J = 7.0, 2.0, 2.0 Hz, 1H), 4.59 (s, 2H), 3.49 (t, J = 6.5 Hz, 2H), 3.33 (s, 3H), 2.14 (m, 2H), 1.56 (m, 2H), 1.25 (bs, 14H), 0.99 (dd, J = 3.0 and 2.0 Hz, 4H). ^{13}C NMR: 120.8, 118.4, 96.4, 67.9, 55.0, 31.8, 29.7, 29.6, 29.5, 29.4, 26.2, 2.1, 1.8. Anal. Calcd for $C_{16}H_{30}O_2$: C, 75.54; H, 11.89; O, 12.58. Found: C, 75.44; H, 11.82.

11-cyclopropylideneundecanoic Acid (9). Following the same procedure as for **22a**, treatment of 27 mg (0.1 mmol) of (11-methoxymethoxyundecylidene)cyclopropane (**29**) with 1.5 mL of 10% hydrogen chloride methanolic solution produced a crude that was purified by flash chromatography using a hexanes−EtOAc gradient as the eluent, yielding 21 mg (0.1 mmol, 99%) of a colorless oil identified as 11-cyclopropylideneundecanol that was treated with 4 mL (0.8 mmol) of a 0.2M PDC solution in DMF to yield 18 mg (0.08 mmol, 79%) of 11-cyclopropylideneundecanoic acid (**9**). IR (film): 3300−2900, 3051, 2925, 2854, 1710, 1459, 1417, 1119, 1073, 1043. ^{1}H NMR: 5.73 (ddt, J = 7.0, 2.0 and 2.0 Hz, 1H), 2.32 (t, J = 7.0 Hz, 2H), 2.14 (m, 2H), 1.60 (m, 2H), 1.25 (bs, 12H), 0.99 (dd, J = 3.0 and 2.0 Hz, 4H). ^{13}C NMR: 179.8, 120.8, 118.4, 34.0, 31.8, 29.4, 29.3, 29.2, 29.0, 24.7, 2.1, 1.8. Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78; O, 14.26. Found: C, 74.94, H, 10.77.

11-Cyclopropylideneundecanoic Acid Methyl Ester (10). An analytical sample of 11-cyclopropylideneundecanoic acid methyl ester (**10**) was obtained by treatment of **9** with an ethereal solution of diazomethane. This compound was characterized by GC−MS: m/z 95 (M^+ − 143, 68), 81 (100), 67 (55), 55 (61).

Δ^{11} Desaturation Assays. These experiments were carried out with glands cultured in vitro[15a] using round-bottom-96-well plates. To each well was added a 5 μL drop of incubation medium, and the plates were placed in an incubator at 25 °C. The incubation medium consisted of Grace's saline (135 μL) and a dimethyl sulfoxide solution (15 μL) of the cyclopropane probe (10 mg/mL). Plates were sealed with adherent plastic covers and incubations proceeded for 3 h. After this time, pheromone glands were collected and soaked in chloroform/methanol (2:1) at 25 °C for 1 h. The lipidic extracts thus obtained were base methanolyzed as described elsewhere[3b] to obtain the fatty acid methyl esters that were submitted to GC-MS analysis.

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