Synthesis of Ammonium Analogues of Carbocationic Intermediates in the Conversion of Presqualene Diphosphate to Squalene

Todd L. Capson, Michael D. Thompson, Vyas M. Dixit, Roger G. Gaughan, and C. Dale Poulter*

Departments of Chemistry and Medicinal Chemistry, University of Utah, Salt Lake City, Utah 84112

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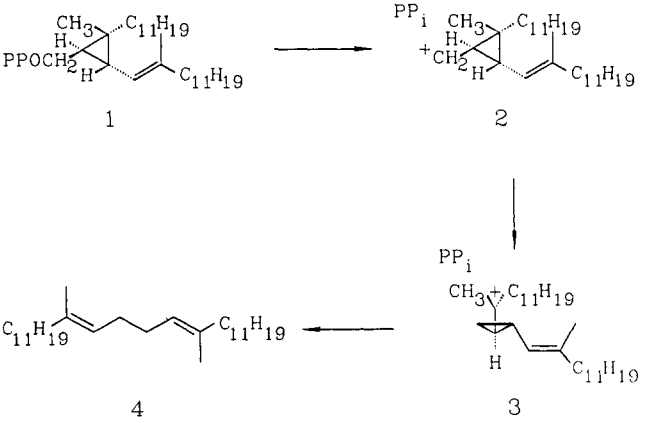
Ammonium analogues **5** and **7** of the primary (**2**) and tertiary (**3**) cyclopropylcarbinyl cations, respectively, proposed as reactive intermediates in the enzyme-catalyzed rearrangement of presqualene diphosphate (**1**) to squalene (**4**), were synthesized. The general strategy involved construction of the appropriately substituted cyclopropanecarboxylic acids and introduction of the amino groups by a Curtius rearrangement. When the isocyanates from the Curtius reaction were trapped with (trimethylsilyl)ethanol, the resulting carbamates were easily cleaved with fluoride ion to give excellent yields of the corresponding cyclopropylamines. Amino acid **6**, an analogue of the primary cyclopropylcarbinyl cation–pyrophosphate ion pair generated during the initial step of the rearrangement, was prepared by tethering a phosphonophosphate moiety to the amino group in **5** by a three-carbon bridge.

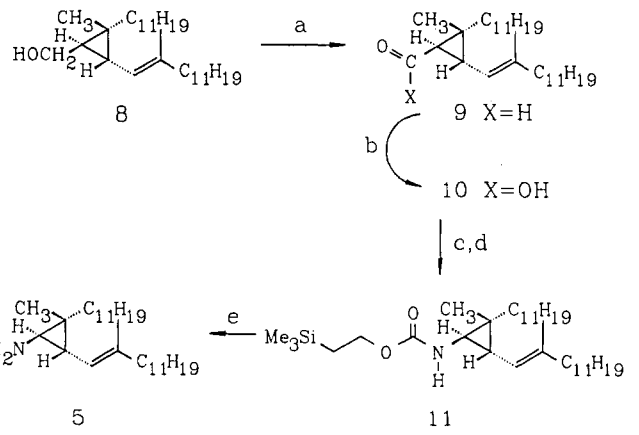
Squalene synthetase (farnesyl-diphosphate:farnesyl-diphosphate farnesyltransferase, EC 2.5.1.21) is the first pathway-specific enzyme in the cholesterol biosynthetic pathway.[1,2] The enzyme is a membrane-bound protein, MW 47 000, and has recently been solubilized and purified to homogeneity.[3,4] Squalene synthetase catalyzes the 1′–1 condensation between two molecules of farnesyl diphosphate to yield the C_{30} triterpene squalene **4**. The transformation occurs in two distinct steps: the insertion of C(1) of one molecule of farnesyl diphosphate into the C(2)–C(3) double bond of the second to generate presqualene diphosphate (**1**), followed by conversion of the cyclopropylcarbinyl intermediate into squalene.

It was recognized by several groups that the reductive rearrangement of **1** to **4** could be rationalized in terms of bond reorganizations typically observed for cyclopropylcarbinyl cations.[5–9] We proposed the sequence for the rearrangement shown in Scheme I.[7] Subsequent model studies revealed that the rearrangement of primary cyclopropylcarbinyl cation **2** to its tertiary isomer **3** was neither kinetically nor thermodynamically favored in solution and that squalene synthetase must exert strict control upon the cationic intermediates to achieve the regiocontrol required for biosynthesis of squalene.[8,10–12] We suggested that regiocontrol was, in fact, achieved as a natural consequence of the orientation between the positively and negatively charged partners in the tight ion pair generated upon cleavage of the carbon–oxygen bond in **1**.[13,14]

Scheme I. Mechanism for Rearrangement of Presqualene Diphosphate to Squalene



Scheme II.[a] Synthesis of Primary Amine 5



[a] (a) $(ClCO)_2$, Et_3N, DMSO; (b) nBu_4NMnO_4; (c) $(PhO)_2PON_3$; (d) $Me_3Si(CH_2)_2OH$; (e) nBu_4NF.

In several recent studies, analogues of carbocations proposed as reactive intermediates or transition states for reactions catalyzed by enzymes in the isoprenoid pathway were synthesized where the positively charged trigonal centers were replaced by sulfonium or ammonium moieties.[15–18] In general, these compounds proved to be potent

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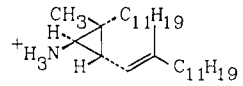
inhibitors. One exception was an ammonium analogue of the tertiary cyclopropylcarbinyl cation **3**, which required inorganic pyrophosphate as a synergistic co-inhibitor in the buffer, presumably to mimic the ion pair created during catalysis.[18] We now report syntheses of primary amine **5** and tertiary amine **7**, whose ammonium salts are



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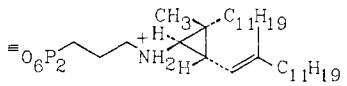

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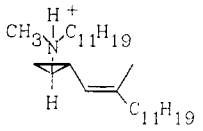

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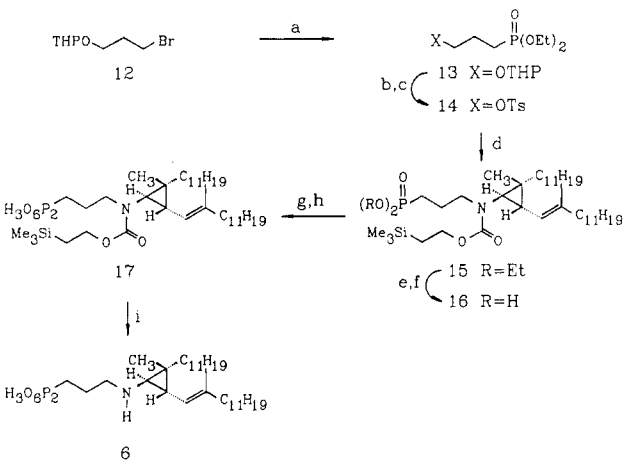
analogues of cations **2** and **3**, respectively, and a novel phosphonophosphate amino acid analogue (**6**) of the primary cation–pyrophosphate ion pair in which the positive and negative partners are tethered covalently. The results of experiments with squalene synthetase will be presented elsewhere.

Results and Discussion

Primary Amine 5. The synthesis of primary amine **5** is outlined in Scheme II. The carbon skeleton was assembled from farnesyl residues by using the cyclopropanation procedure of Altman and co-workers[19] to give presqualene alcohol (**8**), which was subsequently converted to **5** via a Curtius rearrangement. Direct oxidation of **8** to carboxylic acid **10** proceeded in moderate to low yields with a variety of reagents. Initial attempts at two-step conversions by a Swern oxidation[20] of presqualene alcohol to aldehyde **9**, followed by treatment with sodium chlorite as described by Balkrishna et al.,[21] were also disappointing. However, when the oxidation of **9** was carried out with tetrabutylammonium permanganate in pyridine as described by Sala and Sargent,[22] the two-step oxidation of **8** was accomplished in 73% overall yield.

Conversion of acid **10** to the isocyanate was accomplished by using the procedure of Shioiri and co-workers.[23] Treatment of the isocyanate with aqueous tetrahydrofuran and base yielded material with the cyclopropyl skeleton intact that had a strong IR band at 1650 cm^{-1} indicative of formation of a symmetrical urea. Olah et al.[24] had shown that benzyl carbamates were cleaved almost instantaneously at 25 °C with trimethylsilyl iodide generated in situ by treating trimethylsilyl chloride with sodium iodide, and Jung and co-workers[25] also reported rapid cleavage of carbamates by trimethylsilyl iodide. In our hands these

Scheme III.[a] **Synthesis of Amino Acid 6**



[a] (a) $P(OEt)_3$; (b) PPTs; (c) TsCl, DMAP; (d) KH, **11**; (e) Me_3SiBr; (f) H_2O; (g) $COIm_2$; (h) $nBu_4NH_2PO_4$; (i) nBu_4NF.

reagents did not give reproducible results. Often unacceptably low yields of the primary amine were obtained along with side products whose NMR spectra indicated that the cyclopropane ring had been destroyed, presumably because of the sensitivity of the vinylcyclopropyl moiety toward acid. Addition of propene to the reaction mixture failed to adequately correct the problem. We were also unsuccessful in removing the benzyl moieties from a variety of olefin-containing carbamates by catalytic reduction, including transfer hydrogenation using 1,4-cyclohexadiene as a source of hydrogen, without concomitant reduction of the double bonds.

A successful approach was developed[26] based on the observation by Carpino and co-workers[27,28] that (trimethylsilyl)ethyl carbamate containing polymers were cleaved with fluoride to give polyamines. When the isocyanate was trapped with (trimethylsilyl)ethanol, the (trimethylsilyl)ethyl carbamate **11** was readily cleaved upon treatment with 4 equiv of tetrabutylammonium fluoride to give amine **5**.

Amino Acid 6. An analogue of the ion pair produced when squalene synthetase catalyzes cleavage of the carbon–oxygen bond in presqualene diphosphate was constructed by covalently attaching a phosphorus-containing anion to amine **5** with a short tether. Examination of space-filling models suggested that a two-carbon bridge between the cyclopropyl nitrogen and a nonbridging oxygen in inorganic pyrophosphate would be sufficient to permit the analogue to fold into a conformation where an oxygen on the terminal phosphorus was adjacent to the nitrogen. Initial attempts to prepare a 2-aminoethyl diphosphate derivative were abandoned because of the tendency of the system to form aziridines. We then decided to prepare a less reactive phosphonophosphate analogue by joining the cyclopropyl nitrogen directly to phosphorus by a three-carbon bridge.

As outlined in Scheme III, diethyl phosphonate **13** was prepared from bromide **12** by an Arbuzov reaction. The tetrahydropyranyl group was removed, and the resulting alcohol was converted to tosylate **14**. Addition of **14** to the potassium salt of **11** gave N-alkylated phosphonate **15** in good yield. The ester was hydrolyzed by treatment with

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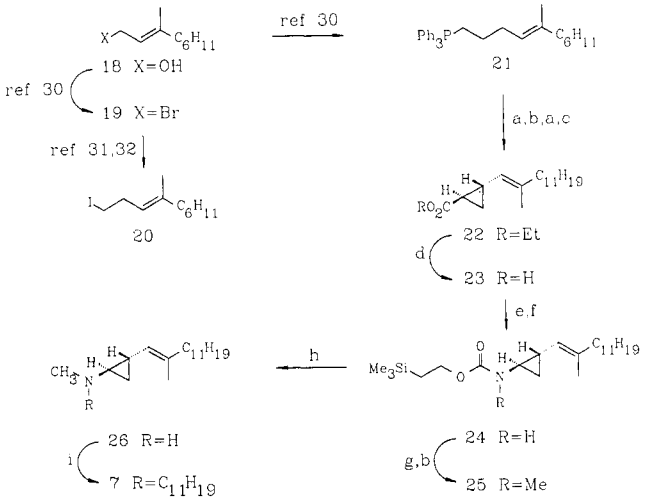
Scheme IV.[a] Synthesis of Tertiary Amine 7



[a] (a) BuLi; (b) MeI; (c) ethyl *trans*-2-formylcyclopropanecarboxylate; (d) KOH, EtOH; (e) $(PhO)_2PON_3$; (f) $Me_3Si(CH_2)_2OH$; (g) KH; (h) nBu_4NF; (i) **20**.

neat bromotrimethylsilane followed by addition of water to give **16**.

Conditions for the conversion of phosphonate **15** to amino acid **6** were established with the chrysanthemyl system,[29] in which the alkyl side chains of the presqualene system are replaced with methyl groups. The procedure of Hoard and Ott,[30] originally developed for the conversion of nucleoside monophosphates to triphosphates, was modified to phosphorylate the phosphonate moiety. The C_{10} analogue of phosphonic acid **15** was activated with carbonyldiimidazole. During the reaction, the ^{31}P singlet of the 27.8 ppm peak disappeared and was replaced with a new peak at 14.2 ppm within 10 min at room temperature. Upon addition of tetra-*n*-butylammonium dihydrogen phosphate and heating to 50 °C, the resonance at 14.2 ppm disappeared to give an AB quartet at 16.4 and −6.5 ppm (J = 24.4 Hz). Treatment with tetrabutylammonium fluoride yielded the C_{10} analogue of amino acid **6** in 28% yield from the phosphonate. The synthetic methodology described above was implemented in the presqualene system. Treatment of **16** with carbonyldiimidazole followed by sequential addition of tetrabutylammonium dihydrogen phosphate, dimethylformamide, and pyridine resulted in clean formation of **17**. Addition of tetrabutylammonium fluoride removed the (trimethylsilyl)ethyl moiety from **17** to yield **6** in 48% yield from **15**.

Tertiary Amine 7. Tertiary amine **7** was obtained by the series of reactions outlined in Scheme IV. The approach involved attachment of an isoprenoid side chain to the formyl carbon in ethyl *trans*-2-formylcyclopropanecarboxylate, conversion of the carboxyl substituent to a carbamate by a Curtius rearrangement similar to the procedure used during the synthesis of **5**, and alkylation of the cyclopropyl nitrogen.

Both isoprenoid side chains in **7** were constructed from geraniol (**18**). The alcohol was converted to bromide **19**,[31] and the one-carbon homologation reported by Hirai and Kishida[32,33] based on nucleophilic displacement with the lithium salt of 2-(methylthio)thiazolide was used to convert **19** to homogeranyl iodide (**20**). In a second set of reactions, **18** was converted to phosphonium salt **21** according to the procedure of Coates and co-workers.[31] In a one-pot sequence, **21** was methylated and converted to the corresponding secondary ylide, which was condensed with the formyl moiety in ethyl *trans*-2-formylcyclopropanecarboxylate to give a 1:1 mixture of *E,E*- and *Z,E*-**22**. The isomers were separated by flash chromatography, and the stereochemistry of the newly formed double bond was assigned from ^{13}C NMR spectra. The vinyl methyl in *E,E*-**22** gave a peak at 16.7 ppm, which was 6.6 ppm upfield of the signal for the corresponding methyl in the *Z,E* isomer, while the vinyl methylene at 32.5 ppm in *Z,E*-**22** resonated upfield of the methylene in *E,E*-**22** by 7.2 ppm. Sterically induced upfield shifts of similar magnitudes were also found by Crombie and co-workers[34] for alkyl groups cis to cyclopropane rings on double bonds in a closely related set of vinylcyclopropyl isomers.

The Curtius rearrangement was used to introduce the nitrogen on the cyclopropane ring as previously described for **11**. Carbamate **24** was obtained by trapping the isocyanate generated upon heating carboxylic acid **23** and diphenyl phosphorazidate in the presence of (trimethylsilyl)ethanol. Treatment of **24** with potassium hydride and alkylation of the corresponding salt with methyl iodide gave **25**. The (trimethylsilyl)ethyl moiety was removed with fluoride, and concomitant decarboxylation gave secondary amine **26**, which was then alkylated with **20** to yield tertiary amine **7**.

Experimental Section

General. Combustion analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. Melting points were obtained on a Thomas-Hoover melting point apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were obtained on Varian EM-390, FT-80, SC-300, or XL-300 spectrometers. ^1H and ^{13}C NMR spectra are reported in parts per million downfield from internal tetramethylsilane (TMS) or external sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) (Aldrich). ^{31}P NMR spectra were referenced to 85% phosphoric acid. Mass spectra (MS) were obtained on VG 770 (routine spectra) and Varian MAT 731 (high-resolution mass spectra, HRMS) mass spectrometers. Fast atom bombardment mass spectra (FABMS) on diphosphates and phosphonophosphates were performed on a VG 770 mass spectrometer using the technique developed by Sharp, Davisson, and Poulter.[35] Infrared (IR) spectra were obtained on Perkin-Elmer 1500 fourier transform and 299 spectrometers and were referenced to the 1601-cm^{-1} absorbance of polystyrene. All absorptions are reported in wave numbers (cm^{-1}). Ultraviolet (UV) measurements were performed on a Gilford 2600 spectrophotometer. The purity of title compounds in the experimental section was established to be >90% by combustion analysis or from NMR (^1H, ^{13}C, ^{31}P) spectra. Unless otherwise indicated, reagents were obtained from Aldrich Chemical Co. Reagent grade hexanes and pentane were purified by acid and base washes, filtration through neutral alumina, and distillation. Reagent grade diethyl ether (ether), tetrahydrofuran, and hexanes for reactions were dried over lithium aluminum hydride followed by distillation from sodium benzophenone ketyl. Methylene chloride and acetonitrile used for reactions were distilled from phosphorus pentoxide. Ethyl acetate was distilled. *N,N*-Dimethylformamide, dimethyl sulfoxide, toluene, triethylamine, and pyridine were distilled from calcium hydride. 2-Butanone was distilled from magnesium sulfate.

***trans*-2-[(3*E*)-4,8-Dimethyl-3,7-nonadienyl]-2-methyl-*trans*-3-[(1*E*,5*E*)-2,6,10-trimethyl-1,5,9-undecatrienyl]-**

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cyclopropanecarbaldehyde (9). Following the procedure of Mancuso et al.,[20] 1.2 mL of methylene chloride and oxalyl chloride (68.0 mg, 0.53 mmol) were combined in a 5-mL flame-dried reaction vial. The solution was cooled to −60 °C, dimethyl sulfoxide (92.5 mg, 1.18 mmol) in 0.24 mL of methylene chloride was added, and the resulting solution was stirred for 2 min. Presqualene alcohol[19] (8, 200 mg, 0.47 mmol) in 0.5 mL of methylene chloride was added, and the mixture was stirred for 25 min at −60 °C. Triethylamine (0.22 mL, 0.16 g, 1.6 mmol) was added, and stirring was continued for 5 min at −60 °C. The cloudy, white suspension was allowed to warm to room temperature over a 45-min period. Ether (1 mL) and 5% sodium carbonate (1 mL) were added. The contents of the vial were transferred to a culture tube and briefly agitated on a vortex mixer. The clear ether layer was transferred to a second culture tube and extracted with saturated sodium chloride. The ether layer was dried over magnesium sulfate and sodium bicarbonate and filtered. Solvent was removed under reduced pressure to afford 182 mg (0.43 mmol, 91%) of a viscous, light-yellow oil, which was used immediately in the following step.

***trans*-2-[(3*E*)-4,8-Dimethyl-3,7-nonadienyl]-2-methyl-*trans*-3-[(1*E*,5*E*)-2,6,10-trimethyl-1,5,9-undecatrienyl]-cyclopropanecarboxylic Acid (10).** Following the procedure of Sala and Sargent,[22] aldehyde 9 (182 mg, 0.43 mmol) from the previous step was dissolved in 1.6 mL of pyridine. Tetra-*n*-butylammonium permanganate (0.24 g, 0.65 mmol) in 2.4 mL of pyridine was added dropwise at room temperature. After addition of each drop of the oxidant, the resulting solution was stirred until the color of the reaction mixture changed from deep purple to dark brown. The progress of the reaction was monitored by TLC (1:1:0.1, v/v/v, hexanes/ethyl acetate/methanol, R_f[9] = 0.65, R_f[10] = 0.27). After 1 h, water (10 mL) was added. Sodium bisulfite (10% w/v in water) was added dropwise until the brown color was no longer visible. The solution was carefully acidified to pH 3 with 2 N HCl. The aqueous phase was extracted with ether. The combined ether layers were dried over magnesium sulfate and filtered. Solvent was removed at reduced pressure to yield 166.0 mg (0.38 mmol, 80%) of a viscous yellow oil. A portion of the material was purified by flash chromatography (1:2, v/v, ethyl acetate/hexanes): ^{1}H NMR (300 MHz, $CDCl_3$) 5.06 (m, 4 H, vinyls), 4.91 (d, J = 8.4 Hz, 1 H, vinyl coupled to C(3′) cyclopropyl), 1.99 (m, 16 H, vinyl methylenes), 1.68 (s, 3 H, vinyl methyls), 1.65 (s, 6 H, vinyl methyls), 1.57 (s, 12 H, vinyl methyls), 1.38 (m, 2 H, cyclopropyls), 1.27 ppm (s, 3 H, cyclopropylmethyl); ^{13}C NMR (75 MHz, $CDCl_3$), 178.70, 139.34, 135.26, 135.15, 131.28, 131.23, 124.30, 123.88, 123.76, 120.57, 39.82, 39.64, 36.43, 34.55, 33.85, 33.79, 29.70, 26.86, 26.78, 26.63, 25.83, 25.11, 17.82, 17.64, 16.97, 16.14, 16.06 ppm; IR (neat) 2960, 2940, 2830, 1690, 1450, 1375, 1250, 1210 cm^{-1}; HRMS m/z calcd 440.3654, obsd 440.3638.

***N*-[[2-(Trimethylsilyl)ethoxy]carbonyl]-*trans*-2-[(3*E*)-4,8-dimethyl-3,7-nonadienyl]-2-methyl-*trans*-3-[(1*E*,5*E*)-2,6,10-trimethyl-1,5,9-undecatrienyl]cyclopropylamine (11).** Acid 10 (29.0 mg, 0.07 mmol) was dissolved in 0.11 mL of toluene. In order, triethylamine (6.7 mg, 0.07 mmol) and diphenyl phosphorazidate (18.2 mg, 0.07 mmol) were added. The solution was heated to 100 °C over a 15-min period. Nitrogen evolution was evident at 70–80 °C and continued as the temperature increased. The reaction mixture was stirred at 100 °C for 20 min, by which time nitrogen evolution had ceased. The clear solution was allowed to cool to 50 °C, and neat 2-(trimethylsilyl)ethanol (15.6 mg, 0.13 mmol) was added. The reaction mixture was stirred overnight at 50 °C. The material was diluted with ether, and the solution was transferred to a culture tube. Dilute sodium hydroxide (1 mL, one pellet of sodium hydroxide/50 mL of water) was added, and the solution was agitated on a vortex mixer. The ether layer was dried over magnesium sulfate and filtered. Solvent was removed at reduced pressure to afford a clear viscous oil. The material was purified by flash chromatography on silica gel (0.8:9.2, v/v, ethyl acetate/hexanes) to yield 30 mg (82% from the acid) of a clear, viscous oil: R_f = 0.37; ^{1}H NMR (300 MHz, $CDCl_3$) 5.28 (m, 4 H, vinyls), 5.02 (d, J = 8.4 Hz, 1 H, vinyl coupled to C(3′) cyclopropyl), 4.50 (br s, 1 H, NH), 4.28 (m, 2 H, methylene adjacent to oxygen), 2.42 (br s, 1 H, C(1′) cyclopropyl), 2.12 (m, 16 H, vinyl methylenes), 1.69, 1.65, 1.60, 1.57 (s, 21 H, vinyl methyls), 1.42 (m, 1 H, C(3′) cyclopropyl), 1.12 (s, 3 H, cyclopropylmethyl), 1.0 (br s, 2 H, methylene adjacent to trimethylsilyl), −0.06 ppm (s, 9 H, trimethylsilyl methyls); ^{13}C NMR (75 MHz, $CDCl_3$) 157.9, 138.6, 135.5, 135.2, 131.6, 124.9, 124.7, 124.5, 121.8, 63.1, 42.5, 39.8, 39.7, 35.1, 31.2, 28.4, 26.8, 26.7, 25.8, 24.8, 17.9, 17.7, 16.9, 16.1, 16.0, −1.48 ppm; IR (CCl_4) 3450, 2950, 2920, 2840, 1700, 1500, 1370, 1245, 1180, 1170 cm^{-1}; HRMS m/z (M − 15) calcd 540.4237, obsd 540.4237; HRMS m/z (M − 28) calcd 527.4159, obsd 527.4164.

***trans*-2-[(3*E*)-4,8-Dimethyl-3,7-nonadienyl]-2-methyl-*trans*-3-[(1*E*,5*E*)-2,6,10-trimethyl-1,5,9-undecatrienyl]-cyclopropylamine (5).** Tetra-*n*-butylammonium fluoride trihydrate (29.3 mg, 0.093 mmol) in 0.05 mL of tetrahydrofuran was added to 12.9 mg (0.023 mmol) of carbamate 11, and the resulting solution was heated to 50 °C with stirring. Water (5 drops) and 0.1 mL of ether were added. The clear, light-brown solution was stirred for 10 min at room temperature. The contents of the vial were transferred to a culture tube containing 2 mL each of ether and water. The suspension was agitated on a vortex mixer, and the ether layer was removed. The aqueous phase was extracted with 2 × 2 mL portions of ether, and the combined ether layers were extracted with three portions of saturated sodium chloride. The ether layer was dried with magnesium sulfate and sodium bicarbonate and filtered. Solvent was removed at reduced pressure to yield 10.1 mg of a clear viscous oil. The material was purified by flash chromatography on silica gel (5:5:1, v/v/v, hexanes/ethyl acetate/methanol) to yield 3.8 mg (40%) of a clear, viscous oil: ^{1}H NMR (300 MHz, $CDCl_3$) 5.08 (m, 4 H, vinyls), 4.84 (d, J = 7.4 Hz, 1 H, vinyl coupled to C(3′) cyclopropyl), 1.99 (m, 16 H, vinyl methylenes), 1.673, 1.669, 1.662, 1.66, 1.58 (s, 21 H, vinyl methyls), 1.17 (s, 3 H, cyclopropylmethyl), 0.8–1.2 ppm (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) 137.49, 135.37, 135.15, 131.68, 131.63, 124.86, 124.74, 124.55, 122.75, 43.84, 39.86, 39.76, 35.68, 27.92, 26.82, 25.78, 24.95, 17.74, 17.29, 16.75, 16.05, 15.95 ppm; IR (neat) 3400, 2970, 2940, 2870, 1740, 1660, 1460, 1380, 1110, 840 cm^{-1}; HRMS m/z (M^+) calcd 411.3865, obsd 411.3865.

Diethyl [3-[(*p*-Tolylsulfonyl)oxy]propyl]phosphonate (14). Following the procedure of Miyashita et al.,[36] 3-bromo-1-propanol (2.0 g, 14 mmol) was dissolved in 50 mL of methylene chloride. Dihydropyran (0.99 mL, 10.8 mmol) and pyridinium *p*-toluenesulfonate (0.18 g, 0.72 mmol) were added, and the solution was stirred at room temperature for 3 h. The reaction mixture was diluted with 100 mL of ether and washed with a half-saturated solution of sodium chloride. The light-yellow organic phase was dried over magnesium sulfate. Solvent was removed at reduced pressure, and the residue was passed through a plug of silica gel by elution with 1:1 hexanes/ether. Solvent was removed at reduced pressure to afford a yellow oil, which was purified by flash chromatography on silica gel (1.5:8.5, v/v, ether/hexanes) to yield 3.12 g (97%) of a clear, viscous oil: ^{1}H NMR (90 MHz, $CDCl_3$) 4.7 (br s, 1 H), 3.0–4.0 (m, 6 H), 2.0 (m, 2 H), 1.0–2.0 ppm (m, 6 H).

THP ether 12 (3.12 g, 14.09 mmol) was dissolved in freshly distilled triethyl phosphite (12.0 mL, 70.0 mmol). The stirred solution was heated at reflux (175 °C) for 5 h. Excess triethyl phosphite was removed at reduced pressure to yield 3.74 g (100%) of a clear, viscous oil, which was used in the following step without purification: ^{1}H NMR (90 MHz, $CDCl_3$) 4.4 (br s, 1 H, acetal proton), 3.9 (dq, $J_{P,H}$ = 11 Hz, $J_{H,H}$ = 11 Hz, 4 H, ethoxymethylenes, 3.3–4.3 (m, 4 H), 1.0–2.0 (m, 10 H), 1.1 ppm (t, J = 11 Hz, 6 H, ethoxymethyls); IR (neat) 2965, 2860, 2845, 1438, 1385, 1240, 1050, 1025, 995, 790 cm^{-1}.

The THP phosphonate 13 (3.74 g, 14.0 mmol) was dissolved in 110 mL of methanol. Pyridinium *p*-toluenesulfonate (0.35 g, 1.4 mmol) was added, and the solution was stirred for 5 h at 50 °C. The solution was allowed to cool to room temperature, and solvent was removed at reduced pressure to yield a white paste, which was dissolved in 50 mL of methylene chloride. To the solution was added a mixture of *p*-toluenesulfonyl chloride (4.0 g, 21.0 mmol) and 4-(dimethylamino)pyridine (2.8 g, 23.1 mmol) dissolved in 50 mL of methylene chloride. The solution was stirred for 5 h at room temperature, and solvent was removed under reduced pressure to yield a white slurry. Ethyl acetate (200 mL) was added, and the solution was extracted with 150 mL of water. The organic layer was dried over magnesium sulfate and filtered. Solvent was removed under reduced pressure to afford a viscous,

(36) Miyashita, N.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772–3774.

yellow oil, which was purified by flash chromatography on silica gel (2:1:1, v/v/v, hexanes/ether/methanol) to yield 3.36 g (69%) of a clear, viscous oil: ^{1}H NMR (90 MHz, $CDCl_3$) 7.8 (d, J = 8 Hz, 2 H), 7.3 (d, J = 8 Hz, 2 H), 4.0 (m, 6 H, methylenes adjacent to oxygen), 2.4 (s, 3 H), 1.3–2.3 (m, 4 H, methylenes at C(1) and C(2)), 1.3 ppm (t, J = 8 Hz, 6 H, methyls); IR (neat) 2980, 2930, 2900, 1760, 1592, 1452, 1440, 1383, 1240, 1186, 1172, 1090, 1050, 1025, 955, 912, 810 cm^{-1}; MS, m/z (relative intensity) 350 (M^+, 21), 195 (33), 179 (42), 155 (31), 151 (29), 143 (57), 123 (100), 91 (92), 41 (50).

Tetrabutylammonium Dihydrogen Phosphate. Phosphoric acid (85 wt %, 1.3 g, 11.3 mmol) was dissolved in 20 mL of distilled, deionized water and titrated to pH 4.67 with 40 wt % aqueous tetrabutylammonium hydroxide. The solution was frozen in a dry ice–2-propanol slurry and lyophilized to yield 3.56 g of a fluffy white hydroscopic solid, which was stored under nitrogen at −20 °C.

Diethyl [3-[*N*-[[2-(Trimethylsilyl)ethoxy]carbonyl]-*N*-[*trans*-2-[(3*E*)-4,8-dimethyl-3,7-nonadienyl]-2-methyl-*trans*-3-[(1*E*,5*E*)-2,6,10-trimethyl-1,5,9-undecatrienyl]-1-cyclopropyl]amino]propyl]phosphonate (15). Mineral oil was removed from a 35% slurry of potassium hydride (5 mg) with ether to yield a gray solid (2.0 mg, 0.050 mmol). Carbamate **11** (13.0 mg, 0.023 mmol) in 0.13 mL of tetrahydrofuran was added, and the reaction mixture was stirred for 1.5 h at room temperature. Tosylate **14** (17 mg, 0.05 mmol) was added, followed by 0.06 mL of tetrahydrofuran. The reaction mixture was stirred for 10 min, at which time it became yellow and viscous. Tetrahydrofuran (0.1 mL) was added to facilitate stirring. The reaction mixture was stirred for 35 min and then quenched by a slow, dropwise addition of methanol. The mixture was diluted with ether and water, the solution was transferred to a culture tube, and the suspension was agitated on a vortex mixer. The ether layer was removed, and the aqueous layer was extracted with two additional portions of ether. The combined ether layers were dried over magnesium sulfate and filtered. Removal of solvent under reduced pressure afforded a clear, viscous oil, which was purified by flash chromatography on silica gel (ethyl acetate) to yield 9.9 mg (61%) of a clear viscous oil: R_f = 0.38; ^{1}H NMR (300 MHz, $CDCl_3$) 5.06 (br s, 4 H, vinyls), 4.84 (d, J = 8.3 Hz, 1 H, vinyl coupled to C(3′) cyclopropyl), 4.08 (m, 6 H, methylenes adjacent to oxygen), 3.57 (m, 1 H, diastereotopic methylene proton adjacent to nitrogen), 3.04 (m, 1 H, diastereotopic methylene proton adjacent to nitrogen), 2.26 (d, J = 4.6 Hz, 1 H, C(1′) cyclopropyl proton), 2.0 (m, 16 H, vinyl methylenes), 1.60–1.80 (m, 5 H, CH_2CH_2P, C(3′) cyclopropyl), 1.650, 1.647, 1.57 (s, 21 H, vinyl methyls), 1.28 (t, J = 7.1 Hz, 6 H, ethoxy methyls), 1.02 (s, 3 H, cyclopropyl methyl), 1.0 (m, 2 H, methylenes adjacent to trimethylsilyl), 0.01 ppm (s, 9 H, trimethylsilyl methyls); ^{13}C NMR (75 MHz, $CDCl_3$) 158.2, 138.2, 135.3, 134.9, 131.4, 124.7, 124.5, 124.2, 121.8, 63.4, 61.5 (d, $J_{P,C}$ = 6 Hz), 48.0, 47.7, 39.6 (d, $J_{P,C}$ = 4 Hz), 35.1, 29.5, 26.6, 25.5, 24.3, 24.1, 22.2, 21.2, 21.1, 17.9 (d, $J_{P,C}$ = 16 Hz), 17.5, 16.6, 16.3, 16.2, 15.8, 15.7, −1.48 ppm; ^{31}P NMR (32.3 MHz, $CDCl_3$) 31.31 ppm (s); IR (CCl_4) 2957, 2927, 1701, 1457, 1405, 1251, 1167, 1061, 1032, 959 cm^{-1}; HRMS m/z (M^+) calcd 733.5230, obsd 733.5238; HRMS m/z (M − 15) calcd 718.4996, obsd 718.4994.

[3-[*N*-[*trans*-2-[(3*E*)-4,8-Dimethyl-3,7-nonadienyl]-2-methyl-*trans*-3-[(1*E*,5*E*)-2,6,10-trimethyl-1,5,9-undecatrienyl]-1-cyclopropyl]amino]propyl]phosphonophosphate (6). Phosphonate **15** (21.0 mg, 0.029 mmol) was dissolved in bromotrimethylsilane (11 μL, 0.086 mmol). The clear solution was stirred for 1 h at room temperature before volatile components were removed under reduced pressure, first on a rotary evaporator and then at 0.5 mmHg, to yield 23.0 mg (97%) of a viscous, clear oil. The residue was dissolved in 1.5 mL of 2:1, v/v, acetone/water, and the resulting solution was stirred for 1 h at room temperature. Acetone was removed under reduced pressure, and acetonitrile was added. Solvent was removed under reduced pressure. The addition of acetonitrile and removal of solvent under reduced pressure was repeated six times to remove residual water. Analysis of the clear sticky oil by ^{31}P NMR showed a single resonance at 37.6 ppm. The ^{1}H NMR spectrum showed that the resonances associated with the ethoxy group were no longer present.

To crude phosphonic acid **16** were added 1,1′-carbonyldiimidazole (5.17 mg, 0.032 mmol) and dimethylformamide (30 μL). The solution was stirred for 10 min at room temperature before tetrabutylammonium dihydrogen phosphate (29.5 mg, 0.087 mmol), dimethylformamide (40 μL), and pyridine (35 μL) were added in sequence. The resulting solution was stirred at room temperature for 16 h. Dimethylformamide (1.3 mL) was added, and ^{31}P NMR of the mixture showed resonances at 8.15 ppm (d, J = 23.3 Hz) and −13.55 ppm (d, J = 23.5 Hz).

Tetra-*n*-butylammonium fluoride trihydrate (0.44 g, 1.4 mmol) was added to crude phosphonophosphate **17**, and the solution was stirred for 1 h at 50 °C. The reaction mixture was allowed to cool to room temperature, and 12 drops of distilled water were added. Gas evolution occurred within 30 s, and stirring was continued for 30 min at room temperature. Solvent was removed at reduced pressure, the residual viscous oil obtained was dissolved in 1 mL of 1:19, v/v, 2-propanol/25 mM ammonium bicarbonate, and the material was applied to a 1.3 × 7.0 cm column of AG 50W-X8 ion-exchange resin (ammonium form). The column was slowly eluted with 2 column volumes of the same buffer. Solvent was removed by lyophilization to yield a light-yellow solid, which was purified by flash chromatography on CF11 cellulose (3:1:1, v/v/v, 2-propanol/tetrahydrofuran/0.1 M ammonium bicarbonate) to yield 9.0 mg (48%) of an off-white amorphous solid: ^{1}H NMR (300 MHz, $CDCl_3$) 5.05 (m, 4 H, vinyls), 4.83 (br s, 1 H, vinyl adjacent to C(3′) cyclopropyl), 0.8–3.0 (unresolved resonances for the ammonium counterions), 3.0–3.9 (m, 4 H), 2.0 (m, 22 H, vinyl methylenes, C(1′) cyclopropyl), 1.67, 1.58 (s, 21 H, vinyl methyls), 1.0–1.6 (13 H, unresolved resonances, CH_2CH_2P, C(3′) cyclopropyl, cyclopropyl methyl); ^{13}C NMR (75 MHz, $CDCl_3$) 135.46, 135.22, 131.23, 131.13, 124.27, 123.82, 39.84, 29.78, 29.53, 26.89, 26.71, 25.78, 17.81, 16.10; ^{31}P NMR (32.3 MHz, $CDCl_3$) 14.6 (d, J = 24.8 Hz, 1 P, phosphonate), 9.25 (br s, 1 P, phosphate); negative ion FABMS, m/z (relative intensity) 612 (M − N_3H_{10}, 22.4), 218 (2.8), 183 (37), 153 (28), 97 (29.1).

Ethyl *trans*-2-[(1*E*,5*E*)-2,6,10-Trimethyl-1,5,9-undecatrienyl]cyclopropanecarboxylate (22). A solution of 5.4 g (9.7 mmol) of (*E*)-(5,9-dimethyl-4,8-decadienyl)triphenylphosphonium iodide (**21**) in 30 mL of anhydrous tetrahydrofuran was cooled to 0 °C. *n*-Butyllithium (9.7 mmol, 4.2 mL of a 2.3 M solution) was added, and the resulting solution was allowed to warm to room temperature. Stirring was continued for 10 min, methyl iodide (1.38 g, 9.7 mmol) was added dropwise, and the resulting solution was stirred for 30 min at room temperature. The reaction mixture was cooled to 0 °C, and a second portion of *n*-butyllithium (9.7 mmol, 4.2 mL of a 2.3 M solution) was added. The solution was allowed to warm to room temperature and then stirred for 10 min. The reaction mixture was cooled to −62 °C, and 1.4 g (9.8 mmol) of ethyl *trans*-2-formyl-1-cyclopropanecarboxylate was added via syringe. Stirring was continued for 15 min at −62 °C. Ether (10 mL) was added, and the solution was allowed to warm to −25 °C. Stirring was continued at −25 °C for 0.5 h before 10 mL of absolute ethanol was added. The resulting clear yellow solution was allowed to warm to room temperature and was stirred overnight. The solution was then poured into 100 mL of ether and extracted with water until the aqueous layer was pH 7. The organic layer was dried over magnesium sulfate and filtered. Solvent was removed at reduced pressure, and the residual viscous oil was passed through a plug of silica gel (5:95, v/v, hexanes/ethyl acetate). Solvent was removed at reduced pressure, and the residual viscous, yellow oil was purified by flash chromatography on silica gel (1:1, v/v, benzene/hexanes). Those fractions containing the pure trans isomer (*E*,*E*-**22**) were pooled to yield 0.5 g (1.6 mmol, 16% from **21**): R_f = 0.55 (1:99, ethyl acetate/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) 5.08 (s, 2 H, vinyls), 4.62 (d, J = 9 Hz, 1 H, vinyl), 4.13 (q, J = 7.0 Hz, 2 H, ethoxy methylenes), 2.01 (m, 8 H, allylic methylenes), 1.15–1.83 (m, 3 H, cyclopropyl protons), 1.74 (s, 3 H, vinyl methyl), 1.69 (s, 3 H, vinyl methyl), 1.23 (t, J = 7.0 Hz, ethoxy methyl), 0.7–1.0 ppm (m, 1 H, cyclopropyl proton); ^{13}C NMR (75 MHz, $CDCl_3$) 173.6, 137.4, 135.0, 131.0, 124.4, 124.2, 123.8, 60.3, 39.7, 39.4, 26.8 26.4, 25.7, 21.9, 21.7, 17.6, 16.7, 16.1, 16.0, 14.3; IR (neat) 2960, 2910, 2850, 1719, 1435, 1400, 1373, 1345, 1293, 1258, 1193, 1165, 1085, 1030, 930 cm^{-1}; MS, m/z (relative intensity) 304.2 (M^+, 6), 95.1 (28), 93.1 (37), 81.1 (43), 69.1 (100). Anal. Calcd for $C_{20}H_{32}O_2$: C, 78.90; H, 10.59. Found: C, 78.77; H, 10.47.

Those fractions containing the pure cis isomer (*Z*,*E*-**22**) were pooled to yield 0.5 g (1.6 mmol, 16% from **21**): R_f = 0.61 (1:99, v/v, ethyl acetate/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) 5.08 (br

s, 2 H, vinyl), 4.56 (d, J = 9 Hz, 1 H, vinyl), 4.09 (q, J = 7.0 Hz, 2 H, ethoxy methylenes), 1.98–2.13 (m, 8 H, allylic methylenes), 1.58–1.69 (m, 12 H, vinyl methyls), 1.11–1.60 (m, 3 H, cyclopropyl protons), 1.22 (t, J = 7.0 Hz, 3 H, ethoxy methyl), 0.84 ppm (m, 1 H, cyclopropyl proton); ^{13}C NMR (75 MHz, $CDCl_3$) 173.7, 137.6, 135.3, 131.0, 125.2, 124.3, 123.7, 60.3, 39.8, 32.5, 26.8, 26.4, 25.7, 23.3, 21.9, 21.6, 17.7, 16.1, 16.0, 14.3 ppm; MS, m/z (relative intensity) 304.3 (M^+, 1.1), 219.1 (11), 95.1 (26), 93.1 (38), 81.1 (40), and 69.1 (100). Anal. Calcd for $C_{20}H_{32}O_2$: C, 78.90; H, 10.59. Found: C, 79.14; H, 10.34.

***trans*-2-[(1*E*,5*E*)-2,6,10-Trimethyl-1,5,9-undecatrienyl]-cyclopropanecarboxylic Acid (23).** Ester **22** (1.12 g, 3.68 mmol) was dissolved in 62 mL of 1.2 M potassium hydroxide in methanol and stirred overnight at room temperature. Methanol was removed at reduced pressure, and the resulting residue was diluted with 1 M hydrochloric acid. The solution was extracted with ether, and the combined ether layers were dried over magnesium sulfate and filtered. Solvent was removed at reduced pressure to yield 0.99 g (98%) of a viscous oil, which was used without purification in the following step: ^{1}H NMR (300 MHz, $CDCl_3$) 12.01 (s, 1 H, OH), 5.29 (m, 2 H, vinyl protons), 4.78 (d, J = 9 Hz, 1 H, vinyl proton), 2.11 (br s, 8 H, allylic methylenes), 1.84 (s, 3 H, vinyl methyl), 1.77 (s, 3 H, vinyl methyl), 1.69 (s, 3 H, vinyl methyl), 1.2–1.7 (m, 2 H, cyclopropyl protons), 0.8–1.1 ppm (m, 2 H, cyclopropyl protons); IR (neat) 3400, 3100 (br), 2960, 2920, 2850, 1690, 1445, 1373, 1295, 1228, 1155, 1105, 1045, 930 cm^{-1}; MS, m/z (relative intensity) 276.0 (M^+, 1.9), 81.0 (47), 69.0 (100); HRMS m/z calcd 276.2085, obsd 276.2088.

***N*-[[2-(Trimethylsilyl)ethoxy]carbonyl]-*trans*-2-[(1*E*,5*E*)-2,6,10-trimethyl-1,5,9-undecatrienyl]cyclopropylamine (24).** To a solution of acid **23** (1.1 g, 3.99 mmol) in 4 mL of anhydrous toluene was added 0.40 g (3.99 mmol) of triethylamine. Diphenyl phosphorazidate (1.1 g, 3.99 mmol) was added, and the resulting solution was heated to 90 °C with stirring. Evolution of gas began as the temperature approached 80 °C. After 2 h, 2-(trimethylsilyl)ethanol (1.0 g, 8.46 mmol) was added, and stirring at 90 °C was continued for 8 h. Solvent was removed under reduced pressure, and the residue obtained was dissolved in 100 mL of ether. After extraction with dilute aqueous sodium hydroxide, the ether layer was dried over magnesium sulfate and filtered. Solvent was removed at reduced pressure, and the residual oil was purified by flash chromatography on silica gel (9:1, v/v, hexanes/ethyl acetate) to yield 1.1 g (71%) of a clear, viscous oil: R_f = 0.28; ^{1}H NMR (300 MHz, $CDCl_3$) 5.18 (t, J = 6.0 Hz, 2 H, vinyls), 4.9 (br s, 1 H, vinyl adjacent to cyclopropyl), 4.7 (d, J = 7.5 Hz, 1 H, NH), 4.15 (t, J = 8.0 Hz, 2 H, methylene adjacent to oxygen), 2.3 (m, 10 H), 1.75 (m, 13 H), 1.05 (m, 4 H), 0.1 ppm (s, 9 H, trimethylsilyl methyls); ^{13}C NMR (75 MHz, $CDCl_3$) 157.52, 136.82, 135.38, 131.53, 127.73, 124.73, 124.66, 124.32, 109.99, 63.12, 39.75, 39.48, 31.23, 26.76, 26.52, 25.69, 17.73, 17.64, 16.64, 15.98, 15.82, −1.56 ppm; IR (neat) 3300, 2945, 2910, 2850, 1700, 1510, 1325, 1245, 1080, 1055, 855, 830 cm^{-1}; MS, m/z (relative intensity) 348 (3.3), 182 (6.5), 101 (10.2), 73 (100), 57 (32.2). Anal. Calcd for $C_{23}H_{41}NO_2Si$: C, 70.59; H, 10.49. Found: C, 70.64; H, 10.54.

***N*-Methyl-*N*-[[2-(trimethylsilyl)ethoxy]carbonyl]-*trans*-2-[(1*E*,5*E*)-2,6,10-trimethyl-1,5,9-undecatrienyl]-cyclopropylamine (25).** Potassium hydride (0.57 g of a 40% suspension in mineral oil) was rinsed with ether, the resulting gray powder was suspended in 1 mL of anhydrous tetrahydrofuran, and a solution of 0.39 g (1.0 mmol) of carbamate **24** in 0.5 mL of tetrahydrofuran was added. The reaction mixture was stirred at room temperature for 2 h before 0.71 g (5.0 mmol) of methyl iodide was added. Stirring was continued for 15 min at room temperature. Ether was added, the soluion was washed with water and dried over magnesium sulfate, and the solvent was removed at reduced pressure. The residue was purified by flash chromatography (95:5, v/v, ethyl acetate/hexanes) to yield 0.39 g (96%) of a clear, viscous oil: ^{1}H NMR (300 MHz, $CDCl_3$) 5.15 (t, J = 6.0 Hz, 2 H, vinyls), 4.7 (d, J = 7.5 Hz, 1 H, NH), 4.2 (t, J = 8.0 Hz, 2 H, methylenes adjacent to oxygen), 2.95 (s, 3 H), 2.2 (m, 22 H), 1.8 (m, 13 H), 1.05 (m, 4 H), 0.15 ppm (s, 9 H, trimethylsilyl methyls); ^{13}C NMR (75 MHz, $CDCl_3$) 158.08, 136.23, 133.33, 131.50, 125.14, 124.63, 124.29, 109.99, 63.44, 39.75, 39.53, 38.35, 34.62, 26.76, 26.52, 25.67, 17.85, 17.63, 16.57, 16.49, 15.96, −1.59 ppm; MS, m/z (relative intensity) 362 (14.4), 292 (5.5), 224 (26.4), 196 (59.4), 132 (10.1), 101 (22.7), 73 (100), 69 (41.6). Anal. Calcd for $C_{24}H_{43}NO_2Si$: C, 71.11; H, 10.37. Found: C, 70.67; H, 10.70.

***N*-Methyl-*trans*-2-[(1*E*,5*E*)-2,6,10-trimethyl-1,5,9-undecatrienyl]cyclopropylamine (26).** Carbamate **25** (0.20 g, 0.5 mmol) was heated with 2.5 mL of a 1 M solution of tetra-*n*-butylammonium fluoride trihydrate in tetrahydrofuran for 30 min at 50 °C. The mixture was allowed to cool to room temperature, and solvent was removed under reduced pressure. The residue was dissolved in 100 mL of ether and extracted in succession with water and saturated sodium chloride. The ether layer was dried over magnesium sulfate and filtered. Solvent was removed at reduced pressure to yield 129 mg (98%) of a clear, viscous oil: ^{1}H NMR (300 MHz, $CDCl_3$) 5.05 (t, J = 6.0 Hz, 2 H, vinyls), 4.55 (d, J = 7.5 Hz, 1 H, vinyl adjacent to cyclopropyl), 2.4 (s, 3 H), 2.0 (m, 8 H), 1.65 (m, 13 H), 0.8 ppm (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) 135.07, 134.82, 126.06, 124.45, 124.19, 109.77, 39.55, 39.31, 35.41, 26.56, 26.34, 25.47, 19.43, 17.43, 16.27, 15.76, 15.23 ppm; IR (neat) 2960, 2920, 2860, 2785, 1645, 1450, 1375, 1150, 1090, 890, 835 cm^{-1}; HRMS m/z calcd 261.2456, obsd 261.2339.

***N*-Methyl-*N*-[(3*E*)-4,8-dimethyl-3,7-nonadienyl]-*trans*-2-[(1*E*,5*E*)-2,6,10-trimethyl-1,5,9-undecatrienyl]cyclopropylamine (7).** A solution of amine **26** (0.15 g, 0.58 mmol), iodide **20** (0.24 mg, 0.87 mmol), and anhydrous potassium carbonate (0.20 g, 1.45 mmol) in 100 mL of acetone was heated at reflux for 24 h. The reaction mixture was allowed to cool to room temperature, and solvent was removed under reduced pressure. The dark-brown residue was suspended in ether, and 20 mL of water was added. The ether layer was dried over magnesium sulfate and filtered. Solvent was removed at reduced pressure, and the residual yellow oil was purified by flash chromatography on silica gel (1:9, v/v, ethyl acetate/hexanes) to yield 85.0 mg (36%) of a light yellow oil: R_f = 0.28; ^{1}H NMR (300 MHz, $CDCl_3$) 5.30 (t, J = 7.0 Hz, 4 H, vinyls), 4.76 (t, J = 10 Hz, 1 H, vinyl adjacent to cyclopropyl ring), 2.7 (m, 2 H, methylene adjacent to nitrogen), 2.5 (m, 2 H), 2.41 (s, 3 H, methyl attached to nitrogen), 2.3 (m, 2 H), 2.09 (br s, 12 H, vinyl methylenes), 1.77 (s, 3 H, vinyl methyl), 1.73 (s, 6 H, vinyl methyls), 1.66 (s, 12 H, vinyl methyls), 1.2–1.6 (m, 1 H, cyclopropyl proton), 0.4–1.0 ppm (m, 2 H, cyclopropyl protons); ^{13}C NMR (75 MHz, $CDCl_3$) 136.0, 135.4, 131.2, 128.3, 126.3, 124.7, 124.6, 122.5, 58.1, 47.3, 42.5, 39.9, 39.8, 39.7, 27.1, 27.0, 26.9, 26.8, 26.3, 25.6, 20.5, 17.7, 16.1, 16.0, 15.9 ppm; MS (electron impact), m/z (relative intensity) 411.3 (M^+, 1.5), 275.2 (21), 274.2 (100), 69.0 (61); HRMS m/z calcd 411.3860, obsd 411.3865.

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Registry No. **5**, 117144-95-3; **5**·H$^+$, 117182-30-6; **6**, 116179-97-6; **7**, 117182-27-1; **7**·H$^+$, 117182-31-7; **8**, 117182-28-2; **9**, 117182-29-3; **10**, 117144-96-4; **11**, 117144-97-5; **12**, 33821-94-2; **12** (alcohol), 627-18-9; **13**, 117144-98-6; **13** (R = H), 55849-69-9; **14**, 117144-99-7; **15**, 117145-00-3; **16**, 117145-01-4; **17**, 117145-02-5; **20**, 22339-13-5; **21**, 32205-44-0; **22**, 83732-42-7; (*Z*,*E*)-**22**, 117182-32-8; **23**, 117145-03-6; **24**, 117145-04-7; **25**, 117145-05-8; **26**, 117145-06-9; ethyl *trans*-2-formylcyclopropanecarboxylate, 13949-93-4.