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α-Phosphono Lactone Analogues of Farnesyl Pyrophosphate: An Asymmetric Synthesis via Ring-Closing Metathesis

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An α-phosphono lactone derivative of farnesol has been prepared, in both racemic and nonracemic forms, to provide a new type of farnesyl pyrophosphate analogue. Attempted preparation of the racemic α-phosphono lactone through rearrangement of a vinyl phosphate derived from the parent lactone resulted in both rearrangement and lactone ring opening, revealing that the farnesyl lactone was not stable to the excess of strong base required for the rearrangement. A procedure for C−P bond formation based on generation of the lactone enolate, reaction with a P(III) reagent, and oxidation was successful in providing the racemic α-phosphono lactone, in part, because only 1 equiv of strong base was required. The same strategy for phosphonate synthesis then was applied to the nonracemic farnesyl lactone, prepared through a sequence including allylation of farnesal with a nonracemic borane reagent, reaction of the product alcohol with acryloyl chloride, and formation of an unsaturated lactone through ring-closing metathesis. A similar strategy gave the corresponding racemic α-phosphono lactam through a six-step sequence from farnesal.

Introduction

α-Phosphono esters and lactones are widely used as synthetic reagents, particularly in the Horner−Wadsworth−Emmons reaction.[1] However, a second motive for study of such compounds derives from their similarity to pyrophosphate esters, compounds which are common intermediates in metabolism.[2] Formal replacement of a phosphate P−O bond with a phosphonate P−C bond is considered to increase metabolic stability while maintaining a structural display similar to that of the phosphate ester.[3] Therefore, α-phosphono acetates have been prepared and tested as inhibitors of a variety of enzymes, including farnesyl protein transferase (FPTase),[4] biotin carboxylase,[5] aspartate carbamoyltransferase,[6] DNA polymerase,[7] and squalene synthase.[8]

Ring systems are often incorporated in molecular design to restrict conformations and/or to serve as a platform for incorporation of other functional groups.[9] For example, cyclobutanones and cyclopropanes have been built on farnesyl chains to obtain potential inhibitors of squalene synthase.[10] Although a number of α-phosphono lactones have been reported, the biological activity of this class of pyrophosphate analogues remains unexplored.

Our interest in the design and synthesis of FPTase inhibitors[11] has prompted an effort to discover different replacements for the diphosphate moiety of farnesyl pyrophosphate (**1**). One such target compound would be a phosphonic acid such as compound **2a**, which presumably could be derived from the more familiar diethyl phosphonate **3a**. Compound **2a** would employ the α-phosphono lactone to mimic a pyrophosphate group, not just in position and polarity but possibly also as a potential leaving group for enzyme-catalyzed nucleophilic displacement.[12] If such enzymatic reactions were observed, the carbon chain of the lactone ring would then serve as a tether to keep the “leaving group” connected. Compounds that could function in this manner might serve as useful probes of both the FPTase mechanism and the impact of attaching modified farnesyl groups to various proteins.[13] In contrast to lactone **2a**, the corresponding lactam **2b**

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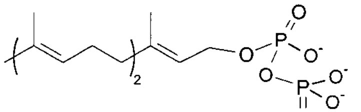
would be expected to have much greater metabolic stability, which might be of value as a control in biological investigations. Again, it is reasonable to assume that the lactam **2b** could be derived from the phosphonate ester **3b**, so the initial goal became preparation of the phosphonate esters **3a** and **3b**.



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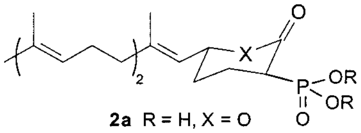
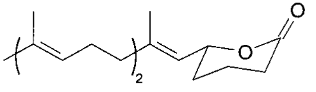


2a R = H, X = O
2b R = H, X = NH
3a R = Et, X = O
3b R = Et, X = NH



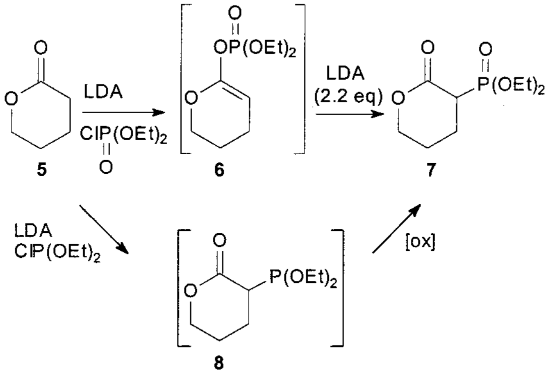
4

α-Phosphono lactones have been prepared from a variety of precursors. For example, they can be made from phosphono acetate derivatives through condensation or radical reaction to form a lactone ring[14] or via the Arbuzov reaction of an α-halo lactone and a trialkyl phosphite.[15] However, preparation of α-phosphono lactones containing the farnesyl chain (e.g., **3a**) might best be approached from the parent lactone **4** through either of two methodologies for C−P bond formation via an intermediate enolate.[16] For example, when lactone **5** was treated with LDA and the resulting enolate was trapped by reaction with diethyl phosphorochloridate, the vinyl phosphate **6** was formed. Upon exposure to LDA, this vinyl phosphate undergoes an intramolecular rearrangement to provide the α-phosphono lactone **7**. Alternatively, the lactone enolate can be trapped on carbon by reaction with diethyl phosphorochloridite, followed by oxidation of the P(III) intermediate **8** to give the α-phosphono lactone **7** (Scheme 1). To extend the potential scope of these procedures and to obtain access to the desired α-phosphono lactone derivatives of farnesol, direct phosphorylation strategies were incorporated in the planned synthesis of the α-phosphono δ-lactone **3a**. Assuming either or both of these strategies would afford the desired phosphonate, the initial synthetic target would be the δ-lactone **4**.

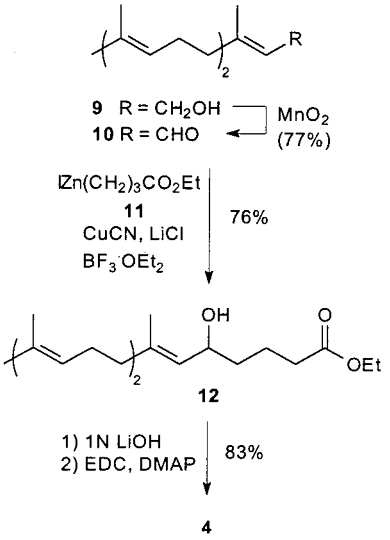
Results and Discussions

Racemic δ-lactone **4** was prepared from commercially available farnesol (**9**) as illustrated in Scheme 2. After oxidation of farnesol (**9**) with MnO_2 to provide farnesal (**10**),[17] reaction with the zinc reagent **11** under Knockel's condition afforded the δ-hydroxy ester **12**.[18] Attempts to convert this ester into the corresponding lactone through an acid-catalyzed intramolecular transesterification were unsuccessful. However, cyclization was accomplished after hydrolysis of the ester to the acid and intramolecular condensation with EDC and DMAP.

SCHEME 1



SCHEME 2



Conversion of lactone **4** into the desired phosphonate **3a** was first attempted through a vinyl phosphate−phosphonate rearrangement, and ^{31}P NMR was used to monitor the reaction. When δ-lactone **4** was treated with LDA and the resulting enolate was trapped by reaction with diethyl phosphorochloridate (Scheme 3), a chemical shift of −6 ppm clearly revealed formation of vinyl phosphate **13**. Upon exposure of this vinyl phosphate to LDA (2.2 equiv) in situ, a phosphonate obviously was formed, as shown by a chemical shift of +25 ppm. However, the ^{1}H and ^{13}C NMR spectra did not support assignment of this phosphonate as the desired rearrangement product **3a**. Instead, interpretation of ^{1}H,

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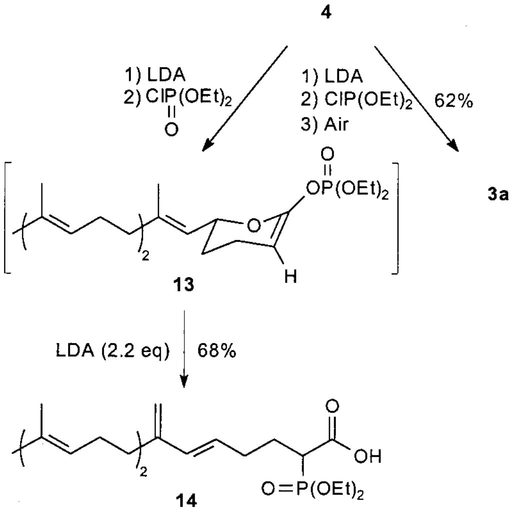
SCHEME 3

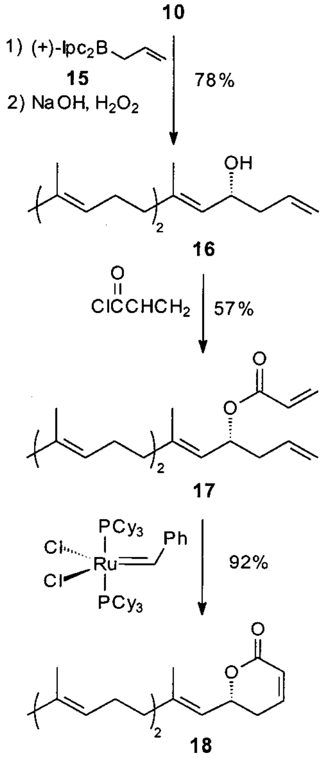


DEPT, ^{13}C, and COSY NMR experiments showed that one allylic methyl group in the farnesyl chain had been converted into a terminal methylene group. Ultimately, this compound was assigned as the α-phosphono acid **14**, a lactone ring-opened product. This result suggested that the presence of excess strong base may be problematic; that is, abstraction of an allylic proton and elimination of the carboxylate would provide this elimination product. Because rearrangement of the vinyl phosphate also had occurred, two reactions must be involved in this process, a vinyl phosphate−phosphonate rearrangement and a lactone ring opening, but the sequence of these reactions was not immediately clear (Scheme 3). It is possible that the sequence starts with abstraction of the vinyl proton of the vinyl phosphate followed by rearrangement, but this would probably require loss of the equivalent of a dianion during the subsequent elimination process. Alternatively, if the elimination takes place first, it would generate an anion where significant charge density could be placed on the α carbon, and this might induce a vinyl phosphate−phosphonate rearrangement. In this context, it is significant that rearrangement of vinyl phosphates derived from acyclic esters has substantial precedent.[16a]

Results from the attempted vinyl phosphate rearrangements demonstrated that the farnesyl lactone **4** does not tolerate an excess of strong base well. Therefore, application of the phosphonate synthesis based on use of a P(III) electrophile became attractive because this strategy requires use of just 1 equiv of strong base. When δ-lactone **4** was treated with 1.1 equiv of LDA and the resulting enolate was trapped by reaction with diethyl phosphorochloridite followed by oxidation, phosphonate **3a** was obtained in good yield (Scheme 3). The product from this sequence was a mixture of diastereomers, in part because of the earlier decision to employ racemic lactone **4**, and attempts to separate the diastereomers to two racemates by column chromatography were unsuccessful. Thus, this study of racemic lactone **4** established a procedure for conversion of the lactone into an α-phosphono lactone, but further studies of the activity of these compounds would benefit from a route to nonracemic preparations of lactone **4**.

Ring-closing metathesis (RCM) has become a well-established strategy for construction of a wide range of cyclic structures.[19] We have found that metathesis of acrylate esters derived from different terpene aldehydes could afford lactones in good yields and with excellent regioselectivities.[20] Because a nonracemic alcohol might be readily obtained from farnesal through use of a borane reagent,[21] it was envisioned that nonracemic δ-lactone **4** could be synthesized by RCM.

SCHEME 4



To explore this strategy, Brown's (+)-*B*-allyldiisopinocamphenylborane (**15**) was prepared from commercially available (+)-*B*-chlorodiisopinocamphenylborane and allylmagnesium bromide.[21] Allylboration of farnesal (**10**) with this reagent provided nonracemic alcohol **16** (Scheme 4). The stereochemistry of this addition initially was assigned by analogy to the general pattern and assuming a six membered ring transition state. Esterification of compound **16** with acryloyl chloride readily provided the acrylate **17,** which was transformed smoothly into the unsaturated lactone **18** through a metathesis reaction.

Several methods have been employed to establish the enantiomeric excess of nonracemic alcohols, including preparation of diastereomeric derivatives through reaction with a chiral reagent [22] or use of HPLC with chiral

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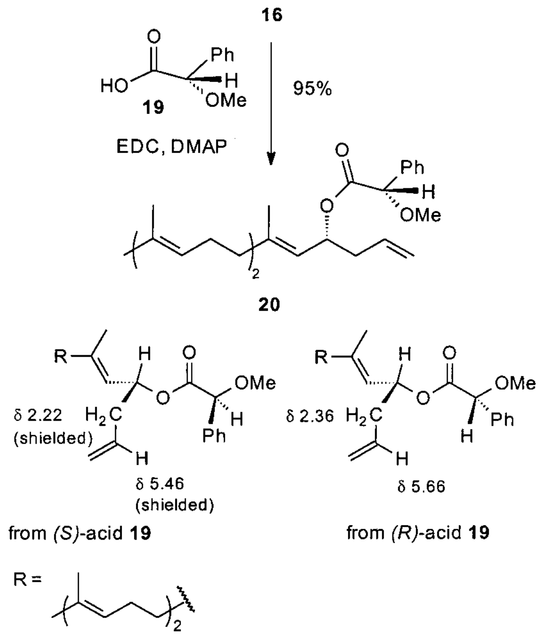
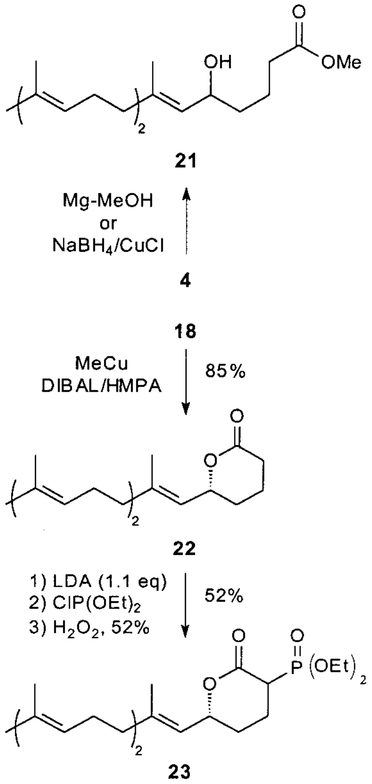
SCHEME 5



SCHEME 6



columns.[23] In this case, alcohol **16** was esterified to a mandelic acid derivative to prepare diastereomers. When racemic *O*-methylmandelic acid was used,[24] methoxy groups in the two diastereomers showed two separate ^{1}H NMR resonances in a 1:1 ratio. When the *S*-(+) acid **19** was used (Scheme 5), the ratio observed for the product ester **20** was 12:1, corresponding to an 85% ee for compound **16**. Furthermore, the ^{1}H NMR spectra of these compounds supported the initial assignment of the R stereochemistry to the major product of the allylboration reaction. In particular, with the ester derived from alcohol **16** and the *S*-(+) acid, resonances for the methylene group of the allyl unit and the adjacent vinylic hydrogen were shifted significantly upfield (from δ 5.66 to 5.46 and from δ 2.36 to 2.22, respectively) relative to the corresponding resonances observed when the nonracemic alcohol **16** was esterified with the racemic acid. According to the standard model based on extended Newman projections,[24] these shifts support assignment of the R stereochemistry to the predominant enantiomer of compound **16**.

In theory, the conjugated lactone **18** could be converted into the desired phosphonate either by conjugate addition of hydride and trapping the intermediate enolate on carbon through reaction with diethyl phosphorochloridite followed by oxidation or through stepwise conjugate reduction to give the saturated lactone followed by enolate formation, reaction with the P(III) reagent, and oxidation. Unfortunately, attempts to apply the potentially more efficient first route through reaction with Stryker's catalyst[25] or CuMe−HMPA−DIBAL[26] were unsuccessful. With respect to the second route, several reduction systems were tested, first with the racemic material (**4**) and then with nonracemic material (Scheme 6). Upon attempted reduction with Mg−MeOH[27] or with $NaBH_4$−CuCl,[28] mixtures were obtained and the ring-opened product **21** was formed, perhaps because of generation of methoxide during the course of the reactions. Successful reduction was effected upon treatment with CuMe−HMPA−DIBAL. While this appears to be the first report of conjugate reduction of a lactone under these conditions, they have been used widely for the reduction of conjugated ketones.[26]

Finally, phosphorylation of the nonracemic lactone **22** was accomplished through formation of the enolate and reaction with diethyl phosphorochloridite as described above. In this case, oxidation with H_2O_2 instead of air appeared to facilitate separation. Two diastereomers of the product **23** were obtained, presumably differing in configuration at the α carbon, and separation of these diastereomers by chromatography on silica gel columns was not readily accomplished. However, it is possible that the separated diastereomers would equilibrate given the acidity of the remaining α hydrogen, so the separation was not pursued.

An α-phosphono lactam analogous to compound **3a** also could be viewed as a farnesyl pyrophosphate analogue, albeit one where displacement would be less likely, so an extension of this approach to preparation of the

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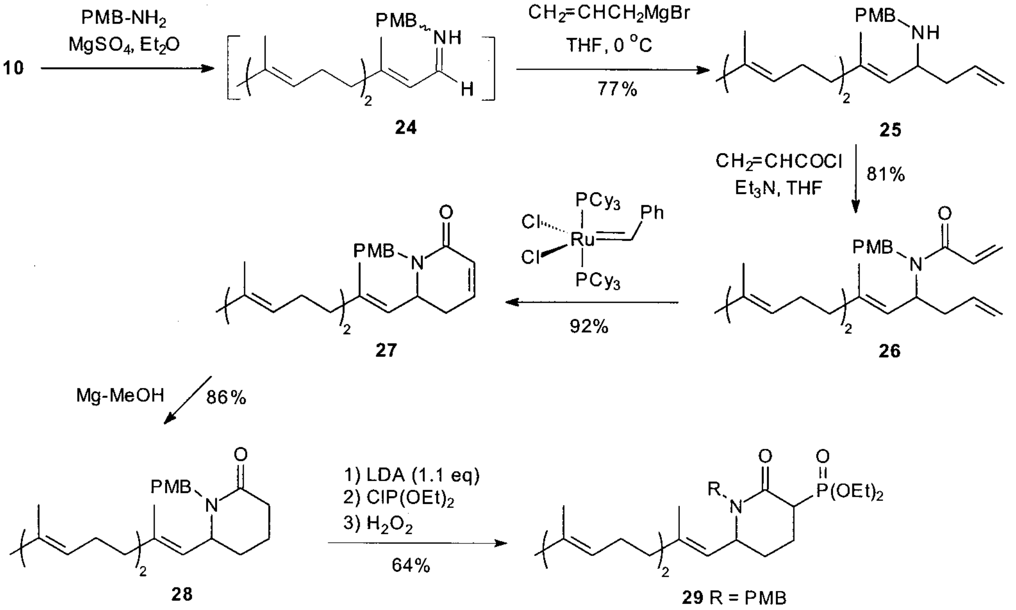
SCHEME 7



corresponding lactam was attempted. To avoid an unfavorable impact of a secondary amide group on the metathesis process,[29] a *p*-methoxybenzyl (PMB) group was incorporated as a protecting group (Scheme 7). Condensation of farnesal (**10**) with *p*-methoxybenzylamine afforded the desired imine **24**, and this intermediate was treated with allylmagnesium bromide without isolation to give the secondary amine **25**. Through a sequence parallel to that used in preparation of lactone **18**,[20] including reaction with acryloyl chloride to give the amide **26** and subsequent metathesis with Grubbs catalyst, the conjugated δ-lactam **27** was obtained in good yield. Conjugate reduction proved to be more straightforward than that with the corresponding lactone **18**, and compound **27** was reduced with Mg−MeOH at room temperature to provide the saturated lactam **28** in good yield. Phosphorylation through formation of the enolate, reaction with diethyl phosphorochloridite, and oxidation with H_2O_2 gave the desired phosphonate **29** as a mixture of diastereomers. In contrast to the difficulty encountered with the separation of the α-phosphono lactone **23**, this mixture could be separated by column chromatography into two racemic pairs. An attempt to remove the PMB group through reaction with CAN was not successful, but it is possible that more forceful conditions or other strategies[30] for this cleavage may yet afford the parent lactam.

These studies have shown that it is possible to prepare an α-phosphono lactone through reaction of the corresponding enolate with an electrophilic phosphorus(III) reagent, even in a case where the vinyl phosphate−phosphonate rearrangement is complicated by a competing elimination. A parallel set of reactions has been used to prepare an analogous α-phosphono lactam. In addition, metathesis can be used to build a nonracemic lactone from farnesal with very good regioselectivity, and conditions for regioselective reduction of the metathesis products have been found. Further studies on the biological activities of the parent phosphonic acids derived from these new phosphonates will be reported in due course.

Experimental Section

Tetrahydrofuran (THF) and diethyl ether were distilled from sodium−benzophenone immediately prior to use, while dichloromethane was freshly distilled from calcium hydride. HMPA was distilled over CaH_2 under vacuum and stored under argon until used. Lithium chloride was dried at 120 °C in vacuo (0.05 mmHg) overnight before use. All nonaqueous reactions were conducted in oven-dried glassware, under an atmosphere of argon, and with magnetic stirring. Flash chromatography was carried out on silica gel with 40 μm average particle diameter. NMR spectra were recorded at 600, 400, or 300 MHz for ^1H with $CDCl_3$ as solvent and $(CH_3)_4Si$ (^1H and ^{13}C) as internal standard unless otherwise noted. All ^{31}P NMR chemical shifts are reported in ppm relative to 85% H_3PO_4 (external standard). High resolution and electron-spray mass spectra were obtained at the University of Iowa Mass Spectrometry Facility. Elemental analyses were performed by Atlantic Microlab, Inc. (Norcross, GA).

5-Hydroxy-7,11,15-trimethyl-6*E*,10*E*,14-hexadecatrienoic Acid Ethyl Ester (12). A suspension of activated zinc dust (980 mg, 15.1 mmol) in THF (1 mL) was treated with 1,2-dibromoethane (42 μL, 0.49 mmol) and then heated gently until boiling was observed. The zinc suspension was stirred a few minutes and heated again, and this process was repeated three times. Chlorotrimethylsilane (30 μL, 0.26 mmol) in THF (0.5 mL) was added dropwise into the suspension. After 15 min, the reaction mixture was warmed to 30 °C and ethyl-4-iodobutyrate[31] (3.08 g, 12.7 mmol) in THF (7 mL) was added dropwise over 20 min. After the addition was complete, the reaction mixture was stirred for 4 h at 40 °C to dissolve most of the zinc dust and give a clear solution of the zinc reagent. This preparation was added to a stirred solution of CuCN/2LiCl, prepared in situ by dissolving CuCN (1.02 g, 11.36 mmol) and LiCl (960 mg, 22.7 mmol) in THF (8 mL) at rt, at −40 °C via cannula. The resulting solution was allowed to

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[30] For example, through reaction with TFA: Chen, P.; Barrish, J. C.; Iwanowicz, E.; Lin, J.; Bednarz, M. S.; Chen, B. C. *Tetrahedron Lett.* **2001**, *42*, 4293−4296.

[31] Bergmann, E. D.; Yaroslavsky, S. *Tetrahedron* **1960**, *11*, 154−157.

warm to 0 °C over 1 h to complete the transmetalation and then cooled to −78 °C. Boron trifluoride etherate (4.32 mL, 34.0 mmol) was added dropwise, and the reaction mixture was allowed to warm to −30 °C, stirred for 30 min at this temperature, and then cooled to −78 °C. Farnesal[17] (**10**, 2.00 g, 9.08 mmol) in THF (2 mL) was added slowly via cannula. The reaction mixture was allowed to warm to −30 °C over 1 h, stirred at this temperature for 15 h, and then stirred for 30 min at 0 °C. After the solution was diluted with ethyl acetate (100 mL), it was treated with saturated NH_4Cl. The mixture was filtered, and the organic layer was separated. The aqueous layer was extracted with ethyl acetate, and the combined organic solution was washed with 10% sodium thiosulfate (10 mL), saturated NH_4Cl, and brine, and finally dried over $MgSO_4$. After concentration in vacuo, purification of the residue by flash column chromatography over silica (hexanes/EtOAc 8:2) yielded compound **12** (2.34 g, 76%): ^{1}H NMR (400 MHz) δ 5.17 (dm, J = 8.6 Hz, 1H), 5.13−5.05 (m, 2H), 4.37 (dt, J = 8.7, 6.2 Hz, 1H), 4.12 (q, J = 7.1 Hz, 2H), 2.32 (t, J = 7.2 Hz, 2H), 2.16−1.94 (m, 8H), 1.75−1.40 (m, 16H), 1.25 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz) δ 173.6, 138.9, 135.4, 131.3, 127.6, 124.3, 123.7, 68.2, 60.2, 39.7, 39.6, 37.0, 34.2, 26.7, 26.3, 25.7, 21.0, 17.7, 16.6, 16.0, 14.2. Anal. Calcd for $C_{21}H_{36}O_3$: C, 74.95; H, 10.78. Found: C, 75.12; H, 10.74.

6-(2′,6′,10′-Trimethyl-1′*E*,5′*E*,9′-undecatrienyl)tetrahydropyran-2-one (4). To a stirred solution of compound **12** (1.00 g, 2.98 mmol) in THF (6 mL) at 0 °C was added 1 N LiOH (6.00 mL, 6.00 mmol). The mixture was stirred at this temperature for 30 min, then diluted with 20 mL of water, and washed with ether. The aqueous phase was separated, acidified with 1 N HCl to pH 3, and then extracted with ethyl acetate. The combined extracts were washed with brine and dried over $MgSO_4$. After evaporation of the solvent, a clear liquid was obtained which was dissolved in CH_2Cl_2 (30 mL) and cooled to 0 °C. 1-(3-Dimethylamino)propyl-3-ethylcarbodiimide hydrogen chloride (EDC, 860 mg, 4.47 mmol) and (dimethylamino)pyridine (DMAP, 180 mg, 1.49 mmol) were added successively. After the reaction was stirred for 10 min at this temperature, the mixture was stirred for 16 h at rt and then concentrated in vacuo. The residue was treated with ether and filtered through a pad of Celite. After evaporation of solvent, the residue was purified by flash column chromatography (hexanes/EtOAc 8:2) to furnish compound **4** (710 mg, 83%): ^{1}H NMR (400 MHz) δ 5.26 (dq, J = 8.6, 1.3 Hz, 1H), 5.13−5.00 (m, 3H), 2.65−2.41 (m, 2H), 2.16−1.81 (m, 12H), 1.71 (d, J = 1.3 Hz, 3H), 1.68 (d, J = 0.9 Hz, 3H), 1.60 (s, 6H); ^{13}C NMR δ 171.7, 141.5, 135.6, 131.4, 124.3, 123.5, 123.0, 77.4, 39.7, 39.4, 29.5, 28.6, 26.7, 26.2, 25.7, 18.6, 17.7, 16.8, 16.0. HRMS (ES) m/z: calcd for $(M + H)^+$ $C_{19}H_{31}O_2$, 291.2324; found, 291.2310.

2-(Diethoxyphosphinyl)-7-methylenyl-11,15-dimethyl-5*E*,10*E*,14-hexadecatrienoic Acid (14). To a solution of LDA (1.10 mmol) in anhyd THF (3 mL) at −78 °C was added dropwise via cannula a solution of lactone **4** (290 mg, 1.00 mmol) in THF (2 mL). After 30 min, HMPA (0.20 mL, 1.15 mmol) and diethyl phosphorochloridate (0.17 mL, 1.15 mmol) were added sequentially, and the resulting mixture was allowed to warm to rt over the course of 30 min. After the reaction mixture was cooled to −78 °C, a solution of LDA (2.2 equiv) in THF (3 mL) was added via cannula, and the reaction mixture was allowed to warm to rt over 2 h. The reaction was quenched by slow addition of a solution of acetic acid in ether (1 M, 15 mL), and the resulting mixture was filtered through a pad of Florisil. Final purification by column chromatography (silica gel, from EtOAc to EtOAc/AcOH 95:5) afforded compound **14** (290 mg, 68%): ^{1}H NMR (300 MHz) δ 11.74 (br s, 1H), 6.08 (d, J = 15.8 Hz, 1H), 5.64 (dt, J = 15.7, 6.6 Hz, 1H), 5.75−5.55 (m, 2H), 4.90 (s, 1H), 4.88 (s, 1H), 4.35−4.05 (m, 4H), 3.01 (ddd, J_{HP} = 23.1, J = 10.2, 3.7 Hz, 1H), 2.36−1.79 (m, 12H), 1.68 (s, 3H), 1.60 (s, 6H), 1.34 (t, J = 7.0 Hz, 3H), 1.33 (t, J = 7.0 Hz, 3H); ^{13}C NMR δ 171.2 (d, J_{CP} = 4.0 Hz), 145.7, 135.4, 133.9, 131.3, 127.6, 124.5, 124.2, 114.2, 63.7 (d, J_{CP} = 6.4 Hz), 63.1 (d, J_{CP} = 6.8 Hz), 45.1 (d, J_{CP} = 130.7 Hz), 39.8, 32.3, 31.4 (d, J_{CP} = 15.2 Hz), 26.9, 26.8, 26.8, 25.8, 17.8, 16.4 (d, J_{CP} = 6.6 Hz, 2C), 16.2; ^{31}P NMR +24.5 ppm. HRMS (ES) m/z: calcd for $(M + Na)^+$ $C_{23}H_{39}O_5NaP$, 449.2433; found, 449.2448.

α-(Diethoxyphosphinyl)-6-(2′,6′,10′-trimethyl-1′*E*,5′*E*,9′-undecatrienyl)tetrahydropyran-2-one (3). A solution of lactone **4** (200 mg, 0.69 mmol) in ether (1 mL) was added dropwise via cannula to a stirred solution of LDA (1.1 equiv), prepared in situ from diisopropylamine (0.11 mL, 0.76 mmol) and *n*-butyllithium in hexanes (2.50 M, 0.30 mL, 0.76 mmol), in anhyd ether (2.5 mL) at −78 °C. After 60 min, HMPA (0.13 mL, 0.76 mmol) and diethyl phosphorochloridite (0.11 mL, 0.76 mmol) were added sequentially, and the resulting mixture was allowed to warm to 0 °C over the course of 2 h. The reaction was quenched by slow addition of acetic acid in ether (1 M, 4 mL), and the resulting mixture was filtered through a pad of Celite. After concentration, the residue was stirred open to the air at rt overnight. Final purification by column chromatography (silica gel, gradient elution from hexanes/EtOAc 1:1 to EtOAc) afforded phosphonate **3** (190 mg, 62%) as a clear oil consisting of a mixture of diastereomers: ^{1}H NMR (400 MHz) δ 5.31−5.19 (m, 3H), 5.12−5.02 (m, 5H), 4.30−4.14 (m, 8H), 3.19−3.06 (m, 2H), 2.42−2.16 (m, 4H), 2.16−1.80 (m, 20 H), 1.72 (d, J = 1.0 Hz, 3H), 1.70 (d, J = 1.5 Hz, 3H), 1.68 (s, 3H), 1.68 (s, 3H), 1.60 (s, 12H), 1.39−1.32 (m, 12H); ^{31}P NMR +23.2, 22.6 ppm.

6,10,14-Trimethyl-1,5*E*,9*E*,13-pentadecatetraen-(4*R*)-4-ol (16). To a stirred suspension of (+)-*B*-chlorodiisopinocampheylborane (3.16 g, 9.88 mmol) in ether (30 mL) was added allylmagnesium bromide in ether (1 M, 9.00 mL, 9.00 mmol) dropwise at −78 °C. The mixture was allowed to warm to rt over the course of 4 h and then stirred for another 2 h. The resulting cloudy white suspension was cooled to −100 °C and treated with farnesal (**10**, 1.66 g, 7.53 mmol) in THF (15 mL). After the reaction was stirred for 4 h at this temperature, the mixture was treated with methanol (1 mL) and allowed to warm to rt. After NaOH (3 N, 7.24 mL) and H_2O_2 (30%, 2.98 mL) were added, the resulting mixture was heated at reflux for 1 h. The organic phase was separated and washed with water (5 mL) and brine (5 mL) and then dried over $MgSO_4$. After concentration in vacuo, purification of the residue by flash chromatography on silica gel (hexanes to hexanes/EtOAc 9:1) afforded the alcohol **16** as a clear oil (1.55 g, 78%): $[\alpha]^{22}_{D}$ = −8.4 (c 1.15, EtOH); both ^{1}H and ^{13}C NMR spectra matched those of racemic **16.**[32]

2-Propenoic Acid, 3,7,11-Trimethyl-(1*R*)-1-(2-propenyl)-2*E*,6*E*,10-dodecatrienyl Ester (17). To a solution of alcohol **16** (1.00 g, 3.81 mmol) and triethylamine (1.59 mL, 11.4 mmol) in THF (25 mL) at 0 °C was added acryloyl chloride (0.62 mL, 7.62 mmol) dropwise. The resulting mixture was stirred at rt overnight and then treated with saturated NH_4Cl (15 mL). Extraction with ether, concentration of the combined extracts in vacuo, and purification by flash chromatography on silica gel (hexanes/EtOAc from 1:0 to 9:1) afforded acrylate ester **17** (690 mg, 57%): $[\alpha]^{25}_{D}$ = +15.6 (c 1.41, $CHCl_3$); ^{1}H NMR (400 MHz) δ 6.37 (dd, J = 17.4, 1.4 Hz, 1H), 6.09 (dd, J = 17.3, 10.6 Hz, 1H), 5.78 (dd, J = 10.3, 1.6 Hz, 1H), 5.80−5.67 (m, 1H), 5.62 (dt, J = 9.0, 6.6 Hz, 1H), 5.19−5.14 (m, 1H), 5.12−5.02 (m, 4H), 2.47−2.30 (m, 2H), 2.15−1.93 (m, 8H), 1.74 (d, J = 1.4 Hz, 3H), 1.68 (d, J = 1.0 Hz, 3H), 1.61−1.58 (m, 6H); ^{13}C NMR (100 MHz) δ 165.6, 140.9, 135.4, 133.4, 131.3, 130.2, 129.0, 124.3, 123.6, 122.8, 117.7, 70.9, 39.7, 39.5, 39.5, 26.7, 26.2, 25.7, 17.7, 16.9, 16.0. Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.90; H, 10.21.

(6*R*)-6-(2,6,10-Trimethyl-1*E*,5*E*,9-undecatrienyl)-5,6-dihydro-2*H*-pyran-2-one (18). To a solution of compound **17** (380 mg, 1.23 mmol) in CH_2Cl_2 (125 mL) at reflux was added dropwise a solution of Grubbs' ruthenium catalyst (100 mg,

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[32] Mechelke, M. M. Ph.D. Thesis, University of Iowa, Iowa City, IA, 1999.

0.12 mmol) in CH_2Cl_2 (5 mL) over the course of 30 min. The resulting mixture was stirred under reflux for 2 h and allowed to cool to rt, and then, DMSO (0.44 mL) was added. After the resulting mixture was stirred at rt for 18 h, concentration in vacuo and purification of the residue by flash chromatography on silica gel (hexanes/EtOAc 8:2) yielded lactone **18** (318 mg, 92%): $[\alpha]^{32}_D = +34.0$ (c 1.54, $CHCl_3$); ^1H NMR (400 MHz) δ 6.88 (ddd, $J = 9.8, 5.3, 3.2$ Hz, 1H), 6.04 (ddd, $J = 9.8, 2.0, 1.4$ Hz, 1H), 5.36 (dq, $J = 8.6, 1.2$ Hz, 1H), 5.16 (ddd, $J = 9.9, 8.6, 5.2$ Hz, 1H), 5.12−5.05 (m, 2H), 2.46−2.30 (m, 2H), 2.17−1.94 (m, 8H), 1.73 (d, $J = 1.3$ Hz, 3H), 1.68 (d, $J = 0.8$ Hz, 3H), 1.60 (s, 6H); ^{13}C NMR (100 MHz) δ 164.5, 144.9, 142.8, 135.7, 131.4, 124.3, 123.4, 121.8, 121.7, 74.9, 39.7, 39.4, 30.0, 26.7, 26.1, 25.7, 17.7, 16.9, 16.0. HRMS (ES) m/z: calcd for $(M + Na)^+$ $C_{19}H_{28}O_2Na$, 311.1987; found, 311.1983.

(*S*)-Methoxyphenylacetic Acid, 3,7,11-Trimethyl-(1*R*)-1-(2-propenyl)-2*E*,6*E*,10-dodecatrienyl Ester (20). To a mixture of alcohol **16** (76 mg, 0.29 mmol), EDC (83 mg, 0.44 mmol), and DMAP (18 mg, 0.15 mmol) in THF (5 mL) was added (*S*)-methoxyphenylacetic acid (**19**, 63 mg, 0.38 mmol), and the mixture was stirred at rt. After 28 h, ether (20 mL) was added and the resulting mixture was filtered and washed with brine. The organic phase was dried over $MgSO_4$, filtered, and concentrated to provide a clear oil. Purification by flash column chromatography (hexanes/EtOAc 95:5) gave compound **20** (113 mg, 95%): ^1H NMR (600 MHz, relaxation delay 30 s) δ 7.45−7.39 (m, 2H), 7.37−7.28 (m, 3H), 5.58 (dt, $J = 9.0, 6.5$ Hz, 1H), 5.51−5.39 (m, 1H), 5.17−4.98 (m, 3H), 4.88−4.84 (m, 1H), 4.84−4.81 (m, 1H), 4.71 (s, 1H), 3.39 (s, 3H), 2.29−2.14 (m, 2H), 2.12−1.90 (m, 8H), 1.70−1.67 (m, 6H), 1.60 (s, 3H), 1.59 (s, 3H); ^{13}C NMR (100 MHz) δ 170.0, 141.6, 136.5, 135.4, 132.8, 131.3, 128.6, 128.5 (2C), 127.3 (2C), 124.3, 123.6, 122.4, 117.7, 82.6, 71.5, 57.2, 39.7, 39.5, 39.2, 26.7, 26.2, 25.7, 17.7, 16.9, 16.0. HRMS (ES) m/z: calcd for $(M + Na)^+$ $C_{27}H_{38}O_3Na$, 433.2719; found, 433.2733.

5-Hydroxy-7,11,15-trimethyl-6*E*,10*E*,14-hexadecatrienoic Acid Methyl Ester (21). Lactone **4** (200 mg, 0.69 mmol) in anhyd MeOH (6 mL) was added to stirred magnesium turnings (170 mg, 7.08 mmol). The mixture was stirred at rt for 3 h until disappearance of the UV spot for the starting material was noted upon TLC analysis. A solution of AcOH in ether (1 N, 25 mL) was added to quench the reaction, and ether (15 mL) was used to dilute the mixture. After filtration, the organic solution was concentrated in vacuo. Final purification by column chromatography (silica gel, hexanes/EtOAc 8:2) gave ester **21** (50 mg, 22%) as a clear oil: ^1H NMR (300 MHz) δ 5.16 (d, $J = 9.0$ Hz, 1H), 5.13−5.04 (m, 2H), 4.36 (dt, $J = 8.8, 6.3$ Hz, 1H), 3.66 (s, 3H), 2.34 (t, $J = 7.1$ Hz, 2H), 2.16−1.91 (m, 8H), 1.76−1.40 (m, 4H), 1.68 (s, 6H), 1.59 (s, 6H). HRMS (EI) m/z: calcd for $(M - H_2O)^+$ $C_{20}H_{32}O_2$, 304.2402; found, 304.2400.

(6*R*)-6-(2′,6′,10′-Trimethyl-1′*E*,5′*E*,9′-undecatrienyl)tetrahydropyran-2-one (22). To a stirred slurry of CuI (28 mg, 0.15 mmol) in THF (10 mL) at −55 °C was added MeLi (1.4 M, 0.11 mL, 0.16 mmol). After the reaction was stirred for 10 min, the mixture was treated with HMPA (0.39 mL, 2.24 mmol) and DIBAL (1 M in hexanes, 1.64 mL, 1.64 mmol) sequentially. The resulting mixture was stirred at this temperature for another 30 min, and then lactone **18** (430 mg, 1.49 mmol) in THF (2 mL) was added via cannula. After the resulting mixture was stirred at −55 °C for 20 h, HCl (1 N, 1.50 mL) was added and the mixture was extracted with ether. After standard workup, final purification by column chromatography (silica gel, hexanes/EtOAc 8:2) gave lactone **22** (360 mg, 84%) as a clear oil: $[\alpha]^{24}_D = -48.0$ (c 1.82, $CHCl_3$); both ^1H and ^{13}C NMR spectra matched those of the racemic compound **4**.

α-(Diethoxyphosphinyl)-(6*R*)-6-(2′,6′,10′-trimethyl-1′*E*,5′*E*,9′-undecatrienyl)tetrahydropyran-2-one (23). Lactone **22** (358 mg, 1.23 mmol) was treated with LDA and diethyl phosphorochloridite as described for preparation of compound **3**. The resulting intermediate was then oxidized by treatment with excess H_2O_2 (30%) at −10 °C for 10 min. The organic phase was separated, washed with brine, and dried over $MgSO_4$. After concentration in vacuo, final purification by column chromatography (silica gel, hexanes/EtOAc 1:1 to EtOAc) gave phosphonate **23** (270 mg, 52%) as a clear oil: ^1H NMR and ^{31}P NMR spectra were consistent with those of compound **3**; ^{13}C NMR δ 166.9 (d, $J_{CP} = 4.2$ Hz), 166.7 (d, $J_{CP} = 4.4$ Hz), 142.4, 141.9, 135.6, 135.6, 131.4 (2C), 124.3 (2C), 123.5, 123.4, 122.5, 122.4, 78.0, 77.5, 63.6 (d, $J_{CP} = 6.9$ Hz), 63.3 (d, $J_{CP} = 6.9$ Hz), 62.7 (d, $J_{CP} = 7.6$ Hz), 62.6 (d, $J_{CP} = 6.9$ Hz), 39.8 (d, $J_{CP} = 135.9$ Hz), 39.7 (2C), 39.4, 39.4, 39.3 (d, $J_{CP} = 138.2$ Hz), 28.3 (d, $J_{CP} = 7.4$ Hz), 26.7 (2C), 26.7 (d, $J_{CP} = 5.4$ Hz), 26.2, 26.1, 25.7 (2C), 20.8 (d, $J_{CP} = 4.5$ Hz), 20.7 (d, $J_{CP} = 4.5$ Hz), 17.7 (s, 2C), 16.9, 16.8, 16.4 (d, $J_{CP} = 6.4$ Hz), 16.4 (d, $J_{CP} = 6.0$ Hz), 16.4 (d, $J_{CP} = 6.4$ Hz), 16.4 (d, $J_{CP} = 6.0$ Hz), 16.0 (2C). HRMS (ES) m/z: calcd for $(M + H)^+$ $C_{23}H_{40}O_5P$, 427.2613; found, 427.2610.

***N*-[3,7,11-Trimethyl-1-(2-propenyl)-2*E*,6*E*,10-dodecatrienyl]-4-methoxybenzylamine (25).** To a suspension of $MgSO_4$ (3.00 g, dried at 130 °C at 0.1 mmHg for 4 h prior to use) and farnesal (**10**, 685 mg, 3.11 mmol) in ether (20 mL) was added 4-methoxybenzylamine (0.44 mL, 3.26 mmol) at 0 °C. The resulting mixture was stirred at this temperature for 2 h and then was filtered and concentrated in vacuo. The residue was dissolved in THF (15 mL), cooled to −40 °C, and then treated with allylmagnesium bromide in ether (1 M, 13 mL). The resulting mixture was stirred for 1 h at −40 °C and then for 2.5 h at −25 °C and then was quenched by addition of saturated NH_4Cl (10 mL). Extraction with ether, concentration of the combined extracts in vacuo, and purification of the residue by flash chromatography (CH_3CN and then MeOH) gave the secondary amine **25** (912 mg, 77%): ^1H NMR (400 MHz) δ 7.19 (dm, $J = 8.6$ Hz, 2H), 6.84 (dm, $J = 8.7$ Hz, 2H), 5.80−5.67 (m, 1H), 5.17−4.98 (m, 5H), 3.78 (s, 3H), 3.74 (d, $J = 13.0$ Hz, 1H), 3.56 (d, $J = 13.0$ Hz, 1H), 3.37 (dt, $J = 9.1, 6.6$ Hz, 1H), 2.26−2.02 (m, 8H), 2.01−1.94 (m, 2H), 1.67 (d, $J = 0.9$ Hz, 3H), 1.61 (s, 3H), 1.59 (s, 3H), 1.58 (s, 3H), 1.47 (br s, 1H); ^{13}C NMR (100 MHz) δ 158.4, 137.4, 135.6, 135.1, 133.0, 131.2, 129.2 (2C), 128.0, 124.3, 124.0, 116.9, 113.7 (2C), 55.2, 54.2, 50.6, 40.7, 39.7 (2C), 26.7, 26.4, 25.7, 17.6, 16.7, 16.0. Anal. Calcd for $C_{26}H_{39}NO$: C, 81.84; H, 10.30; N, 3.67. Found: C, 81.43; H, 10.31; N, 3.74.

***N*-[4-Methoxybenzyl]-*N*-[3,7,11-trimethyl-1-(2-propenyl)-2*E*,6*E*,10-dodecatrienyl]-2-propenamide (26).** According to the procedure described above for compound **17**, the secondary amine **25** (862 mg, 2.26 mmol) was treated with triethylamine (0.94 mL, 6.78 mmol) and acryloyl chloride (0.37 mL, 4.52 mmol). Standard workup and purification of the resulting oil by flash chromatography (hexanes/EtOAc from 9:1 to 85:15) gave amide **26** (790 mg, 81%) as a mixture of rotamers: ^1H NMR (400 MHz, 50 °C) δ 7.09 (br s, 2H), 6.81 (d, $J = 8.6$ Hz, 2H), 6.40−6.30 (m, 2H), 5.76−5.50 (br m, 2H), 5.46−5.25 (m, 1H), 5.16−4.93 (m, 5H), 4.48 (br s, 2H), 3.37 (s, 3H), 2.44−2.28 (br s, 1H), 2.26−2.16 (m, 1H), 2.08−1.88 (m, 8H), 1.67 (d, $J = 1.0$ Hz, 3H), 1.58 (s, 3H), 1.63 (br s, 3H), 1.55 (s, 3H); ^{13}C NMR (100 MHz, 25 °C, for the major rotamer) δ 166.5, 158.6, 141.5, 135.2, 134.9, 131.3, 130.4, 128.5, 128.3, 127.3 (2C), 124.2, 123.8, 122.5, 117.0, 113.8 (2C), 55.2, 51.7, 46.7, 39.7, 39.4, 38.6, 26.7, 26.2, 25.7, 17.7, 17.2, 16.0. Anal. Calcd for $C_{29}H_{41}NO_2$: C, 79.95; H, 9.49; N, 3.22. Found: C, 79.83; H, 9.59; N, 3.43.

1-(4-Methoxybenzyl)-6-(2,6,10-trimethyl-1*E*,5*E*,9-undecatrienyl)-5,6-dihydro-2(1*H*)-pyridinone (27). According to the procedure described above for compound **18**, acrylamide **26** (384 mg, 0.88 mmol) in CH_2Cl_2 (85 mL) was treated with Grubbs' ruthenium catalyst (73 mg, 0.088 mmol) for 1 h to obtain lactam **27** (331 mg, 92%): ^1H NMR (600 MHz) δ 7.18 (m, 2H), 6.84 (m, 2H), 6.43 (ddd, $J = 9.8, 5.4, 2.9$ Hz, 1H), 6.00 (dd, $J = 9.8, 1.8$ Hz, 1H), 5.36 (dd, $J = 9.8, 1.0$ Hz, 1H), 5.29 (d, $J = 14.8$ Hz, 1H), 5.12−5.04 (m, 2H), 4.12 (ddd, $J = 9.7, 7.0, 3.6$ Hz, 1H), 3.79 (s, 3H), 3.69 (d, $J = 14.8$ Hz, 1H), 2.55 (ddt, $J = 17.8, 6.8, 2.9$ Hz, 1H), 2.14 (dt, $J = 17.9, 4.3$ Hz, 1H), 2.11−1.94 (m, 8H), 1.68 (d, J = 0.6 Hz, 3H), 1.60 (s, 3H), 1.60 (s, 3H), 1.52 (d, J = 1.2 Hz, 3H); ^{13}C NMR δ 164.1, 158.7, 138.8, 137.4, 135.4, 131.3, 130.2, 129.2 (2C), 125.0, 124.2, 123.4, 123.1, 113.8 (2C), 55.2, 51.6, 46.1, 39.6, 39.3, 30.5, 26.7, 26.1, 25.6, 17.6, 16.2, 16.0. HRMS (ES) m/z: calcd for (M + H)$^+$ $C_{27}H_{38}NO_2$, 408.2902; found, 408.2901.

1-(4-Methoxyphenylmethyl)-6-(2,6,10-trimethyl-1*E*,5*E*,9-undecatrienyl)piperidin-2-one (28). Lactam **27** (289 mg, 0.71 mmol) in anhyd MeOH (7 mL) was added to stirred magnesium turnings (170 mg, 7.08 mmol). The resulting mixture was stirred at rt for 100 min until disappearance of starting material was noted on TLC analysis. After HCl (1 N, 10 mL) was added to quench the reaction, ether was used to extract the aqueous solution. The combined organic solution was washed with saturated $NaHCO_3$ and then with brine and finally dried over $MgSO_4$. Standard workup and final purification by column chromatography (silica gel, hexanes/EtOAc 7:3) gave the lactam **28** (252 mg, 86%) as a clear oil: ^{1}H NMR (300 MHz) δ 7.13 (m, 2H), 6.82 (m, 2H), 5.34 (d, J = 14.6 Hz, 1H), 5.16 (dq, J = 9.4, 1.2 Hz, 1H), 5.13−5.03 (m, 2H), 4.07−3.92 (m, 1H), 3.79 (s, 3H), 3.60 (d, J = 14.4 Hz, 1H), 2.47 (t, J = 6.5 Hz, 2H), 2.20−1.55 (m, 12H), 1.68 (d, J = 0.9 Hz, 3H), 1.62 (d, J = 0.9 Hz, 3H), 1.59 (s, 3H), 1.51 (d, J = 1.3 Hz, 3H); ^{13}C NMR (75 MHz) δ 170.0, 158.7, 138.4, 135.5, 131.4, 130.0, 129.4 (2C), 125.6, 124.2, 123.6, 113.8 (2C), 55.2, 53.4, 46.2, 39.8, 39.5, 32.6, 29.9, 26.7, 26.1, 25.7, 18.4, 17.7, 16.2, 16.1. HRMS (ES) m/z: calcd for (M + H)$^+$ $C_{27}H_{40}NO_2$, 410.3059; found, 410.3046.

α-(Diethoxyphosphinyl)-1-(4-methoxyphenylmethyl)-6-(2,6,10-trimethyl-1*E*,5*E*,9-undecatrienyl)piperidin-2-one (29). According to the procedure described above for preparation of compound **23**, lactam **28** (217 mg, 0.53 mmol) was treated with LDA (1.1 equiv), with diethyl phosphorochloridite, and then with H_2O_2. Standard workup and purification by column chromatography (silica gel, hexanes/EtOAc 1:1 to EtOAc) gave phosphonate **29** (184 mg, 64%) as a clear oil consisting of a 1:1 mixture of diastereomers along with some recovered compound **28** (0.03 g or 74% yield based on recovered starting material). Anal. Calcd for $C_{31}H_{48}NO_5P$: C, 68.23; H, 8.87; N, 2.57. Found: C, 67.97; H, 8.91; N, 2.62.

A second column chromatography experiment gave the two individual diastereomers as the less polar compound **29a** and the more polar compound **29b** on TLC (EtOAc).

29a: ^{1}H NMR (400 MHz) δ 7.16 (dm, J = 8.6 Hz, 2H), 6.83 (dm, J = 8.8 Hz, 2H), 5.42 (d, J = 14.8 Hz, 1H), 5.13 (dd, J = 9.6, 1.2 Hz, 1H), 5.12−5.06 (m, 2H), 4.36−4.12 (m, 4H), 4.02 (dt, J = 9.3, 5.1 Hz, 1H), 3.78 (s, 3H), 3.69 (d, J = 14.9 Hz, 1H), 3.06 (dt, J_{HP} = 26.5 Hz, J = 5.4 Hz, 1H), 2.22−1.94 (m, 11H), 1.67 (d, J = 0.8 Hz, 3H), 1.61 (d, J = 0.6 Hz, 3H), 1.58−1.50 (m, 1H), 1.60 (s, 3H), 1.46 (d, J = 1.3 Hz, 3H), 1.37 (t, J = 7.1 Hz, 3H), 1.34 (t, J = 7.1 Hz, 3H); ^{13}C NMR δ 165.2 (d, J_{CP} = 5.7 Hz), 158.7, 139.0, 135.6, 131.4, 129.4, 129.1 (2C), 124.9, 124.2, 123.5, 113.8 (2C), 62.8 (d, J_{CP} = 5.7 Hz), 62.1 (d, J_{CP} = 6.9 Hz), 55.2, 53.4, 46.4, 41.8 (d, J_{CP} = 135.2 Hz), 39.8, 39.5, 27.7 (d, J_{CP} = 7.1 Hz), 26.7, 26.1, 25.7, 20.2 (d, J_{CP} = 4.6 Hz), 17.7, 16.5 (d, J_{CP} = 6.1 Hz), 16.4 (d, J_{CP} = 6.0 Hz), 16.2, 16.1; ^{31}P NMR +26.1 ppm.

29b: ^{1}H NMR (400 MHz) δ 7.14 (dm, J = 8.6 Hz, 2H), 6.82 (dm, J = 8.7 Hz, 2H), 5.28 (d, J = 14.4 Hz, 1H), 5.29−5.24 (m, 1H), 5.12−5.06 (m, 2H), 4.36−4.14 (m, 4H), 4.02 (dt, J = 9.4, 5.3 Hz, 1H), 3.78 (s, 3H), 3.75 (dd, J = 14.6, 1.6 Hz, 1H), 3.08 (dt, J_{HP} = 26.8 Hz, J = 7.5 Hz, 1H), 2.34−1.70 (m, 12H), 1.67 (d, J = 0.4 Hz, 3H), 1.61 (s, 3H), 1.59 (s, 3H), 1.53 (d, J = 1.3 Hz, 3H), 1.36 (t, J = 7.0 Hz, 3H), 1.36 (t, J = 7.0 Hz, 3H); ^{13}C NMR δ 165.1 (d, J_{CP} = 4.9 Hz), 158.8, 138.9, 135.5, 131.4, 129.7, 129.5 (2C), 125.0, 124.3, 123.6, 113.8 (2C), 62.9 (d, J_{CP} = 6.7 Hz), 62.0 (d, J_{CP} = 6.6 Hz), 55.2, 53.6, 47.0, 41.9 (d, J_{CP} = 138.5 Hz), 39.8, 39.5, 28.2 (d, J_{CP} = 9.4 Hz), 26.8, 26.3, 25.7, 20.4 (d, J_{CP} = 4.2 Hz), 17.7, 16.5 (d, J_{CP} = 6.2 Hz), 16.4 (d, J_{CP} = 6.3 Hz), 16.2, 16.1; ^{31}P NMR +25.6 ppm.

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Supporting Information Available: ^{1}H and/or ^{13}C NMR spectra for compounds **4**, **14**, **18**, **20**, **21**, **23**, **27**, and **28**. This material is available free of charge via the Internet at http://pubs.acs.org.

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