JOC Article

Preparation of α-Phosphono Lactams via Electrophilic Phosphorus Reagents: An Application in the Synthesis of Lactam-Based Farnesyl Transferase Inhibitors

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Conversion of *N*-alkyl lactams to the corresponding α-phosphono lactams has been investigated through procedures that involve formation of the lactam enolate and reaction with a phosphorus electrophile. With *N*-octylpyrrolidinone, the enolate could be trapped efficiently on oxygen by reaction with diethyl phosphorochloridate, and the resulting vinyl phosphate rearranges smoothly to the desired phosphonate upon treatment with additional LDA. Attempts to apply the same protocol to *N*-farnesyl lactams met with limited success. Studies with an isolated α-phosphono *N*-farnesyl lactam have shown that the farnesyl group is not stable to the excess of strong base required for rearrangement of a vinyl phosphate. However, a series of *N*-farnesyl lactams and imides was converted to the desired phosphonates through formation of the lactam enolate, reaction with diethyl phosphorochloridite, and subsequent oxidation of the phosphorus intermediate to the P(V) state.

α-Phosphono lactams and amides are widely used as synthetic reagents, particularly in the Horner−Wadsworth−Emmons (HWE) reaction.[1] They also attract interest for their potential biological activity because they can serve as surrogates for diphosphate esters and carbamyl phosphate groups, which are important metabolic intermediates.[2] Formal replacement of a P−O bond with a P−C bond is considered to increase metabolic stability.[3] For this reason, various α-phosphono amides have been prepared and tested as inhibitors of farnesyl protein transferase (FPTase)[2a] or geranylgeranyl protein transferase,[4] as a transition-state analogue for aspartate transcarbamylase,[5] and for their toxicity to herpes viruses.[6]

With our interest in the design and synthesis of FPTase inhibitors,[7] we were particularly interested in defining a new bioisoteric replacement for the diphosphate moiety of farnesyl pyrophosphate. FPTase is a zinc metalloenzyme, and it has been shown in some inhibitor design studies that compounds with zinc ligands, hydrogen-bonding potential, and a hydrophobic group are important for their activities.[8] For these reasons, the α-phosphono lactam structure was of new interest to us. On one hand, such structures would employ an α-phosphono amide group to mimic the pyrophosphate group, and on the other hand, incorporation of a ring structure would fix part of the molecular geometry and serve as a template to carry other functional groups.

α-Phosphono lactams can be synthesized from a variety of precursors. Most frequently they have been prepared from (diethoxyphosphinyl)acetic acid derivatives through intramolecular amidation to form a lactam ring.[9] The Arbuzov reaction, in which an α-halolactam is treated with a trialkyl phosphite, also has been used quite often.[10] Both copper(I)-mediated coupling[11] and rhodium(II)-catalyzed C−H insertion[12] have been reported as well.

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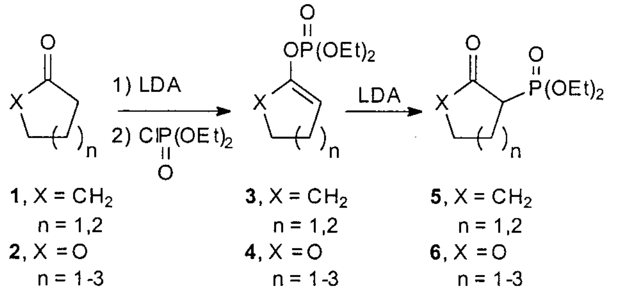
[10] (a) For *N*,*N*-dimethylglycine anhydride, cf.: Burger, K.; Heistracher, E.; Simmerl, R.; Eggersdorfer, M. *Z. Naturforsch., B* **1992**, *47*, 424−433. (b) Chai, C. L. L.; King, A. R. *J. Chem. Res., Miniprint* **1997**, *11*, 2347−2357. (c) For imides, cf: Meanwell, N. A.; Roth, H. R.; Smith, E. C. R.; Wedding, D. L.; Wright, J. J. K. *J. Org. Chem.* **1991**, *56*, 6897−6904. For other α-halo lactams, cf.: (d) Schickli, C. P.; Seebach, D. *Liebigs Ann. Chem.* **1991**, *7*, 655−668. (e) Worley, J. W.; Ratts, K. W.; Cammack, K. L. *J. Org. Chem.* **1975**, *40*, 1731−1734.

10.1021/jo020119l CCC: $22.00

SCHEME 1

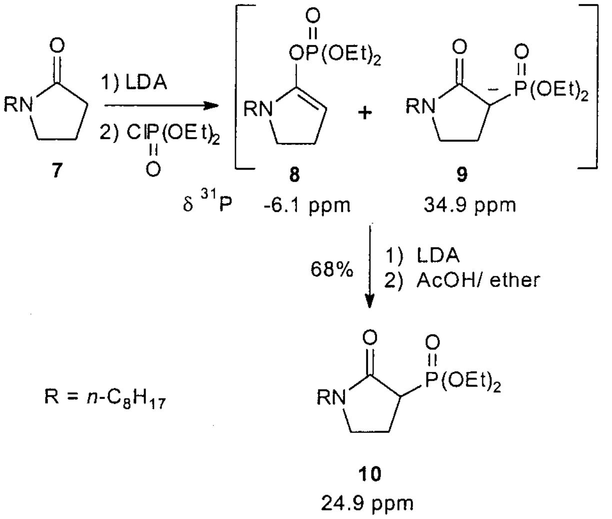


However, for our purposes it appeared more efficient to begin with the core lactam structure and add farnesyl and phosphonyl groups in turn. However, there are fewer known methods that proceed directly from a lactam to an α-phosphono lactam.[13]

For some years we have been interested in the rearrangement of vinyl phosphates to phosphonates (Scheme 1).[14] When the cyclic ketone **1** or the lactone **2** was treated with LDA and the resulting enolate was trapped by reaction with diethyl phosphorochloridate, a vinyl phosphate (**3** or **4**) was formed in good yield. Upon exposure to LDA, these vinyl phosphates rearrange through an intramolecular migration of the diethyl phosphoryl group from oxygen to the α-carbon to provide the keto phosphonate **5** and the α-phosphono lactone **6**, respectively. We postulated that an *N*-alkyl lactam might undergo a similar rearrangement to afford an α-phosphono lactam.

To test the viability of a rearrangement in an *N*-alkyl lactam, commercially available *n*-octylpyrrolidinone (**7**) was selected. After treatment with LDA and subsequent addition of diethyl phosphorochloridate, the ^{31}P NMR spectrum of the reaction mixture showed the presence of the vinyl phosphate **8** and the α-phosphono lactam anion **9** in a 3:1 ratio. Without isolation, this mixture was exposed to additional LDA to give the α-phosphono lactam **10** as the only product after standard workup (Scheme 2).

SCHEME 2



Encouraged by the success of this model reaction, preparation of a series of *N*-farnesyl lactams with different ring sizes and functional groups became the next goal. It has been well documented that alkylation of a primary amide can be realized by reaction of a nitrogen anion with an electrophile such as farnesyl bromide (**11**) or an activated derivative of farnesol (**12**), and many lactams (e.g., **13**−**20**) appropriate for this reaction are readily available (Table 1).[15] Thus, lactams **13**−**16** were treated with potassium *tert*-butoxide in the presence of 18-crown-6, followed by reaction with farnesyl bromide (**11**) to give the *N*-farnesyl lactams **21**−**24** in good yields (Table 1).

When these reaction conditions were applied to lactams **17**−**20**, none of the desired products were formed. In the case of compound **17**, farnesyl *tert*-butyl ether was formed as the only product, suggesting that a stronger base and/or more polar solvent would be needed to make the nitrogen anion more nucleophilic.[16] When compound **17** was treated with NaH and farnesyl bromide in DMF, the desired product **25** was obtained in 80% yield.

With the first imide, compound **18**, attempted reaction with potassium *tert*-butoxide and farnesyl bromide gave only recovered imide. When this reaction was conducted in DMF with K_2CO_3 and 18-crown-6 at elevated temperature, the desired product **26** was formed in just 16% yield. This low yield may result from diminished negative charge on nitrogen due to the more extensive delocalization. However, this delocalization also contributes to increased acidity of the parent imide, which made it possible to employ a Mitsunobu reaction.[17] Under general Mitsunobu conditions, farnesol (**12**) reacted with succinimide (**18**) to afford the desired product **26** in 85% yield. Through similar reactions, the imide derivatives **27** and **28** were synthesized in moderate to good yields from imides **19** and **20**.

With this series of *N*-farnesyl compounds in hand, attention was turned to their use in the synthesis of the corresponding phosphonates. Given the successful rearrangement of the vinyl phosphate **8**, the same approach was applied to lactams **22** and **23** with HMPA added to aid in formation of the vinyl phosphate[14b] as well as to serve as an internal standard for monitoring the reaction process by ^{31}P NMR. On the basis of the NMR analysis, the vinyl phosphates **29** and **30** were formed in ratios of 0.26:1 and 0.60:1 relative to the HMPA (Scheme 3), which

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(12) Okada, Y.; Minami, T.; Miyamoto, M.; Otaguro, T.; Sawasaki, S.; Ichikawa, J. *Heteroat. Chem.* **1995**, *6*, 195−210.

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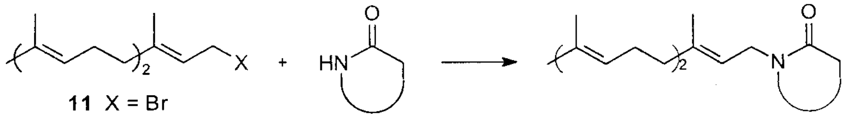
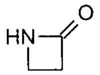
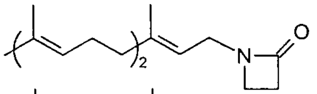
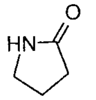
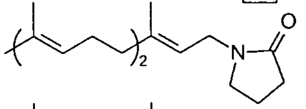
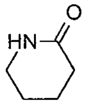
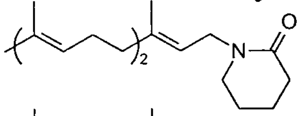
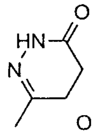
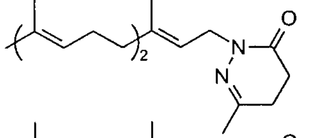
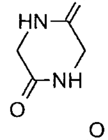
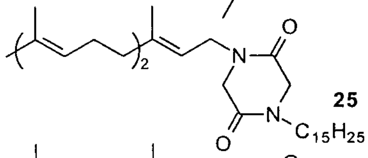
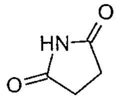
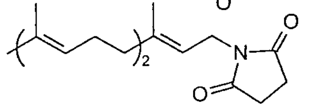
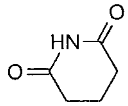
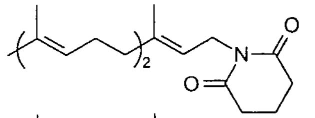
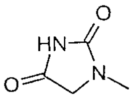
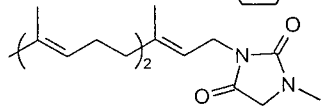
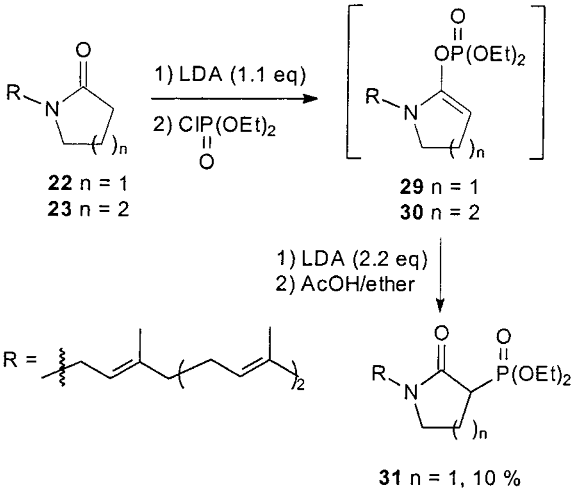
TABLE 1. Synthesis of *N*-Farnesyl Lactams



11 X = Br
12 X = OH
13-20
21-28

X	Lactam	Reaction Conditions	*N*-Farnesyl Lactams	Yield
Br	 **13**	KO^{t}Bu, 18-Cr-6	 **21**	52%
Br	 **14**	KO^{t}Bu, 18-Cr-6	 **22**	86%
Br	 **15**	KO^{t}Bu, 18-Cr-6	 **23**	76%
Br	 **16**	KO^{t}Bu, 18-Cr-6	 **24**	87%
Br	 **17**	NaH, DMF	 **25**	80%
OH	 **18**	DEAD, PPh$_3$	 **26**	85%
OH	 **19**	DEAD, PPh$_3$	 **27**	57%
OH	 **20**	DEAD, PPh$_3$	 **28**	75%

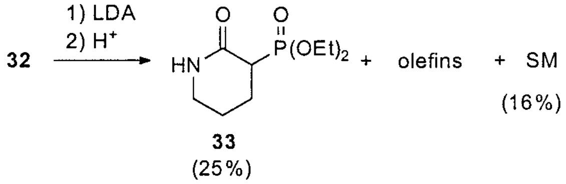
SCHEME 3



22 n = 1
23 n = 2
29 n = 1
30 n = 2
31 n = 1, 10 %
32 n = 2, 32%

are not as high as observed with the corresponding lactone substrates.[14b] Separate treatment of each of these reaction mixtures with additional LDA (2.2 equiv) led to consumption of the vinyl phosphates on the basis of ^{31}P NMR and formation of the phosphonates **31** and **32** albeit in low yields.

SCHEME 4



33
(25%)

TLC analysis of the reaction mixtures indicated that olefins were formed in the second step of every trial. This suggests that intermediates **29** and **30** and/or products **31** and **32** were not stable under the strongly basic reaction conditions. To test this possibility, compound **32** was treated with 2.2 equiv of LDA under the typical reaction conditions (Scheme 4). In this experiment, compound **32** was recovered in only 16% yield, together with 25% of the parent α-phosphono lactam **33**. These results supported the conclusion that compound **32** is not

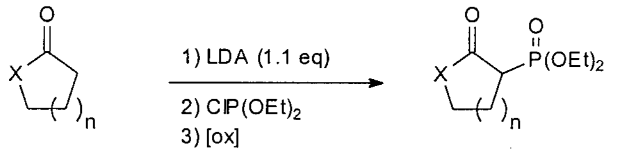
SCHEME 5

$$\mathbf{22} \xrightarrow[\text{2) ClP(O)(OEt)}_2]{\text{1) LDA (2.2 eq)}^{13a}} \mathbf{31}\ (61\%)$$

$$\mathbf{23} \xrightarrow[\text{2) ClP(O)(OEt)}_2]{\text{1) LDA (2.2 eq)}^{13a}} \mathbf{32}\ (36\%)$$

$$\mathbf{22} \xrightarrow[\text{2) ClP(O)(OEt)}_2]{\text{1) LDA, LiCl}^{18}} \mathbf{31}\ (30\%)$$

SCHEME 6



1, X = CH$_2$
n = 1-3, 8
2, X = O
n = 1-3, 9

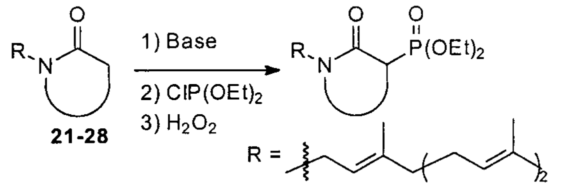
5, X = CH$_2$
n = 1-3, 8
6, X = O
n = 1-3, 9

stable in LDA solution, and this instability was time dependent. Abstraction of an allylic proton from the farnesyl group, followed by loss of an amide anion, would explain this decomposition and still be consistent with the observation of a successful rearrangement with the *n*-octyl lactam **7**, which carries only a saturated alkyl group. Unfortunately, this view suggested that successful rearrangements would be difficult with the other *N*-farnesyl lactams of Table 1.

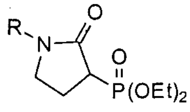
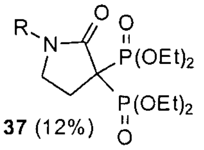
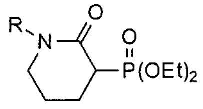
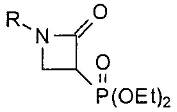
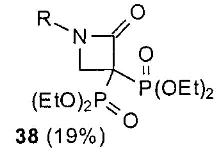
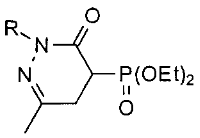
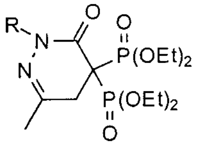
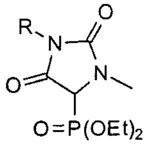
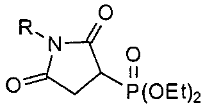
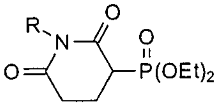
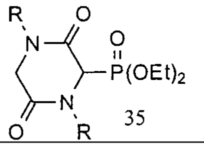
Conditions used by others to prepare phosphono lactams through the lactam enolate also were examined with some of these substrates, and met with limited success. For example, according to conditions reported by Collignon and Savignac,[13a] compounds **22** and **23** were treated first with 2.2 equiv of LDA and the reactions were quenched by addition of diethyl phosphorochloridate (Scheme 5). With the five-membered ring lactam **22**, this reaction gave phosphonate **31** in 61% yield. With the six-membered ring lactam **23**, however, the yield was low and addition of HMPA did not result in improved yield. Treatment of lactam **22** with LDA, LiCl, and diethyl phosphorochloridate under conditions parallel to those reported by Meyers[18] for alkylation of amide enolates did give the desired phosphonate, but only in 30% yield along with recovered starting material (Scheme 5).

Over the past few years, a different strategy has been developed for the synthesis of β-keto phosphonates[19a] and α-phosphono lactones[19] that involves reaction of an enolate with diethyl phosphorochloridite followed by oxidation to provide the desired phosphonate products **5** and **6** (Scheme 6) rather than direct use of a P(V) reagent. Because the P(III) procedure requires only enough base to make the enolate, it became attractive to explore this methodology with these *N*-farnesyl lactams. In the initial trials, after formation of the enolates through reaction of compounds **22** and **23** with strong base, treatment with (EtO)$_2$PCl, and air oxidation, the desired phosphonates were obtained in ~40% yield. When H$_2$O$_2$[20] was used for oxidation of the P(III) intermediate, purification was simplified, the yields were significantly improved, and phosphonates **31** and **32** were obtained in 75% and 60% yield (Table 2). Azetidinone **21** was converted to phosphonate **34** in modest yield by this strategy, but compounds **24** and **28** gave the corresponding phosphonates **35** and **36** in good yields. With compound **24**, only one phosphonate regioisomer was observed even though there

TABLE 2. Synthesis of α-Phosphono *N*-Farnesyl Lactams



21-28

Base	Lactam	Product(s) (% yield)	
LDA	**22**	 **31** (75%)	 **37** (12%)
LDA	**23**	 **32** (60%)	
LDA	**21**	 **34** (24%)	 **38** (19%)
LDA	**24**	 **35** (79%)	 **39** (5%)
LDA	**28**		**36** (68%)
LHMDS	**26**		**40** (71%)
LHMDS	**27**		**41** (70%)
LHMDS	**25**	 35	**42** (62%)

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(18) (a) Myers, A. G.; Yang, B. H.; Chen, H.; Gleason, J. L. *J. Am. Chem. Soc.* **1994**, *116*, 9361–9362. (b) Ruck, K. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 433–435.

(19) (a) Lee, K.; Wiemer, D. F. *J. Org. Chem.* **1991**, *56*, 5556–5560. (b) Boeckman, R. K., Jr.; Kamenecka, T. M.; Nelson, S. G.; Pruit, J. R.; Barta, T. E. *Tetrahedron Lett.* **1991**, *32*, 2581–2584. (c) Lee, K.; Jackson, J. A.; Wiemer, D. F. *J. Org. Chem.* **1993**, *58*, 5967–5971.

(20) Evans, D. A.; Gage, J. R.; Leighton, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 9434–9453.

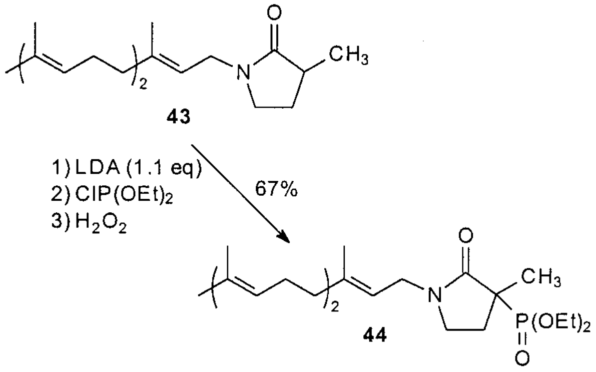
may be two sites for proton abstraction. The regiochemistry of phosphonate **35** was supported by extensive NMR experiments. In particular, in an HMBC experiment the imine methyl hydrogens were correlated to C5, and C5 could be unambiguously assigned as a methylene group on the basis of ^{1}H NMR and HMQC data.

It was also noteworthy that bisphosphonates were formed in some of these reactions, even though they were observed in generally small amounts. The structures of the bisphosphonates were established unambiguously by NMR. Especially informative were the triplets observed as a result of P−C coupling in the ^{13}C NMR spectra, where the direct C−P attachment resulted in a large J (∼150 Hz) and the adjacent carbonyl carbons displayed much smaller J values (∼6−7 Hz). With the five-membered lactam **22**, the bisphosphonate **37** was always a minor product, and with the *N*-farnesyl β-lactam **21**, the bisphosphonate **38** was a minor product (6%) when HMPA was used as a cosolvent. In the absence of HMPA, the mono- and bisphosphonates **34** and **38** were obtained in similar yields (24% and 19%, respectively). When these conditions were applied to lactam **24**, a small amount of the bisphosphonate **39** was obtained.

Preliminary studies with compounds **26** and **27** under the conditions described above were disappointing. Complex mixtures were obtained with monophosphonates isolated in low yields. Efforts to optimize the reaction conditions with these substrates included replacing LDA with other bases, changing the sequence of reagent addition, and varying the temperature for enolate formation. For compound **26**, the best yield of compound **40** (71%) was obtained through use of a slight deficiency of LHMDS (0.99 equiv) at −100 °C with inverse addition. For compound **27** when 0.99 equiv of LHMDS was used with inverse addition, and enolate formation was conducted at −78 °C, the desired phosphonate **41** was formed in 70% yield. With compound **25**, no reaction was observed at −100 °C, and at −10 °C, a complex mixture was formed and phosphonate **42** was isolated in just 25% yield. The yield was finally improved to 62% when enolate formation was carried out at −40 °C. These findings suggest that general statements about optimum reaction conditions must be made with great care, but that reasonable yields of the α-phosphono lactams have been obtained in all of the cases examined thus far.

Finally, the new *N*-farnesyl lactam **43** was prepared to probe the differences between the procedures for phosphonate synthesis based on the P(V) reagent. In contrast to the results described above for compound **22** (Scheme 5), when lactam **43** was treated with 2.2 equiv of LDA and then diethyl phosphorochloridate, there was no evidence for phosphonate formation in the ^{31}P NMR spectrum of the reaction mixture. This may support the view that phosphonate formation requires formation of a vinyl phosphate anion, which of course is prevented by the presence of the methyl substituent in compound **43**. In any event, the phosphonate **44** was obtained through the P(III) approach in 67% yield (Scheme 7), demonstrating that the enolate can be formed under these conditions and that even highly substituted phosphonates may be accessible via this strategy.

SCHEME 7



In conclusion, these studies have shown that it is possible to prepare a variety of α-phosphono lactams and imides through reaction of the corresponding enolates with electrophilic phosphorus reagents. The farnesyl group does not tolerate well the strongly basic conditions necessary to bring about a vinyl phosphate−phosphonate rearrangement. However, a number of *N*-farnesyl lactams and imides have been converted to the corresponding phosphonates through reaction of the enolate with diethyl phosphorochloridite and subsequent oxidation. This finding is especially of interest for phosphorylation of compounds which contain base labile groups or bear a substituent at the α position.

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. 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 a 40 μm average particle diameter. NMR spectra were recorded at 600, 400, or 300 MHz for ^{1}H with $CDCl_3$ as solvent and $(CH_3)_4Si$ (^{1}H and ^{13}C) as internal standard unless otherwise noted. The ^{31}P NMR chemical shifts are reported in parts per million relative to that of 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).

1-*n*-Octyl-3-(diethoxyphosphinyl)-2-pyrrolidinone (10). To a solution of LDA [3.77 mmol, prepared in situ from diisopropylamine (0.56 mL) and *n*-BuLi (1.46 mL, 2.58 M in hexane)] in anhydrous THF (15 mL) at −78 °C was added dropwise via cannula a solution of 1-*n*-octyl-2-pyrrolidinone (676 mg, 3.43 mmol) in THF (2 mL). After 30 min, HMPA (0.71 mL, 4.11 mmol) and diethyl phosphorochloridate (0.59 mL, 4.11 mmol) were added sequentially, and the resulting mixture was allowed to warm to room temperature over the course of 30 min. After the reaction mixture was cooled to −78 °C, a solution of LDA (1.1 equiv in 15 mL of THF) was added via cannula, and the reaction mixture was allowed to warm to room temperature over 2 h. The reaction was quenched by slow addition of a solution of acetic acid in diethyl ether (1 M, 4.4 equiv), and the resulting mixture was filtered through a pad of Florisil. Final purification by column chromatography (silica gel, from EtOAc to EtOAc/CH_3CN, 1:1) afforded compound **10** (776 mg, 68%) as a clear oil: ^{1}H NMR (300 MHz) δ 4.33−4.10 (m, 4H), 3.51 (q, J = 8.3 Hz, 1H), 3.39−3.18 (m, 3H), 2.94 (ddd, J_{HP} = 21.7 Hz, J = 10.1, 5.3 Hz, 1H), 2.50−2.20 (m, 2H), 1.58−1.43 (m, 2H), 1.39−1.19 (m, 16H), 0.92−0.83 (m, 3H); ^{13}C NMR (75 MHz) δ 169.0 (d, J_{CP} = 3.6 Hz), 63.0 (d, J_{CP} = 7.0 Hz), 62.2 (d, J_{CP} = 6.1 Hz), 45.8 (d, J_{CP} = 4.0 Hz), 43.0, 41.2 (d, J_{CP} = 142.5 Hz), 31.8, 29.2, 29.2, 27.2, 26.7, 22.6, 20.5 (d, J_{CP} = 3.6 Hz), 16.5 (d, J_{CP} = 5.5 Hz), 16.4 (d, J_{CP} = 5.0 Hz), 14.0; ^{31}P

NMR (121 MHz) 25.3 ppm. Anal. Calcd for $C_{16}H_{32}NO_4P$: C, 57.64; H, 9.67; N, 4.20. Found: C, 57.59; H, 9.85; N, 4.28.

1-(3′,7′,11′-Trimethyl-2′(*E*),6′(*E*),10′-dodecatrienyl)-2-azetidinone (21). General Procedure for the Preparation of *N*-Farnesyl Lactams 21−24. A mixture of 2-azetidinone (**13**; 142 mg, 2.00 mmol), potassium *tert*-butoxide (380 mg, 3.20 mmol), and 18-crown-6 (53 mg, 0.20 mmol) in ether (20 mL) was stirred at room temperature for 45 min and then cooled in an ice bath. Farnesyl bromide (**11**; 0.81 mL, 3.00 mmol) was added dropwise, and the mixture was stirred at room temperature for 16 h. The mixture was filtered through a pad of Celite, the filtrate was concentrated in vacuo, and the resulting oil was purified by flash chromatography (1:1 hexanes:EtOAc) to give 280 mg (52%) of compound **21** as a clear oil: ^{1}H NMR (400 MHz) δ 5.17 (tq, J = 7.2, 1.2 Hz, 1H), 5.12−5.05 (m, 2H), 3.81 (d, J = 7.2 Hz, 2H), 3.16 (t, J = 4.0 Hz, 2H), 2.89 (t, J = 4.0 Hz, 2H), 2.15−1.94 (m, 8H), 1.70−1.66 (m, 6H), 1.60 (s, 6H); ^{13}C NMR (75 MHz) δ 167.2, 141.0, 135.5, 131.4, 124.2, 123.6, 117.2, 39.7, 39.5, 39.4, 38.2, 36.5, 26.7, 26.2, 25.7, 17.7, 16.2, 16.0; HRMS (ES) *m*/*z* calcd for $C_{18}H_{30}NO$ (M^+ + H) 276.2327, found 276.2343.

1-(3′,7′,11′-Trimethyl-2′(*E*),6′(*E*),10′-dodecatrienyl)-2-pyrrolidinone (22). According to the general procedure, 2-pyrrolidinone (**14**; 500 mg, 5.87 mmol) was treated with farnesyl bromide to afford compound **22** (1.46 g, 86%) as a clear oil: ^{1}H NMR (400 MHz) δ 5.16−5.05 (m, 3H), 3.86 (d, J = 7.2 Hz, 2H), 3.28 (t, J = 7.1 Hz, 2H), 2.35 (t, J = 8.2 Hz, 2H), 2.14−1.93 (m, 10H), 1.66 (s, 6H), 1.57 (s, 6H); ^{13}C NMR (100 MHz) δ 174.4, 140.4, 135.3, 131.3, 124.2, 123.7, 118.5, 46.4, 40.0, 39.7, 39.5, 31.0, 26.7, 26.2, 25.7, 17.7, 17.6, 16.2, 16.0. Anal. Calcd for $C_{19}H_{31}NO{\cdot}0.5H_2O$: C, 76.46; H, 10.81; N, 4.69. Found: C, 76.32; H, 10.55; N, 4.73.

1-(3′,7′,11′-Trimethyl-2′(*E*),6′(*E*),10′-dodecatrienyl)-2-piperidinone (23). According to the general procedure, 2-piperidinone (**15**; 1.00 g, 10.09 mmol) was treated with farnesyl bromide to afford lactam **23** (2.31 g, 76%) as a clear oil: ^{1}H NMR (400 MHz) δ 5.17−5.05 (m, 3H), 4.02 (d, J = 7.0 Hz, 2H), 3.24−3.17 (m, 2H), 2.41−2.34 (m, 2H), 2.14−1.92 (m, 8H), 1.81−1.74 (m, 4H), 1.68 (s, 6H), 1.60 (s, 6H); ^{13}C NMR (100 MHz) δ 169.3, 139.8, 135.3, 131.3, 124.3, 123.8, 119.5, 46.9, 44.0, 39.7, 39.6, 32.4, 26.8, 26.3, 25.7, 23.3, 21.5, 17.7, 16.2, 16.0. Anal. Calcd for $C_{20}H_{33}NO$: C, 79.15; H, 10.96; N, 4.62. Found: C, 79.24; H, 10.96; N, 4.71.

2-(3′,7′,11′-Trimethyl-2′(*E*),6′(*E*),10′-dodecatrienyl)-6-methyl-4,5-dihydro-3(2*H*)-pyridazinone (24). According to the general procedure, 4,5-dihydro-3(2*H*)-pyridazinone monohydrate (**16**; 260 mg, 2.00 mmol) was treated with farnesyl bromide to afford lactam **24** (550 mg, 87%) as a clear oil: ^{1}H NMR (400 MHz) δ 5.26 (tq, J = 6.5, 1.2 Hz, 1H), 5.13−5.05 (m, 2H), 4.32 (d, J = 6.6 Hz, 2H), 2.49−2.39 (m, 4H), 2.13−1.93 (m, 11H), 1.73 (m, 3H), 1.68 (d, J = 0.9 Hz, 3H), 1.60 (s, 3H), 1.59 (d, J = 1.0 Hz, 3H); ^{13}C NMR (75 MHz) δ 164.6, 153.1, 139.1, 135.1, 131.3, 124.4, 124.0, 119.5, 46.1, 39.7, 39.6, 26.9, 26.7, 26.4 (2C), 25.7, 23.2, 17.7, 16.5, 16.0. Anal. Calcd for $C_{20}H_{32}N_2O$: C, 75.90; H, 10.19; N, 8.85. Found: C, 75.90; H, 10.23; N, 8.84.

1,4-Bis(3′,7′,11′-trimethyl-2′(*E*),6′(*E*),10′-dodecatrienyl)-2,5-piperazinedione (25). NaH (140 mg, 3.62 mmol, 60% in mineral oil) was added to a stirred solution of 2,5-piperazinedione (**17**; 190 mg, 1.66 mmol) in DMF (5 mL) at room temperature, and the mixture was stirred at this temperature for 30 min. Farnesyl bromide (1.00 mL, 3.69 mmol) was added dropwise via syringe over 10 min. The resulting mixture was allowed to stir for 4 h at room temperature, poured into satd NH_4Cl (5 mL), and thoroughly extracted with diethyl ether. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (hexanes/EtOAc, from 9:1 to 1:1) to give compound **25** (700 mg, 80%) as a white solid: ^{1}H NMR (300 MHz) δ 5.17−5.03 (m, 6H), 4.04 (d, J = 7.5 Hz, 4H), 3.90 (s, 4H), 2.15−1.91 (m, 16H), 1.71 (s, 3H), 1.71 (s, 3H), 1.68 (s, 3H), 1.68 (s, 3H), 1.60 (s, 12H); ^{13}C NMR (75 MHz) δ 163.1 (2C), 142.5 (2C), 135.6 (2C), 131.4 (2C), 124.3 (2C), 123.5 (2C), 116.9 (2C), 48.9 (2C), 42.8 (2C), 39.7 (2C), 39.6 (2C), 26.7 (2C), 26.3 (2C), 25.7 (2C), 17.7 (2C), 16.4 (2C), 16.0 (2C). Anal. Calcd for $C_{34}H_{54}N_2O_2$: C, 78.11; H, 10.41; N, 5.36. Found: C, 77.93; H, 10.49; N, 5.33.

Representative Procedure for the Preparation of *N*-Farnesyl Imides 26−28. Synthesis of 1-(3′,7′,11′-Trimethyl-2′(*E*),6′(*E*),10′-dodecatrienyl)-2,5-pyrrolidinedione (26). To a solution of succinimide (**18**; 190 mg, 1.88 mmol), PPh_3 (640 mg, 2.44 mmol), and farnesol (**12**; 500 mg, 2.25 mmol) in THF (10 mL) was added dropwise at 0 °C diethyl azodicarboxylate (0.38 mL, 2.44 mmol). The mixture was stirred at room temperature for 24 h, and then concentrated in vacuo. The residue was triturated with hexanes, and the organic extracts were concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexanes/EtOAc, from 1:0 to 7:3) to give compound **26** (494 mg, 85%): ^{1}H NMR (300 MHz) δ 5.25−5.00 (m, 3H), 4.10 (d, J = 7.3 Hz, 2H), 2.69 (s, 4H), 2.15−1.85 (m, 8H), 1.78 (d, J = 0.7 Hz, 3H), 1.68 (s, 3H), 1.60 (s, 3H), 1.58 (s, 3H); ^{13}C NMR (75 MHz) δ 176.9 (2C), 141.0, 135.4, 131.3, 124.3, 123.6, 117.2, 39.7, 39.5, 36.7, 28.2 (2C), 26.7, 26.2, 25.7, 17.7, 16.4, 16.0. Anal. Calcd for $C_{19}H_{29}NO_2$: C, 75.21; H, 9.63; N, 4.62. Found: C, 74.92; H, 9.69; N, 4.58.

1-(3′,7′,11′-Trimethyl-2′(*E*),6′(*E*),10′-dodecatrienyl)-2,6-piperidinedione (27). According to the procedure described above for compound **26**, 2,6-piperidinedione (**19**; 430 mg, 3.75 mmol) was treated with farnesol and the product was purified by flash chromatography on silica gel (CH_2Cl_2) to give compound **27** (690 mg, 57%) as a clear oil: ^{1}H NMR (400 MHz) δ 5.12−5.00 (m, 3H), 4.34 (d, J = 6.9 Hz, 2H), 2.61 (t, J = 6.6 Hz, 4H), 2.08−1.85 (m, 10H), 1.74 (s, 3H), 1.65 (d, J = 1.0 Hz, 3H), 1.57 (s, 3H), 1.55 (s, 3H); ^{13}C NMR (100 MHz) δ 172.3 (2C), 139.8, 135.1, 131.3, 124.3, 123.8, 118.8, 39.7, 39.6, 37.7, 32.9 (2C), 26.7, 26.3, 25.7, 17.7, 17.2, 16.3, 16.0. Anal. Calcd for $C_{20}H_{31}NO_2$: C, 75.67; H, 9.84; N, 4.41. Found: C, 75.68; H, 9.94; N, 4.55.

1-Methyl-3-(3′,7′,11′-trimethyl-2′(*E*),6′(*E*),10′-dodecatrienyl)-2,4-imidazolidine dione (28). According to the procedure described above for compound **26**, 1-methyl-2,4-imidazolidinedione (**20**; 1.00 g, 8.77 mmol) was treated with farnesol and the product was purified by flash chromatography on silica gel (hexanes/EtOAc, from 9:1 to 5:5) to afford compound **28** (1.60 g, 75%) as a clear oil: ^{1}H NMR (400 MHz) δ 5.25−5.18 (m, 1H), 5.11−5.03 (m, 2H), 4.10 (d, J = 7.1 Hz, 2H), 3.83 (s, 2H), 2.99 (s, 3H), 2.12−1.92 (m, 8H), 1.78 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H), 1.58 (s, 3H); ^{13}C NMR (100 MHz) δ 169.5, 156.8, 140.8, 135.3, 131.3, 124.3, 123.7, 117.6, 51.8, 39.7, 39.5, 36.8, 29.6, 26.7, 26.2, 25.7, 17.7, 16.4, 16.0; HRMS (ES) *m*/*z* calcd for $C_{19}H_{31}N_2O_2$ (M^+ + H) 319.2386, found 319.2397.

1-(3′,7′,11′-Trimethyl-2′(*E*),6′(*E*),10′-dodecatrienyl)-3-(diethoxyphosphinyl)-2-pyrrolidinone (31). Synthesis of Phosphonate 31 via Vinyl Phosphate−Phosphonate Rearrangement. To a solution of LDA (1.1 equiv) in anhydrous THF (10 mL) at −78 °C was added dropwise via cannula a solution of lactam **22** (940 mg, 3.26 mmol, 1.0 equiv) in THF (2 mL). After 30 min, HMPA (0.68 mL, 1.20 equiv) and diethyl phosphorochloridate (0.56 mL, 1.20 equiv) were added in sequence, and the resulting mixture was allowed to warm to room temperature over the course of 30 min. After the reaction mixture was cooled to −78 °C, a solution of LDA (2.2 equiv) in THF (15 mL) was added via cannula, and the reaction mixture was allowed to warm to room temperature over 2 h. The reaction then was quenched by slow addition of a solution of acetic acid in diethyl ether (1 M, 32.6 mL, 10 equiv), and the resulting mixture was filtered through a pad of Florisil. Final purification by column chromatography (silica gel, from EtOAc to EtOAc/CH_3CN, 1:1) afforded phosphonate **31** (10%).

Synthesis of Phosphonate 31 via Method B. To a solution of LDA (2.2 equiv) in THF (26 mL) at −78 °C was added dropwise via cannula a stirred solution of lactam **22** (1.30 g, 4.49 mmol, 1.0 equiv) in THF (4 mL). The mixture was stirred at this temperature for 30 min and then at room temperature for 5 min, and then cooled back to −78 °C. After diethyl phosphorochloridate (0.74 mL, 1.15 equiv) was added dropwise via syringe, the resulting mixture was allowed to warm to room temperature over 2 h. The reaction was quenched by slow addition of a solution of acetic acid in diethyl ether (1 M, 15 equiv), and the resulting mixture was filtered through a pad of Florisil. Final purification by column chromatography (silica gel, from EtOAc to EtOAc/CH_3CN, 1:1) afforded phosphonate **31** (1.17 g, 61%).

Synthesis of Phosphonate 31 via Method C. To a suspension of lithium chloride (870 mg, 20.52 mmol, 6 equiv; dried at 150 °C and 0.1 mmHg for 4 h prior to use) in THF (5 mL) was added diisopropylamine (0.55 mL, 3.93 mmol). The resulting suspension was cooled to −78 °C, and a solution of *n*-butyllithium in hexanes (2.58 M, 1.43 mL, 3.69 mmol) was added via syringe. After this mixture was stirred at this temperature for 10 min, it was stirred at 0 °C for 5 min, and then cooled to −78 °C. A solution of lactam **22** (0.99 g, 3.42 mmol) in THF (10 mL) was added to the reaction mixture via cannula. The mixture was stirred at −78 °C for 1 h, at 0 °C for 15 min, and at room temperature for 5 min. After the resulting mixture was cooled to 0 °C, diethyl phosphorochloridate was added. The mixture was stirred overnight and then quenched by addition of acetic acid in diethyl ether (1 M, 10 mL, 10 equiv), and the resulting mixture was filtered through a pad of Florisil. Final purification by column chromatography (silica gel, from EtOAc to EtOAc/CH_3CN, 1:1) afforded phosphonate **31** (430 mg, 30%).

General Procedure for Phosphonate Synthesis via P(III) Electrophiles. Synthesis of Phosphonate 31. A solution of lactam **22** (310 mg, 1.07 mmol, 1.0 equiv) in diethyl ether (2 mL) was added dropwise via cannula to a stirred solution of LDA [1.1 equiv, prepared in situ from diisopropylamine (0.16 mL, 1.18 mmol) and *n*-butyllithium in hexanes (2.50 M, 0.47 mL, 1.18 mmol)] in anhydrous diethyl ether (5 mL) at −78 °C. After 60 min, HMPA (0.21 mL, 0.23 mmol) and diethyl phosphorochloridite (0.18 mL, 0.23 mmol) were added in turn, 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 hydrogen peroxide (30%, 1.21 mL, 10 equiv), and the resulting mixture was stirred vigorously at this temperature for 10 min. The organic phase was separated, washed with brine, and dried ($MgSO_4$). After concentration, final purification by column chromatography on silica gel (from EtOAc to 1:1 EtOAc/CH_3CN) afforded phosphonate **31** (340 mg, 75%) as the major product and then (EtOAc/MeOH, 8:2) a minor product (**37**; 70 mg, 12%) as a clear oil.

Data for the Major Product 31: ^{1}H NMR (600 MHz) δ 5.11 (tq, J = 6.0, 1.2 Hz, 1H), 5.09−5.04 (m, 2H), 4.28−4.13 (m, 4H), 3.95 (dd, J = 14.8, 7.2 Hz, 1H), 3.84 (dd, J = 14.8, 7.2 Hz, 1H), 3.41 (m, 1H), 3.27 (tdd, J = 9.4, 4.4, 2.0 Hz, 1H), 2.93 (ddd, J_{HP} = 21.8 Hz, J = 10.2, 5.4 Hz, 1H), 2.41−2.21 (m, 2H), 2.01−1.93 (m, 8H), 1.67 (s, 6H), 1.59 (s, 3H), 1.58 (s, 3H), 1.36−1.31 (m, 6H); ^{13}C NMR (100 MHz) δ 168.7 (d, J_{CP} = 3.8 Hz), 140.9, 135.4, 131.3, 124.2, 123.6, 118.0, 62.9 (d, J_{CP} = 6.6 Hz), 62.2 (d, J_{CP} = 6.4 Hz), 45.1 (d, J_{CP} = 4.1 Hz), 41.1(d, J_{CP} = 143.8 Hz), 40.0, 39.7, 39.5, 26.7, 26.3, 25.7, 20.3 (d, J_{CP} = 4.4 Hz), 17.6, 16.4 (d, J_{CP} = 6.6 Hz), 16.4 (d, J_{CP} = 5.9 Hz), 16.2, 16.0; ^{31}P NMR (121 MHz) 25.0 ppm. Anal. Calcd for $C_{23}H_{40}NO_4P{\cdot}0.5H_2O$: C, 63.57; H, 9.51; N, 3.22. Found: C, 63.44; H, 9.29; N, 3.29.

Data for the Minor Product 1-(3′,7′,11′-Trimethyl-2′(*E*),6′(*E*),10′-dodecatrienyl)-3,3-bis(diethoxyphosphinyl)-2-pyrrolidinone (37): ^{1}H NMR (300 MHz) δ 5.17−5.03 (m, 3H), 4.38−4.15 (m, 8H), 3.92 (d, J = 7.1 Hz, 2H), 3.37 (t, J = 7.0 Hz, 2H), 2.63 (tt, J_{HP} = 17.5 Hz, J = 6.9 Hz, 2H), 2.14−1.91 (m, 8H), 1.68 (s, 6H), 1.60 (s, 3H), 1.59 (s, 3H), 1.34 (t, J = 7.1 Hz, 12H); ^{13}C NMR (75 MHz) δ 166.2 (t, J_{CP} = 4.6 Hz), 141.1, 135.4, 131.4, 124.3, 123.7, 117.9, 63.7 (d, J_{CP} = 6.5 Hz, 2C), 63.4 (d, J_{CP} = 7.0 Hz, 2C), 52.6 (t, J_{CP} = 135.6 Hz), 44.5 (t, J_{CP} = 3.9 Hz), 40.9, 39.7, 39.6, 26.7, 26.4, 25.7, 24.9 (t, J_{CP} = 4.1 Hz), 17.7, 16.5 (d, J_{CP} = 2.2 Hz, 2C), 16.4 (d, J_{CP} = 2.0 Hz, 2C), 16.2, 16.0; ^{31}P NMR (121 MHz) 19.9 ppm. Anal. Calcd for $C_{27}H_{49}NO_7P_2$: C, 57.74; H, 8.79; N, 2.49. Found: C, 57.50; H, 8.93; N, 2.46.

1-(3′,7′,11′-Trimethyl-2′(*E*),6′(*E*),10′-dodecatrienyl)-3-(diethoxyphosphinyl)-2-piperidinone (32). According to the general procedure described for compound **31**, compound **23** (324 mg, 1.07 mmol) was treated with LDA, diethyl phosphorochloridite, and H_2O_2 to obtain phosphonate **32** (280 mg, 60%) as a clear oil: ^{1}H NMR (400 MHz) δ 5.14 (t, J = 6.8 Hz, 1H), 5.11−5.05 (m, 2H), 4.30−4.10 (m, 5H), 3.94 (dd, J = 14.6, 7.2 Hz, 1H), 3.32−3.16 (m, 2H), 2.98 (dt, J_{HP} = 26.7 Hz, J = 6.7 Hz, 1H), 2.22−1.93 (m, 11H), 1.76−1.64 (m, 7H), 1.60 (s, 3H), 1.59 (s, 3H), 1.34 (t, J = 7.4 Hz, 3H), 1.33 (t, J = 7.3, 3H); ^{13}C NMR (100 MHz) δ 164.4 (d, J_{CP} = 5.0 Hz), 140.2, 135.3, 131.3, 124.3, 123.8, 119.1, 63.0 (d, J_{CP} = 6.9 Hz), 61.9 (d, J_{CP} = 7.2 Hz), 46.7, 44.6, 41.8 (d, J_{CP} = 137.8 Hz), 39.7, 39.6, 26.7, 26.4, 25.7, 23.3(d, J_{CP} = 5.0 Hz), 21.6 (d, J_{CP} = 8.0 Hz), 17.7, 16.5(d, J_{CP} = 6.1 Hz), 16.4 (d, J_{CP} = 6.0 Hz), 16.2, 16.0; ^{31}P NMR (121 MHz) 25.7 ppm. Anal. Calcd for $C_{24}H_{42}NO_4P{\cdot}0.5H_2O$: C, 64.26; H, 9.66; N, 3.12. Found: C, 64.53; H, 9.59; N, 3.19.

3-(Diethoxyphosphinyl)-2-piperidinone (33). A solution of α-phosphono lactam **32** (367 mg, 0.83 mmol) in THF (2 mL) was added dropwise via cannula to a stirred solution of LDA [2.2 equiv, prepared in situ from diisopropylamine (0.27 mL, 1.92 mmol) and *n*-butyllithium in hexanes (2.44 M, 0.75 mL, 1.84 mmol)] in anhydrous THF (5 mL) at −78 °C. The resulting mixture was allowed to warm to room temperature over the course of 2 h, and stirred for another 22 h at this temperature. The reaction was quenched by slow addition of a solution of acetic acid in diethyl ether (1 M, 20 mL, 24 equiv), and the resulting mixture was filtered through a pad of Florisil. Purification of this mixture by column chromatography (silica gel, first with hexanes/EtOAc, 1:1) gave recovered compound **32** (60 mg, 16%). Continued gradient elution (from EtOAc to EtOAc/MeOH, 6:4) afforded the defarnesylated α-phosphono lactam **33** (50 mg, 25%): ^{1}H NMR (300 MHz) δ 6.91 (br, 1H), 4.32−4.07 (m, 4H), 3.45−3.24 (m, 2H), 2.95 (dt, J = 27, 6.7 Hz, 1H), 2.28−1.97 (m, 3H), 1.81−1.62 (m, 1H), 1.34 (t, J = 7.1 Hz, 3H), 1.34 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz) δ 167.2 (d, J_{CP} = 4.6 Hz), 62.8 (d, J_{CP} = 6.4 Hz), 61.9 (d, J_{CP} = 7.2 Hz), 42.0, 41.0 (d, J_{CP} = 137.2 Hz), 22.6 (d, J_{CP} = 4.5 Hz), 20.7 (d, J_{CP} = 7.2 Hz), 16.3 (d, J_{CP} = 6.4 Hz), 16.2 (d, J_{CP} = 6.2 Hz); ^{31}P NMR (121 MHz) 26.3 ppm; HRMS (ES) *m*/*z* calcd for $C_9H_{19}NO_4P$ ($M^+ + H$) 236.1052, found 236.1060.

1-(3′,7′,11′-Trimethyl-2′(*E*),6′(*E*),10′-dodecatrienyl)-3-(diethoxyphosphinyl)-2-azetidinone (34). According to the general procedure for compound **31**, azetidinone **21** (365 mg, 1.32 mmol) was treated with LDA, diethyl phosphorochloridite, and H_2O_2 to afford phosphonate **34** as the major product (151 mg, 28%) and bisphosphonate **38** as the minor product (46 mg, 6%).

Data for the Major Product 34: ^{1}H NMR (300 MHz) δ 5.21−5.13 (m, 1H), 5.13−5.04 (m, 2H), 4.33−4.09 (m, 4H), 3.85 (d, J = 7.2 Hz, 2H), 3.63−3.52 (m, 1H), 3.40−3.33 (m, 2H), 2.18−1.92 (m, 8H), 1.68 (s, 3H), 1.68 (s, 3H), 1.60 (s, 6H), 1.39−1.31 (m, 6H); ^{13}C NMR (75 MHz) δ 161.4 (d, J_{CP} = 7.2 Hz), 142.0, 135.6, 131.4, 124.2, 123.5, 116.5, 62.8 (d, J_{CP} = 6.4 Hz), 62.5 (d, J_{CP} = 6.4 Hz), 46.7 (d, J_{CP} = 147.9 Hz), 39.8 (d, J_{CP} = 1.2 Hz), 39.7, 39.6 (d, J_{CP} = 3.6 Hz), 39.5, 26.7, 26.3, 25.7, 17.7, 16.4 (d, J_{CP} = 6.0 Hz, 2C), 16.3, 16.0; ^{31}P NMR (121 MHz) 21.0 ppm; HRMS (ES) *m*/*z* calcd for $C_{22}H_{39}NO_4P$ ($M^+ + H$) 412.2617, found 412.2624.

Data for the Minor Product 1-(3′,7′,11′-Trimethyl-2′(*E*),6′(*E*),10′-dodecatrienyl)-3,3-bis(diethoxyphosphinyl)-2-azetidinone (38): ^{1}H NMR (400 MHz) δ 5.17 (tq, J = 7.2, 1.2 Hz, 1H), 5.12−5.03 (m, 2H), 4.35−4.10 (m, 8H), 3.88 (d, J = 7.2 Hz, 2H), 3.53 (t, J_{HP} = 7.6 Hz, 2H), 2.16−1.93 (m, 8H), 1.68 (s, 6H), 1.60 (s, 6H), 1.36 (t, J_{HP} = 7.1 Hz, 6H), 1.35 (t, J_{HP} = 7.1 Hz, 6H); ^{13}C NMR (100 MHz) δ 158.5 (t, J_{CP} = 7.2 Hz), 142.2, 135.6, 131.4, 124.3, 123.5, 116.2, 63.6 (m, 2C), 63.6

(m, 2C), 57.9 (t, J_{CP} = 136.8 Hz), 43.0 (t, J_{CP} = 3.7 Hz), 40.2, 39.7, 39.6, 26.7, 26.4, 25.7, 17.7, 16.4 (m, 2C), 16.4 (m, 2C), 16.3, 16.0; ^{31}P NMR (121 MHz) 15.9 ppm; HRMS (ES) *m*/*z* calcd for $C_{26}H_{47}NO_7NaP_2$ (M^+ + Na) 570.2726, found 570.2746.

2-(3′,7′,11′-Trimethyl-2′(*E*),6′(*E*),10′-dodecatrienyl)-3-(diethoxyphosphinyl)-6-methyl-4,5-dihydro-3(2*H*)-pyridazinone (35). According to the general procedure described for compound **31**, compound **24** (300 mg, 0.94 mmol) was treated with LDA, diethyl phosphorochloridite, and H_2O_2 to obtain phosphonate **35** (340 mg, 79%) as a clear oil: ^{1}H NMR (400 MHz) δ 5.30−5.22 (m, 1H), 5.13−5.04 (m, 2H), 4.39 (dd, *J* = 14.8, 6.6 Hz, 1H), 4.29 (dd, *J* = 14.9, 6.4 Hz, 1H), 4.22−4.08 (m, 4H), 3.02 (ddd, J_{HP} = 24.1 Hz, *J* = 8.4, 5.2 Hz, 1H), 2.90−2.63 (m, 2H), 2.13−1.93 (m, 11H), 1.72 (s, 3H), 1.68 (d, *J* = 1.1 Hz, 3H), 1.60 (s, 3H), 1.58 (s, 3H), 1.35 (t, *J* = 7.3 Hz, 3H), 1.31 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz) δ 160.0 (d, J_{CP} = 4.4 Hz), 151.8 (d, J_{CP} = 5.6 Hz), 139.4, 135.2, 131.3, 124.3, 123.9, 119.1, 63.0 (d, J_{CP} = 6.9 Hz), 62.8 (d, J_{CP} = 6.5 Hz), 46.6, 39.7, 39.6, 37.2 (d, J_{CP} = 136.8 Hz), 27.7 (d, J_{CP} = 5.2 Hz), 26.7, 26.4, 25.7, 23.2, 17.7, 16.5, 16.4 (d, J_{CP} = 3.8 Hz), 16.3 (d, J_{CP} = 3.8 Hz), 16.0; ^{31}P NMR (121 MHz) 22.6 ppm; HRMS (ES) *m*/*z* calcd for $C_{24}H_{42}N_2O_4P$ (M^+ + H) 453.2882, found 453.2880.

Data for the Minor Product 2-(3′,7′,11′-Trimethyl-2′(*E*), 6′(*E*),10′-dodecatrienyl)-3,3-bis(diethoxyphosphinyl)-6-methyl-4,5-dihydro-3(2*H*)-pyridazinone (39): yield 30 mg, 5%; clear oil; ^{1}H NMR (400 MHz) δ 5.32−5.23 (m, 1H), 5.15−5.04 (m, 2H), 4.34 (d, *J* = 6.6 Hz, 2H), 4.43−4.10 (m, 8H), 3.05 (t, J_{HP} = 17.6 Hz, 2H), 2.12−1.93 (m, 11H), 1.71 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H), 1.58 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 12H); ^{13}C NMR (100 MHz) δ 158.0 (t, J_{CP} = 5.6 Hz), 150.9 (t, J_{CP} = 7.2 Hz), 139.3, 135.2, 131.3, 124.4, 124.0, 119.1, 64.2 (m, 2C), 63.8 (m, 2C), 48.6 (t, J_{CP} = 131.6 Hz), 47.2, 39.7, 39.7, 32.0 (t, J_{CP} = 5.1 Hz), 26.8, 26.5, 25.7, 23.0, 17.7, 16.6, 16.4 (m, 2C), 16.4 (m, 2C), 16.0; ^{31}P NMR (121 MHz) 18.5 ppm; HRMS (ES) *m*/*z* calcd for $C_{28}H_{51}N_2O_7P_2$ (M^+ + H) 589.3169, found 589.3172.

1-Methyl-3-(3′,7′,11′-trimethyl-2′(*E*),6′(*E*),10′-dodecatrienyl)-5-(diethoxyphosphinyl)-2,4-imidazolidinedione (36). According to the general procedure described for compound **31**, compound **28** (360 mg, 1.13 mmol) was treated with LDA, diethyl phosphorochloridite, and H_2O_2 to obtain phosphonate **36** (350 mg, 68%) as a clear oil: ^{1}H NMR (400 MHz) δ 5.28 (tq, *J* = 7.0, 1.2 Hz, 1H), 5.19−5.11 (m, 2H), 4.38−4.23 (m, 4H), 4.23 (d, J_{HP} = 13.9 Hz, 1H), 4.18 (d, *J* = 7.1 Hz, 2H), 3.20 (s, 3H), 2.19−1.98 (m, 8H), 1.85 (s, 3H), 1.75 (d, *J* = 0.8 Hz, 3H), 1.67 (s, 3H), 1.65 (s, 3H), 1.47 (t, *J* = 7.1 Hz, 3H), 1.38 (t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz) δ 166.2 (d, J_{CP} = 4.4 Hz), 156.6 (d, J_{CP} = 5.7 Hz), 141.3, 135.4, 131.3, 124.3, 123.7, 117.2, 64.3 (d, J_{CP} = 6.9 Hz), 63.8 (d, J_{CP} = 7.1 Hz), 60.1 (d, J_{CP} = 155.8 Hz), 39.7, 39.5, 37.2, 30.0, 26.7, 26.3, 25.7, 17.7, 16.5 (d, J_{CP} = 5.5 Hz), 16.4 (d, J_{CP} = 5.7 Hz), 16.4, 16.0; ^{31}P NMR (121 MHz) 12.6 ppm. Anal. Calcd for $C_{23}H_{39}N_2O_5P$: C, 60.78; H, 8.65; N, 6.16. Found: C, 60.37; H, 8.91; N, 6.18.

1-(3′,7′,11′-Trimethyl-2′(*E*),6′(*E*),10′-dodecatrienyl)-3-(diethoxyphosphinyl)-2,5-pyrrolidinedione (40). A solution of lactam **26** (251 mg, 0.83 mmol) in diethyl ether (9 mL) at −100 °C was treated with LHDMS (1.0 M, 0.82 mL, 0.82 mmol, 0.99 equiv). After 1 h at this temperature, HMPA (0.14 mL, 0.83 mmol, 1.00 equiv) and diethyl phosphorochloridite (0.12 mL, 0.82 mmol, 0.99 equiv) were added sequentially, and the resulting mixture was allowed to warm to 0 °C over the course of 5 h. The reaction was quenched by slow addition of hydrogen peroxide (30%, 0.94 mL, 8.26 mmol, 10 equiv), and the resulting mixture was stirred vigorously at this temperature for 10 min. The organic phase was separated, washed with brine, and dried ($MgSO_4$). After concentration, final purification by column chromatography (silica gel, EtOAc) afforded phosphonate **40** (254 mg, 71%) as a clear oil along with small amounts of starting material (30 mg, or 79% yield of compound **40** based on recovered starting material): ^{1}H NMR (400 MHz) δ 5.19−5.02 (m, 3H), 4.30−4.14 (m, 4H), 4.11 (d, *J* = 7.1 Hz, 2H), 3.27 (ddd, J_{HP} = 23.5 Hz, *J* = 9.5, 4.7 Hz, 1H), 3.06−2.86 (m, 2H), 2.10−1.92 (m, 8H), 1.77 (d, *J* = 1.1 Hz, 3H), 1.68 (d, *J* = 1.0 Hz, 3H), 1.60 (s, 3H), 1.58 (s, 3H), 1.40−1.29 (m, 6H); ^{13}C NMR (100 MHz) δ 174.9 (d, J_{CP} = 6.1 Hz), 172.0 (d, J_{CP} = 5.5 Hz), 141.7, 135.6, 131.5, 124.5, 123.8, 117.0, 63.8 (d, J_{CP} = 6.6 Hz), 63.4 (d, J_{CP} = 6.6 Hz), 40.6, 39.9, 39.6 (d, J_{CP} = 142.7 Hz), 37.5, 30.9 (d, J_{CP} = 3.8 Hz), 26.9, 26.5, 25.9, 17.9, 16.6, 16.6 (d, J_{CP} = 5.6 Hz, 2C), 16.2; ^{31}P NMR (121 MHz) 20.6 ppm. Anal. Calcd for $C_{23}H_{38}NO_5P$: C, 62.85; H, 8.71; N, 3.19. Found: C, 62.81; H, 8.76; N, 3.15.

1-(3′,7′,11′-Trimethyl-2′(*E*),6′(*E*),10′-dodecatrienyl)-3-(diethoxyphosphinyl)-2,6-piperidinedione (41). To a solution of lactam **27** (280 mg, 0.88 mmol) in diethyl ether (9 mL) at −78 °C was added dropwise LHMDS (1.0 M, 0.87 mL, 0.87 mmol, 0.99 equiv). After the solution was stirred at this temperature for 40 min, HMPA (0.15 mL, 0.88 mmol, 1.00 equiv) and diethyl phosphorochloridite (0.13 mL, 0.87 mmol, 0.99 equiv) were added sequentially, and the resulting mixture was allowed to warm to 0 °C over the course of 4 h. The reaction was quenched by slow addition of hydrogen peroxide (30%, 1.00 mL, 8.82 mmol, 10 equiv), and the resulting mixture was stirred vigorously at this temperature for 10 min. The organic phase was separated, washed with brine, and dried ($MgSO_4$). After concentration, final purification by column chromatography (silica gel, EtOAc) afforded phosphonate **41** (280 mg, 71%) as a clear oil along with small amounts of starting material (55 mg, or 87% yield of compound **41** based on recovered starting material): ^{1}H NMR (400 MHz) δ 5.15−5.03 (m, 3H), 4.40 (d, *J* = 6.9 Hz, 2H), 4.24−4.12 (m, 4H), 3.21 (dt, J_{HP} = 25.8 Hz, *J* = 5.0 Hz, 1H), 3.04−2.91 (m, 1H), 2.64 (dt, *J* = 17.7, 5.2 Hz, 1H), 2.37−2.11 (m, 2H), 2.10−1.91 (m, 8H), 1.76 (d, *J* = 1.0 Hz, 3H), 1.68 (d, *J* = 1.0 Hz, 3H), 1.60 (s, 3H), 1.58 (s, 3H), 1.40−1.29 (m, 6H); ^{13}C NMR (100 MHz) δ 171.5, 167.9 (d, J_{CP} = 4.5 Hz), 140.0, 135.2, 131.3, 124.3, 123.8, 118.5, 63.2 (d, J_{CP} = 7.0 Hz), 63.0 (d, J_{CP} = 6.6 Hz), 42.2 (d, J_{CP} = 134.7 Hz), 39.7, 39.6, 38.3, 30.5 (d, J_{CP} = 5.5 Hz), 26.7, 26.4, 25.7, 18.6 (d, J_{CP} = 4.9 Hz), 17.7, 16.4, 16.4 (d, J_{CP} = 6.1 Hz, 2C), 16.0; ^{31}P NMR (121 MHz) 21.6 ppm. Anal. Calcd for $C_{24}H_{40}NO_5P$: C, 63.56; H, 8.89; Found: C, 63.30; H, 8.94.

1,4-Bis(3′,7′,11′-Trimethyl-2′(*E*),6′(*E*),10′-dodecatrienyl)-3-(diethoxyphosphinyl)-2,5-piperazinedione (42). To a solution of lactam **25** (404 mg, 0.77 mmol) in diethyl ether (9 mL) at −40 °C was added dropwise LHMDS (1.0 M, 0.76 mL, 0.76 mmol, 0.99 equiv). After the reaction was stirred for 1 h, the mixture was cooled to −78 °C, HMPA (0.13 mL, 0.77 mmol, 1.00 equiv) and diethyl phosphorochloridite (0.11 mL, 0.76 mmol, 0.99 equiv) were added, and the resulting mixture was allowed to warm to 0 °C over 4 h. The reaction was quenched by slow addition of hydrogen peroxide (30%, 0.87 mL, 7.73 mmol, 10 equiv), and the resulting two-phase mixture was stirred vigorously at this temperature for 10 min. The organic phase was separated, washed with brine, and dried ($MgSO_4$). After concentration, final purification by column chromatography (silica gel, EtOAc/hexanes, 1:1) afforded phosphonate **42** (307 mg, 62%) as a clear oil, along with small amounts of starting material (60 mg, or 72% yield of **42** based on recovered starting material): ^{1}H NMR (300 MHz) δ 5.20−5.00 (m, 6H), 4.79 (dd, *J* = 15.0, 4.9 Hz, 1H), 4.31 (d, J_{HP} = 17.2 Hz, 1H), 4.33−3.88 (m, 7H), 3.78−3.66 (m, 2H), 2.15−1.90 (m, 16H), 1.72 (s, 3H), 1.70 (s, 3H), 1.68 (s, 3H), 1.68 (s, 3H), 1.60 (s, 6H), 1.59 (s, 6H), 1.38 (t, *J* = 7.1 Hz, 3H), 1.34 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz) δ 164.8, 161.3 (d, J_{CP} = 1.2 Hz), 143.5, 142.7, 135.8 (s, 2C), 131.5, 131.5, 124.5, 124.5, 123.7 (s, 2C), 117.3, 117.1, 64.1 (d, J_{CP} = 7.2 Hz), 63.6 (d, J_{CP} = 7.0 Hz), 57.9 (d, J_{CP} = 142.0 Hz), 49.7, 43.7, 42.4, 39.9, 39.9 (s, 2C), 39.9, 26.9 (s, 2C), 26.6, 26.5, 25.9 (s, 2C), 17.9 (s, 2C), 16.7 (d, J_{CP} = 3.4 Hz), 16.6, 16.6 (d, J_{CP} = 3.6 Hz), 16.5, 16.2, 16.2; ^{31}P NMR (121 MHz) 18.0 ppm. Anal. Calcd for $C_{38}H_{63}N_2O_5P$: C, 69.27; H, 9.64; N, 4.25. Found: C, 68.88; H, 9.70; N, 4.34.

1-(3′,7′,11′-Trimethyl-2′(*E*),6′(*E*),10′-dodecatrienyl)-3-methyl-2-pyrrolidinone (43). According to the general procedure for preparation of compound **21**, 3-methyl-2-pyrrolidinone (592 mg, 5.79 mmol) was treated with farnesyl bromide to afford lactam **43**. Purification by flash chromatography on silica gel (hexanes/EtOAc, 2:8 to 1:1) gave lactam **43** (1.61 g, 89%) as a clear oil: ^{1}H NMR (400 MHz) δ 5.16−5.04 (m, 3H), 3.89 (d, J = 7.2 Hz, 2H), 3.27−3.17 (m, 2H), 2.50−2.39 (m, 1H), 2.20 (dddd, J = 12.7, 8.5, 6.7, 4.1 Hz, 1H), 2.14−1.92 (m, 8H), 1.68 (s, 6H), 1.64−1.53 (m, 1H), 1.60 (s, 6H), 1.20 (d, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz) δ 176.8, 140.4, 135.4 131.4, 124.3, 123.7, 118.6, 44.5, 40.2, 39.7, 39.6, 36.8, 27.1, 26.7, 26.3, 25.7, 17.7, 16.4, 16.2, 16.0; HRMS (ES) *m*/*z* calcd for $C_{20}H_{34}NO$ ($M^+ + H$) 304.2640, found 304.2639.

1-(3′,7′,11′-trimethyl-2′(*E*),6′(*E*),10′-dodecatrienyl)-3-methyl-3-(diethoxyphosphinyl)-2-pyrrolidinone (44). According to the general procedure described for compound **31**, compound **43** (444 mg, 1.46 mmol) was treated with LDA, diethyl phosphorochloridite, and H_2O_2 to obtain phosphonate **44** (430 mg, 67%) as a clear oil: ^{1}H NMR (300 MHz) δ 5.20−5.03 (m, 3H), 4.32−4.06 (m, 4H), 3.98 (dd, J = 14.7, 7.0 Hz, 1H), 3.85 (dd, J = 14.7, 7.2 Hz, 1H), 3.47−3.32 (m, 1H), 3.27−3.14 (m, 1H), 2.63 (dddd, J = 18.1, 13.5, 7.7, 3.0 Hz, 1H), 2.20−1.74 (m, 9H), 1.68 (s, 6H), 1.59 (s, 6H), 1.44 (d, J_{HP} = 16.1 Hz, 3H), 1.38−1.28 (m, 6H); ^{13}C NMR (75 MHz) δ 172.2 (d, J_{CP} = 2.4 Hz), 140.8, 135.4, 131.4, 124.3, 123.7, 118.2, 63.0 (d, J_{CP} = 6.6 Hz), 62.4 (d, J_{CP} = 7.2 Hz), 45.5 (d, J_{CP} = 140.2 Hz), 43.7 (d, J_{CP} = 2.4 Hz), 40.7, 39.7, 39.6, 29.6 (d, J_{CP} = 1.7 Hz), 26.7, 26.3, 25.7, 19.6 (d, J_{CP} = 3.1 Hz), 17.7, 16.5, 16.5 (d, J_{CP} = 1.1 Hz), 16.2, 16.0; ^{31}P NMR 28.1 ppm; HRMS (ES) *m*/*z* calcd for $C_{24}H_{43}NO_4P$ ($M^+ + H$) 440.2930, found 440.2944.

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Supporting Information Available: ^{1}H and/or ^{13}C NMR spectra for compounds **21**, **28**, **33**, **34**, **35**, **38**, **39**, **43**, and **44**. This material is available free of charge via the Internet at http://pubs.acs.org.

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