The Synthesis of *P*-Chiral Amino Acid-Derived Phosphonamidic Anhydrides

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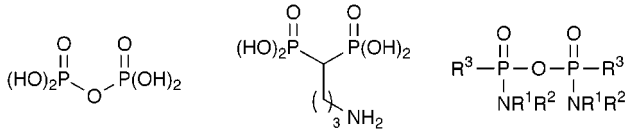
The synthesis of an array of *P*-chiral amino acid-derived phosphonamidic anhydrides is described. These anhydrides are prepared by condensation of allylated amino acids **19**−**22** with methyl- or vinylphosphonic dichlorides **23** or **24** to produce three diastereomeric anhydrides **4**−**11a**−**c** in good to excellent yields. The mechanistic issues concerning anhydride formation are discussed and supported by experimental results. Vinylphosphonamidic anhydrides **8**−**11** are further derivatized via the ring-closing metathesis (RCM) reaction to yield amino acid-derived bicyclic phosphonamidic anhydrides.

Introduction

Anhydrides and their derivatives have a rich history both in terms of their synthetic utility as well as their biological relevance.[1] Anhydrides are widely known to serve as potent inhibitors of a variety of enzymes,[2] with a number of anhydrides recently being reported as potent in-activators of various serine proteases.[3] Pyrophosphonic acid **1** (Scheme 1) and related analogues are a class of phosphorus-based anhydrides that have gained enormous attention over the last 50 years for their ability to serve as potent inhibitors of osteoclastic bone resorption and, therefore, have therapeutic value as osteoporotic agents.[4] Bisphosphonates,[5] synthetic non-hydrolyzable P−C−P analogues of pyrophosphates, are thus far the most effective agents developed for inhibiting osteoclastic bone re-sorption. As a result of the pioneering work of Fleisch,[6] these agents have become the primary players in the fight against osteoporosis, with Alendronate (**2**) now on the market.[7] Bisphosphonic acids have also proven to be powerful inhibitors of squalene synthase,[8] a crucial enzyme in the role of cholesterol biosynthesis. Current efforts in this area are focused on the development of diverse pyrophosphate analogues in hopes of improving their therapeutic profiles.[9]

Scheme 1



1 Pyrophosphoric Acid — **2** Alendronate — **3** Phosphonamidic Anhydrides

Schrader first reported a multitude of unique pyrophosphates during his initial work on phosphorus based insecticides.[10] A class of compounds that we have begun to study are the nitrogen containing phosphonamidic anhydrides **3**. Since the initial report of these anhydrides,[11] an array of analogues have been studied,[12] many of which possess an assortment of chemical and biological attributes including plant regulation,[13] metal chelation,[14] and anti-cholinesterase activity. As part of our program

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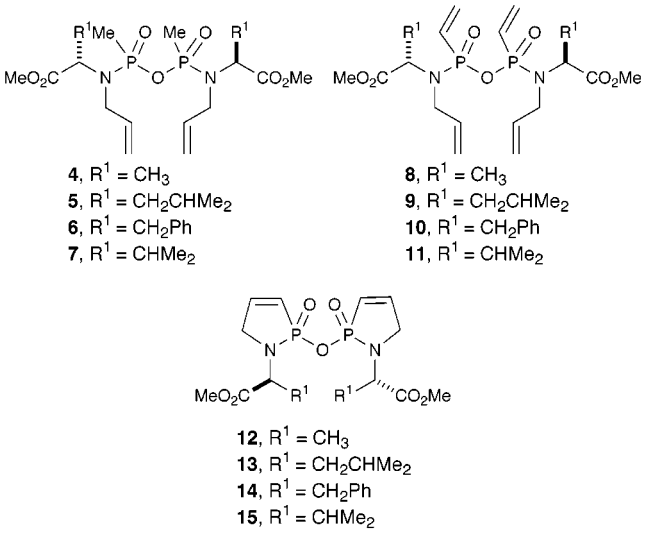
Scheme 2

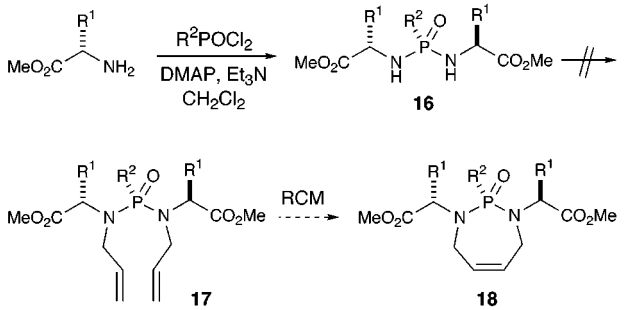


aimed at the development of structurally diverse phosphorus- and sulfur-based compounds,[15] we herein report a concise strategy into a new class of *P*-chiral amino acid-derived phosphonamidic anhydrides **4**−**15** (Scheme 2). These compounds, containing two stereogenic phosphorus atoms, exist as a pair of C_2-symmetric diastereomers and a single pseudo-meso diastereomer.[16] In this initial report, we discuss the convenient synthesis of a multitude of amino acid-based phosphonamidic anhydrides **4**−**15** (Scheme 2) and provide a mechanistic overview for their formation. We feel that this approach provides ample opportunity into the development of potentially useful, chiral, nonracemic phosphonamidic anhydrides.

Results and Discussion

In our continuing effort to synthesize novel *P*-heterocycles,[15] we have targeted a number of cyclic phosphorus containing motifs which can be accessed via the ring-closing metathesis (RCM) reaction (Scheme 3). Recently we reported a similar RCM strategy as a facile method to prepare amino acid-derived C_2-symmetric cyclic sulfamides.[17] Our initial attempts to prepare the cyclic phosphonamide **18** in a similar manner focused on the bis-allylation of the phosphonamide **16**[18] to derive **17**

Scheme 3



followed by ring-closing metathesis (Scheme 3). However, repeated attempts at the bis-allylation of the phosphonamide **16** failed. We next attempted to couple 2.0 equivalents of the α-branched allylated amino acids **19**−**22**[19] with the methyl- or vinylphosphonic dichlorides **23** or **24** (Scheme 4). However, repeated attempts at this coupling resulted only in mono-amination to yield two diastereomeric phosphonamidic chloridates **25**−**32P$_S$*S*** and **25**−**32P$_R$*S*** (Scheme 4). This result is presumable due to steric factors which prevent the bis-coupling of two secondary α-branched amino acids with methyl phosphonic dichloride.[20] These *P*-chiral diastereomers are remarkably stable, and can be isolated and purified by SiO_2 column chromatography in near quantitative yields. The chloridates are consistently formed in an approximate 1:1 ratio as determined by ^{31}P NMR, regardless of the amino acid/phosphonic dichloride combination. Upon standing at ambient temperature, these intermediate chloridates **25**−**32** dimerize over a period of 4 days as monitored by ^{31}P NMR. After water workup, this protocol (method A) yields three diastereomeric phosphonamidic anhydrides: a pseudo-*meso* isomer **4**−**11c**, and a pair of C_2-symmetric diastereomers **4**−**11a,** and **4**−**11b** as assayed by ^{31}P NMR (Table 1), ^{1}H NMR, ^{13}C NMR, and mass spectral analysis. Typical yields of the anhydrides in this original recipe range from 40 to 80%, with the remainder as hydrolyzed phosphonamidic acid.

We recently developed an optimized method (method B) which consistently leads to higher yields. A representative example of this new procedure applied to any of the phosphonamidic chloridates **25**−**32** was as follows: a single diastereomeric mixture of neat phosphonamidic chloridates **30P$_S$*S*** and **30P$_R$*S*** was cooled to 0° and exposed neat to 3.5 equivalents of triethylamine in an inert atmosphere. The reaction mixture was heated to 50° and monitored by TLC until disappearance of the phosphonamidic chloridates (typical reaction time is 30 min). The mixture was partitioned between EtOAc and water to cleanly yield the three diastereomeric anhy-

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(16) We have designated the term "pseudo-*meso*" to the diastereomer which contains an *unlike*-relationship between the two stereogenic phosphorus atoms in the optically active compounds **4**−**15c**. The pair of C_2-symmetric diastereomers contain a *like*-relationship between the two stereogenic phosphorus atoms in the optically active compounds **4**−**15a**,**b**.

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Scheme 4

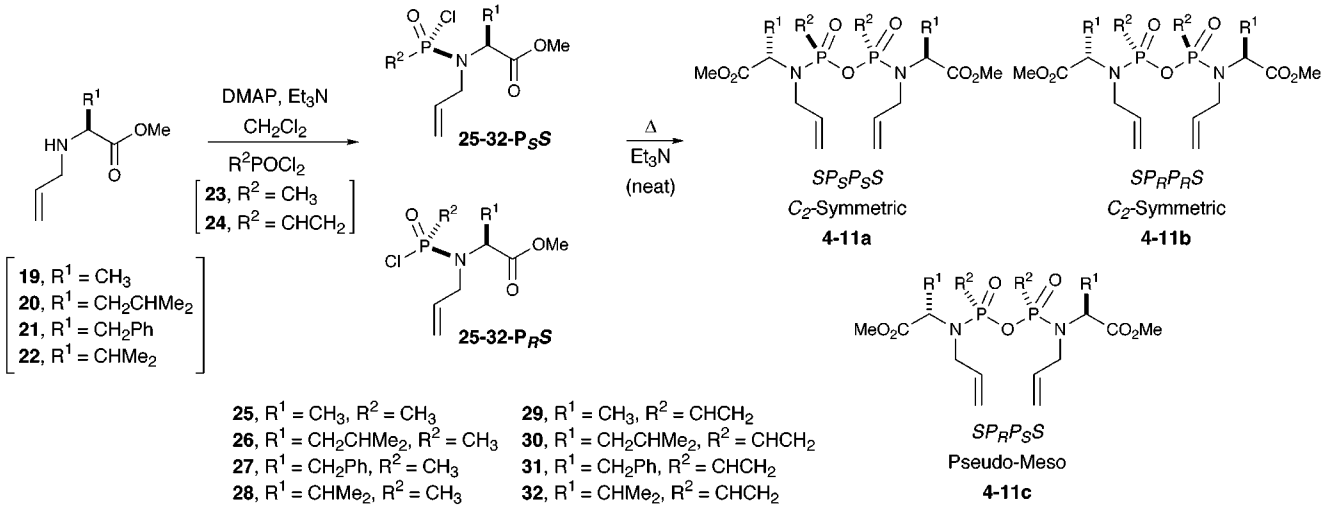

Table 1. ^{31}P NMR Resonances for the C_2-symmetric Phosphonamidic Anhydrides 4−11a,b and the Pseudo-Meso Phosphonamidic Anhydrides 4−11c

				d/*l* pair			pseudo-meso		
Pdt	R^1	R^2	yield (%)	entry	(%)	^{31}P δ	entry	(%)	^{31}P δ (*J*, Hz)
4	CH_3	CH_3	58[a]	**4ab**	31	29.47 29.41	**4c**	27	28.95 (34.4) 28.94 (34.4)
5	CH_2CHMe_2	CH_3	82[b] 72[a]	**5ab**	53	30.14 29.88	**5c**	29	29.19 (35.5) 28.41 (35.5)
6	CH_2Ph	CH_3	49[a]	**6ab**	23	30.10 29.36	**6c**	26	28.96 (36.7) 28.12 (36.7)
7	$CHMe_2$	CH_3	63[a]	**7ab**	43	30.20 29.94	**7c**	20	29.19 (35.4) 28.41 (35.4)
8	CH_3	$CH{=}CH_2$	51[a]	**8ab**	20	16.70 16.69	**8c**	31	16.40 (34.5) 16.25 (34.5)
9	CH_2CHMe_2	$CH{=}CH_2$	52[a] 81[b]	**9ab**	39	17.46 16.80	**9c**	42	16.48 (37.5) 15.78 (37.5)
10	CH_2Ph	$CH{=}CH_2$	55[a]	**10ab**	28	17.56 16.98	**10c**	27	15.90
11	$CHMe_2$	$CH{=}CH_2$	84[a]	**11ab**	44	17.22 16.87	**11c**	40	16.32 (35.9) 15.98 (35.9)

[a] Method A. [b] Method B.

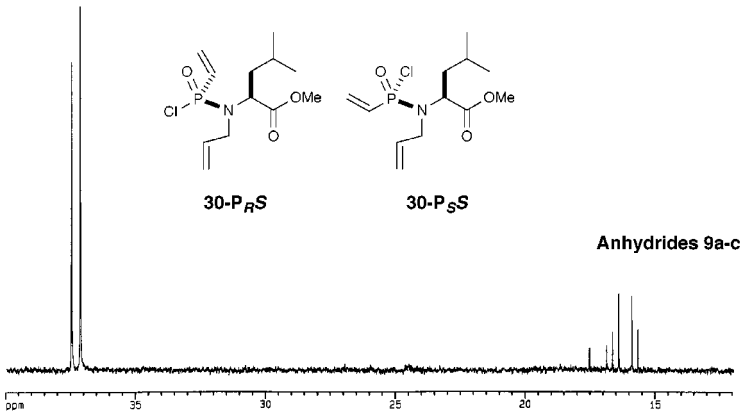

Figure 1. (^{1}H decoupled ^{31}P spectrum) ^{31}P NMR analysis of crude vinylphosphonamidic chloridates **30-P$_R$*S*** and **30-P$_R$*S*** before water workup using method A.

drides **9a**−**c**. Subsequent column chromatography yielded the corresponding pseudo-*meso* compound **9c** and the pair of diastereomers **9a**,**b** (the individual diastereomers **9a**,**b** were difficult to separate from each other). Yields in this improved procedure were typically greater than 80%. All of the anhydrides **4**−**11a**−**c** were slowly hydrolyzed in the presence of moisture, but were stable indefinitely in a number of solvents including chloroform, methylene chloride and DMSO.

We have relied heavily on ^{31}P NMR analysis (Table 1) in attempts to deduce the mechanism of anhydride formation. As seen in Figure 1 (and Table 1), initial formation of the leucine-derived phosphonamidic chloridates **30-P$_R$*S*** and **30-P$_R$*S*** is indicated by the appearance of two downfield singlets (R^2 = CH=CH_2, ∼37−38 ppm; when R^2 = CH_3, ∼47−48 ppm). Upon heating, formation of phosphonamidic anhydrides **9a**−**c** occur, leading to variable ratios of all three diastereomers as evident by

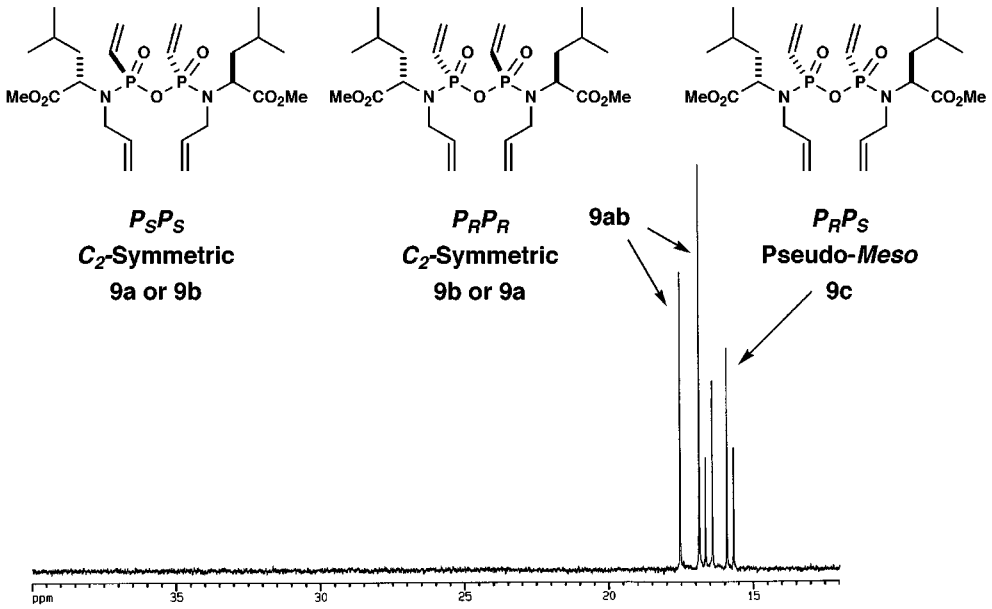

Figure 2. (^{1}H decoupled ^{31}P spectrum) ^{31}P NMR analysis of crude vinylphosphonamidic anhydrides **9a**−**c** after water workup using method A.

the appearance of two singlets (C_2-symmetric diastereomers, **9a,b**) and a pair of doublets (pseudo-*meso*, **9c**) between 15 and 18 ppm. (Figure 2).

Mechanistic Issues

Thus far, mechanistic studies pertaining to the formation of phosphonamidic anhydrides have been limited in the literature. Harger and co-workers have identified various phosphonamidic anhydrides in their eloquent mechanistic studies of base-induced rearrangements of *N*-phosphinoylhydroxylamine derivatives.[21] In addition, Smith, Hirschmann and co-workers have recently addressed mechanistic issues involved in pyrophosphonate anhydride formation associated with their efforts to synthesize phosphonopeptides.[22] While any detailed mechanistic discussion requires further investigation, a reasonable hypothesis for the formation of anhydrides **4**−**11** is depicted in Scheme 5. We propose a mechanism that involves nucleophilic participation from the nitrogen of a phosphonamidic chloridate molecule (**25**−**32**) to directly couple with another phosphonamidic chloridate molecule (**25**−**32**) (Scheme 5). This is in contrast to another plausible mechanism involving direct coupling of a phosphonamidic acid molecule (hydrolyzed **25**−**32**) with another phosphonamidic chloridate molecule (**25**−**32**). The proposed mechanism involves two intermediate trigonal bipyramidal-containing transition states **33** and **35**, rather than a stereocontrolled direct displacement via an S_N2-like transition state. The nonstereospecific addition of water to the phosphoniminium species **34** generates the second trigonal bipyramidal transition state **35** which collapses to yield the 3 diastereomeric anhydrides **4**−**11a**−**c**.

Anhydride formation appears to occur in a nonstereospecific manner, since subjecting each individual chloridate diastereomer to the improved reaction conditions yields the same three diastereomeric anhydrides. Given that the starting chloridate was a single diastereomer of either "like" SP_S or "unlike" SP_R configurations, and that the resulting anhydrides contain both "like" and "unlike" diastereo-relationships, the displacement at phosphorus is not stereoselective. The ratios seen in anhydride formation were typically inconsistent (∼1−3: 1−3 of pseudo-*meso* to diastereomeric C_2-symmetric pair). The nature of the proposed reaction mechanism undoubtedly allows for this inconsistency during anhydride formation.

We have yet to observe ^{31}P NMR peaks corresponding to the intermediate phosphonimidic cations **33** or **34**. Attempts to detect these intermediates were made by monitoring the reaction by ^{31}P NMR over a period of several days. As shown in Figure 3, the dimerization of a mixture of the diastereomeric valine-derived phosphonamidic chloridates **28** (∼1:1 mixture of **28P$_R$*S*** and **28P$_S$*S***), under anhydrous conditions in $CDCl_3$/Et_3N, smoothly progresses over time to yield a pair of C_2-symmetric diastereomers **7a,b** (two singlets) and a single pseudo-*meso* isomer **7c** (pair of doublets). Careful analysis of this spectra shows the presence of two very small, unaccountable, peaks at ∼45.4 ppm (0−20% completion) and 35.9 ppm (>50% completion). Other than these peaks, the reaction appears to proceed cleanly from starting chloridate to product. It is also worth noting that the ^{31}P NMR resonance corresponding to the valine phosphonamidic acid is also not present. We feel that this spectroscopic evidence indicates that our proposed mechanism goes through three short-lived reactive intermediates (**33**-**35**) which may have low relative abundance. Although it may be argued that this reaction cannot proceed past intermediates **33** and **34** under anhydrous conditions, adventitious amounts of water must be present to account for the above observations. We have repeated this experiment several times and have observed the same result each time.

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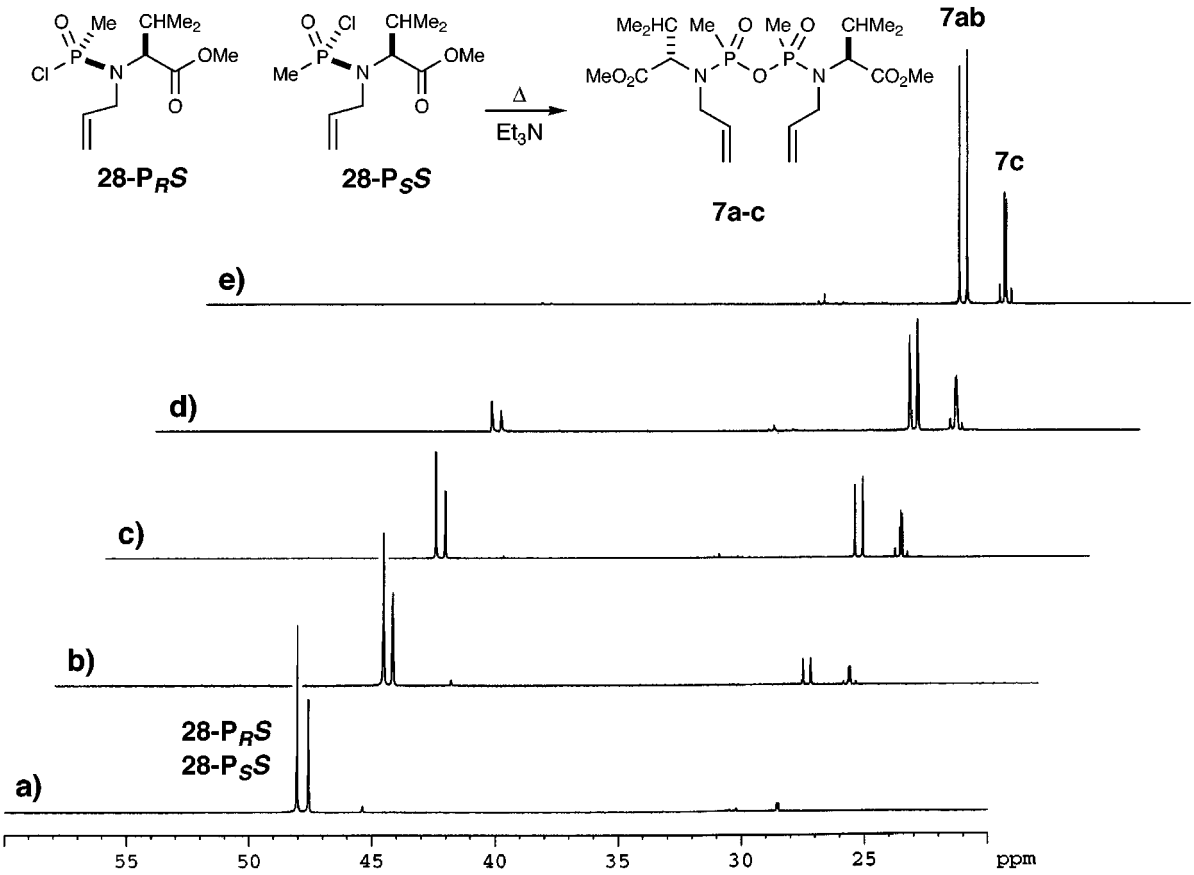
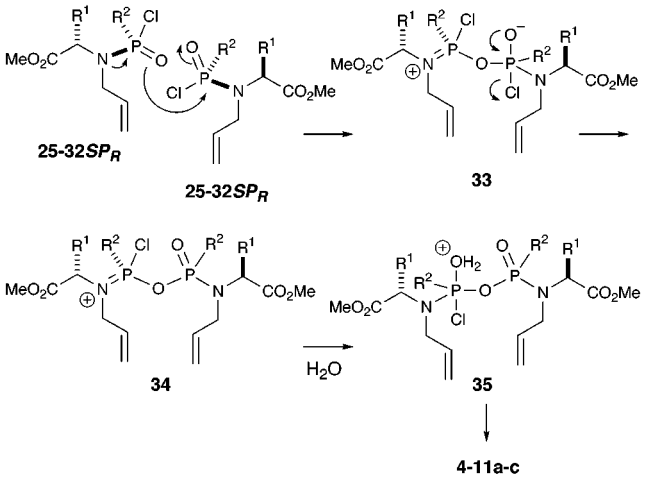
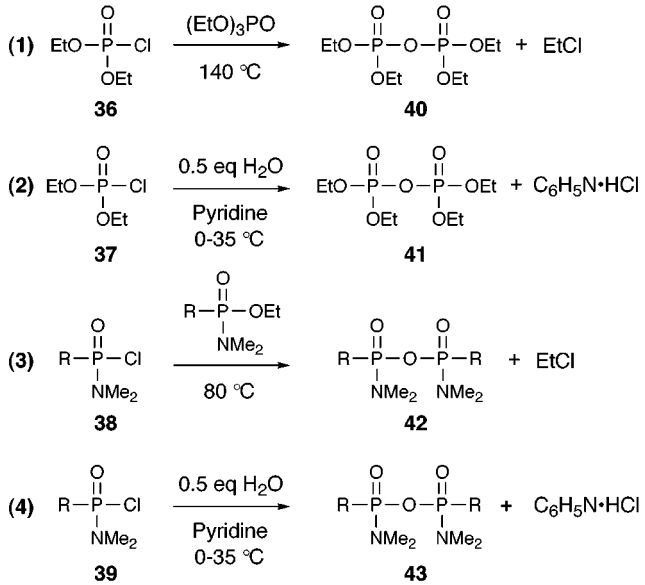


Figure 3. (^{1}H decoupled ^{31}P spectrum) ^{31}P NMR analysis of the dimerization of a mixture of the diastereomeric valine-derived methyl phosphonamidic chloridates **28** (~1:1 mixture of **28-P$_R$S** and **28-P$_R$S**) under anhydrous conditions in $CDCl_3$/Et_3N. The reaction yields a pair of C_2-symmetric diastereomers **7a**,**b** (two singlets) and a single pseudo-meso isomer **7c** (pair of doublets). Intervals at (a) 0%, (b) 20%, (c) 52%, (d) 85%, and (e) 100% indicating the percent-completion of reaction.

Scheme 5

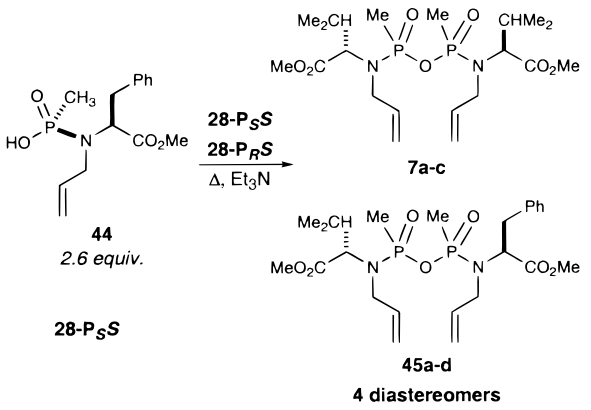


Scheme 6



The mechanism that we have proposed has literature precedence in previously reported pyrophosphate syntheses and two phosphonamidic anhydride syntheses (eqs 1−4, Scheme 6).[14] Both of these earlier reports used the Schrader (eq 1) or the modified Schrader (eq 3) methods to yield the pyrophosphonate **40** or the phosphonamidic anhydride **42**. The reactions in eqs 1 and 3 were run under inert, anhydrous conditions, and must invoke an oxonium or iminium intermediate similar to **31** or **34** in Scheme 5 in order to account for chloroethane formation. In contrast, these reports also utilized the Toy (eq 2) and Holmstedt (eq 4) methods to yield pyrophosphonate **41** or the phosphonamidic anhydride **43**. In eqs 2 and 4, 0.5 equiv of water was deliberately included in order to derive 0.5 equivalents of the corresponding phosphonic acid in situ. This acid is then phosphonylated with the remaining 0.5 equivalent of starting phosphonic chloride to derive either the pyrophosphonate or phosphonamidic anhydride, respectively.

Scheme 7



To further verify our mechanism, a simple cross-coupling experiment between the phenylalanine-derived phosphonamidic acid **44** and the pair of diastereomeric valine-derived phosphonamidic chloridates **28-P$_S$*S*** and **28-P$_R$*S*** was carried out under anhydrous conditions (Scheme 7). As shown in Scheme 7, coupling of 2.6 equivalents of **44** with 1.0 equivalent of **28** gave an ~3:1 ratio of the bis-valine derived phosphonamidic anhydrides **7a**−**c** (3 diastereomers) to the mixed valine-phenylalanine-derived anhydrides **45** (4 diastereomers). We feel that this ratio further supports our proposed mechanism since acid **44** was used in excess, and the resulting mixed phosphonamidic anhydride **45** was still the minor product. These results also indicate that the dimerization of chloridates **28** occurs faster than condensation of acid **44** with chloridate **28**.

Ring-Closing Metathesis Studies

We felt that the vinylphosphonamidic anhydrides **8**−**11** represented attractive scaffolds from which to exploit the RCM reaction. The allylated amino acid vinylphosphonamidic anhydrides **9**−**11** undergo ring closing metathesis using the Grubbs benzylidene catalyst to give products **12**−**15** in excellent yields (>90%). Figure 4 shows the resulting crude ^{1}H decoupled ^{31}P spectrum of the pseudo-*meso* bicyclic RCM product **13c** (note the downfield shift from the starting pseudo-*meso* phosphonamidic anhydride **9c** shown in Figure 2). The cyclic phosphonamidic anhydride motifs **12**−**15** are currently being investigated for both their synthetic and biological utility.

Conclusion

In conclusion, the rapid assembly of these structurally diverse amino acid-derived phosphonamidic anhydrides and their subsequent RCM reactions have been demonstrated. When coupled with the therapeutic potential of anhydrides, pyrophosphates, bisphosphonates, and their derivatives, these compounds represent an exciting new class of phosphorus compounds. We are currently targeting a number of derivatives of the amino acid analogues presented herein and are assaying them for biological activity. These efforts will be reported in due course.

Experimental Section

General Methods. All reactions were carried out in flame- or oven-dried glassware under an argon atmosphere with magnetic stirring. Methylene chloride was purified via one of two ways: by passage through the Solv-Tek purification system employing activated Al_2O_3,[23] or by distillation over CaH_2. Triethylamine was distilled from CaH_2 and stored over KOH. DMAP was purchased from Reilly Chemicals and was not further purified. All amino acid precursors were purchased from Advanced Chem Tech. Deuteriochloroform ($CDCl_3$) was purchased from Cambridge Isotope laboratories and stored over potassium carbonate at room temperature. Mass spectra were performed by the Mass Spectrometry Laboratory at the University of Kansas. Flash column chromatography was performed with Merck silica gel (EM-9385-9, 230−400 mesh). Thin-layer chromatography was performed on silica gel 60F_{254} plates (EM-5715-7, Merck). Visualization of TLC spots was effected using $KMnO_4$ stain.

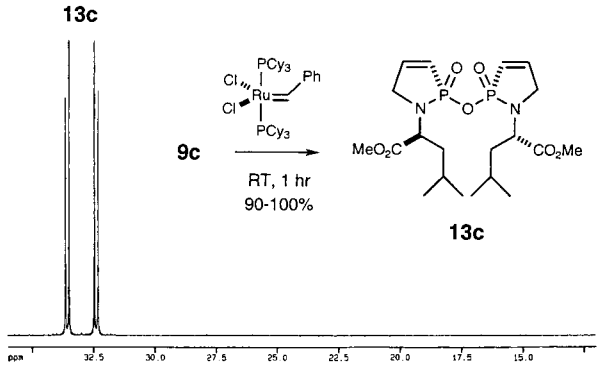


Figure 4. (^{1}H decoupled ^{31}P spectrum) ^{31}P NMR analysis of the crude RCM reaction product **13c** (pair of doublets at 33.55 and 32.38 ppm) after 30 min.

Leucine-Derived Methyl Phosphonamidic Chloridates (26P$_S$*S* and 26P$_R$*S*). To a flame-dried 100 mL round-bottom flask under argon atmosphere was added methylphosphonic dichloride **23** (1.0 mL, 11.04 mmol) and CH_2Cl_2 (20 mL). The reaction flask was cooled to 0 °C, and Et_3N (6.26 mL, 45.0 mmol) was added dropwise, followed by a catalytic amount of DMAP (5 mol %). After stirring at 0 °C for 5 min, 0.98 equiv of allylated leucine methyl ester **20** (2.0 g, 10.82 mmol) in CH_2Cl_2 (5 mL) was added via cannula. The reaction mixture was refluxed and monitored by TLC. Once complete, the reaction mixture was concentrated under reduced pressure, diluted with EtOAc, filtered, and concentrated under reduced pressure. Flash chromatography (SiO_2, 3:1 Hex/EtOAc) gave 2.94 g (95%) of a light yellow oil consisting solely of the 2 diastereomeric chloridates **26P$_S$*S*** and **26P$_R$*S***. Further chromatography (SiO_2, 8:1 Hex/EtOAc) yielded portions of the separated isomers for characterization.

Leucine-derived methyl phosphonamidic chloridate (26P$_S$*S* or 26P$_R$*S*, top *R$_f$*): TLC R_f = 0.39 (1:1 Hex/EtOAc); $[\alpha]^{25} = -42.3°$ (c = 2.44, $CHCl_3$); FTIR 1742, 1445, 1368, 1240 (P=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (dddd, 16.9, 10.2, 6.5, 6.5 Hz, 1H), 5.22 (dd, J = 17.2, 1.2 Hz, 1H), 5.14 (d, J = 10.1 Hz, 1H), 4.40 (ddd, J_{HP} = 12.1 Hz, J_{HH} = 7.5, 7.5 Hz, 1H), 3.75−3.67 (m, 2H), 3.68 (s, 3H), 1.96 (d, J_{HP} = 16.3 Hz, 3H), 1.70 (dd, J = 7.3, 6.3 Hz, 2H), 1.65−1.52 (m, 1H), 0.91 (d, J = 6.4 Hz, 3H), 0.90 (d, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.37, 134.68 (d, J_{CP} = 3.0 Hz), 118.04, 55.87, 52.05, 47.16 (d, J_{CP} = 4.5 Hz), 38.49 (d, J_{CP} = 5.7 Hz), 24.52, 22.65 (d, J_{CP} = 118.9 Hz), 22.65, 21.53; ^{31}P NMR (162 MHz, $CDCl_3$) δ 48.02; HRMS calcd for $C_{11}H_{23}ClNO_3P$ $(M + H)^+$ required 282.1026, found 282.1049.

Leucine-derived methyl phosphonamidic chloridate (26P$_R$*S* or 26P$_S$*S*, bottom R$_f$): TLC R_f = 0.38 (1:1 Hex/EtOAc); $[\alpha]^{25} = -13.1°$ (c = 1.44, $CHCl_3$); FTIR 1742, 1440, 1373, 1245 (P=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81−5.69 (m, 1H), 5.20−5.08 (m, 2H), 4.51 (ddd, J_{HP} = 9.2 Hz,

(23) Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518−1520.

J_{HH} = 6.2, 6.2 Hz, 1H), 3.76−3.66 (m, 2H), 3.62 (s, 3H), 1.98 (d, J_{HP} = 16.0 Hz, 3H), 1.73−1.64 (m, 2H), 1.64−1.51 (m, 1H), 0.89 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.56 (d, J_{CP} = 6.2 Hz), 134.08 (d, J_{CP} = 2.8 Hz), 118.06, 55.35 (d, J_{CP} = 2.0 Hz), 51.97, 46.47 (d, J_{CP} = 5.1 Hz), 37.14 (d, J_{CP} = 2.1 Hz), 24.31, 22.80, 22.28 (d, J_{CP} = 117.3 Hz), 21.20; ^{31}P NMR (162 MHz, $CDCl_3$) δ 47.98; HRMS calcd for $C_{11}H_{23}ClNO_3P$ $(M + H)^+$ required 282.1026, found 282.1047.

Leucine-Derived Methyl Phosphonamidic Anhydrides (5a−c) (Method B). To a neat solution of a mixture of diastereomeric leucine phosphonamidic chloridates **26P*R*S** and **26P*S*S** (260 mg, 0.92 mmol) at 0 °C was added Et_3N (450 μL, 3.22 mmol). The mixture was heated at 45 °C and monitored by TLC and ^{31}P NMR. The resulting salty slurry was diluted with EtOAc (10 mL) and filtered (10 mL) and concentrated under reduced pressure to yield 236 mg (quantitative) of a mixture of the 3 diastereomeric anhydrides as a yellow oil. Flash chromatography (SiO_2, 1:1 Hex/EtOAc) afforded 46 mg (20%) of the pseudo-meso diastereomer **5c**, and 132 mg (56%) of a mixture of C_2-symmetric diastereomers **5a** and **5b**. The mixture was comprised of 16 mg (7%) of a single C_2-symmetric diastereomer **5a** or **5b**, 104 mg (44%) of a mixture of C_2-symmetric diastereomers **5a** and **5b**, and 12 mg (5%) of a sample of C_2-symmetric diastereomer **5b** or **5a** at 90% purity, all as colorless oils.

Pseudo-*meso* leucine-derived methyl phosphonamidic anhydride (5c): TLC R_f = 0.40 (EtOAc); $[\alpha]^{25} = -17.06°$ (c = 0.59, $CHCl_3$); FTIR 1749, 1714, 1422, 1363, 1222 (P═O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87−5.75 (m, 2H), 5.18 (dd, J = 17.1, 1.3 Hz, 1H), 5.14 (dd, J = 17.1, 1.3 Hz, 1H), 5.12−5.06 (m, 2H), 4.49 (ddd, J_{HP} = 10.7 Hz, J_{HH} = 10.7, 5.4 Hz, 1H), 4.34 (ddd, J_{HP} = 9.2 Hz, J_{HH} = 9.2, 5.3 Hz, 1H), 3.75−3.58 (m, 4H), 3.68 (s, 3H), 3.66 (s, 3H), 1.83−1.60 (m, 6H), 1.74 (d, J_{HP} = 16.8 Hz, 3H), 1.69 (d, J_{HP} = 16.7 Hz, 3H), 0.92 (d, J = 6.2 Hz, 6H), 0.91 (d, J = 6.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.67 (d, J_{CP} = 2.2 Hz), 173.20, 135.34, 135.34, 117.77, 117.48, 56.32 (d, J_{CP} = 2.9 Hz), 55.93 (d, J_{CP} = 3.6 Hz), 51.94, 51.90, 47.24 (d, J_{CP} = 4.9 Hz), 46.45 (d, J_{CP} = 4.9 Hz), 38.98 (d, J_{CP} = 3.7 Hz), 37.57 (d, J_{CP} = 2.6 Hz), 24.51, 24.19, 22.95, 22.87, 21.51, 21.33, 15.49 (dd, J_{CP} = 129.5, 4.3 Hz), 14.80 (dd, J_{CP} = 127.7, 4.5 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.19 (d, J_{PP} = 35.5 Hz), 28.41(d, J_{PP} = 35.5 Hz); HRMS calcd for $C_{23}H_{43}N_2O_7P_2$ $(M + H)^+$ required 509.2546, found 509.2545.

***C*$_2$-symmetric leucine-derived methyl phosphonamidic anhydride, single diastereomer (5a or 5b, top *R*$_f$):** TLC R_f = 0.22 (EtOAc); $[\alpha]^{25} = -37.8°$ (c = 0.32, $CHCl_3$); FTIR 1740, 1437, 1387, 1241 (P═O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (dddd, J = 16.9, 10.2, 6.2, 6.2 Hz, 2H), 5.21 (dd, J = 15.9, 1.2 Hz, 2H), 5.12 (dd, J = 9.8, 0.9 Hz, 2H), 4.49−4.42 (m, 2H), 3.79−3.57 (m, 4H), 3.67 (s, 6H), 1.81−1.59 (m, 6H), 1.75 (d, J_{HP} = 17.0 Hz, 6H), 0.94 (d, J = 6.0 Hz, 6H), 0.93 (d, J = 6.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.33, 135.59, 117.62, 56.11, 51.95, 46.95, 38.71, 24.57, 22.94, 21.31, 15.67 (dd, J_{CP} = 130.9, 5.6 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.88; HRMS calcd for $C_{23}H_{43}N_2O_7P_2$ $(M + H)^+$ required 509.2546, found 509.2526.

***C*$_2$-symmetric leucine-derived methyl phosphonamidic anhydride, single diastereomer (5b or 5a, bottom *R*$_f$ at 90% purity):** TLC R_f = 0.22 (EtOAc); $[\alpha]^{25} = -5.0°$ (c = 0.24, $CHCl_3$); FTIR 1740, 1437, 1387, 1241 (P═O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (dddd, J = 16.8, 10.1, 6.6, 6.6 Hz, 2H), 5.17 (dd, J = 16.7, 1.3 Hz, 2H), 5.10 (dd, J = 9.1, 1.0 Hz, 2H), 4.52−4.42 (m, 2H), 3.66−3.54 (m, 4H), 3.68 (s, 6H), 1.80 (d, J_{HP} = 15.8 Hz, 6H), 1.78−1.53 (m, 6H), 0.94 (d, J = 6.0 Hz, 6H), 0.93 (d, J = 6.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.48, 135.13, 117.47, 55.65, 51.91, 46.35, 37.46, 24.34, 22.99, 21.21, 15.27 (dd, J_{CP} = 130.9, 5.6 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 30.14; HRMS calcd for $C_{23}H_{43}N_2O_7P_2$ $(M + H)^+$ required 509.2546, found 509.2561.

Leucine-Derived Vinylphosphonamidic Anhydrides (9a−c). In a procedure similar to that used for the preparation of the methyl anhydrides **5a−c** (method B), a mixture of the diastereomeric vinylchloridates **30P*S*S** and **30P*R*S** (355 mg, 1.21 mmol) was subjected to the conditions of method B. Flash chromatography (SiO_2, 1:1 Hex/EtOAc) afforded 135 mg (42%) of the pseudo-meso diastereomer **9c** and 126 mg (39%) of an inseparable mixture of C_2-symmetric diastereomers **9a** and **9b**, both as colorless oils.

Pseudo-*meso* leucine-derived vinylphosphonamidic anhydride (9c): TLC R_f = 0.68 (EtOAc); $[\alpha]^{25} = -15.59°$ (c = 0.68, $CHCl_3$); FTIR 1740, 1649, 1461, 1438, 1387, 1207 (P═O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.45−6.22 (m, 4H), 6.19−6.11 (m, 1H), 6.06−5.98 (m, 1H), 5.82−5.72 (m, 2H), 5.13 (dd, J = 17.1, 1.2 Hz, 2H), 5.09 (dd, J = 17.1, 1.2 Hz, 2H), 4.46−4.40 (m, 1H), 4.33 (ddd, J = 13.2, 9.5, 5.3 Hz, 1H), 3.64 (s, 3H), 3.64−3.59 (m, 4H), 3.63 (s, 3H), 1.79−1.56 (m, 6H), 0.88 (d, J = 6.3 Hz, 6H), 0.87 (d, J = 6.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.44 (d, J_{CP} = 2.5 Hz), 173.14, 135.05, 135.05, 133.52, 133.52, 128.51 (dd, J_{CP} = 166.4, 8.2 Hz), 128.33 (dd, J_{CP} = 166.4, 9.0 Hz), 117.95, 117.68, 56.08 (d, J_{CP} = 3.4 Hz), 55.68 (d, J_{CP} = 4.3 Hz), 51.85, 51.76, 47.11 (d, J_{CP} = 5.2 Hz), 46.52 (d, J_{CP} = 5.2 Hz), 38.71 (d, J_{CP} = 3.6 Hz), 37.61 (d, J_{CP} = 3.0 Hz), 24.32, 24.06, 22.83, 22.83, 21.50, 21.34; ^{31}P NMR (162 MHz, $CDCl_3$) δ 16.48 (d, J_{PP} = 37.5 Hz), 15.78 (d, J_{PP} = 37.5 Hz); HRMS calcd for $C_{24}H_{43}N_2O_7P_2$ $(M + H)^+$ required 533.2546, found 533.2550.

***C*$_2$-symmetric leucine-derived vinylphosphonamidic anhydrides (9a,b):** characterized as a mixture; TLC R_f = 0.24 (EtOAc); FTIR 1741, 1642, 1613, 1469, 1438, 1370, 1233 (P═O), 1207 (P═O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.37−6.21 (m, 8H), 6.08 (ddd, J = 10.2, 8.6, 4.2 Hz, 2H), 5.94 (ddd, J = 10.2, 8.5, 4.3 Hz, 2H), 5.75−5.65 (m, 4H), 5.11−4.96 (m, 8H), 4.40−4.29 (m, 4H), 3.65−3.51 (m, 8H), 3.57 (s, 6H), 3.56 (s, 6H), 1.74−1.49 (m, 12H), 0.87−0.81 (m, 24H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.05, 172.93, 135.08, 135.01, 133.92, 133.86, 128.18 (dd, J_{CP} = 176.8, 4.9 Hz), 127.98 (dd, J_{CP} = 174.9, 4.1 Hz), 117.59, 117.33, 55.67, 55.50, 51.66, 51.60, 46.62, 46.22, 38.32, 37.49, 24.17, 23.98, 22.71, 22.71, 21.13, 21.05; ^{31}P NMR (162 MHz, $CDCl_3$) δ 17.46, 16.80; HRMS calcd for $C_{24}H_{43}N_2O_7P_2$ $(M + H)^+$ required 533.2546, found 533.2556.

Pseudo-Meso Bicyclic Leucine-Derived Phosphonamidic Anhydride (13c). To a flame-dried 25 mL round-bottom flask were added leucine-derived vinylphosphonamidic anhydride **9c** (88 mg, 0.165 mmol) and CH_2Cl_2 (15 mL). The mixture was stirred, and the system was purged with argon for 10 min using a gas aerating tube. The Grubbs catalyst (6.8 mg, 8 μmol) was added under argon, and the reaction was stirred and monitored for disappearance of starting material. Upon completion, the reaction was concentrated under reduced pressure, passed through a plug of silica using EtOAc, and concentrated under reduced pressure to give a crude oil. Flash chromatography (SiO_2, 100% EtOAc) afforded the bicyclic phosphonamidic anhydride **13c** (75 mg, 96%) as a colorless oil: TLC R_f = 0.20 (EtOAc); $[\alpha]^{25} = +11.1°$ (c = 0.19, $CHCl_3$); FTIR 1742, 1587, 1451, 1390, 1346, 1241 (P═O), 1199 (P═O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11−7.06 (m, 1H), 7.00−6.95 (m, 1H), 6.25 (dd, J = 30.3, 9.0 Hz, 1H), 6.12 (dd, J = 30.2, 9.0 Hz, 1H), 4.47 (ddd, J_{HP} = 9.4 Hz, J_{HH} = 6.5, 6.5 Hz, 1H), 4.29 (ddd, J_{HP} = 7.2 Hz, J_{HH} = 7.2, 7.2 Hz, 1H), 4.17−4.06 (m, 2H), 3.76−3.67 (m, 2 H), 3.67 (s, 3H), 3.65 (s, 3H), 1.67−1.64 (m, 4H), 1.64−1.51 (m, 2H), 0.97 (d, J = 6.3 Hz, 3H), 0.93−0.90 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.60 (d, J_{CP} = 1.2 Hz), 173.13 (d, J_{CP} = 1.9 Hz), 146.15 (d, J_{CP} = 17.0 Hz), 145.75 (d, J_{CP} = 17.4 Hz), 119.24 (d, J_{CP} = 161.9 Hz), 118.62 (dd, J_{CP} = 166.2, 2.9 Hz), 52.20 (d, J_{CP} = 4.1 Hz), 52.04 (d, J_{CP} = 4.5 Hz), 51.84, 51.73, 47.18 (d, J_{CP} = 31.8 Hz), 46.82 (d, J_{CP} = 31.1 Hz), 39.14 (d, J_{CP} = 3.4 Hz), 38.49 (d, J_{CP} = 3.8 Hz), 24.48, 24.47, 23.06, 22.99, 21.28, 21.07; ^{31}P NMR (162 MHz, $CDCl_3$) δ 33.55 (d, J_{PP} = 24.0 Hz), 32.38 (d, J_{PP} = 24.0 Hz); HRMS calcd for $C_{20}H_{35}N_2O_7P_2$ $(M + H)^+$ required 477.1919, found 477.1911.

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Supporting Information Available: Experimental details and spectroscopic data of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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