Synthetic Studies toward the Preparation of Phosphonate Analogs of Sphingomyelin and Ceramide 1-Phosphate Using Pentacovalent Organophospholene Methodology

Cynthia K. McClure,*[,1] Pranab K. Mishra, and Christopher W. Grote[†]

Department of Chemistry and Biochemistry, Montana State University, Bozeman, Montana 59717

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Model studies for the syntheses of phosphonate analogs of sphingomyelin and ceramide 1-phosphate are described. The pentacovalent oxaphospholene **3b** (derived from methyl vinyl ketone and triethyl phosphite) readily condensed with dialkyl azodicarboxylates (R = Et, t-Bu, CH_2CCl_3) to form β-hydrazido γ-ketophosphonates **5** and **8** in excellent yields. Cleavage of the N−N bond in **5a** (R = Et) or **5b** (R = t-Bu) via standard methods was unsuccessful. Upon reduction with $NaBH_4$, **8** produced the oxazolidinone **9** (93%) as a diastereomeric mixture of 3:1. Treatment of **9** with Zn/HOAc/acetone at rt readily cleaved the N−N bond to form **11** (78−83%). Confirmation of stereochemical assignments in **11** (3:1, trans:cis) was accomplished via NOE experiments.

Introduction

Sphingolipids are important membrane components in both animal and plant cells,[2] with the sphingomyelins being one of the major constituents in animal cells (especially nerve cells). Each sphingomyelin consists of a fatty acid, sphingosine residue, and a phosphocholine group. Sphingomyelins have been associated with the regulation of intracellular cholesterol balance, atherosclerosis, musclar dystrophy, leukæmia, a neurological disorder called Niemann−Pick disease, as well as other physiological functions.[2] Sphingomyelinases,[2b,3] the best known being the acidic liposomal human sphingomyelinase, have been shown to cleave the phosphocholine group from the sphingomyelin molecule to produce ceramide, a major player in the sphingomyelin cycle and a known second messenger in cellular signaling.[2bg,4] Further catabolism of ceramide by ceramidases produces a fatty acid and sphingosine,[5] a known inhibitor of protein kinase C, an enzyme critical to cellular regulation and signal transduction.[6]

The importance of sphingomyelins, ceramides, and sphingosines in metabolism and cellular signaling has kept the areas of phospholipid biosynthesis, activation, and catabolism under intense investigation due to the speculative nature of many of the "answers" to these pathways. The recent fundamental questions and problems raised include the lack or dearth of information on (a) the physiological function of ceramide 1-phosphate and sphingosine 1-phosphate in cellular transduction processes; (b) the extent of extracellular activators of sphingomyelin hydrolysis and ceramide generation; (c) the cellular localization of the signaling pool of sphingomyelin, as well as the source of the sphingosine that serves as a modulator; (d) the mechanism of phospholipid activation of sphingolipid hydrolases; and (e) structural information on the active sites in sphingomyelinases, as well as information on their mechanism(s) of action.[1−6]

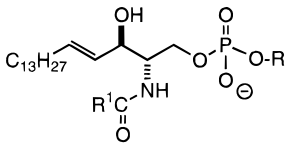

Figure 1.

One way to obtain information relating to the mode of action and active site of an enzyme is to introduce analogs of the natural substrates for structure−activity relationship (SAR) studies. Phosphonate analogs of phosphate groups have been shown to be useful in the investigations of the structure and mechanism of various enzymatic systems.[7] Phosphonate analogs of sphingomyelin and ceramide 1-phosphate would not be able to be cleaved by the enzyme sphingomyelinase due to the nonlabile

* To whom correspondence should be addressed. Phone: 406-994-1779. Fax: 406-994-5407. E-mail: UCHCM@EARTH.OSCS.MONTANA.EDU.

† Current address: Eastman Kodak Co., Chemical Developments Div., Rochester, NY 14652-3619.

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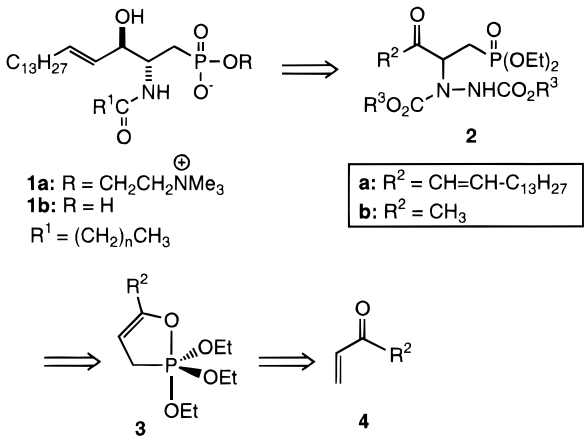
Scheme 1



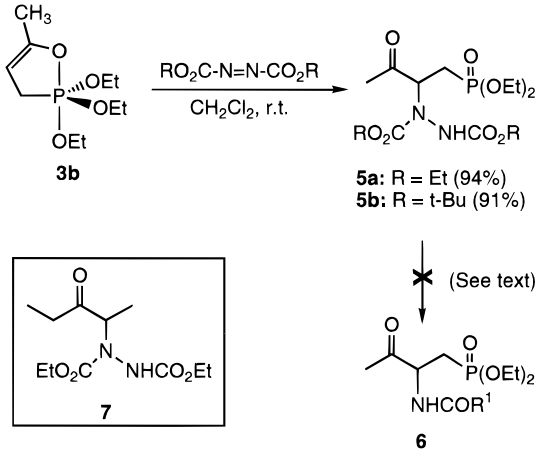
P−C bond and are thus potential inhibitors of this enzyme. These analogs also allow for further analyses of the metabolic processes of sphingomyelin and ceramide.

Since very little is known about the structure of the active site in sphingomyelinase, both isosteric and nonisosteric phosphonate analogs would be useful in SAR studies. We are currently applying our pentacovalent organophospholene methodology[8] to the preparation of nonisosteric phosphonate analogs of the sphingomyelins **1a**, and of ceramide 1-phosphates, **1b**, utilizing dialkyl azodicarboxylates as the electrophilic nitrogen sources (Scheme 1). We report herein our model studies toward this goal utilizing the pentacovalent oxaphospholene **3b** ($R^2 = CH_3$).

Results and Discussion

We have previously reported that the readily available pentacovalent oxaphospholene **3b** (derived from methyl vinyl ketone and triethyl phosphite) condensed with diethyl or di-*tert*-butyl azodicarboxylates (DEAD or DTBAD, respectively) to produce the phosphono-keto-hydrazides **5a,b** in excellent isolated yields[8b,9] (see Scheme 2). In order to achieve our final synthetic goal of the sphingomyelin and ceramide 1-phosphonate analogs, it will be necessary to cleave the N−N bond in the hydrazide.

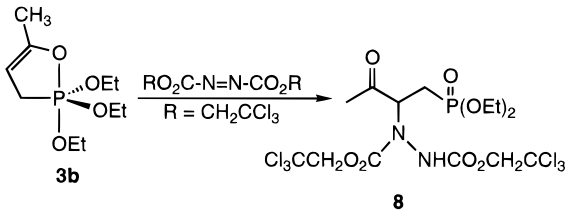
Scheme 2



We initially pursued the cleavage of the N−N bond in the *tert*-butyl derivative **5b**.[9] The standard methods include hydrolysis of the *tert*-butyl esters and subsequent decarboxylation of the carbamic acid to the hydrazine, followed by hydrogenolysis.[10a,c] However, we were unable to isolate any phosphonate-containing products under these conditions for *tert*-butyl ester hydrolysis (TFA, TMS-I), possibly due to hydrolysis of the phosphonate to the phosphonic acid as well (TMS-I). Attempts at reduction of the diethyl hydrazide N−N bond in **5a** using the standard Raney nickel method[10b] (with and without protection of the ketone as a 1,3-dioxolane) led to either reduction of the carbonyl to an alcohol or no reaction (on the protected ketone system).[9] The model α-keto-hydrazide **7** that does not contain a phosphonate group was examined in order to test the efficacy of our Raney nickel. The N−N bond in **7** was readily cleaved under these standard conditions. The phosphonate group therefore appears to have a detrimental effect on this method of cleavage, although we are not clear as to its mode of action. Subjecting **5a** or ketone-protected **5a** to dissolving metal conditions (Na/NH_3/EtOH) induced cleavage of the C−N bond α to the ketone (or protected ketone) and isolation of the dialkyl hydrazide. Dissolving metal conditions are known to produce anions on the carbon α to the phosphonate group.[11] To date, samarium diiodide[10d] (2.1 equiv of SmI_2, MeOH) has not effected the desired cleavage in our hands on the ketone-protected **5a**, with starting material being recovered.

We therefore decided to investigate the use of bis(2,2,2-trichloroethyl) azodicarboxylate in this reaction. Cleavage of the N−N bond in hydrazides possessing a 2,2,2-trichloroethyl group have been accomplished in other systems using very mild Zn/acetic acid/acetone conditions.[12] Reaction of the P(V) **3b** ($R^2 = Me$) with bis(2,2,2-

Table 1.



mode of addition[a]	temp, °C	solvent	% yield of **8**
direct addition	0−rt	CH_2Cl_2	0[b]
direct addition	−78	CH_2Cl_2	5
inverse addition	0−rt	CH_2Cl_2	10
inverse addition	−78	CH_2Cl_2	20
direct addition	0−rt	Et_2O	35
direct addition	−78	Et_2O	55
inverse addition	0−rt	Et_2O	68
inverse addition	−78	Et_2O	87−93

[a] Direct addition: addition of the BTCEAD to the P(V) **3b**. Inverse addition: addition of a solution of **3b** to a solution of BTCEAD at the indicated temperature. [b] Complex mixture of products formed.

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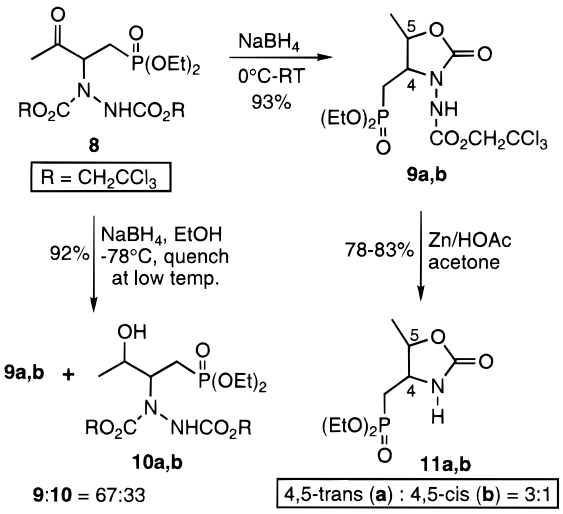
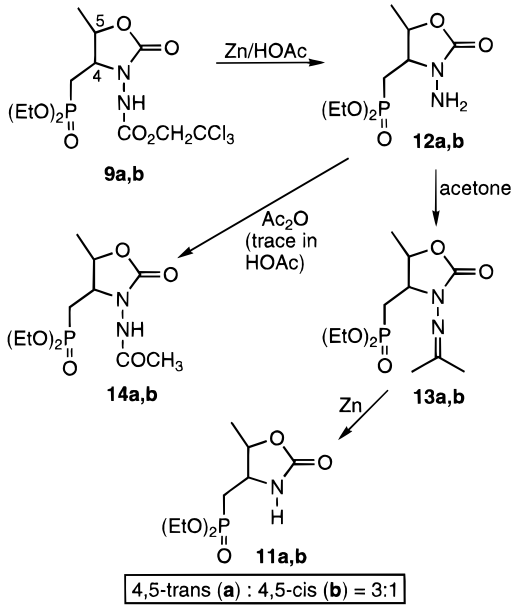
Scheme 3



Scheme 4



trichloroethyl) azodicarboxylate (BTCEAD) under our standard conditions (rt, CH_2Cl_2) used with either diethyl or di-*tert*-butyl azodicarboxylates, however, did not produce any recognizable products. This particular azodicarboxylate was *much more* reactive than DEAD or DTBAD in our condensation reactions. The conditions that were screened for this reaction are shown in Table 1. The best conditions consisted of inverse addition (addition of a solution of the P(V) substrate to a solution of BTCEAD) at −78 °C in diethyl ether. These conditions apparently slowed down the reaction sufficiently to produce clean condensation product, and we could routinely isolate **8** in 87−93% yield.

The key cleavage of the N−N bond in the trichloroethyl hydrazide was subsequently pursued. To avoid any possible problems, the ketone was first reduced to the alcohol using sodium borohydride in ethanol (see Scheme 3). If the reduction was run at 0 °C and warmed to room temperature, a 3:1 (trans:cis) diastereomeric mixture of the oxazolidinones **9a,b** was obtained in excellent yield (93%). Attack of the incipient alkoxide on one of the hydrazide diester carbonyls provided internal protection of the alcohol. Since we were more interested in the N−N bond cleavage at this point, the ratio of diastereomers

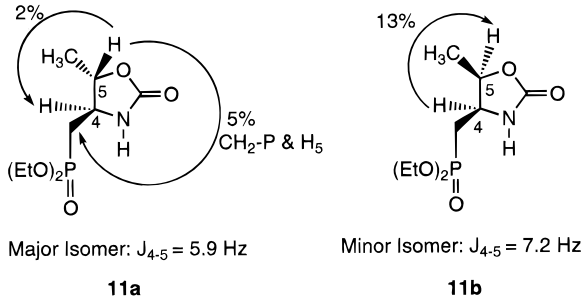


Figure 2.

was not optimized. Running the reduction at −78 °C and quenching at low temperature produced a mixture of the oxazolidinones **9a,b** and the alcohols **10a,b** in 62% and 30% yields, respectively, and both as 3:1 mixtures of diastereomers.

Cleavage of the N−N bond was performed on the 3:1 mixture of diastereomers (**9a,b**) as they were difficult to separate via chromatography at this point. Thus, treatment of the mixture of **9a,b** under LeBlanc's conditions[12] (Zn/HOAc/acetone) did indeed produce the desired N−N bond cleavage to yield a 3:1 diastereomeric mixture of the oxazolidinones, **11a,b**, in excellent isolated yields (78−83%). That the reduction of the N−N bond proceeded according to the mechanism proposed by LeBlanc was evidenced by isolation of the intermediates **12**−**14** (see Scheme 4). Thus, hydrolysis of **9** to the hydrazine derivative **12** occurred first. Condensation with acetone produced the hydrazone derivative **13**, which was then reduced by the zinc to the desired oxazolidinone **11**. Due to a small contaminant of acetic anhydride in our purified acetic acid, we also produced and isolated a small amount of the N-acetylated **14**. The 3:1 diastereomeric ratio was maintained throughout all these transformations. No equilibration between the diastereomers was noted under prolonged reaction times.

The oxazolidinone diastereomers **11a,b** were readily separable via HPLC, and stereochemical assignments were performed at this point. It is known in the literature that 4,5-disubstituted oxazolidinones generally exhibit H4−H5 proton coupling constants where $J_{cis} > J_{trans}$.[13] The major isomer of **11** exhibited $J_{4,5} = 5.9$ Hz, and the minor isomer had $J_{4,5} = 7.3$ Hz. Since these coupling constants were fairly close in magnitude, we confirmed the assignments via nuclear Overhauser effect (NOE) experiments (Figure 2). Irradiation of H4 in the minor isomer induced a 13% NOE in H5. The NOE between H4 and H5 in the major isomer was approximately 2%. An NOE of 5% was seen, however, between H5 and the methylene α to the phosphonate in the major isomer. Thus, the major isomer was the trans isomer **11a**, and the minor isomer was the cis diastereomer **11b**, as predicted by the H4−H5 coupling constants.

We are currently applying these successful condensation and N−N bond cleavage conditions to the real system utilizing the P(V) **3a** produced from the dienone **4a** in order to synthesize the sphingomyelin and ceramide phosphonate derivatives. These results will be reported in due course.

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Experimental Section

General. All phosphites were treated with sodium prior to distillation. Methyl vinyl ketone was treated with solid K_2CO_3 and $CaCl_2$ prior to distillation. Et_2O was distilled from sodium benzophenone ketyl. CH_2Cl_2 was distilled from CaH_2. $CDCl_3$ and acetic acid were distilled from P_2O_5 under argon. Acetone was treated with 4 Å molecular sieves prior to distillation. All reactions were carried out under dry argon atmosphere in oven-dried round bottom flasks. Proton, carbon, and phosphorus NMR spectra were obtained on either 250 or 300 MHz spectrometers as solutions in $CDCl_3$. Proton and carbon NMR chemical shifts are reported in ppm downfield from TMS (or relative to internal $CHCl_3$). ^{31}P spectra are reported in ppm from an external reference of 85% H_3PO_4. Proton NOE data were acquired on a 500 MHz spectrometer. Mass spectra were obtained from a double-focusing mass spectrometer operating at a resolution of 5000. FAB spectra were obtained by using glycerol as a matrix, EI data were obtained by using 70 eV electrons, and CI data were obtained by using NH_3 as a reagent gas at 0.3 torr and source temperature of 150 °C. Column chromatography was performed on silica gel, Merck grade 9385, 230−400 mesh, 60 Å, using a step gradient of CH_3OH in CH_2Cl_2 or EtOAc/hexane. The solvent mixtures used for column chromatography were volume/volume mixtures. R_f values indicated refer to thin layer chromatography on Analtech 2.5 × 10 cm, 250 μm analytical plates coated with silica gel GF. High pressure liquid chromatography was done on a Rainin-60A semipreparative silica gel column. Elemental analyses data were obtained from Robertson Microlit Laboratories, Inc, Madison, NJ.

(±)-Diethyl [2-[*N*,*N*′-Bis[(2,2,2-trichloroethoxy)carbonyl]hydrazido]-3-oxobutyl]phosphonate (8). The oxaphospholene **3b** (0.968 g, 4.098 mmol) was transferred via cannula into a flame-dried flask under Ar and dissolved in dry diethyl ether (15 mL). In a separate flame-dried flask under Ar was placed the bis(2,2,2-trichloroethyl) azodicarboxylate (BTCEAD) (1.875 g, 4.917 mmol) and dissolved in dry diethyl ether (15 mL). The BTCEAD solution was cooled to −78 °C, and the oxaphospholene was added via cannula to the BTCEAD solution over a period of 5 min. After stirring at −78 °C for 12 h, the reaction mixture was hydrolyzed by treatment with pH 7 buffer (15 mL) and allowed to stir for another 2 h at rt. The hydrolyzed product was extracted with EtOAc (3 × 30 mL) and washed with water (10 mL). The combined organic extracts were dried over $MgSO_4$, and the solvent was removed under reduced pressure. Purified product (2.158 g, 3.51 mmol, 91%) was isolated via flash column chromatography using 75 g silica gel, eluting with 40% EtOAc/Hex. R_f 0.33 (50%EtOAc/hex). ^1H NMR: 4.73 (4H, m), 4.08 (5H, m), 2.34 (3H, s), 2.24 (2H, m), 1.31 (6H, m). ^{13}C NMR: 202.3, 154.2, 153.8, 94.6, 94.4, 75.8, 75.1, 62.5 (d, J_{P-C} = 6.3 Hz), 62.2 (d, J_{P-C} = 6.8 Hz), 58.2, 26.8, 22.4 (d, J_{P-C} = 145.6 Hz), 16.3. ^{31}P: 28.1 ppm. IR (neat, cm^{-1}): 3178, 1761, 1725, 1399. HRMS (CI) calcd for $C_{14}H_{22}N_2O_8PCl_6$ $(M + H)^+$ 586.9245, found 586.9247. Anal. Calcd for $C_{14}H_{22}N_2O_8PCl_6$: C, 28.66; H, 3.75; N, 4.77; P, 5.29; Cl, 35.83. Found: C, 28.90; H, 3.70; N, 4.71; P, 5.16; Cl, 35.38.

(4*S,5*R**)-Diethyl [[3-[*N*′-(2,2,2-Trichloroethoxy)carbonyl]amino]-5-methyl-2-oxooxazolidin-4-yl]methyl]phosphonate (9a) and (4*R**,5*R**)-Diethyl [[3-[*N*′-[(2,2,2-trichloroethoxy)carbonyl]amino]-5-methyl-2-oxooxazolidin-4-yl]methyl]phosphonate (9b).** The ketone **8** (0.727 g, 1.24 mmol) was dissolved in dry EtOH (25 mL) in a dry round-bottom flask, and cooled to 0 °C. To this cooled solution was added solid $NaBH_4$ (0.140 g, 3.72 mmol) in one portion. The ice bath was then removed, and the reaction mixture was allowed to stir at rt overnight. The reaction was quenched after 9 h with saturated aqueous NH_4Cl, extracted with Et_2O (3 × 20 mL), and dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. After flash column chromatography (2.5% MeOH/CH_2Cl_2), R_f 0.35 (5% MeOH/CH_2Cl_2), the diastereomeric mixture of oxazolidinones **9a,b** was isolated as a clear oil (0.678 g, 93%, 1.15 mmol). Attempts to separate the diastereomers were not successful at this point. The ratio of isomers **9a**:**9b** = 3:1 by ^1H NMR integration. Major diastereomer, **9a**: ^1H NMR: 8.40 (1H, bs, NH), 4.82 (2H, m), 4.45 (1H, m), 4.12 (4H, m), 3.85 (1H, m), 2.4−1.9 (2H, m), 1.45 (3H, d, J = 6.1 Hz), 1.30 (6H, m). ^{13}C NMR: 155.4, 153.8, 94.7, 76.3, 74.9, 62.2, 59.2, 28.8 (d, J_{P-C} = 140.2 Hz), 19.9, 16.2. Minor diastereomer, **9b**: ^1H NMR: 8.38 (1H, bs, NH), 4.82 (2H, m), 4.35 (1H, m), 4.12 (5H, m), 2.4−1.9 (2H, m), 1.36 (3H, d, J = 6.5 Hz), 1.30 (6H, m). ^{13}C NMR: 155.4, 153.8, 94.7, 74.9, 73.9, 62.2, 55.4, 24.7 (d, J_{P-C} = 143.1 Hz), 19.9. 16.2. ^{31}P: (**9a**) 24.8 ppm; (**9b**) 25.7 ppm. HRMS (CI) calcd for $C_{12}H_{20}N_2O_7PCl_3$ (mixture of **9a,b**) $(M + H)^+$ 441.0152, found 441.0150. Anal. Calcd for $C_{12}H_{20}N_2O_7PCl_3$ (mixture of **9a,b**): C, 32.72; H, 4.54; N, 6.36; P, 7.04; Cl, 23.86. Found: C, 32.63; H, 4.60; N, 6.15; P, 6.20; Cl, 21.91.

(4*S,5*R**)-Diethyl [2-[*N*,*N*′-Bis[(2,2,2-trichloroethoxy)carbonyl]hydrazido]3-hydroxybutyl]phosphonate (10a) and (4*R**,5*R**)-Diethyl [2-[*N*,*N*′-Bis[(2,2,2-trichloroethoxy)carbonyl]hydrazido]-3-hydroxybutyl]phosphonate (10b).** The trichloroketohydrazide **8** (2.17 g, 3.7 mmol) was dissolved in EtOH (60 mL) and cooled to −78 °C. To this cooled solution was added solid $NaBH_4$ (0.451 g, 11.9 mmol). The reaction was allowed to stir at −78 °C for 10 h and then quenched at −78 °C with saturated aqueous NH_4Cl. The mixture was extracted with CH_2Cl_2 (3 × 30 mL) and dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. After gravity column chromatography (1.5−2.5% MeOH/CH_2Cl_2), the 3:1 mixture of alcohols **10a,b**, (0.65 g, 1.11 mmol, 30%) and the diastereomeric mixture of oxazolidinones **9a,b** (1.01 g, 2.29 mmol, 62%) were isolated as clear oils. Attempts to separate the diastereomers of the alcohol were unsuccessful. R_f (alcohol **10**) 0.32 (2.5% MeOH/CH_2Cl_2). ^1H NMR (mixture of **10a,b**): 4.85−4.62 (4H, m), 4.40 (1H, m), 4.20−3.90 (4H, m), 3.51 (1H, m), 2.22−1.75 (2H, m), 1.40−1.26 (6H, m), 1.22 (3H, d, J = 5.7 Hz). ^{13}C NMR: (major isomer, **10a**) 156.6, 154.1, 94.6, 75.5, 68.2 (d, J_{P-C} = 18.4 Hz), 62.4 (d, J_{P-C} = 7.0 Hz), 59.0 , 25.5 (d, J_{P-C} = 143.7 Hz), 18.7, 16.1; (minor isomer, **10b**) 156.6, 154.1, 94.5, 74.9, 68.0 (d, J_{P-C} = 18.40), 62.1 (d, J_{P-C} = 6.5 Hz), 58.9, 25.1 (J_{P-C} = 146.3 Hz), 18.7, 16.1. ^{31}P (mixture of **10a,b**): 28.1. IR (mixture of **10a,b**, neat, cm^{-1}): 3464, 1733, 1652, 1405, 1221, 1026. LRMS (CI) calcd for $C_{14}H_{23}O_8N_2PCl_6$ $(M + H)^+$ 590.9, found 590.9. HRMS by EI on the mixture of **10a,b** was performed on two fragment ions. HRMS (EI) for $C_{12}H_{18}O_7N_2PCl_6$ $(M - OCH_2CH_3)$ 542.8962, found 542.8982. HRMS (EI) for $C_{12}H_{21}O_7N_2PCl_3$ $(M - OCH_2CCl_3)$ 441.0147, found 441.0151.

(4*S,5*R**)-Diethyl [(5-Methyl-2-oxooxazolidin-4-yl)methyl]phosphonate (11a) and (4*R**,5*R**)-Diethyl [(5-Methyl-2-oxooxazolidin-4-yl)methyl]phosphonate (11b).** The 3:1 diastereomeric mixture of oxazolidinones **9a,b** (300 mg, 0.68 mmol) was dissolved in HOAc (3 mL), and Zn dust (1.5 g, 23.3 mmol) was added at rt under Ar over a period of 5 min. After about 4 h, acetone (0.60 mL) was added to the reaction mixture. The reaction mixture was allowed to stir at rt for another 32 h. The reaction mixture was then quenched with 10% aqueous $NaHCO_3$ and tested with litmus paper to be slightly basic. The mixture was extracted with EtOAc (3 × 20 mL) and dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. After gradient HPLC chromatography (10 mL/min, 1.5−4% MeOH/CH_2Cl_2), the N−N cleavage products **11a,b** (105 mg, 0.42 mmol, 62%, R_f 0.30 (3% MeOH/CH_2Cl_2)) were isolated, along with the hydrazines **12a,b** (27 mg, 0.101 mmol, 15%, R_f 0.18 (5% MeOH/CH_2Cl_2)), the hydrazones **13a,b** (13 mg, 0.042 mmol, 6%, R_f 0.32 (5% MeOH/CH_2Cl_2)), and the N′-acetylated hydrazines **14a,b** (32 mg, 0.103 mmol, 14%, R_f 0.28 (5% MeOH/CH_2Cl_2)) as intermediates. The reaction could be coaxed to completion (78−83% of **11a,b**) by addition of another 10−20 equiv of Zn dust and 2 mL of HOAc after the initial 4 h, followed by addition of acetone (0.20−1.0 mL) after a further 12 h. Stirring for another 16−20 h converted the intermediates into the products **11a,b**. The diastereomers **11a** and **11b** could easily be separated by HPLC chromatography in 5.5% MeOH/CH_2Cl_2 (4 mL/min). In the best run, 0.425 g (0.964 mmol) of the oxazolidinones **9a,b** were converted to the following amounts of isolated cleaved products: **11a** (0.15 g, 0.59 mmol, 62.2%), **11b** (0.05 g, 0.199 mmol, 20.7%), and **14a,b** (0.025 g, 0.081 mmol, 8%). Major diastereomer, **11a**: ^1H NMR: 6.20

(1H, bs, NH), 4.30 (1H, app quint, $J = 6.1$ Hz), 4.05 (4H, m), 3.61 (1H, app quint, $J = 6.6$ Hz), 1.94 (2H, dd, $J_{P-H} = 18.1$ Hz, $J_{H-H} = 6.7$ Hz), 1.35 (3H, d, $J = 6.2$ Hz), 1.26 (6H, d, $J = 7.1$ Hz). ^{13}C NMR: 158.00, 78.8 ($J_{P-C} = 14.3$ Hz), 62.0 ($J_{P-C} = 6.5$ Hz), 54.5 ($J_{P-C} = 3.1$ Hz), 31.2 ($J_{P-C} = 139.9$ Hz), 19.5, 16.1. ^{31}P: 26.6. IR (neat, cm $^{-1}$): 3258, 1749, 1241, 1040. Minor diastereomer **11b**: ^{1}H NMR: 5.80 (1H, bs, NH), 4.78 (1H, app quint, $J = 6.4$ Hz), 4.08 (5H, m), 1.86 (2H, dd, $J_{P-H} = 18.6$ Hz, $J_{H-H} = 6.6$ Hz), 1.33 (9H, m). ^{13}C NMR: 158.04, 75.2 ($J_{P-C} = 18.1$ Hz), 62.3 ($J_{P-C} = 6.1$ Hz), 51.0 ($J_{P-C} = 5.0$ Hz), 27.0 ($J_{P-C} = 142.1$), 16.4, 15.0. ^{31}P: 28.5. IR (neat, cm $^{-1}$): 3276, 1760, 1238, 1050. HRMS (CI) calcd for $C_9H_{18}NO_5P$ (**11a,b** mixture) $(M + H)^+$ 252.1000, found 252.1000. Anal. Calcd for $C_9H_{18}NO_5P$ (**11a,b** mixture): C, 43.02; H, 7.17; N, 5.57; P, 12.35. Found: C, 43.13; H, 7.36; N, 5.84; P, 12.26.

(4*S,5*R**)-Diethyl [(3-Amino-5-methyl-2-oxooxazolidin-4-yl)methyl]phosphonate (12a) and (4*R**,5*R**)-Diethyl [(3-Amino-5-methyl-2-oxooxazolidin-4-yl]methyl]phosphonate (12b).** The mixture of the oxazolidinones **9a,b** (0.423 g, 0.96 mmol) was dissolved in HOAc (2 mL). To this stirred solution was added Zn dust (1.5 g, 23.3 mmol) over 5 min. The reaction mixture was stirred overnight for 12 h. The reaction mixture was then quenched with 10% aqueous $NaHCO_3$, tested with litmus paper to be basic, and then extracted with EtOAc (5 × 3 mL). The organic layer was dried with $MgSO_4$ and solvent removed in vacuo to give a crude oil (250 mg). The hydrazines **12a,b** were isolated as a mixture of diastereomers via flash column chromatography (210 mg, 0.786 mmol, 82%). R_f 0.32 (10% MeOH/CH_2Cl_2). A small amount of the N′-acetylated hydrazines **14a,b** was also isolated (45 mg, 0.144 mmol, 15%), R_f 0.28 (5% MeOH/CH_2Cl_2). Major isomer **12a**: ^{1}H NMR: 4.50−4.45 (1H, m), 4.20−3.95 (4H, m), 3.80−3.55 (1H m), 2.32−1.85 (2H, m), 1.45 (3H, d, $J = 6.2$ Hz), 1.25 (6H, m). ^{13}C NMR: 155.5, 69.5, 62.4 (d, $J_{P-C} = 6.8$ Hz), 59.2, 28.7 (d, $J_{P-C} = 140.4$ Hz), 20.0, 16.2. Minor isomer **12b**: ^{1}H NMR: 4.72 (1H, m), 4.30−4.20 (1H, m), 4.20−3.95 (4H, m), 2.32−1.85 (2H, m), 1.35 (3H, d, $J = 6.7$ Hz), 1.25 (6H, m). ^{13}C NMR: 155.5, 68.4, 62.4 (d, $J_{P-C} = 6.8$ Hz), 55.5, 24.7 (d, $J_{P-C} = 142.5$ Hz), 20.0, 16.2. ^{31}P NMR: (**12a**) 24.8; (**12b**) 25.8. HRMS (CI) calcd for $C_9H_{19}N_2O_5P$ (mixture of **12a,b**): $(M + H)^+$ 267.1109, found 267.1108.

(4*S,5*R**)-Diethyl [[3-(Isopropylideneamino)-5-methyl-2-oxooxazolidin-4-yl]methyl]phosphonate (13a) and (4*R**,5*R**)-Diethyl [[3-(Isopropylideneamino)-5-methyl-2-oxooxazolidin-4-yl]methyl]phosphonate (13b).** Major isomer **13a**: ^{1}H NMR: 4.42 (1H, app quint, $J = 6.1$ Hz), 4.09 (4H, m), 3.87 (1H, m), 2.25−1.85 (2H, m), 2.01 (6H, s), 1.51 (3H, d, $J = 6.2$ Hz), 1.30 (6H, m). ^{13}C NMR: 169.4, 155.9, 76.3 (d, $J_{P-C} = 7.7$ Hz), 62.2 (d, $J_{P-C} = 5.8$ Hz), 55.3, 25.3 (d, $J_{P-C} = 143.1$ Hz), 20.6, 16.3 (d, $J_{P-C} = 5.8$ Hz), 15.2. Minor isomer **13b**: ^{1}H NMR: 4.87 (1H, app quint, $J = 6.9$ Hz), 4.33 (1H, app quint, $J = 7.5$ Hz), 4.09 (4H, m), 2.25−1.91 (2H, m), 2.01 (6H, s), 1.38 (3H, d, $J = 6.6$ Hz), 1.30 (6H, m). ^{13}C NMR: 169.6, 156.0, 73.8 (d, $J_{P-C} = 7.7$ Hz), 62.2 (d, $J_{P-C} = 5.8$ Hz), 55.3, 25.3 (d, $J_{P-C} = 145.0$ Hz), 19.8, 16.3 (d, $J_{P-C} = 5.8$ Hz), 15.2. HRMS (FAB) calcd for $C_{12}H_{23}N_2O_5P$ (mixture of **13a,b**) $(M + H)^+$ 307.1424, found 307.2048.

(4*S,5*R**)-Diethyl [(3-(Acetamido)-5-methyl-2-oxooxazolidin-4-yl)methyl]phosphonate (14a) and (4*R**,5*R**)-Diethyl [(3-(Acetamido)-5-methyl-2-oxooxazolidin-4-yl)-methyl]phosphonate (14b).** Major isomer **14a**: ^{1}H NMR: 8.80 (1H, bs, NH), 4.43 (1H, m), 4.04 (4H, m), 3.82 (1H, m), 2.20−1.87 (2H, m), 1.96 (3H, s), 1.47 (1H, d, $J = 6.1$ Hz), 1.26 (6H, m). ^{13}C NMR: 169.6, 155.6, 76.1, 61.9, 58.9, 28.5 ($J_{P-C} = 139.9$ Hz), 20.2, 19.6, 16.0 (d, $J_{P-C} = 5.5$ Hz). Minor Isomer **14b**: ^{1}H NMR: 8.78 (1H, s, NH), 4.70 (1H, m), 4.24 (1H, m), 3.94 (4H, m), 2.20−1.87 (2H, m), 1.96 (3H, s), 1.30 (1H, d, $J = 6.5$Hz), 1.26 (6H, m). ^{13}C NMR: 169.5, 156.1, 73.5, 61.9, 58.9, 24.3 (d, $J_{P-C} = 143.2$ Hz), 20.2, 19.6, 16.0 (d, $J_{P-C} = 5.5$ Hz). IR (mixture of **14a,b**, neat, cm^{-1}) 3234, 1782, 1690, 1236, 1052, 1017. ^{31}P: (**14a**) 25.2 ppm; (**14b**) 26.1 ppm. HRMS (CI) calcd for $C_{11}H_{21}N_2O_6P$ (mixture of **14a,b**): $(M + H)^+ = 309.1216$, found 309.1228. Anal. Calcd for $C_{11}H_{21}N_2O_6P$ (**14a,b** mixture): C, 42.85; H, 6.81; N, 9.09; P, 10.06. Found: C, 42.46; H, 6.68; N, 8.83; P, 9.76.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for compounds **8**−**14** (17 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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