

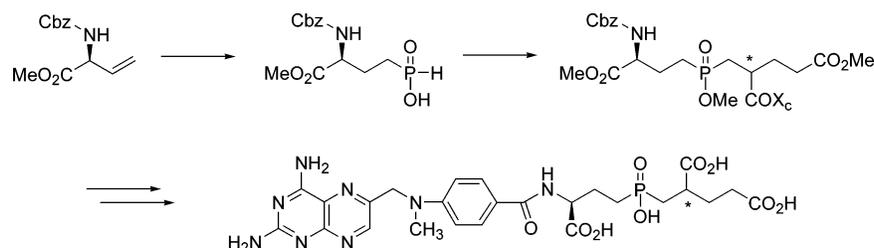
A Stereoselective Synthesis of Phosphinic Acid Phosphapeptides Corresponding to Glutamyl- γ -glutamate and Incorporation into Potent Inhibitors of Folylpoly- γ -glutamyl Synthetase

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Received April 13, 2005



Radical addition of H_3PO_2 to *N*-Cbz-protected vinyl glycine led to the corresponding *H*-phosphinic acid in excellent yield. The non-nucleophilic *H*-phosphinic acid was converted to a nucleophilic P^{III} species, $\text{RP}(\text{OTMS})_2$, which was used in two approaches to the target phosphinic acid containing pseudopeptide. New methodology was developed that led to excellent yields in the reaction of $\text{RP}(\text{OTMS})_2$ with unactivated electrophiles, including an acyclic homoallylic bromide. However, en route to the target pseudopeptide, Arbuzov reaction of $\text{RP}(\text{OTMS})_2$ with a cyclic homoallylic bromide, (*R*)-3-(bromomethyl)-cyclopent-1-ene, led to a rearranged allylic phosphinic acid rather than the desired homoallylic derivative, a putative glutarate surrogate. Conjugate addition of $\text{RP}(\text{OTMS})_2$ to α -methylene glutarate containing a chiral auxiliary resulted in only modest diastereoselectivity. Purification by flash chromatography provided protected derivatives of both diastereomers of the pseudopeptide. Following global deprotection, coupling of (*S*)-H-Glu- γ -[$\Psi(\text{P}(\text{O})(\text{OH})(\text{CH}_2))$]-(*S*)-Glu-OH and (*S*)-H-Glu- γ -[$\Psi(\text{P}(\text{O})(\text{OH})(\text{CH}_2))$]-(*R*)-Glu-OH to (4-amino-4-deoxy-10-methyl)pteroyl azide led to the target compounds for biochemical study as inhibitors of the ATP-dependent ligase, folylpoly- γ -glutamyl synthetase.

Introduction

Folylpoly- γ -glutamate synthetase (FPGS, EC 6.3.2.17) catalyzes the ATP-dependent polyglutamylation of dietary folates and antifolate cancer therapeutics (Scheme 1). The poly- γ -glutamyl metabolites are important cofactors in one-carbon metabolism and are essential for cell growth and survival.¹ Folylpoly- γ -glutamyl derivatives aid in cellular retention of reduced folate cofactors and are better substrates for many of the folate-dependent enzymes employed in one-carbon metabolism.^{2,3}

FPGS is an attractive target for anticancer drug design for many reasons. As noted above, FPGS is required for cell viability, and therefore inhibition of this enzyme is

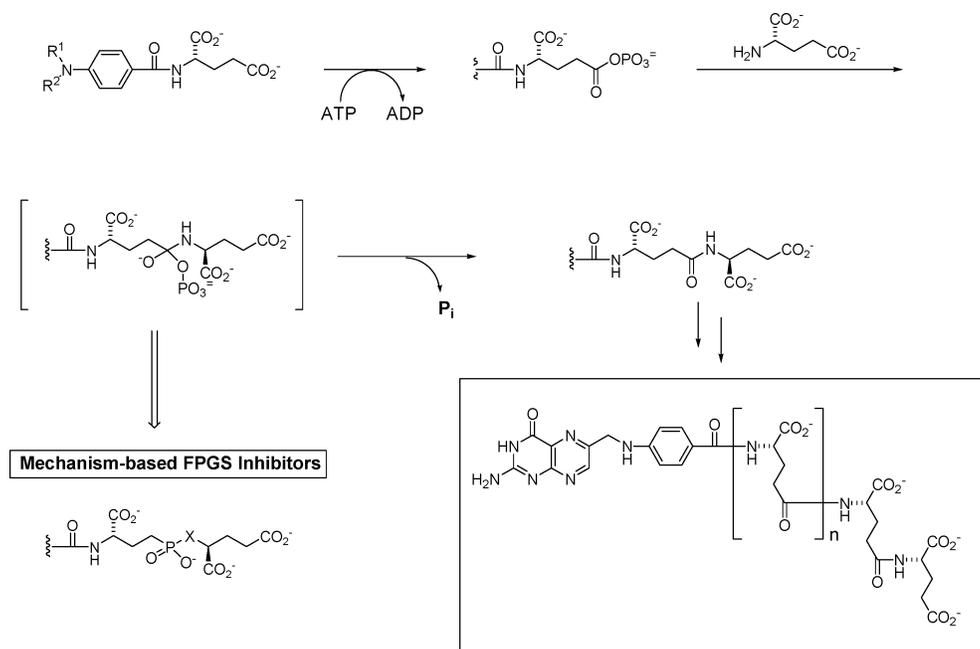
expected to be cytotoxic. In addition, one known mechanism of antifolate resistance is down regulation of FPGS activity,^{4,5} and cells with this type of resistance should be inherently sensitive to FPGS inhibition.⁶ FPGS requires a heterocycle for substrate binding. With the glutamate ligation site being distal to the heterocycle, we^{7,8} and others⁹⁻¹⁶ have shown it is possible to incorporate known heterocyclic inhibitors of other folate-

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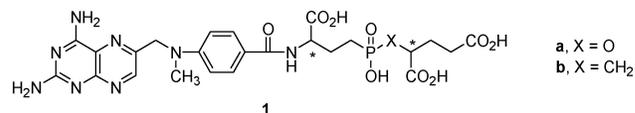
SCHEME 1



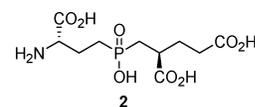
dependent enzymes into the design of FPGS inhibitors. This inhibitor design may allow for the synergistic effect of inhibiting two enzymes in the folate pathway with one drug. Recently, Alimta, a multitargeted antifolate (MTA) known to inhibit dihydrofolate reductase, thymidylate synthetase, and glycineamide ribonucleotide formyltransferase,¹⁷ has been approved for clinical use in the United States. In addition to the clinical importance of FPGS inhibitors, the design of cell-permeable compounds would allow for investigations on the control of intracellular folate cofactor levels by FPGS. Several other proteins are involved in the uptake and/or regulation of intracellular folate concentrations, such as γ -glutamyl hydrolase, the enzyme that cleaves the poly- γ -glutamyl tail,¹⁸ in addition to the folate transporter and reduced folate carrier that aid in cellular uptake of folates and antifolates.¹⁹ Although each of these proteins has been studied in great detail individually, little is known about how the expression levels or levels of activity of these proteins are interrelated or controlled in terms of normal metabolism or in development of drug resistance to antifolates.

Our laboratory has previously reported the use of phosphorus-containing pseudopeptides **1** as inhibitors of FPGS.^{7,8} The phosphorus moiety mimics the tetrahedral intermediate²⁰ in FPGS catalysis (Scheme 1), and these

compounds are very potent inhibitors of FPGS. The phosphonate analogue **1a** (2'S,2''S) inhibits human FPGS



with $K_i = 46$ nM.⁷ More recently, we have published the synthesis and biological evaluation of racemic phosphinate analogues with the most potent being the MTX-phosphinate **1b** ($K_i = 3.1$ nM).^{8,21} This phosphinate is a mixture of racemic diastereomers (2'RS,2''RS) and on the basis of the known stereospecificity of FPGS,² it is likely that only the 2'S,2''S diastereomer inhibits the enzyme and therefore the actual inhibition constant may be subnanomolar. To determine if this hypothesis is correct, a stereoselective synthesis of the phosphinate pseudo-peptide **2** has been investigated.



The most common methods for the generation of phosphorus-carbon (P-C) bonds are often not feasible with highly functionalized molecules.²² Previous efforts to synthesize highly functional phosphorus-containing pseudopeptides of type **2** led to the realization that the best method for the synthesis of the P-C bonds was the in situ generation of P^{III} species and their addition to alkyl halides or Michael acceptors.⁸ Unfortunately, the

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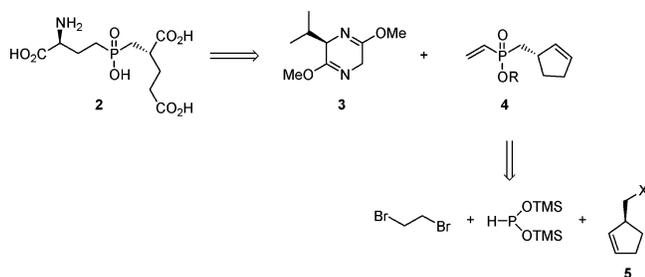
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SCHEME 2



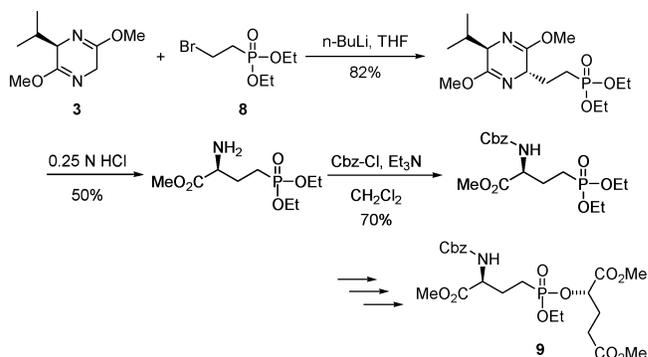
current literature procedures for synthesizing P–C bonds with P^{III} intermediates using alkyl halides are limited to alkyl halides activated by neighboring electron-withdrawing groups^{8,23,24} and are ineffective on unactivated alkyl halides unless forcing conditions are used (i.e., hexamethyl disilazane (HMDS), 110 °C). Recently, Liu et al. have shown that HMDS conditions result in racemization of amino acid stereocenters,²⁵ and often even these harsh conditions result in rather low yields.^{8,26–29} Boyd and Regan reported that the reaction proceeds in good yield at room temperature regardless of the nature of the electrophile,³⁰ but there are no other examples of this in the literature. The lack of suitable methodology for the introduction of carbon–phosphorus bonds into highly functionalized molecules has led us to investigate new protocols for the formation of these bonds.

Results and Discussion

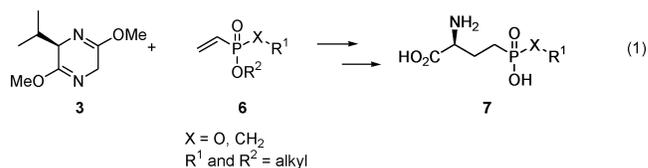
Initially, this research focused on the use of Schollkopf's bis-lactim ether **3**³¹ in the synthesis of phosphinate pseudopeptide **2** (Scheme 2). This approach provides a stereoselective route to the N-terminal amino acid of the pseudopeptide and involves phosphinic acid synthon **4**, containing both the N- and C-terminal P–C bonds of **2**. The phosphinic acid would, in turn, be synthesized via reaction of the nucleophilic P^{III} reagent, (TMSO)₂PH, bis-(trimethylsilyl)-phosphonite (BTSP), and a homoallylic electrophile **5**, containing the carbon backbone of the C-terminal glutaric acid moiety of **2**. Reaction of the resulting *H*-phosphinic acid with 1,2-dibromoethane, again via a bis-TMS derivative, followed by esterification and dehydrohalogenation would provide **4**.⁸

The bis-lactim heterocycle **3** has been used by several research groups^{32–37} in the synthesis of phosphorus-

SCHEME 3



containing amino acids (eq 1, **7**, X = O), and we have used it to set the N-terminal stereocenter in phosphonate pseudopeptide **9** (Scheme 3),³⁸ a precursor of **1a**. Successful use of the β -bromoalkyl phosphonate **8** as a precursor of an α,β -unsaturated phosphonate (eq 1, **6**, X = O, R¹ = R² = Et) was encouraging in terms of the proposed strategy for synthesis of the corresponding phosphinate pseudopeptide **2**.



The installation of various P–O esters, R² (eq 1), either prior to or following formation of the new C-terminal P–C bond (X = CH₂), and the ability to use a variety of alkyl groups, R¹, most notably a glutarate surrogate such as **5** (Scheme 2), was appealing. As will be discussed below in more detail, stereoselective synthesis of the *R*-isomer of the homoallylic alcohol, 3-(hydroxymethyl)-cyclopentene (*ent*-**5**, X = OH), was effected by the method of Maeda and Innouye.³⁹ Conversion of the alcohol to several cyclopentene-based homoallylic electrophiles (*ent*-**5**, X = OMs, OTs, etc.) could be effected by standard methods (see Supporting Information for details). In addition, the reaction of an acyclic homoallylic bromide with BTSP was investigated.

Unfortunately, all efforts to effect formation of the desired P–C bond using standard methodology involving in situ generation of BTSP from HMDS and ammonium hypophosphite (AHP)³⁰ followed by reaction with any of these homoallylic electrophiles led only to very low yields of the desired product, the bis-TMS ester precursor of **6** (eq 1, X = CH₂).³⁸ Surprisingly, the homoallylic electrophiles *ent*-**5** (X = OMs, OTs) were recovered unchanged

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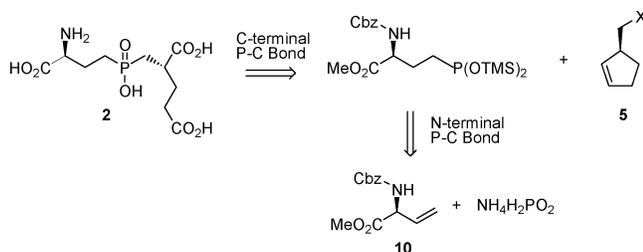
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SCHEME 4



and a yellow-orange solid was formed during the reaction. A review of the literature found very few reports of this byproduct.^{24,40} However, Voronkov et al.⁴⁰ reported the solid to be a polymer of “high phosphorus and silicon content” presumably formed from the polymerization of BTSP. The low yields observed in our research and possibly those encountered in this type of reaction throughout the organophosphorus literature may be due to the complete consumption of BTSP as a result of a competing polymerization reaction prior to completion of P–C bond formation. To test this hypothesis, the acyclic homoallylic bromide, 4-bromo-1-butene, was treated with BTSP in toluene at reflux temperature (110 °C) for 60 h. Only 46% conversion to the bis-TMS precursor of **6** ($R_1 = \text{allyl}$) occurred with concomitant formation of a large amount of orange solid. However, in a subsequent reaction, when a second aliquot of BTSP was added to the reaction mixture after 8 h at reflux temperature and the reaction was allowed to proceed for an additional 18 h at reflux temperature, the desired product was isolated in 92% yield as its methyl ester after treatment with CH_2N_2 (see Supporting Information for details). These results suggested that a more complex phosphite, $R_1\text{CH}_2\text{-P(OTMS)}_2$, derived from the N-terminal portion of the phosphinate-containing pseudopeptide **2**, could be employed under similar conditions (Scheme 4).

At the onset of this research, there were no useful procedures in the literature that would allow for the introduction of the N-terminal P–C as outlined in Scheme 4.⁸ Therefore, initial efforts described above focused on the synthesis of **4**, which contains both the C- and N-terminal P–C bonds, for reaction with **3** (Scheme 2) to provide a stereoselective route to the N-terminal amino acid. However, Montchamp’s group has since described an extremely mild Et_3B -initiated radical addition of AHP to alkenes²⁴ and more recently a palladium-catalyzed cross-coupling of aqueous hypophosphorus acid to alkenes and alkynes.⁴¹ We envisioned that this chemistry could also be performed on protected α -vinyl glycine **10** (Scheme 4).

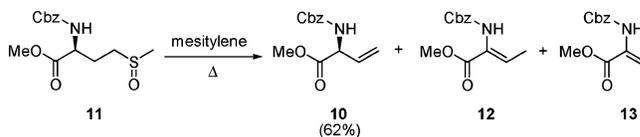
There are numerous syntheses of α -vinyl glycine reported in the literature; however, most suffer either from low yields or low optical purity or are not amenable to scale-up. Rapoport’s large-scale synthesis⁴² was used initially, but during the elimination reaction (**11** \rightarrow **10**), significant double bond migration to form **12** and **13**

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SCHEME 5

TABLE 1. Oxidation/Elimination of **14**

| entry ^a | oxidant | solvent | temp | time, h | yield, % |
|--------------------|--|--------------------------|--------|---------|--------------------|
| 1 | 30% H_2O_2 | THF | rt | 18 | 23–60 ^b |
| 2 | aq NaIO_4 | THF | rt | 18 | 29 |
| 3 | $\text{NaIO}_4/\text{SiO}_2$ | THF | rt | 24 | no reaction |
| 4 | 30% H_2O_2 , Et_3N | THF | rt | 18 | major decomp |
| 5 | 30% H_2O_2 , Pyr | CH_2Cl_2 | reflux | 2 | 83 ^b |
| 6 | 30% H_2O_2 | CH_2Cl_2 | reflux | 5 | 83 ^b |
| 7 | 30% H_2O_2 | THF | 40 °C | 5 | 68 ^b |

^a See Supporting Information for experimental details, entries 1, 2, 6, and 7. ^b Yields based on ≥ 0.5 g (≥ 1.2 mmol) scale reaction.

occurred (Scheme 5).⁴³ The extent of the rearrangement could be limited by carrying out the elimination reaction in solvent (mesitylene, bp 162–164 °C) rather than neat,⁴² to give the desired product in 62% yield after tedious chromatographic separation. The moderate yield and difficult purification made this route undesirable for large-scale preparation of protected α -vinyl glycine. Ultimately, the synthesis of **10** from the corresponding protected phenyl selenide **14**⁴⁴ proved to be the most efficient.⁴⁵

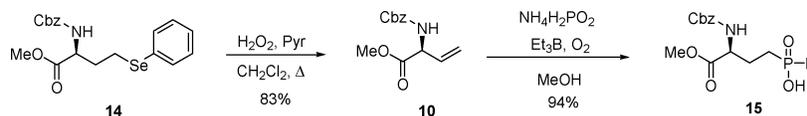
Barton’s group, the first to report the use of **14** as a precursor to α -vinyl glycine,⁴⁴ used ozone to oxidize the selenide prior to a selenoxide elimination to form the olefin. They also reported the use of 30% H_2O_2 as the oxidant, but the yields were much lower than when ozone was employed (56% vs 98%). Wishing to avoid the use of ozone, we have developed a one-pot oxidation/elimination reaction using H_2O_2 as the oxidant. Several reaction conditions and oxidants were investigated, and the results are summarized in Table 1. When the solvent was changed from THF (rt) to CH_2Cl_2 (reflux, 40 °C), the reaction rate and yield of **10** increased dramatically (Table 1, entries 5 and 6). Higher temperatures (THF, reflux temperature 66 °C) resulted in more rearrangement, whereas use of THF at 40 °C resulted in a lower yield (Table 1, entry 7). From this investigation, we conclude that the optimum reaction conditions for the successful one-pot conversion of **14** to **10** are oxidation with H_2O_2 and pyridine in refluxing CH_2Cl_2 (Table 1,

(43) The checkers of the *Organic Synthesis* procedure also reported seeing a large amount of rearrangement but attributed it to the silica gel used during the purification; however, we observed the rearrangement products in the NMR spectra of the crude reaction mixture prior to purification.

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(45) Commercially available *S*-2-amino-butyrolactone was converted to *S*-2-amino-4-bromo-butyric acid using a slight modification of the procedure of Koch and Buchardt (*Synthesis* **1993**, 1065). Following protection of the amino acid, phenyl selenide, **14**, was formed in 98% yield using the method of Barton.⁴⁴ See Supporting Information for details.

SCHEME 6



entry 5). The procedure can easily be scaled up to several grams without appreciable loss of yields. The protected α -vinyl glycine **10** was treated with Et_3B and AHP in methanol at room temperature open to air to give **15** in 94% yield (Scheme 6). This demonstrates that the Montchamp procedure is useful for highly sensitive, functionalized compounds that are prone to racemization and rearrangement.

With the synthesis of **15** completed, the stereoselective synthesis of a synthon that could be elaborated to the C-terminal portion of **2** was required. As noted above (Schemes 3 and 4), a suitably substituted cyclopentene derivative could serve as a glutarate surrogate that could be unmasked by ring-opening oxidation of the double bond. Based upon our previous work,⁸ masking the diacid functionality should allow for a broader range of reaction conditions to be employed for the synthesis of the key P–C bonds. We envisioned that a variety of electrophiles (e.g., **5**, Scheme 4) could be prepared from the corresponding 3-(hydroxymethyl)-cyclopent-1-ene **16** or **17**.⁴⁶ The *R*-stereoisomer **16**, which would lead to the (2*R*) 2-substituted glutarate moiety of **2** analogous to unnatural (2*R*)-glutamic acid, has previously been prepared by Maeda and Inouye.³⁹ A route to the desired *S*-isomer, **17**, was developed that allowed for the use of the same commercially available starting material **18** in the syntheses of **16** and **17** (Scheme 7). Both isomers are desirable for biochemical analysis to assess stereochemical determinants for phosphinic acid inhibitors of FPGS.

Treatment of **18** with Ac_2O and pyridine furnished the unstable enol acetate, which was immediately reduced using the method of Rozzell⁴⁷ (H_2 , 5% Rh/C, 1 atm) to afford the racemic mixture of **20** and **21**. The desired β -hydroxy ester **22** was obtained using Lipase AK “Amano” to selectively hydrolyze only the (2*R*)-acetate **20**, in 45% yield. The original report of this selective hydrolysis by Sakai and co-workers noted only that an unspecified *P. fluorescens* lipase was used,⁴⁸ but the microorganism was subsequently identified as *P. fluorescens* Amano P (Amano Pharmaceutical Co.).⁴⁹ We have found that Lipase AK “Amano” from the same supplier works equally well for this reaction. The resulting alcohol **22** was converted to xanthate **23** in 97% yield. Pyrolysis of **23** furnished ethyl 3-(*S*)-cyclopentenecarboxylate in 78% yield. Reduction of the ester with LiAlH_4 gave the desired (*S*)-(–)-3-(hydroxymethyl)-cyclopent-1-ene (**17**) in 71% yield.

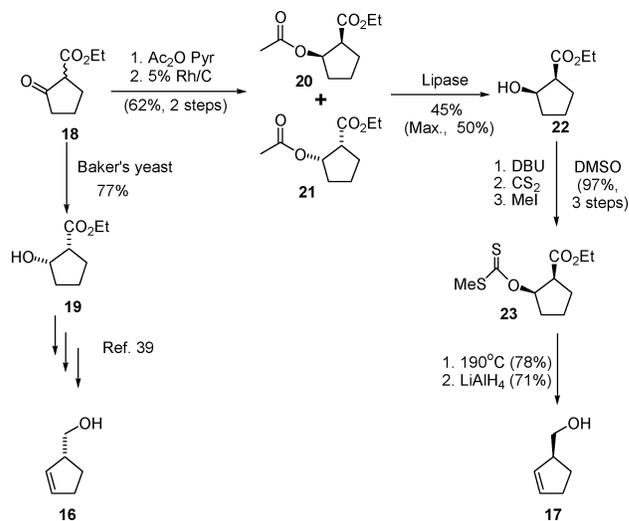
(46) Conversion of the alcohol into a suitable leaving group for P^{III} chemistry proved much more difficult than was anticipated. Compound **16** could easily be converted into the corresponding mesylate or tosylate in good yield by treatment with the corresponding sulfonyl chloride and pyridine. However, the triflate and iodide could be synthesized only in low yield and the resulting product decomposed at room temperature within minutes, presumably through a nonclassical carbocation intermediate. Ultimately, conditions were optimized for synthesis of the corresponding bromide (Table 2). See Supporting Information for details.

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SCHEME 7



The *R*-isomer **16** has been used for numerous model reactions because it is available in larger quantities than the *S*-isomer **17**. This is due to the fact that the C-3 stereocenter of **16** is set via a one-step, enzyme-catalyzed dynamic kinetic resolution, versus three steps required to obtain enantiomerically pure **17**. Given the fact that an acyclic homoallylic bromide, 4-bromo-1-butene, reacted with BTSP in high yield under the optimized conditions described above, synthesis of 3-(bromomethyl)-cyclopent-1-ene was pursued as a key intermediate (Scheme 4, **5**, X = Br). Although nonclassical carbocation rearrangements of 3-(X-methyl)-cyclopent-1-enes have been described,⁵⁰ the synthesis and study of this class of compounds is not well documented in the literature.

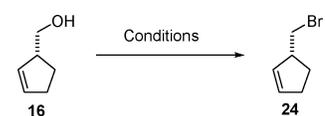
Several different methods for the synthesis of **24**, the *R*-isomer of the desired homoallylic bromide, were investigated and are summarized in Table 2. Initially, treatment of **16** with CBr_4 and PPh_3 in CH_2Cl_2 resulted in yields higher than 100% because an impurity (CHBr_3) could not be removed from the desired product (Table 2, entry 1). The inability to remove CHBr_3 proved detrimental to the P–C bond-forming reactions as will be discussed below. In a previously reported synthesis of the racemic form for use in the study of its possible rearrangement under radical⁵¹ and Grignard⁵² conditions, separation of the desired product from CHBr_3 by GC was effective; however we wished to synthesize **24** on a scale that would not be amenable to GC purification.

Activation of the alcohol via Mitsunobu (or related) conditions followed by bromide displacement (Table 2, entries 2–6) resulted in low yields and/or formation of byproduct(s) that were difficult to separate from **24**. The conversion of **16** to **24** with PPh_3Br_2 was effective (Table

(50) Hanack, M.; Schneider, H. J. *Tetrahedron* **1964**, 20, 1863–1879.

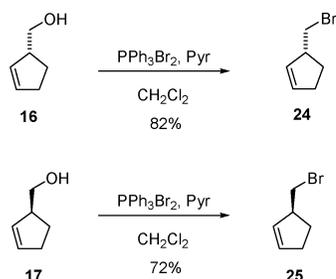
(51) Friedrich, E. C.; Halomstead, R. L. *J. Org. Chem.* **1972**, 37, 2550–2554.

(52) Maercker, A.; Geub, R. *Chem. Ber.* **1973**, 106, 773–797.

TABLE 2. Synthesis of 3-(Bromomethyl)-cyclopent-1-ene


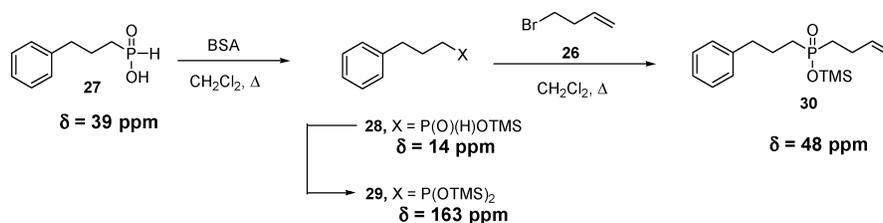
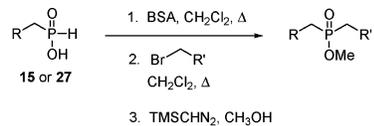
| entry ^a | conditions | solvent | yield, % |
|--------------------|---|---------------------------------|--------------------|
| 1 | CBr ₄ , PPh ₃ | CH ₂ Cl ₂ | >100 ^b |
| 2 | DIAD, PPh ₃ , ZnBr ₂ | THF | 60 |
| 3 | DIAD, PPh ₃ , ZnBr ₂ | CH ₂ Cl ₂ | 0 |
| 4 | DIAD, PPh ₃ , ⁿ Bu ₄ NBr | CH ₂ Cl ₂ | 0 |
| 5 | DDQ, PPh ₃ , ⁿ Bu ₄ NBr | CH ₂ Cl ₂ | 50–87 |
| 6 | NBS, PPh ₃ | CH ₂ Cl ₂ | 75 |
| 7 ^d | PPh ₃ Br ₂ | benzene | 56–80 ^c |
| 8 ^d | PPh ₃ Br ₂ , PPh ₃ | CH ₂ Cl ₂ | 75 |
| 9 ^d | PPh ₃ Br ₂ , Pyr | CH ₂ Cl ₂ | 82 |

^a See Supporting Information for experimental details, entries 1–8. ^b Product contaminated with CHBr₃. ^c Yield highly dependent upon source of PPh₃Br₂. ^d PPh₃Br₂ stoichiometry: entry 7, 1.12 equiv; entries 8 and 9, 1.32 equiv.

SCHEME 8

2, entry 7), but the yields varied when different sources of PPh₃Br₂ were used. Side products formed that lacked the endocyclic double bond, presumably from attack of the olefin by Br₂ or HBr contaminating the reagent. This problem could be overcome by the inclusion of additional PPh₃ in the reaction to consume any excess Br₂ (Table 2, entry 8) or by the addition of pyridine to the reaction mixture (Table 2, entry 9). The latter conditions proved to be more optimal for generation of the bromide and gave the desired product in 82% yield in 1 h. Compound **24** is relatively stable and can be stored for at least 1 month at –20 °C and is stable for 1–2 days at room temperature. However, when left at room temperature for several days, **24** decomposes to a hydrocarbon polymer with no double bond or alkyl bromide evident by NMR. As a result, the prudent course is to prepare **24** just prior to use. The *S*-isomer **25** was also prepared using this method (Scheme 8).

To couple **24**, **25**, or an acyclic analogue, 4-bromo-1-butene (**26**), to **15**, a new method was developed to accomplish the desired P–C bond formation. Although the methods of Boyd and Regan³⁰ and Thottathil²³ are

SCHEME 9**TABLE 3.** BSA-Mediated S_N2 Displacement by Phosphinic Acids


| Entry | H-Phosphinic Acid | Bromide | Product | Yield, % |
|-------|-------------------|---|-----------|----------|
| 1 | 27 | 26 | 31 | 80 |
| 2 | 27 | Br-CH ₂ CH ₂ CH ₂ CH ₂ -CH ₃ | 32 | 92 |
| 3 | 15 | 26 | 33 | 77 |

often cited for the formation of P–C bonds using P^{III} intermediates, their methods suffer from extremely diminished yields when unactivated alkyl halides are used.⁸ In our research, the reactions utilizing a P^{III} coupling methodology were followed routinely by ³¹P NMR, which allowed for the monitoring of all reaction intermediates as shown in Scheme 9.

In a typical literature procedure, the three reagents, an *H*-phosphinic acid, an alkyl halide, and *N,O*-bis-(trimethylsilyl)acetamide (BSA) or TMSI/DIEA (as the TMS source) are added in one pot and the reaction is stirred for several hours at room temperature. Using this procedure, reaction of **26** and the simple phenylpropyl *H*-phosphinic acid **27** to give **30** (Scheme 9) proceeded in only 35% yield even at reflux temperature in CH₂Cl₂ (data not shown).⁵³ However, by performing the P^{III} intermediate at slightly elevated temperatures prior to addition of the alkyl halide, the yields can be greatly improved. Initial conversion of **27** to its TMS ester **28** followed by formation of the P^{III} intermediate **29** and finally formation of the TMS ester of the desired product **30** upon addition of **26** could be monitored by ³¹P NMR and easily quantitated by integration of the corresponding peaks. Monitoring P–C bond formation in this way has allowed us to optimize the coupling of P^{III} species to unactivated alkyl bromides in high yield (Table 3).

However, when **24** (prepared via CBr₄/PPh₃ method, vide supra) was substituted for **26** in the reaction with **15**, the isolated yield of the desired phosphonic acid was only 8%! This low yield appeared to be due to contamination of **24** with bromoform, which was shown to inhibit the alkylation reaction.³⁸ These dramatically differing results led us to explore the other methods for the

synthesis of **24** described above and summarized in Table 2. The use of PPh_3Br_2 and pyridine in CH_2Cl_2 provided the best method for the preparation of **24** without contamination by CHBr_3 , and this method was used to synthesize all of the 3-(bromomethyl)-cyclopent-1-ene derivatives described below. Unfortunately, when **24**, prepared using the PPh_3Br_2 /pyridine method, was used in the BSA-mediated P–C bond-forming reaction, the reaction was very slow, ^{31}P NMR indicated only a 23% conversion after 22 h. An additional 3 equiv of **24** was added in portions over time, but after 48 h only 30% conversion to the desired phosphinic acid derivative was observed by ^{31}P NMR.

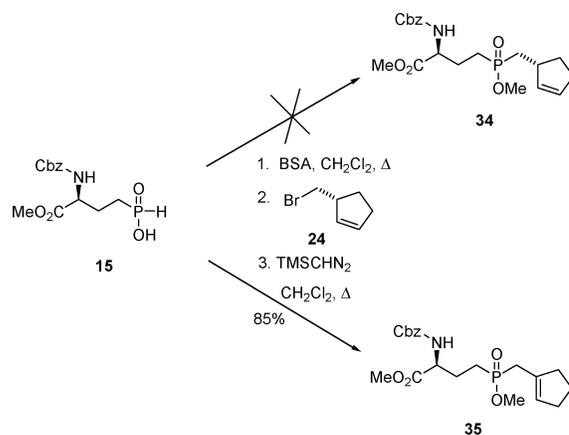
There are two possible explanations for the lower rate of reaction observed with **24**: either the 3-(bromomethyl)-cyclopent-1-ene is not stable to the reaction conditions or the additional steric encumbrance of the electrophile may be retarding the reaction. ^1H NMR of the crude reaction mixture indicated that **24** does not decompose under these conditions. The slower reaction rate and lower yield may be due to the extra substitution at the β -position of **24** compared to that of **26**. To test this hypothesis, 3-(bromomethyl)-cyclopentane was prepared from the commercially available 3-(hydroxymethyl)-cyclopentane using the PPh_3Br_2 /pyridine procedure, and its reaction with **27** was monitored by ^{31}P NMR. After 24 h only 6% conversion was observed, although prolonged reaction (11 days) did result in a conversion of 70% to the desired phosphinic acid. Other changes in reaction conditions (solvent and temperature) did not result in improved rates or yields. In contrast, reaction of **24** with thiophenol (NaH , THF, rt) proceeded smoothly in 4 h to provide the corresponding homoallylic phenylthioether in 60% yield. Similarly, Michaelis–Becker reaction of diethyl phosphite with **24** (Na , THF, reflux temperature) provided the expected cyclopentene-containing phosphonate in 65% yield (M. Ferguson, unpublished results). Therefore, the electrophilicity of **24** is adequate for effective reaction with appropriate nucleophiles.

Reasoning that the reaction with **24** was proceeding, albeit at a slow rate due to steric constraints at the electrophilic center and attenuated nucleophilicity of the P^{III} intermediate, we postulated that both rate and yield could perhaps be enhanced by increasing the equivalents of the alkyl halide. Compound **15**, containing the N-terminal stereocenter, was combined with varying amounts of **24** and BSA, and it was found that yields of greater than 80% (^{31}P NMR) could be obtained by increasing the ratio of **24**/BSA/**15** from 2:3:1 to 10:10:1. Using these optimized conditions, the reaction was complete in 44 h. After purifying the phosphinate ester by silica gel chromatography (85% yield), we discovered that either during the course of the reaction or the workup the double bond had isomerized to give **35** (Scheme 10). The structure of **35** is based on extensive NMR data (^1H , ^{13}C , ^{31}P , COSY, APT, and HETCOR), the key NMR signal being the quaternary carbon of the olefin. The reaction was repeated three times and in each instance **35** was the only product isolated.

A series of control experiments was performed in an attempt to understand the basis for the migration.

(53) After 18 h at room temperature only a very small amount of product (2%) was observed.

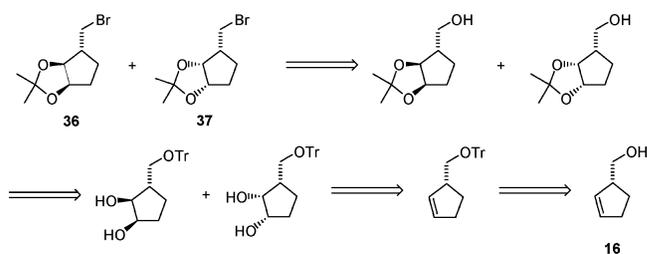
SCHEME 10



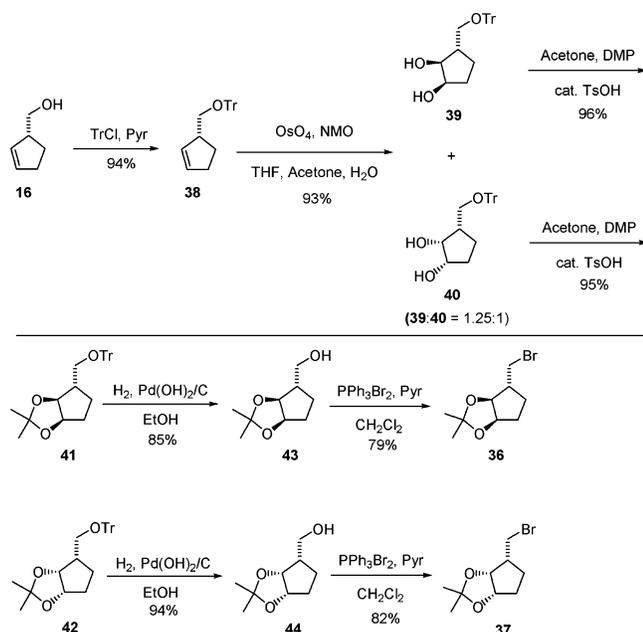
Reaction of **24** with BSA in CH_2Cl_2 at reflux temperature (48h) evaluated stability of the double bond in the starting material under the reaction conditions. Following normal workup (2 M HCl, 1:1 dilution, 15–30 min) to hydrolyze the remaining BSA and the TMS ester of the crude phosphinic acid, **24** was obtained unchanged. A similar reaction was carried out with **24** and **15** in the absence of BSA and again **24** was recovered intact. It is possible that the rearrangement occurs during the acidic workup after the P–C bond is formed, resulting in rearrangement of the desired product, **34**, to the allylic isomer, **35**. To determine if the acidic workup was causing the rearrangement of the initially formed product, the P–C bond-forming reaction was repeated and the reaction was quenched with TBAF to remove the phosphinic acid TMS ester and decompose any remaining BSA in a nonprotic environment. After treatment with TBAF, the reaction was concentrated and NMR was taken of the crude mixture. The NMR spectral data indicated that the rearrangement had occurred even with the basic workup procedure. These results led us to conclude that the rearrangement was occurring during the reaction and that the use of 3-(2-bromomethyl)cyclopent-1-ene (**24** or **25**) was not a viable option for setting the C-terminal P–C bond.

To prevent the double bond migration described above, temporary removal of the olefin was investigated. The most logical choice for this “protection” was to convert the double bond to a diol, which ultimately could be oxidatively cleaved to furnish the desired diacid functionality of the target pseudopeptide. However, the P^{III} intermediate in the P–C bond-forming reaction is not stable to protic reagents or solvents so the diol would have to be further protected as shown retrosynthetically in Scheme 11. Considering the difficulties associated with forming the second P–C bond

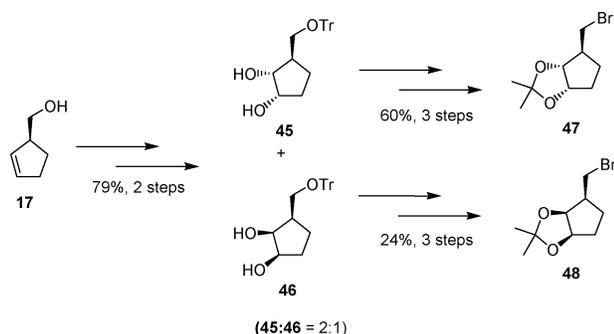
SCHEME 11



SCHEME 12



SCHEME 13



with **24**, the increased steric encumbrance presented by an acetone on the same face of the ring as the leaving group (hereafter referred to as the 2,3-*cis* isomer, e.g., **37**) could be problematic, and therefore the 2,3-*trans* isomer (e.g., **36**) was desired. The most common and highly stereoselective method for the stereoselective formation of diols from olefins is the Sharpless asymmetric dihydroxylation.⁵⁴ Unfortunately, the Sharpless procedure does not provide good asymmetric induction with disubstituted *Z*-olefins.⁵⁵

Reaction of the 3*R* alcohol **16** with trityl chloride in pyridine provided the trityl ether in 94% yield. Oxidation of **38** was first attempted using the classic Upjohn procedure⁵⁶ of catalytic OsO_4 and NaIO_4 , which provided a 90% yield of 1.25:1 mixture of the *trans* and *cis* diols **39** and **40**, respectively (Scheme 12). The use of the trityl protecting group allowed for easy separation of the two isomers. An alternative oxidant, KMnO_4 , gave much better selectivity (2,3-*trans*:2,3-*cis* (**39**:**40**), 6:1) than OsO_4 but the reaction yield was much lower, 64% vs 90%, resulting in formation of about the same amount of the

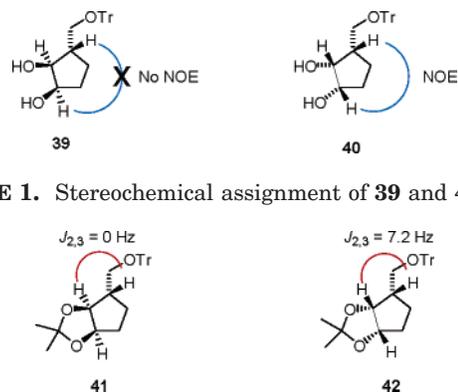


FIGURE 1. Stereochemical assignment of **39** and **40**.

FIGURE 2. Stereochemical assignment of **41** and **42**.

desired 2,3-*trans* product **39** via either route. On the basis of these results, the OsO_4 procedure is favored because of a more facile workup and easier purification of the product than with the KMnO_4 -based oxidation. The 2,3-*cis* and 2,3-*trans* diols were converted to the acetone acetonides by treatment with 2,2-dimethoxypropane, acetone, and catalytic acid in 96% yield for the 2,3-*trans* isomer **41**, and 95% for the 2,3-*cis* isomer **42** (Scheme 12).

The stereochemistry of the two oxidation products **39** and **40** was assigned on the basis of their NOESY NMR spectra (Figure 1). The stereochemical assignment is supported by the NOE cross-peak observed between the protons on C1 and C3 of **40**. There was no NOE observed for the equivalent protons of **39**. The 2,3-*cis* and 2,3-*trans* stereochemistry assigned using the NOESY spectrum of **39** and **40** was further supported by the coupling constant for the C2 and C3 protons on **41** and **42**. For compound **41** the $J_{2,3}$ coupling constant is 0 Hz indicating a dihedral angle of $\sim 90^\circ$ while the coupling constants for the corresponding protons of **42** is 7.2 Hz consistent with a dihedral angle of $\sim 20^\circ$ signifying that both protons are on the same side of the ring (Figure 2).

Several methods for the deprotection of the trityl group were investigated. Deprotection with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ ⁵⁷ or formic acid⁵⁸ resulted in decomposition and low yields. Hydrogenation with 10% Pd/C ⁵⁹ also proved unsuccessful yielding quantitative recovery of starting material. Finally, successful deprotection of the trityl group was accomplished by hydrogenation (40 psi) in the presence of Pearlman's catalyst, $\text{Pd(OH)}_2/\text{C}$, at room temperature. Conversion of the hydroxymethyl acetone acetonides to the corresponding bromomethyl derivatives was carried out using PPh_3Br_2 and pyridine to provide **36** in 79% yield and **37** in 82% yield (Scheme 12). The 2,3-*trans* (**47**) and 2,3-*cis* (**48**) isomers of the bromomethyl acetone acetonides, derived from the 3*S*-homoallylic alcohol **17**, were also prepared using the same methods (Scheme 13). The absolute stereochemistry depicted for **46**, deduced via NMR analysis of this series as described above for **39**–**42**, was confirmed via a crystal structure obtained for the corresponding sulfone.⁶⁰

(56) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 23, 1973–1976.

(57) Cabaret, D.; Wakselman, M. *Can. J. Chem.* **1990**, 68, 2253–2257.

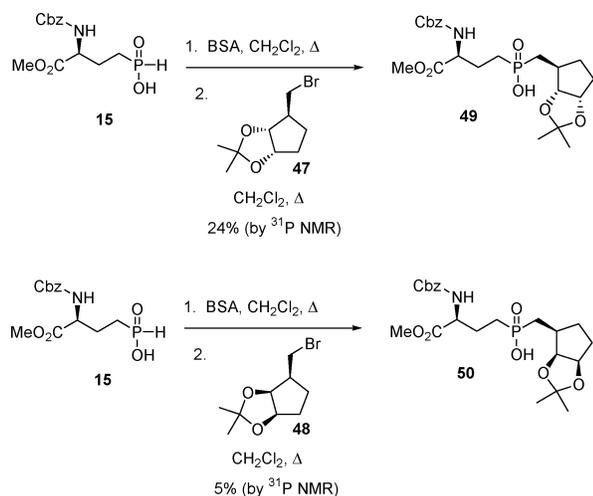
(58) Bessodes, M.; Lomiotis, D.; Antonakis, K. *Tetrahedron Lett.* **1986**, 27, 579–580.

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(55) Wang, L.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, 114, 7568–7570.

SCHEME 14

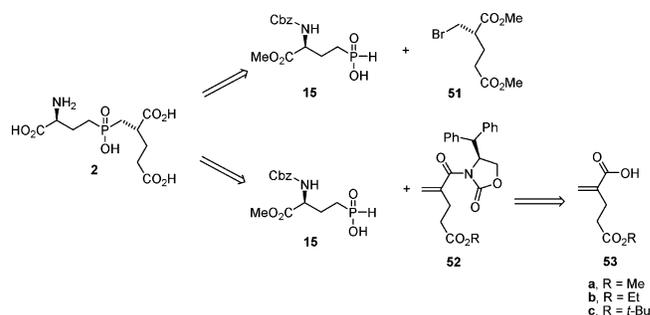


Formation of the second P–C bond using **15** and each of the four bromomethyl acetonides **36**, **37**, **47**, and **48**, proved to be even slower than was the case with the corresponding free olefins **24** or **25** (Scheme 14). After 8 days of heating, the reaction of **15** and **36** went only to 15% completion as determined by ³¹P NMR. Similar results were observed with **37**. The 3*S*-2,3-*trans* isomer **47**, with correct stereochemistry for elaboration to **2**, was then used with longer reaction times in an attempt to force the reaction to completion. Unfortunately, even after 1 month only 24% conversion was observed by ³¹P NMR. As expected, the reaction was even slower on the *S*-2,3-*cis* isomer **48** with less than 5% conversion after several weeks. The low yields of the desired complex phosphinic acids (e.g., **49** and **50**) obtained in the reactions of all isomers of 3-(bromomethyl)-cyclopentane 1,2-acetonides, together with the double bond migration observed with the corresponding cyclopentene (Scheme 10), indicated that (bromomethyl)-cyclopentene derivatives would not be effective glutarate surrogates as proposed in our retrosynthetic analysis for the stereoselective synthesis of the C-terminal C–P bond (Schemes 3 and 4). Therefore, an alternate route to the desired compounds was explored.

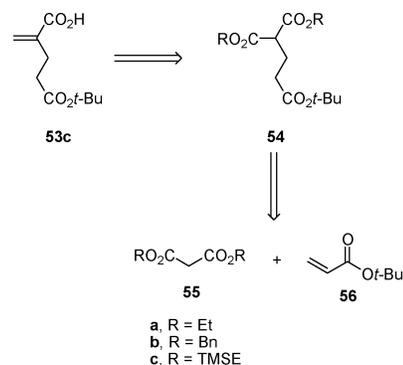
Two possible compounds that could be appended to **15** to furnish the desired product **2** are an acyclic bromomethyl derivative of dimethyl glutarate such as **51** or a methylene glutarate derivative containing a chiral auxiliary such as **52** (Scheme 15). The synthesis of **51** was not pursued because this ring-open form would be as sterically hindered at the β-position as **24** and also would be much more prone to dehydrohalogenation. For this reason, our attention focused on synthesizing the second carbon–phosphorus bond through a stereoselective Michael addition of **15** to **52**. Recently, Liu et al. have shown that the stereoselectivity of this type of Michael addition can be greatly influenced by incorporation of a chiral auxiliary on the α-carboxylate of simple acrylates.²⁵ Compound **53c** was synthesized to investigate this route. A *tert*-butyl ester was chosen as the γ-protecting group to allow for ultimate synthesis of a more versatile dipeptide analogue with N- and C-termini being differentially protected.

(60) Alexander, M. D. Ph.D. Dissertation, University of Michigan, Ann Arbor, MI, 2004.

SCHEME 15

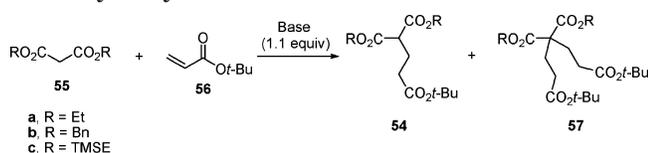


SCHEME 16



Although synthetic routes to both 2-methyleneglutaric acid and the corresponding di-esters are readily available,^{61–68} selective esterification of one of the two acids has been reported only rarely. 2-Methyleneglutaric acid 5-methyl ester **53a** has been prepared electrochemically by the addition of CO₂ to pent-4-ynoic acid methyl ester. However the free acid was not isolated, and instead the product was converted to the dimethyl ester for isolation and purification (38% yield).⁶⁹ As reported in the patent literature, compound **53a** has also been synthesized via an iodine-mediated selective esterification of the non-conjugated carboxylic acid of 2-methyleneglutaric acid.⁷⁰ A retrosynthetic strategy for the formation of 2-methyleneglutaric acid 5-*tert*-butyl ester **53c** is shown in Scheme 16. Compound **54** can be prepared via a Michael reaction of a suitably protected malonate and *tert*-butyl acrylate.⁷¹ We envisioned that **54** could be converted to compound **53c** via a tandem Mannich reaction and in situ decarboxylation.^{25,72} The Michael addition proved to be problematic as several attempted preparations of **54** led also to the α,α-disubstituted malonate **57** (Table 4). Thus, when the anion of diethyl malonate **55a** was generated

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 (70) Mitsubishi Petrochemical Co. Ltd., Japanese Patent 59152347, 1984.
 (71) Makarevic, J.; Skaric, V. *Heterocycles* **1995**, *41*, 1207–1218.

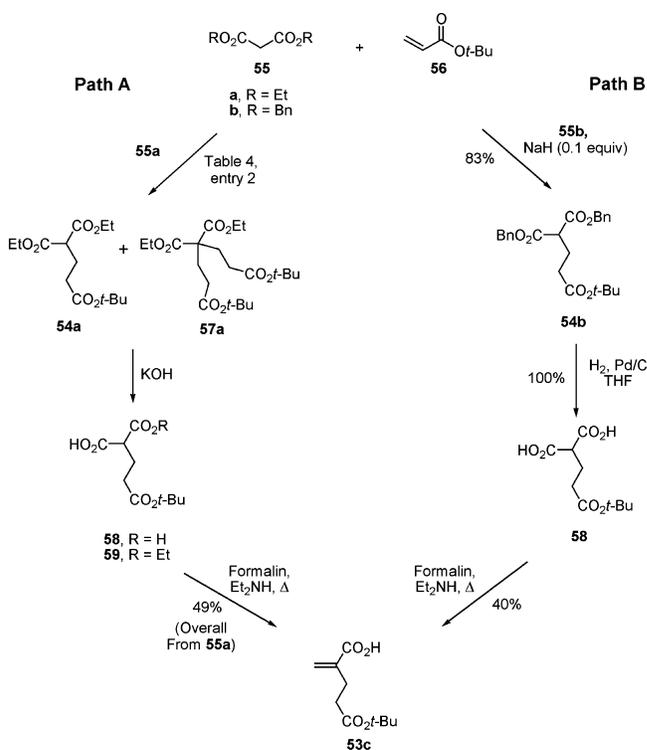
TABLE 4. Michael Reaction of Malonate Esters and *tert*-Butyl Acrylate

| entry ^a | R | base | 54:57 ^b |
|--------------------|------|---|----------------------|
| 1 | Et | NaOEt | mixture |
| 2 | Et | K ₂ CO ₃ ^c | 4:1 |
| 3 | Bn | KOtBu | mixture ^d |
| 4 | Bn | NaH | 2.3:1 |
| 5 | Bn | K ₂ CO ₃ ^c | only 57 |
| 6 | TMSE | K ₂ CO ₃ ^c | 2.4:1 |

^a See Supporting Information for experimental details, entries 4–6. ^b Ratios of individual components based upon NMR integration. ^c Phase-transfer conditions: [(*n*Bu₄)N⁺Br⁻/benzene], reflux. ^d Major component appeared to be the α,γ-disubstituted product based on NMR spectral analysis.

using stoichiometric amounts of NaH, NaOEt, KOt-Bu, or K₂CO₃ under phase-transfer conditions,⁷³ a mixture of products was obtained. The best ratio of desired monosubstituted product **54** to undesired disubstituted product **57** was 4:1 obtained with diethyl malonate (**55a**) and *tert*-butyl acrylate (**56**) using phase-transfer conditions (Table 4, entry 2). However, incomplete cleavage of the ethyl esters was observed when either a stoichiometric amount or slight excess (2.1 equiv) of base was used. The use of a large excess of base resulted in partial cleavage of the *tert*-butyl ester. In an effort to synthesize a substituted malonate containing more labile esters, the reaction of dibenzyl malonate (**55b**) or bis(trimethylsilylethyl) malonate (**55c**) and **56** was investigated. Unfortunately, under a variety of reactions conditions (Table 4, entries 3–6), only unsatisfactory mixtures were obtained. Further transformation of the inseparable mixture of **54a** and **57a** (Table 4, entry 2) was pursued. It was found that, with only an extractive workup, the mixture of hydrolysis products **58** and **59**, could be converted to the desired product **53c** under conditions involving Mannich base formation and decarboxylation, in a respectable overall yield of 49% from **55a** (Scheme 17, Path A). This method provides the desired γ-*tert*-butyl ester **53c** via a route that avoids chromatographic purification of intermediate products.

Considering the significant amount of disubstitution that was observed in all reactions of **55** and **56**, the use of stoichiometric base to deprotonate the malonate is not necessary. Only one example was found in the literature where a catalytic amount of base was used.⁷⁴ Surprisingly, in most literature procedures using stoichiometric base, the reaction is run on large scale and the desired product is purified by distillation.^{75–77} This approach typically results in low yields for this seemingly simple carbon–carbon bond-forming reaction. The addition of **55b** to **56** was repeated using a catalytic amount of NaH (Scheme 17, Path B). NaH was added to a solution of **55b**

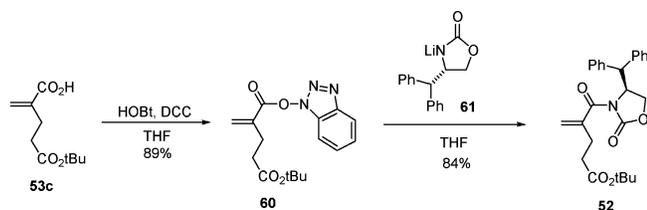
SCHEME 17

in THF, followed by the slow addition of **56** over 30 min. The reaction yielded 83% of the monosubstituted malonate **54b**. The benzyl esters of compound **54b** were removed by catalytic hydrogenation over Pd/C to give **58** in quantitative yield. Sequential formation of a Mannich base followed by decarboxylation gave the desired product **53c** in an unoptimized yield of 40% and provided the required building block for installation of a chiral auxiliary at the α-position.

On the basis of the work of Liu et al.,²⁵ the diphenylmethyl derivative of Evans' oxazolidinone was chosen as the chiral auxiliary. Initially, coupling of the oxazolidinone to the methylene glutarate was attempted via an acid chloride, but this method was not effective. Synthesis of **52** by way of the mixed anhydride using the method of Deslongchamp⁷⁸ was also attempted but furnished the desired product in only 40% yield. The most common method for the synthesis of peptide bonds is the use of carbodiimide coupling reagents in conjunction with HOBt to form the activated ester of the carboxylic acid that is being coupled. Although HOBt esters are usually formed in situ and not isolated, research in our laboratory has demonstrated that higher yields of coupling product can be obtained if the HOBt ester of an aromatic carboxylic acid is first isolated and then reacted with the desired nucleophile.⁶⁰ Yields of the chiral auxiliary coupling perhaps could be increased by HOBt-mediated activation of **53c** and isolation of the HOBt ester. In fact, reaction of **53c** with HOBt and DCC in THF provided the activated ester **60** in 89% yield following silica gel

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SCHEME 18



chromatography (Scheme 18). When **60** was treated with the lithiated anion **61**, compound **52** was isolated in 84% yield. The use of isolated activated esters similar to **60** is rare in the literature, perhaps due to the incorrect assumption that compounds of this type are not stable to silica gel chromatography or to long-term storage. However, we have found that both aromatic and aliphatic HOBt esters are stable to silica gel chromatography and are stable to prolonged (several months) storage at $-20\text{ }^{\circ}\text{C}$.

Using the procedure of Liu et al.,²⁵ the Michael reaction of **52** and a P^{III} species derived from **15** was investigated. When these conditions were used to generate a P^{III} species from **15** and effect subsequent Michael addition to **52**, a 1:1.5 ratio of two diastereomers was detected by HPLC analysis of the crude reaction mixture. The procedure described by Liu et al.²⁵ used TMSCl and DIEA to generate the BTSP nucleophile prior to addition of the Michael acceptor. However, TMSCl and DIEA vapors form copious amounts of a fluffy white solid, and the vapor also reacts with rubber septa, thus rendering this method inconvenient. Because of the low selectivity observed and problems encountered with the use of TMSCl and DIEA, reaction using BSA as the silylating agent was investigated. Reactions of **15** and either methyl acrylate, dimethyl methylene glutarate, or **52** were carried out in the presence of BSA, leading to acceptable yields of the desired products (Table 5).

The modest stereoselectivity of the Michael addition was slightly lower when BSA was used as the silylating agent than when TMSCl/DIEA was used (1.2:1 vs 1.5:1). However, the BSA reaction was much cleaner by ^{31}P NMR and did not have any of the problems associated with TMSCl and DIEA noted above. The BSA reaction can also be performed in one step with all of the reagents added at one time. There was no difference in selectivity regardless of how the reaction was quenched (2 M HCl, abs EtOH, or TFA) or at what temperature (rt, 0, or $-10\text{ }^{\circ}\text{C}$). Based upon these results, the optimized reaction conditions are reaction of **15**, **52**, and BSA at room temperature in CH_2Cl_2 for 24 h followed by quenching with 2 M HCl at room temperature and esterification of the resulting free acid with TMSCHN₂. The resulting product, a 1.2:1 mixture of two diastereomers, **64** and **65**, was obtained in 72% yield, and the two isomers were separated by silica gel chromatography (**A**, higher R_f isomer; **B**, lower R_f isomer).⁷⁹

Using LiOOH to cleave the chiral auxiliary⁸⁰ and then treating the free acid with CH_2N_2 provided fully protected

TABLE 5. BSA-Mediated Conjugate Addition of Phosphinic Acids

| Entry | X | Y | Product | Yield, % |
|-------|--------------------|--|---------|----------|
| 1 | CO ₂ Me | H | | 56 |
| 2 | CO ₂ Me | CH ₂ CH ₂ CO ₂ Me | | 70 |
| 3 | | CH ₂ CH ₂ CO ₂ t-Bu | | 72 |

pseudopeptides **66** and **67** in high yield (Scheme 19). In addition to clean deprotection, this method allows for recovery of the chiral auxiliary in greater than 90% yield by simple extraction of the crude reaction mixture with diethyl ether. Compounds **66** and **67** have the added advantage of being differentially protected at the N- and C-termini, which allows for their future extension into longer chain peptides at either the N-terminus or C-terminus or both. The protected pseudopeptides, **66** and **67**, were globally deprotected by heating at reflux temperature for 12 h in 6 M HCl, leading to the pure phosphinic acids as their HCl salts **68** and **69** in quantitative yield. To complete the synthesis of the target FPGS inhibitors, phosphinic acid pseudopeptides **74** and **75** were coupled to the acyl azide, AMPte-N₃, derived from 4-deoxy-4-amino-10-methylpteroic acid,^{8,11} using the methodology described previously.^{8,81} Subsequent ion exchange chromatography provided the desired products as their triethylammonium salts **70** and **71** in excellent yield.

In conclusion, during the course of investigating a stereoselective synthesis of phosphinic acid based inhibitors of FPGS, improved methodology for the synthesis of P–C bonds between highly functionalized phosphinic acids and unactivated alkyl bromides has been developed. Unfortunately, this procedure led to an unexpected rearrangement when applied to a cyclic homoallylic bromide and was, therefore, ineffective for the synthesis of the target pseudopeptides **70** and **71**. An alternate synthesis was pursued that relied upon the conjugate addition of **15** to **52** and subsequent chromatographic separation of stereochemically pure phosphinate pseudopeptides **64** and **65**. Deprotection of **64** and **65** and the ensuing coupling to 4-amino-4-deoxy-10-methylpteroyl azide completed the synthesis of **70** and **71**.

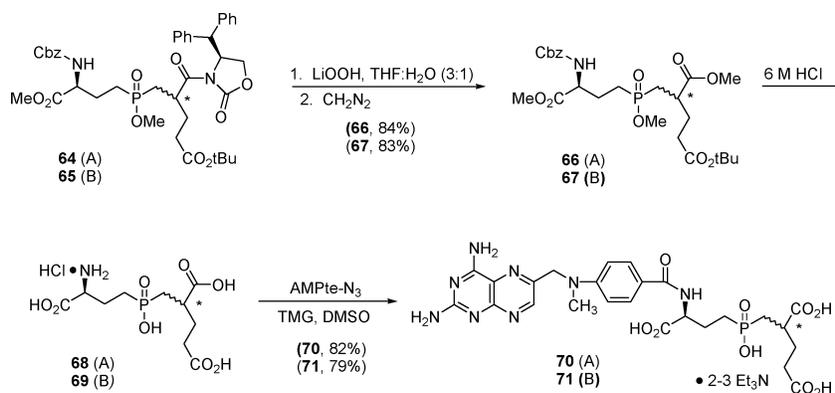
The successful synthesis of phosphinate pseudopeptides **70** and **71**, including the coupling to the 2,4-diaminopteridine heterocycle, provides the first stereochemically pure phosphinate analogues of Glu- γ -Glu for biochemical study as FPGS inhibitors and as potential ligands for crystallographic research. Preliminary biochemical data indicate that **70**, derived from **64** (isomer

(79) Subsequent reactions (Scheme 19) were carried out separately on compounds derived from either **64** (**A** series, even numbers) or **65** (**B** series, odd numbers).

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(81) Luo, J.; Smith, M. D.; Lantrip, D. A.; Wang, S.; Fuchs, P. L. *J. Am. Chem. Soc.* **1997**, *119*, 10004–10013.

SCHEME 19



A, IC_{50} = ca. 5 nM) is the more active inhibitor of the two diastereomers **70** and **71** (W. H. Haile and J. J. McGuire, personal communication) and is the most potent FPGS inhibitor synthesized to date. Although, the configuration of the 2''-stereocenter of **70** and **71** has not been proven, these preliminary biochemical results and the known requirement for L-(2S)glutamate in both the acceptor and donor substrates reported to date strongly suggest that the configuration of the more potent inhibitor, isomer **70**, is 2'S,2''S.

Experimental Section

General Experimental Procedures. See Supporting Information.

N-Cbz-Vinyl Glycine-O-methyl Ester, **10**.

A. Elimination from Sulfoxide **11** (modified Rapoport procedure). A solution of **11** (1.6 g, 5.0 mmol) in mesitylene (20 mL) was heated at reflux temperature for 24 h. After cooling to room temperature, the entire reaction was loaded onto a silica gel column and eluted with hexanes to remove mesitylene and then 4:1 hexanes/EtOAc to elute the product. The fractions containing the desired product were pooled and concentrated to give 0.74 g of **10** (62%): $^1\text{H NMR}$ (CDCl_3) δ 7.36 (m, 5H), 5.91 (ddd, 1H, J = 16.9 Hz, 10.4 Hz, 5.4 Hz), 5.47 (d, 1H, J = 6.0 Hz), 5.36 (dd, 1H, J = 16.9, 1.2 Hz), 5.28 (dd, 1H, J = 10.4, 1.2 Hz), 5.13 (s, 3H), 4.95 (m, 1H). $^{13}\text{C NMR}$ (CDCl_3) δ 171.0, 155.7, 136.3, 132.5, 128.7, 128.4, 128.3, 117.9, 67.3, 56.3, 52.9. $[\alpha]^{24}_{\text{D}}$ -12.3° (c 1.0, MeOH) (lit.⁴⁴ -12.4° (c 0.5, MeOH)).

B. Oxidative Elimination from Selenide **14.** (Table 1, Entry 5) To a solution of **14** (0.5 g, 1.2 mmol) in CH_2Cl_2 (50 mL) were added 30% H_2O_2 (3 mL) and pyridine (3 mL) and the solution was heated at reflux temperature for 2 h. The reaction was cooled to room temperature and then washed with H_2O , saturated aqueous CuSO_4 , 2 M HCl, saturated aqueous NaHCO_3 , and brine (60 mL each). The organic layer was dried over Na_2SO_4 , filtered, and concentrated. The crude product was purified by CombiFlash chromatography to give 0.25 g of **10** as a clear oil (83%). $^1\text{H NMR}$, $^{13}\text{C NMR}$, and optical rotation data were identical to that reported above for **10** prepared by the modified Rapoport procedure. MS (ESI) m/z 272.2 ($[\text{M} + \text{Na}]^+$, 100). HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{15}\text{NO}_4\text{Na}$ 272.0899 $[\text{M} + \text{Na}]^+$, found 272.0895.

(S)-2-Benzoyloxycarbonylamino-4-hydroxyphosphinoylbutyric Acid Methyl Ester, **15.** To a solution of **10** (0.5 g, 2.0 mmol) and $\text{NH}_4\text{H}_2\text{PO}_2$ (0.42 g, 5.0 mmol) in MeOH (2 mL) was added Et_3B (2.0 mL of 1.0 M solution in hexanes, 2.0 mmol) at room temperature. The reaction was stirred vigorously open to the air. The reaction was monitored by $^{31}\text{P NMR}$ (two drops of crude reaction mixture in 0.5 mL CD_3OD), and after 2 h the reaction was complete. The reaction was

concentrated and the crude oil was partitioned between 5% aqueous KHSO_4 (30 mL) and EtOAc (60 mL). The aqueous layer was extracted with EtOAc (2×60 mL) and the combined organic phase was dried over Na_2SO_4 , filtered, and concentrated to give 0.6 g of **15** as a clear oil (85%): $^1\text{H NMR}$ (CDCl_3) δ 7.04 (d, 1H, J_{PH} = 555 Hz), 7.33 (m, 5H), 5.91 (br, H), 5.10 (s, 2H), 4.40 (m, 1H), 3.73 (s, 3H), 2.13 (m, 1H), 2.0–1.8 (overlapping m, 3H). $^{13}\text{C NMR}$ (CDCl_3) δ 172.2, 156.4, 136.4, 129.0, 128.7, 128.6, 67.6, 54.2 (d, J = 16 Hz), 53.1, 25.7 (d, J = 93 Hz), 24.3. $^{31}\text{P NMR}$ (121 MHz, CDCl_3) δ 35.5 Hz. MS (ESI) m/z 338.1 ($[\text{M} + \text{Na}]^+$, 100). HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{18}\text{NO}_6\text{PNa}$ 338.0769 $[\text{M} + \text{Na}]^+$, found 338.0767.

Ethyl (1S,2R)-(-)-2-hydroxycyclopentanecarboxylate, **22.** To a stirring mixture of **20/21** (0.5 g, 2.5 mmol) in 100 mL of phosphate buffer (0.1M, pH 7.0) was added 0.3 g of lipase (Lipase AK "Amano" from *Pseudomonas fluorescens*, Amano Enzyme) and the reaction was stirred at 37°C for 18 h. The reaction was extracted with Et_2O (3×150 mL). The organic layer was dried over Na_2SO_4 , filtered and concentrated. The crude residue was purified by silica gel chromatography (7:3 pentane/Et₂O) to give 0.18 g of **22** as a clear, colorless oil (45% (maximum yield 50%)): $^1\text{H NMR}$ (CDCl_3) δ 4.42 (q, 1H, J = 3.7 Hz), 4.17 (q, 2H, J = 7.1 Hz), 2.66 (m, 1H), 2.07–1.6 (overlapping m, 7H), 1.27 (t, 3H, J = 7.1 Hz). $^{13}\text{C NMR}$ (CDCl_3) δ 175.1, 73.8, 60.7, 49.5, 34.1, 26.5, 22.2, 14.3. $[\alpha]^{24}_{\text{D}}$ -14.1° (c 1.0, CHCl_3) (lit.⁴⁸ -14.3° (c 0.63, CHCl_3)). MS (EI) m/z 101.1 (100), 159.2 ($[\text{M} + \text{H}]^+$, 15). HRMS (EI) calcd for $\text{C}_8\text{H}_{15}\text{O}_3$ 159.1021 $[\text{M} + \text{H}]^+$, found 159.1028.

(1S,2R)-2-((Methylthio)-carboxyoxo)-cyclopentanecarboxylic Acid Ethyl Ester, **23.** To a solution of **22** (0.82 g, 5.0 mmol) in anhydrous DMSO (2.5 mL) was added DBU (0.83 mL, 5.5 mmol) at room temperature and the reaction was stirred for 1 h. Carbon disulfide (33.0 mL, 2.0 mmol) was then added and the reaction was stirred for 1.5 h. Methyl iodide (0.61 mL, 10.0 mmol) was added and the reaction was stirred for 1 h. The reaction was concentrated by rotary evaporation (40 °C, 10 mmHg) and the resulting solution was diluted with CH_2Cl_2 (80 mL) and washed with H_2O (80 mL). The aqueous layer was extracted with CH_2Cl_2 (80 mL). The combined organic layers were washed with brine (40 mL), dried over Na_2SO_4 , filtered and concentrated. The crude material was purified by silica gel chromatography (9:1 hexanes/EtOAc) to give 1.2 g of **23** as an orange oil (97%): $^1\text{H NMR}$ (CDCl_3) δ 6.14 (m, 1H), 4.14 (q, 2H, J = 7.1 Hz) 3.03 (m, 1H), 2.49 (s, 3H), 2.3–2.1 (m, 1H), 2.1–1.8 (m, 4H), 1.8–1.6 (m, 1H), 1.23 (t, 3H, J = 7.1 Hz). $^{13}\text{C NMR}$ (CDCl_3) δ 214.6, 171.4, 86.2, 60.9, 49.2, 32.3, 26.2, 22.4, 18.7, 14.4.

(S)-3-(hydroxymethyl)-cyclopent-1-ene, **17.** Xanthate **23** (2.2 g, 9.0 mmol) was placed in a 100 mL round-bottom flask equipped with a condenser and was heated at 190 °C for 3.5 h. The reaction was allowed to cool to room temperature. The desired product was purified by Kugelrohr distillation (110 °C, 40 mmHg) to give 1.1 g of ethyl (S)-2-cyclopentene-1-carboxylate as a clear oil (85%): $^1\text{H NMR}$ (CDCl_3) δ 5.88 (m, 1H), 5.72

(m, 1H), 4.13 (q, 2H, $J = 7.1$ Hz), 3.53 (m, 1H), 2.6–2.3 (overlapping m, 2H), 2.13 (m, 2H), 1.26 (t, 3H). ^{13}C NMR (CDCl_3) δ 175.4, 134.2, 129.0, 60.9, 53.8, 51.1, 32.6, 26.9, 14.6. $[\alpha]_{\text{D}}^{25}$ -176.4° (c 1.0, CHCl_3). MS (EI) m/z 67.1 ($[\text{M}-\text{CO}_2\text{Et}]^+$, 100), 140.1 ($[\text{M} + \text{H}]^+$, 16). HRMS (EI) calcd for $\text{C}_8\text{H}_{12}\text{O}_2$ 140.0837 $[\text{M}]^+$, found 140.0841.

A solution of Ethyl (*S*)-2-cyclopentene-1-carboxylate (1.1 g, 7.8 mmol) in Et_2O (5 mL) was added dropwise to a stirring suspension of LiAlH_4 (0.41 g, 10.9 mmol) in Et_2O (20 mL) at 0°C under Ar. The reaction was allowed to warm to room temperature and stirred for 4 h. The reaction was quenched using standard workup conditions (0.41 mL H_2O was added, followed by 0.41 mL 15% aqueous NaOH and finally by 1.23 mL H_2O all at 0°C).⁸² The reaction was allowed to warm to room temperature and stirred until all of the excess LiAlH_4 had reacted to form a solid, white precipitate of hydroxides. The precipitate was removed by filtration and washed with Et_2O . The filtrate was concentrated and the crude product was purified by Kugelrohr distillation (20 mmHg, $80\text{--}85^\circ\text{C}$) to give 0.70 g of **17** as a clear oil (92%): ^1H NMR (CDCl_3) δ 5.87 (m, 1H), 5.66 (m, 1H), 3.56 (t, 2H, $J = 5.7$ Hz), 2.92 (m, 1H), 2.35 (m, 2H), 2.01 (m, 1H), 1.64 (m, 1H), 1.40 (t, 1H, $J = 5.7$ Hz). ^{13}C NMR (CDCl_3) δ 133.5, 131.2, 66.6, 48.6, 32.3, 26.1. $[\alpha]_{\text{D}}^{24}$ -152.8° (c 1.44, CHCl_3). MS (EI) m/z 98.1 ($[\text{M}]^+$, 7), 67.0 ($[\text{M} - \text{CH}_2\text{OH}]^+$, 100). HRMS (EI) calcd for $\text{C}_6\text{H}_{10}\text{O}$ 98.0732 $[\text{M}]^+$, found 98.0730.

(R)-3-(Bromomethyl)-cyclopent-1-ene, 24. PPh₃Br₂/Pyr Method. (Table 2, Entry 9) To a suspension of PPh_3Br_2 (1.4 g, 3.3 mmol) in anhydrous CH_2Cl_2 (10 mL) at -10°C was added a solution of **16** (0.25 g, 2.5 mmol) and pyridine (0.33 mL, 4.0 mmol) in anhydrous CH_2Cl_2 (1 mL). The reaction was stirred at -10°C for 10 min and then allowed to warm to room temperature and stir for 1 h. The reaction mixture was filtered through a silica gel plug (pentane) and the fractions containing **24** were pooled and concentrated to give 0.33 g of **24** as a clear, colorless oil (82%): ^1H NMR (CDCl_3) δ 5.87 (m, 1H), 5.65 (m, 1H), 3.35 (m, 2H), 3.13 (m, 1H), 2.35 (overlapping m, 2H), 2.11 (m, 1H), 1.62 (m, 1H). ^{13}C NMR (CDCl_3) δ 133.4, 132.1, 48.4, 38.6, 32.1, 28.9. MS (EI) m/z 160.0 and 162.0 ($[\text{M}]^+$, 6), 67.1 ($[\text{M} - \text{CH}_2\text{Br}]^+$, 100). HRMS (EI) calcd for $\text{C}_6\text{H}_9\text{Br}$ 159.9888 $[\text{M}]^+$, found 159.9882.

(S)-3-(Bromomethyl)-cyclopent-1-ene, 25. To a suspension of PPh_3Br_2 (1.4 g, 3.3 mmol) in anhydrous CH_2Cl_2 (10 mL) at -10°C was added a solution of **17** (0.25 g, 2.5 mmol) and pyridine (0.33 mL, 4.0 mmol) in anhydrous CH_2Cl_2 (1 mL). The reaction was stirred at -10°C for 10 min and then allowed to warm to room temperature and stir for 1 h. The reaction mixture was absorbed onto silica gel (2 g) and loaded onto a silica gel plug. The plug was eluted with pentane and the fractions containing **25** were pooled and concentrated to give 0.31 g of **25** as a clear, colorless oil (79%): ^1H NMR (CDCl_3) δ 5.86 (m, 1H), 5.65 (m, 1H), 3.36 (m, 2H), 3.13 (m, 1H), 2.33 (overlapping m, 2H), 2.10 (m, 1H), 1.62 (m, 1H). ^{13}C NMR (CDCl_3) δ 133.3, 132.1, 48.5, 38.6, 32.0, 28.9. MS (EI) m/z 160.0 and 162.0 ($[\text{M}]^+$, 5), 67.1 ($[\text{M} - \text{CH}_2\text{Br}]^+$, 100). HRMS (EI) calcd for $\text{C}_6\text{H}_9\text{Br}$ 159.9888 $[\text{M}]^+$, found 159.9883.

But-3-enyl-(3-phenyl-propyl)-phosphinic Acid Methyl Ester, 31. A 10 mL round-bottom flask was charged with **27** (0.1 g, 0.5 mmol) and CH_2Cl_2 (3 mL) and equipped with a condenser fitter with a rubber septum. The apparatus was flushed with Ar and fitted with an Ar-filled balloon. BSA (0.38 mL, 1.5 mmol) was added via syringe through the septum. The reaction was heated at reflux temperature for 6 h, after which 4-bromo-1-butene (**26**, 0.1 mL, 1.0 mmol) was added. The reaction was returned to reflux temperature and heated for 18 h, then quenched by stirring vigorously with 2 M HCl (2 mL) for 15 min. The resulting mixture was diluted with CH_2Cl_2 (10 mL) and washed with 2 M HCl (2×5 mL) and H_2O (5 mL). The organic layer was dried over Na_2SO_4 , filtered, and

concentrated. The resulting oil was dissolved in MeOH (3 mL) and treated with TMSCHN_2 (2 M in hexanes) until a persistent yellow color was observed. The reaction was stirred for 30 min at room temperature, then quenched with AcOH and concentrated. The residue was purified by CombiFlash chromatography (95:5 $\text{CHCl}_3/\text{MeOH}$) to give 0.12 g of **31** (80%): ^1H NMR (CDCl_3) δ 7.30–7.16 (m, 5H), 5.80 (m, 1H), 5.00 (m, 2H), 3.67 (d, 3H, $J = 6.3$ Hz), 2.70 (m, 2H), 2.28 (m, 2H), 1.90 (m, 2H), 1.80–1.70 (m, 4H). ^{13}C NMR (CDCl_3) δ 140.9, 137.3, 137.2, 128.58, 128.55, 126.3, 115.4, 51.1, 51.0, 36.8, 36.7, 27.5, 26.5, 25.98, 25.96, 23.67, 23.65. ^{31}P NMR (CDCl_3) δ 58.7.

Pentyl-(3-phenyl-propyl)-phosphinic Acid Methyl Ester, 32. A 10 mL round-bottom flask was charged with **27** (0.1 g, 0.5 mmol) and CH_2Cl_2 (2 mL) and equipped with a reflux temperature condenser fitter with a rubber septum. The apparatus was flushed with Ar and fitted with an Ar-filled balloon. BSA (1.2 mL, 5.0 mmol) was added via syringe through the septum. The reaction was heated at reflux temperature for 4 h. 1-Bromopentane (0.31 mL, 5.0 mmol) was added. The reaction was returned to reflux temperature and heated for 72 h, then quenched by stirring vigorously with 2 M HCl (2 mL) for 15 min. The resulting mixture was diluted with CH_2Cl_2 (10 mL) and washed with 2 M HCl (2×5 mL) and H_2O (5 mL). The organic layer was dried over Na_2SO_4 , filtered, and concentrated. The resulting oil was dissolved in MeOH (3 mL) and treated with TMSCHN_2 (2 M in hexanes) until a persistent yellow color was observed. The reaction was stirred for 30 min at room temperature, then quenched with AcOH and concentrated. The residue was purified by preparative TLC (95:5 $\text{CHCl}_3/\text{MeOH}$) to give 0.12 g of **32** (92%): NMR (CDCl_3) δ 7.31–7.15 (m, 5H), 3.69 (d, 3H, $J = 6.3$ Hz), 2.70 (m, 2H), 1.90 (m, 2H), 1.72–1.62 (m, 4H), 1.62–1.50 (m, 2H), 1.35–1.30 (m, 4H), 0.88 (t, 3H, $J = 6.9$ Hz). ^{13}C NMR (CDCl_3) δ 141.3, 128.9, 128.8, 126.5, 51.3, 51.2, 37.2, 37.0, 33.5, 33.3, 28.4, 27.8, 27.2, 26.6, 24.0, 22.6, 21.9, 21.8, 14.2. ^{31}P NMR (CDCl_3) δ 60.4.

(2S)-2-Benzoyloxycarbonylamino-4-(but-3-enyl-methoxy-phosphinoyl)-butyric Acid Methyl Ester, 33. A solution of **15** (0.10 g, 0.32 mmol) in CH_2Cl_2 (2 mL) freshly dried over MgSO_4 was added to a flame-dried 10 mL round-bottom flask equipped with a stir bar and condenser. BSA (0.32 mL, 1.3 mmol) was added and the reaction was heated at reflux temperature for 4 h, after which **26** (0.1 mL, 0.96 mmol) was added and the reaction was heated at reflux temperature for 22 h. ^{31}P NMR analysis of a 0.1 mL aliquot of the reaction indicated incomplete conversion to the desired product. An additional 0.1 mL BSA was added and the reaction was heated at reflux temperature for 18 h, at which time ^{31}P NMR analysis of a second 0.1 mL aliquot indicated $\sim 90\%$ conversion, and the reaction was allowed to warm to room temperature. 1 M HCl (2 mL) was added and the reaction was stirred vigorously for 30 min. The reaction was then diluted with CH_2Cl_2 (5 mL), and the aqueous layer was extracted with additional CH_2Cl_2 (5 mL). The combined organic layer was washed with 5 M each 1 M HCl, H_2O , and brine, then dried over Na_2SO_4 , filtered, and concentrated. The crude product was dissolved in MeOH and treated with freshly prepared CH_2N_2 until a yellow color persisted. The reaction was stirred for 15 min at room temperature before quenching with AcOH. The crude methyl ester was purified by CombiFlash ($\text{EtOAc}/2\%$ MeOH, 10 g column, 30 mL/min flow rate) to give 0.08 g of **33** as a clear oil (69% isolated yield, 77% corrected yield (10% of the reaction mixture had been removed to monitor reaction progress (^{31}P NMR): ^1H NMR (CDCl_3) δ 7.33 (m, 5H), 5.96–5.74 (overlapping m, 2H), 5.10 (s, 2H), 5.09 (m, 2H), 4.41 (m, 1H), 3.73 (s, 3H), 3.66 (m, 3H), 2.31 (m, 2H), 2.18 (m, 1H), 2.03 (m, 1H), 1.76 (m, 4H). ^{13}C NMR (CDCl_3) δ 172.3, 156.4, 137.4, 137.3, 136.5, 128.9, 128.8, 128.7, 128.6, 128.5, 160.0, 67.5, 54.4, 53.1, 51.5, 27.70, 27.65, 26.98, 26.93, 26.26, 26.23, 25.47, 25.39, 24.45, 24.39, 23.71, 23.68. ^{31}P NMR (CDCl_3) δ 57.4. MS (ESI) m/z 384.2 ($[\text{M} + \text{H}]^+$, 100). HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{27}\text{NO}_6\text{P}$ 384.1576 $[\text{M} + \text{H}]^+$, found 384.1572.

(82) Fieser, L. F.; Fieser, M. In *Reagents for Organic Synthesis*; John Wiley & Sons Inc.: New York, 1967; Vol. 1, p 584.

(2S)-2-Benzoyloxycarbonylamino-4-(cyclopent-1-enyl-methyl-methoxy-phosphinoyl)-butyric Acid Methyl Ester, 35. A solution of **15** (0.1 g, 0.32 mmol) and BSA (0.79 mL, 3.2 mmol) in anhydrous CH₂Cl₂ (2 mL) was heated at reflux temperature for 4 h. A solution of **24** (0.52 g, 3.2 mmol) in anhydrous CH₂Cl₂ (1 mL) was added and the reaction continued at reflux temperature for 44 h. The reaction was cooled to room temperature, 2 M HCl (2 mL) was added and the reaction was vigorously stirred for 30 min. CH₂Cl₂ (5 mL) was added and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (5 mL) and the combined organic layers were dried over Na₂SO₄ and concentrated. The crude oil was dissolved in MeOH (5 mL) and treated with CH₂N₂ until the reaction remained yellow. The reaction was stirred for 15 min at room temperature, then quenched with a drop of AcOH and concentrated. The crude product purified by silica gel chromatography (EtOAc with 2% MeOH) to give 0.12 g of **35** as a clear colorless oil (85%): ¹H NMR (CDCl₃) δ 7.39–7.29 (m, 5H), 5.80 (m, 1H), 5.55 (m, 1H), 5.11 (s, 2H), 4.40 (m, 1H), 3.74 (s, 3H), 3.67 (m, 3H), 2.65 (m, 2H), 2.34 (overlapping m, 4H), 2.18 (m, 1H), 1.95 (m, 1H), 1.89 (m, 2H), 1.8–1.6 (m, 2H). ¹³C NMR (CDCl₃) δ 172.4, 156.4, 136.6, 134.22, 134.16, 130.2, 130.1, 128.9, 128.6, 128.5, 67.1, 54.46, 54.35, 53.0, 51.61, 51.58, 51.56, 51.53, 36.54, 36.52, 33.11, 33.10, 31.83, 31.79, 31.14, 31.09, 25.4, 23.9, 23.82, 23.77, 23.09, 23.03. ³¹P NMR (CDCl₃) δ 54.1. MS (ESI) *m/z* 410.2 ([M + H]⁺, 100). HRMS (ESI) calcd for C₂₀H₂₉NO₆P 410.1733 [M + H]⁺, found 410.1729.

(R)-3-[(phenylthio)methyl]-cyclopent-1-ene. To a suspension of NaH (80% dispersion in mineral oil, 0.019 g, 0.62 mmol) in anhydrous THF (3.5 mL) at 0°C under Ar, PhSH (0.063 mL, 0.62 mmol) was added dropwise over 5 min. The suspension was stirred for 30 min. A solution of **24** (0.10 g, 0.62 mmol) in anhydrous THF (3.5 mL) was added dropwise over 5 min. The reaction was warmed to room temperature and stirred for 4 h, after which it was concentrated and the residue partitioned between H₂O (20 mL) and CH₂Cl₂ (30 mL). The aqueous layer was washed with CH₂Cl₂ (2 × 30 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated to give 0.24 g of crude orange oil. The crude product was purified using a silica gel plug and eluting with pentane to give 0.07 g of (R)-3-[(phenylthio)methyl]-cyclopent-1-ene as a slightly yellow oil. (60%): ¹H NMR (CDCl₃) δ 7.27 (m, 5H), 5.80 (m, 1H), 5.76 (m, 1H), 2.94 (overlapping m, 3H), 2.36 (m, 2H), 2.13 (m, 1H), 1.62 (m, 1H). ¹³C NMR (CDCl₃) δ 137.2, 133.4, 132.1, 129.2, 129.0, 127.6, 125.9, 45.3, 39.7, 32.1, 29.9.

(R)-3-(Tritylxymethyl)-cyclopent-1-ene, 38. To a solution of **16** (0.35, 3.6 mmol) in anhydrous pyridine (4 mL) was added trityl chloride (1.5 g, 5.4 mmol) under Ar and the reaction was stirred at room temperature for 24 h. The reaction was filtered through a silica gel plug (4:1 hexanes/EtOAc) and the filtrate was concentrated to give a mixture of **38** and TrCl. The crude product was purified by silica gel chromatography (95:5 hexanes/EtOAc) to give 1.1 g of **38** (92%): ¹H NMR (CDCl₃) δ 7.6–7.2 (m, 15H), 5.87 (overlapping m, 2H), 3.10 (overlapping m, 3H), 2.39 (m, 2H), 2.11 (m, 1H), 1.61 (m, 1H). ¹³C NMR (CDCl₃) δ 144.6, 132.6, 131.9, 128.9, 128.8, 127.9, 127.8, 127.0, 126.9, 86.3, 67.6, 46.5, 32.0, 26.9. MS (CI) *m/z* 243.1 ([Tr]⁺, 100), 341.2 ([M + H]⁺, 1).

(1R,2S,3S)-3-(Tritylxymethyl)-cyclopentane-1,2-diol, 39, and (1S,2R,3S)-3-(Tritylxymethyl)-cyclopentane-1,2-diol, 40. To a stirring solution of **38** (0.5 g, 1.5 mmol) in 7.5 mL THF, 7.5 mL acetone, and 1 mL H₂O at 0°C was added OsO₄ (0.02 mL of 2.5 wt % in *t*BuOH) followed by NMO (0.35 g, 8.8 mmol). The reaction was stirred at room temperature for 30 h. The reaction was diluted with CH₂Cl₂ (150 mL) and washed with 10% aqueous Na₂SO₃ (100 mL) and NH₄Cl (100 mL). The combined aqueous phases were extracted with CH₂-Cl₂ (2 × 150 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated. The crude residue was purified by silica gel chromatography (2:1 hexanes/EtOAc) to

give 0.30 g of 2,3-*trans* isomer, **39** (53%) and 0.22 g of the 2,3-*cis* isomer, **40** (40%).

Compound **39**: ¹H NMR (CDCl₃) δ 7.6–7.2 (m, 15H), 4.12 (m, 1H), 3.80 (m, 1H), 3.40 (Overlapping m, 2H), 3.15 (Overlapping m, 2H), 2.41 (m, 1H), 2.10 (m, 1H), 1.97 (m, 1H), 1.86 (m, 1H), 1.32 (m, 1H). ¹³C NMR (CDCl₃) δ 143.9, 128.6, 128.5, 127.9, 127.1, 86.9, 78.3, 73.2, 66.5, 43.4, 30.0, 23.4.

Compound **40**: ¹H NMR (CDCl₃) δ 7.5–7.2 (m, 15H), 4.15 (m, 1H), 4.07 (m, 1H), 3.33 (m, 1H), 3.24 (m, 1H), 2.90 (d, 1H, *J* = 3.2 Hz), 2.52 (d, 1H, *J* = 6.7 Hz), 2.29 (m, 1H), 1.85 (m, 1H), 1.7–1.6 (overlapping m, 2H), 1.57 (m, 1H). ¹³C NMR (CDCl₃) δ 143.9, 128.6, 128.1, 127.3, 78.2, 74.6, 74.4, 64.0, 41.4, 30.7, 23.9.

(1R,2S,3S)-3-(Tritylxymethyl)-cyclopentane-1,2-diol Dimethyl Acetonide, 41. To a solution of **39** (0.69 g, 1.8 mmol) in acetone (20 mL) and dimethoxypropane (20 mL) was added TsOH (0.03 g, 0.2 mmol) and the reaction was stirred at room temperature for 10 min. The reaction was diluted with EtOAc (150 mL) and washed with saturated aqueous NaHCO₃ (50 mL) and brine (50 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated. The crude product was purified by silica gel chromatography (95:5 hexanes/EtOAc) to give 0.73 g of **41** (97%): ¹H NMR (CDCl₃) δ 7.6–7.2 (m, 15H), 4.62 (dd, 1H, *J* = 5.4, 5.5), 4.45 (d, 1H, *J* = 5.7 Hz), 3.05 (overlapping m, 2H), 2.50 (m, 1H), 2.09 (m, 1H), 1.83 (m, 1H), 1.8–1.6 (overlapping m, 2H), 1.55 (s, 3H), 1.36 (s, 3H). ¹³C NMR (CDCl₃) δ 144.2, 128.7, 127.8, 127.0, 109.5, 86.6, 83.6, 81.0, 63.7, 46.0, 31.5, 26.6, 25.8, 24.2.

(1S,2R,3S)-3-(Tritylxymethyl)-cyclopentane-1,2-diol Dimethyl Acetonide, 42. To a solution of **40** (0.2 g, 0.53 mmol) in acetone (10 mL) and dimethoxypropane (10 mL) was added TsOH (0.01 g, 0.05 mmol) and the reaction was stirred at room temperature for 15 min. The reaction was diluted with EtOAc (100 mL) and washed with saturated aqueous NaHCO₃ (50 mL) and brine (50 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated. The crude product was purified by silica gel chromatography (95:5 hexanes/EtOAc) to give 0.21 g of **42** (95%): ¹H NMR (CDCl₃) δ 7.6–7.2 (m, 15H), 4.67 (overlapping m, 2H), 3.47 (dd, 1H, *J* = 8.6, 7.3), 3.15 (dd, 1H, *J* = 8.6, 7.2 Hz), 1.92 (m, 1H), 1.85 (m, 1H), 1.69 (m, 1H), 1.5–1.4 (overlapping m, 2H), 1.37 (s, 3H), 1.33 (s, 3H). ¹³C NMR (CDCl₃) δ 144.6, 129.0, 127.9, 126.9, 109.1, 86.5, 81.0, 80.5, 62.8, 45.6, 32.4, 26.1, 26.0, 24.1.

(1R,2S,3S)-3-(Hydroxymethyl)-cyclopentane-1,2-diol Dimethyl Acetonide, 43. To a solution of **41** (0.9 g, 2.2 mmol) in EtOH (100 mL) was added 10% Pd(OH)₂ on carbon (Pearlman's catalyst) (1 g) and the reaction was shaken on a Parr hydrogenator (40 psi H₂) for 8 h. The catalyst was removed by filtering through silica gel using EtOAc as solvent and concentrating the eluant. The crude product was purified by silica gel chromatography (CHCl₃ to elute triphenylmethane, then EtOAc to elute the desired product) to give 0.32 g of **43** (85%): ¹H NMR (CDCl₃) δ 4.65 (dd, 1H, *J* = 4.9, 5.5 Hz), 4.45 (d, 1H, *J* = 5.7 Hz), 3.45 (m, 2H), 2.22 (m, 1H), 1.98 (m, 1H), 1.82 (m, 1H), 1.75 (m, 1H), 1.48 (m, 2H), 1.45 (s, 3H), 1.30 (s, 3H). ¹³C NMR (CDCl₃) δ 110.1, 83.4, 81.0, 63.6, 48.4, 31.3, 26.7, 25.4, 24.3.

(1S,2R,3S)-3-(Hydroxymethyl)-cyclopentane-1,2-diol Dimethyl Acetonide, 44. To a solution of **42** (0.21 g, 0.51 mmol) in EtOH (20 mL) was added 10% Pd(OH)₂ on carbon (Pearlman's catalyst) (0.2 g) and the reaction was shaken on a Parr hydrogenator (40 psi H₂) for 12 h. The catalyst was removed by filtering through silica gel using EtOAc as solvent and concentrating the eluant. The crude product was purified by CombiFlash chromatography (1:1 hexanes/EtOAc) to give 0.08 g of **44** (94%): ¹H NMR (CDCl₃) δ 4.65 (overlapping m, 2H), 3.88 (dd, 1H, *J* = 11.1, 4.2 Hz), 3.77 (dd, 1H, *J* = 11.1, 6.8 Hz), 2.53 (br s, 1H), 1.90–1.75 (overlapping m, 2H), 1.71 (m, 1H), 1.6–1.3 (overlapping m, 2H), 1.44 (s, 3H), 1.30 (s, 3H). ¹³C NMR (CDCl₃) δ 109.5, 81.6, 81.2, 62.1, 46.4, 32.1, 25.9, 24.5, 23.8.

(1R,2S,3R)-3-(Bromomethyl)-cyclopentane-1,2-diol Dimethyl Acetonide, 36. To a suspension of PPh_3Br_2 (0.32 g, 0.75 mmol) in anhydrous CH_2Cl_2 (4 mL) at -10°C was added a solution of **43** (0.10 g, 0.58 mmol) and pyridine (0.08 mL, 0.93 mmol) in anhydrous CH_2Cl_2 (3 mL). The reaction was stirred at -10°C for 10 min and then allowed to warm to room temperature and stir for 2 h. Silica gel (2 g) was added and the reaction was concentrated by rotary evaporation. The dry silica containing the crude reaction mixture was loaded onto a silica gel column. Elution of PPh_3 (98:2 hexanes/EtOAc) followed by the desired product (9:1 hexanes/EtOAc), pooling of product-containing fractions, and removal of solvents in vacuo gave 0.14 g of **36** as a clear oil (79%): $^1\text{H NMR}$ (CDCl_3) δ 4.64 (d, 1H, $J = 5.4$ Hz), 4.41 (d, 1H, $J = 5.6$ Hz), 3.25 (m, 2H), 2.42 (m, 1H), 2.05 (m, 1H), 1.79 (overlapping m, 2H), 1.56 (m, 1H), 1.42 (s, 3H), 1.28 (s, 3H). $^{13}\text{C NMR}$ (CDCl_3) δ 110.1, 83.4, 81.0, 63.6, 48.4, 31.3, 26.7, 25.4, 24.3. MS (CI) m/z 97 ($[\text{M} - \text{Br} - \text{acetone}]^+$, 100), 235.1 ($[\text{M} + \text{H}]^+$, 8). HRMS (CI) calcd for $\text{C}_9\text{H}_{16}\text{BrO}_2$ 235.0334 $[\text{M} + \text{H}]^+$, found 235.0327.

(1S,2R,3R)-3-(Bromomethyl)-cyclopentane-1,2-diol Dimethyl Acetonide, 37. To a suspension of PPh_3Br_2 (0.20 g, 0.46 mmol) in anhydrous CH_2Cl_2 (3 mL) at -10°C was added a solution of **44** (0.06 g, 0.35 mmol) and pyridine (0.04 mL, 0.56 mmol) in anhydrous CH_2Cl_2 (2 mL). The reaction was stirred at -10°C for 10 min and then allowed to warm to room temperature and stir for 2 h. Silica gel (1 g) was added and the reaction was concentrated by rotary evaporation. The dry silica containing the crude reaction mixture was loaded onto a silica gel column. Elution of PPh_3 (98:2 hexanes/EtOAc) followed by the desired product (9:1 hexanes/EtOAc), pooling of product-containing fractions, and removal of solvents in vacuo gave 0.07 g of **37** as a clear oil (82%): $^1\text{H NMR}$ (CDCl_3) δ 4.57 (m, 1H), 4.45 (m, 1H), 1.93 (m, 1H), 1.76 (m, 1H), 1.61 (m, 1H), 1.4–1.3 (overlapping m, 6H), 1.20 (s, 3H). $^{13}\text{C NMR}$ (CDCl_3) δ 109.6, 80.9, 80.2, 48.1, 32.4, 32.0, 31.7, 27.9, 26.0, 24.0, 22.8, 14.3. MS (CI) m/z 97 ($[\text{M} - \text{Br} - \text{acetone}]^+$, 100), 235.1 ($[\text{M} + \text{H}]^+$, 15). HRMS (CI) calcd for $\text{C}_9\text{H}_{16}\text{BrO}_2$ 235.0334 $[\text{M} + \text{H}]^+$, found 235.0328.

(1S,2R,3R)-3-(Trityloxymethyl)-cyclopentane-1,2-diol, 45, and (1R,2S,3R)-3-(Trityloxymethyl)-cyclopentane-1,2-diol, 46. To a solution of **17** (0.5, 5.1 mmol) in anhydrous pyridine (5 mL) was added trityl chloride (2.1 g, 7.7 mmol) under Ar and the reaction was stirred at room temperature for 24 h. The reaction was filtered through a silica gel plug (4:1 hexanes/EtOAc) and the filtrate was concentrated to give a mixture of the desired product and TrCl. The crude product was purified by silica gel chromatography (95:5 hexanes/EtOAc) to give 1.6 g of (*S*)-3-(trityloxymethyl)-cyclopent-1-ene (94%): $^1\text{H NMR}$ (CDCl_3) δ 7.6–7.2 (m, 15H), 5.87 (overlapping m, 2H), 2.99 (overlapping m, 3H), 2.39 (m, 2H), 2.00 (m, 1H), 1.52 (m, 1H). $^{13}\text{C NMR}$ (CDCl_3) δ 144.6, 132.6, 131.9, 128.9, 128.8, 127.9, 127.8, 127.0, 126.9, 86.3, 67.6, 46.5, 32.0, 26.9.

To a stirring solution of (*S*)-3-(trityloxymethyl)-cyclopentene (1.5 g, 4.4 mmol) in 20 mL THF, 20 mL acetone, and 2 mL H_2O at 0°C was added OsO_4 (0.05 mL of 2.5 wt % in *t*BuOH) followed by NMO (1.0 g, 8.8 mmol). The reaction was stirred at room temperature for 36 h. The reaction was diluted with CH_2Cl_2 (300 mL) and washed with 10% aqueous Na_2SO_3 (300 mL) and NH_4Cl (300 mL). The combined aqueous phases were extracted with CH_2Cl_2 (3 \times 200 mL). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated. The crude residue was purified by silica gel chromatography (2:1 hexanes/EtOAc) to give 0.90 g of 2,3-*trans* isomer, **45** (56%), 0.45 g of the 2,3-*cis* isomer, **46** (28%), and 0.29 g overlapping fractions containing a mixture of **45** and **46** (18%).

Compound **45**: $^1\text{H NMR}$ (CDCl_3) δ 7.5–7.2 (m, 15H), 4.15 (m, 1H), 4.07 (m, 1H), 3.33 (m, 1H), 3.24 (m, 1H), 2.90 (d, 1H, $J = 3.2$ Hz), 2.52 (d, 1H, $J = 6.7$ Hz), 2.29 (m, 1H), 1.85 (m, 1H), 1.7–1.6 (overlapping m, 2H), 1.57 (m, 1H). $^{13}\text{C NMR}$ (CDCl_3) δ 143.9, 128.6, 128.1, 127.3, 87.2, 74.6, 74.4, 64.0, 41.4, 30.7, 23.9.

Compound **46**: $^1\text{H NMR}$ (CDCl_3) δ 7.5–7.2 (m, 15H), 4.15 (m, 1H), 4.07 (m, 1H), 3.33 (m, 1H), 3.24 (m, 1H), 2.90 (d, 1H, $J = 3.2$ Hz), 2.52 (d, 1H, $J = 6.7$ Hz), 2.29 (m, 1H), 1.85 (m, 1H), 1.7–1.6 (overlapping m, 2H), 1.57 (m, 1H). $^{13}\text{C NMR}$ (CDCl_3) δ 143.9, 128.6, 128.1, 127.3, 87.2, 74.6, 74.4, 64.0, 41.4, 30.7, 23.9.

(1S,2R,3S)-3-(Bromomethyl)-cyclopentane-1,2-diol Dimethyl Acetonide, 47. To a solution of **45** (0.87 g, 2.3 mmol) in acetone (25 mL) and dimethoxypropane (25 mL) was added TsOH (0.04 g, 0.2 mmol) and the reaction was stirred at room temperature for 15 min. The reaction was diluted with EtOAc (200 mL) and washed with saturated aqueous NaHCO_3 (50 mL) and brine (50 mL). The organic layer was dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by silica gel chromatography (95:5 hexanes/EtOAc) to give 0.91 g of (1*S*,2*R*,3*R*)-3-(trityloxymethyl)-cyclopentane-1,2-diol dimethyl acetonide (96%): $^1\text{H NMR}$ (CDCl_3) δ 4.65 (dd, 1H, $J = 4.9, 5.5$ Hz), 4.45 (d, 1H, $J = 5.7$ Hz), 3.45 (m, 2H), 2.22 (m, 1H), 1.98 (m, 1H), 1.82 (m, 1H), 1.75 (m, 1H), 1.48 (m, 2H), 1.45 (s, 3H), 1.30 (s, 3H). $^{13}\text{C NMR}$ (CDCl_3) δ 110.1, 83.4, 81.0, 63.6, 48.4, 31.3, 26.7, 25.4, 24.3.

To a solution of (1*S*,2*R*,3*R*)-3-(trityloxymethyl)-cyclopentane-1,2-diol dimethyl acetonide (0.9 g, 2.2 mmol) in EtOH (100 mL) was added 10% Pd(OH)₂ on carbon (Pearlman's catalyst) (1 g) and the reaction was shaken on a Parr hydrogenator (40 psi H_2) for 8 h. The catalyst was removed by filtering through silica gel using EtOAc as solvent and concentrating the eluant. The crude product was purified by CombiFlash chromatography (1:1 hexanes/EtOAc) to give 0.32 g of (1*S*,2*R*,3*R*)-3-(hydroxymethyl)-cyclopentane-1,2-diol dimethyl acetonide (85%): $^1\text{H NMR}$ (CDCl_3) δ 4.65 (dd, 1H, $J = 4.9, 5.5$ Hz), 4.45 (d, 1H, $J = 5.7$ Hz), 3.45 (m, 2H), 2.22 (m, 1H), 1.98 (m, 1H), 1.82 (m, 1H), 1.75 (m, 1H), 1.48 (m, 2H), 1.45 (s, 3H), 1.30 (s, 3H). $^{13}\text{C NMR}$ (CDCl_3) δ 110.1, 83.4, 81.0, 63.6, 48.4, 31.3, 26.7, 25.4, 24.3.

To a suspension of PPh_3Br_2 (0.72 g, 1.7 mmol) in anhydrous CH_2Cl_2 (7 mL) at -10°C was added a solution of (1*S*,2*R*,3*R*)-3-(hydroxymethyl)-cyclopentane-1,2-diol dimethyl acetonide (0.22 g, 1.3 mmol) and pyridine (0.72 mL, 1.7 mmol) in anhydrous CH_2Cl_2 (3 mL). The reaction was stirred at -10°C for 10 min and then allowed to warm to room temperature and stir for 2 h. Silica gel (2 g) was added and the reaction was concentrated by rotary evaporation. The dry silica containing the crude reaction mixture was loaded onto a silica gel column. Elution of PPh_3 (98:2 hexanes/EtOAc) followed by the desired product (9:1 hexanes/EtOAc), pooling of product-containing fractions, and removal of solvents in vacuo gave 0.27 g of **47** as a clear oil (87%; 60% overall yield from **45**): $^1\text{H NMR}$ (CDCl_3) δ 4.67 (m, 1H), 4.44 (d, 1H, $J = 5.7$ Hz), 3.28 (m, 2H), 2.46 (m, 1H), 2.08 (m, 1H), 1.9–1.7 (overlapping m, 2H), 1.55 (m, 1H), 1.46 (s, 3H), 1.31 (s, 3H). $^{13}\text{C NMR}$ (CDCl_3) δ 110.4, 84.6, 80.8, 48.3, 34.7, 31.0, 28.0, 26.7, 24.4. MS (CI) m/z 97 ($[\text{M} - \text{Br} - \text{acetone}]^+$, 100), 235.1 ($[\text{M} + \text{H}]^+$, 11). HRMS (CI) calcd for $\text{C}_9\text{H}_{16}\text{BrO}_2$ 235.0334 $[\text{M} + \text{H}]^+$, found 235.0324.

(1R,2S,3S)-3-(Bromomethyl)-cyclopentane-1,2-diol Dimethyl Acetonide, 48. To a solution of **46** (0.4 g, 1.1 mmol) in acetone (15 mL) and dimethoxypropane (15 mL) was added TsOH (0.02 g, 0.1 mmol) and the reaction was stirred at room temperature for 20 min. The reaction was diluted with EtOAc (150 mL) and washed with saturated aqueous NaHCO_3 (50 mL) and brine (50 mL). The organic layer was dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by silica gel chromatography (95:5 hexanes/EtOAc) to give 0.54 g of (1*R*,2*S*,3*R*)-3-(trityloxymethyl)-cyclopentane-1,2-diol dimethyl acetonide (74%): $^1\text{H NMR}$ (CDCl_3) δ 7.6–7.2 (m, 15H), 4.67 (overlapping m, 2H), 3.47 (dd, 1H, $J = 8.6, 7.3$ Hz), 3.15 (dd 1H, $J = 8.6, 7.2$ Hz), 1.92 (m, 1H), 1.85 (m, 1H), 1.69 (m, 1H), 1.5–1.4 (overlapping m, 2H), 1.37 (s, 3H), 1.33 (s, 3H). $^{13}\text{C NMR}$ (CDCl_3) δ 144.6, 129.0, 127.9, 126.9, 109.1, 86.5, 81.0, 80.5, 62.8, 45.6, 32.4, 26.1, 26.0, 24.1.

To a solution of (1*R*,2*S*,3*R*)-3-(trityloxymethyl)-cyclopentane-1,2-diol dimethyl acetonide (0.44 g, 1.1 mmol) in EtOH (75 mL)

was added 10% Pd(OH)₂ on carbon (Pearlman's catalyst) (0.5 g) and the reaction was shaken on a Parr hydrogenator (40 psi H₂) for 12 h. The catalyst was removed by filtering through silica gel using EtOAc as solvent and concentrating the eluent. The crude product was purified by silica gel chromatography (CHCl₃ to elute Ph₃CH then EtOAc to elute the desired product) to give 0.09 g of (1*R*,2*S*,3*R*)-3-(hydroxymethyl)-cyclopentane-1,2-diol dimethyl acetonide (50%): ¹H NMR (CDCl₃) δ 4.65 (overlapping m, 2H), 3.88 (dd, 1H, *J* = 11.1, 4.2 Hz), 3.77 (dd, 1H, *J* = 11.1, 6.8 Hz), 2.53 (br s, 1H), 1.90–1.75 (overlapping m), 1.71(m, 1H), 1.6–1.3 (overlapping m, 2H), 1.44 (s, 3H), 1.30 (s, 3H). ¹H NMR (CDCl₃) δ 109.5, 81.6, 81.2, 62.1, 46.4, 32.1, 25.9, 24.5, 23.8.

To a suspension of PPh₃Br₂ (0.46 g, 1.4 mmol) in anhydrous CH₂Cl₂ (6 mL) at –10 °C was added a solution of (1*R*,2*S*,3*R*)-3-(hydroxymethyl)-cyclopentane-1,2-diol dimethyl acetonide (0.15 g, 0.9 mmol) and pyridine (0.46 mL, 1.1 mmol) in anhydrous CH₂Cl₂ (4 mL). The reaction was stirred at –10 °C for 10 min and then allowed to warm to room temperature and stir for 2 h. Silica gel (2 g) was added and the reaction was concentrated by rotary evaporation. The dry silica containing the crude reaction mixture was loaded onto a silica gel column. Elution of PPh₃ (98:2 hexanes/EtOAc) followed by the desired product (9:1 hexanes/EtOAc), pooling of product-containing fractions, and removal of solvents in vacuo gave 0.27 g of **48** as a clear oil (65%; 24% overall yield from **46**): ¹H NMR (CDCl₃) δ 4.67 (m, 1H), 4.56 (m, 1H), 3.59 (m, 1H), 3.41 (m, 1H), 2.06 (m, 1H), 1.87 (m, 1H), 1.73 (m, 1H), 1.6–1.45 (overlapping m, 2H), 1.43 (s, 3H), 1.31 (s, 3H). MS (CI) *m/z* 97 ([M – Br – acetone]⁺, 100), 235.1 ([M + H]⁺, 25). HRMS (CI) calcd for C₉H₁₆BrO₂ 235.0334 [M + H]⁺, found 235.0323.

2-Methylene-pentanedioic Acid 5-*tert*-Butyl Ester, 53c. A. From 54a/57a. A mixture of **55a** (30.3 g, 189 mmol), **56** (27.7 mL, 189 mmol), K₂CO₃ (26.12 g, 189 mmol) and tetrabutylammonium bromide (0.7 g, 1.9 mmol) in anhydrous benzene (100 mL) was heated at reflux temperature for 12 h. The reaction was filtered and the solvent concentrated to give 53.2 g of crude mixture of **54a** and **57a**. A portion of **54a/57a** was carried on without further purification. ¹H NMR (CDCl₃) δ 4.18 (m, 4H), 3.41 (t, *J* = 7.4 Hz, 1H), 2.35–2.1 (overlapping m, 4H), 1.43 (s, 9H), 1.24 (m, 6H). ¹³C NMR (CDCl₃) δ 171.9, 169.2, 80.8, 61.6, 51.0, 32.9, 28.2, 24.1, 14.2.

To a solution of **54a/57a** (10.0 g) in EtOH (8 mL) was added a solution of KOH (3.6 g, 69.4 mmol) in H₂O (4 mL). The reaction was stirred at room temperature for 18 h. The reaction was extracted with Et₂O (2 × 20 mL). The aqueous layer was acidified to pH 1.0 by the dropwise addition of 6 M HCl and then extracted with Et₂O (3 × 20 mL). The combined organic layer was dried over Na₂SO₄, filtered, and concentrated to give 7.0 g of crude mixture of **58** and **59**, which was carried on without further purification. ¹H NMR (CDCl₃) δ 3.74 (m, 1H), 3.49 (m, 1.4H), 2.37 (m, 2H), 2.19 (m, 2H), 1.43 (s, 9H), 1.22 (m, 3.2H).

To a solution of **58/59** (7.0 g) in formaldehyde (37 wt % in H₂O, 11 mL) was added Et₂NH (4.2 mL, 40.4 mmol) at room temperature. The reaction was heated at reflux temperature for 5 h. The reaction was allowed to cool to room temperature and was diluted with CHCl₃ (50 mL) and saturated aqueous NaHCO₃ (25 mL). The aqueous layer was extracted with CHCl₃ (50 mL). The NaHCO₃ layer was acidified to pH 1.0 with 6 M HCl and extracted with CHCl₃ (100 mL then 50 mL). The organic layer was washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated to give 0.57 g of crude product. The original organic washes were acidified to pH 1.0 with 1 M HCl. The aqueous layer was extracted with CHCl₃ (50 mL). The combined organic layer was washed with H₂O (50 mL) and brine (50 mL), dried over Na₂SO₄, filtered and concentrated to give an additional 3.4 g of crude product. The crude product was combined and purified by silica gel chromatography (8:1 hexanes/EtOAc with 2% AcOH) to give 3.4 g of **53c** as a colorless solid (49% overall from **55a**): mp 61–63 °C. ¹H NMR (CDCl₃) δ 6.34 (s, 1H), 5.73 (s, 1H), 2.61 (t, 2H, *J* = 7.5),

2.47 (t, 2H, *J* = 7.6), 1.45 (s, 9H). ¹³C NMR (CDCl₃) δ 172.4, 172.2, 138.7, 128.1, 80.7, 34.3, 28.2, 27.2. MS (ESI) *m/z* 223.2 ([M + Na]⁺, 100). HRMS (ESI) calcd for C₁₀H₁₆NaO₄ 223.0944 [M + Na]⁺, found 223.0946.

B. From 58. To a suspension of **58** (0.19 g, 0.8 mmol), prepared as described below, in formaldehyde (37 wt % in H₂O, 1 mL) was added Et₂NH (0.11 mL, 1.1 mmol) at room temperature. The reaction was heated at reflux temperature for 2 h and allowed to cool to room temperature and stir overnight. The reaction became homogeneous during reflux and remained so throughout the reaction. The reaction was partitioned between EtOAc (10 mL) and 1 M HCl (5 mL). The aqueous layer was extracted with EtOAc (10 mL) and CHCl₃ (2 × 20 mL). The combined organic layer dried over Na₂SO₄, filtered, and concentrated. The crude product was purified by silica gel chromatography (1:1 hexanes/EtOAc) to give 65 mg of **53c** as a white solid (40%): mp 61–63 °C. ¹H NMR and ¹³C NMR spectral data are identical to those reported above for the sample of **53c** synthesized from the mixture of **54a** and **57a**. HRMS (ESI) calcd for C₁₀H₁₆NaO₄ 223.0944 [M + Na]⁺, found 223.0943.

2-Benzyloxycarbonyl-pentanedioic Acid 1-Benzyl Ester 5-*tert*-Butyl Ester, 54b. To a solution of **55b** (0.57, 2.0 mmol) in anhydrous THF (1 mL) under Ar at room temperature was added NaH (2 mg, 0.1 mmol) in one portion. After the evolution of H₂ gas ceased, **56** (0.15 mL, 1.0 mmol) was added dropwise over a period of 30 min. The reaction was stirred at room temperature under Ar for 3.5 h. The reaction was concentrated and the crude residue was partitioned between EtOAc (10 mL) and saturated aqueous NH₄Cl (5 mL). The organic layer was washed with brine (5 mL), dried over Na₂SO₄, filtered and concentrated. The crude product was purified by CombiFlash chromatography (9:1 hexanes/EtOAc, 120 g column, 80 mL/min flow rate) to give 0.34 g of **55b** as a clear, colorless oil (83%): ¹H NMR (CDCl₃) δ 7.30 (m, 10H), 5.15 (s, 4H), 3.56 (t, 1H, *J* = 6.9 Hz), 2.3–2.1 (overlapping m, 4H), 1.42 (s, 9H). MS (ESI) *m/z* 435.2 [M + Na]⁺.

2-Carboxy-pentanedioic Acid 5-*tert*-Butyl Ester, 58. To a solution of **54b** (0.34 g, 0.82 mmol) in anhydrous THF (10 mL) was added 10% Pd/C and the suspension was purged with H₂ from a balloon for 30 s. The reaction was stirred under H₂ for 5 h. The reaction was filtered through a plug of Celite with EtOAc. The filtrate was concentrated to give 0.19 g of **58** as a clear oil (100%). ¹H NMR (CDCl₃) δ 11.4 (br s, 2H), 4.13 (br m, 1H), 2.4–2.0 (overlapping m, 4H), 1.43 (s, 9H).

2-Methylene-pentanedioic Acid 1-benzotriazol-1-yl Ester 5-*tert*-Butyl Ester, 60. To a solution of **53c** (0.25 g, 1.2 mmol) in anhydrous THF (10 mL) under Ar was added HOBT (0.16 g, 1.2 mmol) followed by DCC (0.25 g, 1.2 mmol) and the reaction was stirred at room temperature for 4 h. The entire reaction was filtered through a column of silica gel with CHCl₃ as solvent. Tubes containing the desired product were pooled and concentrated to give 0.34 g of **60** as a clear oil (89%): ¹H NMR (CDCl₃) δ 8.08 (m, 1H), 7.55 (m, 1H), 7.45 (m, 2H), 6.7 (s, 1H), 6.10 (s, 1H), 2.79 (t, 2H, *J* = 7.3 Hz), 2.57 (t, 2H, *J* = 7.3 Hz), 1.46 (s, 9H). ¹³C NMR (CDCl₃) δ 171.4, 162.7, 143.7, 135.2, 131.4, 128.8, 125.0, 1120.7, 108.5, 33.9, 28.3, 27.6. MS (ESI) *m/z* 283.1([M – *t*Bu + Na]⁺, 100), 318.1([M + H]⁺, 58). HRMS (ESI) calcd for C₁₆H₁₉N₃NaO₄ 340.1273 [M + Na]⁺, found 340.1270.

4-(4-Benzhydryl-2-oxo-oxazolidine-3-carbonyl)-pent-4-enoic Acid *tert*-Butyl Ester, 52. To a solution of (*S*)-(–)-4-(diphenylmethyl)-2-oxazolidinone (0.25 g, 1.0 mmol) in anhydrous THF (5 mL) at –78 °C under Ar was added *n*BuLi (1.6 M in hexanes, 0.63 mL, 1.0 mmol). The reaction was stirred at –78 °C for 30 min. This solution was added via syringe to a solution of **60** (0.32 g, 1.0 mmol) in anhydrous THF (5 mL) cooled to –78 °C. The reaction was stirred at –78 °C for 20 min and then allowed to warm to room temperature and stir for 1 h. The reaction was quenched with saturated aqueous NH₄Cl (3 mL). The organic layer was removed by rotary evaporation and resulting aqueous layer was diluted with H₂O

(5 mL) and extracted with CH_2Cl_2 (2×10 mL). The organic layer was dried over Na_2SO_4 , filtered, and concentrated. The crude product was purified by silica gel chromatography (2:1 hexanes/EtOAc) to give 0.36 g of **52** as a clear oil (84%): ^1H NMR (CDCl_3) δ 7.4–7.1 (m, 10H), 5.40 (m, 1H), 5.29 (s, 1H), 5.11 (s, 1H), 4.66 (d, 1H, $J = 7.2$ Hz), 4.43 (t, 1H, $J = 9.2$ Hz), 4.36 (dd, 1H, $J = 3.5, 9.2$ Hz), 2.48 (m, 2H), 2.29 (m, 2H), 1.43 (s, 9H). ^{13}C NMR (CDCl_3) δ 172.2, 166.7, 146.6, 141.6, 139.3, 138.8, 129.8, 128.4, 128.3, 128.0, 127.9, 127.8, 125.8, 122.4, 80.6, 63.0, 34.3, 28.2, 27.6. MS (ESI) m/z 402.2 ($[\text{M} - t\text{Bu} + \text{Na}]^+$, 100), 458.2 ($[\text{M} + \text{Na}]^+$, 56). HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{29}\text{NNaO}_5$ 458.1943 [$[\text{M} + \text{Na}]^+$], found 458.1941.

(S)-2-Benzylloxycarbonylamino-4-[methoxy-(2-methoxycarbonyl-ethyl)-phosphinoyl]-butyric Acid Methyl Ester, 62. To a solution of **15** (57 mg, 0.18 mmol) in anhydrous CH_2Cl_2 (0.8 mL) was added methyl acrylate (24 μL , 0.27 mmol) and BSA (130 μL , 0.54 mmol) at room temperature. The reaction was stirred under Ar for 20 h. Reaction progress was monitored by ^{31}P NMR. The reaction was quenched with 1 M HCl (1 mL). CH_2Cl_2 (10 mL) was added and the reaction was washed with 1 M HCl (2×10 mL) and H_2O (10 mL). The organic layer was dried over Na_2SO_4 , filtered and concentrated. The crude product was dissolved in MeOH (2 mL) and TMSCHN_2 (2.0 M in hexanes) was added until a persistent yellow color was observed. The reaction was stirred at room temperature for 30 min, then quenched with AcOH and the solution concentrated. The crude material was purified by CombiFlash chromatography (EtOAc w/ 2% MeOH, 4 g column, 18 mL/min flow rate) to give 50 mg of **62** as clear oil. (67%) ^1H NMR (CDCl_3) δ 7.28 (m, 5H), 7.75 (m, 1H), 5.10 (s, 2H), 4.38 (m, 1H), 3.74–3.63 (overlapping, 9H), 2.57 (m, 2H), 2.25–1.80 (overlapping m, 4H), 1.80–1.70 (m, 2H). ^{13}C NMR (CDCl_3) δ 172.82, 172.78, 172.64, 172.60, 172.0, 156.1, 136.2, 128.6, 128.5, 128.4, 128.3, 67.2, 54.18 (d, $J = 3.1$ Hz), 53.97 (d, $J = 3.7$ Hz), 53.8, 52.3, 51.40 (d, $J = 6.6$ Hz), 51.37 (d, $J = 6.6$ Hz), 26.6–26.5 (overlapping), 25.17–25.06 (overlapping), 24.5, 23.4, 23.29, 23.26, 22.2, 22.0. ^{31}P NMR (CDCl_3) 56.2 and 56.1. MS (ESI) m/z 416.1 ($[\text{M} + \text{H}]^+$, 100). HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{27}\text{NO}_8\text{P}$ 416.1474 [$[\text{M} + \text{H}]^+$], found 416.1469.

(S)-2-[(3-Benzylloxycarbonylamino-3-methoxycarbonyl-propyl)-methoxy-phosphinoylmethyl]-pentanedioic Acid Dimethyl Ester, 63. To a solution of **15** (93 mg, 0.29 mmol) in anhydrous CH_2Cl_2 (2 mL) were added 2-methyleneglutarate (76 mg, 0.44 mmol) and BSA (220 μL , 0.87 mmol) at room temperature. The reaction was stirred under Ar for 20 h. Reaction progress was monitored by ^{31}P NMR. The reaction was quenched with 1 M HCl (1 mL). CH_2Cl_2 (8 mL) was added and the reaction was washed with 1 M HCl (2×5 mL) and H_2O (5 mL). The organic layer was dried over Na_2SO_4 , filtered, and concentrated. The crude product was dissolved in MeOH (2 mL) and TMSCHN_2 (2.0 M in hexanes) was added until a persistent yellow color was observed. The solution was stirred for 30 min at room temperature, then quenched with AcOH, and the solution concentrated. The crude material was purified by silica gel chromatography (EtOAc/ 2% MeOH) to give 100 mg of **68** as clear oil, an inseparable mixture of two diastereomers (70%, 1:1 by HPLC): ^1H NMR (CDCl_3) δ 7.23 (m, 5H), 5.80 (m, 1H), 5.08 (s, 2H), 4.37 (m, 1H), 3.7–3.5 (overlapping, 12 H), 2.79 (m, 1H), 2.35–2.05 (overlapping m, 4H), 2.00–1.60 (overlapping m, 3H). ^{13}C NMR (CDCl_3) δ 174.58, 174.55, 172.94, 172.88, 172.85, 171.0, 156.1, 136.2, 128.5, 128.2, 128.1, 67.0, 54.1, 54.0, 53.9, 52.6, 52.2, 51.7, 51.35, 51.31, 51.21, 51.16, 51.11, 38.6, 38.4, 31.16, 31.10, 30.2, 30.0, 29.7, 29.5, 29.2, 29.0, 28.8, 28.7, 24.8, 24.5, 24.2, 24.1, 23.7. ^{31}P NMR (CDCl_3) δ 55.2 and 54.6. MS (ESI) m/z 502.2 ($[\text{M} + \text{H}]^+$, 100). HRMS (ESI) calcd for $\text{C}_{22}\text{H}_{33}\text{NO}_{10}\text{P}$ 502.1842 [$[\text{M} + \text{H}]^+$], found 502.1839.

(3'S)-5-(4-Benzhydryl-2-oxo-oxazolidin-3-yl)-4-[(3'-benzylloxycarbonylamino-3'-methoxy-carbonyl-propyl)-methoxy-phosphinoylmethyl]-5-oxo-pentanoic Acid tert-Butyl Ester, 64 and 65. To a solution of **15** (0.1 g, 0.32 mmol) and **52** (0.15 g, 0.35 mmol) in anhydrous CH_2Cl_2 (4 mL) under Ar was added BSA (0.24 mL, 0.96 mmol) and the reaction was

stirred at room temperature for 15 h. The reaction was quenched with abs EtOH (0.27 mL), which did not fully cleave the TMS esters as indicated by ^{31}P NMR. Two drops of TFA were added and the reaction was stirred at room temperature for 25 min to cleave the remaining esters. The reaction was diluted with CH_2Cl_2 (20 mL) and H_2O (5 mL). The organic layer was washed with brine (5 mL), dried over Na_2SO_4 , filtered, and concentrated. The crude material was dissolved in MeOH (5 mL) treated with TMSCHN_2 until a persistent yellow color was observed. The reaction was stirred at room temperature for 30 min and then quenched with AcOH. The reaction was concentrated and the crude material was purified by silica gel chromatography (4:1 hexanes/EtOAc) to give 90 mg of **64** (higher R_f , isomer **A**) and 85 mg of **65**, (lower R_f , isomer **B**) (combined yield, 72%).

Compound 64: analytical HPLC $t_R = 22.4$ min. ^1H NMR (CDCl_3) δ 7.31 (m, 15H), 5.90 (m, 1H), 5.29 (m, 1H), 5.11 (s, 2H), 4.74 (m, 1H), 4.43 (m, 2H), 4.12 (m, 1H), 3.8–3.6 (overlapping m, 6H), 2.3–1.6 (overlapping m, 11H), 1.42 (s, 9H). ^{13}C NMR (CDCl_3) δ 173.8, 173.7, 173.6, 172.06, 172.04, 131.2, 156.1, 153.3, 139.8, 138.21, 138.16, 136.3, 129.47, 129.39, 128.97, 128.88, 128.77, 128.73, 128.55, 128.49, 128.41, 128.17, 128.15, 127.84, 127.81, 127.2, 80.7, 67.1, 65.3, 65.0, 60.4, 56.74, 56.67, 54.1, 52.67, 52.63, 51.51, 51.46, 51.22, 51.17, 51.14, 50.81, 36.6, 36.4, 32.37, 32.32, 30.9, 29.6, 29.4, 28.9, 28.1, 27.6, 27.3, 25.0, 24.6, 24.2, 23.8. ^{31}P NMR (CDCl_3) δ 55.2 and 54.7. MS (ESI) m/z 730.2 ($[\text{M} - t\text{Bu} + \text{Na}]^+$, 100), 787.3 ($[\text{M} + \text{Na}]^+$, 8). HRMS (ESI) calcd for $\text{C}_{40}\text{H}_{49}\text{N}_2\text{NaO}_{11}\text{P}$ 787.2972 [$[\text{M} + \text{Na}]^+$], found 787.2967.

Compound 65: analytical HPLC $t_R = 23.1$ min. ^1H NMR (CDCl_3) δ 7.27 (m, 15H), 5.90 (m, 1H), 5.42 (m, 1H), 5.10 (s, 2H), 4.54 (m, 1H), 4.43 (m, 2H), 4.12 (m, 1H), 3.8–3.6 (overlapping m, 6H), 2.3–1.6 (overlapping m, 11H), 1.41 (s, 9H), $t\text{Bu}$. ^{31}P NMR (CDCl_3) δ 55.4 and 54.9. MS (ESI) m/z 730.2 ($[\text{M} - t\text{Bu} + \text{Na}]^+$, 100), 787.3 ($[\text{M} + \text{Na}]^+$, 5). HRMS (ESI) calcd for $\text{C}_{40}\text{H}_{49}\text{N}_2\text{NaO}_{11}\text{P}$ 787.2972 [$[\text{M} + \text{Na}]^+$], found 787.2965.

(3'S)-2-[(3'-Benzylloxycarbonylamino-3'-methoxy-carbonyl-propyl)-methoxy-phosphinoylmethyl]-pentane-1,5-dioic Acid 5-tert-Butyl Ester 1-Methyl Ester, 66. To a solution of **64** (0.28 g, 0.37 mmol) in 3:1 THF/ H_2O (4 mL) at 0 °C was added H_2O_2 (0.17 mL, 1.5 mmol) followed by solid LiOH (31 mg, 0.74 mmol). The reaction was stirred at 0 °C for 30 min. The reaction was quenched by the addition of Na_2SO_3 (0.28 g) in H_2O (1 mL). The reaction was extracted with Et_2O (2×20 mL) to recover the chiral auxiliary. The aqueous layer was acidified to pH 1.0 with 2 M HCl and extracted with Et_2O (3×30 mL). The organic layer was concentrated and the crude material dissolved in MeOH (5 mL) and treated with CH_2N_2 until a persistent yellow color was observed. The reaction was stirred at room temperature for 15 min, then quenched with AcOH and concentrated to give 0.17 g of **66** as a clear oil (84%): ^1H NMR (CDCl_3) δ 7.32 (m, 5H), 5.93 (d, 1H, $J = 6.1$), 5.10 (s, 2H), 4.38 (m, 1H), 3.8–3.6 (overlapping m, 9H), 2.84 (m, 1H), 2.3–2.1 (overlapping m, 4H), 1.90 (m, 3H), 1.76 (m, 3H), 1.43 (s, 9H). ^{13}C NMR (CDCl_3) δ 174.71, 174.69, 174.67, 174.65, 172.02, 171.98, 171.78, 171.73, 156.1, 136.3, 128.8, 128.7, 128.5, 128.21, 128.15, 80.70, 80.68, 67.1, 54.2, 54.12, 54.07, 54.0, 52.6, 52.1, 51.34, 51.29, 51.22, 51.17, 51.12, 38.63, 38.61, 38.44, 38.41, 32.63, 32.57, 31.8, 31.2, 30.3, 30.0, 29.5, 29.3, 28.1, 25.6, 24.95, 24.93, 24.86, 24.77, 24.5, 24.4, 24.1, 23.8. ^{31}P NMR (CDCl_3) δ 55.4 and 54.9. MS (ESI) m/z 509.1 ($[\text{M} - t\text{Bu} + \text{Na}]^+$, 100), 566.2 ($[\text{M} + \text{Na}]^+$, 10). HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{38}\text{NNaO}_{10}\text{P}$ 566.2131 [$[\text{M} + \text{Na}]^+$], found 566.2127.

(3'S)-2-[(3'-Benzylloxycarbonylamino-3'-methoxy-carbonyl-propyl)-methoxy-phosphinoylmethyl]-pentane-1,5-dioic Acid 5-tert-Butyl Ester 1-Methyl Ester, 67. To a solution of **65** (0.26 g, 0.34 mmol) in 3:1 THF/ H_2O (4 mL) at 0 °C was added H_2O_2 (0.16 mL, 1.5 mmol) followed by solid LiOH (29 mg, 0.69 mmol). The reaction was stirred at 0 °C for 30 min. The reaction was quenched by the addition of Na_2SO_3 (0.28 g) in H_2O (1 mL). The reaction was extracted with Et_2O (2×20 mL) to recover the chiral auxiliary. The aqueous layer

was acidified to pH 1.0 with 2 M HCl and extracted with Et₂O (3 × 30 mL). The organic layer was concentrated and the crude material dissolved in MeOH (5 mL) and treated with CH₂N₂ until a persistent yellow color was observed. The reaction was stirred at room temperature for 15 min, then quenched with AcOH and concentrated to give 0.15 g of **67** as a clear oil (83%): ¹H NMR (CDCl₃) δ 7.32 (m, 5H), 5.94 (m, 1H), 5.10 (s, 2H), 4.38 (m, 1H), 3.8–3.6 (overlapping m, 9H), 2.80 (m, 1H), 2.3–2.1 (overlapping m, 4H), 1.91 (m, 3H), 1.78 (m, 3H), 1.43 (s, 9H). ¹³C NMR (CDCl₃) δ 174.81, 172.03, 171.75, 171.72, 156.1, 136.3, 128.8, 128.6, 128.5, 128.24, 128.18, 128.05, 126.7, 80.7, 67.1, 54.19, 54.11, 53.99, 52.8, 52.6, 52.19, 52.17, 51.38, 51.34, 51.21, 51.15, 38.62, 38.59, 31.9, 30.3, 29.8, 29.6, 29.14, 29.07, 29.04, 28.1, 24.92, 24.6, 24.2, 23.8. ³¹P NMR (CDCl₃) δ 55.4 and 54.8. MS (ESI) *m/z* 509.1 ([M – *t*Bu + Na]⁺, 100), 566.2 ([M + Na]⁺, 7). HRMS (ESI) calcd for C₂₅H₃₈NNaO₁₀P 566.2131 [M + Na]⁺, found 566.2127.

(3'S)-2-[[[3'-Carboxy-3'-[[4''-[(2''', 4'''-diamino-6''-pteridiny]methyl]methylamino]benzoyl]amino]propyl]-hydroxyphosphinyl]methyl]pentane-1,5-dioic Acid Bis-(triethylamine) Salt, 70. A solution of **66** (45 mg, 0.083 mmol) in 6 M HCl (2 mL) was heated at reflux temperature for 12 h. The reaction was extracted with Et₂O (2 mL) and the aqueous layer was freeze-dried to give 27 mg of **68** as hydroscopic white solid (93%): ¹H NMR (D₂O) δ 4.13 (m, 1H), 2.77 (m, 1H), 2.45 (m, 3H), 2.19 (m, 3H), 1.95 (m, 5H). ³¹P NMR (D₂O) δ 50.3.

To a solution of AMPte-N₃ (20 mg, 0.06 mmol) and **68** (10 mg, 0.03 mmol) in anhydrous DMSO (1 mL) was added tetramethylguanidine (0.022 mL, 0.18 mmol). The reaction was stirred at room temperature for 18 h. The desired product was precipitated by the addition of CH₃CN (10 mL) and collected by centrifugation (9000 rpm × 30 min). The pellet was dried under a stream of N₂ and then purified by ion exchange chromatography (DEAE-cellulose, 0.01 to 1.0 M Et₃NH⁺HCO₃⁻). Fractions containing the desired product were pooled and lyophilized to give 22 mg of **70** as the di-Et₃N salt (83%): analytical HPLC *t*_R = 11.7 min. UV–vis (HPLC diode array, phosphate buffer, pH 7.0/acetoneitrile) λ_{max} 260, 305, 375 nm; (0.1 N HCl) 306 nm; (0.1 N NaOH) 257, 301, 270 nm). ¹H NMR (D₂O) δ 8.61 (s, 1H), 7.66 (d, 2H, *J* = 8.6 Hz), 6.78 (d, 2H, *J* = 8.6 Hz), 4.31 (m, 1H), 3.17 (m, 12H), 2.54 (m, 1H), 2.3–2.0 (overlapping m, 3H), 2.0–1.7 (overlapping m, 4H), 1.60 (m, 3H), 1.24 (m, 18H). ³¹P NMR (D₂O) δ 42.6. MS (ESI) *m/z* 619.2 ([M + H]⁺, 100). HRMS (ESI) calcd for C₂₅H₃₂N₈O₉P 619.2030 [M + H]⁺, found 619.2024.

(3'S)-2-[[[3'-Carboxy-3'-[[4''-[(2''', 4'''-diamino-6''-pteridiny]methyl]methylamino]benzoyl]amino]propyl]-hydroxyphosphinyl]methyl]pentane-1,5-dioic Acid Tris-(triethylamine) Salt, 71. A solution of **67** (48 mg, 0.088 mmol) in 6 M HCl (2 mL) was heated at reflux temperature

for 12 h. The reaction was extracted with Et₂O (2 mL) and the aqueous layer was freeze-dried to give 30 mg of **69** as hydroscopic white solid (97%): ¹H NMR (D₂O) δ 4.14 (m, 1H), 2.77 (m, 1H), 2.43 (m, 3H), 2.19 (m, 3H), 1.95 (m, 5H). ³¹P NMR (D₂O) δ 50.7.

To a solution of AMPte-N₃ (20 mg, 0.06 mmol) and **69** (10 mg, 0.03 mmol) in anhydrous DMSO (2 mL) was added tetramethylguanidine (0.022 mL, 0.18 mmol). The reaction was stirred at room temperature for 18 h. The desired product was precipitated by the addition of CH₃CN (10 mL) and collected by centrifugation (9000 rpm × 30 min). The pellet was dried under a stream of N₂ and then purified by ion exchange chromatography (DEAE-cellulose, 0.01 to 1.0 M Et₃NH⁺HCO₃⁻). Fractions containing the desired product were pooled and lyophilized to give 19 mg of **71** as the tri-Et₃N salt (79%). Analytical HPLC: *t*_R = 9.8 min. UV–vis (HPLC diode array, phosphate buffer, pH 7.0/acetoneitrile) λ_{max} 260, 305, 375 nm; (0.1 N HCl) 306 nm; (0.1 N NaOH) 258, 301, 270 nm). ¹H NMR (D₂O) δ 8.60 (s, 1H), 7.66 (d, 2H, *J* = 8.7 Hz), 6.78 (d, 2H, *J* = 8.7 Hz), 4.29 (m, 1H), 3.17 (m, 18H), 2.48 (m, 1H), 2.2–2.0 (overlapping m, 3H), 1.95 (m, 2H), 1.82 (m, 1H), 1.74 (m, 1H), 1.60 (m, 3H), 1.24 (m, 18H). ³¹P NMR (D₂O) δ 43.0. MS (ESI) *m/z* 619.2 ([M + H]⁺, 100). HRMS (ESI) calcd for C₂₅H₃₂N₈O₉P 619.2030 [M + H]⁺, found 619.2037.

Acknowledgment. This research was supported by a grant from the National Cancer Institute (CA28097). D.M.B. is a trainee in the Pharmacological Sciences Training Program supported by a grant from the National Institutes of General Medical Sciences (GM07767). We are most grateful to Dr. John McGuire and Mr. Bill Haile, Roswell Park Cancer Institute, Buffalo, NY, for their gift of FPGS and for testing of **70** and **71**. We thank Dr. Jean-Luc Montchamp, Texan Christian University, Fort Worth, TX, for helpful discussions on P–C bond formation; and Dr Shoujun Chen, Synta Pharmaceuticals Corp., Lexington, MA, for helpful advice on organophosphorus chemistry. We are also grateful to Amano Pharmaceutical Co. for the generous gift of Lipase AK “Amano”.

Supporting Information Available: Experimental procedures and characterization of compounds *ent*-**5** (X = Ms, Ts, I), **10** (Table 1), **14**, **24** (Table 2), **54b/57b**, **57b**, and **54c/57c**; ¹H and ¹³C spectra for all new compounds described in Experimental Section. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JO0507439