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Design and Synthesis of Diversely Substituted Azacyclic Inhibitors of Endothelin Converting Enzyme

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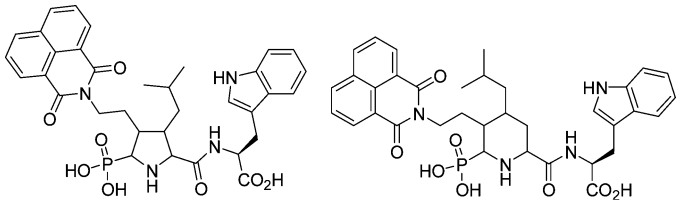

A series of azacyclic phosphonic acids were synthesized from L-pyroglutamic acid, 6-oxo-L-pipecolic acid, and their enantiomers. The objective was to study the effect of constraining acyclic inhibitors of endothelin converting enzyme on inhibitory activity. Potential pharmacophoric tethers were introduced by stereocontrolled reactions to give highly substituted pyrrolidine- and piperidine-α-phosphonic acids. Weak inhibitory activity was observed for one diastereomer in each series having the same relative orientation of substituents.

Introduction

The role of endogenous vasoactive peptides in physiologically important processes has been known for some time.[1] Among these peptides is a family of potent vasoconstrictors acting on smooth muscle tissues and the central nervous system, known as the endothelins.[2] They consist of three isoforms in humans that are encoded by different genes but differ in only a few amino acids.[3] A series of biochemical conversions mediated by endopeptidases converts the initially formed pure proendothelin into big ET-1. Subsequently, endothelin-converting enzyme (ECE) cleaves big ET-1 at the Trp-Val site to produce the 21-amino acid peptide ET-1, which is the most powerful local vasoconstricting peptide known.[4] ET-1 binds to its receptor on a G-coupled protein resulting in the activation of phospholipase C and stimulation of protein kinase C. As a consequence, the concentration of intracellular Ca^{2+} is increased, which in conjunction with other enzymatic events, notably the phosphorylation of the light chain of myosin, leads to the contraction of blood vessels.

Thus, in addition to other targets such as ACE[5] and renin,[6] the inhibition of ECE has been considered as a relevant strategy to control hypertension.[7] The physiopathologic implications of ECE cover a wide range of serious disorders beyond hypertension, such as asthma, renal failure, cancer, and atherosclerosis to mention a few.[8] Another endogenous endopeptidase, NEP (neutral endopeptidase), is responsible for the degradation of natural natriuretic peptide, which is a potent vasodilator. ECE and NEP are zinc metalloproteases that share a substantial degree of homology.[9] Thus, the search for an effective inhibitor of ECE has been the focus of intensive efforts.[7b,10]

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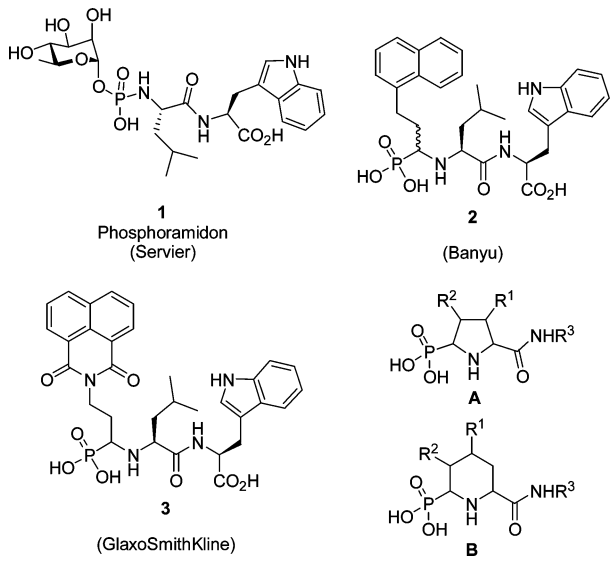
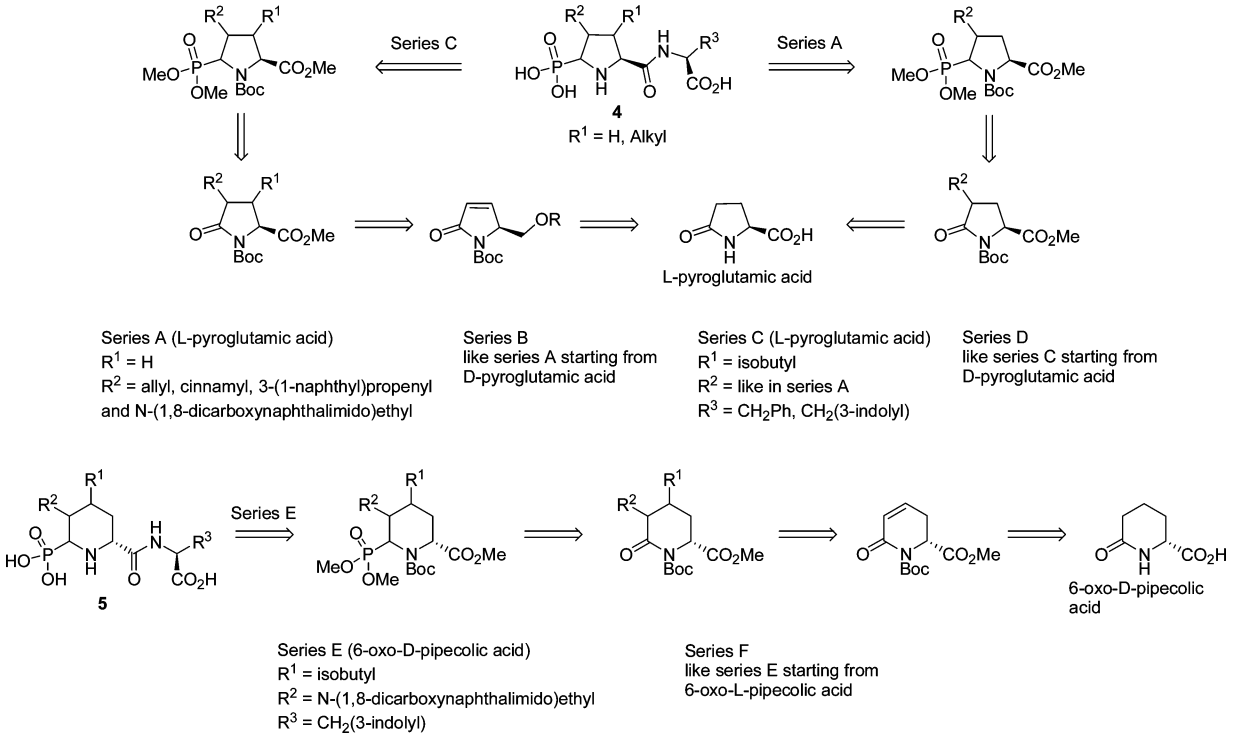


FIGURE 1. Examples of ECE inhibitors and projected constrained analogues **A** and **B**.

The interaction of phosphoramidon **1** (Figure 1), a naturally occurring L-rhammosyl phosphoramidite of Trp-Lys with NEP, has identified specific binding domains in the S_1, S_1', and S_2' sites.[9] Phosphoramidon is also an inhibitor of ECE.[11] Although the ultimate aim is to develop a dual or triple inhibitor, capable of inhibiting ECE, NEP, and ACE,[12] we focused on gaining insights into the functional and stereochemical requirements for inhibitory activity of ECE. Our objective was to synthesize azacyclic compounds related to the α-aminophosphonic acids **2**[7b] and **3**.[7b] Since the 3-dimensional spatial disposition of the various groups in these compounds is not known, we hoped that the stereocontrolled synthesis of individual substituted 5-phosphonoproline amides[13] with stereochemically fixed appendages on a rigid scaffold would provide insights into selective modes of binding.[14] By choosing substituted prolines[15] as the azacyclic core units, we wished to maintain the relative positions of pharmacophores compared to the acyclic models **2** and **3**. In the absence of crystallographic data on the 3-dimensional structure of ECE, we deemed it necessary to address the stereochemical issues related to the arrangement of the pharmacophoric sites by making available *a diverse set of diastereomeric compounds within each enantiomeric series*, as shown in the generic structure **4**. Our choice of a phosphonic acid as a potential zinc chelator was based on known precedents[16] and synthetic convenience adopting a disconnective analysis that was amenable to functional and stereochemical diversity as shown in Scheme 1.

For the series A analogues, stereocontrolled enolate alkylation of an L-pyroglutamic acid[17] ester would introduce the R_2 group at C_4. Sequential introduction of requisite R_1 and R_2 groups via conjugate addition to an α,β-unsaturated lactam derived from pyroglutamic acid[15,18] or 6-oxopipecolic acid,[19] followed by enolate alkylation,[20] respectively, would give analogues in series C and E. The phosphonic acid group in each series would be introduced via the corresponding *N*-acyloxyiminium ions.[21] Functional group adjustments and amide coupling would ultimately produce the 4-substituted or 3,4-disubstituted 5-phosphono-L-prolylamides **4** and 4,5-disubstituted 6-phosphono-D-pipecolic acid amides **5**. An identical sequence starting with D-pyroglutamic acid and 6-oxo-L-pipecolic acid would provide a selection of compounds in the enantiomeric series. Our initial studies focused on the elaboration of a strategy toward obtaining 4-alkyl-5-phosphono-L-proline esters as intermediates corresponding to series A (Scheme 1), relying on an anticipated *anti*-selectivity in the enolate alkylation. Since previous inhibitors in the acyclic series such as **2** and **3** deployed a bulky aromatic group as an α-alkyl appendage, we chose cinnamyl, isobutyl, and *N*-(1,8-dicarboxynaphthalimido)ethyl groups as potential mimics of the presumed hydrophobic P_2' pharmacophore. For

SCHEME 1. Disconnective Strategy toward Diverse Substitution on L-Proline and L-Pipecolic Acid Scaffolds

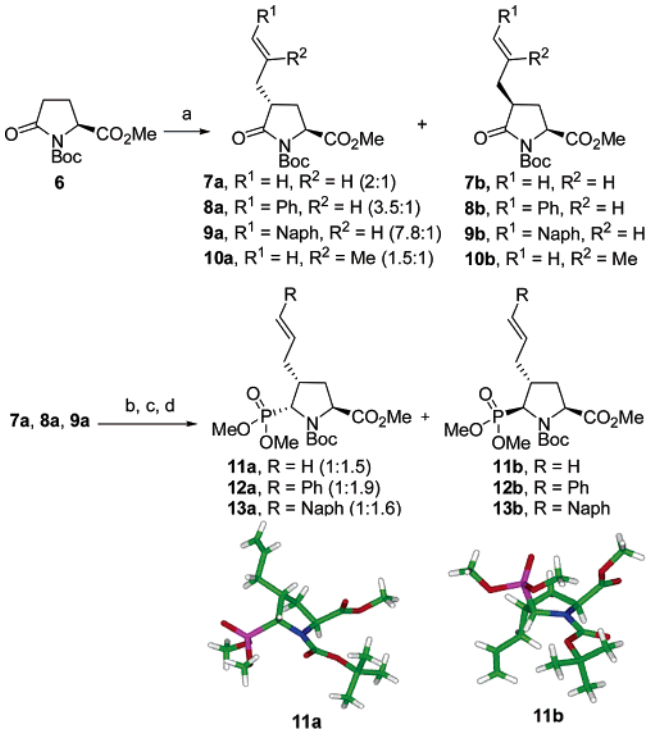


series C, the eventual C_3-substituent was kept constant as an isobutyl group. The above protocol also allowed for the introduction of other zinc-chelating groups such as a carboxylic or hydroxamic acid at C_5.[22]

Results and Discussion

Formation of the Li^+ enolate from L-pyroglutamic acid methyl ester **6** and treatment with allyl iodide afforded a 2:1 mixture of the *trans* and *cis* C_4 allyl derivatives **7a** and **7b**, respectively (Scheme 2). Analogous treatment with cinnamyl bromide afforded a modest *trans*-selectivity to give **8a** and **8b** in a 3.5:1 ratio. On the other hand, treatment of the enolate with the bulkier 1-naphthyl-2-propenyl bromide led to a preponderance of the

SCHEME 2[a]



[a] Reagents and conditions: (a) LiHMDS, RBr, THF, −78 °C, 30−57%; (b) Super Hydride, THF, −78 °C; (c) Ac_2O, Et_3N, DMAP, DCM, rt; (d) $P(OMe)_3$, $BF_3{\cdot}OEt_2$, DCM, −78 °C to rt, 45−80%.

trans-isomer **9a** (*trans*/*cis* ∼8:1). The above diastereomers were easily separable by flash chromatography. Since our aim was to produce a diverse set of diastereomers from a common intermediate within the same enantiomeric series, we did not attempt to optimize the ratios of products. Their ease of separation by chromatography allowed us to prepare sufficient quantities of each diastereomer to pursue the functionalization of the resulting lactams at C_5. Thus, reduction of the lactams **7a**, **8a**, and **9a** with Super hydride,[23] followed by acetylation and treatment with trimethyl phosphite,[24] gave three sets of diastereomeric C_5 dimethylphosphonates **11a**/**11b**, **12a**/**12b**, and **13a**/**13b** in excellent overall yields. In each pair, the proportion of C_2/C_5 *cis*-isomer was favored, ranging from 1.5 to 1.9:1 (as determined by ^1H NMR). Furthermore, the C_5 epimeric dimethyl phosphonates could be separated into individual enantiomerically pure compounds. Their stereochemistry was determined by NOE studies of the respective H_2/H_5 in *cis*-phosphonates and by single-crystal structure determination of the allyl analogues **11a** and **11b** (Scheme 2).

It is of interest that the orientation of the *N*-Boc and ester carbonyl groups in the crystalline solid state were different in the *trans*- and *cis*-phosphonates **11a** and **11b**, respectively. The minimization of $A^{1,2}$ strain between the ester and *N*-Boc groups,[25] coupled with the *trans*- or *cis*-disposition of the dimethylphosphonate, result in significant changes compared

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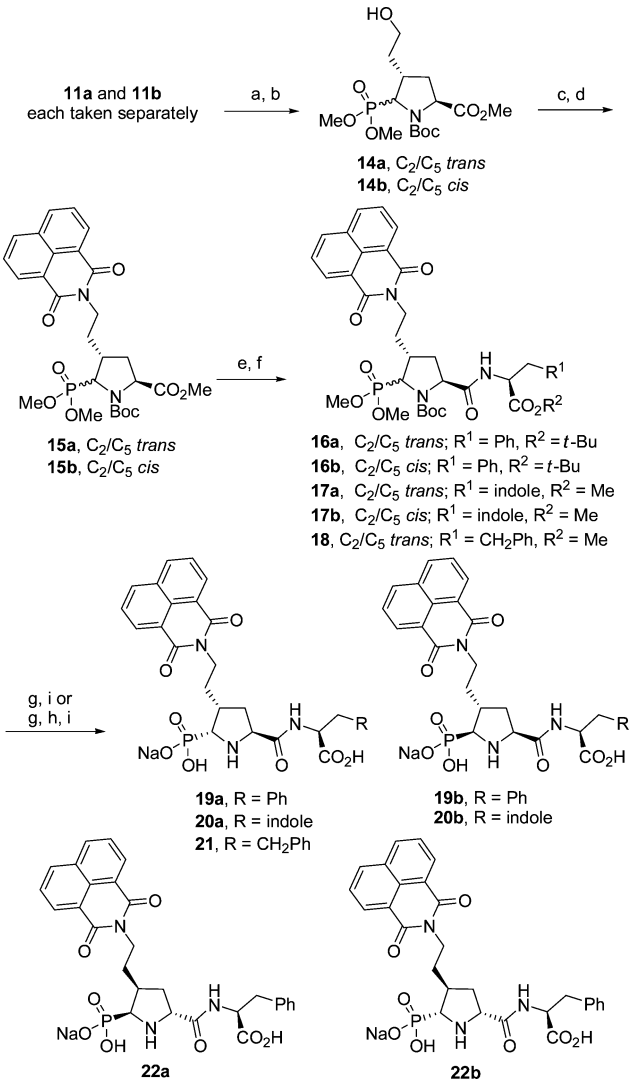
SCHEME 3[a]

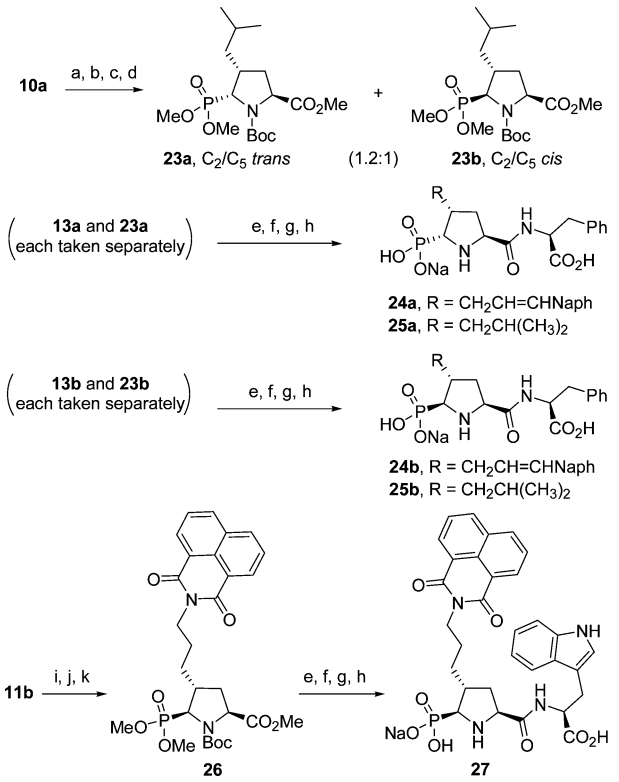


[a] Reagents and conditions: (a) (i) ozone, DCM/MeOH (1:1), −78 °C; (ii) Me_2S, −78 to 0 °C; (b) $NaBH_4$, MeOH, 0 °C to rt, 79−81%; (c) TsCl, Et_3N, DMAP, DCM, rt; (d) *N*-(1,8-dicarboxynaphthalimido) Na^+ salt, DMF, 33−42%; (e) LiOH·H_2O, THF/H_2O/MeOH (5:4:1), 0 °C to rt; (f) *i*-Pr_2NEt, EDCI, HOBt, H-Xaa-OR^2·HCl, DCM, 33−79%; (g) HCl (gas), dioxane, reflux; (h) LiOH·H_2O, THF/H_2O/MeOH (5:4:1), 0 °C to rt; (i) TMSBr, DCM then 1 equiv of NaOH 0.05 M, 38−70%.

to *N*-Boc L-proline.[26] The deviation from planarity is more pronounced in **11a** and **11b** (rms N, C_2, C_3, C_5 = 0.0312 and 0.0505 Å, respectively), compared to *N*-Boc proline (rms C_2, N, C_5, C_4 = 0.018 Å). In both diastereomers **11a** and **11b**, C_4 is puckered out of plane compared to C_3 in *N*-Boc proline. Two rotamers can be observed by ^1H and ^{13}C NMR for several peaks, with a characteristic downfield shift for C_5 in the *trans*-analogue **11a** (C_5 = 58.9 ppm, compared to C_5 = 53.2 ppm for **11b**).

The moderately higher proportion of the C_2/C_5 *cis*-phosphonates in the three series of products **11**−**13** was of interest. In the absence of a C_4 substituent, the attack of nucleophiles on the corresponding *N*-acyloxyiminium ions is expected to be mostly *trans* to the ester group[27] by virtue of its pseudoaxial

SCHEME 4[a]



[a] Reagents and conditions: (a) H_2 (60 psi), $Pd(OH)_2/C$, EtOH, rt; (b) Super Hydride, THF, −78 °C; (c) Ac_2O, Et_3N, DMAP, DCM, rt; (d) $P(OMe)_3$, BF_3·OEt_2, DCM, −78 °C to rt, 69%; (e) LiOH·H_2O, THF/H_2O/MeOH (5:4:1), 0 °C to rt; (f) *i*-Pr_2NEt, EDCI, HOBt, H-Phe-O*t*-Bu·HCl or H-Trp-OMe·HCl, DCM, rt; (g) HCl (gas), dioxane, reflux or LiOH·H_2O, THF/H_2O/MeOH (5:4:1), H-Trp-OMe·HCl; (h) TMSBr, DCM then 1 equiv of NaOH 0.05M, 40−70%; (i) (i) BH_3·THF, THF, 0 °C, (ii) NaOH, H_2O_2 30% v/v, rt; (j) TsCl, Et_3N, DMAP, DCM, rt; (k) *N*-(1,8-dicarboxynaphthalimido) Na^+ salt, DMF, rt, 30%.

orientation due to $A^{1,2}$ strain.[28] However, in the **11**−**13** series, the sterically favored *trans*-approach of trimethyl phosphite is counterbalanced by the presence of the C_4 α-oriented alkyl group. The slight variations in favor of the C_2/C_5 *cis*-phosphonates with increasing bulk of the C_4 alkyl group in going from allyl to cinnamyl or its naphthyl counterpart could be due to a more pronounced vicinal steric effect.

It was of interest to incorporate the imidoyl group, like in structure **3**, in our constrained azacyclic scaffold. The most practical approach was to utilize the diastereomeric unsaturated alkyl appendages at C_4 as precursors. Thus, ozonolysis of **11a** and **11b**, respectively, followed by reduction of the resulting aldehydes with $NaBH_4$, afforded the corresponding 1-hydroxylethyl derivatives **14a** and **14b**, respectively (Scheme 3). Attempts to introduce the naphthalimido group by a Mitsunobu reaction[29] of **14b** were not successful, affording starting alcohol even upon heating to 60 °C. Therefore, a two-step procedure was adopted which consisted of displacing the corresponding tosylates with the Na^+ salt of the imide to afford **15a** and **15b** (Scheme 3). We then proceeded with their elaboration into the intended target structures in this Serie A (Scheme 1). Hydrolysis

(26) See the Supporting Information.

(27) For nucleophilic additions on iminium ions, see: (a) Hanessian, S.; Margarita, R.; Hall, A.; Johnstone, S.; Tremblay, M.; Parlanti, L. *J. Am. Chem. Soc.* **2002**, *124*, 13342−13343. (b) Collado, I.; Ezquerra, J.; Pedregal, C. *J. Org. Chem.* **1995**, *60*, 5011−5015.

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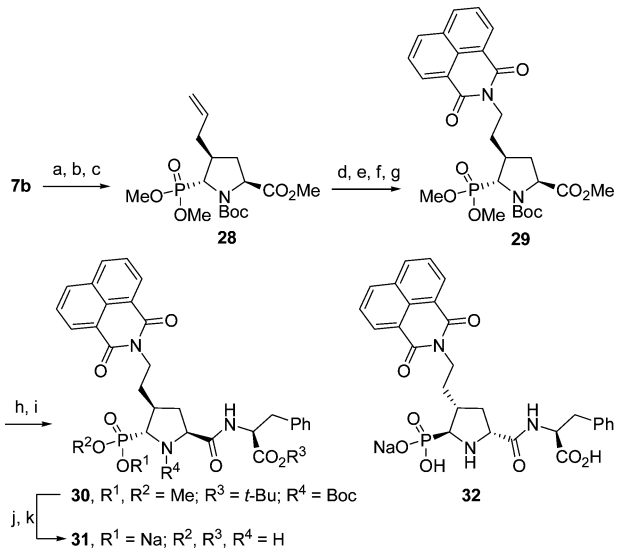
SCHEME 5[a]



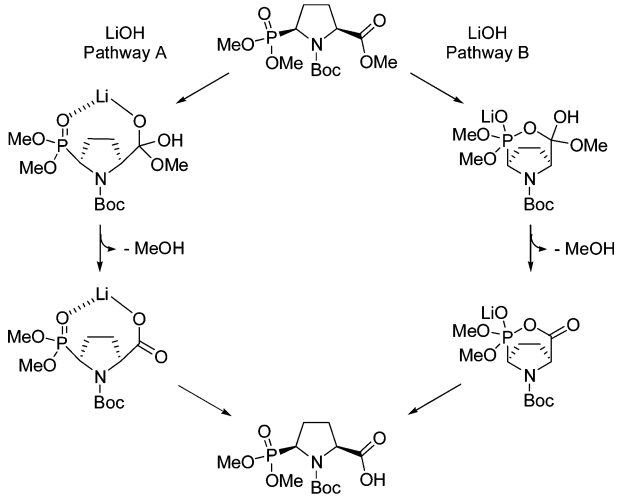
[a] Reagents and conditions: (a) Super Hydride, THF, −78 °C; (b) Ac_2O, Et_3N, DMAP, DCM, rt; (c) $P(OMe)_3$, $BF_3{\cdot}OEt_2$, DCM, −78 °C to rt, 68%; (d) (i) ozone, DCM/MeOH (1:1), −78 °C, (ii) Me_2S, −78 to 0 °C; (e) $NaBH_4$, MeOH, 0 °C to rt, 84%; (f) TsCl, Et_3N, DMAP, DCM, rt; (g) *N*-(1,8-dicarboxynaphthalimido) Na^+ salt, DMF, rt, 42%; (h) $LiOH{\cdot}H_2O$, THF/H_2O/MeOH (5:4:1), rt; (i) *i*-Pr_2NEt, EDCI, HOBt, H−Phe-O*t*-Bu·HCl, DCM, rt, 65%; (j) HCl (gas), dioxane, reflux; (k) TMSBr, DCM then 1 equiv of NaOH 0.05 M, 38%.

of the methyl ester **15a** with LiOH in a mixture of aqueous MeOH and THF required heating at 60 °C for 2 days. The resulting acid was coupled with L-PheO-*t*-Bu in the presence of HOBt and Hunig's base to give the corresponding *tert*-butyl ester **16a**. Similar treatment of **15b** on the other hand, resulted in a surprisingly facile hydrolysis, requiring LiOH at room temperature for only 2 h. Coupling with L-PheO-*t*-Bu gave **16b**. The Trp analogue **17a** and **17b** corresponding to the C_2/C_5 *trans*- and *cis*-isomer, respectively, were prepared as described for **16**. The L-homoPhe analogue **18** corresponding to the C_2/C_5 *trans*-isomer was also prepared. Hydrolysis of the *tert*-butyl esters and the *N*-Boc group in **16a**, **16b**, **17a**, **17b**, and **18** with HCl gas in dioxane, followed by cleavage of the phosphonate with TMSBr,[30] gave, after preparative HPLC, the sodium salts of the first intended prototypes **19a**, **19b**, **20a**, **20b**, and **21**, respectively. Compounds in the diastereomeric series were prepared by the same transformations starting from D-pyroglutamic acid to give **22a** and **22b** (series B).

The same protocol was used to transform the 3-[1-(naphthyl)-propenyl] analogues obtained from **13a** and **13b** and the 4-(isobutyl) counterparts **23a**, **23b** into their PheOH amides **24a**, **24b**, **25a**, and **25b**, respectively (Scheme 4). The homologated analogue **27** was prepared by hydroboration of the allyl intermediate **11b**, followed by tosylation of the resulting alcohol, and introduction of the naphthalimide group to give **26**. Hydrolysis of the methyl ester, peptide coupling, and then cleavage of the phosphonate esters afforded **27**.

Access to different diastereomers in series A was possible from the minor C_2/C_4-*cis* allyl isomer **7b**, which resulted from the enolate alkylation reaction shown in Scheme 2. Thus, formation of the iminium ion from **7b** and treatment with

SCHEME 6. Possible Mechanistic Pathways for Ester Hydrolysis[a]



[a] C_3 substituent omitted for clarity.

trimethyl phosphite gave the C_5-*trans* phosphonate **28** as the predominant product, although it could not be separated from a minor quantity of its C_5-epimer (Scheme 5). Oxidative cleavage of the allyl group and installation of the 1,8-dicarboxynaphthalimido group as described above afforded **29**. Cleavage of the methyl ester, peptide coupling to **30**, and deprotection gave enantiopure **31**. The same transformations were effected starting from D-pyroglutamic acid to afford **32** (series B).

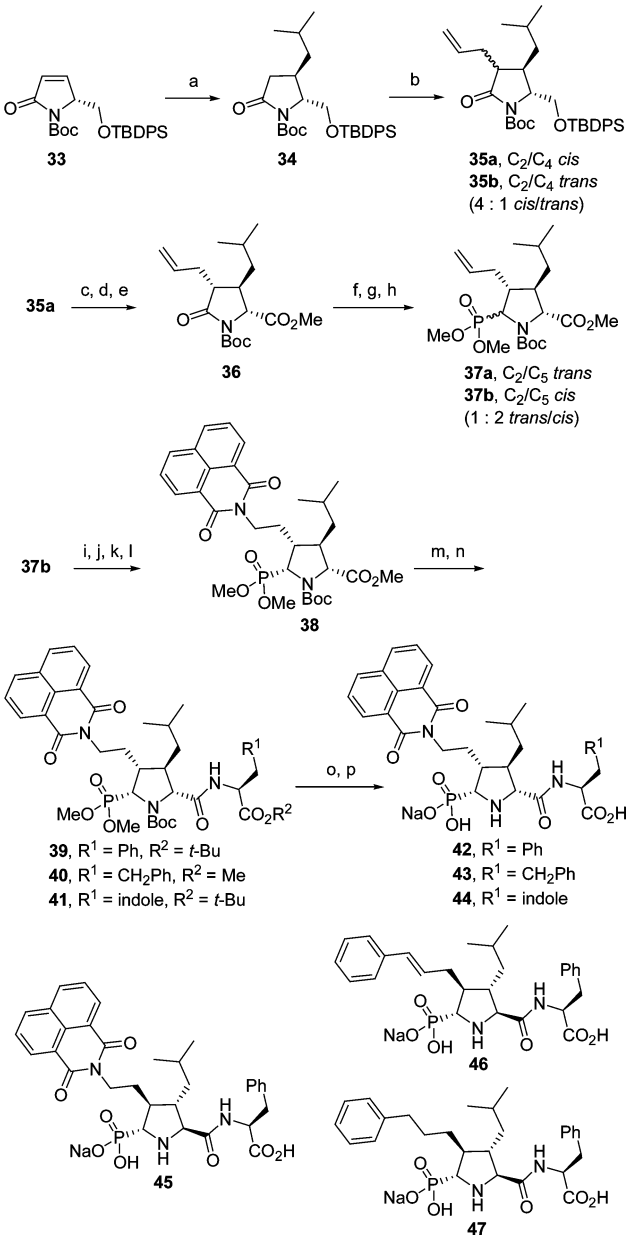
Before proceeding to the synthesis of analogues in series C, we studied the course of basic hydrolysis of *trans*- and *cis*-phosphonates esters **11a** and **11b**, respectively. As observed also for the C_4 naphthalimido series **15a** and **15b**, the *cis*-isomer **11b** was cleaved to the acid with 2 equiv of LiOH/THF−H_2O within 2 h at room temperature. The *trans*-isomer **11a** required 60 °C for 2 days. The reaction course was followed by ^{31}P NMR for both compounds.[31] Thus, for **11a** the signal corresponding to the starting ester at 26.6 ppm diminished gradually in favor of a new peak at 27.9 ppm corresponding to the carboxylic acid, whereas for **11b**, two ^{31}P peaks, corresponding to rotamers of the carboxylic acid, appear at 28.0 and 27.7 ppm within 5 min at room temperature and continued to grow until the starting ester was no longer observed after 1 h. It is possible that the hydrolysis of the *cis*-ester is accelerated due to anchimeric assistance from the favorably disposed phosphonate **11b**. Alternatively, Li^+-chelated tetrahedral intermediates may be favored in the *cis*-ester (Scheme 6). We are not aware of similar acceleration effects in the hydrolysis of mixed carboxylic phosphonic esters in which proximity may play a role. The distance of the P═O oxygen atom from the carbonyl of the ester in the X-ray crystal structure of **11b** is 3.99 Å. However, it is speculative to extrapolate such a proximity effect in solution.

We then turned our attention to the preparation of 3,4-disubstituted proline 5-phosphonic acids (series C and D). Since this involved the elaboration of three new vicinal stereogenic centers starting with D- and L-pyroglutamic acids, we

(30) (a) McKenna, C. E.; Higa, M. T.; Cheung, N. H.; McKenna, M.-C. *Tetrahedron Lett.* **1977**, *18*, 155−158. (b) Rabinowitz, R. *J. Org. Chem.* **1963**, *28*, 2975−2978.

(31) For related ^{31}P NMR values, see: (a) Davis, F. A.; Wu, Y.; Xu, H.; Zhang, J. *Org. Lett.* **2004**, *6*, 4523−4525. (b) Pietri, S.; Miollan, M.; Martel, S.; Le Moigne, F.; Blaive, B.; Culcasi, M. *J. Biol. Chem.* **2000**, *275*, 19505−19512.

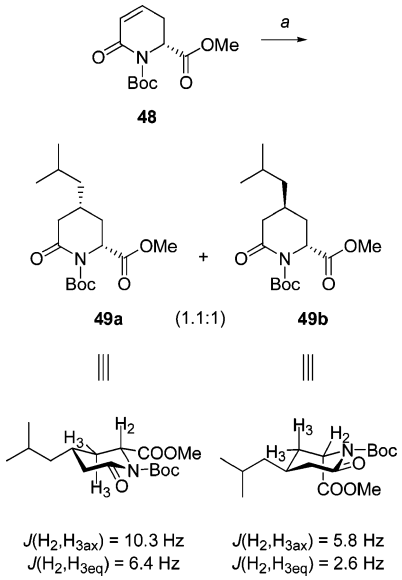
SCHEME 7[a]



[a] Reagents and conditions: (a) $(CH_3)_2CHCH_2MgBr$, CuI cat., Et_2O, −20 °C, 87%; (b) LiHMDS, allyl iodide, −78 °C, 46%; (c) TBAF, AcOH, THF, rt; (d) Jones' reagent, acetone, rt; (e) CH_2N_2, Et_2O, 0 °C, 65%; (f) Super Hydride, THF, −78 °C; (g) Ac_2O, Et_3N, DMAP, DCM, rt; (h) $P(OMe)_3$, $BF_3{\cdot}OEt_2$, DCM, −78 °C to rt, 87%; (i) i. ozone, DCM/MeOH (1:1), −78 °C; ii. Me_2S, −78 to 0 °C; (j) $NaBH_4$, MeOH, 0 °C to rt; (k) TsCl, Et_3N, DMAP, DCM, rt; (l) *N*-(1,8-dicarboxynaphthalimido) Na^+ salt, DMF, rt, 27%; (m) $LiOH{\cdot}H_2O$, THF/H_2O/MeOH (5:4:1), rt; (n) *i*-Pr_2NEt, EDCI, HOBt, H-Xaa-$OR^2{\cdot}HCl$, DCM, rt, 42−52%; (o) HCl (gas), dioxane, reflux or $LiOH{\cdot}H_2O$, THF/H_2O/MeOH (5:4:1), rt; (q) TMSBr, DCM then 1 equiv of NaOH 0.05M, 78−82%.

directed our effort toward the development of methodology and stereochemical feasibility first. Thus, the readily available 3,4-unsaturated lactam **33**[15,32] was treated with isobutylmagnesiocuprate to give the *trans*-adduct **34** as the only isomer (Scheme 7). Formation of the Li^+ enolate and alkylation with allyl iodide gave the *trans*/*trans*-adduct **35a** and its C_4 epimer **35b** in a 4:1 ratio, respectively. Desilylation of the major isomer **35a** with fluoride ion, followed by a Jones oxidation[33] and esterification, gave the corresponding ester **36** in good yield. Formation of the *N*-acyliminium ion and treatment with trimethyl phosphite gave the *trans*/*trans*/*trans*-product **37a** and the C_5 epimer **37b** in a 1:2 ratio, respectively. Oxidative cleavage of the allyl group in **37b**, reduction to the primary alcohol and displacement of the corresponding tosylate with the Na^+ salt of the 1,8-dicarboxynaphthalimido group, afforded the adduct **38**. Hydrolysis of the ester, followed by coupling with L-Phe-(O-*t*-Bu), L-homoPhe(OMe), or L-Trp(O-*t*-Bu), and deprotection as described previously, gave the intended phosphonic acids **42**, **43**, and **44**, respectively. The analogues **45**, **46**, and **47** were obtained starting from L-pyroglutamic acid (series C).

SCHEME 8[a]



[a] Reagents and conditions: (a) *i*-BuMgBr, $CuBr{\cdot}Me_2S$, Et_2O, −40 °C, 85%.

The elaboration of the pipecolic acid in series E (Scheme 1) presented challenges regarding the stereocontrolled introduction of the requisite substituents. The readily available[19b,34] 6-oxo-4,5-dehydro-D-pipecolic acid ester **48** was treated with isobutylmagnesiocuprate to give the mixture of 4-isobutyl adducts **49a** and **49b** in a 1.1:1 ratio as shown in Scheme 8.

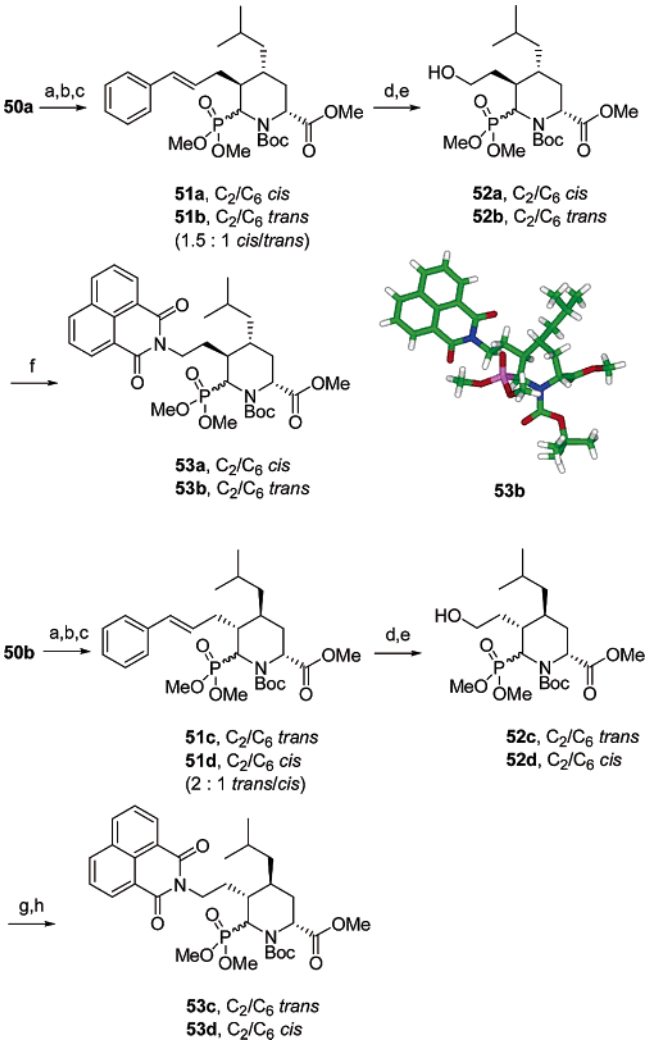
Their stereochemistry was unambiguously assigned from detailed ^1H NMR analysis. Since the isomers could not be separated by column chromatography, we proceeded with the alkylation of the lactam enolates of a mixture of **49a** and **49b**. The yield and selectivity of alkylation with cinnamyl bromide was found to be highly dependent on the solvent and countercation present (Table 1). The best condition for 4,5-*trans* product **50a** was a mixture of THF and DME (1:1) in conjunction with LiHMDS. This led to a 2:1 separable mixture of **50a** and **50b**, each in high diastereomeric excess (Table 1, entry 7). The recovered lactam (25%) was enriched in the *trans*-isomer **49b**.

(32) (a) Acevedo, C. M.; Kogut, E. F.; Lipton, M. A. *Tetrahedron* **2001**, *57*, 6353−6359. (b) Woo, K.-C.; Jones, K. *Tetrahedron Lett.* **1991**, *32*, 6949−6952. (c) Ohfune, Y.; Tomita, M. *J. Am. Chem. Soc.* **1982**, *104*, 3511−3513.

(33) For recent references, see: (a) Jao, E.; Bogen, S.; Saksena, A. K.; Girijavallabhan, V. *Tetrahedron Lett.* **2003**, *44*, 5033−5035. (b) Flamant-Robin, C.; Wang, Q.; Chiaroni, A.; Sasaki, N. A. *Tetrahedron* **2002**, *58*, 10475−10484. (c) Hanessian, S.; Ninkovic, S. *J. Org. Chem.* **1996**, *61*, 5418−5424.

(34) Davies, C. E.; Heightman, T. D.; Hermitage, S. A.; Moloney, M. G. *Synth. Commun.* **1996**, *26*, 687−696.

SCHEME 9[a]



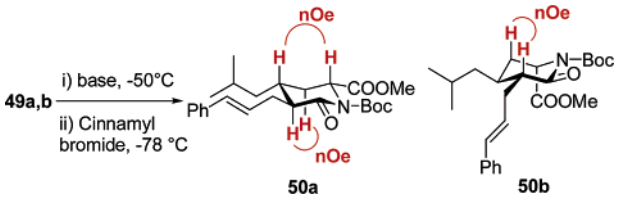
[a] Reagents and conditions: (a) (i) Super Hydride, THF, −78 °C, (ii) H_2O_2, 0 °C; (b) Ac_2O, Et_3N, DMAP, DCM, rt; (c) $P(OMe)_3$, $BF_3{\cdot}Et_2O$, DCM, −78 °C to rt, 81−94%; (d) (i) ozone, DCM/MeOH (1:1), −78 °C, (ii) Me_2S, −78 °C to 0 °C; (e) $NaBH_4$, MeOH, rt, 79−87%; (f) *N*-1,8-dicarboxynaphthalimide, PPh_3, methyl azodicarboxylate, THF, rt, 86−87%; (g) TsCl, Et_3N, DMAP, DCM, rt; (h) *N*-(1,8-dicarboxynaphthalimido) Na^+ salt, DMF, rt, 42−60%.

Other combinations of solvent and bases led to inferior results, especially in the case of NaHMDS. The structures of **50a** and **50b** were determined by NOE measurements (Table 1).

With **50a** and **50b** in hand, we proceeded to their elaboration into the intended target compounds in this series (Scheme 9). Thus, formation of the *N*-Boc iminium ion from **50a** and treatment with $P(OMe)_3$ in the presence of $BF_3{\cdot}Et_2O$ as previously described afforded a 1.5:1 separable mixture of C_2/C_6 *cis*- and *trans*-dimethylphosphonates **51a** and **51b** in excellent yield (Scheme 9). Each isomer was subjected to ozonolysis, and hydride reduction of the resulting aldehyde to give alcohols **52a** and **52b**. A Mitsunobu reaction with 1,8-dicarboxynaphthalimide was highly successful in this series to afford **53a** and **53b**. An analogous sequence was performed on the diastereomeric **50b**. The alcohols **52c** and **52d** did not react under Mitsunobu conditions, but displacement of the corresponding tosylates afforded **53c** and **53d** (Scheme 9).

Compounds **53a** and **53b** were individually converted into the diastereomeric protected indolyl amides **54a** and **54b** in good

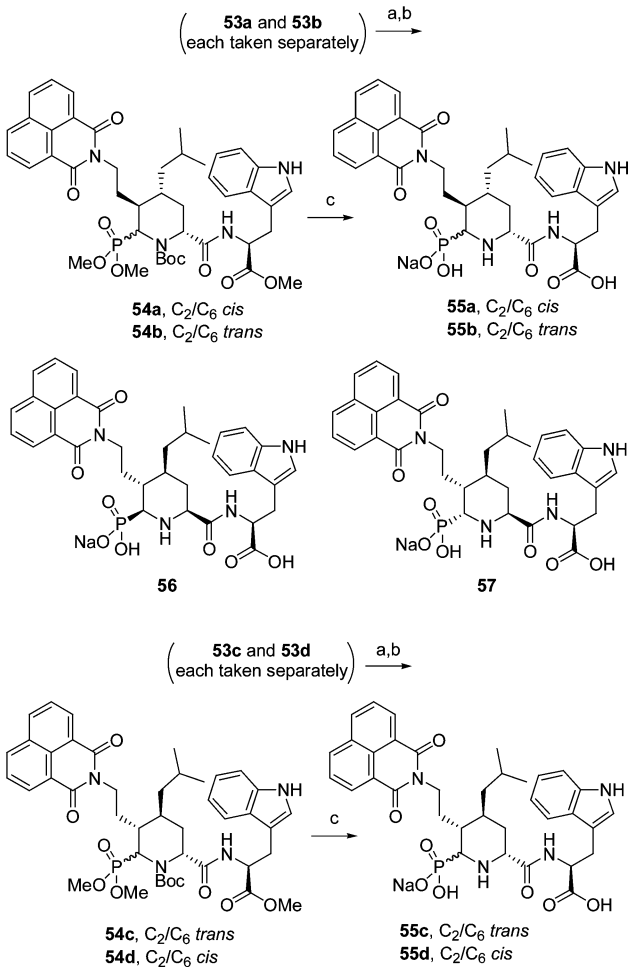
TABLE 1. Counterion and Solvent Study for Preparation of 50a and 50b



			yield (%)		
entry	solvents	base	**50a** (ratio)[a]	**50b** (ratio)[a]	**49** (ratio)[a]
1	THF	LiHMDS	44 (>98:2)	17 (72:28)	21 (0:100)
2	THF	LiHMDS	17 (>98:2)	13 (75:25)	50 (20:80)[b]
3	THF/DME (1:1)	LiHMDS	48 (>98:2)	24 (80:20)	26 (5:95)
4	THF/DME (1:1)	NaHMDS	11 (>98:2)	10 (79:21)	56[c]
5	THF/DME (1:10)	LiHMDS	37 (>98:2)	15 (88:12)	43 (30:70)
6	Et_2O/DME (1:10)	LiHMDS	25 (>98:2)	15 (91:9)	51 (37:63)
7	THF/DME (1:1)	LiHMDS	48 (>98:2)	25 (90:10)	25 (5:95)[d]

[a] Ratio determined by ^1H NMR analysis. [b] Only 0.6 equiv of cinnamyl bromide was used. [c] Not determined. [d] Cinnamyl bromide in THF was added over 30 min using a syringe pump.

SCHEME 10[a]



[a] Reagents and conditions: (a) $LiOH{\cdot}H_2O$, $THF/H_2O/MeOH$ (5:4:1), 50 °C; (b) H-Trp-OMe·HCl, EDCI, HOBt, DIEA, DMF, rt, 67−82%; (c) (i) $LiOH{\cdot}H_2O$, $THF/H_2O/MeOH$ (5:4:1), 0 °C, (ii) TMSBr, CH_2Cl_2, rt, then 1 equiv of NaOH 0.05 M, 68−95%.

yields (Scheme 10). Deprotection of the ester groups and purification by column chromatography afforded **55a** and **55b** respectively. The diastereomeric pairs series **54c**/**55c** and **54d**/**55d** were similarly prepared as were two representative com-

pounds **56** and **57** starting from the enantiomeric 6-oxo-L-pipecolic acid (Series F).

Conclusions

Biological testing of the phosphonic acids as inhibitors of ECE did not reveal a distinct SAR. However, two compounds stood out with promising results. The analogues **44** and **55d**, each originating from D-pyroglutamic acid and 6-oxo-D-pipecolic acid, respectively, showed 91% and 98% inhibition of ECE at 10^{-5} M.[35] Clearly, the expected improved binding of the constrained analogues was not observed despite a high level of stereochemical diversity. This may in part be due to nonoptimal deployment of the pharmacophoric group on the rigid 5- and 6-membered scaffolds compared to the acyclic inhibitors shown in Figure 1.

Experimental Section

(2*S*,4*R*)-4-Allyl-5-oxopyrrolidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester (7a) and (2*S*,4*S*)-4-Allyl-5-oxopyrrolidine-1,2-dicarboxylic acid 1-*tert*-Butyl Ester 2-Methyl Ester (7b). Lactam **6** (2.6 g, 10.7 mmol) was placed in a flame-dried, argon-filled flask, dissolved in dry THF (100 mL), and cooled to −78 °C. LiHMDS (11.8 mL, 11.8 mmol) was introduced as a 1 M solution in THF over 30 min (hypodermic syringe). The solution was stirred (30 min) prior to the addition of a solution of allyl bromide (1.39 mL, 16.0 mmol) in THF (160 mL), precooled to 0 °C, via a cannula. The solution was then stirred at −78 °C until completion (monitored by TLC). A saturated solution of $NaHCO_3$ was added, and the solution was allowed to reach rt. The aqueous layer was extracted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting oil was purified by flash column chromatography (hexanes/EtOAc, 9:1) to yield the two alkylated compounds **7a** and **7b** (2:1 in favor of **7a**). For **7a**: 1.2 g (40%); $[\alpha]_D$ −32.4 (*c* 1.0, $CHCl_3$); IR (neat/NaCl) 2961, 1793, 1752, 1718, 1317 cm^{-1};^{1}H NMR (300 MHz, $CDCl_3$) δ 5.65 (m, 1H), 5.01 (dd, 2H, J = 6.4, 13.6 Hz), 4.48 (dd. 1H, J = 1.6, 9.6 Hz), 3.69 (s, 3H), 2.65 (m, 1H), 2.52 (m, 1H), 2.12 (m, 2H), 1.95 (m, 1H), 1.41 (s, 9H); ^{13}C (100 MHz, $CDCl_3$) δ 174.7, 172.2, 149.8, 134.7, 118.2, 84.0, 57.3, 52.9, 41.6, 34.8, 28.3, 28.1; LRMS (FAB, NBA, *m*/*z*) 283, 183. For **7b**: 611 mg (20%); $[\alpha]_D$ +12.0 (*c* 3.5, $CHCl_3$); IR (neat/NaCl) 2981, 1792, 1752, 1719, 1320 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.68 (m, 1H), 5.08 (dd, 2H, J = 7.0, 13.0 Hz), 4.50 (dd. 1H, J = 1.8, 6.9 Hz), 3.78 (s, 3H), 2.68 (m, 2H), 2.45 (m, 1H), 2.20 (m, 1H), 1.78 (m, 1H), 1.47 (s, 9H); ^{13}C (100 MHz, $CDCl_3$) δ 174.4, 171.9, 149.1, 134.4, 117.6, 83.6, 57.3, 52.4, 41.9, 35.0, 27.7, 26.7; LRMS (FAB, NBA, *m*/*z*) 284, 228, 184.

(2*S*,4*R*)-5-Oxo-4-(3-phenylallyl)pyrrolidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester (8a) and (2*S*,4*S*)-5-Oxo-4-(3-phenylallyl)pyrrolidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester (8b). Following the preparation of **7a** and **7b** gave compounds **8a** and **8b** (3.5:1 in favor of **8a**). For **8a**: 5.1 g (57%); mp 107 °C; $[\alpha]_D$ −33.3 (*c* 1.3, $CHCl_3$); IR (neat/NaCl) 2981, 1792, 1751, 1717, 1318 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34−7.25 (m, 5H), 6.45 (d, 1H, J = 15.8 Hz), 6.11 (m, 1H), 4.55 (dd, 1H, J = 1.6, 9.4 Hz), 3.75 (s, 3H), 2.78 (m, 2H), 2.39 (m, 1H), 2.16 (m, 1H), 2.08 (m, 1H), 1.48 (s, 9H); ^{13}C (100 MHz, $CDCl_3$) δ 174.1, 171.6, 149.2, 136.7, 132.8, 128.1, 127.3, 125.9, 125.6, 83.4, 56.8, 52.4, 41.4, 33.3, 28.1, 27.7; LRMS (FAB, NBA, *m*/*z*) 360, 304, 260; HRMS for $C_{20}H_{25}NO_5$, (MH^+) calcd 360.183778, obsd 360.182100. For **8b**: 1.5 g (16%); $[\alpha]_D$ −47.2 (*c* 1.0, $CHCl_3$); IR (neat/NaCl) 2981, 1791, 1751, 1718, 1318, 1150 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.21 (m, 5H), 6.42 (d, 1H, J = 15.8 Hz), 6.21−6.08 (m, 1H), 4.52 (dd, 1H, J = 6.9, 8.8 Hz), 3.72 (s, 3H), 2.86−2.69 (m, 2H), 2.53−2.35 (m, 2H), 1.87−1.71 (m, 1H), 1.50 (s, 9H); ^{13}C (100 MHz, $CDCl_3$) δ 174.4, 171.9, 149.2, 136.8, 132.9, 128.5, 127.4, 126.1, 126.0, 83.8, 57.3, 52.5, 42.5, 34.4, 27.8, 26.7.

(2*S*,4*R*)- 4-(3-Naphthalen-1-ylallyl)-5-oxopyrrolidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester (9a) and (2*S*,4*S*)-4-(3-Naphthalen-1-ylallyl)-5-oxopyrrolidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester (9b). Following the preparation of **7a** and **7b** gave compounds **9a** and **9b** (7.8:1 in favor of **9a**). For **9a**: 1.1 g (63%); $[\alpha]_D$ −20.7 (*c* 0.7, $CHCl_3$); IR (neat/NaCl) 2981, 1790, 1750, 1717, 1314 cm^{-1}; ^{1}H (300 MHz, $CDCl_3$) δ 8.06 (d, 1H, J = 8.8 Hz), 7.84 (d, 1H, J = 7.2 Hz), 7.80 (m, 1H), 7.50 (m, 3H), 7.36 (m, 1H), 7.20 (d, 1H, J = 15.5 Hz), 6.15 (m, 1H), 4.59 (d, 1H, J = 9.4 Hz), 3.77 (s, 3H), 2.90 (m, 2H), 2.52 (m, 1H), 2.27−2.08 (m, 2H), 1.50 (s, 9H); ^{13}C (100 MHz, $CDCl_3$) δ 174.2, 171.7, 149.3, 134.6, 133.4, 130.9, 130.3, 129.0, 128.4, 127.7, 126.0, 125.7, 125.5, 123.7, 83.6, 56.9, 52.5, 41.6, 33.8, 27.8, 27.6; LRMS (FAB, NBA, *m*/*z*) 409, 309; HRMS for $C_{24}H_{27}NO_5$ calcd 409.188923, obsd 409.187996. For **9b**: 141 mg (8%);^{1}H (300 MHz, $CDCl_3$) δ 8.14 (d, 1H, J = 7.2 Hz), 7.82 (d, 1H, J = 7.2 Hz), 7.77 (d, 1H, J = 7.0 Hz), 7.61−7.40 (m, 4H), 7.19 (m, 1H), 6.16 (m, 1H), 4.57 (m, 1H), 3.75 (s, 3H), 2.98−2.78 (m, 2H), 2.61−2.46 (m, 2H), 1.94−1.81 (m, 1H), 1.51 (s, 9H); LRMS (FAB, NBA, *m*/*z*) 409; HRMS for $C_{24}H_{27}NO_5$ calcd 409.188923, obsd 409.188142.

(2*S*,4*R*)-4-(2-Methylallyl)-5-oxopyrrolidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester (10a) and (2*S*,4*S*)-4-(2-Methylallyl)-5-oxopyrrolidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester (10b). Following the preparation of **7a** and **7b** gave compounds **10a** and **10b** (1.5:1 in favor of **10a**). For **10a**: 620 mg (30%); as a white solid; mp 55 °C; $[\alpha]_D$ −41.0 (*c* 2.0, $CHCl_3$); IR (neat/NaCl) 2979, 1792, 1751, 1717 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 4.60 (d, 2H, J = 23.8 Hz), 4.54 (dd, 1H, J = 1.7, 9.6 Hz), 3.66 (s, 3H), 2.67 (m, 1H), 2.54 (dd, 1H, J = 3.7, 14.4 Hz), 2.05 (dddd, 1H, J = 1.7, 8.6, 13.5, 22.2 Hz), 1.89 (m, 1H), 1.82 (m, 1H), 1.58 (s, 3H), 1.37 (s, 9H); ^{13}C (100 MHz, $CDCl_3$) δ 174.3, 171.5, 148.9, 141.7, 112.2, 83.1, 56.5, 52.1, 39.6, 38.5, 27.8, 27.4, 21.7; LRMS (FAB, NBA, *m*/*z*) 297, 250, 197, 241; HRMS for $C_{15}H_{23}NO_5$ calcd 297.157623, obsd 297.158752. For **10b**: 413 mg (20%); as an amorphous solid; IR (neat/ NaCl) 2981, 1792, 1752, 1719 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 4.68 (d, 2H, J = 40.8 Hz), 4.47 (dd, 1H, J = 6.5, 9.0 Hz), 3.72 (s, 3H), 2.68 (m, 1H), 2.59 (dd, 1H, J = 3.7, 14.5 Hz), 2.40 (ddd, 1H, J = 9.1, 9.1, 13.3 Hz), 2.06 (dd, 1H, J = 11.1, 14.4 Hz), 1.65 (s, 3H), 1.64 (m, 1H), 1.43 (s, 9H); ^{13}C (100 MHz, $CDCl_3$) δ 174.8, 171.9, 149.1, 141.9, 112.6, 83.5, 57.2, 52.3, 40.6, 39.1, 27.7, 26.7, 21.7; LRMS (FAB, NBA, *m*/*z*) 298, 242, 198.

(2*S*,4*R*,5*R*)-4-Allyl-5-(dimethoxyphosphoryl)pyrrolidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester (11a) and (2*S*,4*R*,5*S*)-4-Allyl-5-(dimethoxyphosphoryl)pyrrolidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester (11b). Lactam **7a** (500 mg, 1.77 mmol) was placed in a flame-dried, argon-filled flask, dissolved in dry THF (10 mL), and cooled to −78 °C. A 1 M solution of $LiEt_3BH$ (2.12 mL, 2.12 mmol) in THF was added dropwise over 30 min (hypodermic syringe). After being stirred for 2 h, the reaction was quenched by addition of saturated $NaHCO_3$ and allowed to reach 0 °C. A few drops of H_2O_2 (30% v/v) were added, and the mixture was stirred for 1 h at 0 °C. The solvents were evaporated and replaced by CH_2Cl_2, and the organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo at rt to give the crude hemiacetal which was directly used in the next step. The residue was dissolved in CH_2Cl_2 (6 mL) and cooled to 0 °C prior to the addition of Et_3N (740 μL, 5.31 mmol), Ac_2O (501 μL, 5.31 mmol), and a catalytic amount of DMAP. The mixture was allowed to reach rt and stirred for 16 h, and then the reaction was quenched by the addition of saturated $NaHCO_3$, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo at rt to furnish an oil which was directly

(35) See the Supporting Information.

used in the next step. The crude oil and $P(OMe)_3$ (417 μL, 3.54 mmol) were dissolved in CH_2Cl_2 (20 mL) and cooled to −78 °C. Then, $BF_3{\cdot}OEt_2$ (449 μL, 3.54 mmol) was introduced by dropwise addition, and the solution was stirred for 1 h at −78 °C, 1 h at 0 °C and 1 h at rt. Water was added to the mixture, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (hexanes/EtOAc, 1:1) to give the two phosphonates **11a** and **11b** (1.5:1 in favor of **11b**). For **11a**: 193 mg (29%, three steps); mp 108 °C; $[\alpha]_D$ −9.4 (*c* 1.0, $CHCl_3$); IR (neat/NaCl) 3478, 2958, 1749, 1711, 1381 cm^{-1}; for a mixture of two rotamers ^1H NMR (300 MHz, $CDCl_3$) δ 5.77 (m, 1H), 5.05 (m, 2H), 4.41 (dd, 0.70H, J = 2.6, 7.5 Hz), 4.30 (m, 1.30H), 3.73 (d, 3H, J = 10.4 Hz), 3.70 (d, 3H, J = 10.5 Hz), 3.69 (s, 3H), 2.66 (m, 1H), 2.55 (m, 2H), 2.25 (m, 1H), 1.92 (m, 1H), 1.44 (s, 3H), 1.36 (s, 6H); ^{13}C (100 MHz, $CDCl_3$) δ 173.4, 153.1, 136.2 and 130.4, 116.3, 80.9 and 80.7, 58.9 and 58.6, 56.1, 55.2, 53.2 (d), 52.3, 40.2 and 39.0, 34.8, 33.2, 28.1 and 27.9; ^{31}P (161.3 MHz, $CDCl_3$) δ 26.1 (minor rotamer), 24.9 (major rotamer); LRMS (FAB, NBA, *m*/*z*) 377, 378; HRMS for $C_{16}H_{28}NO_7P$ calcd 377.160341, obsd 377.159649. For **11b**: 293 mg (44%, three steps); mp 68 °C; $[\alpha]_D$ +1.5 (*c* 1.0, $CHCl_3$); IR (neat/NaCl) 3481, 2957, 1761, 1739, 1703, 1382 cm^{-1}; for a mixture of two rotamers^1H NMR (300 MHz, $CDCl_3$) δ 5.72 (m, 1H), 5.06 (m, 2H) 4.35−4.26 (m, 1H), 4.04 (m, 1H), 3.83 (d, 3H, J = 10.3 Hz), 3.76 (d, 3H, J = 10.5 Hz), 3.71 (s, 3H), 2.57 (m, 1H), 2.48 (m, 1H), 2.08 (m, 3H), 1.43 (s, 3H), 1.40 (s, 6H); ^{13}C (100 MHz, $CDCl_3$) δ 173.4 and 173.0, 155.4 and 154.8, 135.6, 118.6, 81.4, 59.2, 58.9 (d), 54.3, 52.9, 52.3, 39.7 and 39.0, 38.2 and 38.0, 33.9 and 33.2, 28.4 and 28.2; ^{31}P (161.3 MHz, $CDCl_3$) δ 25.5; LRMS (FAB, NBA, *m*/*z*) 377, 378; HRMS for $C_{16}H_{28}NO_7P$ calcd 377.160341, obsd 377.159546.

(2*S*,4*R*,5*R*)-5-(Dimethoxyphosphoryl)-4-(3-phenylallyl)pyrrolidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester (12a) and (2*S*,4*R*,5*S*)-5-(Dimethoxyphosphoryl)-4-(3-phenylallyl)pyrrolidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester (12b). Following the preparation of **11a** and **11b** gave compounds **12a** and **12b** (1.9:1 in favor of **12b**). For **12a**: 1.72 g (28%, three steps); as a white solid; mp 121 °C; $[\alpha]_D$ −1.4 (*c* 1.0, $CHCl_3$); IR (neat/NaCl) 3468, 2956, 1748, 1704, 1382 cm^{-1}; for a mixture of two rotamers ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 (m, 4H), 7.12 (m, 1H), 6.48 (d, 1H, J = 13.3 Hz), 6.10 (m, 1H), 4.46 (dd, 1H, J = 2.5, 7.2 Hz), 4.32 (m, 1H), 3.76−3.74 (m, 6H), 3.68 (s, 3H), 2.70−2.68 (m, 1H), 2.63−2.43 (m, 3H), 1.98 (m, 1H), 1.46 (s, 3H), 1.38 (s, 6H); ^{13}C (100 MHz, $CDCl_3$) δ 173.9 and 173.5, 154.2 and 153.6, 137.8, 132.2, 128.9, 128.3, 127.6, 126.4, 81.4 and 81.2, 59.4, 56.3 (d), 53.7, 52.8, 52.5, 41.1 and 39.9, 35.4, 33.1, 28.6 and 28.4; ^{31}P (161.3 Mz, $CDCl_3$) δ 25.2 (minor rotamer), 24.9 (major rotamer); HRMS for $C_{22}H_{32}NO_7P$ (MH^+) calcd 454.19946, obsd 454.20050. For **12b**: 3.32 g (53%, three steps); as a colorless oil; $[\alpha]_D$ +3.6 (*c* 0.8, $CHCl_3$); IR (neat/NaCl) 3473, 2956, 1760, 1702, 1381 cm^{-1}; for a mixture of two rotamers ^1H NMR (300 MHz, $CDCl_3$) δ 7.34−7.26 (m, 4H), 7.21 (m, 1H), 6.44 (d, 1H, J = 15.1 Hz), 6.10 (dd, 1H, J = 6.7, 15.1 Hz), 4.33 (m, 1H), 4.13 (m, 1H), 3.88 (d, 3H, J = 10.3 Hz), 3.74 (s, 3H), 3.36 (d, 3H, J = 10.5 Hz), 2.71 (m, 1H), 2.53 (m, 1H), 2.27 (m, 2H), 2.18 (m, 1H), 1.59 (s, 3H), 1.41 (s, 6H); ^{13}C (100 MHz, $CDCl_3$) δ 172.8, 154.2, 137.4, 133.5, 133.3, 128.9, 127.8, 126.5, 81.4, 59.3, 59.2 (d), 54.4, 53.0 (d), 52.5, 39.5, 37.8 and 37.6, 34.1, 28.6 and 28.4; ^{31}P (161.3 MHz, $CDCl_3$) δ 25.5; HRMS for $C_{22}H_{32}NO_7P$ (MH^+) calcd 454.19946, obsd 454.19820.

(2*S*,4*R*,5*R*)-5-(Dimethoxyphosphoryl)-4-(3-naphthalen-1-ylallyl)pyrrolidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester (13a) and (2*S*,4*R*,5*S*)-5-(Dimethoxyphosphoryl)-4-(3-naphthalen-1-ylallyl)pyrrolidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester (13b). Following the preparation of **11a** and **11b** gave compounds **13a** and **13b** (1.6:1 in favor of **13b**). For **13a**: 152 mg (25%, three steps); $[\alpha]_D$ +20.0 (*c* 1.1, $CHCl_3$); for a mixture of two rotamers ^1H (300 MHz, $CDCl_3$) δ 8.09 (d, 1H, J = 8.8 Hz), 7.83 (d, 1H, J = 3.05 Hz), 7.80 (d, 1H, J = 2.1 Hz), 7.53−7.38 (m, 4H), 7.21 (d, 1H, J = 15.5 Hz), 6.18 (m, 1H), 4.53 (dd, 1H, J = 2.7, 7.2 Hz), 4.34 (d, 1H, J = 8.2 Hz), 3.81−3.77 (m, 6H),3.69 (s, 3H), 2.80 (m, 2H), 2.59 (m, 2H), 2.03 (m, 1H), 1.48 (s, 3H), 1.40 (s, 6H); ^{13}C (100 MHz, $CDCl_3$) δ 173.4, 153.1, 134.9, 133.4, 131.1, 130.9, 128.9, 128.3, 127.5, 125.8, 125.6, 125.5, 123.7, 123.5, 80.7, 58.9, 56.9 (d), 53.3, 52.3, 52.2, 39.4, 34.9, 33.2, 28.1 and 27.9; LRMS (FAB, NBA, *m*/*z*) 503, 447, 270; HRMS for $C_{26}H_{34}NO_7P$ (MH^+) calcd 503.207291, obsd 503.206184. **13b**: 249 mg (40%, three steps); $[\alpha]_D$ +0.8 (*c* 1.0, $CHCl_3$); for a mixture of two rotamers ^1H (300 MHz, $CDCl_3$) δ 8.04 (d, 1H, J = 8.2 Hz), 7.80 (d, 1H, J = 8.3 Hz), 7.72 (d, 1H, J = 8.0 Hz), 7.50−7.36 (m, 4H), 7.15 (d, 1H, J = 15.4 Hz), 6.08 (m, 1H), 4.40 (m, 1H), 4.20 (m, 1H), 3.87 (d, 3H, J = 10.3 Hz), 3.78 (d, 3H, J = 11.8 Hz), 3.72 (s, 3H), 2.76 (m, 1H), 2.59 (m, 1H), 2.34 (m, 2H), 2.21 (m, 1H), 1.44 (s, 3H), 1.38 (s, 6H); ^{31}P (161.3 MHz, $CDCl_3$) δ 25.8; LRMS (FAB, NBA, *m*/*z*) 505, 448, 294; HRMS for $C_{26}H_{34}NO_7P$ (MH^+) calcd 504.215116, obsd 504.214216.

(2*S*,4*R*,5*R*)-5-(Dimethoxyphosphoryl)-4-(2-hydroxyethyl)pyrrolidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester (14a). The phosphonate **11a** (385 mg, 1.02 mmol) was dissolved in a mixture of CH_2Cl_2/MeOH 1:1 (10 mL) and cooled to −78 °C. After 15 min, ozone was bubbled until a light blue coloration of the solution persisted. The ozone flow was stopped and replaced by argon until the solution turned colorless. Then, Me_2S (150 μL, 2.04 mmol) was added, and the resulting mixture was allowed to reach 0 °C and then stirred for 1 h. After addition of saturated $NaHCO_3$, the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The formed benzaldehyde was removed by filtration through a plug of silica gel (hexanes/EtOAc, 8:2). The pure aldehyde was dissolved in anhydrous MeOH (0.1 M) and placed under argon at 0 °C. After portionwise addition of $NaBH_4$ (77 mg, 2.04 mmol), the mixture was allowed to reach rt and was stirred until completion (monitored by TLC). The reaction was quenched by addition of saturated NH_4Cl. The organic solvents were removed by evaporation, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated to furnish the desired alcohol **14a** as a colorless oil which was used as a crude in the next step, (315 mg, 81%, two steps): for a mixture of two rotamers ^1H NMR (300 MHz, $CDCl_3$) δ 4.49 (dd, 1H, J = 2.0, 8.2 Hz), 4.19 (d, 1H, J = 9.6 Hz), 3.72−3.64 (m, 9H), 3.59−3.52 (m, 2H), 2.81−2.56 (m, 1H), 2.45−2.33 (m, 1H), 2.13−1.87 (m, 2H), 1.75−1.65 (m, 1H), 1.39 (s, 3H), 1.32 (s, 6H).

(2*S*,4*R*,5*S*)-5-(Dimethoxyphosphoryl)-4-(2-hydroxyethyl)pyrrolidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester (14b). Following the preparation of **14a** gave compound **14b** as a colorless oil: 286 mg (79%, two steps); $[\alpha]_D$ +16.1 (*c* 1.1, $CHCl_3$); for a mixture of two rotamers ^1H NMR (300 MHz, $CDCl_3$) δ 4.40 (t, 1H, J = 8.8 Hz), 4.10 (m, 1H), 3.88 (m, 3H), 3.80 (d, 3H, J = 10.6 Hz), 3.74 (s, 3H), 3.62 (t, 2H, J = 6.1 Hz), 2.64 (m, 1H), 2.43 (m, 1H), 2.18 (m, 1H), 1.58 (m, 2H), 1.50 (s, 3H), 1.44 (s, 6H); ^{13}C (100 MHz, $CDCl_3$) δ 172.3, 153.8, 80.9, 59.9, 58.8 and 57.7, 53.2 (d), 51.9, 36.5, 36.5, 36.2, 34.6 and 33.9, 28.0; ^{31}P (161.3 MHz, $CDCl_3$) δ 27.1; LRMS (FAB, NBA, *m*/*z*) 381, 325, 272, 216; HRMS for $C_{15}H_{28}NO_8P$ calcd 381.155256, obsd 381.154572.

(2*S*,4*R*,5*R*)-5-(Dimethoxyphosphoryl)-4-[2-(1,3-dioxo-1*H*,3*H*-benzo[*de*]isoquinolin-2-yl)ethyl]pyrrolidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester (15a). To a solution of the alcohol **14a** (530 mg, 1.39 mmol) in dry CH_2Cl_2 (3 mL) at 0 °C were added TsCl (292 mg, 1.53 mmol), Et_3N (213 μL, 1.53 mmol), and a catalytic amount of DMAP. The resulting mixture was allowed to reach rt and was stirred for 24 h. The reaction was quenched by addition of saturated NH_4Cl, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to yield the desired tosylate, which was used without further purification. Then, NaH (222 mg, 5.56 mmol, 60%

dispersion in oil), washed three times with dry hexanes, was suspended in dry DMF. The mixture was cooled to 0 °C prior to the addition of 1,8-dicarboxynaphthalimide (1.23 g, 6.25 mmol). After 30 min, a solution of the tosylate in dry DMF was introduced via a cannula, and the resulting suspension was stirred for 48 h at rt. After evaporation of DMF, H_2O was added to the residue, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The excess of reagent was removed by flash chromatography (hexanes/EtOAc, 1:1) prior to the recovery of the desired compound (hexanes/EtOAc, 3:7) **15a**, (210 mg, 27%, two steps): mp 58 °C; $[\alpha]_D$ −8.1 (*c* 0.9, $CHCl_3$); IR (neat/NaCl) 2956, 1747, 1701, 1667, 1366 cm^{-1}; for a mixture of rotamers ^1H NMR (300 MHz, $CDCl_3$) δ 8.47 (dd, 2H, J = 7.2 Hz), 8.13 (d, 2H, J = 8.2 Hz), 7.66 (t, 2H, J = 7.8 Hz), 4.41 (dd, 1H, J = 2.5, 7.2 Hz), 4.32 (dd, 1H, J = 7.9, 13.5 Hz), 4.25−3.97 (m, 2H), 3.73 (d, 3H, J = 4.9 Hz), 3.70 (d, 3H, J = 7.2 Hz), 3.67 (s, 3H), 2.58 (m, 2H), 2.22 (m, 2H), 1.88 (m, 1H), 1.41 (s, 3H), 1.33 (s, 6H); ^{13}C (100 MHz, $CDCl_3$) δ 173.2 and 172.9, 163.9, 153.6 and 153.0, 133.8, 131.3, 130.9, 127.8, 126.7, 122.3, 80.7 and 80.5, 58.6, 55.9 (d), 53.0 (d), 52.4 (d), 51.9, 38.8, 38.0 and 37.0, 34.8, 30.4, 27.8 and 27.4; ^{31}P (161.3 MHz, $CDCl_3$) δ 25.16 (minor rotamer), 25.48 (major rotamer); LRMS (FAB, NBA, *m*/*z*) 561, 505, 351, 326; HRMS for $C_{27}H_{33}N_2O_9P$ (MH^+) calcd 561.200195, obsd 561.199200.

(2*S*,4*R*,5*S*)-5-(Dimethoxyphosphoryl)-4-[2-(1,3-dioxo-1*H*,3*H*-benzo[*de*]isoquinolin-2-yl)ethyl]pyrrolidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester (15b). Following the preparation of **15a** gave compound **15b**, 92 mg (42%, two steps): $[\alpha]_D$ +5.3 (*c* 0.9, $CHCl_3$); IR (neat/NaCl) 2957, 2360, 1700, 1661, 1367 cm^{-1}; for a mixture of two rotamers ^1H NMR (300 MHz, $CDCl_3$) δ 5.58 (dd, 2H, J = 1.1, 7.5 Hz), 8.22 (dd, 2H, J = 1.1, 8.5 Hz), 7.77 (t, 2H, J = 7.5 Hz), 4.43 (m, 1H), 4.25 (m, 2H), 4.19 (m, 1H), 3.87 (d, 3H, J = 10.8 Hz), 3.76 (d, 3H, J = 10.9 Hz), 3.74 (s, 3H), 2.63 (m, 2H), 2.38 (m, 1H), 1.90−1.62 (m, 2H), 1.51 (s, 3H), 1.41 (s, 6H); ^{13}C (100 MHz, $CDCl_3$) δ 172.3 and 172.0, 164.0, 153.7, 134.6 and 134.1, 131.5, 131.2 and 130.9, 128.1, 126.9, 122.4, 81.1 and 80.9, 59.8 (d), 58.6 and 58.4, 54.0, 52.5, 51.9, 38.2, 37.5, 33.5, 31.7, 28.1; ^{31}P (161.3 MHz, $CDCl_3$) δ 25.2; LRMS (FAB, NBA, *m*/*z*) 561, 460, 410; HRMS for $C_{27}H_{33}N_2O_9P$ (MH^+) calcd 561.200195, obsd 561.198600.

(2*R*,3*R*,5*S*)-5-[(1*S*)-*tert*-Butoxycarbonyl-2-phenylethylcarbamoyl]-2-(dimethoxyphosphoryl)-3-[2-(1,3-dioxo-1*H*,3*H*-benzo[*de*]-isoquinolin-2-yl)ethyl]pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (16a). The methyl ester **15a** (147 mg, 0.26 mmol) was dissolved in THF/H_2O/MeOH 5:4:1 (3 mL) and cooled to 0 °C. LiOH·H_2O (22 mg, 0.52 mmol) was added, and the solution was stirred for 2 h at rt. In the case of the C_2/C_5 *trans* derivatives the hydrolysis was done at 60 °C over 48 h. The aqueous layer was washed with CH_2Cl_2, acidified to pH 3 with HCl 1 N, and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to give the carboxylic acid, which was used in the next step without further purification. The HCl salt of H-Phe-O*t*-Bu (81 mg, 0.31 mmol) was suspended in CH_2Cl_2 (1.5 mL) at 0 °C. Diisopropylethylamine (54 μL, 0.31 mmol) was added, followed by HOBt (50 mg, 0.37 mmol) and a solution of the described carboxylic acid in CH_2Cl_2 (1.5 mL). The resulting mixture was stirred for 15 min at 0 °C, and EDCI (65 mg, 0.34 mmol) was added. The solution was stirred for 16 h at rt. The organic layer was washed with saturated $NaHCO_3$, 1 N HCl, and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography (CH_2Cl_2/MeOH, 10:0 to 9.8:0.2) afforded pure **16a** (65 mg, 33%, two steps) as a white solid: mp 79−82 °C; $[\alpha]_D$ +2.3 (*c* 1.1, $CHCl_3$); IR (neat/NaCl) 2955, 1721, 1500 cm^{-1}; for a mixture of two rotamers ^1H NMR (300 MHz, $CDCl_3$) δ 8.54 (m, 2H), 8.18 (d, 2H, J = 8.2 Hz), 7.72 (m, 2H), 7.26 (m, 3H), 7.16 (m, 2H), 6.23 (bd, 0.30H), 6.05 (bd, 0.70H), 4.68 (m, 1H), 4.51 (d, 0.70H, J = 7.4 Hz), 4.45 (d, 0.30H, J = 7.5 Hz), 4.20 (m, 3H), 3.75 (d, 3H, J = 10.4 Hz), 3.73 (d, 3H, J = 10.2 Hz), 3.12 (dd, 1H, J = 5.7, 13.8 Hz), 2.97 (m, 1H), 2.57 (m, 2H), 2.22 (m, 2H), 1.97 (m, 1H), 1.47 (s, 3H), 1.35 (s, 6H), 1.33 (s, 9H); ^{13}C (100 MHz, $CDCl_3$) δ 172.0, 170.5 and 170.4, 164.0, 153.3, 136.3, 133.8, 131.5, 131.2, 129.8, 129.3, 128.4, 128.2, 126.9, 122.6, 82.4 and 82.2, 80.8 and 80.7, 60.4 and 60.2, 56.2 (d), 53.9 and 53.7, 53.1 (d), 52.3 (d), 39.2 and 39.1, 38.7 and 38.6, 37.2, 35.8, 34.6, 28.2 and 27.9, 28.1; ^{31}P (161.3 MHz, $CDCl_3$) δ 25.7 (major rotamer), 25.3 (minor rotamer); LRMS (FAB, NBA, *m*/*z*) 750, 650, 484; HRMS for $C_{39}H_{48}N_3O_{10}P$ (MH^+) calcd 750.315559, obsd 750.317400.

(2*S*,3*R*,5*S*)-5-[(1*S*)-*tert*-Butoxycarbonyl-2-phenylethylcarbamoyl]-2-(dimethoxyphosphoryl)-3-[2-(1,3-dioxo-1*H*,3*H*-benzo[*de*]-isoquinolin-2-yl)ethyl]pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (16b). Following the preparation of **16a** gave compound **16b** as a white foam, 65 mg (79%, two steps): $[\alpha]_D$ +3.0 (*c* 1.3, $CHCl_3$); IR (neat/NaCl) 3279, 2977, 1735, 1701, 1663 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.75 (d, 2H, J = 7.3 Hz), 8.20 (d, 2H, J = 8.3 Hz), 7.73 (dd, 2H, J = 7.4, 8.1 Hz), 7.25 (m, 5H), 4.75 (m, 1H), 4.30 (t, 1H, J = 7.5 Hz), 4.15 (m, 2H), 4.02 (m, 1H), 3.82 (d, 3H, J = 10.5 Hz), 3.75 (d, 3H, J = 10.6 Hz), 3.09 (dd, 1H, J = 6.8, 13.7 Hz), 3.00 (dd, 1H, J = 8.0, 13.7 Hz), 2.49 (m, 1H), 2.29 (m, 1H), 2.15−1.86 (m, 2H), 1.66 (m, 1H), 1.42 (s, 9H), 1.33 (s, 9H); ^{13}C (100 MHz, $CDCl_3$) δ 172.3, 171.0, 164.3, 154.8, 137.4, 134.4, 131.9, 131.6, 129.9, 128.7, 128.5, 127.3, 126.9, 122.9, 82.1, 81.6, 62.8, 61.3, 59.1, 54.0, 53.1, 39.0, 38.7, 38.1, 35.0, 32.2, 28.4, 28.3; ^{31}P (161.3 MHz, $CDCl_3$) δ 29.5; LRMS (FAB, NBA, *m*/*z*) 750, 540, 484.

(2*R*,3*R*,5*S*)-2-(Dimethoxyphosphoryl)-3-[2-(1,3-dioxo-1*H*,3*H*-benzo[*de*]isoquinolin-2-yl)ethyl]-5-[2-(3*H*-inden-1-yl)-(1*S*)-methoxycarbonylethylcarbamoyl]pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (17a). Following the preparation of **16a** gave compound **17a**, 26 mg (36%, two steps): $[\alpha]_D$ +27.4 (*c* 1.2, $CHCl_3$); IR (neat/NaCl) 3284, 2953, 1702, 1699, 1660 cm^{-1}; for a mixture of two rotamers ^1H NMR (300 MHz, CDCl3) δ 8.62 (d, 2H, J = 7.3 Hz), 8.20 (d, 2H, J = 8.2 Hz), 7.78 (m, 2H), 7.56 (m, 1H), 7.38 (m, 1H), 7.18−7.01 (m, 3H), 6.32 (d, 0.4H), 6.04 (d, 0.6H), 4.81 (m, 1H), 4.27−4.10 (m, 3H), 4.02 (m, 1H), 3.80−3.68 (m, 9H), 3.33 (m, 2H), 2.55 (m, 1H), 2.20 (m, 2H), 1.92 (m, 2H), 1.59 (s, 3H), 1.34 (s, 6H); ^{13}C (100 MHz, $CDCl_3$) δ 172.2, 172.0, 168.5, 153.6 and 153.0, 136.4, 134.0, 131.5, 128.1, 127.4, 123.1, 121.8, 119.8, 118.2, 111.6, 109.3, 81.0, 60.3, 57.0, 54.9, 53.1, 52.8, 52.3, 39.4, 37.7, 35.7, 34.7, 29.6, 28.1 and 27.4; ^{31}P (161.3 MHz, $CDCl_3$) δ 25.6 (minor rotamer), 25.0 (major rotamer); LRMS (FAB, NBA, *m*/*z*) 747, 647.

(2*S*,3*R*,5*S*)-2-(Dimethoxy-phosphoryl)-3-[2-(1,3-dioxo-1*H*,3*H*-benzo[*de*]isoquinolin-2-yl)ethyl]-5-[2-(3*H*-inden-1-yl)-(1*S*)-methoxycarbonylethylcarbamoyl]pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (17b). Following the preparation of **16a** gave compound **17b** as a yellow foam, 63 mg (74%, two steps): mp 45 °C; $[\alpha]_D$ −5.5 (*c* 1.0, $CHCl_3$); IR (neat/NaCl) 3285, 2956, 1745, 1700, 1661, 1368 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.75 (bs, 1H), 8.60 (d, 2H, J = 7.2 Hz), 8.37 (bs, 1H), 8.22 (d, 2H, J = 8.2 Hz), 7.76 (t, 2H, J = 7.8 Hz), 7.61 (d, 1H, J = 7.6 Hz), 7.31 (d, 1H, J = 7.6 Hz), 7.12 (m, 3H), 5.06 (m, 1H), 4.38 (t, 1H, J = 5.8 Hz), 4.10 (m, 2H), 3.86 (m, 1H), 3.78 (d, 3H, J = 9.8 Hz), 3.69 (s, 3H), 3.58 (d, 3H, J = 10.7 Hz), 3.40 (dd, 1H, J = 5.03, 14.8 Hz), 3.28 (dd, 1H, J = 8.9, 14.9 Hz), 2.41 (m, 1H), 2.17 (m, 1H), 2.05 (m, 2H), 1.73 (m, 1H), 1.44 (s, 9H); ^{13}C (100 MHz, $CDCl_3$) δ 172.8, 172.4, 164.5, 154.7, 136.7, 134.6, 132.0, 131.8, 128.5, 127.8, 127.4, 123.5, 122.8, 122.2, 119.6, 119.2, 111.5, 111.3, 82.1, 62.0 (d), 59.2, 54.7, 52.6, 52.5, 39.1, 39.0, 38.6, 35.6, 31.9, 28.4; ^{31}P (161.3 MHz, $CDCl_3$) δ 30.3; LRMS (FAB, NBA, *m*/*z*) 747, 537, 307; HRMS for $C_{38}H_{43}N_4O_{10}P$ (MH^+) calcd 747.279508, obsd 747.277900.

(2*R*,3*R*,5*S*)-2-(Dimethoxyphosphoryl)-3-[2-(1,3-dioxo-1*H*,3*H*-benzo[*de*]isoquinolin-2-yl)ethyl]-5-[(1*S*)-methoxycarbonyl-3-phenylpropylcarbamoyl]pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (18). Following the preparation of **16a** gave compound **18**, 25 mg (35%, two steps): $[\alpha]_D$ +5.3 (*c* 1.2, $CHCl_3$); IR (neat/NaCl) 3282, 2954, 1744, 1701, 1663 cm^{-1}; for a mixture of two rotamers ^1H NMR (300 MHz, $CDCl_3$) δ 8.56 (m, 2H), 8.18 (m, 2H), 7.73

(m, 2H), 7.29−7.13 (m, 5H), 4.66 (m, 1H), 4.50 (dd, 1H, J = 7.5, 17.2 Hz), 4.29−4.20 (m, 3H), 3.83−3.70 (m, 9H), 2.73−2.63 (m, 3H), 2.31−2.16 (m, 3H), 2.16−2.02 (m, 1H), 2.02−1.91 (m, 2H), 1.45 (s, 9H); ^{13}C (100 MHz, $CDCl_3$) δ 172.6, 172.5, 171.9, 164.1, 153.7 (d), 140.7 (d), 133.8, 131.2, 128.7, 128.5, 128.3, 126.9, 126.1 (d), 122.7, 80.8 (d), 60.3, 57.0 (d), 55.8 (d), 52.7 (d), 52.4, 39.0, 37.9 (d), 35.0 (d), 34.6, 31.5 (d), 30.9, 28.2, 27.6; ^{31}P (161.3 MHz, $CDCl_3$) δ 25.8 (major rotamer), 25.2 (minor rotamer); LRMS (FAB, NBA, *m*/*z*) 722, 623, 513.

(2*S*,4*R*,5*R*)-(2*S*)-({4-[2-(1,3-Dioxo-1*H*,3*H*-benzo[*de*]isoquinolin-2-yl)ethyl]-5-phosphonopyrrolidine-2-carbonyl}amino)-3-phenylpropionic Acid (19a). The phosphonate **16a** (60 mg, 0.08 mmol) was placed in a flame-dried flask and dissolved in dry dioxane (1 mL). After bubbling of HCl for 1 h, the solution was refluxed for 6 h and stirred at rt until completion. The solvent was evaporated and replaced by CH_2Cl_2. The suspension was cooled to 0 °C, and TMSBr (42 μL, 0.32 mmol) was added dropwise. The solution was stirred for 24−48 h (monitored by TLC). The solvent was removed, and deionized H_2O (few mL) was added. The resulting suspension was stirred in the cold room (4 °C) for 16 h. The suspension was transferred in a conic 2 mL Eppendorf tube and centrifuged at 4 °C for 10 min. The supernatant was removed and replaced by fresh H_2O, and the same operation was repeated twice. The amorphous solid was suspended in 2 mL of deionized H_2O, and the pH value was adjusted to 7 by addition of an aqueous solution of NaOH 0.05 M (1.6 mL, 0.08 mmol). The solution was filtered on a 0.45 μm filter and lyophilized to give **19a**. Purification by preparative C_{18} RP-HPLC gave a yellow foam (7 mg, 15%): $[\alpha]_D$ −78.7 (*c* 0.5, H_2O); IR (KBr) 3433, 1698, 1656, 1591 cm^{-1}; ^{1}H NMR (300 MHz, D_2O) δ 8.15 (m, 4H), 7.58 (t, 2H, J = 7.7 Hz), 7.24 (m, 2H), 7.11 (m, 3H), 4.70 (dd, 1H, J = 2.3, 3.2 Hz), 4.35 (dd, 1H,, J = 5.1, 9.0 Hz), 4.24 (dd, 1H,, J = 5.4, 9.5 Hz), 3.88 (t, 2H, J = 6.5 Hz), 3.48 (dd, 1H, J = 9.2, 6.0 Hz), 3.10 (dd, 1H, J = 5.0, 13.9 Hz), 2.87 (dd, 1H, J = 9.1, 13.9 Hz), 2.39 (m, 1H), 2.18 (m, 1H), 2.10 (m, 1H), 1.90 (m, 1H), 1.62 (m, 1H); ^{13}C (100 MHz, D_2O) δ 178.4, 171.8, 166.2, 138.6, 136.0, 132.4, 131.7, 130.0, 129.3, 127.9, 127.6, 127.5, 121.5, 61.8, 59.6, 57.6, 40.0, 38.8, 38.2, 35.0, 27.7; ^{31}P (161.3 MHz, D_2O) δ 11.6; LRMS (FAB, NBA, *m*/*z*) 565, 549, 485.

(2*S*,4*R*,5*S*)-(2*S*)-({4-[2-(1,3-Dioxo-1*H*,3*H*-benzo[*de*]isoquinolin-2-yl)ethyl]-5-phosphonopyrrolidine-2-carbonyl}amino)-3-phenylpropionic Acid (19b). Following the preparation of **19a** gave compound **19b**, 30 mg (64%, two steps): IR (KBr) 3443, 1697, 1656, 1591, 1456 cm^{-1}; ^{1}H NMR (300 MHz, D_2O) δ 8.24 (d, 2H, J = 8.2 Hz), 8.17 (d, 2H, J = 7.7 Hz), 7.63 (t, 2H, J = 8.2 Hz), 7.33 (t, 2H, J = 7.5 Hz), 7.25 (t, 3H, J = 9.2 Hz), 4.45 (dd, 1H, J = 5.2 8.9 Hz), 4.36 (dd, 1H, J = 5.1, 9.5 Hz), 3.99 (m, 1H), 3.87 (m, 1H), 3.26 (t, 1H, J = 10.0 Hz), 3.21 (dd, 1H, J = 5.4, 14.1 Hz), 2.98 (dd, 1H, J = 8.8, 13.6 Hz), 2.44 (m, 1H), 2.34 (m, 1H), 2.23 (m, 1H), 2.13 (m, 1H), 1.54 (m, 1H); ^{13}C (100 MHz, D_2O) δ 178.0, 169.2, 165.3, 138.6, 135.7, 131.9, 131.1, 130.0, 129.8, 129.4, 127.6, 126.9, 120.7, 62.6, 61.2, 59.9, 39.4, 38.6, 38.0, 36.4, 30.0; ^{31}P (161.3 MHz, D_2O) δ 10.8; LRMS (FAB, NBA, *m*/*z*) 566.

(2*S*,4*R*,5*R*)-(2*S*)-({4-[2-(1,3-Dioxo-1*H*,3*H*-benzo[*de*]isoquinolin-2-yl)ethyl]-5-phosphonopyrrolidine-2-carbonyl}amino)-3-(1*H*-indol-3-yl)propionic Acid (20a). Following the preparation of **16a** and the preparation of **19a** gave compound **20a**, 16 mg (80%, four steps): $[\alpha]_D$ −3.2 (*c* 0.4, H_2O); IR (KBr) 3413, 2926, 1698, 1654, 1590 cm^{-1}; ^{1}H NMR (300 MHz, D_2O) δ 8.02 (m, 2H), 7.56 (m, 2H), 7.44 (m, 1H), 7.24 (m, 1H), 7.04 (m, 2H), 6.95 (m, 2H), 6.72 (m, 1H), 4.42 (m, 1H), 3.85 (m, 2H), 3.48 (m, 2H), 3.02 (m, 2H), 2.07 (m, 2H), 1.98 (m, 1H), 1.70−1.25 (m, 2H); ^{13}C (100 MHz, D_2O) δ 179.2, 175.6, 166.1, 136.6, 135.7, 132.1, 131.0, 128.0, 127.7, 126.9, 124.7, 122.3, 121.2, 119.7, 119.1, 112.4, 111.0, 62.3, 59.6, 56.3, 40.4, 38.6, 35.0, 28.3; ^{31}P (161.3 MHz, D_2O) δ 14.6.

(2*S*,4*R*,5*S*)-(2*S*)-({4-[2-(1,3-Dioxo-1*H*,3*H*-benzo[*de*]isoquinolin-2-yl)ethyl]-5-phosphonopyrrolidine-2-carbonyl}amino)-3-(1*H*-indol-3-yl)propionic Acid (20b). Following the preparation of **16a** and the preparation of **19a** gave compound **20b**; 22 mg (69%, four steps): $[\alpha]_D$ −22.5 (*c* 1.2, H_2O); IR (KBr) 3428, 1654, 1591, 1129 cm^{-1}; ^{1}H NMR (300 MHz, D_2O) δ 8.03 (d, 2H, J = 6.3 Hz), 7.98 (d, 2H, J = 7.5 Hz), 7.67 (d, 1H, J = 7.5 Hz), 7.59 (d, 2H, J = 7.5 Hz), 7.50 (d, 1H, J = 7.0 Hz), 7.17 (m, 2H), 7.08 (t, 1H, J = 6.8 Hz), 4.51 (t, 1H, J = 4.6 Hz), 3.90 (m, 1H), 3.80 (m, 1H), 3.65 (m, 1H), 3.31 (m, 1H), 3.13 (dd, 1H, J = 9.0, 13.5 Hz), 2.97 (t, 1H, J = 8.3 Hz), 2.19 (m, 1H), 2.01 (m, 1H), 1.89 (m, 1H), 1.70 (m, 1H), 1.41 (m, 1H); ^{13}C (100 MHz, D_2O) δ 178.9, 171.6. 165.5, 136.8, 135.6, 131.9, 131.1, 127.9, 127.5, 127.0, 125.1, 122.4, 120.9, 119.9, 119.3, 112.6, 111.3, 63.5, 59.7, 56.8, 39.9, 38.6, 36.3, 31.3, 28.1; ^{31}P (161.3 MHz, D_2O) δ 13.4; LRMS (FAB, NBA, *m*/*z*) 605.

(2*S*,4*R*,5*R*)-(2*S*)-({4-[2-(1,3-Dioxo-1*H*,3*H*-benzo[*de*]isoquinolin-2-yl)ethyl]-5-phosphonopyrrolidine-2-carbonyl}amino)-4-phenylbutyric Acid (21). Following the preparation of **16a** and the preparation of **19a** gave compound **21**, 15 mg (90%, four steps): $[\alpha]_D$ −50.2 (*c* 0.4, H_2O); IR (KBr) 3389, 2927, 1699, 1656, 1591 cm^{-1}; ^{1}H NMR (300 MHz, D_2O) δ 8.07 (m, 3H), 7.53 (m, 3H), 7.03 (m, 3H), 6.82 (m, 2H), 4.15 (m, 1H), 4.01−3.62 (m, 3H), 3.58 (m, 1H), 3.46 (m, 1H), 2.64 (m, 1H), 2.24 (m, 4H), 2.05 (m, 1H), 1.91 (m, 1H), 1.70 (m, 1H); ^{13}C (100 MHz, D_2O) δ 179.4, 175.2, 166.1, 141.8, 135.9, 132.3, 131.5, 129.2, 129.0, 127.7, 127.4, 126.7, 121.1, 61.4 (d), 59.5, 55.5, 40.5, 38.7, 35.6, 34.3, 32.4, 28.0; ^{31}P (161.3 MHz, D_2O) δ 14.0.

(2*R*,4*S*,5*S*)-(2*S*)-({4-[2-(1,3-Dioxo-1*H*,3*H*-benzo[*de*]isoquinolin-2-yl)ethyl]-5-phosphonopyrrolidine-2-carbonyl}amino)-3-phenylpropionic Acid (22a). Prepared following the synthetic sequence for the preparation of **19a**, starting from D-pyroglutamic acid: 36 mg; $[\alpha]_D$ −47.8 (*c* 0.1, H_2O); ^{1}H NMR (300 MHz, D_2O) δ 7.76 (m, 3H), 7.56 (m, 1H), 7.28−7.07 (m, 4H), 6.93 (m, 1H), 6.85 (m, 1H), 6.71 (m, 1H), 4.31 (m, 2H), 3.70 (m, 1H), 3.57 (m, 1H), 3.49 (m, 1H), 3.00 (m, 1H), 2.60 (t, 1H, J = 0.8 Hz), 2.24 (m, 1H), 1.98 (m, 1H), 1.87 (m, 1H), 1.48 (m, 1H), 1.25 (m, 1H); ^{13}C (100 MHz, D_2O) δ 178.1, 169.7, 165.4, 138.0, 135.4, 131.7, 130.4, 129.4, 129.2, 128.6, 127.3, 126.7, 120.6, 60.8, 58.8, 56.5, 39.7, 38.3, 35.1, 30.1, 27.2; ^{31}P (161.3 MHz, D_2O) δ 9.0; LRMS (FAB, NBA, *m*/*z*) 566.

(2*R*,4*S*,5*R*)-(2*S*)-({4-[2-(1,3-Dioxo-1*H*,3*H*-benzo[*de*]isoquinolin-2-yl)ethyl]-5-phosphonopyrrolidine-2-carbonyl}amino)-3-phenylpropionic Acid (22b). Prepared following the synthetic sequence for the preparation of **19b**, starting from D-pyroglutamic acid: 31 mg; $[\alpha]_D$ +14.3 (*c* 0.1, H_2O); ^{1}H NMR (300 MHz, D_2O) δ 7.82 (m, 4H), 7.47−7.01 (m, 7H), 4.59 (m, 1H), 4.31 (m, 1H), 3.69 (m, 1H), 3.60 (m, 1H), 3.24 (m, 1H), 3.05 (m, 1H), 2.84 (m, 1H), 2.06 (m, 3H), 1.75 (m, 1H), 1.35 (m, 1H); ^{13}C (100 MHz, D_2O) δ 178.1, 169.3, 164.8, 138.1, 135.1, 131.3, 130.6, 129.5, 128.9, 127.1, 126.3, 121.2, 120.3, 63.6, 61.9, 58.9, 56.5, 39.4, 38.2, 36.6, 30.5; ^{31}P (161.3 MHz, D_2O) δ 10.3; LRMS (FAB, NBA, *m*/*z*) 566.

(2*S*,4*R*,5*R*)-5-(Dimethoxyphosphoryl)-4-isobutylpyrrolidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester (23a) and (2*S*,4*R*,5*S*)-5-(Dimethoxyphosphoryl)-4-isobutylpyrrolidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester (23b). The lactam **10a** (406 mg, 1.36 mmol) was dissolved in EtOH (15 mL), and a catalytic amount of $Pd(OH)_2$, 20% over carbon, was added. The reaction was kept under 60 psi of H_2 for 3 h at rt. The suspension was filtered through a pad of Celite and concentrated in vacuo to afford the desired intermediate in quantitative yield. Following the procedure for the preparation of **11a** and **11b** gave the two phosphonates **23a** and **23b** (1.2:1 in favor of **23b**). For **23a**: 172 mg (32%, three steps); $[\alpha]_D$ −22.6 (*c* 0.9, $CHCl_3$); IR (neat/NaCl) 2957, 1749, 1712, 1367 cm^{-1}; for a mixture of two rotamers ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.35 (dd, 1H, J = 2.6, 7.8 Hz), 4.24 (m, 1H), 3.71−3.68 (m, 6H), 3.67 (s, 3H), 2.64 (m, 1H), 2.46 (m, 2H), 1.84 (dd, 1H, J = 5.8, 12.6 Hz), 1.54 (m, 2H), 1.42 (s, 3H), 1.35 (s, 6H), 0.86 (d, 3H, J = 6.1 Hz), 0.81 (d, 3H, J = 5.8 Hz); ^{13}C (100 MHz, $CDCl_3$) δ 173.4, 153.0, 80.7 and 80.5, 58.8 and 58.5, 56.6 (d), 53.0, 52.1, 51.9, 37.6, 37.1, 35.1 and 33.9,

28.0 and 27.8, 26.4, 22.8, 22.2; ^{31}P (161.3 MHz, $CDCl_3$) δ 25.7 (minor rotamer), 25.4 (major rotamer); LRMS (FAB, NBA, *m*/*z*) 394, 338, 307; HRMS for $C_{17}H_{32}NO_7P$ (MH^+) calcd 394.199466, obsd 394.199019. For **23b**: 204 mg (37%, three steps); $[\alpha]_D$ +12.7 (*c* 0.8, $CHCl_3$); IR (neat/NaCl) 2958,1761, 1706, 1368 cm^{-1}; for a mixture of two rotamers ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.35 (m, 1H), 4.21 (m, 1H), 3.80 (d, 3H, J = 10.4 Hz), 3.70 (d, 3H, J = 9.8 Hz), 3.66 (s, 3H), 2.52 (m, 2H), 1.96 (m, 1H), 1.52 (m, 1H), 1.42 (s, 3H), 1.36 (s, 6H), 1.18 (m, 1H), 1.10 (m, 1H), 0.85 (d, 3H, J = 3.3 Hz), 0.83 (d, 3H, J = 3.3 Hz); ^{13}C (100 MHz, $CDCl_3$) δ 172.4, 153.9, 80.8, 59.1 (d), 58.7, 53.9, 52.3, 51.8, 42.7 (d), 38.0 and 37.2, 34.4 and 33.5, 28.0, 25.7, 22.3, 22.1; ^{31}P (161.3 MHz, $CDCl_3$) δ 25.7; LRMS (FAB, NBA, *m*/*z*) 394, 338; HRMS for $C_{17}H_{32}NO_7P$ (MH^+) calcd 394.199466, obsd 394.199255.

(2*S*,4*R*,5*R*)-(2*S*)-{[4-(3-Naphthalen-1-ylallyl)-5-phosphonopyrrolidine-2-carbonyl]amino}-3-phenylpropionic Acid (24a). Following the preparation of **16a** and the preparation of **19a** gave compound **24a**, 16 mg (41%, four steps): mp 102 °C; $[\alpha]_D$ −10.6 (*c* 0.9, MeOH); IR (KBr) 3360, 2926, 1676 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 8.15 (m, 1H), 7.83 (d, 1H, J = 7.7 Hz), 7.75 (d, 1H, J = 8.5 Hz), 7.59 (d, 1H, J = 6.2 Hz), 7.48 (m, 3H), 7.24 (m, 5H), 7.10 (m, 1H), 6.23 (m, 1H), 4.68 (dd, 1H, J = 4.6, 9.8 Hz), 4.45 (m, 1H), 3.88 (d, 1H, J = 10.8 Hz), 3.65 (d, 1H, J = 10.4 Hz), 3.31 (t, 1H, J = 1.6 Hz), 3.26 (m, 1H), 2.95 (dd, 1H, J = 10.0, 14.0 Hz), 2.58 (m, 1H), 2.33 (m, 2H); ^{13}C (100 MHz, CD_3OD) δ 172.5, 168.2, 137.9, 136.1, 134.7, 132.0, 129.9, 129.1, 128.5, 126.8, 125.9, 125.7, 123.8, 123.7, 123.6, 59.2, 54.8, 41.1, 36.9, 35.0, 32.8, 29.7; ^{31}P (161.3 MHz, CD_3OD) δ 12.9; LRMS (FAB, NBA, *m*/*z*) 509, 427, 421.

(2*S*,4*R*,5*S*)-(2*S*)-{[4-(3-Naphthalen-1-ylallyl)-5-phosphonopyrrolidine-2-carbonyl]amino}-3-phenylpropionic Acid (24b). Following the preparation of **16a** and the preparation of **19a** gave compound **24b**, 16 mg (40%, four steps): mp 97° C; $[\alpha]_D$ −72.7 (*c* 0.8, MeOH); IR (neat/NaCl) 3360, 2925, 1678 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 8.15 (d, 1H, J = 7.7 Hz), 7.85 (d, 1H, J = 7.4 Hz), 7.77 (d, 1H, J = 8.5 Hz), 7.62 (m, 1H), 7.49 (m, 3H), 7.22 (m, 5H), 7.10 (m, 1H), 6.24 (m, 1H), 4.69 (t, 1H, J = 4.3 Hz), 4.28 (m, 1H), 3.67 (m, 2H), 3.29 (m, 1H), 3.01 (m, 2H), 2.38 (m, 3H); ^{13}C (100 MHz, CD_3OD) δ 173.4, 170.8, 138.3, 136.2, 135.1, 132.4, 131.0, 129.5, 128.7, 127.8, 127.0, 126.7, 126.6, 124.8, 124.7, 60.4, 59.6, 55.7, 37.7, 30.7, 30.1, 24.0; ^{31}P (161.3 MHz, CD_3OD) δ 11.6; LRMS (FAB, NBA, *m*/*z*) 522, 508, 505; HRMS calcd for $C_{27}H_{28}N_2O_6P$ 507.168500, obsd 507.168697.

(2*S*,4*R*,5*R*)-(2*S*)-[(4-Isobutyl-5-phosphonopyrrolidine-2-carbonyl)amino]-3-phenylpropionic Acid (25a). Following the preparation of **16a** and the preparation of **19a** gave compound **25a**, 19 mg (66%, four steps): $[\alpha]_D$ −63.0 (*c* 0.3, H_2O); IR (KBr) 3420, 2959, 1683, 1455 cm^{-1}; ^{1}H NMR (300 MHz, D_2O) δ 7.34−7.16 (m, 5H), 4.55 (d, 1H, J = 1.89 Hz), 4.45 (d, 1H, J = 9.4 Hz), 4.22 (t, 1H, J = 8.7 Hz), 3.22 (dd, 1H, J = 4.4, 14.2 Hz), 3.07 (dd, 1H, J = 4.4, 14.1 Hz), 1.82 (m, 1H), 1.63 (m, 1H), 1.45−1.38 (m, 4H), 0.81 (d, 3H, J = 6.2 Hz), 0.73 (d, 3H, J = 6.2 Hz); ^{13}C (100 MHz, D_2O) δ 178.5, 172.5, 135.3, 130.6, 129.0, 127.9, 61.1 (d), 56.9, 56.7, 38.9, 38.8, 36.5, 32.7, 26.5, 21.4, 24.0; ^{31}P (161.3 MHz, D_2O) δ 14.4; LRMS (FAB, NBA, *m*/*z*) 395, 299.

(2*S*,4*R*,5*S*)-(2*S*)-[(4-Isobutyl-5-phosphonopyrrolidine-2-carbonyl)amino]-3-phenylpropionic Acid (25b). Following the preparation of **16a** and the preparation of **19a** gave compound **25b**, 26 mg (70%, four steps): $[\alpha]_D$ −56.0 (*c* 0.3, H_2O); IR (KBr) 3437, 2957, 1618, 1385 cm^{-1}; ^{1}H NMR (300 MHz, D_2O) δ 7.31 (m, 2H), 7.23 (m, 3H), 4.42 (dd, 1H, J = 5.0, 8.8 Hz), 4.14 (dd, 1H, J = 5.6, 9.5 Hz), 3.17 (dd, 1H, J = 5.05, 13.9 Hz), 2.99 (t, 1H, J = 3.2 Hz), 2.92 (dd, 1H, J = 8.8, 13.9 Hz), 2.28 (m, 1H), 2.20 (m, 1H), 1.99 (m, 1H), 1.52 (m, 2H), 1.14 (m,1H), 0.84 (d, 3H, J = 6.2 Hz), 0.81 (d, 3H, J = 6.0 Hz); ^{13}C (100 MHz, D_2O) δ 178.3, 170.2, 138.5, 130.0, 129.4, 127.6, 63.9 (d), 59.5, 57.8, 42.3, 38.9, 38.2, 36.7, 26.7, 23.9, 21.5; ^{31}P (161.3 MHz, D_2O) δ 11.0; LRMS (FAB, NBA, *m*/*z*) 421, 307; HRMS for $C_{18}H_{26}N_2O_6P$ (MH^+) calcd 421.150445, obsd 421.152400.

(2*S*,4*R*,5*S*)-5-(Dimethoxyphosphoryl)-4-[3-(1,3-dioxo-1*H*,3*H*-benzo[*de*]isoquinolin-2-yl)propyl]pyrrolidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester (26). The olefin **11b** (100 mg, 0.26 mmol) was placed in a flame-dried flask and dissolved in dry THF (4 mL). BH_3·THF (278 μL, 0.28 mmol, 1 M in THF) was slowly added at 0 °C, and the resulting mixture was stirred for 1.5 h. NaOH (344 μL, 0.34 mmol, 1 M in H_2O) was added dropwise, followed by H_2O_2 30% v/v (300 μL, 2.65 mmol). The solution was stirred for 10 min before addition of brine. The aqueous phase was extracted with Et_2O. The combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo to afford the desired alcohol. Following the procedure for the preparation of **15a** gave compound **26** (45 mg, 30%, three steps): $[\alpha]_D$ +5.8 (*c* 1.1, $CHCl_3$); IR (neat/NaCl) 2956, 1759, 1702, 1662 cm^{-1}; for a mixture of two rotamers ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60 (d, 2H, J = 7.2 Hz), 8.22 (d, 2H, J = 8.2 Hz), 7.76 (t, 2H, J = 7.6 Hz), 4.40−4.22 (m, 1H), 4.18 (m, 2H), 4.10−3.95 (m, 1H), 3.86 (d, 3H, J = 10.4 Hz), 3.76 (d, 3H, J = 10.6 Hz), 3.73 (s, 3H), 2.50 (m, 2H), 2.08 (t, 1H, J = 9.7 Hz), 1.80 (m, 3H), 1.55 (m, 1H), 1.42 (s, 9H); ^{13}C (100 MHz, $CDCl_3$) δ 172.3, 164.2, 156.8, 134.0, 131.6, 128.2, 126.9, 122.5, 81.0, 58.7, 58.4, 54.0 (d), 52.5, 52.0, 39.9, 39.8, 33.9, 32.4, 28.1, 26.1; ^{31}P (161.3 MHz, $CDCl_3$) δ 26.3 (major rotamer), 26.2 (minor rotamer); LRMS (FAB, NBA, *m*/*z*) 575; HRMS for $C_{28}H_{35}N_2O_9P$ calcd 575.215845, obsd 575.215957.

(2*S*,4*R*,5*S*)-(2*S*)-({4-[3-(1,3-Dioxo-1*H*,3*H*-benzo[*de*]isoquinolin-2-yl)propyl]-5-phosphonopyrrolidine-2-carbonyl}amino)-3-(1*H*-indol-3-yl)propionic Acid (27). Following the preparations of **16a** and of **19a** gave compound **27**, 11 mg (53%, four steps): $[\alpha]_D$ +2.6 (*c* 0.6, H_2O); IR (KBr) 3402, 2955, 1754, 1701, 1663 cm^{-1}; ^{1}H NMR (300 MHz, D_2O) δ 7.82 (m, 2H), 7.34 (m, 2H), 6.99 (m, 2H), 6.79 (m, 2H), 6.66 (m, 2H), 6.50 (m, 1H), 4.36 (m, 1H), 3.79 (m, 1H), 3.50 (m, 2H), 3.19 (m, 1H), 3.08 (m, 1H), 2.76 (m, 1H), 2.06 (m, 1H), 1.75 (m, 2H), 1.25 (m, 2H), 1.16 (m, 2H); ^{13}C (100 MHz, D_2O) δ 176.6, 172.2, 163.2, 134.0, 133.2, 130.6, 129.5, 127.8, 125.3, 125.1, 122.3, 119.5, 118.5, 117.1, 116.5, 109.4, 108.5, 57.5, 53.9, 38.7, 37.9, 34.3, 28.2, 25.4, 23.8, 16.0; ^{31}P (161.3 MHz, D_2O) δ 14.3.

(2*S*,4*S*)-4-Allyl-5-(dimethoxyphosphoryl)pyrrolidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester (28). Following the preparation of **11** gave compound **28**, 789 mg (68%, three steps, inseparable mixture): IR (neat/NaCl) 3479, 2958, 1761, 1706, 1381 cm^{-1}; for a mixture of two rotamers ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.76 (m, 1H), 5.08 (d, 1H, J = 17.3 Hz), 4.98 (d, 1H, J = 9.9 Hz), 4.29 (m, 1H), 4.18 (m, 1H), 3.87 (d, 3H, J = 10.3 Hz), 3.72 (d, 3H, J = 10.7 Hz), 3.70 (s, 3H), 2.51 (m, 1H), 2.32−2.28 (m, 4H), 1.44 (s, 3H), 1.39 (s, 6H); ^{13}C (100 MHz, $CDCl_3$) δ 172.0, 153.6, 136.1, 116.4, 80.8, 59.4, 57.9, 55.8, 54.0, 51.9, 41.2, 34.4, 33.2, 28.2 and 28.0; ^{31}P (161.3 MHz, $CDCl_3$) δ 25.5; LRMS (FAB, NBA, *m*/*z*) 378, 322; HRMS for $C_{16}H_{28}NO_7P$ (MH^+) calcd 378.168166, obsd 378.169900.

(2*S*,4*S*)-5-(Dimethoxyphosphoryl)-4-[2-(1,3-dioxo-1*H*,3*H*-benzo[*de*]isoquinolin-2-yl)ethyl]pyrrolidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester (29). Following the preparation of **14a** and of **15a** gave compound **29** as a white solid, 355 mg (32%, four steps): IR (neat/NaCl) 3470, 2957, 1757, 1699, 1660, 1366, 1327 cm^{-1}; for a mixture of two rotamers ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55 (m, 2H), 8.19 (m, 2H), 7.70 (m, 2H), 4.35 (m, 1H), 4.25 (m, 2H), 4.08 (m, 1H), 3.88 (d, 3H, J = 10.2 Hz), 3.74 (d, 3H, J = 10.6 Hz), 3.71 (s, 3H), 2.58 (m, 1H), 2.31−2.18 (m, 3H), 2.01 (m, 1H), 1.46 (s, 3H), 1.38 (s, 6H); ^{13}C (100 MHz, $CDCl_3$) δ 172.0, 164.1, 153.5, 133.9, 131.4, 131.2, 128.0, 126.8, 122.4, 80.7 and 80.6, 59.4, 59.2 (d), 55.9, 54.1, 52.1, 38.9, 38.2, 34.6, 33.6, 28.0 and 27.6; ^{31}P (161.3 MHz, $CDCl_3$) δ 24.6 (minor rotamer), 24.4 (major rotamer); LRMS (FAB, NBA, *m*/*z*) 561, 505, 351; HRMS for $C_{27}H_{33}N_2O_9P$ (MH^+) calcd 561.200195, obsd 561.198600.

(2*R*,3*S*,5*S*)-5-[(1*S*)-*tert*-Butoxycarbonyl-2-phenylethylcarbamoyl]-2-(dimethoxyphosphoryl)-3-[2-(1,3-dioxo-1*H*,3*H*-benzo[*de*]-

isoquinolin-2-yl)ethyl]pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (30). Following the preparation of **16a** gave compound **30**, 131 mg (65%, two steps): $[\alpha]_D$ −2.9 (*c* 1.1, $CHCl_3$); mp 82 °C; IR (neat/NaCl) 2978, 1703, 1664, 1364 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.54 (d, 2H, J = 7.2 Hz), 8.18 (d, 2H, J = 7.6 Hz), 7.84 (bs, 1H), 7.72 (t, 2H, J = 7.8 Hz), 7.25 (m, 5H), 4.71 (dd, 1H, J = 7.52 Hz), 4.46 (m, 1H), 4.23 (m, 2H), 4.08 (m, 1H), 3.82−3.79 (m, 6H), 3.02 (d, 2H, J = 7.3 Hz), 2.46−2.35 (m, 2H), 2.25 (m, 1H), 2.11 (m, 1H), 1.95 (m, 1H), 1.38 (s, 9H), 1.28 (s, 9H); ^{13}C (100 MHz, $CDCl_3$) δ 171.9, 170.4, 164.1, 154.4, 136.7, 133.9, 131.5, 131.2, 129.6, 128.2, 128.0, 126.8, 126.5, 122.4, 81.4, 81.2, 63.5, 54.0, 53.7, 52.5, 52.4, 39.3, 39.0, 38.8, 35.9, 28.2, 27.9, 27.1; ^{31}P (161.3 MHz, $CDCl_3$) δ 25.7; LRMS (FAB, NBA, *m*/*z*) 750, 540, 484; HRMS for $C_{39}H_{48}O_{10}N_3P$ (MH^+) calcd 750.315559, obsd 750.318900.

(2*S*,4*S*,5*R*)-(2*S*)-({4-[2-(1,3-Dioxo-1*H*,3*H*-benzo[*de*]isoquinolin-2-yl)ethyl]-5-phosphonopyrrolidine-2-carbonyl}amino)-3-phenylpropionic Acid (31). Following the preparation of **19a** gave compound **31**, 13 mg (38%, two steps): $[\alpha]_D$ −8.2 (*c* 0.4, H_2O); IR (KBr) 3407, 1699, 1658, 1591, 1388 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 8.10 (d, 2H, J = 8.1 Hz), 8.08 (d, 2H, J = 6.9 Hz), 7.55 (t, 2H, J = 7.7 Hz), 7.34−7.29 (m, 2H), 7.10 (m, 2H), 6.94 (t, 1H, J = 6.8 Hz), 4.70 (m, 1H), 4.38 (dd, 1H, J = 5.0, 7.9 Hz), 4.08 (dd, 1H, J = 5.9, 9.7 Hz), 3.77 (t, 2H, J = 7.2 Hz), 3.44 (dd, 1H, J = 7.2, 9.9 Hz), 3.08 (dd, 1H, J = 5.1, 14.0 Hz), 2.90 (dd, 1H, J = 8.1, 14.0 Hz), 2.44 (m, 1H), 2.36 (m, 1H), 2.16−2.08 (m, 2H); ^{13}C (100 MHz, D_2O) δ 178.3, 172.2, 165.8, 138.5, 135.8, 132.1, 131.5, 130.0, 129.2, 127.8, 127.4, 121.2, 62.6, 60.8, 60.0, 40.0, 38.9, 38.4, 35.2, 28.3; ^{31}P (161.3 MHz, D_2O) δ 12.3; LRMS (FAB, NBA, *m*/*z*) 588, 566, 484.

(2*R*,4*R*,5*S*)-(2*S*)-({4-[2-(1,3-Dioxo-1*H*,3*H*-benzo[*de*]isoquinolin-2-yl)ethyl]-5-phosphonopyrrolidine-2-carbonyl}amino)-3-phenylpropionic Acid (32). Prepared following the synthetic sequence for the preparation of **31**, starting from D-pyroglutamic acid: 11 mg; $[\alpha]_D$ +28.6 (*c* 0.05, H_2O); ^1H NMR (300 MHz, D_2O) δ 7.87 (m, 4H), 7.37 (m, 2H), 7.25−7.07 (m, 5H), 4.42 (dd, 1H, J = 5.5, 8.4 Hz), 4.12−4.06 (m, 1H), 3.52 (m, 2H), 3.25 (dd, 1H, J = 6.0, 11.1 Hz), 3.05 (dd, 1H, J = 5.0, 13.7 Hz), 2.79 (dd, 1H, J = 8.5, 13.2 Hz), 2.25 (m, 2H), 2.04−1.95 (m, 1H), 1.65−1.59 (m, 1H), 1.33−1.25 (m, 1H); ^{13}C (100 MHz, D_2O) δ 178.2, 169.7, 165.5, 137.9, 135.3, 131.6, 131.0, 129.6, 128.9, 127.2, 127.0, 121.2, 120.8, 62.7, 59.5, 56.9, 39.2, 38.3, 38.1, 35.1, 27.5; ^{31}P (161.3 MHz, D_2O) δ 9.2; LRMS (FAB, NBA, *m*/*z*) 566.

(2*R*,3*R*)-2-(*tert*-Butyldiphenylsilanyloxymethyl)-3-isobutyl-5-oxopyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (34). A catalytic amount of CuI (232 mg, 1.22 mmol), previously flame-dried under vacuum until bright yellow, was added in one portion to a solution of Me_2CHCH_2MgBr (8.52 mL, 17.0 mmol, 2 M in Et_2O) in dry Et_2O (170 mL) cooled at −20 °C. After 15 min, the solution turned black, and the unsaturated lactam **33** (5.5 g, 12.2 mmol), dissolved in dry Et_2O (120 mL), was added dropwise via a cannula. The mixture was stirred at −20 °C until completion (monitored by TLC ca. 3 h). After addition of saturated NH_4Cl and a 0.5 M solution of NH_4OH, the solution was allowed to reach rt. The aqueous layer was extracted with Et_2O, and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting oil was purified by flash chromatography (hexanes/EtOAc, 8:2) to give **34** (5.4 g, 87%): $[\alpha]_D$ +19.9 (*c* 3.7, $CHCl_3$); IR (neat/NaCl) 3410, 3073, 3050, 2958, 2933, 2900, 2860, 1789, 1753, 1713, 1590, 1568, 1472, 1428, 1392, 1368, 1311, 1257, 1207, 1155, 1113 cm^{-1}; ^1H NMR (300 MHz, $CHCl_3$) δ 7.59 (m, 4H), 7.33−7.25 (m, 6H), 3.88−3.81 (m, 2H), 3.69 (d, 1H, J = 9.2 Hz), 2.86 (dd, 1H, J = 8.8, 17.6 Hz), 2.37 (m, 1H), 2.09 (d, 1H, J = 17.6 Hz), 1.60−1.53 (m, 1H), 1.39 (s, 9H), 1.33−1.21 (m, 2H), 1.01 (s, 9H), 0.85 (d, 6H, J = 6.4 Hz); ^{13}C (100 MHz, $CDCl_3$) δ 175.0, 150.4, 135.9, 133.3, 130.3, 128.3, 83.2, 65.0, 64.8, 44.9, 39.0, 31.4, 28.4, 27.2, 25.7, 23.2, 22.8, 19.6; LRMS (FAB, NBA, *m*/*z*) 410.2.

(3*R*,4*R*,5*R*)-3-Allyl-5-(*tert*-butyldiphenylsilanyloxymethyl)-4-isobutyl-2-oxopyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (35a) and (3*S*,4*R*,5*R*)-3-Allyl-5-(*tert*-butyldiphenylsilanyloxymethyl)-4-isobutyl-2-oxopyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (35b). Following the preparation of **7a** and **7b** gave compounds **35a** and **35b** (4:1 in favor of **35a**). For **35a**: 2.1 g (37%); $[\alpha]_D$ +14.9 (*c* 1.5, $CHCl_3$); IR (neat/NaCl) 3638, 3470, 3074, 3052, 3002, 2959, 2933, 2893, 2860, 1959, 1887, 1822, 1780, 1722, 1591, 1568, 1473, 1429, 1393, 1364, 1305, 1259, 1189, 1153, 1119, 1030 cm^{-1}; ^1H NMR (300 MHz, $CHCl_3$) δ 7.66−7.61 (m, 4H), 7.46−7.35 (m, 6H), 5.82−5.73 (m, 1H), 5.11−5.04 (m, 2H), 3.83−3.69 (m, 3H), 2.60−2.54 (m, 1H), 2.40−2.22 (m, 3H), 1.65−1.56 (m, 1H), 1.42 (s, 9H), 1.38−1.29 (m, 2H), 1.07 (s, 9H), 0.94 (d, 3H, J = 6.3 Hz), 0.89 (d, 3H, J = 6.3 Hz); ^{13}C (100 MHz, $CDCl_3$) δ 175.8, 149.9, 135.5, 132.9, 132.7, 129.7, 127.7, 117.3, 82.7, 64.1, 63.7, 49.6, 46.3, 36.1, 33.8, 27.8, 26.7, 25.1, 22.6, 19.1; LRMS (FAB, NBA, *m*/*z*) 450; HRMS for $C_{33}H_{47}NO_4Si$ (MNa^+) calcd 572.317208, obsd 572.318400. For **35b**: 0.5 g (9%); $[\alpha]_D$ +31.6 (*c* 0.6, $CHCl_3$); IR (neat/NaCl) 3448, 3073, 2958, 1789, 1755, 1714, 1642, 1590, 1560, 1541, 1508, 1472, 1429, 1392, 1369, 1312, 1258, 1157, 1113 cm^{-1}; ^1H NMR (300 MHz, $CHCl_3$) δ 7.69−7.62 (m, 4H), 7.50−7.37 (m, 6H), 5.83 (dddd, 1H, J = 5.8, 7.4, 10.2, 17.4 Hz), 5.17−5.09 (m, 2H), 3.94 (dd, 1H, J = 3.2, 5.7 Hz), 3.86−3.74 (m, 2H), 3.06 (ddd, 1H, J = 4.6, 7.9, 10.8 Hz), 2.62 (ddd, 1H, J = 5.1, 5.1, 15.8 Hz), 2.49 (ddd, 1H, J = 3.8, 8.0, 11.5 Hz), 2.12 (ddd, 1H, J = 7.4, 10.8, 15.6 Hz), 1.72−1.62 (m, 1H), 1.48 (s, 9H), 1.17 (ddd, 2H, J = 3.7, 10.8, 10.8 Hz), 1.07 (s, 9H), 0.96 (d, 3H, J = 6.6 Hz), 0.89 (d, 3H, J = 6.5 Hz); ^{13}C (100 MHz, $CDCl_3$) δ 175.8, 150.8, 136.3, 135.9, 133.2, 130.3, 128.3, 116.6, 83.1, 64.1, 61.6, 45.6, 36.9, 34.9, 29.6, 27.2, 25.6, 24.7, 21.5, 19.6; LRMS (FAB, NBA, *m*/*z*) 450; HRMS for $C_{33}H_{47}NO_4Si$ (MNa^+) calcd 572.317208, obsd 572.315500.

(2*R*,3*R*,4*R*)-4-Allyl-3-isobutyl-5-oxopyrrolidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester (36). Glacial acetic acid (833 μL, 14.6 mmol) and TBAF (4.73 mL, 4.73 mmol, 1 M in THF) were added to a solution of lactam **35a** (2.0 g, 3.64 mmol) in dry THF (72 mL) at rt. The solution was stirred until completion (monitored by TLC, ca. 48 h). An aqueous saturated solution of $NaHCO_3$ was added, and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude alcohol was dissolved in acetone (72 mL), and Jones' reagent was added dropwise until an orange-red color persisted. The solution was stirred at rt until completion (monitored by TLC). A solution of brine was added, and the aqueous layer was extracted with Et_2O and then with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude acid was suspended in dry Et_2O (72 mL) at 0 °C. A freshly prepared CH_2N_2 etheral solution was added dropwise until a yellow color persisted. After 1 h, the solvent was removed in vacuo at rt. Purification by flash chromatography (hexanes/EtOAc, 8:2) gave the desired methyl ester **36** (0.8 g, 65%, three steps): $[\alpha]_D$ −30.7 (*c* 0.8, $CHCl_3$); ^1H NMR (300 MHz, $CHCl_3$) δ 5.73 (m, 1H), 5.10−5.03 (m, 2H), 4.17 (d, 1H, J = 4.3 Hz), 3.77 (s, 3H), 2.55−2.49 (m, 1H), 2.39−2.27 (m, 2H), 2.14−2.07 (m, 1H), 1.76−1.69 (m, 1H), 1.49 (s, 9H), 1.49−1.45 (m, 1H), 1.38−1.31 (m, 1H), 0.93 (d, 3H, J = 6.6 Hz), 0.87 (d, 3H, J = 6.6 Hz); ^{13}C (100 MHz, $CDCl_3$) δ 175.0, 172.6, 149.8, 135.1, 118.4, 84.1, 63.9, 52.8, 49.8, 45.6, 36.8, 35.6, 28.3, 25.5, 23.2, 22.5; LRMS (FAB, NBA, *m*/*z*) 240.1; HRMS for $C_{18}H_{29}NO_5$ (MNa^+) calcd 362.194343, obsd 362.194900.

(2*R*,3*R*,4*R*,5*S*)-4-Allyl-5-(dimethoxyphosphoryl)-3-isobutylpyrrolidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester (37a) and (2*R*,3*R*,4*R*,5*R*)-4-Allyl-5-(dimethoxyphosphoryl)-3-isobutylpyrrolidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester (37b). Following the preparation of **11a** and **11b** gave compounds **37a** and **37b**; (2:1 in favor of **37b**). For **37a**: 262 mg (29%, three steps); $[\alpha]_D$ +36.9 (*c* 2.0, $CHCl_3$); IR (neat/NaCl) 3486, 3078, 2956, 1752, 1706, 1641, 1456, 1392, 1254, 1177 cm^{-1}; for a mixture of two rotamers ^1H NMR (300 MHz, $CHCl_3$) δ 5.60−

5.51 (m, 1H), 4.94−4.88 (m, 2H), 3.94 (m, 1H), 3.84 (d, 1H, J = 3.7 Hz), 3.64−3.59 (m, 9H), 2.34−2.11 (m, 3H), 1.99 (m, 1H), 1.53−1.37 (m, 2H), 1.25 (s, 10H), 0.72 (m, 6H); ^{13}C (100 MHz, $CDCl_3$) δ 173.7 and 173.0, 153.7, 135.9, 118.0, 81.1 and 81.0, 66.4, 60.6, 58.5, 53.5 (d), 53.2 (d), 52.2, 46.8, 45.0 (d), 40.4, 28.3, 25.9, 23.1, 22.3; ^{31}P (161.3 MHz, $CDCl_3$) δ 28.8; LRMS (FAB, NBA, *m*/*z*) 434; HRMS for $C_{20}H_{36}NO_7P$ (MH^+) calcd 434.230766, obsd 434.232700. For **37b**: 544 mg (58%, three steps); $[\alpha]_D$ +36.5 (*c* 1.2, $CHCl_3$); IR (neat/NaCl) 3491, 2957, 2871, 1758, 1707, 1641, 1455, 1387, 1367, 1250, 1175, 1147, 1123 cm^{-1}; for a mixture of two rotamers ^{1}H NMR (300 MHz, $CHCl_3$) δ 5.77−5.66 (m, 1H), 4.94−4.82 (m, 2H), 4.24−4.09 (m, 1H), 3.77−3.63 (m, 4H), 3.57−3.54 (m, 6H), 2.45−2.35 (m, 2H), 2.17−2.12 (m, 1H), 1.92−1.77 (m, 1H), 1.61−1.57 (m, 1H), 1.29−1.16 (s, 11H), 0.81 (d, 3H, J = 6.5 Hz), 0.53 (d, 3H, J = 6.5 Hz); ^{13}C (100 MHz, $CDCl_3$) δ 172.9, 153.6, 137.0, 116.2, 81.1, 66.5, 58.0, 55.9, 54.1, 52.0, 48.4, 45.0, 41.7, 31.8, 28.3, 26.3, 23.9, 22.3; ^{31}P (161.3 MHz, $CDCl_3$) δ 24.6; LRMS (FAB, NBA, *m*/*z*) 434; HRMS for $C_{20}H_{36}NO_7P$ (MH^+) calcd 434.230766, obsd 434.232200.

(2*R*,3*R*,4*R*,5*R*)-5-(Dimethoxyphosphoryl)-4-[2-(1,3-dioxo-1*H*,3*H*-benzo[*de*]isoquinolin-2-yl)ethyl]-3-isobutylpyrrolidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester (38). Following the preparation of **14a** and the preparation of **15a** gave compound **38**, 100 mg (27%, four steps): $[\alpha]_D$ +18.6 (*c* 1.1, $CHCl_3$); IR (neat/NaCl) 3455, 2957, 2361, 1756, 1703, 1663, 1627, 1591, 1439, 1386, 1248, 1175 cm^{-1}; for a mixture of two rotamers ^{1}H NMR (300 MHz, $CHCl_3$) δ 8.54 (d, 2H, J = 7.2 Hz), 8.16 (m, 2H), 7.70 (m, 2H), 4.63−4.58 (m, 1H), 4.41−4.17 (m, 2H), 3.86 (m, 7H), 3.69 (s, 3H), 2.71−2.53 (m, 1H), 2.37−2.15 (m, 1H), 2.08−1.86 (m, 2H), 1.78−1.12 (m, 1H), 1.48 (s, 3H), 1.40 (s, 6H), 1.40−1.18 (m, 2H), 0.85−0.67 (m, 6H); ^{13}C (100 MHz, $CDCl_3$) δ 172.6 and 172.2, 163.9, 156.3 and 153.1, 133.7, 131.4, 131.0, 127.9, 126.7, 122.4, 80.7, 66.0 and 63.5, 57.5, 55.9, 53.9, 51.9, 51.7, 46.3 and 46.1, 44.6 and 44.0, 41.6 and 41.0, 39.4, 28.1 and 28.0, 26.0 and 25.8, 23.5, 21.9; ^{31}P (161.3 MHz, $CDCl_3$) δ 24.4 (major rotamer), 24.1 (minor rotamer); LRMS (FAB, NBA, *m*/*z*) 617; HRMS for $C_{31}H_{41}N_2O_9P$ (MH^+) calcd 617.262795, obsd 617.260922.

(2*R*,3*R*,4*R*,5*R*)-2-[(1*S*)-*tert*-Butoxycarbonyl-2-phenylethylcarbamoyl]-5-(dimethoxyphosphoryl)-4-[2-(1,3-dioxo-1*H*,3*H*-benzo[*de*]isoquinolin-2-yl)ethyl]-3-isobutylpyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (39). Following the preparation of **16a** gave compound **39**, 63 mg (50%, two steps): $[\alpha]_D$ +36.1 (*c* 1.4, $CHCl_3$); IR (neat/NaCl) 3265, 2957, 1737, 1703, 1664, 1627, 1591, 1544, 1498, 1456, 1368, 1236, 1154 cm^{-1}; ^{1}H NMR (300 MHz, $CHCl_3$) δ 8.58 (d, 2H, J = 7.1 Hz), 8.19 (d, 2H, J = 8.1 Hz), 8.13 (bd, 1H), 7.73 (t, 2H, J = 7.5 Hz), 7.23−7.18 (m, 5H), 4.74 (m, 2H), 4.36 (m, 2H), 3.92 (d, 3H, J = 9.3 Hz), 3.74 (m, 1H), 3.67 (d, 3H, J = 10.2 Hz), 3.06−2.99 (m, 2H), 2.54 (m, 1H), 2.21−1.92 (m, 4H), 1.77 (m, 1H), 1.39 (s, 9H), 1.30 (s, 10H), 0.75 (m, 6H); ^{13}C (100 MHz, $CDCl_3$) δ 171.1, 164.6, 154.9, 137.4, 134.3, 132.0, 131.6, 129.8, 128.6, 127.3, 126.9, 123.1, 81.7, 81.6, 71.1, 60.9, 54.3, 53.8, 53.2, 46.5, 41.0, 39.9, 39.0, 28.6, 28.3, 28.2, 27.3, 25.8, 24.2, 22.4; ^{31}P (161.3 MHz, $CDCl_3$) δ 26.5; LRMS (FAB, NBA, *m*/*z*) 807.

(2*R*,3*R*,4*R*,5*R*)-2-[(1*S*)-Methoxycarbonyl-3-phenylpropylcarbamoyl]-5-(dimethoxyphosphoryl)-4-[2-(1,3-dioxo-1*H*,3*H*-benzo[*de*]isoquinolin-2-yl)ethyl]-3-isobutylpyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (40). Following the preparation of **16a** gave compound **40**, 49 mg (52%, two steps): $[\alpha]_D$ +26.9 (*c* 1.3, $CHCl_3$); IR (neat/NaCl) 3267, 2956, 1747, 1702, 1663, 1627, 1591, 1551, 1498, 1455, 1366, 1236, 1173 cm^{-1}; ^{1}H NMR (300 MHz, $CHCl_3$) δ 8.60 (d, 2H, J = 7.3 Hz), 8.58 (bd, 1H), 8.22 (d, 2H, J = 8.1 Hz), 7.76 (t, 2H, J = 7.8 Hz), 7.29−7.14 (m, 5H), 4.77 (m, 1H), 4.57 (ddd, 1H, J = 4.9, 8.4, 8.4 Hz), 4.39 (m, 1H), 4.31 (m, 1H), 3.96 (d, 3H, J = 10.6 Hz), 3.85 (d, 3H, J = 10.5 Hz), 3.84 (m, 1H), 3.65 (s, 3H), 2.71−2.59 (m, 3H), 2.16−1.98 (m, 5H), 1.89−1.78 (m, 1H), 1.43 (bs, 9H), 1.32 (t, 2H, J = 6.8 Hz), 0.78 (m, 6H); ^{13}C (100 MHz, $CDCl_3$) δ 172.9, 164.7, 154.8, 141.4, 134.4, 132.0, 131.7, 128.8, 128.6, 127.4, 126.4, 123.0, 81.5, 70.9, 60.8, 54.5, 53.2, 52.4, 46.6, 42.6, 39.8, 34.6, 32.5, 28.9, 28.6, 27.2, 25.7, 24.4, 22.1; ^{31}P (161.3 MHz, $CDCl_3$) δ 26.9; LRMS (FAB, NBA, *m*/*z*) 777.

(2*R*,3*R*,4*R*,5*R*)-2-[(1*S*)-*tert*-Butoxycarbonyl-2-(1*H*-indol-3-yl)-ethylcarbamoyl]-5-(dimethoxyphosphoryl)-4-[2-(1,3-dioxo-1*H*,3*H*-benzo[*de*]isoquinolin-2-yl)ethyl]-3-isobutylpyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (41). Following the preparation of **16a** gave compound **41**, 35 mg (42%, two steps): $[\alpha]_D$ +34.7 (*c* 1.0, $CHCl_3$); IR (neat/NaCl) 3295, 2957, 1734, 1702, 1662, 1626, 1591, 1537, 1458, 1368, 1236, 1156 cm^{-1}; for a mixture of two rotamers ^{1}H NMR (300 MHz, $CHCl_3$) δ 8.60 (d, 2H, J = 7.2 Hz), 8.21 (d, 2H, J = 8.3 Hz), 7.75 (t, 2H, J = 7.4 Hz), 7.45 (m, 1H), 7.31 (m, 1H), 7.19−7.03 (m, 4H), 4.85 (ddd, 1H, J = 5.5, 5.5, 7.9 Hz), 4.73 (m, 1H), 4.34 (m, 2H), 3.92 (m, 3H), 3.78 (m, 4H), 3.34−3.21 (m, 1H), 3.18 (m, 2H), 2.58 (m, 1H), 2.14 (m, 2H), 1.93 (m, 1H), 1.88−1.77 (m, 1H), 1.58 (m, 1H), 1.39 (s, 9H), 1.25 (s, 9H), 0.98−0.88 (m, 1H), 0.76 (m, 6H); ^{13}C (100 MHz, $CDCl_3$) δ 185.3, 172.5, 171.1, 164.1, 135.9, 133.8, 131.4, 131.1, 128.0, 127.4, 126.8, 122.5, 121.9, 121.7, 119.1, 118.6, 111.1, 110.8, 81.4, 81.2, 70.1, 65.0, 60.2, 53.3, 52.8, 52.6, 45.9, 41.7, 39.3, 28.3, 27.9, 27.6, 26.6, 25.2, 23.7, 21.7; ^{31}P (161.3 MHz, $CDCl_3$) δ 27.4; LRMS (FAB, NBA, *m*/*z*) 846.

(2*R*,3*R*,4*R*,5*R*)-(2*S*)-({4-[2-(1,3-Dioxo-1*H*,3*H*-benzo[*de*]isoquinolin-2-yl)ethyl]-3-isobutyl-5-phosphonopyrrolidine-2-carbonyl}amino)-3-phenylpropionic Acid (42). Following the preparation of **19a** gave compound **42**, 40 mg (82%, two steps): $[\alpha]_D$ +7.1 (*c* 0.2, H_2O); ^{1}H NMR (300 MHz, D_2O) δ 7.72 (d, 2H, J = 6.9 Hz), 7.63 (d, 2H, J = 6.6 Hz), 7.20−7.02 (m, 7H), 4.43 (t, 1H, J = 6.2 Hz), 3.73 (m, 1H), 3.42 (m, 3H), 3.03 (d, 1H, J = 10.1 Hz), 2.89−2.81 (m, 1H), 2.08 (m, 3H), 1.38−1.23 (m, 4H), 0.69 (m, 6H); ^{13}C (100 MHz, D_2O) δ 178.1, 169.8, 164.5, 137.9, 134.9, 131.3, 130.8, 129.4, 129.0, 127.1, 127.0, 126.7, 120.6, 66.1, 61.4, 60.1, 57.0, 47.1, 44.2, 39.3, 37.7, 27.4, 26.0, 22.9, 22.1; ^{31}P (161.3 MHz, D_2O) δ 8.9; LRMS (FAB, NBA, *m*/*z*) 624.

(2*R*,3*R*,4*R*,5*R*)-(2*S*)-({4-[2-(1,3-Dioxo-1*H*,3*H*-benzo[*de*]isoquinolin-2-yl)ethyl]-3-isobutyl-5-phosphonopyrrolidine-2-carbonyl}amino)-4-phenylbutyric Acid (43). Following the preparation of **19a** gave compound **43**, 7 mg (18%, three steps): $[\alpha]_D$ +9.3 (*c* 0.1, H_2O); ^{1}H NMR (300 MHz, $CHCl_3$) δ 7.89 (d, 2H, J = 7.9 Hz), 7.83 (d, 2H, J = 7.0 Hz), 7.36 (t, 1H, J = 7.3 Hz), 7.26 (t, 2H, J = 6.9 Hz), 7.19 (d, 2H, J = 6.3 Hz), 7.12 (d, 2H, J = 7.3 Hz), 4.14 (dd, 1H, J = 4.0, 9.0 Hz), 3.80 (m, 1H), 3.73−3.68 (m, 1H), 3.66−3.61 (m, 1H), 3.49 (dd, 1H, J = 5.5, 12.7 Hz), 2.53−2.38 (m, 2H), 2.28 (m, 2H), 2.18−2.14 (m, 1H), 1.96−1.87 (m, 1H), 1.86−1.81 (m, 1H), 1.78−1.62 (m, 1H), 1.47 (t, 1H, J = 7.6 Hz), 1.40−1.31 (m, 1H), 1.16−1.11 (m, 1H), 0.97 (d, 3H, J = 6.5 Hz), 0.77 (d, 3H, J = 6.7 Hz); ^{13}C (100 MHz, $CDCl_3$) δ 178.8, 165.0, 160.8, 141.9, 135.2, 131.7, 129.1, 128.9, 127.3, 127.2, 126.6, 120.9, 66.2, 61.2, 55.6, 45.3, 44.6, 39.5, 34.4, 32.4, 27.2, 25.9, 22.6, 22.3; ^{31}P (161.3 MHz, $CDCl_3$) δ 8.9; LRMS (FAB, NBA, *m*/*z*) 637.

(2*R*,3*R*,4*R*,5*R*)-(2*S*)-({4-[2-(1,3-Dioxo-1*H*,3*H*-benzo[*de*]isoquinolin-2-yl)ethyl]-3-isobutyl-5-phosphonopyrrolidine-2-carbonyl}amino)-3-(1*H*-indol-3-yl)propionic Acid (44). Following the preparation of **19a** gave compound **43**, 26 mg (86%, two steps): $[\alpha]_D$ +11.1 (*c* 0.1, H_2O); ^{1}H NMR (300 MHz, $CHCl_3$) δ 8.31 (d, 2H, J = 7.4 Hz), 8.27 (d, 2H, J = 8.2 Hz), 7.71 (t, 2H, J = 7.6 Hz), 7.53 (d, 1H, J = 8.0 Hz), 7.19 (s, 1H), 7.10 (d, 1H, J = 8.7 Hz), 6.61 (t, 1H, J = 6.5 Hz), 6.52 (t, 1H, J = 7.3 Hz), 4.56 (dd, 1H, J = 4.1, 9.6 Hz), 3.92 (d, 1H, J = 1.7 Hz), 3.56−3.48 (m, 1H), 3.30 (dd, 1H, J = 4.2, 14.8 Hz), 2.99 (dd, 1H, J = 10.5, 15.2 Hz), 2.28−2.23 (m, 1H), 2.17−2.12 (m, 1H), 1.89−1.83 (m, 1H), 1.58−1.49 (m, 2H), 1.45−1.28 (m, 2H), 1.25 (d, 2H, J = 6.9 Hz), 0.81 (d, 3H, J = 6.3 Hz), 0.71 (d, 3H, J = 6.4 Hz); ^{13}C (100 MHz, D_2O) δ 178.4, 172.4, 163.9, 162.1, 135.6, 134.1, 130.5, 130.0, 126.6, 126.3, 126.0, 123.1, 121.0, 119.9, 118.3, 117.8, 111.0, 109.6, 66.8 (d), 60.9, 59.5, 55.4, 47.2 (d), 45.0, 44.1, 38.9, 27.4, 27.1, 25.2, 22.8, 22.2, 21.8, 21.3; ^{31}P (161.3 MHz, $CDCl_3$) δ 8.5; LRMS (FAB, NBA, *m*/*z*) 683.1.

(2*S*,3*S*,4*S*,5*R*)-(2*S*)-({4-[2-(1,3-Dioxo-1*H*,3*H*-benzo[*de*]isoquinolin-2-yl)ethyl]-3-isobutyl-5-phosphonopyrrolidine-2-carbonyl}-amino)-3-phenylpropionic Acid (45). Prepared following the synthetic sequence for the preparation of **42**, starting from L-pyroglutamic acid: 5 mg; $[\alpha]_D$ −79.0 (*c* 0.2, H_2O); IR (KBr) 3453, 1654, 1465 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 8.25 (m, 4H), 7.68 (m, 2H), 6.98 (m, 2H), 6.84 (m, 2H), 6.59 (m, 1H), 4.24 (dd, 1H, J = 4.8, 7.3 Hz), 3.85−3.80 (m, 2H), 3.60 (s, 1H), 3.55 (dd, 1H, J = 6.1, 9.7 Hz), 2.98 (dd, 1H, J = 4.4, 13.8 Hz), 2.86 (dd, 1H, J = 7.7, 14.1 Hz), 2.35 (m, 1H), 2.21 (m, 1H), 2.05 (m, 1H), 1.59 (m, 1H), 1.38 (t, 2H, J = 7.2 Hz), 1.22 (m, 1H), 0.91 (d, 3H, J = 6.4 Hz), 0.80 (d, 3H, J = 6.4 Hz); ^{13}C (100 MHz, D_2O) δ 178.0, 174.3, 165.7, 138.1, 136.0, 132.3, 131.8, 129.7, 128.9, 127.9, 127.7, 126.9, 121.5, 66.2 (d), 60.9, 57.5, 47.5, 45.3, 44.3, 39.9, 38.2, 28.7, 26.2, 22.9, 22.7; ^{31}P (161.3 MHz, D_2O) δ 14.8; LRMS (FAB, NBA, *m*/*z*) 622.

(2*S*,3*S*,4*S*,5*R*)-(2*S*)-{[3-Isobutyl-4-(3-phenylallyl)-5-phosphonopyrrolidine-2-carbonyl]amino}-3-phenylpropionic Acid (46). Following the synthetic sequence for the preparation of **37b**, starting from L-pyroglutamic acid and using cinnamoyl bromide instead of allyl bromide gave a phosphonate which, following sequentially the preparation of **16a** and **19a**, gave **46**: 24 mg; $[\alpha]_D$ −0.4 (*c* 0.8, H_2O); IR (KBr) 3429, 1619, 1222 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 7.37 (m, 3H), 7.32 (m, 2H), 7.21 (m, 5H), 6.23 (d, 2H, J = 16.0 Hz), 6.14 (m, 1H), 4.36 (dd, 1H, J = 4.8, 8.5 Hz), 3.71 (d, 1H, J = 4.1 Hz), 3.60 (dd, 1H, J = 6.2, 11.5 Hz), 3.19 (dd, 1H, J = 5.0, 14.1 Hz), 2.98 (dd, 1H, J = 8.5, 14.0 Hz), 2.73 (d, 1H, J = 13.7 Hz), 2.30−2.24 (m, 2H), 1.99 (td, 1H, J = 9.8, 13.6 Hz), 0.71 (d, 3H, J = 6.5 Hz), 0.62 (d, 3H, J = 6.4 Hz); ^{13}C (100 MHz, D_2O) δ 177.5, 170.4, 138.6, 138.1, 133.1, 130.0, 129.6, 129.4, 128.1, 127.5, 126.9, 66.6, 61.1, 57.7, 58.0, 45.9 (d), 44.6, 38.1, 33.9, 26.2, 23.1, 21.7; ^{31}P (161.3 MHz, D_2O) δ 10.03; LRMS (FAB, NBA, *m*/*z*) 515, 433.

(2*S*,3*S*,4*S*,5*R*)-(2*S*)-{[3-Isobutyl-4-(3-phenylpropyl)-5-phosphonopyrrolidine-2-carbonyl]amino}-3-phenylpropionic Acid (47). Following the preparation of **23b** starting from **46** gave compound **47**: 13 mg; $[\alpha]_D$ −59.0 (*c* 0.6, H_2O); IR (neat/NaCl) 3434, 2927, 1638, 1455, 1385 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 7.47−7.06 (m, 10H), 4.87 (m, 1H), 3.71 (m, 1H), 3.56 (m, 1H), 3.13 (m, 1H), 2.96 (m, 1H), 2.64 (m, 2H), 2.47 (m, 1H), 2.12 (m, 1H), 1.84 (m, 1H), 1.52 (m, 3H), 1.22 (m, 2H), 1.10 (m, 1H), 0.76 (s, 6H); ^{13}C (100 MHz, D_2O) δ 177.4, 169.5, 143.7, 138.4, 130.0, 129.4, 127.6, 126.7, 66.2, 60.1, 57.6, 46.6, 46.2, 44.5, 38.0, 35.7, 29.9, 29.1, 26.3, 22.9, 22.2; ^{31}P (161.3 MHz, D_2O) δ 9.61; LRMS (FAB, NBA, *m*/*z*) 517, 435.

(2*R*,4*R*)- and (2*R*,4*S*)-4-Isobutyl-6-oxopiperidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester (49a and 49b). A solution of *i*-BuMgBr (7.83 mL, 15.7 mmol, 2 M in Et_2O) was added dropwise to a suspension of CuBr·SMe_2 (160 mg, 0.78 mmol) in Et_2O (10 mL) at −40 °C. The suspension was stirred for 1 h prior to the addition of **48** (2.0 g, 7.83 mmol) in solution Et_2O (5 mL). The mixture was stirred for an additional 5 h and quenched by the addition of saturated NH_4Cl. The resulting mixture was diluted with water and extracted twice with Et_2O. The combined organic layers were dried over Na_2SO_4, filtered, and evaporated to give a colorless oil. Purification by flash column chromatography (hexanes/EtOAc, 8:2) gave compounds **49a** and **49b** as an inseparable mixture, (2.09 g, 85%, 1.1:1 in favor of **49a**): colorless oil; $[\alpha]_D$ +15.6 (*c* 1.1, $CHCl_3$); IR (neat/NaCl) 2957, 1780, 1748, 1715, 1456, 1368, 1287, 1143 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 4.70 (dd, 1H, J = 2.6, 5.8 Hz, **49b**), 4.54 (dd, 1H, J = 6.4, 10.3 Hz, **49a**), 3.74 (s, 3H, **49b**), 3.73 (s, 3H, **49a**), 2.67−2.62 (m, 1H, **49b**), 2.61−2.57 (m, 1H, **49a**), 2.32−2.26 (m, 1H, **49a**), 2.23−2.18 (m, 1H, **49b**), 2.07−2.00 (m, 2H), 1.95−1.81 (m, 2H), 1.65−1.56 (m, 4H), 1.47 (s, 9H, **49a**), 1.47 (s, 9H, **49b**), 1.15−1.08 (m, 4H), 0.86 (d, 3H, J = 2.3 Hz, **49a**), 0.85 (d, 3H, J = 2.1 Hz, **49a**), 0.84 (d, 3H, J = 6.6 Hz, **49b**), 0.81 (d, 3H, J = 6.6 Hz, **49b**); ^{13}C (100 MHz, $CDCl_3$) δ 172.0, 171.9, 170.1, 169.8, 152.0, 151.8, 83.6, 83.4, 58.5, 58.0, 52.4, 52.3, 44.7, 44.6, 41.3, 41.2, 32.5, 31.7, 28.8, 27.7, 27.7, 27.4, 24.6, 24.4, 22.5, 22.4, 22.3, 22.3; LCMS (MNa^+) 336.1; HRMS for $C_{16}H_{27}NO_5$ (MH^+) calcd 314.19620, obsd 314.19682; (MNa^+) calcd 336.17814, obsd 336.17885.

(2*R*,4*R*,5*S*)-4-Isobutyl-6-oxo-5-(3-phenylallyl)piperidine-1,2-dicarboxylic Acid 1-*tert*-Butyl 2-Methyl Ester (50a) and (2*R*,4*S*,5*R*)-4-Isobutyl-6-oxo-5-(3-phenylallyl)piperidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester (50b). The diastereomeric mixture of **49a** and **49b** (244 mg, 0.78 mmol) was placed in an argon-filled round-bottom flask, dissolved in THF/DME 1:1 (5 mL), and cooled to −78 °C. LiHMDS (934 μL, 0.93 mmol) was introduced as a 1 M solution in THF via a hypodermic syringe. The solution was allowed to reach −50 °C and stirred for 2.5 h. After the solution was cooled to −78 °C, cinnamoyl bromide (230 mg, 1.17 mmol) in solution in THF (2 mL) was added over 30 min using a syringe pump. After 4 h, the reaction was quenched by the addition of an excess of saturated NH_4Cl. The mixture was allowed to reach rt and vigorously stirred for few minutes. The THF was evaporated and replaced by EtOAc, which was washed with water. The organic layer was dried over Na_2SO_4, filtered, concentrated, and purified by flash column chromatography (CH_2Cl_2/Et_2O, 95:5) to give **50a** and **50b**. For **50a**: 160 mg (48%, sole diastereomer); colorless oil; $[\alpha]_D$ +52.3 (*c* 1.1, $CHCl_3$); IR (neat/NaCl) 2956, 1778, 1748, 1715, 1598, 1448, 1368, 1288, 1153 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 7.35−7.27 (m, 4H), 7.24−7.20 (m, 1H), 6.45 (d, 1H, J = 15.7 Hz), 6.16 (ddd, 1H, J = 6.4, 8.5, 15.6 Hz), 4.54 (dd, 1H, J = 6.0, 9.3 Hz), 3.76 (s, 3H), 2.95−2.89 (m, 1H), 2.59−2.52 (m, 1H), 2.35−2.29 (m, 2H), 1.90−1.81 (m, 1H), 1.71−1.64 (m, 1H), 1.62−1.57 (m, 1H), 1.50 (s, 9H), 1.39 (ddd, 1H, J = 3.3, 10.3, 13.6 Hz), 1.10 (ddd, 1H, J = 3.8, 10.5, 13.6 Hz), 0.94 (d, 3H, J = 6.6 Hz), 0.86 (d, 3H, J = 6.5 Hz); ^{13}C (100 MHz, $CDCl_3$) δ 172.8, 172.0, 151.7, 137.2, 132.9, 128.3, 127.0, 126.1, 126.0, 83.4, 57.9, 52.2, 50.1, 42.7, 32.6, 31.6, 30.0, 27.7, 24.9, 23.9, 21.3; LCMS (MNa^+) 452.1. For **50b**: 84 mg (25%, inseparable mixture with the corresponding diastereomer, 9:1); colorless oil; $[\alpha]_D$ −4.4 (*c* 0.9, $CHCl_3$); IR (neat/NaCl) 2955, 1778, 1748, 1715, 1598, 1448, 1368, 1288, 1153 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 7.37−7.35 (m, 2H), 7.30−7.26 (m, 2H), 7.20−7.17 (m, 1H), 6.40 (d, 1H, J = 15.7 Hz), 6.18 (ddd, 1H, J = 6.0, 8.8, 15.6 Hz), 4.72 (dd, 1H, J = 3.3, 5.1 Hz), 3.56 (s, 3H), 3.06−3.00 (m, 1H), 2.56−2.49 (m, 1H), 2.34 (dt, 1H, J = 13.4, 2.9 Hz), 2.30−2.25 (m, 1H), 1.75−1.69 (m, 1H), 1.68−1.59 (m, 2H), 1.51 (s, 9H), 1.35 (ddd, 1H, J = 3.1, 10.4, 13.6 Hz), 1.07 (ddd, 1H, J = 4.2, 10.0, 13.7 Hz), 0.92 (d, 3H, J = 6.6 Hz), 0.76 (d, 3H, J = 6.5 Hz); ^{13}C (100 MHz, $CDCl_3$) δ 172.1, 171.5, 152.0, 137.1, 132.0, 128.0, 126.6, 126.5, 125.7, 83.1, 57.4, 52.0, 50.0, 42.5, 32.2, 30.2, 29.7, 27.5, 24.5, 23.6, 20.8; LCMS (MNa^+) 452.0.

(2*R*,4*R*,5*S*,6*R*)-6-(Dimethoxyphosphoryl)-4-isobutyl-5-(3-phenylallyl)piperidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester (51a) and (2*R*,4*R*,5*S*,6*S*)-6-(Dimethoxyphosphoryl)-4-isobutyl-5-(3-phenylallyl)piperidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester (51b). Following the preparation of **11a** and **11b** gave compounds **51a** and **51b** (1.5:1 in favor of **51a**) as colorless oils. For **51a**: 92 mg (58%, three steps); $[\alpha]_D$ −24.9 (*c* 1.0, $CHCl_3$); IR (neat/NaCl) 2955, 1760, 1700, 1455, 1382, 1254, 1170, 1032 cm^{-1}; for a mixture of two rotamers ^1H (400 MHz, $CDCl_3$) δ 7.34−7.17 (m, 5H), 6.46 (d, 1H, J = 15.7 Hz), 6.19−6.13 (m, 1H), 4.69 (d, 0.67H, J = 21.6 Hz), 4.50 (d, 0.33H, J = 22.0 Hz), 4.27 (dd, 0.33H, J = 6.6, 12.4 Hz), 4.13 (dd, 0.67H, J = 5.7, 12.9 Hz), 3.85 (d, 3H, J = 10.6 Hz), 3.73−3.66 (m, 6H), 2.47−2.38 (m, 1H), 2.30−2.11 (m, 3H), 2.03−1.92 (m, 2H), 1.74−1.61 (m, 1H), 1.44 (s, 3H), 1.41 (s, 6H), 1.34−1.27 (m, 2H), 0.93 (d, 3H, J = 6.5 Hz), 0.87 (d, 3H, J = 6.5 Hz); ^{13}C (100 MHz, $CDCl_3$) δ 172.2, 154.6, 137.3 and 137.0, 133.2 and 133.0, 128.4 and 128.2, 126.9, 126.3, 126.0 and 125.8, 80.9 and 80.8, 56.8 and 56.0, 53.6 (d), 52.2 (d), 51.7 and 51.6, 49.2 and 48.6 (d), 44.4, 41.2 and 41.0 (d), 38.3 and 38.2 (d), 34.2 and 33.4, 29.5, 28.1 and 27.8, 25.1 and 25.0, 23.8, 21.5; ^{31}P (161.3 MHz, $CDCl_3$) δ 28.0 (major rotamer), 27.7 (minor rotamer); LCMS (MH^+) 524.9, (MNa^+) 546.1; HRMS for $C_{27}H_{42}NO_7P$ (MH^+) calcd 524.27717,

obsd 524.27738; (MNa^+) calcd 546.25911, obsd 546.25901. For **51b**: 60 mg (38%, three steps); $[\alpha]_D$ +1.4 (*c* 0.9, $CHCl_3$); IR (neat/NaCl) 2955, 1751, 1700, 1454, 1384, 1250, 1169, 1033 cm^{-1}; for a mixture of two rotamers ^1H (400 MHz, $CDCl_3$) δ 7.37−7.28 (m, 4H), 7.25−7.19 (m, 1H), 6.50 (d, 1H, J = 15.7 Hz), 6.27−6.19 (m, 1H), 4.70 (dd, 0.67H, J = 5.0, 13.1 Hz), 4.58 (dd, 0.33H, J = 3.6, 12.8 Hz), 4.40−4.36 (m, 1H), 3.79 (d, 3H, J = 9.1 Hz), 3.77 (d, 3H, J = 8.7 Hz), 3.74 (s, 3H), 2.61−2.40 (m, 2H), 2.15−2.05 (m, 1H), 2.03−1.94 (m, 2H), 1.92−1.85 (m, 1H), 1.69−1.57 (m, 1H), 1.43 (s, 3H), 1.42 (s, 6H), 1.21−1.14 (m, 1H), 0.97−0.92 (m, 1H), 0.89 (d, 3H, J = 6.6 Hz), 0.85 (d, 3H, J = 6.5 Hz); ^{13}C (100 MHz, $CDCl_3$) δ 174.1, 154.2, 137.3, 132.2 and 132.0, 128.3, 127.8, 126.9, 126.0, 80.7, 53.6 and 53.3, 53.0 (d), 52.2 (d), 51.7, 50.0 (d), 42.8 and 42.7, 42.2, 34.5 and 33.5, 31.1, 29.5, 28.0, 25.3, 24.1, 21.2;^{31}P (161.3 MHz, $CDCl_3$) δ 29.3 (major rotamer), 29.1 (minor rotamer); LCMS (MH^+) 524.3; HRMS for $C_{27}H_{42}NO_7P$ (MH^+) calcd 524.27717, obsd 524.27691; (MNa^+) calcd 546.25911, obsd 546.25814.

(2*R*,4*S*,5*R*,6*S*)-6-(Dimethoxyphosphoryl)-4-isobutyl-5-(3-phenylallyl)piperidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester (51c) and (2*R*,4*S*,5*R*,6*R*)-6-(Dimethoxyphosphoryl)-4-isobutyl-5-(3-phenylallyl)piperidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester (51d). Following the preparation of **11a** and **11b** gave compounds **51c** and **51d** (2:1 in favor of **51c**) as colorless oils. For **51c**: 206 mg (54%, three steps); $[\alpha]_D$ −65.3 (*c* 1.1, $CHCl_3$); IR (neat/NaCl) 2955, 1755, 1699, 1455, 1390, 1253, 1174, 1033 cm^{-1}; for a mixture of two rotamers ^1H (400 MHz, $CDCl_3$) δ 7.37−7.35 (m, 2H), 7.32−7.25 (m, 2H), 7.23−7.16 (m, 1H), 6.50 (d, 1H, J = 15.8 Hz), 6.25−6.16 (m, 1H), 4.69 (d, 0.60H, J = 18.6 Hz), 4.50 (d, 0.40H, J = 18.5 Hz), 4.39−4.36 (m, 1H), 3.74−3.65 (m, 9H), 2.53−2.34 (m, 3H), 2.00−1.77 (m, 2H), 1.65−1.54 (m, 1H), 1.41−1.39 (m, 1H), 1.41 (s, 5H), 1.39 (s, 4H), 1.33−1.26 (m, 2H), 0.91−0.88 (m, 3H), 0.79 (d, 1.20H, J = 6.5 Hz), 0.76 (d, 1.80H, J = 6.5 Hz); ^{13}C (100 MHz, $CDCl_3$) δ 173.1 and 172.3, 154.7 and 154.3, 137.2 and 136.9, 132.9 and 132.6, 128.2 and 128.0, 127.5 and 127.2, 126.8 and 126.6, 125.8 and 125.6, 80.6 and 80.5, 55.5 and 54.8, 52.7 and 52.6 (d), 52.4 and 52.3 (d), 51.6 and 51.4, 49.0 and 48.3 (d), 44.5 and 44.4, 40.5 and 40.6 (d), 38.1 and 38.0 (d), 30.4 and 30.0, 28.0, 27.7 and 27.6, 24.7 and 24.6, 23.4 and 23.3, 21.0 and 20.9;^{31}P (161.3 MHz, $CDCl_3$) δ 29.1 (minor rotamer), 29.0 (major rotamer); LCMS (MNa^+) 546.1; HRMS for $C_{27}H_{42}NO_7P$ (MH^+) calcd 524.27717, obsd 524.27716; (MNa^+) calcd 546.25911, obsd 546.25835. For **51d**: 104 mg (27%, three steps); $[\alpha]_D$ −3.8 (*c* 1.0, $CHCl_3$); IR (neat/NaCl) 2954, 1757, 1700, 1454, 1392, 1254, 1166, 1033 cm^{-1}; for a mixture of two rotamers ^1H (400 MHz, $CDCl_3$) δ 7.36−7.26 (m, 4H), 7.21−7.17 (m, 1H), 6.46 (d, 1H, J = 15.6 Hz), 6.24−6.19 (m, 1H), 4.69 (dd, 0.70H, J = 5.5, 17.2 Hz), 4.59−4.53 (m, 0.30H), 4.30−4.27 (m, 0.30H), 4.15−4.10 (m, 0.70H), 3.88 (d, 3H, J = 10.6 Hz), 3.78−3.75 (m, 3H), 3.73 (s, 0.77H), 3.72 (s, 2.24H), 2.70−2.61 (m, 1H), 2.57−2.41 (m, 2H), 1.98−1.90 (m, 1H), 1.70−1.54 (m, 3H), 1.41 (s, 9H), 1.25−1.18 (m, 2H), 0.91 (d, 3H, J = 6.6 Hz), 0.85 (d, 3H, J = 6.4 Hz); ^{13}C (100 MHz, $CDCl_3$) δ 172.8, 154.3, 137.1, 131.8, 128.1, 127.7, 126.7, 125.7, 81.1, 53.6 (d), 52.6, 51.6 (d), 51.6, 50.2 (d), 44.7, 42.4, 34.5, 30.9, 28.5, 27.7, 25.1, 23.8, 20.9;^{31}P (161.3 MHz, $CDCl_3$) δ 26.8 (major rotamer), 26.4 (minor rotamer); LCMS (MH^+) 524.0, (MNa^+) 546.1; HRMS for $C_{27}H_{42}NO_7P$ (MH^+) calcd 524.27717, obsd 524.27706; (MNa^+) calcd 546.25911, obsd 546.25925.

(2*R*,4*R*,5*S*,6*R*)-6-(Dimethoxyphosphoryl)-5-(2-hydroxyethyl)-4-isobutylpiperidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester (52a). Following the preparation of **14a** gave compound **52a**, 144 mg (84%, two steps), as a colorless oil: $[\alpha]_D$ −34.2 (*c* 1.0, $CHCl_3$); IR (neat/NaCl) 3423, 2956, 1760, 1698, 1456, 1388, 1252, 1172, 1044 cm^{-1}; for a mixture of two rotamers ^1H (400 MHz, $CDCl_3$) δ 4.71 (d, 0.67H, J = 20.4 Hz), 4.64 (d, 0.33H, J = 22.5 Hz), 4.35 (dd, 0.33H, J = 6.8, 12.7 Hz), 4.20 (dd, 0.67H, J = 6.3, 12.7 Hz), 3.81 (d, 3H, J = 10.6 Hz), 3.77 (d, 3H, J = 10.9 Hz), 3.76−3.68 (m, 2H), 3.71 (s, 3H), 3.23 (bs, 1H), 2.09−2.03 (m, 1H), 1.96−1.78 (m, 3H), 1.70−1.60 (m, 1H), 1.48 (s, 2H), 1.42 (s, 7H), 1.36−1.10 (m, 4H), 0.90 (d, 3H, J = 6.6 Hz), 0.85 (d, 3H, J = 6.4 Hz); ^{13}C (100 MHz, $CDCl_3$) δ 172.6, 155.6, 81.7, 59.4, 56.9 and 55.9, 53.9 and 53.8 (d), 53.5 and 53.3 (d), 52.3 and 52.1, 49.9 and 48.1 (d), 44.3, 38.6 and 37.7 (d), 37.7 and 37.6, 35.5 and 35.2, 29.0, 28.7 and 28.5, 25.8, 24.4, 21.9; ^{31}P (161.3 MHz, $CDCl_3$) δ 29.7 (major rotamer), 29.1 (minor rotamer).

(2*R*,4*R*,5*S*,6*S*)-6-(Dimethoxyphosphoryl)-5-(2-hydroxyethyl)-4-isobutylpiperidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester (52b). Following the preparation of **14a** gave compounds **52b**, 163 mg (79%, two steps), as a colorless oil: $[\alpha]_D$ −12.7 (*c* 1.0, $CHCl_3$); IR (neat/NaCl) 3423, 2955, 1751, 1698, 1456, 1390, 1254, 1176, 1056 cm^{-1}; for a mixture of two rotamers ^1H (400 MHz, $CDCl_3$) δ 4.75 (dd, 0.67H, J = 5.1, 14.0 Hz), 4.63 (dd, 0.33H, J = 4.1, 13.1 Hz), 4.32−4.28 (m, 1H), 3.74 (d, 3H, J = 6.0 Hz), 3.72 (d, 3H, J = 5.8 Hz), 3.71−3.66 (m, 2H), 3.68 (s, 3H), 3.05 (bs, 1H), 2.51−2.43 (m, 0.67H), 2.36−2.29 (m, 0.33H), 2.08−1.98 (m, 1H), 1.96−1.66 (m, 4H), 1.63−1.51 (m, 1H), 1.44 (s, 3H), 1.38 (s, 6H), 1.08−1.02 (m, 1H), 0.87−0.81 (m, 1H), 0.83 (d, 3H, J = 6.5 Hz), 0.79 (d, 3H, J = 6.4 Hz); ^{13}C (100 MHz, $CDCl_3$) δ 174.6, 154.9, 81.6 and 81.3, 61.4 and 61.0, 54.0, 53.4 (d), 53.0 (d), 52.4 and 52.3, 50.7 (d), 43.2 and 43.1, 38.6 (d), 34.0, 31.6, 28.5, 28.1, 25.8 and 25.6, 24.6, 21.6; ^{31}P (161.3 MHz, $CDCl_3$) δ 29.6.

(2*R*,4*S*,5*R*,6*S*)-6-(Dimethoxyphosphoryl)-5-(2-hydroxyethyl)-4-isobutylpiperidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester (52c). Following the preparation of **14a** gave compounds **52c**, 75 mg (87%, two steps), as a colorless oil: $[\alpha]_D$ +31.0 (*c* 1.0, $CHCl_3$); IR (neat/NaCl) 3428, 2956, 1751, 1705, 1455, 1384, 1178, 1036 cm^{-1}; for a mixture of two rotamers ^1H (400 MHz, $CDCl_3$) δ 4.63 (dd, 0.77H, J = 1.4, 17.9 Hz), 4.50 (dd, 0.23H, J = 1.0, 18.6 Hz), 4.31−4.29 (m, 1H), 3.74 (d, 3H, J = 6.7 Hz), 3.74−3.70 (m, 2H), 3.71 (d, 3H, J = 6.8 Hz), 3.69 (s, 0.64H), 3.68 (s, 2.36H), 2.81 (bs, 1H), 2.21−2.13 (m, 1H), 1.97−1.88 (m, 1H), 1.81−1.72 (m, 2H), 1.66−1.50 (m, 2H), 1.43 (s, 2H), 1.37 (s, 7H), 1.30−1.19 (m, 2H), 1.17−1.10 (m, 1H), 0.84 (d, 3H, J = 6.6 Hz), 0.72 (d, 3H, J = 6.5 Hz); ^{13}C (100 MHz, $CDCl_3$) δ 173.1, 154.6, 80.9 and 80.8, 59.3 and 58.9, 55.3 and 54.5, 53.0 and 52.8 (d), 52.6 and 52.5 (d), 51.7 and 51.5, 48.0 (d), 44.0 and 43.7, 36.9 (d), 36.6 (d), 30.3 and 30.1, 27.8 and 27.6, 28.2, 24.8, 23.4, 20.8; ^{31}P (161.3 MHz, $CDCl_3$) δ 29.9 (major rotamer), 29.5 (minor rotamer).

(2*R*,4*S*,5*R*,6*R*)-6-(Dimethoxyphosphoryl)-5-(2-hydrox-ethyl)-4-isobutylpiperidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester (52d). Following the preparation of **14a** gave compounds **52d**, 70 mg (81%, two steps), as a colorless oil: $[\alpha]_D$ +17.5 (*c* 1.0, $CHCl_3$); IR (neat/NaCl) 3421, 2955, 1755, 1700, 1456, 1392, 1254, 1171, 1034 cm^{-1}; for a mixture of two rotamers ^1H (400 MHz, $CDCl_3$) δ 4.78 (dd, 1H, J = 5.3, 17.6 Hz), 4.42−4.39 (m, 0.22H), 4.20−4.17 (m, 0.76H), 3.82 (d, 3H, J = 10.6 Hz), 3.73 (d, 3H, J = 10.6 Hz), 3.76−3.70 (m, 2H), 3.69 (s, 3H), 2.59−2.51 (m, 2H), 1.93−1.85 (m, 1H), 1.84−1.75 (m, 2H), 1.74−1.57 (m, 2H), 1.55−1.48 (m, 1H), 1.46 (s, 2.13H), 1.41 (s, 6.85H), 1.16−1.12 (m, 2H), 0.90 (d, 3H, J = 6.6 Hz), 0.84 (d, 3H, J = 6.4 Hz); ^{13}C (100 MHz, $CDCl_3$) δ 172.6, 154.4, 81.1, 60.3, 53.1 (d), 52.5, 52.0 (d), 51.4, 50.0 (d), 42.2, 40.4 (d), 33.0, 30.7, 28.7, 27.8 and 27.7, 25.0, 23.8, 20.9; ^{31}P (161.3 MHz, $CDCl_3$) δ 27.6.

(2*R*,4*R*,5*S*,6*R*)-6-(Dimethoxyphosphoryl)-5-[2-(1,3-dioxo-1*H*,3*H*-benzo[*de*]isoquinolin-2-yl)ethyl]-4-isobutylpiperidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester (53a). 1,8-Dicarboxynaphthalimide (32 mg, 0.16 mmol) and PPh_3 (43 mg, 0.16 mmol) were added to a solution of **52a** (37 mg, 0.08 mmol) in THF (2 mL). The resulting suspension was cooled to 0 °C prior to the dropwise addition of a solution of methyl azodicarboxylate (24 mg, 0.16 mmol) in THF (0.5 mL). The solution was stirred overnight with a slow increase of temperature from 0 °C to rt. The suspension was filtered off, and the solid was washed with EtOAc. The filtrate was evaporated to afford a residue, which was purified by flash column chromatography (hexanes/EtOAc, 1:9) to give **53a**

as a colorless oil (45 mg, 87%): $[\alpha]_D$ −25.7 (*c* 0.9, $CHCl_3$); IR (neat/NaCl) 2958, 1750, 1700, 1663, 1591, 1438, 1366, 1237, 1175, 1033 cm^{-1}; for a mixture of two rotamers ^1H (400 MHz, $CDCl_3$) δ 8.60−8.58 (m, 2H), 8.22−8.19 (m, 2H), 7.77−7.72 (m, 2H), 4.77 (dd, 1H, J = 12.6, 21.3 Hz), 4.30−4.05 (m, 3H), 3.93−3.87 (m, 3H), 3.77 (d, 3H, J = 10.5 Hz), 3.73 (s, 3H), 2.18−2.07 (m, 1H), 1.95−1.82 (m, 3H), 1.74−1.65 (m, 1H), 1.60 (s, 4.5H), 1.42 (s, 4.5H), 1.35−1.29 (m, 4H), 0.93−0.86 (m, 6H); ^{13}C (100 MHz, $CDCl_3$) δ 172.3 and 171.6, 163.7 and 163.6, 154.9 and 154.7, 133.8 and 133.7, 131.5 and 131.4, 131.0, 128.0, 126.7, 122.5, 81.3 and 81.0, 56.6 and 55.8, 53.8 (d), 52.3 (d), 51.7 and 51.6, 50.6 and 49.6 (d), 44.8 and 44.0, 39.9 and 39.5 (d), 37.8 and 37.5, 34.2 and 34.0, 28.1, 28.1 and 27.9, 27.7, 25.1 and 25.0, 23.8, 21.3; ^{31}P (161.3 MHz, $CDCl_3$) δ 27.7; LCMS (MNa^+) 653.2; HRMS for $C_{32}H_{43}N_2O_9P$ (MH^+) calcd 631.27789, obsd 631.27656; (MNa^+) calcd 653.25984, obsd 653.25818.

(2*R*,4*R*,5*S*,6*S*)-6-(Dimethoxyphosphoryl)-5-[2-(1,3-dioxo-1*H*,3*H*-benzo[*de*]isoquinolin-2-yl)ethyl]-4-isobutylpiperidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester (53b). Following the preparation of **53a** gave compounds **53b** as a white solid, 60 mg (86%): $[\alpha]_D$ −9.3 (*c* 1.0, $CHCl_3$); mp 154−156 °C; IR (neat/NaCl) 2954, 1750, 1700, 1662, 1590, 1436, 1367, 1235, 1175, 1030 cm^{-1}; for a mixture of two rotamers ^1H (400 MHz, $CDCl_3$) δ 8.57 (d, 2H, J = 7.2 Hz), 8.19 (m, 2H), 7.75−7.70 (m, 2H), 4.90−4.84 (m, 1H), 4.46−4.10 (m, 3H), 3.91 (d, 1.67H, J = 10.9 Hz), 3.86 (d, 1.33H, J = 10.9 Hz), 3.79 (d, 3H, J = 10.4 Hz), 3.66 (s, 1.67H), 3.60 (s, 1.33H), 2.60−2.52 (m, 0.55H), 2.42−2.35 (m, 0.45H), 2.03−1.87 (m, 4H), 1.53 (s, 4H), 1.42 (s, 5H), 1.29−1.19 (m, 2H), 1.14−1.06 (m, 1H), 0.83−0.73 (m, 7H); ^{13}C (100 MHz, $CDCl_3$) δ 174.4 and 174.0, 164.4 and 164.3, 155.1 and 154.9, 134.3 and 134.2, 132.0, 131.6, 128.5, 127.3, 123.2 and 123.1, 81.5 and 81.3, 54.2, 54.0 and 53.7 (d), 53.8 (d), 52.8 and 52.6 (d), 52.3, 43.2 and 43.0, 40.6 and 40.4 (d), 39.6 and 39.2, 31.9 and 31.7, 29.7, 28.6, 28.2, 25.8 and 25.6, 24.6, 21.6; ^{31}P (161.3 MHz, $CDCl_3$) δ 29.1 (minor rotamer), 28.9 (major rotamer); LCMS (MNa^+) 653.0; HRMS for $C_{32}H_{43}N_2O_9P$ (MH^+) calcd 631.27789, obsd 631.27702; (MNa^+) calcd 653.25984, obsd 653.25859.

(2*R*,4*S*,5*R*,6*S*)-6-(Dimethoxyphosphoryl)-5-[2-(1,3-dioxo-1*H*,3*H*-benzo[*de*]isoquinolin-2-yl)ethyl]-4-isobutylpiperidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester (53c). Following the preparation of **15a** gave compounds **53c** as a colorless oil, 39 mg (47%, two steps): $[\alpha]_D$ +19.8 (*c* 1.2, $CHCl_3$); IR (neat/NaCl) 2955, 1749, 1701, 1662, 1591, 1438, 1367, 1237, 1175, 1033 cm^{-1}; for a mixture of two rotamers ^1H (400 MHz, $CDCl_3$) δ 8.59 (m, 2H), 8.22−8.18 (m, 2H), 7.77−7.71 (m, 2H), 4.76 (dd, 1H, J = 9.2, 18.4 Hz), 4.38 (dd, 1H, J = 6.8, 14.6 Hz), 4.29−4.19 (m, 2H), 3.81−3.77 (m, 6H), 3.73 (s, 1.60H), 3.70 (s, 1.40H), 2.43−2.31 (m, 1H), 2.04−1.82 (m, 4H), 1.58 (s, 4.20H), 1.51−1.45 (m, 1H), 1.41 (s, 4.80H), 1.32−1.26 (m, 2H), 0.88 (m, 3H), 0.79 (d, 3H, J = 6.5 Hz); ^{13}C (100 MHz, $CDCl_3$) δ 173.1 and 172.3, 163.5 and 163.4, 154.9 and 154.4, 133.5 and 133.4, 131.2, 130.7 and 130.6, 127.8, 126.5, 122.4, 81.1 and 80.6, 55.6 and 54.9, 53.0 and 52.8 (d), 52.5 and 52.4 (d), 51.6 and 51.5, 51.0 and 49.4 (d), 44.7 and 44.2, 39.1 and 38.9 (d), 37.6 and 37.5, 33.3 and 32.6 (d), 30.0, 28.1, 27.8 and 27.7, 24.7 and 24.6, 23.5 and 23.4, 20.8; ^{31}P (161.3 MHz, $CDCl_3$) δ 29.0 (major rotamer), 28.8 (minor rotamer); LCMS (MNa^+) 653.1; HRMS for $C_{32}H_{43}N_2O_9P$ (MH^+) calcd 631.27789, obsd 631.27816; (MNa^+) calcd 653.25984, obsd 653.26048.

(2*R*,4*S*,5*R*,6*R*)-6-(Dimethoxyphosphoryl)-5-[2-(1,3-dioxo-1*H*,3*H*-benzo[*de*]isoquinolin-2-yl)ethyl]-4-isobutylpiperidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester (53d). Following the preparation of **15a** gave compounds **53d** as a colorless oil, 59 mg (73%, two steps): $[\alpha]_D$ +24.5 (*c* 1.0, $CHCl_3$); IR (neat/NaCl) 2955, 1755, 1701, 1662, 1591, 1439, 1366, 1243, 1175, 1036 cm^{-1}; for a mixture of two rotamers ^1H (400 MHz, $CDCl_3$) δ 8.56 (d, 2H, J = 7.2 Hz), 8.21−8.17 (m, 2H), 7.76−7.70 (m, 2H), 4.98 (dd, 0.40H, J = 4.9, 16.8 Hz), 4.85 (dd, 0.60H, J = 5.0, 17.4 Hz), 4.45−4.30 (m, 1H), 4.27−4.09 (m, 2H), 3.93−3.83 (m, 6H), 3.70 (s, 3H), 2.70−2.56 (m, 1H), 2.14−1.81 (m, 4H), 1.56 (s, 4H), 1.44 (s, 5H), 1.25−1.00 (m, 3H), 0.93−0.80 (m, 7H); ^{13}C (100 MHz, $CDCl_3$) δ 172.8 and 172.4, 163.8 and 163.6, 154.5 and 154.3, 133.6 and 133.4, 131.2, 130.8, 127.8, 126.6 and 126.5, 122.3 and 122.2, 81.0 and 80.8, 53.8 and 53.5 (d), 52.6, 51.9 and 51.5 (d), 51.6 and 51.5, 51.3 and 50.0 (d), 42.8 and 41.5 (d), 42.2 and 42.0, 38.8 and 38.0, 31.0 and 30.5, 29.2 and 28.8, 28.5 and 28.4, 27.8 and 27.7, 25.0 and 24.8, 23.8, 20.9; ^{31}P (161.3 MHz, $CDCl_3$) δ 26.7 (minor rotamer), 26.5 (major rotamer); LCMS (MH^+) 631.5, (MNa^+) 653.5; HRMS for $C_{32}H_{43}N_2O_9P$ (MH^+) calcd 631.27789, obsd 631.27768; (MNa^+) calcd 653.25984, obsd 653.25961.

(2*R*,3*S*,4*R*,6*R*)-2-(Dimethoxyphosphoryl)-3-[2-(1,3-dioxo-1*H*,3*H*-benzo[*de*]isoquinolin-2-yl)ethyl]-6-[2-(1*H*-indol-3-yl)-(1*S*)-methoxycarbonylethylcarbamoyl]-4-isobutylpiperidine-1-carboxylic Acid *tert*-Butyl Ester (54a). Compound **53a** (32 mg, 0.05 mmol) was dissolved in a mixture of THF/H_2O/MeOH 5:4:1 (1 mL). LiOH·H_2O (4 mg, 0.10 mmol) was added, and the solution was stirred for 24 h at 50 °C. The organic layer was extracted with CH_2Cl_2, and the aqueous layer was acidified to pH 3 with 1 N $KHSO_4$. The aqueous phase was extracted with EtOAc, washed with brine, dried over Na_2SO_4, and concentrated in vacuo to give the crude carboxylic acid used in the next step without further purification. Diisopropylethylamine (25 μL, 0.14 mmol) was added dropwise to a solution of the acid, EDC (14 mg, 0.07 mmol), HOBt (10 mg, 0.07 mmol) and HCl·H-Trp-OMe (19 mg, 0.07 mmol) in DMF (2 mL) at rt. The solution was stirred for 16 h before quenching by addition of saturated NH_4Cl. The solution was extracted with EtOAc and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (CH_2Cl_2/MeOH, 95:5) to give **54a** (34 mg, 86%) as a yellowish oil: $[\alpha]_D$ −26.5 (*c* 1.0, $CHCl_3$); IR (neat/NaCl) 3288, 2955, 1747, 1700, 1661, 1591, 1438, 1367, 1234, 1052 cm^{-1}; for a mixture of two rotamers ^1H (400 MHz, $CDCl_3$) δ 8.66 (bd, 1H), 8.57 (d, 2H, J = 7.3 Hz), 8.20−8.18 (m, 2H), 8.36 (bs, 1H), 7.73 (t, 2H, J = 7.8 Hz), 7.64−7.55 (m, 1H), 7.34−7.32 (m, 2H), 7.13 (t, 1H, J = 7.1 Hz), 7.07 (t, 1H, J = 7.2 Hz), 4.94−4.82 (m, 1.3H), 4.68−4.63 (m, 0.7H), 4.22−4.18 (m, 2H), 4.00−3.79 (m, 7H), 3.67 (s, 2H), 3.57 (s, 1H), 3.31 (dd, 1H, J = 14.6, 5.4 Hz), 3.20 (dd, 1H, J = 14.6, 8.8 Hz), 2.20−2.08 (m, 1H), 2.01−1.79 (m, 2H), 1.78−1.59 (m, 3H), 1.52 (s, 2.6H), 1.33−1.23 (m, 3H), 1.09 (s, 6.4H), 0.89−0.83 (m, 6H); ^{13}C (100 MHz, $CDCl_3$) δ 173.3, 172.9, 163.5, 155.1, 136.0, 133.6, 131.2, 130.8, 127.7, 126.8, 126.5, 123.5, 122.2, 121.5, 118.9, 118.1, 110.8, 110.2, 81.4, 59.6, 53.6, 53.1 (d), 52.9 (d), 51.6, 49.3 (d), 45.1, 39.4 (d), 37.6, 34.6, 34.0 (d), 29.2, 27.4, 27.2, 24.6, 23.6, 21.0; ^{31}P (161.3 MHz, $CDCl_3$) δ 31.3 (major rotamer), 30.5 (minor rotamer); LCMS (MH^+) 817.2, (MNa^+) 839.2; HRMS for $C_{43}H_{53}N_4O_{10}P$ (MH^+) calcd 817.35721, obsd 817.35755; (MNa^+) calcd 839.33915, obsd 839.34013.

(2*S*,3*S*,4*R*,6*R*)-2-(Dimethoxyphosphoryl)-3-[2-(1,3-dioxo-1*H*,3*H*-benzo[*de*]isoquinolin-2-yl)ethyl]-6-[2-(1*H*-indol-3-yl)-(1*S*)-methoxycarbonylethylcarbamoyl]-4-isobutylpiperidine-1-carboxylic Acid *tert*-Butyl Ester (54b). Following the preparation of **54a** gave compounds **54b** as a yellowish oil, 89 mg (78%, two steps): $[\alpha]_D$ −10.6 (*c* 1.0, $CHCl_3$); IR (neat/NaCl) 3289, 2954, 2244, 1744, 1662, 1591, 1439, 1386, 1236, 1175, 1034 cm^{-1}; for a mixture of rotamers ^1H (400 MHz, $CDCl_3$) δ 8.59 (d, 2H, J = 7.2 Hz), 8.31−8.29 (bd, 1H), 8.22−8.20 (m, 3H), 7.77−7.73 (m, 2H), 7.62−7.60 (m, 1H), 7.32−7.30 (bd, 1H), 7.18 (bs, 1H), 7.14 (t, 1H, J = 7.2 Hz), 7.07 (t, 1H, J = 7.1 Hz), 4.96−4.89 (m, 2H), 4.24−4.12 (m, 3H), 3.76−3.72 (m, 6H), 3.59 (s, 3H), 3.33 (dd, 1H, J = 6.5, 14.8 Hz), 3.26 (dd, 1H, J = 6.8, 14.6 Hz), 2.08−1.64 (m, 9H), 1.39 (s, 6H), 1.25 (s, 3H), 0.90 (d, 3H, J = 6.3 Hz), 0.84 (d, 3H, J = 6.4 Hz); ^{13}C (100 MHz, $CDCl_3$) δ 173.3, 172.9, 163.7, 155.3, 135.8, 133.8, 131.4, 131.0, 128.0, 127.5, 126.8, 123.1, 122.5, 121.6, 119.1, 118.7, 110.7, 110.4, 81.8, 60.1, 53.4, 52.8 (d), 52.7 (d), 51.8, 49.5 (d), 45.3, 39.7 (d), 37.8, 34.8, 34.2 (d), 29.5, 28.1, 27.8, 24.8, 23.8, 21.3; ^{31}P (161.3 MHz, $CDCl_3$) δ 29.2 (major rotamer), 29.0 (minor

rotamer); LCMS (MNa^+) 839.2; HRMS for $C_{43}H_{53}N_4O_{10}P$ (MH^+) calcd 817.35721, obsd 817.35747; (MNa^+) calcd 839.33915, obsd 839.33967.

(2*S*,3*R*,4*S*,6*R*)-2-(Dimethoxyphosphoryl)-3-[2-(1,3-dioxo-1*H*,3*H*-benzo[*de*]isoquinolin-2-yl)ethyl]-6-[2-(1*H*-indol-3-yl)-(1*S*)-methoxycarbonylethylcarbamoyl]-4-isobutylpiperidine-1-carboxylic Acid *tert*-Butyl Ester (54c). Following the preparation of **54a** gave compounds **54c** as a yellowish oil, 23 mg (67%, two steps): $[\alpha]_D$ +75.6 (*c* 1.0, $CHCl_3$); IR (neat/NaCl) 3279, 2955, 1744, 1699, 1661, 1591, 1439, 1367, 1236, 1174, 1034 cm^{-1}; for a mixture of rotamers ^1H (400 MHz, $CDCl_3$) δ 9.00 (bs, 1H), 8.69−8.62 (m, 2H), 8.29−8.25 (m, 2H), 7.83−7.77 (m, 2H), 7.44−7.42 (bd, 1H), 7.17−7.15 (m, 1H), 7.00−6.85 (m, 3H), 6.56−6.52 (m, 1H), 4.93−4.83 (m, 1H), 4.76 (d, 0.66H, J = 17.6 Hz), 4.70 (d, 0.34H, J = 17.6 Hz), 4.31−4.12 (m, 3H), 3.82−3.76 (m, 6H), 3.48 (s, 2H), 3.46−3.37 (m, 1H), 3.35 (s, 1H), 3.14−3.07 (m, 1H), 2.24−2.11 (m, 1H), 2.01−1.62 (m, 5H), 1.55 (s, 3H), 1.55−1.48 (m, 1H), 1.39 (s, 6H), 1.29−1.21 (m, 2H), 0.84−0.80 (m, 3H), 0.67 (d, 1H, J = 6.4 Hz), 0.63 (d, 2H, J = 6.5 Hz); ^{13}C (100 MHz, $CDCl_3$) δ 172.0, 171.7, 164.1, 156.1, 136.1, 134.1, 131.5, 131.2, 128.0, 126.9, 122.8, 122.5, 121.9, 118.3, 119.2, 110.9, 109.0, 81.9, 57.8, 53.0 (d), 52.8 (d), 52.1 and 51.6, 51.0 (d), 50.8, 45.4, 39.2 (d), 38.9, 32.7 (d), 30.8, 28.8, 28.0 and 27.9, 27.8, 24.8, 23.7, 21.1; ^{31}P (161.3 MHz, $CDCl_3$) δ 29.7 (minor rotamer), 29.5 (major rotamer); LCMS (MNa^+) 839.2; HRMS for $C_{43}H_{53}N_4O_{10}P$ (MH^+) calcd 817.35721, obsd 817.35697; (MNa^+) calcd 839.33915, obsd 839.33882.

(2*R*,3*R*,4*S*,6*R*)-2-(Dimethoxyphosphoryl)-3-[2-(1,3-dioxo-1*H*,3*H*-benzo[*de*]isoquinolin-2-yl)ethyl]-6-[2-(1*H*-indol-3-yl)-(1*S*)-methoxycarbonylethylcarbamoyl]-4-isobutylpiperidine-1-carboxylic Acid *tert*-Butyl Ester (54d). Following the preparation of **54a** gave compounds **54d** as a yellowish oil, 55 mg (77%, two steps): $[\alpha]_D$ +7.2 (*c* 1.0, $CHCl_3$); IR (neat/NaCl) 3270, 2955, 1745, 1698, 1662, 1591, 1439, 1384, 1234, 1174, 1050 cm^{-1}; appeared as a mixture of rotamers ^1H (400 MHz, $CDCl_3$) δ 8.78 (bd, 1H), 8.60 (d, 2H, J = 7.2 Hz), 8.21 (d, 2H, J = 8.1 Hz), 8.14 (bs, 1H), 7.75 (t, 2H, J = 7.8 Hz), 7.65−7.63 (m, 1H), 7.37 (bs, 1H), 7.31−7.29 (m, 1H), 7.14 (t, 1H, J = 7.4 Hz), 7.11 (t, 1H, J = 7.4 Hz), 4.99−4.93 (m, 1H), 4.62−4.57 (m, 1H), 4.35−4.28 (m, 1H), 4.25−4.18 (m, 1H), 3.97 (d, 3H, J = 11.4 Hz), 3.94 (d, 3H, J = 11.2 Hz), 3.92−3.88 (m, 1H), 3.67 (s, 3H), 3.30 (dd, 1H, J = 4.8, 14.4 Hz), 3.18 (dd, 1H, J = 9.2, 14.5 Hz), 2.12−2.00 (m, 2H), 1.91−1.86 (m, 1H), 1.72−1.55 (m, 3H), 1.47 (m, 1H), 1.05 (s, 9H), 0.86−0.80 (m, 8H); ^{13}C (100 MHz, $CDCl_3$) δ 174.8, 173.8, 164.4, 155.4, 136.7, 134.4, 132.0, 131.7, 128.6, 127.7, 127.3, 124.4, 123.0, 119.7, 118.9, 122.2, 111.4, 111.2, 82.1, 55.6, 54.3, 53.7 (d), 53.6 (d), 52.4, 50.4 (d), 43.5, 43.1, 39.4, 32.3, 30.2, 29.1, 28.1, 27.9, 25.6, 24.3, 21.6; ^{31}P (161.3 MHz, $CDCl_3$) δ 33.4; LCMS (MH^+) 817.2, (MNa^+) 839.2; HRMS for $C_{43}H_{53}N_4O_{10}P$ (MH^+) calcd 817.35721, obsd 817.35750; (MNa^+) calcd 839.33915, obsd 839.33998.

(2*R*,4*R*,5*S*,6*R*)-(2*S*)-({5-[2-(1,3-Dioxo-1*H*,3*H*-benzo[*de*]isoquinolin-2-yl)ethyl]-4-isobutyl-6-phosphonopiperidine-2-carbonyl}-amino)-3-(1*H*-indol-3-yl)propionic Acid (55a). The phosphonate **54a** (100 mg, 0.122 mmol) was dissolved in a mixture of THF/H_2O/MeOH 5:4:1 (2 mL) and cooled to 0 °C. $LiOH\cdot H_2O$ (10 mg, 0.245 mmol) was added, and the solution was stirred at 0 °C until completion (monitoring by TLC). The organic layer was extracted with CH_2Cl_2, and the aqueous layer was acidified to pH 3 with 1 N $KHSO_4$. The aqueous phase was extracted with EtOAc, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The oily residue was dissolved in CH_2Cl_2 and cooled to 0 °C. After dropwise addition of TMSBr (64 μL, 0.488 mmol), the solution was allowed to reach rt and stirred for 48 h. Solvent was removed,and deionized H_2O (few mL) was added. The suspension was stirred in a cold room (4 °C) for 16 h. The suspension was transferred in a conic 2 mL Eppendorf tube and centrifuged at 4 °C for 10 min. The supernatant was removed and replaced by fresh H_2O and the same operation was repeated twice. The amorphous powder was suspended in 2 mL of deionized H_2O and the pH value was adjusted to 7 with an aqueous solution of NaOH 0.05 M (2.44 mL, 0.122 mmol). The solution was filtered through a 0.45 μm filter and lyophilized to give **55a** as a foam (82 mg, 95%): $[\alpha]_D$ −15.8 (*c* 0.5, H_2O); IR (KBr) 3395, 2954, 1700, 1658, 1591, 1441, 1389, 1356, 1238, 1074 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 7.74 (bd, 2H), 7.55 (bd, 2H), 7.14 (m, 2H), 7.04−7.02 (m, 1H), 6.93 (bs, 2H), 6.59−6.55 (m, 1H), 6.50−6.47 (m, 1H), 4.43 (dd, 1H, J = 5.5, 5.8 Hz), 3.84−3.72 (m, 2H), 3.24−3.19 (m, 1H), 2.99−2.86 (m, 2H), 2.77 (t, 1H, J = 10.1 Hz), 1.93−1.81 (m, 2H), 1.37−1.29 (m, 1H), 1.10−0.90 (m, 3H), 0.76−0.69 (m, 1H), 0.56−0.49 (m, 1H), 0.42−0.34 (m, 1H), 0.22 (m, 3H), 0.01 (m, 3H); ^{13}C (100 MHz, D_2O) δ 177.1, 170.2, 163.1, 135.1, 133.9, 130.6, 130.0, 127.1, 126.2, 126.1, 123.5, 120.5, 120.2, 118.2, 117.5, 110.9, 109.4, 58.5, 57.6 (d), 55.2, 40.5, 39.3, 37.3, 34.6, 31.6, 26.5, 25.3, 23.3, 22.8, 19.2; ^{31}P (161.3 MHz, D_2O) δ 10.9; LCMS (MH^+) 675.0, (MNa^+) 697.1; HRMS for $C_{35}H_{39}N_4O_8P$ (MH^+) calcd 675.25783, obsd 675.25819; (MNa^+) calcd 697.23977, obsd 697.24023.

(2*R*,4*R*,5*S*,6*S*)-(2*S*)-({5-[2-(1,3-Dioxo-1*H*,3*H*-benzo[*de*]isoquinolin-2-yl)ethyl]-4-isobutyl-6-phosphonopiperidine-2-carbonyl}-amino)-3-(1*H*-indol-3-yl)propionic Acid (55b). Following the preparation of **55a** gave compound **55b** as a yellowish foam, 42 mg (93%, two steps): $[\alpha]_D$ −47.6 (*c* 0.5, H_2O); IR (KBr) 3403, 2956, 1696, 1657, 1590, 1442, 1386, 1347, 1238, 1179, 1078 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 7.50 (m, 2H), 7.15 (m, 2H), 7.07 (m, 1H), 6.92 (s, 1H), 6.81 (m, 2H), 6.75 (m, 1H), 6.33 (m, 2H), 4.46 (t, 1H, J = 6.4 Hz), 3.95 (bd, 2H), 3.68 (bd, 1H), 3.49 (m, 1H), 3.12 (bd, 1H), 2.90−2.82 (m, 1H), 1.96−1.69 (m, 3H), 1.21−1.02 (m, 2H), 0.87−0.77 (m, 1H), 0.72−0.61 (m, 1H), 0.36 (m, 3H), 0.24 (m, 4H), 0.20−0.00 (m, 1H); ^{13}C (100 MHz, D_2O) δ 177.9, 168.5, 164.2, 135.1, 133.7, 130.3, 129.6, 126.8, 125.9, 125.6, 123.4, 120.3, 119.6, 118.1, 117.7, 110.7, 109.5, 55.2, 54.1 (d), 53.8, 41.5, 38.3, 37.8, 32.0, 30.0, 26.7, 26.1, 23.3, 23.1, 19.9; ^{31}P (161.3 MHz, D_2O) δ 8.7; LCMS (MH^+) 674.9, (MNa^+) 697.1; HRMS for $C_{35}H_{39}N_4O_8P$ (MH^+) calcd 675.25783, obsd 675.25900; (MNa^+) calcd 697.23977, obsd 697.24136.

(2*R*,4*S*,5*R*,6*S*)-(2*S*)-({5-[2-(1,3-Dioxo-1*H*,3*H*-benzo[*de*]isoquinolin-2-yl)ethyl]-4-isobutyl-6-phosphonopiperidine-2-carbonyl}-amino)-3-(1*H*-indol-3-yl)propionic Acid (55c). Following the preparation of **55a** gave compound **55c** as a yellowish foam, 29 mg (93%, two steps): $[\alpha]_D$ +8.8 (*c* 0.5, H_2O); IR (KBr) 3408, 2956, 1698, 1657, 1590, 1442, 1386, 1351, 1237, 1178, 1089 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 7.78 (m, 2H), 7.62 (m, 2H), 7.22 (m, 1H), 7.17 (m, 2H), 6.97 (bs, 2H), 6.60 (m, 2H), 4.50 (m, 1H), 4.06 (m, 1H), 3.60−3.46 (m, 2H), 3.18 (t, 1H, J = 9.0 Hz), 3.04−3.01 (m, 1H), 2.89−2.84 (m, 1H), 1.86−1.78 (m, 1H), 1.62−1.41 (m, 3H), 1.36−1.23 (m, 1H), 1.10−0.82 (m, 3H), 0.73−0.62 (m, 1H), 0.40 (m, 3H), −0.08 (m, 3H); ^{13}C (100 MHz, D_2O) δ 178.1, 168.4, 164.2, 135.5, 134.3, 130.7, 130.2, 126.6, 126.4, 126.2, 122.9, 120.9, 120.1, 118.4, 117.7, 111.0, 109.5, 55.3, 53.5 (d), 53.1, 40.5, 38.1, 36.8, 30.1, 28.1, 26.0, 27.2, 23.2, 23.0, 19.5; ^{31}P (161.3 MHz, D_2O) δ 10.5; LCMS (MH^+) 675.1, (MNa^+) 697.1; HRMS for $C_{35}H_{39}N_4O_8P$ (MH^+) calcd 675.25783, obsd 675.25870; (MNa^+) calcd 697.23977, obsd 697.24019.

(2*R*,4*S*,5*R*,6*R*)-(2*S*)-({5-[2-(1,3-Dioxo-1*H*,3*H*-benzo[*de*]isoquinolin-2-yl)ethyl]-4-isobutyl-6-phosphonopiperidine-2-carbonyl}-amino)-3-(1*H*-indol-3-yl)propionic Acid (55d). Following the preparation of **55a** gave compound **55d** as a yellowish foam, 29 mg (68%, two steps): $[\alpha]_D$ −23.8 (*c* 0.5, H_2O); IR (KBr) 3408, 2957, 1695, 1652, 1590, 1441, 1385, 1352, 1237, 1111 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 7.88 (m, 4H), 7.38−7.34 (m, 2H), 7.16 (d, 1H, J = 7.6 Hz), 6.90 (m, 2H), 6.61 (t, 1H, J = 7.0 Hz), 6.52 (t, 1H, J = 6.6 Hz), 4.43 (dd, 1H, J = 5.3, 8.4 Hz), 3.69−3.60 (m, 1H), 3.58−3.45 (m, 2H), 3.11−2.96 (m, 2H), 2.82 (dd, 1H, J = 8.9, 14.2 Hz), 2.21−2.13 (m, 1H), 1.77−1.73 (m, 1H), 1.41−1.34 (m, 1H), 1.31−1.21 (m, 1H), 1.13−1.03 (m, 2H), 0.96−0.82 (m, 2H), 0.77−0.68 (m, 1H), 0.61 (d, 3H, J = 5.5 Hz), 0.41 (d, 3H, J = 5.3 Hz); ^{13}C (100 MHz, D_2O) δ 177.9, 170.0, 164.2, 135.2, 134.5, 130.9, 130.3, 126.9, 126.5, 126.3, 123.4, 120.7, 120.1, 118.4, 117.8, 110.9, 109.5, 55.1, 54.1 (d), 52.5, 39.4, 39.1, 35.7, 30.2, 26.8, 25.1, 24.4, 24.0, 22.0, 21.0; ^{31}P (161.3 MHz, D_2O) δ 11.0; LCMS (MH^+)

674.8, (MNa^+) 697.1; HRMS for $C_{35}H_{39}N_4O_8P$ (MH^+) calcd 675.25783, obsd 675.25818; (MNa^+) calcd 697.23977, obsd 697.24061.

(2*S*,4*S*,5*R*,6*S*)-(2*S*)-({5-[2-(1,3-Dioxo-1*H*,3*H*-benzo[*de*]isoquinolin-2-yl)ethyl]-4-isobutyl-6-phosphonopiperidine-2-carbonyl}-amino)-3-(1*H*-indol-3-yl)propionic Acid (56). Prepared following the synthetic sequence for the preparation of **55a**, starting from L-oxopipecolic acid: 13 mg; $[\alpha]_D$ −4.3 (*c* 0.5, H_2O); ^1H (400 MHz, D_2O) δ 8.01 (m, 4H), 7.47 (m, 2H), 7.35 (m, 1H), 7.16 (m, 1H), 7.01 (s, 1H), 6.82 (m, 2H), 4.32 (t, 1H, J = 7.0 Hz), 3.98 (m, 1H), 3.78 (m, 1H), 3.12−3.02 (m, 3H), 2.82 (t, 1H, J = 7.0 Hz), 2.05−1.76 (m, 2H), 1.29−0.87 (m, 4H), 0.47−0.28 (m, 2H), 0.21 (m, 3H), 0.04 (m, 1H), 0.01 (m, 3H); ^{31}P (161.3 MHz, D_2O) δ 12.9; LCMS (MNa^+) 697.1; HRMS for $C_{35}H_{39}N_4O_8P$ (MH^+) calcd 675.25783, obsd 675.25757; (MNa^+) calcd 697.23977, obsd 697.23928.

(2*S*,4*S*,5*R*,6*R*)-(2*S*)-({5-[2-(1,3-Dioxo-1*H*,3*H*-benzo[*de*]isoquinolin-2-yl)ethyl]-4-isobutyl-6-phosphonopiperidine-2-carbonyl}-amino)-3-(1*H*-indol-3-yl)propionic Acid (57). Prepared following the synthetic sequence for the preparation of **55a**, starting from L-oxopipecolic acid: 12 mg; $[\alpha]_D$ +17.1 (*c* 0.5, H_2O); ^1H (400 MHz, D_2O) δ 7.92−7.84 (m, 4H), 7.39−7.37 (m, 2H), 7.11 (m, 2H), 7.01 (s, 1H), 6.74 (m, 2H), 4.26−4.24 (m, 1H), 3.87−3.82 (m, 2H), 3.67−3.64 (m, 2H), 1.91 (m, 2H), 1.76 (m, 1H), 1.60 (m, 1H), 1.11−1.03 (m, 5H), 0.50 (d, J = 6.3 Hz, 3H), 0.46 (m, 5H); ^{31}P (161.3 MHz, D_2O) δ 10.3; LCMS (MH^+) 675.1; HRMS for $C_{35}H_{39}N_4O_8P$ (MH^+) calcd 675.25783, obsd 675.25760; (MNa^+) calcd 697.23977, obsd 697.23952.

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Supporting Information Available: Experimental procedures for ECE inhibition determination, ^1H and ^{13}C NMR spectra copies, HPLC profile of final compounds, and X-ray CIF files for **11a**, **11b**, and **53b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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