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Single-Step Ugi Multicomponent Reaction for the Synthesis of Phosphopeptidomimetics

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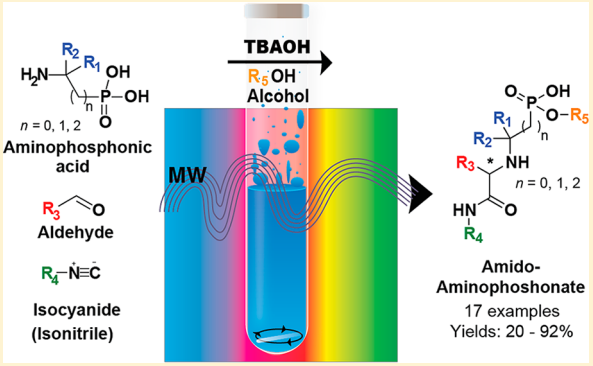
Supporting Information

ABSTRACT: This article describes the design and optimization of an effective microwave-assisted multicomponent reaction to produce a novel class of phosphopeptidomimetic compounds. When using aminophosphonic acids (α, β, γ), aldehydes, and isocyanides as reactants and alcohols as solvents, these building blocks are merged to functionalized amido-aminophosphonate structures in a novel Ugi-type one-pot transformation reaction. A high level of structural diversity can be achieved with this synthetic approach, providing a platform for the production of functionalized building blocks for novel bioactive molecules. The general scope of this multicomponent synthetic protocol is explored by variation of reaction parameters together with an evaluation of a diverse set of reaction substrates. The applicability of this reaction has been demonstrated by the synthesis of 17 distinct compounds giving yields in the range of 20−92%.



INTRODUCTION

Amino acids play a key role in biochemistry, constituting the structural units of peptides, proteins and enzymes. As phosphorus analogues of amino acids, aminophosphonic acids can efficiently act as biomimetics undergoing competing interactions at the active site of enzymes and cell receptors.[1−4]

In addition, phosphonates have demonstrated to be effective chelating agents,[5] capable of controlling the uptake or the removal of metal ions in living systems.[3] These unique characteristics render aminophosphonic acids and phosphonates of considerable biological and pharmacological interest, with applications as antitumor,[6−10] neuroactive,[8,11] antihypertensive,[8,12] antimicrobial,[8,13,14] herbicidal[1,8] and imaging agents.[15]

In the past decades, a significant progress in the field of molecular biology together with the development of high-throughput drug screening methodologies have led to an ever-increasing demand for prospective drug candidates. In this context multicomponent reactions (MCRs), because of their efficiency, ease of automation along with their chemical diversity-generating power, have attracted the attention of the academic and industrial research community.[16,17] Within the class of MCRs, those based on the peculiar reactivity of isocyanides, and in particular the Ugi reaction, have been among the most widely used.[18−24]

Typically, Ugi four component reactions (U-4-CR) provide access to peptide-like derivatives by a one pot condensation of an aldehyde, an amine, a carboxylic acid and an isocyanide.[19,25]

Effective variations of the U-4-CR are the Ugi five-center four-component reaction (U-5C-4CR) and the Ugi-4-center-3-component reaction (U-4C-3CR). In these intramolecular versions of the Ugi reaction α- and β-amino acids are used as bifunctional reactants, the former to generate 1,1-iminodicarboxylic acids[26,27] and the latter providing alicyclic β-lactams.[28,29] The exact mechanism of such reactions has not been disclosed yet; however, it has been postulated that in both cases the reaction evolves through a cyclic intermediate (6- and 7-membered ring, respectively; vide infra).[30] In the case of β-amino carboxylic acids, a lactam structure is generated via ring contraction of a 7-membered intermediate (U-4C-3CR), while with α-amino acids, the intermediate cannot undergo such reaction, and methanol (used as solvent) acts as nucleophile generating iminodicarboxylic adducts.[26,27] These synthetic procedures are restricted to amino carboxylic acids and typically are carried out at low temperature (−30 °C, 0 °C or rt) and require extended reaction times (often in the range of days).

Ugi reaction with aminophosphonic acids has not been proposed yet. However, a related reaction using an aldehyde bearing a phosphate group has been attempted by Sutherland and co-workers.[31] In this former contribution, the extension of the Ugi reaction to phosphate compounds failed (while it was successfully applied to the Passerini reaction) because of an intramolecular trapping of the nitrilium ion by the phosphate

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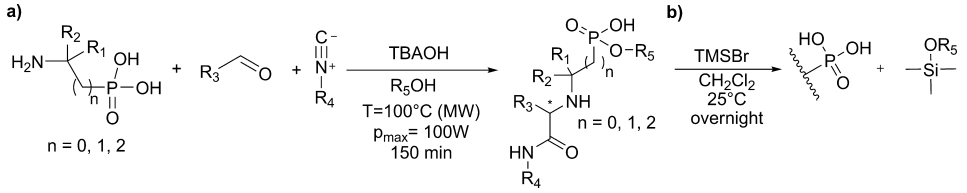
Scheme 1. Reaction Scheme and Conditions of Phospho Ugi Reaction (a) And the Hydrolysis of the Generated Ugi Products (b)



reactant that leads to a different reaction mechanism. Herein, we can show that by the current chemistry the Ugi reaction can be extended to phosphonic acid substrates, starting from aminophosphonic acids to access a novel class of amido-aminophosphonate molecules in an easy and selective way. The newly developed method makes use of microwave heating in order to enhance reaction rates,[32] generating the corresponding amido-aminophosphonate products from α-, β- and γ-aminophosphonic acid, aldehyde, isocyanide and alcohol via U-5C-4CR. As an extension of our work we also describe conditions for quantitative hydrolysis of this novel class of monoalkyl phosphonate compounds to generate the corresponding phosphonic acids (Scheme 1).

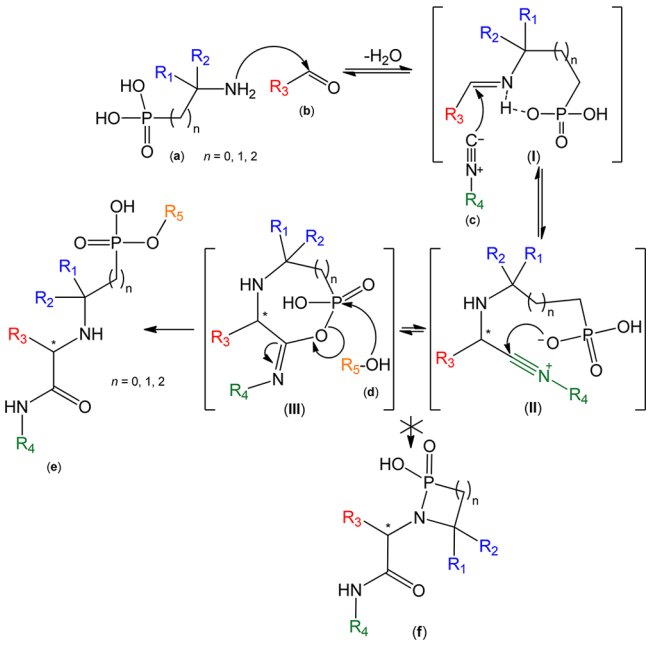
Moreover, as application of the presented combinatorial approach, new zwitterionic chromatographic selectors were designed and prepared adopting the synthetic strategy described in this contribution, as reported elsewhere.[33]

RESULTS AND DISCUSSION

Reaction Mechanism. A reaction mechanism similar to that suggested by Ugi et al.[26,27] for amino carboxylic acids can be proposed (Scheme 2).

In the first step of the cascade reaction, the amino group of the aminophosphonic acid (**a**) condenses with the aldehyde (**b**) to form the imine intermediate (**I**). The Schiff's base is then protonated by the phosphonic acid group followed by addition of the isocyanide (**c**) to create a nitrilium intermediate (**II**).[34] Subsequently, the nucleophilic attack of the phosphonate anion generates an *O*-phosphorylimine intermediate (**III**), which is then subjected to nucleophilic attack by the solvent (**d**; alcohol, fifth reacting center), followed by a Mumm rearrangement to the corresponding racemic 1-(1-alkylcarboxamidoalkan-2-yl-amino)alkylphosphonic acid monoalkylester derivative (**e**). NMR and X-ray analysis confirmed the molecular structure postulated by the reaction mechanism (the crystallographic structure is available in the Supporting Information).

Scheme 2. Postulated Reaction Mechanism of the Phospho Ugi Reaction



Synthesis Optimization. As mentioned above Ugi-5C-4CRs with amino acids are typically carried out at low temperature (starting at −30 °C and then gradually warmed up to ambient temperature[26]) and require extended reaction times (in the range of 24−48 h) to generate the corresponding 1,1-iminodicarboxylic acids in good yields. However, under such conditions, we did not observe the formation of the corresponding 1-amido 1-aminophosphonate derivatives when aminophosphonic acids were employed as reactants. Thus, reaction conditions were optimized using a single set of substrates, namely, (2-aminopropane-2-yl)phosphonic acid, benzaldehyde and 2,6-dimethylphenyl isocyanide using methanol as solvent (Table 1). In the course of the optimization studies, we systematically evaluated the impact of temperature, mode of heating, solvent and ion-pairing reagents using reversed phase liquid chromatography coupled to mass spectrometry (RPLC−MS) for reaction monitoring. The results of these investigations are summarized in Table 1.

Starting from the conditions described by Ugi et al.,[26] increasing the temperature up to 50 °C we could obtain the desired product in 35% yield after two days of reaction. Given this rather low reaction rate, we decided to employ microwave (MW) heating[35] in order to increase the heat-exchange efficacy and thus shorten the reaction time. The acceleration of the reaction proved to be significant; employing MW heating under the same temperature and reaction conditions as for the oil bath approach, the reaction time could be reduced from 2 days to 90 min at comparable yields (compare Table 1 entries 5 and 10). Increasing the reaction temperature to 100 °C with slightly prolonged reaction time provided the best results. A maximal yield of 45% was achieved with a temperature of 100 °C under microwave heating for 150 min (maximum power set to 100 W).

In the following experiments we evaluated the influence of the reaction medium. We employed apolar and dipolar aprotic solvents under MW heating at 100 °C (Table 1). Reactions performed in dichloromethane (DCM) or toluene gave origin to a heterogeneous system in which the aminophosphonic acid remained mostly dispersed as precipitate and did not enter the reaction (therefore no product was detected). When instead DMSO and trifluoroethanol were tested, a part of the aminophosphonic acid substrate was dissolved; however, after reaction the RPLC−MS analysis revealed the formation of

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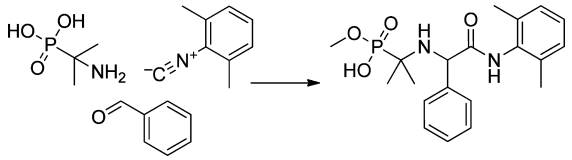
Table 1. Optimization of Reaction Conditions[a]



entry	solvent	T [°C][b]	time [min]	MW [W]	yield [%][c]
1	MeOH	−30 to 0	2 days[d]	–	0
2	MeOH	0	2 days[d]	–	0
3	MeOH	25	2 days[d]	–	0
4	MeOH	40	2 days[d]	–	20
5	MeOH	50	2 days[d]	–	35
6	DCM	100	30	100	0[e]
7	Toluene	100	30	100	0[e]
8	DMSO	100	30	100	0[e]
9	CF_3CH_2OH	100	30	100	2[f]
10	MeOH	50	90	100	28
11	MeOH	75	90	125	33
12	MeOH	100	30	100	38
13	MeOH	100	90	100	42
14	MeOH	100	90	50	42
15	MeOH	100	90	150	41
16	MeOH	100	150	100	45
17	MeOH	125	90	100	37
18	MeOH	150	90	100	15

[a]All reactions were carried out with (2-aminopropane-2-yl) phosphonic acid (0.2 mmol), benzaldehyde (0.3 mmol), 2,6-dimethylphenylisocyanide (0.3 mmol) in the indicated solvent (2 mL). [b]Temperature measured via external sensor. [c]Determined through calibrated RPLC−MS analysis. [d]Conventional heating. [e]The yield refers to the corresponding mono-amido-aminophosphonate or amido-aminophosphonic acid. [f]The yield refers to the corresponding mono-2,2,2,-trifluoroethyl amido-aminophosphonate.

several side products. In the case of trifluoroethanol, small percentages (ca. 2%) of the corresponding monoester of the amido-aminophosphonate target product were detected, while no product was observed in DMSO. The use of trifluoroethanol is reported to maximize intramolecular attack in Ugi type reaction,[36] enhancing the rates of formation of the lactam product (Scheme 2, **f**). However, under the studied conditions this effect was observed neither for α nor for β amino-phosphonic acids (Table 1 entry 9, data for β aminophosphonic acids are not shown).

Among the solvents tested, methanol was the only solvent in which the reaction led to the formation of the target compound in reasonable yields. Although relatively low molar concentrations of the aminophosphonic acid (0.1 M) in the adopted reaction conditions were used, after the reaction part of the reactant remained as solid. We therefore concluded that reaction yields could have been impaired by the poor solubility of the zwitterionic aminophosphonic acids. Thus, we decided to introduce an ion-pairing reagent to enhance solubility of these reactants. Both acidic (methanolic HCl, acetic acid, trifluoro-acetic acid) and basic (NaOH, *N*,*N*-diisopropylethylamine DIPEA, tetrabutylammonium hydroxide TBAOH) additives enhanced the solubility of aminophosphonic acids; however, their influence on the product formation was different. The results, summarized in Table 2, indicate that protonation of the amino group in an acidic environment hinders the initial nucleophilic attack of the amino group at the carbonyl group of the aldehyde. This behavior diminishes the benefit of higher

Table 2. Effect of Ion-Pairing Agent and Its Concentration on the Ugi-5C-4CR[a]

entry	ion pairing agent	mol equiv[b]	yield [%][c]
1	–		45
2	CH_3COOH	0.5	2
3	HCl	0.5	0
4	TFA	0.5	0
5	NaOH	0.5	16
6	DIPEA	0.5	21
7	TBAOH[d]	0.1	58
8	TBAOH[d]	0.3	71
9	TBAOH[d]	0.5	79
10	TBAOH[d]	1.0	12

[a]All the reactions were carried out with the same reactants and the same concentrations as in Table 1 in MeOH (2 mL) for 150 min at 100 °C with maximum MW of 100 W. [b]Rel. to the aminophosphonic acid. [c]Determined by calibrated RPLC−MS analysis. [d]TBAOH, tetrabutylammonium hydroxide.

solubility of the substrate given by acidic media. Thus, basic media are favorable for the synthesis.

Among NaOH, DIPEA and TBAOH, the best results were achieved using the latter in a molar ratio of 1:2 with respect to the aminophosphonic acid (Table 2 entry 9). This finding suggests that strong organic bases capable of forming free ion-pairs with the phosphonic acid functional group do not represent an impediment to intramolecular cyclization.

The purification of this new type of monoalkyl amido-aminophosphonate compounds can be accomplished employing column chromatography on silica (Table 3 product **6**) or liquid−liquid extraction (Table 3 product **8**). Alternatively, chiral anion exchange chromatography employing quinine or quinidine carbamate phases[37] can be chosen as a general purification process to obtain the target compounds in their enantiomerically pure forms with high chemical and stereo-chemical purity as well as good recovery. The comparison of structurally related compounds (Table 3 products **5** and **6**) shows that chiral anion exchange chromatography and column chromatography purification approaches provided similar yields (66 and 71%, respectively). The first approach, however, has the advantage that, besides removal of unreacted educts and chemical impurities, single enantiomers can be isolated in a single step purification process. A detailed description of the basis of retention and the mechanism of enantioseparation for the products generated by the synthetic approach presented herein is published elsewhere.[38]

Effect of Substrates on the Reaction. On the basis of the established optimized reaction conditions (summarized in Scheme 1), we explored the synthetic scope using a variety of aldehydes, isocyanides and aminophosphonic acids (Table 3). We did not observe significant differences in the reactivity of aliphatic and aromatic aldehydes or isonitriles. Partial reaction diasteroselectivity was observed when chiral aminophosphonic acids were adopted, with higher *d.e.* (diastereomeric excess) values given by bulkier substrate (Table 3 product **9** with respect to **7**, **10**, **13**). In contrast to what was previously reported by Ugi et al. using L-amino acids under different reaction conditions,[26,27] we did not observe enhancement of diastereomeric excess when enantiomerically pure amino-phosphonic acid reactants were employed (chromatograms of the diastereomer and enantiomer separation of Table 3 product

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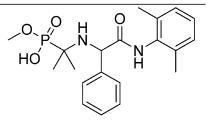
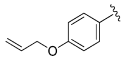
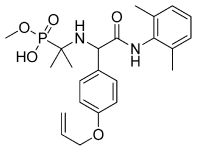
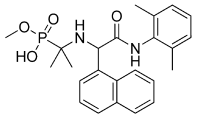
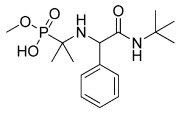
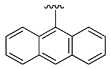
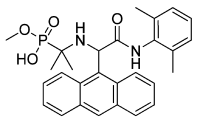
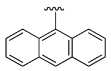
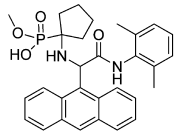
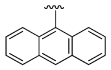
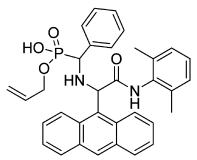
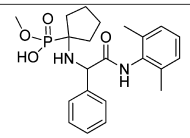
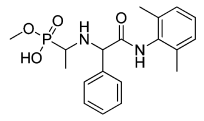
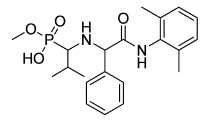
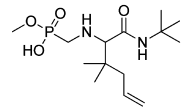
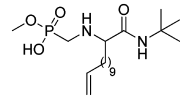
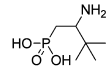
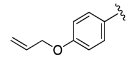
Table 3. Ugi-5C-4CR Reaction Yields (Related to Starting Aminophosphonic Acid) For Reaction in MeOH with Different Aminophosphonic Acids, Aldehydes, and Isocyanides (Compound Numbers Refer to Products)

Aminophosphonic acid (R^1, R^2)	Aldehyde (R^3)	Isocyanide (R^4)	Product
R^1,R^2= CH_3, *n*= 1			 **1** Y: 71 % [a], 66% [b]
R^1,R^2= CH_3, *n*= 1			 **2** Y: 50 % [b]
R^1,R^2= CH_3, *n*= 1			 **3** Y: 66 % [b]
R^1,R^2= CH_3, *n*= 1			 **4** Y: 80 %[b]
R^1,R^2= CH_3, *n*= 1			 **5** Y: 66 % [b]
			 **6** Y: 71 % [c]
R^1= Ph, R^2= H, *n*= 1			 **7** Y: 32 % [b] [d] 44 % *de*

Aminophosphonic acid (R^1, R^2)	Aldehyde (R^3)	Isocyanide (R^4)	Product
			 **8** Y: 66 % [e]
R^1=CH_3, R^2=H, *n*= 1			 **9** Y: 34 % [b] 9 % *de*
R^1=$CH(CH_3)_2$, R^2=H, *n*= 1			 **10** Y: 55 % [b] 48 % *de*
R^1, R^2=H, *n*= 1			 **11** Y: 92 % [b]
R^1, R^2=H, *n*= 1			 **12** Y: 68 % [b]
			**13** Y: 43 % [b] 68 % *de*

[a]Liquid−liquid extraction (H_2O/DCM) followed by evaporation under a vacuum and crystallization in toluene [b]Chiral anion-exchange chromatography with quindine carbamate based column; mobile phase compositions are reported in the compound characterization section [c]Silica flash chromatography with DCM/MeOH (2:1; v/v) as mobile phase [d]Reaction performed in allyl alcohol [e]Liquid−liquid extraction (H_2O/DCM) followed by evaporation under a vacuum.

9 obtained from racemic and enantiomerically pure reactants are reported in ref 38).

Surprisingly, the use of aminophosphonic acids of a different spacer length between the amino and the phosphonic acid group (α-, β- and γ-aminophosphonic acids, Table 4 product **16**, **17**, **18**) affected the product formation only in terms of yield but not the general reaction mechanism. In contrast, it has been reported that β- or γ-amino carboxylic acids in Ugi reactions provided only lactam structures (undergoing U-4C-3CR instead of U-5C-4CR).[28,29] No phosphonamidate lactam product (Scheme 2, **f**) was generated under the conditions reported here. The lack of cyclization in the final product could be attributed to higher thermodynamic stability of the 1-(1-alkylcarboxamidoalkan-2-yl-amino)alkylphosphonic acid mono-

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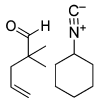
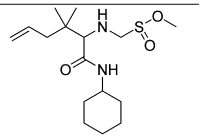
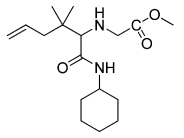
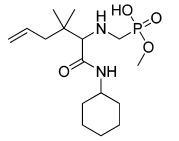
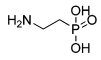
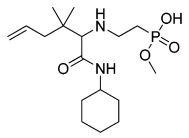
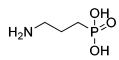
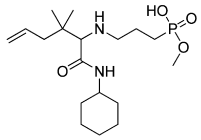
Table 4. Influence of the Type and Length of the Amino Acid Component on the Reaction Yield

Reaction mixture	Amino Acid	Product
		 **14** Y: 0 % [a]
		 **15** Y: 21 % [b]
		 **16** Y: 92 % [b]
		 **17** Y: 42 % [b]
		 **18** Y: 20% [b]

[a]No product according to RPLC−MS measurement. [b]Chiral anion-exchange chromatography with quinidine carbamate based column; mobile phase compositions are reported in the compound characterization section.

alkylester structure (Scheme 2, **e**) with respect to its phosphonamidate lactam equivalent (Scheme 2, **f**). Additionally, using high temperature, pressure and pH, the reactivity of methanol in the methanolysis reaction of the cyclic intermediate (Scheme 2, **III**) is much higher than under reported conditions.[28,29]

Although no lactam product was detected, we observed a marked decrease in reaction yield when aminophosphonic acids with longer spacer length between the amino and the phosphonic acid group were employed. Reaction rates declined in the order α- > β- > γ-aminophosphonic acids (cf. Table 4 product **16**, **17**, **18**). A possible explanation for the decrease of yield in this order is that 6-membered rings of the cyclic intermediate III (Scheme 2) as resulting for α-amino phosphonic acids are more favorable than larger rings such as 7- and 8-membered rings for β- and γ-aminophosphonic acids, respectively.

In the course of this study, we also investigated the efficiency of the established MCR reaction scheme upon replacing the aminophosphonic acid component by different types of amino acids (carboxylic and sulfonic acid moieties; Table 4 product **15** and **14**). The reaction protocol was successful for amino carboxylic acids, although with lower yields.[27] However, the protocol failed to produce detectable amounts of products when aminosulfonic acids were employed as reactant.

Although it has been reported that the UGI-5C-4CR can work well with nucleophiles other than methanol such as other alcohols, primary or secondary amines, the only example reported in literature are with trifunctional amino acids such as lysine,[26] homoserine[39] or bifunctional aldehydes such as glycolaldehyde.[36] In order to assess the possibility of generating further molecular diversity via the phosphoester residue (R_5), we tested allyl alcohol as the reaction solvent. The incorporation of this solvent into the product was indeed confirmed (Table 3 product **7**) Also other alcohols were tested as reaction solvent, and LC−MS confirmed incorporation of the alcoholic component in the product (LC−MS analysis of product derived by reaction mixture in 2-propanol and benzyl alcohol are reported[38]). However, yields were generally lower with solvents different from methanol, indicating that probably a specific optimization of the reaction conditions has to be performed to improve the reaction rate and yield when another solvent is used.

Hydrolysis of Phosphonic Acid Ester. In order to quantitatively obtain phosphonic acid derivatives of the amido-aminophosphonate compounds without the risk of hydrolysis of the amide bond, we tested various conditions,[12,40] monitoring the product formation with LC−MS. The use of trimethylsilyl bromide in dichloromethane proved to be the most convenient and efficient method (Scheme 1b). Under these conditions, quantitative yields were obtained, and the integrity of the stereogenic center(s) within the substrates remained unaffected (products **19**, **20**, **21** after hydrolysis of Table 3 products **1**, **12**, **16** respectively; more details are reported in the Supporting Information).

■ CONCLUSIONS

In summary, we devised a generally applicable multicomponent reaction protocol that enables synthesis of amido-aminophosphonate structures in a fast and efficient manner from α-, β-, γ- aminophosphonic acids, aldehydes, isocyanides and methanol. We investigated the influence of structural variation of reactants, temperature, reaction time, and solvent on the yield of the product. The established protocol can be used with a large variety of substrates providing corresponding amido-aminophosphonates in moderate to high yields. This novel type of Ugi five center four component reaction opens up the possibility to obtain libraries of phosphopeptidomimetic compounds as new lead structures with potential bioactivity.

■ EXPERIMENTAL SECTION

Materials. (2-Aminopropane-2-yl)phosphonic acid, (1-aminocyclopentyl)phosphonic acid, (1-aminoethyl)phosphonic acid, [amino(phenyl)methyl]phosphonic acid, (1-aminopropyl)phosphonic acid were of a purity grade of at least 97% and supplied by Acros Organics (Geel, Belgium). (1-Aminomethyl)phosphonic acid (98%) was purchased from Epsilon Chimie (Brest-Guipavas, France). (1-Amino-2-methylpropyl)phosphonic acid and (2-amino-3,3-dimethylbutyl)phosphonic acid were synthesized according to literature procedure.[41]

General Methods. Microwave-assisted reactions were performed in sealed glass vials using a temperature and pressure controlled microwave (90801 CEM discovery system) operated through Chem Driver Software 3.6.0. Temperature was measured via external sensor and set to 100 °C. The microwave reactor was operated under stirring

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in "discovery mode", the maximum power set to 100 W, and maximum pressure to 20 bar. The ramp time was set to 2 min, and the given conditions were maintained for 150 min.

^{1}H, ^{13}C, ^{31}P NMR spectra were acquired at 25 °C in CD_3OD if not specified differently; ^{31}P NMR spectra are ^{1}H decoupled and referenced using 85% phosphoric acid. Chemical shifts (δ) are given in parts per million (ppm) and the coupling constants (J) in Hertz (Hz). COSY, HSQC and HMBC experiments were performed in order to clarify the assignment of ^{1}H and ^{13}C resonances.

Mass spectrometric detection was carried out using an electrospray interface (ESI) on an ion trap. High-resolution mass spectra (HRMS) were recorded by direct injection (2 μL of a 2 μM solution in water/acetonitrile 50:50 v/v and 0.1% formic acid) with a TOF instrument equipped with an electrospray ion source in negative mode (flow rate 10 μL/min, source voltage −3.5 kV, sheath gas flow 10 units, capillary temperature 250 °C). The high-resolution mass spectrometer was calibrated prior to measurements with a calibration mixture.

All reaction batches were characterized adopting reversed-phase (RP) chromatography using gradient elution chromatography (mobile phase A: H_2O containing 0.1% (v/v) formic acid, mobile phase B: MeOH containing 0.1% (v/v) formic acid; gradient: 20−100% B in 20 min). The flow rate adopted was 0.4 mL/min at 25 °C, the sample injection volume 2.5 μL and detection was performed at 214 nm. In order to evaluate the results from the synthesis optimization in a quick manner without purifying each batch, we experimentally determined the linear relationship presented between the chromatographic peak area and the compound quantity for compound **1**. The obtained linear correlation was $y = 267.26x - 37.705$ with $R^2 = 0.9993$

The preparative HPLC purification and enantioseparation was carried out on a preparative column (250 × 16 mm ID) packed with 100 Å, 10 μm silica gel modified with *tert*-butylcarbamoylquinidine selector[37] (prototype of CHIRALPAK QD-AX) from Chiral Technologies Europe (Illkirch, France). The mobile phase composition is specified in the compound characterization. Flow rate was set up to 20 mL/min. The injection volume was up to 5 mL per run and the detection was carried out at 210, 220, 240, and 254 nm.

In the X-ray crystal structure analysis all hydrogen atoms were clearly identified in the difference map; C−H were then placed in calculated positions and refined using a riding model, and N−H were freely refined. Measurements were performed at room temperature. Cell determined at 300 K: a = 9.504(37), b = 12.129(52), c = 13.321(55), α = 108.346(83), β = 96.052(72), γ = 95.623(82).

General Procedure for the Synthesis of Amido-aminophosphonate Derivatives (1−18). The aminophosphonic acid (1 mol equiv; final molar concentration in the reaction mixture of 0.25 M) and the selected aldehyde (1.5 mol equiv) were dissolved in MeOH in a microwave glass vial. Tetrabutylammonium hydroxide (0.5 equiv from 1 M methanolic solution) and isocyanide (1.5 mol equiv) were sequentially added to this mixture. The microwave reaction vial was sealed, heated and stirred under microwave irradiation at 100 °C for 150 min. In case of the presence of residual unreacted substrates (generally constituted by the unreacted aminophosphonic acid), the reaction mixture was filtered. The filtrate was evaporated under reduced pressure, and the crude residue was purified by column chromatography or chiral anion exchange chromatography, giving viscous oils or solids as products.

Reaction products purified by chiral anion-exchange chromatography (Table 3 purification procedure a) followed by evaporation of the mobile phase under a vacuum were typically obtained as formate salts due to excess of formic acid in the mobile phase. When the formic acid concentration of the eluent was not high enough to allow dissociation of the tetrabutylammonium phosphonate ion-pair or the ion-pair was very strong, the tetrabutylammonium salt was typically isolated. Products from liquid−liquid extraction and subsequent crystallization (Table 3 purification procedure b) were obtained as zwitterionic compounds without any counterion. The same is valid when a crystallization step was performed after chiral anion-exchange chromatography or column chromatography, while it does not apply to liquid−liquid extraction per se (Table 3, purification procedure e). Another purification procedure was silica flash chromatography (Table 3 purification procedure c) with MeOH/DCM mixtures as eluents. Since eluents contained no acidic or basic additives, the mobile phase was not capable of dissociating the tetrabutylammonium ion-pairs in the course of the purification procedure, and these compounds were therefore isolated as tetrabutylammonium salts.

Methyl [2-({1-[(2,6-dimethylphenyl)carbamoyl]-1-phenylmethyl}-amino)propane-2-yl]phosphonate (in zwitterionc form) (Table 3, product 1). Compound **1** was prepared from (2-aminopropane-2-yl)phosphonic acid (39 mg, 0.24 mmol), benzaldehyde (38 mg, 0.36 mmol) and 2,6-dimethylphenyl isocyanide (47 mg, 0.36 mmol). Purification was done by preparative chromatography on CHIRALPAK QD-AX; k_1 = 2.82; k_2 = 3.08 (mobile phase MeOH/ACN 50/50; v/v containing 25 mM formic acid, apparent pH adjusted in mixture to 4 with NH_4OH). The product was obtained as a sticky solid (yield 79 mg, 0.21 mmol, 82%; purification procedure a). An alternative purification procedure consisted of liquid−liquid extraction (H_2O/DCM) followed by evaporation under a vacuum and crystallization in toluene (yield 66%; purification procedure b).

Optical rotation: first eluted enantiomer from CHIRALPAK QD-AX $[\alpha]^{rt}$ Na (589 nm) 64.2; Hg (578 nm) 67.5; (546 nm) 79.1; (436 nm) 148.1 (c = 1.02 g/100 mL, methanol), ee >99%; second eluted enantiomer $[\alpha]^{rt}$ Na (589 nm) −71.5; Hg (578 nm) −73.8; (546 nm) −85.2; (436 nm) −153.7 (c = 1.03 g/100 mL, methanol), ee 74%. A fraction of the second eluted enantiomer was redissolved in DMSO and allowed to concentrate slowly at rt to give crystals suitable for X-ray analysis (Supporting Information). The absolute configuration was not determined because of the centrosymmetric nature of the obtained crystal (cocrystallization of the two enantiomers; triclinic $P\bar{1}$ crystal system). The NMR, IR and MS characterization of the compound was performed on its second eluting enantiomer: ^{1}H NMR (400 MHz, CD_3OD, 25 °C) δ 7.61 (d, ^{3}J (H,H) = 7.3 Hz; 2H; Ar−H), 7.40 (m, 3 H; Ar−H), 7.04 (m, 3 H; Ar−H), 5.94 (s, 1 H; C*H*−NH), 3.67 (d, ^{3}J (H,P) = 9.9 Hz, 3 H; OCH_3), 2.06 (bs, 6 H; 2 × Ar−CH_3), 1.46 (d, ^{3}J (H,P) = 13.6 Hz, 6 H; −NH−C(CH_3)$_2$) ppm; ^{13}C NMR (100 MHz, CD_3OD, 25 °C) δ 170.2 (C═O), 136.5 (Cq), 132.5 (Cq), 132.3 (Cq), 130.2 (Ar−CH), 129.7 (Ar−CH), 129.2 (Ar−CH), 128.6 (Ar−CH), 61.1 (d, J = 6 Hz, CH), 60.9−59.4 (J = 143 Hz −C(CH_3)$_2$), 52.3−52.2 (J = 7 Hz, OCH_3), 23.5 (CH_3), 22.4 (CH_3), 20.4 (Ar−CH_3) ppm; ^{31}P NMR (162 MHz, CD_3OD) 18.92 ppm; FT-IR $\tilde{\nu}$ = 3248, 3037, 2794, 1665, 1600−1400, 1296 cm^{-1}; MS (ESI) m/z 389.2 [M − H]$^-$; HRMS (ESI-TOF) m/z [M − H]$^-$ Calcd for $C_{20}H_{26}N_2O_4P$ 389.1629, found [M − H]$^-$ 389.1640.

Methyl [2-({1-[(2,6-dimethylphenyl)carbamoyl]-1-(4-allyloxyphenyl)methyl}amino)propane-2-yl]phosphonate (as formate salt) (Table 3, product 2). Compound **2** was prepared from (2-aminopropane-2-yl)phosphonic acid (100 mg, 0.64 mmol), 4-allyloxybenzaldehyde (155 mg, 0.96 mmol) and 2,6-dimethylphenyl isocyanide (125 mg, 0.96 mmol). Purification was performed by preparative HPLC on CHIRALPAK QD-AX; k_1 = 3.23; k_2 = 3.51 (mobile phase MeOH/ACN 50/50; v/v containing 25 mM formic acid, apparent pH adjusted in mixture to 4 with NH_4OH). The product was isolated as a sticky solid (yield 138 mg, 0.64 mmol; 50%). The NMR, IR and MS characterization of the compound was performed on its second eluting enantiomer. From the NMR signals we observed the presence of residual formic acid from the anion exchange purification process: ^{1}H NMR (400 MHz, CD_3OD, 25 °C) δ 7.6 (d, ^{3}J(H,H) = 8.15 Hz, 2H; Ar−H), 7.1 (m, ^{3}J(H,H) = 6 Hz, 5H; Ar−H), 6.1 (m, ^{3}J(H,H) = 5.4 Hz, 1H; —CH_2—C*H*═CH_2) 5.7 (s, 1H; C*H*−NH), 5.4, 5.3 (each 1H, dq, $^{3}J(H,H)_1$ = 17.3 Hz, $^{3}J(H,H)_2$ = 3.0 Hz, CH_2—CH═CH_2), 4.6 (dt, $^{3}J(H,H)_1$ = 5.1 Hz, $^{3}J(H,P)_2$ = 1.5 Hz; 2H; CH_2−CH═CH_2), 3.7 (d, ^{3}J(H,H) = 10 Hz, 3H; OCH_3), 2.0 (bs, 6 H; 2 × Ar−CH_3), 1.54 (dd,$^{3}J(H,H)_1$ = 12.9 Hz, $^{3}J(H,P)_2$ = 6.3 Hz 6 H; −NH−C(CH_3)$_2$) ppm; ^{13}C NMR (101 MHz, MeOD, 27 °C) δ 170.2 (C═O), 161.6 (Cq), 137.3 (Cq), 135.0 (Ar−CH), 135.0 (Cq), 131.6 (Ar−CH), 131.6 (Ar−CH), 129.1 (Ar−CH), 128.7 (Cq), 118.1 (CH_2), 116.9 (Ar−CH), 70.2 (CH_2), 62.1 ($J_{C,P}$ = 6 Hz, CH), 53.0−52.9 ($J_{C,P}$ = 6 Hz, OCH_3), 24.0 (CH_3), 22.4 (CH_3), 18.8 (Ar−CH_3) ppm; ^{31}P NMR (162 MHz, CD_3OD, TMS) δ 18.98 ppm; FT-IR $\tilde{\nu}$ = 3250, 3200, 3025, 2863, 1667, 1600−1400, 1327 cm^{-1} MS (ESI) m/z 445.1 [M − H]; HRMS (ESI-TOF) m/z [M − H]$^-$ Calcd for

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$C_{23}H_{30}N_2O_5P$ 445.1891, found 445.1903; $[M + Na - 2H]^-$ Calcd for $C_{23}H_{29}N_2O_5PNa$ 467.1717, found 467.1724.

*Methyl [2-({1-[(2,6-dimethylphenyl)carbamoyl]-1-(1-naphthyl)-methyl}amino)propane-2-yl]phosphonate (as formate salt) (Table 3, product **3**).* Product **3** was prepared from (2-aminopropane-2-yl)phosphonic acid (117 mg, 0.75 mmol), 1-naphthaldehyde (174 mg, 1.12 mmol) and 2,6-dimethylphenyl isocyanide (146 mg, 1.12 mmol). Purification was performed by preparative chromatography on CHIRALPAK QD-AX; k_1 = 2.53; k_2 = 5.12 (mobile phase MeOH containing 50 mM formic acid, apparent pH adjusted to 5 with NH_4OH). The target compound was obtained as a sticky solid (yield 216 mg, 0.49 mmol; 66%). Optical rotation: first eluted enantiomer from CHIRALPAK QD-AX $[\alpha]^{rt}$ Na (589 nm) 16.6; Hg (578 nm) 18.7; (546 nm) 21.5, (436 nm), 44.7 (c = 1.48 g/100 mL, methanol), ee 99%; second eluted enantiomer $[\alpha]^{rt}$ Na (589 nm) −17.8; Hg (578 nm) −17.8; (546 nm) −21.2; (436 nm) −36.6 (c = 0.96 g/100 mL, methanol), ee 90% . The NMR, IR and MS characterization of the compound was performed on its second eluting enantiomer. From the NMR signals we observed the presence of residual formic acid from the anion exchange purification process: ^{1}H NMR (400 MHz, CD_3OD, 25 °C, TMS) δ 7.9 (m, 3 H; Ar−H), 7.6 (m, 1H; Ar−H), 7.5 (m; 2H; Ar−H), 7.0 (m, 4H, Ar−H), 5.9 (s, 1H; C*H*−NH), 3.62 (d, ^3J(H,P) = 9.6 Hz, 3H; OCH_3), 1.97 (bs, 6H; 2 × Ar−CH_3), 1.33 (m, 6H; −NH−C(CH_3)$_2$) ppm; ^{13}C NMR (101 MHz, MeOD, 27 °C) δ 173.6 (C═O), 137.0 (Cq), 135.8 (Cq), 132.2 (Cq), 130.3 (Ar−CH), 130.0 (Ar−CH), 129.1 (Ar−CH), 128.4 (Ar−CH), 127.7 (Ar−CH), 127.1 (Ar−CH), 126.5 (Ar−CH), 125.5 (Ar−CH), 58.4−56.9 ($J_{C,P}$ = 152.1 Hz, (CH_3)C), 52.2 (2 × CH), 23.5 ($J_{C,P}$ = 4 Hz, CH_3), 18.7 (Ar−CH_3) ppm; ^{31}P NMR (162 MHz, CD_3OD) δ 25.12 ppm; FT-IR $\tilde{\nu}$ = 3180, 2970, 2794, 1705, 1600−1400, 1342 cm^{-1}; MS (ESI) m/z 439.2 $[M - H]^-$; HRMS (ESI-TOF) m/z $[M - H]^-$ Calcd for $C_{24}H_{28}N_2O_4P$ 439.1786, found 439.1793.

*Methyl [2-({1-[(tert-butyl)carbamoyl]-1-phenylmethyl}amino)-propane-2-yl]phosphonate (as tetrabutylammonium salt) (Table 3, product **4**).* Prepared from (2-aminopropane-2-yl)phosphonic acid (125 mg, 0.8 mmol), benzaldehyde (127 mg, 1.2 mmol) and *tert*-butyl isocyanide (99 mg, 1.2 mmol). Purification was performed by preparative chromatography on CHIRALPAK QD-AX; k_1 = 1.50; k_2 = 1.72 (mobile phase MeOH containing 15 mM formic acid, apparent pH adjusted to 5 with NH_4OH). Compound **4** was obtained as tetrabutylammonium salt as a sticky solid (yield 214 mg, 0.44 mmol 80%). The NMR, IR and MS characterization of the compound was performed on its second eluting enantiomer: ^{1}H NMR (400 MHz, CD_3OD, 25 °C, TMS) δ 7.5 (m, 2H; Ar−H), 7.4 (m, 3H; Ar−H), 5.15 (s, 1H; C*H*−NH) 3.7 (d, ^3J(H,P) = 9.83 Hz, 3H; OCH_3), 1.39−1.30 (m, 6H; −NH−C(CH_3)$_2$), 1.23 (s, 9H; C(CH_3)$_3$) ppm; ^{13}C NMR (101 MHz, MeOD, 27 °C) δ 175.6 (C═O), 138.0 (Ar−C), 130.1 (Ar−CH), 129.4 (Ar−CH), 62.1 (CH), 58.0 (Cq), 52.4−52.3 ($J_{C,P}$ = 7 Hz, CH), 52.3 (Cq), 28.6 (CH_3), 23.4 (CH_3), 21.8 (Ar−CH_3) ppm; ^{31}P NMR (162 MHz, CD_3OD) δ 21.11 ppm; FT-IR $\tilde{\nu}$ = 3457, 3002, 2876, 1738, 1600−1400, 1367 cm^{-1}; MS (ESI) m/z 341.2 $[M - H]^-$; HRMS (ESI-TOF) m/z $[M - H]^-$ Calcd for $C_{16}H_{26}N_2O_4P$ 341.1629, found 341.1641.

*Methyl [2-({1-[(2,6-dimethylphenyl)carbamoyl]-1-(anthracene-9-yl)methyl}amino)propane-2-yl]phosphonate (as tetrabutylammonium salt) (Table 3, product **5**).* Prepared from (2-aminopropane-2-yl)phosphonic acid (104 mg, 0.66 mmol), 9-anthracene carboxaldehyde (204 mg, 0.99 mmol) and 2,6-dimethylphenyl isocyanide (130 mg, 0.99 mmol). Purification by preparative chromatography on CHIRALPAK QD-AX; k_1 = 3.05; k_2 = 7.51 (mobile phase MeOH containing 75 mM formic acid, apparent pH adjusted to 4 with NH_4OH) provided compound **5** as tetrabutylammonium salt as a sticky solid (yield 213 mg, 0.44 mmol, 66%). Optical rotation: first eluted enantiomer from CHIRALPAK QD-AX $[\alpha]^{rt}$ Na (589 nm) 59.3; Hg (578 nm) 64.6; (546 nm) 77.8, (436 nm) 201.3 (c = 0.57 g/100 mL, methanol), ee 99%; second eluted enantiomer $[\alpha]^{rt}$ Na (589 nm) −26.3; Hg (578 nm) −87.3; (546 nm) −102.6; (436 nm) −232.9 (c = 0.39 g/100 mL, methanol), ee 95%. The NMR, IR and MS characterization of the compound was performed on the second eluting enantiomer: ^{1}H NMR (400 MHz, CD_3OD, 25 °C, TMS) δ 8.80(d, ^3J(H,H) = 8.61 Hz, 1H; Ar−H), 8.64 (s; 1H, Ar−H), 8.48 (d, ^3J(H,H) = 8.43 Hz, 1H; Ar−H), 8.15(t, ^3J(H,H) = 9.50 Hz, 2H; Ar−H), 7.73 (t, ^3J(H,H) = 8.41 Hz, 1H; Ar−H), 7.58 (m, 2H; Ar−H), 7.05 (m, 3H; Ar−H), 6.47 (s, 1H; C*H*−NH), 3.62 (d, ^3J(H,P) = 10.33 Hz, 3H; OCH_3), 2.14(bs, 6H; 2 × Ar−CH_3), 1.33(m, 6H; −NH−C(CH_3)$_2$) ppm; ^{13}C NMR (101 MHz, MeOD, 27 °C) δ 170.9 (C═O), 137.1 (Cq), 136.1 (Cq), 132.3 (Cq), 131.1 (Cq), 129.5 (Ar−CH), 129.3 (Cq), 128.1 (Ar−CH), 127.4 (Ar−CH), 126.9 (Ar−CH),125.1 (Ar−CH), 59.9−59.8 ($J_{C,P}$ = 101 Hz, (CH_3)C), 57.7 (CH), 52.7(CH_3), 23.8 (CH_3), 23.2 (CH_3), 18.8 (Ar−CH_3) ppm; ^{31}P NMR (162 MHz, CD_3OD) δ 24.20 ppm; FT-IR $\tilde{\nu}$ = 3255, 2969, 2873, 1739, 1600−1400 1366 cm^{-1}; MS (ESI) m/z 489.1 $[M - H]^-$; HRMS (ESI-TOF) m/z $[M - H]^-$ Calcd for $C_{28}H_{30}N_2O_4P$ 489.1942, found 489.1941.

*Methyl [1-({1-[(2,6-dimethylphenyl)carbamoyl]-1-(anthracene-9-yl)methyl}amino)cyclopentane-1-yl]phosphonate (as tetrabutylammonium salt) (Table 3, product **6**).* Prepared from (1-aminocyclopentyl)phosphonic acid (200 mg, 1.27 mmol), 9-anthracene carboxaldehyde (391 mg, 1.9 mmol) and 2,6-dimethylphenyl isocyanide (248 mg, 1.9 mmol). Purification by silica flash chromatography (purification procedure c); R_f = 0.38 (MeOH/DCM 1:2; v/v). Compound **6** was obtained as tetrabutylammonium salt as a red powder (yield 465 mg, 0.90 mmol; 71%). The NMR, IR and MS characterization of the compound was performed on the racemic mixture of the target compound: ^{1}H NMR (400 MHz, CD_3OD, 25 °C, TMS) δ 8.6 (d, ^3J(H,H) = 9.2 Hz, 2H; Ar−H), 8.5 (t, ^3J(H,H) = 5.5 Hz, 2H; Ar−H), 8.1(t, ^3J(H,H) = 8.8 Hz, 2H; Ar−H), 7.6 (m, 1H; Ar−H), 7.5 (m, 3H; Ar−H), 7.0(m, 3 H; Ar−H), 6.5 (s, 1H; C*H*−NH), 3.7(d, ^3J(H,P) = 9.6 Hz, 3H; −OCH_3) 2.3 (s, 6H; 2 × Ar−CH_3), 2.1−1.70 (m, 4H; −CH_2−CH_2−CH_2−CH_2−), 1.55−1.40, 1.32−1.20 (m, 4H; −CH_2−CH_2−CH_2−CH_2−) ppm; ^{13}C NMR (101 MHz, MeOD, 27 °C) δ 176.4 (C═O), 137.2 (Cq), 135.9 (Cq), 133.5 (Cq), 133.2 (Cq), 130.9 (Ar−CH), 130.5 (Cq), 130.3 (Ar−CH), 129.0 (Ar−CH), 128.2 (Ar−CH), 126.5 (Ar−H), 67.6−66.1 ($J_{C,P}$ = 160 Hz, C(CH_2)$_2$), 57.9 ($J_{C,P}$ = 7 Hz, OCH_3), 51.75 (CH), 37.2−33.9 ($J_{C,P}$ = 330 Hz, CH_2), 24.74 (CH_2), 20.66 (CH_3) ppm; ^{31}P NMR (162 MHz, CD_3OD) δ 27.88 ppm; FT-IR $\tilde{\nu}$ = 3457, 3016, 2801, 1739, 1600−1400, 1367 cm^{-1}; MS (ESI) m/z 515.6 $[M - H]^-$; HRMS (ESI-TOF) m/z $[M - H]^-$ Calcd for $C_{30}H_{32}N_2O_4P$ 515.2099, found 515.2101.

*2-Propen-1-yl [1-({1-[(2,6-dimethylphenyl)carbamoyl]-1-(anthracene-9-yl)methyl}amino) phenylmethyl]phosphonate (in zwitterionic form) (Table 3, product **7**).* Prepared from [amino(phenyl)-methyl]phosphonic acid (700 mg, 3.8 mmol), to which 3 mL of methanolic tetrabutylammonium hydroxide solution (1M, 3 mmol) were added and sonicated for 5 min. The obtained yellowish solution was dried under a vacuum overnight and dissolved in 5 mL of allyl alcohol, and 2.5 mL were transferred into a microwave reaction flask. To the solution [amino(phenyl)methyl]phosphonic acid (350 mg, 1.9 mmol), 9-anthracene carboxaldehyde (500 mg, 2.4 mmol) and 2,6-dimethylphenyl isocyanide (500 mg, 3.8 mmol) and allyl alcohol (2 mL) were added. The vial was sealed, and the reaction was stirred under microwave irradiation at 100 °C for 250 min. After this time a darkly yellow solution with a precipitate was observed. The supernatant was transferred into a round-bottom flask. To the precipitate the remaining [amino(phenyl)methyl]phosphonic acid−TBAOH solution (2.5 mL) was added, and fresh aldehyde, isocyanide and allyl alcohol components were added. The reaction then proceeded under the same reaction conditions reported above. The supernatants obtained from the reactions were collected in a round flask and evaporated to dryness under a vacuum and subsequently dissolved in methanol. Purification by preparative chromatography on CHIRALPAK QD-AX; k_1 = 9, k_2 = 15, k_3 = 24, k_4 = 32 (mobile phase MeOH containing 100 mM formic acid and 50 mM ammonium formate) provided compound **7** as a sticky solid (yield 180 mg, 0.32 mmol, 32%). The NMR, IR and MS characterization of the compound was performed on its fourth eluting isomer: ^{1}H NMR (600 MHz, MeOD) δ 8.61 (s, 1H; Ar−H), 8.50 (d, ^3J(H,H) = 8.73 Hz, 1H; Ar−H,), 8.30 (m; 1H; Ar−H), 8.21−8.02 (dd, ^3J(H,H)$_1$ = 8 Hz, ^3J(H,H)$_2$ = 46 Hz, 2H; Ar−H), 7.88 (m, 1H; Ar−H), 7.74 (d, ^3J(H,H) = 9 Hz,

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1H; Ar−H), 7.62−7.36 (m, 8H; Ar−H), 7.16−6.99 (m, 4H, Ar−H), 5.81 (s,1H; C*H*−NH), 5.31 (m,1H; CH_2—C*H*=CH_2), 4.58−4.83 (m, 2H; CH_2—CH=C*H*$_2$), 3.95, 3.66 (each m, 1H; —C*H*$_2$—CH=CH_2), 3.75 (d, ^3J(H,H) = 17 Hz, 1H; NH−C*H*−P), 2.27 (s, 6H; 2 × Ar−CH_3) ppm; ^{13}C NMR (151 MHz, MeOD) δ 174.3 (C=O), 137.6 (CH−allyl), 137.2 (Cq),135.6 (Cq), 135.3 (Cq), 133.7 (Cq), 133.5 (Cq), 132.9 (Cq), 131.2 (Ar−CH), 131.0 (Ar−CH), 130.7 (Ar−CH), 130.4 (Ar−CH), 130.1 (Ar−CH), 129.5 (Ar−CH), 129.2 (Ar−CH), 129.0 (Ar−CH), 128.4 (Ar−CH), 127.9 (Ar−CH), 126.2 (Ar−CH), 125.5 (Ar−CH), 124.4 (Ar−CH), 116.4 (CH−allyl), 66.8, 66.7 ($J_{C,P}$ = 6 Hz, CH), 61.9, 60.97 ($J_{C,P}$ = 158 Hz, CH−(Ph)), 58.7, 58.6 ($J_{C,P}$ = 14.5 Hz, O−CH), 19.0 (Ar−CH_3) ppm; ^{31}P NMR (162 MHz, CD_3OD) δ 16.47 ppm; FT-IR $\tilde{\nu}$ = 3457, 3016, 2801, 1739, 1600−1400, 1367 cm^{-1}; MS (ESI) *m*/*z* 563.6 [M − H]$^-$; HRMS (ESI-TOF) *m*/*z* [M − H]$^-$ Calcd for $C_{34}H_{32}N_2O_4P$ 563.2099, found 563.2089.

*Methyl [1-({1-[(2,6-dimethylphenyl)carbamoyl]-1-(phenyl)-methyl}amino)cyclopentane-1-yl]phosphonate (as tetrabutylammonium salt) (Table 3, product **8**).* Prepared from (1-aminocyclopentyl)phosphonic acid (102 mg, 0.65 mmol), benzaldehyde (103 mg, 0.97 mmol) and 2,6-dimethylphenyl isocyanide (127 mg, 0.97 mmol). Purification by liquid extraction (H_2O/DCM) (purification procedure b) followed by evaporation of the aqueous phase under a vacuum provided compound **8** as tetrabutylammonium salt in form of a sticky solid (yield 216 mg, 0.49 mmol, 66%). The NMR, IR and MS characterization of the compound was performed on the racemic mixture of the target compound: ^{1}H NMR (400 MHz, CD_3OD, 25 °C, TMS) δ 7.7(m, ^3J(H,H) = 3.8 Hz, 2H; Ar−H), 7.5 (m, ^3J(H,H) = 2.8 Hz, 3H; Ar−H), 7.0 (m, ^3J(H,H) = 7.1 Hz, 3H; Ar−H), 6.1 (s, 1H; C*H*−NH), 3.7(d, ^3J(H,H) = 9.9 Hz, 3H; −OCH_3), 2.34 (m, 4H; −C*H*$_2$−CH_2−CH_2−C*H*$_2$−), 1.96 (s, 6H; 2 × Ar−CH_3) 1.84 (m, 1H; −CH_2−C*H*$_2$−C*H*$_2$−CH_2−) ppm^{13}C NMR (101 MHz, $CDCl_3$, 27 °C) δ 168.4 (C=O), 136.9 (Cq), 135.0 (Cq), 134.4 (Cq), 131.2 (Ar−H), 130.4 (Ar−H), 130.2 (Ar−H), 129.2 (Ar−H), 128.8 (Ar−H), 71.6−70.1 ($J_{C,P}$ = 151.5 Hz, C$(CH_2)_2$, 63.0 (OCH_3), 52.3−52.2 ($J_{C,P}$ = 7 Hz, CH), 35.6−33.1 (CH_2), 24.8 (CH_2), 18.2 (Ar−CH_3) ppm; ^{31}P NMR (162 MHz, CD_3OD) δ 18.86; 2.39 ppm. The presence of a second peak in the ^{31}P NMR indicates the presence of unreacted aminophosphonic acid. The product was therefore further purified by reversed-phase SPE. For this purpose, a reversed-phase C-18 SPE (500 mg cartridge) column was first rinsed with MeOH (3 column volumes) and then conditioned with water (3 volumes). Afterward, the sample dissolved in water (1 mL) was applied. Thereby, compound **8** was captured on the SPE column. After washing with 2 column volumes of water, the product was eluted using MeOH. The collected fraction was dried under a vacuum leading to a white solid: ^{31}P NMR (162 MHz, CD_3OD) δ 18.86; MS (ESI) *m*/*z* 415.4 [M − H]$^-$; FT-IR $\tilde{\nu}$ = 3248, 3037, 2794, 1665, 1600−1400, 1296 cm^{-1}; HRMS (ESI-TOF) *m*/*z* [M − H]$^-$ Calcd for $C_{22}H_{28}N_2O_4P$ 415.1786, found 415.1798.

*Methyl [1-({1-[(2,6-dimethylphenyl)carbamoyl]-1-(phenyl)-methyl}amino)ethane-1-yl]phosphonate (in zwitterionic form) (Table 3, product **9**).* Prepared from (1-aminoethyl)phosphonic acid (117 mg, 0.94 mmol), benzaldehyde (149 mg, 1.41 mmol) and 2,6-dimethylphenyl isocyanide (184 mg, 1.41 mmol). Purification was performed by preparative chromatography on CHIRALPAK QD-AX; $k_{1,2}$ = 2.52; $k_{3,4}$ = 4.5 (mobile phase MeOH containing 50 mM formic acid, apparent pH adjusted to 4 with NH_4OH). Compound **9** was obtained as tetrabutylammonium salt as a sticky solid (yield 123 mg, 0.33 mmol, 34%). The NMR, IR and MS characterization of the compound was performed on a sample containing the target compound as mixture 1:6 of its first and second eluting diastereomers: ^{1}H NMR (400 MHz, CD_3OD, 25 °C, TMS) δ 7.65 (m, 2H; Ar−H), 7.42 (m, 3H; Ar−H), 6.98(m, 3H; Ar−H), 5.63 (s, 1H; −C*H*−NH−), 3.55 (d, ^3J(H,H) = 10.70 Hz, 3H; −OCH_3), 1.89 (m, bs, 6H; 2 × Ar−CH_3), 1.44 (q, ^3J(H,H) = 7.41 Hz, 3H; −NH−CH−C*H*$_3$); 1.33 (dd, $^3J(H,H)_1$ = 14.1 Hz, $^3J(H,H)_2$ = 7.3 Hz, 1H; −NH−C*H*−CH_3) ppm; ^{13}C NMR (101 MHz, MeOD, 27 °C) δ 167.9 (C=O), 137.3 (Cq), 134.7 (Cq), 133.6 (Cq), 132.0 (Ar−H), 131.0 (Ar−H), 130.6 (Ar−H), 129.6 (Ar−H), 129.2 (Ar−H), 63.6 ($J_{C,P}$ = 4 Hz, CH), 52.9 ($J_{C,P}$ = 6 Hz, CH), 51.8−50.4 ($J_{C,P}$ = 143 Hz, OCH_3), 18.5, 14.3 (Ar−CH_3) ppm; ^{31}P NMR (162 MHz, CD_3OD) δ 15.00, 14.64, 12.50, 12.21 ppm; the presence of multiple ^{31}P NMR signals is a result of the diastereomeric nature of the sample and of the coexisting free zwitterionic and tetrabutylammonium salt form of the analyte; FT-IR $\tilde{\nu}$ = 3456, 2969, 2794, 1665, 1600−1400, 1296 cm^{-1}; MS (ESI) *m*/*z* 375.4 [M − H]$^-$; HRMS (ESI-TOF) *m*/*z* [M − H]$^-$ Calcd for $C_{19}H_{24}N_2O_4P$ 375.1473, found 375.1480.

*Methyl [1-({1-[(2,6-dimethylphenyl)carbamoyl]-1-(phenyl)-methyl}amino)-2-methylpropane-1-yl]phosphonate (in zwitterionic form) (Table 3, product **10**).* Prepared from (1-amino-2-methylpropyl)phosphonic acid (115 mg, 0.75 mmol), benzaldehyde (119 mg, 1.12 mmol) and 2,6-dimethylphenyl isocyanide (146 mg, 1.12 mmol). Purification by preparative chromatography on CHIRALPAK QD-AX; $k_{1,2}$ = 2.75; $k_{3,4}$ = 4.08 (mobile phase MeOH containing 25 mM formic acid, apparent pH adjusted to 4 with NH_4OH) provided compound **10** in form of a sticky solid (yield 197 mg, 0.49 mmol 65%). The NMR, IR and MS characterization of the compound was performed on a sample containing the target compound as mixture 1:1 of its first and second eluting diastereomers: ^{1}H NMR (400 MHz, CD_3OD, 25 °C, TMS) δ 7.76 (m, 2H; Ar−H), 7.53 (m, 3H; Ar−H), 7.06 (m, 3H; Ar−H), 5.80 (s, 1H; −C*H*−NH−), 3.67 (d, ^3J(H,H) = 10,78 Hz, 3H; −OCH_3), 3.06 (m, 1H; NH−C*H*−$(CH_3)_2$), 1.89 (bs, 6H; 2 × Ar−CH_3), 1,44 (bs, 6H; NH−CH−(C*H*$_3$)$_2$) ppm; ^{13}C NMR (101 MHz, MeOD, 27 °C) δ 166.4 (C=O), 136.1 (Cq), 135.7 (Cq), 132.8 (Cq) 130.4 (Ar−CH), 130.1 (Ar−CH), 129.5 (Ar−CH), 128.2 (Ar−CH), 125.4 (Ar−CH), 64.9 (CH), 63.2−61.8 (C(CH$(CH_3)_2$), 51.2−50.6 ($J_{C,P}$ = 70 Hz, OCH_3), 29.6 (CH(CH_3), 22.9 (CH_3), 21.1 (CH_3), 17.8 (Ar−CH_3), 17.3 (Ar−CH_3) ppm; ^{31}P NMR (162 MHz, CD_3OD) δ 30.90, 15.04 ppm; FT-IR $\tilde{\nu}$ = 3456, 2969, 2874, 1740, 1600−1400, 1367 cm^{-1}; MS (ESI) *m*/*z* 404.4 [M − H]$^-$403.2; HRMS (ESI-TOF) *m*/*z* [M − H]$^-$ Calcd for $C_{21}H_{28}N_2O_4P$ 403.1786 [M − H]$^-$, found 403.1800.

*Methyl [({1-[(tert-butyl)carbamoyl]-2,2-dimethylpent-4-en-1-yl}-amino)methyl]phosphonate (as formate salt) (Table 3, product **11**).* Prepared from (aminomethyl)phosphonic acid (500 mg, 4.50 mmol), 2,2-dimethyl pentanal (756 mg, 6.75 mmol) and *tert*-butyl isocyanide (560 mg, 6.75 mmol). The supernatant solution was after reaction transferred into a round-bottom flask, while white precipitate (constituted by the unreacted aminophosphonic acid) was allowed to react under same conditions reported before with another aliquot of aldehyde and isonitrile in TBAOH solution for another 150 min. The two solutions were combined and evaporated to dryness under a vacuum, and the crude product was purified by chiral anion-exchange chromatography. Purification was performed by preparative chromatography on CHIRALPAK QD-AX; $k_{1,2}$ = 2.67 (mobile phase MeOH/ACN containing 12.5 mM formic acid, apparent pH adjusted in the mixture to 4 with NH_4OH). Compound **11** was obtained as formate salt as a sticky solid (yield 1330 mg, 4.16 mmol, 93%). The NMR, IR and MS characterization of the compound was performed on the mixture of all stereoisomers of the target compound: ^{1}H NMR (400 MHz, CD_3OD, 25 °C, TMS) δ 5.90 (m, 1H; —CH_2—C*H*=CH_2), 5.15 (m, 2H; —CH_2—CH=C*H*$_2$), 3.80 (s, 1H; −CH−NH−), 3.63 (d, ^3J(H,H) = 10.33 Hz, 3H; −OCH_3), 3.07, 2.80 (each m, 1H; —C*H*$_2$—CH=CH_2), 2.23 (m, 2H; −NH−C*H*$_2$−P), 1.38 (s, 9H; −C(CH_3)), 1.06 (d, ^3J(H,H) = 7.10 Hz, 6H; −C$(CH_2)_2$) ppm; ^{13}C NMR (101 MHz, MeOD, 27 °C) δ 167.2 (C=O), 134.5 (CH−Allyl), 119.6 (CH_2−Allyl), 70.3 ($J_{C,P}$ = 4 Hz, CH), 53.0 (C $(CH_3)_3$, 52.3 ($J_{C,P}$ = 7 Hz, OCH_3), 44.2 (CH_2), 37.4 (CH_2), 28.7 (C$(CH_3)_3$), 24.8 (Cq), 24.1−23.3 ($J_{C,P}$ = 70 Hz, CH_2) ppm; ^{31}P NMR (162 MHz, CD_3OD) δ 11.87 ppm; FT-IR $\tilde{\nu}$ = 3456, 2969, 2794, 1665,1600−1400,1296 cm^{-1}; MS (ESI) *m*/*z* 318.9 [M − H]$^-$; HRMS (ESI-TOF) *m*/*z* [M − H]$^-$ Calcd for $C_{14}H_{28}N_2O_4P$ 319.1786, found 319.1795.

*Methyl [({1-[(tert-butyl)carbamoyl]-dodec-11-en-1-yl}amino)-methyl]phosphonate (as formate salt) (Table 3, product **12**).* Prepared from (aminomethyl)phosphonic acid (639 mg, 5.77 mmol), 10-undecenal (1453 mg, 8.65 mmol) and *tert*-butyl isocyanide (718 mg, 8.65 mmol). Purification by preparative chromatography on CHIRALPAK QD-AX; $k_{1,2}$ = 3.78 (mobile phase MeOH containing 25 mM formic acid, apparent pH adjusted to 4 with NH_4OH) provided compound **12** as formate salt as a sticky solid (yield 1.47 g, 3.9 mmol,

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68%). The NMR, IR and MS characterization of the compound was performed on the racemic mixture of the target compound: ^{1}H NMR (400 MHz, CD_3OD, 25 °C, TMS) δ 5.81 (m, 1H; —CH_2—CH=CH_2), 4.97 (m, 2H; —CH_2—CH=CH_2), 3.61 (d, ^3J(H,H) = 11.11 Hz, 3H; −OCH_3), 3.36 (s, 1H; −CH−NH−), 2.98 (m, 2H; −NH−CH_2−P), 2.06 (m, 2H; —CH_2—CH=CH_2), 1.84 (m, 2H; −CH_2−CH−NH−),1.38 (m, 12H; −$(CH_2)_6$−), 1.33 (m, 9H; −C$(CH_3)_3$) ppm; ^{13}C NMR (101 MHz, MeOD, 27 °C) δ 168.1 (C=O), 140.1 (CH−Allyl), 114.7 (CH_2−Allyl), 62.8 (CH), 52.8 (Cq), 52.3 (OCH_3), 42.5−41.1 ($J_{C,P}$ = 140 Hz, CH_2), 34.8 (CH_2), 31.6 (CH_2), 30.3 (CH_2), 30.1 (CH_2), 28.8 (CH_3), 25.7 (CH_2) ppm; ^{31}P NMR (162 MHz, CD_3OD) δ 11.19 ppm; FT-IR $\tilde{\nu}$ = 3470, 3002, 2769, 1661,1600−1400, 1280 cm^{-1}; MS (ESI) m/z 389.5 [M − H]$^-$; HRMS (ESI-TOF) m/z [M − H]$^-$ Calcd for $C_{19}H_{38}N_2O_4P$ 389.2568, found 389.2572.

*Methyl [2-({1-[(2,6-dimethylphenyl)carbamoyl]-1-(4-allyloxyphenyl)methyl}amino)-3,3-dimethylbutane-1-yl]-phosphonate (in zwitterionic form) (Table 3, product **13**).* Prepared from (2-amino-3,3-dimethylbutyl)phosphonic acid (125 mg, 0.69 mmol), benzaldehyde (109 mg, 1.03 mmol) and 2,6-dimethylphenyl isocyanide (135 mg, 1.03 mmol). Purification was performed by preparative chromatography on CHIRALPAK QD-AX; $k_{1,2}$ = 1.4; k_3 = 3.74; k_4 = 4.05 (mobile phase MeOH containing 15 mM formic acid, apparent pH adjusted to 4 with NH_4OH). Compound **13** was obtained in zwitterionic form as a sticky solid (yield 175 mg, 0.37 mmol, 43%). Optical rotation: third eluted stereoisomer from CHIRALPAK QD-AX [α]^{rt} Na (589 nm) 78; Hg (578 nm) 83; (546 nm) 98; (436 nm) 191 (c = 1.02 g/100 mL, methanol), ee >99%; fourth eluted stereoisomer [α]^{rt} Na (589 nm) −69; Hg (578 nm) −68; (546 nm) −81; (436 nm) −146 (c = 1.03 g/100 mL, methanol), ee 97%. The NMR, IR and MS characterization of the compound was performed on the racemic mixture of the target compound: ^{1}H NMR (400 MHz, CD_3OD, 25 °C, TMS) δ 7.73 (d, ^3J(H,H) = 8.83, 2H; Ar−H), 7.06 (m, 5H; Ar−H), 6.07 (m, 1H; —O—CH_2—CH=CH_2), 5.74 (s, 1H; −CH−NH−), 5.41, 5.27 (each d, ^3J(H,H) = 1.66, 1H; —O—CH_2—CH=CH_2), 4.62 (d, ^3J(H,H) = 5.01, 2H; —O—CH_2—CH=CH_2), 3.65 (d, ^3J(H,H) = 10.63 Hz, 3H; −OCH_3), 3.30 (m, 1H; −NH−CH−CH_2P−), 2.06 (bs, 6H; 2 × Ar−CH_3), 1.93,1.30 (each m, 1H; −NH−CH−CH_2−P−), 0.89 (s, 9H; −C$(CH_3)_3$) ppm; ^{13}C NMR (101 MHz, MeOD, 27 °C) δ 161.7 (C=O; Cq), 137.1 (Cq), 134.7 (Cq), 134.5 (CH−Allyl), 132.4 (Ar−CH), 131.4 (Ar−CH), 129.1 (Ar−CH), 128.6 (Ar−CH), 117.8 (CH_2−Allyl), 116.5 (Ar−CH), 69.9 (CH_2), 64.4 (CH), 63.4 ($J_{C,P}$ = 5 Hz, CH), 51.8 ($J_{C,P}$ = 6 Hz, OCH_3), 35.6−35.5 ($J_{C,P}$ = 11 Hz, CH), 26.6 (CH_3), 18.4 (Ar−CH_3) ppm; ^{31}P NMR (162 MHz, CD_3OD) δ 23.49 ppm; FT-IR $\tilde{\nu}$ = 3457, 3016, 2795,1739, 1600−1400, 1367 cm^{-1}; MS (ESI) m/z 487.5 [M − H]$^-$; HRMS (ESI-TOF) m/z [M − H]$^-$ Calcd for $C_{26}H_{36}N_2O_5P$ 487.2361, found 487.2371.

*Methyl [({1-[(cyclohexyl)carbamoyl]-2,2-dimethylpent-4-en-1-yl}-amino)methyl]phosphonate (as formate salt) (Table 4, product **16**).* Prepared from (aminomethyl)phosphonic acid (111 mg, 1.0 mmol), 2,2-dimethyl pentanal (168 mg, 1.5 mmol) and *tert*-butyl isocyanide (124 mg, 1.5 mmol). Purification by preparative chromatography on CHIRALPAK QD-AX; $k_{1,2}$ = 2.82 (mobile phase MeOH containing 15 mM formic acid, apparent pH adjusted to 4 with NH_4OH) provided compound **16** as formate salt as a sticky solid (yield 317 mg, 0.92 mmol, 91.53%). The NMR, IR and MS characterization of the compound was performed on its fourth eluting isomer: ^{1}H NMR (400 MHz, CD_3OD, 25 °C, TMS) δ 5.90 (m, 1H; —CH_2—CH=CH_2), 5.14 (m, 2H; —CH_2—CH=CH_2), 3.83 (s, 1H; −CH−NH−), 3.75 (m, 1H; O=C—NH—CH cyHex), 3.61 (d, 3H; ^3J(H,p) = 10.17 Hz −OCH_3), 3.07, 2.81 (each m, 1H; −NH−CH_2−P−), 2.22 (m, 2H; CH_2 cyHex), 1.89,1.78 (each m, 1H; —CH_2—CH=CH_2), 1.65 (m, 4H; 2 × CH_2 cyHex), 1.06 (d, ^3J(H,H) = 10.77 Hz, 6H; −C$(CH_3)_2$) ppm; ^{13}C NMR (101 MHz, MeOD, 27 °C) δ 167.3 (C=O), 134.5 (CH−Allyl), 119.6 (CH_2−Allyl), 69.7 (CH), 50.3 (CH), 44.3 (CH_2), 37.4 (CH_2), 33.6 ($J_{C,P}$ = 5 Hz, CH_2), 26.5 (CH), 26.0 (CH_2), 24.2 (CH), 23.5 (CH_3) ppm; ^{31}P NMR (162 MHz, CD_3OD) δ 12.1 ppm; FT-IR $\tilde{\nu}$ = 3526, 2888, 1785, 1377 cm^{-1}; MS (ESI) m/z 345.4 [M − H]$^-$; HRMS (ESI-TOF) m/z [M − H]$^-$ Calcd for $C_{16}H_{30}N_2O_4P$ 345.1949 [M − H]$^-$, found 345.1954.

*Methyl [(2-{1-[(cyclohexyl)carbamoyl]-2,2-dimethylpent-4-en-1-yl}amino)ethyl]phosphonate (in zwitterionic form) (Table 4, product **17**).* Prepared from (aminoethyl)phosphonic acid (100 mg, 0.80 mmol), 2,2-dimethyl pentanal (134 mg, 1.2 mmol) and *tert*-butyl isocyanide (100 mg, 1.2 mmol). Purification was performed by preparative chromatography on CHIRALPAK QD-AX; k_1 = 1.35 (mobile phase MeOH containing 15 mM formic acid, apparent pH adjusted to 4 with NH_4OH). Compound **17** was obtained in zwitterionic form as a sticky solid (yield 122 mg, 0.34 mmol, 42%): ^{1}H NMR (400 MHz, CD_3OD, 25 °C, TMS) δ 5.87 (m, 1H; —CH_2—CH=CH_2), 5.19 (m, 2H; —CH_2—CH=CH_2), 3.74 (d, ^3J(H,H) = 11.60, 3H; −OCH_3), 3.66 (s, 1H; −CH−NH−), 3.31 (m, 2H; O=C—NH—CH cyHex), 3.21 (m, 2H; −NH−CH_2−CH_2−P−), 2.25 (m, 4H; 2 × CH_2 cyHex), 1.90, 1.77 (each m,1H; —CH_2—CH=CH_2), 1.64 (m, 1H; −NH−CH_2−CH_2−P−), 1.32 (m, 5H; −NH−CH_2−CH_2−P−; 2 × CH_2 cyHex), 1.10 (d, ^3J(H,H) = 9.6 Hz, 6H; −C$(CH_3)_2$) ppm; ^{13}C NMR (101 MHz, MeOD, 27 °C) δ 166.7 (C=O), 134.4 (CH−Allyl), 119.9 (CH_2−Allyl), 69.2 (CH), 51.7 ($J_{C,P}$ = 7 Hz, OCH_3), 50.3 (CH), 44.2 (CH_2), 37.4 (CH_2), 33.6 ($J_{C,P}$ = 5 Hz, CH_2), 26.5 (CH), 26.0 (CH_2), 24.2 (CH), 23.7 (CH_3), 23.6 (CH_3) ppm; ^{31}P NMR (162 MHz, CD_3OD) δ 26.47 ppm; FT-IR $\tilde{\nu}$ = 3526, 2888, 1785, 1377 cm^{-1}; MS (ESI) m/z 359.4 [M − H]$^-$; HRMS (ESI-TOF) m/z [M − H]$^-$ Calcd for $C_{17}H_{32}N_2O_4P$ 359.2105, found 359.2082.

*Methyl [(3-{1-[(cyclohexyl)carbamoyl]-2,2-dimethylpent-4-en-1-yl}amino)propyl]phosphonate (as formate salt) (Table 4, product **18**).* Prepared from (aminopropyl)phosphonic acid (100 mg, 0.72 mmol), 2,2-dimethyl pentanal (121 mg, 1.08 mmol) and *tert*-butyl isocyanide (90 mg, 1.08 mmol). Purification by preparative chromatography on CHIRALPAK QD-AX; $k_{1,2}$ = 1.28 (mobile phase MeOH containing 15 mM formic acid, apparent pH adjusted to 4 with NH_4OH) provided compound **18** as formate salt as a sticky solid (yield 55 mg, 0.15 mmol, 20%). The NMR, IR and MS characterization of the compound was performed on the racemic mixture of the target compound: ^{1}H NMR (400 MHz, CD_3OD, 25 °C, TMS) δ 5.87 (m, 1H; —CH_2—CH=CH_2), 5.17 (dd, ^3J(H,H)$_1$ = 10.88 Hz, ^3J(H,H)$_2$ = 2.17 Hz, 2H; −CH_2−CH=CH_2), 3.73 (m, 1H; O=C—NH—CH cyHex), 3.57 (d, ^3J(H,H) = 10.33 Hz, 3H; −OCH_3), 3.04, 2.91 (each m, 1H; −NH−CH_2−CH_2−CH_2−P−), 2.25 (d, ^3J(H,H) = 7.06, 2H; —CH_2—CH=CH_2), 1.88 (m, 2H; CH_2 cyHex), 1.76 (m, 2H; NH−CH_2−CH_2−CH_2−P−), 1.63 (m, 2H; NH−CH_2−CH_2−CH_2−P−), 1.37 (m, 4H; 2 × CH_2 cyHex), 1,09 (d, 6H; −C$(CH_3)_2$), ppm ^{13}C NMR (101 MHz, MeOD, 27 °C) δ 166.16 (C=O), 134.1 (CH−Allyl), 120.1 (CH_2−Allyl), 69.2 (CH), 52.9−52, 8 ($J_{C,P}$ = 10 Hz, OCH_3), 50.5 (CH), 44.2 (CH_2), 43.8 (CH_2), 37.4 (CH_2), 33.6 ($J_{C,P}$ = 5 Hz, CH_2), 26.5 (CH), 26.0 (CH_2), 24.1 (CH), 23.9 (CH_3), 23.6 (CH_3) ppm; ^{31}P NMR (162 MHz, CD_3OD) δ 26.65 ppm; FT-IR $\tilde{\nu}$ = 3526, 2888, 1785, 1377 ν cm^{-1}; MS (ESI) m/z 373.4 [M − H]$^-$; HRMS (ESI-TOF) m/z [M − H]$^-$ Calcd for $C_{18}H_{34}N_2O_4P$ 373.2262, found 373.2270.

General Procedure for the Hydrolysis of the Amido-aminophosphonic Acid Methyl Ester Derivatives. A solution of purified monomethyl ester of Table 3 compound **1** (24 mg, 0.061 mmol) in dry dichloromethane (CH_2Cl_2, 2.25 mL) was sonicated for about 1 min. Bromotrimethylsilane ($BrSiMe_3$, 0.183 mmol, 3 mol equiv) was added dropwise, and the reaction was allowed to react for 15 h at 25 °C. After removal of the solvent under reduced pressure methanol (5 mL) was added. The solution was heated at 50 °C for 2 h and afterward concentrated under a high vacuum to obtain the hydrobromide salt of the respective aminophosphonic acid derivative as yellow solid in quantitative yield (in order to remove the hydrobromide salt, a solid phase extraction (SPE) procedure was successfully applied to product **19**, see below).

(Carboxymethyl)[1-(cyclohexylcarbamoyl)-2,2-dimethylpent-4-en-1-yl]ammonium bromide. It was prepared from Table 4, product **15** (50 mg), following the general procedure of Ugi 5C-4CR reported above. The dried crude product was hydrolyzed following the procedure reported above using a larger excess of the reactant bromotrimethylsilane (6 equiv). The dried reaction mixture was purified through chiral anion-exchange chromatography on CHIR-

ALPAK QD-AX; $k_{1,2}$ = 1.8 (MeOH/ACN 50/50; v/v containing 25 mM formic acid, apparent pH adjusted in mixture to 4 with NH_4OH): ^{1}H NMR (400 MHz, CD_3OD, 25 °C, TMS) δ 5.88 (m, 1H; —CH_2—CH=CH_2), 5.15 (m, 2H; —CH_2—CH=CH_2), 3.72 (m, 1H; O=C—NH—CH cyHex), 3.69 (s, 1H; −CH−NH−), 3.31, 3.13 (each d, ^3J(H,H) = 14.65 Hz, 1H; −NH−CH_2−P−), 2.24 (m, 2H; CH_2 cyHex), 1.87 (m, 2H; —CH_2—CH=CH_2; CH_2 cyHex), 1.30 (m, 6H; CH_2 cyHex), 1,09 (d, ^3J(H,H) = 17.09 Hz, 6H; −$C(CH_3)_2$) ppm; ^{13}C NMR (101 MHz, MeOD, 27 °C) δ 167.2 (C=O), 134.4 (CH−Allyl), 119.6 (CH_2−Allyl), 70.0 ($J_{C,P}$ = 3 Hz, CH), 59.5 ($J_{C,P}$ = 5 Hz, OCH_3), 50.4 (CH), 44.2 (CH_2), 43.5 (CH_2), 42.1 (CH_2), 37.4 (CH_2), 33.6 ($J_{C,P}$ = 8 Hz, CH_2), 26.5 (CH), 26.0 (CH_2), 24.1 (CH_3), 23.4 (CH_3) ppm; FT-IR $\tilde{\nu}$ = 3456, 2969, 2874, 1740, 1367 cm^{-1}; MS (ESI) m/z 295.0 [M − H]$^-$; HRMS (ESI-TOF) m/z [M − H]$^-$ Calcd for $C_{16}H_{27}N_2O_3$ 295.2027, found 295.2050.

*[2-({[(2,6-Dimethylphenyl)carbamoyl](phenyl)methyl}amino)-propane-2-yl]phosphonic acid (product **19**; from the hydrolysis of Table 3, product **1**, 24 mg).* The raw product **19** was desalted by reversed-phase SPE. For this purpose, a reversed-phase C-18 SPE (500 mg cartridge) column was first rinsed with MeOH (3 column volumes) and then conditioned with water (3 volumes). Afterward, the sample dissolved in water (1 mL) was applied. Thereby, compound **19** was captured on the SPE column. After washing with 2 column volumes of water, the product was eluted using MeOH. The collected fraction was dried under a vacuum leading to a white solid (yield 22 mg, 0.059 mmol, 94%): ^{1}H NMR (400 MHz, CD_3OD, 25 °C, TMS) δ 7.73 (m, 2H; Ar−H), 7.50 (t, ^3J(H,H) = 3.9 Hz, 2H; Ar−H), 7.04 (m, 3H; Ar−H), 6.04 (s, 1H; −CH−NH−), 2.12−1.95 (bs, 6H; 2 × Ar−CH_3), 1.58 (t, ^3J(H,H) = 13.36 Hz, 6H; −NH−C(CH_3)$_2$) ppm; ^{13}C NMR (100 MHz, CD_3OD, 25 °C, TMS) δ 168.2 (C=O), 137.0 (Cq), 134.9 (Cq), 134.3 (Cq), 131.2 (Ar−CH), 130.2 (Ar−CH), 129.7 (Ar−CH), 129.6 (Ar−CH), 128.8 (Ar−CH), 62.3 (d, $J_{C,P}$ = 6 Hz, CH), 59.2, 57.7 ($J_{C,P}$ = 152 Hz −$C(CH_3)_2$), 23.7 (CH_3), 21.7 (CH_3), 19.0 (Ar−CH_3) ppm; ^{31}P NMR (162 MHz, CD_3OD) δ 15.03 ppm; FT-IR $\tilde{\nu}$ = 3248, 3037, 2794,1665, 1600−1400, 1296 cm^{-1}; MS (ESI) m/z 375.4 [M − H]$^-$; HRMS (ESI-TOF) m/z [M − H]$^-$ Calcd for $C_{19}H_{24}N_2O_4P$ 375.1479, found 375.1493; [M + Na − 2H]$^-$ Calcd for $C_{19}H_{23}N_2O_4PNa$ 397.1299, found 397.1310.

*({[1-(tert-Butylcarbamoyl)-2,2-dimethylpent-4-en-1-yl]amino}-methyl)phosphonic acid (**20**; from the hydrolysis of Table 3, product **11**).* ^{1}H NMR (400 MHz, CD_3OD, 25 °C, TMS) δ 5.90 (m, 1H; —CH_2—CH=CH_2), 5.15 (m, 2H; —CH_2—CH=CH_2), 3.80 (s, 1H; −CH−NH−), 3.63 (d, ^3J(H,H) = 10.33 Hz, 3H;), 3.23, 3.05 (each m, 1H; −NH−CH_2−P−), 2.21, 2.03 (each m, 1H; —CH_2—CH=CH_2), 2.03 (d, ^3J(H,H) = 16.14 Hz, 1H;), 1.38 (s, 9H; —O=C—NH—C(CH_3)$_3$), 1.06 (d, ^3J(H,H) = 7.10 Hz, 6H; −C(CH_3)$_2$) ppm; ^{13}C NMR (101 MHz, MeOD, 27 °C) δ 166.1 (C=O), 134.1 (CH−Allyl), 119.9 (CH_2−Allyl), 70.1 ($J_{C,P}$ = 4 Hz, CH), 53.4 (C(CH_3)$_3$, 44.1 (CH_2), 37.5 (CH_2), 28.4 (C(CH_3)$_3$), 24.9 (Cq), 24.0−23.2 ($J_{C,P}$ = 74 Hz, CH_2) ppm; ^{31}P NMR (162 MHz, CD_3OD) δ 12.10 ppm; FT-IR $\tilde{\nu}$ = 3456, 2969, 2794, 1665,1600−1400,1296 cm^{-1}; MS (ESI) m/z 305.4 [M − H]$^-$; HRMS (ESI-TOF) m/z [M + Na]$^+$ Calcd for $C_{13}H_{27}N_2O_4PNa$ 329.1601, found 329.1594.

*({[1-(tert-Butylcarbamoyl)undec-10-en-1-yl]amino}methyl)-phosphonic acid (**21**, from the hydrolysis of Table 3, product **12**).* ^{1}H NMR (400 MHz, CD_3OD, 25 °C) δ 5.81 (m, 1H; —CH_2—CH=CH_2), 4.97 (m, 2H; —CH_2—CH=CH_2), 2.98 (m, 2H; −NH−CH_2−P), 2.36 (s, 1H; −CH−NH−) 2.06 (m, 2H; —CH_2—CH=CH_2), 1.84 (m, 2H; −CH_2−CH−NH−),1.38 (m, 23H; −$(CH_2)_6$−; −C(CH_3)$_3$) ppm; ^{13}C NMR (101 MHz, MeOD, 27 °C) δ 168.6 (C=O), 140.6 (CH−Allyl), 115.4 (CH_2−Allyl), 63.3 (CH), 52.8 (Cq), 42.7−41.3 ($J_{C,P}$ = 140 Hz, CH_2), 34.9 (CH_2), 31.6 (CH_2), 30.3 (CH_2), 30.2 (CH_2), 28.6 (CH_3), 25.5 (CH_2) ppm; ^{31}P NMR (162 MHz, CD_3OD) δ 8.44 ppm; FT-IR $\tilde{\nu}$ = 3470, 3002, 2769, 1661, 1600−1400, 1280 cm^{-1}; MS (ESI) m/z 361.2 [M − H]$^-$; HRMS (ESI-TOF) m/z [M − H]$^-$ Calcd for $C_{17}H_{34}N_2O_4P$ 361.2262, found 361.2258.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

X-ray and NMR characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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