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Lithiated Alkylidenebis(phosphonates): Reactive Phosphorus Intermediates in the Synthesis of 3-Amino-1-alkenylphosphonates

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ABSTRACT: *An efficient and stereoselective-synthesis of 3-amino-1-alkenylphosphonates by a direct procedure involving alkylidene diphosphorylation of nucleophiles followed by a Horner–Emmons olefination of aminoaldehydes is reported. The versatility of the method is illustrated by the preparation of P-monoglycosyl-, P-diglycosyl 3-aminoalkenyl-, and alkylphosphonates.* © 2008 Wiley Periodicals, Inc. Heteroatom Chem 19:461–469, 2008; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20450

INTRODUCTION

Many aminophosphonate derivatives have attracted particular interest, and they have found broad applications in many areas of medicine and agriculture [1]. For some of these compounds, biological activity seems to be linked to the presence of a metabolically stable aminophosphorylated residue within their structure. For instance, 3-aminophosphonates are the analogues of 2-aminoethyl phosphates in which the scissile O—P bond is replaced by a C—P bond and therefore, they are resistant to the phosphohydrolase action.

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Thus 3-aminoalkenyl- and 3-aminoalkyl phosphonates have been the subject of recent studies, and they have been prepared as analogues of sphingosine-1-phosphate [2], dihydrosphingosine-1-phosphate [3], and sphingomyelin [4]. Sphingosine (or 4-sphingenine), dihydrosphingosine (or sphinganine), and phytosphingosine (or 4-hydroxy sphinganine) are the major long-chain bases of ceramide, sphingomyelin, and glycosphingolipids [5].

These sphingolipid metabolites act both intracellularly and extracellularly to cause numerous and significant biological responses [6]. The bioactivity of the sphingolipid metabolites is regulated by the presence of the phosphate group. Indeed, the phosphorylated form is often antagonistic to the unphosphorylated form. For example, sphingosine is an essential regulatory component of stress responses associated with cell growth arrest, apoptosis, inhibition of protein kinase C, and calcium releasing and decreasing of thermotolerance. In contrast, sphingosine-1-phosphate has been implicated in cellular proliferation and survival with stimulation of growth, suppression of apoptosis, regulation of motility, and calcium, and increasing of thermotolerance [7]. It has been suggested that the control of the dynamic balance between intracellular sphingosine-1-phosphate and sphingosine may provide the basis for the development of novel therapeutics. The understanding of the catalytic mechanism of the hydrolysis of the phosphoester linkage of sphingosine-1-phosphate or other

sphingolipids such as sphinganine-1-phosphate, phytosphingosine-1-phosphate, and sphingomyelin has inspired recent extensive studies [2–4].

Also, 3-aminophosphonate analogues of other lipid mediators such as lysophosphatidic acids have recently attracted considerable attention because of their potential as LPA (lysophosphatidic acid or 2-O-acyl-*sn*-glycero-3-phosphate) receptor agonists or antagonists [8].

In addition, aminophosphonic acids are the most important substitutes for the corresponding amino acids and there is considerable interest in the chemical modification of amino acids to better understand the biological significance of their derivatives. It has been shown that 3-aminophosphonic derivatives were interesting as peptidomimetics of D-Ala-D-Ala [9], D-alanyl phosphate [10], 3-amino-2-mercapto-carboxylic acids [11], (S)-glutamic [12], and pyroglutamic acids [13]. Several 3-aminoalkenylphosphic acids and their analogues have been described as inhibitors of D-Ala-D-Ala-ligase [9,10], metallopeptidase [11], NMDA (N-methyl-D-aspartic acid)-receptor ligands [13], and human rhinovirus 3C protease [14].

Owing to the biological importance of the 3-aminophosphonate moiety, a versatile strategy, which allows the introduction of a large variety of substituents is of a particular interest.

Herein, we report an efficient and rapid method for the preparation of 1-, 3-substituted 3-amino-1-alkenyl- and 3-amino-1-alkylphosphonates and P-mono- or P-diglycosyl 3-amino-1-alkenyl- and 3-amino-1-alkylphosphonates.

RESULTS AND DISCUSSION

Common methods for the synthesis of (3-amino-1-alkenyl)phosphonates involve the acid-catalyzed rearrangement of allylic α-hydroxyphosphonates [15] with secondary amines, the Pd(0) and Ni(II) catalyzed intermolecular allylic amination of α-acetoxy-2-alkenylphosphonates [16], the thermal rearrangement of trichloroacetimidic esters of allylic α-hydroxy phosphonates [17], or allylic α-azido phosphonates [18]. These strategies cannot be applied to substituted (3-amino-1-alkenyl) phosphonates because of the difficulties relating to the preparation of the starting reagents, severe reaction conditions, and the lack of the ability to control the regioselectivity, stereoselectivity, and stereospecificity of rearrangements. Another route to these compounds involves the addition of imines to the alkynylphosphonate titanium(II) complexes [19]. A similar process to prepare unsubstituted aminoalkenylphosphonates is based on the addition of the lithiated carbanion, derived from diethyl ethynyl phosphonate, to an alanine Schiff base [20].

Finally, several examples of (*E*)-(3-amino-1-alkenyl)phosphonates have been prepared by the Horner-Emmons reaction between N-protected aminoaldehydes and the carbanion derived from tetraethyl methylenebisphosphonate. However, this strategy has not been investigated extensively and only a few reports are available in the literature describing the design of novel enzymatic inhibitors [2a–2d, 8–11,13,14].

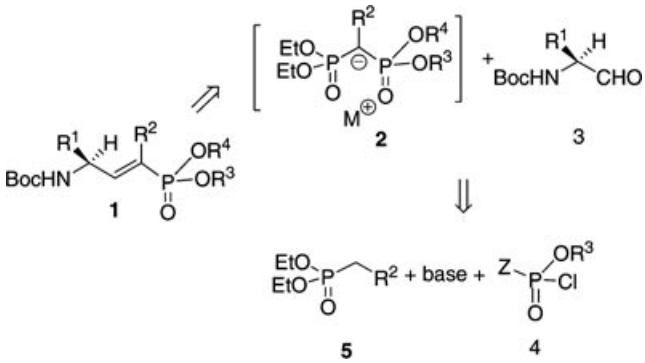
In continuation of our studies on the Horner type-reactions [21] and on chiral alkylidene diphosphorylated derivatives [22], here we present a rapid and simple access to 3-amino-1-alkenylphosphonates **1**.

The strategy involves a one-pot sequence based on a regioselective Horner-Emmons olefination involving alkylidene bis(phosphonic) anions **2** and aminoaldehydes **3**. As previously described [22], the intermediates **2** were generated in situ by a selective phosphonomethylation of chlorophosphorylated substrates **4** using the carbanions derived from diethyl alkylphosphonates **5** (Scheme 1).

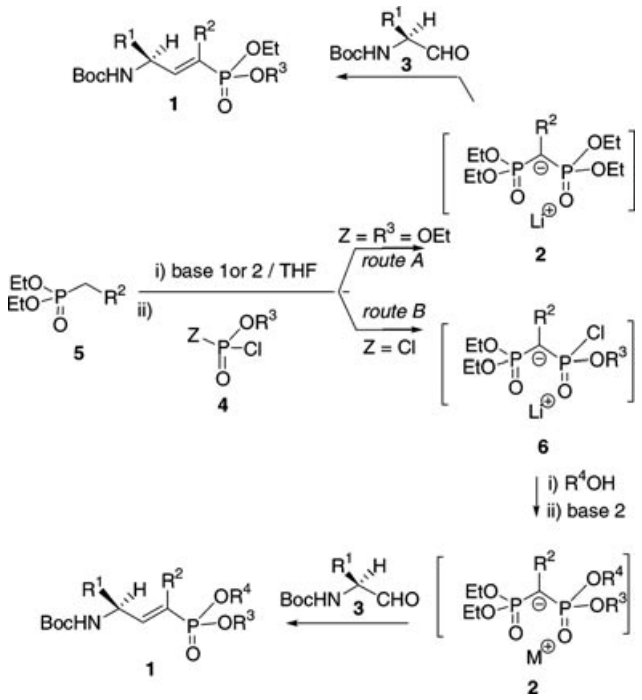
The detailed mechanism of the process depends on the nature of the Z group (Scheme 2). When Z = OEt, the intermediate anions **2** were formed directly by the successive addition of a solution of LDA (2 equivalents/base 2) onto diethyl alkylphosphonates **5** and diethyl phosphorochloridate **4** (R^3 = OEt) in THF at −70°C (route A).

When Z = Cl, the intermediate anions **2** were obtained after the alcoholysis of the chlorine atom of the intermediates **6** and addition of one supplementary equivalent of base (route B). The anions **6** were generated by successive addition of a solution of BuLi (2 equivalents/base 1) onto diethyl alkylphosphonates **5** and ethyl phosphorochloridate **4**.

For both routes, aminoaldehydes were introduced onto the nonisolated intermediates **2**, which reacted via a Horner-Emmons carbonyl olefination



SCHEME 1



SCHEME 2

to give the desired 3-amino-1-alkenylphosphonates **1**. The results are summarized in Table 1.

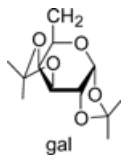
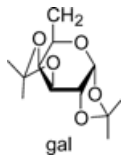
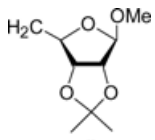
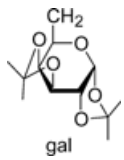
Route A

The addition of an aminoaldehyde **3** onto the generated in situ lithiated anions **2** led to the formation of the expected amino-1-alkenylphosphonates **1** when room temperature was attained. After the removal of the salts and chromatography, **1** was obtained in satisfactory yield and purity (Table 1). This synthesis starting from the easily available substrates, diethyl alkylphosphonates **5**, and the diethyl phosphorochloridate (**4**, R^3 = OEt) worked well with a wide range of aminoaldehydes, and in addition a substituent on the R^2 position (**1b**, R^2 = Me) was tolerated under the reaction conditions. The simplicity of the experimental procedure should be noted; this one-pot synthesis that proceeds by sequential metallation, substitution, metallation, and carbonylolefination represents a significant improvement for the preparation of 3-amino-1-alkenylphosphonates **1**.

All compounds **1** were fully characterized on the basis of their ^{1}H, ^{13}C, and ^{31}P NMR, IR, and MS spectra. Characteristic signals in the ^{1}H NMR spectrum of **1a–1d** are the signals corresponding to the CH alkene with a typical downfield shift for an *E* configuration (δ = 6.76–6.34 ppm).

In every case, the preferential configuration of the newly formed double bond was *E*. The formation of only one isomer is typical of the Horner-Emmons

TABLE 1 Synthesis of 3-amino-1-alkenylphosphonates **1** via a Horner-Emmons carbonyl olefination of aminoaldehydes **3**

Compound **1**	R^1	R^2	R^3	R^4	*Z*	*Route*	*Base 1*	*Base 2*	*E/Z ratio*	*Yield%*
1a				Et	EtO	A	LDA	LDA	>99[a]	60
1a	Me	H	Et	CF_3CH_2	Cl	B	BuLi	LDA	>95[b]	60
1a				CF_3CH_2	Cl	B	BuLi	KH	>95[b]	30
1b	Me	Me	Et	Et	EtO	A	LDA	LDA	>99[a]	57
1c	Bn	H	Et	Et	EtO	A	LDA	LDA	>99[a]	70
1d	^{i}Bu	H	Et	Et	EtO	A	LDA	LDA	>99[a]	63
1e	Me	H	Et	 gal	Cl	B	BuLi	LDA	>99[a]	45
1f	Bn	H	Et	 gal	Cl	B	BuLi	LDA	>99[a]	50
1g	Me	H	 rib	 gal	Cl	B	BuLi	LDA	>99[a]	42

[a]Only *E*-aminophosphonates **1** were detected in ^{1}H-NMR.
[b]Traces of *Z*-aminophosphonates **1** were detected in ^{1}H-NMR.

reactions with aminoaldehydes and diethyl phosphonates [21d].

Route B

In preliminary attempts to tailor Z-selectivity, we introduced a trifluoroethoxy group on a phosphorus atom (**1a**, $R^4 = CF_3CH_2$). It appeared that **2** behaved very specifically and the *E*-stereoselectivity was conserved, despite the presence of the trifluoroethoxy group. The use of potassium hydride in THF led to **1a** in only poor yield and did not modify the *E*/*Z* ratio. Thus, the traditional parameters (cation and electronic effect) did not affect the stereoselectivity of the Horner reaction. As a result, the reaction was generally studied with BuLi as base 1 and LDA as base 2.

The various compounds summarized in Table 1 demonstrated the generality of the method. 3-amino-1-alkenylphosphonates bearing linear (**1a** and **1b** R^1 = Me; **1a–1d**, R^2 = H, Me; **1a–1d,** R^3 = Et) and ramified (**1c**, R^1 = Bn; **1d**, $R^1 = {}^i$Bu) substituents were compatible with the procedure. The product **1** was obtained satisfactorily with 57%–70% overall yield after chromatography.

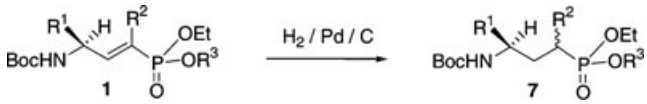
With the complete one-pot synthesis of 3-amino-1-alkenylphosphonates **1** in hand, our attention was turned to the possible preparation of the first P-mono and then P,P-diglycosyl 3-amino-1-alkenylphosphonates **1e–1g** in this way.

The methodology used ethyl or D-ribosyl phosphorodichloridate as dichlorophosphorylated substrate **4** (R^3 = Et, rib, Z = Cl) and subsequently protected D-galactose as nucleophile (R^4 = gal). The incorporation of one or two glycosyl residues smoothly modified the efficiency of the procedure. The sequential in situ reaction led to **1e–1g** with reasonable yields (50%–42%). The regioselectivity of the reaction was shown to be in favor of alkenes **1e–1g**: clearly the steric hindrance of the glycosyl residues oriented the regioselectivity of the olefination and allowed the exclusive removal of the diethyl phosphono group.

The reaction led to the creation of a phosphorus stereogenic center, and both diastereomers were observed by ^{31}P and ^{13} C NMR (ratio 1/1).

This sequential in situ reaction proved to be an efficient synthetic method for the preparation of functional aminoalkenylphosphonates **1**.

In addition, the preparation of aminoalkenylphosphonates **1e–1g** with a chiral phosphorus atom confirmed the synthetic potential of the method and the obtained compounds are of particular interest for further biological applications.

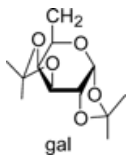
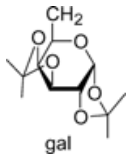


SCHEME 3

The synthesis of the saturated α-aminophosphonates **7** can also be achieved in excellent yields, by catalytic hydrogenation of the 3-amino-1-alkenylphosphonates **1** (Scheme 3 and Table 2). In sharp contrast with the hydrogenation of the vinylogous aminoester Boc—NH—CHMe—CH=CMe—COOMe [23], no diastereoselectivity was observed with the analogous aminophosphonate Boc—NH—CHMe—CH=CMe—P(O)$(OEt)_2$ **7b**. This result is quite surprising, because it could be supposed that the (S) configuration of the *N*-α-ethyl carbon would involve a diastereoselective hydrogenation of the aminophosphonate **7b**. As a consequence, it appeared that the concept of 1,3-allylic strain could not be applied to the hydrogenation of the 3-aminobutenyl phosphonate **7b**.

Because the natural metabolites of the sphingomyelin cycle include either a carbohydrate moiety or a phosphorylated group linked to a sphingosine unit, the synthesis of aminophosphonates with a glycosyl moiety represents an interesting possibility. With this aim, we have also studied the catalytic hydrogenation of **1e** and **1f**, a priori the most difficult examples, having steric hindrance on the phosphorus atom. It is noteworthy that these hydrogenations carried out in the presence of palladium on charcoal (10%), in EtOH, at room temperature were

TABLE 2 Catalytic hydrogenation of the 3-amino-1-alkenylphosphonates **1**

Compound	R^1	R^2	R^3	*Diastereomeric ratio*	*Yield%*
7a	Me	H	Et	–	96
7b	Me	Me	Et	1/1	95
7c	Bn	H	Et	–	97
7d	^{i}Bu	H	Et	–	96
7e	Me	H	 gal	1/1	95
7f	Bn	H	 gal	1/1	93

very efficient (93%–95%). ^{31}P NMR of the galactosyl aminophosphonates **7e** and **7f** indicated the presence of two diastereomers (diastereomeric ratio 1/1).

In summary, we developed a rapid and efficient one-step synthesis of various aminoalkenylphosphonates starting from readily available phosphonates and phosphorochloridates. In addition, the presented methodology allowed the preparation of the P-mono and *P*,*P*-diglycosyl-3-amino-1-alkenylphosphonates.

Moreover, the saturated α-aminophosphonates can be obtained easily by the catalytic hydrogenation of aminoalkenylphosphonates. These compounds are important building blocks in organic synthesis and in the preparation of biologically active compounds.

EXPERIMENTAL

NMR experiments were recorded on Bruker spectrometers (AM 400, DRX 400). Chemical shifts (δ) are reported in ppm and referenced to initial TMS (δ 0.0) for ^{1}H NMR and $CDCl_3$ (δ 77.0) for ^{13}C NMR; coupling constants (J) are quoted in hertz; two-dimensional techniques were also used to assist in structural elucidation. Diastereomer ratios were determined on the basis of ^{31}P NMR of the crude products. IR spectra were recorded on a Nicolet 210 FT-IR spectrometer, and only the most representative frequencies (cm^{-1}) are reported. Mass spectra (ESI) were obtained with LCM Waters-Micromass/zq spectrometer. Merck silica gel 60 (230–400 mesh) was used as stationary phase for column chromatography. TLC (Merck Kieselgel 60, F254) was viewed using a UV light (254 nm). Optical rotations were measured on Bellingham-Stanley ADP 220 polarimeter. All reactions were conduced in oven-dried glassware under inert atmosphere of nitrogen. All solvents were purified according to standard procedures.

Preparation of γ-Aminovinylphosphonates **1**

Route A. A 100-mL four-necked flask equipped with a thermometer and dropping funnel, was charged with a solution of $(EtO)_2P(O)CH_2R^2$ **5** (3.6 mmol in 10 mL of dry THF) and after cooling down to −78°C an LDA (7.2 mmol) was gradually injected. The reaction mixture was allowed to warm to −70°C and stirred at that temperature for 1h. After that time a solution of $(EtO)_2P(O)Cl$ **4** (0.52 mL, 3.6 mmol, in 10 mL of dry THF) was added dropwise. The mixture was stirred for 2 h at −70°C, then allowed to warm to −50°C and stirred, for 1 h at that temperature before warming to room temperature (r.t.), where the mixture was stirred for an additional 1 h. After that time, the reaction was again cooled down to −70°C and then the appropriate aminoaldehyde **3** (3.6 mmol, in 10 mL of dry THF) was added dropwise. After the addition was complete, the reaction was left to warm slowly to r.t. and then stirred at that temperature over a period of 12 h. After that time, the reaction was quenched with water (20 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried (Na_2SO_4) and filtered, and the solvent was removed on the rotary evaporator affording the crude product that was further purified by column chromatography.

Route B. To a dry 100-mL four-necked flask equipped with a thermometer and dropping funnel, dry THF (10 mL) was added and after cooling down to −50°C an *n*-BuLi (6.0 mL, 9.0 mmol, 1.5 M in hexane) was gradually injected. This mixture was cooled down to −78°C before adding dropwise the solution of $(EtO)_2P(O)CH_3$ **5** (1.32 mL, 9.0 mmol, in 10 mL of dry THF). After stirring, the reaction mixture for 30 min. at −78°C, the solution of $ZP(O)Cl_2$ **4** (4.5 mmol, in 10 mL of dry THF) was added dropwise, and the stirring was continued for 2.5 h at that temperature. After that time, a solution of appropriate alcohol (4.5 mmol, in 10 mL of dry THF) was added dropwise and after stirring for 15 min at −78°C the reaction mixture was allowed to warm slowly to r.t. over a period of 4 h. Then the reaction mixture was again cooled down to −78°C and LDA (3.6 mmol) was gradually injected and after 20 min the appropriate aminoaldehyde **3** (3.6 mmol, in 10 mL of dry THF) was added dropwise. The reaction mixture was left to warm to r.t. and then stirred at that temperature over a period of 12 h. After that time, the reaction was cooled down to −50°C and quenched with water (15 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried (Na_2SO_4) and filtered, and the solvent was removed on the rotary evaporator affording the crude product that was further purified by column chromatography.

Compound **1a**. Colourless oil; R_f (0.21 AcOEt/hexane 8:1); $[\alpha]^{23}{}_{D=}$ −22.0 (*c* 0.5, CH_2Cl_2) ^{1}H NMR ($CDCl_3$) δ_H (ppm): 6.73–6.62 (m, 1H, CH=), 5.73 (m, 1H, P(O)CH=), 4.63 (bs, 1H, NH), 4.34 (bs, 1H, CH), 4.08–4.01 (m, 4H, $(OCH_2CH_3)_2$, 1.41 (s, 9 H, $C(CH_3)_3$), 1.29 (t, 6 H, $(OCH_2CH_3)_2$, $^3J_{HH}$ = 8.7 Hz), 1.29 (d, 3 H, CH_3, $^4J_{HH}$ = 4.5 Hz). ^{13}C NMR ($CDCl_3$; 100 MHz) δ_C (ppm): 154.86 (s, NHCO), 153.63 (d, CH=, $^2J_{CP}$ = 5.1 Hz), 116.58 (d, CH=, $^1J_{CP}$ = 187 Hz), 61.77 (s, OCH_2), 48.27 (d, CH, $^3J_{CP}$ = 21.8 Hz), 28.29 (s, $C(CH_3)_3$), 20.04 (s, CH_3), 16.35 (d,

CH_2CH_3, $^3J_{CP} = 6.4$ Hz). ^{31}P NMR ($CDCl_3$; 170 MHz) δ_P (ppm): 19.1 (s). IR, ν_{max} (film) cm^{-1}: 3283 (NH), 1716 (C=O), 1634 (C=C), 1029 (P=O), 973 (P–O). SM (ESI > 0.40V): 330.3 $[M + Na]^+$.

Compound **1b**. Colourless oil; R_f (0.38 AcOEt/Hexane 4:1); $[\alpha]^{23}{}_{D=} -6.0$ (*c* 1.0, CH_2Cl_2) ^1H NMR ($CDCl_3$) δ_H (ppm): 6.34 (dd, 1H, CH=, $^3J_{HH}$ = 5.25 Hz), 4.97 (bs, 1H, NH), 4.47 (bs, 1H, CH), 4.03–3.92 (m, 4H, $(OCH_2CH_3)_2$), 1.82 (d, 3H, CH_3 C=, $^4J_{HH} = 9.25$ Hz), 1.35 (s, 9H, $C(CH_3)_3$), 1.26–1.21 (m, 6H, $(OCH_2CH_3)_2$), 1.15 (d, 3H, CH_3, $^4J_{HH} = 4.25$ Hz). ^{13}C NMR ($CDCl_3$; 100 MHz) δ_C (ppm): 154.98 (s, NHCO), 147.43 (d, CH=, $^2J_{CP} = 8.0$ Hz), 125.74 (d, CH=, $^1J_{CP} = 175.5$ Hz), 61.66 (s, OCH_2), 48.46 (d, CH, $^3J_{CP} = 21.6$ Hz), 28.26 (s, $C(CH_3)_3$), 20.28 (s, CH_3), 16.25 (d, CH_2CH_3, $^3J_{CP} = 6.1$ Hz), 12.59 (d, CH_3 C=, $^2J_{CP} = 9.6$ Hz). ^{31}P NMR ($CDCl_3$; 170 MHz) δ_P (ppm): 21.2 (s). IR, ν_{max} (film) cm^{-1}: 3200 (NH), 1705 (C=O), 1639 (C=C), 1000 (P=O), 970 (P–O). SM (ESI > 0.40V): 344.3 $[M + Na]^+$.

Compound **1c**. Colourless oil; R_f (0.35 AcOEt/hexane 2:1), $[\alpha]^{23}{}_{D=} -6.0$ (*c* 0.5, CH_2Cl_2), ^1H NMR ($CDCl_3$) δ_H (ppm): 7.24–7.08 (m, 5H, ArH), 6.70–6.60 (m, 1H, CH=), 5.65–5.60 (m, 1H, P(O)CH=), 4.53 (bs, 2H, NH, CH), 3.98–3.89 (m, 4H, $(OCH_2CH_3)_2$), 2.82 (bs, 2H, CH_2Ph), 1.32 (s, 9H, $C(CH_3)_3$), 1.23–1.18 (m, 6H, $(OCH_2CH_3)_2$). ^{13}C NMR ($CDCl_3$; 100 MHz) δ_C (ppm): 154.92 (s, NHCO), 151.87 (d, CH=, $^2J_{CP} = 5.4$ Hz), 136.37, 129.41, 128.55, 126.85 (C_{arm}), 117.96 (d, CH=, $^1J_{CP}$ = 185 Hz), 61.81 (s, OCH_2), 53.65 (bs, CH), 40.61 (s, CH_2Ph), 28.26 (s, $C(CH_3)_3$), 16.34 (d, CH_2CH_3, $^3J_{CP}$ = 5.8 Hz). ^{31}P NMR ($CDCl_3$; 170 MHz) δ_P (ppm): 18.1 (s). IR, ν_{max} (film) cm^{-1}: 3277 (NH), 1721 (C=O), 1634 (C=C), 1024 (P=O), 963 (P–O). SM (ESI > 0.40V): 406.4 $[M + Na]^+$.

Compound **1d**. Colourless oil; R_f (0.44 AcOEt/hexane 2:1), $[\alpha]^{23}{}_{D=} -18.0$ (*c* 0.5, CH_2Cl_2), ^1H NMR ($CDCl_3$) δ_H (ppm): 6.64–6.53 (m, 1H, CH=), 5.75–5.65 (m, 1H, P(O)CH=), 4.51 (bs, 1H, NH), 4.24 (bs, 1H, CH), 4.01–3.98 (m, 4H, $(OCH_2CH_3)_2$), 1.64–1.59 (m, 1H, $CH(CH_3)_2$), 1.36 (s, 9H, $C(CH_3)_3$), 1.20–1.25 (m, 2H, $CHCH_2$), 1.26 (t, 6H, $(OCH_2CH_3)_2$), $^3J_{HH} = 9.0$ Hz), 0.87 (d, 6H, $CH(CH_3)_2$, $^3J_{HH} = 4.25$ Hz). ^{13}C NMR ($CDCl_3$; 100 MHz) δ_C (ppm): 155.05 (s, NHCO), 153.40 (d, CH=, $^2J_{CP} = 5.0$ Hz), 116.72 (d, CH=, $^1J_{CP} = 186$ Hz), 61.69 (s, OCH_2), 51.11 (d, CH, $^3J_{CP} = 21.5$ Hz), 43.41 (s, $CHCH_2$), 28.24 (s, $C(CH_3)_3$), 24.66 (s, $CH(CH_3)_2$), 22.71 (s, $(CH_3)_2$), 16.29 (d, CH_2CH_3, $^3J_{CP} = 6.3$ Hz). ^{31}P NMR ($CDCl_3$; 170 MHz) δ_P (ppm): 18.7 (s). IR, ν_{max} (film) cm^{-1}: 3272 (NH), 1721 (C=O), 1629 (C=C), 1024 (P=O), 963 (P–O). SM (ESI > 0.40V): 372.3 $[M + Na]^+$.

Compound **1e** *(diastereomers)*. Colourless oil; R_f (0.45 AcOEt/hexane 4:1), $[\alpha]^{23}{}_{D=} -37.50$ (*c* 0.8, CH_2Cl_2), ^1H NMR ($CDCl_3$) δ_H (ppm): 6.69–6.55 (m, 1H, CH=), 5.67–5.57 (m, 1H, P(O)CH=), 5.52 (d, 1H, H_1, $^3J_{HH} = 5.2$ Hz), 4.90 (bs, 1H, NH), 4.62–4.59 (m, 1H, CH), 4.56–4.53 (m, H_2, 1H), 4.28–3.91 (m, 7H, H_3, H_4, H_5, OCH_2CH_3, OCH_2Gal), 1.48 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.34 (s, 9H, $C(CH_3)_3$), 1.25 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 1.22–1.19 (m, 3H, OCH_2CH_3), 1.10–1.07 (m, 3H, CH_3). ^{13}C NMR ($CDCl_3$; 100 MHz) δ_C (ppm): *diastereomer 1*: 155.62 (s, NHCO), 151.97 (d, CH=, $^2J_{CP} = 5.2$ Hz), 117.81 (d, CH=, $^1J_{CP} = 182$ Hz), 109.74 (s, $C(CH_3)_2$), 108.83 (s, $C(CH_3)_2$), 96.24 (s, C_1), 70.67 (s, C_4), 70.45 (s, C_3), 70.32 (s, C_2), 67.37 (d, C_5, $^3J_{CP} = 5.8$ Hz), 64.65 (d, C_6, $^2J_{CP} = 5.0$ Hz), 61.90 (m, OCH_2), 47.05 (bs, CH), 28.40 (s, $C(CH_3)_3$), 26.00 (s, CH_3), 25.90 (s, CH_3), 24.95 (s, CH_3), 24.47 (s, CH_3), 21.30 (s, CH_3), 16.42 (m, CH_2CH_3). *diastereomer 2*: 155.50 (s, NHCO), 151.95 (d, CH=, $^2J_{CP} = 4.9$ Hz), 117.78 (d, CH=, $^1J_{CP} = 184$ Hz), 109.74 (s, $C(CH_3)_2$), 108.83 (s, $C(CH_3)_2$), 96.24 (s, C_1), 70.67 (s, C_4), 70.45 (s, C_3), 70.32 (s, C_2), 67.67 (d, C_5, $^3J_{CP} = 6.0$ Hz), 65.47 (d, C_6, $^2J_{CP} = 5.5$ Hz), 61.25 (m, OCH_2), 47.07 (bs, CH), 28.40 (s, $C(CH_3)_3$), 26.00 (s, CH_3), 25.90 (s, CH_3), 24.95 (s, CH_3), 24.47 (s, CH_3), 21.30 (s, CH_3), 16.42 (m, CH_2CH_3). ^{31}P NMR ($CDCl_3$; 170 MHz) δ_P (ppm): 18.7 (s) and 18.3 (s) (in ratio 1:1). IR, ν_{max} (film) cm^{-1}: 3207 (NH), 1720 (C=O), 1578 (C=C), 1254 (P=O), 978 (P–O). SM (ESI >0.40V): 544.2 $[M + Na]^+$.

Compound **1f** *(diastereomers)*. Colourless oil; R_f (0.47 AcOEt/hexane 4:1), $[\alpha]^{23}{}_{D=} -29.28$ (*c* 1.4, CH_2Cl_2), ^1H NMR ($CDCl_3$) δ_H (ppm): 7.24–7.08 (m, 5H, ArH), 6.70–6.59 (m, 1H, CH=), 5.70–5.56 (m, 1H, P(O)CH=), 5.46 (d, 1H, H_1, $^3J_{HH} = 5.2$ Hz), 4.76–4.72 (m, 1H, NH), 4.54–4.51 (m, 1H, CH), 4.25–4.23 (m, H_2, 1H), 4.20–3.90 (m, 7H, H_3, H_4, H_5, OCH_2CH_3, OCH_2Gal), 2.82–2.77 (m, 2H, CH_2Ph), 1.45 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.31 (s, 9H, $C(CH_3)_3$), 1.25 (s, 3H, CH_3), 1.22–1.17 (m, 6H, OCH_2CH_3). ^{13}C NMR ($CDCl_3$; 100 MHz) δ_C (ppm): *diastereomer 1*: 154.96 (s, NHCO), 151.96 (d, CH=, $^2J_{CP} = 5.0$ Hz), 136.37, 129.38 128.83, 126.77 (C_{arm}), 117.80 (d, CH=, $^1J_{CP} = 185$ Hz), 109.74 (s, $C(CH_3)_2$), 108.83 (s, $C(CH_3)_2$), 96.22 (s, C_1), 70.66 (s, C_4), 70.60 (s, C_3), 70.38 (s, C_2), 67.06 (d, C_5, $^3J_{CP} = 6.6$ Hz), 64.35 (d, C_6,$^2J_{CP} = 5.6$ Hz), 61.75 (m, OCH_2), 53.53 (bs, CH), 40.61 (bs, CH_2Ph), 28.24 (s, $C(CH_3)_3$), 25.99 (s, CH_3), 25.91 (s, CH_3), 24.92 (s, CH_3), 24.42 (s, CH_3), 16.30 (m, CH_2CH_3). *diastereomer 2*: 154.96 (s, NHCO), 152.12 (d, CH=, $^2J_{CP} = 5.0$ Hz), 136.37,

129.38 128.83, 126.77 (C_{arm}), 117.40 (d, CH=, $^1J_{CP}$ = 184 Hz), 109.74 (s, $C(CH_3)_2$), 108.83 (s, $C(CH_3)_2$), 96.22 (s, C_1), 70.66 (s, C_4), 70.60 (s, C_3), 70.38 (s, C_2), 67.41 (d, C_5, $^3J_{CP}$ = 6.4 Hz), 64.83 (d, C_6,$^2J_{CP}$ = 5.4 Hz), 61.97 (m, OCH_2), 53.53 (bs, CH), 40.61 (bs, CH_2Ph), 28.24 (s, $C(CH_3)_3$), 25.99 (s, CH_3), 25.91 (s, CH_3), 24.92 (s, CH_3), 24.42 (s, CH_3), 16.30 (m, CH_2CH_3). ^{31}P NMR ($CDCl_3$; 170 MHz) δ_P (ppm): 18.9 (s) and 18.4 (s) (in ratio 1:1). IR, ν_{max} (film) cm^{-1}: 3257 (NH), 1715 (C=O), 1582 (C=C), 1031 (P=O), 976 (P—O). SM (ESI > 0.40V): 620.6 $[M + Na]^+$.

Compound **1g** *(diastereomers).* Colourless oil; R_f (0.35 AcOEt/hexane 4:1), $[\alpha]^{23}{}_{D=}$ −51.67 (*c* 0.6, CH_2Cl_2), ^{1}H NMR ($CDCl_3$) δ_H (ppm): 6.76–6.62 (m, 1H, CH=), 5.81–5.70 (m, 1H, P(O)CH=), 5.49–5.46 (m, 1H, H_1), 4.88 (s, 1H, H_1Rib), 4.70 (bs, 1H, NH), 4.67–4.62 (m, 2H, H_2, H_4Rib), 4.55–4.50 (m, 1H, H_3Rib), 4.34 (bs, 1H, CH), 4.26–4.20 (m, 1H, H_2Rib), 4.219–3.90 (m, 7H, H_3, H_4, H_5 OCH_2Rib, OCH_2Gal), 3.23 (s, 3H, OCH_3), 1.47 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.37 (s, 9H, $C(CH_3)_3$), 1.26 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 1.98–1.18 (m, 3H, CH_3). ^{13}C NMR ($CDCl_3$; 100 MHz) δ_C (ppm): *diastereomer 1*: 154.90 (s, NHCO), 154.36 (d, CH=, $^2J_{CP}$ = 5.0 Hz), 116.13 (d, CH=, $^1J_{CP}$ = 182 Hz), 112.57 (s, $C(CH_3)_2$), 109.62 (s, C_1Rib), 109.74 (s, $C(CH_3)_2$), 108.83 (s, $C(CH_3)_2$), 96.22 (s, C_1), 85.09 (s, C_2Rib), 81.66 (s, C_3Rib), 79.66 (s, C_4Rib), 70.69 (s, C_4), 70.64 (s, C_3), 70.36 (s, C_2), 67.17 (s, C_5Rib), 67.38 (d, C_5, $^3J_{CP}$ = 5.7 Hz), 65.23 (d, C_6,$^2J_{CP}$ = 5.3 Hz), 55.02 (s, OCH_3), 48.10 (bs, CH), 28.35 (s, $C(CH_3)_3$), 25.99 (s, CH_3), 24.95 (s, CH_3), 24.42 (s, CH_3), 20.17 (s, CH_3). *diastereomer 2*: 154.90 (s, NHCO), 154.36 (d, CH=, $^2J_{CP}$ = 5.0 Hz), 116.13 (d, CH=, $^1J_{CP}$ = 182 Hz), 112.57 (s, $C(CH_3)_2$), 109.62 (s, C_1Rib), 109.74 (s, $C(CH_3)_2$), 108.83 (s, $C(CH_3)_2$), 96.22 (s, C_1), 85.09 (s, C_2Rib), 81.66 (s, C_3Rib), 79.66 (s, C_4Rib), 70.69 (s, C_4), 70.64 (s, C_3), 70.36 (s, C_2), 67.17 (s, C_5Rib), 67.19 (d, C_5, $^3J_{CP}$ = 6.0 Hz), 64.97 (d, C_6,$^2J_{CP}$ = 6.1 Hz), 55.02 (s, OCH_3), 48.10 (bs, CH), 28.35 (s, $C(CH_3)_3$), 26.39 (s, CH_3), 25.99 (s, CH_3), 24.95 (s, CH_3), 24.42 (s, CH_3), 20.17 (s, CH_3). ^{31}P NMR ($CDCl_3$; 170 MHz) δ_P (ppm): 19.8 (s) and 19.2 (s) (in ratio 1:1). IR, ν_{max} (film) cm^{-1}: 3157 (NH), 1721 (C=O), 1557 (C=C), 1070 (P=O), 1004 (P—O). SM (ESI > 0.40V): 702.6 $[M + Na]^+$.

General Procedure for the Hydrogenolysis of the Aminoalkenylphosphonates **1**

Hydrogenolysis was carried out in standard conditions using Pd/C 10% and H_2 (30 bars). The starting material was dissolved in dry EtOH (15 mL). Pd/C was added (10% with respect to the mass of the starting material), and after 12 h under H_2 (30 bars) the mixture was filtered through a celite and evaporated to give crude product that did not required any further purification.

Compound **7a**. Colourless oil; $[\alpha]^{23}{}_{D=}$ −6.36 (*c* 1.1, CH_2Cl_2) ^{1}H NMR ($CDCl_3$) δ_H (ppm): 4.44 (bs, 1H, NH), 4.07–3.97 (m, 4H, $(OCH_2CH_3)_2$), 3.59 (bs, 1H, CH), 1.80–1.50 (m, 4H, CH_2CH_2), 1.36 (s, 9H, $C(CH_3)_3$), 1.27 (t, 6H, $(OCH_2CH_3)_2$), $^3J_{HH}$ = 8.0 Hz), 1.08 (d, 3H, CH_3, $^4J_{HH}$ = 4.0 Hz). ^{13}C NMR ($CDCl_3$; 100 MHz) δ_C (ppm): 155.40 (s, NHCO), 61.54 (s, OCH_2), 46.94 (d, CH, $^3J_{CP}$ = 17.8 Hz), 29.88 (d, CH_2, $^2J_{CP}$ = 4.5 Hz), 28.35 (s, $C(CH_3)_3$), 23.12 (d, $CH_2P(O)^1J_{CP}$ = 141 Hz), 21.09 (s, CH_3), 16.44 (d, CH_2CH_3, $^3J_{CP}$ = 5.9 Hz). ^{31}P NMR ($CDCl_3$; 170 MHz) δ_P (ppm): 32.2 (s). IR, ν_{max} (film) cm^{-1}: 3288 (NH), 1710 (C=O), 1055 (P=O), 958 (P—O). SM (ESI > 0.40V): 332.3 $[M + Na]^+$.

Compound **7b** *(diastereomers).* Colourless oil; $[\alpha]^{23}{}_{D=}$ −3.0 (*c* 1.0, CH_2Cl_2) ^{1}H NMR ($CDCl_3$) δ_H (ppm): 4.63 (bs, 1H, NH), 4.44 (bs, 1H, CHP(O)), 4.83–3.98 (m, 4H, $(OCH_2CH_3)_2$), 3.73 (bs, 1H, NCH), 1.85–1.65 (m, 2H, CH_2), 1.3 (s, 9H, $C(CH_3)_3$), 1.27–1.23 (m, 6H, $(OCH_2CH_3)_2$), 1.2–1.1 (m, 3H, $CHCH_3P(O)$ *diastereomer 1*), 1.00–1.05 (m, 3H, $CHCH_3P(O)$ *diastereomer 2*), 1.04 (d, 3H, CH_3, $^4J_{HH}$ = 4.0Hz). ^{13}C NMR ($CDCl_3$; 100 MHz) δ_C (ppm): *diastereomer 1*: 155.57 (s, NHCO), 61.70 (s, OCH_2), 44.73 (bs, CHP(O)), 48.70 (d, CH, $^3J_{CP}$ = 15.5 Hz), 37.45 (s, CH_2), 28.37 (s, $C(CH_3)_3$), 20.14 (s, CH_3), 16.47 (d, $(OCH_2CH_3)_2$, $^3J_{CP}$ = 6.0 Hz), 13.51 (d, $CH_3CP(O)$, $^2J_{CP}$ = 9.0 Hz). *diastereomer 2*: 155.12 (s, NHCO), 61.70 (s, OCH_2), 44.73 (bs, CHP(O)), 48.70 (d, CH, $^3J_{CP}$ = 15.5 Hz), 37.30 (s, CH_2), 28.37 (s, $C(CH_3)_3$), 20.14 (s, CH_3), 16.47 (d, $(OCH_2CH_3)_2$, $^3J_{CP}$ = 6.0 Hz), 12.94 (d, $CH_3CP(O)$, $^2J_{CP}$ = 9.0 Hz). ^{31}P NMR ($CDCl_3$; 170 MHz) δ_P (ppm): 35.1 (s) and 35.32 (s) (in ratio 1:1). IR, ν_{max} (film) cm^{-1}: 3288 (NH), 1710 (C=O), 1055 (P=O), 958 (P—O). SM (ESI > 0.40V): 346.3 $[M + Na]^+$.

Compound **7c**. Colourless oil; $[\alpha]^{23}{}_{D=}$ −1.92 (*c* 0.52, CH_2Cl_2), ^{1}H NMR ($CDCl_3$) δ_H (ppm): 7.23–7.09 (m, 5H, ArH), 4.39 (bs, 1H, NH), 4.04–3.94 (m, 4H, $(OCH_2CH_3)_2$), 3.75 (bs, 1H, CH), 2.73–2.64 (m, 2H, CH_2Ph), 1.80–1.50 (m, 4H, CH_2CH_2), 1.32 (s, 9H, $C(CH_3)_3$), 1.25–1.21 (m, 6H, $(OCH_2CH_3)_2$). ^{13}C NMR ($CDCl_3$; 100 MHz) δ_C (ppm): 155.53 (s, NHCO), 137.66, 129.42, 128.44, 126.48 (C_{arm}), 61.64 (s, OCH_2), 53.25 (bs, CH), 41.45 (s, CH_2Ph), 28.34 (s, $C(CH_3)_3$), 23.20 (s, CH_2), 21.79 (s, CH_2), 16.47 (d, $(OCH_2CH_3)_2$, $^3J_{CP}$ = 5.0 Hz). ^{31}P NMR ($CDCl_3$; 170 MHz) δ_P (ppm): 32.20 (s). IR, ν_{max} (film) cm^{-1}: 3283

(NH), 1710 (C=O), 1034 (P=O), 963 (P–O). SM (ESI > 0.40V): 408.1 $[M + Na]^+$.

Compound **7d**. Colourless oil; $[\alpha]^{23}{}_{D=} -16.36$ (*c* 1.1, CH_2Cl_2), ^{1}H NMR ($CDCl_3$) δ_H (ppm): 4.33 (bs, 1H, NH), 4.07–4.04 (m, 4H, $(OCH_2CH_3)_2$), 3.62 (bs, 1H, CH), 1.76–1.52 (m, 5H, $CH_2CH_2P(O)$, $CH(CH_3)_2$), 1.40 (s, 9H, $C(CH_3)_3$), 1.33 (t, 6H, $(OCH_2CH_3)_2$), $^3J_{HH} = 9.0$ Hz), 1.26–1.20 (m, 2H, $CHCH_2$), 0.89 (d, 6H, $CH(CH_3)_2$, $^3J_{HH} = 4.25$ Hz). ^{13}C NMR ($CDCl_3$; 100 MHz) δ_C (ppm): 155.64 (s, NHCO), 61.52 (s, OCH_2), 49.24 (d, CH, $^3J_{CP} = 21.0$ Hz), 44.77 (s, $CHCH_2$), 28.35 (s, $C(CH_3)_3$), 24.71 (s, $CH(CH_3)_2$), 23.02 (s, $(CH_3)_2$), 22.18 (s, CH_2), 21.50 (s, CH_2), 16.46 (d, $(OCH_2CH_3)_2$, $^3J_{CP} = 6.0$ Hz). ^{31}P NMR ($CDCl_3$; 170 MHz) δ_P (ppm): 32.58 (s). IR, ν_{max} (film) cm^{-1}: 3283 (NH), 1716 (C=O), 1034 (P=O), 968 (P–O). SM (ESI > 0.40 V): 374.2 $[M + Na]^+$.

Compound **7e** *(diastereomers)*. Colourless oil; $[\alpha]^{23}{}_{D=} -27.50$ (*c* 0.4, CH_2Cl_2), ^{1}H NMR ($CDCl_3$) δ_H (ppm): 5.52 (d, 1H, H_1, $^3J_{HH} = 5.2$ Hz), 4.93 (bs, 1H, NH), 4.56–4.53 (m, H_2, 1H), 4.28–3.91 (m, 7H, H_3, H_4, H_5, OCH_2CH_3, OCH_2Gal), 3.58 (bs, 1H, CH), 1.89–1.55 (m, 4H, CH_2CH_2), 1.47 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 1.36 (s, 9H, $C(CH_3)_3$), 1.28 (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 1.25–1.22 (m, 3H, OCH_2CH_3), 1.08–1.06 (m, 3H, CH_3). ^{13}C NMR ($CDCl_3$; 100 MHz) δ_C (ppm): *diastereomer 1*: 155.63 (s, NHCO), 109.71 (s, $C(CH_3)_2$), 108.79 (s, $C(CH_3)_2$), 96.26 (s, C_1), 70.66 (s, C_4), 70.43 (s, C_3), 70.34 (s, C_2), 67.34 (d, C_5, $^3J_{CP} = 6.0$ Hz), 64.70 (d, C_6, $^2J_{CP} = 5.2$ Hz), 61.96 (m, OCH_2), 47.07 (bs, CH), 28.44 (s, $C(CH_3)_3$), 26.02 (s, CH_3), 25.95 (s, CH_3), 24.93 (s, CH_3), 24.44 (s, CH_3), 23.53 (s, CH_2), 23.09 (s, CH_2), 21.37 (s, CH_3), 16.45 (m, CH_2CH_3). *diastereomer 2*: 155.48 (s, NHCO), 109.71 (s, $C(CH_3)_2$), 108.79 (s, $C(CH_3)_2$), 96.26 (s, C_1), 70.66 (s, C_4), 70.43 (s, C_3), 70.34 (s, C_2), 67.83 (d, C_5, $^3J_{CP} = 6.2$ Hz), 65.49 (d, C_6, $^2J_{CP} = 5.3$ Hz), 61.12 (m, OCH_2), 47.07 (bs, CH), 28.44 (s, $C(CH_3)_3$), 26.02 (s, CH_3), 25.95 (s, CH_3), 24.93 (s, CH_3), 24.44 (s, CH_3), 23.53 (s, CH_2), 23.09 (s, CH_2), 21.85 (s, CH_3), 16.11 (m, CH_2CH_3). ^{31}P NMR ($CDCl_3$; 170 MHz) δ_P (ppm): 33.4 (s) and 32.7 (s) (in ratio 1:1). IR, ν_{max} (film) cm^{-1}: 1716 (C=O), 1250 (P=O), 1004 (P–O). SM (ESI > 0.40V): 546.5 $[M + Na]^+$.

Compound **7f** *(diastereomers)*. Colourless oil; $[\alpha]^{23}{}_{D=} -27.00$ (*c* 1.0, CH_2Cl_2), ^{1}H NMR ($CDCl_3$) δ_H (ppm): 7.23–7.09 (m, 5H, ArH), 5.47 (d, 1H, H_1, $^3J_{HH} = 5.0$ Hz), 4.60–4.55 (m, H_2, 1H), 4.53 (bs, 1H, NH), 4.26–3.95 (m, 7H, H_3, H_4, H_5, OCH_2CH_3, OCH_2Gal), 4.77 (bs, 1H, CH), 2.70–2.68 (m, 2H, CH_2Ph), 1.80–1.47 (m, 4H, CH_2CH_2), 1.36 (s, 3H, CH_3), 1.32 (s, 9H, $C(CH_3)_3$), 1.25 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 1.22 (s, 3H, CH_3), 1.21–1.17 (m, 3H, OCH_2CH_3). ^{13}C NMR ($CDCl_3$; 100 MHz) δ_C (ppm): *diastereomer 1*: 155.66 (s, NHCO), 129.51, 129.41 128.43, 126.47 (C_{arm}), 109.74 (s, $C(CH_3)_2$), 108.83 (s, $C(CH_3)_2$), 96.24 (s, C_1), 70.77 (s, C_4), 70.69 (s, C_3), 70.34 (s, C_2), 67.30 (d, C_5, $^3J_{CP} = 6.2$ Hz), 64.76 (d, C_6, $^2J_{CP} = 5.5$ Hz), 61.70 (m, OCH_2), 52.50 (bs, CH), 41.47 (bs, CH_2Ph), 28.38 (s, $C(CH_3)_3$), 25.96 (s, CH_3), 25.93 (s, CH_3), 24.88 (s, CH_3), 24.45 (s, CH_3), 23.18 (s, CH_2), 21.77 (s, CH_2), 16.46 (m, CH_2CH_3). *diastereomer 2*: 155.58 (s, NHCO), 129.51, 129.41 128.43, 126.47 (C_{arm}), 109.74 (s, $C(CH_3)_2$), 108.83 (s, $C(CH_3)_2$), 96.24 (s, C_1), 70.77 (s, C_4), 70.69 (s, C_3), 70.34 (s, C_2), 67.37 (d, C_5, $^3J_{CP} = 6.4$ Hz), 64.20 (d, C_6, $^2J_{CP} = 5.3$ Hz), 61.70 (m, OCH_2), 52.50 (bs, CH), 41.47 (bs, CH_2Ph), 28.38 (s, $C(CH_3)_3$), 25.96 (s, CH_3), 25.93 (s, CH_3), 24.88 (s, CH_3), 24.45 (s, CH_3), 23.18 (s, CH_2), 21.77 (s, CH_2), 16.46 (m, CH_2CH_3). ^{31}P NMR ($CDCl_3$; 170 MHz) δ_P (ppm): 33.4 (s) and 32.6 (s) (in ratio 1:1). IR, ν_{max} (film) cm^{-1}: 3303 (NH), 1716 (C=O), 1173 (P=O), 986 (P–O). SM (ESI > 0.40V): 622.6 $[M + Na]^+$.

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