Article

Synthesis of Four Enantiomers of (1-Amino-3-Hydroxypropane-1,3-Diyl)Diphosphonic Acid as Diphosphonate Analogues of 4-Hydroxyglutamic Acid

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Abstract: All the enantiomers of (1-amino-3-hydroxypropane-1,3-diyl)diphosphonic acid, newly design phosphonate analogues of 4-hydroxyglutamic acids, were obtained. The synthetic strategy involved Abramov reactions of diethyl (R)- and (S)-1-(N-Boc-amino)-3-oxopropylphosphonates with diethyl phosphite, separation of diastereoisomeric [1-(N-Boc-amino)-3-hydroxypropane-1,3-diyl]diphosphonates as O-protected esters, followed by their hydrolysis to the enantiomeric phosphonic acids. The absolute configuration of the enantiomeric phosphonates was established by comparing the $^{31}$P NMR chemical shifts of respective (S)-O-methylmandelic acid esters obtained from respective pairs of syn- and anti-[1-(N-Boc-amino)-3-hydroxypropane-1,3-diyl]diphosphonates according to the Spilling rule.

Keywords: Abramov reaction; phosphonates; glutamic acid analogues; absolute configuration

1. Introduction

As analogues of naturally occurring α-amino acids, α-aminophosphonic acids are pharmacologically significant as they can mimic transition states of several biological processes such as peptide hydrolysis. Owing to the tetrahedral structure of the phosphonic residue, they can act as enzyme inhibitors or antibiotics [1–4]. Moreover, their activity often depends on the absolute configuration at Cα in α-aminophosphonic acids. Over decades, a vast number of phosphonate analogues of α-amino acids have been synthesized with the intention to study their biological properties (Figure 1). Among them, analogues of glutamic acid 1, a major excitatory neurotransmitter in the central nervous system, deserve great consideration. For example, 2-amino-4-phosphonobutanic acid (L-AP4) 2 has been obtained as an analogue of glutamic acid and appeared to be a selective agonist for group III glutamate metabotropic receptors (mGluR) [5–9], whereas its α-methylated analogue (MAP4) 3 acts as a competitive antagonist of mGluR [10,11].

In continuation of our research program directed at the syntheses of enantiomerically pure functionalized aminophosphonates, we focus attention on hydroxyglutamic acids, which are widely available in nature, including plants, however this structure is also found as a part of more complex molecules with important biological properties. As expected, the presence of an additional hydroxy group in the glutamic acid framework may have a positive impact on the activity of its analogues. Thus, (2S,4S)-4-hydroxyglutamic acid 4 exhibited potency at mGlu$_{1a}$R and mGlu$_{8a}$R similar to that of L-glutamic acid [12], and its isomer (2S,4R)-4 demonstrated a significant preference for the NMDA (N-methyl-D-aspartic acid) receptor [13].

Inspired by these observations we considered the synthesis of all four enantiomerically pure diphosphonic acids 5 (Figure 2).
Our synthetic strategy relied on the formation of the C–P bond by the addition of diethyl phosphite to (R)- and (S)-1-amino-2-oxoethyl phosphonates 7, available from the enantiomerically pure N-(1-phenylethyl)-C-(diethoxyphosphoryl)nitrone (S)-10 already described by our research group (Scheme 1) [14].

2. Results and Discussion

The enantiomerically pure aldehydes (R)-7 and (S)-7 were synthesized starting from the nitrone (S)-10 following the reaction sequence depicted in Scheme 2, and their configurational stability was proven [14,15]. Cycloaddition of the nitrone (S)-10 to allyl alcohol in the presence of MgBr₂ led to the formation of an inseparable 1:1 mixture of isoxazolidines (3R,5R,1'S)-9 and (3S,5S,1'S)-9. They were successfully separated as O-acetyl derivatives from which the starting compounds (3R,5R,1'S)-9 and (3S,5S,1'S)-9 were recovered after ammonolysis. Subsequent catalytic hydrogenation in the presence of Boc₂O produced the N-Boc-aminodiols (1R,3R)-8 and (1S,3S)-8, respectively, which upon treatment with sodium metaperiodate, gave the aldehydes (R)-7 and (S)-7.

The aldehyde (R)-7 was subjected to the Abramov reaction with diethyl phosphite in the presence of catalytic amounts of triethylamine to afford a 1:1 mixture of diastereoisomeric diphenosphonates (1R,3S)-6 and (1R,3R)-6 (Scheme 3). Attempts to separate the diastereoisomeric mixture of diphenosphonates by column (silica gel) and high performance liquid chromatography (HPLC) appeared fruitless as the fractions collected were only...
enriched for the respective isomers (up to 90%). The ratio of diastereoisomers was established on the basis of $^{31}$P NMR spectra of the crude product. Since two phosphonyl groups are installed in the structure of compound 6, two signals were identified for each of the respective diastereoisomeric diphosphonates (1R,3S)-6 ($\delta^{31}$P = 25.26 and 23.58 ppm) and (1R,3R)-6 ($\delta^{31}$P = 24.60 and 24.01 ppm).

![Scheme 3](image)

Scheme 3. Synthesis of the diphosphonates (1R,3S)-6 and (1R,3R)-6. Reagents and conditions: (a) H3PO4(OEt)2, NEt3, rt, 48 h.

Separation of the diastereoisomeric mixture of 3-hydroxydiphosphonates 6 was achieved by their transformation into O-protected derivatives (Scheme 4). Thus, a 1:1 mixture of compounds (1R,3S)-6 and (1R,3R)-6 was esterified with acetic anhydride in the presence of triethylamine and catalytic amounts of DMAP (4-dimethylaminopyridine) to form the O-acetyl derivatives (1R,3S)-11 and (1R,3R)-11, which were then successfully separated by HPLC into a faster eluting diastereoisomer (1R,3S)-11 (22%) and a late-eluting one (1R,3R)-11 (40%). Alternatively, a 1:1 mixture of diphosphonates (1R,3S)-6 and (1R,3R)-6 was benzoylated with p-nitrobenzoyl chloride to produce the derivatives (1R,3S)-12 and (1R,3R)-12, and their separation by HPLC allowed isolation of pure isomer (1R,3S)-12 (21%) followed by (1R,3R)-12 (31%). Finally, the O-protected derivatives 11 and 12 were efficiently hydrolysed to produce the phosphonic acids (1R,3S)-5 and (1R,3R)-5.

![Scheme 4](image)

Scheme 4. Reagents and conditions: (a) Ac2O, Et3N, DMAP, 2 h, rt; (b) $p$-NO2-C6H4C(O)Cl, Et3N, DMAP, CH2Cl2, 4 h, rt; (c) 5M HCl, 6 h, reflux, propylene oxide [81% from (1R,3S)-11 and 84% from (1R,3R)-11; 53% from (1R,3S)-12 and 60% from (1R,3R)-12].

To complete the full set of stereoisomeric phosphonic acids 5, the aldehyde (S)-7 was used to synthesize diphosphonates (1S,3R)-6 and (1S,3S)-6, which were subsequently O-protected as the respective esters 11 or 12, and then transformed into the final acids (1S,3R)-5 and (1S,3S)-5 by application of an analogous reaction sequence (Scheme 5).

Since enantiomerically pure aldehydes were used for the synthesis of the respective diphosphonates, i.e., (R)-7 to obtain (1R,3S)-6 and (1R,3R)-6, and (S)-7 to obtain (1S,3R)-6 and (1S,3S)-6, the absolute configuration at C1 in the isomeric compounds 6 can be arbitrarily assigned. In order to unambiguously determine the absolute configuration at C3, it was therefore necessary to establish the relative configuration between C1 and C3 for the diastereoisomeric pairs of the respective diphosphonates, namely, (1R,3S)-6 and (1R,3R)-6, and (1S,3R)-6 and (1S,3S)-6.
In assigning the relative configurations of the diastereoisomeric diphosphonates (1S,3R)-6 and (1R,3R)-6, and (1S,3R)-6 and (1S,3R)-6, we took advantage of the known stereochemical outcome of the cycloaddition of N-benzyl-C-(diethoxyphosphoryl)nitron 13 with vinylphosphonate leading to the formation of a 76:12:12 mixture of the respective racemic isoxazolidines, trans-14 (δ31P = 21.32 and 20.77 ppm), cis-14 (δ31P = 20.81 and 19.49 ppm), and trans-15 (δ31P = 27.42 and 21.15 ppm, both as doublets with J value 32.4 Hz), with trans-14 predominating (Scheme 6) [16,17]. From this mixture, the major diastereoisomeric (isoxazolidine-3,5-diy1)-3,5-disphosphonate trans-14 [(3R/3S,5R/S)-14] and its 3,4-disubstituted regioisomer trans-15 [(3R/3S,5S/R)-15] were isolated on a silica gel column followed by HPLC with 17% and 3.5% yields, respectively. Compound trans-14 was then efficiently transformed into anti-6 via hydrogenolysis in the presence of Boc2O. The transformation of compound trans-14 into 6 proceeded without changes in configuration of the stereogenic centres, thus the relative configuration between substituents at C1 and C3 in racemic diphosphonate anti-6 [(1R/3S,3R/6] could be established unequivocally (Scheme 6), and therefore, the same applied to the anti-configured enantiomeric pair of diphosphonates (1R,3R)-6 and (1S,3S)-6 (Schemes 3 and 5). The addition of diethyl phosphite to aldehyde (R)-7 or (S)-7, results in the formation of the corresponding syn-adduct 6 in addition to the isomeric anti-6 product (stereochemical outcome of Abramov reaction). Consequently, the absolute configuration of the other pair of enantiomeric diphosphonates obtained from (R)-7 and (S)-7 were assigned as (1R,3S)-6 and (1S,3R)-6, respectively (Schemes 3 and 5).
Scheme 6. Cycloaddition of nitrone 13 to vinylphosphonate and transformation of cycloadduct trans-14 into anti-5. Reagents and conditions: (a) vinylphosphonate, 60 °C, 48 h; (b) H2, 20% Pd(OH)2/C, 48 h, rt.

To gather additional evidence of the absolute configurations at C3 in the respective 3-hydroxydiphosphonates 6, the racemic compound anti-6 [(1R,3R,3R)-6] available from isoxazolidine trans-14 [(3R,5R,5R)-14] was transformed into a diastereoisomeric mixture of O-methylmandelate derivatives (1R,3R,1′S)-16 (δ31P = 24.34 and 18.42 ppm) and (1S,3S,1′S)-16 (δ31P = 23.98 and 19.32 ppm) via esterification with (S)-O-methylmandelic acid [18] in the presence of DCC (N,N′-dicyclohexylcarbodiimide) [19] (Scheme 7). Although separation of the diastereoisomeric O-methylmandelates was tedious with HPLC, mainly due to problems with removal of dicyclohexylurea (DCU), sufficient amounts of the diastereoisomers were obtained to collect their 1H and 31P NMR spectra (see Supplementary Materials), i.e., (1R,3R,1′S)-16 eluted faster than (1R,3S,1′S)-16 (Scheme 4). Moreover, the O-methylmandelates 16 appeared unstable, even at −4 °C.

Scheme 7. Synthesis of (S)-O-methylmandelate derivatives (1R,3R,1′S)-16 and (1S,3S,1′S)-16. Reactions and conditions: (a) (S)-PhCH(OCH3)COOH, DCC, DMAP, CH2Cl2, rt, 24 h [14% for (1R,3R,1′S)-16 and 10% for (1S,3S,1′S)-16].

To synthesize all diastereoisomeric (S)-O-methylmandelic acid esters of the 3-hydroxydiphosphonates 6, analogous reactions were performed on the respective mixtures of diastereoisomeric phosphonates 6 obtained directly from enantiomerically pure aldehydes (Schemes 3 and 5). Thus, a mixture of the 3-hydroxydiphosphonates (1R,3S)-6 and (1R,3R)-6 obtained from aldehyde (R)-7 was converted into (S)-O-methylmandelates (1R,3S,1′S)-16 and (1R,3R,1′S)-16, whereas esters (1S,3R,1′S)-16 and (1S,3S,1′S)-16 were synthesized from the 3-hydroxydiphosphonates (1S,3R)-6 and (1S,3S)-6 produced from aldehyde (S)-7 (Figure 3).
Based on extensive configurational studies of the α-hydroxyphosphonates, Spilling and co-workers concluded that $^{31}$P NMR chemical shifts for the (R)-O-methylmandelate esters of (S)-α-hydroxyphosphonates appear in a higher field compared to the signals for the (R)-O-methylmandelates of enantiomeric (R)-alcohols [20]. Accordingly, (S)-O-methylmandelates of (R)-α-hydroxyphosphonates are expected to absorb in a higher field than (S)-O-methylmandelates of (S)-α-hydroxyphosphonates. Indeed, this general rule worked well for our 3-hydroxydiphosphonates 6 (Figure 3). Thus, the $^{31}$P nucleus at C3 in (S)-O-methylmandelate (1R,3R,1′S)-16 resonates in a higher field ($\delta^{31}$P = 18.42 ppm) compared to the diastereoisomeric ester (1S,3S,1′S)-16 ($\delta^{31}$P = 19.34 ppm) obtained from the enantiomeric α-hydroxydiphosphonate (1S,3S)-6. Similarly, a lower value for the $^{31}$P NMR chemical shift of the phosphorus atom at C3 in (S)-O-methylmandelate (1S,3R,1′S)-16 ($\delta^{31}$P = 19.14 ppm) was observed in comparison to the respective signal for (1R,3S,1′S)-16 ($\delta^{31}$P = 19.14 ppm). Thereby, comparison of the $^{31}$P NMR chemical shifts for the respective pairs of (S)-O-methylmandelic acid esters of enantiomeric hydroxydiphosphonates, i.e., (1R,3R,1′S)-16 and (1S,3S,1′S)-16, and (1S,3R,1′S)-16 and (1R,3S,1′S)-16, provided unambiguous evidence for the already established absolute configurations of the isomeric 1-amino-3-hydroxydiphosphonates (1R,3R)-6, (1S,3S)-6, (1S,3R)-6, and (1R,3S)-6, respectively.

3. Materials and Methods
3.1. General Information

NMR spectra were measured in chloroform-$d$ (CDCl$_3$), benzene-$d$6 (C$_6$H$_6$), or deuterium oxide (D$_2$O) on a Bruker Avance III (600 MHz). Solvent signals or TMS were used as internal references for $^1$H and $^{13}$C chemical shifts (ppm). $^{31}$P signals were referenced through the solvent lock (2H) signal according to the IUPAC recommended secondary referencing method and the manufacturer’s protocols (an analogous protocol was used for $^{13}$C NMR spectra recorded in D$_2$O). Coupling constants $J$ are given in Hz. The NMR experiments were conducted at 300K with the following parameters: $^1$H NMR spectra were acquired at 600.26 MHz using 30°-pulses (zg30), a spectral width of 12,335.5 Hz, acquisition time 2.6564 s, collecting an average of 16 scans, a relaxation delay of 1.0 sec, a pulse width...
9.4 μs; 13C NMR were acquired at 150.95 MHz with 30°-pulses ( zgppg30), a spectral width of 36,057.7 Hz, acquisition time 0.9088 s, collecting an average of 8192 scans, a relaxation delay of 2.0 s, a pulse width 10.5 μs; 31P NMR were acquired at 242.98 MHz with 30°-pulses ( zgppg30), a spectral width of 96,153.8 Hz, acquisition time 0.3408 s, collecting an average of 128 scans, a relaxation delay of 2.0 s, a pulse width 13.7 μs. IR spectroscopic data were measured on an Bruker Alpha-T FT-IR spectrometer. Melting points were determined with a Boetius apparatus and are uncorrected. Elemental analyses were performed by the Microanalytical Laboratory of the Faculty of Pharmacy (Medical University of Lodz) with a Perkin Elmer PE 2400 CHNS analyzer, and their results were found to be in good agreement (±0.3%) with the calculated values. Polarimetric measurements were conducted with an Optical Activity PolAAr 3001 apparatus. HPLC separations were performed using a Waters HPLC system consisting of binary HPLC pump (Waters 2545), a diode array detector (Waters 2998) and an auto sampler (Waters 2767), and an XBridge C18 column OBD, 19 × 100 mm with a particle size of 5 μm. The following adsorbents were used: column chromatography, Merck silica gel 60 (70–230 mesh); analytical TLC, Merck TLC plastic sheets silica gel 60 F254. TLC plates were developed in chloroform–methanol and chloroform–isopropanol solvent systems. Visualization of spots was achieved with iodine vapours. All solvents were purified by methods described in the literature.

3.2. General Procedure for the Synthesis of (1R,3S)-6 and (1R,3R)-6 or (1S,3R)-6 and (1S,3S)-6

Crude aldehyde (R)-7 or (S)-7 (1.0 mmol) and diethyl phosphate (5.0 mmol) containing triethylamine (0.1 mmol) were left at room temperature for 48 h. The crude product was purified on a silica gel column with chloroform-methanol (100:1 v/v) to give an inseparable mixture of diphosphonates (1R,3S)-6 and (1R,3R)-6 or (1S,3R)-6 and (1S,3S)-6.

Tetraethyl (1R,3S)- and (1R,3R)-[1-(N-Boc-amino)-3-hydroxypropane-1,3-diyl]diphosphonate [(1R,3S)-6 and (1R,3R)-6]. From aldehyde (R)-7 (0.292 g, 0.897 mmol), an inseparable mixture of diphosphonates (1R,3R)-6 and (1R,3S)-6 (0.296 g, 76%) was obtained. 31P NMR (243 MHz, CDCl3): δ = 25.26 [(1R,3S)-6], 24.60 [d, J = 8.0 Hz, (1R,3R)-6], 24.03 [d, J = 8.0 Hz, (1R,3R)-6], 23.58 [(1R,3S)-6]. Anal. Calcd. for C16H35NO3P2: 0.25 H2O: C, 42.53; H, 7.92; N, 3.10. Found: C, 42.33; H, 7.91; N, 3.02.

Tetraethyl (1S,3R)- and (1S,3S)-[1-(N-Boc-amino)-3-hydroxypropane-1,3-diyl]diphosphonate [(1S,3S)-6 and (1S,3R)-6]. From aldehyde (S)-7 (0.308 g, 0.950 mmol), an inseparable mixture of diphosphonates (1S,3S)-6 and (1S,3R)-6 (0.298 g, 72%) was obtained. 31P NMR (243 MHz, CDCl3): δ = 25.26 [(1S,3S)-6], 24.60 [d, J = 8.0 Hz, (1S,3R)-6], 24.03 [d, J = 8.0 Hz, (1S,3R)-6], 23.58 [(1S,3S)-6]. Anal. Calcd. for C16H35NO3P2: 0.25 H2O: C, 42.53; H, 7.92; N, 3.10. Found: C, 42.38; H, 8.11; N, 3.18.

3.3. General Procedure for the Synthesis of Tetraethyl [1-(N-Boc-amino)-3- Acetoxypropane-1,3-Diyl]Diphosphonate 11

A 1:1 mixture of diphosphonates (1R,3R)-6 and (1R,3S)-6 or (1S,3S)-6 and (1S,3R)-6, acetic anhydride (1.5 mmol), triethylamine (2.0 mmol), and catalytic amounts of DMAP (1 crystal) in methylene chloride (1 mL) were stirred at room temperature for 4 h. The reaction mixture was washed with water (3 × 5 mL), dried over MgSO4, concentrated in vacuo and chromatographed on a silica gel column with chloroform-isopropanol (100:1 v/v). Diastereoisomers were separated by HPLC with a mobile phase of water-acetonitrile (70:30, v/v) at a flow rate of 17 mL/min to yield (1R,3R)-11 and (1R,3S)-11 or (1S,3S)-11 and (1S,3R)-11.

3.3.1. Synthesis of (1R,3S)-11 and (1R,3R)-11

From a 1:1 mixture of 3-hydroxydiposphonates (1R,3S)-6 and (1R,3R)-6 (0.149 g, 0.345 mmol), compound (1R,3S)-11 (0.037 g, 22%) was obtained followed by (1R,3R)-11 (0.067 g, 40%).

Tetraethyl (1R,3S)-[1-(N-Boc-amino)-3-acetoxypropane-1,3-diyl]diphosphonate [(1R,3S)-11]. Colourless oil; tR = 10.69 min. [α]D20 = +3.27 (c 1.04, CHCl3). IR (film): ν = 3483, 3249,
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1H NMR (600 MHz, CDCl3): δ = 5.38 (ddd, 1H, J = 4.7 Hz, J = 8.9 Hz, J = 13.7 Hz, H3), 4.92 (d, 1H 3 J = 10.3 Hz, NH), 2.14 (d, 1H, J = 8.9 Hz, CH3), 1.45 (s, 1H, J = 5.7 Hz, CH2), 1.36–1.26 (m, 2H, 3J = 13.7 Hz), 0.89–0.84 (m, 4H, CH2). 31P NMR (125 MHz, CDCl3): δ = 19.83 (d, 2JCCCP = 4.2 Hz), 19.53 (d, 2JCCCP = 3.9 Hz). Anal. Calcd. for C18H37NO10P2: C, 44.12; H, 7.95; N, 2.91.

3.3.2. Synthesis of (1S,3R)-11 and (1S,5S)-11

From a 1:1 mixture of 3-hydroxydiphosphonates (1S,3R)-6 and (1S,5S)-6 (0.098 g, 0.227 mmol), compound (1S,3R)-11 (0.022 g, 20%) was obtained followed by (1R,3R)-11 (0.036 g, 32%).

Tetraethyl (1S,3R)-1-[N-Boc-amino]-3-acetoxypropene-1,3-diyldiphosphonate ([1S,3R]-11)

[enantiomer of (1R,3S)-11]. Colourless oil; tR = 10.69 min. [α]20D = −3.45 (c 1.10, CHCl3). Anal. Calcd. for C18H37NO10P2 × 0.25 H2O: C, 44.18; H, 7.62; N, 2.86. Found: C, 44.00; H, 7.88; N, 2.96.

Tetraethyl (1S,3S)-1-[N-Boc-amino]-3-acetoxypropene-1,3-diyldiphosphonate ([1S,3S]-11)

[enantiomer of (1R,3R)-11]. White amorphous solid; tR = 12.67 min. [α]20D = +20.30 (c 1.01, CHCl3). Anal. Calcd. for C18H37NO10P2: C, 44.18; H, 7.62; N, 2.86. Found: C, 44.11; H, 7.85; N, 2.97.

3.4. General Procedure for the Synthesis of Tetraethyl [1-(N-Boc-amino)-3-(4-Nitrobenzoyloxy)Propene-1,3-Diyldiphosphonate 12

A 1:1 mixture of diphosphonates (1R,3R)-6 and (1S,3R)-6 or (1S,3S)-6 and (1S,3R)-6, 4-nitrobenzoyl chloride (1.5 mmol), and triethylamine (2.0 mmol) containing DMAP (1 crystal) in methylene chloride (1 mL) was stirred at room temperature for 4 h. The reaction mixture was washed with water (3 × 5 mL), dried over Na2SO4, concentrated in vacuo and chromatographed on a silica gel column with dichloromethane-isopropanol (100:1 v/v). Diastereoisomers were separated by HPLC with a mobile phase of water-acetonitrile (64:38, v/v) at a flow rate of 17 mL/min to yield (1R,3R)-12 and (1R,3S)-12 or (1S,3S)-12 and (1S,3R)-12.

3.4.1. Synthesis of (1R,3S)-12 and (1R,3R)-12

From a 1:1 mixture of 3-hydroxydiphosphonates (1R,3R)-6 and (1R,3S)-6 (0.099 g, 0.229 mmol), compound (1R,3S)-12 (0.029 g, 21%) was obtained followed by (1R,3R)-12 (0.043 g, 31%).
Tetraethyl (1R,3S)-[1-(N-Boc-amino)-3-(4-nitrobenzoyloxy)propane-1,3-diyl]diphosphonate [(1R,3S)-12]. Yellowish oil; \( t_R = 14.89 \text{ min.} \) \( [\alpha]_{D}^{20} = -4.60 \) (c 2.65, CHCl\(_3\)). IR (film): \( \nu = 3290, 3050, 2982, 2932, 1739, 1704, 1500, 1368, 1243, 1053, 716 \text{ cm}^{-1} \). \(^1\)H NMR (600 MHz, CDCl\(_3\)): \( \delta = 8.33 \) (d, 2H, \( J = 8.8 \text{ Hz} \)), 6.28 (s, 2H), 8.22 (d, 2H, \( J = 8.8 \text{ Hz} \)). 13C NMR (151 MHz, CDCl\(_3\)): \( \delta = 136.34 \) (d, \( J_{CCP} = 2.5 \text{ Hz} \)), 155.00 (d, \( J_{CNC} = 4.3 \text{ Hz} \)), 150.80, 135.16, 131.00, 123.76, 60.57, 64.38 (dd, \( J_{CP} = 167.7 \text{ Hz} \)), 13.59 (d, \( J_{CCP} = 13.5 \text{ Hz} \)).

3.4.2. Synthesis of (1R,3S)-[(1-(N-Boc-amino)-3-(4-nitrobenzoyloxy)propane-1,3-diyl]diphosphonate [(1R,3S)-12]. White amorphous solid; \( t_R = 18.14 \text{ min.} \) \( [\alpha]_{D}^{20} = -41.34 \) (c 0.82, CHCl\(_3\)). Mp = 125–126 \( ^\circ \text{C} \). IR (KBr): \( \nu = 3288, 3049, 2982, 2930, 1740, 1704, 1500, 1368, 1243, 1053, 716 \text{ cm}^{-1} \). 1H NMR (600 MHz, CDCl\(_3\)): \( \delta = 8.32 \) (d, 2H, \( J = 8.8 \text{ Hz} \)), 6.28 (s, 2H), 8.22 (d, 2H, \( J = 8.8 \text{ Hz} \)). 13C NMR (151 MHz, CDCl\(_3\)): \( \delta = 136.34 \) (d, \( J_{CCP} = 2.5 \text{ Hz} \)), 155.00 (d, \( J_{CNC} = 4.3 \text{ Hz} \)), 150.80, 135.16, 131.00, 123.76, 60.57, 64.38 (dd, \( J_{CP} = 167.7 \text{ Hz} \)), 13.59 (d, \( J_{CCP} = 13.5 \text{ Hz} \)).

3.5. General Procedure for the Hydrolysis of 11 or 12

A solution of the respective enantiomers of compound 11 or 12 (1.0 mmol) in 5M HCl (15 mL) was refluxed for 6 h. The solvent was removed under reduced pressure, and the residue was suspended in mixture of methanol-water (15 mL) and neutralized with propylene oxide and concentrated in vacuo. The residue was dissolved in 10 mL deionised water. Compounds (1S,3S)-5 and (1R,3R)-5 were precipitated by adding isopropanol; compounds (1S,3R)-5 and (1R,3S)-5 were precipitated by adding methanol.

(1R,3S)-(1-amino-3-hydroxypropane-1,3-diyl)diphosphonic acid [(1R,3S)-5]. From compound (1R,3S)-11 (0.05 g, 0.10 mmol), diphosphonic acid (1R,3S)-5 (0.019 g, 0.081 mmol, 53%) was obtained. White amorphous solid. Mp > 290 \( ^\circ \text{C} \). IR (KBr): \( \nu = 3390, 3241, 2960, 2932, 1651, 1519, 1454, 1167, 1081, 919, 809, 723 \text{ cm}^{-1} \). \(^1\)H
Molecules was obtained. White amorphous solid. Mp > 290 °C. IR (KBr): v = 3406, 3252, 2960, 2926, 2855, 1636, 1532, 1438, 1165, 1062, 912, 717 cm⁻¹. [α]D²⁰ = −9.71 (c 0.68, 5% NH₃). ¹H NMR (600 MHz, D₂O): δ = 3.81 (dd, 1H, J = 9.9 Hz, J = 13.1 Hz, CHP), 3.43 (dd, 1H, J = 3.2 Hz, J = 10.3 Hz, J = 13.6 Hz, CHP), 2.18–2.10 (m, 1H), 2.08–2.00 (m, 1H). ¹³C NMR (151 MHz, D₂O): δ = 65.45 (dd, ¹JC = 157.0 Hz, ³JCPC = 11.3 Hz), 46.55 (dd, ¹JC = 137.3 Hz, ³JCPC = 12.2 Hz), 30.02. ³¹P NMR (243 MHz, D₂O); δ = 18.97 and 12.89. Anal. Calcd. for C₃H₁₁NO₁₁P₂·0.25 H₂O: C, 15.04; H, 4.84; N, 5.85. Found: C, 15.12; H, 4.87; N, 5.84.

(1R,3R)-(1-amino-3-hydroxypropene-1,3-diyldiphosphonic acid [1(R,3R)-5]. From compound (1R,3R)-11 (0.043 g, 0.088 mmol), diphosphonic acid (1R,3R)-5 (0.017 g, 84%) was obtained.

(1S,3S)-(1-amino-3-hydroxypropene-1,3-diyldiphosphonic acid [(1S,3S)-5] (enantamer of (1R,3S)-5). From compound (1S,3S)-11 (0.054 g, 0.11 mmol), diphosphonic acid (1R,3S)-5 (0.022 g, 86%) was obtained as a white amorphous solid. Mp > 290 °C. [α]D = −4.64 (c 0.56, 5% NH₃). Anal. Calcd. for C₃H₁₁NO₁₁P₂·0.25 H₂O: C, 15.04; H, 4.84; N, 5.85. Found: C, 15.19; H, 4.89; N, 5.87.

(1S,5S)-(1-amino-3-hydroxypropene-1,3-diyldiphosphonic acid [(1S,5S)-5] (enantamer of (1R,3S)-5). From compound (1S,5S)-11 (0.052 g, 0.106 mmol), diphosphonic acid (1S,3S)-5 (0.017 g, 69%) was obtained as a white amorphous solid. Mp > 290 °C. [α]D = +8.62 (c 0.83, 5% NH₃). Anal. Calcd. for C₃H₁₁NO₁₁P₂·0.25 H₂O: C, 15.04; H, 4.84; N, 5.85. Found: C, 15.21; H, 4.85; N, 5.86.

3.6. Cycloaddition of Nitroene 13 to Vinylphosphonate

Nitroene 13 (0.710 g, 2.617 mmol) and vinylphosphonate (0.389 mL, 2.617 mmol) were stirred in toluene (3.0 mL) at 60 °C for 48 h. All volatiles were removed in vacuo and the crude products were subjected to purification on a silica gel column with chloroform-isopropanol (100:1, v/v) to yield (3R/S,5R/S)-14 [anti-14] (0.331 g, 17%). The residue was separated by HPLC with a mobile phase of water-isopropanol (80:20, v/w) at a flow rate of 17 mL/min to yield (3R/S,4S/R)-15 [anti-15] (0.040 g, 3.5%).

Tetraethyl (3R/S,5R/S)-(2-benzylisoxazolidine-3,5-diyldiphosphonate [(3R/S,5R/S)-14]. Colourless oil. IR (film): ν = 3477, 2984, 2931, 2911, 1650, 1246, 1048, 1025, 970 cm⁻¹. ¹H NMR (CDCl₃, 600 MHz): δ = 7.14 (d, J = 7.3 Hz, 2H), 7.30 (d, J = 7.8 Hz, 1H), 4.36 (d, 1H, JAB = 13.8 Hz, H₂CH₂Ph), 3.49 (dt, 1H, J = 8.3 Hz, J = 2.1 Hz, HCS), 4.25–4.08 (m, 4 × CH₂OP and H₃CH₂OP), 3.46 (dd, 1H, J = 4.9 Hz, J = 6.4 Hz, J = 8.3 Hz, HCS), 2.91–2.80 (m, 2H, H₂CH₂ and H₂C4). ¹³C NMR (CDCl₃, 151 MHz): δ = 137.00, 129.49, 128.31, 127.51, 72.56 (dd, ¹JC = 167.7 Hz, ³JCPC = 6.1 Hz, C5), 63.42 (d, ²JCOP = 6.5 Hz), 63.28 (d, ²JCOP = 6.5 Hz), 63.05 (d, J = 8.0 Hz), 62.92 (d, ²JCOP = 6.9 Hz), 62.60 (d, ²JCOP = 6.9 Hz), 61.23 (d, ¹JC = 170.8 Hz, ³JCPC = 5.8 Hz, C3), 33.45, 16.62 (d, ³JCOP = 6.5 Hz), 16.53 (d, ³JCOP = 6.5 Hz). ³¹P NMR (243 MHz, CDCl₃): δ = 21.32 and 20.77. Anal. Calcd. for C₁₈H₁₄O₂P₂·0.25 H₂O: C, 49.15; H, 7.22; N, 3.19. Found: C, 49.06; H, 7.07; N, 3.27.

Tetraethyl (3R/S,4S/R)-(2-benzylisoxazolidine-3,4-diyldiphosphonate [(3R/S,4S/R)-15]. Colourless oil; Rₚ = 14.13 min. ¹H NMR (600 MHz, CDCl₃): δ = 7.43 (d, J = 6.9 Hz, 1H), 7.33 (t, J = 7.4 Hz, 1H), 7.28 (d, J = 7.4 Hz, 1H), 4.28 (dd, ³JC = 15.1 Hz, ³JC = 8.9 Hz, J = 7.0 Hz, 1H, H₂C5), 4.23 (d, JAB = 12.9 Hz, 1H), 4.21–4.14 (m, 8H, 4 × CH₂OP), 4.08 (d, JAB = 12.9 Hz, 1H), 4.08–4.03 (m, 1H, H₂C5), 3.59 (dd, ²JC = 21.0 Hz, ³JC = 7.2 Hz, ³JC = 5.5 Hz, 1H, HCS), 3.26–3.11 (m, 1H, H₄C₄), 1.36 (t, ³JC = 7.1 Hz, 6H, 2 × CH₃CH₂OP), 1.30 (t, ³JC = 7.1 Hz, 3H, H₂CH₂OP), 1.27 (t, ³JC = 7.1 Hz, 3H, H₂CH₂OP). ¹³C NMR (151 MHz, CDCl₃): δ = 136.54, 129.46, 128.35, 127.60, 66.57, 63.24 (d, ²JCOP = 7.0 Hz), 63.15 (d, ²JCOP = 6.6 Hz), 62.72 (d, ²JCOP = 6.6 Hz), 62.45 (d, ²JCOP = 6.6 Hz), 61.37 (d, J = 177.1 Hz), 41.95 (d, J = 147.1 Hz),
16.64 (d, JCCOP = 3.6 Hz), 16.57 (d, JCCOP = 5.2 Hz). 31P NMR (243 MHz, CDCl3): δ = 27.42 (d, JPPCCP = 32.4 Hz), 21.15 (d, JPCCP = 32.4 Hz). Anal. Calcd. C18H31NO3P2: C, 49.66 H, 7.18; N, 3.22. Found: C, 49.55 H, 7.02; N, 3.12.

3.7. Synthesis of (1R,3R,S)-6 [Anti-6] from (3R/S,5R/S)-6 [Anti-14]
A solution of isoxazolidine (3R/S,5R/S)-14 (0.046 g, 0.020 mmol) and Boc₂O (0.023 g, 0.020 mmol) was kept under atmospheric pressure of hydrogen over 20% PdOH-C (5 mg) at room temperature for 2 days. The suspension was filtered through a layer of celite. The solution was concentrated, and the residue was chromatographed on a silica gel column with chloroform–isopropanol (100:1, v/v) to yield (1R/S,3R/S)-6 [anti-6] (0.032 g, 74%) as a colourless oil.

(1R/S,3R/S)-[1-(N-Boc-amino)-3-hydroxypropane-1,3-diyl]diphasphonate [(1R/S,3R/S)-6]. Colourless oil. IR (film): ν = 3417, 2931, 1698, 1393, 1368. 1232, 1166, 1046, 1026 cm⁻¹. 1H NMR (CDCl3, 600 MHz): δ = 5.00 (dd, 1H, J = 10.8 Hz, J = 4.6 Hz, NH), 4.30–4.15 (m, 9H, 4νH), 4.10 (d, 1H, J = 21.7 Hz, OH), 3.98 (dd, 1H, J = 11.7 Hz, J = 11.3 Hz, HCO), 2.23–2.15 (m, 1H, H₂C₂), 2.01–1.98 (m, 1H, H₂C₂), 1.47 (s, 9H, 3 × CH₃), 1.38–1.34 (m, 12H, 4 × CH₂CH₂OP). 13C NMR (151 MHz, CDCl₃): δ = 156.79 (d, JPCCP = 9.0 Hz), 81.04, 63.80 (dd, JPC = 170.6 Hz, JPPCCP = 13.2 Hz), 63.02 (d, JCCOP = 7.0 Hz), 62.79 (d, JCCOP = 2.2 Hz), 62.73 (d, JCCOP = 6.8 Hz), 43.66 (dd, JPC = 158.0 Hz, JPPCCP = 16.1 Hz), 32.72 (dd, JPC = 4.1 Hz, JPPCCP = 4.0 Hz), 28.20, 16.50 (d, JCCOP = 2.9 Hz), 16.46 (d, JCCOP = 2.9 Hz), 16.41 (d, JCCOP = 5.7 Hz), 16.34 (d, JCCOP = 5.7 Hz). 31P NMR (CDCl₃, 243 MHz): δ = 24.59 (d, JPCCCP = 8.0 Hz), 24.93 (d, JPCCCP = 8.0 Hz). 1H NMR (600 MHz, CD₂Cl₂): δ = 5.86 (d, 3J = 10.0 Hz, 1H, NH), 5.36 (s, 1H, OH), 4.75 (ddt, J = 17.8 Hz, 3J = 10.0 Hz, J = 3.2 Hz, 1H, CH₂N), 4.41 (t, J = 10.1 Hz, 1H, CHO), 4.19–4.04 (m, 4H, 2 × CH₂OP), 4.02–3.87 (m, 4H, 2 × CH₂OP), 2.64–2.53 (m, 1H, H₃CH₂), 2.42–2.33 (m, 1H, H₃CH₂), 1.37 (s, 9H, 3 × CH₃), 1.11 (t, 3J = 7.1 Hz, 3H, CH₃CH₂OP), 1.10 (t, 3J = 7.1 Hz, 3H, CH₃CH₂OP), 1.04 (t, 3J = 7.1 Hz, 3H, CH₃CH₂OP), 1.03 (t, 3J = 7.1 Hz, 3H, CH₃CH₂OP). 13C NMR (151 MHz, CD₂Cl₂): δ = 169.04, 154.28 (dd, 3JCCOP = 5.8 Hz), 79.37, 64.45 (dd, 3JPC = 155.1 Hz, JPPCCP = 13.9 Hz), 62.44 (d, JCCOP = 6.8 Hz), 62.25 (d, JCCOP = 6.5 Hz), 62.15 (d, JCCOP = 6.3 Hz), 44.26 (dd, JPC = 156.1, JPPCCP = 15.7 Hz), 32.48, 27.96, 16.22 (d, JCCOP = 5.3 Hz), 16.08 (d, JCCOP = 5.2 Hz), 15.99 (d, JCCOP = 5.7 Hz). 31P NMR (243 MHz, CD₂Cl₂): δ = 25.33 (d, JPPCCP = 7.1 Hz), 24.56 (d, JPCCP = 7.1 Hz). Anal. Calcd. for C₁₆H₃₅NO₃P₂ × 0.25 H₂O: C, 42.53; H, 7.92; N, 3.10. Found: C, 42.38; H, 8.11; N, 3.09.

3.8. General Procedure for Esterification of 3-Hydroxydiphasphonates 6 with (S)-O-Methylmandelic Acid
To a solution of diphosphonate (1R/S,3R/S)-6 or an appropriate mixture of diphosphonates (1R,3S)-6 and (1R,3R)-6 or (1S,3R)-6 and (1S,3S)-6 (1.00 mmol) in methylene chloride (3.5 mL), (S)-2-methoxy-2-phenylacetic acid (1.75 mmol), DCC (1.75 mmol) and DMAP (0.10 mmol) were added. This mixture was stirred at room temperature for 24 h. The reaction mixture was filtered off and concentrated in vacuo and chromatographed on a silica gel column with chloroform-isopropanol (100:1, v/v) and a flow rate of 17 mL/min.

3.8.1. Esterification of (1R/S,3R/S)-6 with (S)-O-Methylmandelic Acid
From 3-hydroxydiphasphonate (1R/S,3R/S)-6 (0.134 g, 0.585 mmol), (S)-O-methylmandelate (1R,3R,1′S)-16 (0.026 g, 14%) was obtained followed by diastereoisomer (1S,3S,1′S)-16 (0.018 g, 10%) after separation by HPLC with a mobile phase of water-acetonitrile (63:37, v/v) and a flow rate of 17 mL/min.

Mandelate (1R,3R,1′S)-16: white amorphous solid; tR = 15.77 min. 1H NMR (600 MHz, CD₂Cl₂): δ = 7.52 (d, 2H, 3J = 7.3 Hz), 7.08 (t, 2H, 3J = 7.6 Hz), 7.00 (t, 1H, 3J = 7.6 Hz), 6.05 (d, 3J = 10.0 Hz, HNBOc), 5.84 (ddd, 1H, 3J = 1.4 Hz, 3J = 1.4 Hz, 3J = 7.7 Hz, 3J = 9.7 Hz, H3C3), 4.88 (s, 1H, HCOC₃H), 4.58 (dddd, 1H, 3J = 3.2 Hz, 3J = 10.0 Hz, 3J = 7.7 Hz, 3J = 9.7 Hz, H1C1), 4.09–3.97 (m, 4H, 2 × CH₂OP), 3.95–3.84 (m, 2H, CH₂OP), 3.69–3.57 (m, 2H, CH₂OP), 3.54 (s, 3H, OCH₃), 2.79–2.72 (m, 1H, H₃C₂), 2.67–2.61 (m, 1H, H₃C₂), 1.46 (s, 9H, 3 × CH₃),
1.11 (t, 3H, δ = 7.1 Hz, CH₂CH₂OP), 1.07 (t, 3H, δ = 7.1 Hz, CH₂CH₂OP), 0.93 (t, 3H, δ = 7.1 Hz, CH₂CH₂OP), 0.89 (t, 3H, δ = 7.1 Hz, CH₂CH₂OP). ³¹P NMR (243 MHz, CDCl₃): δ = 24.72 (d, ⁴PCCCP = 7.9 Hz), 19.18 (d, ⁴PCCCP = 7.9 Hz). ³¹P NMR (243 MHz, CDCI₃): δ = 24.34 (d, J = 7.9 Hz), 18.42 (d, J = 7.9 Hz).

Mandelate (1S,3S,1’S)-16: white amorphous solid; tᵣ = 17.86 min. ¹H NMR (CDCl₃, 600 MHz): δ = 7.62 (d, 2H, δ = 7.4 Hz), 7.17–7.15 (m, 2H), 7.05 (t, 1H, δ = 7.4 Hz), 5.87–5.83 (m, 1H, H₃C), 5.26 (d, δ = 10.4 Hz, H₃C), 4.90 (s, 1H, HCOCH₃), 4.44–4.37 (m, 1H, HCl), 3.99–3.80 (m, 8H, 4 × CH₂OP), 3.39 (s, 3H, OCH₃), 2.84–2.77 (m, 1H, Hα-C2), 2.57–2.50 (m, 1H, Hβ-C2), 1.43 (s, 9H, 3 × CH₃), 1.03 (t, 6H, J = 7.0 Hz, 2 × CH₃CH₂OP), 0.97 (t, 3H, J = 7.0 Hz, CH₃CH₂OP), 0.91 (t, 3H, J = 7.0 Hz, CH₃CH₂OP). ³¹P NMR (CDCl₃, 243 MHz): δ = 24.31 (d, ⁴PCCCP = 7.5 Hz), 19.72 (d, ⁴PCCCP = 7.5 Hz). ³¹P NMR (CDCl₃, 243 MHz): δ = 23.98 (d, ⁴PCCCP = 7.6 Hz), 19.34 (d, ⁴PCCCP = 7.6 Hz).

3.8.2. Esterification of (1R,3R)-6 and (1R,3S)-6 with (S)-O-Methylmandelic Acid

From a 1:1 mixture of 3-hydroxydiphosphonates (1R,3R)-6 and (1R,3S)-6 (0.262 g, 0.585 mmol), (S)-O-methylmandelate (1R,3R,1’S)-16 (0.010 g, 3%) was obtained followed by diastereoisomer (1R,3S,1’S)-16 (0.010 g, 8%) after separation by HPLC with a mobile phase of water-acetonitrile (61:38.5:8, v/v/v) and a flow rate of 17 mL/min.

Mandelate (1R,3S,1’S)-16: white amorphous solid; tᵣ = 12.56 min. ³¹P NMR (243 MHz, CDCl₃): δ = 24.34 (d, J = 7.9 Hz), 18.42 (d, J = 7.9 Hz).

Mandelate (1R,3S,1’S)-16: colorless oil; tᵣ = 14.12 min. ¹H NMR (CDCl₃, 600 MHz, CDCl₃): δ = 7.63 (d, J = 7.5 Hz, 1H), 7.05 (t, J = 7.4 Hz, 1H), 5.96 (q, J = 7.8 Hz, 1H, H₃C), 5.32 (d, J = 8.6 Hz, 1H, NH), 4.83 (s, 1H, HCOCH₃), 4.53 (dq, J = 16.6, 7.5 Hz, 1H), 3.28 (s, 1H, OCH₃), 2.85–2.74 (m, 1H, Hα-C2), 2.30–2.17 (m, 1H, Hβ-C2), 1.41 (s, 9H, 3 × CH₃), 1.10–0.96 (m, 12H, 4 × CH₂CH₂OP). ³¹P NMR (CDCl₃, 243 MHz): δ = 23.77, 19.72. ³¹P NMR (243 MHz, CDCl₃): δ = 23.38, 19.14.

3.8.3. Esterification of (1S,3S)-6 and (1S,3R)-6 with (S)-O-Methylmandelic Acid

From a mixture of 3-hydroxydiphosphonates (1S,3S)-6 and (1S,3R)-6 (0.088 g, 0.200 mmol), (S)-O-methylmandelate (1S,3R,1’S)-16 (0.036 g, 36%) was obtained followed by diastereoisomer (1S,3S,1’S)-16 (0.031 g, 31%) after separation by HPLC with a mobile phase of water-acetonitrile (60:40, v/v) at a flow rate of 17 mL/min.

Mandelate (1S,3R,1’S)-16: colourless oil; tᵣ = 9.06 min. ¹H NMR (CDCl₃, 600 MHz, CDCl₃): δ = 7.57 (d, J = 7.4 Hz, 2H), 7.11 (t, J = 7.4 Hz, 1H), 7.02 (t, J = 7.4 Hz, 1H), 5.97 (q, J = 8.0 Hz, 1H, H₃C), 5.52 (d, J = 5.7 Hz, NH), 4.91 (s, 1H, HCOCH₃), 4.68–4.55 (m, 1H), 4.08–3.90 (m, 4H), 3.92–3.84 (m, 2H), 3.78 (qd, J = 7.4 Hz, J = 3.4 Hz, 1H), 3.72–3.61 (m, 1H), 3.38 (3H, OCH₃), 2.91–2.79 (m, 1H, H₂C₂), 2.40–2.25 (m, 1H, H₂C₂), 1.41 (s, 9H, 3 × CH₃), 1.07 (t, J = 7.0 Hz, 3H, CH₃CH₂OP), 1.04 (t, J = 7.0 Hz, 3H, CH₃CH₂OP), 0.93 (t, J = 7.0 Hz, 6H, 2 × CH₂CH₂OP). ³¹P NMR (CDCl₃, 243 MHz, CDCl₃): δ = 24.00, 19.22. ³¹P NMR (243 MHz, CDCl₃): δ = 23.61, 18.42.

Mandelate (1S,3S,1’S)-16: white amorphous solid; tᵣ = 10.82 min. ³¹P NMR (CDCl₃, 243 MHz, CDCl₃): δ = 23.98 (d, ⁴PCCCP = 7.6 Hz), 19.34 (d, ⁴PCCCP = 7.6 Hz).

4. Conclusions

The nucleophilic addition reactions of aldehydes (R)-7 and (S)-7 with diethyl phosphite provided inseparable mixtures of diastereoisomeric diphosphonates (1R,3S)-6 and (1R,3R)-6, and (1S,3R)-6 and (1S,3S)-6, respectively. Diastereoisomeric 3-hydroxydiphosphonates 6 were then efficiently separated as O-acetates or O-p-nitrobenzoates and then hydrolysed to the designed phosphonic acids (1R,3S)-5, (1R,3R)-5, (1S,3R)-5, and (1S,3S)-5 as diphosphonate analogues of 4-hydroxyglutamic acids.
Supplementary Materials: The following are available online at https://www.mdpi.com/2073-4409/27/9/2699/s1, Figure S1: 31P NMR Spectrum for (1R,S)-6 and (1R,3)R-6 in CDCl3, Figure S2: 1H NMR Spectrum for (1R,S)-11 in CDCl3, Figure S3: 13C NMR Spectrum for (1R,S)-11 in CDCl3, Figure S4: 31P NMR Spectrum for (1R,S)-11 in CDCl3, Figure S5: 1H NMR Spectrum for (1R,3R)-11 in CDCl3, Figure S6: 13C NMR Spectrum for (1R,3R)-11 in CDCl3, Figure S7: 31P NMR Spectrum for (1R,3R)-11 in CDCl3, Figure S8: 1H NMR Spectrum for (1R,3R)-12 in CDCl3, Figure S9: 13C NMR Spectrum for (1R,3S)-12 in CDCl3, Figure S10: 31P NMR Spectrum for (1R,3S)-12 in CDCl3, Figure S11: 1H NMR Spectrum for (1R,3R)-12 in CDCl3, Figure S12: 13C NMR Spectrum for (1R,3R)-12 in CDCl3, Figure S13: 31P NMR Spectrum for (1R,3R)-12 in CDCl3, Figure S14: 1H NMR Spectrum for (1R,3R)-4 in D2O, Figure S15: 13C NMR Spectrum for (1R,3R)-4 in D2O, Figure S16: 31P NMR Spectrum for (1R,3R)-4 in D2O, Figure S17: 1H NMR Spectrum for (1R,3S)-4 in D2O, Figure S18: 13C NMR Spectrum for (1R,3S)-4 in D2O, Figure S19: 31P NMR Spectrum for (1R,3S)-4 in D2O, Figure S20: 1H NMR Spectrum for trans-14 in CDCl3, Figure S21: 13C NMR Spectrum for trans-14 in CDCl3, Figure S22: 31P NMR Spectrum for trans-14 in CDCl3, Figure S23: 1H NMR Spectrum for trans-15 in CDCl3, Figure S24: 13C NMR Spectrum for trans-15 in CDCl3, Figure S25: 31P NMR Spectrum for trans-15 in CDCl3, Figure S26: 1H NMR Spectrum for (1R/S,3R/S)-6 [anti-6] in CDCl3, Figure S27: 13C NMR Spectrum for (1R/S,3R/S)-6 [anti-6] in CDCl3, Figure S28: 1H NMR Spectrum for (1R/S,3R/S)-6 [anti-6] in CDCl3, Figure S29: 1H NMR Spectrum for (1R/S,3R/S)-6 [anti-6] in C6D6, Figure S30: 13C NMR Spectrum for (1R/S,3R/S)-6 [anti-6] in C6D6, Figure S31: 31P NMR Spectrum for (1R/S,3R/S)-6 [anti-6] in C6D6, Figure S32: 1H NMR Spectrum for (1R,3R,1’S)-16 in C6D6, Figure S33: 31P NMR Spectrum for (1R,3R,1’S)-16 in C6D6, Figure S34: 1H NMR Spectrum for (1R,3R,1’S)-16 in CDCl3, Figure S35: 1H NMR Spectrum for (1S,3S,1’S)-16 in C6D6, Figure S36: 31P NMR Spectrum for (1S,3S,1’S)-16 in C6D6, Figure S37: 31P NMR Spectrum for (1S,3S,1’S)-16 in CDCl3, Figure S38: 1H NMR Spectrum for (1S,3S,1’S)-16 in C6D6, Figure S39: 31P NMR Spectrum for (1S,3S,1’S)-16 in C6D6, Figure S40: 31P NMR Spectrum for (1S,3S,1’S)-16 in CDCl3, Figure S41: 1H NMR Spectrum for (1S,3R,1’S)-16 in C6D6, Figure S42: 31P NMR Spectrum for (1S,3R,1’S)-16 in C6D6, Figure S43: 31P NMR Spectrum for (1S,3R,1’S)-16 in CDCl3, Figure S44: Separation of (1R,3S)-11 and (1R,3R)-11 by preparative HPLC, Figure S45: Separation of (1S,3R)-11 and (1S,3S)-11 by preparative HPLC, Figure S46: Separation of (1R,3S)-12 and (1R,3R)-12 by preparative HPLC, Figure S47: Separation of (1S,3R)-12 and (1S,3S)-12 by preparative HPLC, Figure S48: Separation of trans-14 and trans-15 by preparative HPLC, Figure S49: Separation of (1R,3R,1’S)-16 and (1S,3S,1’S)-16 by preparative HPLC, Figure S50: Separation of (1R,3R,1’S)-16 and (1R,3S,1’S)-16 by preparative HPLC, Figure S51: Separation of (1S,3S,1’S)-16 and (1S,3R,1’S)-16 by preparative HPLC.

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Abbreviations

DCC N,N’-dicyclohexylcarbodiimide
DCU dicyclohexylurea
DMAP 4-dimethylaminopyridine
HPLC high performance liquid chromatography
L-AP4 L(±)-2-amino-4-phosphonobutyric acid
MgBr2-etherate magnesium bromide ethyl etherate
mGluR  glutamate metabotropic receptors
mGlu1a R  metabotropic glutamate 1a receptor
mGlu8a R  metabotropic glutamate 8a receptor
MAP4  (S)-2-Amino-2-methyl-4-phosphonobutyric acid
NMDA  N-methyl-D-aspartic acid
rt  room temperature

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