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Aminophosphonates and aminophosphonic acids with tetrasubstituted stereogenic center: diastereoselective synthesis from cyclic ketimines†

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New chiral tetrasubstituted aminophosphonic acid derivatives of hexahydroquinoxalin-2(1*H*)-one were synthesised *via* highly diastereoselective hydrophosphonylation of the corresponding imines with tris(trimethylsilyl) phosphite as phosphorus nucleophile. High asymmetric induction, good yields, mild reaction conditions, and ease of purification of the final products are the key advantages of the presented protocol.

Introduction

Among nitrogen-containing heterocycles, cyclic imines constitute an important class of compounds used as synthetic intermediates in the preparation of pharmaceuticals and agrochemicals.[1,2] 2-Substituted cyclic ketimines are particularly useful starting materials for asymmetric transformations leading to the formation of tetrasubstituted carbon stereocenters. Most reactions described thus far involve five-membered derivatives, though Nenajdenko *et al.* reported on the aza-Henry[3] and Ugi[4,5] reactions performed with six- and seven-membered rings as well. Likewise, a series of 2-alkyl- and 2-aryl-imines of various ring size were reacted with C_2F_5Li to give pentafluoroethyl-substituted, racemic products in moderate yields.[6] Nenajdenko's group described also a route to tetrazole-derived cyclic amines *via* azido-Ugi reaction of 2-substituted cyclic imines.[7] Importantly, enantioselective reactions of cyclic ketimines in the presence of chiral organocatalysts or transition metal complexes are also described. To that end, Nakamura *et al.* applied 4-aryl-3-oxo-1,2,5-thiadiazol-1,1-oxides in enantioselective aza-Friedel–Crafts reaction with indole derivatives catalysed by chiral imidazoline-phosphoric acid.[8] Whereas Zhang and co-workers reported a highly enantioselective transformations of cyclic *N*-sulfonylketimines catalyzed by chiral palladium (addition of arylboronic acids),[9] cobalt (allylation),[10] and ruthenium/copper complexes (Mannich reaction).[11]

On the other hand, synthesis of compounds having an optically active quaternary stereocenters attached to the phosphorus atom attracts considerable attention since they can act as scaffolds widely present in pharmaceuticals and biologically active compounds, especially in enzyme inhibitors (Fig. 1).[12] The latter very often include tailored peptide structures with incorporated tetrasubstituted α-aminophosphonic acids, as they are known to increase the rigidity of such structures improving their biological activity.[13] An attractive approach for the construction of such compounds is the addition of P-nucleophiles to ketimines. However, asymmetric synthesis of derivatives bearing a tetrasubstituted stereocenter *via* functionalized ketimines remains elusive, due to their lower reactivity than aldimines and difficulty in enantiofacial discrimination.[14] Although few elegant approaches to these targets have been reported in the literature,[15–18] access to configurationally and conformationally rigid α-amino phosphonates is still challenging. Shibasaki *et al.* developed a catalytic asymmetric hydrophosphonylation of 5-membered cyclic imine (thiazoline derivative).[15,16] Cyclic α-aminophosphonates were obtained in moderate to high yields and high enantioselectivity when a chiral heterobimetalic lanthanoid complex was used as a catalyst. In turn, organocatalytic hydrophosphonylation of *N*-acyl ketimines generated *in situ* from 3-aryl-3-hydroxylisoindolones was reported by Suneja *et al.*[17]

Effective and asymmetric preparation of tetrasubstituted aminophophonates is therefore of high importance for the

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†Electronic supplementary information (ESI) available: Details of DFT calculations; X-ray diffraction analysis; experimental procedures and full characterization data for all previously unreported compounds. CCDC 1903889 (**4a**) 1903892 (**4e**) and 1915269 (**3fa**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9ob01346f

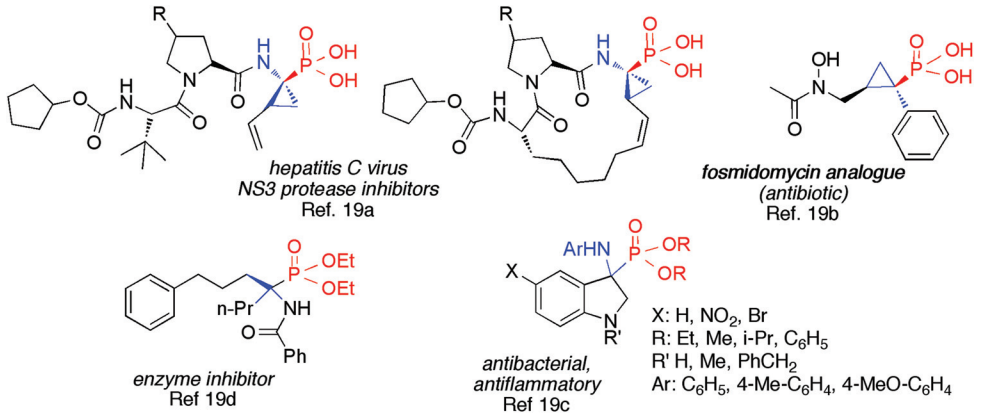


Fig. 1 Selected bioactive compounds with tetrasubstituted stereocenters attached to the phosphorus atom.[19]

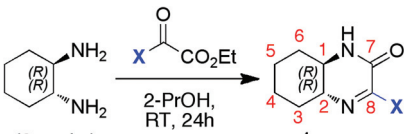
preparation of biologically active compounds. In that respect and in line with our interest in developing new synthetic protocols and the synthesis of phosphorus-containing heterocycles,[20] herein we present our recent results on asymmetric nucleophilic addition of tris(trimethylsilyl) phosphite to ketimines (substituted hexahydroquinoxalin-2(1*H*)-one derivatives) as an effective route leading to chiral bicyclic aminophosphonates and aminophosphonic acids with tetrasubstituted stereocenter.

Results and discussion

In our previous work we reported on the efficient hydrophosphonylation of enantiomerically pure hexahydroquinoxalin-2(1*H*)-one with a wide range of phosphorus nucleophiles under mild reaction conditions.[21] Unfortunately, the diastereoselectivity of the process was rather unsatisfactory. Hereby, we decided to introduce a substituent at the reaction center of the imine substrate to cause a steric hindrance and preclude a possible epimerization of the reaction intermediates. To this end, various enantiomerically pure hexahydroquinoxalin-2(1*H*)-one derivatives were prepared from (1*R*,2*R*)-1,2,-diaminocyclohexane and α-ketoesters using a modified procedure described for the reaction with ethyl glyoxylate.[21] After stirring in 2-propanol for 24 hours at room temperature, desired substituted imines were isolated in good yields (57–93%, Table 1). All imines were obtained for the first time as pure (1*R*,2*R*) enantiomers.

We have selected imine **1a** as model substrate for the phosphorylation reaction. During optimization of the reaction conditions, we have quickly discovered that the reaction required elevated temperature to produce the desired aminophosphonate in good yield. This was due to the presence of additional substituent at the iminic carbon atom and thus increased steric hindrance at the reaction centre. The reaction time of 1 h in toluene at 80 °C was established as optimal (Table 2). Under such conditions imine **1a** reacted readily with both diethyl- (**2a**) and diisopropyl- (**2b**) H-phosphonates affording desired bicyclic aminophosphonates **3aa** and **3ab** in 78 and

Table 1 Synthesis of imines **1**[a]



No	X=	Ketimine	Yield, %
1	Methyl	**1a**	89
2	Isopropyl	**1b**	93
3	Phenyl	**1c**	57
4	4-Cyanophenyl	**1d**	89
5	Phenethyl	**1e**	70

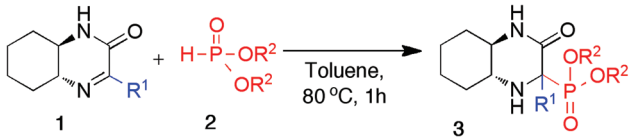
[a] (1*R*,2*R*)-1,2-Diaminocyclohexane (2.00 mmol), ketoester (1.00 mmol), 2-PrOH (4 ml), RT, 24 h.

80% yield, respectively (Table 2, entries 1 and 2). Extending the substrate scope to imines **1b** and **1c** afforded the desired products **3ba** and **3bb** (Table 2, entries 3 and 4) and **3ca** and **3cb** (Table 2, entries 5 and 6) in very good yields.

We expected that the use of chiral imines **1a–c** with a sterically crowded reaction centre and H-phosphonate **2b** with bulky diisopropyl groups should lead to very good diastereoselectivity in the formation of the desired bicyclic aminophosphonates. However, the diastereomeric ratio (dr) in all products was only moderate (dr 83 : 17 in the best case). Additionally, the obtained diastereomers were non-separable neither by chromatography nor by crystallization.

We have therefore decided to apply a different phosphorus nucleophile in the reaction with imines **1**. We have selected the tris(trimethylsilyl)phosphite [$P(OSiMe_3)_3$] as commercially available, stable and affordable reagent.[22] To our satisfaction, reaction of imines **1a–f** with [$P(OSiMe_3)_3$] afforded directly the desired aminophosphonic acids with excellent diastereoselectivies (Table 3) and under mild reaction conditions. Imine **1f** was prepared *via* Horner–Wadsworth–Emmons (HWE) reaction between isovaleraldehyde and hexahydroquinoxalin-2(1*H*)-one

Table 2 Reaction of imines **1** with H-phosphonates **2**[a]

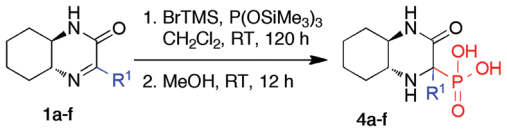


1 2 3

Entry	Imine **1**	R^1	H-Phosphonate **2**	R^2	Product **3**	Yield[b] (%)	dr[c]
1	**1a**	Me	**2a**	Et	**3aa**	78	71 : 29
2	**1a**	Me	**2b**	iPr	**3ab**	80	68 : 32
3	**1b**	iPr	**2a**	Et	**3ba**	93	74 : 26
4	**1b**	iPr	**2b**	iPr	**3bb**	95	83 : 17
5	**1c**	Ph	**2a**	Et	**3ca**	89	83 : 17
6	**1c**	Ph	**2b**	iPr	**3cb**	85	85 : 15

[a] Reaction conditions: Imine (1.00 mmol), H-phosphonate (1.00 mmol), toluene (30 mL), 80 °C, 1 h. [b] Yield of pure product after chromatographic purification. [c] Ratio of diastereoisomers established based on ^{31}P NMR of the crude reaction mixture and did not change during the purification step.

Table 3 Reaction of $[P(OSiMe_3)_3]$ with substituted hexahydroquinoxalin-2(1*H*)-one derivatives **1a–f** – substrate scope[a]



1a-f 4a-f

Entry	R^1	Imine	Product	Yield[b] (%)	dr (%)
1	CH_3	**1a**	**4a**	80	>98 : 2[c,d]
2	i-Pr	**1b**	**4b**	99	>98 : 2[c,d]
3	Ph	**1c**	**4c**	80	>98 : 2[d] (85 : 15)[c]
4	4-Cyanophenyl	**1d**	**4d**	75	>98 : 2[d] (88 : 12)[c]
5	Phenethyl	**1e**	**4e**	70	>98 : 2[d] (89 : 11)[c]
6	Isopentyl	**1f**	**4f**	65	>98 : 2[c,d]

[a] Reaction conditions: Imine (1.00 mmol), $P(OSiMe_3)_3$ (1.10 mmol), BrTMS (1.10 mmol), CH_2Cl_2 (20 ml), RT, 120 h then MeOH (15 ml), RT, 12 h. [b] Yield of pure product after crystallization. [c] Ratio of diastereoisomers established based on ^{31}P NMR of the crude reaction mixture. [d] Pure major diastereoisomer isolated after simple recrystallization.

derived dimethylphosphonate, as previously described by us (see ESI† for details).[21]

It has to be noted that during preliminary tests we observed that activation of the imine is required to obtain good yields of the desired product. For that purpose, we have used bromotrimethylsilane (BrTMS) that reacted with the imine forming an iminium cation[23] that was found to be more reactive towards tris(trimethylsilyl) phosphite. Pure major diastereoisomers **4a–f** were isolated after simple recrystallization of the crude products. A palette of substituted hexahydroquinoxalin-2(1*H*)-one derivatives with structurally varied aliphatic substituents such as methyl- (**1a**) or bulkier isopropyl- (**1b**) and isopentyl- (**1f**) groups were tolerated under the reaction conditions leading to the desired aminophosphonic acids with good to excellent yields and very good diastereoselectivity (Table 3, entries 1, 2 and 6). Likewise, aromatic (**1c**, **1e**) and substituted aromatic (**1d**) groups were tolerated under the reaction conditions.

The observed high asymmetric induction is supported by the DFT calculations performed for imine **1a** as a model substrate (see ESI† for details). Two main factors play an important role on the stereoselectivity of formation of major epimeric product **4a** (with *R* configuration on the new stereogenic C atom): the relative stabilities of products and the curve of the C–P bond dissociation energy. The calculations show that the **4a** epimer is more stable by 15 kJ mol^{-1}, and its dissociation energy is higher (50 kJ mol^{-1} *vs.* 20 kJ mol^{-1} for a **4a** with *S* configuration on the new stereogenic C atom).

The results of the DFT simulations were confirmed by X-ray diffraction analysis (see ESI† for details). The absolute configuration of the newly formed asymmetric carbon stereocenter was unambiguously assigned for compounds **4a** and **4e**. The molecule of each compound bears two chiral centers inherited in the synthetic pathway that possess *R* configuration. The analysis of molecular structure revealed that a new chiral center has *R* configuration in major diastereomers of **4a** and **4e** (Fig. 2).

Finally, to demonstrate the utility of the developed methodology based of nucleophilic addition of tris(trimethylsilyl) phosphite to substituted hexahydroquinoxalin-2(1*H*)-one

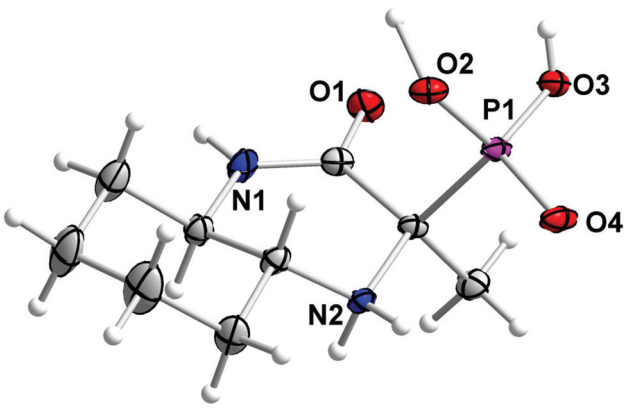
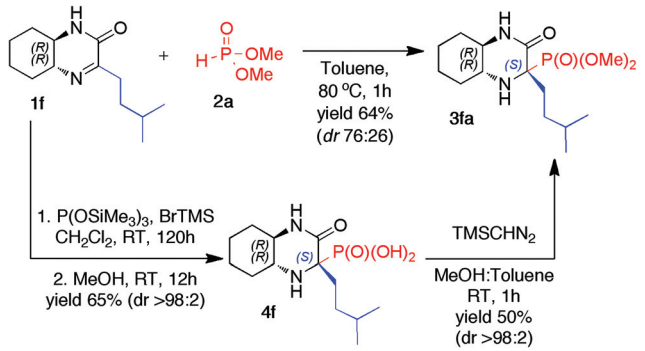


Fig. 2 Molecular structure of **4a** (a zwitterion found in a solid state).



Scheme 1 Preparation of pure diasteroisomer of aminophosphonate ester **3fa**.

derivatives we prepared a single diasteroisomer of aminophosphonate **3fa** (Scheme 1).

This was done by esterification of the earlier prepared diasteoreomerically pure aminophosphonic acid **4f** employing trimethylsilyldiazomethane ($TMSCHN_2$).[24] The configuration at the new stereogenic C atom in aminophosphonate **3fa** was *S* as assigned by X-ray diffraction analysis (see ESI† for details). Importantly, the direct hydrophosphonylation of imine **1f** yielded a non-separable mixture of diastereomers of aminophosphonate **3fa**.

Conclusions

In summary, we have reported on the asymmetric nucleophilic addition of tris(trimethylsilyl)phosphite to variety of substituted hexahydroquinoxalin-2(1*H*)-one derivatives leading to new chiral bicyclic aminophosphonic acids comprising a tetrasubstituted stereogenic center with remarkably high diastereoselectivity (up to >98 : 2 dr). The developed methodology is featured with broad substrate scope, mild reaction conditions, high yield and easy isolation and purification of the final product by simple crystallization. Furthermore, we have demonstrated that the obtained diastereomerically pure aminophosphonic acids can be easily transformed into optically pure aminophosphonate esters without racemisation showing the utility of the developed protocol. Further application of this strategy is under active investigation in our laboratory. The obtained chiral quaternary aminophosphonic acids are currently tested for biological activity and the results will be reported in due course.

Experimental section

General information

Melting points were determined on the Schmelzpunkt Bestimmer Apotec melting-point apparatus using the standard open capillary method and are uncorrected. ^{1}H, ^{13}C and ^{31}P NMR spectra were collected on Jeol 400yh, Bruker Avance III 500 and Bruker Avance II 600 instruments. NMR spectra recorded in $CDCl_3$, D_2O and DMSO-d_6 were referenced to the respective residual ^{1}H or ^{13}C signals of the solvents. The reported *J* values are those observed from the splitting patterns in the spectrum and may not reflect the true coupling constant values. NOESY experiments were carried out at 293 K. Infrared spectra (4000–400 cm^{-1}) were collected on a PerkinElmer 2000 FTIR spectrophotometer. High resolution mass spectra were collected using electrospray ionization on Waters LCT Premier XE TOF instrument. Optical rotations were measured using an Optical Activity Ltd. Model AA-5 automatic polarimeter; $[\alpha]^{D}$ values are given in 10^{-1} deg cm^2 g^{-1}. Chromatographic separations were performed on silica gel 60 (70–230 mesh). Thin layer chromatography was carried out using silica gel 60 precoated plates.

General procedure for synthesis of cyclic imines 1a–e. (1*R*,2*R*)-1,2-Diaminocyclohexane (2.00 mmol, 228 mg, 2.00 equiv.) was dissolved in 2-PrOH (4 ml). To the stirred solution was added a ketone ester (1.00 mmol, 1.00 equiv.) and the mixture was stirred for 24 hours at room temperature (293 K). The solvent was removed *in vacuo* and the product was purified by silica gel column chromatography (eluent: CH_2Cl_2/MeOH 97 : 3 v/v).

Procedure for synthesis of cyclic imine 1f. Sodium hydride (60% dispersion in mineral oil, 1.20 mmol, 48.0 mg, 1.20 equiv.) was dispersed in anhydrous THF (10 ml) under argon atmosphere. A mixture was cooled to 273 K in an ice bath and then dimethyl-[(1*R*,6*R*)-3-oxo-2,5-diazabicyclo[4.4.0]dec-4-yl] phosphonate (1.00 mmol, 262 mg, 1.00 equiv.) was added. The mixture was stirred for 30 minutes. Isovaleraldehyde was added (1.00 mmol, 107 µl, 1.00 equiv.) and the reaction continued for 30 minutes in 273 K and then for 30 minutes in room temperature. Reaction mixture was washed with Et_2O (20 ml) and saturated $NaHCO_3$ solution (20 ml). The organic layer was dried (Na_2SO_4), filtered and evaporated under reduced pressure.

General procedure for synthesis of dialkyl aminophosphonic acid esters 3aa–cb. Imine (1.00 mmol, 1.00 equiv.) was dissolved in toluene (30 ml), mixed with appropriate H-phosphonate (1.00 mmol, 1.00 equiv.) and the resulting mixture was stirred for 1 h at 80 °C. After that time the resulting crude product was purified by column chromatography (eluent: CH_2Cl_2/MeOH 98 : 2 v/v).

Procedure for synthesis of dialkyl aminophosphonic acid ester 3fa. The procedure of esterification of the earlier prepared aminophosphonic acid **4f** employing trimethylsilyldiazomethane ($TMSCHN_2$) can be found in the literature.[24]

General procedure for synthesis of acids 4a–f. To the solution of imine (1.00 mmol, 1.00 equiv.) in CH_2Cl_2 (8 ml) bromotrimethylsilane (1.10 mmol, 0.145 ml, 1.10 equiv.) and subsequently tris(trimethylsilyl) phosphite (1.10 mmol, 0.367 ml, 1.10 equiv.) were added. The resulting reaction mixture was flushed with argon and stirred for 120 h at room temperature and afterwards the solvent was removed under reduced pressure. The resulting residue was dissolved in methanol (10 ml) and stirred for 12 h at room temperature. After that time the solvent was removed under reduced

pressure, and the product was purified by washing with methanol (3 × 2 ml) or by crystallization (abs. EtOH/Et_2O 1 : 5 v/v), yielding the desired product as a colorless solid.

4-Methyl-(1R,6R)-3-oxo-2,5-diazabicyclo[4.4.0]dec-4-ene ***(1a)***. Colorless solid; 148 mg; yield = 89%; mp. 169–170 °C; $[\alpha]_D^{20}$ −178 (*c* 0.55, CH_2Cl_2); IR (KBr): 573, 773, 1204, 1358, 1450, 1625, 1663, 1686, 2861, 2933, 2949, 3226 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.63 (br. s, 1H), 3.11 (td, J = 11.5, 3.7 Hz, 1H), 2.97–3.06 (m, 1H), 2.24–2.32 (m, 1H), 2.19 (d, J = 2.5 Hz, 3H), 1.83–1.92 (m, 2H), 1.75–1.78 (m, 1H), 1.22–1.44 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.0, 159.0, 62.5, 54.5, 31.8, 31.1, 25.3, 23.7, 21.0; HRMS (ESI-TOF) calcd for $C_9H_{15}N_2O$ $[M + H]^+$ *m*/*z*: 167.1184, found: 167.1176.

4-Isopropyl-(1R,6R)-3-oxo-2,5-diazabicyclo[4.4.0]dec-4-ene ***(1b)***. Colorless solid; 180 mg; yield = 93%; mp. 125–127 °C; $[\alpha]_D^{20}$ −166 (*c* 0.67, CH_2Cl_2); IR (KBr): 572, 807, 1068, 1361, 1446, 1627, 1683, 2865, 2930, 3064, 3192 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 6.50 (br. s, 1H), 3.25 (dsep, J = 7.0, 1.1 Hz, 1H), 3.02–3.09 (m, 2H), 2.35–2.37 (m, 1H), 1.80–1.94 (m, 3H), 1.33–1.42 (m, 4H), 1.17 (d, J = 7.0 Hz, 3H), 1.11 (d, J = 7.0 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 169.3, 158.6, 62.4, 54.1, 31.9, 31.1, 30.7, 25.2, 23.7, 20.6, 19.3; HRMS (ESI-TOF) calcd for $C_{11}H_{19}N_2O$ $[M + H]^+$ *m*/*z*: 195.1497, found: 195.1489.

4-Phenyl-(1R,6R)-3-oxo-2,5-diazabicyclo[4.4.0]dec-4-ene ***(1c)***. Colorless solid; 130 mg; yield = 57%; mp. 143–144 °C; $[\alpha]_D^{20}$ −239 (*c* 0.82, CH_2Cl_2); IR (KBr): 688, 696, 739, 809, 1259, 1359, 1446, 1574, 1595, 1683, 2861, 2934, 3084, 3189, 3320, 3480 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.90 (dd, J = 8.1, 1.5 Hz, 2H), 7.36–7.44 (m, 3H), 6.99 (br. s, 1H), 3.16–3.23 (m, 2H), 2.38–2.44 (m, 1H), 1.78–1.99 (m, 3H), 1.17–1.54 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.6, 158.5, 135.2, 130.4, 129.0 (2C overlapped), 128.1 (2C overlapped), 63.1, 54.1, 31.9, 31.0, 25.3, 23.8; HRMS (ESI-TOF) calcd for $C_{14}H_{17}N_2O$ $[M + H]^+$ *m*/*z*: 229.1341, found: 229.1349.

4-((1R,6R)-3-Oxo-2,5-diazabicyclo[4.4.0]dec-4-yl-4-ene)-benzonitrile ***(1d)***. Off-white solid; 225 mg; yield = 89%; mp. 184–186 °C; $[\alpha]_D^{20}$ −333 (*c* 0.48, CH_2Cl_2); IR (KBr): 848, 854, 1254, 1363, 1586, 1673, 2229, 2857, 2940, 3066, 3080, 3185 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.04–8.07 (m, 2H), 7.65–7.68 (m, 2H), 6.66 (br. s, 1H), 3.19–3.29 (m, 2H), 2.24–2.45 (m, 1H), 1.81–2.00 (m, 3H), 1.24–1.49 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.9, 157.6, 139.1, 131.9 (2C overlapped), 129.7 (2C overlapped), 118.7, 113.7, 63.6, 54.2, 31.7, 31.0, 25.3, 23.7; HRMS (ESI-TOF) calcd for $C_{15}H_{16}N_3O$ $[M + H]^+$ *m*/*z*: 254.1293, found: 254.1299.

4-Phenethyl-(1R,6R)-3-oxo-2,5-diazabicyclo[4.4.0]dec-4-ene ***(1e)***. Pale yellow solid; 180 mg; yield = 70%; mp. 127–128 °C; $[\alpha]_D^{20}$ −110 (*c* 0.55, CH_2Cl_2); IR (KBr): 499, 711, 756, 1358, 1624, 1678, 2863, 2934, 3064, 3188 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.14–7.28 (m, 5H), 6.52 (br. s, 1H), 2.82–3.03 (m, 6H), 2.29–2.32 (m, 1H), 1.76–1.90 (m, 3H), 1.25–1.41 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.9, 158.6, 141.5, 128.7 (2C overlapped), 128.4 (2C overlapped), 126.0, 62.6, 54.4, 35.4, 32.7, 31.2, 31.1, 25.3, 23.8; HRMS (ESI-TOF) calcd for $C_{16}H_{21}N_2O$ $[M + H]^+$ *m*/*z*: 257.1654, found: 257.1647.

4-Isopentyl-[(1R,6R)-3-oxo-2,5-diazabicyclo[4.4.0]dec-4-ene] ***(1f)***. Yellow solid; 210 mg; 94% yield; mp. 98–101 °C; $[\alpha]_{20}^{D}$ −36 (*c* 0.22, CH_2Cl_2); IR (nujol): 1093, 1367, 1456, 1652, 1683, 2924, 3208 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.00 (br. s, 1H), 3.04–3.08 (m, 2H), 2.59–2.65 (m, 1H), 2.45–2.53 (m, 1H), 2.27–2.31 (m, 1H), 1.75–1.89 (m, 3H), 1.59 (sept., J = 6.72, 1H), 1.20–1.47 (m, 6H), 0.89 (d, J = 6.72, 6H), ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.3, 158.9, 62.4, 54.3, 35.7, 31.8, 31.0, 29.7, 28.2, 25.3, 23.8, 22.6, 22.4; HRMS (ESI-TOF) calcd for $C_{13}H_{23}N_2O$ $[M + H]^+$ *m*/*z*: 223.1810, found: 223.1805.

*Diethyl-[4-methyl-(1R,6R)-3-oxo-2,5-diazabicyclo[4.4.0]dec-4-yl]-phosphonate (****3aa****).* Colorless solid; 237 mg; 78% yield in a diastereomeric ratio = 71 : 29; IR (KBr): 962, 1026, 1056, 1229, 1451, 1670, 2857, 2929, 3448 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.92 (s, dia_{maj}, 1H), 5.85 (s, dia_{min}, 1H), 4.09–4.29 (m, dia_{maj} + dia_{min}, 8H), 3.05–3.16 (m, dia_{maj} + dia_{min}, 2H), 2.96–3.05 (m, dia_{maj} + dia_{min}, 2H), 1.68–2.10 (m, dia_{maj} + dia_{min}, 10H), 1.63 (d, J = 16.5 Hz, dia_{min}, 3H), 1.55 (d, J = 15.9 Hz, dia_{maj}, 3H), 1.13–1.43 (m, dia_{maj} + dia_{min}, 20H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.7 (dia_{min}), 169.7 (dia_{maj}), 64.3 (d, J = 6.9 Hz, dia_{min}), 63.4 (d, J = 6.9 Hz, dia_{maj}), 63.2 (d, J = 7.5 Hz, dia_{min}), 63.2 (d, J = 8 Hz, dia_{maj}), 61.9 (d, J = 133.2 Hz, dia_{maj}), 61.8 (d, J = 162.6 Hz, dia_{min}), 58.0 (dia_{maj}), 57.8 (dia_{min}), 54.9 (dia_{maj}), 54.4 (d, J = 10.3 Hz, dia_{min}), 31.0 (dia_{min}), 31.0 (dia_{maj}), 30.6 (dia_{maj}), 30.4 (dia_{min}), 24.5 (dia_{min}), 24.4 (dia_{maj}), 23.8 (dia_{maj}), 23.8 (dia_{maj}), 23.7 (dia_{min}), 22.1 (dia_{min}), 16.7 (dia_{min}), 16.6 (dia_{min}), 16.6 (dia_{maj}), 16.6 (dia_{maj}); ^{31}P NMR (162 MHz, $CDCl_3$): δ 25.0 (m, dia_{maj}), 22.4 (m, dia_{min}); HRMS (ESI-TOF): calcd for $C_{13}H_{26}N_2O_4P$ $[M + H]^+$ *m*/*z*: 305.1630, found: 305.1626.

*Diisopropyl-[4-methyl-(1R,6R)-3-oxo-2,5-diazabicyclo[4.4.0]dec-4-yl]-phosphonate (****3ab****).* Colorless solid; 266 mg; 80% yield in a diastereomeric ratio = 68 : 32; IR (KBr): 990, 1214, 1227, 1345, 1373, 1455, 1469, 1670, 2861, 2934, 2980, 3197, 3279 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 6.95–7.05 (s, br, 1H), 4.60–4.74 (m, 2H), 3.02–3.13 (m, 1H), 2.85–2.96 (m, 1H), 1.90–2.30 (br. s, 1H), 1.96–1.75 (m, 4H), 1.44 (d, J = 15.9 Hz, 3H), 0.41–0.56 (m, 16H); ^{13}C NMR (100 MHz, $CDCl_3$): 170.1, 72.1 (d, J = 6.9 Hz),71.4 (d, J = 7.5 Hz, 61.8 (d, J = 134.2 Hz), 57.9, 54.6, 30.7, 30.6, 24.5 (d, J = 1.7 Hz), 24.4, 24.2 (d, J = 2.9 Hz), 23.9, 23.9 (d, J = 8.6 Hz), 23.8 (d, J = 9.7 Hz), 22.1; ^{31}P NMR (162 MHz, $CDCl_3$): δ 22.8 (qt, J = 15.9, 6.5 Hz); HRMS (ESI-TOF): calcd for $C_{15}H_{30}N_2O_4P$ $[M + H]^+$ *m*/*z*: 333.1943, found: 333.1948.

*Diethyl-[4-isopropyl-(1R,6R)-3-oxo-2,5-diazabicyclo[4.4.0]dec-4-yl]-phosphonate (****3ba****).* Colorless solid; 308 mg; 93% yield in a diastereomeric ratio = 74 : 26; IR (KBr): 948, 960, 1030, 1052, 1226, 1342, 1454, 1668, 2939, 2980, 3200, 3323 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 6.22 (br. s, 1H), 6.20 (br. s, 1H), 4.08–4.26 (m, 8H), 2.94–3.08 (m, 3H), 2.63–2.77 (m, 1H), 2.55–2.63 (m, 2H), 2.01 (br. s, 2H), 1.71–1.85 (m, 8H), 1.16–1.38 (m, 20H), 1.04 (d, J = 6.7 Hz, 3H), 0.97 (d, J = 6.7 Hz, 6H), 0.93 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 169.5, 169.4, 69.4 (d, J = 128.1 Hz), 68.2 (d, J = 152.2 Hz), 63.7 (d, J = 7.5 Hz), 63.6 (d, J = 7.5 Hz), 63.2 (d, J = 6.9 Hz), 62.7 (d, J = 6.3 Hz), 57.2 (d, J = 8.0 Hz), 57.1 (d, J = 6.9 Hz), 56.5, 54.9, 34.2, 33.8, 30.8, 30.7, 30.5, 24.4, 24.3, 23.8, 23.7, 19.6, 19.5, 17.5, 17.3, 17.2, 17.0, 16.7, 16.6, 16.6; $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ 25.6, 21.9; $C_{15}H_{29}N_2O_4PNa$ $[M + Na]^+$ *m*/*z*: 355.1763, found: 355.1753.

*Diisopropyl-[4-isopropyl-(1R,6R)-3-oxo-2,5-diazabicyclo[4.4.0]dec-4-yl]-phosphonate (**3bb**).* Colorless solid; 341 mg; 95% yield in a diastereomeric ratio = 83 : 17; IR (KBr): 806, 1068, 1360, 1447, 1622, 1683, 2866, 2936, 3193 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 6.01 (br. s, 1H), 5.93 (br. s, 1H), 4.78 (sept, J = 6.1 Hz, 1H), 4.77 (sept, J = 6.1 Hz, 1H), 4.09–4.17 (m, 2H), 3.09–3.15 (m, 1H), 2.90–3.08 (m, 3H), 2.76–2.84 (m, 1H), 2.59–2.67 (m, 1H), 1.90 (br. s, 2H), 1.67–1.79 (m, 4H), 1.23–1.39 (m, 36H), 1.01 (d, J = 6.7 Hz, 3H), 0.91–0.96 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): 170.1, 169.9, 72.0 (d, J = 8.0 Hz), 71.8 (d, J = 8.0 Hz), 71.3, 69.4 (d, J = 128.7 Hz, 2C overlapped), 57.2, 57.1, 56.9, 56.7, 54.5, 34.1, 33.8, 30.9, 30.8, 30.6, 24.4 (2C overlapped), 24.39, 24.3 (2C overlapped), 23.9, 23.88 (2C overlapped), 23.8 (2C overlapped), 23.7, 19.6, 19.5, 17.5, 17.4, 17.2, 17.0; $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ 23.6, 20.3; $C_{17}H_{33}N_2O_4PNa$ $[M + Na]^+$ m/z: 383.2076, found: 383.2087.

*Diethyl-[4-phenyl-(1R,6R)-3-oxo-2,5-diazabicyclo[4.4.0]dec-4-yl]-phosphonate (**3ca**).* Colorless solid; 325 mg; 89% yield in a diastereomeric ratio = 83 : 17; IR (Nujol): 1029, 1204, 1342, 1394, 1450, 1674, 2426, 3891 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.97–8.02 (m, 1H), 7.88–7.92 (m, 2H), 7.70–7.75 (m, 1H), 7.23–7.36 (m, 6H), 6.34 (br. s, 1H), 6.32 (br. s, 1H), 4.20–4.27 (m, 2H), 4.10–4.23 (m, 2H), 3.90–4.05 (m, 2H), 3.77–3.85 (m, 2H), 3.17–3.28 (m, 2H), 2.96–3.12 (m, 1H), 2.52 (br. s, 2H), 2.29–2.34 (m, 1H), 1.93–1.96 (m, 2H), 1.56–1.78 (m, 6H) 1.42–1.10 (m, 8H), 1.28 (t, J = 7.3 Hz, 3H), 1.25 (t, J = 7.03 Hz, 3H), 1.18 (t, J = 7.3 Hz, 3H), 1.11 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 167.7, 167.5, 137.6, 136.4, 128.5, 128.49, 128.1, 128.04, 128.01, 127.9, 127.8, 127.78, 127.3, 127.2, 68.7 (d, J = 159.7 Hz), 67.7 (d, J = 140.2 Hz) 64.6 (d, J = 6.9 Hz), 64.1, 64.0, 63.99, 63.9, 63.8, 58.6, 56.7, 56.0, 53.6 (d, J = 11.5 Hz), 30.9, 30.87, 30.6, 30.2, 24.5, 24.4, 23.7, 23.69, 16.5 (q, J = 9.8 Hz), 16.4 (q, J = 10.3 Hz); $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ 21.3, 19.1; HRMS (ESI-TOF): calcd for $C_{18}H_{28}N_2O_4P$ $[M + H]^+$ m/z: 367.1787, found: 367.1781.

*Diisopropyl-[4-phenyl-(1R,6R)-3-oxo-2,5-diazabicyclo[4.4.0]dec-4-yl]-phosphonate (**3cb**).* Colorless solid; 310 mg; 85% yield in a diastereomeric ratio = 85 : 15; IR (KBr): 986, 1106, 1228, 1345, 1373, 1385, 1447, 1671, 2861, 2934, 2979, 3207 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.89–7.93 (m, 2H), 7.69–7.72 (m, 2H), 7.23–7.35 (m, 6H), 6.11 (br. s, 1H), 6.01 (br. s, 1H), 4.89 (oct., J = 6.7 Hz, 1H), 4.75 (oct., J = 6.7 Hz, 1H), 4.59 (oct., J = 6.7 Hz, 1H), 4.53 (oct., J = 6.7 Hz, 1H), 3.21–3.25 (m, 1H), 3.11–3.12 (m, 1H), 2.93–3.02 (m, 1H), 2.48 (br. s, 2H), 2.26–2.32 (m, 1H), 1.66–1.92 (m, 8H), 1.31 (d, J = 6.1 Hz, 3H), 1.28 (d, J = 6.1 Hz, 3H), 1.27 (d, J = 6.1 Hz, 3H), 1.21 (d, J = 6.4 Hz, 3H), 1.19 (d, J = 6.4 Hz, 3H), 1.18 (d, J = 6.7 Hz, 3H), 1.16 (d, J = 6.7 Hz, 3H), 1.11–1.44 (m, 8H) 1.01 (d, J = 6.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.2, 167.9 (d, J = 5.8 Hz), 138.4, 137.0 (d, J = 2.9 Hz), 128.2 (d, J = 2.3 Hz), 127.95 (2C overlapped), 127.9 (2C overlapped), 127.85 (d, J = 1.7 Hz, 2C overlapped), 127.7 (d, J = 2.3 Hz), 127.6 (d, J = 1.7 Hz), 127.4 (d, J = 5.2 Hz), 72.9 (d, J = 7.5 Hz), 72.5 (d, J = 7.5 Hz, 2C overlapped), 72.4 (d, J = 8.0 Hz), 68.8 (d, J = 160.3 Hz), 67.8 (d, J = 140.8 Hz), 58.6, 56.9, 55.7, 53.5 (d, J = 12.1 Hz), 30.9, 30.8, 30.7, 30.3, 24.5 (d, J = 5.8 Hz), 24.4 (3C overlapped), 24.3 (d, J = 1.7 Hz), 24.2 (d, J = 2.9 Hz), 24.1 (d, J = 3.5 Hz), 23.8 (2C overlapped), 23.6 (d, J = 5.8 Hz), 23.57 (d, J = 5.8 Hz), 23.4 (d, J = 5.8 Hz); $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ 19.6, 17.3; HRMS (ESI-TOF) calcd for $C_{20}H_{31}N_2O_4PNa$ $[M + Na]^+$ m/z: 417.1919, found: 417.1917.

*Dimethyl-[4-isopentyl-(1R,4S,6R)-3-oxo-2,5-diazabicyclo[4.4.0]dec-4-yl]-phosphonate (**3fa**).* Colorless solid; 57 mg; yield = 52% in a diastereomeric ratio >98 : 2; mp. 139–141 °C; $[\alpha]_D^{20}$ +30 (c 0.10, CH_2Cl_2); IR (KBr): 774, 833, 1037, 1062, 1217, 1351, 1468, 1662, 2868, 2952, 3258 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.85 (br. s, 1H), 3.84 (dd, J = 20.2, 10.4 Hz, 6H), 3.10–3.16 (m, 1H), 2.56–2.61 (m, 1H), 2.20–2.32 (m, 1H), 1.72–1.89 (m, 6H), 1.53 (non, J = 6.7 Hz, 1H), 1.18–1.38 (m, 6H), 0.90 (d, J = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.8, 65.3 (d, J = 158.6 Hz), 57.2, 56.2 (d, J = 9.2 Hz), 55.2 (d, J = 7.5 Hz), 54.0 (d, J = 7.5 Hz), 33.7, 32.8 (d, J = 9.8 Hz), 30.8, 30.7, 28.5, 24.3, 23.6, 22.8, 22.5; $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ 24.2; HRMS (ESI-TOF) calcd for $C_{15}H_{30}N_2O_4P$ $[M + H]^+$ m/z: 333.1943, found: 333.1938.

*[4-Methyl-(1R,4R,6R)-3-oxo-2,5-diazabicyclo[4.4.0]dec-4-yl]-phosphonic acid (**4a**).* Colorless solid; 198 mg; yield = 80% in a diastereomeric ratio >98 : 2; mp. 270–271 °C; $[\alpha]_D^{20}$ −44 (c 0.43, H_2O); IR (KBr): 821, 932, 1116, 1455, 1467, 1606, 1670, 2924, 2948, 3426 cm^{-1}; ^1H NMR (600 MHz, D_2O): δ 3.55–3.60 (m, 1H), 3.35–3.42 (m, 1H); 1.90–2.01 (m, 2H), 1.65–1.70 (m, 2H), 1.61 (dd, J = 12.8, 4.9 Hz, 3H), 1.22–1.46 (m, 4H); ^{13}C NMR (151 MHz, D_2O): δ 168.6, 63.0 (d, J_{C-P} = 189.9 Hz), 55.3, 54.1, 30.2, 27.1, 23.7, 22.5, 19.3; ^{31}P NMR (243 MHz, D_2O): δ 9.7 (q, J = 13.1 Hz); HRMS (ESI-TOF) calcd for $C_9H_{18}N_2O_4P$ $[M + H]^+$ m/z: 249.1004 found: 249.1016.

*[4-Isopropyl-(1R,4S,6R)-3-oxo-2,5-diazabicyclo[4.4.0]dec-4-yl]-phosphonic acid (**4b**).* Colorless solid; 273 mg; 99% yield in a diastereomeric ratio >98 : 2; mp. 220–222 °C; $[\alpha]_D^{20}$ −55 (c 0.15, H_2O); IR (KBr): 912, 1042, 1083, 1218, 1342, 1661, 2933, 3425 cm^{-1}; ^1H NMR (400 MHz, D_2O): δ 3.44–3.51 (m, 1H), 3.34–3.40 (m, 1H), 2.80 (dhept, J = 7.0 Hz, J = 6.7 Hz, 1H), 2.07–2.10 (m, 1H), 1.95–1.97 (m, 1H), 1.76–1.79 (m, 1H), 1.66–1.69 (m, 1H), 1.48–1.57 (m, 1H), 1.37–1.56 (m, 3H), 1.02 (d, J = 7.3 Hz, 3H), 0.92 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, D_2O): δ 168.1 (d, J = 2.3 Hz), 71.3 (d, J = 126.4 Hz), 56.4, 52.5, 32.2, 30.4, 26.6, 23.6, 22.4, 16.4 (d, J = 10.3 Hz), 16.1; ^{31}P NMR (162 MHz, D_2O): δ 8.9 (d, J = 6.5 Hz); HRMS (ESI-TOF) calcd for $C_{11}H_{22}N_2O_4P$ $[M + H]^+$ m/z: 277.1317, found: 277.1319.

*[4-Phenyl-(1R,6R)-3-oxo-2,5-diazabicyclo[4.4.0]dec-4-yl]-phosphonic acid (**4c**).* Colorless solid; 248 mg; 80% yield in a diastereomeric ratio >98 : 2 (diastereomeric ratio of crude product 85 : 15); mp. 196–198 °C; $[\alpha]_D^{20}$ −35 (c 0.29, H_2O); IR (KBr): 909, 1087, 1239, 1349, 1447, 1460, 1591, 1646, 2865, 2939, 3369 cm^{-1}; ^1H NMR (600 MHz, D_2O): δ 7.36–7.55 (m, 5H), 3.63–3.66 (m, 1H), 3.40–3.45 (m, 1H), 1.99–2.10 (m, 2H), 1.68–1.76 (m, 2H), 0.87–1.40 (m, 4H); ^{13}C NMR (151 MHz, D_2O): δ 166.7, 133.8 129.5, 129.1, 128.3, 69.7 (d, J = 185.8 Hz), 55.8, 53.0, 30.3, 27.0, 23.5, 22.5; $^{31}P\{^1H\}$ NMR (243 MHz, D_2O): δ 8.5; HRMS (ESI-TOF) calcd for $C_{14}H_{20}N_2O_4P$ $[M + H]^+$ m/z: 311.1161, found: 311.1155.

*[4-(4-Cyanophenyl)-(1R,6R)-3-oxo-2,5-diazabicyclo[4.4.0]dec-4-yl]-phosphonic acid (**4d**).* Colorless solid; 251 mg; 75% yield in a

diastereomeric ratio >98 : 2 (diastereomeric ratio of crude product 88 : 12); mp. 176–178 °C; $[\alpha]_D^{20}$+18 (*c* 0.11, H_2O); IR (KBr): 564, 1312, 1335, 1455, 1575, 1669, 2231, 2946, 3421 cm^{-1}; ^1H NMR (400 MHz, D_2O): δ 7.71–7.81 (m, 4H), 3.46–3.57 (m, 1H), 2.81–2.91 (m, 1H), 1.91–2.01 (m, 1H), 1.79–1.88 (m, 1H), 1.55–1.72 (m, 2H), 1.02–1.50 (m, 4H); ^{13}C NMR (100 MHz, D_2O): δ 166.7, 138.0 (d, J = 4.2 Hz), 133.1 (2C), 129.7, 129.7, 118.8, 112.6, 69.1 (d, J = 128.1 Hz), 54.3 (d, J = 3.5 Hz), 53.2, 30.5, 26.6, 23.5, 22.4; $^{31}P\{^1H\}$ NMR (243 MHz, D_2O): δ 7.5; HRMS (ESI-TOF): calcd for $C_{15}H_{17}N_3O_4P$ $[M - H]^-$ *m*/*z* 334.0957, found: 334.0959.

*[4-Phenethyl-(1R,4R,6R)-3-oxo-2,5-diazabicyclo[4.4.0]dec-4-yl]-phosphonic acid (**4e**).* Colorless solid; 237 mg; 70% yield in a diastereomeric ratio >98 : 2 (diastereomeric ratio of crude product 89 : 11); mp. 224–225 °C; $[\alpha]_D^{20}$ +15 (*c* 0.13, DMSO); IR (KBr): 703, 930, 1110, 1458, 1605, 1669, 2938 cm^{-1}; ^1H NMR (400 MHz, D_2O): δ 7.68 (br. s, 1H), 7.12–7.25 (m, 5H), 3.19–3.22 (m, 1H), 2.96–3.01 (m, 2H), 2.36–2.46 (m, 2H), 2.25–2.28 (m, 1H), 1.62–1.90 (m, 5H), 1.07–1.26 (m, 4H); ^{13}C NMR (100 MHz, D_2O): δ 168.8, 142.9, 128.8 (2C overlapped), 128.7 (2C overlapped), 126.1, 65.4 (d, J = 125.8 Hz), 56.2, 55.0, 38.2, 30.9, 30.1, 30.06, 24.6, 23.8; $^{31}P\{^1H\}$ NMR (162 MHz, D_2O): δ 17.2; HRMS (ESI-TOF) calcd for $C_{16}H_{24}N_2O_4PNa$ $[M + H]^+$ *m*/*z*: 339.1474, found: 339.1462.

*[4-Isopentyl-(1R,4S,6R)-3-oxo-2,5-diazabicyclo[4.4.0]dec-4-yl]-phosphonic acid (**4f**).* Colorless solid; 198 mg; 65% yield in a diastereomeric ratio >98 : 2; mp. 226–227 °C; $[\alpha]_D^{20}$ −46 (*c* 0.54, H_2O); IR (KBr): 922, 1103, 1165, 1353, 1461, 1607, 1672, 2871, 2954, 3203, 3403 cm^{-1}; ^1H NMR (400 MHz, D_2O): δ 3.52 (dt, J = 11.0, 4.0 Hz, 1H), 3.35 (dt, J = 10.4, 4.0 Hz, 1H), 1.90–2.16 (m, 4H), 1.64–1.76 (m, 2H), 1.18–1.48 (m, 6H), 1.06 (sep, J = 4.9 Hz, 1H), 0.75 (dd, J = 6.4, 4.0 Hz, 6H); ^{13}C NMR (151 MHz, D_2O): δ 168.3, 66.8 (d, J = 126.4 Hz), 55.9, 52.9, 31.8, 31.6 (d, J = 4.6 Hz), 30.4, 27.9, 26.9, 23.6, 22.5, 21.5, 21.5; ^{31}P NMR (162 MHz, D_2O): δ 8.9 (dd, J = 18.7, 5.6 Hz); HRMS (ESI-TOF) calcd for $C_{13}H_{25}N_2O_4PNa$ $[M + Na]^+$ *m*/*z*: 327.1450, found: 327.1474.

Conflicts of interest

There are no conflicts to declare.

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