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# Polycyclic phosphonic acid derivatives obtained by a [4+2] cycloaddition strategy using phosphonodienes

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ABSTRACT

A practical route is described for the preparation of 1-phosphono-3(4-di)-substituted-1,3-butadienes based on the Horner–Wadsworth–Emmons (HWE) reaction. Their reactivity in the Diels–Alder (DA) reaction with three selected dienophiles is studied and compared to diethyl 1-phosphono-1,3-butadiene. A particular attention is given to the P-deprotection of cycloadducts from dibenzyl phosphonodienes. New phosphonated bicycles and tricycles have been obtained using this HWE/DA reaction sequence.



## 1. Introduction

Our continuous interest in the Diels–Alder (DA) reactions of 1-phosphono-1,3-butadiene (**1a**) leads us to consider 3(4)-alkyl-substituted derivatives to (i) possibly increase the diene reactivity by conformational and electron-donating effects, and (ii) provide an entry into cyclic dienes and consequently into unprecedented polycyclic phosphonated DA cycloadducts.

Different methods are described in the literature for the preparation of 1-phosphono-3-alkyl-1,3-butadienes. Generally they use multistep synthesis giving low overall yields and/or mixtures of regioisomers. Phosphochloration reaction,[1] modification of phosphonoepoxides,[2] transformations of phosphonocyclopropenes[3] are the major routes for the preparation of these dienes. Organometallic processes, such as selective reduction of conjugated alkynes by hydride in the presence of In(III),[4] and catalyzed Michaelis–Arbuzov reaction on bromodienes[5] are other methods. Lastly, classical Michaelis–Arbuzov reaction followed by acetate elimination[6] and addition of dialkyl phosphite on propargyl alcohols and alkynes in the presence of Ni(0) or Pd(II) catalyst[7,8] lead to mixtures of 1-phosphonodienes and 2-phosphonodienes, which are not easily separable. 1-Phosphono-4-alkyl-1,3-butadienes are mainly obtained by isomerization of 1-phosphono-alkynes with Pd(0) catalyst[9] and Horner–Wadsworth–Emmons (HWE) condensation of conjugated aldehydes with methylenediphosphonate.[10] All these methods are generally applied to dimethyl and diethyl phosphonates.

The aim of this work is to propose the same strategy for the preparation of 3 and/or 4-substituted 1-phosphono-1,3-butadienes, and to illustrate the reactivity of these dienes in Diels–Alder (DA) cycloadditions with three reactive dienophiles, previously identified as good partners towards diethyl 1-phosphono-1,3-butadiene (**1a**).[11] The access to cycloadducts with a free phosphonic acid group by dibenzyl phosphonate deprotection is also reported. Lastly, the ability of some ethyl phosphonate cycloadducts to coordinate metal cations is illustrated.

## 2. Results and discussion

### 2.1. Synthesis of dienes 1a–f

A limited number of protecting groups of the phosphonate moiety is reported in the current literature for an easy access to free phosphonic acid derivatives.[12] The most common phosphonate ester is the diethyl phosphonate, because it is of practical handling and relative stability. The usual deprotection method[13] using

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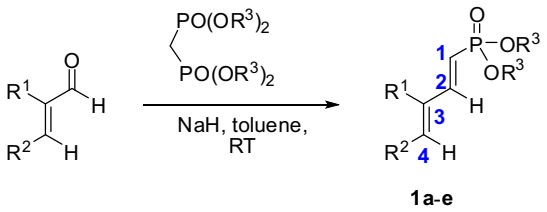
trimethylsilyl bromide as $SN_2$ reagent, followed by methanolysis, was found incompatible with the stability of succinimide derivatives (i.e., DA cycloadducts on maleimides) in our previous studies.[11] Acid hydrolysis of dialkylphosphonates could not be envisaged as an alternative method on imide derivatives. The use of 2-cyanoethyl phosphonate, usually cleaved at pH 10, was discarded.[14] The allyl protecting group was avoided,[15] because of its possible reaction as dienophile in the DA cycloaddition of phosphonodienes. 2,2,2-Trichloroethyl and trialkylsilylethyl groups were not envisaged because their deprotection conditions (zinc in acetic acid[16] and fluoride treatment,[17] respectively) are considered too hard. So, the benzyl group was selected for its soft deprotection by catalytic hydrogenation in neutral conditions.[18]

Previously, our group has synthesized, in two steps on a multigram scale, diethyl 1-phosphono-1,3-butadiene (**1a**) via the Michaelis–Arbuzov reaction between triethylphosphite and (*E*)-1,4-dichlorobut-2-ene followed by hydrochloride elimination with a hindered base (DBU).[19] The same route cannot be applied for the preparation of dibenzyl phosphonodienes. Indeed, the Michaelis–Arbuzov reaction between tribenzylphosphite and halogenoalkanes was previously reported to be weakly efficient because of the formation of a by-product, i.e., benzyl halide, which reacts more easily with tribenzylphosphite than the alkyl halide of interest.[20]

Dibenzyl 1-phosphono-1,3-butadiene (**1b**) was initially prepared from diethyl 1-phosphono-1,3-butadiene (**1a**) in three steps.[21] Diethyl phosphonate was first dealkylated by an excess of trimethylsilyl bromide, then the trimethylsilyl groups were replaced with chlorine atoms by the action of oxalyl chloride and the formal transesterification was finally achieved with benzyl alcohol in the presence of pyridine as a base. This indirect route towards dibenzyl phosphonodienes requires thus the previous preparation of the corresponding diethyl phosphonodienes. However, only the diene **1a** is easily synthesized with good yields from (*E*)-1,4-dichlorobut-2-ene; no general preparation of mono- or disubstituted phosphonodienes in positions 3 and/or 4 is described so far.

Diethyl 1-phosphono-4-alkenyl-1,3-butadienes were obtained as intermediates during the preparation of phosphoantigens.[10] The synthesis consists in a Horner–Wadsworth–Emmons (HWE) reaction between conjugated aldehydes and tetraethyl methylenediphosphonate in the presence of a base, a method generally applied to the synthesis of simple phosphonated olefins.[22] The convergent synthesis of 1-phosphonodienes by HWE reaction remains to be explored as a general strategy.

HWE reaction was tested in our hands for the preparation of the reference diene **1a** from acrolein and tetraethyl methylenediphosphonate (easily accessible from diethylphosphite and methylene chloride[23]) (Scheme 1). Using potassium carbonate as a base, no reaction was observed but polymerization of acrolein occurred. The diene **1a** was obtained with good yields, as a single *E*-stereoisomer, when sodium hydride was used as a base in toluene solution at room temperature. The same procedure did not work with ketones, such as methylvinylketone.




**Scheme 1.** Preparation of 1-phosphono-1,3-butadienes by Horner–Wadsworth–Emmons (HWE) reaction.

For the preparation of dibenzyl phosphonodiene **1b**, we carried out the HWE reaction with acrolein and tetrabenzyl methylenediphosphonate prepared from tetrachloromethylenediphosphonate using a known procedure.[24] The diene **1b** (Table 1) was recovered in moderate yield as a single *E*-stereosiomer, after purification by chromatography on silica gel. This one-step synthesis is more efficient than the transesterification method from diene **1a**.

**Table 1**
Yields of dienes **1a**–**e**, *E*:*Z* ratio from $^1$H NMR and energy difference between the *s-cis* and *s-trans* conformers of the (*E*)-isomer

| $R^1$ | $R^2$ | $R^3$ | Cmpd | Yields (%) | *E*:*Z* | $\Delta E_{rel}$ (kcal mol$^{-1}$)[a] |
|---|---|---|---|---|---|---|
| H | H | Et | **1a** | 78 | 100:0 | 3.4 |
| H | H | Bn | **1b** | 51 | 100:0 | 3.3 |
| Me | H | Et | **1c** | 79 | 87:13 | 3.7 |
| $-(CH_2)_4-$ | | Et | **1d** | 82 | 97:3 | 3.8 |
| Me | H | Bn | **1e** | 19 | 87:13 | n.d. |
| $-(CH_2)_4-$ | | Bn | **1f** | <5 | n.d. | n.d. |

[a] B3LYP-D/6-31+G**(THF)/B3LYP/6-31G**; n.d.=not determined.

The HWE methodology was further exemplified using two commercially available α,β-unsaturated aldehydes, namely methacrylaldehyde and cyclohex-1-encarbaldehyde, for the preparation of representative 3,(4-di)-substituted 1-phosphono-1,3-butadienes. In the diethyl phosphonate series, good yields of purified dienes **1c** and **1d** were obtained, in the form of two geometrical isomers, non separable by column chromatography (Scheme 1, Table 1). In the dibenzyl phosphonate series, the yields of dienes **1e** and **1f** decreased dramatically. HWE reaction is very sensitive to steric hindrance; the presence of an alkyl substituent in position 3/4 of the conjugated aldehyde prevents the attack of bulky dibenzyl phosphonated anion.

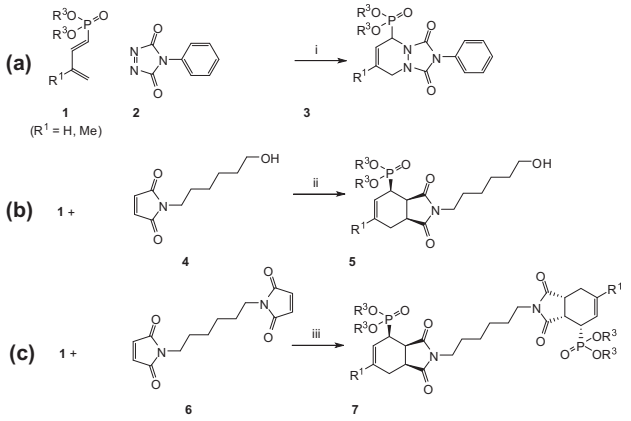
The *E*:*Z* ratio of dienes **1** could be experimentally determined from $^1$H NMR spectra: the major (or exclusive) isomer *E* shows the H-1 and the H-2 protons at 5.42–5.74 ppm and 6.99–7.15 ppm, respectively, while the very minor isomer *Z* presents these protons at 5.72–5.84 ppm and 6.66–6.87 ppm, respectively.

Since the concerted DA cycloaddition proceeds from the *s-cis* conformer of the diene, we have computed the relative energy of *s-cis* and *s-trans* conformers of *E*-**1a**–**d** using DFT methods (Fig. 1). The nature of the phosphonate ester and the presence of substituents at C-3/C-4 do not influence significantly the conformational equilibrium (Table 1). $\Delta E_{rel}$, i.e., $\Delta E_{cis}-\Delta E_{trans}$, was found between 3.3 and 3.8 kcal mol$^{-1}$, suggesting that all these dienes should have a similar DA reactivity under thermal activation.

**Fig. 1.** *s-trans*/*s-cis* equilibrium of (*E*)-**1**.

## 2.2. [4+2] cycloadditions of dienes 1

4-Phenyl-4*H*-1,2,4-triazoline-3,5-dione (**2**) and two *N*-substituted maleimides (**4**[25] and **6**[26]) have been selected as representative dienophiles for the DA reactions with dienes **1** (Scheme 2 and Fig. 2). Cycloadducts could be obtained and purified from dienes **1a**–**d** (Table 2); diene **1e** reacted with **2** only and the corresponding cycloadduct could not be purified. Microwave activation did not improve the yields in all series of experiments.



**Scheme 2.** [4+2] cycloadditions of dienes **1a**–**c** on three representative dienophiles. Conditions (i) DCE, reflux, 1–1 h 30 min; (ii) neat, 120 °C, 6–8 h; (iii) neat, 140 °C, 6–8 h.

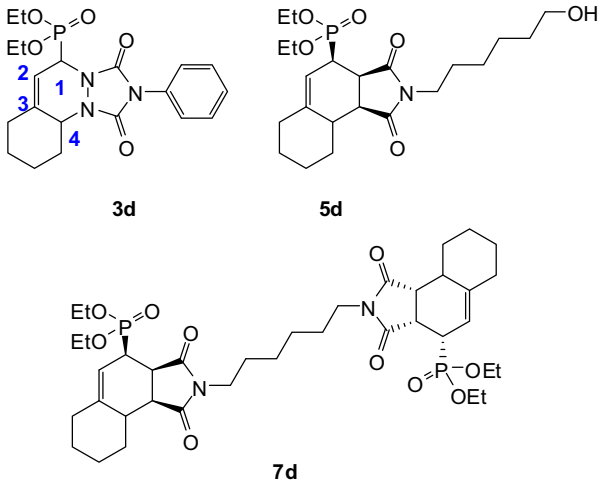


**Fig. 2.** Tricyclic products obtained from diene **1d** cycloadditions.

**Table 2**
Yields of pure cycloadducts **3**, **5** and **7**

| Entry | $R^1$ | $R^2$ | $R^3$ | Cmpd | Yields (%) |
|---|---|---|---|---|---|
| 1 | H | H | Et | **3a** | 83[11] |
| 2 | H | H | Bn | **3b** | 82 |
| 3 | Me | H | Et | **3c** | 52 |
| 4 | $-(CH_2)_4-$ | | Et | **3d** | 53 |
| 5 | H | H | Et | **5a** | 56[11d] |
| 6 | H | H | Bn | **5b** | 50 |
| 7 | Me | H | Et | **5c** | 37 |
| 8 | $-(CH_2)_4-$ | | Et | **5d** | 45 |
| 9 | H | H | Et | **7a** | 16[a,11d] |
| 10 | H | H | Bn | **7b** | 37 |
| 11 | Me | H | Et | **7c** | 34 |
| 12 | $-(CH_2)_4-$ | | Et | **7d** | 17 |

[a] Purification problems.

Based on the isolated yields of cycloadducts **3**, **5**, **7**, the heterodienophile **2** appeared more reactive than the maleimides **4** and **6**. Cycloadducts **3** were formed within 1 h 30 min by heating **2** and **1** in 1,2-dichloroethane at reflux. Cycloadducts **5** and **7** were obtained from neat mixtures of **1** with **4** and **6**, respectively, maintained at 120 °C and 140 °C during 6–8 h. Under these conditions, competition with the diene dimerization occured,[27] leading to very arduous chromatographic purifications.

Unsubstituted dienes **1a** and **1b** reacted similarly (Table 2, entries 1–2, 5–6 and 9–10): the nature of the phosphonate ester ($R^3$=Et, Bn) has no influence on reactivity. The monosubstituted diene **1c** ($R^1$=Me) gave bicyclic adducts with moderate yields (Scheme 2, Table 2, entries 3, 7 and 11), while the disubstituted diene **1d** ($R^1$=$R^2$=$-(CH_2)_4-$) led to tricyclic adducts with moderate to low yields (Fig. 2, Table 2, entries 4, 8 and 12). By following the cycloaddition reactions of diene **1c**,**d** by NMR spectroscopy, it was clear that the *Z*-isomers did not react. This observation could partially explain the lower yields of cycloadducts collected with substituted dienes, combined with purification difficulties.

The all-*cis* relative stereochemistry of the cycloadducts **5** and **7** could be determined from typical coupling constant values in $^1$H NMR. For cycloadduct **5b** as an example, $^3J_{6,P}$=21.1 Hz, $^3J_{1,6}$=5.8 Hz and $^3J_{5,6}$=8.9 Hz correspond to dihedral angles of 130° ($H_6-C_6-C_1-P$), 49° ($H_1-C_1-C_6-H_6$) and 37° ($H_6-C_6-C_5-H_5$), respectively. Compounds **5** are thus obtained as racemic mixtures of single diastereoisomers. In principle, compounds **7** are racemic mixtures of two diastereoisomers. Despite a lot of experimental conditions tested, HPLC traces did not reveal peaks splitting. The separation of diastereoisomers **7** was not possible.

Only the tricycle **3d** could be crystallized for single crystal X-ray diffraction analysis. As shown in Fig. 3, the triazole cycle is planar (rms error 0.004 Å) making an angle of 44.1(2)° with the attached benzene ring. The heterocyclic six-membered ring is in an envelope (*E*) form (Cremer and Pople: puckering amplitude ($Q$)= 0.434(4) Å, $\theta$=57.3(7)°, $\phi$=54.5(7)°) with the nitrogen atom at the junction displaced from the plane on the opposite side of the phosphorous atom, which is in the axial position. The cyclohexane moiety is in a chair conformation (Cremer and Pople: puckering amplitude ($Q$)=0.586(6) Å, $\theta$=4.7(6)°, $\phi$=282(8)°). The rms deviations between the different molecules in the asymmetric unit (between 0.0955 Å and 0.6090 Å, see Table 2 in Supplementary data for more details), means that the molecules display the same geometrical features. The largest deviations are thus found around the $OCH_2CH_3$ groups attached to the phosphorus atom, which show disorder in half of the molecules. Looking closely at the crystal packing one could observe compound **3d** to crystallize as a loose ensemble/dimer of two identical enantiomers, connected by a pseudo-2-fold axis; the driving force for this arrangement is believed to be the optimal shape packing of this pair. This arrangement is also believed to cause the high $Z'$=6 value. Characteristic bond and angle information are given as Supplementary data.

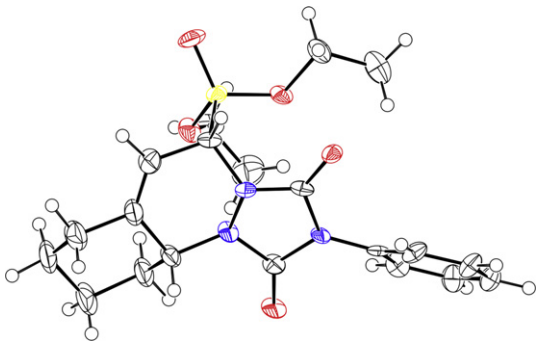


**Fig. 3.** Ortep representation of the cycloadduct **3d**, showing thermal displacement ellipsoides at the 50% probability level.

By hydrogenation in the presence of Pd/C catalyst, the dibenzyl phosphonate group of cycloadducts **3b**, **5b** and **7b** was quantitatively deprotected, giving access to the phosphonic acid derivatives **8**, **9** and **10** (Fig. 4). As expected, the C=C double bond was also reduced.

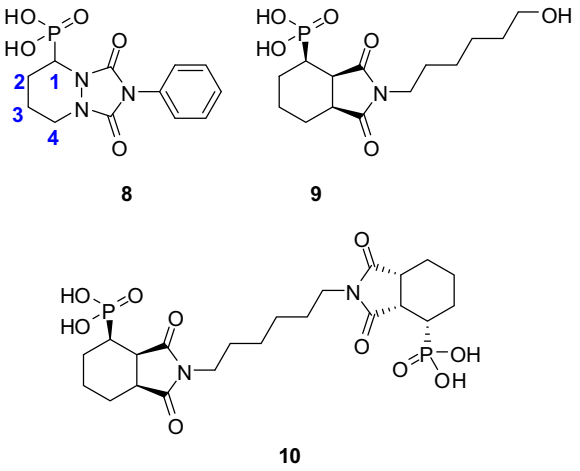



**Fig. 4.** Phosphonic acid derivatives obtained by hydrogenolysis of dibenzyl phosphonate precursors **3b**, **5b** and **7b**.

### 2.3. Metal coordination study

The dimer-like cycloadducts **7a**, **7c** and **7d** (L) have been tested for coordination with di- ($Ca^{2+}$, $Co^{2+}$, $Fe^{2+}$, $Mg^{2+}$, $Ni^{2+}$, $Zn^{2+}$) and trivalent ($Eu^{3+}$, $Gd^{3+}$, $La^{3+}$, $Lu^{3+}$) cations (M) in solution, using ESI-HRMS as the analytical tool according to a procedure described in precedent works.[11] All the complexes identified by ESI-HRMS were monocharged and possessed the [L:M], i.e., one ligand for one metal cation, stoichiometry. The coordination sphere of metallic cations was completed with one or two poorly coordinating counter-anion(s), that is, one perchlorate anion in the case of divalent metal and two nitrate anions in the case of trivalent metal. The tables of identified complexes (experimental and calculated masses, atomic compositions, and relative abundances) are given in Supplementary data (Tables 4–6 in Supplementary data S64–S65). The structures of the coordination complexes are confirmed by the isotopic distributions, as illustrated in Fig. 5 with the zinc (part A) and gadolinium (part B) complexes of **7a**. The observed patterns are identical to the calculated ones.

The ratios of complexes $[LM(II)ClO_4]^+$ and $[LM(III)(NO_3)_2]^+$ versus the respective free metal salts gave a qualitative idea of the coordination capacity of the ligands **7**. We found the following order: **7a**>**7c**>**7d**, meaning that the steric hindrance is unfavourable to the coordination. All the $M^{3+}$ cations are more efficiently coordinated than $M^{2+}$ cations, and amongst the $M^{2+}$ cations, complexes with $Zn^{2+}$, $Co^{2+}$ and $Fe^{2+}$ are favoured. A possible structure of [L:M] complex of the ligand **7a** with gadolinium is depicted in Fig. 6.

## 3. Conclusion

1-Phosphono-3(4-di)-substituted-1,3-butadienes **1a**–**f** were prepared by Horner–Wadsworth–Emmons (HWE) reaction between dialkyl methylenediphosphonate and α,β-unsaturated aldehydes with good to moderate yields depending on the nature of the phosphonate ester. Dibenzyl phosphonate dienes (**1b**, **1e**, **1f**), which are the most useful reagents in the context of DA cycloadducts deprotection, were less efficiently synthesized than the corresponding diethyl phosphonates (**1a**, **1c**, **1d**). The HWE reaction appears sensitive to the steric bulkiness of both partners, the diphosphonate anion and the α,β-unsaturated aldehyde. The instability of benzyl esters under strong basic conditions (NaH) could also handicap the HWE condensation in the dibenzyl phosphonate series. Diels–Alder (DA) reaction between these dienes **1a**–**e** and reactive dienophiles **2**, **4** and **6** gave access to original bicyclic and

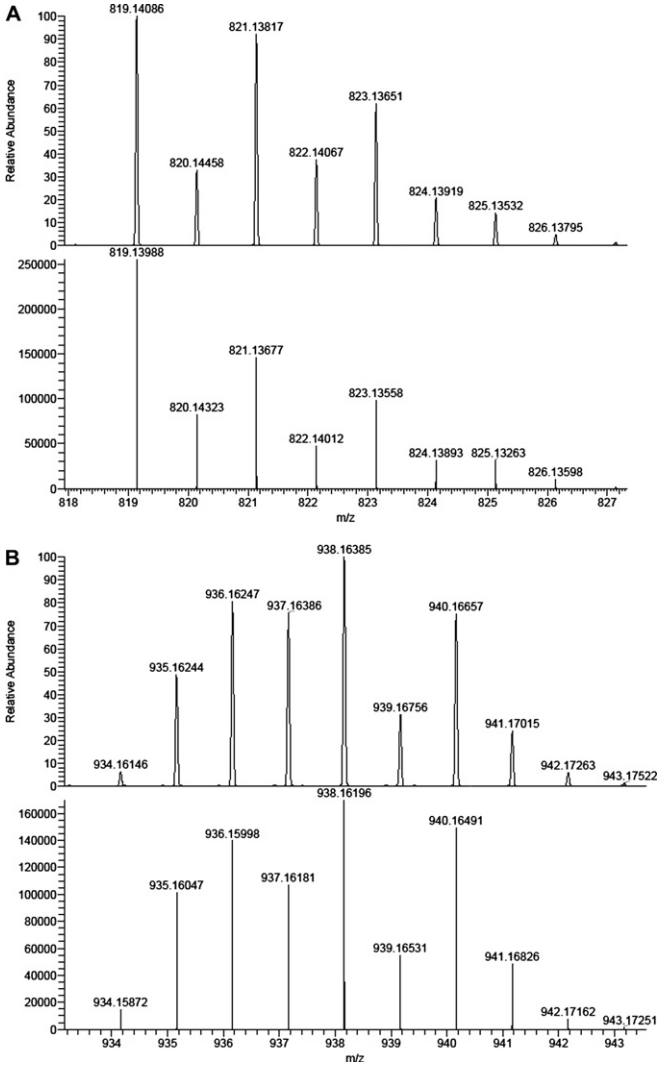



**Fig. 5.** Experimental (at the top) and theoretical (at the bottom) isotopic distribution of: part A: [Zn: **7a**] coordination complex (with atomic composition: $C_{30}H_{46}O_{14}N_2ClP_2Zn$). Part B: [Gd: **7a**] coordination complex (with atomic composition: $C_{30}H_{46}O_{16}N_4GdP_2$).

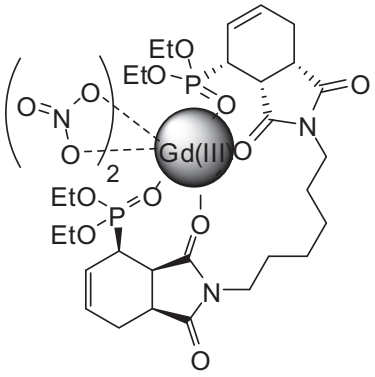



**Fig. 6.** Postulated structure of [**7a**: Gd] coordination complex.

tricyclic cycloadducts **3**, **5** and **7**. In the case of *N*-substituted maleimide dienophiles, the bicyclic structures present a half-cage shape due to the all-*cis* relative stereochemistry of the substituents, resulting from the cycloaddition mechanism (*cis*-stereospecificity, *ortho* and *endo* rules of DA reaction). The novel

phosphonic derivatives **8**–**10** were obtained in two steps from diene **1b**: a Diels–Alder reaction followed by the catalytic hydrogenolysis of dibenzyl phosphonates. The synthesis of pure phosphonic acids remains a difficult task; in spite of moderate yields of final products, the use of dibenzyl phosphonodiene seems to be the best approach. The coordination properties of the ethyl phosphonates **7** towards $M^{2+}$ and $M^{3+}$ cations have been demonstrated in solution.

## 4. Experimental section

### 4.1. Materials and methods

Experiments were performed under an atmosphere of dry argon. The chemicals purchased from Acros Organic, Alfa Aesar and Sigma–Aldrich were of reagent grade and used without purification. TLC analyses were performed on aluminium plates coated with silica gel Merck 60 F-254 and flash column chromatographies over silica gel (230–400 mesh). Visualization of TLC plates was performed under a UV lamp (254 nm), and using *p*-anisaldehyde or $KMnO_4$. Analytical grade solvents were used for reactions and solvents used for column chromatographies were technical solvents distilled before use. Reactions under microwave heating were conducted in sealed tubes using MicroSYNTH equipment (Milestone Srl). NMR spectra were recorded on a Bruker AVANCE II 300 spectrometer operating at 300 MHz for $^1$H, 75 MHz for $^{13}$C and 121 MHz for $^{31}$P and on a Bruker AVANCE II 500 spectrometer operating at 500 MHz for $^1$H, 125 MHz for $^{13}$C and 202 MHz for $^{31}$P. Chemical shifts were reported in parts per million from tetramethylsilane as the internal standard ($\delta$=0.0 ppm) for the $^1$H spectra. The internal standard was deuterated chloroform for the $^{13}$C spectra ($\delta$=77.16 ppm). $^{31}$P downfield shifts ($\delta$) were expressed with a positive sign, using 85% $H_3PO_4$ in $H_2O$ as external standard. Spectra were reported as follows: chemical shift ($\delta$ ppm), multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet), coupling constants (Hertz), integration, and assignment. The atom numbering used for NMR descriptions is given in Scheme 2; the dienyl protons were assigned as the protons number 1–4 because this motif was common for all the cycloadducts. Melting points (mp) were determined on a Büchi B-540 apparatus calibrated with caffeine, vanillin and phenacetin. Infrared spectra (IR) were recorded by transmittance with a Schimadzu FTIR-8400S equipment and the absorption bands are reported in $cm^{-1}$. Products were analyzed as thin films deposited on a Se–Zn crystal by evaporation from $CHCl_3$ solutions. The intensity of peaks was noted by (w), (m) and (s), respectively, for weak, medium and strong. Mass spectra (MS) were recorded with a LCQ Finnigan MAT and the masses are reported in Dalton. High Resolution Mass Spectrometry analyses (MALDI-TOF HRMS) were carried out at the University College London using Waters Maldi microMX equipment with an α-cyano-4-hydroxycinnamic acid matrix.

### 4.2. General procedure for the preparation of dienes 1

To a suspension of sodium hydride (1.2 equiv) in dry toluene (6.8 mL/mmol) was added tetraethyl methylenediphosphonate ($R^3$=Et) or tetrabenzyl methylenediphosphonate ($R^3$=Bn) (1.2 equiv) at room temperature. After about 15 min (end of gaseous dihydrogen evolution), a solution of aldehyde (acrolein, methacrylaldehyde or 1-cyclohexen-1-carboxyaldehyde) (1 equiv) in dry toluene (0.1 mL/mmol of acrolein, 4.0 mL/mmol of methacrylaldehyde and 1.4 mL/mmol of 1-cyclohexen-1-carboxyaldehyde) was added dropwise to the solution of sodium salt of tetraalkyl methylenediphosphonate and the mixture was stirred for two additional hours. After addition of water (2–3 mL/mmol), the aqueous layer was extracted with dichloromethane (4×7 mL, $R^3$=Bn) or ethyl acetate (4×5 mL, $R^3$=Et), and the combined organic portions were dried over magnesium sulfate. Filtration and concentration under reduced pressure gave the crude diene **1**, which is purified by silica gel chromatography with ethyl acetate.

*4.2.1. 1-Diethylphosphono-1,3-butadiene (**1a**).* NaH (60%, dispersed in oil, 28 mg, 0.694 mmol), tetraethyl methylenediphosphonate (0.20 g, 0.694 mmol) in toluene (4.7 mL) and acrolein (41 μL, 32 mg, 0.578 mmol) in toluene (2.3 mL) furnished the title compound as yellowish oil (86 mg, 78%). The spectral data were in agreement with the literature.[10,19]

*4.2.2. 1-Dibenzylphosphono-1,3-butadiene (**1b**).* NaH (60% oil dispersed, 0.15 g, 3.65 mmol) tetrabenzyl methylenediphosphonate (1.96 g, 3.65 mmol) in toluene (8 mL), and acrolein (213 μL, 0.17 g, 3.04 mmol) in toluene (8 mL) furnished the title compound as a yellowish oil (0.49 g, 51%). $R_f$ [silica gel, toluene/ethyl acetate (5:2)]=0.6. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 7.33 (m, CH(Ph), 10H), 7.07 (ddd, $^3J_{2,P}$=21.2 Hz, $^3J_{1,2}$=16.9 Hz and $^3J_{2,3}$=10.6 Hz, C(2)–H, 1H), 6.36 (dt, $^3J_{3,4a}$=17.2 Hz and $^3J_{2,3}$=$^3J_{3,4b}$=10.3 Hz, C(3)–H, 1H), 5.72 (dd, $^2J_{1,P}$=19.1 Hz and $^3J_{1,2}$=17.0 Hz, C(1)–H, 1H), 5.50 (d, $^3J_{3,4a}$=17.0 Hz, C(4)–Ha, 1H), 5.43 (d, $^3J_{3,4b}$=9.9 Hz, C(4)–Hb, 1H), 5.03 (d, $^3J_{H,P}$=8.0 Hz, $PO(OCH_2Ph)_2$, 4H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 149.2 (d, $^2J_{2,P}$=5.8 Hz, C(2)), 136.3 (d, $^3J_{C,P}$=6.6 Hz, Cq(Ph)), 135.7 (d, $^3J_{3,P}$=27.2 Hz, C(3)), 128.6 (s, CH(Ph)), 128.5 (s, CH(Ph)), 128.0 (s, CH(Ph)), 125.3 (s, C(4)), 117.7 (d, $^1J_{1,P}$=190.8 Hz, C(1)), 67.4 (d, $^2J_{C,P}$=5.4 Hz, $OCH_2$). For other data, see Ref. 21.

*4.2.3. 1-Diethylphosphono-3-methyl-1,3-butadiene (**1c**).* NaH (60%, dispersed in oil, 28 mg, 0.693 mmol), tetraethyl methylenediphosphonate (200 mg, 0.693 mmol) in toluene (4.7 mL) and methacrylaldehyde (90%, 54 μL, 41 mg, 0.577 mmol) in toluene (2.3 mL) furnished the title compound as a mixture of stereoisomers (*E*:*Z*=87:13) not separated by column chromatography, as a yellow oil (93.3 mg, 79%). $R_f$ [silica gel, ethyl acetate]=0.5. IR ($\nu$, $cm^{-1}$): 3031 (m), 2923 (m), 1623 (w, C=C), 1591 (m, C=C), 1497 (w), 1456 (m, C=C), 1377 (m), 1231 (s, P=O), 1217 (s, P=O), 1014 (s, P–O), 991 (s, P–O), 735 (s), 696 (s). HRMS (MALDI-TOF, positive mode) *m*/*z* (%) [M+H]: calcd for $C_9H_{18}O_3P$: 205.0994, found: 205.0987 (37); [M–$CH_2$=$CH_2$]: 177.0644 (19); [M–2$CH_2$=$CH_2$]: 149.0318 (100); [M–$CH_2$=$CH_2$–$H_2O$]: 131.0250 (17).

*E*-Isomer (major): $^1$H NMR (500 MHz, $CDCl_3$) $\delta$: 7.18 (dd, $^3J_{2,P}$=22.0 Hz and $^3J_{1,2}$=17.3 Hz, C(2)–H, 1H), 5.68 (t, $^2J_{1,P}$=$^3J_{1,2}$=17.9 Hz, C(1)–H, 1H), 5.34 (m, C(4)–H, 1H), 5.32 (s, C(4)–H, 1H), 4.12–4.07 (m, $PO(OCH_2CH_3)_2$, 4H), 1.88 (s, $CH_3$, 3H), 1.34 (t, $^3J_{H,H}$=7.1 Hz, $PO(OCH_2CH_3)_2$, 6H). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$: 151.2 (d, $^2J_{2,P}$=5.9 Hz, C(2)), 140.8 (d, $^3J_{3,P}$=23.6 Hz, C(3)), 123.8 (s, C(4)), 124.7 (d, $^1J_{1,P}$=189.6 Hz, C(1)), 61.8 (d, $^2J_{C,P}$=5.2 Hz, $PO(OCH_2CH_3)_2$), 17.8 (s, $CH_3$), 16.4 (d, $^3J_{C,P}$=6.3 Hz, $PO(OCH_2CH_3)_2$). $^{31}$P NMR (202 MHz, $CDCl_3$) $\delta$: 20.49.

*Z*-Isomer (minor): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 6.95–6.79 (m, C(4)–H, 1H), 6.66 (dd, $^3J_{2,P}$=22.8 Hz and $^3J_{1,2}$=17.1 Hz, C(2)–H, 1H), 6.16 (s, C(4)–H, 1H), 5.72 (dd, $^2J_{1,P}$=20.4 Hz and $^3J_{1,2}$=17.1 Hz, C(1)–H, 1H), 4.12–4.07 (m, $PO(OCH_2CH_3)_2$, 4H), 1.88 (s, $CH_3$, 3H), 1.34 (t, $^3J_{H,H}$=7.1 Hz, $PO(OCH_2CH_3)_2$, 6H). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$: 155.0 (d, $^2J_{2,P}$=4.8 Hz, C(2)), 136.4 (s, C(4)), 115.2 (d, $^1J_{1,P}$=185.4 Hz, C(1)), 107.8 (s, C(3)), 61.8 (d, $^2J_{C,P}$=5.2 Hz, $PO(OCH_2CH_3)_2$), 17.8 (s, $CH_3$), 16.4 (d, $^3J_{C,P}$=6.3 Hz, $PO(OCH_2CH_3)_2$). $^{31}$P NMR (202 MHz, $CDCl_3$) $\delta$: 19.82.

*4.2.4. Diethyl-2-cyclohexenylvinylphosphonate (**1d**).* NaH (60%, dispersed in oil, 87 mg, 2.178 mmol), tetraethyl methylenediphosphonate (1.17 g, 2.178 mmol) in toluene (5.0 mL) and 1-cyclohexen-1-carboxyaldehyde (207 μL, 0.20 g, 1.815 mmol) in toluene (2.5 mL) furnished the title compound as a mixture of

stereoisomers (*E*:*Z*=97:3), not separated by column chromatography, as a yellowish oil (362 mg, 82%). $R_f$ [silica gel, ethyl acetate]=0.7. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$: 6.99 (dd, $^3J_{2,P}$=22.9 Hz and $^3J_{1,2}$=17.4 Hz, C(2)–H, 1H), 6.03 (m, C(4)–H, 1H), 5.42 (t, $^2J_{1,P}$=$^3J_{1,2}$=17.0 Hz, C(1)–H, 1H), 4.00–3.96 (m, PO(O*CH*$_2$CH$_3$)$_2$, 4H), 2.13–2.06 (m, CH(4)–*CH*$_2$ or C(3)–*CH*$_2$, 2H), 2.06–1.98 (m, C(3)–*CH*$_2$ or CH(4)–*CH*$_2$, 2H), 1.63–1.55 (m, CH(4)–CH$_2$–*CH*$_2$ or C(3)–CH$_2$–*CH*$_2$, 2H), 1.55–1.47 (m, C(3)–CH$_2$–*CH*$_2$ or CH(4)–CH$_2$–*CH*$_2$, 2H),1.25–1.20 (m, PO(OCH$_2$*CH*$_3$)$_2$, 6H). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$: 152.3 (d, $^2J_{2,P}$=6.1 Hz, C(2)), 138.2 (s, C(4)), 135.5 (d, $^3J_{3,P}$=23.4 Hz, C(3)), 109.2 (d, $^1J_{1,P}$=190.8 Hz, C(1)), 61.6 (d, $^2J$=5.2 Hz, PO(O*CH*$_2$CH$_3$)$_2$), 26.2 (s, CH(4)–*CH*$_2$ or C(3)–*CH*$_2$), 23.8 (s, C(3)–*CH*$_2$ or CH(4)–*CH*$_2$), 22.0 (s, CH(4)–CH$_2$–*CH*$_2$ or C(3)–CH$_2$–*CH*$_2$), 21.9 (s, C(3)–CH$_2$–*CH*$_2$ or CH(4)–CH$_2$–*CH*$_2$), 16.3 (d, $^3J$=5.9 Hz, PO(OCH$_2$*CH*$_3$)$_2$). $^{31}$P NMR (202 MHz, $CDCl_3$) $\delta$: 21.97. IR ($\nu$, cm$^{-1}$): 2941 (m), 1632 (s, C=C), 1595 (s, C=C), 1479 (w), 1444 (w), 1393 (m), 1246 (s, P=O), 1211 (m, P=O), 1013 (s, P–O), 945 (s, P–O), 849 (s), 793 (s), 733 (s). HRMS (MALDI-TOF, positive mode) *m*/*z* (%) [M+H]: calcd for $C_{12}H_{22}O_3P$: 245.1307, found: 245.1313 (68); [M–CH$_3$]: 230.0955 (64); [M+H–CH$_2$=CH$_2$]: 217.1001 (34); [M+H–2CH$_2$=CH$_2$]: 189.0696 (100); [M+H–2CH$_2$=CH$_2$–H$_2$O]: 171.0580 (10).

*4.2.5. 1-Dibenzyl-3-methyl-1,3-butadiene (**1e**).* NaH (60%, dispersed in oil, 18 mg, 0.446 mmol), tetrabenzyl methylenediphosphonate (0.239 g, 0.446 mmol) in toluene (3 mL) and methacrylaldehyde (90%, 34 μL, 0.026 g, 0.371 mmol) in toluene (1,5 mL) afforded the title compound as a mixture of stereoisomer (*E*:*Z*=87:13), not separated by column chromatography, as a yellow oil (23 mg, 19%). $R_f$ [silica gel, toluene/ethyl acetate, 5:2]=0.3. IR ($\nu$, cm$^{-1}$): 2980 (m), 2906 (m), 1626 (w, C=C), 1591 (m, C=C), 1479 (w, C=C), 1442 (m, C=C), 1392 (m), 1294 (w), 1244 (s, P=O), 1211 (s, P=O), 1163 (m), 1013 (s, P–O), 964 (s, P–O), 854 (s), 829 (m), 752 (s), 696 (s). HRMS (MALDI-TOF, positive mode) *m*/*z* (%) [M+Na]: calcd for $C_{19}H_{21}O_3PNa$: 351.1126, found: 351.1115 (100); [M+H]: 329.1308 (48).

*E*-Isomer (major): $^1$H NMR (500 MHz, $CDCl_3$) $\delta$: 7.31–7.37 (m, CH(Ph), 10H), 7.15 (dd, $^3J_{2,P}$=22.4 Hz and $^3J_{1,2}$=17.3 Hz, C(2)–H, 1H), 5.63 (dd, $^2J_{1,P}$=18.9 Hz and $^3J_{1,2}$=17.3 Hz, C(1)–H, 1H), 5.31 (m, C(4)–H, 1H), 5.28 (s, C(4)–H′, 1H), 5.05 (d, $^3J_{H,P}$=8.2 Hz, PO(O*CH*$_2$Ph)$_2$, 4H), 1.79 (s, CH$_3$, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$: 153.95 (d, $^2J_{2,P}$=6.0 Hz, C(2)), 140.73 (d, $^3J_{3,P}$=24.1 Hz, C(3)), 136.29 (d, $^3J_{C,P}$=11.8 Hz, Cq(Ph)), 128.55 (s, CH(Ph)), 128.37 (s, CH(Ph)), 127.92 (s, CH(Ph)), 124.03 (s, C(4)), 113.88 (d, $^1J_{1,P}$=190.5 Hz, C(1)), 67.33 (d, $^2J_{C,P}$=5.4 Hz, PO(O*CH*$_2$Ph)$_2$), 17.63 (s, CH$_3$). $^{31}$P NMR (202 MHz, $CDCl_3$) $\delta$: 21.53.

*Z*-Isomer (minor): $^1$H NMR (500 MHz, $CDCl_3$) $\delta$: 7.31–7.37 (m, CH(Ph), 10H), 6.87 (ddt, $^3J_{2,P}$=28.3 Hz, $^3J_{1,2}$=17.0 Hz and $^4J_{2,4}$=5.7 Hz, C(2)–H, 1H), 5.84 (dd, $^2J_{1,P}$=20.9 Hz and $^3J_{1,2}$=17.1 Hz, C(1)–H, 1H), 6.66 (dd, $^2J_{4,4'}$=23.2 Hz and $^4J_{2,4}$=1.7 Hz, C(4)–H, 1H), 6.12 (dd, $^4J_{4,H}$=2.8 Hz and $^4J_{2,4}$=1.6 Hz, C(4)–H′, 1H), 5.05 (d, $^3J_{H,P}$=8.2 Hz, PO(O*CH*$_2$Ph)$_2$, 4H), 1.79 (s, CH$_3$, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$: 153.95 (d, $^2J_{2,P}$=6.0 Hz, C(2)), 140.73 (d, $^3J_{3,P}$=24.1 Hz, C(3)), 136.29 (d, $^3J_{C,P}$=11.8 Hz, Cq(Ph)), 128.55 (s, CH(Ph)), 128.37 (s, CH(Ph)), 127.92 (s, CH(Ph)), 124.03 (s, C(4)), 113.88 (d, $^1J_{1,P}$=190.5 Hz, C(1)), 67.33 (d, $^2J_{C,P}$=5.4 Hz, PO(O*CH*$_2$Ph)$_2$), 17.63 (s, CH$_3$). $^{31}$P NMR (121 MHz, $CDCl_3$) $\delta$: 20.85.

### 4.3. General procedure for the Diels–Alder reaction with N=N dienophile 2

A solution of 4-phenyl-4*H*-1,2,4-triazole-3,5-dione **2** (1 equiv) and diene **1b**, **1c** or **1d** (1 equiv), in 1,2-dichloroethane (4.6 mL/mmol) was stirred under vigourous reflux for 1 h 30 min (R$^3$=Bn) or 1 h (R$^3$=Et). The reaction mixture was then concentrated under reduced pressure and directly purified by column chromatography on silica gel. The reaction of **2** and diene **1a**, giving the cycloadduct **3a**, has been described previously.[11a]

*4.3.1. Dibenzyl 2,3,5,8-tetrahydro-1,3-dioxo-2-phenyl-1H-[1,2,4]triazol-[1,2-a]pyridazin-5-yl-5-phosphonate (**3b**).* Diene **1b** (123.0 mg, 0.391 mmol) and 4-phenyl-4*H*-1,2,4-triazole-3,5-dione **2** (68.5 mg, 0.391 mmol) in 1,2-dichloroethane (1.8 mL) furnished the title compound as a white solid (156 mg, 82%). $R_f$ [silica gel, ethyl acetate]=0.4. Mp (°C): 124.1. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$: 7.43–7.35 (m, CH(Ph), 5H), 7.31 (br s, CH(Ph), 10H), 6.05 (ddq, $^3J_{2,3}$=10.1 Hz, $^3J_{3,4}$=6.0 Hz and $^3J_{3,4'}$=$^4J_{3,P}$=$^4J_{1,3}$=2.4 Hz, C(3)–H, 1H), 5.97 (dddd, $^3J_{2,3}$=10.4 Hz, $^4J_{2,P}$=6.9 Hz, $^3J_{1,2}$=3.7 Hz and $^4J_{2,4}$=1.8 Hz, C(2)–H, 1H), 5.08 (dd, $^3J_{H,P}$=8.0 Hz and $^4J_{H,H}$=1.7 Hz, *CH*$_2$–Ph, 2H), 5.06 (t, $^3J_{H,P}$=$^4J_{H,H}$=8.8 Hz, *CH*$_2$–Ph, 2H), 4.99 (dddt, $^2J_{1,P}$=14.7 Hz, $^3J_{1,2}$=4.9 Hz, $^4J_{1,3}$=2.3 Hz and $^5J_{1,4}$=$^5J_{1,4'}$=1.6 Hz, C(1)–H, 1H), 4.18 (dddd, $^2J_{4,4'}$=16.9 Hz, $^3J_{3,4}$=6.0 Hz, $^5J_{4,P}$=2.5 Hz and $^4J_{2,4}$=1.6 Hz, C(4)–H, 1H), 3.98 (ddq, $^2J_{4,4'}$=16.9 Hz, $^3J_{3,4'}$=2.5 Hz and $^4J_{4',P}$=$^4J_{2,4'}$=$^5J_{1,4}$=1.6 Hz, C(4)–H′, 1H). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$: 153.0 (s, C=O), 151.1 (s, C=O), 135.6 (d, $^3J_{C,P}$=5.7 Hz, Cq(Ph)), 131.1 (s, Cq(Ph)), 129.1 (s, CH(Ph)), 128.7 (s, CH(Ph)), 128.7 (d, $^5J_{C,P}$=1.9 Hz, CH(Ph)), 128.3 (d, $^4J_{C,P}$=5.2 Hz, CH(Ph)), 128.2 (s, CH(Ph)), 128.2 (s, CH(Ph)), 125.1 (d, $^3J_{3,P}$=10.0 Hz, C(3)), 118.9 (d, $^2J_{2,P}$=5.2 Hz, C(2)), 68.7 (d, $^2J_{C,P}$=7.1 Hz, *CH*$_2$–Ph), 68.6 (d, $^2J_{C,P}$=6.4 Hz, *CH*$_2$–Ph), 51.6 (d, $^1J_{1,P}$=139.1 Hz, C(1)), 44.2 (d, $^4J_{4,P}$=3.1 Hz, C(4)). $^{31}$P NMR (202 MHz, $CDCl_3$) $\delta$: 18.90. IR ($\nu$, cm$^{-1}$): 3100–2800 (large band, w, OH), 2000–1665 (w, Ph), 1778 (s, C=O), 1715 (s, C=O), 1693 (s, C=C (Ph)), 1599 (m, CH=CH), 1502 (s), 1456 (m), 1410 (s), 1298 (m), 1245 (m, P=O), 1138 (m), 1030 (s, P–O), 1007 (s), 993 (s, P–O), 914 (m), 873 (m), 848 (m), 736 (s), 721 (s). HRMS (MALDI-TOF, positive mode) *m*/*z* (%) [M+Na]: calcd for $C_{26}H_{24}N_3O_5PNa$: 512.1351, found: 512.1340 (100).

*4.3.2. Diethyl (1a, 2a, 6, 9)-tetrahydro-8-methyl -4-phenyl-1,2,4]triazolo-[**1a**, 2-a]-pyridazinyl-6-phosphonate-3,5-dione (**3c**).* 4-Phenyl-4*H*-1,2,4-triazole-3,5-dione **2** (0.191 g, 1.09 mmol) and diene **1c** (0.223 g, 1.09 mmol) in 1,2-dichloroethane (5.0 mL) afforded the title compound as a yellow oil (0.216 g, 52%). $R_f$ [silica gel, ethyl acetate]=0.4. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$: 7.53 (dd, $^3J_{H,H}$=8.3 Hz and $^4J_{H,H}$=1.2 Hz, CH(Ph), 2H), 7.47 (tt, $^3J_{H,H}$=7.9 Hz and $^4J_{H,H}$=1.3 Hz, CH(Ph), 2H), 7.37 (td, $^3J_{H,H}$=7.3 Hz and $^4J_{H,H}$=1.3 Hz, CH(Ph), 1H), 5.80 (br s, C(2)–H, 1H), 4.90 (dddq, $^2J_{4,4'}$=13.7 Hz, $^5J_{4,P}$=3.9 Hz, $^4J_{2,4}$=2.6 Hz and $^4J_{4,H}$=1.3 Hz, C(4)–H, 1H), 4.23–4.21 (m, C(1)–H, 1H), 4.21–4.11 (m, PO(O*CH*$_2$CH$_3$)$_2$, 4H), 3.97–3.93 (m, C(4)–H′, 1H), 1.90 (d, $^4J_{H,H}$=1.3 Hz, CH$_3$), 1.31 (br t, $^3J$=6.9 Hz, PO(OCH$_2$*CH*$_3$)$_2$, 6H). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$: 152.5 (s, C=O), 150.5 (s, C=O), 131.2 (s, Cq(Ph)), 131.1 (d, $^3J_{3,P}$=10.1 Hz, C(3)), 129.0 (s, CH(Ph)), 128.0 (s, CH(Ph)), 125.4 (s, CH(Ph)), 113.2 (d, $^2J_{2,P}$=5.1 Hz, C(2)), 63.2 (d, $^2J_{C,P}$=7.1 Hz, PO(O*CH*$_2$CH$_3$)$_2$), 63.0 (d, $^2J_{C,P}$=6.4 Hz, PO(O*CH*$_2$CH$_3$)$_2$), 50.7 (d, $^1J_{1,P}$=141.1 Hz, C(1)), 47.1 (d, $^4J_{4,P}$=2.6 Hz, C(4)), 20.1 (s, CH$_3$), 16.3 (d, $^3J_{C,P}$=5.6, PO(OCH$_2$*CH*$_3$)$_2$), 16.2 (d, $^3J_{C,P}$=5.8 Hz, PO(OCH$_2$*CH*$_3$)$_2$). $^{31}$P NMR (202 MHz, $CDCl_3$) $\delta$: 18.32. IR ($\nu$, cm$^{-1}$): 2979 (w), 1778 (s, C=O), 1699 (s, C=O), 1599 (w), 1502 (s), 1407 (s), 1286 (s), 1252 (s, P=O), 1161 (m), 1138 (s), 1007 (s, P–O), 951 (s, P–O), 914 (s), 852 (m), 766 (s), 714 (s), 690 (s) HRMS (MALDI-TOF, positive mode) *m*/*z* (%) [M+Na]: calcd for $C_{17}H_{22}N_3O_5PNa$: 402.1195, found: 402.1182 (100); [M+H]: 380.1349 (14); [M–PO(OEt)$_2$]: 242.0930 (45).

*4.3.3. Diethyl-2,3,5,7,8,9,10,10a-octahydro-1,3-dioxo-2-phenyl-1H-[1,2,4]triazolo[1,2a]cinnolin-5-yl-phosphonate (**3d**).* 4-Phenyl-4*H*-1,2,4-triazole-3,5-dione **2** (0.124 g, 0.71 mmol) and diene **1d** (0.174 g, 0.71 mmol) in 1,2-dichloroethane (3.3 mL) afforded the title compound as white needles (0.158 g, 53%). $R_f$ [silica gel, ethyl acetate]=0.4. Mp (°C): 103.3–104.4. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$: 7.52 (br d, $^3J_{H,H}$=8.1 Hz, CH(Ph), 1H), 7.46 (br t, $^3J_{H,H}$=7.9 Hz, CH(Ph), 1H), 7.36 (td, $^3J_{H,H}$=7.3 Hz and $^4J_{H,H}$=1.2 Hz, CH(Ph), 2H), 5.77 (dt,

$^{3}J_{1,2}$=5.4 Hz and $^{3}J_{2,P}$=$^{4}J_{2,H}$=1.7 Hz, C(2)–H, 1H), 4.91 (ddt, $^{1}J_{1,P}$=14.6 Hz, $^{3}J_{1,2}$=5.1 Hz and $^{5}J_{1,H}$=2.5 Hz, C(1)–H, 1H), 4.22 (m, PO(O*CH*$_2$CH$_3$)$_2$, 2H), 4.20 (m, PO(O*CH*$_2$CH$_3$)$_2$, 2H), 4.17 (dtd, $^{3}J_{H,4}$=14.1 Hz, $^{4}J_{H,4}$=7.0 Hz and $^{4}J_{2,4}$=4.1 Hz, C(4), 1H), 3.00 (dq, $^{3}J_{H,H}$=11.8 Hz and $^{3}J_{H,H}$=$^{4}J_{H,H}$=2.3 Hz, C(4)–*CH*$_2$, 1H), 2.51 (dt, $^{2}J_{H,H}$=13.8 Hz and $^{3}J_{H,H}$=1.7 Hz, C(3)–*CH*$_2$, 1H), 2.08 (dq, $^{2}J_{H,H}$=13.6 Hz and $^{3}J_{H,H}$=$^{4}J_{H,H}$=6.0 Hz, C(3)–*CH*$_2$, 1H), 1.91–1.84 (m, C(3)–CH$_2$–*CH*$_2$, 2H), 1.62 (qd, $^{2}J_{H,H}$=12.1 Hz and $^{3}J_{H,H}$=2.4 Hz, C(4)–CH$_2$–*CH*$_2$, 1H), 1.55 (qt, $^{2}J_{H,H}$=13.5 Hz and $^{3}J_{H,H}$=2.9 Hz, C(4)–CH$_2$–*CH*$_2$, 1H), 1.37 (qt, $^{2}J_{H,H}$=13.4 Hz and $^{3}J_{H,H}$=$^{4}J_{H,H}$=4.1 Hz, C(4)–*CH*$_2$, 1H), 1.34 (t, $^{3}J_{H,H}$=7.6 Hz, PO(OCH$_2$*CH*$_3$)$_2$, 3H), 1.33 (t, $^{3}J_{H,H}$=7.8 Hz, PO(OCH$_2$*CH*$_3$)$_2$, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 153.4 (s, C=O), 149.2 (s, C=O), 138.5 (d, $^{3}J_{3,P}$=10.1 Hz, C(3)), 131.4 (s, Cq(Ph)), 129.2 (s, CH(Ph)), 128.2 (s, CH(Ph)), 125.6 (s, CH(Ph)), 109.8 (d, $^{2}J_{2,P}$=4.5 Hz, C(2)), 63.4 (d, $^{2}J_{C,P}$=6.3 Hz, PO(O*CH*$_2$CH$_3$)$_2$), 63.1 (d, $^{2}J_{C,P}$=7.3 Hz, PO(O*CH*$_2$CH$_3$)$_2$), 58.6 (d, $^{4}J_{4,P}$=2.8 Hz, C(4)), 49.5 (d, $^{1}J_{1,P}$=142.7 Hz, C(1)), 34.0 (d, $^{5}J_{C,P}$=2.1 Hz, C(3)–CH$_2$–*CH*$_2$), 33.4 (s, C(4)–*CH*$_2$), 27.2 (d, $^{4}J_{C,P}$=3.4 Hz, C(3)–*CH*$_2$), 23.8 (s, C(4)–CH$_2$–*CH*$_2$), 16.6 (d, $^{3}J_{C,P}$=5.7 Hz, PO(OCH$_2$*CH*$_3$)$_2$), 16.5 (d, $^{3}J_{C,P}$=5.9 Hz, PO(OCH$_2$*CH*$_3$)$_2$). $^{31}$P NMR (202 MHz, CDCl$_3$) $\delta$: 18.00. IR ($\nu$, cm$^{-1}$): 3000–2750 (large band, w), 1771 (s, C=O), 1703 (s, C=O),1599 (w), 1502 (s), 1408 (s), 1290 (s), 1249 (s, P=O), 1142 (m), 1043 (s, P–O), 955 (s, P–O), 798 (s),767 (s). HRMS (MALDI-TOF, positive mode) *m*/*z* (%) [M+Na]: calcd for $C_{20}H_{26}N_3O_5NaP$: 442.1508, found: 442.1507 (71); [M+H]: 420.1665 (19); [M–HPO(OEt)$_2$]: 282.1243 (100).

### 4.4. General procedure for Diels–Alder reaction with C=C dienophile 4

A neat mixture of diene **1b**, **1c** or **1d** (1 equiv) and *N*-(6-hydroxyhexyl)maleimide **4** (1 equiv) was vigorously stirred at 120 °C for 6–8 h. The oily mixture was directly purified by column chromatography on silica gel. The reaction of **4** and diene **1a**, giving the cycloadduct **5a**, has been described previously.[11d]

*4.4.1. Dibenzyl 2,3,3a,4,7,7a-hexahydro-2-(6-hydroxyhexyl)-1,3-dioxo-1H-isoindol-4-yl-4-phosphonate (**5b**).* *N*-(6-Hydroxyhexyl)-maleimide **4** (189 mg, 0.957 mmol) and diene **1b** (301 mg, 0.957 mmol) yielded the title compound as a yellow oil (246 mg, 50%). $R_f$ [silica gel, ethyl acetate]=0.4. $^{1}$H NMR (500 MHz, CDCl$_3$) $\delta$: 7.27–7.35 (m, CH(Ph), 5H), 6.03 (dtd, $^{3}J_{2,3}$=9.1 Hz, $^{3}J_{3,4'}$=$^{4}J_{3,H}$=4.8 Hz, $^{4}J_{3,P}$=1.3 Hz, C(3)–H, 1H), 5.97 (tdd, $^{3}J_{2,3}$=$^{3}J_{2,P}$=9.3 Hz, $^{3}J_{1,2}$=4.9 Hz and $^{4}J_{2,4}$=1.5 Hz, C(2)–H, 1H), 5.08 (dd, $^{3}J_{H,P}$=9.3 Hz and $^{2}J_{H,H}$=7.7 Hz, *CH*$_2$Ph, 1H), 5.05 (dd, $^{3}J_{H,P}$=11.8 Hz and $^{2}J_{H,H}$=11.7 Hz, C*H*$_2$Ph, 1H), 4.99 (dd, $^{3}J_{H,P}$=9.4 Hz and $^{2}J_{H,H}$=7.8 Hz, *CH*$_2$Ph, 1H), 4.90 (dd, $^{3}J_{H,P}$=11.8 Hz and $^{2}J_{H,H}$=11.7 Hz, *CH*$_2$Ph, 1H), 3.57 (t, $^{3}J_{H,H}$=6.5 Hz, *CH*$_2$OH, 2H), 3.42 (q, $^{3}J_{H,H}$=6.9 Hz, N*CH*$_2$, 2H), 3.40 (ddd, $^{3}J_{6,P}$=21.1 Hz, $^{3}J_{5,6}$=8.7 Hz and $^{3}J_{1,6}$=5.8 Hz, C(6)–H, 1H), 3.08 (ddd, $^{3}J_{4',5}$=$^{3}J_{5,6}$=8.9 Hz and $^{3}J_{4,5}$=3.7 Hz, C(5)–H, 1H), 2.91 (dt, $^{2}J_{1,P}$=23.3 Hz, $^{3}J_{1,2}$=$^{3}J_{1,6}$=5.4 Hz, C(1)–H, 1H), 2.69 (m, C(4)–H, 1H), 2.20 (dddt, $^{2}J_{4,4'}$=13.8 Hz, $^{3}J_{4',5}$=8.4 Hz, $^{3}J_{3,4'}$=4.4 Hz and $^{4}J_{4',P}$=$^{4}J_{2,4'}$=1.9 Hz, C(4)–H′, 1H), 1.51 (tt, $^{3}J_{H,H}$=7.0 Hz and $^{3}J_{H,H}$=6.3 Hz, NCH$_2$*CH*$_2$ or *CH*$_2$CH$_2$OH, 2H), 1.50 (tt, $^{3}J_{H,H}$=6.9 Hz and $^{3}J_{H,H}$=6.4 Hz, *CH*$_2$CH$_2$OH or NCH$_2$*CH*$_2$, 2H), 1.31 (quint., $^{3}J_{H,H}$=7.3, N(CH$_2$)$_2$*CH*$_2$ or *CH*$_2$(CH$_2$)$_2$O, 2H), 1.23 (quint., $^{3}J_{H,H}$=7.3, *CH*$_2$(CH$_2$)$_2$O or N(CH$_2$)$_2$*CH*$_2$, 2H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 179.1 (s, C=O), 176.5 (d, $^{3}J_{C,P}$=4.3 Hz, C=O), 136.5 (d, $^{3}J_{C,P}$=5.8 Hz, Cq(Ph)), 136.2 (d, $^{3}J_{C,P}$=6.0 Hz, Cq(Ph)), 130.5 (d, $^{3}J_{3,P}$=13.1 Hz, C(3)), 128.6 (s, CH(Ph)), 128.43 (s, CH(Ph)), 128.4 (s, CH(Ph)), 128.3 (s, CH(Ph)), 128.2 (s, CH(Ph)), 124.6 (d, $^{2}J_{2,P}$=6.8 Hz, C(2)), 68.6 (d, $^{2}J_{C,P}$=6.6 Hz, *CH*$_2$Ph), 67.6 (d, $^{2}J_{C,P}$=6.8 Hz, *CH*$_2$Ph), 62.4 (s, *CH*$_2$OH), 40.7 (d, $^{2}J_{6,P}$=3.1 Hz, C(6)), 39.1 (d, $^{3}J_{5,P}$=11.0 Hz, C(5)), 38.9 (s, N*CH*$_2$), 34.4 (d, $^{1}J_{1,P}$=148.7 Hz, C(1)), 32.5 (s, *CH*$_2$CH$_2$OH), 27.5 (s, NCH$_2$*CH*$_2$), 26.3 (s, *CH*$_2$(CH$_2$)$_2$OH), 25.1 (s, N(CH$_2$)$_2$*CH*$_2$), 23.4 (s, C(4)). $^{31}$P NMR (202 MHz, CDCl$_3$) $\delta$: 27.46. IR ($\nu$, cm$^{-1}$): 3500–3100 (large band, m, OH), 2945 (m), 2856 (m), 1774 (m, C=O), 1693 (s, C=O), 1456 (m), 1402 (s), 1371 (m), 1346 (m), 1252 (s), 1226 (s, P=O), 1080 (s, P–O), 955 (s, P–O), 733 (s), 696 (s). HRMS (MALDI-TOF, positive mode) *m*/*z* (%) [M+Na]: calcd for $C_{28}H_{34}NO_6PNa$: 534.2021, found: 534.2012 (100); [M+H]: 512.2150 (36).

*4.4.2. Diethyl (1,1a,3,3a,4,7)-hexahydro-2-(6-hydroxyhexyl)-5-methyl-2H-isoindol-4-phosphonate-1,3-dione (**5c**).* *N*-(6-Hydroxyhexyl)-maleimide **4** (0.185 g, 0.935 mmol) and diene **1c** (0.191 g, 0.935 mmol) yielded the title compound as a yellow oil (0.140 g, 37%). $R_f$ [silica gel, ethyl acetate/acetone, 1:1]=0.4. $^{1}$H NMR (500 MHz, CDCl$_3$) $\delta$: 5.64 (dd, $^{3}J_{2,P}$=7.2 Hz, $^{3}J_{1,2}$=6.0 Hz, C(2)–H, 1H), 4.22–4.05 (m, PO(O*CH*$_2$CH$_3$)$_2$, 4H), 3.59 (t, $^{3}J_{H,H}$=6.3 Hz, *CH*$_2$OH, 2H), 3.51–3.43 (m, N*CH*$_2$, 2H), 3.32 (ddd, $^{3}J_{6,P}$=15.8 Hz, $^{3}J_{5,6}$=9.2 Hz and $^{3}J_{1,6}$=6.4 Hz, C(6)–H, 1H), 3.13 (td, $^{3}J_{5,6}$=$^{3}J_{4',5}$=8.8 Hz and $^{3}J_{4,5}$=3.9 Hz, C(5)–H, 1H), 2.87 (dt, $^{3}J_{1,P}$=22.3 Hz, and $^{3}J_{1,2}$=$^{3}J_{1,6}$=5.3 Hz, C(1)–H, 1H), 2.64 (dt, $^{2}J_{4,4'}$=15.9 Hz, $^{3}J_{4,5}$=$^{4}J_{4,H}$=2.8 Hz, C(4)–H, 1H), 2.26 (dd, $^{2}J_{4,4'}$=15.7 Hz and $^{3}J_{4',5}$=8.6 Hz, C(4)–H′, 1H), 1.80 (s, CH$_3$, 3H), 1.54 (tt, $^{3}J_{H,H}$=7.4 Hz and $^{3}J_{H,H}$=7.0 Hz, NCH$_2$*CH*$_2$ and *CH*$_2$CH$_2$O, 4H), 1.40–1.34 (m, *CH*$_2$(CH$_2$)$_2$OH, 2H), 1.32 (t, $^{3}J_{H,H}$=7.1 Hz, PO(OCH$_2$CH$_3$)$_2$, 3H), 1.31 (t, $^{3}J_{H,H}$=7.0 Hz, PO(OCH$_2$CH$_3$)$_2$, 3H), 1.30–1.23 (m, N(CH$_2$)$_2$*CH*$_2$, 2H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 179.1 (s, C=O), 176.5 (d, $^{3}J_{C,P}$=4.3 Hz, C=O), 139.2 (d, $^{3}J_{3,P}$=12.9 Hz, C(3)), 116.9 (d, $^{2}J_{2,P}$=7.1 Hz, C(2)), 62.9 (d, $^{2}J_{C,P}$=6.7 Hz, PO(O*CH*$_2$CH$_3$)$_2$), 62.2 (s, *CH*$_2$OH), 61.8 (d, $^{2}J_{C,P}$=7.0 Hz, PO(O*CH*$_2$CH$_3$)$_2$), 40.5 (d, $^{2}J_{6,P}$=3.0 Hz, C(6)), 39.3 (d, $^{3}J_{5,P}$=10.3 Hz, C(5)), 38.7 (s, N*CH*$_2$), 34.4 (d, $^{1}J_{1,P}$=147.8 Hz, C(1)), 32.4 (s, *CH*$_2$CH$_2$OH), 28.3 (s, *CH*$_2$(CH$_2$)$_2$OH), 27.3 (s, NCH$_2$*CH*$_2$), 26.2 (s, N(CH$_2$)$_2$*CH*$_2$), 25.1 (s, CH$_3$), 23.4 (s, C(4)), 16.3 (d, $^{3}J_{C,P}$=6.3 Hz, PO(OCH$_2$*CH*$_3$)$_2$), 16.3 (d, $^{3}J_{C,P}$=6.6 Hz, PO(OCH$_2$*CH*$_3$)$_2$). $^{31}$P NMR (202 MHz, CDCl$_3$) $\delta$: 26.87. IR ($\nu$, cm$^{-1}$): 3600–3000 (large band, m, OH), 2923 (m), 2854 (m), 1776 (w, C=O), 1688 (s, C=O), 1439 (m), 1402 (s), 1369 (m), 1346 (m), 1244 (m, P=O), 1221 (m), 1159 (m), 1016 (s, P–O), 960 (s, P–O), 791 (m), 751 (s), 731 (s). HRMS (MALDI-TOF, positive mode) *m*/*z* (%) [M+Na]: calcd for $C_{19}H_{32}NO_6PNa$: 424.1865, found: 424.1860 (100); [M+H]: 402.2010 (46).

*4.4.3. Preparation of diethyl-1a,3a,4,5,5a,6,7,8,9,9a-decahydro-2-(6-hydroxyhexyl)-1,3-dioxo-1H-benzo[e]isoindol-4-yl-4-phosphonate (**5d**).* *N*-(6-Hydroxyhexyl)-maleimide (80.7 mg, 0.409 mmol) **4** and diene **1d** (100 mg, 0.409 mmol) yielded the title compound as a pale yellow oil (81.7 mg, 45%). $R_f$ [silica gel, ethyl acetate/acetone, 1:2]=0.4. $^{1}$H NMR (500 MHz, CDCl$_3$) $\delta$: 5.59 (td, $^{3}J_{2,P}$=$^{3}J_{1,2}$=4.3 Hz, $^{4}J_{2,H}$=1.7 Hz, C(2)–H, 1H), 4.60–4.24 (m, PO(O*CH*$_2$CH$_3$)$_2$, 4H), 3.59 (t, $^{3}J_{H,H}$=6.5 Hz, *CH*$_2$OH, 2H), 3.42 (t, $^{3}J_{H,H}$=7.1 Hz, N*CH*$_2$, 2H), 3.35 (ddd, $^{3}J_{6,P}$=13.5 Hz, $^{3}J_{5,6}$=8.0 Hz and $^{3}J_{1,6}$=6.1 Hz, C(6)–H, 1H), 3.11 (t, $^{3}J_{4,5}$=$^{3}J_{5,6}$=8.5 Hz, C(5)–H, 1H), 2.80 (dt, $^{2}J_{1,P}$=24.4 Hz and $^{3}J_{1,2}$=$^{3}J_{1,6}$=5.0 Hz, C(1)–H, 1H), 2.34 (t, $^{3}J_{4,H}$=11.7 Hz, C(4)–H, 1H), 2.24–2.19 (m, C(3)–*CH*$_2$, 1H), 2.13–2.05 (m, C(3)–(CH$_2$)$_2$*CH*$_2$, 2H), 1.88–1.79 (m, C(4)–*CH*$_2$, 2H), 1.66–1.57 (m, C(3)–*CH*$_2$, 1H), 1.52 (tt, $^{3}J_{H,H}$=7.2 Hz and $^{3}J_{H,H}$=7.3 Hz, C(3)–CH$_2$*CH*$_2$, NCH$_2$*CH*$_2$ and *CH*$_2$CH$_2$OH, 6H), 1.4–1.33 (m, N(CH$_2$)$_2$*CH*$_2$, 2H), 1.32 (t, $^{3}J_{H,H}$=7.1 Hz, PO(OCH$_2$*CH*$_3$)$_2$, 3H), 1.31 (t, $^{3}J_{H,H}$=7.1 Hz, PO(OCH$_2$*CH*$_3$)$_2$, 3H), 1.27–1.23 (m, *CH*$_2$(CH$_2$)$_2$OH and *CH*$_2$CH$_2$OH, 4H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 177.0 (s, C=O), 176.2 (d, $^{3}J_{C,P}$=4.3 Hz, C=O), 144.8 (d, $^{3}J_{3,P}$=12.8 Hz, C(3)), 114.0 (d, $^{2}J_{2,P}$=6.7 Hz, C(2)), 63.0 (d, $^{2}J_{C,P}$=6.7 Hz, PO(O*CH*$_2$CH$_3$)$_2$), 62.3 (s, *CH*$_2$OH), 61.9 (d, $^{2}J_{C,P}$=6.9 Hz, PO(O*CH*$_2$CH$_3$)$_2$), 42.5 (d, $^{2}J_{5,P}$=10.2 Hz, C(5)), 41.2 (d, $^{3}J_{6,P}$=2.9 Hz, C(6)), 38.5 (s, NCH$_2$), 37.0 (s, C(4)), 33.9 (d, $^{1}J_{1,P}$=148.4 Hz, C(1)), 32.5 (s, NCH$_2$*CH*$_2$ or *CH*$_2$CH$_2$OH), 31.6 (s, C(3)–CH$_2$*CH*$_2$ or C(4)CH$_2$*CH*$_2$), 27.5 (s, NCH$_2$*CH*$_2$ or *CH*$_2$CH$_2$OH), 26.3 (s, C(3)–CH$_2$*CH*$_2$ or C(4)–CH$_2$*CH*$_2$), 26.00 (s, C(4)–*CH*$_2$), 25.2 (s, N(CH$_2$)$_2$*CH*$_2$ or *CH*$_2$(CH$_2$)$_2$OH), 23.7 (s, N(CH$_2$)$_2$*CH*$_2$ or *CH*$_2$(CH$_2$)$_2$OH or C(4)), 23.7 (s, C(4) or, N(CH$_2$)$_2$*CH*$_2$ or *CH*$_2$(CH$_2$)$_2$OH), 16.5 (d, $^{3}J_{C,P}$=6.3 Hz, PO(OCH$_2$*CH*$_3$)$_2$), 16.4 (d, $^{3}J_{C,P}$=6.4 Hz, PO(OCH$_2$*CH*$_3$)$_2$). $^{31}$P NMR (202 MHz, CDCl$_3$) $\delta$: 27.03. IR ($\nu$, cm$^{-1}$): 3800–3000 (large band, w, OH), 3000–2800

(large band, m), 1776 (w, C=O), 1699 (s, C=O), 1439 (m), 1402 (m), 1369 (m), 1346 (m), 1238 (m, P=O), 1163 (m), 1051 (s), 1028 (s, P–O), 959 (s, P–O), 794 (m), 721 (s). HRMS (MALDI-TOF, positive mode) *m/z* (%) [M+Na]: calcd for $C_{22}H_{36}NO_6PNa$: 464.2178, found: 464.2197 (100)); [M+H]: 442.2416 (29).

### 4.5. General procedure for the Diels–Alder reaction with bis-maleimide 6

A neat mixture of pure diene **1b**, **1c** or **1d** (2 equiv) and maleimide **6** (1 equiv) was vigorously stirred at 140 °C for 6–8 h. The oily mixture was directly purified by column chromatography. The reaction of **6** and diene **1a**, giving the cycloadduct **7a**, has been described previously.[11d]

*4.5.1. Dibenzyl (1,1a,3,3a,4,7)-hexahydro-2-(hexyl)-bis-2H-isoindol-4-phosphonate-1,3-dione (**7b**).* *N,N*-Hexamethylene-bis-maleimide **6** (99 mg, 0.358 mmol) and diene **1b** (225 mg, 0.358 mmol) yielded the title compound as a yellow oil (119 mg, 37%). $R_f$ [silica gel, ethyl acetate/acetone (1:1)]=0.5. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$: 7.34–7.27 (m, CH(Ph), 20H), 6.05–5.99 (m, C(3)–H, 2H), 5.98 (ddd, $^3J_{2,3}$=9.1 Hz, $^3J_{1,2}$=4.8 Hz and $^4J_{2,4}$=1.4 Hz, C(2)–H, 2H), 5.11 (dd, $^2J_{H,P}$=11.8 Hz and $^2J_{H,H}$=7.6 Hz, $CH_2$Ph, 2H), 5.07 (dd, $^2J$=11.8 Hz and $^2J$=9.5 Hz, $CH_2$Ph, 2H), 4.98 (dd, $^2J_{H,P}$=11.7 Hz and $^2J_{H,H}$=9.4 Hz, $CH_2$Ph, 2H), 4.89 (dd, $^2J_{H,P}$=11.8 Hz and $^2J_{H,H}$=7.9 Hz, $CH_2$Ph, 2H), 3.41 (dddd, $^3J_{6,P}$=15.6 Hz, $^3J_{5,6}$=9.3 Hz, $^3J_{1,6}$=6.0 Hz and $^4J_{4,6}$=1.2 Hz, C(6)–H, 2H), 3.36 (dt, $^3J_{H,H}$=7.3 Hz and $^3J_{H,H}$=3.7 Hz, N$CH_2$, 4H), 3.10 (ddd, $^3J_{4',5}$=$^3J_{5,6}$=9.0 Hz and $^4J_{5,P}$=3.5 Hz, C(5)–H, 2H), 2.91 (dt, $^2J_{1,P}$=23.2 Hz, $^3J_{1,2}$=$^3J_{1,6}$=5.2 Hz, C(1)–H, 2H), 2.69 (ddd, $^2J_{4,4'}$=15.7 Hz and $^3J_{4,5}$=$^3J_{3,4}$=$^5J_{4,P}$=3.5 Hz, C(4)–H, 2H), 2.23–2.17 (m, C(4)–H′, 2H), 1.45 (tt, $^3J_{H,H}$=6.2 Hz and $^3J_{H,H}$=6.1 Hz, $NCH_2CH_2$, 4H), 1.19–1.16 (m, $N(CH_2)_2CH_2$, 4H). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$: 179.0 (s, C=O), 176.5 (d, $^3J_{C,P}$=4.4 Hz, C=O), 136.6 (d, $^3J_{C,P}$=5.8 Hz, Cq(Ph)), 136.3 (d, $^3J_{C,P}$=6.0 Hz, Cq(Ph)), 130.5 (d, $^3J_{3,P}$=13.1 Hz, C(3)), 128.6 (s, CH(Ph)), 128.4 (d, $^4J_{C,P}$=2.3 Hz, CH(Ph)), 128.3 (s, CH(Ph)), 128.2 (s, CH(Ph)), 124.7 (d, $^2J_{2,P}$=6.8 Hz, C(2)), 68.6 (d, $^2J_{C,P}$=6.0 Hz, $CH_2$Ph), 67.5 (d, $^2J_{C,P}$=6.8 Hz, $CH_2$Ph), 40.8 (d, $^2J_{6,P}$=3.4 Hz, C(6)), 39.1 (d, $^3J_{5,P}$=11.1 Hz, C(5)), 38.9 (s, N$CH_2$), 34.5 (d, $^1J_{1,P}$=148.7 Hz, C(1)), 27.4 (s, $NCH_2CH_2$), 26.3 (s, $N(CH_2)_2CH_2$), 23.4 (s, C(4)). $^{31}$P NMR (202 MHz, $CDCl_3$) $\delta$: 27.42. IR ($\nu$, $cm^{-1}$): 1776 (w, C=O), 1699 (s, C=O), 1498 (w), 1438 (w), 1402 (m), 1265 (m, P=O), 1151 (w), 1036 (s, P–O), 1024 (s), 997 (s, P–O), 906 (s), 725 (s), 702 (s). HRMS (MALDI-TOF, positive mode) *m/z* (%) [M+H]: calcd for $C_{50}H_{55}N_2O_{10}P_2$: 905.3332, found: 905.3323 (100).

*4.5.2. Diethyl (1,1a,3,3a,4,7)-hexahydro-2-(hexyl)-bis-2H-isoindol-4-phosphonate-1,3-dione (**7c**).* *N,N*-Hexamethylene-bis-maleimide **6** (98.4 mg, 0.356 mmol) and diene **1c** (145.2 mg, 0.711 mmol) yielded the title compound as a yellow oil (83.62 mg, 34%), after column chromatography [silica gel: $CH_3CN$ then $CH_3CN$+methanol gradient (1–10%)]. $R_f$ [silica gel, $CH_3CN$+10% MeOH]=0.2. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$: 5.64 (t, $^3J_{1,2}$=$^3J_{2,P}$=6.4 Hz, C(2)–H, 2H), 4.23–4.13 (m PO(O$CH_2CH_3$)$_2$, 4H), 4.13–4.10 (m PO(O$CH_2CH_3$)$_2$, 4H), 3.44 (t, $^3J_{H,H}$=6.4 Hz, N$CH_2$, 4H), 3.32 (ddd, $^3J_{6,P}$=16.2 Hz, $^3J_{5,6}$=9.1 Hz and $^3J_{1,6}$=6.0 Hz, C(6)–H, 2H), 3.12 (td, $^3J_{4',5}$=$^3J_{5,6}$=8.7 Hz and $^3J_{4,5}$=3.0 Hz, C(5)–H, 2H), 2.87 (dt, $^1J_{1,P}$=23.6 Hz and $^3J_{1,6}$=$^3J_{1,2}$=5.3 Hz, C(1)–H, 2H), 2.64 (dd, $^2J_{4,4'}$=15.9 Hz and $^3J_{4,H}$=2.3 Hz, C(4)–H, 2H), 2.25 (dd, $^2J_{4,4'}$=15.6 Hz and $^3J_{4',H}$=8.7 Hz, C(4)–H′, 2H), 1.79 (s, $CH_3$, 3H), 1.52 (tt, $^3J_{H,H}$=5.5 Hz and $^3J_{H,H}$=4.7 Hz, $NCH_2CH_2$, 2H), 1.32 (t, $^3J_{H,H}$=6.8 Hz, PO(O$CH_2CH_3$)$_2$, 6H), 1.31 (t, $^3J_{H,H}$=7.0 Hz, PO(O$CH_2CH_3$)$_2$, 6H), 1.28–1.20 (m, $N(CH_2)_2CH_2$, 4H). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$: 178.8 (s, C=O), 176.4 (s, C=O), 138.9 (d, $^3J_{3,P}$=12.5 Hz, C(3)), 116.8 (d, $^2J_{2,P}$=6.8 Hz, C(2)), 62.6 (d, $^2J_{C,P}$=3.6 Hz, PO(O$CH_2CH_3$)$_2$), 61.5 (d, $^2J_{C,P}$=5.6 Hz, PO(O$CH_2CH_3$)$_2$), 40.4 (s, C(6)), 39.1 (d, $^3J_{5,P}$=9.9 Hz, C(5)), 38.5 (s, N$CH_2$), 34.3 (d, $^1J_{1,P}$=147.5 Hz, C(1)), 28.0 (s, $NCH_2CH_2$), 27.1 (s, $N(CH_2)_2CH_2$), 26.0 (s, $CH_3$), 23.3 (s, C(4)), 16.4 (d, $^3J_{C,P}$=5.9 Hz, PO(O$CH_2CH_3$)$_2$), 16.2 (d, $^3J_{C,P}$=6.6 Hz, PO(O$CH_2CH_3$)$_2$). $^{31}$P NMR (202 MHz, $CDCl_3$) $\delta$: 26.71. IR ($\nu$, $cm^{-1}$): 2982 (m), 2974 (m), 1774 (m, C=O), 1693 (s, C=O), 1431 (m), 1402 (s), 1348 (m), 1246 (s, P=O), 1221 (s, P=O), 1053 (s), 1018 (m, P–O), 959 (s, P–O), 793 (s), 743 (s). HRMS (MALDI-TOF, positive mode) *m/z* (%) [M+Na]: calcd for $C_{32}H_{50}N_2O_{10}P_2Na$: 707.2838, found: 707.2828 (100); [M+H]: 685.2965 (28).

*4.5.3. Diethyl-1a,3a,4,5,5a,6,7,8,9,9a-decahydro-2-(hexyl)-bis-1,3-dioxo-1H-1,3dioxo-1H-benzoisoindol-4-yl-4-phosphonate (**7d**).* *N,N*-Hexamethylen-bis-maleimide **6** (0.226 g, 0.819 mmol) and diene **1d** (0.452 g, 1.637 mmol) yielded the title compound as a yellow oil (0.105 g, 17%), after column chromatography [silica gel: ethyl acetate: acetone: 1:1 then ethyl/acetone: 1:1+5% MeOH]. $R_f$ [silica gel, ethyl acetate/acetone, 1:1+5% MeOH]=0.4. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$: 5.64–5.55 (m, C(2)–H), 4.29–4.16 (m, PO(O$CH_2CH_3$)$_2$, 2H), 4.16–4.09 (m, PO(O$CH_2CH_3$)$_2$, 2H), 3.40 (t, $^3J_{H,H}$=7.2 Hz, N$CH_2$, 2H), 3.36 (m, $^3J_{6,P}$=14.0 Hz and $^3J_{1,6}$=6.8 Hz, C(6)–H, 1H), 3.12 (t, $^3J_{4,5}$=$^3J_{5,6}$=8.4 Hz, C(5)–H, 1H), 2.81 (d, $^3J_{1,P}$=24.3 Hz, C(1)–H, 1H), 2.35 (t, $^3J_{4,H}$=7.5 Hz, C(4)–H, 1H), 2.25–2.19 (m, C(3)–$CH_2$, 1H), 2.18–2.10 (m, C(4)–$CH_2CH_2$, 2H), 2.09–2.04 (m, C(3)–$CH_2$, 1H), 1.85 (t, $^3J_{H,H}$=10.7 Hz, C(4)–$CH_2$, 2H), 1.68–1.57 (m, C(3)–$CH_2CH_2$, 2H), 1.56–1.43 (m, $NCH_2CH_2$, 2H), 1.33 (t, $^3J_{H,H}$=7.1 Hz, PO(O$CH_2CH_3$)$_2$, 2H), 1.30 (t, $^3J_{H,H}$=7.1 Hz, PO(O$CH_2CH_3$)$_2$, 2H), 1.26–1.22 (m, $N(CH_2)_2CH_2$, 2H). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$: 176.9 (s, C=O), 176.2 (d, $^3J_{C,P}$=4.0 Hz, C=O), 144.7 (d, $^3J_{3,P}$=12.9 Hz, C(3)), 114.1 (d, $^2J_{2,P}$=6.1 Hz, C(2)), 63.0 (d, $^2J_{C,P}$=6.6 Hz, PO(O$CH_2CH_3$)$_2$), 61.8 (d, $^2J$=6.8 Hz, PO(O$CH_2CH_3$)$_2$), 42.4 (d, $^3J_{5,P}$=9.8 Hz, C(5)), 41.2 (d, $^2J_{6,P}$=3.0 Hz, C(6)), 38.5 (s, N$CH_2$), 37.0 (s, C(4)), 34.0 (d, $^1J_{1,P}$=148.0 Hz, C(1)), 31.7 (s, C(3)–$CH_2$), 27.4 (s, $NCH_2CH_2$, 26.3 (s, $N(CH_2)_2CH_2$), 26.1 (s, C(4)–$CH_2CH_2$), 23.8 (s, C(3)–$CH_2CH_2$ or C(4)–$CH_2$), 23.8 (s, C(4)–$CH_2$ or C(3)–$CH_2CH_2$), 16.5 (d, $^3J_{C,P}$=6.5 Hz, PO(O$CH_2CH_3$)$_2$), 16.4 (d, $^3J_{C,P}$=6.8 Hz, PO(O$CH_2CH_3$)$_2$). $^{31}$P NMR (202 MHz, $CDCl_3$) $\delta$: 26.87. IR ($\nu$, $cm^{-1}$): 3000–2800 (large band, w), 1771 (m, C=O), 1694 (s, C=O), 1437 (m), 1398 (m), 1366 (s), 1220 (m, P=O), 1163 (m), 1016 (s, P–O), 957 (s, P–O), 908 (s), 793 (m), 723 (s). HRMS (MALDI-TOF, positive mode) *m/z* (%) [M+Na]: calcd for $C_{38}H_{58}N_2O_{10}P_2Na$: 787.3464, found: 787.3448 (100); [M+H]: 765.36 (14).

### 4.6. General procedure for the catalytic hydrogenation

A mixture of dibenzyl phosphono-cycloadduct **3b**, **5b** or **7b** (1 equiv), Pd/C (10%, 0.1 equiv) and tetrahydrofurane (2 mL/0.1 mmol) was stirred at room temperature overnight under 1 atm of $H_2$. The reaction mixture was then filtered over a Celite© pad and rinced with a $CH_2Cl_2$/MeOH (1:1) solution (10 mL/0.1 mmol). The solvent was removed under reduced pressure.

*4.6.1. Hexahydro-1,3-dioxo-2-phenyl-1H-[1,2,4]triazol-[1,2-a]pyridazin-5-yl-5-phosphonic acid (**8**).* Reduction of the cycloadduct **3b** (215.0 mg, 0.439 mmol) yielded the title compound as a white powder (136.0 mg, 100%). $^1$H NMR (500 MHz, $D_2O$) $\delta$: 7.58–7.50 (m, CH(Ph), 3H), 7.42 (dd, $^3J_{H,H}$=7.1 Hz and $^4J_{H,H}$=1.4 Hz, CH(Ph), 2H), 4.48 (dd, $^2J_{4,4'}$=11.1 Hz and $^3J_{3,4}$=5.6 Hz, C(4)–H, 1H), 4.05 (d, $^1J_{1,P}$=10.3 Hz, C(1)–H, 1H), 3.27 (td, $^2J_{4,4'}$=$^3J_{3,4}$=12.0 Hz and $^3J_{3',4}$=3.5 Hz, C(4)–H, 1H), 2.29–2.24 (m, C(3)–H, 2H), 2.11–1.97 (m, C(2)–H, 1H), 1.89–1.86 (m, C(2)–H′, 1H). $^{13}$C NMR (125 MHz, MeOD) $\delta$: 154.8 (s, C=O), 152.9 (s, C=O), 132.8 (s, Cq(Ph)), 130.0 (s, CH(Ph)), 129.4 (s, CH(Ph)), 127.4 (s, CH(Ph)), 51.5 (d, $^1J_{1,P}$=146.4 Hz, C(1)), 45.4 (s, C(4)), 24.1 (s, C(2)), 20.26 (s, C(3)). $^{31}$P NMR (121 MHz, MeOD) $\delta$: 19.46. IR ($\nu$, $cm^{-1}$): 3421–3061 (large band, m, OH), 2926 (m), 2839 (w), 1759 (m, C=O), 1693 (s, C=O), 1502 (m), 1416 (m), 1300 (m), 1151 (m, P=O), 1065 (w, P–O), 920 (w, P–O), 766 (m), 690 (s). MS (ESI, negative mode) *m/z* (%)642.98 (14) [2M–H–Na],

620.76 (38) [2M−2H], 310.12, 280.13 (100) [M−H]; MS (ESI, positive mode) *m*/*z* (%)=333.98 (100) [M+Na], 311.96 (35) [M+H]. HRMS (MALDI-TOF, negative mode) *m*/*z* (%) [M−H]: calcd: for $C_{12}H_{13}N_3O_5P$ 310.0593, found: 310.0595 (100).

*4.6.2. Hexahydro-2-(6-hydroxyhexyl)-1,3-dioxo-1H-isoindol-4-yl-4-phosphonic acid (**9**).* Reduction of the cycloadduct **5b** (80.16 mg, 0.157 mmol) yielded the title compound as a colourless oil (52.24 mg, 100%). $^1$H NMR (500 MHz, $D_2O$) $\delta$: 3.56 (t, $^3J_{H,H}$=6.5 Hz, $CH_2$OH, 2H), 3.49 (t, $^3J_{H,H}$=7.1 Hz, N$CH_2$, 2H), 3.48−3.44 (m, $^3J_{5,6}$=7.7 Hz, C(6)−H, 1H), 3.09 (ddd, $^3J_{5,6}$=$^3J_{4,5}$=$^3J_{4',5}$=7.3 Hz, C(5)−H, 1H), 2.31−2.31 (m, C(1)−H, 1H), 2.04−1.98 (m, C(2)−H or C(3)−H, 2H), 1.97−1.91 (m, C(3)−H or C(2)−H, 2H), 1.53−1.47 (m, $CH_2CH_2$OH, NC$H_2CH_2$, N$(CH_2)_2CH_2$ and $CH_2(CH_2)_2$OH, 8H), 1.39−1.30 (m, C(4)−H, 1H), 1.30−1.22 (m, C(4)−H′, 1H). $^{13}$C NMR (125 MHz, MeOH d) $\delta$: 181.3 (s, C=O), 181.1 (s, C=O), 62.8 (s, $CH_2$OH), 42.3 (d, $^3J_{6,P}$=9.5 Hz, C(6)), 41.9 (s, C(5)), 39.5 (s, N$CH_2$), 33.4 (s, $CH_2CH_2$OH), 28.6 (s, NC$H_2CH_2$), 27.7 (s, N$(CH_2)_2CH_2$ or $CH_2(CH_2)_2$OH), 27.1 (d, $^1J_{1,P}$=164.0 Hz, C(1)), 26.4 (s, $CH_2(CH_2)_2$OH N$(CH_2)_2CH_2$), 26.0 (s, C(4)), 22.5 (s, C(3)), 21.8 (d, $^2J_{2,P}$=13.6 Hz, C(2)). $^{31}$P NMR (121 MHz, MeOH d) $\delta$: 27.02. IR ($\nu$, cm$^{-1}$): 3607−3148 (large band, m, OH), 2931 (m), 2866 (m), 1767 (m, C=O), 1693 (s, C=O), 1437 (m), 1405 (m), 1344 (m), 1250 (w), 1221 (w), 1163 (m, P=O), 1061 (w, P−O), 978 (w), 920 (w, P−O), 866 (w). MS (ESI, positive mode) *m*/*z* (%)=688.82 (100) [2M+Na], 666.83 (23) [2M+H], 356.14 (45) [M+Na], 334.13 (17) [M+H]; MS (ESI, negative mode) *m*/*z* (%)=687.00 (100) [2M−H+Na], 665.11 (38) [2M], 332.13 (84) [M−H]. HRMS (MALDI-TOF, positive mode) *m*/*z* (%) [M+Na]: calcd for $C_{14}H_{24}NO_6PNa$: 356.1239, found: 356.1226 (97); [M+H]: 334.1404 (87); [M−$H_2O$] 316.1297 (100).

*4.6.3. Hexahydro-2-(hexyl)-bis-2H-isoindol-4-phosphonic acid-1,3-dione (**10**).* Reduction of the cycloadduct **7b** (48.7 mg, 0.053 mmol) yielded the title compound as a colourless oil (28.9 mg, 100%). $^1$H NMR (500 MHz, $D_2O$) $\delta$: 3.49 (t, $^3J_{H,H}$=7.1 Hz, N$CH_2$, 4H), 3.46 (dt, $^3J_{5,6}$=7.8 Hz and $^3J_{4,5}$=$^3J_{4',5}$=3.9 Hz, C(5)−H, 2H), 3.09 (q, $^3J_{5,6}$=$^3J_{1,6}$=$^3J_{6,P}$=7.3 Hz, C(6)−H, 2H), 2.15 (ddt, $^2J_{1,P}$=23.7 Hz, $^3J_{1,6}$=13.3 Hz and $^3J_{1,2}$=4.4 Hz, C(1)−H, 2H), 2.02 (tt, $^3J_{H,H}$=6.2 Hz and $^3J_{H,H}$=6.3 Hz, NC$H_2CH_2$, 4H), 1.98 (ddt, $^3J_{2,P}$=13.6 Hz and $^3J_{1,2}$=4.6 Hz, C(2)−H, 2H), 1.55−1.50 (m, C(3)−H, 2H), 1.50−1.44 (m, C(4)−H, 2H), 1.40−1.31 (m, C(4)−H′, 2H), 1.30−1.26 (m, N$(CH_2)_2CH_2$, 4H). $^{13}$C NMR (125 MHz, MeOD) $\delta$: 181.9 (s, C=O), 181.6 (s, C=O), 42.6 (d, $^2J_{6,P}$=11.6 Hz, C(6)), 42.4 (s, C(5)), 39.3 (s, N$CH_2$), 28.1 (s, NC$H_2CH_2$), 27.6 (d, $^1J_{1,P}$=138.9 Hz, C(1)), 27.1 (s, N$(CH_2)_2CH_2$), 26.2 (d, $^3J_{3,P}$=4.3 Hz; C(3)), 23.0 (s, C(4)), 22.00 (d, $^2J_{2,P}$=12.8 Hz, C(2)). $^{31}$P NMR (121 MHz, MeOD) $\delta$: 24.62. IR ($\nu$, cm$^{-1}$): 3545−3231 (large band, m, OH), 2933 (m), 2862 (w), 1769 (m, C=O), 1697 (s, C=O), 1441 (m), 1404 (m), 1342 (m), 1161 (m, P=O), 1061 (m, P−O), 912 (m, P−O), 868 (w). MS (ESI, negative mode) *m*/*z* (%)=547.10 (100) [M−H], 529.12 (15) [M−$H_2O$]. HRMS (MALDI-TOF negative mode) *m*/*z* (%) [M−H] calcd for $C_{22}H_{33}N_2O_{10}P_2$: 547.1610, found: 547.1620 (100); [M−H−HPO$(OH)_2$]: 465.1773 (14).

### 4.7. Computational details

Calculations have been performed using the Jaguar 7.5 pseudospectral program package.[28] All species have been fully optimized. Geometry optimization was carried out using the well established B3LYP hybrid density functional[29] as implemented in Jaguar with the standard split valence polarized 6-31G** basis.[30]

Energies were obtained by single point energy calculations at the B3LYP-D level of theory (thus including an approximation correction for dispersion[31]) using the larger 6-31+G** basis, using ORCA package.[32] Solvation effects were estimated using the conductor-like screening model (COSMO) as implemented in ORCA, using the parameters appropriate for THF.

### 4.8. Crystal data

Compound **3d** was crystallized from diethyl ether. Crystal dimensions 0.27×0.12×0.08 (colourless), monoclinic *Cc*, a=8.03210(17) Å, *b*=47.3353(8) Å, *c*=32.9636(9) Å, $\beta$=96.786(2)°, *V*=12445.0(5) Å$^3$, *Z*=24, Z′=6, $\rho_{calcd}$=1.343 g cm$^{-3}$, 2$\theta$=50.48°, $\mu$(MoK$\alpha$)=0.169 cm$^{-1}$, Rigaku Ultra X 18 rotating anode, Zr filter, Mar345 image plate, *T*=150 K, 35,522 measured reflections, 20,068 unique. Data (224 images $\Delta\phi$=0.7°) were integrated with the chrysalis software and corrected for absorption by SADABS. The structure was twinned (180° rotation around the *c**) and was refined accordingly (twin fraction 68/32%).

The structure was solved by direct methods (SHELXS) and refined by full-matrix least squares on |F$^2$| (SHELXL).[33] Non-hydrogen atoms were anisotropically refined and the hydrogen atoms were placed on calculated positions with temperature factors fixed at 1.2 times $U_{eq}$ of the parent atoms and 1.5 times $U_{eq}$ for methyl groups, $R_1$=0.0554 (for 16,375 with $I>2\sigma(I)$), $\omega R_2$=0.1093, $\omega R_2$ (all data)= 0.1195, max/min. residual electron density 0.367/−0.295 e Å$^{-3}$.

### 4.9. ESI-HRMS

ESI-HRMS analyses were performed with a LTQ-Orbitrap XL hybrid mass spectrometer (Thermo Fisher Scientific, Bremen, Germany). Data were acquired in the positive ion mode, using a full-scan MS with a mass range of 200−2000 *m*/*z*. The orbitrap operated at 30,000 resolution [FWHM (full width at half maximum) definition]. All experimental data were acquired, along with a daily external calibration prior to the data acquisition. The appropriate tuning of the electrospray ion source was done to ensure the preservation of the complexes formed in the solution, but to avoid the detection of adducts formed during the ESI process.[34] The following electrospray inlet conditions were applied: flow rate, 200 μL min$^{-1}$; spray voltage, 5 kV; sheath gas ($N_2$) flow rate, 20 a.u.; auxiliary gas ($N_2$) flow rate, 20 a.u.; capillary temperature, 275 °C; capillary voltage, 45 V; and tube lens, 80 V. The salts, which were purchased from Aldrich, Alpha, or Acros, were of the highest quality available and vacuum dried at room temperature over $P_2O_5$ prior to use. Ethanol from Fisher (absolute) was used for the MS experiments. For all experiments, the concentration of the ligand was approximately 0.5 mM with 5 equiv of cation.

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## Supplementary data

NMR spectra of compounds **1b**–**e**, **3b**–**d**, **5b**–**d**, **7b**–**d** and **8**–**10**, crystal data, and HRMS-ESI analysis of complexes with $M^{2+}$ and $M^{3+}$ are given as Supplementary data. Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.tet.2012.11.059.

## References and notes

1. Anisimov, K. N.; Kolobova, N. E. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1956**, 943–946.
2. Ryabov, B. V.; Ionin, B. I.; Petrov, A. A. *J. Gen. Chem. USSR* **1988**, *58*, 969–983.
3. Welter, W.; Hartmann, A.; Regitz, M. *Chem. Ber.* **1978**, *111*, 3068–3085.
4. Wang, C.; Pan, Y.; Yang, D. *J. Organomet. Chem.* **2005**, *690*, 1705–1709.
5. (a) Axelrad, G.; Laosooksathit, S.; Engel, R. *J. Org. Chem.* **1981**, *46*, 5200–5204; (b) Axelrad, G.; Laosooksathit, S.; Engel, R. *Synth. Commun.* **1980**, *10*, 933–937.

6. Åkermark, B.; Nystroem, J. E.; Rein, T.; Baeckvall, J.-E.; Helquist, P.; Aslanian, R. *Tetrahedron Lett.* **1984**, *25*, 5719–5722.
7. Han, L. B.; Ono, Y.; Yazawa, H. *Org. Lett.* **2005**, *7*, 2909–2911.
8. Han, L. B.; Tanaka, M. *J. Am. Chem. Soc.* **1996**, *118*, 1571–1572.
9. Azab, A. A.; Al Aziz Quntar, A.; Abed, T.; Srebnik, M. *Heterocycles* **2010**, *82*, 417–429.
10. Zgani, I.; Menut, C.; Seman, M.; Gallois, V.; Laffont, V.; Liautard, J.; Liautard, J. P.; Criton, M.; Montero, J. L. *J. Med. Chem.* **2004**, *47*, 4600–4612.
11. (a) Villemin, E.; Elias, B.; Robiette, R.; Herent, M. F.; Habib-Jiwan, J. L.; Marchand-Brynaert, J. *Tetrahedron Lett.* **2011**, *52*, 5140–5144; (b) Monbaliu, J. C.; Villemin, E.; Elias, B.; Marchand-Brynaert, J. In *Target in Heterocyclic Systems (THS)*; Attonasi, O. A., Spinelli, D., Eds.; 2010; Vol. 14, pp 49–79; (c) Villemin, E.; Marchand-Brynaert, J. *Synthesis* **2012**, *44*, 1923–1927; (d) Villemin, E.; Herent, M.-F.; Marchand-Brynaert, J. *Eur. J. Org. Chem.* **2012**, *31*, 6165–6178.
12. (a) Greene, T. W. *Protecting Groups in Organic Synthesis*; J. Wiley&Sons: New York, NY, 1980; (b) Eckstein, F. Protection of Phosphoric and Related Acid In *Protective Groups*; Mc Omie, J. F. W., Ed.; Plenum: New York and London, 1973; Chapter 6, pp 217–234; (c) Kocienski, P. J. *Protecting Groups*, 3rd ed.; Georg Thieme: Stuttgart, 2005.
13. Mc Kenna, C. E.; Higa, M. T.; Cheung, N. H.; Mc Kenna, M.-C. *Tetrahedron Lett.* **1977**, *18*, 155–158.
14. Goldstein, J. A.; McKenna, C. E.; Westheimer, F. H. *J. Am. Chem. Soc.* **1976**, *98*, 7327–7332.
15. (a) Rammler, D. H.; Yengoyan, L.; Paul, A. V.; Bax, P. C. *Biochemistry* **1967**, *6*, 1828–1837; (b) Kamber, M.; Just, G. *Can. J. Chem.* **1985**, *63*, 823–827; (c) Guibé, F. *Tetrahedron* **1998**, *54*, 2967–3042.
16. (a) Eckstein, F.; Rizk, I. *Angew. Chem., Int. Ed. Engl.* **1967**, *79*, 695–696; (b) Letsinger, R. L.; Lunsford, W. B. *J. Am. Chem. Soc.* **1976**, *98*, 3655–3661.
17. (a) Chao, H.-G.; Bernatowicz, M. S.; Reiss, P. D.; Matsueda, G. R. *J. Org. Chem.* **1994**, *59*, 6687–6691; (b) Sawabe, A.; Filla, S. A.; Masamune, S. *Tetrahedron Lett.* **1992**, *33*, 7685–7686.
18. (a) Atherton, F. A.; Openshaw, H. T.; Todd, A. R. *J. Chem. Soc.* **1945**, 382–385; (b) Todd, A. R. *Angew. Chem.* **1948**, *60A*, 69–70.
19. Monbaliu, J. C.; Marchand-Brynaert, J. *Synthesis* **2009**, *11*, 1876–1880.
20. Saady, L.; Lebeau, C.; Mioskowski. *Tetrahedron Lett.* **1995**, *36*, 5183–5186.
21. Monbaliu, J. C.; Marchand-Brynaert, J.; Tinant, B. *J. Org. Chem.* **2010**, *75*, 5478–5486.
22. (a) Wadsworth, W. S.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, 1733–1738; (b) Huller, T. L. *Tetrahedron Lett.* **1967**, *49*, 4921–4923; (c) Rambaud, M.; del Vecchio, A.; Villieras, J. *Synth. Commun.* **1984**, *14*, 833–841.
23. (a) Hormi, O. E. O.; Pajunen, E. O.; Avall, A. K. C.; Pennanen, P. *Synth. Commun.* **1990**, *20*, 1865–1867; (b) Petrov, K. A.; Chauzov, V. A.; Agafonov, S. V. *Usp. Khim.* **1982**, *51*, 412–437.
24. Page, P. C. B.; McKenzie, M. J.; Gallagher, J. A. *J. Org. Chem.* **2001**, *66*, 3704–3708.
25. Keller, K. A.; Guo, J.; Punna, S.; Finn, M. G. *Tetrahedron Lett.* **2005**, *46*, 1181–1184.
26. Cheronis, J. C.; Whalley, E. T.; Nguyen, K. T.; Eubanks, E. D.; Allen, L. G.; Duggan, M. J.; Loy, S. D.; Bohnan, K. A.; Blodgett, J. K. *J. Med. Chem.* **1992**, *35*, 1563–1572.
27. Griffin, C. E.; Daniewski, W. M. *J. Org. Chem.* **1970**, *35*, 1691–1693.
28. Jaguar. *Version 7.5*; Schrödinger, LLC: New York, NY, 2008.
29. Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652; (b) Francl, M. M.; Pietro, W. J.; Hehre, W. J.; Binkley, J. S.; Gordon, M. S.; DeFrees, D. J.; Pople, J. A. *J. Chem. Phys.* **1982**, *77*, 3654–3665.
30. Hehre, W. J.; Ditchfield, R.; Pople, J. A. *J. Chem. Phys.* **1972**, *56*, 2257–2261.
31. Grimme, S. *J. Comput. Chem.* **2006**, *27*, 1787–1799.
32. Neese, F. *ORCA, An Ab Initio, DFT, and Semienpirical Electronic Structure Package, Version 2.7.0*; Universität Boon: Germany, 2010.
33. Sheldrick, G. M. *Acta Crystallogr.* **2008**, *A64*, 112–122.
34. Beck, J.; Maton, L.; Habib Jiwan, J. L.; Marchand-Brynaert, J. *Amino Acids* **2011**, *40*, 679–689.