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[4+2] Cycloaddition of 1-aminodienes and 2-substituted vinylphosphonates: application to asymmetric synthesis of 3-amino-5-phosphono-1-cyclohexene derivatives

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Abstract—*N*-Butadienylsuccinimide (**1**), *iso*-propyl *N*-butadienyl-(*S*)-pyroglutamate (**5**) and *N*-butadienyl-(*R*)-4-phenyloxazolidin-2-one (**6**) reacted with vinylphosphonates, vicinally-substituted (**2**) by electronwithdrawing groups (CO_2Me, CN, COMe), to furnish [4+2] cycloadducts (**3**–**4**,**7**–**10**, and **11**–**14**) in moderate to good yields (40–88%). The reactions were highly selective: regioselectivity of 95–100%, endoselectivity of 75–92% and facial selectivity of 80–95%. The major diastereoisomers were fully characterized by ^1H and ^{13}C NMR spectroscopy. © 2003 Elsevier Science Ltd. All rights reserved.

1. Introduction

Aminophosphonic derivatives are endowed with various and important biological activities,[1] bioisosteres of the natural α and β-aminoacids representing the most developed families. However, the search of novel drug candidates, particularly in the field of neurotransmitters antagonists, raised up a growing interest in γ-aminophosphonic derivatives (glutamate analogs).[1] Only a few specific methods are described towards such compounds, most often based on the addition of carbanions derived from α-aminoacids onto vinylphosphonates (method also exploited in asymmetric version).[2]

We are interested in the development of a general strategy for the synthesis of aminophosphonic derivatives by using regio- and stereocontrolled [4+2] cycloadditions of respectively amino- and phosphoryl-substituted partners (or inversely).[3] We have already demonstrated the validity of this methodology by the synthesis of β-aminophosphonic derivatives resulting from the cycloaddition of 1-aminodienes and geminally-substituted vinylphosphonates (Scheme (1-I)).[3,4] The initially formed cyclohexene derivatives could be transformed into a series of substituted β-aminophosphonic acids.[5] Efficient asymmetric synthesis was also performed by using homochiral 1-aminodienes.[6]

This study led us to question about the 'substituent effect' played by a phosphonate group on the reactivity in Diels–Alder cycloadditions.[7] It appeared that $PO(OH)_2$ is a slightly activating group, mainly by polarization effect, and thus behaves differently from CO_2H which is known to exercise important inductive and mesomeric effects. Accordingly, dialkyl vinylphosphonates are bad dienophiles,[8] and require the presence of a second activating substituent (EWG, electron withdrawing group) to efficiently react with dienes in [4+2] cycloadditions.[9] Since the regioselectivity of the Diels–Alder reaction is governed by the most electron-withdrawing substituent,[10] geminally and vicinally-substituted vinylphosphonates will give cycloadducts with 1-aminodienes displaying the amino and phosphoryl substituents in the relative positions *ortho* (β-aminophosphonic derivatives) and *meta* (γ-aminophosphonic derivatives), respectively (Scheme 1). In this paper, we illustrate the cycloaddition of 1-aminodienes (non chiral and homochirals) with representative vicinally-substituted vinylphosphonates (activating group=CO_2Me, CN, COMe) in view to prepare (chiral) γ-aminophosphonocyclohexene derivatives (Scheme (1-II)).

2. Results and discussion

1,3-Butadienylsuccinimide **1**[11] reacted with *trans* vinylphosphonates **2** in refluxing acetonitrile for 5 days (Scheme 2). Methyl 3-(diethoxyphosphoryl)acrylate **2a**[12] and 3-(diethoxyphosphoryl)acrylonitrile **2b**[12] have been prepared, according to a literature protocol, from methyl 2-chloroacrylate and 2-chloroacrylonitrile, respectively,

Keywords: Diels–Alder cycloaddition; chiral 1-aminodiene; vinylphosphonate; asymmetric synthesis; γ-aminophosphonic derivatives.

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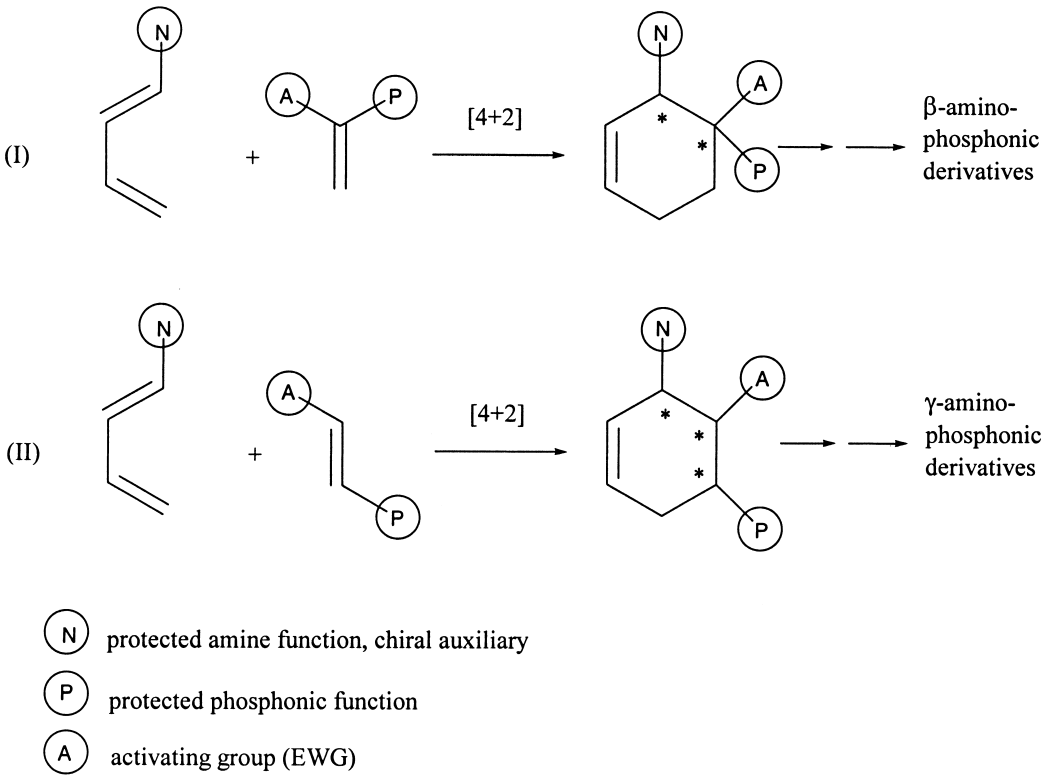
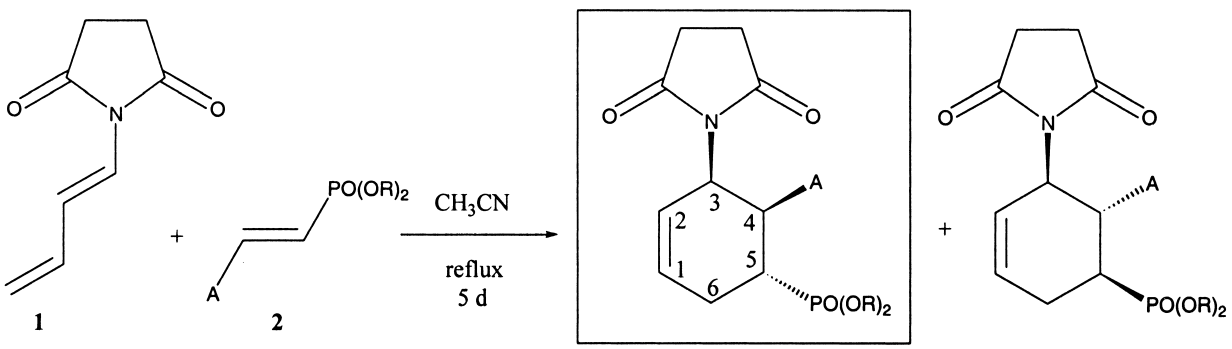


Scheme 1. General strategy of Diels–Alder cycloaddition.

treated with diethylphosphite, triethylamine and chlorotrimethylsilane. 1-(Di(*m*)ethoxyphosphoryl)-1-buten-3-one **2c**[13] was obtained following McClure et al. from methyl vinyl ketone successively treated with tri(m)ethylphosphite, bromine and triethylamine.

GC analysis (see Section 4) of the crude reaction mixtures gave the different selectivities. As expected, the very high or total regioselectivity (97:3 (**a**), 91:9 (**b**) and 100:0 (**c**); Scheme 2) was in favour of the activating substituent A placed in position C(4) and the phosphonate group in position C(5). Thus, the directing substituent A occupies the *ortho* position regarding the diene amino-substituent. Moreover, the high stereoselectivity of 80:20 (**a**), 75:25 (**b**) and 90:10 (**c**), respectively, was in favour of the *endo* isomer **3** over the *exo* isomer **4** (Scheme 2), the best selectivity corresponding to the most electron-withdrawing substituent A. Our experimental selectivities are in good agreement with the 'frontier molecular orbitals' theory applied to pericyclic reactions.[14]

After purification by flash chromatography on silica gel, the major isomers, recovered in moderate yields, were fully characterized by NMR spectroscopy. The *endo* isomers



a A = CO_2Me — **a** 80 / 20 (48%)

b A = CN — **b** 75 / 25 (38%)

c A = COMe — **c** 90 / 10 (58%)

Scheme 2. Cycloaddition of vinylphosphonates and 1-aminodiene.

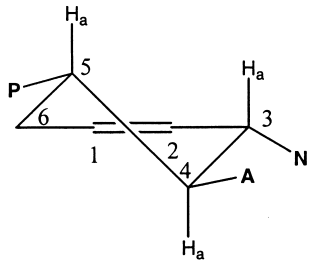
3a–c (conformer I) showed a typical coupling constant of 5–6 Hz between H(3) and H(4); the corresponding protons in the *exo* isomers **4a–c** gave a value of 10–11 Hz. The *trans* relationship of the substituents A and phosphonate group was confirmed by the high coupling constant value (11–13 Hz) between H(4) and H(5). In both stereoisomers, the pseudo-equatorial conformation of the phosphonate group was attributed on the basis of the high coupling constant value of 12–15 Hz between P and C(3)[4] (Fig. 1).

We further considered the use of homochiral 1-aminodienes in the [4+2] cycloadditions with activated vinylphosphonates **2**. The use of pyroglutamates as chiral auxiliaries was first described by M. B. Smith et al.[15] and then well developed by J. Strieth and A. Defoin[16] in hetero-Diels–Alder reactions. More recently, dienes substituted by homochiral oxazolidinones were also described.[17–19]

We have already analysed the facial selectivity of *iso*-propyl *N*-butadienyl-(*S*)-pyroglutamate (**5**) and *N*-butadienyl-(*R*)-4-phenyloxazolidin-2-one (**6**) on the basis of ab initio calculations.[6] The absolute configuration of 3-amino-cyclohexene derivatives obtained by Diels–Alder reaction of dienes **5–6** should result from the approach of the dienophile from the less hindered face of the *cis*-oid diene presenting a *s-trans* conformation, as depicted in Figure 2, around the N–C(1) bond; this conformation is favoured over the *s-cis* conformation by an extended electronic delocalisation and a stabilizing interaction between the dipoles of the dienyl and heterocyclic moieties, despite the fact that hydrogen bonding interaction could stabilize the *s-cis* conformer.[6] Our theoretical model predicted the preferred (*R*) configuration of the amino substituent on the cycloadducts. This has been confirmed experimentally for the cycloadditions of trimethyl 2-phosphonoacrylate (geminally-substituted dienophile) with diene **5** by NMR analysis of the major diastereoisomer (nuclear Overhauser effect (NOE) between H(7) and H(5a); Figure 3: X=CH_2 and R=CO_2*i*Pr),[6a] and with diene **6** by X-ray diffraction analysis of a monocrystal of the major diastereoisomer (Fig. 3: X=O and R=Ph).[6b,20]

Now, dienes **5**[11] and **6**[18] were similarly engaged in cycloaddition reactions with *vicinally*-substituted dienophiles **2a–c** (Scheme 3). The reactions were conducted in refluxing acetonitrile for several days and analysed by GC analysis (Table 1). The regioselectivity was almost complete (activating group A and phosphonate substituent respectively in *ortho*- and *meta* positions regarding the amino substituent). Four diastereoisomers were detected (no

EXO-stereoisomer

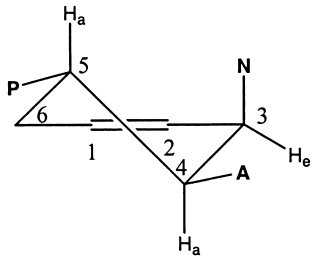


$^3J_{H(3)-H(4)} = 10.0 - 10.5$ Hz

$^3J_{H(4)-H(5)} = 12.0 - 12.5$ Hz

$^3J_{P-C(3)} = 15.5 - 17.5$ Hz

ENDO-stereoisomer (conformer I)

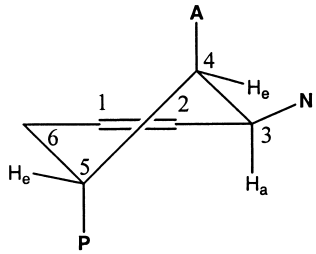


$^3J_{H(3)-H(4)} = 5.5 - 6.5$ Hz

$^3J_{H(4)-H(5)} = 11.5 - 13.5$ Hz

$^3J_{P-C(3)} = 12.5 - 14.5$ Hz

ENDO-stereoisomer (conformer II)

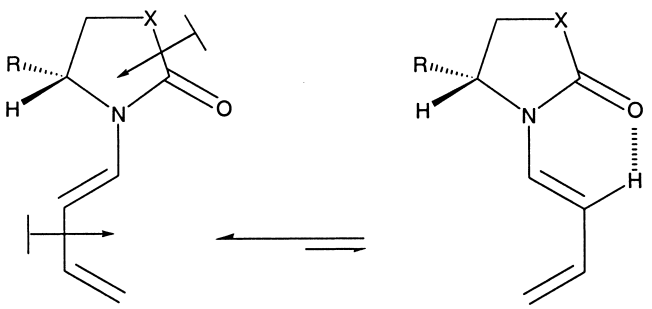


$^3J_{H(3)-H(4)} = 5.9 - 10$ Hz

$^3J_{H(4)-H(5)} = 6.0 - 6.5$ Hz

$^3J_{P-C(3)} = 3.5 - 4.0$ Hz

Figure 1. Typical coupling constant values.



s-trans *s-cis*

(*S*)-**5** : X = CH_2; R = CO_2*i*Pr

(*R*)-**6** : X = O; R = Ph

Figure 2. Chiral 1-aminodienes.

change of relative ratios in the function of reaction time) with a high selectivity in favour of the stereoisomers *endo* **7a–c** and **11a–c** (Scheme 3 and Table 1). The structures have been established after chromatographic purification and NMR analysis. Pure samples of the major diastereoisomers and mixtures of minor diastereoisomers (in various ratios) revealed structural features already identified (Fig. 1). The absolute configuration (3*R*) of the major isomers was attributed by analogy with our previous results.[6,20]

For cycloadducts **7a** (A=CO_2Me) and **7c** (A=COMe) (Table 1; Scheme 3) obtained by reaction of diene (*S*)-**5**, the equatorial positions of the phosphonate and carbonyl substituents and the pseudoaxial position of the pyrrolidinone moiety, corresponding to the conformer I of the major *endo* stereoisomers, were confirmed by the typical coupling constant values of H(3)–H(4) (*J*=5.9–6.1 Hz), H(4)–H(5) (*J*=12.5 Hz) and P–C(3) (*J*=14.3 Hz) (Fig. 1). In the case of **7b** (A=CN), a conformational change occurred, as firmly indicated by the P–C(3) coupling constant value of 3.5 Hz

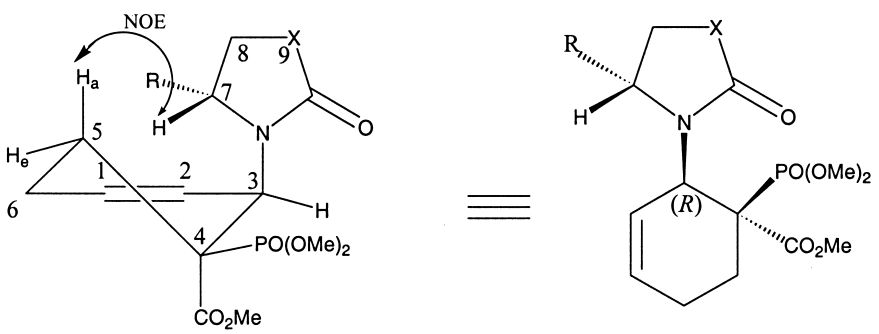
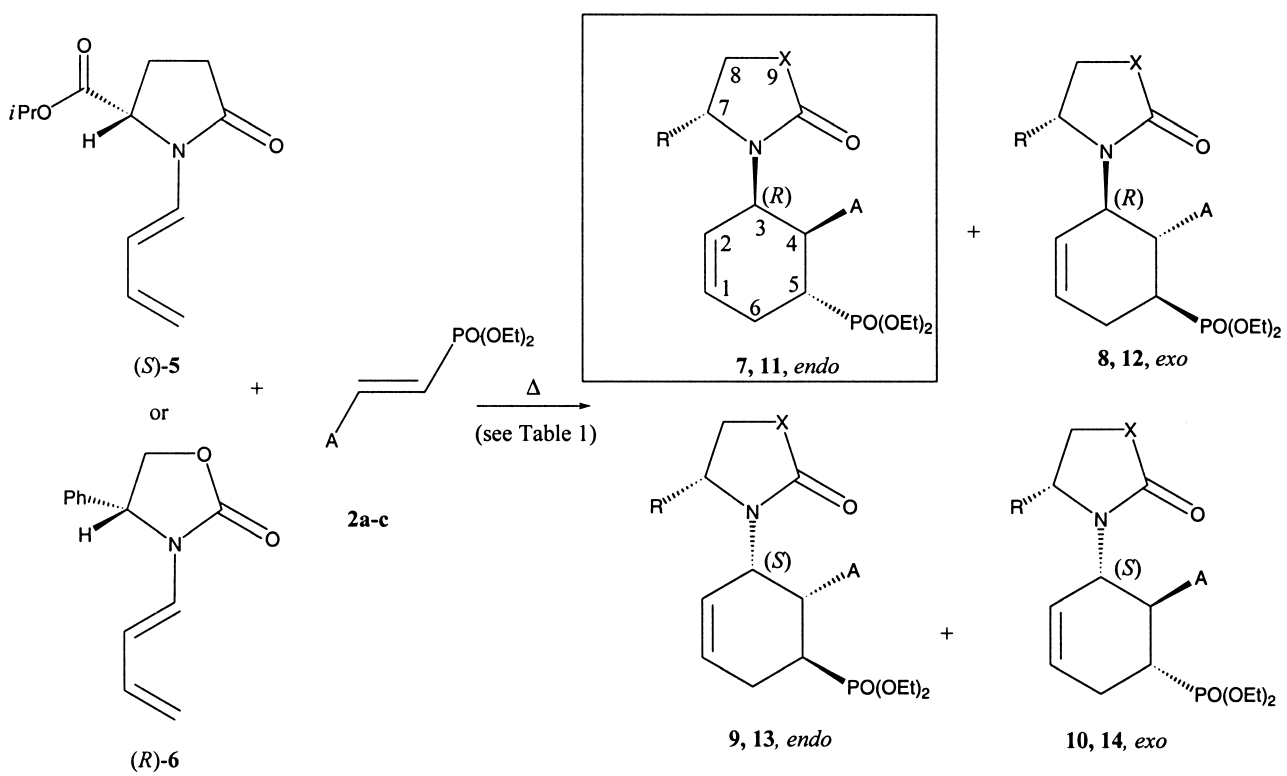


Figure 3. Attribution of (3*R*) configuration.



Scheme 3. Cycloadditions of chiral 1-amino-dienes and vinylphosphonates (see Table 1).

Table 1. Description of the cycloadducts (see Scheme 3)

Cycloadditions		Products			Ratio of diastereoisomers (product number)[a]	Selectivity	
Reagents	Conditions[b]	R	X	Yield (%)[c]		*endo* (%)	Facial (%)[d]
5+**2a**	14d	CO_2iPr	CH_2	82	75 (**7a**)/19 (**8a**)/6 (**9a**)/0 (**10a**)	81	92.6
5+**2b**	19d	CO_2iPr	CH_2	88	78 (**7b**)/12 (**8b**)/8 (**9b**)/2 (**10b**)[e]	86	90.7
5+**2c**	2d[f]	CO_2iPr	CH_2	50	81 (**7c**)/6 (**8c**)/6 (**9c**)/7 (**10c**)[g]	87	93.1
6+**2a**	8d	Ph	O	69	62 (**11a**)/17 (**12a**)/14 (**13a**)/7 (**14a**)	76	81.6
6+**2b**	15d	Ph	O	59	81 (**11b**)/14 (**12b**+**13b**)/5 (**14b**)	>85	>85
6+**2c**	3d	Ph	O	63	87 (**11c**)/7 (**12c**)/5 (**13c**)/1 (**14c**)	92	94.6

[a] Determined on the crude mixture by GC analysis (one regioisomer).
[b] Reflux in acetonitrile.
[c] Isolated yield after flash chromatography on silica gel (mixture of stereoisomers).
[d] Facial selectivity calculated for the *endo* isomers.
[e] Regioisomers in the 97/3 ratio; diastereoisomers of the major regioisomer.
[f] Reflux in toluene.
[g] Regioisomers in the 95/5 ratio; diastereoisomers of the major regioisomer.

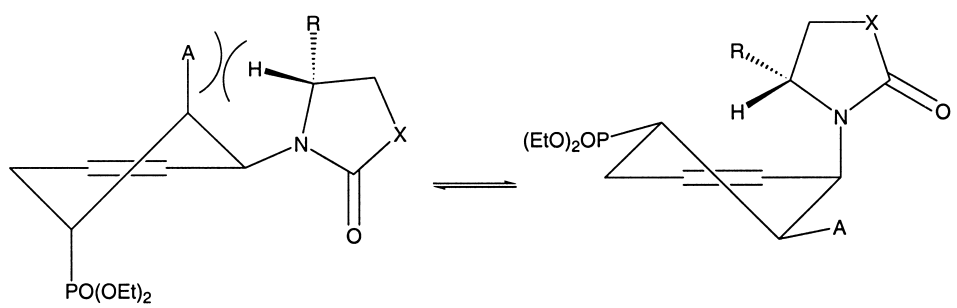
which is characteristic of a phosphonate substituent in pseudoaxial position;[21] accordingly, the pyrrolidinone moiety appears in equatorial position and the cyano group in pseudoaxial position, corresponding to the conformer II of the major *endo* stereoisomer (Fig. 1). In this situation, $J_{H(4)-H(5)}$ became 6.0 Hz (equatorial–equatorial coupling) instead of 12.5 Hz as in conformer I (axial–axial coupling). The major *exo* isomer **8a** (A=CO_2Me) was characterized by two axial–axial coupling constants for the protons on substituted carbons (H(3), H(4) and H(5)); all the substituents being in equatorial positions, the P–C(3) coupling constant was high[21] (17.5 Hz) (Fig. 1).

Fortunately, the four diastereoisomers formed by the cycloaddition of diene (*R*)-**6** with dienophile **2a** (A=CO_2Me), namely cyclohexene derivatives **11a**,**12a**,**13a** and **14a** (Scheme 3; Table 1), could be identified by ^{1}H and ^{13}C NMR spectroscopy (see Section 4). The major *endo* diastereoisomer **11a** showed the characteristic features of conformer I ($J_{H(3)-H(4)}$=6 Hz; $J_{H(4)-H(5)}$=12 Hz and $J_{P-C(3)}$=12.3 Hz). The structure of the major *exo* diastereoisomer **12a** was attributed on the basis of axial–axial coupling constant values for protons H(3)–H(4) and H(5)–H(6); the P–C(3) coupling (*J*=15.7 Hz) was typical of the phosphonate group in pseudoequatorial position[20] (Fig. 1). The minor *endo* diastereoisomer **13a** differed from **11a** mainly by a shielding of the protons H(4), H(3), and H(7): respectively 2.81, 4.68 and 4.67 δ instead of 3.02, 4.84 and 5.01 δ. A similar effect was observed for the minor *exo* diastereoisomer **14a** (H(7): 4.77 δ) comparatively to **12a** (H(7): 4.88 δ).

The major diastereoisomer **11c** (A=COMe) obtained by cycloaddition of diene (*R*)-**6** with **2c** (A=COMe) exhibited the same structural characteristics as **11a** (*endo* isomer; conformer I). On the other hand, the major diastereoisomer **11b** (A=CN) resulting from the reaction with **2b** (A=CN) presented a different conformation, as previously observed for the corresponding cycloadduct **7b** (A=CN) with diene (*S*)-**5**. The P–C(5) coupling constant value of 4.0 Hz indicated a pseudoaxial position of the phosphonate group[21] (*endo* isomer; conformer II). This most probably results from unfavourable steric interactions between the most bulky substituents A (CO_2Me and COMe, but not CN) and the proton H(7) of the chiral auxiliary (Fig. 4). We have already shown, by semi-empirical calculations, that the presence of a bulky *endo* substituent in the *ortho* position regarding the amino heterocycle makes the conformer I more stable than the conformer II.[6a]

3. Conclusion

We have demonstrated the validity of a novel approach towards 3-amino-5-phosphono-1-cyclohexene derivatives based on the regio- and stereocontrolled Diels–Alder cycloaddition of *N*-protected 1-amino-dienes and β-substituted vinylphosphonates. This constitutes an original



conformer II (A = CN) conformer I (A = CO_2Me, COMe)

Figure 4. Preferred *endo* conformer.

strategy for the synthesis of precursors of constrained γ-aminophosphonic compounds as glutamate analogs,[22] useful in the search of neuroactive molecules. By using chiral 1-amino-dienes, we could obtain a major *endo* diastereoisomer with a good facial selectivity of 80–95% (see Table 1); this isomer was well separated by chromatography on silica gel. Since the chiral diene (*S*)-**6** is also accessible,[18] the enantiomers of cyclohexenes **11a**–**c** should be similarly prepared. Further transformations of the cycloadducts, such as selective hydrolysis of phosphonic and carboxylic esters,[5] epoxidation, dihydroxylation, and oxidative cleavage of the cyclohexene double bond,[5] and deprotection of the imide[5] or oxazolidone moiety[23] are known reactions.

Optimization of the facial selectivity is currently under investigation, on the basis of designed structural modification of the oxazolidine chiral auxiliary.[6b]

4. Experimental

4.1. General

Reagents and solvents were purchased from Aldrich and Acros. IR spectral measurements were carried out with a Bio-RAD FTS-135 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded with a Brucker AM-500 spectrometer. All signals were expressed as ppm down field from tetramethylsilane used as an internal standard (δ-value). The carbon spectra were H–C decoupled; thus, the coupling constant values indicated correspond to P–C coupling. For the major stereoisomers, all protons and carbons could be assigned; the structural attributions were controlled by selective decoupling experiments. For the minor stereoisomers, only the firmly attributed signals have been reported (signals not masked by others). Mass spectra were taken with a Finnigan MAT-TSQ 70 apparatus. High resolution mass spectra were performed at University Mons-Hainaut by Prof. R. Flammang. The microanalyses were performed at University College London by Dr A. Stones. GC analyses were performed on CE instruments GC-8000 TOP and HRGC-5300 with FID detector, under 70 kPA of He, and a temperature of 150–225°C by an increase of 5°C/min. Columns used were MN OPTIMAS (*l*=30 m; *d*=0.25 mm) and Chirasil DEX CB (*l*=30 m; *d*=0.25 mm).

4.1.1. 3-Succinimido-4-methoxycarbonyl-5-diethoxyphosphoryl-1-cyclohexene. *N*-Buta-1,3-dienylsuccinimide **1** (71 mg, 0.47 mmol, 1 equiv.) and methyl 3-(diethoxyphosphoryl)acrylate **2a**[12] (104 mg, 0.47 mmol, 1 equiv.) dissolved in acetonitrile (4 mL) were heated at reflux for 4 days. GC analysis (MN OPTIMAS column) gave the following peaks (t_R, min): 30.6 (**3a**) and 31.2 (**4a**), corresponding to 97%, and 26.3 and 37.2, corresponding to 3% (other regioisomers). After solvent evaporation, the crude mixture was purified by flash chromatography on silica gel with AcOEt as eluent (R_f=0.15). An 80:20 mixture of **3a** and **4a** isomers was obtained (84 mg, 48%) as a pale brown oil. IR (cm^{-1}): 2984, 1707, 1248; ^{1}H NMR (500 MHz, $CDCl_3$): **3a** (*endo* isomer) δ 1.25 (6H, m, $PO(OCH_2CH_3)_2$); 2.33 (1H, m, H-6a); 2.39 (1H, m, H-6b); 2.61 (4H, s, CH_2–CH_2); 2.87 (1H, dddd, *J*=16.8, 6.4, 10.3, 11.9 Hz, H-5); 3.02 (1H, ddd, *J*=11.9, 7.0, 5.6 Hz, H-4); 3.56 (3H, s, $COOCH_3$); 4.02 (4H, m, $PO(OCH_2CH_3)_2$); 4.89 (1H, d, *J*=5.6 Hz, H-3); 5.50 (1H, m, H-2); 6.04 (1H, m, H-1). **4a** (*exo* isomer) δ 2.60 (1H, m, H-5); 2.61 (4H, m, CH_2–CH_2); 3.24 (1H, m, H-4); 3.60 (3H, s, $COOCH_3$); 4.94 (1H, d, H-3); 5.36 (1H, m, H-2); 5.86 (1H, m, H-1). ^{13}C NMR (125 MHz, $CDCl_3$): **3a** (*endo* isomer) δ 16.1 (s, $PO(OCH_2CH_3)_2$); 23.9 (d, *J*=5.4 Hz, C-6); 27.8 (s, CH_2–CH_2); 29.7 (d, *J*=143.0 Hz, C-5); 42.9 (d, *J*=3.0 Hz, C-4), 44.7 (d, *J*=12.4 Hz, C-3); 51.9 (s, $COOCH_3$); 61.6 and 61.8 (d and d, *J*=7.1 Hz, $PO(OCH_2CH_3)_2$); 120.0 (s, C-2); 130.2 (d, *J*=12.4 Hz, C-1); 171.8 (d, *J*=5.4 Hz, $COOCH_3$); 177.3 (s, NCO). **4a** (*exo* isomer) δ 16.1 (s, $PO(OCH_2CH_3)_2$); 24.0 (d, *J*=5.4 Hz, C-6); 27.8 (s, CH_2–CH_2); 33.4 (d, *J*=143.0 Hz, C-5); 42.1 (d, *J*=3.0 Hz, C-4), 50.2 (d, *J*=17.6 Hz, C-3); 51.9 (s, $COOCH_3$); 61.7 and 62.2 (d and d, *J*=7.1 Hz, $PO(OCH_2CH_3)_2$); 124.3 (s, C-2); 127.6 (d, *J*=16.0 Hz, C-1); 171.1 (d, *J*=5.4 Hz, $COOCH_3$); 176.1 (s, NCO). MS *m*/*z* (EI) 373 $(M)^{\cdot+}$, 167, 138. HRMS (EI): found 373.1297; $C_{16}H_{24}NO_7P$ requires 373.1290.

4.1.2. 3-Succinimido-4-cyano-5-diethoxyphosphoryl-1-cyclohexene. *N*-Buta-1,3-dienylsuccinimide **1** (160 mg, 1.06 mmol, 1 equiv.) and 3-(diethoxyphosphoryl)acrylonitrile **2b**[12] (200 mg, 1.06 mmol, 1 equiv.) dissolved in acetonitrile (4 mL) were heated at reflux for 3 days, an excess of *N*-buta-1,3-dienylsuccinimide **1** (160 mg) was added and heating was continued for 2 days. GC analysis (MN OPTIMAS column) gave the following peaks (t_R, min): 31.3 (**3b**) and 32.4 (**4b**), corresponding to 91%, and 24.5 and 26.6, corresponding to 9% (other regioisomers). After solvent evaporation, the crude mixture was purified by flash chromatography on silica gel with AcOEt as eluent (R_f=0.15). A 75:25 mixture of **3b** and **4b** isomers was obtained (137 mg, 38%) as a pale brown oil. IR (cm^{-1}): 2985, 2245, 1706, 1239; ^{1}H NMR (500 MHz, $CDCl_3$): **3b** (*endo* isomer) δ 1.36 (6H, m, $PO(OCH_2CH_3)_2$); 2.29 (1H, m, H-6a); 2.61 (4H, s, CH_2–CH_2); 2.65 (1H, m, H-6b); 2.79 (1H, dddd, *J*=16.8, 5.3, 10.3, 11.4 Hz, H-5); 3.04 (1H, ddd, *J*=11.4, 6.5, 6.5 Hz, H-4); 4.20 (4H, m, $PO(OCH_2CH_3)_2$); 5.05 (1H, d, *J*=6.5 Hz, H-3); 5.55 (1H, m, H-2); 6.11 (1H, m, H-1). **4b** (*exo* isomer) δ 1.36 (6H, m, $PO(OCH_2CH_3)_2$), 2.79 (4H, s, CH_2–CH_2); 4.20 (4H, m, $PO(OCH_2CH_3)_2$); 5.03 (1H, d, *J*=10.3 Hz, H-3); 5.40 (1H, m, H-2); 5.94 (1H, m, H-1). ^{13}C NMR (125 MHz, $CDCl_3$): **3b** (*endo* isomer) δ 16.3 (s, $PO(OCH_2CH_3)_2$); 27.9 (d, *J*=3.5 Hz, C-6); 27.9 (s, CH_2–CH_2); 30.8 (d, *J*=148.0 Hz, C-5); 31.1 (d, *J*=5.3 Hz, C-4), 44.7 (d, *J*=10.5 Hz, C-3); 62.5 and 62.6 (d and d, *J*=7.2 Hz, $PO(OCH_2CH_3)_2$); 117.3 (d, *J*=5.3 Hz, CN); 120.5 (s, C-2); 129.7 (d, *J*=14.1 Hz, C-1); 176.6 (s, NCO). **4b** (*exo* isomer) δ 16.3 (s, $PO(OCH_2CH_3)_2$); 24.7 (d, *J*=5.3 Hz, C-6); 27.9 (s, CH_2–CH_2); 28.7 (d, *J*=5.3 Hz, C-4); 34.1 (d, *J*=148.0 Hz, C-5); 50.2 (d, *J*=16.0 Hz, C-3); 62.5 and 62.6 (d and d, *J*=7.2 Hz, $PO(OCH_2CH_3)_2$); 117.6 (d, *J*=3.5 Hz, CN); 124.1 (s, C-2); 128.4 (d, *J*=16.0 Hz, C-1); 176.1 (s, NCO). MS *m*/*z* (EI) 341 $(M)^+$, 163, 100. HRMS (EI): found 340.1182; $C_{15}H_{21}N_2O_5P$ requires 340.1188.

4.1.3. 3-Succinimido-4-methylcarbonyl-5-dimethoxyphosphoryl-1-cyclohexene. *N*-Buta-1,3-dienylsuccinimide **1** (200 mg, 1.3 mmol, 1 equiv.) and 1-(dimethoxyphosphoryl)but-1-ene-3-one **2c**[13] (285 mg, 1.61 mmol,

1.2 equiv.) dissolved in acetonitrile (2 mL) were heated at reflux for 5 days. After solvent evaporation, the crude mixture was purified by flash chromatography on silica gel with CH_2Cl_2/isopropanol 98:2 as eluent (R_f with CH_2Cl_2/isopropanol 95:5=0.33). A 90:10 mixture of **3c** and **4c** isomers was obtained (248 mg, 58%) as a pale yellow oil. IR (cm^{-1}): 2955, 1774, 1704, 1249; ^1H NMR (500 MHz, $CDCl_3$): **3c** (*endo* isomer) δ 2.25 (3H, s, $COCH_3$); 2.33 (1H, ddd, J=11.3, 18.6, 6.1 Hz, H-6a); 2.57 (1H, ddd, J=6.1, 18.6, 6.1 Hz, H-6b); 2.60 (4H, s, CH_2-CH_2); 2.97 (1H, dddd, J=16.5, 11.3, 6.1, 12.5 Hz, H-5); 3.30 (1H, ddd, J=6.1, 12.5, 6.1 Hz, H-4); 3.62 (6H, d, J=11 Hz, $PO(OCH_3)_2$); 4.86 (1H, dddd, J=6.1, 2.7, 2.4, 5.2 Hz, H-3); 5.50 (1H, m, H-2); 6.07 (1H, m, H-1). **4c** (*exo* isomer) δ 3.79 (1H, ddd, J=10.7, 12.5, 5.2 Hz, H-4); 4.93 (1H, d, H-3); 5.34 (1H, m, H-2); 5.86 (1H, m, H-1). ^{13}C NMR (125 MHz, $CDCl_3$): **3c** (*endo* isomer) δ 24.5 (d, J=3.6 Hz, C-6); 27.8 (s, CH_2-CH_2); 28.8 (d, J=142.0 Hz, C-5); 31.8 (s, $COCH_3$), 43.9 (d, J=14.3 Hz, C-3); 49.1 (d, J=3.6 Hz, C-4); 52.8 and 53.7 (d, J=8.3 and 6.9 Hz, $PO(OCH_3)_2$); 120.0 (s, C-2); 130.7 (d, J=14.3 Hz, C-1); 177.4 (s, NCO); 208.2 (s, $COCH_3$). MS *m/z* (EI) 329 $(M)^{\cdot+}$, 314. Anal. calcd for $C_{14}H_{20}NO_6P$: C, 51.07; H, 6.12; N, 4.25; found: C, 51.01; H, 6.11; N, 4.15.

4.1.4. 3-[2′-(*S*)-(*i*-Propyloxycarbonyl)pyrrolidin-2-on-1-yl]-4-methoxycarbonyl-5-diethoxy phosphoryl-1-cyclohexene. *i*-Propyl *N*-butadienyl-(*S*)-pyroglutamate **5** (200 mg, 0.9 mmol, 1 equiv.) and methyl 3-(diethoxyphosphoryl)acrylate **2a** (199 mg, 0.9 mmol, 1 equiv.) dissolved in acetonitrile (2 mL) were heated at reflux for 8 days. Then, an excess of diene (100 mg) was added and heating was continued for 6 days. GC analysis (MN OPTIMAS column) gave the following peaks (t_R, min): 72.8 (**7a**), 73.9 (**8a**), 72.9 (**9a**). After solvent evaporation, the crude mixture was purified by flash chromatography on silica gel with AcOEt/isopropanol 90:10 as eluent (R_f=0.30). A 75/19/6/0 mixture of stereoisomers was obtained (311 mg, 82%) as a yellow oil. IR (cm^{-1}): 2983, 1735, 1236; ^1H NMR (500 MHz, $CDCl_3$): **7a** (major *endo* isomer) δ 1.21 and 1.22 (6H, d and d, J=6.2 and 6.2 Hz, $CH(CH_3)_2$); 1.30 (6H, m, $PO(OCH_2CH_3)_2$); 1.81–2.63 (7H, m, H-5, H-6, H-8 and H-9); 3.02 (1H, ddd, J=8.2, 12.4, 5.9 Hz, H-4); 3.63 (3H, s, $COOCH_3$); 4.07 (4H, m, $PO(OCH_2CH_3)_2$); 4.25 (1H, m, H-7); 4.98 (1H, tt, J=6.2, 5.9 Hz, $CH(CH_3)_2$); 5.06 (1H, m, H-3); 5.57 (1H, m, H-2); 5.92 (1H, m, H-1). **8a** (major *exo* isomer) δ 1.21 and 1.22 (6H, m and m, $CH(CH_3)_2$); 1.30 (6H, m, $PO(OCH_2CH_3)_2$); 1.81–2.63 (7H, m, H-5, H-6, H-8 and H-9); 2.76 (1H, ddd, J=5.3, 12.1, 10.5 Hz, H-4); 3.66 (3H, s, $COOCH_3$); 4.07 (4H, m, $PO(OCH_2CH_3)_2$); 4.17 (1H, m, H-7); 4.98 (1H, m, $CH(CH_3)_2$); 5.13 (1H, m, H-3); 5.47 (1H, m, H-2); 5.75 (1H, m, H-1). ^{13}C NMR (125 MHz, $CDCl_3$): **7a** (major *endo* isomer) δ 16.1 and 16.2 (s, $PO(OCH_2CH_3)_2$); 21.4 and 21.5 (s, $CH(CH_3)_2$); 23.4 (d, J=3.6 Hz, C-6); 24.0 (s, C-8); 29.0 (s, C-9); 29.9 (d, J=147.0 Hz, C-5); 43.6 (d, J=5.4 Hz, C-4); 44.8 (d, J=12.4 Hz, C-3); 52.0 (s, $COOCH_3$); 59.6 (s, C-7); 61.9 and 68.7 (d and d, J=6.2 and 6.2 Hz, $PO(OCH_2CH_3)_2$); 122.9 (s, C-2); 130.1 (d, J=12.4 Hz, C-1); 172.0 (s, $COOCH_3$); 172.6 (s, $COOCH(CH_3)_2$); 175.6 (NCO). **8a** (major *exo* isomer) δ 16.2 (s, $PO(OCH_2CH_3)_2$); 21.4 and 21.6 (s, $CH(CH_3)_2$); 24.1 (d, J=5.4 Hz, C-6); 24.2 (s, C-8); 29.3 (s, C-9); 33.3 (d, J=145.0 Hz, C-5); 42.9 (d, J=3.6 Hz, C-4); 51.3 (d, J=17.6 Hz, C-3); 52.0 (s, $COOCH_3$); 56.7 (s, C-7); 62.0 and 62.3 (d and d, J=7.2 and 7.2 Hz, $PO(OCH_2CH_3)_2$); 69.1 (s, $CH(CH_3)_2$); 125.6 (s, C-2); 128.1 (d, J=16.0 Hz, C-1); 172.0 (s, $COOCH_3$); 172.2 (s, $COOCH(CH_3)_2$); 175.5 (NCO). MS *m/z* (EI) 445 $(M)^{\cdot+}$, 276, 83. HRMS (EI): found 445.1854; $C_{20}H_{32}NO_8P$ requires 445.1865.

4.1.5. 3-[2′-(*S*)-(*i*-Propyloxycarbonyl)pyrrolidin-2-on-1-yl]-4-cyano-5-diethoxyphosphoryl-1-cyclohexene. *i*-Propyl *N*-butadienyl-(*S*)-pyroglutamate **5** (200 mg, 0.89 mmol, 1 equiv.) and 3-(diethoxyphosphoryl)acrylonitrile **2b** (169 mg, 0.90 mmol, 1 equiv.) dissolved in acetonitrile (2 mL) were heated at reflux for 8 days. Then, an excess of diene (100 mg) was added and heating was continued for 11 days. GC analysis (MN OPTIMAS column) gave the following peaks (t_R, min): 35.8 (**7b**), 39.4 (**8b**), 37.8 (**9b**) and 40.0 (**10b**), corresponding to 97%, and 30.4, 30.8 and 33.1 corresponding to 3% (other regioisomers). After solvent evaporation, the crude mixture was purified by flash chromatography on silica gel with AcOEt/isopropanol 95:5 as eluent (R_f=0.30). A 78/12/8/3 mixture of stereoisomers was obtained (325 mg, 88%) as a brown oil. IR (cm^{-1}): 2983, 2343, 1735, 1702, 1206; ^1H NMR (500 MHz, $CDCl_3$): **7b** (major *endo* isomer) δ 1.26 and 1.27 (6H, d and d, J=6.2 and 6.2 Hz, $CH(CH_3)_2$); 1.36 (6H, m, $PO(OCH_2CH_3)_2$); 2.01–2.74 (7H, m, H-5, H-6, H-8 and H-9); 3.68 (1H, ddd, J=6.4, 6.4, 5.9 Hz, H-4); 4.19 (4H, m, $PO(OCH_2CH_3)_2$); 4.40 (1H, m, H-7); 5.06 (1H, tt, J=6.2, 6.2 Hz, $CH(CH_3)_2$); 5.16 (1H, ddd, J=5.9, 2.4, 3.3 Hz, H-3); 5.53 (1H, dddd, J=10.3, 2.4, 2.4, 2.4 Hz, H-2); 5.96 (1H, dddd, J=10.3, 3.3, 3.3, 3.3 Hz, H-1). ^{13}C NMR (125 MHz, $CDCl_3$): **7b** (major *endo* isomer) δ 16.3 and 16.4 (s and s, $PO(OCH_2CH_3)_2$); 21.4 and 21.5 (s, $CH(CH_3)_2$); 21.6 (d, J=12.4 Hz, C-6); 24.9 (s, C-8); 29.1 (s, C-9); 30.1 (d, J=6.5 Hz, C-4); 32.0 (d, J=146.0 Hz, C-5); 46.2 (d, J=3.5 Hz, C-3); 58.7 (s, C-7); 62.4 and 63.2 (d and d, J=7.2 and 7.2 Hz, $PO(OCH_2CH_3)_2$); 69.3 (s, $CH(CH_3)_2$); 118.3 (d, J=19.4 Hz; CN); 122.1 (s, C-2); 129.4 (d, J=5.4 Hz, C-1); 172.3 (s, $COOCH(CH_3)_2$); 175.8 (NCO). MS *m/z* (EI) 413 $(M+1)^+$, 172. HRMS (EI): found 412.1756; $C_{19}H_{29}N_2O_6P$ requires 412.1763.

4.1.6. 3-[2′-(*S*)-(*i*-Propyloxycarbonyl)pyrrolidin-2-on-1-yl]-4-methylcarbonyl-5-diethoxy phosphoryl-1-cyclohexene. *i*-Propyl *N*-butadienyl-(*S*)-pyroglutamate **5** (393 mg, 1.76 mmol, 1.5 equiv.) and 1-(diethoxyphosphoryl)but-1-ene-3-one **2c** (242 mg, 1.17 mmol, 1 equiv.) dissolved in toluene (4 mL) were heated at reflux for 2 days. GC analysis (Chirasil DEX CB column) gave the following peaks (t_R, min): 43.8 (**7c**), 53.2 (**8c**), 46.7 (**9c**) and 50.3 (**10c**), corresponding to 95%; other regioisomers were visible, corresponding to 5%. After solvent evaporation, the crude mixture was purified by flash chromatography on silica gel with AcOEt/isopropanol 90:10 as eluent (R_f=0.39). An 81/6/6/7 mixture of stereoisomers was obtained (245 mg, 50%) as a pale yellow oil. IR (cm^{-1}): 2982, 2937, 1738, 1699, 1405, 1285, 1199, 1106, 1052, 1025, 968; ^1H NMR (500 MHz, $CDCl_3$): **7c** (major *endo* isomer) δ 1.22 (6H, m, $CH(CH_3)_2$); 1.29 and 1.31 (6H, two t, J=7.3 Hz, $PO(OCH_2CH_3)_2$); 1.85 and 2.22 (2H, two m, H-9a and H-9b); 2.28 (1H, m, H-8a); 2.30 (3H, s, $COCH_3$); 2.35 (1H, m, H-6a); 2.50 (2H, m, H-8b and H-6b); 2.58 (1H,

dddd, J=18.9, 12.5, 11.5, 6.7 Hz, H-5); 3.26 (1H, ddd, J=12.5, 8.9, 6.1 Hz, H-4); 4.06 (4H, m, PO(OCH_2CH$_3$)$_2$); 4.17 (1H, d, J=8.8 Hz, H-7); 4.98 (1H, m, CH(CH$_3$)$_2$), 5.14 (1H, ddd, J=6.1, 5.3, 2.0 Hz, H-3), 5.57 (1H, m, H-2), 5.93 (1H, m, H-1). ^{13}C NMR (125 MHz, CDCl$_3$): **7c** (major *endo* isomer) δ 16.1 and 16.2 (two s, PO(OCH$_2$CH_3)$_2$); 21.4 and 21.5 (two s, CH(CH_3)$_2$); 23.8 (d, J=5.2 Hz, C-6); 24.0 (s, C-8); 28.9 (s, C-9); 29.4 (d, J=141.0 Hz, C-5); 31.5 (s, COCH_3); 43.9 (d, J=14.3 Hz, C-3); 59.4 (s, C-7); 61.8 and 61.9 (two d, J=7.2 Hz, PO(OCH$_2$CH$_3$)$_2$); 68.7 (s, CH(CH$_3$)$_2$); 123.1 (s, C-2); 130.3 (d, J=14.1 Hz, C-1); 172.6 (s, NCO); 175.8 (s, COOCH(CH$_3$)$_2$), 207.7 (s, COCH$_3$). MS m/z (EI) 429 (M^{+}), 386, 149. HRMS (EI): found 429.1911; $C_{20}H_{32}NO_7P$ requires 429.1916.

4.1.7. 3-[4′-(*R*)-(Phenyl)oxazolidin-2-on-1-yl]-4-methyloxycarbonyl-5-diethoxyphosphoryl-1-cyclohexene. *N*-Butadienyl-(*R*)-4-phenyloxazolidin-2-one **6** (200 mg, 0.93 mmol, 1 equiv.) and methyl 3-(diethoxyphosphoryl)-acrylate **2a** (93 mg, 0.90 mmol, 1 equiv.) dissolved in acetonitrile (2 mL) were heated at reflux for 8 days. GC analysis (MN OPTIMAS column) gave the following peaks (t_R, min): 53.3 (**11a**), 54.7 (**12a**), 54.1 (**13a**) and 53.9 (**14a**). After solvent evaporation, the crude mixture was purified by flash chromatography on silica gel with AcOEt/isopropanol 95:5 as eluent (R_f=0.30). A 61/17/14/7 mixture of stereoisomers was obtained (201 mg, 69%) as a colourless oil. IR (cm^{-1}): 2983, 1750, 1248; ^{1}H NMR (500 MHz, CDCl$_3$): **11a** (major *endo* stereoisomer) δ 1.30 and 1.31 (6H, m, PO(OCH$_2$CH_3)$_2$); 2.04–2.39 (2H, m, H-6); 2.55 (1H, ddd, J=18.4, 6.4, 12.0 Hz, H-5); 3.02 (1H, ddd, J=7.8, 12.0, 6.0 Hz, H-4); 3.72 (3H, s, COOCH_3); 3.90–4.23 (5H, m, H-8a and PO(OCH_2CH$_3$)$_2$); 4.61 (1H, dd, J=9.0, 8.7 Hz, H-8b); 4.84 (1H, m, H-3); 5.01 (1H, dd, J=4.3, 8.7 Hz, H-7); 5.10 (1H, m, H-2); 5.41 (1H, m, H-1); 7.15–7.45 (5H, m, Ph). **12a** (major *exo* isomer) δ 1.30 and 1.31 (6H, m, PO(OCH$_2$CH_3)$_2$); 2.04–2.39 (2H, m, H-6); 2.45 (1H, ddd, J=17.7, 5.7, 12.1 Hz, H-5); 3.07 (1H, ddd, J=5.6, 12.1, 10.5 Hz, H-4); 3.75 (3H, s, COOCH_3); 3.90–4.23 (5H, m, H-8a and PO(OCH_2CH$_3$)$_2$); 4.57 (1H, dd, J=9.0, 8.7 Hz, H-8b); 4.68 (1H, m, H-3); 4.88 (1H, dd, J=6.2, 8.7 Hz, H-7); 5.07 (1H, m, H-2); 5.37 (1H, m, H-1); 7.1.45 (5H, m, Ph). **13a** (minor *endo* isomer) δ 1.30 and 1.31 (6H, m, PO(OCH$_2$CH_3)$_2$); 2.04–2.39 (3H, m, H-5 and H-6); 2.81 (1H, m, H-4); 3.70 (3H, s, COOCH_3); 3.90–4.26 (5H, m, H-8a and PO(OCH_2CH$_3$)$_2$); 4.55 (1H, m, H-8b); 4.67 (1H, dd, J=6.8, 8.7 Hz, H-7); 4.68 (1H, m, H-3); 5.46 (1H, m, H-2); 5.79 (1H, m, H-1); 7.15–7.45 (5H, m, Ph). **14a** (minor *exo* isomer) δ 1.30 and 1.31 (6H, m, PO(OCH$_2$CH_3)$_2$); 2.04–2.39 (3H, m, H-4, H-5 and H-6); 3.73 (3H, s, COOCH_3); 3.90–4.23 (5H, m, H-8a and PO(OCH_2CH$_3$)$_2$); 4.58 (1H, dd, J=9.0, 8.7 Hz, H-8b); 4.77 (1H, dd, H-7); 5.66 (1H, m, H-2); 5.91 (1H, m, H-1); 7.15–7.45 (5H, m, Ph). ^{13}C NMR (125 MHz, CDCl$_3$): **11a** (major *endo* isomer) δ 16.2 (s, PO(OCH$_2$CH_3)$_2$); 23.3 (d, J=5.4 Hz, C-6); 30.6 (d, J=143.0 Hz, C-5); 43.7 (d, J=3.5 Hz, C-4); 47.6 (d, J=3.5 Hz, C-3); 52.2 (s, COOCH_3); 59.4 (s, C-7); 61.9 and 62.2 (d and d, J=7.2 and 7.2 Hz, PO(OCH$_2$CH$_3$)$_2$); 70.9 (s, C-8); 123.5 (s, C-2); 126.7, 128.7 and 128.4 (s, s and s, Ph); 128.0 (d, J=12.4 Hz, C-1); 140.9 (s, CHPh); 158.3 (s, NCOO); 172.3 (s, COOCH$_3$). **12a** (major *exo* isomer) δ 16.2 (s, PO(OCH$_2$CH_3)$_2$); 23.8 (d, J=5.4 Hz, C-6); 33.2 (d, J=143.0 Hz, C-5); 42.8 (d, J=3.5 Hz, C-4); 52.1 (s, COOCH_3); 53.6 (d, J=15.7 Hz, C-3); 57.6 (s, C-7); 62.2 (d, J=7.2 Hz, PO(OCH$_2$CH$_3$)$_2$); 70.2 (s, C-8); 125.7 (s, C-2); 127.4, 128.8 and 129.0 (s, s and s, Ph); 128.3 (d, J=12.4 Hz, C-1); 138.8 (s, CHPh); 157.7 (s, NCOO); 173.4 (s, COOCH$_3$). **13a** (minor *endo* isomer) δ 16.2 (s, PO(OCH$_2$CH_3)$_2$); 24.4 (d, J=5.4 Hz, C-6); 34.1 (d, J=143.0 Hz, C-5); 42.9 (d, J=3.5 Hz, C-4); 52.1 (s, COOCH_3); 53.7 (d, J=17.6 Hz, C-3); 60.5 (s, C-7); 61.5 and 61.8 (d and d, J=7.2, 7.2 Hz, PO(OCH$_2$CH$_3$)$_2$); 69.8 (s, C-8); 125.8 (s, C-2); 126.3 (d, J=16.0 Hz, C-1); 127.8, 129.0 and 129.0 (s, s and s, Ph); 138.0 (s, CHPh); 156.7 (s, NCOO); 172.3 (s, COOCH$_3$). **14a** (minor *exo* isomer) δ 16.2 (s, PO(OCH$_2$CH_3)$_2$); 22.5 (d, J=5.4 Hz, C-6); 29.1 (d, J=143.0 Hz, C-5); 41.7 (d, J=3.5 Hz, C-4); 48.6 (d, J=10.0 Hz, C-3); 52.1 (s, COOCH_3); 60.6 (s, C-7); 61.6 and 61.7 (d, J=7.2, 7.2 Hz, PO(OCH$_2$CH$_3$)$_2$); 69.8 (s, C-8); 122.2 (s, C-2); 127.9, 129.1 and 129.2 (s, s and s, Ph); 138.4 (s, CHPh); 157.9 (s, NCOO); 171.5 (s, COOCH$_3$). MS m/z (EI) 437 (M^{+}), 276. HRMS (EI): found 437.1603; $C_{21}H_{28}NO_7P$ requires 437.1601.

4.1.8. 3-[4′-(*R*)-(Phenyl)oxazolidin-2-on-1-yl]-4-cyano-5-diethoxyphosphoryl-1-cyclohexene. *N*-Butadienyl-(*R*)-4-phenyloxazolidin-2-one **6** (300 mg, 1.39 mmol, 1 equiv.) and 3-(diethoxyphosphoryl)acrylonitrile **2b** (264 mg, 1.39 mmol, 1 equiv.) dissolved in acetonitrile (2 mL) were heated at reflux for 5 days. Then, an excess of diene (180 mg) was added and heating was continued for 7 days. This operation was started again and heating was continued for 7 days. GC analysis (MN OPTIMAS column) gave the following peaks (t_R, min): 44.7 (**11b**), 52.6 (**12b**+**13b**) and 51.5 (**14b**). After solvent evaporation, the crude mixture was purified by flash chromatography on silica gel with AcOEt/isopropanol 70:30 as eluent (R_f with AcOEt/isopropanol 97:3=0.30). An 84/14/5 mixture of stereoisomers was obtained (330 mg, 59%) as a pale brown oil. IR (cm^{-1}): 3026, 2984, 2244, 1755, 1242; ^{1}H NMR (500 MHz, CDCl$_3$): **11b** (major *endo* isomer) δ 1.28–1.34 (6H, m, PO(OCH$_2$-CH_3)$_2$); 2.25–2.38 (2H, m, H-6); 2.51–2.65 (1H, m, H-5); 3.69 (1H, ddd, J=6.0, 6.0, 12.0 Hz, H-4); 3.90–4.23 (5H, m, H-8a and PO(OCH_2CH$_3$)$_2$); 4.68 (1H, dd, J=8.5, 8.5 Hz, H-8b); 4.91 (1H, m, H-3); 5.07 (1H, dd, J=3.5, 8.5 Hz, H-7); 5.19 (1H, ddd, J=3.5, 10.5 Hz, H-2); 5.66 (1H, m, H-2); 7.20–7.45 (5H, m, Ph). ^{13}C NMR (125 MHz, CDCl$_3$): **11b** (major *endo* isomer) δ 16.3 and 16.4 (s, PO(OCH$_2$-CH$_3$)$_2$); 21.4 (d, J=3.1 Hz, C-6); 30.2 (d, J=5.8 Hz, C-4); 32.9 (d, J=145.2 Hz, C-5); 48.6 (d, J=4.0 Hz, C-3); 58.7 (s, C-7); 62.5 and 63.2 (d and d, J=6.9 and 6.9 Hz, PO(OCH_2-CH$_3$)$_2$); 71.3 (s, C-8); 122.0 (s, CN); 126.2 (s, C-2); 128.2 (d, J=4.2 Hz, C-1); 127.6, 128.8 and 129.2 (s, s and s, Ph); 140.5 (s, CHPh); 157.8 (s, NCOO). MS m/z (EI) 405 (M+1)$^{+}$, 59. HRMS (EI): found 405.1593; $C_{20}H_{26}N_2O_5P$ requires 405.1579.

4.1.9. 3-[4′-(*R*)-(Phenyl)oxazolidin-2-on-1-yl]-4-methylcarbonyl-5-diethoxyphosphoryl-1-cyclohexene. *N*-Butadienyl-(*R*)-4-phenyloxazolidin-2-one **6** (200 mg, 0.9 mmol, 1.2 equiv.) and 1-(diethoxyphosphoryl)-but-1-ene-3-one **2c** (160 mg, 0.77 mmol, 1 equiv.) dissolved in acetonitrile (2 mL) were heated at reflux for 3 days. GC analysis (MN OPTIMAS column) gave the following peaks (t_R, min): 60.0 (**11c**), 69.5 (**12c**), 65.0 (**13c**) and 54.4 (**14c**). After solvent evaporation, the crude mixture was purified by flash

chromatography on silica gel with AcOEt as eluent (R_f with AcOEt=0.21). A 87/7/5/1 mixture of isomers was obtained (205 mg, 63%) as an amorphous white solid. IR (cm^{-1}): 3035, 2976, 1734, 1712, 1250; ^1H NMR (500 MHz, $CDCl_3$): **11c** (major *endo* isomer) δ 1.32 (6H, m, $PO(OCH_2CH_3)_2$); 2.21 and 2.30 (2H, m, H-6); 2.38 (3H, s, $COCH_3$); 2.59 (1H, m, H-5); 3.26 (1H, ddd, J=6.6, 6.6, 13.2 Hz, H-4); 4.06 (3H, m, H-8a and $PO(OCH_2CH_3)_2$); 4.10 (2H, m, $PO(OCH_2CH_3)_2$); 4.62 (1H, dd, J=8.4, 8.4 Hz, H-8b); 4.91 (1H, m, H-3); 4.96 (1H, m, H-7); 5.09 (1H, m, H-2); 5.39 (1H, m, H-1); 7.15–7.35 (5H, m, Ph). ^{13}C NMR (125 MHz, $CDCl_3$): **11c** (major *endo* isomer) δ 16.2 and 16.3 (d and d, J=5.3 and 5.3 Hz, $PO(OCH_2CH_3)_2$); 23.7 (d, J=3.5 Hz, C-6); 30.2 (d, J=143.0 Hz, C-5); 32.0 (s, $COCH_3$); 46.8 (d, J=12.3 Hz, C-3); 49.9 (d, J=3.5 Hz, C-4); 59.2 (s, C-7); 61.8 and 62.0 (d and d, J=7.2 and 7.2 Hz, $PO(OCH_2CH_3)_2$); 70.7 (s, C-8); 123.8 (s, C-2); 128.0 (d, J=14.1 Hz, C-1); 126.8–128.4–128.7 (s, Ph); 141.0 (s, CHPh); 158.6 (s, NCOO) 208.5 (s, $COCH_3$). MS m/z (EI) 421 $(M)^{\cdot+}$, 378, 240. HRMS (EI): found 421.1660; $C_{21}H_{28}NO_6P$ requires 421.1654.

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