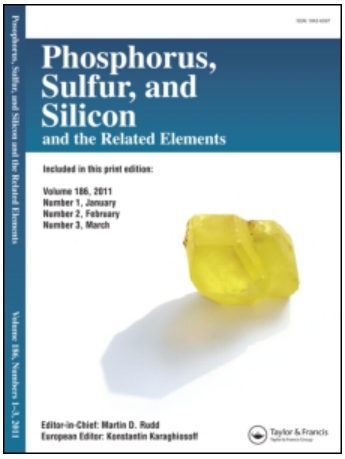

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STEREOCHEMISTRY AND CONFORMATION OF AMIDO-PHOSPHONOCYCLOHEXENE DERIVATIVES, ASSIGNED BY NMR AND X-RAY DIFFRACTION ANALYSES

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STEREOCHEMISTRY AND CONFORMATION OF AMIDO-PHOSPHONOCYCLOHEXENE DERIVATIVES, ASSIGNED BY NMR AND X-RAY DIFFRACTION ANALYSES

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(Received June 18, 2003)

*Stereochemistry (absolute or relative) of four compounds have been established by x-ray diffraction analysis, namely: 3(R)-[4′(R)-(phenyl)-oxazolidin-2-one-1-yl]-4(S)-dimethoxyphosphoryl-4-methoxycarbonyl-1-cyclohexene (**7**), 3(R)-[4′-(R)-(phenyl)-oxazolidin-2-thione-1-yl]-4(S)-dimethoxyphosphoryl-4-methoxycarbonyl-1-cyclohexene (**8**), methyl 1-dimethoxyphosphoryl-2-succinimido-3,4-epoxy-cyclohexane-1-carboxylate (**9**), and 3-succinimido-4-methylcarbonyl-5-dimethoxyphosphoryl-1-cyclohexene (**10**). The ring conformations deduced from NMR analysis were thus fully confirmed.*

Keywords: Amido-phosphonic derivative; asymmetric synthesis; conformational analysis; Diels-Alder reaction; NMR analysis; x-ray structure

Aminophosphonic derivatives are recognized as an important class of pharmacologically active molecules effective in several deseases.[1] Many general synthetic strategies have been developed toward α-aminophosphonic acids that could be readily extended to the preparation of chiral compounds.[1] On the other hand, β- and γ-aminophosphonic derivatives were obtained only via punctual methods. For that reason, our laboratory became interested[2–8] some years ago, in the synthesis of such compounds by using a general and versatile approach based on the Diels-Alder reaction, a highly controlled

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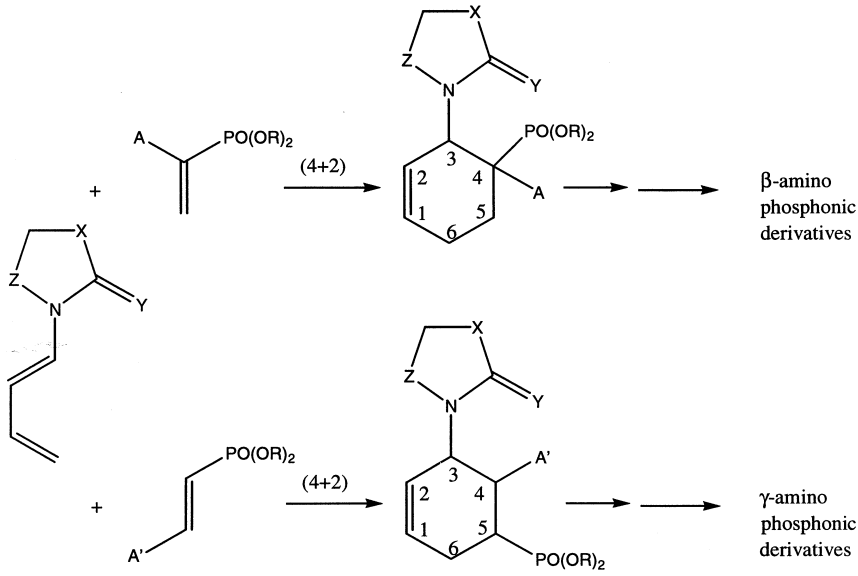


X: CH_2; Y: O; Z: C=O, diene **1**

X: O; Y: O; Z: CHPh(*R*), diene **2**

X: O; Y: S; Z: CHPh(*R*), diene **3**

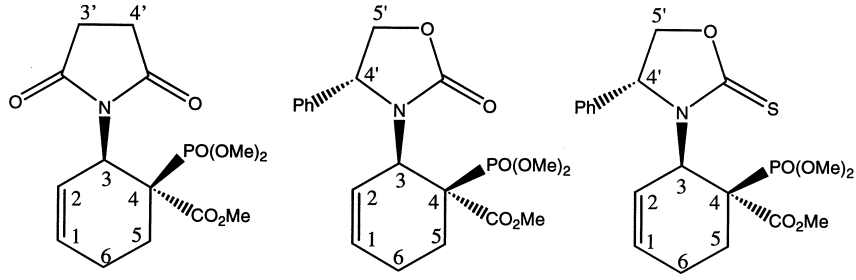
A: CO_2Me; R = Me, dienophile **4**

A': COMe; R = Me, dienophile **5**

SCHEME 1 (4 + 2) Cycloadditions of 1-aminodienes with vinylphosphonates.

reaction with possible developments in asymmetric synthesis. Thus, the regio- and stereocontrolled cycloadditions of 1-aminodienes (**1–3**) with *geminally*- and *vicinally*-substituted vinylphosphonates (**4–5**) furnished, respectively, 3-amido-4-phosphono and 3-amido-5-phosphono-1-cyclohexene derivatives, considered as precursors[5] of the corresponding β- and γ-aminophosphonic acids (Scheme 1). The relative or absolute configurations of the major diastereoisomers have been established by ^1H and ^{13}C NMR spectroscopy on the basis of typical H—H, P—H, and P—C coupling constant values[9] and, in one case, by NOE effect.[6] Now, we confirm the structures by x-ray diffraction analysis of monocrystals.

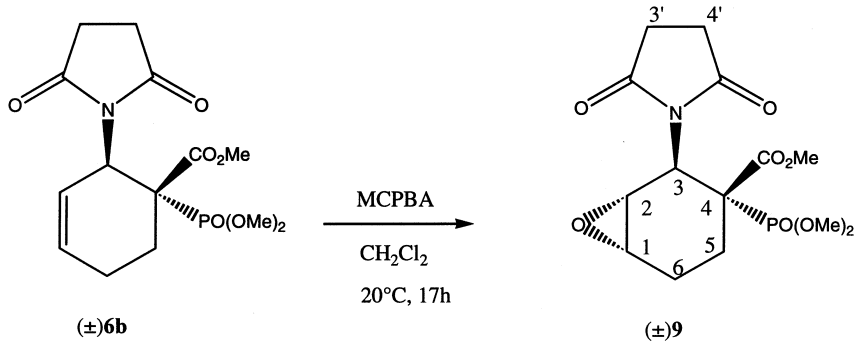
We already have established the preferred *endo* configuration, i.e., the *cis* relationship between the N- and P-substituents, for the cycloadduct **6a** (Scheme 2) obtained by reaction of 1,3-butadienylsuccinimide (**1**) with trimethyl 2-phosphonoacrylate (**4**).[3] In this paper, we



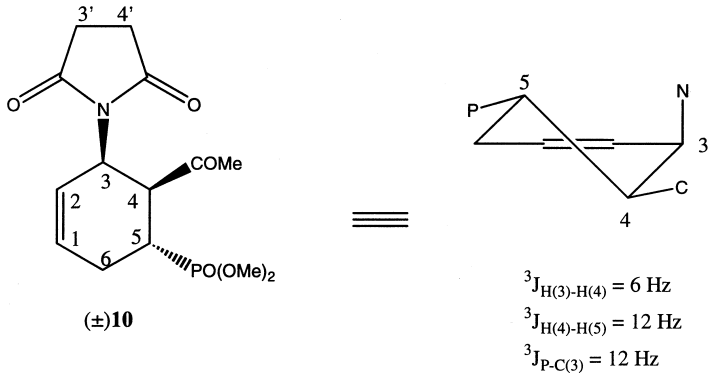
SCHEME 2 Structures of β-amino-phosphonocyclohexene derivatives.

further discuss the structural assignment of cycloadducts **7** and **8** (Scheme 2) resulting from the reaction of the same dienophile **4** with homochiral aminodienes, respectively *N*-butadienyl-(*R*)-4-phenyloxazolidin-2-one (**2**) and *N*-butadienyl-(*R*)-4-phenyloxazolidin-2-thione (**3**).[7–8] The stereoselectivity of the epoxidation reaction of cyclohexene **6b** also is demonstrated[5] (Scheme 3); and lastly, the structural assignment of the cycloadduct **10** formed by reaction of diene 1 with 1-(dimethoxyphosphoryl)-1-buten-3-one (**5**) is well established[2,8] (Scheme 4).

From the x-ray data collected with compounds **6–10**, we could further validate general guidelines based on NMR coupling constant values for the stereochemical and conformational analysis of substituted phosphono-cyclohexene derivatives.



SCHEME 3 Structure of an epoxycyclohexane derivative.



SCHEME 4 Structure of a γ-amino-phosphonocyclohexene derivative.

RESULTS AND DISCUSSION

Cycloadditions of 1-aminodienes (**1**, **2**, and **3**) and trimethyl 2-phosphonoacrylate (**4**) gave cyclohexene derivatives as mixtures of diastereoisomers (Table II); major isomers are, respectively **6a**,[3] (4′*R*)-7, and (4′*R*)-8 (Scheme 2). The facial selectivity induced by the chiral auxiliaries (4*R*)-phenyl-oxazolidin-2-one and (4*R*)-phenyl-oxazolidin-2-thione has been predicted by theoretical methods[6,7] and presently confirmed by the analysis of the crystal structures of **7** and **8**. From the ORTEP views (Figures 1 and 2),[10] phosphonate and oxazolidinone

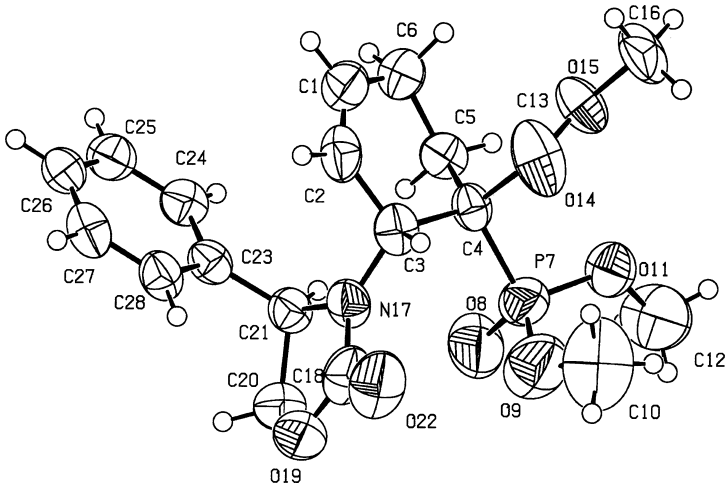


FIGURE 1 ORTEP view of compound **7**.

TABLE I Data Collection and Refinement Parameters

	7	**8**	**9**	**10**
Formula	$C_{19}H_{24}NO_7P$	$C_{19}H_{24}NO_6PS$	$C_{14}H_{20}NO_8P$	$C_{14}H_{20}NO_6P$
Mr	414.36	425.42	361.28	329.28
System	Orthorhombic	Orthorhombic	Monoclinic	Orthorhombic
Space group	$P2_12_12_1$	$P2_12_12_1$	$P2_{1/n}$	*Pbca*
a/Å	6.932(2)	7.141(2)	7.792(2)	9.948(3)
b/Å	14.858(3)	14.995(3)	14.727(4)	16.498(5)
c/Å	19.364(5)	19.070(5)	14.339(4)	18.914(6)
β/°	90	90	96.51(2)	90
V/Å^3	1994.4(9)	2042.0(9)	1634.8(8)	3104(2)
D_x g cm^{-3}	1.36	1.38	1.47	1.41
Z	4	4	4	8
F(000)	864	896	760	1392
μ/mm^{-1}	0.179	0.272	0.211	0.206
Crystal size/mm	0.25 × 0.12 × 0.0.10	0.32 × 0.10 × 0.08	0.32 × 0.24 × 0.20	0.50 × 0.40 × 0.40
$2\theta_{max}$ (°) for data coll.	47	49	55	52.5
Range of *hkl*	$-7 \le h \le 7$ $-16 \le k \le 16$ $-21 \le l \le 21$	$-8 \le h \le 8$ $-17 \le k \le 17$ $-21 \le l \le 22$	$0 \le h \le 10$ $0 \le k \le 19$ $-18 \le l \le 18$	$-12 \le h \le 12$ $-20 \le k \le 20$ $-23 \le l \le 23$
No. of. refl.	10674	21105	13685	34501
No. of unique (Rint)	2949(0.067)	3364(0.069)	3695(0.045)	3164(0.054)
No. of obs. refl. [$I \ge 2\sigma$ (I)]	2688	3230	3463	2902
U for H at (Å^2)	0.125	0.082	0.094	0.083
No. of param.	255	255	261	261
R (R all data)	0.076 (0.081)	0.062(0.064)	0.048(0.049)	0.053(0.055)
ωR (all data)	0.207	0.175	0.131	0.156
Abs. struc par	0.1(3)	0.05(1)	—	—
S	1.061	1.063	1.067	1.057
(Δ/σ)	0.000(1)	0.001(1)	0.001(1)	0.000(1)
$\Delta\rho$ (max, min) (eÅ^{-3})	0.62, −0.34	1.04, −0.45	0.32, −0.31	0.42, −0.31

(thione) substituents are mutally *cis* in both cycloadducts, corresponding to conformers in which the phosphoryl group occupies a pseudo-equatorial position and the heterocyclic auxiliary a pseudo-axial position. This was deduced previously from the P—C(3) and P—C(6) coupling constant values, respectively of 5.2–5.4 Hz and 12.1 Hz, in good agreement with the recorded values for **6a**[3] and with the calculated values based on the Karplus curve adapted to phosphorus derivatives.[9] The experimental dihedral angle P—C(4)—C(3)—H(3) of 79(1)°–81(1)° is compatible with the absence of coupling between P and H(3) in such *endo* conformers (Table III). Moreover, the absolute configuration of the

TABLE II Description of the Cycloadducts

Entry	Reaction of cycloadd.[a]	Products[b]		Ratio of stereoisomers[c,d]	Selectivity	
		Total yield	Major isomer		*endo* (%)	facial (%)
1	**1** + **4** (48 h)	93	50	65(**6a**)/35(**6b**)	65[e]	/
2	**2** + **4** (15 h)	85	60	76(**7**)/14/10/0	84[e]	90
3	**3** + **4** (15 h)	93	67	84(**8**)/16/0/0	84[e]	>99.8[g]
4	**1** + **5** (5 d)	58	38	90(**10**)/10	90[f]	/

[a] Reflux in CH_3CN (time).
[b] Isolated yield after chromatography on silica gel (%).
[c] Determined from GC, HPLC, or ^1H NMR analysis of the crude reaction mixtures.
[d] The regioselectivity was complete.
[e] The *endo* stereoisomer displays *N* and *P* substituents in the relative *cis* configuration.
[f] The *endo* stereoisomer displays *N* and *C* substituents in the relative *cis* configuration.
[g] Limit of detection of GC analysis.

induced C(3) chiral center was unambiguously proved to be (*R*) in both structures **7** and **8**, while C(4) was found to be (S).

The structure of epoxide **9** (Scheme 3) derived from cycloadduct 6b (minor diastereoisomer from the cycloaddition of diene **1** with trimethyl 2-phosphonoacrylate) has been proposed[5] on the basis of ^1H NMR analysis. The *trans* relationship between the oxirane ring and the succinimido substituent was inferred from the absence of coupling between H(2) and H(3). The *cis* relationship between H(3) and the phosphoryl group was deduced from the H(3)—P coupling constant value of 14.9 Hz

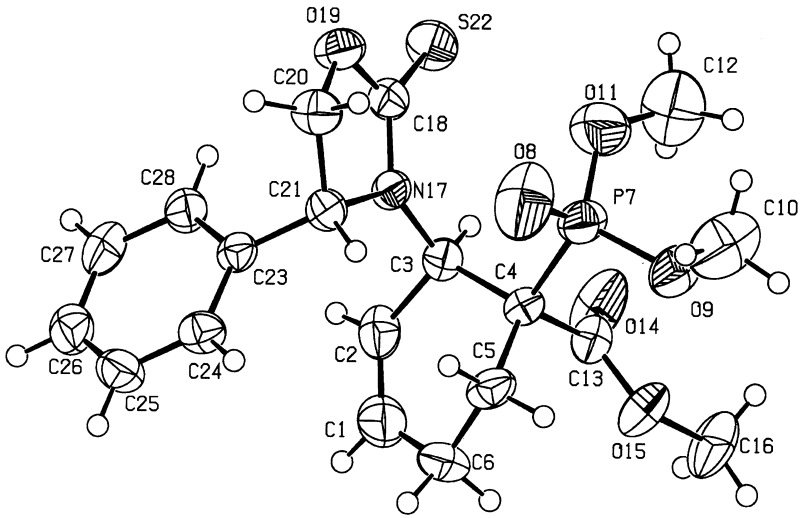
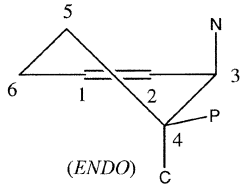
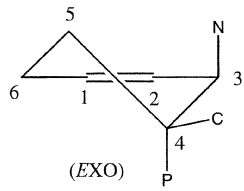


FIGURE 2 ORTEP view of compound **8**.

TABLE III Typical Coupling Constant Values J_{P-H} and J_{P-C} (Hz)



(*ENDO*)



(*EXO*)

Cpd	$^3J_{P-H(3)}$	$^2J_{P-C(3)}$	$^3J_{P-C(6)}$	$^1J_{P-C(4)}$
6a	0	5.4	12.6	133.2
6b	13.9	0	5.4	134.5
7	0(79°)[a]	5.2	12.1(179°)[a]	146.5
8	0(81°)[a]	5.4	12.1(179°)[a]	133.0
9	14.4(44°)[a]	5.4	12.6(178°)[a]	140.0

[a]Dihedral angle observed in the crystal structure, σ in the range 1–2°.

corresponding to a calculated dihedral angle about 40°.[9] The crystal structure of **9** fully confirmed the previous structural assignment: the observed P—C(4)—C(3)—H(3) dihedral angle is 44(1)°. The ORTEP view (Figure 3)[10] clearly shows that epoxide, succinimide and phosphonate motifs are all *trans* with respect to each other.

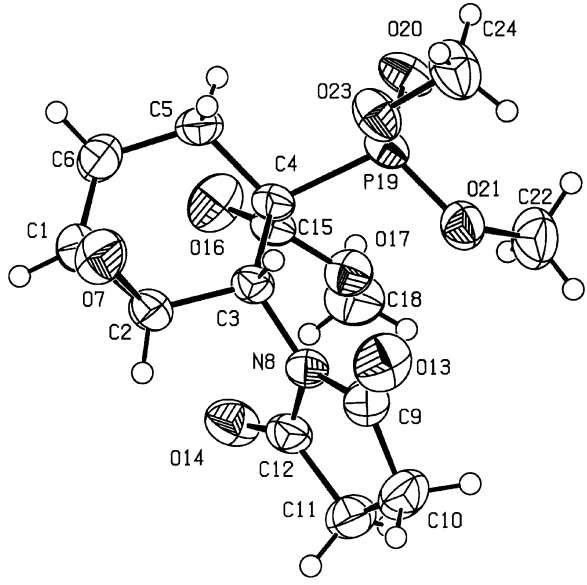


FIGURE 3 ORTEP view of compound **9**.

The last structure analyzed in this article resulted from the cycloaddition of diene **1** onto β-substituted vinylphosphonate **5** (Table II). One regioisomer was obtained in which the most electronwithdrawing substituent (COMe) occupies the *ortho* position regarding the succinimido group; in the major stereoisomer, this substituent is *cis* with respect to the succinimido group (*endo* isomer **10**, Scheme 4). This structure was proposed[2,8] on the basis of typical H—H and P—C coupling constant values shown in Scheme 4. The respective equatorial-axial and axial-axial positions of protons H(3)—H(4) and H(4)—H(5) were deduced from their coupling constant values of 6 Hz and 12 Hz. The pseudo-equatorial position of the phosphoryl group was inferred from the P—C(3) coupling constant of 12 Hz, similar to the corresponding P—C(6) value of compounds **7–8** (see Table III). The crystal structure of **10**, pictured in Figure 4,[10] shows that both the phosphoryl and carbonyl substituents occupy a pseudo-equatorial position, while the heterocycle occupies a pseudo-axial position as in structures **7–8**.

Selected bond lengths and bond angles are compared for the four molecules in Table IV. The P—C, P=O, and P—O distances are similar to the values reported for 3-succinimido-4-dimethylphosphono-4-methoxycarbonyl-l-cyclohexene (**6a**); they are in the range of the mean values, calculated over 62 structures, of these bond lengths, 1.460,

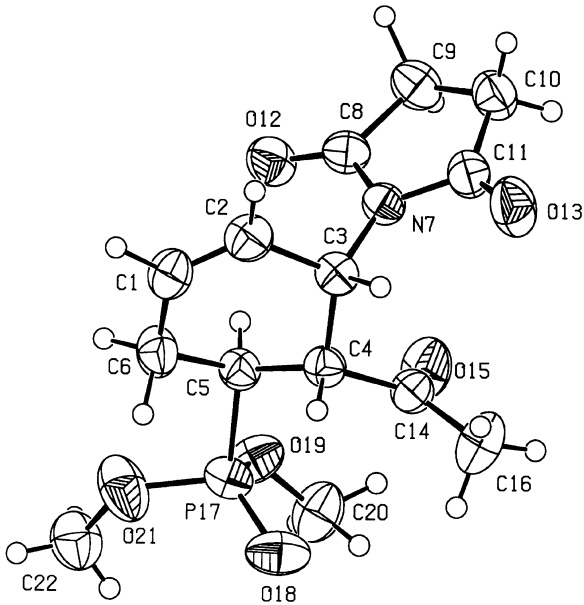


FIGURE 4 ORTEP view of compound **10**.

TABLE IV Comparison of Selected Bond Lengths (Å) and Angles (°)

	7	**8**	**9**	**10**
C1═C2	1.310(9)	1.309(7)	1.455(2)	1.318(3)
C2─C3	1.505(8)	1.502(6)	1.526(2)	1.507(3)
C3─C4	1.562(7)	1.555(5)	1.567(2)	1.555(2)
C4─C5	1.527(6)	1.536(5)	1.556(2)	1.538(2)
C5─C6	1.520(8)	1.509(8)	1.529(2)	1.545(3)
C6─C1	1.495(10)	1.483(9)	1.487(3)	1.497(3)
C3─N	1.458(7)	1.467(5)	1.459(2)	1.478(2)
C4(5)─P	1.821(5)	1.847(4)	1.839(1)	1.817(2)
C4─Cester	1.564(7)	1.532(5)	1.537(2)	1.524(2)
P═O	1.464(7)	1.505(5)	1.463(1)	1.461(2)
P─O	1.507(6)	1.507(6)	1.567(1)	1.576(1°
P─O	1.554(4)	1.554(3)	1.574(1)	1.578(2)
C6─C1─C2	125.3(6)	124.7(5)	120.3(1)	124.3(2)
C3─C1─C2	123.7(5)	123.9(4)	122.5(1)	123.4(2)
C2─C3─C4	110.5(4)	110.4(3)	114.3(1)	111.9(1)
C3─C4─C5	111.4(4)	111.7(3)	106.6(1)	112.3(1)
C4─C5─C6	111.8(5)	110.6(4)	114.1(1)	108.5(1)
C5─C6─C1	112.2(5)	113.2(4)	112.7(1)	112.9(2)
C2─C3─N	112.2(4)	111.4(3)	109.3(1)	110.9(1)
C4─C3─N	114.7(4)	115.0(3)	115.8(1)	114.7(1)
C3─C4─P	111.1(3)	110.7(3)	112.4(3)	111.7(1)
C5─C4─P	108.5(3)	107.6(3)	106.8(1)	110.6(1)

1.563, 1.815 Å respectively.[3] However, the observed values of P═O in 7 and of one of the single P─O bonds in molecules **7** and **8**, differ significantly from the average; we have no explanation for these differences.

For all the four structures the conformation of the cyclohexene ring is a half-chair with the twofold axis passing through the C1─C2 locked bond (Table V). We have calculated the asymmetry

TABLE V Comparison of the Cyclohexene Endocyclic Torsion Angles (°; $\sigma = 1°$)

	7	**8**	**9**	**10**
C6─C1─C2─C3	3	3	4	−3
C1─C2─C3─C4	15	14	−18	−10
C2─C3─C4─C5	−45	−44	44	42
C3─C4─C5─C6	59	59	−62	−60
C4─C5─C6─C1	−40	−41	50	46
C5─C6─C1─C2	10	11	−20	−16
ΔC_2(1–2)(°)	**5.0**	**3.0**	**4.4**	**5.1**

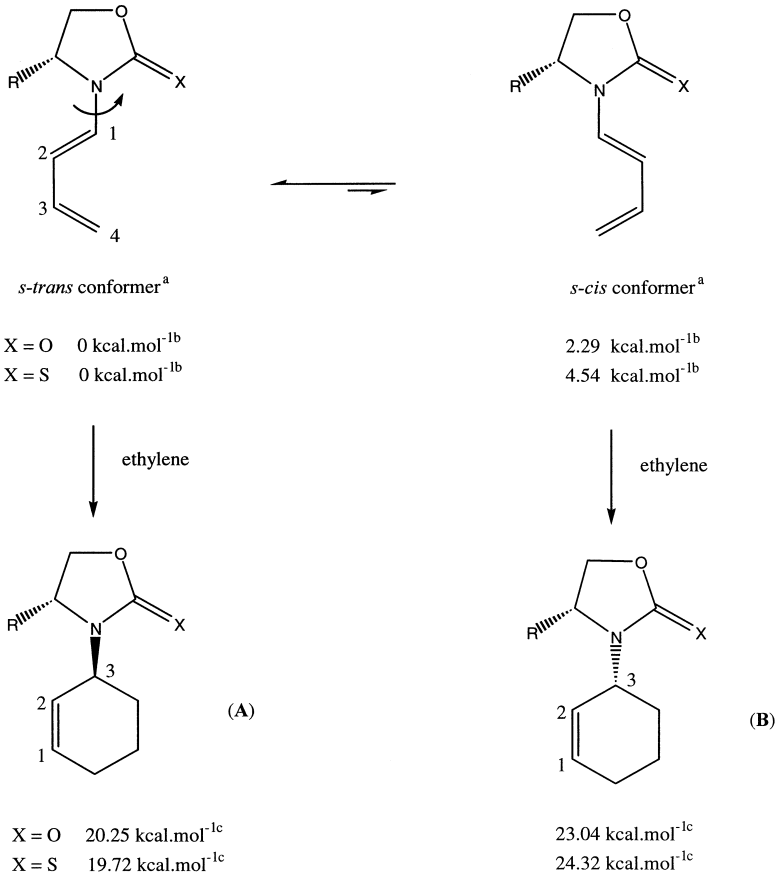
parameter from a perfect half-chair conformation by using the procedure of Duax et al.;[11] it is in the range 3–5° indicating only small deformations from the perfect conformation. In 3-succinimido-4-dimethylphosphono-4-methoxycarbonyl-l-cyclohexene (**6a**), the same conformation with $\Delta C_{2(1-2)} = 7.1°$ was reported.[3] For **7** and **8**, the five-membered heterocycle and the O=P—O groupment are parallel to each other: the dihedral angle between the best mean planes is 3° in both molecules. In **9**, this orientation is not observed.

CONCLUSION

This work has definitively confirmed the structure of representative cyclohexene derivatives obtained by (4 + 2) cycloaddition of 1-aminodienes with vinylphosphonate dienophiles.

In the case of 1-aminodienes substituted with a chiral auxiliary (**2**, **3**), the absolute configuration of the C(3) chiral center created by the Diels-Alder reaction has been established and, fortunately, corresponded to our theoretical predictions. The formed major (**7**) or exclusive (**8**) diastereoisomers by cycloaddition to trimethyl 2-phosphonoacrylate result from the approach of the dienophile from the less hindered face of the diene in its reactive *s-trans* conformation, the most stable conformation by *ab initio* calculations (Scheme 5).[7] The transition state (TS) energy was also lower for the cycloaddition of this conformer, leading to the diastereoisomer **A** of the cyclohexene compound. The facial discrimination was predicted to be higher for the chiral auxiliary with X=S comparatively to X=O (Scheme 5);[7,8] this is in perfect agreement with our experimental results. Thus the previous structural assignments (relative configurations) based on NMR data[3,6,8] are fully validated. In the β-amido-phosphono-cyclohexene series (see Scheme 1), two coupling constant values are very characteristic of the major *endo* diastereoisomers (N- and P-substituents in pseudo-axial and pseudo-equatorial positions, respectively), namely $^2J_{P—C(3)} = 5.2–5.4$ Hz and $^3J_{P—C(6)} \geq 12.1$ Hz. Very few data are available in the previous literature about NMR analysis of functionalized cyclohexenes bearing a phosphonate substituent;[12–14] the strong dependence of $^3J_{P—C}$ coupling constant on the P—C—C—C dihedral angle[15,16] also was used for structural determination.

Further stereoselective reactions performed on the C=C double bond of these cycloadducts[5] are governed by steric factors, as illustrated with the formation of epoxide **9** (Scheme 3); the *trans* relationship between the oxirane and N-substituents results from the attack of the cyclohexene from the less hindered face of the molecule.



[a] *trans* and *cis* relationship are considered between the dienyl moiety and the *N*-heterocycle (N-C(1) rotation).

[b] Relative energies of both conformers calculated at the B3LYP/6-31G** level.

[c] Relative transition state energies (reaction with ethylene) calculated at the B3LYP/6-31G** level. $\Delta E^{\neq} = E_{(TS)} - E$ (reactants with diene in the *s-trans* conformation).

SCHEME 5 Theoretical evaluation of the facial selectivity induced by chiral 1-aminodienes.

Lastly, the complete structural analysis of one representative (**10**) of the γ-amido-phosphono-cyclohexene series (see Scheme 1), opens the route toward new developments, particulary in asymmetric synthesis, since the induced C(3) chiral center should be (*R*) as in compounds **7** and **8**. The relative configurations of the N-, C- and P-substituents are in agreement with the usual rules of the Diels-Alder reaction (*ortho*- and *endo*-selectivities). Here, also, the pseudo-axial position of the

N-substituent and the pseudo-equatorial position of the P-substituent (relative *trans* configuration) gives as $^{3}J_{P-C(3)}$ characteristic coupling constant value of 12 Hz, as predicted from the literature.[15,16]

EXPERIMENTAL

Materials

The syntheses of dienes and dienophiles, and the cycloaddition procedures are described in previous publications.[3–8]

3-[4′-(R)-(phenyl)-oxazolidin-2-one-l-yl]-4-dimethoxyphosphoryl-4-methoxycarbonyl-1-cyclohexene (**7**). m.p.: 182–183°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 1.86 (ddd, 1H, J = 19.0, 5.5 and 5.5 Hz, H-6a), 2.14 (m, 1H, H-6b), 2.30 (m, 1H, H-5a), 2.51 (ddd, 1H, J = 13.5, 4.5 and 4.5 Hz, H-5b), 3.74 (s, 3H, OMe), 3.84 and 3.86 (two d, 6H, J = 4.5 Hz, $(OMe)_2$), 4.13 (dd, 1H, J = 8 and 2 Hz, H-5a′), 4.69 (dd, 1H, J = 8 and 8 Hz, H-5b′), 5.03 (m, 1H, H-2), 5.16 (dd, 1H, J = 10.5 and 5.5 Hz, H-1), 5.69 (dd, 1H, J = 8 and 2 Hz, H-4′), 6.54 (d, 1H, J = 5 Hz, H-3), 7.20–7.30 (m, 5H, Ph). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 21.0 (d, J = 12.1 Hz, C-6), 22.5 (C-5), 48.9 (d, J = 5.2 Hz, C-3), 52.9 (d, J = 146.5 Hz, C-4), 53.0 (OMe), 53.4 and 54.6 (two d, J = 5.0 and 6.6 Hz, $(OMe)_2$), 58.9 (C-4′), 70.9 (C-5′), 123.9 (d, J = 8.9 Hz, C-2), 126.8, 128.2 and 128.5 (CH_{Ar}), 128.8 (C-1), 141.7 (C_{Ar}), 158.2 (CO carbamate), 168.8 (d, J = 6.6 Hz, CO ester). For x-ray analysis: crystallization by slow evaporation from toluene; $[\alpha]_D^{20}$: −265.9 (c = 0.8, $CHCl_3$).

3-[4′-(*R*)-(phenyl)-oxazolidin-2-thione-l-yl]-4-dimethoxyphosphoryl-4-methoxycarbonyl-1-cyclohexene (**8**). m.p.: 190–191°C; ^{1}H NMR (500 MHz, $CDCI_3$): δ (ppm) 1.87 (m, 1H, H-6a), 2.12 (m, 1H, H-6b), 2.32 (m, 1H, H-5a), 2.52 (ddd, 1H, J = 13.5, 6.5 and 6.5 Hz, H-5b), 3.77 (s, 3H, OMe), 3.84 and 3.86 (two d, 6H, J = 6.5 Hz, $(OMe)_2$), 4.33 (d, 1H, J = 8 Hz, H-5a′), 4.80 (dd, 1H, J = 8 and 8 Hz, H-5b′), 5.10 (m, 1H, H-2), 5.16 (m, 1H, H-1), 5.62 (d, 1H, J = 8 Hz H-4′), 6.35 (s, 1H, H-3), 7.20–7.30 (m, 5H, Ph). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 21.0 (d, J = 12.1 Hz, C-6), 22.2 (C-5), 52.6 (d, J = 133 Hz, C-4), 53.1 (d, J = 5.4 Hz, C-3), 53.2 (OMe), 53.8 and 54.3 (two d, J = 8.0 and 6.9 Hz, $(OMe)_2$), 62.5 (C-4′), 74.9 (C-5′), 122.7 (d, J = 8.9 Hz, C-2), 126.7, 128.6 and 128.7 (CH_{Ar}), 128.9 (C-1), 140.4 (C_{Ar}), 168.8 (d, J = 7.2 Hz, CO ester), 189.4 (CS). For x-ray analysis: crystallization by slow evaporation from toluene; $[\alpha]_D^{20}$: −245.2 (c = 0.9, $CHCl_3$).

Methyl 1-dimethoxyphosphoryl-2-succinimido-3,4-epoxy-cyclohexane-1-carboxylate (**9**). m.p.: 152–153°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 1.88–2.10 (m, 2H, H-5), 2.10–2.62 (m, 2H, H-6), 2.63 (ddd, 1H,

J = 18.2, 9.1 and 5.3 Hz, H-3a′ or 4a′), 2.69 (ddd, 1H, J = 18.2, 10.1 and 4.4 Hz, H-3b′ or 4b′), 2.76 (ddd, 1H, J = 18.2, 9.1 and 4.4 Hz, H-4a′ or 3a′), 2.87 (ddd, 1H, J = 18.2, 10.1 and 5.3 Hz, H-4b′ or 3b′), 3.14 (dd, 1H, J = 4 and 4 Hz, H-2), 3.40 (m, 1H, H-1), 3.68 (s, 3H, OMe), 3.72 and 3.76 (two d, 6H, J = 10.7 Hz, $(OMe)_2$), 4.82 (d, 1H, J = 14.4 Hz, H-3). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 20.4 (d, J = 12.6 Hz, C-6), 21.5 (d, J = 5.4 Hz, C-5), 27.7 (C-3′ or 4′), 28.4 (C-4′ or 3′), 47.3 (d, J = 140 Hz, C-4), 47.7 (d, J = 5.4 Hz, C-3), 52.7 (OMe), 52.9 (C-1), 53.4 and 54.3 (two d, J = 7.2 Hz, $(OMe)_2$), 53.5 (d, J = 10.8 Hz, C-2), 168.9 (CO ester), 174.9 (CO imide), 177.4 (CO imide) For x-ray analysis: crystallization by slow evaporation from toluene.

3-Succinimido-4-methylcarbonyl-5-dimethoxyphosphoryl-1-cyclohexene (**10**). m.p.: 135–136°C; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 2.25 (s, 3H, Me), 2.33 (ddd, 1H, J = 18.6, 14.0 and 11.3 Hz, H-6a), 2.57 (ddd, 1H, J = 18.6, 6.1 and 6.1 Hz, H-6b), 2.60 (s, 4H, CH_2—CH_2), 2.97 (dddd, 1H, J = 16.5, 12.5, 11.3 and 6.1 Hz, H-5), 3.30 (ddd, 1H, J = 12.5, 6.1 and 6.1 Hz, H-4), 3.62 (d, 6H, J = 11 Hz, $(OMe)_2$), 4.86 (dddd, 1H, J = 6.1, 5.2, 2.7 and 2.4 Hz, H-3), 5.50 (dddd, 1H, J = 10.1, 5.2, 2.1 and 2.1 Hz, H-2), 6.07 (ddddd, 1H, J = 10.1, 5.2, 2.7, 2.7 and 2.7 Hz, H-1). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 24.5 (d, J = 3.6 Hz, C-6), 27.7 (CH_2-CH_2), 28.8 (d, J = 142 Hz, C-5), 31.8 (Me), 43.9 (d, J = 14.3 Hz, C-3), 49.1 (d, J = 3.6 Hz, C-4), 120.0 (C-2), 130.7 (d, J = 14.3 Hz, C-1), 177.4 (CO imide), 208.2 (CO ketone). For x-ray analysis: crystallization by slow evaporation from toluene.

Methods

The NMR spectra were recorded under standard conditions on a Bruker AM500 spectrometer with 3.000 computer using a 5 mm ^1H and ^{13}C probe at room temperature (25°C). The $CDCl_3$ solvent provided an internal deuterium lock signal and an internal spectral reference (76.9 ppm for ^{13}C). The reported chemical shifts and coupling constants are accurate to 0.1 ppm and 0.1 Hz respectively. The assignments were confirmed by selective H—H and H—C irradiations.

For the four structures, the x-ray intensity data were collected at room temperature with a MAR345 image plate detector using MoKα ($\lambda = 0.71069$ Å) monochromatized radiation. The crystal data and the data collection parameters are summarized in Table I. The unit cell parameters were refined using all the collected spots after the integration process. Figures are drawn in the ORTEP style.[10] All the four structures were solved by direct methods with SHELXS97[17] and refined by full-matrix least-squares on F^2 using SHELXL97.[10] All the nonhydrogen atoms were refined with anisotropic temperature factors. The

hydrogen atoms were located from Fourier difference or calculated with AFIX and included in the refinement with a common isotropic temperature factor. The details of the refinement and the final R indices are presented at Table I. In each structure the largest peak in the final Fourier difference synthesis is located near a heavy atom.

The details of the four structures have been deposited with the Cambridge Crystallographic data Centre, no. CCDC204151–204154.

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