Asymmetric synthesis of β- and γ-amidophosphonates by Diels–Alder reaction using chiral aminodiene: theoretical and experimental study of the facial selectivity of chiral *N*-dienyl lactam

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Asymmetric [4 + 2] cycloaddition of optically pure 1-aminodiene **1** onto substituted phosphonodienophiles **2** and **4** provided respectively chiral β- and γ-amidophosphonocyclohexenes with good selectivities. The absolute stereochemistry of the major diastereoisomer was experimentally proved by NMR experiments and the facial selectivity of diene **1** is discussed on the basis of *ab initio* calculations.

Introduction

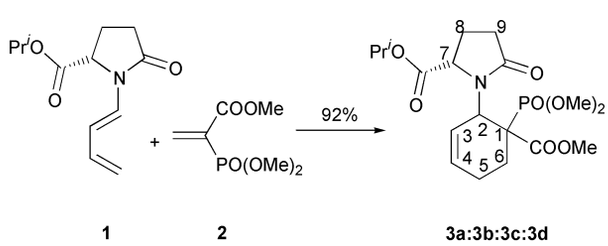
Aminophosphonic derivatives constitute an important class of compounds that exhibit numerous and various biological activities.[1,2] Among them the most developed are the α-aminophosphonic acids, the direct analogues of the usual amino acids, for which many methods of synthesis have already been proposed, including efficient asymmetric syntheses.[1b,3,4] Nevertheless, various naturally occurring aminophosphonates are known to contain the amino function in a position other than the α one. Moreover, in many cases 'non-alpha' aminophosphonic derivatives have been shown to possess specific and interesting properties[1c,2] as bioregulators, antibiotics, enzyme inhibitors, complexing agents, additives, pH indicators,[5] *etc.* However, only a few asymmetric syntheses of β- and γ-aminophosphonates have been disclosed at this time.[1d,6] We have previously reported on the synthesis of racemic chiral β-imidophosphonocyclohexenes obtained by [4 + 2] cycloaddition reactions between trialkyl 2-phosphonoacrylates and *N*-buta-1,3-dienylsuccinimide;[7,8] oxidative ring-opening of the cycloadducts and functional group deprotections furnished β-aminoalkyl phosphonic acids.[9] Now, we have further developed this strategy for the asymmetric synthesis of optically active β- and γ-amidophosphonates by using a chiral partner in the Diels–Alder reactions. Chiral phosphonodienophiles and their reactions with standard non-functionalized dienes have been recently described in a single publication: the diastereoselectivities were moderate.[10] We selected the reversed approach, based on the use of a chiral aminodiene.

Recently, some chiral aminodienes have been described in the literature.[11,12] Among the optically active 1-aminodienes, the *N*-dienyl pyroglutamate derivatives are reported to be very efficient.[13,14] Smith *et al.* first presented the cyclisation of ethyl *N*-dienyl pyroglutamates onto acrylic derivatives with good facial selectivities.[13] Defoin *et al.* then described hetero-Diels–Alder reactions of chiral *N*-dienyl lactams with acylnitroso dienophiles (with single and double asymmetric induction).[14] However, the facial selectivity of chiral *N*-dienyl pyroglutamates towards carbonated dienophiles was neither proved experimentally, nor theoretically examined.

We report here on the asymmetric synthesis of β- and γ-amidophosphonate derivatives by addition of enantiomerically pure isopropyl *N*-dienyl pyroglutamate onto *geminally*- or *vicinally*-substituted phosphonodienophiles. The facial selectivity of the chiral *N*-dienyl pyroglutamate partner has been established and explained for the first time by *ab initio* calculations.

Results and discussion

According to our preliminary work,[7–9] vinylphosphonates are poorly reactive dienophiles and require to be activated by an electron withdrawing substituent to react with *N*-protected 1-aminodienes. Thus the cyclisation of isopropyl *N*-dienyl-L-pyroglutamate **1** with trimethyl 2-phosphonoacrylate **2** in refluxing acetonitrile provided four diastereoisomers **3a–d** in 92% yield (Scheme 1) which could be separated by semi-



Scheme 1 Asymmetric synthesis of β-amidophosphonocyclohexene.

preparative HPLC and analysed by gas chromatography (GC), ^{1}H and ^{13}C NMR spectroscopy. The isomer ratio of 2 : 73 : 8 : 17 was determined by GC on the crude mixture; the products are thermally stable.

The diastereoisomers **3a** and **3b** exhibited heteronuclear P–C(5) and P–C(2) coupling constants of respectively 12.6 and 5.4 Hz (Fig. 1). As already demonstrated on similar structures, these values are characteristic of an equatorial position of the phosphonic group.[7,15] On the other hand the values of these coupling constants for the diastereoisomers **3c** and **3d** were typical of an axial position of the phosphorus.

With the aim of determining the conformation of the amine moiety and, subsequently, its relative stereochemistry towards the phosphorus group (*endo*/*exo* configuration), we have performed theoretical calculations[16] (PM3) on the relative stabilities of each conformer of the four diastereoisomers **3a–d**. As shown by the calculated relative energies of the two half-chair conformers of the cyclohexene ring for each diastereoisomer,

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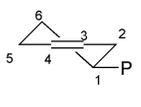
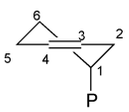
Table 1 Relative calculated energies (PM3) of the two half-chair conformers of each cyclohexene **3a**–**d** (kcal mol^{-1})

(C1,C2) configuration	*N*-pseudoaxial	*N*-pseudoequatorial
(*R*,*R*)	0.00	2.82
(*S*,*R*)	0.37	8.98
(*S*,*S*)	0.78	1.77
(*R*,*S*)	1.55	8.78



3a and **3b**



3c and **3d**

$^2J_{P\text{-}C(2)}$ = 5.4 Hz $^3J_{P\text{-}C(5)}$ = 12.6 Hz

$^2J_{P\text{-}C(2)}$ = 0 Hz $^3J_{P\text{-}C(5)}$ = 3.6-5.4 Hz

Fig. 1 Characteristic heteronuclear C–P coupling constants for diastereoisomers **3a**–**d**.

the pseudoaxial position of the lactam moiety is always preferred (Table 1). On similar structures with a succinimide group in position 2, the pseudoaxial conformation of this substituent has been experimentally confirmed by X-ray diffraction analysis.[7] These results led to attribution of the *endo*- and *exo*-stereochemistry respectively to **3a**,**b** and **3c**,**d** diastereoisomers, considering the phosphonate group as the directing substituent. Accordingly, the *endo*-selectivity was 75 : 25.

As far as *N*-protected 1-aminodienes are concerned, the authors generally admitted that the carbonyl group on the amide[13] or carbamate nitrogen[11e] preferentially adopts the *anti* conformation, away from the dienyl moiety. They speculated that the *syn* orientation of the dienyl carbons towards the carbonyl function should be higher in energy due to steric interactions between the oxygen of the lactam and the hydrogen of the dienyl group. Since this difference in energy was expected to be maintained at the transition states of the cycloaddition, the cyclisation of the *syn* conformer of the diene should be disfavoured. We calculated the relative energies (B3LYP 6-31G**)[16] of the two conformers (*syn* and *anti*) of *N*-dienyl pyroglutamic acid and of two relevant transition states[17] of the reaction between this model of diene **1** and ethylene (Scheme 2). The results obtained showed that the cyclisation of the *anti* conformer should be indeed preferred.

In our opinion, the higher energy (2.96 kcal mol^{-1}) of the *syn* conformer compared to the *trans* conformer of the diene has two causes: (1) a disfavouring steric interaction between the oxygen of the carbonyl function and the hydrogen on C(2) of the diene as previously predicted, but also (2) a less important stabilisation by electronic delocalisation in the *syn* conformer. A *syn* conformation between two conjugated double bonds indeed decreases the conjugation, comparatively to the *anti* conformer, for electronic reasons.[18,19]

However, the structures of the transition states (Fig. 2) and the larger difference in energy between those (3.56 kcal mol^{-1}) in comparison to the difference between the two conformers of the diene showed that the facial selectivity cannot be fully explained only by these two effects. The difference in energy between the two transition states is indeed increased by a steric interaction in TS2 between the dienophile and the hydrogen atom of the chiral centre that induces a rotation of the lactam function (dihedral angle C(2)–N–C(6)–C(7) = 22.2°), diminishing the overlap between the lactam and the dienyl moiety, and then reducing over again the possibility of stabilisation by electronic delocalisation.

The predicted facial selectivity was experimentally confirmed by the observation of a nuclear Overhauser effect (NOE) between H(6a) and H(7) in the major diastereoisomer **3b** (Fig. 3). This NOE established clearly the *pseudoaxial* conformation of the lactam moiety, *i.e.* the *R* configuration of carbon C(2); this effect could not be present in the case of *S* configuration for this carbon atom, as can be shown by a theoretical conformational study (PM3).[16] Thus, NOE combined with the heteronuclear C–P coupling constants confirmed unambiguously the absolute configuration C1(*S*)–C2(*R*) of the major diastereoisomer **3b**. Accordingly, the diastereoselectivity of *endo* (**a**,**b**) and *exo* (**c**,**d**) stereoisomers of the β-amidophosphonocyclohexenes **3** was respectively 97% and 68%.

Asymmetric γ-amidophosphonocyclohexenes **5** could be similarly obtained by using β-acetyl vinyl phosphonate **4**[20] as dienophile. McClure[21] has already observed that this dienophile reacts with electron rich 1-substituted dienes, such as 1-acetoxybutadiene, to provide cycloadducts with the carbonyl group of the dienophile in the *ortho*-position with respect to the donor group of the diene. Thus the cyclisation of **4** with the chiral aminodiene **1** in toluene at reflux provided the cycloadduct **5** with excellent regioselectivity (95 : 5) and good

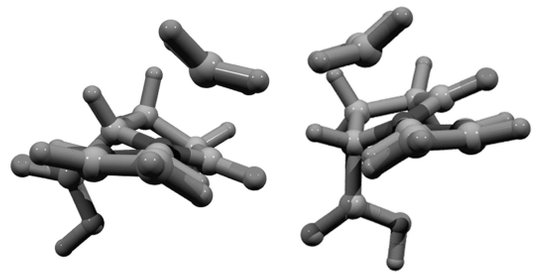


Fig. 2 Structures of two relevant transition[17] states of the cycloaddition of ethylene and *N*-dienyl pyroglutamic acid: left: **TS1**, 20.04 kcal mol^{-1} (dihedral angle C(2)–N–C(6)–C(7) = 168.7°); right: **TS2**, 23.60 kcal mol^{-1} (dihedral angle C(2)–N–C(6)–C(7) = 22.2°).

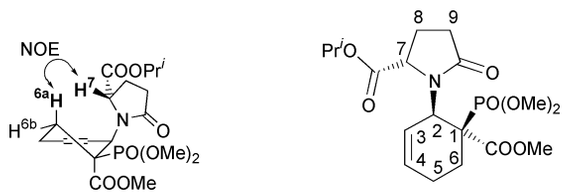
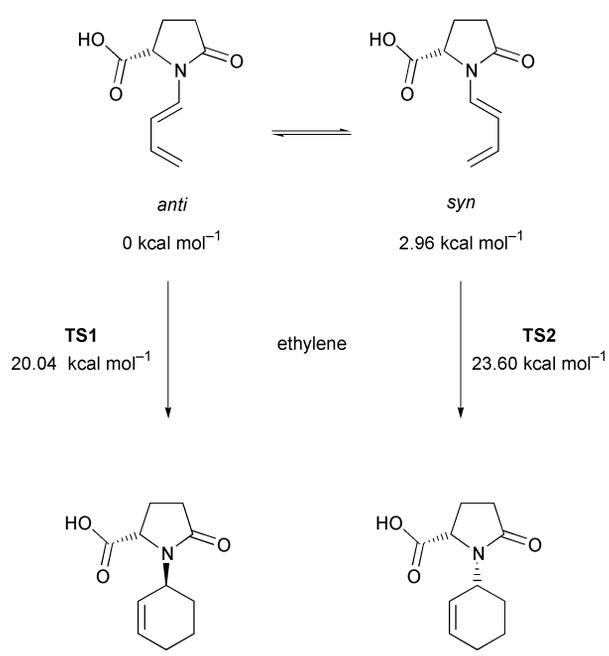
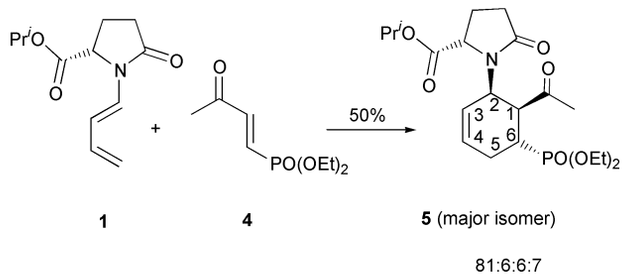


Fig. 3 Determination of absolute configuration of C(2) by NOE for **3b**.



Scheme 2 Facial selectivity of *N*-dienyl pyroglutamic acid in Diels–Alder reaction with ethylene: relative energies of *syn* and *anti* conformers of the diene and corresponding transition states.



Scheme 3 Asymmetric synthesis of γ-amidophosphonocyclohexene.

diastereoselectivity according to the GC and NMR analyses (Scheme 3). The experimental ratio of stereoisomers **5** of 81 : 6 : 6 : 7 corresponds to an *endo* selectivity of 87% and a facial selectivity, for the *endo*-stereoisomer of γ-amidophosphonocyclohexene **5**, of 93%.

The *endo* configuration can be easily attributed to the major diastereoisomer by the observation of a coupling constant of 6.1 Hz between H(1) and H(2). The value of 12.5 Hz for the coupling constant between H(1) and H(6) confirmed the *trans* relative configuration between the acetyl and phosphonate functions. The facial selectivity, *i.e.* the *R* configuration at C(2), was attributed by similarity to the cyclisation of diene **1** with trimethyl 2-phosphonoacrylate **2**.

Conclusions

The results reported here illustrate an easy asymmetric synthesis of chiral β- and γ-amidophosphonocyclohexene derivatives that could be further functionalized[9] or transformed by ring-opening into interesting glutamate analogues.[1] For the first time, the facial selectivity of the diene **1** has been theoretically explained. This comprehension of the factors governing the facial selectivity should allow us to develop more efficient chiral 1-aminodienes. Our current investigations concern the cycloaddition of phosphonodienophiles with chiral oxazolidinone-containing dienes for which excellent facial selectivities have been recently reported.[11e]

Experimental

General

Reagents and solvents were purchased from Acros or Aldrich. The IR spectra were taken with a Perkin-Elmer 1710 instrument and calibrated with polystyrene. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-500 spectrometer, in $CDCl_3$ solution; chemical shifts are reported in ppm (δ) downfield from internal Me_4Si (J in Hz). The high resolution mass spectra (HRMS) were measured in the laboratory of Professor Flammang (université Mons-Hainaut). Gas chromatography (GC) analyses were realised on a CE instrument HRGC-5300 (column Chirasil DEX CB). HPLC analyses and separations were performed on NOVAPAK AD columns with a UV-detector at 220 nm. Optical rotation values are given in 10 deg mL cm^{-1} g^{-1}.

Isopropyl (2*S*)-1-[(1*R*)-1-methoxycarbonyl-1-(dimethoxyphosphoryl)cyclohex-3-en-2-yl]-5-oxopyrrolidine-2-carboxylate

A solution of aminodiene **1** (360 mg, 1.61 mmol) and dienophile **2** (275 mg, 1.34 mmol) in acetonitrile (4 mL) was stirred at reflux. After 48 h, a supplement of **2** (137 mg, 0.67 mmol) was added and the solution was stirred for 24 h. After removal of CH_3CN, the mixture was passed through a column of silica gel (elution with 90 : 10 AcOEt–Pr^{i}OH) to afford a mixture of **3a**–**d** (430 mg, 92%) as a colourless oil. The crude mixture when analysed by chiral gas chromatography revealed an isomer ratio of 2 : 73 : 8 : 17 (given in order of retention time). Pure fractions of the diastereoisomers **3b** and **3d**, and a mixture of **3a** and **3c** (40 : 60) were obtained by semipreparative HPLC. **3a**–**d**: HRMS calcd for $C_{18}H_{28}NO_8P$: 417.155256, Found: 417.155891; ν_{max}/cm^{-1} 1740 (C=O), 1700 (C=O); GC (150⟶225 °C at 5 °C min^{-1}): t_R = 35.2, 36.2, 37.1 and 39.5 min; HPLC (hexane–Pr^{i}OH 70 : 30, 1 mL min^{-1}, 25 °C, 220 nm): t_R = 7.5, 9.9 and 11.2 min. **3b**: $[\alpha]_D^{20}$ −11.75 (*c* 0.72 in $CHCl_3$); δ_H(500 MHz, $CDCl_3$, 20 °C, TMS) 1.16 (3H, d, *J* 7.0, C*H*$_3$-CH), 1.17 (d, 3H, *J* 7.0, C*H*$_3$-CH), 1.82 (m, 1H, *H*-CHCHN), 2.10 (m, 1H, *H*-CHCH=CH), 2.20 (m, 2H, *H*-CHCP and *H*-CHCH=CH), 2.44 (m, 1H, *H*-CHCP), 2.29 (m, 1H, *H*-CHCON), 2.54 (m, 1H, *H*-CHCON), 3.69 (d, 3H, J_{H-P} 11.0, MeOP), 3.72 (s, 3H, MeOC=O), 3.75 (d, 3H, J_{H-P} 11.0, MeOP), 4.53 (d, 1H, *J* 8.2, HCCOO), 4.91 (qq, 1H, *J* 7.0, $HCMe_2$), 5.42 (ddd, 1H, *J* 5.5, 10.1, J_{H-P} 4.2, *H*-C=CHCH_2), 5.71 (m, 1H, *H*-CN-CH=CH), 5.75 (m, 1H, *H*-C=CHCHN); δ_C(125 MHz, $CDCl_3$, 20 °C, TMS) 21.0, 21.3, 21.4, 22.5, 23.6, 28.9, 46.0 (J_{C-P} 5.4), 52.4 (J_{C-P} 133.0), 52.9, 53.4 (J_{C-P} 7.2), 54.0 (J_{C-P} 7.2), 59.2, 68.4, 123.3, 130.9, 169.0 (J_{C-P} 7.2), 172.8, 175.8.

Isopropyl (2*S*)-1-[(5*R*,6*S*)-6-acetyl-5-(diethoxyphosphoryl)-cyclohex-2-en-1-yl]-5-oxopyrrolidine-2-carboxylate

A solution of aminodiene **1** (393 mg, 1.76 mmol) and dienophile **4** (242 mg, 1.17 mmol) in toluene (4 mL) was stirred at reflux for 48 h. The solvent was removed under reduced pressure. The crude mixture was analysed by chiral gas chromatography as above and revealed an isomer ratio of 81 : 6 : 6 : 7. The residue was purified by column chromatography on silica gel (elution with 90 : 10 AcOEt–Pr^{i}OH) to afford the four diastereoisomers **5** (245 mg, 50%) as a yellow oil: HRMS calcd for $C_{20}H_{32}NO_7P$: 429.191641, Found: 429.191071; δ_H of the major isomer (500 MHz, $CDCl_3$, 20 °C, TMS) 1.22 (m, 6H, (C*H*$_3$)$_2$CH), 1.29 (t, 3H, *J* 7.3, C*H*$_3$-CH$_2$), 1.31 (t, 3H, *J* 7.3, C*H*$_3$-CH$_2$), 1.85 (m, 1H, *H*-CON), 2.22 (m, 1H, *H*-CON), 2.28 (m, 1H, *H*-CHCHCOO), 2.30 (s, 3H, MeC=O), 2.35 (m, 1H, *H*-CHCH=CH), 2.50 (m, 2H, *H*-CHCH=CH and *H*-CHCHCOO), 2.58 (dddd, 1H, *J* 6.7, 11.5, 12.5, J_{H-P} 18.9, *H*-CP), 3.26 (ddd, 1H, *J* 6.1, 12.5, J_{H-P} 8.9, *H*-CC=O), 4.06 (m, 4H, C*H*$_2$-OP), 4.17 (d, 1H, *J* 8.8, *H*-CCOO), 4.98 (m, 1H, *H*-CMe$_2$), 5.14 (ddd, 1H, *J* 2.0, *J* 5.3, 6.1, *H*-CCH=CH), 5.57 (m, 1H, *H*C=CHCH$_2$), 5.93 (m, 1H, *H*C=CHCHN); δ_C of the major isomer (125 MHz, $CDCl_3$, 20 °C, TMS) 16.15 (J_{C-P} 7.2), 16.23 (J_{C-P} 7.2), 21.44, 21.52, 23.77 (J_{C-P} 5.2), 24.02, 28.94, 29.43 (J_{C-P} 141.0), 31.5, 43.94 (J_{C-P} 14.3), 49.62 (J_{C-P} 3.5), 59.40, 61.77 (J_{C-P} 7.2), 61.91 (J_{C-P} 7.2), 68.71, 123.11, 130.27 (J_{C-P} 14.1), 172.60, 175.81, 207.69; ν_{max}/cm^{-1} 1738 (C=O), 1699 (C=O); GC of the major isomer (150⟶225 °C at 5 °C min^{-1}): t_R = 43.8 min (other diastereoisomers at 46.7, 50.3 and 53.2 min).

Theoretical methods

All calculations were performed using the Gaussian 98[16] program package. For the conformers of cyclohexenes **3a**–**d**, all structures were fully optimized with the PM3 method. The structure of *N*-dienyl pyroglutamic acid and of the transition states under investigation have been studied at the B3LYP level using the 6-31G(d,p) basis set. Analytical normal mode frequency calculations were performed for all of the optimized structures. The correctness of the curvature and their eigenvector were checked in order to guarantee the quality of the obtained results. Intrinsic reaction coordinate (IRC) calculations were performed on both transition states to ensure that the identified transition structures lie along the correct reaction coordinates and connect effectively the reactants to the products.

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