Cycloaddition Reactions of Phosphorylated 1,2-Diaza-1,3-butadienes with Olefins: Regioselective Synthesis of Pyridazine Derivatives

Francisco Palacios,*[a] Domitila Aparicio,[a] Yago López,[a] Jesús M. de los Santos,[a] and Concepción Alonso[a]

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The aza-Diels–Alder reaction of 4-phosphinyl- and 4-phosphonyl-1,2-diaza-1,3-butadienes with styrene, cyclopentadiene, dihydrofuran and norbornadiene is reported. Monocyclic, bicyclic and polycyclic tetrahydropyridazines containing a phosphane oxide or a phosphonate substituent are obtained. The formation of cycloadducts can be explained by an *endo* transition state in the cycloaddition process of these heterodienes with styrene, cyclopentadiene, dihydrofuran, and by means of an *exo* transition state in the case of norbornadiene.

Introduction

The Diels–Alder reaction has both enabled and shaped the art and science of synthesis in recent years, and azabutadienes have proved to be efficient heterodienes in aza-Diels–Alder processes.[1,2] 1,2-Diaza-1,3-butadienes (**III**, Figure 1) are widely used intermediates in organic synthesis,[3,4] and theoretical calculations [at the Becke3LYP/6-31G(d) computational level] have shown that they are more efficient dienes than 1- (**I**) and 2-azabutadienes (**II**, Figure 1) for the formation of heterocycles by aza-Diels–Alder processes.[5] Some examples of the use of 1,2-diaza-1,3-butadienes (**III**) both in Diels–Alder reactions with electron-poor dienophiles[6] and also in inverse-demand Diels–Alder reactions with electron-rich dienophiles[7] have been described. However, as far as we know no example of an aza-Diels–Alder reaction of 1,2-diaza-1,3-butadienes (**IV**, Figure 1), containing a phosphorus substituent, has been reported. It is known that phosphorus substituents regulate important biological functions,[8] and that molecular modifications involving the introduction of organophosphorus functionalities in simple synthons could be very interesting from a synthetic point of view because they can be useful substrates for the preparation of biologically active compounds.

We have previously described the synthesis of 2-aza-[9] and 1,2-diaza-1,3-butadienes,[10] as well as new strategies for the preparation of three-,[11] five-,[12] and six-membered[13] phosphorus-substituted nitrogen heterocycles from functionalised phosphane oxides and phosphonates, and the application of phosphorus-substituted hydrazones[14] as starting materials for the preparation of acyclic and cyclic compounds. Recently, we described the preparation of new phosphorylated conjugated aza-alkenes[15] (**IV**, Figure 2) and the preparation of α-aminophosphorus derivatives (**V**, Figure 2) by Michael addition of amines to these substrates. As a continuation of our work on the cycloaddition reaction of azadienes[9] and on the preparation of phosphorus-substituted heterocycles,[11–13] here we aim to explore the behaviour of heterodienes, such as 4-phosphinyl-**IV** (R = Ph) and 4-phosphonyl 1,2-diaza-1,3-butadienes **IV** (R = OEt), towards olefins for the preparation of the phosphorus-substituted heterocycles (**VI**, Figure 2). The effect of optically active substituents[16] at the terminal nitrogen atom (N-1) is also reported.

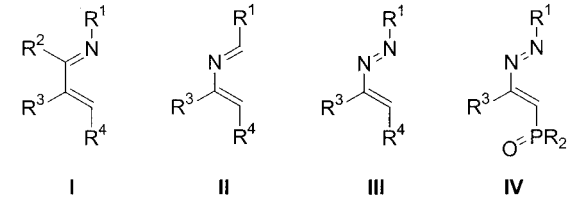

Figure 1. 1- and 2-azadienes **I** and **II** and 1,2-diazadienes **III** and **IV**.

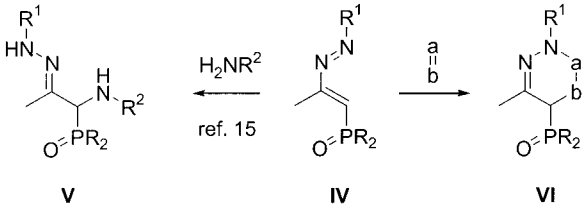

Figure 2. Reactivity pattern of phosphorylated 1,2-diazadienes.

[a] Facultad de Farmacia, Departamento de Química Orgánica I, Universidad del País Vasco
Apartado 450, 01080, Vitoria, Spain
Fax: +34-945-013-049
E-mail: qoppagaf@vf.ehu.es

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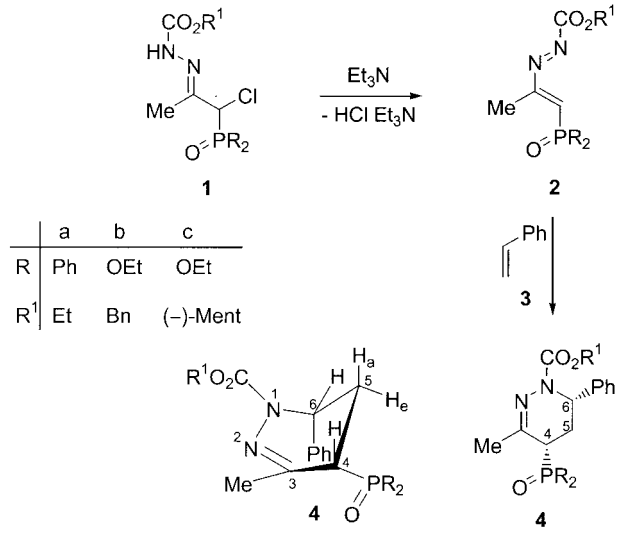
Results and Discussion

Reaction of 1,2-Diaza-1,3-butadienes 2 with Acyclic and Cyclic Alkenes

Initially, the behaviour of diazabutadienes **2** (Scheme 1) as heterodienes with electron-poor dienophiles such as diethyl acetylenedicarboxylate, diethyl azodicarboxylate or tetracyanoethylene was explored. However, the formation of cycloadducts was not observed in these reactions and the starting materials were recovered. The presence of electron-withdrawing groups at the terminal nitrogen (N-1) and carbon atoms (C-4) of the azo-ene system of the 1,2-diaza-1,3-butadienes **2** suggested that inverse-demand aza-Diels–Alder reactions with electron-rich dienophiles[7] could be favoured. For this reason, we explored the reaction with styrene. Highly coloured 4-phosphinyl-1,2-diaza-1,3-butadiene (**2a**; R = Ph), obtained as a mixture of the *E*- and *Z*-isomers in a ratio of 85:15, was generated in situ from chlorohydrazones **1** (R = Ph, R^1 = Et) in the presence of triethylamine[15] (Scheme 1). Addition of styrene (**3**) to 1,2-diaza-1,3-butadiene **2a** led to the formation of tetrahydropyridazylphosphane oxide (**4a**; R = Ph, R^1 = Et) in moderate yield (66%) and in a regioselective fashion (Scheme 1).



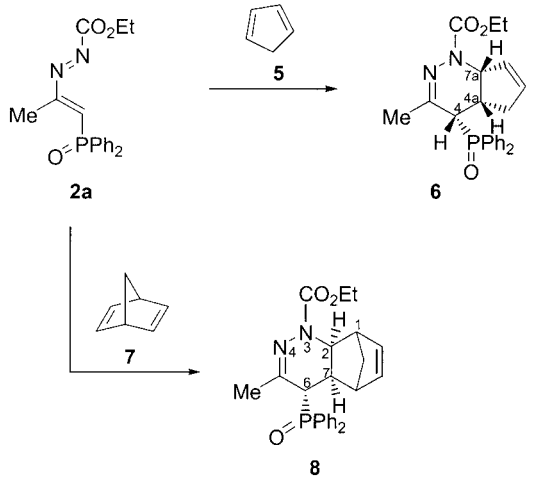
Scheme 1.

Spectroscopic data, including NOE experiments, were in agreement with the assigned structure of compound **4a**. The ^{1}H NMR spectrum of **4a** shows multiplets at δ_H = 2.0 and 2.4 for the H-5 ($^2J_{H,H}$ = 13.2 Hz) protons and at δ_H = 2.92 ppm for H-4 ($^3J_{H,H}$ = 11.6 and 4.6 Hz), while H–6 appears as a broad singlet at δ_H = 5.56 ppm. Difference experiments (NOE), either between H-4 and H-5a (4.3%) when H-4 was irradiated or between H-6 and both H-5a (2.4%) and H-5e (3.7%) when H-6 was irradiated, as well as the coupling constants observed, are all consistent with a semi-boat conformation with the axial phenyl group at the 6-position and the equatorial diphenylphosphane oxide group (R = Ph) at the 4-position, with a *cis* configuration between protons H-4 and H-5a ($^3J_{H,H}$ = 11.6 Hz) and a *trans* configuration between protons H-4 and H-5e ($^3J_{H,H}$ = 4.6 Hz).[7a] The formation of this cycloadduct **4a** could be explained by an aza-Diels–Alder reaction with an *endo* approach of the styrene to the heterodiene **2a** (Scheme 1).

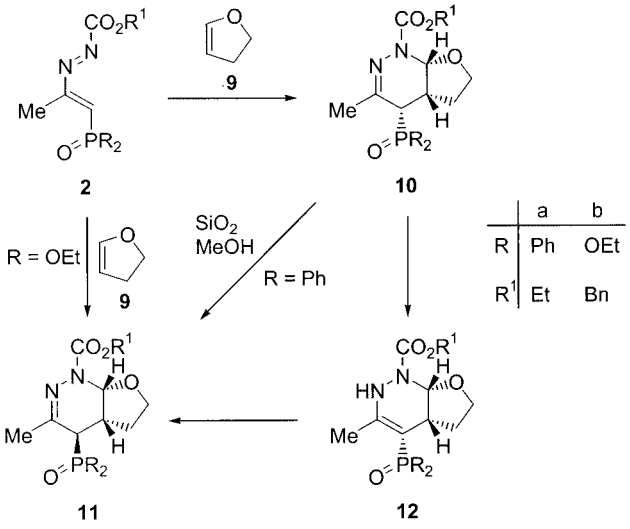
This process was extended to 4-phosphonyl-1-benzyloxycarbonyl-1,2-diaza-1,3-butadiene (**2b**; R = OEt, R^1 = Bn) and, in a similar way to that described before, the tetrahydropyridazyl phosphonate (**4b**; R = OEt, R^1 = Bn) was obtained in 58% yield. As far as we know, this process represents the first example of a [4+2] cycloaddition reaction of 1,2-diaza-1,3-butadienes containing phosphorus substituents (Scheme 1). We next explored the influence of the presence of an optically active group[16] [(–)-menthyloxycarbonyl] at the terminal nitrogen atom (N-1) of 1,2-diazadienes **2**. Reaction of styrene with 1,2-diazadiene **2c** [R = OEt, R^1 = (–)-Ment], generated "in situ" from chlorohydrazone **1c**, gave the *endo*-cycloadduct [**4c**; R = OEt, R^1 = (–)-Ment] in a 1:1 diastereoisomeric ratio (Scheme 1). The proportion of diastereoisomers was determined from the ^{31}P NMR spectrum of the crude reaction mixture. This result suggests that the chiral group at the nitrogen atom of the 1,2-diazadiene has negligible influence on the cycloaddition process. Pyridazines constitute an important class of compounds with interest in organic and medicinal chemistry.[17,18] However, only one example of the preparation of pyridazines containing phosphorus substituents has been described[19] by reaction of diazoalkyl-1,3-dipoles and cyclopropenyl derivatives. Therefore, as far as we know, this strategy represents the first synthesis of tetrahydropyridazines containing a phosphinyl or a phosphonyl group as substituent, as well as the first example of an aza-Diels–Alder reaction of the phosphorylated 1,2-diaza-1,3-butadienes **2**.

We also studied the cycloaddition of cyclic olefins to diazaalkenes **2**. The addition of cyclopentadiene **5** to 1,2-diaza-1,3-butadiene **2a** led to the formation of the functionalised *endo* bicyclic cycloadduct **6** (yield of isolated compound 69%, Scheme 2). As before, the structure of compound **6** was assigned on the basis of NMR spectroscopic data, including NOE experiments, and MS data. The ^{1}H NMR spectrum of **6** shows multiplets at δ_H = 3.07 ppm for H-4a, δ_H = 3.26 ppm for H-4 and at δ_H = 5.19 ppm for H-7a. The vicinal coupling constants ($^3J_{H,H}$) of 9.3 Hz between H-4a and H-7a and 3.5 Hz between H-4 and H-4a support the *cis* orientation[7a,20] of the three protons H-4, H-4a and H-7a. In the ^{13}C NMR spectrum the absence of vicinal coupling constants ($^3J_{P,C}$) between C-5 and the phosphorus atom also suggests the *cis* configuration of the phosphane oxide group and the cyclopentene ring.[21]

A different behaviour was observed when **2a** was treated with a strained olefin such as norbornadiene, as only the *exo* tricyclic pyridazine derivative **8**, instead of the *endo* cycloadduct as before, was obtained. Its vicinal coupling constants ($^3J_{H\text{-}2,H\text{-}7}$ = 9.3 Hz and $^3J_{P,C\text{-}8}$ = 11.0 Hz) are consistent with the *cis*-ring juncture of the fused polycyclic compound[20,21] and with the *exo* structure in a similar way to that reported for cycloadducts derived from norbornadiene and azides (1,3-cycloadition)[22] or 2-aza-1,3-butadienes (aza-Diels–Alder).[23] This strategy represents the first ex-



Scheme 2.



Scheme 3.

ample of the synthesis of bicyclic and polycyclic tetrahydropyridazylphosphane oxides (R = Ph) or phosphonates (R = OEt).

Reaction of 1,2-Diaza-1,3-butadienes 2 with Electron-Rich Dienophiles

Finally, we studied the inverse-demand aza-Diels–Alder reaction of 1,2-diaza-1,3-butadienes **2** with an electron-rich dienophile such as dihydrofuran **9**. Treatment of 4-phosphinyl-1,2-diaza-1,3-butadiene (**2a**; R = Ph, R^1 = Et) with dihydrofuran in the absence of solvent led to the formation of the functionalised bicyclic pyridazine (**10a**; R = Ph, R^1 = Et) in a regio- and stereoselective fashion, since no traces of regioisomer with the oxygen atom at the 5-position were observed and a very high proportion (>97%) of the *endo* isomer was detected spectroscopically (^{1}H and ^{31}P NMR) in the crude reaction mixture and isolated (yield 65%, Scheme 3). The spectroscopic data are in agreement with the assigned structure of compound **10a**. The vicinal coupling constant between H-4a and H-7a ($^3J_{H,H}$ = 8.9 Hz) and the absence of vicinal coupling constants ($^3J_{P,C}$) between C-5 and the phosphorus atom support the *cis* orientation of the three protons H-4, H-4a and H-7a.

Bicyclic pyridazine **10a** was easily epimerised at C-4 upon treatment with silica gel (SiO_2) in methanol, and the corresponding pyridazinylphosphane oxide (**11a**; R = Ph, R^1 = Et) with a *cis* configuration of the phosphane oxide group at the 4-position and H-4a was obtained. A coupling constant ($^3J_{H,H}$) of 7.8 Hz between H-4a and H-7a supported the *cis* orientation of these protons, while the vicinal coupling constant ($^3J_{P,C}$) of 11.5 Hz observed in the ^{13}C NMR spectrum between C-5 and the phosphorus atom supports the *trans* configuration of the phosphane oxide group and the tetrahydrofuran ring.[21] Similar epimerisations of *N*-ethoxycarbonyl- and *N*-tosylpyridazine derivatives have been described previously[24] and the formation of the new pyridazine derivative **11a** could be explained by means of an enehydrazinic intermediate **12** and subsequent tautomerisation with formation of the pyridazine **11a**.[25] In a similar way, in the case of the 1,2-diaza-1,3-butadiene containing a phosphonate group at the 4-position, the bicyclic pyridazine (**10b**; R = OEt, R^1 = Bn) was obtained in a regio- and stereoselective fashion. However, this pyrazine could not be isolated and, after treatment with silica gel (SiO_2) in methanol, the corresponding epimerised pyridazinylphosphane oxide (**11b**; R = OEt, R^1 = Bn) was obtained (yield 72%, Scheme 3).

In conclusion, 1-alkoxycarbonyl-1,2-diaza-1,3-butadienes containing a phosphane oxide group (**2a**) or a phosphonate group (**2b** and **2c**) at the 4-position can be used as heterodienes in aza-Diels–Alder reactions, not only with simple (styrene), cyclic (cyclopentadiene) and strained (norbornadiene) olefins but also with an electron-rich dienophile (dihydrofuran) to give monocyclic, bicyclic and polycyclic pyrazine derivatives containing phosphinyl or phosphonyl substituents. Whereas *endo* cycloadducts are obtained in the case of styrene, cyclopentadiene and dihydrofuran, in the case of the strained olefin (norbornadiene) only an *exo* cycloadduct can be isolated. The functionalized pyridazine derivatives obtained may be interesting substrates in organic and medicinal chemistry.[17,18]

Experimental Section

General: Solvents for extraction and chromatography were of technical grade. All solvents used in reactions were freshly distilled. All other reagents were recrystallised or distilled as necessary. All reactions were performed under an atmosphere of dry nitrogen. Analytical TLC was performed with silica gel 60 F_{254} plates. Visualisation was accomplished by UV light or $KMnO_4$ solution. Flash chromatography was carried out on silica gel 60 (230–400 mesh). Melting points are uncorrected. ^{1}H (300 MHz), ^{13}C (75 MHz) and ^{31}P NMR (120 MHz) spectra were recorded on a 300 MHz spectrometer using tetramethylsilane (TMS; δ = 0.00 ppm) or chloroform (δ = 7.24 ppm) as an internal reference in $CDCl_3$ solutions for ^{1}H NMR spectra, or chloroform (δ = 77.0 ppm) as an internal reference in $CDCl_3$ solutions for ^{13}C NMR spectra, and phosphoric

acid (85%) for ^{31}P NMR spectra. Chemical shifts (δ) are given in ppm. Coupling constants (J) are reported in hertz. Low-resolution mass spectra (MS) were obtained at 50–70 eV by electron impact (EI) or chemical ionisation (CI). Data are reported in the form m/z (intensity relative to base = 100). Infrared spectra (IR) were taken on an IRFT spectrometer, and were obtained as solids in KBr or as neat oils in NaCl. Peaks are reported in cm^{-1}. Chlorohydrazones **1**[15] and 1,2-diaza-1,3-butadienes **2**[15] were synthesised according to literature procedures.

General Procedure for the aza-Diels–Alder Reactions. Synthesis of a Pyridazine Derivative: Triethylamine (0.21 mL, 1.5 mmol) was added dropwise under a nitrogen atmosphere to a solution of chlorohydrazone **1** (1 mmol) in dry CH_2Cl_2 (5 mL) at room temperature. The mixture was stirred at this temperature for 30 min. The crude mixture was then diluted with CH_2Cl_2 (4 mL), washed with H_2O (2 × 4 mL) and the aqueous phase was extracted twice with CH_2Cl_2 (4 mL). The solvent was dried over $MgSO_4$ and the solvents evaporated under vacuum. Diazaalkenes **2** were then treated with the appropriate dienophile (2 mL/mmol) under a nitrogen atmosphere at room temperature for 1–2 d. The crude product was purified by crystallisation or flash chromatography (silica gel).

Ethyl (±)-(4*S,6*S**)-4-(Diphenylphosphinoyl)-3-methyl-6-phenyl-5,6-dihydro-4*H*-pyridazine-1-carboxylate (4a):** Obtained as a white solid from **1a** (0.38 g, 1 mmol) and styrene **3** (2 mL) as described in the general procedure. The crude product was purified by crystallisation from diethyl ether. Yield: 0.29 g (66%); m.p. 113–114 °C. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.25 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, CH_3), 1.95–2.07 [m, 4 H, CH_3 and C(5)-H_a], 2.32–2.48 [m, $^3J_{H,H}$ = 4.6, $^2J_{H,H}$ = 13.2 Hz, 1 H, C(5)-H_e], 2.87–2.98 [m, $^3J_{H,H}$ = 4.6, $^3J_{H,H}$ = 11.6 Hz, 1 H, C(4)-H], 4.21–4.28 (m, 2 H, CH_2), 5.56 [br. s, 1 H, C(6)-H], 6.98–7.75 (m, 15 H, arom) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 14.4, 25.1, 27.4, 34.6 (d, $^1J_{P,C}$ = 69.0 Hz), 53.4 (d, $^3J_{P,C}$ = 9.6 Hz), 62.6, 125.1–139.6 (m), 144.9, (d, $^2J_{P,C}$ = 3.0 Hz), 153.9 ppm. ^{31}P NMR (120 MHz, $CDCl_3$, 25 °C): δ = 31.2 ppm. IR (KBr): $\tilde{\nu}$ = 1116, 1314, 1440, 1692, 2912, 2972 cm^{-1}. MS (CI): m/z (%) = 447 (100) [M^+ + 1]. $C_{26}H_{27}N_2O_3P$ (446): calcd. C 69.94, H 6.10, N 6.27; found C 70.15, H 6.08, N 6.25.

Benzyl (±)-(4*S,6*S**)-4-(Diethoxyphosphoryl)-3-methyl-6-phenyl-5,6-dihydro-4*H*-pyridazine-1-carboxylate (4b):** Obtained as an oil from **1b** (0.38 g, 1 mmol) and styrene **3** (2 mL) as described in the general procedure. The crude product was purified by flash chromatography (silica gel, AcOEt/hexanes, 70:30). Yield: 0.26 g (58%). ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.25–1.34 (m, 6 H, 2 × CH_3), 2.22–2.40 [m, 6 H, CH_3, C(4)-H and C(5)-H_2], 4.06–4.15 (m, 4 H, 2 × CH_2), 5.24 (s, 2 H, CH_2), 5.59–5.60 [m, 1 H, C(6)-H], 7.05–7.33 (m, 10 H, arom) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 15.9, 16.0, 23.7, 26.7, 31.8 (d, $^1J_{P,C}$ = 145.0 Hz), 52.9 (d, $^3J_{P,C}$ = 11.1 Hz), 62.0 (d, $^2J_{P,C}$ = 6.5 Hz), 62.6 (d, $^2J_{P,C}$ = 7.1 Hz), 67.4, 124.7–139.2 (m), 144.4 (d, $^2J_{P,C}$ = 3.6 Hz), 153.4 ppm. ^{31}P NMR (120 MHz, $CDCl_3$, 25 °C): δ = 25.6 ppm. IR (NaCl): $\tilde{\nu}$ = 1029, 1248, 1414, 1699, 2985 cm^{-1}. MS (CI): m/z (%) = 445 (100) [M^+ + 1]. $C_{23}H_{29}N_2O_5P$ (444): calcd. C 62.15, H 6.58, N 6.30; found C 62.32, H 6.60, N 6.32.

Menthyl (±)-(4*S,6*S**)-4-(Diethoxyphosphoryl)-3-methyl-6-phenyl-5,6-dihydro-4*H*-pyridazine-1-carboxylate (4c):** Obtained as an oil from **1c** (0.43 g, 1 mmol) and styrene **3** (2 mL) as described in the general procedure. The crude product was purified by flash chromatography (silica gel, AcOEt/hexanes, 50:50). Yield: 0.26 g (53%). ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 0.73–2.37 [m, 29 H, menthyl group, 2 × CH_3 and C(5)-H_2], 4.00–4.15 (m, 1 H, CH_2), 4.50–4.63 [m, 1 H, C(menthyl group)-H], 5.47 [br. s, 1 H, C(6)-H], 7.00–7.27 (m, 5 H, arom) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 15.2, 21.6, 22.6, 23.3, 23.7, 26.2, 26.7, 26.8, 30.8, 30.9, 31.8 (d, $^1J_{P,C}$ = 155.6 Hz), 33.7, 33.8, 40.2, 40.7, 46.5, 53.4 (d, $^3J_{P,C}$ = 13.0 Hz), 61.9–62.5 (m), 75.9–76.1 (m), 124.6–139.9 (m), 141.7, 143.5, 153.0, 153.2 ppm. ^{31}P NMR (120 MHz, $CDCl_3$, 25 °C): δ = 25.7, 25.9 ppm. IR (NaCl): $\tilde{\nu}$ = 1043, 1169, 1255, 1407, 1706, 2939 cm^{-1}. MS (CI): m/z (%) = 493 (100) [M^+ + 1]. $C_{26}H_{41}N_2O_5P$ (492): calcd. C 63.40, H 8.39, N 5.69; found C 63.51, H 8.38, N 5.67.

Ethyl (±)-(4*S,4a*S**,7a*R**)-4-(Diphenylphosphinoyl)-3-methyl-4,4a,5,7a-tetrahydrocyclopenta[*c*]pyridazine-1-carboxylate (6):** Obtained as a white solid from **1a** (0.38 g, 1 mmol) and cyclopentadiene **5** (2 mL) as described in the general procedure. The crude product was purified by crystallisation from diethyl ether. Yield: 0.28 g (69%); m.p. 174–175 °C. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.35 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, CH_3), 2.14 (s, 3 H, CH_3), 2.47–2.55 [m, 1 H, C(5)-H], 2.72–2.79 [m, 1 H, C(5)-H], 3.03–3.11 [m, 1 H, C(4a)-H], 3.26 [m, $^3J_{H,H}$ = 3.5 Hz, 1 H, C(4)-H], 4.29–4.32 (m, 2 H, CH_2), 5.19 [m, $^3J_{H,H}$ = 9.3 Hz, 1 H, C(7a)-H], 5.68 [s, 1 H, C(7)-H], 5.81 [s, 1 H, C(6)-H], 7.49–7.89 (m, 10 H, arom) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 14.6, 24.1, 35.8, 39.1, 39.6 (d, $^1J_{P,C}$ = 80.1 Hz), 62.4, 65.8 (d, $^3J_{P,C}$ = 11.1 Hz), 127.8–135.4 (m), 155.2, 159.7 ppm. ^{31}P NMR (120 MHz, $CDCl_3$, 25 °C): δ = 27.1 ppm. IR (KBr): $\tilde{\nu}$ = 1293, 1424, 1500, 1699, 2866, 2965, 3429 cm^{-1}. MS (CI): m/z (%) = 409 (100) [M^+ + 1]. $C_{23}H_{25}N_2O_3P$ (408): calcd. C 67.64, H 6.17, N 6.86; found C 67.72, H 6.19, N 6.88.

Ethyl (±)-(2*S,6*S**,7*R**)-6-(Diphenylphosphinoyl)-5-methyl-3,4-diazatricyclo[6.2.1.$0^{2,7}$]undeca-4,9-diene-3-carboxylate (8):** Obtained as an oil from **1a** (0.38 g, 1 mmol) and norbornadiene **7** (2 mL) as described in the general procedure. The crude product was purified by flash chromatography (silica gel, AcOEt). Yield: 0.25 g (58%). ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.29 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, CH_3), 1.42–1.63 [m, 2 H, C(11)-H_2], 2.03 (s, 3 H, CH_3), 2.67 [d, $^3J_{H,H}$ = 9.3 Hz, 1 H, C(7)-H], 2.72 [s, 1 H, C(1)-H], 2.88 [s, 1 H, C(8)-H], 3.34 [d, $^1J_{P,C}$ = 21.9 Hz, 1 H, C(6)-H], 3.37–3.45 [m, 1 H, C(2)-H], 4.10–4.20 (m, 2 H, CH_2), 6.10–6.24 [m, 2 H, C(6)–H and C(7)-H], 7.48–7.81 (m, 10 H, arom) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 14.5, 25.8, 38.8, 44.5, 45.4 (d, $^1J_{P,C}$ = 59.4 Hz), 51.0, 51.2 (d, $^3J_{P,C}$ = 11.0 Hz), 52.3, 61.8, 128.3–139.8 (m), 137.2, 140.0, 151.5 (d, $^2J_{P,C}$ = 5.1 Hz), 153.5 ppm. ^{31}P NMR (120 MHz, $CDCl_3$, 25 °C): δ = 29.9 ppm. IR (KBr): $\tilde{\nu}$ = 1268, 1334, 1407, 1669, 2979, 3054 cm^{-1}. MS (CI): m/z (%) = 435 (100) [M^+ + 1]. $C_{25}H_{27}N_2O_3P$ (434): calcd. C 69.11, H 6.26, N 6.45; found C 68.97, H 6.24, N 6.48.

Ethyl (±)-(4*S,4a*S**,7a*R**)-4-(Diphenylphosphinoyl)-3-methyl-4a,5,6,7a-tetrahydro-4*H*-furo[2,3-*c*]pyridazine-1-carboxylate (10a):** Obtained as a white solid from **1a** (0.38 g, 1 mmol) and 2,3-dihydrofuran **9** (2 mL) as described in the general procedure. The crude product was purified by crystallisation from diethyl ether. Yield: 0.27 g (65%); m.p. 153–154 °C. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.36 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, CH_3), 2.17–2.23 [m, 5 H, CH_3 and C(5)-H_2], 2.74–2.81 [m, 1 H, C(4a)-H], 3.22–3.25 [m, 1 H, C(4)-H], 3.64–3.89 [m, 2 H, C(6)-H_2], 4.31–4.39 (m, 2 H, CH_2), 6.04 [d, $^3J_{H,H}$ = 8.9 Hz, 1 H, C(7a)-H], 7.51–7.90 (m, 10 H, arom) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 14.4, 23.7, 27.8, 38.3 (d, $^1J_{P,C}$ = 76.0 Hz), 39.9, 62.7, 68.3, 86.9 (d, $^3J_{P,C}$ = 13.1 Hz), 128.4, 133.4 (m), 154.8, 158.3 ppm. ^{31}P NMR (120 MHz, $CDCl_3$, 25 °C): δ = 26.7 ppm. IR (KBr): $\tilde{\nu}$ = 1320, 1444, 1692, 1685, 2878, 3125 cm^{-1}. MS (CI): m/z (%) = 413 (100) [M^+ + 1]. $C_{22}H_{25}N_2O_4P$ (412): calcd. C 64.07, H 6.11, N 6.79; found C 64.25, H 6.13, N 6.81.

Synthesis of Ethyl (±)-(4*R,4a*S**,7a*R**)-4-(Diphenylphosphinoyl)-3-methyl-4a,5,6,7a-tetrahydro-4*H*-furo[2,3-*c*]pyridazine-1-carboxylate**

(11a): The crude product **10a** was dissolved in MeOH (6 mL) and silica gel (0.2 g) was added. The suspension was stirred at room temperature for 1 d. The solvent was then evaporated under vacuum and the crude product was purified by flash chromatography (silica gel, AcOEt) and crystallised from diethyl ether to obtain **11a** as a white solid. M.p. 168–170 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.29 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, CH_3), 1.65–1.73 [m, 1 H, C(5)-H], 1.84 (m, 3 H, CH_3), 2.17–2.29 [m, 1 H, C(5)-H], 3.29–3.48 [m, 2 H, C(4)-H and C(4a)-H], 3.70–3.89 [m, 2 H, C(6)-H_2], 4.15–4.22 (m, 2 H, CH_2), 5.47 [d, $^3J_{H,H}$ = 7.8 Hz, 1 H, C(7a)-H], 7.49–7.87 (m, 10 H, arom) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 14.4, 25.5, 32.3 (d, $^3J_{P,C}$ = 11.5 Hz), 37.0, 44.6 (d, $^1J_{P,C}$ = 60.4 Hz), 62.1, 66.4, 81.5, 128.2–132.5 (m), 149.5 (d, $^2J_{P,C}$ = 4.0 Hz), 153.3 ppm. ^{31}P NMR (120 MHz, $CDCl_3$, 25 °C): δ = 26.0 ppm. IR (KBr): $\tilde{\nu}$ = 1314, 1440, 1692, 1712, 2866, 2992, 3409 cm^{-1}. MS (CI): *m*/*z* (%) = 413 (100) [M^+ + 1]. $C_{22}H_{25}N_2O_4P$ (412): calcd. C 64.07, H 6.11, N 6.79; found C 64.21, H 6.09, N 6.82.

Benzyl (±)-(4*R,4a*S**,7a*R**)-4-(Diethoxyphosphoryl)-3-methyl-4a,5,6,7a-tetrahydro-4*H*-furo[2,3-*c*]pyridazine-1-carboxylate (11b):** According to the general procedure, **11a** was obtained as an oil from **1b** (0.38 g, 1 mmol) and 2,3-dihydrofuran **9** (2 mL). The crude product was purified by flash chromatography (silica gel, AcOEt) and crystallised from diethyl ether. Yield: 0.30 g (72%). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.06–1.30 (m, 6 H, CH_3), 1.57–1.60 [m, 1 H, C(5)-H], 2.15–2.19 [m, 4 H, CH_3 and C(5)-H], 2.69 [d, $^2J_{P,H}$ = 25.9 Hz, 1 H, C(4)-H], 3.06–3.15 [m, 1 H, C(4a)-H], 3.71–4.11 [m, 6 H, 2 × CH_2 and C(6)-H_2], 5.10–5.26 (m, 2 H, CH_2), 5.82 [d, $^3J_{H,H}$ = 7.9 Hz, 1 H, C(7a)-H], 7.19–7.40 (m, 5 H, arom) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 16.0, 24.9, 31.9 (d, $^3J_{P,C}$ = 15.1 Hz), 36.9 (d, $^2J_{P,C}$ = 4.5 Hz), 39.9 (d, $^1J_{PC}$ = 135.5 Hz), 62.6 (d, $^2J_{P,C}$ = 7.1 Hz), 63.1 (d, $^2J_{PC}$ = 6.7 Hz), 66.6, 67.6, 81.7, 127.9–136.4 (m), 149.7 (d, $^2J_{P,C}$ = 7.6 Hz), 153.8 ppm. ^{31}P NMR (120 MHz, $CDCl_3$, 25 °C): δ = 21.6 ppm. IR (NaCl): $\tilde{\nu}$ = 1248, 1407, 1706, 3005, 3429 cm^{-1}. MS (CI): *m*/*z* (%) = 411 (100) [M^+ + 1]. $C_{19}H_{27}N_2O_6P$ (410): calcd. C 55.60, H 6.63, N 6.83; found C 55.82, H 6.61, N 6.85.

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[1] For reviews see: a) E. M. Stocking, R. M. Williams, *Angew. Chem. Int. Ed.* **2003**, *42*, 3078–3115; b) K. C. Nicolau, S. A. Snyder, T. Montagnon, G. Vassilikogiannakis, *Angew. Chem. Int. Ed.* **2002**, *41*, 1669–1698; c) S. Jayakumar, M. P. S. Ishar, M. P. Mahajan, *Tetrahedron* **2002**, *58*, 379–471; d) P. Buonora, J.-C. Olsen, T. Oh, *Tetrahedron* **2001**, *57*, 6099–6138; e) E. J. Corey, A. Guzman-Perez, *Angew. Chem. Int. Ed.* **1998**, *37*, 388–401; f) L. F. Tietze, G. Kettschau, *Top. Curr. Chem.***1997**, *189*, 1–120; g) L. Ghosez, in *Stereocontrolled Organic Synthesis*, Blackwell, Oxford, **1994**, pp. 193–233.

[2] For recent contributions, see: a) K. C. Nicolau, M. Nevalainen, B. S. Safina, M. Zak, S. Bulat, *Angew. Chem. Int. Ed.* **2002**, *41*, 1941–1945; b) C. J. Moody, R. A. Hughes, S. P. Thompson, L. Alcaraz, *Chem. Commun*. **2002**, 1760–1761; c) D. Ntirampebura, L. Ghosez, *Synthesis* **2002**, 2043–2052; d) V. B. Genisson, P. Nebois, M. Domard, H. Fillion, *Chem. Pharm. Bull.* **2000**, *48*, 893–894; e) E. Jnoff, L. Ghosez, *J. Am. Chem. Soc.* **1999**, *121*, 2617–2618.

[3] For reviews see: a) O. A. Attanasi, P. Filippone, *Synlett* **1997**, 1128–1140; b) J. G. Schantl, in *Houben-Weyl. Methoden der Organische Chemie* (Eds.: H. Kropf, E. Schaumann), Thieme, Stuttgart, **1990**, vol. E15 p. 909; c) O. A. Attanasi, L. Caglioti, *Org. Prep. Proced. Int.* **1988**, *18*, 299–327.

[4] For recent contributions see: a) O. A. Attanasi, L. de Crescentini, G. Favi, P. Filippone, G. Giorgi, F. Mantenilli, S. Santeusanio, *J. Org. Chem.* **2003**, *68*, 1947–1953; b) A. Arcadi, O. A. Attanasi, G. Giorgi, P. Filippone, E. Rossi, S. Santeusanio, *Tetrahedron Lett.* **2003**, *44*, 8391–8394; c) O. A. Attanasi, G. Favi, P. Filippone, G. Giorgi, B. Stanovnik, J. Svete, *Synlett* **2003**, 995–996; d) E. Rossi, A. Arcadi, G. Abbiati, O. A. Attanasi, L. de Crescentini, *Angew. Chem. Int. Ed.* **2002**, *41*, 1400–1402; e) O. A. Attanasi, L. de Crescentini, G. Favi, P. Filippone, F. Mantenilli, S. Santeusanio, *J. Org. Chem*. **2002**, *67*, 8178–8181; f) M. Avalos, R. Babiano, P. Cintas, F. R. Clemente, R. Gordillo, J. L. Jiménez, J. C. Palacios, *J. Org. Chem.* **2001**, *66*, 5139–5145.

[5] M. Avalos, R. Babiano, F. R. Clemente, P. Cintas, R. Gordillo, J. L. Jiménez, J. C. Palacios, *J. Org. Chem*. **2000**, *65*, 8251–8259.

[6] a) M. Avalos, R. Babiano, P. Cintas, F. R. Clemente, R. Gordillo, J. L. Jiménez, J. C. Palacios, *J. Org. Chem.* **2002**, *67*, 2241–2251; b) R. K. Boeckman Jr., P. Ge, J. E. Reed, *Org. Lett.* **2001**, *3*, 3647–3650; c) K. Banert, M. Hagedorn, *Tetrahedron Lett.* **1992**, *33*, 7331–7334; d) G. Ferguson, A. J. Lough, D. Mackay, G. Weeratunga, *J. Chem. Soc., Perkin Trans. 1* **1991**, 3361–3369.

[7] a) O. A. Attanasi, L. de Crescentini, P. Filippone, F. Fringelli, F. Mantenilli, M. Metteucci, O. Piermatti, F. Pizzo, *Helv. Chim. Acta* **2001**, *84*, 513–525; b) M. Avalos, R. Babiano, P. Cintas, F. R. Clemente, J. L. Jiménez, J. C. Palacios, J. B. Sánchez, *J. Org. Chem.* **1999**, *64*, 6297–6305; c) M. S. South, T. L. Jakuboski, M. D. Westmeyer, D. R. Dukesherer, *J. Org. Chem.* **1996**, *61*, 8921–8934; d) S. J. Clarke, T. L. Gilchrist, A. Lemos, T. G. Roberts, *Tetrahedron* **1991**, *47*, 5615–5624; e) T. L. Gilchrist, J. A. Stevens, B. Parton, *J. Chem. Soc., Perkin Trans. 1* **1985**, 1741–1745; f) S. Sommer, *Tetrahedron Lett.* **1977**, *1*, 117–120.

[8] For reviews see: a) R. Engel, in *Handbook of Organophosphorus Chemistry*, M. Dekker, Inc., New York, **1992**; b) P. Kafarski, B. Lejezak, *Phosphorus Sulfur* **1991**, *63*, 193–215; c) R. E. Hoagland, in *Biologically Active Natural Products* (Ed.: H. G. Culter), ACS Symposium Series 380. American Chemical Society, Washington DC, **1988**, p. 182; d) A. D. F. Toy, E. N. Walsh, in *Phosphorus Chemistry in Everyday Living*, American Chemical Society, Washington DC, **1987**, p. 333.

[9] a) F. Palacios, E. Herrán, G. Rubiales, *J. Org. Chem.***2002**, *67*, 2131–2135; b) F. Palacios, C. Alonso, P. Amezua, G. Rubiales, *J. Org. Chem.* **2002**, *67*, 1941–1946; c) F. Palacios, E. Herrán, G. Rubiales, *J. Org. Chem.* **1999**, *64*, 6239–6246; d) F. Palacios, C. Alonso, G. Rubiales, *J. Org. Chem.* **1997**, *62*, 1146–1154.

[10] F. Palacios, D. Aparicio, J. M. de los Santos, *Tetrahedron* **1999**, *55*, 13767–13778.

[11] a) F. Palacios, A. M. Ochoa de Retana, J. I. Gil, R. López de Munain, *Org. Lett.* **2002**, *4*, 2405–2408; b) F. Palacios, D. Aparicio, A. M. Ochoa de Retana, J. M. de los Santos, J. I. Gil, J. M. Alonso, *J. Org. Chem.* **2002**, *67*, 7283–7288; c) F. Palacios, A. M. Ochoa de Retana, E. Martínez de Marigorta, J. M. de los Santos, *Eur. J. Org. Chem.* **2001**, 2401–2414; d) F. Palacios, A. M. Ochoa de Retana, J. I. Gil, J. M. Ezpeleta, *J. Org. Chem.* **2000**, *65*, 3213–3217.

[12] a) F. Palacios, A. M. Ochoa de Retana, J. Pagalday, *Eur. J. Org. Chem.* **2003**, 913–919; b) F. Palacios, A. M. Ochoa de Retana, J. I. Gil, J. M. Alonso, *Tetrahedron: Asymmetry* **2002**, *13*, 2541–2552; c) F. Palacios, A. M. Ochoa de Retana, J. Pagalday, *Tetrahedron* **1999**, *55*, 14 451–14 458; d) F. Palacios, J. Pagalday, V. Piquet, F. Dahan, A. Baceiredo, G. Bertrand, *J. Org. Chem.* **1997**, *62*, 292–296.

[13] a) F. Palacios, A. M. Ochoa de Retana, J. I. Gil, R. López de Munain, *Org. Lett.* **2002**, *4*, 2405–2408; b) F. Palacios, D. Aparicio, J. Vicario, *Eur. J. Org. Chem.* **2002**, 4131–4136; c) F. Palacios, A. M. Ochoa de Retana, J. Oyarzabal, *Tetrahedron* **1999**, *55*, 5947–5964; d) F. Palacios, D. Aparicio, A. M. Ochoa de Retana, J. García, J. Oyarzabal, *Tetrahedron* **1999**, *55*, 3105–3116.

[14] a) F. Palacios, D. Aparicio, J. M. de los Santos, J. Vicario, *Tetrahedron* **2001**, *57*, 1961–1972; b) F. Palacios, D. Aparicio, J. M. de los Santos, A. Baceiredo, G. Bertrand, *Tetrahedron* **2000**, *56*, 663–669; c) F. Palacios, D. Aparicio, A. M. Ochoa de Retana, J. M. de los Santos, J. García, J. Oyarzabal, *Tetrahedron* **1999**, *55*, 3105–3116; d) F. Palacios, D. Aparicio, J. M. de los Santos, *Tetrahedron* **1996**, *52*, 3123–4132; e) F. Palacios, D. Aparicio, J. M. de los Santos, *Tetrahedron* **1994**, *50*, 12 727–12 742.

[15] F. Palacios, D. Aparicio, Y. López, J. M. de los Santos, *Tetrahedron Lett.* **2004**, *60*, 4345–4348.

[16] Only the preparation and some reactions of chiral azaalkenes containing a carbohydrate template at C-4 have been described.[7b]

[17] For recent reviews see: a) G. H. C. Woo, J. K. Snyder, Z. K. Wan, *Prog. Heterocycl. Chem.* **2002**, *14*, 279–309; b) J. Parrick, C. J. G. Shaw, L. K. Mehta, in *Rodd's Chemistry of Carbon Compounds*, 2nd ed., Elsevier, Amsterdam, **2000**, vol. 4 (Pt. I–J), pp. 1–69; c) P. Kolar, M. Tisler, *Adv. Heterocycl. Chem.* **1999**, *75*, 167–241.

[18] For recent contributions, see: a) S. Raghavan, K. Anuradha, *Synlett* **2003**, 711–713; b) U. Ghosh, D. Ganessunker, V. J. Sattigeri, K. E. Carlson, D. J. Mortensen, B. S. Katzenellenbogen, J. A. Katzenellenbogen, *Bioorg. Med. Chem.* **2003**, *11*, 629–657; c) C. Fruit, A. Turck, N. Ple, L. Mojovic, G. Queguiner, *Tetrahedron* **2002**, *58*, 2743–2753.

[19] a) H. Heydt, P. Eisenbarth, K. Feith, K. Urgast, G. Maas, M. Regitz, *Isr. J. Chem.* **1986**, *27*, 96–104; b) P. Eisenbarth, M. Regitz, *Chem. Ber.* **1984**, *117*, 445–454.

[20] a) R. J. Abrahamn, J. Fisher, P Loftus, in *Introduction to NMR Spectroscopy*, Wiley, Chichester, **1990**; b) R. Casas, T. Parella, V. Branchadell, A. Oliva, R. M. Ortuño, A. Guingaut, *Tetrahedron* **1992**, *48*, 2659–2671.

[21] L. D. Quin, in *Phosphorus-31 NMR Spectroscopy in Stereochemical Analysis* (Eds.: J. G. Verkade, L. D. Quin), VCH Publishers, Florida, **1987**, pp. 391–424.

[22] a) T. Sasaki, S. Eguchi, M. Yamaguchi, T. Esaki, *J. Org. Chem.* **1981**, *46*, 1800–1804; b) R. Huisgen, L. Möbius, G. Müller, H. Stangl, G. Szeimies, J. M. Vernon, *Chem. Ber.* **1965**, *98*, 3992–4013.

[23] F. Palacios, I. Pérez de Heredia, G. Rubiales, *J. Org. Chem.* **1995**, *60*, 2384–2390.

[24] S. J. Clarke, T. L. Davies, T. L. Gilchrist, *J. Chem. Soc., Perkin Trans. 1* **1983**, 1803–1807.

[25] MM2 calculations[26] show pyridazine **11a** to be 20.09 kcal mol^{-1} more stable than pyridazine **10a**.

[26] CS Chem3D Pro®. *Molecular Modelling and Analysis.* Version 3.5. CambridgeSoft Corporation, **1999**.

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