Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 5441–5447

TETRAHEDRON

Synthesis of dimethylphosphorylamino diazo esters by a selective tandem Staudinger/Arbuzov rearrangement sequence of azido diazo esters with trimethylphosphite

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Received 5 December 2002; revised 29 May 2003; accepted 29 May 2003

Abstract—γ-Azido-α-diazo-β-keto esters react selectively with trimethylphosphite by a tandem Staudinger/Arbuzov rearrangement sequence, furnishing γ-(dimethylphosphorylamino)-α-diazo-β-keto esters in good yield under mild conditions. Collected X-ray data for the novel diazo phosphoramides confirm the proposed chemoselectivity. © 2003 Elsevier Science Ltd. All rights reserved.

1. Introduction

Organic azides are extremely valuable intermediates for the synthesis of many nitrogen-containing molecules,[1–3] including heterocycles and natural products.[4–9] The reactivity of azido compounds has received increasing interest over the past two decades, particularly their reactions with tertiary phosphorus reagents which afford phosphorus–nitrogen ylides (the Staudinger reaction).[10] These versatile intermediates[11,12] can be further converted to important nitrogenated compounds such as amines, carboxamides, phosphoramides, imines and azadienes, among others,[13–16] usually in high yield and with pronounced chemoselectivity.

α-Diazo carbonyl compounds are also widely used in organic synthesis for the preparation of heterocyclic and carbocyclic rings[17–21] commonly related to natural products as well as for the preparation of pharmacologically active compounds.[22–27] The chemistry of the isoelectronic azido and diazo functionalities are somewhat related, given that azides can be considered as a diazo group bonded to a nitrogen atom.[18] Surprisingly, the chemical behavior of compounds that contain both a diazo and azido group in the same molecule has seldom been explored.[28–31] Moreover, the chemoselective transformation of an azido group in the presence of a diazo functionality, as far as we can tell, has not been described in the literature.

We recently reported the synthesis of γ-azido-α-diazo-δ-hydroxy-β-keto esters **1** and **2** by an aldol-type reaction of the azido diazo ester **3** with aldehydes mediated by DABCO. This condensation reaction proceeded under mild conditions and in high yield (Scheme 1).[32] γ-Azido-α-diazo-δ-hydroxy-β-keto esters **1** and **2** were subsequently converted to 2-azido-3-furanones **4** and **5**, respectively, through a rhodium(II) catalyzed intramolecular OH-insertion followed by a [3,3] sigmatropic rearrangement of the transient allylic azide.[33] Chemoselective transformations of the multiple functional groups present in azido diazo esters **1**–**3** and their further application to the synthesis of more elaborated structures not only has the potential of being synthetically useful, but also represents a challenge since various selectivity issues need to be addressed. Herein, we describe the chemical behavior of azido diazo esters towards phosphorus(III) reagents and the first chemoselective synthesis of diazo phosphoramides using a Staudinger reaction with trimethylphosphite.

2. Results and discussion

Azido diazo esters **3**, **6** and **7** (Scheme 1)[32] as well as vinyl azide **8** (Scheme 2) were chosen as model substrates for representative reactions with triphenylphosphine, tributylphosphine and trimethylphosphite. Compound **8** was obtained in 68% yield from a Hemetsberger–Knittel reaction[34] of diazo azide **3** with benzaldehyde mediated by piperidinium acetate in ethanol for 60 h at rt. The presence of both diazo and azido groups in structure **8** was confirmed by characteristic IR bands at 2140 and 2110 cm^{-1}, respectively. The presence of a large band at 1720 cm^{-1} and a medium one at 1620 cm^{-1} indicate the existence of carbonyl groups as well a conjugated olefin. Conclusive assignment for **8** came from its ^{13}C NMR

Keywords: azido diazo esters; Staudinger reaction; diazo phosphoramide.
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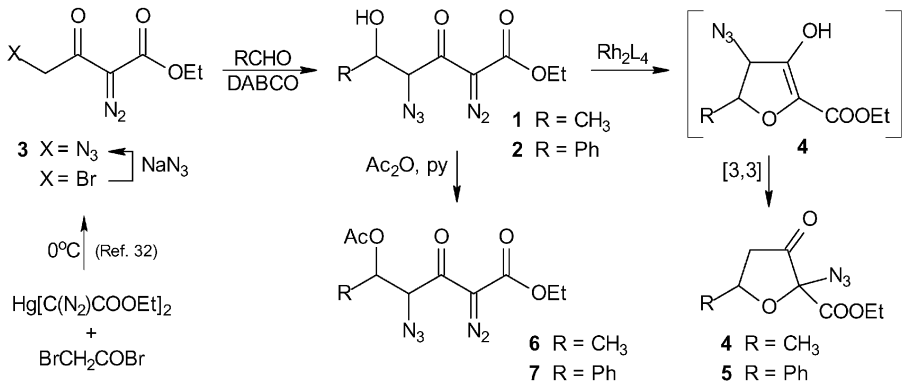
doi:10.1016/S0040-4020(03)00856-1

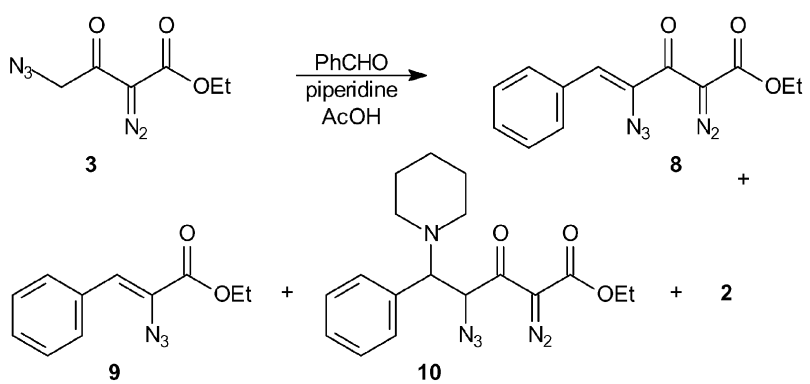


Scheme 1.

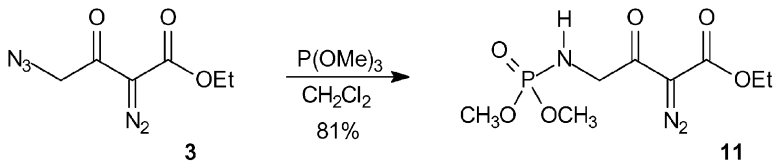
spectrum, which showed two carbonyl peaks at δ 160–180 and two unsaturated carbon atoms at δ 126–133. Also, a singlet at δ 6.42 in the ^{1}H NMR spectrum, characteristic of a β-olefinic proton *cis* to the carbonyl group, favors the proposed double bond geometry as being *Z*.[35–37] Furthermore, the mass spectrum of the protonated compound confirmed the expected molecular weight (MH^+=287).

In addition to vinyl azide **8**, four by-products were also isolated in minor (5–10%) quantities after column chromatography, in the following order of elution: the known ethyl (*Z*)-2-azidocinnamate **9** (5% yield),[37] γ-azido-α-diazo-β-keto-δ-*N*-piperidinyl ester **10** as a single diastereoisomer (8% yield), and the aldol product **2**[32] as a 1:1 diastereomeric mixture (8% yield). *N*-Piperidinyl derivative **10** was characterized by its spectroscopic data, which shows a similar NMR pattern to the structurally related aldol **2** and acetylated derivative **7**.[32] The relative configuration of the two stereogenic centers in **10** was suggested by its ^{1}H NMR spectrum, which shows two methine protons as doublets (4.16 and 5.60 ppm) with a large coupling constant (J=11 Hz) characteristic of the *anti* configuration.[32,38,39] Interestingly, when diazo azide **3** was treated with benzaldehyde/piperidinium acetate in ethanol for shorter periods of time (48 h), only the vinyl azide **8** and hydroxy ester **2** were formed (58 and 30% yield, respectively). *N*-Piperidinyl derivative **10** was formed in trace amounts (less than 5%), but none of the azido-cinnamate **9** could be detected in the crude reaction nor isolated by column chromatography. In a control experiment, aldol **2** (1:1 diastereomeric mixture) was submitted to the same reaction conditions, affording, aside from unreacted starting material, only trace amounts of vinyl azide **8** and the *N*-piperidinyl derivative **10**, together with decomposition products. When vinyl azide **8** was treated with benzaldehyde/piperidinium acetate, it was slowly converted to azido-cinnamate **9** and also produced unknown decomposition products. These observations suggest that hydroxy ester **2** is being formed by an aldol reaction of diazo azido ester **3** with benzaldehyde in the basic media,[37,39] while *N*-piperidinyl ester **10** is produced either by a condensation between **3** and the piperidinium ion of the aldehyde[34] or by a Michael addition of piperidine to vinyl azide **8**. Vinyl azide **8** could come about by a dehydration of hydroxy ester **2** or by piperidine elimination from **10**.[34] Finally, azido-cinnamate **9** is most likely derived by a slow solvolysis of the pre-formed vinyl azide **8** in ethanolic media,[32] or possibly from a nucleophilic acyl cleavage reaction which is characteristic of diazo ketones.[40] The above results clearly depict a complex equilibrium among the involved species, hence only a tentative explanation for the product distribution can be made at this moment.

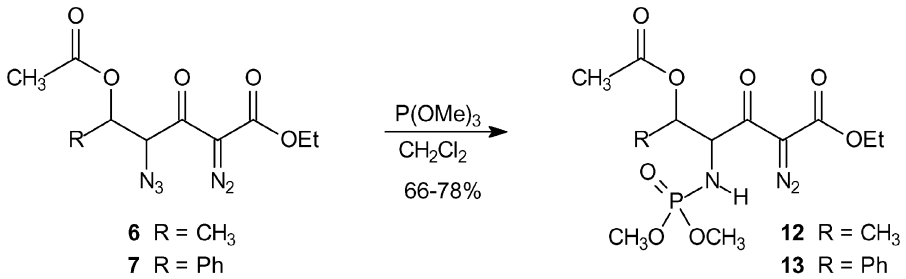
In order to evaluate the chemical reactivity of azido diazo esters **3**, **6**, **7** and **8** towards phosphorus(III) reagents, each compound was initially treated with triphenylphosphine at rt. All the reactions were monitored by IR spectroscopy, whereby the disappearance (or shifting) of the azido and diazo bands (2100–2110 and 2135–2145 cm^{-1}, respectively) were monitored. Reactions were rapid in all cases; after 1–2 h at rt or at 0°C all the starting materials were consumed. The IR of the crude reaction mixture showed a strong band that had been shifted to 2125 cm^{-1}, indicating that both the azido and diazo groups are reactive under these



Scheme 2.



Scheme 3.



Scheme 4.

conditions. However, product purification by column chromatography led to extensive decomposition of preformed adducts. Trapping any elusive iminophosphorane intermediates with acetaldehyde[11] was also unsuccessful as a complex mixture of products was observed. It is interesting to note that when azido diazo **3** was treated with the more reactive tributylphosphine reagent, the reaction followed another course. After stirring for 15 min at 0°C, the diazo band at 2140 cm^{-1} had totally disappeared, suggesting the formation of a phosphazine from the diazo group, with retention of the azido functionality.[30,31] However, isolation of this product was not possible due to its low thermal stability.

While the outcome of the reaction of phosphines with the selected azido diazo compounds was disappointing, much more consistent results were obtained by using trimethylphosphite. The reaction of $P(OMe)_3$ with **3** gave rise to a slow but very selective disappearance of the band located at 2105 cm^{-1}, and cleanly produced the diazo phosphoramide **11** after stirring for 24 h at rt (Scheme 3). Compound **11** was stable to chromatography, allowing its purification and complete characterization. The presence of a NH-P moiety was evident by IR bands at 3340 and 3230 cm^{-1}, a D_2O-exchangeable ^1H NMR signal at 3.40 ppm (coupling with phosphorus) and a singlet at 11.2 ppm in the ^{31}P NMR, a chemical shift characteristic for the $R-NH-P(O)(OR')_2$ group.[41,42] Phosphoramide **11** is most likely formed by an initially generated phosphorimide intermediate [$R-N{=}P(OMe)_3$], followed by an Arbuzov rearrangement with subsequent elimination of methanol.[11,41]

Although vinyl azide **8** underwent decomposition in the presence of trimethylphosphite, diazo azido esters **6** and **7** reacted smoothly with $P(OMe)_3$, affording phosphoramides **12** and **13**, respectively, in good yield after flash chromatography (Scheme 4). The stereogenic centres in azido esters **6** and **7** are not directly involved in the transformation, therefore, the diastereomeric ratios observed for substrates and products are always identical. For instance, diastereomerically-enriched azido diazo esters generated diastereomerically-enriched diazo phosphoramides, no epimerization being involved. The relative stereochemistry that was assigned to phosphoramides **12** and **13** was again based on a ^1H NMR analysis, which showed characteristic coupling constants for the *anti*- (8.0 Hz) and *syn*- (2.0 Hz) isomers of ethyl 5-acetoxy-2-diazo-4-(dimethylphosphorylamino)-5-phenyl-3-oxopentanoate (**13**).[38]

The *syn* and *anti* isomers of phosphoramide **12** and the *syn*-phosphoramide **13** were purified by silica gel column chromatography, and were submitted to careful crystallization in ethyl ether, furnishing triclinic monocrystals whose structures were then resolved by X-ray crystallography (Figs. 1–3). The ORTEP structures for *anti*-**12**, *syn*-**12** and *syn*-**13** unambiguously confirms the stereochemistry that had previously been assigned by ^1H NMR spectroscopy. The obvious presence of the diazo and the phosphoramide groups in these structures by IR spectroscopy, clearly demonstrates the chemoselectivity of the reaction of azido diazo compounds with trimethylphosphite. The uncommon occurrence of compounds that contain both diazo and phosphoramide groups within the same molecule is also worthy of mention, as only one related report in the literature has appeared to date.[43] Prior to our work, no

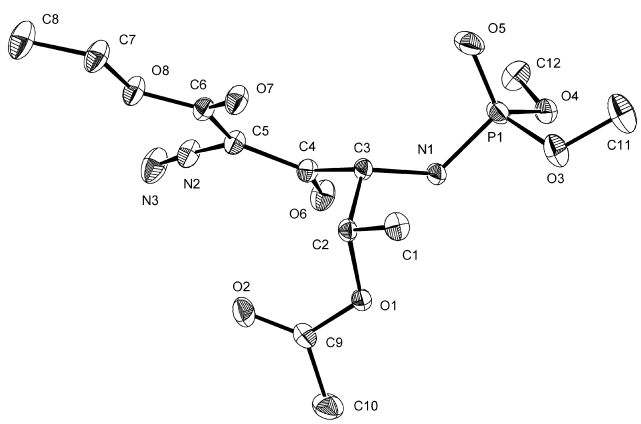


Figure 1. View of the structure of *syn*-**12** with labeling scheme and the ellipsoids with 50% of the probability level. Hydrogen atoms were omitted for clarity.

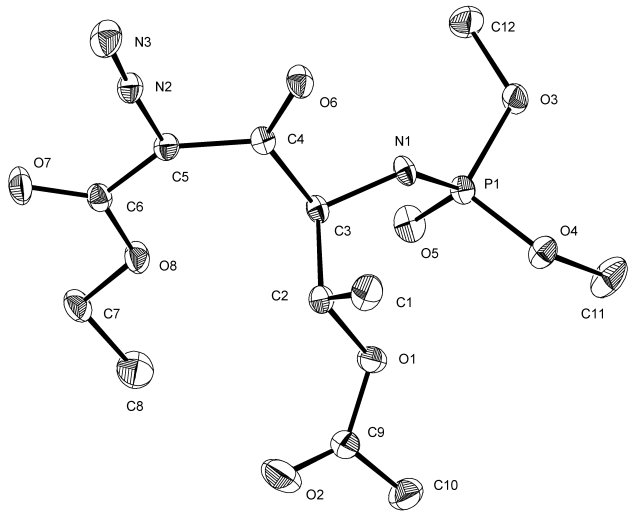


Figure 2. View of the structure of *anti*-**12** with labeling scheme and the ellipsoids with 50% of the probability level. Hydrogen atoms were omitted for clarity.

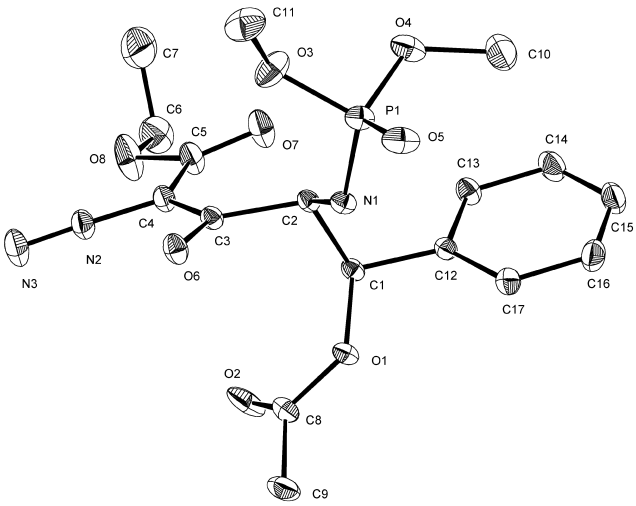


Figure 3. View of the structure of *syn*-**13** with labeling scheme and the ellipsoids with 50% of the probability level. Hydrogen atoms were omitted for clarity.

general method had previously been available to access these compounds, and no X-ray data had been reported for them.

3. Conclusion

The easily available γ-azido-α-diazo-β-keto esters **3**, **6** and **8** were found to undergo selective reaction with trimethylphosphite to give diazo phosphoramides in good yield under mild conditions. The overall process involves a novel tandem Staudinger/Arbuzov rearrangement sequence. The structures of the resulting products were fully confirmed by X-ray crystal data, which establishes the relative stereochemistry present in compounds **12** and **13**. These diazo phosphoramides represent new stable multifunctional compounds, and studies dealing with their reactivity and other chemical properties are currently being investigated.

4. Experimental

4.1. General considerations

All chemicals were of reagent grade and were used as received. Melting points are uncorrected. ^{1}H NMR (300 MHz), ^{13}C NMR (75 MHz) and ^{31}P NMR (162 MHz) spectra were recorded in $CDCl_3$ solution, using tetramethylsilane as internal standard for ^{1}H and ^{13}C NMR, and triphenylphosphate as external standard for ^{31}P NMR. Infrared spectra were acquired using KBr for solids and film for liquid samples. Mass spectra were determined at an ionizing voltage of 70 eV. X-Ray were collected with an automatic X-Ray Diffractometer for monocrystals ENRAF NONIUS CAD-4. Column chromatography utilized silica gel (Aldrich, 100–200 mesh particle size). Azido diazo compounds **3**, **6** and **7** were prepared according to the described method.[32]

4.1.1. Ethyl (*Z*)-4-azido-2-diazo-3-oxo-4-phenylpentenoate (8). To a solution containing 0.72 g (3.6 mmol) of 4-azido-2-diazo-3-oxo-butanoate (**3**) and 0.75 mL (7.4 mmol) of benzaldehyde in 10 mL of absolute ethanol under argon at 25°C was added 0.52 g (3.6 mmol) of piperidinium acetate. After stirring for 60 h in the dark, the reaction mixture was diluted with CH_2Cl_2, washed with H_2O, 10% HCl and H_2O again, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The yellow oil obtained was submitted to chromatography (hexane/ethyl eter 3:1) to give five compounds, in order of elution:

4.1.2. Ethyl (*Z*)-2-azidocinnamate (9).[37] Clear oil (5% yield); IR (neat) 2120, 1712 and 1618 cm^{-1}; ^{1}H NMR: δ 1.38 (t, 3H, J=7.0 Hz), 4.35 (q, 2H, J=7.0 Hz), 6.88 (s, 1H), 7.36 (m, 3H) and 7.81 (m, 2H); ^{13}C NMR: δ 14.2, 62.3, 125.3, 125.8, 128.5 (2C), 129.4, 130.6 (2C), 133.2 and 163.5; MS for $C_{11}H_{11}N_3O_2$: 218 (MH^+).

4.1.3. Ethyl 4-azido-2-diazo-3-oxo-5-phenyl-5-(*N*-piperidinyl)-pentanoate (10). Colorless solid (8% yield); mp 81–83°C; IR (neat) 2142, 2100, 1716 and 1657 cm^{-1}; ^{1}H NMR: δ 1.20 (m, 2H), 1.36 (t, 3H, J=7.0 Hz), 1.42 (m, 4H), 2.10 (m, 2H), 2.51 (m, 2H), 4.19 (d, 1H, J=11.0 Hz), 4.32 (q, 2H, J=7.0 Hz), 5.60 (d, 1H, J=11.0 Hz) and 7.20–7.45 (m, 5H); ^{13}C NMR: δ 14.4, 24.1, 26.6 (2C), 51.5 (2C), 58.8, 61.8, 71.2, 127.9, 128.1 (2C), 129.2 (2C), 133.4, 161.2 and 190.5; MS for $C_{18}H_{22}N_6O_3$: 371 (MH^+).

4.1.4. Ethyl (*Z*)-4-azido-2-diazo-3-oxo-4-phenylpentenoate (8). Clear oil (69% yield); IR (neat) 2140, 2110, 1720 and 1620 cm^{-1}; ^{1}H NMR: δ 1.28 (t, 3H, J=7.0 Hz), 4.29 (q, 2H, J=7.0 Hz), 6.42 (s, 1H), 7.34 (m, 3H) and 7.77 (m, 2H); ^{13}C NMR: δ 14.3, 62.0, 75.9, 126.4, 128.5 (2C), 129.5, 130.5 (2C), 130.8, 132.9, 160.5 and 180.8; MS for $C_{13}H_{11}N_5O_3$: 287 (MH^+).

4.1.5. Ethyl 4-azido-2-diazo-5-hydroxy-3-oxo-5-phenylpentanoate (2). Clear oil, mixture of *syn*, *anti* diastereoisomers (1:1 ratio, 8% combined yield; spectral data identical to Ref. 32).

4.1.6. Ethyl 2-diazo-4-(dimethylphosphorylamino)-3-oxobutanoate (11). To a solution containing 50 mg

(0.25 mmol) of ethyl 4-azido-2-diazo-3-oxobutanoate (**3**) in 1.5 mL of dry CH_2Cl_2 under argon at 25°C was added 0.03 mL (0.25 mmol) of trimethylphosphite. After stirring for 24 h the reaction mixture was diluted with CH_2Cl_2, washed with H_2O, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was filtered through a Celite-silica gel plug using ethyl acetate as the eluent and the filtrate was concentrated under reduced pressure to give 56 mg (81%) of ethyl 2-diazo-4-(dimethylphosphorylamino)-3-oxo-butanoate (**11**) as a clear yellow oil; IR (neat) 3340, 3230, 2140, 1715 and 1662 cm^{-1}; ^1H NMR: δ 1.33 (t, 3H, J=7.0 Hz), 3.40 (br, 1H, D_2O exchange), 3.72 (d, 6H, J=11.0 Hz), 4.20 (dd, 2H, J=9.0, 6.0 Hz), and 4.31 (q, 2H, J=7.0 Hz); ^{13}C NMR: δ 14.2, 49.1, 53.2 (d, J=5.5 Hz), 61.8, 160.8, and 188.3 (d, J=7.5 Hz); ^{31}P NMR: δ 11.2; HRMS calcd for $C_8H_{15}N_3O_6P$ (MH^+): 280.0698. Found: 280.0694.

4.1.7. Ethyl 5-acetoxy-2-diazo-4-(dimethylphosphorylamino)-3-oxohexanoate (12). To a solution containing 3.0 g (10.5 mmol) of ethyl 5-acetoxy-4-azido-2-diazo-3-oxohexanoate (**6**; *syn*/*anti*~2:1) in 50 mL of dry CH_2Cl_2 under argon at 25°C was added 1.25 mL (10.6 mmol) of trimethylphosphite. After stirring for 22 h the reaction mixture was concentrated under reduced pressure and the resulting residue was purified by chromatography (ethyl eter/ethyl acetate 9:1) to give phosphorylamino derivative **12** (*syn*/*anti*~2:1; 78% combined yield).

The isolated *syn* isomer was recrystallized from ethyl ether to give pale yellow crystals; mp 79–80°C; IR (neat) 3340, 3220, 2140, 1742, 1710 and 1664 cm^{-1}; ^1H NMR: δ 1.32 (t, 3H, J=7.0 Hz), 1.37 (d, 3H, J=6.0 Hz), 1.96 (s, 3H), 3.62 (m, 1H), 3.69 (m, 6H), 4.29 (q, 2H, J=7.0 Hz), 4.79 (t, 1H, J=10.0 Hz) and 5.27 (q, 1H, J=6.0 Hz); ^{13}C NMR: δ 14.2, 17.4, 20.9, 53.3–53.4 (m, 2C), 60.2, 61.9, 69.6 (d, J=6.5 Hz), 161.0, 170.1 and 189.5; ^{31}P NMR: δ 27.98; HRMS calcd for $C_{12}H_{20}N_3O_8P$ (MH^+): 366.1067. Found: 366.1066. Anal. calcd for $C_{12}H_{20}N_3O_8P$: C, 39.46; H, 5.52; N, 11.50. Found: C, 39.53; H, 5.52; N, 11.46.

The isolated *anti* isomer was recrystallized from ethyl ether to give pale yellow crystals; mp 74–75°C; IR (neat) 3330, 3210, 2140, 1742, 1715 and 1655 cm^{-1}; ^1H NMR: δ 1.17 (d, 3H, J=6.0 Hz), 1.32 (t, 3H, J=7.0 Hz), 2.03 (s, 3H), 3.67 (d, 3H, J=11.0 Hz), 3.72 (d, 3H, J=11.0 Hz), 3.80 (dd, 1H, J=9.5, 10 Hz), 4.31 (q, 2H, J=7.0 Hz), 4.98 (ddd, 1H, J=5.0, 6.0, 9.5 Hz) and 5.05 (m, 1H); ^{13}C NMR: δ 14.2, 14.8, 21.1, 53.3–53.4 (m, 2C), 59.7, 62.1, 70.0 (d, J=6.5 Hz), 160.4, 169.7 and 189.2 (d, J=3.5 Hz); ^{31}P NMR: δ 27.46. Anal. calcd for $C_{12}H_{20}N_3O_8P$: C, 39.46; H, 5.52; N, 11.50. Found: C, 39.59; H, 5.46; N, 11.57.

4.1.8. Ethyl 5-acetoxy-2-diazo-4-(dimethylphosphorylamino)-5-phenyl-3-oxopentanoate (13). To a solution containing 2.55 g (7.4 mmol) of ethyl 5-acetoxy-4-azido-2-diazo-3-oxo-5-phenylpentanoate (**7**; *syn*/*anti*~3:1) in 45 mL of dry CH_2Cl_2 under argon at 25°C was added 1.0 mL (8.5 mmol) of trimethylphosphite. After stirring for 18 h the reaction mixture was concentrated under reduced pressure and the resulting residue was purified by chromatography (ethyl eter/ethyl acetate 9:1) to give phosphorylamino derivative **13** (*syn*/*anti*~3:1; 66% combined yield).

The isolated *syn* isomer was recrystallized from ethyl ether to give pale yellow crystals; mp 127–128°C; IR (neat) 3340, 3210, 2142, 1746, 1708 and 1664 cm^{-1}; ^1H NMR: δ 1.36 (t, 3H, J=7.0 Hz), 2.10 (s, 3H), 3.02 (d, 3H, J=11.0 Hz), 3.37 (d, 3H, J=11.0 Hz), 3.72 (dd, 1H, J=9.5, 10.5 Hz), 4.37 (q, 2H, J=7.0 Hz), 5.05 (ddd, 1H, J=1.5, 2.0, 10.5 Hz), 6.31 (d, 1H, J=1.5 Hz) and 7.25–7.55 (m, 5H); ^{13}C NMR: δ 14.3, 20.8, 52.6 (d, J=5.5 Hz), 53.0 (d, J=5.5 Hz), 61.7, 62.0, 73.2 (d, J=7.5 Hz), 126.3 (2C), 128.0, 128.3 (2C), 137.0, 161.1, 169.6 and 189.3; ^{31}P NMR: δ 27.36. Anal. calcd for $C_{17}H_{22}N_3O_8P$: C, 47.78; H, 5.19; N, 9.83. Found: C, 47.93; H, 5.19; N, 9.81.

The *anti* isomer was obtained impure, even after many recrystallizations: ^1H NMR: δ 1.35 (m, 3H), 2.02 (s, 3H), 3.31 (d, 3H, J=11.0 Hz), 3.51 (d, 3H, J=11.0 Hz), 4.35 (m, 2H), 5.21 (m, 1H), 5.81 (d, 1H, J=8.0 Hz) and 7.20–7.60 (m, 5H).

4.2. X-Ray crystallography

The intensities for all compounds were collected on a CAD4 diffractometer, at rt, with graphite-monochromated Mo K_α radiation (λ=0.71073 Å). The unit cell parameters were defined on the setting angles of 25 centered reflections in the

Table 1. Selected bond lengths (Å) and angles (°) for *syn*-**12** isomer

P1–O5	1.448(3)
P1–O4	1.559(2)
P1–O3	1.600(3)
P1–N1	1.613(2)
N1–C3	1.445(3)
N2–N3	1.110(4)
N2–C5	1.338(4)
O1–C9	1.344(4)
O1–C2	1.453(3)
O8–C6	1.334(4)
O8–C7	1.469(4)
C2–C3	1.538(4)
C3–C4	1.533(4)
C4–C5	1.455(4)
O5–P1–O4	116.88(15)
O5–P1–O3	115.87(19)
O4–P1–O3	98.03(14)
O5–P1–N1	113.20(14)
O4–P1–N1	107.43(13)
O3–P1–N1	103.64(14)
C3–N1–P1	124.16(19)
N3–N2–C5	175.2(3)
C9–O1–C2	118.2(2)
C6–O8–C7	116.3(3)
O1–C2–C1	107.1(2)
O1–C2–C3	108.2(2)
C1–C2–C3	112.5(2)
N1–C3–C4	109.6(2)
N1–C3–C2	112.1(2)
C4–C3–C2	110.8(2)
O6–C4–C5	120.6(3)
O6–C4–C3	121.4(3)
C5–C4–C3	117.9(3)
N2–C5–C4	112.4(3)
N2–C5–C6	116.5(3)
C4–C5–C6	130.9(3)
O7–C6–O8	124.5(3)
O7–C6–C5	124.2(3)
O8–C6–C5	111.3(3)

Table 2. Selected bond lengths (Å) and angles (°) for *anti*-**12** isomer

P1–O5	1.462(1)
P1–O4	1.573(1)
P1–O3	1.583(1)
P1–N1	1.623(1)
N1–C3	1.450(2)
N2–N3	1.106(2)
N2–C5	1.352(2)
O1–C9	1.325(2)
O1–C2	1.451(2)
O7–C6	1.205(2)
C2–C3	1.539(3)
C3–C4	1.527(2)
C4–C5	1.453(2)
C5–C6	1.465(3)
O5–P1–O4	115.73(8)
O5–P1–O3	114.78(8)
O4–P1–O3	99.49(7)
O5–P1–N1	113.58(8)
O4–P1–N1	106.18(7)
O3–P1–N1	105.63(7)
C3–N1–P1	123.88(12)
N3–N2–C5	175.29(19)
C9–O1–C2	119.71(16)
O1–C2–C1	109.57(16)
O1–C2–C3	103.85(14)
C1–C2–C3	114.19(16)
N1–C3–C4	108.42(14)
N1–C3–C2	112.99(15)
C4–C3–C2	108.84(14)
O6–C4–C5	119.47(16)
O6–C4–C3	120.62(15)
C5–C4–C3	119.87(15)
N2–C5–C4	111.59(15)
N2–C5–C6	112.88(15)
C4–C5–C6	135.39(16)

Table 3. Selected bond lengths (Å) and angles (°) for *syn*-**13** isomer

P1–O5	1.460(2)
P1–O4	1.551(3)
P1–O3	1.562(3)
P1–N1	1.611(2)
O1–C8	1.326(4)
O1–C1	1.445(3)
N1–C2	1.447(3)
N2–N3	1.106(4)
N2–C4	1.333(4)
C1–C12	1.504(4)
C1–C2	1.537(4)
C2–C3	1.532(4)
C3–C4	1.468(4)
C4–C5	1.444(5)
O5–P1–O4	114.53(17)
O5–P1–O3	115.34(18)
O4–P1–O3	98.7(2)
O5–P1–N1	112.50(14)
O4–P1–N1	108.11(14)
O3–P1–N1	106.53(17)
C8–O1–C1	119.7(3)
C2–N1–P1	125.50(19)
N3–N2–C4	175.9(3)
O1–C1–C12	109.0(2)
O1–C1–C2	107.5(2)
C12–C1–C2	111.8(2)
N1–C2–C3	111.6(2)
N1–C2–C1	110.6(2)
C3–C2–C1	109.4(2)
O6–C3–C4	120.2(3)
O6–C3–C2	122.0(3)
C4–C3–C2	117.7(2)
N2–C4–C5	117.0(3)
N2–C4–C3	112.5(3)
C5–C4–C3	130.5(3)
O7–C5–O8	124.6(3)
O7–C5–C4	124.1(3)
O8–C5–C4	111.3(3)

θ range from 9.60 to 14.00°. The intensities data were collected using $\omega/2\theta$ scan technique. Intensity control was carried out using three standards reflections, which were measured at regular intervals and no significant loss of intensity was observed during the data collection. The collected reflections were corrected for Lorentz and polarization effects.[44] No absorption correction was applied. The structures were solved by direct methods with SHELXS97[45] and refined by full-matrix least-squares procedure based on F^2 with SHELXL97.[46] H atoms attached to C atoms were placed at idealized positions, with C–H distances and U_{eq} values taken from the default settings of the refinement program. H atoms of the amine groups were found from difference Fourier maps and treated as riding atoms. Non-hydrogen atoms were refined with anisotropic displacement parameters. Selected bond lengths and angles are listed in Tables 1–3.

4.2.1. *syn*-12 Isomer. $C_{12}H_{20}N_3O_8P$, FW=365.28, Triclinic, *P*-1, a=8.908(2) Å, b=10.649(2) Å, c=10.877(3) Å, α=72.26(2)°, β=70.72(2)°, γ=72.90(2)°, V=905.9(4) Å^3, Z=2, D_{calc}=1.339 g/cm^3, μ=0.194 mm^{-1}, crystal 0.50×0.43×0.26 mm, 3403 reflections collected, unique 3218 [R_{int}=0.0096], 218 refined parameters, GOOF=1.047, final indices $R_{[I>2\sigma(I)]}$=0.057 and wR_2=0.187 (all data).

4.2.2. *anti*-12 Isomer. $C_{12}H_{20}N_3O_8P$, FW=365.28, Triclinic, *P*-1, a=6.727(1) Å, b=10.681(1) Å, c=12.382(2) Å, α=78.15(1)°, β=83.61(1)°, γ=86.48(1)°, V=864.6(2) Å^3, Z=2, D_{calc}=1.403 g/cm^3, μ=0.203 mm^{-1}, crystal 0.50×0.46×0.26 mm, 3345 reflections collected, unique 3060 [R_{int}=0.0184], 219 refined parameters, extinction coef.=0.018(3), GOOF=1.036, final indices $R_{[I>2\sigma(I)]}$=0.038 and wR_2=0.1113 (all data).

4.2.3. *syn*-13 Isomer. $C_{17}H_{22}N_3O_8P$, FW=427.35, Triclinic, *P*-1, a=8.422(5) Å, b=10.407(2) Å, c=12.859(2) Å, α=88.35(1)°, β=87.08(2)°, γ=73.50(3)°, V=1079.1(7) Å^3, Z=2, D_{calc}=1.315 g/cm^3, μ=0.174 mm^{-1}, crystal 0.50×0.50×0.33 mm, 4111 reflections collected, unique 3826 [R_{int}=0.0119], 302 refined parameters, extinction coef.=0.034(4), GOOF=1.073, final indices $R_{[I>2\sigma(I)]}$=0.0594 and wR_2=0.1754 (all data). Two disorders were observed in this structure. The oxygen atom of the carboxylic moiety (O2 in Fig. 3) was found disordered over three positions, where the site occupancies for the disordered atom were refined and fixed at 0.56 for one position and 0.22 for two positions. One terminal carbon atom of the dimethylphosphorylamino group (C11 in Fig. 3) also occupies three alternative positions, for which the occupancies factors were also refined and they were fixed at 0.40, 0.30 and 0.30.

Acknowledgements

The authors are grateful to Central de Análises (Departamento de Química, UFSC) for X-ray analysis and to

National Institutes of Health (GM59384 and GM60003) for generous support of this work. GPS is grateful to CNPq for a Predoctoral fellowship.

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