Facile diastereoselective synthesis of phosphonate esters bearing cyclic or acyclic amides

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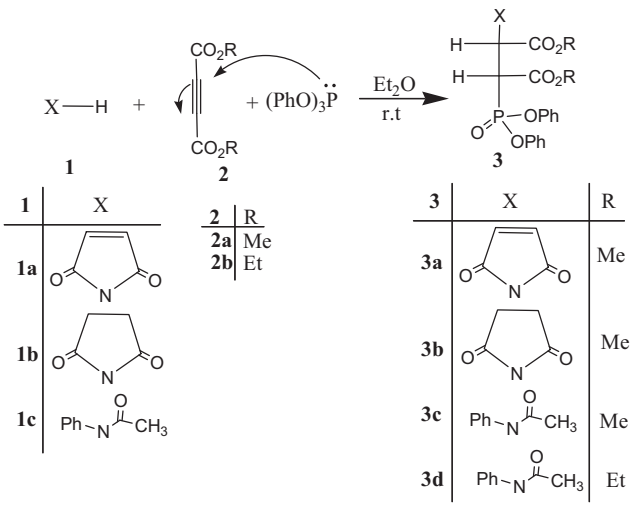
Phosphonate esters were obtained in excellent yields from a 1:1:1 addition reaction between triphenyl phosphite, dialkyl acetylenedicarboxylate and NH acids (maleimide, succinimide and *N*-phenylacetamide). The stereochemistry was established by solution NMR and single X-ray crystallography for two of the phosphonate esters. Dynamic effects of the maleimide moiety was observed and determined by ^{1}H and ^{13}C NMR. The free energy of activation is established for the rotation of the maleimide moiety around the N-C bond in dimethyl (*2S*,3R**)-2-(2,5-dioxo-2,5-dihydropyrrol-1-yl)-3-(diphenoxyphosphoryl)butanedioate as 47 ± 2 kJ/mol.

Keywords: phosphonate esters, diastereoselective synthesis, conformational analysis

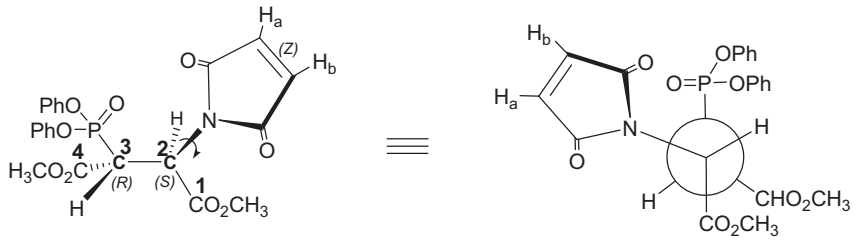
Multi-component 'one pot' syntheses are increasingly used in the preparation of diverse molecular compounds.[1-3] This approach offers an efficient method to accessing important molecules for a variety of applications. Phosphonate esters are important class of compounds obtained by sequential addition reaction of trivalent phosphite with α,β-unsaturated carbonyl molecules in the presence of C–H or N–H acids.[4,5] Phosphonate esters are biologically active and the stereoisomerism has subtle differences in the biological activity and toxicological profile.[6-9] Extensive studies on the biological significance of phosphonate derivatives is established as nucleoside analogues of biologically important nucleotides.[10,11] Furthermore, erucylphosphocholine is an alkylphosphocholine derivative of phosphonates found to have cytostatic activity against leukemic cell lines.[12,13] The preparation of phosphonate esters compounds having two chiral centres via a one pot reaction methodology is well-established.[14] Synthetic routes to adducts of trivalent phosphorus nucleophile and α,β-unsaturated carbonyl compounds in the presence of a proton source such as alcohol, phenol or primary amine are relatively well documented.[17-21] In contrast, related condensation of phosphonate using phosphite is less explored with only few reports in the literature.[22-24] Herein we report the synthesis of maleimide, succinimide and *N*-phenylacetamide phosphonate esters, **3a**–**d**. The phosphonate esters, **3a**–**d** were prepared from the reaction of triphenyl phosphite with dialkyl acetylendicarboxylates **2**, and concomitant protonation of the reactive 1:1 adduct by cyclic or acyclic NH acids, **1a**–**c**. The vinyl phosphonium salt intermediate produced was subsequently attacked by the nitrogen nucleophile, which when hydrolysed produced mainly one diastereoisomer of the phosphonate ester, **3** in good yield (Scheme 1).



Scheme 1

The reaction of dialkyl acetylenedicarboxylate (DMAD) and triphenyl phosphite with N-H acids (maleimide or succinimide or *N*-phenylacetamide) produces a single diastereoisomer **3** in good yield. The structure of the adduct **3a**–**d** is characterised by mass spectrometry, FTIR, ^{1}H/^{13}C NMR spectroscopy and single X-ray diffraction, Fig. 1 (see Experimental).

In taking product **3a** as a model for the prepared compounds, the ^{1}H NMR spectrum of **3a** shows signals for the vicinal methine protons as separate two sets of quartets. The vicinal proton–proton coupling constant ($^3J_{HH}$) can be obtained from the Karplus equation as a function of the torsion angle.[25-28] Typically J_{gauche} or J_{anti} configuration give rise to distinct coupling constants which vary between 1.5 Hz and 10–14 Hz



2S, 3R (3a) and mirror image

Fig. 1 Structure and assignment of the stereochemistry for **3a** along with the Newman projection.

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respectively.[25] Observation of $^3J_{HH}$ = 11.6 Hz for the vicinal protons in compound **3a** confirms an *anti* arrangement for these protons. In addition, compound **3a** possesses two stereogenic centres and hence two diastereoisomers with an *anti* C_H–C_H arrangement are possible. The presence of phosphorus (^{31}P) nucleus in compound **3a** assisted in identifying its configuration by analysing the long range coupling signals of phosphorus (^{31}P) nucleus with neighbouring protons (^{1}H) and carbons (^{13}C) nuclei (see Experimental). The carbon–phosphorus three bond range coupling constant $^3J_{PC}$ is associated with the *anti* or the *cis* configuration (transoid coupling being larger than cisoid coupling).[17] The Karplus relationship can be derived from literature data for organophosphorus compounds with tri- or penta-valent phosphorus environment.[28] The observation of $^3J_{PC}$ = 19.4 Hz (δ 168.1 ppm) for the distal ester carbonyl group for **3a** is in agreement with an *anti* arrangement along the P–CH–CH–C(O) bond. This assignment was reinforced with the smaller coupling of the phosphorus to the proximal ester carbonyl group, $^2J_{PC}$ = 7.9 Hz (δ 166.4 ppm), Fig. 1.

Structural determination by single X-ray diffraction for compound **3a** and **3d** confirms the configuration assignment by ^{1}H and ^{13}C NMR, Fig. 2. Both structures of phosphonate ester **3a** and **3d** are devoid of solvent molecules with the asymmetric unit contains a complete unique molecule.

Dynamic NMR spectroscopy enables the study of conformational analysis and determination of energy barrier of interconversion.[29] The technique allows investigation of conformational equilibriums in ring systems including saturated and unsaturated heterocyclic ring compounds.[29-31] Dynamic ^{1}H NMR is performed on phosphonate ester **3a** in order to ascertain the dynamic effects and the energy barrier for the rotation of the maleimide moiety. The variable temperature ^{1}H NMR spectrum for compound **3a** in $CDCl_3$ displays a sharp singlet for protons H_a and H_b of the maleimide (δ 6.7 ppm) at room temperature which shows broadening upon lowering the temperature, Fig. 3.

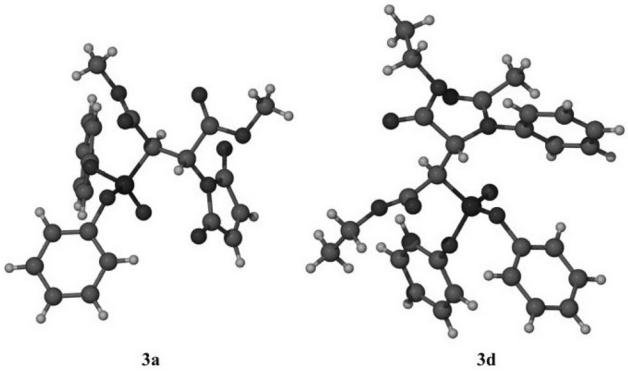

Fig. 2 X-ray single crystal structure of **3a** (*2S*,3R**), **3d** (*2S*,3R**) with their respective configuration: stick representation showing the single diastereoisomers, and the arrangement of the groups in respect to the stereogenic centres.

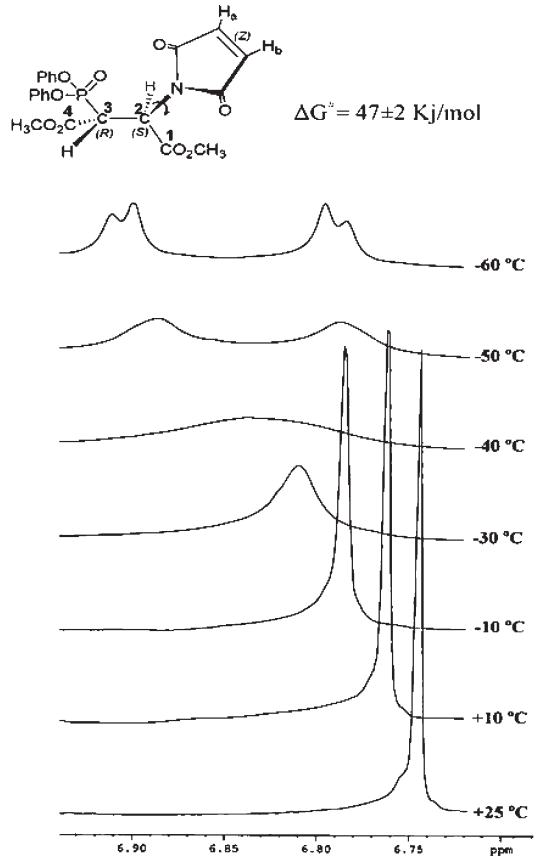

Fig. 3 Schematic representation of the restricted rotation around the N-C single bond of the maleimide moiety in **3a** (VT ^{1}H NMR depicting only the protons in the maleimide).

At T_c = –40 ± 1°C in $CDCl_3$ we observed coalescence for the protons H_a and H_b of the maleimide moiety as a broad signal which converts to two sets of broad doublets at –60°C. This behaviour is fully reversible on warming to room temperature and also supported by ^{13}C dynamic NMR. This phenomena is attributed to the restricted rotation around the C–N single bond for the maleimide ring.[31,32]

The variable temperature NMR spectra allowed the determination of the free-energy barrier (if not the enthalpy or entropy of activation) for the dynamic process in **3a**. From coalescence signal attributed to the maleimide proton and using the expression $k = \pi\lambda\upsilon/\sqrt{2}$, we calculated the first-order rate constant (k) for the dynamic NMR effect of 133 s^{-1} at 233°K. Application of the absolute rate theory with a transmission coefficient of 1 gives a free-energy of activation ($\Delta G^{\neq}$) 47± 2 kJ mol^{-1} where all sources of errors are estimated and included (Table 1).[24] The experimental data available are not suitable for obtaining meaningful values for $\Delta H^{\neq}$ and $\Delta S^{\neq}$ although the errors in $\Delta G^{\neq}$ are not large.[24]

In conclusion, we have successfully carried a facile diastereo-selective synthesis of cyclic and acyclic NH acids derivatives of phosphonate ester **3a**–**d** from the reaction

Table 1 VT ^{1}H NMR selected chemical shifts (δ in ppm, CDCl3) and activation energy parameter (kJ/mol) for **3a**

Entry	Temp. /°C	Resonance ^{1}H NMR	Resonance (CH_a–CH_b)		δ(Hz) ^{1}H NMR	K/s^{-1}	T_c/k	ΔG#/kJ/mol
		(CH_a–CH_b)	(CH_a–CH_b)	2*C=O* of maleimide ring				
3a	+ 25	6.75	134.60	169.14	60	133	233	47±2
	–60	6.79, 6.91	134.87, 135.06	168.71, 170.65				

between dialkyl acetylenedicarboxylate and NH acids **1a–c** in the presence of triphenyl phosphite at room temperature. The simplicity and the diastreoselectivity of this good yielding one-pot procedure under mild conditions are notable. The observed dynamic effects in **3a** are attributed to the restricted rotation around the C–N single bond or inversion at the nitrogen atom in the maleimide ring. The calculated free energy of activation ($\Delta G^{\neq}$) in **3a** for the dynamic process is 47± 2 kJ/mol.

Experimental

All the materials and solvents were obtained from Merck Chemical Company (Germany) and Fluka (Switzerland) and used without further purification. Melting points were determined in open capillary tubes on an Electrothermal 9100 melting point apparatus. FTIR spectra were recorded on a Shimadzu-IR 470 spectrophotometer. ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on a Bruker DRX-500 Avance spectrometer in $CDCl_3$ at 500.1, 125.8 and 202.4 MHz, respectively. X-ray diffracted intensities were measured from a single crystal 0.25 × 0.24 × 0.22 mm of **3a** at 100 K on an Oxford Diffraction Gemini-R Ultra CCD diffractometer using monochromatised Cu-K_α (λ = 1.54178Å). Whereas, X-ray diffracted intensities were measured from a single crystal 0.27 × 0.17 × 0.16 mm of **3d** at 100 K on an Oxford Diffraction Xcalibur-S CCD diffractometer using monochromatised Mo-K_α (λ = 0.71073). Data were corrected for Lorentz and polarisation effects and absorption correction applied using multiple symmetry equivalent reflections. The structures were solved by direct method and refined on F^2 using SHELX-97 crystallographic package. A full matrix least-squares refinement procedure was used, minimising $w(F_o^2–F_c^2)$, with $w=[\sigma^2(F_o^2)+(AP)^2+BP]^{-1}$, where $P=(F_o^2+2F_c^2)/3$. Agreement factors (R = $\Sigma||F_o|-|F_c||/\Sigma|F_o|$, $wR2$ = $\{\Sigma[w(F_o^2–F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{1/2}$ and GOF = $\{\Sigma[w(F_o^2–F_c^2)^2]/(n–p)\}^{1/2}$ are cited, where n is the number of reflections and p the total number of parameters refined). All non-hydrogen atoms were refined anisotropically. Positions of hydrogen atoms were localised from difference Fourier synthesis and their atomic parameters were constrained to the bonded atoms during the refinement.

Mass spectrometry measurements were performed on a Micromass Autospec Mass Spectrometer and on Shimadzu GC/MSQP 1100 EX mass spectrometer operating at an ionisation potential of 70 eV. Elemental analysis (CHN) was performed using ThermoFinigan Flash EA1112 and Elementar equipments.

Typical procedure for the preparation of **3a–d**

Dimethyl (2S,3R*)-2-(2,5-dioxo-2,5-dihydropyrrol-1-yl)-3-(diphenoxyphosphoryl)butanedioate* **(3a):** To a magnetically stirred solution of triphenylphosphite (0.31 g, 1 mmol) and maleimide (0.097 g, 1 mmol) in diethyl ether (5 ml) was added dimethyl acetylenedicarboxylate (1 mmol) dropwise over 3 minutes at room temperature and reaction mixture was then allowed to stir for 2 h. The ether was removed under reduced pressure and the residue was purified by crystallisation using diethyl ether-hexane. The product **3a** was obtained as white crystals, 0.4 g, yield 84%, m.p. 95–97°C. IR (KBr): 1730 (C=O of ester), 1705 (C=O of maleimide), 1590 (C=C) Cm^{-1}. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 3.7, 3.8 (2 × s, 6H, $2OCH_3$), 4.4 (dd, 1H, $^2J_{HP}$ = 20.9 Hz, $^3J_{HH}$ = 11.6 Hz, P– CH), 5.7 (dd, 1H, $^3J_{HP}$ = 5.5 Hz, $^3J_{HH}$ = 11.6 Hz, P-C-CH), 6.75 (s, 2H, 2CH of maleimide), 7.1–7.3 (m, 10H, Ar); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 44.8 (d, $^1J_{CP}$ = 134.6 Hz, P–^{13}CH), 48.9 (d, $^2J_{CP}$ = 4.5 Hz, P–CH–^{13}CH), 53.2, 53.5 (2 × s, $2OCH_3$), 120.3, 120.5 (2d, $^3J_{CP}$ = 4.5 Hz, 2 C_{ortho} of $2C_6H_5$), 125.5, 125.6 (2 C_{para} of $2C_6H_5$), 129.7, 129.8 (2C_{meta} of $2C_6H_5$), 134.6 (s, HC=CH of maleimide), 149.5 (d, $^2J_{CP}$ = 10.0 Hz, C_{ipso} of C_6H_5), 150.0 (d, $^3J_{CP}$ = 8.4 Hz, C_{ipso} of C_6H_5), 166.4 (d, $^2J_{CP}$ = 7.9 Hz, C=O ester), 168.1 (d, $^3J_{CP}$ = 19.4 Hz, C=O ester), ^{31}P NMR (202.4 MHz, $CDCl_3$): δ 9.9 [– $(PhO)_2{}^{31}P$ = O], MS (EI, 70eV): *m/z* (%) = 474 (25) [M$^+$], 380 (60) [M$^+$– PhOH], 285 (23) [M$^+$ – 2PhOH], 255 (15) [M + –CH_3O –$2C_6H_5OH$], 77 (100) [Ph]. Microanalysis for $C_{22}H_{20}NO_9P$ (473) Calcd: C 55.8, H 4.2 and N 3.0%; Found: 55.5, H 4.1, and N 3.2%.

Dimethyl (2S,3R*)-2-(2,5-dioxopyrrolidino-1-yl)-3-(diphenoxyphosphoryl)butanedioate* **(3b)**: The product 3b was obtained as white powder, 0.43 g, yield 90%, m.p. 114–116°C. IR (KBr) (ν_{max}, cm^{-1}): 1742 and 1712 (C=O), 1587 (C=C), 1279 (P = O). ^{1}H NMR (300.1 MHz, $CDCl_3$): 2.72 (s, 4H, $2CH_2$), 3.73 and 3.87 (2 × s, 6H, $2OCH_3$), 4.43 (dd, 1H, $^2J_{PH}$ = 21.3 Hz, $^3J_{HH}$ = 11.5 Hz, P–CH), 5.78 (dd, 1H, $^3J_{PH}$ = 5.1 Hz, $^3J_{HH}$ = 11.5 Hz, P–CH–C*H*), 7.11–7.34 (m, 10H, 2 C_6H_5). ^{13}C NMR (125.8 MHz, $CDCl_3$): 28.11 (s, CH_2–CH_2), 43.36 (d, $^1J_{PC}$ = 132.8 Hz, P–*C*H), 49.23 (s, $2OCH_3$), 53.31 (d, $^2J_{PC}$ = 17.02 Hz, P–C–*C*H), 120.21 and 120.52 (2d, $^3J_{PC}$ = 4.4 Hz, C_{ortho} of $2C_6H_5$), 125.70 and 125.82 (C_{para} of $2C_6H_5$), 129.85 and 129.89 (C_{meta} of $2C_6H_5$), 149.31 and 149.88 (2d, $^2J_{PC}$ = 10.1 Hz, C_{ipso} of $2C_6H_5$), 166.31 (d, $^2J_{PC}$ = 7.9 Hz, C=O), 167.79 (d, $^3J_{PC}$ = 19.7 Hz, C=O), 176.31(s, C=O of Succinimide). ^{31}P NMR (202.4 MHz, $CDCl_3$): 10.05 [s, $(PhO)_2P$(= O)]. MS (EI, 70eV): *m/z* (%): 381 (M$^+$– PhOH, 35), 282 (M$^+$–$C_4H_5NO_2$ and PhOH, 30), 222 (285–CH_3CO_2H, 65), 223 94 (PhOH, 88), 77(C_6H_5, 100). ^{31}P NMR (202.4 MHz, $CDCl_3$): δ 10.05 [– $(PhO)_2{}^{31}P$ = O]. MS (EI$^+$, 70 eV) for $C_{22}H_{22}NO_9P$, ([M] +): calcd: 475.1; found: 475.0 (90%). Microanalysis for $C_{22}H_{22}NO_9P$ (475) Calcd: C 55.6, H 4.6 and N 3.0%; Found: 55.4, H 4.2, and N 3.3%.

Dimethyl (2S,3R*)-2-(N-phenylacetamido)-3-(diphenoxyphosphoryl) butanedioate* **(3c):** The product **3c** was obtained as colourless crystals (by crystallisation from diethyl ether-ethanol), 0.48 g, yield 94%, m.p.137–139°C; FTIR (KBr): 1736, 1734 (2C=O of esters), 1666 (C=O of amide) 1591 (C=C) Cm^{-1}; ^{1}H NMR (300.1355 MHz, $CDCl_3$): δ 1.9 (s, 3H, CH_3, acyl group), 3.76 (s, 3H, OCH_3), 3.8 (s, 3H, OCH_3), 4.76 (dd, 1H, $^2J_{PH}$ = 21.3 Hz, $^3J_{HH}$ = 10.7 Hz, P– C*H*), 5.2 (dd, 1H, $^3J_{PH}$ = 5.4 Hz, $^3J_{HH}$ = 10.7 Hz, P–C–C*H*), 6.9–7.6 (m, 15H, Ar), ^{13}C NMR (75.47 MHz, $CDCl_3$): δ 22.9 (s, CH_3 of N–CO–CH_3), 49.2 (d, $^1J_{PC}$ = 135.5 Hz, P–^{13}CH), 53.13, 53.35 (2 × s, $2CH_3$ of two ester groups), 62.6 (d, $^2J_{PC}$ = 3.6 Hz, P–CH–^{13}CH), 120.3, 120.5 (2d, $^3J_{PC}$ = 4.5 Hz, 2 C_{ortho} of $2C_6H_5$), 125.41, 125.54 (2 × s, $2C_{para}$ of $2OC_6H_5$), 128.09 (s, C_{ortho} of N–C_6H_5), 128.12 (s, C_{para} of N–C_6H_5), 129.5 (C_{meta} of N–C_6H_5), 129.8, 129.9 (2 × s, C_{meta} of $2C_6H_5$), 143.6 (s, C_{ipso} of N–C_6H_5), 149.98 (d, $^2J_{PC}$ = 9.8 Hz, Cipso of OC_6H_5), 150.3 (d, $^2J_{PC}$ = 8.8 Hz, C_{ipso} of OC_6H_5), 167.7 (d, $^2J_{PC}$ = 7.4, C=O ester), 170.2 (d, $^3J_{PC}$ = 19.8 Hz, C=O ester), 172.6 (s, C=O of Acyl); ^{31}P NMR (121.496 MHz, $CDCl_3$): δ 11.5 [– $(PhO)_2{}^{31}P$ = O]. MS (EI$^+$, 70 eV) for C26H26NO8P, ([M + 1] +): calcd: 511.14; found: 511.0 (5%), 512.0 (100%). Microanalysis for C26H26NO8P (511) Calcd: C 61.0, H 5.1 and N 2.7%; Found: 60.8, H 5.0, and N 3.0%.

Diethyl (2S,3R*)-2-(N-phenylacetamido)-3-(diphenoxyphosphoryl) butanedioate* **(3d):** Colourless crystals, 0.49 g, yield 90%, m.p. 129–131°C; FTIR (KBr): 1743, 1727 (2C=O of esters), 1668 (C=O of amide) 1595 (C=C) Cm^{-1}; ^{1}H NMR (300.135 MHz, $CDCl_3$): δ 1.24 (t, $^3J_{HH}$ = 7 Hz, 3H, CH_3 of Et), 1.3 (t, $^3J_{HH}$ = 7 Hz, 3H, CH_3 of Et), 1.9 (s, 3H, CH_3 of acyl group), 4.18–4.32 (m, 4H, $2CH_2$ of 2Et), 4.76 (dd, 1H, $^2J_{PH}$ = 21.3 Hz, $^3J_{HH}$ = 10.7 Hz, P– C*H*), 5.13 (dd, 1H, $^3J_{PH}$ = 5.1 Hz, $^3J_{HH}$ = 10.7 Hz, P–C–C*H*), 6.9–7.7 (m, 15H, Ar), ^{13}C NMR (75.47 MHz, $CDCl_3$): δ 14.0, 14.2 (2 × s, CH_3 of 2Et), 22.9 (s, CH_3 of N–CO–CH_3), 46.4 (d, $^1J_{PC}$ = 135.0 Hz, P–^{13}CH), 62.2, 62.4 (2 × s, $2OCH_2$ of ester), 62.7 (d, $^2J_{PC}$ = 1.8 Hz, P–CH–^{13}CH), 120.3, 120.5 (2d, $^3J_{PC}$ = 4.6 Hz, $2C_{ortho}$ of $2C_6H_5$), 125.36, 125.46 (2 × s, $2C_{para}$ of $2OC_6H_5$), 128.0 (s, C_{ortho} of N–C_6H_5), 128.15 (s, C_{para} of N–C_6H_5), 129.4 (C_{meta} of N–C_6H_5), 129.8, 129.9 (2 × s, C_{meta} of $2C_6H_5$), 143.8 (C_{ipso} of N–C_6H_5), 150.0 (d, $^2J_{PC}$ = 9.6 Hz, C_{ipso} of OC_6H_5), 150.4 (d, $^2J_{PC}$ = 8.7 Hz, Cipso of OC_6H_5), 167.1 (d, $^2J_{PC}$ = 7.4, C=O ester), 169.5 (d, $^3J_{PC}$ = 19.7 Hz, C=O ester), 172.5 (s, C=O of Acyl); ^{31}P NMR (121.496 MHz, $CDCl_3$): δ 11.8 [– $(PhO)_2{}^{31}P$ = O]. MS (EI$^+$, 70 eV) for $C_{28}H_{30}NO_8P$, ([M + 1] +): calcd: 539.17; found: 539.0 (3%), 540.0 (100%). Microanalysis for $C_{28}H_{30}NO_8P$ (539) Calcd: C 62.3, H 5.6 and N 2.6%; Found: 62.0, H 5.4, and N 2.5%.

Crystal data

$C_{22}H_{20}NO_9P$ (**3a**), M = 473.36, F(000) = 984 e, monoclinic, $P2_1/n$ (No. 14), Z = 4, T = 100(2) K, a = 13.745(2), b = 9.219(2), c = 18.900(2) Å, β = 109.23(2)°, V = 2261.3(6) Å^3; D_c = 1.402 g cm^{-3}; μ_{Cu} = 1.553 mm^{-1}; $\sin\theta/\lambda_{max}$ = 0.5878; N(unique) = 3843 (merged from 56667, R_{int} = 0.0309, R_{sig} = 0.0115), N_o ($I > 2\sigma(I)$) = 3397; R = 0.0417, $wR2$ = 0.1185 (A,B = 0.08, 1.02), GOF = 1.003; $|\Delta\rho_{max}|$ = 0.42(5) e Å^{-3}. CCDC 647943.

$C_{28}H_{30}NO_8P$ (**3d**), M = 539.50, F(000) = 443.38 e, triclinic, P-1 (No. 2), Z = 2, T = 100(2) K, a = 10.3285(3), b = 10.6318(3), c = 13.3918(3) Å, α = 111.871(2), β = 97.270(2), γ = 93.492(2)°, V = 1344.39(6) Å^3; D_c = 1.333 g cm^{-3}; μ_{Mo} = 0.153 mm^{-1}; $\sin\theta/\lambda_{max}$ = 0.7035; N(unique) = 7829 (merged from 39308, R_{int} = 0.0287, R_{sig} = 0.0335), N_o ($I > 2\sigma(I)$) = 5713; R = 0.0363, $wR2$ = 0.0994 (A,B = 0.069, 0.0), GOF = 1.000; $|\Delta\rho_{max}|$ = 0.38(5) e Å^{-3}. CCDC 656078.

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