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Synthetic and structural study of 4-phosphacyclohexanones and 3-aza-7-phosphabicyclo[3.3.1]nonan-9-ones

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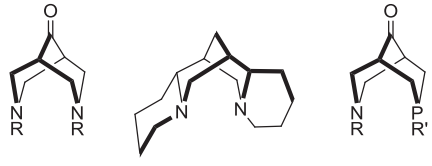
ABSTRACT

The synthesis of bicyclic phosphorus–nitrogen (PN) compounds containing the rigid bicyclo[3.3.1]nonan-9-one framework was attempted using the Mannich condensation reaction of four different phosphorinanone classes with amines and aldehydes. Three different isomers of 4-*tert*-butyl-2,6-di(methoxycarbonyl)-3,5-bis(*p*-dimethylaminophenyl)-4-phosphacyclohexanone were obtained from the Michael addition reaction of *tert*-butylphosphine with 2,4-di(methoxycarbonyl)-1,5-bis(*p*-dimethylaminophenyl)penta-1,4-dien-3-one. The reaction of the all-equatorial isomer with methylamine and formaldehyde produced the bicyclic PN compound 7-*tert*-butyl-1,5-di(methoxycarbonyl)-6,8-bis(*p*-dimethylaminophenyl)-3-methyl-3-aza-7-phosphabicyclo[3.3.1]nonan-9-one. The identical Mannich reaction of the enol tautomer also yielded the same product, as well as the PN compound 4-*tert*-butyl-6-methoxycarbonyl-5-(*p*-dimethylaminophenyl)-2-methyl-2-aza-4-phosphacyclohexanone and the *E*/*Z* isomers of 3-(*p*-dimethylaminophenyl)methyl-2-propenoate. The newly synthesised 3-aza-7-phosphabicyclo[3.3.1]nonan-9-one PN compound adopts a chair–chair conformation both in solution and the solid state.

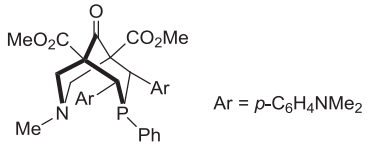
1. Introduction

A prominent group of compounds containing the bicyclo[3.3.1]nonan-9-one framework are the bispidinones (**1**).[1,2] These are simplified bis-nitrogen derivatives of the natural product sparteine[3] (**2**) with a carbonyl group at the bridging position. Bispidinones were first reported by Mannich and Mohs[4] in 1930 and have since formed an active area of research due to their synthetic simplicity, potential biological activity[5–8] and versatility as chelating ligands for transition metals.[9–12]



1 **2** **3**

Bispidinone derivatives, where one nitrogen atom has been replaced with oxygen,[13] sulfur[14,15] or selenium[16] have attracted attention for their interesting stereochemical aspects and potential medicinal properties. Recently we reported the synthesis of phosphorus–nitrogen derivatives (**3**), which adopt a rigid chair–chair conformation both in solution and the solid state, and are preorganised for coordination to transition metals via both donor atoms.[17] A specific example is 1,5-di(methoxycarbonyl)-6,8-bis(*p*-dimethylaminophenyl)-3-methyl-7-phenyl-3-aza-7-phosphabicyclo[3.3.1]nonan-9-one (**4**).



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Our continued interest in developing this novel class of PN compounds has led us to present here a detailed study on the design and synthesis of new analogues with different substitution patterns around the bicyclic backbone.

2. Results and discussion

2.1. Phosphorinanone synthesis

The synthesis of the bicyclic PN derivatives consists of two steps. Firstly a *P*-Michael[18] addition reaction between an αβ-unsaturated carbonyl compound and an aryl- or alkylphosphine (or a derivative) produces a phosphorinanone (4-phosphacyclohexanone)

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intermediate. In the second step the intermediate is combined with an aldehyde and a primary amine in a Mannich[19,20] condensation reaction to give the bicyclic PN compound.

Four different phosphorinanone classes (Fig. 1) were examined in this work. The six-membered phosphorinanone rings varied in the substituents at the 2,6- and 3,5-positions with respect to the carbonyl moiety, as well as different groups on the phosphorus atom.

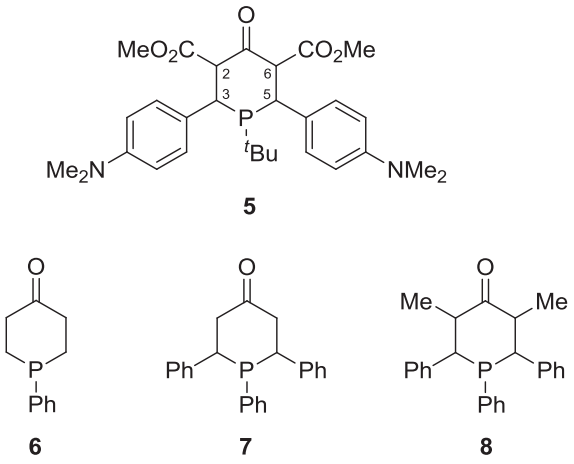


Fig. 1. Different phosphorinanone compounds.

The *P*-Michael addition reaction of dienone **9** with *tert*-butylphosphine in pyridine at room temperature yielded phosphorinanones **5a** and **5b** in a 2:1 ratio based on isolated yields (Scheme 1). Most of compound **5a** precipitated from the reaction mixture as a white solid, while isomer **5b** remained in solution. Removal of solvent and several cycles of crystallisation from hot methanol yielded **5b** as air stable fine white needles. The filtrate still contained small amounts of **5a** and **5b** plus potentially other isomers as evident from the signals in the ^{1}H and ^{31}P NMR spectra. The isolation of the other isomers was not practical as they were present in very small amounts.

Isomer **5a** exists in the ketone form with normal IR carbonyl stretches for a ketone at 1707 cm^{-1} and an ester at 1755 cm^{-1}. The ^{31}P NMR spectrum showed one resonance at 13.0 ppm (Table 1), while the ^{1}H NMR spectrum of **5a** in C_6D_6 was simple owing to the presence of a plane of symmetry in the molecule (Table 2). The pairs of equivalent protons H_3/H_5 and H_2/H_6 appeared as doublets of doublets at 3.59 and 3.97 ppm, respectively, each with J_{HH} coupling of 12.7 Hz. This large diaxial coupling constant indicates that the bulky methoxycarbonyl and dimethylaminophenyl groups are in equatorial positions. Two doublets were observed at 6.62 and 7.21 ppm for the eight aromatic protons in a ratio of 1:1, implying that both of the aryl rings are rotating freely.

Table 1
^{31}P NMR data of key compounds[a]

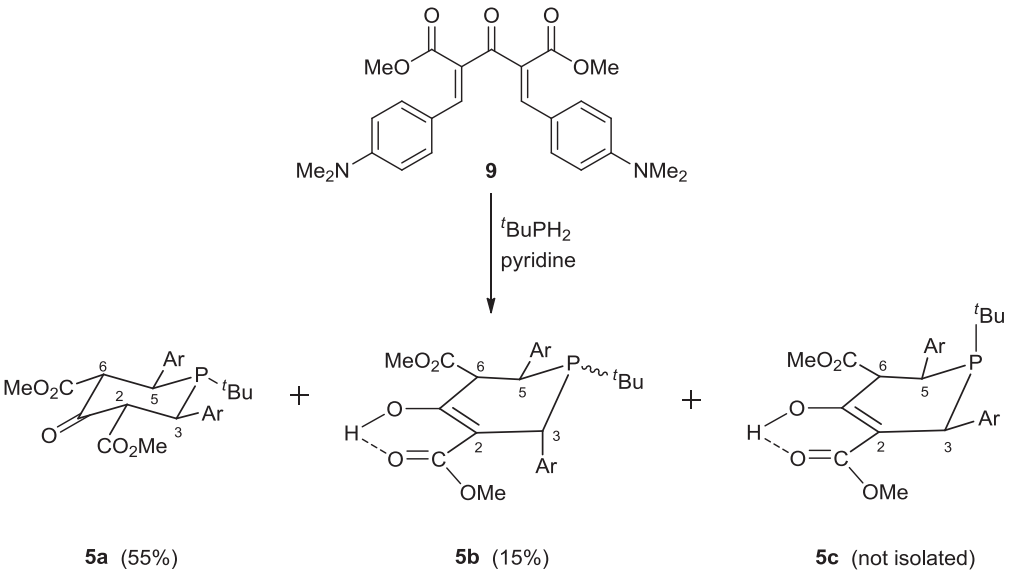
Compound	δ (ppm)	Solvent
5a	13.0	$CDCl_3$
5b	6.0	$CDCl_3$
5c	17.5	$CDCl_3$
10	8.4	C_6D_6
11	−3.5	C_6D_6

[a] All signals are referenced with respect to 85% aqueous H_3PO_4, 300 MHz.

Table 2
^{1}H NMR data of phosphorinanone isomers **5a**–**c**[a]

Group	5a	5b	5c
H_2	3.97 (dd, 12.7 Hz, 5.4 Hz)	–	–
H_3	3.59 (dd, 12.7 Hz, 5.9 Hz)	3.90 (m)	4.13 (s)
H_5	3.59 (dd, 12.7 Hz, 5.9 Hz)	3.90 (m)	3.78 (dd, 12.6 Hz, 3.2 Hz)
H_6	3.97 (dd, 12.7 Hz, 5.4 Hz)	4.28 (d, 5.9 Hz)	4.42 (dd, 12.6 Hz, 1.0 Hz)
OMe	3.51 (s)	3.62 (s) 3.66 (s)	3.58 (s) 3.61 (s)
NMe_2	2.91 (s)	2.91 (br s) 2.95 (br s)	2.90 (s)
Bu^t	0.63 (d, 10.7 Hz)	0.52 (d, 11.6 Hz)	0.96 (d, 11.3 Hz)
OH	–	12.84 (s)	13.13 (s)

[a] Spectra obtained in $CDCl_3$. Chemical shifts in ppm. Multiplicity and coupling constants given in parentheses.



Scheme 1. Synthesis of 2,6-diester phosphorinanones.

From previous conformational analysis work on six-membered phosphacycles,[21,22] the bulky *tert*-butyl group on phosphorus is expected to occupy an equatorial position in isomer **5a**. Quin et al.[21] showed that 1-R-phosphorinanes (R=CH_3, C_2H_5, *i*-C_3H_7, C_6H_5) gave a single ^{31}P NMR signal at 300 K, but on lowering the temperature, separate sharp signals for the axial-R and equatorial-R conformers were observed. However, in the case of 1-*tert*-butylphosphorinane only one signal was observed over the entire temperature range (129–300 K) corresponding to the equatorial conformer. Moreover, Pringle and co-authors found that the *tert*-butyl group in 4-*tert*-butyl-3,5-diphenyl-4-phosphorinanone also occupied an equatorial position.[22] The strong preference of the *tert*-butyl group for the equatorial position may be attributed to its large size. The ^{13}C NMR data of **5a** is summarised in Table 3.

Table 3
^{13}C NMR data of phosphorinanone isomers **5a**–**c**[a]

Group	5a	5b	5c
C_1	199.4 (d, 3.4 Hz)	168.3 (d, 6.2 Hz)	169.9 (s)
C_2	65.4 (d, 15.8 Hz)	103.8 (d, 9.0 Hz)	99.9 (d, 2.8 Hz)
C_3	42.3 (d, 19.7 Hz)	35.2 (d, 24.1 Hz)	34.5 (d, 13.5 Hz)
C_5	42.3 (d, 19.7 Hz)	36.5 (d, 19.1 Hz)	34.3 (d, 21.3 Hz)
C_6	65.4 (d, 15.8 Hz)	57.3 (d, 17.4 Hz)	48.1 (d, 2.0 Hz)
COO	168.2 (d, 10.6 Hz)	172.6 (d, 13.2 Hz)	172.6 (d, 6.7 Hz)
		172.8 (d, 6.7 Hz)	173.1 (s)
OMe	52.1 (s)	52.4 (s)	52.0 (s)
		52.6 (s)	
NMe_2	40.6 (s)	40.7 (br s)	40.0 (s)
		40.8 (br s)	
$C(\mathbf{C}H_3)_3$	28.7 (d, 10.1 Hz)	27.6 (d, 12.3 Hz)	29.8 (d, 13.7 Hz)
$\mathbf{C}(CH_3)_3$	30.9 (d, 20.6 Hz)	30.2 (d, 21.3 Hz)	31.7 (d, 30.9 Hz)

[a] Spectra obtained in $CDCl_3$. Chemical shifts in ppm. Multiplicity and coupling constants given in parentheses.

As a result of keto–enol tautomerism, phosphorinanone isomer **5b** was isolated in the enol form. The IR spectrum showed a broad enolic OH stretch at 3453 cm^{-1} and a group of bands at 1644, 1610 and 1519 cm^{-1} associated with the carbonyl groups. Compound **5b** is asymmetric, as two non-equivalent methoxy and dimethylamino signals were observed in the ^{1}H NMR spectrum (Table 2). The enolic proton resonated at 12.84 ppm, while the signals for H_5 and H_6 overlapped to give a multiplet centred at approximately 3.90 ppm (Fig. 2). Thus, useful stereochemical information from the magnitude of vicinal and phosphorus couplings for H_5 and H_6 were instead obtained from a coupled HSQC spectrum.[23–25]

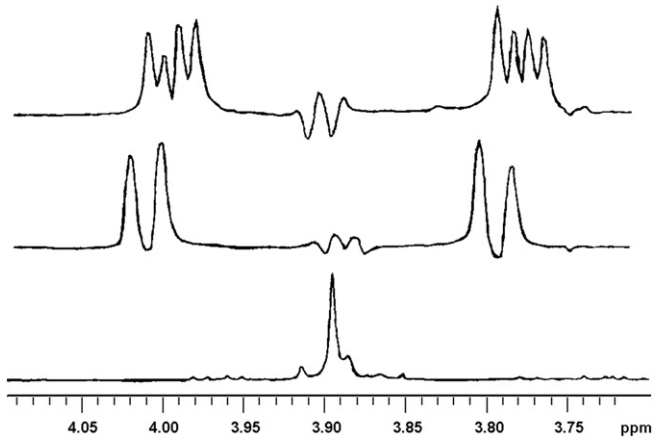


Fig. 2. Expanded-scale displays of the ^{1}H NMR spectrum of phosphorinanone isomer **5b** (bottom), and 1D traces from a coupled HSQC spectrum of **5b** at the frequency of the corresponding carbon atoms for H_5 (top) and H_6 (centre), $CDCl_3$, 600 MHz.

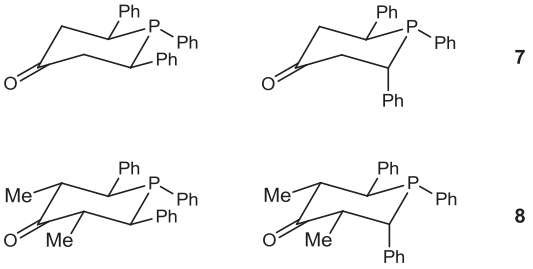
A coupled HSQC experiment is performed in the absence of broadband ^{13}C decoupling and with an extended acquisition time as compared with a regular HSQC. Extraction of 1D traces from the coupled HSQC spectrum at the carbon frequency allows the observation of proton multiplets with high resolution nearly equal to that of a conventional proton spectrum. The resolution is further enhanced by the increased acquisition time. The primary doublet splitting is due to the large $^1J_{CH}$ coupling constant as a result of coupling to ^{13}C nuclei. Residual coupling constants can also be measured from the 1D traces as second-order effects caused by strong proton–proton coupling is eliminated. In ^{1}H NMR spectra, complex coupling patterns result from strongly coupled ^{1}H–^{12}C–^{12}C–^{1}H spin systems. In the coupled HSQC experiment these strong couplings are removed and only coupling from ^{1}H–^{13}C–^{12}C–^{1}H units are observed. Consequently, undistorted first-order multiplets are restored from which proton–proton and proton–phosphorus coupling constants can be extracted.

The 1D traces (Fig. 2) from the coupled HSQC spectrum of **5b** showed H_5 as a doublet of doublets (J_{HH}=11.4 Hz, J_{PH}=6.3 Hz) and H_6 as a doublet with J_{HH} of 12.4 Hz, indicating a diaxial arrangement. Nothing can be said about the configuration at C_3 because of the isolated position of H_3, and also as NOE experiments proved inconclusive. The signals for the eight aromatic protons overlapped to give four resonances in a ratio of 3:3:1:1. This suggests that one of the dimethylaminophenyl rings is rotating freely to give rise to two signals each integrating for two protons, while the other group is experiencing restricted rotation resulting in four resonances integrating for one proton each. Since the orientation of H5 and H6 is diaxial, the dimethylaminophenyl ring at position 5 is in an equatorial position and would be free to rotate according to a stereomodel of **5b**. By contrast, the other ring on the enol side of the molecule at position 3 would be restricted in rotation if it was in an axial position and would give rise to four signals in the ^{1}H NMR spectrum. As this was the case, the H_3 proton must therefore be in an equatorial position while the dimethylaminophenyl group is axial. The observation of two signals for the dimethylaminophenyl groups is consistent with the proposed structure.

Considering that isomer **5b** represents the first example of a phosphorinanone isolated in the enol form, the orientation of the *tert*-butyl group on phosphorus is difficult to determine. Meanwhile, keto–enol tautomerism has been observed in nitrogen[26] and sulfur[27] analogues of the phosphorinanones. Isomer **5b** resonated at 6.0 ppm in the ^{31}P NMR spectrum (Table 1), and the ^{13}C NMR data is reported in Table 3.

In addition, NMR analysis of the filtrate showed a complete set of signals corresponding to a second enolic isomer (**5c**), which resonated at 17.5 ppm in the ^{31}P NMR spectrum (Table 1). The dimethylaminophenyl and the methoxycarbonyl groups at positions 5 and 6 are both equatorial because a large diaxial coupling constant of 12.7 Hz was observed between H_5 and H_6 (Table 2). The H_3 proton displayed no phosphorus coupling, resonating as a singlet at 4.13 ppm. Meanwhile, four signals in a ratio of 2:2:2:2 were observed for the aromatic protons, suggesting free rotation for both of the dimethylaminophenyl rings. To assign a molecular structure to the minor enolic isomer **5c**, the configuration at C_3 is very important. As free rotation was observed for the aryl groups, the dimethylaminophenyl group at position 3 must be equatorial. So far the substituent arrangement in isomer **5c** is the same as isomer **5a**. However, since samples containing **5a** are very stable in solution over long periods of time, the possibility of **5c** being the enol tautomer of **5a** can be ruled out. Consequently, for the enolic isomer **5c** to be different from **5a**, the *tert*-butyl group on phosphorus atom has to be in an axial position, even though such an arrangement has not been observed before. The ^{13}C NMR data for **5c** is compiled in Table 3.

Phosphorinanones **6**,[28] **7**[22,29,30] and **8**[31] were prepared by known literature methods. Mixtures of isomers were obtained for **7** and **8**, which were used in the Mannich reactions.

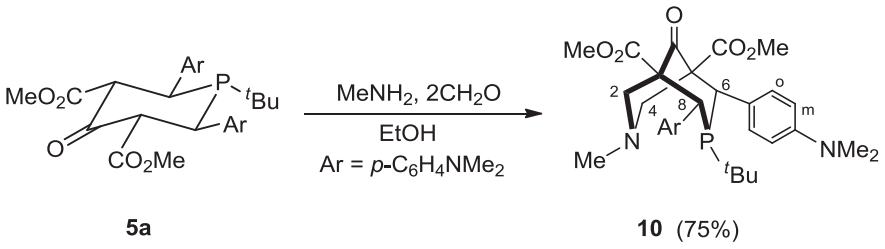


2.2. Synthesis of 3-aza-7-phosphabicyclo[3.3.1]nonan-9-ones

The Mannich reaction of isomer **5a** with methylamine and 2 equiv of formaldehyde in ethanol produced the bicyclic PN compound **10** in good yield (Scheme 2). Compound **10** was obtained as white needles and was air stable.

The Mannich reaction of the enol phosphorinanone isomer **5b** with formaldehyde and methylamine in ethanol gave highly unexpected results (Scheme 3). Removal of ethanol and washing the resulting yellow residue with diethyl ether several times yielded the symmetrical PN compound **10** (26%). The ether wash still contained small amounts of **10**. Taking the ether wash to dryness and washing the residue with hexane successfully separated the other products. The hexane-insoluble solid was identified as a new six-membered phosphorus–nitrogen compound (**11**) produced in low yield (13%) and contaminated with compound **10**. Although **11** is air stable, the use of flash column chromatography for its purification was not successful as it decomposed on the column. It could, however, be further purified by washing several times with small volumes of ethyl acetate, which dissolved most of PN compound **10,** along with small amounts of **11**. The hexane wash contained the *E*/*Z* isomers of 3-(*p*-dimethylaminophenyl)methyl-2-propenoate (37%) (**12**), with the *E* isomer being dominant.

PN compound **11** was characterised by IR and NMR spectroscopy and mass spectrometry. Elemental analysis could not be performed due to contamination with **10**, but HRESIMS analysis confirmed the molecular formula of compound **11**. The IR spectrum of **11** showed



5a **10** (75%)

Scheme 2. Synthesis of bicyclic PN compound **10**.

The ^{1}H NMR spectrum of **10** in C_6D_6 showed only half of the signals expected for this PN compound, implying symmetrical positions for the methoxycarbonyl and dimethylaminophenyl substituents, and for $H_{6/8}$ and $H_{2/4}$. Four broad doublets between 6 and 9 ppm were observed, indicating that the phenyl protons are magnetically inequivalent as a result of restricted rotation about the C–C bond. This was confirmed by variable temperature ^{1}H NMR experiments ranging from 20 to 70 °C. The signals corresponding to the *m*-protons between 6 and 7 ppm gradually collapsed and coalesced at 60 °C (300 MHz). The ^{31}P NMR spectrum showed a single peak at 8.4 ppm (Table 1), and the IR spectrum was dominated by two carbonyl stretches at 1712 and 1733 cm^{-1} corresponding to the ketone and ester groups, respectively.

Crystals of PN compound **10** were grown by the slow evaporation of a C_6D_6 solution. The solid state crystal structure shows a perfect mirror symmetrical chair–chair conformation with the methoxycarbonyl, dimethylaminophenyl, methyl and *tert*-butyl substituents in equatorial sites (Fig. 3). This conformation is favourable for metal complexation via both donor atoms to form a complex with a stable tricyclic quasi-adamantane structure. The equatorial 6,8-dimethylaminophenyl groups are constrained by the bicyclic framework to be in close proximity to the metal, which could lead to unusual coordination chemistry. Furthermore, the X-ray crystal structure also shows the unique out-of-plane protection that would be provided to coordinated metals by the dimethylaminophenyl groups.

The crystallographic dimensions of **10** are very similar to the previously reported phenyl analogue.[17] For example, the intramolecular distance between the phosphorus and nitrogen donor atoms is 2.9 Å in both PN compounds. This distance is the same as the average NN distance in bispidinone compounds.[12]

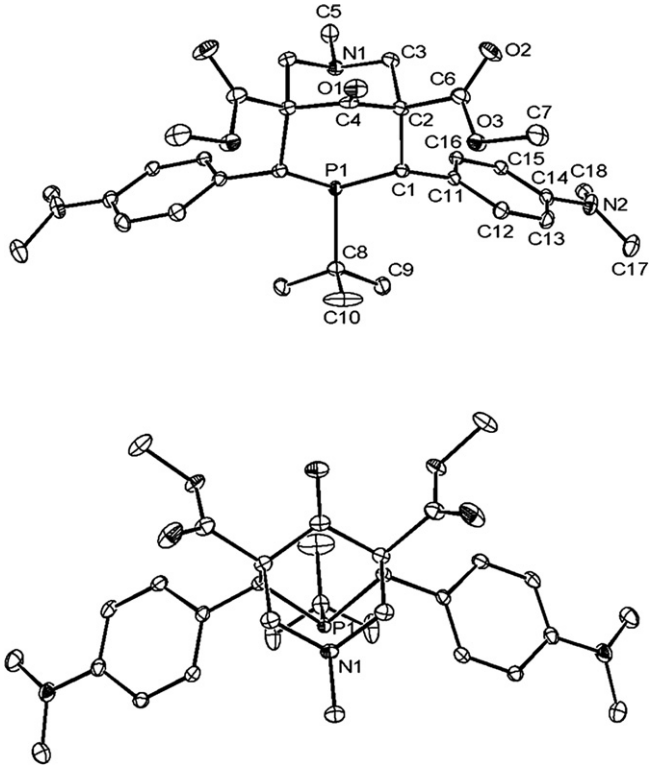
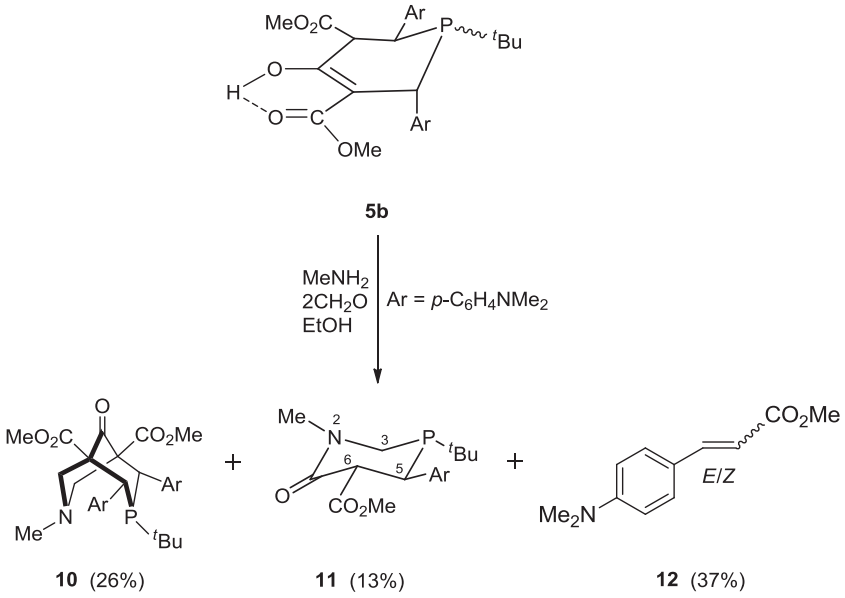


Fig. 3. ORTEP diagrams of PN compound **10** (30% thermal ellipsoids). Hydrogen atoms omitted for clarity.



Scheme 3. Mannich reaction of phosphorinanone isomer **5b**.

a carbonyl stretch at 1744 cm^{-1} and an amide stretch at 1655 cm^{-1}. The phosphorus atom in **11** resonated at -3.5 ppm in the ^{31}P NMR spectrum in $CDCl_3$ (Table 1). In the ^{1}H NMR spectrum, the axial and equatorial protons of the CH_2 group each appeared as a doublet of doublets at 2.84 and 3.03 ppm, respectively (J_{HH}=14.5 Hz). The phosphorus coupling constants were vastly different between the two protons; 18.0 Hz for the proton at 3.03 ppm and only 2.6 Hz for its geminal partner. The protons in positions 5 and 6 were in a diaxial arrangement with a J_{HH} of 12.8 Hz, indicating that the methoxycarbonyl and dimethylaminophenyl groups are in equatorial positions. The *tert*-butyl group is expected to occupy an equatorial position.[21,22]

The results obtained from the Mannich reaction of **5b** are puzzling. Firstly, through the use of an asymmetric phosphorinanone, such as isomer **5b** in the Mannich reaction, we hoped to produce an asymmetric PN compound. As this was not the case, formation of the symmetric PN compound **10** implies that some sort of isomerisation about the stereogenic centres in phosphorinanone **5b** had taken place during the double Mannich reaction.

Similar epimerisation has previously been noted in bispidinone chemistry whereby the thermodynamically most stable product forms under double Mannich reaction conditions.[32,33] These findings have been rationalised in terms of invoking either a retro-Michael reaction or a retro-Mannich reaction. Therefore, the formation of PN compound **10** from phosphorinanone **5b** under the double Mannich reaction conditions can also be attributed to the same reasons as for the nitrogen analogues.

Secondly, formation of compound **11** suggests that a side reaction occurred under the Mannich conditions, which had not been observed before. Thirdly, the observation of the *E*/*Z* isomers of compound **12** could be the result of the side reaction, or perhaps the result of the complete decomposition of phosphorinanone **5b** under such reaction conditions. Consequently, the behaviour of phosphorinanone isomer **5b** under the Mannich conditions used is very difficult to understand.

The synthesis of bicyclic PN compounds from phosphorinanones **6** and **7** was attempted using the Mannich reaction. Many products were obtained from the reactions, as shown by a plethora of signals in the ^{31}P NMR spectrum. Varying the amine, aldehyde, solvent and reaction time gave similar results. All efforts were made to purify the products, including the use of column chromatography, and extensive NMR analyses were performed on the mixture of products, but no reasonable conclusions could be drawn about the successful synthesis of bicyclic PN compounds in these cases.

Samples containing the two isomers of phosphorinanone **8** were subjected to typical Mannich reaction conditions. No reaction was observed between the phosphorinanone isomers and methylamine and formaldehyde in ethanol over different reaction times. Addition of either acid or base (as the Mannich reaction can be done under acidic or basic conditions) resulted only in the isomerisation of the starting material to the more stable symmetric isomer, presumably via a reverse Michael reaction. The use of different amines, aldehydes and solvents was also unsuccessful. The failure of the Mannich reactions was surprising as analogous bispidinone compounds with methyl substituents at the α-positions to the central carbonyl group have been reported.[9,10] Such bispidinones were prepared by the Mannich condensation reaction with the aldehyde, ketone and amine components present in the reaction mixture in a 4:1:2 ratio. However the yields were very low, never exceeding 18%. This suggests that diethyl ketone is not effective as the ketonic substrate in these syntheses. The methyl groups could be deactivating the α-positions to the carbonyl group, hence disfavouring a double Mannich reaction. Further support for such a hypothesis came from work published by Omarov et al.[34] They report the successful condensation of 3,5-diphenylpiperidinone and 2-methyl-3,5-diphenylpiperidinone to the corresponding bispidinone compounds, but 2,6-dimethyl-3,5-diphenylpiperidinone did not react at all. These observations suggest that a double Mannich reaction using diethyl ketone can be performed if the synthesis is carried out in one pot. However, the Mannich reaction is unsuccessful when 2,6-dimethyl piperidinones are used as the starting materials. As the results of this work have shown, the same is true for the isomers of phosphorinanone **8**.

To investigate the degree of reactivity of the α-positions to the central carbonyl group in the dimethyl phosphorinanone isomers of **8**, a series of small scale exchange experiments were performed using different electrophiles and reaction conditions. The only successful experiment was an H/D exchange in the presence of NaOMe. In light of these results, it is not surprising that a complex double Mannich reaction was never observed with **8**.

3. Conclusions

The synthesis of phosphorus–nitrogen compounds containing the 3-aza-7-phosphabicyclo[3.3.1]nonan-9-one framework via the Mannich reaction proved to be challenging. The nature of the substituents at the α-positions to the central carbonyl group in the phosphorinanone compounds had a significant effect on the success of the double Mannich reaction. This was demonstrated by the 2,6-diester phosphorinanone system, from which the only PN bicyclic compound was produced. The electron-withdrawing ester groups enhanced the acidic character of the α-CH protons, and also resonance stabilised the enol form of the phosphorinanones. The presence of methyl substituents at the α-positions was detrimental to the success of the Mannich reaction, as illustrated by the 2,6-dimethyl phosphorinanone system. The lack of reactivity can be attributed to the electron-donating nature of the methyl groups and their inability to stabilise the enol form of the phosphorianones. The remaining 3,5-diphenyl and 4-phenyl phosphorinanone systems had no α-substituents, but ascertaining whether the synthesis of any bicyclic PN compounds had been achieved was still difficult. Overall, these results suggest that a combination of steric and electronic factors govern the success of a double Mannich reaction in the different phosphorinanone systems examined in this work.

The newly synthesised bicyclic PN compound **10** adopted a rigid chair–chair conformation both in solution and the solid state. In reactions with transition metals this structural feature presets a bidentate capability and ensures that the nitrogen donor group remains in close proximity to the metal centre in non-chelating situations. The coordination chemistry of the novel PN ligand with transition metals is described elsewhere.[35]

4. Experimental

4.1. General information

All reactions and manipulation of products and reagents were carried out under an inert nitrogen atmosphere using standard Schlenk techniques unless otherwise stated. Analytical grade reagents and high purity solvents were degassed and purged with nitrogen gas before use, except for diethyl ether, which was dried by refluxing over sodium/benzophenone ketyl. NMR spectra were recorded using a Varian Unity Inova 300 (300 MHz for ^{1}H, 75 MHz for ^{13}C and 121 MHz for ^{31}P), a Varian Unity Inova 500 (500 MHz for ^{1}H and 125 MHz for ^{13}C), or a Varian DirectDrive 600 (600 MHz for ^{1}H and 150 MHz for ^{13}C) spectrometers. The 600 MHz instrument was equipped with a Varian inverse-detected triple-resonance HCN cold probe operating at 25 K. All direct-detected ^{1}H and ^{13}C chemical shifts were referenced to the residual solvent peak. NMR samples were prepared under an inert nitrogen atmosphere, unless otherwise stated, using C_6D_6 and $CDCl_3$. All NMR solvents were degassed before use. Variable temperature NMR experiments were carried out in C_6D_6 using Varian Unity Inova 300 MHz NMR spectrometer. Infrared spectra were recorded with a Perkin–Elmer Spectrum One FT-IR spectrophotometer using pressed KBr discs. Microanalyses were performed by The Campbell Microanalytical Laboratory at Otago University (Dunedin, NZ). Melting points were recorded on a Gallenkamp Melting Point Apparatus under vacuum unless otherwise stated. Single crystal X-ray diffraction data were recorded by the X-ray Crystallography Laboratory at the University of Canterbury (Christchurch, NZ). Electrospray ionisation mass spectra were either recorded on a PE Biosystem Mariner 5158 TOF mass spectrometer at Victoria University, or performed by the GlycoSyn QC laboratory at Industrial Research Limited (Wellington, NZ) using a Waters Q-TOF Premier Tandem mass spectrometer.

4.2. X-ray structure determination

Diffraction data for **10** were collected using Bruker CCD diffractometers with Mo Kα radiation (0.71073 Å) from a fine-focus sealed tube with graphite monochromator, using phi and omega scans. Multi-scan absorption corrections were applied. The structure was solved by direct methods and full-matrix least squares refinement, with anisotropic thermal parameters for all non-H atoms. Hydrogen atoms are in calculated positions and refined using a riding model with SHELXL defaults. Molecular drawings were made using ORTEP3.

4.3. Synthesis of compounds

*4.3.1. 4-tert-Butyl-2,6-di(methoxycarbonyl)-3,5-bis(p-dimethylaminophenyl)-4-phosphacyclohexanones (**5a**–**c**).* Dibenzylideneacetone derivative **9** (3.6 g, 8.2 mmol) was dissolved in pyridine (30 mL). To the solution, *tert*-butylphosphine (1.1 g, 12.3 mmol) was quickly added. The reaction mixture was stirred at room temperature for 1 day in a closed vessel to prevent ^{t}BuPH$_2$ from escaping. Over time a white solid precipitated out. The solid was filtered in the air, washed with diethyl ether then dried in vacuo to give the first batch of phosphorinanone isomer **5a**. The filtrate was reduced to dryness in vacuo to give a yellow foam. Washing the foam with diethyl ether yielded a second batch of **5a** as a white solid.

The diethyl ether wash was reduced to dryness in vacuo and the yellow solid was recrystallised from hot methanol in the air to produce white crystalline fine needles of **5b**. The yield can be increased by several cycles of crystallisations of the filtrates from hot methanol. Sometimes residual **5a** co-crystallised with **5b** as off-white spherical aggregates, which could be physically separated from the needles. The final mother liquor contained small amounts of **5a**–**c** and several other isomers as shown by ^{1}H and ^{31}P NMR spectra. It was impractical to separate the remaining isomers.

Compound **5a**: yield 2.4 g, 55%; decomposition at 200 °C. IR (KBr) ν_{max} 1755, 1707, 1610 and 1520 cm^{-1}; ^{1}H NMR δ (500 MHz, $CDCl_3$): 0.63 (d, J_{PH}=10.7 Hz, 9H, ^{t}Bu), 2.91 (s, 12H, NMe_2), 3.51 (s, 6H, OMe), 3.59 (dd, J_{PH}=12.7 Hz, J_{HH}=5.9 Hz, 2H, PCH), 3.97 (dd, J_{PH}=12.7 Hz, J_{HH}=5.4 Hz, 2H, PCCH), 6.62 (d, J_{HH}=8.5 Hz, 4H, *m*-H), 7.21 (d, J_{HH}=8.5 Hz, 4H, *o*-H); ^{13}C NMR δ (125 MHz, $CDCl_3$): 28.7 (d, J_{PC}=10.1 Hz, C**Me**$_3$), 30.9 (d, J_{PC}=20.6 Hz, **C**Me_3), 40.6 (s, NMe_2), 42.3 (d, J_{PC}=19.7 Hz, PCH), 52.1 (s, OMe), 65.4 (d, J_{PC}=16.1 Hz, P**C**CH), 112.7 (s, *m*-C_6H_4), 127.7 (d, J_{PC}=8.2 Hz, C_6H_4), 129.9 (d, J_{PC}=8.2 Hz, *o*-C_6H_4), 149.6 (s, *p*-C_6H_4), 168.2 (d, J_{PC}=10.6 Hz, COO), 199.4 (d, J_{PC}=3.4 Hz, CO); ^{31}P NMR δ (121 MHz; $CDCl_3$): 13.0; HRMS calcd for $C_{29}H_{40}N_2O_5P$ $[M+H]^+$: *m*/*z*=527.2675; found: 527.2661; Anal. Calcd for $C_{29}H_{39}N_2O_5P$: C, 66.1; H, 7.5; N, 5.3; found: C, 66.2; H, 7.7; N, 5.4.

Compound **5b**: yield 0.64 g, 15%; decomposition at 170 °C. IR (KBr) ν_{max} 3453, 1735, 1644, 1610 and 1519 cm^{-1}; ^{1}H NMR δ (600 MHz, $CDCl_3$): 0.52 (d, J_{PH}=11.6 Hz, 9H, ^{t}Bu), 2.91 (br s, 6H, NMe_2), 2.95 (br s, 6H, NMe_2), 3.62 (s, 3H, OMe), 3.66 (s, 3H, OMe), 3.90 (m, 2H, PCH/PCCH), 4.28 (d, J_{PH}=5.9 Hz, 1H, PCH), 6.51 (br s, 1H, *m*-C_6H_4), 6.74 (br s, 3H, *m*-C_6H_4), 6.91 (br s, 1H, *o*-C_6H_4), 7.40 (br s, 3H, *o*-C_6H_4), 12.84 (s, 1H, OH); ^{13}C NMR δ (150 MHz, $CDCl_3$): 27.6 (d, J_{PC}=12.3 Hz, CMe_3), 30.2 (d, J_{PC}=21.3 Hz, CMe_3), 35.2 (d, J_{PC}=24.1 Hz, PCH), 36.5 (d, J_{PC}=19.1 Hz, PCH), 40.7 (br s, NMe_2), 40.8 (br s, NMe_2), 52.4 (s, OMe), 52.6 (s, OMe), 57.3 (d, J_{PC}=17.4 Hz, PCCH), 103.8 (d, J_{PC}=9.0 Hz, C=COH), 112.0 (br s, *m*-C_6H_4), 112.5 (br s, *m*-C_6H_4), 113.7 (br s, *m*-C_6H_4), 127.1 (br s, C_6H_4), 128.5 (br s, C_6H_4), 128.9 (br s, *o*-C_6H_4), 130.6 (br s, *o*-C_6H_4), 149.1 (br s, *p*-C_6H_4), 149.7 (br s, *p*-C_6H_4), 168.3 (d, J_{PC}=6.2 Hz, C=COH), 172.6 (d, J_{PC}=13.2 Hz, COO), 172.8 (d, J_{PC}=6.7 Hz, COO); ^{31}P NMR δ (121 MHz; $CDCl_3$): 6.0; HRMS calcd for $C_{29}H_{40}N_2O_5P$ $[M+H]^+$: *m*/*z*=527.2675; found: 527.2677; Anal. Calcd for $C_{29}H_{39}N_2O_5P$: C, 66.1; H, 7.5; N, 5.3; found: C, 66.3; H, 7.6; N, 5.4.

Compound **5c**: this phosphorinanone isomer was not isolated. ^{1}H NMR δ (600 MHz, $CDCl_3$): 0.96 (d, J_{PH}=11.3 Hz, 9H, ^{t}Bu), 2.90 (s, 12H, NMe_2), 3.58 (s, 3H, OMe), 3.61 (s, 3H, OMe), 3.78 (dd, J_{HH}=12.6 Hz, J_{PH}=3.2 Hz, 1H, PCH), 4.13 (s, 1H, PCH), 4.42 (dd, J_{HH}=12.6 Hz, J_{PH}=1.0 Hz, 1H, PCCH), 6.57 (d, J_{HH}=8.8 Hz, 2H, *m*-C_6H_4), 6.72 (m, 2H, *m*-C_6H_4), 7.13 (d, J_{HH}=8.7 Hz, 2H, *o*-C_6H_4), 7.24 (m, 2H, *o*-C_6H_4), 13.13 (s, 1H, OH); ^{13}C NMR δ (150 MHz, $CDCl_3$): 29.8 (d, J_{PC}=13.7 Hz, C**Me**$_3$), 31.7 (d, J_{PC}=30.9 Hz, **C**Me_3), 34.3 (d, J_{PC}=21.3 Hz, PCH), 34.5 (d, J_{PC}=13.5 Hz, PCH), 40.0 (s, NMe_2), 52.0 (s, OMe), 48.1 (d, J_{PC}=2.0 Hz, PC**C**H), 99.9 (d, J_{PC}=2.8 Hz, **C**=COH), 112.0 (s, *m*-C_6H_4), 126.0 (d, J_{PC}=6.7 Hz, C_6H_4), 130.8 (d, J_{PC}=11.8 Hz, C_6H_4), 128.4 (d, J_{PC}=5.9 Hz, *o*-C_6H_4), 128.7 (d, J_{PC}=5.9 Hz, *o*-C_6H_4), 148.7 (m, *p*-C_6H_4), 169.9 (s, C=**C**OH), 172.6 (d, J_{PC}=6.7 Hz, COO), 173.1 (s, COO); ^{31}P NMR δ (121 MHz; $CDCl_3$): 17.5.

*4.3.2. 7-tert-Butyl-1,5-di(methoxycarbonyl)-6,8-bis(p-dimethylaminophenyl)-3-methyl-3-aza-7-phosphabicyclo[3.3.1]nonan-9-one (**10**).* Phosphorinanone isomer **5a** (1.7 g, 3.2 mmol), methylamine (0.30 mL, 3.2 mmol) and formaldehyde (0.51 mL, 6.3 mmol) were combined in absolute ethanol (30 mL). The reaction mixture was heated under reflux for one day. Colourless needles crystallised out of the yellow reaction mixture as it cooled to room temperature. The needles were filtered in the air, washed with cold ethanol and dried in vacuo (1.83 g, 75%); decomposition at 200 °C. IR (KBr) ν_{max} 1733, 1712, 1612, 1521, 1360 and 1264 cm^{-1}; ^{1}H NMR δ (300 MHz, C_6D_6): 0.86 (d, J_{PH}=9.8 Hz, 9H, ^{t}Bu), 2.30 (s, 3H, NMe), 2.48 (s, 12H, NMe_2), 2.91 (d, J_{HH}=12.0 Hz, 2H, CH_2), 3.44 (s, 6H, OMe), 3.56 (d, J_{HH}=12.5 Hz, 2H, CH_2), 4.44 (d, J_{PH}=5.4 Hz, 2H, PCH), 6.32 (br d, J_{HH}=7.8 Hz, 2H, *m*-H), 6.69 (br d, J_{HH}=6.7 Hz, 2H, *m*-H), 7.27 (br d, J_{HH}=8.1 Hz, 2H, *o*-H), 8.17 (br d, J_{HH}=8.6 Hz, 2H, *o*-H); ^{13}C NMR δ (75 MHz, C_6D_6): 28.1 (d, J_{PC}=13.4 Hz, C**Me**$_3$), 31.4 (d, J_{PC}=27.5 Hz, **C**Me_3), 39.9 (s, NMe_2), 43.0 (d, J_{PC}=28.4 Hz, PCH), 44.1 (s, NMe), 51.6 (s, OMe), 60.7 (s, CH_2), 65.8 (d, J_{PC}=1.4 Hz, PCH**C**), 112.2 (br s, *m*-C_6H_4), 112.4 (br d, J_{PC}=1.3 Hz, *m*-C_6H_4), 132.1 (br d, J_{PC}=3.4 Hz, C_6H_4), 133.1 (br d, J_{PC}=1.8 Hz, *o*-C_6H_4), 133.4 (br d, J_{PC}=2.0 Hz, *o*-C_6H_4), 149.7 (d, J_{PC}=1.7 Hz, *p*-C_6H_4), 169.7 (d, J_{PC}=2.2 Hz, COO), 205.2 (d, J_{PC}=2.5 Hz, CO); ^{31}P NMR δ (121 MHz; C_6D_6): 8.4; HRMS calcd for $C_{32}H_{45}N_3O_5P$ $[M+H]^+$: *m*/*z*=582.3096; found: 582.3086; Anal. Calcd for $C_{32}H_{44}N_3O_5P$: C, 66.1; H, 7.6; N, 7.2; found: C, 65.7; H, 7.6; N, 7.0.

*4.3.3. Mannich reaction of phosphorinanone isomer **5b**.* Phosphorinanone isomer **5b** (1.0 g, 1.9 mmol), methylamine (0.16 mL, 1.9 mmol) and formaldehyde (0.28 mL, 3.8 mmol) were combined in absolute ethanol (100 mL). The reaction mixture was heated under reflux for 1 day. Large colourless crystals of **10** crystallised out of the yellow reaction mixture as it cooled to room temperature. The crystals were filtered, washed with ethanol and dried in the air. All solvent was removed from the filtrate to give a yellow solid. Washing the solid with ethanol removed most of the yellow colouration to leave behind **10** as a white solid. Taking the filtrate to dryness again and washing the resulting yellow solid with diethyl ether gave another batch of compound **10** bringing the total yield to 0.29 g, 26%. The yields calculated from this reaction are based on the number of moles of phosphorinanone **5b**.

The diethyl ether filtrate was taken to dryness and the resulting yellow residue was washed with hexane. This successfully separated the other products from this reaction. The hexane-insoluble white solid was identified as PN compound **11** but the solid was contaminated with **10**. The white solid was further purified by washing with small volumes of ethyl acetate to give up to 90% pure sample of compound **11** (0.09 g, 13%). The hexane wash contained the *E*/*Z* isomers of compound **12** (0.27 g, 37%, *E*/*Z* 9:1).

*4.3.4. 4-tert-Butyl-6-methoxycarbonyl-5-(p-dimethylaminophenyl)-2-methyl-2-aza-4-phosphacyclohexanone (**11**).* Melting point and elemental analysis data could not be obtained due to contamination with compound **10**. IR (KBr) ν_{max} 1744, 1655, 1612, 1520, 1351 and 1164 cm^{-1}; ^{1}H NMR δ (500 MHz, C_6D_6): 0.79 (d, J_{PH}=11.5 Hz, 9H, ^{t}Bu), 2.45 (s, 6H, NMe_2), 2.68 (s, 3H, NMe), 2.84 (dd, J_{HH}=14.5 Hz, J_{PH}=2.6 Hz, 1H, CH_2), 3.03 (dd, J_{PH}=18.0 Hz, J_{HH}=14.5 Hz, 1H, CH_2), 3.32 (s, 3H, OMe), 3.67 (dd, J_{HH}=12.8 Hz, J_{PH}=7.2 Hz, 1H, PCH), 3.90 (dd, J_{HH}=12.8 Hz, J_{PH}=5.3 Hz, 1H, PCCH), 6.55 (d, J_{HH}=8.8 Hz, 2H, *m*-H), 7.32 (d, J_{HH}=8.8 Hz, 2H, *o*-H); ^{13}C NMR δ (150 MHz, C_6D_6): 27.4 (d, J_{PC}=13.0 Hz, C**Me**$_3$), 29.2 (d, J_{PC}=18.7 Hz, **C**Me_3), 36.6 (s, NMe), 39.2 (d, J_{PC}=17.3 Hz, PCH), 40.0 (s, NMe_2), 43.3 (d, J_{PC}=27.8 Hz, CH_2), 51.7 (s, OMe), 57.6 (d, J_{PC}=8.6 Hz, PCH**C**), 112.9 (s, *m*-C_6H_4), 129.0 (d, J_{PC}=13.4 Hz, C_6H_4), 130.0 (d, J_{PC}=8.6 Hz, *o*-C_6H_4), 149.5 (d, J_{PC}=1.9 Hz, *p*-C_6H_4), 167.6 (s, CO), 169.7 (d, J_{PC}=9.1 Hz, COO); ^{31}P NMR δ (121 MHz; C_6D_6): −3.5; HRMS calcd for $C_{19}H_{30}N_2O_3P$ $[M+H]^+$: *m*/*z*=365.1994; found: 365.1997.

Supplementary data

CCDC 839378 contains the supplementary crystallographic data for compound **10**. This information can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; e-mail: deposit@ccdc.cam.sc.uk. Supplementary data related to this article can be found online at doi:10.1016/j.tet.2012.04.038.

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