An improved, versatile synthesis of the $GABA_C$ antagonists (1,2,5,6-tetrahydropyridin-4-yl)methylphosphinic acid (TPMPA) and (piperidin-4-yl)methylphosphinic acid (P4MPA)

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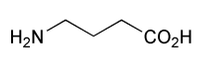
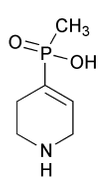
A simple, versatile and economical synthesis of the highly selective $GABA_C$ antagonist (1,2,5,6-tetrahydropyridin-4-yl)methylphosphinic acid (TPMPA) and the saturated analogue P4MPA is described. TPMPA is prepared in high yield in five steps *via* a palladium catalysed C–P bond forming reaction.

Introduction

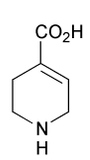
γ-Aminobutyric acid, GABA (**1**), is the major inhibitory neurotransmitter in the mammalian central nervous system (CNS). Currently, three classes of GABA receptors have been characterised ($GABA_A$, $GABA_B$, and $GABA_C$) which have a variety of roles in many CNS processes and are thus of pharmacological interest.[1,2] Several phosphinic and alkylphosphinic acids have been reported to act as potent and selective agonists at $GABA_B$ and competitive antagonists at $GABA_C$ receptors.[3–5] The methylphosphinic acid analogue (1,2,5,6-tetrahydropyridin-4-yl)methylphosphinic acid (TPMPA) (**2**), of the $GABA_A$ receptor agonist isoguvacine (**3**) has been shown to be a potent and selective competitive antagonist at $GABA_C$ receptors.[6,7] We now report a simple and versatile synthesis of TPMPA and its saturated analogue (piperidin-4-yl)methylphosphinic acid (P4MPA) (**4**), also a potent antagonist at $GABA_C$ receptors.[8]



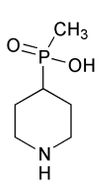
GABA **1**



TPMPA **2**



Isoguvacine **3**



P4MPA **4**

One of the greatest challenges in organophosphorus chemistry is the formation of carbon–phosphorus bonds. The most common C–P bond forming reaction is the Michaelis–Arbuzov reaction, which involves a reaction between an alkyl halide and a trialkyl or dialkyl phosphite.[9] However, this reaction usually gives acceptable yields only when primary alkyl halides are used as substrates. An alternative to the Michaelis–Arbuzov reaction is the Pudovik addition of alkyl phosphinates or phosphonates to aldehydes or ketones resulting in hydroxyphosphinate or hydroxyphosphonate compounds. The disadvantage of this reaction is the possible need to remove the hydroxy group depending upon the desired product. Therefore, the use of Heck-type palladium catalysed coupling reactions to form C–P bonds is of considerable interest. Although there are some examples in the literature of palladium catalysed C–P bond formation, these are mainly restricted to the preparation of arylphosphines[10–13] and arylphosphine oxides.[14]

The previously reported syntheses of TPMPA require a Mannich cyclisation to give an iodotetrahydropyridinyl intermediate prior to the Heck type coupling with an alkyl methylphosphinate to form the C–P bond.[7,15] An alternative synthesis of the related compound P4MPA (**4**) forms the C–P bond *via* a base-catalysed Pudovik addition of ethyl methylphosphinate.[16] A deoxygenation step is then necessary to afford the desired phosphinic ester. Our investigation has shown that the palladium catalysed coupling of methylphosphinate esters proceeds well on aryl iodides. Thus, this extends the scope of this important C–P bond forming reaction. We now report a simple, versatile and high yielding synthesis of TPMPA (**2**) and P4MPA (**4**) starting from 4-iodopyridine (**5**).[17] This synthesis has two major advantages over the previously reported syntheses: the starting materials are relatively inexpensive making this route suitable for large scale preparations, and ring-substituted TPMPA analogues are now easily accessible by starting with the appropriately substituted 4-iodopyridine.

Results and discussion

4-Iodopyridine (**5**)[17] couples smoothly with isopropyl methylphosphinate[18] in the presence of 5 mol% $Pd(PPh_3)_4$ and 1,4-diazobicyclo[2.2.2]octane (DABCO) at 70 °C to yield isopropyl (pyridin-4-yl)methylphosphinate (**6**) (Scheme 1). Reaction temperatures above 70 °C result in appreciable amounts of starting material being converted to pyridine. Highest yields were achieved by adding the catalyst in two portions of 2.5 mol%.

Treatment of **6** with methyl iodide in toluene afforded quantitatively the *N*-methylpyridinium iodide as a bright yellow salt (**7**) which was smoothly reduced with sodium borohydride in

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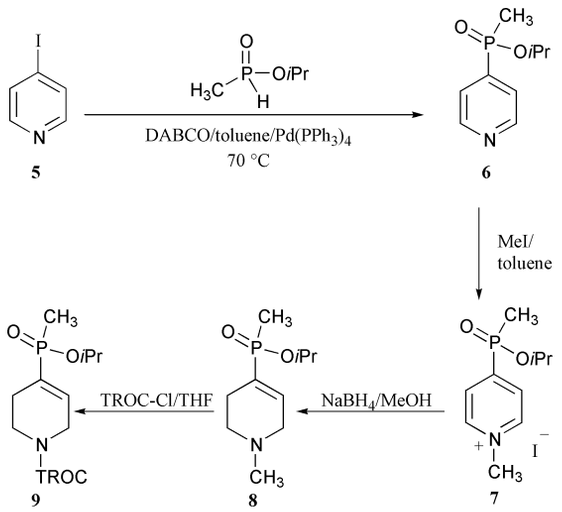
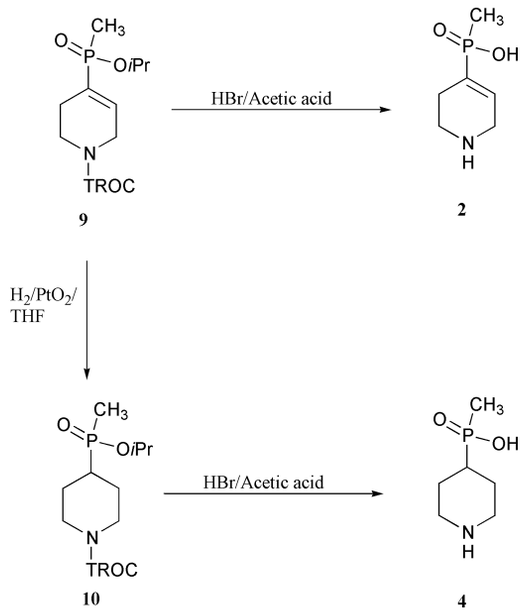


Scheme 1

methanol to give isopropyl (1-methyl-1,2,5,6-tetrahydropyridin-4-yl)methylphosphinate (**8**) in high yield. Conversion to the *N*-TROC derivative (**9**) was achieved in good yield with 2,2,2-trichloroethyl chloroformate in a procedure similar to that previously described for the *N*-benzyl protected analogue.[7] The complexity of the ^{1}H and ^{13}C NMR spectrum of **9** can be rationalised in terms of rotameric contributions.

Hydrogenation of **9** (Scheme 2) at one atmosphere using PtO_2



Scheme 2

gave the TROC protected P4MPA derivative (**10**) with a minimum of the concomitant reduction and partial deprotection of the TROC group that was the major product at higher pressures and/or longer reaction times. Deprotection of both **9** and **10** was achieved by refluxing in aqueous HBr and acetic acid. Purification of the crude products by ion exchange chromatography (Dowex 50 H^+ form, eluting with 1 M pyridine) and recrystallisation from ethanol–water afforded pure samples of TPMPA (**2**) and P4MPA (**4**) respectively.

Conclusion

An investigation of the palladium catalysed coupling of phosphinates with iodopyridines has afforded a rapid and efficient synthesis of the potent and selective $GABA_C$ antagonist TPMPA (**2**) and the saturated analogue P4MPA (**4**). The key steps in this synthesis are the palladium catalysed C–P bond forming reaction, followed by the formation and reduction of the iodopyridinium salt. In addition to economic advantages, this synthetic route also offers a potential synthesis of ring substituted analogues of TPMPA and P4MPA starting with the appropriately substituted iodopyridine.

Experimental

Melting points were determined using a Reichert hot-stage melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded at 300 MHz using a Varian Gemini 300 instrument. Chemical shifts (δ_H) are quoted in parts per million (ppm), referenced internally to tetramethylsilane (TMS) at 0 ppm. Coupling constants (J) are reported in hertz; dm indicates a doublet of multiplets where the doublet relates to ^{31}P coupling. ^{13}C NMR spectra were recorded at 75.46 MHz on a Varian Gemini 300 instrument. Chemical shifts (δ_C) are quoted in ppm, referenced to $CDCl_3$ at 77.0 ppm. ^{31}P NMR spectra were recorded at 121 MHz on a Varian Gemini 300 instrument and referenced externally to 85% H_3PO_4. Low resolution mass spectra were recorded on a Finnigan/MAT TSQ 7000 LCMS/MS spectrometer; only molecular ions (M^+) and major peaks are reported, with intensities quoted as percentages of the base peak. High resolution mass spectra were recorded on a Micromass QT of II in the Department of Chemistry at the University of Wollongong; all samples were run using electrospray ionisation (ESI) with ions measured as protonated molecular ions MH^+. Microanalyses were performed in the Department of Marine Biology at the University of Sydney. Thin layer chromatography (TLC) was performed on aluminium backed plates pre-coated with silica (0.2 mm, $60F_{254}$) which were developed using one or more of the following agents: UV fluorescence (254 nm), alkaline potassium permanganate solution (0.5% w/v), or ninhydrin (0.2% w/v). Flash vacuum chromatography was performed on silica gel (Merck silica gel 60H particle size 5–40 μm). Chemicals were purchased from Aldrich at the highest available grade. Tetrahydrofuran was distilled under nitrogen from sodium–benzophenone.

Isopropyl (pyridin-4-yl)methylphosphinate (6)

To a solution of DABCO (9.8 g, 87.8 mmol), 4-iodopyridine (6 g, 29.3 mmol) and isopropyl methylphosphinate (5.4 g, 43.95 mmol) in anhydrous toluene (300 cm^3) was added tetrakis-(triphenylphosphine)palladium(0) (850 mg, 2.5 mol%). The reaction mixture was heated at 70 °C under an atmosphere of nitrogen for 18 h at which time a second portion of tetrakis-(triphenylphosphine)palladium(0) (850 mg, 2.5 mol%) was added and heating continued for a further 36 h. The reaction mixture was filtered while still warm and the filtrate concentrated under reduced pressure. Purification by short column vacuum chromatography on silica gel (ethanol–ethyl acetate; 15 : 85) yielded the purified product as a pale yellow solid (4.2 g, 85%): mp 87–88 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.78 (2H, m, Ar*H*), 7.64 (2H, dm, J = 11.7 Hz, Ar*H*), 4.51 (1H, d of septet, J = 8.9, 6.2 Hz, OC*H*), 1.65 (3H, d, J_{HCP} = 14.7 Hz, PCH_3), 1.39 and 1.17 (2 × 3H, d, J = 6.2 Hz); ^{13}C NMR (75.46 MHz, $CDCl_3$) 15.5 (P*C*H$_3$, d, J_{CP} = 103.6 Hz), 23.9 and 24.5 (POCH(*C*H$_3$)$_2$, d, $^{3}J_{POCC}$ = 4.8 and 3.4 Hz respectively), 70.5 (PO*C*H(CH$_3$)$_2$, d, $^{2}J_{POC}$ = 6.6 Hz), 124.8 (Ar, d, $^{2}J_{PC}$ = 8.3 Hz), 140.9 (Ar, d, J = 119.3 Hz), 150.1 (Ar, d, $^{3}J_{PC}$ = 10.3 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) 38.2; MS (CI, CH_4) *m*/*z* 200 (96%) (MH^+), 158 (100); (ESI) 200.0839 (MH^+ − $C_9H_{15}NO_2P$ requires 200.0840).

4-[Isopropoxy(methyl)phosphoryl]-1-methylpyridinium iodide (7)

A solution of isopropyl (pyridin-4-yl)methylphosphinate (**6**) (2.2 g, 11.05 mmol) in anhydrous toluene (30 cm^3) was treated

with methyl iodide (7 g, 49 mmol) and the reaction mixture heated at 45 °C for 72 h. The reaction mixture was cooled and the salt allowed to settle. The solvent was decanted and the yellow salt was washed with diethyl ether (3 × 20 cm^3). Residual diethyl ether was removed under reduced pressure yielding 4-[isopropoxy(methyl)phosphoryl]-1-methylpyridinium iodide in quantitative yield which was used without further purification in the following reaction: mp 156 °C decomposed; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.45 (2H, m, Ar*H*), 8.40 (2H, dm, J = 10.8 Hz, Ar*H*), 4.78 (3H, s, NCH_3), 4.69 (1H, d of septet, J = 9, 6 Hz, OC*H*), 1.80 (3H, d, J_{HCP} = 15 Hz, PCH_3), 1.42 and 1.25 (2 × 3H, d, J = 6 Hz, CH_3CH); ^{13}C NMR (75.46 MHz, $CDCl_3$) 15.4 (P*C*H_3, d, J_{CP} = 104.8 Hz), 24.2 and 24.3 (POCH(*C*H_3)$_2$, d, $^3J_{POCC}$ = 3.8 and 4.7 Hz respectively), 50.1 (N*C*H_3), 72.4 (PO*C*H(CH$_3$)$_2$, d, $^2J_{POC}$ = 6.6 Hz), 129.6 (Ar, d, $^2J_{PC}$ = 9.7 Hz), 145.96 (Ar, d, $^3J_{PC}$ = 9.9 Hz), 150.7 (Ar, d, J_{PC} = 112.5 Hz) (Found C, 35.34; H, 5.05; N, 4.08; $C_{10}H_{17}INO_2P$ requires C, 35.21; H, 5.02; N, 4.11%).

Isopropyl (1-methyl-1,2,5,6-tetrahydropyridin-4-yl)methylphosphinate (8)

A stirred solution of 4-[isopropoxy(methyl)phosphoryl]-1-methylpyridinium iodide (**7**) (3.7 g, 11.05 mmol) in methanol (100 cm^3) was cooled to 0 °C and $NaBH_4$ (1.68 g, 44.2 mmol) was added in portions over a period of 1 h. The reaction mixture was allowed to warm to room temperature and stirring was continued for 12 h. The methanol was removed under reduced pressure and the residue partitioned between dichloromethane (60 cm^3) and water (25 cm^3). The dichloromethane layer was separated and the aqueous layer further extracted with dichloromethane (3 × 30 cm^3). The combined organic layers were washed with water (25 cm^3) and brine (30 cm^3), dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo* to yield crude product. The oil was purified by short column vacuum chromatography on silica gel (ethyl acetate containing 10% ethanol) to afford the desired isopropyl (1-methyl-1,2,5,6-tetrahydropyridin-4-yl)methylphosphinate (2.0 g, 86%), ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.67 (1H, dm, J = 18.9 Hz, C*H*=C), 4.48 (1H, d of septet, J = 8.7, 6.3 Hz, OC*H*), 3.22–2.98 (2H, m, NCH_2C=C), 2.66–2.57 and 2.55–2.45 (each 1H, m, NCH_2CH$_2$), 2.38 (1H, s, NCH_3), 2.36–2.28 (2H, m, NCH$_2$CH_2), 1.43 (3H, d, J = 14.1 Hz, PCH_3), 1.33 and 1.24 (each 3H, d, J = 6.3 Hz, CH_3CH); ^{13}C NMR (75.46 MHz, $CDCl_3$) 13.2 (d, J = 100.8 Hz), 24.0 (d, $^3J_{POCC}$ = 4.9 Hz), 24.4 (d, $^3J_{POCC}$ = 3.3 Hz), 25.5 (d, $^2J_{PC}$ = 10 Hz), 45.4 (d, $^5J_{PCCCNC}$ = 1.6 Hz), 51.1 (d, $^3J_{PC}$ = 9.4 Hz), 54.6 (d, J = 15.2 Hz), 128.77 (d, J = 124 Hz), 139.3 (d, $^2J_{PC}$ = 8.1 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) 40.8; MS (CI, CH_4) *m*/*z* 218 (100%) (MH^+), 176 (38); (ESI) 218.1304 ($MH^+ - C_{10}H_{21}NO_2P$ requires 218.1310).

Isopropyl [1-(2,2,2-trichloroethoxycarbonyl)-1,2,5,6-tetrahydropyridin-4-yl]methylphosphinate (9)

2,2,2-Trichloroethyl chloroformate (2.2 g, 10.1 mmol) was added in one portion to a stirred solution of isopropyl (1,2,5,6-tetrahydropyridin-4-yl)methylphosphinate (**7**) (2.00 g, 9.2 mmol) in anhydrous tetrahydrofuran (20 cm^3) under a N_2 atmosphere and the reaction mixture was stirred at room temperature (20 °C) for 20 h. The small amount of solid which precipitated was filtered off and the filtrate concentrated under reduced pressure. The residue was purified by short column vacuum chromatography on silica gel (ethyl acetate containing 10% ethanol) to afford the desired product as an off-white solid. Recrystallisation from hexane gave pure isopropyl [1-(2,2,2-trichloroethoxycarbonyl)-1,2,5,6-tetrahydropyridin-4-yl]methylphosphinate as small white needles (1.42 g, 52%): mp 98–99 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.72 (1H, dm, J = 19.5 Hz, C*H*=C), 4.78 (2H, s, NCH_2CCl$_3$), 4.58 (1H, d of septet, J = 8.8, 6.2 Hz, OC*H*), 4.07–4.34 (2H, m, NCH_2C=C), 3.71–3.83 and 3.49–3.66 (each 1H, m, NCH_2CH$_2$), 2.25–2.45 (2H, m, NCH$_2$CH_2), 1.49 (3H, d, J = 14.2 Hz, PCH_3), 1.35 and 1.26 (each 3H, d, J = 6.2 Hz, CH_3CH); ^{13}C NMR (75.46 MHz, $CDCl_3$) 13.9 (d, J_{PC} = 101 Hz), 24.1 (d, $^3J_{POCC}$ = 4.7 Hz), 24.5 (d, $^3J_{POCC}$ = 3.5 Hz), 24.3* and 24.7* (each d, J^3_{POCC} = 9.2 Hz), 40.2* and 40.5* (each d, $^2J_{PC}$ = 8.0 Hz), 44.1* and 44.4* (each d, $^3J_{PC}$ = 15.2 Hz), 69.3, 75.2, 95.5 (d, J = 6.4 Hz), 131.1 (d, J_{PC} = 124 Hz), 136.8*, 137.2*, 153.3*, and 153.6 (each d, J = 7.5 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) 32.4; MS (CI, CH_4) *m*/*z* 378/380/382/384 (in correct isotopic abundances) (MH^+); (ESI) 378.0184 ($MH^+ - C_{12}H_{20}Cl_3NO_4P$ requires 378.0196).

Note: * signifies probable contributions from discrete rotamers in solution, although not confirmed by variable temperature (VT) experiments.

(1,2,5,6-Tetrahydropyridin-4-yl)methylphosphinic acid (TPMPA) (2)

A solution of isopropyl [1-(2,2,2-trichloroethoxycarbonyl)-1,2,5,6-tetrahydropyridin-4-yl]methylphosphinate (1.42 g, 3.74 mmol) in 48% aq. HBr (20 cm^3) and glacial acetic acid (20 cm^3) was refluxed gently for 30 h. The mixture was concentrated under reduced pressure and final traces of residual acid removed by the sequential addition of water and concentration under reduced pressure (several cycles). The final residue was purified by ion-exchange chromatography (Dowex AG 50W). The column was eluted initially with distilled water (200 cm^3) until the eluent was neutral. Further elution with 1 M aqueous pyridine gave a ninhydrin +ve fraction which was concentrated under reduced pressure. The final traces of pyridine were removed by the sequential addition of water and concentration as described above to afford crude TPMPA as an off-white solid in quantitative yield. Recrystallisation from ethanol–water and vacuum drying gave pure TPMPA (**2**): mp 252–254 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 6.32 (1H, dm, J = 17.4 Hz, C*H*=C), 3.71 (2H, m, NCH_2C=C), 3.28 (2H, dt, J = *ca.* 0.8, 6.0 Hz, NCH_2CH$_2$), 2.49–2.57 (2H, m, NCH$_2$CH_2), 1.25 (3H, d, J = 13.9 Hz); ^{13}C NMR (D_2O, 75.46 MHz, referenced to internal dioxane at 67.4 ppm) 15.5 (d, J_{PC} = 98 Hz, P*C*H$_3$), 21.9 (d, $^2J_{PC}$ = 10.2 Hz), 41.3 (d, $^3J_{PC}$ = 7.9 Hz), 42.8 (d, $^3J_{PC}$ = 14.5 Hz), 127.2 (d, $^2J_{PC}$ = 9.0 Hz), 136.5 (d, J_{PC} = 122 Hz, P*C*H); MS (CI, CH_4) *m*/*z* 162 (MH^+); (ESI) 162.0674 ($MH^+ - C_6H_{15}NO_2P$ requires 162.0684).

Isopropyl [1-(2,2,2-trichloroethoxycarbonyl)piperidin-4-yl]-methylphosphinate (10)

Platinum oxide ($PtO_2 \cdot H_2O$) (25 mg) was added to a solution of isopropyl [1-(2,2,2-trichloroethoxycarbonyl)-1,2,5,6-tetrahydropyridin-4-yl]methylphosphinate (475 mg, 1.25 mmol) in anhydrous tetrahydrofuran (10 cm^3) and the mixture was stirred under H_2 (1 atm) at room temperature for 40 minutes. The catalyst was removed by filtration through Celite and the filtrate concentrated to a viscous, colourless oil which slowly crystallised to a colourless solid on standing: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.77 and 4.75 (both 1H, total 2H, AB system, *C*H_2CCl$_3$), 4.69 (1H, d of septet, J = 8.4, 6.2 Hz, OC*H*), 4.29–4.39 (2H, m, H_B of NCH_2), 2.74–2.95 (2H, m, H_A of NCH_2), 1.89–2.03 (2H, m, H_B of NCH$_2$CH_2), 1.75–1.87 (1H, m, PC*H*), 1.47–1.67 (2H, m, H_A of NCH$_2$CH_2), 1.43 (3H, d, J = 13.1 Hz, PCH_3), 1.32 and 1.30 (both 3H, d, J = 6.2 Hz, CHCH_3); ^{13}C NMR ($CDCl_3$, 75.46 MHz) 12.0 (d, J_{PC} = 89.5 Hz, P*C*H$_3$), 24.2 (d, $^3J_{POCC}$ = 3.6 Hz, CH*C*H$_3$), 24.3 (d, $^3J_{POCC}$ = 4.1 Hz, CH*C*H$_3$), 24.7 (br s, NCH$_2$*C*H$_2$), 37.0 (d, J_{PC} = 99.5 Hz, P*C*H), 44.3 (d, $^3J_{PC}$ = 15.0 Hz, N*C*H$_2$), 68.9 (d, $^2J_{POC}$ = 6.0 Hz, O*C*H), 75.0 (O*C*H$_2$), 95.6 (*C*Cl$_3$), 153.2 (*C*=O); MS (CI, CH_4) *m*/*z* 380/382/384 (isotopic MH^+); (ESI) 380.0363 ($MH^+ - C_{12}H_{22}Cl_3NO_4P$ requires 380.0352).

(Piperidin-4-yl)methylphosphinic acid (P4MPA) (4)

A solution of isopropyl [1-(2,2,2-trichloroethoxycarbonyl)-

piperidin-4-yl]methylphosphinate (477 mg, 1.25 mmol) was deprotected by hydrolysis as described above for the preparation of TPMPA (**2**) to afford crude P4MPA as an off-white solid in quantitative yield. Recrystallisation from ethanol–water and vacuum drying gave pure P4MPA monohydrate (**4**): mp 289–291 °C; ^{1}H NMR (300 MHz, D_2O, referenced to DOH at 4.75 ppm) δ 3.43–3.51 (2H, m, H_B of NCH_2CH_2), 2.96 (2H, (apparent?) dt, J = 3.0, 12.8 Hz, H_A of NCH_2CH_2), 2.00–2.08 (2H, m, H_B of NCH_2CH_2), 1.56–1.82 (3H, 2 × overlapping m, H_A of NCH_2CH_2 and PC*H*), 1.18 (3H, d, J = 13.2 Hz, PCH_3); ^{13}C NMR (D_2O, 75.46 MHz, referenced to internal dioxane at 67.4 ppm) 13.6 (d, J_{PC} = 91.5 Hz, PCH_3), 23.1 (NCH_2CH_2), 36.0 (d, J_{PC} = 96 Hz, PCH), 44.8 (d, $^{3}J_{PC}$ = 14.2 Hz, NCH_2); (CI, CH_4) *m/z* 164 (MH^+), (ESI) 164.0829 ($MH^+ - C_6H_{15}NO_2P$ requires 164.0840) (Found C, 39.73; H, 8.92; N, 7.67; $C_6H_{14}NO_2P{\cdot}H_2O$ requires C, 39.78; H, 8.90; N, 7.73%).

Acknowledgements

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