Diastereoselective synthesis of (±)-(3-aminocyclopentane)alkylphosphinic acids, conformationally restricted analogues of GABA

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A divergent synthesis of both diastereoisomers of (±)-(3-aminocyclopentane)alkylphosphinic acid is described. Both diastereoisomers are obtained in 5 steps from the key (±)-(3-hydroxycyclopent-1-ene)alkylphosphinate esters which are prepared *via* a palladium catalysed C–P bond forming reaction.

Introduction

γ-Aminobutyric acid, GABA (Fig. 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 $GABA_C$). These have a variety of roles in many CNS processes, *e.g.* memory and learning and in the pathophysiology of diseases such as epilepsy, and are thus of considerable clinical and pharmacological interest.[1,2] A number of phosphinic and alkylphosphinic acids have been synthesised and several of these (Fig. 1) have been shown to act potently as agonists at $GABA_B$ receptors and as competitive antagonists at $GABA_C$ receptors.[3–8]

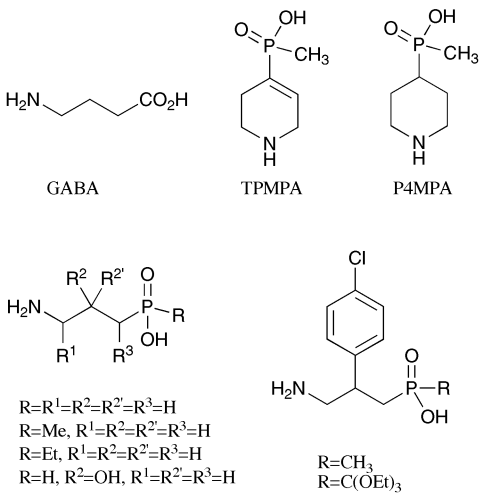

Fig. 1

With the exception of TPMPA and P4MPA, all the currently known phosphinic and methylphosphinic acid analogues of GABA are straight chain analogues which have conformational flexibility comparable to that of the endogenous ligand. Since much useful structure–activity information can be gained from the actions of small, conformationally restricted compounds, we undertook the preparation of (±)-(3-aminocyclopentane)alkylphosphinic acid analogues of GABA.

One of the greatest difficulties in the synthesis of carbocyclic organophosphorous compounds is the formation of the carbon–phosphorous (C–P) bond. A number of recent papers have indicated that the Heck-type palladium catalysed coupling reaction of alkenyl halides with alkyl phosphinates[9–11] and anilinium hypophosphite[12] are of considerable synthetic utility in the formation of C–P bonds. We now report the stereodivergent synthesis of (±)-(3-aminocyclopentane)alkylphosphinic acids *via* a palladium(0) catalysed coupling of a substituted iodocyclopentene and alkyl phosphinates to form the C–P bond.

Discussion

3-Iodo-2-cyclopenten-1-one (**1**) was prepared in high yield by a previously described method.[13] Although palladium catalysed coupling reactions have been reported to occur in high yields on a wide variety of substrates,[14] all attempts in our laboratory to carry out the modified Heck reaction of isopropyl methylphosphinate[15] with 3-iodocyclopent-2-enone (**1**) or 3-iodocyclopent-2-enol (**2**) were unsuccessful. However, *in situ* protection of the hydroxyl moiety as the trimethylsilyl ether followed by reaction under modified Heck conditions allowed the palladium catalysed coupling of the alkylphosphinate ester to proceed smoothly. Addition of ethanol to the reaction mixture at the completion of the reaction facilitated the hydrolysis of the silyl ether affording high yields of the required (±)-(3-hydroxycyclopent-1-ene)alkylphosphinates (**3** and **4**) which are the key intermediates in this stereodivergent synthesis (Scheme 1). The introduction of the TBDMS protecting group at this stage in the synthesis was investigated. However, the silyl ether was inseparable under a variety of chromatographic conditions from a by-product of reaction, resulting in a product that could not be purified. Thus it was expedient to continue to use the labile TMS ether as a temporary protecting group to facilitate the coupling reaction.

Preliminary experiments on the hydrogenation of isopropyl (±)-(3-hydroxycyclopent-1-ene)methylphosphinate (**3**) produced a 3 : 2 mixture of the *cis* : *trans* products, as determined by integration of both the P-CH_3 methyl and C*H*OH peaks in the ^{1}H NMR spectrum. The slight inequality in the ratio of the two products

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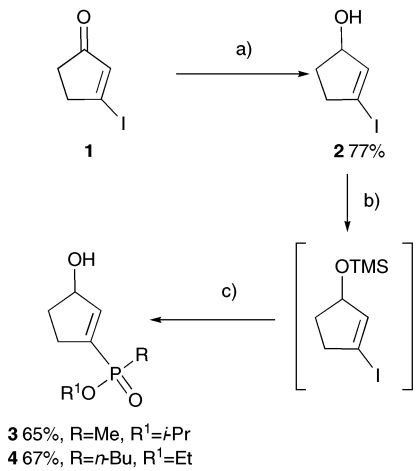
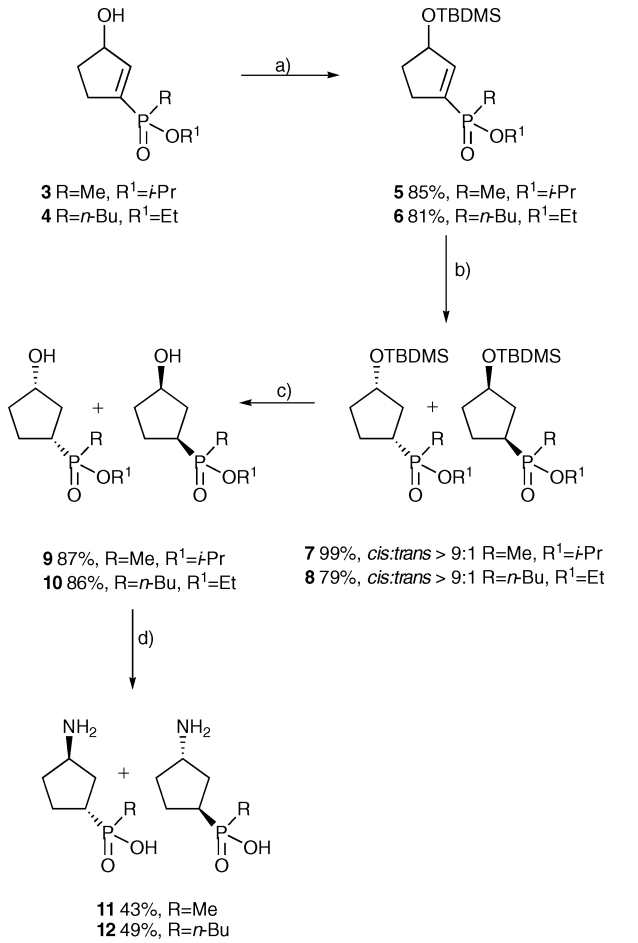


Scheme 1 *Reagents and conditions*: a) $NaBH_4$, EtOH; 0 °C to room temperature; b) TMSCl, DABCO, toluene; 0 °C to room temperature; c) i) DABCO, $Pd(PPh_3)_4$, $HP(O)(OR^1)R$; 70 °C; ii) EtOH.

indicated that the steric requirements of the hydroxyl were having a directing effect on the hydrogenation. This prompted us to investigate the effect of the sterically demanding *tert*-butydimethylsilyl substituent as a means to direct the hydrogenation of the double bond. Reaction of isopropyl (±)-(3-hydroxycyclopent-1-ene)methylphosphinate with *tert*-butyldimethylsilyl chloride in the presence of triethylamine and DMAP (Scheme 2) gave the TBDMS ether (**5**) in high yield.[16] Hydrogenation of the TBDMS protected cyclopentenol over palladium on carbon at 10 psi yielded the desired cyclopentane (**7**). This was determined to be predominantly the *cis* diastereoisomer based on a previous literature precedent in which the hydrogenation of 1,3 disubstituted cyclopent-2-enes had been shown to give the *cis* isomer when the 3-substituent is sterically demanding.[17] Hydrogenation at higher pressures resulted in some cleaving of the reactive allylic C–O bond. ^{1}H NMR analysis showed a diastereomeric ratio of greater than 9 : 1 *cis* : *trans* for the both the methyl and butyl products. The minor *trans* isomer could be easily removed by chromatography on silica gel.

Deprotection of the (±)-*cis*-*tert*-butylsilyl ethers (**7** and **8**) by treatment with TBAF afforded the (±)-*cis*-alcohols (**9** and **10** respectively) in high yield. Reaction of the alcohols under Mitsunobu conditions,[18] resulting in inversion of stereochemistry at the 3-position, yielded the (±)-*trans* isomers. Acid hydrolysis of the intermediate esters with subsequent purification by ion exchange chromatography provided (±)-*trans*-(3-aminocyclopentane)methylphosphinic acid (**11**) and (±)-*trans*-(3-aminocyclopentane)butylphosphinic acid (**12**) in good yield which were purified by ion exchange chromatography.

A related strategy was applied to the synthesis of (±)-(*cis*-3-aminocyclopentane)alkylphosphinic acids (Scheme 3). However, in this synthesis, a Mitsunobu reaction was performed at the start of the sequence on alkyl (±)-(3-hydroxycyclopent-1-ene)alkylphosphinate (**3** and **4**) to yield (±)-alkyl (3-aminocyclopent-1-ene)alkylphosphinates (**13** and **14** respectively). The amine moiety was then protected as the *tert*-butyloxycarbonylamide (BOC) (**15** and **16**) which provided the steric bulk to direct the approach of hydrogen. The hydrogenation was carried out over PtO_2 at 40 psi affording the (±)-*cis*-*N*-*tert*-



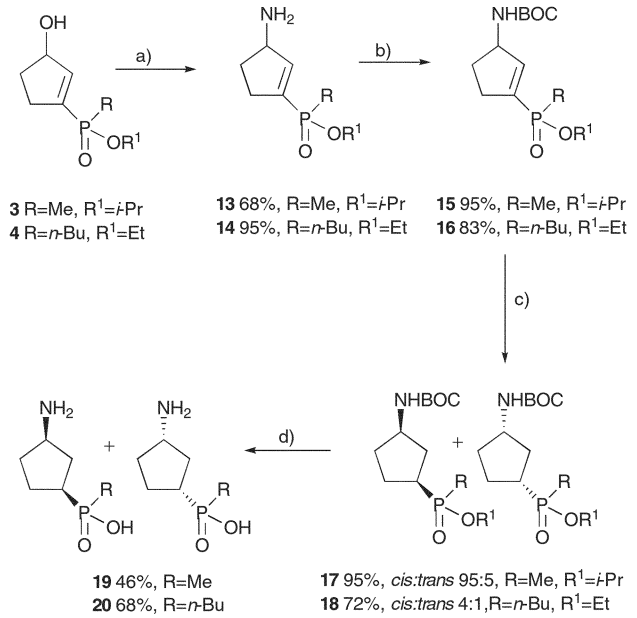
Scheme 2 *Reagents and conditions*: a) TBDMSCl, DMAP, Et_3N, DMF; 0 °C to room temperature, 12 h; b) H_2, Pd/C, MeOH; 10 psi; c) TBAF, THF; room temperature, 12 h; d) i) HN_3, PPh_3, DEAD, THF; 0 °C to room temperature, 12 h, 50 °C, 3 h; ii) 6 M HCl; reflux 36 h; iii) Dowex 50 (H^+).

butyloxycarbonyl cyclopentanes (**17** and **18**) in quantitative yield and a diastereomeric ratio of 95 : 5 *cis* : *trans* for the P-methyl compound **17**. However, in the case of the P-butyl compound, less strict stereochemical control of the *cis* : *trans* ratio was achieved with a ratio of 4 : 1 *cis* : *trans* being common. However, in both cases the minor diastereoisomer was readily separated by silica gel chromatography.

Concurrent deprotection of the phosphinic ester and the *N*-butyloxycarbonylamide was carried out in refluxing aqueous HCl. Purification by ion exchange chromatography and recrystallisation yielded the desired (±)-*cis*-(3-aminocyclopentane)methylphosphinic and (±)-*cis*-(3-aminocyclopentane)butylphosphinic acids (**19** and **20**).

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 spectrometer. Chemical shifts (δ_H) are quoted in parts per million (ppm), referenced internally to tetramethylsilane (TMS) at 0 ppm in $CDCl_3$ and referenced externally to tetramethylsilane (TMS) at



Scheme 3 *Reagents and conditions*: a) HN_3, PPh_3, DEAD, THF; 0 °C to room temperature, 12 h, 50 °C, 3 h; b) $(BOC)_2O$, NaOH, H_2O; c) H_2, PtO_2, MeOH, 40 psi; d) i) 6 M HCl; reflux 36 h; ii) Dowex 50 (H^+).

0 ppm in D_2O. Coupling constants (J) are reported in Hertz. ^{13}C NMR spectra were recorded at 75 MHz on a Varian Gemini 300 spectrometer. Chemical shifts (δ_C) are quoted in ppm and referenced to $CDCl_3$ at 77.0 ppm. ^{31}P NMR spectra were recorded at 121 MHz on a Varian Gemini 300 spectrometer 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^+ or MH^+) and major peaks are reported with intensities quoted as percentages of the base peak. High resolution mass spectra were recorded on a Micromass QTof II spectrometer with all samples being run using electrospray ionisation (ESI) with ions measured as protonated molecular ions (MH^+) or a Bruker Daltonics BioApexII spectrometer with a 7 T superconducting magnet and an Analytica ESI source with all samples being run using electrospray ionisation (ESI) with ions measured as (MNa^+). Thin layer chromatography (TLC) was performed on Merck 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. THF was distilled under nitrogen from sodium–benzophenone.

Unless otherwise noted, the duplication of peaks in the NMR spectra arise from the presence of diastereoisomers associated with the chirality of the phosphorous atom in the phosphinic ester.

(±)-3-Iodo-2-cyclopenten-1-ol (2)

A solution of 3-iodo-2-cyclopenten-1-one (**1**) (16.5 g, 79.3 mmol) in ethanol (250 cm^3) was cooled to 0 °C and sodium borohydride (1.5 g, 39.6 mmol) was added in small portions over 1 hour. When the addition was complete the reaction was monitored *via* TLC as the temperature returned to room temperature. When the reaction was complete, indicated *via* TLC, acetone (25 cm^3) was added and the solvent removed *in vacuo*. The residue was partitioned between DCM (200 cm^3) and water (35 cm^3) and the aqueous layer was further extracted with DCM (3 × 50 cm^3). The combined organic layers were washed with brine (50 cm^3), dried over anhydrous magnesium sulfate, filtered and the solvent removed *in vacuo* to afford the title compound (**6**) (sufficiently pure by ^1H NMR spectroscopy) as a pale yellow oil (12.70 g, 77%): ^1H NMR (300 MHz, $CDCl_3$) δ 1.76 and 2.35 (2H, m, C(4)-*H* and C(4)-*H′*), 2.58 and 2.83 (2H, m, C(5)-*H* and C(5)-*H′*), 3.70 (1H, m, C(1)-*H*), 4.71 (1H, br. s, C(1)-O*H*), 6.23 (1H, s, C(2)-*H*).

(±)-Isopropyl (3-hydroxycyclopent-1-ene)methylphosphinate (3)

To a solution of DABCO (11.8 g, 105 mmol) and (±)-3-iodo-2-cyclopenten-1-ol (**2**, 5.5 g, 26.3 mmol) in anhydrous toluene (300 cm^3) was added trimethylsilyl chloride (3 g, 27.6 mmol). The reaction mixture was stirred at room temperature for 15 min, after which time isopropyl methylphosphinate[15] (4.8 g, 39.4 mmol) and tetrakis(triphenylphosphine)palladium(0) (760 mg, 2.5 mol%) were added. The reaction mixture was heated at 70 °C for 24 h after which time a second portion of tetrakis(triphenylphosphine)palladium(0) (760 mg, 2.5 mol%) was added and heating continued for a further 24 h. The reaction mixture was filtered while still hot and aqueous ethanol (50 cm^3) added to the filtrate, which was then concentrated *in vacuo.* The product was isolated by short column vacuum chromatography on silica gel (15% ethanol–ethyl acetate) to yield the title compound (**3**) as a slightly coloured oil (3.5 g, 65%): ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (3H, t, $J = 6.4$, OCHCH_3), 1.327 and 1.333 (3H, 2 × d, $J = 6.2$ and 6.2 Hz, OCHCH_3), 1.49 and 1.51 (3H, 2 × d, $J =$ 14.4 and 14.4 Hz, PCH_3), 1.76–1.92 (1H, m, C(5)-*H*), 2.33–2.52 (2H, m, C(5)-*H′* and C(4)-*H*), 2.60–2.78 (1H, m, C(4)-*H′*), 4.55 (1H, m, OC*H*CH_3), 4.95 (1H, m, C(3)-*H*), 6.57 (1H, m, C(2)-*H*); ^{13}C NMR (75.46 MHz, $CDCl_3$) δ 13.8 and 14.0 (P*C*H_3, d, $J_{PC} =$ 101 and 101 Hz), 23.88 and 23.91 (POC*C*H_3, d, $^3J_{POCC} = 4.9$ and 4.6 Hz), 24.31 (POC*C*H_3, overlapping d, $^3J_{POCC} = 3.4$ Hz) 26.89 and 26.91 (*C*(4), d, $^3J_{PC} = 12.8$ and 12.5 Hz), 29.27 and 29.35 (*C*(5), d, $^2J_{PC} = 8.8$ and 8.6 Hz), 76.94 and 73.65 (PO*C*HCH_3, d, $^2J_{POC} = 6.0$ and 6.3 Hz), 76.94 and 77.18 (*C*(3), d, $^3J_{PC} = 5.0$ and 7.5 Hz), 138.11 and 138.22 (*C*(1), d, $J_{PC} = 126$ and 126 Hz), 147.54 (*C*(2), d, $J = 10.6$ Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ 38.9, 39.0; MS (CI, CH_4) m/z 207 (100%) (MH^+); (ESI) 207.1154 (MH^+ − $C_9H_{20}O_3$ requires 207.1150).

(±)-Ethyl (3-hydroxycyclopent-1-ene)butylphosphinate (4)

Compound **4** was prepared from (±)-3-iodo-2-cyclopenten-1-ol (**2**, 6.35 g, 30.4 mmol) and ethyl butylphosphinate[4] (6.83 g, 45.5 mmol) as described above. The product was isolated by short column vacuum chromatography on silica gel (10% ethanol–ethyl acetate) to yield the title compound (**4**) as a pale yellow oil (4.74 g, 67%): ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (3H, 2 coincidental t, $J = 7.2$ $PCH_2CH_2CH_2CH_3$), 1.17–1.89 (10H, m, C(5)-*H′*, $POCH_2CH_3$, $PCH_2CH_2CH_2CH_3$, $PCH_2CH_2CH_2CH_3$, $PCH_2CH_2CH_2CH_3$), 2.37 (2H, m, C(5)-*H* and C(4)-*H′*), 2.62 (1H, m, C(4)-*H*), 3.45 (1H, br. s, O*H*), 4.02 (2H, m, $POCH_2CH_3$), 4.95 (1H, m, C(3)-*H*), 6.62 (1H, d, $J = 9.7$, C(2)-*H*); ^{13}C

NMR (75.46 MHz, $CDCl_3$) δ 13.45 ($PCH_2CH_2CH_2\mathit{C}H_3$, s), 16.39 and 16.47 ($POCH_2\mathit{C}H_3$, d, $^3J_{POCC}$ = 6.2 Hz,), 23.32 and 23.36 ($PCH_2\mathit{C}H_2CH_2CH_3$, d, $^2J_{PC}$ = 3.4 Hz), 23.64 and 23.86 ($PCH_2CH_2\mathit{C}H_2CH_3$, d, $^3J_{PC}$ = 16 Hz), 27.10 and 28.30 ($P\mathit{C}H_2CH_2CH_2CH_3$, d, J_{PC} = 90.2 Hz,), 31.65 and 31.80 (*C*(4), d, $^3J_{PC}$ = 11.7 Hz), 33.89 and 33.95 (*C*(5), d, $^2J_{PC}$ = 4.6 Hz), 60.55 ($PO\mathit{C}H_2CH_3$, d, $^2J_{POC}$ = 6.3 Hz), 76.61 and 77.03 (*C*(3), d, $^3J_{PC}$ = 31.6 Hz), 136.94 and 138.51 (*C*(1), d, J_{PC} = 117.3 Hz), 148.81 (*C*(2), s); ^{31}P NMR (121 MHz, $CDCl_3$) δ 43.93 and 44.18; MS (CI, CH_4) *m/z* 233.1 (100%) (MH^+), 215 (47), 261 (18); (ESI) 255.1121 ($MNa^+ - C_{11}H_{21}O_3PNa$ requires 255.1126).

(±)-Isopropyl [3-(*tert*-butyldimethylsilyloxy)cyclopent-1-ene]methylphosphinate (5)

A solution of (±)-isopropyl (3-hydroxycyclopent-1-ene)methylphosphinate (**3**) (3.5 g, 17.2 mmol) in anhydrous DMF (60 cm^3) was treated with *tert*-butyldimethylsilyl chloride (2.85 g, 18.9 mmol), triethylamine (3.6 g, 34.3 mmol) and DMAP (250 mg). The reaction mixture was stirred at room temperature for 16 h, after which time the solvent was removed *in vacuo.* The residue was partitioned between DCM (50 cm^3) and water (30 cm^3) and the aqueous layer was further extracted with DCM (3 × 20 cm^3). The combined organic layers were washed with water (2 × 30 cm^3) and brine (40 cm^3), dried over anhydrous Na_2SO_4, filtered and the solvent removed under reduced pressure. The crude product was purified by short column vacuum chromatography on silica gel (5% ethanol–ethyl acetate) to yield the title compound (**5**) as a colourless oil (4.62 g, 85%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.065 and 0.067 (6H, 2 × s, $Si(C\mathit{H}_3)_2$), 0.870 and 0.874 (9H, 2 × s, $SiC(C\mathit{H}_3)_3$), 1.22 and 1.24 (3H, 2 × d, J = 6.3 and 6.3 Hz, $OCHC\mathit{H}_3$), 1.31 and 1.33 (3H, 2 × d, J = 6.0 and 6.0 Hz, $OCHC\mathit{H}_3$), 1.45 and 1.49 (3H, 2 × d, J = 14.4 and 14.4 Hz, $PC\mathit{H}_3$), 1.69–1.83 (1H, m, C(5)-*H*), 2.24–2.46 (2H, m, C(5)-*H*′ and C(4)-*H*), 2.54–2.68 (1H, m, C(4)-*H*′), 4.55 (1H, m, $OC\mathit{H}CH_3$), 4.95 (1H, m, C(3)-*H*), 6.46 (1H, m, C(2)-*H*); ^{13}C NMR (75.46 MHz, $CDCl_3$) δ −4.81 and −4.75 ($Si(\mathit{C}H_3)_2$, 2 × s), 14.0 and 14.19 ($P\mathit{C}H_3$, d, J_{PC} = 101.3 and 101.8 Hz), 18.07 and 18.10 ($Si\mathit{C}(CH_3)_3$, 2 × s), 23.90 and 23.96 ($POC\mathit{C}H_3$, 2 × d, $^3J_{POCC}$ = 4.8 Hz), 24.43 ($POC\mathit{C}H_3$, overlapping d, $^3J_{POCC}$ = 3.3 Hz), 25.76 ($SiC(\mathit{C}H_3)_3$, br. s), 31.34 (*C*(4), d, $^3J_{PC}$ = 11.5 Hz), 34.42 and 34.55 (*C*(5), 2 × d, $^2J_{PC}$ = 9.5 Hz), 68.95 and 68.99 ($PO\mathit{C}HCH_3$, d, $^2J_{POC}$ = 6.5 and 5.9 Hz), 77.98 and 78.24 (*C*(3), d, $^3J_{PC}$ = 6.9 and 6.7 Hz), 137.78 and 138.08 (*C*(2), d, J_{PC} = 125.0 and 125.6 Hz), 147.2 (*C*(1), d, J = 10.7 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ 38.1, 38.5; MS (CI, CH_4) *m/z* 319 (87%) (MH^+), 185 (100); (ESI) 319.1869 ($MH^+ - C_{15}H_{32}O_3PSi$ requires 319.1858).

(±)-Ethyl [3-(*tert*-butyldimethylsilyloxy)cyclopent-1-ene]butylphosphinate (6)

Compound **6** was prepared from (±)-isopropyl (3-hydroxycyclopent-1-ene)butylphosphinate (**4**) (3.66 g, 15.8 mmol) as described above. The crude product was purified by short column vacuum chromatography on silica gel (15% ethanol–ethyl acetate) to yield the desired title compound (**6**) as a colourless oil (4.42 g, 81%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.09 (6H, s, $Si(C\mathit{H}_3)_2$), 0.89 (9H, s, $SiC(C\mathit{H}_3)_3$), 0.91 and 0.93 (3H, 2 × d, J = 7.2 and 7.2 Hz, $PCH_2CH_2CH_2C\mathit{H}_3$), 1.22–1.83 (9H, m, $POCH_2C\mathit{H}_3$, $PC\mathit{H}_2CH_2CH_2CH_3$, $PCH_2C\mathit{H}_2CH_2CH_3$, $PCH_2CH_2C\mathit{H}_2CH_3$), 2.26–2.72 (4H, m, C(4)-*H*, C(4)-*H*′, C(5)-*H* and C(5)-*H*′), 3.84–4.19 (2H, m, $POC\mathit{H}_2CH_3$), 4.97 (1H, m, C(3)-*H*), 6.50 and 6.54 (1H, 2 × d, J = 9.6 and 9.6 Hz, C(2)-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.81 and −4.74 ($Si(\mathit{C}H_3)_2$, 2 × s), 13.48 ($PCH_2CH_2CH_2\mathit{C}H_3$, s), 16.43 and 16.51 ($Si\mathit{C}(CH_3)_3$, 2 × s), 18.08 ($POCH_2\mathit{C}H_3$, s), 23.43 ($PCH_2\mathit{C}H_2CH_2CH_3$, t, $^2J_{PC}$ = 3.2 and 3.2 Hz), 23.69 and 23.90 ($PCH_2CH_2\mathit{C}H_2CH_3$, d, $^3J_{PC}$ = 15.9 Hz), 25.75 ($SiC(\mathit{C}H_3)_3$, s), 27.22 and 28.54 ($P\mathit{C}H_2CH_2CH_2CH_3$, 2 × d, J_{PC} = 99.6 and 99.0 Hz), 31.55 and 31.70 (*C*(4), 2 × d, $^3J_{PC}$ = 11.6 and 11.6 Hz), 34.54 (*C*(5), t, $^2J_{PC}$ = 8.25 and 8.55 Hz), 60.15 ($PO\mathit{C}H_2CH_3$, 2 × d, $^2J_{POC}$ = 6.30 and 6.83 Hz), 77.97 and 78.22 (*C*(3), d, $^3J_{PC}$ = 18.45 Hz), 136.64 and 138.24 (*C*(1), 2 × d, J_{PC} = 119.78 and 120.1 Hz), 148.51 (*C*(2), d, $^2J_{PC}$ = 9.4 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ 42.77 and 43.15; MS (CI, CH_4) *m/z* 347.2 (16%) (MH^+), 215 (100), 375 (44); (ESI) 369.1987 ($MNa^+ - C_{17}H_{35}O_3PSiNa$ requires 369.1991).

(±)-*cis*-Isopropyl [3-(*tert*-butyldimethylsilyloxy)-cyclopentane]methylphosphinate (7)

A solution of isopropyl [3-(*tert*-butyldimethylsilyloxy)cyclopent-1-ene]methylphosphinate (**5**) (3.4 g, 10.7 mmol) in methanol (30 cm^3) was hydrogenated over palladium on carbon (50 mg) at 40 psi for 3 h. The catalyst was removed by filtration through Celite which was washed with methanol (3 × 30 cm^3). The solvent was removed *in vacuo* to yield the desired product in quantitative yield (>90% *cis* isomer (**7**) by NMR spectroscopy) which was used in the next step without further purification (3.4 g, 99%) (data for *cis* isomer only is reported): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.076 (6H, s), 0.90 (9H, s), 1.32 (6H, d, J = 6.1 Hz, $OCHC\mathit{H}_3$), 1.44 (3H, d, J = 13.2 Hz, $PC\mathit{H}_3$), 1.63–1.81 (3H, m, C(5)-*H*, C(5)-*H*′ and C(1)-*H*), 1.82–1.99 (2H, m, C(2)-*H* and C(4)-*H*), 2.09–2.21 (2H, m, C(2)-*H*′ and C(4)-*H*′), 4.26 (1H, m, C(3)-*H*), 4.65 (1H, m, $OC\mathit{H}CH_3$); ^{13}C NMR (75.46 MHz, $CDCl_3$) δ −4.96 ($Si(\mathit{C}H_3)_2$, br. s), 11.07 and 12.28 ($P\mathit{C}H_3$, d, J_{PC} = 91.0 and 91.0 Hz), 17.89 ($OSi\mathit{C}(CH_3)_3$, s), 23.99 and 24.01 (*C*5, s), 24.20 ($POC(\mathit{C}H_3)_3$, br. d, J = 4.0 Hz), 25.68 ($OSiC(\mathit{C}H_3)_3$, br. s), 35.78 and 35.81 (*C*(2), s), 35.91 and 36.11 (*C*(4), br. s,), 36.11 and 36.17 (*C*(1), d, J_{PC} = 99.6 and 100.7 Hz), 68.25 ($PO\mathit{C}H\mathit{C}H_3$, br. d, $^2J_{POC}$ = 6.6 Hz), 73.80 (*C*(3), d, $^3J_{PC}$ = 11.5 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ 57.9, 58.1; MS (CI) *m/z* 321 (91%) (MH^+), 187 (100), 145 (75); (ESI) 321.2012 ($MH^+ - C_{15}H_{34}O_3PSi$ requires 321.2015).

(±)-*cis*-Ethyl [3-(*tert*-butyldimethylsilyloxy)-cyclopentane]butylphosphinate (8)

Compound **8** was prepared from [3-(*tert*-butyldimethylsilyloxy)-cyclopentenyl]butylphosphinate (**6**) (3.20 g, 9.23 mmol) as described above in quantitative yield (>90% *cis* isomer (**8**) by NMR spectroscopy) as a colourless oil, which was used in the next step without further purification (2.55 g, 79%) (data for *cis* isomer only is reported): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.05 (6H, s, $Si(C\mathit{H}_3)_2$), 0.89 (9H, s, $SiC(C\mathit{H}_3)_3$), 0.90 and 0.92 (3H, 2 × d, J = 7.2 and 9.3 Hz, $PCH_2CH_2CH_2C\mathit{H}_3$), 1.23–2.21 (16H, m, C(1)-*H*, C(2)-*H*, C(2)-*H*′, C(4)-*H*, C(4)-*H*′, C(5)-*H* and C(5)-*H*′, $POCH_2C\mathit{H}_3$, $PC\mathit{H}_2CH_2CH_2CH_3$, $PCH_2C\mathit{H}_2CH_2CH_3$, $PCH_2CH_2C\mathit{H}_2CH_3$), 3.99–4.35 (3H, m, $POC\mathit{H}_2CH_3$, C(3)-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.89 and −4.87 ($Si(\mathit{C}H_3)_2$, 2 × s),

13.51 ($PCH_2CH_2CH_2CH_3$, s), 16.63 and 16.70 ($SiC(CH_3)_3$, 2 × s), 17.98 ($POCH_2CH_3$, s), 23.60 and 23.77 ($PCH_2CH_2CH_2CH_3$, 2 × d, $^3J_{PC}$ = 12.8 and 13.1 Hz), 23.91 (*C*(5), s), 24.10 ($PCH_2CH_2CH_2CH_3$, s), 25.74 ($SiC(CH_3)_3$, s), 25.26 and 26.47 ($PCH_2CH_2CH_2CH_3$, 2 × d, J_{PC} = 89.1 and 92.2 Hz), 34.88 and 36.51 (*C*(1), 2 × d, J_{PC} = 94.5 and 94.7 Hz), 35.78 and 35.58 (*C*(4), d, $^3J_{PC}$ = 15.4 Hz), 35.86 (*C*(2), s), 60.05 ($POCH_2CH_3$, 2 × d, $^2J_{POC}$ = 5.9 and 6.3 Hz), 73.81 and 73.97 (*C*(3), 2 × d, $^3J_{PC}$ = 11.9 and 11.9 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ 60.26 and 60.43; MS (CI, CH_4) *m*/*z* 349 (100%) (MH^+), 333 (40), 291 (36), 350 (23); (ESI) 371.2143 ($MNa^+ - C_{17}H_{37}O_3PSiNa$ requires 371.2147).

(±)-*cis*-Isopropyl (3-hydroxycyclopentane)methylphosphinate (9)

To a solution of (±)-*cis*-isopropyl [3-(*tert*-butyldimethylsilyloxy)-cyclopentane]methylphosphinate (**7**) (3.2 g, 10 mmol) in anhydrous THF (30 cm^3) was added tetrabutylammonium fluoride (11 cm^3 of a 1 M solution in THF). The reaction mixture was stirred at room temperature for 12 h at which time the solvent was removed *in vacuo.* The crude product was purified by short column vacuum chromatography on silica gel (15% ethanol–ethyl acetate); earlier fractions contained the *trans* isomer, later fractions contained the desired *cis* (**9**) isomer which was isolated as a colourless oil (1.8 g, 87%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 and 1.31 (6H, d, *J* = 6.3 and 6.3 Hz, $OCHCH_3$), 1.45 (3H, d, *J* = 13.2 Hz, PCH_3), 1.61–2.32 (6H, m, C(1)-*H*, C(2)-*H*, C(2)-*H*′, C(4)-*H*, C(4)-*H*′ and C(5)-*H*), 4.26 (1H, m, C(3)-*H*), 4.61 (1H, m, $OCHCH_3$); ^{13}C NMR (75.46 MHz, $CDCl_3$) δ 12.15 and 12.76 (PCH_3, d, J_{PC} = 90.2 and 89.9 Hz), 23.62 (*C*(5)), 24.20 and 24.24 ($POCCH_3$, 2 × d, $^3J_{POCC}$ = 3.3 Hz), 35.24 and 35.29 (*C*(2, s), 35.81 and 35.89 (*C*(1), d, J_{PC} = 97.9 and 98.5 Hz), 35.98 and 36.01 (*C*(4), d, $^3J_{PC}$ = 7.2 and 7.5 Hz), 69.11 and 69.12 ($POCHCH_3$, d, $^2J_{POC}$ = 6.9 and 6.9 Hz), 72.8 and 73.3 (*C*(3), d, $^3J_{PC}$ = 4.1 and 4.9 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ 59.4, 59.7; MS (CI, CH_4) *m*/*z* 207 (100%) (MH^+), 190 (98); (ESI) 207.1154 ($MH^+ - C_9H_{20}O_3P$ requires 207.1150).

(±)-*cis*-Ethyl (3-hydroxycyclopentane)butylphosphinate (10)

Compound **10** was prepared from (±)-*cis*-ethyl [3-(*tert*-butyldimethylsilyloxy)cyclopentane]butylphosphinate (**8**) (2.40 g, 6.89 mmol) as described above. The crude product was purified by short column vacuum chromatography on silica gel (15% ethanol–ethyl acetate); earlier fractions contained the *trans* isomer, later fractions contained the desired title *cis* isomer (**10**) as a colourless oil (1.39 g, 86%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (3H, 2 × d, *J* = 7.2 and 7.5 Hz, $PCH_2CH_2CH_2CH_3$), 1.20–2.38 (16H, m, C(1)-*H*, C(2)-*H*, C(2)-*H*′, C(4)-*H*, C(4)-*H*′, C(5)-*H* and C(5)-*H*′, $POCH_2CH_3$, $PCH_2CH_2CH_2CH_3$, $PCH_2CH_2CH_2CH_3$, $PCH_2CH_2CH_2CH_3$), 3.98–4.40 (4H, m, $POCH_2CH_3$, C(3)-O*H*, C(3)-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.35 ($PCH_2CH_2CH_2CH_3$, s), 16.50 and 16.57 ($POCH_2CH_3$, d, $^3J_{PC}$ = 5.4 Hz), 22.89 and 22.95 (*C*(5), d, $^2J_{PC}$ = 4.3 Hz), 23.42 and 23.68 ($PCH_2CH_2CH_2CH_3$, d, $^3J_{PC}$ = 19.4 Hz,), 23.87 ($PCH_2CH_2CH_2CH_3$, s), 25.45–27.29 (*C*(1), 2 × d, J_{PC} = 88.2 and 87.9 Hz), 33.99 and 34.08 (*C*(4), d, $^3J_{PC}$ = 6.5 Hz), 35.38 (*C*(2), s), 60.57 and 60.66 ($POCH_2CH_3$, 2 × d, $^2J_{POC}$ = 6.8 and 6.8 Hz), 72.58 and 73.07 (*C*(3), 2 × d, $^3J_{PC}$ = 36.2 and 37.3 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ 62.99 and 63.02; MS (CI, CH_4) *m*/*z* 235.1 (100%) (MH^+), 217 (50), 263 (21), 189 (16), (ESI) 257.1277 ($MNa^+ - C_{11}H_{23}O_3PNa$ requires 257.1282).

(±)-*trans*-(3-Aminocyclopentane)methylphosphinic acid (11)

To a stirred solution of (±)-*cis*-isopropyl (3-hydroxycyclopentane)methylphosphinate (**9**) (1.6 g, 7.8 mmol), DEAD (2.5 cm^3, 17.05 mmol) and HN_3 (8.2 cm^3 of a 1.9 M solution in benzene) in anhydrous THF (70 cm^3) under an atmosphere of N_2 at 0 °C was added triphenylphosphine (8.15 g, 31.2 mmol) in small portions over a period of 1 h. The reaction mixture was allowed to warm to room temperature and stirring continued for 12 h. The reaction mixture was then heated to 50 °C for 3 h after which time water (2 cm^3) was added and heating continued for a further 2 h. The reaction mixture was cooled to room temperature and the solvent removed *in vacuo.* The residue was partitioned between aqueous HCl (1 M, 30 cm^3) and DCM (30 cm^3). The organic layer was separated and further extracted with aqueous HCl (2 × 30 cm^3). The combined aqueous fractions were washed with DCM (2 × 30 cm^3) and concentrated *in vacuo.* The crude amino ester hydrochloride salt was hydrolysed by refluxing in aqueous HCl (6 M) for 30 h after which time the reaction mixture was cooled to room temperature and the aqueous HCl removed under reduced pressure. The crude product was purified by ion exchange chromatography (Dowex 50, H^+), eluting first with water until the eluate was colourless and pH 7. On further elution with aqueous pyridine (1 M), ninhydrin positive fractions were combined and the solvent removed *in vacuo* giving an off-white foam. Recrystallisation from ethanol–acetone followed by drying over P_2O_5 gave the desired product (**11**) (0.68 g, 43%): ^{1}H NMR (300 MHz, D_2O) δ 1.17 (3H, d, *J* = 12.3 Hz, PCH_3), 1.52–2.06 (7H, m, C(1)-*H*, C(2)-*H*, C(2)-*H*′, C(4)-*H*, C(4)-*H*′, C(5)-*H* and C(5)-*H*′), 3.73 (1H, m, *C*(3)-*H*); ^{13}C NMR (75.46 MHz, D_2O) δ 13.16 (PCH_3, d, J_{PC} = 91.6 Hz), 25.10 (*C*(5)), 31.31 (*C*(2)) 31.50 (*C*(4), d, $^3J_{PC}$ = 11.4 Hz), 37.34 (*C*(1), d, J_{PC} = 98.2 Hz), 52.40 (*C*(3), d, $^3J_{PC}$ = 9.7 Hz); ^{31}P NMR (121 MHz, D_2O) δ 45.9; MS (CI, CH4) *m*/*z* 164 (38%) (MH^+), 147 (30), 105 (100); (ESI) 164.0821 ($MH^+ - C_6H_{15}NO_2P$ requires 164.0840).

(±)-*trans*-(3-Aminocyclopentane)butylphosphinic acid (12)

Compound **12** was prepared from (±)-*trans*-ethyl (3-hydroxycyclopentane)butylphosphinate (**10**) (1.24 g, 5.29 mmol) as described above. The crude product was purified by ion exchange chromatography (Dowex 50, H^+), eluting first with water until the eluate was colourless and the pH 7. On further elution with aqueous pyridine (1 M), ninhydrin positive fractions were combined and the solvent was removed *in vacuo.* The residual traces of pyridine were removed by repeatedly redissolving the compound in water (20 cm^3) and re-evaporating (3 times). Recrystallisation from ethanol–acetone followed by drying gave the desired title compound (**12**) as a pale yellow solid (535 mg, 49%); mp (decomp.) 145–148 °C; ^{1}H NMR (300 M Hz, D_2O) δ 0.78 (3H, t, *J* = 7.2 and 7.2 Hz, $PCH_2CH_2CH_2CH_3$), 1.02–2.24 (13H, m, C(1)-*H*, C(2)-*H*, C(2)-*H*′, C(4)-*H*, C(4)-*H*′, C(5)-*H* and C(5)-*H*′, $PCH_2CH_2CH_2CH_3$, $PCH_2CH_2CH_2CH_3$, $PCH_2CH_2CH_2CH_3$), 3.61 (1H, m, C(3)-*H*); ^{13}C NMR (75 MHz, D_2O) δ 13.45 ($PCH_2CH_2CH_2CH_3$, s), 24.08 and 24.29 ($PCH_2CH_2CH_2CH_3$, d, $^3J_{PC}$ = 15.5 Hz), 24.29 and 24.35 $PCH_2CH_2CH_2CH_3$, d,

$^2J_{PC}$ = 5.2 Hz), 25.31 (*C*(5)s,), 27.90 and 29.11 (P*C*H$_2$CH$_2$-CH$_2$CH$_3$, d, J_{PC} = 91.0 Hz), 31.38 (*C*(2), s), 31.72 and 31.84 (*C*(4), d, $^3J_{PC}$ = 9.5 Hz), 35.90 and 37.16 (*C*(1), d, J_{PC} = 95.0 Hz), 52.76 and 52.90 (*C*(3), d, $^3J_{PC}$ = 10.6 Hz); ^{31}P NMR (121 MHz, D$_2$O) δ 51.41; MS (ESI) *m/z* 206 (28%) (MH$^+$), 166 (100); (ESI) 228.1129 (MNa$^+$ − $C_9H_{20}NO_2PNa$ requires 228.1124).

(±)-Isopropyl (3-aminocyclopent-1-ene)methylphosphinate (13)

To a solution of (±)-isopropyl (3-hydroxycyclopent-1-ene)methylphosphinate (**3**) (2.5 g, 12.25 mmol), DEAD (4.0 cm^3, 26.95 mmol) and HN_3 (12.9 cm^3 of a 1.9 M solution in benzene) in anhydrous THF (100 cm^3) at 0 °C was added triphenylphosphine (12.8 g, 49 mmol) in small portions over a period of 1 h. The reaction mixture was allowed to warm to room temperature and stirring continued for 12 h. The reaction mixture was then heated to 50 °C for 3 h after which time water (2 cm^3) was added and heating continued for a further 2 h. The reaction mixture was cooled to room temperature and the solvent removed *in vacuo.* The residue was partitioned between HCl (1 M, 40 cm^3) and DCM (40 cm^3). The organic layer was separated and further extracted with water (3 × 30 cm^3). The combined aqueous fractions were washed with DCM (2 × 30 cm^3) and concentrated *in vacuo.* The crude product was purified by ion exchange chromatography (Dowex 50 H$^+$ form), eluting first with water until the eluate was neutral and then with aqueous ammonium hydroxide (1 M) combining ninhydrin positive fractions. The solvent was removed *in vacuo* to yield the title compound as a pale yellow oil (**13**) (1.71 g, 68%): ^{1}H NMR (300 MHz, CD$_3$OD) δ 1.26 and 1.27 (3H, d, J = 6.0 and 6.0 Hz, POCHC*H*$_3$), 1.31 and 1.32 (3H, d, J = 6.3 and 6.3 Hz, POCHC*H*$_3$), 1.51 and 1.53 (3H, d, J = 14.4 and 14.1 Hz, PC*H*$_3$), 1.59–1.79 (1H, m, C(4)-*H*), 2.33–2.55 (2H, m, C(5)-*H*, C(5)-*H′*), 2.54–2.72 (1H, m, C(4)-*H′*), 4.05 (1H, m, C(3)-*H*), 4.48 (1H, m, C(2)-*H*), 6.52 (1H, dm, J = 9.9 Hz, PCC*H*), ^{13}C NMR (75.46 MHz, CD$_3$OD) δ 13.92 and 14.10 (P*C*H$_3$, d, J_{PC} = 102.1 and 101.6 Hz), 24.54 and 24.60 (POCH*C*H$_3$, 2 × d, $^3J_{POCC}$ = 4.6 Hz), 24.9 (POCH*C*H$_3$, d, $^3J_{POCC}$ = 3.4 Hz), 32.86 and 32.88 (*C*(4), d, $^3J_{PC}$ = 12.6 and 12.3 Hz), 35.0 and 35.13 (*C*(5), 2 × d, $^2J_{PC}$ = 10.0 Hz), 59.83 and 60.07 (PO*C*HCH$_3$, d, $^2J_{POC}$ = 5.7 and 5.7 Hz), 71.36 and 71.39 (*C*(3), d, $^3J_{PC}$ = 6.3 and 6.3 Hz), 137.96 (*C*(1), d, J_{PC} = 125.7 Hz), 150.84 and 150.95 (*C*(2), d, $^2J_{PC}$ = 10.9 and 11.1 Hz); ^{31}P NMR (121 MHz, CD$_3$OD) δ 45.9; MS (EI) *m/z* 204 (38%) (MH$^+$), 147 (30), 105 (100); (ESI) 204.1151 (MH$^+$ − $C_9H_{19}NO_2P$ requires 204.1153).

(±)-Ethyl (3-aminocyclopent-1-ene)butylphosphinate (14)

Compound **14** was prepared from (±)-ethyl (3-hydroxycyclopent-1-ene)butylphosphinate (**4**) (2.98 g, 12.8 mmol) as described above. Recrystallisation from ethanol–acetone followed by drying gave the desired title compound (**12**) as a pale yellow oil (2.82 g, 95%): ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.88 (3H, 2 × d, J = 6.9 and 7.5 Hz, PCH$_2$CH$_2$CH$_2$C*H*$_3$), 0.91 (3H, 2 × d, J = 7.2 and 7.2 Hz, PCH$_2$CH$_2$CH$_2$C*H*$_3$), 1.21–1.98 (9H, m, POCH$_2$C*H*$_3$, PC*H*$_2$CH$_2$CH$_2$CH$_3$, PCH$_2$C*H*$_2$CH$_2$CH$_3$, PCH$_2$CH$_2$C*H*$_2$CH$_3$), 2.38–2.71 (4H, m, C(4)-*H*, C(4)-*H′*, C(5)-*H* and C(5)-*H′*), 3.87–4.31 (5H, m, POC*H*$_2$CH$_3$, C(3)-N*H*$_2$, C(3)-*H*), 6.51 (1H, d, J = 9.6 Hz, C(2)-*H*); ^{13}C NMR (75 MHz, CDCl$_3$) δ 13.43 (PCH$_2$CH$_2$CH$_2$*C*H$_3$, s), 16.39 and 16.47 (POCH$_2$*C*H$_3$, d, $^3J_{POCC}$ = 6.0 Hz), 23.41 and 23.46 (PCH$_2$*C*H$_2$CH$_2$CH$_3$, 2 × d, $^2J_{PC}$ = 3.4 and 3.8 Hz), 23.63 and 23.84 (PCH$_2$CH$_2$*C*H$_2$CH$_3$, d, $^3J_{PC}$ = 15.9 Hz), 27.15 and 28.47 (P*C*H$_2$CH$_2$CH$_2$CH$_3$, 2 × d, J_{PC} = 99.0 and 99.0 Hz), 31.93 and 32.09 (*C*(4), 2 × d, $^3J_{PC}$ = 11.6 and 11.7 Hz), 34.93 and 35.04 (*C*(5), 2 × d, $^2J_{PC}$ = 8.3 and 8.6 Hz), 58.86 and 59.09 (*C*(3), 2 × d, $^3J_{PC}$ = 17.0 and 17.3 Hz), 60.11 and 60.19 (PO*C*H$_2$CH$_3$, d, $^2J_{POC}$ = 6.2 Hz), 135.63 and 137.72 (*C*(1), d, J_{PC} = 156.8 Hz), 150.47 and 150.66 (2 × d, $^2J_{PC}$ = 13.9 and 14.00 Hz, *C*(2)); ^{31}P NMR (121 MHz, CDCl$_3$) δ 43.18 and 43.28; MS (CI, CH$_4$) *m/z* 232 (16%) (MH$^+$), 215 (100); (ESI) 254.1281 (MNa$^+$ − $C_{11}H_{22}NO_4PNa$ requires 254.1286).

(±)-Isopropyl [3-(*tert*-butyloxycarbonyl)aminocyclopent-1-ene]methylphosphinate (15)

To a solution of (±)-isopropyl (3-aminocyclopent-1-ene)methylphosphinate (**13**) (1.5 g, 7.4 mmol) in aqueous sodium hydroxide (326 mg, 8.15 mmol in 25 cm^3) was added di-*tert*-butyl dicarbonate (1.78 g, 8.15 mmol). The reaction mixture was stirred at room temperature for 16 h after which time the aqueous solution was extracted with DCM (4 × 30 cm^3). The crude product was purified by short column vacuum chromatography on silica gel (15% ethanol–ethyl acetate) to yield the desired product (**15**) as a colourless oil (2.1 g, 95%): ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.24 (3H, 2 × d, J = 6.3 Hz, POCHC*H*$_3$), 1.32 (3H, d, J = 6.3 Hz, POCHC*H*$_3$), 1.44 (9H, br. s, C(C*H*$_3$)$_3$), 1.48 and 1.49 (3H, d, J = 14.7 and 14.1 Hz, PC*H*$_3$), 1.58–1.75 (1H, m, C(4)-*H*), 2.41–2.72 (3H, m, C(5)-*H*, C(5)-*H′* and C(4)-*H′*), 4.53 (2H, m, POC*H*CH$_3$ and N*H*C(CH$_3$)$_3$), 4.84 (1H, br. m, C(3)-*H*), 6.43 (1H, m, C(2)-*H*); ^{13}C NMR (75 MHz, CDCl$_3$) δ 14.18 and 14.35 (P*C*H$_3$, d, J_{PC} = 101 and 101 Hz), 24.09 and 24.14 (POCH*C*H$_3$, 2 × d, $^3J_{POCC}$ = 3.9 Hz), 24.49 (POCH*C*H$_3$, d, $^3J_{POCC}$ = 3.4 Hz), 28.4 (C(*C*H$_3$)$_3$), 31.61 (*C*(4), d, $^3J_{PC}$ = 11.6 Hz), 32.45 and 32.52 (*C*(5), 2 × d, $^2J_{PC}$ = 5.0 Hz), 57.64 and 57.87 (*C*(CH)$_3$, br. s), 69.26 (PO*C*HCH$_3$, d, $^2J_{POC}$ = 6.4 Hz), 79.65 (*C*(3), br. s), 139.11 and 139.20 (*C*(1), d, J_{PC} = 127.5 and 128.6 Hz), 145.0 (*C*(2), d, $^2J_{PC}$ = 11.3 Hz), 155.12 (C=O); ^{31}P NMR (121 MHz, CDCl$_3$) δ 56.70, 56.75; MS (EI) *m/z* 304 (38%) (MH$^+$), 147 (30), 105 (100); (ESI) 304.1681 (MH$^+$ − $C_{14}H_{26}NO_4P$ requires 304.1678).

(±)-Ethyl [3-(*tert*-butyloxycarbonyl)aminocyclopent-1-ene]butylphosphinate (16)

Compound **16** was prepared from (±)-ethyl (3-aminocyclopent-1-ene)butylphosphinate (**14**) (2.67 g, 11.5 mmol) as described above. The crude product was purified by short column vacuum chromatography on silica gel (15% ethanol–ethyl acetate) to yield the desired title compound (**16**) as a colourless oil (3.18 g, 83%): ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.91 (3H, 2 × d, J = 6.0 and 6.3 Hz, PCH$_2$CH$_2$CH$_2$C*H*$_3$), 1.20–1.84 (18H, m, POCH$_2$C*H*$_3$, PC*H*$_2$CH$_2$CH$_2$CH$_3$, PCH$_2$C*H*$_2$CH$_2$CH$_3$, PCH$_2$CH$_2$C*H*$_2$CH$_3$, C(C*H*$_3$)$_3$), 2.39–2.73 (4H, m, C(4)-*H*, C(4)-*H′*, C(5)-*H* and C(5)-*H′*), 3.87–4.18 (2H, m, POC*H*$_2$CH$_3$,), 4.58 (1H, m, C(3)-N*H*), 4.85 (1H, m, C(3)-*H*), 6.48 (1H, m, C(2)-*H*); ^{13}C NMR (75 MHz, CDCl$_3$) δ 13.53 (PCH$_2$CH$_2$CH$_2$*C*H$_3$, s), 16.52 and 16.60 (POCH$_2$*C*H$_3$, d, $^3J_{POCC}$ = 6.2 Hz), 23.52 and 23.56 (PCH$_2$*C*H$_2$CH$_2$CH$_3$, d, $^2J_{PC}$ = 3.7 Hz), 23.74 and 23.95 (PCH$_2$CH$_2$*C*H$_2$CH$_3$, d, $^3J_{PC}$ = 16.0 Hz), 27.34 and 28.66 (P*C*H$_2$CH$_2$CH$_2$CH$_3$, 2 × d, J_{PC} = 99.0 and 99.3 Hz), 28.36

($C(CH_3)_3$, s), 31.84 and 31.99 ($C(4)$, 2 × d, $^3J_{PC}$ = 11.1 and 11.6 Hz), 32.42 and 32.53 ($C(5)$, d, $^2J_{PC}$ = 8.3 Hz), 57.82 (m, $C(CH_3)_3$), 57.82 and 58.29 ($C(3)$, d, $^3J_{PC}$ = 35.6 Hz), 60.29 and 60.38 ($POCH_2CH_3$, d, $^2J_{POC}$ = 6.5 Hz), 137.95 and 139.54 ($C(1)$, d, J_{PC} = 119.3 Hz), 145.97 and 146.19 ($C(2)$, 2 × d, $^2J_{PC}$ = 16.2 and 16.5 Hz), 155.06 (s, C=O); ^{31}P NMR (121 MHz, $CDCl_3$) δ 42.53 and 42.65; MS (CI, CH_4) m/z 332 (32%) (MH^+), 276 (100), 215 (25); (ESI) 354.1805 ($MNa^+ - C_{16}H_{30}NO_4PNa$ requires 354.1810).

(±)-*cis*-Isopropyl [3-(*tert*-butyloxycarbonyl)aminocyclopentane]-methylphosphinate (17)

A solution of isopropyl [3-(*tert*-butyloxycarbonyl)aminocyclopent-1-ene]methylphosphinate (**15**) (3.4 g, 10.7 mmol) in methanol (30 cm^3) was hydrogenated over platinum oxide (50 mg) at 40 psi for 3 h. The catalyst was removed by filtration through Celite and then washed with methanol (3 × 30 cm^3). The solvent was removed *in vacuo* and the crude product was purified by short column vacuum chromatography on silica gel (15% ethanol–ethyl acetate) to yield the desired *cis* isomer (**17**) as a colourless oil (2.1 g, 95%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (3H, 2 × d, J = 6.3 Hz, $POCHC\mathit{H}_3$), 1.32 (3H, d, J = 6.3 Hz, $POCHC\mathit{H}_3$), 1.44 (9H, br. s, $C(C\mathit{H}_3)_3$), 1.48 and 1.49 (3H, d, J = 14.7 and 14.1 Hz, $PC\mathit{H}_3$), 1.58–1.75 (2H, m, C(2)-*H*, C(4)-*H*), 2.41–2.72 (5H, m, C(1)-*H*, C(2)-*H′*, C(4)-*H′*, C(5)-*H* and C(5)-*H′*), 4.53 (2H, m, $POC\mathit{H}CH_3$ and N*H*), 4.84 (1H, br. m, C(3)-*H*); ^{13}C NMR (75.46 MHz, $CDCl_3$) δ 12.78 and 12.96 (PCH_3, d, J_{PC} = 89.0 and 89.6 Hz), 23.58 ($C(5)$), 24.16 and 24.25 ($POCHCH_3$, d, $^3J_{POCC}$ = 3.4 and 3.9 Hz), 28.35 ($C(CH_3)_3$), 33.05 ($C(2)$, s), 33.51 and 33.61 ($C(4)$, 2 × d, $^3J_{PC}$ = 8.0 Hz), 35.85 and 35.93 ($C(1)$, d, J_{PC} = 100.2 and 100.1 Hz), 52.21 ($C(CH)_3$, br. s), 68.76 and 68.81 ($POCHCH_3$, d, $^2J_{POC}$ = 6.9 and 6.9 Hz), 79.2 ($C(3)$, br. d, $^3J_{PC}$ = 5.0 Hz), 155.32 and 155.35 (C=O, s); ^{31}P NMR (121 MHz, $CDCl_3$) δ 56.70, 56.75; MS (EI) m/z 277 (38%) (MH^+), 306 (30); (ESI) 306.1821 ($MH^+ - C_{14}H_{28}NO_4P$ requires 306.1834).

(±)-*cis*-Ethyl [3-(*tert*-butyloxycarbonyl)aminocyclopentane]-butylphosphinate (18)

Compound **18** was prepared from (±)-ethyl [3-(*tert*-butyloxycarbonyl)aminocyclopent-1-ene]butylphosphinate (**16**) (2.95 g, 8.90 mmol) as described above. The solvent was removed *in vacuo* to yield the desired title compound (**14**) in quantitative yield as a 4 : 1 mixture of *cis* : *trans* (by NMR spectroscopy), the isomers were separated by silica gel vacuum chromatography to yield (**18**) as a colourless oil (2.14 g, 72%) (data for *cis* isomer only is reported): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (3H, 2 × d, J = 6.9 and 7.2 Hz, $PCH_2CH_2CH_2C\mathit{H}_3$), 1.21–2.32 (25H, m, C(1)-*H*, C(2)-*H*, C(2)-*H′*, C(4)-*H*, C(4)-*H′*, C(5)-*H* and C(5)-*H′*, $POCH_2C\mathit{H}_3$, $PC\mathit{H}_2CH_2CH_2CH_3$, $PCH_2C\mathit{H}_2CH_2CH_3$, $PCH_2CH_2C\mathit{H}_2CH_3$, $C(C\mathit{H}_3)_3$), 4.13 (4H, m, $OC\mathit{H}_2CH_3$, C(3)-N*H*, C(3)-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.49 ($PCH_2CH_2CH_2\mathit{C}H_3$, s), 16.65 ($POCH_2\mathit{C}H_3$, d, $^3J_{POCC}$ = 4.0 Hz), 23.61 ($C(5)$, s), 23.85 ($PCH_2\mathit{C}H_2CH_2CH_3$, s), 23.88 and 24.04 ($PCH_2CH_2\mathit{C}H_2CH_3$, d, $^3J_{PC}$ = 12.5 Hz), 26.34 and 27.50 ($P\mathit{C}H_2CH_2CH_2CH_3$, 2 × d, J_{PC} = 87.1 and 87.4 Hz), 28.38 ($C(\mathit{C}H_3)_3$, s), 33.02 ($C(2)$, s), 33.50 and 33.63 ($C(4)$, 2 × d, $^3J_{PC}$ = 9.1 and 10.0 Hz), 34.24 and 35.50 ($C(1)$, 2 × d, J_{PC} = 94.4 and 94.7 Hz), 52.25 ($C(CH_3)_3$, br. s,), 60.45 and 60.54 ($POCH_2CH_3$, d, $^2J_{POC}$ = 6.8 Hz), 78.79 and 79.11 ($C(3)$, d, $^3J_{PC}$ = 24.2 Hz,), 155.42 (s, C=O); ^{31}P NMR (121 MHz, $CDCl_3$) δ 59.85 and 60.99; MS (CI, CH_4) m/z 334.0 (12%) (MH^+), 234.2 (100); (ESI) 356.1961 ($MNa^+ - C_{16}H_{32}O_4PNa$ requires 356.1967).

(±)-*cis*-(3-Aminocyclopentane)methylphosphinic acid (19)

(±)-*cis*-Isopropyl [3-(*tert*-butyloxycarbonyl)aminocyclopentane]-methylphosphinate (**17**) (2.1 g, 9.6 mmol) was dissolved in aqueous HCl (6 M, 40 cm^3) and the solution heated at reflux for 30 h. After cooling, the solution was evaporated to dryness under reduced pressure. The residue was dissolved in water (10 cm^3) and applied to an ion exchange column (Dowex 50, H^+ form). The column was eluted with water until the eluate was colourless and pH neutral and then eluted with aqueous pyridine (1 M). Ninhydrin positive fractions were combined and evaporated to dryness under reduced pressure. Residual traces of pyridine were removed by repeatedly redissolving the compound in water (20 cm^3) and re-evaporating (3 times). Recrystallisation from ethanol–acetone and drying gave the title compound (**19**) as an off white solid (1 g, 46%): ^{1}H NMR (300 MHz, D_2O) δ 1.27 (3H, d, J = 12.9 Hz, $PC\mathit{H}_3$), 1.56–2.27 (7H, m, C(1)-*H*, C(2)-*H*, C(2)-*H′*, C(4)-*H*, C(4)-*H′*, C(5)-*H* and C(5)-*H′*), 3.59 (1H, m, C(3)-*H*); ^{13}C NMR (75.46 MHz, D_2O) 13.02 ($P\mathit{C}H_3$, d, J_{PC} = 92.0 Hz), 23.9 ($C(5)$), 30.50 ($C(4)$, d, $^3J_{PC}$ = 7.5 Hz), 31.55 ($C(2)$), 37.20 ($C(1)$, d, J_{PC} = 97.3 Hz), 52.29 ($C(3)$, d, $^3J_{PC}$ = 9.3 Hz); ^{31}P NMR (121 MHz, D_2O) δ 45.9; MS (CI, CH_4) m/z 164 (38%) (MH^+), 147 (30), 105 (100); (ESI) 164.0822 ($MH^+ - C_6H_{15}NO_2P$ requires 164.0840).

(±)-*cis*-(3-Aminocyclopentane)butylphosphinic acid (20)

A solution of (±)-*cis*-ethyl [3-(*tert*-butyloxycarbonyl)aminocyclopentane]butylphosphinate (**18**) (1.07 g, 3.21 mmol) was dissolved in aqueous HCl (6 M, 40 cm^3) and the solution heated at reflux for 30 hours. After cooling, the solution was evaporated to dryness under reduced pressure. The residue was dissolved in water (10 cm^3) and applied to an ion exchange column (Dowex 50, H^+). The column was eluted with water until the eluate was colourless and the pH 7. On further elution with aqueous pyridine (1 M), ninhydrin positive fractions were collected and the solvent removed *in vacuo*. Residual traces of pyridine were removed by repeatedly redissolving the compound in water (20 cm^3) and re-evaporating (3 times). Recrystallisation from ethanol–acetone followed by drying gave the desired title compound (**20**) as an off white solid (450 mg, 68%): mp (decomp.) 180–183 °C; ^{1}H NMR (300 MHz, D_2O) δ 0.68 (3H, 2 × d, J = 6.9 and 7.2 Hz, $PCH_2CH_2CH_2C\mathit{H}_3$), 1.02–2.43 (13H, m, C(1)-*H*, C(2)-*H*, C(2)-*H′*, C(4)-*H*, C(4)-*H′*, C(5)-*H* and C(5)-*H′*, $PC\mathit{H}_2CH_2CH_2CH_3$, $PCH_2C\mathit{H}_2CH_2CH_3$, $PCH_2CH_2C\mathit{H}_2CH_3$), 3.56 (1H, m, C(3)-*H*); ^{13}C NMR (75 MHz, D_2O) δ 13.46 ($PCH_2CH_2CH_2\mathit{C}H_3$, s), 24.11 and 24.31 ($PCH_2CH_2\mathit{C}H_2CH_3$, d, $^3J_{PC}$ = 15.2 Hz), 24.31 ($C(5)$, s), 24.53 and 24.56 ($PCH_2\mathit{C}H_2CH_2CH_3$, d, $^2J_{PC}$ = 2.9 Hz), 27.96 and 29.17 ($P\mathit{C}H_2CH_2CH_2CH_3$, d, J_{PC} = 91.3 Hz), 31.12 and 31.20 ($C(2)$, d, $^2J_{PC}$ = 6.3 Hz), 31.95 (s, $C(4)$), 36.14 and 37.38 ($C(1)$, d, J_{PC} = 93.3 Hz), 52.97 and 52.88 ($C(3)$, d, $^3J_{PC}$ = 7.2 Hz); ^{31}P NMR (121 MHz, D_2O) δ 50.74; MS (ESI) m/z 205 (37%) (MH^+), 102 (12); (ESI) 228.1129 ($MNa^+ - C_9H_{20}NO_2PNa$ requires 228.1124).

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