Organic & Biomolecular Chemistry

RSC Publishing

PAPER

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2013, **11**, 119

Synthesis of a phosphinate analogue of the anti-tumour phosphate di-ester perifosine *via* sequential radical processes†

Marios S. Markoulides and Andrew C. Regan*

Received 13th December 2011,
Accepted 2nd October 2012

DOI: 10.1039/c2ob26395e

www.rsc.org/obc

An efficient synthesis of a phosphinate analogue of the anti-tumour phosphate di-ester perifosine is described (6 steps and 50% overall yield). The two phosphorus–carbon bonds in the perifosine analogue were prepared by sequential double radical hydrophosphinylation processes. This is the first example of a phosphinate analogue of perifosine, designed to be resistant to hydrolysis by phospholipid-metabolizing enzymes.

Introduction

Alkyl phospholipids were synthesized in the late 1960s as metabolically stable analogues of lysophosphatidylcholine.[1] Several of these synthetic analogues turned out to be potent immune modulators, but surprisingly some of these lipids also exhibited anti-tumour activities both *in vitro* and *in vivo* in a rather selective way.[2] In the late 1980s, Eibl and Unger identified miltefosine **1** as the minimal structural requirement for the anti-tumour activity of synthetic analogues of phospholipids (Fig. 1).[3] Remarkably, in addition to their initial anti-tumour action they have also been shown to be potentially useful for other therapeutic indications, which make synthetic analogues of phospholipids a fascinating family of compounds with several potential biomedical applications.[4]

Since then, new classes of alkyl phospholipids with promising biological activities have been synthesized and amongst these, the heterocyclic derivative perifosine **3** constitutes a second generation derivative of miltefosine **1**, with potent anti-tumour activity (Fig. 1).[5]

Synthetic analogues of phospholipids display two important advantages: (a) they target the plasma membrane rather than directly interacting with cellular DNA, and (b) they reveal a strong apoptosis-inducing ability.[4b,6] Whereas malignant cells are highly sensitive to the lethal action of synthetic phospholipids, normal cells may remain relatively unaffected, illustrating the potentially selective anti-tumour properties of these type of compounds.[3]

However, one disadvantage is that the presence of the phosphate diester group results in them being prone to biodegradation by phospholipid-metabolizing enzymes such as phospholipases C[7] and D.[8] Replacement of both of the O–P bonds of the phosphate diester in miltefosine **1** or perifosine **3** with two C–P bonds would result in phosphinate analogues **2** and **4**, which should be resistant to hydrolysis by phospholipid-metabolizing enzymes (Fig. 1).

We have recently reported the synthesis of phosphinate analogues **2b–d** of miltefosine **1**, using a free-radical addition reaction to form the first phosphorus–carbon bond, and the

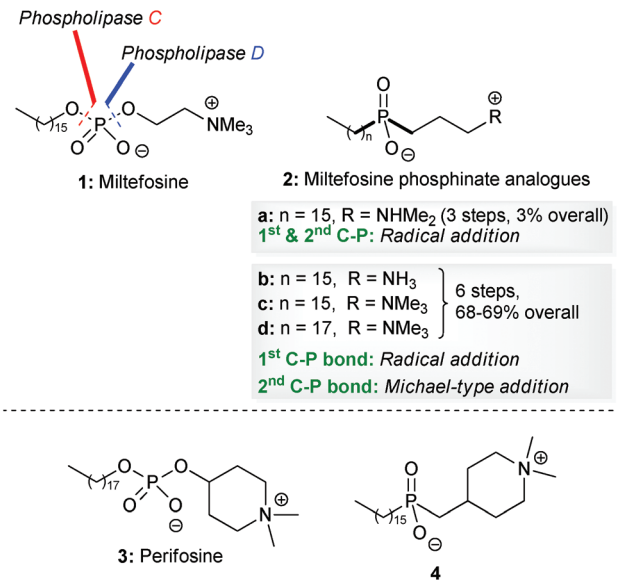
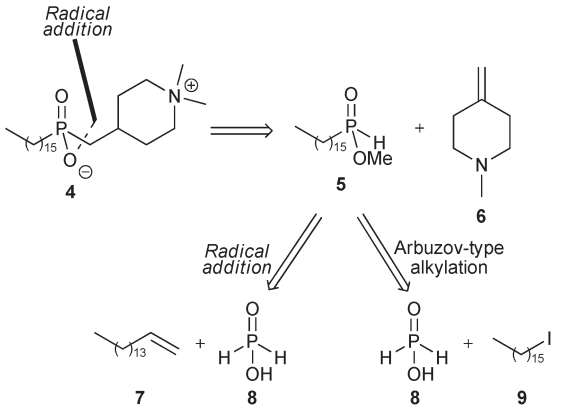


Fig. 1 Structures of miltefosine **1**, perifosine **3** and phosphinate analogues of miltefosine **2** and perifosine **4**.

School of Chemistry, The University of Manchester, Oxford Road, Manchester, M13 9PL, UK. E-mail: andrew.regan@manchester.ac.uk; Fax: +44 (0) 161 275 4617; Tel: +44 (0) 161 275 4617

†Electronic supplementary information (ESI) available: Copies of ^{1}H, ^{13}C and ^{31}P NMR spectra. See DOI: 10.1039/c2ob26395e



Scheme 1 Retrosynthetic analyses of **4**.

conjugate addition reaction of a silyl phosphonite to form the second.[9]

During the synthesis of miltefosine analogues **2b–d**, an alternative approach to compound **2a** was also examined, involving two radical addition reactions, which had the attraction of requiring fewer steps overall. However the sequential radical approach proved to be low yielding, and no improvement was obtained upon modifying the conditions.[9]

In this paper we describe an efficient synthesis of the phosphinate analogue **4** of perifosine **3**, involving two sequential radical hydrophosphinylation reactions to construct both of the carbon–phosphorus bonds. To the best of our knowledge, the phosphinate function has never been used in the synthesis of perifosine analogues, despite its close structural analogy. We have also carried out further investigations into the sequential radical approach to analogue **2a** of miltefosine **1**.

The retrosynthetic analysis of **4** is shown in Scheme 1. Disconnection of the first phosphorus–carbon bond suggested that this might be formed by regioselective free-radical addition of mono-alkylphosphinic ester **5** to the exo-methylene piperidine derivative **6**. Phosphinate **5** is then a common intermediate for further analysis by two approaches, and our previous work on alkylation of trivalent silyl-phosphonite derivatives[10] suggested that one possibility for preparation of **5** would be by the Arbuzov-type alkylation of a silyl derivative of hypophosphorous acid **8** with hexadecyl iodide **9**.

An alternative approach to **4** envisioned the use of two sequential radical hydrophosphinylation addition reactions, where the carbon–phosphorus bond in intermediate **5** would also be constructed using a free-radical addition, here involving reaction of hypophosphorous acid **8** with 1-hexadecene **7**.

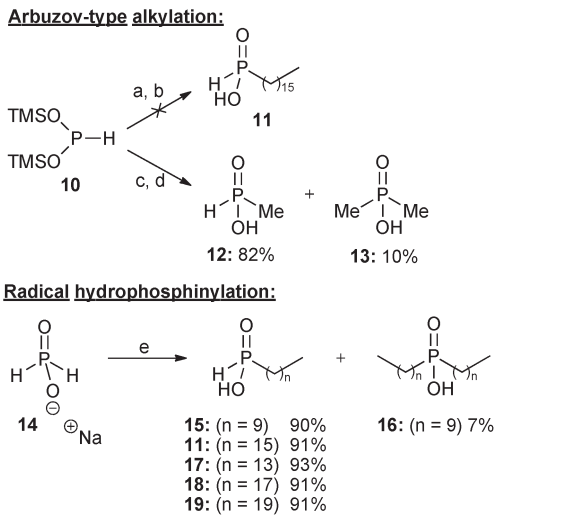
The formation of mono-substituted phosphinic acids by free-radical addition of **8** or its salts to terminal alkenes has been known for some time.[11] Nifant'ev[12] developed the reaction using peroxide initiators; more recently AIBN has been employed with either the acid **8**[13] or its esters,[14] and the use of the combination of triethylborane and air is also effective.[15] Changing the ratio of hypophosphorous acid **8** to the alkene can be used to influence the formation of either mono-substituted or *symmetrical* disubstituted phosphinic acids.[16]

There are relatively few examples of the formation of the second C–P bond in *unsymmetrical* disubstituted phosphinic acids by radical addition of mono-substituted *H*-phosphinates to alkenes.[11,17] These reactions are often inefficient, probably due to the higher P–H bond dissociation energy, and often require a wastefully large excess of the alkene component.[11] Phenyl *H*-phosphinates are more reactive than alkyl analogues,[17a] perhaps because the phenyl group can stabilise the adjacent phosphorus-centred radical.[11]

Nevertheless, there has been very little investigation of the use of sequential radical addition reactions to two different alkenes in order to form both phosphorus–carbon bonds in unsymmetrical disubstituted phosphinic acids.[18] In the area of biological targets, there has been one report of this approach being employed to prepare a precursor for a phosphinate analogue of a dinucleotide.[19]

Results and discussion

As experienced in our previous work,[9] attempts to alkylate bis (trimethylsilyl)phosphonite (BTSP) **10** with hexadecyl iodide **9** were not successful using our Arbuzov-type alkylation protocol (Scheme 2).[10a] In spite of extensive experimentation involving different solvents, including DCM, diglyme, benzene, and toluene, reaction without any solvent under neat conditions, and also modification of the conditions (changing the ratio of BTSP **10** to **9**, and also temperature from room temperature to reflux), there was no improvement in yields. Although in some solvents (*e.g.* benzene or toluene) BTSP **10** was stable (thus allowing for longer reaction times), this did not improve the results. In more polar solvents (*e.g.* DCM) decomposition of BTSP **10** was observed to occur much more readily.



Scheme 2 *Reagents and conditions*: (a) hexadecyl iodide, CH_2Cl_2, 0 °C to reflux, 2 days; (b) THF–H_3O^+, 0 °C to rt, 2 hours; (c) methyl iodide (0.33 eq), CH_2Cl_2, 0 °C, 2 hours, then rt, 12 hours; (d) THF–H_3O^+, 0 °C to rt, 2 hours; (e) terminal alkene, conc. H_2SO_4, AIBN or VAZO-88, EtOH, reflux, 1 day.

The alkylation reaction was also repeated with greater success using methyl iodide[10a] and three equivalents of BTSP **10** (Scheme 2), resulting in formation of monomethyl phosphinic acid **12** in 82% yield together with a small amount of the corresponding dimethyl phosphinic acid **13**. It appears that whereas alkylation of silyl phosphonite **10** with short-chain alkyl bromides and iodides is successful,[10a] long-chain iodides are problematic,[10b] even when reacted neat or in various solvents, and at elevated temperatures.

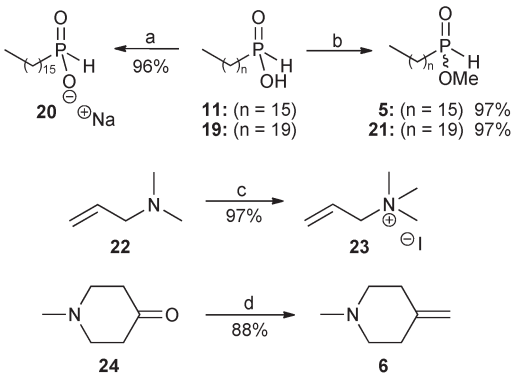
Having confirmed that the Arbuzov-type approach was unsuccessful, attention was then turned to free radical hydrophosphinylation reactions. Several long chain mono-alkyl phosphinic acids **11**,[9] **15**, **17**, **18**[9] and **19** were conveniently prepared in high yields by free radical addition of sodium hypophosphite **14** to the appropriate terminal alkenes (Scheme 2).[9,13] Sodium hypophosphite **14** could be employed in either anhydrous form or as the monohydrate (depending on availability), and with essentially equivalent results. Because of changes in commercial availability VAZO-88 was sometimes used instead of AIBN as the radical initiator. In the case where 1-decene was used as the alkene, a small quantity (7%) of the corresponding disubstituted product **16** was also formed, and it may be that this is a result of less steric hindrance in the second radical addition than with the longer alkenes, where bis-addition was not observed.

Terminal alkenes with even numbers of carbon atoms were utilised in Scheme 2 because of their greater availability and lower cost. The consistently high yields obtained with alkenes ranging from 16 to 20 carbon atoms suggest that radical hydrophosphinylation reactions of alkenes with an odd number of carbons would be equally successful. It is not expected that changing the lengths of such long alkyl chains by one carbon atom would significantly alter the biological activities,[1b] however odd-numbered alkyl groups could be investigated in future work if desired.

In view of the very low yield (3%) obtained in our previous report[9] for the radical hydrophosphinylation reaction between hexadecylphosphinic acid **11** and *N*,*N*-dimethylallylamine **22**, further investigation of this methodology was undertaken by varying the phosphinate component between the acid forms (**11** and **19**), sodium salt **20**, and methyl esters (**5** and **21**). The alkene component was also varied between the tertiary allyl amine **22** and the corresponding quaternary ammonium salt **23** (Scheme 3).

Sodium hexadecylphosphinate **20** was prepared from the acid **11** using sodium ethoxide. The coupling constant of the P–H doublet in the ^{1}H NMR spectrum of sodium hexadecylphosphinate **20** was 486.5 Hz, reduced from the value found in hexadecylphosphinic acid **11**, which was 539.7 Hz.[9] The phosphorus NMR signal at δ 37.96 for **11**[9] was also moved upfield to δ 27.97 for **20**, as would be expected for a hypophosphite salt.

The mono-alkyl phosphinic acids **11** and **19** were then converted into their methyl esters **5** and **21** with trimethyl orthoformate.[9,20] The ^{1}H NMR spectrum of **5** displayed a new doublet at δ 3.72 ($^3J_{P-H}$ = 11.9 Hz) attributable to the methyl ester group, and the signal for the corresponding carbon atom



Scheme 3 *Reagents and conditions*: (a) NaH, EtOH, 0 °C, 20 minutes, then rt, 30 minutes; (b) trimethyl orthoformate, reflux, 3.5 days; (c) methyl iodide, Et_2O, rt, 3 hours; (d) NaH, dry DMSO, 75 °C, 45 minutes, then 0 °C, methyltriphenylphosphonium bromide in dry DMSO, then rt, 10 minutes, then **24**, rt, 30 minutes.

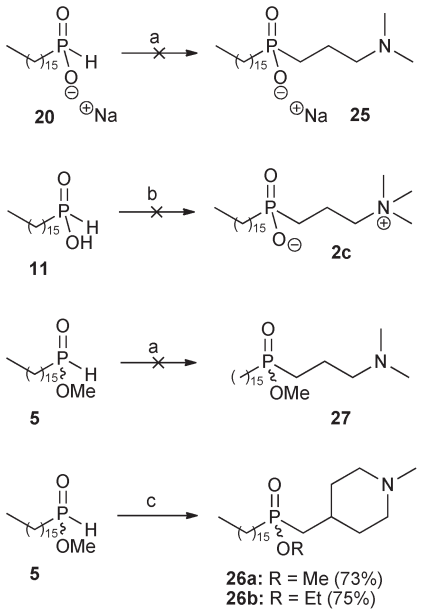
also appeared in the ^{13}C NMR spectrum as a doublet at δ 52.68 ($^2J_{C-P}$ = 6.4 Hz). The ^{31}P NMR spectrum displayed a signal at δ 42.10, downfield from the corresponding signal in the starting material **11** (δ 37.96). For the longer chain alkylphosphinic acids **11** (C-16),[9] **18** (C-18)[9] and **19** (C-20), the doublet attributable to the first carbon atom directly bonded to phosphorus could not be observed in the ^{13}C NMR spectra, probably because it was hidden by other carbon signals of similar frequency. In the case of methyl hexadecylphosphinate **5** this doublet was separated and appeared at δ 28.47 ($^1J_{C-P}$ = 92.7 Hz). Methyl icosylphosphinate **21** showed analogous spectroscopic data to **5**.

Next, *N*,*N*,*N*-trimethylallylammonium iodide **23** was conveniently prepared in 97% yield by the reaction of *N*,*N*-dimethylallylamine **22** with methyl iodide in diethyl ether at room temperature.

Finally, for the preparation of the perifosine analogue **4**, the alkene precursor required for the second radical hydrophosphinylation reaction was the exo-methylene piperidine **6**, and this was prepared in 88% yield by a Wittig reaction on the piperidinone **24** using dimsyl sodium as a base[21] (Scheme 3). The use of alternative conditions involving butyl lithium as a base[22] gave unsatisfactory results in our hands.

The second radical hydrophosphinylation addition reaction was then investigated between the sodium phosphinate **20** and the tertiary amine **22**, the phosphinic acid **11** and the quaternary ammonium salt **23**, and the methyl phosphinate ester **5** with tertiary amine **22** (Scheme 4). However, all attempts to form the disubstituted products **25**, **2c** and **27** proved to be unsuccessful. Extensive repetition and variation of the procedures did not improve the results, and in all of the attempts the starting materials were substantially recovered at the end of the reaction.

However, much better results were obtained in the synthesis of the perifosine analogue **4**. The radical hydrophosphinylation addition reaction between methyl hexadecylphosphinate **5** and 1-methyl-4-methylene-piperidine **6** afforded the disubstituted phosphinate **26a** in 73% yield

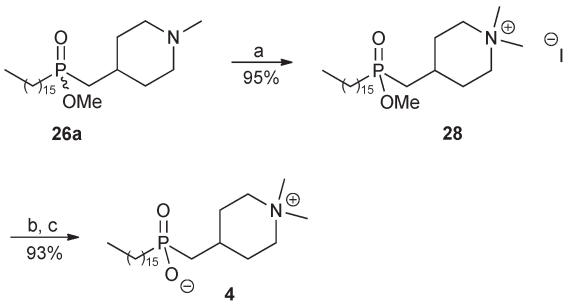


Scheme 4 *Reagents and conditions*: (a) **22** (xs), MeOH, AIBN (xs), reflux, 6 days; (b) **23** (xs), EtOH, AIBN (xs), reflux, 6 days; (c) **6** (1 eq), AIBN (1.6 eq), MeOH (for **26a**) or EtOH (for **26b**), reflux, 3 days.

(Scheme 4). Remarkably, only one equivalent of the alkene **6** was required in this reaction, in contrast to the large excesses of alkenes often required for radical addition of mono-substituted *H*-phosphinates.[11] This successful radical hydrophosphinylation involving methyl ester **5** to give **26a** differed markedly from the very low-yielding radical addition of the corresponding unprotected phosphinic acid **11** to tertiary amine **22**, which was reported in our previous work.[9] The three unsuccessful radical hydrophosphinylation reactions in Scheme 4 were also originally aimed at the synthesis of the miltefosine analogues **2**, and the failure of these reactions required us to resort to our previously-developed methodology of conjugate addition of silyl phosphonites in order complete that synthesis.[9] Here, the successful radical reaction of the exo-methylene-piperidine **6**, in contrast to those of the mono-substituted terminal alkenes **22** and **23**, may be a result of alkene **6** being a disubstituted terminal alkene, so that the intermediate radical formed after the addition step is tertiary (and therefore more stable than the secondary radicals which would be formed from the mono-substituted terminal alkenes). An additional factor may be that in the alkenes **22** and **23** the electronegative nitrogen atom is only two bonds away from the radical centre formed during the addition step, whereas for alkene **6** it is more remote, being three bonds removed.

The successful hydrophosphinylation reaction between **5** and **6** was repeated in a higher boiling alcohol in an attempt to increase the yield. The only differences observed when ethanol (EtOH) was used as the solvent were that the product obtained was the corresponding transesterified ethyl ester **26b**, and in a slightly improved yield of 75%.

The synthesis of phosphinate analogue **4** of perifosine was then completed as shown in Scheme 5. Quaternisation of the



Scheme 5 *Reagents and conditions*: (a) methyl iodide, anhydrous K_2CO_3, MeOH–$CHCl_3$, reflux, 1 day; (b) TMSI, CH_2Cl_2, rt, overnight; (c) MeOH, rt, 30 minutes.

tertiary amine **26a** with excess methyl iodide in the presence of anhydrous K_2CO_3 afforded the desired ammonium salt **28** in 95% yield. Finally, cleavage of the methyl ester group in **28** was achieved by treatment with iodotrimethylsilane (TMSI)[9,23] followed by methanolysis, to afford the ammonium phosphinate inner salt **4** in 93% yield.

The proton-decoupled ^{31}P NMR spectrum of ester **28** displayed a signal at δ 57.06, whereas that of the zwitterion **4** displayed a signal which was shifted upfield to δ 52.85. Upon addition of one drop of concentrated hydrochloric acid to the same NMR tube containing **4** in CD_3OD, the phosphorus signal moved downfield from δ 52.85 to 58.06, corresponding to protonation of P–$O^{(-)}$ to P–OH (see the ESI†). After the ^{31}P NMR spectroscopic study the hydrochloride salt of **4** was converted back to the inner salt **4** by co-evaporation with MeOH, followed by pumping under high vacuum.

Conclusions

In summary, an efficient synthetic strategy has been developed for the synthesis of a phosphinate analogue **4** of the anti-tumour agent perifosine **3**, making use of two radical hydrophosphinylation steps to form both of the carbon–phosphorus bonds. The second hydrophosphinylation in particular is unusual in that it is efficient and does not employ an excess of the alkene, which is important here because the alkene is a functionalised synthetic intermediate. Overall, the synthesis of the C16 alkyl phosphinate analogue **5** proceeded in six steps and 50% overall yield. By suitable modification of the two alkenes employed, further non-hydrolysable analogues may be designed in order to investigate biological structure-activity relationships.

Experimental section

General information

All reagents and solvents were purchased from commercial sources and either used as supplied or purified using the appropriate standard procedures.[24] Column chromatography was carried out using Merck silica gel 60H (40–60 nm,

230–300 mesh). Thin-layer chromatography (TLC) was carried out using glass, aluminum or plastic plates coated with Merck $HF_{254/366}$ silica gel. Visualisation was achieved by viewing under a 254 nm ultraviolet (UV) light source and/or by immersion in solutions of potassium permanganate ($KMnO_4$), anisaldehyde, phosphomolybdic acid (PMA) or ninhydrin, followed by heating. Electron impact/chemical ionisation (EI/CI) mass spectra were recorded on a Micromass Trio 2000 spectrometer. Electrospray (ES±) mass spectra were recorded on a Micromass Platform II spectrometer. High resolution mass spectra were recorded on a Thermo Finnigan MAT95XP spectrometer. Infrared (IR) spectra were recorded either on a PerkinElmer FT-IR RX1 as evaporated films (from deuteriochloroform $CDCl_3$ or dichloromethane DCM) on sodium chloride (NaCl) plates or on a PerkinElmer FT-IR ATIR BX spectrometer, and bands are quoted in cm^{-1}. NMR spectra were recorded using deuterated chloroform ($CDCl_3$) as solvent unless otherwise stated. ^1H NMR spectra were recorded either on a Bruker Avance II$^+$ 500 (500 MHz), Bruker Avance III 400 (400 MHz), Varian INOVA Unity 300 (300 MHz) or on a Bruker Avance 200 (200 MHz) spectrometer. Residual non-deuterated solvent was used as the internal standard. Chemical shifts (δ_H) are quoted in parts per million (ppm) downfield from tetramethylsilane (TMS). ^{13}C NMR spectra were recorded either on a Bruker Avance II$^+$ 500 at 125 MHz, Bruker Avance III 400 at 100 MHz or on a Varian INOVA Unity 300 at 75 MHz spectrometer, using a carbon signal of the solvent as the internal standard. Chemical shifts (δ_C) are quoted in parts per million (ppm) downfield from tetramethylsilane (TMS). ^{31}P NMR spectra were recorded either on a Bruker Avance III 400 at 162 MHz or on a Bruker Avance 200 spectrometer at 81 MHz. Chemical shifts for phosphorus (δ_P) are reported in parts per million (ppm) on the δ scale relative to phosphoric acid as the external standard. Peak assignments were aided by ^1H–^1H COSY, ^1H–^{13}C HMQC, ^1H–^{13}C HMBC, DEPT-135 and/or DEPT-90, whenever necessary. The resonance multiplicity patterns are described as singlet (s), broad singlet (br s), doublet (d), triplet (t), quartet (q), quintet (quin.), multiplet (m), or combinations of these. Coupling constants (J) are quoted in hertz (Hz). Microanalyses were carried out by the staff of the Microanalytical Laboratory at the School of Chemistry, University of Manchester. Reagents: Copper stabilisers were removed from methyl iodide (MeI) and trimethylsilyl iodide (TMSI) prior to use. 1-Adamantanamine was purified by dissolving it in diethyl ether (Et_2O) and washing the organic layer (three times) with a dilute solution of sodium hydroxide (1 M NaOH). The organic layer was then dried over anhydrous sodium sulfate (anh. Na_2SO_4), and concentrated under reduced pressure to give the compound as a bright white powder. Melting points (mp) were determined either on a Stuart Scientific SMP10 apparatus or on a Reichert (Shandon Scientific) hot stage microscope, and were uncorrected.

Methylphosphinic acid (12). Methyl iodide (0.14 cm^3, 0.32 g, 2.26 mmol) was injected into a two-neck round-bottomed flask containing a cooled solution (0 °C) of bis(trimethylsilyl) phosphonite (BTSP) **10**[9] (1.43 g, 6.78 mmol) in dry dichloromethane (10 cm^3), under an atmosphere of dry nitrogen. The system was stirred at 0 °C for two hours followed by stirring overnight at room temperature. The reaction was filtered and the solvent evaporated under reduced pressure. The residue was cooled to 0 °C and tetrahydrofuran–water (1 : 1, 3 cm^3), acidified with a few drops of concentrated HCl, were added and the solution was stirred for two hours at room temperature. The solvent was removed under reduced pressure and the crude material was washed with hot hexane to afford the product **12** as a yellow oil (0.15 g, 82%). The compound was not purified further. ^1H NMR (300 MHz, $CDCl_3$): δ_H 12.22 (1H, br s, O*H*), 7.34 (1H, dq, $^1J_{P–H}$ = 562.4 Hz, $^3J_{H–H}$ = 2.2 Hz, CH_3PH), 1.65 (3H, dd, $^2J_{P–H}$ = 15.2 Hz, $^3J_{H–H}$ = 2.3 Hz, CH_3PH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 15.58 (d, $^1J_{C–P}$ = 94.4 Hz, CH_3PH). ^{31}P NMR (162 MHz, $CDCl_3$): δ_P 34.36 (CH_3PH).

Dimethylphosphinic acid (13). The compound **13** was obtained during the procedure described above for **12**: the combined hexane washes of **12** were concentrated under reduced pressure to give **13** as a white solid which was purified by the following methods: (a) *via* the adamantanamine derivative:[9] 1-adamantanamine (10.60 mg, 70.17 μmol) and crude dimethylphosphinic acid **13** (6.00 mg, 63.80 μmol) were used. The white solid obtained washed with ethyl acetate to give dimethylphosphinate adamantan-1-yl-ammonium salt (adamantanamine derivative of **13**) as a bright white powder (15.30 mg, 6.24 μmol). The acid was not regenerated due to its water solubility; (b) recrystallization of the white solid (5.00 mg) from ethyl acetate–hexane afforded the product **13** as bright white needles (4.50 mg). From the two purification methods described, the product **13** was obtained as a bright white powder (as the adamantanamine derivate), and as bright white needles (as the free phosphinic acid) (10.40 mg, 10%). mp 83–85 °C (from EtOAc–hexane). R_f = 0.47 (9 : 2.5 : 0.05, $CHCl_3$–MeOH–TFA, stain: PMA). HRMS (ESI−): calculated for $C_2H_6O_2P$ $[M - H]^-$ requires 93.0111; found: 93.0113. IR, ν_{max} (NaCl, evap. film)/cm^{-1}: 2984 (m, CH_3), 2626 (br, PO–H), 1429 (w, CH_3), 1306 (w, CH_3), 1149 (m, P═O), 1062 (br, P–OH), 877 (w, P–O), 646 (w, P–C). ^1H NMR (400 MHz, $CDCl_3$): δ_H 11.25 (1H, br s, O*H*), 1.22 (6H, d, $^2J_{P–H}$ = 14.4 Hz, CH_3PCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 16.42 (d, $^1J_{C–P}$ = 96.0 Hz, CH_3PCH_3). ^{31}P NMR (162 MHz, $CDCl_3$): δ_P 52.42 (CH_3PCH_3). MS (ESI−), m/z (rel. intensity %): 93 ($M - H^-$, 30%).

Dimethylphosphinate adamantan-1-yl-ammonium salt (adamantanamine derivative of 13). mp 181 °C (dec.). Elem. Anal. (%): calculated for $C_{12}H_{24}NO_2P$ requires C, 58.76; H, 9.86; N, 5.71; P, 12.63%; found: C, 58.96; H, 9.85; N, 5.67; P, 12.40%. IR, ν_{max} (NaCl, evap. film)/cm^{-1}: 2972 (w, C–H), 2907 and 2847 (m, C–H), 1624 and 1559 (w, $^+NH_3$), 1456 (w, C–H), 1367 (w, C–H), 1281 (w, C–H), 1148 (s, P═O), 1127 (s, C–N), 1039 (s, P–O), 843 (m, P–O), 725 (w, CH_2), 645 (w, P–C). ^1H NMR (400 MHz, CD_3OD): δ_H 2.07 (3H, br s, 3 × C*H*), 1.79 (6H, d, J = 2.3 Hz, 6 × C*H*), 1.70 (3H, d, J = 12.7 Hz, 3 × C*H*), 1.62 (3H, d, J = 12.1 Hz, 3 × C*H*), 1.14 (6H, d, $^2J_{P–H}$ = 13.6 Hz, CH_3PCH_3). ^{13}C NMR (100 MHz, CD_3OD): δ_C 52.65 (*C*–N), 41.58 (CH_2), 36.52 (CH_2), 30.46 (*C*H), 18.47 (d, $^1J_{C–P}$ = 93.8 Hz, CH_3PCH_3). ^{31}P NMR (162 MHz, CD_3OD, proton-coupled): δ_P 36.66 (sp, $^2J_{P–H}$ = 13.7 Hz, CH_3PCH_3).

Decylphosphinic acid (15). The product **15** was prepared according to the literature procedure[9] with the following modifications: sodium hypophosphite monohydrate ($NaH_2PO_2{\cdot}H_2O$) (80.00 g, 0.75 mol), concentrated sulfuric acid (22.10 cm^3, 40.72 g, 0.42 mol), 1-decene (57.20 cm^3, 42.35 g, 0.30 mol) and 2,2′-azobis(isobutyronitrile) (AIBN) (total of all portions: 8.85 g, 53.91 mmol) were used. Before purification of **15**, the side-product didecylphosphinic acid **16** was removed by recrystallization from ethanol–water (EtOH–H_2O). The filtrate was then concentrated under reduced pressure to give a yellowish solid which was purified as described above for **13**, with the following modifications: (a) 1-adamantanamine (1.44 g, 9.55 mmol) and crude decylphosphinic acid **15** (1.79 g, 8.68 mmol) were used. The white solid obtained was purified by recrystallization from tetrahydrofuran–ethyl acetate to give decylphosphinate adamantan-1-yl-ammonium salt (adamantanamine derivative of **15**) (2.95 g, 8.25 mmol). Regeneration of the acid afforded the product **15** as a bright white powder (1.67 g); (b) recrystallization of the yellowish solid (55.71 g) from acetonitrile afforded the product **17** as a bright white powder (54.30 g). From the two purification methods described, the product **15** was obtained as a bright white powder (55.97 g, 90%). mp 24–25 °C (from acetonitrile). HRMS (ESI−): calculated for $C_{10}H_{22}O_2P$ $[M - H]^-$ requires 205.1363; found: 205.1366. Elem. Anal. (%): calculated for $C_{10}H_{23}O_2P$ requires C, 58.23; H, 11.24; P, 15.02%; found: C, 58.49; H, 11.37; P, 15.28%. IR, ν_{max} (ATIR)/cm^{-1}: 2952 (w, C–H), 2916 (m, C–H), 2846 (m, C–H), 2650 (br, PO–H), 2419 (w, P–H), 1459 (m, C–H), 1292 (w, C–H), 1166 (m, P═O), 1079 and 1051 (m, P–OH), 973 and 946 (s, P–H), 721 (m, CH_2), 675 (w, P–C). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 12.23 (1H, br s, O*H*), 7.1 (1H, dt, $^1J_{P-H}$ = 539.5 Hz, $^3J_{H-H}$ = 1.8 Hz, P*H*), 1.78–1.70 (2H, m, PCH_2), 1.63–1.52 (2H, m, PCH_2CH_2), 1.38 (2H, quin., J = 6.6 Hz, $PCH_2CH_2CH_2$), 1.25 (12H, br s, 6 × CH_2), 0.87 (3H, t, J = 7.1 Hz, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 31.88, 30.43 (d, $^3J_{C-P}$ = 16.0 Hz, $PCH_2CH_2CH_2$), 29.54, 29.36, 29.30, 29.24 (d, $^1J_{C-P}$ = 93.7 Hz, PCH_2), 29.15, 22.68, 20.68 (d, $^2J_{C-P}$ = 2.9 Hz, $PCH_2CH_2CH_2$), 14.10 (CH_3). ^{31}P NMR (162 MHz, $CDCl_3$, proton-coupled): δ_P 37.29 (d quin., $^1J_{P-H}$ = 538.0 Hz, $^2J_{P-H}$ = $^3J_{P-H}$ = 28.4 Hz, CH_2CH_2PH). MS (ESI−), m/z (rel. intensity %): 205 ($M - H^-$, 100%).

Decylphosphinate adamantan-1-yl-ammonium salt (adamantanamine derivative of 15). mp 139–141 °C (from THF–EtOAc). HRMS (ESI−): calculated for $C_{10}H_{22}O_2P$ $[M]^-$ requires 205.1363; found: 205.1373. HRMS (ESI+): calculated for $C_{10}H_{18}N$ $[M]^+$ requires 152.1434; found: 152.1445. Elem. Anal. (%): calculated for $C_{20}H_{40}NO_2P$ requires C, 67.19; H, 11.28; N, 3.92; P, 8.66%; found: C, 67.25; H, 11.33; N, 3.92; P, 8.93%. IR, ν_{max} (ATIR)/cm^{-1}: 2917 (m, C–H), 2850 (m, C–H), 2282 (w, P–H), 1644 and 1626 (br, NH_3^+), 1550 (m, NH_3^+), 1470 (m, C–H), 1456 and 1401 (w, C–H), 1365 (m, C–H), 1311 (w, C–H), 1153 (s, P═O), 1126 (w, C–N), 1039 (s, P–O^-), 990 (w, P–H), 720 (w, CH_2), 690 (w, P–C). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.83 (3H, br s, NH_3), 7.1 (1H, d, $^1J_{P-H}$ = 479.2 Hz, P*H*), 2.11 (3H, br s), 1.94 (6H, br s), 1.66 (6H, br s), 1.52 (4H, br s), 1.35 (2H, br s), 1.24 (12H, br s), 0.87 (3H, t, J = 7.1 Hz, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 50.60 (CNH_3), 40.63, 35.78, 33.22 (d, $^1J_{C-P}$ = 90.8 Hz, PCH_2), 31.90, 31.05 (d, $^3J_{C-P}$ = 16.0 Hz, $PCH_2CH_2CH_2$), 29.64, 29.52, 29.47, 29.33, 29.02, 22.84 (d, $^2J_{C-P}$ = 1.4 Hz, PCH_2CH_2), 22.68, 14.11 (CH_3). ^{31}P NMR (162 MHz, $CDCl_3$): δ_P 25.56 (CH_2PH). MS (ESI−), m/z (rel. intensity %): 205 (M^-, 100%). MS (ESI+), m/z (rel. intensity %): 152 (M^+, 100%).

Didecylphosphinic acid (16). The compound **16** was isolated as a side-product during the procedure described above for **15**: purification of **16** (3.50 g, 10.10 mmol) was carried out according to the procedure described above for **13**, with the following modifications: (a) 1-adamantanamine (36.60 mg, 0.24 mmol) dissolved in acetone (1 cm^3) and crude didecylphosphinic acid **16** (82.30 mg, 0.24 mmol) dissolved in acetone (1 cm^3) were used. The white solid obtained was purified by recrystallization from ethyl acetate–acetone to give didecylphosphinate adamantan-1-yl-ammonium salt (adamantanamine derivative of **16**) as a bright white powder (75.30 mg, 0.15 mmol). Regeneration of the acid afforded the product **16** as a bright white powder (49.00 mg); (b) second recrystallization of the solid (3.42 g) from ethanol–water (EtOH–H_2O) afforded the product **18** as bright white needles (3.35 g). From the two purification methods described, the product **16** was obtained as a bright white powder, and bright white needles (3.40 g, 7%). mp 81–83 °C (from EtOH–H_2O). HRMS (ESI+): calculated for $C_{20}H_{43}O_2NaP$ $[M + Na]^+$ requires 369.2893; found: 369.2906.

Elem. Anal. (%): calculated for $C_{20}H_{43}O_2P$ requires C, 69.32; H, 12.51; P, 8.94%; found: C, 68.96; H, 12.54; P, 8.77%. IR, ν_{max} (NaCl, evap. film)/cm^{-1}: 2951 (m, C–H), 2915 (s, C–H), 2848 (s, C–H), 2600 (br, PO–H), 1470 (m, C–H), 1290 (w, C–H), 1137 (m, P═O), 995 (w, P–OH), 719 (m, CH_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 11.11 (1H, br s, O*H*), 1.71–1.54 (8H, m, $CH_2CH_2PCH_2CH_2$), 1.37 (4H, quin., J = 7.5 Hz, $CH_2CH_2CH_2PCH_2CH_2CH_2$), 1.26 (24H, br s, 12 × CH_2), 0.88 (6H, t, J = 7.0 Hz, 2 × CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 31.92, 30.94 (d, $^3J_{C-P}$ = 15.3 Hz, $PCH_2CH_2CH_2$), 29.62, 29.49, 29.34, 29.23, 28.95 (d, $^1J_{C-P}$ = 91.6 Hz, PCH_2), 22.70, 21.60 (d, $^2J_{C-P}$ = 3.6 Hz, $PCH_2CH_2CH_2$), 14.13 (CH_3). ^{31}P NMR (162 MHz, $CDCl_3$): δ_P 59.51 (CH_2PCH_2). MS (ESI−), m/z (rel. intensity %): 345 ($M - H^-$, 100%).

Didecylphosphinate adamantan-1-yl-ammonium salt (adamantanamine derivative of 16). mp 105–106 °C (from EtOAc–acetone). IR, ν_{max} (NaCl, evap. film)/cm^{-1}: 2918 (s, C–H), 2853 (s, C–H), 2018 (w, NH_3^+), 1621 (m, NH_3^+), 1559 (m, NH_3^+), 1456 (m, C–H), 1408 (w, C–H), 1367 (m, C–H), 1314 (w, C–H), 1142 (s, P═O), 1121 (s, C–N), 1033 (s, P–O^-), 734 (m, CH_2), 645 (w, P–C). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.10 (3H, br s, NH_3), 2.02 (3H, br s), 1.87 (6H, br s), 1.60 (6H, br s), 1.44 (8H, br s), 1.18 (28H, br s), 0.81 (6H, t, J = 7.0 Hz, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 50.26 (CNH_3), 41.11, 35.88, 31.94, 31.56 (d, $^3J_{C-P}$ = 15.2 Hz, $PCH_2CH_2CH_2$), 30.71 (d, $^1J_{C-P}$ = 88.6 Hz, PCH_2), 29.71, 29.63, 29.57, 29.38, 29.15, 24.13, 22.71, 14.13 (CH_3). ^{31}P NMR (162 MHz, $CDCl_3$): δ_P 41.76 (CH_2PCH_2).

Tetradecylphosphinic acid (17). The product **17** was prepared according to the procedure described above for **15**, with the following modifications: sodium hypophosphite monohydrate ($NaH_2PO_2{\cdot}H_2O$) (124.84 g, 1.18 mol), concentrated sulfuric

acid (conc. H_2SO_4) (34.50 cm^3, 63.54 g, 0.65 mol), 1-tetradecene (0.10 dm^3, 77.10 g, 0.39 mol) and 2,2′-azobis(isobutyronitrile) (AIBN) (total of all portions: 13.84 g, 84.29 mmol) were used. Purification of **17** was carried out according to the procedure described above for **13**, with the following modifications: (a) 1-adamantanamine (64.00 mg, 0.42 mmol) and crude tetradecylphosphinic acid **19** (108.80 mg, 0.41 mmol) were used. The white solid obtained was purified by recrystallization from tetrahydrofuran–ethyl acetate (THF–EtOAc) to give tetradecylphosphinate adamantan-1-yl-ammonium salt (adamantanamine derivative of **17**) (161.20 mg, 0.39 mmol) as a bright white powder. Regeneration of the acid afforded the product **17** as a bright white powder (95.00 mg); (b) recrystallization of the yellowish solid (99.89 g) from hexane afforded the product **17** as a bright white powder (95.80 g). From the two purification methods described, the product **17** was obtained as a bright white powder (95.90 g, 93%). mp 52–53 °C (from hexane). HRMS (ESI−): calculated for $C_{14}H_{30}O_2P$ $[M - H]^-$ requires 261.1989; found: 261.1998. Elem. Anal. (%): calculated for $C_{14}H_{31}O_2P$ requires C, 64.09; H, 11.91; P, 11.81%; found: C, 64.31; H, 11.94; P, 11.64%. IR, ν_{max} (ATIR)/cm^{-1}: 2954 (w, C–H), 2915 and 2847 (m, C–H), 2590 (br, PO–H), 2361 (w, P–H), 1468 (m, C–H), 1399, 1308, 1285, 1260, 1236 and 1215 (w, C–H), 1154 (m, P═O), 1075 and 1037 (m, P–OH), 975 and 959 (m, P–H), 720 and 709 (m, CH_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.37 (1H, br s, O*H*), 7.1 (1H, dt, $^1J_{P-H}$ = 540.3 Hz, $^3J_{H-H}$ = 1.7 Hz, P*H*), 1.80–1.72 (2H, m, PCH_2), 1.65–1.54 (2H, m, PCH_2CH_2), 1.40 (2H, quin., J = 6.8 Hz, $PCH_2CH_2CH_2$), 1.26 (20H, br s, 10 × CH_2), 0.89 (3H, t, J = 7.1 Hz, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 31.95, 30.44 (d, $^3J_{C-P}$ = 16.0 Hz, $PCH_2CH_2CH_2$), 29.71, 29.69, 29.67, 29.65, 29.61, 29.38, 29.26 (d, $^1J_{C-P}$ = 93.7 Hz, PCH_2), 29.16, 22.71, 20.63 (d, $^2J_{C-P}$ = 2.9 Hz, $PCH_2CH_2CH_2$), 14.14 (CH_3). ^{31}P NMR (162 MHz, $CDCl_3$, proton-coupled): δ_P 38.11 (d quin., $^1J_{P-H}$ = 539.9 Hz, $^2J_{P-H}$ = $^3J_{P-H}$ = 27.4 Hz, CH_2CH_2PH). MS (ESI−), m/z (rel. intensity %): 261 ($M - H^-$, 100%).

Tetradecylphosphinate adamantan-1-yl-ammonium salt (adamantanamine derivative of 17). mp 152–153 °C (from THF–EtOAc). IR, ν_{max} (NaCl, evap. film)/cm^{-1}: 2913 (s, C–H), 2847 (s, C–H), 2284 and 2249 (m, P–H), 2065 (w, NH_3^+), 1639 and 1621 (m, NH_3^+), 1547 (m, NH_3^+), 1471 (m, C–H), 1453 (m, C–H), 1400 (w, C–H), 1367 (m, C–H), 1349 (w, C–H), 1311 (w, C–H), 1281, 1257 and 1234 (w, C–H), 1207 (m, C–H), 1154 (s, P═O), 1127 (m, C–N), 1042 (s, P–O^-), 976 (m, P–H), 719 (m, CH_2), 690 (m, P–C). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.78 (3H, br s, NH_3), 7.0 (1H, d, $^1J_{P-H}$ = 478.7 Hz, P*H*), 2.04 (3H, br s), 1.88 (6H, br s), 1.60 (6H, br s), 1.46 (4H, br s), 1.29 (2H, br s), 1.17 (20H, br s), 0.81 (3H, t, J = 7.1 Hz, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 50.57 (*C*NH_3), 40.63, 35.79, 33.27 (d, $^1J_{C-P}$ = 90.8 Hz, PCH_2), 31.95, 31.07 (d, $^3J_{C-P}$ = 16.0 Hz, $PCH_2CH_2CH_2$), 29.72, 29.69, 29.67, 29.54, 29.49, 29.39, 29.02, 22.88, 22.71, 14.14 (*C*H_3). ^{31}P NMR (162 MHz, $CDCl_3$): δ_P 25.47 (CH_2PH).

Icosylphosphinic acid (19). The product **19** was prepared according to the procedure described above for **15**, with the following modifications: anhydrous sodium hypophosphite (anh. NaH_2PO_2) (47.04 g, 0.53 mol), concentrated sulfuric acid (conc. H_2SO_4) (15.70 cm^3, 28.84 g, 0.29 mol), 1-icosene (50.00 g, 0.18 mol) and 1,1′-azobis(cyclohexanecarbonitrile) (VAZO-88) (total of all portions: 11.00 g, 45.02 mmol) were used. Purification of **19** was carried out according to the procedure described above for **13**, with the following modifications: (a) 1-adamantanamine (50.80 mg, 0.34 mmol) and crude icosylphosphinic acid **19** (114.20 mg, 0.33 mmol) were used. The white solid obtained was not recrystallized, but was washed with hot ethyl acetate to give icosylphosphinate adamantan-1-yl-ammonium salt (adamantanamine derivative of **19**) (0.16 g, 0.31 mmol) as a bright white soft solid. Regeneration of the acid afforded the product **19** as a bright white powder (0.11 g); (b) recrystallization of the yellowish solid (57.89 g) from hexane afforded the product **19** as a bright white fine powder (56.10 g). From the two purification methods described, the product **19** was obtained as a bright white fine powder (56.21 g, 91%). mp 72–73 °C (from hexane). HRMS (ESI−): calculated for $C_{20}H_{42}O_2P$ $[M - H]^-$ requires 345.2928; found: 345.2946. Elem. Anal. (%): calculated for $C_{20}H_{43}O_2P$ requires C, 69.32; H, 12.51; P, 8.94%; found: C, 69.36; H, 12.32; P, 9.24%. IR, ν_{max} (ATIR)/cm^{-1}: 2968, 2927, 2873, 1458 and 1371 (m, C–H), 1269 and 1197 (w, C–H), 1154 (w, P═O), 1086 and 1047 (s, P–OH), 945 (w, P–H), 736 (m, CH_2), 699 (m, P–C). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 10.73 (1H, br s, O*H*), 7.1 (1H, dt, $^1J_{P-H}$ = 540.4 Hz, $^3J_{H-H}$ = 1.9 Hz, P*H*), 1.80–1.73 (2H, m, PCH_2), 1.65–1.56 (2H, m, PCH_2CH_2), 1.41 (2H, quin., J = 7.0 Hz, $PCH_2CH_2CH_2$), 1.27 (32H, br s, 16 × CH_2), 0.90 (3H, t, J = 6.9 Hz, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 31.95, 30.44 (d, $^3J_{C-P}$ = 16.4 Hz, $PCH_2CH_2CH_2$), 29.72, 29.70, 29.68, 29.66, 29.61, 29.38, 29.16, 28.96, 22.71, 20.59 (d, $^2J_{C-P}$ = 3.7 Hz, $PCH_2CH_2CH_2$), 14.13 (*C*H_3). ^{31}P NMR (162 MHz, $CDCl_3$, proton-coupled): δ_P 38.39 (d quin., $^1J_{P-H}$ = 539.9 Hz, $^2J_{P-H}$ = $^3J_{P-H}$ = 27.4 Hz, CH_2CH_2PH). MS (ESI−), m/z (rel. intensity %): 345 ($M - H^-$, 100%).

Icosylphosphinate adamantan-1-yl-ammonium salt (adamantanamine derivative of 19). mp 148–149 °C. Elem. Anal. (%): calculated for $C_{30}H_{60}NO_2P$ requires C, 72.39; H, 12.15; N, 2.81; P, 6.22%; found: C, 72.27; H, 12.11; N, 2.70; P, 6.40%. IR, ν_{max} (NaCl, evap. film)/cm^{-1}: 2921 (br, NH_3^+), 2919 and 2849 (s, C–H), 2286 and 2249 (m, P–H), 1638 (w, NH_3^+), 1548 (m, NH_3^+), 1470 and 1457 (m, C–H), 1400 (w, C–H), 1365 (m, C–H), 1350, 1310, 1277, 1265, 1250, 1233 and 1216 (w, C–H), 1154 (s, P═O), 1127 (w, C–N), 1040 (s, P–O^-), 985 (w, P–H), 720 (w, CH_2), 690 (w, P–C). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.82 (3H, br s, NH_3), 7.0 (1H, d, $^1J_{P-H}$ = 479.5 Hz, P*H*), 2.04 (3H, br s), 1.88 (6H, br s), 1.60 (6H, br s), 1.46 (4H, br s), 1.29 (2H, br s), 1.18 (32H, br s), 0.81 (3H, t, J = 7.1 Hz, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 50.48 (*C*NH_3), 40.53, 35.81, 33.23 (d, $^1J_{C-P}$ = 90.4 Hz, PCH_2), 31.95, 31.09 (d, $^3J_{C-P}$ = 15.8 Hz, $PCH_2CH_2CH_2$), 29.74, 29.69, 29.56, 29.51, 29.39, 29.02, 22.84, 22.71, 14.14 (*C*H_3). ^{31}P NMR (162 MHz, $CDCl_3$): δ_P 25.69 (CH_2PH).

Sodium hexadecylphosphinate (20). Ethanol (30 cm^3) was cooled to 0 °C under an atmosphere of dry nitrogen with stirring, and sodium hydride (0.14 g, 3.62 mmol, 60 wt% in mineral oil) was slowly added over 20 minutes. A solution of hexadecylphosphinic acid **11** (1.00 g, 3.44 mmol) in ethanol

(30 cm^3) was then injected slowly and the reaction mixture left stirring for 30 minutes at room temperature. Removal of the solvent under reduced pressure gave a white solid which was purified by recrystallization from methanol–tetrahydrofuran to afford the product **20** as a bright white powder (1.03 g, 96%). mp 161–162 °C (from MeOH–THF). HRMS (ESI+): calculated for $C_{16}H_{34}O_2Na_2P$ $[M + Na]^+$ requires 335.2086; found: 335.2090. IR, ν_{max} (ATIR)/cm^{-1}: 2973 (s, C–H), 2886 and 1415 (m, C–H), 1335, 1322 and 1274 (w, C–H), 1192 (w, P═O), 1086 and 1049 (s, P–O), 879 (m, P–H), 721 (w, CH_2), 680 (w, P–H). ^{1}H NMR (400 MHz, CD_3OD): δ_H 6.98 (1H, d, $^1J_{P-H}$ = 486.5 Hz, P*H*), 1.57–1.37 (6H, m, 3 × CH_2), 1.30 (24H, br s, 12 × CH_2), 0.91 (3H, t, J = 7.0 Hz, CH_3). ^{13}C NMR (100 MHz, CD_3OD): δ_C 34.22, 33.32, 33.14, 32.18 (d, $^3J_{C-P}$ = 16.0 Hz, *C*$H_2$$CH_2$$CH_2$P), 30.86, 30.84, 30.69, 30.56, 30.54, 23.80, 23.12 (d, $^2J_{C-P}$ = 2.2 Hz, CH_2CH_2*C*H_2P), 14.53 (*C*H_3). ^{31}P NMR (162 MHz, CD_3OD, proton-decoupled): δ_P 27.95 (CH_2*P*H). MS (ESI+), *m*/*z* (rel. intensity %): 335 ($M + Na^+$, 100%).

Methyl hexadecylphosphinate (5). Trimethyl orthoformate (180.80 cm^3, 175.39 g, 1.65 mol) was injected into a round-bottomed flask containing hexadecylphosphinic acid **11** (12.00 g, 41.32 mmol), under a dry nitrogen atmosphere. The reaction mixture was refluxed and monitored by means of ^{1}H and ^{31}P NMR spectroscopy. After 3.5 days, when all of starting material had been consumed, the reaction mixture was allowed to cool at room temperature. Removal of solvent under reduced pressure gave a yellowish solid which was purified by column chromatography on silica gel (9.5 : 0.5, $CHCl_3$–MeOH, stain: PMA) to afford the product **5** as a white solid (12.14 g, 97%). mp 41–43 °C. R_f = 0.44 (9.5 : 0.5, $CHCl_3$–MeOH, stain: PMA). HRMS (ESI+): calculated for $C_{17}H_{41}O_2NP$ $[M + NH_4^+]^+$ requires 322.2869; found: 322.2869. IR, ν_{max} (NaCl, evap. film)/cm^{-1}: 2949 (w, C–H), 2917, 2849 and 1467 (m, C–H), 1234 (w, C–H), 1217 (w, P–OC), 1194 (w, P═O), 1035 (w, P–O–C), 951 (w, P–H), 722 (w, CH_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 6.98 (1H, dt, $^1J_{P-H}$ = 527.9 Hz, $^3J_{H-H}$ = 2.0 Hz, P*H*), 3.72 (3H, d, $^3J_{P-H}$ = 11.9 Hz, POCH_3), 1.75–1.67 (2H, m, CH_2P), 1.57–1.47 (2H, m, C$H_2$$CH_2$P), 1.32 (2H, quin., J = 6.8 Hz, C$H_2$$CH_2$$CH_2$P), 1.18 (24H, br s, 12 × CH_2), 0.81 (3H, t, J = 6.8 Hz, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 52.68 (d, $^2J_{C-P}$ = 6.4 Hz, POCH_3), 31.90, 30.42 (d, $^3J_{C-P}$ = 15.5 Hz, *C*$H_2$$CH_2$$CH_2$P), 29.66, 29.64, 29.59, 29.54, 29.35, 29.29, 29.08, 28.47 (d, $^1J_{C-P}$ = 92.7 Hz, CH_2CH_2*C*H_2P), 22.67, 20.63 (d, $^2J_{C-P}$ = 1.8 Hz, CH_2*C*$H_2$$CH_2$P), 14.10 (*C*$H_3$). ^{31}P NMR (162 MHz, $CDCl_3$, proton-coupled): δ_P 42.10 (dm, $^1J_{P-H}$ = 528.2 Hz, CH_2*P*H). MS (ESI+), *m*/*z* (rel. intensity %): 322 ($M + NH_4^+$, 100%).

Methyl icosylphosphinate (21). The product **21** was prepared according to the procedure described above for **5**, with the following modifications: trimethyl orthoformate (118.50 cm^3, 114.90 g, 1.08 mol) and icosylphosphinic acid **19** (9.38 g, 27.07 mmol) were used. The crude solid obtained was purified by column chromatography on silica gel (9.5 : 0.5, $CHCl_3$–MeOH, stain: PMA) to afford the product **21** as a white solid (9.47 g, 97%). mp 56–58 °C.

R_f = 0.44 (9.5 : 0.5, $CHCl_3$–MeOH, stain: PMA). HRMS (ESI+): calculated for $C_{21}H_{45}O_2NaP$ $[M + Na^+]^+$ requires 383.3049; found: 383.3054. IR, ν_{max} (NaCl, evap. film)/cm^{-1}: 2935 (m, C–H), 2917 and 2850 (s, C–H), 2346 (w, P–H), 1467 and 1236 (m, C–H), 1208 (m, P–OC), 1175 (w, P═O), 1037 (m, P–O–C), 954 (m, P–H), 802 and 789 (w, P–O–C), 721 (w, CH_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 6.72 (1H, dt, $^1J_{P-H}$ = 528.1 Hz, $^3J_{H-H}$ = 1.8 Hz, P*H*), 3.46 (3H, d, $^3J_{P-H}$ = 11.6 Hz, POCH_3), 1.49–1.41 (2H, m, CH_2P), 1.32–1.21 (2H, m, C$H_2$$CH_2$P), 1.07 (2H, quin., J = 7.0 Hz, C$H_2$$CH_2$$CH_2$P), 0.93 (32H, br s, 16 × CH_2), 0.55 (3H, t, J = 7.0 Hz, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 52.64 (d, $^2J_{C-P}$ = 6.5 Hz, POCH_3), 31.88, 30.38 (d, $^3J_{C-P}$ = 16.0 Hz, *C*$H_2$$CH_2$$CH_2$P), 29.66, 29.64, 29.62, 29.57, 29.51, 29.33, 29.27, 29.06, 28.45 (d, $^1J_{C-P}$ = 93.0 Hz, CH_2CH_2*C*H_2P), 22.63, 20.60 (d, $^2J_{C-P}$ = 2.9 Hz, CH_2*C*$H_2$$CH_2$P), 14.05 (*C*$H_3$). ^{31}P NMR (162 MHz, $CDCl_3$, proton-coupled): δ_P 41.94 (dm, $^1J_{P-H}$ = 528.1 Hz, CH_2*P*H). MS (ESI+), *m*/*z* (rel. intensity %): 361 ($M + H^+$, 60%), 383 ($M + Na^+$, 100%).

N,*N*,*N*-Trimethylallylammonium iodide (23). Methyl iodide (10.51 cm^3, 23.97 g, 0.17 mol) was added dropwise into a stirred solution of *N*,*N*-dimethylallylamine **22** (2.00 cm^3, 1.44 g, 16.89 mmol) in diethyl ether (40 cm^3), at room temperature. After addition the mixture was stirred for three hours at room temperature, under an atmosphere of dry nitrogen. The reaction mixture was then filtered under suction on a Buchner funnel to give a white solid which was purified by recrystallization from iPrOH–THF to afford the product **23** as bright white needles (3.70 g, 97%). mp 104–105 °C (from iPrOH–THF). HRMS (ESI+): calculated for $C_6H_{14}N$ $[M]^+$ requires 100.1121; found: 100.1124. Elem. Anal. (%): calculated for $C_6H_{14}IN$ requires C, 31.73; H, 6.21; I, 55.88; N, 6.17%; found: C, 31.60; H, 6.35; I, 55.60; N, 6.10%. IR, ν_{max} (ATIR)/cm^{-1}: 3009 (w,═C–H), 2944 (w, C–H), 1639 (w, C═C), 1473 (s, C–H), 1405 (m,═C–H), 1369 (w, C–H), 1126 (w, C–N), 1008 (m,═C–H), 956 and 890 (s,═C–H). ^{1}H NMR (500 MHz, CD_3OD): δ_H 5.75 (1H, ddt, J = 17.1, 9.8, 7.6 Hz, –C*H*═), 5.38 (1H, d, J = 16.7 Hz,═CH_2), 5.34 (1H, d, J = 10.1 Hz,═CH_2), 3.71 (2H, d, J = 7.2 Hz, NCH_2), 2.80 (9H, s, 3 × NCH_3). ^{13}C NMR (100 MHz, CD_3OD): δ_C 129.8 (═*C*H_2), 126.7 (–*C*H═), 69.44 (NCH_2), 53.59 (NCH_3). MS (ESI+), *m*/*z* (rel. intensity %): 100 (M^+, 20%).

1-Methyl-4-methylenepiperidine (6). The product **6** was prepared according to the literature procedure[21] with the following modifications: sodium hydride (0.78 g, 19.44 mmol, 60 wt % in mineral oil) was suspended in dry dimethylsulfoxide (20 cm^3) and was stirred for 45 minutes at an elevated temperature of 75 °C, under an atmosphere of dry nitrogen. The solution was cooled to 0 °C. Into this mixture a solution of methyltriphenylphosphonium bromide (6.95 g, 19.44 mmol) in dry dimethylsulfoxide (14 cm^3) was injected, and the system was stirred for 10 minutes at room temperature. 1-Methylpiperidin-4-one **24** (2.04 cm^3, 2.00 g, 17.67 mmol) was then added and the mixture was stirred for 30 minutes at room temperature. The reaction mixture was distilled at 75 °C/100 mbar to afford the product **6** as a colourless oil (1.73 g, 88%). R_f = 0.59 (10 : 3, $CHCl_3$–MeOH, stain: ninhydrin). HRMS (ESI+): calculated for $C_7H_{14}N$ $[M + H]^+$ requires 112.1121; found: 112.1111. IR, ν_{max} (ATIR)/cm^{-1}: 3079 (w,═C–

H), 2939 and 2848 (m, C–H), 2781 (m, N–CH_2), 1653 (m, C=C), 1436, 1371, 1282, 1268 and 1222 (m, C–H), 1135 (m, C–N), 1014 and 887 (s,=C–H). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 4.58 (2H, t, $^4J_{H-H}$ = 1.0 Hz,=CH_2), 2.32 (4H, t, J = 6.3 Hz, 2 × CH_2N), 2.19 (3H, s, NCH_3), 2.17 (4H, t, J = 5.5 Hz, 2 × =CCH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 145.6 (>C=), 107.9 (=CH$_2$), 57.01 (CH$_2$N), 46.04 (NCH_3), 34.49 (=CCH$_2$). MS (ESI+), m/z (rel. intensity %): 112 (M + H$^+$, 100%).

Methyl [(1-methylpiperidin-4-yl)methyl](hexadecyl)phosphinate (26A). 1-Methyl-4-methylene-piperidine **6** (0.37 g, 3.29 mmol) and 2,2′-azobis(isobutyronitrile) (AIBN) (0.30 g, 1.82 mmol) were added into a stirred solution of methyl hexadecylphosphinate **5** (1.00 g, 3.29 mmol) in methanol (20 cm^3), and the mixture was refluxed for three days, under a dry nitrogen atmosphere. During this time another two portions of AIBN (2 × 0.30 g, 3.65 mmol) were added into the reaction mixture, with a 24 hours time difference between each portion. The cooled mixture was then concentrated under reduced pressure to give an orange-yellow solid which was purified by column chromatography on silica gel (8 : 1 : 0.05, $CHCl_3$–MeOH–conc. NH_4OH, stain: ninhydrin) to afford the product **26a** as a colourless oil (1.00 g, 73%). R_f = 0.28 (8 : 1 : 0.05, $CHCl_3$–MeOH–conc. NH_4OH, stain: ninhydrin). HRMS (ESI+): calculated for $C_{24}H_{51}O_2NP$ [M + H]$^+$ requires 416.3652; found: 416.3649. IR, ν_{max} (NaCl, evap. film)/cm^{-1}: 2925 and 2853 (s, C–H), 2780 (m, N–CH_2), 1463 (m, C–H), 1279 (w, C–H), 1207 (m, P–OC), 1194 (m, P=O), 1142 (w, C–N), 1039 (m, P–O–C), 822 and 804 (w, P–O–C), 719 (w, CH_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 3.62 (3H, d, $^3J_{P-H}$ = 10.4 Hz, POCH_3), 2.84 (2H, apparent d, J = 11.1 Hz, 2 × CHN), 2.25 (3H, s, NCH_3), 1.99 (2H, apparent dd, J = 11.7, 1.6 Hz, 2 × CHN), 1.86–1.78 (2H, m), 1.67–1.55 (5H, m), 1.50–1.39 (4H, m), 1.34–1.25 (2H, m), 1.19 (24H, br s, 12 × CH_2), 0.81 (3H, t, J = 7.1 Hz, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 54.43 (CH$_2$N), 49.70 (d, $^2J_{C-P}$ = 6.6 Hz, POCH$_3$), 44.98 (NCH$_3$), 33.01 (d, $^1J_{C-P}$ = 89.5 Hz, PCH$_2$), 32.38, 30.93, 29.90 (d, $^3J_{C-P}$ = 15.4 Hz), 28.69, 28.67, 28.63, 28.59, 28.38, 28.36, 28.18, 28.12, 27.30, 21.69, 21.11, 13.13 (CH$_3$). ^{31}P NMR (162 MHz, $CDCl_3$): δ_P 58.02 (CH_2PCH_2). MS (ESI+), m/z (rel. intensity %): 416 (M + H$^+$, 10%).

Ethyl (1-methylpiperidin-4-yl)methyl(hexadecyl)phosphinate (26B). The product **26b** was prepared according to the procedure described above for **26a**, with the following modifications: methyl hexadecylphosphinate **5** (0.20 g, 0.66 mmol), 1-methyl-4-methylene-piperidine **6** (73.00 mg, 0.66 mmol) and 2,2′-azobis(isobutyronitrile) (AIBN) (total of all portions: 0.16 g, 0.99 mmol) in ethanol (5 cm^3) were used. The crude residue obtained was purified by column chromatography on silica gel (8 : 1 : 0.05, $CHCl_3$–MeOH–conc. NH_4OH, stain: ninhydrin) to afford the product **26b** as a colourless oil (0.21 g, 75%). R_f = 0.28 (8 : 1 : 0.05, $CHCl_3$–MeOH–conc. NH_4OH, stain: ninhydrin). HRMS (ESI+): calculated for $C_{25}H_{53}O_2NP$ [M + H]$^+$ requires 430.3808; found: 430.3806. IR, ν_{max} (NaCl, evap. film)/cm^{-1}: 2927 and 2852 (m, C–H), 2782 (w, N–CH_2), 1465, 1460 and 1277 (w, C–H), 1218 (w, P–OC), 1193 (m, P=O), 1143 (w, C–N), 1040 (m, P–O–C), 823 (w, P–O–C), 718 (w, CH_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 4.02–3.92 (2H, m, POCH_2), 2.75 (2H, d, J = 11.4 Hz, 2 × CHN), 2.18 (3H, s, NCH_3), 1.89 (2H, dd, J = 11.8, 1.8 Hz, 2 × CHN), 1.83–1.77 (2H, m), 1.69–1.55 (5H, m), 1.53–1.42 (2H, m), 1.37–1.28 (4H, m), 1.24 (3H, t, J = 7.1 Hz, POCH$_2$CH_3), 1.19 (24H, br s, 12 × CH_2), 0.81 (3H, t, J = 6.9 Hz, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 59.83 (d, $^2J_{C-P}$ = 6.5 Hz, POCH$_2$), 55.62 (CH$_2$N), 46.36 (NCH$_3$), 34.62 (d, $^1J_{C-P}$ = 89.4 Hz, PCH$_2$), 33.89, 31.92, 30.90 (d, $^3J_{C-P}$ = 15.3 Hz), 29.79 (d, $^2J_{C-P}$ = 3.6 Hz), 29.69, 29.66, 29.65, 29.63, 29.58, 29.38, 29.36, 29.12, 28.80, 22.69, 22.12 (d, $^2J_{C-P}$ = 3.6 Hz), 16.71 (d, $^3J_{C-P}$ = 5.8 Hz, POCH$_2$$CH_3$), 14.13 ($CH_3$). ^{31}P NMR (162 MHz, $CDCl_3$): δ_P 56.58 (CH_2PCH_2). MS (ESI+), m/z (rel. intensity %): 430 (M + H$^+$, 100%), 452 (M + Na$^+$, 95%).

4-[(Hexadecyl(methoxy)phosphoryl)methyl]-1,1-dimethylpiperidinium iodide (28). Methyl iodide (0.54 cm^3, 1.23 g, 8.66 mmol) and anhydrous potassium carbonate (0.40 g, 2.89 mmol) were added into a stirred solution of methyl (1-methylpiperidin-4-yl)methyl(hexadecyl)phosphinate **26a** (0.12 g, 0.29 mmol), in methanol–chloroform (2 : 1, 10 cm^3). The mixture was refluxed under a dry nitrogen atmosphere and monitored by means of thin-layer chromatography (10 : 2 : 0.2, $CHCl_3$–MeOH–conc. NH_4OH, stain: ninhydrin) and ^{1}H NMR spectroscopy. After one day of refluxing the reaction mixture cooled to room temperature and the solvent evaporated under reduced pressure. The residue was then re-dissolved in chloroform and filtered. The filtrate was concentrated under reduced pressure to give a yellow solid which was purified by recrystallization from tetrahydrofuran–ethyl acetate to afford the product **28** as a bright white powder (0.15 g, 95%). mp 233–234 °C (dec.) (from THF–EtOAc). R_f = 0.32 (6.5 : 2.5 : 0.3, $CHCl_3$–MeOH–conc. NH_4OH, stain: ninhydrin). HRMS (ESI+): calculated for $C_{25}H_{53}O_2NP$ [M]$^+$ requires 430.3808; found: 430.3827. IR, ν_{max} (NaCl, evap. film)/cm^{-1}: 2916, 2852 and 1468 (m, C–H), 1409 (w, $^+$NMe$_2$), 1304 (w, C–H), 1207 (m, P–OC), 1191 (m, P=O), 1040 (m, P–O–C), 954 (w, $^+$NMe$_2$), 823 and 814 (w, P–O–C), 718 (w, CH_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 3.76 (2H, d, J = 12.6 Hz, 2 × CHN), 3.64 (3H, d, $^3J_{P-H}$ = 10.6 Hz, POCH_3), 3.60 (2H, dd, J = 12.4, 2.5 Hz, 2 × CHN), 3.49 (3H, s, NCH_3), 3.37 (3H, s, NCH_3), 2.30–2.15 (1H, m), 2.12–2.06 (2H, m), 1.98–1.87 (2H, m), 1.85–1.75 (2H, m), 1.71–1.61 (2H, m), 1.54–1.42 (2H, m), 1.37–1.27 (2H, m), 1.19 (24H, br s, 12 × CH_2), 0.81 (3H, t, J = 7.0 Hz, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 61.56 (CH$_2$N), 55.23 (NCH$_3$), 50.20 (d, $^2J_{C-P}$ = 6.6 Hz, POCH$_3$), 47.57 (NCH$_3$), 31.41 (d, $^1J_{C-P}$ = 90.2 Hz, PCH$_2$), 30.93, 29.87 (d, $^3J_{C-P}$ = 14.7 Hz), 28.71, 28.70, 28.67, 28.62, 28.44, 28.37, 28.19, 27.78 (d, $^1J_{C-P}$ = 88.8 Hz, PCH$_2$), 26.63 (d, $^2J_{C-P}$ = 4.4 Hz), 26.48, 26.39, 26.33, 26.25, 21.70, 21.08 (d, $^2J_{C-P}$ = 4.4 Hz), 13.15 (CH$_3$). ^{31}P NMR (162 MHz, $CDCl_3$): δ_P 57.05 (CH_2PCH_2). MS (ESI+), m/z (rel. intensity %): 430 (M$^+$, 100%).

[(1,1-Dimethylpiperidinium-4-yl)methyl](hexadecyl)phosphinate; inner salt (4). Trimethylsilyl iodide (TMSI) (0.037 cm^3, 51.30 mg, 0.26 mmol) was injected into a stirred solution of 4-[(hexadecyl-(methoxy)phosphoryl)methyl]-1,1-dimethylpiperidinium iodide **28** (28.60 mg, 51.30 μmol) in dry dichloromethane (5 cm^3) at room temperature, under a dry nitrogen atmosphere. The mixture was stirred overnight at room temperature, methanol (3 cm^3) was then injected and the solution was stirred for an

additional 30 minutes. Removal of the solvent under reduced pressure gave dark orange solid which was purified by recrystallization from tetrahydrofuran to afford the product **4** as a bright white powder (19.50 mg, 93%). mp 213–214 °C (from THF). HRMS (ESI+): calculated for $C_{24}H_{51}O_2NP$ $[M + H]^+$ requires 416.3652; found: 416.3664. IR, ν_{max} (NaCl, evap. film)/cm^{-1}: 2916 and 2852 (m, C–H), 1465 (w, C–H), 1406 (w, $^+NMe_2$), 1301 and 1212 (w, C–H), 1161 (w, P═O), 1134 (w, C–N), 1035 (w, P–O), 954 (w, $^+NMe_2$), 720 (w, CH_2). ^1H NMR (400 MHz, CD_3OD): δ_H 3.39 (2H, d, J = 12.6 Hz, 2 × C*H*N), 3.29 (2H, dd, J = 12.7, 2.5 Hz, 2 × C*H*N), 3.07 (3H, s, NCH_3), 3.03 (3H, s, NCH_3), 2.00–1.97 (3H, m), 1.80–1.69 (4H, m), 1.67–1.59 (2H, m), 1.55–1.44 (2H, m), 1.33 (2H, quin., J = 6.5 Hz, CH_2CH$_2$CH$_2$P), 1.19 (24H, br s, 12 × CH_2), 0.81 (3H, t, J = 7.0 Hz, CH_3). ^{13}C NMR (100 MHz, 328.1 K, CD_3OD): δ_C 63.69 (*C*H$_2$N), 56.79 (N*C*H$_3$), 48.81 (N*C*H$_3$), 35.00 (d, $^1J_{C-P}$ = 89.5 Hz, P*C*H$_2$), 33.02, 31.96 (d, $^3J_{C-P}$ = 14.7 Hz), 30.74, 30.70, 30.54, 30.39, 30.29, 29.12, 28.80, 28.71, 23.67, 22.96 (d, $^2J_{C-P}$ = 3.7 Hz), 14.41 (*C*H$_3$). ^{31}P NMR (162 MHz, CD_3OD): δ_P 52.85 (CH$_2$*P*CH$_2$). MS (ESI+), m/z (rel. intensity %): 416 ($M + H^+$, 100%), 438 ($M + Na^+$, 90%).

4-((Hexadecyl(hydroxy)phosphoryl)methyl)-1,1-dimethylpiperidinium chloride (hydrochloride salt of 4). Into the NMR tube containing (1,1-dimethylpiperidinium-4-yl)methyl(hexadecyl)phosphinate; inner salt **4** in CD_3OD, one drop of concentrated hydrochloric acid was added. After ^{31}P NMR study the product (hydrochloride salt of **4**) was converted back to the inner salt **4** by co-evaporation with methanol followed by evaporation of final solvent traces under high vacuum. ^{31}P NMR (162 MHz, CD_3OD): δ_P 58.06 (*P*OH).

Acknowledgements

We gratefully acknowledge the University of Manchester and the A. G. Leventis Foundation (Cyprus) for financial support and Dr C. I. F. Watt at Manchester for valuable assistance and helpful discussions.

Notes and references

1 (*a*) H. Brachwitz and C. Vollgraf, *Pharmacol. Ther.*, 1995, **66**, 39–82; (*b*) W. J. Houlihan, M. Lohmeyer, P. Workman and S. H. Cheon, *Med. Res. Rev.*, 1995, **15**, 157–223.

2 (*a*) G. S. Tarnowski, I. M. Mountain, C. C. Stock, P. G. Munder, H. U. Weltzien and O. Westphal, *Cancer Res.*, 1978, **38**, 339–344; (*b*) P. G. Munder, M. Modolell, R. Andreesen, H. U. Weltzien and O. Westphal, *Springer Semin. Immunopathol.*, 1979, **2**, 187–203; (*c*) D. Berkovic, *Gen. Pharmacol.*, 1998, **31**, 511–517.

3 H. Eibl and C. Unger, *Cancer Treat. Rev.*, 1990, **17**, 233–242.

4 (*a*) F. Mollinedo, *Expert Opin. Ther. Pat.*, 2007, **17**, 385–405; (*b*) S. R. Vink, W. J. van Blitterswijk, J. H. M. Schellens and M. Verheij, *Cancer Treat. Rev.*, 2007, **33**, 191–202.

5 (*a*) J. Stekar, P. Hilgard, R. Voegeli, H. R. Maurer, J. Engel, B. Kutscher, G. Nößner and W. Schumacher, *Cancer Chemother. Pharmacol.*, 1993, **32**, 437–444; (*b*) P. Hilgard, T. Klenner, J. Stekar, G. Nössner, B. Kutscher and J. Engel, *Eur. J. Cancer*, 1997, **33**, 442–446.

6 C. Oberle, U. Massing and H. F. Krug, *Biol. Chem.*, 2005, **386**, 237–245.

7 V. Jendrossek and R. Handrick, *Curr. Med. Chem.: Anti-Cancer Agents*, 2003, **3**, 343–353.

8 R. Ulbrich-Hofmann, A. Lerchner, M. Oblozinsky and L. Bezakova, *Biotechnol. Lett.*, 2005, **27**, 535–5439.

9 M. S. Markoulides and A. C. Regan, *Tetrahedron Lett.*, 2011, **52**, 2954–2956.

10 (*a*) E. A. Boyd, K. James and A. C. Regan, *Tetrahedron Lett.*, 1994, **35**, 4223; (*b*) E. L. Ravaschino, R. Docampo and J. B. Rodriguez, *J. Med. Chem.*, 2006, **49**, 426–435.

11 L. Coudray and J.-L. Montchamp, *Eur. J. Org. Chem.*, 2008, 3601–3613.

12 (*a*) E. E. Nifant'ev and M. P. Koroteev, *J. Gen. Chem. USSR (Engl. Trans.)*, 1967, **37**, 1293; (*b*) E. E. Nifant'ev, R. K. Magdeeva and N. P. Shchepet'eva, *J. Gen. Chem. USSR (Engl. Trans.)*, 1980, **50**, 1416.

13 (*a*) D. S. Karanewsky, M. C. Badia, D. W. Cushman, J. M. DeForrest, T. Dejneka, M. J. Loots, M. G. Perri, E. W. Petrillo Jr. and J. R. Powell, *J. Med. Chem.*, 1988, **31**, 204–212; (*b*) N. G. Anderson, M. L. Coradetti, J. A. Cronin, M. L. Davies, M. B. Gardineer, A. S. Kotnis, D. A. Lust and V. A. Palaniswamy, *Org. Process Res. Dev.*, 1997, **1**, 315–319; (*c*) Y. Feng and J. K. Coward, *J. Med. Chem.*, 2006, **49**, 770–778; (*d*) C. Selvam, N. Oueslati, I. A. Lemasson, I. Brabet, D. Rigault, T. Courtiol, S. Cesarini, N. Triballeau, H.-O. Bertrand, C. Goudet, J.-P. Pin and F. C. Acher, *J. Med. Chem.*, 2010, **53**, 2797–2813.

14 M. I. Antczak and J.-L. Montchamp, *Synthesis*, 2006, 3080–3084.

15 S. Deprèle and J.-L. Montchamp, *J. Org. Chem.*, 2001, **66**, 6745–6755.

16 For a recent example see: A. F. Parsons and A. Wright, *Synlett*, 2008, 2142–2146.

17 For examples, see: (*a*) L.-B. Han and C.-Q. Zhao, *J. Org. Chem.*, 2005, **70**, 10121–10123; (*b*) S. R. Piettre, *Tetrahedron Lett.*, 1996, **37**, 2233–2236; (*c*) H.-J. Zeiss, *Tetrahedron*, 1992, **48**, 8263–8270; (*d*) J. G. Dingwall and B. Tuck, *J. Chem. Soc., Perkin Trans. 1*, 1986, 2081–2090; (*e*) M. Finke and H.-J. Kleiner, *Liebigs Ann. Chem.*, 1974, 741–750; (*f*) L. P. Reiff and H. S. Aaron, *J. Am. Chem. Soc.*, 1970, **92**, 5275–5276.

18 For an example, see: A. Gautier, G. Garipova, C. Salcedo, S. Balieu and S. R. Piettre, *Angew. Chem., Int. Ed.*, 2004, **43**, 5963–5967.

19 O. Dubert, A. Gautier, E. Condamine and S. R. Piettre, *Org. Lett.*, 2002, **4**, 359–362.

20 S. J. Fitch, *J. Am. Chem. Soc.*, 1964, **86**, 61–64.

21 A. M. Schmidt and P. Eilbracht, *J. Org. Chem.*, 2005, **70**, 5528–5535.

22 E. W. Della and P. A. Smith, *J. Org. Chem.*, 1999, **64**, 1798–1806.
23 (*a*) J. Zygmunt, P. Kafarski and P. Mastalerz, *Synthesis*, 1978, 609–612; (*b*) S. A. Biller, C. Forster, E. M. Gordon, T. Harrity, L. C. Rich, J. C. Marretta and C. P. Ciosek Jr., *J. Med. Chem.*, 1991, **34**, 1912–1914.
24 (*a*) D. D. Perrin and W. L. F. Armarego, *Purification of Laboratory Chemicals*, Butterworth-Heinemann, Oxford, UK, 4th edn, 1996; (*b*) B. S. Furniss, A. J. Hannaford, P. W. G. Smith and A. R. Tatchell, *Vogel's Textbook of Practical Organic Chemistry*, Pearson Education, Harlow, Essex, UK, 5th edn, 1989.