Synthesis of alkyldibenzophosphole 5-oxides

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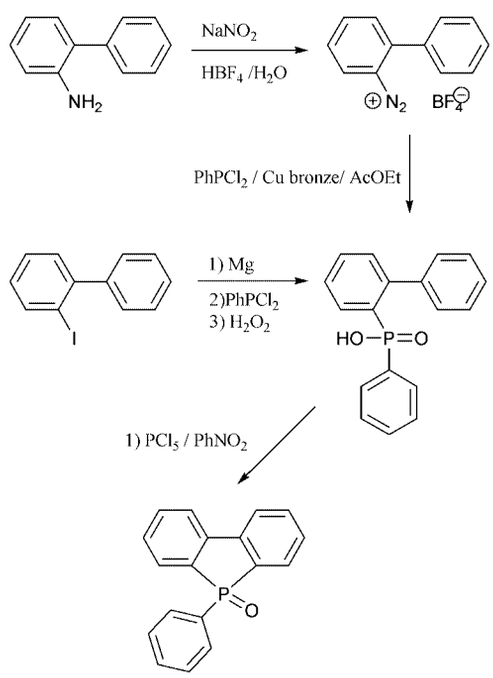
The synthesis of 5-alkyl-5*H*-dibenzophosphole 5-oxides has been re-studied. Ethyl-, dodecenyl- and heptadecyl-dibenzophosphole oxides have been synthesised by the alkylation of the P-methylide generated by lithiation of 5-methyl-5*H*-dibenzophosphole 5-oxide. An improved method for the synthesis of the latter oxide is also described.

Introduction

Our research group is interested in the physical properties of certain 5-long-chain alkyl-5*H*-dibenzophospholes. However, the synthesis of suitable molecules for our aims remains unresolved.

In spite of the common use of dibenzophosphole as a ligand, there are no high yield syntheses of this compound and/or its derivatives in the literature. The Cornforth[1] method is suitable for some symmetrically disubstituted-5-hydroxy-5*H*-dibenzophosphole 5-oxides, but it is difficult to generalise this method to products of a different pattern of substitution and, furthermore, the introduction of a long chain alkyl group onto the phosphorus atom requires several steps. A set of methods[1–3] using 2,2′-dibromobiphenyls as starting material is in all cases appropriate only for systems without substituents on the aromatic rings and/or with a phenyl group on the phosphorus atom, and the adaptation of such methods to our requirements involves starting materials that are difficult to prepare; furthermore, the described global yields are very low. Attempts to generalise the Freedman and Doak method[4] were unsuccessful. Probably, the most widely used method is that described by Hoffmann,[5] consisting of the treatment of tetraphenylphosphonium bromide with lithium diethylamide. The conversion of the obtained 5-phenyl-5*H*-dibenzophosphole into 5-methyl-5*H*-dibenzophosphole is described by Ezzell and Freedman[6] by treatment with lithium and methyl iodide; however, the described global yield from the commercial tetraphenylphosphonium bromide into 5-methyl-5*H*-dibenzophosphole is only 27% and the method is impossible to generalise to systems substituted in the benzene rings. The method described by Campbell *et al.*[7]—formation of biphenyl-2-ylphenylphosphinic acid and its cyclisation by reaction with phosphorus pentachloride (Scheme 1)—has only been applied with a phenyl substituent on the phosphorus atom and it has not been used recently. However, we thought that this method would probably be the easiest to adapt to our needs and despite the very low global yields—in some cases 3%—we decided to modify it in order to develop a new procedure for the general synthesis of 5-alkyl-5*H*-dibenzophospholes.



Scheme 1

Results and discussion

The main problems observed in the development of the Campbell's method were:

a) When the target is the previously undescribed product biphenyl-2-ylmethylphosphinic acid, dichloromethylphosphine (toxic, volatile and difficult to manage) must be used in order to obtain 5-methyl-5*H*-dibenzophosphole 5-oxide. With a 1.5 : 1 proportion of dichloromethylphosphine–biphenyl-2-ylbromomagnesium the only product isolated after oxidation, and with a good yield (76%), was bis(biphenyl-2-yl)methylphosphine oxide, the product of double condensation of the organometallic compound and dichloromethylphosphine, and none of the desired compound.

b) The alternative preparation of the biphenyl-2-ylmethylphosphinic acid *via* diazonium salt, dichloromethylphosphine and copper as catalyst yielded the acid but it showed a yield which depended critically on the temperature, order of reagent addition, reaction time, proportion of copper, *etc.*, erratically changing the yield even between identical experiments.

c) The cyclisation of the biphenyl-2-ylmethylphosphinic acid to 5-methyl-5*H*-dibenzophosphole 5-oxide with phosphorus pentachloride took place with a very low yield. This reaction only worked with nitrobenzene as solvent but steam distillation as described led to the small amount of product unexpectedly being reconverted into the phosphinic acid showing that the formation of the P–C bond was perfectly reversible, at least in this family of compounds and under the conditions used.

We have developed the method described in Scheme 2. The preparation of biphenyl-2-ylmethylphosphinic acid is a one-pot process in three steps.

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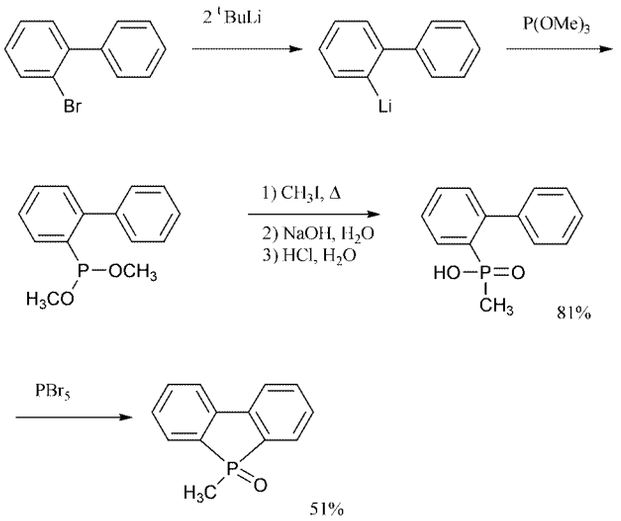


Scheme 2

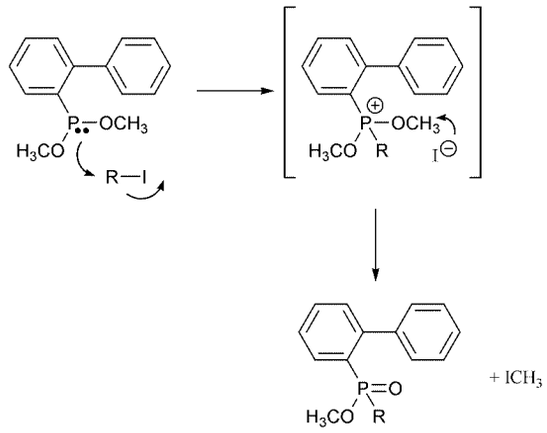
Firstly preparation of biphenyl-2-yllithium was achieved by reaction of 2-bromobiphenyl and 2 equivalents of *tert*-butyllithium in anhydrous tetrahydrofuran. Secondly, biphenyl-2-yllithium was reacted with an excess—at least 10 equivalents—of trimethyl phosphite and yielded dimethyl biphenyl-2-ylphosphonite. Excess of reagent was used to avoid the condensation of two units of organolithium with one molecule of trimethyl phosphite; such an excess was not a problem because of the low price of the reagent used and its easy removal from the reaction mixture by low pressure distillation. It is important to avoid contact of the compound with air to prevent the very fast oxidation to the phosphonate. Finally, reaction of the dry residue of the latter step with methyl iodide under Arbuzov conditions was carried out.[8]

The second part of the method was the cyclisation of the biphenyl-2-ylmethylphosphinic acid to 5-methyl-5*H*-dibenzophosphole 5-oxide with phosphorus pentabromide at 100 °C for 60 hours with nitrobenzene as solvent. The desired product was obtained very pure in 51% yield after removal of the solvent by low pressure distillation, treatment of the crude with dilute sodium hydroxide and extraction with methylene chloride to separate the starting acid. Attempts to use antimonium pentachloride instead of the other cyclisation reagents were unsuccessful and led to the total destruction of the starting material. The use of a variety of solvents other than nitrobenzene was also inadequate.

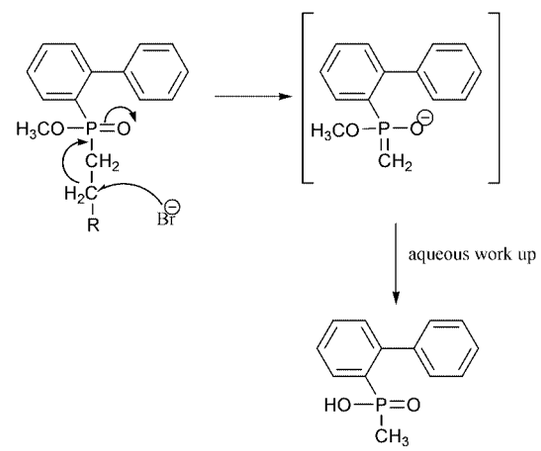
Our method, in contrast to that described by Campbell *et al.*, is clean, with reasonable global yield (40% compared with 3%) and easily reproducible.

The second problem to solve was the introduction of a long alkyl chain on the phosphorus atom. The first idea was to apply the Arbuzov reaction but with a long chain alkyl iodide instead of methyl iodide. However, methyl iodide was quickly formed (Scheme 3) and reacted with the phosphonite due to its relative higher reactivity compared with the long chain alkyl iodide, yielding the biphenyl-2-ylmethylphosphinic acid as the only product, which is identical to when methyl iodide is used as reagent.

The apparent solution was to use an excess of alkyl iodide and to heat the reaction mixture above the boiling point of methyl iodide in order to remove it as fast as it is formed. Under these conditions the desired compound was formed. Unfortunately, when the resulting compounds were treated with phosphorus pentabromide or pentachloride for cyclisation, the long alkyl chain broke, probably by the attack of bromide ion as indicated in Scheme 4, and biphenyl-2-ylmethylphosphinic acid was obtained as the only product. However, this fact can be considered as evidence of the existence of a stable anionic intermediate with evident synthetic interest.

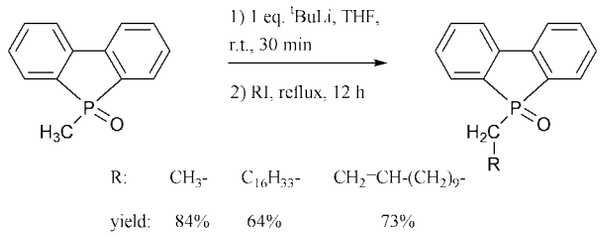


Scheme 3



Scheme 4

We applied such an idea to solve the problem of the introduction of a long alkyl chain onto the 5*H*-dibenzophosphole 5-oxide phosphorus atom by alkylation of the 5-methyl-5*H*-dibenzophosphole 5-oxide as shown in Scheme 5. This method



Scheme 5

is very scarce in the literature[9] and there are no examples for this family of compounds.

This reaction only took place with alkyl iodides, not with chlorides or bromides, and the use of n-BuLi led to biphenyl-2-ylbutylmethylphosphine oxide. The possibility of the introduction of a variety of alkyl chains onto the phosphorus atom from a common starting compound is a feature of great interest in many cases.

Conclusion

We have developed a new procedure for the synthesis of 5-methyl-5*H*-dibenzophosphole 5-oxides with considerably higher yields than the ones described until now. Furthermore, the introduction of a long alkyl group onto the phosphorus atom by reaction between an alkyl iodide and the ylide formed by treatment of 5-methyl-5*H*-dibenzophosphole 5-oxide with a base is also described.

Experimental

General

Melting points were determined in a Köfler apparatus provided with a Reichert Thermovar microscope and are uncorrected. TLC was carried out on SiO_2 (Silica Gel 60 F_{254}, Merck 0.063–0.200 mm) and spots were located with UV light. Flash chromatography was carried out on SiO_2 (Silica Gel 60 A CC, Merck). Organic extracts were dried over anhydrous $MgSO_4$, and solutions were evaporated under reduced pressure with a rotatory evaporator. IR spectra were recorded on a Nicolet 510 FT-IR spectrometer. NMR spectra were measured with Varian Gemini-200 (200 MHz) and Varian Gemini-300 (300 MHz) spectrometers; data are given in δ/ppm, referenced to TMS and J values are given in Hz. Mass spectra were measured in the electron impact (EI) or chemical impact (CI, NH_3) modes with a Hewlett-Packard 5988A spectrometer. High resolution mass spectra were performed on an Autospec/VG by the Departament de Química Orgànica Biològica (C.S.I.C.), Barcelona.

Biphenyl-2-ylmethylphosphinic acid

Commercial ^{t}BuLi (1.7 M, 7 ml) was added to a solution of 2-bromobiphenyl (1.12 g, 4.8 mmol) in anhydrous THF (20 ml), cooled to −78 °C and maintained under an inert atmosphere. The mixture was stirred for 30 min and then trimethyl phosphite (7 ml, 57.6 mmol) was added. After complete addition the cooling bath was retired and the reaction stirred for 1 h. The solvent and excess trimethyl phosphite were removed to yield a residue formed by a yellow oil and a white solid. To this mixture methyl iodide (1 ml) was added and maintaining the inert atmosphere the reaction was refluxed for 12 h, then cooled and extracted with CH_2Cl_2 and 5% NaOH (3 × 5 ml). The aqueous basic layer was acidified with 5% HCl and extracted with CH_2Cl_2. The organic layer was dried, the solvent removed and the biphenyl-2-ylmethylphosphinic acid (904 mg, 81%) was isolated as a white solid; mp 113–115 °C (from CH_2Cl_2); ν_{max} (film)/cm^{-1} 3058 (arC–H s), 2921 (C–H s), 2624 (PO–H s, broad), 2250 (POH combination vibration, broad), 1136 (P=O s), 971 (P–OH s); δ_H ($CDCl_3$, 300 MHz) 10.90 (s, H^8, 1H), 8.09 (ddd, H^3, 1H, J_{H-P} 13.1, J_{H3-H4} 7.7, J_{H3-H5} 1.5), 7.55–7.25 (m, $H^{4,5,6,2',3',4',5',6'}$, 8H), 1.05 (d, H^7, 3H, J_{H-P} 14.7); δ_C ($CDCl_3$, 75 MHz) 145.20 (d, C^1, J_{C-P} 12.5), 140.89 (d, $C^{1'}$, J_{C-P} 4.2), 132.13 (d, C^6, J_{C-P} 8.2), 131.57 (d, C^5, J_{C-P} 2.7), 131.55 (d, C^2, J_{C-P} 127.5), 131.03 (d, C^3, J_{C-P} 11.9), 129.92 (s, $C^{3'+5'}$), 127.81 (s, $C^{2'+4'+6'}$), 126.96 (d, C^4, J_{C-P} 11.9), 16.61 (d, C^7, J_{C-P} 107.6); δ_P ($CDCl_3$, 121 MHz): 37.63 (s); m/z (CI, NH_3) 232.0647 (M^+). $C_{13}H_{13}O_2P$ requires 232.0653, 250 (M + 18, 100%), 233 (M + 1, 7%); (EI) 232 (M^+, 45%), 231 (M − 1, 100%).

5-Methyl-5*H*-dibenzophosphole 5-oxide

Phosphorus pentabromide (535 mg, 1.24 mmol) was added to a solution of biphenyl-2-ylmethylphosphinic acid (101 mg, 0.44 mmol) in nitrobenzene (3 ml) under an inert atmosphere. The mixture was heated at 100 °C for 60 h; then the nitrobenzene was removed by vacuum distillation (approx. 60 °C, 2 mmHg). The residue was extracted with CH_2Cl_2 and 5% NaOH (3 × 5 ml). The organic layer was dried and evaporated, yielding a brown solid that was purified by column chromatography eluting with CH_2Cl_2–CH_3OH, 96:4. The 5-methyl-5*H*-dibenzophosphole 5-oxide was isolated as a white solid (47 mg, 51%); mp 90–91 °C (from CH_2Cl_2) (lit.,[6] 89–91 °C); ν_{max} (film)/cm^{-1} 3056 (arC–H s), 1175 (P=O s); δ_H ($CDCl_3$, 300 MHz) 7.87 (dddd, H^4, 2H, J_{H-P} 9.6, J_{H3-H4} 7.5, J_{H2-H4} 1.2, J_{H1-H4} 0.9), 7.79 (dddd, H^1, 2H, J_{H1-H2} 7.8, J_{H-P} 2.7, J_{H1-H3} 0.9, J_{H1-H4} 0.9), 7.59 (dddd, H^2, 2H, J_{H1-H2} 7.8, J_{H2-H3} 7.5, J_{H-P} 1.5, J_{H2-H4} 1.2), 7.44 (dddd, H^3, 2H, J_{H3-H4} 7.5, J_{H2-H3} 7.5, J_{H-P} 3.6, J_{H1-H3} 0.9), 1.85 (d, H^{14}, 3H, J_{H-P} 13.8); δ_C ($CDCl_3$, 75 MHz) 140.54 (d, C^{10}, J_{C-P} 21.5), 133.17 (d, C^2, J_{C-P} 1.8), 132.48 (d, C^{12}, J_{C-P} 103.2), 129.14 (d, C^4, J_{C-P} 11.0), 128.82 (d, C^3, J_{C-P} 9.7), 121.18 (d, C^1, J_{C-P} 9.7), 16.19 (d, C^{14}, J_{C-P} 70.7); δ_P ($CDCl_3$, 121 MHz) 37.23 (s); m/z (CI, NH_3) 215 (M + 1, 84%), 232 (M + 18, 100%); (EI) 214 (M^+, 35%), 199 ($M^+ - CH_3$, 100%).

5-Ethyl-5*H*-dibenzophosphole 5-oxide

Commercial ^{t}BuLi (1.7 M, 0.36 ml) was added to a solution of 5-methyl-5*H*-dibenzophosphole 5-oxide (132 mg, 0.62 mmol) in anhydrous THF (10 ml) and the mixture was stirred for 30 min at room temperature under an inert atmosphere. Then, methyl iodide (38 µl, 87 mg, 0.62 mmol) was added to the red solution formed and stirred overnight at room temperature. The solvent was removed and the residue was purified by column chromatography, eluting firstly with CH_2Cl_2 to remove apolar impurities present in the crude mixture and after with CH_2Cl_2–CH_3OH, 96:4 yielding 5-ethyl-5*H*-dibenzophosphole 5-oxide (117 mg, 84%) as an oil; ν_{max} (film)/cm^{-1} 3056 (arC–H s), 2967 (C–H s), 1194 (P=O s); δ_H ($CDCl_3$, 200 MHz) 7.84 (dddd, H^4, 2H, J_{H-P} 9.6, J_{H3-H4} 7.5, J_{H2-H4} 1.2, J_{H1-H4} 0.9), 7.79 (dddd, H^1, 2H, J_{H1-H2} 7.8, J_{H-P} 2.7, J_{H1-H3} 0.9, J_{H1-H4} 0.9), 7.59 (dddd, H^2, 2H, J_{H1-H2} 7.8, J_{H2-H3} 7.5, J_{H-P} 1.5, J_{H2-H4} 1.2), 7.43 (dddd, H^3, 2H, J_{H3-H4} 7.5, J_{H2-H3} 7.5, J_{H-P} 3.6, J_{H1-H3} 0.9), 2.12 (dq, CH_2, 2H, J_{H-P} 13.8, $J_{H14-H15}$ 7.6), 1.07 (dt, CH_3, 3H, J_{H-P} 18.8, $J_{H14-H15}$ 7.6); δ_C ($CDCl_3$, 50 MHz) 141.16 (d, C^{10}, J_{C-P} 20.5), 133.07 (d, C^2, J_{C-P} 2.3), 129.23 (d, C^4, J_{C-P} 10.9), 129.02 (d, C^3, J_{C-P} 9.6), 121.08 (d, C^1, J_{C-P} 9.6), 23.19 (d, C14, J_{C-P} 70.1), 6.23 (d, C15, J_{C-P} 4.1); δ_P ($CDCl_3$, 121 MHz) 46.11 (s); m/z (CI, NH_3) 228.0711 (M^+). $C_{14}H_{13}OP$ requires 228.0704, 229 (M + 1, 100%), 246 (M + 18, 71%).

5-Heptadecyl-5*H*-dibenzophosphole 5-oxide

Commercial ^{t}BuLi (1.7 M, 0.46 ml) was added to a solution of 5-methyl-5*H*-dibenzophosphole 5-oxide (153 mg, 0.72 mmol) in anhydrous THF (10 ml) and the mixture was stirred for 30 min at room temperature under an inert atmosphere. Then, hexadecyl iodide (377 mg, 1.1 mmol) was added to the red solution formed and the mixture refluxed for 15 h. The solvent was removed and the residue was purified by column chromatography, eluting firstly with CH_2Cl_2 to remove apolar impurities present in the crude mixture and after with CH_2Cl_2–CH_3OH, 96:4 yielding 5-heptadecyl-5*H*-dibenzophosphole 5-oxide (200 mg, 64%) as an oil; ν_{max} (film)/cm^{-1} 3056 (arC–H s), 2925 (C–H s), 1204 (P=O s); δ_H ($CDCl_3$, 300 MHz) 7.84 (dddd, H^4, 2H, J_{H-P} 9.6, J_{H3-H4} 7.5, J_{H2-H4} 1.2, J_{H1-H4} 0.9), 7.78 (dddd, H^1, 2H, J_{H1-H2} 7.8, J_{H-P} 2.7, J_{H1-H3} 0.9, J_{H1-H4} 0.9), 7.58 (dddd, H^2, 2H, J_{H1-H2} 7.8, J_{H2-H3} 7.5, J_{H-P} 1.5, J_{H2-H4} 1.2), 7.42 (dddd, H^3, 2H, J_{H3-H4} 7.5, J_{H2-H3} 7.5, J_{H-P} 3.6, J_{H1-H3} 0.9), 2.12–0.85 (complex signal, H^{14-30}, 35H); δ_C ($CDCl_3$, 75 MHz) 141.14 (d, C^{10}, J_{C-P} 20.3), 133.06 (d, C^2, J_{C-P} 2.2), 129.30 (d, C^4, J_{C-P} 9.4), 129.05 (d, C^3, J_{C-P} 10.6), 121.13 (d, C^1, J_{C-P} 9.7), [31.88, 30.89, 30.70, 29.64, 29.47, 29.31, 29.26, 28.94] ($C^{14,16-28}$), 22.64 (C^{29}), 22.02 (d, C^{15}, J_{C-P} 3.7), 14.07 (C^{30}); δ_P ($CDCl_3$, 121 MHz) 44.02 (s); m/z (CI, NH_3) 438.3044 (M^+). $C_{27}H_{41}OP$ requires 438.3038, 439 (M + 1, 100%), 456 (M + 18, 10%).

5-(Dodec-11-enyl)dibenzophosphole 5-oxide

Commercial ^{t}BuLi (1.7 M, 0.44 ml) was added to a solution of 5-methyl-5*H*-dibenzophosphole 5-oxide (146 mg, 0.69 mmol) in anhydrous THF (10 ml) containing a catalytic amount (5 mg) of KI and the mixture was stirred for 30 min at room temperature under an inert atmosphere. Then undec-10-enyl bromide (240 mg, 1 mmol) was added to the red solution formed and the mixture refluxed for 15 h. The solvent was removed and the residue was purified by column chromatography, eluting firstly with CH_2Cl_2 to remove apolar impurities present in the crude and after with CH_2Cl_2–CH_3OH, 96:4 yielding 5-(dodec-11-enyl)dibenzophosphole 5-oxide (182 mg, 73%) as an oil; ν_{max} (film)/cm^{-1} 3058 (arC–H s), 2927 (C–H s), 1202 (P=O s);

δ_H ($CDCl_3$, 300 MHz) 7.82 (dddd, H^4, 2H, J_{H-P} 9.6, J_{H3-H4} 7.5, J_{H2-H4} 1.2, J_{H1-H4} 0.9), 7.79 (dddd, H^1, 2H, J_{H1-H2} 7.8, J_{H-P} 2.7, J_{H1-H3} 0.9, J_{H1-H4} 0.9), 7.58 (dddd, H^2, 2H, J_{H1-H2} 7.8, J_{H2-H3} 7.5, J_{H-P} 1.5, J_{H2-H4} 1.2), 7.43 (dddd, H^3, 2H, J_{H3-H4} 7.5, J_{H2-H3} 7.5, J_{H-P} 3.6, J_{H1-H3} 0.9), 5.80 (complex signal, H^{24}, 1H), 4.96 (complex signal, H^{25}, 2H), 2.17–0.99 (complex signal, H^{14-23}, 20H); δ_C ($CDCl_3$, 75 MHz) 141.09 (d, C^{10}, J_{C-P} 20.6), 139.09 (C^{24}), 133.01 (d, C^2, J_{C-P} 2.2), 129.30 (d, C^3, J_{C-P} 9.4), 129.01 (d, C^4, J_{C-P} 10.7), 121.10 (d, C^1, J_{C-P} 9.5), 114.02 (C^{25}), 33.69 (C^{23}), 30.28 (d, C^{14}, J_{C-P} 83.5) [30.64, 29.34, 29.29, 29.18, 28.99, 28.87, 28.82] (C^{16-22}), 21.99 (d, C^{15}, J_{C-P} 3.7); δ_P ($CDCl_3$, 121 MHz) 44.04 (s); *m/z* (CI, NH_3) 366.2118 (M^+); $C_{24}H_{31}OP$ requires 366.2112. 367 (M + 1, 100%), 384 (M + 18, 7%).

Acknowledgements

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