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Synthesis and Characterization of Some P-Menthylphosphetanes, a New Class of Electron-rich Chiral Phosphines

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Abstract : 1-Menthyl substituted phosphetane oxides **4** and **6** are prepared either by starting from (menthyl)PCl_2 and an appropriate olefin, or by reacting (menthyl)MgCl with a 1-chlorophosphetane. Highly selective alkylation and halogenation reactions of the corresponding anions **4'** afford α-substituted derivatives in diastereomerically pure form. Reductions of the phosphetane oxides with $HSiCl_3$,Et_3N proceed with retention of configuration about the phosphorus atom. The described procedure provide an access to a wide range of optically pure phosphines of known stereochemistry.

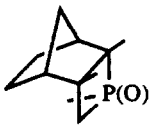
Introduction

The successful development of the asymmetric version of many transition metal catalyzed reactions is dependent upon the design and synthesis of new chiral ligands and, *inter alia*, of new chiral phosphines. Hundreds of chiral phosphines have been described in the literature[1], most of them being P-arylsubstituted species with a chiral backbone and achiral phosphorus. Several detailed studies in this field have defined a class of ligands which are well adapted to enantioselective catalysis : these are generally fairly rigid, bidentate, C_2 symmetric phosphines bearing two aryl substituents on phosphorus. Important representatives of this family are Kagan's DIOP, Noyori's BINAP and their analogues.

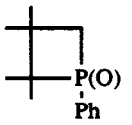
Comparatively, very little is known concerning the catalytic activity of basic phosphines such as trialkylphosphines, on their structural requirements for good asymmetric induction and on the relationship between chirality at phosphorus and enantioselectivity. In order to contribute to a better understanding of this field, we are, initially, attempting to develop simple and flexible preparations of new families of optically active monophosphines, which are chiral on both phosphorus and carbon atoms.

Cyclic phosphines seem to offer some significant advantages over their acyclic analogues, in that the restricted number of possible conformations allows a better definition of the relative position of the various substituents and, thus, a better understarting of the chiral environment at phosphorus. Moreover, the restricted rotational freedom of the ligand is expected to improve enantioselectivity. The synthesis and use of enantiomerically pure five membered rings - phospholanes - have been successfully developed by M.J. Burk[2] and J.C. Fiaud[3] ; who have both specifically targetted species with C_2 symmetry and achiral phosphorus. On the other hand, optically active four-membered rings - phosphetanes - have been largely neglected in the recent literature : only phosphetane oxide **1**[4], obtained from (+) camphene, in unknown

optical yield, and compound 2[5] have been briefly mentioned.



1 $[\alpha]_D = -9.4°$

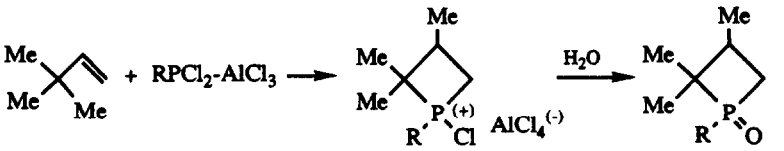


2 $[\alpha]_D = +37.1°$

We now describe a general protocol for the synthesis of diastereomerically pure phosphetanes, by using an enantiomerically pure menthyl group, bound to the phosphorus atom, to generate an easily separable diastereomeric pair. While P-menthylphosphetanes are unknown, P-menthyldialkylphosphines have been reported as efficient ligands in nickel catalyzed codimerizations of ethylene on cycloocta-1,3-diene or norbornene[6].

Results and Discussion

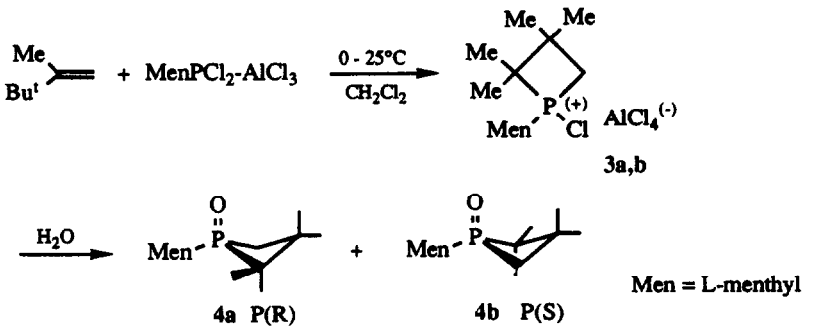
The preparations leading to the phosphetane system are few in number.[7] The most general approach is still to date the McBride synthesis : the reaction between a branched olefin and the $RPCl_2.AlCl_3$ complex, shown in scheme 1.



Scheme 1

The same approach can be applied to the synthesis of menthyl-substituted phosphetane oxides by using (L-menthyl)PCl_2 and an appropriate olefin as starting materials.

When 2,3,3-trimethyl-1-butene was reacted with the $MenPCl_2.AlCl_3$ complex (scheme 2), the two isomeric phosphetanium salts 3a,b were formed (δ ^{31}P 125 and 118 ppm) in equal amount. Hydrolysis afforded the phosphetane oxides 4a,b in a 1:1 ratio, according to ^{31}P NMR spectroscopy of the reaction mixture.



Scheme 2

Column chromatography on neutral alumina yields a mixture of the phosphetane oxides **4a** + **4b** in 48% total yield. Fractional crystallization from pentane allows separation of the two diastereoisomers : oxide **4a** (^{31}P NMR (C_6D_6) δ = 62.7 ppm) is recovered first ; the oxide **4b** is obtained in the pure state after two recrystallizations of the mother liquor (^{31}P NMR (C_6D_6) δ = 57.7 ppm).

The phosphorus configuration was established by an X-ray study of the phosphetane oxide **4a** : as shown in figure 1, the oxide **4a** has an (R) configuration at phosphorus.

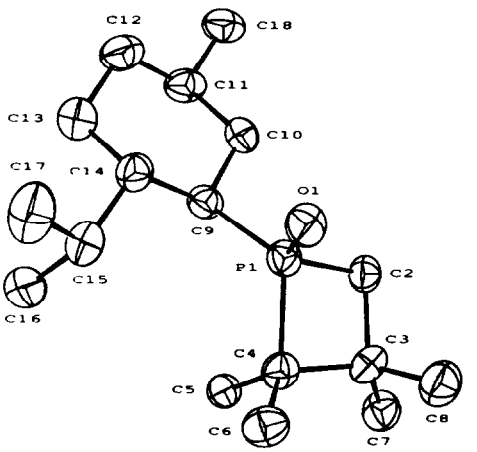


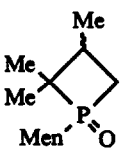
Figure 1. ORTEP drawing of the phosphetane oxide **4a**

Selected bond distances and angles are listed in table 1. All structural data are comparable to those found in other phosphetane ring systems.[8] As expected the phosphetane oxide 4a exhibits puckering of the four membered ring (dihedral angle between the planes C(2)-P-C(4) and C(2)-C(3)-C(4) is 17.6°) and has the bulky menthyl substituent in a pseudoequatorial position (where it lowers cross-ring interactions between substituents on C(3) and P).

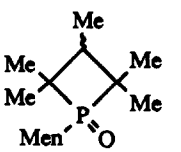
Table 1 : Selected Bond Distances (Å) and Angles (deg) for Compound 4a.

P-C(2)	1.806(5)	C(2)-P-C(4)	79.9(2)
P-C(4)	1.852(6)	P-C(2)-C(3)	89.7(3)
C(2)-C(3)	1.570(8)	C(2)-C(3)-C(4)	96.3(4)
C(3)-C(4)	1.584(8)	C(3)-C(4)-P	87.7(3)
P-C(9)	1.818(5)	C(9)-P-C(4)	117.6(2)
P-O	1.490(4)	C(9)-P-C(2)	112.6(3)

An attempt was made to apply reaction (1) to the synthesis of 1-menthyl-2,2,3-trimethylphosphetane oxides by reacting $MenPCl_2$ with 3,3-dimethyl-1-butene. Unfortunately the four possible diastereoisomers of 5 are formed (^{31}P NMR δ = 68.4, 62.6, 62.2 and 57.0 ppm) in equimolar ratios, thus precluding the isolation of pure compounds in reasonable yields.

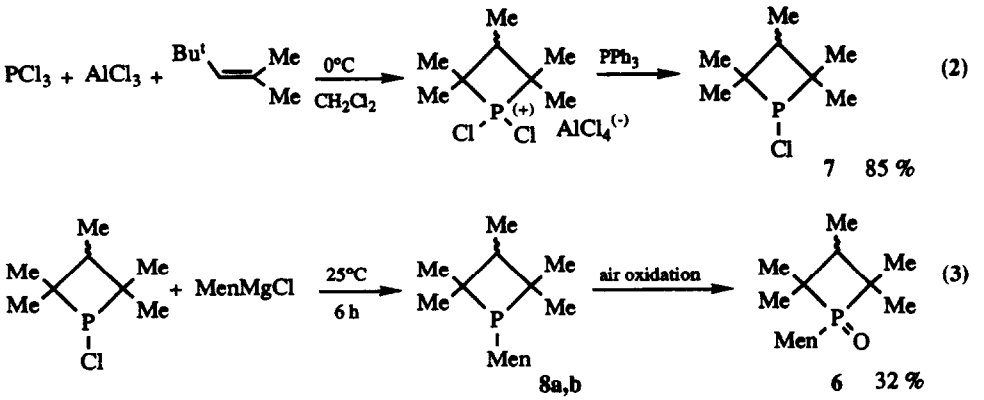


5



6

To expand the scope of our approach we also tried the synthesis of the 1-menthyl-2,2,3,4,4-pentamethyl phosphetane oxide 6, with achiral phosphorus, by the same method. Only a small amount of the desired product was formed : as mentioned by S.E. Cremer in the case of $tBuPCl_2$[9], hindered dichlorophosphine.$AlCl_3$ adducts do not react cleanly with hindered olefins such as 2,4,4-trimethyl-2-pentene.However, compound 6 is accessible through the two step synthesis shown in scheme 3.

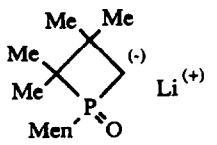


Scheme 3

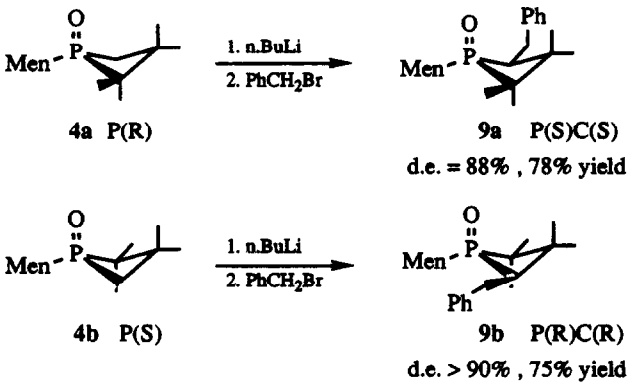
The 1-chlorophosphetane 7[10] is formed as a mixture of two isomers in a 2:1 ratio (^{31}P NMR δ = 170.8 and 150.4 ppm), the major being the trans isomer. After distillation, the chlorophosphetane 7 was reacted with MenMgCl to give the phosphetane 8 (^{31}P NMR δ = 48.8 (major) and 49.3 ppm), together with some side-products. Air oxidation was employed in order to facilitate the isolation of the major isomer in a pure form by column chromatography and crystallization. The isolated oxide 6a is the cis derivative according to a comparison of its ^{1}H NMR data with those of analogous P-tert-butyl substituted ring systems of known stereochemistry[9], as would be expected from its synthesis (Grignard nucleophilic substitution on the chlorophosphane).

The two synthetic approaches defined in scheme 2 and 3 can probably be transposed to the preparation of other P-menthylphosphetane oxides by using different olefins as starting materials. Nevertheless we preferred to examine the synthesis of new phosphetane oxides through transformations of the oxides 4a and 4b, as stereospecific α-functionalization of these ring systems could give rise to an entire family of chiral phosphetanes in both the P(R) and P(S) series. To the best of our knowledge, no such functionalization of the carbon atoms of a preformed phosphetane ring has ever been reported.

The preliminary work reported here concerns highly selective alkylation and halogenation reactions of the chiral phosphorus stabilized anions 4'.



The phosphetane oxides 4a and 4b were reacted separately with nBuLi at -78°C in THF and alkylated with benzylbromide at low temperature (scheme 4).



(4)

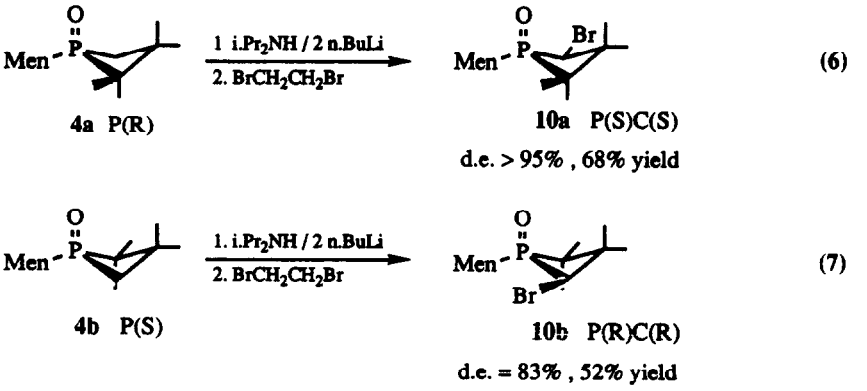
(5)

Scheme 4

Reaction conditions were not optimized ; some starting material was still present together with a few ring opening side products. The diastereomeric excess was established by ^{31}P NMR spectroscopy of the reaction mixture and the minor isomer was not fully characterized. The deprotonation-alkylation reaction is not accompanied by a detectable epimerization at phosphorus, as already mentioned in the case of acyclic phosphine oxide anions.[11] Unlike the acyclic anions the stereoselectivity of these alkylations is very high, probably due to sterical contraints in the hindered four membered ring. The steric bulk of the groups directly attached to phosphorus has also proved to be the key structural element for highly stereoselective alkylations in five membered phosphorus heterocycles.[12] For some recent work on the stereoselective alkylations of chiral, phosphorus-stabilized carbanions see also ref 13.

NMR data of 9a,b do not permit a definitive stereochemical assignment, but it seems reasonable to assume a trans diequatorial relationship between the menthyl and benzyl groups, that is a P(S)C(S) and P(R)C(R) configuration for 9a and 9b respectively. The NMR data of the corresponding P(III) derivatives (see below) confirm such an assignement : the small $^{2}J_{PH}$ coupling (7.2 Hz) must be associated with an hydrogen trans to the phosphorus doublet; additionally, the large $^{2}J_{CP}$ coupling for the $\underline{C}H_2Ph$ carbon (18.2 and 17.7 Hertz) corresponds to a cis relationship between the benzyl group and the phosphorus doublet.[14]

α-Halogenation of the phosphetane oxides 4a and 4b has been performed through a lithium/bromine exchange reaction, using dibromoethane as halogen source (scheme 5).

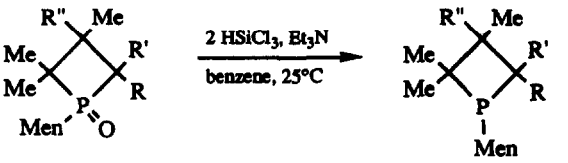


Scheme 5

An excess LDA is required to reduce the quantity of starting material in the final mixture, as it may otherwise be formed by reprotonation of the anion 4' by the more acidic final product. Optimization of the reaction conditions, via the choice of more efficient bases is in progress. Reaction (6) appears to be totally stereospecific according to the ^{31}P NMR analysis of the reaction mixture, while two isomers (trans and cis isomers in a 92:8 ratio) are formed from **4b**. The bromo derivatives **10a** and **10b** are assumed to be the trans diequatorial stereoisomers with P(S) C(S) and P(R) C(R) configurations for **10a** and **10b** respectively, as implied by the ^{1}H NMR data of the corresponding P(III) derivatives (see below). The 2-bromo-1-menthyl-3,3,4,4-tetramethylphosphetane oxide **10a** is almost insoluble in pentane and is easily purified by pentane washing of the crude product obtained after extraction of the reaction mixture with dichloromethane. The oxide **10b** was purified by crystallization. More detailed studies are required in order to confirm and to explain the poorer stereoselectivity of reaction (7), with respect to reaction (6) ; the chiral menthyl group bound to phosphorus could be responsible for the different behavior of **4a** with respect to **4b**.

Both scheme 4 and 5 are intended to show a new general methodology for the highly stereoselective functionalization of the ring carbon of phosphetane oxides by electrophilic reagents. The bromo derivatives **10a** and **10b** could be used further, as starting materials for the introduction of nucleophiles into the same cyclic systems. Moreover, the described approach to diastereomerically and optically pure phosphetane oxides will provide an access to a wide range of optically pure phosphines of known stereochemistry, as reduction of phosphetane oxides by the $HSiCl_3$.amine complex is expected to proceed with retention of configuration about the phosphorus atom.[15]

Phosphetane oxides **4a**, **4b**, **6a**, **9a** and **9b** have been reduced to the corresponding phosphetanes by using 2 equivalents of the $HSiCl_3.Et_3N$ complex in benzene at room temperature (scheme 6).



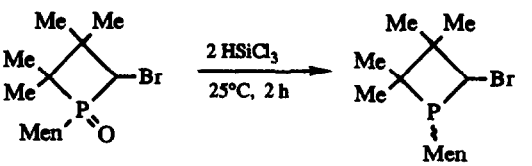
(8)

		$\delta^{31}P$ (C_6D_6)		$\delta^{31}P$ (C_6D_6)
R = R' = H, R" = Me	**4a**	62.7	**11a**	17.6
	4b	57.7	**11b**	8.7
R = CH_2Ph, R' = H, R" = Me	**9a**	68.8	**12a**	32.1
	9b	64.5	**12b**	26.9
R = R' = Me, R" = H	**6a**	67.9	**8a**	48.6

Scheme 6

All reductions are quantitative and totally stereospecific, according to ^{31}P NMR analysis of the crude reaction mixtures. The final products were filtered through a short silicagel column with hexane or hexane-ether (96:4) as eluent, before NMR characterization. Yields ranging form 46% to 80% are obtained after chromatography : these will almost certainly be higher when working on a bigger scale, given the lesser influence of accidental exposure to air during larger scale purification.

The same reducing agent, the $HSiCl_3$, NEt_3 complex, did not give reproducible results when applied to the reduction of the α-bromophosphetane oxides **10a** and **10b** ; a detrimental unfluence of adventitious excess triethylamine seems to be responsible. On the other hand, $HSiCl_3$ reduces the oxide **10a** cleanly to phosphetane **13a**, with the expected retention of the phosphorus configuration (scheme 7). The $HSiCl_3$ reduction of an α-bromophosphetane oxide has already been reported.[16]



(9)

$\delta^{31}P$ (C_6D_6)		$\delta^{31}P$ (C_6D_6)	
10a	64.3	**13a**	45.1
10b	61.7	**13b**	41.4 + **13a** (85:15)

Scheme 7

Under the same reaction conditions, the reduction of **10b** gives a mixture of two isomeric phosphetanes **13b** and **13a** in a 85:15 ratio. **13b** was characterized only by ^1H NMR in a mixture with **13a**. The different behavior of **10a** and **10b** towards $HSiCl_3$ will to be examined more carefully and other reducing agents or conditions will be tested in order to improve stereoselectivity.

Concerning the characterization of the above phosphetanes and phosphetane oxides, the presence of the menthyl group bound to phosphorus makes the complete assignment of the NMR signals somewhat difficult. Nevertheless, most of them have been tentatively assigned by the usual NMR techniques (^1H, ^{31}P decoupling and ^{13}C-DEPT spectra) and by comparison with literature data. The most significant ^1H and ^{13}C NMR data are reported in tables 2 and 3.

Table 2 : Selected ^1H NMR Data for Phosphetane Oxides and P(III) Phosphetanes[a]

Compound	CH_3-7	CH_3-5	CH_3-6	CH_3-8
4a	0.73	0.84 [18.4]	1.15 [16.6]	1.29
4b	0.75	0.93 [16.9]	1.18 [16.1]	1.34
9a	0.72	0.88 [17.5]	1.10 [16.1]	1.33
9b	0.64	0.98 [16.6]	1.16 [15.7]	1.37
10a	0.71	0.74 [17.9]	1.04 [16.2]	1.44
10b	0.70	0.81 [17.0]	1.07 [15.4]	1.46
11a	0.82	1.15 [4.6]	1.13 [15.5]	1.32
11b	0.82	1.22 [4.3]	1.13 [15.5]	1.31
12a	0.72	1.13 [3.5]	1.08 [15.1]	1.26
12b	0.53	1.20 [4.2]	1.07 [15.2]	1.30
13a	0.76	0.92 [4.4]	1.04 [15.1]	1.39
13b	0.77	1.01 [4.0]	1.05 [15.1]	1.40

[a] spectra measured in C_6D_6 ; $\delta[J_{PC}]$: chemical shifts in ppm, coupling constants in Hz
Additional NMR data are given in the experimental section

Table 3 : Selected ^{13}C NMR Data for Phosphetane Oxides and P(III) Phosphetanes[a]

Compound	C-2	C-3	C-4	PCH(Men)
4a	41.7 [51.1]	36.4 [12.3]	49.7 [55.1]	40.3 [43.5]
4b	46.1 [47.4]	38.5 [14.0]	49.2 [58.0]	42.0 [45.5]
9a	52.7 [51.7]	41.8 [11.6]	48.5 [53.6]	40.0 [40.8]
9b	53.4 [48.7]	42.8 [15]	48.1 [56.2]	45.3 [39.5]
10a	51.3 [45.6]	44.5 [6.7]	48.3 [52.6]	41.8 [45.6]
10b	55.2 [40.5]	45.8 [7.7]	47.2 [56.3]	43.7 [45.5]
6a	44.0 [55.1]	47.4 [12.9]	46.7 [55.0]	40.7 [34.2]
11a	37.0 [9]	39.8 (d)[b]	39.4 (d)[b]	37.2 [29.1]
11b	39.9 [16.9]	41.3 (d)	38.9 (d)	39.4 [31.1]
12a	42.5	43.0 [5.3]	36.6 [2.5]	36.0 [31.4]
12b	43.6 [2.9]	44.1 [5.7]	36.7 [4.6]	40.4 [33.4]
13a	53.4 [9.2]	46.2 [9.6]	39.6 [2.9]	38.1 [30.9]
8a	33.8 [2.7]	49.5 [7.2]	35.4 [4.9]	37.6 [34.2]

[a] spectra measured in C_6D_6 ; δ [J_{PC}] : chemical shifts in ppm, J_{PC} coupling constants in Hz
[b] d = unresolved doublet
Additional NMR data are given in the experimental section
In P(III) phosphetanes C3/C4 chemical shifts may be reversed

^1H and ^{13}C NMR spectra have been interpreted on the basis of the known relationships between geometric features and NMR shieldings or couplings.[17]

In phosphetane oxides, the methyl groups attached to α-carbons are strongly coupled to ^{31}P, but the orientation of oxygen has a small influence on $^3J_{PH}$. The methyl assignment is more reliably accomplished on the basis of shielding differences, the methyls cis to oxygen being the more deshielded.

In the P(III) phosphetane serie, the $^3J_{PH}$ coupling constant is controlled by the orientation of the lone pair: greater coupling occurs when the lone pair is cis to the methyl substituent. The same stereospecific effect of the orientation of the lone pair orbital on phosphorus is observed on both $^2J_{PC}$ and $^3J_{PC}$ coupling constants (see experimental section).

In summary, we have shown that P-menthyl phosphetanes are a new class of chiral phosphines, which is easily accessible in an enantiomerically pure form. Highly selective reactions of the phosphorus stabilized phosphetane anion offer a simple way of modifying the phosphorus environment. This will enable us to examine the properties of phosphetanes, as chiral ligands, as a function of electronic or stereochemical changes in the phosphorus environment.

Experimental Section

All manipulations were performed under an argon atmosphere in dry solvents. NMR spectra were recorded on a Bruker AC 200 SY spectrometer operating at 200.13 MHz for ^1H, 50.32 MHz for ^{13}C and 81.01 MHz for ^{31}P. Mass spectra were obtained at 70 eV with a Shimadzu GC-MS QP 1000 instrument by the direct inlet method. The ^{31}P chemical shifts are reported relative to external 85% H_3PO_4.

1-Menthyl-2,2,3,3-tetramethylphosphetane oxide 4a,b

To 3.5g (26.3 mmol) of aluminium chloride in 50 mL of methylene chloride was added at 0°C a solution of 6.0g (25 mmol) of L-menthyl dichlorophosphine[18] in CH_2Cl_2. After about 20 min the solution became homogeneous ; a solution of 2,3,3-trimethyl-1-butene (3.5 mL, 25 mmol) in CH_2Cl_2 was then added at 0°C. The reaction mixture was warmed, stirred at room temperature for 2.5h and then hydrolyzed at 0°C with about 10 mL of distilled water. The organic layer was separated, washed with dilute sodium bicarbonate and with water and finally dried over $MgSO_4$. The final product was purified by column chromatography on neutral alumina with ether as eluent. A 1:1 mixture of phosphetane oxides **4a,b** was obtained (3.4g, 48%). The solid was recrystallized from pentane to give pure **4a** (1.2g). **4b** (0.9g) was obtained from the mother liquor after two recrystallization from pentane. The remaining **4a** and **4b** can be obtained later by further crystallization.

4a : colorless solid ; m.p. 152°C ; ^1H NMR (C_6D_6) δ 0.75 (d, $^3J_{HH}$ = 6.8, Me), 0.86 (d, $^3J_{HH}$ = 6.2, Me), 1.07 (d, $^3J_{HH}$ = 6.7, Me), 1.0-2.0 (m) ; ^{13}C NMR (C_6D_6) δ 17.3 (Me), 18.2 (Me), 21.4 (Me), 22.1 (Me), 22.7 (Me), 24.5 (d, J_{CP} = 10.6, CH_2), 25.5 (d, J_{CP} = 18.4, Me), 26.9 (d, J_{CP} = 4.0, Me), 30.8 (CH), 33.4 (d, J_{CP} = 12.8, CH), 34.1 (CH_2), 34.4 (CH_2), 41.2 (CH); MS m/e 284 (M, 94%), 269 (M-Me, 55%), 146 (M-$C_{10}H_{18}$, 100%); Anal. Calc. for $C_{17}H_{33}OP$: C, 71.79 ; H, 11.69. Found : C, 71.64 ; H, 11.82.

4b : colorless solid ; m.p. 117°C ; ^1H NMR (C_6D_6) δ 0.70 (d, $^3J_{HH}$ = 6.8, Me), 0.83 (d, $^3J_{HH}$ = 6.4, Me), 0.93 (d, $^3J_{HH}$ = 6.7, Me), 1.6 (m, 5H), 2.0 (m, 5H) ; ^{13}C NMR (C_6D_6) δ 16.1 (Me), 18.7 (Me), 20.9 (Me), 21.7 (Me), 22.7 (Me), 24.7 (d, J_{CP} = 10.0, CH_2), 25.1 (d, J_{CP} = 19.3, Me), 26.9 (Me), 28.7 (CH), 33.0 (d, J_{CP} = 12.1, CH), 34.8 (CH_2), 35.0 (CH_2), 42.7 (CH).

1-Chloro-2,2 ,3,4,4-pentamethylphosphetane 7

To a slurry of 7.3g (54.8 mmol) of commercial anhydrous aluminium chloride was added 5.0 mL (50 mmol) of PCl_3. The mixture was cooled to 0°C and 7.8 mL (50 mmol) of 2,4,4-trimethyl 2-pentene were added. After stirring for 2h, a solution of triphenylphosphine (13.1g, 50 mmol) in CH_2Cl_2 was added at 0°C. The mixture was stirred at room temperature for 0.5h and then diluted with pentane. A yellow oil (mostly $Ph_3PCl^+AlCl_4^-$) separated ; the supernatant liquid was removed and stripped of solvent. The residual oil

was distilled in a kugelrohr apparatus at 120°C (20 mm Hg). 7.6g of 7 (85% yield) were obtained as a mixture of two isomers : NMR ^{31}P δ = 170.8 and 150.5 ppm. The ^{1}H NMR spectrum agreed with that already reported (see ref.9).

1-Menthyl-2,2,3,4,4-pentamethylphosphetane oxide 6

MenMgCl was prepared from 0.58g (24 mmol) of magnesium (50 mesh) and 3.8g (22 mmol) of (-) menthyl chloride in THF. The Grignard solution was then added to a stirred solution of 7 (2.0g, 11 mmol) in THF at room temperature. Excess MenMgCl is required and the reaction is completed after about 6h at room temperature. The reaction mixture was hydrolized at 0°C with distilled water, and extracted with ether under argon. Two isomeric menthyl phosphetanes 6 are formed (NMR ^{31}P δ = 49.4 and 48.8 (major isomer) ppm), together with some side-products. The ether solution was allowed to oxidize by exposure to air and then chromatographed on neutral alumina column. Elution with an hexane-ether gradient (from 90:10 to 30:70) afforded 1.0g (32%) of pure 6a (cis isomer).

6a : colorless solid ; m.p. 160°C (pentane) ; ^{1}H NMR (C_6D_6) δ 0.59 (dd, $^{3}J_{HH}$ = 7.2, $^{4}J_{HP}$ = 1.0, PCCHMe), 0.73 (d, $^{3}J_{HH}$ = 6.8, Me), 0.83 (d, $^{3}J_{HH}$ = 6.4, Me), 0.95 (d, $^{3}J_{HP}$ = 17.5, PCMe), 0.99 (d, $^{3}J_{HP}$ = 16.0, PCMe), 1.01 (d, $^{3}J_{HH}$ = 6.0, Me), 1.25 (d, $^{3}J_{HP}$ = 15.6, PCMe), 1.27 (d, $^{3}J_{HP}$ = 15.0, PCMe), 2.20 (qd, $^{3}J_{HH}$ = 7.2, $^{3}J_{HP}$ = 2.3, CHMe) ; ^{13}C NMR (C_6D_6) δ 7.2 (d, J_{CP} = 18.4, CHMe), 17.6 (Me), 18.9 (Me), 19.2 (Me) 22.1 (Me), 23 (unresolved, 2 Me), 23.7 (d, J_{CP} = 3.5, Me), 24.8 (d, J_{CP} = 9.9, CH_2), 30.2 (d, J_{CP} = 2.6, CH), 33.14 (d, J_{CP} = 11.8, CH), 34.7 (2 CH_2), 41.8 (CH) ; MS m/e 298 (M, 79%), 160 (M-$C_{10}H_{18}$, 100%) ; Anal. Calcd. for $C_{18}H_{35}OP$: C, 72.44 ; H, 11.82. Found : C, 72.47 ; H, 12.06.

Alkylation procedure (scheme 4)

nBuLi (0.96 mL, 1.6M solution in hexane, 1.5 mmol) was added to a THF solution of phosphetane oxide **4a** (or **4b**) (0.40g, 1.4 mmol) at -78°C. After a few minutes 0.18 mL (1.5 mmol) of benzylbromide were added. After 15 min at -78°C the reaction mixture was warmed to room temperature and checked by ^{31}P NMR. By starting from the phosphetane oxide **4a** we observed two ^{31}P NMR signals, at δ 74.1 and 71.2 ppm (THF) in a 94:6 ratio. Phosphetane oxide **4b** gave more than 98% of the benzylsubstituted phosphetane with δ ^{31}P = 67.5 ppm (THF). Some starting material is still present in both cases.

After hydrolysis and extraction with ether, the final product was purified by chromatography on alumina with hexane-ether (60:40) as eluent.

4-Benzyl-1-menthyl-2,2,3,3-tetramethylphosphetane oxide 9a

Yield 0.41g (78%) ; colorless solid ; m.p. 146°C (pentane) ; ^{1}H NMR (C_6D_6) δ 0.61 (d, $^{3}J_{HH}$ = 6.1, Me), 0.74 (d, $^{3}J_{HH}$ = 6.6, Me), 1.05 (d, $^{3}J_{HH}$ = 6.7, Me), 1.5 (m, 3H), 1.9 (m, 3H), 2.25 (dt, $^{3}J_{HH}$ = 9.5, $^{3}J_{HH}$ = 5.8, $^{2}J_{HP}$ = 5.8, PCHCH$_2$Ph), 2.73 (AB, J_{AB} = 13.7, $^{3}J_{HH}$ = 5.8, $^{3}J_{HP}$ = 24.7, 1H, CH$_2$Ph), 3.12 (AB, J_{AB} = 13.7, $^{3}J_{HH}$ = 9.5, $^{3}J_{HP}$ = 11.2, 1H, CH$_2$Ph), 7.0-7.2 (m, Ph) ; ^{13}C NMR (C_6D_6) δ 16.9 (J_{CP} = 3.1, Me), 17.2 (Me), 21.8 (Me), 22.1 (Me), 22.2 (Me), 22.6 (Me), 24.3 (J_{CP} = 22.9, Me), 24.5 (J_{CP} = 10.1, CH_2), 29.8 ($^{2}J_{CP}$ = 4.7, CH$_2$Ph), 30.6 (J_{CP} = 2.8, CH), 33.1 (J_{CP} = 12.5, CH), 34.4 (CH_2), 34.6 (CH_2), 41.2 (CH), 141.7 ($^{3}J_{CP}$ = 5.4, C(Ph)) ; MS m/e 375 (M+1, 100%), 359 (M-Me, 33%), 283 (M-PhCH$_2$, 56%), 159 (67%), 91 (PhCH$_2$, 82%) ; Anal. Calcd. for $C_{24}H_{39}OP$: C, 76.96 ; H, 10.50. Found : C, 76.93 ; H, 10.61.

4-Benzyl-1-menthyl-2,2,3,3-tetramethylphosphetane oxide 9b

Yield 0.40g (75%) ; colorless solid : m.p. 159°C (pentane) ; ^{1}H NMR (C_6D_6) δ 0.77 (d, $^{3}J_{HH}$ = 6.6, Me), 0.80 (d, $^{3}J_{HH}$ = 7.7, Me), 0.86 (d, $^{3}J_{HH}$ = 6.8, Me), 1.53 (m, 2H), 1.7 (m, 2H), 2.07 (m, 1H, CHMe), 2.59 (pseudo q, $^{3}J_{HH} \simeq {}^{2}J_{HP} \simeq$ 7.2, PCHCH$_2$Ph), 2.86 (m, AB, J_{AB} = 14.0, $^{3}J_{HH}$ = 7.2, $^{3}J_{HP}$ = 17.4, 1H, CH$_2$Ph), 3.16 (m, AB, J_{AB} = 14.0, $^{3}J_{HH}$ = 7.2, $^{3}J_{HP}$ = 10.9, 1H, CH$_2$Ph), 7.0-7.3 (m, Ph) ; ^{13}C NMR (C_6D_6) δ 15.9 (Me), 18.1 (J_{CP} = 3.6, Me), 21.0 (Me), 21.6 (Me), 22.1 (Me), 22.7 (Me), 24.8 (J_{CP} = 22.1, Me), 25.0 (J_{CP} = 10.5, CH_2), 30.3 (J_{CP} = 4.1, CH), 33.4 (J_{CP} = 12.3, CH), 34.8 (CH_2), 36.2 (CH_2), 43.0 (J_{CP} = 2.7, CH), 141.5 ($^{3}J_{CP}$ = 9.2, C(Ph)) ; MS m/e 374 (M, 30%), 331 (M-C_3H_7, 23%), 290 (M-C_6H_{12}, 100%).

Bromination procedure (scheme 5)

nBuLi (1.38 mL, 2.2 mmol) was added at -78°C to a solution containing 0.30g (1.1 mmol) of phosphetane oxide **4a** (or **4b**) and 0.15 mL (1.1 mmol) of diisopropylamine in THF. After a few minutes, 1,2-dibromoethane (0.27 mL, 3.1 mmol) was added and the reaction mixture was stirred at -78°C for 1h. The reaction mixture was warmed to about 0°C and hydrolyzed with distilled water (some side-products are

formed when the reaction mixture is warmed to room temperature before hydrolysis). After extraction with dichloromethane the organic phase was washed with water and evaporated to dryness to give a colorless solid.

2-Bromo-1-menthyl-3,3,4,4-tetramethylphosphetane oxide 10a

The crude reaction product was washed with pentane in order to remove the unreacted starting material. The remaining solid consisted of pure **10a** (according to ^{31}P NMR). It was recrystallized from a CH_2Cl_2-pentane mixture.

Yield 0.26g (68%) ; colorless solid, m.p. 226°C (dec) ; ^1H NMR (C_6D_6) δ 0.69 (d, $^3J_{HH}$ = 6.9, Me), 0.87 (d, $^3J_{HH}$ = 6.4, Me), 1.00 (d, $^3J_{HH}$ = 6.7, Me), 1.4-2.0 (m), 3.63 (s, CHBr) ; ^{13}C NMR (C_6D_6) δ 17.2 (Me), 18.1 (J_{CP} = 3.1, Me), 21.4 (Me), 22.0 (Me), 22.5 (Me), 22.5 (J_{CP} = 21.4, Me), 24.2 (J_{CP} =11.2, CH_2), 24.7 (Me), 31.3 (J_{CP} = 3.7, CH), 33.3 (J_{CP} =12.3, CH), 33.7 (J_{CP} = 2.7, CH_2), 34.0 (CH_2), 41.0 (J_{CP} = 2.4, CH); MS (^{79}Br) m/e 362 (M, 19%), 283 (M-Br, 100%). Anal. Calcd. for $C_{17}H_{32}BrOP$: C, 56.20 ; H, 8.88. Found : C, 56.83 ; H, 9.12.

2-Bromo-1-menthyl-3,3,4,4-tetramethylphosphetane oxide 10b

The final product was purified by crystallization from a pentane-ether mixture.

Yield 0.20g (52%) ; colorless solid, m.p. 177°C ; ^1H NMR (C_6D_6) δ 0.75 (d, $^3J_{HH}$ = 7.2, Me), 0.79 (d, $^3J_{HH}$ = 6.6, Me), 0.97 (d, $^3J_{HH}$ = 6.7, Me), 1.6 (m, 6H), 1.8 (m, 1H), 2.4 (m, 1H, C<u>H</u>Me$_2$), 4.01 (s, CHBr) ; ^{13}C NMR (C_6D_6) δ 15.9 (Me), 18.9 (J_{CP} = 4.3, Me), 21.1 (Me), 21.7 (Me), 22.5 (J_{CP} = 21.5, Me), 22.6 (Me), 24.4 (J_{CP} = 11.9, CH_2), 24.8 (Me), 30.2 (J_{CP} = 2.8, CH), 33.0 (J_{CP} = 12.8, CH), 34.6 (CH_2), 35.0 (J_{CP} = 2.3, CH_2), 42.0 (J_{CP} = 3.5, CH).

A minor isomer was detected in the reaction mixture : ^{31}P NMR (C_6D_6) δ 64.1 ppm ; ^1H NMR (C_6D_6) δ 4.37 (s, CHBr) ppm.

Reduction procedure (scheme 6 and 7)

The phosphetane oxide (1.0 mmol) was dissolved in dry benzene (10 mL) and triethylamine (2 mmol, 0.28 mL) was added. The mixture was cooled to 5°C and treated with trichloro-silane (0.20 mL, 2 mmol). The solution was warmed to room temperature and monitored by ^{31}P NMR. Reaction times vary between a few minutes (for **4a,b**) to 2.5h (for **9a,b**). The solution was then cooled to 5°C and 20% aqueous sodium hydroxide solution (2 mL) was added dropwise.

The organic layer was directly chromatographed on a short silica gel column with hexane-ether 96:4 as eluent, under argon.

The reduction of the α-bromophosphetane oxides **10a,b** followed the same procedure, without addition of triethylamine.

1-Menthyl-2,2,3,3-tetramethylphosphetane 11a

Yield 0.18g (67%). Air sensitive, colorless solid ; ^1H NMR (C_6D_6) δ 0.78 (d, $^3J_{HH}$ = 6.8, Me), 0.88 (d, $^3J_{HH}$ = 6.5, Me), 0.99 (d, $^3J_{HH}$ = 6.8, Me) ; ^{13}C NMR (C_6D_6) δ 17.1 (Me), 22.7-22.9 (unresolved, 3 Me), 24.3 ($^2J_{CP}$ = 22.7, Me), 25.4 (J_{CP} = 10.0, CH_2), 26.2 (J_{CP} = 4.9, Me), 27.3 ($^3J_{CP}$ = 9.7, Me), 29.7 (CH_2), 30.5 ($^3J_{CP}$ = 11.7, C<u>H</u>Me$_2$), 33.8 ($^3J_{CP}$ = 6.7, C<u>H</u>Me), 35.3 (CH_2), 49.0 ($^2J_{CP}$ = 22.6, C<u>H</u>CHMe$_2$) ; MS m/e 268 (M, 19%), 253 (M-Me, 32%), 212 (Men PCMe$_2$, 44%), 184 (Men P CH_2, 100%).

1-Menthyl-2,2,3,3-tetramethylphosphetane 11b

Yield 0.12g (46%). Air sensitive, colorless solid ; ^1H NMR (C_6D_6) δ 0.76 (d, $^3J_{HH}$ = 6.8, Me), 0.85 (d, $^3J_{HH}$ = 6.4, Me), 0.90 (d, $^3J_{HH}$ = 6.9, Me), 1.54 (<u>A</u>B, $^2J_{AB}$ = 10.9, $^2J_{HP}$ = 18.5, 1H, PCH_2), 1.86 (m, PCH), 1.95 (A<u>B</u>, $^2J_{AB}$ = 10.9, $^2J_{HP}$ = 6.6, 1H, PCH_2) ; ^{13}C NMR (C_6D_6) δ 16.1 (Me), 20.8 (J_{CP} = 4.6, Me), 22.2 (Me), 23.0 (Me), 25.5 ($^2J_{CP}$ = 25.5, Me), 25.4 (CH_2), 25.8 (Me), 27.1 ($^3J_{CP}$ = 10.7, Me), 29.6 ($^3J_{CP}$ = 7.1, C<u>H</u>Me), 33.0 (CH_2), 33.1 ($^3J_{CP}$ = 10.4, C<u>H</u>Me$_2$), 35.5 (CH_2), 48.3 ($^2J_{CP}$ = 13.2, C<u>H</u>CHMe$_2$).

4-Benzyl-1-menthyl-2,2,3,3-tetramethylphosphetane 12a

Yield 0.29g (80%). Colorless solid. ^1H NMR (C_6D_6) δ 0.12 (m, J_{HH} = 13.6, J_{HH} = 12.4, J = 12.4, J = 5.5, 1H), 0.69 (d, $^3J_{HH}$ = 6.3, Me), 0.74 (d, $^3J_{HH}$ = 6, Me), 0.96 (d, $^3J_{HH}$ = 6.8, Me), 1.6 (m, 3H), 1.9 (m, 1H), 2.72 (pseudo q, J ~ 7.3, P<u>C</u>HCH_2Ph), 2.6-2.9 (m, 2H, CH_2Ph), 7.0-7.2 (m, Ph) ; ^{13}C NMR (C_6D_6) δ 16.7 (Me), 22.4 ($^3J_{CP}$ = 10.5, Me), 22.6 (Me), 22.9 (Me), 23.0 (J_{CP} = 7.0, Me), 24.0 ($^2J_{CP}$ = 23.0, Me), 25.1 (J_{CP} = 6.8, Me), 25.4 (J_{CP} = 9.9, CH_2), 29.9 ($^3J_{CP}$ = 14.0, C<u>H</u>Me$_2$), 33.7 ($^3J_{CP}$ = 4.9, C<u>H</u>Me), 35.1 (CH_2), 36.9

($^2J_{CP}$ = 18.2, $\underline{C}H_2Ph$), 37.3 (J_{CP} = 4.5, CH_2), 48.7 ($^2J_{CP}$ = 22.8, $\underline{CH}CHMe_2$), 142.2 ($^3J_{CP}$ = 6.0, C(Ph)) ; MS m/e 358 (M, 15%), 274 (MenPCHCH$_2$Ph, 53%), 212 (MenPCMe$_2$, 79%), 170 (MenP, 100%).

4-Benzyl-1-menthyl-2,2,3,3-tetramethylphosphetane 12b
Yield 0.23g (65%). Colorless solid. ^{1}H NMR (C_6D_6) δ 0.81 (d, $^3J_{HH}$ = 6.8, Me), 0.86 (d, $^3J_{HH}$ = 6.4, Me), 0.88 (d, $^3J_{HH}$ = 6.8, Me), 1.97 (m, J = 2.9, 6.3, 11.4, 11.4, 1H, PCH), 2.6-3.0 (m, 3H, P$\underline{C}H\underline{C}H_2$Ph + PCH$\underline{C}H_2$Ph), 7.0-7.2 (m, Ph) ; ^{13}C NMR (C_6D_6) δ 15.8 (Me), 21.1 (J_{CP} = 4.6, Me), 21.9 ($^3J_{CP}$ = 11.5, Me), 21.9 (Me), 23.0 (Me), 25.2 ($^2J_{CP}$ = 15.3, Me), 25.3 (CH_2), 25.5 (Me), 30.8 ($^3J_{CP}$ = 7.4, $\underline{C}HMe$), 33.4 ($^3J_{CP}$ = 10.1, $\underline{C}HMe_2$), 35.5 (CH_2), 36.2 ($^2J_{CP}$ = 17.7, $\underline{C}H_2Ph$), 39.8 (J_{CP} = 15.1, CH_2), 47.6 ($^2J_{CP}$ = 11.2, $\underline{C}HCHMe_2$), 142.8 ($^3J_{CP}$ = 11.1, C(Ph)).

2-Bromo-1-menthyl-3,3,4,4-tetramethylphosphetane 13a
Yield 0.16g (47%). Colorless solid. ^{1}H NMR (C_6D_6) δ 0.67 (d, $^3J_{HH}$ = 6.8, Me), 0.91 (d, $^3J_{HH}$ = 6.6, 6H, Me), 4.04 (d, $^2J_{HP}$ = 6.4, CHBr) ; ^{13}C NMR (C_6D_6) δ 16.8 (Me), 22.4 (Me), 22.6 (J_{CP} = 4.4, Me), 22.7 (Me), 23.2 (J_{CP} = 5.6, Me), 24.8 ($^2J_{CP}$ = 24.5, Me), 25.1 (J_{CP} = 10.3, CH_2), 25.5 ($^3J_{CP}$ = 11.3, Me), 30.8 ($^3J_{CP}$ = 12.2, $\underline{C}HMe_2$), 33.7 ($^3J_{CP}$ = 6.1, $\underline{C}HMe$), 34.8 (CH_2), 36.2 (J_{CP} = 6.0, CH_2), 48.3 ($^2J_{CP}$ = 22.6, $\underline{C}HCHMe_2$); MS m/e (^{79}Br) 346 (M, 6%), 331 (M-Me, 6%), 303 (M-CHMe$_2$, 21%), 290 (M-C_4H_8, 22%), 267 (M-Br, 87%), 262 (MenPCHBr, 17%), 212 (MenPCMe$_2$, 100%).

2-Bromo-1-menthyl-3,3,4,4-tetramethylphosphetane 13b
Phosphetane 13b was characterized by ^{1}H NMR spectroscopy, in a 85:15 mixture with 13a.13b : ^{1}H NMR (C_6D_6) δ 0.80 (d,$^3J_{HH}$ = 6.1, Me), 0.84 (d, $^3J_{HH}$ = 6.6, Me), 0.97 (d, $^3J_{HH}$ = 6.8, Me), 1.9 (m, 1H, PCH), 2.15 (m, 1H), 4.36 (d, $^2J_{HP}$ = 6.4 Hz, CHBr).

1-Menthyl-2,2,3,4,4-tetramethylphosphetane 8a
Yield 0.25g (90%) ; colorless solid. ^{1}H NMR (C_6D_6) δ 0.73 (dd, $^3J_{HH}$ = 7.2, $^4J_{HP}$ = 0.5, CH $\underline{Me}$), 0.77 (d, $^3J_{HH}$ = 7.0, Me), 0.86 (d, $^3J_{HH}$ = 6.4, Me), 0.96 (d, $^3J_{HH}$ = 6.8, Me), 1.17 (d, $^3J_{HP}$ = 4.7, Me), 1.20 (d, $^3J_{HP}$ = 4.8, Me), 1.23 (d, $^3J_{HP}$ = 17.1, Me), 1.25 (d, $^3J_{HP}$ = 16.6, Me), 1.92 (m, J = 3.3, 7.2, 11.2, $^2J_{HP}$ = 11.2, 1H, PCH), 2.15 (qd, $^3J_{HH}$ = 7.2, $^3J_{HP}$ = 3.7, C$\underline{H}$Me) ; ^{13}C NMR (C_6D_6) δ 8.1 ($^3J_{CP}$ = 12.6, PCCH$\underline{Me}$), 17.8 (Me), 19.8 ($^2J_{CP}$ = 5.3, PCMe), 21.0 ($^2J_{CP}$ = 5.6, PCMe), 22.7 (Me), 23.1 (Me), 25.5 (J_{CP} = 9.1, CH_2), 30.44 (J_{CP} = 7.0, $\underline{C}HMe$), 31.8 ($^2J_{CP}$ = 25.8, PCMe), 33.3 ($^2J_{CP}$ = 25.2, PCMe), 33.2 ($^3J_{CP}$ = 9.2, $\underline{C}HMe_2$), 33.8 ($^1J_{CP}$ = 2.7, P$\underline{C}Me_2$), 35.4 ($^1J_{CP}$ unresolved, P$\underline{C}Me_2$), 35.4 (CH_2), 37.6 ($^1J_{CP}$ = 34.2, PCH), 38.1 (J_{CP} = 13.1, CH_2), 48.8 ($^2J_{CP}$ = 17.8, $\underline{C}HCHMe_2$), 49.5 ($^2J_{CP}$ = 7.2, PC$\underline{C}$HMe) ; MS m/e 282 (M, 5%), 267 (M-Me, 7%), 212 (MenPCMe$_2$, 100%).

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