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Phosphorus Ylide Chemistry Investigated for Dihydrotachysterol$_2$ Metabolite Side-Chain Synthesis The Wittig Approach

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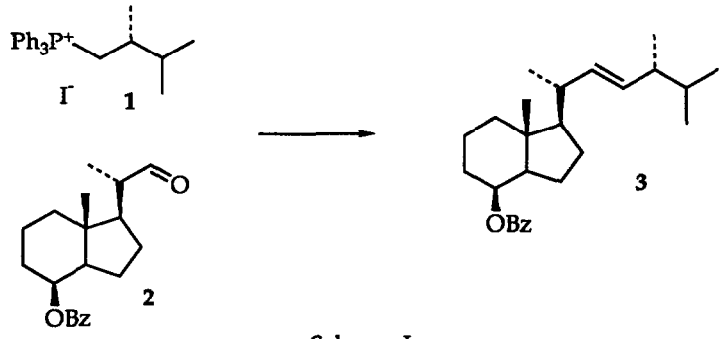
Abstract: The behaviour of the γ-oxido ylide of R-(3-hydroxy-2,3-dimethylbutyl)triphenylphosphonium iodide **4**, *to be used in the 25-hydroxylated DHT$_2$ side-chain synthesis, was studied. The synthesis of the chiral phosponium salt* **4** *was done in an overall yield of 73%. Condensation of the ylide with benzaldehyde afforded the E olefin* **11** *in a 70% yield; no Z isomer was detected. Furthermore, some other useful phosphonium salts were synthesised.*

INTRODUCTION

The Wittig reaction plays a prominent role in natural product synthesis.[1-4] Many of these syntheses make use of the stereospecific behaviour of the condensation of a phosphorus ylide (R_3P^+-C^-HR) with the substrate, usually an aldehyde. In general, "non-stabilised" ylides react with aldehydes to give predominantly Z alkenes, whereas "stabilised" ylides mainly afford E olefines. "Semi-stabilised" ylides usually give no high preference one way or the other.[5] The stereochemistry of these reactions can be influenced by the solvent, temperature, cation, and depends on the type of aldehyde.[6]

The report by Salmond *et al.*,[7] which describes the unusual E stereoselective behaviour of γ-oxido ylides, initiated several synthetic enterprises based on this procedure.[8-11] In the field of vitamin D_2 chemistry, however, the application of the Wittig reaction in the preparation of the side-chain is rather limited. Kocienski and co-workers reported a synthesis of the Windaus and Grundmann's ketone (compound **3** is the protected form of the corresponding alcohol) in which they attempted the use of the Wittig reaction in the preparation of the side-chain (scheme I).[12]



Scheme I.

However, their synthesis of the requisite phosphonium salt **1** did only partially succeed, and therefore this method of side-chain preparation was not further investigated.

As we are interested in 25-hydroxydihydrotachysterol$_2$ and some of its derivatives, a study on phosphonium salt synthesis, and their stereoselective behaviour in the condensation with a model substrate (benzaldehyde) was initiated.

RESULTS and DISCUSSION

The phosphonium salt, needed for the synthesis of 25-hydroxylated DHT$_2$, is depicted in figure 1 (compound **4**). The preparation of target compound **4** was thought to be possible by using the commercially available S-(+)-methyl 2-methyl-3-hydroxypropanoate.

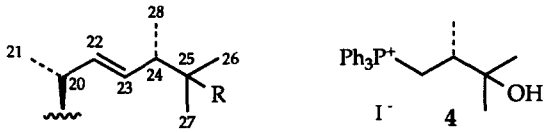
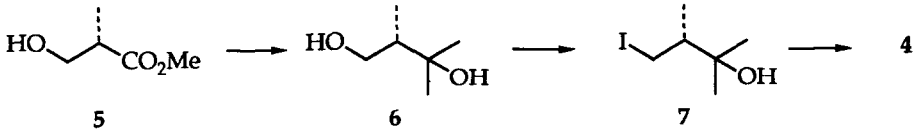


Figure 1.

The starting material already contains the C^{24} stereogenic centre (the DHT$_2$ side-chain is also depicted in figure 1 for convenience). A straightforward reaction scheme was conceived (scheme II). A reaction path somewhat similar to scheme II is mentioned in a 1989 European patent.[13] In this case, however, a sulfone is prepared instead of a phosphonium salt, and the *E* C^{22}-C^{23} double bond is introduced via a sulfone addition[12] and a Julia elimination[14] process.



Scheme II.

The preparation of diol **6** was carried out by treating ester **5** with 3 equivalents of MeMgBr, *without* the prior protection of the primary hydroxy group.[13] In order to verify the enantioselectivity of the reaction the acetate of the primary hydroxy group of **6** was prepared. It showed a satisfactory rotation (see experimental section).[15] The iodine was introduced via the tosylate of the primary hydroxy group of diol **6**. The conversion of the intermediary iodide **7** into the corresponding phosphonium salt was thought to be the most challenging part of the route.[12] We made several attempts using various solvents. A phosphonium salt was formed indeed, but NMR spectroscopy showed that the compound was the dehydrated phosphonium salt **8**.

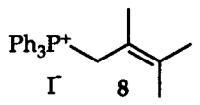


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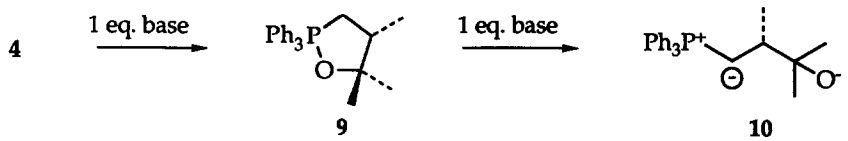
Figure 2.

In the literature a synthesis of a phosphonium salt analogous to our target compound was reported.[11] We tried the same reaction conditions. Target compound **4** was isolated in a reasonable yield, but side-product **8** was still present (about 25%). When the reaction was carried out with 8 equivalents of triphenylphosphine, phosphonium salt **4** was isolated in quantitative yield. The overall yield of the synthesis, starting from ester **5**, is 73%. The crystal structure of compound **4** confirmed the expected absolute configuration of the C^{24} stereogenic centre.[16]

The Wittig reaction with our phosphonium salt was explored under a variety of conditions with benzaldehyde as the model substrate. To examine the formation of the phosphorus ylide ^{31}P NMR spectroscopy was used. The phosphonium salt was suspended in dry THF, after which BuLi (2 equivalents) was added. Addition of the first equivalent of BuLi gave a signal in the pentavalent phosphorus region, namely at -62 ppm. This indicates the formation of an oxaphospholane (**9**).[17,18] Oxaphospholane **9** was synthesised by us separately[17] and fully characterised.



9 **10**

Scheme III.

The reaction with the second equivalent of BuLi was much slower; after four hours oxaphospholane **9** was still present according to ^{31}P NMR. An explanation for this rather sluggish reaction might be that the CH_2 moiety in the oxaphospholane ring (figure 3 is a 3D presentation of the possible structure)[19] is, to some extent, shielded off from the BuLi aggregate.

Since BuLi reacts with THF at room temperature,[20] the temperature of the reaction mixture had to be kept below 0°C. Both above mentioned reasons might be the cause (among others) of the observed sluggish reaction.

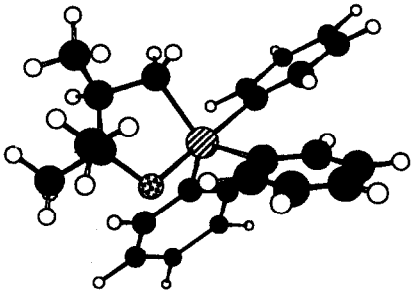


Figure 3.

The ylide appeared on the ^{31}P NMR spectrum as a multitude of peaks between 18 and 23 ppm. A similar ^{31}P NMR behaviour for γ-oxido ylide Ph_3P^+-$C^-H(CH_2)_2O^-Li^+$ has been observed by Maryanoff *et al.*.[18] This suggests that, when the ylide and oxido centres are in close proximity, a variety of slowly (on the NMR time-scale) interconverting structures exist, possibly as a result of variously interacting aggregates.[18] The condensation with benzaldehyde was sluggish. Olefin **11** was obtained in a low yield. No Z isomer was isolated, and triphenylphosphine was retrieved.

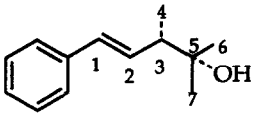


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Figure 4.

In order to improve these results, some other solvents and bases were tested. Major progress was obtained in diethyl ether when MeLi (1.6 M (0.4% LiCl) in diethyl ether) was used. The ylide was formed within 2.5 h at room temperature, as was observed with ^{31}P NMR (the spectrum differed considerably from the ^{31}P spectrum taken in THF, *vide infra*). Although MeLi is a weaker base than BuLi, it forms a smaller aggregate[21] which might be an explanation for the observed improvement, considering the rationale of the "shielded" CH_2 moiety of **9**. The condensation reaction in ether with benzaldehyde was extremely fast and afforded the E olefin (**11**) in a 70% yield. Again no Z isomer was observed.

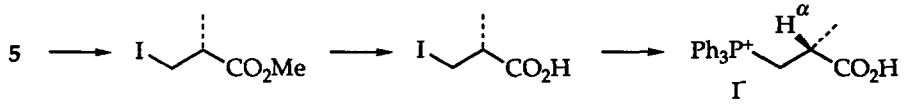
The ^{31}P NMR spectrum of the diethyl ether solution of the ylide was quite different (a broad singlet at 22 ppm) from the ^{31}P spectrum of the ylide dissolved in THF (a multitude of peaks between 18 and 23 ppm). The ylide was therefore generated in ether as well as in THF, either with BuLi or MeLi. The ^{31}P NMR spectra were recorded and they exhibited the expected characteristics. Ether was replaced by THF, and the ylide appeared as a multitude of peaks between 18 and 23 ppm. This experiment was repeated with the ylide generated in THF. Replacement of THF by ether resulted in a broad singlet at 22 ppm. When an ylide solution in THF was heated in the NMR probe the multiplet between 18 and 23 ppm changed into the broad singlet at 22 ppm. These observations support the idea of the interconverting ylide aggregate

structures,[18] which, apparently, are stabilised better in THF than in diethyl ether.

As described in our earlier report,[22] the actual condensation of ylide **10** with aldehyde **2** proceeded successfully; only the *E* isomer was observed and was isolated in a 45-50% yield.

The Wittig reaction proved to be a valuable tool for the stereoselective introduction of a 25-hydroxylated side-chain. This result spurred us on to investigate other types of ylides reported to induce high *E* stereoselectivities, and which are suitable for DHT_2 metabolite side-chain synthesis. This survey was done in order to devise a phosphonium salt comparable to **4** which, on condensation with aldehyde **2**, would render a DHT_2 analogue suitable for the introduction of a radioactive moiety.

Phosphorus ylides containing a carboxylate moiety are reported to induce an unusually high *E* stereoselectivity in reaction with aldehydes.[18] Ester **5** was used as the starting compound again. The ester group, however, had to be left intact in the first two steps of the reaction path (the formation of the tosylate of the primary hydroxy group (98%) of ester **5**, followed by the conversion of the tosylate moiety into the iodide **12** (85%)), as the free carboxylic acid would compete with the primary hydroxy group. Once the iodide was synthesised, the cleavage of the ester was performed with Me_3SiCl and NaI in acetonitrile.[23] The ester **12** was cleaved in a 90% yield, and compound **14** was synthesised quantitatively.



12 **13** **14**

Scheme IV.

Treatment of phosphonium salt **14** with all kinds of bases in different solvents all resulted in a fast triphenylphosphine elimination. Presumably deprotonation at the α-carbon atom had taken place. Published methods for the generation of β-carboxy ylides did not seem suitable to us[2,24] and therefore we decided to develop an alternative approach.

To prevent the abstraction of the α-proton a sterically hindered base was evaluated. For this purpose lithium 2,2,6,6-tetramethylpiperidide (LTMP) was used (prepared from TMP and BuLi in THF at -80°C). LTMP was added to a THF suspension of compound **14** at -20°C (in ether a fast triphenylphosphine elimination was observed), after which the temperature of the reaction mixture was allowed to rise *slowly* to 20°C. No pentavalent phosphorus compound (compare **9**) was observed.[25] The ylide appeared on the ^{31}P NMR as numerous peaks between 5 and 45 ppm. Condensation with benzaldehyde afforded **15** in a 70% yield. No *Z* isomer was observed.

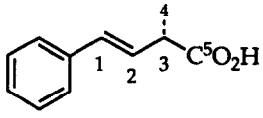


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Figure 5.

Phosphonium salt **14** is under current investigation in the coupling with aldehyde **2**. The synthesis of phosphonium salt **1** was also considered. rac-2,3-Dimethyl-1-butanol was used as the starting material. The rac-phosphonium salt **1** was synthesised in the same way as **4** in a 80% overall yield. We are currently trying to reproduce the original ideas of Kocienski *et al.* in the preparation of compound **3**.[12]

EXPERIMENTAL SECTION

Glassware was dried with the flame while being evacuated. All reactions were carried out under nitrogen with magnetic stirring. Standard Schlenk techniques were used where mentioned. Solvents were freshly distilled before use from the appropiate drying agents. Column chromatography was performed on SiO_2. Proton NMR spectra were recorded at 300 MHz on a Bruker AC300 spectrometer with $CDCl_3$ as solvent and internal standard, chemical shifts being reported as ppm downfield from Me_4Si. Coupling constants *J* are reported in Hz. Carbon-13 NMR spectra were obtained on a Bruker AC300 at 75.4 MHz with $CDCl_3$ as solvent and internal standard. Phosphorus-31 NMR spectra were recorded at 80.9 MHz on a Bruker AC200 spectrometer; chemical shifts are referenced to 85% H_3PO_4 (external). Mass spectroscopy (FAB) was performed on a Jeol-JMS-AX505W mass spectrometer with a Hewlett-Packard 9000 data system.

S-2,3-Dimethyl-1,3-butanediol 6

A solution of S-(+)-methyl 2-methyl-3-hydroxy propanoate **5** (23.6 g, 0.2 mol) in 100 ml of ether was added to an diethyl ether solution (750 ml) of 0.7 mol of MeMgBr while keeping the temperature between 15°C and 23°C. Occasional cooling with an ice bath was necessary. After completion of this addition the reaction mixture was stirred for an additional 2 h at room temperature. Ice, and an aqueous HCl solution (5%) were added until the water layer was pH4. The aqueous layer was continuously extracted with ether during 24 h, and the extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The product was distilled at reduced pressure (0.1 mm Hg, 72°C) to afford **6** in a 87% yield (20.5 g); n_D^{20}=1.4460. The acetate of the primary hydroxy group of diol **6** had a specific rotation of $[\alpha]_D$ -27.6°.[15] ^1H NMR (proton numbering as in compound **4**, table 2): δ 4.18 (2H's, broad s, 2 OH's), δ 3.62 (2H's, m, H^1 and H^2), δ 1.74 (1H, m, H^3), δ 1.18 (3H's, s, CH_3^5 or CH_3^6), δ 1.11 (3H's, s, CH_3^5 or CH_3^6), δ 0.78 (3H's, d, CH_3^4, $^3J_{4\text{-}3}$=7.10); ^{13}C NMR (carbon numbering as in compound **4**, table 1): δ 74.4 (C^4), δ 65.8 (C^1), δ 43.7 (C^2), δ 29.4 (C^5 or C^6), δ 23.8 (C^5 or C^6), δ 12.9 (C^3).

The 1-tosylate of diol 6

Diol **6** (20.5 g, 0.174 mol) was dissolved in 200 ml of pyridine. The solution was cooled to -15°C, and tosyl chloride (35.3 g, 0.185 mol) was added. The reaction mixture was kept in the refrigerator (-4°C) for 14 h. Addition of ice resulted in a suspension, which was thoroughly extracted with ether (5×40 ml). The combined organic extracts were washed with water, 5% aqueous HCl solution, and water (2 times, 20 ml each), and dried over $MgSO_4$. Removal of the ether *in vacuo*

afforded the primary mono-tosylate in a 98% yield (46.5 g, 0.171 mol) as a viscous oil. ^{13}C NMR (carbon numbering as in compound **4**, table 1): δ 144.7 (C^{ar}_{ipso}-SO_3R), δ 132.7 (C^{ar}_{ipso}-CH_3), δ 129.7 ($2C^{ar\,2}$ or $2C^{ar\,3}$), δ 127.7 ($2C^{ar\,2}$ or $2C^{ar\,3}$), δ 72.6 (C^1), δ 71.7 (C^4), δ 43.2 (C^2), δ 28.3 (C^5 or C^6), δ 25.8 (C^5 or C^6), δ 21.5 ($CH_3{}^{ar}$), δ 12.9 (C^3).

R-4-Iodo-2,3-dimethyl-2-butanol 7

The tosylate (46.5 g, 0.171 mol) was added to a LiI (26.8 g, 0.2 mol, anhydrous) solution in THF (350 ml). The clear solution was heated under reflux for 15 min. The resulting yellow suspension was filtered off, and the residue was thoroughly washed with ether. The organic solution was washed with a saturated aqueous NH_4Cl solution and dried over $MgSO_4$. The solvents were removed *in vacuo* to give compound **7** in a 85% yield (33.2 g, 0.146 mol). ^{13}C NMR (carbon numbering as in compound **4**, table 1): δ 73.0 (C^4), δ 47.5 (C^2), δ 28.4 (C^5 or C^6), δ 25.0 (C^5 or C^6), δ 16.0 (C^1), δ 11.1 (C^3).

R-(+)-(2,3-Dimethylbutyl)triphenylphosphonium iodide 4

The iodide **7** (33.2 g, 0.146 mol) was added to a solution of triphenylphosphine (314.4 g, 1.2 mol) in 1000 ml of acetonitrile. The mixture was heated under reflux during 40 h. The acetonitrile was subsequently removed *in vacuo* to give a white solid. Diethyl ether was added (500 ml) and the resulting slurry was stirred for 2 h in order to dissolve the triphenylphosphine. Filtration afforded a sticky white solid which was again stirred with ether (500 ml) for 2 h. This procedure was repeated until a fine white powder remained. This powder was filtered off, and the filtrate was dried *in vacuo* yielding the pure phosphonium salt **4** quantitatively (71.0 g, 0.145 mol). The overall yield of the phosphonium salt synthesis is 73%. Specific rotation $[\alpha]_D$= +6.85°. Comprehensive NMR data are given in table 1 and 2. MS, *m /e* 363 (M^+-I^-, 100), 345 (40), 303 (35), 262 (50), 185 (40), 108 (30), 59 (35).

R-(+)-4,5,5-Trimethyl-2,2,2-triphenyl-1,2-oxaphospholane 9

Phosphonium salt **4** (1,96 g, 0.004 mol) was added to a NaH (0.12 g, 0.005 mol) suspension in THF (25 ml; the NaH was washed 5 times with pentane to remove the oil). H_2 gas immediately evolved from the suspension, and the reaction mixture became clear. During 1 h the THF solution was heated under reflux. A small amount of grey solid precipitated. The THF was removed *in vacuo*, and to the remaining solid dry hexane was added. The suspension was filtered under N_2, and a clear colourless solution was obtained. After evaporation of the hexane, an off-white sticky solid remained (crystallisation failed). The oxaphospholane was obtained quantitatively (1.42 g, 0.0039 mol). Specific rotation $[\alpha]_D$= +49.14°. For NMR data see table 1 and 2.

rac-(2,3-Dimethylbutyl)triphenylphosphonium iodide 1

This compound was prepared in the same manner as phosphonium salt **4**, starting with commercially available rac-2,3-dimethyl-1-butanol. The overall yield of this three step synthesis was

80%. The spectroscopic details of the phosphorus compound are presented in table 1 and 2. MS *m /e* 347 (M^+-I^-, 100), 303 (5), 262 (8), 183 (10), 108 (5), 91 (4), 43 (5).

R-(+)-(2-Carboxypropyl)triphenylphosphonium iodide 14

S-(+)-methyl 2-methyl-3-hydroxypropanoate **5** was used as the starting compound for this synthesis. The primary hydroxy group was converted into an iodide as described for compound **7** in a 83% yield. R-methyl 3-iodo-2-methylpropanoate (6.0 g, 0.026 mol) was subsequently added to a suspension of dry NaI (15.6 g, 0.104 mol) in acetonitrile (150 ml), after which trimethylsilyl chloride (11.3 g, 0.104 mol) was added. A fine white precipitate (NaCl) was formed immediately. The reaction mixture was heated under reflux for 85 h. Subsequently, water was added (50 ml) at room temperature. The resulting clear solution was stirred for another 2 h. Ether (3×50 ml) was added to extract the reaction mixture. Subsequently, the combined ether layers were washed with a small amount of brine (10 ml) and an equally small amount of a 15% aqueous $Na_2S_2O_8$ solution to remove the iodine. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. This yielded the pure R-3-iodo-2-methylpropanoic acid in 90% (5.0 g, 0.023 mol).
^{1}H NMR (proton numbering as in compound **14**, table 2): δ 7.86 (1H, broad s, H^7), δ 3.36 (1H, q, H^1, $^2J_{1-2}$= 9.94, $^2J_{1-3}$= 6.44), δ 3.25 (1H, q, H^2, $^2J_{2-1}$= 9.97, $^3J_{2-3}$= 6.12), δ 2.81 (1H, s, H^3, $^3J_{3-1}$= 6.45, $^3J_{3-2}$= 6.24, $^3J_{3-4}$= 6.95), δ 1.29 (3H, d, CH_3^4, $^3J_{4-3}$= 7.00); ^{13}C NMR (carbon numbering as in compound **14**, table 1): δ 179.8 (C^4), δ 41.9 (C^2), δ 17.9 (C^3), δ 6.0 (C^1).

The synthesis of the carboxy acid phosphonium salt was done in the same way as described for phosphonium salt **4**. The remaining white reaction product was washed with diethyl ether until phosphonium salt **14** persisted as a fine white powder. The phosphorus compound was obtained in a quantitative yield (10.9 g, 0.023 mol). Specific rotation $[\alpha]_D$= +2.01°. NMR details are depicted in table 1 and 2. MS *m /e* 349 (M^+-I^-, 95), 307 (25), 289 (15), 183 (10), 154 (100), 136 (70), 107 (25), 77 (20), 65 (10).

Ylide Formation from Phosphonium Salt 4

Phosphonium salt **4** (0.98 g, 0.002 mol) was suspended in THF or diethyl ether (5 ml of the appropiate solvent) in a 25 ml Schlenk vessel, after which 2 equivalents of the base (BuLi or MeLi) were added at -20°C. The temperature of the reaction mixture was allowed to rise slowly to 20°C (in the case of THF-BuLi 0°C). Stirring was continued for 2.5 h at room temperature.

Ylide Formation from phosphonium Salt 14

Phosphonium salt **14** (0.95 g, 0.002 mol) was suspended in THF (5 ml) in a 25 ml Schlenk vessel, after which 2 equivalents of lithium 2,2,6,6-tetramethylpiperidide (LTMP) in THF were slowly added at -20°C. LTMP was prepared in dry THF by adding an equimolar amount of BuLi to a solution of TMP at -80°C and stirred for 30 min at -50°C. A yellow suspension was formed. The temperature of the reaction mixture was allowed to rise *slowly* to room temperature, and the yellow suspension changed to a clear solution with a dark red colour over a period of 3 h.

^{31}P NMR Spectroscopic Experiments

The ylides (0.001 mol) were prepared as described above in a smaller amount of solvent (1 ml of the appropiate solvent). The red ylide solutions were carefully transferred into a 5-mm NMR tube (under N_2) containing dry C_6D_6 as the deuterated solvent. The ^{31}P NMR spectrum was examined under broad-band proton decoupling conditions. The THF ylide solution (made from phosphonium salt **4**) was heated in the probe to investigate the behaviour of the postulated interconverting ylide aggregate structures at elevated temperatures. The probe was heated to a maximum of 323 K.

Wittig Reaction of the Ylide from Phosphonium Salt 4 with Benzaldehyde

The ylide (0.002 mol) was prepared in diethyl ether from **4** and 2 equivalents of MeLi in 2.5 h as described above. At -30°C benzaldehyde (0.21 g, 0.002 mol), dissolved in 1 ml ether, was added, immediately dissipating the red ylide colour. The resulting cream coloured reaction mixture was stirred for 1 h at -20°C. Subsequently, the suspension temperature was allowed to rise to 20°C, after which stirring was continued for an additional 20 h. Water (10 ml) and a 2.5% aqueous HCl solution were added until pH4. The water layer was thoroughly extracted with ether. The organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed on silica gel (25% EtOAc/hexane) affording the expected *E* olefin **11** in a 70% yield (0.27 g, 0.0014 mol). ^{1}H NMR (the numbering is indicated in figure 4): δ 7.50-7.00 (5H, m, H^{ar}), δ 6.45 (1H, d, H^1, $^3J_{1\text{-}2}$= 15.90), δ 6.21 (1H, dd, H^2, $^3J_{2\text{-}1}$= 15.87, $^3J_{2\text{-}3}$= 8.74), δ 2.37 (1H, m, H^3, $^3J_{3\text{-}2}$= 8.78, $^3J_{3\text{-}4}$= 6.88), δ 1.75 (1H, broad s, OH), δ 1.24 (3H, s, CH_3^6 or CH_3^7), δ 1.22 (3H, s CH_3^6 or CH_3^7), δ 1.14(3H, d, CH_3^4, $^3J_{4\text{-}3}$= 6.90). ^{13}C NMR (the numbering is depicted in figure 6): δ 137.3 (C^{ar}_{ipso}), δ 132.1 (C^{ar}_{para} or C^2), δ 131.2 (C^{ar}_{para} or C^2), δ 128.5 ($2C^{ar}_{meta}$), δ 127.1 (C^1), δ 126.1 ($2C^{ar}_{ortho}$), δ 72.6 (C^5), δ 48.6 (C^3), δ 27.0 (C^6or C^7), δ 26.8 (C^6 or C^7), δ 15.4 (C^4).

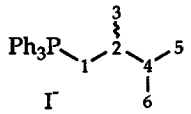
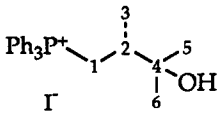
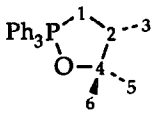
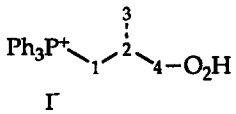
Wittig Reaction of the Ylide from Phosphonium Salt 14 with Benzaldehyde

The ylide (0.002 mol) was prepared from **14** with 2 equivalents of lithium 2,2,6,6-tetramethylpiperidide (dissolved in THF) as described above. At -30°C benzaldehyde (0.21 g, 0.002 mol), dissolved in 1 ml THF, was added, causing an instantaneous dissipation of the red ylide colour. After 1 h the temperature of the resulting yellow suspension was allowed to rise to room temperature, and stirred for an additional 20 h. Water (10 ml), and an aqueous HCl solution (2.5%) were added until pH4. The solution was extracted thoroughly with ether, and the ether layers were dried over $MgSO_4$. The solvents were removed under reduced pressure affording a residue that was chromatographed on SiO_2 (50% EtOAc/hexane). *E* olefin **15** was obtained in a 70% yield (0.24 g, 0.0014 mol). ^{1}H NMR (the numbering of the protons is indicated in figure 4): δ 8.68 (1H, broad s, COOH), δ 7.50-7.00 (5H, m, H^{ar}), δ 6.56 (1H, d, H^1, $^3J_{1\text{-}2}$= 15.99, δ 6.33 (1H, dd, H^2, $^3J_{2\text{-}1}$= 15.93, $^3J_{2\text{-}3}$= 7.89), δ 3.39 (1H, quintet, H^3, $^4J_{3\text{-}1}$= 0.97, $^3J_{3\text{-}2}$= 7.84, $^3J_{3\text{-}4}$= 7.04), δ 1.44 (3H, d, CH_3^4, $^3J_{4\text{-}3}$= 7.04); ^{13}C NMR (the numbers of the carbon atoms are depicted in figure 5): δ 180.9 (C^5), δ 136.6 (C^{ar}_{ipso}), δ 131.6 (C^2), δ 128.3 (C^{ar}_{para} or C^1), δ 127.9 ($2C^{ar}_{meta}$), δ 127.6 (C^{ar}_{para} or C^1), δ 126.3 ($2C^{ar}_{ortho}$), δ 43.0 (C^3), δ 17.2 (C^4).

Wittig Reaction of the Ylide from Phosphonium Salt 4 with aldehyde 2

The ylide from phosphonium salt **4** (4.9 g, 0.01 mol) was made as described above. The aldehyde **2** (2.4 g, 0.0075 mol), dissolved in ether, was added to the ylide at -40°C, causing an instantaneous dissipation of the red ylide colour, after which the reaction mixture was stirred at -40°C for 2 h. The resulting yellow suspension was stirred for an additional 20 h at room temperature. Water and an aqueous HCl solution (2.5%) were added until pH4. The resulting mixture was thoroughly extracted with ether, and the combined ether layers were dried over $MgSO_4$. The solvents were removed under reduced pressure affording a yellow coloured residue, which was chromatographed on SiO_2 with 20% EtOAc/hexane. The desired compound was isolated in a 45% yield (1.3 g, 0.0034 mol). ^1H NMR (conventional steroid numbering is used): δ 8.04 (2H, m, H^{ar}), δ 7.45 (3H, m, H^{ar}), δ 5.39 (1H, broad s , H^{8}), δ 5.31 (1H, m, H^{22} and H^{23}), δ 2.1 (4H, m), δ 1.9-1.4 (11H, m), δ 1.14 (3H, s, CH_3^{26} or CH_3^{27}), δ 1.12 (3H, s, CH_3^{26} or CH_3^{27}), δ 1.05 (3H, s, CH_3^{18}), δ 1.03 (3H, d, CH_3^{21} or CH_3^{28}, ^3J= 6.6), δ 0.98 (3H, d, CH_3^{21} or CH_3^{28}, ^3J= 6.9); ^{13}C NMR (conventional steroid numbering is used): δ 166.3 (Ph-(C=O)-OR), δ 138.4 (C^{23}), δ 132.6 (C^{ar}_{para}-COOR), δ 130.7 (C^{ar}_{ipso}-COOR), δ 129.4 (C^{ar}_{ortho}-COOR), δ 129.3 (C^{22}), δ 128.2 (C^{ar}_{meta}-COOR), δ 72.1 (C^{25}), δ 72.0 (C^{8}), δ 56.0 (C^{17}), δ 51.5 (C^{14}), δ 47.9 (C^{24}), δ 41.7 (C^{13}), δ 39.8 (C^{12} or C^{20}), δ 39.7 (C^{12} or C^{20}), δ 30.4 (C^{9}), δ 27.4 (C^{16}), δ 26.7 (C^{26} or C^{27}), δ 26.5 (C^{26} or C^{27}), δ 22.5 (C^{15}), δ 20.5 (C^{21}), δ 17.9 (C^{11}), δ 15.4 (C^{28}), δ 13.6 (C^{18}).

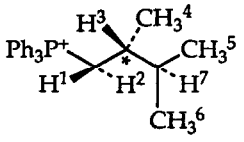
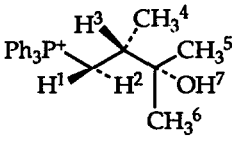
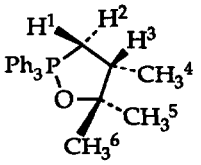
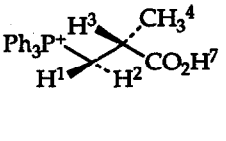
Table 1. ^{31}P and ^{13}C NMR Data of the Phosphorus Compounds

Compound	**1**	**4**	**9**	**14**
				
P [a]	24.6	24.1	-61.6	23.4
C^1 [b]	27.7 ($^1J_{C\text{-}P}$: 48.9)[c]	24.5 ($^1J_{C\text{-}P}$: 51.5)	37.8 ($^1J_{C\text{-}P}$: 95.5)	26.0 ($^1J_{C\text{-}P}$: 52.3)
C^2	33.7 ($^2J_{C\text{-}P}$: 4.2)	38.8 ($^2J_{C\text{-}P}$: 4.3)	39.2 ($^2J_{C\text{-}P}$: 5.3)	34.8 ($^2J_{C\text{-}P}$: 3.2)
C^3	15.9 ($^3J_{C\text{-}P}$: 4.4)	16.1	15.8 ($^3J_{C\text{-}P}$: 23.1)	20.1 ($^3J_{C\text{-}P}$: 12.1)
C^4	33.2 ($^3J_{C\text{-}P}$: 10.9)	72.7 ($^3J_{C\text{-}P}$: 11.8)	74.3	175.6 ($^3J_{C\text{-}P}$: 4.2)
C^5	19.9[d]	28.6[d]	29.2[d] ($^4J_{C\text{-}P}$: 2.9)	-
C^6	16.9[d]	22.9[d]	24.1[d]	-
C^{ar}_{ipso}	118.2 ($^1J_{C\text{-}P}$: 85.4)	118.0 ($^1J_{C\text{-}P}$: 85.5)	148.3 ($^1J_{C\text{-}P}$: 101.0)	117.3 ($^1J_{C\text{-}P}$: 86.1)
C^{ar}_{ortho}	133.3 ($^2J_{C\text{-}P}$: 9.9)	133.0 ($^2J_{C\text{-}P}$: 10.0)	[e]	133.6 ($^2J_{C\text{-}P}$: 10.2)

$C^{ar}{}_{meta}$	130.3 ($^3J_{C\text{-}P}$: 12.4)	129.8 ($^3J_{C\text{-}P}$: 12.5)	e	130.4 ($^3J_{C\text{-}P}$: 12.6)
$C^{ar}{}_{para}$	134.9 ($^4J_{C\text{-}P}$: 2.9)	134.3 ($^4J_{C\text{-}P}$: 2.9)	e	135.2 ($^4J_{C\text{-}P}$: 2.9)

[a] δ values in ppm are referenced to 85% H_3PO_4 (external). [b] δ values in ppm downfield to $SiMe_4$, and $CDCl_3$ as solvent and internal standard (77.01 ppm), except for compound 8 (C_6D_6 as solvent and internal standard, 128.03 ppm). [c] *J* values in Hz. [d] These values may be interchanged. [e] No positive assignment could be made. Five signals are observed at 131.9 ppm, 131.7 ppm, 127.5 ppm, 127.4 ppm, and at 127.3 ppm.

Table 2. ^{1}H NMR Data of the Phosphorus Compounds.

	1	4	9	14
				
H^{1} [a]	3.38 (m)	4.23 (dd $^2J_{1\text{-}2}$: 15.60 $^2J_{1\text{-}P}$: 15.60)[b]	2.71 (m $^2J_{1\text{-}2}$: 17.88 $^2J_{1\text{-}P}$: 16.07)	3.85 (m $^2J_{1\text{-}2}$: 12.16 $^2J_{1\text{-}P}$: 13.26)
H^2	3.38 (m)	2.73 (m $^2J_{2\text{-}1}$: 15.60 $^2J_{2\text{-}3}$: 9.85 $^2J_{2\text{-}P}$: 15.60	2.32 (m $^2J_{2\text{-}1}$: 17.82	3.64 (m $^2J_{2\text{-}1}$: 12.18 $^2J_{2\text{-}P}$: 13.28)
H^3	1.79 (m $^3J_{3\text{-}4}$: 6.81)	2.03 (m $^3J_{3\text{-}2}$: 9.82 $^3J_{3\text{-}4}$: 6.84 $^3J_{3\text{-}P}$: 16.32	2.02 (m $^3J_{3\text{-}4}$: 6.75)	3.10 (m $^3J_{3\text{-}4}$: 7.11)
H^4	0.73 (d $^3J_{4\text{-}3}$: 6.81)	0.46 (d $^3J_{4\text{-}3}$: 6.84)	0.86 (dd $^3J_{4\text{-}3}$: 6.80 $^4J_{4\text{-}P}$: 1.05	1.40 (dd $^3J_{4\text{-}3}$: 7.11 $^4J_{4\text{-}P}$: 1.52)
H^5	0.84 (d $^3J_{5\text{-}7}$: 6.73)[c]	1.24 (s)[c]	0.94 (s)[c]	-
H^6	0.79 (d $^3J_{6\text{-}7}$: 6.76)[c]	1.20 (s)[c]	0.92 (s)[c]	-
H^7	1.67 (m $^3J_{7\text{-}5}$: 6.73 $^3J_{7\text{-}6}$: 6.76)	3.80 (s broad)	-	8.77 (s broad)
H^{ar}	7.73 (m 15H's)	7.83 (m 6H's) 7.67 (m 9H's)	7.49 (m 6H's) 7.02 (m 9H's)	7.70 (m 15H's)

[a] δ values in ppm downfield to $SiMe_4$, and $CDCl_3$ as solvent and internal standard (7.26 ppm), except for compound 8 (C_6D_6 as solvent and internal standard, 7.16 ppm). [b] *J* values in Hz. Some values were determined with ^{1}H homonuclear decoupling NMR. The proton-phosphorus coupling constants corresponded with values reported in: Gorenstein, D. G. *Prog. NMR Spectr.* **1983**, *16*, 1-98. [c] Values may be interchanged. * The phosphonium salt consists of both the R and the S enantiomers.

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