UNUSUAL COURSE OF THE REACTION OF ALLYL PHOSPHINE OXIDES WITH THE GRUNDMANN KETONE

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GRAPHICAL ABSTRACT

Abstract This article describes efficient preparation of isomeric allyl phosphine oxides possessing a protected cyclohexanediol fragment. Their base-catalyzed interconversions are examined and reactions with the Grundmann ketone provide an adduct containing the rearranged vinyl phosphine oxide moiety, instead of 19-norvitamin D₃ analogs, the expected products of the Horner–Wittig process.

Keywords Allyl phosphine oxide; Grundmann ketone; vinyl phosphine oxide

INTRODUCTION

Since its discovery in 1954[1] the Wittig reaction has been considered as one of the most versatile methods of alkene synthesis.[2–4] Compared to other related Wittig-type olefinations, the Horner variant of this process[5–7] was particularly
useful and found numerous applications in the controlled synthesis of 1,3-dienes as well as other conjugated polyenic systems. Allyl phosphine oxides are relatively readily accessible compounds, their metallation easily occurs at low temperatures (−78 °C), and the high nucleophilicity of the generated anions facilitates their subsequent reaction with the carbonyl compounds. The elimination of lithium phosphinate by-product occurs below room temperature and, as a consequence, such Horner–Wittig reactions usually proceed smoothly, providing the conjugated dienes in good yield with complete retention of configuration of the double bonds present in the substrates.[8,9] Therefore, this useful carbonyl olefination method was commonly applied in the syntheses of polyene isoprenoids and other polyunsaturated compounds. Besides, in the past four decades it has become one of the most frequently utilized synthetic approaches for the construction of the intercyclic 5,7-diene unit (B-seco ring) of the vitamin D derivatives.[10–12]

The method was developed by Lythgoe et al., who prepared the allyl phosphine oxide 1 (Fig. 1) as the A-ring fragment and coupled its lithio anion with the Windaus–Grundmann ketone 3 (C/D ring synthon) to give, after hydroxyl deprotection, vitamin D₃ (8).[13] An analogous approach, condensation of the lithiated phosphine oxide 2 with the protected hydroxy ketone 4, was used by Hoffmann–La Roche chemists as the final step of their total synthesis of 1α,25-dihydroxyvitamin D₃ (calcitriol, 9),[14] and later it was utilized by many other research groups for the preparation of related compounds.[12] Because, not surprisingly, the Horner–Wittig method was also successfully applied during the preparation of 19-nor-calcitriol

![Figure 1. Structures of vitamin D₃ (8), calcitriol (9), and 19-norcalcitriol analogs and the building blocks for their syntheses.](image-url)
(10; coupling of 6 and 4)\textsuperscript{15} and its numerous analogs,\textsuperscript{16} we have decided to use this process for the planned synthesis of 1α,25-dihydroxy-6-methyl-19-norvitamin D\textsubscript{3} (11). The required synthons for this convergent synthesis would be the phosphine oxide 7 and the known bicyclic ketone 5.\textsuperscript{17} We were encouraged by the literature data indicating that anions of allyl phosphine oxides possessing alkyl substituents at β-carbon (trisubstituted double bond) react with aldehydes and ketones in a normal fashion yielding the corresponding hydroxy phosphine oxides as the primary products.\textsuperscript{18,19}

**RESULTS AND DISCUSSION**

The synthesis of the A-ring fragment 7 started from the transformation of the known ketone 12 (Scheme 1), being easily accessible from the commercial (1R,3R,4S,5R)-(-)-quinic acid,\textsuperscript{15} to the unsaturated aldehyde 13 using the method elaborated by Corey.\textsuperscript{20} The reduction of the latter gave the allyl alcohol 14, which was subsequently converted via a three-step reaction sequence: tosylation, followed by treatment with diphenylphosphine anion and hydrogen peroxide oxidation, into the desired phosphate oxide 7. However, the attempted Horner–Wittig coupling of its anion, generated with n-butyllithium, with the Grundmann ketone 5, did not provide the expected protected 19-norvitamin D\textsubscript{3} analog 16. Instead, the polar product was obtained and investigated by spectroscopic methods supported by molecular modeling. The structure 15 of the synthesized product was established by mass spectrometry (MS), infrared (IR), and \textsuperscript{1}H and \textsuperscript{13}C measurements; NMR signal assignments were assisted by nuclear Overhauser effect (NOE) difference, correlation spectroscopy (COSY), heteronuclear single quantum coherence (HSQC), spin decoupling experiments, and inspecting the couplings to \textsuperscript{31}P. Because the mass spectrum of the obtained compound was characterized by molecular ion at \textit{m/z} 978, corresponding to the molecular formula of C\textsubscript{57}H\textsubscript{99}O\textsubscript{5}P\textsubscript{3}Si\textsubscript{3}, and the IR spectrum revealed absorption bands at 3476, 3313 cm\textsuperscript{-1}, indicating a presence of a hydroxy group, the structure of adduct should be considered as hydrindanol fragment with attached phosphine oxide moiety. In the \textsuperscript{1}H NMR spectrum, the chemical shift of the single

![Scheme 1. Synthesis of the allyl phosphine oxide 7 and its reaction with the Grundmann ketone 5.](image-url)
olefinic proton signal at δ 5.93 and magnitude of its coupling to $^{31}$P ($^2J_{P,H-3'''} = 25.9$ Hz) strongly supported vinyl phosphine oxide structure.[21] Two doublets at 1.95 and 2.74 ($J \sim 12$ Hz) and a broad triplet at 3.31 ($J = 12.0$ Hz) can be assigned to the allyl protons at C-1" and C-1"", respectively (Fig. 2). Large vicinal couplings of the latter indicate its axial disposition[22] and, therefore, existence of one strongly favored conformation of the silylated cyclohexanediol ring. A strong shift to the one chair conformer is also evident from the comparison of vicinal coupling constants of the multiplets at δ 4.21 (1H, br s) and 4.03 (tt, $J = 10.5, 4.2$ Hz), derived from the equatorially and axially,[22] respectively, oriented hydrogens from the oxygen bearing C-3"" and C-5"". E-Configuration of the double bond was established by the $^1$H NOE difference experiment involving irradiation of olefinic H-3"". In addition to strong enhancement (14%) of the signal derived from the phenyl ring protons, smaller enhancements (8%, 2%, and 2%) of the signals originating from the protons located at C-2"" and C-6"" were also observed.

The structure of the product 15 indicated that instead of the allyl anion A, the rearranged allyl anion B participated in the nucleophilic attack on the carbonyl group of 5. To further explore this subject it seemed reasonable to synthesize the isomeric allyl phosphine oxide 23 (Scheme 2) and examine its reaction with the Grundmann ketone. The $\alpha,\beta$-unsaturated ester 17, prepared from the cyclohexanone 12, served as the starting material. Catalytic hydrogenation of the double bond in 17 gave the saturated ester 18 that was subsequently $\alpha$-methylated and then $\alpha$-phenylselenated.
to form the compound 20 as an epimeric mixture. The selenoxide elimination was accomplished by the treatment of 20 with 30% \( \text{H}_2\text{O}_2 \) in the presence of a catalytic amount of acetic acid\[^{23}\] to form the \( \alpha,\beta \)-unsaturated ester 21. The obtained ester was reduced to the allyl alcohol 22, which was in turn transformed into the desired phosphine oxide 23.

Attempted Horner–Wittig reaction of the Grundmann ketone 5 with the lithiated compound 23 furnished the same product that was obtained when the isomeric phosphine oxide 7 was used (Scheme 3). This result is obviously a consequence of deprotonation of the phosphine oxide 23 and formation of an allyl anion B that adds its less hindered \( \gamma \)-end to the carbonyl group of the Grundmann ketone.
Formulation of such anions was confirmed in separate experiments involving treatment of the phosphine oxides 7 and 23 with n-butyllithium, followed by addition of water (Scheme 3). The obtained equilibrium mixtures were composed of the starting material and the rearranged vinyl phosphine oxide 24 (8:1 and 1:8, respectively). Undoubtedly, the phosphine oxide 7 after its treatment with n-BuLi is first converted to the anion A, which is probably too hindered to react with the ketone 5. Instead, this anion can then detach a proton from another molecule, forming the vinyl phosphine oxide 24, which after deprotonation is converted to the anion B. Finally, the less hindered end of the latter anion attacks the carbonyl group from the less hindered side of the hydrindanone molecule, providing the adduct 15.

Furthermore, we have observed that an excess of n-BuLi (1.82 eq) used in the reaction of the phosphine oxide 23 with the ketone 5 resulted in formation of epimeric compounds 25a and 25b (Scheme 4), having a stereogenic center at phosphorus atom.[24]

EXPERIMENTAL

Optical rotations were measured in chloroform using a Perkin-Elmer 241 polarimeter at 24°C. Infrared spectra were recorded on a Perkin-Elmer FT-IR Spectrum 2000 spectrophotometer in KBr or CHCl₃. Ultraviolet spectra were obtained on a Perkin-Elmer Lambda 3B ultraviolet–visible (UV-vis) spectrophotometer in 100% ethanol (EtOH). The ¹H and ¹³C nuclear magnetic resonance spectra were taken on Varian Unity Plus 200 MHz, Bruker DMX 500, and Varian 700 Active Shield spectrometers in deuteriochloroform. Chemical shifts are reported downfield to Me₄Si (δ 0.00) as an internal standard. High-resolution mass spectra were recorded on LCT (TOF) or Mass Quattro LC spectrometers. High-performance liquid chromatography (HPLC) was performed on a Waters Associates liquid chromatograph equipped with a model 486 tunable absorbance detector or Shimadzu UFLS liquid chromatograph equipped with SPD-20A tunable absorbance detector.

2-[(3’R,5’R)-3’,5’-Bis[(tert-butyldimethylsilyl)oxy]cyclohexylidene]-propionaldehyde (13)

LDA (2 M; 0.42 mmol, 0.21 mL) was slowly added to a solution of TMSCH(CH₃)CH=N-t-Bu (83 mg, 0.42 mmol) in anhydrous THF (4 mL) under
argon at 0 °C. The reaction was stirred at this temperature for 30 min and then cooled to −78 °C. A solution of the cyclohexanone 12 (100 mg, 0.28 mmol) in anhydrous THF (4 mL) was siphoned into the reaction flask. The reaction was allowed to reach −20 °C during 4 h and then quenched with water. Solid oxalic acid was added to bring the pH value to 4.5, and stirring was continued for 30 min. The reaction mixture was poured into brine and extracted with ether. The organic extracts were washed with diluted NaHCO₃ and brine, dried (MgSO₄), and evaporated to give an oily residue, which was purified by flash chromatography. Elution with hexane/ethyl acetate (95:5) gave the semisolid 13 (102 mg, 92%).

2-[(3′R,5′R)-3′,5′-Bis[tert-butyldimethylsilyloxy]cyclohexylidene]propan-1-ol (14)

Diisobutylaluminum hydride (1 M in toluene; 16.43 mmol, 16.43 mL) was slowly added to a stirred solution of the aldehyde 13 (0.90 g, 2.26 mmol) in toluene/methylene chloride (2:1, 15 mL) at −78 °C under argon. Stirring was continued at −78 °C under argon for 2 h. The mixture was quenched by slow addition of potassium sodium tartrate (2 N, 4 mL), aqueous HCl (2 N, 4 mL), and water (16 mL) and then diluted with methylene chloride (30 mL) and extracted with methylene chloride. The organic layers were washed with diluted (ca. 1%) HCl and brine, dried (Na₂SO₄), and evaporated. The residue was purified by flash chromatography. Elution with hexane/Et₂O (96:4) gave the semicrystalline allylic alcohol 14 (877 mg, 97%).

[2-[(3′R,5′)-3′,5′-Bis[tert-butyldimethylsilyloxy]cyclohexylidene]propyl]-diphenyl-phosphine oxide (7)

n-BuLi (1.6 M; 1.46 mmol, 0.91 mL) was added to a solution of the alcohol 14 (531 mg, 1.33 mmol) in anhydrous THF (9 mL) under argon at 0 °C. Freshly recrystallized tosyl chloride (254 mg, 1.33 mmol) was dissolved in anhydrous THF (1 mL) and added to the solution of the alcohol and n-BuLi. The mixture was stirred at 0 °C for 15 min. In another dry flask, n-BuLi (1.6 M; 2.65 mmol, 1.66 mL) was added to Ph₂PH (2.65 mmol, 0.46 mL) in anhydrous THF (4 mL) under argon at 0 °C with stirring. The red solution was siphoned under argon pressure (ca. one-half of the solution was added). The resulting mixture was stirred at 0 °C for an additional 2 h and quenched by addition of one drop of water. Solvents were evaporated off under reduced pressure, and the residue was redissolved in methylene chloride (4 mL) and stirred with 10% H₂O₂ (0.8 mL) at 0 °C for 1 h. The organic layer was separated, washed with cold aqueous sodium sulfite and water, dried (MgSO₄), and evaporated. The residue was purified by flash chromatography. Elution with hexane/Et₂O (96:4) gave the semicrystalline phosphine oxide 7 (628 mg, 81%).

(1R,4R,7aR)-4-[(E)-2""-[(3""R,5""R)-3"",5""-Bis[tert-butyldimethylsilyloxy]-cyclo-hexyl]-3""-[(diphenyl-phosphinoyl)-allyl]-1-[(R)-1',5'-dimethyl-5""-[(triethylsilyloxy)-hexyl]-7a-methyl-octahydro-inden-4-ol (15)

n-BuLi (1.6 M; 0.19 mmol, 0.12 mL) was slowly added to a solution of the phosphine oxide 7 (103 mg, 0.18 mmol) in anhydrous THF (4 mL) under argon at
0°C. The solution turned deep orange. The mixture was cooled to −78°C, and a precooled solution of the protected hydroxy ketone 5 (62 mg, 0.16 mmol) in anhydrous THF (0.5 mL) was slowly added. The mixture was stirred under argon at −78°C for 1 h and at 0°C for 18 h. Ethyl acetate was added, and the organic phase was washed with brine, dried (MgSO4), and evaporated. The residue was purified by flash chromatography with hexane/Et2O (6:4) as an eluent. Final purification was achieved by HPLC (9.4 mm × 25 cm Zorbax-Sil column, 4 mL/min) using the hexane/ethyl acetate (9:1) solvent system. The adduct 15 was collected at Rv 34 mL (129 mg, 76%).

2-[(3'R,5'R)-3',5'-Bis[(tert-butyldimethylsilyl)oxy]cyclohexylidene]acetlic Acid Methyl Ester (17)

LDA (2 M; 3.88 mmol, 1.94 mL) was slowly added to a solution of TMSCH2COOMe (4.08 mmol, 0.67 mL) in anhydrous THF (18 mL) under argon at −78°C and stirred for 30 min. A solution of the cyclohexanone 12 (500 mg, 1.94 mmol) in anhydrous THF (12 mL) was siphoned into the reaction flask. The reaction was allowed to reach −40°C during 2 h, poured into brine, and extracted with ether. The combined organic extracts were dried (MgSO4) and evaporated to give an oily residue which was purified by flash chromatography. Elution with hexane/Et2O (98:2) gave the semisolid 17 (566 mg, 98%).

[(3'R,5'R)-3',5'-Bis[(tert-butyldimethylsilyl)oxy]cyclohexyl]-acetic Acid Methyl Ester (18)

Pd/C (10%, 49 mg) was added to a solution of the α,β-unsaturated ester 17 (490 mg, 1.18 mmol) in ethyl acetate under argon. Argon was removed and the reaction was stirred under hydrogen for 6 h, when the next portion of a catalyst was added. The reaction mixture was stirred for 19 h, and the suspension was filtered through a small pad of silica, washed with ethyl acetate, and concentrated. The residue was purified by flash chromatography. Elution with hexane/Et2O (98:2) gave the ester 18 (48 mg, 99%) as a colorless oil.

2-[(3'R,5'R)-3',5'-Bis[(tert-butyldimethylsilyl)oxy]cyclohexyl]-propionic Acid Methyl Ester (19)

LDA (2 M; 0.62 mmol, 0.31 mL) was added to a solution of the compound 18 (200 mg, 0.48 mmol) in anhydrous THF (3 mL) under argon at −78°C. The solution was warmed to −40°C and, after 30 min, N,N'-dimethylpropylene urea (DMPU) (0.58 mmol, 0.07 mL) was added. The reaction was allowed to reach −20°C and stirred at this temperature for 1 h. Then it was cooled to −78°C and methyl iodide (4.8 mmol, 0.30 mL) was added. The reaction mixture was allowed to reach −20°C during 1 h, stirred at this temperature for 2 h, poured into 0.1 N HCl, and extracted with ether. The organic extracts were washed with diluted NaHCO3 and brine, dried (MgSO4), and evaporated to give an oily residue, which was purified by flash chromatography. Elution with hexane/Et2O (99:1) gave the ester 19 (194 mg, 94%; mixture of epimers) as a colorless oil.
2-[(3'R,5'R)-3',5'-Bis[(tert-butyldimethylsilyl)oxy]cyclohexyl]-2-phenylselenyl-propionic Acid Methyl Ester (20)

LDA (2 M; 0.32 mmol, 0.16 mL) was added to a solution of the compound 19 (96 mg, 0.22 mmol) in anhydrous THF (1 mL) under argon at −78 °C. The solution was warmed to −40 °C and after 30 min DMPU (0.27 mmol, 0.032 mL) was added. The reaction was allowed to reach −20 °C and stirred at this temperature for 1 h. Then it was cooled to −78 °C and diphenyl diselenide (0.27 mmol, 51 mg) was added. The reaction mixture was allowed to reach −20 °C during 1 h and stirred at this temperature for 4 h, poured into 0.1 N HCl, and extracted with ether. The organic extracts were washed with diluted NaHCO₃ and brine, dried (MgSO₄), and evaporated to give a yellow oily residue, which was purified by flash chromatography. Elution with hexane/Et₂O (99.5:0.5) gave 20 (98 mg, 75%) as an oily mixture of epimers.

2-[(3'R,5'R)-3',5'-Bis[(tert-butyldimethylsilyl)oxy]cyclohexyl]acrylic Acid Methyl Ester (21)

Hydrogen peroxide (30%, 0.09 mL) was added to a solution of the phenylselenyl compound 20 (72 mg, 0.12 mmol) in THF (1 mL) containing acetic acid (0.02 mL) at 0 °C. The mixture was stirred for 1 h, poured into cold saturated sodium bicarbonate solution, and extracted with ether. The combined organic extracts were washed with brine, dried (MgSO₄), and evaporated to give an oily residue, which was purified by flash chromatography. Elution with hexane/Et₂O (99:1) gave the ester 21 (44 mg, 84%) as a colorless oil.

2-[(3',5'R)-3',5'-Bis[(tert-butyldimethylsilyl)oxy]cyclohexyl]prop-2-en-1-ol (22)

Diisobutylaluminum hydride (1 M in toluene; 0.43 mmol, 0.43 mL) was slowly added to a stirred solution of the ester 21 (0.026 g, 0.06 mmol) in toluene/methylene chloride (2:1, 1.5 mL) at −78 °C under argon. Stirring was continued at −78 °C under argon for 2 h. The mixture was quenched by slow addition of potassium sodium tartrate (2 N, 2 mL), aqueous HCl (2 N, 2 mL), and water (8 mL), then diluted with methylene chloride (12 mL), and extracted with methylene chloride. The organic layers were washed with diluted (ca. 1%) HCl and brine, dried (MgSO₄), and evaporated. The residue was purified by flash chromatography. Elution with hexane/Et₂O (96:4) gave semicrystalline allyl alcohol 22 (24 mg, 96%).

2-[(3',5'R)-3',5'-Bis[(tert-butyldimethylsilyl)oxy]cyclohexyl]prop-2-en-1-ol diphenyl-phosphine Oxide (23)

n-BuLi (1.6 M; 0.058 mmol, 0.036 mL) was added to a solution of the alcohol 22 (21 mg, 0.053 mmol) in anhydrous THF (0.5 mL) under argon at 0 °C. Freshly recrystallized tosyl chloride (11 mg, 0.057 mmol) was dissolved in anhydrous THF (0.5 mL) and added to the alcohol-n-BuLi solution. The mixture was stirred at 0 °C for 15 min. In another dry flask n-BuLi (1.6 M; 0.11 mmol, 0.07 mL) was added to Ph₂PH (18.3 µL, 0.105 mmol) in anhydrous THF (2 mL) under argon at 0 °C with
stirring. The red solution was siphoned under argon pressure (ca. one-half solution was added). The resulting mixture was stirred at 0°C for an additional 2h and quenched by addition of one drop of water. Solvents were evaporated under reduced pressure, and the residue was redissolved in methylene chloride (1mL) and stirred with 10% H2O2 (0.2mL) at 0°C for 1h. The organic layer was separated, washed with cold aqueous sodium sulfite and water, dried (MgSO4), and evaporated. The residue was purified by flash chromatography. Elution with hexane/ethyl acetate (6:4) gave semicrystalline phosphine oxide 23 (26mg, 84%).

\[ [2\{(3'R,5'R)-3',5'-Bis\{[\text{tert-butyldimethylsilyl}]oxy\}-cyclohexyl\}prop-1-en]diphenyl-phosphine \text{Oxide (24)} \]

\( n\)-BuLi (1.6 M; 0.027 mmol, 0.017 mL) was slowly added to a solution of phosphine oxide 23 (10mg, 0.017 mmol) in anhydrous THF (0.5mL) under argon at 0°C. The solution turned orange. The mixture was stirred under argon at 0°C overnight. Ethyl acetate was added, and the organic phase was washed with brine, dried (MgSO4), and evaporated. The residue was purified by HPLC (9.4mm × 25cm Zorbax-Sil column, 4mL/min). Elution with hexane/ethyl acetate (6:4) gave 1:8 mixture of the starting material (Rv 18mL) and the rearranged phosphine oxide 24 (Rv 19mL).

\( [1R,4R,7aR]-4\{[E]-2\{(3''R,5''R)-3'',5''-Bis\{[\text{tert-butyldimethylsilyl}]oxy\}-cyclohexyl\}3''-((\text{diphenyl-phosphinoyl}-allyl)-1\{(R)-1',5'-dimethyl-5'\{(\text{triethylsilyl})oxy\}-hexyl\}-7a\text{-methyl-octahydro-inden-4-ol (15)} \]

The reaction of the protected hydroxy ketone 5 with an anion of the phosphine oxide 23, generated with \( n\)-BuLi, was performed as described for the analogous reaction of the isomeric phosphine oxide 7. The crude product was purified by flash chromatography to give the adduct 15 in 66% yield.

\( [1R,4R,7aR]-4\{[E]-2\{(3''R,5''R)-3'',5''-Bis\{[\text{tert-butyldimethylsilyl}]oxy\}-cyclohexyl\}3''-((\text{butyl-phenyl-phosphinoyl})-allyl)-1\{(R)-1',5'-dimethyl-5'\{(\text{triethylsilyl})oxy\}-hexyl\}-7a\text{-methyl-octahydro-inden-4-ol (25a and 25b)} \]

\( n\)-BuLi (1.6 M; 0.062 mmol, 0.039 mL) was slowly added to a solution of phosphine oxide 23 (33mg, 0.056 mmol) in anhydrous THF (0.5mL) under argon at 0°C. The solution turned deep orange. After 5 min, the next portion of \( n\)-BuLi (1.6 M; 0.04 mmol, 0.025mL) was added, the mixture was cooled to −78°C, and a precooled solution of the protected hydroxy ketone 5 (33mg, 0.084 mmol) in anhydrous THF (0.5mL) was slowly added. The mixture was stirred under argon at −78°C for 1h and at 0°C for 18h. Ethyl acetate was added, and the organic phase was washed with brine, dried (MgSO4), and evaporated. The residue was purified by flash chromatography. Elution
with hexane/Et$_2$O (6:4) gave epimeric compounds $25a$ (13 mg, 24%) and $25b$ (14 mg, 26%).

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**SUPPORTING INFORMATION**

Supplemental data for this article can be accessed on the publisher’s website.

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