Efficient Synthesis of the A-Ring Phosphine Oxide Building Block Useful for 1α,25-Dihydroxy Vitamin D₃ and Analogues

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The 1α-hydroxy A-ring phosphine oxide 1, a useful building block for vitamin D analogues, was synthesized from (S)-carvone in nine synthetic operations and a single chromatographic purification in 25% overall yield. The synthesis features two novel efficient synthetic transformations: the Criegee rearrangement of α-methoxy hydroperoxyacetate 10 in methanol to obtain directly the desired secondary 3β-alcohol 11 and the highly chemo- and stereoselective isomerization of dienoate ester (E)-7 to the 1α-allylic alcohol with an exocyclic double bond (E)-8. Further insight into the selectivity control of the latter rearrangement was obtained from the reactions of (Z)-epimeric substrates. The new synthetic approach leading to the 1α-hydroxy epimers complements our previously reported synthesis of the corresponding 1β-epimers, thus producing all stereoisomers of these versatile building blocks efficiently from carvone.

Introduction

The hormonally active metabolite of vitamin D₃, 1α,25-dihydroxy vitamin D₃ (3),¹ has a broad spectrum of potent biological activities that spreads across several important therapeutic areas such as dermatology, metabolic diseases, oncology, and autoimmune diseases.² However, 3 is also a regulator of calcium homeostasis causing dose-limiting hypercalcemia and related side effects, which have thus far restricted its clinical use. The search for structural analogues with attenuated calcemic effect and improved target selectivity has led to increased synthetic activity in the field.³ Through these efforts a number of practical synthetic routes have been developed, mostly starting from steroid precursors or vitamin D₃.⁴ More recently, however, extensive modifications of the side chain and the CD-ring portion of the molecule have led to new structures, which diverge significantly from the natural motif and so cannot be easily derived from natural precursors.⁵ Hence, in many cases the classic approaches have become impractical and an efficient de novo synthesis of such analogues is highly desirable.

The known total syntheses are inherently convergent on the basis of the final coupling of the A-ring and the CD-ring fragments, which are separately synthesized.⁶ Thus, a versatile and reliable method was pioneered by Lythgoe⁷ that proceeded by the direct construction of the conjugated triene system with complete stereoselectivity² via Wittig–Horner coupling of the A-ring phosphine oxide 1⁸ with a CD-ring ketone of type 2 (Scheme 1).⁹ Subsequently, this modular approach has been applied consistently for the synthesis of a multitude of analogues with modified CD-rings and side chains while retaining the natural A-ring fragment intact by using the phosphine oxide building block 1.¹⁰

Unfortunately, however, the known preparations of 1 are long and tedious, discouraging the practical application...


(2) (a) 1st International Conference on Chemistry and Biology of Vitamin D Analogues, Steroids-Special Issue 2001, 60, 127-472; (b) Vitamin D Endocrine System: Structural, Biological, Genetic and Clinical Aspects; Norman, A. W.; Bouillon, R., Thomassen, M., Eds.; University of California Riverside: Riverside, CA, 2000; (c) Vitamin D, Chemistry, Biology and Clinical Applications of the Steroid Hormone; Norman, A. W.; Bouillon, R., Thomassen, M., Eds.; University of California Riverside: Riverside, CA, 1997; (d) Bouillon, R.; Okamura, W. H.; Norman, A. W. Endocrine Rev. 1995, 16, 200.


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Scheme 1

bond. Instead, it requires several additional steps, multiple chromatographic purifications, and use of Martin’s sulfurane for the dehydration.

As previously reported,14 we have devised a very efficient isomerization of the epoxide moiety of the respective 1β-dieneoxide (E)-ester to the corresponding dienol using palladium catalysis. Thus, we anticipated that if an efficient synthesis of the requisite 1α-dieneoxide (E)-7 could be achieved, its palladium-catalyzed isomerization would directly give the desired dienol (E)-8.

Herein, we report a new, very efficient process for the preparation of the key building block 1 that minimizes intermediate isolation and purification steps.

Results and Discussion

The 1α-dieneoxide 7 was expediently obtained from 1α-carvone oxide 9 without intermediate purification, as outlined in Scheme 3.

The stereoselective epoxidation of (S)-carvone has been previously described, leading to 9 as the major diastereomer, in 89% yield.15 Nevertheless, following the known procedure, we had to use a large excess of 3 equiv of 30% hydrogen peroxide and 0.5 equiv of sodium hydroxide in methanol at temperatures from −15 °C to 0 °C to effect complete reaction. The low reaction temperature is required as the product slowly decomposes under these strongly basic reaction conditions. To reduce the amounts of oxidant and base, tert-butyl hydroperoxide was examined as a substitute for hydrogen peroxide. It was found that only 1.22 equiv of 70% aqueous tert-butyl hydroperoxide and 0.1 equiv of 25% sodium methoxide in methanol as the base source were needed to complete the reaction and obtain cleanly the ca. 15−20:1 mixture of diastereomers in 94% yield. The desired product, 9, was then isolated in 80% yield by low-temperature (below −30 °C) crystallization from hexane,16 resulting in essentially complete removal of the minor 1β-isomer.


(16) At ambient temperature 9 is a yellow oil, as its mp is below 0 °C.
The subsequent Criegee rearrangement\textsuperscript{17} of peracetoate 10 was key to the successful oxidative cleavage of the isopropenyl group in 9 to unmask the requisite 3β-alcohol. Ozonolysis of 9 at −70 °C in the presence of methanol and in situ acetylation of the hydroperoxide intermediate 15 gave crude peracetoate 10, which could be used directly for the Criegee rearrangement.

As it is not desirable to isolate these unstable intermediates, the one-pot process required considerable optimization. Excess methanol is necessary during the ozonolysis to trap the short-lived carbonyl oxide intermediate 14, which is formed via retro 1,3-dipolar cycloaddition from ozonide 13. In the absence of methanol, 14 undergoes recombination with formaldehyde to give the thermally more stable ozonide 16. However, since excess methanol would interfere with the subsequent acylation of 15 to 10, it is beneficial to minimize the amount of methanol in the process. It was found that clean formation of 15 could be achieved with only 4 equiv of methanol in dichloromethane. When methanol was further reduced to 3 equiv the reaction was not as clean presumably due to competitive formation of ozonide 16, leading to formation of the corresponding methyl ketone as a major byproduct.

The hydroperoxide 15 thus obtained was acetylated in situ at −5 °C with 7 equiv each of acetic anhydride and triethylamine in the presence of a catalytic amount of DMAP. Acetylation at a higher temperature (e.g., at room temperature) gave a product of a much darker color. The reaction was quenched with methanol at a low temperature and extracted with hexane. The extracts were washed to remove acidic and basic byproducts, which are otherwise detrimental in the subsequent rearrangement step.

Crude peracetoate 10 thus obtained could then be used advantageously for the Criegee rearrangement, after solvent exchange, without further purification. Indeed, the stereospecific rearrangement of peracetoate 10 proceeded cleanly in methanol at 37 °C to give directly the desired secondary alcohol 11. Remarkably, alcohol 11 was the single product isolated, even at a lower temperature of 20 °C, and its acetate was never observed when the reaction was run in methanol. In contrast, with nonpolar aprotic solvents such as dichloromethane or chloroform, the reaction was sluggish and produced a complex mixture of products.

The rearrangement of related α-methoxy hydroperoxyacetates has been previously carried out in aprotic solvents such as dichloromethane,\textsuperscript{18} where the corresponding acetate of the alcohol product was obtained predominantly upon prolonged reflux. The alcohol, usually the minor product under these conditions, was produced from hydrolysis of the acetate on aqueous workup. Thus, it has been postulated that a dioxonium ion intermediate such as 17 should suffer demethylation by nucleophilic attack of its acetate counterion to generate the acetate of the alcohol, and methyl acetate as a byproduct.

In methanol, however, the transient intermediate 17 should be swiftly trapped to produce acetic acid and orthoacetate 18 instead, which would then rapidly un-
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dego acetic acid-catalyzed methanolysis to yield cleanly alcohol 11 along with trimethyl orthoacetate as the byproduct. A substantial rate acceleration in methanol should normally result from the stabilization of the highly polarized transition state leading to the dioxonium ion 17 in this polar solvent.

Indeed, 1H NMR analysis of a reaction run in deuteriomethanol (CD3OD) revealed the clean formation of 11, without accumulation of intermediates, while producing three additional singlet peaks. These peaks were assigned to CH3OD (δ 3.35 ppm, originating from the methoxy group in 10), CH3CO2H (δ 1.99 ppm, originating from the acetoxy group in 10), and CH3CO(OCD3) (δ 1.40 ppm). As a reference, trimethyl orthoacetate (δ 3.24 and 1.40 ppm) in CD3OD slowly produced two peaks at 3.35 ppm (CH3OD) and 1.40 ppm. Methanol and acetic acid in CD3OD have peaks at 3.35 and 1.99 ppm, respectively.

The direct formation of alcohol 11 from the rearrangement of 10, when carried out in methanol, is synthetically significant because it has been reported that 11 could not be produced from its acetate by either chemical or enzymatic hydrolysis due to the facile elimination of the acetoxy group. In fact, attempts to produce the acetate for reference purpose, by acetylation of 11, failed completely due to elimination.

After solvent exchange with acetonitrile, alcohol 11 was then silylated without isolation to give ketone 12 (Scheme 3). The relatively volatile silyl byproducts were removed at 45 °C under high vacuum, and crude 12, thus obtained in 82% yield from epoxide 9, was directly subjected to the Wittig–Horner reaction yielding the desired dieneoxide 7. The olefination was carried out using 2.2 equiv of triethyl phosphonoacetate and 1.8 equiv of lithium hydride in a concentrated THF solution at the lower temperature of 11 °C to minimize elimination of the silyloxy group.

Under these conditions, 7 was obtained in 76% yield as a mixture of E/Z epimers in a ratio of 8.5:1. However, a slight variation in yield in the range of 70–85% was noted with reaction time, which also affected the E/Z ratio of products. Thus, the E/Z ratio varied accordingly from 9:1 to 7:1, with higher yields correlating with lower selectivity, suggesting that selective decomposition of the minor (Z)-epimer was occurring under the reaction conditions. The concentration of the reaction mixture also affected the E/Z ratio, as a 2-fold dilution resulted in a ca. 2-fold decrease in selectivity for the (E)-epimer. Other phosphanoacetates, i.e., (EtO)2P(O)CH2CO2Me, (EtO)2P(O)CH2CO2Et, (Me2N)2P(O)CH2CO2Et, and (Me2N)2P(O)CH2CO2Et, as well as (EtO)2P(O)CH2CN were examined but gave lower yields and selectivities.

We have previously described the palladium-catalyzed isomerization of the corresponding 1β-dieneoxide (E)-esters, which produced dienols exclusively over enones when using a fluoro alcohol cocatalyst. However, the effects of the relative configuration of the double bond and C-1 of the substrates on selectivity had not been clarified. When 1α-dieneoxide 7 as a 7:1 mixture of E/Z epimers was subjected to the same reaction conditions, an 88:12 mixture of (E)-dienol 8 and enone 19 was obtained, while the corresponding (Z)-dienol product was not observed. This unexpected result warranted further examination.

Since the E/Z-ratio of the starting materials used seemed to correspond exactly to the ratio of these two products (see Table 1, entries 1–3), the pure epimers (E)-7 and (Z)-7, as well as the related tert-butyl esters (E)-20 and (Z)-20, and nitriles (E)-23 and (Z)-23 were separately prepared in an attempt to clarify the issue.

Indeed as expected, the (E)-ester substrates, ethyl ester (E)-7 and tert-butyl ester (E)-20, gave the (E)-dienols, (E)-8 and (E)-21, respectively (Table 1), with high selectivities (>99:1) as previously noted for the corresponding 1β-epimers. However, the (Z)-esters, (Z)-7 and (Z)-20, gave the corresponding enones 19 and 22 as the major products. Moreover, the minor products from the rearrangement of the (Z)-esters were the (E)-dienols, (E)-8 and (E)-21, respectively, while the epimeric (Z)-dienols were undetectable. In contrast, however, the epimeric nitriles 23 rearranged in a stereospecific fashion, as (E)-23 gave only dienol (E)-24, (Z)-23 gave dienol (Z)-24 exclusively, and the corresponding enone 25 was never observed. These results suggested that the inverse selectivity for the palladium-catalyzed isomerization of the (Z)-esters may be due to a different coordination of palladium, which is available for the (Z)-esters, but not for the (E)-esters and the nitriles. Hence, for the (Z)-esters, unlike the (E)-esters, internal coordination of the ester carboxyl to the allylic palladium such as in intermediate 26 would promote the sterically favored equilibration of 26 to the palladium enolate 27 with concomitant loss of stereochemistry at the exocyclic double bond. Subsequent
elimination from 27 would occur via enolate 28 to form enone 19 preferentially, along with a lesser amount of the corresponding dienol (E)-8. As this internal equilibration is not possible for the nitrile (Z)-23, stereospecific isomerization leads to dienol (Z)-24 exclusively by β-hydride elimination from the methyl group as previously described.

While high selectivity was achieved with the pure (E)-epimer 7, the separation of the E/Z epimers was not practical. Thus, in practice, the mixture was subjected to the rearrangement conditions, and after solvent exchange with DMF, the resulting mixture of dienol (E)-8 and enone 19 was subjected to silylation (Scheme 4). Since dienol (E)-8 was converted to the nonpolar product (E)-5, while the polar enone 19 remained unchanged, pure (E)-5 was then isolated, by simple silica gel filtration, in 64% yield over the three steps from epoxysketone 12.

DIBALH reduction of ester (E)-5 in hexane uneventfully produced allylic alcohol (E)-6, which was photoisomerized to (Z)-6 in tert-butyl methyl ether, in the presence of a sensitizer. With 10 mol % of 9-fluorenone, greater than 98.7% conversion was achieved. However, this sensitizer was difficult to remove from the product without chromatography. Hence, other sensitizers were evaluated, and 9-fluorenone-4-carboxylic acid was found to be equally effective as 9-fluorenone but easily removed from the product by filtration through silica gel. Thus, after photolysis with 10 mol % of 9-fluorenone-4-carboxylic acid followed by filtration, crystallization from acetonitrile afforded the known13 alcohol (Z)-6 in greater than 99% purity.

The isomeric 9-fluorenone-2-carboxylic acid and 9-fluorenone-1-carboxylic acid were less effective as sensitizers in this reaction, giving 98.2 and 96.9% conversion, respectively. 9-Anthracencarboxylic acid was virtually inactive. Alternatively, the previously described photoisomerization of ester (E)-513 was examined but was found to be inefficient. For instance, with 9-fluorenone and 9-acetylanthracene the highest conversions achieved were 88.8 and 11.7%, respectively.

Alcohol (Z)-6 was converted to the desired phosphine oxide 1 as previously described.23 Crude phosphine oxide 1 was crystallized from a mixture of hexane and cyclohexane as 2:1 solvate with cyclohexane, mp 54–55 °C. However, because recovery from this crystallization (ca. 60%) was modest, its chromatographic purification was preferred instead, increasing the yield of 1 to 84% over these two steps.

In summary, we have developed a new practical preparation of the vitamin D building block 1, which is useful for the synthesis of many vitamin D analogues bearing this structural motif via the dependable Lythgoe method. The process uses inexpensive (S)-carvone as the starting material, is scalable, and requires a minimal number of chromatographic purification steps. Using this process, we obtained the key precursor (E)-7 in five synthetic operations and 42% overall yield from (S)-carvone, which compares very favorably to previous syntheses.11 Ultimately, phosphine oxide 1 is obtained in nine synthetic operations and 25% overall yield from (S)-carvone, requiring only one chromatographic purification, that of the final product 1. While carvone oxide 9 and alcohol (Z)-6 were crystallized, intermediate purification, where necessary (as of 7, (E)-5, (E)- and (Z)-6), could be achieved by simple filtration through silica to remove polar impurities, obviating extensive chromatographic separation.

The present synthesis affording the 1α-hydroxy A-ring alcohols 6 with the E- and Z-configuration of the substituents...
tuted exocyclic double bond, complements our previously reported synthesis of the corresponding 1β-epimers, thus making all stereoisomers of the versatile A-ring phosphine oxide building blocks readily available from the respective enantiomers of carveone.

**Experimental Section**

**General Materials and Procedures.** All reactions were performed in dried glassware under a positive pressure of nitrogen. Water-sensitive reagents and chromatography fractions were concentrated using a rotary evaporator at approximately 10 Torr using a diaphragm pump and then at high vacuum to approximately 0.01 Torr using an oil pump. TLC analysis was performed using silica gel 60 F254 precoated glass plates (EM Science) and detected by UV254 or phosphomolybdic acid (PMA) stain. 1H NMR spectra were recorded at 300 MHz. CDCl3 was used with basic alumina prior to use. Melting points were obtained on a capillary melting point apparatus and are uncorrected. A Polyemetric Laboratories Ozoneator model T-816 instrument was used to generate ozoneized air (shell pressure = 6 PSIG; flow rate = 4 LPM; 110 V). Commercial grade reagents and solvents were used without further purification, except as indicated. Silica gel 60, particle size 0.040–0.063 mm (230–400 mesis), was used. The preparation of diphenylphosphine oxide has been previously described.

(1S,4S,5S,8S)-1-Methyl-4-(1-methylthienyl)-7-oxabicyclo[4.1.0]heptan-2-one (9). A 70% solution of tert-butyl hydroperoxide in water (105 g, 81.6 mmol) was cooled to 5 °C, and a 25% solution of sodium methoxide in methanol (15 mL, 65.3 mmol) was added in one portion. A mild exotherm ensued and the temperature of the mixture to 7 °C. After the mixture was cooled to 5 °C, a mixture of (S)-carvone (100 g, 696 mmol) and methanol (40 mL) was added dropwise over 2 h while maintaining the reaction temperature between 3 and 6 °C. The mixture was stirred at 3 °C for 3 h. At this point, TLC analysis indicated ca. 80% conversion. After the mixture was stored in an ice–water bath in a refrigerator overnight. TLC analysis indicated the presence of only a trace amount of starting material. Then, 5% aqueous sodium bicarbonate (200 mL) was added over 10 min while maintaining the temperature of the mixture below 10 °C. The mixture was cooled to 3 °C, and an aqueous sodium dithionite solution, prepared by dissolving 85% sodium dithionite (12 g, Stenchik) in water and dilution to 100 mL, was added over 7 min while maintaining the temperature of the mixture below 12 °C. After 10 min, the cooling bath was removed. After stirring for 30 min, the mixture was extracted with tert-butyl methyl ether (2 × 100 mL). The combined organic extracts were washed with a mixture of saturated aqueous NaHCO3 (100 mL) and saturated aqueous NaCl (100 mL), dried over Na2SO4, and concentrated to dryness at 30 °C under reduced pressure. The residue was dissolved in hexane (100 mL), and the resulting solution was concentrated to dryness at 35 °C under reduced pressure, and additional acetone (40 mL) was added. The resulting solution was again concentrated to dryness at 35 °C under reduced pressure, and then acetone (35 mL) and imidazole (29.5 g, 435 mmol) were added. After the mixture was stirred with an ice–water bath, tert-butyl methyl ether (125 mL) was added. The mixture was then stirred for 5 min, ice-water (55 mL) was added and the mixture was extracted with hexanes (2 × 50 mL). The combined organic extracts were washed with a 2.3% v/v mixture of methanol and water (50 mL), dried over Na2SO4, and concentrated to dryness at 40 °C under reduced pressure. Further drying of the residue at 46 °C and 0.4 mmHg for 1 h gave 25.2 g (81.7% from 9) of crude 12 as a pale yellow oil. The material, which according to NMR analysis contained silanol (ca. 2%; δ 0.09 ppm) and siloxane (ca. 12%; δ 0.00 ppm) byproducts, was used directly in the next step without further purification. TLC (40:21) dichloromethane–ethyl acetate–methanol; PMA stain; Rf = 0.8, Rf = 0.11 = 0.4, and Rf = 0.12 = 0.35.

**Ethyl 2-[[1S,4S,5S,8S]-1-Methyl-7-oxa-4-[[1S,4S,5S,8S]-1-Methyl-7-oxabicyclo[4.1.0]heptan-2-yliide]acetate (7).** Caution! When handling lithium hydride powder, use a protective mask to prevent accidental inhalation. A mixture of lithium hydride (1.41 g, 177 mmol) and trichloro(2.1 equiv) phosphopheneacetonitrile (4.3 mL, 216 mmol) in THF (45 mL) was heated slowly to 55 °C (Caution! Exotherm), and then the heating bath was removed. An exotherm ensued, which raised the temperature of the mixture to 69 °C over 5 min. The temperature of the mixture slowly decreased to 66 °C over 55
min. and a clear solution resulted. Approximately 25 mL of THF was then removed by distillation at 50–55 °C under a slightly reduced pressure.24 After the resulting mixture was cooled to 3 °C with an ice water bath, crude 12 as obtained above (25 mg, 40% yield) was added in one portion over 30 min while maintaining the temperature of the reaction mixture below -65 °C. This resulting mixture was then stirred under nitrogen at -70 °C for 30 min. TLC analysis indicated complete reaction. The cooling bath was removed, and the reaction mixture was allowed to warm to 0 °C. While the mixture was cooled with an ice-water bath, cold water (380 mL) was added slowly over 5 min (Caution! Gas evolution). The cooling bath was then removed, and the mixture was stirred at room temperature for 1.5 h. The resulting suspension was diluted with EtOAc (300 mL), and the mixture was washed with 0.25 M HCl (2 x 300 mL), causing most of the solids to dissolve. The combined aqueous washes were diluted with 0.5 N HCl (120 mL), decreasing the pH from 5 to 2, and then extracted with EtOAc (300 mL). The organic phase and extract were combined, washed with saturated aqueous NaCl solution (300 mL), dried over MgSO4, and concentrated to dryness at 35 °C under reduced pressure to give 27.5 g (94.5%) of (E)-6 as a colorless solid. TLC of hexane–EtOAc–short-wave UV detection and PMA stain: Rf 0.5, Rf (E)-6 = 0.0.75 (2.7 g, 92.9 mmol) was dissolved in hexane (250 mL). After the mixture was cooled to -75 °C, a solution of 1 M Dibal-H in toluene (157 mL) was added in one portion over 45 min while maintaining the temperature of the reaction mixture below -65 °C. This resulting mixture was then stirred under nitrogen at -70 °C for 30 min. TLC analysis indicated complete reaction. The cooling bath was removed, and the reaction mixture was allowed to warm to 0 °C. While the mixture was cooled with an ice-water bath, cold water (380 mL) was added slowly over 5 min (Caution! Gas evolution). The cooling bath was then removed, and the mixture was stirred at room temperature for 1.5 h. The resulting suspension was diluted with EtOAc (300 mL), and the mixture was washed with 0.25 M HCl (2 x 300 mL), causing most of the solids to dissolve. The combined aqueous washes were diluted with 0.5 N HCl (120 mL), decreasing the pH from 5 to 2, and then extracted with EtOAc (300 mL). The organic phase and extract were combined, washed with saturated aqueous NaCl solution (300 mL), dried over MgSO4, and concentrated to dryness at 35 °C under reduced pressure to give 27.5 g (94.5%) of (E)-6 as a colorless solid. TLC of hexane–EtOAc–short-wave UV detection and PMA stain: Rf 0.5, Rf (E)-6 = 0.0.75 (2.7 g, 92.9 mmol) was dissolved in hexane (250 mL). A color change from deep purple to yellow, as well as disappearance of purple particles, indicates complete catalyst formation. Preparation in a more dilute solution is not recommended as it makes it more difficult for the active catalyst to form. Then, 1.3-bis-(1,1,3,3,3,3-hexafluoro-2-hydroxypropyl)benzene (0.37 mL, 1.5 mmol) was added. The slurry became red-orange. After three minutes of stirring at ambient temperature (19 °C), a solution of crude 7, as obtained above (24.4 g, 74.9 mmol in toluene) in toluene (100 mL) prepared under nitrogen, was added to the catalyst solution via cannula using a slight positive nitrogen pressure. After 10 minutes of stirring at ambient temperature, under a slight positive pressure of nitrogen, the reaction mixture was heated to 16 h at 40 °C. TLC analysis indicated complete reaction. The mixture was concentrated on a rotary evaporator at -40 °C under reduced pressure to remove most of the toluene. The resulting brown oil was dissolved in THF (80 mL) and the resulting solution was cooled in an ice-water bath; then, imidazole (6.12 g, 89.8 mmol) followed by tert-butyl chloride (61.6 g, 989.9 mmol) was added. After 10 min, the cooling bath was removed and stirring was continued at room temperature for 16 h. TLC analysis indicated complete reaction. The reaction mixture was diluted with hexane (300 mL) and washed with water (2 x 150 mL). The combined aqueous washes were extracted with hexane (2 x 100 mL), and the combined extracts were also washed with water (2 x 50 mL). The organic phase and extracts were then combined, dried over MgSO4, and concentrated to dryness under reduced pressure. The residue was dissolved in toluene (100 mL) and filtered through silica gel (200 g). The silica plug was then washed with 98:2 v/v hexanes–EtOAc (1.5 L), and the combined filtrate and washes were concentrated to dryness under reduced pressure. The residue was further dried under high vacuum for 1 h to give 27.7 g (84.0%) of (E)-7 as a colorless oil. TLC (3:1 petroleum ether–EtOAc–short-wave UV detection and PMA stain): Rf 0.8 = 0.45, Rf (E)-7 = 0.9, Rf (E)-8 = 0.85, Rf (E)-7 = 0.9, and Rf (E)-6 = 0.7.

24 When the reaction was carried out without removal of the THF, the subsequent reaction was slow and the E/Z ratio of the product was lower (<1:1).

25 This material contained, by HPLC analysis, (E)-8 (Rf = 17.6 min), ca. 11% of the enone byproduct 19 (Rf = 10.2 min), and ca. 1.4% of the 1,8-epimer of (E)-8 (Rf = 13.4 min).
thick suspension was stirred at room temperature for 1 h. TLC analysis indicated complete reaction. Then, the reaction mixture was diluted with hexanes (150 mL) and washed consecutively with ice-cold 0.25 N HCl (2 x 250 mL) and water (2 x 250 mL). The combined aqueous washes were back-extracted with hexanes (2 x 100 mL). The organic extracts were combined, washed with saturated aqueous NaCl solution (150 mL), dried over MgSO\(_4\), and concentrated to dryness at 30 °C under reduced pressure. The residual mixture was then purged with nitrogen for 15 min to give 19.2 g (overweight) of crude product as a slightly hazy, yellow oil. This material solidified upon being stored overnight in the freezer and was directly used to the next step without further purification. This product is relatively unstable at room temperature and, therefore, should be stored in the freezer. TLC (9:1 hexanes–EtOAc; short-wave UV detection and PMA stain): \( R_f (2) = 0.2 \) and chloride product \( R_f = 0.6 \).

\[(\text{Z}-[\text{S,S,R}-\text{5-Bis[[(1,1-di-methylethyl)dimethylsilyl]oxy]}\text{2-methylenecyclohexylidene]}\text{-ethyl}]\text{diphosphine Oxide (I),}^{13}\text{DMF (170 mL)}\text{ and sodium hydride, 60% dispersion in mineral oil (2.02 g, 50.6 mmol), were combined in a reaction flask. Then, diphosphine oxide (10.2 g, 50.6 mmol) was added in one portion. Gas evolution was observed, and a mild exotherm raised the temperature of the mixture to 28 °C. The mixture was stirred for 50 min at room temperature to give a slightly cloudy yellow solution. After the solution was cooled to \(-45^\circ\text{C}\) with a dry ice–acetone bath, a solution of the crude product from the previous step (19.2 g, 45.2 mmol in theory) in DMF (70 mL) was added dropwise over 25 min while maintaining the temperature of the reaction mixture below \(-35^\circ\text{C}\). The reaction mixture was stirred for 1.5 h at temperatures from \(-30\) to \(-35^\circ\text{C}\) and then allowed to warm to 0 °C and stirred at that temperature for 30 min. TLC analysis indicated complete reaction. The reaction mixture was diluted with diethyl ether (500 mL) and washed with water (2 x 200 mL). The combined aqueous washes were extracted with diethyl ether (2 x 150 mL), and these extracts were also washed with water (2 x 200 mL). The organic phase and extracts were then combined, dried over MgSO\(_4\), and concentrated at 35 °C under reduced pressure to give 26.2 g of a cloudy yellow oil. This material was dissolved in hexanes (50 mL), and the resulting solution was filtered through silica gel (150 g). The silica plug was then washed consecutively with hexane (200 mL), 9:1 hexanes–EtOAc (1.5 L), 8:2 hexanes–EtOAc (1.5 L), and 7:3 hexanes–EtOAc (1.5 L). The appropriate fractions were combined and concentrated to dryness at 35 °C under reduced pressure. The residue was further dried under high vacuum to give 22.3 g (83.7% over two steps) of I as a colorless foam. TLC (1:1 hexanes–EtOAc; short-wave UV detection and PMA stain): \( R_f \) chloride substrate = 0.95 and \( R_f \) I = 0.45.

Supporting Information Available: 'H NMR spectra of nine compounds, obtained as indicated in the Experimental Section. This material is available free of charge via the Internet at http://pubs.acs.org.

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