Efficient Synthesis of the A-Ring Phosphine Oxide Building Block Useful for 1α,25-Dihydroxy Vitamin D_3 and Analogues

Andrzej R. Daniewski, Lisa M. Garofalo, Stanley D. Hutchings, Marek M. Kabat, Wen Liu, Masami Okabe, Roumen Radinov,* and George P. Yiannikouros

Chemical Synthesis - Process Research, Non-Clinical Development, Pre-Clinical Research and Development, Hoffmann−La Roche, Inc., Nutley, New Jersey 07110

roumen.radinov@roche.com

Received September 28, 2001

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 3*β*-alcohol **11** and the highly chemo- and stereoselective isomerization of dieneoxide 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 1*β*-epimers, thus producing all stereoisomers of these versatile building blocks efficiently from carvone.

Introduction

The hormonally active metabolite of vitamin D_3, 1α,-25-dihydroxy vitamin D_3 (**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 specificity 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 D_2.[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.[3] Thus, a versatile and reliable method was pioneered by Lythgoe[6] that proceeded by the direct construction of the conjugated triene system with complete stereoselectivity[7] via Wittig−Horner coupling of the A-ring phosphine oxide **1**[8] 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 applica-

---

[1] The α and *β* designations and atom numbering used in the text follow the conventional steroid nomenclature; see: Rose, I. A.; Hanson, K. R.; Wilkinson, K. D.; Wimmer, M. J. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 2439.

[2] (a) 1st International Conference on Chemistry and Biology of Vitamin D Analogues, *Steroids-Special Issue* **2001**, *66*, 127−472. (b) *Vitamin D Endocrine System: Structural, Biological, Genetic and Clinical Aspects*; Norman, A. W., Bouillon, R., Thomasset, 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., Thomasset, M., Eds.; University of California Riverside: Riverside, CA, 1997. (d) Bouillon, R.; Okamura, W. H.; Norman, A. W. *Endocrine Rev.* **1995**, *16*, 200.

[3] For reviews, see: (a) Zhu, G.-D.; Okamura, W. H. *Chem. Rev.* **1995**, *95*, 1877. (b) Dai, H.; Posner, G. H. *Synthesis* **1994**, 1383.

[4] Okabe, M. Chemistry of Vitamin D: A Challenging Field for Process Research. In *Process Chemistry in the Pharmaceutical Industry*; Gadamasetti, K. G., Ed.; Marcel Dekker: New York, Basel, 1999; pp 73−89.

[5] (a) Guyton, K. Z.; Kensler, T. W.; Posner, G. H. *Annu. Rev. Pharmacol. Toxicol.* **2001**, *41*, 421. (b) Gabriëls, S.; Van Haver, D.; Vandewalle, M.; De Clercq, P.; Verstuyf, A.; Bouillon, R. *Chem. Eur. J.* **2001**, *7*, 520. (c) Uskoković, M. R.; Studzinski, G. P.; Gardner, J. P.; Reddy, S. G.; Campbell, M. J.; Koeffler, H. P. *Curr. Pharm. Des.* **1997**, *3*, 99.

[6] Lythgoe, B.; Moran, T. A.; Nambudiry, M. E. N.; Tideswell, J.; Write, P. W. *J. Chem. Soc., Perkin Trans. 1* **1978**, 590.

[7] Kociensky, P. J.; Lythgoe, B.; Waterhouse, I. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1045.

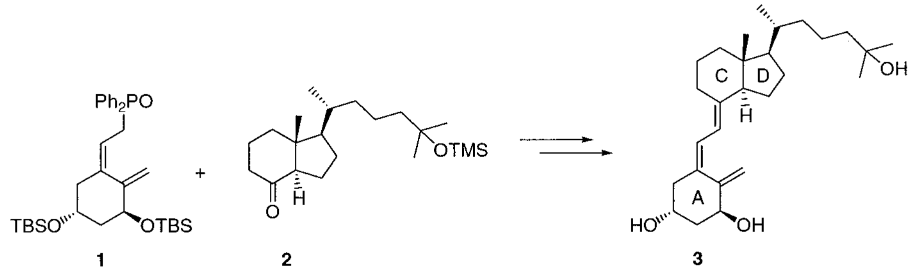
[8] Baggiolini, E. G.; Iacobelli, J. A.; Hennessy, B. M.; Uskoković, M. R. *J. Am. Chem. Soc.* **1982**, *104*, 2945.

[9] For recent syntheses of the CD-ring ketone fragment, see: (a) Daniewski, A. R.; Liu, W. *J. Org. Chem.* **2001**, *66*, 626. (b) Van Gool, M.; Vandewalle, M. *Eur. J. Org. Chem.* **2000**, 3427. (c) Fall, Y.; Vitale, C.; Mouriño, A. *Tetrahedron Lett.* **2000**, *41*, 7337. (d) Stork, G.; Ra, C. S. *Bull. Korean Chem. Soc.* **1997**, *18*, 137. (e) Jankowski, P.; Marczak, S.; Wicha, J. *Tetrahedron* **1998**, *54*, 12071 and references therein.

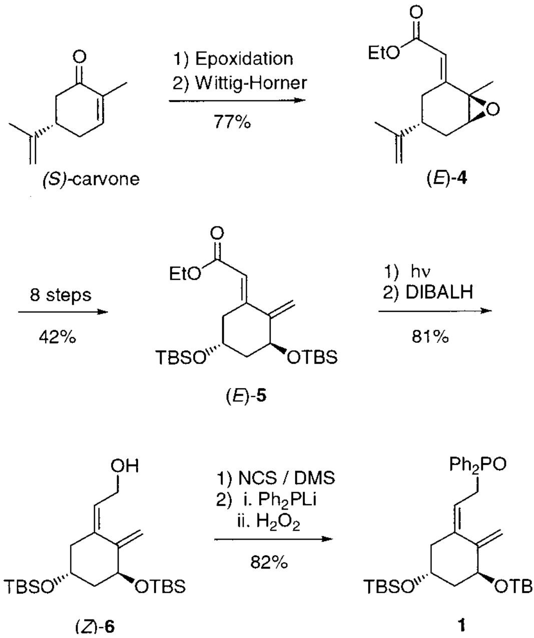
[10] For recent examples, see: (a) Calverley, M. J. *Steroids* **2001**, *66*, 249. (b) Norman, A. W.; Manchand, P. S.; Uskoković, M. R.; Okamura, W. H.; Takeuchi, J. A.; Bishop, J. E.; Hisatake, J.-I.; Koeffler, H. P.; Peleg, S. *J. Med. Chem.* **2000**, *43*, 2719. (c) Sestelo, J. P.; Mouriño, A.; Sarandeses, L. A. *J. Org. Chem.* **2000**, *65*, 8290. (d) Fernández-Gacio, A.; Vitale, C.; Mouriño, A. *J. Org. Chem.* **2000**, *65*, 6978. (e) Zhou, X.; Zhu, G.-D.; Van Haver, D.; Vandewalle, M.; De Clercq, P. J.; Verstuyf, A.; Bouillon, R. *J. Med. Chem.* **1999**, *42*, 3539. (f) Posner, G. H.; Wang, Q.; Han, G.; Lee, J. K.; Crawford, K.; Zand, S.; Brem, H.; Peleg, S.; Dolan, P.; Kensler, T. W. *J. Med. Chem.* **1999**, *42*, 3425. (g) de los Angeles Rey, M.; Martínez-Pérez, J. A.; Fernández-Gacio, A.; Halkes, K.; Fall, Y.; Granja, J.; Mouriño, A. *J. Org. Chem.* **1999**, *64*, 3196. (h) Grue-Sørensen, G.; Hansen, C. M. *Bioorg. Med. Chem.* **1998**, *6*, 2029.

10.1021/jo0161577 CCC: $22.00 © 2002 American Chemical Society
Published on Web 02/09/2002

Scheme 1



Scheme 2

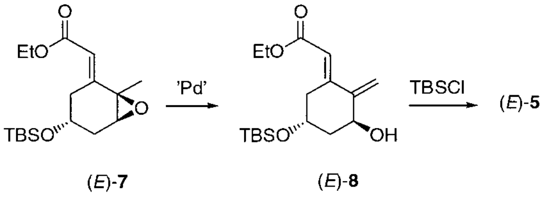


tion of this useful approach. Thus, while many ingenious syntheses of **1** have been reported,[11] only very recently has a synthesis of less than 10 steps been realized.[12] Furthermore, these preparations involve multiple isolations and chromatographic purifications, rendering them unacceptable for larger kilo-scale production.

The seminal Baggiolini–Usković synthesis (Scheme 2),[13] while affording **1** in an overall yield of 21% from (*S*)-carvone, requires 14 steps and at least eight chromatographic purifications. In this approach, the conversion of the 1α-epoxide (*E*)-**4**, obtained in two steps from (*S*)-carvone, to the silylated diol (*E*)-**5** required eight steps. Whereas oxidative degradation of the isopropenyl substituent was accomplished in three steps, four steps were needed for the formal isomerization of the dieneoxide moiety in **4** to the allylic alcohol, with an exocyclic double bond, in compound **5**.

Indeed, the apparent shortcoming of this process is the inability to convert the epoxide moiety in (*E*)-**4** directly into the desired allylic alcohol with an exocyclic double 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.

---

(11) For recent syntheses of **1**, see: (a) Hatakeyama, S.; Okano, T.; Maeyama, J.; Esumi, T.; Hiyamizu, H.; Iwabuchi, Y.; Nakagawa, K.; Ozono, K.; Kawase, A.; Kubodera, N. *Bioorg. Med. Chem.* **2001**, *9*, 403. (b) Miyata, O.; Nakajima, E.; Naito, T. *Chem. Pharm. Bull.* **2001**, *49*, 213. (c) Koiwa, M.; Hareau, G. P. J.; Sato, F. *Tetrahedron Lett.* **2000**, *41*, 2389. (d) Anné, S.; Wu, Y.; Vandewalle, M. *Synlett* **1999**, 1435 and references therein. For earlier syntheses, see ref 3.

(12) Hiyamitzu, H.; Ooi, H.; Inomoto, Y.; Esumi, T.; Iwabuchi, Y.; Hatakeyama, S. *Org. Lett.* **2001**, *3*, 473.

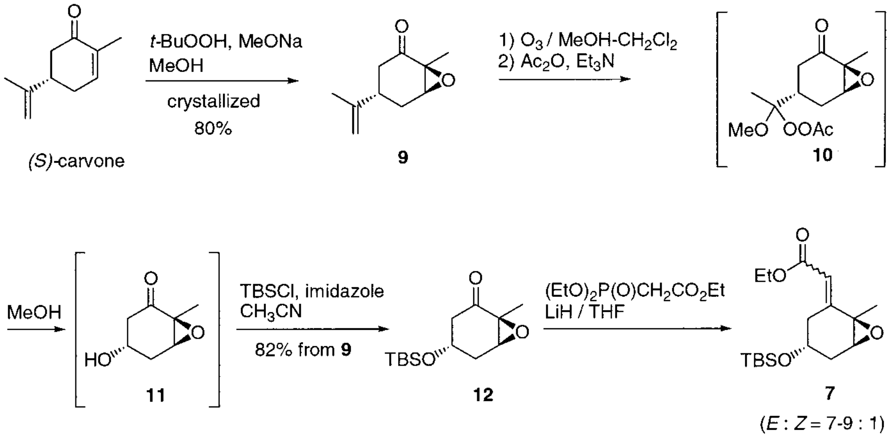
(13) Baggiolini, E. G.; Iacobelli, J. A.; Hennessy, B. M.; Batcho, A. D.; Sereno, J. F.; Usković, M. R. *J. Org. Chem.* **1986**, *51*, 3098.

(14) Kabat, M. M.; Garofalo, L. M.; Daniewski, A. R.; Hutchings, S. D.; Liu, W.; Okabe, M.; Radinov, R.; Zhou, Y. *J. Org. Chem.* **2001**, *66*, 6141.

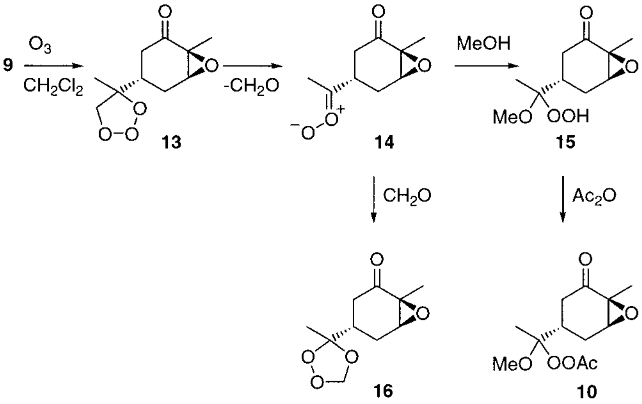
(15) (a) Klein, E.; Ohloff, G. *Tetrahedron* **1963**, *19*, 1091. (b) Okamura, W. H.; Aurrecoechea, J. M.; Gibbs, R. A.; Norman, A. W. *J. Org. Chem.* **1989**, *54*, 4072.

(16) At ambient temperature **9** is a yellow oil, as its mp is below 0 °C.

Scheme 3



The subsequent Criegee rearrangement[17] of peracetate **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 peracetate **10**, which could be used directly for the Criegee rearrangement.

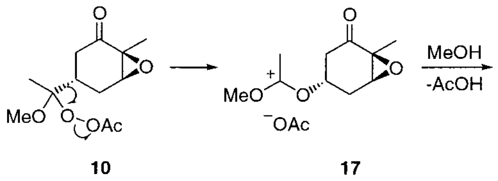


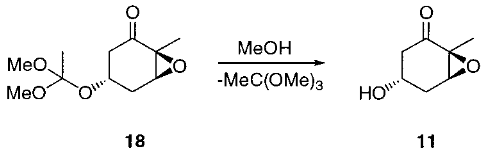
As it is not desirable to isolate these unstable intermediates, the *one-pot* process required considerable optimization. Excess methanol is necessary during the ozonolysis to trap the short-lived carbonyl oxide intermediate **14**, which is formed via retro 1,3-dipolar cycloaddition from ozonide **13**. 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. Acylation 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 peracetate **10** thus obtained could then be used advantageously for the Criegee rearrangement, after solvent exchange, without further purification. Indeed, the stereospecific rearrangement of peracetate **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,[18] where the corresponding acetate of the alcohol product was obtained predominantly upon prolonged reflux. The alcohol, usually the minor product under those conditions, was produced from hydrolysis of the acetate on aqueous workup. Thus, it has been postulated that a dioxenium 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-

---

[17] (a) Criegee, R.; Kaspar, R. *J. Liebigs Ann. Chem.* **1948**, *560*, 127. (b) Criegee, R. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 745.

[18] Schreiber, S. L.; Liew, W.-F. *Tetrahedron Lett.* **1983**, *24*, 2363.

dergo acetic acid-catalyzed methanolysis to yield cleanly alcohol **11** along with trimethyl orthoacetate as the byproduct.[19] A substantial rate acceleration in methanol should normally result[17a] from the stabilization of the highly polarized transition state leading to the dioxenium ion **17** in this polar solvent.

Indeed, ^{1}H NMR analysis of a reaction run in deuteriomethanol (CD_3OD) revealed the clean formation of **11**, without accumulation of intermediates, while producing three additional singlet peaks. These peaks were assigned to CH_3OD (δ 3.35 ppm, originating from the methoxy group in **10**), CH_3CO_2D (δ 1.99 ppm, originating from the acetoxy group in **10**), and $CH_3C(OCD_3)_3$ (δ 1.40 ppm). As a reference, trimethyl orthoacetate (δ 3.24 and 1.40 ppm) in CD_3OD slowly produced two peaks at 3.35 ppm (CH_3OD) and 1.40 ppm. Methanol and acetic acid in CD_3OD have peaks at 3.35 and 1.99 ppm, respectively.

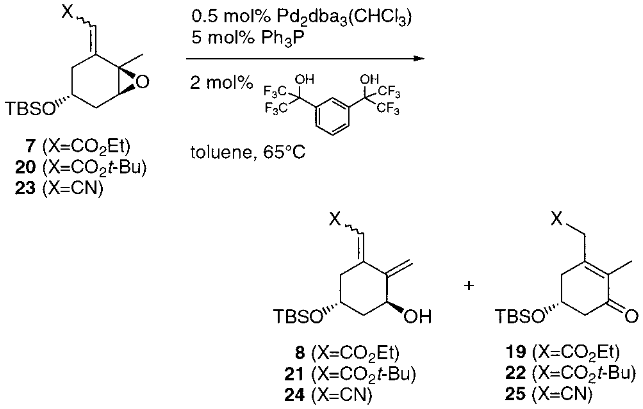
The direct formation of alcohol **11** from the rearrangement of **10**, when carried out in methanol, is synthetically significant because it has been reported[20] that **11** could not be produced from its acetate by either chemical or enzymatic hydrolysis due to the facile elimination of the acetoxy group. In fact, attempts to produce the acetate for reference purpose, by acylation 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.[21]

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 phoshonoacetates, i.e., $(EtO)_2P(O)CH_2CO_2Me$, $(EtO)_2P(O)CH_2CO_2t\text{-Bu}$, $(MeO)_2P(O)CH_2CO_2Me$, and $(i\text{-PrO})_2P(O)CH_2CO_2Et$, as well as $(EtO)_2P(O)CH_2CN$ were examined but gave lower yields and selectivities.

We have previously described[14] 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.

Table I.



entry	X (substrate)	*E*:*Z* of substrate	*E*:*Z* of product	dieneol:enone[a]
1	CO_2Et (**7**)	4:1	*E* only: (*E*)-**8**	80:20 (**8**:**19**)
2	CO_2Et (**7**)	7:1	*E* only: (*E*)-**8**	88:12 (**8**:**19**)
3	CO_2Et (**7**)	9:1	*E* only: (*E*)-**8**	90:10 (**8**:**19**)
4	CO_2Et (**7**)	*E* only	*E* only: (*E*)-**8**	>99:1 (**8**:**19**)
5	CO_2Et (**7**)	*Z* only	*E* only: (*E*)-**8**	14:86 (**8**:**19**)
6	CO_2t-Bu (**20**)	*E* only	*E* only: (*E*)-**21**	>99:1 (**21**:**22**)
7	CO_2t-Bu (**20**)	*Z* only	*E* only: (*E*)-**21**	8:92 (**21**:**22**)
8	CN (**23**)	*E* only	*E* only: (*E*)-**24**	>99:1 (**24**:**25**)
9	CN (**23**)	*Z* only	***Z* only**: (*Z*)-**24**	>99:1 (**24**:**25**)

[a] HPLC analysis was performed on a Nucleosil 5 μm, 4.6 × 250 mm column with 2% 2-propanol in hexane at 0.5 mL/min. Percentages given are the area percentages of the corresponding peaks detected at 220 nm.

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.[14] 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 carbonyl 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

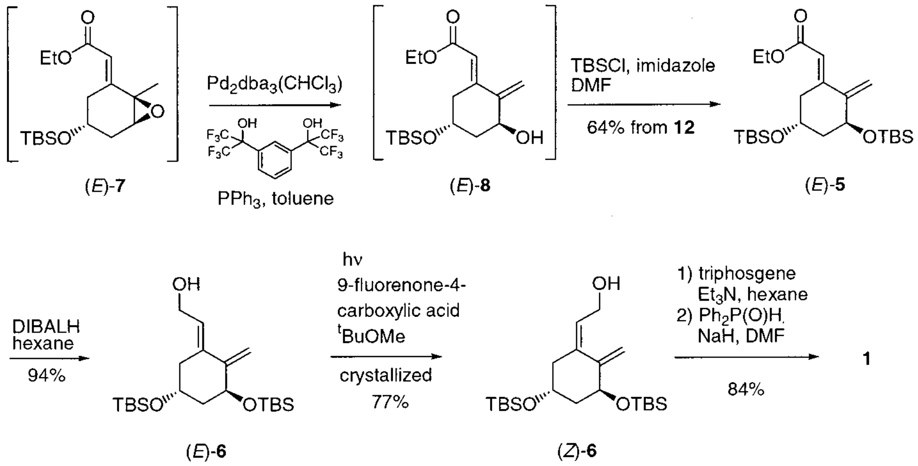
---

[19] The ionic decomposition of 2-methoxy-2-propyl per-*p*-nitrobenzoate in methanol has been reported to produce quantitatively *methyl acetate* and *p*-nitrobenzoic acid: Hedaya, E.; Winstein, S. *Tetrahedron Lett.* **1962**, 563.

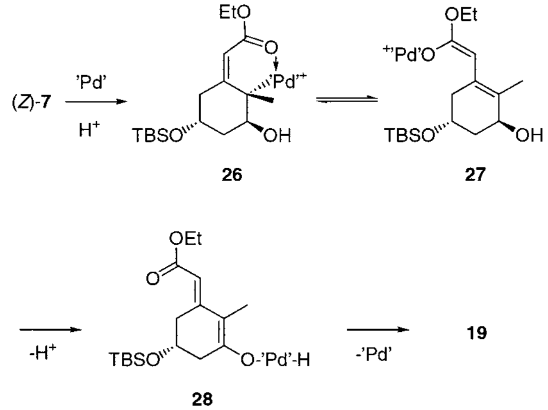
[20] De Brabander, J.; Kulkarni, B. A.; Garcia-Lopez, R.; Vandewalle, M. *Bull. Soc. Chim. Belg.* **1997**, *106*, 665.

[21] When sodium ethoxide was used as the base, significant amounts of *tert*-butyldimethylsilanol were produced via elimination.

Scheme 4



elimination from **27** would occur via enolate **28** to form enone **19** preferentially,[22] 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.[14]



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 epoxyketone **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 known[13] 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-Anthracenecarboxylic acid was virtually inactive. Alternatively, the previously described photoisomerization of ester (*E*)-**5**[13] 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 a 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 scaleable, 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 substi-

---

[22] Coordination of the cationic palladium in ester enolate **27** to the 1α-OH group is likely to favor the β-hydride migration yielding enolate **28** (cf. ref 14). For an elimination of a palladium *O*-enolate to enone in the context of an intramolecular redox reaction, see: Högenauer, K.; Mulzer, J. *Org. Lett.* **2001**, *3*, 1495.

[23] For improved preparation of A-ring phosphine oxides from allylic alcohols, see: Daniewski, A. R.; Garofalo, L. M.; Kabat, M. M. *Synth. Commun.* **2002**, in press.

tuted exocyclic double bond, complements our previously reported synthesis of the corresponding 1β-epimers,[14] thus making all stereoisomers of the versatile A-ring phosphine oxide building blocks readily available[23] from the respective enantiomers of carvone.

Experimental Section

General Materials and Procedures. All reactions were performed in dried glassware under a positive pressure of nitrogen. Reaction extracts 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 F$_{254}$ precoated glass plates (EM Science) and detected by UV$_{254}$ or phosphomolybdic acid (PMA) stain. ^{1}H NMR spectra were recorded at 300 MHz. CDCl$_3$ was treated with basic alumina prior to use. Melting points were obtained on a capillary melting point apparatus and are uncorrected. A Polymetrics Laboratory Ozonator model T-816 instrument was used to generate ozonized air (shell pressure = 6 PSIG; flow rate = 4 LPM; 110 V). Commercial grade reagents and solvents were used without purification, except as indicated. Silica gel 60, particle size 0.040−0.063 mm (230−400 mesh), was used. The preparation of diphenylphosphine oxide has been previously described.[14]

(1*S*,4*S*,6*S*)-1-Methyl-4-(1-methylethenyl)-7-oxabicyclo[4.1.0]heptan-2-one (9).[15] A 70% solution of *tert*-butyl hydroperoxide in water (105 g, 816 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 raised the temperature of the mixture to 7 °C. After the mixture was cooled to 5 °C, a mixture of (*S*)-carvone (100 g, 666 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, *Stench!*) 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 NaHCO$_3$ (100 mL) and saturated aqueous NaCl (100 mL), dried over Na$_2$SO$_4$, 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 30 °C under reduced pressure. The resulting yellow oil was dissolved in hexane (500 mL), and the stirred solution was cooled with a dry ice−acetone bath. At −30 °C, crystallization commenced to give a thick suspension. The mixture was then diluted further with hexane (100 mL). After the mixture was stirred at −70 °C for 15 min, the solid was collected by filtration using a sintered glass filter (pre-cooled with dry ice) and quickly washed with cold (pre-cooled to −70 °C) hexane (200 mL). Then, the solid was allowed to melt at ambient temperature. The resulting oil was filtered through the glass filter, which was rinsed with hexane (50 mL). The combined filtrate and washes were concentrated at 30 °C under reduced pressure. The resulting residue was dried at room temperature for 1.5 h under high vacuum to give 88.0 g (79.5%) of **9** as a pale yellow oil. NMR analysis of this material indicated the presence of a trace amount of the 1β-diastereomer, while the mother liquor of the crystallization was found to contain a 2:1 mixture of **9** and its 1β-diastereomer. TLC (9:1 hexanes−ethyl acetate; short-wave UV detection): R_f (*S*)-carvone = 0.4 and R_f **9** = 0.35.

(1*S*,4*S*,6*S*)-4-(1-Acetylhydroperoxy-1-methoxyethyl)-1-methyl-7-oxabicyclo[4.1.0]heptan-2-one (10). A solution of **9** (20.0 g, 120 mmol) and methanol (20 mL, 494 mmol) in dichloromethane (200 mL) was cooled with a dry ice/acetone bath; the nitrogen inlet tube was replaced with a gas dispersion tube, and the gas outlet tube was connected to a trap through a wide 4 mm i.d. tube immersed in a 1 M solution of potassium iodide (2 L). Then, ozonized air (4 LPM) was continuously passed through the reaction mixture at −68 ± 3 °C. The reaction turned pale blue after 65 min, indicating complete reaction. Then, excess ozone was removed by purging with nitrogen (4 LPM) for 30 min, and the mixture was allowed to warm to 14 °C over 40 min to ensure complete conversion of the initially formed ozonide **14** to the desired hydroperoxide **15**. Then, the mixture was cooled to −25 °C, and triethylamine (117 mL, 839 mmol) was added over 5 min while maintaining the temperature of the mixture below −25 °C. Then, DMAP (2.0 g, 16.4 mmol) was added in one portion, followed by the slow addition of acetic anhydride (79.6 mL, 843 mmol) over 10 min while maintaining the reaction temperature between −25 and −38 °C. The mixture was allowed to warm to −8 °C over 30 min and stirred at −7 ± 1 °C for 1.5 h. TLC analysis indicated complete reaction. The reaction was quenched by the slow addition (over 7 min) of methanol (33 mL) while maintaining the temperature of the mixture below 10 °C. After stirring at 5 °C for 5 min, the mixture was diluted with hexane (220 mL), washed consecutively with 10% aqueous citric acid (2 × 150 mL) and saturated aqueous KHCO$_3$ (2 × 80 mL), dried over Na$_2$SO$_4$, and concentrated to dryness at 30 °C under reduced pressure to give 38.2 g (overweight) of crude **10** as a yellow oil. This material is relatively unstable and was immediately used in the next step without further purification. TLC (2:1 hexanes−EtOAc; PMA stain): R_f **9** = 0.8 and R_f **15** = 0.45. TLC (40:2:1 dichloromethane−ethyl acetate−methanol; PMA stain): R_f **15** = 0.4 and R_f **10** = 0.8.

(1*S*,4*S*,6*S*)-4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-1-methyl-7-oxabicyclo[4.1.0]heptan-2-one (12). Crude **10** as obtained above (38.2 g, 120 mmol in theory) and NaOAc (2 g, 24.4 mmol) in methanol (245 mL) were stirred at 37 °C overnight. TLC analysis indicated complete reaction. Then, the mixture was concentrated to dryness at 39 °C, and the residue (29 g) was dissolved in acetonitrile (40 mL). The resulting solution was concentrated to dryness at 35 °C under reduced pressure, and additional acetonitrile (40 mL) was added. The resulting solution was again concentrated to dryness at 35 °C under reduced pressure, and then acetonitrile (35 mL) and imidazole (29.5 g, 433 mmol) were added. After the mixture was cooled with an ice−water bath, *tert*-butylchlorodimethylsilane (32.6 g, 217 mmol) was added. The cold bath was removed, and the mixture was stirred at room temperature for 4 h. TLC analysis indicated the presence of only a trace amount of **11**. The reaction was quenched by the addition of methanol (10 mL). A mild exotherm ensued, which raised the temperature of the mixture by 2 °C. After the mixture was 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 Na$_2$SO$_4$, 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. This 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 (40:2:1 dichloromethane−ethyl acetate−methanol; PMA stain): R_f **10** = 0.8, R_f **11** = 0.4, and R_f **12** = 0.95.

Ethyl 2-[(1*S*,4*S*,6*S*)-1-Methyl-7-oxa-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-bicyclo[4.1.0]hept-2-ylidene]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 triethyl phosphonoacetate (43.3 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 (25.2 g, 98.4 mmol in theory) was added in one portion with the aid of THF (15 mL). The mixture was stirred at 5−6 °C for 90 min, at 11 °C for 18 h, and at 24 °C for 2 h. TLC analysis indicated complete reaction. Then, the mixture was diluted with 8:1 v/v hexanes−EtOAc (100 mL), washed with water (3 × 36 mL), and concentrated to dryness at 38 °C under reduced pressure. The residue was dissolved in hexane (115 mL) and filtered through silica gel (50 g). The silica plug was then washed with 8:1 v/v hexanes−EtOAc (191 mL), and the combined filtrate and washes were concentrated to dryness at 37 °C under reduced pressure. The residue was further dried under high vacuum for 1 h to give 24.4 g (76.1%) of crude **7** as a yellow oil. ^{1}H NMR analysis indicated this material to be a 8.5:1 mixture of *E*/*Z* epimers. This material was used directly in the next step without further purification. TLC (3:1 dichloromethane−hexane; short-wave UV detection and PMA stain): R_f **12** = 0.55, R_f (*E*)-**7** = 0.45, and R_f (*Z*)-**7** = 0.35.

Ethyl (2*E*)-2-[(3*S*,5*R*)-3,5-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-methylene-cyclohexylidene]acetate ((*E*)-5).[13] Tris(dibenzylideneacetone)dipalladium(0)−chloroform adduct (388 mg, 0.375 mmol) and triphenylphosphine (985 mg, 3.75 mmol) were combined in a reaction flask. The flask was evacuated and refilled with nitrogen three times, and then toluene (23 mL) was added via a syringe. The resulting deep purple mixture was stirred at ambient temperature for 1 h to give a yellow slurry (*Note: It is critical to allow enough time, usually from 30 min to 1 h, for the formation of the active catalyst before proceeding with the reaction. 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-(1,1,1,3,3,3-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 theory) 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 for 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[25] was dissolved in DMF (80 mL), and the resulting solution was cooled in an ice−water bath; then, imidazole (6.12 g, 89.8 mmol) followed by *tert*-butylchlorodimethylsilane (13.5 g, 89.8 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 × 150 mL). The combined aqueous washes were extracted with hexane (2 × 100 mL), and the combined extracts were also washed with water (2 × 50 mL). The organic phase and extracts were then combined, dried over $MgSO_4$, and concentrated to dryness under reduced pressure. The residue was dissolved in hexane (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*)-**5** as a colorless oil. TLC (3:1 petroleum ether−Et_2O; short-wave UV detection and PMA stain): R_f **8** = 0.45, R_f **5** = 0.9, R_f **7** = 0.85, R_f **19** = 0.6, and R_f of dba = 0.7.

(2*E*)-2-[(3*S*,5*R*)-3,5-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-methylenecyclohexylidene]-ethanol ((*E*)-6). (*E*)-**5** (27.7 g, 62.9 mmol) was dissolved in hexane (250 mL). After the mixture was cooled to −75 °C, a solution of 1 M DIBALH in hexanes (157 mL, 157 mmol) was added dropwise 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 N HCl (2 × 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 $MgSO_4$, and concentrated to dryness at 35 °C under reduced pressure to give 27 g of the crude product. This material was dissolved in hexane (25 mL) and filtered through silica gel (25 g). The silica plug was then washed with 10−100% EtOAc−hexane, and the combined filtrate and washes were concentrated to dryness at 35 °C under reduced pressure. The residue was further dried under high vacuum to give 23.7 g (94.5%) of (*E*)-**6** as a colorless solid. TLC (9:1 hexanes−EtOAc; short-wave UV detection and PMA stain): R_f (*E*)-**5** = 0.6 and R_f (*E*)-**6** = 0.2.

(2*Z*)-2-[(3*S*,5*R*)-3,5-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-methylenecyclohexylidene]-ethanol ((*Z*)-6).[13] A 500 mL photoreaction vessel equipped with a cooling jacket, Pyrex immersion well, nitrogen inlet tube (immersed deep into the reaction mixture), and outlet bubbler was charged with crude (*E*)-**6** as obtained above (23.7 g, 59.4 mmol), *tert*-butyl methyl ether (100 mL), and a solution of 9-fluorenone-4-carboxylic acid (1.33 g, 5.94 mmol) in *tert*-butyl methyl ether (150 mL). While water was rapidly passed through the well and the reaction vessel was immersed in a 15 °C water bath, the above solution was irradiated with a 450 W medium-pressure mercury lamp through a uranium filter. During the photolysis, nitrogen was continuously bubbled through the reaction solution via the inlet tube. The reaction was monitored by HPLC analysis, which indicated that a photostationary state was reached at 98.6% conversion after 6 h of irradiation. The reaction mixture was concentrated to dryness at 30 °C under reduced pressure and then dried under high vacuum for 30 min. The residue was dissolved in 9:1 hexanes−EtOAc (50 mL) and filtered through silica gel (50 g). The silica plug was then washed with 9:1 EtOAc−hexane (750 mL), and the combined filtrate and washes were concentrated to dryness at 35 °C under reduced pressure. The residue was further dried under high vacuum to give 21.2 g (89.3%) of crude (*Z*)-**6** as an off-white solid. This material was dissolved in acetonitrile (22 mL) at reflux, and the resulting solution was stored in a freezer at −20 °C overnight. The resulting solid was collected by filtration, washed with ice-cold acetonitrile (3 × 3 mL), and dried by suction and then under vacuum to give 18.3 g (77.2%) of (*Z*)-**6** as a colorless solid, mp 68−70 °C. HPLC analysis indicated that this material contained 0.36% of (*E*)-**6** and 0.24% of the 1β-epimer. HPLC (column = ES SI 3 μm, 5 × 150 mm; mobile phase = 7% THF in heptane at 1 mL/min; detection at 220 nm): R_t (*Z*)-**6** = 10.5, R_t (*E*)-**6** = 11.9, R_t = 13.3 (1β-epimer) min.

[[(1*R*,3*S*,5*Z*)-5-(2-Chloroethylidene)-4-methylene-1,3-cyclohexanediyl]bis(oxy)]bis(1,1-dimethylethyl)dimethylsilane.[13] *Caution! This reaction should be performed in a well-ventilated hood.* (*Z*)-**6** (18.2 g, 45.6 mmol), hexanes (250 mL), and triphosgene (6.76 g, 22.8 mmol) were combined in a reaction flask. The resulting solution was then cooled with an ice−water bath, and after a clear solution resulted, triethylamine (22.3 mL, 160 mmol) was added dropwise over 10 min with vigorous stirring. After the mixture was stirred at 5 °C for 20 min, the cooling bath was removed and the resulting

---

[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 (<7:1).

[25] This material contained, by HPLC analysis, (*E*)-**8** (R_t = 17.6 min), ca. 11% of the enone byproduct **19** (R_t = 10.2 min), and ca. 1.4% of the **1**β-epimer of (*E*)-**8** (R_t = 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 × 250 mL) and water (2 × 250 mL). The combined aqueous washes were back-extracted with hexanes (2 × 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 (*Z*)-**6** = 0.2 and chloride product $R_f = 0.6$.

[(2*Z*)-2-[(3*S*,5*R*)-5-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-methylenecyclohexylidene]-ethyl]diphenylphosphine Oxide (1).[13] DMF (170 mL) and sodium hydride, 60% dispersion in mineral oil (2.02 g, 50.6 mmol), were combined in a reaction flask. Then, diphenylphosphine 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 °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 °C. The reaction mixture was stirred for 1.5 h at temperatures from −30 to −35 °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 × 200 mL). The combined aqueous washes were extracted with diethyl ether (2 × 150 mL), and these extracts were also washed with water (2 × 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 L), 8:2 hexanes−EtOAc (1 L), and 7:3 hexanes−EtOAc (1 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 **1** 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 **1** = 0.45.

Supporting Information Available: ^{1}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.

JO0161577