A Short, Efficient Copper-Mediated Synthesis of 1α,25-Dihydroxyvitamin D_2 (1α,25-Dihydroxyergocalciferol) and C-24 Analogs[1,2]

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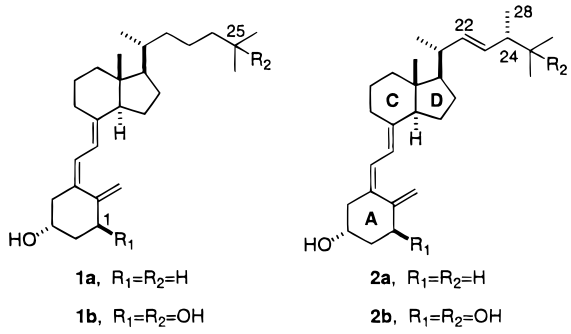
Two synthetic routes to the nonnatural hormone 1α,25-dihydroxyergocalciferol [**2b**, 1α,25-$(OH)_2$-D_2] and analogs modified at C-24 have been developed both starting from aldehyde **7b**. Key steps in route A (eight steps, ≈38% overall yield from **7b**) are (1) stereoselective addition of (*E*)-vinyllithium reagent **8c** to aldehyde **7b**; and (2) S_N2' *anti*-displacement of the allylic phosphate of **5e** by organocuprates derived from Grignard reagents and CuCN in the presence of LiCl. Key steps in route B (eight steps from **7b**, 48% overall yield) are (1) Wittig−Horner type coupling between ketone **22**, which bears an allylic phosphate group on the side chain, and the ylide derived from the Lythgoe−Roche phosphine oxide to form the vitamin D triene unit; and (2) efficient S_N2' *anti*-displacement of the phosphate group of **23** by the organocuprate derived from MeMgCl, CuCN, and LiCl, without affecting the labile vitamin D triene system, to give, after deprotection, 1α,25-$(OH)_2$-D_2. Route B is particularly attractive as an approach to diverse C-24 vitamin D analogs for biological screening.

Introduction

Vitamin D_3 (**1a**, colecalciferol, Figure 1) is hydroxylated in the liver and the kidney to its hormonally active form 1α,25-dihydroxyvitamin D_3 [**1b**, calcitriol, 1α,25-$(OH)_2$-D_3], which regulates calcium homeostasis and bone mineralization.[3] Calcitriol also promotes cell-differentiation and inhibits the proliferation of malignant cells, suppresses tumor growth, inhibits metastasis, and prolongs survival[4] in cancer patients.[5] It has also been used in the treatment of several other human diseases, including osteoporosis,[6] psoriasis,[7] and AIDS.[8] For some years, the nonnatural vitamin D_2 (**2a**, ergocalciferol) has been administered to humans and domestic animals[3,9] on the assumption that its metabolism and biological activity parallel those of vitamin D.[10] There is now strong evidence that vitamin D_2 also undergoes a double hydroxylation to produce 1α,25-dihydroxyvitamin D_2 [**2b**, 1α,25-$(OH)_2$-D_2],[10−13] although other metabolites can be formed as a result of hydroxylations at C-24, C-26, and C-28.[14] 1α,25-Dihydroxyvitamin D_2 also induces cell-differentiation and inhibits the proliferation of a number of tumor cell lines, including leukemic cells.[15] Unfortunately, **1b** and **2b** cause hypercalcemia in treated pa-



1a, $R_1=R_2=H$ **2a**, $R_1=R_2=H$

1b, $R_1=R_2=OH$ **2b**, $R_1=R_2=OH$

Figure 1.

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(1) This paper is dedicated to Professor Dieter Seebach in honor of his 60th birthday.

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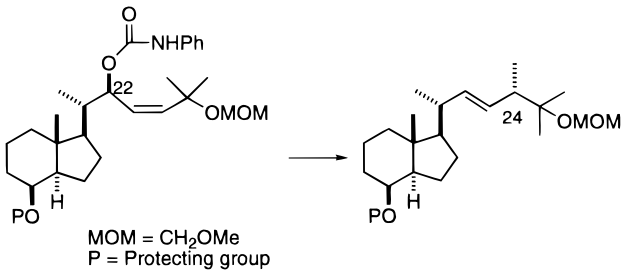
tients, making the therapeutic window of efficacy quite narrow. For this reason, there is increasing interest in the development of new vitamin D analogs with strong cell-differentiating and weak calcemic effects. Most analogs examined to date belong to the natural vitamin D_3 series rather than the vitamin D_2 series,[16] although analogs have been reported that preserve structural features of vitamin D_2 such as the $C_{22}-C_{23}$ double bond[17] or both this double bond and the C-24 methyl group.[18,19]

Interest in the biological evaluation of vitamin D_2 metabolites and analogs has led to the development of several synthetic approaches to these compounds. Among the methods that have been used for the introduction of vitamin D_2 and 25-OH-D_2 side chains[20] are the Wittig reaction,[21] the Julia olefination,[7b,19a,22] the solvolysis of cyclopropylcarbinyl precursors,[23] the chemistry of $Zr(C_5H_5)_2$ on vinylcyclopropanes,[24] the chemistry of isoxazolidines derived from nitrones,[25] the Ramberg−Bäcklund reaction,[26] and the Claisen rearrangement.[27] During the last decade we have synthesized 25-hydroxyvitamin D_2 (**2c**)[28a] and 1α,25-dihydroxyvitamin D_2 (**2b**),[28b] introducing the 24-methyl group by S_N2' *syn*-displacement of *Z*-allylic phenyl carbamates by $Li_2Cu_3Me_5$ (Scheme 1). Drawbacks to this approach are (1) the need to use chiral reducing agents or to open chiral dioxanones or acetal templates in order to introduce the allylic *22R*-hydroxy configuration; and (2) difficulties with the introduction of alkyl groups other than methyl by S_N2' *syn*-displacement of the carbamate by an alkyl cuprate.[29]

Scheme 1



Here we describe two short, practical synthetic routes to 1α,25-dihydroxyvitamin D_2 and its analogs modified at C-24.

Synthetic Plan

As an extension of our previous work on the synthesis of vitamin D_2 metabolites and analogs, we initially envisaged the synthesis of the target 1α,25-$(OH)_2$-D_2 analogs modified at C-24 by the retrosynthetic analysis depicted in route A of Scheme 2. This approach takes advantage of the ready availability of aldehyde **7** by degradation of commercially available vitamin D_2 (**2a**).[27,28b,c] A key step in this approach is the S_N2' *anti*-alkylation by cuprates[30] of (*E*)-allylic systems of type **5**, which would be derived from stereoselective reaction of aldehyde **7** with the appropriate vinyl carbanion[31] followed by esterification. In preliminary studies using semirigid allylic systems, similar regio- and stereochemical results were obtained for the alkylation of simple secondary allylic phosphate esters, pivalates, and benzoates under Goering conditions (RMgX with a catalytic amount of CuCN),[32] phosphates giving higher yields on reaction products.[33] This result, combined with the fact that Yamamoto and co-workers have also reported that

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(17) Some interesting analogs of this type are (a) Calcipotriol (MC-903), which is used for the topical treatment of psoriasis; see Calverley, M. J.; Jones, G. Vitamin D. In Antitumor Steroids; Blickenstaff, R. T., Ed., Academic Press: San Diego, 1992. (b) (22*E*,25*R*)-1α,25,26-$(OH)_3$-Δ^{22}-D_3, which has been identified as a potential antiosteoporotic agent; see Drezner, M. K.; Nesbitt, T. In *Vitamin D: Gene Regulation, Structure-function Analysis and Clinical Application*; Norman, A. W., Bouillon, R., Thomasset, M., Eds.; Walter de Gruyter: Berlin, 1991; p 816. (c) EB-1089, which inhibits the growth of breast cancer cells *in vitro* and *in vivo*; see Binderup, L. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1891.

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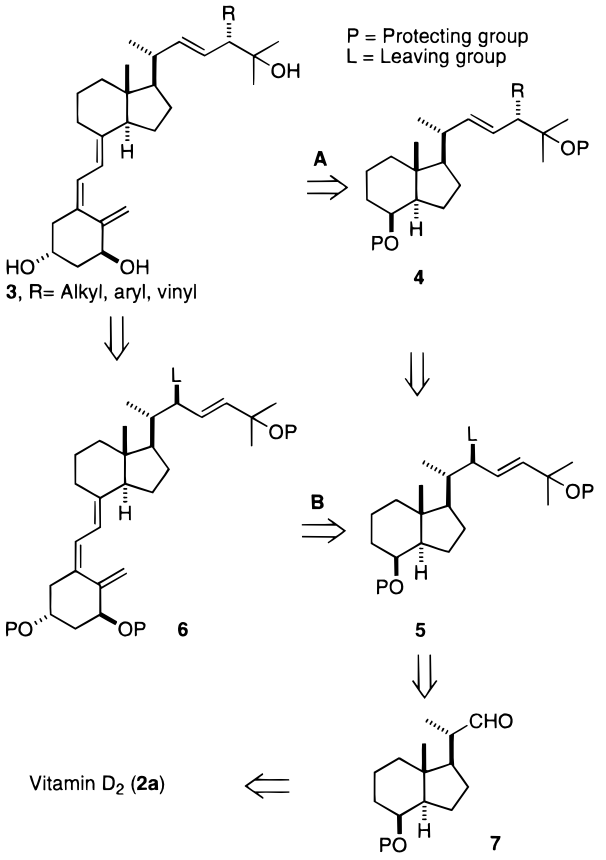
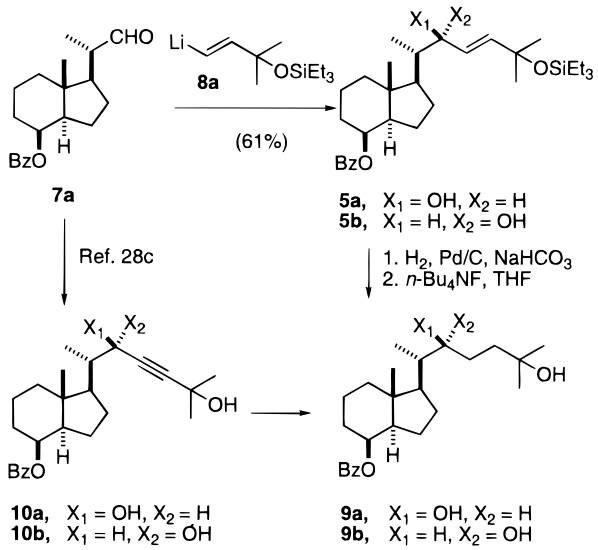
Scheme 2



Scheme 3



allylic phosphates react efficiently in an S_N2' *anti* fashion with cuprates derived from magnesium reagents,[30a] led us to examine the utility of a phosphate leaving group first. The synthetic plan also includes a second approach (route B), in which the copper chemistry is carried out on an allylic system of type **6**, which contains the fully assembled vitamin D triene unit. This approach has the advantage that it would allow for the preparation of several vitamin D_2 analogs modified at C-24 in a short period of time simply by reacting different cuprates with **6**, albeit with the risk of destroying the labile vitamin D triene unit. Since synthesis of vitamin D_2 analogs **3** by both routes was envisaged to pass through **5**, this compound was our first synthetic target.

Results and Discussion

1. Formation of the CD Side Chain Fragment (Route A). Our experiments started from aldehyde **7a**[27,28b,c] which was treated with the vinyllithium reagent **8a** prepared using methodology developed by Salomon and co-workers[34] (Scheme 3). At best, slow addition of **8a** (4.5 mmol) to aldehyde **7a** (3.2 mmol, THF, −78 °C) led to a chromatographically separable 6.7:1 mixture of allylic alcohols **5a** and **5b** in 61% yield. The stereochemistry of these alcohols at C-22 was established by comparison of the ^{1}H and ^{13}C NMR spectra of the corresponding deprotected, saturated compounds **9a** and **9b** with authentic samples prepared from the known propargylic alcohols **10a** and **10b**.[28c]

The fact that reaction of vinyllithium reagent **8a** with aldehyde **7a** provided the desired Cram alcohol **5a** as the major product in only moderate yield led us to replace the potentially labile benzoate protecting group with a silyl group. In order to selectively remove this silyl protecting group before introducing the vitamin D triene system by the Wittig−Horner olefination method,[20b] it was also necessary to replace the protecting group at C-25 (Scheme 4). To this end, the requisite lithium reagent **8c** was conveniently prepared in two steps from the protected propargylic alcohol **11**.[28c] Irradiation of **11** in the presence of Bu_3SnH and AIBN led to the formation of the vinyltin reagent **8b**, which was converted to the desired vinyllithium reagent **8c** by treatment with *n*-butyllithium. After some experimentation, we found that addition of **8c** (3.3 mmol) to a solution of aldehyde **7b**[35] (0.3 g, 0.94 mmol) in Et_2O at −78 °C afforded a chromatographically separable 7:1 mixture of epimeric alcohols **5c** and **5d** in 88% yield. The stereochemistry of **5c** and **5d** at C-22 was established by comparison of their ^{1}H NMR spectra with those of **5a** and **5b**. Attempts to scale up this procedure to 1.5 g (4.6 mmol) of aldehyde **7b** resulted in lower yields; however, this setback was easily overcome by adding a cooled (−85 °C) solution of the aldehyde to a −78 °C cooled solution of the lithium reagent. With the (22*R*)-alcohol **5c** in hand, we next attempted the preparation of the phosphate **5e**, using Murahashi reaction conditions [$(EtO)_2POCl$, py, CH_2Cl_2].[36] This procedure gave unexpectedly low yields (≈40%) due to elimination of the phosphate group. However, deprotonation of alcohol **5c** with *n*-butyllithium in Et_2O at −78 °C, followed by reaction of the resulting lithium alkoxide with diethyl chlorophosphate at −78 °C, led to the formation of the desired phosphate **5e** in 93% yield.

The stage was now set for studying the reaction of allylic phosphate **5e** with organocuprates. For construction of 25-OH-D_2 side chain, we first tried Goering reaction conditions [MeMgCl (20 equiv), CuCN (2 equiv), Et_2O, 0 °C → rt].[32] Under these conditions alkylation was not regioselective, affording an inseparable roughly 1:1

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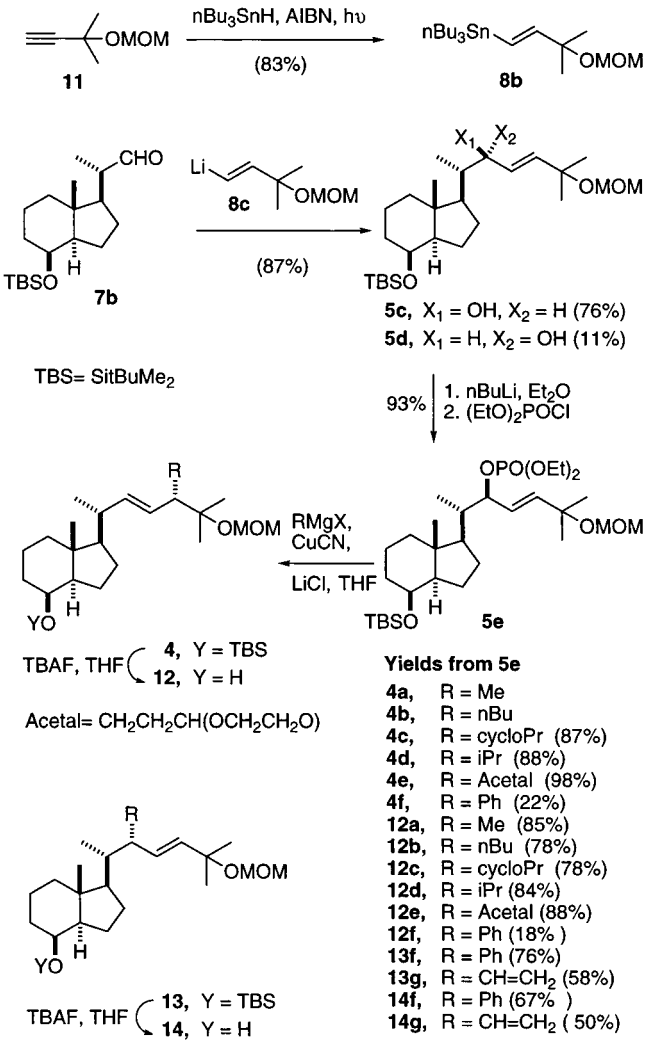
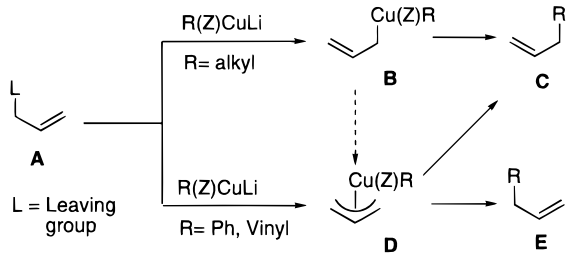
Scheme 4



mixture of the S_N2' and S_N2 products **4a** and **13a**, respectively, in 86%. However, under Yamamoto conditions [MeMgCl (10 equiv), CuCN·2LiCl (10 equiv), THF, −78 °C],[30a,37] the alkylation was highly regioselective, affording, after deprotection (Bu_4NF, THF, 60 °C), the S_N2' *anti*-product **12a**[28b] in 85% yield (Scheme 4). Encouraged by this result, we examined the reaction of **5e** with sp^3-organocopper reagents bearing other alkyl groups. Introduction of the *n*-butyl group under the same reaction conditions occurred with a high degree of regioselectivity to give, after deprotection,[38] compound **12b** (78%). Likewise, the use of Grignard reagents [c-PrMgBr, *i*-PrMgCl, and $(OCH_2CH_2O)CHCH_2CH_2MgBr$][39] gave **4c** (87%), **4d** (88%), and **4e** (98%), respectively, as the only compounds detectable by ^1H and ^{13}C NMR. However when phosphate **5e** was treated with sp^2-copper reagents under the same reaction, partial or total loss of S_N2' regioselectivity occurred. Thus, treatment of **5e** with the cuprate derived from PhMgCl gave a separable 1:3.4 mixture of **4f** (S_N2' *anti*) and **13f** (S_N2) in 98% yield, and reaction of **5e** with CH_2=CHMgBr gave only the S_N2 product **13g** in 58% yield. This type of behavior in the reactions of sp^2-organocopper reagents with allylic systems was also described by other authors.[30b,31a,b,40,41]

Scheme 5. Goering's Mechanism for the Reaction of Cuprates with Allylic Esters



The above results can be rationalized by the mechanism proposed by Goering,[41a] in which the allylic ester and alkyl cuprate initially form a σ-allylic copper complex **B** (Scheme 5) that can undergo reductive elimination to the S_N2' product **C** faster than it isomerizes to the π-allylic complex **D**. By contrast, aryl and vinyl cuprates form the π-allylic complex **D** from which both S_N2 product **E** and the S_N2' product **C** may be formed.

2. Synthesis of Vitamin D Analogs. For assembly of the triene unit of the target vitamin D_2 analogs modified at C-24, we chose the Lythgoe−Roche phosphine oxide approach.[20b,25] This mild, convergent and direct method requires ketones **15**, corresponding to the CD-side chain fragments, and the phosphine oxide **17**, corresponding to the A-ring fragment (Scheme 6). The requisite ketones **15b**−**f** were prepared in 92−98% yields from the corresponding 8β-hydroxy-precursors **12b**−**f**. Treatment of the phosphine oxide **17**[20i−k,42] with phenyllithium at −78 °C,[43] followed by Lythgoe-type coupling[20b,25] of the resulting anion with each of the CD side chain ketone fragments, provided the corresponding protected vitamin D analogs **18c**−**f**. Cleavage of the protecting groups using the cationic ion-exchange resin AG50 WX4 in MeOH afforded a complex mixture of partially deprotected products, resulting in the desired vitamin D analogs in low yield after long reaction times. However, cleavage of the *tert*-butyldimethylsilyl groups of **18c**−**f** by reaction with tetrabutylammonium fluoride, followed by treatment of each of the resulting crude diols with AG50 WX4 resin in MeOH, afforded the vitamin D analogs **19c**,**d**,**f** in high yield (≈55%, in three steps from ketones **15**). The formation of **19e** as a mixture of diastereomers can be inferred to be due to transketalization following deprotection. In a similar manner ketones **16f**,**g**, prepared from **14f**,**g**, were converted to protected analogues **20f**,**g**. Desilylation followed by methanolysis of the OMOM group of **20f**,**g** in the presence of the acidic resin afforded the 25-methoxyvitamin D analogs **21f**,**g**.[44]

3. Exploration of Route B. Synthesis of 1α,25-dihydroxyvitamin D_2 (Scheme 7). Route A allowed

(37) While this work was in progress, a catalytic version of the Yamamoto reaction appeared. See ref 30b.

(38) Small amounts of S_N2 regioisomers and other stereoisomers with *Z* configuration at the double bond were chromatographically removed after desilylation.

(39) The compound with a 3,3-(ethylendioxy)propyl group was prepared as a precursor for the preparation of affinity columns for the purification of the receptor of 1α,25-dihydroxyvitamin D_3 hormone receptor.

(40) Marino, J. P.; Fernández de la Pradilla, R.; Laborde, E. *J. Org. Chem.* **1987**, *52*, 4898.

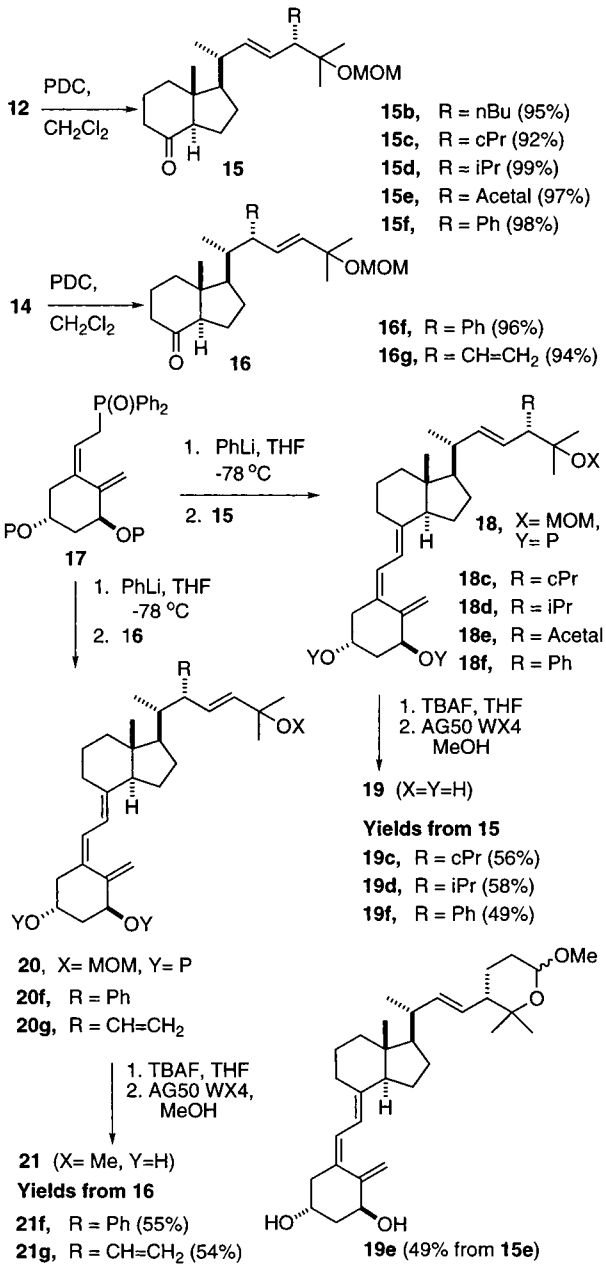
(41) (a) Underiner, T. L.; Paisley, S. D.; Schmitter, J.; Lesheski, L.; Goering, H. L. *J. Org. Chem.* **1989**, *54*, 2369. (b) Underiner, T. L.; Goering, H. L. *Ibid.* **1991**, *56*, 2563.

(42) Mouriño, A.; Torneiro, M.; Vitale, C.; Fernández, S.; Pérez-Sestelo, J.; Anné, S.; Gregorio, C. Efficient and Versatile Synthesis of A-Ring Precursors of 1α,25-Dihydroxyvitamin D_3 and Analogues. Application to the Synthesis of Lythgoe-Roche Phosphine Oxide. *Tetrahedron Lett.* **1997**, *38*, 4713.

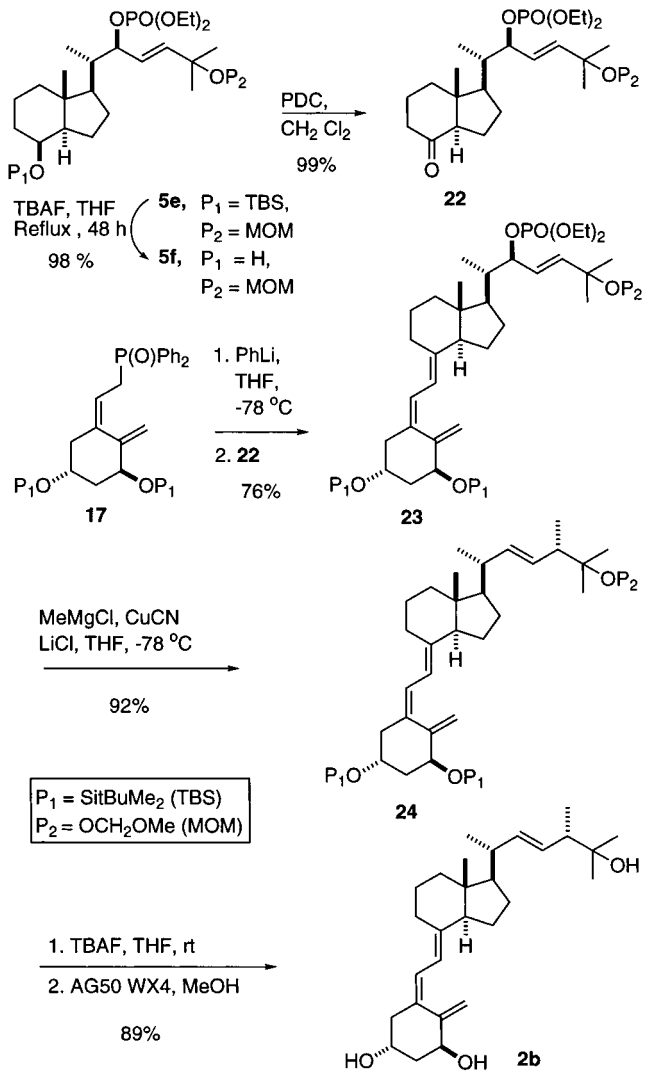
(43) Posner, G. H.; Johnson, N. *J. Org. Chem.* **1994**, *59*, 7855.

(44) Efforts to drive the reaction to the desired 1α,25-dihydroxyvitamin D analogs using MeOH−H_2O or THF−H_2O have not been carried out.

Scheme 6



Scheme 7



the efficient preparation of several 1α,25-dihydroxyvitamin D_2 analogs modified at C-24, but required individual preparation of each CD-side chain vitamin D fragment prior to Wittig−Horner coupling with the A-ring phosphine oxide.[45] In route B, the use of a ready-assembled vitamin D triene moiety with a (22*R*)-phosphate group on the side chain (**23**) should serve for the preparation of numerous 1α,25-dihydroxyvitamin D_2 analogs modified at the side chain, simply by reacting it with different cuprates. To test the feasibility of the Wittig−Horner coupling step, a THF solution of ketone **22** prepared from **5e** in 97% was treated at −78 °C with a THF solution of the ylide resulting from metalation of phosphine oxide **17**. We were pleased to find that this reaction afforded the desired phosphate **23** in 76% yield. Next, we examined the possibility of incorporating alkyl groups in the side chain by S_N2' *anti*-displacement of the phosphate group by alkyl cuprates. To test the feasibility of this step we chose 1α,25-dihydroxyergocalciferol (**2b**) as the synthetic target. Treatment of phosphate **23** with the cuprate derived from MeMgCl and CuCN in the presence of LiCl afforded **24** as the only product (92% yield). Removal of the silyl groups with tetra-*n*-butylammonium fluoride, and the MOM protecting-group with AG50 WX4 resin in methanol, gave the nonnatural hormone 1α,25-dihydroxyergocalciferol (**2b**) (89%, two steps).

In summary, we have developed two short, efficient approaches to the synthesis of 1α,25-dihydroxyergocalciferol and its analogs modified at C-24. In route A, an allylic phosphate bearing the CD-ring fragment of vitamin D undergoes S_N2' *anti*-displacement by an organocuprate and is then coupled with the A-ring fragment by the Horner−Wittig olefination method, affording analogs of 1α,25-dihydroxyergocalciferol with an alkyl substituent at C-24 (eight steps and ≈38% average overall yield from aldehyde **7b**). In route B, an allylic phosphate bearing the ready-assembled vitamin D triene unit undergoes S_N2' *anti*-displacement by an organocuprate. As an example, the organocuprate derived from MeMgCl afforded 1α,25-dihydroxyergocalciferol in eight steps and 48% overall yield from aldehyde **7b**. Route B is particularly attractive since it offers the possibility of preparing, from a single starting allylic phosphate (**23**), a variety of C-24 analogs of vitamin D_2 for biological screening.

(45) Previous experiments carried out in our laboratory indicate that the Wittig−Horner type coupling gives the vitamin D triene unit in low yield when the amount of CD-side chain fragment used is lower than 50 mg.

Experimental Section

General. All reactions involving oxygen- or moisture-sensitive compounds were carried out under a dry argon atmosphere. Reaction temperatures refer to external bath temperatures. All dry solvents were distilled under argon immediately prior to use. Tetrahydrofuran (THF) and ether (Et_2O) were distilled from Na/benzophenone. Dichloromethane (CH_2Cl_2) was distilled from P_2O_5. The concentrations of commercially available solutions of organolithium reagents (Aldrich) were checked by titration using diphenylacetic acid.[47] Liquid reagents or solutions of reagents were added by syringe or cannula. The analytical grade cation exchange resin AG50 WX4 was supplied by BioRad. Organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated with a rotary evaporator at aspirator pressure (20-30 mmHg). Reactions were monitored by thin layer chromatography (TLC) using aluminum Merck 60 silica gel plates (0.2 mm thickness). After ultraviolet illumination at 254 nm, the plates were visualized by immersion in a solution of phosphomolybdic acid in MeOH (5%), followed by heating. Column chromatography was performed with Merck 60 (230−400 mesh) silica gel.[48] All NMR spectra were measured as solutions in $CDCl_3$ unless otherwise stated. Chemical shifts are reported as δ units (ppm) downfield from tetramethylsilane (δ 0.0) using residual solvent signal as an internal standard: δ 7.26 (^{1}H), 77.0 triplet (^{13}C). All coupling constants are measured in hertz units (Hz). DEPT was used to assign carbon types. Unless otherwise noted, mass spectra were measured using electron impact ionization at 70 eV.

(22*R*,23*E*)-8*β*-(Benzoyloxy)-25-[(triethylsilyl)oxy]-des-A,B-cholest-23-en-22-ol (5a) and (22*S*,23*E*)-8*β*-(Benzoyloxy)-25-[(triethylsilyl)oxy]-des-A,B-cholest-23-en-22-ol (5b). *n*-Butyllithium (1.83 mL, 2.46 M in hexanes, 4.50 mmol) was slowly added to a solution of (1*E*)-3-methyl-1-(tributylstannyl)-3-[(triethylsilyl)oxy]-1-butene[34] (2.21 g, 3.21 mmol) in tetrahydrofuran (10 mL) at −78 °C. After stirring for 4 h, the solution was slowly cannulated into a solution of aldehyde **7a** (1.01 g, 3.21 mmol) in tetrahydrofuran (10 mL) at −78 °C. After 2 h, the reaction was quenched by dropwise addition of MeOH. After warming to rt, the mixture was concentrated in vacuo. Flash chromatography (2.5 × 20 cm; eluent, 6−8% EtOAc−hexanes) afforded a 6.7:1 mixture of **5a** and **5b** (1 g, 60% combined yield). HPLC separation of an aliquot (Phenomenex Zorbasil 10 × 250 mm column; eluent 1% 2-propanol−hexanes, Φ = 1.5 mL/min) gave **5a** [t_R = 25.2 min, R_f = 0.69 (30% EtOAc−hexanes), colorless oil], and **5b** [t_R = 22.1 min, R_f = 0.70 (30% EtOAc−hexanes), colorless oil]. **5a**. ^{1}H NMR: 8.07−7.41 (5H, m, Ar), 5.74 (1H, d, J = 15.7, H-24), 5.68 (1H, dd, J = 15.7, 4.51, H-23), 5.42 (1H, br s, H-8), 4.26 (1H, br s, H-22), 1.31 (3H, s, CH_3-26), 1.30 (3H, s, CH_3-27), 1.06 (3H, s, CH_3-18), 0.94 [9H, t, J = 7.9, Si(CH_2CH_3)$_3$], 0.91 (3H, d, J = 6.04, CH_3-21), 0.57 [6H, q, J = 7.9, Si(CH_2CH_3)$_3$]. ^{13}C NMR: 166.52 (C=O), 138.88 (CH-23 or 24), 132.68 (CH=), 131.00 (C=), 129.59 (CH=), 128.78 (CH-23 or 24), 128.36 (CH=), 73.54, 72.79 (C-25), 72.17, 52.85, 51.56, 42.79 (C-13), 41.11, 39.86 (CH_2), 30.75 (C-26), 30.51 (CH_2), 30.43 (C-27), 26.61 (CH_2), 22.57 (CH_2), 17.96 (CH_2), 13.38, 11.86, 6.93 [Si(CH_2CH_3)$_3$], 6.65 [Si(CH_2CH_3)$_3$]. Anal. Calcd for $C_{31}H_{50}O_4Si$: C, 72.33; H, 9.79. Found: C, 72.40; H, 9.55. **5b**. ^{1}H NMR: 8.07−7.41 (5H, m, Ar), 5.78 (1H, d, J = 15.5, H-24), 5.63 (1H, dd, J = 15.5, 7.0, H-23), 5.41 (1H, br s, H-8), 4.19 (1H, dd, J = 7.0, 3.6, H-22), 1.32 (3H, s, CH_3-26), 1.31 (3H, s, CH_3-27), 1.07 (3H, s, CH_3-18), 0.97 (3H, d, J = 6.14, CH_3-21), 0.96 [9H, t, J = 7.8, Si(CH_2CH_3)$_3$], 0.59 [6H, q, J = 7.8, Si(CH_2CH_3)$_3$]. ^{13}C NMR: 166.56 (C=O), 141.65 (CH-23 or 24), 132.75 (CH=), 130.99 (C=), 129.62 (CH=), 128.42 (CH=), 124.58 (CH-23 or 24), 74.00, 72.90 (C-25), 72.01, 53.49, 51.39, 42.16 (C-13), 41.78, 39.95 (CH_2), 30.84 (C-26 or 27), 30.59 (CH_2), 30.48 (C-26 or 27), 26.51 (CH_2), 22.76 (CH_2), 17.96 (CH_2), 13.53, 12.29, 7.03 [Si(CH_2CH_3)$_3$], 7.73 [Si(CH_2CH_3)$_3$]. HRMS calcd for $C_{31}H_{50}O_4Si$ 514.3478, found 514.3478.

(22*S*)-8*β*-(Benzoyloxy)-des-A,B-cholestane-22,25-diol (9a). A mixture of diol **10a** (40 mg, 0.10 mmol), Pd/C (10%, 5 mg), and $NaHCO_3$ (12 mg, 0.14 mmol) in dioxane was hydrogenated at balloon pressure for 12 h. EtOAc (10 mL) was added, and the mixture was filtered through a short path of Celite. Concentration in vacuo and flash chromatography of the concentrate (1 × 15 cm; eluent, 30−50% EtOAc−hexanes), afforded diol **9a** [35 mg, R_f = 0.2 (40% EtOAc−hexanes), white solid, mp 35−37 °C]. ^{1}H NMR: 8.07−7.40 (5H, m, Ar), 5.41 (1H, br s, H-8), 3.65 (1H, m, H-22), 1.24 (3H, s, CH_3-26), 1.23 (3H, s, CH_3-27), 0.95 (3H, s, CH_3-18), 0.94 (3H, d, J = 6.29, CH_3-21). ^{13}C NMR: 166.56 (C=O), 13 2.72 (Ar), 130.98 (Ar), 129.59 (Ar), 128.38 (Ar), 73.99, 72.19, 70.72, 52.96, 51.57, 41.79, 40.75, 40.50, 39.95, 30.51, 30.18, 29.90, 28.98, 26.57, 22.52, 17.98, 13.41, 11.57. HRMS calcd for $C_{25}H_{38}O_4$ 402.2770, found 402.2766.

(22*R*)-8*β*-(Benzoyloxy)-des-A,B-cholestane-22,25-diol (9b). Procedure as above. **9b** [81%, R_f = 0.25 (50% EtOAc−hexanes), white solid]. ^{1}H NMR: 8.07−7.41 (5H, m, Ar), 5.42 (1H, br s, H-8), 3.65 (1H, m, H-22), 1.25 (3H, s, CH_3-26), 1.24 (3H, s, CH_3-27), 1.05 (3H, s, CH_3-18), 0.96 (3H, d, J = 6.73, CH_3-21). ^{13}C NMR: 166.56 (C=O), 132.73 (Ar), 130.94 (Ar), 129.59 (Ar), 128.40 (Ar), 74.13, 71.98, 70.74, 53.68, 51.31, 42.16, 41.95, 42.01, 39.95, 30.56, 29.97, 29.15, 26.30, 24.43, 22.65, 17.96, 13.43, 12.27. HRMS: calcd for $C_{25}H_{38}O_4$ 402.2770, found 402.2771.

Preparation of 9a and 9b from a Mixture of 5a and 5b. A mixture of **5a** and **5b** (50 mg, 0.097 mmol), Pd/C (10%, 5 mg), and $NaHCO_3$ (12 mg, 0.14 mmol) in dioxane (2.5 mL) was hydrogenated at balloon pressure for 24 h. EtOAc (10 mL) was added, and the mixture was filtered through a short path of Celite. After concentration in vacuo, the residue was dissolved in THF (1 mL). Tetrabutylammonium fluoride (TBAF, 0.5 mL, 0.55 mmol, 1.1 M in THF) was added. After stirring for 24 h, the mixture was concentrated in vacuo. The residue was extracted with Et_2O. The combined organic phases were washed with saturated NaCl, dried, filtered, and concentrated in vacuo. Comparison of the spectral data of the mixture (^{1}H NMR and ^{13}C NMR) with those obtained above for **9a** and **9b** shows that **9a** is the major component.

(1*E*)-3-[(Methoxymethyl)oxy]-3-methyl-1-(tributylstannyl)-1-butene (8b). A mixture of compound **11** (0.50 g, 3.90 mmol), Bu_3SnH (1.51 g, 1.4 mL, 5.20 mmol), and AIBN (20 mg) was irradiated with a 300 W tungsten lamp at rt for 15 min and at 95 °C for 6 h. The mixture was slowly cooled to rt. Flash chromatography (1.5 × 15 cm; eluent, 0−0.7% EtOAc−hexanes) gave tin derivative **8b** [1.36 g, 83%, R_f = 0.4 (10% EtOAc−hexanes), colorless liquid, bp 120 °C/1 mmHg]. ^{1}H NMR: 6.02 (2H, AB, J = 19.5, HC=CH), 4.63 (2H, s, OCH_2O), 3.35 (3H, s, OCH_3), 1.47 [6H, m, Sn(CH_2-)$_3$], 1.30 (6H, s, 2 CH_3), 1.29 [6H, m, Sn(CH_2CH_2-)$_3$], 0.91−0.85 [15H, m, (-CH_2CH_3)$_3$]. ^{13}C NMR: 153.26 (CH=), 126.58 (CH=), 91.97 (OCH_2O), 77.76 (*C*OMOM), 54.98 (OCH_3), 29.01 [Sn(CH_2-)$_3$], 27.12 [Sn(CH_2CH_2-)$_3$], 26.75 [C(CH_3)$_2$], 13.55 [(-CH_3)$_3$], 9.42 [(-CH_2CH_3)$_3$]. Anal. Calcd for $C_{19}H_{40}O_2Sn$: C, 54.44; H, 9.62. Found: C, 54.16; H, 9.25.

(22*R*,23*E*)-8*β*-[(*tert*-Butyldimethylsilyl)oxy]-25-[(methoxymethyl)oxy]-des-A,B-cholest-23-en-22-ol (5c). *n*-Butyllithium (3 mL, 2.38 M in hexanes, 7.11 mmol) was slowly added to tin compound **8b** (2.98 g, 7.11 mmol, freshly bulb to bulb distilled) in Et_2O (19 mL) at −78 °C. After stirring for 4 h, the reaction mixture was cooled to −85 °C. A solution of aldehyde **7b** (1.49 g, 4.59 mmol) in Et_2O (36 mL) was cannulated over 15 min. After stirring for 2 h, the reaction was quenched by dropwise addition of MeOH. The mixture was allowed to warm to rt and then was poured into a mixture of saturated NaCl and HCl (10%) and extracted with Et_2O. The combined organic extracts were dried, filtered, and concentrated in vacuo. Medium pressure liquid chromatography (5 × 45 cm; eluent 10% EtOAc−hexanes) gave alcohol **5c** [1.58 g, 76%, R_f = 0.61 (30% EtOAc−hexanes)] as a colorless oil which crystallizes upon standing in the refrigerator during several days (mp 49 °C), and **5d** [0.24 g, 11%; R_f = 0.57 (30% EtOAc−hexanes); colorless oil]. **5c**. ^{1}H NMR: 5.66 (1H, d, J = 16.1, H-24), 5.58 (1H, dd, J = 16.1, 3.5, H-23), 4.62 (2H, s, OCH_2O), 4.25 (1H, br s, H-22), 3.98 (1H, br s, H-8), 3.33 (3H,

(46) Attempts to carry out this type of transformation using other cuprates have not been pursued although similar results are expected.
(47) Kofron, W. G.; Badawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879.
(48) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

s, OCH_3), 1.31 (6H, s, CH_3-26 and 27), 0.90 (3H, s, CH_3-18), 0.86 [9H, s, $SiC(CH_3)_3$], 0.82 (3H, d, J = 5.93, CH_3-21), −0.01 (3H, s, $SiCH_3$), −0.03 (3H, s, $SiCH_3$). ^{13}C NMR: 135.00 (CH═), 132.58 (CH═), 91.75 (OCH_2O), 75.88 (C-25), 73.35 (69.41), 54.95 (OCH_3), 53.13, 52.98, 41.95 (C-13), 40.81, 40.60 (CH_2), 34.35 (CH_2), 27.32, 27.24 (C-26 and 27), 26.81 (CH_2), 25.74 [$SiC(CH_3)_3$], 22.93 (CH_2), 17.94 [$SiC(CH_3)_3$], 13.57, 11.78, −4.89 ($SiCH_3$), −5,26 ($SiCH_3$). Anal. Calcd for $C_{26}H_{50}O_4Si$: C, 68.67; H, 11.08. Found: C, 68.62; H, 10.86.

(22*R*,23*E*)-8*β*-[(*tert*-Butyldimethylsilyl)oxy]-25-[(methoxymethyl)oxy]-des-A,B-cholest-23-en-22-ol Diethyl Phosphate (5e). *n*-Butyllithium (1.26 mL, 2.38 M in hexanes, 3.0 mmol) was slowly added to alcohol **5c** (1.24 g, 2.71 mmol) in Et_2O (25 mL) at −78 °C. After stirring for 15 min, diethyl chlorophosphate (0.43 mL, 0.52 g, 3.0 mmol, freshly distilled twice from P_2O_5 under vacuum) was added. After stirring for 3 h, the reaction mixture was poured into a mixtured of saturated NaCl and ice. The mixture was extracted with Et_2O. The combined ethereal extracts were dried, filtered, and concentrated in vacuo. Flash chromatography of the concentrate (2 × 20 cm; eluent 15−30% EtOAc−hexanes) afforded phosphate **5e** (1.50 g, 93%; R_f = 0.3 (30% EtOAc−hexanes)] as a colorless liquid. ^{1}H NMR: 5.71 (1H, d, J = 15.95, H-24), 5.60 (1H, dd, J = 15.95, 5.0, H-23), 4.89 (1H, br t, J = 6.0, H-22), 4.64 (2H, s, OCH_2O), 4.14−3.97 (4H, m, J = 7.2, $P(OCH_2CH_3)_2$], 1.32 (6H, s, CH_3-26 and 27), 0.91 (3H, d, J = 6.33, CH_3-21), 0.90 (3H, s, CH_3-18), 0.87 [9H, s, $SiC(CH_3)_3$], −0.01 (3H, s, $SiCH_3$), −0.02 (3H, s, $SiCH_3$). ^{13}C NMR: 137.50 (CH═), 128.04 (CH═), 91.74 (OCH_2O), 81.16 (d, J = 6.9, C-22), 75.50 (C-25), 69.23, 63.23 (q, J = 2.8, $P(OCH_2CH_3)_2$], 54.85 (OCH_3), 52.92, 52.53, 41.91 (C-13), 41.83, 40.49 (CH_2), 34.18 (CH_2), 27.06 (C-26 and 27), 26.75 (CH_2), 25.59 [$SiC(CH_3)_3$], 22.84 (CH_2), 17.79 [$SiC(CH_3)_3$], 17.41 (CH_2), 15.95 [q, J = 3.5, $P(OCH_2CH_3)_2$], 13.32, 12.16, −5.04 ($SiCH_3$), −5.40 ($SiCH_3$). Anal. Calcd for $C_{30}H_{59}O_7PSi$: C, 60.99; H, 10.06. Found: C, 61.42; H, 10.07.

(22*E*,24*S*)-[(*tert*-Butyldimethylsilyl)oxy]-25-[(methoxymethyl)oxy]-24-methyl-des-A,B-cholest-22-en-8*β*-ol (4a) and (22*E*,24*S*)-25-[(Methoxymethyl)oxy]-24-methyl-des-A,B-cholest-22-en-8*β*-ol (12a). A mixture of CuCN (63 mg, 0.70 mmol, Aldrich) and LiCl (59 mg, 1.4 mmol) in THF (2 mL) was stirred to effect solution. After cooling to −78 °C, methylmagnesium chloride (0.235 mL, 3 M in THF, 0.7 mmol) was added dropwise. The cooling bath was removed, and the mixture was stirred for 10 min. After cooling to −78 °C, a solution of phosphate **5e** (43 mg, 0.073 mmol, dried over P_2O_5) in THF (1.5 mL) was cannulated into the cuprate suspension. After stirring for 6 h, the reaction mixture was slowly warmed to rt (12 h). The reaction was quenched dropwise with saturated aqueous NH_4Cl. After stirring for 10 min, the mixture was extracted with hexanes. The combined organic extracts were dried, filtered, and concentrated in vacuo to afford **4a** [30 mg, 91%; R_f = 0.8 (10% EtOAc−hexanes)] as a viscous oil which was treated with tetrabutylammonium fluoride (2.3 mL, 1.1 M in THF, 2.5 mmol). The reaction mixture was stirred for 8 days at rt, and for 20 h at 60 °C, and was then poured into a saturated $NaHCO_3$ solution and extracted with Et_2O. The ethereal extracts were dried, filtered, and concentrated in vacuo. Flash chromatography of the concentrate (1 × 10cm; eluent 12% EtOAc−hexanes) afforded alcohol **12a**[28b,c] [21 mg, 0.062 mmol, 85%, R_f = 0.35 (10% EtOAc−hexanes)] as a viscous oil which crystallizes on standing for several days in the refrigerator (mp 56−57 °C).

Compounds 4c, 4d, 4e, 12c, 12d, 12e. These compounds were prepared as above. The starting alkylmagnesium bromides were prepared from bromocyclopropane, 2-bromopropane, and 2-(2-bromoethyl)-1,3-dioxolane, respectively.

General Procedure for the Preparation of Ketones 15b−f and 16f,g. A mixture of alcohols **12b−f** or **14f**,**g** (0.28 mmol), pyridinium dichromate[49] (314 mg, 0.84 mmol), and a crystal of pyridinium tosylate in dry CH_2Cl_2 (6 mL) were stirred at rt for 5 h. After adding Et_2O (20 mL), the mixture was stirred for 30 min, filtered through Celite, and concentrated in vacuo. Flash chromatography gave ketones **15b−f** or **16f**,**g** in high yields (92−99%).

(22*E*,24*S*)-24-*n*-Butyl-25-[(methoxymethyl)oxy]-des-A,B-cholest-22-en-8-one (15b): 95%, R_f = 0.4 (25% EtOAc−hexanes), colorless viscous oil. ^{1}H NMR: 5.24 (1H, dd, J = 15.2, 8.8, H-22 or 23), 5.11 (1H, dd, J = 15.2, 9.2, H-22 or 23), 4.70 (2H, AB, J = 7.0, OCH_2O), 3.36 (3H, s, OCH_3), 1.18 (3H, s, CH_3-26), 1.13 (3H, s, CH_3-27), 1.06 (3H, d, J = 6.9, CH_3-21), 0.88 [3H, t, J = 6.9, $(CH_2)_3CH_3$], 0.66 (3H, s, CH_3-18). ^{13}C NMR: 211.69 (C═O), 138.63 (CH-23), 128.99 (CH-22), 90.87 (OCH_2O), 78.16 (C-25), 62.02 (CH-14), 56.41 (CH-17), 55.12 (OCH_3), 53.20 (CH-24), 49.73 (C-13), 40.96 (CH_2-9), 40.07 (CH-20), 38.88 (CH-12), 30.23 (CH_2), 28.23 (CH_2), 27.94 (CH_2-16), 25.53 (CH_3-26), 24.07 (CH_2-11), 23.21 (CH_3-27), 22.67 (CH_2), 20.94 (CH_3-21), 19.15 (CH_2-15), 14.14 [$CH_3(CH_2)_3$], 12.68 (CH_3-18). HRMS calcd for $C_{24}H_{42}O_3 - CH_3$ 363.2899, found 363.2897.

(22*R*,23*E*)-22-Phenyl-25-[(methoxymethyl)oxy]-des-A,B-cholest-23-en-8-one (16f): 96%, R_f = 0.4 (25% EtOAc−hexanes), colorless oil. ^{1}H NMR: 7.32−7.27 (m, 2H, Ar), 7.20−7.16 (3H, m, Ar), 5.95 (1H, dd, J = 15.7, 10, H-23), 5.66 (1H, d, J = 15.7, H-24), 4.50 (2H, AB, J = 7.0, OCH_2O), 3.53 (1H, dd, J = 10, 2.6, H-22), 3.37 (3H, s, OCH_3). ^{13}C NMR: 211.65 (C═O), 144.65 (C═), 138.64 (CH-23), 128.22 (2CH═), 127.86 (2CH═),126.77 (CH═), 125.88 (CH-24), 91.88 (CH_2), 76.24 (C), 61.99 (CH), 55.10 (CH_3), 54.89 (CH), 50.22 (CH), 49.81 (C), 42.28 (CH), 40.95 (CH_2), 39.07 (CH_2), 28.14 (CH_3), 27.66 (CH_2), 27.18 (CH_3), 24.03 (CH_2), 19.24 (CH_2), 13.60 (CH_3), 12.59 (CH_3). HRMS: calcd for $C_{26}H_{38}O_3 - CH_3$ 383.2586, found 383.2594.

General Procedure for the Coupling Reaction between the CD Ring Ketone and the Phosphine Oxide A Ring. Phosphine oxide **17** (1 g, 1.718 mmol) was purified by flash chromatography (3 × 30 cm; eluent, HPLC grade Et_2O). After concentration in vacuo, the phosphine oxide was transferred to a 100 mL round bottomed flask with hexanes (15 mL). Concentration in vacuo gave a solid which was dissolved in hexanes (30 mL). After concentration in vacuo, the phosphine oxide was vacuum dried over P_2O_5 for 12 h. The round bottomed flask containing pure **17** (0.907 g, 1.558 mmol) and activated molecular sieves (4 Å) was fitted with a septum cap. Dry THF (15 mL, distilled under argon) was added. This freshly prepared 0.104 M solution of phosphine oxide in THF was used in the next experiments.

Phenyllithium (0.416 mmol, 0.231 mL, 1.8 M in cyclohexane−Et_2O) was cannulated dropwise into a THF solution of phosphine oxide **17** (0.395 mmol, 3.8 mL, 0.104 M) at −78 °C. The deep red solution was stirred at −78 °C for 10 min. A cooled (−78 °C) solution of the CD ring ketone (**15c−f** and **16f**,**g**, 0.208 mmol, dried over P_2O_5 for 12 h in vacuo) in THF (1.4 mL) was cannulated dropwise. The red solution was stirred in the dark at −78 °C for 3 h and then warmed to −65 °C over 30 min. The reaction was quenched with aqueous sodium and potassium tartrate (0.9 mL, 2 M) and aqueous potassium carbonate (5 mL). The mixture was allowed to warm to rt and extracted with CH_2Cl_2. The organic layer was dried, filtered, and concentrated in vacuo. Flash chromatography of the concentrate (2 × 20 cm; eluent, 1% EtOAc−hexanes) afforded the protected vitamin D analog (**18c−f** and **20f**,**g**) which was treated with tetrabutylammonium fluoride (3.5 mL, 2.887 mmol, 0.83 M in THF). The mixture was stirred in the dark overnight at rt and concentrated in vacuo. The concentrate was dissolved in Et_2O, washed with brine, dried, filtered, and concentrated in vacuo. Flash chromatography of the concentrate (2 × 20 cm; eluent, Et_2O) gave the corresponding desilylated vitamin D analog, which was dissolved in MeOH and treated with resin AG50 WX4 (1.76 g, previously washed with MeOH). The mixture was stirred in the dark at rt overnight and filtered. The solids were washed with EtOAc. The combined liquids were concentrated in vacuo. Flash chromatography of the concentrate (1.5 × 10 cm; eluent, 20% Et_2O−hexanes) afforded the vitamin D analog (**19c−f** and **21f**,**g**) (49−64%, three steps from ketones **15** and **16**).

(24*S*)-24-Cyclopropyl-1α,25-dihydroxy-28-norvitamin D$_2$ (19c): 56%, R_f = 0.1 (60%, Et_2O−hexanes), mp 145 °C. ^{1}H NMR (CD_2Cl_2): 6.34 and 6.00 (2H, AB, J = 11.2, H-6 and 7), 5.30−5.27 (2H, m, H-22 and 23), 5.26 (1H, s, H-19), 4.94 (1H,

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s, H-19), 4.36 (1H, dd, J = 6.5, 4.4, H-1), 4.15 (1H, m, H-3), 2.82 (1H, d, J = 12.5), 2.53 (1H, dd, J = 13.3, 2.66), 2.25 (1H, dd, J = 13.3, 6.5), 1.19 (3H, s, CH_3-26), 1.16 (3H, s, CH_3-27), 1.02 (3H, d, J = 6.6, CH_3-21), 0.73 (1H, m, c-Pr), 0.55 (3H, s, CH_3-18), 0.53 (1H, m, c-Pr), 0.36 (1H, m, c-Pr), 0.22 (1H, m, c-Pr), 0.02 (1H, m, c-Pr). ^{13}C NMR (CD_2Cl_2): 148.41 (C═), 143.12 (C═), 140.28 (CH═), 133.90 (C═), 127.22 (CH═), 124.83 (CH═), 117.49 (CH═), 111.74 (CH_2-19), 73.29 (C), 71.04, 67.06, 58.89, 56.72, 56.48, 46.11 (C), 45.66 (CH_2), 43.28 (CH_2), 40.94 (CH_2), 40.72, 29.34 (CH_2), 28.24 (CH_2), 27.84, 27.41, 23.93 (CH_2), 22.63 (CH_2), 21.23, 12.33, 11.67, 6.11 (CH_2), 2.54 (CH_2). HRMS calcd for $C_{30}H_{46}O_3$ 454.3447, found 454.3461.

Acetal 19e: 49%, R_f = 0.2 (60% Et_2O−hexanes), mp 120 °C. ^{1}H NMR (CD_2Cl_2): 6.33 and 5.99 (2H, AB, J = 11.2, H-6 and 7), 5.30−5.26 (1H, m, H-22 or 23), 5.27 (1H, s, H-19), 5.12 (1H, dd, J = 15.3, 8.4, H-22 or 23), 4.93 (1H, s, H-19), 4.60 (0.4H, d, J = 1.4, OCHO), 4.44 (0.6H, dd, J = 9.5, 2.4, OCHO), 4.35 (1H, m, H-1), 4.14 (1H, m, H-3), 3.34 (1.9H, s, OCH_3), 3.32 (1.1H, s, OCH_3), 2.82 (1H, d, J = 12.4), 2.52 (1H, dd, J = 13.4, 3.5), 2.25 (1H, dd, J = 13.4, 6.6), 1.17 (3H, s, CH_3-26), 1.12 (1.1H, s, CH_3-27), 1.08 (1.9H, s, CH_3-27), 0.99 (3H, d, J = 6.6, CH_3-21), 0.53 (3H, s, CH_3-18). ^{13}C NMR (CD_2Cl_2): 148.45 (C═), 143.01 (C═), 142.98 (C═), 138.77 (CH═), 138.19 (CH═), 134.02 (C═), 133.99 (C═), 129.05 (CH═), 128.46 (CH═), 124.76 (CH═), 117.53 (CH═), 111.70 (CH_2-19), 99.08 (CH), 98.41 (CH), 76.26 (C), 75.47 (C), 70.95, 67.03, 56.70, 56.65, 55.59, 55.14, 49.12, 48.68, 46.13 (C), 45.63 (CH_2), 43.32 (CH_2), 40.77, 40.72 (CH_2), 40.69, 31.53 (CH_2), 30.40 (CH_2), 29.74, 29.70, 29.35 (CH_2), 28.05 (CH_2), 25.91 (CH_2), 23.92 (CH_2), 23.35, 22.58 (CH_2), 22.11 (CH_2), 20.99, 19.66, 12.34. HRMS calcd for $C_{31}H_{48}O_4$ 484.3553, found 484.3580.

(22*S*,23*E*)-1α-Hydroxy-25-methoxy-22-phenyl-23-dehydrovitamin D_3 (21f): 55%, R_f = 0.2 (40% EtOAc−hexanes), mp 90 °C. ^{1}H NMR (CD_2Cl_2): 7.27−7.14 (5H, m, Ar), 6.35 and 6.03 (2H, AB, J = 11.2, H-6 and 7), 5.89 (1H, dd, J = 15.8, 10.3, H-23), 5.55 (1H, d, J = 15.8, H-24), 5.29 (1H, d, J = 1.4, H-19), 4.96 (1H, s, H-19), 4.36 (1H, m, H-1), 4.15 (1H, m, H-3), 3.5 (1H, d, J = 10.3, H-22), 3.14 (3H, s, OCH_3), 2.80 (1H, d, J = 12), 2.52 (1H, d, J = 13), 2.25 (1H, dd, J = 13.0, 6.5), 1.29 (3H, s, CH_3-26), 1.27 (3H, s, CH_3-27), 0.80 (3H, d, J = 6.8, CH_3-21), 0.57 (3H, s, CH_3-18). ^{13}C NMR (CD_2Cl_2): 148.43 (C═), 145.66 (C═), 142.99 (C═), 138.69 (CH═), 133.96 (C═), 128.33 (CH═), 128.27 (CH═), 127.51 (CH═), 125.92 (CH═), 124.84 (CH═), 117.61 (CH═), 111.76 (CH_2-19), 75.20 (C), 71.08, 67.08, 56.74, 55.13, 50.67, 50.50, 46.14 (C), 45.68 (CH_2), 43.34 (CH_2), 43.20, 40.90 (CH_2), 29.32 (CH_2), 27.97 (CH_2), 26.78, 25.77, 23.89 (CH_2), 22.64 (CH_2), 13.69, 12.11. HRMS calcd for $C_{34}H_{48}O_3$ 504.3603, found 504.3632.

(22*R*,23*E*)-8β-Hydroxy-25-[(methoxymethyl)oxy]-des-A,B-cholest-23-en-22-yl Diethyl Phosphate (5f). Tetrabutylammonium fluoride (695 mg, 2.66 mmol) was added to a solution of phosphate **5e** (157 mg, 0.266 mmol) in THF (2.5 mL). The mixture was refluxed for 48 h and then allowed to reach rt. The reaction was quenched with saturated NH_4Cl. The mixture was extracted with Et_2O. The combined organic extracts were dried, filtered, and concentrated in vacuo. Flash chromatography of the concentrate (1.5 × 10 cm; eluent 70% EtOAc−hexanes) afforded phosphate **5f** [117 mg, 97%; R_f = 0.4 (50% Et_2O−hexanes)] as a colorless oil. ^{1}H NMR: 5.76 (1H, d, J = 15.99, H-24), 5.60 (1H, dd, J = 15.99, 5.24, H-23), 4.85 (1H, br t, J = 6.0, H-22), 4.63 (2H, s, OCH_2O), 4.14−3.99 [4H, m, J = 7.2, P(OC*H*$_2$CH$_3$)$_2$], 4.04 (1H, br s, H-8), 3.33 (3H, s, OCH_3), 1.35−1.23 [6H, m, P(OCH$_2$C*H*$_3$)$_2$], 1.32 (6H, s, CH_3-26 and 27), 0.92 (3H, s, CH_3-18), 0.91 (3H, d, J = 6.28, CH_3-21). ^{13}C NMR: 137.65 (CH═), 127.72 (CH═), 91.56 (OCH_2O), 81.14 (d, J = 5.7, C-22), 75.31 (C-25), 68.19, 63.13 [q, J = 3.08, P(OC*H*$_2$CH$_3$)$_2$], 54.61 (OCH_3), 52.67, 52.48, 41.74 (C-13), 41.58, 40.43 (CH_2), 33.61 (CH_2), 26.91 (CH_3-26 and 27), 26.61 (CH_2), 22.37 (CH_2), 17.28 (CH_2), 15.79 [q, J = 3.9, P(OCH$_2$C*H*$_3$)$_2$], 13.03, 12.05. HRMS FAB calcd for $C_{24}H_{45}O_7PNa$ 499.2800, found 499.2796.

(22*R*,23*E*)-25-[(Methoxymethyl)oxy]-8-oxo-des-A,B-cholest-23-en-22-yl Diethyl Phosphate (22). A mixture of alcohol **5f** (69 mg, 0.151 mmol), pyridinium dichromate (171 mg, 0.453 mmol), and a crystal of pyridinium *p*-toluenesulfonate in CH_2Cl_2 (1.5 mL) was stirred at rt for 3 h. The mixture was diluted with Et_2O, stirred at rt for 30 min, filtered through Celite, and concentrated in vacuo. Flash chromatography of the concentrate (1 × 8 cm; eluent, 40% EtOAc−hexanes) afforded ketone **22** [68 mg, 99%, R_f = 0.5 (70% EtOAc−hexanes)] as a colorless viscous oil. ^{1}H NMR: 5.73 (1H, d, J = 16.0, H-24), 5.61 (1H, dd, J = 5.40, 16.0, H-23), 4.86 (1H, br t, H-22), 4.62 (2H, AB, OCH_2O), 4.06 [4H, m, P(OC*H*$_2$CH$_3$)$_2$], 3.32 (3H, s, OCH_3), 1.30 (6H, s, CH_3-26 and 27), 1.28 [6H, m, P(OCH$_2$C*H*$_3$)$_2$], 0.74 (3H, d, J = 6.74, CH_3-21), 0.61 (3H, s, CH_3-18). ^{13}C NMR: 211.41 (C═O), 137.93 (CH═), 127.46 (CH═), 91.69 (OCH_2O), 80.82 (d, CH_2-22), 75.49 (C-25), 63.41 [m, P(OC*H*$_2$CH$_3$)$_2$], 61.69, 54.91, 52.48, 49.47 (C-13), 42.04, 41.95, 40.75 (CH_2), 38.75 (CH_2), 27.05, 23.80 (CH_2), 18.96 (CH_2), 15.95 [t, P(OCH$_2$C*H*$_3$)$_2$], 12.41, 12.19. HRMS FAB calcd for $C_{24}H_{43}O_7PNa$ 497.2644, found 497.2631.

Diethyl Phosphate 23. Phenyllithium (1.05 mmol, 0.526 mL, 2 M in cyclohexane−Et_2O) was cannulated dropwise into a solution of phosphine oxide **17** (1.25 mmol, 6.13 mL, 0.204 M in THF) at −78 °C. The deep red solution was stirred at −78 °C for 1 h. A cooled (−78 °C) solution of the CD ring ketone **22** (300 mg, 0.660 mmol) in THF (5 mL) was cannulated dropwise. The red solution was stirred in the dark at −78 °C for 3 h and then warmed to −30 °C for 1 h. The reaction was quenched with saturated NH_4Cl. The mixture was extracted with Et_2O. The combined organic phases were dried, filtered, and concentrated. The concentrate was purified by flash chromatography (2.5 × 15 cm, eluent, 0−10% EtOAc−hexanes) to give **23** [420 mg, 76%, R_f = 0.7 (60% EtOAc−hexanes)] as a colorless oil. ^{1}H NMR: 6.25 and 6.03 (2H, *AB*, J = 11.21, H-6 and 7), 5.72 (1H, d, J = 15.95, H-24), 5.64 (1H, dd, J = 5.69, 15.95, H-23), 5.18 (1H, s, H-19), 4.87 (1H, br t, H-22), 4.84 (1H, d, J = 2.33, H-19), 4.61 (2H, AB, OCH_2O), 4.37 (1H, m), 4.18 (1H, m), 4.11−3.97 [4H, m, P(OC*H*$_2$CH$_3$)$_2$], 3.30 (3H, s, OCH_3), 1.30 (6H, s, CH_3-26 and 27), 1.32−1.26 [6H, m, P(OCH$_2$C*H*$_3$)$_2$], 0.95 (3H, d, J = 6.67, CH_3-21), 0.86 [18H, s, 2SiC(CH$_3$)$_3$], 0.53 (3H, s, CH_3-18), 0.05 [12H, 3s, 4Si(CH$_3$)$_2$]. ^{13}C NMR: 148.90 (C═), 141.21 (C═), 138.21 (CH═), 135.75 (C═), 128.42 (CH═), 123.43 (CH═), 118.45 (CH═), 111.51 (CH_2-19), 91.21 (OCH_2O), 81.59 (d, CH-22), 75.90 (C-25), 72.43, 67.99, 63.83 [m, P(OC*H*$_2$CH$_3$)$_2$], 56.74, 55.19, 53.00, 46.43 (CH_2), 46.02 (C-13), 45.29 (CH_2), 43.13, 43.08, 40.98 (CH_2), 29.25 (CH_2), 27.69 (CH_2), 27.44, 27.41, 26.16, 26.03 [2Si*C*(CH$_3$)$_3$], 23.90 (CH_2), 22.61 (CH_2), 18.53 (SiC), 18.42 (SiC), 16.43 [t, P(OCH$_2$C*H*$_3$)$_2$], 12.87, 12.00, −4.54 ($SiCH_3$), −4.58 ($SiCH_3$), −4.67 ($SiCH_3$), −4.88 ($SiCH_3$). HRMS FAB calcd for $C_{45}H_{83}O_8Si_2PNa$ 861.5261, found 861.5241.

1α-[(*tert*-Buthyldimethylsilyl)oxy]-25-[(methoxymethyl)oxy]-vitamin D_2 *tert*-Buthyldimethylsilyl Ether (24). A mixture of CuCN (323 mg, 3.61 mmol, Aldrich) and LiCl (306 mg, 7.2 mmol) in THF (20 mL) was stirred to effect a homogeneous solution. After cooling to −78 °C, MeMgCl (1.2 mL, 3 M in THF, 3.61 mmol) was added dropwise. After stirring for 15 min, a solution of phosphate **23** (303 mg, 0.361 mmol) in THF (7 mL) was added via cannula. The mixture was stirred for 10 h at −78 °C and then allowed to reach for 12 h. The reaction was quenched with drops of saturated NH_4Cl. The mixture was diluted with Et_2O and saturated NH_4Cl. The aqueous phase was extracted with Et_2O. The combined organic phases were dried, filtered, and concentrated. Flash chromatography of the concentrate (2.5 × 15 cm; eluent, 1% EtOAc−hexanes) afforded protected vitamin D_2 **24**[28c] [232 mg, 92%, R_f = 0.7 (80% EtOAc−hexanes)]. ^{1}H NMR: 6.25 and 6.02 (2H, AB, J = 11.23, H-6 and 7), 5.32 (1H, dd, J = 15.2, 7.9, H-22 or H-23), 5.24 (1H, dd, J = 15.2, 8.25, H-22 or H-23), 5.18 (1H, d, J = 1.79, H-19), 4.84 (1H, d, J = 2.44, H-19), 4.66 (2H, *AB*, OCH_2O), 4.37 (1H, m), 4.18 (1H, m), 3.31 (3H, s, OCH_3), 1.14 (3H, s, CH_3-26), 1.10 (3H, s, CH_3-27), 1.01 (3H, d, J = 6.53, CH_3-21), 0.96 (3H, d, J = 7.01, CH_3-28), 0.87 [18H, s, SiC(CH$_3$)$_3$], 0.54 (3H, s, CH_3-18), 0.06−0.05 [12H, 3s, 4Si(CH$_3$)$_2$].

1α,25-dihydroxyvitamin D_2 (2b). Tetrabutylammonium fluoride (4 mmol, 4 mL, 1 M in THF) was added to a solution of **24** (102 mg, 0.146 mmol) in THF (2 mL). The mixture was stirred in the dark for 12 h. Saturated NH_4Cl was added, and the mixture was extracted with Et_2O. The combined organic phases were dried, filtered, and concentrated. The residue was

dissolved in MeOH (10 mL) and treated with resin AG50 WX4 (3 g, previously washed with MeOH). The mixture was stirred in the dark at rt for 5 h, filtered, and concentrated. The residue was flash chromatographed (1 × 10 cm; eluent, 50% EtOAc−hexanes) to afford 1α,25-dihydroxyvitamin D_2 (**2b**)[28c] [55 mg, 89%, $R_f = 0.2$ (50% EtOAc−hexanes)]. ^{1}H NMR: 6.34 and 5.99 (2H, AB, $J = 11.27$, H-6 and 7), 5.36−5.29 (2H, m, H-22 and 23), 5.26 (1H, br s, H-19), 4.94 (1H, br s, H-19), 4.35 (1H, m), 4.14 (1H, m), 3.31 (3H, s, OCH_3), 1.10 (3H, s, CH_3-26), 1.08 (3H, s, CH_3-27), 1.01 (3H, d, $J = 6.51$, CH_3-21), 0.96 (3H, d, $J = 6.70$, CH_3-28), 0.54 (3H, s, CH_3-18).

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of all compounds, and experimental details for the preparation of compounds **4b**, **12b**, **4c**, **12c**, **4d**, **12d**, **4e**, **12e**, **4f**, **12f**, **13f**, **14f**, **13g**, **14g**, **15c**, **15d**, **15e**, **15f**, **16g**, **19d**, **19f**, **21g** (50 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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