New Synthetic Strategies to Vitamin D Analogues Modified at the Side Chain and D Ring. Synthesis of 1α,25-Dihydroxy-16-ene-vitamin D_3 and C-20 Analogues[1]

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Two efficient synthetic routes to 1α,25-dihydroxy-16-ene-vitamin D_3 (**4a**) and their C-20 analogues (**3** and **4**) have been developed. Key features common to both routes A and B are the introduction of side chains functionalized at C20 (**17**, **21**, **19**, and **25**). In route A the CD side chain fragments **5** and **6** are prepared by S_N2' syn displacement of allylic carbamates **8** and **9** (X = OCONHPh) by $Li_2Cu_3R_5$. The triene unit is then constructed by assembling the latter fragments with the A-ring fragment using the Wittig−Horner method (average yield of vitamin D analogue 35%, 11−13 steps from ketone **11**). In route B, the S_N2' syn displacement of the carbamate moiety by $Li_2Cu_3R_5$ is carried out on intermediates **12** and **13**, both of which bear the vitamin D triene unit (average yield of vitamin D analogue 27%, 13−15 steps from ketone **11**). The latter route is particularly attractive as an approach to diverse C-20 vitamin D analogues for biological screening.

Introduction

1α,25-Dihydroxyvitamin D_3 [1α,25-$(OH)_2$-D_3, calcitriol (**1**), Figure 1], the hormonally active form of vitamin D_3 (**2**), besides regulating the homeostasis of calcium and classical bone mineralization, also promotes cellular differentiation and induces some biological functions related to the immunological system.[2−4] Extensive structure−function studies have shown that it is possible to modify the calcitriol structure to obtain vitamin D_3 analogues that are capable of inducing, in a selective manner, the biological functions related to the same hormone.[3,5] In this way, for example, in the past decade analogues have been developed that strongly induce cellular differentiation with very low secondary calcemic effects.[2,3] Such analogues are of potential interest as drugs in the treatment of a wide range of illnesses such as psoriasis, leukemia, breast cancer, prostate cancer, and AIDS.[3,4] The fact that some vitamin D analogues with a nonnatural configuration at C20 of the side chain, or with a double bond at C16−C17 of ring D, bind more strongly to VDR (vitamin D receptor) and induce significant cell differentiation[3] led us to focus our interest on developing strategies for the synthesis of 1α,25-dihydroxy-16-ene-vitamin D_3 analogues bearing substituents (alkyl, aryl) at C20 with the natural or nonnatural configuration at this position (**4** and **3** respectively, Scheme 1) with the aim of carrying out structure−activity studies. Previous synthetic routes to vitamin D_3 analogues with the nonnatural configuration at C20 and with a double bond at C16−C17 were respectively carried out at Leo Pharmaceutical Co. (Denmark)[6] and Hoffmann La Roche (Nutley, NJ).[7]

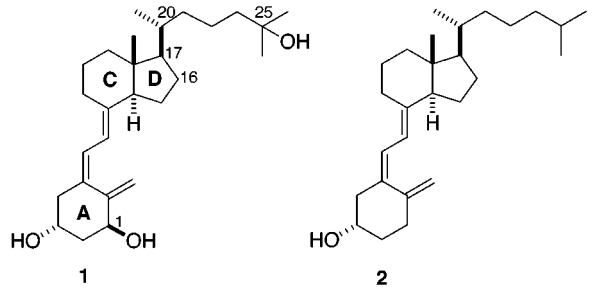

Figure 1.

Synthetic Plan

Our initial retrosynthetic plan (route A, Scheme 1) for vitamin D_3 analogues **3** and **4** starts with ketone **11**.[8] The key step in this approach is the regio- and stereoselective

(1) This work was taken in part from the doctoral theses of María de los Angeles Rey and José Antonio Martínez (University of Santiago de Compostela) and was partially presented at the XVII Conference on Isoprenoids (Kracow, Poland, 1997).

(2) (a) Norman, A. W.; Litwack, G. *Hormones*; Academic Press: San Diego, 1997. (b) Feldman, D.; Glorieux, F. H.; Pike, J. W. *Vitamin D*; Academic Press: San Diego, 1997.

(3) Bouillon, R.; Okamura, W. H.; Norman, A. W. Structure−Function Relationships in the Vitamin D Endocrine System. *Endocrine Rev.* **1995**, *16*, 200.

(4) *Vitamin D: Chemistry, Biology and Clinical Applications of the Steroid Hormone*; Norman, A. W., Bouillon, R., Thomasset, M., Eds.; Vitamin D Workshop, Inc: Riverside, CA, 1997.

(5) Calverley, M. J.; Jones, G. *Antitumor Steroids*; Blikenstaff, R. T., Ed.; Academic Press: New York, 1992; p 193.

(6) (a) Calverley, M. J.; Binderup, E.; Binderup, L. 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 163. (b) Binderup, L.; Latini, S.; Binderup, E.; Bretting, C.; Calverley, M. J.; Hansen, K. *Biochem. Pharmacol.* **1991**, *42*, 1569.

(7) (a) Uskoković, M. R.; Baggiolini, E.; Shiuey, S. J.; Iacobelli, J.; Hennessy, B.; Kiegiel, J.; Daniewski, A. R.; Pizzolato, G.; Courtney, L. F.; Horst, R. L. 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 139. (b) Daehne, W.; Hansen, C. M.; Hansen, D.; Mathiasen, I. S. In *Vitamin D: Chemistry, Biology and Clinical Applications of the Steroid Hormone*; Norman, A. W., Bouillon, R., Thomasset, M., Eds.; Vitamin D Workshop, Inc: Riverside, CA, 1997; p 81. (c) Posner, G. H. In *Vitamin D: Chemistry, Biology and Clinical Applications of the Steroid Hormone*; Norman, A. W., Bouillon, R., Thomasset, M., Eds.; Vitamin D Workshop, Inc: Riverside, CA, 1997; p 65 and references therein.

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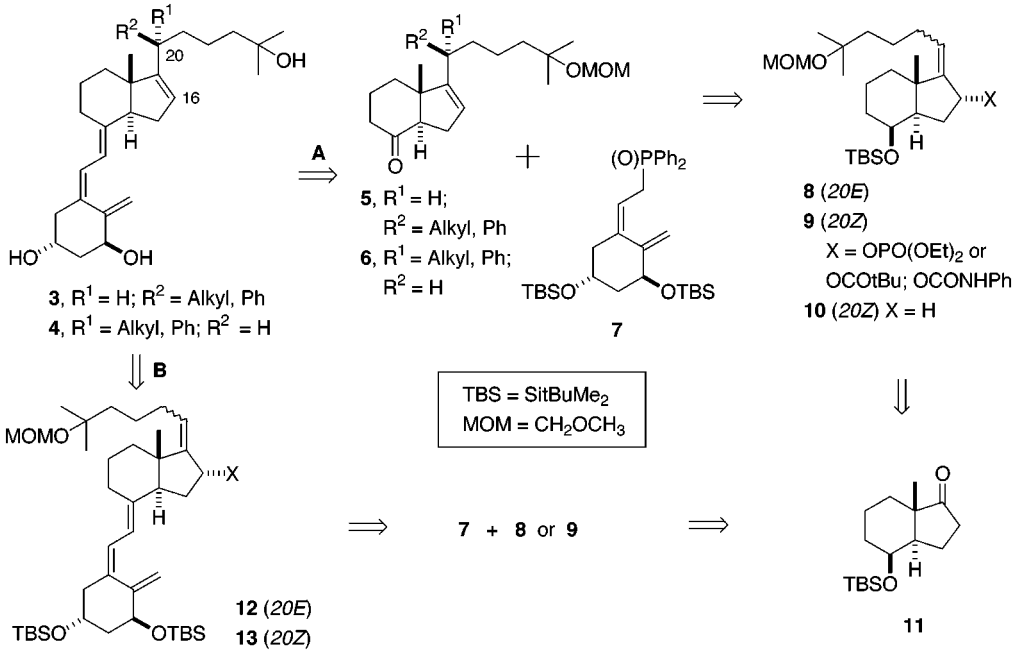
Scheme 1



S_N2' allylic alkylation by cuprates of compounds **8** or **9** (*X* = pivaloate, phosphate or carbamate).[9,10] Compounds **5**, precursors of vitamin D analogues **3** (nonnatural configuration at C20), would be prepared by S_N2' anti displacement of the pivaloate or phosphate group of **9** or by S_N2' syn displacement of the carbamate group of **8** by cuprates. On the other hand, the S_N2' anti displacement of the pivaloate or phosphate group of **8** or the S_N2' syn displacement of the carbamate group of **9** by cuprates would afford compounds **6**, which are precursors of **4** (natural configuration at C20). It was envisaged that the required allylic derivatives **8** and **9** would be synthesized from ketone **11** by successive olefination and regio- and stereoselective allylic oxidation. Finally, the vitamin D triene system of the target analogues **3** and **4** would be elaborated using the Lythgoe−Hoffmann La Roche Wittig−Horner coupling between the upper part (ketones **5** or **6**) and anion of phosphine oxide **7** corresponding to the A-ring fragment.[11]

The alternative route B also starts with ketone **11**, but the cuprate chemistry would be carried out after the introduction of the triene unit. The inherent advantage of this route over route A is that it would allow the preparation of vitamin D_3 analogues **3** and **4** without the need to carry out the Wittig−Horner coupling for each analogue. The viability of this approach is linked to the uncertainty associated with the construction of the triene system of **12** and **13** from **8** and **9**, respectively, using the above Lythgoe−Hoffmann La Roche approach and the S_N2' displacement with cuprates of the allylic ester or carbamate groups of **12** and **13**, which bear the labile vitamin D triene system.

Results and Discussion

Exploration of Route A. Synthesis of Vitamin D Analogues with Nonnatural Configuration at C20. This route starts with ketone **11** (Scheme 2). Initial attempts to introduce the $C_{17}-C_{20}$ *Z*-double bond using phosphonium salts **14a** and **14b** were hampered by the production of significant amounts of elimination products.[12,13] An attempt to produce **16b** by employing **15a** resulted in the formation of a known cyclic ylide.[13] However, treatment of ketone **11** with the ylide prepared by reaction of phosphonium salt **15b** with *t*-BuOK in benzene stereoselectively gave the desired *Z* olefin **16a** in 75% yield.[14] A crucial point in this step was the distillation of the crude mixture to remove byproducts. The *Z* geometry of the newly introduced double bond was first confirmed by comparison of the ^{1}H NMR spectrum

(8) Fernández, B.; Martínez-Pérez, J. A.; Granja, J. R.; Castedo, L.; Mouriño, A. *J. Org. Chem.* **1992**, *57*, 3173.

(9) For the construction of vitamin D side chains via S_N2' syn-displacement of allylic carbamates by cuprates, see: (a) Sardina, F. J.; Mouriño, A.; Castedo, L. *Tetrahedron Lett.* **1983**, *24*, 4477. (b) Sardina, F. J.; Mouriño, A.; Castedo, L. *J. Org. Chem.* **1986**, *51*, 1264. (c) Maestro, M. A.; Castedo, L.; Mouriño, A. *J. Org. Chem.* **1992**, *57*, 5208. (d) Granja, J. R.; Castedo, L.; Mouriño, A. *J. Org. Chem.* **1993**, *58*, 124. (e) For the use of S_N2' anti-displacement of allylic phosphates by cuprates, see: Torneiro, M.; Fall, Y.; Castedo, L.; Mouriño; A. *J. Org. Chem.* **1997**, *62*, 6344. (f) For elaboration of steroidal side chains by S_N2' anti-displacement of allylic pivaloates, see: Schmuff, N. R.; Trost, B. M. *J. Org. Chem.* **1983**, *48*, 1404. (g) For construction of steroidal side chains with natural and nonnatural configurations at C20 using palladium-catalyzed allylic alkylation, see: (h) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1976**, *98*, 630. (i) Trost, B. M.; Matsumura, Y. *J. Org. Chem.* **1977**, *42*, 2036. (j) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1978**, *100*, 3435.

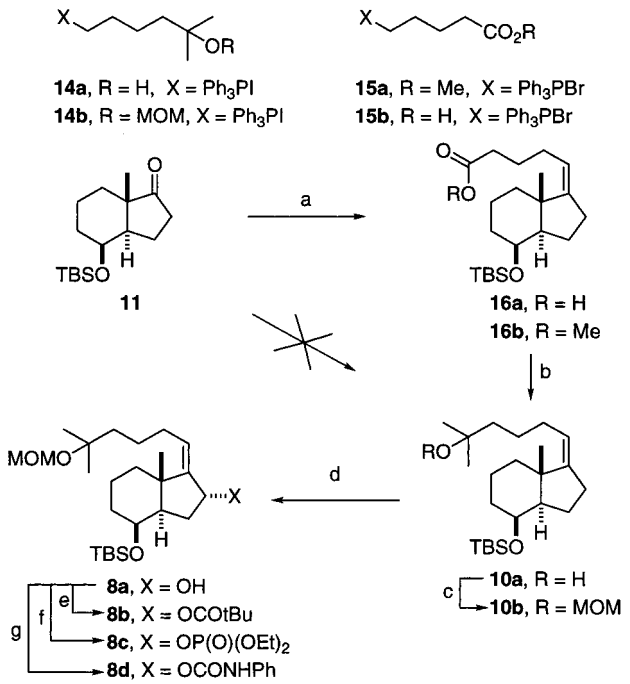
(10) For the stereochemistry of alkylation of allylic carbamates with cuprates, see: (a) Gallina, C.; Ciattini, P. G. *J. Am. Chem. Soc.* **1979**, *101*, 1035. (b) Gallina, C. *Tetrahedron Lett.* **1982**, *23*, 3093. (c) Goering, H. L.; Kantner, S. S.; Tseng, C. C. *J. Org. Chem.* **1983**, *48*, 715.

(11) For reviews on the synthesis of vitamin D metabolites and analogues, see: (a) Pardo, R.; Santelli, M. *Bull. Soc. Chim. Fr.* **1985**, 98. (b) Quinkert, G. Vitamin D Active Compounds. Part I. *Synform* **1985**, *3*, 41; (c) Part II. *Ibid.* **1986**, *4*, 131; (d) Part III. *Ibid.* **1987**, *5*, 1. (e) Wilson, S. R.; Yasmin, A. Stereoselective Synthesis of Vitamin D. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman., Ed.; Elsevier: Amsterdam, 1992; Vol. 10, p 43. (f) Dai, H.; Posner, G. H. *Synthesis* **1994**, 1383. (g) Schmalz, H.-G. *Nachr. Chem. Tech. Lab.* **1994**, *42*, 397. (h) Zhu, G.-D.; Okamura, W. H. *Chem. Rev.* **1995**, *95*, 1877.

(12) For the use of similar salts in the preparation of unsaturated fatty acids, see: Bergelson, L. D.; Shemyakin, M. M. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 250.

(13) House, H. O.; Badad, H. *J. Org. Chem.* **1963**, *28*, 90.

Scheme 2[a]



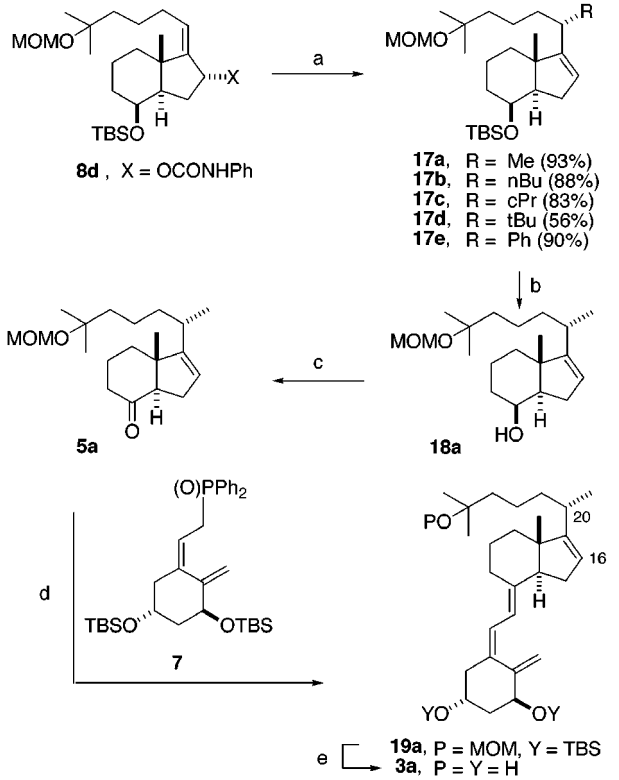
[a] Key: (a) **15b**, *t*-BuOK, PhH, reflux, 75%; (b) MeLi, THF, 0 °C, workup; MeLi, THF, 0 °C, 85%; (c) MOMCl, *i*-Pr_2NEt, DMAP, CH_2Cl_2, 92%; (d) SeO_2, *t*-BuOOH, CH_2Cl_2, 93%; (e) *t*-BuCOCl, DMAP, py, 96%; (f) *n*-BuLi, Et_2O; $(EtO)_2P(O)Cl$; (g) PhNCO, DMAP, py, −10 °C, 97%.

of the compound in question with that of a similar compound in the steroid series[15] and vide infra with that of the *E* isomer. Methylation of acid **16a** with methyllithium to give tertiary alcohol **10a** (85%) was followed by protection with chloromethyl methyl ether (ClMOM) to give **10b** (92%).

Stereoselective hydroxylation at C16 was accomplished under Sharpless conditions (SeO_2, *t*-BuOOH)[16] to give allylic alcohol **8a** in 93% yield. We then proceeded to prepare pivaloate **8b** and phosphate **8c** to test their propensity to undergo the S_N2' anti displacement using cuprates. Pivaloate **8b** was prepared in 96% yield from **8a** [*t*-BuCOCl, DMAP, Py]. Previously, Trost and coworkers[9f] showed that similar steroidal *E* allylic pivaloates undergo S_N2' anti displacement of the ester group on reaction with cyanocuprates to produce C20-alkylated compounds in high yield. Disappointingly, treatment of **8b** with MeCuCNLi (Et_2O, −20 °C, 24 h) resulted only in starting material, and treatment with BuCuCNLi (Et_2O, −20 °C, 48 h) produced the desired C20-alkylated compound with the natural configuration (20*R*) in only 9% yield.[17] The failure to introduce an alkyl substituent at C20 was attributed to steric hindrance produced by the side chain and C18-methyl group.

We have recently demonstrated the synthetic utility of allylic phosphates in the construction of vitamin D side

Scheme 3[a]



[a] Key: (a) preparation of **17a**, $Li_2Cu_3Me_5$, Et_2O, 0 °C; preparation of **17b**−**e**, $Li_2Cu_3R_5$, Et_2O, −78 °C; (b) *n*-Bu_4NF, THF, reflux, 98%; (c) PDC, PPTS, CH_2Cl_2, 97%; (d) **7**, *n*-BuLi, THF, −78 °C, 92%; (e) *n*-Bu_4NF, THF; AG50W-X4, MeOH, 88%.

chains by the S_N2' anti pathway[9e,18] and therefore considered the possibility of effecting such a transformation on compound **8c** to produce vitamin D analogues with the natural configuration at C20. However, neat phosphate **8c**, prepared from **8a** (*n*-BuLi, Et_2O, −78 °C), was quite unstable both on standing and under flash chromatography conditions. Attempts to achieve the S_N2' anti displacement of the phosphate group by treatment of a freshly prepared solution of **8c** in Et_2O with a suspension of the cuprate derived from MeMgCl [9 equiv, CuCN (0.6 equiv), LiCl (1.2 equiv)][19] in THF at −78 °C were unsuccessful, leading only to extensive decomposition.

At this point, we decided to explore carbamate **8d** for the preparation of the vitamin D analogues with the nonnatural configuration at C20 (**3**). This carbamate was prepared in 97% yield by reaction of allylic alcohol **8a** with phenylisocyanate in pyridine at −10 °C.[20] On the basis of an S_N2'-syn-facial mode of displacement of the nucleofuge, we expected that reaction of high order cuprates with carbamate **8d** would take place through the less hindered α-face to produce **17** with the nonnatural configuration 20*S* (Scheme 3).[9] This proved to be the case, and compounds **17a**−**e** were smoothly obtained in high yields by reaction of **8d** with $Li_2Cu_3R_5$. This observation is in contrast to the low yields reported by Trost[9f] using other types of cuprates on steroidal allylic carbam-

(14) (a) Only traces of the *E* isomer (<2%) were detected by ^1H NMR of the crude reaction mixture. (b) For the preparation of 1α,25-dihydroxyvitamin D_3 analogues with a fixed torsion angle (C16−17−20−22) using compound **16b**, see: Martínez-Pérez, J. A.; Sarandeses, L.; Granja, J.; Palenzuela, J. A.; Mouriño, A. *Tetrahedron Lett.* **1998**, *39*, 4725.

(15) Pumar, M. C.; Mouriño, A.; Castedo, L. *An. Quím.* **1988**, *84*, 105.

(16) Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 5526.

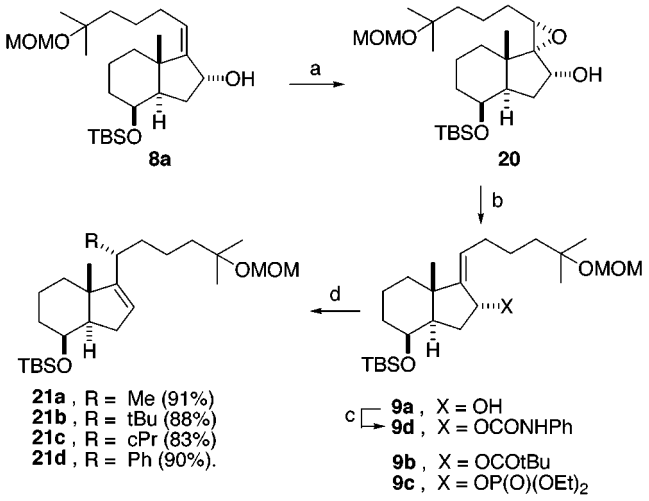
(17) Attempts to effect S_N2' anti-selective alkylation using either RCuMgX or R_2CuLi failed. In the case of RCuMgX (RMgX/CuCN, Et_2O, 0 °C) only deprotection of the pivaloate group occurred.

(18) For previous results in the alkylation of simple semirigid systems, see: (a) Tseng, C. C.; Paisley, S. D.; Goering, H. L. *J. Org. Chem.* **1986**, *51*, 2884. (b) Tseng, C. C.; Yen, S.-J.; Goering, H. L. *Ibid.* **1986**, *51*, 2892 and references therein.

(19) Yanagisawa, A.; Nomura, N.; Yamamoto, H. *Synlett* **1993**, 689.

(20) When the reaction was carried out at higher temperatures a substantial amount of the epimer at C16 was obtained, presumably by an 1,3-sigmatropic rearrangement of the carbamate group.

Scheme 4[a]



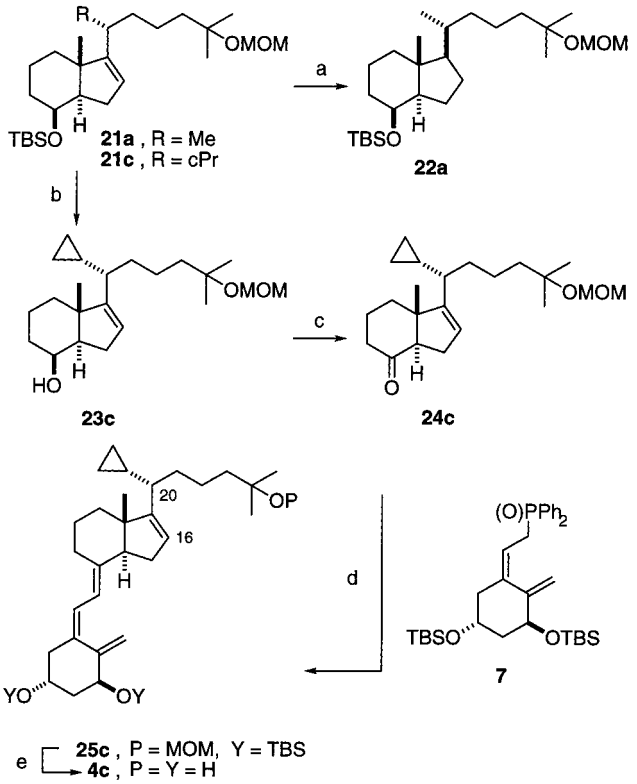
[a] Key: (a) *m*-CPBA, $NaHCO_3$, $CH_2Cl_2-H_2O$, 86%; (b) $LiPPh_2$, THF, 0 °C; MeI, 88% (two steps); (c) PhNCO, DMAP, py, −10 °C, 84%; (d) $Li_2Cu_3R_5$, Et_2O, 0 °C.

ates. As an example of the utility of this approach in the synthesis of vitamin D analogues with the nonnatural configuration at C20, we proceeded to prepare **3a** from **17a**. Cleavage of the silyl ether protecting group to give alcohol **18a** was followed by PDC oxidation to afford ketone **5a**. The Lythgoe−Roche approach[11] was chosen to introduce the triene unit. Treatment of the phosphine oxide **7**[11] with butyllithium, followed by reaction of the resulting anion with ketone **5a**, provided the protected vitamin D analogue **19a**. Removal of the silyl protecting groups by reaction with tetrabutylammonium fluoride, followed by exposure of the resulting crude diol to the cationic ion-exchange resin AG50 W-X4 in MeOH, afforded the vitamin D analogue **3a**[7b] (71% overall yield from carbamate **8d**).

Exploration of Route A. Synthesis of Vitamin D Analogues with the Natural Configuration at C20. Encouraged by the results described above for the synthesis of vitamin D analogues with the nonnatural configuration at C20, we selected the S_N2' syn displacement by cuprates of the carbamate group of **9d** to synthesize vitamin D analogues **4**, with the natural configuration at C20, rather than the alternative S_N2' anti pathway on *Z* pivaloate **9b** or *Z* phosphate **9c** (Scheme 4). The requisite carbamate **9d** was prepared from the allylic alcohol **8a** using the double-bond isomerization method of Vedejs and co-workers.[21] Stereoselective epoxidation of the allylic alcohol **8a** using *m*-chloroperbenzoic acid in CH_2Cl_2-saturated $NaHCO_3$ gave epoxide **20** (86%). Small amounts of β-epoxide were easily removed by flash chromatography. Opening of the epoxy ring with lithium diphenylphosphine in THF, followed by addition of methyl iodide, afforded *Z* olefin **9a** (88%) through syn-elimination of the oxaphosphetane intermediate formed in situ. Carbamate **9d** was prepared in 84% yield as described above. As expected, treatment of carbamate **9d** with different high-order cuprates ($Li_2Cu_3R_5$) gave compounds **21a**−**d**, with the natural configuration at C20, as single isomers in high yields. Further examples of the usefulness of this approach are that (i) compound **21c** was efficiently converted to vitamin D analogue **4c** in 66% yield (five steps, Scheme 5) and (ii)

(21) Vedejs, E.; Fuchs, P. L. *J. Am. Chem. Soc.* **1971**, *93*, 4070.

Scheme 5[a]



[a] Key: (a) H_2, 5% Pd/C, EtOAc, 90%; (b) *n*-Bu_4NF, THF, reflux, 99%; (c) PDC, PPTS, CH_2Cl_2, 96%; (d) **7**, *n*-BuLi, THF, −78 °C, 89%; (e) *n*-Bu_4NF, THF; AG50W-X4, MeOH, 78% (two steps).

hydrogenation of **21a** gave a 90% yield of the known intermediate **22**, which bears the CD side-chain fragment of the important hormone 1α,25-dihydroxyvitamin D_3 (**1**).[2,3,4]

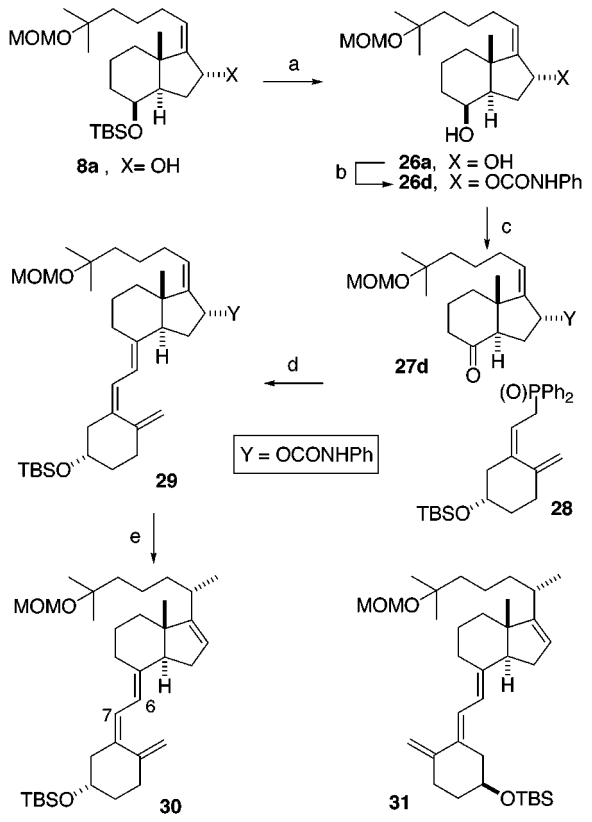
Exploration of Route B. As the next step in this synthetic study we explored the more convenient route B to prepare vitamin D analogues **3** and **4** (Scheme 1). The easy availability of phosphine oxide **28** (Scheme 6), by degradation of vitamin D_3,[9b,22] led us to first examine this convergent approach in the synthesis of the protected vitamin D_3 analogue **30**. Desilylation of **8a** with tetrabutylammoniun fluoride in THF at reflux for 24 h gave diol **26a** in 99% yield.[23] Selective formation of carbamate **26d** could be effected in 88% yield by treatment of **26a** with phenyl isocyanate (1.1 equiv). On treatment with pyridinium dicromate, **26d** provided ketone **27d** (92%). The stage was now set for the introduction of the triene system. Generation of the anion of phosphine oxide **28** using *n*-BuLi, followed by addition of ketone **27d** (1/3 equiv), did indeed afford the desired compound **29** bearing the carbamate moiety, although only in moderate yield (54%). The next step was also crucial to test the feasibility of this approach. When **29** was treated with $Li_2Cu_3Me_5$, prepared from CuI, an inseparable 1:1 mixture of the desired protected vitamin D_3 derivative **30** and its 5,6-trans isomer **31** were identified on the basis of the observation of AB patterns, corresponding to vinylic protons H6 and H7, in the ^1H NMR spectrum.[24]

(22) Toh, H. T.; Okamura, W. H. *J. Org. Chem.* **1983**, *48*, 1414.

(23) Attempts to achieve selective desilylation of carbamate **8d** (Scheme 3) to produce **26d** were problematic and also gave diol **26a**.

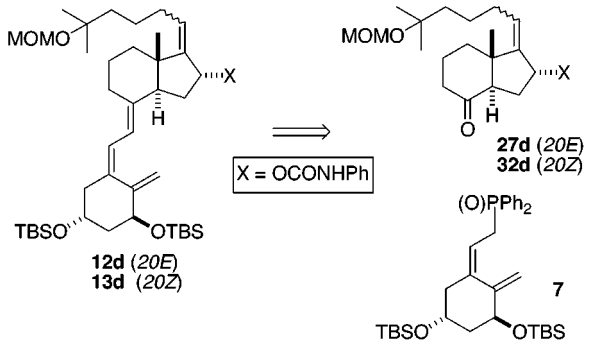
(24) ^1H NMR ($CDCl_3$, 250 MHz): **30**, δ = 6.09, 6.16 (2 H, J = 11.2 Hz, H6 and H7); **31**, δ = 5.95; 6.48 (2 H, J = 11.3 Hz, H6 and H7).

Scheme 6[a]



[a] Key: (a) *n*-Bu_4NF, THF, reflux, 24 h, 99%; (b) PhNCO, DMAP, py, −25 °C, 89%; (c) PDC, PPTS, CH_2Cl_2, 92%; (d) **28**, *n*-BuLi, THF, −78 °C, 54%; (e) $Li_2Cu_3Me_5$, Et_2O, 0 °C, 89%.

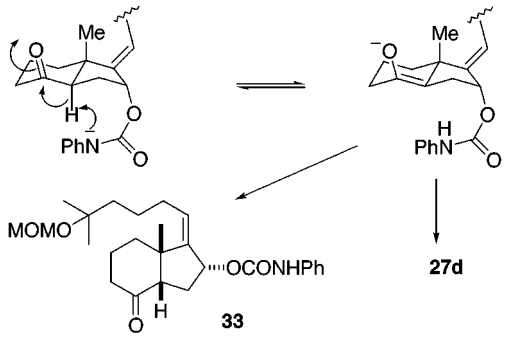
Scheme 7



The formation of the 5,6-trans isomer **31** is in accord with the presence of traces of iodine in the reaction mixture.[25] When the higher order cuprate $Li_2Cu_3Me_5$ (prepared from CuBr) was employed, the vitamin D_3 derivative **30** was produced exclusively (89% isolated yield). The results obtained in this initial exploratory work on route B encouraged us to pursue the synthesis of our target vitamin D analogues **3** and **4** using this route (Scheme 7).

Synthesis of Vitamin D Analogues with the Nonnatural and Natural Configuration at C20 by Route B. An important aspect of the synthesis of vitamin D analogues **3** (nonnatural configuration at C20) was the formation of the protected vitamin D derivative **12d** (Scheme 1, X = OCONHPh), which bears the appropriate

Scheme 8



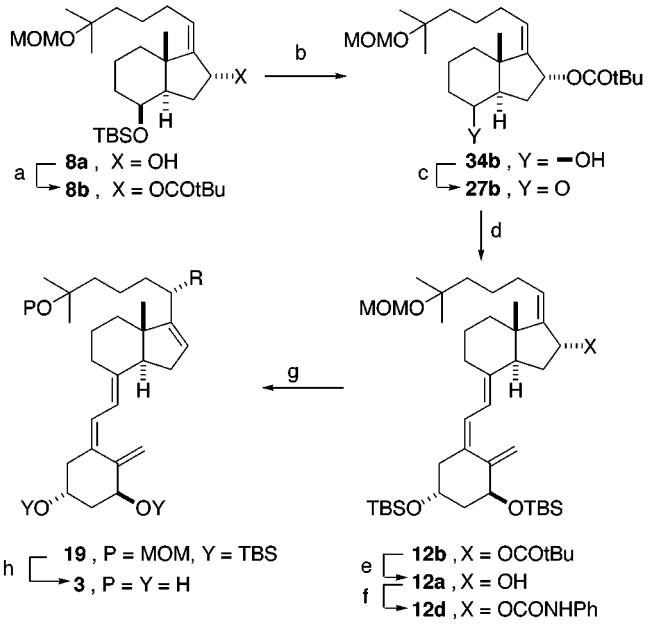
appendage on the D ring to allow the introduction of different substituents at C20 through S_N2' syn displacement. Transformation of carbamate **27d** to **12d** (Scheme 7) proved to be more challenging than anticipated. Treatment of the anion of **7** with ketone **27d** (1/3 equiv) gave, at best, a 30% yield of **12d**. Analysis of the crude reaction products by ^1H NMR spectroscopy revealed the presence of starting material **27d** [$\delta = 0.84$ (3 H, Me18)] and its epimer at carbon C14 **33** [$\delta = 1.31$ (3 H, Me18)]. The unexpected formation of **33** supports the hypothesis that the anion generated from **7** attacks the carbamate moiety and the resulting anion induces the formation of the thermodynamic enolate by intramolecular hydrogen abstraction (Scheme 8). Ultimately, protonation of the enolate during the reaction or upon workup gives rise to **27d** and **33**.[26]

In an effort to improve the yield of **12d** we planned an alternative, though longer, route employing pivaloate **27b** (Scheme 9) to overcome the problem of epimerization at C14 during the Wittig−Horner coupling reaction. Treatment of alcohol **8a** with pivaloyl chloride (*t*-BuCOCl) in the presence of 4-(dimethylamino)pyridine (DMAP) as a catalyst in pyridine, followed by desilylation of the resulting ester **8b** with tetrabutylammonium fluoride in THF, gave alcohol **34b** (88% two steps). Treatment of **34b** with pyridinium dicromate (PDC) in the presence of pyridinium *p*-toluenesulfonate (PPTS) in CH_2Cl_2 afforded the desired ketone **27b** (98%). The Wittig−Horner coupling between ketone **27b** and the anion prepared by reaction of **7** with *n*-BuLi took place cleanly to afford protected vitamin D analogues **12b** in 93% yield. Reduction of the ester group in **12b** with $LiAlH_4$ gave alcohol **12a** (94%), which was subjected to carbamoylation using phenyl isocyanate in the presence of DMAP in pyridine to afford the required allylic carbamate **12d** (98%). We were pleased to find that reaction of **12d** with the high order cuprates $Li_2Cu_3R_5$ (R = Me, *n*-Bu, Ph) proceeded cleanly to provide the desired protected vitamins D analogues (**19a**, **19b**, and **19c**) (87% average yield). These intermediates were successively treated with tetrabutylammonium fluoride and AG 50W-X4 cationic resin to give the 20-substituted vitamin D analogues (**3a**−**c**) (83% average yield).

(25) For equilibration of the vitamin D triene system to the 5,6-trans isomer in the presence of traces of iodine, see ref 9c and references therein.

(26) The anion of **7** was generated using *n*-BuLi. The use of the anion generated from **7** by means of *N*-sodium hexamethyldisilazane resulted in a higher degree of epimerization at C14 and a lower yield of the reaction product **12d**.

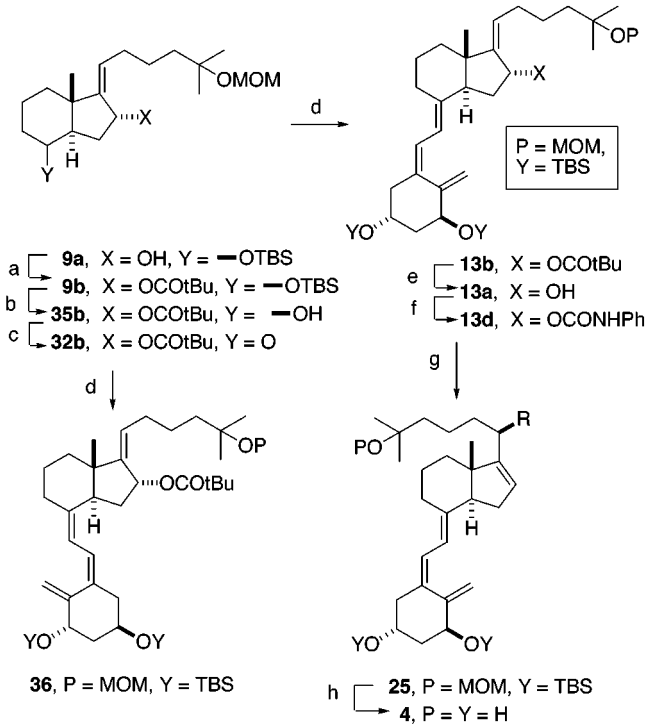
Scheme 9[a]



[a] Key: (a) *t*-BuCOCl, py, DMAP, 96%; (b) *n*-Bu_4NF, THF, reflux, 92%; (c) PDC, PPTS, CH_2Cl_2, 98%; (d) **7**, *n*-BuLi, THF, −78 °C; **27b**, THF, 93%; (e) $LiAlH_4$, THF, 0 °C, 94%; (f) PhNCO, DMAP, py, −20 °C, 98%; (g) $Li_2Cu_3R_5$, Et_2O, −78 °C [**19a** (R = Me, 82%), **19b** (R = *n*-Bu, 93%), **19c** (R = Ph, 85%)]; (h) *n*-Bu_4NF, THF; AG50W-X4, MeOH [**3a** (R = Me, 88%), **3b** (R = *n*-Bu, 80%), **3c** (R = Ph, 81%)].

Next we proceeded with the synthesis of vitamin D_3 analogues with the natural configuration at C20 (**4**). As above, we first examined the Wittig−Horner coupling between ketone **32d**[27] (1/3 equiv) and the anion of phosphine oxide **7** (Scheme 7). In this case, the desired precursor of vitamin D analogues **13d** was produced only in 26% yield. Analysis of the crude reaction products by ^{1}H NMR spectroscopy revealed the presence of starting ketone **32d** and its epimer at C14. This result led us to introduce the carbamate group after formation of the triene unit. Esterification of alcohol **9a** to pivaloate **9b**, followed by desilylation and oxidation, provided ketone **32b** (93% over the three steps) (Scheme 10). The Wittig−Horner coupling afforded the protected vitamin D analogue **13b** in a lower than expected yield (71%). In this case, a minor side product was isolated (20%) and tentatively identified as the nonnatural protected vitamin D analogue **36** by comparison of its ^{1}H NMR spectrum with those of similar compounds.[28] The formation of **36** is probably due to steric hindrance caused by the attacking phosphine oxide anion and the pivaloyl moiety.[29] Replacement of the pivaloate group by the carbamate group, as described above, afforded **13d** in 89% yield. Carbamate **13d** was subjected to reaction with $Li_2Cu_3R_5$, prepared from CuBr, and cleanly produced the protected vitamin D analogues with the natural configuration at C20 (82% average yield) by S_N2' syn displacement of the carbamoyl moiety. Removal of the silyl and methoxymethyl protecting groups of **25** using the method described above gave the desired vitamin D analogues **4b** and **4c** (81% average yield).

Scheme 10[a]



[a] Key: (a) *t*-BuCOCl, DMAP, py, 97%; (b) *n*-Bu_4NF, THF, 65 °C, 97%; (c) PDC, PPTS, CH_2Cl_2, 99%; (d) **7**, *n*-BuLi, THF, −78 °C; **32b**, THF, 71%; (e) $LiAlH_4$, THF, 0 °C, 92%; (f) PhNCO, DMAP, py, −20 °C, 97%; (g) $Li_2Cu_3R_5$, Et_2O, −78 °C [**25b** (R = Ph, 89%), **25c** (R = c-Pr, 92%)]; (h) *n*-Bu_4NF, AG50W-X4, MeOH, [**4b** (R = Ph, 84%), **4c** (R = c-Pr, 78%)].

In summary, we have developed two efficient approaches to 1α,25-dihydroxy-16-ene-vitamin D_3 and its analogues at C20. Key features of these approaches are the stereo- and regiocontrolled cuprate S_N2' syn addition to allylic carbamates. In route A, the cuprate chemistry is carried out before the introduction of the vitamin D triene unit (average yield of vitamin D analogue 35%, 11−13 steps from ketone **11**). In route B, the cuprate chemistry is carried out on intermediates that already bear the vitamin D triene unit and the allylic carbamate system (average yield of vitamin D analogue 27%, 13−15 steps from ketone **11**). The second route is particularly attractive since the Wittig−Horner coupling to introduce the triene unit is carried out only once. The new synthetic strategies also serve to provide access to the important hormone 1α,25-dihydroxyvitamin D_3 and its analogues with C17−C20 unsaturated side chains.

Experimental Section

General Methods. 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), ether (Et_2O), and benzene were distilled from Na/benzophenone. Dichloromethane (CH_2Cl_2) was distilled from P_2O_5. Absolute MeOH was distilled from Mg turnings. Pyridine was distilled from KOH. *i*-Pr_2NH and Et_3N were redistilled from CaH_2. Copper(I) iodide (CuI) was purified by heating in a saturated aqueous solution of KI followed by hot filtration and precipitation with water/ether, and the resulting solid was dried in vacuo over

(27) Ketone **32d** (X = OCONHPh, Y = O, Scheme 10) was prepared in 83% overall yield by the sequence: **9a** → **35a** (X = OH, Y = −OH) → **35d** (X = OCONHPh, Y = −OH).

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(29) Molecular mechanics calculations (CS Chem 3D Pro. 1986−1987 CambridgeSoft Corp.) indicate that the pivaloyl group in **32b** is orientated more to the convex face than in **27b**.

P_2O_5.[30] Copper(I) bromide was purified by dissolving in commercial HBr (48%) followed by precipitation with water and filtration, and the resulting solid was dried in vacuo over P_2O_5.[31] Both of these reagents were handled under argon in the absence of light. 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 using a rotary evaporator at aspirator pressure (20−30 mmHg). Reactions were monitored by thin-layer chromatography (TLC) using aluminum-backed 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. Flash column chromatography was performed with Merck 60 (230−400 mesh) silica gel.[32] All NMR spectra were measured as solutions in $CDCl_3$ unless otherwise stated. Chemical shifts are reported on the δ scale (ppm) downfield from tetramethylsilane ($\delta = 0.0$) using the residual solvent signal as an internal standard: $\delta = 7.26$ (^{1}H), 77.0 triplet (^{13}C). All coupling constants are measured in hertz (Hz). DEPT was used to assign carbon types. The electron-impact mass spectra were measured at 70 eV and FAB mass spectra were recorded using a bis(2-hydroxyethyl) disulfide matrix. High-performance liquid chromatography (HPLC) was performed using a Zorbax-sil 10/250 column and a programmable multiwavelength detector.

(4-Carboxybutyl)triphenylphosphonium Bromide (15b).[33] To a solution of 5-bromovaleric acid (10 g, 55.25 mmol) in acetonitrile (25 mL) was added Ph_3P (16 g, 60.77 mmol). The resulting mixture was stirred at 80 °C for 24 h and then concentrated. The white residue was washed with benzene, hexanes, and Et_2O and dried to give 23.55 g of **15b** (96%, white solid). ^{1}H NMR: 1.70 (2 H, m, H_2), 1.91 (2 H, q, H_3, $J = 6.9$ Hz), 2.58 (2 H, t, H_4, $J = 6.9$ Hz), 3.61 (2 H, m, H_1), 7.73 and 7.78 (5 H, m, Ar).

(17*Z*)-8*β*-[(*tert*-Butyldimethylsilyl)oxy]-des-A,B-21,26,27-trinorcholest-17(20)-en-25-oic Acid (16a). A solution of (4-carboxybutyl)triphenylphosphonium bromide (55.6 g, 125.4 mmol) and *t*-BuOK (42.2 g, 376.2 mmol) in benzene (250 mL) was refluxed for 2 h, and then a solution of ketone **11** (10.1 g, 35.8 mmol) in dry benzene (65 mL) was added by syringe. After being stirred for 36 h at 80 °C, the mixture was washed with water, and the aqueous phase was acidified with HCl (10%) and extracted with EtOAc. The combined organic extracts were dried, filtered, and concentrated in vacuo. The residue was flash chromatographed (4% EtOAc/hexanes) to give 9.83 g of **16a** [75%, $R_f = 0.3$ (20% EtOAc/hexanes), white solid]. ^{1}H NMR: 0.01 and 0.02 (6 H, 2 s, Me_2Si), 0.89 (9 H, s, *t*-BuSi), 1.09 (3 H, s, C_{18}-CH_3), 2.17 (4 H, m, $2H_{22}$ and $H_{16,14}$), 2.36 (2 H, t, $2H_{24}$, $J = 7.7$ Hz), 2.38 (1 H, m, H_{16}), 4.07 (1 H, d, H_8, $J = 1.8$ Hz), 4.90 (1 H, tt, H_{20}, $J = 7.4$ Hz, 1.9 Hz). ^{13}C NMR: −5.2 (CH_3), −4.9 (CH_3), 17.8 (C), 17.9 (CH_2), 20.1 (CH_3), 23.7 (CH_2), 25.6 (CH_2), 25.7 ($3CH_3$), 26.6 (CH_2), 30.5 (CH_2), 33.6 (CH_2), 34.3 (CH_2), 38.1 (CH_2), 44.1 (C), 52.7 (CH), 69.7 (CH), 117.6 (CH═), 151.2 (C═), 180.5 (C). HRMS: calcd for $C_{21}H_{38}O_3Si$ 366.2590, found 366.2595.

(17*Z*)-8*β*-[(*tert*-Butyldimethylsilyl)oxy]-des-A,B-21-norcholest-17(20)-en-25-ol (10a). A solution of MeLi (1.5 M in Et_2O, 26.6 mL, 39.9 mmol) was added dropwise to a solution of **16a** (6.8 g, 18.6 mmol) in dry THF (70 mL) at 0 °C. The mixture was stirred at room temperature for 12 h and quenched slowly with ice. The mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried, filtered, and concentrated in vacuo. The residue was dried overnight under vacuum and directely used in the next step.

A solution of MeLi (1.5 M in Et_2O, 37.2 mL, 55.8 mmol) was added to a solution of the above crude mixture in dry THF (70 mL) at −78 °C. After 3 h, the mixture was allowed to warm to room temperature over a 3 h period. The reaction was quenched at −78 °C with an aqueous saturated solution of NaCl. The mixture was extracted with EtOAc, and the combined organic fractions were dried, filtered, and concentrated in vacuo. The residue was flash chromatographed (7% EtOAc/hexanes) to give 6 g of alcohol **10a** [85%, $R_f = 0.5$ (20% EtOAc/hexanes), colorless oil]. ^{1}H NMR: 0.008 and 0.01 (6 H, 2 s, Me_2Si), 0.88 (9 H, s, *t*-BuSi), 1.09 (3 H, s, C_{18}-CH_3), 1.20 (6 H, s, $C_{26,27}$-$2CH_3$), 2.19 (4 H, m, $2H_{22}$ and $H_{16,14}$), 2.39 (1 H, m, H_{16}), 4.07 (1 H, d, H_8, $J = 1.9$ Hz), 4.93 (1 H, tt, H_{20}, $J = 7.4$ Hz, 2.0 Hz). ^{13}C NMR: −5.2 (CH_3), −4.9 (CH_3), 17.9 (C), 18.0 (CH_2), 20.1 (CH_3), 23.7 (CH_2), 25.5 (CH_2), 25.8 (3 CH_3), 27.7 (2 CH_3), 29.2 (CH_2), 30.5 (CH_2), 34.3 (CH_2), 38.2 (CH_2), 43.7 (CH_2), 44.1 (C), 52.7 (CH), 69.7 (CH), 71.0 (C), 118.8 (CH═), 150.3 (C═). HRMS: calcd for $C_{23}H_{44}O_2Si$ 380.3110, found 380.3126.

(17*Z*)-8*β*-[(*tert*-Butyldimethylsilyl)oxy]-25-[(methoxymethyl)oxy]-des-A,B-21-norcholest-17(20)-ene (10b). ClMOM (2.5 mL, 43.6 mmol) was added to a solution of **10a** (5.5 g, 14.6 mmol), DMAP (0.12 g, 1 mmol), and *i*-Pr_2NEt (7.5 mL) in CH_2Cl_2 (120 mL) at 0 °C. The reaction mixture was stirred for 24 h and quenched with ice and an aqueous solution of HCl (10%). The resulting mixture was extracted with CH_2Cl_2. The organic phase was washed with H_2O, dried (Na_2SO_4), and filtered. Concentration afforded a residue that was flash chromatographed (4% EtOAc/hexanes) to give 5.7 g of **10b** [92%, $R_f = 0.7$ (15% EtOAc/hexanes), colorless oil]. ^{1}H NMR: −0.01 (6 H, 2 s, Me_2Si), 0.87 (9 H, s, *t*-BuSi), 1.08 (3 H, s, C_{18}−CH_3), 1.18 (6 H, s, $C_{26,27}$-$2CH_3$), 2.16 (4 H, m, $2H_{22}$ and $H_{16,14}$), 2.39 (1 H, m, H_{16}), 3.34 (3 H, s, MeO), 4.05 (1 H, d, H_8, $J = 1.9$ Hz), 4.67 (2 H, s, OCH_2O), 4.92 (1 H, tt, H_{20}, $J = 7.4$ Hz, 2.0 Hz). ^{13}C NMR: -5.2 (CH_3), −4.9 (CH_3), 17.9 (C), 18.0 (CH_2), 20.0 (CH_3), 23.7 (CH_2), 25.2 (CH_2), 25.7 (3 CH_3), 26.3 (2 CH_3), 27.8 (CH_2), 30.5 (CH_2), 34.4 (CH_2), 38.2 (CH_2), 43.8 (CH_2), 44.1 (C), 52.7 (CH), 54.9 (CH_3), 69.8 (CH), 76.2 (C), 91.0 (CH_2), 120.0 (CH═), 150.1 (C═). HRMS: calcd for $C_{25}H_{48}O_3Si - CH_3$ 409.3138, found 409.3137.

(17*E*)-8*β*-[(*tert*-Butyldimethylsilyl)oxy]-25-[(methoxymethyl)oxy]-des-A,B-21-norcholest-17(20)-en-16α-ol (8a). A solution of *t*-BuOOH (3 M in toluene, 6.8 mL, 20.5 mmol) was added to a suspension of SeO_2 (1.1 g, 10.3 mmol, freshly sublimated) in CH_2Cl_2 (30 mL) at 0 °C. After 1 h, a solution of **10b** (5.7 g, 13.4 mmol) in CH_2Cl_2 (130 mL) was added slowly via cannula, and the mixture was stirred at room temperature for 6 h. The reaction was quenched with an aqueous solution of NaOH (10%). The aqueous portion was extracted with CH_2Cl_2, and the combined organic fractions were dried, filtered, and concentrated in vacuo. Flash chromatography (10% EtOAc/hexanes) afforded 5.5 g of **8a** [90%, $R_f = 0.43$ (20% EtOAc/hexanes), colorless oil]. ^{1}H NMR: 0.01 and 0.02 (6 H, 2 s, Me_2Si), 0.88 (9 H, s, *t*-BuSi), 1.09 (3 H, s, C_{18}−CH_3), 1.20 (6 H, s, $C_{26,27}$-$2CH_3$), 2.12−2.22 (3 H, m, $2H_{22}$ and H_{14}), 3.36 (3 H, s, MeO), 4.09 (1 H, d, H_8, $J = 1.9$ Hz), 4.44 (1 H, d, H_{16}, $J = 6.0$ Hz), 4.67 (2 H, s, OCH_2O), 5.38 (1 H, dt, H_{20}, $J = 7.4$ Hz, 1.1 Hz). ^{13}C NMR: −5.2 (CH_3Si), −4.9 (CH_3Si), 17.8 (CH_2), 17.9 (C), 20.9 (CH_3), 24.6 (CH_2), 25.7 (CH_3), 26.3 (CH_3), 27.7 (CH_2), 34.2 (CH_2), 34.7 (CH_2), 38.3 (CH_2), 41.5 (CH_2), 44.3 (C), 49.1 (CH), 55.1 (CH_3), 69.4 (CH), 73.6 (CH), 76.2 (C), 91.0 (CH_2), 124.4 (CH═), 155.6 (C═). HRMS: calcd for $C_{25}H_{48}O_4Si - H_2O$ 422.3216. found 422.3212. Anal. Calcd for $C_{25}H_{48}O_4Si$: C, 68.13; H, 10.97. Found: C, 68.02; H, 11.49.

(20*S*)-8*β*-[(*tert*-Butyldimethylsilyl)oxy]-17a,20-epoxy-25-[(methoxymethyl)oxy]-des-A,B-21-norcholestan-16α-ol (20). Pure *m*-CPBA (430 mg, 2.51 mmol) was added portionwise to a cooled (0 °C) biphasic mixture of **8a** (1 g, 2.27 mmol) and $NaHCO_3$ (1.18 g, 13.79 mmol) in 3:1 CH_2Cl_2/H_2O (32 mL). The resulting mixture was stirred at room temperature for 5 h in the absence of light and then treated with HCl (10%). The aqueous phase was extracted with CH_2Cl_2, and the combined organic fractions were dried, filtered, and concentrated in vacuo. The resulting residue was flash chromatographed (10% EtOAc/hexanes) to give 886 mg of **20** [86%, $R_f = 0.67$ (30% EtOAc/hexanes), colorless oil]. ^{1}H NMR: −0.01 (6 H, 2 s, Me_2Si), 0.87 (9 H, s, *t*-BuSi), 1.11 (3 H, s, C_{18}-CH_3), 1.21 (6 H, s, $C_{26,27}$-$2CH_3$), 2.04 (1 H, m, H_{14}), 2.92 (1 H, m,

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H_{20}), 3.35 (3 H, s, MeO), 4.03 (1 H, d, H_8, J = 2.3 Hz), 4.69 (2 H, s, OCH_2O), 4.19 (1 H, t, H_{16}, J = 6.8 Hz). ^{13}C NMR: −5.1 (CH_3Si), −4.9 (CH_3Si), 16.8 (CH_2), 17.8 (CH_3), 18.0 (C), 21.8 (CH_2), 25.6 (CH_3), 26.2 (CH_3), 28.8 (CH_2), 33.7 (CH_2), 33.8 (CH_2), 34.5 (CH_2), 41.4 (CH_2), 41.7 (C), 47.7 (CH), 55.0 (CH_3), 62.0 (CH), 69.3 (CH), 69.4 (CH), 73.8 (C), 76.1 (C), 91.0 (CH_2). HRMS: calcd for $C_{25}H_{48}O_5Si$ 456.3271, found 456.3262.

(17*Z*)-8*β*-[(*tert*-Butyldimethylsilyl)oxy]-25-[(methoxymethyl)oxy]-des-A,B-21-norcholest-17(20)-en-16α-ol (9a). A solution of *n*-BuLi (2.5 m in hexanes, 2.15 mL, 5.34 mmol) was added to a solution of $HPPh_2$ (860 mL, 4.95 mmol) in THF (7 mL) at 0 °C. The red solution was stirred at room temperature for 4 h, and then epoxide **20** (860 mg, 1.88 mmol) in THF (7 mL) was added dropwise via syringe. After 48 h, the reaction mixture was cooled at 0 °C and treated with MeI (620 mL, 8.88 mmol). After an additional 4 h of stirring, H_2O was added, and the aqueous portion was extracted with Et_2O. The combined organic fractions were dried, filtered, and concentrated in vacuo, and the residue was flash chromatographed (8% EtOAc/hexanes) to give 733 mg of **9a** [88%, R_f = 0.44 (20% EtOAc/hexanes), white solid]. ^{1}H NMR: 0.11 (3 H, s, MeSi), 0.21 (3 H, s, MeSi), 0.87 (9 H, s, *t*-BuSi), 0.98 (3 H, s, C_{18}−CH_3), 1.21 (6 H, s, $C_{26,27}$-$2CH_3$), 2.02 (1 H, m, H_{14}), 3.36 (3 H, s, MeO), 4.12 (1 H, d, H_8, J = 2.2 Hz), 4.69 (2 H, s, OCH_2O), 4.74 (1 H, m, H_{16}), 5.16 (1 H, t, H_{20}, J = 7.4 Hz). ^{13}C NMR: −5.2 (CH_3Si), −4.9 (CH_3Si), 17.7 (CH_2), 17.9 (C), 20.9 (CH_2), 23.7 (CH_3), 24.5 (CH_2), 25.7 (CH_3), 26.3 (CH_3), 29.3 (CH_2), 34.5 (CH_2), 35.5 (CH_2), 37.4 (CH_2), 41.3 (CH_2), 43.7 (C), 48.4 (CH), 55.0 (CH_3), 69.2 (CH), 70.6 (CH), 76.3 (C), 91.0 (CH_2), 122.1 (CH═), 155.6 (C═). HRMS: calcd for $C_{25}H_{47}O_4Si$ − H 439.3243, found 439.3235.

(17*E*)-8*β*-[(*tert*-Butyldimethylsilyl)oxy]-25-[(methoxymethyl)oxy]-16α-[(phenylcarbamoyl)oxy]-des-A,B-21-norcholest-17(20)-ene (8d). A solution of **8a** (600 mg, 1.4 mmol) in Py (9 mL) was treated with DMAP (15 mg) and PhNCO (0.49 mL, 4.63 mmol) at −10 °C. After 12 h, the reaction was treated with an aqueous saturated solution of $NaHCO_3$. The resulting mixture was filtered and the residue washed with Et_2O. The combined organic extracts were washed successively with HCl (10%), H_2O, and an aqueous saturated solution of $CuSO_4$ and H_2O. The ethereal extract was dried, filtered, and concentrated in vacuo. Flash chromatography (4% EtOAc/hexanes) afforded 740 mg of pure **8d** [97%, R_f = 0.66 (20% EtOAc/hexanes), white foam]. ^{1}H NMR: 0.01 and 0.02 (6 H, 2 s, Me_2Si), 0.88 (9 H, s, *t*-BuSi), 1.14 (3 H, s, C_{18}−CH_3), 1.20 (6 H, s, $C_{26,27}$-$2CH_3$), 2.04−2.22 (3 H, m, $2H_{22}$ and H_{14}), 3.36 (3 H, s, MeO), 4.09 (1 H, d, H_8, J = 1.9 Hz), 4.70 (2 H, s, OCH_2O), 5.43 (1 H, dt, H_{20}, J = 7.4 Hz, 1.8 Hz), 5.49 (1H, dd, H_{16}, J = 6.2 Hz, 1.3 Hz), 6.80 (1H, br s, NH), 7.01−7.41 (5H, m, Ar). ^{13}C NMR: −5.1 (CH_3Si), −4.9 (CH_3Si), 17.6 (CH_2), 17.9 (C), 20.6 (CH_3), 24.6 (CH_2), 25.7 (CH_3), 26.3 (CH_3), 26.4 (CH_3), 27.6 (CH_2), 31.7 (CH_2), 34.1 (CH_2), 37.8 (CH_2), 41.1 (CH_2), 43.6 (C), 48.6 (CH), 55.0 (CH_3), 68.8 (CH), 76.2 (C), 77.3 (CH), 91.0 (CH_2), 118.5 (CH Ar), 123.2 (CH═), 126.1 (CH-Ar), 129.0 (CH-Ar), 138.3 (C-Ar), 149.3 (C═O), 154.0 (C═). HRMS: calcd for $C_{32}H_{53}NO_5Si$ 559.3693, found 559.3677. Anal. Calcd for $C_{32}H_{53}NO_5Si$: C, 68.65; H, 9.54; N, 2.50. Found: C, 69.01; H, 9.95; N, 2.64.

A similar procedure was used to prepare compound **9d** [84%, R_f = 0.68 (20% EtOAc/hexanes), white solid].

(20*S*)-8*β*-[(*tert*-Butyldimethylsilyl)oxy]-25-[(methoxymethyl)oxy]-des-A,B-cholest-16-ene (17a). A solution of MeLi (1.6 M in Et_2O, 1.2 mL, 1.92 mmol) was added via syringe to a suspension of CuI (184 mg, 0.96 mmol) in Et_2O (9 mL) at 0 °C. After 1 h, a solution of **8d** (180 mg, 0.31 mmol) in Et_2O (6 mL) was added, and the mixture was stirred at room temperature for 6 h in the dark. The reaction was quenched with aqueous NH_4Cl, and the mixture was extracted with Et_2O. The combined ethereal layers were washed with saturated solution of $NaHCO_3$, dried, and concentrated in vacuo. The residue was flash chromatographed (3% EtOAc/hexanes) to give 130 mg of **17a** [93%, R_f = 0.79 (20% EtOAc/hexanes), colorless oil]. ^{1}H NMR: 0.01 (6 H, s, Me_2Si), 0.85 (9 H, s, *t*-BuSi), 1.02 (3 H, s, C_{18}-CH_3), 1.03 (3 H, d, C_{21}-CH_3, J = 6.8 Hz), 1.19 (6 H, s, $C_{26,27}$-$2CH_3$), 2.05−2.24 (3 H, m, $2H_{22}$ and H_{14}), 3.36 (3 H, s, MeO), 4.09 (1 H, m, H_8), 4.70 (2 H, s, OCH_2O), 5.29 (1 H, t, H_{16}, J = 1.2 Hz). ^{13}C NMR: −5.2 (CH_3Si), −4.8 (CH_3Si), 17.9 (C), 18.0 (CH_2), 19.8 (CH_3), 21.9 (CH_3), 22.8 (CH_2), 25.9 (CH_3), 26.4 (CH_3), 30.9 (CH_2), 31.0 (CH), 34.8 (CH_2), 35.9 (CH_2), 38.1 (CH_2), 42.0 (CH_2), 46.6 (C), 55.0 (CH_3), 55.1 (CH), 69.2 (CH), 76.3 (C), 90.9 (CH_2), 120.1 (CH═), 161.0 (C═). HRMS: calcd for $C_{26}H_{50}O_3Si$ 438.3529, found 438.3520.

A similar procedure was used to prepare compound **21a** [91%, R_f = 0.81 (20% EtOAc/hexanes), colorless oil].

(20*S*)-8*β*-[(*tert*-Butyldimethylsilyl)oxy]-25-[(methoxymethyl)oxy]-21-propyl-des-A,B-cholest-16-ene (17b). A solution of *n*-BuLi (2.5 M in hexane, 1.59 mL, 3.97 mmol) was added by syringe to a suspension of CuI (379 mg, 1.99 mmol) in Et_2O (8 mL) at −78 °C. After 1 h, a solution of **8d** (150 mg, 0.26 mmol) in Et_2O (4 mL) was added, and then the mixture was allowed to warm to room temperature and stirred for 12 h in the dark. The reaction was quenched with aqueous NH_4Cl, and the mixture was extracted with Et_2O. The combined ethereal layers were washed with saturated solution of $NaHCO_3$, dried, and concentrated in vacuo. The residue was flash chromatographed (2% EtOAc/hexanes) to give 113 mg of **17b** [88%, R_f = 0.76 (20% EtOAc/hexanes), colorless oil]. ^{1}H NMR: 0.04 (6 H, s, Me_2Si), 0.85 (9 H, s, *t*-BuSi), 0.85 (2 H, t, C_{21}-CH_3), 0.98 (3 H, s, C_{18}-CH_3), 1.18 (6 H, s, $C_{26,27}$-$2CH_3$), 1.59−1.98 (3 H, m, $2H_{15}$ and H_{20}), 2.22 (1 H, m, H_{14}), 3.38 (3 H, s, MeO), 4.06 (1 H, m, H_8), 4.69 (2 H, s, OCH_2O), 5.22 (1 H, H_{16}, t, J = 1.1 Hz). ^{13}C NMR: −5.1 (CH_3Si), −4.8 (CH_3Si), 14.1 (CH_3), 18.1 (CH_2), 19.1 (CH_3), 21.5 (CH_2), 23.0 (C), 23.1 (CH_2), 25.8 (CH_3), 26.4 (CH_3), 26.5 (CH_3), 29.9 (CH_2), 30.9 (CH_2), 33.9 (CH_2), 34.8 (CH_2), 35.7 (CH_2), 36.3 (CH_2), 36.9 (CH), 42.1 (CH_2), 46.7 (C), 55.0 (CH_3), 55.1 (CH), 69.2 (CH), 76.4 (C), 91.0 (CH_2), 120.6 (CH═), 158.7 (C═); HRMS: calcd for $C_{29}H_{56}O_3Si$ 480.3999, found 480.3979.

A similar procedure was used to prepare compounds **17e**, **17d**, **17c**,[34] **21b**, and **21c**. **17e**, **17d**, and **17c** were prepared from **8d**; **21b** and **21c** were prepared from **9d**. **17e** [90%, R_f = 0.72 (20% EtOAc/hexanes), colorless oil]. **17d** [56%, R_f = 0.81 (20% EtOAc/hexanes), colorless oil. **17c** [83%, R_f = 0.74 (20% EtOAc/hexanes), colorless oil]. **21b** [90%, R_f = 0.80 (20% EtOAc/hexanes), colorless oil]. **21c** [85%, R_f = 0.76 (20% EtOAc/hexanes), colorless oil].

8*β*-[(*tert*-Butyldimethylsilyl)oxy]-25-[(methoxymethyl)oxy]-des-A,B-cholestane (22a). A suspension of **21a** (100 mg, 0.23 mmol) and Pd/C (5%, 25 mg) in EtOAc (3 mL) was stirred under H_2 gas at balloon pressure. After being stirred for 12 h, the resulting suspension was filtered through a short column of Celite, and the solvent was removed under reduced pressure to afford a residue that was flash chromatographed (4% EtOAc/hexanes) to give 90.5 mg of **22a** [90%, R_f = 0.81 (20% EtOAc/hexanes), colorless oil]. ^{1}H NMR: −0.015 and −0.01 (6 H, 2s, Me_2Si), 0.86 (3 H, d, C_{21}-CH_3, J = 2.0 Hz), 0.88 (9 H, s, *t*-BuSi), 0.89 (3 H, s, C_{18}-CH_3), 1.20 (6 H, s, $C_{26,27}$-$2CH_3$), 2.92 (1 H, m, H_{14}), 3.35 (3 H, s, MeO), 3.98 (1 H, m, H_8), 4.69 (2 H, s, OCH_2O). ^{13}C NMR: −5.2 (CH_3Si), −4.8 (CH_3Si), 13.6 (CH_3), 17.6 (CH_2), 17.7 (C), 18.5 (CH_3), 20.4 (CH_2), 23.0 (CH_2), 25.7 (CH_3), 26.2 (CH_3), 26.3 (CH_3), 27.3 (CH_2), 34.4 (CH_2), 35.2 (CH), 36.3 (CH_2), 40.7 (CH_2), 42.1 (C), 42.2 (CH_2), 53.0 (CH), 55.0 (CH_3), 56.8 (CH), 69.4 (CH), 76.3 (C), 90.9 (CH_2). HRMS: calcd for $C_{26}H_{53}O_3Si$ + H 441.3781, found 441.3764.

(20*S*)-25-[(Methoxymethyl)oxy]-des-A,B-cholest-16-en-8*β*-ol (18a). A solution of TBAF (1 M in THF, 790 mL, 0.79 mmol) was added by syringe to **17a** (70 mg, 0.16 mmol) in THF (0.5 mL). The resulting mixture was refluxed for 12 h and then treated with $NaHCO_3$. The aqueous phase was extracted with Et_2O, and the combined ethereal fractions were dried, filtered, and concentrated in vacuo. The residue was flash chromatographed (10% EtOAc/hexanes) to give 50.6 mg of **18a** [98%, R_f = 0.53 (20% EtOAc/hexanes), colorless oil]. ^{1}H NMR: 1.02 (3 H, s, C_{18}-CH_3), 1.03 (3 H, s, H_{21}-CH_3), 1.17 (6 H, s, $C_{26,27}$-$2CH_3$), 2.05−2.28 (4 H, m, $2H_{15}$ and $H_{20,14}$), 3.33 (3 H, s, MeO), 4.09 (1 H, m, H_8), 4.66 (2 H, s, OCH_2O), 5.30 (1 H, t, H_{16}, J = 1.2 Hz); ^{13}C NMR: 17.7 (CH_2), 18.6 (CH_3), 21.1 (CH_3), 21.7 (CH_2), 26.3 (CH_3-26 and 27), 30.2 (CH_2), 30.4 (CH), 33.8 (CH_2), 35.4 (CH_2), 38.0 (CH_2), 41.9 (CH_2), 46.6 (C), 54.1 (OCH_3), 55.0

(CH), 69.1 (CH), 76.3 (C), 90.9 (OCH_2O), 120.2 (CH═), 160.8 (C═). HRMS: calcd for $C_{20}H_{36}O_3$ 324.2664, found 324.2656.

A similar procedure was used to prepare compound **23c** [99%, $R_f = 0.44$ (10% EtOAc/hexanes), colorless oil].

(20*S*)-25-[(Methoxymethyl)oxy]-des-A,B-cholest-16-en-8-one (5a). PDC (109 mg, 0.29 mmol) was added to a solution of **18a** (34 mg, 0.105 mmol) in CH_2Cl_2 (1.5 mL). After 6 h, the resulting suspension was filtered through Celite and concentrated to give a residue that was flash chromatographed (10% EtOAc/hexanes) to afford 33 mg of pure **5a** [97%, $R_f = 0.62$ (20% EtOAc/hexanes), colorless oil]. ^{1}H NMR: 0.80 (3 H, s, C_{18}-CH_3), 1.05 (3 H, d, C_{21}-CH_3 $J = 1.2$ Hz), 1.19 (6 H, s, $C_{26,27}$-$2CH_3$), 2.24−2.46 (5 H, m, $2H_{9,15}$ and H_{20}), 2.80 (1 H, dd, H_{20}, $J = 10.6$, 6.4 Hz), 3.35 (3 H, s, MeO), 4.68 (2 H, s, OCH_2O), 5.28 (1 H, t, H_{16}, $J = 1.2$ Hz). ^{13}C NMR: 17.5 (CH_2), 21.1 (CH_3), 21.8 (CH_2), 23.9 (CH_2), 26.3 (CH_3-26 and 27), 27.0 (CH_2), 34.4 (CH_2), 37.6 (CH_2), 40.4 (CH_2), 41.9 (CH_2), 54.0 (C), 55.0 (OCH_3), 63.0 (CH), 76.2 (C), 91.0 (OCH_2O), 120.4 (CH═), 158.8 (C═), 211.2 (C═O). HRMS: calcd for $C_{20}H_{34}O_3$ + Na 345.2407, found 345.2406.

A similar procedure was used to prepare compound **24c** [96%, $R_f = 0.57$ (10% EtOAc/hexanes), colorless oil].

(20*S*)-1α-[(*tert*-Butyldimethylsilyl)oxy]-16-en-25-[(methoxymethyl)oxy]vitamin D_3 *tert*-Butyldimethylsilyl Ether (19a). Phosphine oxide **7** (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 that 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 **7** (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 0.1 M solution of phosphine oxide in THF was used in the next experiments.

A solution of *n*-BuLi (2.1 M in hexane, 105 mL, 0.220 mmol) was added dropwise via syringe to a solution of the phosphine oxide **7** (0.216 mmol, 2.1 mL, 0.1 M) at −78 °C. The resulting deep red solution was stirred at −78 °C for 1 h followed by the slow addition of the ketone **5a** (35 mg, 0.11 mmol) in THF (1.5 mL). The red solution was stirred in the dark at −78 °C for 3 h and then warmed to −40 °C over 2 h. The reaction was quenched with H_2O. The mixture was extracted with Et_2O, and the combined organic fractions were washed with brine, dried, filtered, and concentrated in vacuo. The residue was flash chromatographed (1% EtOAc/hexanes) to give 68 mg of **19a** [92%, $R_f = 0.77$ (20% EtOAc/hexanes), white solid]. ^{1}H NMR: 0.05 (6 H, s, Me_2Si), 0.06 (6 H, s, Me_2Si), 0.68 (3 H, s, C_{18}-CH_3), 0.86 (9 H, s, *t*-BuSi), 0.87 (9 H, s, *t*-BuSi), 1.04 (3 H, d, C_{21}-CH_3, $J = 6.8$ Hz), 1.16 (6 H, s, $C_{26,27}$-$2CH_3$), 2.81 (1 H, m, H_{14}), 3.29 (3 H, s, MeO), 4.19 (1 H, m, H_3), 4.37 (1 H, m, H_1), 4.64 (2 H, s, OCH_2O), 4.86 (1 H, br s, H_{19Z}), 5.19 (1 H, br s, H_{19E}), 5.31 (1 H, m, H_{16}), 6.12 and 6.26 (2 H, AB pattern, H_6 and H_7, $J = 11.7$ Hz). ^{13}C NMR: −4.9 ($SiCH_3$), −4.7 ($SiCH_3$), −4.6 ($SiCH_3$), −4.5 ($SiCH_3$), 17.5 (CH_3), 18.4 (C), 18.5 (C), 21.5 (CH_3), 22.3 (CH_2), 23.9 (CH_2), 26.0 (CH_3-*t*Bu), 26.5 (CH_3-26 and 27), 29.0 (CH_2), 29.8 (CH_2), 32.6 (CH), 35.9 (CH_2), 38.2 (CH_2), 42.5 (CH_2), 45.4 (CH_2), 46.5 (CH_2), 50.6 (C), 55.1 (OCH_3), 58.8 (CH), 68.1 (CH), 72.5 (CH), 76.4 (C), 91.4 (OCH_2O), 111.5 (CH_2═), 118.3 (CH═), 120.8 (CH═), 123.6 (CH═), 135.7 (C═), 141.1 (C═), 149.1 (C═), 161.4 (C═).

A similar procedure was used to prepare compound **25c** [89%, $R_f = 0.65$ (10% EtOAc/hexanes), white solid].

(20*S*)-1α,25-Dihydroxy-16-ene-vitamin D_3 (3a). A solution of TBAF (1 M in THF, 840 mL, 0.84 mmol) was added via syringe to a solution of **19a** (31 mg, 0.045 mmol) in THF (0.3 mL). After the solution was stirred at room temperature for 12 h in the dark, a saturated solution of NH_4Cl was added, and the resulting mixture was extracted with Et_2O. The combined organic extracts were dried, filtered, and concentrated in vacuo to give a residue that was used directly in the next step.

A suspension of the above crude mixture in deoxygenated MeOH (3 mL) was stirred with cationic resin AG 50W-X4 (450 mg, prewashed with MeOH) at room temperature for 5 h in the dark. Filtration and concentration gave a residue that was flash chromatographed (50% EtOAc/hexanes) to afford 16 mg of pure vitamin D analogue **3a** [88%, $R_f = 0.35$ (50% EtOAc/hexanes)]. ^{1}H NMR: 0.69 (3 H, s, C_{18}-CH_3), 1.03 (3 H, d, C_{21}-CH_3, $J = 6.8$ Hz), 1.15 (6 H, s, $C_{26,27}$-$2CH_3$), 2.81 (1 H, m, H_{14}), 4.15 (1 H, m, H_3), 4.38 (1 H, m, H_1), 4.90 (1 H, br s, H_{19Z}), 5.27 (1 H, br s, H_{19E}), 5.30 (1 H, m, H_{16}), 6.09 and 6.35 (2 H, AB pattern, H_6 and H_7, $J = 11.7$ Hz). ^{13}C NMR: 16.4 (CH_3), 20.5 (CH_3), 22.0 (CH_2), 23.3 (CH_2), 27.8 (CH_3-26 and 27), 28.4 (CH_2), 29.0 (CH_2), 32.0 (CH), 35.3 (CH_2), 37.7 (CH_2), 42.4 (CH_2), 43.7 (CH_2), 44.8 (CH_2), 50.0 (C), 58.2 (CH), 66.0 (CH), 70.1 (C and CH), 110.7 (CH_2═), 117.5 (CH═), 120.1 (CH═), 123.5 (CH═), 134.4 (C═), 140.7 (C═), 148.4 (C═), 160.6 (C═). HRMS: calcd for $C_{27}H_{42}O_3$ 414.3134, found 414.3146.

A similar procedure was used to prepare compounds **3b**, **3c**, **4b**, and **4c**. **3b** [80%, $R_f = 0.20$ (50% EtOAc/hexanes), white solid]. **3c** [81% *Rf*= 0.21 (50% EtOAc/hexanes), white solid]. **4b** [84%, $R_f = 0.21$ (50% EtOAc/hexanes), white solid]. **4c** [78%, $R_f = 0.21$ (50% EtOAc/hexanes), white solid].

(17*E*)-25-[(Methoxymethyl)oxy]-des-A,B-21-norcholest-17(20)-ene-8β,16α-diol (26a). A solution of TBAF (1 M in THF, 10.6 mL, 10.6 mmol) was added via syringe to a solution of **8a** (900 mg, 2.04 mmol) in THF (2 mL). The resulting mixture was refluxed for 24 h, and then a saturated solution of $NaHCO_3$ was added. The aqueous phase was extracted with Et_2O. The combined organic extracts were dried, filtered, and concentrated in vacuo. The residue was flash chromatographed (50% EtOAc/hexanes) to afford 660 mg of **26a** [99%, $R_f = 0.18$ (40% EtOAc/hexanes), colorless oil]. ^{1}H NMR: 1.12 (3 H, s, C_{18}-CH_3), 1.21 (6 H, s, $C_{26,27}$-$2CH_3$), 2.14−2.21 (3 H, m, $2H_{22}$ and H_{14}), 3.35 (3 H, s, MeO), 4.19 (1 H, m, H_8), 4.48 (1 H, d, H_{16}, $J = 5.7$ Hz), 4.69 (2 H, s, OCH_2O), 5.41 (1 H, dt, H_{20}, $J = 6.4$, 1.0 Hz). ^{13}C NMR: 17.6 (CH_2), 20.6 (CH_3), 24.6 (CH_2), 26.2 (CH_3-26 and 27), 27.7 (CH_2), 33.6 (CH_2), 34.2 (CH_2), 38.1 (CH_2), 41.4 (CH_2), 44.0 (C), 48.7 (CH), 54.9 (OCH_3), 69.1 (CH), 73.2 (CH), 76.1 (C), 91.9 (CH_2), 124.6 (CH═), 154.9 (C═). HRMS: calcd for $C_{19}H_{34}O_4$ + Na 349.2355, found 349.2366. Anal. Calcd for $C_{19}H_{34}O_4$: C, 69.90; H, 10.49. Found: C, 69.32; H, 10.87.

A similar procedure was used to prepare compound **35a** [99%, $R_f = 0.20$ (40% EtOAc/hexanes), colorless oil].

(17*E*)-25-[(Methoxymethyl)oxy]-16α-[phenylcarbamoyl)oxy]-des-A,B-21-norcholest-17(20)-en-8β-ol (26d). A solution of **26a** (268 mg, 0.82 mmol) in Py (5 mL) was treated with DMAP (15 mg) and PhNCO (110 mL, 0.98 mmol) at −25 °C. After 20 h, the reaction was treated with an aqueous saturated solution of $NaHCO_3$. The resulting mixture was filtered, and the residue washed with Et_2O. The combined organic extracts were washed successively with HCl (10%), H_2O, and aqueous saturated solution of $CuSO_4$ and H_2O. The ethereal extract was dried, filtered, and concentrated in vacuo. Flash chromatography (10% EtOAc/hexanes) afforded 325 mg of pure **26d** [89%, $R_f = 0.34$ (20% EtOAc/hexanes), colorless oil]. ^{1}H NMR: 1.17 (3 H, s, C_{18}−CH_3), 1.20 (6 H, s, $C_{26,27}$-$2CH_3$), 2.11−2.25 (3 H, m, $2H_{22}$ and H_{14}), 3.35 (3 H, s, MeO), 4.18 (1 H, m, H_8), 4.70 (2 H, s, OCH_2O), 5.49 (2 H, m, H_{20} and H_{16}), 6.77 (1 H, br s, NH), 7.04−7.40 (5 H, m, Ar). ^{13}C NMR: 17.6 (CH_2), 21.0 (CH_3), 24.9 (CH_2), 26.9 (CH_3-26 and 27), 28.3 (CH_2), 32.9 (CH_2), 34.5 (CH_2), 38.2 (CH_2), 41.4 (CH_2), 44.2 (C), 49.6 (CH), 55.1 (OCH_3), 69.3 (CH), 75.2 (CH), 76.3 (C), 90.9 (OCH_2O), 119.4 (2 CH═Ar), 124.2 (CH═Ar), 127.1 (CH═), 129.5 (2 CH═Ar), 138.4 (C═Ar), 149.9 (C═), 154.2 (C═O). HRMS: calcd for $C_{26}H_{39}NO_5$ + Na 468.2726, found 468.2740. Anal. Calcd for $C_{26}H_{39}NO_5$: C, 70.08; H, 8.82; N, 3.14. Found: C, 69.62; H, 9.11; N, 3.14.

A similar procedure was used to prepare compound **35d** [85%, $R_f = 0.35$ (20% EtOAc/hexanes), colorless oil].

(17*E*)-25-[(Methoxymethyl)oxy]-16α-[phenylcarbamoyl)oxy]-des-A,B-21-norcholest-17(20)-en-8-one (27d). PDC (971 mg, 2.60 mmol) was added to a solution of **26d** (378 mg, 0.85 mmol) and PPTS (10 mg) in CH_2Cl_2 (15 mL). After 6 h, the resulting suspension was filtered through Celite and concentrated to give a residue that was flash chromatographed (5% EtOAc/hexanes) to afford 347 mg of pure **27d** [92%, $R_f =$ 0.45 (40% EtOAc/hexanes), colorless oil]. ^{1}H NMR: 0.84 (3 H,

s, C_{18}-CH_3), 1.16 (6 H, s, $C_{26,27}$-2CH_3), 2.90 (1 H, dd, H_{14}, J = 12.8, 5.5 Hz), 3.31 (3 H, s, MeO), 4.68 (1 H, s, OCH_2O), 5.50 (1 H, d, H_{16}, J = 5.7 Hz), 5.65 (2 H, t, H_{20}, J = 7.5 Hz), 6.85 (1 H, br s, NH), 7.21−7.38 (5 H, m, Ar). ^{13}C NMR: 19.1 (CH_3), 23.5 (CH_2), 24.2 (CH_2), 26.2 (CH_3), 26.3 (CH_3), 28.2 (CH_2), 29.0 (CH_2), 36.5 (CH_2), 40.5 (CH_2), 41.4 (CH_2), 49.7 (C), 54.9 (OCH_3), 58.7 (CH), 76.0 (C), 77.0 (CH), 90.9 (OCH_2O), 118.7 (2 CH═Ar), 123.3 (CH═Ar), 129.0 (CH═), 129.8 (2 CH═Ar), 138.2 (C═Ar), 147.4 (C═), 153.4 (NC═O), 210.2 (C═O). HRMS: calcd for $C_{26}H_{37}NO_5$ + Na 466.2569, found 466.2569.

A similar procedure was used to prepare compound **32d** [99%, R_f = 0.46 (40% EtOAc/hexanes), colorless oil].

(17*E*)-17(20)-Ene-25-[(methoxymethyl)oxy]-16α-[phenylcarbamoyl)oxy]-21-norvitamin D$_3$ *tert*-Butyldimethylsilyl Ether (29). A solution of *n*-BuLi (2.1 M in hexane, 1.40 mL, 2.94 mmol) was added dropwise via syringe to a solution of the phosphine oxide **28** (1.34 g, 2.97 mmol) in THF (30 mL) at −78 °C. The resulting deep red solution was stirred for 1 h followed by the slow addition of the ketone **27d** (347 mg, 0.78 mmol) in THF (5 mL). The resulting solution was stirred for 3 h and then allowed to warm to −40 °C. After 2 h, the reaction mixture was quenched with H_2O. The mixture was extracted with Et_2O, and the combined organic fractions were washed with brine, dried, filtered, and concentrated in vacuo. The residue was flash chromatographed (1−50% EtOAc/hexanes) to give 287 mg of **29** [54%, R_f = 0.66 (20% EtOAc/hexanes), white solid] and of phosphine **28**. ^{1}H NMR: 0.055 (3 H, s, MeSi), 0.06 (3 H, s, MeSi), 0.80 (3 H, s, C_{18}-CH_3), 0.88 (9 H, s, *t*-BuSi), 1.20 (6 H, s, $C_{26,27}$-2CH_3), 2.85 (1 H, m, H_{14}), 3.29 (3 H, s, MeO), 4.82 (1 H, m, H_3), 4.64 (2 H, s, OCH_2O), 4.75 (1 H, br s, H_{19Z}), 5.01 (1 H, br s, H_{19E}), 5.45 (1 H, d, H_{16}, J = 5.8 Hz), 5.60 (1 H, t, H_{20}, J = 7.5 Hz), 6.01 and 6.15 (2 H, AB pattern, H_6 and H_7, J = 11.4 Hz), 6.67 (1 H, br s, NH), 6.99−7.39 (5 H, m, Ar). ^{13}C NMR: −4.5 ($SiCH_3$), 18.4 (CSi), 18.5 (CH_3), 23.6 (CH_2), 24.8 (CH_2), 26.0 (CH_3-26 and 27), 26.5 (CH_3), 26.6 (CH_3), 28.6 (CH_2), 29.0 (CH_2), 32.1 (CH_2), 32.9 (CH_2), 36.7 (CH_2), 38.4 (CH_2), 41.7 (CH_2), 46.9 (CH_2), 47.2 (C), 53.7 (CH), 55.2 (CH_3), 70.9 (CH), 76.4 (C), 78.1 (CH), 91.4 (CH_2), 112.5 (CH_2═), 118.9 (2 CH═Ar), 121.5 (CH═), 123.5 (CH═Ar), 129.4 (CH═), 129.7 (CH═Ar), 137.8 (C═Ar), 139.4 (C═), 139.8 (C═), 146.1 (C═), 149.6 (C═), 154.2 (NC═O).

(20*S*)-16-Ene-25-[(methoxymethyl)oxy]vitamin D$_3$ *tert*-Butyldimethylsilyl Ether (30). A solution of MeLi (1.5 M in Et_2O, 160 mL, 0.24 mmol) was added via syringe to a suspension of CuBr (21 mg, 0.15 mmol) in Et_2O (1 mL) at 0 °C. After 1 h, a solution of **29** (33 mg, 0.05 mmol) in Et_2O (1 mL) was added, and the mixture was stirred at room temperature for 5 h in the dark. The reaction was quenched with aqueous NH_4Cl, and the mixture was extracted with Et_2O. The combined ethereal layers were washed with a saturated solution of $NaHCO_3$, dried, and concentrated in vacuo. The residue was flash chromatographed (3% EtOAc/hexanes) to give 24 mg of **30** [89%, R_f = 0.67 (20% EtOAc/hexanes), white solid]. ^{1}H NMR: 0.04 (3 H, s, MeSi), 0.05 (3 H, s, MeSi), 0.67 (3 H, s, C_{18}-CH_3), 0.87 (9 H, s, *t*-BuSi), 1.02 (3 H, d, C_{21}-CH_3, J = 6.9 Hz), 1.16 (6 H, s, $C_{26,27}$-2CH_3), 2.80 (1 H, dd, H_{14}, J = 12.5, 4.4 Hz), 3.29 (3 H, s, MeO), 3.84 (1 H, m, H_3), 4.63 (2 H, s, OCH_2O), 4.76 (1 H, d, H_{19Z}, J = 1.6 Hz), 5.01 (1 H, d, H_{19E}, J = 1.2 Hz), 5.30 (1 H, br s, H_{16}), 6.09 and 6.16 (2 H, AB pattern, H_6 and H_7, J = 11.2 Hz). ^{13}C NMR: −4.6 ($SiCH_3$), −4.5 ($SiCH_3$), 17.4 (CH_3), 18.4 (CSi), 21.4 (CH_3), 22.3 (CH_2), 23.9 (CH_2), 26.0 (CH_3 *t*Bu), 26.5 (CH_3-26 and 27), 29.0 (CH_2), 29.7 (CH_2), 32.5 (CH), 32.9 (CH_2), 35.8 (CH_2), 36.7 (CH_2), 38.1 (CH_2), 42.3 (CH_2), 47.1 (CH_2), 50.5 (C), 55.1 (OCH_3), 58.6 (CH), 70.8 (CH), 76.3 (C), 91.2 (OCH_2O), 112.2 (CH_2═), 118.0 (CH═), 120.6 (CH═), 121.8 (CH═), 138.8 (C═), 141.4 (C═), 146.0 (C═), 161.1 (C═). HRMS: calcd for $C_{35}H_{60}O_3Si$ 556.4311, found 556.4298.

(17*E*)-1α-[(*tert*-Butyldimethylsilyl)oxy]-17(20)-en-25-[(methoxymethyl)oxy]-16α-[(phenylcarbamoyl)oxy]-21-norvitamin D$_3$ *tert*-Butyldimethylsilyl Ether (12d). A solution of *n*-BuLi (2.15 M in hexanes, 1.1 mL, 2.36 mmol) was added dropwise via syringe to a THF solution of the phosphine oxide **7** (2.30 mmol, 2.30 mL, 1 M) at −78 °C. The resulting reddish solution was stirred for 1 h followed by the slow addition of the ketone **27d** (362 mg, 0.82 mmol) in THF (2 mL). The resulting solution was stirred for 1 h and then allowed to warm to −20 °C. After 3 h, the reaction mixture was quenched with H_2O. The mixture was extracted with Et_2O, and the combined organic fractions were washed with brine, dried, filtered, and concentrated in vacuo. The residue was flash chromatographed (1−50% EtOAc/hexanes) to give 198 mg of **12d** [30%, R_f = 0.68 (20% EtOAc/hexanes), white solid]. ^{1}H NMR: 0.07 (12 H, s, 2 Me_2Si), 0.78 (3 H, s, C_{18}-CH_3), 0.88 (18 H, s, 2 *t*-BuSi), 1.18 (6 H, s, $C_{26,27}$-2CH_3), 2.85 (1 H, m, H_{14}), 3.31 (3 H, s, MeO), 4.21 (1 H, m, H_3), 4.38 (1 H, m, H_1), 4.67 (2 H, s, OCH_2O), 4.85 (1 H, br s, H_{19Z}), 5.19 (1 H, br s, H_{19E}), 5.48 (1 H, d, H_{16}, J = 5.1 Hz), 5.62 (1 H, t, H_{20} J = 7.3 Hz), 6.03 and 6.27 (2 H, AB pattern, H_6 and H_7, J = 11.0 Hz), 6.94 (1 H, br s, NH), 7.03 (1 H, m, Ar), 7.26−7.41 (4 H, Ar, m). ^{13}C NMR: −4.5 ($SiCH_3$), −4.4 ($SiCH_3$), 18.4 (CSi), 18.5 (CH_3), 23.6 (CH_2), 24.9 (CH_2), 26.1 (CH_3 *t*Bu), 26.6 (CH_3), 26.6 (CH_3), 28.6 (CH_2), 29.0 (CH_2), 32.0 (CH_2), 38.5 (CH_2), 41.7 (CH_2), 45.3 (CH_2), 46.6 (CH_2), 47.0 (C), 53.8 (CH), 55.2 (OCH_3), 68.0 (CH), 72.7 (CH), 76.4 (C), 78.1 (CH), 91.4 (OCH_2O), 112.1 (CH_2═), 118.9 (2 CH═Ar), 123.3 (CH═Ar), 123.5 (CH═), 129.4 (2 CH═Ar), 129.8 (CH═), 136.4 (C═), 139.1 (C═Ar), 139.6 (C═), 148.7 (C═), 149.8 (C═), 154.2 (NC═O). HRMS: calcd for $C_{47}H_{77}NO_6Si_2$ + Na 830.5187, found 830.5168.

A similar procedure was used to prepare compound **13d** [26%, R_f = 0.73 (20% EtOAc/hexanes), white solid].

(17*E*)-8β-[(*tert*-Butyldimethylsilyl)oxy]-16α-[(2′,2′-dimethylpropanoyl)oxy]-25-[(methoxymethyl)oxy]-des-A,B-21-norcholest-17(20)-ene (8b). A solution of **8a** (450 mg, 1.02 mmol) in Py (16 mL) was treated with DMAP (10 mg) and pivaloyl chloride (0.63 mL, 5.1 mmol) at 0 °C. After 14 h, the reaction was treated with aqueous HCl (10%). The mixture was extracted with Et_2O, and the combined organic layers were washed sequentially with HCl (10%), H_2O, and an aqueous saturated solution of $CuSO_4$ and H_2O. The etheral extract was dried, filtered, and concentrated in vacuo. Flash chromatography (5% EtOAc/hexanes)afforded 514 mg of pure **8b** [96%, R_f = 0.73 (20% EtOAc/hexanes), colorless oil]. ^{1}H NMR: 0.01 and 0.02 (6 H, 2 s, Me_2Si), 0.88 (9 H, s, *t*-BuSi), 1.11 (3 H, s, C_{18}-CH_3), 1.18 (9 H, s, *t*-BuCO), 1.20 (6 H, s, $C_{26,27}$-2CH_3), 2.00−2.23 (3 H, m, 2H_{22} and H_{14}), 3.36 (3 H, s, MeO), 4.08 (1 H, m, H_8), 4.69 (2 H, s, OCH_2O), 5.23 (1 H, dt, H_{20}, J = 7.6 Hz, 1.3 Hz), 5.47 (1H, dd, H_{16}, J = 6.3 Hz, 1.3 Hz). ^{13}C NMR: −5.2 ($SiCH_3$), −4.9 ($SiCH_3$), 17.7 (CH_2), 17.9 (CSi), 21.1 (CH_3), 24.6 (CH_2), 25.7 (CH_3 *t*BuSi), 26.2 (CH_3-26 and -27), 27.1 (CH_3 Piv), 27.6 (CH_2), 32.5 (CH_2), 34.1 (CH_2), 38.2 (CH_2), 38.3 (C), 41.5 (CH_2), 44.2 (C), 49.6 (CH), 55.0 (OCH_3), 69.2 (CH), 75.4 (CH), 76.2 (C), 90.9 (OCH_2O), 125.4 (CH═), 149.8 (C═), 178.5 (C═O). HRMS: calcd for $C_{30}H_{56}O_5Si$ + Na 547.3794, found 547.3775.

A similar procedure was used to prepare compound **9b** [97%, R_f = 0.72 (20% EtOAc/hexanes), colorless oil].

(17*E*)-16α-[(2′,2′-Dimethylpropanoyl)oxy]-25-[(methoxymethyl)oxy]-des-A,B-21-norcholest-17(20)-en-8β-ol(34b). A solution of TBAF (1 M in THF, 4.65 mL, 4.65 mmol) was added via syringe to a solution of **8b** (400 mg, 0.76 mmol) in THF (1 mL). The resulting mixture was refluxed for 20 h, and then a saturated solution of $NaHCO_3$ was added. The aqueous phase was extracted with Et_2O. The combined organic extracts were dried, filtered, and concentrated in vacuo. The residue was flash chromatographed (15% EtOAc/hexanes) to afford 288 mg of **34b** [92%, R_f = 0.26 (30% EtOAc/hexanes), colorless oil]. ^{1}H NMR: 1.14 (3 H, s, C_{18}-CH_3), 1.17 (9 H, s, *t*-BuCO), 1.19 (6 H, s, $C_{26,27}$-2CH_3), 2.03−2.21 (3 H, m, 2H_{22} and H_{14}), 3.34 (3 H, s, MeO), 4.16 (1 H, m, H_8), 4.68 (2 H, s, OCH_2O), 5.27 (1 H, dt, H_{20}, J = 7.5 Hz, 1.3 Hz), 5.50 (1H, d, H_{16}, J = 6.4 Hz). ^{13}C NMR: 17.5 (CH_2), 20.7 (CH_3), 24.5 (CH_2), 26.2 (CH_3-26 and 27), 27.0 (CH_3 Piv), 27.6 (CH_2), 32.0 (CH_2), 33.5 (CH_2), 37.9 (CH_2), 38.5 (C), 41.5 (CH_2), 43.9 (C), 49.2 (CH), 55.0 (OCH_3), 69.0 (CH), 75.1 (CH), 76.1 (C), 90.9 (OCH_2O), 126.0 (CH═), 149.4 (C═), 178.5 (C═O). HRMS: calcd for $C_{24}H_{42}O_5$ + Na 433.2930, found 433.2938.

A similar procedure was used to prepare compound **35b** [97%, R_f = 0.27 (30% EtOAc/hexanes), colorless oil].

(17*E*)-16α-[(2′,2′-Dimethylpropanoyl)oxy]-25-[(methoxymethyl)oxy]-des-A,B-21-norcholest-17(20)-en-8-one (27b). PDC (428 mg, 1.15 mmol) was added to a solution of **34b** (145 mg, 0.35 mmol) in CH_2Cl_2 (1.5 mL). After 12 h, the resulting suspension was filtered through Celite and concentrated to give a residue that was flash chromatographed (10% EtOAc/hexanes) to afford 142 mg of pure **27b** [98%, $R_f = 0.72$ (40% EtOAc/hexanes), colorless oil]. ^{1}H NMR: 0.84 (3 H, s, C_{18}-CH_3), 1.13 (9 H, s, *t*-BuCO), 1.16 (6 H, s, $C_{26,27}$-2CH_3), 2.87 (1 H, dd, H_{14}, $J = 11.5, 5.2$ Hz), 3.28 (3 H, s, MeO), 4.63 (2 H, s, OCH_2O), 5.46 (1 H, dt, H_{20}, $J = 7.5, 1.3$ Hz), 5.50 (1 H, d, H_{16}, $J = 6.4$ Hz). ^{13}C NMR: 19.3 (CH_3), 24.0 (CH_2), 24.7 (CH_2), 26.4 (CH_3-26 and -27), 27.2 (CH_3 Piv), 28.5 (CH_2), 29.3 (CH_2), 37.0 (CH_2), 38.8 (C), 41.0 (CH_2), 41.9 (CH_2), 50.2 (C), 55.2 (OCH_3), 59.2 (CH), 76.0 (CH), 76.2 (C), 91.3 (OCH_2O), 129.5 (CH═), 148.2 (C═), 178.2 (C═O), 210.6 (C═O). HRMS: calcd for $C_{24}H_{40}O_5$ + Na 431.2773, found 431.2755. Anal. Calcd for $C_{24}H_{40}O_5$: C, 70.55; H, 9.87. Found: C, 70.24; H, 10.16.

A similar procedure was used to prepare compound **32b** [99%, $R_f = 0.70$ (40% EtOAc/hexanes), colorless oil].

(17*E*)-1α-[(*tert*-Butyldimethylsilyl)oxy]-16α-[(2′,2′-dimethylpropanoyl)oxy]-17(20)-en-25-[(methoxymethyl)oxy]-vitamin D_3 *tert*-Butyldimethylsilyl Ether (12b). A solution of *n*-BuLi (2.5 M in hexanes, 170 mL, 0.43 mmol) was added dropwise by syringe to a THF solution of the phosphine oxide **7** (0.49 mmol, 0.49 mL, 1 M) at −78 °C. The resulting deep red solution was stirred for 1 h followed by the slow addition of the ketone **27b** (97 mg, 0.24 mmol) in THF (3.5 mL). The resulting solution was stirred for 4 h and then allowed to warm to −40 °C. After 2 h, the reaction mixture was quenched with H_2O. The mixture was extracted with Et_2O, and the combined organic fractions were washed with brine, dried, filtered, and concentrated in vacuo. The residue was flash chromatographed (1−50% EtOAc/hexanes) to give 170 mg of **12b** [93%, $R_f = 0.77$ (20% EtOAc/hexanes), colorless oil]. ^{1}H NMR: 0.06 (12 H, s, 2 Me_2Si), 0.75 (3 H, s, C_{18}-CH_3), 0.87 (18 H, s, 2 *t*-BuSi), 1.15 (9 H, s, *t*-BuCO), 1.16 (6 H, s, $C_{26,27}$-2CH_3), 2.85 (1 H, m, H_{14}), 3.29 (3 H, s, MeO), 4.18 (1 H, m, H_3), 4.38 (1 H, m, H_1), 4.64 (2 H, s, OCH_2O), 4.84 (1 H, br s, H_{19Z}), 5.18 (1 H, br s, H_{19E}), 5.30 (1 H, m, H_{16}), 5.44 (1 H, d, H_{20}, $J = 7.0$ Hz), 5.99 and 6.25 (2 H, AB pattern, H_6 and H_7, $J = 11.1$ Hz). ^{13}C NMR: −4.9 ($SiCH_3$), −4.7 ($SiCH_3$), −4.6 ($SiCH_3$), −4.5 ($SiCH_3$), 18.5 (CH_3), 23.6 (CH_2), 24.9 (CH_3), 26.0 (CH_3 *t*-BuSi), 26.5 (CH_3-26 and -27), 27.3 (CH_3 Piv), 28.6 (CH_2), 29.0 (CH_2), 31.8 (CH_2), 38.4 (CH_2), 38.8 (CH_2), 41.9 (CH_2), 45.3 (CH_2), 46.5 (CH_2), 47.0 (C), 53.7 (CH), 55.1 (OCH_3), 67.9 (CH), 72.6 (CH), 76.3 (CH), 76.5 (CH), 91.3 (OCH_2O), 111.9 (CH_2═), 118.7 (CH═), 123.3 (CH═), 128.9 (CH═), 136.3 (C═), 139.9 (C═), 148.8 (C═), 150.0 (C═), 178.4 (C═O). HRMS: calcd for $C_{45}H_{80}O_6Si_2$ + Na 795.5391, found 795.5384.

A similar procedure was used to prepare compound **13b** [71%, $R_f = 0.78$ (20% EtOAc/hexanes), colorless oil].

(17*E*)-1α-[(*tert*-Butyldimethylsilyl)oxy]-17(20)-en-16α-hydroxy-25-[(methoxymethyl)oxy]vitamin D_3 *tert*-Butyldimethylsilyl Ether (12a). A solution of $LiAlH_4$ (1 M in THF, 180 mL, 0.18 mmol) was added dropwise by syringe to a solution of pivaloate **12b** (140 mg, 0.18 mmol) in THF (2.5 mL) at 0 °C. After 1 h, the reaction mixture was cooled to −78 °C and quenched with ice. The resulting mixture was stirred at room temperature for 15 min, and the aqueous phase was extracted with EtOAc. The combined organic layers were dried, filtered, and concentrated in vacuo. The residue was flash chromatographed (40% EtOAc/hexanes) to afford 117 mg of compound **12a** [94%, $R_f = 0.36$ (20% EtOAc/hexanes), colorless oil]. ^{1}H NMR: 0.08 (6 H, s, Me_2Si), 0.09 (6 H, s, Me_2Si), 0.74 (3 H, s, C_{18}-CH_3), 0.89 (9 H, s, *t*-BuSi), 0.90 (9 H, s, *t*-BuSi), 1.20 (6 H, s, $C_{26,27}$-2CH_3), 2.83 (1 H, m, H_{14}), 3.33 (3 H, s, MeO), 4.21 (1 H, m, H_3), 4.41 (1 H, m, H_1), 4.67 (2 H, s, OCH_2O), 4.88 (1 H, d, H_{19Z}, $J = 2.0$ Hz), 5.22 (1 H, d, H_{19E}, $J = 1.4$ Hz), 5.33 (1 H, m, H_{16}), 5.52 (1 H, d, H_{20}, $J = 7.1$ Hz), 6.04 and 6.27 (2 H, AB pattern, H_6 and H_7, $J = 11.1$ Hz). ^{13}C NMR: −4.9 ($SiCH_3$), −4.6 ($SiCH_3$), −4.56 ($SiCH_3$), −4.5 ($SiCH_3$), 18.4 (CH_3), 18.5 (CSi), 23.7 (CH_2), 25.0 (CH_2), 26.0 (CH_3 *t*-BuSi), 26.5 (CH_3-26 and 27), 28.6 (CH_2), 29.0 (CH_2), 33.9 (CH_2), 38.5 (CH_2), 41.9 (CH_2), 45.3 (CH_2), 46.4 (CH_2), 47.1 (C), 53.3 (CH), 55.2 (OCH_3), 68.0 (CH), 72.5 (CH), 74.6 (CH), 76.4 (C), 91.4 (OCH_2O), 111.7 (CH_2═), 118.7 (CH═), 123.4 (CH═), 127.0 (CH═), 136.1 (C═), 140.2 (C═), 148.9 (C═), 155.3 (C═). HRMS: calcd for $C_{40}H_{72}O_5Si_2$ + Na 711.4816, found 711.4826.

A similar procedure was used to prepare compound **13a** [92%, $R_f = 0.38$ (20% EtOAc/hexanes), colorless oil].

(17*E*)-1α-[(*tert*-Butyldimethylsilyl)oxy]-17(20)-en-25-[(methoxymethyl)oxy]16α-[(phenylcarbamoyl)oxy]vitamin D_3 *tert*-Butyldimethylsilyl Ether (12d). A solution of **12a** (100 mg, 0.15 mmol) in Py (1 mL) was treated with DMAP (5 mg) and PhNCO (80 mL, 0.73 mmol) at −20 °C. After 14 h, the reaction was treated with an aqueous saturated solution of $NaHCO_3$ (10 mL). The resulting mixture was filtered and the residue washed with Et_2O. The combined organic extracts were washed successively with HCl (10%), H_2O, and an aqueous saturated solution of $CuSO_4$ and H_2O. The ethereal extract was dried (Na_2SO_4), filtered, and concentrated in vacuo. The resulting residue was flash chromatographed (4% EtOAc/hexanes) to produce 115 mg of pure **12d** (97%).

A similar procedure was used to prepare compound **13d** [97%].

(20*S*)-1α-[(*tert*-Butyldimethylsilyl)oxy]-16-en-25-[(methoxymethyl)oxy]-21-propylvitamin D_3 *tert*-Butyldimethylsilyl Ether (19b). A solution of *n*-BuLi (2.25 M in hexane, 260 mL, 0.59 mmol) was added by syringe to a suspension of CuBr (78 mg, 0.54 mmol) in Et_2O (3.5 mL) at −78 °C. After 1 h, a solution of **12d** (50 mg, 0.06 mmol) in Et_2O (1.5 mL) was added, and then the mixture was allowed to warm to room temperature and stirred for 12 h in the dark. The reaction was quenched with a saturated aqueous solution of NH_4Cl, and the mixture was extracted with Et_2O. The combined ethereal layers were washed with a saturated solution of $NaHCO_3$, dried, and concentrated in vacuo. The residue was flash chromatographed (2% EtOAc/hexanes) to give 38 mg of **19b** [93%, $R_f = 0.82$ (20% EtOAc/hexanes), colorless oil]. ^{1}H NMR: −0.14 (3 H, s, MeSi), −0.10 (3 H, s, MeSi), 0.05 (3 H, s, MeSi), 0.06 (3 H, s, MeSi), 0.62 (3 H, s, C_{18}-CH_3), 0.86 (18 H, s, 2 *t*-BuSi), 0.87 (2 H, m, H_{21}), 1.15 (6 H, s, $C_{26,27}$-2CH_3), 2.81 (1 H, m, H_{14}), 3.29 (3 H, s, MeO), 4.18 (1 H, m, H_3), 4.37 (1 H, m, H_1), 4.63 (2 H, s, OCH_2O), 4.85 (1 H, d, H_{19Z}, $J = 2.5$ Hz), 5.19 (1 H, br s, H_{19E}), 5.27 (1 H, br s, H_{16}), 6.10 and 6.25 (2 H, AB pattern, H_6 and H_7, $J = 11.1$ Hz). ^{13}C NMR: −4.9 ($SiCH_3$), −4.7 ($SiCH_3$), −4.6 ($SiCH_3$), 14.3 (CH_3), 17.2 (CH_3), 18.4 (C), 18.5 (C), 22.0 (CH_2), 23.3 (CH_2), 24.0 (CH_2), 26.0 (6 CH_3, *t*-BuSi), 26.6 (2 CH_3), 29.0 (CH_2), 29.8 (CH_2), 30.1 (CH_2), 34.4 (CH_2), 35.8 (CH_2), 36.2 (CH_2), 38.6 (CH), 42.5 (CH_2), 45.3 (CH_2), 46.4 (CH_2), 50.5 (C), 55.2 (OCH_3), 58.8 (CH), 68.0 (CH), 72.3 (CH), 76.5 (C), 91.3 (OCH_2O), 111.5 (CH_2═), 118.2 (CH═), 121.7 (CH═), 123.6 (CH═), 135.7 (C═), 141.2 (C═), 149.1 (C═), 158.9 (C═).

Similar procedures were used to prepare compounds**19a**, **19c**, **25b**, and **25c**.[34] **19a** and **19c** were prepared from **12d**; **25b** and **25c** were prepared from **13d**. **19a** (82%). **19c** [85%, $R_f = 0.81$ (20% EtOAc/hexanes)]. **25b** [89%, $R_f = 0.82$ (20% EtOAc/hexanes), colorless oil]. **25c** (92%).

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Supporting Information Available: ^{1}H and ^{13}C NMR (including DEPT) spectra of all compounds and molecular mechanics calculation for compounds **27b** and **35b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(34) The starting cyclopropyllithium was prepared from cyclopropyl bromide and *tert*-butyllithium.