Synthesis of Vitamin D_3 and Calcitriol Dimers as Potential Chemical Inducers of Vitamin D Receptor Dimerization

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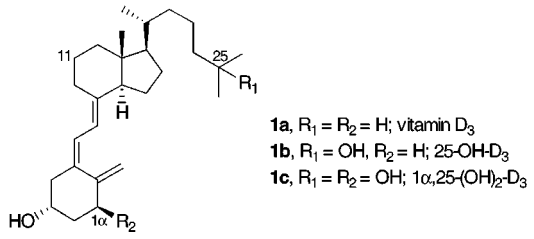
The design and synthesis of vitamin D_3 dimers **2** and **3** and 1α,25-dihydroxyvitamin D_3 (calcitriol) dimers **4** and **5** are described. The dimers were designed with a view to doubly binding the vitamin D receptor (VDR) and inducing the receptor homodimerization. In the dimers the units are linked through the C-11 position in ring C by an alkyl side chain of six or 10 carbon atoms, far from the hydroxy groups responsible for the VDR binding. The linker is formed by olefin metathesis of an olefinic side chain at the C-11 position introduced by stereoselective cuprate addition. The synthesis, which is both short and convergent, uses the Wittig−Horner approach to construct the vitamin D triene system and allows the preparation of dimers with a linker of modulated length with the purpose of optimizing the vitamin D_3−VDR interaction.

Introduction

Vitamin D_3 (**1a**), through its hormonally active form 1α,25-$(OH)_2$-vitamin D_3 (calcitriol, **1c**), is responsible for a broad-ranging of biological activity that includes the regulation of calcium and phosphorus metabolism, the promotion of cellular differentiation processes, the inhibition of the proliferation of various tumor cells and some functions related to the immune system.[1] The biological activity of vitamin D_3 is associated with the interaction of calcitriol with the vitamin D_3 protein receptor (VDR), a member of the nuclear receptor superfamily,[2] through a genomic pathway. Calcitriol interacts with the DNA in the cell nucleus as a complex with the VDR and this activates the signal transduction processes. During the interaction, the VDR can exist as a homodimer (VDR−VDR) or as a heterodimer with the retinoid X receptor (VDR−RXR).[3] The synthesis of vitamin D_3 analogues that can selectively induce the homo- or heterodimerization of the VDR is of interest to understand the role of dimeric VDR structures in the activation of gene transcription.[4]

It has recently been shown that dimeric molecular ligands with the ability to bind two protein receptors simultaneously can induce the receptor's dimerization,



1a, $R_1 = R_2 = H$; vitamin D_3
1b, $R_1 = OH$, $R_2 = H$; 25-OH-D_3
1c, $R_1 = R_2 = OH$; 1α,25-$(OH)_2$-D_3

which leads to the activation of different signal transduction pathways by proximity or allosteric interactions.[5,6] These compounds have been coined by Schreiber and Crabtree as chemical inducers of dimerization (CIDs)[7] and representative examples are the dimers of the immunosuppressive agents FK506 (FK1012) and cyclosporin A [$(CyA)_2$], which are able to activate several cellular processes such apoptosis.[8] Molecular dimers have also been useful to produce selective chemical responses in the case of phorbol[9] and to study divalent interactions in other structures such as cyclodextrins[10] or vancomycin.[11] In the vitamin D research area we envisioned the synthesis of vitamin D_3 dimers as chemical inducers of VDR homodimerization with a view to exploring and

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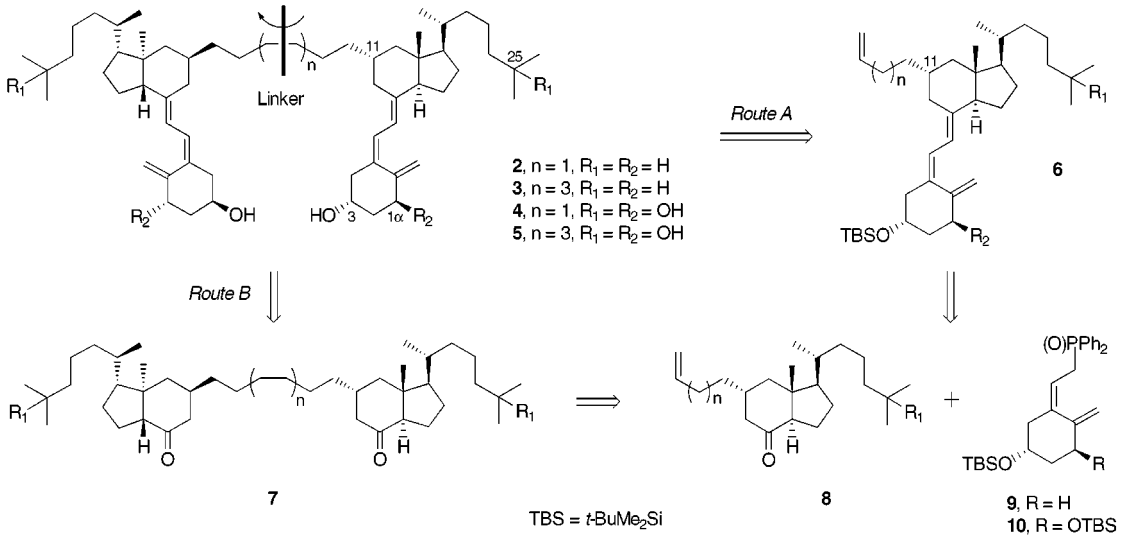
Scheme 1



possibly exploiting their role in transcription control. In this, a full account,[12] we report in detail the synthesis of dimeric vitamin D_3 and calcitriol structures linked through the C-11 position by a carbon side chain of modulated size.

Results and Discussion

In the design of vitamin D_3 dimeric structures that could be capable of doubly binding the VDR, we considered some essential structure/function relationships: (a) the hydroxy groups at the C-3, C-1α and C-25 positions are part of the VDR binding domain,[1e] (b) the triene system is a fundamental structural feature,[13] and (c) the introduction of polar groups dramatically alters the biological activity.[1d] In addition, we reasoned that the linker should be sufficiently flexible to permit complete interaction of each monomer with the VDR. For this reason, we were interested in a synthetic route that would allow the preparation of linkers of variable length to optimize the binding with the VDR. In the past, different types of linkers have been used for the preparation of molecular dimers and these include a carbamate bond formed by reaction of a free hydroxy group with *p*-xylylenediamine and phosgene in the dimer of cyclosporine,[4] an ester group formed by a hydroxy group of phorbol and a diacid of variable length,[7] or a carbon−carbon bond from metathesis of a terminal olefin, e.g., in FK1012.[14]

With these findings in mind, and considering the absence of functionality in the vitamin D structure to effect a direct dimerization, we envisaged the synthesis of a dimeric vitamin D_3 molecule consisting of two moieties linked by a carbon chain attached to each calcitriol at ring C, thus providing a nonpolar linker attached far from the hydroxy groups responsible in the interaction with the VDR.[1e] The linker could be made by metathesis of a terminal olefin conveniently inserted at the C-11 position. The C-11 position can be functionalized by cuprate addition to a suitable enone.[15] This strategy serves to incorporate side chains of different lengths, to optimize the protein binding. The synthesis was focused toward vitamin D_3 dimers (**2** and **3**) and calcitriol dimers (**4** and **5**) with variable linker lengths (n = 1 and 3). A vitamin D dimer could be transformed into calcitriol dimer in the metabolic route. The retrosynthetic analysis is depicted in Scheme 1. Route A involves dimerization by metathesis of vitamin D_3 analogue **6** conveniently functionalized at C-11. The vitamin D triene unit is formed by a Wittig−Horner reaction[16] between ketone **8** which contains the C−D fragment and the anion of phosphine oxide **9**[17] or **10**[18] which contains the A ring. The alternative route B involves direct Wittig−Horner coupling of dimeric ketone **7** with the anion of phosphine oxide **9** or **10**. The dimeric ketone **7** can be prepared by olefin metathesis of ketone **8** and subsequent hydrogenation.

Synthesis of Vitamin D_3 Dimers. In our synthetic venture, we first decided to explore route A to prepare a dimer of vitamin D_3 (**1a**). The synthesis starts with Grundmann's ketone **11** (Scheme 2),[19] which was converted to enone **12**[20] (80% yield) by known procedures.[15a,c] Treatment of **12** with the cuprate prepared from 4-bromo-1-butene by treatment with *t*-BuLi and the complex CuI/*n*-Bu_3P at −78 °C, gave **13** in high yield (85%) as a single stereoisomer, as detected by ^{1}H NMR spectroscopy. The conjugate addition of the cuprates derived from 6-bromo-1-hexene or bromoethylene to enone **12** led to the stereoselective formation of ketones **14** and **15** (95% and 85% yields, respectively). These compounds possess, respectively, olefinic side chains two carbons longer and two carbons shorter than in **13**.

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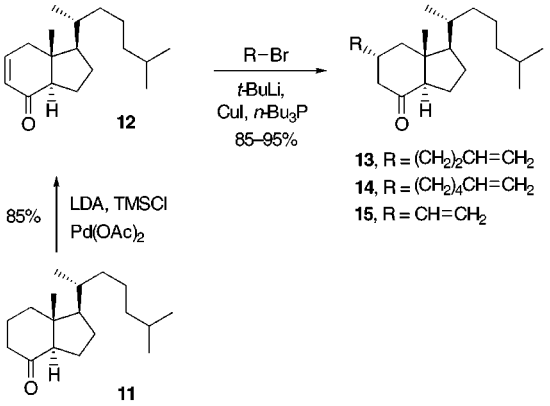
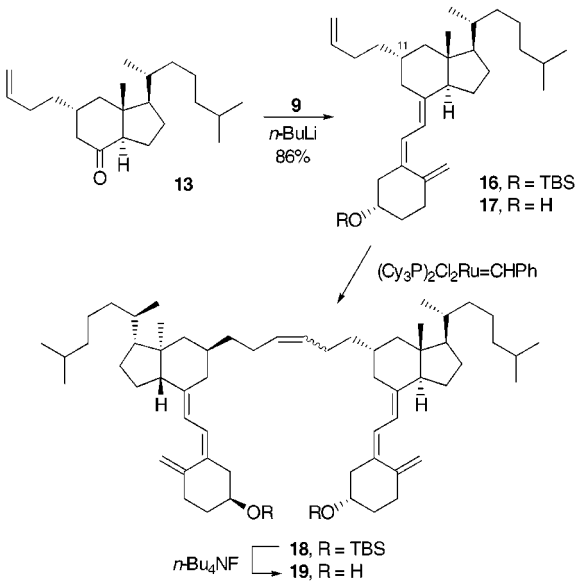
Scheme 2



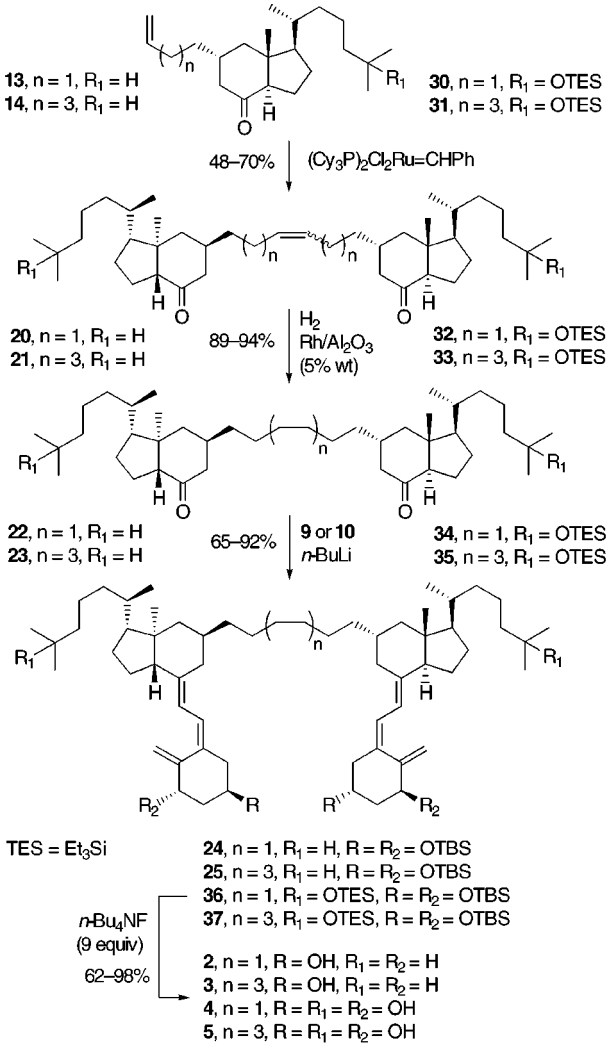
Having obtained the C-11 functionalized ketones **13**−**15**, we proceeded to construct the vitamin D triene system following approach A. Wittig−Horner reaction of **13** (Scheme 3) with the anion derived from treatment of phosphine oxide **9** with *n*-BuLi at −78 °C afforded the vitamin D_3 analogue **16** in 86% yield. Treatment of **16** with a catalytic amount of the ruthenium carbene $(Cy_3P)_2Cl_2RuCHPh$ (10 mol %)[21] at room temperature for 4 h gave the dimer **18** (with loss of ethylene) as a mixture of geometric isomers along with unreacted vitamin **16** in a 1:1 ratio. It was gratifying to see that the labile vitamin D triene system survives the olefin metathesis reaction. Treatment of the mixture **16**-**18** with *n*-Bu_4NF (TBAF) allowed the isolation of the vitamin D_3 dimer **19** in 74% yield (two steps) as a mixture of geometric isomers (8:1 ratio), and vitamin **17** in 18% yield. Unfortunately, attempts to selectively hydrogenate the nonconjugate double bond in **19** using different catalysts and reaction conditions led to saturated products. Despite this problem, this synthetic route allowed us to synthesize **19** as the first known vitamin D_3 dimer.

Scheme 3



These results led us to explore route B (Scheme 1), as an alternative way to prepare our target compounds **2**−**5**. Treatment of ketone **13** (Scheme 4) with Grubbs catalyst[21] (10 mol %) at room temperature for 24 h gave the dimeric ketone **20** in 63% yield as a mixture of geometric isomers without any detectable epimerization at C-14 by ^{1}H NMR. The recovered unreacted ketone **13** (30%) was again submitted to olefin metathesis. The ratio of **20** isomers varies from 2:1 to 8:1 depending on the concentration and temperature used. Similarly, metathesis of ketone **14**, with an olefinic side chain two carbons longer, afforded dimeric ketone **21** in similar yield and stereoselectivity. Interestingly, when vinyl ketone **15** (Scheme 2) was subjected to the same olefin metathesis reaction conditions, the reaction failed leading to the recovery of starting material presumably due to steric hindrance.

Scheme 4



Hydrogenation of dimeric ketone **20** at atmospheric pressure in the presence of catalytic amounts of Rh/Al_2O_3 (5 wt %) for 12 h gave **22** in 91% yield. Wittig−Horner reaction between ketone **22** and the anion generated by treatment of phosphine oxide **10** (4.0 equiv) with *n*-BuLi at −78 °C, provided the protected vitamin **24** in 85% yield. Desilylation of **24** with *n*-Bu_4NF (3 equiv), in the absence of light, at room temperature for 24 h gave the desired vitamin D_3 dimer **2** (90%). Following the same protocol as for **2**, vitamin D_3 dimer **3** was prepared in three steps from dimeric ketone **21** in 82% overall yield.

Synthesis of Calcitriol Dimers. Bearing in mind the experience gained during the preparation of the vitamin

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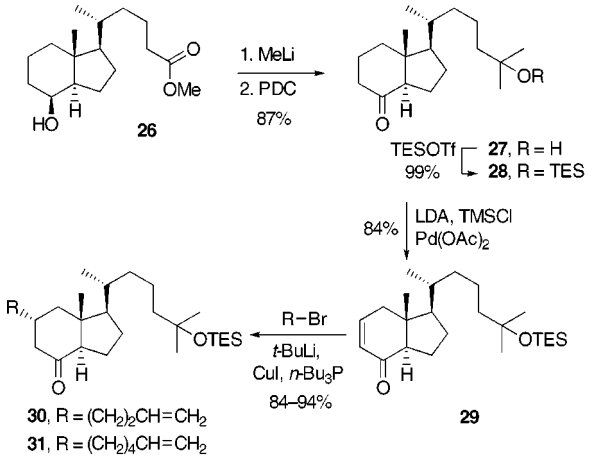
Scheme 5



D_3 dimers, we focused our efforts on the preparation of calcitriol dimers following approach B. The synthesis of dimers **4** and **5** (Scheme 1) requires the introduction of C-25 and C-1α hydroxyl groups. The synthesis starts with known ester **26** (Scheme 5).[22] Addition of MeLi (3 equiv), followed by oxidation with PDC and protection with Et_3-SiOTf (TESOTf) at −78 °C, afforded ketone **28**[23] (86% three steps) (Scheme 5). Treatment of **28** under Saegusa reaction conditions,[15a,c,24] led to the formation of enone **29** in 84% yield. Stereoselective conjugate addition of the respective cuprates derived from 4-bromo-1-butene and 6-bromo-1-hexene to enone **29** afforded ketones **30** or **31** in high yield (84−94%) as the only stereoisomers detected by ^{1}H NMR. Olefin metathesis of **30** or **31** with Grubbs catalyst in CH_2Cl_2 at room temperature for 24 h afforded the dimeric ketones **32** or **33** as a mixture of geometric isomers without detectable epimerization at C-14 by ^{1}H NMR. As above, the stereoselectivity observed in the reaction products (2:1 to 8:1) depends on the reaction conditions such as concentration and temperature. The mixture of isomers was converted to a single product (**34** or **35**) in 89−94% yield by catalytic hydrogenation at atmospheric pressure using Rh/Al_2O_3 (5 wt %).

With the dimeric ketones **34** and **35** in hand, we proceeded to the stereoselective construction of the vitamin D triene system (Scheme 4). A double Wittig−Horner reaction of **34** with the anion formed from the 1α-hydroxylated phosphine oxide **10** (3.0 equiv), gave protected dimer **36** in 71% yield. Removal of the six silyl protecting groups of **36**, in the absence of light, with *n*-Bu_4NF (9 equiv) in THF at room temperature during 24 h afforded calcitriol dimer **4** in 67% yield. Calcitriol dimer **5** was prepared as above by Wittig−Horner reaction of **35** with the anion of **10** followed by one step deprotection with *n*-Bu_4NF (40% two steps). Overall, the synthesis of the first known calcitriol dimers **4** and **5** were achieved from known ketone **28** in six steps and 25% overall yield.

Conclusions

We have designed and synthesized the first generation of vitamin D_3 and calcitriol dimers. The moieties are linked at the C-11 position, far from the hydroxy groups involved in the VDR binding, with an alkyl chain of modulated length with the purpose of optimizing the calcitriol−VDR interaction. The synthetic strategy, which is both short and convergent, uses the Wittig−Horner approach for the construction of the vitamin D triene system, a stereoselective cuprate addition and a key ruthenium olefin metathesis for the linker construction. This work opens the door to new vitamin D homo- and heterodimers.

Experimental Section

General Materials and Methods. Unless otherwise stated, all reactions were conducted in flame-dried glassware under a positive pressure of argon. 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 the sodium ketyl of benzophenone. Dichloromethane (CH_2Cl_2) and acetonitrile were distilled from P_2O_5. For the metathesis reactions CH_2Cl_2 was degassed and filtered through basic alumina prior to use. $(Cy_3P)_2Cl_2RuCHPh$ was purchased from Strem Chemicals and used directly. Absolute MeOH was distilled from Mg turnings. Copper iodide was purified by recrystallization from saturated potasium iodide solution.[25] Organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated using a rotary evaporator at aspirator pressure (20−30 mmHg). For reactions where a component was added by cannula, the total volume of solvent is given. Usually the compound was dissolved in 80% of that volume and the flask was then rinsed with the remaining 20% of fresh solvent. Thin-layer chromatography was effected on silica gel 60 F_{254} (layer thickness 0.2 mm) and components were located by observation under UV light and/or by treating the plates with a phosphomolybdic acid or *p*-anisaldehyde reagent followed by heating. Flash column chromatography was performed on silica gel 60 (230−400 mesh) by Still's method.[26] ^{1}H NMR spectra were recorded on a 200 MHz spectrometer and ^{13}C NMR spectra at 50 MHz.

11α-(3-Buten-1-yl)-de-*A,B*-cholestan-8-one (13). A solution of 4-bromo-1-butene (145 μL, 1.43 mmol) in Et_2O (3 mL) was added dropwise over a 15 min period to a cooled (−85 °C) solution of *t*-BuLi (1.7 mL, 1.75 M). After 40 min of stirring, a solution of the complex CuI/*n*-Bu_3P in Et_2O [previously prepared by addition of *n*-Bu_3P (176 μL, 0.72 mmol) to a solution of CuI (137 mg, 0.72 mmol) in Et_2O (4 mL) at room temperature] was transferred by cannula into the reaction mixture. The mixture was warmed to −50 °C during 1 h and cooled to −78 °C, and a solution of the enone **12** (94 mg, 0.36 mmol) in Et_2O (5 mL) was added by cannula over a 10 min. The reaction was allowed to reach −20 °C (1 h) and quenched with a few drops of a saturated solution of NH_4Cl. The mixture was poured into a separatory funnel with Et_2O (50 mL), washed with a saturated solution of NH_4Cl (30 mL), and the organic phase was dried, filtered and concentrated in vacuo. The residue was purified by flash chromatography (2% AcOEt/hexanes) to give 97 mg of ketone **13** [85%, R_f = 0.4 (10% AcOEt/hexanes), colorless oil]: $[\alpha]^{27}_D = +21.5$ (*c* 0.6, $CHCl_3$); IR (neat) 3020, 2950, 1750, 1425 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.64 (s, 3H), 0.87 (d, *J* = 6.4 Hz, 6H), 0.97 (d, *J* = 5.9 Hz, 3H), 2.40 (m, 2H), 4.95 (d, *J* = 13.2 Hz, 1H), 5.02 (d, *J* = 17.1 Hz, 1H), 5.78 (ddt, *J* = 17.1, 13.2, 6.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.2, 18.5, 18.7, 22.3, 22.6, 24.0, 27.5, 27.7, 31.2, 35.3, 35.7, 35.8, 36.6, 39.4, 46.2, 47.5, 49.1, 56.6, 61.9, 114.8, 138.3, 211.3; MS (EI, 70 eV) *m*/*z* 318 (M^+, 6); HRMS calcd for $C_{22}H_{38}O$ 318.2923 (M^+), found 318.2913.

11α-(5-Hexen-1-yl)-de-*A,B*-cholestan-8-one (14). Following the same experimental procedure as for **13**, enone **12** (183 mg, 0.70 mmol) was treated with the cuprate prepared from 6-bromo-1-hexene (0.37 mL, 2.79 mmol), *t*-BuLi (1.69 mL, 1.65

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(26) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

M), and CuI (218 mg, 1.15 mmol) to give, after purification by flash chromatography (2% AcOEt/hexanes), 229 mg of **14** [95%, R_f = 0.5 (15% AcOEt/hexanes), colorless oil]: $[\alpha]^{28}_D$ = +15.7 (*c* 0.4, $CHCl_3$); IR (neat) 3030, 2980, 1750, 1510, 1425 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.64 (s, 3H), 0.87 (d, *J* = 6.4 Hz, 6H), 0.97 (d, *J* = 5.9 Hz, 3H), 2.45 (m, 2H), 4.95 (d, *J* = 10.5 Hz, 1H), 5.04 (d, *J* = 17.1 Hz, 1H), 5.80 (ddt, *J* = 17.1, 10.5, 6.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.2, 18.8, 18.9, 22.5, 22.8, 23.7, 26.5, 27.6, 28.0, 29.0, 33.6, 35.5, 36.0, 36.6, 37.3, 39.4, 46.5, 47.7, 49.2, 56.6, 61.9, 114.4, 138.8, 211.5; HRMS calcd for $C_{24}H_{42}O$ 346.3236 (M^+), found 346.3236.

(5*E*,7*Z*)-3*β*-[(*tert*-Butyldimethylsilyl)oxy]-11α-(3-buten-1-yl)-9,10-secocholesta-5,7,10(19)-triene (16). To a solution of the phosphine oxide **9** (150 mg, 0.31 mmol) in THF (7 mL) at −78 °C was added dropwise a solution of *n*-BuLi in hexanes (118 μL, 0.28 mmol). The reaction was warmed to 0 °C and, after 15 min, cooled again to −78 °C. A solution of **13** (50 mg, 0.157 mmol) in THF (3 mL) was added by cannula. The mixture was stirred and warmed to −35 °C. The reaction was quenched with a saturated solution of NH_4Cl (1 mL) and then poured into a separatory funnel with Et_2O (30 mL). The organic layer was washed with a saturated solution of NH_4Cl (20 mL), dried, filtered and concentrated with protection from light. The residue was purified by flash chromatography (10% Et_2O/hexanes) to afford 73 mg of vitamin **16** [84%, R_f = 0.8 (10% AcOEt/hexanes), colorless oil]: $[\alpha]^{25}_D$ = +45.6 (*c* 1.5, $CHCl_3$); ^1H NMR (CD_2Cl_2) δ 0.06 (s, 3H), 0.07 (s, 3H), 0.52 (s, 3H), 0.86 (d, *J* = 7.3 Hz, 6H), 0.88 (s, 9H), 0.94 (d, *J* = 5.8 Hz, 3H), 2.89 (m, 1H), 3.84 (m, 1H), 4.76 and 5.01 (2 br s, 2H), 4.91, 4.96 and 5.06 (3 m, 2H), 5.83 (ddt, *J* = 17.1, 10.3, 6.8 Hz, 1H), 6.00 and 6.19 (2 d, AB system, *J* = 11.2 Hz, 2H); ^{13}C NMR (CD_2Cl_2) δ −4.6, −4.5, 12.9, 18.4, 19.1, 22.3, 22.7, 22.9, 24.2, 26.0, 28.3, 28.4, 31.9, 33.0, 34.5, 36.1, 36.5, 36.7, 37.2, 39.9, 46.1, 47.1, 47.8, 56.7, 56.9, 70.8, 112.2, 114.2, 118.1, 121.7, 136.8, 139.7, 141.2, 146.0; HRMS calcd for $C_{37}H_{64}OSi$ 552.4726 (M^+), found 552.4715.

(5*E*,7*Z*)-11α,11′α-(3-Hexene-1,6-diyl)bis-9,10-secocholesta-5,7,10(19)-trien-3*β*-ol (19). To a solution of the vitamin **16** (35 mg, 0.063 mmol) in CH_2Cl_2 (1 mL), protected from light in a Schlenk tube, was added $(Cy_3P)_2Cl_2RuCHPh$ (6 mg, 10%). The resulting mixture was stirred for 2 h and purified by flash chromatography (5% Et_2O/hexanes) to give 35 mg of a mixture of dimer **18** and starting vitamin **16** (1:1 ratio). The mixture was dissolved in THF (3 mL) and treated with a solution *n*-Bu_4NF in THF (88 μL, 1 M). After being stirred for 24 h, the mixture was concentrated in vacuo and the residue was purified by flash chromatography (25% AcOEt/hexanes) to afford 20 mg of dimer **19** [74%, R_f = 0.2 (40% AcOEt/hexanes), white foam] and 5 mg of the vitamin **17** (18%). **19**: ^1H NMR (CD_2Cl_2) δ 0.51 (s, 6H), 0.85 (d, *J* = 6.8 Hz, 12H), 0.93 (d, *J* = 5.9 Hz, 6H), 2.87 (m, 2H), 3.89 (m, 2H), 4.78 and 5.02 (2 br s, 4H), 5.42 (m, 2H), 6.01 and 6.24 (2 d, AB system, *J* = 11.2 Hz, 4H); ^{13}C NMR (CD_2Cl_2) δ 12.9, 19.1, 22.4, 22.7, 22.9, 24.2, 28.3, 28.4, 30.6, 32.4, 34.5, 35.7, 36.2, 36.5, 37.9, 39.8, 46.2, 46.3, 47.7, 56.8, 56.9, 69.5, 112.4, 117.8, 122.5, 130.7, 135.8, 141.8, 145.8; HRMS (FAB) calcd for $C_{60}H_{96}O_2$ 848.7410 (M^+), found 848.7412. **17**: $[\alpha]^{28}_D$ = +18.3 (*c* 0.6, $CHCl_3$); ^1H NMR (CD_2Cl_2) δ 0.52 (s, 3H), 0.85 (d, *J* = 6.3 Hz, 6H), 0.93 (d, *J* = 6.3 Hz, 3H), 2.89 (m, 1H), 3.87 (m, 1H), 4.78 and 5.04 (2 br s, 2H), 4.90, 4.96 and 5.05 (3 m, 2H), 5.83 (ddt, *J* = 17.1, 10.3, 6.8 Hz, 1H), 6.01 and 6.24 (2 d, AB system, *J* = 11.2 Hz, 2H); ^{13}C NMR (CD_2Cl_2) δ 12.8, 19.1, 22.4, 22.7, 22.9, 24.2, 25.8, 28.3, 28.4, 31.9, 32.4, 34.6, 35.7, 36.1, 36.4, 36.5, 37.2, 39.8, 46.1, 46.3, 47.8, 56.8, 56.9, 69.5, 112.4, 114.2, 117.9, 122.4, 135.9, 139.7, 141.7, 145.8; MS (FAB) *m*/*z* 439 (M^+ + 1, 87), 438 (M^+, 100); HRMS calcd for $C_{31}H_{50}O$ 438.3862 (M^+), found 438.3870.

11α,11′α-(3-Hexene-1,6-diyl)bis-de-*A*,*B*-cholestan-8-one (20). To a solution of **13** (30 mg, 0.094 mmol) in CH_2Cl_2 (5 mL) in a Schlenk tube was added $(Cy_3P)_2Cl_2RuCHPh$ (9 mg, 10%). The mixture was stirred for 24 h, concentrated, and purified by flash chromatography (5% AcOEt/hexanes) to afford 18 mg of dimeric ketone **20** [63%, R_f = 0.5 (10% AcOEt/hexanes), colorless oil] as mixture of isomers in 5:1 ratio, and 9 mg of starting ketone **13** (30%). **20** (major isomer): IR (neat) 2950, 1720, 1425 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.63 (s, 6H), 0.87 (d, *J* = 6.4 Hz, 12H), 0.96 (d, *J* = 5.4 Hz, 6H), 2.39 (m, 4H), 5.38 (t, *J* = 3.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 13.2, 18.8, 18.9, 22.5, 22.8, 23.7, 27.8, 28.0, 30.0, 35.5, 35.9, 36.0, 37.2, 39.4, 46.2, 47.6, 49.2, 56.5, 61.9, 130.1, 211.5; MS (EI, 70 eV) *m*/*z* 609 (M^+ + 1, 3) 608 (M^+, 7), 173 (100); HRMS calcd for $C_{42}H_{72}O_2$ 608.5532 (M^+), found 608.5540.

11α,11′α-(5-Decene-1,10-diyl)bis-de-*A*,*B*-cholestan-8-one (21). Following the same experimental procedure as for **20**, a solution of ketone **14** (50 mg 0.144 mmol) in CH_2Cl_2 (2 mL) afforded, after purification by flash chromatography (10% AcOEt/hexanes), 32 mg of **21** as a 5:1 isomeric mixture [67%, R_f = 0.4 (10% AcOEt/hexanes), colorless oil]. **21** (major isomer): IR (neat) 2940, 1720, 1460, 1380, 960 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.64 (s, 6H), 0.87 (d, *J* = 6.4 Hz, 12H), 0.96 (d, *J* = 5.4 Hz, 6H), 2.41 (m, 4H), 5.37 (t, *J* = 3.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 13.2, 18.8, 18.9, 22.5, 22.8, 23.7, 26.5, 27.8, 27.9, 29.6, 32.5, 35.5, 36.0, 36.7, 37.4, 39.4, 46.5, 47.7, 49.2, 56.5, 61.9, 130.3, 211.7; HRMS (FAB) calcd for $C_{46}H_{82}O_2$ 664.6172 (M^+ + 1), found 664.6158.

11α,11′α-(1,6-Hexanediyl)bis-de-*A*,*B*-cholestan-8-one (22). To a solution of diketone **20** (60 mg, 0.1 mmol) in MeOH (7 mL) under an H_2 atmosphere was added a catalytic amount of the complex Rh/Al_2O_3 (5 wt %). The mixture was stirred overnight, concentrated in vacuo and purified by flash chromatography (4% AcOEt/hexanes) to afford 55 mg of ketone **22** [91%, R_f = 0.5 (10% AcOEt/hexanes)]: IR (neat) 2950, 1710, 1420, 960 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.63 (s, 6H), 0.86 (d, *J* = 6.8 Hz, 12H), 0.95 (d, *J* = 5.7 Hz, 6H), 2.38 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 13.2, 18.8, 18.9, 22.5, 22.8, 23.7, 27.0, 27.8, 28.0, 29.7, 35.5, 35.9, 36.7, 37.5, 39.4, 46.4, 47.7, 49.2, 56.5, 61.9, 211.7; MS (FAB) *m*/*z* 611 (M^+ + 1, 100), 593 (M^+ − CH_3, 17); HRMS (FAB) calcd for $C_{42}H_{75}O_2$, 611.5767 (M^+ + 1), found 611.5739.

11α,11′α-(1,10-Decanediyl)bis-de-*A*,*B*-cholestan-8-one (23). Following the same experimental procedure as for **22**, hydrogenation of diketone **21** (25 mg, 0.038 mmol) with Rh/Al_2O_3 (5 wt %) in MeOH (5 mL) afforded, after purification (7% AcOEt/hexanes), 23 mg of **23** [91%, R_f = 0.6 (15% AcOEt/hexanes), white solid]: IR (neat) 2940, 1725, 1460, 1380 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.64 (s, 6H), 0.87 (d, *J* = 6.4 Hz, 12H), 0.96 (d, *J* = 5.4 Hz, 6H), 1.26 (s, 23H), 2.39 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 13.2, 18.8, 18.9, 22.5, 22.8, 23.7, 27.1, 27.8, 28.0, 29.6, 29.7, 35.5, 36.0, 36.7, 37.5, 39.4, 46.5, 47.8, 49.2, 56.5, 61.9, 211.6; MS (FAB) *m*/*z* 668 (M^+ + 2, 10), 667 (M^+ + 1, 21), 288 (100); HRMS (FAB) calcd for $C_{46}H_{82}O_2$ 666.6315 (M^+), found 666.6318.

(5*E*,7*Z*)-1α,11′α-(1,6-Hexanediyl)bis-9,10-secocholesta-5,7,10(19)-trien-3*β*-ol (2). To a solution of the phosphine oxide **9** (90 mg, 0.2 mmol) in THF (7 mL), at −78 °C, was added dropwise a solution of *n*-BuLi in hexanes (100 μL, 2.0 M, 0.20 mmol). The reaction was warmed to 0 °C and, after 15 min, cooled again to −78 °C. A solution of **22** (30 mg, 0.049 mmol) in THF (3 mL) was then added by cannula. The mixture was stirred and warmed to −50 °C. The reaction was quenched with a saturated solution of NH_4Cl (1 mL). The mixture was poured into a separatory funnel with Et_2O (50 mL) and washed with a saturated solution of NH_4Cl (30 mL). The organic layer was dried, filtered and concentrated in vacuo with protection from the light. The residue was purified by flash chromatography (1% AcOEt/hexanes) to afford 45 mg of the protected vitamin D_3 dimer **24** [85%, R_f = 0.8 (10% AcOEt/hexanes), colorless oil]: ^1H NMR (CD_2Cl_2) δ 0.06 (s, 6H), 0.07 (s, 6H), 0.53 (s, 6H), 0.86 (d, *J* = 7.0 Hz, 12H), 0.88 (s, 18H), 0.94 (d, *J* = 5.9 Hz, 6H), 2.55 (m, 2H), 2.84 (m, 2H), 3.84 (m, 2H), 4.78 (d, *J* = 2.4 Hz, 2H), 5.03 (d, *J* = 2.4 Hz, 2H), 6.00 and 6.20 (2 d, AB system, *J* = 11.2 Hz, 4H); ^{13}C NMR (CD_2Cl_2) δ −4.57, −4.51, 12.9, 18.4, 19.1, 22.4, 22.7, 22.9, 24.2, 26.0, 27.6, 28.3, 28.4, 30.4, 32.9, 35.1, 36.3, 36.5, 36.7, 38.2, 39.9, 46.1, 47.1, 48.0, 56.8, 56.9, 70.8, 112.2, 118.0, 121.8, 136.6, 141.4, 146.0.

To a solution of **24** (45 mg) in THF (5 mL), with protection from the light, was added *n*-$Bu_4NF{\cdot}H_2O$ (42 mg, 0.16 mmol). The solution was stirred for 24 h, poured into a separatory funnel with AcOEt (30 mL) and washed with a saturated solution of NaCl (30 mL). The organic layer was dried, filtered and concentrated in vacuo. The residue was purified by flash

chromatography (30% AcOEt/hexanes) to afford 32 mg of vitamin D_3 dimer **2** [90%, $R_f = 0.4$ (60% AcOEt/hexanes), white foam]: $[\alpha]^{26}_D = +14.1$ (*c* 0.2, $CHCl_3$); ^{1}H NMR (CD_2Cl_2) δ 0.53 (s, 6H), 0.86 (d, $J = 6.3$ Hz, 12H), 0.93 (d, $J = 5.9$ Hz, 6H), 1.31 (m, 12H), 2.55 (m, 2H), 2.89 (m, 2H), 3.87 (m, 2H), 4.78 (d, $J = 2.9$ Hz, 2H), 5.03 (d, $J = 2.4$ Hz, 2H), 6.24 and 6.01 (2 d, AB system, $J = 11.2$ Hz, 4H); ^{13}C NMR (CD_2Cl_2) δ 12.9, 19.1, 22.4, 22.7, 22.9, 24.2, 27.5, 28.3, 30.3, 32.4, 35.2, 35.7, 36.3, 36.5, 38.2, 39.8, 46.2, 46.3, 48.1, 56.8, 57.0, 69.5 112.4, 117.8, 122.5, 135.8, 141.9, 145.8; MS (FAB) *m*/*z* 850 (M^+, 75); HRMS (FAB) calcd for $C_{60}H_{98}O_2$ 850.7567 (M^+), found 850.7601.

(5*E*,7*Z*)-1α,11′α-(1,10-Decanediyl)bis-9,10-secocholesta-5,7,10(19)-trien-3*β*-ol (3). Following the same experimental procedure as for **2**, reaction of diketone **23** (56 mg, 0.084 mmol) with the anion prepared from phosphine oxide **9** (152 mg, 0.34 mmol) and *n*-BuLi in hexanes (187 μL, 1.71 M, 0.31 mmol) afforded, after purification by flash chromatography (1% AcOEt/hexanes), 88 mg of **25** [92%, $R_f = 0.8$ (15% AcOEt/hexanes), colorless oil]: ^{1}H NMR (CD_2Cl_2) δ 0.06 (s, 12H), 0.53 (s, 6H), 0.86 (d, $J = 7.3$ Hz, 12H), 0.88 (s, 18H), 0.93 (d, $J = 5.9$ Hz, 6H), 2.42 (m, 2H), 2.85 (m, 2H), 3.86 (m, 2H), 4.75 (d, $J = 3$ Hz, 2H), 5.00 (d, $J = 3$ Hz, 2H), 5.99 and 6.19 (2 d, AB system, $J = 11.2$, Hz, 4H); ^{13}C NMR (CD_2Cl_2) δ −4.6, −4.5, 12.9, 18.4, 19.1, 22.4, 22.7, 22.9, 24.2, 26.0, 27.6, 28.3, 28.4, 30.1, 30.4, 32.9, 35.1, 36.3, 36.5, 36.7, 38.2, 39.9, 46.1, 47.1, 48.0, 56.8, 57.0, 70.8, 112.2, 118.0, 121.7, 136.7, 141.4, 146.0.

Deprotection of **25** (32 mg, 0.028 mmol) with *n*-$Bu_4NF{\cdot}H_2O$ (35 mg, 0.11 mmol), following the same experimental procedure as for **2**, afforded, after purification by flash chromatography (AcOEt), 25 mg of **3** [98%, $R_f = 0.8$ (70% AcOEt/hexanes), white foam]: $[\alpha]^{29}_D = +11.1$ (*c* 0.6, $CHCl_3$); ^{1}H NMR (CD_2Cl_2) δ 0.53 (s, 6H), 0.86 (d, $J = 6.3$ Hz, 12H), 0.93 (d, $J = 5.9$ Hz, 6H), 2.55 (m, 2H), 2.89 (m, 2H), 3.87 (m, 2H), 4.78 (d, $J = 2.9$ Hz, 2H), 5.03 (d, $J = 2.4$ Hz, 2H), 6.24 and 6.01 (2 d, AB system, $J = 11.2$, Hz, 4H); ^{13}C NMR (CD_2Cl_2) δ 19.1, 199, 22.4, 22,7, 22.9, 23.1, 24.2, 27.6, 28.3, 28.4, 30.1, 30.4, 32.3, 32.4, 35.2, 35.7, 36.3, 36.4, 36.5, 38.2, 39.9, 46.2, 46.3, 48.1, 56,8, 57.0, 69.5, 112.4, 117.8, 122.5, 135.7, 142.0, 145.8; MS (FAB) *m*/*z* 907 (M^+, 25); HRMS (FAB) calcd for $C_{64}H_{107}O_2$ 907.8271 ($M^+ + 1$), found 907.8260.

25-Hydroxy-de-*A*,*B*-cholestan-8-one (27).[27] To a −45 °C cooled solution of ester **26** (502 mg, 1.78 mmol) in THF (15 mL) a solution of MeLi in Et_2O (3.9 mL, 1.5 M, 5.94 mmol) was added dropwise (10 min). The reaction mixture was stirred for 30 min, quenched by addition of MeOH (1 mL), and then warmed to room temperature. The reaction mixture was poured into a separatory funnel with Et_2O (30 mL) and washed successively with a saturated solution of $NaHCO_3$ (30 mL) and NaCl (30 mL). The organic layer was dried, filtered and concentrated in vacuo, and the crude was purified by flash chromatography (30% EtOAc/hexanes) to afford 445 mg [89%, $R_f = 0.4$ (50% AcOEt/hexanes), white solid] of a diol which was inmediately oxidized to ketone **27**: ^{1}H NMR ($CDCl_3$) δ 0.92 (d, $J = 7.1$ Hz, 3H), 0.94 (s, 3H), 1.22 (s, 6H), 4.08 (m, 1H).

A mixture of the freshly prepared diol (445 mg, 1.58 mmol) and PDC (1.92 g, 5.11 mmol) in CH_2Cl_2 (30 mL) was stirred for 6 h. Et_2O (50 mL) was added and the resulting mixture was stirrred for 10 min. The mixture was filtered through Celite and the solids were washed with Et_2O (2 × 40 mL). The filtrate was concentrated in vacuo and residue was purified by flash chromatography (25% EtOAc/hexanes), to afford 432 mg of **27** [98%, $R_f = 0.5$ (50% AcOEt/hexanes), colorless oil]: ^{1}H NMR ($CDCl_3$) δ 0.62 (s, 3H), 0.95 (d, $J = 6.2$ Hz, 3H), 1.20 (s, 6H), 2.45 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 12.5, 18.7, 19.0, 20.7, 24.1, 27.5, 29.2, 29.4, 35.5, 36.2, 39.0, 41.0, 42.3, 49.9, 56.6, 62.0, 71.0, 212.2.

25-[(Triethylsilyl)oxy]de-A,B-cholestan-8-one (28). To a solution of **27** (440 mg, 1.57 mmol) in CH_2Cl_2 (30 mL), at −78 °C, was added dropwise 2,6-lutidine (0.74 mL, 6.29 mmol) and Et_3SiOTf (0.53 mL, 2.36 mmol) and the resulting mixture was stirred for 30 min at −78 °C and warmed to room temperature. The mixture was poured into a separatory funnel with CH_2Cl_2 (50 mL), and successively washed with 2% H_2SO_4 (50 mL), a saturated solution of $NaHCO_3$ (50 mL) and water (50 mL). The organic phase was dried, filtered and concentrated in vacuo, and the resulting crude was purified by flash chromatography (6% EtOAc/hexanes) to afford 613 mg of **28** [99%, $R_f = 0.7$ (50% AcOEt/hexanes), colorless oil]: $[\alpha]^{28}_D = +6.5$ (*c* 1.7, $CHCl_3$); IR (neat) 2950, 1730, 750 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 0.59 (q, $J = 7.9$ Hz, 6H), 0.65 (s, 3H), 0.91 (t, $J = 7.9$ Hz, 9H), 0.93 (d, $J = 5.6$ Hz, 3H),1.16 (s, 6 H), 2.27 (m, 1 H), 2.45 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 6.7, 7.1, 12.4, 18.6, 19.0, 20.6, 24.0, 27.4, 29.7, 29.9, 35.4, 36.2, 38.9, 40.9, 45.4, 49.9, 56.7, 61.9, 73.3, 212.2.

25-[(Triethylsilyl)oxy]de-*A*,*B*-cholest-9(11)-en-8-one (29). A solution of ketone **28** (500 mg, 1.27 mmol) in THF (6 mL) was added dropwise (30 min) by cannula to a cooled (−75 °C) solution of LDA (1.52 mmol) in THF (4 mL). After stirring for 30 min, TMSCl (210 μL, 1.64 mmol) was added by syringe and the reaction mixture was warmed to room temperature and concentrated in vacuo. The residue was dissolved in Et_2O (25 mL), the solution was dried, filtered and concentrated in vacuo. The residue was dissolved in CH_3CN/THF (10 mL, 3:2), and $Pd(OAc)_2$ (285 mg, 1.27 mmol) was added. The resulting mixture was stirred for 24 h, filtered through Celite and concentrated in vacuo. The residue was purified by flash chromatography (5% AcOEt/hexanes) to afford 420 mg of enone **29** [84%, $R_f = 0.4$ (15% AcOEt/hexanes), colorless oil]: $[\alpha]^{28}_D = +8.7$ (*c* 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.56 (q, $J = 7.8$ Hz, 6H), 0.76 (s, 3H), 0.92 (d, $J = 6.8$ Hz, 3H), 0.94 (t, $J = 7.5$ Hz, 9H), 1.19 (s, 6H), 2.3−2.7 (m, 3H), 5.98 (dd, $J = 9.0$, 2.9 Hz, 1H), 6.75 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 6.2, 6.8, 7.1, 7.4, 11.9, 18.4, 19.4, 20.6, 27.4, 29.8, 30.0, 35.0, 35.4, 36.1, 42.9, 45.4, 47.5, 56.7, 59.2, 63.5, 73.3, 129.5, 135.2, 147.6, 202.0; HRMS calcd for $C_{24}H_{44}O_2Si$ 392.3111 ($M^+ + 1$), found 449.3123.

11α-(3-Buten-1-yl)-25-[(triethylsilyl)oxy]de-*A*,*B*-cholestan-8-one (30). Following the same experimental procedure as for **13**, reaction of enone **29** (250 mg, 0.64 mmol) with the cuprate generated from 4-bromo-1-butene (260 mL, 2.55 mmol), *t*-BuLi (1.54 mL, 2.55 mmol) and CuI/*n*-Bu_3P (1.275 mmol) afforded, after purification by flash chromatography (2% AcOEt/hexanes), 240 mg of **30** [84%, $R_f = 0.5$ (15% AcOEt/hexanes), colorless oil]: $[\alpha]^{25}_D = +7.2$ (*c* 0.5, $CHCl_3$); IR (neat) 3070, 2950, 1715, 1470, 1390, 910 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.56 (q, $J = 8.3$ Hz, 6H), 0.94 (t, $J = 6.8$ Hz, 9H), 0.96 (d, $J = 6.4$ Hz, 3H), 1.19 (s, 3H), 2.40 (m, 2H), 4.96 (d, $J = 13.2$ Hz, 1H), 5.01 (d, $J = 17.1$ Hz, 1H), 5.79 (ddt, $J = 17.1$, 13.2, 6.8 Hz, 1H); ^{13}C NMR (CD_2Cl_2) δ 6.8, 7.1, 13.2, 13.8, 18.7, 18.9, 20.7, 27.0, 27.8, 29.8, 30.0, 31.3, 35.5, 36.0, 36.2, 36.5, 45.4, 46.2, 47.6, 49.1, 56.5, 61.9, 73.4, 114.7, 138.3, 211.4; MS (FAB) *m*/*z* 449 ($M^+ + 1$, 13), 317 (100); HRMS (FAB) calcd for $C_{28}H_{53}O_2Si$ 449.3815 ($M^+ + 1$), found 449.3828.

11α-(5-Hexene-1-yl)-25-[(triethylsilyl)oxy]-de-*A*,*B*-cholestan-8-one (31). Following the same experimental procedure as for **13**, reaction of enone **29** (190 mg, 0.48 mmol) with the cuprate generated from 6-bromo-1-hexene (260 mL, 1.94 mmol), *t*-BuLi (1.17 mL, 2.55 mmol) and CuI/*n*-Bu_3P (0.97 mmol) afforded, after purification by flash chromatography (2% AcOEt/hexanes), 218 mg of **31** [94%, $R_f = 0.5$ (15% AcOEt/hexanes), colorless oil]: $[\alpha]^{26}_D = +10.7$ (*c* 0.3, $CHCl_3$); IR (neat) 3080, 2950, 1725, 1460, 1380, 1230, 1050, 740 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 0.58 (q, $J = 7.6$ Hz, 6H,), 0.64 (s, 3H), 0.93 (t, $J = 7.8$ Hz, 12H), 0.96 (d, $J = 6.4$ Hz, 3H), 1.19 (s, 6H), 4.95 (d, $J = 10.3$ Hz, 1H), 5.04 (d, $J = 17.6$ Hz, 1H), 5.81 (ddt, $J = 17.6$, 10.3, 6.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 6.7, 7.1, 13.2, 18.8, 18.9, 20.7, 25.0, 25.1, 26.5, 27.7, 29.0, 29.8, 30.0, 33.6, 35.4, 35.8, 36.2, 36.6, 37.3, 45.4, 46.4, 47.7, 49.2, 114.4, 138.8, 211.5; MS (FAB) *m*/*z* 477 ($M^+ + 1$, 54), 475 ($M^+ - 1$, 100); HRMS (FAB) calcd for $C_{30}H_{57}O_2Si$ 477.4128 ($M^+ + 1$), found 477.4138.

11α,11′α-(3-Hexene-1,6-diyl)bis-25-[(triethylsilyl)oxy]-de-*A*,*B*-cholestan-8-one (32). A solution of ketone **30** (50 mg 0.11 mmol) in CH_2Cl_2 (2 mL) was treated following the same experimental procedure as for **20**, to afford, after purification by flash chromatography (8% AcOEt/hexanes), 34 mg of **32** [70%, $R_f = 0.4$ (20% AcOEt/hexanes), colorless oil] as a 5:1 isomeric mixture. **32** (major isomer): IR (neat) 3000, 1720,

(27) Curci, R.; Detomaso, A.; Prencipe, T.; Carpenter, G. *J. Am. Chem. Soc.* **1994**, *116*, 8112.

1450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.56 (q, $J = 7.8$ Hz, 12H), 0.64 (s, 6H), 0.94 (t, $J = 7.8$ Hz, 18H), 0.97 (d, $J = 7.3$ Hz, 6H), 1.19 (s, 12H), 2.40 (m, 4H), 5.38 (t, $J = 3.6$ Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 6.8, 7.1, 13.2, 18.8, 18.9, 20.7, 27.7, 29.7, 30.0, 30.1, 35.5, 36.0, 37.2, 45.4, 46.2, 47.6, 49.1, 56.5, 61.9, 73.4, 129.5, 130.1, 211.5; HRMS (FAB) calcd for $C_{52}H_{95}O_4Si_2$ 839.6769 ($M^+ - C_2H_5$), found 839.6751.

11α,11′α-(5-Decene-1,10-diyl)bis-25-[(triethylsilyl)oxy]-de-*A,B*-cholestan-8-one (33). Following the same experimental procedure as for **20**, ketone **31** (60 mg, 0.126 mmol) in CH_2Cl_2 (2 mL) afforded, after purification by flash chromatography (5% AcOEt/hexanes), 28 mg of **33** [48%, $R_f = 0.4$ (10% AcOEt/hexanes), colorless oil] as a isomeric mixture. **33** (major isomer): IR (neat) 2950, 1710, 1450, 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.58 (q, $J = 7.6$ Hz, 12H), 0.64 (s, 6H), 0.93 (t, $J = 7.6$ Hz, 18H), 0.97 (d, $J = 7.3$ Hz, 6H), 1.19 (s, 12H), 2.35 (m, 4H), 5.38 (t, $J = 3.9$ Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 6.8, 13.2, 18.8, 18.9, 20.7, 26.5, 27.1, 27.7, 29.7, 29.8, 30.0, 32.5, 35.5, 36.3, 36.8, 37.4, 45.4, 46.5, 47.7, 49.2, 56.6, 61.9, 73.4, 130.3, 211.6; MS (FAB) *m/z* 948 [$(M + Na)^+$, 1], 896 ($M^+ - C_2H_5$, 1), 297 (100).

11α,11′α-(1,6-Hexanediyl)bis-25-[(triethylsilyl)oxy]-de-*A,B*-cholestan-8-one (34). Following the same experimental procedure as for **22**, dimeric ketone **32** (18 mg, 0.021 mmol) afforded, after purification (4% AcOEt/hexanes), 16 mg of **34** [89%, $R_f = 0.5$ (15% AcOEt/hexanes), colorless oil]: $[\alpha]^{27}_D = +9.4$ (*c* 0.2, $CHCl_3$); IR (neat) 2950, 1720, 1410, 1230, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.56 (q, $J = 7.6$ Hz, 12H), 0.64 (s, 6H), 0.95 (t, $J = 7.6$ Hz, 18H), 0.96 (d, $J = 5.6$ Hz, 6H), 1.19 (s, 12H), 2.40 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 6.8, 7.1, 13.2, 18.8, 18.9, 20.7, 27.2, 27.8, 29.7, 29.8, 30.0, 35.5, 36.2, 36.7, 37.5, 45.4, 46.4, 47.8, 49.2, 56.5, 61.9, 73.4, 211.7; HRMS (FAB) calcd for $C_{52}H_{97}O_4Si_2$ 841.6925 ($M^+ - C_2H_5$), found 841.6898.

11α,11′α-(1,10-Decanediyl)bis-25-[(triethylsilyl)oxy]-de-*A,B*-cholestan-8-one (35). Following the same experimental procedure as for **20**, dimeric ketone **33** (50 mg, 0.054 mmol) afforded after purification (6% AcOEt/hexanes), 47 mg of **35** [94%, $R_f = 0.5$ (15% AcOEt/hexanes), colorless oil]: IR (neat) 2925, 1720, 1410, 1230, 775 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.57 (c, $J = 7.8$ Hz, 12H), 0.65 (s, 6H), 0.92 (t, $J = 7.8$ Hz, 18H), 0.95 (d, $J = 7.8$ Hz, 6H), 1.19 (s, 12H), 2.41 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 6.8, 7.1, 13.2, 18,8, 18.9, 20.7, 27.1, 27.8, 29.6, 29.7, 29.8, 30.0, 35.5, 36.3, 36.7, 37.6, 45.4, 46.5, 47.8, 49.2, 56.6, 61.9, 73.4, 211.6; HRMS (FAB) calcd for $C_{56}H_{105}O_4Si_2$ 897.7551 ($M^+ - C_2H_5$), found 897.7555.

(5*E*,7*Z*)-11α,11′α-(1,6-Hexanediyl)bis-9,10-secocholesta-5,7,10(19)-triene-1α,3*β*,25-triol (4). To a solution of the phosphine oxide **10** (40 mg, 0.06 mmol) in THF (5 mL) at −78 °C, was added dropwise a solution of *n*-BuLi in hexanes (40 μL, 1.75 M, 0.07 mmol). The reaction was warmed to 0 °C and, after 15 min, cooled again to −78 °C. A solution of **34** (16 mg, 0.018 mmol) in THF (3 mL) was added by cannula. The mixture was stirred and warmed to −50 °C. The reaction was quenched with MeOH (1 mL). The mixture was poured into a separatory funnel with AcOEt (40 mL) and washed with a saturated solution of NaCl (30 mL). The organic layer was dried, filtered and concentrated under reduced pressure with protection from the light. The residue was purified by flash chromatography (2% Et_2O/hexanes) to afford 21 mg of the protected calcitriol dimer **36** [71%, $R_f = 0.8$ (10% Et_2O/hexanes), colorless oil]: ^1H NMR (CD_2Cl_2) δ 0.06 (s, 12H), 0.52 (s, 6H), 0.56 (q, $J = 8.3$ Hz, 12H), 0.86 (d, $J = 7.3$ Hz, 6H), 0.87 (s, 18H), 0.93 (t, $J = 8.3$ Hz, 18H), 1.18 (s, 12H), 2.42 (m, 2H), 2.87 (m, 2H), 4.19 (m, 2H), 4.38 (m, 2H), 4.83 (d, $J = 3$ Hz, 2H), 5.18 (d, $J = 3$ Hz, 2H), 6.01 and 6.2 (2 d, AB system, $J = 11.2$ Hz, 4H).

To a solution of **36** (21 mg, 0.013 mmol) in THF (7 mL), with protection from the light, was added *n*-$Bu_4NF{\cdot}H_2O$ (41 mg, 0.13 mmol) in one portion. After stirring for 24 h, the reaction mixture was poured into a separatory funnel with AcOEt (30 mL) and washed with a saturated solution of NaCl (30 mL). The organic layer was dried, filtered and concentrated in vacuo. The residue was purified by flash chromatography (AcOEt) to afford 8 mg of the calcitriol dimer **4** [67%, $R_f = 0.2$ (100% AcOEt), white solid]: $[\alpha]^{26}_D = +34.2$ (*c* 0.2, $CHCl_3$); ^1H NMR (CD_3OD) δ 0.57 (s, 6H), 0.98 (d, $J = 5.8$ Hz, 6H), 1.16 (s, 12H), 2.52 (m, 2H), 2.91 (m, 2H), 4.12 (m, 2H), 4.34 (t, $J = 5.3$ Hz, 2H), 4.90 (s, 2H), 5.29 (s, 2H), 6.06 and 6.32 (2 d, AB system, $J = 11.3$ Hz, 4H); ^{13}C NMR (CD_3OD) δ 13.2, 19.5, 21.9, 22.9, 28.1, 29.1, 29.2, 30.8, 35.9, 37.1, 37.5, 37.7, 38.8, 43.7, 45.3, 46.1, 46.9, 57.8, 67.4, 71.4, 111.9, 118.9, 124.8, 135.8, 141.8, 149.8; MS (FAB) *m/z* 938 [$(M + Na)^+$, 3]; HRMS (FAB) calcd for $C_{60}H_{98}O_6Na$ 937.7261 [$(M + Na)^+$], found 937.7232.

(5*E*,7*Z*)-11α,11′α-(1,10-Decanediyl)bis-9,10-secocholesta-5,7,10(19)-triene-1α,3*β*,25-triol (5). Following the same experimental procedure as for **4**, reaction of diketone **35** (19 mg, 0.021 mmol) with the anion formed from phosphine oxide **10** (55 mg, 0.09 mmol) and *n*-BuLi in hexanes (35 μL, 2.24 M, 0.08 mmol) afforded, after purification by flash chromatography (1% AcOEt/hexanes), 22 mg of **37** [65%, $R_f = 0.8$ (15% AcOEt/hexanes), colorless oil]: ^1H NMR (CD_2Cl_2) δ 0.06 (s, 12H), 0.52 (s, 6H), 0.56 (q, $J = 8.3$ Hz, 12H), 0.86 (d, $J = 7.3$ Hz, 6H), 0.87 (s, 18H), 0.93 (t, $J = 8.3$ Hz, 18H), 1.18 (s, 12H), 2.42 (m, 2H), 2.87 (m, 2H), 4.19 (m, 2H), 4.38 (m, 2H), 4.83 (d, $J = 3$ Hz, 2H), 5.18 (d, $J = 3$ Hz, 2H), 6.01 and 6.2 (2 d, AB system, $J = 11.2$ Hz, 4H).

Deprotection of **37** (22 mg, 0.013 mmol) with *n*-$Bu_4NF{\cdot}H_2O$ (50 mg, 0.12 mmol), following the same experimental procedure as for **4**, afforded, after purification by flash chromatography (AcOEt), 8 mg of **5** [62%, $R_f = 0.4$ (10% MeOH/AcOEt), colorless oil]: ^1H NMR (CD_3OD) δ (0.57 (s, 6H), 0.98 (d, $J = 5.9$ Hz, 6H), 1.16 (s, 12H), 2.56 (m, 2H), 2.91 (m, 2H), 4.12 (m, 2H), 4.35 (t, $J = 5.8$ Hz, 2H), 4.90 (br s, 2H), 5.29 (br s, 2H), 6.07 and 6.32 (2 d, AB system, $J = 11.2$ Hz, 4H); ^{13}C NMR (CD_3OD) δ 11.8, 18.0, 20.4, 21.6, 26.7, 27.6, 27.8, 29.1, 29.4, 34.5, 35.6, 36.0, 36.5, 37.4, 42.2, 43.8, 44.6, 45.5, 46.2, 56.4, 65.9, 69.9, 70.0, 110.5, 117.5, 123.3, 134.3, 140.3, 148.3; HRMS (FAB) calcd for $C_{64}H_{106}O_6$ 970.7989 (M^+), found 970.8223.

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Supporting Information Available: ^1H NMR and ^{13}C NMR for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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