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Synthesis and Biological Activity of Two C-7 Methyl Analogues of Vitamin D

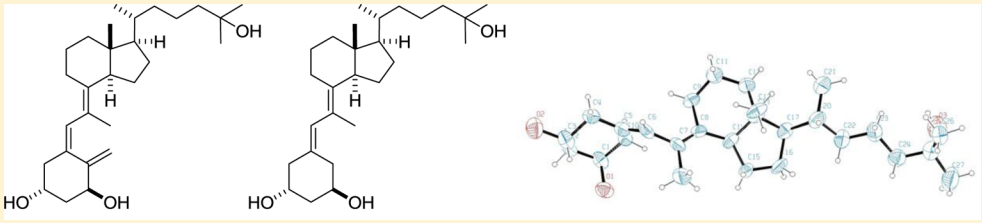
Katarzyna Sokolowska,[†,∥] Diego Carballa,[‡,∥] Samuel Seoane,[§] Román Pérez-Fernández,[§] Antonio Mouriño,*[,‡] and Rafal R. Sicinski*[,†]

[†]Department of Chemistry, University of Warsaw, Pasteura 1, 02-093 Warsaw, Poland

[‡]Departamento de Química Orgánica, Laboratorio de Investigación Ignacio Ribas, Universidad de Santiago de Compostela, 15782 Santiago de Compostela, Spain

[§]Departamento de Fisiología, Centro de Investigación en Medicina Molecular y Enfermedades Crónicas (CIMUS), Universidad de Santiago de Compostela, 15782 Santiago de Compostela, Spain

Supporting Information



ABSTRACT: Two novel vitamin D analogues of the hormone 1α,25-$(OH)_2D_3$ modified at C-7, namely, 7-methyl-1α,25-$(OH)_2D_3$ (**12**) and 7-methyl-1α,25-$(OH)_2$-19-nor-D_3 (**26**), were synthesized and biologically evaluated to gain further insights into the structure−function relationships of vitamin D. Key steps in the synthesis of **12** include the functionalization at C-7 by an efficient regioselective hydrostannylation of an allene precursor, and the construction of the triene framework by a palladium-catalyzed intramolecular cyclization-Suzuki−Miyaura coupling cascade. Since the calcitriol analogue **12** was prone to conversion into its previtamin D form by thermal equilibration, the corresponding 19-nor-compound **26** was also synthesized. The diene moiety of compound **26** was constructed by a modified Julia coupling. UV data as well as X-ray analysis indicate that introduction of the methyl group at C-7 results in a significant deviation from planarity of the 5,7-diene moiety. The new vitamin D analogues **12** and **26** retained good VDR binding ability.

INTRODUCTION

1α,25-Dihydroxyvitamin D_3 [calcitriol, 1α,25-$(OH)_2D_3$ (**4**); Figure 1] is the major metabolite of vitamin D_3 (**1**) formed in living organisms (mammals and birds) by two sequential enzymatic oxidations: 25-hydroxylation converting the vitamin **1** into 25-OH-D_3 (**2**), the major metabolite circulating in the blood, and then 1α-hydroxylation of the latter occurring in the kidney.[1] Calcitriol, 1α,25-$(OH)_2D_3$, is responsible for regulation of more than 200 genes that are involved not only in mineral homeostasis, the classical area of the natural hormone action, but also in cellular differentiation and proliferation, angiogenesis, and apoptosis.[2] It has also been established that 1α,25-$(OH)_2D_3$ is involved in the immune[3] and nervous systems.[4] These various physiological effects of calcitriol are mediated through the vitamin D receptor (VDR),[5] which belongs to the superfamily of nuclear receptors.[6]

Because the VDR is widely distributed in the living organisms and its presence has been confirmed in more than 30 different tissues and cell lines,[7] it is highly probable that the physiological role of calcitriol is even broader. To date, more than 3000 vitamin D compounds have been prepared and tested in search for analogues displaying selective biological profiles (for instance, high anticancer properties and low or negligible calcemic activity).[8] Structural changes of 1α,25-$(OH)_2D_3$ were introduced practically in all positions of its carbon skeleton. However, apart from changes in double bond configurations, a very limited number of analogues with substituents at the triene moiety has been developed. Sheves and Mazur synthesized 6-methyl-vitamin D_3 (**3**) in 1976 and reported its tendency to undergo isomerization to the respective previtamin D form **7**;[9] a few years later, this analogue was also prepared by Yamada's group.[10] As an extension of these studies, we described the synthesis of 1α-hydroxy-6-methyl-vitamin D_3 (**5**) and 6-methyl-calcitriol (**6**) in 2005 and 2010, respectively.[11] Similarly as in the case of **3**, these 6-methylated vitamins very easily equilibrated to their respective previtamin D forms **8** and **9**. Recently, 1α,25-dihydroxy-6-methyl-19-norvitamin D_3 (**10**) and some other 6-substituted 19-norcalcitriol analogues have been prepared by our[12] and Japanese groups.[13] Since the synthesis of 7-substituted calcitriol analogues has never been described (only the 7-fluoro compound **11** in the 19-nor series

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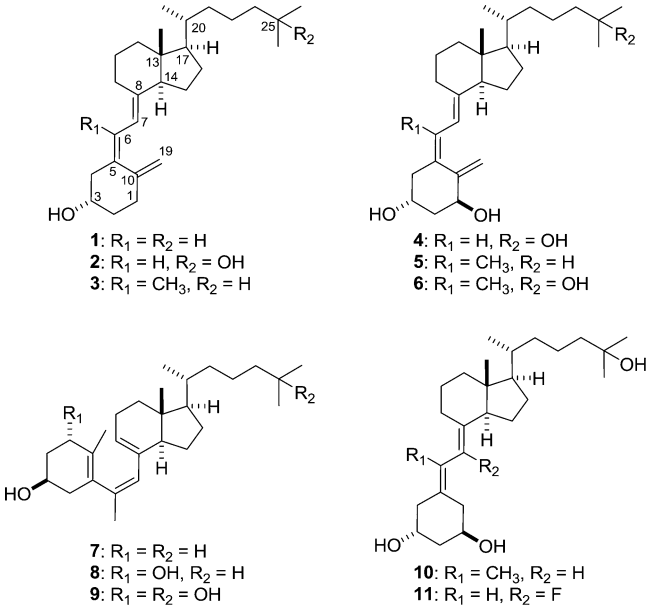


Figure 1. . Chemical structures of vitamin D_3 (**1**), 25-OH-D_3 (**2**), 1α,25-$(OH)_2D_3$ (calcitriol, **4**), and their analogues with substituted B-*seco* ring.

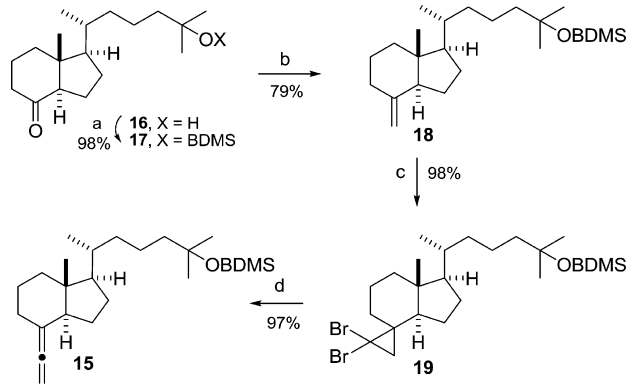
was reported[13] in the patent literature), we have turned our attention to such modification of the vitamin D triene moiety.

RESULTS AND DISCUSSION

We have recently demonstrated the utility of a Pd(0)-catalyzed intramolecular cyclization-Suzuki–Miyaura coupling cascade for the construction of the vitamin D triene system.[11c,14] As an extension of this work, we considered the possibility of using this methodology as a key step in the synthesis of yet unexplored analogues of the natural hormone 1α,25-dihydroxyvitamin D_3 with substituents at C-7. Our plan for the synthesis of the target vitamin D analogue **12** (Scheme 1), possessing a methyl group at C-7, entails a Pd(0)-catalyzed closure of enoltriflate **14**, followed by coupling of the resulting palladium intermediate with boronate **13**. We conceived that the required boronate **13** might be prepared from allene **15**. This reasoning was based on previous results of Yamamoto *et al.* describing that the Pt(0)-catalyzed hydroboration of vinylidene-cyclohexane in the presence of phospine ligands provides the Markovnikov internal boronate in good yield.[15]

Our studies began with the synthesis of allene **15** (Scheme 2) following Okamura's method.[16] 25-Hydroxy-Grundmann's ketone **16**[11b,c,17] was silylated with benzyldimethylsilyl chloride to afford protected ketone **17**. Wittig reaction on ketone **17** to give olefin **18** was followed by cyclopropanation to afford dibromide **19**, which, upon treatment with methyllithium, gave

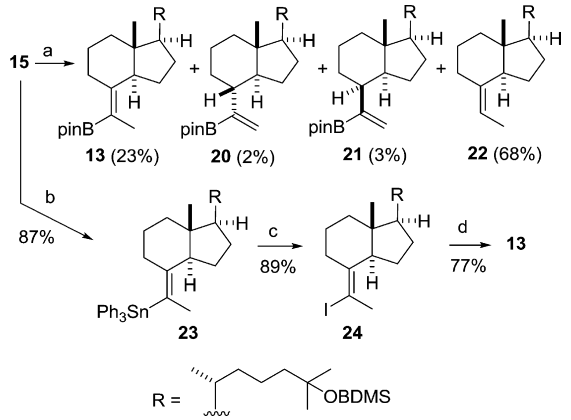
Scheme 2. Synthesis of Protected Allene 15[a]



[a]Reagents and conditions: (a) $Me_2BnSiCl$, Im, DMAP, DMF, rt, 0 °C, 2 h; (b) $Ph_3P{=}CH_2$, THF, 90 °C, 15 min; (c) KO*t*Bu, $CHBr_3$, hexanes, 0 °C, 2 h, rt, 2 h; (d) MeLi, Et_2O, 0 °C.

the desired allene **15** in high yield. Unfortunately, the catalytic hydroboration of **15** with pinacolborane in the presence of $Pt(dba)_2$[18] as the catalyst and tris(trimethoxyphenyl)phosphine as the ligand[15] afforded the desired boronate **13** (Scheme 3) in

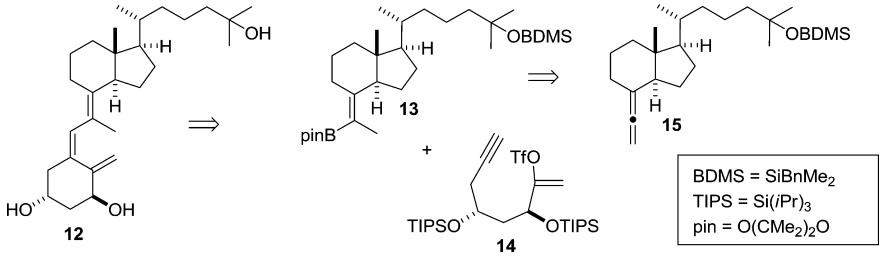
Scheme 3. Synthesis of Boronate 13 from Allene 15[a]



[a]Reagents and conditions: (a) pinBH, $Pt(dba)_2$, TTMPP, PhMe, 50 °C, 14 h; (b) Ph_3SnH, Et_3B, PhMe, rt, 4 h; (c) *N*-Iodosuccinimide, CH_2Cl_2, rt, 1 h; (d) *n*HexLi, $B(OiPr)_3$, THF-PhMe, −78 °C, 30 min; pinacol, rt, 24 h.

only 23% yield, together with stereoisomers **20** (2%) and **21** (3%), and the protonated compound **22** (68%). The use of catecholborane or 9-borabicyclo[3.3.1]nonane as an alternative borane gave a complex mixture of reaction products with no desired boronate **13** detected. The stereochemistry of isomers

Scheme 1. Retrosynthesis of the Target Vitamin D_3 Analogue 12



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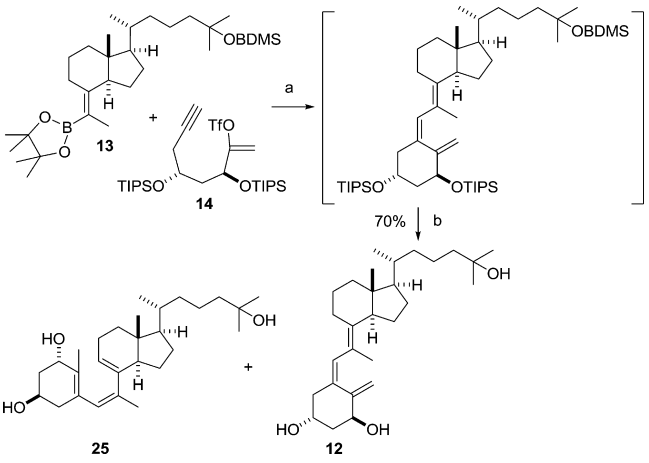
20 and **21** was proposed on the basis of NOE experiments (see the Supporting Information).

Radical hydrostannation of allenes has been previously studied.[19] The Fish, Oshima, Mitchell, and Myers groups have reported that free radical hydrostannation of substituted allenes with trimethyltin hydride[19a,c] or triphenyltin hydride[19b,d] can afford, in certain cases, the most substituted vinylstannane in moderate yield. On the basis of these observations, we expected that hydrostannation of allene **15** would likely provide the desired vinylstannane **23**, which would serve to prepare boronate **13** through vinyl iodide **24** (Scheme 3). Treatment of a mixture of allene **15** and a catalytic amount of triethylborane with triphenyltin hydride[20] in toluene afforded vinylstannane **23** as the only isolable product in 87% yield. We believe that steric factors play a key role in determining the high regioselectivity and yield of the reaction. The availability of the vinylstanne **23** gave us the opportunity to test the Stille coupling with enoltriflate **14**. Unfortunately, heating the reaction mixture in the presence of LiCl and a catalytic amount of $Pd(PPh_3)_4$ in THF led to the recovery of starting materials. At this point, we became aware that the Ph_3Sn group is not usual as a nontransferable organic fragment in Stille coupling reactions. Attempts to prepare the corresponding tri-*n*-butylstannane by reaction of allene **15** with nBu_3SnH were unsuccessful.[21] Therefore, we decided to proceed with the planned synthesis of analogue **12**. Exposure of the vinylstannane **23** to *N*-iodosuccinimide afforded the vinyl iodide **24** in 89% yield. Attempts to prepare boronate **13** by Pd(0)-catalyzed coupling with bis(pinacolato)diboron were unsuccessful, presumably due to unfavorable steric interactions. However, the desired boronate **13** could be prepared in 77% yield from iodide **24** by the sequence: metalation, treatment with triisopropyl borate, and transesterification with pinacol.[22] With boronate **13** in hand, we set out to explore the proposed Pd(0)-catalyzed approach to the target vitamin D analogue **12** (Scheme 4). Thus, an aqueous-THF mixture of boronate **13**, enoltriflate **14**, potassium phosphate, and a catalytic amount of bis(triphenylphosphine)palladium dichloride was vigorously stirred at room temperature for 8 h to provide the protected vitamin D analogue, which was worked up and immediately desilylated with nBu_4NF to give the desired target 1α,25-dihydroxy-7-methyl-vitamin D_3 (**12**) in 70% yield over the two steps after chromatography (ratio of vitamin/previtamin = 4:1). The vitamin structure of **12** was demonstrated by NOE experiments (H9β-H6-H4; 7CH_3-H19*E*). The observation of the previtamin D form **25** in the reaction mixture led us to explore the thermal stability of **12** with a view on biological testing.

Scheme 4. Synthesis of 1α,25-Dihydroxy-7-methyl-vitamin D_3 (12)[a]



[a]Reagents and conditions: (a) $PdCl_2(PPh_3)_2$, K_3PO_4, THF−H_2O, rt, 8 h; (b) nBu_4NF, THF, 10 h.

The obtained mixture (4:1) of the vitamin D analogue **12** and its previtamin D isomer **25** was subjected to separation by HPLC. Then, compound **12** was dissolved in CD_3OD and stirred at room temperature to study its thermal conversion. The following vitamin D−previtamin D ratios were observed: 24 h (1:0.3), 48 h (1:0.7), 78 h (1:1.5), 138 h (1:4.1), 178 h (1:13). These results indicate that the vitamin D analogue **12** is slowly transformed into its more stable previtamin D form **25**. Compound **12** was subjected to biological testing immediately upon its isolation.

A strong bias toward the previtamin form observed for 7-methyl calcitriol encouraged us to prepare its 19-nor analogue **26** (Scheme 5) in which such equilibration is not possible.[23] As a key retrospective step leading to the target compound, we envisioned the Julia olefination between sulfone **27** and the known[24] protected dihydroxyketone **28**. Such a synthetic strategy, elaborated by Kittaka et al.,[25] was successfully used by us in the preparation of 19-norcalcitriol analogues with A-ring modifications.[26] The CD fragment required for this coupling would be obtained from the hydrindane compound **29** substituted with a cyanoethylidene group. Our synthesis of **27** began with Horner−Emmons reaction on the known,[27] TES-protected 25-hydroxy-Grundmann's ketone **30** (Scheme 6) with diethylcyanomethylphosphonate anion to provide a 9:1 mixture of nitrile **31** and its *Z*-isomer in almost quantitative yield. Alkylation of this mixture with methyl iodide, using LDA for nitrile deprotonation, furnished the mixture of methylated nitrile **29** together with its geometrical isomer. Thus, only the desired monoalkylation process occurred in this case. That is somewhat surprising, because similar reactions described in the literature resulted in formation of mixtures of mono- and dimethylated nitriles (the latter with a double bond shifted to the γ,δ-position).[28,29] Reduction of these compounds with DIBAL-H, followed by chromatographical separation of products, afforded the desired α,β-unsaturated aldehyde **32**. Reduction of this compound with $NaBH_4$ gave the allylic alcohol **33**, which was transformed into the allylic sulfone **27** by Kittaka's procedure.[24] Thus, Mitsunobu reaction on **33** with 2-mercaptobenzothiazole, followed by oxidation of the formed sulfide, gave the allylic sulfone **27**. With this compound in hand, we performed a modified Julia olefination by coupling of its anion, generated with LiHMDS, with the protected ketone **28**, prepared from quinic acid as previously described.[23] Julia coupling, as above, was an efficient process providing the expected protected 19-norvitamin D compound **34** in 82% yield. Deprotection of **34** with nBu_4NF and HPLC separation gave 1α,25-dihydroxy-7-methyl-19-norvitamin D_3 (**26**). The UV absorption maximum of this product (λ_{max} 240 nm, ε = 5800), blue-shifted in comparison with that of 1α,25-dihydroxy-19-norvitamins by ca. 12 nm, as well as a lower extinction coefficient value, seemed to indicate a significant deviation of the intercyclic diene moiety from planarity (a large blue shift of the UV absorbance maximum was also observed for the 6-methyl-substituted analogue of the natural hormone).[30] This fact could, in turn, decrease the ability of the synthesized analogue to bind VDR and affect its biological activity.

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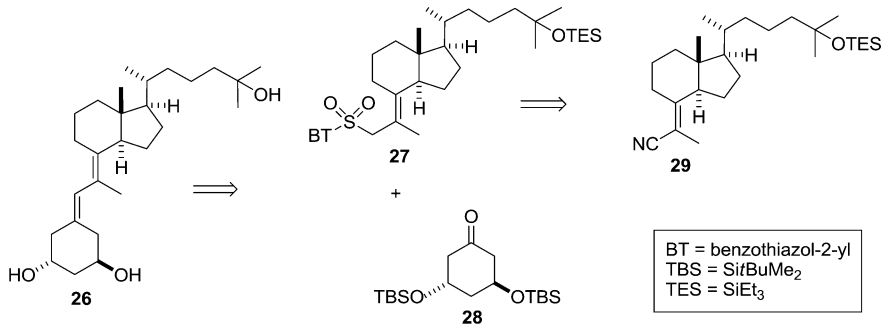
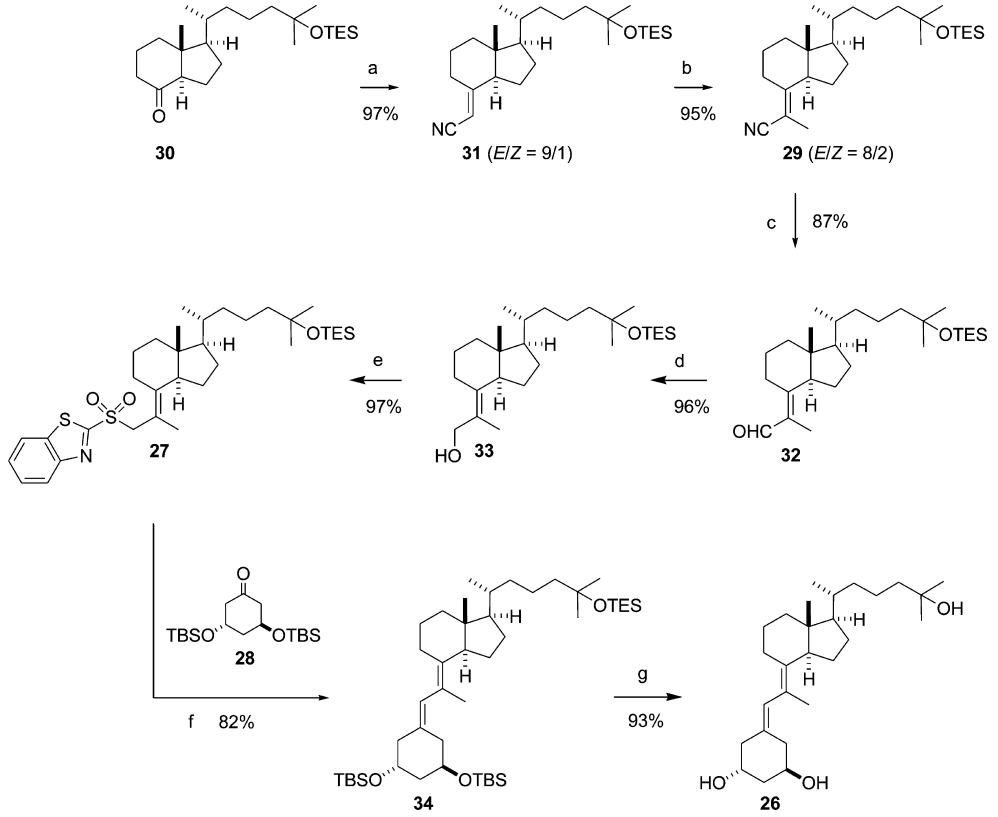
Scheme 5. Retrosynthesis of the Target Vitamin D_3 Analogue 26



Scheme 6. Synthesis of 1α,25-Dihydroxy-7-methyl-19-norvitamin D_3 (26)[a]



[a]Reagents and conditions: (a) NaH, $(EtO)_2P(O)CH_2CN$, THF, 0 °C to rt; (b) LDA, MeI, DMPU, THF, −78 to 0 °C; (c) iBu_2AlH-H, toluene, −78 °C; (d) $NaBH_4$, MeOH, 0 °C to rt; (e) 2-mercaptobenzothiazole, DIAD, Ph_3P, CH_2Cl_2, 0 °C, then $(NH_4)_6Mo_7O_{24} \times 4H_2O$, 30% H_2O_2, EtOH, 0 °C to rt; (f) LiHMDS, ketone **28**, THF, −78 to −30 °C; (g) nBu_4NF, THF, rt.

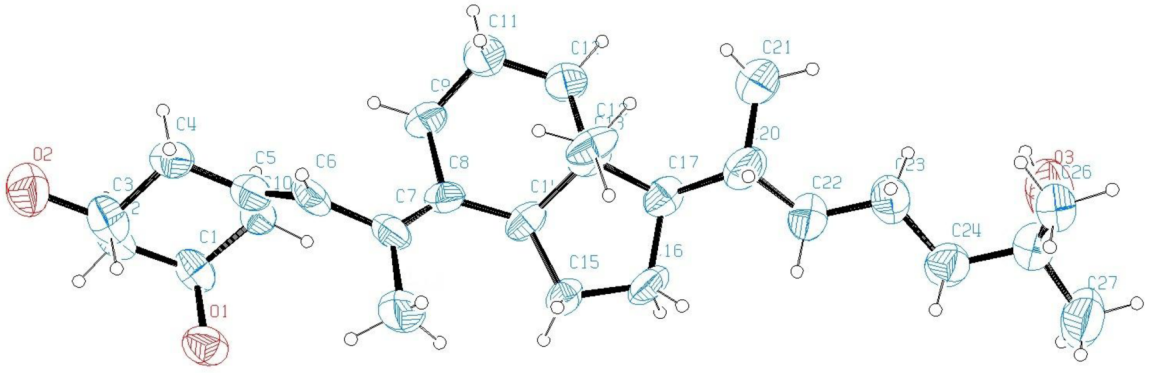


Figure 2. ORTEP drawing derived from the single-crystal X-ray analysis of **19**-norvitamin **26**.

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Literature data prove that the natural hormone[31] and the vast majority of other 1α-hydroxylated vitamin D compounds adopt in the crystalline state exclusively the β-form of their A rings (with an exception of tacalcitol monohydrate[32] and calcipotriol anhydrate[33]) characterized by equatorial and axial disposition of 1α- and 3β-hydroxyls, respectively, whereas the 5,7-diene fragment of their B-*seco* rings is almost planar. Crystallographic data from the growing number of solved crystalline complexes of the vitamin D receptor (VDR) and vitamin D analogues[34] indicate the *s-trans* conformation of the ligand's intercyclic C(5)=C(6)−C(7)=C(8) diene moiety, exhibiting a torsion angle of ca. −150°. In the VDR ligand binding pocket, this part of the vitamin D molecule is tightly packed in the hydrophobic channel formed by Ser 275 and Trp 286 on one side and Leu 233 on the other side.[35]

Our molecular modeling studies of 19-norvitamin **26**, carried out using the PCModel (v9.0, Serena Software, Bloomington, IN) program, led to two low-energy conformers of similar steric energies, but significantly different intercyclic torsion angles (ca. 74° and −105°). In order to confirm the distortion of the conjugated 5,7-diene fragment in **26**, we attempted to crystallize this compound. After successful crystallization from ethyl formate, the structure of the analogue was solved using single-crystal X-ray diffraction. The ORTEP representation of the solid-state conformation of **26** is shown in Figure 2. Interestingly, the cyclohexane ring A of the analogue adopts exclusively the α-chair form. Moreover, the intercyclic 5,7-diene bridge significantly departs from planarity, as is evident from the value (74.9°) of C(5−6−7−8) torsion angle.

The synthesized vitamin D compounds, possessing 7-methyl substituents, were assessed for their biological in vitro activities (Table 1). The VDR binding affinity[36] of compound **12** was approximately 1 order of magnitude smaller in comparison with 1α,25-$(OH)_2D_3$, whereas 19-nor analogue **26** was 15 times less potent. The activity of the vitamins **12** and **26** in inducing transcription of a vitamin D target gene was examined using the 24-hydroxylase (CYP-24) promoter.[37] Both compound **12** and calcitriol induced a dose-dependent activation of the CYP24A1 gene, as measured by luciferase activity, but the former was 4 times less potent. Rather unexpectedly, the 19-nor compound **26** showed transcriptional activity decreased by 3 orders of magnitude. Obtaining an explanation for the intriguing differences in biological potency of the two tested vitamin D analogues would require further investigation.

Table 1. VDR Binding Properties and Transcriptional Activities of the Vitamin D Analogues 12 and 26

	VDR binding		24-OHase transcription	
compd no.	ED_{50} (M)	ratio	ED_{50} (M)	ratio
4	5.5×10^{-9}	1	4.5×10^{-9}	1
12	5×10^{-8}	9	2×10^{-8}	4
4	2×10^{-10}	1	3×10^{-10}	1
26	3×10^{-9}	15	4×10^{-7}	1300

CONCLUSIONS

The goal of the presented studies was to broaden structure−activity relationships in calcitriol analogues and explore the previously unknown alteration of the vitamin D skeleton, namely, introduction of an alkyl group into C-7. Two novel vitamin D compounds have been efficiently synthesized, 7-methyl-calcitriol (**12**) and the corresponding compound lacking a 19-exomethylene moiety, 7-methyl-19-norcalcitriol (**26**). Key steps in the synthesis of **12** include the functionalization at C-7 by an efficient regioselective hydrostannylation of an allene precursor, and the construction of the triene framework by a palladium-catalyzed intramolecular cyclization-Suzuki−Miyaura coupling cascade. The diene moiety of compound **26** was constructed by a modified Julia coupling. The structures of obtained vitamin D analogues have been established by spectroscopic methods together with X-ray diffraction studies, which confirmed a significant distortion of the 5,7-diene fragment in the latter analogue, predicted on the basis of its molecular modeling. Significant deviation from planarity must also be present in the intercyclic diene bridge of compound **12**, as evident from its UV spectrum, which significantly differs from that of the parent calcitriol (**4**). Also, in comparison with the natural hormone, 7-methyl calcitriol has an increased tendency to undergo isomerization to its previtamin form. Interestingly, a similar shift to the previtamin D form was observed in 6-methylated vitamin D compounds **3**, **5**, and **6**, which were also characterized by the anomalous UV spectra. 7-Methyl calcitriol (**12**) showed similar activity as calcitriol in all biological assays. However, rather to our surprise, its counterpart **26**, lacking the 10-exomethylene group, was characterized by drastically reduced biological potency. In conclusion, our results demonstrate that substitution of C-7 with the methyl group modulates the biological action of the vitamin D analogues and this structural modification, unknown to date, can be of some interest only in compounds possessing the intact 5,7,10(19)-triene system.

EXPERIMENTAL SECTION

(1*R*,3a*R*,7a*R*)-1-[(*R*)-5′-(Benzyldimethylsilyl)oxy-1′,5′-(dimethyl)hexyl]-7a-methyl-octahydro-inden-4-one (17). Imidazole (1.04 g, 15.32 mmol), DMAP (156 mg, 1.28 mmol), and benzyldimethylsilyl chloride (1.4 mL, 7.68 mmol) were successively added to a solution of **16** (1.8 g, 6.42 mmol) in dry DMF (40 mL). The mixture was stirred at rt for 2 h. The reaction was quenched by the addition of H_2O (50 mL). The aqueous phase was extracted with *tert*-butyl methyl ether (3 × 30 mL). The combined organic phases were dried and concentrated. The residue was purified by flash chromatography (SiO_2, 5% EtOAc/hexanes) to give protected hydroxy ketone **17** (2.66 g, 97%, colorless oil): $[\alpha]_D^{25}$ +4.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.24−6.97 (5H, m), 2.44 (1H, dd, *J* = 11.4, 7.5 Hz), 2.13 (2H, s), 1.19 (6H, s), 0.95 (3H, d, *J* = 5.7 Hz), 0.64 (3H, s), 0.08 (6H, s); ^{13}C NMR (63 MHz, $CDCl_3$) δ 211.7 (C), 139.6 (C), 128.2 (CH), 127.8 (CH), 123.7 (CH), 74.1 (C), 61.7 (CH), 56.5 (CH), 49.7 (C), 45.0 (CH_2), 40.8 (CH_2), 38.8 (CH_2), 36.1 (CH_2), 35.3 (CH), 29.8 (CH_3), 29.7 (CH_3), 28.7 (CH_2), 27.4 (CH_2), 23.9 (CH_2), 20.5 (CH_2), 18.9 (CH_2), 18.5 (CH_3), 12.3 (CH_3), 0.5 (CH_3); IR (film) 3022, 2959, 2874, 1715, 1600; HRMS (EI^+) exact mass calculated for $C_{27}H_{44}O_2Si$ $(M)^+$ 428.3111, measured 428.3119.

(1*R*,3a*R*,7a*R*)-1-[(*R*)-(Benzyldimethylsilyl)oxy-1′,5′-(dimethyl)hexyl]-7a-methyl-4-methylene-octahydro-indene (18). A solution of *n*BuLi in hexanes (5.7 mL, 1.42 M, 8.07 mmol) was added dropwise to a suspension of Ph_3PCH_3Br (2.88 g, 8.07 mmol) in dry THF (35 mL). The mixture was heated at 90 °C, and a solution of **17** (2.66 g, 6.21 mmol) in dry THF (25 mL) was transferred via cannula. The reaction mixture was stirred at the same temperature for 15 min and then allowed to reach rt. The mixture was washed with saturated NH_4Cl (30 mL). The THF was removed in vacuo, and the aqueous phase was extracted with hexanes (3 × 20 mL). The combined organic phases were dried and concentrated. The residue was purified by flash chromatography (SiO_2, hexanes) to give **18** (2.09 g, 79%, colorless oil): $[\alpha]_D^{25}$ +55.1 (*c* 1.1, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.25−7.01 (5H, m), 4.78 (1H, d, *J* = 1.6 Hz), 4.51 (1H, d, *J* = 1.6 Hz), 2.36−2.24 (1H, m), 2.17 (2H, s), 1.22 (6H, s),

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0.97 (3H, d, J = 6.2 Hz), 0.61 (3H, s), 0.12 (6H, s); ^{13}C NMR (63 MHz, $CDCl_3$) δ 149.5 (C), 139.8 (C), 128.4 (CH), 127.9 (CH), 123.8 (CH), 105.0 (CH_2), 74.3 (C), 56.4 (CH), 55.3 (CH), 45.2 (CH_2), 45.0 (C), 40.2 (CH_2), 36.4 (CH_2), 36.1 (CH), 35.4 (CH_2), 29.9 (CH_3), 29.8 (CH_3), 28.8 (CH_2), 27.7 (CH_2), 23.8 (CH_2), 22.2 (CH_2), 20.8 (CH_2), 18.8 (CH_3), 11.7 (CH_3), 0.7 (CH_3); IR (film) 2945, 2874, 1650; HRMS (EI$^+$) exact mass calculated for $C_{28}H_{46}OSi$ (M)$^+$ 426.3318, measured 426.3326.

(1*R*,3a*R*,7a*R*)-1-[(*R*)-(Benzyldimethylsilyl)oxy-1′,5′-(dimethyl) shyhexyl]-7a-methyl-4-ethenylidene-octahydro-indene (15). KO*t*Bu (5.5 g, 49.0 mmol) was added to a solution of **18** (2.09 g, 4.9 mmol) in dry hexanes (50 mL). The suspension was cooled to 0 °C, and $CHBr_3$ (4.3 mL, 49.0 mmol) was slowly added dropwise over a period of 2 h. The reaction mixture was stirred at rt for 2 h. The reaction was quenched by the addition of H_2O (50 mL). The aqueous phase was extracted with hexanes (3 × 25 mL). The combined organic phases were dried and concentrated. The excess of $CHBr_3$ was removed by distillation under reduced pressure (30 mmHg, 60 °C) to give 2,2-dibromospiro[cyclopropane-1,4′-(1′*R*,3a′*R*,7a′*R*)-1′-[(*R*)-(benzyldimethylsilyl)oxy-1″,5″-(dimethyl)hexyl]-7a′-methyl-octahydro-indene] (**19**, 2.87 g, 98%, pale yellowish oil) that was used in the next reaction without further purification: $[\alpha]_D^{25}$ −13.3 (c 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.24−7.00 (5H, m), 2.13 (2H, s), 1.19 (6H, s), 0.95 (3H, d, J = 6.5 Hz), 0.70 (3H, s), 0.08 (6H, s); ^{13}C NMR (63 MHz, $CDCl_3$) δ 139.8 (C), 128.4 (CH), 127.9 (CH), 123.8 (CH), 74.3 (C), 55.0 (CH), 51.3 (CH), 46.9 (C), 45.2 (CH_2), 39.2 (CH_2), 38.4 (CH_2), 36.5 (C), 36.3 (CH_2), 35.2 (CH), 33.5 (C), 29.9 (CH_3), 29.8 (CH_3), 29.3 (CH_2), 28.9 (CH_2), 27.6 (CH_2), 24.3 (CH_2), 21.6 (CH_2), 20.8 (CH_2), 18.9 (CH_3), 12.2 (CH_3), 0.7 (CH_3); IR (film) 3081, 3060, 3024, 2951, 2931, 2868, 1935, 1715, 1601.

A solution of MeLi in Et_2O (9 mL, 1.6 M, 14.37 mmol) was slowly added dropwise to a 0 °C cooled solution of **19** (2.87 g, 4.79 mmol) in Et_2O over a period of 1.5 h. H_2O (2 mL) was slowly added dropwise. The mixture was diluted with H_2O (50 mL), and the resulting mixture was extracted with hexanes (3 × 25 mL). The combined organic phases were dried and concentrated. The residue was purified by flash chromatography (SiO_2, hexanes) to give **15** (2.04 g, 97%, colorless oil): $[\alpha]_D^{25}$ +43.9 (c 1.4, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.24−7.01 (5H, m), 4.63 (2H, t, J = 4.1 Hz), 2.38−2.25 (1H, m), 2.13 (2H, s), 1.18 (6H, s), 0.92 (3H, d, J = 6.4 Hz), 0.65 (3H, s), 0.07 (6H, s); ^{13}C NMR (63 MHz, $CDCl_3$) δ 203.4 (C), 139.9 (C), 128.4 (CH), 128.0 (CH), 123.9 (CH), 101.9 (C), 74.6 (CH_2), 74.4 (C), 56.1 (CH), 51.8 (CH), 45.3 (CH_2), 44.5 (C), 40.0 (CH_2), 36.5 (CH_2), 36.2 (CH), 31.0 (CH_2), 29.9 (CH_3), 29.8 (CH_3), 27.7 (CH_2), 23.3 (CH_2), 22.8 (CH_2), 20.8 (CH_2), 18.8 (CH_3), 11.9 (CH_3), 0.7 (CH_3); IR (film) 3082, 3060, 2948, 1962, 1602; HRMS (EI$^+$) exact mass calculated for $C_{29}H_{46}OSi$ (M)$^+$ 438.3318, measured 438.3297.

(1*R*,3a*R*,7a*R*,*Z*)-1-[(*R*)-(Benzyldimethylsilyl)oxy-1′,5′-(dimethyl)hexyl]-7a-methyl-4-[1″-(4‴,4‴,5‴,5‴-tetramethyl-1‴,3‴-dioxa-2‴-borolan-2‴-yl)ethylidene]-octahydro-indene (13) by Pt(0)-Catalyzed Hydroboration of Allene 15. Tris(2,4,6-trimethoxyphenyl)phosphine (10 mg, 0.02 mmol), a solution of allene **15** (140 mg, 0.319 mmol) in dry toluene (3 mL), and pinacolborane (70 μL, 0.478 mmol) were successively added to a suspension of $Pt(dba)_2$ (6 mg, 0.01 mmol) in dry toluene (2 mL). The reaction mixture was stirred at 50 °C for 14 h and then concentrated in vacuo. Purification of the residue by flash chromatography (SiO_2, 2% EtOAc/hexanes) afforded the compound **22** (95 mg, 68%, colorless oil), and a mixture of compounds, which were separated by HPLC (21.2 × 250 mm Luna Silica column, 10 mL/min, 5% EtOAc/hexanes) to give the minor isomers **20** (4 mg, 2%, Rv 90 mL) and **21** (5 mg, 3%, Rv 93 mL), and the boronate **13** (41 mg, 23%, Rv 102 mL).

13: $[\alpha]_D^{25}$ +58.6 (c 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23−7.01 (5H, m), 2.74 (1H, d), 2.13 (2H, s), 1.78 (3H, s), 1.28 (12H, s), 1.18 (6H, s), 0.94 (3H, d, J = 6.2 Hz), 0.73 (3H, s), 0.08 (6H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.4 (C); 139.9 (C); 128.4 (CH); 127.9 (CH), 123.8 (CH), 82.8 (C), 74.4 (C), 58.5 (CH), 55.2 (CH), 47.4 (C), 45.3 (CH_2), 41.5 (CH_2), 37.4 (CH_2), 36.5 (CH_2), 36.2 (CH), 29.9 (CH_3), 29.8 (CH_3), 28.9 (CH_2), 28.4 (CH_2), 26.5 (CH_2), 25.0 (CH_2), 24.8 (CH_3), 24.7 (CH_3), 20.9 (CH_2), 19.2 (CH_3), 16.0 (CH_3), 12.9 (CH_3), 0.7 (CH_3), (the C peak near the boron atom is missing); IR (film) 3080, 2930, 1712; HRMS (EI$^+$) exact mass calculated for $C_{35}H_{59}BO_3Si$ (M)$^+$ 566.4327, measured 566.4321.

20: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.24−703 (5H, m; H-Ph), 5.70 and 5.57 (1H and 1H, each d, J = 3.3 Hz; 2″-H_2), 2.12 (2H, s; C$\underline{H}_2$Ph), 1.25 (12H, s; 4‴-$(CH_3)_2$ and 5‴-$(CH_3)_2$), 1.17 (6H, s; 5′-CH_3 and 6′-H_3), 0.92 (3H, d, J = 6.5 Hz; 1′-CH_3), 0.72 (3H, s; 7a-CH_3), 0.07 (6H, s; Me_2Si); ^{13}C NMR (63 MHz, $CDCl_3$) δ 139.9 (C; Ph), 128.4 (CH; Ph), 128.0 (CH; Ph), 127.3 (CH_2; C-2″), 123.8 (CH; Ph), 83.0 (C; C-4‴ and C-5‴), 74.4 (C; C-5′), 56.3 (CH), 54.0 (CH), 45.3 (CH_2), 43.1 (CH), 43.0 (C; C-7a), 40.1 (CH_2), 36.5 (CH_2), 35.8(CH), 32.9 (CH_2), 30.0 and (CH_3; 5′-CH_3 and C-6′), 28.9 (CH_2), 27.7 (CH_2), 24.9 (CH_2), 24.7 (CH_3; 4‴-$(CH_3)_2$ and 5‴-$(CH_3)_2$), 22.3 (CH_2), 20.9 (CH_2), 18.7 (CH_3), 11.7 (CH_3), 0.7 (CH_3; Me_2Si), (the C peak near the boron atom is missing).

21: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.24−6.99 (5H, m; H-Ph), 5.77 (2H, s; 2″-H_2), 2.12 (2H, s; C$\underline{H}_2$Ph), 1.32−1.22 (12H, s; 4‴-$(CH_3)_2$ and 5‴-$(CH_3)_2$), 1.17 (6H, s; 5′-CH_3 and 6′-H_3), 0.97 (3H, d, J = 6.5 Hz; 1′-CH_3), 0.68 (3H, s; 7a-CH_3), 0.07 (6H, s; Me_2Si). ^{13}C NMR (63 MHz, $CDCl_3$) δ 139.9 (C; Ph), 128.4 (CH; Ph), 127.9 (CH; Ph), 126.2 (CH_2; C-2″), 123.8 (CH; Ph), 83.3 (C; C-4‴ and C-5‴), 74.4 (C; C-5′), 56.7 (CH), 51.7 (CH), 45.3 (CH_2), 43.4 (C; C-7a), 40.9 (CH_2), 39.0 (CH), 36.4 (CH_2), 35.5 (CH), 29.9 and 29.8 (CH_3; 5′-CH_3 and C-6′), 29.3 (CH_2), 28.9 (CH_2), 27.6 (CH_2), 25.8 (CH_2), 24.9 and 24.5 (CH_3; 4‴-$(CH_3)_2$ and 5‴-$(CH_3)_2$), 20.8 (CH_2), 20.0 (CH_2), 18.7 (CH_3), 12.7 (CH_3), 0.7 (CH_3; Me_2Si), (the C peak near the boron atom is missing).

22: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.25−7.04 (5H, m), 5.32 (1H, q, J = 7.1 Hz), 2.16 (2H, s), 1.69 (3H, d, J = 7.1 Hz), 1.22 (6H, s), 0.97 (3H, d, J = 6.3 Hz), 0.72 (3H, s), 0.11 (6H, s); ^{13}C NMR (63 MHz, $CDCl_3$) δ 139.9 (C), 139.0 (C), 128.4 (CH), 127.9 (CH), 123.8 (CH), 117.4 (CH), 74.4 (C), 55.7 (CH), 55.0 (CH), 46.0 (C), 45.3 (CH_2), 41.0 (CH_2), 38.9 (CH_2), 36.6 (CH_2), 36.3 (CH), 29.9 (CH_3), 29.8 (CH_3), 28.9 (CH_2), 28.5 (CH_2), 25.6 (CH_2), 24.2 (CH_2), 20.9 (CH_2), 19.1 (CH_3), 13.6 (CH_3), 12.4 (CH_3), 0.67 (CH_3); HRMS (EI$^+$) exact mass calculated for $C_{29}H_{48}OSi$ (M)$^+$ 440.3474, measured 440.3469.

(1*R*,3a*R*,7a*R*,*E*)-1-[(*R*)-(Benzyldimethylsilyl)oxy-1′,5′-(dimethyl)hexyl]-7a-methyl-4-(1″-iodoethyliden)-octahydro-indene (24). A solution of **15** (250 mg, 0.57 mmol) in dry toluene and a solution of Et_3B in THF (60 μL, 1 M, 0.06 mmol) were successively added to a solution of Ph_3SnH[19d] (240 mg, 0.684 mmol) in dry toluene (4 mL). The reaction mixture was stirred at rt for 4 h and then concentrated. Purification of the residue by flash chromatography (SiO_2 washed with 1% Et_3N/hexanes, hexanes) afforded (1*R*,3a*R*,7a*R*,*E*)-1-[(*R*)-(benzyldimethylsilyl)oxy-1′,5′-(dimethyl)-hexyl]-7a-methyl-4-[1″-(triphenylstannyl)ethylidene]-octahydro-indene (**23**, 390 mg, 87%, colorless oil): $[\alpha]_D^{25}$ +61.2 (c 1.4, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.77−7.47 (6H, m), 7.47−7.29 (9H, m), 7.25−6.99 (5H, m), 2.15 (2H, s), 2.10 (3H, s), 1.21 (6H, s), 0.96 (3H, d, J = 7.5 Hz), 0.83 (3H, s), 0.10 (6H, s); ^{13}C NMR (63 MHz, $CDCl_3$) δ 150.4 (C), 140.7 (C), 139.9 (C), 137.1 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 128.0 (CH), 127.3 (C), 123.9 (CH), 74.4 (C), 58.8 (CH), 54.9 (CH), 47.1 (C), 45.2 (CH_2), 43.6 (CH_2), 40.9 (CH_2), 36.5 (CH_2), 36.2 (CH), 30.0 (CH_3), 29.9 (CH_3), 28.9 (CH_2), 28.5 (CH_2), 26.9 (CH_2), 24.3 (CH_2), 21.8 (CH_3), 21.0 (CH_2), 19.2 (CH_3), 12.9 (CH_3), 0.7 (CH_3).

N-Iodosuccinimide (128 mg, 0.568 mmol) was added to a solution of **23** (390 mg, 0.494 mmol) in dry CH_2Cl_2 (15 mL). The reaction mixture was stirred at rt for 1 h. The reaction was quenched by the addition of H_2O (15 mL), and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were dried and concentrated. The residue was purified by flash chromatography (SiO_2, 2% Et_2O/hexanes) to give vinyl iodide **24** (250 mg, 89%, colorless oil): $[\alpha]_D^{25}$ +76.2 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25−7.04 (5H, m; Ph-H), 2.88 (1H, broad dt, J = 13.6, 3.0 Hz; 5β-H), 2.76 (3H, s; 2″-H_3), 2.17 (2H, s; C$\underline{H}_2$Ph), 1.22 (6H, s; 5′-CH_3 and 6′-H_3), 0.98 (3H, d, J = 6.2 Hz; 1′-CH_3), 0.72 (3H, s; 7a-CH_3), 0.12 (6H, s; Me_2Si); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.1 (C), 139.8 (C; Ph), 128.4 (CH; Ph), 127.9 (CH; Ph), 123.8 (CH; Ph), 95.5 (C),

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74.3 (C; C-5′), 56.2 (CH), 54.5 (CH), 47.1 (C, C-7a), 46.0 (CH_2), 45.2 (CH_2), 40.7 (CH_2), 36.4 (CH_2), 36.1 (CH), 32.4 (CH_3), 29.9 and 29.8 (CH_3; 5′-CH_3 and C-6′), 28.8 (CH_2), 28.2 (CH_2), 27.2 (CH_2), 23.5 (CH_2), 20.9 (CH_2), 19.1 (CH_3), 12.8 (CH_3), 0.7 (CH_3; Me_2Si); IR (film) 3081, 2946, 1929 cm^{-1}. HRMS (EI^+) exact mass calculated for $C_{28}H_{44}IOSi$ $(M - CH_3)^+$ 551.2206, measured 551.2192.

(1*R*,3a*R*,7a*R*,*Z*)-1-[(*R*)-(Benzyldimethylsilyl)oxy-1′,5′-(dimethyl)hexyl]-7a-methyl-4-[1″-(4‴,4‴,5‴,5‴-tetramethyl-1‴,3‴-dioxa-2‴-borolan-2‴-yl)ethylidene]-octahydro-indene (13) from Vinyl Iodide 24. A solution of *n*HexLi in hexanes (93 μL, 2.2 M, 0.203 mmol) was added dropwise to a −78 °C cooled solution of **24** (105 mg, 0.185 mmol) and B(*i*PrO)$_3$ (55 μL, 0.241 mmol) in dry THF (1 mL) and dry toluene (3 mL). The reaction mixture was stirred at −78 °C for 1 h; then, pinacol (33 mg, 0.278 mmol) was added and the mixture was stirred at rt for 24 h. The reaction was quenched by addition of H_2O (15 mL) and saturated NH_4Cl (5 mL). The aqueous phase was extracted with EtOAc (3 × 15 mL), and the combined organic phases were dried and concentrated. The residue was purified by flash chromatography (SiO_2, 1% EtOAc/hexanes) to afford compound **22** (17 mg, 21%) and the desired vinylboronate **13** (81 mg, 77%, colorless oil).

1α,25-Dihydroxy-7-methyl-vitamin D$_3$ (12). Aqueous K_3PO_4 (2 M, 4 mL) and $PdCl_2(PPh_3)_2$ (5 mg, 0.006 mmol) were successively added to a solution of boronate **13** (75 mg, 0.132 mmol) and enoltriflate **14** (87 mg, 0.145 mmol) in THF (6 mL). The reaction mixture was vigorously stirred at rt for 8 h. Water (10 mL) was added, and the aqueous phase was extracted with ethyl ether (3 × 5 mL). The combined organic phases were dried and concentrated. The residue was dissolved in dry THF (5 mL), and then a solution of tetrabutylammonium fluoride in THF (1.2 mL, 1 M, 1.19 mmol) was added. The reaction mixture was stirred at rt for 10 h. The reaction was quenched by the addition of H_2O (20 mL), and the aqueous phase was extracted with ethyl acetate (3 × 15 mL). The combined organic phases were dried and concentrated. The residue was purified by flash chromatography (SiO_2, 5−20% *i*PrOH/hexanes) to give the vitamin **12** (40 mg, 70%, white foam) contaminated with its previtamin form **25**. Further purification by HPLC (10 × 250 mm Luna Silica column, 4 mL/min, 15% *i*PrOH/hexanes) provided analytically pure (>95%) samples of **12** (Rv 177 mL) and **25** (Rv 215 mL), which were used for biological assays.

12: UV (96% EtOH) λ_{max} (ε) 258 nm (11800 mol^{-1} m^3 cm^{-1}); ^{1}H NMR (CD_3OD, 400 MHz) δ 6.07 (1H, s; 6-H), 5.10 and 4.97 (1H and 1H, each s; 19-H_2), 4.41 (1H, dd, J = 9.0, 4.4 Hz; 1β- or 3α-H), 4.18−4.12 (1H, m; 1β- or 3α-H), 2.75−2.68 (1H, m; 9β-H), 2.41 (1H, broad d, J∼ 13.2 Hz), 2.24 (1H, dd, J = 13.2, 5.3 Hz), 1.80 (3H, s; 7-CH_3), 1.16 (6H, s; 26- and 27-H_3), 0.96 (3H, d, J = 6.4 Hz; 21-H_3), 0.70 (3H, s; 18-H_3); ^{13}C NMR (CD_3OD, 101 MHz): 150.9, 135.6, 135.5, 133.5, 126.3, 110.0, 71.5, 70.2, 67.5, 58.1, 56.5, 48.2, 45.3, 45.1, 43.6, 42.9, 37.9, 37.6, 34.6, 29.4, 29.3, 29.1, 28.1, 24.9, 22.0, 19.8, 19.7, 13.3; IR (KBr) 3356, 2939, 2870, 1635; HRMS (ESI-TOF$^+$) exact mass calculated for $C_{28}H_{46}O_3Na$ $(M + Na)^+$ 453.3339, measured 453.3323.

25: UV (96% EtOH) λ_{max} (ε) 252 nm (5800 mol^{-1} m^3 cm^{-1}); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.80 (1H, s), 5.31−5.26 (1H, m), 4.18 (1H, br s), 4.05−3.96 (1H, m), 2.38 (1H, dd, J = 16.6, 4.3 Hz), 1.83 (3H, s), 1.77 (3H, s), 1.22 (6H, s), 0.96 (3H, d, J = 6.5 Hz), 0.75(3H, s);^{13}C NMR ($CDCl_3$, 63 MHz) δ 140.3 (C), 139.8 (C), 130.3 (C), 129.4 (C), 124.5 (CH), 123.2 (CH), 71.1 (C), 70.9 (CH), 64.3 (CH), 54.2 (CH), 50.3 (CH), 44.3 (CH_2), 42.3 (C), 40.6 (CH_2), 39.7 (CH_2), 36.3 (CH_2), 36.0 (CH), 36.0 (CH_2), 29.3 (CH_3), 29.1 (CH_3), 28.2 (CH_2), 25.6 (CH_3), 24.5 (CH_2), 23.3 (CH_2), 20.7 (CH_2), 18.8 (CH_3), 17.4 (CH_3), 11.6 (CH_3); HRMS (ESI-TOF$^+$) exact mass calculated for $C_{28}H_{46}O_3Na$ $(M + Na)^+$ 453.3339, measured 453.3329.

[(1′*R*,3a′*S*,7a′*R*)-1′-[(*R*)-1″,5″-Dimethyl-5″-[(triethylsilyl)oxy]-hexyl]-7a′-methyloctahydro-inden-(4′*E*)-ylidene]-acetonitrile (31). $(EtO)_2P(O)CH_2CN$ (0.195 mL, 1.22 mmol) was added to a suspension of NaH (28 mg, 1.17 mmol) in dry THF (6 mL) at 0 °C. The reaction mixture was stirred at rt for 1 h and cooled to 0 °C; then, a solution of the protected hydroxy ketone **30** (150 mg, 0.38 mmol) in dry THF (4 mL) was added and the stirring was continued at rt for 18 h. The mixture was diluted with ethyl ether (50 mL) and poured into brine (100 mL). The organic phase was separated, dried, and concentrated. The residue was purified by flash chromatography (SiO_2, 1% EtOAc/hexanes) to afford nitrile **31** (154 mg, 97%, colorless oil, contaminated with ca. 10% of its 4′*Z*-isomer): ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.89 (1H, t, J = 2.0 Hz), 2.93 (1H, dm, J = 13.5 Hz), 1.19 (6H, s), 0.95 (9H, t, J = 7.8 Hz), 0.94 (3H, d, J ∼ 6 Hz), 0.56 (6H, q, J = 7.8 Hz), 0.56 (3H, s); minor 4′*Z*-isomer: δ (selected signals) 5.20 (br s), 0.69 (s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.0 (C), 117.5 (C), 90.9 (CH), 73.5 (C), 56.6 (CH), 56.2 (CH), 52.6 (CH_2), 47.4 (C), 45.6 (CH_2), 39.7 (CH_2), 36.5 (CH_2), 36.0 (CH), 33.1 (CH_2), 30.2 (CH_3), 30.0 (CH_3), 27.5 (CH_2), 23.8 (CH_2), 21.9 (CH_2), 20.9 (CH_2), 18.9 (CH_3), 12.1 (CH_3), 7.3 (CH_3), 7.0 (CH_2); HRMS (ESI) exact mass calculated for $C_{26}H_{47}NOSiNa$ $(M + Na)^+$ 440.3325, measured 440.3329.

2-[(1′*R*,3a′*R*,7a′*R*)-1′-[(*R*)-1″,5″-Dimethyl-5″-[(triethylsilyl)-oxy]hexyl]-7a′-methyloctahydro-inden-(4′*E*)-ylidene]-propionitrile (29). A solution of LDA in THF/heptane/ethylbenzene (1.08 mL, 2 M, 2.16 mmol) was added to a solution of nitrile **31** (500 mg, 1.20 mmol) in dry THF (30 mL) under argon at −78 °C. The reaction was allowed to reach 0 °C. Then, it was cooled to −78 °C, and DMPU (260 μL, 0.22 mmol) was added dropwise. The solution was stirred at the same temperature for 30 min, and MeI (150 μL, 2.40 mmol) was added. The reaction mixture was allowed to reach 0 °C during 4 h, and it was stirred at this temperature for 1 h, poured into brine (50 mL), and extracted with ethyl ether (3 × 30 mL). The combined organic phases were dried and concentrated. The residue was purified by flash chromatography (SiO_2, 0.5% Et_2O/hexanes) to afford nitrile **29** (490 mg, 95%, colorless oil, contaminated with ca. 20% of its 4′*Z*-isomer): ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.99 (1H, dm, J ∼ 13.0 Hz), 1.98 (3H, br s), 1.19 (6H, s), 0.94 (9H, t, J = 8.0 Hz), 0.94 (3H, d, J ∼ 6 Hz), 0.67 (3H, s), 0.56 (6H, q, J = 8.0 Hz); minor 4′*Z*-isomer: δ (selected signals) 2.64 (m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 158.6 (C), 121.3 (C), 102.4 (C), 73.6 (C), 56.9 (CH), 55.2 (CH), 48.7 (C), 45.7 (CH_2), 40.7 (CH_2), 37.2 (CH_2), 36.6 (CH_2), 36.2 (CH), 30.2 (CH_3), 30.0 (CH_3), 28.3 (CH_2), 25.8 (CH_2), 24.3 (CH_2), 21.0 (CH_2), 19.2 (CH_3), 17.0 (CH_3), 12.9 (CH_3), 7.3 (CH_3), 7.0 (CH_2); HRMS (ESI) exact mass calculated for $C_{27}H_{49}NOSiNa$ $(M + Na)^+$ 454.3481, measured 454.3478.

2-[(1′*R*,3a′*R*,7a′*R*)-1′-[(*R*)-1″,5″-Dimethyl-5″-[(triethylsilyl)-oxy]hexyl]-7a′-methyloctahydro-inden-(4′*E*)-ylidene]-propionaldehyde (32). A solution of diisobutylaluminum hydride in toluene (2.25 mL, 1 M, 2.25 mmol) was added to a stirred solution of nitrile **29** (487 mg, 1.13 mmol) in dry toluene/CH_2Cl_2 (2:1, 15 mL) at −78 °C under argon. The mixture was stirred at −78 °C for 1 h, and then it was quenched by the addition of potassium sodium tartrate (2 mL, 2 N), aqueous HCl (2 mL, 2 N), and H_2O (12 mL). The mixture was poured into brine (100 mL) and extracted with ethyl acetate/ethyl ether (2:1, 3 × 30 mL). The combined organic phases were washed with diluted $NaHCO_3$ and brine, dried, and concentrated. The residue was purified by flash chromatography (SiO_2, 6% Et_2O/hexanes) to afford pure aldehyde **32** (426 mg, 87%, colorless semisolid): $[\alpha]_D^{25}$ +113.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 10.24 (1H, s), 3.54 (1H, br d), 1.87 (3H, s), 1.19 (6H, s), 0.95 (3H, d, J ∼ 6 Hz), 0.95 (9H, br t, J = 8.0 Hz), 0.73 (3H, s), 0.56 (6H, br q, J = 8.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 192.2 (CH), 162.2 (C), 131.9 (C), 73.6 (C), 59.4 (CH), 55.8 (CH), 49.8 (C), 45.7 (CH_2), 41.5 (CH_2), 36.7 (CH_2), 36.2 (CH), 30.8 (CH_2), 30.2 (CH_3), 30.0 (CH_3), 28.4 (CH_2), 26.5 (CH_2), 25.5 (CH_2), 21.1 (CH_2), 19.3 (CH_3), 13.1 (CH_3), 11.6 (CH_3), 7.3 (CH_3), 7.0 (CH_2). HRMS (ESI) exact mass calculated for $C_{27}H_{50}O_2SiNa$ $(M + Na)^+$ 457.3478, measured 457.3475.

2-[(1′*R*,3a′*R*,7a′*R*)-1′-[(*R*)-1″,5″-Dimethyl-5″-[(triethylsilyl)-oxy]hexyl]-7a′-methyloctahydro-inden-(4′*E*)-ylidene]-propan-1-ol (33). $NaBH_4$ (60 mg, 1.59 mmol) was added to a stirred solution of aldehyde **32** (426 mg, 0.98 mmol) in dry methanol (6 mL) at 0 °C under argon. The reaction mixture was allowed to reach rt during 1 h, and it was stirred at this temperature for additional 1 h. The reaction was quenched by addition of saturated aqueous solution of NH_4Cl, poured into brine (100 mL), and extracted with dichloromethane (3 × 30 mL). The combined extracts were washed with brine, dried, and

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concentrated. The residue was purified by flash chromatography (SiO_2, 10% EtOAc/hexanes) to afford pure alcohol **33** (411 mg, 96%, colorless semisolid): $[\alpha]_D^{25}$ +65.6 (*c* 0.9, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 4.02 (1H, d, *J* = 11.2 Hz), 4.22 (1H, d, *J* = 11.2 Hz), 2.75 (1H, br dd, *J* ∼11.0, 4.0 Hz), 1.87 (3H, s), 1.19 (6H, s), 0.95 (9H, br t, *J* = 7.9 Hz), 0.94 (3H, d, *J* ∼ 6 Hz), 0.67 (3H, s), 0.58 (6H, br q, *J* = 7.9 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 137.8 (C), 126.9 (C), 73.7 (C), 66.2 (CH_2), 55.4 (CH), 47.3 (C), 45.7 (CH), 41.7 (CH_2), 36.8 (CH), 36.4 (CH_2), 32.5 (CH_2), 30.2 (CH_3), 30.0 (CH_3), 29.9 (CH_2), 28.5 (CH_2), 27.3 (CH_2), 24.7 (CH_2), 21.1 (CH_2), 19.3 (CH_3), 18.2 (CH_3), 12.9 (CH_3), 7.3 (CH_3), 7.0 (CH_2); HRMS (ESI) exact mass calculated for $C_{27}H_{52}O_2SiNa$ $(M + Na)^+$ 459.3634, measured 459.3642.

2-{2′-[(1″*R*,3a″*R*,7a″*R*)-1″-[(*R*)-1‴,5‴-Dimethyl-5‴-[(triethylsilyl)oxy]hexyl]-7a″-methyl-octahydro-inden-(4″*E*)-ylidene]-propane-1′-sulfonyl}-benzothiazole (27). A solution of allylic alcohol **33** (132 mg, 0.30 mmol) in dry dichloromethane (1 mL) was added to a solution of 2-mercaptobenzotriazole (73 mg, 0.44 mmol) and Ph_3P (114 mg, 0.44 mmol) in dry dichloromethane (1 mL) at 0 °C. Then, DIAD (84 μL, 0.30 mmol) was added and the reaction mixture was stirred at 0 °C for 2 h. The solvent was evaporated, the residue was dissolved in ethanol (1.6 mL) and cooled to 0 °C, and 30% H_2O_2 (180 μL) was added, followed by $(NH_4)_6Mo_7O_{24} \times 4H_2O$ (73 mg, 0.06 mmol). The mixture was stirred at rt for 4 h, poured into cold saturated aqueous solution of Na_2SO_3, and extracted with ethyl acetate. The combined organic phases were washed with brine, dried, and evaporated. The residue was purified by flash chromatography (SiO_2, 15% EtOAc/hexanes) to give an oily product (152 mg) that was dissolved in dry CH_2Cl_2 (5 mL). 2,6-Lutidine (56 μL, 0.48 mmol) was added at −78 °C, and the mixture was stirred for 30 min at this temperature. Then, triethylsilyltrifluoromethanesulfonate (100 μL, 0.45 mmol) was added and the mixture was stirred at −78 °C for 1 h. The reaction was quenched by addition of a diluted aqueous solution of $NaHCO_3$. The mixture was poured into brine (100 mL) and extracted with dichloromethane (3 × 30 mL). The combined organic phases were washed with brine, dried, and evaporated. The residue was purified by flash chromatography (SiO_2, 5% EtOAc/hexanes) to afford pure sulfone **27** (181 mg, 97%, colorless oil): $[\alpha]_D^{25}$ +50.6 (*c* 1.3, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 8.23 (1H, m), 8.01 (1H, m), 7.63 (2H, m), 4.47 (1H, d), 4.25 (1H, d), 2.63 (1H, br d, *J* ∼12 Hz), 1.95 (3H, br s), 1.18 (6H, s), 0.94 (9H, t, *J* = 8.0 Hz), 0.90 (3H, d, *J* = 6.2 Hz), 0.61 (3H, s), 0.56 (6H, q, *J* = 8.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 166.9 (C), 153.0 (C), 145.5 (C), 137.2 (C), 128.1 (CH), 127.8 (CH), 125.6 (CH), 122.5 (CH), 113.3 (C), 73.6 (C), 62.5 (CH_2), 57.5 (CH), 55.1 (CH), 47.8 (C), 45.7 (CH_2), 41.3 (CH_2), 36.7 (CH_2), 36.3 (CH), 33.8 (CH_2), 30.2 (CH_3), 30.0 (CH_3), 28.4 (CH_2), 27.2 (CH_2), 24.2 (CH_2), 21.3 (CH_3), 21.1 (CH_2), 19.3 (CH_3), 12.9 (CH_3), 7.3 (CH_3), 6.98(CH_2); HRMS (ESI) exact mass calculated for $C_{34}H_{55}NO_3S_2SiNa$ $(M + Na)^+$ 640.3290, measured 640.3276.

1α-[(*tert*-Butyldimethylsilyl)oxy]-25-[(triethylsilyl)oxy]-7-methyl-19-norvitamin D_3 *tert*-Butyldimethylsilyl Ether (34). A solution of LiHMDS in THF (0.19 mL, 1 M, 0.19 mmol) was added to a solution of sulfone **27** (120 mg, 0.19 mmol) in dry THF (0.6 mL) at −78 °C under argon. The solution turned deep red. The mixture was stirred at −78 °C for 1 h, and a solution of the ketone **28** (60 mg, 0.17 mmol) in dry THF (1.5 mL) was added. The stirring was continued at −78 °C for 2 h, and the reaction mixture was allowed to warm slowly to −30 °C. After stirring for an additional 30 min at −30 °C, it was poured into saturated NH_4Cl (50 mL) and extracted with ethyl acetate (2 × 10 mL) and hexanes (10 mL). The combined organic phases were washed with brine, dried, and concentrated. The yellow oily residue was purified by flash chromatography (SiO_2, hexanes) to provide a protected vitamin **34** (71 mg, 56%; 82% based on recovered starting material). Further elution with 3% EtOAc/hexanes gave unreacted sulfone **27** (51 mg).

34: ^1H NMR (200 MHz, $CDCl_3$) δ 5.66 (1H, s), 4.12 (1H, m, *w*/2 = 11 Hz), 3.98 (1H, m, *w*/2 = 21 Hz), 2.64 (1H, m), 2.53 (1H, dd, *J* = 12.4, 3.4 Hz), 1.73 (3H, s), 1.19 (6H, s), 0.95 (9H, t, *J* = 8.0 Hz), 0.94 (3H, d, *J* ∼ 6.5 Hz), 0.87 (9H, s), 0.86 (9H, s), 0.71 (3H, s), 0.56 (6H, q, *J* = 8.0 Hz), 0.03 (12H, br s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 134.0 (C), 132.1 (C), 131.2 (CH), 125.3 (C), 73.7 (C), 68.2 (CH), 67.9 (CH), 56.8 (CH), 55.3 (CH), 46.9 (C), 45.7 (CH_2), 43.7 (CH_2), 43.4 (CH_2), 41.8 (CH_2), 39.3 (CH_2), 36.8 (CH_2), 36.5 (CH), 34.1 (CH_2), 30.2 (CH_3), 30.0 (CH_3), 28.6 (CH_2), 27.3 (CH_2), 26.2 (CH_3), 25.9 (CH_3), 23.9 (CH_2), 21.2 (CH_2), 19.8 (CH_3), 19.4 (CH_3), 18.5 (C), 18.2 (C), 13.2 (CH_3), 7.4 (CH_3), 7.0 (CH_2), −4.50 (CH_3), −4.56 (CH_3), −4.61 (CH_3), −4.74 (CH_3); HRMS (ESI) exact mass calculated for $C_{45}H_{88}O_3Si_3Na$ $(M + Na)^+$ 783.5939, measured 783.5953.

1α,25-Dihydroxy-7-methyl-19-norvitamin D_3 (26). A solution of tetrabutylammonium fluoride in THF (3.7 mL, 1 M, 3.7 mmol) was added to a solution of the protected vitamin D_3 analogue **34** (47 mg, 0.062 mmol) in anhydrous THF (3.5 mL) at rt. The reaction mixture was stirred overnight and quenched by addition of brine (50 mL), extracted with ethyl acetate (3 × 15 mL), dried, and concentrated. The residue was purified by HPLC (9.4 × 250 mm Luna Silica column, 4 mL/min, 18% *i*PrOH/hexanes). The deprotected vitamin **26** was collected at Rv 62 mL. Final purification was achieved by reversed-phase HPLC (9.4 × 250 mm Zorbax-C18 column, 3 mL/min, 10% H_2O/MeOH). Analytically pure (>95%) vitamin **26** (24 mg, 93%) was collected at Rv 29 mL: mp 129−130 °C (from HCOOEt); UV (96% EtOH) $\lambda_{max}(\varepsilon)$ 240 nm (5800 mol^{-1} m^3 cm^{-1}) 240 nm; ^1H NMR (500 MHz, $CDCl_3$) δ 5.91 (1H, s), 4.13 (1H, m, *w*/2 = 15 Hz), 4.02 (1H, m, *w*/2 = 19 Hz), 2.54 (1H, m), 2.43 (1H, m), 1.76 (3H, s), 1.22 (6H, s), 0.95 (3H, d, *J* = 6.2 Hz), 0.70 (3H, s); ^{13}C NMR (125 MHz) δ 134.9 (C), 133.5 (CH), 130.6 (C), 124.5 (C), 71.3 (C), 67.5 (CH), 67.2 (CH), 56.7 (CH), 55.2 (CH), 46.9, 44.6, 43.6, 42.0, 41.6, 38.2, 36.7, 36.4, 33.9, 29.9, 29.5 (CH_3), 29.4 (CH_3), 28.6, 27.2, 23.8, 21.1, 19.9 (CH_3), 19.3 (CH_3), 13.1 (CH_3); HRMS (ESI) exact mass calculated for $C_{27}H_{46}O_3Na$ $(M + Na)^+$ 441.3345, measured 441.3347. Crystals of compound **26** were obtained after crystallization from ethyl formate, and they were characterized by an X-ray analysis.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General experimental methods, spectra (^1H and ^{13}C NMR) of the synthesized compounds, NOE spectra of compounds **20**, **21**, **24**, and **12**, thermal isomerization of 1α,25-dihydroxy-7-methylvitamin D_3 (**12**), and crystallographic studies of compound **26**. This material is available free of charge via the Internet at http://pubs.acs.org. CCDC 1032407 contains the supplementary crystallographic data for this article. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

■ AUTHOR INFORMATION

Corresponding Authors

*Phone: +34 981 563100, ext. 14254. Fax: +34 983 595012. E-mail: antonio.mourino@usc.es (A.M.).

*Phone: +48 228220211, ext. 216. Fax: +48 22822 5996. E-mail: rasici@chem.uw.edu.pl (R.R.S.)

Author Contributions

‖K.S. and D.C. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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