# 6-*s*-*cis* Locked Analogues of the Steroid Hormone 1α,25-Dihydroxyvitamin $D_3$. Synthesis of Novel A-Ring Stereoisomeric 1,25-Dihydroxy-3-*epi*-19-*nor*-previtamin $D_3$ Derivatives

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Efficient syntheses of A-ring synthons **24** and **32** are described from hydroxy ester **16**, which is easily available on a preparative scale from (−)-quinic acid. Key features of the syntheses were (a) the ability to selectively perform desilylations in the presence of *p*-nitrobenzoate esters and (b) the excellent yield and complete stereospecificity with which the configuration of alcohols **16**, **18**, and **26** could be inverted under Mitsunobu conditions. Thus, A-ring synthons **24** and **32** were both prepared in 35−38% yield (eight steps) from the common precursor **16**. The coupling of A-ring synthons **24** and **32** with the appropriate CD-ring/side chain fragment **7** provides access to novel 6-*s*-*cis* locked analogues of steroid hormone 1α,25-dihydroxyvitamin $D_3$: 1α,25-dihydroxy-3-*epi*-19-*nor*-previtamin $D_3$ (**37**) and 1*β*,25-dihydroxy-3-*epi*-19-*nor*-previtamin $D_3$ (**38**), which are unable to undergo rearrangement to the respective vitamin D form by virtue of the absence of the C-19 methyl group. Compounds **37** and **38** can be used as tools for studying the genomic and nongenomic mechanisms of action of the previtamin form of the hormone 1α,25-dihydroxyvitamin $D_3$.

## Introduction

Vitamin $D_3$ is successively hydroxylated in the liver (at C-25) and then in the kidney (at C-1α) to produce the *seco*-B steroid 1α,25-dihydroxyvitamin $D_3$ [1α,25-$(OH)_2$-$D_3$] (**1**, Scheme 1), which is the hormonally active form of vitamin D. This metabolite exhibits a much broader spectrum of biological activities than originally thought, beyond its classic functions as a steroid hormone in regulating intestinal calcium absorption (ICA) and bone calcium mobilization (BCM), via genomic mechanisms[1] by interaction with a nuclear/cytosol vitamin D receptor (n-VDR) to regulate gene transcription. 1α,25-$(OH)_2$-$D_3$ also affects the human immune system, inhibits cell proliferation, and promotes cellular differentiation.[2]

There is clear evidence that this secosteroid can also generate biological responses via nongenomic pathways[3] by interaction with a membrane vitamin D receptor (m-VDR), which generates rapid biological responses believed to be independent of direct interaction with the genome. These include the rapid stimulation of intestinal $Ca^{2+}$ transport, a process known as transcaltachia.[4] The efficacy of 1α,25 analogues as chemotherapeutic agents in a variety of human disease states is extremely promising,[5] including both nongenomic and genomic pathways.

**Scheme 1**

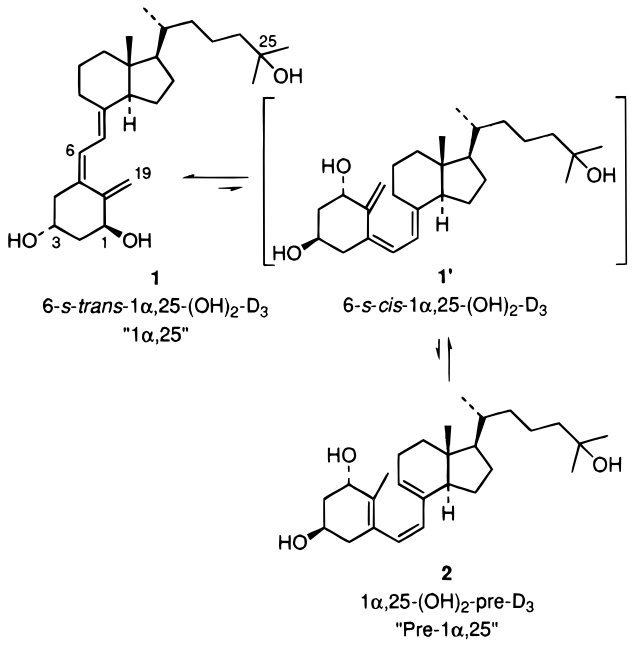


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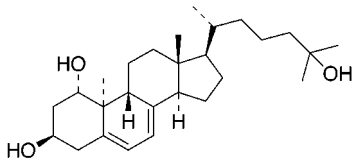
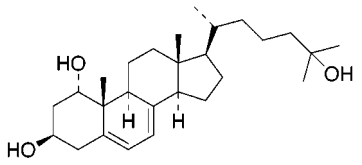
**Chart 1**



**3**
1α,25-$(OH)_2$-Lumisterol

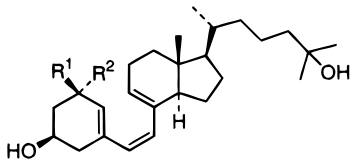


**4**
1α,25-$(OH)_2$-7-Dehydrocholesterol

1α,25-$(OH)_2$-$D_3$ exists as two conformationally interequilibrating forms (6-*s*-*trans* **1** and a minor form 6-*s*-*cis* **1′**), which are present in slow chemical equilibrium (5−10%) with 1α,25-dihydroxyprevitamin $D_3$ [1α,25-$(OH)_2$-pre-$D_3$] (**2**). Pure pre-1α,25 standing in solution rearranges to 1α,25 with a half-life of 13.5 h at 37 °C, whereas when the C-19 methyl group is deuterated,[6] rearrangement proceeds with a half-life of 81 h. However, whereas 1α,25 is significantly more active than pre-1α,25 (in a pentadeuterated form)[6] in assays reflecting genomic responses, the latter was equally as active as 1α,25 in assays for measuring nongenomic effects.[7] Thus, 6-*s*-*cis*-1α,25 (**1′**) was proposed as the active conformer in eliciting nongenomic effects, with pre-1α,25 (**2**) simply behaving as an excellent analogue of this conformer.[8] 1α,-25-$(OH)_2$-Lumisterol (**3**, Chart 1), a 6-*s*-*cis* analogue,[9] has been established to be equally active in eliciting the nongenomic activity of transcaltachia as both pre-1α,25 and 1α,25. In contrast, in terms of both transcaltachia and binding to m-VDR, 1α,25-$(OH)_2$-7-dehydrocholesterol (**4**) is less active than 1α,25-lumisterol. Thus, there is a significant level of stereoselectivity in mediating these nongenomic responses. Different analogues can induce different shapes of protein, resulting in different conformations of the protein-analogue complex, each leading to different biological responses. It became of interest, then, to prepare locked analogues of the 6-*s*-*cis* conformer of 1α,25, incapable of isomerizing to its 6-*s*-*trans* conformation, which is thermodynamically more stable.

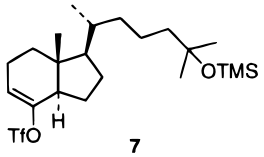
Our efforts have been aimed at synthesizing the A-ring diastereomers of 1α,25-$(OH)_2$-19-*nor*-pre-$D_3$, which are unable to undergo rearrangement to the respective vitamin D form by virtue of the absence of the C-19 methyl group. We have already reported[10a] the synthesis of 1α,25-$(OH)_2$-19-*nor*-pre-$D_3$ (**5**) and 1*β*,25-$(OH)_2$-19-*nor*-pre-$D_3$ (**6**) (Chart 2) through the coupling of CD-ring

**Chart 2**

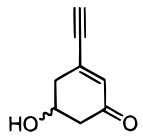


**5**, $R^1$= H; $R^2$= OH
1α,25-$(OH)_2$-19-*nor*-pre-$D_3$

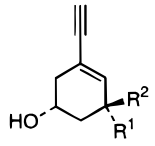
**6**, $R^1$= OH; $R^2$= H
1β,25-$(OH)_2$-19-*nor*-pre-$D_3$



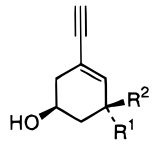
**7**



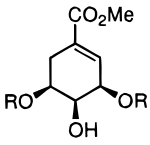
(*R*)-**12**
(*S*)-**12**



**8**, $R^1$= H; $R^2$= OH
**9**, $R^1$= OH; $R^2$= H



**10**, $R^1$= H; $R^2$= OH
**11**, $R^1$= OH; $R^2$= H



**13**, R= H
**14**, R= TBDMS

triflate **7** with A-ring silyl-protected precursors of **8** and **9**, respectively. Spectral data for these compounds are collected in the Supporting Information. To develop useful vitamin D analogues to understand the mechanism of the action of the steroid hormone 1α,25-$(OH)_2$-$D_3$, as a result of the importance of A-ring stereochemistry for binding the ligand to the hormone receptor and as a part of our research program,[10] we need to complete the A-ring stereoisomeric series of 1,25-$(OH)_2$-19-*nor*-pre-$D_3$. It is the purpose of this article to describe the preparation of the appropriate A-ring precursors **10** and **11** to allow us access to novel 1,25-$(OH)_2$-3-*epi*-19-*nor*-pre-$D_3$ analogues **37** and **38** (Scheme 4). As starting material we use (−)-quinic acid, an inexpensive and commercial available compound.

## Results and Discussion

**A-Ring Syntheses.** In a previous communication,[10a] we described the synthesis of A-ring stereoisomeric synthons **8** and **9** (Chart 2) through an efficient sequence in high overall yield from (−)-quinic acid. Key features of this approach were the selective deprotection of a disilyl ether in an α,*β*-unsaturated ester derivative and the excellent yield of the Mitsunobu reaction, which takes place with total inversion of configuration. To prepare the two other remaining stereoisomers of A-ring synthons (3*S*,5*S*)-**10** and (3*R*,5*S*)-**11**, stereoselective reduction of hydroxy ketone (*S*)-**12** with sodium triacetoxyborohydride[11] to prepare **11** and with sodium borohydride to prepare **10** was chosen as a reasonable approach. Com-

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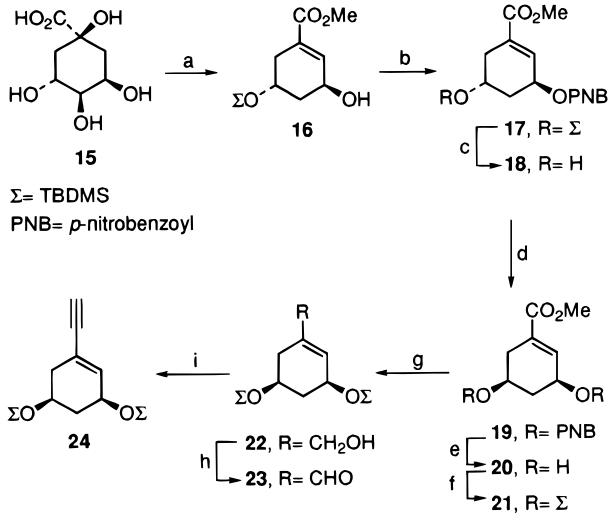
pound (*S*)-**12** was expected to form by inversion of (*R*)-**12**, which is readily obtained from **8** by selective Dess−Martin oxidation of the allylic OH group. However a problem arose when attempts to invert the configuration of the OH group in (*R*)-**12** were found to consistently lead to spontaneous aromatization.

Another rational but unsuccessful strategy was the synthesis of diol (3*S*,5*S*)-**10** through 3,5-disilyl-protected compound **14**. (−)-Methyl 5-*epi*-shikimate **13** was obtained[10c] on a large scale in five steps in 60% overall yield from shikimic acid or alternatively from (−)-quinic acid. Dess−Martin oxidation of the allylic alcohol in **10** provided the (*S*)-hydroxy ketone **12**, which by simple treatment with sodium triacetoxyborohydride[11] gave exclusively the A-ring stereoisomer (3*R*,5*S*)-**11**. Here, however, a problem was encountered when we tried to apply Barton's procedure[12] to remove the C-4 hydroxyl group in **14**. At the beginning, we followed a procedure similar to that for (3*S*,5*R*)-**8**,[13] in which the A-ring has the natural *anti* configuration. In our case, as a result of the steric hindrance of the 4-hydroxyl group in compound **14**, it was not possible to introduce the phenoxythionocarbonate group with the corresponding chloride in DMAP. It was necessary to use stronger conditions (bases such as NaH or $^t$BuOK), but in these cases migrations of the *O*-silyl group were observed. Alternative methods of removing the hydroxyl group at C-4, such as its transformation into a good leaving group (by tosylation or mesylation) and subsequent removal with hydride, were also unsatisfactory.

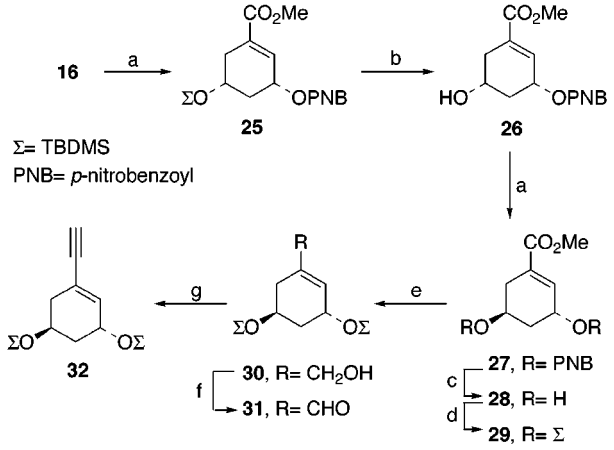
At this point, we decided to change our strategy, taking into account the availability of compound **16** (Scheme 2) through the selective deprotection of the allylic hydroxyl group of the corresponding disilyl derivative, an intermediate in the route to A-ring synthon **9**. Full experimental details for the conversion of (−)-quinic acid to key starting material **16**, as well as full spectral data for all compounds involved in this route are shown in the Supporting Information section. To synthesize A-ring precursors (3*S*,5*S*)-**10** and (3*R*,5*S*)-**11**, we have used the efficient pathways shown in Schemes 2 and 3, respectively. A-Ring protected synthon (3*S*,5*S*)-**24** was prepared via the allylic alcohol **16**, which was synthesized as previously described in eight steps with 31% overall yield from (−)-quinic acid.[10a] To perform the subsequent transformations, the OH group at C-5 had to be free and the OH group at C-3 had to be protected. Because of the impossibility of selectively deprotecting the C-5 hydroxyl group of the fully protected precursor of ester **16**, protection of the allylic alcohol is required. From various possibilities, we chose to convert **16** to the *p*-nitrobenzoate ester **17** on the basis that the same ester will be obtained after Mitsunobu reaction[14] over compound **18** and also would be stable under acid-catalyzed desilylation conditions. Thus, reaction of **16** with *p*-nitrobenzoyl chloride (PNBCl) in pyridine gave an almost quantitative yield of **17**, and subsequent treatment with HCl in MeOH afforded **18**. This was fortunate, as attempted desilylation with TBAF was unsuccessful as a result of the fact that

**Scheme 2**




(a) Reference 10a. (b) PNBCl, Py. (c) HCl conc., MeOH. (d) $PPh_3$, DIAD, PNBOH, THF. (e) MeONa, MeOH. (f) TBDMSCl, imidazole, $CH_2Cl_2$. (g) DIBAL-H, toluene. (h) PCC, $CH_2Cl_2$. (i) $TMSCHN_2$, $^n$BuLi, THF.

**Scheme 3**




(a) $PPh_3$, DIAD, PNBOH, THF. (b) HCl conc., MeOH. (c) MeONa, MeOH. (d) TBDMSCl, imidazole, $CH_2Cl_2$. (e) DIBAL-H, toluene. (f) PCC, $CH_2Cl_2$. (g) $TMSCHN_2$, $^n$BuLi, THF.

fluoride ion in THF was a sufficiently strong base to lead to migration of the PNB group, giving a mixture of 3- and 5-OPNB esters. To invert the C-5 hydroxyl group in **18**, we applied Mitsunobu's procedure with *p*-nitrobenzoic acid in THF. The completely inverted di-PNB ester **19** was obtained with 85% yield. Methanolysis of the PNB esters was carried out at 0 °C with 0.7 equiv of NaOMe. Protection of the resulting diol **20** was necessary to afford the desired transformation from methyl ester to alkyne and to couple this A-ring fragment with CD-ring/side chain synthon **7**. When the OH group was left unprotected, the yield of coupled product decreased significantly. Transformation of the ester **21** into the aldehyde **23** was best carried via a two-step sequence: reduction with DIBAL-H followed by oxidation with pyridinium chlorochromate (PCC). Formation of the enyne **24** was accomplished in a good yield by reaction with trimethylsilyldiazomethane. The overall yield of **24** from **16** via this eight-step sequence was 38%.

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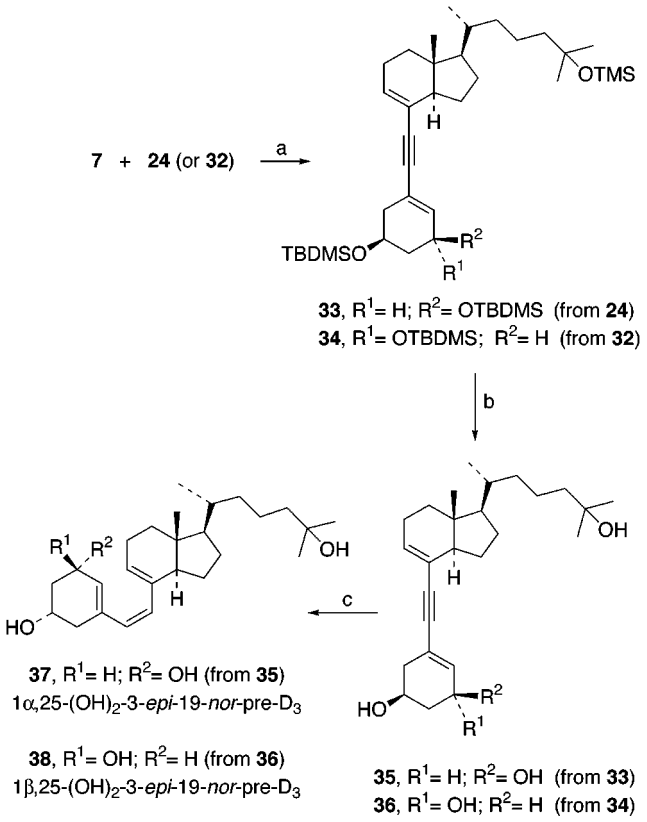
(14) (a) Hughes, D. L. *Org. Prep. Proc. Int.* **1996**, *28*, 127−164. (b) Mitsunobu, O. *Synthesis* **1981**, 1−28.

**Scheme 4**




(a) $Pd(PPh_3)_2(OAc)_2$, CuI, $Et_2NH$, DMF. (b) TBAF, THF. (c) $H_2$, Lindlar cat., quinoline, MeOH.

We envisaged that the synthesis of **32** could be achieved by simultaneous inversions both OH groups in the corresponding diol of **16**. However, although the Mitsunobu process gave the desired inversion at both C-3 and C-5, the yield was very poor and large amounts of starting material were recovered. As a result, we turned our attention to carrying out the inversion stepwise. Thus, **16** under standard Mitsunobu conditions with *p*-nitrobenzoic acid resulted in esterification of the alcohol with total inversion of configuration (Scheme 3). Cleavage of the silyl group in **25** with HCl in MeOH yielded **26**; as in the case of **17**, TBAF treatment led to PNB migrations and thus was not useful. Inversion of the desilylated OH group by reaction with *p*-nitrobenzoic acid under Mitsunobu conditions provided diester **27**, in which both C-3 and C-5 have undergone inversion. $^1$H NMR spectra of the product at each step showed the presence of only one diastereoisomer and confirmed that both Mitsunobu reactions proceeded with complete inversion. Methanolysis and the previously described reaction sequence from **20** to **24** was followed to obtain enyne **32** in 35% overall yield starting from **16**.

**Syntheses of Previtamin D Analogues.** To synthesize stable previtamin analogues **37** and **38** (Scheme 4), we used a convergent route[15] starting from the protected A-ring synthon precursors **24** or **32** and the known CD-triflate **7**.[16] The synthesis of the CD-ring/side chain fragment was accomplished through ozonolysis of vitamin $D_3$ to obtain Grundmann's ketone,[17] which was oxidized at the 25-position (steroid numbering) and then protected as a trimethylsilyl ether. Posterior kinetic enol formation afforded triflate **7**. A-Ring synthons **24** or **32** were coupled to CD-triflate **7** in the presence of bis[triphenylphosphine]-palladium(II) acetate−copper(I) iodide catalyst and diethylamine in DMF. The resulting silyloxy dienynes **33** or **34** were deprotected with TBAF to afford the trihydroxydienynes **35** or **36**, respectively. Careful catalytic hydrogenation of triols **35** or **36** in MeOH, in the presence of Lindlar catalyst and quinoline, generated 3-*epi*-previtamins **37** or **38**.

The structural assignment of the compounds described in this paper is based on the analysis of their $^1$H and $^{13}$C NMR spectra and DEPT experiments. The correct assignment was confirmed by $^1$H−$^{13}$C heteronuclear correlation experiments.

In summary, we have developed a novel and practical route to A-ring precursors **24** and **32** from a single intermediate (**16**) easily available on a preparative scale from (−)-quinic acid. Key features of the synthesis were the ability to selectively deprotect silyl ethers in the presence of *p*-nitrobenzoate esters and the excellent yield and stereoselectivity of the Mitsunobu reaction, which occurs with complete inversion. Coupling of **24** and **32** to the appropriate CD-ring/side chain fragment **7** provided access to the novel 6-*s*-*cis*-3-*epi* locked analogues **37** and **38**. These syntheses will allow the effect of stereochemistry at C-1 and C-3 on the biological activity of 1,25-$(OH)_2$-19-*nor*-pre-$D_3$ to be studied.

## Experimental Section[18]

**General.** Reagents were purchased from Aldrich or Fluka. Solvents were distilled over an appropriate desiccant under nitrogen. Syntheses of CD-triflate **7**[16] and allylic alcohol **16**[10a] were previously reported.

**Methyl (3*S*,5*R*)-5-[(*tert*-Butyldimethylsilyl)oxy]-3-[(*p*-nitrophenylcarbonyl)oxy]cyclohex-1-enecarboxylate (17).** *p*-Nitrobenzoyl chloride (1.15 g, 6.22 mmol) was added in portions to a stirred solution of compound **16** (1.00 g, 3.11 mmol) in pyridine (10 mL) at 0 °C under nitrogen atmosphere. The mixture was stirred for 1 h at room temperature, then diluted with water, and extracted with methylene chloride. The combined organic layers were evaporated under reduced pressure to leave a residue which was purified by flash chromatography (10% EtOAc/hexane) to obtain 1.32 g (98%) of benzoate ester **17**: $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 0.08 (s, 3H, *Me*Si), 0.09 (s, 3H, *Me*Si), 0.88 (s, 9H, $Me_3$CSi), 1.92 (ddd, 1H, $H_{4a}$, $^2J_{HH}$ 13.4, $^3J_{HH}$ 6.4, 2.7 Hz) 2.11 (ddd, 1H, $H_{4e}$, $^2J_{HH}$ 13.4, $^3J_{HH}$ 8.0, 5.4 Hz), 2.30 (dddd, 1H, $H_{6a'}$, $^2J_{HH}$ 18.2, $^3J_{HH}$ 5.6, $^4J_{HH}$ 1.9, 1.9 Hz), 2.64 (dddd, 1H, $H_{6e'}$, $^2J_{HH}$ 18.2, $^3J_{HH}$ 4.5, $^4J_{HH}$ 2.0, 2.0 Hz), 3.76 (s, 3H, O*Me*), 4.26 (m, 1H, $H_5$), 5.86 (m, 1H, $H_3$), 6.94 (ddd, 1H, $H_2$, $^3J_{HH}$ 1.9, $^4J_{HH}$ 1.9, 1.9 Hz), and 8.22 (m, 4H, Ar*H*); HRMS calcd for $C_{17}H_{20}NO_7Si$ ($M^+ - {}^t$Bu) 378.1009, found 378.0990.

**Methyl (3*S*,5*R*)-5-Hydroxy-3-[(*p*-nitrophenylcarbonyl)-oxy]-cyclohex-1-enecarboxylate (18).** To a solution of **17** (1.00 g, 2.23 mmol) in methanol (5 mL) were added 2 drops of concentrated HCl. After being stirred at room temperature for 2 h, the reaction mixture was evaporated; yield 630 mg

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(18) For all products, full spectral data are given in the Supporting Information and selected $^1$H and $^{13}$C NMR signals are also presented in the Experimental Section. The purity of compounds was estimated by a combination of GC and/or HPLC and NMR analysis. The level of purity is indicated by the inclusion of copies of $^1$H and $^{13}$C NMR spectra in the Supporting Information.

(88%): $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 2.00−2.20 (m, 2H, $H_4$), 2.32 (m, 1H, $H_{6a'}$, $^2J_{HH}$ 12.0, $^3J_{HH}$ 4.2 Hz), 2.60 (br s, 1H, OH), 2.78 (m, 1H, $H_{6e'}$, $^2J_{HH}$ 12.0, $^3J_{HH}$ 3.0 Hz), 3.75 (s, 3H, O*Me*), 4.32 (m, 1H, $H_5$), 5.87 (m, 1H, $H_3$), 6.95 (m, 1H, $H_2$), and 8.21 (m, 4H, Ar*H*); HRMS calcd for $C_{15}H_{15}NO_7$ ($M^+$) 321.0848, found 321.0849.

**Methyl (3*S*,5*S*)-3,5-Di[(*p*-nitrophenylcarbonyl)oxy]-cyclohex-1-enecarboxylate (19).** To a stirred solution of **18** (710 mg, 2.21 mmol) in THF (30 mL) at 0 °C under nitrogen were added $PPh_3$ (638 mg, 2.43 mmol), 4-nitrobenzoic acid (428 mg, 2.43 mmol), and diisopropyl azodicarboxylate (0.47 mL, 2.43 mmol). The mixture was stirred for 2 h at room temperature and then evaporated under reduced pressure to leave a residue which was purified by flash chromatography (gradient eluent 10−40% EtOAc/hexane); yield 884 mg (85%): $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 2.27−2.37 (m, 1H, $H_{4a}$), 2.51−2.59 (m, 1H, $H_{4e}$), 2.64−2.74 (m, 1H, $H_{6a'}$), 2.87−2.93 (m, 1H, $H_{6e'}$), 3.79 (s, 3H, O*Me*), 5.46 (m, 1H, $H_5$), 5.88 (m, 1H, $H_3$), 7.03 (m, 1H, $H_2$), and 8.05−8.24 (m, 8H, Ar*H*); HRMS calcd for $C_{21}H_{14}N_2O_9$ ($M^+$ − MeOH) 438.0699, found 438.0702.

**Methyl (3*S*,5*S*)-3,5-Dihydroxycyclohex-1-enecarboxylate (20).** A solution of MeONa in MeOH, prepared in situ by addition of Na (46 mg, 2.00 mmol) to MeOH (2 mL), was added dropwise to a solution of **19** (800 mg, 1.70 mmol) in MeOH (4 mL). The reaction was stirred at room temperature under nitrogen, until TLC showed the disappearance of starting material. The mixture was neutralized with solid $NH_4Cl$ and the solvent was evaporated. The residue was purified by flash chromatography (gradient eluent 60−80% EtOAc/hexane), and the product was dried in vacuo; yield 204 mg (70%): $^1$H NMR (MeOH-$d_4$, 200 MHz) $\delta$ 1.67 (ddd, 1$H_{4a}$, $^2J_{HH}$ 11.8, $^3J_{HH}$ 11.8, 9.8 Hz), 2.25 (dddd, 1H, $H_{6a'}$, $^2J_{HH}$ 17.0, $^3J_{HH}$ 9.2, $^4J_{HH}$ 3.6, 2.7 Hz), 2.45 (m, 1H, $H_{4e}$), 2.85 (dddd, 1H, $H_{6e'}$,$^2J_{HH}$ 17.0, $^3J_{HH}$ 5.6, $^4J_{HH}$ 3.2, 1.7 Hz), 3.93 (s, 3H, O*Me*), 4.03 (dddd, 1H, $H_5$, $^3J_{HH}$ 9.8, 5.9, 3.3, 2.1 Hz), 4.58 (m, 1H, $H_3$), and 7.06 (m, 1H, $H_2$); HRMS calcd for $C_8H_{12}O_4$ ($M^+$) 172.0736, found 172.0739.

**Methyl (3*S*,5*S*)-3,5-Di[(*tert*-butyldimethylsilyl)oxy]-cyclohex-1-enecarboxylate (21).** TBDMSCl (900 mg, 6.38 mmol) was added to a solution of **20** (580 mg, 3.37 mmol) and imidazole (459 mg, 6.38 mmol) in $CH_2Cl_2$ (5 mL) at 0 °C under nitrogen. The reaction mixture was stirred at room temperature for 2 h, diluted with $CH_2Cl_2$ and washed with water. The aqueous layer was extracted with $CH_2Cl_2$ and the combined organic layers were dried ($Na_2SO_4$) and evaporated in a vacuum. The residue was purified by flash chromatography (5% EtOAc/hexane); yield 1.31 g (97%): $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 0.06 (s, 6H, 2*Me*Si), 0.08 (s, 3H, *Me*Si), 0.09 (s, 3H, *Me*Si), 0.88 (s, 9H, *Me*$_3$CSi), 0.89 (s, 9H, *Me*$_3$CSi), 1.58 (ddd, 1H, $H_{4a}$, $^2J_{HH}$ 12.0, $^3J_{HH}$ 10.4, 10.4 Hz), 2.10 (m, 2H, $H_{4e}$ + $H_{6a'}$), 2.60 (dd, 1H, $H_{6e'}$, $^2J_{HH}$ 17.2, $^3J_{HH}$ 5.6 Hz), 3.72 (s, 3H, O*Me*), 3.80 (m, 1H, $H_5$), 4.43 (m, 1H, $H_3$), and 6.67 (m, 1H, $H_2$); HRMS calcd for $C_{20}H_{40}O_4Si_2$ ($M^+$) 400.2465, found 400.2457.

**(3*S*,5*S*)-3,5-Di[(*tert*-butyldimethylsilyl)oxy]-1-hydroxymethylcyclohex-1-ene (22).** DIBAL-H (7.4 mL of 1.0 M in toluene, 7.48 mmol) was added dropwise under nitrogen to a solution of **21** (1.00 g, 2.48 mmol) in anhydrous toluene (20 mL) at −78 °C, and the reaction was stirred for 2 h at the same temperature. $NH_4Cl$ (aqueous) was added (∼2 mL) and the mixture was warmed to room temperature, diluted with $Et_2O$, and filtered through a short column of silica gel, using additional $Et_2O$ to elute the column. The filtrate was concentrated and the residue further purified by flash chromatography (gradient eluent 5−10% EtOAc/hexane); yield 887 mg (96%): $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 0.05 (s, 3H, *Me*Si), 0.06 (s, 3H, *Me*Si), 0.07 (s, 3H, *Me*Si), 0.08 (s, 3H, *Me*Si), 0.87 (s, 9H, *Me*$_3$CSi), 0.88 (s, 9H, *Me*$_3$CSi), 1.55 (ddd, 1H, $H_{4a}$, $^2J_{HH}$ 12.0, $^3J_{HH}$ 10.0, 10.0 Hz), 1.93−2.20 (m, 3H, $H_{4e}$ + 2$H_6$), 2.35 (br s, OH), 3.80 (m, 1H, $H_5$), 3.96 (m, 2H, $H_7$), 4.36 (m, 1H, $H_3$), and 5.52 (m, 1H, $H_2$); HRMS calcd for $C_{15}H_{31}O_3Si_2$ ($M^+$ − $^t$Bu), found 315.1810.

**(3*S*,5*S*)-3,5-Di[(*tert*-butyldimethylsilyl)oxy]cyclohex-1-enecarbaldehyde (23).** PCC (1.16 mg, 5.36 mmol) was added to a solution of compound **22** (1.00 g, 2.68 mmol) in anhydrous $CH_2Cl_2$ (5 mL). The reaction mixture was stirred at room temperature for 2 h under nitrogen. $Et_2O$ was added and the gummy residue was filtered through a short column of fluorosil. The filtrate was concentrated to afford 990 mg of **23**, whose purity was sufficiently pure for direct use in the next step. This aldehyde is unstable and could only be kept a couple of days in the refrigerator under nitrogen. **23**: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 0.07 (s, 6H, 2*Me*Si), 0.11 (s, 3H, *Me*Si), 0.13 (s, 3H, *Me*Si), 0.89 (s, 9H, *Me*$_3$CSi), 0.91 (s, 9H, *Me*$_3$CSi), 1.67 (ddd, 1H, $H_{4a}$, $^2J_{HH}$ 12.0, $^3J_{HH}$ 12.0, 10.2 Hz), 1.98 (dddd, 1H, $H_{6a'}$, $^2J_{HH}$ 17.2, $^3J_{HH}$ 9.6, $^4J_{HH}$ 2.8, 2.8 Hz), 2.18 (m, 1H, $H_{4e}$), 2.61 (dd, 1H, $H_{6e'}$, $^2J_{HH}$ 17.4, $^3J_{HH}$ 5.2 Hz), 3.84 (dddd, 1H, $H_5$, $^3J_{HH}$ 12.0, 9.2, 5.5, 3.5 Hz), 4.55 (dddd, 1H, $H_3$, $^3J_{HH}$ 10.0, 5.7, 3.9, 1.9 Hz), 6.50 (m, 1H, $H_2$), and 9.50 (s, 1H, $H_7$).

**(3*S*,5*S*)-3,5-Di[(*tert*-butyldimethylsilyl)oxy]-1-ethynylcyclohex-1-ene (24).** $^n$BuLi (1.8 mL of 1.6 M in hexane, 2.88 mmol) was added to a solution of trimethylsilyldiazomethane (1.32 mL of 2.0 M in hexane, 2.64 mmol) in THF (2 mL) at −78 °C under nitrogen. To this solution was added compound **23** (900 mg, 2.4 mmol) in THF (2 mL). The reaction mixture was stirred at −78 °C for 1 h and then was allowed to reach room temperature overnight. The THF was evaporated and the residue was poured into water/EtOAc. The aqueous layer was extracted with EtOAc, washed with brine, dried ($Na_2SO_4$), and evaporated in a vacuum. A subsequent flash chromatography (gradient eluent 1−10% EtOAc/hexane) afforded 660 mg (75% yield from **22**) of compound **24**: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 0.07 (s, 3H, *Me*Si), 0.07 (s, 3H, *Me*Si), 0.08 (s, 3H, *Me*Si), 0.09 (s, 3H, *Me*Si), 0.89 (s, 9H, *Me*$_3$CSi), 0.90 (s, 9H, *Me*$_3$CSi), 1.57 (ddd, 1H, $H_{4a}$, $^2J_{HH}$ 12.0, $^3J_{HH}$ 12.0, 10.2 Hz), 2.07−2.20 (m, 2H, $H_{4e}$ + $H_{6a'}$), 2.33 (m, 1H, $H_{6e'}$), 2.85 (s, 1H, $H_8$), 3.81 (dddd, 1H, $H_5$, $^3J_{HH}$ 12.0, 9.4, 5.7, 3.5 Hz), 4.38 (m, 1H, $H_3$), and 5.97 (m, 1H, $H_2$); HRMS calcd for $C_{16}H_{29}O_2Si_2$ ($M^+$ − $^t$Bu) 309.1706, found 319.1707.

**Methyl (3*R*,5*R*)-5-[(*tert*-Butyldimethylsilyl)oxy]-3-[(*p*-nitrophenylcarbonyl)oxy]cyclohex-1-enecarboxylate (25).** The same procedure as the one described for **19** yielded **25** (98%): $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 0.02 (s, 3H, *Me*Si), 0.03 (s, 3H, *Me*Si), 0.81 (s, 9H, *Me*$_3$CSi), 1.78 (ddd, 1H, $H_{4a}$, $^2J_{HH}$ 13.2, $^3J_{HH}$ 11.5, 11.5 Hz), 2.20 (dddd, 1H, $H_{6a'}$, $^2J_{HH}$ 17.6, $^3J_{HH}$ 5.7, 3.2, $^4J_{HH}$ 3.2 Hz), 2.33 (m, 1H, $H_{4e}$), 2.64 (dd, 1H, $H_{6e'}$, $^2J_{HH}$ 17.6, $^3J_{HH}$ 4.3 Hz), 3.70 (s, 3H, O*Me*), 3.97 (m, 1H, $H_5$), 5.74 (m, 1H, $H_3$), 6.77 (m, 1H, $H_2$), and 8.16 (m, 4H, Ar*H*); HRMS calcd for $C_{17}H_{20}NO_7Si$ ($M^+$ − $^t$Bu) 378.1009, found 378.1002.

**Methyl (3*R*,5*R*)-5-Hydroxy-3-[(*p*-nitrophenylcarbonyl)-oxy]-cyclohex-1-enecarboxylate (26).** The same procedure as the one described for **18** yielded **26** (85%): $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 1.93 (ddd, $H_{4a}$, $^2J_{HH}$ 12.4, $^3J_{HH}$ 10.8, 8.1 Hz), 2.42 (m, 2H, $H_{4e}$+$H_{6a'}$), 2.78 (dd, 1H, $H_{6e'}$, $^2J_{HH}$ 17.5, $^3J_{HH}$ 5.2 Hz), 3.70 (s, 3H, O*Me*), 4.16 (m, 1H, $H_5$), 5.82 (m, 1H, $H_3$), 6.91 (m, 1H, $H_2$), and 8.25 (m, 4H, Ar*H*); HRMS calcd for $C_{15}H_{15}NO_7$ ($M^+$): 321.0848, found 321.0856.

**Methyl (3*R*,5*S*)-3,5-Di[(*p*-nitrophenylcarbonyl)oxy]-cyclohex-1-enecarboxylate (27).** The same procedure as the one described for **19** yielded **27** (85%): $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 2.25 (ddd, 1H, $H_{4a}$, $^2J_{HH}$ 13.6, $^3J_{HH}$ 6.4, 2.9 Hz), 2.42 (ddd, 1H, $H_{4e}$, $^2J_{HH}$ 13.6, $^3J_{HH}$ 8.1, 5.5 Hz), 2.61 (dddd, 1H, $H_{6a'}$, $^2J_{HH}$ 18.5, $^3J_{HH}$ 5.9, $^4J_{HH}$ 1.8, 1.8 Hz), 2.97 (dddd, 1H, $H_{6e'}$, $^2J_{HH}$ 18.5, $^3J_{HH}$ 4.9, $^4J_{HH}$ 2.0, 2.0 Hz), 3.78 (s, 3H, O*Me*), 5.62 (m, 1H, $H_5$), 5.94 (m, 1H, $H_3$), 7.05 (ddd, 1H, $H_2$, $^3J_{HH}$ 3.7, $^4J_{HH}$ 1.9, 1.9 Hz), and 8.19 (m, 8H, Ar*H*); HRMS calcd for $C_{21}H_{14}N_2O_9$ ($M^+$ − MeOH) 438.0699, found 438.0703.

**Methyl (3*R*,5*S*)-3,5-Dihydroxycyclohex-1-enecarboxylate (28).** The same procedure as the one described for **20** yielded **28** (75%): $^1$H NMR (MeOH-$d_4$, 300 MHz) $\delta$ 1.95 (ddd, 1H, $H_4$, $^2J_{HH}$ 13.2, $^3J_{HH}$ 6.4, 2.8 Hz), 2.09 (ddd, 1H, $H_4$, $^2J_{HH}$ 13.2, $^3J_{HH}$ 8.1, 5.3 Hz), 2.35 (dddd, 1H, $H_6$, $^2J_{HH}$ 17.8, $^3J_{HH}$ 6.1, $^4J_{HH}$ 2.0, 2.0 Hz), 2.79 (dddd, 1H, $H_6$, $^2J_{HH}$ 17.8, $^3J_{HH}$ 4.6, $^4J_{HH}$ 2.0, 2.0 Hz), 3.94 (s, 3H, O*Me*), 4.32 (m, 1H, $H_5$), 4.66 (m, 1H, $H_3$), and 7.06 (m, 1H, $H_2$); HRMS calcd for $C_8H_8O_2$ ($M^+$ − $2H_2O$) 136.0524, found 136.0495.

**Methyl (3*R*,5*S*)-3,5-Di[(*tert*-butyldimethylsilyl)oxy]-cyclohex-1-enecarboxylate (29).** The same procedure as the one described for **21** yielded **29** (96%): $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 0.06 (s, 6H, 2*Me*Si), 0.07 (s, 3H, *Me*Si), 0.09 (s, 3H, *Me*Si), 0.86 (s, 9H, *Me*$_3$CSi), 0.90 (s, 9H, *Me*$_3$CSi), 1.69 (ddd,

1H, $H_{4a}$, $^2J_{HH}$ 12.9, $^3J_{HH}$ 6.4, 2.8 Hz), 1.81 (ddd, 1H, $H_{4e}$, $^2J_{HH}$ 12.9, $^3J_{HH}$ 7.9, 4.9 Hz), 2.15 (dd, 1H, $H_{6a'}$, $^2J_{HH}$ 17.8, $^3J_{HH}$ 5.6 Hz), 2.54 (dd, 1H, $H_{6e'}$, $^2J_{HH}$ 17.8, $^3J_{HH}$ 4.5 Hz), 3.74 (s, 3H, O*Me*), 4.19 (dddd, 1H, $H_5$, $^3J_{HH}$ 7.3, 5.5, 4.9, 2.6 Hz), 4.54 (m, 1H, $H_3$), and 6.79 (m, 1H, $H_2$); HRMS calcd for $C_{20}H_{40}O_4Si_2$ ($M^+$) 400.2465, found 400.2456.

**(3*R*,5*S*)-3,5-Di[(*tert*-butyldimethylsilyl)oxy]-1-hydroxymethylcyclohex-1-ene (30).** The same procedure as the one described for **22** yielded **30** (97%): $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 0.05 (s, 3H, *Me*Si), 0.06 (s, 3H, *Me*Si), 0.07 (s, 6H, 2*Me*Si), 0.87 (s, 9H, $Me_3$CSi), 0.88 (s, 9H, $Me_3$CSi), 1.73 (m, 2H, $H_4$), 1.90 (dd, 1H, $H_{6a'}$, $^2J_{HH}$ 17.0, $^3J_{HH}$ 7.1 Hz), 2.12 (br s, OH), 2.22 (dd, 1H, $H_{6e'}$, $^2J_{HH}$ 17.0, $^3J_{HH}$ 4.8 Hz), 3.98 (m, 2H, $H_7$), 4.16 (m, 1H, $H_5$), 4.40 (ddd, 1H, $H_3$, $^3J_{HH}$ 8.3, 4.6, 4.6 Hz), and 5.63 (m, 1H, $H_2$); HRMS calcd for $C_{19}H_{38}O_2Si_2$ ($M^+ - H_2O$) 354.2410, found 354.2411.

**(3*R*,5*S*)-3,5-Di[(*tert*-butyldimethylsilyl)oxy]cyclohex-1-enecarbaldehyde (31).** The same procedure as the one described for **23** yielded **31** (100%): $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 0.04 (s, 3H, *Me*Si), 0.06 (s, 3H, *Me*Si), 0.11 (s, 3H, *Me*Si), 0.12 (s, 3H, *Me*Si), 0.85 (s, 9H, $Me_3$CSi), 0.91 (s, 9H, $Me_3$CSi), 1.70 (ddd, 1H, $H_{4a}$, $^2J_{HH}$ 12.8, $^3J_{HH}$ 7.3, 2.3 Hz), 1.94 (ddd, 1H, $H_{4e}$, $^2J_{HH}$ 12.5, $^3J_{HH}$ 7.1, 6.0 Hz), 2.13 (dd, 1H, $H_{6a'}$, $^2J_{HH}$ 18.0, $^3J_{HH}$ 4.2 Hz), 2.41 (ddd, 1H, $H_{6e'}$, $^2J_{HH}$ 17.9, $^3J_{HH}$ 4.3, $^4J_{HH}$ 2.1 Hz), 4.22 (m, 1H, $H_5$), 4.70 (m, 1H, $H_3$), 6.62 (m, 1H, $H_2$), and 9.49 (s, 1H, $H_7$).

**(3*R*,5*S*)-3,5-Di[(*tert*-butyldimethylsilyl)oxy]-1-ethynylcyclohex-1-ene (32).** The same procedure as the one described for **24** yielded **32** (70% from **30**): $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 0.07 (s, 6H, 2*Me*Si), 0.08 (s, 6H, 2*Me*Si), 0.89 (s, 9H, $Me_3$Si), 0.90 (s, 9H, $Me_3$Si), 1.74 (m, 2H, $H_4$), 2.06 (dd, 1H, $H_{6a'}$, $^2J_{HH}$ 16.1, $^3J_{HH}$ 6.3 Hz), 2.39 (dd, 1H, $H_{6e'}$, $^2J_{HH}$ 16.1, $^3J_{HH}$ 3.1 Hz), 2.82 (s, 1H, $H_8$), 4.15 (m, 1H, $H_5$), 4.43 (m, 1H, $H_3$), and 6.07 (m, 1H, $H_2$); HRMS calcd for $C_{20}H_{38}O_2Si_2$ ($M^+$) 366.2410, found 366.2411.

**1α,25-Dihydroxy-6,7-dehydro-3-*epi*-19-*nor*-previtamin $D_3$ (35).** CuI (4 mg, 0.02 mmol), $Pd(PPh_3)_2(OAc)_2$ (5 mg, 0.01 mmol) and $Et_2NH$ (1 mL) were added to a solution of **7** (105 mg, 0.22 mmol) and **24** (81 mg, 0.24 mmol) in DMF (1 mL). The reaction mixture was stirred at room temperature for 1 h under nitrogen atmosphere and then poured into water and extracted with diethyl ether. The combined ether fractions were washed with brine, dried over $Na_2SO_4$, filtered and concentrated to give 165 mg of crude **33**, which was sufficiently pure for the next step. Although it was possible to purify this compound by flash chromatography, it decomposed in a few hours.

TBAF (1.2 mL of 1.0 M in THF, 1.2 mmol) was added to a solution of the crude **33** in THF (4 mL) at 0 °C and the reaction was stirred at room temperature for 12 h. THF was evaporated and the crude residue was poured into water/EtOAc. The aqueous layer was extracted with EtOAc and the combined organic layers were dried ($Na_2SO_4$) and evaporated in a vacuum. Flash chromatography of the crude (85% EtOAc/hexane) afforded 61 mg (70%) of triol **35**: $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 0.67 (s, 3H, *Me*-18), 0.93 (d, 3H, *Me*-21, $^3J_{HH}$ 6.4 Hz), 1.19 (s, 6H, *Me*-26 + *Me*-27), 1.00−1.60 (m, 12H), 1.70−2.80 (m, 12H), 4.20 (m, 1H, $H_3$), 4.27 (m, 1H, $H_1$), 5.96 (m, 1H, $H_9$ or $H_{10}$), and 6.13 (m, 1H, $H_9$ or $H_{10}$); HRMS calcd for $C_{26}H_{40}O_3$ ($M^+$) 400.2977, found 400.2994.

**1β,25-Dihydroxy-6,7-dehydro-3-*epi*-19-*nor*-previtamin $D_3$ (36).** The same procedure as the one described for **35** yielded **36** (75% from **32**): $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 0.67 (s, 3H, *Me*-18), 0.94 (d, 3H, *Me*-21, $^3J_{HH}$ 6.7 Hz), 1.20 (s, 6H, *Me*-26 + *Me*-27), 1.00−1.50 (m, 12H), 1.60−2.20 (m, 11H), 2.5 (dd, 1H, $^3J_{HH}$ 17.4, 4.8 Hz), 4.14 (m, 1H, $H_3$), 4.44 (m, 1H, $H_1$), 5.97 (dd, 1H, $H_9$, $^3J_{HH}$ 6.5, 3.4 Hz), and 6.03 (m, 1H, $H_{10}$); HRMS calcd for $C_{26}H_{40}O_3$ ($M^+$) 400.2977, found 400.2986.

**1α,25-Dihydroxy-3-*epi*-19-*nor*-previtamin $D_3$ (37).** A flask containing Lindlar catalyst (32 mg) was exposed to a positive pressure of hydrogen gas (balloon). MeOH (1 mL) was added and the mixture was cooled to 0 °C. To this suspension was added quinoline (0.24 mL, 0.17 M in hexane) and **35** (20 mg, 0.05 mmol) in MeOH (2 mL). The reaction was stirred at 20−25 °C and was carefully monitored by TLC (20% $^i$PrOH/hexane) to avoid over-reduction. After 3 h the mixture was filtered on Celite and concentrated to afford a residual oil which was purified by flash chromatography (gradient eluent 10−15% $^i$PrOH/hexane) to afford 14 mg (70%) of previtamin **37**: $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 0.71 (s, 3H, *Me*-18), 0.95 (d, 3H, *Me*-21, $^3J_{HH}$ 6.5 Hz), 1.21 (s, 6H, *Me*-26 + *Me*-27), 1.00−2.50 (m, 24H), 4.18 (m, 1H, $H_3$), 4.31 (m, 1H, $H_1$), 5.40 (m, 1H), and 5.82 (m, 3H); HRMS calcd for $C_{26}H_{40}O_2$ ($M^+ - H_2O$) 384.3028, found 384.3020.

**1β,25-Dihydroxy-3-*epi*-19-*nor*-previtamin $D_3$ (38).** The same procedure as the one described for **37** yielded **38** (75%): $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 0.65 (s, 3H, *Me*-18), 0.90 (d, 3H, *Me*-21, $^3J_{HH}$ 6.6 Hz), 1.16 (s, 6H, *Me*-26 + *Me*-27), 0.90−2.50 (m, 24H), 4.06 (m, 1H, $H_3$), 4.41 (m, 1H, $H_1$), 5.35 (m, 1H), and 5.79 (m, 3H); HRMS calcd for $C_{26}H_{42}O_3$ ($M^+$) 402.3134, found 402.3125.

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**Supporting Information Available:** Complete $^1$H and $^{13}$C NMR spectral data in addition to mp, optical rotations, IR, microanalysis, and MS (and/or HRMS) data. This material is available free of charge via the Internet at http://pubs.acs.org.

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