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Novel Heteroatom-containing Vitamin D₃ Analogs: Efficient Synthesis of 1 α ,25-Dihydroxyvitamin D₃-26,23-lactam

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Abstract: Vitamin D₃ and its synthetic analogs are promising compounds for controlling various types of cell differentiation. In this article, we describe the synthesis of novel vitamin D₃ analogs containing heteroatoms in their side chains – so-called vitamin D₃ lactam analogs – via 1,3-dipolar cycloaddition reaction as a key step.

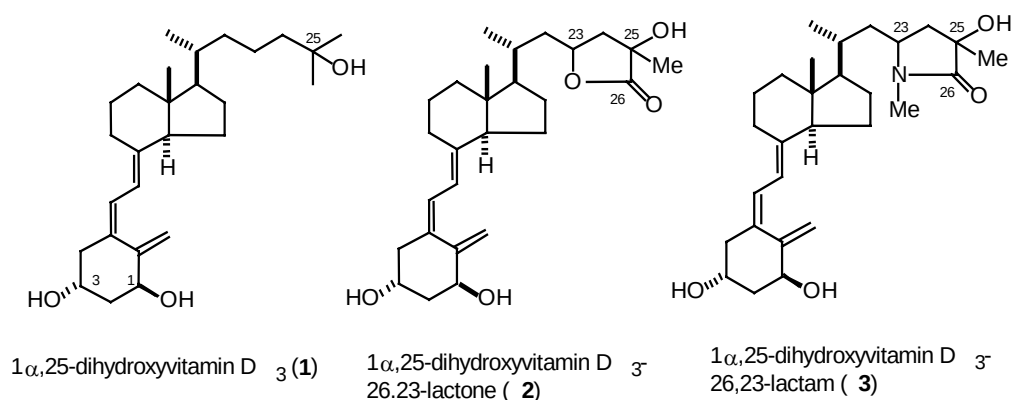
Keywords: Vitamin D₃, Vitamin D₃ analog, lactam, 1,3-dipolar cycloaddition reaction

Introduction

1 α ,25-Dihydroxyvitamin D₃ (**1**) has a wide variety of biological activities including the regulation of calcium homeostasis and the control of cellular growth, differentiation and apoptosis [1]. Though many analogs of **1** have been synthesized so far, only a few analogs containing nitrogen atoms in their structures have been reported. In the course of our recent studies towards the development of novel vitamin D₃ analogs, we focused on one of the major metabolites of **1**, so-called (23S, 25R)-1 α ,25-dihydroxyvitamin D₃-26,23-lactone (**2a**) which inhibits bone resorption induced by **1**, while it has very weak binding affinity against vitamin D nuclear receptor [2]. Interestingly, each of the diastereomers of **2a**, that are (23S,25S)-(**2b**), (23R,25R)-(**2c**), and (23R,25S)-(**2d**), has different biological activities. On the basis of the structure of **2**, we have designed 1 α ,25-dihydroxyvitamin D₃-26,23-lactam (**3**) as a

novel vitamin D₃ analog. Herein we report the efficient synthesis of (23*S*,25*R*)-1 α ,25-dihydroxyvitamin D₃-26,23-lactam (**3a**) including its A-ring and CD-ring synthons.

Figure 1



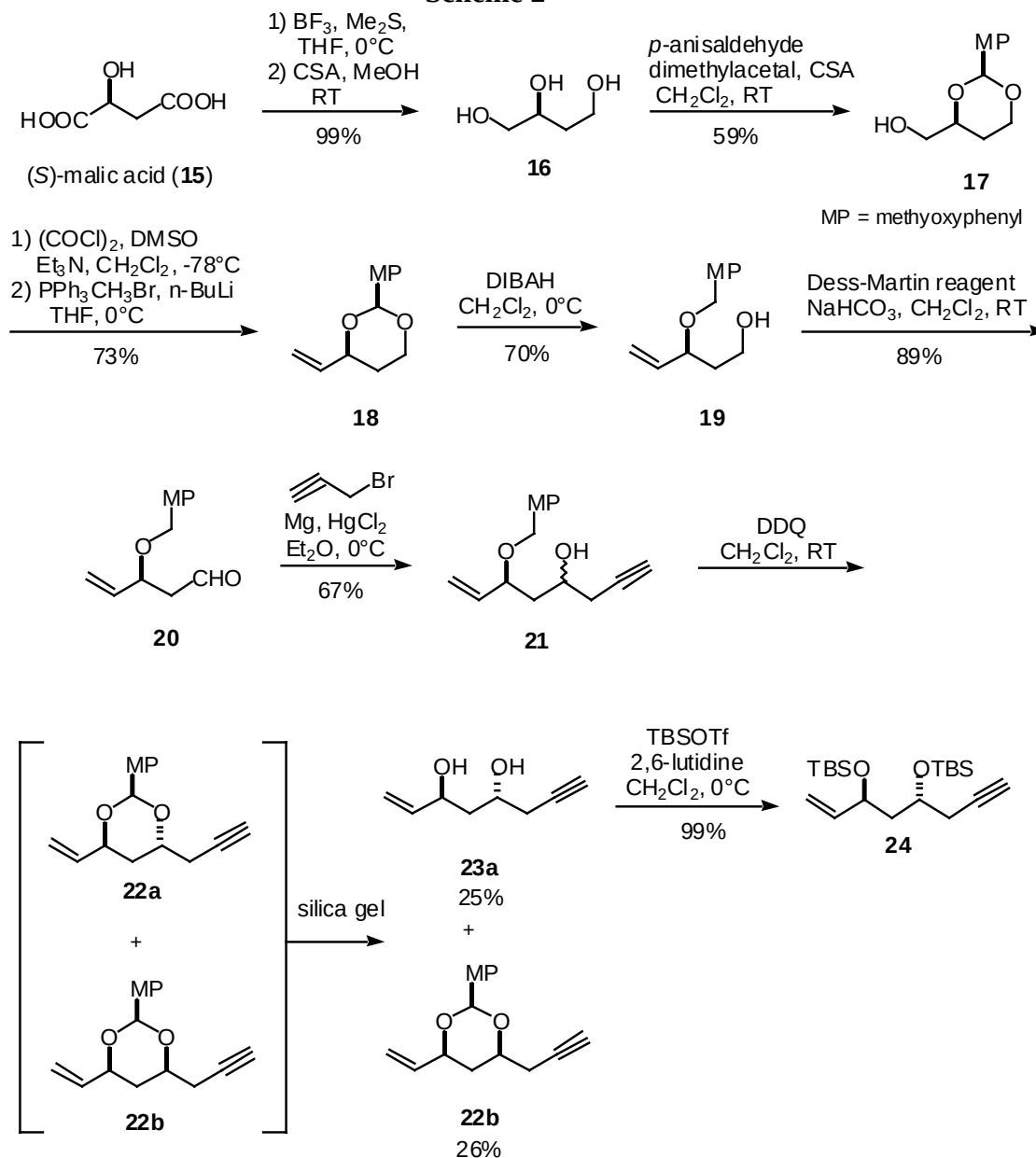
Results and Discussion

1. Synthesis of CD-ring synthon **14**

The synthesis of CD-ring synthon **14** for **3a** is summarized in **Scheme 1**. The reaction of the Inhoffen-Lythgoe diol (**5**), prepared from vitamin D₂ (**4**), with *p*-toluenesulfonyl chloride and DMAP followed by protection of the secondary alcohol with TBSOTf and 2,6-lutidine gave silyl ether **6** in 75% yield (2 steps). The tosylate **6** was converted into the aldehyde **8** with the following stepwise reaction: 1) cyanide formation with sodium cyanide and 2) reduction of the resulting cyanide with DIBAH [3]. The aldehyde **8** was reacted with *N*-methylhydroxy amine to give nitrone **9**, which was subsequently reacted with methyl methacrylate (**10**) to give the four possible diastereomers of isoxazolidine **11**. These diastereomers were separated with HPLC and **11a**, **11b**, **11c** and **11d** were thus obtained in 26, 28, 10 and 10% yields, respectively [4]. The stereochemistries of these compounds were confirmed by NMR techniques. One of the isomers, **11a**, which has (23*S*,25*S*)-stereochemistry, was then carried on to the CD-ring synthon **14**. Thus, the removal of the TBS group of **11a** with *p*-toluenesulfonic acid in methanol and reduction of the N-O bond with hydrogen in the presence of palladium on carbon gave lactam **12** in 80% yield. The secondary alcohol of **12** was oxidized with TPAP-NMO [5] conditions and tertiary alcohol was protected with TMS ether by TMS-imidazole to give ketone **13** in 80%. Finally, the Wittig reaction of **13** under the Trost's conditions [6] gave vinyl bromide **14** in 25% yield while the ketone **13** was recovered in 52%.

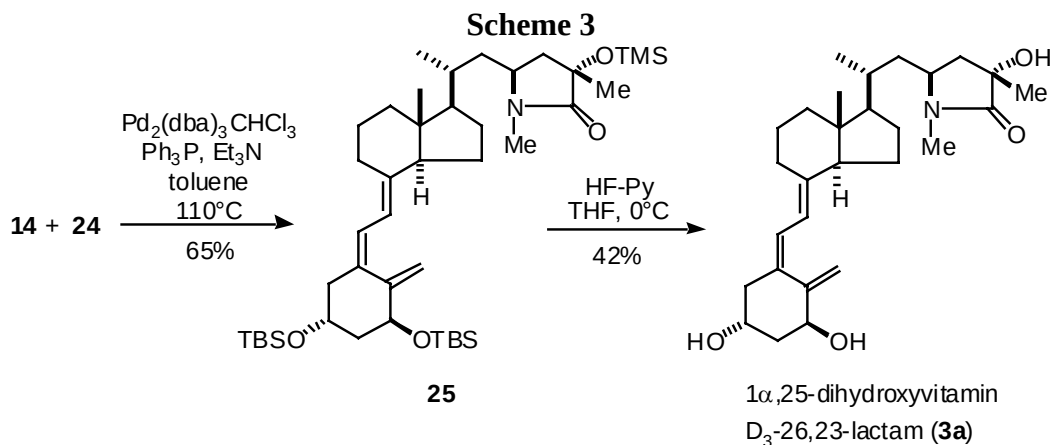
yield. The *p*-methoxybenzylidene acetal of **18** was selectively reduced with DIBAH at 0°C [7] gave alcohol **19** in 70% yield. The oxidation of the primary alcohol of **19** with Dess-Martin reagent [8] followed by propargylation with propargyl bromide and magnesium in the presence of a catalytic amount of mercury chloride gave **21** in 67% yield as a 1:1 mixture of diastereomers. The reaction of **21** with DDQ and subsequent purification on silica gel column gave deprotected diol **23a** via acetal **22a** and acetal **22b** in 25% and 26% yield, respectively. The diol **23a** was reacted with TBSOTf and 2,6-lutidine gave silyl ether **24** in 99% yield.

Scheme 2



With the vinyl bromide **14** (CD-ring synthon) and eneyne **24** (A-ring synthon) in hand, coupling reaction of these segments were examined based upon the palladium catalyzed reaction conditions [6,9]. Coupling reaction of **14** and **24** in the presence of catalytic amount of $\text{Pd}_2(\text{dba})_3\text{CHCl}_3$ and triphenylphosphine in toluene-triethylamine under the reflux conditions gave **25** in 65% yield.

Deprotection of the hydroxyl protecting group was finally performed with HF-pyridine to give (23S,25S)-1 α ,25-dihydroxyvitamin D₃-26,23-lactam (**3a**) in 42% yield.



Conclusions

In summary, we have designed and synthesized the novel vitamin D₃ analog **3a** having the lactam moiety on its CD-ring side chain. Our synthesis of **3a** features: 1) 1,3-dipolar cycloaddition reaction between **9** and **10**, followed by the reduction of an isoxazolidine to form the lactam moiety for **14** and 2) palladium catalyzed coupling reaction of CD-ring synthon **14** and A-ring synthon **24**. Since this method provides a variety of vitamin D₃ lactam analogs, synthetic efforts towards these, including (23R,25R)-(**3b**), (23R,25S)-(**3c**), and (23S,25R)-(**3d**), continue. Furthermore, the evaluation of the biological activities of synthetic analogs **3** in our laboratories is planned.

Experimental

General

Optical rotations were recorded with a JASCO DIP-370 polarimeter. IR spectra were measured with a JASCO VALOR-III FT-IR spectrophotometer. ^1H - and ^{13}C -NMR spectra were recorded on JNM- α 500 instruments at 500 and 125 MHz, respectively. Mass spectra were recorded on JEOL JMA-HX110 spectrometers.

(8S,20R)-De-A,B-8-Hydroxy-20-(hydroxymethyl)pregnane (**5**). Vitamin D₂ (**4**) (5.00 g, 12.63 mmol) was dissolved in CH_2Cl_2 (170 mL), and MeOH (70 mL) was added. After cooling to -78°C , a stream of ozone was passed to the solution for 1 h. The remaining ozone was purged with a stream of N_2 . After warming up to 0°C , NaBH_4 (1.43g, 37.8 mmol) was added and stirred for 1h. The reaction mixture was then acidified by adding 2N HCl and extracted with CH_2Cl_2 . The organic layer was washed with water, dried over MgSO_4 , filtered and concentrated *in vacuo*. The residue was chromatographed on silica gel (6:1 hexane - ethyl acetate) to give diol **5** (2.8g, 75%) as a white solid.

$^1\text{H-NMR}$ (CDCl_3) δ 4.09 (d, $J = 2.6$ Hz, 1H), 3.64 (dd, $J = 3.3, 10.6$ Hz, 1H), 3.39 (dd, $J = 6.6, 10.6$ Hz, 1H), 1.99 (dd, $J = 2.6, 13.2$ Hz, 1H), 1.12~1.92 (m, 14H), 1.03 (d, $J = 6.6$ Hz, 3H), 0.002 (s, 3H).

(8*S*,20*R*)-De-A,B-8-(*tert*-Butyldimethylsilyl)oxy-20-[(*p*-tolylsulfonyl)oxymethyl]pregnane (**6**). DMAP (3.7 g, 30.2 mmol) and *p*-TsCl (3.8 g, 19.63 mmol) was added to a solution of **5** (3.2 g, 15.10 mmol) in CH_2Cl_2 (45 mL). After stirring overnight at room temperature, the reaction mixture was poured into water (110 mL) and extracted with CH_2Cl_2 . The organic layer was washed with water, dried over MgSO_4 , filtered and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (70 mL) and then 2,6-lutidine (4.5 mL, 38.99 mmol) and TBSOTf (5.3 mL, 23.11 mmol) was added. After stirring at room temperature for 30 min, the solution was cooled to 0°C , satuated NaHCO_3 was added and extracted with CH_2Cl_2 . The organic layer was dried over MgSO_4 and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane) to give **5** as a colorless oil (4.29 g, 99%). $^1\text{H-NMR}$ (CDCl_3) δ 9.72 (dd, $J = 1.3, 3.3$ Hz, 1H), 3.99 (d, $J = 2.6$ Hz, 1H), 2.43 (m, 1H), 1.93 (m, 1H), 1.78 (m, 2H), 1.66 (m, 1H), 1.56 (m, 1H), 1.35 (m, 3H), 1.25 (m, 2H), 1.11 (m, 2H), 1.00 (d, $J = 6.3$ Hz, 3H), 0.96 (s, 3H), 0.89 (s, 9H), 0.01 (s, 3H), 0.002 (s, 3H).

(8*S*,20*R*)-De-A,B-8-(*tert*-Butyldimethylsilyl)oxy-20-(cyanomethyl)pregnane (**7**). To a solution of **6** (2.00 g, 4.17 mmol) in DMSO (30 mL) was added NaCN (270 mg, 5.42 mmol) and the resulting mixture was heated at 90°C for 1 h. The reaction mixture was poured into water (60 mL) and the organics were extracted with ethyl acetate. The extracts were washed with water and brine, dried over MgSO_4 , filtered and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane) to give **7** (1.02 g, 72%) as a colorless oil. $^1\text{H-NMR}$ (CDCl_3) δ 4.01 (d, $J = 2.6$ Hz, 1H), 2.34 (dd, $J = 4.0, 16.5$ Hz, 1H), 2.23 (dd, $J = 6.6, 16.5$ Hz, 1H), 1.10~2.00 (m, 20H), 1.14 (d, $J = 6.6$ Hz, 3H), 0.93 (s, 3H), 0.89 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H).

(8*S*,20*R*)-De-A,B-8-(*tert*-Butyldimethylsilyl)oxy-20-(formylmethyl)pregnane (**8**). To a solution of DIBAH (1M in hexane) (6.1 mL, 6.1 mmol) in CH_2Cl_2 (20 mL) was added a solution of **7** (1.02 g, 3.05 mmol) in CH_2Cl_2 (25 mL) at 0°C with dropwise and the mixture was stirred for 1 h. The reaction mixture was quenched by the addition of saturated NH_4Cl solution, and the resulting mixture was diluted with ether, and then stirred for another 30 min. The mixture was dried over MgSO_4 and filtered through a pad of Celite, and the filtrates were concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane) to give aldehyde **8** (595 mg, 58%) as a colorless oil. $^1\text{H-NMR}$ (CDCl_3) δ 9.75 (dd, $J = 1.3, 3.3$ Hz, 1H), 4.00 (d, $J = 2.6$ Hz, 1H), 2.46 (dd, $J = 2.0, 13.5$ Hz, 1H), 1.03~2.20 (m, 20H), 1.00 (d, $J = 6.3$ Hz, 3H), 0.96 (s, 3H), 0.89 (s, 9H), 0.01 (s, 3H), 0.002 (s, 3H).

(8*S*,20*R*)-De-A,B-8-(*tert*-Butyldimethylsilyl)oxy-20-[4-(2,5-dimethyl-5-isoxazolidinecarboxylic acid methyl ester)methyl]pregnane (**11**). To a mixture of **8** (595 mg, 2.66 mmol) in CH_2Cl_2 (8 mL) was added *N*-methyl hydroxylamine hydrochloride (184 mg, 3.19 mmol) and Et_3N (1.0 mL), and the

resulting mixture was stirred at room temperature for 3 h. To the reaction mixture was added saturated NaHCO_3 , and the mixture was extracted with CH_2Cl_2 . The organic layer was dried over MgSO_4 and concentrated *in vacuo*. The residue was dissolved in toluene (17 mL) and methyl methacrylate (**10**) (1.0 mL, 9.32 mmol) was added, and the resulting mixture was heated at 90°C for 2 h. The reaction mixture was concentrated *in vacuo*, and the residue was purified by HPLC using a PEGASIL Silica 60-5 column (ϕ 20x150 mm, Senshu Pak.) and elution with 15% ethyl acetate in hexane to give **11a** (316.6 mg, 26%), **11b** (343.6 mg, 28%), **11c** (116.5 mg, 10%) and **11d** (125.5 mg, 10%), respectively.

11a (23S, 25S): $[\alpha]_D^{24} = +112.4^\circ$ (c 1.1, CHCl_3); $^1\text{H-NMR}$ (CDCl_3) δ 3.98 (br s, 1H), 3.76 (s, 3H), 2.67 (s, 3H), 2.57 (br s, 1H), 2.46 (dd, $J = 3.0, 13.1$ Hz, 1H), 2.24 (dd, $J = 7.0, 13.1$ Hz, 1H), 1.94 (br d, $J = 13.1$ Hz, 1H), 1.79 (m, 2H), 1.65 (m, 2H), 1.54 (m, 1H), 1.47 (s, 3H), 1.39 (m, 4H), 1.21 (m, 2H), 1.11 (m, 2H), 1.01 (m, 1H), 0.92 (d, $J = 8.2$ Hz, 3H), 0.91 (s, 3H), 0.88 (s, 6H), -0.01 (d, $J = 7.0$ Hz, 9H); $^{13}\text{C-NMR}$ (CDCl_3) δ 175.67, 77.25, 76.99, 76.74, 69.36, 66.95, 57.37, 53.03, 52.57, 45.87, 43.27, 42.17, 40.73, 38.06, 34.35, 34.03, 27.61, 25.77, 24.37, 23.01, 18.85, 17.99, 17.61, 13.74, -4.82, -5.21; IR (neat) 3318, 2952, 2856, 1738 cm^{-1} ; m/z 468 ($\text{M}+\text{H}$) $^+$.

11b (23R, 25R): $[\alpha]_D^{24} = -26.7^\circ$ (c 1.0, CHCl_3); $^1\text{H-NMR}$ (CDCl_3) δ 3.98 (br s, 1H), 3.75 (s, 3H), 2.68 (s, 3H), 2.57 (dd, $J = 9.0, 12.2$ Hz, 1H), 2.51 (br s, 1H), 2.30 (m, 1H), 1.94 (br d, $J = 12.2$ Hz, 1H), 1.80 (m, 2H), 1.64 (m, 2H), 1.52 (m, 1H), 1.47 (s, 3H), 1.33 (m, 3H), 1.23 (m, 3H), 1.13 (m, 2H), 1.00 (m, 1H), 0.92 (d, $J = 6.0$ Hz, 3H), 0.90 (s, 3H), 0.87 (s, 6H), -0.01 (d, $J = 7.1$ Hz, 9H); $^{13}\text{C-NMR}$ (CDCl_3) δ 175.69, 69.35, 68.00, 57.42, 52.97, 52.54, 47.64, 43.93, 42.22, 40.66, 38.83, 34.52, 34.34, 27.56, 25.77, 24.29, 23.02, 19.60, 17.99, 17.60, 13.65, -4.83, -5.21; IR (neat) 3287, 2951, 2857, 1738 cm^{-1} ; m/z 468 ($\text{M}+\text{H}$) $^+$.

11c (23S, 25R): $[\alpha]_D^{24} = +62.5^\circ$ (c 1.0, CHCl_3); $^1\text{H-NMR}$ (CDCl_3) δ 3.98 (br s, 1H), 3.76 (s, 3H), 2.85 (dd, $J = 6.1, 13.1$ Hz, 1H), 2.70 (s, 3H), 2.00 (m, 1H), 1.86 (m, 1H), 1.66 (br d, $J = 12.2$ Hz, 1H), 1.57-1.42 (m, 1H), 1.52 (s, 3H), 1.37-0.99 (m, 12H), 0.91 (s, 3H), 0.89 (d, $J = 16.3$ Hz, 3H), 0.88 (s, 6H), -0.01 (d, $J = 7.2$ Hz, 9H); $^{13}\text{C-NMR}$ (CDCl_3) δ 174.47, 77.24, 76.99, 76.74, 69.36, 66.78, 57.31, 53.02, 52.50, 46.82, 43.84, 42.18, 40.69, 38.38, 37.60, 34.34, 34.14, 29.66, 27.66, 25.77, 24.92, 24.83, 23.00, 22.62, 19.05, 18.90, 18.00, 17.60, 14.08, 13.72, -4.81, -5.21; IR (neat) 3790, 2951, 2856, 2777, 1739 cm^{-1} ; m/z 468 ($\text{M}+\text{H}$) $^+$.

11d (23R, 25S): $[\alpha]_D^{24} = +16.9$ (c 1.1, CHCl_3); $^1\text{H-NMR}$ (CDCl_3) δ 3.98 (br s, 1H), 3.76 (s, 3H), 2.91 (dd, $J = 6.1, 12.1$ Hz, 1H), 1.95-1.91 (m, 2H), 1.81-1.76 (m, 2H), 1.70-1.64 (m, 2H), 1.59-1.47 (m, 2H), 1.51 (s, 3H), 1.37-1.20 (m, 6H), 1.12-0.97 (m, 3H), 0.92 (d, $J = 9.2$ Hz, 3H), 0.91 (s, 3H), 0.88 (s, 6H), -0.01 (d, $J = 7.1$ Hz, 9H); $^{13}\text{C-NMR}$ (CDCl_3) δ 174.84, 77.25, 76.99, 76.74, 69.38, 67.03, 57.42, 53.01, 52.48, 47.77, 44.88, 42.24, 40.68, 39.26, 34.37, 34.06, 31.56, 29.67, 27.51, 25.78, 24.86, 23.03, 22.62, 19.39, 18.00, 17.61, 14.08, 13.68, -4.81, -5.19; IR (neat) 3307, 2951, 2856, 2360, 1738 cm^{-1} ; m/z 468 ($\text{M}+\text{H}$) $^+$.

(8*S*,20*R*,23*S*,25*S*)-De-A,B-8,25-Dihydroxy-cholestane-26,23-*N*-methyl lactam (**12**). To a solution of **11a** (316.6 mg, 0.68 mmol) in MeOH (25 mL) was added a catalytic amount of p-TsOH and the resulting mixture was stirred for 12 h. The reaction mixture was diluted with ethyl acetate and the saturated NaHCO₃ was added. The resulting mixture was extracted with ethyl acetate and the organics was washed with brine, dried over MgSO₄, filtered and concentrated in vacuo. The residue was chromatographed on silica gel (5:1 hexane:ethyl acetate) to give the alcohol (218.7 mg, 91%) as a colorless oil. $[\alpha]_D^{24} = +145.9$ (c 1.0, CHCl₃); ¹H-NMR (CDCl₃) δ 3.98 (br s, 1H), 3.68 (s, 3H), 2.58 (s, 3H), 2.49 (br s, 1H), 2.38 (dd, *J* = 9.0, 13.0 Hz, 1H), 2.15 (dd, *J* = 8.2, 13.0 Hz, 1H), 1.90 (br d, *J* = 13.0 Hz, 1H), 1.80-1.69 (m, 3H), 1.54-0.93 (m, 11H), 1.39 (s, 3H), 0.84 (d, *J* = 6.3 Hz, 3H), 0.84 (s, 3H); ¹³C-NMR (CDCl₃) δ 175.71, 69.26, 66.90, 57.24, 52.60, 52.59, 45.83, 43.28, 41.91, 40.41, 38.06, 34.03, 33.54, 27.45, 24.36, 22.47, 18.77, 17.38, 13.51; IR (neat) 3526, 2948, 2867, 2360, 1737 cm⁻¹; *m/z* 354 (M+H)⁺. A mixture of the alcohol (218.7 mg, 0.62 mmol) and 10% Pd/C (100 mg) in EtOH (15 mL) was stirred under H₂ atmosphere for 12 h. The reaction mixture was filtered through a pad of Celite and the filtrates were concentrated *in vacuo* to give **12** (180 mg, 90%) as a colorless oil. $[\alpha]_D^{24} = +145.9^\circ$ (c 1.0, CHCl₃); ¹H-NMR (CDCl₃) δ 3.98 (br s, 1H), 3.68 (s, 3H), 2.58 (s, 3H), 2.49 (br s, 1H), 2.38 (dd, *J* = 9.0, 13.1 Hz, 1H), 2.15 (dd, *J* = 8.0, 13.1 Hz, 1H), 1.90 (br d, *J* = 13.1 Hz, 1H), 1.80-1.69 (m, 3H), 1.54-0.93 (m, 11H), 1.39 (s, 3H), 0.84 (d, *J* = 6.0 Hz, 3H), 0.84 (s, 3H); ¹³C-NMR (CDCl₃) δ 175.71, 69.26, 66.90, 57.24, 52.60, 52.59, 45.83, 43.28, 41.91, 40.41, 38.06, 34.03, 33.54, 27.45, 24.36, 22.47, 18.77, 17.38, 13.51; IR (neat) 3381, 2936, 2867, 2242, 1680 cm⁻¹; *m/z* 324 (M+H)⁺.

(20*R*,23*S*,25*S*)-De-A,B-25-Trimethylsilylhydroxy-cholestane-8-one-26,23-*N*-methyl lactam (**13**). To a solution of **12** (212 mg, 0.66 mmol) in CH₂Cl₂ (5 mL) was added tetra-*n*-propylammonium perruthenate (12 mg, 0.66 mmol), 4-methylmorpholine N-oxide (310 mg, 2.64 mmol) and molecular sieves 4A powder, and the whole mixture was stirred for 2 h at room temperature. The reaction mixture was loaded on the silica gel column chromatography (1:2 hexane - ethyl acetate) to give the ketone (219 mg, quant. yield) as a colorless oil. A mixture of the ketone (95 mg, 0.3 mmol) and TMS-imidazole (0.22 mL, 1.5 mmol) in CH₂Cl₂ (5 mL) was stirred for 12 h at room temperature. The reaction mixture was cooled at 0°C and water was added to the mixture. The organic layer was extracted with CH₂Cl₂, and the extracts were dried over MgSO₄, filtered and concentrated *in vacuo*. The residue was chromatographed on silica gel (2:1 hexane - ethyl acetate) to give **13** (107 mg, 91%) as a colorless oil. $[\alpha]_D^{24} = +36.0^\circ$ (c 1.0, CHCl₃); ¹H-NMR (CDCl₃) δ 3.55(m, 1H), 2.78 (s, 3H), 2.46 (dd, *J* = 8.0, 12.0 Hz, 1H), 2.32-1.20 (m, 19H), 1.02 (d, *J* = 6.1 Hz, 3H), 0.66 (s, 3H), 0.11 (s, 9H); ¹³C-NMR (CDCl₃) δ 211.49, 174.56, 76.24, 61.95, 57.11, 53.90, 49.81, 43.41, 40.89, 39.74, 39.03, 32.47, 27.94, 27.70, 25.54, 23.96, 19.04, 18.68, 12.53, 1.75; IR (neat) 3035, 2957, 2360, 1705 cm⁻¹; *m/z* 394 (M+H)⁺.

(7*E*)-(20*R*,23*S*,25*S*)-De-A,B-8-Bromomethylidene-25-trimethylsilylhydroxy-cholestane-26,23-*N*-methyl lactam (**14**). To an emulsion of bromomethyltriphenylphosphonium bromide (327 mg, 0.75 mmol) in toluene (2 mL) was added lithium hexamethyldisilazane (1 M in THF) (0.74 mL, 0.74 mmol) at -78°C

and the mixture was warmed up to 0°C and stirred for 10 min. After cooling to -78°C, to the resulting solution was added **13** (60.1 mg, 0.15 mmol) in toluene (1 mL) with dropwise, and the mixture was stirred at the same temperature for 2 h. To the reaction mixture was added saturated NH₄Cl and warmed up to room temperature. The resulting mixture was extracted with ethyl acetate and the organic layer was washed with brine, dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane) to give **14** (8.4 mg, 12%) and **13** (32 mg, 52%) was recovered. $[\alpha]^{24}_{\text{D}} = +79.47^\circ$ (c 0.9, CHCl₃); ¹H-NMR (CDCl₃) δ 5.56 (s, 1H), 3.45 (m, 1H), 2.80 (m, 1H), 2.68 (s, 3H), 2.19 (dd, *J* = 6.0, 12.2 Hz, 1H), 1.94-1.10 (m, 18H), 0.90 (d, *J* = 6.0 Hz, 3H), 0.49 (s, 3H), 0.02 (s, 9H); ¹³C-NMR (CDCl₃) δ 174.79, 144.73, 97.70, 56.27, 55.89, 53.93, 45.52, 43.38, 39.90, 39.80, 32.92, 30.97, 29.69, 28.01, 27.70, 25.58, 22.48, 21.98, 18.76, 11.87; IR (neat) 3734, 2952, 1700, 1635, 1507 cm⁻¹; *m/z* 470, 472 (M+H)⁺.

(2*S*)-2,4-Diol butanol anisilidene (**17**). To a solution of boranemethyl sulfide complex (100 mL, 1 mol) in THF (200 mL) was added the solution of (*S*)-malic acid (**15**) (50 g, 373 mmol) in THF (400 mL) at 0°C with dropwise over 3 h, and the resulting mixture was stirred for another 12 h at room temperature. The reaction mixture was re-cooled to 0°C and MeOH (400 mL) was added. The organics were evaporated *in vacuo* and the residue was dissolved in MeOH (300 mL) and evaporated *in vacuo*. The same sequences (addition of MeOH and concentration of organics) were repeated three times. The residue was dissolved in MeOH (300 mL) and *p*-TsOH (200 mg) was added, and the mixture was evaporated *in vacuo* to give **16** (50.63 g, 99%) as a colorless oil. To a solution of **16** (15 g, 141 mmol) in MeOH (240 mL) was added CSA (3.3 g, 14 mmol) and the mixture was heated at 90°C for 1 h. The resulting mixture was cooled to room temperature, and the organics were evaporated *in vacuo*. The residue was dissolved in CH₂Cl₂ and 4-methoxybenzaldehyde dimethylacetal (30 mL, 170 mmol) was added to the solution, and the resulting mixture was stirred for 6 h. To the reaction mixture was added saturated NaHCO₃, and the organic layer was extracted with ethyl acetate and washed with brine. The aqueous layer was extracted twice with ethyl acetate. The combined organic layers were dried over MgSO₄, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (2:1 hexane - ethyl acetate) to give **17** (18.23 g, 26%) as a pale yellow oil.

(3*S*)-3,5-Diol-1-pentene anisilidene (**18**). To a solution of (COCl)₂ (6.0 mL, 67.4 mmol) in CH₂Cl₂ (50 mL) was added DMSO (12.0 mL, 168.5 mmol) dropwise at -78°C and the mixture was stirred for 15 min. To the resulting mixture was added **17** (8.23 g, 33.7 mmol) in CH₂Cl₂ (100 mL) and the mixture was stirred for 40 min. Et₃N (470 mL, 337 mmol) was added and whole mixture was warmed to room temperature, and then stirred for another 30 min. Water (20 mL) was added and the organic layer was extracted with ethyl acetate. The extracts were washed with brine, dried over MgSO₄, filtered and evaporated *in vacuo*. The residue in THF solution was added to a solution of methylphosphoniumylide in THF prepared from methylphosphonium bromide (16.6 g, 46.5 mmol) and *n*-BuLi (1.5 M in hexane, 30 mL, 45 mmol) in THF (250 mL) at 0°C and the whole mixture was stirred at 0°C for 30 min and at room temperature for another 1 h. After cooling to 0°C, water was added, and the organics were

extracted with ethyl acetate. The extracts were washed with brine, dried over MgSO_4 , filtered and evaporated *in vacuo*. The residue was chromatographed on silica gel (10:1 hexane - ethyl acetate) to give **18** (2.77 g, 38%) as a colorless oil. $^1\text{H-NMR}$ (CDCl_3) δ 7.44 (d, $J = 10.0$ Hz, 2H), 6.88 (d, $J = 10.0$ Hz, 2H), 5.99 (m, 1H), 5.58 (s, 1H), 5.38 (dd, $J = 13.1, 1.0$ Hz, 1H), 5.19 (dd, $J = 13.1, 1.0$ Hz, 1H), 4.36 (dd, $J = 12.2, 6.3$ Hz, 1H), 4.28 (m, 1H), 4.00 (m, 1H), 3.80 (s, 3H), 1.92 (m, 1H), 1.60 (m, 1H).

(3*S*)-3-Methoxyphenylmethyloxy-5-hydroxy-1-pentene (**19**). To a solution of **18** (2.77 g, 12.6 mmol) in CH_2Cl_2 (130 mL) was added DIBAH (0.95 M in hexane, 66 mL, 63 mmol) dropwise at -20°C and the mixture was stirred for 2 h. 2-Propanol was added, then water and silica gel. The resulting slurry was diluted with ethyl acetate and stirred at room temperature for another 1 h. The slurry was filtered through a pad of Celite and the filtrates were concentrated *in vacuo*. The residue was purified by silica gel column chromatography (10:1 hexane - ethyl acetate) to give **19** (1.15 g, 41%) as a colorless oil. $^1\text{H-NMR}$ (CDCl_3) δ 7.14 (d, $J = 9.3$ Hz, 2H), 6.77 (d, $J = 9.3$ Hz, 2H), 5.68 (m, 1H), 5.17 (m, 2H), 4.46 (d, $J = 12.2$ Hz, 2H), 4.20 (d, $J = 12.2$ Hz, 2H), 3.90 (m, 1H), 3.70 (s, 3H), 3.65 (m, 1H), 1.75 (m, 1H), 1.67 (m, 1H).

(3*S*)-3-[(Methoxyphenylmethyloxy)-5-formyl-1-pentene (**20**). A mixture of **19** (1.15 g, 5.17 mmol), NaHCO_3 (1.7 g, 20.68 mmol) and Dess-Martin periodinane (4.4 g, 10.34 mmol) in CH_2Cl_2 (45 mL) was stirred for 1 h. The reaction mixture was directly loaded on a silica gel column (10:1 hexane - ethyl acetate) and purified to give **20** (990 mg, 89%) as a colorless oil. $^1\text{H-NMR}$ (CDCl_3) δ 9.48 (s, 1H), 7.15 (d, $J = 10.1$ Hz, 2H), 6.77 (d, $J = 10.1$ Hz, 2H), 5.50 (m, 1H), 5.04 (d, $J = 17.4$ Hz, 1H), 4.97 (d, $J = 10.1$ Hz, 1H), 4.41 (d, $J = 13.2$ Hz, 1H), 4.19 (d, $J = 13.2$ Hz, 1H), 4.00 (m, 1H), 2.35 (m, 1H), 2.2 (m, 1H).

(3*S*)-3-[(Methoxyphenylmethyloxy)-5-hydroxy-1-octen-7-yne (**21**). To a mixture of Mg (220 mg, 2.25 mmol) and HgCl_2 (25 mg, 0.09 mmol) in ether (40 mL) was added propargyl bromide (0.75 mL, 9.9 mmol) at room temperature until the Mg was dissolved. The mixture was cooled to 0°C , and **20** (495 mg, 2.25 mmol) in ether (25 mL) was added dropwise. After being stirred for 15 min, saturated NH_4Cl solution was added to the reaction mixture. The organics were extracted with ethyl acetate and washed with brine. The extracts were dried over MgSO_4 , filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (8:1 hexane - ethyl acetate) to give **21** (393.1 mg, 67%) as a colorless oil.

(3*S*,5*R*)-3,5-Dihydroxy-1-octen-7-yne (**23a**). To a solution of **21** (741.5 mg, 2.8 mmol) in CH_2Cl_2 (50 mL) was added DDQ (953 mg, 4.2 mmol) at room temperature. After being stirred for 1 h, the reaction mixture was quenched by the addition of saturated NaHCO_3 . The mixture was extracted with CH_2Cl_2 , dried over MgSO_4 , filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (8:1 hexane - ethyl acetate) to give **23a** (98.7 mg, 25%) and **22b** (189 mg, 26%) as colorless oils. **23a**: $^1\text{H-NMR}$ (CDCl_3) δ 5.94 (m, 1H), 5.31 (d, $J = 10.2$ Hz, 2H), 5.17 (d, $J = 10.2$ Hz,

2H), 4.49 (m, 1H), 4.41 (m, 1H), 4.11 (m, 1H), 4.05 (m, 1H), 2.41 (m, 2H), 2.16 (m, 1H), 1.86 (m, 1H), 1.73 (m, 1H).

(3*S*,5*R*)-3,5-Di[(*t*-butyldimethylsilyl)oxyl]-1-octen-7-yne (**24**). To a solution of **23a** (98.7 mg, 0.70 mmol) in CH₂Cl₂ (7 mL) was added 2,6-lutidine (0.25 mL, 2.1 mmol) and TBSOTf (0.4 mL, 1.75 mmol) at 0°C and the mixture was stirred for 30 min at room temperature. The reaction mixture was re-cooled to 0°C, and saturated NaHCO₃ was added. The organics were extracted with CH₂Cl₂ and the extracts were dried over MgSO₄, filtered and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane) to give **24** (248.2 mg, 96%) as a colorless oil. $[\alpha]_D^{24} = -5.19^\circ$ (c 0.7, CHCl₃); ¹H-NMR (CDCl₃) δ 5.57 (m, 1H), 5.04 (d, *J* = 17.4 Hz, 1H), 4.94 (d, *J* = 10.1 Hz, 1H), 4.11 (m, 1H), 3.82 (m, 1H), 2.25 (m, 2H), 1.87 (m, 1H), 1.81-1.53 (m, 2H), 1.44 (s, 1H), 0.78 (m, 18H), 0.03 (m, 12H); ¹³C-NMR (CDCl₃) δ 141.90, 114.25, 81.47, 71.65, 70.07, 68.13, 45.89, 27.98, 25.92, 25.85, -3.76, -4.15, -4.45, -4.58; IR (neat) 3315, 2956, 2930, 2888, 2858, 1749, 1624, 1508 cm⁻¹; *m/z* 369 (M+H)⁺.

(2*S*,25*S*)-1α,3-Di[(*t*-butyldimethylsilyl)oxyl]-25-(trimethylsilyl)oxyl vitamin D₃ 26,23-*N*-methyl lactam (**25**). A mixture of Pd₂(dba)₃CHCl₃ (2 mg, 0.002 mmol), PPh₃ (5 mg, 0.19 mmol) and Et₃N (0.8 mL) in toluene (0.8 mL) was stirred for 10 min at room temperature. To the resulting mixture was added **14** (13.8 mg, 0.03 mmol) and **24** (8 mg, 0.02 mmol) in toluene (0.8 mL) dropwise, and the whole mixture was heated at 110°C for 4 h. The reaction mixture was diluted with hexane and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane) to give **25** (9.4 mg, 62%) as a colorless oil. Ketone **14** (4.7 mg, 33%) and enyne **24** were recovered (2.7 mg, 37%).

(2*S*,25*S*)-1α,25-Dihydroxy vitamin D₃-26,23-*N*-methyl lactam (**3a**). A mixture of **25** (4.7 mg, 0.0062 mmol) and HF pyridine (1 mL) in THF (2 mL) at 0°C was stirred for 6 h. The reaction mixture was quenched with saturated NaHCO₃ and the organics were extracted with ethyl acetate. The extracts were dried over MgSO₄, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (9:1 CHCl₃-MeOH) to give **3a** as a pale yellow oil (1.5 mg, 53%). ¹H-NMR (CDCl₃) δ 6.37 (d, *J* = 11.5 Hz, 1H), 6.02 (d, *J* = 11.1 Hz, 1H), 5.33 (s, 1H), 4.99 (s, 1H), 4.43 (br s, 1H), 4.23 (br s, 1H), 2.82 (s, 3H), 2.61-0.70 (m, 33H), 0.99 (d, *J* = 6.4 Hz, 3H), 0.58 (s, 3H); *m/z* 458(M+H)⁺.

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