Synthesis of Diastereomers of 1,3-cis-25-Dihydroxy-19-norvitamin D₃

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1β,3β,25-Dihydroxy-19-norvitamin D₃ (4a) and 1α,3α,25-dihydroxy-19-norvitamin D₃ (4b) were synthesized by employing a new A-ring synthons, (1R,3S)-3-((tert-butyldimethylsilyl)oxy)-5-oxocyclohexyl benzoate (19), which was derived from α-(−)-quinic acid in 12 steps. The A-ring was coupled with the circular dichroism (CD) ring by means of Julia–Kocienski olefination to construct the diene unit. The structures of the products were confirmed by 1H-NMR and nuclear Overhauser effect (NOE) experiments.

Key words 19-norvitamin D₃; cis-A ring synthons; Julia–Kocienski coupling

Results and Discussion

Synthesis of ketone 6 is illustrated in Chart 2. 1,3,5-Cyclohexanetriol (7) was reacted with the phenylboronic acid in toluene under reflux to give the boronate, whose free hydroxy group was then protected as benzene ester by reaction with benzyl chloride in the presence of triethylamine, affording 8 in 76% yield (2 steps). The boronate ester in 8 was hydrolyzed using pinacol in the presence of BF₃·Et₂O and the free hydroxy groups were protected as tert-butylidemethylsilyl (TBS) ether using TBS chloride in the presence of triethylamine and tetrabutylammonium bromide (TBAB), affording 9 in 52% yield. After hydrolysis of benzoyl group in 9 with sodium hydroxide in methanol, the resulting hydroxy group was oxidized with pyridinium chlorochromate (PCC) to give ketone 6 in 56% yield.

With ketone 6 in hand, the CD ring synthons 5 and ketone 6 were coupled using lithium bis(trimethylsilyl)amide

1α,25-Dihydroxyvitamin D₃ (2, Fig. 1; also known as calcitriol), which is the hormonally active form of vitamin D₃ (1) in mammals, regulates calcium and phosphorus homeostasis, and also has antiproliferative, cell differentiation-inducing and immune-regulatory activities. It is used to treat hyperproliferative disorders, but its clinical utility is limited by side effects such as hypercalcemia and hypercalciuria, which are induced at clinically effective doses. Hence, there is a need for structural development to separate these biological activities.

19-Norvitamin D₃ (3) was first reported by DeLuca and colleagues in 1990, and has a characteristic biological activity profile, exhibiting high differentiation potency towards various malignant tissues with a substantially reduced calcemic effect. Since then, there have been many synthetic studies of 3, mainly focusing on the A-ring synthons. We recently reported a new synthetic strategy. We are particularly interested in structural derivatization involving the C1 and C3 hydroxy groups, whose geometries are believed to be crucial for antiproliferative activity. Herein, we described syntheses of 1β,3β,25-dihydroxy-19-norvitamin D₃ (4a) and 1α,3α,25-dihydroxy-19-norvitamin D₃ (4b), using a newly developed methodology to obtain the 1,3-cis-type A-ring synthons 19.
(LiHMDS) in tetrahydrofuran (THF) to give 10 in 98% yield as a 1:1 mixture of diastereomers 10a and 10b (Chart 3). However, separation of these two diastereomers was difficult. Moreover, the chemical shifts of H at C1 and C3 of these two isomers 10a and 10b overlapped ($\delta = 3.6–3.9$ ppm), and structural identification of these isomers was problematic. Therefore, we decided to modify the hydroxy protecting groups at the A-ring in order to obtain products with different polarity, which would be more easily separable.

Specifically, we planned to change one silyl ether to benzoate ester in ketone 6 to obtain 19. The strongly electron-withdrawing nature of the benzoate group would make the adjacent C1–H more deshielded than its C3 counterpart, which should enable an easy identification of both H’s in $^1$H-NMR. This group was also expected to induce some polarity difference between the two target compounds, enabling us to separate them easily on a preparative scale. Thus, we attempted selective deprotection of one TBS group in 6 using tetrabutylammonium fluoride (TBAF) (1 eq) or hydrogen fluoride·pyridine (HF·Py) (1 eq). However, $\beta$-elimination and subsequent aromatization reaction took place to generate 12 and 13, respectively (Chart 4). These results led us to develop a new route to synthesize an A-ring synthon with different hydroxy protecting groups at the C1 and C3 positions (19).

We started our synthesis of 19 from 14, which can be obtained from $\alpha$-$(\pm)$-quinic acid in five steps (Chart 5). The diol in 14 was protected with benzaldehyde dimethylacetal to give acetal 15 in 82% yield. We found that selective deprotection of one TBS group in 15 proceeded upon slow addition of TBAF in THF (1 eq) at 0°C to give a mixture of four stereoisomers 16 in 70% yield. This mixture of isomers was oxidized with tetrapropylammonium perruthenate-N-methylmorpholine-N-oxide (TPAP-NMO) to give ketone 17 (a mixture of four isomers). Various conditions were investigated for the stereoselective reduction of ketone 17 to 1,3-cis alcohol 18. Among them, diisobutylaluminium hydride (DIBAL)-H in the presence of ZnCl$_2$ was effective, and 1,3-cis alcohol 18 (more polar) was obtained in 67% yield, together with 1,3-trans alcohol 16 (less polar, 29%) after silica gel column separation.

After protection of the hydroxy group in 18 as benzoate by reaction with benzoyl chloride and triethylamine, deprotection of benzylidene acetal under hydrogenation conditions in the presence of palladium hydroxide followed by oxidative cleavage of the resulting diol with NaIO$_4$ aqueous solution in...
methanol afforded ketone 19. Coupling reaction of CD-ring synthon 5 with ketone 19 was performed to give 20a and b. These two diastereomers were separable by silica gel column chromatography, affording 20a and b in 36 and 35% yield, respectively. The structures of these isomers were confirmed by 1H-NMR and nuclear Overhauser effect correlated spectroscopy (NOESY) (Chart 6).

These isomers were converted to 1,3-cis-19-nor vitamin D₃ 4a and b in 56 and 59% yield, respectively, by reaction with potassium carbonate in methanol–THF followed by deprotection of silyl ethers with HF·Py.

**Conclusion**

In conclusion, synthesis of 1,3-cis-19-nor type A-ring synthon from 1,3,5-cyclohexanetriol was problematic due to the difficulty of separation and identification of the 1,3-cis-19-nor vitamin D₃ isomers 4a and b. A simple strategic modification to protect one hydroxy group with benzoate afforded A-ring synthon 19. Finally, 4a and b were synthesized by Julia–Kocienski olefination of this A-ring synthon and a circular dichroism (CD) ring synthon, thus opening up a new route that should be available to build a library of 1,3 modified 1,3-cis-19-nor type vitamin D derivatives in a convergent manner.

**Experimental**

All reactions have been carried out in dry solvents, and under inert atmosphere unless otherwise mentioned. Reagents were purchased from Sigma-Aldrich (St. Louis, MO, U.S.A.), TCI and Wako Pure Chemical Industries, Ltd. (Osaka, Japan). Flash chromatography was performed on silica gel 60 (spherical, particle size 40–100 mm; Kanto (Tokyo, Japan)). 1H-NMR spectra have been recorded in deuteriochloroform at 300 and 400 MHz using JMT 300 and JNM-ECX 400 spectrometers, whereas 13C-NMR spectra have been recorded at 75 and 100 MHz using same spectrometers. The spectra are referenced internally according to residual solvent signal of CDCl₃ (1H-NMR: δ = 7.26 ppm; 13C-NMR: δ = 77.0 ppm).

For mixture of diastereomers NMR of single pure diastereomer or the peaks for major isomers is reported, in other cases diastereomeric protons have been reported in italics. Mass spectra were recorded on a JMS-T100X (JEOL) spectrometer in electrospray ionization (ESI)-MS mode using methanol as solvent.

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for 4 h at room temperature, then the solvent was evaporated off under reduced pressure, the left over gum was dissolved in methanol and evaporated under reduced pressure, this process was repeated for five times, and then the left over sticky substance was treated as the crude for the next step. The crude product was dissolved in N,N-dimethylformamide (DMF) (15.5 mL) at 0°C. To the mixture was added tetrabutyl ammonium bromide (48 mg, 0.15 mmol), N,N-dimethyl-4-aminopyridine (DMAP) (189 mg, 1.55 mmol), and TBSCl (2.34 g, 15.5 mmol), then triethylamine (0.59 mL, 434 mg, 4.27 mmol) was added dropwise, after the addition was over the reaction was raised at room temperature, and allowed to stand at room temperature for 15 h. After the reaction was finished, water (75 mL) was added to the reaction, and then the aqueous layer was extracted with CH₂Cl₂ for three times. The combined organic layer was washed with water for three times, and then was washed with brine, dried over MgSO₄, filtered and evaporated in vacuo. The residue was purified by silica gel column (5% ethyl acetate–hexanes) to give 9 (372 mg, 2 steps 52%).

**Spectral Data for 9**

1H-NMR (300 MHz, CDCl₃): δ: 7.60–7.33 (5H, m), 5.06–4.89 (1H, m), 3.74–3.63 (2H, m), 2.56–2.50 (1H, m), 3.92–3.68 (1H, m), 2.28 (2.17) (1H, d, J = 11.9Hz), 1.97–1.84 (3H, m), 1.67–1.59 (1H, m), 1.48–1.34 (1H, m), 0.90 (1H, d, J = 5.9Hz), 0.10–0.05 (12H, q, J = 6.4Hz); 13C-NMR (75 MHz, CDCl₃): δ: 138.71 (138.11), 129.29 (129.15), 128.43, 126.79 (126.58), 102.57 (101.49), 81.52 (80.99), 75.29, 67.38 (67.16), 66.09 (65.83), 46.34 (44.42), 42.73 (42.68), 41.89 (41.80), 25.99, 25.89, 18.27, 18.05, −4.54, −4.83. HR-MS ESI: m/z: Calcd for C₂₅H₄₄NaO₄Si₂: 501.2832 [M+Na]+. Found: 501.2805.

**Spectral Data for 16**

1H-NMR (300 MHz, CDCl₃): δ: 7.50–7.46 (2H, m), 7.40–7.36 (3H, m), 5.85 (1H, s), 4.34–4.26 (1H, m), 4.17–4.08 (1H, m), 4.02 (1H, d, J = 8.6Hz), 3.80 (1H, d, J = 8.9Hz), 2.07 (1H, d, J = 3.4, 13.4, Hz), 2.00–1.66 (5H, m), 0.89 (9H, s), 0.09 (6H, s); 13C-NMR (75 MHz, CDCl₃): δ: 137.63, 129.56, 128.52, 126.73, 103.22, 82.46, 67.20, 65.11, 44.29, 42.31, 40.06, 25.43, 18.19, −4.69, −4.73. HR-MS ESI: m/z: Calcd for C₂₅H₄₂NaO₄Si₂: 387.1976 [M+Na]+. Found: 387.1994.

**Spectral Data for 17**

1H-NMR (300 MHz, CDCl₃): δ: 7.46–7.42 (2H, m), 7.39–7.35 (3H, m), 5.88 (1H, s), 4.39–4.31 (1H, m), 4.00 (1H, d, J = 8.6Hz), 3.78 (1H, d, J = 8.6Hz), 2.69–2.60 (3H, m), 2.43–2.31 (2H, m), 2.03–1.96 (1H, m), 0.87 (9H, s), 0.05 (6H, s); 13C-NMR (75 MHz, CDCl₃): δ: 206.06, 137.78, 129.46, 128.50, 126.55, 103.25, 81.18, 75.25, 66.86, 50.16, 49.75, 43.54, 25.83, 18.10, −4.78, −4.82. HR-MS ESI: m/z: Calcd for C₂₅H₄₄NaO₄Si₂: 385.1811 [M+Na]+. Found: 385.1851.

**Combined organic layer was washed with water and brine, dried on MgSO₄, filtered and evaporated in vacuo. The residue was purified on silica gel column (2% ethyl acetate–hexanes) to give 15 (2.54 g, 82%) as a mixture of two diastereomers.**

**Spectral Data for 15**

1H-NMR (300 MHz, CDCl₃): δ: 7.50–7.46 (2H, m), 7.41–7.34 (3H, m), 5.92 (5.81) (1H, s), 4.26–4.25 (1H, m), 4.08–3.98 (2H, m), 3.92–3.68 (1H, m), 2.28 (2.17) (1H, d, J = 11.9Hz), 1.97–1.84 (3H, m), 1.67–1.59 (1H, m), 1.48–1.34 (1H, m), 0.90 (1H, d, J = 5.9Hz); 13C-NMR (75 MHz, CDCl₃): δ: 138.71 (138.11), 129.29 (129.15), 128.43, 126.79 (126.58), 102.57 (101.49), 81.52 (80.99), 75.29, 67.38 (67.16), 66.09 (65.83), 46.34 (44.42), 42.73 (42.68), 41.89 (41.80), 25.99, 25.89, 18.27, 18.05, −4.54, −4.83. HR-MS ESI: m/z: Calcd for C₃₀H₄₀Na₂O₄Si₂: 501.2832 [M+Na]+. Found: 501.2805.
−78°C, and the resultant mixture was warmed to room temperature. Then, saturated Rochelle salt solution (5.2 mL) was added, and allowed to stir for 30 min. The aqueous layer was extracted with CH₂Cl₂ for three times. The combined organic layer was washed with saturated Rochelle salt and brine, dried over MgSO₄, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel column (6–8, 9–10% ethyl acetate–hexanes) to give trans alcohols 16 (less polar, 115 mg, 29%) and cis alcohols 18 (more polar, 226 mg, 67%).

Spectral Data for 18

1H-NMR (300 MHz, CDCl₃) δ: 7.48–7.44 (2H, m), 7.41–7.32 (3H, m), 5.85 (1H, s), 4.13–4.02 (3H, m), 3.85 (1H, d, J = 8.3 Hz), 2.13–2.00 (3H, m), 1.64–1.43 (3H, m), 0.89 (9H, s), 0.07 (6H, s); 13C-NMR (75 MHz, CDCl₃) δ: 137.91, 129.47, 128.49, 126.79, 103.35, 80.40, 67.35, 66.71, 44.36, 42.91, 42.34, 25.94, 18.19, −4.69, −4.76. HR-MS ESI: m/z: Calcd for C₁₉H₂₈Na₁O₄Si: 371.1655. Found: 371.1654.

(1R,3S)-3-[(tert-Butyldimethylsilyloxy)-5-oxocyclohexyl]benzoate (19) To a solution of cis alcohols 18 (219 mg, 0.6 mmol) in CH₂Cl₂ (5 mL) was added benzyl chloride (0.15 mL, 186 mg, 1.32 mmol), triethylamine (0.24 mL, 182 mg, 1.3 mmol), and a saturated aqueous solution of NaIO₄ (542 mg, 2.53 mmol, 0.62 mL) was added, and the reaction mixture was stirred for 2.5 h, then the reaction mixture was raised to 78°C, and the resultant mixture was warmed to room temperature. Then, saturated Rochelle salt solution (5.2 mL) was added, and the reaction mixture was allowed to stir overnight. To the reaction mixture was added saturated NH₄Cl, and the aqueous layer was extracted with CH₂Cl₂ for three times. The combined extracts were washed with water and brine, dried over MgSO₄, filtered, and concentrated in vacuo. The residue was chromatographed on the silica gel column (5% ethyl acetate–hexane) to give ketone 20a (18 mg, 36%) and 20b (17 mg, 35%).

Spectral Data for 20a

1H-NMR (400 MHz, CDCl₃) δ: 8.05 (2H, d, J = 6.9 Hz), 7.55 (1H, t, J = 7.3 Hz), 7.44 (2H, t, J = 7.8 Hz), 6.26 (1H, d, J = 10.9 Hz), 5.80 (1H, d, J = 11.5 Hz), 4.91–4.90 (1H, m), 3.71–3.67 (1H, m), 3.13 (1H, dd, J = 4.6, 12.8 Hz), 2.80 (1H, d, J = 11.5 Hz), 2.45 (1H, d, J = 4.6, 13.1 Hz), 2.36 (1H, m), 2.14 (1H, t, J = 11.9 Hz), 2.02–1.86 (3H, m), 1.67–1.60 (4H, m), 1.41–1.24 (13H, m), 1.17 (6H, s), 0.96–0.82 (22H, m), 0.58–0.52 (9H, m), 0.07 (6H, d, J = 6.9 Hz), 13C-NMR (100 MHz, CDCl₃) δ: 165.98, 143.35, 132.99, 130.65, 130.38, 130.72, 129.72, 128.42, 123.05, 115.57, 73.59, 70.49, 68.76, 56.73, 56.46, 46.45, 45.94, 45.62, 41.85, 40.62, 36.55, 36.22, 33.74, 30.11, 29.93, 28.97, 27.73, 25.95, 23.59, 22.39, 20.94, 18.92, 18.21, 12.26, 7.24, 6.91, −4.48, −4.54. HR-MS ESI: m/z: Calcd for C₁₉H₂₉NaO₂Si: 759.5180 [M+N+]. Found: 759.5180.

Spectral Data for 20b

1H-NMR (400 MHz, CDCl₃) δ: 8.04 (2H, d, J = 7.3 Hz), 7.55 (1H, t, J = 7.8 Hz), 7.44 (2H, t, J = 7.8 Hz), 6.29 (1H, d, J = 10.9 Hz), 5.84 (1H, d, J = 11.5 Hz), 4.91–4.88 (1H, m), 3.62–3.58 (1H, m), 2.99 (1H, dd, J = 4.6, 10.9 Hz), 2.79 (1H, d, J = 12.4 Hz), 2.66 (1H, dd, J = 4.6, 12.4 Hz), 2.37–2.34 (1H, br), 2.25–2.20 (1H, t, J = 11.5 Hz), 2.02–1.66 (9H, m), 1.43–1.30 (7H, m), 1.19 (6H, s), 0.96–0.83 (23H, m), 0.59–0.53 (9H, m), 0.09–0.07 (6H, d, J = 8.2 Hz), 13C-NMR (100 MHz, CDCl₃) δ: 165.96, 143.38, 132.96, 130.62, 130.38, 129.68, 128.39, 123.05, 115.54, 73.56, 71.04, 68.60, 56.73, 56.41, 45.84, 45.61, 42.07, 41.76, 40.56, 38.32, 36.53, 36.23, 30.09, 29.92, 29.79, 28.99, 27.78, 25.96, 23.63, 22.23, 20.93, 18.91, 18.29, 12.15, 7.22, 6.89, −4.59, −4.67. HR-MS ESI: m/z: Calcd for C₁₉H₂₉NaO₂Si: 759.5180 [M+N+]. Found: 759.5170.

(1R,3S,5,E)-5-[(E)-2-[(1R,7aR)-7a-methyl-1-[(R)-6-methyl-6-[(triethylsilyloxy)heptan-2-yl]hexahydro-1H-inden-4(2H)-ylidene]ethylidene]cyclohexene-1,3-diol (4a) To a solution of 20a (18 mg, 24 µmol) in MeOH (0.6 mL) and THF (2.4 mL) was added K₂CO₃ (5 mg, 36 µmol) and kept for 20 min. The mixture was added saturated NaH₂O₂, and aqueous layer was extracted with ethyl acetate for three times. The combined organic layer was washed with water and brine, dried over MgSO₄, filtered, and concentrated in vacuo. The residue was purifed by silica gel column (10% ethyl acetate–hexanes) to give alcohol, which was then dissolved in THF (1 mL), and HF·Py (181 mg, 0.16 mL, 6.3 mmol) was added, and the reaction mixture was stirred for 2.5 h, then the mixture was raised to room temperature and allowed to stand for 10 min. To the reaction mixture was added water, and extracted with ether for three times. The combined extracts were washed with brine, dried over MgSO₄, filtered, and concentrated in vacuo. The residue was first eluted using 3% MeOH–CH₂Cl₂ on a silica gel column, and then
again purified on a preparative TLC plate using 5% MeOH–CH₂Cl₂ as the mobile phase to give 4a (5 mg, 56%).

Spectral Data for 4a

$^{1}$H-NMR (400 MHz, CDCl₃) $\delta$: 6.23 (1H, d, J=10.9 Hz), 5.86 (1H, d, J=11.5 Hz), 3.91 (2H, m), 2.82 (1H, dd, J=10.3, 4.1 Hz), 2.59 (1H, dd, J=11.5, 3.7 Hz), 2.49 (1H, dd, J=13.3, 3.7 Hz), 2.43–2.38 (1H, m), 2.13–2.14 (27H, m), 2.13–2.12 (27H, m), 1.22 (6H, s), 0.94 (3H, d, J=6.4 Hz), 0.55 (3H, s); $^{13}$C-NMR (100 MHz, CDCl₃) $\delta$: 142.89, 130.21, 123.82, 115.48, 71.22, 68.92, 68.65, 56.41, 45.87, 45.23, 44.50, 41.33, 40.59, 36.95, 36.48, 36.20, 29.46, 29.28, 28.99, 27.95, 23.57, 22.37, 20.89, 18.89, 12.16. HR-MS ESI: m/z: Calcd for C₂₆H₄₄NaO₃; 427.3188 [M+Na]$^+$; Found: 427.3172.

(1R,3S,Z)-5-[(E)-2-[(1R,7aR)-1-[(R)-6-Hydroxy-6-methylheptan-2-yl]-7a-methylhexahydro-1'H-inden-4(2H)-ylidenemethylidene]cyclohexane-1,3-diol (4b) Similar to 20a, compound 20b (17 mg, 24 μmol) in MeOH (0.6 mL) and THF (2.4 mL) was added K₂CO₃ (4.9 mg, 36 μmol) and the resulting mixture was stirred for 24 h at room temperature. The residue was purified by silica gel column, and then the residue was washed with water and brine, dried over MgSO₄, and filtered and concentrated in vacuo. The residue was purified by silica gel column (10% ethyl acetate–hexanes) to give alcohol, which was then dissolved in THF (1 mL), and HF·Py (0.16 mL) was added, and the resulting mixture was stirred for 24 h at room temperature. To the reaction mixture was added saturated Na₂S₄O₆, and aqueous layer was extracted with ethyl acetate for three times. The combined organic layer was washed with water and brine, dried over MgSO₄, filtered and concentrated in vacuo. The residue was first eluted using 3% MeOH–CH₂Cl₂ on a silica gel column, and then again purified on a preparative TLC plate using 5% MeOH–CH₂Cl₂ as the mobile phase to give 4b (5.5 mg, 59%).

Spectral Data for 4b

$^{1}$H-NMR (400 MHz, CDCl₃) $\delta$: 6.34 (1H, d, J=10.9 Hz), 5.87 (1H, d, J=11.5 Hz), 4.01 (2H, br), 2.83 (1H, dd, J=4.6, 10.3 Hz), 2.58 (1H, dd, J=6.4, 13.5 Hz), 2.32–2.24 (3H, m), 2.04–1.97 (3H, m), 1.91–1.84 (2H, m), 1.72–1.21 (23H, m), 0.94 (3H, d, J=6.4 Hz), 0.55 (3H, s); $^{13}$C-NMR (100 MHz, CDCl₃) $\delta$: 142.89, 130.05, 124.14, 115.44, 71.22, 68.96, 68.77, 56.58, 56.39, 45.85, 45.14, 44.50, 40.56, 40.36, 36.76, 36.47, 36.20, 29.44, 29.31, 29.02, 27.78, 25.60, 22.37, 20.90, 18.89, 12.17. HR-MS ESI: m/z: Calcd for C₂₆H₄₄NaO₃; 427.3188 [M+Na]$^+$; Found: 427.3196.

Conflict of Interest The authors declare no conflict of interest.

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