Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 7826

www.rsc.org/obc

PAPER

Synthesis of vitamin D_3 derivatives with nitrogen-linked substituents at A-ring C-2 and evaluation of their vitamin D receptor-mediated transcriptional activity†

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Received 24th May 2012, Accepted 3rd August 2012
DOI: 10.1039/c2ob26017d

Binding of a series of novel 1α,25-dihydroxyvitamin D_3 (1,25-VD_3) derivatives, having a nitrogen-linked substituent at the 2α- or 2β-position of the A-ring (2-*N*-substituted compounds), with the vitamin D receptor (VDR) was investigated by means of computational docking studies. Selected compounds were synthesized by coupling A-ring synthons **6** and/or **7** with CD-ring-bearing bromomethylene **5** under Trost's conditions. The 2α- and 2β-stereoisomers of the A-ring synthons were synthesized from L-serine (**8**) as a single chiral source by installing vinyl and propargyl groups at opposite ends of the molecule. The activity of the obtained compounds was evaluated by means of a luciferase-based VDR transcriptional activity assay in NIH3T3 cells. Relatively small substituents incorporating a hydrogen-bonding donor, *i.e.*, NHAc and NHMs, were effective for eliciting VDR transcriptional activity, and 2β-NHMs-1,25-VD_3 (**Xa**) showed the highest activity, being more potent than 1,25-VD_3. Derivatives with bulky substituents were inactive. These new insights into the structure–activity relationships of 1,25-VD_3 derivatives may be helpful in separating the various biological activities of 1,25-VD_3 and in generating novel therapeutic drug candidates.

1. Introduction

1α,25-Dihydroxyvitamin D_3 (**1**) (1,25-VD_3) (Fig. 1), the active metabolite of vitamin D_3, plays central roles in various biological processes, acting *via* its specific receptor, *i.e.*, vitamin D receptor (VDR), which is a member of the nuclear receptor (NR) superfamily.[1] 1,25-VD_3 modulates bone metabolism,[2] cell proliferation and cell differentiation.[3] These characteristic biological activities deeply relate with various diseases, including osteoporosis, cancer, secondary hyperparathyroidism and psoriasis.[4] Since 1,25-VD_3 and related compounds are promising candidates for the treatment of these diseases, thousands of vitamin D derivatives have been synthesized in attempts to separate and/or enhance their biological activities,[5] and some of these compounds are in clinical use.[5a–c,e] In recent structure–activity relationship studies of vitamin D, much attention has been paid to modification of the A-ring.[5b,c,e,6] This ring contains the 1α- and 3β-hydroxyl groups, which have important interactions with VDR at Ser237 and Arg274 (for the 1α-hydroxyl group) and at Ser278 and Tyr143 (for the 3β-hydroxyl group), as determined by X-ray analysis.[10] The X-ray structure also indicated the presence of an unoccupied region in the binding site of VDR near the location of C2 of the A-ring of 1,25-VD_3. Therefore, introduction of substituents at C2 in the A-ring may alter the strength or the mode of interaction of the ligand with VDR, which may lead to conformational change of VDR, as well as changes in the characteristic biological activities. In fact, modification at the C2 position with oxygen- or carbon-containing groups has been intensively explored, and the resulting derivatives were reported to show characteristic and/or new biological activities.[7–9] For example, introduction of a 2α-hydroxypropyl[8] or 2α-methyl[9] group increased the binding affinity for VDR by 4- and 3-fold, respectively. These analogs also showed extremely high calcium-mobilizing activity, having 7 and 500 times higher potency than 1,25-VD_3 (**1**), respectively.[7] Further, introduction of a 2β-hydroxypropoxy group afforded a compound (ED-71; **2**) that appears to increase the bone mineral density in osteoporotic patients

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†Electronic supplementary information (ESI) available. See DOI: 10.1039/c2ob26017d

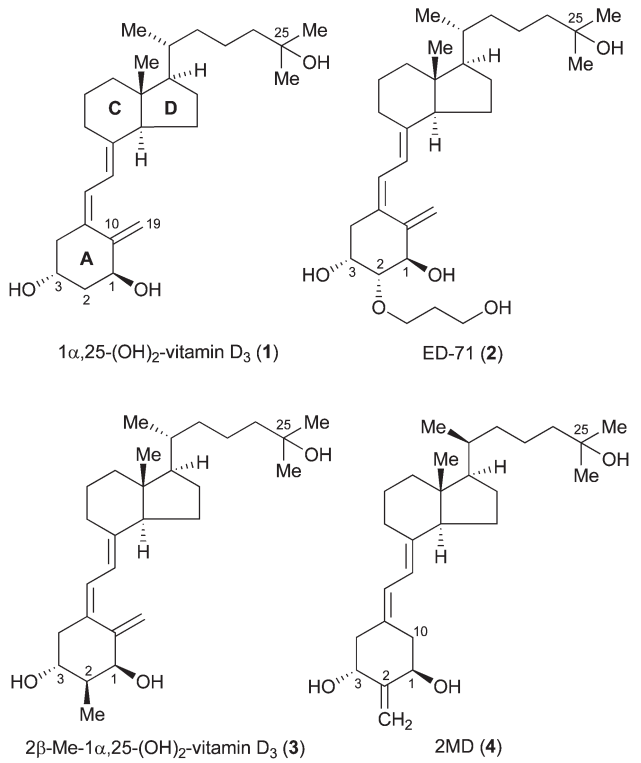


Fig. 1 Structures of 1α,25-dihydroxyvitamin D_3 and its synthetic analogs modified at the C2 position.

without significant side effects.[11] An analog of 2MD (**4**) having a methylene group at C2 also caused a bone mass increment without inducing hypercalcemia.[12] These results clearly show the potential of modifications at the C2 position in the A-ring of the vitamin D skeleton for eliciting a broad range of biological activities.

Here, we focused on installing nitrogen-linked functional groups at C2 in the A-ring to obtain 2-*N*-substituted compounds. Nitrogen has a different electrostatic field from oxygen or carbon, as well as a different number of substituents and different bond angles. Therefore, vitamin D derivatives with *N*-substituents at the C2 position can be expected to show different VDR-binding modes from the corresponding oxygen and/or carbon-substituted vitamin D derivatives, and so might have characteristically different biological activities.[13]

Firstly, we carried out docking studies of various 2-*N*-substituted vitamin D derivatives, **I** ~ **X** (Fig. 2), with the AF2 domain of VDR using the Glide (Schrödinger, LLC).[14,15] The docking scores are summarized in Table 1.[16]

In the case of 2α-*N*-monoalkyl groups (category **I**, **Ia–Ie**), higher stabilization was seen as the bulkiness increased from methyl to *n*-butyl group, but a remarkably low stabilization score was obtained for the *N*-benzyl-substituted derivative (**Ie**), probably because of steric hindrance. A similar trend was observed in the case of 2α-*N*,*N*′-dialkyl substitution (category **II**). The 2α-*N*,*N*′-diethyl-substituted derivative (**IIb**) was well docked with the AF2 domain (see Fig. 3(a)). Among the compounds in category **II**, no poses were obtained for the bulky *N*,*N*′-di-*n*-butyl- and *N*,*N*′-dibenzyl-substituted compounds (**IId** and **IIe**). Substitution of a 2α-*N*-amide group (category **III**) resulted in relatively low calculated affinity for VDR. The docking result for the 2α-*N*-benzoyl derivative (**IIIc**) is illustrated in Fig. 3(b). The sterically hindered phenyl group in **IIIc** reduces the stability as a result of steric interaction with Lys240 of VDR. Moderate stabilization scores were obtained for carbamate-substituted derivatives (category **IV**). The 2α-*N*-acyl and carbamate groups showed no significant interaction of their carbonyl groups with amino acid residues of VDR. In the case of 2α-*N*-sulfonamide substitution (category **V**), no poses were obtained except for the *N*-methanesulfonamide derivative **Va**. This compound **Va** was well docked with VDR (see Fig. 3(c)), and it showed greater stabilization than 1,25-VD_3.

The 2β-*N*-substituted derivatives (categories **VI–X**) showed similar trends to the case of 2α-*N*-substitution. 2β-*N*-monoalkyl groups (**VIa–d**), a 2β-*N*-acetyl group (**VIIIa**) and especially a *N*-methanesulfonyl group (**Xa**) were effective for stabilization of VDR. From the docking model (Fig. 3(d)), it appears that a hydrogen-bonding interaction between the sulfonyl group in **Xa** and Arg274 contributes to the stabilization.

Based upon these docking calculations, we selected **IIb**, **IId–e**, **IIIa–c**, **IVd**, **Va–d**, **VIIe**, **VIIIa**, and **Xa** as synthetic targets.

2. Synthesis of 2-*N*-substituted vitamin D derivatives

Palladium-catalyzed coupling reaction of vinyl bromide **5** (CD-ring) with an ene–yne-type A-ring synthon was developed by Trost for the synthesis of 2-*N*-substituted vitamin D derivatives.[17] We planned to synthesize A-ring precursors of 2α- and 2β-*N*-substituted ene–ynes **6** and **7** from L-serine (**8**) as a single chiral source by switching the positions of the vinyl and propargyl groups, as depicted in Scheme 1.

A-ring synthons for 2α-*N*-substituted-1,25-VD_3 derivatives **14–24** were synthesized from the key amine intermediate **13** (Scheme 2). Optically active allyl alcohol **9** was obtained from L-serine (**8**) according to Katsumura's method.[18] The hydroxyl group of **9** was protected with TBS ether to give bis-TBS ether **10** in 93% yield. The primary TBS group in **10** was selectively deprotected with 1% HCl in ethanol to give alcohol **11**. In this reaction, the diol was co-generated in 23% yield, with 16% recovery of the starting bis-TBS ether **10**. The diol was quantitatively transformed back to the starting bis-TBS ether **10** with TBSOTf and 2,6-lutidine. Oxidation of the hydroxyl group under Swern conditions followed by reaction with propargyl Grignard reagent gave the alcohol as a 1 : 1 mixture of diastereomers,[19] which were separated by column chromatography on silica gel to give **12** in 53% yield from **11**. The TBS ether and Boc group in **12** were deprotected with TFA, and resulting diol was protected as TBS ether with TBSOTf and 2,6-lutidine to afford the key amine intermediate **13** in 75% yield. *N*,*N*′-Dialkyl A-ring synthons **14–16** were synthesized in 51–60% yields by reductive amination with the corresponding aldehydes. In the case of NBn_2-substituted **16**, *N*-alkylation of amine **13** with benzyl bromide in the presence of potassium carbonate was more effective than a reductive amination protocol. *N*-Acyl derivatives **17–19** were synthesized by reaction with acyl halide or acyl anhydride in 90–96% yields. *N*-Sulfonamide derivatives **20–23** were synthesized by reaction of sulfonyl chloride in the

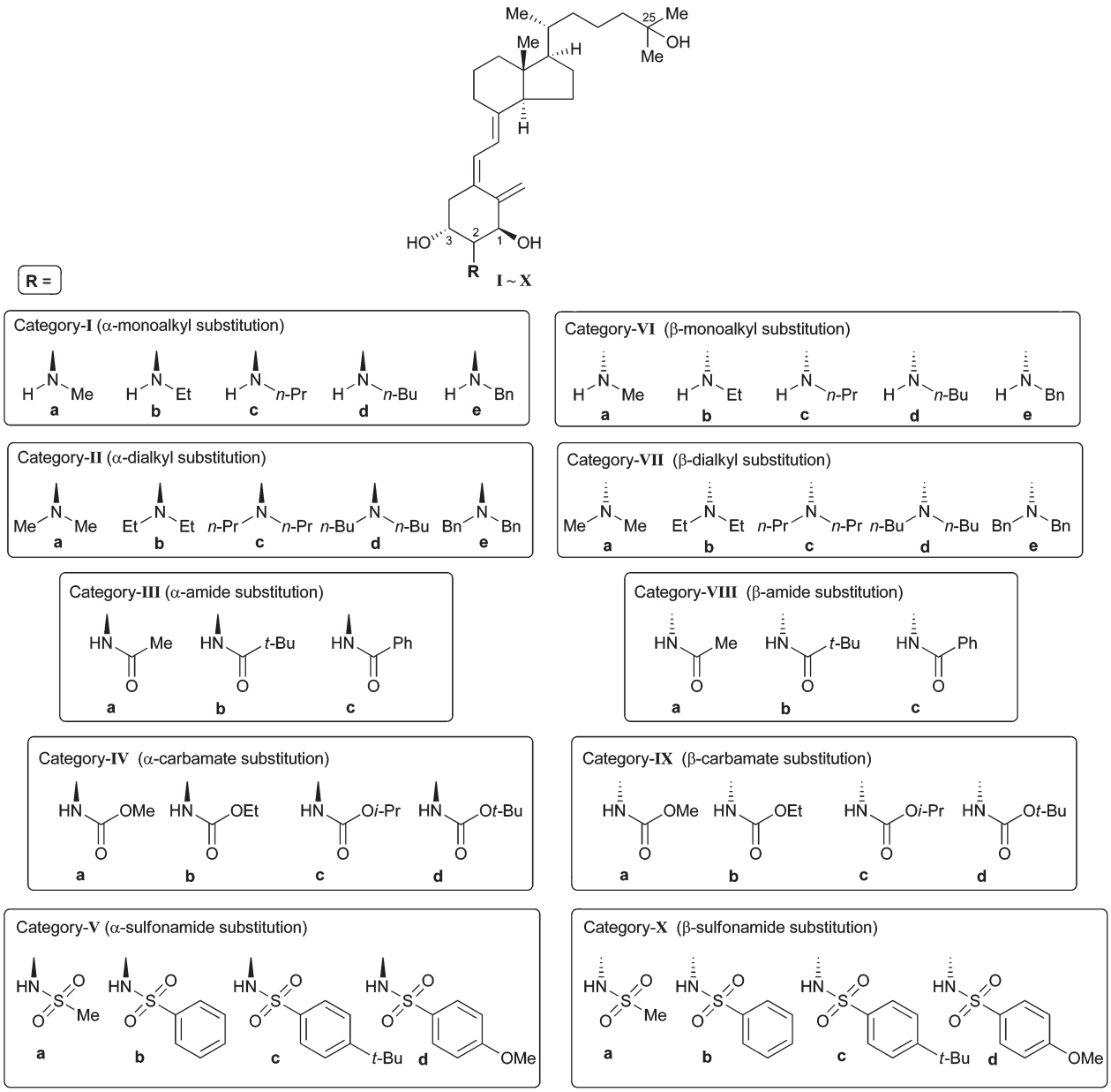
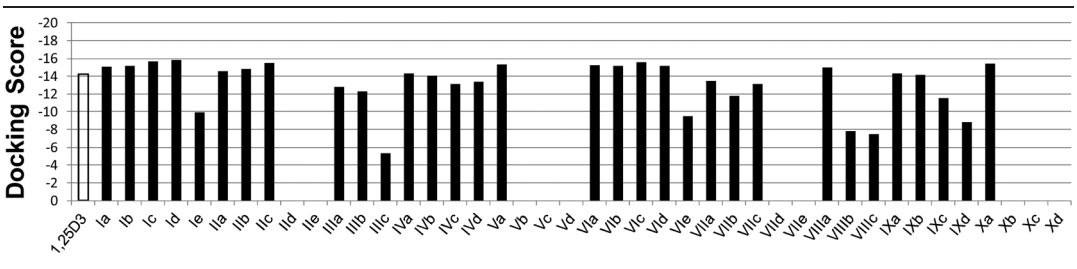


Fig. 2 Structures of 2-*N*-substituted vitamin D_3 derivatives.

Table 1 Docking scores of 2-*N*-substituted vitamin D_3 derivatives with the AF2 domain of VDR calculated with Glide XP



presence of triethylamine in 80–95% yields. The *N*-carbamate derivative **24** was synthesized from **12** by silylation with TBSOTf and 2,6-lutidine in 38% yield.

Other A-ring synthons with 2β stereochemistry **32–34** were also synthesized from L-serine (**8**) (Scheme 3). Optically active Weinreb amide **25**,[20] derived from L-serine (**8**), was reacted with

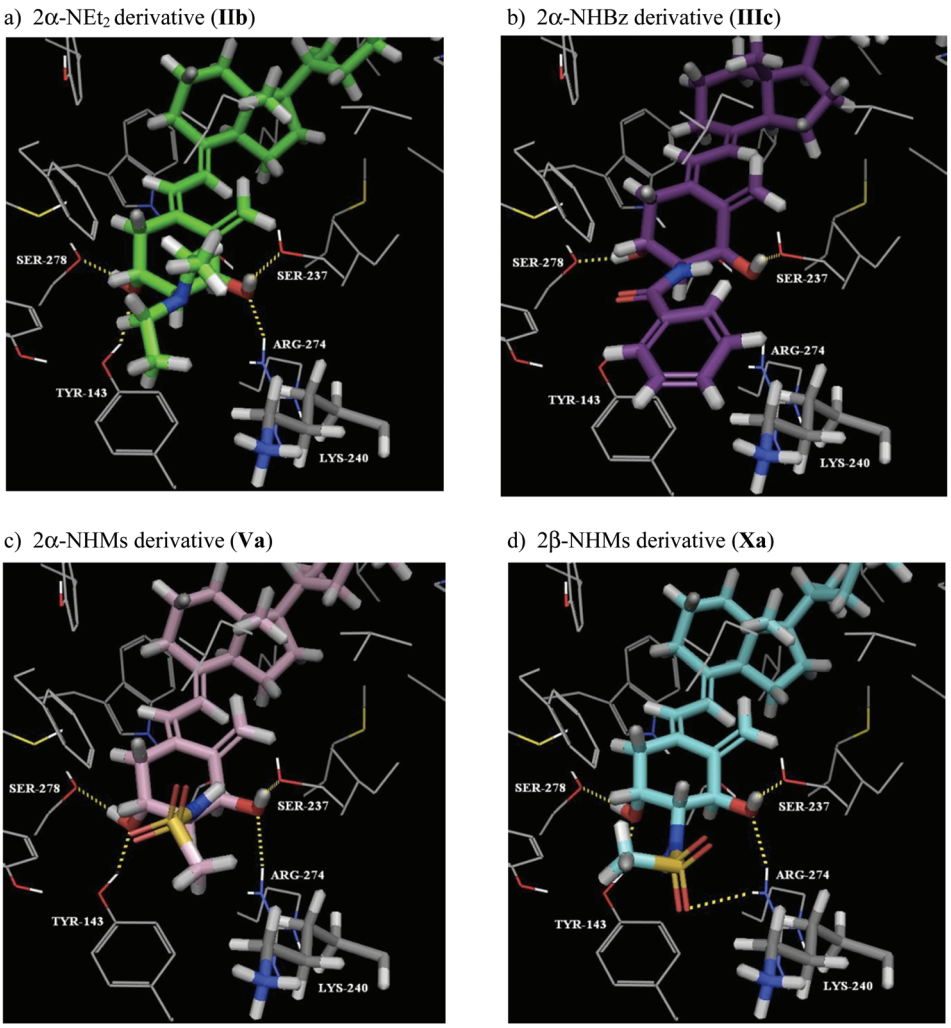


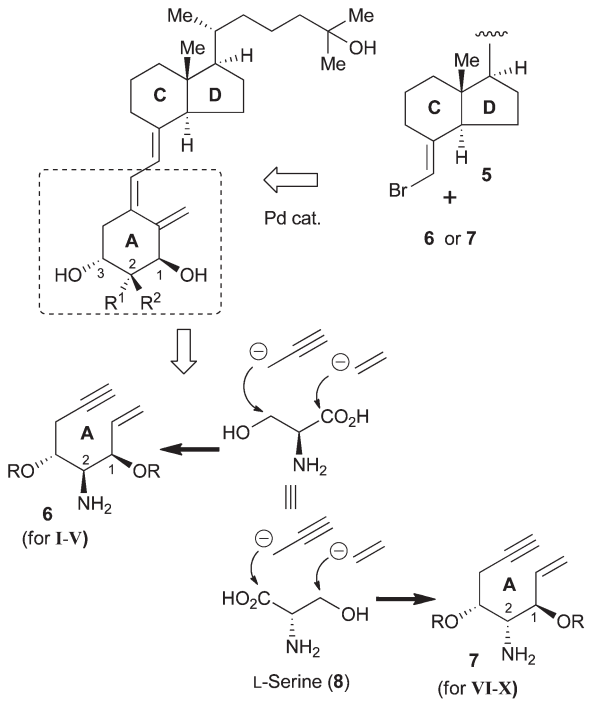
Fig. 3 Selected docking models of 2-*N*-substituted 1,25-VD_3 with the AF2 domain of VDR calculated with Autodock.

vinyl magnesium bromide to give vinyl ketone **26** in 85% yield. Reduction of the ketone with zinc borohydride proceeded stereoselectively, affording the alcohol as a single stereoisomer,[21] whose hydroxyl group was protected as TBS ether to give **27** in 89% yield in 2 steps. Ozonolysis of the vinyl group of **27** followed by reduction of the resulting ozonide with sodium borohydride gave the alcohol, which was treated with methanesulfonyl chloride followed by TBAF to give epoxide **28** in 76% yield in 3 steps.[22] Opening reaction of the epoxide was carried out with trimethylsilyl acetylide in the presence of $BF_3{\cdot}Et_2O$, and the resulting hydroxyl group was protected with *tert*-butyldiphenyl chloride (TBDPSCl) to give TBDPS ether **29** in 87% yield. The acetonide in **29** was deprotected with bismuth tribromide,[24] and the alcohol was oxidized with TPAP to give the aldehyde, which was subsequently reacted with vinylmagnesium bromide to give alcohol **30** as a mixture of two diastereomers (dr = 1 : 1) in 59% yield in 3 steps. After separation of the diastereomers on a silica gel column, deprotection of the TBDPS and TMS groups and the Boc group was conducted with TBAF and TFA, respectively, to give the diol, whose hydroxyl groups were protected as TBS ethers to give amine **31** in 61% yield. This key intermediate was converted into *N*,*N*′-dibenzyl **32**, *N*-acetyl **33** and *N*-methanesulfonyl **34** by following the same procedures described for the synthesis of the corresponding 2α-stereoisomers of A-ring synthons **16**, **17**, and **20**.

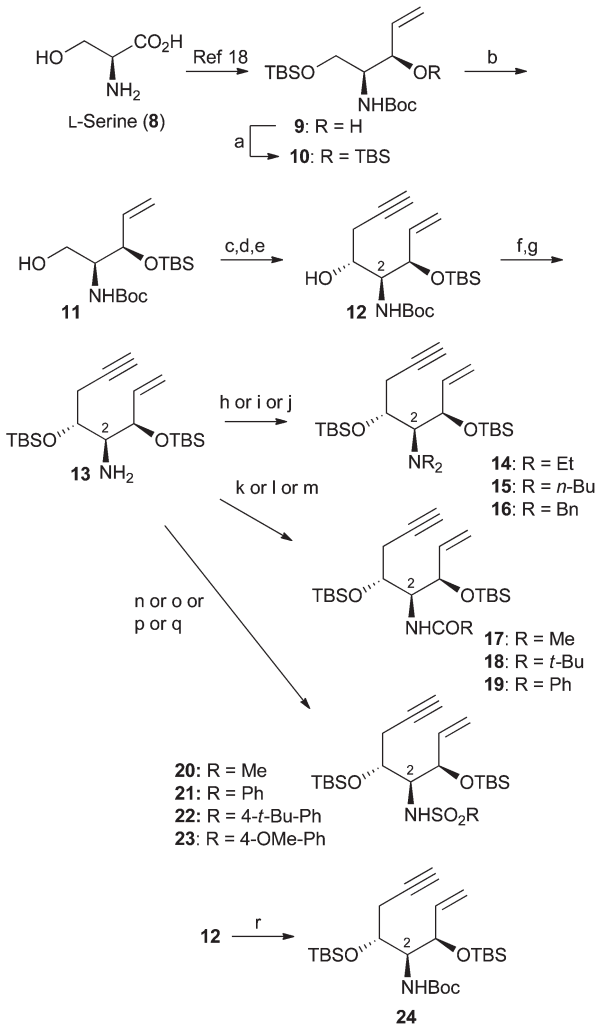
With the *N*-substituted A-ring synthons with 2α and 2β stereochemistry, **14–24** and **32–34**, in hand, these A-ring precursors were coupled with the CD-ring bromomethylene **5** in the presence of $Pd(PPh_3)_4$,[17] and the resulting TBS-protected coupling products were deprotected with TBAF or HF–Et_3N (Scheme 4) to afford the 2α-*N*-substituted vitamin D_3 derivatives **II–V**. 2β-*N*-Substituted 1,25-VD_3 derivatives **VIIe**, **VIIIa** and **Xa** were also obtained in 33, 17 and 21% yields, respectively.[25]

3. Evaluation of VDR-mediated transcription-activating activity of 2-*N*-substituted 1,25-VD_3 derivatives

The biological activities of these 2-*N*-substituted 1,25-VD_3 derivatives were evaluated by means of a luciferase-based VDR transcriptional activity assay in NIH3T3 cells.[26] NIH3T3 cells



Scheme 1 Synthetic plan for A-ring synthons **6** and **7** of 2-*N*-substituted vitamin D_3 derivatives.



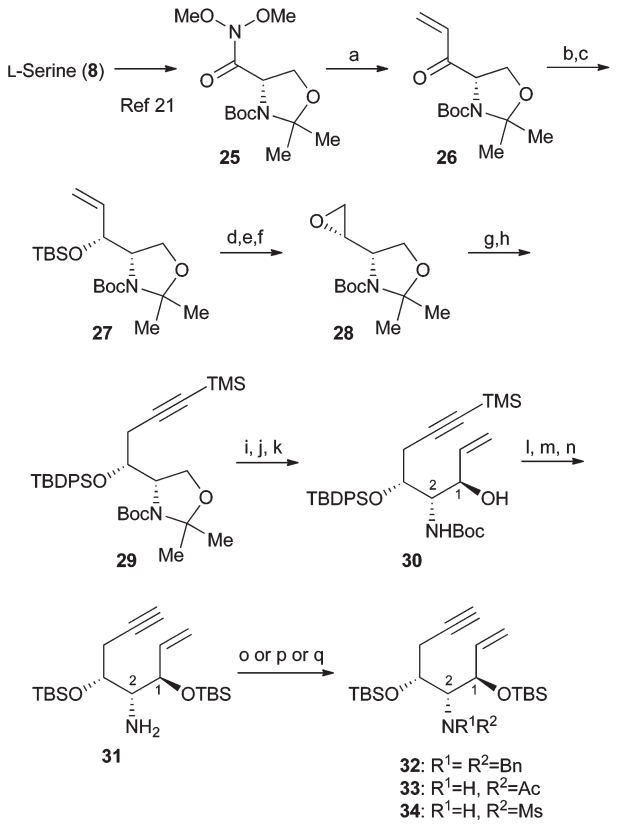
Scheme 2 Synthesis of 2α-*N*-substituted A-ring synthons **14–24**. (a) TBSCl, imidazole, DMAP, DMF, rt, 93%; (b) 1% HCl, EtOH, rt, 60% (diol was generated in 23% yield, with 16% recovery of starting bis-TBS ether **10**); (c) $(COCl)_2$, DMSO, *i*-Pr_2NEt, CH_2Cl_2, −78 °C to 0 °C; (d) propargyl magnesium bromide, THF, 0 °C; (e) Separation with silica gel column, 53% (C3 isomer 35%); (f) 20% TFA–CH_2Cl_2, 0 °C to rt; (g) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to rt, 75% (2 steps); (h) acetoaldehyde (6 eq), $NaBH_3CN$, then AcOH, CH_3CN, 0 °C to rt, 51%; (i) *n*-butylaldehyde (6 eq), $NaBH_3CN$, then AcOH, CH_3CN, 0 °C to rt, 59%; (j) BnBr, K_2CO_3, CH_3CN, 80 °C, 60%; (k) acetic anhydride, rt, 94%; (l) pivaloyl chloride, triethylamine, CH_2Cl_2, 0 °C to rt, 96%; (m) benzoic anhydride, triethylamine, THF, 0 °C to rt, 90%; (n) methanesulfonyl chloride, triethylamine, CH_2Cl_2, 0 °C to rt, 95%; (o) benzenesulfonyl chloride, triethylamine, CH_2Cl_2, rt, 83%; (p) 4-*t*-butylbenzenesulfonyl chloride, triethylamine, THF, rt, 80%; (q) 4-methoxybenzenesulfonyl chloride, triethylamine, THF, rt, 93%; (r) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 38%.

were transfected with pDR3-Luc and pGL4.74 [hLuc/TK] normalizing vectors, then treated with 1,25-VD_3 or compounds (100 nM **IIb**, **IId–e**, **IIIa–c**, **IVd**, **Va–d**, **VIIe**, **VIIIa**, and **Xa**), and the luciferase activity was measured. The relative intensities of the luciferase activity of compounds *versus* the control or 1,25-VD_3 are summarized in Fig. 4.

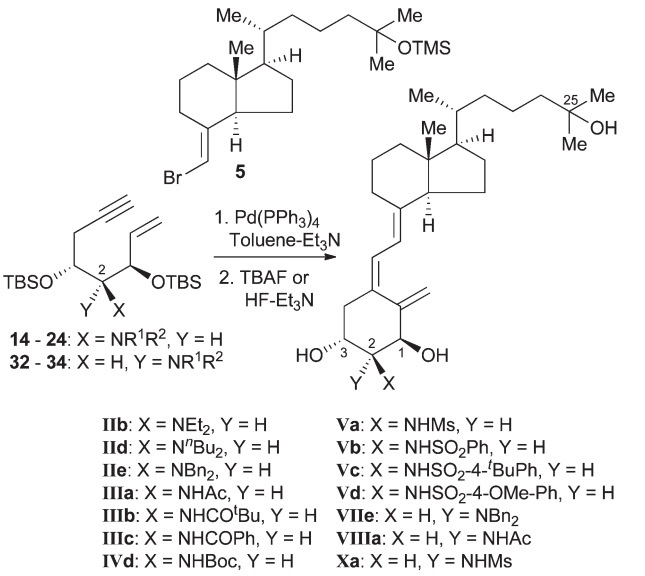
Among the compounds tested, 2α-NHAc-1,25-VD_3 (**IIIa**) showed similar activity to 1,25-VD_3, while **IVd** and **Va**, bearing NHBoc and NHMs groups at 2α, showed moderate activity. Among the 2β stereoisomers, the 2β-*N*-acetyl derivative (**VIIIa**), which effectively stabilized VDR in the docking studies, showed potent activity nearly equal to that of 1,25-VD_3. However, 2β-NHMs-1,25-VD_3 (**Xa**), which appeared to exhibit a hydrogen-bonding interaction with Arg274 of VDR in the docking studies, showed the highest transcriptional activity among the derivatives synthesized, being slightly more potent than VD_3. These derivatives all have a hydrogen-bond-donating group at the C2 position, so hydrogen bonding seems to be important for VDR transcriptional activity. Indeed, 2α-NEt_2-1,25-VD_3 (**IIb**), which cannot form a hydrogen bond, induced no transcriptional activity, although it could be well docked with VDR by calculation. Steric hindrance is also an important factor. Compounds **IIe** and **VIIe** bearing bulky *N*,*N*′-Bn_2 groups at the 2α- and 2β-position, respectively, gave no calculated docking poses with VDR, and also failed to induce transcriptional activity. On the other hand, $NHSO_2Ar$ can act as a hydrogen bond donor, but it is a bulky group, and it induced only low transcriptional activity. Thus, it appears that 2-*N*-substituted 1,25-VD_3 derivatives with a relatively small substituent group that has hydrogen-bond donor capability are effective for eliciting VDR transcriptional activity.

4. Conclusion

In summary, we carried out computational docking with VDR for a series of novel 2α- and 2β-*N*-substituted 1,25-VD_3 derivatives. Based on the results, 14 compounds were selected and synthesized. A-Ring synthons for both stereoisomers were synthesized from L-serine (**8**) as a single chiral source by installing vinyl and propargyl groups at opposite ends of the molecule.



Scheme 3 Synthesis of 2β-substituted A-ring synthons **32**–**34**. (a) vinyl magnesium bromide, THF, 0 °C, 85%; (b) $Zn(BH_4)_2$, Et_2O, −30 °C; (c) TBSCl, imidazole, DMAP, DMF, rt, 89% (2 steps); (d) O_3, CH_2Cl_2, MeOH, −78 °C, then $NaBH_4$, −78 °C to rt; (e) MsCl, triethylamine, CH_2Cl_2, 0 °C, 94% (2 steps); (f) TBAF, THF, rt, 81%; (g) trimethylsilyl acetylene, *n*-BuLi, $BF_3{\cdot}Et_2O$, THF, −78 °C, 90%; (h) TBDPSCl, imidazole, DMF, rt to 40 °C, 97%; (i) $BiBr_3$, CH_3CN–H_2O, rt, 91%; (j) TPAP, NMO, MS-4A, CH_2Cl_2, rt, 92%; (k) vinyl magnesium bromide, THF, 0 °C, then separation (α-isomer: 35%, β-isomer: 35%); (l) TBAF, THF, rt, 89%; (m) 20% TFA–CH_2Cl_2, 0 °C to rt; (n) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to rt, 69% (2 steps); (o) BnBr, K_2CO_3, CH_3CN, NaI, 80 °C, 54%; (p) Ac_2O, rt, 99%; (q) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 84%.



Scheme 4 Synthesis of 2α-*N*-substituted 1,25-VD_3 derivatives; **IIb** (NEt_2), 20%; **IId** (N-nBu_2), 10%; **IIe** (NBn_2), 10%; **IIIa** (NHAc), 9%; **IIIb** (NHCO-*t*Bu), 57%; **IIIc** (NHCOPh), 25%; **IVd** (NHBoc), 20%; **Va** ($NHSO_2Me$), 57%; **Vb** ($NHSO_2Ph$), 5%; **Vc** ($NHSO_2$-4-*t*BuPh), 8%; **Vd** ($NHSO_2$-4-OMe-Ph), 6%. Synthesis of 2β-*N*-substituted 1,25-VD_3 derivatives; **VIIe** (NBn_2), 33%; VIIIa (NHAc), 17%; **Xa** ($NHSO_2Me$), 21%.

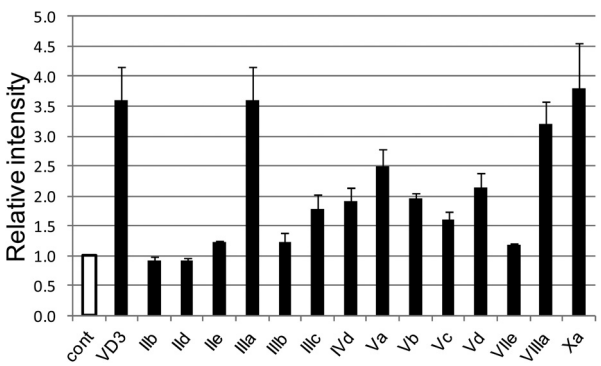


Fig. 4 Results of dual-luciferase reporter assay for 2-*N*-substituted 1,25-VD_3 derivatives. Data are expressed as the means ± SEM.

These A-rings were coupled with CD-ring bromomethylene **5** according to Trost's protocol to afford the target compounds. In a dual-luciferase reporter assay, **IIIa**, **VIIIa** and **Xa** showed similar activity to 1,25-VD_3. Our results indicate that 2-*N*-substituted 1,25-VD_3 derivatives with a relatively small substituent group that has the potential to form a hydrogen bond with the receptor are effective for eliciting VDR transcriptional activity. Further structural development studies and evaluation of various VDR-mediated biological activities of our compounds are in progress.

Experimental

General

Flash chromatography was performed on Silica gel 60 (spherical, particle size 40–100 μm; Kanto). Optical rotations were measured on a JASCO P-2200 polarimeter. ^1H and ^{13}C NMR spectra were recorded on JEOL JNM-ECA 500, JNM-ECX 400 or JMTC 300. The spectra are referenced internally according to residual solvent signals of $CDCl_3$ (^1H NMR; δ = 7.26 ppm, ^{13}C NMR; δ = 77.0 ppm). Data for ^1H NMR are recorded as follows: chemical shift (δ, ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad), integration, coupling constant (Hz). Data for ^{13}C NMR are reported in terms of chemical shift (δ, ppm). Mass spectra were recorded on JEOL JMS-T100X spectrometer with ESI-MS mode using methanol as solvent.

Bis-TBS ether 10. To a solution of **9** (16.7 mmol) in DMF (50 mL) was added imidazole (2.7 g, 40.1 mmol), DMAP (204 mg, 1.67 mmol) and TBSCl (3 g, 20.0 mmol), and the mixture was stirred for 24 h at room temperature. To the reaction mixture was added H_2O and then it was extracted with ethyl

acetate. The organic layer was washed with H_2O and brine, and the extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (hexane–ethyl acetate = 100 : 1) to give **10** (6.9 g, 15.5 mmol, 93%). $[\alpha]_D^{22}$ = +3.4 (*c* 1.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76–5.90 (m, 1H), 5.10–5.28 (m, 2H), 4.62 (d, *J* = 7.3 Hz, 1H), 4.27 (brs, 1H), 3.76 (m, 1H), 3.69–3.55 (m, 2H), 1.42 (s, 9H), 0.89 (s, 9H), 0.88 (s, 9H), 0.07–0.01 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6, 138.3, 116.2, 79.0, 73.1, 61.3, 56.4, 28.4, 25.8, 18.2, 18.1, −5.3, −5.5; HRMS: calcd for $C_{22}H_{47}NO_4Si_2Na$, 468.2941; found, 468.2940.

Alcohol 11. A solution of **10** (3.2 g, 7.18 mmol) in HCl and ethanol (1 : 99, 240 mL) was stirred for 15 min at room temperature. To the reaction mixture was added saturated $NaHCO_3$, then it was concentrated *in vacuo*. The residue was extracted with ethyl acetate and the organic layer was washed with H_2O and brine, and dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (hexane–ethyl acetate = 4 : 1) to give **11** (1.43 g, 4.31 mmol, 60%). $[\alpha]_D^{22}$ = −20.8 (*c* 5.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.88–5.79 (m, 1H), 5.40–5.18 (m, 3H), 4.52 (s, 1H), 3.97 (d, *J* = 11.4 Hz, 1H), 3.60–3.45 (m, 2H), 1.43 (s, 9H), 0.91–0.86 (m, 9H), 0.08–0.02 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.7, 137.5, 116.3, 79.5, 76.0, 61.9, 54.6, 28.3, 25.7, 25.6, 18.0, −3.6; HRMS: calcd for $C_{16}H_{33}NO_4SiNa$, 354.2077; found, 354.2060.

Alcohol 12. To a solution of $(COCl)_2$ (0.6 mL, 7.29 mmol) in dichloromethane (30 mL) was added DMSO (1 mL, 14.3 mmol) dropwise at −78 °C. The reaction mixture was stirred for 10 min at −78 °C, and to the mixture was added dropwise a solution of **11** (1.05 g, 3.17 mmol) in dichloromethane (20 mL). The reaction mixture was stirred for 1.5 h at −78 °C, and diisopropylethylamine (5 mL, 28.5 mmol) was added. The resulting mixture was warmed to room temperature for 30 min. To the reaction mixture was added 1 N HCl, and the mixture was extracted with dichloromethane. The extracts were washed with H_2O, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give aldehyde. To a prepared solution of propargyl magnesium bromide (1 M in THF, 17 mL, 17.1 mmol) was added aldehyde in THF (15 mL) at 0 °C, and the mixture was stirred for 40 min. The resulting mixture was quenched by 1 N HCl at 0 °C and extracted with ethyl acetate. The organic layer was washed with H_2O and brine, and the extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (hexane–ethyl acetate = 13 : 1) to give **12** (148 mg, 0.296 mmol, 53% from **11**). $[\alpha]_D^{22}$ = −25.6 (*c* 2.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.90–5.82 (m, 1H), 5.39–5.20 (m, 3H), 4.61–4.57 (m, 1H), 4.27 (t, *J* = 6.9 Hz, 1H), 3.61 (s, 1H), 3.58 (dd, *J* = 8.9, 2.0 Hz, 1H), 2.35 (ddd, *J* = 58.3, 16.5, 2.9 Hz, 2H), 2.01 (t, *J* = 2.9 Hz, 1H), 1.44 (s, 9H), 0.91 (s, 9H), 0.08 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.6, 137.2, 116.7, 80.5, 79.6, 76.6, 70.1, 68.3, 55.0, 28.4, 25.8, 23.6, 18.0, −4.8, −5.3; HRMS: calcd for $C_{19}H_{35}NO_4SiNa$, 392.2233; found, 392.2267.

Amine 13. A solution of **12** (298 mg, 0.81 mmol) in TFA and dichloromethane (1 : 4, 8 mL) was stirred at 0 °C for 5 min and room temperature for 1 h. The reaction mixture was concentrated *in vacuo* to give diol. To a solution of the resulting diol in dichloromethane (8 mL) was added 2,6-lutidine (0.6 mL, 4.84 mmol) and TBSOTf (0.6 mL, 2.42 mmol), and the mixture was stirred at 0 °C for 40 min. To the reaction mixture was added saturated $NaHCO_3$, then it was extracted with ethyl acetate. The organic layer was washed with H_2O and brine, and dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (hexane–ethyl acetate = 40 : 1) to give **13** (250 mg, 0.65 mmol, 75% from **12**). $[\alpha]_D^{24}$ = −3.6 (*c* 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83–5.74 (m, 1H), 5.26–5.17 (m, 2H), 4.10–4.04 (m, 1H), 3.95 (t, *J* = 7.4 Hz), 2.86 (dd, *J* = 6.9, 2.8 Hz, 1H), 2.65–2.32 (m, 2H), 1.99 (t, *J* = 2.7 Hz, 1H), 0.91–0.88 (m, 18H), 0.12–0.03 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 117.8, 81.2, 76.4, 70.4, 70.2, 58.3, 25.9, 24.9, 18.1, −3.3, −4.0; HRMS: calcd for $C_{20}H_{42}NO_2Si_2$, 384.2754; found, 384.2725.

2α-*N*-Ethylamine 14. To a solution of **13** (100 mg, 0.26 mmol) in acetonitrile (2.6 mL) was added acetoaldehyde (88 μL, 1.56 mmol) and $NaBH_3CN$ (41 mg, 0.65 mmol) at room temperature, and the mixture was stirred for 50 min. To the reaction mixture was added acetic acid until the pH of the mixture reached 3. The resulting mixture was stirred for 1.5 h and quenched by saturated $NaHCO_3$. The reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine, and the extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (hexane–ethyl acetate = 100 : 1) to give **14** (58 mg, 0.13 mmol, 51%). $[\alpha]_D^{20}$ = +4.8 (*c* 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.98–5.87 (m, 1H), 5.28–5.12 (m, 2H), 4.38 (t, *J* = 8.9 Hz, 1H), 4.28–422 (m, 1H), 2.88–2.74 (m, 4H), 2.65–2.57 (m, 2H), 2.28–2.20 (m, 1H), 1.95 (t, *J* = 2.8 Hz, 1H), 0.97 (t, *J* = 7.1 Hz, 6H), 0.9–0.86 (m, 18H), 0.13–0.02 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.9, 117.2, 82.4, 74.3, 72.3, 69.8, 67.0, 47.9, 26.0, 24.4, 18.1, 16.4, −2.4, −4.1, −4.6; HRMS: calcd for $C_{24}H_{50}NO_2Si_2$, 440.3380; found, 440.3353.

2α-*N*-*n*-Butylamine 15. To a solution of **13** (100 mg, 0.26 mmol) in acetonitrile (2.6 mL) was added *n*-butylaldehyde (140 μL, 1.56 mmol) and $NaBH_3CN$ (41 mg, 0.65 mmol) at room temperature, and the mixture was stirred for 1 h. To the reaction mixture was added acetic acid until the pH of the mixture reached 3. The resulting mixture was stirred for 1 h and quenched by saturated $NaHCO_3$. The reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine, and the extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (hexane–ethyl acetate = 100 : 1) to give **15** (76 mg, 0.15 mmol, 59%). $[\alpha]_D^{21}$ = +1.6 (*c* 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.03–5.88 (m, 1H), 5.30–5.12 (m, 2H), 4.40 (t, *J* = 8.6 Hz, 1H), 4.28–4.20 (m, 1H), 2.89–2.62 (m, 5H), 2.60–2.49 (m, 2H), 2.31–2.21 (m, 1H), 1.95 (t, *J* = 2.5 Hz, 1H), 1.42–1.30 (m, 4H), 1.29–1.14 (m, 4H), 0.84–0.92 (m, 24H), 0.15–0.02 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.9, 117.1, 82.5, 74.6, 72.5, 69.9, 67.6, 54.6, 33.3, 26.0, 24.6, 20.5, 18.1, −2.4, −4.1; HRMS: calcd for $C_{28}H_{58}NO_2Si_2$, 496.4006; found, 496.4010.

2α-*N*,*N*′-Dibenzylamine 16. To a solution of **13** (100 mg, 0.26 mmol) in acetonitrile (3 mL) was added K_2CO_3 (360 mg,

2.61 mmol) and BnBr (0.13 mL, 2.61 mmol) at room temperature, and the mixture was stirred at 80 °C for 10 h. To the resulting mixture was added saturated NH_4Cl, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, and the extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (hexane–ethyl acetate = 100 : 1) to give **16** (89 mg, 0.16 mmol, 60%). $[\alpha]_D^{24}$ = −14.4 (*c* 3.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.16 (m, 10H), 6.08–5.97 (m, 1H), 5.44–5.27 (m, 2H), 4.54 (t, *J* = 8.7 Hz, 1H), 4.s35–4.29 (m, 1H), 3.96 (dd, *J* = 134.7, 13.8 Hz, 4H), 2.91 (dd, *J* = 8.5, 2.6 Hz, 1H), 2.67–2.58 (m, 1H), 2.39–2.31 (m, 1H), 1.68 (t, *J* = 2.5 Hz, 1H), 0.89 (s, 9H), 0.82 (s, 9H), 0.13–0.03 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.0, 140.9, 129.4, 127.9, 126.5, 117.6, 81.6, 75.1, 72.8, 69.8, 63.8, 56.5, 25.9, 18.1, −2.5, −4.0, −4.5; HRMS: calcd for $C_{34}H_{54}NO_2Si_2$, 564.3693; found, 564.3682.

2α-*N*-Acetylamine 17. A solution of **13** (66 mg, 0.17 mmol) in acetic anhydride (0.5 mL) was stirred for 15 min at room temperature. The resulting mixture was concentrated *in vacuo* to give **17** (69 mg, 0.16 mmol, 94%). $[\alpha]_D^{25}$ = −12.8 (*c* 0.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.91–5.82 (m, 1H), 5.69 (d, *J* = 9.7 Hz, 1H), 5.15–5.03 (m, 2H), 4.32–4.27 (m, 1H), 4.11 (t, *J* = 9.2 Hz, 1H), 3.96 (t, *J* = 8.6 Hz, 1H), 2.40–2.26 (m, 2H), 2.02 (t, J = 2.6 Hz, 1H), 1.94 (s, 3H), 0.92 (s, 9H), 0.88 (s, 9H), 0.14 (d, *J* = 4.0 Hz, 6H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8, 139.4, 117.4, 75.9, 70.9, 68.7, 55.8, 25.9, 25.4, 23.6, 18.1, −2.9, −4.0, −4.6; HRMS: calcd for $C_{22}H_{43}NO_3Si_2Na$, 448.2679; found 448.2674.

2α-*N*-Pivaloylamine 18. To a solution of **13** (60 mg, 0.16 mmol) in dichloromethane (1.6 mL) was added Et_3N (33 μL, 0.23 mmol) and pivaloyl chloride (23 μL, 0.19 mmol) at room temperature, and the mixture was stirred for 4 h. To the reaction mixture was added saturated NH_4Cl, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, and the extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (hexane–ethyl acetate = 20 : 1) to give **18** (71 mg, 0.15 mmol, 96%). $[\alpha]_D^{27}$ = −1.6 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.03 (d, *J* = 9.1 Hz, 1H), 5.91–5.80 (m, 1H), 5.11–5.01 (m, 2H), 4.34–4.29 (m, 1H), 4.06 (t, *J* = 9.2 Hz, 1H), 3.93 (t, *J* = 8.7 Hz, 1H), 2.31–2.24 (m, 2H), 2.00 (t, *J* = 2.8 Hz, 1H), 1.14 (s, 9H), 0.92 (s, 9H), 0.88 (s, 9H), 0.14 (s, 6H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7, 139.5, 117.2, 80.4, 76.2, 70.9, 69.1, 55.1, 38.7, 27.6, 25.9, 25.4, 18.0, −2.9, −4.0, −4.5, −4.6; HRMS: calcd for $C_{25}H_{49}NO_3Si_2Na$, 490.3149; found, 490.3123.

2α-*N*-Benzoylamine 19. To a solution of **13** (120 mg, 0.31 mmol) in THF (3 mL) was added triethylamine (90 μL, 0.63 mmol) and benzoic anhydride (106 mg, 0.47 mmol) at room temperature, and the mixture was stirred for 15 min. To the resulting mixture was added saturated NH_4Cl, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, and the extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (hexane–ethyl acetate = 20 : 1) to give **19** (136 mg, 0.28 mmol, 90%). $[\alpha]_D^{25}$ = −17.2 (*c* 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74–7.68 (m, 2H), 7.50–7.38 (m, 3H), 6.54 (d, *J* = 9.7 Hz, 1H), 6.01–5.91 (m, 1H), 5.14–5.06 (m, 2H), 4.42–4.38 (m, 1H), 4.34 (t, *J* = 9.2 Hz, 1H), 4.09 (t, *J* = 8.7 Hz, 1H), 2.47–2.30 (m, 2H), 2.00 (t, *J* = 2.7 Hz, 1H), 0.95 (s, 9H), 0.90 (s, 9H), 0.17 (d, *J* = 5.5 Hz, 6H), 0.68 (d, *J* = 1.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 139.3, 135.0, 131.3, 128.6, 126.7, 117.7, 80.2, 76.1, 71.0, 69.1, 56.1, 25.9, 25.6, 18.1, −2.9, −4.0, −4.6; HRMS: calcd for $C_{27}H_{45}NO_3Si_2Na$, 510.2836; found, 510.2806.

2α-*N*-Methanesulfonylamine 20. To a solution of **13** (60 mg, 0.16 mmol) in dichloromethane (2 mL) was added triethylamine (53 μL, 0.37 mmol) and methanesulfonyl chloride (15 μL, 0.19 mmol) at 0 °C, and the mixture was stirred for 40 min at room temperature. To the resulting mixture was added saturated $NaHCO_3$, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, and the extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (hexane–ethyl acetate = 20 : 1) to give **20** (69 mg, 0.19 mmol, 95%). $[\alpha]_D^{26}$ = −5.0 (*c* 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.94–5.84 (m, 1H), 5.32–5.23 (m, 2H), 4.65 (d, *J* = 9.2 Hz, 1H), 4.23–4.17 (m, 1H), 4.11 (t, *J* = 6.9 Hz, 1H), 3.77–3.70 (m, 1H), 3.03 (s, 3H), 2.58–2.48 (m, 1H), 2.41–2.33 (m, 1H), 2.07 (t, *J* = 2.8 Hz, 1H), 0.89 (d, *J* = 1.8 Hz, 18H), 0.13 (d, *J* = 5.5 Hz, 6H), 0.08 (d, *J* = 5.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 118.2, 79.9, 75.6, 71.5, 69.9, 60.5, 42.7, 25.8, 25.1, 18.2, 18.0, −3.5, −4.0, −4.6; HRMS: calcd for $C_{21}H_{43}NO_4SSi_2Na$, 484.2349; found, 484.2358.

2α-*N*-Benzenesulfonylamine 21. To a solution of **13** (110 mg, 0.29 mmol) in dichloromethane (3 mL) was added triethylamine (0.1 mL, 0.69 mmol) and benzenesulfonyl chloride (45 μL, 0.34 mmol) at room temperature, and the mixture was stirred for 6 h. The reaction mixture was diluted with H_2O and extracted with ethyl acetate. The organic layer was washed with brine, and the extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (hexane–ethyl acetate = 40 : 1) to give **21** (124 mg, 0.24 mmol, 83%). $[\alpha]_D^{18}$ = −26.5 (*c* 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91–7.85 (m, 2H), 7.59–7.44 (m, 3H), 5.74–5.62 (m, 1H), 5.13–4.85 (m, 2H), 4.15 (q, *J* = 4.6 Hz, 1H), 4.00 (t, *J* = 7.8 Hz, 1H), 3.58 (t, *J* = 8.3 Hz, 1H), 2.14–206 (m, 1H), 1.98 (t, *J* = 2.5 Hz, 1H), 1.93–1.83 (m, 1H), 0.86 (s, 18H), 0.07 (d, *J* = 5.5 Hz, 6H), 0.02 (d, *J* = 3.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.8, 138.7, 132.4, 128.9, 127.0, 118.1, 80.2, 75.7, 71.1, 69.4, 59.9, 24.8, 18.1, 18.0, −3.3, −4.3, −4.5, −4.7; HRMS: calcd for $C_{26}H_{45}NO_4SSi_2Na$, 546.2506; found, 546.2500.

2α-*N*-(4-*tert*-Butyl)-benzenesulfonylamine 22. To a solution of **13** (65 mg, 0.17 mmol) in THF (2 mL) was added triethylamine (57 μL, 0.41 mmol), 4-*tert*-butyl-benzenesulfonyl chloride (47 mg, 0.20 mmol) at room temperature, and the mixture was stirred for 8 h. The reaction mixture was warmed to 60 °C and stirred additional 8 h. The resulting mixture was diluted with H_2O at room temperature and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, and the extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography

(hexane–ethyl acetate = 30 : 1) to give **22** (78.9 mg, 0.14 mmol, 80%). $[\alpha]_D^{19}$ = −18.7 (*c* 2.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82–7.76 (m, 2H), 7.51–7.45 (m, 2H), 5.74–5.59 (m, 1H), 5.12–4.85 (m, 2H), 4.16–4.09 (m, 1H), 4.01 (t, *J* = 7.6 Hz, 1H), 3.58–3.48 (m, 1H), 2.16–1.92 (m, 3H), 1.33 (s, 9H), 0.86 (d, *J* = 1.4 Hz, 18H), 0.60 (s, 6H), 0.01 (d, *J* = 3.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 138.7, 126.9, 125.8, 117.8, 80.4, 75.6, 70.9, 69.6, 59.9, 35.1, 31.1, 25.8, 24.8, 18.1, 18.0, −3.3, −4.3, −4.5, −4.7; HRMS: calcd for $C_{30}H_{53}NO_4SSi_2Na$, 602.3132; found, 602.3137.

2α-*N*-(4-Methoxy)-benzenesulfonylamine 23. To a solution of **13** (90 mg, 0.24 mmol) in THF (2 mL) was added triethylamine (79 μL, 0.56 mmol) and 4-methoxybenzenesulfonyl chloride (58 mg, 0.28 mmol) at room temperature, and the mixture was stirred for 3 h. To the reaction mixture was added saturated NH_4Cl, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, and the extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (hexane–ethyl acetate = 15 : 1) to give **23** (122 mg, 0.22 mmol, 93%). $[\alpha]_D^{18}$ = −27.2 (*c* 2.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 9.0 Hz, 2H), 6.94 (d, *J* = 8.9 Hz, 2H), 5.77–5.62 (m, 1H), 5.14–5.03 (m, 2H), 4.84 (d, *J* = 8.9 Hz, 1H), 4.19–4.11 (m, 1H), 4.01 (t, *J* = 7.7 Hz, 1H), 3.86 (s, 3H), 3.58–3.49 (m, 1H), 2.18–1.89 (m, 3H), 0.86 (s, 18H), 0.07 (d, *J* = 2.4 Hz, 6H), 0.02 (d, *J* = 3.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6, 138.8, 133.6, 129.2, 118.0, 114.0, 80.4, 75.7, 71.0, 69.4, 59.8, 55.6, 25.9, 24.9, 18.1, 18.0, −3.3, −4.3, −4.5, −4.7; HRMS: calcd for $C_{27}H_{47}NO_5SSi_2Na$, 576.2611; found, 576.2606.

2α-*N*-*tert*-Butoxycarbonylamine 24. To a solution of **12** (124 mg, 0.34 mmol) in dichloromethane (3 mL) was added 2,6-lutidine (78 μL, 0.67 mmol) and TBSOTf (85 μL, 0.37 mmol) at 0 °C, and the mixture was stirred for 50 min at room temperature. To the resulting mixture was added 2,6-lutidine (40 μL) and TBSOTf (50 μL) additionally at room temperature. The reaction mixture was diluted with H_2O, and extracted with ethyl acetate. The organic layer was washed with brine, and the extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (hexane–ethyl acetate = 50 : 1) to give **24** (62.4 mg, 0.13 mmol, 38%). $[\alpha]_D^{24}$ = −20.7 (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.95–5.83 (m, 1H), 5.15–5.08 (m, 2H), 4.69 (d, *J* = 10.1 Hz, 1H), 4.29–4.22 (m, 1H), 3.97 (t, *J* = 8.7 Hz, 1H), 3.78 (t, *J* = 9.2 Hz, 1H), 2.47–2.25 (m, 2H), 2.01 (t, J = 2.7 Hz, 1H), 1.41 (s, 9H), 0.91 (s, 9H), 0.88 (s, 9H), 0.12 (d, *J* = 4.6 Hz, 6H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 139.4, 117.4, 80.6, 78.9, 76.0, 70.7, 69.2, 57.2, 28.4, 25.9, 25.2, 18.1, −2.9, −4.1, −4.5, −4.6; HRMS: calcd for $C_{25}H_{49}NO_4Si_2Na$, 506.3098; found, 506.3075.

Vinyl ketone 26. To a solution of **25** (5.80 g, 20.1 mmol) in THF (40 mL) was added vinylmagnesium bromide (1 M in THF, 25 mL, 25 mmol) at 0 °C, and the mixture was stirred for 2 h at room temperature. The resulting mixture was quenched by 1 N HCl at 0 °C and extracted with ethyl acetate. The organic layer was washed with brine, and the extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (hexane–ethyl acetate = 10 : 1) to give **26** (4.37 g, 17.1 mmol, 85%). $[\alpha]_D^{20}$ = −33.0 (*c* 0.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.56 (ddd, *J* = 10.3, 17.2, 17.2 Hz, 1H), 6.34 (dd, *J* = 4.4, 17.2 Hz, 1H), 5.85 (dd, *J* = 1.3, 10.3 Hz, 1H), 4.78–4.53 (m, 1H), 4.23–4.13 (m, 1H), 4.00–3.98 (m, 1H), 1.72–1.34 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.7 151.3 131.8 129.9 95.2 80.7 65.6 63.9 28.3 28.2; HRMS: (ESI, M + Na^+) calcd for $C_{13}H_{21}NO_4Na$, 278.1368; found, 278.1360.

TBS ether 27. To a solution of **26** (334.5 mg, 1.31 mmol) in diethyl ether (13 mL) was added a 0.18 M diethyl ether solution of $Zn(BH_4)_2$ (5 mL) at −20 °C, and the mixture was stirred for 1 h. To the resulting mixture was added 1 N HCl at 0 °C and the mixture was extracted with ethyl acetate. The extracts were washed with brine, and the organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give alcohol (328.7 mg). To a solution of the resulting alcohol (328.7 mg) in DMF (2 mL) was added imidazole (215 mg, 3.16 mmol), TBSCl (238 mg, 1.58 mmol) and DMAP (16 mg, 0.132 mmol) at room temperature, and the mixture was stirred for 5 h. To the reaction mixture was added saturated $NaHCO_3$, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, and the extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (hexane–ethyl acetate = 50 : 1) to give **27** (434.7 mg, 1.17 mmol, 89% from **26**). $[\alpha]_D^{21}$ = −34.9 (*c* 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.84–5.67 (m, 1H), 5.28–5.04 (m, 2H), 4.59–4.21 (m, 1H), 4.03 (d, *J* = 5.1 Hz, 1H), 3.90–3.83 (m, 1H), 3.83–3.71 (m, 1H), 1.46 (s, 9H), 0.88 (s, 9H), 0.00 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.7, 152.1, 139.2, 138.9, 116.2, 115.5, 94.2, 94.0, 79.9, 79.7, 74.3, 71.9, 64.3, 63.1, 61.6, 61.4, 28.4, 26.7, 25.9, 25.8, 25.2, 23.2, 18.0, −4.4, −4.6; HRMS: (ESI, M + Na^+) calcd for $C_{19}H_{37}NO_4SiNa$, 394.2389; found, 394.2387.

Epoxide 28. A solution of **27** (3.12 g, 8.4 mmol) in dichloromethane (40 mL) and methanol (40 mL) was treated with ozone at −78 °C with stirring for 40 min. Then $NaBH_4$ (1.9 g, 50.4 mmol) was added to the resulting mixture, which was warmed up slowly to room temperature over 12 h. To the reaction mixture was added 3 N HCl, and the organic layer was extracted with dichloromethane. The extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give alcohol (3.2 g). To a solution of the alcohol (3.2 g) in dichloromethane (30 mL) was added triethylamine (1.8 mL, 12.6 mmol) and methanesulfonyl chloride (1.3 mL, 16.8 mmol) at room temperature, and the mixture was stirred for 1.5 h. The resulting mixture was diluted with H_2O and extracted with dichloromethane, and the extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (hexane–ethyl acetate = 10 : 1) to give mesylate (3.59 g, 7.91 mmol, 94% from **27**). To a solution of mesylate (175.3 mg, 0.386 mmol) in THF (5 mL) was added TBAF (505 mg, 1.93 mmol) at room temperature, and the mixture was stirred for 10 min. To the reaction mixture was added saturated NH_4Cl, and the organic layer was extracted with ethyl acetate. The extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (hexane–ethyl acetate = 20 : 1) to give **28** (75.8 mg,

0.311 mmol, 81%). $[\alpha]_D^{22}$ = +12.5 (*c* 1.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 4.10–3.95 (m, 2H), 3.61–3.38 (m, 1H), 3.00 (s, 1H), 2.89 (s, 1H), 2.86–2.70 (m, 1H), 1.69–1.42 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.3, 151.7, 94.3, 93.7, 80.4, 80.0, 66.0, 65.4, 59.2, 58.9, 52.3, 51.9, 48.3, 48.2, 28.3, 28.2, 27.4, 26.6, 24.2, 23.0; HRMS: (ESI, M + Na^+) calcd for $C_{12}H_{21}NO_4Na$, 266.1368; found, 266.1361.

Silyl ether 29. To a solution of trimethylsilylacetylene (1.6 mL, 11.3 mmol) in THF (45 mL) was added *n*-butyllithium (1.6 M in hexane, 6.8 mL, 11.3 mmol) at 0 °C, and the mixture was stirred for 10 min. To the reaction mixture was added a solution of **28** (1.83 g, 7.53 mmol) in THF (15 mL) and BF_3–Et_2O (1.9 mL, 15.0 mmol) at −78 °C. After being stirred for 1 h, triethylamine (10 mL, 75.2 mmol) was added to the resulting mixture. The reaction mixture was warmed to room temperature, and concentrated *in vacuo*. The residue was filtered through a pad of silica gel using ethyl acetate to give alcohol (2.32 g, 6.78 mmol, 90%). To a solution of alcohol (2.21 g, 6.47 mmol) in DMF (1 mL) was added imidazole (1.7 g, 25.9 mmol) and TBDPSCl (2.5 mL, 9.71 mmol) at room temperature, and the mixture was stirred at 40 °C for 8 h. To the reaction mixture was added saturated $NaHCO_3$, and the organic layer was extracted with ethyl acetate. The extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (hexane–ethyl acetate = 100 : 1) to give **29** (3.63 g, 6.26 mmol, 97%). $[\alpha]_D^{17}$ = −61.0 (*c* 1.7, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.75–7.67 (m, 4H), 7.45–7.34 (m, 6H), 4.46 (dd, *J* = 8.3, 2.1 Hz, 1H), 4.33–4.20 (m, 1H), 4.04–3.91 (m, 2H), 2.23–2.12 (m, 2H), 1.59–1.35 (m, 15H), 1.08 (s, 9H), 0.12 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.2, 152.4, 135.8, 135.7, 134.7, 134.2, 129.7, 129.6, 127.6, 127.5, 103.6, 103.1, 94.3, 93.6, 87.2, 79.9, 71.2, 70.7, 63.5, 62.3, 61.1, 28.4, 27.0, 26.4, 19.4, −0.06; HRMS: (ESI, M + Na^+) calcd for $C_{33}H_{49}NO_4Si_2Na$, 602.3097; found, 602.3079.

Allyl alcohol 30. To a solution of **29** (3.63 g, 6.26 mmol) in acetonitrile (40 mL) was bismuth tribromide (281 mg, 0.626 mmol) at room temperature, and the mixture was stirred for 1 h. To the reaction mixture was added H_2O (0.1 mL) at room temperature and the mixture was stirred for 30 min. To the resulting mixture was added saturated $NaHCO_3$, and the organic layer was extracted with ethyl acetate. The extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (hexane–ethyl acetate = 10 : 1) to give alcohol (3.09 g, 5.72 mmol, 91%). To a solution of the alcohol (322 mg, 0.596 mmol) in dichloromethane (6 mL) was added NMO (83 mg, 0.709 mmol) and MS 4Å (330 mg) at room temperature, then TPAP (23 mg, 0.0656 mmol) was added and the resulting mixture was stirred for 20 min. The reaction mixture was filtered through a pad of silica gel using ethyl acetate, and eluted fractions were concentrated *in vacuo* to give aldehyde (297.1 mg, 0.550 mmol, 92%). To a solution of the aldehyde (212.4 mg, 0.513 mmol) in THF (5 mL) was added vinylmagnesium bromide (1 M in THF, 1.5 mL, 1.5 mmol) at 0 °C, and the mixture was stirred for 30 min. To the reaction mixture was added 1 N HCl at 0 °C, and organic layer was extracted with ethyl acetate. The extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (hexane–ethyl acetate = 20 : 1) to give **30** (79.3 mg, 0.179 mmol, 35%). $[\alpha]_D^{25}$ = −12.8 (*c* 1.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.70–768 (m, 4H), 7.49–7.38 (m, 6H), 5.78 (ddd, *J* = 16.6, 10.9, 5.4 Hz, 1H), 5.39–5.29 (m, 2H), 5.16 (d, *J* = 10.3 Hz, 1H), 4.81–4.78 (m, 1H), 4.12–4.09 (m, 1H), 3.76–3.74 (m, 1H), 2.41 (dd, *J* = 17.7 6.3 Hz, 1H), 2.34 (dd, *J* = 17.7, 4.6 Hz, 1H), 1.40 (s, 9H), 1.10 (s, 9H), 0.13 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.9, 137.2, 135.8, 132.8, 132.1, 130.1, 127.8, 115.8, 102.3, 88.2, 79.2, 73.0, 70.9, 56.9, 28.3, 26.9, 25.5, 19.3, −0.12; HRMS: (ESI, M + Na^+) calcd for $C_{32}H_{47}NO_4Si_2Na$, 588.2941; found, 588.2934.

Amine 31. To a solution of **30** (665.4 mg, 1.18 mmol) in THF (10 mL) was added TBAF (771 mg, 2.95 mmol) at room temperature, and the mixture was stirred for 40 min. To the reaction mixture was added saturated NH_4Cl, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, and the extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (hexane–ethyl acetate = 2 : 1) to give diol (268.6 mg, 1.05 mmol, 89%). To the diol (268.6 mg, 1.05 mmol) was added a mixed solution of TFA and dichloromethane (1 : 4, 5 mL) at 0 °C, and the mixture was stirred for 2 h at room temperature. The reaction mixture was concentrated *in vacuo* to give diol (309.3 mg). To a solution of the diol (309.3 mg) in dichloromethane (3 mL) was added 2,6-lutidine (1.4 mL, 12.6 mmol) and TBSOTf (1.2 mL, 5.25 mmol) at 0 °C, and the mixture was stirred for 8 h at room temperature. To the reaction mixture was added saturated $NaHCO_3$, and extracted with ethyl acetate. The organic layer was washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (hexane–ethyl acetate = 50 : 1) to give **31** (278.1 mg, 0.726 mmol, 69% from the diol). $[\alpha]_D^{19}$ = −1.9 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.87 (ddd, *J* = 17.4, 10.5, 7.3 Hz, 1H), 5.21 (d, *J* = 17.4 Hz, 1H), 5.16 (d, *J* = 10.5 Hz, 1H), 4.12 (dd, *J* = 5.9, 7.3 Hz, 1H), 3.82 (ddd, *J* = 4.4, 4.4, 6.7 Hz, 1H), 2.83 (dd, *J* = 4.58, 5.50 Hz, 1H), 2.53 (dd, *J* = 17.4, 6.87, 2.75 Hz, 1H), 2.44 (dd, *J* = 17.4, 4.58, 2.75 Hz, 1H), 1.93 (t, *J* = 2.75 Hz, 1H), 0.89 (s, 9H), 0.88 (s, 9H), 0.11 (s, 3H), 0.075 (s, 3H), 0.068 (s, 3H), 0.030 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.3, 116.5, 82.4, 75.0, 71.8, 69.8, 61.0, 25.9, 25.8, 22.5, 18.1, 18.0, −3.5, −3.7, −4.6, −4.7; HRMS: (ESI, M + H^+) calcd for $C_{20}H_{42}NO_2Si_2$, 384.2754; found, 384.2745.

2β-*N*,*N*′-Dibenzylamine 32. To a solution of **31** (30.4 mg, 0.0792 mmol) in acetonitrile (1 mL) was added K_2CO_3 (66 mg, 0.475 mmol) and BnBr (38 μL, 0.317 mmol) at room temperature, and the mixture was stirred for 1 h at 80 °C. To the reaction mixture was added NaI (14 mg, 0.095 mmol) at room temperature, and the mixture was stirred at 80 °C for 21 h. To the reaction mixture was added saturated NH_4Cl at room temperature, and organic layer was extracted with ethyl acetate. The extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (hexane–ethyl acetate = 100 : 1) to give **32** (24 mg,

0.0426 mmol, 54%). $[\alpha]_D^{26}$ = +6.8 (*c* 0.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.38–7.14 (m, 10H), 6.08 (ddd, *J* = 7.91, 10.3, 17.5 Hz, 1H), 5.16 (d, *J* = 17.2 Hz, 1H), 4.99 (d, *J* = 9.9 Hz, 1H), 4.65 (dd, *J* = 5.1, 7.9 Hz, 1H), 4.28 (ddd, *J* = 4.8, 5.1, 7.4 Hz, 1H), 4.09 (d, *J* = 14.1 Hz, 2H), 3.84 (d, *J* = 13.8, 2H), 2.96 (dd, *J* = 4.8, 5.1 Hz, 1H), 2.76 (dd, *J* = 2.7, 7.2, 16.8 Hz, 1H), 2.34 (ddd, *J* = 2.7, 5.1, 16.8 Hz, 1H), 1.77 (t, *J* = 2.7 Hz, 1H), 0.90 (s, 9H), 0.87 (s, 9H), 0.085 (s, 3H), 0.060 (s, 3H), 0.044 (s, 3H), 0.040 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.9, 140.9, 129.1, 128.1, 126.6, 115.2, 76.4, 73.1, 70.8, 69.8, 64.7, 56.0, 53.5, 29.8, 26.3, 26.1, 18.3, −3.3, −3.4, −4.2, −4.4; HRMS: (ESI, M + H^+) calcd for $C_{34}H_{54}NO_2Si_2$, 564.3693; found, 564.3648.

2β-*N*-Acetylamine 33. A solution of **31** (127.6 mg, 0.333 mmol) in acetic anhydride (0.3 mL) was stirred for 20 min at room temperature. The reaction mixture was concentrated *in vacuo* to give **33** (140.1 mg, 0.329 mmol, 99%). $[\alpha]_D^{17}$ = +8.90 (*c* 0.6, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.87 (d, *J* = 9.6 Hz, 1H), 5.80 (ddd, *J* = 17.4, 10.1, 7.3 Hz, 1H), 5.19 (d, *J* = 17.4 Hz, 1H), 5.11 (d, *J* = 10.1 Hz, 1H), 4.48 (d, *J* = 7.3 Hz, 1H), 3.97 (ddd, *J* = 9.6, 7.8, 1.8 Hz, 1H), 3.93–3.87 (m, 1H), 2.56 (ddd, *J* = 16.9, 6.4, 2.8 Hz, 1H), 2.36 (ddd, *J* = 16.9, 5.0, 2.8 Hz, 1H), 2.02 (t, *J* = 2.7 Hz, 1H), 2.00 (s, 3H), 0.91 (s, 9H), 0.90 (s, 9H), 0.14 (s, 3H), 0.12 (s, 3H), 0.098 (s, 3H), 0.056 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9, 138.6, 116.2, 81.8, 72.4, 71.5, 70.3, 58.2, 24.8, 23.4, 18.1, 18.0, −4.4, −4.6; HRMS: (ESI, M + Na^+) calcd for $C_{22}H_{43}NO_3Si_2Na$, 448.2679; found, 448.2667.

2β-*N*-Methanesulfonylamine 34. To a solution of **31** (92.8 mg, 0.242 mmol) in dichloromethane (2 mL) was added triethylamine (81 μL, 0.581 mmol) and methanesulfonyl chloride (22 μL, 0.290 mmol) at room temperature, and the mixture was stirred for 15 min. The resulting mixture was quenched with saturated NH_4Cl and extracted with ethyl acetate. The organic layer was washed with brine, and the extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (hexane–ethyl acetate = 30 : 1) to give **34** (94.2 mg, 0.204 mmol, 84%). $[\alpha]_D^{18}$ = +15.2 (*c* 0.9, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.94 (ddd, *J* = 7.2, 10.3, 17.2 Hz, 1H), 5.25 (d, *J* = 17.2 Hz, 1H), 5.22 (d, *J* = 10.3 Hz, 1H), 4.85 (d, *J* = 8.9 Hz, 1H), 4.42 (dd, *J* = 2.4, 7.2 Hz, 1H), 3.91 (dd, *J* = 5.16, 10.6 Hz, 1H), 3.53 (ddd, *J* = 2.7, 5.5, 8.6, Hz, 1H), 3.08 (s, 3H), 2.59 (ddd, *J* = 2.4, 5.1, 17.2 Hz, 1H), 2.47 (ddd, *J* = 2.7, 5.1, 17.2 Hz, 1H), 208–2.02 (m, 1H), 0.91 (s, 9H), 0.89 (s, 9H), 0.15 (s, 3H), 0.12 (s, 3H), 0.088 (s, 3H), 0.059 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 116.9, 81.1, 73.3, 71.3, 62.5, 42.3, 25.8, 25.7, 24.1, 18.0, −3.8, −4.1, −4.5, −4.7; HRMS: (ESI, M + Na^+) calcd for $C_{21}H_{43}NO_4SSi_2Na$, 484.2349; found, 484.2368.

2α-*N*,*N*′-Diethyl-1α-25(OH)$_2$ vitamin D$_3$ (IIb). To a solution of **5** (37 mg, 0.09 mmol) and **14** (45 mg, 0.10 mmol) in toluene and triethylamine (1 : 1, 2 mL) was added $Pd(PPh_3)_4$ (about 50 mg) at room temperature. The resulting mixture was stirred at room temperature for 15 min and 90 °C for 2 h. The reaction mixture was cooled to room temperature, and diluted with ethyl acetate, filtered through a pad of Celite, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (hexane–ethyl acetate = 50 : 1) to give bis silylether. To a solution of in THF (3 mL) was added TBAF (71 mg, 0.27 mmol) at room temperature, and the mixture was stirred at 60 °C for 3 h. To the reaction mixture was added saturated NH_4Cl at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography ($CHCl_3$–methanol = 5 : 1) to give **IIb** (8 mg, 0.02 mmol, 22%). $[\alpha]_D^{22}$ = +9.6 (*c* 0.6, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.42 (d, *J* = 11.5 Hz, 1H), 5.94 (d, *J* = 11.0 Hz, 1H), 5.32 (s, 1H), 5.00 (s, 1H), 4.45–4.35 (m, 1H), 4.20–4.31 (m, 1H), 3.79–3.36 (m, 5H), 2.84–2.75 (m, 1H), 2.44 (t, *J* = 11.9 Hz, 1H), 2.25–0.70 (m, 37H), 0.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.8, 143.6, 130.6, 125.5, 117.3, 117.1, 71.5, 70.0, 69.0, 65.3, 56.5, 56.3, 47.8, 45.9, 44.6, 44.4, 40.5, 36.3, 36.1, 29.5, 29.2, 29.1, 27.6, 23.4, 22.1, 20.8, 18.8, 12.1; HRMS: calcd for $C_{31}H_{54}NO_3$ 488.4104; found, 488.4078.

2α-*N*-Substituted vitamin D$_3$ derivatives IId–e, IIIa–c, IVd, Va–d. As described for **IIb**, **IId–e**, **IIIa–c**, **IVd** and **Va–d** were obtained from the corresponding A-ring synthons (**15–24**).

2α-*N*,*N*′-Dibutyl-1α-25(OH)$_2$ vitamin D$_3$ (IId). $[\alpha]_D^{23}$ = +20.7 (*c* 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.49 (d, *J* = 10.8 Hz, 1H), 5.94 (d, *J* = 10.9 Hz, 1H), 5.30 (s, 1H), 5.02 (s, 1H), 4.63 (s, 1H), 4.15–4.29 (m, 1H), 3.35–2.72 (m, 9H), 2.40–2.25 (m, 1H), 2.20–0.70 (m, 42H), 0.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.1, 132.1, 130.9, 128.5, 126.1, 116.7, 72.5, 71.1, 68.4, 64.5, 56.5, 56.3, 51.0, 45.9, 44.4, 43.7, 40.5, 36.4, 36.1, 31.9, 29.7, 29.6, 29.4, 29.1, 27.6, 23.5, 22.7, 22.2, 20.9, 20.8, 18.8, 14.1, 14.0, 12.1; HRMS: calcd for $C_{35}H_{62}NO_3$, 544.4730; found, 544.4711.

2α-*N*,*N*′-Dibenzyl-1α-25(OH)$_2$ vitamin D$_3$ (IIe). $[\alpha]_D^{31}$ = +18.3 (*c* 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.18 (m, 10H), 6.47 (d, *J* = 11.4 Hz, 1H), 5.94 (d, *J* = 11.4 Hz, 1H), 5.21 (d, *J* = 1.9 Hz, 1H), 4.89 (d, *J* = 1.8 Hz, 1H), 4.66 (d, *J* = 1.8 Hz, 1H), 4.26–4.08 (m, 2H), 3.93 (dd, *J* = 178.4, 13.7 Hz, 4H), 2.82 (d, *J* = 12.4 Hz, 1H), 2.76 (dd, *J* = 13.1, 5.3 Hz, 1H), 2.60 (dd, *J* = 10.1, 2.3 Hz, 1H), 2.18–0.68 (m, 30 H), 0.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.0, 139.5, 131.5, 129.1, 127.1, 126.1, 116.7, 114.3, 72.3, 71.1, 66.1, 64.1, 56.5, 56.3, 54.5, 45.9, 44.4, 43.3, 40.4, 36.4, 36.1, 29.4, 29.3, 29.2, 27.6, 23.4, 22.2, 20.8, 18.8, 12.1; HRMS: calcd. for $C_{41}H_{57}NO_3Na$, 634.4236; found, 634.4231.

2α-*N*-Acetyl-1α-25(OH)$_2$ vitamin D$_3$ (IIIa). $[\alpha]_D^{26}$ = +62.8 (*c* 0.6, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.46 (d, *J* = 11.4 Hz, 1H), 6.28 (d, *J* = 8.3 Hz, 1H), 5.93 (d, *J* = 11.5 Hz, 1H), 5.35 (d, *J* = 1.8 Hz, 1H), 5.09 (d, *J* = 1.9 Hz, 1H), 4.31 (d, *J* = 3.3 Hz, 1H), 4.03–3.96 (m, 1H), 3.89 (ddd, *J* = 9.7, 9.7, 4.6 Hz, 1H), 2.83 (d, *J* = 12.8 Hz, 1H), 2.70 (dd, *J* = 13.7, 4.6 Hz, 1H), 2.34–2.25 (m, 1H), 2.08 (s, 3H), 2.08–0.80 (m, 30H), 0.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 144.5, 144.0, 130.7, 126.1, 117.0, 116.6, 74.7, 71.1, 70.6, 58.1, 56.4, 56.3, 45.9, 44.3, 43.4, 40.4, 36.4, 36.1, 29.5, 29.4, 29.2, 27.6, 23.5, 23.4, 22.2, 20.8, 18.8, 12.1; HRMS: calcd for $C_{29}H_{47}NO_4Na$, 496.3403; found, 496.3399.

2α-*N*-Pivaloyl-1α-25(OH)$_2$ vitamin D$_3$ (IIIb). $[\alpha]_D^{23}$ = +37.5 (*c* 1.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.48–6.37 (m, 2H), 5.94 (d, *J* = 11.4 Hz, 1H), 5.35 (s, 1H), 5.08 (s, 1H), 4.33 (d, *J* = 3.2 Hz, 1H), 4.05–3.93 (m, 1H), 3.93–3.84 (m, 1H), 2.82 (d, *J* = 12.3 Hz, 1H), 2.65 (dd, *J* = 13.5, 4.4 Hz, 1H), 2.30 (t, *J* = 11.4 Hz, 1H), 2.05–0.80 (m, 39H), 0.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.8, 144.2, 132.1, 128.5, 125.8, 116.7, 116.4, 74.2, 71.1, 70.8, 57.8, 56.4, 56.3, 45.9, 44.3, 43.2, 40.4, 38.9, 36.3, 36.1, 29.5, 29.3, 29.2, 27.7, 27.6, 23.5, 22.2, 20.8, 18.8, 12.0; HRMS: calcd for $C_{32}H_{53}NO_4Na$, 538.3872; found, 538.3834.

2α-*N*-Benzoyl-1α-25(OH)$_2$ vitamin D$_3$ (IIIc). $[\alpha]_D^{23}$ = +26.2 (*c* 1.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89–7.31 (m, 5H), 6.98 (d, *J* = 8.0 Hz, 1H), 6.46 (d, *J* = 11.4 Hz, 1H), 5.97 (d, *J* = 11.4 Hz, 1H), 5.38 (s, 1H), 5.12 (s, 1H), 4.45 (d, *J* = 3.4 Hz, 1H), 4.25–4.17 (m, 1H), 4.09–4.00 (m, 1H), 2.83 (t, *J* = 13.1 Hz, 1H), 2.71 (dd, *J* = 13.8, 4.6 Hz, 1H), 2.36 (t, *J* = 11.8 Hz, 1H), 2.23–0.80 (m, 30H), 0.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 144.1, 132.5, 132.0, 131.8, 131.0, 128.5, 127.2, 125.8, 116.8, 74.3, 71.1, 70.4, 58.5, 56.4, 56.3, 45.9, 44.3, 43.2, 40.4, 36.3, 36.1, 29.4, 29.3, 29.1, 27.6, 23.5, 22.2, 20.8, 18.8, 12.1; HRMS: calcd for $C_{34}H_{49}NO_4Na$, 558.3559; found, 558.3540.

2α-*N*-*tert*-Butoxycarbonyl-1α-25(OH)$_2$ vitamin D$_3$ (IVd). $[\alpha]_D^{31}$ = +44.7 (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.44 (d, *J* = 11.0 Hz, 1H), 5.94 (d, *J* = 11.0 Hz, 1H), 5.35 (s, 1H), 5.07 (s, 1H), 4.35 (d, *J* = 2.7 Hz, 1H), 3.92–3.84 (m, 1H), 3.73–3.64 (m, 1H), 2.82 (d, *J* = 12.8 Hz, 1H), 2.67 (dd, *J* = 13.5, 4.8 Hz, 1H), 2.27 (t, *J* = 11.5 Hz, 1H), 2.06–0.72 (m, 30H), 1.46 (s, 9H), 0.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2, 144.3, 144.1, 131.1, 128.0, 125.8, 116.7, 80.4, 74.7, 71.1, 70.5, 59.1, 56.4, 56.3, 45.9, 44.3, 43.2, 40.4, 36.3, 36.1, 29.7, 29.3, 29.2, 28.3, 27.6, 23.4, 22.2, 20.8, 18.8, 12.1; HRMS: calcd for $C_{32}H_{53}NO_5Na$, 554.3821; found, 554.3814.

2α-*N*-Methanesulfonyl-1α-25(OH)$_2$ vitamin D$_3$ (Va). $[\alpha]_D^{14}$ = +29.4 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.45 (d, *J* = 11.5 Hz, 1H), 5.93 (d, *J* = 11.4 Hz, 1H), 5.39 (s, 1H), 5.12 (s, 1H), 5.01 (d, *J* = 8.3 Hz, 1H), 4.47 (s, 1H), 4.00–3.87 (m, 1H), 3.51–3.38 (m, 1H), 3.01 (s, 3H), 2.82 (d, *J* = 11.9 Hz, 1H), 2.70 (dd, *J* = 13.5, 4.3 Hz, 1H), 2.35–2.20 (m, 1H), 2.10–0.75 (m, 30H), 0.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.6, 143.9, 130.3, 126.0, 116.9, 116.5, 74.2, 71.1, 69.3, 61.9, 56.5, 56.3, 46.0, 44.4, 42.1, 41.4, 40.4, 36.3, 36.1, 29.7, 29.4, 29.3, 27.6, 23.5, 22.2, 20.8, 18.8, 12.1; HRMS: calcd for $C_{28}H_{47}NO_5SNa$, 532.3073; found, 532.3076.

2α-*N*-Benzenesulfonyl-1α-25(OH)$_2$ vitamin D$_3$ (Vb). $[\alpha]_D^{17}$ = +29.2 (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.8 Hz, 1H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 2H), 6.42 (d, *J* = 11.4 Hz, 1H), 5.87 (d, *J* = 11.5 Hz, 1H), 5.31 (d, *J* = 8.3 Hz, 1H), 5.15 (s, 1H), 5.02 (d, *J* = 1.3 Hz, 1H), 3.94 (s, 1H), 3.91–3.81 (m, 1H), 3.23 (ddd, *J* = 8.7, 8.7, 3.2 Hz, 1H), 2.79 (d, *J* = 12.8 Hz, 1H), 2.67 (dd, *J* = 13.6, 4.9 Hz, 1H), 2.32 (s, 1H), 2.20 (t, *J* = 11.7 Hz, 1H), 2.05–0.82 (m, 30H), 0.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.6, 143.7, 140.3, 133.0, 130.2, 129.3, 127.1, 126.1, 116.9, 116.5, 73.4, 71.1, 68.7, 62.0, 56.4, 56.3, 45.9, 44.3, 41.6, 40.4, 36.3, 36.0, 29.3, 29.2, 29.1, 27.6, 23.4, 22.1, 20.8, 18.8, 12.1; HRMS: calcd for $C_{33}H_{49}NO_5SNa$, 594.3229; found, 594.3271.

2α-*N*-(4-*tert*-Butyl)-benzenesulfonyl-1α-25(OH)$_2$ vitamin D$_3$ (Vc). $[\alpha]_D^{18}$ = +12.0 (*c* 0.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.6 Hz, 2H), 7.55 (t, *J* = 8.6 Hz, 2H), 6.42 (d, *J* = 11.5 Hz, 1H), 5.87 (d, *J* = 10.9 Hz, 1H), 5.24 (d, *J* = 8.6 Hz, 1H), 5.11 (d, *J* = 1.7 Hz, 1H), 5.01 (d, *J* = 1.7 Hz, 1H), 3.90 (d, *J* = 3.5 Hz, 1H), 3.86 (ddd, *J* = 13.7, 9.1, 4.6 Hz, 1H), 3.22 (dt, *J* = 8.6, 3.4 Hz, 1H), 2.79 (d, *J* = 12.6 Hz, 1H), 2.68 (dd, *J* = 13.8, 4.6 Hz, 1H), 2.21 (t, *J* = 11.8 Hz, 1H), 2.10–0.60 (m, 39H), 0.50 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.9, 144.6, 143.8, 137.1, 130.2, 127.0, 126.3, 126.2, 116.8, 116.5, 73.4, 71.1, 68.7, 61.9, 56.4, 56.3, 45.9, 44.4, 41.6, 40.4, 36.3, 36.1, 31.6, 31.1, 29.4, 29.2, 29.1, 27.6, 23.5, 22.1, 20.8, 18.8, 12.0; HRMS: calcd for $C_{37}H_{57}NO_5SNa$, 650.3855; found, 650.3858.

2α-*N*-(4-Methoxy)-benzenesulfonyl-1α-25(OH)$_2$ vitamin D$_3$ (Vd). $[\alpha]_D^{20}$ = +12.2 (*c* 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 9.1 Hz, 2H), 7.00 (d, *J* = 8.6 Hz, 2H), 6.42 (d, *J* = 11.5 Hz, 1H), 5.87 (d, *J* = 11.5 Hz, 1H), 5.22 (d, *J* = 8.6 Hz, 1H), 5.18 (s, 1H), 5.03 (d, *J* = 1.1 Hz, 1H), 3.99 (d, *J* = 3.5 Hz, 1H), 3.88 (s, 3H), 3.88–3.81 (m, 1H), 3.19 (dt, *J* = 8.6, 3.5 Hz, 1H), 2.79 (d, *J* = 13.2 Hz, 1H), 2.67 (dd, *J* = 13.2, 4.6 Hz, 1H), 2.20 (t, *J* = 11.8 Hz, 1H), 2.10–0.60 (m, 39H), 0.50 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.1, 144.6, 143.8, 131.7, 130.3, 129.3, 126.1, 116.9, 116.5, 114.4, 73.4, 71.1, 68.7, 61.9, 56.4, 56.3, 55.6, 45.9, 44.3, 41.6, 40.4, 36.3, 36.0, 29.3, 29.2, 29.1, 27.6, 23.5, 22.1, 20.8, 18.8, 12.0; HRMS: calcd for $C_{34}H_{51}NO_6SNa$, 624.3335; found, 624.3337.

2β-*N*,*N*′-Dibenzyl-1α-25(OH)$_2$ vitamin D$_3$ (VIIe). To a solution of **5** (40 mg, 0.0346 mmol) and **32** (42 mg, 0.0737 mmol) in toluene and triethylamine (1 : 1, 2 mL) was added $Pd(PPh_3)_4$ (about 50 mg) at room temperature. The resulting mixture was stirred at room temperature for 15 min, then 100 °C for 3 h. The resulting mixture was cooled to room temperature, and diluted with ethyl acetate, filtered through a pad of Celite, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (hexane–ethyl acetate = 20 : 1) to give bis silylether. To a solution of bis silylether in THF (1.0 mL) was added HF–Et_3N (1.0 mL), and the mixture was stirred for 15 h. To the reaction mixture was added saturated $NaHCO_3$, and the mixture was stirred for 30 min. The resulting mixture was extracted with ethyl acetate, and the organic layer was washed with brine. The extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography ($CHCl_3$–MeOH = 9 : 1) to give **VIIe** (8.7 mg, 0.0142 mmol, 21%). $[\alpha]_D^{18}$ = −35.3 (*c* 0.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7.24 (m, 10H), 6.34 (d, *J* = 10.8 Hz, 1H), 6.08 (d, *J* = 10.8 Hz, 1H), 5.46 (s, 1H), 4.94 (s, 1H), 4.52 (s, 1H), 4.44 (d, *J* = 10.8 Hz, 1H), 4.16 (d, *J* = 13.7 Hz, 2H), 3.66 (d, *J* = 13.7 Hz, 2H), 2.80 (dd, *J* = 3.4, 12.6 Hz, 1H), 2.56 (d, *J* = 10.8 Hz, 1H), 2.38–0.83 (m, 26H), 0.93 (d, *J* = 5.7 Hz, 3H), 0.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.7, 139.4, 131.7, 131.0, 128.8, 128.5, 127.1, 126.2, 116.9, 110.4, 71.0, 66.6, 66.0, 65.8, 56.4, 56.3, 54.2, 50.9, 45.9, 44.3, 40.3, 36.3,

36.0, 31.9, 29.6, 29.3, 29.2, 27.6, 23.7, 22.2, 20.7, 18.8, 11.8; HRMS: (ESI, M + H^+) calcd for $C_{41}H_{58}NO_3$, 612.4416; found, 612.4422.

2β-*N*-Substituted vitamin D derivatives VIIIa and Xa. As described for **VIIe**, **VIIIa** and **Xa** were obtained from the corresponding A-ring synthons (**33** and **34**), respectively.

2β-*N*-Acetyl-1α-25(OH)$_2$ vitamin D$_3$ (VIIIa). $[\alpha]_D^{20}$ = −15.6 (*c* 0.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.39–6.33 (m, 2H), 6.03 (d, *J* = 11.4 Hz, 1H), 5.59 (s, 1H), 5.09 (s, 1H), 4.13–4.04 (m, 2H), 3.96–3.89 (m, 1H), 2.80 (d, *J* = 10.8 Hz, 1H), 2.61 (d, *J* = 13.1 Hz, 1H), 2.15 (d, *J* = 14.3 Hz, 1H), 2.08 (s, 3H), 2.20–0.84 (m, 24H), 0.93 (d, *J* = 5.1 Hz, 3H), 0.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 145.1, 144.1, 131.0, 125.9, 116.7, 112.2, 73.7, 71.0, 69.4, 58.4, 56.5, 56.3, 46.0, 44.3, 42.4, 40.3, 36.3, 36.0, 29.6, 29.3, 29.2, 27.5, 23.7, 23.3, 22.1, 20.7, 18.8, 11.8; HRMS: (ESI, M + Na^+) calcd for $C_{29}H_{47}NO_4Na$, 496.3402; found, 496.3405.

2β-*N*-Methanesulfonyl-1α-25(OH)$_2$ vitamin D$_3$ (Xa). $[\alpha]_D^{21}$ = −41.4 (*c* 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.35 (d, *J* = 10.9 Hz, 1H), 6.00 (d, *J* = 11.4 Hz, 1H), 5.52 (s, 1H), 5.24 (d, *J* = 8.24 Hz, 1H), 5.12 (s, 1H), 4.23–4.14 (m, 2H), 3.39–3.32 (m, 1H), 3.09 (s, 3H), 2.80 (d, *J* = 10.9 Hz, 1H), 2.57 (d, *J* = 14.6 Hz, 1H), 2.44 (d, *J* = 14.2 Hz, 1H), 2.09–0.84 (m, 24H), 0.93 (d, *J* = 5.9 Hz, 3H), 0.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.5, 144.1, 130.9, 125.7, 116.6, 112.3, 71.6, 71.1, 69.8, 62.6, 56.5, 56.3, 46.0, 44.3, 42.0, 41.4, 40.3, 36.3, 36.0, 29.6, 29.3, 29.2, 27.5, 23.7, 22.3, 20.7, 18.8, 11.8; HRMS: (ESI, M + Na^+) calcd for $C_{28}H_{47}NO_5SNa$, 532.3072; found, 532.3089.

Acknowledgements

This study was supported in part by the Advanced research for medical products Mining Programme of the National Institute of Biomedical Innovation (NIBIO) and Grant-in Aid for Scientific Research on Innovative Areas.

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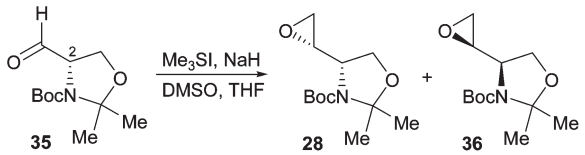
(Scheme 3) afforded **28** as a sole product. $[\alpha]_D^{22}$ = +12.5 (*c* 1.1, $CHCl_3$).



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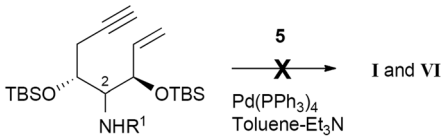

R^1 = Me, Et, *n*-Pr, *n*-Bu, Bn

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