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Design, Synthesis, Evaluation, and Structure of Vitamin D Analogues with Furan Side Chains

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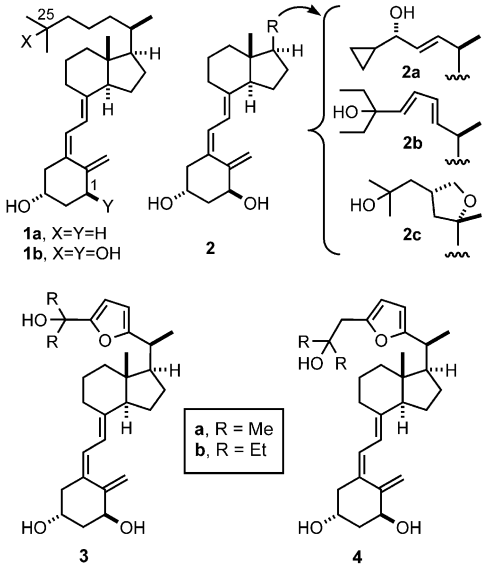
Dedicated to Dr. Noburu Kubodera on the occasion of his retirement

Abstract: Based on the crystal structures of human vitamin D receptor (hVDR) bound to 1α,25-dihydroxy-vitamin D_3 (1,25D) and superagonist ligands, we previously designed new superagonist ligands with a tetrahydrofuran ring at the side chain that optimize the aliphatic side-chain conformation through an entropy benefit. Following a similar strategy, four novel vitamin D analogues with aromatic furan side chains (**3a**, **3b**, **4a**, **4b**) have now been developed. The triene system has been constructed by an efficient stereoselective intramolecular cyclization of an enol triflate (A-ring precursor) followed by a Suzuki–Miyaura coupling of the resulting intermediate with an alkenyl boronic ester (CD-side chain, upper fragment). The furan side chains have been constructed by gold chemistry. These analogues exhibit significant pro-differentiation effects and transactivation potency. The crystal structure of **3a** in a complex with the ligand-binding domain of hVDR revealed that the side-chain furanic ring adopts two conformations.

Keywords: cell adhesion · furans · gold · synthesis design · vitamin D analogues

Introduction

Vitamin D_3 (**1a**), before eliciting its biological functions, must be dihydroxylated to its active metabolite 1α,25-dihydroxy-vitamin D_3 (**1b**, 1,25D, calcitriol), which induces gene expression by signaling through the nuclear vitamin D receptor transcription factor (VDR). The *seco*-steroid hormone 1,25D regulates a plethora of biological functions, including calcium homeostasis, cell proliferation and differentiation, and immunomodulation.[1]



Although the applicability of 1,25D is at present limited due to the parallel induction of hypercalcemia, its properties open perspectives for the treatment of several diseases, including osteoporosis, cancer, psoriasis, arthritis, and type 1 diabetes.[2,3] As a result, a great deal of attention is being focused on the synthesis of vitamin D analogues with selective properties, although few have proceeded beyond the preclinical stage.[4,5] Most of these analogues have been modified at the side chain, as exemplified by calcipotriol[6] (**2a**, MC903, Dovonex, Leo Pharmaceuticals, Denmark), used topically for the treatment of psoriasis[7] and seocalcitol (**2b**, EB1089,

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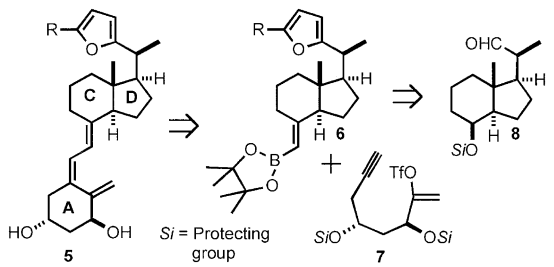
Leo Pharmaceuticals, Denmark), a potent inhibitor of cell proliferation.[8]

All synthetic vitamin D analogues that crystallize in complexes with the VDR ligand-binding domain (LBD) have been shown to be anchored by the same residues in the ligand-binding pocket (LBP), with the hydroxyl moieties at the A-ring and the side chain located in identical positions and forming identical hydrogen bonds.[9,10] On the basis of docking studies using the crystal structure of an engineered active ligand-binding domain of the human vitamin D receptor (hVDR LBD) bound to 1,25 D[9] and to agonist ligands,[10] we have recently designed the new superagonist analogue **2c**, the conformation of which in the binding pocket is stabilized by a side-chain tetrahydrofuran unit.[11] Attracted by the potent biological activities of **2b**,[8] which possesses a conjugated double bond in the side chain, and superagonist **2c**,[11] and to further study the correlation between in silico ligand design and biological activity, we designed the new analogues **3** and **4**, which possess a rigid side-chain fragment in the form of a furan ring and bind significantly more efficiently to the hVDR in silico than the natural hormone 1,25 D.[12,13] We describe herein the synthesis of the four analogues **3a**,**b** and **4a**,**b**. In addition, we present the results of investigations of their biological behavior and structural studies.

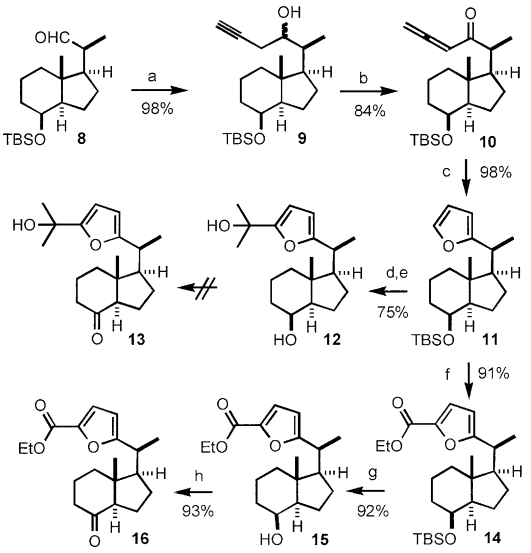
Results and Discussion

General retrosynthesis of analogues 3 and 4: The general synthetic strategy for the synthesis of vitamin D analogues **3a**, **3b**, **4a**, and **4b** (depicted as the general structure **5**) follows the convergent strategy recently developed in our laboratory (Scheme 1).[14] In this route, the triene system is constructed by an efficient stereoselective intramolecular cyclization of an enol triflate (A-ring precursor **7**)[15] followed in situ by a Suzuki–Miyaura coupling of the resulting palladium intermediate with an alkenyl boronic ester (CD-side chain upper fragment, **6**). We envisaged the preparation of the boronate ester **6** from the known protected aldehyde **8**[16] using gold chemistry to introduce the furan ring.



Scheme 1. General retrosynthesis of the target vitamin D_3 analogues.

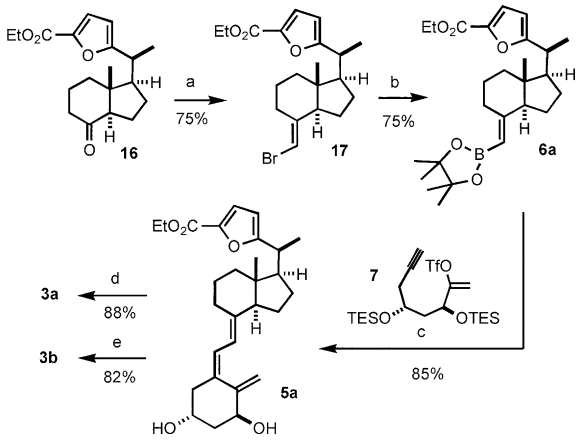
Preliminary studies on the conversion of furan **11** into ketone **13** were not very promising. Deprotonation of the furan ring with butyllithium and subsequent reaction of the resulting lithium anion with acetone furnished, after desilylation with tetrabutylammonium fluoride (TBAF),[22] diol **12** (75%, two steps, Scheme 2). Unfortunately, several attempts



Scheme 2. Synthesis of furan **11** and furanic ketone **16**. Reagents and conditions: a) HC_2CH_2ZnBr, THF, 0°C, 1 h, RT, 1.5 h, 98%; b) DMP, CH_2Cl_2, RT, 1.5 h, 84%; c) Et_3PAuCl (3 mol%), THF, then $AgNO_3$ (3 mol%), RT, 4 h, 98%; d) *n*BuLi, THF, RT, 2 h, −78°C, acetone, −78°C to RT, 80%; e) TBAF, THF, 50°C, 72 h, 94%; f) *n*BuLi, THF, 0°C, 2 h, −78°C, then $ClCO_2Et$, THF, −78°C to RT, 91%; g) HF (48%, 50 drops), CH_3CN, RT, 36 h, 92%; h) DMP, CH_2Cl_2, RT, 3.5 h, 93%. TBS = $SiMe_2tBu$. DMP = Dess–Martin periodinane. THF = tetrahydrofuran. TBAF = nBu_4NF.

to selectively oxidize alcohol **12** to the desired ketone **13** under different reaction conditions were unsuccessful.[23] These results prompted us to attempt the installation of the hydroxylated side chain at the end of the synthesis. Considering that the ester group tolerates the reaction conditions chosen to introduce the vitamin D triene system,[14] we selected this functionality instead of the previous tertiary hydroxy group to continue the synthesis. The required ester **14** was prepared in 91% yield by reaction of the lithium anion of **11** with ethyl chloroformate. Removal of the TBS group (HF/CH_3CN) and oxidation of the resulting alcohol (DMP/CH_2Cl_2) afforded the desired upper ketone **16** (85% yield over the two steps; 62% yield from aldehyde **8**, six steps).

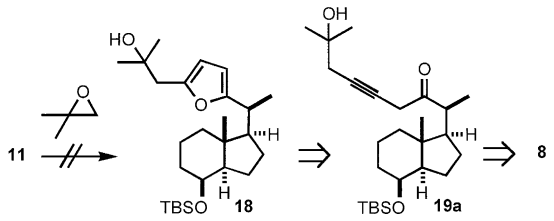
Completion of the synthesis of analogues **3a** and **3b** is illustrated in Scheme 3. Wittig reaction of **16** with ylide $Ph_3P{=}CHBr$[14] afforded alkenyl bromide **17** (75%), which was treated with bis(pinacolato)diboron in the presence of [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II)–dichloromethane complex as catalyst and tricyclohexylphosphine as ligand to provide the desired boronate **6a** in 75% yield. With the requisite upper boronate **6a** in hand, we next proceeded to install the triene unit. Treatment of an equimolar mixture of **6a** and **7** in aqueous K_3PO_4 (2 M)/THF with a catalytic amount of $[PdCl_2(Ph_3P)_2]$ (5 mol%) at RT for 1 h delivered, after desilylation with hydrogen fluoride,



Scheme 3. Functionalization of the furan ring and synthesis of analogues **3a** and **3b**. Reagents and conditions: a) $Ph_3P{=}CHBr$, toluene, −15 to 0 °C, 75 %; b) $[PdCl_2(dppf)_2]{\cdot}CH_2Cl_2$, Cy_3P, KOAc, Pin_2B_2, DMSO, 80 °C, 2.5 h, 75 %; c) $[PdCl_2(Ph_3P)_2]$, K_3PO_4, THF/H_2O, RT, 1 h; HF (48 %, 5 drops), CH_3CN, 15 min, 85 %; d) MeLi, THF, −78 °C to RT, 12 h, 88 %; e) EtMgBr, THF, −78 °C, 15 min, RT, 3 h, 82 %. TES = $SiEt_3$. dppf = 1,1′-bis(diphenylphosphino)ferrocene.

the ester **5a** (85 % yield, two steps). The ester **5a** is a suitable intermediate for further functionalization at the side chain with the possibility of isotopic labeling. Finally, the target analogue **3a** was obtained in 88 % yield by treatment of ester **5a** with methyllithium in THF (33 % overall yield from aldehyde **8**, eleven steps). Replacing methyllithium by ethylmagnesium bromide furnished the vitamin D analogue **3b** (31 % overall yield from aldehyde **8**, eleven steps).

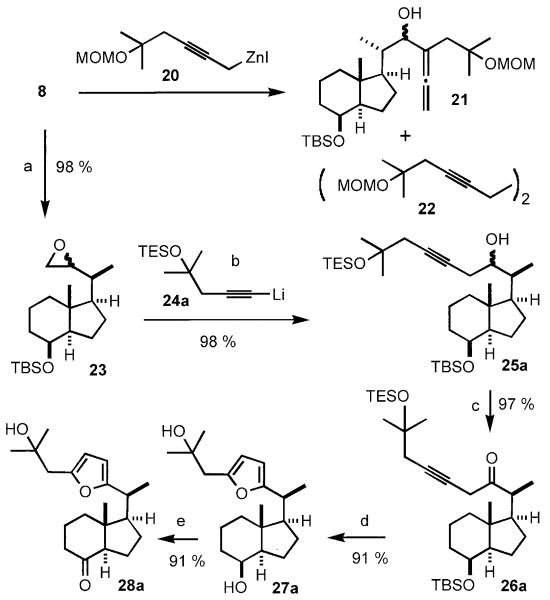
Synthesis of vitamin D analogues 4a and 4b: Our synthetic efforts were first focused on alcohol **18**, which contains the side chain of the target analogues **4** (Scheme 4). Unfortu-



Scheme 4. Retrosynthesis of **12a** from aldehyde **8**.

nately, our efforts to obtain **18** by treatment of the lithium or copper anion of **11** with isobutylene oxide resulted only in recovery of the starting material.[24] As an alternative, we next focused our attention on the Au^{III}-assisted transformation of propargyl ketones into furans, as previously observed by Hashmi and co-workers.[20] Thus, furan **18** was envisaged as being accessible from ketone **19a**, which in turn would be prepared from aldehyde **8**.

As shown in Scheme 5, our initial efforts to obtain a diastereomeric mixture of propargylic alcohols **25a** by reaction of aldehyde **8** with propargyl zinc **20** produced a mixture of

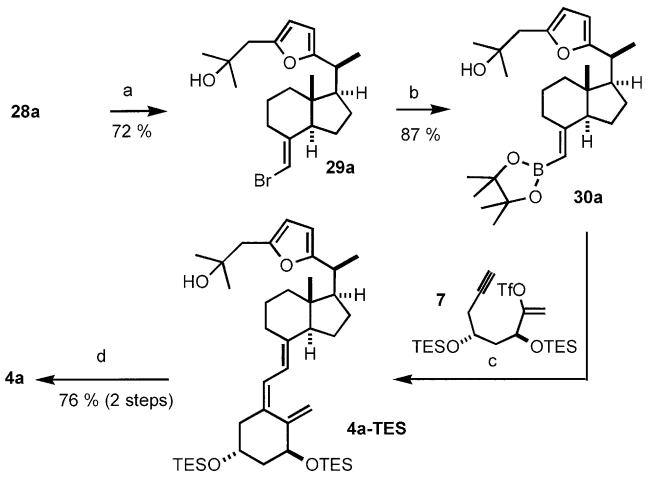


Scheme 5. Synthesis of the upper ketone **26a**. Reagents and conditions: a) MeLi addition to **8** in $ClCH_2I$, THF, −78 °C, 30 min, RT, 1.5 h, 98 %; b) **22** and $F_3B{\cdot}OEt_2$, THF, addition to **23a**, −78 °C to RT, 12 h, 98 %; c) DMP, CH_2Cl_2, RT, 1.5 h, 91 %; d) $AuCl_3$, THF, RT, 15 min; TBAF, THF, 50 °C, 4 days, 91 %; e) DMP, CH_2Cl_2, RT, 1.5 h, 91 %.

the unwanted allene **21** and dimer **22**. However, the desired alcohols **25a** could be obtained in 96 % yield through a two-step sequence, which involved treatment of a mixture of chloroiodomethane and **8** with methyllithium, followed by opening of the resultant epoxide **23**[25] with the lithium alkynide **24a** in the presence of boron trifluoride diethyl etherate. Oxidation of alcohols **25a** with Dess–Martin periodinane proceeded smoothly to produce ketone **26a** (97 % yield) accompanied by a trace amount of the corresponding isomeric allenone. As previously planned, exposure of ketone **26a** to gold(III) chloride furnished, after desilylation (TBAF), the desired diol **27a** (91 % yield over the two steps). Diol **27a** was then oxidized with Dess–Martin periodinane to generate ketone **28a** (91 % yield).

Scheme 6 depicts the completion of the synthesis of **4a** following the same sequence of reactions as above. Olefination of ketone **28a** with $Ph_3P{=}CHBr$ provided the alkenyl bromide **29a** (72 %), exposure of which to Pin_2B_2 in the presence of $[PdCl_2(dppf)_2]{\cdot}CH_2Cl_2$ as catalyst and Cy_3P as a ligand, furnished the expected boronate **30a** (87 %). The cyclization–coupling cascade between enol triflate **7** and boronate **30a** proceeded smoothly under the standard reaction conditions indicated in Scheme 3 to provide, after desilylation (HF/CH_3CN), the desired analogue **4a** in 76 % yield (nine steps, 36.7 % overall yield from aldehyde **8**). Analogue **4b** was synthesized in 26.6 % yield from aldehyde **8** employing the same sequence of reactions.[26]

Biological activity: The biological activities of the four vitamin D analogues (**3a**, **3b**, **4a**, **4b**) were assayed in human SW480-ADH colon cancer cells. These cells express endoge-



Scheme 6. Synthesis of **4a**. Reagents and conditions: a) $Ph_3P{=}CHBr$, toluene, −15 to 0 °C, 72 %; b) $[PdCl_2(dppf)_2]{\cdot}CH_2Cl_2$, Cy_3P, KOAc, Pin_2B_2, DMSO, 80 °C, 3 h, 87 %; c) $[PdCl_2(Ph_3P)_2]$, K_3PO_4, THF/H_2O, RT, 1 h; d) HF (48 %, 5 drops), CH_3CN, 20 min, 76 % (two steps).

nous VDR and respond to 1,25 D treatment by inhibition of proliferation and differentiation to an epithelial phenotype.[27] The ability of the four derivatives to activate VDR was first examined by their capacity to induce in SW480-ADH cells a morphological change towards a differentiated adhesive phenotype. All four compounds displayed a similar effect to that of 1,25 D when assayed at 10^{-7} M, leading to the formation of compact epitheloid islands (Figure 1 A). We subsequently studied the effect of the analogues in increasing the cellular content of VDR in comparison with that exerted by 1,25 D, an effect that is believed to be a consequence of both transcriptional and post-transcriptional mechanisms.[28] Western blot analyses showed that they were all able to increase the VDR protein level with comparable potency to that of 1,25 D (Figure 1 B). Moreover, and in line with the induction of intercellular adhesion, all four compounds caused an increase in the amount of E-cadherin, the crucial component of *adherens junctions* structures at the plasma membrane that is mainly responsible for intercellular adhesion in epithelia. E-Cadherin has been shown to be induced by 1,25 D through the activation of a rapid extranuclear signaling pathway that is required for CDH1/E-cadherin gene transcription.[29] Thus, our results indicate that compounds **3a**, **3b**, **4a**, and **4b** are able to activate both non-genomic and genomic VDR actions.

Finally, we examined the ability of the compounds to induce VDR transcriptional activity in transactivation experiments using cells that were transfected with a plasmid encoding the luciferase reporter gene under the control of a vitamin D response element (VDRE; Figure 1 C). Analogues **3a** and **4a** showed potencies slightly lower than but comparable to that of 1,25 D, whereas analogues **3b** and **4b** were an order of magnitude less potent. All in all, these results show that our compounds efficiently bind VDR in vivo, inducing its ability to interact with target genes and to activate transcription from a consensus VDRE, with the variable potency observed in the assays being attributable to gene- or sequence-specific differences.

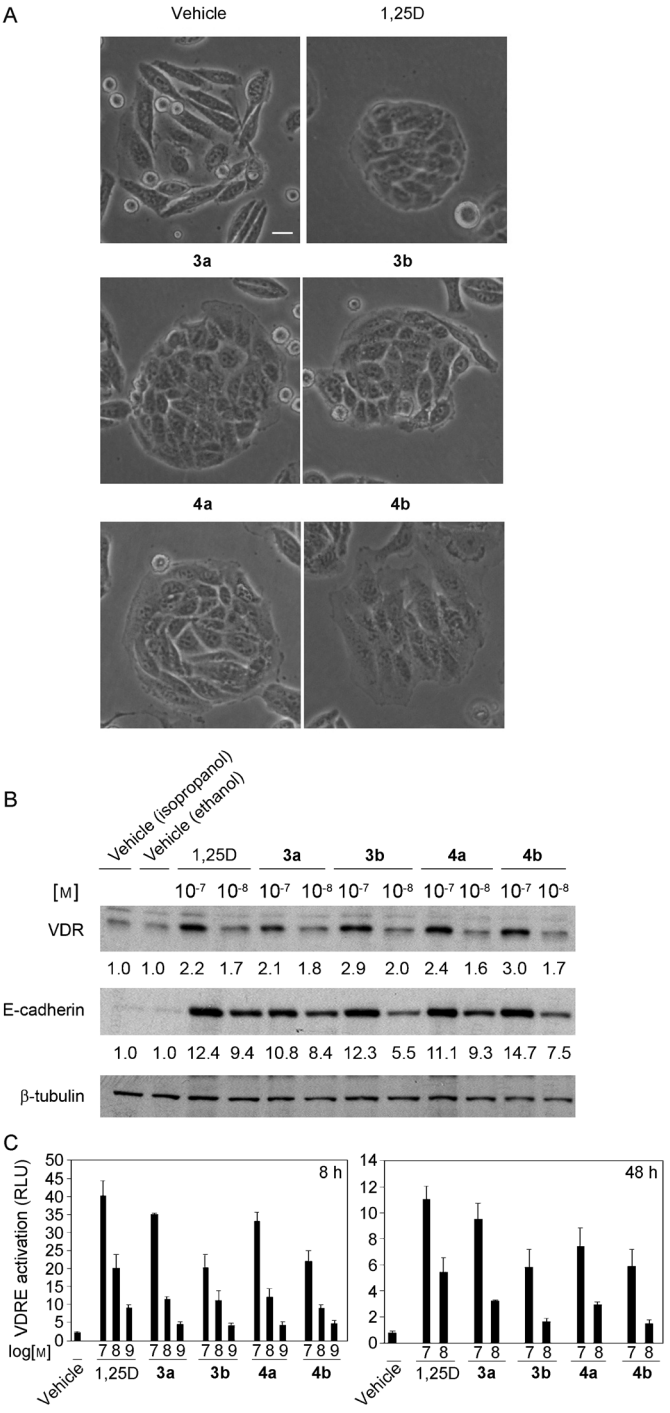


Figure 1. Biological assays of **3a**, **3b**, **4a**, and **4b**. Numbers below tracks correspond to the values of E-cadherin and VDR protein expression levels normalized to that of β-tubulin in 1,25 D- and analogues-treated versus vehicle-treated cells. RLU = relative luciferase units.

Crystal structure of 3a bound to the hVDR ligand-binding domain (PDB ID: 3TKC): To gain insight into structure–function relationships, we solved the crystal structure of the

hVDR LBD bound to **3a** at a resolution of 1.75 Å (Table S1 in the Supporting Information). The complex hVDR LBD/**3a** displays the canonical agonist conformation of all previously reported structures of VDR bound to agonist and superagonist ligands, with helix H12 folded in the agonistic position.[9–11] The ligand is buried in the predominantly hydrophobic pocket and adopts the same orientation as the natural ligand. In contrast to all previous structures of hVDR LBD complexes, the side chain of the bound **3a** ligand adopts two conformations, X and Y (Figure 2). Their relative occupancies refined by PHENIX.REFINE were evaluated as 60% and 40% for conformations **3a**-X and **3a**-Y, respectively.

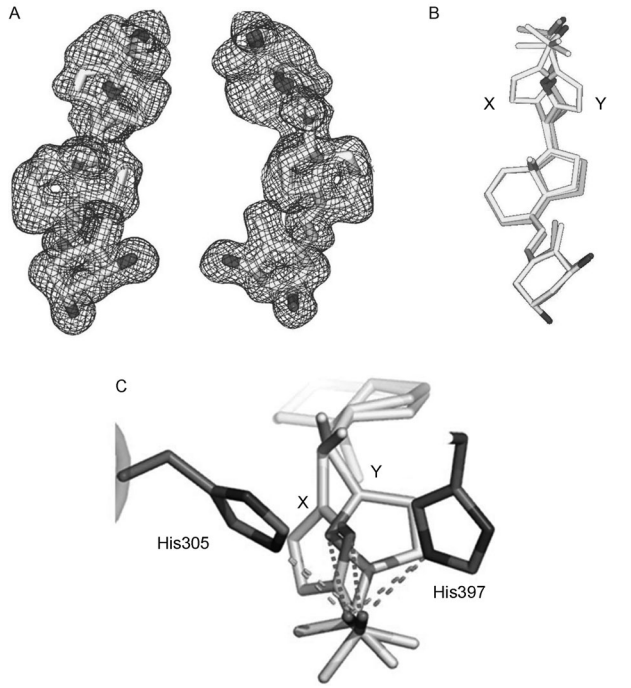


Figure 2. Conformations of **3a** bound to VDR. A) Two views of **3a** (in white) in the $2F_o-F_c$ electron density omit map contoured at 1.0 σ. B) Superimposition of the two conformations X and Y of **3a** (light grey) with that of 1,25D (grey). C) Intermolecular and intramolecular hydrogen bonds around the side chain of **3a**. X and Y are the two conformations of the side chain of **3a**.

In the two conformations, the A, seco-B, and C/D rings form identical hydrogen-bonding interactions as previously described for the hVDR LBD/1α,25$(OH)_2D_3$ complex. The presence of an oxygen atom in the tetrahydrofuran ring in the vicinity of the 25-OH group of the side chain of **3a** favors an intramolecular hydrogen bond (darker grey central dashed lines in Figure 2C; distances are 3.07 Å in the **3a**-X conformation and 2.81 Å in the **3b**-Y conformation). Consequently, the side chain of **3a** is more flexible in the LBP and the hydrophobic and electrostatic environment stabilizes two distinct conformations. The distances between the Nε2 of His305 and the 25-OH of the ligand are 2.73, 3.02, and 2.82 Å for **3a**-X, **3a**-Y, and 1α,25$(OH)_2D_3$, respectively, and the distances between the Nε2 of His397 and 25-OH are 2.91, 2.68, and 2.81 Å for **3a**-X, **3a**-Y, and 1α,25$(OH)_2D_3$, respectively. Additional van der Waals interactions stabilize each conformation. Thus, the flexibility of compound **3a**, illustrated by the presence of two distinct conformations of the furan ring in the LBP, may explain the slightly lower agonist property of this molecule.

Conclusion

We have designed by docking and efficiently synthesized four novel 1α,25-dihydroxy-vitamin D_3 analogues with furan side chains. Key features of our work include the use of a Pd^0-catalyzed cyclization–coupling cascade for the stereoselective construction of the triene unit from an enol triflate (A-ring precursor) and an alkenyl boronate (CD-side chain fragment), and an Au^{III}-catalyzed intramolecular construction of the side-chain furan unit. These analogues efficiently bind the vitamin D receptor (VDR) in vivo to induce VDR transcriptional activity. Analogues **3a** and **4a** showed comparable potency to that of 1,25D, whereas analogues **3b** and **4b** were an order of magnitude less potent. All four compounds exerted a similar effect in human SW480-ADH colon cancer cells as the natural hormone at concentrations of 10^{-7} M. In contrast to all previous structures of hVDR LBD complexes, the side chain of the bound ligand **3a** adopts two conformations. The slightly lower agonist potency of **3a** in comparison with 1,25D may be explained in terms of intramolecular hydrogen-bonding between the hydroxy group of the side chain and the oxygen of the furan ring, which diminishes the intermolecular interaction of the analogue with His305 and His397 of the VDR.

Experimental Section

General: Details of the general materials and methods have been provided elsewhere.[12,14] For details concerning the preparation of compounds **8**, **23**, **28a**, **29a**, **30a**, **4a**, **26b**, **17b**, **28b**, **29b**, **30b**, and **4b**, see the Supporting Information.

8β-[(*tert*-Butyldimethylsilyl)oxy]-de-A,B-26,27-dinor-24-cholestyn-22-ol (9): A suspension of Zn (0.197 g, 3.01 mmol, 7 equiv) in dry THF (10 mL) was heated at reflux for 10 min. 1,2-Dibromoethane (0.03 mL, 0.345 mmol, 0.8 equiv) was then added. The suspension was heated at reflux for 10 min and then cooled to 0°C, whereupon propargyl bromide (0.16 mL, 1.5 mmol, 3.5 equiv) was added dropwise. The resulting mixture was stirred in the dark for 1 h at 0°C. A solution of aldehyde **8** (0.156 g, 0.43 mmol, 1 equiv) in THF (4 mL) was then added via a cannula. The mixture was stirred for 1 h at 0°C and for 1.5 h at RT. The reaction was then quenched with saturated aqueous NH_4Cl solution (10 mL). The aqueous phase was extracted with Et_2O (3×10 mL) and the combined organic phases were dried, filtered, and concentrated. The residue was purified by flash chromatography (SiO_2, 1×12 cm, 5% EtOAc/hexanes) to give a mixture of isomers **9** [0.154 g, 0.42 mmol, 98%, R_f=0.44 (20% EtOAc/hexanes), colorless oil]. ^{1}H NMR (400 MHz, $CDCl_3$): δ= 4.00 (m, 1H; H-8), 3.90 (m, 1H; H-22), 2.44 (ddd, J=16.6, 8.1, 2.6 Hz, 1H; H-23), 2.24 (ddd, J=16.6, 5.8, 2.6 Hz, 1H; H-23), 2.03 (t, J=2.6 Hz, 1H; H-25), 0.92 (s, 3H; H-18), 0.89–0.88 (m, 12H; Me_3CSi and H-21), 0.00 (s, 3H; MeSi), −0.01 ppm (s, 3H; MeSi); ^{13}C NMR (100 MHz, $CDCl_3$): δ=81.8 (C; C-24), 71.8 (CH; C-22), 70.2 (CH; C-25), 69.4 (CH;

C-8), 53.2 (CH; C-17), 53.0 (CH; C-14), 42.1 (C; C-13), 40.7 (CH_2; C-12), 39.1 (CH; C-20), 34.4 (CH_2; C-9), 26.8 (CH_2; C-11), 25.8 ($3\times CH_3$; Me_3CSi), 25.4 (CH_2; C-23), 22.9 (CH_2; C-15), 18.0 (C; CSi), 17.6 (CH_2; C-16), 13.6 (CH_3; C-18), 11.3 (CH_3; C-21), −4.8 (CH_3; MeSi), −5.2 ppm (CH_3; MeSi); IR (film): $\tilde{\nu}=3446$, 3313 cm^{-1}; HRMS (EI^+): m/z: calcd for $[C_{22}H_{39}OSi]^+$: 347.2770 $[M]^+$; found 347.2773.

8β-[(*tert*-Butyldimethylsilyl)oxy]-de-A,B-26,27-dinor-23(24),24(25)-cholesdien-22-one (10): Dess–Martin periodinane (DMP, 0.641 g, 1.51 mmol, 1.2 equiv) was added to a solution of **9** (0.460 g, 1.26 mmol, 1 equiv) in dry CH_2Cl_2 (15 mL). After stirring at RT for 1.5 h, the reaction was quenched with saturated aqueous NaCl solution (15 mL). The aqueous phase was extracted with CH_2Cl_2 (3×15 mL) and the combined organic phases were dried, filtered, and concentrated. The residue was purified by flash chromatography (SiO_2, 3×7 cm, hexanes) to give **10** [0.403 g, 1.07 mmol, 84%, $R_f=0.68$ (20% EtOAc/hexanes), pale-yellow solid]. M.p. 99–101 °C (CH_2Cl_2/hexanes); ^1H NMR (250 MHz, $CDCl_3$): $\delta=5.72$ (t, $J=6.5$ Hz, 1H; H-23), 5.22 (m, 2H; H-25), 3.99 (m, 1H; H-8), 3.08 (dq, $J=10.5$, 6.8 Hz, 1H; H-20), 1.06 (d, $J=6.6$ Hz, 3H; H-21), 0.92 (s, 3H, H-18), 0.87 (s, 9H; Me_3CSi), −0.01 (s, 3H; MeSi), −0.03 ppm (s, 3H; MeSi); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta=216.7$ (C; C-24), 204.7 (C; C-22), 96.6 (CH; C-23), 79.3 (CH_2; C-25), 69.2 (CH; C-8), 53.0 (CH; C-17), 52.3 (CH; C-14), 43.9 (CH; C-20), 42.3 (C; C-13), 40.5 (CH_2; C-12), 34.3 (CH_2; C-9), 26.5 (CH_2; C-15), 25.8 ($3\times CH_3$; Me_3CSi), 23.1 (CH_2; C-16), 18.0 (C; CSi), 17.6 (CH_2; C-11), 17.1 (CH_3; C-21), 13.9 (CH_3; C-18), −4.8 (CH_3; MeSi), −5.2 ppm (CH_3; MeSi); IR (film): $\tilde{\nu}=1967$, 1677 cm^{-1}; HRMS (CI^+): m/z: calcd for $[C_{22}H_{39}O_2Si]^+$: 363.2719 $[M+H]^+$; found 363.2729.

8β-[(*tert*-Butyldimethylsilyl)oxy]-(20*S*)-de-A,B-(2-furyl)pregnane (11): A solution of **10** (0.082 g, 0.225 mmol, 1 equiv) in dry THF (5 mL) was added dropwise via a cannula to a solution of Et_3PAuCl (2.4 mg, 0.007 mmol, 3 mol%) in THF (5 mL). $AgNO_3$ (1.2 mg, 0.007 mmol, 3 mol%) was added and the reaction mixture was stirred in the dark at RT for 4 h. Et_2O (15 mL) was then added, and the mixture was filtered through Celite, washing with further Et_2O (50 mL). The collected organic phase was washed with saturated aqueous NaCl solution (40 mL), dried, filtered, and concentrated. The residue was purified by flash chromatography (SiO_2, 1×10 cm, hexanes) to afford **11** [0.08 g, 0.22 mmol, 98%, $R_f=0.72$ (10% EtOAc/hexanes), colorless oil]. ^1H NMR (250 MHz, $CDCl_3$): $\delta=7.26$ (d, $J=1.3$ Hz, 1H; H-25), 6.25 (dd, $J=3$, 1.9 Hz, 1H; H-24), 5.90 (d, $J=3$ Hz, 1H; H-23), 4.02 (m, 1H; H-8), 2.70 (dq, $J=10.6$, 6.9 Hz, 1H; H-20), 1.24 (d, $J=6.8$ Hz, 3H; H-21), 1.00 (s, 3H; H-18), 0.90 (s, 9H; Me_3CSi), 0.03 (s, 3H; MeSi), 0.01 ppm (s, 3H; MeSi); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta=161.6$ (C; C-22), 140.0 (CH; C-25), 109.7 (CH; C-24), 103.2 (CH; C-23), 69.4 (CH; C-8), 55.8 (CH; C-17), 53.0 (CH; C-14), 42.1 (C; C-13), 40.6 (CH_2; C-12), 35.8 (CH; C-20), 34.4 (CH_2; C-9), 27.6 (CH_2; C-15), 25.8 ($3\times CH_3$; Me_3CSi), 23.0 (CH_2; C-16), 19.7 (CH_3; C-21), 18.0 (C; CSi), 17.7 (CH_2; C-11), 13.7 (CH_3; C-18), −4.8 (CH_3; MeSi), −5.1 ppm (CH_3; MeSi); IR (film): $\tilde{\nu}=2933$, 2858 cm^{-1}; elemental analysis calcd (%) for $C_{22}H_{38}O_2Si$: C 72.87, H 10.56; found: C 72.60, H 10.83.

(20*S*)-De-A,B-[5-(2-hydroxypropan-2-yl)furan-2-yl]-8β-pregnanol (12): A solution of *n*BuLi in hexanes (0.25 mL, 2.24 M, 0.56 mmol, 1.2 equiv) was added dropwise to a solution of **11** (0.170 g, 0.47 mmol, 1 equiv) in dry THF (5 mL) at −78 °C. The mixture was allowed to warm to 0 °C, stirred for 2 h, and then cooled to −78 °C once more. Dry acetone (0.14 mL, 1.86 mmol, 4 equiv) was added dropwise, and the reaction mixture was allowed to warm slowly to RT. The reaction was quenched with saturated aqueous NH_4Cl solution (10 mL) and Et_2O (10 mL), and the aqueous phase was extracted with Et_2O (3×15 mL). The combined organic phases were dried, filtered, and concentrated. The residue was purified by flash chromatography (SiO_2, 2×10 cm, 10% EtOAc/hexanes) to afford **12-TBS** [0.156 g, 0.37 mmol, 80%, $R_f=0.26$ (10% EtOAc/hexanes), colorless oil]. ^1H NMR (250 MHz, $CDCl_3$): $\delta=6.02$ (d, $J=3.1$ Hz, 1H; H-24), 5.80 (d, $J=3.1$ Hz, 1H; H-23), 4.00 (m, 1H; H-8), 2.70 (dq, $J=10.6$, 6.9 Hz, 1H; H-20), 1.56 (s, 6H; H-27 and H-28), 1.23 (d, $J=6.9$ Hz, 3H; H-21), 0.98 (s, 3H; H-18), 0.89 (s, 9H; Me_3CSi), 0.01 (s, 3H; MeSi), −0.01 ppm (s, 3H; MeSi); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta=160.8$ (C; C-25), 157.5 (C; C-22), 103.6 (CH; C-24), 103.5 (CH; C-23), 69.4 (CH; C-8), 68.7 (C; C-26), 56.0 (CH; C-17), 53.0 (CH; C-14), 42.1 (C; C-13), 40.6 (CH_2; C-12), 35.8 (CH; C-20), 34.4 (CH_2; C-9), 28.6 (CH_3; C-27 and C-28), 27.3 (CH_2, C-15), 25.8 ($3\times CH_3$; Me_3CSi), 23.0 (CH_2; C-16), 19.7 (CH_3; C-21), 18.0 (C; C-Si), 17.7 (CH_2; C-11), 13.7 (CH_3; C-18), −4.8 (CH_3; MeSi), −5.2 ppm (CH_3; MeSi). A solution of TBAF in THF (3.1 mL, 1 M, 3 mmol, 5 equiv) was added to a solution of **12-TBS** (0.260 g, 0.619 mmol, 1 equiv) in dry THF (10 mL), and the mixture was heated at 50 °C for 72 h. The reaction was then quenched at RT with saturated aqueous NH_4Cl solution (10 mL) and Et_2O (5 mL), and the aqueous phase was extracted with Et_2O (3×15 mL). The combined organic phases were dried, filtered, and concentrated. The residue was purified by flash chromatography (SiO_2, 2.5×10 cm, 10% EtOAc/hexanes) to give **12** [0.178 g, 0.583 mmol, 94%, $R_f=0.26$ (hexanes), colorless oil]. ^1H NMR (250 MHz, $CDCl_3$): $\delta=6.01$ (d, $J=3.1$ Hz, 1H; H-24), 5.80 (d, $J=3.1$ Hz, 1H; H-23), 4.06 (m, 1H; H-8), 2.70 (dq, $J=10.3$, 6.9 Hz, 1H; H-20), 1.55 (s, 6H; H-27 and H-28), 1.23 (d, $J=6.9$ Hz, 3H; H-21), 0.99 ppm (s, 3H; H-18); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta=160.4$ (C; C-25), 157.6 (C; C-22), 103.6 (CH; C-23 and C-24), 69.2 (CH; C-8), 68.6 (COH; C-26), 55.8 (CH; C-17), 52.4 (CH; C-14), 41.7 (C; C-13), 40.2 (CH_2; C-12), 35.7 (CH; C-20), 33.5 (CH_2; C-9), 28.5 (CH_3; C-27 and C-28), 27.1 (CH_2; C-15), 22.4 (CH_2; C-16), 19.7 (CH_3; C-21), 17.4 (CH_2; C-11), 13.4 ppm (CH_3; C-18); HRMS (CI^+): m/z: calcd for $[C_{19}H_{31}O_3]^+$: 307.2273 $[M+H]^+$; found 307.2271.

8β-[(*tert*-Butyldimethylsilyl)oxy]-(20*S*)-de-A,B-[(5-ethyloxycarbonyl)furan-2-yl]pregnane (14): A solution of *n*BuLi in hexanes (2.4 mL, 2.3 M, 5.51 mmol, 1.3 equiv) was added to a solution of **11** (1.53 g, 4.24 mmol, 1 equiv) in dry THF (20 mL) at 0 °C. The mixture was stirred for 2 h and then cooled to −78 °C, whereupon ethyl chloroformate (2 mL, 21.2 mmol, 5 equiv) was slowly added dropwise. The reaction mixture was allowed to warm to RT overnight. The reaction was then quenched with saturated aqueous NaCl solution (20 mL) and Et_2O (20 mL), and the aqueous phase was extracted with Et_2O (3×20 mL). The combined organic phases were dried, filtered, and concentrated. The residue was purified by flash chromatography (SiO_2, 3×6 cm, 3% EtOAc/hexanes) to afford **14** [1.68 g, 3.87 mmol, 91%, $R_f=0.7$ (10% EtOAc/hexanes), colorless oil]. ^1H NMR (250 MHz, $CDCl_3$): $\delta=7.04$ (d, $J=3.3$ Hz, 1H; H-24), 6.02 (d, $J=3.3$ Hz, 1H; H-23), 4.32 (q, $J=7.1$ Hz, 2H; -OCH_2CH$_3$), 3.97 (m, 1H; H-8), 2.80 (m, 1H; H-20), 1.35 (t, $J=7.1$ Hz, 3H; CH_3CH$_2$O-), 1.26 (d, $J=7.1$ Hz, 3H; H-21), 0.98 (s, 3H; H-18), 0.88 (s, 9H; Me_3CSi), 0.00 (s, 3H; MeSi), −0.02 ppm (s, 3H; MeSi); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta=$ 166.5 (C; COOEt), 159.0 (C, C-22), 142.5 (C; C-25), 118.0 (CH; C-24), 106.1 (CH; C-23), 69.3 (CH; C-8), 60.5 (CH_2; -OCH_2CH$_3$), 55.2 (CH; C-17), 52.8 (CH; C-14), 42.2 (C; C-13), 40.5 (CH_2; C-12), 36.3 (CH; C-20), 34.3 (CH_2; C-9), 27.3 (CH_2; C-15), 25.8 ($3\times CH_3$; Me_3CSi), 22.9 (CH_2; C-16), 19.5 (CH_3; C-21), 18.0 (C; C-Si), 17.6 (CH_2; C-11), 14.4 (CH_3; CH_3CH$_2$O-), 13.7 (CH_3; C-18), −4.8 (CH_3; MeSi), −5.2 ppm (CH_3; MeSi); IR (film): $\tilde{\nu}=2934$, 1729 cm^{-1}; HRMS (CI^+): m/z: calcd for $[C_{25}H_{43}O_4Si]^+$: 435.2931 $[M+H]^+$; found 435.2935.

(20*S*)-De-A,B-[(5-ethyloxycarbonyl)furan-2-yl]-8β-pregnanol (15): Aqueous HF (48%, 50 drops) was added to a solution of **14** (0.430 g, 1 mmol, 1 equiv) in CH_3CN (20 mL) and the mixture was stirred at RT for 36 h. The reaction was quenched by the slow addition of saturated aqueous $NaHCO_3$ solution (20 mL) (CAUTION: CO_2 evolution) and Et_2O (20 mL). The aqueous phase was extracted with EtOAc (4×20 mL) and the combined organic phases were dried, filtered, and concentrated. The residue was purified by flash chromatography (SiO_2, 3.5×10 cm, 20% EtOAc/hexanes) to give **15** [0.294 g, 0.92 mmol, 92%, $R_f=0.3$ (20% EtOAc/hexanes), colorless oil]. ^1H NMR (250 MHz, $CDCl_3$): $\delta=7.03$ (d, $J=3.1$ Hz, 1H; H-24), 6.02 (d, $J=3.1$ Hz, 1H; H-23), 4.30 (q, $J=7.1$ Hz, 2H; -OCH_2CH$_3$), 4.05 (s, 1H; H-8), 2.79 (m, 1H; H-20), 1.32 (t, $J=$ 7.1 Hz, 3H; CH_3CH$_2$O-), 1.24 (d, $J=7$ Hz, 3H; H-21), 0.98 ppm (s, 3H; H-18); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta=166.2$ (C; COOEt), 158.9 (C; C-22), 142.5 (C; C-25), 118.8 (CH; C-24), 106.1 (CH; C-23), 69.0 (CH; C-8), 60.5 (CH_2; -OCH_2CH$_3$), 55.0 (CH; C-17), 52.4 (CH; C-14), 41.9 (C; C-13), 40.1 (CH_2; C-12), 36.2 (CH; C-20), 33.5 (CH_2; C-9), 27.1 (CH_2; C-15), 22.3 (CH_2; C-16), 19.4 (CH_3; C-21), 17.4 (CH_2; C-11), 14.3 (CH_3; CH_3CH$_2$O-), 13.4 ppm (CH_3; C-18); IR (film): $\tilde{\nu}=3529$, 1712 cm^{-1}; HRMS (CI^+): m/z: calcd for $[C_{19}H_{29}O_4]^+$: 321.2069 $[M+H]^+$; found 321.2066.

(20*S*)-De-A,B-[(5-ethyloxycarbonyl)furan-2-yl]-8-pregnanone (16): Dess–Martin periodinane (0.528 g, 1.24 mmol, 1.5 equiv) was added to a solution of **15** (0.266 g, 0.83 mmol, 1 equiv) in dry CH_2Cl_2 (12 mL) and the mixture was stirred at RT for 3.5 h. The reaction was then quenched with saturated aqueous NaCl solution (20 mL), and the resulting mixture was stirred for 30 min. The aqueous phase was extracted with Et_2O (3× 20 mL) and the combined organic phases were dried, filtered, and concentrated. The residue was purified by flash chromatography (SiO_2, 2× 8 cm, 10% EtOAc/hexanes) to afford **16** [0.245 g, 0.77 mmol, 93%, R_f= 0.47 (10% EtOAc/hexanes), colorless oil]. ^{1}H NMR (250 MHz, $CDCl_3$): δ=7.03 (d, J=3.3 Hz, 1H; H-24), 6.05 (d, J=3.3 Hz, 1H; H-23), 4.31 (q, J=7.1 Hz, 2H; -OCH_2CH$_3$), 2.81 (dq, J=10.5, 6.9 Hz, 1H; H-20), 2.47 (dd, J=11.5, 7.2 Hz, 1H; H-14), 1.34 (t, J=7.1 Hz, 3H, CH_3CH$_2$O-), 1.24 (d, J=7.2 Hz, 3H; H-21), 0.63 ppm (s, 3H; H-18); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=211.3 (C; C-8), 165.2 (C; COOEt), 158.8 (C; C-22), 142.7 (C; C-25), 118.7 (CH; C-24), 106.4 (CH; C-23), 61.6 (CH; C-14), 60.6 (CH_2; -OCH_2CH$_3$), 55.0 (CH; C-17), 49.6 (C; C-13), 40.8 (CH_2; C-12), 38.6 (CH_2; C-9), 36.3 (CH_2; C-20), 27.3 (CH_2; C-15), 23.9 (CH_2; C-16), 19.5 (CH_3; C-21), 18.9 (CH_2; C-11), 14.3 (CH_3; CH_3CH$_2$O-), 12.4 ppm (CH_3; C-18); IR (film): $\tilde{\nu}$=2961, 1714 cm^{-1}; HRMS (CI$^+$): m/z: calcd for $[C_{19}H_{26}O_4]^+$: 319.1909 $[M+H]^+$; found 319.1907.

(20*S*),(8*E*)-Bromomethylene-de-A,B-[(5-ethyloxycarbonyl)furan-2-yl]-pregnane (17): A suspension of (Ph_3PCH_2Br)Br (2.023 g, 4.640 mmol, 8 equiv) in dry toluene (15 mL) was sonicated for 30 min and then cooled to −15°C. KO*t*Bu (0.454 g, 4.060 mmol, 7 equiv) was added and the mixture was stirred for 2 h. A solution of ketone **16** (0.185 g, 0.58 mmol, 1 equiv) in toluene (15 mL) was then added, and the resulting mixture was allowed to warm slowly to 0°C. The reaction was quenched with saturated aqueous NH_4Cl solution (1 mL), and the mixture was filtered through a layer of silica gel. The silica was washed with Et_2O (3×20 mL) and the resulting filtrate was concentrated. The residue was purified by flash chromatography (SiO_2, 2×12 cm, 1% EtOAc/hexanes) to afford **17** [0.172 g, 0.435 mmol, 75%, R_f=0.58 (10% EtOAc/hexanes), yellow oil]. ^{1}H NMR (250 MHz, $CDCl_3$): δ=7.04 (d, J=3.3 Hz, 1H; H-24), 6.04 (d, J=3.3 Hz, 1H; H-23), 5.62 (s, 1H; H-7), 4.31 (q, J=7.1 Hz, 2H; -OCH_2CH$_3$), 2.86 (m, 1H; H-9), 2.81 (dq, J=10.7, 7.1 Hz, 1H; H-20), 1.83 (q, J=9.4 Hz, 1H; H-17), 1.33 (t, J=7.1 Hz, 3H; CH_3CH$_2$O-), 1.28 (d, J=6.9 Hz, 3H; H-21), 0.60 ppm (s, 3H; H-18); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=165.9 (C; COOEt), 159.0 (C; C-22), 144.7 (C; C-8), 142.7 (C; C-25), 118.8 (CH; C-24), 106.4 (CH; C-23), 97.8 (CH; C-7), 60.6 (CH_2; -OCH_2CH$_3$), 55.7 (CH; C-14), 54.3 (CH; C-17), 45.5 (C; C-13), 40.0 (CH_2; C-12), 36.8 (CH_2; C-20), 31.0 (CH_2; C-9), 27.4 (CH_2; C-11), 22.5 (CH_2; C-16), 22.0 (CH_2; C-15), 19.7 (CH_3; C-21), 14.4 (CH_3; CH_3CH$_2$O-), 11.9 ppm (CH_3; C-18); IR (film): $\tilde{\nu}$=2947, 1726 cm^{-1}; HRMS (CI$^+$): m/z: calcd for $[C_{20}H_{28}O_3Br]^+$: 398.1235 $[M+H]^+$; found 398.1221.

(20*S*)-De-A,B-[(5-ethyloxycarbonyl)furan-2-yl]-(8*E*)-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methylene]pregnane (6a): Cy_3P (5.2 mg, 0.0186 mmol, 0.06 equiv) and $[PdCl_2(dppf)_2]\cdot CH_2Cl_2$ (7.7 mg, 0.0094 mmol, 0.03 equiv) were dissolved in dry DMSO (3 mL) and the mixture was stirred for 20 min. A solution of **17** (0.120 g, 0.31 mmol, 1 equiv) in DMSO (2 mL) was then added via a cannula. KOAc (0.091 g, 0.930 mmol, 3 equiv) and Pin_2B_2 (0.157 g, 0.62 mmol, 2 equiv) were then successively added. The reaction mixture was heated at 80°C for 2.5 h, then cooled to RT, and the reaction was quenched by the addition of H_2O (10 mL) and Et_2O (10 mL). The aqueous phase was extracted with Et_2O (3×30 mL) and the combined organic phases were dried, filtered, and concentrated. The residue was purified by flash chromatography (SiO_2, 2×7 cm, 2–5% EtOAc/hexanes) to give **6a** [0.103 g, 0.233 mmol, 75%, R_f=0.42 (10% EtOAc/hexanes), yellow oil]. ^{1}H NMR (250 MHz, $CDCl_3$): δ=7.04 (d, J=3.4 Hz, 1H; H-24), 6.04 (d, J=3.4 Hz, 1H; H-23), 4.89 (s, 1H; H-7), 4.32 (q, J=7.1 Hz, 2H; -OCH_2CH$_3$), 3.18 (dd, J=13.2, 2.9 Hz; H-9), 2.82 (dq, J=10.5, 6.9 Hz, 1H; H-20), 1.34 (t, J=7.1 Hz, 3H; CH_3CH$_2$O-), 1.29 (d, J=6.9 Hz, 3H; H-21), 1.25 (s, 12H; CH_3-pinacol), 0.60 ppm (s, 3H; H-18); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=166.1 (C; COOEt), 165.4 (C; C-8), 158.9 (C; C-22), 142.5 (C; C-25), 118.8 (CH; C-24), 106.2 (CH; C-23), 82.5 (C; COB), 60.5 (CH_2; -OCH_2CH$_3$), 57.7 (CH; C-14), 55.2 (CH; C-17), 46.2 (C; C-13), 40.2 (CH_2; C-12), 36.9 (CH_2; C-20), 33.1 (CH_2; C-9), 27.3 (CH_2; C-16), 24.8 (2×CH_3; CH_3-pinacol), 24.7 (2×CH_3; CH_3-pinacol), 24.2 (CH_2; C-11), 22.1 (CH_2; C-15), 19.6 (CH_3; C-21), 14.4 (CH_3; CH_3CH$_2$O-), 12.0 ppm (CH_3; C-18); IR (film): $\tilde{\nu}$=2975, 1727 cm^{-1}; HRMS (CI$^+$): m/z: calcd for $[C_{26}H_{40}O_5B]^+$: 443.2969 $[M+H]^+$; found 443.2954.

(20*S*)-[(5-Ethyloxycarbonyl)furan-2-yl]-22,23,24,25,26,27-hexanor-1α-hydroxy-vitamin D$_3$ (5a): Aqueous K_3PO_4 (1.5 mL, 2 M) was added to a solution of **6a** (0.060 g, 0.135 mmol, 1 equiv) and **7** (0.077 g, 0.149 mmol, 1.1 equiv) in THF (3 mL). $[PdCl_2(Ph_3P)_2]$ (4.7 mg, 0.0068 mmol, 0.05 equiv) was added and the reaction mixture was stirred vigorously for 1 h in the dark. The reaction was then quenched by the addition of H_2O (10 mL) and Et_2O (10 mL). The aqueous phase was extracted with Et_2O (3×10 mL), and the combined organic phases were dried, filtered, and concentrated. The residue was redissolved in CH_3CN (3 mL), and then HF (48%, 5 drops) was added by means of a syringe. After stirring the solution for 20 min, the reaction was quenched with saturated aqueous $NaHCO_3$ solution (10 mL) and EtOAc (10 mL). The aqueous phase was extracted with EtOAc (5×15 mL), and the combined organic phases were dried, filtered, and concentrated. The residue was purified by flash chromatography (SiO_2, 2.5×10 cm, 60% EtOAc/hexanes) to give **5a** [0.052 g, 0.114 mmol, 85%, R_f=0.3 (60% EtOAc/hexanes), white foam]. ^{1}H NMR (500 MHz, CD_2Cl_2): δ=7.05 (d, J=3.4 Hz, 1H; H-24), 6.36 (d, J=11.2 Hz, 1H; H-6), 6.05 (d, J=3.4 Hz, 1H; H-23), 6.00 (d, J=11.2 Hz, 1H; H-7), 5.30 (s, 1H; H-19), 4.97 (s, 1H; H-19), 4.41 (m, 1H; H-1), 4.32 (q, J=7.1 Hz, 2H; -OCH_2CH$_3$), 4.21 (m, 1H; H-3), 1.35 (t, J=7.1 Hz, 3H; CH_3CH$_2$O), 1.28 (d, J=7 Hz, 3H; H-21), 0.59 ppm (s, 3H; H-18); ^{13}C NMR (126 MHz, CD_2Cl_2): δ=166.2 (CO; C-26), 158.9 (C; C-22), 147.5 (C; C-10), 142.4 (C; C-25), 142.2 (C; C-8), 133.4 (C; C-5), 124.5 (CH; C-6), 118.8 (CH; C-24), 117.3 (CH; C-7), 111.7 (CH_2; C-19), 106.2 (CH; C-23), 70.7 (CH; C-1), 66.6 (CH; C-3), 60.5 (CH_2; OCH_2CH$_3$), 56.0 (CH; C-17), 54.7 (CH; C-14), 45.7 (C; C-13), 45.0 (CH_2; C-4), 42.7 (CH_2; C-2), 40.1 (CH_2; C-12), 38.9 (CH; C-20), 29.0 (CH_2; C-9), 27.3 (CH_2; C-16), 23.3 (CH_2; C-11), 22.1 (CH_2; C-15), 19.7 (CH_3; C-21), 14.3 (CH_3; CH_3CH$_2$O), 11.9 ppm (CH_3; C-18); IR ($CHCl_3$): $\tilde{\nu}$=3412, 2933, 1712 cm^{-1}; HRMS (ESI-TOF): m/z: calcd for $[C_{28}H_{38}O_5Na]^+$: 477.2611 $[M+Na]^+$; found 477.2604.

(20*S*)-[5-(2-Hydroxypropan-2-yl)furan-2-yl]-22,23,24,25,26,27-hexanor-1α-hydroxy-vitamin D$_3$ (3a): A solution of MeLi in Et_2O (1.15 mL, 1.6 M, 1.85 mmol, 5 equiv) was added by means of a syringe to a solution of **5a** (0.168 g, 0.37 mmol, 1 equiv) in dry THF (20 mL) at −78°C. The resulting solution was stirred at −78°C for 6 h and then allowed to warm to RT overnight. The reaction was quenched by the slow addition of saturated aqueous NH_4Cl solution (10 mL) followed by EtOAc (10 mL). The aqueous phase was extracted with EtOAc (5×15 mL) and the combined organic phases were dried, filtered, and concentrated. The residue was purified by flash chromatography (SiO_2, 2×8 cm, 70% EtOAc/hexanes) to afford **3a** [0.143 g, 0.325 mmol, 88%, R_f=0.15 (60% EtOAc/hexanes), amorphous solid]. M.p. 84–86°C (Et_2O/hexanes); $[\alpha]_D^{25}$=0.88 (c=1.3 in 96% EtOH); ^{1}H NMR (500 MHz, CD_2Cl_2): δ=6.38 (d, J=11.2 Hz, 1H; H-6), 6.04 (d, J=3.1 Hz, 1H; H-24), 6.02 (d, J=11.2 Hz, 1H; H-7), 5.83 (d, J=3 Hz, 1H; H-23), 5.31 (s, 1H; H-19*E*), 4.99 (s, 1H; H-19*Z*), 4.42 (m, 1H; H-1), 4.22 (m, 1H; H-3), 2.72 (dq, J=10.1, 6.9 Hz, 1H; H-20), 1.56 (s, 6H; H-27 and H-28), 1.26 (d, J=6.8 Hz, 3H; H-21), 0.59 ppm (s, 3H; H-18); ^{13}C NMR (CD_2Cl_2, 126 MHz): δ=160.4 (C; C-25), 157.6 (C; C-22), 147.6 (C; C-10), 142.8 (C; C-8), 133.1 (C; C-5), 124.8 (CH; C-6), 117.2 (CH; C-7), 111.8 (CH_2; C-19), 104.0 (CH; C-24), 103.8 (CH; C-23), 70.8 (CH; C-1), 69.9 (COH; C-26), 66.8 (CH; C-3), 56.2 (CH; C-17), 55.6 (CH; C-14), 45.8 (C; C-13), 45.2 (CH_2; C-4), 42.8 (CH_2; C-2), 40.2 (CH_2; C-12), 36.3 (CH; C-20), 29.0 (CH_2; C-9), 28.6 (2×CH_3; C-27 and C-28), 27.4 (CH_2; C-16), 23.5 (CH_2; C-11), 22.2 (CH_2; C-15), 20.0 (CH_3; C-21), 12.0 ppm (CH_3; C-18); IR ($CHCl_3$): $\tilde{\nu}$=3405, 2961 cm^{-1}; UV (96% EtOH): λ_{max} (ε)=220 nm (18500), λ=266 nm (14500 mol^{-1} m^3 cm^{-1}), λ_{min}=250 nm; HRMS (ESI-TOF): m/z: calcd for $[C_{28}H_{40}O_4Na]^+$: 463.2819 $[M+Na]^+$; found 463.2822.

(20*S*)-[5-(3-Hydroxypentan-3-yl)furan-2-yl]-22,23,24,25,26,27-hexanor-1α-hydroxy-vitamin D$_3$ (3b): A solution of EtMgBr in Et_2O (0.22 mL, 3 M, 0.66 mmol, 6 equiv) was added by means of a syringe to a solution of **5a** (0.052 g, 0.11 mmol, 1 equiv) in dry THF (8 mL) at −78°C. The mixture was stirred at −78°C for 15 min and at RT for 3 h. The reaction was then quenched by the slow addition of saturated aqueous NH_4Cl solution

(10 mL) followed by EtOAc (10 mL). The aqueous phase was extracted with EtOAc (5×15 mL) and the combined organic phases were dried, filtered, and concentrated. The residue was purified by flash chromatography (SiO_2, 1.5×6 cm, 70% EtOAc/hexanes) to give **3b** [0.042 g, 0.089 mmol, 82%, R_f=0.2 (60% EtOAc/hexanes), amorphous solid]. M.p. 66–68°C (Et_2O/hexanes); $[\alpha]_D^{25}$=1.06 (c=2.1 in 96% EtOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ=6.36 (d, J=11.2 Hz, 1H; H-6), 6.03 (d, J=3 Hz, 1H; H-24), 6.00 (d, J=11.2 Hz, 1H; H-7), 5.80 (d, J=3 Hz, 1H; H-23), 5.30 (s, 1H; H-19*E*), 4.97 (s, 1H; H-19*Z*), 4.40 (m, 1H; H-1), 4.20 (m, 1H; H-3), 2.69 (dq, J=10.1, 6.8 Hz, 1H; H-20), 1.24 (d, J=6.9 Hz, 3H; H-21), 0.81 (t, J=7.4 Hz, 6H; 2×CH_3CH_2), 0.58 ppm (s, 3H; CH_3-18); ^{13}C NMR (126 MHz, $CDCl_3$): δ=160.1 (C; C-25), 155.9 (C; C-22), 147.6 (C; C-10), 142.7 (C; C-8), 133.2 (C; C-5), 124.7 (CH; C-6), 117.2 (CH; C-7), 111.8 (CH_2; C-19), 105.5 (CH; C-24), 103.7 (CH; C-23), 74.9 (COH; C-26), 70.7 (CH; C-1), 66.7 (CH; C-3), 56.1 (CH; C-17), 55.6 (CH; C-14), 45.7 (C; C-13), 45.1 (CH_2; C-4), 42.8 (CH_2; C-2), 40.2 (CH_2; C-12), 36.3 (CH; C-20), 31.7 (2×CH_2; C-27 and C-29), 29.0 (CH_2; C-9), 27.6 (CH_2; C-16), 23.5 (CH_2; C-11), 22.2 (CH_2; C-15), 20.0 (CH_3; C-21), 12.0 (CH_3; C-18), 7.9 ppm (2×CH_3; -CH_2CH_3); IR ($CHCl_3$): $\tilde{\nu}$=3386, 2925 cm^{-1}; UV (96% EtOH): λ_{max} (ε)=218 nm (18900), λ=266 nm (14600 mol^{-1} m^3 cm^{-1}), λ_{min}=245 nm; HRMS (ESI-TOF): m/z: calcd for $[C_{30}H_{43}O_3]^+$: 451.3194 $[M-OH]^+$; found 451.3207.

8β-[(*tert*-Butyldimethylsilyl)oxy]-de-A,B-22,23-epoxy-24-norcolane (23): A solution of MeLi in Et_2O (1.92 mL, 1.6 M, 3.08 mmol, 2 equiv) was added dropwise over 30 min to a solution of **8** (0.500 g, 1.54 mmol, 1 equiv) and $ClCH_2I$ (0.223 mL, 3.08 mmol, 2 equiv) in dry THF (10 mL) at −78°C. The reaction mixture was stirred at −78°C for 30 min and then at RT for 1.5 h. The reaction was stopped by the addition of Et_2O (10 mL) and brine (10 mL). The aqueous phase was extracted with Et_2O (3×15 mL) and the combined organic phases were dried, filtered, and concentrated. The residue was purified by flash chromatography (SiO_2, 3×10 cm, 5% EtOAc/hexanes) to afford a mixture of diastereoisomers **23**[25] [0.513 g, 1.51 mmol, 98%, R_f=0.78 (2% Et_2O/hexanes, two runs), white foam].

8β-[(*tert*-Butyldimethylsilyl)oxy]-de-A,B-26,27-dinor-25-[2-methyl-(2-triethylsilyloxy)prop-2-yl]-24-cholestin-22-ol (25a): A solution of **24a** was prepared at −78°C by the addition of a solution of *n*BuLi in hexanes (0.82 mL, 2.5 M, 2.05 mmol, 2.5 equiv) to the corresponding alkyne (0.600 g, 2.83 mmol, 3.5 equiv) in dry THF (10 mL) followed by stirring for 40 min. $F_3B{\cdot}OEt_2$ (0.520 mL, 4.10 mmol, 5 equiv) and a solution of **23** (0.280 g, 0.82 mmol, 1 equiv) in THF (5 mL) were then successively added dropwise. The reaction mixture was allowed to warm to RT overnight. The reaction was then quenched by the addition of saturated aqueous NaCl solution (10 mL) and Et_2O (10 mL). The aqueous phase was extracted with Et_2O (4×15 mL), and the combined organic phases were dried, filtered, and concentrated. The residue was purified by flash chromatography (SiO_2, 3×10 cm, 2% EtOAc/hexanes) to give a mixture of alcohols **25a** [0.441 g, 0.80 mmol, 98%, R_f=0.39 (10% EtOAc/hexanes), oil]. ^{1}H NMR (250 MHz, $CDCl_3$): δ=4.00 (s, 1H; H-8), 3.84 (t, J=6.8 Hz, 1H; H-22), 2.41 (dd, J=16.2, 7.9 Hz, 1H; H-23), 2.31 (s, 2H; H-26), 2.23 (dd, J=16.2, 5.9 Hz, 1H; H-23), 1.29 (s, 6H; H-28 and H-29), 0.94 (t, J=7.9 Hz, 9H; CH_3CH_2Si), 0.91 (s, 3H; H-18), 0.89–0.87 (m, 12H; Me_3CSi and H-21), 0.57 (q, J=7.9 Hz, 6H; CH_3CH_2Si), 0.01 (s, 3H; MeSi), 0.00 ppm (s, 3H; MeSi); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=80.2 (C; C-25), 78.6 (C; C-24), 73.1 (COH; C-27), 72.0 (CH; C-22), 69.4 (CH; C-8), 53.2 (CH; C-14), 52.9 (CH; C-17), 42.0 (C; C-13), 40.7 (CH_2; C-12), 38.9 (CH; C-20), 35.4 (CH_2; C-26), 34.4 (CH_2; C-9), 29.4 (2×CH_3; C-28 and C-29), 26.7 (CH_2; C-16), 25.8 (3×CH_3; Me_3CSi and CH_2; C-23), 22.9 (CH_2; C-15), 18.0 (C; C-Si), 17.7 (CH_2; C-11), 13.6 (CH_3; C-18), 11.3 (CH_3; C-21), 7.0 (2×CH_3; CH_3CH_2Si), 6.6 (2×CH_2; CH_3CH_2Si), −4.8 (CH_3; MeSi), −5.2 ppm (CH_3; MeSi); HRMS (CI$^+$): m/z: calcd for $[C_{34}H_{67}O_3Si_2]^+$: 579.4629 $[M+H]^+$; found 579.4634.

8β-[(*tert*-Butyldimethylsilyl)oxy]-de-A,B-26,27-dinor-25-[2-methyl-(2-triethylsilyloxy)-prop-2-yl]-24-cholestin-22-one (26a): Dess–Martin periodinane (0.284 g, 0.66 mmol, 1.3 equiv) was added to a solution of **25a** (0.280 g, 0.509 mmol, 1 equiv) in dry CH_2Cl_2 (15 mL) and the reaction mixture was stirred at RT for 1.5 h. The reaction was then quenched by the addition of saturated aqueous NaCl solution (15 mL). The aqueous phase was extracted with TBME (4×15 mL) and the combined organic phases were dried, filtered, and concentrated. The residue was purified by flash chromatography (SiO_2, 2.5×8 cm, 2% EtOAc/hexanes) to give **26a** [0.270 g, 0.492 mmol, 97%, R_f=0.43 (30% EtOAc/hexanes), pale-yellow oil], slightly contaminated with its allenic ketone. ^{1}H NMR (250 MHz, $CDCl_3$): δ=4.00 (m, 1H; H-8), 3.24 (t, J=2.2 Hz, 1H; H-23), 2.85 (dq, J=10.7, 6.8 Hz, 1H; H-20), 2.35 (t, J=2.2 Hz, 2H; H-26), 1.31 (s, 6H; H-28 and H-29), 1.10 (d, J=6.8 Hz, 3H; H-21), 0.97–0.91 (m, J=7.9 Hz, 12H; CH_3CH_2Si and H-18), 0.88 (s, 9H; Me_3Si), 0.61–0.54 (m, 6H; CH_3CH_2Si), 0.00 (s, 3H; MeSi), −0.02 ppm (s, 3H; MeSi); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=208.8 (CO; C-22), 82.5 (C; C-25), 74.0 (C; C-24), 73.1 (COH; C-27), 69.2 (CH; C-8), 52.6 (CH; C-14), 52.4 (CH; C-17), 46.9 (CH; C-20), 42.2 (C; C-13), 40.5 (CH_2; C-12), 35.5 (CH_2; C-26), 34.3 (CH_2; C-9), 33.8 (CH_2; C-23), 29.4 (2×CH_3; C-28 and C-29), 26.6 (CH_2; C-16), 25.8 (3×CH_3; Me_3CSi), 23.2 (CH_2; C-15), 18.0 (C; C-Si), 17.6 (CH_2; C-11), 16.6 (CH_3; C-21), 14.0 (CH_3; C-18), 7.0 (2×CH_3; CH_3CH_2Si), 6.6 (2×CH_2; CH_3CH_2Si), −4.8 (CH_3; MeSi), −5.2 ppm (CH_3; MeSi); HRMS (CI$^+$): m/z: calcd for $[C_{36}H_{70}O_3Si_2]^+$: 564.4394 $[M+H]^+$; found 564.4387.

(20*S*)-De-A,B-[5-(2-hydroxy-2-methylpropan-1-yl)furan-2-yl]-8β-pregnanol (27a): $AuCl_3$ (4.4 mg, 0.014 mmol, 0.03 equiv) was added to a solution of **26a** (0.265 g, 0.48 mmol, 1 equiv) in dry THF (10 mL) and the reaction mixture was stirred at RT for 15 min. Saturated aqueous NaCl solution (10 mL) and TBME (10 mL) were then successively added, and the aqueous phase was extracted with TBME (4×10 mL). The combined organic phases were dried, filtered, and concentrated. The residue was redissolved in THF (15 mL), and then TBAF (1.5 mL, 1 M, 1.5 mmol, 3 equiv) was added. The reaction mixture was heated at 50°C for 4 days. Saturated NH_4Cl (15 mL) and EtOAc (15 mL) were then successively added, and the aqueous phase was extracted with EtOAc (3×15 mL). The combined organic phases were dried, filtered, and concentrated. The residue was purified by flash chromatography (SiO_2, 2.5×8 cm, 20% EtOAc/hexanes) to give **27a** [0.140 g, 0.44 mmol, 91%, R_f=0.4 (40% EtOAc/hexanes), white amorphous solid]. M.p. 69–71°C (CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ=5.96 (d, J=2.9 Hz, 1H; H-24), 5.82 (d, J=2.9 Hz, 1H; H-23), 4.06 (m, 1H; H-8), 2.73 (s, 2H; H-26), 2.67 (dq, J=10.5, 7.1 Hz, 1H; H-20), 1.22 (s, 9H; H-21, H-28 and H-29), 0.99 ppm (s, 3H; H-18); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=160.4 (C; C-25), 150 (C; C-22), 107.9 (C; C-24), 103.9 (CH; C-23), 70.4 (COH; C-27), 69.9 (CH; C-8), 55.5 (CH; C-14), 52.4 (CH; C-17), 42.0 (CH_2; C-26), 41.6 (C; C-13), 40.1 (CH_2; C-12), 35.7 (CH; C-20), 33.4 (CH_2; C-9), 28.8 (2×CH_3; C-28 and C-29), 27.3 (CH_2; C-16), 22.3 (CH_2; C-15), 19.6 (CH_3; C-21), 17.3 (CH_2; C-11), 13.4 ppm (CH_3; C-18); IR (film): $\tilde{\nu}$=3377, 2935 cm^{-1}; elemental analysis calcd (%) for $C_{20}H_{32}O_3$: C 74.96, H 10.06; found: C 74.90, H 10.35.

(20*S*)-De-A,B-[5-(2-hydroxy-2-methylpropan-1-yl)furan-2-yl]-8b-pregnone (28a): Procedure as for **16. 28a** [91%, R_f=0.4 (40% EtOAc/hexanes), colorless oil]. ^{1}H NMR (250 MHz, $CDCl_3$): δ=5.96 (s, 1H; H-24), 5.84 (s, 1H; H-23), 2.73 (s, 2H; H-26), 2.69 (m, 1H; H-20), 2.48 (dd, J=11.5, 7 Hz; 1H, H-14), 1.27 (d, J=6.3 Hz, 3H; H-21), 1.21 (s, 6H; H-28 and H-29), 0.68 ppm (s, 3H; H-18); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=211.7 (C=O; C-8), 159.6 (C; C-25), 150.3 (C; C-22), 108.1 (C; C-24), 104.4 (CH; C-23), 70.4 (COH; C-27), 61.8 (CH; C-14), 55.5 (CH; C-17), 49.6 (C; C-13), 42.1 (CH_2; C-26), 40.8 (CH_2; C-12), 36.7 (CH_2; C-9), 35.8 (CH; C-20), 28.9 (2×CH_3, C-28 and C-29), 27.5 (CH_2; C-16), 24.0 (CH_2; C-15), 19.8 (CH_3; C-21), 18.9 (CH_2; C-11), 12.4 ppm (CH_3; C-18). IR (film): $\tilde{\nu}$=3468, 2935, 1712 cm^{-1}; HRMS (CI$^+$): m/z: calcd for $[C_{20}H_{30}O_2]^+$: 302.2246 $[M-H_2O]^+$; found 302.2252.

(20*S*),(8*E*)-Bromomethylene-de-A,B-[5-(2-hydroxy-2-methylpropan-1-yl)-furan-2-yl]pregnane (29a): Procedure as for **17. 29a** [0.164 g, 0.417 mmol, 72%, R_f=0.4 (20% EtOAc/hexanes), yellow oil]. ^{1}H NMR (250 MHz, $CDCl_3$): δ=5.97 (d, J=2.9 Hz, 1H; H-24), 5.84 (d, J=2.9 Hz, 1H; H-23), 5.64 (s, 1H; H-7), 2.74 (s, 2H; H-26), 2.69 (m, 1H; H-20), 1.25 (d, J=6.9 Hz, 3H; H-21), 1.22 (s, 6H; H-28 and H-29), 0.61 ppm (s, 3H; H-18); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=160.2 (C; C-25), 150.2 (C; C-22), 144.8 (C; C-8), 108.1 (C; C-24), 104.2 (CH; C-23), 97.6 (CH; C-7), 70.5 (COH; C-27), 55.7 (CH; C-14), 54.7 (CH; C-17), 45.3 (C; C-13), 42.1 (CH_2; C-26), 39.6 (CH_2; C-12), 36.3 (CH; C-20), 31.0 (CH_2; C-9), 29.0 (2×CH_3; C-

28 and C-29), 27.6 (CH_2; C-15), 22.5 (CH_2; C-16), 21.9 (CH_2; C-11), 20.0 (CH_3; C-21), 11.8 ppm (CH_3; C-18); IR (film): $\tilde{\nu}$ = 3418, 2965 cm^{-1}; HRMS (CI^+): *m/z*: calcd for $[C_{21}H_{31}O_2Br]^+$: 396.1487 $[M+H]^+$; found 396.1485.

(20*S*),(8*E*)-De-A,B-[5-(2-hydroxy-2-methylpropan-1-yl)furan-2-yl]-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methylene]pregnane (30a): Procedure as for **6a. 30a** [87%, R_f = 0.34 (20% EtOAc/hexanes), oil]. ^1H NMR (250 MHz, $CDCl_3$): δ = 5.96 (d, *J* = 2.9 Hz, 1H; H-24), 5.83 (d, *J* = 2.9 Hz, 1H; H-23), 4.90 (s, 1H; H-7), 3.18 (dd, *J* = 13.3, 3 Hz; 1H, H-9), 2.73 (s, 2H; H-26), 2.67 (dq, *J* = 10.5, 7 Hz, 1H; H-20), 1.26–1.21 (m, 21H; H-21, H-28, H-29, and 4×Me-pinacol), 0.59 ppm (s, 3H; H-18); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 165.7 (C; C-8), 160.5 (C; C-25), 150.0 (C; C-22), 108.0 (C; C-24), 104.1 (CH; C-23), 82.5 (CO; pinacol), 70.4 (COH; C-27), 57.8 (CH; C-14), 55.7 (CH; C-17), 46.0 (C; C-13), 42.1 (CH_2; C-26), 40.2 (CH_2; C-12), 36.4 (CH; C-20), 33.1 (CH_2; C-9), 28.9 (2×CH_3; C-28 and C-29), 27.4 (CH_2; C-16), 24.9 (2×CH_3; Me-pinacol), 24.8 (2×CH_3; Me-pinacol), 24.2 (CH_2; C-15), 22.1 (CH_2; C-11), 20.0 (CH_3; C-21), 12.0 ppm (CH_3; C-18); IR (film): $\tilde{\nu}$ = 3459, 2974 cm^{-1}; HRMS (CI^+): *m/z*: calcd for $[C_{27}H_{44}O_4B]^+$: 443.3333 $[M+H]^+$; found 443.3337.

(20*S*)-[5-(2-Hydroxy-2-methylpropan-1-yl)furan-2-yl]-22,23,24,25,26,27-hexanor-1α-hydroxy-vitamin D_3 (4a): Procedure as for **3a. 4a** [76%, R_f = 0.11 (50% EtOAc/hexanes), amorphous white solid]; m.p. 77–79 °C (Et_2O/hexanes); $[\alpha]_D^{25}$ = 1.2 (*c* = 2.9 in 96% EtOH; ^1H NMR (500 MHz, $CDCl_3$): δ = 6.36 (d, *J* = 11.2 Hz, 1H; H-6), 6.00 (d, *J* = 11.2 Hz, 1H; H-7), 5.96 (d, *J* = 2.9 Hz, 1H; H-24), 5.83 (d, *J* = 2.9 Hz, 1H; H-23), 5.30 (s, 1H; H-19*E*), 4.97 (s, 1H; H-19*Z*), 4.40 (m, 1H; H-1), 4.21 (m, 1H; H-3), 2.83 (dd, *J* = 12.3, 3.4 Hz, 1H; H-9), 2.73 (s, 2H; H-26), 2.68 (m, 1H; H-20), 2.58 (dd, *J* = 13.3, 2.5 Hz, 1H; H-4), 2.30 (dd, *J* = 13.3, 6.5 Hz, 1H; H-4), 1.24 (d, *J* = 6.9 Hz, 3H; H-21), 1.21 (s, 6H; H-28 and H-29), 0.59 ppm (s, 3H; CH_3-18); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 160.4 (C; C-25), 150.1 (C; C-22), 147.6 (C; C-10), 142.6 (C; C-8), 133.2 (C; C-5), 124.7 (CH; C-6), 117.2 (CH; C-7), 111.8 (CH_2; C-19), 108.1 (CH; C-24), 104.1 (CH; C-23), 70.7 (CH; C-1), 70.5 (COH; C-27), 66.7 (CH; C-3), 56.2 (CH; C-17), 55.4 (CH; C-14), 45.7 (C; C-13), 45.2 (CH_2; C-4), 42.8 (CH_2; C-2), 42.1 (C; C-26), 40.2 (CH_2; C-12), 36.4 (CH; C-20), 28.9 (CH_2; C-9), 28.8 (2×CH_3; C-28 and C-29), 27.6 (CH_2; C-16), 23.5 (CH_2; C-11), 22.1 (CH_2; C-15), 20.0 (CH_3; C-21), 12.0 ppm (CH_3; C-18); IR ($CHCl_3$): $\tilde{\nu}$ = 3346, 2954 cm^{-1}; UV (96% EtOH): λ_{max} (ε) = 218 nm (18900), λ = 266 nm (15000 $mol^{-1}m^3cm^{-1}$), λ_{min} = 246 nm; HRMS (ESI-TOF): *m/z*: calcd for $[C_{29}H_{43}O_4]^+$: 455.3156 $[M]^+$; found 455.3155.

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