A Practical Synthesis of 14-*epi*-19-*nor*-1α,25-Dihydroxyvitamin D_3 Analogues and Their A-ring Epimers

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A practical synthesis of (2*S*,3a*S*,4a*S*)-2-*tert*-butyldimethylsilyloxybicyclo[3.1.0]hexane-3a-carbaldehyde (**14a**) and diastereoisomers, starting from *all-cis* methyl 3,5-dihydroxy-1-cyclohexanecarboxylate (**24**) is described. Coupling with appropriate *cis*-hydrindanes produces the title compounds. TX 522, a member of this series, is currently in phase II clinical studies for the treatment of psoriasis. The key step involves the coupling of **14** and **16** with the respective *cis*-hydrindanes **9** and **7**.

Introduction

It is now well established that the hormonally active form of vitamin D_3, 1α,25-dihydroxyvitamin D_3 [**1a**; 1α,25$(OH)_2D_3$] may generate biological responses by regulation of gene transcription.[1] The discovery of the presence of specific vitamin D receptors in over 30 tissue types has stimulated investigation into the possible functions of 1α,25$(OH)_2D_3$ (**1a**) outside its classical role in bone calcium homeostasis. The hormone was found to be capable of regulating cell proliferation and differentiation of a variety of immunological and malignant cells. The major drawback regarding its use is the high toxicity associated with the calcemic effect, which prevents the application of pharmaceutical doses. Current research is therefore aimed not only at the synthesis of analogues with superagonistic potency but, in particular, at the decoupling of the effects on cell differentiation from calcemic effects.[1,2] A large number of analogues incorporating modifications in the A-ring, in the CD-ring fragment and, especially, in the side chain have been synthesized and tested biologically.[1] Some years ago, we embarked on an extensive study of the structure-function relationship, focussing on the least studied part of the module: the central CD-ring region.[3,4]

Among other modifications, we observed that 14-epimers such as **2** (KS 532) and **3** (TX 522) induce interesting physiological activities; they are also among the best analogues known in that they show smaller hypercalcemic effects than **1a**.[3,5] TX 522 is currently in phase II clinical trials for the treatment of psoriasis. Because of the *cis*-fused nature of the central hydrindane, these analogues must be of the 19-*nor* type (Figure 1). Indeed, unlike in the natural series (such as **1a**),[6] the vitamin D-previtamin D equilibrium induced by the 1,7-sigmatropic rearrangement is, in this case, largely shifted towards the previtamin form (**4**:**5**, for example; ratio circa 5:95).[7,8] It is noteworthy that the removal of the 19-exomethylene function is in itself beneficial; 19-*nor*-1α,25-dihydroxyvitamin D_3 (**1b**) shows a smaller calcemic effect (v = 10% of **1a**) while retaining good cell-differentiating properties.[9,10]

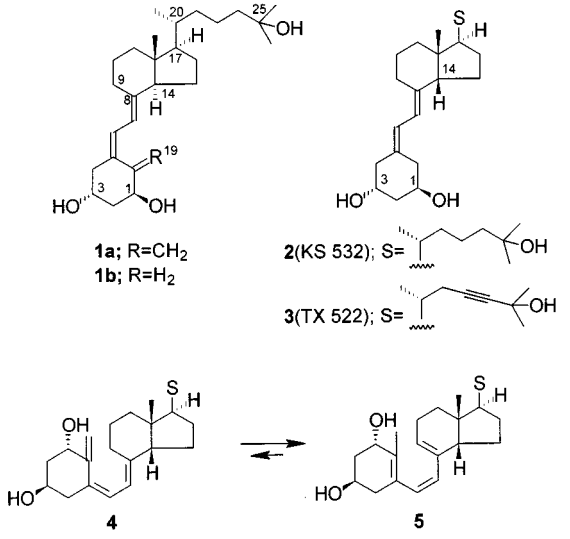

Figure 1

We now wish to report a practical approach applicable to the large-scale production of 14-*epi*-19-*nor* vitamin D_3 analogues, illustrated by the synthesis of **2** and **3** and their 1- and 3-*epi* analogues. The convergent construction of the vitamin D skeleton is based on the cyclovitamin strategy (Scheme 1).[11]

This concept is an alternative to the more widely used Lythoe coupling process[12] involving a Horner–Wittig olefination between the 8-C ketones **6** or **7** (vitamin D numbering) and a phosphane oxide such as **11** and **12**. The

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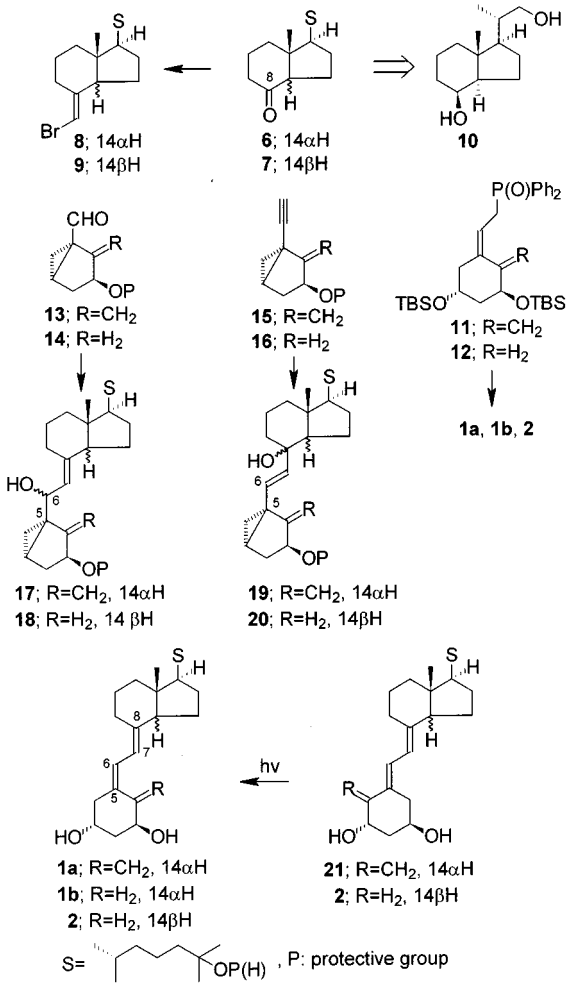


Scheme 1

cyclovitamin approach is based on reaction of **6** (**7**) or **8** (**9**) with **15** (**16**) or **13** (**14**), respectively, and was developed by Kametani et al.,[13] Wilson et al.,[14] and Uskokovic et al.[15] for the synthesis of **1a**. The cyclopropyl alcohol **17** and its vinylogue **19** are then subjected to an acid-catalyzed stereoselective solvolysis, which gives **1a** with the desired 3-α and 7,8-*E* configurations. However, because of a rotation about the 5,6 bond in **17** and **19**, or in the corresponding homoallylic cation intermediate, solvolysis results (after water interception) in a mixture of **1a** and its 5,6-*E* isomer **21** in at best a 4:1 ratio, depending on substituents and reaction conditions.[16]

It is evident that this does not apply to the synthesis of 19-*nor* analogues such as **1b**, **2**, or **3**, in which the A-ring has a C_2 axis of symmetry. This marked advantage prompted us to select the cyclovitamin strategy for the synthesis of 19-*nor* analogues. Furthermore, a large-scale synthesis of the A-ring precursors **14** and **16** could, at the outset, be shorter and more efficient than a synthesis of **12**, the precursor in the Lythgoe coupling, for which DeLuca et al.[9] have developed a synthesis starting from (−)-quinic acid (**22**). We have already reported in preliminary form the synthesis of the 19-*nor* vitamin D_3 analogues **1b** and **2** by this cyclovitamin strategy.[17]

Here we report a practical synthesis of the bicyclo[3.1.0]-cyclohexane precursor **14**, applicable to large-scale production. Our previously described syntheses, starting from **22**,[17a] **23**,[17b] or **24** (Figure 2),[17c] showed several drawbacks relating to scaling up or purification.

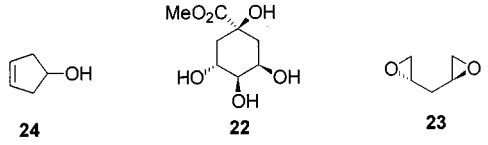
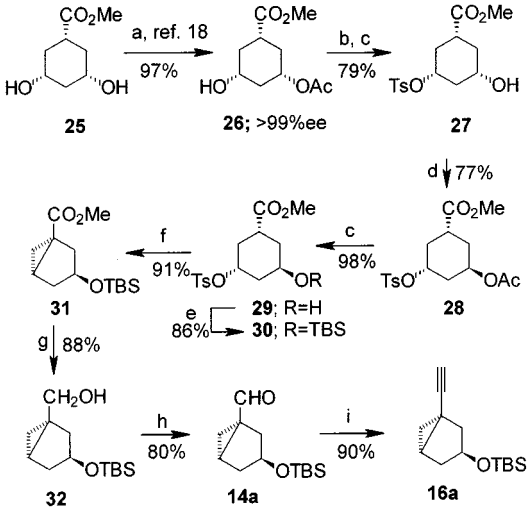


Figure 2

The *cis*-fused 8-C ketones **7** (steroid numbering) can be obtained by base-catalyzed equilibration of **6**.[4] The *trans*-fused isomers **6** are generally produced from the Inhoffen−Lythgoe diol **10**[18] (from ozonolysis of vitamin D_2, Scheme 4).

Results and Discussion

The current synthesis is centered around methyl *all-cis*-3,5-dihydroxy-cyclohexanecarboxylate (**25**)[19,20] as the starting material (Scheme 2). In contrast to (−)-quinic acid (**22**), this possesses only the three essential functions, thus minimizing the number of functional group transformations necessary.



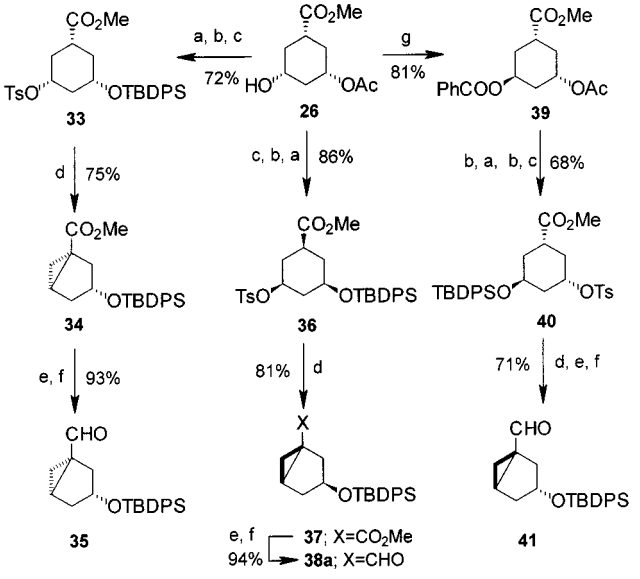
Scheme 2. (a) PPL (*Porcine pancreas lipase*), room temp., 24 h, dark; (b) TsCl, Et_3N, DMAP, 0 °C → room temp., 23 h; (c) K_2CO_3, MeOH, room temp., 0.5 h; (d) AcOH, Ph_3P, DEAD, toluene, 0 °C → room temp., 0.5 h; (e) TBSCl, imidazole, DMF, room temp., 1.5 h; (f) *t*BuOK, *t*BuOH, 60 °C, 1 h; (g) DIBAL-H, toluene, −70 °C, 1.5 h; (h) PCC, CH_2Cl_2, room temp., 1 h; (i) $(MeO)_2$-P(O)CHN_2, *t*BuOK, THF, −78 °C → room temp., 16 h

We have already described the asymmetrization of **25** by a PPL-catalyzed transesterification (PPL: porcine pancreas lipase) with vinyl acetate, which afforded crystalline, enanti-

opure **26** in high yield (Scheme 2).[20] The excellent result of this key step provided an efficient route to **14a**. The tosylation of **26**, followed by acetate methanolysis, gave the alcohol **27**. An inversion under Mitsunobu conditions[21] then afforded **28**. Acetic acid was selected as the nucleophile once we observed that acetate **28** crystallized more easily than other esters such as benzoate.[17a] Another advantage of the presence of the acetate function compared to a benzoate is the fact that methyl acetate can be removed after methanolysis by evaporation, thereby leaving **29** in a state sufficiently pure for hydroxy group protection, giving **30**. Intramolecular alkylation of the ester enolate of **30** gave the bicyclic product **31**. The ester was finally converted into the aldehyde **14a** by a two-step reduction-oxidation procedure, by way of **32**.

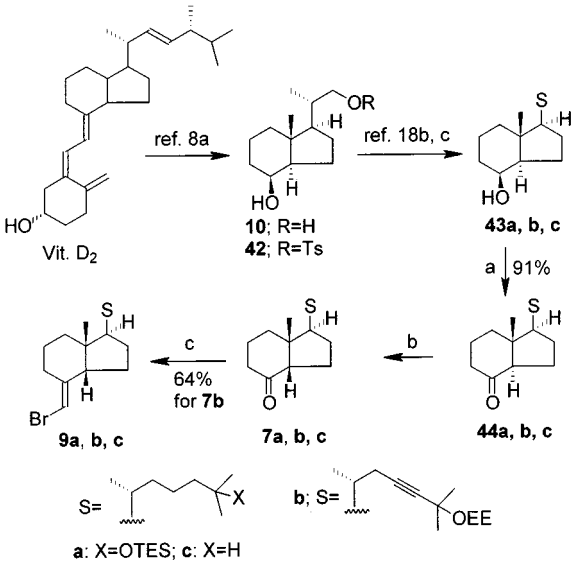
The overall yield of the nine-step sequence, starting from **25** (800 g), is 32%. Only four chromatographic purification steps are needed; intermediates **25**, **26**, **27**, **28**, and **30** are crystalline. Aldehyde **14a** is the 19-*nor*-A-ring precursor, suitable for coupling with vinylic bromide **9**. It can also be smoothly converted into alkyne **16a** by Seyferth's method,[22] using dimethyl diazomethylphosphonate.[23]

An important feature of the key intermediate **26** is the fact that it permits easy access to the stereoisomers of **14** simply by changing the order of the reaction sequence depicted in Scheme 2 and deleting the inversion step for the synthesis of **35** and **38a** (Scheme 3). The inversion of **26** was performed with benzoic acid as the nucleophile in order to allow selective methanolysis of the acetate function in **39**. Both the TBS- and TBDPS-protected series were prepared. Only the TBDPS-protected A-ring analogues are described here as these enabled the structure determination of the 1- and 3-epi analogues of **3** (vide infra).



Scheme 3. (a) TsCl, Et_3N, DMAP (cat.), CH_2Cl_2, room temp.; (b) K_2CO_3, MeOH, room temp.; (c) TBDPSCl, imidazole, DMF, room temp.; (d) *t*BuOK, *t*BuOH/THF, 55−60 °C; (e) DIBAL-H, CH_2Cl_2, −78 → −55 °C; (f) PCC, CH_2Cl_2, room temp., 1 h; (g) $PhCO_2H$, DEAD, Ph_3P, THF

We next undertook the construction of the CD-ring fragments **7** and **9** (Scheme 4). Ozonolysis of vitamin D_2 and subsequent side-chain formation, via the monotosylate **42** of the Lythgoe−Inhoffen diol **10**, producing **43a**, **43b**, and **43c**, is well documented.[18] After oxidation to ketones **44a**, **44b**, and **44c**, a base-catalyzed epimerization to the thermodynamically more stable *cis*-fused hydrindanes resulted in an equilibrium mixture of **44a**, **44b**, and **44c** and **7a**, **7b**, and **7c**, in a ratio of 15:85.

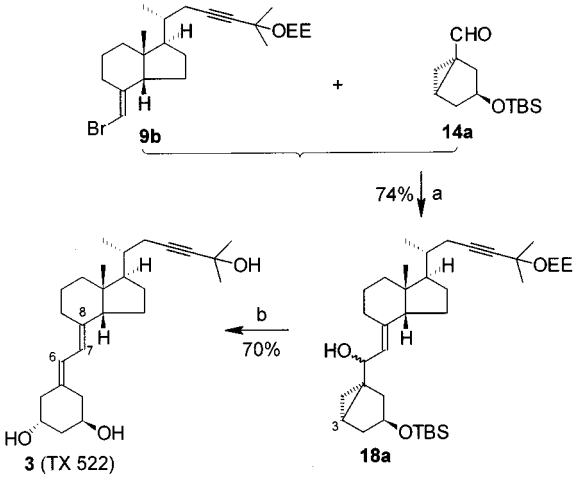


Scheme 4. (a) TPAP, NMO, 4 Å mol. sieves, CH_2Cl_2, room temp.; (b) NaOMe, MeOH, room temp., 24 h; (c) $Ph_3P^+CH_2Br.Br^-$, KHMDS, THF, −78 °C → room temp., 3 h; TES = triethylsilyl, EE = ethoxyethyl

The subsequent formation of a vinylic bromide **8** has been described by Trost et al. for the *trans*-fused ketone **44a**;[24] an *E*/*Z* ratio of 30:1 was found when NaHMDS was used as the base. Under identical conditions, the 14-epimer **7a** gave **9a**, together with the *Z* isomer, in only a 3.5:1 ratio. We found that under more dilute conditions and using the bulkier potassium counterion, a ratio of 40:1 in favor of the *E* isomers **9a**, **9b**, and **9c** could be obtained.

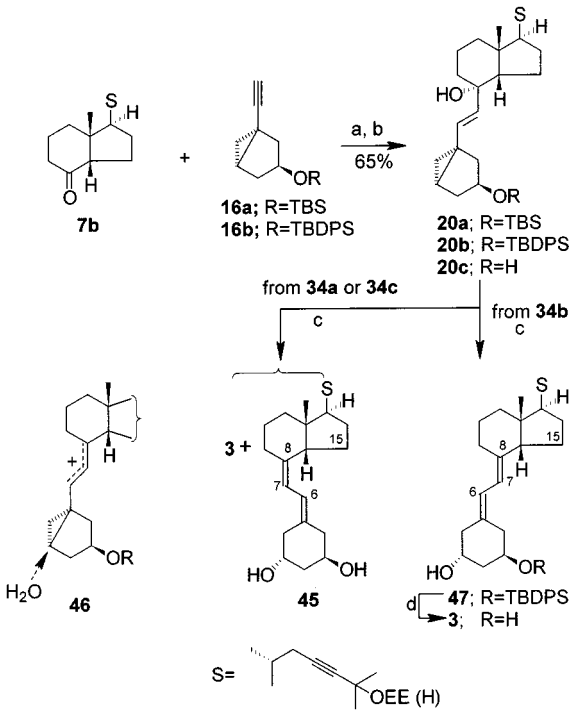
A structure determination was carried out on **9c** as there are no side-chain protons above δ = 2 in its ^1H NMR spectrum, unlike in **9a** and **9b**. The ^1H NMR spectrum of the crude mixture **9c** showed two singlets at δ = 5.87 and 5.05 (ratio 40:1) for the vinylic proton. An NOE enhancement was observed between the major singlet and the signal at δ = 2.21 (dd, *J* = 3.8, 5.2 Hz, 14-H). The assignment of 14-H is straightforward; the two other allylic protons (9-H) are found at δ = 2.50 and δ = 2.10, respectively, and a COSY-2D experiment established their proximity relationship. This proved the desired *E* geometry for the major isomer, later confirmed by the ultimate synthesis of the title compounds. It is noteworthy that while the vinylic protons in the *cis*-fused compounds **9** are downfield (δ = 5.87) of their *Z* isomer counterparts (δ = 5.05), the *trans*-fused vinylic bromide **8** (*E* isomer) vinylic proton is upfield (δ = 5.62) of that of the *Z* isomer (δ = 5.92).[24]

With the "upper" and "lower" fragments in hand, we turned our attention to the construction of the vitamin D skeleton by the two "cyclovitamin" approaches depicted in Scheme 1. The preferred method (100 g scale) consists of coupling the aldehyde **14a** with the vinylic lithium derivative of **9b** (Scheme 5). An acid-catalyzed solvolysis of the resulting **18a** (epimeric ratio, 1:1), involving stereoselective attack of water at 3-C and concomitant hydrolysis of the TBS ether, gave **3** (TX 522). The 7,8-*E* geometry is preserved, in contrast to the solvolysis of **20a** (vide infra, Scheme 6). TX 522 can easily been crystallized, which is not a given for 1α,25-dihydroxyvitamin D_3 analogues. About 2 to 5% of the 7,8-*Z* isomer (vide infra) was found in the mother liquor. The structure of TX 522 was proven by X-ray analysis.[25] Compound **2** (KS 532) was obtained similarly, starting from **9a**.



Scheme 5. (a) *t*BuLi, THF, −70 °C, 1 h; (b) PTSA, dioxane/H_2O (1:1), 40−60 °C, 4 h

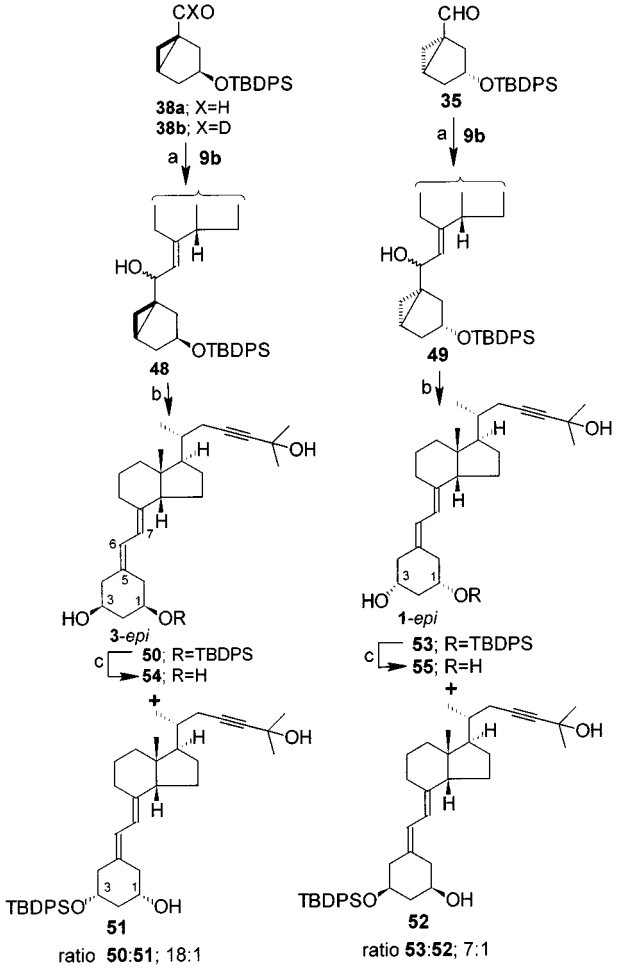
The alternative route, investigated concomitantly, involves treatment of the lithiated alkyne **16a** with ketone **7b** (Scheme 6) to give the propargylic alcohol, which was subsequently reduced to the *E* allylic alcohol **20a**. This reduction had previously[17a] been performed under Corey's conditions,[26] using $LiAlH_4$ in the presence of an excess of NaOMe to avoid allene formation. Under these conditions, however, this side reaction was still observed. We later found that Red-Al is very suitable for this reduction, with no allene being formed.[17b] Surprisingly, the acid-catalyzed solvolysis of **20a** — the vinylogue of the cyclopropyl alcohol **18a** — and concomitant deprotection of **47** gave **3**, together with the 7,8-*Z* isomer **45**, in a 4:6 ratio. This result stands in sharp contrast to that obtained for **18a** (Scheme 5) and to the synthesis of 19-*nor*-1α,25-dihydroxyvitamin D_3 (**1b**), starting from **44a**, in which only the desired *E* isomer was formed.[17a] It appears that the more flexible *cis*-hydrindane in **20a** does not provide steric control (substitution around 14-C) for *E* geometry formation. A solvolysis performed on **20c** (after deprotection of **20a**) also gave the same result. The different outcomes of the solvolyses of **18a** and **20a** seem to demonstrate that the generally accepted mechanism[16] by way of the allylic cation **46** is not valid. It does, however, hold for the *trans*-fused series, in which the synthesis of **1b** by either of the two approaches gives the same result.[17b] It is thus more likely that the discrepancy between the solvolysis of **18a** and that of **20a** is due to the presence of the 7,8 bond rotamer of **20a** with 6-C already turned towards the D-ring. Indeed, as a consequence of an *exo* attack on the *cis*-hydrindanone **7b**, the 8-C substituent in **20a** is most probably β-oriented, which results in low steric hindrance with 15-C.



Scheme 6. (a) *n*BuLi, THF, −50 °C → room temp., 1 h; (b) [$MeOCH_2CH_2O)_2AlH_2$]Na, Et_2O, room temp., 12 h; (c) PTSA, dioxane/H_2O (1:1), 63 °C, 3 h; (d) TBAF, THF, room temp.

A spectacular solution to this problem was found on changing the protective group to a TBDPS ether, which is stable under the solvolysis conditions. The solvolysis of **20b** (obtained from **16b**) indeed afforded the *E* isomer **47** almost exclusively, giving the desired **3** after deprotection. The bulky protective group thus seems to be crucial for inducing the 7,8-*E* geometry in 14-*epi* analogues; GC analysis showed the presence of about 2−5% of the 7,8-*Z* isomer **45**. The reaction conditions for the solvolysis of **18a** and **20b** are rather critical; long reaction times and/or addition of too large quantities of solid PTSA to the solution gave enhanced formation of the 7,8-*Z* isomers and reduced the yield through increased formation of by-products. This was confirmed by the equilibration of **3** with PTSA in $CDCl_3$, which resulted after three days at room temperature in an *E*/*Z* ratio of 5:1. It is noteworthy that 19-*nor*-1α,25-dihydroxyvitamin D_3 (**1b**) does not exhibit this behavior, thus demonstrating the importance of the steric hindrance between 6-C and 15-C. It is interesting to note that, in the ^1H NMR spectra of 19-*nor*-14-*epi* analogues such as **2** and **3** (several examples; see also **54** and **55** in Scheme 7), the dd

pattern of the vinylic protons in the 7,8-*E* epimers is consistently found at about δ = 6.05 and 6.25 (Δδ = 0.2) while the 7,8-*Z* epimers give δ = 6.12 and 6.22 (Δδ = 0.1). This observation can be used for structure determination.



Scheme 7. (a) *t*BuLi, THF, −70 °C, 1 h; (b) PTSA, dioxane/H_2O (1:1), 40−60 °C, 4 h; (c): TBAF, THF, room temp.

We now turned our attention to the synthesis of the 3-*epi*- and 1-*epi*-analogues **54** and **55** of TX 522. The aldehydes **38a** and **35** are potential A-ring analogues (Scheme 7). Unlike in the synthesis of **3** (TX 522), the outcome of the solvolytic step is now no longer straightforward. Indeed it proceeds by way of two rotamers around the 5,6 bond (Figure 3; **i** and **ii** for **48**), in equilibrium with each other. For the formation of **3**, in which the A-ring has a pseudo-C_2 axis of symmetry, this is of no consequence. As the A-rings in **54** and **55** possess pseudo-planes of symmetry, attack of water on the rotamers **i** and **ii** will, in principle, produce a mixture of the 1- and 3-epimers. The rotamers **i** and **ii** of **48**, for example, will produce **50** (3-*epi*) and **51** (1-*epi*), respectively, and hence **54** and **55**. The same argument holds for **49**; the rotamer shown, for example, will ultimately produce **55** by way of regioisomer **53**. Evidently, one rotamer might be more populated. As shown in Scheme 1, this is the case in the synthesis of **1a**, in which the solvolysis of the cyclovitamin precursor **17** produces, at best, a mixture of **1a** (5,6-*Z*) and **21** (5,6-*E*) in a 4:1 ratio.[15]

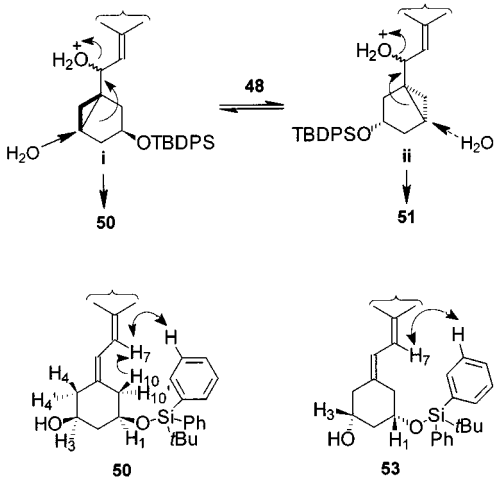


Figure 3

It is evident that distinguishing the epimers **54** and **55** by spectrometric methods would be an almost impossible task. For the structure determination the A-ring the oxy-functions must be differentiated from each other, and therefore a TBDPS protecting group, stable under the solvolysis conditions (vide supra), is needed. Remarkably, the solvolysis of **48** gave a mixture of **50** and **51** in an 18:1 ratio, thus indicating a large preference towards a mechanism via rotamer **i**. Selectivity, albeit lower, in favor of the 1-epimer **53** was also observed in the case of **49** (**52**:**53**, ratio 1:7). The solvolysis was also performed on the separated 6-C isomers of **48** and **49**; both gave the same result.

The structure of **50** was proven by NOE and COSY-2D experiments. In order to assign the NMR signals for the vinylic protons 6-H and 7-H (AB system; δ = 6.21 and δ = 5.71; *J* = 12.0 Hz) unambiguously, 6-deuterated **50** was synthesized, starting from **38b** (from **37**; $LiAlD_4$ reduction and subsequent oxidation: see Scheme 3). The ^1H NMR spectrum of the deuterated product showed the singlet for 7-H at δ = 5.70. The observation of a NOE enhancement between 7-H and an aromatic proton in the TBDPS group (Figure 3) is by itself practically a proof for the structure **50**. COSY-2D experiments led to the same conclusion; 1-H (δ = 3.85) and 3-H (δ = 4.05) were easily distinguished as a coupling with the hydroxy proton was observed for 3-H. This allowed us to locate the protons at 4-C (coupling with 3-H) and 10-C (coupling with 1-H). An NOE enhancement established a proximity relation between 7-H and 10-H. Localization of the protons in the trichloroacetate of **50** was also performed. For 3-H a chemical shift from δ = 4.05 to δ = 4.60 was observed and COSY-2D experiments and NOE enhancement (7-H, 10-H) corroborated with those obtained for **50**.

An NOE enhancement between 7-H and an aromatic proton of the TBDPS protective group was also observed in **53**. The vinylic protons in **50** and **53** (1-C OTBDPS) are

found at δ = 6.21 (6-H), and δ = 5.71 (7-H), in contrast to the values of δ = 6.25 and δ = 6.05 for **54** and **55** (also **2** and **3**). The upfield shift of 7-H is probably due to the anisotropy of a phenyl group of the TBDPS ether, which is in fact confirmed by the observed NOE enhancement. In the regioisomers (3-C OTBDPS) **51** and **52**, 6-H and 7-H show almost the same chemical shift (δ = 6.08). The smaller upfield shift (δ = 6.25 to δ = 6.08) of 6-H can also be explained by the anisotropy of the TBDPS group.

The antiproliferative activities of TX 522 and KS 532 have been described.[5] The biological activities of other 14-*epi*-19-*nor* analogues, in combination with other structural variations (side chain, A-ring), will be described elsewhere.

In conclusion, it can be stated that the cyclovitamin strategy is a valuable tool for the synthesis of 19-*nor* analogues. The A-ring precursors **14**, **35**, **38a**, and **41** are easily accessible and the remarkable stereoselectivity of the solvolytic step opens possibilities for the synthesis of 19-*nor* analogues also modified at the 1-, 2-, and 3-positions.

Experimental Section

General: All reactions were carried out under an argon or nitrogen atmosphere with magnetic stirring. All solvents were purified or dried according to standard procedures. Solutions were dried over $MgSO_4$. The solvent was removed from the filtered solutions on a rotary evaporator. Column chromatography separations were performed with silica gel; eluents are given in brackets. HPLC separations were performed on a Knauer 64, a Waters 6000 A, or a Kontron 420 delivery system with RI detection; eluents are given in brackets. − Optical rotations were measured with a Perkin−Elmer 421 polarimeter. − IR spectra were recorded on a Perkin−Elmer FTIR-1600 spectrometer. − Mass spectra were recorded on a HP-5988 spectrometer. − The ^{1}H NMR spectra were recorded at 200 MHz (Varian Gemini), or at 500 MHz (WH Bruker), the chemical shifts are expressed in ppm relative to TMS and coupling constants are given in Hz. − X-ray analysis of TX 522 was performed by Prof. Dr. J. P. Declercq at UCL (Louvain-la-Neuve, Belgium).

Methyl (1*R*,3*S*,5*R*)-3-Hydroxy-5-tosyloxycyclohexanecarboxylate (27): TsCl (375 g, 1.974 mmol) was added to a solution of **26** (250 g, 1.157 mmol) and DMAP (2.53 g) in NEt_3 (1.5 L) at 0 °C. The solution was stirred for 1 h at 0 °C and then for 22 h at room temp. The reaction was quenched with H_2O (4.5 L) and the precipitate was filtered off. The crude product was crystallized from *i*PrOH, affording the tosylate (375 g, 87.6%) as white crystals; m.p. 83.1 °C, R_f = 0.65 (toluene/dioxane, 85:15). A suspension of this tosylate (716 g, 1.932 mmol) and K_2CO_3 (134 g, 0.903 mmol) in MeOH (6 L) was stirred for 30 min. at room temp. and was then poured into H_2O (40 L). The precipitate was filtered off and dried to give **27** (575.6 g, 90.6%); m.p. 98.4 °C, R_f = 0.25 (toluene/dioxane, 85:15). − $[\alpha]_D^{25}$ = −19.0 (*c* = 1.0, EtOH). − IR (KBr): $\tilde{\nu}$ = 3447, 1719, 1176 cm^{-1}. − UV (EtOH): λ_{max} = 225 nm (ε = 11935). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.34 (q, *J* = 12.1 Hz, 1 H), 1.45 (q, *J* = 11.5 Hz, 1 H), 2.31 (tt, *J* = 13, 3.5 Hz, 1 H), 2.45 (s, 3 H), 3.61 (m, 1 H), 3.68 (s, 3 H), 4.41 (tt, *J* = 11.4 Hz, 1 H), 7.35 (d, *J* = 8.2 Hz, 2 H), 7.79 (d, *J* = 8.2 Hz, 2 H).

Methyl (1*R*,3*R*,5*R*)-3-Acetoxy-5-tosyloxycyclohexanecarboxylate (28): DEAD (175 mL, 1.114 mmol) was added at 0 °C to a solution of **27** (293.7 g, 0.891 mmol), PPh_3 (295 g, 1.122 mmol), and glacial HOAc (66 mL, 1.3 mmol) in toluene (2.9 L). The mixture was stirred at room temp. for 30 min. After filtration, the precipitate was washed with cold toluene and the filtrate was concentrated. Toluene was added to the crude product and the solution was filtered through a pad of silica gel (30−70 M). Elution (toluene/EtOAc, 8:2) afforded (after concentration) crude **28**, which was crystallized from *i*PrOH to give the pure product (254.2 g, 77%) as white crystals; m.p. 83.1 °C, R_f = 0.64 (toluene/dioxane, 85:15). − $[\alpha]_D^{25}$ = −35.6 (*c* = 1, EtOH). − IR (KBr): $\tilde{\nu}$ = 1739, 1120 cm^{-1}. − UV (EtOH): λ_{max} = 345 nm (ε = 12800). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.60 (m, 4 H), 2.00 (s, 3 H), 2.10 (m, 1 H), 2.35 (m, 1 H), 2.47 (s, 3 H), 2.73 (m, 1 H), 3.7 (s, 3 H), 4.75 (m, 1 H), 5.20 (m, 1 H), 7.35 (d, *J* = 8.5 Hz, 2 H), 7.80 (d, *J* = 8.5 Hz, 2 H).

Methyl (1*R*,3*R*,5*R*)-3-*tert*-Butyldimethylsilyloxy-5-tosyloxycyclohexanecarboxylate (30): K_2CO_3 (52.5 g, 22.9 mmol) was added to a suspension of crude **28** (300 g, 0.81 mmol) in MeOH (3 L). The mixture was stirred for 30 min. at room temp. and was then poured into brine (12 L). The aqueous layer was extracted with toluene. The combined organic layers were dried, filtered, and concentrated, affording **29** (260.6 g, 98%) as an oil: R_f = 0.35 (heptane/EtOAc, 4:6).

TBS-Cl (149.58 g, 0.992 mmol) was added to a solution of **29** (259.6 g, 0.79 mmol) and imidazole (67.71 g, 0.990 mmol) in dry DMF (1.3 L). The mixture was stirred at room temp. for 1.5 h, and was then poured into H_2O and extracted with toluene. The combined organic layers were washed with H_2O and concentrated. The crude product was crystallized from heptane to afford **30** (304.5 g, 86%): m.p. 68.2 °C, R_f = 0.5 (heptane/EtOAc, 7:3). − $[\alpha]_D^{25}$ = −41.6 (*c* = 1.0, EtOH). − IR (KBr): $\tilde{\nu}$ = 2853, 1726, 1436, 1359, 1173, 831 cm^{-1}. − UV (EtOH): λ_{max} = 225 nm (ε = 12390). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.02 (s, 3 H), 0.05 (s, 3 H), 0.82 (s, 9 H), 1.50 (m, 3 H), 1.60 (m, 1 H), 1.86 (m, 1 H), 2.31 (m, 1 H), 2.45 (s, 3 H), 2.81 (dt, *J* = 12.5, 3.7 Hz, 1 H), 3.69 (s, 3 H), 4.19 (m, 1 H), 4.72 (dt, *J* = 11.3, 4.5 Hz, 1 H), 7.68 (d, *J* = 8.5 Hz, 2 H), 7.76 (d, *J* = 8.5 Hz, 2 H).

Methyl (2*S*,3*aS*,4*aS*)-2-*tert*-Butyldimethylsilyloxybicyclo[3.1.0]hexane-3a-carboxylate (31): A solution of *t*BuOK in *t*BuOH (1 M, 1.02 L) was added slowly over 1 h to a stirred solution of **30** (378.5 g, 856 mmol) in *t*BuOH at 64 °C. After 5 min. the suspension was cooled to 30 °C and a saturated solution of NH_4Cl (3 L) was added. After 10 min. the aqueous phase was extracted with *i*Pr_2O. The organic layer was washed with H_2O, dried, filtered, and concentrated. Flash chromatography (heptane/EtOH, 7:3) gave **31** (211.3 g, 91.3%) as a yellow oil: R_f = 0.5 (heptane/EtOAc, 8:2), b.p. (760 Torr) 135 °C. − $[\alpha]_D^{25}$ = −43.0 (*c* = 1.04, EtOH). − IR (film): $\tilde{\nu}$ = 1726, 1458, 1437, 1254, 837 cm^{-1}. − UV (EtOH): λ_{max} = 201 nm (ε = 742). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.01 (s, 6 H), 0.67 (t, *J* = 5.1 Hz, 1 H), 0.87 (s, 9 H), 1.28 (dd, *J* = 8.5, 5.0 Hz, 1 H), 1.77 (m, 1 H), 1.81 (m, 1 H), 2.07 (dd, *J* = 12.0, 7.1 Hz, 1 H), 2.14 (dd, *J* = 12.9, 8.2 Hz, 1 H), 2.20 (dd, *J* = 12.9, 9.2 Hz, 1 H), 3.66 (s, 3 H), 3.93 (m, 1 H). − $C_{14}H_{26}O_3Si$ (270.44): calcd. C 62.16, H 9.71; found C 62.27, H 9.81.

(2*S*,3*aS*,4*aS*)-2-*tert*-Butyldimethylsilyloxy-3a-(hydroxymethyl)bicyclo[3.1.0]hexane (32): A solution of DIBAL-H in toluene (1.5 M, 1.25 L) was added at −70 °C over 1.5 h to a solution of **31** (207.5 g, 768 mmol) in toluene (2.1 L). After completion of this addition, a saturated solution of potassium sodium tartrate was slowly added and the temp. was raised to 0 °C. After stirring for 2 h the reaction mixture was extracted with toluene. The organic layers were dried and concentrated to give **32** (142.9 g, 88%) as a yellow oil: R_f =

0.15 (heptane/EtOAc, 8:2). − $[\alpha]_D^{25}$ = −14.0 (*c* = 1.37, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3355, 1471, 1255, 835, 774 cm^{-1}. − ^1H NMR (500 MHz, $CDCl_3$): δ = 0.2 (s, 6 H), 0.51 (dd, *J* = 8.4, 5.1 Hz, 1 H), 0.89 (s, 9 H), 1.18 (ddd, *J* = 8.2, 4.2, 4.2 Hz, 1 H), 1.21 (m, 1 H), 1.80 (m, 2 H), 1.92 (d, *J* = 13.2 Hz, 1 H), 2.01 (m, 2 H), 3.54 (m, 2 H), 4.03 (m, 1 H).

(2*S*,3*aS*,4*aS*)-2-(*tert*-Butyldimethylsilyloxy)bicyclo[3.1.0]hexane-3a-carbaldehyde (14a): PCC (100.8 g, 0.467 mmol) was added at room temp. to a solution of **32** (102.6 g, 0.423 mmol) in CH_2Cl_2 (1 L). The mixture was stirred vigorously for 1 h. The temperature went up to 35 °C, then decreased to 25 °C. The suspension was filtered through a pad of Celite and washed with CH_2Cl_2 and iPr_2O. The organic layer was washed successively with H_2O, a saturated $NaHCO_3$ solution, and with H_2O to pH 6−7. The combined organic layers were dried, filtered, and concentrated. The residue was purified by flash chromatography on Florisil (heptane/EtOAc, 95:5) to give **14a** as a yellow oil (81.56 g, 80.2%): R_f = 0.47 (heptane/EtOAc, 8:2). − $[\alpha]_D^{25}$ = −49.4 (*c* = 1.06, EtOH). − IR (KBr): $\tilde{\nu}$ = 1726, 1253, 1119, 838 cm^{-1}. − UV (EtOH): λ_{max} = 204 nm (ε = 6292). − ^1H NMR (500 MHz, $CDCl_3$): δ = 0 (s, 6 H), 0.87 (s, 9 H), 0.97 (dd, *J* = 5.6, 5.3 Hz, 1 H), 1.35 (dd, *J* = 8.8, 5.6 Hz, 1 H), 1.80 (ddd, *J* = 13.0, 8.0, 5.1 Hz, 1 H), 1.93 (ddd, *J* = 8.3, 5.3, 5.1 Hz, 1 H), 2.10 (dd, *J* = 13.0, 7.2 Hz, 1 H), 2.13 (dd, *J* = 13.0, 7.2 Hz, 1 H), 2.17 (ddd, *J* = 13.0, 8.0, 1.1 Hz, 1 H), 4.04 (m, 1 H), 8.9 (s, 1 H).

Methyl (1*R*,3*S*,5*R*)-3-*tert*-(Butyldiphenylsilyloxy)-5-tosyloxycyclohexanecarboxylate (33): This compound was prepared from **26** in 3 steps as described for **26** to **27** and **29** to **30** (TBDPS-Cl instead of TBS-Cl). Oil, yield 72%. R_f = 0.36 (isooctane/Et_2O, 1:1). − $[\alpha]_D^{25}$ = −3.0 (*c* = 1.04, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 2932, 2857, 1736, 1428, 1364, 1177, 1107, 929, 822, 703, 665 cm^{-1}. − ^1H NMR (500 MHz, $CDCl_3$): δ = 1.00 (s, 9 H), 1.9−2.1 (m, 4 H), 2.14 (), 2.43 (s, 3 H), 3.46 (tt, *J* = 4.0, 11.0 Hz, 1 H), 3.63 (s, 3 H), 4.16 (tt, *J* = 4, 12 Hz, 1 H), 7.28 (d, *J* = 8.4 Hz, 2 H), 7.36 (t, *J* = 8.0 Hz, 4 H), 7.44 (q, *J* = 7.0 Hz, 2 H), 7.57 (m, 4 H), 7.69 (d, *J* = 8.3 Hz, 2 H).

Methyl (2*R*,3*aS*,4*aS*)-2-(*tert*-Butyldiphenylsilyloxy)bicyclo[3.1.0]hexane-3a-carboxylate (34): This compound was prepared from **33** as described for **31** from **30**. Oil, yield 75%. R_f = 0.60 (isooctane/Et_2O, 1:1). − $[\alpha]_D^{25}$ = −30.8 (*c* = 0.46, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 2932, 2857, 1723, 1589, 1472, 1428, 1297, 1148, 1112, 1088, 702 cm^{-1}. − ^1H NMR (500 MHz, $CDCl_3$): δ = 1.03 (s, 9 H), 1.50 (dm, *J* = 9.0 Hz, 1 H), 1.63 (dd, *J* = 4, 5 Hz, 1 H), 1.82 (d, *J* = 14.0 Hz, 1 H), 1.87 (dt, *J* = 5, 9 Hz, 1 H), 1.96 (dd, *J* = 6, 14 Hz, 1 H), 1.99 (d, *J* = 14.0 Hz, 1 H), 2.37 (ddd, *J* = 1, 6.4, 14 Hz, 1 H), 3.63 (s, 3 H), 4.36 (t, 6.1 Hz, 1 H), 7.37 (t, *J* = 7.0 Hz, 4 H), 7.42 (t, *J* = 7.0 Hz, 2 H), 7.61 (dd, *J* = 1, 7 Hz, 4 H).

(2*R*,3*aS*,4*aS*)-2-(*tert*-Butyldiphenylsilyloxy)bicyclo[3.1.0]hexane-3a-carbaldehyde (35): This compound was prepared from **34** as described for **14a** from **31**. Oil, yield 93%. R_f = 0.51 (isooctane/Et_2O, 1:1). − $[\alpha]_D^{25}$ = −35.3 (*c* = 1.6, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 2931, 1701, 1589, 1472, 1196, 1008, 822, 702 cm^{-1}. − ^1H NMR (500 MHz, $CDCl_3$): δ = 1.04 (s, 9 H), 1.87 (dd, *J* = 3.4, 11.5 Hz, 2 H), 1.93−1.99 (m, 3 H), 2.39 (ddd, *J* = 1.0, 6.3, 14.3 Hz, 1 H), 4.40(t, *J* = 6.2 Hz, 1 H), 7.36−7.62 (m, 10 H), 8.86 (s, 1 H).

Methyl (1*S*,3*R*,5*S*)-3-(*tert*-Butyldiphenylsilyloxy)-5-tosyloxycyclohexanecarboxylate (36): This compound was prepared from **26** in 3 steps as described for **29** to **30** (TBDPS-Cl instead of TBS-Cl) and **26** to **27**. Viscous oil, yield 94%. R_f = 0.20 (isooctane/EtOAc, 85:15). − $[\alpha]_D^{25}$ = +2.7 (*c* = 1.17, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 2955, 1738, 1363, 1178, 1111, 824, 704 cm^{-1}. − ^1H NMR (500 MHz, $CDCl_3$): δ = 0.98 (s, 9 H), 1.42 (q, *J* = 11.3 Hz, 1 H), 1.52 (m, 2 H), 1.99−2.15 (m, 4 H), 2.48 (s, 3 H), 3.46 (dt, *J* = 11.1, 4.1 Hz, 1 H), 3.63 (s, 3 H), 4.16 (dt, *J* = 11.6, 4.6 Hz, 1 H), 7.26−7.46 (m, 10 H).

Methyl (2*S*,3*aR*,4a*R*)-2-(*tert*-Butyldiphenylsilyloxy)bicyclo[3.1.0]-hexane-3a-carboxylate (37): This compound was prepared from **36** as described for **31** from **30**. Viscous oil, yield 81%. R_f = 0.34 (isooctane/EtOAc, 100:5). − $[\alpha]_D^{25}$ = 32.0 (*c* = 1.71, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 3287, 2934, 1732, 1457, 1281, 1017 cm^{-1}. − ^1H NMR (500 MHz, $CDCl_3$): δ = 1.01 (s, 9 H), 1.50 (m, 1 H), 1.63 (t, *J* = 5.1 Hz, 1 H), 1.82 (d, *J* = 13.9 Hz, 1 H), 1.87 (dt, *J* = 9.4, 5.1 Hz, 1 H), 1.96 (dd, *J* = 14.3, 5.5 Hz, 1 H), 1.99 (d, *J* = 14.3 Hz, 1 H), 2.37 (ddd, *J* = 14.2, 5.4, 1.2 Hz, 1 H), 3.63 (s, 3 H), 4.36 (t, *J* = 6.1 Hz, 1 H), 7.36 (t, *J* = 7.8 Hz, 4 H), 7.42 (t, *J* = 7.9, 2 H), 7.62 (dd, *J* = 7.9, 1.2 Hz, 4 H).

(2*S*,3*aR*,4aR)-2-(*tert*-Butyldiphenylsilyloxy)bicyclo[3.1.0]hexane-3a-carbaldehyde (38a): This compound was prepared from **37** in 2 steps as described for **14a** from **31**. Viscous oil, yield 96%. R_f = 0.47 (isooctane/Et_2O, 1:1), $[\alpha]_D^{25}$ = +34.4 (*c* = 1.6, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 2956, 1704, 1590, 1472, 1428, 1112, 1072, 822, 702 cm^{-1}. − ^1H NMR (500 MHz, $CDCl_3$): δ = 1.04 (s, 9 H), 1.53 (m, 1 H), 1.86 (m, 2 H), 1.97 (m, 3 H), 2.39 (dd, *J* = 14, 6.0 Hz, 1 H), 4.40 (t, *J* = 6.0 Hz, 1 H), 7.37−7.62 (m, 10 H), 8.85 (s, 1 H).

Methyl (1*R*,3*S*,5*S*)-3-Acetoxy-5-benzoyloxycyclohexanecarboxylate (39): This compound was prepared from **26** as described for **27** to **28** ($PhCO_2H$ instead of HOAc). Viscous oil, yield 81%. R_f = 0.35 (isooctane/EtOAc, 7:3), $[\alpha]_D$ = +42.3 (*c* = 0.82, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 2953, 1735, 1600, 1450, 1369, 1314, 1275, 1237, 1108, 1038, 1024, 713 cm^{-1}. − ^1H NMR (500 MHz, $CDCl_3$): δ = 1.53 (m, 1 H), 1.68 (m, 1 H), 1.76 (m, 1 H), 2.04 (s, 3 H), 2.27 (t, *J* = 15.7 Hz, 2 H), 2.42 (d, *J* = 12.5 Hz, 1 H), 2.91 (dt, *J* = 5.1, 3.7 Hz, 1 H), 3.68 (s, 3 H), 5.15 (m, 1 H), 5.56 (t, *J* = 3.1 Hz, 1 H), 7.45 (d, *J* = 8.2 Hz, 2 H), 7.58 (t, *J* = 8.2 Hz, 1 H), 8.05 (d, *J* = 8.5 Hz, 2 H).

Methyl (1*S*,3*S*,5*S*)-3-(*tert*-Butyldiphenylsilyloxy)-5-tosyloxycyclohexanecarboxylate (40): This compound was prepared from **39** in 4 steps as described for **28** to **29**, **27** to **28**, **28** to **29**; 3 h, and **29** to **30** (TBDPS-Cl instead of TBS-Cl). Viscous oil, yield 68%. R_f = 0.42 (isooctane/EtOAc, 8:2). − $[\alpha]_D^{25}$ = +7.8 (*c* = 1.31, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 2954, 1731, 1272, 1176, 1107, 945, 813, 713, 664 cm^{-1}. − ^1H NMR (500 MHz, $CDCl_3$): δ = 1.01 (s, 9 H), 1.29 (m, 3 H), 1.60 (m, 1 H), 1.84 (d, *J* = 12.7 Hz, 1 H), 2.37 (d, *J* = 12.4 Hz, 1 H), 2.45 (s, 3 H), 2.95 (dt, *J* = 3.3, 12.7 Hz, 1 H), 3.68 (s, 3 H), 4.84 (m, 1 H), 7.25−7.53 (m, 14 H).

(2*R*,3*aR*,4aR)-2-(*tert*-Butyldiphenylsilyloxy)bicyclo[3.1.0]hexane-3a-carbaldehyde (41): This compound was prepared from **40** in 3 steps as described for **14a** from **31**. Viscous oil, yield 71%. R_f = 0.28 (isooctane/EtAcO, 94:6). − $[\alpha]_D^{25}$ = +91.5 (*c* = 0.47, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 2931, 2857, 1708, 1472, 1388, 1362, 1200, 1113, 1093, 1036, 901, 823, 742, 612 cm^{-1}. − ^1H NMR (500 MHz, $CDCl_3$): δ = 0.74 (t, *J* = 5.4 Hz, 1 H), 1.02 (s, 9 H), 1.22 (m, 1 H), 2.01 (m, 2 H), 1.89 (m, 2 H), 2.29 (dd, *J* = 12.9, 8.1 Hz, 1 H), 3.98 (m, 1 H), 7.35−7.65 (m, 10 H), 8.87 (s, 1 H).

(2*S*,3*aS*,4*aS*)-2-*tert*-Butyldimethylsilyloxy-3a-ethynylbicyclo[3.1.0]-hexane (16a): *t*BuOK (1.26 mL, 1.26 mmol, 1.0 M solution in THF) was added dropwise at −78 °C to a solution of $(MeO)_2P(O)CHN_2$ (188 mg, 1.253 mmol) in THF (3 mL). The mixture was stirred at −78 °C for 20 min. until the yellow color persisted. Aldehyde **14a** (380 mg, 1.043 mmol) in THF (3 mL) was then slowly added, and stirring was continued overnight, the temp. rising from −78 °C to

room temp. The reaction was quenched by addition of H_2O (10 mL) and Et_2O (20 mL). The organic phase was separated and the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic layers were dried, filtered, and concentrated. The residue was purified by HPLC (hexane/EtOAc 96:4), affording **16a** (338 mg, 90%) as a colorless oil. R_f = 0.10 (hexane), $[\alpha]_D^{25}$ = −47.3 (c = 0.81, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 3315, 2941, 2856, 2113, 1472, 1385, 1119, 1095, 902, 836, 776 cm^{-1}. − ^1H NMR (500 MHz, $CDCl_3$): δ = 0.01 (s, 6 H), 0.55 (dd, J = 4.9, 4.9 Hz, 1 H), 0.88 (s, 9 H), 0.81 (dd, J = 8.1, 4.9 Hz, 1 H), 1.60 (ddd, J = 8.3, 4.9, 4.9, 1 H), 1.83 (ddd, J = 12.7, 8.1, 4.9 Hz, 1 H), 1.90 (ddd, J = 12.5, 8.3, 1.0 Hz, 1 H), 1.92 (s, 1 H), 2.05 (dd, J = 12.7, 7.1 Hz, 1 H), 2.28 (dd, J = 12.5, 7.1 Hz, 1 H), 3.84 (m, 1 H).

(1*R*)-(1α,3aα,7aα)-1-[6-(1-Ethoxyethoxy)-1,6-dimethylhex-3-ynyl]-7a-methyloctahydroinden-4-one (7b): A solution of **44b**[3b] (307 g, 0.88 mmol) in 0.15% MeONa/MeOH (3 L) was stirred at 50 °C. for 2.5 h. Filtration, solvent removal, and flash chromatographic separation (hexane/EtOAc, 75:25) gave *cis*-hydrindane **7b** (224.1, 73%). R_f = 0.48 (hexane/EtOAc, 8:2). − IR (film): $\tilde{\nu}$ = 1708, 1464, 1443, 1378, 1253, 1160, 1124, 1081, 1053, 976, 930, 850 cm^{-1}. − ^1H NMR (200 MHz, $CDCl_3$): δ = 1.05 (s, 3 H), 1.06 (d, J = 6.5 Hz, 3 H), 1.18 (t, J = 7.0 Hz, 3 H), 1.32 (d, J = 5.3 Hz, 3 H), 1.43 (s, 3 H), 1.49 (s, 3 H), 1.72−2.40 (m, 15 H), 3.40−3.72 m, 2 H), 5.08 (q, J = 5.2 Hz, 1 H).

44b: R_f = 0.41 (hexane/EtOAc, 8:2). − IR (film): $\tilde{\nu}$ = 1715, 1462, 1378, 1160, 1124, 1080, 10853, 1053, 975, 837, 736 cm^{-1}. − ^1H NMR (500 MHz, $CDCl_3$): δ = 0.65 (s, 3 H), 1.10 (d, J = 6.0 Hz, 3 H), 1.19 (t, J = 7.1 Hz, 3 H), 1.34 (d, J = 5.2 Hz, 3 H), 1.45 (s, 3 H), 1.51 (s, 3 H), 1.55−2.15 (m, 11 H), 2.25 (m, 3 H), 2.46 (dd, J = 7.5, 11.7 Hz, 1 H), 3.50 (dq, J = 7.0, 9.2 Hz, 1 H), 3.67 (dq, J = 7.1, 9.2 Hz, 1 H), 5.12 (q, J = 5.2 Hz, 1 H). − C_{22} H_{36} O_3: calcd. C 75.75, H 10.34; found C 75.80, H 10.10.

(*E*)-(1*R*,4*aR*,7*aR*)-4-Bromomethylidene-1-[5-(1-ethoxyethoxy-1,5-dimethylhex-3-ynyl]-7a-methyloctahydroindene (9b): A solution of potassium bis(trimethylsilyl)amide (177.58 g, 0.890 mmol) in THF (800 mL) was slowly added at −30 °C to a solution of (bromomethyl)triphenylphosphonium bromide (396.5 g, 0.909 mmol) in THF (1.25 L), cooled to −30 °C. After this had stirred at 0 °C for 1.5 h, a solution of **7b** (125.15 g, 0.359 mmol) in THF (170 mL) was slowly added and stirring at 0 °C was continued for 2.5 h. H_2O (1 L) was then slowly added, while maintaining the temp. ≥ 20 °C. After extraction (3 ×) with a mixture of heptane/EtOAc/Et_3N (5 L/0.5 L/2.8 mL), the combined organic layers were washed with brine to pH ≈ 7 and then dried, filtered, and concentrated. The residue was purified by flash chromatography (heptane/EtOAc/Et_3N, 99:1:0.05) to afford **9b** (96.9 g, 64%) as an oil. − $[\alpha]_D^{25}$ = +30.7 (c = 1.16, $CDCl_3$). − IR (film): $\tilde{\nu}$ = 2932, 1614, 1453, 1378, 1250, 1157, 1118, 1081, 1029, 975 cm^{-1}. − ^1H NMR (360 MHz, $CDCl_3$): δ = 0.95 (s, 3 H), 1.04 (d, J = 6.4 Hz, 3 H), 1.19 (t, J = 7.0 Hz, 3 H), 1.33 (d, J = 5.2 Hz, 3 H), 1.44 (s, 3 H), 1.55 (s, 3 H), 1.60−2.0 (m, 15 H), 2.20 (m, 3 H), 2.41 (m, 1 H), 3.49 (dq, J = 7.2, 9.1 Hz, 1 H), 3.68 (dq, J = 7.2, 9.1 Hz, 1 H), 5.11 (br. q, J = 5.2 Hz, 1 H), 5.88 (br. s, 1 H).

(*E*)-(1*R*,4*aR*,7aR)-4-Bromomethylidene-1-[1,5-dimethylhexyl]-7a-methyloctahydroindene (9c): This compound was prepared from **7c** as described for **7b** to **9b**. Oil, 70% yield. R_f = 0.75 (hexane/EtOAc, 9:1). − ^1H NMR (500 MHz, $CDCl_3$): δ = 0.87 (d, J = 6.6 Hz, 3 H), 0.88 (d, J = 6.6 Hz, 3 H), 0.90 (d, J = 6.5 Hz, 3 H), 0.95 (s, 3 H), 1.0−2.0 (m, 17 H), 2.10 (m, 1 H), 2.21 (dd, J = 3.8, 5.2 Hz, 1 H), 2.50 (ddd, J = 2.4, 2.4, 7.2 Hz, 1 H), 5.87 (br. s, 1 H). − IR (film): $\tilde{\nu}$ = 2950, 2912, 2871, 1631, 1467, 1379, 1262, 946.5, 885, 844, 772, 699 cm^{-1}.

Intermediate 18a: A solution of *t*BuLi in pentane (c = 1.7 M, 273.6 mL, 0.465 mmol) was added dropwise to a solution of **9b** (95.23 g, 0.224 mmol) in THF (1.14 L), cooled to −70 °C. After this had stirred for 1.5 h, a solution of **14a** (63.67 g, 0.265 mmol) in THF (440 mL) was slowly added and stirring was continued for 1 h. More **14a** (22.75 g, 0.095 mmol) was then added. After 40 min. the reaction was carefully quenched with an aqueous solution of NH_4Cl (534 g in 1.9 L).The product was extracted with EtOAc (3 times, 2.7 L in total). The combined organic layers were washed with brine to pH 7, dried, filtered, and concentrated. Purification by flash chromatography (heptane/EtOAc/Et_3N, 85:15:0.05) gave the epimers **18a** (97.7 g, 74%, ratio 1:1) as an oil. R_f = 0.30 (heptane/EtOAc/Et_3N, 8:2:0.05). − ^1H NMR (200 MHz): δ = 0.4 (s, 6 h), 0.1 (t, J = 4.6 Hz, 1 H), 0.21 (m, 1 H), 0.60 (m, 1 H), 0.86 (s, 9 H), 0.95 (s, 3 H), 1.03 (d, J = 6.3 Hz, 3 H), 1.15 (t, J = 7.4 Hz, 3 H), 1.20−1.30 (m, 3 H), 1.31 (d, J = 5.0 Hz, 3 H), 1.41 (s, 3 H), 1.48 (s, 3 H), 1.50−2.2 (m, 16 H), 3.48 (m, 1 H), 3.63 (m, 1 H), 4.01 (m, 2 H), 4.21 (d, J = 8.5 Hz, 0.5 H), 4.41 (d, J = 8.5 Hz, 0.5 H), 5.09−5.13 (m, 2 H).

TX 522 (3) from 18a: PTSA (3.69 g in 2.9 mL dioxane/H_2O, 3:1) was added dropwise (30 min) to a solution of **18a** (97.36 g, 0.24 mmol) in dioxane/H_2O (3:1, 1 L). The solution was stirred in the dark for 2 h at 60 °C and was then cooled to room temp. Another portion of PTSA (27.17 g) was added and stirring was continued for 1 h at 40 °C. After addition of H_2O (4 L) and extraction with EtOAc, the combined organic layers were washed with saturated $NaHCO_3$ solution to pH≈7 and with H_2O, dried, filtered, and concentrated. Purification by flash chromatography (CH_2Cl_2/MeOH, 95:5) gave **3**, which was crystallized from *i*Pr_2O/EtOH (100:1, 600 mL), yielding a first batch (39.45 g). Concentration of the mother liquor and crystallization gave a second batch (6.67 g, total yield 70%). M.p. 118 °C, R_f = 0.3 (EtOAc). − UV (MeOH): λ_{max} = 258, 249, 241 nm. − IR (film): $\tilde{\nu}$ = 3379, 2927, 2292, 2225, 1609, 1452, 1374, 1262, 1125, 1087, 1044, 863, 801, 738 cm^{-1}. − ^1H NMR (360 MHz, $CDCl_3$): δ = 0.96 (s, 3 H), 1.02 (d, J = 6.5 Hz, 3 H), 1.30 (m, 3 H), 1.50 (s, 6 H), 1.51−2.32 (m, 18 H), 2.39 (dt, J = 5.2, 14.5 Hz, 1 H), 2.48 (dd, J = 3.6, 13.3 Hz, 1 H), 2.69 (dd, J = 3.8, 13.3 Hz, 1 H), 4.09 (m, 2 H), 6.04 (d, J = 11.3 Hz, 1 H), 6.25 (d, J = 11.3 Hz, 1 H). − $C_{26}H_{40}O_3$: calcd. C 77.07, H 9.28; found C 77.46, H 10.01.

14-*epi*-1α,25-Dihydroxy-19-norvitamin D_3 (2): This compound was prepared from **9a** as described for **9b** to **3**. R_f = 0.39 (CH_2Cl_2/MeOH, 9:1). − UV (MeOH): λ_{max} = 244 nm. − IR (film): $\tilde{\nu}$ = 3377 (br. s), 3050, 2931, 1610, 1454, 1376, 1265, 1214, 1152, 1049, 976, 938, 909 cm^{-1}. − ^1H NMR (500 MHz, $CDCl_3$): δ = 0.88 (d, J = 6.6 Hz, 3 H), 0.93 (s, 3 H), 1.05 (m, 1 H), 1.23 (s, 6 H), 1.30−1.73 m, 17 H), 1.85 (m, 2 H), 1.91 (m, 1 H), 2.14 (m, 3 H), 2.29 (dd, J = 7.8, 13.3 Hz, 1 H), 2.47 (m, 2 H), 2.69 (dd, J = 3.8, 13.3 Hz, 1 H), 4.09 (m, 2 H), 6.04 (d, J = 11.2 Hz, 1 H), 6.26 (d, J = 11.2 Hz, 1 H).

Allylic Alcohol 20b: *n*BuLi (0.718 mL, 2.5 M in hexane, 1.80 mmol) was added dropwise to a solution of **16b** (647 mg, 1.80 mmol) in dry THF (10 mL), cooled to −78 °C. The solution was stirred at room temp. for 20 min. Compound **7b** (308 mg, 0.88 mmol) in dry THF (5 mL) was then added dropwise, and stirring was continued for 20 min. The mixture was diluted with Et_2O, washed with brine, dried, filtered, and concentrated. Purification by HPLC (hexane/EtOAc, 9:1) gave the propargylic alcohol (500 mg, 80%) as an oil, together with recovery of excess **16b** (325 mg). R_f = 0.40 (hexane/EtOAc, 8:2). Red-Al (1.6 mL, 3.5 M in toluene) was added at 0 °C to a solution of the resulting propargylic alcohol (500 mg, 0.706 mmol) in dry Et_2O (15 mL), and stirring was continued over-

night at room temp. The solution was quenched with a saturated solution of NH_4Cl and brine, and extracted with Et_2O. The combined organic layers were dried, filtered, and concentrated. Purification by HPLC (hexane/EtOAc, 9:1) afforded **20b** (396 mg, 79%) as an oil. R_f = 0.41 (hexane/EtOAc, 8:2). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.30 (t, 4.7 Hz, 1 H), 0.41 (dd, *J* = 5.3, 8.1 Hz, 1 H), 0.87 (s, 3 H), 0.87 (m, 2 H), 1.03 (s, 9 H), 1.09 (d, *J* = 6.2 Hz, 3 H), 1.20 (t, *J* = 7.2 Hz, 3 H), 1.25 (m, 3 H), 1.31 (d, *J* = 5.1 Hz, 3 H), 1.51 (s, 3 H), 1.60 (s, 3 H), 1.60−2.15 (m, 11 H), 2.25 (br. d, *J* = 16.0 Hz, 1 H), 3.51 (dq, *J* = 7.2, 9.1 Hz, 1 H), 3.69 (dq, *J* = 7.2, 9.1 Hz, 1 H), 3.94 (m, 1 H), 5.31 (dd, *J* = 16.0 Hz, 1 H), 5.33 (d, *J* = 16.0 Hz, 1 H), 7.37 (m, 4 H), 7.40 (m, 2 H), 7.65 (m, 4 H).

Allylic Alcohol 20a: This compound was prepared from **7b** and **16a** as described for **20b**. R_f = 0.32 (hexane/EtOAc, 9:1). − IR: $\tilde{\nu}$ = 3492, 2932, 2235, 1660, 1470, 1454, 1379, 1256, 1118, 1092, 972, 837 cm^{-1}. − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.02 (s, 3 H), 0.04 (s, 3 H), 0.53 (m, 2 H), 0.86 (s, 9 H), 0.87 (s, 3 H), 1.08 (d, *J* = 6.4 Hz, 3 H), 1.19 (t, *J* = 7.0 Hz, 3 H), 1.20−1.30 (m, 2 H), 1.33 (d, *J* = 5.3 Hz, 3 H), 1.41 (m, 3 H), 1.44 (s, 3 H), 1.51 (s, 3 H), 1.55−2.24 (m, 16 H), 3.50 (m, 1 H), 3.69 (m, 1 H), 3.95 (m, 1 H), 5.15 (m, 1 H), 5.33 (s, 2 H).

TX 522 (3) from 20b: PTSA (35 mg, 0.3equiv.) in dioxane/H_2O (8 mL, 5:3) was added to a solution of **20b** (440 mg, 0.620 mmol) in dioxane (5 mL) and the mixture was stirred at 55−60 °C for 2 h. After dilution with Et_2O, the solution was washed with a saturated aqueous solution of $NaHCO_3$ to pH 7 and then with H_2O, dried, filtered, and concentrated. Purification by HPLC (isooctane/EtOAc, 85:15) gave **47** (318 mg, 80.4%) as an oil. R_f = 0.24 (isooctane/EtOAc, 7:3). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.95 (s, 3 H), 1.05 (d, *J* = 6.2 Hz, 3 H), 1.06 (s, 9 H), 1.50(s, 6 H), 1.50−2.40 (m, 19 H), 4.06 (m, 1 H), 4.14 (m, 1 H), 5.63 (d, *J* = 11.3 Hz, 1 H), 6.11 (d, *J* = 11.3 Hz, 1 H), 7.33−7.44 (m, 6 H), 7.61−7.73 (4 H). A solution of **47** (318 mg, 0.498 mmol) and TBAF (10 mL, 1 M in THF) in THF (5 mL) was stirred at room temp. for 2 days. After dilution with Et_2O (50 mL) the solution was washed with H_2O, dried, filtered, and concentrated. HPLC purification (as above) gave **3** (199 mg, quant.).

Compound 48, Intermediate for 3-*epi* Analogues: This compound was prepared from **38a** as described for **18a** from **14a**. The epimers (ratio circa 1:1) were separated by column chromatography (isooctane/Et_2O, 1:12 → 1:4). C-6 configuration undetermined:

Compound 48: More polar R_f = 0.37 (isooctane/Et_2O, 1:1). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.66 (m, 1 H), 0.92 (s, 3 H), 1.02 (d, *J* = 6.2 Hz, 3 H), 1.03 (s, 9 H), 1.19 (t, *J* = 6.0 Hz, 3 H), 1.30 (m, 3 H), 1.33 (d, *J* = 4.8 Hz, 3 H), 1.44 (s, 3 H), 1.50 (s, 3 H), 2.18 (m, 1 H), 2.25 (dd, *J* = 2, 16 Hz, 1 H), 3.49 (dq, *J* = 7, 9 Hz, 1 H), 3.69 (dq, *J* = 7, 9 Hz, 1 H), 4.23 (d, *J* = 8.4 Hz, 1 H), 4.36 (br. t, *J* = 6.0 Hz, 1 H), 5.12 (d, *J* = 8.4 Hz, 1 H), 5.13 (q, *J* = 4.8 Hz, 1 H), 7.36 (t, *J* = 7.0 Hz, 4 H), 7.41 (t, *J* = 7.0 Hz, 2 H), 7.62 (d, *J* = 7.0 Hz, 4 H).

Compound 48: Less polar: R_f = 0.43 (isooctane/Et_2O, 1:1). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.66 (m, 1 H), 0.94 (s, 3 H), 1.01 (d, *J* = 6.7 Hz, 3 H), 1.03 (s, 9 H), 1.18 (t, *J* = 5.9 Hz, 3 H), 1.30 (m, 3 H), 1.33 (d, 5.2 Hz, 3 H), 1.43 (s, 3 H), 1.50 (s, 3 H), 1.50−2.20 (m, 17 H), 2.21 (m, 1 H), 2.25 (br. d, *J* = 16.0 Hz, 1 H), 3.49 (dq, *J* = 7, 9 Hz, 1 H), 3.68 (dq, *J* = 7, 9 Hz, 1 H), 4.30 (d, *J* = 8.5 Hz, 1 H), 4.31 (br. t, *J* = 6.0 Hz, 1 H), 5.11 (q, *J* = 5.2 Hz, 1 H), 5.14 (d, *J* = 8.5 Hz, 1 H), 7.36 (t, *J* = 7.0 Hz, 4 H), 7.41 (t, *J* = 7.0 Hz, 2 H), 7.62 (d, *J* = 7.0 Hz, 4 H).

Solvolysis of 48: This was as described for **3** from **18a**. HPLC separation (isooctane/Et_2O/MeOH/CH_2Cl_2, 100:100:1:20) gave **50**, **51**, and the 7,8-*Z* isomer of **50** (ratio 36:2:1; 72% total yield). **Compound 50:** HPLC retention time: 10.4 min. − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.95 (s, 3 H), 1.05 (d, *J* = 6.2 Hz, 3 H), 1.06 (s, 9 H), 1.30 (m, 3 H), 1.51 (s, 6 H), 1.53−2.45 (m, 19 H), 3.85 (m, 1 H), 4.05 (m, 1 H), 5.71 (d, *J* = 11.2 Hz,1 H), 6.21 (d, *J* = 11.2 Hz, 1 H), 7.39 (m, 4 H), 7.44 (m, 2 H), 7.65 (dd, *J* = 1, 7 Hz, 2 H), 7.71 (dd, *J* = 1, 7 Hz, 2 H).

Compound 51: HPLC retention time: 12.2 min. − UV (MeOH): λ_{max} = 219, 243, 251, 260. − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.94 (s, 3 H), 1.02 (d, *J* = 6.3 Hz, 3 H), 1.05 (s, 9 H), 1.30 (m, 3 H), 1.49 (s, 3 H), 1.50 (s, 3 H), 1.52−2.45 (m, 19 H), 3.84 (m, 1 H), 3.98 (m, 1 H), 6.06 (d, *J* = 12.0 Hz, 1 H), 6.08 (d, *J* = 12.0 Hz, 1 H), 7.38 (t, *J* = 7.0 Hz, 4 H), 7.43 (m, 2 H), 7.67 (m, 4 H).

7,8-*Z* Epimer of 50: HPLC retention time: 7.8 min. − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.98 (s, 3 H), 1.06 (s and d, 12 H), 1.30 (m, 3 H), 1.47 (s, 3 H), 1.51 (s, 3 H), 1.52−2.63 (m, 15 H), 2.64 (m, 2 H), 3.90 (m, 1 H), 4.02 (m, 1 H), 6.05 (d, *J* = 11.0 Hz, 1 H), 6.17 (d, *J* = 11.0 Hz, 1 H), 7.41 (m, 4 H), 7.46 (m, 2 H), 7.66 (d, *J* = 8.0 Hz, 2 H), 7.72 (d, *J* = 8.0 Hz, 2 H).

6-Deuterio-48: This compound was prepared from **38b** as described for **48** from **38a**. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.95 (s, 3 H), 1.05 (s and d 12 H), 1.57 (s, 6 H), 1.70−2.20 (m, 17 H), 2.27−2.40(m, 4 H), 2.46 (m, 1 H), 3.09 (d, *J* =8.4 Hz, 1 H), 3.85 (br. s, 1 H), 4.05 (br. s, 1 H), 5.72 (s, 1 H), 7.36−7.48 (m, 6 H), 7.66 (d, *J* = 7.1 Hz, 2 H), 7.72 (d, *J* = 7.1 Hz, 2 H).

3,14-*Bis*-*epi*-19-nor-23-yn-1α,25-dihydroxy Vitamin D_3 (54): This compound was prepared from **50** as described for **3** from **47**. R_f = 0.2 (MeOH/CH_2Cl_2, 1:20). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.96 (s, 3 H), 1.02 (d, *J* = 6.6 Hz, 3 H), 1.30 (m, 5 H), 1.50(s, 6 H), 1.51−2.20 (m, 16 H), 2.25 (dd, *J* = 3.8, 16.6 Hz, 1 H), 2.29 (dd, *J* = 6.2, 13.4 Hz, 1 H), 2.55 (dd, *J* = 6.2, 13.6 Hz, 1 H), 3.99 (m, 2 H), 6.07 (d, *J* = 11.3 Hz, 1 H), 6.27 (d, *J* = 11.3 Hz, 1 H).

7,8-*Z* Isomer of 54: R_f = 0.2 (MeOH/CH_2Cl_2, 1:20). − UV (MeOH): λ_{max} = 242, 250, 259 nm. − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.98 (s, 3 H), 1.03 (d, *J* = 6.5 Hz, 3 H), 1.41 (m, 2 H), 1.51 (s, 6 H), 1.52−2.45 (m, 18 H), 2.47 (dd, *J* = 2, 14 Hz, 2 H), 2.55 (m, 1 H), 2.68 (t, *J* = 10.0 Hz, 1 H), 3.98 (m, 2 H), 6.13 (d, *J* = 11.1 Hz, 1 H), 6.22 (d, *J* = 11.4 Hz, 1 H).

Compound 53, Intermediate for 1-*epi* Analogues: This compound was prepared from **35** in 2 steps as described for **50** and **51** from **38a**. Ratio **53/52**, 7:1. **Compound 53**, HPLC retention time: 10.8 min. (Et_2O/isooctane/MeOH/CH_2Cl_2, 100:100:1:20). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.94 (s, 3 H), 1.04 (s, 9 H), 1.05 (d, *J* = 6.0 Hz, 3 H), 1.30 (m, 3 H), 1.52 (s, 6 H), 1.78 (m, 1 H), 1.80- 2.30 (m, 17 H), 2.37 (m, 1 H), 2.46 (m, 1 H), 3.85 (m, 1 H); 4.06 (m, 1 H), 5.71 (d, *J* = 11.3 Hz, 1 H), 6.21 (d, *J* = 11.3 Hz, 1 H), 7.38 (br. t, *J* = 7.0 Hz, 4 H), 7.45 (m, 2 H), 7.65 (d, *J* = 6.8 Hz, 2 H), 7.71 (d, *J* = 6.81 Hz, 2 H).

Compound 52: HPLC retention time: 12.8 min. (Et_2O/isooctane/MeOH/CH_2Cl_2, 100:100:1:20). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.97 (s, 3 H), 1.03 (d, *J* = 6.53 Hz, 3 H), 1.6 (s, 9 H), 1.30 (m, 3 H), 1.49 (s, 6 H), 1.50−2.20 (m, 16 H), 2.25 (dd, *J* = 3.4, 16.4 Hz, 1 H), 2.41(m, 2 H), 2.56 (m, 1 H), 3.83 (m, 1 H), 3.98 (m, 1 H), 6.08 (s, 2 H), 7.38 (t, *J* = 7.0 Hz, 4 H), 7.44 (br. t, *J* = 7.0 Hz, 2 H), 7.66 (d, *J* = 6.92 Hz, 2 H), 7.70 (d, *J* = 7.03 Hz, 2 H).

14-*epi*-19-*nor*-23-yn-1β,25-dihydroxy Vitamin D_3 (55): This compound was prepared from **53** as described for **3** from **47**. R_f = 0.2 (MeOH/CH_2Cl_2, 1:20). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.95 (s, 3 H), 1.02 (d, *J* = 6.6 Hz, 3 H), 1.30 (m, 5 H), 1.50(s, 6 H),

1.51−2.0 (m, 13 H), 2.04 (dd, J = 8, 9 Hz, 1 H), 2.10 (dd, J = 8, 9 Hz, 1 H), 2.27 (dd, J = 4, 13 Hz, 1 H), 2.30 (dd, J = 6, 13 Hz, 1 H), 2.41 (m, 1 H), 2.59 (m, 1 H), 4.01 (m, 2 H), 6.06 (d, J = 11.5 Hz, 1 H), 6.27 (d, J = 11.5 Hz, 1 H).

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