Synthesis of 2-Methyl and Ethyl-Substituted 19-*nor*-1α,25-Dihydroxyvitamin D_3 Analogues via the Cyclovitamin Strategy

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The synthesis of several 19-*nor*-2-alkyl-1α,25-dihydroxyvitamin D_3 analogues (**5**–**14**) is described following the cyclovitamin strategy. Starting from *all-cis* methyl 3,5-dihydroxy-4-alkyl-1-cyclohexanecarboxylate (**29**), the eight stereoisomeric A-ring-precursor 2-*tert*-butyldiphenylsilyloxy-3α-formyl-1-alkylbicyclo[3.1.0]hexanes (**39**, **44**, **46**, **63**, **65**, **67**, **69**, **71**) were prepared in two series: **a** (R = methyl) and **b** (R = ethyl). In particular, from the coupling of **39** and the lithiated compounds derived from the CD-ring bromides **20** and **21** possessing the natural or the 23-yne side chain, the title derivatives **5**–**14** were synthesized.

Introduction

The hormonally active form of vitamin D_3, 1α,25-dihydroxyvitamin D_3 [**1**, 1α,25$(OH)_2D_3$] generates 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$(OH)_2D_3$ (**1**) 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 decoupling 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] It is now well established that removal of the 19-exomethylene function is beneficial; 19-*nor*-1α,25-dihydroxyvitamin D_3 (**2**) displays a smaller calcemic effect (10% of **1**) while retaining good cell-differentiating properties.[3,4] We have further observed that, among other modifications, 14-epimers such as **3** and **4** induce interesting physiological activities; they are also among the best analogues known in that they show smaller hypercalcemic effects (circa 0.1% of **1**).[5–8] In continuation of our research on the structure-activity relationship of 19-*nor* compounds, we report the synthesis of 19-*nor*-2-methyl- and 2-ethyl-substituted analogues with both natural and 14-*epi*-CD ring systems and with the natural or 23-yne (20*R* and 20*S*) side chain (Figure 1).

Considerable attention has been devoted to 2-substituted analogues of 1α,25-dihydroxyvitamin D_3.[9] In the 19-*nor* series, the synthesis of **5a**, **6a**, the corresponding 2-hydroxymethyl analogues, and their 20-epimers has been described via a Horner–Wittig reaction, known as the Lythgoe coupling,[10] involving phosphane oxides such as **15** and **16** (Scheme 1).[11,12] Mikami et al.[12b] synthesized the A-ring precursor **16** for **5a** in a stereoselective fashion. DeLuca et al.[11] obtained a 1:1 mixture of **5a** and **6a** upon nonselective catalytic hydrogenation of 2-methylene-19-*nor*-1α,25-dihydroxyvitamin D_3 (from **15**) and separation by reversed phase HPLC. Application of the Lythgoe strategy in a stereoselective synthesis involving a 19-*nor*-2-substituted phosphane oxide (steroid numbering) such as **16** is hampered by the fact that this particular A-ring precursor no longer possesses a pseudo C_2 axis of symmetry as in **17**; consequently, a control element[12b] for the 5,6-double bond geometry relative to the configuration at C-2 is required.

We decided to study a convergent synthesis of the title compounds via the cyclovitamin approach, for which we had some precedent for selectivity during the solvolytic step[8] (vide infra, Scheme 1). This concept is an alternative to the more widely used Lythgoe coupling process[10] involving C-8 ketones such as **18** or **19** (vitamin D numbering).

The cyclovitamin approach is based on reaction of **20** or **21** with **23** or **24**, respectively, and was developed by Kametani et al.,[13] Wilson et al.,[14] and Uskokovic et al.[15] for

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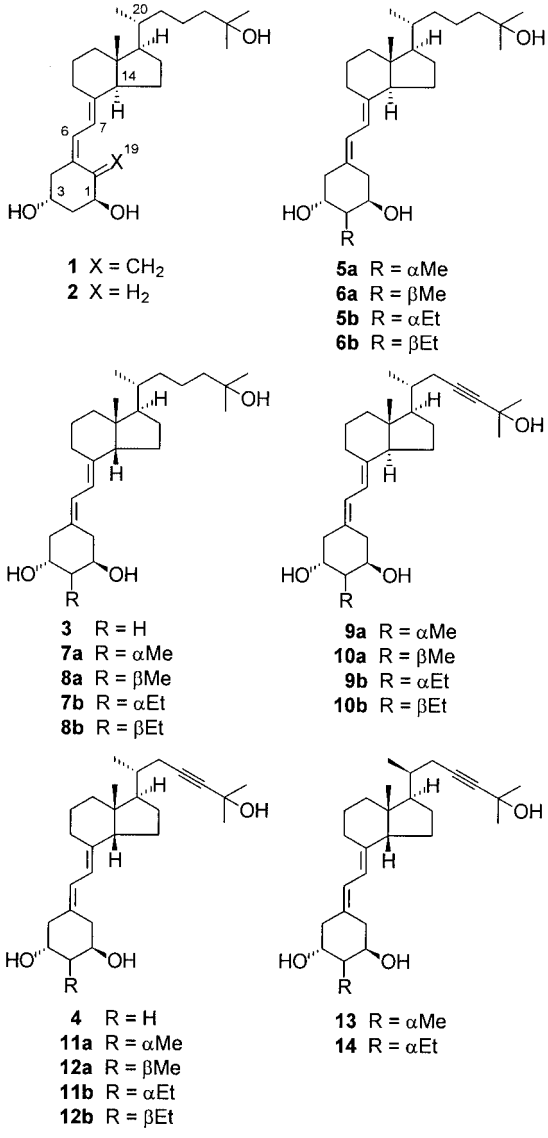
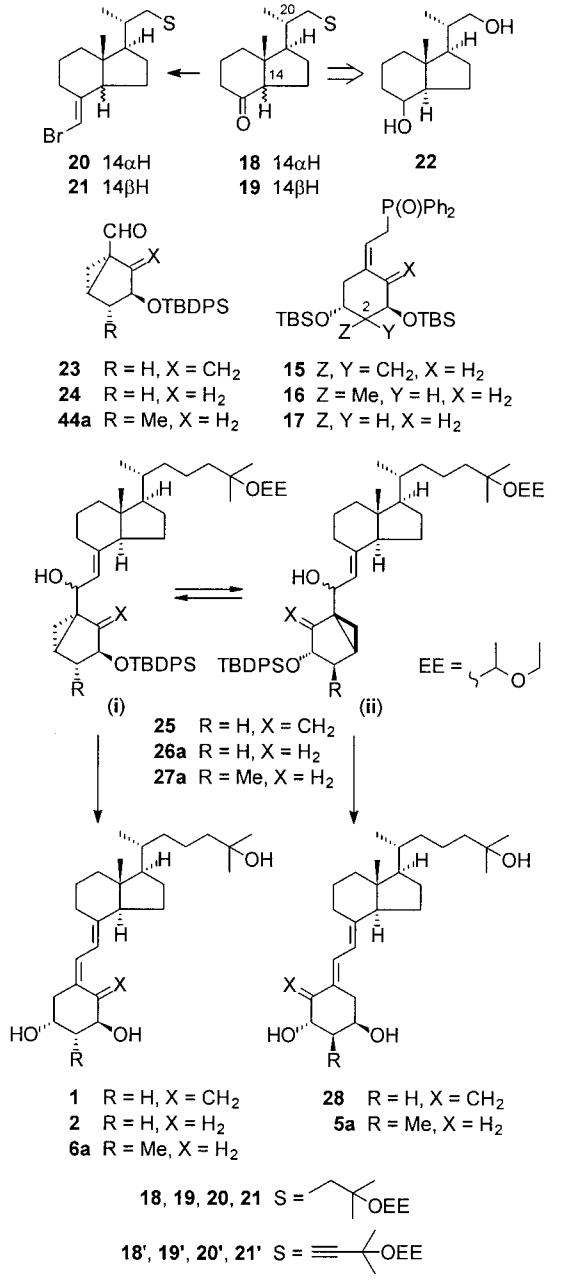


Figure 1. 1α,25-Dihydroxyvitamin D_3 analogues.



Scheme 1. Synthetic intermediates en route to 1α,25-dihydroxyvitamin D_3 analogues.

the synthesis of **1**, and by our group for the synthesis of 19-*nor* analogues such as **2**, **3** and **4**.[7,8] The intermediate cyclopropyl alcohols such as **25**, **26a** or **27a** are then subjected to an acid-catalyzed stereoselective solvolysis, which may proceed via two rotamers around the 5,6-double bond, in equilibrium with each other. For example, starting from **20** and **23**, rotamer **i** of **25** gives **1** with the desired 3β and 5,6-*Z* configurations, while rotamer **ii** leads to 5,6-*E* isomer **28**. Depending on substituents and reaction conditions, the observed **1**:**28** ratio is at best 4:1.[16] Evidently this is of no consequence for the synthesis (starting from **24**) of 19-*nor* analogues such as **2** in which the A-ring has a pseudo-C_2 axis of symmetry. After introduction of a substituent at C-2, as in **27a** (from **44a**), a mixture of epimers **5a** and **6a** could occur; however, one rotamer might be more populated. We have found this to be the case during solvolysis directed towards 1- and/or 3-epimers of **2**, where this symmetry element is also absent, giving selectivities up to 18:1.[8] We observed that the bulky TBDPS protective group is highly influential for this excellent ratio.[17b] This selectivity gave us the incentive for exploring the cyclovitamin approach for the synthesis of the title compounds.

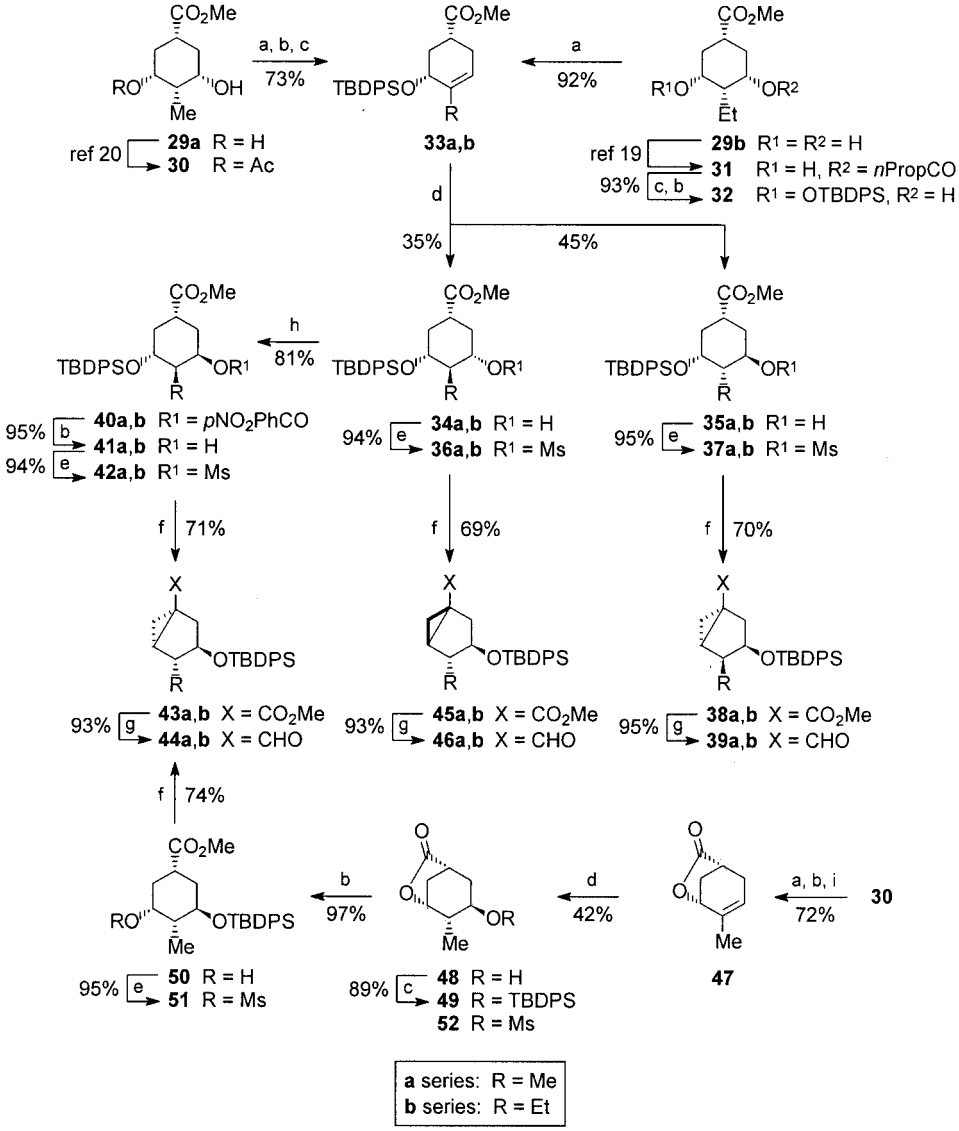
The "upper fragments" **20** and **21**, with both the natural and 23-yne side chains, have already been described.[8] The *cis*-fused C-8 ketones **19** (steroid numbering) can be obtained by base-catalyzed equilibration of **18**.[8,17] The *trans*-fused isomers are generally produced from the Inhoffen–Lythgoe diol **22**.[18] The synthesis of vinylic bromide **20** was first reported by Trost et al.[19] and by us in the case of the *cis*-fused hydrindane **21**.[8,17b] The precursor for the 20*S*-analogues **13** and **14** were obtained from the previously described 20-epimer of **19**′.[7]

Results and Discussion

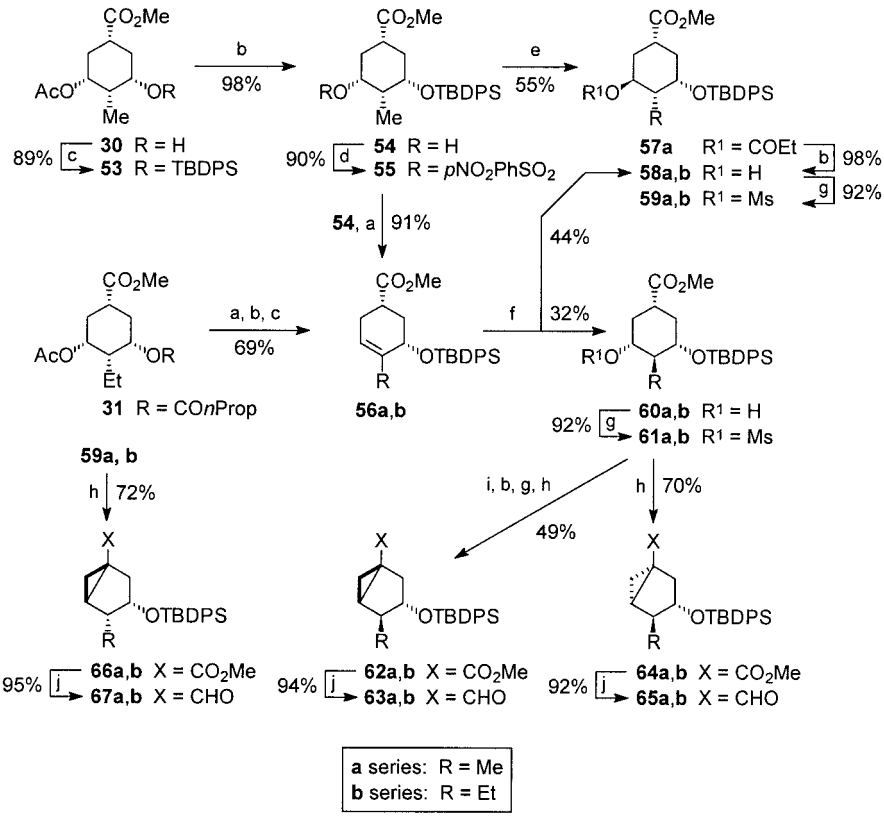
The present report concentrates on the synthesis of the bicyclo[3.1.0]hexane A-ring precursors such as **44a** (R = Me; **a**-series) and its epimers and homologues (R = Et; **b**-series). The synthesis starts from methyl *all-cis*-3,5-dihydroxy-4-methyl-cyclohexanecarboxylate (**29a**) and the 4-ethyl homologue **29b** for which we have already described the enzyme-catalyzed asymmetrization.[20]

Transesterification of **29a** with vinyl acetate, employing SAM II, afforded enantiopure **30** in high yield. For the ethyl-substituted series, the corresponding dibutyrate of **29b** was the best substrate; CCL- or SAM II-mediated monohydrolysis to **31** is completely enantiotoposelective (see Scheme 2; CCL is lipase type II from *Candida cyclindracea*, SAM II is lipase from *Pseudomonas fluorescens*). An important feature of key intermediates **30** and **31** is the fact that they permit access to all stereoisomeric bicyclic A-ring precursors. Essential transformations are (i) inversions directed towards the required relative configuration(s) at C-1, C-2 and C-3 (steroid numbering) and (ii) cyclopropane ring formation via a leaving group at an oxy-substituent. As **30** and **31** belong to different enantiomeric series, the order of the initial steps must be inverted (e.g. **30** → **33a**; a,b,c and **31** → **33b**; c,b,a) for the synthesis of homologues with identical absolute configuration. The yields and conditions given in Schemes 2, 3 and 4 are for methyl-substituted products (**a**); similar results were observed for the 2-ethyl homologues (**b**).

We have previously found that in the case of 4-unsubstituted 3,5-dihydroxy-cyclohexanecarboxylates,[8] inversions under Mitsunobu conditions[21] gave excellent results. How-



Scheme 2. (a) DIAD, Ph_3P, THF, room temperature, 3 h, (b) 0.5 equiv. K_2CO_3, MeOH, room temperature, 6 h; (c) TBDPSCl, imidazole, DMAP (cat.), DMF, room temperature, 10 h; (d) BH_3, THF, 0 °C, 2.5 h; ii) H_2O_2, satd. $NaHCO_3$, 0.5 h; (e) MsCl, Et_3N, CH_2Cl_2, 0 °C, 3 h; (f) *t*BuOK, *t*BuOH/THF (3:2), 45–50 °C, 0.5 h; (g) i) $LiAlH_4$, THF, 0 °C, 1.5 h; ii) TPAP, NMO, CH_2Cl_2, room temperature, 0.5 h; (h) pNO_2PhCO_2H, DIAD, Ph_3P, THF, room temperature, 24 h; (i) PPTS, PhH, 80 °C, 24 h.



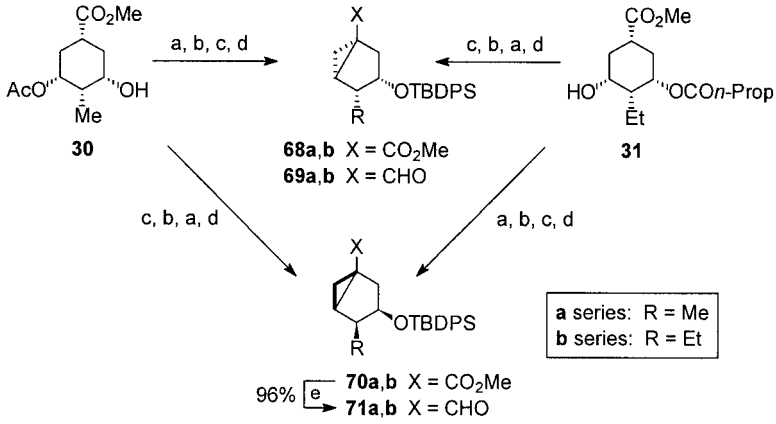
Scheme 3. (a) DIAD, Ph_3P, THF, room temperature, 3 h; (b) 0.5 equiv. K_2CO_3, MeOH, room temperature, 6 h; (c) TBDPSCl, imidazole, DMAP (cat.), DMF, room temperature, 10 h; (d) pNO_2PhSO_2Cl, Et_3N, DMAP (cat.), CH_2Cl_2, room temperature, 10 h; (e) $EtCO_2Cs$, 18-crown-6, toluene, 110 °C, 4 h; (f) i) BH_3, THF, 0 °C, 2.5 h; ii) H_2O_2, satd. $NaHCO_3$, 0.5 h; (g) MsCl, Et_3N, cat. DMAP, CH_2Cl_2, 0 °C, 3 h; (h) *t*BuOK, *t*BuOH/THF (3:2), 45–50 °C, 0.5 h; (i) pNO_2PhCO_2H, DIAD, Ph_3P, THF, room temperature, 24 h; (j) i) $LiAlH_4$, THF, 0 °C, 1.5 h; ii) TPAP, NMO, 4-Å mol. sieves, CH_2Cl_2, room temperature, 0.5 h.

ever, when the hydroxy function is flanked by a *cis*-vicinal alkyl substituent, facile *anti*-elimination occurs in high yield, as is shown by the reaction of acetate **30** to **32a** (91% yield of substituted cyclohexene) and of **32** to **33b**. We later observed that in the case of a vicinal *trans*-relation, the Mitsunobu inversion proceeds normally (see transformation **34a**,**b** to **40a**,**b**, Scheme 2).

Although we found that inversion of the *p*-nitrophenylsulfonate derivatives with cesium propionate[22] (see, for example **55** to **57a** in Scheme 3) provides an acceptable stereoselective transformation, we decided to exploit the easy formation of cyclohexene intermediates. Hydroboration of **33a**,**b** was nonselective and afforded a separable mixture (circa 1:1) of **34a**,**b** and **35a**,**b**. Both diastereoisomers are suitable for further transformation. The mesylates **37a**,**b** led, upon base-mediated cyclopropane formation and subsequent conversion of the ester functions in **38a**,**b** into formyl groups, to **39a**,**b**, the precursors for the 2α-alkyl-19-*nor*-1α,25-dihydroxyvitamin D_3 analogues **5a**,**b**, **7a**,**b**, **9a**,**b** and **11a**,**b**. On the other hand, Mitsunobu inversion of the hydroxy groups in **34a**,**b** opens, via **41a**,**b**, a route to **44a**,**b**, the precursors for the epimeric 2β-alkyl vitamin D_3 analogues **6a**,**b**, **8a**,**b**, **10a**,**b** and **12a**,**b**. Finally, mesylation of **34a**,**b** followed by cyclopropane formation and ester reduction afforded **46a**,**b**, the precursors for analogues with a 1α,2β,3α configuration.

We also investigated stereoselective routes via lactonic key intermediates. For example, hydroboration of lactone **47**, available from mono-acetate **30** (3 steps), gave **48** in rather low yield, which was due to concomitant lactone reduction. After protection of the hydroxy function, **49** is an intermediate, via **50** and **51**, for the previously-described A-ring precursor **44a**. Likewise, it is clear that after initial mesylation of **48**, mesylate **52** is a potential intermediate for **37a** and hence for precursor **39a**. Despite the problem associated with the hydroboration step of **47**, this represents an acceptable route for the synthesis of a particular vitamin D_3 analogue. Because of the present purpose to synthesize and evaluate all stereoisomers, the route via cyclohexenes **33a**,**b** and **56a**,**b** (in Scheme 3) was selected.

The enantiomers (**63a**,**b**, **65a**,**b** and **67a**,**b**, respectively) of the A-ring precursors **46a**,**b**, **39a**,**b** and **44a**,**b** can be constructed via **56a**,**b** (Scheme 3) upon applying the same set of reactions described in Scheme 2. Key intermediates **56a**,**b**, the enantiomers of **33a**,**b**, were obtained from monoesters **30** and **31b** by inverting the order of the initial 3-step sequence shown in Scheme 2. Hydroboration of **56a**,**b** gave separable mixtures of **58a**,**b** (intermediates for **67a**,**b**) and



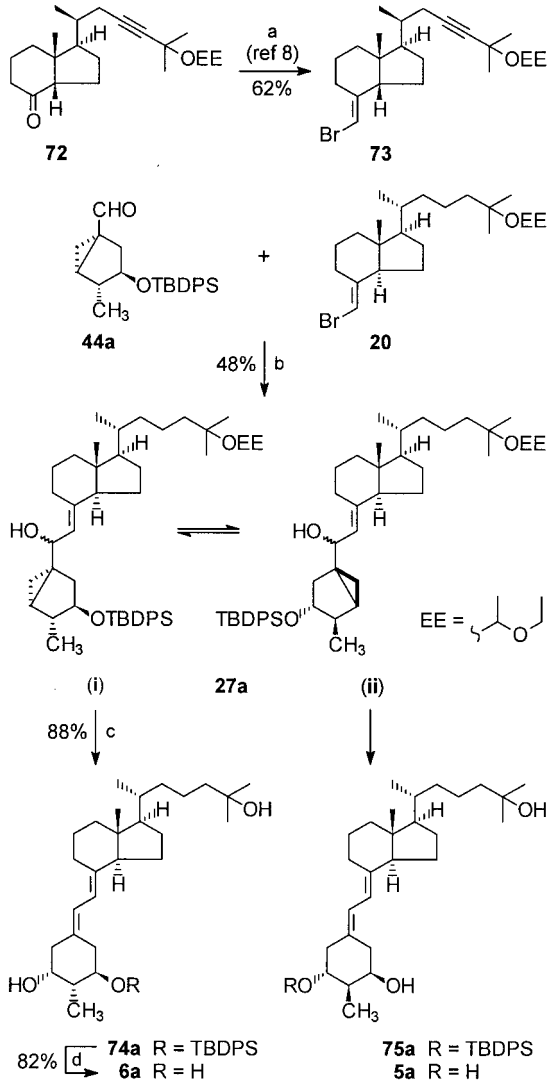
Scheme 4. (a) TBDPSCl, imidazole, DMAP (cat.), DMF, room temperature, 10 h; (b) 0.5 equiv. K_2CO_3, MeOH, room temperature,10 h; (c) MsCl, Et_3N, DMAP (cat.), CH_2Cl_2, 0 °C, 3 h; (d) *t*BuOK, *t*BuOH/THF, 45–50 °C, 0.5 h; (e) i) $LiAlH_4$, THF, 0 °C, 1.5 h; ii) TPAP, NMO, CH_2Cl_2, room temperature, 0.5 h.

60a,**b**. The mesylates **61a**,**b** of the latter led to A-ring precursors **65a**,**b**, while initial Mitsunobu inversion of **60a**,**b** (81% yield) opened the route to **63a**,**b**.

As mentioned above, an alternative for the abortive Mitsunobu reaction when the hydroxy function is flanked by a *cis*-vicinal 4-alkyl substituent consists of inversion of the corresponding *p*-nitrophenylsulfonate with cesium propionate.[22] Thus, **54** led, via **55**, to **57a**, the intermediate for A-ring precursor **67a**.

The synthesis of the two remaining stereoisomers **69a**,**b** and **71a**,**b** (Scheme 4) does not require an inversion step. Thus **69a** was obtained starting from **30** via protection, hydrolysis, mesylation and cyclopropane formation; **69b** was formed from **31** upon changing the order of the reaction sequence. Again, adapting the same set of reactions led to enantiomers **71a**,**b**.

With the A-ring precursors in hand, we turned our attention to the construction of the vitamin D_3 skeleton by the cyclovitamin D strategy described in Scheme 1. The vinylic bromide **73** (Scheme 5), precursor for the (20*S*)-analogues **13** and **14**, was obtained from ketone **72**[7] as described for **21′**.[8,17b] Reaction of the aldehydes (e.g. **44a**) with the vinylic lithium derivative of **20**[8] led to **27a** as a 1:1 epimeric mixture at C-6[23] (Scheme 5). The subsequent acid-catalyzed solvolysis involving stereoselective attack of water proceeds by way of two rotamers, **i** and **ii**, around the 5,6-bond (see also Scheme 1) in equilibrium with each other. It is clear that reaction via rotamer **i** of **27a** will lead to the introduction of a hydroxy group at C-3 (**74a** and hence **6a**), while rotamer **ii** will introduce a C-1 hydroxy group (**75a** and hence **5a**). In order to be able to distinguish the stereoisomers **5a** and **6a**, the TBDPS protective group was chosen at the origin, as it is stable under the solvolysis conditions. As anticipated, and in parallel with previous observations,[8] the major product **27a** arises from attack at C-3; **74a** and **75a** were formed in a 88:12 ratio. This ratio was somewhat more pronounced in the *cis*-CD ring (14-*epi*) series; the sequence starting from **44a** and **21** led to the 1-TBDPS ether of **8a** and the 3-TBDPS ether of **7a** in a 94:6 ratio. This



Scheme 5. (a) $Ph_3P^+CH_2Br\ Br^-$, KHMDS, THF, 0 to 20 °C, 4 h; (b) *t*BuLi, –70 to –10 °C, THF, 1 h; (c) PTSA, dioxane/H_2O (1:1), 55–60 °C, 4 h; (d) TBAF, THF, room temperature, 72 h.

Table 1. Selected ^{1}H NMR spectroscopic data of 1α,25-dihydroxyvitamin D_3 analogues and their 1- and 3-TBDPS ethers (δ in ppm).

1α,25-$(OH)_2$ Vitamin D_3 analogues				1-OTBDPS					[a]	3-OTBDPS			
	H-6	H-7	H-1 or H-3	H-6	H-7	(H-6–H-7) $\Delta\delta$	H-1	H-3	%	H-6	H-7	(H-6–H-7) $\Delta\delta$	H-1 or H-3
5a	6.37	5.83	3.96, 3.61	6.19	5.61	0.58	4.10	3.82	88	5.99	5.77	0.22	4.15, 3.75
5b	6.38	5.83	4.14, 3.63	6.17	5.59	0.58	4.15	3.95	83	5.94	5.84	0.09	4.10, 3.89
6a	6.26	5.87	3.90, 3.51	6.14	5.46	0.58	3.72	3.94	88	6.06	5.89	0.17	4.05, 3.82
6b	6.26	5.87	4.09, 3.54	6.14	5.46	0.68	3.77	4.12	83	5.94	5.84	0.10	4.10, 3.87
7a	6.31	6.01	3.94, 3.59	6.08	5.54	0.54	4.07	3.83	94	[b]			
7b	6.32	6.01	4.15, 3.64	6.06	5.50	0.56	4.12	3.96	94	[b]			
8a	6.19	6.05	3.90, 3.52	6.01	5.29	0.72	3.69	3.93	94	[b]			
8b	6.19	6.06	4.09, 3.50	6.01	5.28	0.73	3.75	4.11	92	[b]			
9a	6.36	5.82	3.96, 3.61	6.18	5.59	0.57	4.10	3.81	87	5.98	5.78	0.20	4.00, 3.72
9b	6.38	5.83	4.14, 3.64	6.17	5.58	0.59	4.15	3.94	87	5.97	5.76	0.21	4.15, 3.88
10a	6.44	6.04	4.07, 3.55	6.14	5.47	0.67	3.73	3.95	90	5.91	5.82	0.09	4.01, 3.79
10b	6.26	5.87	4.10, 3.55	6.04	5.47	0.67	3.79	4.12	83	5.94	5.85	0.09	4.11, 3.86
11a	6.30	6.02	3.98, 3.60	6.07	5.54	0.53	4.09	3.84	94	5.70	5.47	0.23	3.97, 3.72
11b	6.31	6.03	4.15, 3.64	6.05	5.52	0.53	4.14	3.96	93	5.68	5.48	0.20	4.15, 3.76
12a	6.19	6.06	3.89, 3.54	6.00	5.31	0.69	3.73	3.95	94	6.02	5.83	0.19	4.14, 3.81
12b	6.19	6.07	4.10, 3.57	6.05	5.31	0.74	3.77	4.11	92	6.04	5.84	0.20	4.27, 3.90
13	6.30	6.01	3.96, 3.60	6.06	5.54	0.52	4.07	3.83	91				
14	6.32	6.02	4.15, 3.63	6.05	5.51	0.54	4.13	3.96	75				
1-*epi*-9a	6.31	6.08	3.95, 3.90	6.25	5.69	0.56	4.07	3.74	93	6.13	5.99	0.14	4.00, 3.81
1-*epi*-10a	6.32	6.08	3.96, 3.90	6.24	5.67	0.57	4.09	3.73	88	6.12	6.00	0.12	3.99, 3.81

[a]% of 1-OTBDPS ether found in the mixture obtained after solvolysis (step b in Scheme 5). [b] Insufficient product.

difference between *trans*- and *cis*-fused hydrindanes was consistently found (Table 1) and was independent of the configuration of the bicyclic A-ring fragment.

The structure of **74a** was proven by NOE and COSY-2D experiments. The vinylic protons 6-H and 7-H (AB system; δ = 6.14 and δ = 5.46; J = 11.3 Hz)[24] gave an NOE enhancement with the 4-protons and with 10α-H, respectively. The assignment of protons 4 and 10α followed from the observation of an NOE enhancement with 1-H (δ = 3.72 ppm) and 3-H (δ = 3.94 ppm), respectively. Localization of the latter protons follows from the trichloroacetate of **74a**. For 3-H, a chemical shift from δ = 3.94 to δ = 5.17 was observed, and COSY-2D experiments and NOE enhancements correlated with those obtained for **74a**. These results are in full agreement with those obtained for the 14-*epi*, 19-*nor* analogues unsubstituted at C-2 such as **3** and its 1- and/or 3-epimers.[8]

It is noteworthy that for the 1-OTBDPS ether series 1-H is downfield relative to 3-H for the isomers with a 2α-substituent (**5**α, **7**α, **9**α, **11**α, **13**α, **14**α), while a reversed situation is observed for the 2β-substituted isomers **6**β, **8**β, **10**β and **12**β (see Table 1). Identical observations have been made for the stereoisomers with varying C-1, C-2 and C-3 configurations in both the 2-methyl and 2-ethyl-substituted series.

In a few cases in the 14-*epi* series an NOE enhancement between 7-H and an aromatic proton of the 1-OTBDPS substituent was also observed, which by itself is a structural proof. The simplest tool for structural identification in these series is provided by a consistent upfield chemical shift of 7-H in 1-OTBDPS ethers for which 6-H and 7-H give a $\Delta\delta$ = 0.5–0.7 (Table 1). This upfield shift is probably due to the anisotropy of a phenyl group of the TBDPS ether, which is in fact confirmed by the observed NOE enhancement (7-H, H-Ar). The regioisomers (3-OTBDPS) show the signals for 6-H and 7-H closer together ($\Delta\delta$ = 0.1–0.3) with now a small upfield shift for 6-H compared to the δ-values observed for the unprotected title compounds. Finally, TBDPS ether cleavage led to the 2-substituted analogues **5** to **13**.

It is generally accepted that the presence of the 1α-hydroxy function is essential for receptor binding and biological activity and that these properties are influenced by the substitution pattern (see, for example **1** vs. **2**) and the derived conformational behaviour of the A-ring. Therefore, in order to investigate the A-ring conformation–biological activity relationships we decided to prepare not only analogues **5** to **14** but also others epimeric at C-1 and C-3. Two examples are 1-*epi*-**9a** and 1-*epi*-**10a** obtained by coupling aldehydes **69a** and **71a**, respectively, (Scheme 4) with vinylic bromide **21′**.

In conclusion, we have shown that the cyclovitamin route occurs in good stereoselectivity. Biological activities will be published elsewhere.

Experimental Section

General Remarks: All reactions were carried out under argon or nitrogen with magnetic stirring. All solvents were purified or dried according to standard procedures. Solutions were dried with anhydrous $MgSO_4$. The solvent was removed from the filtered solutions on a rotary evaporator. Column chromatography separations were performed on silica gel, eluents are given between brackets. HPLC separations were performed on a Knauer 64, a Waters 6000 A or a Kontron 420 delivery system with refractive index detection; eluents are given between brackets. Optical rotations were measured with a Perkin–Elmer 421 polarimeter and at room temperature unless otherwise stated. IR spectra were recorded on a Perkin–Elmer

FTIR-1600 spectrometer and mass spectra on a HP-5988 spectrometer. The ^{1}H NMR spectra were recorded at 500 MHz (WH-Bruker) and ^{13}C NMR spectra at 200 MHz (Varian Gemini), unless otherwise noted. The chemical shifts are expressed in ppm relative to TMS, and coupling constants are in Hz. Elemental analyses were carried out by ICHOR, Université Pierre et Marie Curie (Paris, France).

Methyl (1*R*,5*R*)-5-(*tert*-Butyldiphenylsilyloxy)-4-methyl-3-cyclohexene-1-carboxylate (33a): To a stirred solution of **30** (1.3 g, 5.65 mmol) and Ph_3P (4.5 g, 17.16 mmol in THF, 15 mL), DIAD (3.6 mL, 17.16 mmol, 95%) was added dropwise at 0 °C. After stirring for 3 h at room temperature, the reaction solution was subjected to flash chromatography (pentane/Et_2O, 3:1) affording a colourless oil. The oil was dissolved in a dry MeOH (20 mL), and then treated with K_2CO_3 (0.36 g, 2.61 mmol). After stirring for 6 h, the solution was poured into H_2O/EtOAc and the separated aqueous layer was extracted with EtOAc. The organic extracts were washed, dried and concentrated. Flash chromatography (isooctane/EtOAc, 4:1) gave the cyclohexenol as crystals from *n*-hexane/acetone [m.p. 70–71 °C. R_f = 0.21 (isooctane/EtOAc, 4:1). $[\alpha]_D$ = –21.6 (c = 1.09, $CHCl_3$). $C_9H_{14}O_3$ (170.21): calcd. C 63.51, H 8.29; found C 63.33, H 8.34]. TBDPSCl (1.55 mL, 98%, 5.99 mmol) was added to a solution of the intermediate (0.83 g, 4.88 mmol), imidazole (0.41 g, 6.02 mmol) and a catalytic amount of DMAP in dry DMF (12 mL) at 0 °C. The resulting mixture was stirred for 10 h at room temperature, and was then poured into H_2O/EtOAc, separated, extracted (EtOAc), washed, dried, and the solvents were evaporated. Chromatography (isooctane/EtOAc, 95:5) gave **33a** (1.68 g, 73% overall) as a colourless oil. R_f = 0.42 (isooctane/EtOAc, 9:1). $[\alpha]_D$ = –82.9 (c = 0.79, $CHCl_3$). IR (KBr film): $\tilde{\nu}$ = 2952, 2857, 1738, 1589, 1472, 1428, 1362, 1308, 1247, 1169 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 7.73–7.37 (m, 10 H), 5.39 (m, 1 H), 4.24 (s, 1 H), 3.59 (s, 3 H), 2.39 (m, 1 H), 2.32–2.02 (m, 3 H), 1.75 (m, 1 H), 1.66 (s, 3 H), 1.07 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 175.2, 137.5, 136.1, 134.4, 133.7, 129.6, 127.6, 121.9, 71.4, 51.6, 38.9, 35.2, 27.9, 27.1, 20.2, 19.5 ppm. MS: *m*/*z* (%) = 408 [M$^+$, 1], 354 (8), 351 [M$^+$ – 57, 73], 299 (5), 273 (6), 213 (100), 183 (75), 137 (70). $C_{25}H_{32}O_3Si$ (408.61): calcd. C 73.49, H 7.89; found C 74.16, H 8.32.

Ethyl Homologue 33b: To a stirred solution of monobutyrate **31** (1.9 g, 7.04 mmol), imidazole (1.43 g, 21.03 mmol mmol) and DMAP (44 mg) in dry DMF (15 mL), TBDPSCl (3.6 mL, 98%, 13.57 mmol)was added dropwise. The mixture was stirred at room temperature for 10 h. The solution was poured into H_2O/EtOAc, separated, extracted (EtOAc), washed, dried and concentrated. The residue was dissolved in dry MeOH (80 mL), and K_2CO_3 (324 mg, 2.35 mmol) was added. The mixture was stirred at room temperature for 6 h, and then the solution was poured into H_2O/EtOAc, separated and extracted (EtOAc). The combined organic extracts were washed, dried and concentrated. The residue was purified by flash chromatography (isooctane/EtOAc, 4:1), affording the intermediate alcohol (2.5 g, 81%) as a colourless oil. The oil (1.9 g, 4.32 mmol) was dissolved in dry THF (30 mL) containing Ph_3P (5.77 g, 22.04 mmol). To this solution DIAD (4.1 mL, 22.04 mmol) was added dropwise at 0 °C. After stirring overnight at room temperature the solution was concentrated. The residue was purified by chromatography (isooctane/EtOAc, 95:5), affording **33b** (1.82 g, 92%). R_f = 0.28 (isooctane/EtOAc, 95:5). $[\alpha]_D$ = –74.8 (c = 0.81, $CHCl_3$). IR (KBr film): $\tilde{\nu}$ = 2957, 2857, 1738, 1429, 1246, 1166, 1108, 1064, 935, 895, 821, 740, 704 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 7.73–7.38 (m, 10 H), 5.36 (br. s, 1 H), 4.26 (br. s, 1 H), 3.58 (s, 3 H), 2.36 (m, 1 H), 2.32 (m, 1 H), 2.16 (m, 2 H), 2.02 (m, 2 H), 1.75 (m, 1 H), 1.05 (s, 9 H), 0.87 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 175.1, 136.7, 134.4, 133.5, 129.5, 127.1, 119.7, 70.2, 51.5, 38.7, 35.3, 27.7, 27.0, 25.3, 19.4, 12.3 ppm. MS: *m*/*z* (%) = 422 [M$^+$, 2], 401 (3), 365 (72), 333 (6), 267 (8), 255 (2), 227 (7), 213 (100), 201 (65), 163 (55), 137 (58), 105 (32), 79 (75), 41 (40). $C_{26}H_{34}O_3Si$ (422.64): calcd. C 73.89, H 8.11; found C 73.72, H 8.27.

Hydroboration of 33a,b (General Procedure): To a stirred solution of **33a** (130 mg, 0.319 mmol), in THF (12 mL) was added dropwise a BH_3 solution (380 µL, 1 M in THF, 0.38 mmol) at 0 °C and stirring was continued at 0 °C for 2.5 h, then H_2O_2 (0.5 mL) and satd.$NaHCO_3$ (3 mL) were added. After stirring for 0.5 h, the reaction solution was poured into H_2O/EtOAc and the organic layer was separated. The aqueous layer was extracted (EtOAc), and the combined organic extracts were washed, dried and concentrated. The residue was purified by chromatography (isooctane/EtOAc, 9:1 to 4:1), affording **34a** (48 mg, 35%) and **35a** (61 mg, 45%).

Methyl (1*R*,3*S*,4*R*,5*R*)-5-(*tert*-Butyldiphenylsilyloxy)-3-hydroxy-4-methylcyclohexane-1-carboxylate (34a): R_f = 0.21 (isooctane/EtOAc, 4:1). $[\alpha]_D$ = –51.8 (c = 0.55, $CHCl_3$). IR (KBr film): $\tilde{\nu}$ =3361, 2932, 2858, 1737, 1589, 1403, 1428, 1363, 1282, 1250, 1173, 1111 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 7.70–7.36 (m, 10 H), 3.59 (s, 3 H), 3.25 (m, 1 H), 3.09 (m, 1 H), 2.12–2.05 (m, 2 H), 1.91 (dt, J = 12.7, 4.3 Hz, 1 H), 1.62 (br.s, 1 H), 1.54–1.38 (m, 3 H), 1.07 (d, J = 6.4 Hz, 3 H), 1.05 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 174.6, 135.9, 134.3, 133.6, 129.7, 127.5, 74.8, 73.0, 51.8, 47.9, 37.9, 37.1, 36.8, 27.1, 19.5, 14.5 ppm. MS: *m*/*z* (%) = 409 (M$^+$ – H_2O – H, 1), 369 (M$^+$ – 57, 10), 337 (25), 309 (5), 199 (75), 153 (25), 121 (15), 93 (100). $C_{25}H_{34}O_4Si$ (426.63): calcd. C 70.38, H 8.03; found C 70.16, H 8.14.

Methyl (1*R*,3*R*,4*S*,5*R*)-5-(*tert*-Butyldiphenylsilyloxy)-3-hydroxy-4-methylcyclohexane-1-carboxylate (35a): R_f = 0.19 (isooctane/EtOAc, 4:1). $[\alpha]_D$ = –38.5 (c = 0.69, $CHCl_3$). IR (KBr film): $\tilde{\nu}$ = 3442, 2954, 2893, 2857, 1735, 1715, 1589, 1463, 1427, 1378, 1273, 1196, 1111 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 7.68–7.36 (m, 10 H), 4.17 (dt, J = 10.8, 4.7 Hz, 1 H), 3.89 (d, J = 3.1 Hz, 1 H), 3.63 (s, 3 H), 2.62 (tt, J = 11.8, 4.4 Hz, 1 H), 1.82–1.66 (m, 5 H), 1.59 (br.s, 1 H), 1.06 (s, 9 H), 0.96 (d, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 175.7, 135.8, 134.3, 129.6, 127.5, 72.0, 68.9, 51.7, 41.3, 36.6, 31.4, 29.6, 27.0, 19.3, 10.7 ppm. MS: *m*/*z* (%) = 369 (M$^+$ – 57, 100), 339 (5), 319 (4), 273 (6), 253 (10), 199 (85), 153 (65), 135 (40). $C_{25}H_{34}O_4Si$ (426.63): calcd. C 70.38, H 8.03; found C 70.21, H 8.20.

Ethyl Homologue 34b: R_f = 0.12 (isooctane/EtOAc, 4:1). $[\alpha]_D$ = –51.1 (c = 0.52, $CHCl_3$). IR (KBr film): $\tilde{\nu}$ = 3421, 2956, 2857, 1736, 1508, 1458, 1428, 1363, 1272, 1242 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 7.69–7.36 (m, 10 H), 3.59 (s, 3 H), 3.43 (dt, J = 10.6, 4.3 Hz, 1 H), 3.33 (dt, J = 10.6, 4.3 Hz, 1 H), 2.05 (m, 2 H), 1.92 (d, J = 12.4 Hz, 1 H), 1.78 (m, 1 H), 1.70 (m, 1 H), 1.54–1.41 (m, 4 H), 1.09 (s, 9 H), 0.69 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 175.2, 136.5, 134.8, 133.9, 130.3, 130.1, 128.2, 127.9, 71.3, 69.8, 52.8, 52.3, 38.3, 37.5, 37.3, 27.6, 19.9, 19.1, 9.4 ppm. MS: *m*/*z* (%) = 383 (M$^+$ – 57, 2), 351 (8), 305 (24), 273 (5), 213 (9), 199 (70), 183 (15), 153 (20), 135 (28), 107 (100), 79 (30). $C_{26}H_{36}O_4Si$ (440.65): calcd. C 70.87, H 8.23; found: C 70.50, H 8.33.

Ethyl Homologue 35b: R_f = 0.17 (isooctane/EtOAc, 4:1). $[\alpha]_D$ = –38.9 (c = 0.81, $CHCl_3$). IR (KBr film): $\tilde{\nu}$ = 3453, 2958, 2858, 1736, 1589, 1460, 1428, 1382, 1255, 1172, 1195, 1110 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 7.67–7.37 (m, 10 H), 4.18 (dt, J = 11.7, 4.6 Hz, 1 H), 4.02 (d, J = 2.8 Hz, 1 H), 3.63 (s, 3 H), 2.60 (m, 1 H), 1.95 (m, 1 H), 1.80 (dt, J = 12.6, 4.1 Hz, 1 H), 1.65–1.45 (m, 5 H), 1.05 (s, 9 H), 0.87 (m, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 176.2, 136.3, 134.8, 134.7, 130.1, 130.0, 128.0, 69.3, 52.1, 49.1, 36.8, 32.6, 30.0, 27.4, 19.7, 17.6, 13.3 ppm. MS: *m*/*z* (%) = 383 (M$^+$ – 57, 90), 351 (6),

333 (5), 305 (4), 273 (10), 213 (50), 199 (100), 183 (58), 153 (60), 135 (65), 107 (48). $C_{26}H_{36}O_4Si$ (440.65): calcd. C 70.87, H 8.23; found C 70.75, H 8.33.

Methyl (1*R*,3*R*,4*R*,5*R*)-5-(*tert*-Butyldiphenylsilyloxy)-3-hydroxy-4-methylcyclohexane-1-carboxylate (41a): To a stirred solution of **34a** (0.55 g, 1.29 mmol), *p*-NO_2PhCO_2H (0.26 g, 1.56 mmol) and Ph_3P (0.41 g, 1.56 mmol) in THF (15 mL) was added DIAD (323 μL, 95%, 1.56 mmol) dropwise at room temperature. After stirring for 24 h, the solution was subjected to flash chromatography (isooctane/EtOAc, 7:3). After concentration, the residue was purified by chromatography (isooctane/EtOAc, 92:8) to give **40a** (0.60 g, 81%). R_f = 0.24 (isooctane/EtOAc, 4:1). $[\alpha]_D$ = –61.4 (*c* = 0.30, $CHCl_3$). IR (KBr film): $\tilde{\nu}$ = 2957, 2858, 1729, 1608, 1529, 1461, 1428, 1349, 1273, 1243 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 8.23 (dd, *J* = 8.8, 1.4 Hz, 2 H), 7.83 (dd, *J* = 8.8, 1.4 Hz, 2 H), 7.75 (dd, *J* = 8.0, 1.4 Hz, 2 H), 7.71 (dd, *J* = 8.0, 1.4 Hz, 2 H), 7.52–7.40 (m, 6 H), 5.33 (d, *J* = 2.2 Hz, 1 H), 3.73 (dt, *J* = 10.6, 4.2 Hz, 1 H), 3.60 (s, 3 H), 2.46 (tt, *J* = 9.1, 3.5 Hz, 1 H), 2.17 (m, 2 H), 1.86 (m, 1 H), 1.73 (dt, *J* = 12.5, 2.2 Hz, 1 H), 1.68 (q, *J* = 12.5 Hz, 1 H), 1.08 (s, 9 H), 0.94 (d, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 174.6, 163.6, 150.4, 136.2, 135.4, 134.4, 133.3, 130.5, 129.7, 127.6, 127.5, 123.5, 75.9, 72.4, 51.9, 42.5, 37.3, 37.2, 30.1, 27.1, 19.4, 14.8 ppm. MS: *m*/*z* (%) = 544 (M^+ – 31, 1), 518 (M^+ – 57, 31), 488 (2), 442 (1), 409 (1), 348 (19), 302 (11), 273 (10), 213 (68), 183 (48), 150 (100). $C_{32}H_{37}O_7NSi$ (575.73): calcd. C 66.76, H 6.48, N 2.43; found C 66.39, H 6.50, N 2.43. A mixture of **40a** (0.59 g, 1.03 mmol) and K_2CO_3 (71 mg, 0.51 mmol) in a dry MeOH (12 mL) was stirred for 6 h at room temperature, and then poured into H_2O/EtOAc, separated and extracted. The organic extracts were washed, dried and concentrated. Flash chromatography (isooctane/EtOAc, 4:1) gave **41a** (0.42 g, 95%) as a colourless oil. R_f = 0.21 (isooctane/EtOAc, 4:1). $[\alpha]_D$ = –72.5 (*c* = 0.50, $CHCl_3$). IR (KBr film): $\tilde{\nu}$ = 3500, 3071, 2956, 2858, 1736, 1462, 1428, 1195, 1111, 1084 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.71–7.35 (m, 10 H), 3.99 (d, *J* = 3.5 Hz, 1 H), 3.75 (dt, *J* = 10.5, 4.3 Hz, 1 H), 3.58 (s, 3 H), 2.59 (tt, *J* = 12.2, 3.6 Hz, 1 H), 1.97–1.91 (m, 2 H), 1.66–1.57 (m, 2 H), 1.49 (m, 1 H), 1.05 (s, 9 H), 1.02 (d, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 175.6, 135.9, 134.7, 133.9, 129.5, 127.5, 72.3, 71.1, 51.6, 43.6, 37.2, 36.4, 35.1, 27.1, 19.5, 14.9 ppm. MS: *m*/*z* (%) = 395 (M^+ – 31, 4), 370 (24), 369 (M^+ – 57, 100), 337 (10), 291 (6), 259 (8), 221 (4), 215 (74), 199 (84), 183 (64), 153 (71), 105 (58), 77 (72).

Ethyl Homologue 41b: Compound **41b** was synthesized from **34b** via **40b** as described for **41a**. R_f = 0.22 (isooctane/EtOAc, 4:1). $[\alpha]_D$ = –63.4 (*c* = 0.71, $CHCl_3$). IR (KBr film): $\tilde{\nu}$ = 3506, 3071, 2956, 2858, 1736, 1472, 1428, 1361, 1266, 1176, 1110 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.67–7.35 (m, 10 H), 4.2 (d, *J* = 3.2 Hz, 1 H), 3.78 (m, 1 H), 3.58 (s, 3 H), 2.57 (m, 1 H), 1.94 (dt, *J* = 13.1, 3.6 Hz, 2 H), 1.60–1.50 (m, 2 H), 1.43 (br. s, 1 H), 1.33 (m, 1 H), 1.13 (m, 2 H), 1.05 (s, 9 H), 0.86 (t, *J* = 7.5 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 175.6, 136.0, 129.6, 129.5, 127.5, 127.4, 71.5, 66.4, 51.6, 50.2, 37.2, 36.2, 35.0, 27.1, 19.7, 19.5, 11.3 ppm. MS: *m*/*z* (%) = 383 (M^+ – 57, 100), 351 (6), 305 (4), 273 (8), 199 (90), 153 (45), 135 (50), 77 (65), 57 (68). $C_{26}H_{36}O_4Si$ (440.65): calcd. C 70.87, H 8.23; found C 71.02, H 8.20.

(1*R*,5*R*)-4-Methyl-6-oxabicyclo[3.2.1]oct-3-en-7-one (47): A solution of **30** (0.36 g, 2.12 mmol) and PPTS (0.49 g, 1.95 mmol) in benzene (25 mL) was stirred at 80 °C for 24 h. The reaction mixture was cooled, diluted with Et_2O and washed with satd. aqueous $NaHCO_3$ and brine. The organic extracts were dried, and the solvents were evaporated. The residue was purified by flash chromatography (isooctane/EtOAc, 4:1), affording **47** (0.19 g, 85%) as colourless crystals from *n*-hexane/acetone. M.p. 47–48 °C. R_f = 0.21 (isooctane/EtOAc, 9:1). $[\alpha]_D$ = +130.1 (*c* = 0.89, $CHCl_3$). IR (KBr film): $\tilde{\nu}$ = 2915, 2855, 1778, 1449, 1436, 1219, 1147, 1116 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 5.43 (br. s, 1 H), 4.53 (d, *J* = 5.2 Hz, 1 H), 2.85 (t, *J* = 3.5 Hz, 1 H), 2.48–2.33 (m, 3 H), 2.06 (d, *J* = 11.1 Hz, 1 H), 1.81 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 179.5, 137.5, 122.2, 78.0, 37.6, 34.4, 28.4, 21.1 ppm. MS: *m*/*z* (%) = 165 (M^+ + 1, 1), 155 (1), 139 (4), 139 (23), 119 (4), 109 (10), 94 (30), 79 (100).

(1*R*,3*R*,4*S*,5*R*)-3-Hydroxy-4-methyl-6-oxabicyclo[3.2.1]octan-7-one (48): The synthesis of **48** was carried out as described for the hydroboration of **33a**, yielding colourless crystals from *n*-hexane/acetone (42%). M.p. 128–129 °C. R_f = 0.21 (isooctane/EtOAc, 1:1). $[\alpha]_D$ = –109.3 (*c* = 0.97, $CHCl_3$). IR (KBr film): $\tilde{\nu}$ = 3448, 2933, 1766, 1359, 1273, 1227 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 4.56 (d, *J* = 5.9 Hz, 1 H), 3.57 (m, 1 H), 2.70 (br. s, 1 H), 2.41 (m, 1 H), 2.32 (m, 1 H), 2.16 (br. s, 1 H), 1.84 (d, *J* = 11.7 Hz, 1 H), 1.65 (m, 1 H), 1.58 (m, 1 H), 1.19 (d, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 178.3, 82.8, 71.5, 42.4, 37.9, 37.6, 35.5, 16.1 ppm. MS: *m*/*z* (%) = 182 (M^+, 1), 161 (5), 154 (4), 128 (14), 113 (48), 97 (54), 67 (50), 55 (100). $C_8H_{12}O_3$ (156.18): calcd. C 61.52, H 7.74; found C 59.92, H 7.78.

Methyl (1*S*,3*R*,4*R*,5*R*)-3-(*tert*-Butyldiphenylsilyloxy)-6-hydroxy-5-methylcyclohexane-1-carboxylate (50): The synthesis of **50** was carried out from **48** as described for **32** from **31**. The yield for the 2 steps was 86%. R_f = 0.21 (isooctane/EtOAc, 4:1). $[\alpha]_D$ = –7.1 (*c* = 0.41, $CHCl_3$). IR (KBr film): $\tilde{\nu}$ = 3445, 2953, 2858, 1734, 1684, 1653, 1559, 1540, 1428, 1362, 1256, 1195 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.66–7.35 (m, 10 H), 4.25 (dt, *J* = 10.7, 6.7 Hz, 1 H), 3.94 (m, 1 H), 3.63 (s, 3 H), 2.92 (m, 1 H), 1.98 (m, 1 H), 1.93 (dt, *J* = 10.1, 6.5 Hz, 1 H), 1.68–1.60 (m, 3 H), 1.05 (s, 9 H), 0.77 (d, *J* = 7.3 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 176.0, 135.7, 133.9, 129.7, 127.6, 73.0, 68.3, 51.8, 41.1, 36.9, 31.4, 30.5, 26.9, 19.3, 10.5 ppm. MS: *m*/*z* (%) = 369 (M^+ – 57, 14), 337 (45), 291 (8), 259 (11), 199 (92), 169 (83), 137 (100), 93 (47). $C_{25}H_{34}O_4Si$ (426.63): calcd. C 70.38, H 8.03; found C 69.93, H 8.22.

Methyl (1*S*,5*S*)-5-(*tert*-Butyldiphenylsilyloxy)-4-methyl-3-cyclohexene-1-carboxylate (56a): The synthesis of **56a** was carried out from **30** via **53** and **54** as described for **33b** from **31**. The yield for the 3 steps was 81%. R_f = 0.30 (isooctane/EtOAc, 9:1). $[\alpha]_D$ = +81.9 (*c* = 1.91, $CHCl_3$). IR (KBr film): $\tilde{\nu}$ = 3070, 2952, 2855, 1738, 1472, 1433, 1428, 1362, 1308, 1247 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.73–7.36 (m, 10 H), 5.39 (t, *J* = 1.8 Hz, 1 H), 4.24 (br. s, 1 H), 3.59 (s, 3 H), 2.38 (m, 1 H), 2.22–2.04 (m, 3 H), 1.75 (m, 1 H), 1.66 (s, 3 H), 1.07 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 175.1, 137.4, 134.4, 133.7, 129.6, 127.6, 121.9, 71.4, 51.6, 38.8, 36.2, 27.9, 27.1, 20.2, 19.5 ppm. MS: *m*/*z* (%) = 408 [M^+, 1], 387 (6), 351 (M^+ – 57, 95), 319 (6), 299 (5), 273 (6), 227 (5), 213 (100), 183 (75), 137 (50), 77 (65).

Ethyl Homologue 56b: R_f = 0.37 (isooctane/EtOAc, 9:1). $[\alpha]_D$ = +74.2 (*c* = 1.09, $CHCl_3$). IR (KBr film): $\tilde{\nu}$ = 2959, 2857, 1738, 1652, 1589, 1456, 1428, 1388, 1246 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.72–7.38 (m, 10 H), 5.37 (m, 1 H), 4.26 (br. s, 1 H), 3.58 (s, 3 H), 2.35 (m, 1 H), 2.30–1.98 (m, 5 H), 1.75 (m, 1 H), 1.05 (s, 9 H), 0.87 (t, *J* = 7.4 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 175.1, 136.7, 134.4, 133.5, 129.5, 127.1, 119.7, 70.2, 51.5, 38.7, 35.3, 27.7, 27.0, 25.3, 19.4, 12.3 ppm. MS: *m*/*z* (%) = 422 (M^+, 2), 401 (3), 365 (88), 333 (8), 287 (9), 255 (3), 227 (7), 213 (90), 183 (50), 137 (58), 107 (45), 79 (100).

Hydroboration of 56a,b: The syntheses of **56a**,**b** were carried out as described for **34a**,**b** and **35a**,**b** from **33a**,**b**.

Methyl (1*S*,3*S*,4*R*,5*S*)-3-(*tert*-Butyldiphenylsilyloxy)-5-hydroxy-4-methylcyclohexane-1-carboxylate (58a): R_f = 0.18 (isooctane/

EtOAc, 4:1). $[\alpha]_D$ = +40.5 (c = 0.66, $CHCl_3$). IR (KBr film): $\tilde{\nu}$ = 3452, 3070, 2953, 2857, 1735, 1717, 1427, 1379, 1272, 1195 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.68–7.36 (m, 10 H), 4.17 (dt, J = 10.8, 4.7 Hz, 1 H), 3.89 (d, J = 2.7 Hz, 1 H), 3.63 (s, 3 H), 2.62 (m, 1 H), 1.81–1.67 (m, 5 H), 1.56 (br. s, 1 H), 1.06 (s, 9 H), 0.96 (d, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 175.7, 135.8, 134.4, 129.7, 127.6, 72.0, 68.9, 56.9, 51.7, 41.3, 36.6, 31.4, 29.6, 27.0, 19.3, 10.6 ppm. MS: m/z (%) = 425 (M^+ – 1, 1), 385 (2), 369 (M^+ – 57, 100), 337 (5), 291 (4), 259 (10), 221 (4), 199 (85), 153 (65).

Methyl (1*S*,3*S*,4*S*,5*R*)-3-(*tert*-Butyldiphenylsilyloxy)-5-hydroxy-4-methylcyclohexane-1-carboxylate (60a): R_f = 0.15 (isooctane/EtOAc, 4:1). $[\alpha]_D$ = +51.2 (c = 0.53, $CHCl_3$). IR (KBr film): $\tilde{\nu}$ = 3444, 3070, 2952, 2857, 1736, 1459, 1427, 1361, 1282, 1249, 1172 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.69–7.36 (m, 10 H), 3.59 (s, 3 H), 3.25 (m, 1 H), 3.08 (m, 1 H), 2.11–2.05 (m, 2 H), 1.92 (d, J = 13.0 Hz, 1 H), 1.53–1.44 (m, 4 H), 1.08 (d, J = 6.4 Hz, 3 H), 1.05 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 174.5, 135.9, 134.3, 133.6, 129.7, 129.6, 127.6, 127.5, 74.8, 73.0, 51.8, 47.9, 37.9, 37.1, 36.8, 30.1, 27.0, 19.4, 14.5 ppm. MS: m/z (%) = 369 (M^+ – 57, 5), 337 (8), 291 (45), 259 (4), 247 (3), 199 (72), 153 (28), 121 (25), 93 (100).

Ethyl Homologue 58b: R_f = 0.17 (isooctane/EtOAc, 4:1). $[\alpha]_D$ = +38.0 (c = 1.13, $CHCl_3$). IR (KBr film): $\tilde{\nu}$ = 3453, 2958, 2858, 1736, 1589, 1460, 1428, 1382, 1255 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.67–7.37 (m, 10 H), 4.18 (dt, J = 11.7, 4.6 Hz, 1 H), 4.02 (d, J = 2.8 Hz, 1 H), 3.63 (s, 3 H), 2.60 (m, 1 H), 1.95 (m, 1 H), 1.80 (dt, J = 12.6, 4.1 Hz, 1 H), 1.65–1.45 (m, 6 H), 1.05 (s, 9 H), 0.87 (m, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 176.2, 136.3, 134.8, 134.7, 130.1, 130.0, 128.0, 69.3, 52.1, 49.1, 36.8, 32.6, 30.0, 27.4, 19.7, 17.6, 13.3 ppm. MS: m/z (%) = 383 (M^+ – 57, 100), 351 (4), 287 (6), 273 (7), 213 (55), 199 (95), 183 (55), 153 (50), 107 (35), 55 (86).

Ethyl Homologue 60b: R_f = 0.12 (isooctane/EtOAc, 4:1). $[\alpha]_D$ = +50.7 (c = 0.52, $CHCl_3$). IR (KBr film): $\tilde{\nu}$ = 3421, 2956, 2857, 1736, 1508, 1458, 1428, 1363, 1272, 1242, 1169, 1110, 1040, 1007, 866, 822, 740, 703, 612 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.69–7.36 (m, 10 H), 3.59 (s, 3 H), 3.43 (dt, J = 10.6, 4.3 Hz, 1 H), 3.33 (dt, J = 10.6, 4.3 Hz, 1 H), 2.05 (m, 2 H), 1.92 (d, J = 12.4 Hz, 1 H), 1.78 (m, 1 H), 1.70 (m, 1 H) 1.54–1.41 (m, 3 H), 1.09 (s, 9 H), 0.89 (m, 1 H), 0.69 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 175.2, 136.5, 134.8, 133.9, 130.3, 130.1, 128.2, 127.9, 71.3, 69.8, 52.8, 52.3, 38.3, 37.5, 37.3, 27.6, 19.9, 19.1, 9.4 ppm. MS: m/z (%) = 383 (M^+ – 57, 3), 351 (9), 305 (32), 273 (6), 199 (64), 183 (15), 153 (18), 135 (35), 107 (100), 79 (35).

Methyl (1*S*,3*S*,4*R*,5*S*)-3-(*tert*-Butyldiphenylsilyloxy)-4-methylcyclohexane-1-carboxylate (58a)

(1) 55: To a stirred solution of **54** (0.21 g, 0.49 mmol), Et_3N (172 μL, 1.23 mmol) and DMAP (6 mg, 0.05 mmol) in CH_2Cl_2 (8 mL) was added *p*-nitrobenzenesulfonyl chloride (136 mg, 0.61 mmol) at 0 °C and stirring was continued for 10 h. The solution was submitted to flash chromatography (isooctane/EtOAc, 9:1) to give **55** (0.27 g, 90%). R_f = 0.27 (isooctane/EtOAc, 4:1). $[\alpha]_D$ = –3.2 (c = 0.40, $CHCl_3$). IR (KBr film): $\tilde{\nu}$ = 3072, 2955, 2858, 1737, 1608, 1535, 1428, 1351, 1288, 1251, 1187 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 8.35 (dd, J = 7.1, 1.7 Hz, 2 H), 7.99 (dd, J = 7.1, 1.7 Hz, 2 H), 7.60–7.35 (m, 10 H), 4.39 (dt, J = 12.1, 4.7 Hz, 1 H), 3.63 (s, 3 H), 3.62 (m, 1 H), 2.17 (m, 1 H), 2.05 (dt, J = 12.9, 1.7 Hz, 1 H), 1.88 (m, 1 H), 1.79 (m, 1 H), 1.73 (m, 1 H), 1.66 (m, 1 H), 1.03 (s, 9 H), 1.00 (d, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 173.4, 150.5, 142.9, 135.6, 133.4, 129.9, 128.8, 127.7, 124.4, 81.9, 70.6, 52.1, 39.5, 37.4, 30.1, 27.8, 26.8, 19.1, 5.4 ppm. MS: m/z (%) = 554 (M^+ – 57, 21), 494 (2), 416 (3), 384 (57), 351 (32), 304 (9), 258 (7), 213 (67), 153 (49), 93 (100). $C_{31}H_{37}O_8SiNS$ (611.79): calcd. C 60.86, H 6.09, N 2.29; found C 61.09, H 6.30, N 2.29.

(2) 57a: To a stirred solution of **55** (0.22 g, 0.36 mmol) and 18-crown-6 (476 mg, 1.80 mmol) was added freshly prepared $EtCO_2Cs$ (371 mg, 1.80 mmol). The mixture was stirred at 110 °C for 2.5 h, and then cooled to room temperature. The mixture was diluted with EtOAc, washed and concentrated. Column chromatography (isooctane/EtOAc, 100:4) afforded **57a** (95 mg, 55%), together with the elimination product. R_f = 0.26 (isooctane/EtOAc, 4:1). $[\alpha]_D$ = +30.7 (c = 0.79, $CHCl_3$). IR (KBr film): $\tilde{\nu}$ = 3049, 2954, 2858, 1738, 1463, 1428, 1274, 1189, 1112 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.67–7.34 (m, 10 H), 4.90 (d, J = 2.9 Hz, 1 H), 3.98 (dt, J = 11.6, 4.7 Hz, 1 H), 3.65 (s, 3 H), 2.48 (m, 1 H), 2.14–1.99 (m, 2 H), 1.93 (m, 1 H), 1.87 (dt, J = 12.8, 4.2 Hz, 1 H), 1.93–1.81 (m, 3 H), 1.06 (s, 9 H), 1.04 (d, J = 7.3 Hz, 3 H), 0.97 (t, J = 7.6 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 175.1, 173.1, 135.8, 133.9, 129.7, 127.5, 74.1, 69.1, 51.8, 38.0, 37.3, 30.9, 27.7, 26.9, 26.7, 19.2, 9.9, 9.0 ppm. MS: m/z (%) = 451 (M^+ – 31, 2), 425 (M^+ – 57, 21), 386 (1), 351 (15), 291 (3), 255 (27), 199 (29), 183 (19), 135 (21), 93 (26). $C_{28}H_{38}O_5Si$ (482.69): calcd. C 69.67, H 7.94; found C 69.82, H 7.82.

(3) 58a: Methanolysis of **57a** as described for **32** gave **58a** in 98% yield.

Mesylate Formation (General Procedure): To a stirred solution of the hydroxy compound and Et_3N (1.5 equiv.) in CH_2Cl_2 (0.04–0.05 mmol/mL) was added dropwise MsCl (1.2 equiv.) at 0 °C, and the stirring was continued for 3 h. The solution was subjected to flash chromatography (isooctane/EtOAc, 7:3). The residue was purified by HPLC (isooctane/EtOAc, 9:1) to give the corresponding mesylate (circa 95%).

Methyl Bicyclo[3.1.0]hexane-1-carboxylate Formation (General Procedure): To a stirred solution of the mesylate (0.03–0.05 mmol/mL) in *t*BuOH/THF (3:2) was added dropwise *t*BuOK (1 M *in t*BuOH, 1.2 equiv.) at 45–50 °C, and stirring was continued for 0.5 h. The solution was poured into H_2O/EtOAc, and then the organic layer was separated. The aqueous layer was extracted with EtOAc and the combined organic extracts were washed, dried and concentrated. The residue was purified by flash chromatography (isooctane/EtOAc, circa 100:3) affording the bicyclic product (circa 70%).

(a) Methyl (1*S*,3*R*,4*S*,5*S*)-3-(*tert*-Butyldiphenylsilyloxy)-4-methylbicyclo[3.1.0]hexane-1-carboxylate (38a): R_f = 0.24 (isooctane/EtOAc, 97:3). $[\alpha]_D$ = –53.8 (c = 0.65, $CHCl_3$). IR (KBr film): $\tilde{\nu}$ = 2957, 2858, 1724, 1472, 1428, 1367, 1292, 1222, 1149 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.65–7.36 (m, 10 H), 3.84 (m, 1 H), 3.64 (s, 3 H), 2.24 (dd, J = 12.5, 8.5 Hz, 1 H), 2.03 (dd, J = 13.5, 6.6 Hz, 1 H), 1.93 (dd, J = 12.7, 7.2 Hz, 1 H), 1.59 (m, 1 H), 1.18 (dd, J = 8.4, 4.8 Hz, 1 H), 1.05 (d, J = 6.9 Hz, 3 H), 1.05 (s, 9 H), 0.56 (t, J = 5.2 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 174.9, 135.7, 133.9, 129.6, 127.6, 72.9, 51.8, 37.2, 34.1, 33.3, 27.2, 27.0, 19.4, 19.5, 15.1 ppm. MS: m/z (%) = 408 (M^+, 1), 353 (M^+ – 57, 21), 351 (87), 296 (13), 237 (8), 213 (100), 183 (58), 135 (61), 77 (67). $C_{25}H_{32}O_3Si$ (408.61): calcd. C 73.49, H 7.89; found C 73.57, H 8.04. Enantiomer (**66a**): $[\alpha]_D$ = +52.2 (c = 0.76, $CHCl_3$).

Ethyl Homologue 38b: R_f = 0.28 (isooctane/EtOAc, 95:5). $[\alpha]_D$ = –36.2 (c = 1.04, $CHCl_3$). IR (KBr film): $\tilde{\nu}$ = 2958, 1724, 1428, 1366, 1233, 1158 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.67–7.38 (m, 10 H), 3.87 (q, J = 7.2 Hz, 1 H), 3.64 (s, 3 H), 2.18 (m, 1 H), 1.92 (m, 1 H), 1.75 (m, 1 H), 1.56 (s, 2 H), 1.22 (m, 2 H), 1.05 (s, 9 H), 0.96 (t, J = 7.4 Hz, 3 H), 0.55 (t, J = 5.1 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 175.1, 135.8, 135.7, 134.0, 129.8, 127.7, 73.1, 51.8, 44.1, 34.3, 31.4, 27.5, 27.0, 21.3, 19.3, 18.5, 12.0 ppm. MS: m/z (%) = 422 (M^+, 27), 365 (M^+ – 57, 26), 337 (3), 287 (5), 213 (40), 199 (52), 153 (22), 135 (100), 79 (35), 57 (25). $C_{26}H_{34}O_3Si$ (422.63): calcd. C

73.89, H 8.11; found C 73.72, H 8.31. Enantiomer (**66b**): $[\alpha]_D$ = +36.5 (*c* = 1.07, $CHCl_3$).

(b) Methyl (1*S*,3*R*,4*S*,5*S*)-3-(*tert*-Butyldiphenylsilyloxy)-4-methylbicyclo[3.1.0]hexane-1-carboxylate (43a): R_f = 0.21 (isooctane/EtOAc, 100:3). $[\alpha]_D$ = –100.4 (*c* = 1.15, $CHCl_3$). IR (KBr film): $\tilde{\nu}$ = 3048, 2956, 2858, 1727, 1589, 1472, 1428, 1369, 1346, 1259, 1199 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.65–7.35 (m, 10 H), 3.63 (s, 3 H), 3.30 (dd, *J* = 12.3, 7.4 Hz, 1 H), 2.27–2.19 (m, 2 H), 1.99 (dd, *J* = 12.8, 7.1 Hz, 1 H), 1.78 (dt, *J* = 8.6, 5.2 Hz, 1 H), 1.07 (m, 1 H), 1.04 (s, 9 H), 0.87 (d, *J* = 6.6 Hz, 3 H), 0.45 (t, *J* = 5.1 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 174.8, 135.9, 134.0, 129.6, 127.5, 77.4, 51.6, 41.7, 36.4, 32.3, 26.9, 26.7, 19.2, 15.9, 15.5 ppm. MS: *m*/*z* (%) = 408 (M^+, 5), 377 (6), 351 (M^+ – 57, 65), 317 (6), 273 (5), 225 (4), 213 (100), 183 (43), 135 (40), 84 (72). $C_{25}H_{32}O_3Si$ (408.61): calcd. C 73.49, H 7.89; found C 73.32, H 8.01. Enantiomer (**62a**): $[\alpha]_D$ = +99.5 (*c* = 0.72, $CHCl_3$). $C_{25}H_{32}O_3Si$ (408.61): calcd. C 73.49, H 7.89; found C 73.47, H 8.06.

Ethyl Homologue 43b: R_f = 0.28 (isooctane/EtOAc, 95:5). $[\alpha]_D$ = –102.9 (*c* = 0.65, $CHCl_3$). IR (KBr film): $\tilde{\nu}$ = 2957, 2857, 1725, 1589, 1461, 1428, 1371, 1327, 1262, 1197, 1154 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.68–7.35 (m, 10 H), 3.63 (s, 3 H), 3.37 (q, *J* = 8.1 Hz, 1 H), 2.21 (m, 2 H), 2.09 (m, 1 H), 1.98 (dd, *J* = 12.8, 7.1 Hz, 1 H), 1.86 (dt, *J* = 8.6, 5.1 Hz, 1 H), 1.08 (q, *J* = 5.0 Hz, 2 H), 1.05 (s, 9 H), 0.90 (t, *J* = 7.1 Hz, 3 H), 0.45 (t, *J* = 5.1 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 175.2, 136.2, 134.3, 129.9, 127.8, 127.7, 76.4, 51.9, 49.3, 36.6, 30.4, 27.3, 26.9, 24.2, 19.5, 16.5, 13.0 ppm. MS: *m*/*z* (%) = 422 (M^+, 1), 407 (2), 365 (M^+ – 57, 75), 309 (4), 213 (90), 199 (20), 183 (35), 135 (30), 77 (45), 41 (48). $C_{26}H_{34}O_3Si$ (422.63): calcd.C 73.89; H 8.11; found C 73.70, H 8.25. Enantiomer **(62b):** $[\alpha]_D$ = +103.5 (*c* = 0.72, $CHCl_3$).

(c) Methyl (1*R*,3*R*,4*R*,5*R*)-2-(*tert*-Butyldiphenylsilyloxy)-4-methylbicyclo[3.1.0]hexane-1-carboxylate (45a): R_f = 0.21 (isooctane/EtOAc, 100:3). $[\alpha]_D$ = +7.1 (*c* = 0.58, $CHCl_3$). IR (KBr film): $\tilde{\nu}$ = 3071, 2956, 2858, 1724, 1589, 1472, 1428, 1390, 1366, 1292, 1222, 1190, 1151, 1112 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.62–7.36 (m, 10 H), 3.89 (d, *J* = 6.3 Hz, 1 H), 3.64 (s, 3 H), 2.45 (dd, *J* = 14.3, 6.2 Hz, 1 H), 2.03 (m, 1 H), 1.94 (d, *J* = 14.3 Hz, 1 H), 1.69 (d, *J* = 1.3 Hz, 1 H), 1.66 (t, *J* = 7.7 Hz, 1 H), 1.47 (m, 1 H), 1.05 (s, 9 H), 0.66 (d, *J* = 7.4 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 175.4, 135.9, 134.2, 129.8, 127.8, 80.7, 51.8, 44.7, 36.7, 35.9, 30.9, 27.1, 20.9, 19.4, 19.0 ppm. MS: *m*/*z* (%) = 408 (M^+, 4), 377 (7), 351 (M^+ – 57, 43), 319 (7), 273 (8), 245 (16), 199 (47), 153 (41), 121 (100), 77 (58). $C_{25}H_{32}O_3Si$ (408.61): calcd. C 73.49, H 7.89; found C 73.36, H 8.01. Enantiomer (**64a**): $[\alpha]_D$ = –7.4 (*c* = 0.70, $CHCl_3$). $C_{25}H_{32}O_3Si$ (408.61): calcd. C 73.49, H 7.89; found C 73.67, H 8.02.

Ethyl Homologue 45b: R_f = 0.26 (isooctane/EtOAc, 95:5). $[\alpha]_D$ = +16.1 (*c* = 1.05, $CHCl_3$). IR (KBr film): $\tilde{\nu}$ = 2959, 2858, 1723, 1560, 1428, 1365, 1297, 1274, 1220, 1150 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.67–7.37 (m, 10 H), 3.96 (d, *J* = 6.6 Hz, 1 H), 3.64 (s, 3 H), 2.37 (m, 1 H), 1.94 (d, *J* = 14.2 Hz, 1 H), 1.83 (t, *J* = 7.3 Hz, 1 H), 1.73 (m, 1 H), 1.68 (t, *J* = 5.2 Hz, 1 H), 1.48 (m, 1 H), 1.03 (s, 9 H), 0.94 (m, 2 H), 0.63 (t, *J* = 7.5 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 174.8, 135.5, 135.4, 129.2, 127.2, 127.1, 78.5, 51.2, 35.9, 34.2, 30.2, 29.6, 26.5, 26.1, 20.3, 18.5, 11.3 ppm. MS: *m*/*z* (%) = 422 (M^+, 2), 365 (M^+ – 57, 82), 213 (100), 199 (20), 183 (40), 153 (10), 135 (60), 77 (42), 49 (70). $C_{26}H_{34}O_3Si$ (422.63): calcd. C 73.89, H 8.11; found C 73.77, H 8.19. Enantiomer **(64b):** $[\alpha]_D$ = –15.9 (*c* = 0.70, $CHCl_3$).

(d) Methyl (1*S*,3*S*,4*R*,5*S*)-2-(*tert*-Butyldiphenylsilyloxy)-4-methylbicyclo[3.1.0]hexane-1-carboxylate (68a): R_f = 0.33 (isooctane/EtOAc, 9:1). $[\alpha]_D$ = –13.2 (*c* = 1.61, $CHCl_3$). IR (KBr film): $\tilde{\nu}$ = 2931, 1724, 1428, 1288, 1224, 1147 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.63–7.36 (m, 10 H), 4.19 (t, *J* = 6.0 Hz, 1 H), 3.62 (s, 3 H), 2.30 (m, 2 H), 1.97 (d, *J* = 14.2 Hz, 1 H), 1.85 (m, 1 H), 1.64 (t, *J* = 4.6 Hz, 1 H), 1.35 (dd, *J* = 8.7, 3.9 Hz, 1 H), 1.09 (s, 9 H), 0.99 (d, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR (CDCl3): δ = 175.1, 136.0, 134.1, 133.6, 129.5, 127.5, 75.0, 51.4, 40.4, 38.1, 35.4, 29.5, 27.0, 19.2, 18.4, 12.9 ppm. MS: *m*/*z* (%) = 408 (M^+), 377, 351, 319, 273, 245, 199, 158, 153, 121 (100), 77, 57. Enantiomer (**70a**): $[\alpha]_D$ = +13.9 (*c* = 0.65, $CHCl_3$). $C_{25}H_{32}O_3Si$ (408.61): calcd. C 73.49, H 7.89; found C 73.41, H 8.13.

Ethyl Homologue 68b: R_f = 0.28 (cyclohexane/EtOAc, 94:6). $[\alpha]_D$ = –29.4 (*c* = 0.61, $CHCl_3$). IR (KBr film): $\tilde{\nu}$ = 2958, 1723, 1427, 1366, 1298, 1224, 1148 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.63–7.35 (m, 10 H), 4.18 (t, *J* = 5.9 Hz, 1 H), 3.61 (s, 3 H), 2.26 (m, 1 H), 2.06 (m, 1 H), 1.98 (d, *J* = 14.3 Hz, 1 H), 1.92 (m, 1 H), 1.67 (t, *J* = 4.3 Hz, 1 H), 1.48 (m, 2 H), 1.36 (dd, *J* = 12.1, 3.9 Hz, 1 H), 1.05 (s, 9 H), 0.89 (t, *J* = 7.4 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 175.3, 136.1, 134.3, 133.5, 129.6, 127.5, 74.6, 51.6, 48.3, 37.8, 33.3, 29.9, 27.1, 20.9, 19.3, 18.5, 13.3 ppm. MS: *m*/*z* (%) = 422 (M^+, 2), 391 (4), 365 (M^+- 57, 40), 337 (8), 287 (12), 259 (10), 225 (8), 199 (65), 135 (100), 105 (38). Enantiomer (**70b**): $[\alpha]_D$ = +28.4 (*c* = 0.75, $CHCl_3$).

(1*S*,3*S*,4*S*,5*S*)-3-(*tert*-Butyldiphenylsilyloxy)-4-methylbicyclo[3.1.0]-hexane-1-carbaldehyde (39a) (General Procedure): To a solution of **38a** (132 mg, 0.324 mmol) in THF (10 mL) at 0 °C was added dropwise $LiAlH_4$ (485 μL, 0.485 mmol, 1 M in THF). The mixture was stirred at 0 °C for 1.5 h, and then EtOAc (3 mL) was added. After stirring for 0.5 h, the reaction was quenched with a minimum of H_2O. The mixture was filtered through Celite and the filtrate was dried and concentrated. The residue was purified by flash chromatography (isooctane/EtOAc, 4:1) to afford the primary alcohol (120 mg, 97%) as a colourless oil. R_f = 0.21 (isooctane/EtOAc, 4:1). $[\alpha]_D$ = –4.6 (*c* = 0.35, $CHCl_3$). IR (KBr film): $\tilde{\nu}$ = 3332, 3070, 2930, 2858, 1472, 1428, 1390, 1219, 1112, 1008 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.66–7.35 (m, 10 H), 3.91 (m, 1 H), 3.52 (d, *J* = 2.0 Hz, 2 H), 2.03 (m, 1 H), 1.91–1.82 (m, 2 H), 1.45 (br. s, 1 H), 1.05 (s, 9 H), 1.04 (d, *J* = 7.7 Hz, 3 H), 0.92 (m, 1 H), 0.27 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 137.6, 134.2, 129.6, 127.5, 73.4, 68.6, 37.5, 35.0, 29.9, 27.9, 26.9, 19.2, 15.3, 13.5 ppm. MS: *m*/*z* (%) = 380 (M^+, 1), 363 (1), 323 (M^+ – 57, 11), 305 (4), 267 (2), 245 (21), 227 (9), 199 (100), 152 (4), 135 (12), 107 (85). $C_{24}H_{32}O_2Si$ (380.60): calcd. C 75.74, H 8.47; found C 75.34, H 8.62. The intermediate alcohol (100 mg, 0.263 mmol) was dissolved in CH_2Cl_2 (10 mL) containing NMO (48 mg, 97%, 0.397 mmol) and 4-Å molecular sieves (130 mg), and then TPAP (9.5 mg, 97%, 0.03 mmol) was added. The mixture was stirred at room temperature for 0.5 h, and then was subjected to flash chromatography (isooctane/EtOAc, 4:1). Evaporation of the solvents and column chromatography (isooctane/EtOAc, 9:1) afforded **39a** (93 mg, 95%) as a colourless oil. R_f = 0.22 (isooctane/EtOAc, 95:5). $[\alpha]_D$ = –49.4 (*c* = 0.99, $CHCl_3$). IR (KBr film): $\tilde{\nu}$ = 2931, 2858, 1702, 1459, 1427, 1389, 1219 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 8.80 (s, 1 H), 7.65–7.37 (m, 10 H), 3.93 (m, 1 H), 2.24 (dd, *J* = 12.9, 9.3 Hz, 1 H), 2.13 (m, 1 H), 1.81 (dd, *J* = 12.9, 7.2 Hz, 1 H), 1.68 (dd, *J* = 8.9, 5.6 Hz, 1 H), 1.20 (dd, *J* = 8.8, 6.0 Hz, 1 H), 1.05 (s, 9 H), 1.03 (d, *J* = 8.1 Hz, 3 H), 0.86 (t, *J* = 5.6 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 200.1, 135.7, 133.8, 129.7, 127.6, 72.7, 37.9, 36.7, 32.7, 30.6, 26.8, 19.2, 17.6, 14.7 ppm. MS: *m*/*z* (%) = 321 (M^+ – 57, 86), 305 (7), 279 (14), 243 (20), 199 (100), 181 (35), 139 (68), 105 (58), 77 (64).

Ethyl Homologue 39b: R_f = 0.28 (isooctane/EtOAc, 9:1). $[\alpha]_D$ = –33.3 (*c* = 0.57, $CHCl_3$). IR (KBr film): $\tilde{\nu}$ = 3070, 2960, 2857, 2711, 1700, 1472, 1428, 1389, 1270, 1217, 1175, 1111, 1027 cm^{-1}. ^1H

NMR ($CDCl_3$): δ = 8.81 (s, 1 H), 7.64–7.35 (m, 10 H), 3.95 (q, J = 7.8 Hz, 1 H), 2.19 (m, 1 H), 1.91–1.78 (m, 4 H), 1.25 (m, 1 H), 1.17 (m, 1 H), 1.05 (s, 9 H), 0.95 (t, J = 7.2 Hz, 3 H), 0.84 (t, J = 5.6 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 200.0, 135.7, 135.5, 133.7, 129.7, 129.6, 127.6, 73.1, 43.6, 38.2, 31.7, 30.1, 26.8, 20.9, 19.1, 17.6, 11.7 ppm. MS: m/z (%) = 335 (M^+ – 57, 55), 280 (10), 257 (18), 227 (15), 199 (100), 181 (30), 139 (50), 105 (45), 77 (65). $C_{25}H_{32}O_2Si$ (392.60): calcd. C 76.48, H 8.21; found C 76.32, H 8.40.

(1*S*,3*R*,4*R*,5*S*)-3-(*tert*-Butyldiphenylsilyloxy)-4-methylbicyclo[3.1.0]-hexane-1-carbaldehyde (44a): Compound **44a** was synthesized from **43a** as described for **39a** in 93% yield as a colourless oil. R_f = 0.38 (isooctane/EtOAc, 4:1). $[\alpha]_D$ = –109.3 (c = 0.16, $CHCl_3$). IR (KBr film): $\tilde{\nu}$ = 3048, 2958, 2858, 1702, 1589, 1472, 1428, 1389, 1362, 1252, 1182, 1112, 1086 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 8.78 (s, 1 H), 7.65–7.35 (m, 10 H), 3.39 (dd, J = 15.5, 7.8 Hz, 1 H), 2.26–2.22 (m, 2 H), 1.88 (m, 2 H), 1.08 (m, 1 H), 1.05 (s, 9 H), 0.93 (d, J = 7.7 Hz, 3 H), 0.75 (t, J = 5.5 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 199.9, 135.9, 133.8, 129.7, 127.6, 77.3, 41.5, 37.4, 33.7, 30.8, 26.9, 19.1, 15.7, 15.2 ppm. MS: m/z (%) = 321 (M^+ – 57, 48), 319 (8), 309 (11), 259 (24), 199 (100), 181 (40), 153 (20).

Ethyl Homologue 44b: R_f = 0.34 (isooctane/EtOAc, 9:1). $[\alpha]_D$ = –110.9 (c = 0.53, $CHCl_3$). IR (KBr film): $\tilde{\nu}$ = 3070, 2959, 2857, 2710, 1704, 1462, 1428, 1257 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 8.80 (s, 1 H), 7.64–7.35 (m, 10 H), 3.46 (q, J = 7.3 Hz, 1 H), 2.21 (t, J = 11.3 Hz, 1 H), 2.09 (br. s, 1 H), 1.96 (d, J = 5.1 Hz, 1 H), 1.87 (m, 1 H), 1.62 (m, 2 H), 1.12 (s, 1 H), 1.04 (s, 9 H), 0.90 (t, J = 7.2 Hz, 3 H), 0.74 (t, J = 5.6 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 199.6, 135.8, 133.8, 129.6, 127.4, 75.9, 48.7, 37.2, 33.6, 28.6, 26.8, 23.9, 19.1, 15.3, 12.6 ppm. MS: m/z (%) = 335 (M^+ – 57, 50), 279 (4), 227 (10), 199 (100), 181 (20), 139 (45), 105 (32), 77 (60).

(*E*)-(1*R*,3a*R*,7a*R*)-4-Bromomethylidene-1-[(1*S*)-5-(1-ethoxyethoxy)-1,5-dimethylhex-3-ynyl]-7a-methyloctahydroindene (73): Compound **73** was obtained from **72** as described for the 20(*R*) epimer in ref.[8]. R_f = 0.65 (isooctane/ethyl acetate, 4:1). $[\alpha]_D^{25}$ = +20.7 (c = 0.75, acetone). IR (KBr film): $\tilde{\nu}$ = 2978, 2234, 1455, 1381, 1252, 1195, 1122, 1081, 1052, 976 cm^{-1}. ^1H NMR (300 MHz, [D$_6$]benzene): δ = 5.54 (br. s, 1 H), 5.25 (br. q, J = 4.9 Hz, 1 H), 3.50 (dq, J = 7.2, 9.1 Hz, 1 H), 3.38 (dq, J = 7.2, 9.1 Hz, 1 H), 2.40 (m, 1 H), 1.80 (m, 3 H), 0.7–1.5 (m, series of H), 1.47 (s, 3 H), 1.36 (s, 3 H), 1.29 (d, J = 5.4 Hz, 3 H), 1.03 (t, J = 7.0 Hz, 3 H), 0.68 (d, J = 6.4 Hz, 3 H), 0.56 (s, 3 H) ppm.

2β-Methyl-19-*nor*-1α,25-dihydroxyvitamin D$_3$ (6a) (General Procedure): To a stirred solution of **20** (65 mg, 0.151 mmol) in THF (2.0 mL) was added dropwise *t*BuLi (197 μL, 1.7 M in pentane, 0.334 mmol) at –78 °C. After stirring at –78 °C for 1 h, the reaction was warmed to –10 °C and was stirred for 0.5 h. The solution was cooled down to –78 °C again, and then a solution of **44a** (80 mg, 0.212 mmol) in THF (1.5 mL) was added dropwise. The reaction was stirred at –78 °C for 1 h, and then the reaction was quenched by addition of satd. NH_4Cl. The solution was diluted with Et_2O, washed with saturated $NaHCO_3$ and brine, dried and concentrated. The residue was purified by flash chromatography (isooctane/EtOAc, 94:1) to afford intermediate **27a** (53 mg, 48%) as a colourless oil. The intermediate oil (53 mg, 0.073 mmol) was dissolved in dioxane/H_2O (3:1, 4 mL) containing PTSA (4 mg, 0.023 mmol). The mixture was stirred in the dark at 55–60 °C for 4 h and then the solution was diluted with Et_2O, washed with saturated $NaHCO_3$ and brine), dried and concentrated. The residue was purified by HPLC (isooctane/EtOAc, 4:1), affording **74a** (38 mg) and **75a** (5 mg) in 88% yield. **74a:** R_f = 0.22 (isooctane/EtOAc, 4:1). $[\alpha]_D$ = –15.7 (c = 0.76, $CHCl_3$). IR (KBr film): $\tilde{\nu}$ = 3394, 2942, 1616, 1471, 1428, 1377, 1110 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.71–7.35 (m, 10 H), 6.14 (d, J = 11.3 Hz, 1 H), 5.46 (d, J = 11.3 Hz, 1 H), 3.94 (m, 1 H), 3.72 (td, J = 8.9, 4.2 Hz, 1 H), 2.72 (m, 1 H), 2.66 (dd, J = 13.3, 4.0 Hz, 1 H), 2.37–2.44 (m, 2 H), 2.25 (dd, J = 13.6, 5.2 Hz, 1 H), 2.05–1.85 (m, 4 H), 1.80 (m, 1 H), 1.70–1.60 (m, 3 H), 1.50–1.24 (m, 13 H), 1.23 (s, 6 H), 1.07 (s, 9 H), 1.03 (d, J = 6.9 Hz, 3 H), 0.93 (d, J = 6.5 Hz, 3 H), 0.45 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 142.2, 135.9, 134.8, 134.2, 132.1, 129.6, 127.5, 122.9, 115.4, 73.9, 71.4, 71.1, 56.5, 56.2, 45.6, 44.4, 43.3, 40.4, 36.5, 36.4, 36.1, 30.1, 29.2, 28.8, 27.7, 27.1, 25.5, 22.5, 22.3, 20.8, 19.4, 18.8, 14.0, 11.9 ppm. MS: m/z (%) = 656 (M^+, 1), 638 (M^+ – 18, 1), 600 (M^+ – *t*Bu + H, 1), 581 (3), 563 (2), 503 (3), 472 (1), 400 (4), 365 (6), 321 (9), 239 (11), 199 (100), 149 (19), 135 (52), 59 (88). **75a**: R_f = 0.19 (isooctane/EtOAc, 4:1). $[\alpha]_D$ = +18.3 (c = 0.31, $CHCl_3$). IR (KBr film): $\tilde{\nu}$ = 3405, 3071, 2958, 2879, 1459, 1429, 1376, 1217, 1147, 1076, 1053 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.71–7.36 (m, 10 H), 5.99 (d, J = 11.2 Hz, 1 H), 5.77 (d, J = 11.2 Hz, 1 H), 4.00 (m, 1 H), 3.71 (td, J = 8.1, 4.2 Hz, 1 H), 2.68 (dd, J = 13.8, 5.1 Hz, 1 H), 2.58 (dd, J = 13.7, 5.9 Hz, 1 H), 2.29 (dd, J = 13.7, 3.7 Hz, 1 H), 2.23 (dd, J = 13.1, 3.9 Hz, 1 H), 2.07–1.82 (m, 5 H), 1.68–1.23 (m, 17 H), 1.22 (s, 6 H), 1.05 (s, 9 H), 1.03 (d, J = 6.7 Hz, 3 H), 0.93 (d, J = 6.5 Hz, 3 H), 0.51 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 142.3, 135.9, 134.9, 133.0, 129.5, 127.5, 123.4, 115.4, 74.4, 71.3, 71.1, 56.5, 56.2, 45.7, 44.4, 44.0, 40.5, 36.4, 36.1, 34.8, 30.1, 29.4, 28.8, 27.6, 27.0, 25.4, 23.4, 22.2, 20.8, 19.4, 18.8, 13.6, 12.0 ppm. MS: m/z (%) = 656 (M^+, 1), 599 (M^+ – *t*Bu, 1), 581 (3), 521 (1), 468 (1), 400 (1), 365 (6), 325 (5), 245 (8), 199 (61), 183 (18), 135 (42), 59 (100). A solution of **74a** (27 mg, 0.041 mmol) in THF (0.5 mL) was treated with TBAF (3.5 mL, 1 M in THF). After stirring at room temperature in the dark for 72 h, the solution was subjected to flash chromatography (isooctane/EtOAc, 1:1). The residue was purified by HPLC (isooctane/EtOAc, 3:2) affording **6a** (11 mg, 82%). R_f = 0.21 (isooctane/EtOAc, 1:1). IR (KBr): $\tilde{\nu}$ = 3422, 2946, 1618, 1452, 1376, 1350, 1150, 1056 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 6.26 (d, J = 11.2 Hz, 1 H), 5.87 (d, J = 11.2 Hz, 1 H), 3.51 (td, J = 10.1, 4.7 Hz, 1 H), 3.08 (dd, J = 12.9, 4.0 Hz, 1 H), 2.79 (dd, J = 12.9, 4.0 Hz, 1 H), 2.44 (d, J = 13.1 Hz, 1 H), 2.37 (m, 1 H), 2.04–1.98 (m, 3 H), 1.90 (t, J = 10.7 Hz, 2 H), 1.80–1.23 (m, 18 H), 1.22 (s, 6 H), 1.14 (d, J = 6.8 Hz, 3 H), 0.94 (d, J = 6.5 Hz, 3 H), 0.55 (s, 3 H) ppm. MS: m/z (%) = 418 (M^+, 9), 400 (6), 385 (4), 357 (5), 317 (2), 289 (6), 245 (8), 203 (4), 189 (6), 149 (27), 135 (41), 84 (58), 59 (100).

2α-Methyl-19-*nor*-1α,25-dihydroxyvitamin D$_3$ (5a): R_f = 0.18 (isooctane/EtOAc, 1:1). $[\alpha]_D$ = +26.6 (c = 0.14, $CHCl_3$). IR (KBr film): $\tilde{\nu}$ = 3354, 2958, 1454, 1054 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 6.37 (d, J = 11.3 Hz, 1 H), 5.83 (d, J = 11.3 Hz, 1 H), 3.96 (m, 1 H), 3.61 (td, J = 9.4, 4.6 Hz, 1 H), 3.20 (m, 2 H), 3.02 (dt, J = 12.0, 4.8 Hz, 2 H), 2.80 (dd, J = 13.6, 4.3 Hz, 2 H), 2.60 (dd, J = 12.9, 4.4 Hz, 1 H), 2.23 (d, J = 12.6 Hz, 1 H), 2.14 (t, J = 10.3 Hz, 1 H), 2.06–1.20 (m, 18 H), 1.22 (s, 6 H), 1.14 (d, J = 6.9 Hz, 3 H), 0.98 (d, J = 7.4 Hz, 3 H), 0.54 (s, 3 H) ppm. MS: m/z (%) = 418 (M^+, 1), 400 (M^+ – H_2O, 18), 382 (6), 340 (22), 295 (12), 271 (9), 233 (32), 191 (22), 149 (85), 135 (25), 92 (100).

Ethyl Homologue 5b: R_f = 0.18 (isooctane/EtOAc, 3:2). $[\alpha]_D$ = +28.0 (c = 0.21, $CHCl_3$). IR (KBr film): $\tilde{\nu}$ = 3389, 2958, 1454, 1188, 1045 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 6.38 (d, J = 11.3 Hz, 1 H), 5.83 (d, J = 11.3 Hz, 1 H), 4.14 (m, 1 H), 3.63 (m, 1 H), 2.87 (dd, J = 13.9, 4.0 Hz, 1 H), 2.80 (dd, J = 12.7, 4.5 Hz, 1 H), 2.61 (dd, J = 12.5, 4.1 Hz, 1 H), 2.20–1.22 (m, 24 H), 1.21 (s, 6 H), 1.00 (t, J = 7.4 Hz, 3 H), 0.91 (d, J = 6.7 Hz, 3 H), 0.53 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 143.3, 131.5, 124.1, 115.4, 71.7, 71.3, 68.0, 56.7, 56.5, 50.9, 45.9, 45.5, 44.6, 40.6, 36.5, 36.2, 35.7, 30.2, 29.5, 29.1, 27.8, 25.6, 23.6, 22.4, 20.9, 18.9, 12.2, 11.8 ppm. MS: m/z (%)

= 432 (M^+, 1), 414 (6), 371 (2), 303 (5), 267 (6), 245 (8), 208 (6), 173 (10), 149 (30), 133 (40), 81 (65), 55 (100).

Ethyl Homologue 6b: R_f = 0.22 (isooctane/EtOAc, 3:2). $[\alpha]_D$ = +42.1 (c = 0.32, $CHCl_3$). IR (KBr film): $\tilde{\nu}$ = 3378, 2959, 1454, 1378 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 6.26 (d, J = 11.3 Hz, 1 H), 5.87 (d, J = 11.3 Hz, 1 H), 4.09 (m, 1 H), 3.54 (m, 1 H), 3.10 (dd, J = 12.7, 4.3 Hz, 1 H), 2.80 (dd, J = 12.8, 4.5 Hz, 1 H), 2.38 (m, 2 H), 2.05–1.25 (m, 25 H), 1.22 (s, 6 H), 1.00 (t, J = 7.4 Hz, 3 H), 0.94 (d, J = 6.5 Hz, 3 H), 0.54 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 143.1, 131.4, 123.5, 115.4, 71.2, 67.7, 56.6, 56.4, 51.5, 45.9, 44.5, 44.2, 40.6, 37.9, 36.5, 36.2, 31.0, 29.5, 29.3, 29.1, 27.8, 23.6, 22.4, 20.9, 20.3, 18.9, 12.2, 11.7 ppm. MS: m/z (%) = 432 (M^+, 1), 414 (5), 303 (8), 267 (8), 245 (15), 208 (5), 173 (5), 135 (30), 105 (35), 81 (70), 59 (100).

14-*epi*-2α-Methyl-19-*nor*-1α,25-dihydroxyvitamin D_3 (7a): R_f = 0.20 (isooctane/EtOAc, 1:1). $[\alpha]_D$ = +61.1 (c = 0.34, $CHCl_3$). IR (KBr film): $\tilde{\nu}$ = 3384, 2960, 1455, 1379, 1147, 1043 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 6.31 (d, J = 11.2 Hz, 1 H), 6.01 (d, J = 11.2 Hz, 1 H), 3.97 (dd, J = 5.6, 2.4 Hz, 1 H), 3.59 (td, J = 9.5, 4.6 Hz, 1 H), 2.84 (dd, J = 13.9, 4.6 Hz, 1 H), 2.59 (dd, J = 12.8, 4.4 Hz, 1 H), 2.47(dt, J = 14.6, 5.1 Hz, 1 H), 2.21 (d, J = 13.7 Hz, 1 H), 2.15–2.08 (m, 2 H), 1.88–1.21 (m, 22 H), 1.22 (s, 6 H), 1.14 (d, J = 6.9 Hz, 3 H), 0.92 (s, 3 H), 0.88 (d, J = 6.7 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 143.4, 131.6, 124.2, 118.5, 72.4, 71.6, 71.1, 57.8, 54.6, 45.3, 44.9, 44.4, 43.9, 37.9, 35.5, 34.5, 34.0, 29.9, 29.4, 29.2, 26.8, 24.8, 22.3, 21.9, 21.7, 19.8, 13.6 ppm. MS: m/z (%) = 418 (M^+, 1), 400 ($M^+ - H_2O$, 22), 387 (7), 357 (4), 340 (5), 289 (14), 271 (21), 245 (19), 191 (17), 147 (29), 133 (38), 81 (59), 59 (100).

Ethyl Homologue 7b: R_f = 0.20 (isooctane/EtOAc, 3:2). $[\alpha]_D$ = +34.4 (c = 0.48, $CHCl_3$). IR (KBr film): $\tilde{\nu}$ = 3372, 2958, 1464, 1378, 1190, 1044 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 6.32 (d, J = 11.3 Hz, 1 H), 6.01 (d, J = 11.3 Hz, 1 H), 4.15 (br. s, 1 H), 3.64 (m, 1 H), 2.92 (m, 1 H), 2.59 (m, 1 H), 2.47 (m, 1 H), 2.18–2.05 (m, 3 H), 1.86–1.24 (m, 23 H), 1.22 (s, 6 H), 1.00 (t, J = 7.4 Hz, 3 H), 0.89 (d, J = 6.8 Hz, 3 H), 0.86 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 143.5, 131.6, 124.2, 118.7, 71.6, 71.2, 68.0, 58.0, 54.7, 51.0, 45.6, 45.4, 44.5, 38.0, 35.7, 34.7, 34.1, 30.0, 29.5, 29.3, 27.0, 24.9, 22.3, 22.0, 21.8, 20.0, 19.8, 11.8 ppm. MS: m/z (%) = 432 (M^+, 2), 414 (15), 386 (4), 265 (5), 245 (10), 199 (20), 161 (15), 135 (30), 81 (50), 55 (100).

14-*epi*-2β-Methyl-19-*nor*-1α,25-dihydroxyvitamin D_3 (8a): R_f = 0.18 (isooctane/EtOAc, 1:1). $[\alpha]_D$ = +38.7 (c = 0.40, $CHCl_3$). IR (KBr film): $\tilde{\nu}$ = 3382, 2958, 1455, 1377, 1212, 1045 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 6.19 (d, J = 11.2 Hz, 1 H), 6.05 (d, J = 11.2 Hz, 1 H), 3.90 (dd, J = 6.2, 3.0 Hz, 1 H), 3.52 (td, J = 10.1, 4.6 Hz, 1 H), 3.08 (dd, J = 12.9, 4.4 Hz, 1 H), 2.41–2.48 (m, 2 H), 2.33 (dd, J = 13.2, 4.2 Hz, 1 H), 2.15–2.03 (m, 2 H), 1.94–1.80 (m, 2 H), 1.72–1.23 (m, 19 H), 1.22 (s, 6 H), 1.13 (d, J = 6.9 Hz, 3 H), 0.92 (s, 3 H), 0.88 (d, J = 6.7 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 143.2, 131.6, 123.7, 118.6, 71.9, 71.7, 71.1, 57.9, 54.6, 45.4, 44.4, 44.1, 43.9, 37.9, 37.4, 34.5, 34.0, 29.8, 29.4, 29.2, 26.8, 24.8, 22.4, 21.8, 21.6, 19.8, 14.0 ppm. MS: m/z (%) = 418 (M^+, 1), 401 ($M^+ - H_2O + H$, 1), 387 (2), 357 (4), 370 (1), 293 (1), 292 (5), 260 (2), 199 (35), 183 (11), 153 (25), 111(28), 93 (100).

Ethyl Homologue 8b: R_f = 0.21 (isooctane/EtOAc, 3:2). $[\alpha]_D$ = +17.0 (c = 0.15, $CHCl_3$). IR (KBr film): $\tilde{\nu}$ = 3369, 2958, 1455, 1378, 1190, 1044 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 6.19 (d, J = 11.2 Hz, 1 H), 6.06 (d, J = 11.3 Hz, 1 H), 4.09 (m, 1 H), 3.50 (m, 1 H), 3.11 (dd, J = 12.7, 4.2 Hz, 1 H), 2.97 (m, 1 H), 2.47 (m, 1 H), 2.38 (m, 1 H), 2.18–1.25 (m, 25 H), 1.22 (s, 6 H), 0.99 (t, J = 7.4 Hz, 3 H), 0.90 (d, J = 6.7 Hz, 3 H), 0.88 (s, 3 H) ppm. MS: m/z (%) = 432 (M^+, 2), 414 (28), 381 (4), 301 (4), 267 (8), 245 (10), 199 (30), 149 (30), 105 (50), 81 (70), 59 (100).

2α-Methyl-19-*nor*-23-yne-1α,25-dihydroxyvitamin D_3 (9a): R_f = 0.18 (isooctane/EtOAc, 1:1). $[\alpha]_D$ = +42.7 (c = 0.11, $CHCl_3$). IR (KBr film): $\tilde{\nu}$ = 3368, 2929, 1614, 1454, 1377, 1261, 1166, 1024 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 6.36 (d, J = 11.1 Hz, 1 H), 5.82 (d, J = 11.1 Hz, 1 H), 3.96 (br. s, 1 H), 3.61 (m, 1 H), 2.80 (d, J = 14.1 Hz, 2 H), 2.60 (d, J = 12.8 Hz, 1 H), 2.28–1.52 (m, 17 H), 1.51 (s, 6 H), 1.38–1.25 (m, 3 H), 1.13 (d, J = 6.7 Hz, 3 H), 1.06 (d, J = 6.3 Hz, 3 H), 0.54 (s, 3 H) ppm. MS: m/z (%) = 414 (M^+, 14), 396 ($M^+ - H_2O$, 8), 381 (7), 353 (4), 317 (12), 267 (3), 241 (9), 199 (13), 185 (16), 161 (21), 105 (37), 84 (52), 43 (100).

Ethyl Homologue 9b: R_f = 0.18 (isooctane/EtOAc, 3:2). $[\alpha]_D$ = +23.1 (c = 0.26, $CHCl_3$). IR (KBr film): $\tilde{\nu}$ = 3367, 2958, 2238, 1455, 1378, 1167 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 6.38 (d, J = 11.2 Hz, 1 H), 5.83 (d, J = 11.1 Hz, 1 H), 4.14 (m, 1 H), 3.64 (td, J = 9.8, 4.8 Hz, 1 H), 2.97 (m, 1 H), 2.87 (dd, J = 13.9, 4.3 Hz, 1 H), 2.80 (dd, J = 12.8, 4.5 Hz, 1 H), 2.30–1.51 (m, 17 H), 1.50 (s, 6 H), 1.46–1.25 (m, 5 H), 1.06 (d, J = 6.6 Hz, 3 H), 0.98 (t, J = 7.4 Hz, 3 H), 0.54 (s, 3 H) ppm. MS: m/z (%) = 428 (M^+, 2), 410 (10), 370 (8), 331 (5), 313 (8), 295 (4), 241 (3), 199 (8), 161 (20), 149 (40), 91 (40), 43 (100).

2β-Methyl-19-*nor*-23-yne-1α,25-dihydroxyvitamin D_3 (10a): R_f = 0.18 (isooctane/EtOAc, 1:1). $[\alpha]_D$ = +28.2 (c = 0.37, $CHCl_3$). IR (KBr film): $\tilde{\nu}$ = 3380, 2930, 1455, 1377, 1346, 1166, 1041 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 6.44 (d, J = 11.3 Hz, 1 H), 6.04 (d, J = 11.3 Hz, 1 H), 4.07 (dd, J = 4.1, 3.0 Hz, 1 H), 3.68 (td, J = 10.1, 4.8 Hz, 1 H), 3.24 (dd, J = 12.9, 3.8 Hz, 1 H), 2.97 (dd, J = 12.9, 4.4 Hz, 1 H), 2.60 (d, J = 3.6 Hz, 1 H), 2.51 (dd, J = 13.8, 3.4 Hz, 1 H), 2.44 (dd, J = 16.6, 3.4 Hz, 1 H), 2.26–2.16 (m, 5 H), 2.07 (m, 2 H), 1.68 (s, 6 H), 1.88–1.66 (m, 8 H), 1.52–1.41 (m, 3 H), 1.31 (d, J = 6.8 Hz, 3 H), 1.24 (d, J = 6.5 Hz, 3 H), 0.72 (s, 3 H) ppm. MS: m/z (%) = 414 (M^+, 18), 396 ($M^+ - H_2O$, 8), 376 (7), 356 (4), 353 (1), 317 (15), 267 (4), 241 (9), 199 (21), 173 (23), 161 (25), 105 (42), 91 (53), 43 (100).

Ethyl Homologue 10b: R_f = 0.19 (isooctane/EtOAc, 3:2). $[\alpha]_D$ = +24.9 (c = 0.54, $CHCl_3$). IR (KBr film): $\tilde{\nu}$ = 3378, 2930, 1454, 1166, 1039 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 6.26 (d, J = 11.2 Hz, 1 H), 5.87 (d, J = 11.2 Hz, 1 H), 4.10 (m, 1 H), 3.55 (m, 1 H), 3.10 (dd, J = 12.9, 4.1 Hz, 1 H), 2.80 (dd, J = 12.5, 4.2 Hz, 1 H), 2.40–1.53 (m, 18 H), 1.52 (s, 6 H), 1.50–1.24 (m, 5 H), 1.07 (d, J = 6.5 Hz, 3 H), 1.00 (t, J = 7.4 Hz, 3 H), 0.56 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 142.6, 131.6, 123.4, 115.5, 86.1, 81.3, 71.2, 67.6, 65.4, 56.3, 55.7, 51.0, 45.7, 44.1, 40.4, 37.9, 36.0, 31.9, 30.1, 29.0, 27.7, 25.7, 23.5, 22.3, 20.2, 19.2, 12.2, 11.6 ppm. MS: m/z (%) = 428 (M^+, 1), 410 (2), 370 (4), 331 (3), 267 (3), 241 (4), 199 (8), 173 (8), 149 (20), 105 (30), 91 (45), 43 (100).

14-*epi*-2α-Methyl-19-*nor*-23-yne-1α,25-dihydroxyvitamin D_3 (11a): R_f = 0.19 (isooctane/EtOAc, 1:1). $[\alpha]_D$ = +55.1 (c = 0.11, $CHCl_3$). IR (KBr film): $\tilde{\nu}$ = 3362, 2959, 2929, 1450, 1376, 1329, 1243, 1175, 1127 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 6.30 (d, J = 11.3 Hz, 1 H), 6.02 (d, J = 11.3 Hz, 1 H), 3.98 (m, 1 H), 3.60 (td, J = 9.4, 4.6 Hz, 1 H), 2.83 (dd, J = 13.9, 4.6 Hz, 1 H), 2.59 (dd, J = 12.8, 4.3 Hz, 1 H), 2.41 (dt, J = 12.5, 3.8 Hz, 1 H), 2.27–1.99 (m, 5 H), 1.87 (m, 1 H), 1.76–1.52 (m, 11 H), 1.49 (s, 6 H), 1.33–1.25 (m, 3 H), 1.13 (d, J = 6.7 Hz, 3 H), 1.02 (d, J = 6.5 Hz, 3 H), 0.95 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 142.9, 131.9, 124.1, 118.5, 86.1, 81.7, 72.5, 71.6, 65.4, 57.7, 52.6, 44.9, 44.9, 43.9, 37.7, 35.5, 33.9, 31.7, 31.7, 29.4, 27.9, 25.2, 24.5, 22.5, 21.8, 20.0, 13.6 ppm. MS: m/z (%) = 653 ($M^+ + H$, 1), 634 ($M^+ - H_2O$, 5), 597 ($M^+ - 57 + H$, 2), 459 (1), 385 (4), 361 (3), 335 (3), 267 (4), 199 (90), 183 (38), 135 (75), 43 (100).

Ethyl Homologue 11b: R_f = 0.24 (isooctane/EtOAc, 3:2). $[\alpha]_D$ = +22.3 (c = 0.38, $CHCl_3$). IR (KBr film): $\tilde{\nu}$ = 3370, 2958, 2874, 2233, 1731, 1614, 1462, 1378, 1337, 1240, 1167 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 6.31 (d, J = 11.3 Hz, 1 H), 6.03 (d, J = 11.3 Hz, 1 H), 4.15 (m, 1 H), 3.64 (m, 1 H), 2.89 (m, 1 H), 2.60 (dd, J = 12.8, 4.3 Hz, 1 H), 2.45–1.51 (m, 18 H), 1.50 (s, 6 H), 1.40–1.25 (m, 5 H), 1.02 (t, J = 7.4 Hz, 3 H), 0.91 (d, J = 6.9 Hz, 3 H), 0.88 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 143.1, 132.1, 124.2, 118.7, 86.2, 81.8, 71.7, 68.0, 57.9, 53.3, 52.8, 51.0, 45.6, 45.1, 37.9, 35.8, 34.2, 31.9, 30.2, 29.5, 28.2, 25.6, 25.3, 24.7, 22.7, 21.9, 20.2, 11.9 ppm. MS: m/z (%) = 428 (M^+, 2), 410 (M^+ – 18, 8), 370 (5), 313 (5), 277 (6), 199 (30), 149 (35), 142 (30), 91 (50), 43 (100).

14-*epi*-2β-Methyl-19-*nor*-23-yne-1α,25-dihydroxyvitamin D_3 (12a): R_f = 0.18 (isooctane/EtOAc, 1:1). $[\alpha]_D$ = +43.8 (c = 0.21, $CHCl_3$). IR (KBr film): $\tilde{\nu}$ = 3358, 2929, 1455, 1377, 1338, 1239, 1166 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 6.19 (d, J = 11.4 Hz, 1 H), 6.06 (d, J = 11.4 Hz, 1 H), 3.89 (dd, J = 6.3, 3.2 Hz, 1 H), 3.54 (td, J = 10.1, 4.6 Hz, 1 H), 3.07 (dd, J = 12.9, 4.2 Hz, 1 H), 3.01 (m, 1 H), 2.46–2.31 (m, 3 H), 2.23 (dd, J = 16.7, 3.5 Hz, 2 H), 2.15–2.01 (m, 3 H), 1.94–1.86 (m, 2 H), 1.78–1.50 (m, 8 H), 1.49 (s, 6 H), 1.35–1.25 (m, 3 H), 1.14 (d, J = 6.7 Hz, 3 H), 1.03 (d, J = 6.6 Hz, 3 H), 0.88 (s, 3 H) ppm. MS: m/z (%) = 652 (M^+, 1), 634 ($M^+ - H_2O$ + 1, 6), 594 (M^+ – 57 + H, 2), 537 (3), 459 (2), 396 (1), 378 (4), 321 (5), 261 (6), 199 (100), 183 (27), 135 (72).

Ethyl Homologue 12b: R_f = 0.22 (isooctane/EtOAc, 3:2). $[\alpha]_D$ = +8.9 (c = 0.69, $CHCl_3$). IR (KBr film): $\tilde{\nu}$ = 3381, 2958, 2233, 1454, 1383, 1166 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 6.19 (d, J = 11.3 Hz, 1 H), 6.07 (d, J = 11.3 Hz, 1 H), 4.10 (m, 1 H), 3.57 (m, 1 H), 3.10 (dd, J = 12.8, 4.3 Hz, 1 H), 2.97 (m, 1 H), 2.38 (m, 2 H), 2.22 (m, 2 H), 2.15–2.00 (m, 3 H), 1.94–1.86 (m, 2 H), 1.84–1.51 (m, 9 H), 1.50 (s, 6 H), 1.45–1.24 (m, 5 H), 0.98 (t, J = 7.5 Hz, 3 H), 0.90 (d, J = 6.7 Hz, 3 H), 0.88 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 142.8, 132.1, 123.5, 118.3, 86.3, 81.6, 71.0, 67.7, 57.8, 52.0, 51.0, 45.1, 44.1, 37.9, 37.8, 34.0, 31.9, 31.7, 30.1, 28.8, 28.2, 25.5, 24.8, 22.6, 22.0, 20.2, 19.9, 11.6 ppm. MS: m/z (%) = 428 (M^+, 2), 410 (6), 313 (4), 277 (4), 241 (4), 199 (15), 173 (10), 149 (30), 105 (25), 91 (40), 43 (100).

14,20-Bis-*epi*-2α-methyl-19-*nor*-23-yne-1α,25-dihydroxyvitamin D_3 (13): R_f = 0.17 (isooctane/EtOAc, 1:1). $[\alpha]_D$ = –3 (c = 0.1, $CHCl_3$). IR (KBr film): $\tilde{\nu}$ = 3365, 2929, 2228, 1441, 1244, 1020 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.30 (d, J = 11 Hz, 1 H), 6.01 (d, J = 11 Hz, 1 H), 3.96 (m, 1 H), 3.60 (td, J = 9.4, 4.6 Hz, 1 H), 2.83 (dd, J = 14, 4.8 Hz, 1 H), 2.59 (dd, J = 12.8, 4.1 Hz, 1 H), 2.41 (dt, J = 14.8, 4.8 Hz, 1 H), 2.23–1.99 (m, 5 H), 1.87 (m, 1 H), 1.76–1.52 (m, 11 H), 1.49 (s, 6 H), 1.38–1.24 (m, 3 H), 1.14 (d, J = 6.8 Hz, 1 H), 0.91 (d, J = 6.6 Hz, 3 H), 0.88 (s, 3 H) ppm.

14,20-Bis-*epi*-2α-ethyl-19-*nor*-23-yne-1α,25-dihydroxyvitamin D_3 (14): R_f = 0.30 (isooctane/EtOAc, 1:1). $[\alpha]_D$ = –4 (c = 0.05, $CHCl_3$). IR (KBr film): $\tilde{\nu}$ = 3335, 2948, 2286, 1452, 1152, 1026 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.32 (d, J = 11.6 Hz, 1 H), 6.02 (d, J = 11.6 Hz, 1 H), 4.15 (m, 1 H), 3.63 (td, J = 9.5, 4.2 Hz, 1 H), 2.89 (dd, J = 14.8, 5.2 Hz, 1 H), 2.59 (m, 1 H), 2.48 (dd, J = 14.3, 4.9 Hz, 1 H), 2.18–1.30 (series of H), 1.49 (s, 6 H), 1.38–1.2 (m, 5 H), 1.01 (t, J = 7.4 Hz, 3 H), 0.94 (d, J = 6.7 Hz, 3 H), 0.88 (s, 3 H) ppm.

3,14-*bisepi*-2α-Methyl-19-*nor*-23-yne-1α,25-dihydroxyvitamin-D_3 (1-*epi*-9a): R_f = 0.21 (isooctane/EtOAc, 3:2). $[\alpha]_D$ +53.11 (c = 0.31, $CHCl_3$). IR (KBr film): $\tilde{\nu}$ = 3345, 2928, 1455, 1362, 1232, 1167, 1103, 1067, 1038, 944, 874, 750 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 6.31 (d, J = 11.3 Hz, 1 H), 6.08 (d, J = 11.3 Hz, 1 H), 3.95 (d, J = 2.1 Hz, 1 H), 3.90 (d, J = 2.9 Hz, 1 H), 3.05 (d, J = 14.1 Hz, 1 H), 2.49–2.40 (m, 4 H), 2.26–1.50 (m, 15 H), 1.49 (s, 6 H), 1.31–1.23 (m, 3 H), 1.19 (d, J = 7.2 Hz, 3 H), 1.01 (d, J = 6.7 Hz, 3 H), 0.96 (s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 142.2, 129.8, 125.0, 118.7, 86.0, 81.8, 73.3, 73.1, 65.4, 57.4, 52.6, 44.9, 44.9, 38.9, 37.6, 36.5, 33.9, 31.7, 31.7, 29.3, 27.8, 25.1, 24.4, 22.4, 21.8, 20.1, 14.5 ppm. MS: m/z (%) = 414 (M^+, 1), 396, ($M^+ - H_2O$, 9), 381 (5), 363 (7), 356 (4), 299 (7), 267 (8), 241 (9), 213 (12), 185 (14), 147 (21), 107 (21), 107 (26), 91 (45), 43 (100).

1,14-*bisepi*-2β-Methyl-19-*nor*-23-yne-1α,25-dihydroxyvitamin-D_3 (1-*epi*-10a): R_f = 0.21 (isooctane/EtOAc, 4:1). $[\alpha]_D$ +20.42 (c = 0.31, $CHCl_3$). IR (KBr film): $\tilde{\nu}$ = 3353, 2930, 1611, 1455, 1376, 1169, 1070, 1028, 988, 948, 882, 729 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 6.32 (d, J = 11.3 Hz, 1 H), 6.08 (d, J = 11.3 Hz, 1 H), 3.96 (br. s, 1 H), 3.90 (br. s, 1 H), 3.06 (dd, J = 14.1, 3.2 Hz, 1 H), 2.49–2.38 (m, 3 H), 2.25–1.50(m, 16 H), 1.49 (s, 6 H), 1.32–1.24 (m, 3 H), 1.18 (d, J = 7.2 Hz, 3 H), 1.02 (d, J = 6.6 Hz, 3 H), 0.95 (s, 3 H) ppm. MS: m/z (%) = 396 ($M^+ - H_2O$, 24), 378 (8), 335 (2), 299 (13), 267 (12), 241 (13), 199 (18), 185 (20), 145 (21), 105 (51), 91 (74), 43 (100).

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[24] For assignment of the chemical shift values for H-6 and H-7 in 19-*nor* analogues, see ref.[8].

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