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The First Convergent Synthesis of 1α,24(*R*)-Dihydroxyvitamin D3 *via* Diastereoselective Isopropylation and Alkylative Enyne Cyclization

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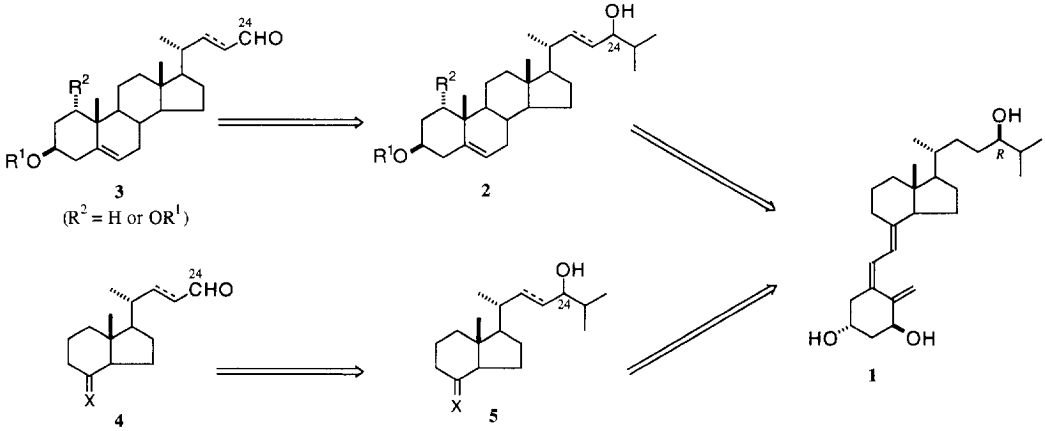
Abstract: An efficient covergent synthesis of 1α,24(*R*)-dihydroxyvitamin D_3 (**1**) has been achieved using the palladium-catalyzed alkylative enyne cyclization reaction. This is the first example of the convergent coupling procedure to synthesize 1α,24(*R*)-dihydroxyvitamin D_3 (**1**). The CD-ring synthons were successfully obtained *via* the diastereoselective addition of diisopropylzinc to CD-ring 24-aldehyde precursors in the presence of a chiral β-amino alcohol with high diastereoselectivities.

INTRODUCTION

1α,24(*R*)-Dihydroxyvitamin D_3[1] (**1**), an active analogue of vitamin D_3, inhibits the growth of keratinocytes, induces keratinocyte differentiation[2] with less hypercalcemic activity, and is used as a therapeutic drug for psoriasis. The 1α,24(*R*)-dihydroxyvitamin D_3 (**1**) was reported to be synthesized from 1α,24(*R*)-dihydroxycholesterol (**2**, $R^2 = OR^1$, R^1 = H), which was obtained through the chromatographic separation of a 24(*R*) and 24(*S*) diastereomeric mixture.[3] Recently, we have reported[4] a new methodology for the synthesis of 1α,24(*R*)-dihydroxyvitamin D_3 (**1**), which employed a diastereoselective isopropylation of steroidal 24-aldehyde precursors (**3**) with diisopropylzinc in the presence of certain chiral β-amino alcohols to obtain 24(*R*)-hydroxycholesterol skeletons (**2**) as outlined in Scheme 1. In this previous study, 24-hydroxycholesterol derivatives (**2**) were found to be obtained with high diastereoselectivities (up to 98.8% de) in good yields (up to 80 %) when 20 mol% of β-amino alcohol was used. α,β-Unsaturated steroidal 24-aldehydes (**3**) were also found to provide the isopropylated adducts (**2**), in much higher yields than saturated



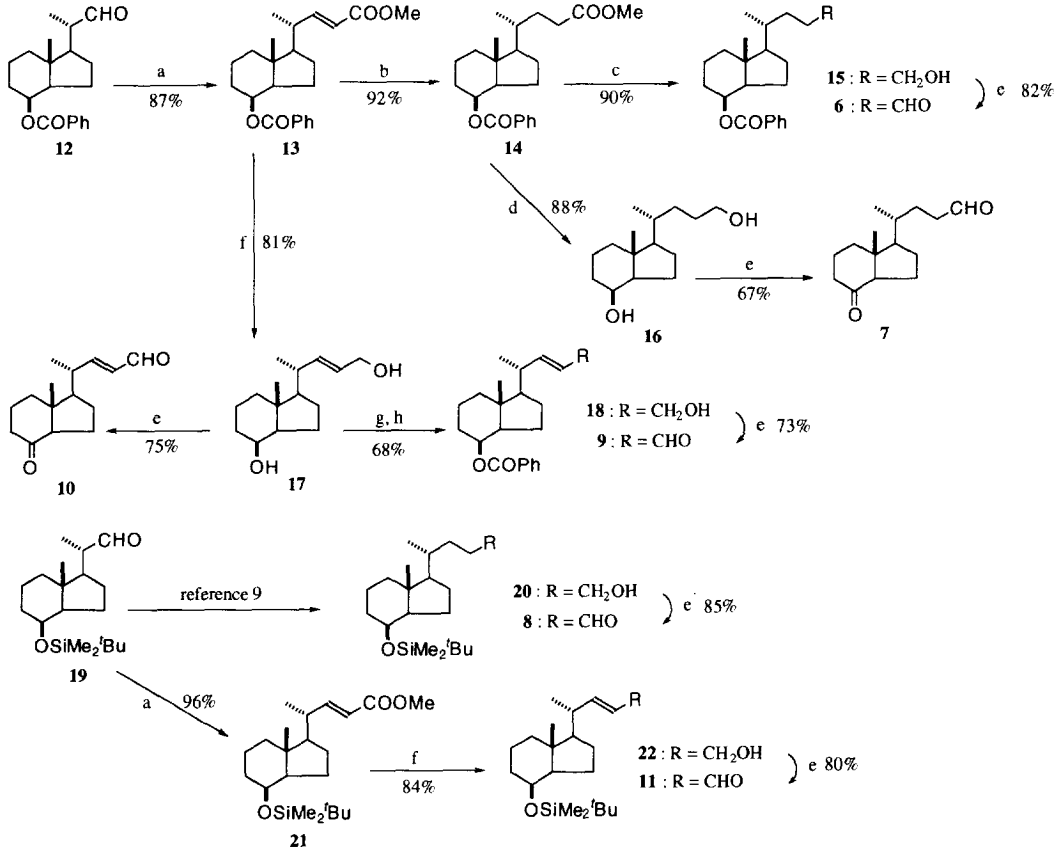
Scheme 1.

steroidal aldehydes.[4] The obtained 24(*R*)-hydroxycholesterol derivatives (**2**) are known to be converted into 1α,24(*R*)-dihydroxyvitamin D_3 (**1**) *via* a biomimetic synthetic methodology, which involves a photochemical cleavage of the corresponding 7,8-didehydrocholesterol derivatives, followed by a thermal isomerization reaction.[1,5]

The diastereoselective isopropylation of diisopropylzinc in the presence of certain chiral β-amino alcohols is applicable to a convergent synthetic approach,[6] which is more suitable for the large scale preparation of vitamin D_3 skeletons than biomimetic methods. We report herein the diastereoselective isopropylation reaction with CD-ring 24-aldehydes (**4**, steroidal nomenclature) and the synthesis of 1α,24(*R*)-dihydroxyvitamin D_3 (**1**) from the obtained isopropylated adducts (**5**) through the palladium-catalyzed alkylative enyne cyclization reaction.[6a]

RESULTS AND DISCUSSION

Preparation of starting CD-ring aldehydes as substrates for asymmetric isopropylation

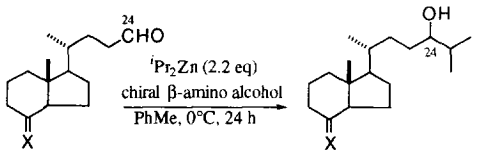


Scheme 2. Reagents : a) Ph_3P=CHCOOMe ; b) H_2, Pd/C ; c) $LiAl(O^tBu)_3H$; d) LAH ; e) $(COCl)_2$, DMSO, NEt_3 ; f) DIBAH ; g) PhCOCl ; h) KOH

Three saturated CD-ring 24-aldehydes, **6**, **7**, and **8**, and three α,β-unsaturated aldehydes, **9**, **10**, and **11**, were prepared as substrates for the asymmetric isopropylation starting from easily available synthons **12**[7], **19**[8], and **20**[9] as summarized in Scheme 2.

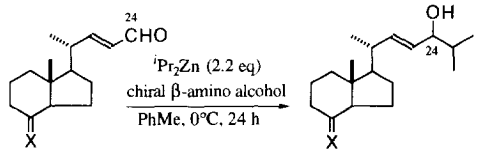
Reaction of CD-ring aldehydes with diisopropylzinc

In the cases of CD-ring 24-aldehydes instead of steroidal 24-aldehydes, similar diastereoselective isopropylation reactions proceeded in the presence of (-)-(*N*,*N*)-dibutylamino-1-phenylpropane-1-ol ((-)-DBNE)[10] as a chiral β-amino alcohol, which was found to be an effective catalyst for 24-steroidal aldehydes. In the reaction of the saturated CD-ring aldehyde **6**, only a 36% yield of the isopropylated product **23** was obtained together with the reduced product **15** (11%) in the presence of 5 mol% (-)-DBNE. The diastereomeric ratio of the product **23** was determined to be **23R**:**23S** = 95.0:5.0 by HPLC analysis (entry 1). In the presence of 20 mol% (-)-DBNE, the isopropylated product **23** was obtained in 65% yield with a high diastereoselectivity (98.0:2.0, entry 2).



6; X = α-H, β-OCOPh
7; X = O
8; X = α-H, β-OSiMe$_2$^{t}Bu

23; X = α-H, β-OCOPh
26; X = O
24; X = α-H, β-OSiMe$_2$^{t}Bu



9; X = α-H, β-OCOPh
10; X = O
11; X = α-H, β-OSiMe$_2$^{t}Bu

27; X = α-H, β-OCOPh
29; X = O
28; X = α-H, β-OSiMe$_2$^{t}Bu

In order to examine the influence of the protecting group of the hydroxy group at the C-8 position of the CD-ring aldehyde **6**, the 8-silyloxy aldehyde **8** was subjected to a similar addition reaction to afford the isopropylated product **24** in 52 % yield. The diastereomeric ratio of the product **24** was determined to be **25R**:**25S** = 98.3:1.7 by HPLC analysis of the derived dibenzoate **25**, indicating that the protecting group of the hydroxy group at the C-8 position did not affect the reaction products (entry 3). The 8-oxo aldehyde **7** also gave the corresponding isopropylated adduct **26** in 49% yield, the diastereomeric ratio of which was determined to be **25R**:**25S** = 98.1:1.9 by HPLC analysis of the converted dibenzoate **25** (entry 4).

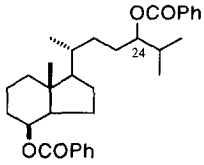
The α,β-unsaturated aldehyde **9** was similarly allowed to react with diisopropylzinc in the presence of 20 mol% (-)-DBNE to afford the isopropylated adduct **27** in 89% yield accompanied by the reduced product **18** (4%), the diastereomeric ratio (24*R*-isomer : 24*S*-isomer) of which was determined to be 4.8:95.2 by HPLC analysis of the mono benzoate **23** derived from the product **27** by hydrogenation (entry 5). Even in the presence of 5 mol% (-)-DBNE, a similar addition reaction of diisopropylzinc with the aldehyde **9** resulted in the formation of the isopropylated adduct **27** in 95% yield with a satisfactory diastereomeric ratio of 5.0:95.0 (entry 6).

Both the α,β-unsaturated aldehydes, **10** and **11**, also reacted with diisopropylzinc to provide the corresponding isopropylated adducts, **28** and **29**, in 89% yields with high diastereoselectivities (96.0:4.0 and 95.4:4.6), respectively (entries 7 and 8).

Table 1. Reaction of CD-Ring Aldehydes with $^{i}Pr_2Zn$

entry	aldehyde	chiral β-amino alcohol		isopropylated adduct (%)	reduced product (%)	R : S
1	**6**	(-)-DBNE	5 mol%	36%	11%	95.0 : 5.0
2	**6**	(-)-DBNE	20 mol%	65%	4%	98.0 : 2.0
3	**8**	(-)-DBNE	20 mol%	52%	6%	98.3 : 1.7
4	**7**	(-)-DBNE	20 mol%	49%	*	98.1 : 1.9
5	**9**	(-)-DBNE	20 mol%	89%	4%	4.8 : 95.2
6	**9**	(-)-DBNE	5 mol%	95%	2%	5.0 : 95.0
7	**11**	(-)-DBNE	20 mol%	89%	2%	4.0 : 96.0
8	**10**	(-)-DBNE	20 mol%	89%	*	4.6 : 95.4
9	**9**	(-)-DPNE	20 mol%	95%	3%	5.0 : 95.0
10	**9**	(-)-DANE	20 mol%	91%	2%	4.9 : 95.1
11	**9**	(+)-DPMPM	20 mol%	88%	3%	9.0 : 91.0
12	**9**	(+)-DMDPE	20 mol%	75%	1%	6.7 : 93.3
13	**9**	(-)-DAIB	20 mol%	94%	3%	4.1 : 95.9

* not measured



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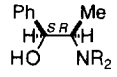
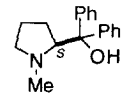
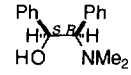


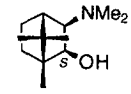
(-)-DPNE : R = Pr
(-)-DBNE : R = Bu
(-)-DANE : R = C_5H_{11}



(-)-DPMPM



(-)-DMDPE



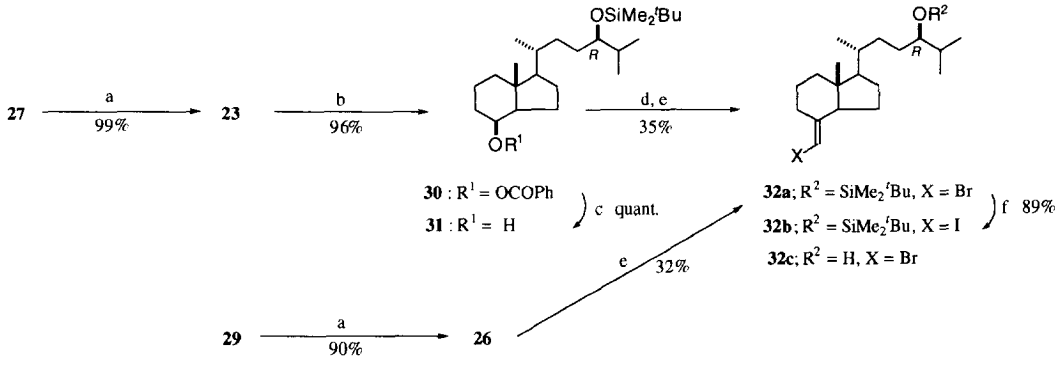
(-)-DAIB

In order to find out a further effective chiral ligand, several chiral β-amino alcohols were tested for the asymmetric isopropylation of the α,β-unsaturated aldehyde **9** in the amount of 20 mol% catalyst. (-)-(*N,N*)-Dipropylamino-1-phenylpropane-1-ol ((-)-DPNE), which was reported to be the best catalyst for the reaction of benzaldehyde with diisopropylzinc among the (-)-(*N,N*)-dialkylamino-1-phenylpropane-1-ols,[10] afforded the isopropylated product **27** in 95% yield with a high diastereoselectivity (95.0:5.0) (entry 9). (-)-(*N,N*)-Dipentylamino-1-phenylpropane-1-ol ((-)-DANE),[10] gave a 91% yield of the isopropylated adduct **27** also with high diastereoselectivity (95.1:4.9) (entry 10). These results showed that the *N*-alkyl (C3-C5) substituents of (-)-(*N,N*)-dialkylamino-1-phenylpropane-1-ol could not affect the present isopropylation reaction, different from the cases[10] of benzaldehyde. Both (+)-diphenyl(1-methylpyrrolidine-2-yl)methanol ((+)-DPMPM)[11] and (+)-(*N,N*)-dimethylamino-1,2-diphenylethanol ((+)-DMDPE)[12] resulted in lower yields with somewhat lower diastereoselectivities (entries 11 and 12). The use of (-)-3-*exo*-(dimethylamino)-isoborneol ((-)-DAIB),[13] which accomplished the best result in the cases of steroidal aldehydes, gave a similar result to the use of (-)-DBNE in the yield and the diastereoselectivity.

In addition, the obtained products, **26** and **29**, along with their precursors, **23**, **24**, **27** and **28**, were useful key intermediates to construct the vitamin D_3 skeleton by Wittig-Horner coupling methods.[6b-d,6i]

Synthesis of 1α,24(R)-dihydroxyvitamin D_3 (**1**) *from diastereoselective isopropylated products.*

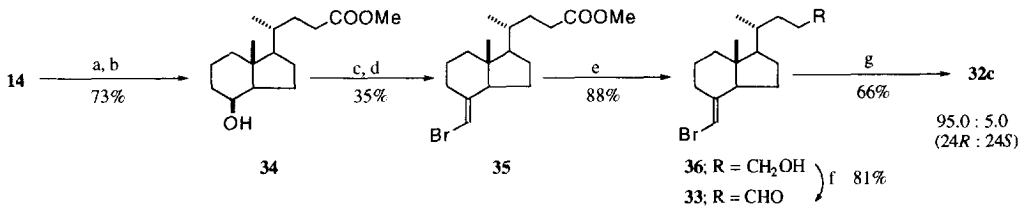
The key synthons **32a-c** for the palladium-catalyzed alkylative enyne cyclization reaction were prepared from the obtained isopropylated products, **23**, **26**, **27**, and **29** as outlined in Scheme 3.



Scheme 3. Reagents : a) H_2, Pt/C ; b) ^{t}BuMe$_2$SiCl ; c) DIBAH ; d) PCC ; e) $Ph_3P^+CH_2Br\ Br^-$, NaN(TMS)$_2$; f) ^{t}BuLi, I_2

Silylation of the alcohol **23** (**23R**:**23S** = 95.0:5.0) provided the silylated ether **30** (96%), which was reduced by diisobutylaluminum hydride to yield the alcohol **31**. Oxidation of the obtained alcohol **31** with pyridinium chlorochromate, followed by Wittig reaction of the resulting ketone gave the vinyl bromide **32a** (35% in 3 steps).[6a] The vinyl iodide **32b** was also obtained in 89% yield by treatment of the vinyl bromide **32a** with ^{t}BuLi and then iodine. The 24-hydroxy vinyl bromide **32c** was prepared in 32% yield through the Wittig reaction of the isopropylated adduct **26**.

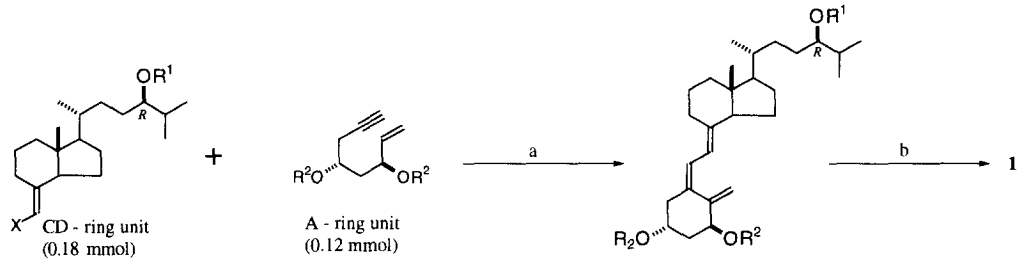
The 24-hydroxy vinyl bromide **32c** was also synthesized by the diastereoselective isopropylation reaction of the bromomethylene 24-aldehydes **33**, which were obtained from the diester **14** through **34**, **35**, **36**, and, **33** in 6 steps as summarized in Scheme 4. The asymmetric isopropylation reaction of the obtained bromomethylenated aldehyde **33** by a similar procedure using (-)-DBNE furnished the isopropylated product **32c** as a diastereomeric mixture in 66% yield. The diasteromeric ratio of **32c** was determined to be **25R**:**25S** = 95.0:5.0 by HPLC analysis after the conversion into the corresponding dibenzoate **25** *via* ozonolysis and benzoylation.



Scheme 4. Reagents : a) NaOH ; b) MeOH, H^+ ; c) PCC ; d) $Ph_3P^+CH_2Br\ Br^-$, NaN(TMS)$_2$; e) LAH ; f) $(COCl)_2$, DMSO, NEt_3 ; g) ^{i}Pr$_2$Zn, (-)-DBNE

We examined the palladium-catalyzed alkylative enyne cyclization reaction of the CD-ring vinyl halides **32** with the A-ring enynes **37** (Scheme 5). The dihydroxy enyne **37f** was prepared according to the cited reference.[14a] The bissilylated enynes **37a-e** were obtained by silylation of the dihydroxy enyne **37f** with the corresponding trialkylsilyl chlorides in the usual manner. The *tert*-butyldimethylsilylated enyne **37a**[14] and the excess vinyl bromide **32a** were allowed to react in the presence of $Pd(OAc)_2$ as a coupling catalyst according to B. M. Trost's procedure[6] to afford the silylated vitamin D_3 derivative **38a** in 55% yield (based on **37a**) (Table 2, entry 1). When $Pd_2(dba)_3$ was used as a catalyst, the coupling product **38a** was obtained in 58% yield, whereas the yield of the product **38a** was improved up to 67% (based on **32a**) by the use of an excess amount of **37a** (entry 2). Both Pd-catalysts, $Pd(OAc)_2$ and $Pd_2(dba)_3$, were found to be used in the cyclization reaction without essential differences in product yields. The vinyl iodide **32b** was found to react sufficiently even at 100°C to give the coupling product **38a** in 48% yield (entry 3). The product yields were improved up to 69% using $[PdCl(\eta^3\text{-}C_3H_5)]_2$ as a catalyst, as well as using heptane instead of toluene as a solvent (63%) and using the diisopropylethylamine instead of triethylamine (59%) (entries 4, 5, and 6). Reaction of the 24-hydroxy vinyl bromide **32c** with the enyne **37a** resulted in the formation of the coupling product **38b** in a high yield (70%) (entry 7). This result indicated that the protection of the hydroxy group on the CD-ring side chain was not necessary at all.

To study the effect of the protecting groups of the A-ring enyne **37**, four additional silylated enynes **37b-e** were subjected to the cyclization reaction. In the reaction of two silylated enynes, **37b** and **37c**, with the CD-ring vinyl bromide **32a**, the corresponding cyclized coupling products, **38c** and **38d**, were obtained in satisfactory yields (66% and 67%), respectively (entries 8 and 9). On the other hand, the coupling reaction of the other two silylated enynes, **37d** and **37e**, with the CD-ring vinyl bromide **32a** resulted in poor yields of the products, **38e** and **38f**, respectively (entries 10 and 11). Furthermore, a similar cyclization reaction of the unprotected enyne **37f** gave no coupling product at all (entry 12). These results disclosed that the protection of the enyne diol **37f** was necessary to give the coupling product and that the selection of the protecting groups of **37f** affected the product yields.



32a; $R^1 = SiMe_2{}^tBu$, X = Br
32b; $R^1 = SiMe_2{}^tBu$, X = I
32c; R^1 = H, X = Br

37a; $R^2 = SiMe_2{}^tBu$
37b; $R^2 = SiEt_3$
37c; $R^2 = SiPr_3$
37d; $R^2 = SiMe_3$
37e; $R^2 = SiPh_2{}^tBu$
37f; R^2 = H

38a; $R^1 = R^2 = SiMe_2{}^tBu$
38b; R^1 = H, $R^2 = SiMe_2{}^tBu$
38c; $R^1 = SiMe_2{}^tBu$, $R^2 = SiEt_3$
38d; $R^1 = SiMe_2{}^tBu$, $R^2 = SiPr_3$
38e; $R^1 = SiMe_2{}^tBu$, $R^2 = SiMe_3$
38f; $R^1 = SiMe_2{}^tBu$, $R^2 = SiPh_2{}^tBu$

Scheme 5. Reagents : a) Pd catalyst, PPh_3, amine ; b) pyridinium *p*-toluenesulfonate

Table 2. Palladium-Catalyzed Alkylative Enyne Cyclization Reaction

entry	CD-ring unit	A-ring unit	Pd catalyst*[1]	solvent	amine	temperature	reaction time	yield(%)*[2]
1	**32a**	**37a**	$Pd(OAc)_2$	toluene	NEt_3	120°C	4 h	55%
2	**32a**	**37a**	$Pd_2(dba)_3$	toluene	NEt_3	120°C	3 h	58% (67%*[3])
3	**32b**	**37a**	$Pd(OAc)_2$	toluene	NEt_3	100°C	2 h	48%
4	**32b**	**37a**	$[PdCl(\eta^3\text{-}C_3H_5)]_2$	toluene	NEt_3	100°C	2 h	69%
5	**32b**	**37a**	$Pd(OAc)_2$	heptane	NEt_3	100°C	2 h	63%
6	**32b**	**37a**	$Pd(OAc)_2$	toluene	$^iPr_2NEt$	100°C	2 h	59%
7	**32c**	**37a**	$Pd_2(dba)_3$	toluene	NEt_3	120°C	2 h	70%
8	**32a**	**37b**	$Pd_2(dba)_3$	toluene	NEt_3	120°C	3 h	66%
9	**32a**	**37c**	$Pd_2(dba)_3$	toluene	NEt_3	120°C	3 h	67%
10	**32a**	**37d**	$Pd_2(dba)_3$	toluene	NEt_3	120°C	3 h	15%
11	**32a**	**37e**	$Pd_2(dba)_3$	toluene	NEt_3	120°C	3 h	12%
12	**32a**	**37f**	$Pd_2(dba)_3$	toluene	NEt_3	120°C	3 h	0%

*[1] PPh_3 : Pd catalyst = 4 : 1, A-ring unit : Pd catalyst = 1 : 0.1 *[2] isolated yield (based on A-ring-unit)

*[3] CD-ring unit (0.12 mmol) and A-ring unit (0.24 mmol) were used (yields were based on CD-ring unit).

Desilylation of the obtained silylated vitamin D_3 derivative **38a**, prepared from a diastereomeric mixture (**23R**:**23S** = 95.0:5.0) with pyridinium *p*-toluenesulfonate afforded the 1α,24(*R*)-dihydroxyvitamin D_3 (**1**) in 75 % yield, which contained 5% of the 1α,24(*S*)-dihydroxyvitamin D_3. Recrystallization of the obtained product **1** from aqueous methanol furnished almost the pure 1α,24(*R*)-dihydroxyvitamin D_3 monohydrate (>99% purity), which could be supplied as a medicinal material without further purification. The obtained 1α,24(*R*)-dihydroxyvitamin D_3 monohydrate was completely identical with the authentic sample prepared through the biomimetic synthetic route using a steroidal starting material.[1]

CONCLUSION

In conclusion, the highly diastereoselective isopropylation[4] of steroidal 24-aldehydes **3** as starting substrates for a biomimetic synthetic procedure was extended to CD-ring aldehydes **4** to afford the isopropylated products **5** in good yields. The obtained isopropylated CD-ring products are useful key intermediates for the synthesis of 1α,24(*R*)-dihydroxyvitamin D_3 by coupling reactions with A-ring moieties.[6] We succeeded in the first convergent synthesis of 1α,24(*R*)-dihydroxyvitamin D_3 in a stereoselective manner using the palladium-catalyzed alkylative enyne cyclization method. In the present coupling reaction, it was found that the vinyl iodide as a CD-ring synthon was preferable to the corresponding vinyl bromide and that different protecting groups of the enyne substrates as an A-ring source significantly affected the product yields.

EXPERIMENTAL

IR spectra were recorded on a Shimadzu 8100M spectrometer. NMR spectra were obtained using a VARIAN GEMINI 200 (200 MHz) spectrometer with $CDCl_3$. Chemical shifts and coupling constants (*J*) are given in ppm relative to internal tetramethylsilane and Hz, respectively. The following abbreviations are used: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), b (broad). Mass spectra (MS) were taken at 70 eV using a HP 5971 mass spectrometer. For high-performance liquid chromatography (HPLC) analysis, a Shimadzu Model LC-6A equipped with a Shimadzu SPD-6A UV detector (254 nm) and a

Shimadzu C-R3A chromatopac was employed. Melting points were taken with a Mettler FP 81 and are uncorrected. A toluene solution of diisopropylzinc was purchased from Trichemical Inc.

Preparation of starting CD-ring aldehydes.

De-A,B-8β-(benzoyloxy)cholan-24-al (6).

A mixture of de-A,B-8β-(benzoyloxy)-23,24-dinorcholan-22-al (**12**, 0.57 g, 1.75 mmol) and methyl (triphenylphosphoranylidene)acetate (1.50 g, 4.49 mmol) in toluene (75 ml) was heated at 80°C for 39 h. The reaction mixture was concentrated *in vacuo* and the residue was chromatographed on silica gel (100 g) using hexane and Et_2O (40:1 up to 20:1) to provide methyl (22*E*)-de-A,B-8β-(benzoyloxy)chol-22-en-24-oate (**13**, 0.57 g, 1.53 mmol, 87%); IR (neat): 2940, 1712, 1650, 1440, 1424, 1260, 1164, 1104 cm^{-1}; ^1H NMR: δ 1.07 (s, 3H), 1.10 (d, 3H, J = 6 Hz), 1.15-2.45 (m, 13H), 2.05-2.35 (m, 1H), 3.70 (s, 3H), 5.41 (b, 1H), 5.75 (d, 1H, J = 14 Hz), 6.84 (dd, 1H, J = 6, 14 Hz), 7.40-7.60 (m, 3H), 8.00-8.10 (m, 2H); MS (*m/z*): 370 (M^+).

A 10% Pd/C catalyst (85 mg) was added to a solution of the above product **13** (570 mg, 1.54 mmol) in EtOH (8.5 ml). The resulting mixture was stirred at room temperature for 2 h under a hydrogen atmosphere. The catalyst was filtered off and the resulting filtrate was concentrated to yield a crude product, which was chromatographed on silica gel (100 g) with hexane and EtOAc (40:1 up to 20:1) yielding methyl de-A,B-8β-(benzoyloxy)cholan-24-oate (**14**, 530 mg, 1.42 mmol, 92%); IR (neat): 2930, 1702, 1420, 1260, 1152, 1103 cm^{-1}; ^1H NMR: δ 0.95 (d, 3H, J = 6 Hz), 1.04 (s, 3H), 1.10-2.45 (m, 15H), 3.67 (s, 3H), 5.41 (b, 1H), 7.4-7.6 (m, 3H), 8.0-8.1 (m, 2H); MS (*m/z*): 372 (M^+).

The obtained ester **14** (530 mg, 1.42 mmol) was reacted with $LiAl(O^tBu)_3H$ (3.24 g, 12.73 mmol) in THF at room temperature for 62 h. A 1 N HCl solution (150 ml) was added, and the resulting mixture was extracted with EtOAc (150 ml). The extract was washed with brine (150 ml). After drying ($MgSO_4$), filtration, and evaporation, the obtained crude product was chromatographed on silica gel (100 g) using hexane and EtOAc (20:1 up to 3:1) to give de-A,B-8β-(benzoyloxy)cholan-24-ol (**15**, 440 mg, 1.28 mmol, 90%); IR (neat): 3340, 2910, 1705, 1256, 1104 cm^{-1}; ^1H NMR: δ 0.96 (d, 3H, J = 6 Hz), 1.05 (s, 3H), 1.05-2.15 (m, 15H), 3.62 (t, 3H, J = 6 Hz), 5.42 (b, 1H), 7.40-7.60 (m, 3H), 8.00-8.10 (m, 2H); MS (*m/z*): 344 (M^+).

Dimethylsulfoxide (0.73 ml, 10.29 mmol) was added dropwise at -50°C to a solution of oxalyl chloride (0.44 ml, 5.13 mmol) in CH_2Cl_2 (12 ml). The resulting mixture was stirred at -50°C for 1 h . A solution of **15** (430 mg, 1.25 mmol) in CH_2Cl_2 (3 ml) was added dropwise and the reaction mixture was stirred at -50°C for 30 min. Triethylamine (1.80 ml, 13.01 mmol) was added and the resulting mixture was stirred at 0-25°C for 1 h. A saturated aqueous NH_4Cl solution (100 ml) was poured into the mixture, which was extracted with CH_2Cl_2 (150 ml). The extract was washed with 1 N HCl solution (100 ml), a saturated aqueous $NaHCO_3$ solution (100 ml), and then brine (100 ml). Drying ($MgSO_4$), filtration, and evaporation of the solvent gave a crude product, which was chromatographed on silica gel (20 g) with hexane and EtOAc (40:1 up to 15:1) to give de-A,B-8β-(benzoyloxy)cholan-24-al (**6**, 350 mg, 1.02 mmol, 82%); IR (neat): 2930, 1704, 1440, 1308, 1260, 1105, 1062 cm^{-1}; ^1H NMR: δ 0.95 (d, 3H, J = 6 Hz), 1.05 (s, 3H), 1.05-2.15 (m, 13H), 2.25-2.55 (m, 2H), 5.42 (b, 1H), 7.60-7.80 (m, 3H), 8.00-8.10 (m, 2H), 9.78 (t, 1H, J = 3 Hz); MS (*m/z*): 220 (M-122)$^+$; High-resolution MS for $C_{22}H_{30}O_3$ (M^+): Calcd. *m/z*: 342.2195; Found: 342.2135.

De-A,B-8-oxocholan-24-al (7)

To a stirred suspension of $LiAlH_4$ (143 mg, 14.28 mmol) in THF (3 ml) was added a solution of the above ester **14** (401 mg, 1.08 mmol) in THF (2 ml) at room temperature. After stirring for 6 h, water was added dropwise and the resulting mixture was poured into a mixture of 1 N HCl solution (100 ml) and EtOAc (100 ml). The separated organic layer was washed with brine and then dried over $MgSO_4$. After filtration and removal of the solvent, the residual product was chromatographed on silica gel (100 g) eluting with hexane and EtOAc (10:1 up to 1:1) to give de-A,B-cholan-8β,24-diol (**16**, 227 mg, 0.95 mmol, 88%); mp: 102.0-106.0°C (hexane-EtOAc); IR (KBr): 3275, 2910, 1430, 1345, 1055, 1025 cm^{-1}; ^1H NMR: δ 0.88 (d, 3H, J = 6 Hz), 0.92 (s, 3H), 0.95-2.05 (m, 15H), 3.61 (t, 2H, J = 6 Hz), 4.07 (b, 1H); MS (*m/z*): 225 (M-15)$^+$.

The aldehyde **7** (150 mg, 0.64 mmol) was obtained from the above diol **16** (227 mg, 0.95 mmol) by a procedure similar to the aldehyde **6** in 67% yield; IR (neat): 2940, 1702, 1375 cm^{-1}; ^1H NMR: δ 0.90 (d, 3H, J = 6 Hz), 1.03 (s, 3H), 1.05-2.55 (m, 15H), 9.75 (t, 1H, J = 3 Hz); MS (*m/z*): 236 (M^+); High-resolution MS for $C_{15}H_{24}O_2$ (M^+): Calcd. *m/z*: 236.1776; Found: 236.1759.

(22*E*)-De-A,B-8β-(benzoyloxy)chol-22-en-24-al (9)

To a solution of the α,β-unsaturated ester **13** (500 mg, 1.35 mmol) in toluene (60 ml) was added at -78°C a 1.0 M solution of $^iBu_2AlH$ (11 ml, 11 mmol). After stirring at -78°C for 3 h, a 1 N HCl solution (100 ml) was added. Extraction (EtOAc), washing (1 N HCl solution and brine), drying ($MgSO_4$) and concentration afforded a crude product, which was chromatographed on silica gel (30 g) using hexane and EtOAc (10:1 up to 1:1) to give (22*E*)-de-A,B-chol-22-en-8β,24-diol (**17**, 260 mg, 1.09 mmol, 81%); mp: 93.5-97.0°C (hexane-EtOAc); IR (KBr): 3480, 2973, 2887, 2849, 1474, 1456, 1447, 1326, 1076 cm^{-1}; ^1H NMR: δ 0.94 (s, 3H), 1.02 (d, 3H, J = 6 Hz), 1.05-2.20 (m, 13H), 4.00-4.10 (b, 1H), 5.45-5.65 (m, 2H); MS (*m/z*): 238 (M^+).

To a solution of the diol **17** (260 mg, 1.06 mmol) in CH_2Cl_2 (8 ml) was added 4-dimethylaminopyridine (1.48 g, 12.13 mmol) and benzoyl chloride (1.17 ml, 10.08mmol) at room temperature. After stirring at 40°C for 1 h, a 1 N HCl solution (100 ml) was added and the resulting mixture was extracted with EtOAc (100 ml). Usual work-up (washing, drying, filtration, and evaporation) gave a crude benzoylated product, which was treated with KOH (1.70 g, 30.4 mmol) in EtOH (15 ml) at room temperature. The reaction mixture was stirred at 35°C for 20 min and then poured into a 1 N HCl solution (100 ml). After usual treatment of the reaction mixture, chromatographic separation on silica gel (25 g) with hexane and Et_2O (4:1 up to 2:1) yielded (22*E*)-de-A,B-8β-(benzoyloxy)chol-22-en-24-ol (**18**, 254 mg, 0.74 mmol, 68%); IR (neat): 3400, 2948, 1717, 1269, 1113 cm^{-1}; ^1H NMR: δ 1.05 (d, 3H, J = 6 Hz), 1.07 (s, 3H), 1.10-2.30 (m, 13H), 4.08 (b, 2H), 5.40 (b, 1H), 5.50-5.60 (m, 2H), 7.40-7.60 (m, 3H), 8.00-8.10 (m, 2H); MS (*m/z*): 342 (M^+).

The above alcohol **18** (226 mg, 0.66 mmol) was converted into the aldehyde **9** (164 mg, 0.48 mmol) by a procedure similar to the aldehyde **6** in 73% yield; mp: 121.0-122.5°C (hexane-EtOAc); IR (KBr): 2930, 1707, 1684, 1480. 1471, 1314, 1270, 1260,

1111, 1073 cm^{-1}; ^1H NMR: δ 1.07 (s, 3H), 1.17 (d, 3H, *J* = 6 Hz), 1.20-2.55 (m, 13H), 5.43 (b, 1H), 6.07 (dd, 1H, *J* = 6, 14 Hz), 6.73 (dd, 1H, *J* = 6, 14 Hz), 7.40-7.65 (m, 3H), 8.00-8.10 (m, 2H), 9.51 (d, 1H, *J* = 6 Hz); MS (*m/z*): 340 (M^+); High-resolution MS for $C_{22}H_{28}O_3$ (M^+): Calcd. *m/z*: 340.2038; Found: 340.2031.

(22*E*)-De-A,B-8-oxocholl-22-en-24-al (10)

The aldehyde **10** (109 mg, 0.47 mmol) was obtained from the above alcohol **17** (150 mg, 0.63 mmol) by a procedure similar to the aldehyde **6** in 75% yield; mp: 117.0-121.5°C (hexane-EtOAc); IR (KBr): 2980, 2816, 2745, 1705, 1682, 1480, 1422, 1150, 1123 cm^{-1}; ^1H NMR: δ 0.60 (s, 3H), 1.18 (d, 3H, *J* = 6 Hz), 1.20-2.55 (m, 13H), 6.09 (dd, 1H, *J* = 6, 14 Hz), 6.73 (dd, 1H, *J* = 6, 14 Hz), 9.50 (d, 1H, *J* = 6 Hz); MS (*m/z*): 234 (M^+); High-resolution MS for $C_{15}H_{22}O_2$ (M^+): Calcd. *m/z*: 234.1619; Found: 334.1567.

De-A,B-8β-(*tert*-butyldimethylsilyloxy)cholan-24-al (8)

The aldehyde **8** (211 mg, 0.60 mmol) was obtained from the alcohol de-A,B-8β-(*tert*-butyldimethylsilyloxy)cholan-24-ol (**20**, 250 mg, 0.70 mmol) by a procedure similar to the aldehyde **6** in 85% yield; IR (KBr): 2910, 1718, 1450, 1240 cm^{-1}; ^1H NMR: δ -0.02 (s, 3H), 0.00 (s, 3H), 0.80-0.95 (m, 15H), 0.95-2.00 (m, 13H), 2.15-2.55 (m, 2H), 9.78 (t, 1H, *J* = 3 Hz); MS (*m/z*): 337 (M-15)$^+$; High-resolution MS for $C_{18}H_{35}OSi$ (M-57)$^+$; Calcd. *m/z*: 295.2457; Found: 295.2446.

(22*E*)-De-A,B-8β-(*tert*-butyldimethylsilyloxy)chol-22-en-24-al (11)

Methyl (22*E*)-de-A,B-8β-(*tert*-butyldimethylsilyloxy)chol-22-en-24-oate (**21**, 0.74 g, 1.95 mmol) was obtained from de-A,B-8β-(*tert*-butyldimethylsilyloxy)-23,24-dinorcholan-22-al (**19**, 0.66 g, 2.03 mmol) by a procedure similar to the α,β-unsaturated ester **13** in 96% yield; mp: 76.0-79.5°C (hexane-EtOAc); IR (KBr): 2982, 2950, 1725, 1458, 1335, 1240, 1169, 1145 cm^{-1}; ^1H NMR: δ 0.05 (s, 3H), 0.07 (s, 3H), 0.93 (s, 9H), 1.01 (s, 3H), 1.13 (d, 3H, *J* = 6 Hz), 1.20-2.40 (m, 13H), 3.78 (s, 3H), 4.07 (b, 1H), 5.80 (d, 1H, *J* = 14 Hz), 6.90 (dd, 1H, *J* = 6, 14 Hz); MS (*m/z*): 380 (M^+).

(22*E*)-De-A,B-8β-(*tert*-butyldimethylsilyloxy)chol-22-en-24-ol (**22**, 361 mg, 0.97 mmol) was obtained from the above ester **21** (440 mg, 1.16 mmol) by a procedure similar to the diol **17** in 84% yield; mp: 69.0-70.0°C (hexane-EtOAc); IR (KBr): 3300, 2920, 2860, 1472, 1460, 1372, 1252, 1165, 1102 cm^{-1}; ^1H NMR: δ -0.01 (s, 3H), 0.01 (s, 3H), 0.88 (s, 9H), 0.93 (s, 3H), 1.02 (d, 3H, *J* = 6 Hz), 1.05-2.20 (m, 13H), 4.00 (b, 2H), 4.07 (b, 2H), 5.50-5.60 (m, 2H); MS (*m/z*): 350 (M^+); Found: C, 71.13; H, 11.49; $C_{21}H_{40}O_2Si$ requires C, 71.53; H, 11.43.

The α,β-unsaturated aldehyde **11** (288 mg, 0.82 mmol) was obtained from the above alcohol **22** (340 mg, 1.03 mmol) by a procedure similar to the aldehyde **6** in 80% yield; mp: 57.5-58.0°C (hexane-EtOAc); IR (KBr): 2950, 2860, 1690, 1460, 1252, 1120, 1110 cm^{-1}; ^1H NMR: δ 0.00 (s, 3H), 0.02 (s, 3H), 0.88 (s, 9H), 0.99 (s, 3H), 1.12 (d, 3H, *J* = 6 Hz), 1.15-2.10 (m, 12H), 2.30-2.50 (m, 1H), 4.02 (b, 1H), 6.05 (dd, 1H, *J* = 6, 14 Hz), 6.73 (dd, 1H, *J* = 6, 14 Hz), 9.49 (t, 1H, *J* = 6 Hz); MS (*m/z*): 350 (M^+); High-resolution MS for $C_{21}H_{38}O_2Si$ (M^+): Calcd. *m/z*: 350.2641; Found: 350.2688.

General procedure for the asymmetric addition of diisopropylzinc to CD-ring aldehydes

To a solution of **an aldehyde** (0.25 mmol) and **a chiral β-amino alcohol** (0.05 mmol) in toluene (2 ml) was added at 0°C a 0.87 M toluene solution of diisopropylzinc (0.63 ml, 0.55 mmol), and the resulting mixture was stirred for 24 h. After a 0.5 N HCl solution was added, the mixture was extracted with EtOAc (20 ml). The separated extract was washed with a saturated aqueous $NaHCO_3$ solution (20 ml) and brine (20 ml). Drying over $MgSO_4$ and filtration followed by evaporation of the solvent gave a crude product, which was subjected to silica gel chromatography (20 g) with hexane and EtOAc (50:1 up to 1:1), providing **the corresponding isopropylated adduct** as a diastereomeric mixture together with the reduced product. The results are summarized in Table 1.

De-A,B-8β-(benzoyloxy)cholest-24-ol (23, 62 mg, 0.16 mmol) was obtained from the aldehyde **6** (85 mg, 0.25 mmol) in 65% yield accompanied by a reduced product **15** (3 mg, 0.01 mmol, 4%) in the presence of (-)-DBNE; IR (neat): 3500, 2870, 1710, 1265, 1110 cm^{-1}; ^1H NMR: δ 0.85-1.00 (m, 9H), 1.05 (s, 3H), 1.1-2.15 (m, 18H), 3.25-3.40 (m, 1H), 5.42 (b, 1H), 7.40-7.60 (m, 3H), 8.00-8.15 (m, 1H); MS (*m/z*): 386 (M^+); High-resolution MS for $C_{25}H_{38}O_3$ (M^+): Calcd. *m/z*: 386.2820; Found: 386.2845.

De-A,B-8β-(*tert*-butyldimethylsilyloxy)cholest-24-ol (24, 52 mg, 0.13 mmol) was obtained from the aldehyde **8** (88 mg, 0.25 mmol) in 52% yield accompanied by a reduced product **20** (5 mg, 0.02 mmol, 6%) in the presence of (-)-DBNE; mp: 41.0-45.0°C (hexane-EtOAc); IR (neat): 3375, 2900, 1450, 1242, 1016 cm^{-1}; ^1H NMR: δ -0.02 (s, 3H), 0.00 (s, 3H), 0.8-0.95 (m, 21H), 0.95-2.50 (m, 18H), 3.35-3.45 (m, 1H), 3.97 (b, 1H); MS (*m/z*): 381 (M-15)$^+$.

De-A,B-8-oxocholest-24-ol (26, 34 mg, 0.12 mmol) was obtained from the aldehyde **7** (59 mg, 0.25 mmol) in 49% yield in the presence of (-)-DBNE; mp: 59.0-63.0°C (hexane-EtOAc); IR (neat): 3440, 2925, 1680 cm^{-1}; ^1H NMR: δ 0.63 (s, 3H), 0.95 (d, 3H, *J* = 6 Hz), 0.95-2.50 (m, 18H), 3.62 (t, 1H, *J* = 6 Hz); MS (*m/z*): 280 (M^+); High-resolution MS for $C_{18}H_{32}O_2$ (M^+): Calcd. *m/z*: 280.2401; Found: 280.2325.

(*E*)-De-A,B-8β-(benzoyloxy)cholest-22-en-24-ol (27, 85 mg, 0.22 mmol) was obtained from the aldehyde **9** (85 mg, 0.25 mmol) in 89% yield accompanied by a reduced product **18** (3 mg, 0.01 mmol, 4%) in the presence of (-)-DBNE; IR (neat): 3500, 2953, 2870, 1717, 1410, 1314, 1113 cm^{-1}; ^1H NMR: δ 0.85-1.00 (m, 9H), 1.1-2.40 (m, 18H), 3.80 (t, 1H, *J* = 6 Hz), 5.43 (b, 1H), 5.40-5.65 (m, 2H), 7.40-7.60 (m, 3H), 8.00-8.10 (m, 1H); MS (*m/z*): 384 (M^+); High-resolution MS for $C_{25}H_{36}O_3$(M^+): Calcd. *m/z*: 384.2664; Found: 384.2703.

(*E*)-De-A,B-8β-(*tert*-butyldimethylsilyloxy)cholest-22-en-24-ol (**28**, 88 mg, 0.22 mmol) was obtained from the aldehyde **11** (88 mg, 0.25 mmol) in 89% yield accompanied by a reduced product **22** (2mg, 0.01 mmol, 2%) in the presence of (-)-DBNE; mp: 57.5-58.0°C (hexane-ethyl acetate); IR (KBr): 3380, 2950, 2930, 2859, 1472, 1374, 1252, 1165, 1082 cm^{-1}; ^1H NMR: δ -0.02 (s, 3H), 0.00 (s, 3H), 0.8-0.95 (m, 9H), 0.87 (s, 9H), 1.01 (d, 3H, *J* = 6 Hz), 1.05-2.15 (m, 16H), 3.73 (t, 1H, *J* = 6 Hz), 4.00 (b, 1H), 5.35-5.55 (m, 2H); MS (*m/z*): 379 (M^+); High-resolution MS for $C_{24}H_{46}O_2Si$ (M^+): Calcd. *m/z*: 394.3267; Found: 394.3227.

(*E*)-De-AB-8-oxocholest-22-en-24-ol (**29**, 60 mg, 0.22 mmol) was obtained from the aldehyde **10** (59 mg, 0.25 mmol) in 89% yield in the presence of (-)-DBNE; IR (neat): 3450, 2957, 2874, 1715, 1458, 1381, 1024 cm^{-1}; ^1H NMR: δ 0.62 (s, 3H), 0.8-0.95 (m, 6H), 1.05 (d, 3H, *J* = 6 Hz), 1.10-2.50 (m, 16H), 3.73 (t, 1H, *J* = 6Hz), 5.30-5.55 (m, 2H); MS (*m/z*): 278 (M^+); High-resolution MS for $C_{15}H_{22}O_2$ (M^+): Calcd. *m/z*: 278.2245; Found: 278.2245.

Determination of the diastereomeric ratio of the isopropylated adducts

A typical procedure for the determination of the diastereomeric ratios of the isopropylated adducts is as follows. After conversion of the isopropylated to the diols, the obtained alcohols were acylated with benzoyl chloride in pyridine to provide the corresponding benzoate. The obtained benzoate was subjected to HPLC analysis to estimate the diastereomeric ratio by comparison of the peak areas of the 24R- and 24S-benzoates. The results of the asymmetric isopropylation reactions of CD-ring aldehydes with diisopropylzinc under various conditions are summarized in Table 1.

Determination of the diastereomeric ratios of the isopropylated adduct 23.

The isopropylated adduct **23** was subjected to HPLC analysis (Zorbax Sil 25 cm x 4.6 mm I.D.) using hexane-CH_2Cl_2-EtOH (90:10:0.3) as a mobile phase at 2.0 ml/min to estimate the ratio of **23R** and **23S** (**23R**; 16.9 min, **23S**; 15.5 min).

Determination of the diastereomeric ratios of the isopropylated adduct 24.

Pyridinium-hydrogen fluoride (0.2 ml) was added at room temperature to a solution of the diastereomeric mixture of **24** (13 mg) in acetonitrile (0.5 ml). After stirring at room temperature for 2 h, the usual work-up yielded a crude product. To a solution of the resulting crude product and 4-dimethylaminopyridine (75 mg) in CH_2Cl_2 (0.5 ml) was added benzoyl chloride (0.06 ml) at room temperature. After stirring at room temperature for 18 h, usual treatment of the resulting mixture gave a crude product, which was purified by column chromatography on silica gel (10 g) with hexane and EtOAc (40:1) yielding the corresponding dibenzoate **25** (13 mg) as a diastereomeric mixture. The dibenzoate **25** was subjected to HPLC analysis (Zorbax Sil 25 cm x 4.6 mm I.D.) using hexane-CH_2Cl_2-EtOH (90:10:0.1) as a mobile phase at 2.0 ml/min to estimate the ratio of the 24*R*- and 24*S*-dibenzoates (24*R*-isomer; 12.2 min, 24*S*-isomer; 13.3 min); **25**; IR (neat): 3060, 1720, 1710, 1270, 1110 cm^{-1}; ^1H NMR: δ 0.75-1.05 (m, 12H), 1.05-2.15 (m, 18H), 4.90-5.05 (m, 1H), 5.35-5.45 (m, 1H), 7.35-7.60 (m, 6H), 7.95-8.10 (m, 4H); MS (*m/z*): 368 $(M-122)^+$; High-resolution MS for $C_{25}H_{36}O_2$ (M^+): Calcd. *m/z*: 368.2715; Found: 368.2699.

Determination of the diastereomeric ratios of the isopropylated adduct 26.

The isopropylated adduct **26** (6 mg) was treated at room temperature with $LiAl(O^tBu)_3H$ (10 mg) in THF (0.5 ml). The usual work-up gave a crude alcohol, which was similarly converted into the dibenzoate **25** (10 mg) by benzoylation with benzoyl chloride and pyridine. The diastereomeric ratios were evaluated by a similar HPLC analysis of the dibenzoate **25**.

Determination of the diastereomeric ratios of the isopropylated adduct 27.

A mixture of the isopropylated adduct **27** (9.6 mg, 0.025 mmol) and a 10% Pd/C (2 mg) in EtOH (1 ml) was stirred at room temperature for 1 h under a hydrogen atomosphere. The catalyst was filtered off and the resulting filtrate was evaporated to provide the reduced product **23** (9.6 mg, 0.025 mmol, 99%), which was subjected to HPLC analysis as mentioned above to estimate the diastereomeric ratio of the product **27**.

Determination of the diastereomeric ratios of the isopropylated adduct 28.

The isopropylated adduct **28** (10 mg) was similarly hydrogenated like the benzoate **27** to give a crude alcohol **24**, which was converted into the dibenzoate **25** (6 mg) as mentioned above. The dibenzoate **25** was subjected to HPLC analysis to determine the diastereomeric ratios of the product **28**.

Determination of the diastereomeric ratios of the isopropylated adduct 29.

The carbonyl group of the isopropylated adduct **29** (13 mg) was reduced in a manner similar to the ketone **26** followed by hydogenation like the benzoate **27** to afford a crude diol, which was analogously benzoylated to give the dibenzoate **25** (14 mg). The obtained dibenzoate **25** was subjected to HPLC analysis as described above to estimate the diastereomeric ratio of the product **29**.

Synthesis of 1α,24(R)-dihydroxyvitamin D_3

(24*R*)-De-A,B-8β-(benzoyloxy)cholest-24-ol *tert*-butyldimethylsilyl ether (30).

To a solution of (24*R*)-de-A,B-8β-(benzoyloxy)cholest-24-ol **23** (1.19 g, 3.09 mmol; 24*R*:24*S* = 95.0:5.0) in DMF (16 ml) was added *tert*-butylchlorodimethylsilane (1.29 g, 8.57 mmol) and imidazole (1.36 g, 20.0 mmol) at 0°C, and the resulting mixture was stirred at room temperature for 18 h. A saturated aqueous $NaHCO_3$ solution (100 ml) was added and the resulting mixture was extracted with EtOAc (2 x 100 ml). Usual work-up of the extract gave a crude silylated product, which was chromatographed on silica gel (40 g) eluting with hexane and EtOAc (40:1) to yield the silylated ether **30** (1.48 g, 2.96 mmol, 96%); IR (neat): 2950, 2860, 1717, 1471, 1464, 1453, 1267, 1111, 1069 cm^{-1}; ^1H NMR: δ 0.03 (s, 6H), 0.80-1.00 (m, 18H), 1.05 (s, 3H), 1.05-2.15 (m,

18H), 3.30-3.40 (m, 1H), 5.35-5.45 (m, 1H), 7.35-7.60 (m, 6H), 8.00-8.10 (m, 4H); MS (*m/z*): 500 (M^+); High-resolution MS for $C_{31}H_{52}O_3Si$ (M^+): Calcd. *m/z*: 500.3686; Found: 500.3744.

(24*R*)-De-A,B-8β-hydroxycholest-24-ol *tert*-butyldimethylsilyl ether (31).

To a solution of the silylated ether **30** (4.52 g, 9.04 mmol) in toluene (200 ml) was added at -78°C a 1.0 M hexane solution of $^iBu_2AlH$ (39 ml, 39 mmol). After stirring at -78°C for 1 h, a 2 N HCl solution (300 ml) was added, and the resulting mixture was extracted with EtOAc (2 x 300 ml). After usual work-up, an obtained crude product was chromatographed on silica gel (130 g) using hexane and EtOAc (30:1 up to 20:1) to give quantitatively the silylated alcohol **31** (3.57 g, 9.03 mmol); IR (neat): 3630, 2953, 1746, 1732, 1471, 1371, 1250, 1051 cm^{-1}; ^1H NMR: δ 0.03 (s, 3H), 0.04 (s, 3H), 0.80-0.95 (m, 21H), 1.05-2.10 (m, 18H), 3.30-3.40 (m, 1H), 4.05-4.10 (m, 1H); MS (*m/z*): 353 $(M-43)^+$; High-resolution MS for $C_{24}H_{47}O_2Si$ $(M-1)^+$: Calcd. *m/z*: 395.3346; Found: 395.3293.

(*E*)-(24*R*)-De-A,B-8-bromomethylenecholest-24-ol *tert*-butyldimethylsilyl ether (32a).

Pyridinium chlorochromate (1.31 g, 6.09 mmol) was added to a solution of the silylated alcohol **31** (804 mg, 2.13 mmol) in CH_2Cl_2 (40 ml) at room temperature. The resulting suspension was stirred for 1 h and then filtered through a small pad of silica gel, which was washed with a mixture of hexane and EtOAc (1:1). Concentration of the filtrate and washings *in vacuo* gave a crude ketone (730 mg), which was allowed to react without further purification. To a suspension of (bromomethylene)-triphenylphosphonium bromide in THF (20 ml) was added at -20°C a 1.0 M THF solution of sodium hexamethyldisilazide (5.0 ml, 5.0 mmol) and then a 1.0 M THF solution of potassium *tert*-butoxide (5.0 ml, 5.0 mmol). After stirring for 30 min, to the cooled suspension was added at -60°C a solution of the above crude ketone in THF (5 ml). After stirring at room temperature for 1 h, hexane was added and the resulting suspension was filtered through a small pad of silica gel, which was washed with a mixture of hexane and EtOAc (1:1). After concentration of the filtrate and washings, the residue was chromatograhed on silica gel (60 g) with hexane to give the vinyl bromide **32a** (338 mg, 0.74 mmol, 35% in two steps); IR (neat): 2940, 2910, 2840, 1458, 1378, 1244 cm^{-1}; ^1H NMR: δ 0.04 (s, 6H), 0.57 (s, 3H), 0.8-0.95 (m, 18H), 1.05-2.10 (m, 17H), 2.85-2.95 (m, 1H), 3.33-3.43 (m, 1H), 5.65 (m, 1H); MS (*m/z*): 470 (M^+), 472 (M^+); High-resolution MS for $C_{25}H_{45}BrO_2Si$ (M^+): Calcd. *m/z*: 470.2580; Found: 470.2498.

(*E*)-(24*R*)-De-A,B-8-iodomethylenecholest-24-ol *tert*-butyldimethylsilyl ether (32b).

To a solution of the vinyl bromide **32a** (498 mg, 0.61 mmol) in Et_2O (7 ml) was added at -78°C a 1.6 M pentane solution of *t*-BuLi (2.6 ml, 4.16 mmol). The mixture was stirred at -78°C for 1 h, then a saturated etherial solution of iodine was added dropwise until a brown color persisted. After stirring for 30 min, the mixture was warmed up to room temperature and then brine (30 ml) was added. After extraction, washing, drying, filtration, and then evaporation of the solvent, an obtained crude product was chromatographed on silica gel (35 g) using hexane to give the vinyl iodide (**32b**, 490 mg, 0.54 mmol, 89%); IR (neat): 1509, 1456, 1254 cm^{-1}; ^1H NMR: δ 0.04 (s, 6H), 0.56 (s, 3H), 0.8-0.95 (m, 18H), 1.05-2.10 (m, 18H), 2.65-2.80 (m, 1H), 3.33-3.43 (m, 1H), 5.60 (m, 1H); MS (*m/z*): 378 $(M-140)^+$.

(*E*)-(24*R*)-De-A,B-8-bromomethylenecholest-24-ol (32c)

A mixture of the isopropylated adduct **29** (268 mg, 0.96 mmol) and PtO_2 (30 mg) in EtOH (5 ml) was stirred at room temperature for 30 min under a hydrogen atomosphere. The catalyst was filtered off and the resulting filtrate was evaporated to provide a crude product, which was chromatographed on silica gel (30 g) using hexane and EtOAc (4:1 up to 2:1) to give the hydrogenated product **26** (242 mg, 0.86 mmol, 90%). This product **26** was identical with the product **26** obtained from the aldehyde **7** by the above-mentioned asymmetric isopropylation reaction.

The ketone **26** (95 mg, 0.36 mmol) was also converted into the vinyl bromide **32c** (37 mg, 0.11 mmol) by a procedure similar to the vinyl bromide **32a** in 32% yield; IR (neat): 3370, 3070, 1625, 1460, 1375, 1260 cm^{-1}; ^1H NMR: δ 0.56 (s, 3H), 0.70-1.00 (m, 9H), 1.10-1.80 (m, 15H), 1.80-2.10 (m, 3H), 2.80-2.95 (m, 1H), 3.25-3.40 (m, 1H), 5.65 (m, 1H); MS (*m/z*): 356 (M^+), 358 (M^+).

This vinyl bromide **32c** was also synthesized as follow.

To the solution of NaOH (14.5 g, 0.36 mol) in water (30 ml) and MeOH (30 ml), was added a THF (60 ml) solution of the diester **14** (4.09 g, 11.37 mmol) at room temperature. After stirring at 40°C for 24 h, a saturated aqueous NH_4Cl solution (150 ml) was added and then conc. HCl was added to acidify the solution. The resulting mixture was extracted with EtOAc (2 x 200 ml). Usual work-up gave a crude acid, which was allowed to react without further purification. To a solution of the above crude acid in MeOH (200 ml), a few drops of conc. H_2SO_4 were added and the resulting solution was refluxed for 24 h. After cooling the reaction mixture to room temperature, a saturated aqueous $NaHCO_3$ solution (30 ml) was added and then extracted with EtOAc (2 x 80 ml). Drying, filtration, and evaporation gave a crude silylated product, which was chromatographed on silica gel (330 g) with hexane and EtOAc (40:1) to yield methyl de-A,B-8β-hydroxychol-24-oate **34** (2.13 g, 8.34 mmol, 73%); mp: 44-46°C (hexane-EtOAc); IR (KBr): 3500, 2920, 2850, 1720, 1423, 1243, 1160 cm^{-1}; ^1H NMR: δ 0.90 (d, 3H, *J* = 6 Hz), 0.92 (s, 3H), 1.00-2.45 (m, 15H), 3.66 (s, 3H), 4.08 (b, 1H); MS (*m/z*): 268 (M^+).

The hydroxy ester **34** (2.35 g, 9.18 mmol) was converted into (*E*)-de-A,B-8β-bromomethylenechol-24-oate **35** (1.12 g, 3.38 mmol) in 37 % yield by a procedure similar to the silyl ester **31**; IR (neat): 2940, 2860, 1738, 1423, 1372, 1260, 1164 cm^{-1}; ^1H NMR: δ 0.58 (s, 3H), 0.95 (d, 3H, *J* = 6 Hz), 1.15-2.45 (m, 13H), 2.80-2.90 (m, 2H), 3.68 (s, 3H), 5.62 (b, 1H); MS (*m/z*): 342 (M^+), 344 (M^+).

The bromomethylene ester **35** (1.62 g, 4.89 mmol) was reacted with $LiAlH_4$ (760 mg, 20.0 mmol) in THF (100 ml) at room temperature for 2 h. To the reaction mixture, a saturated aqueous Na_2SO_4 solution was added dropwise. Drying, filtration, and evaporation gave a crude silylated product, which was chromatographed on silica gel (40 g) with hexane and EtOAc (30:1 up tp 2:1) to afford (*E*)-de-A,B-8β-bromomethylenechol-24-ol **36** (1.30 g, 4.30 mmol, 88%); IR (neat): 3330, 2930, 2860, 1460, 1440, 1374, 1053 cm^{-1}; ^1H NMR: δ 0.57 (s, 3H), 0.94 (d, 3H, *J* = 6 Hz), 1.00-2.10 (m, 13H), 2.80-2.90 (m, 2H), 3.62 (t, 2H, *J* = 6 Hz), 5.63 (b, 1H); MS (*m/z*): 314 (M^+), 316 (M^+); High-resolution MS for $C_{16}H_{27}BrO$ $(M-79)^+$: Calcd. *m/z*: 235.2062; Found: 235.2003.

(*E*)-de-A,B-8β-bromomethylenechol-24-al **33** (1.20g, 3.98 mmol) was obtained from the above alcohol **36** (1.50 g, 4.94 mmol) by a procedure similar to the aldehyde **6** in 81% yield; IR (neat): 2940, 2860, 1722, 1460, 1440, 1378, 1273, 1258 cm^{-1}; ^1H NMR: δ 0.57 (s, 3H), 0.93 (d, 3H, *J* = 6 Hz), 1.15-2.55 (m, 13H), 2.80-2.90 (m, 2H), 5.66 (b, 1H), 9.79 (t, 1H, *J* = 3 Hz); MS (*m/z*): 312 (M^+), 314 (M^+); High-resolution MS for $C_{16}H_{25}BrO$ $(M-79)^+$: Calcd. *m/z*: 233.1905; Found: 233.1942.

The aldehyde **33** (113 mg, 0.375 mmol) was subjected to the above-mentioned asymmetric isopropylation reaction using (-)-DBNE as a catalyst to give the isopropylated product **32c** (86 mg, 0.249 mmol) in 66% yield together with the reduced product **36** (12 mg, 0.04 mmol). This product **32c** was identical with the product **32c** obtained from the isopropylated adduct **26** by the above-mentioned bromomethylenation reaction. To determine the diastereomeric ratio, the solution of the above-obtained isopropylated adduct **32c** (*ca.* 19 mg) in a mixture of CH_2Cl_2 (3 ml) and MeOH (1 ml) was treated with ozone at -78°C until a blue color appeared. The resulting solution was purged with N_2 and then $NaBH_4$ (20 mg) was added. After the reaction mixture was warmed up to room temperature, additional $NaBH_4$ (3 x 20 mg) was added. After stirring for 24 h, a 0.5 N HCl solution (30 ml) was added. The resulting mixture was extracted with EtOAc (50 ml). After washing, drying, filtration, and evaporation, an obtained crude alcohol was similarly converted into the dibenzoate **25** (22 mg) by the benzoylation with benzoyl chloride and pyridine. The diastereomeric ratio was evaluated by a similar HPLC analysis of the dibenzoate **25** to be 95.0:5.0 (**25R**:**25S**).

General procedure for the synthesis of 3(S),5(R)-dihydroxy-1-octen-7-yne bissilyl ethers (**37a-e**).

To a solution of 3(*S*),5(*R*)-dihydroxy-1-octen-7-yne[14a] **37f** (0.25 g, 1.79 mmol) in CH_2Cl_2 (4 ml) was added the corresponding trisubstituted silylchloride (5.5 mmol) and imidazole (0.76 g, 11.3 mmol) at room temperature, and the resulting mixture was refluxed for 4 h. After cooling to room temperature, water (20 ml) was added and the resulting mixture was extracted with EtOAc (2 x 20 ml). Usual work-up gave a crude silylated product, which was chromatographed on silica gel (50 g) with hexane and toluene (10:1-5:1) to give the bissilylated ether (**37a-e**).

3(*S*),5(*R*)-bis(*tert*-butyldimethylsilyloxy)-1-octen-7-yne (37a): 90% yield; IR (neat): 2965, 2940, 2865, 1476, 1465, 1368, 1280, 1100 cm^{-1}; ^1H NMR: δ 0.03 (s, 3H), 0.05 (s, 3H), 0.07 (s, 3H), 0.08 (s, 3H), 0.89 (s, 18H), 1.60-1.75 (m, 1H), 1.80-2.00 (m, 2H), 2.30-2.40 (m, 2H), 3.85-4.00 (m, 1H), 4.15 (b, 1H), 5.00-5.20 (m, 2H), 5.75-5.95 (m, 1H); MS (*m/z*): $311(M-57)^+$.

3(*S*),5(*R*)-bis(triethylsilyloxy)-1-octen-7-yne (37b): 91% yield; IR (neat): 2955, 1458, 1472, 1377, 1240, 1096 cm^{-1}; ^1H NMR: δ 0.50-0.70 (m, 12H), 0.90-1.10 (m, 18H), 1.25-1.50 (m, 12H), 1.60-1.75 (m, 1H), 1.80-2.00 (m, 2H), 2.30-2.40 (m, 2H), 3.85-4.00 (m, 1H), 4.15-4.30 (m, 1H), 5.00-5.20 (m, 2H), 5.70-5.90 (m, 1H); MS (*m/z*): 368 (M^+); High-resolution MS for $C_{20}H_{46}O_2Si_2$ (M^+): Calcd. *m/z*: 368.2567; Found: 368.2614.

3(*S*),5(*R*)-bis(tripropylsilyloxy)-1-octen-7-yne (37c): 96% yield; IR (neat): 2955, 1462, 1408, 1375, 1333, 1206 cm^{-1}; ^1H NMR:δ 0.55-0.70 (m, 12H), 0.85-1.00 (m, 18H), 1.55-1.70 (m, 1H), 1.80-2.05 (m, 2H), 2.35-2.45 (m, 2H), 3.85-4.00 (m, 1H), 4.15-4.25 (m, 1H), 5.00-5.20 (m, 2H), 5.75-5.95 (m, 1H); MS (*m/z*): 452 (M^+); High-resolution MS for $C_{26}H_{52}O_2Si_2$ (M^+): Calcd. *m/z*: 452.3506; Found: 452.3485.

3(*S*),5(*R*)-bis(trimethylsilyloxy)-1-octen-7-yne (37d): 69% yield; IR (neat): 2957, 1509, 1474, 1252 cm^{-1}; ^1H NMR: δ 0.12 (s, 9H), 0.17 (s, 9H), 1.50-1.85 (m, 2H), 1.95-2.05 (m, 2H), 2.30-2.40 (m, 2H), 3.90-4.10 (m, 1H), 4.20-4.30 (m, 1H), 5.00-5.20 (m, 2H), 5.70-5.90 (m, 1H); MS (*m/z*): 284 (M^+).

3(*S*),5(*R*)-bis(*tert*-butyldiphenylsilyloxy)-1-octen-7-yne (37e): 79% yield; IR (neat): 2959, 2893, 1487, 1427, 1111 cm^{-1}; ^1H NMR: δ 0.99 (s, 9H), 1.01 (s, 9H), 1.65-1.85 (m, 2H), 1.95-2.20 (m, 3H), 3.75-3.90 (m, 1H), 4.05-4.20 (m, 1H), 4.60-4.75 (m, 2H), 5.40-5.60 (m, 1H), 7.25-7.50 (m, 12H), 7.55-7.70 (m, 8H); MS (*m/z*): 360 $(M-256)^+$.

General procedure for the palladium-catalyzed alkylative enyne cyclization reaction.

After a mixture of Pd catalyst (0.018 mmol) and Ph_3P (38 mg, 0.15 mmol) in a mixture of toluene (1 ml) and Et_3N (2 ml) was stirred at room temperature for 30 min, a solution of **the vinyl halide 32** (0.18 mmol) and **the 3(*S*),5(*R*)-dihydroxy-1-octen-7-yne derivative 37** (0.12 mmol) in toluene (1 ml) was added. The resulting mixture was stirred at 100-120°C untill no enyne derivative was detected and then filtered through a small pad of silica gel, which was washed with Et_2O. After evaporation of the solvent, the residual product was chromatographed on silica gel (20 g) with hexane and toluene (40:1 up to 5:1) to give **the coupling product 38**.

1α,24(*R*)-Dihydroxyvitamin D3 tris(*tert*-butyldimethylsilyl) ether (38a); 55-69% yield; IR (neat): 2955, 2857, 1472, 1362, 1256, 1084 cm^{-1}; ^1H NMR: δ 0.03 (s, 3H), 0.05 (s, 3H), 0.07 (s, 12H), 0.53 (s, 3H), 0.80-0.95 (m, 36H), 1.20-3.00 (m, 22H), 3.30-3.40 (m, 1H), 4.15-4.25 (m, 1H), 4.35-4.45 (m, 1H), 4.85-4.90 (m, 1H), 5.15-5.20 (m, 1H), 6.02 (d, 1H, *J* = 12 Hz), 6.25 (d, 1H, *J* = 12 Hz); MS (*m/z*): 776 (M^+); High-resolution MS for $C_{35}H_{75}O_3Si_3$ $(M-131)^+$: Calcd. *m/z*: 627.5024; Found: 627.5046.

1α,24(*R*)-Dihydroxyvitamin D3 1,3-bis(*tert*-butyldimethylsilyl) ether (38b); 70% yield; IR (neat): 2920, 1472, 1458, 1362, 1252 cm^{-1}; ^1H NMR: δ 0.07 (s, 12H), 0.53 (s, 3H), 0.80-1.00 (m, 27H), 1.20-3.00 (m, 22H), 3.25-3.40 (m, 1H), 4.10-4.25 (m, 1H), 4.30-4.40 (m, 1H), 4.85-4.90 (m, 1H), 5.15-5.20 (m, 1H), 6.02 (d, 1H, *J* = 12 Hz), 6.23 (d, 1H, *J* = 12 Hz); MS (*m/z*): 644 (M^+); High-resolution MS for $C_{39}H_{72}O_3Si_2$ $(M-132)^+$: Calcd *m/z*: 512.4060; Found: 512.4055.

1α-(Triethylsilyloxy)-24(*R*)-(*tert*-butyldimethylsilyloxy)vitamin D3 triethylsilyl ether (38c); 66% yield; IR (neat): 2920, 1471, 1458, 1417, 1250 cm^{-1}; ^1H NMR: δ 0.04 (s, 3H), 0.05 (s, 3H), 0.50-0.75 (m, 21H), 0.80-1.00 (m, 45H), 1.20-3.00 (m, 22H), 3.35-3.45 (m, 1H), 4.15-4.25 (m, 1H), 4.35-4.45 (m, 1H), 4.85-4.90 (m, 1H), 5.20-5.25 (m, 1H), 6.05 (d, 1H, *J* = 12 Hz), 6.27 (d, 1H, *J* = 12 Hz); MS (*m/z*): 758 (M^+).

1α-(Tripropylsilyloxy)-24(*R*)-(*tert*-butyldimethylsilyloxy)vitamin D3 tripropylsilyl ether (38d); 67% yield; IR (neat): 2930, 1508, 1473 cm^{-1}; ^1H NMR: δ 0.03 (s, 3H), 0.04 (s, 3H), 0.50-0.75 (m, 21H), 0.80-1.10 (m, 45H), 1.20-3.00 (m, 40H), 3.30-3.45 (m, 1H), 4.15-4.30 (m, 1H), 4.35-4.45 (m, 1H), 4.85-4.90 (m, 1H), 5.20-5.25 (m, 1H), 6.05 (d, 1H, *J* = 12 Hz), 6.25 (d, 1H, *J* = 12 Hz); MS (*m/z*): 799 $(M-43)^+$.

1α-(Trimethylsilyloxy)-24(*R*)-(*tert*-butyldimethylsilyloxy)vitamin D3 trimethylsilyl ether (38e); 15% yield; IR (neat): 2960, 1559, 1509, 1473, 1250 cm^{-1}; ^1H NMR: δ 0.03 (s, 6H), 0.13 (s, 12H), 0.54 (s, 3H), 0.80-1.00 (m, 18H), 1.10-2.50 (m, 21H), 2.80-2.90 (m, 1H), 3.30-3.40 (m, 1H), 4.10-4.25 (m, 1H), 4.30-4.40 (m, 1H), 4.85-4.90 (m, 1H), 5.15-5.20 (m, 1H), 6.04 (d, 1H, *J* = 12 Hz), 6.28 (d, 1H, *J* = 12 Hz); MS (*m/z*): 674 (M^+).

1α-(*tert*-Butyldiphenylsilyloxy)-24(*R*)-(*tert*-butyldimethylsilyloxy)vitamin D3 *tert*-butyldiphenylsilyl ether (38f); 12% yield; IR (neat): 1559, 1522, 1473, 1458 cm^{-1}; ^1H NMR: δ 0.04 (s, 3H), 0.06 (s, 3H), 0.51 (s, 3H), 0.85-2.85 (m, 31H), 3.30-3.45 (m, 1H), 4.20-4.35 (m, 1H), 4.50-4.60 (m, 1H), 4.80-4.85 (m, 1H), 5.05-5.10 (m, 1H), 6.01 (d, 1H, *J* = 12 Hz), 6.12 (d, 1H, *J* = 12 Hz); MS (*m/z*): 750 $(M-256)^+$.

1α,24(*R*)-Dihydroxyvitamin D3 (1)

To a solution of the coupling product **38a** (obtained from a 95.0:5.0 mixture of 24*R*-isomer and 24*S*-isomer, 94 mg, 0.13 mmol) in MeOH (45 ml) was added pyridinium *p*-toluenesulfonate (polymer bound, 225 mg, *ca.* 0.9 mmol) at room temperature. After stirring for 16 h, the reaction mixture was filtered through a small pad of alumina, which was washed with EtOAc. Evaporation gave a crude product, which was subjected to silica gel chromatography (20 g) with hexane and EtOAc (5:1 up to 1:2) providing a crude 1α,24(*R*)-dihydroxyvitamin D_3 (1, 38 mg, 0.09 mmol, 75%). After recrystalization from MeOH and water, 1α,24(*R*)-dihydroxyvitamin D_3 monohydrate (22 mg, 0.05 mmol) contaminated with only 0.9% of 1α,24(*S*)-dihydroxyvitamin D_3 isomer was obtained. The diastereomeric ratio was estimated by HPLC analysis (YMC AM303, 25 cm x 4.6 mm I.D.) using a mixture of MeOH-water (4:1) as a mobile phase at 1.0 ml/min. (24*R*-isomer; 18.5 min, 24*S*-isomer; 19.5 min); mp: 96.5-100.0°C (MeOH-water); $[\alpha]_D^{20}$= +54 (*c* 0.05, EtOH); IR (KBr): 3315, 2872, 2740, 1472, 1043 cm^{-1}; ^1H NMR: δ 0.56 (s, 3H), 0.80-1.00 (m, 9H), 1.15-2.85 (m, 22H), 3.30-3.45 (m, 1H), 4.15-4.30 (m, 1H), 4.40-4.50 (m, 1H), 5.00 (b, 1H), 5.30 (b, 1H), 6.02 (d, 1H, *J* = 12 Hz), 6.39 (d, 1H, *J* = 12 Hz); MS (*m/z*): 416 (M^+).

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