Registry No.—1, 56469-10-4; 2, 56469-11-5; 3, 56469-12-6; 4, 56469-13-7; 5, 56469-14-8; 6, 51022-71-0; 6a, 61617-09-2; 6b, 61664-39-9; 7, 56469-15-9; 7a, 61664-40-2; 8a, 19890-02-9; 8a acetate, 19890-04-1; 8b, 22339-08-8; 8b acetate, 39863-91-7; 9a, 61597-27-1; 9b, 61597-28-2; 10a, 61597-29-3; 10b, 61597-30-6; 11a, 61597-31-7; 11b, 61604-70-4; 12a, 61597-32-8; 12b, 61597-33-9; 13a, 61617-10-5; 13b, 61617-11-6; 16b, 35408-03-8; 17a, 28239-05-6; 18a, 61597-34-0; 19b, 61597-35-1; 20b, 61597-36-2; 21, 100-06-1; 22, 7428-99-1; 23, 61597-37-3; 24, 500-66-3; 25, 16964-51-5; 26, 16964-48-0; 27, 61597-38-4; 28, 61597-39-5; 30, 54584-38-2; 31, 61597-40-8; 32, 61597-41-9; 33, 61597-42-0; diethyl 2-acetylglutarate, 1501-06-0; 7-(1,1-dimethylheptyl)-5-hydroxy-4-methyl-2-oxo-2*H*-1-benzopyran-3-propionic acid, 61597-43-1; ethylene glycol, 107-21-1; (−)-α-pinene, 7785-26-4; (+)-α-pinene, 7785-70-8; Ac_2O, 108-24-7; 2,2-dimethyl-1,3-propanediol, 126-30-7.

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(23) If water is omitted, the yield of **7** is reduced to 18%.

Studies on Vitamin D (Calciferol) and Its Analogues. 12. Structural and Synthetic Studies of 5,6-*trans*-Vitamin D_3 and the Stereoisomers of 10,19-Dihydrovitamin D_3 Including Dihydrotachysterol$_3$[1,2]

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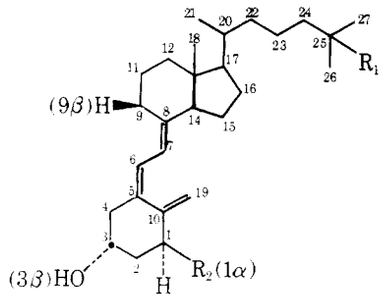
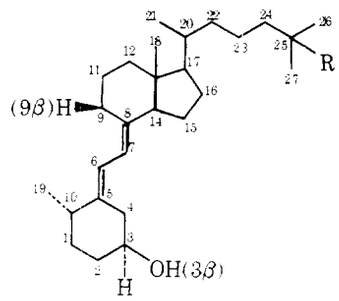
Catalytic hydrogenation of 5,6-*trans*-vitamin D_3 (**3a**, 5*E*-D_3) afforded the previously unknown C_{10} epimer of dihydrotachysterol$_3$ (**2a**, DHT_3 or 10*S*-b), 10*R*,19-dihydro-5*E*-vitamin D_3 (10*R*-b). Reaction of **3a** with 9-borabicyclo[3.3.1]nonane (9-BBN) produced the 9-BBN/**3a** adduct, which upon treatment with acetic acid produced low yields of equal amounts of **2a** and its C_{10} epimer 10*R*-b. When the 9-BBN/**3a** adduct was oxidized with basic hydrogen peroxide, good yields of the 19-hydroxy counterparts of 10*S*-b and 10*R*-b, **7a** and **7b**, respectively, were produced. The 9-BBN/**1a** adduct, produced similarly by treating vitamin D_3 (**1a**) with 9-BBN, reacted with acetic acid to afford 10*S*,19- (10*S*-a) and 10*R*,19-dihydrovitamin D_3 (10*R*-a), which differ from 10*S*-b and 10*R*-b, respectively, in their Δ^5-double bond configurations. Basic hydrogen peroxide treatment of the 9-BBN/**1a** adduct gave good yields of the 19-hydroxy derivatives of 10*S*-a and 10*R*-a, **8a** and **8b**, respectively. The stereoisomeric 10*S*-a, 10*R*-a, 10*S*-b (**2a**), and 10*R*-b vitamin D analogues are also labeled DHV_3-II, DHV_3-III, DHT_3, and DHV_3-IV, respectively, in this study. The stereochemistries and conformations of the A ring of the five analogues (5*E*-D_3, 10*S*-a, 10*R*-a, 10*S*-b, and 10*R*-b) have been studied by two ^1H NMR methods: correlation of the observed coupling constants with the limiting values for the two conformers (coupling constant method) and computer analysis of the 300-MHz tris(dipivalomethanato)europium(III) [Eu(dpm)$_3$] shifted spectra (the lanthanide induced shift or LIS method). The reduction products of vitamin D_3 (**1a**) are clearly identifiable by both methods as the 10*S*-a and 10*R*-a isomers. By contrast the LIS method only partially serves to distinguish the stereochemistries assigned to the reduction products of 5*E*-D_3 (**3a**). The LIS method distinguishes DHT_3 as the 10*S*-b isomer but its epimer is equally well assigned by this method to the 10*S*-b or 10*R*-b diastereomers. Coupling constants do not help in the latter case either. Thus NMR methods must be used with a great deal of care especially when only one epimer of a fluxional molecule is available for study. Both epimers were fortunately available in this study. The A ring of these steroids is dynamically equilibrated between two chair conformers and both methods were in good agreement as regards their A-ring chair population ratios. The 10*S*-a and 10*R*-a isomers were strongly biased in single (~95%) but opposite chair conformers with the C_{10} methyl group axial in both cases. The clinically useful analogue 10*S*-b (DHT_3) also exists principally (~90%) as only one conformer (C_{10} methyl and C_3 hydroxyl equatorial), while its epimer 10*R*-b exists as an approximately equimolar mixture of two A-ring chairlike conformers. Lastly, 5*E*-D_3 is biased (~70%) in favor of the chair possessing the equatorial hydroxyl.

In order to evaluate further the structural requirements necessary for optimal or minimal vitamin D activity and thus obtain more information concerning its mode of action, we have directed our attention toward the synthesis and biological evaluation of analogues of vitamin D_3 (**1a**) and its principal metabolites, 25-hydroxyvitamin D_3 (**1b**) and 1α,25-dihydroxyvitamin D_3 (**1c**).[4] The latter, **1c**, is considered to be the active functional form of vitamin D_3. Among the most

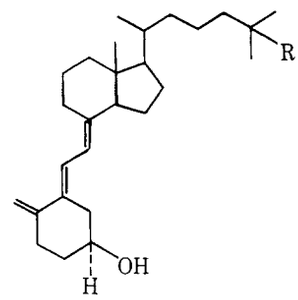


1a, $R_1 = R_2 = H$
b, $R_1 = OH$; $R_2 = H$
c, $R_1 = R_2 = OH$

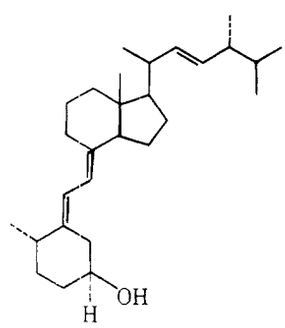
interesting vitamin D analogues are dihydrotachysterol$_3$ (**2a**, DHT_3)[5] and 5,6-*trans*-vitamin D_3 (**3a**, 5*E*-D_3).[6] Both substances are being used clinically and in fact dihydrotachysterol$_2$ (**4**, DHT_2)[7] was marketed as early as 1934 under the trade name A.T.10 by E. Merck (Darmstadt) as an antitetany agent.[8] The biological activity of DHT_3 (**2a**) and 5*E*-D_3 (**3a**)



2a, R = H
b, R = OH



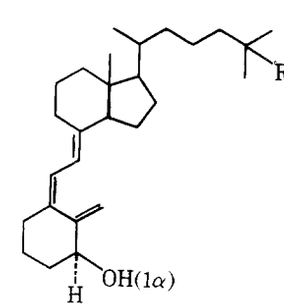
3a, R = H
b, R = OH



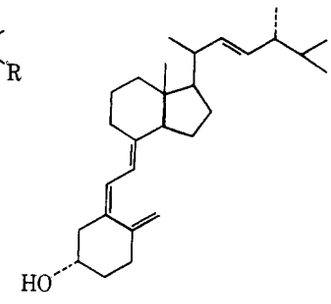
4

in anephric animals has been attributed to the presence of a pseudo-1α-OH group.[9,10] The 3β-OH of **2a** and **3a** are spatially oriented in a topology similar to the key 1α-OH group of the natural hormone **1c**. It is suggested that the 3β-OH in **2a** and **3a** can mimic the function of the 1α-OH group of **1c**. The unusual importance of the 1α-OH group to the function of vitamin D was recently emphasized by the observation of high biological potency for 3-deoxy-1α-hydroxyvitamin D_3 (**5a**),[11] which lacks both the 3β- and 25-OH groups of **1c**. It also appears that **5a** as well **2a** and **3a** are 25-hydroxylated to **5b**,[12] **2b**,[13] and **3b**,[14] respectively, prior to their elicitation of a biological response (intestinal calcium absorption). In order for analogues to retain significant biological properties, it seems evident that a hydroxyl located in a position corresponding topologically to the 3β positior of **1a** is less important and that the $C_{10(19)}$ bond can be located in an unnatural position as in **2** and **3**.

The preparation of DHT_2 (**4**)[7] appears to have been first described by von Werder as a minor component of the sodium–propanol reduction of vitamin D_2 (**6**). This reduction involves not only the saturation of the 10,19 double bond of



5a, R = H
b, R = OH



6

6 but also the *Z* to *E* isomerization of its Δ^5 double bond. The nature of this reduction is such that there remains stereochemical ambiguity in the configuration at C_{10} as well as in the Δ^5 and Δ^7 double bonds. There are thus eight diastereomeric possibilities (shown in Figure 1 for the vitamin D_3 series) for the stereochemistry of **4**. The 10,19-dihydro products resulting from the catalytic hydrogenation of **6** were labeled dihydrovitamin D_2-II (DHV_2-II, major) and dihydrovitamin D_2-IV (DHV_2-IV, minor) by Schubert.[15] The major isomer DHV_2-II appears to differ from DHT_2 only in the configuration of the Δ^5 double bond.[7c] The minor isomer DHV_2-IV is considered by von Werder to differ from DHT_2 only in the configuration at C_{10}.[16,17] However, Westerhof and Keverling-Buisman consider perhaps more logically that DHV_2-II and DHV_2-IV are merely C_{10} configurational isomers.[17,18] Additional substances, DT 66 and dihydrovitamin D_2-III,[15,18] both possessing the UV triplet centered near 250 nm characteristic of DHT_2, DHV_2-II, and DHV_2-IV, have also been described.

In the vitamin D_3 side chain series, only DHT_3 (**2a**) and DHV_3-II (the major catalytic hydrogenation product of **1a**)[5] appear to have been described. It was of some interest that DHT_3, which possesses the natural vitamin D_3 side chain, proved to be significantly more active than DHT_2.[5,19] In a recent preliminary communication, we suggested on the basis of ^1H NMR studies that the configuration of DHT_3 at C_{10} is *S* (the 10*S*-b isomer shown in Figure 1).[20] It became apparent that investigations of the other 10,19-dihydrovitamin D_3s (DHV_3s) would provide more rigorous evidence for the configuration assigned to DHT_3 and that these DHV_3s would also be of interest in their own right from a biological standpoint. In Figure 1, we have categorized the eight DHV_3s according to their diene geometry (a, 5*Z*,7*E*; b, 5*E*,7*E*; c, 5*Z*,7*Z*; d, 5*E*,7*Z*) and their C_{10} configuration (10*S* or 10*R*). DHT_3 and DHV_3-II are the 10*S*-b and 10*S*-a stereoisomers, respectively. In our studies, we have *labeled* DHV_3-III and DHV_3-IV as the 10*R*-a and 10*R*-b isomers, respectively.[17]

Our interest in the stereoisomeric DHV_3s (Figure 1) also stems from our recently proposed structure-function model.[10] From ^1H NMR studies, we determined that the A ring of **1c** is partitioned between a ~55/45 equilibrium mixture of chairlike conformers favoring the chair with the 1α-OH group equatorially oriented.[20,21] Our model elaborates on the thesis that only one of the two A-ring chair conformations of **1c** binds optimally to its receptor protein. One way to test this hypothesis is through the study of a series of 1α-hydroxylated (or pseudo-1α-hydroxylated) analogues whose A rings are biased in one conformation or the other. Such a series includes DHT_3 (**2a**), its hitherto unreported C_{10} epimer DHV_3-IV, and 5*E*-D_3 (**3a**). In this paper, we report on the detailed stereochemical and A-ring conformational analysis of these (10*S*-b, 10*R*-b, and 5*E*-D_3) and related stereoisomers (10*S*-a and 10*R*-a). Synthetic studies of these five substances and related derivatives are also described.

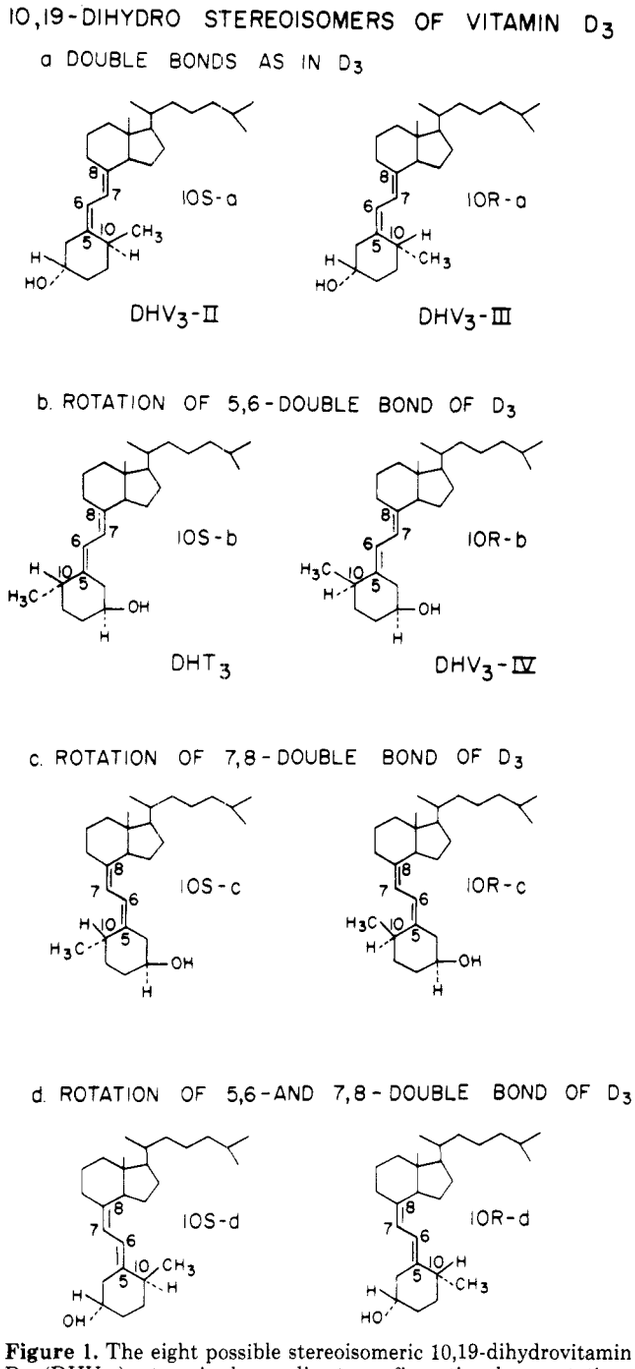
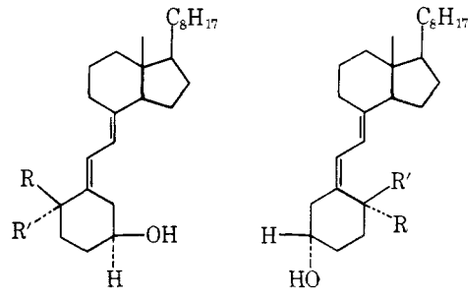


Figure 1. The eight possible stereoisomeric 10,19-dihydrovitamin D_3s (DHV_3s) categorized according to configurational permutations about C_5 (*Z* or *E*), C_7 (*Z* or *E*) and C_{10} (*R* or *S*) after reduction of the 10,19 double bond of vitamin D_3 (**1a**): a, 5*Z*,7*E*; b, 5*E*,7*E*; c, 5*Z*,7*Z*; d, 5*E*,7*Z*. See footnote 17 for an important comment corcerning the DHV_3-III and DHV_3-IV labels.

Results

Catalytic hydrogenation (ethanol, 5% rhodium on carbon) of the analogue 5*E*-D_3 (**3a**), prepared in ~60% purified yield by iodine-catalyzed isomerization of vitamin D_3 (**1a**),[6,22] afforded the 10*R*-b isomer (DHV_3-IV) in 28% yield along with trace amounts of the 10*S*-b isomer (DHT_3, **2a**).[23] The latter was characterized by TLC and UV spectroscopy, but it was not isolated in pure form. Hydroboration (9-borabicyclo[3.3.1]nonane, 9-BBN)[24] of **3a** followed by acetic acid treatment afforded a ~1:1 mixture of the 10*S*-b and 10*R*-b isomers isolated pure in ~6% yields each. The hydroboration step appears to occur in high yield as determined by UV analysis.[25] When the **3a**/9-BBN adduct was reacted with basic hydrogen peroxide, a 64% yield of a 60/40 mixture of **7a** and **7b**, the 19-OH counterpart of the 10*S*-b and 10*R*-b isomers, respectively, was obtained. When the parent vitamin D_3 (**1a**)



7a, R′ = CH_2OH; R = H 8a, R′ = CH_2OH; R = H
b, R = CH_2OH; R′ = H b, R = CH_2OH; R′ = H

was subjected to 9-BBN,[24] an organoborane intermediate again appeared to be formed (by UV analysis) in high yield. Acetic acid decomposition of the **1a**/9-BBN adduct afforded a 31% yield of a mixture of the 10*S*-a (DHV_3-II) and 10*R*-a (DHV_3-III) isomers.[25] Treatment of the borane adduct with basic hydrogen peroxide afforded a 70% yield of a mixture of their 19-hydroxy counterparts, **8a** and **8b**, respectively.

In all cases, separation of stereoisomers was achieved by chromatography over silica gel and the homogeneity of each stereoisomer could be ascertained by ^1H NMR spectroscopy or better by analytical thin layer chromatography. There was no evidence to indicate that the hydroboration reactions led to isomerization of either the Δ^5 or Δ^7 double bond. Only two isomers could be isolated from each of the four hydroboration sequences (acetic acid or peroxide treatment of the 9-BBN adducts of **3a** or **1a**). All the 10,19-dihydrovitamins and their 19-hydroxy counterparts studied exhibited a characteristic ultraviolet triplet (λ_{max} 240, 250, 260 nm) as well as appropriate mass spectral and infrared data. It should be noted that the conjugated diene is nearly planar as attested to by the ultraviolet (λ_{max} 250 nm; calculated by Woodward's rules, 245 nm) and NMR ($J_{6,7} \sim 11.2$ Hz)[21] spectra. It is logical that all of the DHVs reported be assigned the 7*E* rather than the 7*Z* geometry (Figure 1). Molecular models imply that the diene component of the putative 7*Z* isomers (c and d isomers of Figure 1) should be nonplanar as a result of steric congestion between the C_6 and the C_{14} protons. In line with the conformational analysis results described below, the thin layer chromatography R_f value for the C_{10} epimeric pairs of stereoisomers was always larger for the isomers whose A ring was partitioned by a larger extent toward the chair possessing an axial 3β-hydroxyl (see below).

The conformations of the A rings of 5*E*-D_3 (**3a**) and the four 10,19-dihydrovitamin (10*S*-a, 10*R*-a, 10*S*-b, and 10*R*-b, Figure 1) isomers were studied by the two ^1H NMR methods described earlier.[21a] They include correlation of the observed averaged coupling constants with the limiting values for the two chair forms of D_3, and computer analysis of the 300-MHz tris(dipivalomethanato)europium(III) [Eu(dpm)$_3$] shifted spectra. The 300-MHz high-resolution ^1H NMR spectra are given in Figure 2 for the five analogues; a typical lanthanide induced shift (LIS) titration curve, as exemplified by that for the clinically important 10*S*-b (DHT_3, **2a**) stereoisomer, is shown in Figure 3; and finally, the NMR spectral parameters for the five substances including the observed and calculated LIS geometric shifts[26] are given in Table I. The ^1H NMR spectral parameters of the four 19-hydroxy forms (**7** and **8**) are summarized in the Experimental Section.

Discussion

The 9-BBN/HOAc reductions in each case (**1a** or **3a**) gave only two products. Therefore a complete and exhaustive

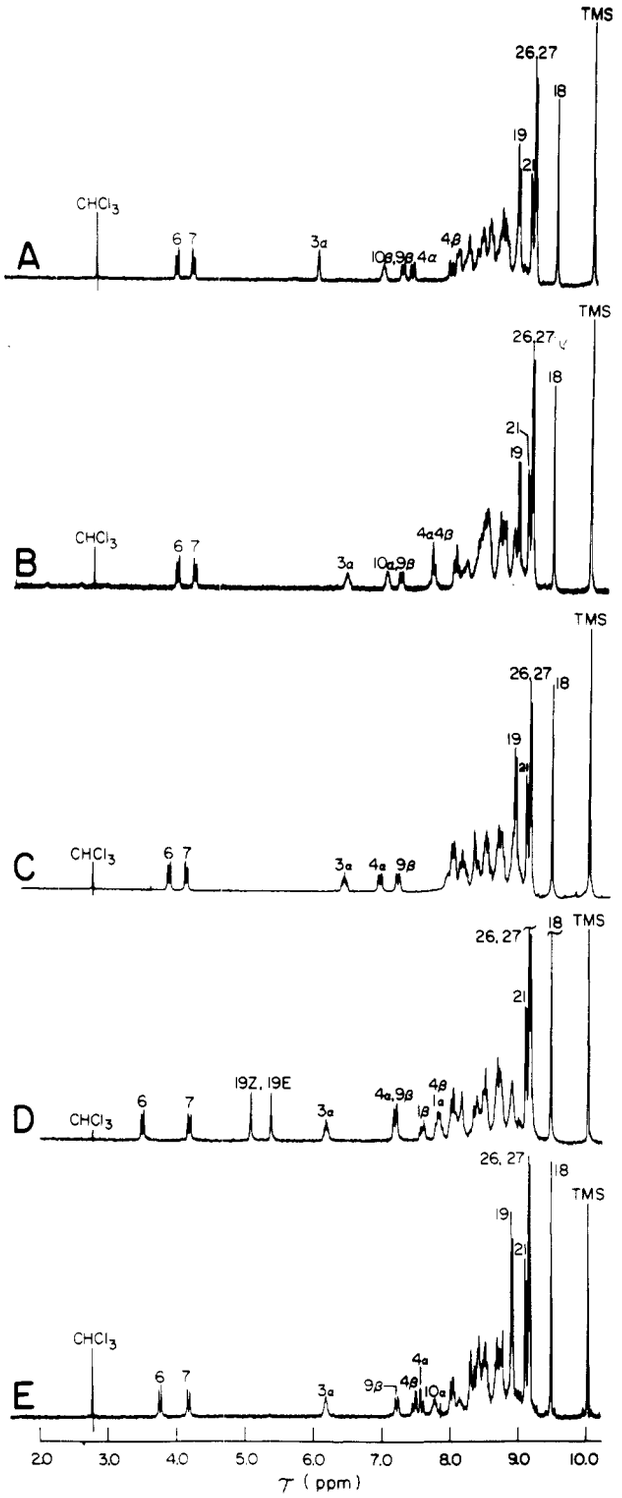


Figure 2. ^1H NMR spectra at 300 MHz of (A) 10*S*-a (DHV_3-II), (B) 10*R*-a (DHV_3-III), (C) 10*S*-b (DHT_3, **2a**), (D) 5*E*-D_3 (**3a**), and (E) 10*R*-b (DHV_3-IV) in deuteriochloroform solvent. Tetramethylsilane and chloroform ($CHCl_3$) (2180 Hz apart) appear as internal standards. See Figure 3 for the lanthanide induced shift spectra for DHT_3. The observable chemical shifts and coupling constants are given in Table I.

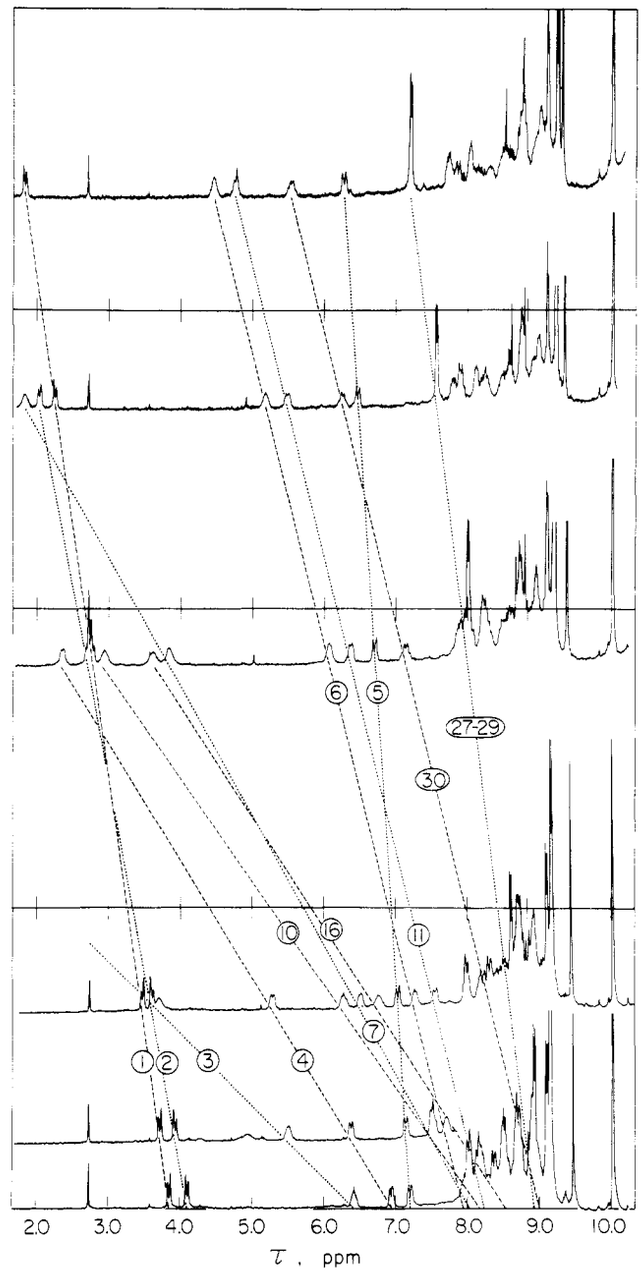


Figure 3. A titration of dihydrotachysterol$_3$ (10*S*-b, **2a**) with tris-(dipivalomethanato)europium(III) [Eu(dpm)$_3$]. The titration of DHT_3 was carried out by adding small increments of solid Eu(dpm)$_3$ to DHT_3 in deuteriochloroform until a near equimolar mixture of steroid and shift reagent was obtained. ^1H NMR spectra (300 MHz) were recorded immediately after each incremental addition of Eu(dpm)$_3$. The vertical scale represents increasing amounts of shift reagent and the dotted lines denote those shifts, which, among others, could be unambiguously followed. The numbers refer to those resonances followed listed in increasing field. The geometric shifts (observed and calculated) are tabulated in Table I. The unshifted spectrum is given in Figure 2C.

analysis of the structures requires that we test the four possible permutations of two compounds with two spectra. When this is done, the spectra can be assigned to compounds as detailed in Table II at the 99.5% confidence[26b] level for the 5*E* series and at the 99.9% confidence[26b] level for the 5*Z* series.

Reduction of **1a** gave two products having spectra A and B (Figure 2). When spectrum A is analyzed, assuming structure 10*R*-a (DHV_3-III), a 9.0% residual for fit of LIS data obtains. Conversely, a 2.75% residual results assuming the 10*S*-a (DHV_3-II) stereochemistry. Likewise when spectrum B is analyzed based on 10*S*-a vs. 10*R*-a stereochemistries residuals of 7.1 and 4.7% result. Assignment of stereochemistries to spectra can now be made using the *R*-ratio test of Hamilton.[26b] Although the above cases are clear cut, the assignment to spectra C and E present a more difficult problem. If LIS titration C is fit to the 10*R*-b configuration, a residual of 4.2% is obtained as against a residual of 2.2% for the 10*S*-b configuration. However, both configurations (10*S*-b and 10*R*-b) fit

Table I. Summary of NMR Results[a]

Line	Assignment[b]	Chemical Shift, τ	Fine Structure (Hz)	Geom. Obs.	Shift Cal.[c]
A. 10S-a					
1	H-6	3.93	d(11.2)	100	100
2	H-7	4.18	d(11.2)	57	66
3	H-3α	5.98	q(~3)[e]	397	399
4	H-10β	6.93	br m	96	106
5	H-9β	7.22	d(12.0)	22	37
6	H-4α	7.36	d(14.3)	128	127
7	H-4β	7.91	d(14.3)	243	244
8	H-2β	8.14[d]	--	227	222
9	H-2α	8.21[d]	--	135	141
10	H-1β	8.40[d]	--	230	228
11	H-1α	8.60[d]	--	101	106
12-31	others	7.9-9.2	--	--	--
32-34	CH_3-19	8.90	d(7.0)	68	64
35-37	CH_3-21	9.08	d(6.0)	--	--
38-43	$(CH_3)_2$-26,27	9.13	d(6.6)	--	--
44-46	CH_3-18	9.46	s	16	15[f]
B. 10R-a					
1	H-6	3.97	d(11)	59	59
2	H-7	4.23	d(11)	48	45
3	H-3α	6.43	m	579	579
4	H-10α	7.03	br m	86	90
5	H-9β	7.22	d(12)	5	4
6	H-4α	7.66	dd(13.0, 4.0)	320	322
7	H-4β	7.72	dd(13.0, 10.5)	387	403
8	H-2α	8.17[d]	--	346	329
9	H-1β	8.42[d]	--	115	122
10	H-1α	8.47[d]	--	144	140
11	H-2β	8.50[d]	--	386	369
12-31	others	7.9-9.2	--	--	--
32-34	CH_3-19	8.94	d(7)	102	130
35-37	CH_3-21	9.08	d(6)	--	--
38-43	$(CH_3)_2$-26,27	9.13	d(7)	--	--
44-46	CH_3-18	9.46	s	7	-8[f]
C. 10S-b					
1	H-6	3.82	d(11.2)	106	94
2	H-7	4.07	d(11.2)	124	126
3	H-3α	6.39	dddd(10.0,10.0,4.1,4.1)	665	661
4	H-4α	6.92	d(12.2)	407	397
5	H-9β	7.18	d(12.0)	44	42
6	H-10β	7.91	br d (~12)[g]	165	176
7	H-2α	8.01[d]	--	369	376
8	H-4β	8.12	dd(~10.0,~12.2)	464	464
9	H-1β	8.21[d]	m	164	167
10	H-2β	8.51[d]	--	432	435
11	H-1α	9.00[d]	br ddd(~12,~12,~12)[g]	163	154
12-31	others	7.9-9.3	--	--	--
32-34	CH_3-19	8.91	d(6.5)	82	84
35-37	CH_3-21	9.08	d(6.3)	--	--
38-43	$(CH_3)_2$-26,27	9.13	d(6.5)	--	--
44-46	CH_3-18	9.45	s	10	19[f]
D. 5E-D_3					
1	H-6	3.48	d(11.2)	85	80
2	H-7	4.16	d(11.2)	102	100
3	H-19Z	5.05	br	78	87
4	H-19E	5.35	br	72	83
5	H-3α	6.14	dddd(8.5,8.5,4.1,4.1)	582	578
6	H-4α	7.16	br d(13.8)[g]	314	316
7	H-9β	7.16	d(12.0)[g]	39	34
8	H-1β	7.56	ddd(14.0,~5.0,~5.0)	161	167
9	H-4β	7.79	dd(13.8,8.5)	404	395
10	H-1α	7.83	br d(14)	139	127
11	H-2α	8.06[d]	--	300	302
12	H-2β	8.42[d]	--	363	367
13-32	other	7.9-9.3	--	--	--
33-35	CH_3-21	9.08	d(6.2)	--	--
36-41	$(CH_3)_2$-26,27	9.13	d(6.7)	--	--
42-44	CH_3-18	9.43	s	4	9
E. 10R-b					
1	H-6	3.76	d(11.2)	125	121
2	H-7	4.17	d(11.2)	179	157
3	H-3α	6.18	ddd(7.0,~4.4,~4.4)	693	683
4	H-9β	7.21	d(12.0)	51	59
5	H-4β	7.47	dd(13.5,7.0)	468	443
6	H-4α	7.58	dd(13.5,3.5)	301	312
7	H-10α	7.77	pseudo-sextet(~6-7)	157	140
8	H-1α	8.33[d]	--	151	146
9	H-2α	8.33[d]	--	293	284
10	H-2β	8.46[d]	--	397	395
11	H-1β	8.63[d]	--	257	270
12-31	others	7.9-9.3	--	--	--
32-34	CH_3-19	8.88	d(6.9)	101	138
35-37	CH_3-21	9.08	d(6.2)	--	--
38-43	$(CH_3)_2$-26,27	9.13	d(6.6)	--	--
44-46	CH_3-18	9.46	s	-11	15[f]

[a] Varian HR300, 24°, in $DCCl_3$ with $HCCl_3$ and TMS standards. [b] The numbering scheme is defined in 1 and 2. [c] The 'PSEUDO' optimized structures gave the following: 10S-a, Eu-O = 2.55(2)Å, Eu-O-C = 105(3)°, Eu-O-C-$H_{3\alpha}$ torsion angle 1(2)°, % axial 3β-OH conformer 94(3) with a residual error, R, of 2.75% based on all data for protons whose geometric shifts are calculated; 10R-a, Eu-O = 2.89(9)Å, Eu-O-C = 114(3)°, Eu-O-C-$H_{3\alpha}$ torsion angle 6(6)°, % axial 3β-OH conformer 8(5) with R = 4.66%; 10S-b, Eu-O = 2.94(6)Å, Eu-O-C = 123(2)°, Eu-O-C-$H_{3\alpha}$ torsion angle -14(3)°, % axial 3β-OH conformer 11(2) with R = 2.21%; 5E-D_3: Eu-O = 2.87(6)Å, Eu-O-C = 118(2)°, Eu-O-C-$H_{3\alpha}$ torsion angle ~9(3)°, % axial 3β-OH conformer 24(3) with R = 2.56%; 10R-b: Eu-O = 2.77(14)Å, Eu-O-C = 117(5)°, Eu-O-C-$H_{3\alpha}$ torsion angle -18(7)°, % axial 3β-OH conformer 58(6) with R = 5.76%. [d] Extrapolated from LIS spectra (not directly observable). [e] H-3α appears as a pseudo-quintet at 60 MHz with an average J ~ 3 Hz while at 300 MHz, the resonance was broad with $w_{\frac{1}{2}}$ ~ 4.2 Hz. [f] Uncertainty in the CH_3-18 coordinate due to perturbation of seco-B ring conformation by CH_3-19 gives rise to a large error in calculated shifts, but does not effect the determined A ring conformers and assignments. [g] From LIS spectra at high resolution.

Table II. Conformational Population Ratios for the A Ring

	Coupling constant[a,b]	LIS[a,c]
A. 10S-a isomer (DHV_3-II)	100 (6), ax	94 (3), ax
B. 10R-a isomer (DHV_3-III)	6 (6), ax	8 (5), ax
C. 10S-b isomer (DHT_3, **2a**)	88 (6), eq	89 (2), eq
D. 5,6-*trans*-D_3(5E-D_3, **3a**)	69 (5), eq	76 (3), eq
E. 10R-b isomer (DHV_3-IV)	50 (5), eq	42 (6), eq

[a] The expression $J_{3\alpha,4\beta} = \lambda J_{ee} + (1-\lambda)J_{aa}$ where λ is the mole fraction of the conformer with the A-ring hydroxyl axial (ax) or equatorial (eq) and the values of $J_{ee} \sim 3$ Hz and $J_{aa} \sim 11$ Hz taken from the work of Anet (see ref 27). The conformational population percentage refers to the orientation of the hydroxyl group (ax or eq) as calculated by either method. [b] The values in parentheses are standard errors computed by assuming linear propagation of errors with a standard error of 0.5 Hz in J_{ee} and J_{aa}, and 0.1 Hz in $J_{3\alpha,4\beta}$. [c] The values in parentheses are standard deviations from the LIS calculated PSEUDO least-squares fit (see Table I and ref 21a).

the LIS titration E to the same 5.6% residual. Clearly spectrum C is representative of the 10S-b stereochemistry and further the coupling constant parameter ($J_{3\alpha,4\beta} \sim 10.1$ Hz) is consistent only with this assignment. By elimination the 10R-b configuration is assigned to spectrum E. Thus if we only had isolated 10R-b, structure analysis would not have been possible by our ^{1}H NMR methods. The importance of examining both epimers in studies of this kind cannot be overemphasized.

Figure 4 gives a graphical description of the two chair conformations available to 5E-D_3 and to each of the four dihydrovitamin D_3 stereoisomers. The population ratios determined by the LIS studies are in good agreement with those estimated from correlating the observed coupling constants (Table II). For the latter, the values of Anet[27] for cyclohexanol ($J_{aa} \sim 11$ Hz and $J_{ee} \sim J_{ea} \approx 3$ Hz) were used.

Of special interest is the observation that both the 10S-a and 10R-a stereoisomers exist in conformations which place the methyl groups almost exclusively axial. As Schubert[15] originally hypothesized for DHV_2-II, a side chain analogue of the 10S-a isomer, this observation for both the 10S-a and 10R-a stereoisomers can be attributed to the steric repulsion between the C_{19} and C_7 protons when the C_{19} methyl is equatorially oriented. Thus, the 10S-a isomer, which possesses a trans relationship between the C_{19} methyl and 3β-OH, has its OH group oriented almost entirely axially, just the opposite of what would have been predicted from simple cyclohexane models.[28] The C_{19} methyl and 3β-OH of the 10R-a isomer are cis to one another, which orients its 3β-OH almost completely equatorially.

The unusual significance of the A-ring hydroxyl (3β- or pseudo-1α-OH) of 10S-b (**2a**, DHT_3), whose C_{10} configuration is definitively established to be S in this paper, and 5E-D_3 (**3a**) was emphasized earlier in this report. These previously known substances, **2a** and **3a**, along with the new 10R-b (DHV_3-IV) isomer reported herein constitute a series which exhibits decreasing equatorial 3β-OH (pseudo-1α-OH) character. They contain ~90, ~70, and ~50%, respectively, of the equatorial 3β conformer (Figure 4, Table II).

In preliminary in vivo (chicks) intestinal calcium transport assays,[19] the biological activities have been observed to follow the order 5E-$D_3 \gtrsim$ 10S-b > 10R-b while the 10S-a and 10R-a isomers exhibited no activity at all. The interpretation of the biological activity results is complicated because the 10S-b isomer (DHT_3) and 5E-D_3, and presumably the 10R-b isomer (DHV_3-IV), are known to be metabolized (25-hydroxylated)

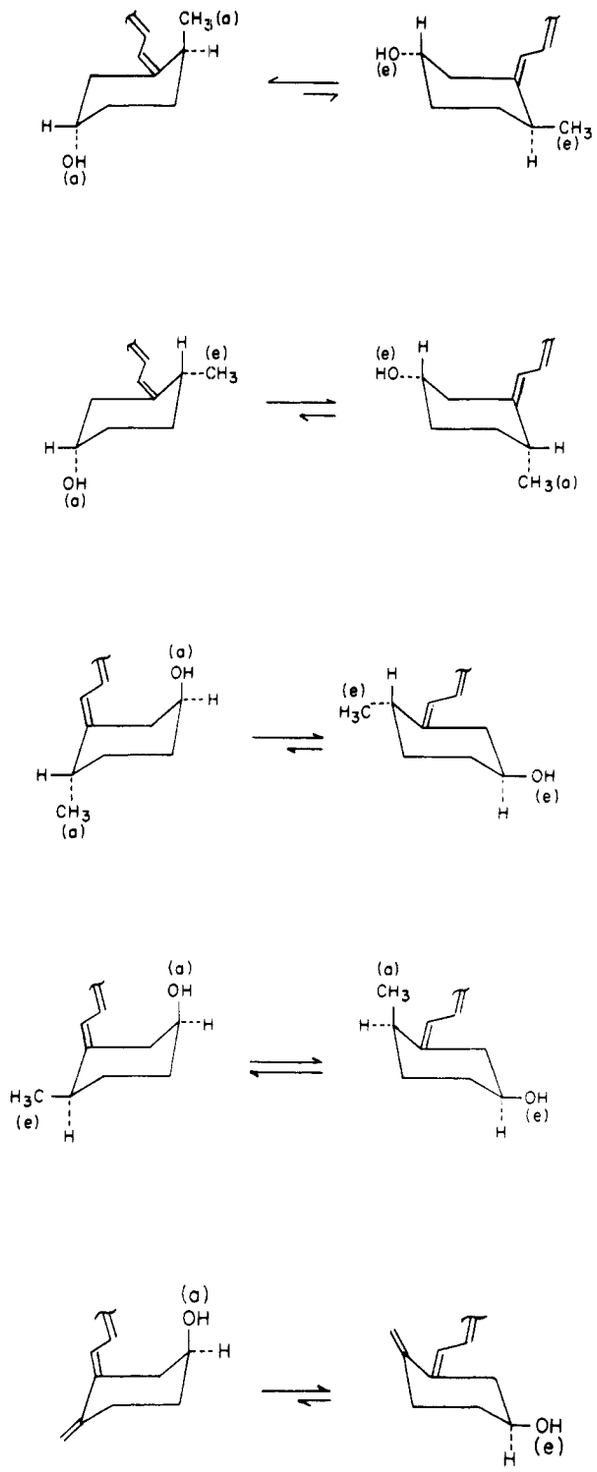


Figure 4. Representations (top to bottom) of the dynamically equilibrating pairs of chair conformers available to the A ring of 10*S*-a (DHV_3-II), 10*R*-a (DHV_3-III), 10*S*-b (DHT_3, **2a**), 10*R*-b (DHV_3-IV), and 5*E*-D_3 (**3a**). See Table II for a comparison of the A-ring population ratios as determined by the two ^1H NMR methods (coupling constants and LIS).

prior to eliciting their physiological action at the intestine.[13,14] Thus the biological activity order observed for 5*E*-D_3, 10*S*-b, and 10*R*-b reflects rates of metabolism (and transport) as well.[29] It would be more meaningful to compare analogues already possessing the 25-hydroxyl group. Further studies from this laboratory are being directed toward the synthesis of these 25-OH counterparts by the methods described in this report and a detailed study of their biological activities.

Experimental Section

General. Ultraviolet spectra (UV, ethanol) were taken on a Beckman DBGT spectrophotometer; ^1H nuclear magnetic resonance spectra (NMR, deuteriochloroform with tetramethylsilane at τ 10.00) were taken on a Varian HR300 spectrometer unless otherwise indicated; mass spectra were taken on a Finnigan 1015C mass spectrometer at 70 eV (parent and base peaks and peaks with >10% intensity at m/e >100 are given); infrared spectra (IR, carbon tetrachloride) were taken on a Perkin-Elmer 621 spectrophotometer; melting points (uncorrected) were taken on a Thomas-Hoover capillary apparatus. Dry tetrahydrofuran (THF) refers to solvent freshly distilled from lithium aluminum hydride; lbpe refers to redistilled reagent 30–60 °C low-boiling petroleum ether; 9-BBN is a 0.5 M solution of 9-borabicyclo[3.3.1]nonane in THF (Aldrich Chemical Co.). Silica gel for column chromatography was Baker Analyzed reagent (60–200 mesh). Silica gel G (EM reagents, type 60) was used for thin layer chromatography (TLC, 0.25 mm analytical plates).

Crystalline vitamin D_3 was purchased from Aldrich Chemical Co. or obtained as a gift from Philips-Duphar (Weesp, the Netherlands). The latter firm also provided the sample of dihydrotachysterol$_3$ used in our initial NMR studies. Tris(dipivalomethanato)europium(III) [Eu(dpm)$_3$] was used directly as purchased from Ventron, Inc. Tris-(dipivalomethanoto)lanthanum(III) [La(dpm)$_3$] was synthesized by the method of Eisentraut and Sievers[30] as modified by Selbin et al.[31] (in vacuo mp 237–245 °C, lit.[30] 238–248 °C).

Preparation of 5*E*-Vitamin D_3 (5*E*-D_3, 5,6-*trans*-Vitamin D_3, 3a). A solution of iodine (5.7 mL of a stock solution containing 0.22 mg iodine/mL lbpe) was added to lbpe (500 mL). Vitamin D_3 (**1a**, 503 mg, 1.31 mmol) was added to the above dilute iodine solution and the mixture was allowed to stand for 1 h at ambient temperature. The reaction was quenched by vigorous shaking with 1% aqueous sodium bisulfite (100 mL). The separated organic layer was washed with water (2 × 100 mL) and then dried (Na_2SO_4). After filtering and concentrating under vacuum, the resulting residue was chromatographed on a dry column of silica gel (60 × 2.5 cm column; isopropyl ether; 11-mL fractions); fractions 2–7 contained 5*E*-D_3 [**3a**, 317 mg (63%), white foam]; fractions 8–13 consisted of starting material (**1a**), contaminated by a small amount of 5*E*-D_3 (164 mg, 33%). The 5*E*-vitamin D_3 was sufficiently pure for subsequent reactions: TLC (isopropyl ether, R_f 0.50) and NMR (see Table I and Figure 2) indicated that the material was homogeneous.

Catalytic Hydrogenation of 3a. Preparation of 10*R*(19)-Dihydro-5*E*-vitamin D_3 (10*R*-b or DHV_3-IV). A stirred suspension of 5% rhodium on carbon (29 mg) in ethanol (23 mL) containing 5*E*-D_3 (**3a**, 227 mg, 0.59 mmol) was allowed to absorb 1.08 molar equiv of hydrogen (25 min) at ambient temperature and pressure. Removal of catalyst and solvent afforded a residue which was chromatographed (silica gel, 20 g, linear gradient between 0–20% ether/lbpe, 10-mL fractions). Fractions 32–38 were combined and concentrated to afford TLC and NMR homogeneous 10*R*-b (DHV_3-IV) in 28% yield (63 mg). The product was identical with that described below. Later fractions of the chromatography afforded material exhibiting a UV spectrum and TLC R_f value identical with those of an authentic specimen of DHT_3 (10*S*-b, **2a**). The DHT_3, however, was present in very small amounts and it could not be isolated pure.

Hydroboration of Vitamin D_3 (1a) and 5*E*-D_3 (3a). A solution of 9-BBN (32 mL, 16 mmol) in THF was added dropwise (syringe) to crystalline **1a** (2.00 g, 5.21 mmol) (nitrogen atmosphere, room temperature, magnetic stirring) whereupon immediate hydrogen evolution was observed to occur. After 1.5 h, the resulting clear solution was quenched (methanol, 5 mL) and then allowed to stand for 15 min. UV analysis indicated that the 10(19)-boron adduct was formed in essentially quantitative yield (solution A).

The 10(19)-boron adduct of 5*E*-D_3 (**3a**) in THF after methanol quench was prepared in an exactly analogous manner (solution B). Again UV analysis indicated that the boron intermediate had been formed nearly quantitatively.

Preparation of 19-Hydroxy-10*S*(19)- (19-OH-10*S*-b, 19-OHDHT$_3$, 7a) and 19-Hydroxy-10*R*(19)-dihydro-5*E*-vitamin D_3 (19-OH-10*R*-b, 19-OHDHV$_3$-IV, 7b). Solution B (9-BBN in THF, 14 mL, 7 mmol; **3a**, 530 mg, 1.38 mmol/4 mL of THF; 5 mL of methanol) was cooled (ice) and then aqueous NaOH (6 M, 2 mL) and 30% H_2O_2 (4 mL, dropwise) were added sequentially. The ice bath was removed and then the mixture was heated (55 °C, 1 h). The cooled mixture was transferred to a separatory funnel, diluted with saturated aqueous K_2CO_3 (50 mL), and then extracted with ether (2 × 50 mL). The combined ether extract was dried (Na_2SO_4) and then concentrated (vacuum) to afford a white, foamy residue. Chromatography of the residue on silica gel (ether) afforded a pure mixture of **7a** and

7b (353 mg, 64%) in a 60/40 ratio (determined by NMR). Careful chromatography (silica gel, 2.5 × 65 cm column, ether–lbpe, 10-mL fractions) of the prepurified mixture afforded fractions containing completely homogeneous **7a** or **7b.**

7a (19-OH-10*S*-b, 19-OHDHT$_3$): noncrystalline, white foam, 91 mg; TLC, ethyl acetate, R_f 0.54; NMR τ 3.72 and 4.10 ($H_{6,7}$, AB q, $J \sim 11$ Hz), 6.15 and 6.37 (2 H_{19}, AB q; A, dd, $J \sim 10$, 7.5 Hz; B, dd, $J \sim 10$, 6 Hz), 6.21 ($H_{3\alpha}$, m), 7.20 ($H_{4\alpha}$, dd, $J \sim 12$, 4 Hz), 7.23 ($H_{9\beta}$, d, $J \sim 12$ Hz), 7.72 ($H_{10\alpha}$, m), 7.78 ($H_{4\beta}$, d, $J \sim 13.8$ Hz), 9.08 (C_{21} CH_3, d, $J \sim 6$ Hz), 9.13 ($C_{26,27}$ 2 CH_3, d, $J \sim 7$ Hz), 9.45 (C_{18} CH_3, s); UV λ_{max} 242.5 nm (ϵ 28 800), 251 (32 800), 261 (22 000); IR ν_{max} 3360 cm^{-1}; mass spectrum *m/e* (rel intensity) 402 (M, 5.8), 384 (M − H_2O, 1.4), 109 (18), 105 (12), 43 (base).

7b (19-OH-10*R*-b, 19-OHDHV$_3$-IV): noncrystalline, white foam, 52 mg; TLC, ethyl acetate, R_f 0.51; NMR τ 3.66 and 4.12 ($H_{6,7}$, AB q, $J \sim 11$ Hz), 6.23 and 6.43 (2 H_{19}, AB q; A, $J \sim 10$, 10 Hz; B, $J \sim 10$, 6 Hz), 6.33 ($H_{3\alpha}$, m) 7.15 ($H_{4\alpha}$, d, $J \sim 11$ Hz), 7.21 ($H_{9\beta}$, d, $J \sim 11$ Hz), 7.66 ($H_{10\beta}$, m), 9.08 ($C_{21}CH_3$, d, $J \sim 6.5$ Hz), 9.13 ($C_{26,27}$ 2 CH_3, d, $J \sim 6.5$ Hz), 9.45 (C_{18} CH_3, s); UV λ_{max} 242.5 nm (ϵ 32 800), 251 (37 000), 260.5 (25 000); IR ν_{max} 3380 cm^{-1}; mass spectrum *m/e* (rel intensity) 402 (M, 4.7), 384 (M − H_2O, 0.2), 107 (12), 105 (11), 43 (base).

Preparation of 10*S*,19- (10*S*-b, DHT$_3$, 2a) and 10*R*,19-Dihydro-5*E*-vitamin D$_3$ (10*R*-b, DHV$_3$-IV) by Hydroboration. Solution B (9-BBN in THF, 20 mL, 10 mmol; **3a,** 946 mg, 2.46 mmol/5 mL of THF; 5 mL of methanol) was concentrated under vacuum. Freshly distilled acetic acid (15 mL) and acetic anhydride (5 mL) were added to the residue and the mixture refluxed (2 h, nitrogen). The cooled mixture was poured into water (50 mL) and then extracted with ether. The ether layer was washed repeatedly with saturated aqueous $NaHCO_3$ (until the acetic acid was removed) and then water. After dyring and concentrating the organic layer, a light green solid residue remained which was taken up in lbpe (25 mL). The resulting white precipitate was removed by filtration. The filtrate was concentrated and then the lbpe precipitation procedure was repeated until no precipitate was observable upon dissolving the residue in lbpe. The soluble residue was chromatographed (silica gel, lbpe and 5% ether–lbpe) and fractions containing products (mainly as acetates; UV, TLC) were pooled and concentrated. The residue was saponified (5% KOH/methanol, 25 mL, and THF, 9 mL; overnight, nitrogen) and then worked up conventionally with water and ether. The ether solution was dried and concentrated to afford the product mixture residue. Careful chromatography (silica gel, 2.5 × 64 cm, 250-mL portions of 0, 2.5, 5, 7.5% ether–lbpe and 750 mL of 10% ether–lbpe, 15-mL fractions) of the residue afforded excellent separation of the stereoisomers.

Fractions 67–77 were combined and concentrated to yield 10*R*-b (DHV$_3$-IV): clear, colorless oil, 60 mg (6.3%); TLC, isopropyl ether, R_f 0.52; NMR, see Figure 2E and Table I; UV λ_{max} 241.5 nm (ϵ 25 600), 250 (28 800), 259 (19 900); IR ν_{max} 3360 cm^{-1}; mass spectrum *m/e* (rel intensity) 386 (M, 22), 273 (12), 255 (10), 147 (12), 135 (14), 121 (19), 119 (13), 109 (11), 107 (17), 105 (13), 43 (base).

Fractions 80–90 upon similar treatment afforded 10*S*-b (DHT$_3$, **2a**): colorless solid, 64 mg (6.7%); TLC, isopropyl ether, R_f 0.47; NMR, see Figure 2C and Table I; UV λ_{max} 241.5 nm (ϵ 25 900), 250 (29 800), and 259 (20 400); IR ν_{max} 3360 cm^{-1}; mass spectrum *m/e* (rel intensity) 386 (M, 11), 147 (11), 135 (16), 121 (13), 119 (13), 109 (10), 107 (22), 105 (14), 43 (base). Comparison of the sample to an authentic specimen obtained from Philips-Duphar proved that they were identical.

Preparation of 19-Hydroxy-10*S*(19)- (19-OH-10*S*-a, 19-OHDHV$_3$-II, 8a) and 19-Hydroxy-10*R*(19)-dihydrovitamin D$_3$ (19-OH-10*R*-a, 19-OHDHV$_3$-III, 8b). Solution A (9-BBN in THF, 10.4 mL, 5.2 mmol; **1a** 500 mg, 1.3 mmol; 5 mL of methanol) was ice cooled and then 6 M aqueous NaOH (1.1 mL) and 30% H_2O_2 (2.2 mL, dropwise) were added sequentially. The stirred mixture was heated for 1 h (55 °C), cooled, diluted with saturated aqueous K_2CO_3 (25 mL), and then extracted with ether. The ether extract was dried (Na_2SO_4), filtered, and then concentrated. The residue was taken up in ether (50 mL) and then the solution cooled (freezer) to precipitate most of the cyclooctanediol. The cold mixture was filtered and then the filtrate was concentrated to afford a white foam which was chromatographed (silica gel, 2.5 × 60 cm; 250 mL each of 75, 85, and 95% ether–lbpe followed by 500 mL of ether, 15-mL fractions).

Combination and concentration of fractions 19–29 afforded pure **8a** (19-OH-10*S*-a, 19-OHDHV$_3$-II): white foam, 230 mg (44%); TLC, ethyl acetate, R_f 0.59; NMR τ 3.64 and 4.12 ($H_{6,7}$, AB q, $J \sim 11$ Hz), 5.94 ($H_{3\alpha}$, m), 6.29 and 6.38 (2 H_{19}, AB q; A, dd, $J \sim 10.3$, 9.2 Hz; B, dd, $J \sim 10.3$, 7.0 Hz), 6.87 ($H_{10\beta}$, m), 7.21 ($H_{9\beta}$, d, $J \sim 12.0$ Hz), 7.43 ($H_{4\beta}$, br. d, $J \sim 14.5$ Hz), 7.82 ($H_{4\alpha}$, d, $J \sim 14.5$ Hz), 9.09 (C_{21} CH_3, d, $J \sim 6$ Hz), 9.13 ($C_{26,27}$ 2 CH_3, d, $J \sim 7$ Hz), 9.48 (C_{18} CH_3, s); UV, λ_{max} 243 nm (ϵ 32 500), 251.5 (36 900), 261 (24 700); IR ν_{max} 3340 cm^{-1}; mass spectrum *m/e* rel intensity) 402 (M, 8), 121 (10), 119 (10), 109 (30), 107 (12), 105 (16), 43 (base).

Fractions 31–49 afforded 60 mg of pure **8b** (19-OH-10*R*-a, 19-OHDHV$_3$-III). Fractions 50–90 were combined and concentrated to a small volume and left in the cold overnight to allow precipitation of additional cyclooctanediol. The decanted liquid phase was concentrated and then rechromatographed (silica gel, 2.5 × 64 cm; 1000 mL of ether, 15-mL fractions). Combination and concentration afforded additional (74 mg) pure product: white foam, 134 mg (25.6%); TLC, ethyl acetate, R_f 0.43; NMR τ 3.72 and 4.20 ($H_{6,7}$, AB q, $J_{AB} \sim 12$ Hz), 6.39 ($H_{3\alpha}$, m), 6.34 and 6.39 (2 H_{19}, AB q; A, dd, $J \sim 11.5$, 9.0 Hz; B, dd, $J \sim 11.5$, 7.8 Hz), 6.99 ($H_{10\alpha}$, m), 7.21 ($H_{9\beta}$, d, $J \sim 12$ Hz), 7.58 ($H_{4\alpha}$, dd, $J \sim 13.0$, 4 Hz), 7.81 ($H_{4\beta}$, dd, $J \sim 13.0$, 10.5 Hz), 9.08 (C_{21} CH_3, d, $J \sim 6$ Hz), 9.12 ($C_{26,27}$ 2 CH_3, d, $J \sim 7$ Hz), 9.45 (C_{18} CH_3, s); UV λ_{max} 243 nm (ϵ 27 800), 251 (32 200), 261 (21 400); IR ν_{max} 3350 cm^{-1}; mass spectrum *m/e* (rel intensity) 402 (M, 1.9), 127 (11), 109 (21), 108 (14), 107 (18), 57 (base), 43 (69).

Preparation of 10*S*,19- (10*S*-a, DHV$_3$-II) and 10*R*,19-Dihydrovitamin D$_3$ (10*R*-a, DHV$_3$-III) by Hydroboration. After solution A (9-BBN in THF, 32 mL, 16 mmol; **1a,** 2.00 g, 5.2 mmol; 5 mL of methanol) was concentrated under vacuum, acetic acid (60 mL) and acetic anhydride (20 mL) were added to the residue and then the mixture was heated (~135 °C, 2 h, nitrogen). The cooled mixture was poured into water (200 mL) and then extracted with ether. The ether phase was backwashed repeatedly with saturated aqueous $NaHCO_3$ (until the acetic acid was removed) and then water. After drying (Na_2SO_4) and concentrating the ether solution, the resulting semisolid residue was taken up in lbpe (100 mL). The colorless, insoluble material was removed by filtration and washed with additional lbpe. The filtrate and washings were combined, dried (Na_2SO_4), and concentrated to yield a viscous residue which was chromatographed (silica gel, 2.5 × 63 cm; ~1000 mL of 0–10% ether–lbpe) to yield after pooling and concentrating appropriate fractions (by UV, TLC) a colorless residue consisting of acetates of the desired products. After saponification (5% KOH/methanol, 300 mL; overnight, ambient temperature, nitrogen) and conventional workup, a residue consisting mainly of the desired alcohol mixture was obtained. The residue was chromatographed (dry silica gel column, 2.5 × 64 cm, isopropyl ether, 15-mL fractions) to afford a pure mixture of the 10*S*-a and 10*R*-a stereoisomers (629 mg, 31.3%). Rechromatography (dry silica gel column, 2.0 × 170 cm, isopropyl ether, 10-mL fractions) of the product mixture effected good separation.

Fractions 7–14 were pooled and concentrated to afford pure 10*S*-a (DHV$_3$-II): oil, 322 mg (16%); TLC, isopropyl ether, R_f 0.43; NMR, see Figure 2A and Table I; UV λ_{max} 241.5 nm (ϵ 26 800), 250 (30 800), 259.5 (21 000); IR ν_{max} 3360 cm^{-1}; mass spectrum *m/e* (rel intensity) 386 (m, 12), 121 (21), 109 (10), 105 (18), 43 (base).

Fractions 15–17 were found to contain 56 mg (3%) of a mixture of the 10*S*-a and 10*R*-a isomers.

Fractions 18–28 upon similar treatment afforded pure 10*R*-a (DHV$_3$-III): oil, 202 mg (10%); TLC, isopropyl ether, R_f 0.32; NMR, see Figure 2B and Table I; UV λ_{max} 241.5 nm (ϵ 28 100), 250 (32 400), 259 (21 700); IR ν_{max} 3340 cm^{-1}; mass spectrum *m/e* (rel intensity) 386 (M, 5), 121 (8), 110 (11), 43 (12).

Shift Reagent Titration. Titration of 10*S*-a (DHV$_3$-II), 10*R*-a (DHV$_3$-III), 10*S*-b (DHT$_3$, **2a**), 5*E*-D$_3$ (**3a**), and 10*R*-b (DHV$_3$-IV) was carried out by adding ~3–5-mg increments of solid Eu(dpm)$_3$ to the NMR sample tubes containing ~20 mg of vitamin/0.5 mL of deuteriochloroform. NMR spectra were recorded immediately after each incremental addition of Eu(dpm)$_3$.

Diamagnetic Correction. In order to test the possibility of complexation shifts and whether the Eu(dpm)$_3$ magnetic probe influences the conformational equilibria of the A ring, La (DPM)$_3$, a diamagnetic analogue of Eu(dpm)$_3$, was introduced (0.3 molar equiv) to each of the vitamin samples (ca. 20 mg in 0.5 mL of $CDCl_3$). No detectable differences were noted for observable coupling constants. Very slight diamagnetic shifts were noted only for the $H_{3\alpha}$ and $H_{4\alpha,\beta}$ resonances, and therefore no corrections to the data were made prior to the LIS calculation.

Computational Procedures. The program PSEUDO, described elsewhere,[21a,32] was used in the interactive mode for all calculations. Parameters varied were the Eu–O distance, the Eu–O–C angle, the Eu–O–C–$H_{3\alpha}$ torsion angle, and the conformational populations. The values obtained are listed in footnote *c* of Table I.

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Registry No.—**1a,** 67-97-0; **1a** BBN adduct, 62077-03-6; **2a,** 57885-34-4; **3a,** 22350-41-0; **3a** BBN adduct, 62077-04-7; **7a,** 62077-05-8; **7b,** 62107-42-0; **8a,** 62077-06-9; **8b,** 62107-43-1; DHV_3-II, 62107-44-2; DHV_3-III, 62107-45-3; DHV_3-IV, 22481-38-5; 9-BBN, 280-64-8.

Supplementary Material Available. Tables giving the atom coordinates and geometric shifts used in the LIS calculations as well as the computer optimized parameters (11 pages). Ordering information is given on any current masthead page.

References and Notes

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(2) This study was supported by USPHS Grants AM-16595 and AM-9012 and by a grant from the Intramural Research Fund of the University of California, Riverside.
(3) (a) Department of Chemistry; (b) Department of Biochemistry and recipient of a USPHS Career Development Award (AM-13654).
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(22) A convenient purification procedure using dry column chromatography is described in the Experimental Section.
(23) No previous studies concerning the reduction of 5*E*-D_3 appear to have been reported. Raney nickel W-2 was the catalyst employed by the earlier workers (ref 5, 15, 16, 18) for the reduction of vitamins D_3 (**1a**) and D_2 (**6**). Attempted reduction of 5*E*-D_3 with this nickel catalyst also produced 10*R*-b, but the yields were lower and the purification was substantially more difficult as a result of contaminating overreduction products and starting material. We observed the formation of 10*S*-a (DHV_3-II), as previously reported (ref 5), upon catalytic reduction of **1a** with the Raney nickel catalyst as well as with the rhodium catalyst. We did not observe formation of detectable amounts of a second stereoisomer (i.e., 10*R*-a). Similar results were obtained when vitamin D_2 (**6**) was reduced employing these catalysts.
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