Studies on Vitamin D (Calciferol) and Its Analogues. 14. On The 10,19-Dihydrovitamins Related to Vitamin D_2 Including Dihydrotachysterol$_2$[1,2]

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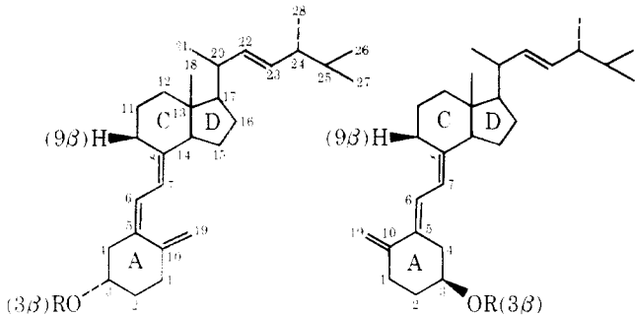
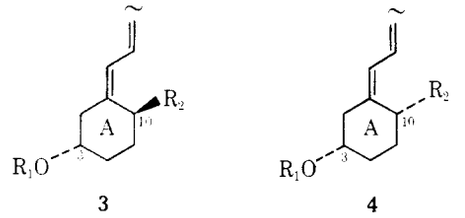
Vitamin D_2 (**1a**), its benzoate (**1b**), 5,6-*trans*-vitamin D_2 (**2a**), and its benzoate (**2b**) were each treated with 9-borabicyclo[3.3.1]nonane and then oxidized with basic hydrogen peroxide to afford the following pairs of stereoisomeric 10,19-dihydrovitamin D_2's: **3a–4a, 3b–4b, 5a–6a,** and **5b–6b,** respectively. Catalytic reduction of **1a** and **2a** afforded the stereoisomeric pairs **3d–4d** and **5d–6d,** respectively. The four benzoyloxy alcohols **3b–6b** were each individually converted to their *p*-toluenesulfonates **3c–6c,** respectively, and then each diester was subjected to lithium triethylborohydride reduction to afford **3d, 7, 5d,** and **8,** respectively. Finally, saponification of **4b** produced **4a** and **6b** gave **6a.** How these chemical transformations including spectral analyses definitively establish the absolute configurations of **3–6** is discussed. The relationship of **3d–6d** to the substances referred to in the old literature as DHT_2, DHV_2-II, DHV_2-III, DHV_2-IV, and DT-66 is also discussed.

Vitamin D_2 (**1a,** ergocalciferol)[4] is utilized extensively as a dietary supplement in foods. Two of its analogues, (5*E*)-vitamin D_2 (**2a**)[5] and dihydrotachysterol$_2$ (**5d,** DHT_2),

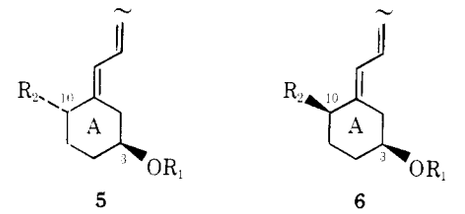


1a, R = H; **b**, R = C_6H_5CO **2a**, R = H; **b**, R = C_6H_5CO

have found clinical applications. In fact **5d** was marketed as early as 1934 under the trade name A. T. 10 by E. Merck (Darmstadt) as an antitetany agent.[6] This substance (**5d**) is one of the four possible stereoisomers (**3d–6d**) which could result from saturation of the 10,19 double bond of **1a** and **2a.** The corresponding stereoisomers in the natural vitamin D_3 series have recently been fully characterized[1b] by this laboratory, but there remained uncertainty in the identity of the 10,19-dihydrovitamins in the D_2 series referred to in the older literature as DHT_2, DHV_2-II, DHV_2-III, DHV_2-IV, and DT-66.[7,8] This paper not only describes the full stereo-



3 **4**



5 **6**

a, R_1 = H; R_2 = CH_2OH
b, R_1 = C_6H_5CO; R_2 = CH_2OH
c, R_1 = C_6H_5CO; R_2 = $CH_2OSO_2C_6H_4$-*p*-CH_3
d, R_1 = H; R_2 = CH_3

Scheme I. Chemical Transformations[a]

1a $\xrightarrow{a}$ (3a, 43%) + (4a, 43%)	(1)
2a $\xrightarrow{a}$ (5a, 33%) + (6a, 39%)	(2)
1b $\xrightarrow{a}$ (4b, 51%) + (3b, 33%)	(3)
2b $\xrightarrow{a}$ (6b, 39%) + (5b, 18%)	(4)
1a $\xrightarrow{b}$ (3d, 54%) + (4d, 35%)	(5)
2a $\xrightarrow{b}$ (6d, 25%) + (5d, 35%)	(6)
4b $\xrightarrow{c}$ 4a (not 3a)	(7)
6b $\xrightarrow{c}$ 6a (not 5a)	(8)
3b $\xrightarrow{d, e}$ 7	(9)
3b $\xrightarrow{d, e}$ 3d (not 4d)	(10)
6b $\xrightarrow{d, e}$ 8	(11)
5b $\xrightarrow{d, e}$ 5d (not 6d)	(12)

[a] The absolute yields of products are given in parentheses. The first product given of each pair in eq 1–6 corresponds to the less polar component obtained under the column chromatography conditions used for the separation. Reactions: (a) 9-BBN, HO^-/H_2O_2; (b) $H_2/C_6H_6/[(C_6H_5)_3P]_3$-RhCl; (c) KOH/CH_3OH; (d) *p*-TsCl, C_5H_5N; (e) $Li(CH_3CH_2)_3BH$.

structural characterization of **3d–6d** and related derivatives but also delineates improved synthetic procedures incorporating a strategy that should allow the convenient preparations of new 19-substituted dihydrovitamins with potential antagonist properties.[9]

Results and Discussion

The chemical transformations carried out in this study are outlined in Scheme I. The following observations are pertinent:

(1) Each of the reactions (catalytic hydrogenation[8] or hydroboration–oxidation[1b]) of **1** and **2** results in two and only two stereoisomeric products. Thus the stereochemical integrity of the $\Delta^{5,7}$-diene is retained in each case (eq 1–6).

(2) Equations 7, 8, 10, and 12 prove that members of each of the following triads possess the same relative stereochemistry: **3a–3b–3d, 4a–4b–4d, 5a–5b–5d,** and **6a–6b–6d.**

(3) Our earlier ^{1}H-NMR results[1b] in the vitamin D_3 series of dihydrovitamins lend considerable confidence on the basis of spectral comparisons to the C_{10} configurational assignments given to the four monoalcohols **3d–6d.** The transformations given in eq 9–12 now also provide definitive chemical evidence for these assignments. This requires, of course, that the structures of the cyclization products **7** and **8** are assigned correctly. Their spectral data (NMR, UV, MS) are certainly in line with the assigned structures and moreover this kind of

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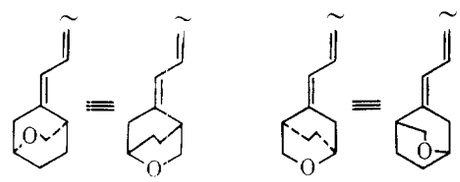
Table I. Chemical Shifts and Bandwidths of the $H_{3\alpha}$ Resonance

	Registry no.	$\tau_{H_{3\alpha}}$	$\sim W_{3\alpha}$, Hz
(5*Z*,7*E*-dienes)			
Trans (CH_3, OH), **3d**	65377-86-8	5.97	7.7
Cis (CH_3, OH), **4d**	65377-87-9	6.4	20
Trans (CH_2OH, OH), **3a**	75338-35-4	5.92	9
Cis (CH_2OH, OH), **4a**	65377-88-0	(6.2–6.6)[a]	*b*
Trans (CH_2OH, OBz), **3b**	65338-36-5	4.67	9
Cis (CH_2OH, OBz), **4b**	65377-89-1	5.0	23
Trans (CH_2OTs, OBz), **3c**	65338-37-6	~4.8	<12
Cis (CH_2OTs, OBz), **4c**	65377-90-4	5.08	23
(5*E*,7*E*-dienes)			
Trans (CH_3, OH), **5d**	67-96-9	6.4	24
Cis (CH_3, OH), **6d**	65377-91-5	6.15	14
rans (CH_2OH, OH), **5a**	65338-38-7	~6.2	*b*
Cis (CH_2OH, OH), **6a**	65377-92-6	~6.3	*b*
Trans (CH_2OH, OBz), **5b**	65338-39-8	~4.8	*b*
Cis (CH_2OH, OBz), **6b**	65377-93-7	~4.9	*b*
Trans (CH_2OTs, OBz), **5c**	65338-40-1	~4.95	>16.5
Cis (CH_2OTs, OBz), **6c**	65377-94-8	~4.95	≳13.5

[a] Includes resonances due to $2H_{19}$. [b] Not measurable.

cyclization is not only logical but also has analogy in the synthesis of the parent 2-oxabicyclo[2.2.2]octane.[10]



7 8

These results reveal that the stereochemistries assigned to **5a** and **6a** (in the vitamin D_3 series)[4] in the previous study[1b] were based on incorrect ^{1}H-NMR analyses.[11] The pertinent ^{1}H-NMR spectral characteristics are discussed in the next paragraph. We emphasize here that the assignments given in the previous paper *are correct*[1b] as a result of yet a second (transposition) error.[11]

Table I summarizes the chemical shifts and bandwidths for the resonance due to $H_{3\alpha}$ for dihydrovitamins **3–6.** For the (5*Z*,7*E*)-dienes derived from **1** it is evident that the trans isomers consistently exhibit their $H_{3\alpha}$ resonance at lower fields (more equatorial character)[12] than the cis isomers. Moreover, the bandwidth of this resonance is consistently smaller (more equatorial character) for the trans isomers than for the cis. Thus the chemical shifts and bandwidths support our earlier conformational analyses of these systems.[1b] For the (5*E*,7*E*)-dienes derived from **2,** the relative chemical shifts and bandwidths for the monoalcohols **5d** and **6d** are in line with their conformational properties (**5d** exhibits more axial 3α-H character than **6d**). The remaining derivatives (**5a–c** and **6a–c**) do not exhibit analogous results and the NMR data (Table I) therefore do not allow stereochemical assignments to be made. The chemical correlations (Scheme I) however establish the absolute configurations of **5a–c** and **6a–c.**

The final subject in this paper deals with the identity of DHT_2, DHV_2-II, DHV_2-III, DHV_2-IV, and DT_{66} referred to in the older literature. It is clear that DHT_2,[6a,e,f,h,i] DHV_2-II,[6c,d,g–i,k] and DHV_2-IV[6e,g,h,k,8] are **5d, 3d,** and **4d,** respectively. As pointed out by von Werder,[6g] DT_{66}[6e] is probably impure DHT_2. It follows that DHV_2-III described by Schubert[6e,8] must have been **6d** or an impure sample of one of the other isomers. Our **6d** exhibited mp 108–110 °C (acetone) and $[\alpha]^{25}_D$ +60.4° (*c* 0.83, ethanol); Schubert's DHV_2-III[6e,8] exhibited mp 50–55 °C (90% methanol) and $[\alpha]_D$ +85° (0.8%, ethanol). From the literature descriptions[6] and from our own experience, it is quite apparent that these dihydrovitamins crystallize erratically and poorly if at all.[13] We made no further attempts to correlate our **6d** with Schubert's DHV_2-III. This study, however, does provide all four unsubstituted DHV's (**3d–6d**) of unequivocally established stereochemistry. We consider the chapter[6j] on the identities of the 10,19-dihydrovitamins of the vitamin D_2 series closed.

Experimental Section

General. Ultraviolet spectra (UV), ^{1}H nuclear magnetic resonance spectra (NMR), and mass spectra (MS) are summarized in Table II (see Supplementary Material paragraph): melting points (mp, uncorrected), Thomas-Hoover capillary apparatus. Dry tetrahydrofuran (THF), freshly distilled (nitrogen) from $LiAlH_4$; lbpe, redistilled 30–60 °C low-boiling petroleum ether; 9-BBN, 0.5 M solution of 9-borabicyclo[3.3.1]nonane in THF (Aldrich Chemical Co.); silica gel for column chromatography, Baker Analyzed reagent (60–200 mesh); alumina for chromatography, Woelm neutral grade III; silica gel G (EM reagents, type 60) for thin layer chromatography (TLC, 0.25 mm analytical plates); alumina for TLC (aluminum oxide G, EM reagents type 60/E). Crystalline vitamin D_2 and dihydrotachysterol$_2$ (DHT_2) were obtained as gifts from Philips-Duphar (Weesp, the Netherlands).

Vitamin D_2 Benzoate (1b). Vitamin D_2 (**1a,** 8.0 g, 16.5 mmol), dry pyridine (40 mL), benzoyl chloride (4.8 g, 4 mL, 38.5 mmol), 45 min (N_2). Standard workup, crystallization (acetone–95% ethanol): 9.06 g (90%); mp 88–90 °C; TLC (silica gel, isopropyl ether), **1a/1b** R_f 0.3/0.6.

5,6-*trans*-Vitamin D_2 (2a).[5] To a solution of **1a** (1 g) in dry ether (1 L) was added iodine (5 mL of a solution containing 20 mg of iodine in 100 mL of ether). After standing for 2.5 h at room temperature (fluorescent room lights), 3 drops of pyridine was added and then the mixture was concentrated under vacuum. The residue was chromatographed on a dry column of silica gel (50 g, pretreated with 4 drops of pyridine; 1.2-cm diameter column) using isopropyl ether (200 mL treated with 2 drops of pyridine). Yield after concentration was 70% (pure by NMR and TLC) of a foam: TLC (alumina, isopropyl ether), **1a/2a** R_f 0.22/0.44.

5,6-*trans*-Vitamin D_2 Benzoate (2b). The benzoate of **2a** was prepared by the method described above for converting **1a** to **1b** except that the reaction time was longer (~2 h) and the residual product after work up was passed through a short column of silica gel (5% ether–lbpe). The residual foam (~quantitative) was found to be pure by NMR and TLC (silica gel, benzene): **2a/2b** R_f 0.39/0.70.

19-Hydroxy-[10*S*(19)]-(3a) and 19-Hydroxy-[10*R*(19)]-dihydrovitamin D_2 (4a). A solution of 9-BBN (11 mL, 0.5 M, 5.5 mmol) in THF was added (syringe) to crystalline **1a** (1.0 g, 2.5 mmol) under nitrogen at room temperature with magnetic stirring. After 2 hr, the resulting clear solution was quenched (H_2O, 5 mL) and then allowed to stand for 15 min. The mixture was cooled (ice) and then aqueous NaOH (1.85 mL, 3 M) and H_2O_2 (1.85 mL, 30%) were added successively (syringe). The mixture was heated (55 °C, 1 h), cooled, and then worked up with pentane and water. The pentane layer afforded a residue which was chromatographed (90 g silica gel, 2 × 120 cm column, 60% ether–lbpe to 100% ether) to afford after thorough drying **3a** (445 mg, 43%; foam, mp 53–6 °C; crystallization from 90% ethanol, mp 66–70 °C) and **4a** (446 mg, 43%; foam, mp 56–60 °C; could not be crystallized). Each of the isomers was completely homogeneous to TLC (silica gel, 30% acetone–benzene: **3a,** R_f 0.36; **4a,** R_f 0.20). Spectroscopic data (Table II) and chemical correlations (below) established configurational assignments.

19-Hydroxy-[10*S*(19)]-(5a) and 19-Hydroxy-[10*R*(19)]-dihydro-(5*E*)-vitamin D_2 (6a). The procedure of the preceding experiment was followed using the following quantities of material: 5,6-*trans*-D_2 (**2a,** 0.68 g, 1.71 mmol) and 9-BBN in THF (7.6 mL, 0.5 M, 3.8 mmol); water (3 mL for quenching); aqueous NaOH (1.25 mL, 3 M) and 30% H_2O_2 (1.25 mL) for oxidation; pentane–water for workup. The residue from the pentane layer was carefully chromatographed (alumina, 1.5 × 70 cm column, 60% ether–lbpe to ether to 2% methanol–ether) to afford after thorough drying **5a** (232 mg, 33%; foam, double mp 52–60 and 121–123 °C; crystallization from isopropyl ether, mp 129–30 °C) and **6a** (275 mg, 39%; foam, mp 59–62 °C; could not be crystallized). TLC (ether, alumina; silica gel was ineffective) revealed that the materials were homogeneous: **5a** R_f 0.36 and **6a** R_f 0.32. Spectroscopic data (Table II) and, most importantly, the chemical correlations showed that **5a** is the trans isomer and **6a** is the cis isomer.

19-Hydroxy-[10*S*(19)]-(3b) and 19-Hydroxy-[10*R*(19)]-dihydrovitamin D_2 Benzoate (4b). The 9-BBN/THF solution (11.4 mmol, 22.8 mL, 0.5 M) was added (syringe, 6 min) to D_2 benzoate (**1b**, 4.1 g, 8.2 mmol) under nitrogen. The resulting clear solution was stirred at ambient for 2 h and then the ice cooled reaction mixture was quenched with methanol (10.8 mL). After adding aqueous NaOH (1.92 mL, 6 M) and 30% H_2O_2 (3.84 mL) to the ice cooled mixture, the mixture was stirred at room temperature for 30 min. After work-up (pentane–water) and concentration, the resulting residue was chromatographed (160 g of silica gel, lbpe to 20% ether–lbpe) to afford an excellent separation of **4b** (2.14 g, 51%, mp 60–65 °C) and **3b** (1.39 g, 33%, mp 55–60 °C). Neither isomer could be crystallized although both proved to be homogeneous by TLC (silica gel, isopropyl ether): **4b** R_f 0.55 and **3b** R_f 0.40. Spectral (Table II) and chemical correlations established their stereochemistries.

19-Hydroxy-[10*S*(19)]-(5b) and 19-Hydroxy-[10*R*(19)]-dihydro-(5*E*)-vitamin D_2 Benzoate (6b). The procedure was essentially the same as that described in the preceding experiment except that the oxidation step was carried out for a longer reaction time (1 h at room temperature and then 0.5 h at 40 °C). The quantities of materials were as follows: 5,6-*trans*-D_2 benzoate (**2b**, 1.48 g, 2.94 mmol); 9-BBN/THF (8.2 mL, 4.10 mmol, 0.5 M); methanol (3 mL) quench; oxidation with aqueous NaOH (0.7 mL, 6 M) and 30% H_2O_2 (1.4 mL). After standard work-up (pentane–water), the residual product was chromatographed (85 g, 5% $AgNO_3$ impregnated silica gel, 2-cm diameter column, dry column method, chloroform) to afford after thorough drying **6b** (600 mg, 39%) and **5b** (270 mg, 18%). TLC ($AgNO_3$–silica gel, isopropyl ether) showed **6b** R_f 0.37 and **5b** R_f 0.25.

The less polar isomer was rechromatographed (silica gel, 40 g, 1.5-cm diameter column, lbpe to 30% ether–lbpe) to afford a white foam (540 mg, mp 54–58 °C). This substance was identified as the cis isomer **6b** by spectral (Table II) and chemical correlations.

The more polar isomer was similarly chromatographed to afford a colorless foam (mp 53–59 °C). It was characterized spectrally (Table II) and chemically as **5b**, the trans isomer.

Tosylation of the Hydroxybenzoates 3b, 4b, 5b, and 6b to the 3β-Benzoyloxy-19-*p*-toluenesulfonates 3c, 4c, 5c, and 6c. The procedure for **6c** is exemplary. A mixture of hydroxybenzoate isomer **6b** (150 mg, 0.29 mmol), *p*-toluenesulfonyl chloride (185 mg, 1.16 mmol, crystallized), and dry pyridine (1.5 mL, freshly distilled) was left under nitrogen in the refrigerator overnight. Ice water was added, the residual solid was gravity filtered several times, and then the product was rinsed thoroughly with water. The solid was taken up in ether and worked up conventionally to afford (after drying under high vacuum) **6c** as a solid (180 mg, 93%, mp ~50–56 °C) which could not be crystallized.

Tosylation of **5b: 5b** (133 mg, 0.26 mmol), *p*-toluenesulfonyl chloride (164 mg, 1.03 mmol), pyridine (1.3 mL); overnight (refrigerator); 174 mg (quantitative) of **5c** with mp ~50–58 °C. See Table II.

Tosylation of **4b: 4b** (300 mg, 0.58 mmol), *p*-toluenesulfonyl chloride (370 mg, 2.32 mmol), pyridine (2.5 mL); 6 h at room temperature; 367 mg (94%) of **4c** with mp ~50–57 °C. See Table II.

Tosylation of **3b: 3b** (300 mg, 0.58 mmol), *p*-toluenesulfonyl chloride (370 mg, 2.23 mmol), pyridine (2.5 mL); 4 h at room temperature; 389 mg (~quantitative) of **3c** with mp ~50–57 °C. See Table II.

Their spectral properties (Table II) were in accord with the structural assignments. These spectral data and the chemical correlations described below established their stereochemistries. Their TLC behavior was as follows: **3c/4c**, silica gel, 25% ether–lbpe, R_f 0.39/0.56; **5c/6c**, 10% $AgNO_3$–silica gel, 25% ether–lbpe, R_f 0.42/0.39.

Reduction of Benzoyloxytosylate 3c to [10*S*(19)]-Dihydrovitamin D_2 (3d). Lithium triethylborohydride/THF (1.05 mL, 1.05 mmol, 1.05 M, Aldrich)[14] was added (syringe) to **3c** (100 mg, 0.15 mmol) under nitrogen with ice cooling. The bath was removed and the solution was stirred at reflux for 2 h. Water (0.5 mL), aqueous NaOH (0.35 mL), and 30% H_2O_2 (0.35 mL) were added successively to the ice cooled solution and then the reaction mixture was refluxed for 0.5 h. The cooled reaction mixture was worked up with pentane–water by conventional methods. The vacuum dried solid residue **3d** (51 mg, 86%) proved homogeneous by NMR (Table II) and TLC. Crystallization (acetone) afforded material with mp 104–5 °C (lit. mp 102.5–106.5,[6d] 108 °C,[6g] liquid[6k]). The **3d** prepared in this way was identical[8] to that prepared by catalytic reduction of vitamin D_2 (see below).

Reduction of Benzoyloxytosylate 4c to the Ether 7. The cis isomer **4c** (100 mg, 0.15 mmol) was reduced essentially as described in the preceding experiment except the reaction was carried out at room temperature for 1 h, methanol (0.5 mL) was used instead of water to quench the excess hydride, and a conventional ether–water (instead of pentane–water) work-up was utilized. As described below for **6c**, it appears that the procedure of the preceding experiment is superior. The resulting residue from this experiment was chromatographed (silica gel, 20 g, 10% ether–lbpe) to afford after vacuum drying 35 mg (59%, oil) of a material assigned the cyclic ether structure **7** on the basis of spectral data (Table II).[11]

Reduction of Benzoyloxytosylate 5c to Dihydrotachysterol$_2$ (5d). The tosylate **5c** (135 mg, 0.20 mmol) was reduced with lithium triethylborohydride in precisely the same way as described for **3c** above to afford after chromatography (silica gel, 1 × 55 cm column, lbpe to 10% ether–lbpe) 21 mg (26%) of TLC (silica gel, benzene; comparison with authentic **5d**) pure **5d.** Crystallization (methanol) afforded material with mp 123–125 °C (authentic commercial specimen, mp 122–123.5 °C;[7] mmp 124–125 °C; lit. mp 128,[6g] 125–127,[6e] 131–133 °C[6h,i]). NMR data are summarized in Table II; $[\alpha]^{25}_D$ +90.4° (*c* 0.83 g/100 mL 95% EtOH).

Reduction of Benzoyloxytosylate 6c to the Ether 8. Using the procedure of the preceding section, **6c** (140 mg, 0.21 mmol) was reduced to afford after vacuum drying a TLC homogeneous substance (70 mg, 85%, oil) assigned the cyclic ether structure **8** on the basis of spectral data (Table II).

Saponification of 6b to the Diol 6a. The ester **6b** (40 mg) described above in a mixture of 5% KOH–CH_3OH (5 mL) and THF (1 mL) was refluxed under nitrogen for 2 h. Standard workup afforded material with properties (TLC–alumina/ether, NMR) identical to the diol isomer **6a** and clearly different from the diol isomer **5a** described earlier.

Saponification of 4b to the Diol 4a. The ester **4b** (40 mg) described earlier was saponified as in the preceding experiment to afford a substance identical (TLC-30% acetone in benzene/silica gel, NMR) to the diol cis isomer **4a** which is clearly different from trans isomer **3a.**

Catalytic Hydrogenation of Vitamin D_2 (1a) to [10*S*(19)]-(3d) and [10*R*(19)]-Dihydrovitamin D_2 (4d). Vitamin D_2 (**1a**, 350 mg, 0.88 mmol) and $[(C_6H_5)_3P]_3RhCl$ (87 mg) in benzene (40 mL, freshly distilled from potassium under nitrogen) were subjected to hydrogenation (1 atm) for 14 h at room temperature by which time hydrogen uptake had essentially ceased.[6k,8] Benzene was removed under vacuum and the residue was taken up in pentane. The latter was washed thoroughly with water, filtered, and then dried (Na_2SO_4). The filtered and concentrated organic phase left a residue (394 mg) which was chromatographed (dry column, 1.5 × 120 cm column of silica gel, 8 mL fractions, 30% ether–lbpe). Fractions 4–10 afforded TLC pure **3d** (190 mg, 54%). Fractions 11–25 were combined and concentrated to afford a residue which was rechromatographed (dry column, 1.5 × 70 cm silica gel, 6 mL fractions, 25% ether–lbpe): fractions 4–6 contained small amounts of **3d;** fractions 8–21 contained TLC pure **4d** (122 mg, 35%).

Crystallization (acetone) of **3d** afforded material with mp 100–102 °C. It proved to be identical (NMR, TLC, mp) to the trans isomer **3d** described earlier in this paper.

Crystallization (90% acetone–H_2O) of **4d** afforded material with mp 83.5–86 °C (lit.[6h,i] mp 85–7 °C from petroleum ether, mp 60–65[6h,i] or 61 °C[6k] from CH_3OH). The combined yield of TLC pure **3d** and **3d** was 89%. Spectral data (NMR) for both **3d** and **4d** are summarized in Table II. Their TLC behavior (**3d/4d**, R_f's) was as follows: isopropyl ether–silica gel (0.40, 0.33); isopropyl ether–5% $AgNO_3$ silica gel (0.35/0.50).

Catalytic Hydrogenation of 5,6-*trans*-Vitamin D_2 (2a) to [10*S*(19)]-, Dihydrotachysterol$_2$) (5d), and [10*R*(19)]-Dihydro-(5*E*)-vitamin D_2 (6d). The reduction (5,6-*trans*-D_2, **2a**, 639 mg; catalyst, 160 mg; benzene, 70 mL; overnight) and work-up (pentane–water) was carried out as described in the preceding section. Dry column chromatography (silica gel, 2.2 × 160 cm, 30% ether–lbpe) afforded TLC pure **6d** [160 mg, 25%; crystallization from acetone gave crystals with mp 108–110 °C, $[\alpha]^{25}_D$ +60.4° (*c* 0.83 g/100 mL 95% EtOH)] and impure **5d** (271 mg). Rechromatography of impure **5d** (alumina, 1.5 × 70 cm, 15% ether–lbpe to 75% ether–lbpe) afforded TLC pure **5d** (215 mg, 34%; crystallization from methanol gave mp 122.5–123.5 °C). Silica gel TLC using 25% ether–lbpe effectively resolved the two stereoisomers: **6d** R_f 0.22 and **5d** R_f 0.16.

The more polar isomer proved to be identical by TLC (alumina, 50% ether–lbpe; silica gel, isopropyl ether), mmp (122.5–123.5 °C), and NMR (Table II) to the dihydrotachysterol$_2$ (**5d,** mp 122–123 °C) prepared by reduction of **5c** described earlier. See earlier section for $[\alpha]^{25}_D$.

The less polar isomer is assigned stereostructure **6d** on the basis of its spectral characteristics (Table II, including a comparison of its NMR spectrum to that of the corresponding stereoisomer in the vitamin D_3 series[4] previously reported by this laboratory)[1b] and the

chemical correlations described above.

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Registry No.—**1a,** 50-14-6; **1b,** 65338-41-2; **2a,** 65377-95-9; **2b,** 65338-42-3; **7,** 65338-43-4; **8,** 65338-44-5; benzoyl chloride, 98-88-4; Ts-Cl, 98-59-9.

Supplementary Material Available: Table II giving the NMR, UV, and/or MS data for the 18 compounds **3–6, 7,** and **8** (5 pages). Ordering information is given on any current masthead page.

References and Notes

(1) (a) For Paper 13 in this series, see W. H. Okamura, M. N. Mitra, M. R. Pirio, A. Mouriño, S. C. Carey, and A. W. Norman, *J. Org. Chem.*, **43,** 574 (1978); (b) see paper 12 for a related study of 10,19-dihydrovitamins, W. H. Okamura, M. L. Hammond, A. Rego, A. W. Norman, and R. M. Wing, *J. Org. Chem.*, **42,** 2284 (1977).
(2) This study was supported by USPHS Grant AM-16595 and by a grant from the Intramural Research Fund of the University of California, Riverside.
(3) Spanish Ministry of Education and Science Postdoctoral Fellow.
(4) Vitamin D_3 (cholecalciferol), a prohormone which possesses the C_8H_{17} side chain of cholesterol, is actually the naturally occurring form of vitamin D.
(5) A. Verloop, A. L. Koevoet, and E. Havinga, *Recl. Trav. Chim. Pays-Bas,* **74,** 1125 (1955).
(6) For articles related to the preparation and characterization of the 10,19-dihydrovitamins of the vitamin D_2 series, see: (a) F. von Werder, *Z. Physiol. Chem.*, **260,** 119 (1939); (b) K. Schubert, *Naturwissenschaften,* **41,** 231 (1954); (c) K. Schubert, *Biochem. Z.,* **326,** 132 (1954); (d) K. Schubert, *ibid.,* **327,** 507 (1956); (e) K. Schubert and K. Wehrberger, *ibid.,* **328,** 199 (1956); (f) P. Westerhof and J. A. Keverling Buisman, *Recl. Trav. Chim. Pays-Bas,* **75,** 453 (1956); (g) F. von Werder, *Justus Liebigs Ann. Chem.*, **603,** 15 (1957); (h) P. Westerhof and J. A. Keverling Buisman, *Recl. Trav. Chim. Pays-Bas,* **76,** 679 (1957); (i) P. Westerhof and J. A. Keverling Buisman, *ibid.,* **78,** 659 (1959); (j) L. F. Fieser and M. Fieser, "Steroids", Reinhold, New York, N.Y., 1959, pp 143–6; (k) A. G. M. Barrett, D. H. R. Barton, R. A. Russell, and D. A. Widdowson, *J. Chem. Soc., Perkin Trans. 1,* 631 (1977).
(7) Commercial dihydrotachysterol$_2$ (**5d**) clearly has the stereostructure shown as determined by comparison of its 300 MHz ^{1}H-NMR spectrum with that of dihydrotachysterol$_3$ (vitamin D_3 side chain) (ref 1b).
(8) The two products (**3d** and **4d**) obtained by saturating the 10,19 double bond of vitamin D_2 have been labeled in our laboratory as DHV$_2$-II and DHV$_2$-III, respectively. Other workers (ref 6e,h,i,k) refer to **4d** as DHV$_2$-IV while our laboratory (see also ref 6g,j) labels **6d,** the C_{10} epimer of dihydrotachysterol$_2$ (**5d**), as DHV$_2$-IV. See footnote 17 of ref 1b. While this study was in progress, Barett et al. (ref 6k) reported the fact that catalytic reduction of **1a** results in only two products: DHV$_2$-II (**3d**) and DHV$_2$-IV (**4d** or what we call DHV$_2$-III).
(9) M. L. Hammond, A. Mouriño, P. Blair, W. Wecksler, R. L. Johnson, A. W. Norman, and W. H. Okamura, "Vitamin D: Biochemical, Chemical and Clinical Aspects Related to Calcium Metabolism", A. W. Norman, K. Schaefer, J. W. Coburn, H. F. DeLuca, D. Fraser, H. G. Grigoleit, and D. v. Herrath, Ed., W. De Gruyter Publisher, Berlin, 1977, pp 1–4.
(10) T. A. Giudici and T. C. Bruice, *J. Org. Chem.*, **35,** 2386 (1970).
(11) It appears that we reversed the **5a–6a** assignments in writing the earlier manuscript (ref 1b). As a result of a double error, the assigned stereochemistries and product ratios as given in ref 1b are correct.
(12) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed, Pergamon Press, Oxford, 1969, pp 239 and 288.
(13) For this reason, homogeneity of the various DHV's was established by TLC under several sets of conditions. NMR and high resolution mass spectral data are given in Table II.
(14) S. Krishnamurthy and H. C. Brown, *J. Org. Chem.*, **41,** 3064 (1976); see also, R. W. Holder and M. G. Matturro, *ibid.*, **42,** 2166 (1977).

Stereochemical Assignment of (*E*)- and (*Z*)-2-(1-Naphthyl)-1-phenylpropene and Their Photocyclization to 5-Methylchrysene

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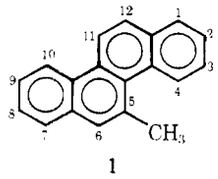
Dehydration of 2-(1-naphthyl)-1-phenyl-2-propanol (**3**) gave varying ratios of (*E*)-2-(1-naphthyl)-1-phenylpropene (**4**), (*Z*)-2-(1-naphthyl)-1-phenylpropene (**5**), and 2-(1-naphthyl)-3-phenylpropene (**6**), depending upon conditions and choice of reagent. Assignment of configuration to these alkenes by UV and ^{1}H NMR spectroscopy was equivocal, but unambiguous assignment was made through comparison of chemical shifts in the ^{1}H NMR spectra of the cis diols and the corresponding cyclic phenylboronates prepared from **4** and **5**. Photocyclization of **4** or **5** gave 5-methylchrysene (**1**), whereas **6** was inert.

The environmental carcinogen 5-methylchrysene (**1**), which occurs in the biologically active neutral subfractions of tobacco smoke, is more carcinogenic on mouse skin than any of the other monomethylchrysene isomers or chrysene itself.[2] The carcinogenic activity of **1** is comparable to that of benzo[*a*]pyrene.[3] 5-Methylchrysene is also more mutagenic towards *S. typhimurium* than the other monomethylchrysenes.[4]

Previous syntheses[2a,5] of **1** involved multistep routes and gave low yields, none exceeding 5%. In order to continue carcinogenicity studies of **1**, a more efficient synthesis was needed. Photocyclization of the appropriately substituted alkene[6] appeared to be a more suitable route. We now report a shorter and improved synthesis (20% yield) of **1** via UV irradiation of (*E*)- or (*Z*)-2-(1-naphthyl)-1-phenylpropene (**4** and **5**, respectively) in the presence of iodine and oxygen as shown in Scheme I.



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Treatment of 1-acetonaphthone with benzylmagnesium chloride gave **3** in 75% yield. Dehydration of **3** was performed under a variety of conditions in an attempt to control the ratio of the resulting alkenes.[7] In all cases, GC analyses[8] indicated the three products shown in Table I.

During dehydration of **3** in refluxing benzene with Amberlyst-15 (A-15) resin,[9] the ratio of alkenes **4/5/6** (48:9:43) remained fairly constant while alcohol **3** was still present. After **3** was consumed, the concentration of exo alkene **6** decreased rapidly with simultaneous increase of **4** to a maximum of 57%. Alkene **4** then slowly diminished as the concentration of **5** increased. After 36 h, the ratio **4/5/6** (54:45:1)[10] stabilized

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