Two New Vitamin D Isomers. Formation of (3S,10R)-(Z,Z)-9,10-Secocholesta-5,7,14-trien-3-ol and Its 10S-Epimer from *cis*-Isotachysterol$_3$ via Facile [1,7] Sigmatropic Rearrangements

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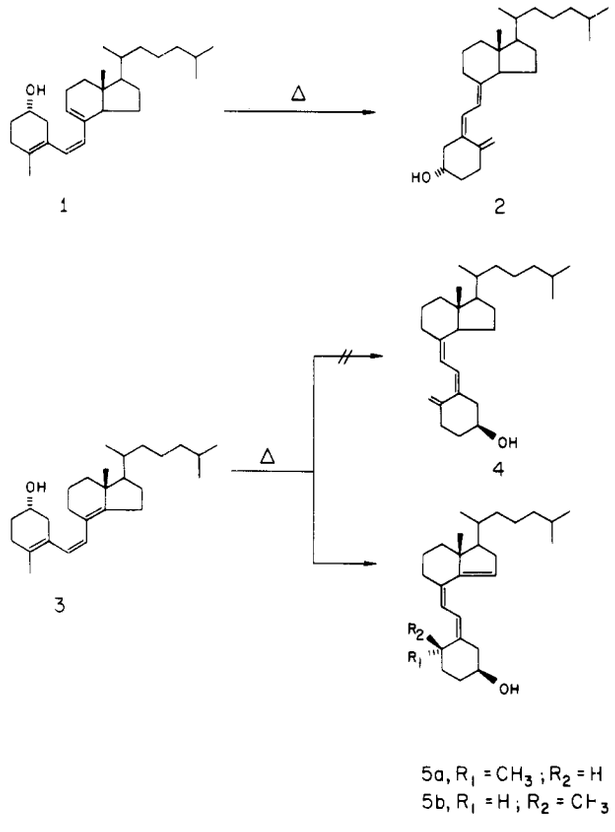
Warming a solution of (3S)-(Z)-9,10-secocholesta-5(10),6,8(14)-trien-3-ol (*cis*-isotachysterol$_3$) in decane produced two new isomers of vitamin D_3: (3S,10S)-(Z,Z)-9,10-secocholesta-5,7,14-trien-3-ol (**5a**) and (3S,10R)-(Z,Z)-9,10-secocholesta-5,7,14-trien-3-ol (**5b**). The reaction has been shown to be reversible, and to occur via an intramolecular [1,7] hydrogen transfer. Stereochemistry at C-10 was assigned by chemical correlation with dihydrotachysterol, and double bond geometry was deduced from NMR data and mechanistic considerations. Activation parameters for the reactions to **5a** and **5b**, calculated from kinetic data, are $\Delta H^{\ddagger} = 23.0 \pm 1.2$ kcal/mol, $\Delta S^{\ddagger} = -16.3 \pm 3.3$ eu and $\Delta H^{\ddagger} = 23.2 \pm 1.2$ kcal/mol, $\Delta S^{\ddagger} = -17.1 \pm 3.4$ eu, respectively.

For the past decade work in our laboratories has focused on the isolation and characterization of biologically active vitamin D metabolites. Since metabolite identification depends heavily on spectral correlations, we have, as part of our general program, prepared most of the known triene isomers of vitamin D, for which required spectral data were often not available, because their original syntheses[1,2] predated the advent of modern spectroscopic techniques. One of these compounds, *cis*-isotachysterol, was originally described by Verloop et al.[3] who noted that prolonged heating (60 °C) of a methanol solution of this compound produced a shift of the UV absorption maximum from 253 to 265 nm and an increase in absorption intensity. A spectral change of this kind is reminiscent of that occurring in the thermal isomerization of previtamin D (**1**) to vitamin D (**2**) via a [1,7]sigmatropic shift. In the case of *cis*-isotachysterol$_3$ (**3**), an exactly analogous rearrangement (C-19 → C-14 H migration) would yield the new and unusual vitamin D isomer(s) **4** (C-14 stereochemistry *R* or *S*, or both) featuring (5Z,7Z) double-bond geometry. A reinvestigation of this reaction has now shown that *cis*-isotachysterol$_3$ (**3**) undergoes an alternative sigmatropic rearrangement involving intramolecular hydrogen transfer from C-15 to C-10 and resulting exclusively in (3S,10S)-(Z,Z)-9,10-secocholesta-5,7,14-trien-3-ol (**5a**) and its (10R)-epimer (**5b**).

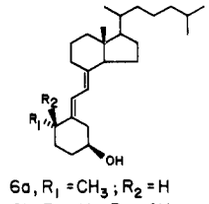


5a, $R_1 = CH_3$; $R_2 = H$
5b, $R_1 = H$; $R_2 = CH_3$

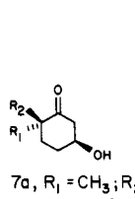
Results and Discussion

In refluxing toluene, *cis*-isotachysterol$_3$ (**3**) was smoothly converted to two products (**5a,b**) which were separated by preparative TLC. High resolution mass spectrometry showed them to be isomers of the starting material ($C_{27}H_{44}O$) and both exhibited the UV absorption maximum of a conjugated triene chromophore (273 nm). The NMR spectra indicated three olefinic protons (two as an isolated AB pattern, the third coupled to two other protons) and an additional secondary methyl instead of the olefinic methyl of the starting material. Given the structure of **3** and the conditions of its conversion to **5a** and **5b**, the spectral evidence required that both products be $\Delta^{5,7,14}$-trienes differing in configuration at C-10. Stereochemistry at C-10 was established by chemical correlation to dihydrotachysterol$_2$ (DHT_2),[4] an historically important reduction product of vitamin D_2. Ozonolysis of **5a** gave β-hydroxy ketone **7a**, identical (as determined by combined GC/MS) with the ozonolysis product obtained from DHT_2 for which the (10S) configuration has been established.[5,6] Ozonolysis of **5b**, on the other hand, furnished hydroxy ketone **7b**, exhibiting a mass spectrum nearly identical to that of **7a**, but clearly distinguished from the latter by GC retention time. These correlations establish the (10S) and (10R) configurations for **5a** and **5b**, respectively, and confirm the C-5 terminus of the triene system for both isomers.

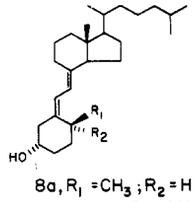
The major difference between the strikingly similar ^{1}H-NMR spectra of the two new isomers is that between the chemical shifts of the 3α protons. This difference allowed assignment of the stereochemistry of the 5,6-double bond by spectral correlation with dihydrovitamins **6a,b** and **8a,b**. The 3α proton of **5a** occurs at δ 4.05, very similar to that found for **8a** (4.02 ppm),[6] but not to that observed for **6a** (3.61 ppm).[6] Analogously, the 3α proton of **5b** resonates at δ 3.52, similar



6a, $R_1 = CH_3$; $R_2 = H$
6b, $R_1 = H$; $R_2 = CH_3$



7a, $R_1 = CH_3$; $R_2 = H$
7b, $R_1 = H$; $R_2 = CH_3$



8a, $R_1 = CH_3$; $R_2 = H$
8b, $R_1 = H$; $R_2 = CH_3$

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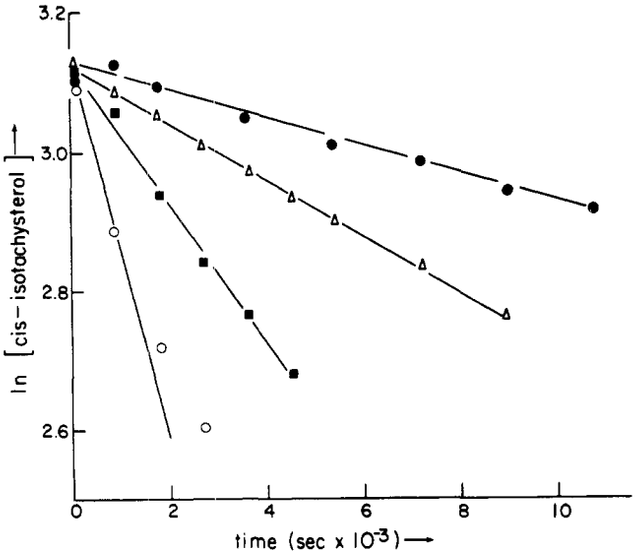


Figure 1. Kinetics of the decrease of *cis*-isotachysterol$_3$ concentration with time at 80 (●), 90 (△), 100 (■), and 110 °C (○). The reaction was run in decane under nitrogen gas; the ordinate represents the natural log of the starting material concentration in arbitrary units.

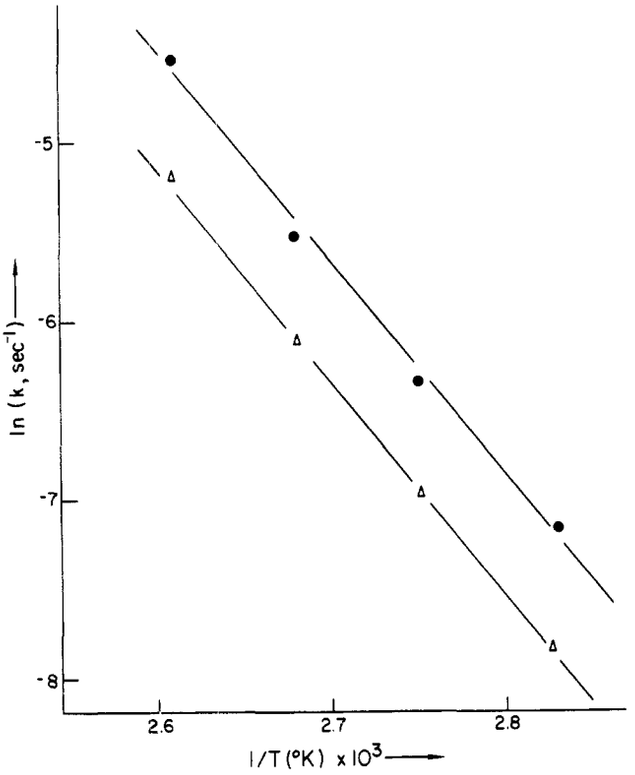


Figure 2. Arrhenius plot of rate constants for formation of isomer **5a** (●) and isomer **5b** (△) from *cis*-isotachysterol$_3$ in decane solutions at 80, 90, 100, and 110 °C.

to that found for **8b** (3.57 ppm),[6] but not to that observed for **6b** (3.82 ppm).[6] These comparisons indicate (5*Z*) stereochemistry for both triene isomers. Since both products arise by intramolecular hydrogen migration (see next paragraph), the known geometric requirement for an antarafacial transition state in [1,7]sigmatropic rearrangements[7] dictates the (7*Z*) geometry for the central double bond in both compounds; structures **5a** and **5b**, therefore, define the reaction products.

To examine the mechanism of the rearrangement, *cis*-isotachysterol$_3$ was heated in CH_3OD. Products **5a** and **5b** were isolated by preparative TLC, and the isotopic composition of their molecular ions was determined by mass spectrometry. As expected for an intramolecular hydrogen transfer, no deuterium was incorporated into the products (Table I). The reversibility of the reaction was demonstrated by heating a solution of **5a** in xylene and isolating **3** and **5b**.

Table I. Mass Spectral Intensities[a] of M, M + 1, and M + 2 for Trienes 5a and 5b Formed Thermally from 3 in CH_3OD

m/e	*cis*-isotachysterol$_3$ (3)	triene **5a**	triene **5b**
384	100.0	100.0	100.0
385	30.8	3/5	30.7
386	5.7	5.5	5.7

[a] Each value represents the mean of three measurements with the intensity of *m/e* 384 taken as 100.

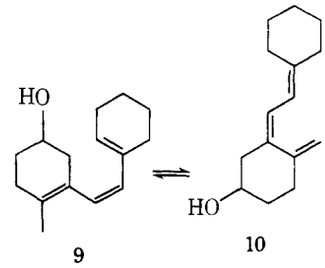
Table II. Comparison of Kinetics of Thermal Rearrangements.

rearrangement	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu
3 → **5a**[f]	23.0 ± 1.2[a]	−16.3 ± 3.3[a]
3[d] → **5b**[g]	23.2 ± 1.2[a]	−17.1 ± 3.4[a]
1[e] → **2**[h]	18.5 ± 0.1[b]	−21.8 ± 0.4[b]
9 → **10**	21.6 ± 0.2[c]	−17.2[c]

[a] Calculated for 95 °C. [b] Calculated from data in ref 10 for 70 °C. [c] Reference 11. [d] Registry no. 66966-15-2. [e] Registry no. 1173-13-3. [f] Registry no. 66901-52-8. [g] Registry no. 66966-16-3. [h] Registry no. 67-97-0.

The kinetics of the reaction were examined at 80, 90, 100, and 110 °C in decane solutions. The decrease in starting material concentration (Figure 1) followed first-order kinetics except at later times for the higher temperatures where the influence of back reaction was evident. Triene isomer **5a** was formed 1.9–2.0 times faster than triene isomer **5b**. The activation parameters (Table II) show that the formation of isomer **5a** is favored over **5b** kinetically. Isomer **5b** is, however, the major product. At 120 °C, the equilibrium mixture in decane consists of 24% of **5a**, 36% of **3**, and 40% of **5b**. Thus isomer **5b** is thermodynamically preferred over **5a** by 0.4 kcal/mol ($\Delta F°$). For both isomers, the C-10 methyl would be almost exclusively axial to minimize the severe steric interaction between the C-19 and C-7 protons. This conformational bias has been experimentally confirmed for compounds **8a** and **8b**.[6] Thus, the C-3 hydroxyl would be forced into an axial orientation in **5a** and an equatorial one in **5b**, accounting for the thermodynamic stability of the latter. The *A* value of 0.5 kcal/mol for the equatorial preference of an hydroxyl substituent on a cyclohexane ring in nonpolar solvents supports this interpretation.[8]

The activation parameters for the conversion of **3** → **5a** + **5b** calculated from our kinetic results are in accord with data for other [1,7]sigmatropic rearrangements in analogous systems. Table II lists the corresponding values for the previtamin D_3 (**1**) to vitamin D_3 (**2**) reaction, one of the earliest



9 10

known [1,7]sigmatropic isomerizations,[9,10] and for the reaction of triene **9** to its isomer **10**, studied by Schlatmann et al.[11] The large negative entropy of activation reflects the high degree of order in the transition state. Since the activation parameters for the isomerization of **1** → **2** and **9** → **10** compare so closely to those found for the formation of trienes **5a** and **5b** from **3**, it is reasonable to assume that the same type of mechanism applies to each case. Unlike the reaction from **3** to **5a** and **5b**, however, the conversion of **1** to **2** involves two transition states (transfer of one of the C-19 hydrogens to either the α or the β face of the 8,9-double bond in **1**) that lead to the same product.[12]

Experimental Section

Mass spectra were obtained on an AEI Model MS-902 mass spectrometer at 70 eV using a direct probe for introduction of samples (source temperature, 110–130 °C above ambient); high resolution mass spectra were measured on the same instrument coupled to an AEI Model DS-50 data system and using perfluorokerosene as an internal mass standard. UV absorption spectra were recorded on a Beckman Model 25 instrument. NMR spectra were taken on a Bruker 270 MHz FT spectrometer using $CDCl_3$ as solvent and tetramethylsilane as internal standard. GC–MS was carried out on a Varian Model 2740 gas chromatograph coupled to a Dupont 21-491 B mass spectrometer. For analytical TLC, air-dried silica gel G plates (5 × 20 cm, 0.25 mm thick) were used. For preparative TLC, 20 × 20 cm plates covered with a 0.75 mm thick layer of silica gel H and silica gel PF-254 (1:1) were used. HPLC was performed on a Dupont 830 liquid chromatograph with a Waters Model U6K injector and 254 nm detector; a Partisil-10 column (0.46 × 50 cm, Whatman) was operated at 800 psig which gave a flow rate of 2.2 mL/min using 1% 2-propanol in hexane as solvent. Ozone was produced with a Supelco microozonator. Commercial Skellysolve B was distilled and the fraction boiling between 67 and 69 °C was used. Dihydrotachysterol$_2$ was a generous gift from the Philips Duphar Co., Amsterdam; methanol-d_1 (99% D) was purchased from Stohler Isotope Chemicals.

***cis*-Isotachysterol$_3$ (3).** An ether solution (200 mL) of 56.7 mg of isotachysterol$_3$ [(3*S*)-(*E*)-9,10-secocholesta-5(10),6,8,(14)-trien-3-ol, prepared from vitamin D_3 (**2**) by the procedure of Murray et al.[13]] was irradiated under N_2 for 35 min using an ice bath, vigorous stirring, Vycor filter, water-cooled quartz irradiation apparatus, and a mercury-arc lamp (Hanau TQ 150 Zz). The solvent was removed by evaporation and the resulting residue was purified on a 20 × 20 cm silica gel preparative TLC plate. After developing the plate four times with 10% ethyl acetate in Skellysolve B two bands were eluted with ethyl acetate. The bottom band was starting material (identical to isotachysterol$_3$ by UV, MS, GC, and TLC) while the top zone, after flash evaporation of solvent, gave 14 mg (25%) of *cis*-isotachysterol$_3$ (**3**) as a clear oil: UV (EtOH) λ_{max} 253 nm (ϵ 13 000); NMR ($CDCl_3$) δ 5.83 and 5.80 (AB, J = 12.7 Hz, 2 H, C-6,7), 3.90 (m, 1 H, C-3), 1.80 (s, 3 H, C-19), 0.94 (d, J = 6.3 Hz, 3 H, C-21), 0.88 (s, 3 H, C-18), 0.87 (d, J = 6.6 Hz, 6 H, C-26,27); mass spectrum, *m/e* (relative intensity) 384 (M^+, 100), 369 (21), 271 (51), 253 (25), 217 (22), 199 (18), 81 (40); M^+, *m/e* calcd for $C_{27}H_{44}O$ 384.3393, found 384.3380; homogeneous on TLC (R_f 0.54, 15% ethyl acetate in Skellysolve B) and LC (t_R = 4.90 min); two peaks are observed on GC[14] (Lit. UV (ether) λ_{max} 253 nm (ϵ 15 000)[3]).

Preparation of Isomers 5a and 5b. A solution of 9.5 mg of *cis*-isotachysterol$_3$ (**3**) in 10 mL of toluene was refluxed under nitrogen for 3 h. The solvent was removed by flash evaporation and the resulting oil was purified by preparative silica gel TLC. The plate was developed with 15% ethyl acetate in Skellysolve B and two bands were eluted with ethyl acetate. The top band gave triene isomer **5a** (1.8 mg, 19%) as an oil: UV (EtOH) λ_{max} 273 nm (ϵ 18 000); NMR ($CDCl_3$) δ 6.21 and 6.13 (AB, J = 11.4 Hz, 2 H, C-6 and C-7), 5.48 (dd, J = 2.9 and 1.8 Hz, 1 H, C-15), 4.05 (m, 1 H, C-3), 1.10 (d, J = 7 Hz, 3 H, C-19), 0.93 (d, J = 6.3 Hz, 3 H, C-21), 0.88 (d, J = 6.3 Hz, 6 H, C-26,27), 0.87 (s, 3 H, C-18); mass spectrum, *m/e* (relative intensity) 384 (M^+, 100), 369 (18), 351 (13), 271 (40), 253 (22), 244 (33), 159 (22), 145 (23), 133 (40); M^+, *m/e* calcd for $C_{27}H_{44}O$ 384.3393, found 384.3375; homogeneous on TLC (R_f 0.77, 15% ethyl acetate in Skellysolve B) and LC (t_R = 2.71 min); GC[14] gave two peaks. The bottom band was reapplied to a silica gel preparative TLC plate which was developed three times using 10% ethyl acetate in Skellysolve. B. Two zones were eluted with ethyl acetate. The upper zone gave 2.7 mg (28%) of starting material (identical to authentic *cis*-isotachysterol$_3$ by UV, TLC, and NMR), and the lower zone gave triene isomer **5b** (2.9 mg, 31%) as an oil: UV (EtOH) λ_{max} 273 nm (ϵ 19 000); NMR ($CDCl_3$) δ 6.14 and 6.05 (AB, J = 11 Hz, 2 H, C-6 and C-7), 5.49 (dd, J = 3 and 2 Hz, 1 H, C-15), 3.52 (m, 1 H, C-3), 1.08 (d, J = 7 Hz, 3 H, C-19), 0.93 (d, J = 6 Hz, 3 H, C-21), 0.88 (d, J = 6 Hz, 6 H, C-26,27), 0.86 (s, 3 H, C-18); mass spectrum, *m/e* (relative intensity) 384 (M^+, 100), 369 (19), 351 (13), 271 (42), 253 (22), 244 (20), 159 (22), 145 (23), 133 (28); M^+, *m/e* calcd for $C_{27}H_{44}O$ 384.3393, found 384.3387; homogeneous on TLC (R_f 0.51, 15% ethyl acetate in Skellysolve B) and LC (t_R = 5.51 min); GC gave two peaks.[14]

Ozonolysis of Compounds 5a, 5b, and DHT$_2$.[4] A sample (20 μg) of each compound was dissolved in 50 μL of dichloromethane containing 100 μg of pyridine, cooled with a dry ice/2-propanol bath, and ozonized to excess. After sparging with nitrogen, the samples were directly examined by combined GC–MS using a 2 mm × 1 m glass column packed with 3% OV-225 on Varaport 30, 100/120 mesh, operated isothermally at 90 °C at a He flow rate of 27 mL/min. From DHT$_2$, β-hydroxy ketone **7a** was obtained [t_R = 7.4 min; *m/e* (relative intensity) 128 (M^+, 10), 110 (2), 82 (12), 74 (100), 71 (30)]. Triene isomer **5a** also gave **7a** [t_R = 7.4 min; *m/e* (rel intensity) 128 (M^+, 12), 110 (1), 82 (10), 74 (100), 71 (32); 70% yield relative to the amount of **7a** formed from DHT$_2$]. The more polar isomer **5b** gave **7b** [t_R = 8.5 min; *m/e* (rel intensity) 128 (M^+, 17), 110 (3), 82 (11), 74 (100), 71 (38); 85% yield relative to the amount of **7a** formed from DHT$_2$].[15] Under the GC conditions chosen, only the most volatile degradation products (i.e., **7a,b**) are eluted; the higher molecular weight products formed by ozonolysis of **5a,b** or DHT$_2$ require elevated temperatures for elution. Coinjection of ozonolysis products from **5a** and DHT$_2$ gave a single peak with t_R = 7.4 min, while coinjection of the products from **5b** and DHT$_2$ gave two peaks (t_R's = 7.5 and 8.7 min).

Deuterium Incorporation Study. To a Pyrex tube was added 1.0 mg of *cis*-isotachysterol$_3$ (**3**) in 0.30 mL of CH_3OD. After freezing the solvent in liquid nitrogen, the tube was sealed and heated to 110 °C for 3 h. The solvent was removed and 0.3 mL of CH_3OH was added and then evaporated. The products were purified by preparative TLC as described above. This gave, as evidenced by UV absorption, 0.21 mg of isomer **5a**, 0.16 mg of starting material (**3**), and 0.23 mg of isomer **5b**. Mass spectral analysis of these two products and a sample of starting material that had never been exposed to CH_3OD is summarized in Table I.

Reaction Reversibility. Isomer **5a** (1.8 mg) was dissolved in 1.0 mL of xylene and heated to 125 °C for 2.5 h. After evaporation of solvent, the residue was purified by preparative TLC as described above. This gave 0.31 mg of starting material **5a**, 0.47 mg of **3**, and 0.43 mg of **5b**. Product identity was confirmed by UV, TLC, and NMR; product amounts were quantitated by UV.

Kinetic Experiments. A solution of *cis*-isotachysterol$_3$ (**3**) in *n*-decane was diluted twentyfold with *n*-decane preheated to the desired temperature. The reaction was maintained under nitrogen; temperature was controlled with an oil bath and thermostat. The starting material concentration was initially 0.05 mg/mL. At the indicated times (Figure 1) an aliquot was removed, cooled, then analyzed by LC as described above. The decrease in the peak height of *cis*-isotachysterol$_3$ on the LC trace was followed versus time. Semilogarithmic plots of these data were made (Figure 1), and the slope of the resulting line for each temperature gave the sum of the forward rate constants. The LC trace was calibrated with standards of **5a** and **5b** of known concentration. This allowed measurement of the ratio of the amounts of **5a** to **5b** (based on peak heights of **5a** and **5b** on LC traces of aliquots taken at early time points) and directly gave the ratio of the two forward rate constants.[16] Knowing the ratios and the sums, the two rate constants were calculated for each temperature and fitted to a linear equation (Figure 2). Slopes, intercepts, and the errors in these measurements were determined by the method of Cleland.[17] Thermodynamic parameters (Table II) were derived from the slopes and intercepts as done by Havinga and co-workers.[11]

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Registry No.—7a, 66901-50-6; **7b,** 66901-51-7; DHT$_2$, 67-96-9; isotachysterol$_3$, 22350-43-2.

References and Notes

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(4) Replacement of the cholesterol side chain in structure **6a** with the side chain

of ergosterol gives dihydrotachysterol$_2$ (DHT_2). Structure **6a** is that of dihydrotachysterol$_3$ (DHT_3).
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(14) Isomerization of vitamin D trienes under GC conditions is a common observation. GC of **3** (2 mm × 2 m glass column packed with 3% OV-101 on Chromosorb 30 100/120 mesh; nitrogen flow rate 30 mL/min; oven held isothermally at 260 °C) gave two peaks with retention times of 3.2 and 8.0 min. Interestingly, GC of either **5a** or **5b** gave the same trace as found for **3**. In all three traces, the ratio of peak heights of the 3.2 to the 8.0 min peak was about 2.5/1. GC–MS of **3** showed that both peaks were isomers of nominal parent mass 384. The early peak showed *m/e* (rel intensity) 384 (M^+, 18), 351 (36), 309 (41), 283 (35), 145 (35), 124 (32), 43 (100). The late peak gave 384 (M^+, 47), 369 (20), 271 (48), 253 (42), 199 (35), 81 (85), 43 (100).
(15) A minor component at t_R = 6.7 min was also found in this sample; its parent ion at *m/e* 110 and fragmentation pattern suggest that it is methylcyclohexenone, the dehydration product of **7b**.
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Effective Biomimetic Route to D(+)-Pantothenate Using Asymmetric Hydrogenation Catalyzed by a Chiral Rhodium Complex in the Key Step

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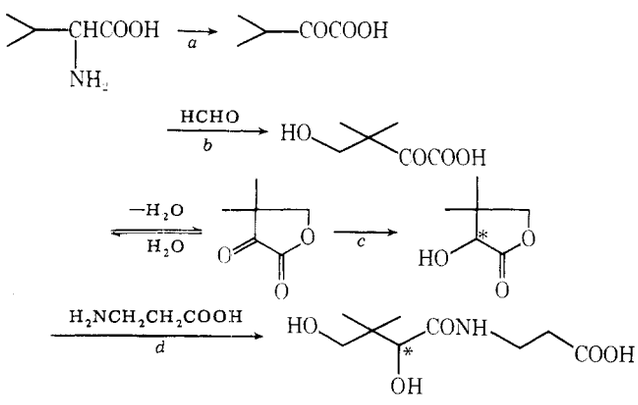
Asymmetric synthesis of D(+)-pantothenate from ketopantoyl lactone following a biomimetic route using asymmetric hydrogenation in the key step is described. The asymmetric hydrogenation of ketopantoyl lactone was effectively catalyzed by a rhodium complex with BPPM as chiral ligand to afford D(−)-pantoyl lactone with 86.7% optical purity under optimum conditions. This was further recrystallized to give the pure lactone in good yield. The pure D(−)-pantoyl lactone thus obtained was converted to ethyl D(+)-pantothenate by reacting with β-alanine ethyl ester.

Pantothenic acid is a member of the B complex vitamins and is an important constituent of Coenzyme A. Pantothenic acid is converted to pantetheine, which further reacts with adenosine triphosphate (ATP) to form Coenzyme A. The biosynthesis of pantothenic acid from valine has been postulated to involve[1,2] (a) the oxidative deamination of valine to α-ketoisovaleric acid, (b) the hydroxymethylation of this acid to form ketopantoyl lactone, (c) the asymmetric reduction of ketopantoyl lactone to pantoyl lactone, and (d) the coupling of pantoyl lactone with β-alanine to give pantothenic acid

Scheme I



[a] Transaminase. [b] Ketopantoaldolase. [c] Reductase. [d] Pantothenate synthetase.

(Scheme I). Among these processes, step c is the most significant since only D(+)-pantothenic acid derived from D(−)-pantoyl lactone has biological activity.[3] Although the biological synthesis of D(+)-pantothenic acid has been reported using microbial reduction of ketopantoyl lactone to pantoyl lactone,[4] no attempts have been made on the chemical asymmetric synthesis of this substance following the biosynthetic route. We have found that a rhodium complex with a chiral pyrrolidinodiphosphine, (2*S*,4*S*)-*N*-*tert*-butoxycarbonyl-4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidine (BPPM),[5] displays a high chiral recognition ability comparable to that of microorganisms, and thus the chiral rhodium complex can be considered as a functional biomimetic model of the ketopantoyl lactone reductase. We wish to present here an effective biomimetic route to D(+)-pantothenic acid using a catalytic asymmetric hydrogenation in the key step as an application of the successful hydrogenation of α-keto esters catalyzed by neutral rhodium complexes with phosphine ligands.[6]

One of the key compounds in the biosynthetic route is ketopantoyl lactone since the asymmetric reduction of this compound is the characteristic process in biological systems. This eliminates the need for the optical resolution of racemic pantoyl lactone as employed in the commercial synthesis of D(+)-pantothenic acid derivatives.[7] As the formation of ketopantoyl lactone is not restricted to enzymatic process but a simple aldol condensation, we started the asymmetric synthesis from ketopantoyl lactone.

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