Calcd for $C_6H_8N_2O_2$·HCl: C, 40.81; H, 5.14; N, 15.86. Found: C, 40.46; H, 5.12; N, 16.10.

Methyl 2-Methyl-5-oxo-3,4-dehydropyrrolidine-2-carboxylate (10). An aqueous solution of 2.72 g of the hydrochloride **9a** was treated with aqueous NH_4OH until the pH of the solution reached 7. Evaporation of the solvent at reduced pressure at 30 °C afforded a solid residue which was extracted many times with $CHCl_3$. The organic extracts were combined and concentrated in vacuo. Bulb-to-bulb distillation of the residue gave 2.48 g (80%) of **10** which crystallized spontaneously: bp 105 °C (0.02 mm); mp 64 °C; ^1H NMR (D_2O) δ 166 (s, 3, CH_3), 3.56 (s, 3, OCH_3), 6.65 (AB, 2, J_{AB} = 6 Hz, ν_{AB} = 71 Hz, HC=CH); IR (Nujol) 3300, 1741, 1670 cm^{-1}. Anal. Calcd for $C_7H_9NO_3$: C, 54.18; H, 5.86; N, 9.03. Found: C, 54.22; H, 5.99; N, 9.05.

2-Methyl-5-oxo-3,4-dehydropyrrolidine-2-carboxamide (11). To a solution of 200 mg of **10** in 2 mL of water was added at 0 °C 50 mL of aqueous NH_4OH (6 M). After the mixture was stirred for 5 min, the solvent was evaporated at reduced pressure at 20 °C to give 170 mg (95%) of **11**. The analytical sample was prepared by recrystallization from water–ethanol: mp 195 °C; ^1H NMR (D_2O) δ 1.53 (s, 3, CH_3), 6.0 (d, 1, J = 5 Hz, HC=C), 7.16 (d, 1, J = 5 Hz, C=CH); IR (Nujol) 1690 cm^{-1}. Anal. Calcd for $C_6H_8N_2O_2$: C, 51.41; H, 5.76; N, 19.99. Found: C, 51.23; H, 5.75; N, 20.00.

Hydrolysis of 9b under Basic Conditions. To a solution of 17 mg (0.098 mmol) of **9b** in 0.3 mL of D_2O was added at 0 °C 32 mg of a solution of 40% NaOD in D_2O (about 3 equiv). The hydrolysis reaction was followed by NMR spectroscopy by monitoring the disappearance of the singlet at δ 3.66 corresponding to the methyl ester group and the apparition of a new singlet at δ 3.30 assignable to CH_3OD. The hydrolysis was complete within 5 min. At that time, the NMR spectrum displayed the following signals: δ 1.36 (s, 3, CH_3), 3.30 (s, 3, CH_3OD), 5.8 (s, 2, HC=CH).

2-(Benzylideneamino)glutarimide (15). A solution of 2.67 g (0.010 mol) of 2-(amino(carbobenzoxy))glutarimide in 80 mL of THF was stirred for 12 h under an atmosphere of H_2 in presence of 0.450 g of Pd/C (5%). The catalyst was separated by filtration. To the filtrate was added 1 g (0.0094 mol) of benzaldehyde and the resulting mixture was stirred at room temperature for 3 h. The residue obtained after evaporation of the solvent was dissolved in chloroform. The organic phase was washed with water and dried over $MgSO_4$. Concentration and recrystallization from dichloromethane–pentane afforded 1.2 g (59%) of **15**: mp 137 °C; ^1H NMR ($CDCl_3$) δ 2.30 (m, 2, CH_2), 2.60–3.40 (m, 2, CH_2C=O), 4.13 (t, 1, J = 5 Hz, OCCHN=), 7.85 (s, 1, NH), 7.18–7.84 (m, 5, C_6H_5), 8.40 (s, 1, N=CH); IR ($CHCl_3$) 3220, 1705, 1645 cm^{-1}. Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.64; H, 5.60; N, 12.95. Found: C, 66.30; H, 5.60; N, 13.11.

2-Amino-2-methylglutarimide Hydrochloride Monohydrate (16). To a solution of lithium diisopropylamide (4 mmol) in THF at −70 °C was added slowly 432 mg (2 mmol) of **15** in 5 mL of THF. The reaction mixture was stirred for 1 h and then 568 mg (4 mmol) of CH_3I was added. The cooling bath was removed and after the mixture was stirred for 12 h at room temperature, the reaction was quenched with water. Isolation of the product by ether extraction and recrystallization from chloroform–pentane afforded 150 mg (33%) of 2-benzylideneamino-2-methylglutarimide [^1H NMR ($CDCl_3$) δ 1.55 (s, 3, CH_3), 2.47 (m, 4, CH_2), 7.07–7.70 (m, 5, C_6H_5), 8.16 (s, 1, NH), 8.18 (s, 1, N=CH)]. A solution of the above Schiff base in ether was treated with aqueous HCl (1 M). After stirring for 1 h at room temperature, the aqueous phase was decanted and concentrated at reduced pressure. Recrystallization of the residue from water afforded 60 mg of **16**: mp 250 °C; ^1H NMR (D_2O) δ 1.67 (s, 3, CH_3), 2.18–3.10 (m, 4, CH_2); IR (Nujol) 1720 cm^{-1}. Anal. Calcd for $C_6H_{10}N_2O_2$·HCl·H_2O: C, 36.63; H, 6.67; N, 14.24. Found: C, 36.47; H, 6.77; N, 14.26.

Catalytic Hydrogenation of 14. A solution of 35 mg (0.2 mmol) of **14** in 3 mL of water was stirred under H_2 at atmospheric pressure in presence of 5 mg of Pd/C (5%) for 1 h. The catalyst was filtered. Recrystallization from water of the residue obtained after concentration of the filtrate afforded 30 mg of material whose chromatographic, spectroscopic, and physical properties were identical with those of **16**.

Registry No. 1, 40216-71-5; **2a**, 73838-85-4; **2b**, 73838-86-5; **2c**, 73838-87-6; **3a**, 73855-18-2; **4a**, 6213-89-4; **4b**, 6213-87-2; **4c**, 72330-65-5; **4d**, 73838-88-7; **4e**, 41866-26-6; **5a**, 1609-92-3; **5b**, 6214-22-8; **5c**, 41866-46-0; **5d**, 73838-89-8; **6a**, 73838-90-1; **6b**, 73838-91-2; **6c**, 73838-92-3; **7a**, 73838-93-4; **7b**, 73838-94-5; **7c**, 73838-95-6; **7d**, 73838-96-7; **8a**, 73838-97-8; **9a**, 73838-98-9; **9b**, 73838-99-0; **10**, 73839-00-6; **11**, 73839-01-7; **12**, 73839-02-8; **13**, 73839-03-9; **14**, 73839-04-0; **15**, 73839-05-1; **16**, 73839-06-2; propiolic acid, 471-25-0; bis(trimethylsilyl)acetamide, 10416-58-7; 2-(amino(carbobenzoxy))-glutarimide, 24666-55-5.

Direct C(1) Hydroxylation of Vitamin D_3 and Related Compounds

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A direct synthesis of C(1) hydroxylated vitamin D analogues from the corresponding vitamin D precursors has been developed. Allylic oxidation of 3,5-cyclovitamin D derivatives, readily obtained from the buffered solvolysis of vitamin D tosylates, with selenium dioxide yields 1α-hydroxylated 3,5-cyclovitamin D compounds which are smoothly converted to the desired 1α-hydroxyvitamin D derivatives by acid-catalyzed cycloreversion. Application of this scheme to vitamin D_3 (**1a**), 25-hydroxyvitamin D_3 (**1b**), and vitamin D_2 (**1c**) affords the 1α-hydroxy products in ~20% overall yield.

The recent markedly increased activity in vitamin D synthetic chemistry can be directly traced to the isolation and structural characterization of the metabolic components of the vitamin D endocrine system.[1] Because of their possible therapeutic value in treating disorders of calcium and phosphorus metabolism, vitamin D metabolites and in particular 1α-hydroxylated analogues represent attractive synthetic targets which should be readily available for biomedical research. Classical synthetic routes to 1α-hydroxylated vitamin D derivatives have involved preparation of a suitably substituted Δ^5 steroidal precursor and conversion to the corresponding 5,7-diene provitamin followed by the well-known photochemical and thermal isomerizations to the vitamin analogue.[2] The disadvantages associated with an approach of this type, namely, complex reaction mixtures and difficult separations, have prompted us to explore a conceptually at-

(1) H. F. DeLuca and H. K. Schnoes, *Annu. Rev. Biochem.*, **45**, 631 (1976).

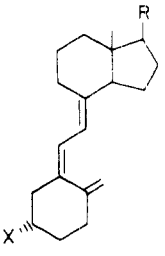
(2) P. E. Georghiou, *Chem. Rev.*, **77**, 83 (1977).

0022-3263/80/1945-3253$01.00/0

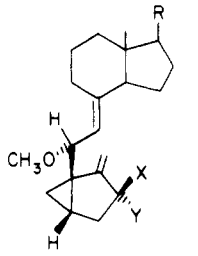
tractive alternative synthetic pathway to 1α-hydroxylated vitamins. Our investigations have been concerned with the direct C-1 allylic hydroxylation of vitamin D substrates, and we wish to report here an experimentally simple procedure of broad scope which affords the corresponding 1α-hydroxylated analogues in 15–20% overall yields.

The direct allylic oxidation of vitamin D faces certain problems with respect to the chemospecificity, regiospecificity, and stereospecificity of the reaction. The presence of an easily isomerized conjugated triene in the substrate requires that the chemospecific allylic oxidant be active in either neutral or basic solutions and show little tendency to attack olefinic bonds. With four allylic centers on the vitamin D molecule, regiospecific attack at the C(1) position seems improbable, and to further complicate matters a stereoisomeric mixture of alcohols would be expected.

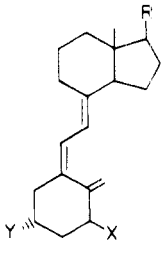
It was quickly established that chromium(VI) oxide species, even though effective allylic oxidants as a molecular complex with pyridine,[3] readily attacked the olefinic system of the vitamin and therefore were not suitable. The triene was found to be inert to an allylic oxidizing system of selenium dioxide and *tert*-butyl hydroperoxide;[4] however, overoxidation, cis/trans double bond isomerization, and lack of stereoselectivity resulted in rather low yields of isolated 1α-hydroxylated vitamin D (**10a**) product.[5]



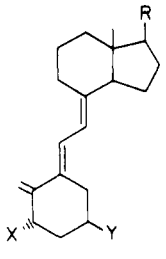
1 X = OH
2 X = OTs



3 X = Y = H
4 X,Y = O
5 X = OH, Y = H
6 X = OAc, Y = H



7 X = OAc, Y = OH
8 X = Y = OAc
9 X = OH, Y = OAc
10 X = Y = OH

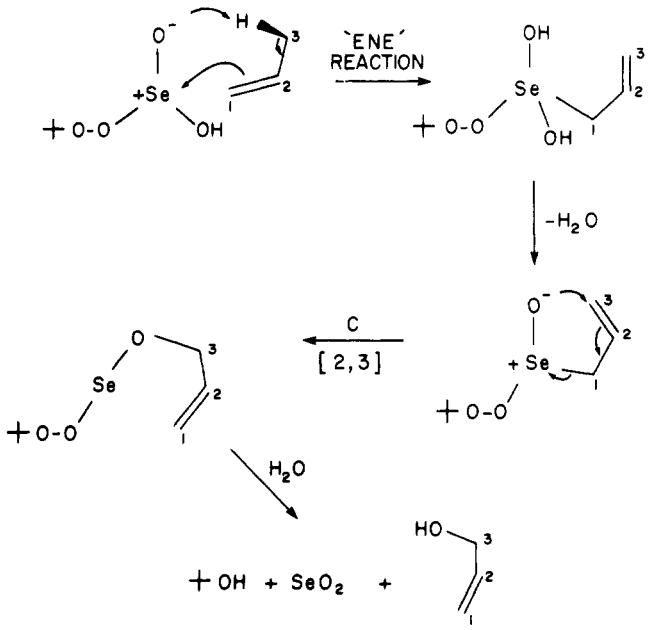


11 X = OAc, Y = OH
12 X = Y = OAc
13 X = OH, Y = OAc
14 X = Y = OH

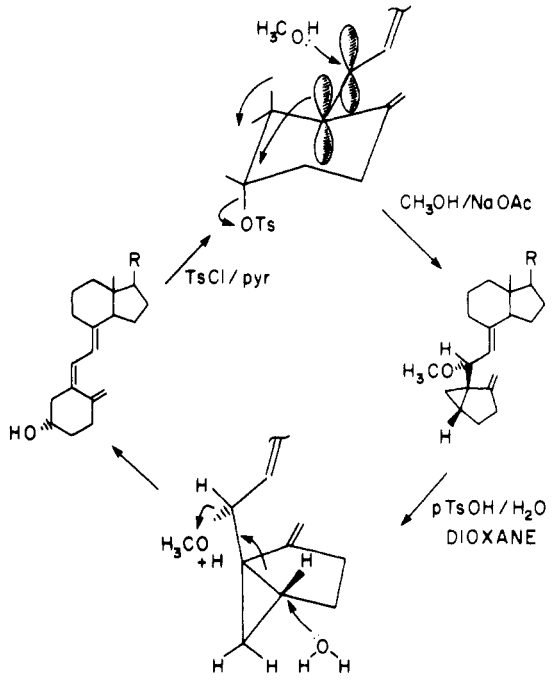
R = a) b) OH c)

(3) W. G. Dauben, M. Lorber, and D. S. Fullerton, *J. Org. Chem.*, **34**, 3587 (1969).
(4) M. A. Umbreit and K. B. Sharpless, *J. Am. Chem. Soc.*, **99**, 5526 (1977).
(5) H. E. Paaren, D. E. Hamer, H. K. Schnoes, and H. F. DeLuca, *Proc. Natl. Acad. Sci. U.S.A.*, **75**, 2080 (1978); B. Pelc, *Steroids*, **30**, 193 (1977).

Scheme I



Scheme II



The mechanism of selenium dioxide allylic oxidation has been shown to proceed initially through an "ene"-type reaction (Scheme I) in which the allylic proton is abstracted, the double bond isomerized, and a selenium–carbon bond formed.[6] The resulting organoselenium intermediate then undergoes a concerted [2,3] fragmentation, yielding the allylic alcohol of the original olefinic system.[7] Because of this "ene" pathway, the rate of oxidation can be affected by stereoelectronic factors and the stereochemistry of the product influenced by steric factors.[8]

As a simple modification of the basic vitamin skeleton, formation of the cyclovitamin derivative as originally reported for the case of vitamin D_3 by Sheves and Mazur[9]

(6) D. Arigoni, A. Vasella, H. P. Jensen, and K. B. Sharpless, *J. Am. Chem. Soc.*, **95**, 7917 (1973).
(7) K. B. Sharpless and R. F. Lauer, *J. Am. Chem. Soc.*, **94**, 7154 (1972).
(8) H. M. R. Hoffman, *Angew. Chem., Int. Ed. Engl.*, **8**, 566 (1969).
(9) M. Sheves and Y. Mazur, *J. Am. Chem. Soc.*, **97**, 6249 (1975).

provided an alternative substrate for the oxidation. Formed from the buffered solvolysis of vitamin D_3 tosylate (**2a**), the cyclovitamin **3a** is easily reconverted with aqueous acid to the vitamin with retention of C(3)-hydroxyl group stereochemistry (Scheme II).[9]

This type of homoallylic displacement reaction is directly analogous to the well-known i-steroid rearrangement of cholesteryl tosylate,[10] which has been used as an effective means to protect the 5,6-olefin during certain chemical transformations of the steroid.[2] In the case of vitamin D, formation of the 3,5-cyclo derivative not only deconjugates the reactive triene system but also fixes the C(1) target site in a rigid bicyclic system in which the β face of the A ring is shielded by the presence of the cyclopropyl moiety.

The oxidation of cyclovitamin D_3 (**3a**) with SeO_2/t-BuOOH was extremely rapid in comparison to the similar reaction on the vitamin (~20 times faster at 25 °C). Two products were isolated in 50 and 20% yields by preparative TLC. The major, more polar component was identified as the 1α-hydroxycyclovitamin **5a**[11] and the minor less polar component was found to be the 1-ketocyclovitamin **4a**. 1β-Hydroxycyclovitamin was detected in some reactions and particularly at lower reaction temperatures (5–10 °C) in less than 5% yield.

The remarkable rate increase for the oxidation of the cyclovitamin is no doubt due to the conformationally rigid pseudoaxial orientation of the 1α-hydrogen. This situation results in maximized orbital overlap for the developing π system during the initial "ene" step of the reaction. By increasing the reactivity of the C(1) allylic position in the cyclovitamin analogue, a high degree of regioselectivity was obtained.

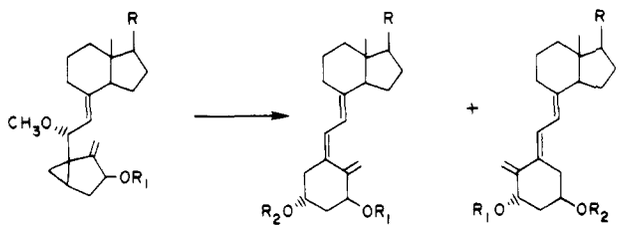
The stereospecificity of the oxidation can be accounted for by the angular orientation of the cyclopropyl ring which effectively prevents oxidant approach from the β face of the A ring.

Cycloreversion of the 1α-hydroxycyclovitamin (1α-OH-cyclo) **5a** catalyzed by *p*-TsOH in 90% aqueous dioxane yielded nonpolar products probably resulting from elimination of the acid-labile allylic hydroxyl functionality at C(1). As a protective measure, 1α-OH-cyclo-D_3 was quantitatively acetylated with Ac_2O/pyridine at 55 °C for 2.0 h. When subjected to the same cycloreversion condition, 0.3 equiv of *p*-TsOH in 90% aqueous dioxane at 55 °C, the reaction was complete in 15 min and gave a 40% yield of 5,6-*cis*-1α-acetoxyvitamin D_3 (**7a**) and a 10% yield of 5,6-*trans*-1α-acetoxyvitamin D_3 (**11a**) after preparative TLC. The other products formed in the reaction were of similar polarity to the decomposition products encountered in the attempted cycloreversion of the unprotected 1α-OH-cyclo-D_3.

In an attempt to minimize secondary decomposition reactions, we performed the cycloreversion using glacial acetic acid as a proton source and nucleophile. After 15 min at 55 °C all of the 1α-acetoxycyclovitamin had been consumed, and NMR analysis revealed a 3:1 cis/trans ratio of the diacetoxyvitamins **8a** and **12a** had been produced in an overall 70% yield.

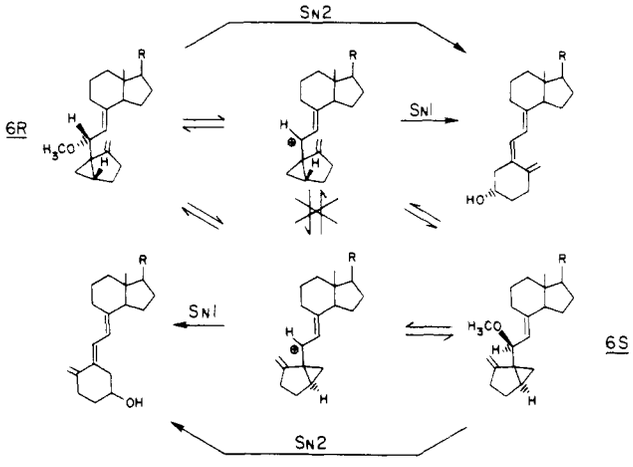
Even though the use of the mild organic acid increased the yield, separation of the 5,6-cis and 5,6-trans isomers as either the 1,3-diacetates or the 1,3-diols proved extremely difficult because of the symmetrical distribution

Table I. Conditions and Results for the Cycloreversion of 1α-Functionalized Cyclovitamins



R_1	catalyst/nucleophile	R_2	% cis	% trans
$COCH_3$	*p*-TsOH/H_2O	H	40	10
$COCH_3$	HOAc	$COCH_3$	52	18
$COCH_3$	1. HCO_2H, 2. $NaHCO_3$	H	46	22
$COCH_3$	*p*-TsOH/Me_2SO	H	42	8
H	HOAc	$COCH_3$	55	20

Scheme III



of A-ring polarity. The asymmetric polarity present in the 1α-acetoxy-3β-hydroxy cis/trans isomers was necessary for effective chromatographic separation.

By use of 98% formic acid in the cycloreversion followed by selective $NaHCO_3$ hydrolysis of the 3β-formate ester, the benefits of mild organic acid catalysis could be obtained in addition to an easily separated cis/trans isomeric mixture. Heating the 1α-acetoxycyclovitamin **6a** in 98% HCO_2H/THF (1:1) at 55 °C for 15 min produced a mixture of the crude *cis*- and *trans*-3β-(formyloxy)vitamins which were hydrolyzed with 10% aqueous $NaHCO_3$ in methanol to the corresponding 3β-hydroxy analogues. Preparative TLC gave a 2:1 ratio of the **7a** and **11a** isomers in an overall 68% yield.

The variation of the cis/trans isomer ratio in the cycloreversion reaction seems to correlate with the nucleophilic strength of the medium (Table I). The higher cis/trans ratio, 4:1, is obtained with water as the attacking nucleophile while lower ratios, 3:1 and 2:1, are produced with the weaker nucleophiles acetic acid and formic acid.

Because the cycloreversion step can occur from either a concerted S_N2-type or ionic S_N1-type transition state, solvent nucleophilicity would be expected to affect the cis/trans product ratio (Scheme III). In a concerted transition state where the protonated (6*R*)-methoxy group of the cyclovitamin departs simultaneously with the nucleophilic attack at the 3β position, cis triene stereochemistry must be the result. If the protonated (6*R*)-methoxy group dissociates from the cyclovitamin in a unimolecular process, a cyclopropylcarbinyl cation is the result.[9,12]

(10) N. L. Wendler in "Molecular Rearrangements", Vol. 2, P. De-Mayo, Ed., Wiley-Interscience, New York, 1964, p 1075.

(11) The overall yield of 1α-hydroxy-3,5-cyclovitamin D_3 can be optimized to 65% by stopping the oxidation at the appearance of the 1-keto oxidation product and recycling unreacted starting material.

(12) M. Sheves and Y. Mazur, *Tetrahedron Lett.*, 1913 (1976).

Although evidence suggests that this species is not free to rotate about the 5,6-bond,[13] it can nevertheless recombine in a nonstereospecific manner with a molecule of solvent at C(6) to give either an *R* or *S* configuration or cyclorevert via 3β attack to the cis triene isomer. Similarly, the 6*S*-substituted cyclovitamin can only produce the trans triene system by either a concerted S_N2 or a solvolytic S_N1 process.

Therefore, the amount of trans vitamin formed during the cycloreversion is directly related to a transition state with a high degree of carbonium ion character and which would be favored in solvents of low nucleophilicity.

When Me_2SO was used as a cosolvent in the formic acid catalyzed cycloreversion of 1α-acetoxy-3,5-cyclovitamin D_3, the 3β-hydroxy-1α-acetoxy cis and trans vitamin isomers **7a** and **11a** were obtained directly in a 5:1 ratio after 5 h at 55 °C. These 3β-hydroxy analogues could arise from either hydrolysis of an intermediate formate ester during the reaction or workup hydrolysis of a 3β-alkoxysulfonium species which might be present if Me_2SO acts as the nucleophile in the reaction.

To differentiate between these two possible mechanisms, we conducted the cycloreversion reaction in Me_2SO with a small amount of anhydrous *p*-TsOH as the acid catalyst. Under these conditions the 3β-hydroxy-1α-acetoxy isomers were again obtained. It therefore seems that the oxygen of the 3β-hydroxy group was donated by Me_2SO.

Subsequent studies on the cycloreversion process have shown that protection of the 1α-hydroxy function is unnecessary when the reaction is conducted in the presence of a mild organic acid such as glacial acetic or formic acid. This approach simplifies the overall scheme by avoiding the protection and hydrolysis steps and yields the easily separated *cis*- and *trans*-3β-*O*-acyl-1α-hydroxyvitamin analogues. For example, 1α-hydroxycyclovitamin D_3 (**5a**) was smoothly converted to *cis*-1α-hydroxyvitamin D_3 acetate (**9a**) and *trans*-1α-hydroxyvitamin D_3 acetate (**13a**) in 55 and 20% yields, respectively, by treatment with glacial acetic acid for 15 min at 55 °C.

Utilization of this direct cycloreversion reaction makes it possible to conduct the entire 1α-hydroxylation scheme, from starting vitamin to final 1α-hydroxyvitamin, with only two chromatographic purification steps: after the oxidation and again after the cycloreversion.

The advantage of having two cycloreversion schemes is that either a 1α-acylated or a 3β-acylated 1,3-dihydroxyvitamin derivative can be produced, thus providing useful intermediates for further selective chemical transformations of the vitamin molecule.

Experimental Section

Mass spectra were run on an AEI/MS9 at 70 eV. UV spectra were taken in absolute ethanol on a Beckman Model 24 spectrophotometer. Proton NMR spectra were recorded with a Bruker WH-270 pulse Fourier transform instrument in $CDCl_3$ solutions with $CHCl_3$ as an internal standard.

Vitamin D_3 Tosylate (2a). To a stirred solution of 100 mg of vitamin D_3 (**1a**) in 2.0 mL of dry pyridine was added 120 mg of freshly recrystallized *p*-toluenesulfonyl chloride. The reaction was allowed to proceed at 5 °C until all the starting material had been consumed (~24 h) and was then quenched by pouring the mixture over ice/saturated $NaHCO_3$ with stirring. After 15 min the excess tosyl chloride had decomposed, and the aqueous suspension was extracted with ether (3 × 30 mL). The combined organic extracts were washed with 3% HCl (2 × 30 mL), saturated $NaHCO_3$ (1 × 50 mL), and saturated NaCl (1 × 50 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude tosylate was suitable for use in the following solvolysis reaction or it could be crystallized from ether/pentane, giving a solid with a melting point of 113–115 °C dec.

3,5-Cyclovitamin D_3 (3a). To a stirring solution of 50 mL of anhydrous methanol was added 500 mg of finely divided $NaHCO_3$ and 100 mg of vitamin D_3 tosylate (**2a**). The mixture was heated to 55 °C for 8 h or until all of the tosylate had been solvolyzed, cooled to room temperature, and concentrated in vacuo to ~15 mL. The reaction concentrate was diluted with 100 mL of Et_2O, washed with water (3 × 30 mL), dried over $MgSO_4$, and concentrated in vacuo. Silica gel TLC (20 × 20 cm plates, 750-μm silica gel) in 1:9 ethyl acetate/hexanes yielded 60 mg of 3,5-cyclovitamin D_3 (**3a**): mass spectrum, *m/e* (relative intensity) 398 (M^+, 20), 366 (100), 253 (45), 247 (30), 135 (50); NMR δ 0.53 (3 H, s, 18-H_3), 0.74 (1 H, m, 3-H), 0.86 (6 H, d, J = 6.2 Hz, 26-H_3 and 27-H_3), 0.92 (3 H, d, J = 6.2 Hz, 21-H_3), 3.26 (3 H, s, (6*R*)-OCH_3), 4.17 (1 H, d, J = 9.5 Hz, 6-H), 4.88 (1 H, m (sharp), (19*Z*)-H), 4.98 (1 H, d, J = 9.5 Hz, 7-H), 5.05 (1 H, m (sharp), (19*E*)-H).

1α-Hydroxy-3,5-cyclovitamin D_3 (5a). To a stirred suspension of 14 mg (0.12 mmol) of SeO_2 in 10 mL of dry CH_2Cl_2 was added 70 μL (0.5 mmol) of *tert*-butyl hydroperoxide (bp 34 °C at 25 mm). After being stirred for 0.5 h at room temperature, the reaction mixture was diluted with 40 mL of CH_2Cl_2 and cooled to 15 °C, and 90 mg (0.23 mmol) of 3,5-cyclovitamin D_3 (**3a**) was added in 10 mL of CH_2Cl_2. The reaction was warmed to room temperature and continued until all the starting material had been consumed (~30–45 min). The mixture was transfered to a separatory funnel and quenched by shaking vigorously with 30 mL of 10% NaOH. The crude mixture was diluted with 150 mL of Et_2O, and the phases were separated. The organic phase was washed with 10% NaOH (2 × 30 mL) and water (2 × 60 mL), dried over $MgSO_4$, and concentrated to a heavy oil in vacuo. Preparative TLC (20 × 20 cm plates, 750-μm silica gel) in 3:7 ethyl acetate/hexanes afforded 47 mg (50% yield) of 1α-hydroxy-3,5-cyclovitamin D_3 (**5a**): mass spectrum, *m/e* (relative intensity) 414 (M^+, 30), 382 (70), 341 (35), 269 (20), 247 (45), 135 (65); NMR δ 0.53 (3 H, s, 18-H_3), 0.61 (1 H, m, 3-H), 0.86 (6 H, d, J = 6.2 Hz, 26-H_3 and 27-H_3), 0.92 (3 H, d, J = 6.2 Hz, 21-H_3), 3.26 (3 H, s, (6*R*)-OCH_3), 4.18 (1 H, d, J = 9.0 Hz, 6-H), 4.22 (1 H, m, 1-H), 4.95 (1 H, d, J = 9.0 Hz, 7-H), 5.17 (1 H, d, J = 2.2 Hz, (19*Z*)-H), 5.25 (1 H, d, J = 22 hZ, (19*E*)-H). An 18-mg sample (20% yield) of 1-oxo-3,5-cyclovitamin D_3 (**4a**) was also obtained: UV λ_{max} 248 nm (ε 3500); mass spectrum, *m/e* (relative intensity) 412 (M^+, 40), 380 (50), 267 (20), 247 (25), 133 (100); NMR δ 0.49 (3 H, s, 18-H_3), 0.58 (1 H, m, 3-H), 0.87 (6 H, d, J = 6.6 Hz, 26-H_3 and 27-H_3), 0.93 (3 H, d, J = 6.2 Hz, 21-H_3), 3.30(3 H, s, (6*R*)-OCH_3), 4.06 (1 H, d, J = 9.0 Hz, 7-H), 5.02 (1 H, d, J = 9.0 Hz, 7-H), 5.62 (1 H, m (sharp), (19*Z*)-H), 6.04 (1 H, m (sharp), (19*E*)-H).

1α-Acetoxy-3,5-cyclovitamin D_3 (6a). A solution of 30 mg of 1α-hydroxy-3,5-cyclovitamin D_3 (**5a**) in 0.5 mL of pyridine was added to a mixture of 0.5 mL of acetic anhydride and 1.0 mL of pyridine. The reaction was heated to 55 °C for 2.0 h and then quenched with ice/saturated $NaHCO_3$. After neutralization, the aqueous mixture was extracted with ether (3 × 25 mL). The combined organic extracts were then washed with water (3 × 20 mL), dried over $MgSO_4$, and concentrated in vacuo with a benzene azeotrope to remove any residual pyridine to yield 32 mg of 1α-acetoxy-3,5-cyclovitamin D_3 (**6a**): mass spectrum, *m/e* (relative intensity) 456 (M^+, 20), 424 (20), 364 (60); NMR δ 0.54 (3 H, s, 18-H_3), 0.87 (6 H, d, J = 6.6 Hz, 26-H_3 and 27-H_3), 0.94 (3 H, d, J = 6.2 Hz, 21-H_3), 2.10 (3 H, s, 1-$OCOCH_3$), 3.26 (3 H, s, (6*R*)-OCH_3), 4.19 (1 H, d, J = 9.2 Hz, 6-H), 4.96 (2 H, m, (19*Z*)-H and 7-H), 5.23 (1 H, m, 1-H), 5.25 (1 H, m (sharp), (19*E*)-H).

Cycloreversion of 1α-Acetoxy-3,5-cyclovitamin D_3 (6a). (a) *p*-Toluenesulfonic Acid Catalyzed. A solution of 13 mg of 1α-acetoxy-3,5-cyclovitamin D_3 (**6a**) in 3.0 mL of a 3:1 mixture of 1,4-dioxane/H_2O was treated with 2.0 mg of *p*-toluenesulfonic acid in 40 μL of H_2O and heated to 55 °C for 15 min. The reaction was poured into ice/saturated $NaHCO_3$ and extracted with ether (2 × 20 mL). The ether extracts were washed with H_2O (2 × 20 mL), dried over $MgSO_4$, and concentrated in vacuo. Preparative

(13) (a) H. G. Riche, Jr., in "Carbonium Ions", Vol. 3, G. A. Olah and P. v. R. Schleyer, Eds., Wiley-Interscience, New York, 1972, pp 1274–1280; (b) L. Radom, D. Poppinger, and R. C. Haddon, *ibid.*, Vol. 5, 1977, pp 2378–2381.

TLC (750-μm silica gel, 20 × 20 cm plates) in 3:7 ethyl acetate/hexanes gave 5.4 mg (40%) of 1α-acetoxyvitamin D_3 (**7a**): UV λ_{max} 264 nm, shoulder at 244 nm; mass spectrum, *m/e* (relative intensity) 442 (M^+, 75), 382 (70), 269 (15), 134 (100); NMR δ 0.52 (3 H, s, 18-H_3), 0.86 (6 H, d, *J* = 5.5 Hz, 26-H_3 and 27-H_3), 0.91 (3 h, d, *J* = 5.9 Hz, 21-H_3), 2.03 (3 H, s, 1-$OCOCH_3$), 4.19 (1 H, m, 3-H), 5.04 (1 H, d, *J* = 1.5 Hz, (19*Z*)-H), 5.31 (1 H, m (sharp), (19*E*)-H), 5.49 (1 H, m, 1-H), 5.93 (1 H, d, *J* = 11.2 Hz, 7-H), 6.37 (1 H, d, *J* = 11.2 Hz, 6-H). A 1.5-mg sample (10% yield) of 5,6-*trans*-1α-acetoxyvitamin D_3 (**11a**) was also obtained: UV λ_{max} 273 nm; mass spectrum, *m/e* (relative intensity) 442 (M^+, 85), 382 (60), 269 (25), 134 (100); NMR δ 0.56 (3 H, s, 18-H_3), 0.87 (6 H, d, *J* = 6.2 Hz, 26-H_3 and 27-H_3), 0.92 (3 H, d, *J* = 6.2 Hz, 21-H_3), 2.00 (3 H, s, 1-$OCOCH_3$), 4.18 (1 H, m, 3-H), 4.97 (1 H, m (sharp), (19*Z*)-H), 5.13 (1 H, m (sharp), (19*E*)-H), 5.6 (1 H, m, 1-H), 5.88 (1 H, d, *J* = 11.2 Hz, 7-H), 6.58 (1 H, d, *J* = 11.2 Hz, 6-H).

(b) Glacial Acetic Acid Catalyzed. A solution of 10 mg of 1α-acetoxy-3,5-cyclovitamin D_3 (**6a**) in 400 μL of glacial HOAc was heated to 55 °C for 15 min and then slowly added to a stirring solution of ice/saturated $NaHCO_3$. The neutralized mixture was extracted with ether (3 × 20 mL), and the combined organic extracts were washed with one 30-mL portion of saturated $NaHCO_3$ and one 30-mL portion of saturated NaCl, dried over $MgSO_4$, and concentrated in vacuo. Preparative TLC (silica gel, 750 μm; plates) 10 × 20 cm in 2:8 ethyl acetate/hexanes gave 7.5 mg (70% yield) of a 2.8:1 mixture (by NMR analysis) of 5,6-*cis*- and 5,6-*trans*-1α-acetoxyvitamin D_3 acetates (**8a** and **12a**).

(c) Formic Acid Catalyzed, $NaHCO_3$ Hydrolysis. To a solution of 10 mg of 1α-acetoxy-3,5-cyclovitamin D_3 (**6a**) in 1.0 mL of dry THF was added 0.5 mL of 97% HCO_2H. The reaction was then heated to 55 °C for 15 min and quenched by addition to ice/saturated $NaHCO_3$. The neutralized reaction mixture was extracted with ether (3 × 20 mL), and the combined organic fractions were washed with saturated $NaHCO_3$ (1 × 30 mL) and water (1 × 30 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude oily residue was dissolved in 1.0 mL of MeOH/THF (1:1) and treated with 200 μL of saturated $NaHCO_3$ solution for 45 min. The reaction was then diluted with 10 mL of H_2O and extracted with ether (2 × 30 mL). The organic solution was washed once with 20 mL of H_2O, dried over $MgSO_4$, and concentrated in vacuo. Chromatography of the crude mixture on a 10 × 20 cm plate of 750-μm silica gel developed in 2:8 ethyl acetate/hexanes gave a 44% yield of 1α-acetoxyvitamin D_3 (**7a**) and a 21% yield of the 5,6-trans isomer (**11a**).

(d) Formic Acid/Me_2SO Catalyzed Cycloreversion. A stirring solution of 10 mg of 1α-acetoxy-3,5-cyclovitamin D_3 (**6a**) in 300 μL of dry distilled Me_2SO was treated with 200 μL of a 1:1 mixture of Me_2SO and 97% HCO_2H and heated to 55 °C for 4 h. The reaction was then quenched with ice/saturated $NaHCO_3$ and extracted with ether (3 × 20 mL). The organic extracts were combined, washed with saturated $NaHCO_3$ and water, dried over $MgSO_4$, and concentrated to an oil in vacuo which was chromatographed (10 × 20 cm, 750-μm silica gel plate) to yield 40% of 1α-acetoxyvitamin D_3 (**7a**) and 8% of 5,6-*trans*-1α-acetoxyvitamin D_3 (**11a**).

(e) *p*-Toluenesulfonic Acid/Me_2SO Catalyzed. Anhydrous benzene was added to 4.0 mg of *p*-TsOH·H_2O, and the solution was concentrated to dryness in vacuo. This procedure was repeated twice to yield anhydrous *p*-toluenesulfonic acid. A solution of 10 mg of 1α-acetoxy-3,5-cyclovitamin D_3 (**6a**) in 800 μL of anhydrous Me_2SO was added to the anhydrous *p*-TsOH, and the reaction was heated to 55 °C for 15 min. After the mixture was quenched with ice/saturated $NaHCO_3$ and extracted with ether, the combined organic extracts were washed with water and dried over $MgSO_4$. Chromatography of the crude oil obtained after evaporation of the solvent in vacuo yielded 5,6-*cis*- and 5,6-*trans*-1α-acetoxyvitamins D_3 (**7a** and **11a**).

Glacial Acetic Acid Catalyzed Cycloreversion of 1α-Hydroxy-3,5-cyclovitamin D_3 (5a). A solution of 20 mg of 1α-hydroxy-3,5-cyclovitamin D_3 (**5a**) in 0.5 mL of glacial acetic acid was heated to 55 °C for 15 min and then carefully poured over ice/saturated $NaHCO_3$. The neutralized solution was extracted with ether (3 × 20 mL), and the combined extracts were washed with saturated $NaHCO_3$ and H_2O and dried over $MgSO_4$. After concentration in vacuo, the crude oil was chromatographed (10 × 20 cm, 750-μm silica gel plates; 3:7 ethyl acetate/hexanes) to give 11.7 mg (55% yield) of 1α-hydroxyvitamin D_3 3-acetate (**9a**): UV λ_{max} 264 nm; mass spectrum, *m/e* (relative intensity) 442 (M^+, 40), 382 (65), 364 (15), 269 (20), 134 (100); NMR δ 0.54 (3 H, s, 18-H_3), 0.86 (6 h, d, *J* = 6.6 Hz, 26-H_3 and 27-H), 0.92 (3 H, d, *J* = 6.0 Hz, 21-H_3), 2.04 (3 H, s, 3-$OCOCH_3$), 4.41 (1 H, m, 1-H), 5.02 (1 H, m (sharp), (19*Z*)-H), 5.21 (1 H, m, 3-H), 5.34 (1 H, m (sharp), 19*E*)-H), 6.02 (1 H, d, *J* = 11.1 Hz, 7-H), 6.34 (1 H, d, *J* = 11.1 Hz, 6-H). A 4.3-mg sample (20% yield) of 5,6-*trans*-1α-hydroxyvitamin D_3 3-acetate (**13a**) was also obtained: UV λ_{max} 273 nm; mass spectrum, *m/e* (relative intensity) 442 (M^+, 10), 382 (80), 269 (23), 134 (100); NMR δ 0.56 (3 H, s, 18-H_3), 0.87 (6 H, d, *J* = 6.3 Hz, 26-H_3 and 27-H_3), 0.92 (3 H, d, *J* = 6.1 Hz, 21-H_3), 2.03 (3 H, s, 3-OCOCH3), 4.49 (1 H, m, 1-H), 4.99 (1 H, m (sharp), (19*Z*)-H), 5.13 (1 H, m (sharp), (19*E*)-H), 5.25 (1 H, m, 3-H), 5.80 (1 H, d, *J* = 11.4 Hz, 7-H), 6.57 (1 H, d, *J* = 11.4 Hz, 6-H).

1α-Hydroxyvitamin D_3 (10a) and 5,6-*trans*-1α-hydroxyvitamin D_3 (14a). Treatment of either 1α-hydroxyvitamin D_3 acetate or 1α-acetoxyvitamin D_3 with 10% methanolic NaOH in ethanol for 1.0 h at 40 °C provided 1α-hydroxyvitamin D_3 (**10a**) which can be crystallized from pentane/ether and is identical in all respects with an authentic sample. Similar treatment of either 5,6-*trans*-1α-hydroxyvitamin D_3 acetate or 5,6-*trans*-1α-acetoxyvitamin D_3 gave 5,6-*trans*-1α-hydroxyvitamin D_3 (**14a**): UV λ_{max} 273 nm (ε 23 000); mass spectrum, *m/e* (relative intensity) 400 (M^+, 12), 382 (8), 152 (42), 134 (100); NMR δ 0.56 (3 H, s, 18-H_3), 0.87 (6 H, d, *J* = 6.6 Hz, 26-H_3 and 27-H_3), 0.93 (3 H, d, *J* = 6.0 Hz, 21-H_3), 4.24 (1 H, m, 3-H), 4.50 (1 H, m, 1-H), 4.97 (1 H, m (sharp), (19*Z*)-H), 5.12 (1 H, m (sharp), (19*E*)-H), 5.89 (1 H, d, *J* = 11.4 Hz, 7-H), 6.58 (1 H, d, *J* = 11.4 Hz, 6-H).

1α,25-Dihydroxy-3,5-cyclovitamin D_3 (5b). A solution of 100 mg of 25-hydroxyvitamin D_3 (**1b**) and 150 mg of *p*-toluenesulfonyl chloride in 0.5 mL of dry pyridine was allowed to react for 24 h at 3 °C and was then quenched with saturated $NaHCO_3$. The aqueous phase was extracted with ether (2 × 30 mL), and the ether extracts were washed with saturated $NaHCO_3$ (3 × 10 mL), 3% HCl (2 × 10 mL), and H_2O (1 × 30 mL) and dried over $MgSO_4$. The solvent was removed in vacuo and the crude 25-hydroxyvitamin D_3 tosylate (**2b**) taken up in 25 mL of anhydrous methanol containing 200 mg of finely divided $NaHCO_3$. The stirred solution was heated to 55 °C for 8.0 h, cooled, concentrated to 5 mL, diluted with 50 mL of ether, and washed with water (3 × 30 mL). After being dried over $MgSO_4$, the ether solution was concentrated in vacuo to an oil which was >75% 25-hydroxy-3,5-cyclovitamin D_3 (**3b**) and suitable for the following oxidation.

To a stirring suspension of 7.0 mg of SeO_2 in 10 mL of CH_2Cl_2 was added 23 μL of *t*-BuOOH (bp 34 °C at 25 mm). When homogeneous, the reaction was diluted with 10 mL of CH_2Cl_2, and the crude 25-hydroxy-3,5-cyclovitamin **3b** in 10 mL of CH_2Cl_2 was added slowly. At the first appearance of overoxidation products, the reaction was transferred to a separatory funnel containing 30 mL of 10% NaOH and vigorously shaken. To the quenched reaction mixture was added 100 mL of ether, and the phases were separated. The organic phase was washed with 10% NaOH (3 × 30 mL) and water (3 × 30 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude oil was chromatographed in 4:6 ethyl acetate/hexanes (20 × 20 cm, 750-μm silica gel plate), giving 43 mg (40% yield) of 1α,25-dihydroxy-3,5-cyclovitamin D_3 (**5b**): mass spectrum, *m/e* (relative intensity) 430 (M^+, 15), 412 (12), 380 (35), 269 (10), 59 (100); NMR δ 0.53 (3 H, s, 18-H_3), 0.61 (1 H, m, 3-H), 0.93 (3 H, d, *J* = 6.2 Hz, 21-H_3), 1.21 (6 H, s, 26-H_3 and 27-H_3), 3.25 (3 H, s, (6*R*)-OCH_3), 4.17 (1 H, d, *J* = 9.2 Hz, 6-H), 4.20 (1 H, m, 1-H), 4.95 (1 H, d, *J* =9.2 Hz, 7-H), 5.19 (1 H, d, *J* = 1.9 Hz, (19*Z*)-H), 5.22 (1 H, d, *J* = 1.9 Hz, (19*E*)-H).

Glacial Acetic Acid Catalyzed Cycloreversion of 1α,25-Dihydroxy-3,5-cyclovitamin D_3. A solution of 16 mg of 1α,25-dihydroxy-3,5-cyclovitamin D_3 (**5b**) in 0.8 mL of glacial HOAc was heated to 55 °C for 15 min, cooled, and poured over ice/saturated $NaHCO_3$. The neutralized solution was extracted with ether (3 × 15 mL), and the ether extracts were washed with saturated $NaHCO_3$ (1 × 40 mL) and water (1 × 40 mL), dried over $MgSO_4$, and concentrated in vacuo. High-pressure LC of the crude mixture (7% 2-propanol/hexane, 6.2 mm × 25 cm Zorbax Sil column) afforded 8.2 mg (48% yield) of 1α,25-dihydroxyvitamin D_3 3-acetate (**9b**): UV λ_{max} 264 nm; mass spectrum, *m/e* (relative intensity) 458 (M^+, 30), 398 (70), 380 (15),

134 (100), 59 (80); NMR δ 0.55 (3 H, s, 18-H_3), 0.92 (3 H, d, J = 6.0 Hz, 21-H_3), 1.22 (6 H, s, 26-H_3 and 27-H_3), 2.04 (3 H, s, 3-$OCOCH_3$), 4.38 (1 H, m, 1-H), 5.00 (1 H, m (sharp), (19*Z*)-H), 5.20 (1 H, m, 3-H), 5.34 (1 H, m (sharp), (19*E*)-H), 6.06 (1 H, d, J = 11.6 Hz, 7-H), 6.42 (1 H, d, J = 11.6 Hz, 6-H). A 3.6-mg sample (20% yield) of 5,6-*trans*-1α,25-dihydroxyvitamin D_3 3-acetate (**13b**) was also obtained: UV λ_{max} 273 nm; mass spectrum, m/e (relative intensity) 458 (M^+, 10), 398 (85), 380 (25), 134 (100), 59 (85); NMR δ 0.54 (3 H, s, 18-H_3), 0.92 (3 H, d, J = 6.0 Hz, 21-H_3), 1.23 (6 H, s, 26-H_3 and 27-H_3), 2.03 (3 H, s, 3-$OCOCH_3$), 4.50 (1 H, m, 1-H), 4.96 (1 H, m (sharp), (19*Z*)-H), 5.10 (1 H, m (sharp), (19*E*)-H), 5.28 (1 H, m, 3-H), 5.80 (1 H, d, J = 11.4 Hz, 7-H), 6.55 (1 H, d, J = 11.4 Hz, 6-H).

1α,25-Dihydroxyvitamin D_3 (10b) and 5,6-*trans*-1α,25-Dihydroxyvitamin D_3 (14b). Hydrolysis of 5,6-*cis*-1α,25-dihydroxyvitamin D_3 acetate with 10% NaOH in methanol for 1.0 h at 55 °C gave 1α,25-dihydroxyvitamin D_3 (**10b**) which was identical in all respects with an authentic sample. By treatment of 5,6-*trans*-1α,25-dihydroxyvitamin D_3 3-acetate as above, 5,6-*trans*-1α,25-dihydroxyvitamin D_3 (**14b**) was obtained: mp 168–171 °C; UV λ_{max} 273 nm (ε 21 600); mass spectrum, m/e (relative intensity) 416 (M^+, 15), 398 (8), 152 (40), 134 (100), 59 (95); NMR δ 0.55 (3 H, s, 18-H_3), 0.92 (3 H, d, J = 6.0 Hz, 21-H_3), 1.23 (6 H, s, 26-H_3 and 27-H_3), 4.22 (1 H, m, 3-H), 4.53 (1 H, m, 1-H), 4.95 (1 H, m (sharp), (19*Z*)-H), 5.12 (1 H, m (sharp), (19*E*)-H), 5.85 (1 H, d, J = 11.4 Hz, 7-H), 6.55 (1 H, d, J = 11.4 Hz, 6-H).

1α-Hydroxy-3,5-cyclovitamin D_2 (5c). A solution of 100 mg of vitamin D_2 (**1c**) and 100 mg of *p*-toluenesulfonyl chloride in 400 μL of dry pyridine was allowed to react for 30 h at 3 °C and was then quenched with ice/saturated $NaHCO_3$. The aqueous mixture was extracted with ether (3 × 30 mL), and the combined organic extracts were washed with saturated $NaHCO_3$ (1 × 40 mL), 3% HCl (2 × 20 mL), saturated $NaHCO_3$ (1 × 20 mL), and H_2O (1 × 40 mL) and dried over $MgSO_4$. After solvent removal in vacuo, the crude vitamin D_2 tosylate (**2c**) was taken up in 20 mL of anhydrous methanol containing 300 mg of finely divided $NaHCO_3$ and the mixture heated to 55 °C for 8 h. After concentration of the reaction mixture to ~5 mL, it was diluted with 50 mL of ether and washed with water (3 × 30 mL). The organic phase was dried over $MgSO_4$ and concentrated in vacuo to an oil which was >75% 3,5-cyclovitamin D_2 (**3c**) and suitable for the following oxidation.

A mixture of 10.1 mg of SeO_2 in 10 mL of CH_2Cl_2 was treated with 33 μL of *t*-BuOOH (bp 34 °C at 25 mm) and stirred at room temperature until homogeneous. The reaction was diluted with an additional 10 mL of CH_2Cl_2, and the crude 3,5-cyclovitamin D_2 (**3c**) in 5 mL of CH_2Cl_2 was added slowly. After 50 min the reaction mixture was transferred to a separatory funnel and shaken vigorously with 25 mL of 10% NaOH. The quenched reaction mixture was diluted with 100 mL of ether, and the phases were separated. The organic phase was washed with 10% NaOH (3 × 20 mL) and water (2 × 30 mL), dried over $MgSO_4$, and concentrated in vacuo to an oil which was chromatographed on a silica gel thin-layer plate (20 × 20 cm; 750 μm silica gel) developed in 3:7 ethyl acetate/hexanes to yield 40 mg of 1α-hydroxy-3,5-cyclovitamin D_2 (**5c**): mass spectrum, m/e (relative intensity) 426 (M^+, 55), 394 (75), 353 (30), 269 (40), 135 (95); NMR δ 0.53 (3 H, s, 18-H_3), 0.63 (1 H, m, 3-H), 0.82 and 0.84 (6, dd, J = 4.4 Hz, 26-H_3 and 27-H_3), 0.92 (3 H, d, J = 6.0 Hz, 21-H_3), 1.02 (3 H, d, J = 6.4 Hz, 28-H_3), 3.26 (3 H, s, (6*R*)-OCH_3), 4.18 (1 H, d, J = 9.6 Hz, 6-H), 4.21 (1 H, m, 1-H), 4.94 (1 H, d, J = 9.6 Hz, 7-H), 5.17 (1 H, m (sharp), (19*Z*)-H), 5.19 (2 H, m, 22-H and 23-H), 5.24 (1 H, m (sharp), (19*E*)-H).

Glacial Acetic Acid Catalyzed Cycloreversion of 1α-Hydroxy-3,5-cyclovitamin D_2. A solution of 20 mg of 1α-hydroxy-3,5-cyclovitamin D_2 (**5c**) in 800 μL of glacial acetic acid was heated to 55 °C for 15 min and then poured carefully over ice/saturated $NaHCO_3$. The neutralized solution was extracted with ether (3 × 20 mL), and the combined organic extracts were washed with water (2 × 20 mL) and dried over $MgSO_4$. The solvent was removed in vacuo and the oily product chromatographed on a silica gel TLC plate (20 × 20 cm; 750 μm silica gel) developed in 3:7 ethyl acetate/hexanes to yield 10.2 mg (48%) of 1α-hydroxyvitamin D_2 3-acetate (**9c**): UV λ_{max} 264 nm (17 200); mass spectrum, m/e (relative intensity) 454 (M^+, 70), 394 (60), 376 (20), 269 (35), 134 (100); NMR δ 0.53 (3 H, s, 18-H_3), 0.82 and 0.84 (6 H, dd, J = 4.4 Hz, 26-H_3 and 27-H_3), 0.92 (3 H, d, J = 6.0 Hz, 21-H_3), 1.02 (3 H, d, J = 6.4 Hz, 28-H_3), 2.03 (3 H, s, 3-$OCOCH_3$), 4.42 (1 H, m, 1-H), 5.02 (1 H, m (sharp), (19*Z*)-H), 5.22 (3 H, m, 3-H, 22-H and 23-H), 5.36 (1 H, m (sharp), (19*E*)-H), 6.04 (1 H, d, J = 11.1 Hz, 7-H), 6.38 (1 H, d, J = 11.1 Hz, 6-H). A 4.7-mg sample (22% yield) of 5,6-*trans*-1α-hydroxyvitamin D_2 3-acetate (**13c**) was also obtained: UV λ_{max} 272 nm; mass spectrum, m/e (relative intensity) 454 (M^+, 20), 394 (80), 376 (10), 269 (25), 134 (100); NMR δ 0.54 (3 H, s, 18-H_3), 0.82 and 0.84 (6 H, dd, J = 4.4 Hz, 26-H_3 and 27-H_3), 0.92 (3 H, d, J = 6.0 Hz, 21-H_3), 1.02 (3 H, d, J = 6.4 Hz, 28-H_3), 2.03 (3 H, s, $OCOCH_3$), 4.49 (1 H, m, 1-H), 4.99 (1 H, m (sharp), (19*Z*)-H), 5.15 (1 H, m (sharp), (19*E*)-H), 5.20 (3 H, m, 3-H, 22-H, and 23-H), 5.80 (1 H, d, J = 11.4 Hz, 7-H), 6.59 (1 H, d, J = 11.4 Hz, 6-H).

1α-Hydroxyvitamin D_2 (10c) and 5,6-*trans*-1α-Hydroxyvitamin D_2 (14c). Hydrolysis of 5,6-*cis*-1α-hydroxyvitamin D_2 acetate (**9c**) with 10% NaOH in ethanol at 50 °C for 1.0 h under N_2 produced 1α-hydroxyvitamin D_2 (**10c**): mp 138–140 °C; UV λ_{max} 265 nm (ε 18 300); mass spectrum, m/e (relative intensity) 412 (M^+, 18), 394 (10), 376 (6), 152 (55), 134 (100); NMR δ 0.55 (3 H, s, 18-H_3), 0.82 and 0.84 (6 H, dd, J = 4.4 Hz, 26-H_3 and 27-H_3), 0.92 (3 H, d, J = 6.0 Hz, 21-H_3), 1.02 (3 H, d, J = 6.6 Hz, 28-H_3), 4.23 (1 H, m, 3-H), 4.42 (1 H, m, 1-H), 5.00 (1 H, m (sharp), (19*Z*)-H), 5.20 (2 H, m, 22-H and 23-H), 5.32 (1 H, m (sharp), (19*E*)-H), 6.02 (1 H, d, J = 11.1 Hz, 7-H), 6.38 (1 H, d, J = 11.1 Hz, 6-H).

Similar treatment of 5,6-*trans*-1α-hydroxyvitamin D_2 acetate (**13c**) produced 5,6-*trans*-1α-hydroxyvitamin D_2 (**14c**): UV λ_{max} 273 nm (ε 22 500); mass spectrum, m/e (relative intensity) 412 (M^+, 25), 394 (60), 376 (10), 152 (60), 134 (100); NMR δ 0.56 (3 H, s, 18-H_3), 0.82 and 0.84 (6 H, dd, J = 4.4 Hz, 26-H_3 and 27-H_3), 0.92 (3 H, d, J = 6.0 Hz, 21-H_3), 1.02 (3 H, d, J = 6.6 Hz, 28-H_3), 4.24 (1 H, m, 3-H), 4.53 (1 H, m, 1-H), 4.97 (1 H, m (sharp), (19*Z*)-H), 5.12 (1 H, m (sharp), (19*E*)-H), 5.20 (2 H, m, 22-H and 23-H), 5.92 (1 H, d, J = 11.4 Hz, 7-H), 6.60 (1 H, d, J = 11.4 Hz, 6-H).

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