H), 5.44 (m, C-6 H), 4.93 (m, C-3α H), 1.08 (s, C-10 Me), 1.02 (s, C-13 Me) (calcd,[15a,29] 1.086 and 1.010, respectively).

Anal. Calcd for $C_{34}H_{48}N_2O_6$: C, 70.31; H, 8.33; N, 4.82. Found: C, 70.63; H, 8.16; N, 4.77.

5α,14β-Cholestan-3β-ol (7a). A. The acetate **1f** (180 mg) was dissolved in acetic acid (20 ml) and hydrogenated over PtO_2 (20 mg) at room temperature and atmospheric pressure. After the stoichiometric hydrogen was taken up, the catalyst was removed by filtration and the filtrate was concentrated to dryness. The solution of the residue in ether was washed acid free with 5% $NaHCO_3$ solution, dried over Na_2SO_4, and evaporated. The residue was chromatographed on silica gel G–Celite (50:50 v/v). The hexane–benzene eluates (95:5 v/v) were concentrated to dryness to yield acetate **7b:** oil; ir 1730 cm^{-1}; NMR δ 4.9 (m, C-3α H), 2.03 (s, CH_3CO), 0.95 (s, C-13 Me), 0.84 (s, C-10 Me) (calcd,[15a,d] 0.950 and 0.800, respectively); GLC (240 °C) rrt 0.87 (rrt of **7c**, 1).

After saponification of **7b** with methanolic KOH, the oily alcohol **7a** was obtained, mass spectrum (GLC) *m/e* 388 (M^+).

Anal. Calcd for $C_{27}H_{48}O$: C, 83.43; H, 12.45. Found: C, 83.32; H, 12.30.

The alcohol **7a** was transformed as usual into 3,5-dinitrobenzoate **7d:** mp 155–156 °C from acetone; $[\alpha]^{21}D$ +38°; ir 3120, 1740 cm^{-1}.

Anal. Calcd for $C_{34}H_{50}N_2O_6$: C, 70.07; H, 8.65; N, 4.81. Found: C, 70.10; H, 8.79; N, 4.51.

B. Compound **8**[3] (300 mg) and $NaBH_4$ (600 mg) were dissolved in methanol (20 ml) and refluxed for 4 h. The solution was worked up as usual to yield oily **7a,** which after esterification was transformed into 3,5-dinitrobenzoate **7d** (260 mg), mp 155–156 °C.

C. The alcohol **9** (950 mg) in dyglime (50 ml) was hydroborated under the same conditions described for the preparation of propionate **1d.** After addition of propionic acid the mixture was heated at 140 °C for 48 h, at which time the solution was worked up as above. The residue was chromatographed on silica gel G–Celite (50:50 v/v).

Fractions eluted with hexane–benzene (95:5 v/v) (420 mg) contained a mixture of propionates **7e** and **7f** (GLC and GLC–mass spectrometry). Upon standing of their solution at −15 °C for 12 h and filtration of crystalline material the mother liquor was evaporated to yield propionate **7f** (250 mg) as an oil: ir 1730 cm^{-1}; mass spectrum (GLC) *m/e* 444 (M^+), 370, 355, 290, 257, 230, 217, 216, 215.

Compound **7f** was saponified to alcohol **7a,** which was transformed into 3,5-dinitrobenzoate **7d,** mp 155–156 °C.

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Registry No.—**1b,** 57759-45-2; **1c,** 633-31-8; **1d,** 57759-46-3; **1f,** 57759-47-4; **1h,** 57759-48-5; **3,** 57679-64-8; **4,** 57674-64-3; **5d,** 57674-65-4; **6,** 57674-66-5; **7a,** 57759-49-6; **7b,** 57759-50-9; **7d,** 57759-51-0; **7e,** 57674-67-6; **7f,** 57759-52-1; **8,** 57674-68-7; **9** 566-99-4; 7-dehydrocholesteryl tosylate, 57674-69-8; trimethylsilyl chloride, 75-77-4.

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Synthesis of 3-*epi*-Cholecalciferol and 5,6-*trans*-3-*epi*-Cholecalciferol

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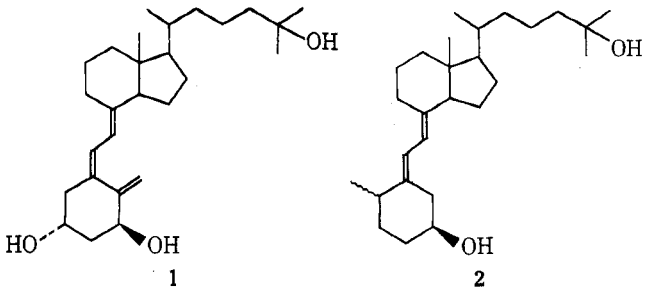
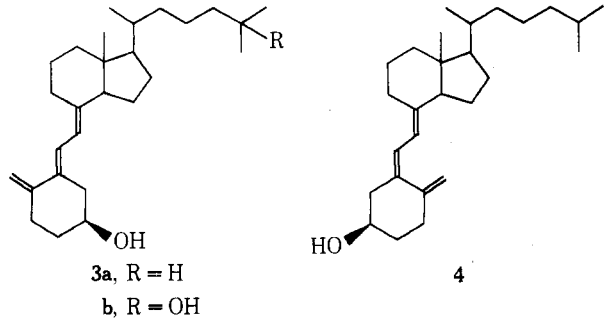
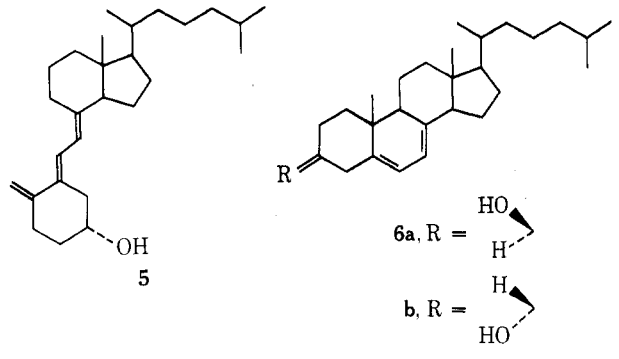
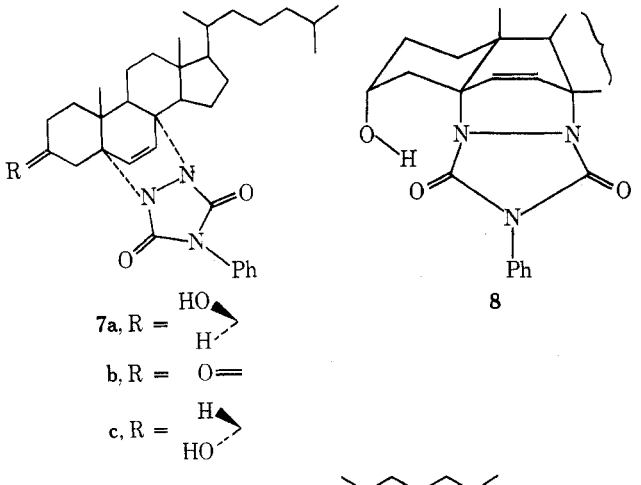
It is now known that vitamin D_3 undergoes a two-stage metabolic process involving hydroxylation, first at C-25 (occurring in liver), then at the C-1α position (in kidney) to produce what is apparently the final biologically active form, 1α,25-dihydroxycholecalciferol (I).[1] Recent studies on synthetic ring A analogs of vitamin D_3 and its hydroxylated metabolites have provided considerable information on structure–activity relationships in such compounds. In particular, the continued presence of intestinal calcium transport ability, even in nephrectomized rats, of 25-hydroxydihydrotachysterol (**2**), 5,6-*trans*-cholecalciferol (**3a**), and 5,6-*trans*-25-hydroxycholecalciferol (**3b**), suggests that the principal requirement for such activity may be the presence of a hydroxyl group in ring A having approximately the same position, relative to the transoid diene system, as that of the 1α-hydroxyl in the normal metabolite, **1**.[1b] Further, such results suggest that the 3β-hydroxyl of **1** may be of little importance in determining the biological activity of vitamin D_3 derivatives. This is supported by the recent finding that 3-deoxy-1α-hydroxycholecalciferol exhibits high biological activity and produced a greater maximum in intestinal calcium transport than did the natural metabolite.[2a] Furthermore, 3-methoxy-1α-hydroxycholecalciferol has pronounced intestinal calcium transport activity in vitamin D deficient rats.[1b]

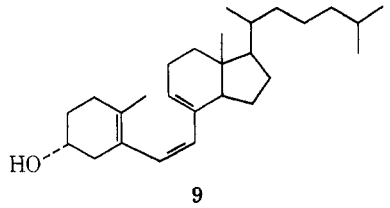
In order to provide further information on the relationships between structure and biological function in ring A analogues of cholecalciferol, we undertook syntheses of the analogues in which the configuration of the 3-hydroxyl group is inverted, namely 3-*epi*-cholecalciferol (**4**) and 5,6-*trans*-3-*epi*-cholecalciferol (**5**). The latter is of particular interest because it possesses a hydroxyl in the same relative position as the 1β-hydroxyl of the (as yet) unknown 3-deoxy-1β-hydroxycholecalciferol. The hydroxyl will also be similar in location to that of the biologically active 3-











deoxy-1α-hydroxycholecalciferol. The hydroxyls may be expected to be primarily equatorial (although some axial alcohol will be present),[2b,c] and thus nearly identically located with respect to the transoid diene system.

The desired compounds **4** and **5** were previously synthesized by Inhoffen[3] and co-workers, but were apparently not tested for biological activity. In the present work, **4** and **5** were prepared by a considerably easier route, from a readily available precursor.

7-Dehydrocholesterol (**6a**) was treated with 4-phenyl-1,2,4-triazoline-3,5-dione to yield, essentially quantitatively, adduct **7a**,[4] which upon treatment with Jones reagent gave the ketone in good yield. Part of our motivation for pursuing this route was the supposition that **7b** could be dehydrogenated to the Δ^1 analogue, which might serve as a suitable precursor of 1α-hydroxy-7-dehydrocholesterol. However, we have not as yet been able to carry out this desired transformation. On treatment with sodium borohydride, ketone **7b** gave the 3α-alcohol, **7c**, as the main product, the bulky triazolinedione moiety providing steric interference with the usual α-attack by this reductant. Although a small amount of the 3β-alcohol **7a** was formed, the separation of 3β and 3α isomers in this case was remarkably easy, the 3α isomer being considerably less polar on silica gel than the 3β isomer. This fact is readily rationalized when it is considered that the 3α-hydroxyl is capable of forming a strong intramolecular hydrogen bond with the 5α-nitrogen, as in **8**. This has the effect of lessening the interaction of the hydroxyl with the absorbent material. In the ir spectrum (CCl_4) of **7c**, a broad absorption band for a bonded hydroxyl, ν_{max} 3450 cm^{-1}, persists practically unchanged over the concentration range of 0.2–0.004 M. In contrast, in the ir of the 3β-alcohol **7a**, the hydroxyl absorption changes over this concentration range from primarily bonded (ν_{max} 3460 cm^{-1}, broad) to nonbonded (ν_{max} 3695, 3640, sharp) with only weak hydrogen-bonded hydroxyl absorption remaining.

Upon treatment of the 3α-hydroxyl adduct **7c** with lithium aluminum hydride, cholesta-5,7-dien-3α-ol[5] (**6b**) was formed as expected,[6] although the yield was not high. Photolysis[7] of **6b** gave a mixture from which the main product, 3-*epi*-precholecalciferol (**9**), was isolated by preparative TLC. This was then thermally isomerized to 3-*epi*-cholecalciferol (**4**). A portion of **4** was further isomerized with iodine in petrol[8] to 5,6-*trans*-3-*epi*-cholecalciferol (**5**). The uv and NMR spectra (see Experimental Section) of compounds **6b**, **9**, **4**, and **5** supported the structures shown, and were closely analogous to the spectra of the corresponding 3β-hydroxy compounds.[9]

Compounds **4** and **5** are currently being examined for biological activity and the results will be published elsewhere.

Experimental Section

Melting points were taken on a hot stage apparatus and are uncorrected. Ir spectra were taken on a Perkin-Elmer Model 337 spectrometer. Uv spectra were taken on a Beckman DB-G spectrometer. NMR spectra were obtained using a Varian A-60 instrument. Camag Kieselgel DF-O was used for thin layer chromatography (TLC). Microanalyses were performed by Chemalytics, Inc., Tempe, Ariz.

7-Dehydrocholesterol–4-Phenyl-1,2,4-triazoline-3,5-dione Adduct (7a). This was prepared by addition of 4-phenyl-1,2,4-triazoline-3,5-dione (1.79 g, 10 mmol) in ethyl acetate (20 ml) to 7-dehydrocholesterol (3.84 g, 10 mmol) in ethyl acetate (20 ml) in an ice bath. The solution was evaporated and the product crystallized from MeOH as needles: mp 155 °C (lit.[3] 155 °C); $[\alpha]^{25}D$ −91° (*c* 1.4, $CHCl_3$); ν_{max} (CCl_4) (0.2 M) 3450 (br), 1755, 1698, 1400, 1291, 1155, 1078, 1043, 1018, 690 cm^{-1}; NMR ($CDCl_3$) δ 0.77 (3 H, s), 0.79 (3 H, s), 0.8–3.5 (35 H, m), 4.35 (1 H, broad m), 6.10 and 6.34 (2 H, AB, J_{AB} = 8 Hz), 7.34 (5 H, br s).

Cholesta-5,7-dien-3-one–4-Phenyl-1,2,4-triazoline-3,5-dione Adduct (7b). 7-Dehydrocholesterol adduct **7a** (3.2 g, 5.7 mmol) in acetone (320 ml) at room temperature was treated with Jones reagent (8 M, 3 ml, 24 mmol) added with stirring over 15 min. Water (200 ml) was added followed by 5% $NaHSO_3$ (30 ml), and the mixture was extracted with ether. The extract was washed with 5% $NaHSO_3$ and saturated NaCl, dried (Na_2SO_4), and evaporated to yield the crude product, **7b**, crystallized from MeOH as prisms: mp 141–144 °C; $[\alpha]^{28}D$ −77° (*c* 1.0, $CHCl_3$); ν_{max} ($CHCl_3$) 1750, 1725 (sh), 1690, 1600, 1400 cm^{-1}; NMR ($CDCl_3$) δ 0.70 (3 H,

s), 0.8–2.8 (35 H, m), 2.76 (4α H) and 3.65 (4β H) (2 H, AB, J_{AB} = 19 Hz), 6.25 and 6.62 (2 H, AB, J_{AB} = 8 Hz), 7.54 (5 H, br s).

Anal. Calcd for $C_{35}H_{47}N_3O_3$: C, 75.37; H, 8.49. Found: C, 75.60; H, 8.64.

Cholesta-5,7-dien-3α-ol-4-Phenyl-1,2,4-triazoline-3,5-dione Adduct (7c). Ketone **7b** (3.0 g, 5.4 mmol) in MeOH (85 ml) and $CHCl_3$ (20 ml) was treated at room temperature with sodium borohydride (3 g, 0.12 mol) added over 40 min. After stirring for 2 h at room temperature, ether (400 ml) was added. The solution was washed with dilute HCl and saturated NaCl, dried (Na_2SO_4), and evaporated to a gum. The product was isolated by preparative TLC (EtOAc–hexane, 1:2) giving **7c**, 1.1 g, crystallized from MeOH as needles: mp 186–188 °C; $[\alpha]^{28}D$ −94° (*c* 1.0, $CHCl_3$); ν_{max} ($CHCl_3$) 3430 (br), 1750, 1690, 1420, 1395, 1167, 1152, 1085, 690 cm^{-1}; NMR ($CDCl_3$) δ 0.79 (3 H, s), 0.85–3.0 (37 H, m), 4.25 (1 H, m), 5.27 (1 H, br s, D_2O exchangeable), 6.23 and 6.49 (2 H, AB, J_{AB} = 8 Hz), 7.42 (5 H, br s).

Anal. Calcd for $C_{35}H_{49}N_3O_3$: C, 74.82; H, 8.83. Found: C, 75.10; H, 8.82.

Cholesta-5,7-dien-3α-ol (6b). 3-Epi adduct **7c** (553 mg, 1.02 mmol) in anhydrous THF (50 ml) was refluxed with $LiAlH_4$ (500 mg, 13.2 mmol) under N_2 in the dark for 11 h. After standing for 8 h at room temperature, the mixture was cooled in ice, and ethyl acetate (5 ml) was added dropwise followed by H_2O (1 ml) and ether (100 ml). The mixture was dried (Na_2SO_4), filtered, and evaporated to a semicrystalline residue. The major product was isolated by preparative TLC (ethyl acetate–hexane, 1:4, R_f 0.6) giving **6b**, 191 mg, as needles from MeOH: mp 128–130 °C; $[\alpha]^{30}D$ −51° (*c* 1.0, $CHCl_3$); ν_{max} ($CHCl_3$) 3620, 3450 (br), 1480, 1400, 1005 cm^{-1}; λ_{max} (EtOH) 252 nm (infl, ε 4260), 262 (infl, 7180), 269 (9550), 280 (10 500), 291 (6150); NMR ($CDCl_3$) δ 0.62 (3 H, s), 0.81 (3 H, s), 0.9–2.5 (35 H, m), 4.10 (1 H, dd, $J_1 = J_2$ = 3 Hz), 5.40 and 5.66 (2 H, AB, J_{AB} = 6 Hz, further coupled with *J* = 2 Hz).

Anal. Calcd for $C_{27}H_{44}O$: C, 84.56; H, 11.49. Found: C, 84.31; H, 11.53.

3-*epi*-Precholecalciferol (9). 3-*epi*-7-Dehydrocholesterol (**6b**, 191 mg) in ether (400 ml), in a quartz reaction vessel equipped with an inlet for rapid flushing with N_2, was irradiated for 30 min in a Rayonet RPR-100 reactor equipped with RPR-3000 Å lamps. The solution was then evaporated in vacuo at room temperature to an oil. The major product was isolated by preparative TLC (ethyl acetate–hexane, 1:9, R_f 0.5) giving 3-*epi*-precholecalciferol (**9**): 95 mg (glass); $[\alpha]^{28}D$ +34° (*c* 1.9, $CHCl_3$); ν_{max} ($CHCl_3$) 3620, 3450 (br), 1450, 1380, 1218, 1035 cm^{-1}; λ_{max} (EtOH) 260 nm (8200); NMR ($CDCl_3$) δ 0.71 (3 H, s), 0.84 (3 H, d, *J* = 6 Hz), 0.7–2.8 (34 H, m), 3.91 (1 H, m), 5.56 (1 H, br s), 5.71 and 6.03 (2 H, AB, J_{AB} = 12 Hz).

3-*epi*-Cholecalciferol (4). The 3-*epi*-precholecalciferol (93 mg) was refluxed for 3 h in benzene (20 ml) and MeOH (2 ml) under N_2 in the dark. The solution was evaporated in vacuo to a glass which was separated by preparative TLC (EtOAc–hexane, 1:9, R_f 0.4) giving **4**; 65 mg; $[\alpha]^{26}D$ −5.4° (*c* 2, $CHCl_3$); ν_{max} ($CHCl_3$) 3630, 3450 (br), 1480, 1450, 1395, 1050, 910 cm^{-1}; λ_{max} (EtOH) 264 nm (ε 17 000); NMR ($CDCl_3$) δ 0.55 (3 H, s), 0.87 (3 H, d, *J* = 6 Hz), 1.0–3.0 (33 H, m), 3.94 (1 H, m), 4.90 (1 H, d, *J* = 3 Hz), 5.12 (1 H, br s, $W_{1/2}$ = 5 Hz), 6.09 and 6.34 (2 H, AB, J_{AB} = 12 Hz).

5,6-*trans*-3-*epi*-Cholecalciferol (5). 3-*epi*-Cholecalciferol (**4**, 30 mg) in petroleum ether (bp 35–60 °C, 40 ml) was treated with a solution of iodine (1 mg) in petroleum ether (10 ml) for 2 h in "diffuse daylight"[7] (the flask was placed near a window on a bright, hazy day at noon). After evaporation of the solvent in vacuo, the product was separated by preparative TLC (ethyl acetate–hexane, 1:9) giving recovered **4** (15 mg) and the faster running **5** (10 mg), as a noncrystalline glass: $[\alpha]^{26}D$ +34° (*c* 1, $CHCl_3$); λ_{max} (EtOH) 272 nm (ε 22 000); NMR ($CDCl_3$) δ 0.54 (3 H, s), 0.8–3.3 (36 H, complex multiplet), 3.9 (1 H, broad m), 4.71 (1 H, br s), 5.00 (1 H, br s), 5.88 and 6.62 (2 H, AB, J_{AB} = 12 Hz).

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Registry No.—**4**, 57651-82-8; **5**, 57651-83-9; **6a**, 434-16-2; **6b**, 57651-84-0; **7a**, 57637-86-2; **7b**, 57637-87-3; **7c**, 57651-85-1; **9**, 57651-22-6; 4-phenyl-1,2,4-triazoline-3,5-dione, 15988-11-1.

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A Facile Synthesis of the Cyclohexyl Constituents of the Boll Weevil Sex Pheromone

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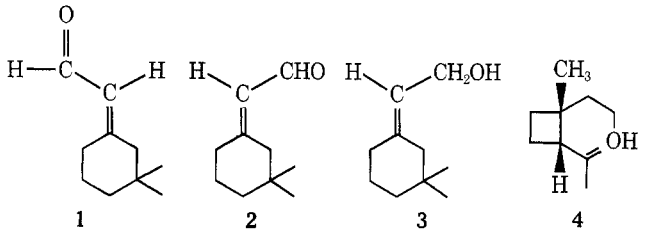
The four monoterpene compounds [(*E*)-3,3-dimethyl-$\Delta^{1,\alpha}$-cyclohexaneacetaldehyde (**1**), (*Z*)-3,3-dimethyl-$\Delta^{1,\alpha}$-cyclohexaneacetaldehyde (**2**), (*Z*)-3,3-dimethyl-$\Delta^{1,\beta}$-cyclohexaneethanol (**3**), and (+)-*cis*-2-isopropenyl-1-methylcyclobutaneethanol (**4**)] that comprise the pheromone of



1 2 3 4

male boll weevil *Anthonomus grandis* Boheman were identified and first synthesized by Tumlinson et al.[1] These sex attractants are currently of considerable interest since they may provide a generally nontoxic method of surveying and controlling boll weevil population.[1] The growing concern over the environmental pollution and ecological imbalance caused by insecticides has further stimulated interest in this area. The commercial importance of these sex attractants prompted us to develop an efficient, high-yield synthesis of these compounds.[2,3] This paper describes a facile route from commercially available 3-methyl-2-cyclohexenone to the *E* and *Z* aldehyde components (**1** and **2**) in 80% overall yield. Separation of the aldehyde mixture,[4] followed by reduction of aldehyde **2** with $NaBH_4$ or 9-BBN, affords a route to the component *Z* alcohol (**3**) in an essentially quantitative yield. Scheme I outlines the synthesis of sex pheromone components **1**, **2**, and **3**.

The known 3,3-dimethylcyclohexanone (**6**), the same intermediate utilized in the previous syntheses,[1,2] was prepared from commercially available 3-methyl-2-cyclohexenone (**5**) by conjugate addition of lithium dimethylcopper in 98% yield.[5] Addition of lithium acetylide–ethylenedi-