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Registry No. **1a**, 3709-27-1; **1b**, 130296-61-6; **1c**, 61958-46-1; **1d**, 88466-67-5; **1e**, 90734-81-9; **1f**, 3709-18-0; **2a**, 130296-62-7; **2b**, 130296-63-8; **2c**, 130296-64-9; **2d**, 130296-65-0; **2e**, 130296-66-1; **2f**, 130296-67-2; (diacetoxyiodo)benzene, 3240-34-4.

A Novel Convergent Synthesis of (+)-1α,25-Dihydroxyvitamin D_3 Using a Chromium(II)-Mediated Coupling Reaction

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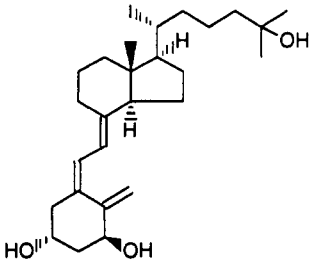
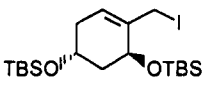
Of the known vitamin D_3 metabolites, 1α,25-dihydroxyvitamin D_3 (1) is known to play a central role in the maintenance of calcium homeostasis. More recently, this hormone has also been found to induce cellular differentiation of human meyloid leukemia cells.[1] These findings, therefore, have spurred much research on the syntheses[2] of 1 and its analogues due to the potential utility of 1 in the treatment of certain cancers.

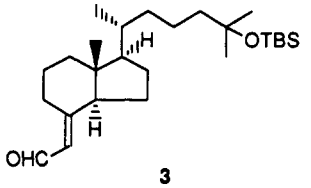
We have recently reported[3] that chromium(II)-mediated addition[4] of the allyl iodide **2**, prepared from (*R*)-(−)-carvone in 10 steps (46% yield), to [(*p*-methoxybenzyl)oxy]acetaldehyde proceeded with complete threo selectivity in almost quantitative yield. This observation prompted us to investigate a new convergent synthesis of **1** which relies on chromium(II)-mediated coupling of the A-ring fragment **2** and the C/D-ring fragment **3**.



1



2



3

TBS = ^{t}BuMe$_2$Si–

The known keto alcohol **4**, easily obtained from the Inhoffen–Lythgoe diol[5] according to Castedo's procedure,[6] was converted to alcohol **7** by sequential Grignard reaction, monoacetylation, silylation, and DIBAL reduction (79% overall yield). After oxidation of **7**, the resulting ketone (**8**) was directly transformed into the α,β-unsaturated aldehyde **3** by reaction with lithiated *N*-*tert*-butyl-2-(trimethylsilyl)acetaldimine followed by acid hydrolysis[7] (88% overall yield).

Reaction of iodide **2** with aldehyde **3** in the presence of chromium(II) species, prepared in situ by LAH reduction of chromium(III) chloride,[4] led to a highly diastereoselective coupling to give alcohol **9** as the sole product.[8] It is worthy of note that, in this particular case, at least 1.5 equiv of aldehyde **3** should be used because concomitant reduction of **3** to alcohol **10** always takes place. In order to make purification easy, the crude reaction mixture was reduced with DIBAL to give alcohol **9** (83% yield) along with **10** (67% yield based on the excess of **3** used), oxidation of which allowed us to recover starting aldehyde **3** in quantitative yield. The observed excellent diastereoselectivity of this chromium(II)-mediated coupling reaction can be explained by assuming the transition state resembling **11**.[3,4]

It was anticipated at this point that the construction of the conjugated triene of **1** might be achieved by stereo- and regioselective dehydration through an E_2 elimination process. However, this transformation turned out to be very difficult. For example, the usual dehydrating agents (e.g. methanesulfonyl chloride/DMAP, thionyl chloride, or phosphorus oxychloride in pyridine) gave a >10:1 mixture of the unconjugated triene **13** and the conjugated triene **12**. In our hands the best method of converting **9** to 1α,25-dihydroxyvitamin D_3 (**1**) involved dehydration catalyzed by copper(II) sulfate on silica gel[9] followed by deprotection. Thus, heating **9** with the catalyst at 50 °C in benzene gave an inseparable mixture of **12** and **13** which, upon desilylation using hydrofluoric acid, furnished **1** and **14** in a ratio of 3:5 in 90% yield. The synthetic 1α,25-dihydroxyvitamin D_3 (**1**), mp 117–118 °C (lit.[10] mp 118–119 °C), $[\alpha]^{29}_D$ +47.8° (*c* 1.00, EtOH) [lit.[10] $[\alpha]_D$ +47.9° (*c* 0.5, EtOH)], exhibited spectral properties (^{1}H NMR, IR, MS) in accord with those reported.[10]

Although improvement of the dehydration step will be necessary in order for the present synthetic route to be translated into a more practical process, this synthetic study provides a new method of potential value in the synthesis of **1** and related vitamin D_3 metabolites.

Experimental Section

General. Melting points were measured on a micro-hot stage apparatus and are uncorrected. Optical rotations were measured with a JASCO-DIP-370 polarimeter. ^{1}H NMR spectra were re-

(1) Ikekawa, N.; Fujimoto, Y. *J. Synth. Org. Chem. Jpn.* **1988**, *46*, 455 and references therein.

(2) For reviews on recent synthetic endeavors in vitamin D field, see: (a) Pardo, R.; Stantelli, M. *Bull. Soc. Chim. Fr.* **1985**, *98*. (b) Kametani, T.; Furukawa, H. *Med. Res. Rev.* **1987**, *7*, 147.

(3) Hatakeyama, S.; Numata, H.; Osanai, K.; Takano, S. *J. Org. Chem.* **1989**, *54*, 3515.

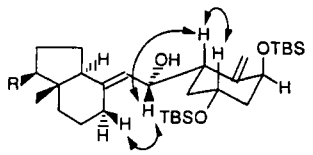
(4) For reviews on Cr(II)-mediated addition of an allylic halide to an aldehyde, see: (a) Hiyama, T. *J. Synth. Org. Chem. Jpn.* **1981**, *39*, 81. (b) Takai, K.; Utimoto, K. *J. Synth. Org. Chem. Jpn.* **1988**, *46*, 66.

(5) For the synthesis of Inhoffen–Lythgoe diol and its derivatives, see: Hatakeyama, S.; Numata, H.; Osanai, K.; Takano, S. *J. Chem. Soc., Chem. Commun.* **1989**, 1843 and references therein.

(6) Castedo, L.; Mascareñas, J. L.; Mouriño, A.; Sarandeses, L. A. *Tetrahedron Lett.* **1988**, *29*, 1203.

(7) (a) Corey, E. J.; Enders, D.; Bock, M. *Tetrahedron Lett.* **1976**, 7. (b) Shau, J.-H.; Reusch, W. *J. Org. Chem.* **1980**, *45*, 2013.

(8) MnO_2 oxidation of **9** followed by $NaBH_4$ reduction of the resulting enone gave a 5:1 mixture of **9** and its epimer whose ^{1}H NMR (500 MHz) spectra allowed us to conclude that the Cr(II)-mediated reaction proceeded with complete diastereoselectivity. The stereochemistry of **9** was determined on the basis of mechanistic considerations in addition to NOE experiments (500-MHz ^{1}H NMR) (the significant NOE's are shown below).



(9) Nishiguchi, T.; Machida, N.; Yamamoto, E. *Tetrahedron Lett.* **1987**, *28*, 4565.

(10) Baggiolini, E. G.; Iacobelli, J. A.; Hennessy, B. M.; Batcho, A. D.; Sereno, J. F.; Uskokovič, M. R. *J. Org. Chem.* **1986**, *51*, 3098.

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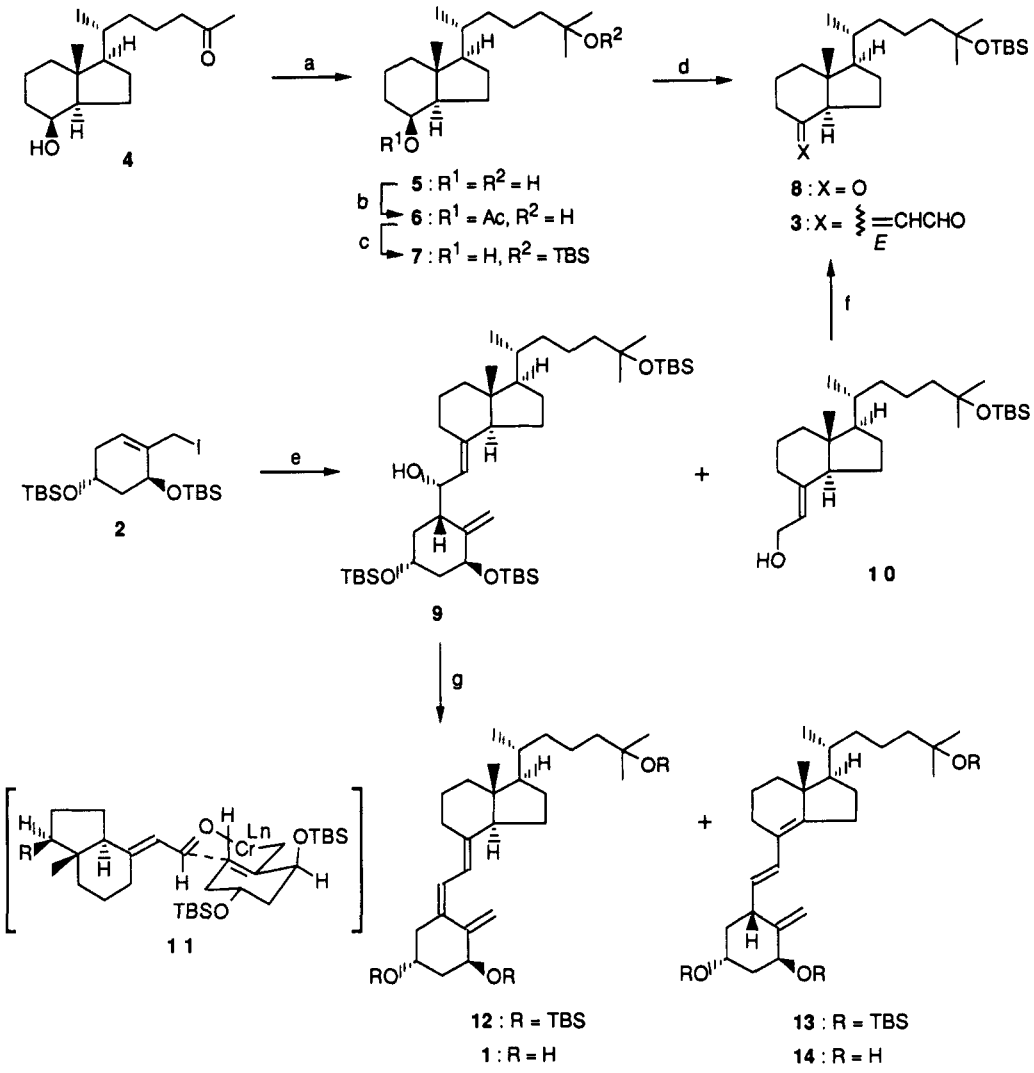
Scheme I[a]



[a] (a) MeMgI, Et_2O, 92%; (b) Ac_2O, pyridine, 91%; (c) (i) TBSOTf, 2,6-lutidine, CH_2Cl_2, (ii) DIBAL, CH_2Cl_2, −78 °C, 94%; (d) (i) PCC, CH_2Cl_2, (ii) ^{t}BuN=CHCH$_2$TMS, LDA, THF, −78 °C → −20 °C then 5% $(CO_2H)_2$, 88%; (e) (i) 1.5 equiv of **3**, 6 equiv of $CrCl_3$, 3 equiv of LAH, THF, (ii) DIBAL, CH_2Cl_2, −50 °C, 83% (**10**: 67% based on the excess of **3**); (f) MnO_2, CH_2Cl_2, 99%; (g) (i) $CuSO_4/SiO_2$, benzene, 50 °C, (ii) 46% HF–MeOH–THF (1:2:2 v/v), 90% (1:14 = 3:5).

corded in $CDCl_3$. All extracts were dried over anhydrous $MgSO_4$ and evaporated with rotary evaporator at ca. 30 Torr. Chromatographic purifications were carried out with Daisogel IR-60 (63/210 μm) (column) and Merck silica gel 60 PF_{254} (thin layer).

[1*R*-[1β(*R),3aα,4β,7aβ]]-Octahydro-4-hydroxy-α,α,ε,7a-tetramethyl-1*H*-indene-1-pentanol (5).** To a stirred solution of MeMgI in Et_2O (20 mL), prepared from Mg (460 mg, 18.93 mmol) and methyl iodide (1.2 mL, 19.17 mmol), at 0 °C was added a solution of ketone **4**[6] (868 mg, 3.26 mmol) in tetrahydrofuran (THF) (20 mL). After 1 h, the reaction mixture was quenched with saturated NH_4Cl, filtered through Celite, and partitioned. The organic layer was washed with saturated NaCl, dried, concentrated, and chromatographed on silica gel. Elution with 1:1 Et_2O–hexane gave diol **5** (841 mg, 92%) as a colorless solid: mp 90–91 °C (from hexane–CH_2Cl_2); $[\alpha]_D$ +48.9° (*c* 0.547, EtOH) [lit.[10] mp 90–91 °C; $[\alpha]_D$ +51.4° (*c* 0.2, EtOH)]. The spectral data (^{1}H NMR, IR, MS) are identical with those reported.[10]

[1*R*-[1β(*R),3aα,4β,7aβ]]-Octahydro-4-acetoxy-α,α,ε,7a-tetramethyl-1*H*-indene-1-pentanol (6).** A solution of diol **5** (432 mg, 1.53 mmol) and acetic anhydride (0.8 mL, 5.53 mmol) in pyridine (8 mL) was stirred at room temperature for 4 days. The reaction mixture was poured into ice–water, acidified with concentrated HCl (ca. pH 3), and extracted with Et_2O. The extract was washed with water and saturated NaCl, dried, and concentrated. The residue was chromatographed on silica gel (1:2 Et_2O–hexane) to give acetate **6** (415 mg, 84%; 91% based on the consumed starting material) as a colorless viscous oil: $[\alpha]^{29}_D$ +36.2° (*c* 0.974, $CHCl_3$); IR (neat) 3420, 1738, 1379, 1242, 1160 cm^{-1}; ^{1}H NMR (90 MHz) δ 0.89 (s, 3 H), 0.92 (d, *J* = 7.1 Hz, 3 H), 1.23 (s, 6 H), 2.05 (s, 3 H), 4.14 (br s, 1 H); MS *m/z* 306 ($M^+ - H_2O$, 11), 264 (34), 246 (81), 161 (35), 135 (89), 122 (39), 108 (56), 94 (61), 43 (100); exact mass calcd for $C_{20}H_{34}O_2$ ($M^+ - H_2O$) 306.2559, found 306.2548. Anal. Calcd for $C_{20}H_{36}O_3$: C, 74.01; H, 11.19. Found: C, 73.71; H, 10.94. Also, elution with 1:1 Et_2O–hexane gave starting diol **5** (35 mg, 8%).

[1*R*-[1β(*R),3aα,4β,7aβ]]-Octahydro-1-[5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1,5-dimethylhexyl]-7a-methyl-1*H*-inden-4-ol (7).** To a stirred solution of alcohol **6** (323 mg, 0.10 mmol) in CH_2Cl_2 (5 mL) at 0 °C were added 2,6-lutidine (0.27 mL, 2.33 mmol) and *tert*-butyldimethylsilyl triflate (0.38 mL, 1.66 mmol). After stirring at room temperature for 30 min, the reaction mixture was diluted with Et_2O, washed with 1 N HCl, water, and saturated $NaHCO_3$, dried, and concentrated.

To a stirred solution of crude silylated product (399 mg), a yellow oil, in CH_2Cl_2 (5 mL) at −78 °C was added 1 M diisobutylaluminum hydride (DIBAL) in CH_2Cl_2 (3 mL, 3 mmol). After stirring at −78 °C for 1 h, the reaction mixture was quenched with 10% NaOH (1 mL), allowed to warm to room temperature, and stirred for an additional 30 min. The resulting sludge was removed by filtration through Celite and thoroughly washed with CH_2Cl_2. The combined filtrates were dried, concentrated, and chromatographed on silica gel. Elution with 50:1 hexane–ethyl acetate gave alcohol **7** (372 mg, 94%) as a colorless viscous oil: $[\alpha]^{29}_D$ +28.8° (*c* 0.898, $CHCl_3$); IR (neat) 3400, 1380, 1364, 1258,

1162, 1090, 1047, cm^{-1}; ^{1}H NMR (90 MHz) δ 0.06 (s, 6 H), 0.85 (s, 12 H), 0.89 (d, J = 7.1 Hz 3 H), 1.17 (s, 6 H), 4.07 (br s, 1 H); MS m/z 381 (M$^+$ - Me, 2.4), 191 (25), 173 (60), 135 (42), 109 (35), 95 (47), 81 (36), 75 (100); exact mass calcd for $C_{23}H_{45}O_2Si$ (M$^+$ - Me) 381.3189, found 381.3225. Anal. Calcd for $C_{24}H_{48}O_2Si$: C, 72.66; H, 12.21. Found: C, 72.58; H, 12.03.

[1*R*-[1β(*R),3aα,4β,7aβ]]-Octahydro-4(*E*)-(2-oxoethylidene)-1-[5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1,5-dimethylhexyl]-7a-methyl-1*H*-indene (3).** To a stirred solution of alcohol **7** (525 mg, 1.33 mmol) in CH_2Cl_2 (35 mL) at room temperature was added pyridinium chlorochromate (875 mg, 3.98 mmol). After 1 h, the reaction mixture was diluted with Et_2O and filtered through Florisil. The filtrate was evaporated to leave ketone **8** (520 mg) as a yellow oil, which was used without purification.

To a stirred solution of lithium diisopropylamide (3.50 mmol) in THF (10 mL) at 0 °C was added a solution of *N*-*tert*-butyl-2-(trimethylsilyl)acetaldimine[7a] (544 mg, 3.18 mmol). After 20 min, this mixture was cooled to -78 °C, and a solution of crude **8** (520 mg) in THF (7 mL) was then added. The resulting mixture was permited to warm to -20 °C, stirred for 30 min, and then quenched with 5% oxalic acid (18 mL). After stirring for 1.5 h at room temperature, the reaction mixture was extracted with Et_2O. The extract was washed with water and saturated $NaHCO_3$, dried, concentrated, and chromatographed on silica gel (1:40 Et_2O-hexane) to give aldehyde **3** (486 mg, 88%) as a colorless viscous oil: $[\alpha]^{29}_D$ +102.1° (*c* 1.064, $CHCl_3$); IR (neat) 1675, 1634, 1470, 1380, 1362, 1250, 1044 cm^{-1}; ^{1}H NMR (90 MHz) δ 0.06 (s, 6 H), 0.60 (s, 3 H), 0.85 (s, 12 H), 0.93 (d, J = 5.9 Hz, 3 H), 1.18 (s, 6 H), 3.37 (dd, J = 10.9 and 2.9 Hz, 1 H), 5.73 (dd, J = 8.3 and 1.5 Hz, 1 H), 10.07 (d, J = 8.3 Hz, 1 H); MS m/z 405 (M$^+$ - Me, 3.3), 363 (22), 271 (24), 173 (48), 159 (17), 133 (20), 109 (15), 95 (16), 81 (17), 75 (100); exact mass calcd for $C_{25}H_{45}O_2Si$ (M$^+$ - Me) 405.3189, found 405.3163. Anal. Calcd for $C_{26}H_{48}O_2Si$: C, 74.23; H, 11.51. Found: C, 74.40; H, 11.69.

Cr(II)-Mediated Coupling Reaction of 2 and 3. To a stirred suspension of $LiAlH_4$ (54 mg, 1.43 mmol) in THF (8 mL) at 0 °C was added $CrCl_3$ (453 mg, 2.86 mmol), and the mixture was stirred at 0 °C for 10 min and then at room temperature for 30 min. The resulting black suspension was recooled to 0 °C, and a mixture of **2** (230 mg, 0.48 mmol) and **3** (300 mg, 0.71 mmol) in THF (5 mL) was added. After stirring at 0 °C for 10 min and at room temperature for 45 min, the reaction mixture was quenched with water, diluted with Et_2O, and filtered through Celite to remove the inorganic precipitates. The organic layer of the filtrate was washed with saturated NaCl and then dried. Removal of the solvent left a yellow oil (504 mg) which was reduced with DIBAL as follows in order to simplify purification of **9**. To a stirred solution of the above crude mixture in CH_2Cl_2 (6 mL) at -50 °C was added 1 M DIBAL in CH_2Cl_2 (2 mL, 2 mmol), and stirring was continued at -50 °C for 30 min. The reaction mixture was quenched with 1 N NaOH (1 mL), allowed to warm to room temperature, and stirred for an additional 30 min. The resulting sludge was removed by filtration through Celite and thoroughly washed with CH_2Cl_2. The combined filtrates were dried, concentrated, and chromatographed on silica gel. Elution with 1:40 Et_2O-hexane gave alcohol **9** (307 mg, 83%) as a colorless viscous oil: $[\alpha]^{29}_D$ +29.8° (*c* 0.646, $CHCl_3$); IR (neat) 3420, 1470, 1363, 1382, 1255, 1105, 1080, 1040, 1005 cm^{-1}; ^{1}H NMR (500 MHz) δ 0.06 (s, 6 H), 0.07 (s, 3 H), 0.08 (s, 3 H), 0.10 (2 s, 6 H), 0.56 (s, 3 H), 0.85 (s, 9 H), 0.90 (s, 9 H), 0.91 (s, 12 H), 0.93 (d, J = 6.7 Hz, 3 H), 1.17 (s, 3 H), 1.18 (s, 3 H), 2.53 (q, J = 5.5 Hz, 1 H), 2.62 (br d, J = 11.6 Hz, 1 H), 3.50 (br s, 1 H, exchangeable with D_2O), 4.23 (m, 1 H), 4.58 (dd, J = 4.9 and 8.5 Hz, 1 H), 4.66 (br dd, J = 7.3 and 4.3 Hz, 1 H), 4.82 (s, 1 H), 5.05 (d, J = 8.5 Hz, 1 H), 5.10 (s, 1 H); MS m/z 758 (M$^+$ - H_2O, 3) 626 (20), 569 (10), 494 (5), 379 (10), 356 (9), 355 (9), 299 (10), 289 (12), 271 (8), 248 (18), 167 (37), 147 (11), 133 (10), 109 (9), 95 (14), 93 (14), 81 (12), 75 (100); exact mass calcd for $C_{45}H_{86}O_3Si_3$ (M$^+$ - H_2O) 758.5885, found 758.5908. Further elution with 1:6 Et_2O-hexane gave alcohol **10** (67 mg, 67% based on the excess of **3**) as a colorless oil: $[\alpha]^{29}_D$ +49.1° (*c* 0.978, $CHCl_3$); IR (neat) 3360, 1466, 1364, 1382, 1255, 1150, 1042 cm^{-1}; ^{1}H NMR (90 MHz) δ 0.06 (s, 6 H), 0.56 (s, 3 H), 0.85 (s, 12 H), 0.92 (d, J = 6.4 Hz, 3 H), 1.18 (s, 6H), 2.65 (br dd, J = 10.0 Hz and 2.8 Hz, 1 H), 4.20 (d, J = 7.3 Hz, 2 H), 5.22 (t, J = 7.3 Hz, 1 H); MS m/z 407 (M$^+$ - Me, 4), 273 (23), 217 (66), 173 (59), 161 (28), 149 (16), 135 (29), 121 (26), 109 (27), 95 (31), 81 (31), 75 (100); exact mass calcd for $C_{25}H_{47}O_2Si$ (M$^+$ - Me) 407.3345, found 407.3334.

Oxidation of this alcohol **10** (30 mg, 0.07 mmol) with activated MnO_2 (300 mg) in CH_2Cl_2 (5 mL) at room temperature for 1 h gave practically pure starting aldehyde **3** (29.6 mg, 99%).

1α,25-Dihydroxyvitamin D$_3$ (1). A mixture of alcohol **9** (66.6 mg, 0.09 mmol) and $CuSO_4$ on SiO_2 (3.14 mmol/g) (30 mg, 0.09 mmol) in benzene (10 mL) was heated at 50 °C for 1.5 h. After cooling to room temperature, the reaction mixture was filtered through Celite, and the catalyst was thoroughly washed with Et_2O. The combined filtrates were evaporated to dryness to give a yellow viscous oil (65.3 mg). The residue was dissolved in a mixture of 46% HF (1 mL), MeOH (2 mL), and THF (2 mL). After being stirred at room temperature for 5 h, the reaction mixture was basified with saturated $NaHCO_3$, extracted with CH_2Cl_2, dried, and concentrated. Purification by preparative TLC developed twice with Et_2O afforded 1α,25-dihydroxyvitamin D$_3$ (**1**) (11.6 mg, 33%) and **14** (20.4 mg, 57%).

1α,25-Dihydroxyvitamin D$_3$ (**1**) was obtained as the less polar component, colorless plates (recrystallized from methyl formate): mp 117-118 °C (lit.[10] mp 118-119 °C); $[\alpha]^{29}_D$ +47.8° (*c* 1.00, EtOH) [lit.[10] $[\alpha]^{29}_D$ +47.9° (*c* 0.5, EtOH)]; IR (Nujol) 3290, 1143, 1072, 1055, 905 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$ + CD_3OD) δ 0.54 (s, 3 H), 0.94 (d, J = 6.1 Hz, 3 H), 1.20 (s, 6 H), 2.30 (dd, J = 13.4 and 6.7 Hz, 1 H), 2.56 (dd, J = 13.4 and 3.7 Hz, 1 H), 2.83 (dd, J = 12.8 and 4.0 Hz, 1 H), 4.17 (m, 1 H), 4.39 (dd, J = 8.0 and 4.9 Hz), 4.99 (s, 1 H), 5.32 (s, 1 H), 6.06 (d, J = 11.0 Hz, 1 H), 6.36 (d, J = 11.0 Hz, 1 H); MS m/z 416 (M$^+$, 5), 398 (9), 380(7), 285 (5), 174 (7), 159 (10), 152 (20), 134 (100), 119 (11), 105 (24); exact mass calcd for $C_{27}H_{44}O_3$ (M$^+$) 416.3290, found 416.3328. These spectral data are in accord with those reported.[10]

The more polar isomer (**14**) was obtained as a colorless amorphous solid: $[\alpha]^{29}_D$ +92.3° (*c* 1.285, EtOH); IR (neat) 3390, 1650, 1600, 1460, 1375, 1260, 1210, 1050, 1030, 970, 905 cm^{-1}; NMR (500 MHz) δ 0.90 (s, 3 H), 0.97 (d, J = 6.7 Hz, 3 H), 1.24 (s, 6 H), 3.22 (m, 1 H), 4.27 (m, 1 H), 4.50 (t, J = 3.4 Hz, 1 H), 4.79 (s, 1 H), 4.96 (s, 1 H), 5.55 (dd, J = 15.9 and 7.9 Hz, 1 H), 6.32 (d, J = 15.9 Hz, 1 H); MS m/z 416 (M$^+$, 3), 398 (3), 167 (43), 149 (100), 123 (28), 113 (17), 99 (26); exact mass calcd for $C_{27}H_{44}O_3$ (M$^+$) 416.3290, found 416.3270.

Supplementary Material Available: ^{1}H NMR spectra for **1**, **3**, **9**, **10**, and **14** (17 pages). Ordering information is given on any current masthead page.

Novel Rearrangement of 8-Methyltricyclo[6.4.0.0^{1,4}]dodecan-5-ones to Angularly Fused and Spiro-Annulated Tricyclic Ketones

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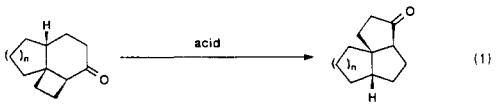
Recently we reported that 5,6-disubstituted bicyclo[4.2.0]octan-2-ones such as **1** rearrange under the action of acid catalysts through a new pathway to give bicyclo[3.3.0]octanones such as **2** (eq 1).[1] Total syntheses of some



(1)

1 n = 1, 2, 3 2

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0022-3263/91/1956-0463$02.50/0