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Synthesis of Cuauhtemone

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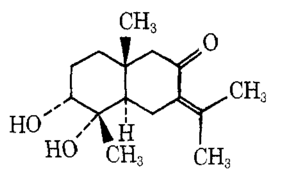
The sesquiterpenoid growth inhibitor cuauhtemone (1) has been synthesized starting from the monoethylene ketal of cyclohexane-1,4-dione. The stereochemistry of the ring A diol system has been introduced by osmium tetroxide hydroxylation. This reaction though stereoselective appears to be less susceptible to steric hindrance than the corresponding epoxidation process. The isopropylidene side chain of cuauhtemone is introduced by addition of methyllithium to the enolate of a β-keto ester followed by dehydration.

Cuauhtemone is a sesquiterpenoid dihydroxy ketone isolated from the Mexican medicinal shrub "Cuauhtematl" [*Pluchea odorate* (compositae)].[1,2] It has been reported to inhibit the growth of corn and bean seeds. The structure of the natural product was proven by a combination of magnetic resonance[1] and x-ray spectroscopic[2] techniques leading to the formulation 1 for cuauhtemone. This report describes a total synthesis of racemic 1.



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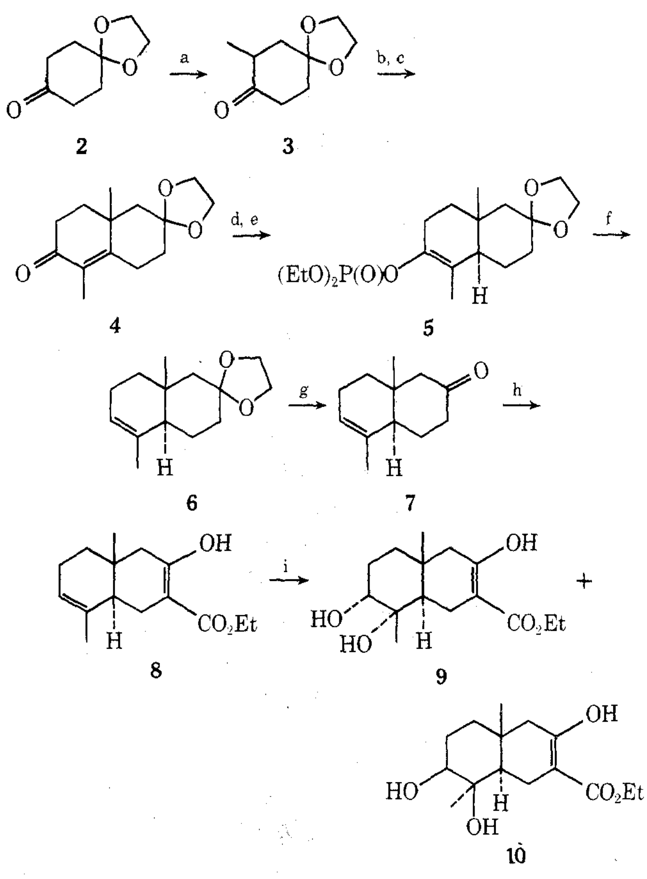
Our initial synthetic goal was the bicyclic olefin ketal 6 shown in Scheme I. This intermediate incorporates the necessary trans-fused ring system and it provides appropriate sites for the introduction of both the diol function and the isopropylidene groups of the cuauhtemone molecule. The preparation of 6 was carried out as shown in Scheme I starting from the monoethylene ketal of cyclohexane-1,4-dione (2).[3] Monomethylation of 2 in the form of its pyrrolidine enamine[4] afforded **3**. The latter was annelated with ethyl vinyl ketone employing potassium hydroxide in methanol for the Michael stage and pyrrolidine in refluxing benzene for the aldol closure step. The product 4 has been previously prepared by Narang and Dutta[5] using a β-chloro ketone as the vinyl ketone equivalent, and subsequent to the onset of our work its preparation and that of ketal 6 as well have also been described by Miller and Behare.[6] The latter workers carried out the annelation using a β-dialkylamino ketone as the source of the vinyl ketone. In all cases, however, the percent conversion of 3 is less than 40%.

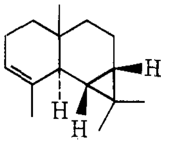
We established the trans fusion for the ring junction of cuauhtemone in a manner similar to that later reported by Miller and Behare.[6] The ketal enone 4 was reduced with lithium in ammonia and the resulting enolate was trapped as the enolphosphonate 5.[7] Further reduction of 5 with lithium in ammonia–ethylamine–*tert*-butyl alcohol[7] gave the desired olefin ketal **6**.

Scheme I



Step a, C_4H_9N, CH_3I; b, $CH_3CH_2COCH{=}CH_2$, KOH, CH_3OH; c, C_4H_9N; d, Li, NH_3; e, $(EtO)_2POCl$; f, Li, NH_3, $EtNH_2$, *t*-BuOH; g, H_2O–HOAc; h, $(EtO)_2CO$, NaH; i, OsO_4

The cis α-diol moiety of cuauhtemone was introduced by osmium tetroxide oxidation. The reaction of a double bond with this reagent is generally assumed to be subject to significant steric control, and hydroxylation of 6 and related compounds was expected to yield overwhelmingly if not uniquely the required α-diol system. Steric accessibility certainly seems to be the prime factor in the regioselective hydroxylation of dienes. In the synthesis of longifolene by Corey and co-workers[8] the accessibity of an exocyclic double bond compared to an equally substituted endocyclic one provided the means for selective formation of an unsaturated 1,2-glycol. The variation in stereoselectivity shown by osmium tetroxide toward octalin substrates appears to be quite great, however. For example, **20**, an intermediate in the synthesis of maaliol,[9] affords a 3:1 ratio of β- to α-diols despite the hindrance to



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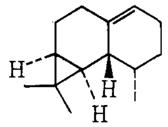

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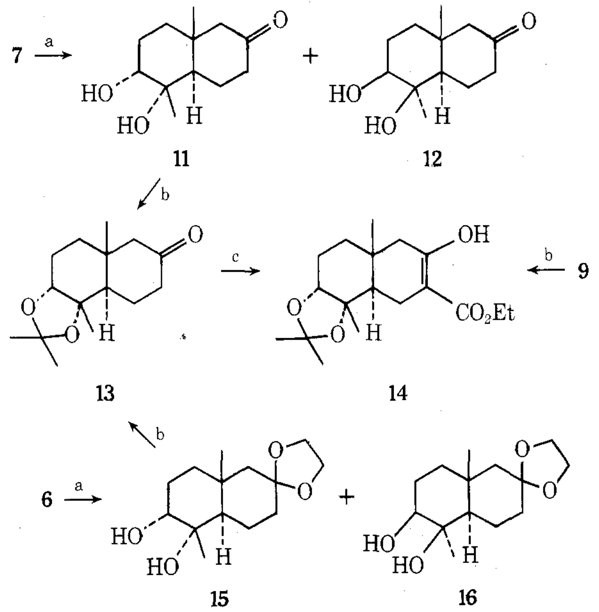
β-attack provided by the angular methyl group. In contrast the related olefin **21** employed in a synthesis of aromadendrene[10] afforded the β-diol exclusively. In the present work we have encountered a relatively low selectivity with osmium tetroxide, and as described below our results suggest that osmium tetroxide has a lower steric requirement than a peracid in reaction with a double bond.

Three compounds in the cuauhtemone series were subjected to the hydroxylation reaction: the olefin ketal **6**, the keto olefin **7** prepared from **6** by acetic acid catalyzed hydrolysis of the ketal function, and the enolic β-keto ester **8** prepared from **7** by condensation with diethyl carbonate in the presence of sodium hydride. Exposure of the keto olefin **7** to the hydroxylation reagent provided a 30% yield of the isomeric cis diols **11** and **12** in a ratio of 3.5:1 (Scheme II). The stereochemical

Scheme II



Step a, OsO_4; b, CH_3COCH_3, $CuSO_4$; c, $(EtO)_2CO$, NaH

assignments of **11** and **12** follow from comparison of the chemical shifts of the methyl groups and the C-3 (secondary hydroxyl position) protons in the NMR spectra of the two isomers. Thus for the major diol **11** the angular methyl shows a singlet at 0.87 ppm, the C-4 methyl shows a singlet at 1.14 ppm, and the signal for the C-3 methine proton appears as a multiplet at 3.64 ppm with a half-band width of 7 Hz. All three of these signals are shifted in the expected manner in the spectrum of the minor isomer **12**. The deshielding effect of the C-4 axial hydroxyl on the angular methyl is observed by a shift of the methyl resonance to 1.02 ppm while the C-4 methyl group being equatorial in **12** is observed at 1.32 ppm. The signal for the C-3 proton is again observed as a multiplet but by virtue of the axial conformation of this proton in **12** the half-band width of the multiplet is increased to 25 Hz. The chemical shift of this axial proton is also found at higher field, 3.38 ppm, relative to the methine proton of **11**. Hydroxylation of the olefin β-keto ester **8** afforded similar results: a 64% yield of diols **9** and **10** in a ratio of 3:1. The two series were also correlated by the conversions shown in Scheme II. Treatment of the major diol **11** obtained from the keto olefin **7** with acetone in the presence of cupric sulfate gave the acetonide **13**. Condensation of the latter with diethyl carbonate afforded the β-keto ester **14**. The latter was identical with the acetonide obtained from **9** after reaction with acetone.

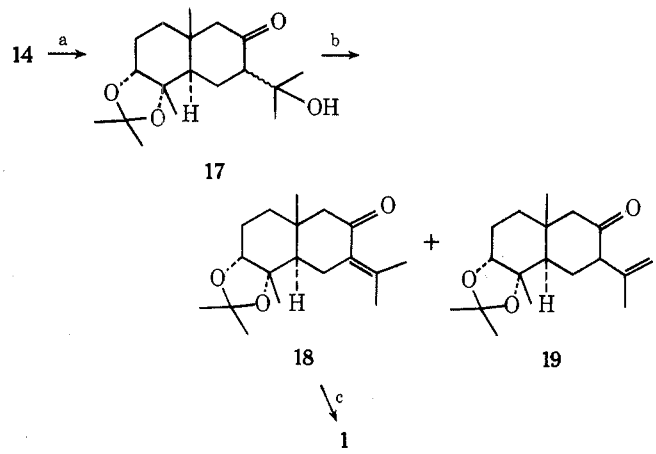
In the case of the ketal olefin **6** we anticipated that the presence of an additional axial substituent, the ketal oxygen, would reinforce the hindrance to attack on the β face of the double bond provided by the angular methyl group. Although the hydroxylation of **6** proceeded quantitatively the increase in selectivity was small. Analysis of the reaction mixture after conversion of the diol products **15** and **16** to acetonide derivatives indicated that the ratio of α- to β-attack was 4:1.

In contrast to our results with osmium tetroxide Miller and Behare[6] found that epoxidation of **6** with *m*-chloroperbenzoic acid in methylene chloride afforded a single epoxide in high yield. This product resulted from exclusive attack at the less hindered α face of the olefin ketal. They also observed total stereoselectivity in a model system lacking the ketal function. The steric requirement for approach of osmium tetroxide to a double bond, therefore, may be considerably less than that of a seemingly smaller reagent, a peracid. An alternative explanation, that the transition state for the hydroxylation may more closely resemble product rather than starting material and thus be controlled by conformational interactions of the product, has been suggested previously by Buchi.[9]

Our original plan for the synthesis of cuauhtemone called for the use of the cis α-diol obtained from hydroxylation of the olefin ketal **6**. We anticipated the possibility that the conditions necessary for cleavage of the ketal function might also cause the tertiary hydroxyl group to undergo elimination. It was found, however, that the mixture of diols, **15** and **16** obtained from **6** could be directly converted to the keto acetonide **13** and its β isomer by treatment with acetone containing copper sulfate and a catalytic amount of *p*-toluenesulfonic acid. What was not anticipated, however, was that chromatography of the diols **15** and **16** or of the corresponding acetonides would not efficiently separate them. We turned, therefore, to the separable major diols **9** and **11** obtained from hydroxylation of the keto olefin **7** and the β-keto ester **8**.

As described previously **9** and **11** were converted to the same acetonide β-keto ester **14**. As shown in Scheme III **14** was treated with sodium hydride to produce the corresponding enolate and the latter was then treated with excess methyllithium.[11] The addition reaction proved to be extremely sluggish. Despite prolonged reaction times a 56% yield of ketol **17** based on recovery of 50% of the starting β-keto ester was the maximum that could be obtained. In addition ketol **17** was sufficiently unstable that conversion of this material to cuauhtemone was undertaken without extensive preliminary purification. Accordingly ketol **17** was subjected to dehydration employing thionyl chloride in pyridine. Chromatography of the product yielded a mixture of the conjugated enone acetonide **18** and its nonconjugated isomer **19**. After purification by silica gel chromatography enone **18** was subjected to acid conditions for the hydrolysis of the acetonide function. Chromatography of the reaction mixture afforded racemic

Scheme III



Step a, NaH, CH_3Li; b, $SOCl_2$–C_5H_5N; c, H_2O–HOAc

cuauhtemone (1). The infrared, ultraviolet, mass, ^{1}H NMR, and ^{13}C NMR spectra of the synthetic material were identical in all respects with those of the natural product kindly provided by Professor K. Nakanishi of Columbia University.

Experimental Section

Infrared spectra were recorded with Perkin-Elmer Model 137-b and Model 257 spectrophotometers. Peak positions are reported in reciprocal centimeters. Proton magnetic resonance spectra were recorded with a Varian Associates T-60 and a JEOL 100-MHz spectrometer, and ^{13}C spectra with a Varian Associates CFT-20 instrument. Tetramethylsilane was used as an internal standard throughout and chemical shifts are reported in parts per million from this standard. Ultraviolet spectra were obtained with a Cary 14 spectrophotometer. Both nominal and precise mass spectra were obtained on a Varian Associates M-66 spectrometer. Melting points are uncorrected. Combustion analyses were obtained from Atlantic Microlab, Inc., Atlanta, Ga. All solvents used were of reagent grade and were purified by standard procedures. All reactions were carried out under an argon atmosphere. Except where noted all chromatography was carried out using Mallinckrodt CC-7 special silica gel.

2-Methyl-4-ethylenedioxycyclohexanone (3). Cyclohexane-1,4-dione monoethylene ketal[3] (23.4 g, 0.15 mol) was converted to its pyrrolidine enamine and treated with 57.0 g (0.4 mol) of methyl iodide according to the method of Stork et al.[4] to yield 13.7 g (46%) of **3:** bp 103 °C (2.5 mm) [lit. 70–72 °C (0.2 mm)]; ir ($CHCl_3$) 1713 cm^{-1}; NMR ($CDCl_3$) 1.02 (d, 3 H, J = 6 Hz), 4.02 ppm (s, 4 H).

Enone Ketal 4. A mixture of 10.46 g (60 mmol) of **3**, 6.72 g (80 mmol) of ethyl vinyl ketone, and approximately 0.2 g of solid potassium hydroxide in 130 ml of methanol was heated under reflux for 4 h. After removal of excess ethyl vinyl ketone and methanol in vacuo 200 ml of benzene was added, followed by distillation of ca. 50 ml of benzene to remove traces of water. Pyrrolidine (1 ml) was then added and heating at reflux was continued for an additional 10 h. The residue obtained after workup was chromatographed on silica gel to yield 5.28 g (37%) of **4:** mp 54–54.5 °C (lit.[5] 61–62 °C); ir ($CHCl_3$) 1653, 1608 cm^{-1}; uv (CH_3OH) 254 nm; NMR ($CDCl_3$) 1.35 (s, 3 H), 1.80 (s, 3 H), 3.9–4.1 ppm (m, 4 H).

Enol Phosphonate 5. Following the procedure of Ireland,[7] **4** (8.05 g, 34 mmol) was added to 150 ml of dry ammonia in a 250-ml three-neck flask fitted with a stirrer and dry ice condenser. Lithium (0.7 g, 0.1 g-atom) was added in portions to the cold (−78 °C) solution over a 20-min period. The mixture was stirred for an additional 1 h and the ammonia then evaporated. The resulting gray mass was treated with 12.1 g (0.07 mol) of diethyl chlorophosphate at 0 °C and stirred for 1 h. After careful addition of water the product was extracted into ether, the ether solution washed to neutrality, and the solvent dried ($MgSO_4$). Removal of the solvent gave 9.02 g of crude material which was chromatographed on silica gel. Elution with ether–benzene gave 8.57 g (67%) of the phosphonate **5:** ir ($CHCl_3$) 1700, 1655, 1265, 1035 cm^{-1}; NMR ($CDCl_3$) 0.99 (s, 3 H), 1.35 (t, 6 H, J = 7 Hz), 1.58 (s, 3 H), 3.94 (s, 4 H), 4.17 ppm (q, 4 H).

Anal. Calcd for $C_{18}H_{31}O_6P$: C, 57.74;H, 8.35. Found: C, 57.58; H, 8.30.

Olefin Ketal 6. Lithium (2.8 g, 0.4 g, 23 mmol) in small pieces was added to a mixture of 100 ml of ethylamine, 100 ml of anhydrous ammonia, 15 ml of *tert*-butyl alcohol, and 8.57 g (23 mmol) of the enol phosphonate **5.** After stirring for 1.5 h at −55 °C the ammonia and ethylamine were evaporated, 100 ml of ether was added, and excess lithium was destroyed by cautious addition of water. Evaporation of ether solvent following standard workup and chromatography on silica gel afforded 3.5 g (69%) of the olefin ketal **6:**[6] NMR ($CDCl_3$) 0.8–0.3 (m, 11 H), 1.00 (s, 3 H), 1.70 (s, 3 H), 4.10 (m, 4 H), 5.45 ppm (m, 1 H).

Hydroxylation of 6. The ketal olefin **6** (0.297 g, 1.34 mmol) was dissolved in 20 ml of dry ether containing 2 ml of dry pyridine. To the cold solution (0 °C) was added 0.34 g (1.34 mmol) of osmium tetroxide.[10] The reaction mixture was allowed to warm to room temperature and left for 5 days. Ether was removed in vacuo, additional pyridine (5 ml) added, and 5 g of $NaHSO_3$ in 15 ml of water was added at 0 °C. The mixture was then stirred for 1.5 h at room temperature. The product was extracted into chloroform and the solvent dried (Na_2SO_4) and removed to afford 0.38 g of crude diols. Chromatography of the crude product on silica gel gave 0.34 g of a mixture of **15** and **16.**

The mixture of diols **15** and **16** (0.092 mg, 0.36 mmol) was dissolved in 20 ml of dry acetone. Anhydrous cupric sulfate[12] (5 g) and *p*-toluenesulfonic acid (0.028 mg) were added and the mixture was heated at reflux for 2 h. Solid material was filtered. The *p*-toluenesulfonic acid was removed by stirring with K_2CO_3 for 30 min, the solution was again filtered, and the acetone was evaporated. Chromatography on silica gel again failed to effect separation. A mixture of **13** and the isomeric β-acetonide (0.07 g) was obtained. Analysis by GLC on SE-30 at 150 °C showed **13** to be the predominant product with a ratio of 4:1.

Keto Olefin 7. Ketal olefin **6** (7.64 g, 0.034 mol) was dissolved in 100 ml of 85% aqueous acetic acid and the solution was heated at 100 °C for 1.5 h. Water and acetic acid were removed in vacuo and the product taken up in ether. Washing of the ether with saturated sodium bicarbonate solution followed by drying (Na_2SO_4) and solvent removal yielded an oil which was chromatographed on silica gel to afford 6.0 g (95%) of **7:** ir ($CHCl_3$) 1705, 1655 cm^{-1}; NMR ($CDCl_3$) 0.79 (s, 3 H), 1.69 (s, 3 H), 5.37 ppm (m, 1 H).

Hydroxylation of 7. Keto olefin **7** (0.19 g, 1.07 mmol) was dissolved in 6 ml of dry pyridine at 0 °C to which was added 0.305 g (1.2 mmol) of osmium tetroxide. The mixture was left for 24 h at room temperature in the dark. After cooling again to 0 °C a solution of 0.7 g of sodium bisulfite, 10.5 ml of water, and 6.3 ml of pyridine was added and the mixture left for 1 h. The product was extracted into chloroform and the solvent was dried (Na_2SO_4) and removed to yield 0.18 g of a brown oil. The latter was chromatographed on silica gel. Elution with ether gave 0.015 g (6.7%) of **12:** NMR ($CDCl_3$) 1.02 (s, 3 H), 1.32 (s, 3 H), 3.46 ppm (m, 1 H, ½ band width = 25 Hz). Elution with acetone gave 0.053 g (23%) of **11:** mp 116–116.5 °C; ir ($CHCl_3$) 3520, 3420, 1705 cm^{-1}; NMR ($CDCl_3$) 0.87 (s, 3 H), 1.14 (s, 3 H), 3.64 ppm (m, 1 H ½ band width = 7 Hz).

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.49. Found: C, 67.73; H, 9.49.

Ketoacetonide 13. The cis α-diol **11** (0.18 g, 0.87 mmol) was dissolved in 25 ml of acetone containing 3.1 g of anhydrous cupric sulfate.[12] The mixture was stirred for 6 h at room temperature. Following the usual workup the residue (0.188 g) was chromatographed on silica gel to afford 107 mg (49%) of ketoacetonide **13:** mp 45–47 °C; NMR ($CDCl_3$) 0.83 (s, 3 H), 1.13 (s, 3 H), 1.32 (s, 3 H), 1.45 (s, 3 H), 3.93 ppm (m, 1 H).

Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.17; H. 9.56.

Keto Ester 8. Sodium hydride–mineral oil dispersion (0.387 g) was washed free of the oil with three portions of anhydrous ether. Keto olefin **7** (0.937 g, 5.26 mmol) dissolved in 20 ml of diethyl carbonate was added to the hydride and the mixture was heated with stirring at 85 °C for 4 h. The red solution was cooled to 0 °C and 3 ml of absolute ethanol was added to destroy excess hydride. The solution was then acidified with 10 ml of 10% aqueous acetic acid and worked up in the usual manner to yield 1.26 g (96%) of the enolic β-keto ester **8:** ir ($CHCl_3$) 1732, 1645, 1610 cm^{-1}; NMR ($CDCl_3$) 0.83 (s, 3 H), 1.32 (t, 3 H, J = 7 Hz), 1.70 (s, 3 H), 4.20 (q, 2 H= J = 7 Hz), 5.42 (m, 1 H), 12.25 (s, 1 H).

Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.78; H, 8.89.

Hydroxylation of 8. Diols 9 and 10. Following the method described previously, keto ester **8** (0.657 g, 2.63 mmol) was treated with 0.678 g (2.67 mmol) of osmium tetroxide in a solution of 2 ml of pyridine and 20 ml of anhydrous ether. The crude product was chromatographed to yield first (50% ether–benzene) 116 mg (16%) of the cis β-diol **9:** NMR ($CDCl_3$) 1.05 (s, 3 H), 1.30 (s, 3 H), 1.32 (t, 3 H, J = 7 Hz), 3.39 (q, 1 H), 4.25 (q, 2 H, J = 7 Hz), 12.13 ppm (s, 1 H). The major product **10** (356 mg, 48%) eluted as an oil with 100% ether: NMR ($CDCl_3$) 0.92 (s 3 H), 1.20 (s, 3 H), 1. t, 3 H, J = 7 Hz), 3.63 (m, 1 H), 4.25 (q, 2 H, J = 7 Hz), 12.10 ppm (s, 1 H).

Anal. Calcd for $C_{15}H_{24}O_5$: C, 63.36; H, 8.51. Found: C, 63.06; H, 8.50.

Acetonide 14. The above diol (35 mg, 0.123 mmol) was treated with acetone–cupric sulfate at 55 °C for 2 h as described previously. Workup and chromatography on silica gel gave 37 mg (93%) of **14:** ir ($CHCl_3$) 1733, 1710, 1655, 1612 cm^{-1}; NMR ($CDCl_3$) 0.87 (s, 3 H), 1.27 (s, 3 H), 1.30 (t, 3 H, J = 7 Hz), 1.35 (s, 3 H), 1.45 (s, 3 H), 3.90 (m, 1 H), 4.18 (q, 2 H, J = 7 Hz), 12.15 ppm (s, 1 H).

Anal. Calcd for $C_{18}H_{28}O_5$: C, 66.64; H, 8.70. Found: C, 66.38; H, 8.69.

Cuauhtemone Acetonide (18). To 33 mg (1.38 mmol) of sodium hydride (from 66 mg of 50% mineral oil dispersion) in 18 ml of ether was added 0.148 g (0.46 mmol) of keto ester acetonide **14.** When hydrogen evolution was complete an ethereal solution of 1.6 M methyllithium[11] (32 mmol) was added at 0 °C over a period of 10 min and the resulting solution was then heated at reflux for 4.5 h. The recooled mixture was then added to 50 ml of an ice-cooled 20% ammonium chloride solution. Following the usual workup removal of the solvent gave 0.135 g of oily product. Rapid chromatography on silica gel gave 70 mg of unreacted keto ester **14** and 40 mg of ketol acetonide **17:** NMR ($CDCl_3$) 0.82 (s, 3 H), 1.22 (s, 3 H), 1.27 (s, 3 H), 1.38 (s, 3 H), 1.53 (s, 3 H), 3.90 (m, 1 H). Recycling of the recovered **14** gave a total of 60 mg of partially purified **17.**

The ketol **17** (60 mg, 0.194 mmol) was dissolved in 10 ml of cold pyridine (0 °C) to which was added 0.2 ml of thionyl chloride.[13] After stirring for 3 h at 0 °C the mixture was added to cold saturated sodium bicarbonate solution. The usual workup (extraction with ether) gave 54 mg of oily product which was chromatographed on silica gel to yield 26 mg of cuauhtemone acetonide (**18**): ir ($CHCl_3$) 1677, 1600 cm^{-1}; NMR ($CDCl_3$) 0.89 (s, 3 H), 1.39 (s, 3 H), 1.50 (s, 3 H), 1.82 (s, 3 H), 1.98 (s, 3 H), 2.19 (s, 3 H), 3.95 ppm (m, 1 H); MS M^+ 292.20133 (calcd for $C_{18}H_{28}O_3$, 292.20377).

Preceding the elution of **18** there was obtained 11 mg of an oil having the spectral characteristics attributable to the isopropenyl isomer **19:** ir ($CHCl_3$) 1707, 1600 cm^{-1}.

Cuauhtemone (1). A solution of 0.38 g of **18** in 5 ml of 80% aqueous acetic acid was warmed to 60 °C for 15 h. The solution was then extracted with methylene chloride and the extracts washed with saturated sodium bicarbonate solution. Removal of the solvent after drying over sodium sulfate afforded 0.34 g of a crude oil. The latter was chromatographed on an EM Reagents size A silica gel 60 prepacked column to give 15 mg of racemic cuauhtemone (**1**):[1] ir ($CHCl_3$) 3530, 2930, 1675, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) 0.92 (s, 3 H), 1.20 (s, 3 H), 1.77 (broad s, 2 H), 1.82 (s, 3 H), 2.01 (s, 3 H), 2.20 (s, 3 H), 2.92 (d, 1 H, J = 12 Hz), 3.63 ppm (t, 1 H, J = 2.0 Hz); ^{13}C NMR ($CDCl_3$) 203.11, 144.37, 131.36, 74.35, 73.07, 60.17, 45.61, 36.29, 32.95, 25.75, 23.41, 22.69, 21.35, 18.62 ppm; uv (CH_3OH) max 254 nm (ϵ 7500); MS M^+ (base peak) 252.1713 (calcd for $C_{15}H_{24}O_3$, 252.1725).

Registry No.—*rac*-**1,** 58616-76-5; **2,** 4746-97-8; **3,** 54316-77-7; **4,** 3944-80-4; **5,** 58540-78-6; **6,** 54316-78-8; **7,** 58540-79-7; **8,** 58540-80-0; **9,** 58540-81-1; **11,** 58540-82-2; **12,** 58540-83-3; **13,** 58540-84-4; **14,** 58540-85-5; **17,** 58540-86-6; **18,** 58540-87-7; **19,** 58540-88-8.

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Studies on the Adduct of 4-Phenyl-1,2,4-triazoline-3,5-dione with Vitamin D_3

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Vitamin D_3 reacted rapidly with 4-phenyl-1,2,4-triazoline-3,5-dione at the $\Delta^{5,10(19)}$-diene system to give the α-face adduct **7** (95%) and β-face adduct **9** (5%). The adduct mixture gave a crystalline ketone **14** with Jones reagent. Ketone **14** was unaffected by HCl in dioxane or ethanol, but gave a dimethyl ketal **15** with HCl in methanol. Sodium borohydride reduction of **14** gave a mixture of **7** and the crystalline epimer **16.** Adduct **7** was unaffected by lithium aluminum hydride or sodium bis(2-methoxyethoxy)aluminum hydride, but reacted with diisobutylaluminum hydride to give a dihydrodeoxy compound **17.** With KOH in ethylene glycol–water, 5,6-*trans*-vitamin D_3 was recovered.

The chemistry of vitamin D has a history of over 50 years.[1] Nonetheless, there remains considerable interest in the chemistry of vitamin D, in particular as a result of recent investigations on the metabolism of vitamin D_3 (**1**) and related compounds.[2] It is now clear that this vitamin undergoes hydroxylation (in the liver) at C-25, followed by hydroxylation (in kidney) at C-1α position to form 1α,25-dihydroxycholecalciferol (**2**), which appears to be the biologically active agent responsible for stimulation of the production of the calcium-binding protein. The activity of **2** is manifested even in nephrectomized rats, which are incapable of carrying out the 1α-hydroxylation step,[3] where in contrast cholecalciferol (**1**) and 25-hydroxycholecalciferol (**3**) are ineffective. The primary requirement for activity in vitamin D analogues appears to be the presence of a 1α-hydroxyl, or, as in 5,6-*trans*-cholecalciferol (**4**), a hydroxyl in the same position, relative to the transoid diene system, as the 1α-hydroxyl.[1a,4] Synthetic 1α-hydroxycholecalciferol (**5**) is now being used in the clinical treatment of nephritic bone disease in humans.[5]

With the foregoing facts in mind, we and many others[6,7] have been studying synthetic routes to the preparation of hydroxylated (or otherwise modified) vitamin D analogues, particularly compounds **2** and **5.** All studies reported to date, with the exception of a total synthesis[8] of **5** have involved the synthesis of steroidal precursors convertible into $\Delta^{5,7}$-steroids, from which the vitamins can be obtained by the usual photochemical–thermal isomerization process. In the present work, we have approached the problem from a different angle, namely via the direct modification of vitamin D_3 itself. Our first objective was the preparation of a derivative in which the heat-, light-, and air-sensitive calciferol triene system is protected in such a way that oxidative reactions, or other trans-