Oxycyclopropanes in Organochemical Synthesis. Total Syntheses of (−)-Valeranone and (±)-Grandisol[1]

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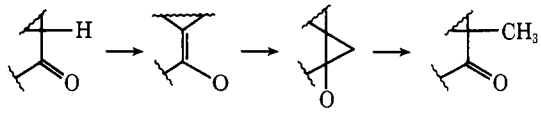
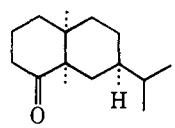
Abstract: A seven-step synthesis of (−)-valeranone from (+)-carvomenthone is presented. It includes the formation of an octalone, containing an α-methoxy-α,β-unsaturated ketone moiety, by Robinson annelation, the stereospecific production of a methoxycyclopropane at a decalin bridgehead, and the acid-induced, quantitative fission of the three-membered ring for the liberation of the angular, α-ketomethyl function of the sesquiterpene. A seven-operation synthesis of (±)-grandisol from 4-methoxy-3,6,6-trimethyl-2,4-cyclohexadienone is described. The reaction scheme includes regiospecific cyclopropanation of the dienone, acid-catalyzed, hydrolytic rearrangement of the product, and five-membered ring opening of the resultant bicyclo[3.2.0]heptanone system.

Some time ago the high-yielding, three-step scheme of transformation of keto compounds into α-methylketo substances by way of oxycyclopropane intermediates (eq A below)



(A)

was shown to be a useful alternative to the classical α-alkylation of keto systems via enolate or enamine intermediates.[4] The new scheme appeared to have a high potential of applicability especially for sterically crowded keto compounds, whose enolate or enamine alkylation might be expected to lead to *O*- or *N*-alkyl products, respectively, in preference to quaternary α-alkylketo compounds. Thus, for example, the introduction of angular methyl groups into polycyclic ketones en route to terpenes or steroids seemed a challenge appropriate for scheme A. As a consequence, valeranone (**1**), a sesquiterpenic ketone



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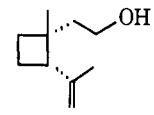

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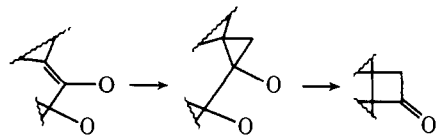
exhibiting the unusual feature of two adjacent quaternary carbon centers each holding an angular methyl group, was chosen as the goal of natural product synthesis for putting the concept to practice.

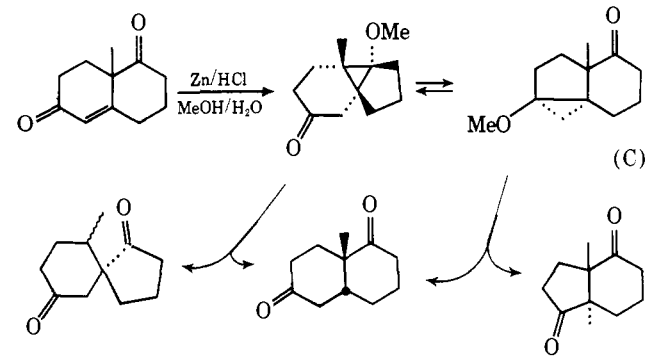
The study of oxycyclopropanes has included α-oxycyclopropylcarbinols, whose facile acid-catalyzed conversion into cyclobutanones,[4-6] a structure change reminiscent of the homo-Favorskii rearrangement,[7] recommended the scheme depicted in eq B for application to natural product synthesis.



(B)

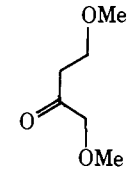
Grandisol (**2**), an unusual cyclobutane-containing, monoterpenic alcohol, was chosen for this purpose.

(−)-Valeranone (1).[8] An early observation of a highly regiospecific protolysis of an oxycyclopropane fused to a perhydroindane nucleus, a transformation which was part of a complex reaction sequence during the Clemmensen reduction of a β-diketone vinylog (eq C, the consequence of the reduction of an octalindione with zinc in methanolic hydrochloric acid),[9] was a good omen for the potential utilization of scheme A for angular methylation. Furthermore, this experience indicated



(C)

that an enol ether incorporated in an isopropylmethyldecalin nucleus capable of being cyclopropanated stereospecifically was needed as an early intermediate in the synthesis of valeranone (**1**). In order to accomplish this initial goal the Robinson annelation reaction was chosen for the construction of the decalin ring system, but an annelating reagent of proper substitution for simultaneous introduction of an enol ether function had to be developed. 1,4-Dimethoxy-2 butanone (**3**)[10] and its



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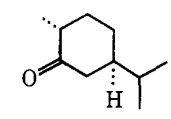

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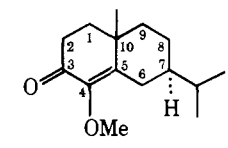

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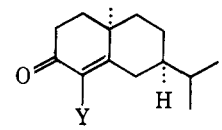
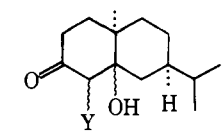


a, Y = OMe
b, Y = H



6 **7**

olefinic counterpart, methoxymethyl vinyl ketone, proved to be excellent annelating agents[11] and thus were available for the task under consideration.

Condensation of ketone **3** with (+)-carvomenthone (**4**) under the influence of ethanolic potassium hydroxide in ether solution[12] yielded a mixture of methoxy enones **5** and **6a** as well as a methoxy ketol of unknown configuration (**7a**). In order to facilitate the differentiation of the conjugated ketones and ascertain the relative configuration of the methyl and isopropyl substituents of the ketol, the latter was demethoxylated by reduction with lithium in ammonia and the resultant ketol (**7b**), a substance which could be prepared also by the hydroxide-induced condensation of (+)-carvomenthone (**4**) with methyl

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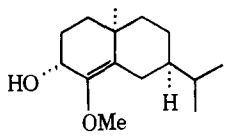
vinyl ketone, dehydrated with acid.[13] The product was shown by spectral means and optical rotatory dispersion measurements to be the enantiomer of an octalone derived from a Robinson annelation of (−)-carvomenthone[14] and hence to possess structure **6b**. This limits the methoxy ketol precursor to the configuration depicted in **7a**. Treatment of the latter with ethanolic potassium hydroxide yielded enone **6a**, thus distinguishing this ketone from its epimer **5**.

Reduction of octalone **6a** with lithium aluminum hydride led to an alcohol to which structure **8** was assigned on the basis of the known, strong predilection of cyclohexenones of type **6b** in the sesqui-, di-, and triterpene as well as steroid fields to yield quasi-equatorial alcohols on hydride reduction. The product was suited ideally for cyclopropanation by the Simmons–Smith procedure,[15] since its enol ether moiety was thus convertible into a methoxycyclopropane and, more importantly, the allylic hydroxy group could be expected to steer the incoming methylene unit cis to it by complexation with the organometallic reagent[16] and hence introduce the proper bridgehead stereochemistry needed for the ultimate goal. Treatment of the enol ether **8** with zinc–copper couple in methylene iodide furnished the tricyclic alcohol **9a**.[17] Jones oxidation of the latter yielded



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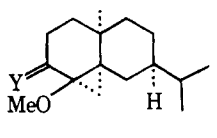
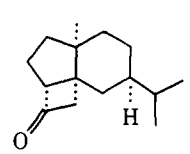


9a, Y = α—OH, β—H
b, Y = O
c, Y = H_2

ketone **9b**,[18] whose Wolff–Kishner reduction gave the tricyclic ether **9c**. Hydrolysis of the methoxycyclopropane by aqueous, methanolic hydrochloric acid afforded natural (−)-valeranone (**1**) in quantitative yield.[19] This completed a seven-step, direct synthesis of the sesquiterpenic ketone.[20]

(±)-Grandisol (2).[21] The cis configuration of the two functionalized side chains of the cyclobutane ring in this monoterpene and the inherent constraint of stable bicyclo[2.2.0]hexanes, bicyclo[3.2.0]heptanes, and bicyclo[4.2.0]octanes to the same steric relationship suggested that the route of synthesis for grandisol (**2**) be based on the fission of a cyclobutane-containing bicycle being a crucial step in the reaction sequence. Furthermore, the latter seemed destined to be a bicyclo[3.2.0]heptane in view of the ease of the rearrangement of α-oxycyclopropylcarbinols into cyclobutanones (eq B), as exemplified by the acid-catalyzed conversions of alcohol **9a** into ketone **10** (see Experimental Section)[22] and **11** into **12**.



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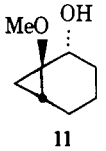

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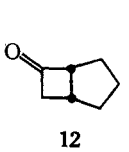

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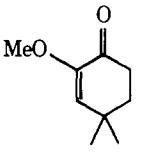
On the assumption of the possibility of the bicycle being assembled with a functional group per ring and that of the cyclobutane moiety being removed preferentially the following organochemical operations were executed.

A recent, four-step reaction sequence (base-induced condensation of isobutyraldehyde with **3**, selenium dioxide oxidation of enone **13**, treatment of dienone **14** with methyllithium, and Collins oxidation of dienol **15**) has made the cyclohexadienone **16** readily available.[23] After many attempts to carry out a Simmons–Smith reaction on this deactivated enol ether, conditions were found for the conversion of **16** into bicyclic ketone **17**. Being an α-oxycyclopropyl ketone vinylog, the latter underwent acid-induced, hydrolytic rearrangement,



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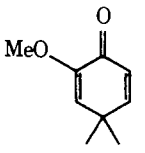

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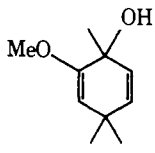

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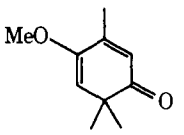

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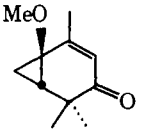

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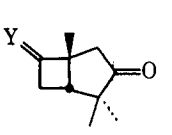
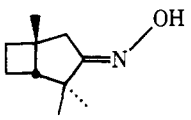


18a, Y = O
b, Y = $S_2(CH_2)_3$
c, Y = H_2

yielding the bicyclo[3.2.0]heptanedione **18a**. Treatment of the diketone with 1,3-propanedithiol and acid, followed by reduction of the resultant thioketal **18b**, produced ketone **18c**, the desired bicycle needed for fragmentation into a grandisol-like skeleton (vide supra).

Oximination of the bicyclo[3.2.0]heptanone **18c** yielded **19**, the solvolysis of whose tosylate in 2,6-lutidine, a sterically demanding base used to optimize deprotonation of one of the methyl groups adjacent to the positive center of the intermediate cation and thus minimize the formation of an isopropylidene cyanide, led to nitrile **20**.[24] Reduction of the latter with



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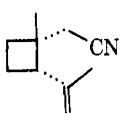

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diisobutylaluminum hydride, hydrolysis of the product, and reduction of the unisolated aldehyde intermediate with lithium aluminum hydride furnished racemic grandisol (**2**).[25,26]

Experimental Section

Melting points were observed on a Reichert micro hotstage and are uncorrected. Infrared and ultraviolet spectra were recorded on Perkin-Elmer 137 and Cary 14 spectrophotometers, respectively. ^1H NMR spectra of deuteriochloroform solutions containing tetramethylsilane as internal standard (δ 0 ppm) were measured on Varian A-60 and HR-220 spectrometers. Optical rotations and rotatory dispersions were run on Rudolph 40 and Jasco ORD/UV-5 polarimeters, respectively. Column chromatography was carried out on alumina from Gebr. Giulini Gmbh. (Ludwigshafen, Germany), 50–200 mesh silica gel from G. F. Smith Chemical Co. (Columbus, Ohio), and Florisil from Matheson Coleman and Bell (Norwood, Ohio). Gas-phase chromatography was performed on Varian Aerograph and Autoprep chromatographs with the use of the following columns: A, ⅛ in. × 10 ft 15% Apiezon L on 60–80 mesh Chromosorb W; B, ⅜ in. × 8 ft 15% Carbowax 20M on 60–80 mesh Chromosorb W; C, ⅛ in. × 10 ft 15% Carbowax 20M on 60–80 mesh Chromosorb W; D, ⅛ in. × 10 ft 10% Carbowax 20M on 60–80 mesh Chromosorb W. Solutions were dried over anhydrous magnesium sulfate and evaporated under vacuum.

5ξ-Hydroxy-7β-isopropyl-10α-methyl-3-decalone (7b). A solution of 3.54 g of methyl vinyl ketone in 25 mL of dry ether was added dropwise over a 35-min period to a stirring solution of 15.80 g of (+)-carvomenthone ($[\alpha]^{18}D$ 26.0° (*c* 2, EtOH)) (**4**) and ethanolic (6 mL) potassium hydroxide (1.10 g) in 80 mL of dry ether under nitrogen at 0 °C. The mixture was stirred for 1.3 h, while warming to room temperature, poured onto ice, and neutralized with concentrated hydrochloric acid. The aqueous layer was extracted with ether and the combined organic solutions were dried and evaporated. Distillation of the residue led to the recovery of 9.05 g of starting ketone (**4**). Chromatography of the residue, 9.14 g, on 550 g of silica gel and elution with hexane up to 9:1 hexane–methylene chloride yielded 1.17 g (13%) of a mixture of enones 4-demethoxy-**5** and **6b**. Elution with 9:1 to 1:1 hexane–methylene chloride gave 2.18 g of a mixture of these enones and ketol and elution with a 1:1 solvent mixture to 100%

methylene chloride furnished 4.02 g (41%) of liquid ketol **7b**: IR (neat) OH 2.80 (s), C=O 5.85 μ (s); ^{1}H NMR δ 0.83 (d, 6, J = 6 Hz, Me_2), 1.18 (s, 3, angular Me), 2.18, 2.80 (AB dd, 2, J = 13 Hz, 4-H_2). Anal. ($C_{14}H_{24}O_2$) C, H.

A solution of 273 mg of ketol **7a** (vide infra) in 25 mL of anhydrous ether was added dropwise over a 10-min period to a solution of 40 mg of lithium in 100 mL of dry liquid ammonia. More lithium, 20 mg, was added to maintain the blue color of the solution and then the ammonia was permitted to evaporate. Water was added and the mixture extracted with ether. The extract was dried and evaporated. Chromatography of the residue, 254 mg, on 10 g of Florisil yielded 189 mg (79%) of liquid ketol **7b**, spectrally identical with the sample above.

7β-Isopropyl-10α-methyl-4-octalin-3-one (6b). A mixture of 3.82 g of ketol **7b**, 0.35 g of *p*-toluenesulfonic acid, and 1.4 g of anhydrous calcium chloride in 150 mL of benzene was refluxed for 1.5 h.[13] It then was filtered and the filtrate washed with saturated sodium bicarbonate and brine solutions, dried, and evaporated. Distillation of the nearly pure enone, 3.19 g (91%), gave partly solid, colorless ketone **6b**: mp 28–28.5 °C; ORD (c 0.30, dioxane, 25 °C) [α]$_{589}$ −45°, [α]$_{370}$ −271°, [α]$_{359}$ −212°, [α]$_{354}$ −238°, [α]$_{344}$ −109°, [α]$_{339}$ −160°, [α]$_{331}$ −81.2°, [α]$_{324}$ −189°, [α]$_{320}$ −177°; IR (neat) C=O 5.99 (s), C=C 6.20 μ (m); ^{1}H NMR δ 0.89 (d, 6, J = 6 Hz, Me_2), 1.26 (s, 3, angular Me), 2.3–2.5 (m, 2, 2-H_2), 5.75 (broad s, 1, olefinic H). Anal. ($C_{14}H_{22}O$) C, H.

5ξ-Hydroxy-7β-isopropyl-4ξ-methoxy-10α-methyl-3-decalone (7a). A solution of 13.20 g of 1,4-dimethoxy-2-butanone (**3**) in 120 mL of dry ether was added dropwise over a 2.3-h period to a stirring solution of 30.80 g of (+)-carvomenthone (**4**) and ethanolic (10 mL) potassium hydroxide (2.4 g) in 120 mL of dry ether under nitrogen at 8 °C. The red mixture was stirred for 3 h, while warming to room temperature, treated with ethereal acetic acid until yellow, and decanted from the red, gummy precipitate. The solution was dried and evaporated and 22.40 g of starting ketone (**4**) recovered by distillation at low temperature. Chromatography of the residue, 13.10 g, on 700 g of alumina, activity IV, and elution with hexane and 9:1 hexane–ether led to 4.50 g of a mixture of enones **5** and **6a** and ketol **7a**. Elution with 1:1 hexane–ether produced 5.00 g (36%) of liquid ketol **7a**: [α]$^{23}_D$ 3.7° (c 1.3, $CHCl_3$); IR (neat) OH 2.81 (s), C=O 5.83 μ (s); ^{1}H NMR δ 0.82 (d, 6, J = 6 Hz, Me_2), 1.25 (s, 3, angular Me), 3.49 (s, 3, OMe), 3.99 (s, 1, OCH). Anal. ($C_{15}H_{26}O_3$) C, H.

7β-Isopropyl-4-methoxy-10α-methyl-4-octalin-3-one (6a). A solution of 5.90 g of ketol **7a** and 3.90 g of potassium hydroxide in 57 mL of ethanol was refluxed under nitrogen for 5 h. The red mixture was treated with ethereal acetic acid until orange and evaporated. Water was added and the stirring mixture extracted with ether. The extract was washed with water, dried, and evaporated. Distillation of the residual oil, 4.35 g, at 0.1 Torr yielded 3.63 g (78%) of liquid enone **6a**: [α]$^{21}_D$ −163° (c 1.0, $CHCl_3$); ORD (c 0.50, dioxane, 25 °C) [α]$_{589}$ −127°, [α]$_{368}$ −138°, [α]$_{360}$ −128°, [α]$_{354}$ −137°, [α]$_{340}$ −66.8°, [α]$_{328}$ 18.3°, [α]$_{326}$ 14.1°, [α]$_{318}$ 50.6°, [α]$_{313}$ 38.0°, [α]$_{308}$ 42.2°, [α]$_{294}$ −4.22°; UV (EtOH) λ$_{max}$ 257 nm (ε 8500); IR (neat) C=O 5.98 (s), C=C 6.23 μ (s); ^{1}H NMR δ 0.88, 0.95 (d, 3 each, J = 6 Hz, Me_2), 1.28 (s, 3, angular Me), 3.60 (s, 3, OMe). Anal. ($C_{15}H_{24}O_2$) C, H.

7β-Isopropyl-4-methoxy-10α-methyl-4-octalin-3α-ol (8). A solution of 1.18 g of enone **6a** in 5 mL of dry ether was added dropwise over a 10-min period to a stirring suspension of 64 mg of lithium aluminum hydride in 10 mL of dry ether and the mixture stirred at room temperature for 3 h. Moist sodium sulfate was added and the mixture shaken vigorously and filtered. Evaporation of the filtrate led to 1.12 g (92%) of viscous, colorless, liquid alcohol **8**: [α$^{24}_D$ 25.7° (c 1.2, $CHCl_3$); IR (neat) OH 2.99 (m), C=C 6.00 μ (w); ^{1}H NMR δ 0.84, 0.95 (d, 3 each, J = 6 Hz, Me_2), 1.14 (s, 3, angular Me), 3.58 (s, 3, OMe), 4.42 (t, 1, J = 7 Hz, OCH). Anal. ($C_{15}H_{26}O_2$) C, H.

7β-Isopropyl-4β-methoxy-10α-methyl-4α,5α-methylene-3α-decalol (9a). A stirring mixture of 1.32 g of zinc–copper couple,[27] 9 mg of iodine, and 6.03 g of methylene iodide in 8 mL of dry ether was refluxed slowly for 45 min. It was kept then at 40 °C and a solution of 1.78 g of alcohol **8** in 5 mL of dry ether added slowly over a 10-min period. The mixture was stirred at 40 °C for 4 h and then cooled. After the addition of 16 mL of saturated ammonium chloride solution the mixture was filtered and the liquid layers were separated. The aqueous solution was extracted with ether and the combined organic solutions were washed with saturated solutions of ammonium chloride, sodium bicarbonate, and sodium chloride, dried, and evaporated. Chromatography of the residual oil, 1.92 g, on 18 g of Florisil yielded 1.70 g (91%) of colorless, liquid alcohol **9a**: [α]$^{21}_D$ −38.9° (c 0.8, $CHCl_3$); IR (neat) OH 2.95 μ (m); ^{1}H NMR δ 0.21, 0.63 (d, 1 each, J = 6 Hz, c-Pr H_2), 0.83 (d, 6, J = 6 Hz, Me_2), 0.91 (s, 3, angular Me), 3.37 (s, 3, OMe). Anal. ($C_{16}H_{28}O_2$) C, H.

7β-Isopropyl-4β-methoxy-10α-methyl-4α,5α-methylene-3-decalone (9b). Jones reagent (2.67 g of chromium trioxide and 2.3 mL of concentrated sulfuric acid diluted to 10 mL with water) was added by titration to a solution of 500 mg of alcohol **9a** in 10 mL of acetone at room temperature and the mixture poured onto ice in 60 mL of ether. Excess sodium carbonate was added, the mixture stirred, and the aqueous layer extracted with ether. The combined organic solutions were washed with saturated brine solution, dried, and evaporated. Chromatography of the residual oil, 420 mg, on 21 g of Florisil yielded 270 mg (54%) of viscous oil which on standing became colorless needles of ketone **9b**: mp 41–42 °C; [α]$^{20}_D$ −39.8° (c 0.8, $CHCl_3$); IR (neat) C=O 5.91 μ (s); ^{1}H NMR δ 0.80, 1.54 (d, 1 each, J = 6 Hz, c-Pr H_2), 0.85 (d, 6, J = 6 Hz, Me_2), 1.12 (s, 3, angular Me), 3.47 (s, 3, OMe). Anal. ($C_{16}H_{26}O_2$) C, H.

7β-Isopropyl-4β-methoxy-10α-methyl-4α,5α-methylenedecalin (9c). A solution of 83 mg of ketone **9b** and 1 mL of 95% hydrazine in 5 mL of diethylene glycol was heated at 120 °C for 1.5 h, then cooled and after the addition of 460 mg of potassium hydroxide pellets refluxed for 4.5 h. The cooled mixture was poured onto ice in 8 mL of concentrated hydrochloric acid, stirred, and extracted with ether. The extract was washed with water, dried, and evaporated, yielding 63 mg (80%) of colorless, liquid ether **9c**. (For analysis a hexane solution was passed through 1 g of Florisil, leading to 40 mg of product.): [α]$^{21}_D$ −55.6° (c 0.8, $CHCl_3$); IR (neat) no OH, C=O, C=C; ^{1}H NMR δ 0.22 (d, 1, J = 6 Hz, c-Pr H), 0.85 (d, 6, J = 6 Hz, Me_2), 0.91 (s, 3, angular Me), 3.24 (s, 3, OMe). Anal. ($C_{16}H_{28}O$) C, H.

(−)-Valeranone (1). A solution of 36 mg of ether **9c** and 3 mL of concentrated hydrochloric acid in 3 mL of methanol was refluxed for 3 h. Water was added and the mixture extracted with ether. The extract was washed with saturated sodium bicarbonate and brine solutions, dried, and evaporated. Chromatography of the residue, 37 mg, on 700 mg of Florisil produced 34 mg (100%) of the natural ketone **1**: [α]$^{20}_D$ −51.9° (c 0.3, $CHCl_3$); IR, ^{1}H NMR spectra, and GC retention time identical with those of an authentic sample.[19]

Cyclobutanone 10. A solution of 138 mg of alcohol **9a** and 1 mL of 6 N hydrochloric acid in 4 mL of methanol was stirred at room temperature for 8 h, diluted with water, and extracted with ether. The extract was washed with saturated sodium bicarbonate and brine solutions and dried. Evaporation yielded 119 mg (99%) of ketone **10**: [α]$^{24}_D$ −81.8° (c 0.9, $CHCl_3$); IR (neat) C=O 5.62 μ (s); ^{1}H NMR δ 0.88, 0.92 (d, 3 each, J = 6 Hz, Me_2), 1.08 (s, 3, angular Me). Anal. ($C_{15}H_{24}O$) C, H.

Alcohol ii.[18,28] A mixture of 720 mg of enone i, prepared by degradation of manool,[29] and 58 mg of lithium aluminum hydride in 45 mL of anhydrous ether was stirred for 4 h, then shaken vigorously with moist sodium sulfate and filtered. Evaporation of the filtrate yielded 730 mg of a gummy alcohol mixture, whose crystallization from ether gave 401 mg (55%) of colorless needles of olefinic alcohol ii: mp 103–105 °C; [α]$^{23}_D$ 8.5° (c 3.3, $CHCl_3$); IR (KBr) OH 2.99 (s), C=C 6.01 μ (w); ^{1}H NMR δ 0.71, 0.82, 0.88 (s, 3 each, Me_3), 1.9–2.3 (m, 3, olefinic CH_2,CH), 4.05 (m, 1, OCH), 5.42 (m, 1, olefinic H). Anal. ($C_{17}H_{28}O$) C, H.

Alcohol iii.[18] A mixture of 325 mg of zinc–copper couple,[27] 3 mg of iodine, and 1.50 g of methylene iodide in 10 mL of anhydrous ether was refluxed for 45 min and 10 mL of tetrahydrofuran added. Upon the further addition of 447 mg of alcohol ii in 10 mL of anhydrous ether the mixture was refluxed for 48 h. A saturated, aqueous ammonium chloride solution, 4 mL, was added, the mixture filtered, and the aqueous layer of the filtrate extracted with ether. The combined organic solutions were washed with saturated ammonium chloride, sodium bicarbonate, and brine solutions, dried, and evaporated. Crystallization of the light yellow, solid residue, 585 mg, from hexane and preparative TLC of the mother liquor on silica gel (elution with chloroform) led to 348 mg (74%) of colorless needles of cyclopropylcarbinol iii: mp 90–90.5 °C; [α]$^{24}_D$ −41.6° (c 0.9, $CHCl_3$); IR (KBr) OH 3.05 (m), 3.11 μ (m); ^{1}H NMR δ 0.25 (t, 1, J = 5 Hz, c-Pr H), 0.42 (m, 1, c-Pr H), 0.87 (s, 9, Me_3), 3.9–4.5 (m, 1, OCH). Anal. ($C_{18}H_{30}O$) C, H.

Ketone iv.[18] Jones reagent (ca. 0.35 mL of a solution of 2.67 g of chromium trioxide, 2.3 mL of sulfuric acid, and enough water to make 10 mL) was added dropwise to a solution of 210 mg of alcohol iii in

6 mL of acetone at −20 °C until an orange tinge was maintained, then stirred for 5 min and poured onto ice and ether. Excess, solid potassium carbonate was added to the stirring mixture and the aqueous solution extracted with ether. The combined organic solutions were washed with saturated brine solution, dried, and evaporated. Crystallization of the residual solid, 206 mg, from ether at −50 °C gave 185 mg (89%) of colorless needles of ketone iv: mp 105–107 °C; $[\alpha]^{24}D$ 13.0° (*c* 0.6, $CHCl_3$); IR (KBr) C=O 5.97 μ (s); ^1H NMR δ 0.85 (s, 3, Me), 0.88 (s, 6, Me_2). Anal. ($C_{18}H_{28}O$) C, H.

1-Methoxy-2,5,5-trimethylbicyclo[4.1.0]hept-2-en-4-one (17). Iodine, two crystals, and after the disappearance of its color 5.00 g of methylene iodide were added to a stirring suspension of 2.00 g of zinc–copper couple[30] in 40 mL of dry ether and the mixture was refluxed under nitrogen for 2 h. A solution of 307 mg of ketone **16**[23] in 5 mL of dry ether was added and the refluxing continued for 20 h. Now 1.06 g of cuprous bromide was added and refluxing maintained for 48 h. The mixture was treated with saturated ammonium chloride solution and decanted and the residue washed with ether. The combined ether solutions were washed with 5% sodium hydroxide and saturated brine solutions, dried, and evaporated. The resultant mixture of starting ketone **16** and desired product (GC column A, 160 °C, 30 mL/min flow: **16,** 2.2 min and **17,** 2.7 min retention times) was resubmitted to the cyclopropanation process and workup. A solution of the crude product and 150 mg of maleic anhydride in 10 mL of dry benzene was kept at 60 °C for 12 h and extracted with 5% sodium hydroxide solution. The extract was washed with ether and the combined organic solutions were washed with saturated brine solution, dried, and evaporated. Chromatography of the residue on silica gel and elution with chloroform gave 287 mg (86%) of liquid ketone **17**: IR (neat) C=O 6.05 (s), C=C 6.29 μ (w); ^1H NMR δ 0.42 (dd, 1, *J* = 6, 3 Hz, c-Pr H), 1.20, 1.25 (s, 3 each, α-CO-Me_2), 1.4–1.6 (m, 2, c-Pr H_2), 2.12 (s, 3, olefinic Me), 3.27 (s, 3, Ome), 5.55 (s, 1, olefinic H). Anal. ($C_{11}H_{16}O_2$) C, H.

2,2,5-Trimethylbicyclo[3.2.0]hepta-3,6-dione (18a). Concentrated hydrochloric acid, 50 mL, was added slowly to a solution of 932 mg of ketone **17** in 70 mL of ether at 0 °C and the mixture then allowed to warm to room temperature and stirred for another 1 h. It was neutralized with potassium hydroxide, while being cooled, and the aqueous layer was extracted with ether. The combined organic solutions were dried and evaporated. Chromatography of the residual oil, 825 mg, on silica gel and elution with ether gave 763 mg (89%) of liquid diketone **18a**: IR (neat) C=O 5.60 (s), 5.75 μ (s); ^1H NMR δ 1.10, 1.17, 1.43 (s, 3 each, Me_3), 2.39 (t, 1, *J* = 8 Hz, H-1), 2.53 (s, 2, 4-CH_2), 2.69, 3.06 (dd, 1 each, *J* = 18, 8 Hz, H_2-7). Anal. ($C_{10}H_{14}O_2$) C, H.

6,6-(1,5-Dithiapentylene)-2,2,5-trimethylbicyclo[3.2.0]heptan-3-one (18b). A mixture of 1.17 g of diketone **18a,** 760 mg of 1,3-propanedithiol, and 635 mg of *p*-toluenesulfonic acid in 35 mL of glacial acetic acid was stirred at room temperature for 6 h. It then was diluted with methylene chloride, extracted with water and saturated brine solution, dried, and evaporated. Chromatography of the residue on silica gel and elution with chloroform and 100:1 chloroform–ether yielded 576 mg of a mixture of dithioketal and undesired monothioketal as well as 1.07 g (60%) of liquid ketone **18b**: IR (neat) C=O 5.74 μ (s); ^1H NMR δ 0.94, 0.97, 1.55 (s, 3 each, Me_3), 1.78 (dd, 1, *J* = 12, 8 Hz, CH), 1.98 (m, 2, H_2-7), 2.41 (d, 1, *J* = 20 Hz, COCH), 2.4–2.9 (m, 6, $(CH_2)_3$), 3.32 (d, 1, *J* = 20 Hz, COCH). Anal. ($C_{13}H_{20}OS_2$) C, H.

A mixture of 576 mg of the dithioketal and unwanted ketothioketal and 14 mL of methyl iodide in 28 mL of water and 140 mL of acetonitrile was kept at 45 °C for 20 h. After evaporation of the volatile, organic substances water was added and the mixture extracted with methylene chloride. The extract was dried and evaporated. Chromatography of the residue, 433 mg, on silica gel and elution with hexane and methylene chloride yielded 276 mg (74%) of dione **18a,** thus increasing the yield of ketoketal **18b** (based on recovered dione) to 77%.

1,4,4-Trimethylbicyclo[3.2.0]heptan-3-one (18c). A mixture of 696 mg of thioketal **18b** and 25 g of Raney nickel in 90 mL of ethanol was stirred at room temperature for 1 h and the solution decanted from the solid and passed through Celite. The nickel and Celite pad were washed exhaustively separately with ether and the combined organic solutions concentrated to a 10-mL volume by distillation through an efficient column. This solution was used without change for the preparation of an oxime (vide infra), but its evaporation and preparative GC of the residue (column B, 175 °C, 160 mL/min flow, 6.5 min retention time) yielded liquid ketone **18c**: IR (neat) C=O 5.74 μ (s); ^1H NMR δ 0.94, 0.97, 1.31 (s, 3 each, Me_3), 1.0–1.3 (m, 2, CH_2), 1.4–2.0 (m, 3, CH_2, CH), 2.30, 2.49 (d, 1 each, *J* = 19 Hz, $COCH_2$). Anal. ($C_{10}H_{16}O$) C, H.

Hydroxylamine hydrochloride, 380 mg, and 380 mg of potassium hydroxide were added to the ethanol solution of ketone **18c**. After refluxing for 2 h the solution was poured into 30 mL of saturated brine solution and extracted with methylene chloride. The extract was dried and evaporated. Crystallization of the residue from aqueous ethanol led to 200 mg (44%) of **18c** oxime (**19**): mp 117–119 °C; ^1H NMR δ 1.05 (s, 6, Me_2), 1.27 (s, 3, Me), 1.4–2.3 (m, 5, $(CH_2)_2$, CH), 2.35, 2.90 (d, 1 each, *J* = 19 Hz, $CNCH_2$).

(*Z*)-1-Cyanomethyl-2-isopropenyl-1-methylcyclobutane (20). A solution of 80 mg of oxime **19** and 191 mg of *p*-toluenesulfonyl chloride in 3 mL of 2,6-lutidine (distilled over barium oxide) was heated under nitrogen at 90 °C for 15 min. It was poured into 0.2 mL of pyridine and 7 mL of 5% sodium hydroxide and extracted with pentane. The extract was washed with water, 5% hydrochloric acid, and 5% sodium hydroxide solutions, dried, and evaporated by fractionation through an efficient distilling column. The residue, 39 mg (55%), consisted of a 7:1 mixture of **20** and its double bond isomer (GC column C, 140 °C, 30 mL/min flow, **20** isomer 3.5 min and **20** 3.9 min retention times), which was separated by preparative GC (column B, 170 °C, 170 mL/min flow); liquid 1-cyanomethyl-2-isopropylidene-1-methylcyclobutane (**20** isomer) (10.0 min retention time); IR (neat) C≡N 4.49 μ (w); ^1H NMR δ 1.34, 1.47, 1.57 (s, 3 each, Me_3), 2.50 (s, 2, CH_2CN)] and liquid nitrile **20** [11.2 min retention time]; IR (neat) C≡N 4.44 (w), C=C 6.07 (w), C=CH_2 11.30 μ (m); ^1H NMR (CCl_4) δ 1.34 (s, 3, Me), 1.65 (s, 3, olefinic Me), 2.00, 2.33 (d, 1 each, *J* = 17 Hz, CH_2CN), 4.60, 4.81 (m, 1 each, olefinic H_2). Anal. ($C_{10}H_{15}N$) C, H, N.

Grandisol (2). A 1.00 M cyclohexane solution of diisobutylaluminum hydride, 0.21 mL, was added to a solution of 28 mg of cyanide **20** in 3 mL of dry pentane at −60 °C and the mixture kept at this temperature for 5 min. It then was allowed to warm to room temperature, kept for 3 h, and treated with 2 mL of saturated ammonium chloride solution. After 20 min of stirring 0.7 mL of a 5% sulfuric acid solution was added, the mixtures were stirred vigorously, and the layers were separated immediately. The aqueous solution was extracted with pentane and the combined organic solutions were dried (Na_2SO_4). GC analysis (column D, 150 °C, 30 mL/min flow) revealed the presence of only one new substance (2.0 min retention time), but no starting nitrile (3.5 min retention time). The dried pentane solution was mixed with an equal volume of anhydrous ether and 8 mg of lithium aluminum hydride added portionwise. The mixture was stirred under nitrogen for 18 h, treated with moist sodium sulfate, stirred, and filtered. GC analysis (column D, 150 °C, 30 mL/min flow) revealed the presence of solely a new substance with 5.6 min retention time. The solution was evaporated by careful fractionation through an efficient distillation column, yielding 20 mg (69%) of liquid alcohol **2**; IR and ^1H NMR spectra and GC retention time identical with those of an authentic sample of grandisol.

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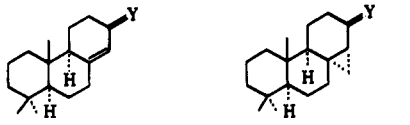

i, Y = O
ii, Y = α—OH, β—H
iii, Y = α—OH, β—H
iv, Y = O

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Oxycyclopropanes in Organochemical Synthesis. Total Syntheses of (±)-α-Cuparenone and (±)-β-Vetivone†

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Abstract: A three-step, cyclopentenone synthesis scheme, involving the cyclopropanation of enol derivatives with diazomethyl ketones, the liberation of γ-dicarbonyl compounds on acid hydrolysis of the resultant β-oxycyclopropyl ketones, and intramolecular aldol condensation of the 1,4-diketo systems, is described. Its application to the synthesis of a prostanoid intermediate (**5**), a spiro[4.5]decenone model (**9**), and an acorane intermediate (**16**) from *n*-butyl vinyl ether, cyclohexanecarboxaldehyde, and 4-methyl-3-cyclohexenecarboxaldehyde, respectively, is illustrated. An eight-step synthesis of (±)-α-cuparenone (**17**) from *p*-cymene is based on this scheme. The latter has been utilized also for a formal synthesis of (±)-β-vetivone (**23**) by an eight-step conversion of 2,6-dimethyl-3-cyclohexenecarboxaldehyde into the spiro[4.5]decenone **24**, previously transformed into the natural ketone.

As a recent, broad study of cyclopropanol derivatives has indicated, their ease of preparation and facility of regiocontrolled fragmentation makes them ideal building blocks in the synthesis of structurally complex substances.[4] The three-step scheme of γ-diketone synthesis outlined in eq A is especially attractive in this connection, since it leads to substances readily transformable into furans in acid and cyclopentenones in base and since furanoid and cyclopentano units are common structure features among naturally occurring substances. The simple syntheses of dihydrojasmone (**1**)[4b] (eq B) and jasmone[5] represent early applications of Scheme A. The present communication illustrates the utilization of β-oxycyclopropyl ketones in the synthesis of cyclopentenones en route to the prostaglandins and acorone as well as to the sesquiterpenic ketones α-cuparenone and β-vetivone.

A Prostaglandin Intermediate.[6] The cyclopentenone ester **5**[7] has served as an intermediate in several prostanoid syntheses. The following three-reaction sequence constitutes an alternate route to this commonly sought substance. The thermal decomposition of diazo ketone **2**, prepared by the consecutive treatments of methyl hydrogen azelate[8] with thionyl

† Dedicated to Professor Robert B. Woodward on the occasion of his 60th birthday.

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