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Synthesis via Chloroketene Adducts. Synthesis of Demethylsesquicarene[1]

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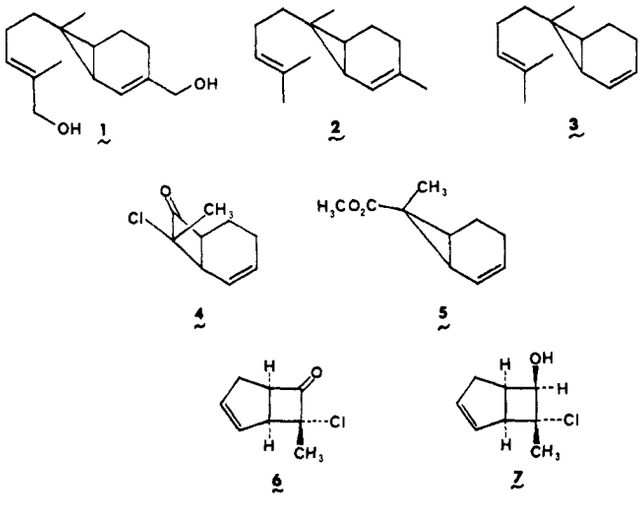
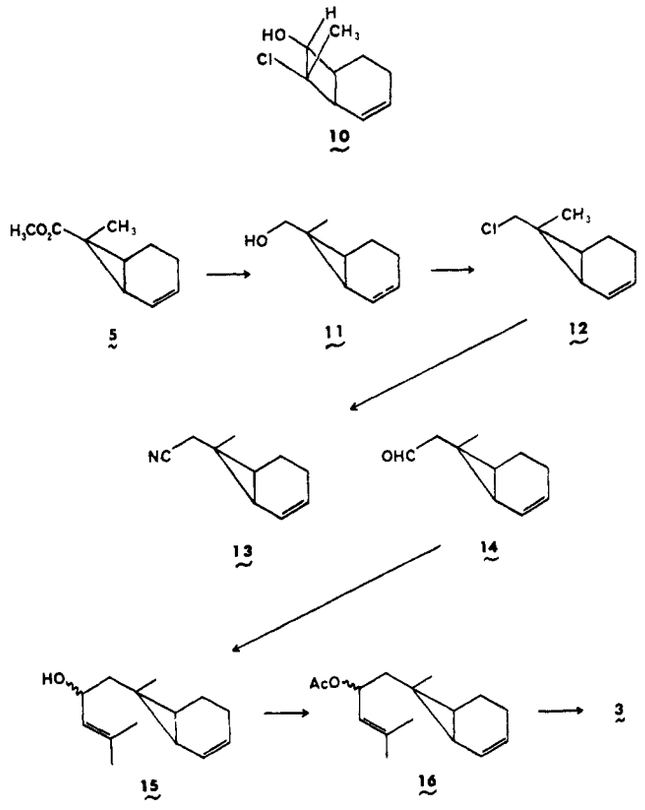
Sirenin (**1**) and sesquicarene (**2**) are novel sesquiterpenes with a carbon skeleton that can be considered an isoprenoid homologue of 2-carene. These compounds have been the object of numerous synthetic studies[2] since the initial reports of their isolation and structure.[3] The major consideration in devising a synthesis of sirenin (**1**) and sesquicarene (**2**) is the introduction of the proper stereochemistry at C-7 in the bicyclo[4.1.0]heptane skeleton. We have utilized the stereospecific ring contraction of chlorocyclobutanone **4** to ester **5** for the total synthesis of demethylsesquicarene (**3**), an analogue of the natural products.

Cyclobutanone ring contractions related to the conversion of **4** → **5** have been well documented.[4] However, at the time of our research, the only examples of this rearrangement with cyclobutanones fused to a six-membered ring had involved cine substitution prior to the ring contraction.[4c] Chlorocyclobutanone **4**[5] was obtained in 47% yield by cycloaddition of methylchloroketene to 1,3-cyclohexadiene followed by column chromatography to remove the *exo*-methyl isomer formed in 10% yield. Our initial attempts to ring contract cyclobutanone **4** following established procedures for ketone **6** were unsuccessful. The facile rearrangement of chloro alcohol **7**[4] led us to investigate this procedure for ring contraction. Reduction of chloro ketone **6** has been effected readily by a number of reducing agents.[4g,h] Chloro ketone **4** could not be reduced cleanly with lithium aluminum hydride, sodium borohydride, lithium tri-*tert*-butoxyaluminum hydride, or sodium diethylaluminum hydride. However, treatment of **4** with aluminum hydride or diisobutylaluminum hydride produced a single alcohol in modest yield (40–50%). Rearrangement of this alcohol using sodium hydroxide in aqueous methanol[4g,h] or sodium nitrate in ethanol[7] gave a cyclobutanone product rather than the desired aldehyde **8**. This result as well as spectral evidence suggests that reduction of ketone **4** gives the exo alcohol **10** rather than the endo alcohol **9** necessary for ring contraction.

The observation that reduction of ketone **4** with charged nucleophiles was unsuccessful but reduction could be effected with the Lewis acids, aluminum hydride, and diisobutyl aluminum hydride led to attempts to rearrange ketone **4** under nonbasic conditions. We found that chlorocyclobutanone **4** could be converted cleanly to ester **5** by refluxing in methanolic silver nitrate for 24 h.[6] There was no evidence that a second isomer was formed in the reaction. The use of the lanthanide shift reagent Eu(fod)$_3$[7] confirmed the exo nature of the carbomethoxy group. Creary has recently reported[8] that this ring contraction can be effected with lithium hydroxide to give the acid corresponding to **5**.

Ester **5** was reduced with lithium aluminum hydride to form alcohol **11** in 97% yield. Alcohol **11** appeared to be stable and could be stored under nitrogen at 0 °C for several weeks. Treatment with carbon tetrachloride and hexamethylphosphorus triamide in ether resulted in formation of chloride **12**.[9] This compound was quite unstable and underwent decomposition upon silica gel chromatography.[10] It generally was not purified but was used directly in the next reaction. Sodium





(or potassium) cyanide in dimethyl sulfoxide at room temperature converted **12** to nitrile **13** in a 30% yield. Although the yield in this step is only modest it did allow formation of a carbon–carbon bond at the C-8 carbon.

Attempts to react isobutenyllithium with nitrile **12** gave a complex mixture of products. Therefore, this nitrile was reduced with diisobutylaluminum hydride and hydrolyzed to give aldehyde **14** in 74% yield.[11] This aldehyde readily formed allylic alcohol **15** in 89% yield upon treatment with isobutenyllithium. Acetylation with acetic anhydride in pyridine formed acetate **16**. Then treatment of **16** with lithium in ethylamine formed demethylsesquicarene (**3**) in 97% yield.[12] It is interesting to note that the vinylcyclopropane portion of the molecule was unaffected by this reduction. The spectral properties of **3** were quite similar to those of sesquicarene. The synthesis of demethylsesquicarene confirms the validity of chloroketene adducts as synthetic intermediates for stereoselective synthesis of the basic sesquicarene skeleton although considerable modification of this scheme may be necessary for application to synthesis of the natural products.

Experimental Section

All compounds prepared in this section are racemic; the prefix *"dl"* is omitted. Infrared spectra were recorded on a Perkin-Elmer Model 237B or Beckmann Instruments Model IR8 spectrophotometer. High-resolution mass spectra were obtained on a CEC Model 21-110 spectrometer under the supervision of Dr. R. Grigsby.

The ^1H NMR spectra were obtained in CCl_4 solution on a Varian Associates T-60 spectrometer. The ^{13}C NMR spectra were obtained in $CDCl_3$ solution in the Fourier transform mode on a JEOL PFT-100 spectrometer system operating at 25.034 MHz (proton resonance frequency 99.539 MHz) and equipped with a Nicolet 1085 data system. All chemical shifts (^1H and ^{13}C) are reported on the δ scale as parts per million downfield from tetramethylsilane (TMS) as internal reference.

Evaporation distillation refers to bulb-to-bulb (Kugelrohr) short-path distillation. The temperatures cited for these distillations are the maximum temperature of the oven during the distillation. "Acid" refers to 10% hydrochloric acid. "Bicarbonate" refers to a saturated aqueous solution of sodium bicarbonate. "Brine" refers to a saturated aqueous solution of sodium chloride. "Concentration" of solvent refers to solvent removal by rotary evaporation at ca. 80 mm. Tetrahydrofuran was distilled from lithium aluminum hydride or the sodium–benzophenone dianion just before use. Anhydrous ether was stored over calcium hydride. Triethylamine was distilled from barium oxide before use. All reactions were performed under a nitrogen atmosphere.

8-*exo*-Chloro-8-*endo*-methyl-*cis*-bicyclo[4.2.0]oct-2-en-7-one (4). The procedure of Brady and Roe[5] was used. A solution of 25.4 g (0.2 mol) of 2-chloropropionyl chloride in 50 mL of pentane was added over a 30-min period to a magnetically stirred solution of 40.0 g (0.5 mol) of 1,3-cyclohexadiene, 20.0 g (0.2 mol) of triethylamine, and 250 mL of pentane. The mixture was stirred for an additional 3 h and then filtered to remove the triethylammonium chloride. After the pentane and remaining cyclohexadiene were removed by rotary evaporation, the cyclohexadiene could be recovered for re-use by fractional distillation. The crude product was chromatographed on 300 g of silica gel (2% ether in hexane). The desired *endo*-methyl isomer was eluted first. Evaporative distillation (100 °C (0.1 mm)) yielded 16.0 g (47%) of adduct **4**: IR (film) 1780 cm^{-1}; ^1H δ 1.5 (s, CH_3), 1.7–2.3 (m, 4 H), 3.2 (dd, C-1 methine), 4.2 (m, C-6 methine), and 6.0 (bs, olefinic protons); ^{13}C NMR δ 205.5 (C-7), 131.6 and 124.2 (C-2 and C-3), 77.1 (C-8), 54.6 (C-6), 40.3 (C-1), 21.3 (C-4 or C-5), 19.3 (C-9), and 18.7 (C-4 or C-5). The *exo*-methyl isomer was obtained in 10% yield (3.5 g) after evaporative distillation: IR (film) 1780 cm^{-1}; ^1H NMR δ 1.9 (s, CH_3), 1.7–2.3 (m, 4 H), 3.0 (dd, C-1 methine), 3.8 (m, C-6 methine), and 5.9 (bs, olefinic protons); ^{13}C NMR δ 206.2 (C-7), 130.0 and 124.7 (C-2 and C-3), 76.1 (C-8), 52.3 (C-6), 37.9 (C-1), 26.3 (C-9), and 21.0 and 19.0 (C-4 and C-5).

7-*endo*-Methyl-7-*exo*-carbomethoxybicyclo[4.1.0]hept-2-ene (5).[7] Silver nitrate (7.5 g, 44.1 mmol) was added to 6.0 g (35.2 mmol) of ketone **4** in 150 mL of methanol, and the solution was refluxed for 24 h. Brine was added, and the mixture was filtered to remove the silver chloride. The oily residue obtained after concentration was dissolved in ether and washed with bicarbonate and brine. The aqueous extracts were washed with ether (2×), and the combined ether solutions were dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed on 150 g of silica gel (2% ether in hexane) to give, after evaporative distillation (110 °C (0.2 mm)), 4.0 g (68%) of ester **5**: IR (film) 1710 cm^{-1}; ^1H NMR δ 1.1 (s, CH_3), 1.3–2.2 (m, 6 H), 3.6 (s, OCH_3), and 5.8 (bs, olefinic protons); ^{13}C NMR δ 175.6 (C-9), 128.9 (C-3), 122.7 (C-2), 51.8 (C-10), 30.8 (C-7), 23.9 and 23.4 (C-1 and C-6), 21.6 (C-4), 15.6 (C-5), and 9.1 (C-8); MS *m/e* (rel intensity) 166 (M^+, 60), 138 (20), 135 (25), 134 (37), 107 (60), 106 (60), 105 (84), 91 (100), 80 (21), 79 (90), 78 (29), 77 (52), 67 (20), 65 (25), 53 (29), 51 (29), 41 (36), 39 (53). Anal.[13] Calcd for $C_{10}H_{14}O_2$: 166.099370. Found: 166.100152 (MS); 4.7 ppm error.

7-Hydroxy-8-*exo*-chloro-8-*endo*-methyl-*cis*-bicyclo[4.2.0]-hept-2-ene (10). To 5 mL of a 25% solution (7.5 mmol) of diisobutylaluminum hydride in 10 mL of toluene was added 1.0 g (5.87 mmol) of ketone **4**. The mixture was stirred under nitrogen at room temperature for 15 min, poured into ether, and washed with acid, water, and brine. The ether solution was dried ($MgSO_4$), filtered, and concentrated. The crude reaction product was chromatographed (silica gel, 2–50% ether in hexane) to give, after evaporative distillation (105 °C (0.1 mm)), 470 mg (46%) of alcohol: IR (film) 3350 cm^{-1}; ^1H NMR δ 1.6 (s, CH_3), 1.0–2.4 (m, 4 H), 2.5–3.0 (m, 2 methine protons and OH), 3.6 (d, J = 7 Hz, CHOH), and 5.8 (bs, olefinic protons). Irradiating the methine region (δ 2.8) caused the doublet to collapse to a singlet. The addition of $Eu(fod)_3$ caused the two methine protons to separate into a doublet for the allylic proton and a lower field multiplet. Irradiation of the proton on the carbon bearing the OH did not affect the doublet but did cause the multiplet to appear as a poor doublet. Irradiation of the multiplet caused both the methine and the –CHO– doublets to collapse into singlets.

7-*endo*-Methyl-7-*exo*-(hydroxymethyl)bicyclo[4.1.0]hept-2-ene (11). To 4.0 g of ester **5** (24 mmol) in 150 mL of tetrahydrofuran was added an excess of lithium aluminum hydride. After 2 h, excess hydride was destroyed by the addition of ethanol. The mixture was poured into ether and washed with saturated ammonium chloride solution until the aluminum salts were removed, and then the ether solution was washed with bicarbonate and brine. The aqueous solutions were washed with ether (2×). The combined ether solutions were dried ($MgSO_4$), filtered, and concentrated. Evaporative distillation (110 °C (0.2 mm)) yielded 3.2 g (97%) of alcohol **11**: IR (film) 3300 cm^{-1}; ^1H NMR δ 1.0 (s, CH_3), 0.9–1.3 (m, 2 methine protons), 1.4–2.2 (m, 4 H), 3.0 (s, OH), 3.3 (s, CH_2OH), and 5.7 (bs, olefinic protons); ^{13}C NMR δ 126.8 (C-3), 124.8 (C-2), 72.6 (C-9), 30.9 (C-7), 22.3 (C-4), 19.3 and 18.6 (C-1 and C-6), 16.5 (C-5), and 10.9 (C-8).

7-*endo*-Methyl-7-*exo*-(chloromethyl)bicyclo[4.1.0]hept-2-ene (12).[10] A solution of 8.1 g (50 mmol) of hexamethylphosphorus triamide in 50 mL of ether was added over a 30-min period to 3.1 g (22.5 mmol) of alcohol **11** in 100 mL of ether and 10 mL of carbon tetrachloride at 0 °C. The solution was stirred overnight and then washed with water (4×) and brine. The ether solution was dried ($MgSO_4$), filtered, and concentrated. This material was used immediately in the next reaction: IR (film) no OH; ^1H NMR δ 3.4 (s, CH_2Cl).

7-*endo*-Methyl-7-*exo*-(cyanomethyl)bicyclo[4.1.0]hept-2-ene (13). Crude chloride **12** from the previous reaction was added to a solution of 5 g of sodium cyanide in 100 mL of dimethyl sulfoxide. This solution was stirred for 10 h, poured into ether, and washed with water (3×) and brine. The aqueous extracts were washed with ether (3×), and the combined ether extracts were dried ($MgSO_4$), filtered, and concentrated. The crude material was chromatographed (silica gel, ether/hexane) and evaporatively distilled (100 °C (0.15 mm)) to yield 1.0 g (30% from **11**) of nitrile **13**: IR (film) 2230 cm^{-1}; ^1H NMR δ 1.1 (s, CH_3), 1.0–1.3 (m, 2 methine protons), 1.4–2.3 (m, 4 H), 2.3 (s, CH_2CN), and 5.8 (bs, olefinic protons); ^{13}C NMR δ 127.6 (C-3), 123.8 (C-2), 118.4 (C-10), 29.8 (C-9), 24.5 (C-7), 21.8 (C-4), 21.1 and 20.4 (C-1 and C-6), 16.1 (C-5), and 13.1 (C-8); MS *m/e* (rel intensity) 147 (M^+, 4), 146 (8), 132 (17), 107 (67), 106 (26), 105 (33), 91 (70), 79 (100), 78 (22), 77 (45), 53 (26), 51 (33), 41 (39), 39 (67). Anal.[13] Calcd for $C_{10}H_{12}N$ ($M^+ - 1$, peak at 147 too weak for measurement): 146.096799. Found: 146.09670 (MS); 3.2 ppm error.

7-*endo*-Methyl-7-*exo*-(formylmethyl)[4.1.0]hept-2-ene (14).[11] Diisobutylaluminum hydride (12 mL of a 20% solution in hexane) was added to 1.0 g (6.8 mmol) of nitrile **13** in 50 mL of hexane at −78 °C. This mixture was stirred for 0.5 h, poured into ether, and washed with dilute sulfuric acid until the aluminum salts were removed. The ether was washed with bicarbonate and brine, dried ($MgSO_4$), filtered, and concentrated. The resultant oil was evaporatively distilled (110 °C (0.2 mm)) to yield 750 mg (74%) of aldehyde **14**: IR (film) 2700 and 1720 cm^{-1}; ^1H NMR δ 1.0 (s, CH_3), 0.9–1.3 (m, 2 methine protons), 1.3–2.2 (m, 4 H), 2.2 (d, J = 4 Hz, CH_2CHO), 5.9 (bs, olefinic protons), and 9.7 (t, J = 4 Hz, CHO); ^{13}C NMR δ 202.6 (C-10), 127.1 (C-3), 124.4

(C-2), 55.9 (C-9), 23.8 (C-7), 22.0 (C-4), 21.0 and 20.3 (C-1 and C-6), 16.4 (C-5), and 13.4 (C-8).

7-*endo*-Methyl-7-*exo*-(2-hydroxy-4-methyl-3-pentenyl)bicyclo[4.1.0]hept-2-ene (15). An ether solution of isobutenyllithium (ca. 20 mmol, prepared from isobutenyl bromide and lithium wire) was added to 750 mg (5.0 mmol) of aldehyde **14** in 10 ml of ether at 0 °C. This mixture was stirred for 6 h and then poured into ether. The ether solution was washed with saturated ammonium chloride solution, bicarbonate, and brine. The ether was dried ($MgSO_4$), filtered, and concentrated. The resulting oil was chromatographed on a short silica gel column (ether/hexane) to yield 920 mg (89%) of alcohol **15**: IR (film) 3350 cm^{-1}; ^1H NMR δ 1.6 (bs, 2 olefinic methyls), 4.5 (m, CHOH), 5.1 (broad doublet, J = 9 Hz, C-1 vinyl proton), and 5.8 (bs, ring olefinic protons); ^{13}C NMR δ 133.8 (C-12), 128.6 (C-3), 126.3 (C-11), 125.2 (C-2), 67.5 (C-10), 50.1 (C-9), 25.9 (C-7 and C-13), 22.2 (C-4), 21.6 and 20.8 (C-1 and C-6), 18.2 (C-14), 16.5 (C-5), and 12.9 (C-8).

7-*endo*-Methyl-7-*exo*-(2-acetoxy-4-methyl-3-pentenyl)bicyclo[4.1.0]hept-2-ene (16). A solution of 540 mg (2.62 mmol) of alcohol **15**, 2 mL of pyridine, and 10 mL of acetic anhydride was refluxed for 3 h. This solution was poured into ether and washed several times with water, bicarbonate, and brine. The aqueous extracts were washed with ether and the combined ether extracts were dried ($MgSO_4$), filtered, and concentrated. The residue was evaporatively distilled (120 °C (0.1 mm)) to yield 550 mg (85%) of acetate **16**: IR (film) 1725 cm^{-1}, no OH; ^1H NMR δ 2.0 (s, O_2CCH_3).

Demethylsesquicarene (3).[12] Acetate **16** (540 mg, 2.18 mmol) was added to 25 mL of ethylamine (distilled from a small piece of sodium) and 60 mg (8.6 mg-atoms) of lithium. This solution was stirred until the lithium had completely reacted and then ammonium chloride was added. The solution was poured into ether and washed with water (3×), acid (2×), bicarbonate, and brine. The ether solution was dried ($MgSO_4$), filtered, and concentrated. The residual oil was evaporatively distilled to yield 400 mg (97%) of product: IR (film) 3040, 1640, 1450, and 1375 cm^{-1}; ^1H NMR δ 0.9 (s, CH_3), 0.7–2.2 (m), 1.60 and 1.65 (s, two olefinic methyls), 5.1 (t, J = 7 Hz, 1 H), and 5.7 ppm (bs, olefinic protons on ring); ^{13}C NMR δ 130.9 (C-12), 127.1 (C-3), 125.8 (C-11), 124.8 (C-2), 43.1 (C-9), 25.7, 22.3, 22.1 21.3, 21.0, 17.6, 16.9, 16.6, and 12.6; MS m/e (rel intensity) 190 (M^+, 7), 121 (19), 107 (55), 105 (50), 93 (33), 91 (38), 82 (21), 81 (21), 80 (19), 79 (67), 77 (26), 69 (60), 67 (29), 55 (43), 53 (24), 41 (100), 39 (33). Anal.[13] Calcd for $C_{14}H_{22}$: 190.172150. Found: 190.171598 (MS); 2.9 ppm error.

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Registry No.—**3**, 63764-90-9; **4**, 63813-94-5; **5**, 63813-95-6; **10**, 63764-91-0; **11**, 63764-92-1; **12**, 63764-93-2; **13**, 63764-94-3; **14**, 63764-95-4; **15**, 63764-96-5; **16**, 63764-97-6; 8-chloro-8-*exo*-methyl-*cis*-bicyclo[4.2.0]oct-2-ene-7-one, 63813-96-7; isobutenyllithium, 29917-94-0.

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Pyridopyrimidines. 8. A Novel Ring Opening during the Acylation of 6-Amino-1,3-dimethyluracil

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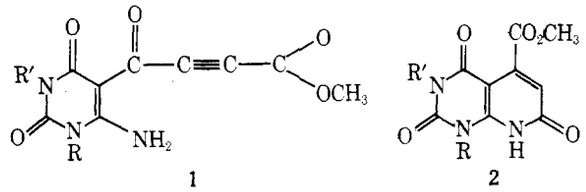
The use of dimethyl acetylenedicarboxylate (DMAD) in the synthesis of pyrido[2,3-*d*]pyrimidines has been the subject of several recent papers.[1-4] During the course of these investigations, it was found that the reaction of 1-alkyl-6-aminouracil derivatives with DMAD under aprotic conditions gave rise to 5-(3-carbomethoxy-2-propynoyl)uracils (**1**).[4] When the same reaction was carried out in a protic solvent (water, methanol), on the other hand, the pyridopyrimidine (**2**) was formed.[1-3]



1 **2**

a, R = R′ = CH_3
b, R = CH_3; R′ = H

In an attempt to gain additional insight into the mechanism of the formation of ketones having the general structure **1**, the reaction of 1,3-dimethyl-6-aminouracil (**3**) with DMAD was followed by ^1H NMR spectroscopy using $(CD_3)_2SO$ as solvent. Spectra were obtained at various time intervals and revealed the disappearance of **3** and the ultimate formation of **1a**. However, a number of additional peaks appeared in the spectrum such that, about 1 h after the initiation of the reaction, the spectrum was a composite of all the peaks (and only the peaks) seen in Figure 1a–c. After 6 h the spectrum (Figure 1c) corresponded to that of the propynoyl adduct **1a**.

The most striking feature of the composite spectrum was the disappearance of one *N*-methyl resonance at δ 3.27 and its replacement by a doublet at δ 2.60. Addition of a small amount of D_2O to the solution caused an immediate collapse of the δ 2.60 doublet to a singlet with the concomitant disap-