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Use of the Ketal Claisen Rearrangement for the Synthesis of Cyclic Sesquiterpenes Containing Quaternary Centers. A Formal Synthesis of Cuparene.

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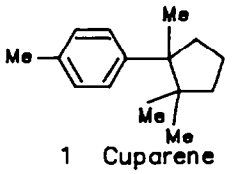
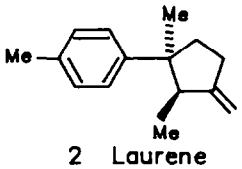
Abstract - We have shown that the ketal based Claisen rearrangement can be useful for generating vicinal quaternary and tertiary-quaternary centers by suitable substitution on the reacting 2-cyclohexenols and cycloalkanone ketal. A rapid and efficient method for preparing hindered cycloalkanone ketals in very pure form is presented, as well as a useful modification for synthesizing the required 2-cyclohexenols from alkyl anisoles with a minimum number of undesired side products.

In considering synthetic routes to the natural products cuparene (**1**), laurene (**2**), bazzanene (**3a**), and trichodiene (**3b**) which would be suitable for the preparation of chiral materials, we were attracted by a reaction sequence that employs a ketal-based modification of the Claisen rearrangement. Although many of the previously reported racemic syntheses of the above mentioned materials[3-5] employed the Claisen rearrangement[6-8] as the key step,these routes proceed via intermediate allyl vinyl ethers which do not contain asymmetric centers, and thus do not allow for stereochemical control of the quaternary carbon atom(s).

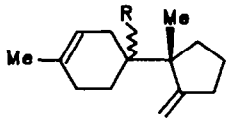
Herein we wish to report the results of using the reaction of an unsymmetrical cyclic ketal with both substituted and unsubstituted 2-cyclohexenols for the preparation of intermediates that have been converted to cuparene (**1**) and laurene (**2**) and could, in principle, be transformed into bazzanene (**3a**) and/or trichodiene (**3b**). The unique molecular framework of these types of compounds together with the central role of trichodiene (**3b**) in trichothecene biosynthesis makes a potentially chiral route to these substrates highly desirable. The additional challenge of introducing two vicinally disposed quaternary centers[9] in bazzanene (**3a**) and trichodiene (**3b**) via the ketal Claisen technology is also present.



1 Cuparene



2 Laurene



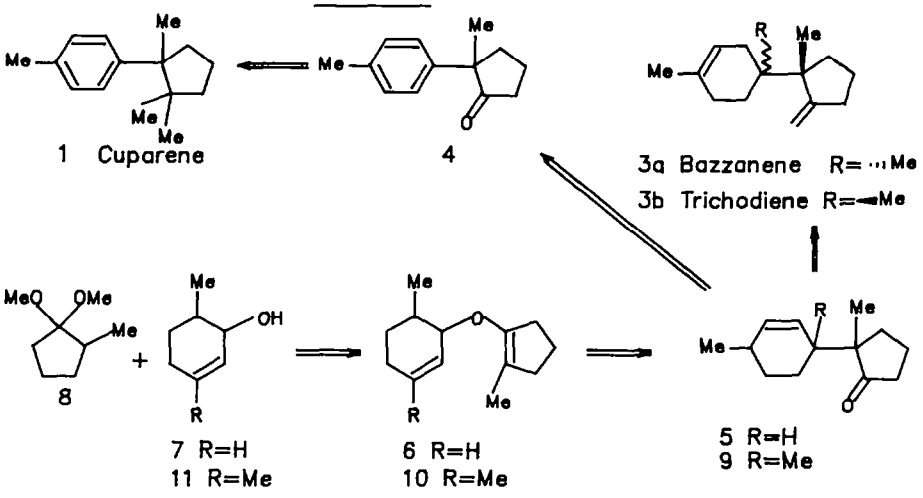
3a Bazzanene R= ···Me

3b Trichodiene R=—Me

The construction of the requisite ring system present in each of these molecules could be derived in a rapid and facile manner by the ketal Claisen rearrangement. The general retrosynthetic plan for the synthesis is shown in **SCHEME I.** The ketone **4** is a known intermediate that has been converted into both cuparene (**1**)[3h] and laurene (**2**).[4c] This material would be derived by the aromatization of the γ,δ-enone **5**, which in turn is the product of Claisen rearrangement of allyl vinyl ether **6**. Compound **6** is to be prepared in situ by the condensation of allylic alcohol **7** and 2-methylcyclopentanone dimethyl ketal (**8**). In a similar fashion, by replacing R=H with R=Me, olefin **9** could provide an entry into the bazzanene (**3a**)-trichodiene (**3b**) family through double bond isomerization and ketone olefination. This path leads back through the Claisen rearrangement of allyl vinyl ether **10**, which is the analogous product of in situ coupling of allylic alcohol **11** with the same ketal **8**.

We have previously found in cases where the ketal portions are part of unsymmetrical cyclic systems,[10] that rearrangement occurs in vast predominance, if not exclusively, to the more substituted carbon. Although no examples were found where the double bond counterparts of the allyl vinyl ether system were both endocyclic and in different rings (eg. see **SCHEME I**), it seems likely from the studies by Daub and coworkers[11] that the presence of substituents on both the ketal and the allylic alcohol pieces

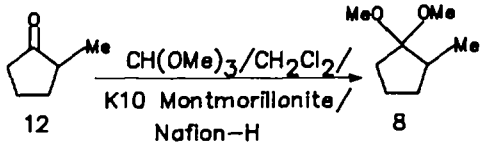
SCHEME I



would retard the rate of the rearrangement.[12] Thus, while the proposed reaction sequence shown in **SCHEME I** appears straightforward, there were sufficient uncertainties to warrant the preliminary synthesis of a cyclic ketone that had previously been converted to cuparene (**1**)[3h] and laurene (**2**).[4c]

A common ingredient necessary for the synthetic work in both this series and others utilizing this approach is the need for an improved synthesis of 2-methylcyclopentanone dimethyl ketal (**8**) and related dimethyl ketals. Attempts to prepare this compound by the standard published methods of ketal formation

SCHEME II

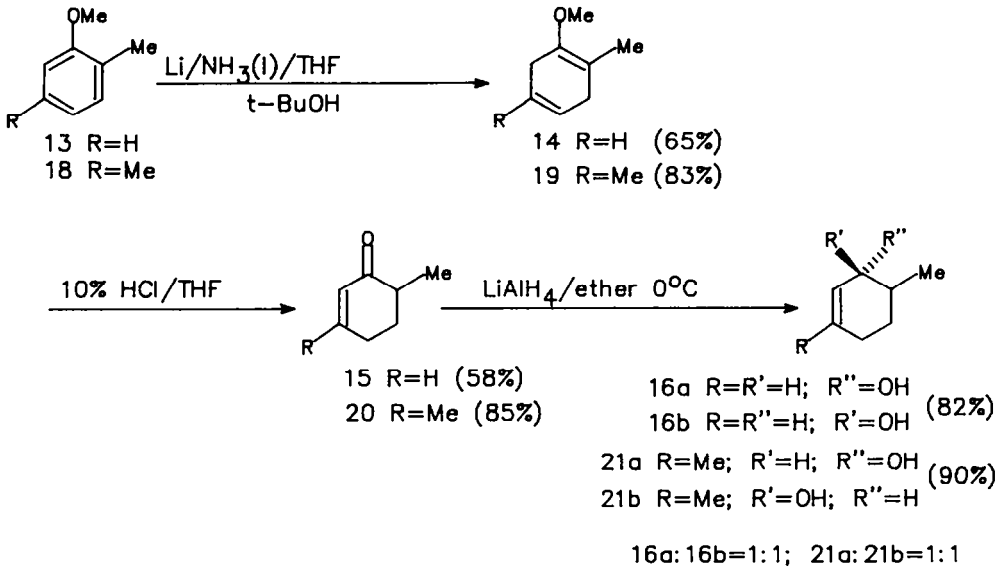


(eg. 2,2-dimethoxypropane/H^+ or $CH(OMe)_3/H^+$) always yielded ketal **8** contaminated with substantial amounts (>20%) starting ketone (**12**) even after a careful fractional distillation, or a very low yield (<20%) of the ketal and significant amounts of polymeric materials. However, we found that treatment of 2-methylcyclopentanone (**12**) with $CH(OMe)_3$/methylene chloride and a 10:1 slurried mixture of K-10 Montmorillonite clay:Nafion-H (**SCHEME II**) for a short time, followed by filtration and distillation afforded the desired 2-methylcyclopentanone dimethyl ketal (**8**) in very pure form in 67% yield. This has proven to be a much superior method of synthesizing this compound. It is also very interesting to note that the use of either the K-10 clay[13] or the Nafion-H[14] alone as the ketalization catalyst gave either incomplete reaction or low yields of the desired ketal **8**.[15]

The allylic alcohols were synthesized in a highly efficient manner as shown in **SCHEME III**, by a modification of the procedure of Stork and White.[16] Birch type reduction (Li/NH_3/THF/t-butanol) of 2-methylanisole (**13**) afforded the dihydroanisole derivative **14** in 65% yield after distillation. In our procedures, we noticed no overreduction problem as previously reported.[17] This is presumably due to the high cosolvent (tetrahydrofuran) dilution in our reaction. This modified procedure eliminated the several extra steps that were previously essential for the complete separation of overreduced products from the desired ones. Treatment of **14** with 10%(aq) HCl in tetrahydrofuran caused enol ether hydrolysis and concommittant olefin isomerization to give the enone **15** in 58% yield after distillation. Subsequent reduction of the enone **15** with lithium aluminum hydride in ether produced a mixture of allylic alcohols **16a & b** in ca. a 1:1 ratio (82%).

This general method was also employed to synthesize the allylic alcohol precursors for the bazzanene (**3a**) and trichodiene (**3b**) probe experiments. As shown in **SCHEME I**, an additional methyl group

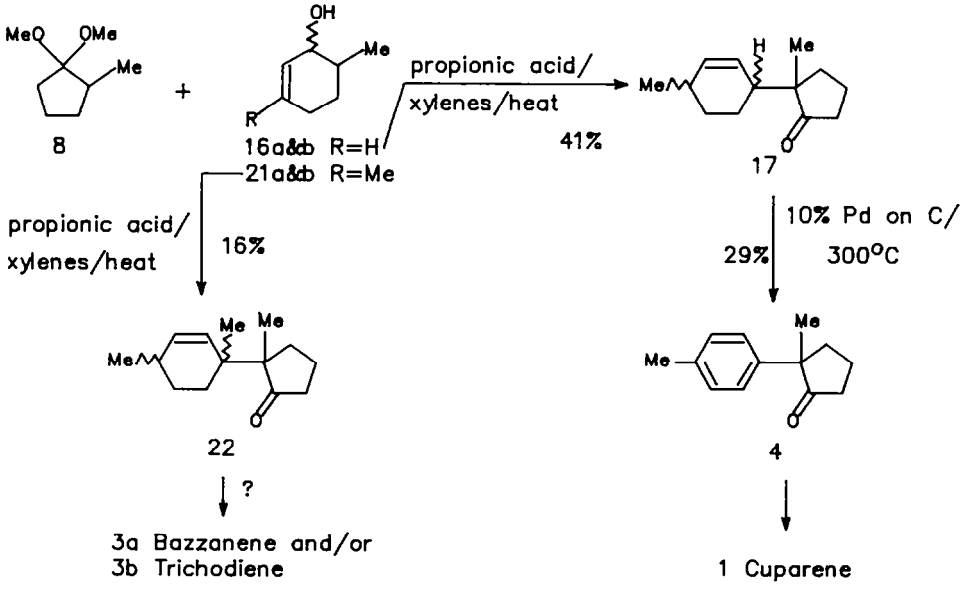
SCHEME III



would be required on the aromatic ring precursor. Thus, Birch type reduction (Li/NH_3/THF/t-butanol) of 2,5-dimethylanisole (**18**) afforded an 83% yield of cyclohexadiene **19**, which was subsequently hydrolyzed and isomerized in one pot (10% HCl(aq)/THF) to the conjugated cyclohexenone **20** (85%). Treatment of enone **20** with $LiAlH_4$/ether/0°C gave allylic alcohols **21a & b** (90% yield) (as approximately a 1:1 mixture of diastereomers by 250MHz 1H NMR analysis) in a 64% overall yield from 2,5-dimethylanisole (**18**).

The ketal Claisen rearrangement sequence was carried out as shown in **SCHEME IV.** In these preliminary experiments, the allylic alcohol mixtures were not separated prior to the rearrangement. The reaction of ketal **8** with allylic alcohols **16a & b** in refluxing xylenes containing a catalytic amount of propionic acid produced the desired γ,δ-enone **17** in 41% yield. Aromatization of this system occurred upon treatment of **17** with 10% Pd on C (sealed tube) to afford the aryl ketone **4** in 29% yield. This material was shown to spectroscopically identical to the compound that has previously been converted into cuparene

SCHEME IV



(1) in one step by Reetz and coworkers,[3h] and into laurene (2) in three steps by Taber and coworkers.[4c] This sequence thereby constitutes a formal synthesis of these natural products in racemic form.

Having demonstrated the efficacy of using this ketal based Claisen rearrangement for building a system with neighboring quaternary and tertiary carbon centers, we examined the possibility of employing this reaction for the synthesis of bazzanene (**3a**)-trichodiene (**3b**), in which two vicinal quaternary centers are present. Therefore, in a similar fashion, the mixture of isomeric alcohols **21a & b** was reacted with 2-methylcyclopentanone dimethyl ketal (**8**) and a catalytic amount of propionic acid to afford a 16% yield of of keto-olefin **22**. This reaction requires that the olefinic termini of the generated allyl vinyl ether both be fully substituted and part of cyclic systems, thus adding more steric congestion in the transition state than in **6**. The relatively low yield of the resulting keto-olefin **22** is probably an indication of this congestion. However, the previous reactions have served well to demonstrate that the ketal Claisen reaction can be used to generate two vicinally disposed hindered carbon atoms in the product,[18] and that the reaction is efficient overall in terms of gross structure, ie. compound **22** contains fourteen of the necessary fifteen carbon atoms found in bazzanene (**3a**) and trichodiene (**3b**). It is also apparent that it is now necessary to focus the synthetic efforts on increasing yields. Nevertheless, these results now make it possible, in principle, to use this rearrangement to try to control the absolute stereochemistry of the quaternary centers and to construct ring systems of this type in few steps.

EXPERIMENTAL

Proton NMR spectra were recorded on either a Varian EM-360A, Varian XL-100 or IBM WP-200 spectrometer using tetramethylsilane (TMS) as an internal standard. Infrared spectra were recorded on a Perkin-Elmer 281 spectrophotometer utilizing the polystyrene 1601.8 cm^{-1} band as the reference. Mass spectra were recorded on either a Bell and Howell 21-492 (70 eV), a Hitachi RMU6E or a VG 7070E spectrometer.

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Elemental analyses were carried out by Dr. Franz Kasler of the University of Maryland.

Flash chromatography refers to the method of Still and co-workers,[19] utilizing E. Merck silica gel 60 (230-400 mesh). Column chromatography (gravity) was carried out using Baker reagent grade silica gel (60-200 mesh). Thin layer chromatography was performed on E. Merck glass supported silica gel 60 (F-254; 0.25mm) plates. Product visualization was done with either vanillan spray (heat), iodine or short wave ultraviolet light as appropriate. Solvent concentrations are given in percent by volume.

Ethyl acetate, hexanes and Skellysolve-F were all distilled prior to use. Benzene, xylenes and methylene chloride were distilled from calcium hydride. Tetrahydrofuran (THF) and ether were distilled from sodium/benzophenone prior to use.

1,1-Dimethoxy-2-methylcyclopentane (8). A mixture of K-10 Montmorillonite clay (Fluka) (10.00 g), Nafion-H (1.00 g), trimethylorthoformate (21.62 g, 0.204 mol) and methylene chloride (95 mL) was stirred at room temperature under a nitrogen atmosphere for 15 min. At this time, a solution of 10.00 g (0.102 mol) of 2-methylcyclopentanone in 5 mL of methylene chloride was added all at once. The mixture was stirred at room temperature for 13 min, then filtered. The filtrate was washed with saturated aq. sodium bicarbonate(50 mL) and water (100 mL). The aqueous layers were backwashed with 25 mL of methylene chloride. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to a clear yellow liquid. The crude ketal was purified by distillation (bp 51-54°C @ 21 mm Hg) to afford 10.09 g (67%) of product as a water white liquid. NMR ($CDCl_3$, 60 MHz) d 0.93 (d, J=6Hz, 3H), 1.10-2.30 (m, 7H), 3.17 (s, 3H), 3.22 (s, 3H) ppm; IR (neat) 2960, 2840, 1455, 1113, 1050 cm^{-1}; Anal. Calcd for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.75; H, 11.40.

1-Methoxy-2-methyl-1,4-cyclohexadiene (14). A flask containing 80 mL of anhydrous ammonia, 80 mL of tetrahydrofuran and 10 mL of t-butanol was stirred rapidly as 1.14 g (0.16 mol) of lithium wire (0.8% Na) was added. The mixture was stirred for 20 min, using a dry ice condenser to maintain the ammonia in the reaction. At this time a solution of 5.00 g (0.04 mol) of 2-methylanisole (**13**) in 2 mL of tetrahydrofuran was added. After 25 min, an additional 5 mL of t-butanol was added. The mixture was stirred until decolorization occurred (ca. 1 h 40 min) and 100 mL of water was cautiously added. The ammonia was allowed to evaporate. The solution was saturated with sodium chloride and extracted with 3 x 100 mL of ether. The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo to a yellow oil. The product was purified by distillation using a short path apparatus (bp 54-56°C @ 13 mm Hg) to give 3.30 g (65%) of the desired diene **14**. NMR ($CDCl_3$, 60 MHz) d 1.60 (s, 3H), 2.70 (br s, 4H), 3.50 (s, 3H), 5.60 (br s, 3H) ppm; IR (neat) 3040, 3000, 2930, 1710, 1150 cm^{-1}; Anal. Calcd for $C_8H_{12}O$: C, 77.38; H, 9.74. Found: C, 77.09; H, 9.75.

6-Methyl-2-cyclohexenone (15). A solution of 0.70 g (5.65 mmol) of enol ether **14** in 4.5 mL of tetrahydrofuran was treated with 0.5 mL of conc. HCl. The reaction mixture was stirred at room temperature for 45 min, then cooled to 0°C and carefully neutralized with saturated sodium bicarbonate. The tetrahydrofuran was evaporated in vacuo and the aqueous extracted with 2 x 10 mL of methylene chloride. The combined methylene chloride layers were dried over anhydrous sodium sulfate and concentrated in vacuo to a yellow oil. Purification by Kugelrohr distillation afforded enone **15** (0.36 g, 58%) as a colorless liquid, bp 66-75 °C @ 24 mm Hg (lit. ref. 16; bp 74-75°C @ 24 mm Hg) NMR ($CDCl_3$, 60 MHz) d 1.13 (d, J=8Hz, 3H), 1.50-2.67 (m, 5H), 5.80-6.07 (m, 1H), 6.73-7.10 (m, 1H) ppm; IR (neat) 2975, 2940, 2880, 1730, 1390 cm^{-1}.

6-Methyl-2-cyclohexen-1-ol (16a&b). A solution of enone **15** (1.22 g, 0.011 mol) in 5 mL of anhydrous ether was

added dropwise to a cold (0°C) stirred suspension of 0.42 g (0.011 mol) of $LiAlH_4$ in 20 mL of anhydrous ether. After the addition was complete, the solution was stirred for 10 min, then carefully quenched with ca. 4 mL of saturated sodium sulfate solution. Anhydrous magnesium sulfate (3 g) was added and the reaction mixture was stirred for an additional 30 min, then filtered and the volatiles concentrated in vacuo to a light yellow oil. This material was purified by Kugelrohr distillation (80°C @ 28 mm Hg) to afford 1.02 g (82%) of a 1:1 mixture (by NMR analysis) of alcohols **16a&b**. NMR ($CDCl_3$, 200 MHz) d 0.98 -1.04 (m of two overlapping doublets, 3H total), 1.21-2.09 (m, 6H), 3.74-3.95 (m containing d, J=6.7 Hz at 3.76 and br s at 3.95, 1H total), 5.48-5.91 (m, 2H) ppm; IR (neat) 3340(broad), 3040, 2940, 1455, 1055 cm^{-1}; m/e 112 (M^+).

2-(4-Methyl-2-cyclohexen-1-yl)-2-methylcyclopentanone (17). A solution of allylic alcohols **16a&b** (0.165 g, 1.47 mmol), ketal **8** (0.576 g, 4.00 mmol), and propionic acid (3 drops) in 3.00 mL of xylenes was heated at reflux under a nitrogen atmosphere for 10 d. A short path distillation head was added and the xylenes and other low boiling materials were removed at reduced pressure (ca. 25 mm Hg). The reddish-brown residue was purified by flash chromatography by eluting with hexanes, followed by 0.5% ether in hexanes to afford 117 mg (41%) of ketone **17** as a colorless oil. R_f=0.40 (4:1 hexanes:ether); NMR ($CDCl_3$, 200 MHz) d 0.95-1.03 (m containing 3H s at 1.00, 6H), 1.07-2.70 (m, 12H), 5.33 (m, 2H) ppm; IR (neat) 3020, 2960, 2935, 2880, 1735, 1455 cm^{-1}; m/e 192 (M^+).

2-Methyl-2-(4-methylphenyl)cyclopentanone (4). Ketone **17** (48 mg, 0.25 mmol) was put in a glass tube with 95 mg of 10% palladium on carbon and the tube was sealed. The tube was immersed in a heating bath held at 300°C and held at that temperature for 50 min. The tube was cooled and opened, the contents taken up in anhydrous ether and filtered through a small pad of celite. The solvent was removed in vacuo leaving a light yellow oil. The crude product was purified by column chromatography using an 8 x 0.5 cm bed of silica and elution with 5 mL of Skellysolve-F followed by 4:1 Skellysolve-F:ether. This procedure afforded 14 mg (29%) of aryl ketone **4**. The spectroscopic data were identical to that reported by McMurry.[4b] NMR ($CDCl_3$, 200 MHz) d 1.37 (s, 3H), 1.93-2.53 (m containing a 3H s at 2.32, 9H), 7.13-7.26 (m, 4H) ppm; IR (neat) 2960, 2930, 1740 cm^{-1}; m/e 188 (M^+).

2-Methoxy-1,4-dimethyl-1,4-cyclohexadiene (19). A mixture of 250 mL of anhydrous ammonia, 250 mL of anhydrous tetrahydrofuran and 15 ml of t-butanol was treated with 3.30 g (0.48 mol) of lithium wire (0.8% Na). The mixture was stirred vigorously for 40 min using a dry ice condenser to maintain the ammonia in the reaction mixture, at which time a solution of 10.00 g (0.074 mol) of 2,5-dimethylanisole (**18**) in 5 mL of tetrahydrofuran was added over ca. a 5 min period. The solution was stirred for 15 min, then an additional 10 mL of t-butanol added. The condenser was removed and the ammonia allowed to evaporate of its own accord over a 24 h period. Solid ammonium chloride (ca. 30 g) and ethanol were used to quench any excess lithium. Ether (700 mL) and water (700 mL) were added and the layers separated. The aqueous layer was extracted with 100 mL of ether. The combined ether layers were washed with 200 mL of saturated ammonium chloride followed by 200 mL of water. The combined aqueous layers were back-extracted with 200 mL of ether. All of the ether layers were combined, dried over anhydrous magnesium sulfate, filtered and the volatiles evaporated in vacuo to give a light yellow oil. The residue was purified by distillation through a 6" Vigreux column to give 8.41 g (83%) of diene **19** as a colorless liquid (bp 71-72 °C @ 11 mm Hg). NMR ($CDCl_3$, 200 MHz) d 1.63 (s, 3H), 1.70 (s, 3H), 2.66 (s, 4H), 3.54 (s, 3H), 5.35 (br s, 1H) ppm; IR (neat) 2940, 2920, 2830, 1715, 1210, 1140 cm^{-1}; Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.29; H, 10.50.

3,6-Dimethyl-2-cyclohexenone (20). A solution of 15 mL of conc. HCl in tetrahydrofuran (135 mL) was added to 40.25 g (0.291 mol) of enol ether **19**. The reaction mixture was stirred vigorously at room temperature for 10 min, then cooled to 0°C and carefully neutralized with saturated sodium bicarbonate. The tetrahydrofuran was evaporated in vacuo and the remaining liquid extracted with 3 x 100 mL of methylene chloride. The combined organic extracts were combined, dried over anhydrous magnesium sulfate and filtered. The volatiles were evaporated in vacuo. The residual oil was purified by fractional distillation using a 6" Vigreux column to give 30.85 g (85%) of enone **20** (bp 81-84°C @ 14 mm Hg) (lit. ref. 20; bp 96-100°C @ 21 mm Hg) as a colorless oil. NMR ($CDCl_3$, 60 MHz) d 1.12 (d, J=6Hz, 3H), 1.61-2.56 (m containing a br s (3H) at 1.93, 8H), 5.82 (br s, 1H) ppm; IR (neat) 2960, 2930, 2860, 1665, 1630, 1375, 1210 cm^{-1}; Anal. Calcd for $C_8H_{12}O$: C, 77.38; H, 9.74. Found: C, 77.08; H, 10.03.

3,6-Dimethyl-2-cyclohexene-1-ol (21a&b). A suspension of $LiAlH_4$ (5.20 g, 0.14 mol) in 240 mL of anhydrous ether was cooled to 0°C stirred as a solution of 17.00 g (0.14 mol) of enone **20** in 10 mL of anhydrous ether was added dropwise over a period of approximately 30 min. After the addition was complete, the reaction was stirred at 0°C for 15 min, then carefully quenched with ca. 10 mL of saturated sodium sulfate. After 30 min, 17g of anhydrous magnesium sulfate was added, and the reaction mixture was filtered. The filtrate was evaporated in vacuo to a clear oil. The residual oil was purified by fractional distillation using a 6" Vigreux column to provide 15.60 g (90%) of a 1:1 mixture of alcohol isomers **21a&b** (by NMR analysis), bp 90-93°C @ 21 mm Hg. NMR ($CDCl_3$, 200 MHz) d 0.95-1.01 (m containing two doublets at 0.97 and 0.99, J=6.3 Hz for each, 3H), 1.20-2.10 (m containing 3H s at 1.65, 9H), 5.34-5.56 (m, 1H) ppm; IR (neat) 3340(br), 2960, 2930, 2870, 1020 cm^{-1}; Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 75.81; H, 11.48.

2-(1,4-Dimethyl-2-cyclohexen-1-yl)-2-methylcyclopentanone (22). A mixture of allylic alcohols **21a&b** (83 mg, 0.66 mmol), ketal **8** (288 mg, 2.00 mmol) and propionic acid (23 mg, 0.31 mmol) in 10 mL of xylenes was heated at reflux under a nitrogen atmosphere for 190 h. The condenser was replaced with a short path distillation apparatus and the low boiling materials were removed at reduced pressure (20-25 mm Hg). The residue was purified by flash chromatography using 0.5% ether in Skellysolve-F as the eluant. Two fractions were collected, the first containing three products (50 mg) R_f=0.41, 0.36 and 0.31 in 4:1 Skellysolve-F:ether, and the second a single product which was identified as the desired product, ketone **22** (22 mg, 16%) at R_f=0.31. NMR ($CDCl_3$, 200MHz) d 0.90-0.94 (m containing 2 doublets centered at 0.91 and 0.92, J=7.0 Hz for each, 3H total), 0.99 (s, 3H), 1.10 (s, 3H), 1.59-2.33 (m, 11H), 5.46 (m, 2H) ppm; IR (neat) 2960, 2930, 2880, 1735 cm^{-1}; Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.51; H, 11.00.

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2) Present address: Exxon Research & Engineering Co, Clinton Township, Route 22 East, Annandale, New Jersey, 08801. This paper is taken in part from the Ph.D. thesis of Steven J. Potlock, University of Maryland, College Park, Maryland, 1985.

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