was refluxed for 45 min, cooled, and added to 1 L of 10% H_2SO_4. The yellow solid which separated was collected, washed with water, and dried to give 10.0 g (92%) of 10-methoxy-7,12-benz[*a*]anthraquinone* (**44**), mp 168–169 °C, suitable for further use. Recrystallization from acetic acid yielded pure **44**, mp 171.5–172.0 °C, with little loss.

7,12-Dihydroxy-7,12-dimethyl-10-methoxy-7,12-dihydrobenz[*a*]anthracene* (45). To a solution of 9.0 g (0.03 mol) of **44** in 270 mL of benzene was added 65 mL (0.09 mol) of 1.4 M CH_3Li in ether during 5 min. After 18 h at reflux, saturated NH_4Cl solution was added and the mixture worked up as usual to yield 9.2 g (95%) of **45**, which showed no carbonyl group in the IR spectrum. A colorless analytical sample, mp 175.5–176.5 °C, was obtained by crystallization from benzene–petroleum ether and benzene alone with little loss.

10-Methoxy-7,12-dimethylbenz[*a*]anthracene (**38**) was obtained by adding a solution of 7.0 g of **45** in 400 mL of methanol dropwise during 25 min to a solution at 0 °C of 75 mL of 70% HI in 100 mL of methanol. After 1 h at 5 °C the solid which had separated was collected and dissolved in 400 mL of dioxane and 30 mL of concentrated HCl. This solution was added to a solution of 70 g of $SnCl_2$ in 300 mL of dioxane and 210 mL of concentrated HCl. On holding at reflux for 30 min the color changed from dark orange-yellow to light yellow. The cooled reaction mixture was added to 3 L of water. The crude solid obtained was dissolved in 70 mL of hexamethylphosphoramide (HMPA) containing a solution of 2 g of NaOH in 5 mL of water and 2 mL of methyl iodide. After 7 h the mixture was diluted with water and the product extracted with ether to yield 4.3 g of solid. Chromatography over basic alumina afforded 4.0 g (62% from **45**) of **38**, mp 135–136 °C (lit.[23] mp 136–137 °C), identical with the **38** produced by the alternate synthesis.

9-Hydroxy-7,12-dimethylbenz[*a*]anthracene* (39) and 10-Hydroxy-7,12-dimethyl-benz[*a*]anthracene (40). Demethylation of **37** and **38** as described[6] afforded 79% of **39** as pale yellow crystals, mp 197–198 °C, and 87% of **40** as pale yellow crystals, mp 133–134 °C (lit.[17] mp 122–123 °C; light tan), respectively, after chromatography and recrystallization.

Registry No.—**1**, 66240-13-9; **2**, 66240-14-0; **3**, 51179-24-9; **4**, 66240-15-1; **5**, 66240-16-2; **6**, 66240-17-3; **7**, 66240-1-4; **8**, 66240-19-5; **9**, 66240-20-8; **10** halide derivative, 66240-21-9; **11** halide derivative, 61735-51-1; **12**, 66240-22-0; **13**, 66240-23-1; **14**, 66240-24-2; **15**, 66240-25-3; **16**, 66240-26-4; **17**, 66240-27-5; **18**, 66240-28-6; **19**, 66240-29-7; **20**, 66240-30-0; **21**, 16277-49-9; **22**, 66240-31-1; **23**, 14760-53-3; **24**, 63216-11-5; *cis*-**25**, 66239-99-4; *trans*-**25**, 66240-00-4; **26**, 66240-01-5; **27**, 66240-02-6; **28**, 57266-83-8; **29**, 53306-04-0; **30**, 32664-13-4; **31**, 17056-94-9; **32**, 66240-03-7; **33**, 66240-04-8; **34**, 66240-05-9; **35**, 53306-06-2; **37**, 62078-52-8; **38**, 62064-35-1; **39**, 66240-06-0; **40**, 62064-38-4; **41**, 66240-07-1; **42**, 66240-08-2; **43**, 66240-09-3; **44**, 66240-10-6; **45**, 66240-11-7; 12-acetoxy-3-methoxybenz[*a*]anthracene, 66240-12-8; 2-methoxy-3-naphthoic acid, 883-62-5; 1-naphthyl bromide, 90-11-9; 4-methoxyphthalic anhydride, 28281-76-7; 4-methoxy-2-(1-naphthoyl)benzoic acid, 62064-28-2; 5-methoxy-2-(1-naphthoyl)benzoic acid, 62064-27-1; 2-[1-hydroxy-1-(1-naphthyl)ethyl]-4-methoxybenzoic acid lactone, 62064-30-6; oxazoline, 504-77-8; methyl 1-naphthyl ketone, 1333-52-4; 4-methoxyphenyl bromide, 104-92-7; 1,2-naphthalic anhydride, 5343-99-7; methyl 1-(4-methoxybenzoyl)-2-naphthoate, 66239-96-1; 1(4-methoxybenzoyl)-2-naphthoic acid, 66239-97-2; 2-(1-hydroxy-4-methoxyphenylmethyl)-1-naphthoic acid lactone, 66239-98-3.

References and Notes

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(2) For a review, see D. M. Jerina and J. W. Daly, "Drug Metabolism from Microbe to Mann", Taylor and Francis, London, 1976, p 13ff. See also D. M. Jerina, H. Yagi, and J. W. Daly, *Heterocycles*, **1**, 267 (1973).
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(19) All melting points are uncorrected. The term "worked up as usual" means that an ether–benzene solution of the products was washed with dilute HCl and/or alkali and then with saturated NaCl and dripped through a cone of anhydrous $MgSO_4$. The solvent was removed on a rotary evaporator, and the residue was treated as indicated. All compounds gave NMR and IR spectra consistant with the formula, and the mass spectra were performed by C. R. Weisenberger on an MS9 instrument made by A.E.I. All new compounds marked with an asterisk gave analyses (by M-H-W Laboratories, Garden City, Mich., and the Galbraith Laboratory, Knoxville, Tenn.) within ±0.30% of theory.
(20) We thank Mr. R. Weisenberger for the mass spectra.
(21) All NMR spectra were taken in $CDCl_3$ using Me_4Si as a standard.
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Structure Relation of Conjugated Cycloalkenones and Their Ketals

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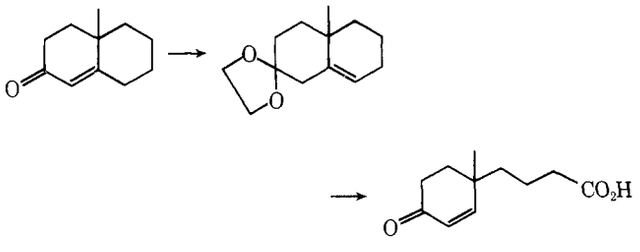
The degree of double bond shift during ketalization was studied on cycloalkenone systems. It was found that the shift was dependent on ring size and the location of substituents.

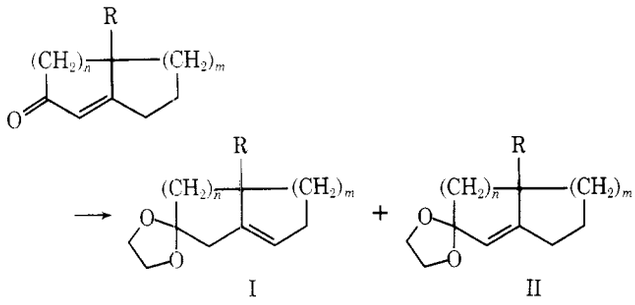
Introduction

In the framework of research carried out in our laboratory,[1] we attempted to develop a new and efficient method for the synthesis of 4,4-disubstituted cycloenones according to Scheme I.

A necessary requirement for success is the shift of the double bond to the β,γ position during the conversion of the ketone into the ketal. The fact that the double bond migrates on ketalization was discovered by Fernholz and Stavely[2] in 1937 and applied in syntheses of natural products.[3,4] Although

Scheme I





I II

ketalization of conjugated enones is a well-established method of protection, the mechanism is not yet fully understood.[5-7] The position of double bonds in substituted cyclic systems is affected mainly by the degree of substitution, conjugation, ring strain, and steric effects.[8,9] This problem has drawn attention for years and is still being studied.[10]

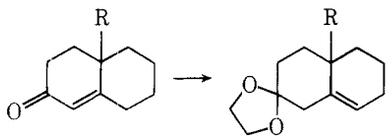
Two additional factors which must be taken into account when discussing the position of the double bond in the ketal are the ketalizing agent, e.g., 1,2-thiol vs. 1,2-diol,[6] and the nature of the acid catalyst.[7,11]

Since the many parameters involved frustrated predictions of the ketal structure we undertook a more systematic study of ketalization of bicyclic enones.

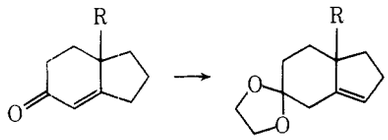
Results and Discussion

In order to facilitate the use of Scheme I as a synthetic method, we studied the ratio of the two isomers potentially formed during ketalization and its dependence upon ring size and substitution. The progress of the reaction was followed by IR and the isomer ratio was determined by NMR.

In bicyclo[4.*x*.0] frameworks, where x = 3 or 4, when the enone is in the six-membered ring and substituted at the β position, the double bond shift on ketalization was complete, as reported by Marshall in **1a**[12] and as found in this work[1] for **1b**,[13] **3a**,[14] and **3b**.[15]



1a,b **2a,b**

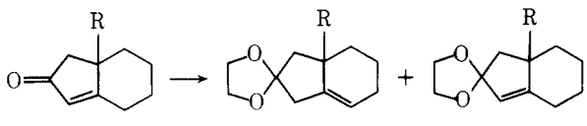


3a,b **4a,b**

a, R = Me; b, R = CO_2Et

This process was carried out in high yield and replacement of the methyl group by a carboethoxy group had no effect on the position of the double bond in the ketals **2b,4b.** This observation enabled us to carry out Scheme I satisfactorily.[16]

Compounds **5a,b**,[15] in which the enone function is located

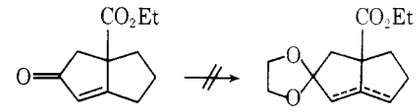


5a,b **6a,b** **7a,b**

a, R = Me; b, R = CO_2Et

in a five-membered ring, were prepared in order to study the effect of ring size on the double bond shift.

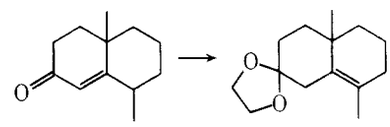
In comparing the cyclopentenone systems to the cyclohexenone systems, we soon learned that the cyclopentenones underwent ketalization more slowly. In order to obtain optimal results refluxing for 48 h was required and the product was always contaminated by starting material. Extending reaction times up to two weeks did not affect the ratio of ketals formed. Bauduin[17] has shown that formation of the ketal of cyclopentanone is less favored than that of cyclohexanone. We emphasize that ketal isomer II is very sensitive to acid hydrolysis, which may even occur when drying a benzene solution of the ketal over anhydrous magnesium sulfate.[11] In fact, we could hydrolyze isomer II with magnesium sulfate in wet benzene in the presence of isomer I and isolate the latter from the starting material by chromatography over basic alumina. Workup of the ketalization mixture under basic conditions, e.g., drying over anhydrous sodium carbonate, enabled us to prepare the ketals free of starting material. Although the structure of the ketal of **5a,b** could not be determined by NMR, we believe the product is **7a,b** based on 10% conversion to the same ketal with catalysis by oxalic acid, which is known to give predominantly α,β-unsaturated ketals, and on analogy.[18] The vinylic proton of the ketal appeared at δ 5.27, which is characteristic of a vinylic proton adjacent to the dioxolane in five-membered rings as seen in Table I. To further observe the influence of the bicyclic system on the location of the double bond in a six-membered ring vs. a five-membered ring, compound **8** was synthesized. To our disappointment we failed to obtain the appropriate ketal.[19]



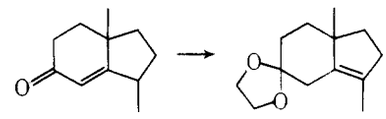
8

It is well known that substituents can influence the location of the double bond in cyclic systems. In order to determine the effect of a γ-methyl substituent on the isomer ratio, the following systems were studied.

In view of previous results for systems **1** and **3**, it was not surprising to observe that compounds **9**[20] and **11** gave ketals

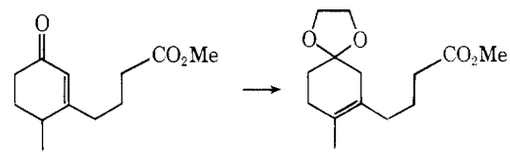


9 **10**



11 **12**

in high yield with complete double bond shift to the more substituted position, as shown unequivocally by NMR spectroscopy. The same behavior was found in monocyclic systems such as Hagemann's ester[21] and **13**[22] in which the double bond shifted completely to the more substituted β,γ position.

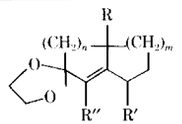
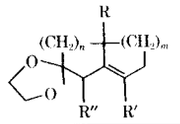


13 **14**

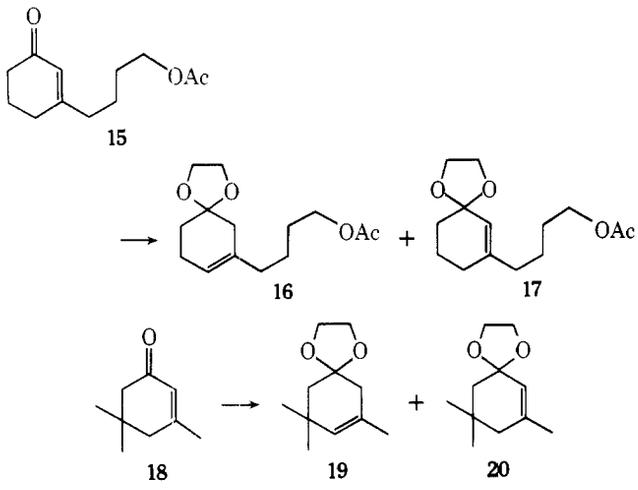
In the absence of a stabilizing γ substituent the double bond shift was found to be partial as observed in **15**[23] and **18.**

Compounds **16** and **17** were obtained in a 1:1 ratio and were separated by chromatography over Florisil. The identity of

Table I

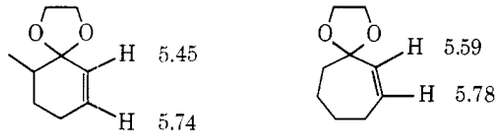
	Registry no.	 R″	(–OCH$_2$–)$_2$	R		 R′	(–OCH$_2$–)$_2$	R	Ketal (s) obtained	Ratio
$n = m = 2$ R = Me; R′ = R″ = H		5.27	3.96	1.1[a]	**2a** 3287-60-3	5.84	3.97	1.1	**2a**	
$n = 2; m = 1$ R = Me; R′ = R″ = H		5.19	3.85	0.98[a]	**4a** 59586-82-2	5.3	3.95	1.07	**4a**	
$n = m = 2$ R = –CO$_2$Et; R′ = R″ = H					**2b** 65898-58-0	5.65	3.97		**2b**	
$n = 2; m = 1$ R = –CO$_2$Et; R′ = R″ = H					**4b** 65898-59-1	5.58	3.93		**4b**	
$n = 1; m = 2$ R = R′ = Me; R″ = H	**30** 65898-52-4	5.25	3.95 R′ = 1.08 (d, 6 Hz)	1.18	**29** 65898-60-4	1.55	3.93 (d)	1.13	**30/29**	3:7
$n = 1; m = 2$ R = R′ = Me; R″ = H	**37** 65898-57-9	5.6		1.19[b]	**36** 65898-61-5	1.58		1.10[b]	**37/36**	3:7
$n = m = 1$ R = R′ = Me; R″ = H	**35** 65898-53-5	5.22	3.92	1.20	**34** 65898-62-6	1.63	3.92	1.1	**35/34**	2:8
$n = 1; m = 2$ R = Me; R′ = R″ = H	**7a** 65898-54-6	5.27	3.93	1.17					**7a**	
$n = 1; m = 2$ R = CO$_2$Et; R′ = R″ = H	**7b** 65898-55-7	5.5	3.95						**7b**	
$n = m = 2$ R = R′ = Me; R″ = H					**10** 65898-63-7	1.63	3.97	1.1	**10**	
$n = 2; m = 1$ R = R′ = Me; R″ = H					**12** 65898-64-8	1.62	3.98	1.03	**12**	
$n = m = 2$ R = R″ = Me; R′ = H	**27** 65898-56-8	1.63	4.05	1.1	**26** 65898-65-9	5.46	4.0 (d) R″ = 1.01 (d, 7 Hz)	1.13	**27/26**	5:5

[a] Reference 7a, solvent $CDCl_3$. [b] 1,3-Dioxane.



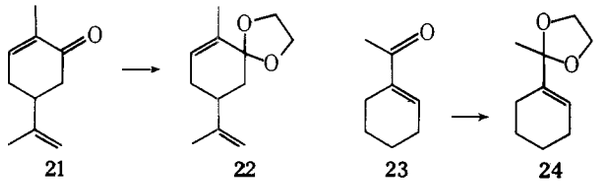
15 16 17 18 19 20

the isomers was determined by the number of allylic protons in the NMR spectra. It is worth noting that the vinylic proton adjacent to the ketal is shielded. The same effect can be seen in the following ketals prepared by Reich.[24]



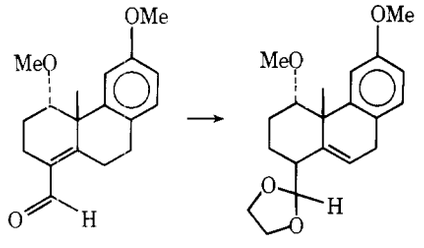
Upon ketalization of isophorone **18**, a mixture of two isomers, **19** and **20**, in the ratio 2:1 was obtained. The structure of the ketals was determined by partial decomposition of one isomer with magnesium sulfate in wet benzene and preparation of the same isomer, **20**, from **18** with fumaric acid[7a] as catalyst. We noticed that in contrast to other cases, the vinylic proton of ketal **19** appeared at higher field than the vinylic proton of isomer **20**, apparently due to the neighboring *gem*-dimethyl group.[25]

The effect of an α substituent was determined in the following monocyclic systems and it was observed that after ketalization the double bond does not shift and is located at the α,β position.

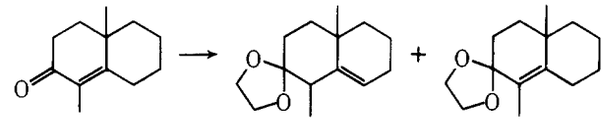


21 22 23 24

In more complex systems, additional factors may be more important than α substitution and the double bond may migrate during ketalization as reported by Wiesner[26] in the following example.



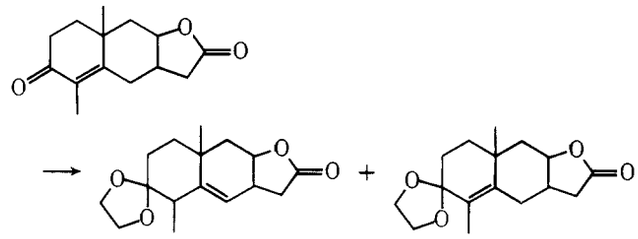
It was interesting to examine bicyclic system **25**[27] in which the enone group is substituted in α and β positions. In this case it was found that two isomers were formed in a 1:1 ratio as determined by NMR.



25 26 27

Treatment of the mixture with magnesium sulfate in wet benzene brought about selective deketalization of **27**, enabling isolation of **26** by chromatography on basic alumina. These results are consistent with Caine's report on a similar system.[28]

From the results discussed so far, it is clear that substituents affect the degree of double bond migration in cyclohexenone



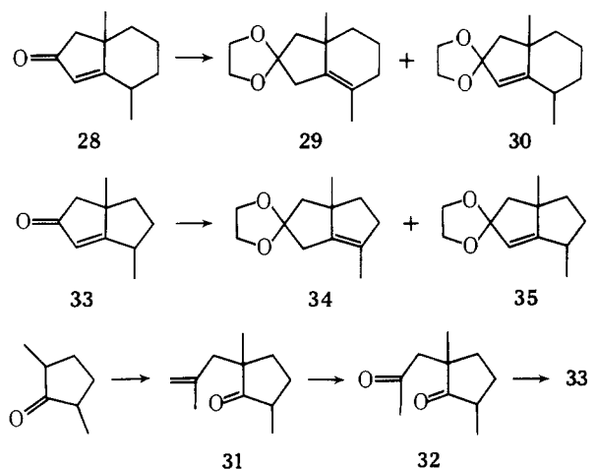
systems during ketalization. In the following bicyclic cyclopentenones the importance of a γ-methyl substituent was studied further.

It was found that 70% of the ketal formed from **28**[29] had undergone double bond migration, in contrast to system **5a** in which no migration took place. The ring size effect was seen by comparing ketalization of systems **28** and **33** (Scheme II). Double bond shifted isomer **34** was 80% of the ketal mixture. These findings are in accord with empirical results for bicyclic [4.3.0] systems that double bonds prefer to be endocyclic to five-membered rings and exocyclic to six-membered rings rather than vice versa.[30]

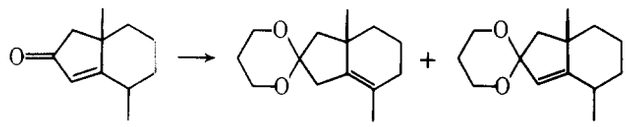
We found that replacing the 1,3-dioxolane ring by a 1,3-dioxane ring had no effect on the degree of migration of the double bond based on the fact that the ratio of the isomers was not affected, although in the NMR spectrum a significant shift was observed, the vinylic proton of **37** appearing at δ 5.60 as opposed to **30** in which it appears at δ 5.25.

In view of the results presented here we can conclude that in bicyclic systems containing enones in a six-membered ring

Scheme II



28 29 30 33 34 35 31 32



28 36 37

the double bond has a strong tendency to shift to the β,γ position on ketalization with a strong acid catalyst.

In order to prevent this shift a stabilizing substituent must be introduced in the α position. On the other hand, in systems containing cyclopentenones the tendency to form the ketal is lower, the double bond does not tend to migrate, and only stabilizing groups in the γ position can cause partial migration.

Experimental Section

Infrared spectra were recorded on Perkin-Elmer 237 in chloroform. The ultraviolet spectra were measured on a Cary 15. The NMR spectra were recorded on a Varian A-60 and Varian T-60 using tetramethylsilane as internal standard.

Mass spectra were determined on an Atlas CH4.

The gas-liquid chromatography was carried out using a Varian Aerograph Model 90-P, carrier gas helium; column 15% XE-60 on Chromosorb Q, ¼ in. × 10 ft, 60–80 mesh.

Materials. 1-Acetyl-1-cyclohexene (Aldrich Chemical) was used without further purification.

2-Acetonyl-2-methylcyclohexanone. A solution of 4.9 g of 2-methyl-2-(2-methylallyl)cyclohexanone[31] was oxidized as described for **32**, yielding 4.9 g of crude oil. After short-path distillation at 65°C (0.1 mm), 3.48 g in 61% yield was collected.

5,6,7,7a-Tetrahydro-4,7a-dimethylindan-2(4*H*)-one (5a).[32] To a solution of 26.6 g of potassium hydroxide in 530 mL of absolute ethanol 3.5 g of 2-acetonyl-2-methylcyclohexanone was added and refluxed under nitrogen for 3 h. The solution was cooled and acidified with 90 mL of 3 N hydrochloric acid diluted with 130 mL of water, and the ethanol was removed under reduced pressure. The oily layer was extracted by four 30-mL portions of ether. The organic layers were combined, washed with 20 mL of brine, and dried over magnesium sulfate and the solvents were removed under reduced pressure to yield 2.8 g of crude **5a**. The crude oil was distilled at 50–60 °C (0.3 mm) to yield 1.3 g of **5a** in 48% total yield.

3,7a-Dimethyl-1,2,3,6,7,7a-hexahydro-5*H*-indan-5-one (11). A sodium methoxide solution was obtained from 7.8 g of sodium and 130 mL of methanol. To the ice-cooled solution was added dropwise 8 g of 2,5-dimethylcyclopentanone and afterwards 8 g of methyl vinyl ketone diluted with 10 mL of methanol was added over 4 h. The solution was allowed to stand overnight under nitrogen. Acidification was carried out with 10% hydrochloric acid, methanol was removed in vacuo, and the product was extracted with three 40-mL portions of methylene chloride. The organic phase was washed with 5% sodium bicarbonate solution and dried over magnesium sulfate. After filtration, the solvent was removed in vacuo, leaving a yellow oil which was distilled at 70 °C (0.1 mm). The 6 g of oil obtained were purified on a 150-g Florisil column, most of the material coming out when the solvent ratio was 1:4 hexane/methylene chloride; 4.8 g of pure compound was obtained: IR 1665 cm^{-1} (α,β-unsaturated ketone); NMR ($CDCl_3$) δ 1.20 (s, 3H, CH_3), 1.33 (d, 3 H, CH_3), 5.82 (m, 1 H, –CO-CH=C–).

Ethyl 2,3,4,5-Tetrahydro-5-oxo-3a-(1*H*)pentalenecarboxylate (8). To a stirred mixture of 0.45 g (19 mmol) of sodium hydride in 30 mL of dry toluene under nitrogen in a three-neck flask was added 0.8 g (3.8 mmol) of ethyl 1-acetonyl-2-oxocyclopentanecarboxylate[33] in 30 mL of toluene during 0.5 h and the reaction was refluxed overnight.

The mixture was cooled and acidified with 5 mL of 2 N hydrochloric acid. The water layer was separated and extracted by four 10-mL portions of ether. The organic layers were combined, washed with 10 mL of brine, and dried over magnesium sulfate. The solvents were removed under reduced pressure to yield 0.6 g of crude **8**.

In bulb-to-bulb distillation of 0.56 g of the crude oil at 50 °C (0.02 mm), 0.45 g was collected containing 55% of **8** according to VPC; the total yield was 57%: IR 1715 (C=O; COO), 1635 cm^{-1} (C=C); NMR ($CDCl_3$) δ 6.03 (t, 1 H, J = 1.5 Hz, vinylic), 4.18 (q, 2 H, J = 7 Hz, $-OCH_2CH_3$), 2.89, 2.31 (AB, 2 H, J = 17 Hz, $COCH_2$), 1.25 (t, 3 H, J = 7 Hz, CH_3CH_2–); MS M^+ 194, calcd 194; main m/e 77, 91, 121, 165; UV λ_{max} (CH_3OH) 232 (ϵ 9.7 × 10^3), 295 nm (ϵ 35). Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.21; H, 7.50.

2-(2-Methylallyl)-2,5-dimethylcyclopentanone (31). To 4.37 g (0.039 mol) of potassium *tert*-butoxide in 80 mL of dry benzene in a 250 mL three-neck flask equipped with a mechanical stirrer, an addition funnel, and a condenser was added 3.56 g (0.31 mol, 4 mL) of 2,5-dimethylcyclopentanone in 10 mL of dry benzene during 10 min.

The mixture was heated to boiling and cooled to room temperature. Methallyl chloride (7.4 g, 0.082 mol) diluted in 10 mL of dry benzene was added during 1.5 h and the mixture stirred overnight at room temperature. The flask was cooled with ice and 20 mL of water and 8.5 mL of hydrochloric acid were added. The aqueous layer was extracted with three 15-mL portions of ether. The combined organic layers were washed with 10 mL of 10% sodium bicarbonate solution and 10 mL of brine and dried over anhydrous magnesium sulfate. After filtration the solvents were removed, yielding 4.7 g of oil.

The product was used in the next step without further purification.

The product was short-path distilled at 78–80 °C (10 mm); the first fraction of 1.4 g was pure **31** as shown by VPC and the second fraction of 7.49 g contained 43% of **31** (total yield 46%): IR 1730 (C(=O)C), 1640 cm^{-1} (C=C); NMR ($CDCl_3$) δ 4.87 (m, 1 H, vinylic), 4.73 (m, 1 H, vinylic), 1.7 (br s, 3 H, CH_3C=C), 0.97 (s, 3 H, $-CCH_3$); MS M^+ 166, calcd 166; main characteristic m/e 41, 55, 81, 96, 111.

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.92. Found: C, 79.08; H, 10.77.

2-Acetonyl-2,5-dimethylcyclopentanone (32). **31** (1.99 g, 0.012 mol) was ozonolyzed in 150 mL of methylene dichloride at −78 °C. The excess of ozone was removed by a stream of nitrogen and the solvent was removed at 0 °C under reduced pressure on a rotary evaporator. To the oily ozonide were added 40 mL of acetone and 1.7 mL of Jones reagent at 0 °C with vigorous stirring. The excess of the oxidizing reagent was decomposed by 2-propanol, and the acetone was removed under reduced pressure. The product was extracted by five 20-mL portions of methylene chloride and washed with 20 mL of sodium bicarbonate and 20 mL of brine. The solvent was removed under reduced pressure, yielding 1.88 g of **32** which was used without further purification in the next step. Short-path distillation, at 80–85 °C (0.8 mm), of the crude product yielded 0.74 g of pure **32** and 0.56 g of a fraction containing 40% of **32** according to VPC (total yield 46%): IR 1735 (cyclic C=O), 1720 cm^- (C=O); NMR ($CDCl_3$) δ 2.7–2.9 (m, 2 H), 2.08 (s, 3 H, $-CCH_3$), 1.02 (d, 3 H, $-CHCH_3$, J = 7 Hz); MS M^+ 168, calcd 168; main m/e 41, 43, 55, 110, 111.

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.62; H, 9.51.

4,5,6,6a-Tetrahydro-4,6a-dimethyl-2(1*H*)-pentalenone (33). Crude **32** (0.5 g, 0.003 mol) and 0.41 g of pyrrolidine were dissolved in 30 mL of dry benzene in a 100-mL flask equipped with a Dean Stark trap. Water removal took place for 24 h under nitrogen, the solvent was evaporated, and 25 mL of benzene, 0.55 g of sodium acetate, 1.1 mL of water, and 1.1 mL of acetic acid were added. The mixture was refluxed for 4 h under nitrogen and cooled to room temperature. The organic layer was separated, washed with 10 mL of 10% hydrochloric acid, 10 mL of 10% sodium bicarbonate, and 10 mL of brine, and dried over magnesium sulfate. The solvent was removed under reduced pressure to yield 0.4 g of crude **33**. Purer **33** was obtained in 30% yield by chromatography over Florisil, eluting with methylene chloride/hexane (1:9): IR 1705 (C=O), 1615 cm^{-1} (C=C); NMR ($CDCl_3$) δ 5.77 (d, 1 H, vinylic), 2.37 (s, 2 H, CH_2C(=O)–), 1.23 (d, 3 H, J = 7 Hz, CH_3CH–), 1.22 (s, 3 H, CH_3); MS M^+ 150, calcd 150; main m/e 41, 43, 79, 80, 108, 135; UV λ_{max} (CH_3OH) 232 (ϵ 1.19 × 10^4), 290 nm (ϵ 160).

Anal. Calcd for $C_{10}H_{14}O$: C, 79.95: H, 9.39. Found: C, 79.39; H, 8.94.

General Ketalization Procedure. Into a flask fitted with a Dean–Stark trap and a reflux condenser with a calcium chloride drying tube were added 2 mmol of ketone, 0.04 g (0.2 mmol) of *p*-toluenesulfonic acid monohydrate, 70 mL of dry benzene, and 2.5 g (40 mmol) of ethylene glycol. The reaction mixture was refluxed overnight or several days. After cooling, anhydrous sodium bicarbonate was added. The mixture was transferred to a separatory funnel containing 20 mL of saturated sodium bicarbonate solution. The aqueous layer was separated and extracted with two 15-mL portions of hexane. The combined organic layers were dried (anhydrous $NaHCO_3$), filtered, and concentrated in vacuo to give an oil in nearly quantitative yield.

Registry No.—5a, 16508-51-3; **8,** 65898-66-0; **11,** 65898-67-1; **31,** 65898-68-2; **32,** 65898-69-3; **33,** 65898-70-6; 2-methyl-2-(2-methylallyl)cyclohexanone, 65898-71-7; 2-acetonyl-2-methylcyclohexanone, 27943-50-6; 2,5-dimethylcyclopentanone, 4041-09-2; methyl

vinyl ketone, 78-94-4; ethyl 1-acetonyl-2-oxocyclopentanecarboxylate, 61771-77-5; methallyl chloride, 563-47-3.

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New Approach to the Synthesis of 4,4-Disubstituted Cycloalkenones

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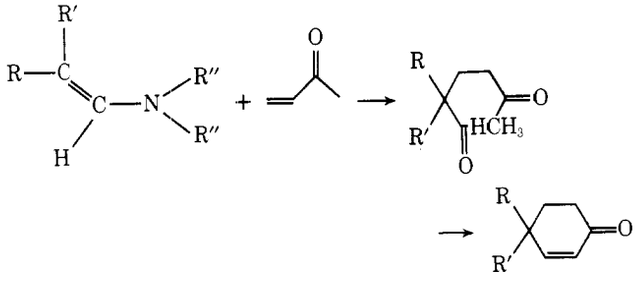
4,4-Disubstituted cycloalkenones were synthesized from appropriate bicyclic systems. The ozonide of each bicyclic system was treated by either the oxidative or the reductive route, giving products which were easily transformed to monocyclic enones. The advantages and limitations of the two routes are described.

Introduction

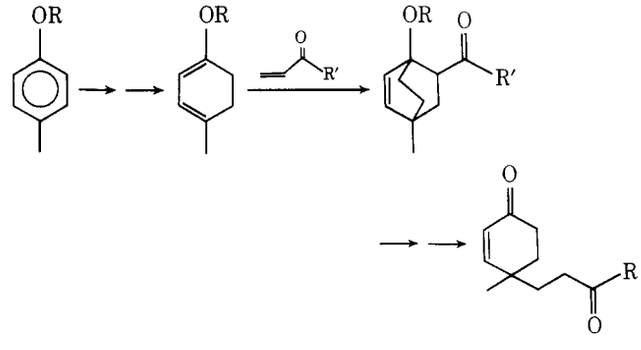
Conjugated cycloalkenone systems are very useful intermediates in synthesis, and therefore, much effort has been invested in developing methods for their preparation. The most common method is annelation, which has been improved and adapted to a wide variety of syntheses.[1] Conjugated 4,4-disubstituted cyclohexenones may be synthesized by many routes, but most of those were tailored to specific problems. Stork[2] has developed a general method consisting of condensation of the enamine with methyl vinyl ketone to produce the desired compound.



This method was applied by Yamada[3] to the synthesis of optically active 4,4-disubstituted cyclohexenones using optically active enamines.

Recently Martin[4] has described a new route to a suitable enamine for this type of annelation, starting with the appropriate ketone and diethyl lithiomorpholinomethyl phosphonate.

Another approach to conjugated cyclohexenones is based on the cleavage of bicyclic systems. For example, the starting material for the synthesis of (±)-Trichodermin was prepared by cleavage of an appropriate bicyclo[4.1.0]heptane by Raphael.[5] Birch[6] suggested a more general method based on the cleavage of bicyclo[2.2.2]octenes which were prepared by Diels–Alder addition to cyclic dienes.



In this report we summarize work in which conjugated 4,4-disubstituted cycloalkenones were prepared from conjugated bicyclic enones. The method consists basically of three steps, the first of which is the shift of the double bond induced by ketalization. The next step is cleavage of the double bond

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