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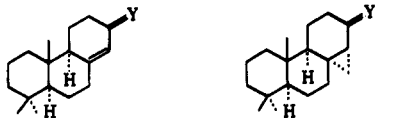
(18) Training for the three-step conversion of the olefinic ketone **6a** into the cyclopropyl ketone **9b** was gained from a prior, similar transformation of the manool-derived, tricyclic ketone I into the tetracyclic ketone IV (see Experimental Section).



i, Y = O
ii, Y = α—OH, β—H

iii, Y = α—OH, β—H
iv, Y = O

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(22) This experiment was based on an early observation of the formation of a cyclobutanone (presumably by catalysis of laboratory acid fumes), when liquid alcohol **9a** was kept relatively unprotected for an extended period of time. Whereas the ketonic product is depicted as a bicyclo[3.2.0]heptanone (**10**), no data precluding an isomeric bicyclo[2.1.1]heptanone structure were acquired. However, the latter configuration is quite unlikely in view of its representation of only occasional, minor side products in the α-oxycyclopropylcarbinol rearrangement.[4-6]
(23) E. Wenkert, N. F. Golob, and R. A. J. Smith, *J. Org. Chem.*, **38**, 4068 (1973).
(24) The preparation of bicyclo[3.2.0]heptanone **18a**, by means other than those reported here, constitutes part of another synthesis of grandisol.[26d] The transformation of the ketone into nitrile **20** paralleled closely the present work, although the conversion of the cyanide into the natural product followed a different path. The authors are indebted to Professor Ayer for communication on this subject prior to publication.
(25) For the isolation, structure determination, and an early synthesis of the natural substance see J. H. Tumlinson, D. D. Hardee, R. C. Gueldner, A. C. Thompson, P. A. Hedin, and J. P. Minyard, *Science*, **166**, 1010 (1969); J. H. Tumlinson, R. C. Gueldner, D. D. Hardee, A. C. Thompson, P. A. Hedin, and J. P. Minyard, *J. Org. Chem.*, **36**, 2616 (1971).
(26) For other syntheses see (a) R. L. Zurflüh, L. L. Durham, V. L. Spain, and J. B. Siddall, *J. Am. Chem. Soc.*, **92**, 425 (1970); (b) R. C. Gueldner, A. C. Thompson, and P. A. Hedin, *J. Org. Chem.*, **37**, 1854 (1972); (c) W. E. Billups, J. H. Cross, and C. V. Smith, *J. Am. Chem. Soc.*, **95**, 3438 (1973); (d) W. A. Ayer and L. M. Browne, *Can. J. Chem.*, **52**, 1352 (1974); (e) G. Stork and J. F. Cohen, *J. Am. Chem. Soc.*, **96**, 5270 (1974); (f) R. L. Cargill and B. W. Wright, *J. Org. Chem.*, **40**, 120 (1975); (g) J. H. Babler, *Tetrahedron Lett.*, 2045 (1975); (h) P. D. Hobbs and P. D. Magnus, *J. Chem. Soc., Chem. Commun.*, 856 (9174); *J. Am. Chem. Soc.*, **98**, 4594 (1976); (i) H. Kosugi, S. Sekiguchi, R. Sekite, and H. Uda, *Bull. Chem. Soc. Jpn.*, **49**, 520 (1976); (j) B. M. Trost and D. E. Keeley, *J. Org. Chem.*, **40**, 2013 (1975); B. M. Trost, D. E. Keeley, H. C. Arndt, and M. J. Bogdanowicz, *J. Am. Chem. Soc.*, **99**, 3088 (1977).
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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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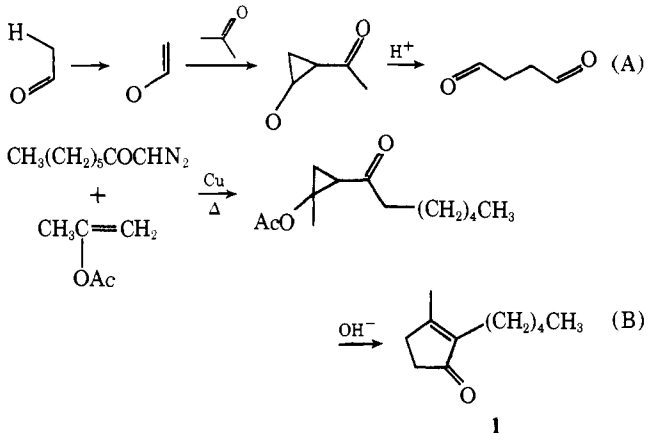

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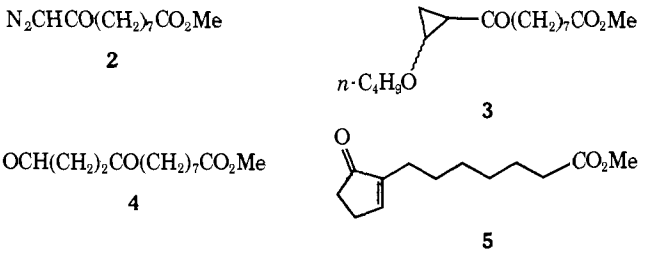
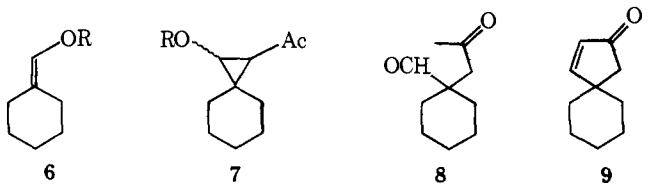
chloride and diazomethane, in *n*-butyl vinyl ether over copper bronze yielded the β-butoxycyclopropyl ketone **3**, whose partial hydrolysis in aqueous acid afforded the aldehydo ketone **4**.[9] Exposure of the latter to methanolic sodium methoxide furnished cyclopentenone **5**.



An Acoranic Sesquiterpene Precursor.[10,11] In connection with the synthesis of β-vetivone (vide infra), a spiro[4.5]decane system, it was of interest to learn whether the scheme of β-oxycyclopropyl ketone preparation and fragmentation was adaptable to the construction of such spiro compounds. Hence the following model study was undertaken.

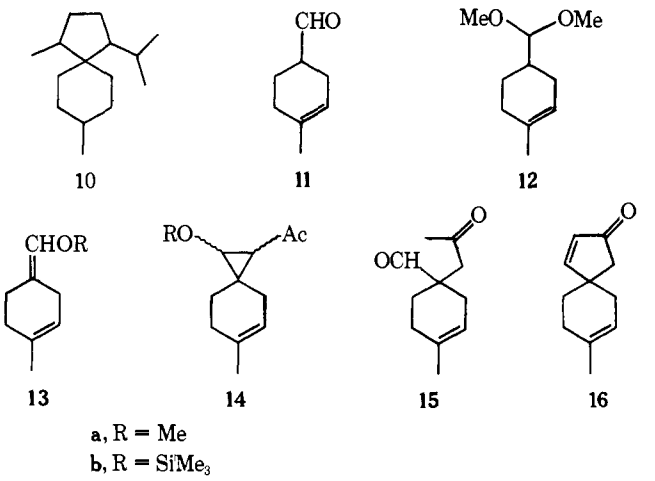
The thermal, copper-catalyzed decomposition of diazoacetone in an enol ether (**6a**) and ester (**6b**) of cyclohexanecarboxaldehyde[4b] yielded ketones **7a** and **7b**, respectively.[10]



a, R = Me
b, R = Ac

Mild acid hydrolysis of **7a** gave aldehydo ketone **8**, whose treatment with methanolic base produced the spiro ketone **9**. The latter was also the product of the interaction of the cyclopropyl ketone **7b** with base.

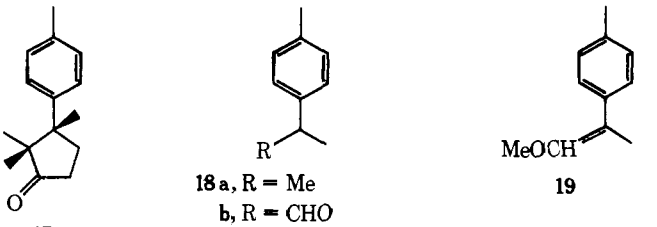
In view of the ease of the two- or three-step construction of the spiro compound, a study of a similar reaction sequence leading to a spiro[4.5]decenone of potential interest in the construction of acoranic sesquiterpenes (cf. skeleton **10**) was executed.[11] Acid-induced ketal-acetal exchange with acetone dimethyl ketal[12] converted 4-methyl-3-cyclohexenecarboxaldehyde (**11**)[13,14] into its acetal (**12**) whose pyrolysis led to enol ether **13a**. Alternatively, treatment of the aldehyde with trimethylsilyl chloride and triethylamine[15] yielded enol ether **13b**. Copper-catalyzed cyclopropanation of these ethers with diazoacetone produced ketones **14a** and **14b**, respectively, and hydrolysis of these substances afforded keto aldehyde **15**, whose base-catalyzed, intramolecular aldol condensation furnished the desired spiro ketone (**16**).[16,17] A most recent



a, R = Me
b, R = SiMe3

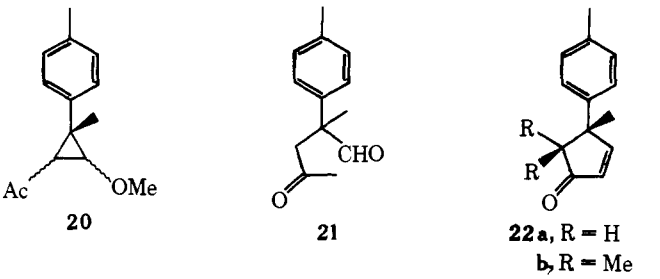
report[18] relates the conversion of the latter, prepared by totally different means from aldehyde **11**, into (±)-acorone.

α-Cuparenone.[10] The tetrasubstituted cyclopentanone structure of the sesquiterpene α-cuparenone (**17**) made the natural substance[19] an ideal goal of synthesis by the β-oxycyclopropyl ketone fragmentation route. As an analysis of the origin of the individual ring carbons in the synthesis of dihydrojasmone[4b] and the above cyclopentenones indicates, the keto and its surrounding α carbons emanate from an α-diazo ketone and the remaining β and β′ carbons of the five-membered rings are derived from an enol derivative. Thus an α-cuparenone synthesis depended on the initial preparation of an enol system based on the *p*-cymene (**18a**) structure.



18a, R = Me
b, R = CHO
c, R = CH(OMe)2

Treatment of α-(*p*-tolyl)propionaldehyde (**18b**), a product of the chromyl chloride oxidation of *p*-cymene (**18a**),[20,21] with trimethyl orthoformate in methanolic acid furnished acetal **18c**, whose acid-induced methanol elimination afforded the enol derivative (**19**) needed for cyclopropanation. Thermal decomposition of diazoacetone in the enol ether **19** in the presence of copper bronze yielded the β-methoxycyclopropyl ketone **20**, whose acid-catalyzed hydrolysis gave keto aldehyde **21**.[22] Base-catalyzed aldol condensation converted the latter



into cyclopentenone **22a**. Alkylation of this ketone with methyl iodide and sodium hydride produced the highly substituted ketone **22b**, whose palladium-catalyzed hydrogenation led to (±)-α-cuparenone (**17**).

β-Vetivone.[10] The spiro[4.5]decene nature of this sesquiterpenic ketone (**23**) and the aforementioned ease of construction of this ring system by way of the β-oxycyclopropyl ketone fragmentation route made this synthesis scheme emi-

nently suitable for the generation of the natural substance.[23] It was decided to limit the goal to spiro[4.5]decenone **24** or its diastereomer on the assumption of these substances being readily convertible into the natural ketone[24] and to maintain a parallelism with the **6** → **9** and **11** → **16** reaction sequences. For these purposes aldehyde **26** was needed as starting material, but was not accessible with facility[25] despite the availability of the double-bond isomer **25a**.[26] Hence the malpositioning of the double bond was ignored initially and the latter aldehyde transformed by the usual means (via acetal **25b**) into its methyl enol ether (**27**). In view of the anticipation of difficulties with acid-catalyzed isomerizations the enol derivative was subjected to equilibrium-controlled, strong base treatment on the assumption of this leading to the stabilized pentadienyl anion **28** and thence to the desired, conjugated dienyl ether **29**. Exposure of diene **27** to potassium *tert*-butoxide in dimethylformamide[27] indeed led to diene **29**, although the formation of hemimellitylene (**30**) as a side product indicated protonation of the intermediate anion **28** to occur even at the oxy carbon site, thereby deconjugating the enol ether system (vide infra).[28]

23 **24** **25a**, $Y_2 = O$; **b**, Y = OMe **26**

27 **28** **29** **30**

The three-step, **25a** → **25b** → **27** → **29** sequence had yielded ready access to the conjugated dienyl ether **29**, the needed starting olefin for the projected four-step buildup of spiro[4.5]decenone **24**. Copper-catalyzed, thermal decomposition of diazoacetone in diene **29** produced a difficultly separable mixture of cyclopropanes, whose hydrolysate revealed it to be a 1:3 combination of bicycles **31** (without stereochemical connotations) and **32**, respectively. Acid-induced hydrolysis led to keto aldehydes **33** and **34**,[29] respectively.

31 **32** **33**

34 **35**

Whereas the latter was a mixture of two stereoisomers, the former dicarbonyl compound was a single entity. This result was consonant with expectation and in support of the stereochemistry of the desired keto aldehyde and its precursor being as depicted in formulas **33** and **31**, respectively, since in the cyclopropanation of diene **29** the involvement of copper and the carbenoid reagent at the unoxygenated double-bond site can be assumed to be affected only minimally by the distant secondary methyl group, the sole stereochemistry-determinant substituent, but at the enol ether site the (in this case) proximate methyl function can be anticipated to exert an optimum steric effect by the suppression of cyclopropanation cis to it.

Treatment of keto aldehyde **33** with base yielded the conjugated ketone **35**,[30] whose hydrogenation in the presence of base furnished the spiro ketone **24**.[23b] The latter's previous conversion into (±)-β-vetivone (**23**)[23b] made the present reaction sequence a formal total synthesis of the sesquiterpenic ketone.

Experimental Section

Melting points were observed on a Reichert micro hot stage and are uncorrected. Infrared spectra and mass spectra were recorded on a Perkin-Elmer 137 spectrophotometer and an AEI MS-9 mass spectrometer, respectively. ^{1}H NMR spectra of deuteriochloroform solutions containing tetramethylsilane as internal standard (δ = 0 ppm) were measured on Varian A-60 and HR-220 spectrometers. Gas-phase chromatography involved Varian Aerograph and Autoprep chromatographs.

Methyl 10-Diazo-9-oxodecanoate (2). A mixture of 50 g of dimethyl azelate and 130 g of azelic acid in 40 mL of di-*n*-butyl ether was stirred and heated at 150 °C until total solution had been achieved. Concentrated hydrochloric acid (10 mL) was added slowly at 120 °C and the solution refluxed for 3 h. After the addition of 56 mL of methanol the solution was refluxed for another 12 h and cooled and low-boiling materials were removed by distillation at ca. 18 Torr up to 125 °C. Distillation of the residue at 125–130 °C (2 Torr) led to the recovery of starting dimethyl azelate and 81 g of colorless methyl hydrogen azelate was obtained at 120–130 °C (0.1 Torr). Thionyl chloride (25 mL) was added dropwise to a solution of 56.0 g of the latter in 50 mL of anhydrous ether and the mixture refluxed for 4 h. Evaporation thereof and distillation of the residue yielded 50.4 g of methyl 8-chlorocarbonyloctanoate, bp 80–84 °C (0.3 Torr) [lit.[8] bp 150–155 °C (15 Torr)]. A solution of 40.0 g of the latter in 150 mL of anhydrous ether was added dropwise to an ice-cold, stirring, ethereal solution of excess diazomethane and the mixture stirred for 12 h, while warming to room temperature. Evaporation yielded 40.0 g of colorless, liquid ester **2**: IR (neat) CN_2 4.78 (s), C=O 5.78 (s), 6.10 μ (s); ^{1}H NMR δ 1.27 (broad s, 6, $(CH_2)_3$), 1.58 (t, 4, J = 8 Hz, $(\beta\text{-}CH_2)_2$), 2.26 (t, 4, J = 8 Hz, $(COCH_2)_2$), 3.51 (s, 3, OMe), 5.57 (s, 1, CHN_2). Anal. ($C_{11}H_{18}O_3N_2$) C, H, N.

Methyl 9-(β-*n*-Butoxycyclopropyl) 9-oxononanoate (3). A solution of 5.00 g of diazo ketone **2** in 20 mL of *n*-butyl vinyl ether was added dropwise over a 4-h period to a refluxing suspension of 1 g of copper bronze in 30 mL of *n*-butoxyethene and the mixture refluxed for 1 h. It then was filtered and the filtrate evaporated. Distillation of the residue yielded 4.10 g of liquid product, whose chromatography on alumina, activity IV, and elution with 3:2 hexane–benzene gave colorless, liquid keto ester **3**: bp 135–137 °C (0.01 Torr); IR (neat) C=O 5.78 (s), 5.93 μ (s); ^{1}H NMR δ 0.90 (t, 3, J = 8 Hz, Me), 1.1–1.7 (m, 16, $(CH_2)_8$), 2.09 (m, 1, COCH), 2.29 (t, 2, J = 8 Hz, CH_2CO_2), 2.48 (m, 2, $COCH_2$), 3.3–3.4 (m, 3, OCH, OCH_2), 3.64 (s, 3, OMe); *m/e* 298.2165 (calcd for $C_{17}H_{30}O_4$, 298.2144).

Methyl 7-(5-Oxocyclopentenyl)heptanoate (5). A mixture of 200 mg of keto ester **3** and 0.4 mL of 1 M hydrochloric acid in 3 mL of tetrahydrofuran was stirred at room temperature for 1.5 h, then diluted with 25 mL of saturated brine solution and extracted exhaustively with ether. The extract was dried (Na_2SO_4), filtered, and evaporated, leaving liquid aldehydo keto ester **4**: IR (neat) OCH 3.69 (w), C=O, 5.77 (s), 5.85 μ (s); ^{1}H NMR δ 1.2–1.6 (m, 10, $(CH_2)_5$), 2.28 (t, 2, J = 8 Hz, CH_2CO_2), 2.44 (t, 2, J = 8 Hz, $COCH_2$), 2.72 (s, 4, $COCH_2CH_2CO$), 3.64 (s, 3, OMe), 9.78 (s, 1, CHO). A mixture of the latter and 1.5 mmol of sodium methoxide in 5 mL of methanol was stirred under nitrogen at room temperature until all aldehyde had

been consumed (TLC monitoring). The red solution was acidified with 1 M hydrochloric acid, diluted with water, and extracted exhaustively with ether. The extract was dried (Na_2SO_4), filtered, and evaporated. Filtration of a methylene chloride solution of the residue through alumina yielded 112 mg of colorless, liquid keto ester **5**: TLC R_f, IR, and ^1H NMR spectra identical with those of an authentic sample.[7]

1-Acetyl-2-methoxyspiro[2.5]octane (7a). Diazoacetone (3.40 g) was added dropwise over a 3-h period to a stirring suspension of 300 mg of copper bronze in 2.40 g of methoxymethylenecyclohexane (**6a**) at 90 °C and the mixture stirred at this temperature for 2 h. After the addition of 25 mL of cyclohexane it was filtered and the solid washed with cyclohexane. Evaporation of the combined solutions yielded 3.5 g of yellow oil, whose fractional distillation led to 1.00 g of starting ether (**6a**) and 1.50 g of colorless, liquid ketone **7a**: bp 65–67 °C (0.6 Torr); IR (neat) C=O 5.91 μ (s); ^1H NMR δ 1.1–1.9 (m, 11, $(CH_2)_5$, CH), 2.28 (s, 3, Me), 3.32 (s, 3, OMe), 3.62 (d, 4, J = 4 Hz, OCH); *m/e* 182.1299 (calcd for $C_{11}H_{18}O_2$, 182.1307).

2-Acetoxy-1-acetylspiro[2.5]octane (7b). Diazoacetone (3.50 g) was added dropwise over a 8-h period to a refluxing suspension of 800 mg of acetoxymethylenecyclohexane (**6b**) and 0.5 g of copper bronze in 15 mL of cyclohexane and the mixture refluxed for another 2 h. It was filtered, the solid washed, and the combined filtrate and washings evaporated. Chromatography of the residual oil (1.4 g) on 30 g of neutral alumina, activity I, and elution with hexane yielded 150 mg of starting ester **6b**. Elution with benzene gave 330 mg of liquid keto ester **7b**: IR (neat) C=O 5.72 (s), 5.85 μ (s); ^1H NMR δ 1.3–2.4 (m, 11, $(CH_2)_5$, CH), 2.05 (s, 3, $MeCO_2$), 2.29 (s, 3, Me), 3.93 (d, <1, J = 7 Hz, minor OCH), 4.42 (d, <1, J = 4 Hz, major OCH); *m/e* 210.1255 (calcd for $C_{12}H_{18}O_3$, 210.1256).

α-Acetonylcyclohexanecarboxaldehyde (8). A mixture of 1.00 g of ketone **7a** and 5 mL of 1 N hydrochloric acid solution in 5 mL of ether was stirred at room temperature for 1 h. The aqueous layer was washed with ether and the combined organic solutions were dried (Na_2SO_4) and evaporated. Chromatography of a benzene solution of the residual oil (920 mg) on Florisil yielded liquid keto aldehyde **8**: IR (neat) CHO 3.72 (w), C=O 5.81 μ (s); ^1H NMR δ 1.3–1.7 (m, 10, $(CH_2)_5$), 2.12 (s, 3, Me), 2.78 (s, 2, $COCH_2$), 9.65 (s, 1, CHO); bissemicarbazone mp 224–225 °C (H_2O–EtOH). Anal. ($C_{12}H_{22}O_2N_6$) C, H, N.

Spiro[4.5]dec-3-en-2-one (9). A mixture of 400 mg of keto aldehyde **8** and 4 mL of 10% potassium hydroxide solution in 4 mL of methanol was stirred at room temperature under nitrogen for 5 h. The alcohol was evaporated under vacuum at low temperature and the residual, aqueous mixture extracted with ether. The extract was dried (Na_2SO_4) and evaporated. Chromatography of a benzene solution of the residual oil on 5 g of neutral alumina, activity I, afforded 343 mg of colorless, liquid ketone **9**: IR (neat) C=O 5.84 (s), C=C 6.29 μ (m); ^1H NMR δ 1.3–1.7 (m, 10, $(CH_2)_5$), 2.21 (s, 2, $COCH_2$), 6.02 (d, 1, J = 6 Hz, olefinic α-H), 7.53 (d, 1, J = 6 Hz, olefinic β-H); semicarbazone mp 187–189 °C (H_2O–EtOH). Anal. ($C_{11}H_{17}ON_3$) C, H, N.

A mixture of 300 mg of keto ester **7b** and 5 mL of 5% potassium hydroxide solution in 5 mL of methanol was stirred at room temperature under nitrogen for 6 h. Workup as above yielded 215 mg of colorless, liquid ketone **9**, spectrally identical with the above sample.

4-Dimethoxymethyl-1-methylcyclohexene (12). A solution of 10.0 g of 4-methyl-3-cyclohexenecarboxaldehyde (**11**), 150 mg of *p*-toluenesulfonic acid, and 150 mL of 2,2-dimethoxypropane in 50 mL of dimethylformamide was refluxed for 3 h, then neutralized with sodium bicarbonate and filtered. The filtrate was concentrated under vacuum, 100 mL of ether added, and the mixture washed with water, dried ($MgSO_4$), and evaporated. Distillation of the residue yielded 13.4 g of liquid acetal **12** (98%): bp 63 °C (0.25 Torr); ^1H NMR (neat) δ 1.62 (broad s, 3, Me), 1.7–2.1 (m, 6, $(CH_2)_3$), 3.26 (s, 6, $(OMe)_2$), 4.07 (d, 1, J = 7 Hz, OCH), 5.39 (m, 1, olefinic H). Anal. ($C_{10}H_{18}O_2$) C, H.

4-Methoxymethylene-1-methylcyclohexene (13a). Crude acetal **12** (6.00 g) was heated at 180 °C up to 2 h past the cessation of methanol evolution. (Pyrolysis of purified acetal leaves the compound unfazed.) Distillation of the residue yielded 4.88 g of ether **13a** (100%): bp 55 °C (0.25 Torr); IR (neat) C=C 5.92 (s), 6.25 μ (w); ^1H NMR (neat) δ 1.61 (broad s, 3, Me), 1.9–2.7 (m, 4, $(CH_2)_2$), 2.50, 2.73 (m, 2 total, diallyl CH_2), 3.46 (s, 3, OMe), 5.33 (m, 1, olefinic H), 5.80 (m, 1, OCH). Anal. ($C_9H_{14}O$) C, H.

1-Methyl-4-trimethylsilyloxymethylenecyclohexene (13b). A solution of 20.5 g of aldehyde **11**, 21.5 g of trimethylsilyl chloride, and 40 g of triethylamine in 60 mL of dimethylformamide was refluxed under nitrogen for 48 h. The suspension was diluted with 150 mL of hexane, washed with 5% sodium bicarbonate solution, dried (Na_2SO_4), and evaporated. Distillation of the residue produced 25.5 g of ether **13b** (78%): bp 47–49 °C (0.35 Torr); IR (neat) C=C 5.95 (m), 6.25 μ (w); ^1H NMR (neat) δ 1.60 (broad s, 3, Me), 1.9–2.4 (m, 4, $(CH_2)_2$), 2.49, 2.74 (m, 2 total, diallyl CH_2), 5.32 (m, 1, olefinic H), 6.09 (m, 1, OCH). Anal. ($C_{11}H_{20}OSi$) C, H.

1-Acetyl-6-methyl-2-trimethylsilyloxyspiro[2.5]oct-5-ene (14b). Diazoacetone (11.0 g) was added dropwise over a 6-h period to a stirring suspension of 1.0 g of bisacetylacetonatocopper(II) and 17.0 g of diene **13b** in 5 mL of hexane under nitrogen at 80 °C and the mixture stirred at 60 °C for 12 h. It was diluted with cyclohexane and filtered and the filtrate was evaporated. Distillation of the residue yielded 6.40 g of starting diene and 6.60 g of cyclopropyl ketone **14b** (30%): bp 84–86 °C (0.25 Torr); IR (neat) C=O 5.83 μ (s); ^1H NMR (neat) δ 1.55 (broad s, 3, Me), 2.05 (s, 3, COMe), 1.6–2.7 (m, 8, $(CH_2)_3$, $(CH)_2$), 5.29 (broad s, 1, olefinic H); *m/e* 252.1554 (calcd for $C_{14}H_{24}O_2Si$, 252.1546).

1-Acetonyl-4-methyl-3-cyclohexenecarboxaldehyde (15). Diazoacetone (7.00 g) was added dropwise over a 5-h period to a stirring suspension of 0.6 g of copper bronze in 3.00 g of diene **13a** under nitrogen at 80 °C and the stirring continued at 80 °C for 12 h. The mixture was diluted with 100 mL of cyclohexane and filtered and the filtrate was evaporated. Slow chromatography of the residue on silica gel led to the recovery of 0.9 g of diene and 1.12 g of keto aldehyde **15** (41%): bp 153–155 °C (2.5 Torr); IR (neat) CHO 3.64 (w), C=O 5.75 (s), 5.82 (s), C=C 6.25 μ (w); ^1H NMR δ 1.65 (broad s, 3, Me), 2.12 (s, 3, COMe), 1.5–2.4 (m, 6, $(CH_2)_3$), 2.74 (s, 2, $COCH_2$), 5.40 (m, 1, olefinic H), 9.80 (s, 1, CHO); *m/e* 180.1155 (calcd for $C_{11}H_{16}O_2$, 180.1150).

Slow chromatography of 6.00 g of cyclopropyl ketone **14b** on silica gel and elution with hexane yielded 4.10 g of keto aldehyde **15** (96%), spectrally identical with the above sample.

8-Methylspiro[4.5]deca-1,7-dien-3-one (16). A mixture of 1.13 g of keto aldehyde **15** and 35 mL of a 0.5 N potassium hydroxide solution in 50 mL of methanol was stirred under nitrogen at room temperature for 4 h and then concentrated under vacuum to half its volume. After the addition of 50 mL of water the mixture was extracted with ether. The extract was washed with water, dried ($MgSO_4$), and evaporated, leaving 960 mg of liquid ketone **16** (94%): bp 118–119 °C (1 Torr); IR (neat) C=O 5.83 (s), C=C 6.18 (w), 6.31 μ (m); ^1H NMR δ 1.71 (broad s, 3, Me), 1.7–2.2 (m, 6, $(CH_2)_3$), 2.20 (s, 2, $COCH_2$), 5.42 (broad s, 1, olefinic H), 6.09 (d, 1, J = 6 Hz, olefinic α-COCH), 7.61 (d, 1, J = 6 Hz, olefinic β-COCH); *m/e* 162.1046 (calcd for $C_{11}H_{14}O$, 162.1045).

Methyl 2,8-Dimethyl-4-methoxy-3-oxaspiro[4.5]deca-1,7-diene-1-carboxylate (i). Methyl α-diazoacetoacetate (7.52 g) was added dropwise over a 5-h period to a stirring suspension of 1 g of freshly prepared copper bronze and 5.00 g of enol ether **13a** in 20 mL of cyclohexane at 80 °C under nitrogen and the mixture stirred at 60 °C for 12 h. It was filtered and the filtrate extracted with hexane (the hexane-insoluble substance being mostly the carbene dimer). The extract was evaporated and the residue chromatographed on 65 g of silica gel. Elution with hexane–benzene yielded 1.5 g of recovered starting enol ether and 2.50 g of a ca. 2:1 stereoisomer mixture of liquid ester i (44%): bp 120–122 °C (0.5 Torr); IR (neat) C=O 5.90 (s), C=C 6.12 (s), 6.30 μ (w); ^1H NMR (CCl_4) δ 1.60 (broad s, 3, cyclohexenyl Me), 1.7–2.5 (m, 6, $(CH_2)_3$), 2.15 (s, 3, Me), 3.33 (s, 3, ether OMe), 3.60 (s, 3, ester OMe), 4.72 (s, <1, minor OCH), 4.97 (s, <1, major OCH), 5.21 (m, 1, olefinic H); *m/e* 252.1356 (calcd for $C_{14}H_{20}O_4$, 252.1361). Anal. ($C_{14}H_{20}O_4$) C, H.

1,1-Dimethoxy-2-(*p*-tolyl)propane (18c). A mixture of 3.80 g of aldehyde **18b**, 8.00 g of trimethyl orthoformate, and 0.05 mL of concentrated sulfuric acid in 50 mL of dry methanol was stirred at room temperature for 48 h. Sodium methoxide (1 g) was added and the mixture evaporated under vacuum. A mixture of the residue in 25 mL of ether was washed with 5% sodium bicarbonate solution and the washings were extracted with ether. The combined ether solutions were dried (Na_2SO_4) and evaporated. Distillation of the residual oil (4.0 g) yielded 3.90 g of colorless, liquid acetal **18c** (78%): ^1H NMR δ 1.25 (d, 3, J = 7 Hz, Me), 2.30 (s, 3, aromatic Me), 2.95 (t, 1, J = 7 Hz, CH), 3.21, 3.33 (s, 3, each, $(OMe)_2$), 4.32 (d, 1, J = 7 Hz, O_2CH), 7.09 (s, 4, aromatic H). Anal. ($C_{12}H_{18}O_2$) C, H.

1-Methoxy-2-(*p*-tolyl)propene (19). A mixture of 3.90 g of acetal

18c and a drop of concentrated sulfuric acid was kept at 45 °C and a 0.3-Torr vacuum for 1 h. Its subsequent distillation yielded 1.77 g of a ca. 15:1 stereoisomer mixture of liquid enol ether **19** (54%): IR (neat) C=C 6.04 μ (m); ^{1}H NMR δ 1.86 (d, <3, J = 1 Hz, minor Me), 1.98 (d, <3, J = 1 Hz, major Me), 2.28 (s, 3, aromatic Me), 3.57 (s, <3, minor OMe), 3.61 (s, <3, major OMe), 6.02 (m, <1, minor olefinic H), 6.35 (q, <1, J = 1 Hz, major olefinic H), 7.11 (m, 4, aromatic H). Anal. ($C_{11}H_{14}O$) C, H.

1-Acetyl-2-methoxy-3-methyl-3-(*p*-tolyl)cyclopropane (20). Diazoacetone (2.30 g) was added dropwise over a 2-h period to a stirring mixture of 0.3 g of freshly prepared copper bronze and 1.77 g of enol ether **19** at 95 °C and the mixture heated for an additional 2 h. After the addition of 25 mL of cyclohexane the mixture was filtered and the solid washed thoroughly with cyclohexane. The combined organic solutions were washed with 5% sodium bicarbonate solution, dried (Na_2SO_4), and evaporated. Chromatography of the residual oil (2.0 g) on 25 g of Florisil and elution with 1:1 cyclohexane–benzene yielded 800 mg of starting ether **19.** Elution with benzene gave 567 mg of a liquid stereoisomer mixture of ketone **20** (44%): IR (neat) C=O 5.90 μ (s); ^{1}H NMR δ 1.52 (s, 3, Me), 2.02 (s, 3, COMe), 2.20 (d, 1, J = 3 Hz, CH), 2.27 (s, 3, aromatic Me), 3.43 (s, 3, OMe), 4.15 (d, 1, J = 3 Hz, OCH), 7.06 (s, 4, aromatic H); *m/e* 218.1306 (calcd for $C_{14}H_{18}O_2$, 218.1307).

2-Methyl-4-oxo-2-(*p*-tolyl)pentanal (21). A mixture of 567 mg of ketone **20** and 5 mL of a 1 N hydrochloric acid solution in 5 mL of ether was stirred for 1 h. The aqueous layer was extracted with ether and the combined ether solutions were washed with 5% sodium bicarbonate solution, dried (Na_2SO_4), and evaporated. Chromatography of the oily residue on 10 g of Florisil and elution with benzene yielded 496 mg of liquid keto aldehyde **21** (92%): IR (neat) CHO 3.73 (w), 5.81 μ (s); ^{1}H NMR δ 1.56 (s, 3, Me), 2.06 (s, 3, COMe), 2.30 (s, 3, aromatic Me), 3.09 (s, 2, CH_2), 7.13 (s, 4, aromatic H), 9.48 (s, 1, CHO); bissemicarbazone mp 229–230 °C (H_2O–EtOH). Anal. ($C_{15}H_{22}O_2N_6$) C, H, N.

4-Methyl-4-(*p*-tolyl)-2-cyclopentenone (22a). A mixture of 496 mg of keto aldehyde **21** and 3 mL of 5% potassium hydroxide solution in 5 mL of methanol was stirred at room temperature under nitrogen for 2 h and then the alcohol evaporated under vacuum. The residue was acidified with 5% hydrochloric acid and extracted with ether. The extract was dried (Na_2SO_4) and evaporated. Chromatography of the oily residue on 10 g of neutral alumina, activity I, and elution with benzene yielded 452 mg of liquid ketone **22a** (99%): IR (neat) C=O 5.85 (s), C=C 6.31 μ (m); ^{1}H NMR δ 1.60 (s, 3, Me), 2.31 (s, 3, aromatic Me), 2.57 (s, 2, CH_2), 6.18 (d, 1, J = 6 Hz, CO-α-H), 7.13 (s, 4, aromatic H), 7.63 (d, 1, J, 6 Hz, CO-β-H); semicarbazone mp 168–169 °C (H_2O–EtOH). Anal. ($C_{14}H_{17}ON_3$) C, H, N.

4-(*p*-Tolyl)-4,5,5-trimethyl-2-cyclopentenone (22b). A solution of 1.87 g of ketone **22a** in 5 mL of dry dimethylformamide was added dropwise over a 0.25-h period to a solution of 0.60 g of sodium hydride in 5 mL of dimethylformamide and the mixture stirred at room temperature under nitrogen for 0.5 h. Methyl iodide (6.84 g) was added dropwise over a 0.25-h period and the mixture stirred at room temperature for 16 h. Methanol (3 mL) was added for the decomposition of excess hydride and the mixture diluted with 50 mL of ether and filtered. The solid was washed exhaustively with ether and the combined organic solutions were evaporated by vacuum, low-temperature distillation. Chromatography of the oily residue on 30 g of neutral alumina, activity I, and elution with 4:1 hexane–benzene yielded 1.60 g of viscous, liquid ketone **22b** (74%): IR (neat) C=O 5.84 (s), C=C 6.28 μ (w); ^{1}H NMR δ 0.53, 1.20, 1.45 (s, 3 each, Me_3), 2.32 (s, 3, aromatic Me), 6.21 (d, 1, J = 6 Hz, CO-α-H), 7.11 (s, 4, aromatic H), 7.72 (d, 1, J = 6 Hz, CO-β-H); *m/e* 214.1357 (calcd for $C_{15}H_{18}O$, 214,1358).

(±)-α-Cuparenone (17). A mixture of 300 mg of ketone **22b,** 30 mg of 10% palladium–charcoal, and 10 mg of piperidine in 5 mL of dry ethanol was stirred at room temperature under 1 atm of hydrogen until the gas uptake had ceased. The mixture was filtered, the catalyst was washed with dry ethanol, and the combined organic solutions were evaporated. Chromatography of the residual oil on 5 g of neutral alumina, activity I, and elution with benzene yielded 280 mg of liquid (±)-α-cuparenone (**17,** 92%): IR and ^{1}H NMR spectrally identical with an authentic specimen;[19] semicarbazone mp 231–232 °C (lit.[19] mp 233–234 °C).

3,5-Dimethyl-4-methoxymethylenecyclohexene (27). A mixture of 5.00 g of 2,6-dimethyl-3-cyclohexenecarboxaldehyde (**25a**),[26] 9.00 g of trimethyl orthoformate, and 0.05 mL of concentrated sulfuric acid in 25 mL of methanol was stirred at room temperature for 24 h and then treated with 1 g of sodium methoxide and evaporated under vacuum. After the addition of 20 mL of water and 20 mL of ether and extraction of the aqueous layer with ether the combined organic solutions were dried (Na_2SO_4). Evaporation of the solution yielded 6.20 g of liquid acetal **25b:** ^{1}H NMR δ 0.96, 1.08 (d, 3 each, J = 6 Hz, Me_2), 0.9–2.3 (m, 5, CH_2, $(CH)_3$), 3.33 (s, 6, $(OMe)_2$), 4.31 (d, 1, J = 7 Hz, O_2CH), 5.54 (m, 2, olefinic H). A mixture of 4.20 g of the latter and 0.05 mL of concentrated sulfuric acid was kept at 40 °C under a 10-Torr vacuum for 1 h. Distillation of the mixture then yielded 3.50 g of liquid enol ether **27** (43% from **25a**): bp 88–90 °C (10 Torr); IR (neat) C=C 5.98 (m), 6.05 μ (w); ^{1}H NMR δ 1.04 (d, 3, J = 6 Hz, Me), 1.05 (d, 3, J = 7 Hz, Me), 1.5–2.4 (m, 4, CH_2, $(CH)_2$), 3.56 (s, 3, OMe), 5.5–5.8 (m, 3, olefinic H). Anal. ($C_{10}H_{16}O$) C, H.

2,4-Dimethyl-3-methoxymethylenecyclohexene (29). A solution of 5.00 g of enol ether **27** and 3.60 g of dry potassium *tert*-butoxide in 25 mL of dry dimethylformamide was kept at 40 °C for 6 h and then poured into 100 mL of cold water and extracted exhaustively with hexane. The extract was washed with water, dried (Na_2SO_4), and evaporated carefully under vacuum. Chromatography of the residue on 100 g of neutral alumina, activity I, and elution with hexane gave 4.70 g of a liquid 3:1 mixture (by GC) of diene **29** (71%) and hydrocarbon **30** (29%). Repeated, fractional distillations afforded hemimellitylene (**30**) [bp 98–100 °C (10 Torr); ^{1}H NMR δ 2.14, 2.26, 2.26 (s, 3 each, Me_3), 6.96 (s, 3, aromatic H)] and dienol ether **29** [bp 110–112 °C (10 Torr); IR (neat) C=C 6.10 (m), 6.20 μ (w); ^{1}H NMR δ 1.01 (d, 3, J = 7 Hz, Me), 1.3–1.8 (m, 2, CH_2), 1.9–2.4 (m, 3, allyl CH_2, CH), 1.99 (broad s, 3, olefinic Me), 3.53 (s, 3, OMe), 5.31 (m, 1, olefinic H), 5.77 (broad s, 1, OCH)]. Anal. ($C_{10}H_{16}O$) C, H.

1-Acetonyl-2,6*c*-dimethyl-2-cyclohexene-(*r*-C^1)-carboxaldehyde (33) and 3-Acetonyl-2,6-dimethyl-2-cyclohexenecarboxaldehyde (34). Diazoacetone (5.80 g) was added dropwise over a 4-h period to a stirring mixture of 0.6 g of freshly prepared copper bronze and 3.53 g of diene **29** at 95 °C and the mixture heated for an additional 2 h. After the addition of 50 mL of cyclohexane and filtration of the mixture the solid was washed with more cyclohexane and the combined organic solutions were evaporated. Chromatography of the residual oil on 50 g of Florisil and elution with hexane led to the recovery of 1.74 g of dienyl ether **29.** Elution with benzene and 1:1 benzene–chloroform yielded 1.96 g of a mixture of cyclopropanes **31** and **32** IR (neat) C=O 5.92 (s), OC=C 6.00 μ (m)], whose instability and ready hydrolysis (especially **32**) was reflected in the slow appearance of a 5.83 μ, saturated carbonyl band in its IR spectrum. As a consequence the mixture was used in the next reaction without further attempts at separation.

A mixture of 1.96 g of the cyclopropane mixture and 10 mL of 1 N hydrochloric acid solution in 10 mL of ether was stirred at room temperature for 6 h. The aqueous layer was washed with ether and the combined organic solutions were dried (Na_2SO_4) and evaporated. Chromatography of the residual oil (1.77 g) on 40 g of Florisil and elution with benzene yielded 390 mg of liquid keto aldehyde **33** (9%, from **29**): IR (neat) CHO 3.70 (s), C=O 5.84 (s), C=C 6.02 μ (w); ^{1}H NMR δ 0.96 (d, 3, J = 6 Hz, Me), 1.48 (d, 3, J = 1 Hz, olefinic Me), 1.3–2.4 (m, 5, $(CH_2)_2$, CH), 2.16 (s, 3, COMe), 2.90 (d, 2, J = 5 Hz, $COCH_2$), 5.91 (m, 1, olefinic H), 9.48 (s, 1, CHO); bissemicarbazone mp 222–223 °C (H_2O–EtOH). Anal. ($C_{14}H_{24}O_2N_6$) C, H, N.

Elution with 1:1 benzene–chloroform gave 1.21 g of liquid keto aldehyde 34 (27%, from **29**): IR (neat) CHO 3.62 (w), C=O 5.82 (s), 6.01 (s), C=C 6.17 μ (m); ^{1}H NMR δ 1.01 (d, <3, J = 7 Hz, major Me), 1.02 (d, <3, J = 7 Hz, minor Me), 1.0–2.3 (m, 6, $(CH_2)_2$, $(CH)_2$), 2.16 (broad s, 3, olefinic Me), 2.21 (s, 3, COMe), 10.06 (s, 1, CHO); bissemicarbazone mp 239–239 °C (H_2O–EtOH). Anal. ($C_{14}H_{24}O_2N_6$) C, H, N.

6,10*t*-Dimethyl-(5*r*-C^1)-spiro[4.5]deca-3,6-dien-2-one (35). A mixture of 290 mg of keto aldehyde **33** and 5 mL of 0.1 N potassium hydroxide solution in 10 mL of methanol was stirred at room temperature under nitrogen for 4 h and then the alcohol evaporated under vacuum. The residue was acidified with 1 N hydrochloric acid solution and extracted with ether. The extract was washed with water, dried (Na_2SO_4), and evaporated. Chromatography of the residual oil (252 mg) on 5 g of Florisil and elution with benzene afforded 242 mg of liquid ketone **35** (95%): IR (5% CH_2Cl_2) C=O 5.84 (s), C=C 5.92 (s), 6.30 μ (m); ^{1}H NMR δ 0.90 (d, 3, J = 7 Hz, Me), 1.0–2.3 (m, 5,

$(CH_2)_2$, CH), 1.51 (t, 3, J = 1 Hz, olefinic Me), 2.32, 2.38 (s, 1 each, $COCH_2$), 5.62 (m, 1, olefinic H), 6.20 (d, 1, J = 6 Hz, CO-α-H), 7.45 (d, 1, J = 6 Hz, CO-β-H); spectra nearly identical with those of an authentic sample.[30] The absence of a comparison sample and of total identity of spectral characteristics required the execution of one more reaction.

6,10*t*-Dimethyl-(5*r*-C[1])-spiro[4.5]dec-6-en-2-one (24). A mixture of 142 mg of ketone **35**, 20 mg of 5% palladium–charcoal, and 0.2 mL of 10% sodium hydroxide solution in 3 mL of 95% ethanol was stirred at room temperature and 1 atm of hydrogen until 18.5 mL of gas had been absorbed. It then was filtered, the catalyst washed with ethanol, and the combined alcohol solution evaporated. The residue was acidified with 1 N hydrochloric acid and extracted with ether. The extract was dried (Na_2SO_4) and evaporated. Chromatography of the residual oil (136 mg) on 4 g of Florisil and elution with 1:1 hexane–benzene yielded 126 mg of liquid ketone **24** (90%): IR (neat) C=O 5.74 (s), C=C 6.11 μ (w); ^{1}H NMR δ 0.92 (d, 3, J = 6 Hz, Me), 1.4–2.3 (m, 11, $(CH_2)_5$, CH), 1.66 (d, 3, J = 2 Hz, olefinic Me), 5.38 (m, 1, olefinic H); spectra nearly identical with those of the Marshall–Johnson ketone **24**[23c] and totally superimposable on those of the Deslongchamps ketone **24**;[32] spectra totally different from those of the Caine–Dawson[33] and Deslongchamps[32] ketone **24** stereoisomer; 2,4-dinitrophenylhydrazone of **24** (lit.[23c] mp 107–109 °C) syn and anti forms, mp 125–127 °C (EtOH, pentane insoluble) (lit.[32] mp 125–127 °C), 149–151 °C (EtOH, pentane soluble) (lit.[32] mp 150–151 °C).

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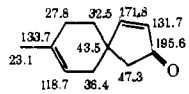
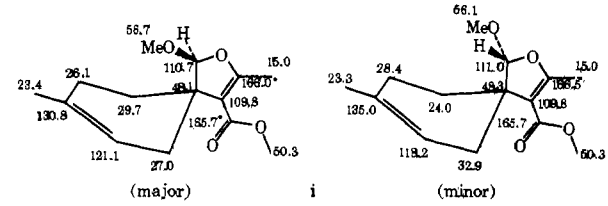
(12) Cf. A. L. Nussbaum, E. Yuan, D. Dincer, and E. P. Olivetto, *J. Org. Chem.*, **26**, 3925 (1961).
(13) G. I. Fray and R. Robinson, *J. Am. Chem. Soc.*, **83**, 249 (1961); E. F. Lutz and G. M. Bailey, *ibid.*, **86**, 3899 (1964).
(14) The Lewis acid catalyzed Diels–Alder reaction between isoprene and acrolein[13] yielded not only aldehyde 11, but also a solid, mp 163 °C, whose spectral properties revealed it to be a symmetrical trioxane trimer (E. Wenkert, A. A. Craveiro, and E. L. Sanchez, unpublished observations), e.g., ^{13}C NMR ($CHCl_3$) δ 24.0 (Me), 24.8 (C-6), 26.8 (C-2), 30.2 (C-5), 38.6 (C-1), 103.4 (O_2CH), 119.1 (C-3), 132.9 ppm (C-4).
(15) Cf. H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, **34**, 2324 (1969).
(16) The carbon shifts of this interesting spiro compound are listed in parts per million downfield from Me_4Si on the following formula (in $CDCl_3$; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm).



(17) The cyclopropanation of enol ether **13a** with ethyl α-diazacetoacetate was attempted, in order to permit elaboration of the product to a spiro ketone like **16**, carboalkoxylated on its α-ketomethylene group and hence structurally closer to the acorane skeleton. However, in analogy with the results of a concurrent study of the copper-assisted interaction of enol derivatives with α-diazo-β-dicarbonyl compounds[4l] the product proved to be dihydro-β-furoic ester i (see Experimental Section), the carbon shifts of whose two stereoisomers are depicted on the following formulas [in parts per million downfield from Me_4Si; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm].



(18) D. A. McCrae and L. Dolby, *J. Org. Chem.*, **42**, 1607 (1977).
(19) For the isolation and structure determination of the ketone see G. L. Chetty and S. Dev, *Tetrahedron Lett.*, 73 (1964); T. Irie, T. Suzuki, S. Ito, and E. Kurosawa, *ibid.*, 3187 (1967); B. Tomita, Y. Hirose, and T. Nakatsuka, *ibid.*, 843 (1968); V. Benesova, *Collect. Czech. Chem. Commun.*, **41**, 3812 (1976). For a previous synthesis see W. Parker, R. Ramage, and R. A. Raphael, *J. Chem. Soc.*, 1558 (1962).
(20) W. Strubell, *J. Prakt. Chem.*, **10**, 349 (1960).
(21) The oxidation has been reported to lead to a 85% yield of aldehyde and to have been performed in ether solution. Reinvestigation revealed the reaction to be more efficient in carbon tetrachloride or methylene chloride solution and furnish at best 40% of the aldehyde and 30% of *p*-methylacetophenone. The aldehyde could be separated from the ketonic product and purified by way of its bisulfite addition product.
(22) This reaction constitutes probably the most dramatic example of the ease of oxygen electron pair release through the cyclopropane carbon network to a neighboring cationic center among all β-oxycyclopropyl ketone transformations into γ-diketo systems[4] in view of the total preference of the **20** → **21** conversion over the otherwise facile fragmentation of the cyclopropane bond linking the keto- and aryl-substituted carbons and the resultant intermediacy of a tertiary, benzyl cation species.
(23) For the isolation and structure determination of the natural ketone see (a) A. St. Pfau and P. A. Plattner, *Helv. Chim. Acta*, **22**, 640 (1939); (b) J. A. Marshall and P. C. Johnson, *J. Am. Chem. Soc.*, **89**, 2750 (1967); (c) *J. Org. Chem.*, **35**, 192 (1970). For previos syntheses of **23** see ref. 23c; G. Stork, R. L. Danheiser, and B. Ganem, *J. Am. Chem. Soc.*, **95**, 3414 (1973); P. M. Mc Curry, Jr., and R. K. Singh, *Tetrahedron Lett.*, 3325 (1973); K. Yamada, H. Nagase, Y. Hayakawa, K. Aoki, and Y. Hirata, *ibid.*, 4963 (1973); G. Bozzato, J. P. Bachmann, and M. Pesaro, *J. Chem. Soc., Chem. Commun.*, 1005 (1974); M. Daighton, C. R. Hughes, and R. Ramage, *ibid.*, 662 (1975); W. G. Dauben and D. J. Hart, *J. Am. Chem. Soc.*, **97**, 1622 (1975); D. Caine, A. A. Boucugnani, S. T. Chao, J. B. Dawson, and P. F. Ingwalson, *J. Org. Chem.*, **41**, 539 (1976); G. Büchi, D. Berthet, R. Decorzant, A. Grieder, and A. Hauser, *ibid.*, **41**, 3208 (1976).
(24) The transformation of stereoisomer **24** into (±)-β-vetivone (**23**) has been accomplished by Marshall and Johnson.[23b]
(25) Treatment of aldehyde **25a** with sulfuric acid at −20 °C gave a 10% yield of its liquid isomer **26** [IR (neat) CHO 3.65 (w), C=O 5.98 (s), C=C 6.12 μ (m); ^{1}H NMR δ 1.01 (d, 3, J = 7 Hz, Me), 1.5–1.8 (m, 4, $(CH_2)_2$), 2.15 (broad s, 3, olefinic Me), 2.1–2.4 (m, 3, allyl CH_2, CH), 10.3 (s, 1, CHO)]. Exposure of the latter to trimethyl orthoformate in methanol in the presence of ammonium nitrate at room temperature yielded an acetal mixture, whose distillation from *p*-toluenesulfonic acid led to dienyl ether **29** [bp 62 °C (3 Torr); IR (neat) C=C 6.02 (w), 6.09 (m), 6.19 μ (w); ^{1}H NMR δ 0.98 (d, 3, J = 7 Hz, Me), 1.4–1.8 (m, 2, CH_2), 1.71 (m, 3, olefinic Me), 1.8–2.3 (m, 3, allyl CH_2, CH), 3.62 (s, 3, OMe), 5.39 (m, 1, olefinic H), 5.99 (broad s, 1, OCH)]. In view of the low yield of the first step this reaction sequence was abandoned.
(26) H. L. Holmes, K. Alcock, D. G. Demianiw, I. W. Robinson, C. E. Rooneg,

and F. A. Sundberg, *Can. J. Res., Sect. B*, **26**, 248 (1948); T. Inukai and S. Miyajima, Japanese Patent 68 08 463 (cl 16c 851) (April 2, 1968); *Chem. Abstr.*, **69**, 96063 (1968).
(27) Cf. C. C. Price and W. H. Snyder, *J. Am. Chem. Soc.*, **83**, 1773 (1961).
(28) The **25a** → **27** → **30** transformation corresponds to the conversion of a carbonyl group into a diene function. The scope of this unusual change of functional groups has been the subject of a recent study (L. N. Moreno, M. S. Dissertation, Rice University, 1976).
(29) Since the carbonyl compound **32**, is a β-oxycyclopropyl ketone vinylog, its regioselective unraveling and transformation into **34** is without surprise. However, it is noteworthy that this fragmentation constitutes the preparation of a 1,6-dicarbonyl compound and thus is of interest in organochemical synthesis. The generality of the **29** → **32** → **34** reaction sequence was the subject of a recent investigation.[4i]
(30) P. J. Kropp, *J. Am. Chem. Soc.*, **87**, 3914 (1965).
(31) This ether is stereoisomeric with the enol ether described in ref 25.
(32) Prepared as an offshoot of the total synthesis of (±)-epihinesol by M. Mongrain, J. Lafontaine, A. Belanger, and P. Deslongchamps, *Can. J. Chem.*, **48**, 3273 (1970) (P. Deslongchamps, private communication).
(33) D. Caine and J. B. Dawson, *Chem. Commun.*, 1232 (1970); D. Caine, A. A. Boucugnani, S. T. Chao, J. B. Dawson, and P. F. Ingwalson, *J. Org. Chem.*, **41**, 1539 (1976).

Measurement of Hydrogen Exchange at the Tyrosine Residues in Ribonuclease A by Stopped-Flow and Ultraviolet Spectroscopy

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Abstract: A time-dependent change in the ultraviolet absorbance at 285 nm of the phenol ring of tyrosine has been observed in a stopped-flow spectrophotometer, when tyrosine was rapidly transferred from water into deuterium oxide (the final tyrosine concentration was about 1 mM). From this experiment, the rate constant (k_e) of the hydrogen-deuterium exchange reaction of the tyrosine OH group has been determined at various pH values and at several temperatures. At pH 6.1 and 11 °C, for example, k_e was found to be as high as 70 s^{-1}. The stopped-flow ultraviolet spectroscopy has also been used for a measurement of hydrogen exchange rates at the six tyrosine residues of bovine pancreatic ribonuclease A.

Introduction

A measurement of the kinetics of the hydrogen exchange reactions of a protein in aqueous solution provides a useful piece of information on the conformation of the protein molecule. For peptide NH groups, such measurements have been made of many proteins, with various methods, by a number of investigators.[2-5] For side-chain hydrogen atoms, on the other hand, such measurements are relatively few; and in addition only tryptophan and histidine residues have so far been subjected to those measurements.[6-9] In this paper, we show that the hydrogen-deuterium exchange reaction of the tyrosine residue can be followed by stopped-flow ultraviolet spectroscopy. The stopped-flow ultraviolet method was first shown by Cross[10,11] to be applicable to a few nucleosides. We have recently shown that this method is useful for the hydrogen exchange study of the tryptophan residues of a protein.[12] The development of this method is of special significance for the tyrosine residue, because the hydrogen exchange rate at the tyrosine hydroxyl group is in general so high that no other methods seem to be easily applicable to its kinetic study. The stopped-flow ultraviolet method is useful not only because it is good for a millisecond exchange reaction but also because it is applicable to a high molecular weight protein in a relatively dilute solution.

Experimental Section

L-Tyrosine was purchased from Wako Pure Chemical Industries, Ltd., and bovine pancreatic ribonuclease A was obtained from Boehlinger Mannhein. Deuterium oxide (99.75%) was purchased from Merck.

The hydrogen and/or deuterium ion concentration of the solution were measured with a Toa Dempa pH meter and a Hitachi-Horiba F7SS pH meter. In this paper, we shall use the notation "pH" even for the deuterium ion concentration of a deuterium oxide solution, and pH-meter readings are always given without any corrections. For adjusting each pH value, HCl or NaOH was used.

Ultraviolet absorption and difference spectra were observed by the use of a Union Giken high-sensitivity spectrophotometer SM-401. The kinetics of the hydrogen-deuterium exchange reactions was examined by the use of a Union Giken stopped-flow spectrophotometer RA-401. This is equipped with a rapid-mixing device of dead time 500 μs, with a cell of optical path length 10 mm, and with an ultraviolet spectrophotometer of focal length 25 cm, sensitivity 0.0004 OD, and response time 0.1 ms. This was connected with a Union-Giken data processor RA-450, a monitor scope, and an *XY* plotter.

Results

Hydrogen-Deuterium Exchange in Free Tyrosine. When L-tyrosine in ^1H_2O is rapidly mixed with ^2H_2O (at pH 6.1 and 11 °C, final concentration is 0.97 mM), a time-dependent decrease of the absorbance at 285 nm is observed as shown in Figure 1(a). A replot of such data, as illustrated in Figure 1(c), shows that the absorbance decrease takes place as a single first-order process. By extrapolating the straight line in Figure 1(c) to zero time, we are able to determine the total absorbance change associated with this first-order process. The total absorbance changes measured in this way at several different wavelengths generate the kinetic difference spectrum shown in Figure 2. In this figure, the equilibrium solvent perturbation difference spectrum, which gives the total effect of ^2H_2O on the spectrum of L-tyrosine, is also shown (curve (b)). The difference between the kinetic difference spectrum and equilibrium solvent perturbation difference spectrum is attributed to a solvent perturbation which takes place during the dead time of the kinetic experiment.[10,11] The equilibrium solvent perturbation difference spectrum has two peaks at about 286 and 279 nm. The magnitude of the perturbation difference spectrum observed here is in an agreement with what was observed by Herkovits and Sorensen.[13]

The first-order process shown in Figure 1 is attributed to the hydrogen-deuterium exchange reaction of the phenol OH group of tyrosine. The rate constant is found to be 70 s^{-1} at pH

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