Intramolecular Photocycloaddition of Substituted Allenes to Conjugated Cyclohexenones

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Substituted allenes linked to cyclohexenones by hydrocarbon chains 1-5 were synthesized and irradiated with UV light. The product structures were determined, and the mechanism of the [2 + 2] cycloaddition is discussed. The possibility of using chiral allene as a template for the synthesis of chiral spiro systems is described.

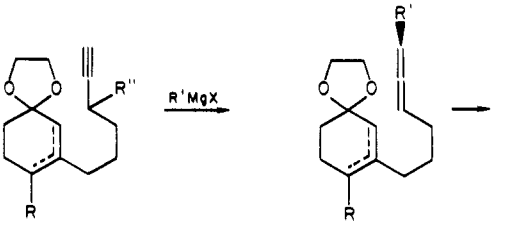
Intermolecular and intramolecular [2 + 2] photocycloadditions are well-known synthetic methods in organic chemistry. In a previous paper,[1] we presented the intramolecular addition of a terminal allene and discussed the factors which influence the regioselectivity. According to Corey's mechanism,[2] a 1,4-diradical is an intermediate which is produced by formation of one new bond. It remains to be determined which of the two new bonds is formed first. Wiesner[3] suggested a rule for the photocycloaddition stereochemistry of allenes to cycloalkenones, and although it is not fully accepted,[4] it was found to be very useful in predicting the structure of the main product. In this paper we shall discuss which one of the two new bonds is formed first. In view of our results which were obtained by irradiating 1,3-disubstituted allenes, it can be concluded that the first bond is formed to carbon β. In addition, we shall describe an attempt to prepare chiral spiro systems by utilizing chiral allenes as templates.

Synthetic Results

The required system was prepared by using two synthetic methods: (1) direct alkylation of the appropriate allenyllithium,[5] a short convenient route, although limited by the availability of the starting materials, and (2) formation of the allenic system by reaction of a Grignard[6] with the corresponding acetylene alkyl sulfonate.

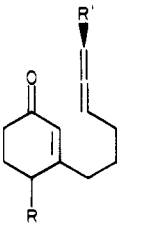
Compounds 1-3 were prepared as described in Scheme I. In the early stages, Crabbé's[7] procedure, using lithium dimethylcopper(I) at -60 °C, was followed to yield the unsubstituted allenic system. Our results are in agreement with a later publication of Crabbé,[8] who found that the reaction may be accompanied by reduction. We based our synthesis on Brandsma's[6] work, forming the allenic function by reacting the appropriate tosylate with a Grignard reagent in the presence of cuprous iodide. Removal of the protecting group under mild acidic conditions enabled isolation of the keto allene 1 in 22% yield. In the preparation of compounds 2 and 3, which were obtained in 36% and 24% yield, respectively, the mesylate (see Experimental Section) and a catalytic amount of copper salt were used since this simplified the workup and improved the yield.

Scheme I



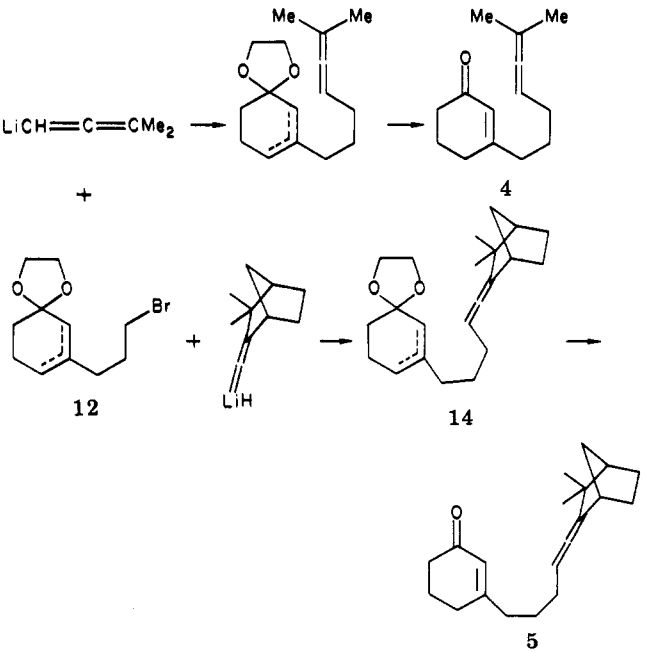
7, R = Me; R'' = OTs; R' = Me
9, R = H; R'' = OMs; R' = *t*-Bu
9, R = H; R'' = OMs; R' = Ph

8, R = R' = Me
10, R = H; R' = *t*-Bu
11, R = H; R' = Ph



1, R = R' = Me
2, R = H; R' = *t*-Bu
3, R = H; R' = Ph

Scheme II



The 1,1-disubstituted allenes were prepared by direct alkylation of allenyllithium (prepared from the corresponding allene and *n*-butyllithium in the presence of hexamethylphosphoramide) with the appropriate bromide, as described in Scheme II. The allenyllithium, prepared

(1) Becker, D.; Harel, Z.; Nagler, M.; Gillon, A. *J. Org. Chem.* **1982**, *47*, 3297.
(2) Corey, E. J.; Bass, I. D.; Mathieu, R.; Mitra, R. B. *J. Am. Chem. Soc.* **1964**, *86*, 5570.
(3) (a) Marini-Bettolo, G.; Sahoo, S. P.; Poulton, G. A.; Tsai, T. Y. R.; Wiesner, K. *Tetrahedron* **1980**, *36*, 719. (b) Wiesner, K. *Ibid.* **1975**, *31*, 1655.
(4) Loutfy, R. O.; de Mayo, P. *J. Am. Chem. Soc.* **1977**, *99*, 3559.
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(6) Vermeer, P.; Meijer, J.; Brandsma, L. *Recl. Trav. Chem. Pays-Bas* **1975**, *94*, 112.
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(8) Luche, J. L.; Barreiro, E.; Dollat, J. M.; Crabbe, P. *Tetrahedron Lett.* **1975**, 4615.

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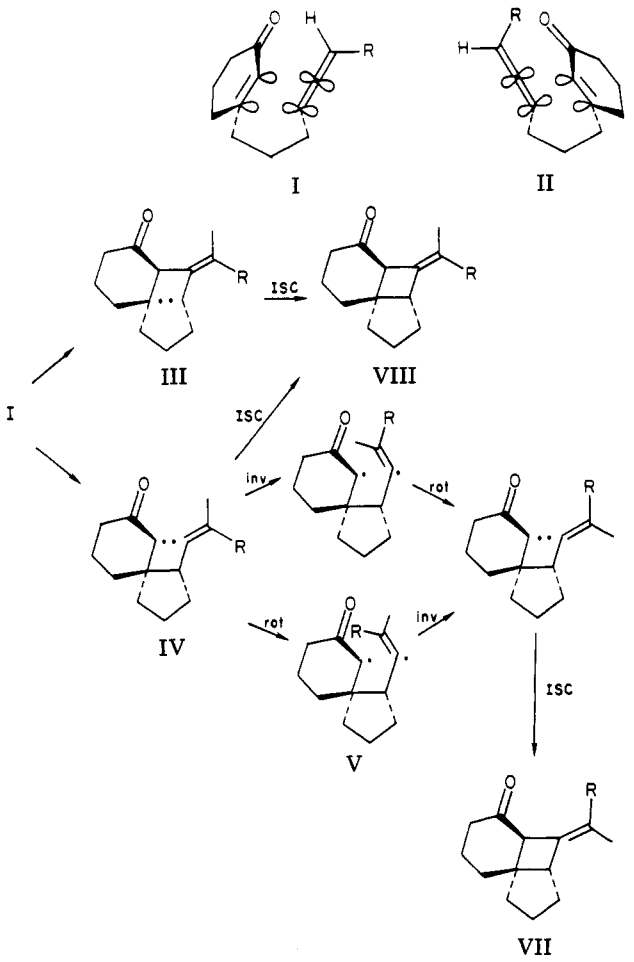
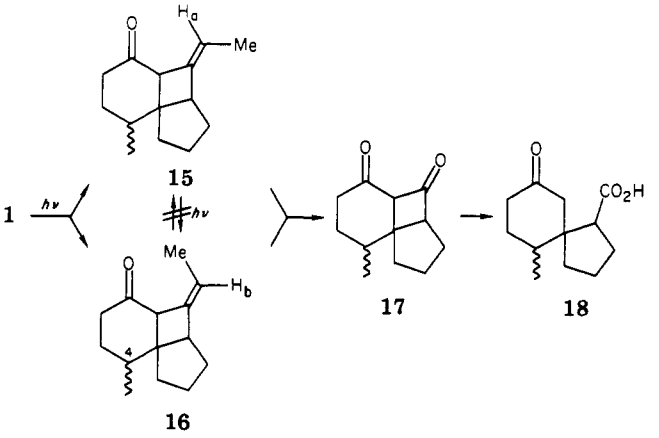
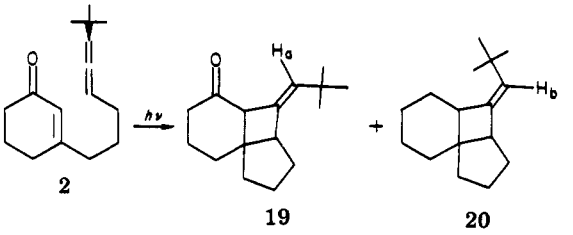
Scheme III



Scheme IV



Scheme V



from commercially available 3-methyl-1,2-butadiene, was condensed with bromo ketal **12**. An attempt to remove the ketal protecting group of the product with hydrochloric acid in methylene chloride–ethanol overnight at room temperature, as used successfully in the prepartion of **21**,[1] failed. Shortening the hydrolysis time, or substituting the hydrochloric acid by oxalic acid, enabled isolation of the keto allene **4** in moderate yield (40%) from the bromide **12**. The camphenylallene[9] was condensed, via the lithium salt, with bromo ketal **12** to give, after hydrolysis, keto allene **5**.

Discussion

It is generally accepted that [2 + 2] photocycloadditions of unsaturated bonds to conjugated cycloalkenones occur via a 1,4-diradical intermediate. Recently it has been suggested, based on new calculations, that the four-membered ring can be formed in one step.[10,11] However, if the 1,4-diradical, which has not been trapped so far, is an intermediate, it remains to be determined which site, C_α or C_β, of the conjugated system will be involved in forming the first new bond. It has been suggested recently[12] that C_α is more frequently the first site to react, but this assumption is open to question. In recent studies on the intermolecular photocycloadditions of ethylene,[13] acetylene,[14] and allene[15] to cyclo enones the authors preferred the assumption that the first new bond is formed at C_β. We planned to study whether the first bond is formed at C_α or C_β in intramolecular [2 + 2] photocycloaddition of 1,3-disubstituted allenes.

The system which was prepared for the investigation of the cycloaddition was designed so that the 1,3-disubstituted allenic function is separated by three carbons from the cyclohexenone moiety since it has been found that in the corresponding terminal allenes[1] the cycloaddition occurred regiospecifically. Assuming that the cycloaddition will form the product via parallel approach, as has been proven to be the case, it still remained to investigate which of the two possible geometrical isomers VII or VIII will be formed. On the basis of model studies it can be seen that of the two possible parallel approaches I and II, I is favored (Scheme III). The configuration of the group R will depend on the mechanism since isomer VIII alone will be formed either by concerted cycloaddition or via diradical III (which will be formed by preliminary bonding to C_α). On the other hand, the isomers VII and VIII will both be formed if diradical VI is an intermediate (initial bonding to C_β). Thus, if the assumption that approach I is highly favored, we have a way of distinguishing between the two possible intial bond formations and hopefully of providing an answer to an old problem.

Compound **1** was irradiated and a mixture of two geometric isomers, **15** and **16**, was isolated in 60% yield. The isomers were formed via a parallel approach as shown by oxidation to the corresponding 1,3-diketone **17**, which in turn was cleaved to give the known keto acid **18**[1] (Scheme IV). The ratio of the epimers at position 4 was found to be 1:2 based on NMR analysis.

The two geometrical isomers **15** and **16** are formed in a 1:1.1 ratio and could be separated by preparative layer chromatography (PLC). It was determined unequivocally

(9) Muhlstadt, M.; Quany Thanh, L.; Graege, J. *Tetrahedron* **1972**, *28*, 4389.
(10) Shaik, S.; Epiotis, N. D. *J. Am. Chem. Soc.* **1978**, *100*, 18.
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(12) Padwa, A. "Organic Photochemistry"; Buldwin, S. W., Ed.; Marcel Dekker: New York, 1981; Vol. 5, p 123.
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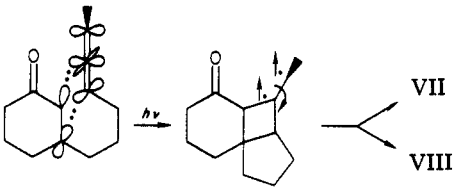
(14) Cargill, R. L.; Bushey, D. F.; Dalton, J. R.; Prasad, R. S.; Dyer, R. D.; Bordner, J. *J. Org. Chem.* **1981**, *46*, 3389.
(15) Blount, J. F.; Gray, G. D.; Atwal, K. S.; Tsai, T. Y. R.; Wiesner, K. *Tetrahedron Lett.* **1980**, *21*, 4413.

Scheme VI



X

that **15** and **16** do not isomerize under the irradiation conditions. The structure of the geometric isomers was determined by NMR analysis, using lanthanide shift reagents (LSRs), and will be discussed later. According to the results described herein, it is possible to assume that the first bond is formed at C_β. However, in order to exclude the possibility that the cycloaddition occurred via approach II, we synthesized the keto allene **2**, since examination of Dreiding models shows that approach II will become even more unfeasable when R = *t*-Bu. Compound **2** was irradiated to give two adducts **19** and **20** (Scheme V) in a 1:1.5 ratio (87% yield). The geometric isomers were separated by PLC, and their structure was determined by NMR. On the basis of the fact that two isomers were formed during the irradiation of **2**, we suggest that at least in [2 + 2] intramolecular photocycloaddition of the system investigated the first bond is formed to C_β.

It has been found in recent studies that triplet 1,4-diradicals can have lifetimes as long as 10^{-4} s,[16] and since it was suggested[17] that spin inversion in triplet diradicals is the rate-determining step in their disappearance, it is reasonable to describe the formation of the two isomers VII and VIII by the following steps. Approach I is highly favored, based on steric hindrance, and will lead to formation of diradical IV which can cyclize after intersystem crossing (ISC) to isomer VIII. On the other hand, diradical IV can also by combination of rotation and vinyl radical inversion[18] form diradical VI which after ISC would cyclize to isomer VII.

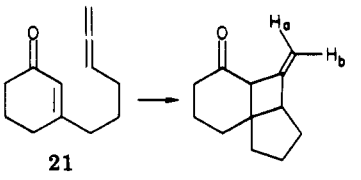
Another possible intermediate that should be considered is the triplet diradical X[19] which would be formed by interaction of the triplet enone with both perpendicular π systems of the allene as shown in Scheme VI.

Diradical X was excluded as a possible intermediate since it was shown that it forms isomers VII and VIII in ratios which are different from those obtained in the cycloaddition. Adducts **15**, **16**, **19**, and **20** were irradiated (λ = 254 nm) in the presence of phenanthrene which is known[20] to sensitize cis–trans isomerization of olefins via a triplet diradical. It was found that under these conditions pure **15** or pure **16** gave a mixture of **15** plus **16** in a 1:2.6 in contrast to the ratio of 1:1.1 obtained in the cyclization. Correspondingly, **19** or **20** gave a 1:16 ratio, while during the cyclization a 1:1.5 ratio was obtained.

The allene reaction with excited enone was shown to occur via the triplet state since quenching with di-*tert*-butyl nitroxide (DBN) obeys the Stern–Volmer relationship, as was found in cyclization of compound **21**. Additional information about the course of the reaction could be obtained by quantum yield measurements.

It is reasonable to assume that all the decay routes of the enone excited states occur at a rate independent of the

Scheme VII



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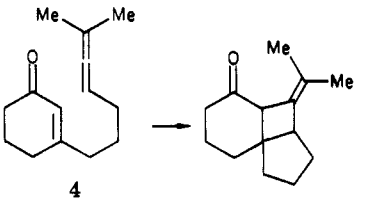
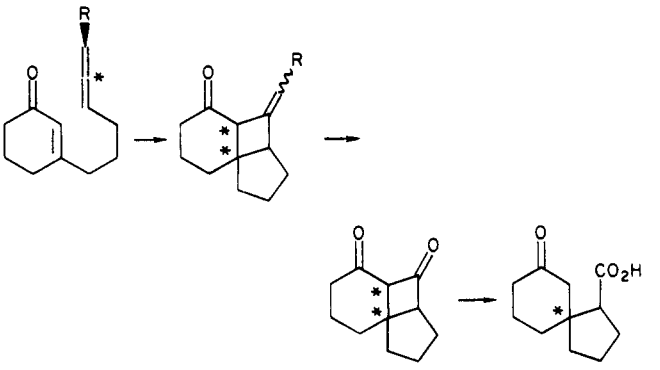
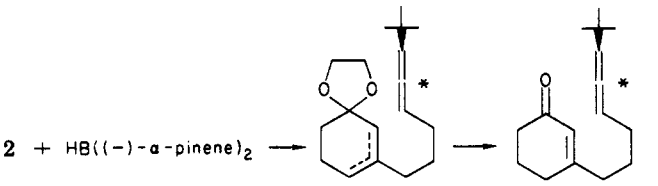


4 23

Scheme VIII



Scheme IX



10 2

nature of the substitutent on the allene. Thus, the quantum yields should provide information on the rates of cyclization.

It was found that the quantum yield for cyclization of **21** to **22**[1] (Scheme VII) was 0.81, while the quantum yields for the monosubstituted compounds **1**-**3** to products were 0.67, 0.63, and 0.60 respectively. These results are in accordance with our assumption of approach I, in which the small hydrogen atom of the allenic system is forced to face the enone. Since compounds **1**–**3** are monosubstituted, the probability for approach I is equal for all, and therefore the quantum yields are nearly identical. A higher quantum yield was found for compound **21** in which approach from both sides of the enone is equally possible. Support could be obtained by irradiation of the 1,1-disubstituted allene **4** which yields **23** in a quantum yield of 0.11, a decrease of 80%. Additional support for this mechanism was obtained from studies of the intramolecular photocycloaddition of olefins to cyclohexenones.[21]

Another method of quantitatively examining the selectivity of the approach of allene to enone is by using optically active allenes. If the cycloaddition occurs mainly from the less hindered face of the allene, the degree of stereoselectivity will be expressed by the ratio of the en-

(16) Wagner, P. J.; Liu, K.; Noguchi, Y. *J. Am. Chem. Soc.* **1981**, *103*, 3837.
(17) Engel, P. S. *Chem. Rev.* **1980**, *80*, 318.
(18) Eliel, E. L.; Allinger, N. L. "Topics in Organic Stereochemistry"; Sirmamura, O., Ed.; Wiley-Interscience: New York, 1969; Vol. 4, p 21.
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(21) To be submitted for publication.

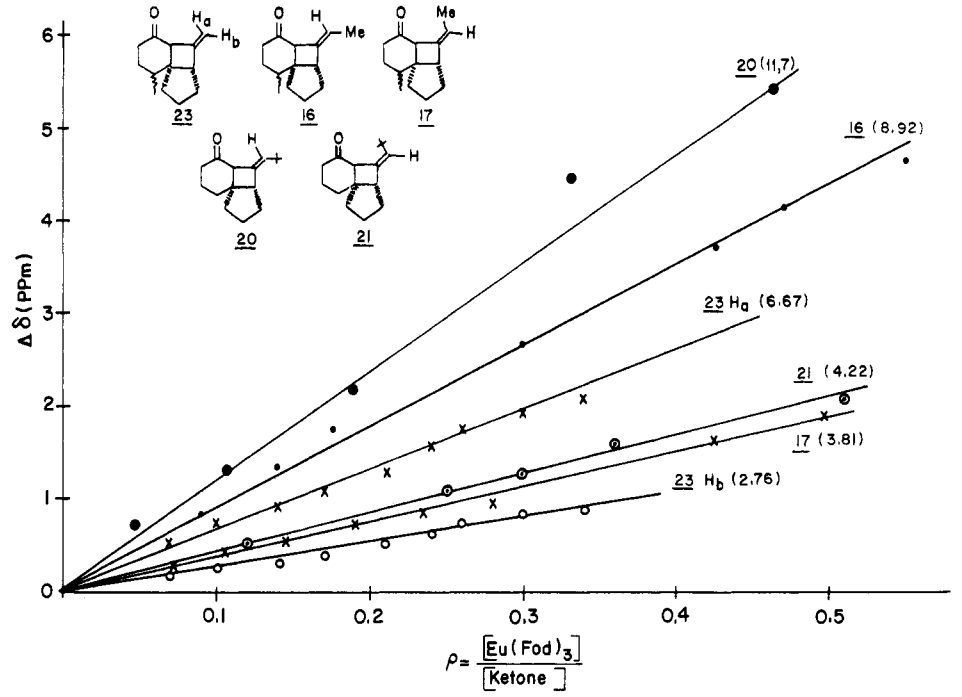


Figure 1.

antiomers in the spiro keto acid which can be obtained from the photoproducts by oxidation and cleavage as described in Scheme VIII.

High stereoselectivity will provide a method for preparation of the optically active keto acid with the required chirality by irradiating the corresponding optically active allene.

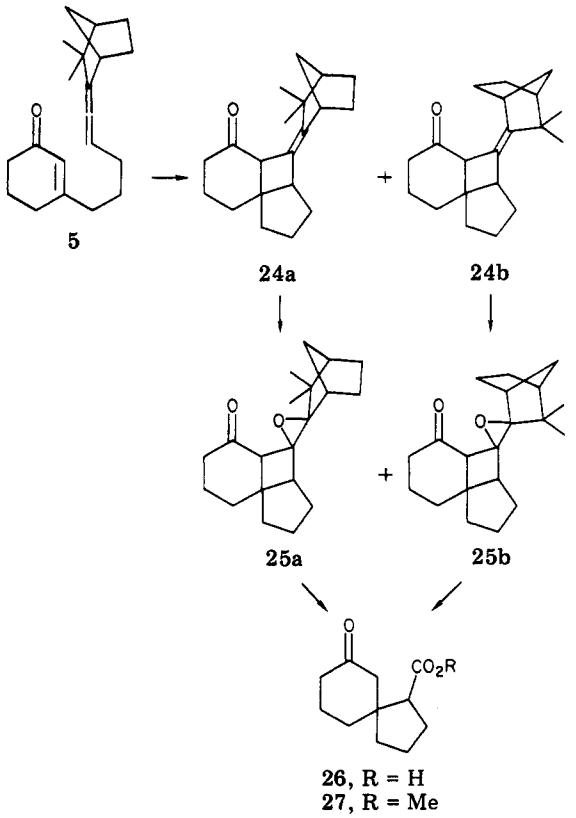
For analytical purposes the allene **2** was enriched in one enantiomer by using partial reduction with an optically active borane complex prepared from borane and (−)-pinene[22] (Scheme IX).

Circular dichroism measurements on the enriched allene **2*** and the products obtained after irradiation indicated optical activity. Since we were not successful in determining the ratio between the enantiomers in the enriched starting material **2*** (optically active LSR or optically active ketals), it was not possible to reach any conclusion about the stereoselectivity.

Another approach to prepare optically active compounds was based on natural starting materials which were commercially available such as (+)-camphene which was converted to the corresponding allene in two steps and condensed with the bromide **12** to give the keto allene **5**. We hoped to separate the two diastereomers which were formed during the alkylation, but all attempts by known methods (chromatography, distillation, crystallization) have failed so far. Despite this failure we examined wheter **5** could be converted to the corresponding keto acid **26** (Scheme X). Keto allene **5** was irradiated to give, in good yield, products **24a** and **24b** which could be transformed without separation to keto acid **26** in moderate yield. It is known that oxidative cleavage of tetrasubstituted olefins does not occur in high yield; two methods, (1) direct ozonolysis of **24** and (2) cleavage via the corresponding epoxides **25a** and **25b**, gave yields of about 50%.

Although we cannot yet report successful results in the preparation of optically active spiro systems using a chiral allene as template, a careful choice of the allenic system might lead to the desired spiro product.

Scheme X



26, R = H
27, R = Me

Structure Determination of the Geometrical Isomers

The structure of the corresponding geometrical isomers was determined by careful study of their NMR spectra in the presence of a lanthanide shift reagent (LSR). Since the structure of the adduct **23** was established unequivocally,[1] we could compare the shifts of its vinylic protons

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(23) Conia, J. M.; Rouessac, F. *Tetrahedron* **1961**, *16*, 45.
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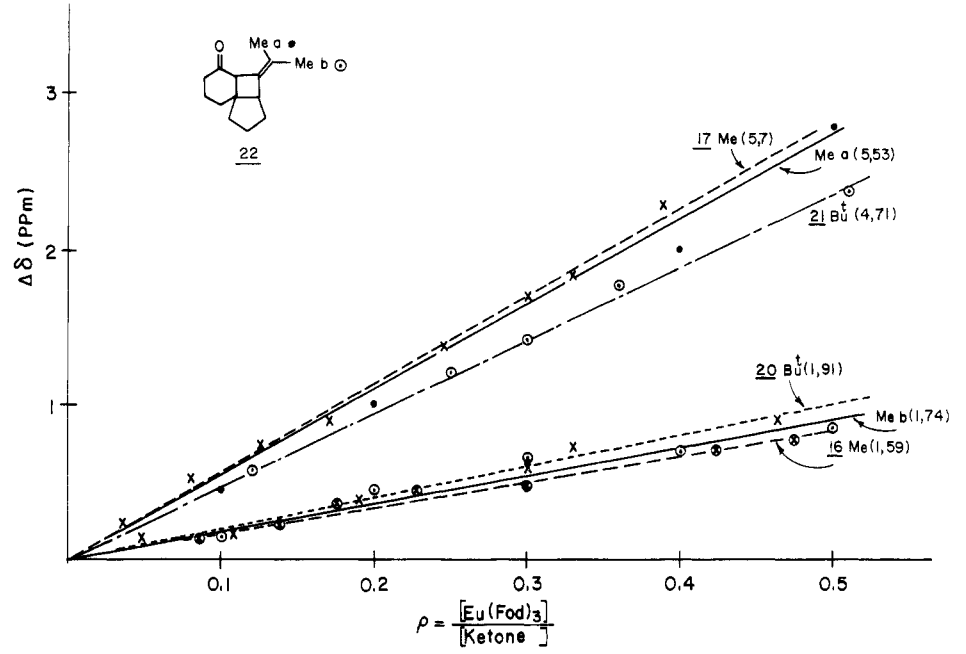

Figure 2.

H_a and H_b to the corresponding vinylic protons in the products of the monosubstituted allenes. It was also possible to check our assignment by comparing the shifts of the two methyl groups of adduct **24** with those of the adducts **16** and **17**.

As can be seen in Figure 1, by a plot of $\Delta\delta$ vs. ρ (moles of $Eu(Fod)_3$/mole of ketone) the shift of H_a is 2.4 times greater than the shift of H_b in **23**. The values of $\Delta\delta$ that were found for the vinylic protons of **17** and **21** were considerably smaller than those found for the vinylic protons of **16** and **20**, and the ratio of slopes from Figure 1 for the pairs **16/17** and **20/21** was found to be 2.3 and 2.7, respectively, which is in good agreement with the 2.4 ratio found for H_a/H_b in **23**. It was possible at that stage to determine the structure of the geometrical isomers, but the assignment was reexamined by comparing the shifts of the alkyl groups as can be seen in Figure 2. The ratio of the slopes for the two methyls in **24** was found to 3.1, and that for the methyls in **17/16** for 3.6. On the basis of this fit we could determine the structure of the geometric isomers with a high degree of confidence.

Experimental Section

General Methods. The (−)-α-pinene and 3-methyl-1,2-butadiene used in this study were obtained from the Fluka Co. The instruments used were as follows: ^1H NMR, Varian T-60; ^{13}C NMR, Bruker WP-60; MS, Varian MAT-711; IR, Perkin-Elmer 257; UV, Cary 15; PLC, preparative separations were effected on 500 μm (20 × 20) plates.

Irradiations were carried out in cyclohexane as the solvent under a nitrogen atmosphere. The commerical cyclohexane was purified by shaking with concentrated sulfuric acid and 10% sodium carbonate, irradiation via quartz with a 450-W Hanovia lamp for 4 h, and distillation. The cyclizations were carried out in concentrations of <0.05 mol by using a 450-W Hanovia lamp and a Pyrex filter (λ > 295 nm). The quantum yileds were measured by actinometry.[25] The reaction was followed by UV absorption of the starting material.

3-(4,5-Heptadienyl)-4-methyl-2-cyclohexen-1-one (1). Cuprus iodide (85 mg, 0.97 mmol) was stirred in a solution of **7**[1] (1.6 g, 4 mmol) in dry ether (10 mL) at 0 °C in a nitrogen atmosphere. An ethereal solution of 1.43 N methylmagnesium bromide (5.5 mL, 7.9 mmol) was slowly added, and the mixture stood for 30 min at room temperature. The reaction mixture was poured into an aqueous solution of ammonium chloride and extracted with ether. The organic solution was dired over anhydrous sodium carbonate, the solvent was removes, and the residue was dissolved in a mixture of methylene chloride (160 mL), ethanol (80 mL), water (3.2 mL), and concentrated hydrochloric acid (6.4 mL) and stirred overnight. The solvents were removed, water (100 mL) was added, the mixture was extracted with methylene chloride (4 × 120 mL) and dried, and the solvent was removed to yield a crude oil which was purified on a Florisil column (64 g) and eluted with hexane–methylene chloride (1:3) to yield 0.185 g (22%) of **1**: IR ($CHCl_3$) 1960 (CH=C=CH), 1655 cm^{-1} (C=C—C=O); NMR (CCl_4) δ 5.7 (s, 1 H), 5.0 (m, 2 H), 1.22 (d, J = 7 Hz, 3 H); UV (hexane) λ_{max} 227 nm (ε 11 000); MS, for $C_{14}H_{20}O$ m/e 204.1514 (theory 204.1514).

Irradiation of 1. A solution of **1** (69 mg, 0.34 mmol) in cyclohexane (150 mL) was irradiated for 1 h. GLC monitoring showed formation of two products in a 1.0:1.1 ratio, and these were separated by PLC (silica; acetone–hexane, 1:4) to yield 22 mg of the more polar product and 20 mg of the less polar one (60%). The products were identified as **15** and **16** correspondingly by NMR with LSR. Spectral data for **15**: IR($CHCl_3$) 1680 (C=O) cm^{-1}; NMR (CCl_4) δ 5.4 (m, 1 H), 3.0 (m, 2 H), 0.92 (d, J = 7 Hz, 3 H); UV (hexane) λ_{max} 297 nm (ε 110.5); MS, for $C_{14}H_{20}O$ m/e 204.1513 (theory 240.1514). For **16**: IR ($CHCl_3$) 1680 (C=O) cm^{-1}; NMR (CCl_4) δ 5.35 (m, 1 H), 3.1 (m, 2 H), 0.92 (d, J = 7 Hz, 3 H); UV (hexane) λ_{max} 308 nm (ε 57.7), 299 (58.5); MS, for $C_{14}H_{20}O$ m/e 204.1516 (theory 204.1514).

Ozonolysis of Photoproducts 15 and 16. Ozonolysis of **15** (17 mg, 0.08 mmol) and **16** (17 mg, 0.08 mmol) was carried out separately in the same manner as described for **22**[1] to yield in both cases the diketone **17**, which was in turn cleaved under mild acidic conditions to the keto acid **18**.[1]

Preparation of 9. A solution of 4-(3-oxo-1-cyclohexeneyl)-butanol[23] (7.9 g, 47 mmol) in dry pyridine (150 mL) was cooled to 0 °C and stirred, and acetyl chloride (6.0 mL, 84 mmol) was added dropwise in a nitrogen atmosphere. The cooling bath was removed for 45 min. The reaction mixture was cooled again, and an additional batch of acetyl chloride (60 mL, 84 mmol) was added. The mixture was then stirred for 1 h at room temperature, poured into water (1 L) and extracted with methylene chloride (4 × 200 mL). The extracts were combined, washed with 10% aqueous hydrochloric acid (2 × 750 mL), and dried, and the solvent was removed. The residue was dissolved in ether and filtered through Celite. Removal of the ether yielded 8.5 g (98%) of the cyclohexenone acetate 4-(3-oxo-1-cyclohexenyl)butyl acetate: IR ($CHCl_3$) 1730 (OAc), 1660 cm^{-1} (C=C—C=O); NMR (CCl_4) δ 5.8

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(s, 1 H), 4.06 (m, 2 H), 2.0 (s, 3 H); MS, for $C_{12}H_{18}O_3$ *m/e* 210.1252 (theory 210.1255). Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.30; H, 8.60.

Ketalization was carried out as described for preparation of **7**[1] (8.3 g, 49.4 mmol), yielding, after chromatography on a Florisil (200 g) column, 4.5 g (45%) of the ketal acetate 4-(1,4-dioxaspiro[4.5]deca-7-en-7-yl)butyl acetate: IR ($CHCl_3$) 1725 cm^{-1} (C=O); NMR (CCl_4) δ 5.36 (m, 1 H), 4.0 (m, 2 H), 3.87 (s, 4 H), 1.97 (s, 3 H); MS, for $C_{14}H_{22}O_4$ *m/e* 254.1493 (theory 254.1518). Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.11; H, 8.72. Found: C, 66.25; H, 8.75.

The ketal acetate was reduced with lithium aluminum hydride as described to yield the ketal alcohol 4-(1,4-dioxaspiro[4.5]-dec-7-en-7-yl)butanol: 92% yield; IR ($CHCl_3$) 3600–3479 cm^{-1} (OH); NMR (CCl_4) δ 5.37 (m, 1 H), 3.92 (s, 4 H), 3.54 (t, J = 6 Hz, 2 H), 2.9 (s, 1 H); MS, for $C_{12}H_{20}O_3$ *m/e* 212.1422 (theory 212.1404). Anal. Calcd for C, 67.89; H, 9.50. Found: C, 68.04; H, 9.82.

The ketal alcohol was oxidized to the corresponding ketal aldehyde 4-(1,4-dioxaspiro[4.5]deca-7-yl)butanal by Corey's procedure: 71% yield; IR ($CHCl_3$) 1720 cm^{-1} (C=O); NMR (CCl_4) δ 9.6 (m, 1 H), 5.4 (m, 1 H), 3.9 (s, 4 H); MS, for $C_{12}H_{18}O_3$ *m/e* 210.1245 (theory 210.1255).

The ketal aldehyde was condensed with lithium acetylide to yield quantitatively 6-(1,4-dioxaspiro[4.5]dec-7-en-7-yl)-1-hexyn-3-ol [IR ($CHCl_3$) 3570 (OH), 3280 cm^{-1} (C≡CH); NMR (CCl_4) δ 5.43 (m, 1 H), 4.33 (m, 1 H), 3.9 (s, 4 H); MS, for $C_{14}H_{20}O_3$ *m/e* 236.1412 (theory 236.1412)] which was converted into the ketal mesylate **9**: 92% yield. IR($CHCl_3$) 3300 (C≡CH), 2130 (C≡C), 1370 cm^{-1} (OSO_2); NMR (CCl_4) δ 5.45 (m, 1 H), 5.17 (m, 1 H), 3.9 (s, 4 H), 3.05 (s, 3 H).

3-(7,7-Dimethyl-4,5-octadienyl)-2-cyclohexen-1-one (2). The keto allene **2** was prepared as described for **1** from the corresponding ketal mesylate **9** (2.1 g, 6.7 mmol) and 0.87 N *tert*-butylmagnesium bromide (11.5 mL, 10 mmol) to yield 0.6 g (36%) of **10**: IR ($CHCl_3$) 1960 (C=C=C) cm^{-1}; NMR (CCl_4) δ 5.37 (m, 1 H), 5.07 (m, 2 H), 3.87 (s, 4 H), 1.02 (s, 9 H); MS, for $C_{18}H_{28}O_2$ *m/e* 276.2079 (theory 276.2089). The ketal allene **10** was quantitatively converted to **2**: IR (CCl_4) 1960 (C=C=C), 1680 cm^{-1} (C=O); NMR ($CDCl_3$) δ 5.94 (s, 1 H), 5.17 (m, 2 H), 1.03 (s, 9 H); UV λ_{max} 227 nm (ϵ 12600); MS, for $C_{16}H_{24}O$ *m/e* 232.1832 (theory 232.1826).

Irradiation of 2. A solution of **2** (0.13 g, 0.56 mmol) in cyclohexane (150 mL) was irradiated for 2 h. GLC monitoring showed formation of two isomers (87%) in a 1.5:1.0 ratio. These were separated by PLC (silica; acetone–hexane, 1:4) to yield 46 mg of **19** [IR ($CHCl_3$) 1960 cm^{-1} (C=O); NMR (CCl_4) δ 5.12 (t, J = 2 Hz, 1 H), 3.15 (m, 1 H), 2.95 (t, J = 3 Hz, 1 H), 1.03 (s, 9 H); UV λ_{max} 297 nm (ϵ 125.6); MS, for $C_{10}H_{24}O$ *m/e* 232.1817 (theory 232.1826)] and 69 mg of **20**; IR ($CHCl_3$) 1690 cm^{-1} (C=O); NMR (CCl_4) δ 5.22 (t, J = 2 Hz, 1 H), 3.25 (t, J = 3 Hz, 1 H), 3.0 (m, 1 H), 1.0 (s, 9 H); UV λ_{max} 301 nm (ϵ 92.3); MS, for $C_{16}H_{24}O$ *m/e* 232.1828 (theory 232.1826). Anal. Calcd for $C_{16}H_{24}O$: C, 82.7; H, 10.41. Found: C, 82.78; H, 10.29.

Asymmetric Hydroboration of 10. A solution of boron trifluoride etherate (0.316 g, 2.22 mmol) in dry diglyme (2 mL) was slowly added to stirred mixture of (−)-α-pinene (0.604 g, 4.44 mmol) and sodium borohydride (70 mg, 1.85 mmol) in diglyme (2 mL) at 0 °C for 4 h. A cold solution of **10** (0.93 g, 3.37 mmol) in diglyme (2 mL) was quickly added, and the mixture was stirred at 0 °C for 17 h, poured into water, and extracted with pentane. Removal of the solvent yielded 1.7 g of crude ketal allene which was chromatographed on a Florisil (70 g) column to yiled 0.4 g of starting material **10**, optically active according to ORD and CD.

3-(6-Phenyl-4,5-hexadienyl)-2-cyclohexen-1-one (3). To a solution of **9** (0.5 g, 1.6 mmol) in 30 mL of dry ether and cuprous iodide (0.05 g, 0.26 mmol) was added 1.66 mL (2 mmol) of phenylmagnesium bromide. Preparation of **3** was carried out as described for **2** in 24% yield: IR ($CHCl_3$) 1960 (HC=C=CH_2), 1685 cm^{-1} (C=C—C=O); NMR (CCl_4) δ 7.26 (s, 5 H), 6.18 (m, 1 H), 5.76 (s, 1 H), 5.55 (m, 1 H); MS, for $C_{18}H_{20}O$ *m/e* 252.3590 (theory 252.3595).

3-(6-Methyl-4,5-heptadienyl)-2-cyclohexen-1-one (4). 3-Methyl-1,2-butadiene (0.1 g, 1.4 mmol) was added to 10 mL of dry tetrahydrofuran and cooled to −78 °C under nitrogen atmosphere. *n*-Butyllithium (1 mL, 1.3 mmol in hexane) was added dropwise followed 15 min later by a solution of the bromo ketal **12** (0.3 g, 1.15 mmol) in 0.5 mL of dry hexamethylphosphoramide which was added to the mixture under stirring. After 30 min, the cooling bath was removed, and 10 mL of water was added when the reaction mixture reached room temperature. The organic phase was extracted with ether (3 × 20 mL), washed with water, and dried, and the solvent was removed to yield 0.27 g of yellow oil which was dissolved in a mixture of 30 mL of methylene chloride, 18 mL of ethanol, 0.8 mL of water, and 1.8 mL of concentrated hydrochloric acid in a nitrogen atmosphere at room temperature and stirred for 2 h. The solvents were removed, 5 mL of water was added, the organic layer was extracted with ether (4 × 10 mL) and dried, and the solvent was again removed to yield 0.2 g of a oily compound. The keto allene was purified by PLC on silica gel eluted with 1:3 acetone–hexane, yielding 0.09 g of **4**: 40% overall yield; IR ($CHCl_3$) 1960 (CH=C=CH_2), 1685 cm^{-1} (=C—C=O); NMR ($CDCl_3$) δ 5.9 (s, 1 H), 4.98 (m, 1 H), 1.62 (d, J = 2 Hz, 6 H); MS, for $C_{14}H_{20}O$ *m/e* 204.1517 (theory 204.1514).

Irradiation of 4. The keto allene **4** (0.12 g, 0.59 mmol) was dissolved in 150 mL of cyclohexane and irradiated for 45 min, with the reaction monitored by GC. Removal of the solvent yielded 0.12 g of an oily mixture which was purified by PLC on silica gel eluted with 1:3 acetone–hexane, yielding 0.075 g (62%) of the product **23**: IR ($CHCl_3$) 1695 cm^{-1} (C=O); MS, for $C_{14}H_{20}O$ *m/e* 204.1501 (theory 204.1514). Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.44; H, 9.84.

Isomerization of Product 15 or 16. Product **15** or **16** (3 mg, 0.016 mmol) and phenanthrene (5 mg, 0.003 mmol) were dissolved in hexane (3 mL) and irradiated at λ = 254 nm (Philips 125W). The mixture reached a steady state after 6 h of irradiation in a nitrogen atmosphere, the ratio of **16**/**15** was determined by GLC to be 1:2.6 respectively.

Isomerization of Product 19 or 20. Isomerization of **19** or **20** was carried out as described for **15**, and the steady-state ratio of **20**/**19** after 16 h of irradiation was found to be 16:1, respectively.

3-[3-[3-(+)-Camphenylallenyl]propyl]-2-cyclohexen-1-one (5). Alkylation of (+)-camphenylallene[24] (1 g, 6.75 mmol) with the bromo ketal **12**[1] was carried out as described for **4**, and the keto allene **5** was isolated: 80% yield; IR ($CHCl_3$) 1915 (CH=C=C), 1660 cm^{-1} (C=C—C=O); NMR (CCl_4) δ 5.74 (s, 1 H), 5.12 (t, 1 H), 1.04 (s, 6 H); MS, for $C_{20}H_{28}O$ *m/e* 284.2132 (theory 284.2139). Anal. Calcd for $C_{20}H_{28}O$: C, 84.45; H, 9.92. Found: C, 84.84; H, 10.20.

Irradiation of 5. The keto allene **5** (88 mg, 0.31 mmol) was dissolved in 150 mL of cyclohexane and irradiated as described for **4**, and the adduct was isolated by PLC (silica gel, eluted with 1:4 acetone–hexane), yielding 49 mg (56%) of the two isomers **24a,b** in a 1:1 ratio: IR ($CHCl_3$) 1690 cm^{-1} (C=O); NMR ($CDCl_3$) for **24a** δ 3.17 (s, 1 H), 3.06 (m, 1 H), 2.70 (m, 1 H), 1.25 (s, 3 H), 1.10 (s, 3 H); for **24b** δ 3.23 (s, 1 H), 3.01 (m, 1 H), 2.78 (7, 1 H) 1.03 (s, 3 H), 0.91 (s, 3 H); MS, for $C_{20}H_{28}O$ isomer **24a** *m/e* 284.2129, for isomer **24b** *m/e* 284.2148 (theory 284.2139).

Cleavage of Products 24a,b via Epoxide 25. *m*-Chloroperbenzoic acid (0.74 g, 4.3 mmol) dissolved in chloroform (11 mL) was added to a solution of the adducts **24a,b** (0.68 g, 2.4 mmol) in chloroform (4 mL) and stirred for 15 min at room temperature. Ether (25 mL) was added, and the solution was washed with 10% aqueous sodium bicarbonate (2 × 10 mL) and dried. The solvents were then removed, yielding 0.65 g (90%) of the crude epoxides **25a,b**: IR ($CHCl_3$) 1690 cm^{-1} (C=O); NMR (CCl_4) δ 2.93 (s, 1 H); MS, for $C_{20}H_{28}O_2$ *m/e* 300.2082 (theory 300.2089).

The crude mixture of epoxides **25a,b** (0.25 g, 0.83 mmol) was dissolved in tetrahydrofuran (20 mL). Periodic acid (15.5 mg) was added and the solution stirred overnight at room temperature. Water (50 mL) was then added, the mixture was extracted with ether (3 × 25 mL), and the organic layers were combined and extracted with (3 × 25 mL) of aqueous 10% sodium hydroxide, acidified with 10% hydrochloric acid, and again extracted with ether. The solvent was removed, yielding 75 mg (47%) of the keto acid **26**. The latter was in turn dissolved in an excess of diazomethane in ether to yield 70 mg of the keto ester **27**: IR ($CHCl_3$) 1720–1705 cm^{-1}; NMR (CCl_4) δ 3.62 (s, 3 H); MS, for $C_{12}H_{18}O_3$ *m/e* 210.1273 (theory 210.1256).

Registry No. 1, 85956-82-7; 2, 85956-83-8; 3, 85956-84-9; 4, 85956-85-0; 5, 85956-86-1; 7, 85956-77-0; 9, 85956-87-2; 10, 85956-79-2; 12, 85956-81-6; 15 (epimer 1), 85956-88-3; 15 (epimer 2), 85944-22-5; 16 (epimer 1), 85994-23-6; 16 (epimer 2), 85994-24-7; 19, 85956-89-4; 20, 85994-25-8; 23, 85956-90-7; 24a, 85956-91-8; 24b, 85994-26-9; 25a, 85956-92-9; 25b, 85994-27-0; 26, 85956-93-0; 27, 85956-94-1; MeBr, 74-83-9; *t*-BuBr, 507-19-7; PhBr, 108-86-1; (+)-camphenylallene, 38996-68-8; 4-(3-oxo-1-cyclohexenyl)butanol, 78877-14-2; 4-(3-oxo-1-cyclohexenyl)butyl acetate, 85956-95-2; 4-(1,4-dioxaspiro[4.5]dec-7-en-7-yl)butyl acetate, 85956-96-3; 4-(1,4-dioxaspiro[4.5]dec-7-en-7-yl)butanol, 85956-97-4; 4-(1,4-dioxaspiro[4.5]dec-7-en-7-yl)butanal, 85956-98-5; lithium acetylide, 1111-64-4; 6-(1,4-dioxaspiro[4.5]dec-7-en-7-yl)-1-hexyn-3-ol, 85956-99-6; 3-methyl-1,2-butadiene, 598-25-4.

Regiospecific Homologation of Unsymmetrical Ketones[1-3]

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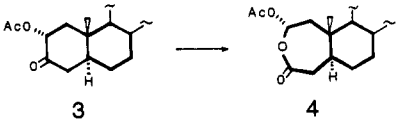
A method has been developed for the regiospecific homologation of unhindered unsymmetrical ketones. The procedure consists of preparation of a pure α-halo ketone, reaction of this derivative with ethyl diazoacetate and boron trifluoride etherate, removal of the halogen by zinc reduction, and finally decarbethoxylation with water at 230 °C or with $CaCl_2 \cdot 2H_2O$ in dimethyl sulfoxide at 150 °C. The method depends on the electron-withdrawing power of the α-halogen to prevent the migration of the attached carbon. *A*-Homo steroid ketones are most conveniently prepared by this method. The reaction of α-acetoxy ketones with ethyl diazoacetate also leads mainly to migration of the unsubstituted α'-carbon atom.

Although the regiospecific homologation of ketones is a potentially valuable synthetic operation, there is no convenient general method for achieving this transformation. Homologation of ketones by diazoalkanes,[4-6] diazoacetic esters,[7,8] or the Tiffeneau–Demjanov reaction[9] proceeds in good yields, but with unsymmetrical ketones these reactions usually give both regioisomers.[4-6,8-13] Some more recently developed procedures also suffer from the disadvantage of giving two isomeric homo products.[14] Even for unsymmetrical ketones which happen to give a single homo product, it might be desirable to prepare the other isomer. Therefore, we have devised a simple method for regiospecific homologation which is applicable to unhindered cyclic and noncyclic ketones.

The stumbling block in the homologation reactions mentioned above is the closely matched migratory aptitudes of the α- and α'-carbon atoms of the ketones. If the migratory tendencies could be further differentiated by the introduction of an α-substituent that could be removed later, a way would be opened to overcome the migratory problem. Recent observations along these lines were encouraging. Thus, while the Baeyer–Villiger oxidation of 5α- and 5β-cholestan-3-one gave nearly equimolar mixtures of both *A*-homo lactones,[10] the oxidation of several α-bromo- and α-chlorocholestan-3-ones, although slower, gave a single α-halo lactone from each reaction, e.g., **1** → **2**.[15,16] Apparently, the electron-withdrawing effect of the α-halogen completely suppressed the migration of the carbon bearing it. In complementary fashion, it was noted that Baeyer–Villiger oxidation of 2α- and 2β-acetoxy-5α-cholestan-3-one also afforded a single product each, but in these cases only the α-acyloxy-bearing carbon atom migrated to oxygen, e.g., **3** → **4**.[17] The cation-stabilizing effect of the unshared oxygen electrons had increased the relative migratory aptitude of the attached carbon.[18]

1 X = Br, Cl **2**



3 **4**

(1) This work is respectfully dedicated to Professor William S. Johnson on the occasion of his 70th birthday.

(2) α-Halo Ketones. 10. For part 9, see E. W. Warnhoff and F. W. Yerhoff, *Heterocycles*, **15**, 777 (1981).

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