Perhydroazulenes. 5. Preparation of Perhydroazul-9(10)-en-4-one[1]

Herbert O. House,* Joseph H. C. Lee, Don VanDerveer, and Jane E. Wissinger

School of Chemistry, Georgia Institute of Technology, Atlanta, Georgia 30332

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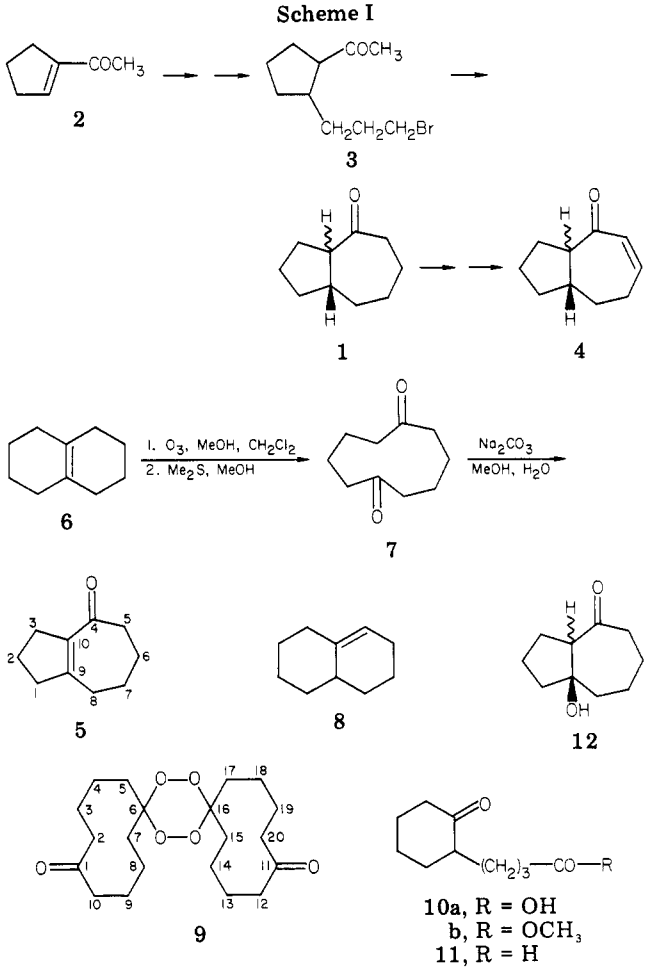
An improved procedure for the preparation of perhydroazul-9(10)-en-4-one is described. Crystal structures were determined for two of the reaction intermediates, 1,6-cyclodecanedione and the cyclic diperoxide derived from 1,6-cyclodecanedione. Measurements of ^{13}C NMR data at various temperatures were used to determine an activation free energy of 14.8 kcal/mol at 298 K for interconversion of the two chair conformers of the cyclic diperoxide.

In our earlier studies of perhydroazulenes[2] we prepared the parent ketone **1** (a mixture of stereoisomers; see Scheme I) from the cyclopentenyl ketone **2** in a three-step sequence involving cyclization of the intermediate bromo ketone **3**. The parent ketone **1** served as a precursor for the enone **4**.[2b] Although the parent ketone **1** could also be considered a likely synthetic precursor for the isomeric enone **5**, an alternative synthetic pathway appeared to be more efficient. In this alternative pathway, first described by Huckel and co-workers,[3,4] the octalin **6** was ozonolyzed to form the diketone **7**. Subsequent intramolecular aldol condensation of the diketone **7** formed the enone **5**.

A detailed procedure has been described[5] for the reduction of naphthalene to a mixture of octalins **6** (80–83% of mixture) and **8** (17–20% of mixture) by the use of a solution of lithium in a mixture of dimethylamine and ethylamine. This procedure was reported to be superior to earlier procedures in which either naphthalene or tetralin was reduced with solutions of lithium in various pure amines (including n-$PrNH_2$).[6] Our subsequent experimentation with these procedures has led us to conclude that reduction of tetralin with a solution of lithium in n-$PrNH_2$ is both experimentally simpler and is a more efficient way to form a mixture of octalins **6** (78%) and **8** (22%) in 88–92% yield.

Although the previously described procedure[5] for the formation of the octalins **6** and **8** also includes an effective procedure for the separation of the two olefins, this separation is not necessary for our application. Reaction of the mixture of octalins with ozone in MeOH can be expected[7] to form a mixture of the crystalline diketone **7** (from octalin **6**), the known[8] acid derivatives **10**, and the keto aldehyde **11** (from octalin **8**). In practice the diketone was readily separated from this mixture by first washing the crude product with aqueous $NaHCO_3$ and then washing the crude product with pentane to leave the relatively insoluble diketone **7**. Further reaction of this partially purified diketone **7** with Na_2CO_3 in boiling aqueous MeOH

Scheme I



formed the enone **5** in 86% yield (73% based on the starting octalin **6**). In one experiment where the crude diketone **7** was heated prior to isolation, some of the known[9] hydroxy ketone **12** was isolated.

The conformation of the solid diketone **7** (see Figure 3) was determined from the crystal structure of the material as illustrated in Figure 1. In one experiment where the octalin mixture was ozonolyzed in CH_2Cl_2 and then treated with aqueous KI rather than Me_2S during the reductive isolation procedure, reduction was incomplete and a portion of the product was isolated as the known,[10] crystalline

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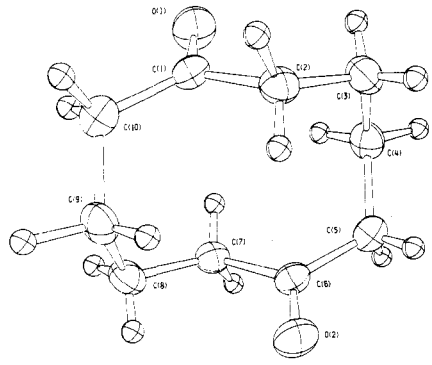

Figure 1. Perspective view of the molecular structure of 1,6-cyclodecanedione.

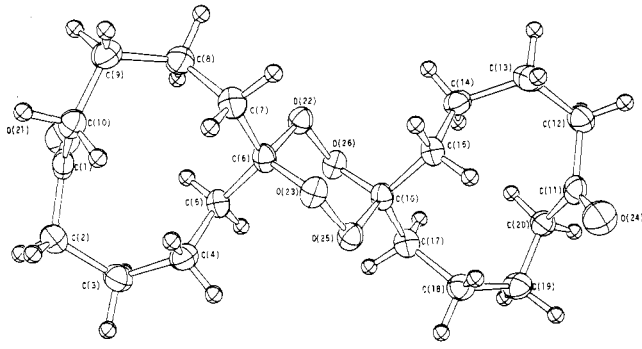

Figure 2. Perspective view of the molecular structure of the dimeric peroxide from 1,6-cyclodecanedione.

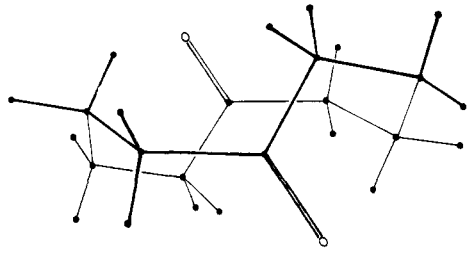

Figure 3. Conformation of crystalline 1,6-cyclodecanedione.

diperoxide **9**. The structure and solid-state conformation of this material were determined by X-ray crystallography as illustrated in Figure 2. In the crystal, the 6-membered tetroxane ring of the diperoxide **9** is present as a chair and each 10-membered ring has a conformation similar to that present in the solid diketone **7**. The diperoxide **9** has a crystallographic center of inversion. The ^{13}C NMR spectrum of the diperoxide **9**, when determined at ca. 35 °C, exhibited a spectrum with fewer than the expected number of lines (see Experimental Section). This spectrum proved to be temperature dependent with coalescence temperatures for several of the lines in the range 337–348 K. The compound in solution is equilibrating between two equivalent chair conformations with a free energy of activation of 14.8 kcal/mol at 298 K. This activation energy value corresponds with values observed (12.6–15.4 kcal/mol at 298 K) for the chair–chair interconversions of other 3,3,6,6-tetrasubstituted 1,2,4,5-tetroxanes.[11]

Experimental Section[12]

Preparation of Δ^9-Octalin (6). To 500 mL of *n*-$PrNH_2$ (bp 49 °C, freshly distilled from Na) was added 27.6 g (209 mmol) of freshly distilled tetralin (bp 83 °C (15 mm)) and 8.8 g of Li (1.26 mol, pieces of wire). The resulting mixture, which ranged in color from yellow to pink to purple, was stirred under an N_2 atmosphere at 25 °C for 6 h. At this time analysis (GLC) of an aliquot of the reaction solution indicated that all of the tetralin had been consumed and that no $\Delta^{2,9}$-hexahydronaphthalene was present. After the reaction mixture had been cooled to 0 °C, solid NH_4Cl was added cautiously to the reaction solution until all the excess Li had been consumed (purple color discharged). Then the bulk of the amine solvent was removed from the mixture by distillation through a Vigreux column. The pale yellow residue was partitioned between H_2O and Et_2O and the organic layer was washed successively with aqueous HCl and with aqueous NaCl. After the ethereal layer had been dried and concentrated, the colorless residue, which was protected from atmospheric oxygen, was distilled under reduced pressure to separate 26.0 g (92%) of a mixture of octalins **6** and **8** as a colorless liquid, bp 76–78 °C (15 mm), n^{25}_D 1.4971. GLC analysis (silicone XE-60 on Chromosorb P, apparatus calibrated with authentic samples) indicated the presence of 22% of octalin **8** (retention time 11.8 min) and 78% of octalin **6** (13.1 min) but no tetralin (31.1 min) or $\Delta^{2,9}$-hexahydronaphthalene (21.9 min). The physical properties and IR and NMR spectra of our product correspond to the values for the same mixture of octalins **6** and **8** [bp 72–77° (14 mm), n^{23}_D 1.4978] formed by the reduction of naphthalene with Li in a mixture of $EtNH_2$ and Me_2NH.[5]

A 7.7-g sample of this mixture of octalins **6** and **8** was fractionally distilled through a 55-cm spinning band column to separte 0.60 g of early fractions (n^{25}_D 1.4923–1.4942) containing (GLC, silicone XE-60 on Chromosorb P at 80 °C) 90–97% of the octalin **8** (retention time 23.6 min) and 3–10% of the decalins (15 and 20.4 min). After separation of 1.00 g of intermediate fractions, the final fractions (5.15 g, n^{25}_D 1.4979, lit.[5] n^{20}_D 1.4990) contained 1–2% of the octalin **8** and 98–99% of the octalin **6** (retention time 27.4 min). Employing *n*-$C_{11}H_{24}$ (retention time 14.2 min) as an internal standard, the GLC response factors were 0.82 for octalin **8** and 0.92 for octalin **6**.

Ozonolysis of the Octalin 6. A. Isolation of the Diketone 7. A stream of O_2 containing 3–4% O_3 was passed through a cold (0 °C) solution of 13.6 g (100 mmol) of a mixture of octalins **6** (78%) and **8** (22%) in 125 mL of MeOH and 25 mL of CH_2Cl_2 for 3.5 h. After the solution had been purged with N_2, 11.0 mL (150 mmol) of Me_2S was added and the solution was allowed to warm to 25 °C with stirring for 1 h. The solvent was removed under reduced pressure and the residual solid was dissolved in CH_2Cl_2 and washed with aqueous $NaHCO_3$. After the organic solution had been dried and concentrated, the residual semisolid was recrystallized from Et_2O to separate 10.4 g (79%) of the crude diketone **7** as a colorless solid, mp 92–100 °C, that contained (NMR analysis) minor amounts of the ketol **12**. An additional recrystallization from Et_2O separated 5.0 g of the diketone **7** as colorless prisms, mp 98–100 °C. Further recrystallization from Et_2O followed by sublimation (40 °C at 0.25 mm) afforded the pure diketone **7** as colorless prisms, mp 99–100 °C [lit. mp 99.5–100.5 °C,[13] 101–102 °C[14]]. The spectral properties of the diketone **7** follow: IR (CCl_4), 1712 cm^{-1} (C=O); ^1H NMR ($CDCl_3$,

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(12) All melting points are corrected and all boiling points are uncorrected. Unless otherwise noted, $MgSO_4$ was employed as a drying agent. The IR spectra were determined with a Perkin-Elmer, Model 299, infrared recording spectrophotometer fitted with a grating. The UV spectra were determined with either a Cary, Model 14, or a Perkin-Elmer, Model 202, recording spectrophotometer. The ^1H NMR spectra were determined at 60 MHz with a Varian Model T-60A, NMR spectrometer or at 300 MHz with a Bruker, Model WM-300, NMR spectrometer. The ^{13}C NMR spectra were determined at 25 MHz with a JEOL, Model PFT-100, NMR spectrometer or at 75 MHz with a Bruker, Model WM-300, NMR spectrometer. The NMR chemical shift values are expressed in δ values (ppm) relative to a Me_4Si internal standard. The mass spectra were obtained with either a Hitachi (Perkin-Elmer), Model RMU-7, or a Varian MAT, Model 112S, mass spectrometer. All reactions involving strong bases or reactive organometallic intermediates were performed under a nitrogen atmosphere.

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300 MHz), δ 2.3–2.4 (8 H, m, CH_2CO), 1.8–1.9 (8 H, m, CH_2); ^{13}C NMR ($CDCl_3$, multiplicity on off-resonance decoupling), 213.6 (s, 2 C atoms), 42.0 (t, 4 C atoms), 23.2 ppm (t, 4 C atoms); mass spectrum, *m/e* (relative intensity), 168 (7, M^+), 150 (32), 111 (45), 97 (45), 85 (53), 84 (77), 83 (26), 81 (30), 68 (30), 67 (31), 57 (32), 56 (29), 55 (100), 43 (25), 41 (41), 39 (23).

The aqueous $NaHCO_3$ extract was acidified with HCl and then extracted successively with CH_2Cl_2 and with $CHCl_3$ to separate 3.7 g of a mixture of Me_2SO and the keto acid **10a**. A 1.7-g portion of this material was washed with H_2O to leave 56 mg of the crude keto acid **10a** as yellow liquid: IR (CCl_4) 2750–3400 (br, associated OH), 1710 cm^{-1} (C=O of ketone and acid).

B. Isolation of the Diperoxide 9. A cold (−78 °C) solution of 15.0 g (110 mmol) of the octalins **6** (ca. 80%) and **8** (ca. 20%) in 100 mL of CH_2Cl_2 was treated with a stream of O_2 containing 3–4% O_3 for 2.75 h at which time a blue color in the solution indicated excess O_3. After the cold solution had been purged with O_2 to remove the excess O_3, a solution of 8.35 g (50 mmol) of KI in 35 mL of H_2O was added and the solution was allowed to warm to 0 °C. The organic solution was washed with $Na_2S_2O_3$ to remove the I_2 and then mixed with 100 mL of aqueous 10% Na_2CO_3. After this mixture had been refluxed for 2 h and then stirred overnight, it was extracted with $CHCl_3$. The organic extract was washed successively with aqueous 1 M HCl and with aqueous NaCl and then dried and concentrated. The dark colored semisolid residue was triturated with Et_2O to separate the crude diperoxide **9** as colorless crystals. Recrystallization from Et_2O afforded 1.9 g (11%) of the diperoxide **9** as colorless prisms, mp 166–168 °C (lit.[10] mp 166 °C); IR ($CHCl_3$) 1703 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 60 MHz) δ 2.3–2.8 (8 H, m, CH_2CO) and 1.0–2.2 (24 H, m, aliphatic CH); mass spectrum (CI), *m/e* (relative intensity), 369 (0.5, M + 1), 185 (23), 169 (23), 151 (100), 143 (44), and 141 (20).

C. Conversion of the Crude Ozonolysis Product to the Enone 5. A stream of O_2 containing 3–4% O_3 was passed through a cold (0 °C) solution of 13.6 g (100 mmol) of the octalins **6** (ca. 80%) and **8** (ca. 20%) in a mixture of 125 mL of MeOH and 25 mL of CH_2Cl_2 for 2.5 h at which time TLC analysis of the reaction mixture indicated that all the olefins **6** and **8** had reacted. After the cold reaction mixture had been purged with N_2 for 15 min, the cold mixture was treated with 11.0 mL (150 mmol) of Me_2S and allowed to warm to 25 °C with stirring during 1 h. Since the reaction mixture still gave a positive test for peroxides, three additional 3.0-mL (27 mmol) aliquots of Me_2S were added and the mixture was allowed to stir overnight. The resulting solution was concentrated under reduced pressure and the residual solid was dissolved in CH_2Cl_2 and washed successively with H_2O and with aqueous $NaHCO_3$. After the organic solution had been dried and concentrated, the residual yellow semisolid was triturated with cold pentane to leave 11.56 g (86%) of the crude diketone **7** as a colorless solid, mp 83–95 °C. A mixture of the crude diketone **7**, 25 mL of MeOH, and 100 mL of aqueous 10% Na_2CO_3 was refluxed under an N_2 atmosphere for 4 h at which time none of the starting diketone **7** remained (IR analysis). The resulting orange solution was extracted continuously with CH_2Cl_2 for 12 h and then the organic extract was dried and concentrated. Distillation of the residual red liquid afforded 8.77 g (73% based on octalin **6**) of the enone **5** as a colorless liquid, bp 56–58 °C (0.17 mm), n^{25}_D 1.5258. This product was identified with a subsequently described sample of the enone **5** by comparison of IR, NMR, and GLC data.

The aqueous $NaHCO_3$ extract from this experiment was acidified with HCl and then continuously extracted with CH_2Cl_2 to separate 1.08 g of liquid containing (NMR analysis) a mixture of Me_2SO and the keto acid **10a**.

In another experiment a 13.1-g sample of the mixture of octalins **6** and **8** was ozonolyzed at 0 °C and then treated with Me_2S. After the crude reaction mixture had been steam distilled and then partitioned between H_2O and Et_2O, the organic products were distilled under reduced pressure. The early fractions contained (GC analysis) mainly the enone **5** while the high-boiling fractions contained the crude ketol **12** that was separated by fractional crystallization as 0.72 g of colorless solid, mp 85–95 °C. Recrystallization from an Et_2O–petroleum ether mixture followed by sublimation (0.5 mm and 25 °C) separated the ketol **12** as colorless prisms: mp 93–95 °C (lit.[9b] mp 94–95 °C, lit.[9a] 96–97 °C); IR (CCl_4) 3600, 3480 (OH), 1700 cm^{-1} (C=O); NMR ($CDCl_3$, 300 MHz) δ 3.15 (1 H, t, *J* = 4.3 Hz, COCH), 2.3–2.6 (3 H, m, aliphatic CH), 2.1–2.2 (1 H, m, aliphatic CH), 1.3–2.0 (11 H, m, OH and aliphatic CH); mass spectrum, *m/e* (relative intensity), 168 (M^+, 5), 150 (28), 111 (24), 107 (21), 95 (23), 84 (28), 83 (32), 81 (29), 79 (25), 68 (34), 67 (46), 55 (100), 43 (51), 42 (25), 41 (71), 39 (51).

Conversion of the Diketone 7 to the Enone 5. A solution of 4.96 g (29.5 mmol) of the freshly recrystallized diketone **7** (mp 98–100 °C) in 15 mL of MeOH and 75 mL of aqueous 10% Na_2CO_3 was refluxed with stirring under an N_2 atmosphere for 2.5 h. The resulting red-black mixture was cooled and then partitioned between H_2O and CH_2Cl_2. After the organic layer had been washed with aqueous NaCl, dried, and concentrated, the residual dark-colored liquid was distilled in a short-path still to separate 3.82 g (86%) of the enone **5** as a colorless liquid, bp 62–63 °C (0.25 mm), n^{25}_D 1.5261 [lit.[15] bp 126–128 °C (15 mm), lit.[16] n^{25}_D 1.5260, 1.5251], that exhibited a single peak on GLC analysis (silicone XE-60 on Chromosorb P). The spectral properties of this enone **5** follow: IR (CCl_4) 1661 (sh), 1648 (conjugated C=O), 1630 cm^{-1} (conjugated C=C); ^1H NMR (300 MHz, $CDCl_3$) δ 2.6–2.7 (6 H, m, CHC=X), 2.5 (2 H, br s, CHC=X), 1.6–1.8 (6 H, m, aliphatic CH); ^{13}C NMR ($CDCl_3$, multiplicity on off-resonance decoupling), 200.9 (s), 158.5 (s), 138.3 (s), 43.7 (t), 41.4 (t), 33.7 (t), 31.4 (t), 25.7 (t), 22.2 (t), 21.1 ppm (t); UV λ_{max} (95% EtOH) 252 nm (ε 22 900), 310 (inflection, ε 79) [lit.[4] UV max 250 nm (ε ca. 20 000), 330 (ε ca. 80)]; mass spectrum, *m/e* (relative intensity) 150 (89, M^+), 122 (24), 121 (82), 108 (100), 96 (27), 93 (74), 91 (31), 80 (42), 79 (95), 77 (44), 65 (21), 41 (27), 39 (44).

^{13}C NMR Measurements on the Diperoxide 9. The numbering scheme used in discussing this spectrum is illustrated in structure **9**. The ^{13}C NMR spectra of solutions of the diperoxide in $CDCl_3$ were measured at 220, 250, 273, 286, 300, and 328 K. In addition spectra were measured in pyridine-d_5 at 353 and 373 K. At the highest temperature (373 K), the spectrum consists of 6 relatively sharp lines: 213.5 (C1, C11), 111.8 (C6, C16), 42.1 (C2, C10, C12, C20), 28.6 (C5, C7, C15, C17), 24.0 (C3, C9, C13, C19), 20.7 ppm (C4, C8, C14, C18). At the lowest temperature (220 K), the spectrum consists of 10 sharp lines: 216.3 (C1, C11), 111.2 (C6, C16), 41.9 and 41.6 (C2, C12 and C10, C20), 27.9 and 24.8 (C5, C15 and C7, C17), 23.1 and 22.4 (C3, C13 and C9, C19), 20.2 and 19.1 ppm (C4, C14 and C8, C18). At ambient temperature (ca. 305 K), the spectrum ($CDCl_3$, multiplicity in off-resonance decoupling) exhibits lines at 214.4 (s), 111.4 (s), 42.0 (t), and 23.5 ppm (t) with additional very broad absorption at ca. 28 and 20 ppm. Standard methods[17,18] were used to determine τ values from measured line separations and measured peak widths at half height employing the peaks for C5, C15, C7, and C17 below the coalescence temperature (348 K) and the peak(s) for C4, C14, C8, and C18 both below and above the coalescence temperature (337 K). From these rate constants at various temperatures, the activation energies for axial–equatorial exchange were calculated by standard methods.[18] The calculated values were: free energy of activation, 14.8 (0.1)[19] kcal/mol at 298 K; enthalpy of activation, 12.5 (0.3) kcal/mol; entropy of activation, 7.5 (1.0) cal/(mol deg); Arrhenius activation energy, 13.2 (0.2) kcal/mol.

Determination of Crystal Structures. A. The Diketone 7. A crystal of the diketone **7** was mounted and data were collected by procedures described in the supplementary material. The crystal belonged to the monoclinic system and the data collected were consistent with only space group $P2_1/n$.[20] From a total of 802 reflections collected in a complete quadrant of data, 733 were accepted as statistically above background. In refinement, described in the supplementary material, 63 parameters were varied

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(20) "International Tables for X-Ray Crystallography"; Kynoch Press: Birmingham, England, 1952; Vol. I. Group $P2_1/n$ is a nonstandard setting for $P2_1/c$ (No. 14).

for the 733 observations. The molecule has a crystallographic center of inversion. The full-matrix least-squares refinement converged at $R = 0.062$ and $R_w = 0.074$. A perspective view of the structure of the diketone **7** is presented in Figure 1 and the final atomic coordinates and thermal parameters are available as supplementary material in Table I.

B. The Diperoxide 9. The supplementary material describes the procedures followed for mounting a crystal of the diperoxide **9** and collecting crystallographic data. The crystal belonged to the orthorhombic system and the data collected were consistent only with space group *Pbca* (No. 61).[20] From a total of 1686 reflections collected in a complete octant of data, 1338 were accepted as statistically above background. In the refinement described in the supplementary material 134 parameters were varied for the 1338 observations. The molecule has a crystallographic center of inversion. The full-matrix least-squares refinement converged at $R = 0.049$ and $R_w = 0.064$. A perspective view of the structure of the diperoxide **9** is presented in Figure 2 and the final atomic coordinates and thermal parameters are available as supplementary material in Table II.

Registry No. **5**, 13031-01-1; **6**, 493-03-8; **7**, 38734-05-3; **9**, 87829-76-3; **10a**, 1838-60-4; **12**, 57479-39-7; tetralin, 119-64-2.

Supplementary Material Available: Descriptions of the determination of crystal structures for the diketone **7** and the diperoxide **9**, including tables of atomic coordinates for each compound (8 pages). Ordering information is given on any masthead page.

Selective γ-Substitution of α,β-Unsaturated Esters via α-Trimethylsilyl β,γ-Unsaturated Esters

Pamela Albaugh-Robertson and John A. Katzenellenbogen*

Department of Chemistry, University of Illinois at Urbana—Champaign, Urbana, Illinois 61801

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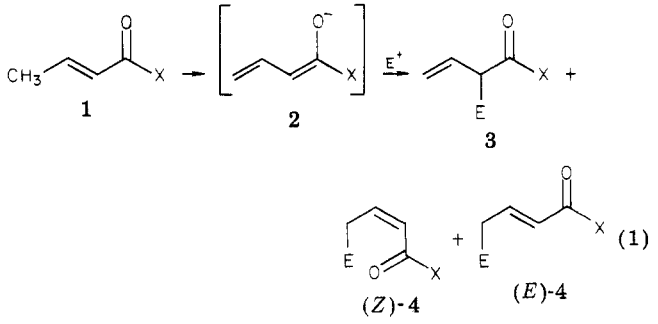
In order to achieve selective γ-substitution of α,β-unsaturated esters, we investigated the directive effect of silicon in the reaction of various electrophiles with α-trimethylsilyl β,γ-unsaturated esters. These esters were prepared by nickel-catalyzed vinylation reactions of the lithium enolate of ethyl α-(trimethylsilyl)acetate. The α-silyl β,γ-unsaturated esters reacted with a variety of electrophiles (aldehydes, ketones, acetals, ketals, acid chlorides, and chloro thioethers) in the presence of Lewis acids (titanium tetrachloride and trimethylsilyl trifluoromethanesulfonate) to give exclusively the γ-substituted product in moderate to good yields. In some cases, the primary substitution products underwent additional conversions under the reaction conditions, such as the cyclization of the δ-hydroxyl or δ-keto enoates to dihydropyrones or pyrones, respectively. These α-silyl β,γ-unsaturated esters are effective reagents for achieving complete γ-selective substitution of α,β-unsaturated ester systems.

Introduction

The synthetic approach to polyisoprenoid systems that involves the direct attachment of intact isoprene units, a process termed "prenologation", is attractive in its conceptual simplicity, but in practice, it suffers from stereochemical and regiochemical ambiguities.[1] One method that has been developed to the point of considerable utility involves the selective γ-substitution of extended enolates (**2**) derived from α,β-unsaturated carbonyl compounds (**1**) (eq 1).[2-22] While the γ substituted product (**4**) displays geometric isomerism, the major task in the approach is to direct electrophilic substitution upon the enol derivative



(1) For a review, see: Cainelli, G.; Cardillo, G. *Acc. Chem. Res.* **1981**, *14*, 89.
(2) For a comprehensive list of references, see those cited in ref 22.
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