racemic diols. The turnover numbers and the enzyme activity recovered at the conclusion of reactions are NAD, 800; HLADH, 10^8 (90–92%); AldDH, 10^7 (84–86%); GluDH, 10^8 (90–91%). The ^{1}H NMR data of compounds **3a–h** and their melting points are as follows. Compound **3a**: δ ($CDCl_3$) 4.0 (d, 2 H, methylene), 4.57 (m, 1 H, methine), 9.0–11.0 (OH, exchangeable with D_2O). Compound **3b**: mp 87–88 °C; δ ($CDCl_3$) 4.73 (dd, 2 H, J_{CHF} = 48 Hz, J_{CHCH} = 3.6 Hz), 5.3 (m, 1 H, methine). Compound **3c**: mp 88–89 °C; δ ($CDCl_3$) 3.86 (d, 2 H, methylene), 4.55 (m, 1 H, methine), 9.0–11.0 (br, OH, exchangeable with D_2O). Compound **3d**: δ ($CDCl_3$) 3.60 (d, 2 H, methylene), 4.55 (m, 1 H, methine), 9.0–11.0 (br, OH, exchangeable with D_2O). Compound **3e**: δ ($CDCl_3$) 1.56 (d, 3 H, CH_3), 4.50 (m, 1 H, methine), 9.0–11.0 (br, OH, exchangeable with D_2O). Compound **3f**: δ (D_2O) 4.24 (dd, 1 H, J_{C2-H} = 7.6 and 4.8 Hz), 3.40 (dd, 1 H, J_{C3-H} = 13.0 and 4.8 Hz), 3.08 (dd, 1 H, J_{C3-H} = 13.0 and 7.6 Hz), other ^{1}H exchangeable with D_2O; mp 199–201 °C. Compound **3g**: δ ($CDCl_3$) 4.8 (dd, 1 H, J_{C2-H} = 7.0, 2.0, and 1.5 Hz), 5.21 (m, 1 H, C4-H), 5.26 (m, 1 H, C4-H), 5.96 (ddd, 1 H, J_{C3-H} = 17.0, 10.0, and 7.0 Hz); bp 128–130 °C (23 mmHg). Compound **3h**: δ ($CDCl_3$) 1.01 (t, 3 H, CH_3), 1.92 (m, 2 H, CH_2), 4.51 (t, 1 H, methine). These constants are essentially consistent with those reported previously.[15]

(*R*)-(+)-α-Methoxy-α-(Trifluoromethyl)phenylacetyl (MTPA) Derivatives of the Methyl Esters of Compounds 3c, 3e, and 3h. The MTPA derivatives were prepared according to the procedures described previously.[4] The intensities of the resonances due to the methoxy protons of the diastermers prepared from racemic **3c**, **3e**, and **3h** (prepared by $NaBH_4$ reduction of the corresponding keto species) and the diastereomers produced from the enzymatic reactions were compared: δ ($CDCl_3$) 3.68 for D-**3c** and 3.63 for L-**3c**; 3.65 for D-**3e** and 3.60 for L-**3e**; 3.62 for L-**3h** and 3.56 for D-**3h**.

Oxidation of Amino Alcohols. For the oxidation of amino alcohols, the same enzymes were used except that the cofactor regeneration system was changed: GluDH/α-ketoglutarate was replaced with cyclohexanone which would oxidize NADH under HLADH catalysis. The amino aldehydes produced in the reaction were transformed in situ to amino acids from which the optical purity was determined. After the reaction was completed, the solution was adjusted to pH 12 with NaOH and extracted continuously with chloroform to remove cyclohexanol and unreacted starting material. The aqueous solution containing enzyme product was concentrated to about 10 mL. After addition of ethanol (50 mL) to the mixture, the amino acid was precipitated as sodium salt which was characterized with ^{1}H NMR, and the spectrum was identical with that of authentic L-serine obtained from Aldrich. The optical purity of compound **3f** was determined to be 96% on the basis of the enzymatic procedures described.

(15) See ref 3. Also, the NMR data of compound **3f** and **3g** are consistent with those reported before: Shimohigashi, Y.; Waki, M.; Izumiya, N. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 949. Appelbaum, J.; Stubbe, J. *Biochemistry* **1975**, *14*, 3908. Some other compounds were made before with no NMR data. Compound **3a**: Wohl, A.; Schellenberg, R. *Chem. Ber.* **1922**, *55*, 1404. Compound **3b**: Gottwald, L. K.; Kum, E. *J. Org. Chem.* **1965**, *30*, 877–879. Compound **3d**: Baer, E.; Robinsen, R. *Can. J. Biochem.* **1971**, *49*, 3005. Compound **3h**: Lindstrom, L. A. *Carbohydr. Res.* **1979**, *69*, 269.

Base-Catalyzed Hydroperoxy Keto Aldehyde Cyclization

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Quinghaosu (**1**),[1] one of the most active antimalarials known,[2] offers a potential new pharmacophore in the unique *endo*-peroxide acetal. Schmid and Hofheinz[3] formed this unit by acid-catalyzed cyclization of a key hydroperoxy keto acetal (**2**) which was produced in an elegant though specialized sequence. A more general route to *endo*-peroxide acetals might be available through the cyclization of hydroperoxy keto aldehydes. These might be obtained by the ozonolysis of allylic hydroperoxides (e.g., **3–5**), which are themselves the product of an ene reaction with singlet oxygen. Unfortunately, allylic alcohols undergo "abnormal ozonolysis"[4] in which both of the olefinic carbon atoms are lost, and it may be anticipated that allylic hydroperoxides will behave similarly. This problem, which must be overcome if the synthesis of hydroperoxy keto aldehydes is to succeed, was circumvented by carrying out the ozonolysis on the derived hydroperoxide *tert*-butyldimethylsilyl ether.

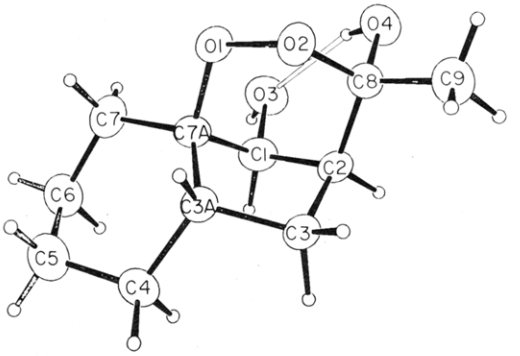
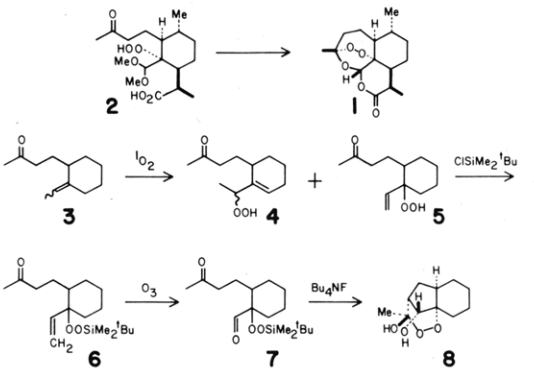


Figure 1. ORTEP plot of the bicyclic *endo*-peroxide.

Scheme I



Keto olefin **3** was available from the action of ethylidenetriphenylphosphorane[5] on methyl 3-(2-oxocyclohex-2-yl)propionate[6] followed by hydrolysis and treatment of the resulting carboxylic acid with methyllithium.[7] Singlet oxygen reacted with **3** to give the unstable allylic hydroperoxide **5** in 81% yield and a compound tentatively identified as its alternate regioisomer **4** in 15% yield. The ^{13}C NMR spectra of **5** and its derived silyl ether **6** indicate that they were obtained, at least predominantly, as single diastereomers. Ozonolysis of **5** gave the product of abnormal ozonolysis, 2-(3-oxobutyl)-cyclohexanone, as expected from the forgoing considerations. In contrast, conversion of the hydroperoxide to the

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0022-3263/85/1950-1994$01.50/0

tert-butyldimethylsilyl ether **6**[8] followed by ozonolysis gave the desired allylic hydroperoxide **7** in protected form. Thus, the ozonolysis of allylic hydroperoxide silyl ethers can produce the α-hydroperoxy carbonyl functionality in protected form.

The stereochemistry of the singlet oxygen reaction was examined after the deprotection. Treatment of **7** with fluoride ion followed by chromatography on silica gel gave a chromatographically homogeneous product as a white crystalline solid (59%).[9] Fractional recrystallization from acetone gave single crystals (needles, mp 151–153 °C) suitable for X-ray analysis. The structure **8** thus obtained is shown in Figure 1. Since the angular oxygen and hydrogen substituents are cis, there was predominant equatorial attack of singlet oxygen on the keto olefin **3** (see Experimental Section).

Under the conditions of the deprotection, the more-substituted enolate of the ketone apparently formed and then cyclized via an aldol reaction to give an intermediate acetylcyclopentanol. Closure of this hydroperoxide onto the acetyl carbonyl completes the generation of this new bicyclic *endo*-peroxide hemiketal. Thus, under basic conditions the rate of the aldol cyclization is at least competitive with the rate of closure of the hydroperoxide onto the acyclic carbonyl. This observation supports the initial steps of the pathway proposed for the decomposition of quinghaosu under mildly basic conditions.[1b]

Experimental Section

General Methods. ^1H and ^{13}C NMR spectra were obtained on a JEOL FX-90Q spectrometer operating at 90 and 22.5 MHz, respectively. IR spectra were recorded on a Beckman Model IR 10. Mass spectra were taken on a DuPont Model 21-490 mass spectrometer in the electron impact mode. Melting points were measured on a Fischer-Johns apparatus, and are uncorrected. Anhydrous tetrahydrofuran and diethyl ether were prepared by distillation from the blue radical anion of benzophenone under nitrogen.

Methyl 3-(2-Ethylidenecyclohex-1-yl)propionate. Sodium hydride (0.516 g of a 60% dispersion in mineral oil, 12.9 mmol) was added to anhydrous dimethyl sulfoxide (60 mL) and the resulting mixture was stirred under nitrogen for 1 h at 60 °C. The resulting yellow solution with a little grey suspension was cooled to room temperature, then solid ethyltriphenylphosphonium bromide (4.8 g, 12.9 mmol) was added in portions and the mixture became a deep red.[5] Methyl 3-(2-oxocyclohex-2-yl)propionate[6] (2.2 g, 12 mmol) was added in one portion via syringe, and the red solution became immediately yellow. After 1 h the solution was diluted with water (100 mL) and then washed with three 150-mL portions of methylene chloride. The combined methylene chloride layers were concentrated under reduced pressure, the residue was dissolved in water–pentane, and then the aqueous layer was washed with three 50-mL portions of pentane. The combined pentane layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure, and the residue was chromatographed on silica gel (25 g) with 5:95 ether–hexane. After combining and concentrating the fractions containing the desired material, there was obtained 0.525 g (20%) of a clear, colorless oil: IR (neat) 2930 (s), 2870 (s), 1740 (s), 1670 (w, sh) and 1160 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.04 (q, J = 6.6 Hz, 1 H), 3.56 (s) and 3.54 (s, combined 3 H), 2.24–1.40 (m, 13 H), 1.50 (d, J = 6.6 Hz) and 1.45 (d, J = 6.6 Hz, combined 3 H); ^{13}C NMR ($CDCl_3$) δ 174.0, 141.1, 140.8, 117.3, 115.3, 51.0, 44.0, 34.7, 33.4, 32.5, 32.3, 31.9, 31.6, 28.4, 27.6, 26.9, 26.7, 25.4, 23.1, 21.2, and 12.3; mass spectrum, m/e (relative abundance) 196 (74), 164 (63), and 136 (52). Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.4; H, 10.3. Found: C, 73.66; H, 10.30.

3-(2-Ethylidenecyclohex-1-yl)propionic Acid. Potassium hydroxide (0.988 g of 85%, 15 mmol) was dissolved in methanol (20 mL), then methyl 3-(2-ethylidenecyclohex-1-yl)propionate (0.678 g, 3.2 mmol) was added in one portion as a solution in methanol (5 mL), and the resulting solution was stirred at room temperature for 24 h. The crude mixture was concentrated under reduced pressure, dissolved in water (75 mL), and then washed with three 15-mL portions of methylene chloride. The aqueous layer was acidified with concentrated hydrochloric acid and then washed with three 20-mL portions of methylene chloride. The final organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 0.596 g (100%) of a clear, colorless oil: IR (neat) 3600–3200 (s, br), and 1700 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 11.30 (br, 1 H), 5.11 (q, J = 6.6 Hz, 1 H), and 2.30–0.88 (m, 16 H, includes 1.56 (d, J = 6.6 Hz)); ^{13}C NMR ($CDCl_3$) δ 180.6, 141.1, 140.8, 117.6, 115.6, 44.1, 34.7, 33.6, 32.5, 32.2, 31.7, 28.5, 27.7, 26.9, 26.6, 25.6, 23.3, 21.3, and 12.4; mass spectrum, m/e (relative abundance) 182 (87), 164 (18), 153 (30), 122 (100).

4-(1-Ethylidenecyclohex-2-yl)-2-butanone (3). 3-(2-Ethylidenecyclohex-1-yl)propionic acid (1.1 g, 6.04 mmol) was dissolved in anhydrous ether (30 mL), and methyllithium (10.6 mL of a 1.25 M solution in ether, 13.25 mmol) was added at 0 °C. The resulting mixture was stirred at room temperature for 24 h and then poured into a well-stirred solution of acetic acid (2.0 mL) in ethyl acetate (60 mL). The resulting organic phase was washed with dilute hydrochloric acid, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was chromatographed on silica gel (15 g) with 1:1 methylene chloride–hexane. After the fractions containing the desired material were combined and concentrated, there was obtained 0.945 g (87%) of a clear, colorless oil: IR (neat) 2920 (s), 2870 (s), 1710 (s), and 1665 (w, sh) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.20 (q, J = 6.6 Hz) and 5.07 (q, J = 6.3 Hz, combined 1 H), 2.36 (m, 2 H), 2.10 (s, 3 H), and 2.07–1.07 (m, 16 H, including 1.55 (d, J = 6.6 Hz) and 1.52 (d, J = 6.6 Hz)); ^{13}C NMR ($CDCl_3$) δ 208.5, 141.4, 141.1, 116.9, 115.0, 43.9, 41.8, 41.4, 34.5, 33.5, 32.5, 31.7, 29.5, 28.4, 27.6, 25.6, 25.4, 23.1, 21.1, 12.4, and 12.2; mass spectrum, m/e (relative abundance) 180 (13), 162 (35), and 122 (100). Anal. Calcd for $C_{12}H_{20}O$: C, 79.9; H, 11.2. Found: C, 79.82; H, 11.06.

The Reaction of 4-(2-Ethylidenecyclohex-1-yl)-2-butanone (3) with Singlet Oxygen. Rose bengal (6.9 mg) and 4-(2-ethylidenecyclohex-1-yl)-2-butanone (0.266 g, 1.47 mmol) were dissolved in acetonitrile (10 mL), and oxygen was bubbled into the well-stirred pink solution. The solution was irradiated through the Pyrex flask with a Kodak carousel projector, and the progress of the reaction was monitored by thin-layer chromatography. After about 1.5 h the starting material was depleted, and the reaction mixture was concentrated under reduced pressure and then chromatographed on silica gel (15 g) with 10:90 ethyl acetate–hexane. The fractions containing the less polar material were combined and concentrated under reduced pressure yielding 0.252 g (81%) of a clear, colorless oil: IR ($CHCl_3$) 3650 (s, br), 1700 (s), and 1640 (w, sh) cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.15 (br s, 1 H), 5.90 (dd, J = 10.7, 17.8 Hz, 1 H), 5.35 (dd, J = 2.0, 17.8 Hz, 1 H), 5.28 (dd, J = 2.2, 10.7 Hz, 1 H), 2.49 (m, 2 H), 2.17 (s, 3 H), and 2.05–0.90 (m, 11 H); ^{13}C NMR ($CDCl_3$) δ 210.6, 135.5, 117.8, 85.7, 41.0, 40.6, 32.4, 30.0, 28.5, 24.9, 23.2, and 22.4. Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.9; H, 9.5. Found: C, 67.64; H, 9.62. The fractions containing a more polar compound were combined and concentrated under reduced pressure to yield 31.9 mg (15%) of a clear, colorless oil: ^1H NMR ($CDCl_3$) δ 8.33 (br s, 1 H), 5.82 (br t, J = 3 Hz, and 5.38 (m) combined 1 H), 4.49 (m, 1 H), 2.48 (m, 2 H), 2.15 (s, 3 H), and 2.10–0.93 (m, 12 H, includes 1.33 (d, J = 6.6 Hz) and 1.25 (d, J = 6.8 Hz).

4-(1-Vinyl-1-hydroperoxycyclohex-1-yl)-2-butanone *tert*-Butyldimethylsilyl Ether (6). The hydroperoxide **5** (221 mg, 1.04 mmol) was added to a solution of imidazole (108 mg, 1.6 mmol) and *tert*-butyldimethylsilyl chloride (226 mg, 1.5 mmol) in DMF (5 mL). The resulting mixture was stirred for 9 h at room temperature, the volatile material was removed at 0.01 mmHg, and the residue was chromatographed on silica gel (15 g) with 1:1 hexane–methylene chloride. Combining and concentrating the fractions containing the desired material afforded 336.6 mg (99%) of a clear, colorless oil: IR ($CHCl_3$) 2940–2860 (s) and 1705 (s) cm^{-1}; ^1H NMR δ 5.92 (dd, J = 10.5, 18.1 Hz, 1 H), 5.23 (dd,

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(9) When pyridine-d_5 was used as solvent, the ^1H NMR spectrum at 300 MHz in the d 4.0–4.7 region (*CH*OH) shows a 7:83:10 ratio for three sets of resonances centered at d 4.62, 4.24, and 4.08 ppm, respectively. See Supplementary Material.

J = 2.3, 18.1 Hz, 1 H), 5.22 (dd, J = 2.3, 10.5 Hz, 1 H), 2.37 (m, 2 H), 2.12 (s, 3 H), 1.91–0.80 (m, 11 H), 0.93 (s, 9 H), and 0.14 and 0.12 (2 s, combined 6 H); ^{13}C NMR ($CDCl_3$) δ 209.3, 136.8, 116.6, 86.1, 42.6, 41.0, 32.7, 29.5, 28.1, 26.3, 24.4, 23.9, 23.0, 18.3, and −5.5. Anal. Calcd for $C_{18}H_{34}O_3Si$: C, 66.2; H, 10.4. Found: C, 65.87; H, 10.25.

1-Hydroperoxy-2-(2-oxobut-4-yl)cyclohexanecarboxaldehyde *tert*-Butyldimethylsilyl Ether (7). The olefin **6** (289.5 mg, 0.916 mmol) was dissolved in methanol (10 mL) and cooled to −78 °C, and ozone was passed into the resulting solution until it turned blue. Dimethyl sulfide (1.0 mL) was added, and the resulting solution was warmed to room temperature, stirred for 7 h, and then concentrated under reduced pressure. The residue was chromatographed on silica gel (15 g) with 15:5:80 ethyl acetate–methylene chloride–hexane. The fractions containing the desired material were combined and concentrated under reduced pressure to yield 226.6 mg (75%) of an unstable, clear, colorless oil: IR (neat) 3550 (w), 2940 (s), 2870 (s), and 1720 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.68 (s, 1 H) and minor isomer 9.93 (s), 2.07 (s, 3 H), 2.1–0.9 (m, 13 H), 0.88 (s, 9 H), and 0.12 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 207.7, 203.9, 89.4, 41.9, 39.5, 29.6, 27.3, 26.3, 26.1, 25.6, 22.6, 21.3, 18.2, and −5.8. Integration of the aldehyde peaks showed at most 10% of the minor isomer.

Cyclization of 1-Hydroperoxy-2-(2-oxobut-4-yl)cyclohexanecarboxaldehyde *tert*-Butyldimethylsilyl Ether. Preparation of 8. The aldehyde **7** (35.3 mg, 0.107 mmol) was dissolved in anhydrous THF (5 mL), and tetra-*n*-butylammonium fluoride (0.2 mL of a 1 M solution in THF, 0.2 mmol) was added. After 3 h at room temperature, the resulting solution was concentrated under reduced pressure and chromatographed on silica gel (10 g) with 30:70 ethyl acetate–hexane. The fractions containing the major product were combined to yield 12.3 mg (57%) of a white, crystalline solid: ^{1}H NMR (pyridine-d_5) δ 5.16 (br s, 2 H, OH), (4.24 (d, J = 5.4 Hz, 1 H) and minor isomers 4.62 (d, J = 5.6 Hz) and 4.08 (d, J = 5.4 Hz),[9] 2.51–0.50 (m, 15 H including 1.42 (s)); ^{13}C NMR (pyridine-d_5) δ 104.4 (s), 85.9 (s), 70.9 (d), 43.6 (d), 37.7 (d), 34.8 (t), 31.9 (t), 27.2 (t), 25.2 (t), 24.6 (q), and 22.0 (t). Crystal data: needles suitable for X-ray diffraction studies were obtained by recrystallization from acetone. Single crystals are monoclinic; space group $P2_1/n$ (no. 14); a = 11.444 (3) Å, b = 5.813 (4) Å, c = 16.351 (3) Å, β = 107.49 (3)°, Z = 4. Three dimensional X-ray diffraction data were collected for 2022 reflections of which 595 were independent, having $4° < 2\theta > 45°$ on a computer-controlled Enraf-Nonius CAD4 X-ray diffractometer with graphite monochromated Mo Kα radiation (λ 0.7107 Å) and $\theta - 2\theta$ scanning technique. The nonhydrogen atoms were located by using the direct methods program MULTAN. Hydrogen atoms were located from a difference Fourier map, and the resulting structure converged at R = 0.035. Tables of the final atomic positional parameters, the atomic thermal parameters, and the bond distances and angles may be found in the supplementary material.

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Registry No. **3**, 96165-23-0; **4**, 96165-24-1; **5**, 96165-25-2; **6**, 96165-26-3; **7**, 96165-27-4; **8**, 96165-28-5; methyl 3-(2-ethylidenecyclohex-1-yl)propionate, 96165-21-8; 3-(2-ethylidenecyclohex-1-yl)propionic acid, 96165-22-9; methyl 3-(2-oxocyclohex-2-yl)propionate, 10407-33-7.

Supplementary Material Available: Proton NMR spectra of **8** at 90 and 300 MHz, carbon spectrum of **8** at 22.5 MHz, tables of positional parameters, temperature factors, bond angles, and distances for **8** as determined by single-crystal X-ray diffraction (9 pages). Ordering information is given on any current masthead page.

Novel Smiles-Type Rearrangement in a Thienamycin Derivative

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Since the discovery of thienamycin,[1] chemical modifications[2] of its C-2 side chain have been investigated extensively to improve its chemical stability[2a] and decrease its metabolism by renal dehydropeptidase I.[3] We have studied the reactivity of the vinyl sulfide system,[4] a moiety of thienamycin, using the thienamycin model compound **1**,[4] and applied the results thus obtained for modification at the 2-position of thienamycin. This report describes the synthesis of the C-2 aza-substituted 1-carbapenem derivative **9** by novel Smiles-type rearrangement.

In the course of studies on the vinyl sulfide system,[4] we became interested in the chemistry of the vinyl sulfonium salt[5] **2**. The sulfide **1** was treated with 1.5 equiv of methyl iodide (MeI) in the presence of 1.2 equiv of silver tetrafluoroborate[6] in nitromethane to afford the sulfonium salt **2**, which was further treated without purification with 1.0 equiv of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dimethyl sulfoxide (Me_2SO) to give the rearranged product **4** in 50% yield from compound **1** (see Scheme I). The structure of compound **4** was supported by NMR, IR, and mass spectra. The NMR spectrum of **4** exhibited a singlet at δ 2.12 (3 H) assignable to the SMe group and a multiplet due to the methylene protons (NCH_2) at δ 3.66–3.83, which was shifted to lower field, in contrast to that of the starting material **1** at δ 3.39. The similar shift to lower field proved to be a common characteristic of all the rearranged products reported here. Compound **4** was assumed to be produced via the intermediate **3** formed by the intramolecular Michael addition,[7] followed by β-elimination[8] as shown in

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