Preparation of 2,2-Dichloro-3(2*H*)-furanone and Its Reactions with Heteronucleophiles

Masahiro Murakami,* Minoru Hayashi, and Yoshihiko Ito*

Department of Synthetic Chemistry, Faculty of Engineering, Kyoto University, Yoshida, Kyoto 606-01, Japan

Received July 26, 1994

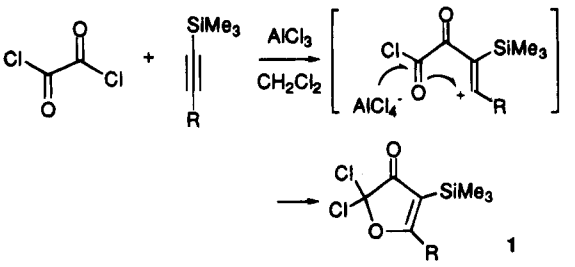
Alkynylsilanes are versatile synthetic building blocks;[1] *e.g.*, acylation with an acyl chloride is efficiently promoted by Lewis acid to produce an alkynyl ketone. Walton and Waugh reported[2] that a [3 + 2] cycloaddition reaction[3] of oxalyl chloride took place with a particular alkynylsilane, *i.e.*, 1,2-bis(trimethylsilyl)ethyne, affording 2,2-dichloro-4,5-bis(trimethylsilyl)-3(2*H*)-furanone in 27% yield. We have recently developed a new synthetic method for alkynylsilanes which employs the SmI_2-mediated coupling of alkyl halides with ethynylsilanes.[4] In the course of our studies on the synthetic utilization of alkynylsilanes, we found that the [3 + 2] cycloaddition reaction of oxalyl chloride proceeds with a variety of alkynylsilanes to give the corresponding 2,2-dichloro-3(2*H*)-furanones. We describe herein the synthesis of 2,2-dichloro-3(2*H*)-furanones (**1**) and their reactions with heteronucleophiles to furnish 2,4-diketo carboxylic acid derivatives. Successful application of this process to the stereoselective syntheses of *cis*-5-alkyl-3-hydroxytetrahydro-2-furanones (**6**) and *cis*-5-alkyl-3-hydroxy-2-pyrrolidones (**13**) is also presented.

Results and Discussion

Oxalyl chloride was treated with alkynylsilanes in the presence of aluminum trichloride in dichloromethane at −78 °C for 3 h. After quenching at that temperature, 2,2-dichloro-3(2*H*)-furanones **1a**–**e** were isolated in moderate to good yields (Table 1, runs 1–5). The [3 + 2] cycloaddition reaction may proceed via initial Friedel-Crafts acylation of a C–C triple bond to form a vinyl cation, which is then attacked intramolecularly by a neighboring carbonyl group.[5] An improved yield of **1h** (86%) was obtained by conducting and quenching the reaction of 1,2-bis(trimethylsilyl)ethyne at −30 °C (run 8). In contrast, ethynyltrimethylsilane gave a poor yield of **1f** (run 6). Furthermore, the cycloaddition reactions with an ordinary internal alkyne (run 10) or with a terminal alkyne (run 9) other than ethynylbenzene (run 7) failed to proceed well. These results suggest that cooperative stabilization of the vinyl cation by both the trimethylsilyl group and the substituent R is required for the cycloaddition reaction to occur. Structures of the 2,2-dichloro-3(2*H*)-furanones were determined by means of ^1H and ^{13}C NMR analysis. In addition, the structure of **1e** was unequivocally determined by an X-ray analysis.[6]

Next, the reactivities of 2,2-dichloro-3(2*H*)-furanones (**1**) toward heteronucleophiles were examined. 2,2-Dichloro-3(2*H*)-furanones (**1**) were fairly stable to water under neutral or acidic conditions and hence could be purified by silica gel chromatography. When a methanol solution of **1** was stirred at room temperature, however, a ring opening reaction took place to afford methyl 2,2-dimethoxy-4-oxoalkanoate (**3**, Table 2). The carbonyl group at the 2-position was selectively protected as a dimethyl ketal. A plausible explanation for this regioselective ketal formation is given by assuming that the epoxyfuran **2** is transiently formed via addition of a methoxy group to the carbonyl group of **1**. The following

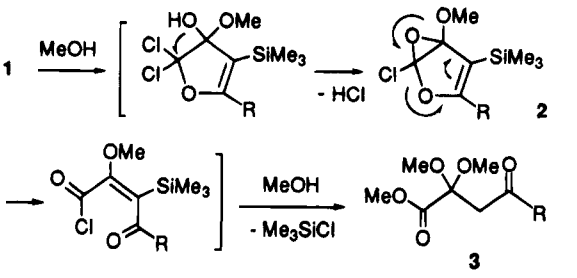
Table 1. Synthesis of 2,2-Dichloro-3(2*H*)-furanones 1



run	R	product	yield,[a] %
1	$PhCH_2CH_2$	**1a**	74
2	*n*-butyl	**1b**	79
3	isobutyl	**1c**	78
4	*sec*-butyl	**1d**	63
5	phenyl	**1e**	91
6	H	**1f**	19
7	*b*	**1g**[c]	70
8	Me_3Si	**1h**	86
9	*d*	*e*	
10	*f*	*e*	

[a] Isolated yield based on oxalyl chloride. [b] Ethynylbenzene was used as the alkyne. [c] The product is 2,2-dichloro-5-phenyl-3(2*H*)-furanone. [d] 1-Octyne was used as the alkyne. [e] A complex mixture was formed. [f] 5-Decyne was used as the alkyne.

Table 2. Synthesis of 2,2-Dimethoxy-4-oxoalkanoates 3



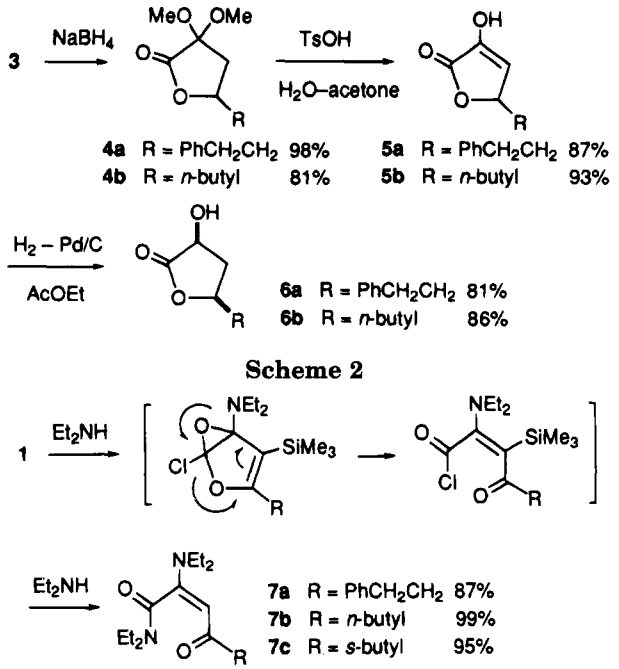
run	R	product	yield,[a] %
1	$PhCH_2CH_2$	**3a**	98
2	*n*-butyl	**3b**	90
3	isobutyl	**3c**	93
4	*sec*-butyl	**3d**	70
5	phenyl[b]	**3e**	73

[a] Isolated yield based on **1**. [b] Reaction temperature of 50 °C.

(1) Colvin, E. W. in *Silicon Reagents in Organic Synthesis*; Academic Press: London, 1988; pp 45–49.
(2) Walton, D. R. M.; Waugh, F. *J. Organomet. Chem.* **1972**, *37*, 45.
(3) For reviews on the thermal and transition metal-mediated [3 + 2] cycloaddition reactions, see: (a) Little, R. D. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds., Pergamon Press: New York, 1991; Vol. 5, Chapter 3.1. (b) Chan, D. M. T. Reference 3a, Chapter 3.2.
(4) Murakami, M.; Hayashi, M.; Ito, Y. *Synlett*, **1994**, 179.
(5) For other examples of the acid-mediated [3 + 2] cycloaddition reaction, see: (a) Morgan, Jr., L. R.; Aubert, C. C. *J. Org. Chem.* **1962**, *27*, 4092. (b) Martin, G. J.; Daviaud, G. *Bull. Soc. Chim. Fr.* **1970**, 3098.
(6) The authors have deposited tables of atomic coordinates, thermal parameters, bond lengths, and bond angles of **1e** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

0022-3263/94/1959-7910$04.50/0

Scheme 1



Scheme 2

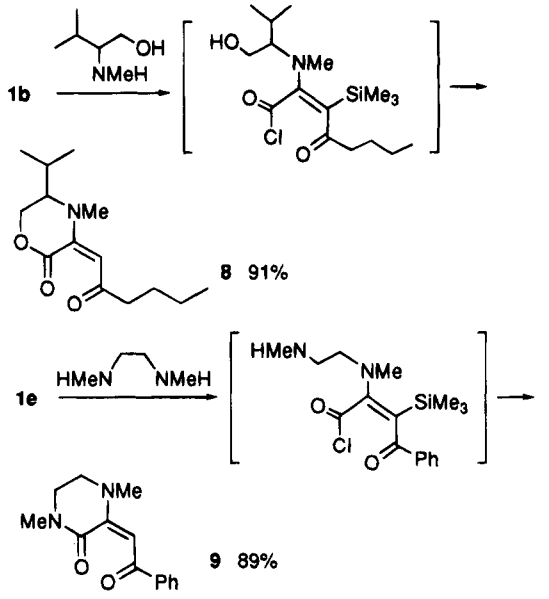
electrocyclic ring opening[7] affords an acid chloride which further reacts with methanol and loses the trimethylsilyl group by methanolysis, leading to the formation of **3**.

Reduction of **3** with $NaBH_4$ gave rise to 4-butanolides **4**, which served to confirm the regiochemistry of the ketal **3** (Scheme 1). 4-Butanolides **4**, on treatment with *p*-toluenesulfonic acid, were hydrolyzed to furnish 2-hydroxy-2-buten-4-olides **5**. Subsequent hydrogenation of the C–C double bond catalyzed by Pd on carbon took place from the less hindered side of the 5-membered ring to produce *cis*-5-alkyl-3-hydroxytetrahydro-2-furanones **6** stereoselectively.[8] The *trans*-isomer was not detected by ^1H NMR. It has been reported that 5-hexyl- and 5-octyl-3-hydroxytetrahydro-2-furanones are potent food intake-control substances for rats.[9] The present procedure offers a novel and convenient method to synthesize similar potential compounds having various substituents at the 5-position in a stereoselective manner.

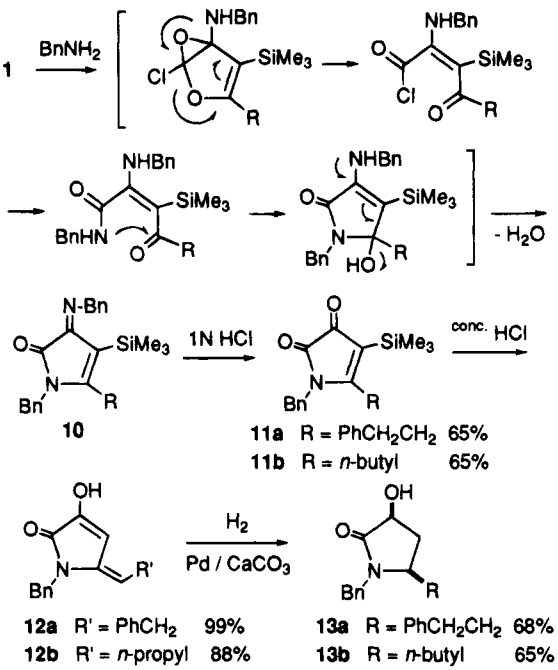
2,2-Dichloro-3(2*H*)-furanones (**1**) underwent a similar nucleophilic attack by amines (Scheme 2). A secondary amine yielded conjugated amides **7**. (*E*)-Geometry of the enamine moieties was unambiguously assigned by means of NOE experiments. This stereoselectivity may also be ascribed to the electrocyclic ring opening mechanism of the epoxyfuran intermediate. The trimethylsilyl group at the 3-position was so labile that it was readily lost during the reaction or the workup procedure, although the reason for this is not clear.

Treatment of **1** with bifunctional amines like a 2-hydroxy amine and a 1,2-diamine yielded the 6-membered heterocyclic compounds **8** and **9**, respectively, as shown in Scheme 3. The enamine moieties also possess (*E*)-geometry.

Scheme 3



Scheme 4



The reaction of **1** with a primary amine led to the stereoselective synthesis of 5-alkyl-3-hydroxy-2-pyrrolidones **13** (Scheme 4). 3-Imino-2-pyrrolidone **10** was formed as the unstable intermediate by the reaction of **1** with benzylamine. The imino group of **10** was easily hydrolyzed by treatment with 1 N aqueous HCl to afford 4-(trimethylsilyl)-4-azoline-2,3-dione **11**. On subsequent treatment with concentrated HCl, *homo*-enolization took place together with loss of the trimethylsilyl group to give 5-alkylidene-3-hydroxy-3-azolin-2-one **12**. The 5-alkylidene moiety of **12** possesses (*E*)-geometry; the substituent R' of **12** is oriented toward the sterically less hindered side. Catalytic hydrogenation of **12** with Pd on $CaCO_3$ produced 5-alkyl-3-hydroxy-3-azolidin-2-one (**13**) stereoselectively. The addition of hydrogen to the conjugated diene system occurred from the same side to furnish the

(7) Similar ring opening reactions of epoxyfurans have been reported; (a) Manfredi, K. P.; Jennings, P. W. *J. Org. Chem.* **1989**, *54*, 5186. (b) Adger, B. M.; Barrett, C.; Brennan, J.; Anthony, M.; McKervey, M. A.; Murray, R. W. *J. Chem. Soc., Chem Commun.* **1991**, 1553. (c) Adam, W.; Peters, K.; Sauter, M. *Synthesis*, **1994**, 111, and references cited therein.

(8) Similar stereoselectivity has been observed in the hydrogenation of 3-benzoyloxy-2-penten-5-olide: Varela, O. J.; Cirelli, A. F.; Lederkremer, R. M. D. *Carbohydr. Res.* **1982**, *100*, 424.

(9) (a) Nakano, T.; Ino, Y.; Nagai, Y. *Chem. Lett.* **1989**, 567. (b) Puthuraya, K.; Oomura, Y.; Shimizu, N. *Brain Research*, **1985**, *332*, 165, and references cited therein.

cis-relationship between the 3-hydroxy and 5-alkyl groups of **13**.

Conclusion

It has been demonstrated that the $AlCl_3$-mediated [3 + 2] cycloaddition reaction of oxalyl chloride takes place with a variety of alkynylsilanes. The resulting 2,2-dichloro-3(2*H*)-furanones are versatile synthetic precursors of 2,4-diketo carboxylic acid derivatives, *cis*-5-alkyl-3-hydroxytetrahydro-2-furanones, and *cis*-5-alkyl-3-hydroxy-2-pyrrolidones. The present reactions, when combined with the SmI_2-mediated coupling reaction previously reported,[3] provide new synthetic routes to these compounds from alkyl halides, ethynylsilanes, and oxalyl chloride.

Experimental Part

General. Column chromatography was performed with silica gel (Wakogel C-200). ^1H and ^{13}C NMR spectra (200 MHz and 50 MHz, respectively) were acquired in chloroform-*d*. Except hydrolysis and hydrogenation, all reactions were performed under dry nitrogen atmosphere.

Unless otherwise noted, materials were obtained from commercial sources. Alkynylsilanes were prepared according to the procedure in the literature.[3] Ether was distilled under N_2 from sodium diphenylketyl, MeOH from $Mg(OMe)_2$, and CH_2Cl_2, AcOEt from CaH_2. Aluminum trichloride was purified by sublimation under reduced pressure and, before use, was ground to powder.

2,2-Dichloro-5-(2-phenylethyl)-4-(trimethylsilyl)-3(2*H*)-furanone (1a). To a stirred solution of 4-phenyl-1-(trimethylsilyl)-1-butyne (2.00 g, 9.9 mmol) and oxalyl chloride (1.09 g, 8.59 mmol) in CH_2Cl_2 (80 mL) at −78 °C was added $AlCl_3$ (2.11 g, 15.8 mmol). After the mixture was stirred at that temperature for 3 h, aqueous HCl (1N, 50 mL) was added in one portion. The mixture was allowed to warm to room temperature and then extracted with CH_2Cl_2. The organic extracts were dried over $MgSO_4$, evaporated, and purified by silica gel column chromatography (Et_2O:hexane = 1:15) to afford **1a** (2.10 g, 74%) as colorless crystals: ^1H NMR δ 0.11 (s, 9 H), 2.80−2.91 (m, 2 H), 2.94−3.05 (m, 2 H), 7.13−7.36 (m, 5 H); ^{13}C NMR δ 1.3, 32.4, 33.1, 100.6, 106.4, 126.8, 128.5, 128.7, 138.9, 190.4, 190.5; IR (neat) 1736, 1596, 1018, 844 cm^{-1}. Anal. Calcd for $C_{15}H_{18}O_2SiCl_2$: C, 54.71; H, 5.51. Found: C, 54.57; H, 5.48.

5-Butyl-2,2-dichloro-4-(trimethylsilyl)-3(2*H*)-furanone (1b). By a procedure similar to that for **1a**, the title compound was obtained in 79% yield from 1-(trimethylsilyl)-1-hexyne (1.54 g, 10.0 mmol), oxalyl chloride (1.05 g, 8.27 mmol), and $AlCl_3$ (2.11 g, 15.8 mmol): ^1H NMR δ 0.27 (s, 9 H), 0.95 (t, J = 7.2 Hz, 3 H), 1.30−1.50 (m, 2 H), 1.56−1.74 (m, 2 H), 2.57 (t, J = 7.7 Hz, 2 H); ^{13}C NMR δ 0.1, 13.7, 22.3, 28.7, 30.8, 100.7, 105.1, 192.4, 195.5; IR (neat) 2968, 1736, 1592, 1018, 842 cm^{-1}. Anal. Calcd for $C_{11}H_{18}O_2SiCl_2$: C, 46.98; H, 6.45. Found: C, 46.95; H, 6.67.

2,2-Dichloro-5-(2-methylpropyl)-4-(trimethylsilyl)-3(2*H*)-furanone (1c). By a procedure similar to that for **1a**, the title compound was obtained in 63% yield from 4-methyl-1-(trimethylsilyl)-1-pentyne (196 mg, 1.27 mmol), oxalyl chloride (128 mg, 1.01 mmol), and $AlCl_3$ (266 mg, 1.99 mmol): ^1H NMR δ 0.29 (s, 9 H), 1.00 (d, J = 6.6 Hz, 6 H); 2.03−2.25 (m, 1 H), 2.46 (t, J = 7.3 Hz, 2 H); ^{13}C NMR δ 1.0, 22.3, 27.2, 39.4, 100.6, 106.0, 191.5, 195.5. Anal. Calcd for $C_{11}H_{18}O_2SiCl_2$: C, 46.98; H, 6.45. Found: C, 47.21; H, 6.49.

2,2-Dichloro-5-(1-methylpropyl)-4-(trimethylsilyl)-3(2*H*)-furanone (1d). By a procedure similar to that for **1a**, the title compound was obtained in 63% yield from 3-methyl-1-(trimethylsilyl)-1-pentyne (100 mg, 0.65 mmol), oxalyl chloride (61 mg, 0.48 mmol), and $AlCl_3$ (133 mg, 1.00 mmol): ^1H NMR δ 0.27 (s, 9 H), 0.90 (t, J = 7.5 Hz, 3 H), 1.23 (d, J = 6.8 Hz, 3 H), 1.40−1.84 (m, 2 H), 2.73−2.92 (m, 1 H); ^{13}C NMR δ −0.8, 11.8, 17.6, 26.7, 37.5, 100.8, 105.0, 195.57, 195.63; HRMS m/e calcd for $C_{11}H_{18}O_2SiCl_2$ 280.0453, found 280.0452.

2,2-Dichloro-5-phenyl-4-(trimethylsilyl)-3(2*H*)-furanone (1e). By a procedure similar to that for **1a**, the title compound was obtained in 91% yield from (2-phenylethynyl)-trimethylsilane (105 mg, 0.60 mmol), oxalyl chloride (62 mg, 0.49 mmol), and $AlCl_3$ (133 mg, 1.00 mmol): ^1H NMR δ 0.24 (s, 9 H); 7.45−7.70 (m, 5 H); ^{13}C NMR δ 0.7, 100.9, 105.6, 128.5, 128.9, 129.4, 133.0, 185.8, 195.3. Anal. Calcd for $C_{13}H_{14}O_2SiCl_2$ C, 51.83; H, 4.68. Found: C, 51.89; H, 4.69. Crystal data: Orthorhombic, space group $Fdd2$, a = 25.470(6) Å, b = 38.518(9) Å, c = 6.045(1) Å, V = 5931(2) Å^3, Z = 16, Dc = 1.35 g·cm^{-3}, $Mo_{K\alpha}$ (λ = 0.71073 Å), μ = 4.54 cm^{-1}.

2,2-Dichloro-4-(trimethylsilyl)-3(2*H*)-furanone (1f). By a procedure similar to that for **1a** except the reaction temperature of −30 °C, the title compound was obtained in 19% yield from ethynyltrimethylsilane (129 mg, 1.31 mmol), oxalyl chloride (135 mg, 1.06 mmol), and $AlCl_3$ (266 mg, 1.99 mmol): ^1H NMR δ 0.33 (s, 9 H); 5.96 (s, 1 H); ^{13}C NMR δ −3.4, 111.2, 192.5, 199.2. Anal. Calcd for $C_7H_{10}O_2SiCl_2$: C, 37.34; H, 4.48. Found: C, 37.51; H, 4.49.

2,2-Dichloro-5-phenyl-3(2*H*)-furanone (1g). By a procedure similar to that for **1a**, the title compound was obtained in 70% yield from ethynylbenzene (69 mg, 0.67 mmol), oxalyl chloride (65 mg, 0.51 mmol), and $AlCl_3$ (133 mg, 1.00 mmol): ^1H NMR δ 6.19 (s, 1 H), 7.45−7.72 (m, 3 H), 7.83−7.92 (m, 2 H); ^{13}C NMR δ 96.4, 101.9, 126.4, 127.7, 129.2, 134.4, 181.3, 190.3. Anal. Calcd for $C_{10}H_6O_2Cl_2$: C, 52.44; H, 2.64. Found: C, 52.37; H, 2.47.

2,2-Dichloro-4,5-bis(trimethylsilyl)-3(2*H*)-furanone (1h). By a procedure similar to that for **1a** except the reaction temperature of −30 °C, the title compound was obtained in 86% yield from 1,2-bis(trimethylsilyl)ethyne (1.06 g, 6.22 mmol), oxalyl chloride (632 mg, 4.98 mmol), and $AlCl_3$ (1.33 g, 10.0 mmol): ^1H NMR δ 0.29 (s, 9 H), 0.37 (s, 9 H); ^{13}C NMR δ −1.6, −0.1, 98.7, 118.4, 197.5, 201.4.[2]

Methyl 2,2-Dimethoxy-4-oxo-6-phenylhexanoate (3a). A solution of **1a** (84 mg, 0.26 mmol) in MeOH (1 mL) was stirred at room temperature for 14 h. The mixture was evaporated and the residue was purified by silica gel column chromatography (Et_2O:hexane = 1:1) to afford **3a** (70 mg, 98%) as colorless oil: ^1H NMR δ 2.72−2.83 (m, 2 H), 2.84−2.95 (m, 2 H), 3.07 (s, 2 H), 3.26 (s, 6 H), 3.81 (s, 3 H), 7.13−7.34 (m, 5 H); ^{13}C NMR δ 29.1, 44.8, 46.7, 49.9, 52.4, 99.4, 125.9, 128.1, 128.3, 140.6, 168.3, 204.5; HRMS m/e calcd for $C_{13}H_{17}O_3$ (M − CO_2Me) 221.1178, found 221.1187.

Methyl 2,2-Dimethoxy-4-oxooctanoate (3b). By a procedure similar to that for **3a**, the title compound was obtained in 90% yield from **1b**: ^1H NMR δ 0.87 (t, J = 7.2 Hz, 3 H), 1.17−1.62 (m, 4 H), 2.42 (t, J = 7.5 Hz, 2 H), 3.07 (s, 2 H), 3.26 (s, 6 H), 3.80 (s, 3 H); ^{13}C NMR δ 13.7, 22.1, 25.4, 43.2, 46.6, 50.0, 52.6, 99.6, 168.6, 206.1. Anal. Calcd for $C_{11}H_{20}O_5$: C, 56.88; H, 8.68. Found: C, 56.87; H, 8.88.

Methyl 2,2-Dimethoxy-6-methyl-4-oxoheptanoate (3c). By a procedure similar to that for **3a**, the title compound was obtained in 93% yield from **1c**: ^1H NMR δ 0.89 (d, J = 6.5 Hz, 6 H), 1.98−2.22 (m, 1 H), 2.29 (d, J = 6.6 Hz, 2 H), 3.06 (s, 2 H), 3.27 (s, 6 H), 3.81 (s, 3 H); ^{13}C NMR δ 22.4, 24.2, 47.0, 50.0, 52.4, 52.7, 100.0, 168.5, 205.4. Anal. Calcd for $C_{11}H_{20}O_5$: C, 56.88; H, 8.68. Found: C, 56.89; H, 8.92.

Methyl 2,2-Dimethoxy-5-methyl-4-oxoheptanoate (3d). By a procedure similar to that for **3a**, the title compound was obtained in 70% yield from **1d**: ^1H NMR δ 0.84 (t, J = 7.4 Hz, 3 H), 1.03 (d, J = 6.8 Hz, 3 H), 1.34 (ddq, J = 14.6, 7.4, 6.8 Hz, 1 H), 1.65 (ddq, J = 14.6, 7.4, 6.8 Hz, 1 H), 2.42 (sextet, J = 6.8 Hz, 1 H), 3.12 (s, 2 H), 3.24 (s, 6 H), 3.78 (s, 3 H); ^{13}C NMR δ 11.4, 15.4, 25.5, 44.8, 48.2, 50.0, 52.5, 100.0, 168.6, 209.2; HRMS m/e calcd for $C_9H_{17}O_3$ (M − CO_2Me) 173.1178, found 173.1186.

Methyl 2,2-Dimethoxy-4-oxo-4-phenylbutanoate (3e). By a procedure similar to that for **3a** except the reaction temperature of 50 °C, the title compound was obtained in 73% yield from **1e**: ^1H NMR δ 3.30 (s, 6 H), 3.68 (s, 2 H), 3.78 (s, 3 H), 7.39−7.62 (m, 3 H), 7.88−7.97 (m, 2 H); ^{13}C NMR δ 42.2, 50.0, 52.5, 99.9, 128.0, 128.6, 133.4, 136.4, 168.6, 194.8; HRMS m/e calcd for $C_{11}H_{13}O_3$ (−CO_2Me) 193.0865, found 193.0872.

2,2-Dimethoxy-6-phenyl-4-hexanolide (4a). To a stirred suspension of $NaBH_4$ (3.3 mg, 0.09 mmol) in MeOH (1.5 mL) at −20 °C was added **3a** (56 mg, 0.20 mmol) in MeOH (0.5 mL). After the mixture was stirred at that temperature for 24 h, aqueous NH_4Cl (20%, 5 mL) was added, and the mixture was extracted with ether. The organic extracts were dried over

$MgSO_4$, evaporated, and purified by silica gel column chromatography (Et_2O:hexane = 1:2) to afford **4a** (49 mg, 98%) as colorless oil: ^1H NMR δ 1.82–2.17 (m, 3 H), 2.47 (dd, J = 12.8, 5.8 Hz, 1 H), 2.62–2.92 (m, 2 H), 3.37 (s, 3 H), 3.39 (s, 3 H), 4.38–4.55 (m, 1 H), 7.15–7.36 (m, 5 H); ^{13}C NMR δ 31.3, 36.9, 39.2, 50.8, 50.9, 76.2, 99.8, 126.2, 128.4, 128.5, 140.5, 169.6. Anal. Calcd for $C_{14}H_{18}O_4$ C, 67.18; H, 7.25. Found: C, 67.13; H, 7.47.

2,2-Dimethoxy-4-octanolide (4b). By a procedure similar to that for **4a**, the title compound was obtained in 81% yield from **3b**: ^1H NMR δ 0.90 (br t, J = 7.2 Hz, 3 H), 1.20–1.84 (m, 6 H), 1.93 (dd, J = 12.7, 8.8 Hz, 1 H), 2.47 (dd, J = 12.7, 5.7 Hz, 1 H), 3.37 (s, 3 H), 3.38 (s, 3 H), 4.37–4.57 (m, 1 H); ^{13}C NMR δ 13.8, 22.3, 27.0, 34.8, 39.3, 50.8, 50.9, 77.2, 100.0, 169.7; HRMS m/e calcd for $C_9H_{15}O_3$ (M − OMe) 171.1021, found 171.1023.

2-Hydroxy-6-phenyl-2-hexen-4-olide (5a). A solution of **4a** (49 mg, 0.20 mmol) and *p*-toluenesulfonic acid monohydrate (188 mg, 0.99 mmol) in acetone (2 mL) and water (3 mL) was heated at 80 °C for 8.5 h. After cooled to room temperature, the mixture was extracted with ether. The organic extracts were dried over $MgSO_4$, evaporated, and purified by silica gel column chromatography (Et_2O:hexane = 1:1) to afford **5a** (35 mg, 87%) as a colorless oil: ^1H NMR δ 1.85–2.20 (m, 2 H), 2.72 (dd, J = 7.6, 13.5 Hz, 1 H), 2.87 (dd, J = 6.6, 13.5 Hz, 1 H), 4.95 (ddd, J = 1.9, 5.0, 7.6 Hz, 1 H), 6.21 (d, J = 1.9 Hz, 1 H), 6.40–7.10 (br, 1 H), 7.14–7.37 (m, 5 H); ^{13}C NMR δ 31.1, 35.8, 78.8, 119.2, 126.3, 128.4, 128.6, 140.3, 142.2, 170.4; HRMS m/e calcd for $C_{12}H_{12}O_3$ 204.0786, found 204.0788.

2-Hydroxy-2-octen-4-olide (5b). By a procedure similar to that for **5a**, the title compound was obtained in 93% yield from **4b**: ^1H NMR δ 0.91 (br t, J = 7.0 Hz, 3 H), 1.20–1.52 (m, 4 H), 1.55–1.84 (m, 2 H), 4.95 (ddd, J = 1.9, 5.5, 7.4 Hz, 1 H), 6.23 (d, J = 1.9 Hz, 1 H), 6.30–7.10 (br, 1 H); ^{13}C NMR δ 13.8, 22.4, 26.8, 33.8, 79.8, 119.2, 142.1, 170.5; HRMS m/e calcd for $C_7H_{12}O_2$ (M − CO) 128.0837, found 128.0830.

(2*S,4*R**)-2-Hydroxy-6-phenyl-4-hexanolide (6a).** A suspension of 5% Pd–C (17 mg) in AcOEt (1 mL) was stirred under H_2 (1 atm) for 1 h at room temperature. Then **5a** (35 mg, 0.17 mmol) in AcOEt (2 mL) was added to the suspension, which was stirred for 18 h. The mixture was filtered through Celite, and after evaporation, the filtrate was purified by silica gel column chromatography (CH_2Cl_2:MeOH = 20:1) to afford **6a** (29 mg, 81%) as colorless oil: ^1H NMR δ 1.83–2.21 (m, 3 H), 2.60–2.93 (m, 3 H), 3.15–3.60 (br, 1 H), 4.35 (ddt, J = 10.2, 8.0, 5.0 Hz, 1 H), 4.54 (dd, J = 11.0, 8.3 Hz, 1 H), 7.15–7.37 (m, 5 H); ^{13}C NMR δ 31.3, 37.0, 68.6, 76.2, 126.3, 128.4, 128.6, 140.4, 177.5; HRMS m/e calcd for $C_{12}H_{14}O_3$ 206.0943, found 206.0947.

(2*S,4*R**)-2-Hydroxy-4-octanolide (6b).** By a procedure similar to that for **6a**, the title compound was obtained in 86% yield from **5b**: ^1H NMR δ 0.91 (t, J = 6.8 Hz, 3 H), 1.20–2.06 (m, 7 H), 2.68 (ddd, J = 12.4, 8.3, 5.2 Hz, 1 H), 3.53 (br s, 1 H), 4.37 (ddt, J = 10.5, 7.1, 5.2 Hz, 1 H), 4.55 (dd, J = 11.0, 8.3 Hz, 1 H); ^{13}C NMR δ 13.8, 22.3, 27.0, 35.0, 37.1, 68.7, 77.3, 177.7.[7b]

(*E*)-*N*,*N*-Diethyl-2-(diethylamino)-4-oxo-6-phenyl-2-hexenamide (7a). To a stirred solution of **1a** (56 mg, 0.17 mmol) in ether (2 mL) at room temperature was added diethylamine (62 mg, 0.85 mmol). After the reaction mixture was stirred for 17 h, the resulting white precipitates were removed by filtration. The filtrate was evaporated and purified by silica gel column chromatography (AcOEt) to afford **7a** (52 mg, 87%): ^1H NMR δ 1.08–1.33 (m, 12 H), 2.85 (t, J = 7.7 Hz, 2 H), 3.10–3.50 (m, 10 H), 5.22 (s, 1 H), 7.13–7.41 (m, 5 H); ^{13}C NMR δ 12.7, 14.5, 31.8, 34.7, 38.5, 42.0, 90.3, 126.1, 128.3, 128.6, 141.0, 166.6, 170.6, 185.0; HRMS m/e calcd for $C_{20}H_{30}N_2O_2$ 330.2307, found 330.2309.

(*E*)-*N*,*N*-Diethyl-2-(diethylamino)-4-oxo-2-octenamide (7b). By a procedure similar to that for **7a**, the title compound was obtained in 99% yield from **1b**: ^1H NMR δ 0.90 (t, J = 7.0 Hz, 3 H), 1.11 (t, J = 7.2 Hz, 6 H), 1.14 (t, J = 7.2 Hz, 6 H), 1.32–1.58 (m, 4 H), 2.94 (br t, J = 7.2 Hz, 2 H), 3.20–3.43 (m, 8 H), 5.09 (s, 1 H). ^{13}C NMR δ 12.6, 13.7, 14.4, 22.9, 29.1, 30.7, 38.4, 41.9, 44.0 (br), 90.2, 167.7, 170.7, 185.0; HRMS m/e calcd for $C_{11}H_{20}NO$ (−$CONEt_2$) 182.1545, found 182.1551.

(*E*)-*N*,*N*-Diethyl-2-(diethylamino)-6-methyl-4-oxo-2-heptenamide (7c). By a procedure similar to that for **7a**, the title compound was obtained in 95% yield from **1c**: ^1H NMR δ 0.96 (d, J = 6.6 Hz, 6 H), 1.11 (t, J = 7.1 Hz, 6 H), 1.14 (t, J = 6.9 Hz, 6 H), 1.76–2.05 (m, 1 H), 2.70–3.20 (br, 2 H), 3.23–3.41 (m, 8 H), 5.15 (s, 1 H). ^{13}C NMR δ 12.6, 14.4, 22.0, 29.0, 36.3, 38.4, 41.9, 44.3, 91.2, 166.6, 170.7, 185.0; HRMS m/e calcd for $C_{11}H_{20}NO$ (M − $CONEt_2$) 182.1545, found 182.1544.

Synthesis of 2-Morphorinone (8). To a stirred solution of *N*-methylvalinol (119 mg, 1.02 mmol) in ether (4 mL) at room temperature was added **1b** (68 mg, 0.24 mmol). The reaction mixture was stirred for 18 h, evaporated, and filtered quickly through a short column of silica gel (Et_2O:hexane = 1:1) to afford **8** (72 mg, 91%): ^1H NMR δ 0.22 (s, 9 H), 0.92 (t, J = 6.3 Hz, 3 H), 0.97 (d, J = 5.8 Hz, 6 H), 1.25–1.75 (m, 4 H), 1.85–2.05 (m, 1 H), 2.24 (s, 3 H), 2.40–2.66 (m, 2 H), 3.15 (dt, J = 4.2, 8.0 Hz, 1 H), 3.98 (t, J = 8.0 Hz, 1 H), 4.18 (t, J = 8.0 Hz, 1 H); ^{13}C NMR δ 0.6, 13.7, 14.9, 19.4, 22.6, 27.5, 29.4, 30.7, 32.1, 65.2, 68.6, 107.1, 116.6, 195.7, 200.5; IR (neat) 2968, 1712, 1566, 842 cm^{-1}. The following column chromatography on silica gel (Et_2O: hexane = 1:1) resulted in protiodesilylation of **8** to afford the corresponding 2-morphorinone: ^1H NMR δ 0.90 (t, J = 7.1 Hz, 3 H), 0.96 (d, J = 7.0 Hz, 3 H), 1.03 (d, J = 7.0 Hz, 3 H), 1.22–1.44 (m, 2 H), 1.50–1.70 (m, 2 H), 2.07–2.32 (m, 1 H), 2.46 (t, J = 7.7 Hz, 2 H), 2.95 (s, 3 H), 3.17 (dt, J = 6.0, 3.7 Hz, 1 H), 4.26 (dd, J = 11.8, 6.0 Hz, 1 H), 4.42 (dd, J = 11.8, 3.7 Hz, 1 H), 6.15 (s, 1 H); ^{13}C NMR δ 13.9, 16.9, 19.0, 22.4, 27.4, 28.9, 43.2, 44.0, 62.6, 65.2, 101.9, 142.6, 163.5, 197.2; HRMS m/e calcd for $C_{14}H_{23}NO_3$ 253.1678, found 253.1676.

Synthesis of Pyrazinone (9). To a stirred solution of **1e** (77 mg, 0.26 mmol) in ether (4 mL) at room temperature was added *N*,*N*′-dimethylethylenediamine (47 mg, 0.50 mmol). The reaction mixture was stirred for 18 h, evaporated, and filtered through a short column of silica gel pretreated with Et_3N (AcOEt:MeOH = 2:1) to afford **9** (72 mg, 89%): ^1H NMR δ −0.22 (s, 9 H), 2.63 (s, 3 H), 3.03 (s, 3 H), 3.67 (t, J = 7.1 Hz, 2 H), 3.98 (t, J = 7.1 Hz, 2 H), 7.26–7.49 (m, 5 H). Recrystallization of **9** from non-dry $CHCl_3$-hexane resulted in protiodesilylation to afford the corresponding pyrazinone: ^1H NMR δ 2.80 (s, 3 H), 3.10 (s, 3 H), 3.62–3.72 (m, 2 H), 3.78–3.90 (m, 2 H), 5.37 (s, 1 H), 7.38–7.52 (m, 5 H); ^{13}C NMR δ 34.0, 41.0, 49.0, 55.5, 107.6, 128.6, 129.2, 130.9, 136.0, 166.5, 170.0, 190.5. Anal. Calcd for $C_{14}H_{16}N_2O_2$ C, 68.83; H, 6.60; N, 11.47. Found: C, 68.61; H, 6.56; N, 11.45.

1-Benzyl-5-butyl-4-(trimethylsilyl)-4-azoline-2,3-dione (11a). To a stirred solution of **1a** (303 mg, 0.92 mmol) in ether (8 mL) at room temperature was added benzylamine (666 mg, 6.22 mmol). After the mixture was stirred for 10 h, aqueous HCl (1N, 20 mL) and ether were added. On vigorous stirring of the mixture, the yellow organic layer turned orange. Then the mixture was extracted with ether. The organic extracts were dried over $MgSO_4$, evaporated, and purified by silica gel column chromatography (Et_2O:hexane = 1:2) to afford **11a** (218 mg, 65%) as orange crystal. ^1H NMR δ 0.24 (s, 9 H), 2.74 (s, 4 H), 4.68 (s, 2 H), 7.03–7.42 (m, 10 H); ^{13}C NMR δ −0.3, 31.2, 35.1, 43.5, 106.8, 126.7, 127.0, 127.97, 128.04, 128.8, 129.1, 136.1, 138.9, 159.7, 179.3, 188.5. Anal. Calcd for $C_{22}H_{25}NO_2Si$ C, 72.69; H, 6.93; N, 3.85. Found: C, 72.45; H, 6.88; N, 3.80.

1-Benzyl-5-butyl-4-(trimethylsilyl)-4-azoline-2,3-dione (11b). By a procedure similar to that for **11a**, the title compound was obtained as orange oil in 65% yield from **1b**: ^1H NMR δ 0.23 (s, 9 H), 0.88 (br t, J = 6.6 Hz, 3 H), 1.32–1.48 (m, 4 H), 2.37–2.52 (m, 2 H), 4.77 (s, 2 H), 7.16–7.43 (m, 5 H); ^{13}C NMR δ 0.3, 13.5, 22.9, 29.2, 31.2, 43.6, 106.0, 126.7, 127.9, 128.9, 136.2, 159.8, 180.7, 188.5; IR (neat) 1754, 1706, 1558 cm^{-1}; HRMS m/e calcd for $C_{18}H_{25}NO_2Si$: 315.1655, found 315.1640.

(*E*)-1-Benzyl-5-(2-phenylethylidene)-3-hydroxy-3-azolin-2-one (12a). To a stirred solution of **11a** (70 mg, 0.19 mmol) in CH_2Cl_2 (2 mL) was added concentrated HCl (0.5 mL). The reaction mixture was stirred for 30 min, and then extracted with CH_2Cl_2. The organic extracts were dried over $MgSO_4$, evaporated, and purified by silica gel column chromatography (Et_2O: hexane = 1:1) to afford **12a** (56 mg, 99%): ^1H NMR δ 3.54 (d, J = 8.0 Hz, 2 H), 4.89 (s, 2 H), 5.46 (d, J = 8.0 Hz, 1 H), 6.29 (s, 1 H), 7.00–7.40 (m, 10 H), 8.40–8.80 (br, 1 H); ^{13}C NMR δ 33.3, 43.1, 100.4, 112.0, 126.4, 126.8, 127.3, 128.2, 128.5, 128.6, 136.6, 136.9, 139.5, 148.1, 165.8; HRMS m/e calcd for $C_{19}H_{17}NO_2$ 291.1259, found 291.1268.

(*E*)-1-Benzyl-5-butylidene-3-hydroxy-3-azolin-2-one (12b). By a procedure similar to that for **12a**, the title compound was obtained in 88% yield from **11b**: ^1H NMR δ 0.83 (t, J = 7.4 Hz, 3 H), 1.38 (sextet, J = 7.4 Hz, 2 H), 2.16 (dt, J = 8.0, 7.4 Hz, 2 H), 4.87 (s, 2 H), 5.28 (t, J = 8.0 Hz, 1 H), 6.17 (s, 1 H), 7.12–7.36 (m, 5 H), 7.70–8.00 (br, 1 H); ^{13}C NMR δ 13.4, 23.1, 29.3,

43.0, 100.6, 114.3, 126.7, 127.3, 128.6, 136.0, 137.0, 147.4, 165.7; HRMS *m/e* calcd for $C_{15}H_{17}NO_2$ 243.1259, found 243.1254.

(3S*,5R*)-1-Benzyl-3-hydroxy-5-(2-phenylethyl)-2-pyrrolidone (13a). A suspension of 5% Pd on $CaCO_3$ (22 mg) in AcOEt (1 mL) was stirred under H_2 (1 atm) for 1 h at room temperature. Then **12a** (20 mg, 0.069 mmol) in AcOEt (3 mL) was added to the mixture, which was stirred for 63 h. The mixture was filtered through Celite. The filtrate was evaporated, and purified by silica gel column chromatography (EtOAc:hexane = 4:1) to afford **13a** (14 mg, 68%) as colorless solid: ^{1}H NMR δ 1.58–1.85 (m, 2 H), 2.08–2.26 (m, 1 H), 2.40–2.75 (m, 3 H), 3.29–3.45 (m, 1 H), 4.05 (d, J = 15.0 Hz, 1 H), 4.07 (d, J = 2.2 Hz, 1 H), 4.41 (dt, J = 8.6, 2.2 Hz, 1 H), 4.98 (d, J = 15.0 Hz, 1 H), 7.03–7.42 (m, 10 H); ^{13}C NMR δ 30.5, 33.8, 34.5, 44.4, 53.2, 69.5, 126.2, 127.7, 127.9, 128.1, 128.5, 128.7, 136.0, 140.7, 175.3. Anal. Calcd for $C_{19}H_{21}NO_2$ C, 77.26; H, 7.17; N, 4.74. Found: C, 77.24; H, 7.15; N, 4.72.

(3S*,5R*)-1-Benzyl-5-butyl-3-hydroxy-2-pyrrolidone (13b). By a procedure similar to that for **13a**, the title compound was obtained in 65% yield from **12b**: ^{1}H NMR δ 0.86 (t, J = 6.8 Hz, 3 H), 1.00–1.45 (m, 6 H), 1.59 (dt, J = 12.6, 8.7 Hz, 1 H), 1.70–1.90 (m, 1 H), 2.52 (ddd, J = 12.6, 8.3, 6.2 Hz, 1 H), 3.25–3.41 (m, 1 H), 4.05 (d, J = 15.0 Hz, 1 H), 4.37 (t, J = 8.7 Hz, 1 H), 4.98 (d, J = 15.0 Hz, 1 H), 7.15–7.38 (m, 5 H). ^{13}C NMR δ 13.9, 22.5, 26.3, 32.6, 33.9, 44.3, 53.6, 69.7, 127.6, 127.9, 128.7, 136.2, 175.2; HRMS *m/e* calcd for $C_{15}H_{21}NO_2$ 247.1572, found 247.1571.

Supplementary Material Available: The details of the X-ray structural determination of **1e**, the ORTEP drawing, and copies of ^{13}C NMR spectra for all compounds not having elemental analyses (18 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.