chloride in 10 mL of dry CH_2Cl_2 was stirred at 0 °C for 0.5 h under nitrogen, then hydrolyzed by 20 mL of 4 N HCl, and extracted four times with 50 mL of CH_2Cl_2. The combined organic layers were washed twice with 50 mL of water, dried over magnesium sulfate, and concentrated under reduced pressure. The remaining solid was chromatographed on silica gel (eluent: cyclohexane/AcOEt, 1/1) to yield 60 mg (90%) of anthraquinone **10a** as a yellow solid, mp 183–184 °C (lit.[19] mp 181–183 °C).

1,5-Dimethoxy-9,10-anthraquinone (10b). A suspension of 60 mg (0.25 mmol) of anthraquinone **10a**, 0.35 mL (5.6 mmol) of methyl iodide, and 376 mg (1.6 mmol) of silver oxide in 7 mL of CH_2Cl_2 was stirred in the dark at room temperature for 41 h and then filtered on Celite. The filtrate was concentrated under reduced pressure, giving 63 mg (100%) of anthraquinone **10b**, mp 240–241 °C, which was identified (mixed melting point) with an authentic sample[20] (lit.[20] mp 241–242 °C).

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Registry No. **1a**, 481-39-0; **1b**, 5196-28-1; **2a**, 71700-93-1; **2b**, 71700-92-0; **3a**, 112740-62-2; **3b**, 105245-47-4; **3c**, 112740-63-3; **4b**, 77189-69-6; **5b**, 69833-10-9; **6**, 105259-49-2; **7**, 63383-46-0; **8**, 112740-64-4; **9**, 112740-65-5; **10a**, 52869-21-3; **10b**, 6448-90-4.

(19) Farbenfabriken Bayer A. G. German Patent 1178441; *Chem. Abstr.* **1964**, *61*, 16027*g*.
(20) Dufraisse, C.; Velluz, L. *Bull. Soc. Chim. Fr.* **1942**, *9*, 171.

A Novel and Efficient Synthesis of 2(5*H*)-Furanone Derivatives

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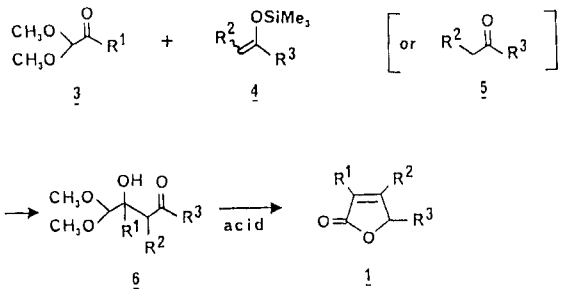
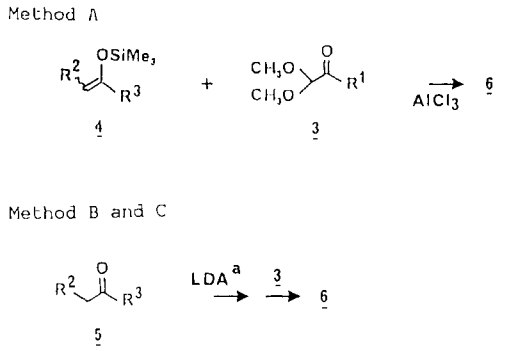
2(5*H*)-Furanones and 5-alkylidene-2(5*H*)-furanones (Δ^2-butenolides) are well-known as basic components of naturally occuring compounds, some of which display a wide range of characteristic physiological properties.[1] In addition, they often serve as useful synthetic intermediates in the stereoselective construction of substituted γ-butyrolactones via conjugate addition or catalytic hydrogenation of the double bond.[2] For example, this approach was used in total syntheses of avenaciolide[3] along with its related compounds[4] and recently has been successfully realized in the stereoselective synthesis of brassinolide.[5] In this work the 5-alkylidene-2(5*H*)-furanone was hydrogenated to the corresponding γ-butyrolactone, providing stereochemical control of four contiguous centers.

Scheme I



Scheme II



[a] 1.1 equiv, R^2 = H, R^3 = CH=C$(CH_3)_2$; 2.2 equiv, R^3 = $CH_2CO_2CH_3$.

Despite the great variety of available synthetic methods,[1,6] scant attention has been paid to practical and efficient synthesis of 3,5-di- or 3,4,5-trisubstituted 2(5*H*)-furanones **1** and 3-alkyl-5-alkylidene-2(5*H*)-furanones **2**.

In this paper, we report a novel and efficient synthesis of 3,5-di- or 3,4,5-trisubstituted 2(5*H*)-furanone analogues **1** in two steps: namely, the cross-aldol condensation of α-keto dimethyl acetal **3** and ketone **5** (or the enol ether equivalent **4**) to lead to the adduct **6**, followed by acid-promoted cyclization of **6** to 2(5*H*)-furanone **1** (as shown in Scheme I).

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(3) Herrmann, J. L.; Berger, M. H.; Schlessinger, R. H. *J. Am. Chem. Soc.* **1979**, *101*, 1544.
(4) Isoavenaciolide: Damon, R. E.; Schlessinger, R. H. *Tetrahedron Lett.* **1975**, 4551. Protolichesterinic acid: Damon, R. E.; Schlessinger, R. H. *Ibid.* **1976**, 1561.
(5) Kametani, T.; Katoh, T.; Tsubuki, M.; Honda, T. *J. Am. Chem. Soc.* **1986**, *108*, 7055.
(6) For reviews of butenolide chemistry: (a) Rao, Y. S. *Chem. Rev.* **1964**, *64*, 353. (b) Rao, Y. S. *Ibid.* **1976**, *76*, 625. (c) Haynes, L. H. *Q. Rev.* **1948**, *2*, 46. (d) Matsumoto, M. *J. Synth. Org. Chem.* **1981**, *39*, 25. For recent methods for the syntheses of 2(5*H*)-furanones: (e) Iwai, K.; Kosugi, H.; Uda, H.; Kawai, M. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 242. (f) Krauser, S. F.; Watterson, A. C., Jr. *J. Org. Chem.* **1978**, *43*, 3400. (g) Schmidt, R. R.; Talbiersky, J. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 204. (h) Berg, A. S.; Kolsaker, P. *Acta Chem. Scand., Ser. B.* **1978**, *32*, 665. (i) Caine, D.; Frobese, S. *Tetrahedron Lett.* **1978**, 5167. (j) Goldsmith, D.; Liotta, D.; Lee, C.; Zima, G. *Ibid.* **1979**, 4801. (k) Corey, E. J.; Schmidt, G. *Ibid.* **1980**, *21*, 731. (l) Pelter, A.; Al-Bayati, R.; Hansel, R.; Dinter, H.; Burke, B. *Ibid.* **1981**, *22*, 1545. (m) Larcheveque, M.; Legueut, C.; Debal, A.; Lallemand, J. Y. *Ibid.* **1981**, *23*, 1595. (n) Brownbridge, P.; Egert, E.; Hunt, P. G.; Kennard, O.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2751. (o) Barbier, P.; Benezra, C. *Ibid.* **1982**, *23*, 3511. (p) Ito, M.; Tsukida, K. *Heterocycles* **1982**, *19*, 1385. (q) Bourguigon, J. J.; Wermuth, C. G. *J. Org. Chem.* **1981**, *46*, 4889. (r) Camps, P.; Cardellach, J.; Font, J.; Ortuno, R. M.; Ponsati, O. *Tetrahedron* **1982**, *38*, 2395. (s) Cardellach, J.; Estopa, C.; Font, J.; Moreno-Manas, M.; Ortuno, R. M.; Sanchez-Ferrando, F.; Valle, S.; Vilamajo, L. *Ibid.* **1982**, *38*, 2377. (t) Saimoto, H.; Shinoda, M.; Matsubara, S.; Ohshima, K.; Hiyama, T.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3088. (u) Goldsmith, D.; Liotta, D.; Saindene, M.; Waykole, L.; Browen, P. *Tetrahedron Lett.* **1983**, *24*, 5835. (v) Nikam, S. S.; Chu, K.-H.; Wang, K. K. *J. Org. Chem.* **1986**, *51*, 745. (w) Hanessian, S.; Hodges, S.; Murray, P. J.; Sahoo, S. P. *J. Chem. Soc., Chem. Commun.* **1986**, 754. (x) Carretero, J. C.; Lombaert, S. D.; Ghosez, L. *Tetrahedron Lett.* **1987**, *28*, 2153. (y) Doyama, K.; Joh, T.; Onitsuka, K.; Shiohara, T.; Takahashi, S. *J. Chem. Soc., Chem. Commun.* **1987**, 649.

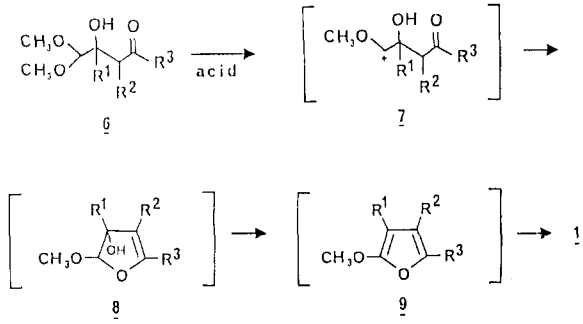
0022-3263/88/1953-1560$01.50/0

Table I. Preparation of Aldol Adducts[a]

entry	α-keto dimethyl acetal, R^1	method	TMS enol ether R^2	TMS enol ether R^3	ketone R^2	ketone R^3	product	yield, %
1	**3a**, Me	A	H	$PhCH_2CH_2$			**6a**	60
2	**3a**, Me	A	H	*p*-Cl-Ph			**6b**	65
3	**3a**, Me	A	H	*t*-Bu			**6c**	57
4	**3a**, Me	A	Me	Et			**6d**	57
5	**3b**, Et	A	H	*t*-Bu			**6e**	53
6	**3a**, Me	B			H	$CH{=}C(Me)_2$	**6f**	62
7	**3a**, Me	C			H	CH_2CO_2Me	**6g**	67
8	**3a**, Me	C			$CH_2CH{=}CH_2$	CH_2CO_2Me	**6h**	73
9	**3c**, Bu	C			H	CH_2CO_2Me	**6i**	70

[a] Conditions are described in this article.

Scheme III



In this method, the alkyl (or aryl) substituents (R^1, R^2, and R^3) can be easily introduced into **1** because R^1 is from the readily accessible α-keto dimethyl acetal **3** and R^2 and R^3 are from ketone **5** or trimethylsilyl enol ether **4**. α-Keto dimethyl acetals can be readily prepared by substitution of the corresponding halides with the anion derived from the *N,N*-dimethylhydrazone of 1,1-dimethoxy-2-propanone, followed by acid hydrolysis.[7]

The first step, the aldol reaction, was conducted with three alternative conditions according to the nature of the ketone employed. (A) Simple ketones were converted to the TMS enol ether and allowed to react with **3** in the presence of $AlCl_3$ (2.2 equiv) at −20 °C ~ 0 °C.[8] (B) α,β-Unsaturated ketones were treated with lithium diisopropylamide at −78 °C and allowed to react with **3** at −78 °C to 0 °C. (C) β-Keto esters were treated with lithium diisopropylamide (2.2 equiv) to generate the dianion,[9] which were allowed to react with **3** at 0 °C (as shown in Scheme II). These results are summarized in Table I. Unfortunately, the reaction between the enolate anion of the simple ketones and α-keto dimethyl acetal **3** was generally found to give mixtures of the aldol adducts.

The second and key step of this synthesis involved an unusual cyclization reaction of the aldol **6** to the 2(5*H*)-furanone **1** and was carried out in acidic conditions. Among several conditions screened, the use of saturated $HCl/CHCl_3$ at 0 °C to room temperature gave the best results in yield, as shown in Table II.

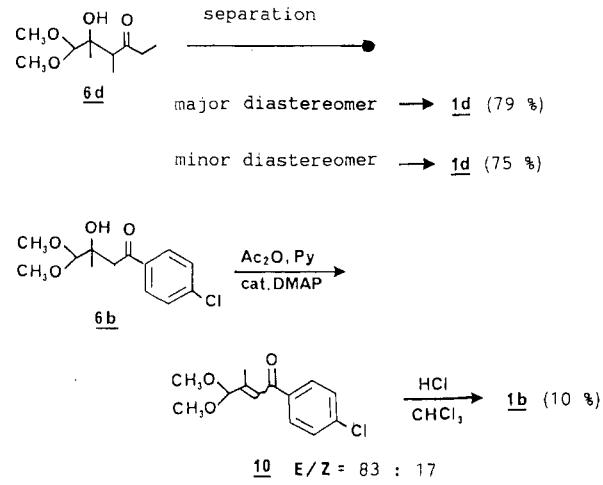
A plausible mechanism[10] to account for this transformation is given in Scheme III. Thus, on treatment of the aldol adduct **6** with acid, carbocation **7** is initially formed because the acetal is the most susceptible function of **6**. The carbocation **7** is in turn expected to cyclize to dihydrofuran **8**, followed by dehydration, to afford furan **9** which is transformed into the 2(5*H*)-furanone **1**.

Table II. Transformation of Aldol Adducts to 2(5*H*)-Furanones

entry	substrate	condition[a]	2(5*H*)-furanone	yield, %
1	**6a**	A	**1a**	82
2	**6a**	B	**1a**	25
3	**6a**	C	**1a**	42
4	**6a**	D	**1a**	58
5	**6b**	A	**1b**	71
6	**6c**	A	**1c**	62
7	**6d**	A	**1d**	78
8	**6e**	A	**1e**	65
9	**6f**	A	**1f**	72
10	**6g**	A	**1g**	78
11	**6h**	A	**1h**	68
12	**6i**	A	**1i**	83

[a] Conditions: (A) saturated $HCl/CHCl_3$, 0 °C ~ r.t.; (B) 1 N HCl/MeOH, 0 °C; (C) $BF_3{\cdot}Et_2O$ (2.0 equiv), 0 °C; (D) CF_3CO_2H (5%)/CH_2Cl_2, 0 °C ~ r.t.

Scheme IV

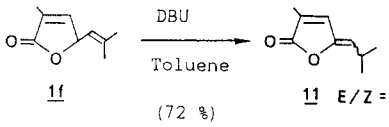


This speculation, i.e., that the cyclization to dihydrofuran **8** precedes the dehydration of the tertiary alcohol in **6**, may be supported by the following experimental results (as shown in Scheme IV). Each of the diastereomers,[11] which were separable by column chromatography, was subjected to the transformation to afford the 2(5*H*)-furanone **1d** in nearly equal yield. When the *E*-rich enone (**10**, E/Z = 83:17)[12] prepared from **6b** was treated

(7) Cuvigny, T.; Normant, H. Synthesis **1977**, 199.
(8) The use of 2.2 equiv of $AlCl_3$ was found to give the best result in yield. This reaction proceeded chemoselectively toward the ketone function of **3** and a similar observation was shown in the reaction between allylsilane and 1,1-dimethoxy-2-propanone: Ojima, I.; Kumagai, M. *Chem. Lett.* **1978**, 575.
(9) (a) Weiler, L. *J. Am. Chem. Soc.* **1970**, *92*, 6702. (b) Weiler, L.; Huckin, S. N. *Can. J. Chem.* **1973**, *52*, 2157.
(10) A similar transformation was reported: Buchi, G.; Minster, M.; Young, J. C. F. *J. Am. Chem. Soc.* **1971**, *93*, 4319.
(11) The faster eluent is the major isomer. The relative stereochemistry (threo/erythro) of the isomers (**6d**) was not assigned.
(12) The assignment and the ratio of *E* or *Z* were determined by ^1H NMR (270 MHz) observation of methyl protones. *E*, δ 2.15 (d, J = 1.7 Hz); *Z*, δ 1.98 (d, J = 2.0 Hz).

with saturated $HCl/CHCl_3$ (the same conditions), the corresponding 2(5*H*)-furanone **1b** was obtained in only 10% yield accompanied by a mixture of other unidentified materials.

Finally, it was found that 5-alkylidene-2(5*H*)-furanone (**11**, E/Z = 22:78)[13] could be successfully obtained from **1f** by base-catalyzed isomerization employing 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).



In summary, novel and practical syntheses of 3,5-di- or 3,4,5-trisubstituted 2(5*H*)-furanone derivatives have been achieved. This method allows the preparation of a variety of the 2(5*H*)-franone derivatives in just two steps and is applicable to a wide range of substrates.

Experimental Section

Melting points were determined on a hot stage microscope apparatus (Yanagimoto) and were uncorrected. ^1H NMR spectra were recorded on a Hitachi R-24 B spectrometer (60 MHz) or JOEL GX-270 spectrometer (270 MHz) using TMS as an internal standard in $CDCl_3$. ^{13}C NMR spectra were recorded on a Hitachi R-90 H spectrometer. IR spectra were determined with a Hitachi 270-30 spectrophotometer. MS and HRMS spectra were obtained with a Hitachi GC/MS M-80 instrument. Microanalytical data were provided by Sumika Analysis Center (Osaka).

1,1-Dimethoxy-2-butanone (3b) was prepared by the known method[7] from 1,1-dimethoxy-2-propanone dimethylhydrazone and iodomethane followed by hydrolysis: bp 125–128 °C/760 mmHg; ^1H NMR δ 4.57 (s, 1 H), 3.40 (s, 6 H), 2.58 (q, 2 H, J = 7 Hz), 1.10 (t, 3 H, J = 7 Hz).

1,1-Dimethoxy-2-heptanone[7] (3c): bp 92–94 °C/11 mmHg; ^1H NMR δ 4.57 (s, 1 H), 3.40 (s, 6H), 2.58 (t, 2 H, J = 7 Hz), 1.10–1.80 (m, 8 H), 0.90 (t, 3 H, J = 7 Hz).

5-Hydroxy-6,6-dimethoxy-5-methyl-1-phenyl-3-hexanone (6a): Typical Procedure of Method A. To a stirred suspension of $AlCl_3$ (2.93 g, 22 mmol) in CH_2Cl_2 (20 mL) was added a solution of 4-phenyl-2-(trimethylsiloxy)-1-butene (2.20 g, 10 mmol) and 1,1-dimethoxy-2-propanone (1.18 g, 10 mmol) at −20 °C, and the resultant mixture was stirred at the same temperature for 1 h. After being stirred at 0 °C for 5 h, the reaction mixture was poured onto ice–water and extracted with CH_2Cl_2 (20 mL × 2). The combined extracts were washed with water, saturated aqueous $NaHCO_3$, and brine and were dried (Na_2SO_4). Removal of the solvent under reduced pressure and flash column chromatography on SiO_2 using $CHCl_3$/EtOAc (20:1) as eluent gave 1.61 g (60%) of **6a** as a colorless liquid: ^1H NMR δ 7.20 (m, 5 H), 4.10 (s, 1 H), 3.48 (s, 3 H), 3.45 (s, 3 H), 2.85 (m, 4 H), 2.83 (d, 1 H, J = 16 Hz), 2.38 (d, 1 H, J = 14 Hz), 1.20 (s, 3 H); IR (film) 3440, 2190, 1700, 1440, 1350, 1060 cm^{-1}. Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.51; H, 8.21.

3-Hydroxy-4,4-dimethoxy-3-methyl-1-(4-chlorophenyl)-1-butanone (6b) (method A): colorless liquid; ^1H NMR δ 7.49 (d, 2 H, J = 10 Hz), 6.90 (d, 2 H, J = 10 Hz), 4.65 (s, 1 H), 3.55 (s, 3 H), 3.50 (s, 3 H), 3.42 (d, 1 H, J = 16 Hz), 2.88 (d, 1 H, J = 16 Hz), 1.30 (s, 3 H); ^{13}C NMR δ 200.1, 139.4, 136.0, 129.7, 128.6, 110.2, 75.3, 57.8, 42.6, 23.4; IR (film) 3550, 3000, 2900, 1700, 1615, 1420, 1120 cm^{-1}. Anal. Calcd for $C_{13}H_{17}ClO_4$: C, 57.25; H, 6.28. Found: C, 57.05; H, 6.20.

5-Hydroxy-6,6-dimethoxy-2,2,5-trimethyl-3-hexanone (6c) (method A): colorless liquid; ^1H NMR δ 5.00 (1 H, s, O*H*), 4.10 (s, 3 H), 3.45 (s, 3 H), 3.42 (s, 3 H), 2.93 (d, 1 H, J = 16 Hz), 2.72 (d, 1 H, J = 16 Hz), 1.65 (s, 9 H), 1.20 (s, 3 H); IR (film) 3450, 3050, 1710, 1450.

5-Hydroxy-6,6-dimethoxy-4,5-dimethyl-3-hexanone (6d) (method A), colorless liquid. Faster eluent (41% yield): ^1H NMR δ 4.30–4.40 (br s, 1 H, O*H*), 3.97 (s, 1 H), 3.45 (s, 3 H), 3.40 (s, 3 H), 3.71 (q, 2 H, J = 8 Hz), 2.30–3.00 (m, 1 H), 1.10 (s, 3 H), 1.05 (d, 3 H, J = 7 Hz), 1.00 (d, 3 H, J = 7 Hz); IR (film) 3470, 3000, 2950, 1710, 1460, 1080 cm^{-1}. Anal. Calcd for $C_{10}H_{20}O_4$: C, 58.80; H, 9.87. Found: C, 59.05; H, 9.85.

Slower eluent (16% yield): ^1H NMR δ 4.10 (s, 1 H), 3.50 (s, 6 H), 3.00–3.10 (br s, 1 H, O*H*), 2.85 (q, 1 H, J = 8 Hz), 2.52 (q, 2 H, J = 8 Hz), 1.20 (s, 3 H), 1.10 (d, 3 H, J = 7 Hz), 1.00 (t, 3 H, J = 7 Hz); IR (film) 3550, 3040, 1730, 1485, 1400, 1100 cm^{-1}. Anal. Found: C, 58.63; H, 9.76.

5-Hydroxy-5-(dimethoxymethyl)-2,2-dimethyl-3-heptanone (6e) (method A): colorless liquid; ^1H NMR δ 4.80 (1 H, s, O*H*), 4.10 (s, 1 H), 3.45 (s, 3 H), 2.95 (d, 1 H, J = 16 Hz), 2.72 (d, 1 H, J = 16 Hz), 1.30–1.70 (m, 2 H), 1.65 (s, 9 H), 0.90 (t, 3 H, J = 7 Hz); IR (film) 3490, 3000, 1705, 1490 cm^{-1}. Anal. Calcd for $C_{12}H_{24}O_4$: C, 62.04; H, 10.41. Found: C, 61.86; H, 10.35.

6-Hydroxy-7,7-dimethoxy-2,6-dimethyl-2-hepten-4-one (6f): Typical Procedure of Method B. To a stirred solution of diisopropylamine (1.11 g, 11 mmol) in THF (20 mL) was added BuLi (6.9 mL, 1.60 M) at 0 °C under a nitrogen atmosphere. After 15 min, the resultant mixture was cooled to −78 °C, and 4-methyl-3-penten-2-one (0.98 g, 10 mmol) in THF (5 mL) was added dropwise, followed by stirring at the same temperature for 1 h. Then 1,1-dimethoxy-2-propanone (1.18 g , 10 mmol) in THF (5 mL) was added dropwise and the reaction mixture was allowed to warm to 0 °C. Saturated aqueous NH_4Cl (50 mL) was added to the reaction mixture, and the mixture was extracted with ether (20 mL × 2). The combined extracts were washed with water and brine and dried ($MgSO_4$). Removal of the solvent under reduced pressure and flash column chromatography on SiO_2 using $CHCl_3$ as eluent gave 1.33 g of **6f** (62%) as a colorless liquid: ^1H NMR δ 6.10 (m, 1 H), 4.30 (s, 1 H, O*H*), 4.10 (s, 1 H), 3.82 (d, 1 H, J = 16 Hz), 3.53 (s, 3 H), 3.50 (s, 3 H), 3.43 (d, 1 H, J = 16 Hz), 2.18 (d, 3 H, J = 1.5 Hz), 1.91 (d, 3 H, J = 1.5 Hz), 1.20 (s, 3 H); IR (film) 3500, 3000, 1680, 1620, 1450, 1100 cm^{-1}. Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 60.98, 9.25.

Methyl 4-Hydroxy-5,5-dimethoxy-4-methyl-2-oxoheptanoate (6g): Typical Procedures of Method C. (According to Weiler's method of the dianion technique.[9]) To a stirred suspension of NaH (0.44 g, 60% mineral oil dispersion, 11 mmol) in THF (20 mL) was added methyl acetoacetate (1.16 g, 10 mmol) in THF (5 mL) at 0 °C under a nitrogen atmosphere. After hydrogen gas was evolved, BuLi (6.9 mL, 1.60 M) was added successively to the reaction mixture at 0 °C. After 15 min, to the resultant solution was added 1,1-dimethoxy-2-propanone (1.18 g, 10 mmol) in THF (10 mL) dropwise, followed by stirring at 0 °C for 30 min. Saturated aqueous NH_4Cl (50 mL) was added to the reaction mixture, and the mixture was extracted with ether (20 mL × 2). The combined extracts were washed with water and brine and dried ($MgSO_4$). Removal of the solvent under reduced pressure and flash column chromatography on SiO_2 using $CHCl_3$/EtOAc (20:1) as eluent gave 1.56 g (67%) of **6g** as a yellow liquid: ^1H NMR δ 4.10 (s, 1 H), 3.70 (s, 3 H), 3.55 (s, 2 H), 3.45 (s, 6 H), 2.90 (d, 1 H, J = 14 Hz), 2.50 (d, 1 H, J = 14 Hz), 1.20 (s, 3 H); IR (film) 3540, 2970, 1760, 1720, 1450, 1335, 1080 cm^{-1}. Anal. Calcd for $C_{10}H_{18}O_6$: C, 51.27; H, 7.75. Found: C, 51.10; H, 7.66.

Methyl 3-allyl-4-hydroxy-5,5-dimethoxy-4-methyl-2-oxoheptanoate (6h) (method C): yellow liquid; ^1H NMR δ 5.30–6.00 (m, 1 H), 4.75–5.15 (m, 2 H), 4.10 (s, 1 H, O*H*), 3.92 (s, 1 H), 3.65 (s, 3 H), 3.45 (s, 3 H), 3.40 (s, 2 H), 2.70–3.30 (m, 1 H); IR (film) 3520, 2950, 1760, 1720, 1620, 1440, 1290, 900 cm^{-1}. Anal. Calcd for $C_{13}H_{22}O_6$: C, 56.92; H, 8.08. Found: C, 56.99; H, 7.98.

Methyl 4-hydroxy-5,5-dimethoxy-4-methyl-2-oxo-4-pentylheptanoate (6i) (method C): yellow liquid; ^1H NMR δ 4.20 (s, 1 H, O*H*), 4.10 (s, 1 H), 3.70 (s, 3 H), 3.50 (s, 3 H), 3.48 (s, 3 H), 2.75 (d, 1 H, J = 16 Hz), 2.28 (d, 1 H, J = 15 Hz), 1.10–1.60 (m, 8 H), 0.90 (t, 3 H, J = 6 Hz); IR (film) 3520, 2975, 1760, 1720, 1450, 1335 cm^{-1}. Anal. Calcd for $C_{14}H_{26}O_6$: C, 57.91; H, 9.03. Found: C, 57.71; H, 8.94.

3-Methyl-5-(phenylethyl)-2(5*H*)-furanone (1a). A Typical Procedure. To a stirred solution of $CHCl_3$ (4 mL) saturated with HCl gas was added 5-hydroxy-6,6-dimethoxy-5-methyl-1-phenyl-3-hexanone (**6a**, 532 mg, 2.0 mmol) in $CHCl_3$ (2 mL) at 0 °C. The resultant mixture was allowed to warm to room temperature and was stirred for 15 min. Then, water was added to

(13) The assignment and the ratio of E or Z were determined by ^1H NMR (270 MHz) observation of ylidene proton. E, δ 5.43 (m); Z, δ 6.23 (m).

the reaction mixture, and the solution was extracted with $CHCl_3$ (10 mL × 2). The combined extracts were washed with water and brine and dried (Na_2SO_4). Removal of the solvent under reduced pressure and column chromatography on SiO_2 using $CHCl_3$ as eluent gave 0.21 g of **1a** as a colorless liquid: ^1H NMR δ 7.20–7.30 (m, 5 H), 7.00 (t, 1 H, J = 1.5 Hz), 4.70–5.00 (m, 1 H), 2.65–2.90 (m, 2 H), 1.95–2.25 (m, 2 H), 1.95 (t, 3 H, J = 1.5 Hz); IR (film) 3040, 2950, 1760, 1660, 1500, 1460, 1100 cm^{-1}; HRMS, calcd for $C_{13}H_{14}O_2$ m/e 202.0995, found m/e 202.0966.

5-(*p*-Chlorophenyl)-3-methyl-2(5*H*)-furanone (1b): white crystals; mp 77–79 °C; ^1H NMR δ 7.10–7.45 (m, 5 H), 7.12 (t, 1 H, J = 2 Hz), 5.85 (t, 1 H, J = 2 Hz), 2.00 (t, 3 H, J = 1.5 Hz); IR (film) 1770, 1675, 1500, 1300, 1100, 1050, 840 cm^{-1}; HRMS, $C_{11}H_9ClO$ m/e 208.0342, found m/e 208.0006.

5-*tert*-Butyl-3-methyl-2(5*H*)-furanone (1c): white crystals; mp 56–56 °C; ^1H NMR δ 7.00 (t, 1 H, J = 1.5 Hz), 4.50 (m, 1 H), 1.92 (t, 3 H, J = 2 Hz), 0.97 (s, 9 H); IR (film), 2950, 1760, 1480, 1380, 1240, 1080 cm^{-1}. Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.98; H, 9.13.

5-Ethyl-3,4-dimethyl-2(5*H*)-furanone[14] **(1d)**: colorless liquid; ^1H NMR δ 4.60–4.90 (m, 1 H), 1.94 (s, 3 H), 1.80 (s, 3 H), 1.10–1.70 (m, 2 H), 0.90 (t, 3 H, J = 8 Hz); IR (film) 3000, 2900, 1760, 1700, 1450, 1340, 1090, 1000 cm^{-1}; HRMS, calcd for $C_8H_{12}O_2$ m/e 140.0838, found m/e 140.0828.

5-*tert*-Butyl-3-ethyl-2(5*H*)-furanone (1e): colorless liquid; ^1H NMR δ 7.05 (t, 1 H, J = 2 Hz), 4.58 (m, 1 H), 2.20–2.50 (m, 2 H), 1.20 (m, 3 H, J = 7 Hz), 0.98 (s, 9 H); IR (film) 2950, 1750, 1700, 1420, 1050 cm^{-1}; HRMS, calcd for $C_{10}H_{16}O_2$ m/e 168.1151, found m/e 168.1140.

3-Methyl-5-prenyl-2(5*H*)-furanone (1f): colorless liquid; ^1H NMR δ 7.05 (t, 1 H, J = 1.5 Hz), 5.38 (m, 1 H), 5.15 (m, 1 H), 1.90 (t, 2 H, J = 2 Hz), 1.72 (s, 3 H), 1.68 (s, 3 H); IR (film) 2950, 2900, 1750, 1440, 1200, 1080 cm^{-1}; HRMS, calcd for $C_9H_{12}O_2$ m/e 152.0838, Found m/e 152.0837.

Methyl 2,5-dihydro-4-methyl-5-oxofuran-2-acetate[15] **(1g)**: colorless liquid; ^1H NMR δ 7.10 (t, 1 H, J = 1.5 Hz), 5.25 (tt, J = 7.5 Hz, J = 1.5 Hz), 3.70 (s, 3 H), 2.65 (d, 2 H, J = 7 Hz), 1.95 (t, 3 H, J = 2 Hz); IR (film) 2970, 1775, 1755, 1670, 1450, 1180, 1060, 870 cm^{-1}.

Methyl 3-allyl-2,5-dihydro-4-methyl-5-oxofuran-2-acetate (1h): colorless liquid; ^1H NMR δ 5.50–6.15 (m, 1 H), 5.20–5.40 (m, 2 H), 5.10 (m, 1 H), 3.70 (s, 3 H), 3.05–3.30 (m, 2 H), 2.92 (dd, 1 H, J = 15 Hz, J = 4.5 Hz), 2.45 (dd, 1 H, J = 16 Hz, J = 8 Hz), 1.85 (d, 3 H, J = 2 Hz); IR (film) 2930, 1735, 1720, 1660, 1440, 1150, 1150, 1040 cm^{-1}. Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71. Found: C, 62.64; H, 6.66.

Methyl 2,5-dihydro-5-oxo-4-phenylfuran-2-acetate (1i): colorless liquid; ^1H NMR δ 7.00 (t, 1 H, J = 1.5 Hz), 5.15 (tt, J = 8 Hz, J = 1.5 Hz), 3.68 (s, 3 H), 2.70 (d, 1 H, J = 4 Hz), 2.58 (d, 1 H, J = 4.5 Hz), 2.10–2.45 (m, 2 H), 1.15–1.70 (m, 6 H), 0.90 (t, 3 H, J = 5.5 Hz); ^{13}C NMR δ 173.0, 169.5, 147.4, 134.7, 77.1, 51.9, 38.0, 31.4, 27.1, 25.2, 22.4, 13.9.; IR (film) 3000, 2960, 1770, 1455, 1190, 1080 cm^{-1}; HRMS, calcd for $C_{12}H_{18}O_4$ m/e 226.1206, found m/e 226.1195.

1-(4-Chlorophenyl)-4,4-dimethoxy-3-methyl-2-buten-1-one (10). To a stirred solution of **6b** (545 mg, 2.0 mmol) and (dimethylamino)pyridine (20 mg, 0.16 mmol) in pyridine (2 mL) was added acetic anhydride (505 mg, 5 mmol) at room temperature, and the resultant mixture was stirred at room temperature for 3 h. Then the reaction mixture was poured onto ice–water and extracted with ether (10 mL × 2). The combined organic phase was washed with saturated aqueous $CuSO_4$ (30 mL × 2), water, and brine and was dried (Na_2SO_4). Removal of the solvent under reduced pressure and flash column chromatography on SiO_2 using C_6H_{14}/Et_2O (3:1) as eluent gave 127 mg (25%) of **10** as a yellow liquid: ^1H NMR δ 7.83 (d, 2 H, J = 10 Hz), 7.34 (d, 2 H, J = 10 Hz), 6.95 (q, 0.83 H, J = 1.7 Hz, *E* form), 6.60 (q, 0.17 H, J = 2.0 Hz, *Z* form), 4.70 (s, 1 H), 3.82 (s, 6 H), 2.15 (d, 2.49 H, J = 1.7 Hz, *E*), 1.98 (d, 0.51 H, J = 2.0 Hz, *Z*). Anal. Calcd for $C_{13}H_{15}O_3Cl$: C, 61.30; H, 5.94. Found: C, 61.02; H, 5.69.

3-Methyl-5-(2-methylpropylidene)-2(5*H*)-furanone (11). A mixture of **1f** (304 mg, 2.0 mmol) and 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) (304 mg, 2.0 mmol) in toluene (5 mL) was refluxed for 3 h and was cooled. Water was added to the reaction mixture, and the mixture was extracted with toluene (10 mL). The organic phase was washed with water and brine and was dried (Na_2SO_4). Removal of the solvent under reduced pressure and flash column chromatography on SiO_2 using C_6H_{14}/Et_2O as eluent gave **11**[13] (218 mg, 72%) as a colorless liquid. Further purification by a preparative thin layer chromatography gave *E* and *Z* isomers as pure compounds. *E* isomer: ^1H NMR δ 7.79 (q, 1 H, J = 1.5 Hz), 6.23 (d, 1 H, J = 7.2 Hz), 2.55 (m, 1 H), 2.10 (d, 3 H, J = 1.5 Hz), 1.65 (d, 6 H, J = 7.0 Hz). Anal. Calcd for $C_9HCl_2O_2$: C, 71.03; H, 7.95. Found: C, 71.22, H, 7.68. *Z* isomer: ^1H NMR δ 7.35 (q, 1 H, J = 1.5 Hz), 5.43 (d, 1 H, J = 8.5 Hz), 2.65 (m, 1 H), 2.15 (d, 3 H, J = 1.5 Hz), 1.65 (d, 6 *H*, J = 7.0 Hz). Anal. Found: C, 70.88; H, 7.85.

Registry No. **1a**, 96250-05-4; **1b**, 85671-08-5; **1c**, 112712-36-4; **1d**, 79379-60-5; **1e**, 112712-37-5; **1f**, 112712-38-6; **1g**, 64198-13-6; **1h**, 112712-39-7; **1i**, 112712-40-0; **3a**, 6342-56-9; **3b**, 6342-57-0; **3c**, 6344-10-1; **4** (R^2 = H, R^3 = $(CH_2)_2Ph$), 59417-89-9; **4** (R^2 = H, R^3 = *p*-Cl-C_6H_4), 58518-76-6; **4** (R^2 = H, R^3 = Bu-*t*), 17510-46-2; **4** (R^2 = Me, R^3 = Et), 17510-47-3; **5** (R^2 = H, R^3 = CH=C(Me)$_2$), 141-79-7; **5** (R^2 = H, R^3 = CH_2CO_2Me), 105-45-3; **5** (R^2 = CH_2-CH=CH_2, R^3 = CH_2CO_2Me), 100636-39-3; **6a**, 112712-27-3; **6b**, 112712-28-4; **6c**, 112712-29-5; **6d** (*R**,*R**), 112712-30-8; **6d** (*R**,*S**), 112712-31-9; **6e**, 112712-32-0; **6f**, 112712-33-1; **6g**, 112712-34-2; **6h**, 92533-59-0; **6i**, 112739-90-9; **10E**, 112712-41-1; **10Z**, 112712-42-2; **11E**, 112712-43-3; **11Z**, 112712-44-4; 1,1-dimethoxy-2-propanone dimethylhydrazone, 62752-81-2; 1,1-dimethoxy-2-heptanone dimethylhydrazone, 112712-35-3.

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Studies on the Acid-Catalyzed Homonuclear Steroidal Diene Isomerization

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As a result of our continued interest in the design and synthesis of mechanism based inhibitors of sterol biosynthesis, we required multigram quantities of (3β,5α,22*E*)-ergosta-8,14,22-trien-3-ol acylated derivatives **1a,b** and the corresponding (3β,5α)-cholesta-8,14-dien-3-ol derivatives **2a,b**. Previous preparations of **1a,b** have generally been based on the pioneering work of Windaus,[1] who observed the acid-catalyzed migration of the 5,7-diene of ergosterol to yield a mixture of trienes. In classic early studies, Fieser[2] and Barton[3] have employed this type of acid-catalyzed rearrangement for the synthesis of **1a,b** and **2a,b** from ergosterol **3a** and 7-dehydrocholesterol (**4a**), respectively, with variable success. They have shown that HCl-catalyzed rearrangements of these steroidal dienes are capricious, particularly in the case of **3a** → **1a**, frequently giving low yields of the desired diene as one component in a difficult to separate mixture of isomers of known and unknown structures.[2g] To our knowledge a detailed study of the HCl-catalyzed homonuclear diene isomerization of **3a,b** and **4a,b** to produce **1a,b** and **2a,b**, respectively, has not been conducted. In addition, anomolous undesired isomers generated in the rearrangement have not been isolated nor have their structures been identified. We have

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