Tropolone Derivatives as Synthetic Intermediates. 1. A Novel Synthetic Method of the Octahydro-2*H*-cyclohepta[*b*]furan-2-one Derivatives†[1]

Masayoshi Ando,*[2a] Naoki Kataoka,[2a] Masafumi Yasunami,[2a] Kahei Takase,[2a] Naonori Hirata,[2b] and Yoshikazu Yanagi[2c]

Department of Chemistry, Faculty of Science, Tohoku University, Aramaki-aza-Aoba, Sendai 980, Japan, and Pesticides Research Laboratory, Sumitomo Chemical Co., Ltd., and Research Laboratories, Sumitomo Pharmaceuticals Co., Ltd., 2-1, 4-Chome, Takatsuka, Takarazuka 665, Japan

Received January 28, 1986

The catalytic hydrogenation of ethyl 8-hydroxy-2-oxo-2*H*-cyclohepta[*b*]furan-3-carboxylate (**1a**), which was derived conveniently from tropolone, gave ethyl (3aα,8aα)-8β-hydroxy-2-oxooctahydro-2*H*-cyclohepta[*b*]furan-3α-carboxylate (**2a**) stereoselectively. The latter was transformed to the octahydro-2*H*-cyclohepta[*b*]furan-2,8-dione derivatives such as **4a**, **4b**, **4c**, **5a**, **5b**, and **5c**, which may be utilized as common synthetic intermediates for guaianolides, pseudoguaianolides, and xanthanolides. The compound **2a** and its deoxy derivative **2b** were also transformed into (3aα,8aα)-3-methyleneoctahydro-2*H*-cyclohepta[*b*]furan-2-one derivatives such as **14a**, **14b**, **14c**, and **16**, which showed significant biological activities as we expected.

Pseudoguaianolides, xanthanolides, and guaianolides are a rapidly expanding group of natural products, comprising to date ca. 400 varieties.[3] Because of their high biological activities, their efficient syntheses are a synthetic challenge that has received much attention.[4] In connection with the general synthetic strategy of those natural products, we envisioned an approach that was based on the tropolone chemistry as shown in Scheme I. The critical step of this approach may be the stereoselective hydrogenation of 2*H*-cyclohepta[*b*]furan-2-one derivatives possessing an oxygen functional group at C_8-position such as **1a**, **1c**, and **1d** to the corresponding octahydro derivatives **2a**, **2c**, and **2d**. Although the catalytic hydrogenation of substituted benzenoid aromatic compounds has been thoroughly investigated for preparative purposes as well as in mechanistic studies,[5] the analogous attempt of catalytic hydrogenation of tropolone derivatives for preparative purpose has not been reported.

In this paper we report the results of catalytic hydrogenation of 2*H*-cyclohepta[*b*]furan-2-one derivatives **1a**, **1b**, **1c**, **1d**, and **1e** into the corresponding octahydro derivatives **2a**, **2b**, **2c**, **2d**, and **2e** and the derivation of resulting **2a** to the octahydro-2*H*-cyclohepta[*b*]furan-2,8-dione derivatives such as **4a**, **4b**, **4c**, **5a**, **5b**, and **5c**, which may be utilized as common synthetic intermediates for pseudoguaianolides, xanthanolides, and guaianolides. We also report the conversion of **2a** and its deoxy derivative **2b** to (3aα,8aα)-3-methyleneoctahydro-2*H*-cyclohepta[*b*]-furan-2-one derivatives such as **14a**, **14b**, **14c**, and **16** and their biological activities.

Results and Discussion

We chose 2*H*-cyclohepta[*b*]furan-2-one derivatives possessing oxygen functional groups at C_8 such as **1a**, **1c**, and **1d** as starting materials and examined their hydrogenation conditions (Table I), since we could prepare them from tropolone in excellent yields by the procedure published from our group.[6] First of all we examined the reduction conditions of ethyl 8-hydroxy-2-oxo-2*H*-cyclohepta[*b*]furan-3-carboxylate (**1a**) to (3aα,8aα)-ethyl 8β-hydroxy-2-oxooctahydro-2*H*-cyclohepta[*b*]furan-3α-carboxylate (**2a**). The best result was given by the catalytic hydrogenation performed at atmospheric pressure in acetic acid in the presence of a Pt/C catalyst that was generated in the reaction mixture of 10% PtO_2 and 50% of activated charcoal by weight on **1a**. Under these conditions, **1a** gave the desired product **2a** in 55% yield as a single stereo-

Scheme I

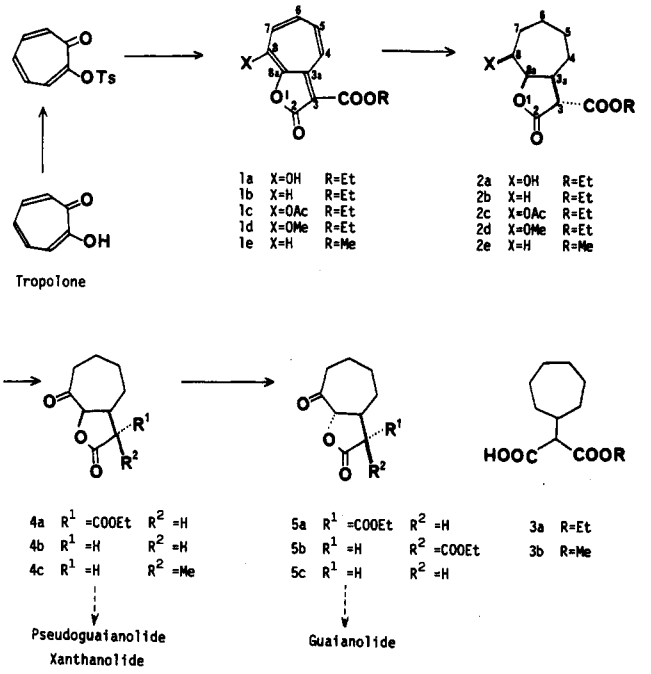

Table I. Catalytic Hydrogenation of 2*H*-Cyclohepta[*b*]furan-2-one Derivatives in the Presence of Platinum on Carbon Catalyst at Atmospheric Pressure

entry	reactant	solvent	products (yield %)
1	**1a**	EtOH	**2a** (50), **2b** (34), **3a** (4)
2	**1a**	AcOH	**2a** (55), **2b** (26), **3a** (5)
3	**1c**	AcOH	**2c** (24), **2b** (45), **3a**[a]
4	**1d**	AcOH	**2d** (61), **2b** (20), **3a**[a]
5	**1b**	EtOH	**2b** (74), **3a** (13)
6	**1b**	AcOH	**2b** (65), **3a**[a]
7	**1e**	AcOH	**2e** (83), **3b** (5)

[a] No attempt to isolate.

† This paper is warmly dedicated to Professor George Büchi on the occasion of his 65th birthday.

(1) A preliminary report of this work was presented at the 49th Annual Meeting of the Chemical Society of Japan, Tokyo, April, 1984; Abstr. No. 1W28.

(2) (a) Department of Chemistry, Faculty of Science, Tohoku University. (b) Pesticides Research Laboratory, Sumitomo Chemical Co., Ltd. (c) Research Laboratories, Sumitomo Pharmaceuticals Co., Ltd.

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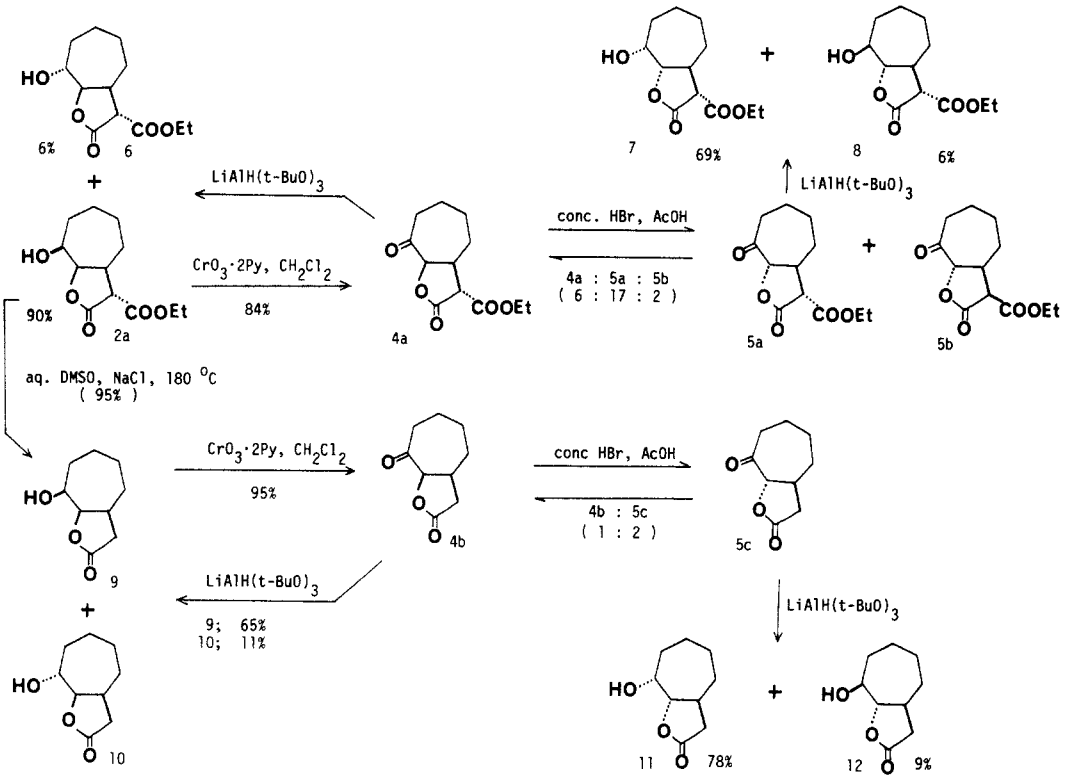
0022-3263/87/1952-1429$01.50/0

Scheme II



isomer accompanied by the minor two products **2b**[7] and **3a**, which were generated by the C–O bond fission under the reaction conditions. The choice of solvent was important. The catalytic hydrogenation of **1a** in the presence of the same catalyst in ethyl acetate or methanol gave the recovered starting material. The ratio of **2a** to **2b** of the reaction products was influenced by the solvent employed as shown in entry 1 and entry 2 in Table I. Then we examined the influence of the substituent at C_8. In the catalytic hydrogenation of the 8-acetoxy derivative (**1c**), the yield of **2b** was markedly increased and the desired (3aα,8aα)-ethyl 8β-acetoxy-2-oxooctahydro-2*H*-cyclohepta[*b*]furan-3α-carboxylate (**2c**) was formed only in 24% yield. The stereochemistries of **2a** and **2c** were related by the fact that **2c** was identical with the acetylation product of **2a**. On the other hand, the 8-methoxy derivative (**1d**) gave the desired (3aα,8aα)-ethyl 8β-methoxy-2-oxooctahydro-2*H*-cyclohepta[*b*]furan-3α-carboxylate (**2d**) in 60% yield in the same conditions. The catalytic hydrogenation of 8-deoxyderivatives **1b** and **1e** in the same conditions above mentioned gave **2b** and **2e**, respectively. The results are summarized in Table I.

Then we attempted several chemical transformations of **2a** (Scheme II). Collins oxidation of **2a** gave a ketone (**4a**), which reverted to **2a** by reduction with LiAlH(*t*-BuO)$_3$ in 90% yield accompanied by 6% yield of the corresponding α-alcohol **6**. Treatment of **4a** with concentrated HBr gave a ca. 6:17:2 equilibrium mixture of **4a** and trans isomers **5a** and **5b**. The isolated **5a** also gave the same equilibrium mixture in the same reaction conditions. Reduction of **5a** with LiAlH(*t*-BuO)$_3$ gave the 8α-alcohol **7** in 69% yield accompanied by a 6% yield of the corresponding β-alcohol **8**. Treatment of **2a** with NaCl in aqueous Me_2SO[8] and successive oxidation of the resulting decarboxylation product **9** with Collins reagent gave a ketone (**4b**), which gave a ca. 1:2 equilibrium mixture of **4b** and the trans isomer **5c** by treatment with concentrated HBr. Reduction of **4b** with LiAlH(*t*-BuO)$_3$ gave the 8β-alcohol **9** in 65% yield accompanied by a 11% yield of the corresponding α-alcohol **10**; on the contrary, the trans-fused ketone **5c** gave an 8α-alcohol **11** in the same conditions in 78% yield accompanied by a 9% yield of the corresponding β-alcohol **12**. It is interesting that the trans-fused octahydro-2*H*-cyclohepta[*b*]furan-2,8-dione derivatives **5a** and **5c** are thermodynamically more stable than the corresponding cis-fused isomers **4a** and **4b**, respectively.

Then our attention was focused on the syntheses of (3aα,8aα)-3-methyleneoctahydro-2*H*-cyclohepta[*b*]furan-2-ones **14a**, **14b**,[7,9] **14c**, and **16** from the interests of their chemical behaviors and biological activities (Scheme III). Hydrolysis of esters **2a** and **2b** gave the corresponding carboxylic acids **13a** and **13b**, which were treated with 30% formalin and diethylamine in refluxing acetic acid[10] to give the desired α-methylene-γ-lactones **14a** and **14b**, respectively. Acetylation of **14a** with acetic anhydride in pyridine in the presence of 4-(dimethylamino)pyridine gave the acetate **14c**. Collins oxidation of **14a** gave the desired ketone **16**. Treatment of **14a** and **14b** with $RhCl_3 \cdot 3H_2O$ in ethanol gave the endocyclic olefins **15a** and **15b**, respectively.[11] The attempt of catalytic hydrogenation of

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(5) Kieboom, A. P. G.; van Rantwijk, F. *Hydrogenation and Hydrogenolysis in Synthetic Organic Chemistry*; Delft University Press: Rotterdam, 1977.
(6) Condensation of 2-[(*p*-tolysulfonyl)oxy]tropone with ethyl malonate in the presence of NaOEt in ethanol gave a mixture of ethyl 8-hydroxy-2-oxo-2*H*-cyclohepta[*b*]furan-3-carboxylate (**1a**, 88%) and its deoxy derivative (**1b**, 11%). The former was converted to the corresponding acetate (**1c**) and methyl ether (**1d**) by the standard conditions: Nozoe, T.; Takase, K.; Kato, M.; Nogi, T. *Tetrahedron* **1971**, *27*, 6023.
(7) Marshall, J. A.; Cohen, N. *J. Org. Chem.* **1965**, *30*, 3475. Herz, W.; Glick, L. A. *J. Org. Chem.* **1963**, *28*, 2970.
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(9) Semmelhack, M. F.; Wu. E. S. C. *J. Am. Chem. Soc.* **1976**, *98*, 3384.
(10) Parker, W. L.; Johnson, F. *J. Org. Chem.* **1973**, *38*, 2489.
(11) Andrieux, J.; Barton, D. H. R.; Patin, H. *J. Chem. Soc., Parkin Trans. 1* **1977**, 359.

Scheme III

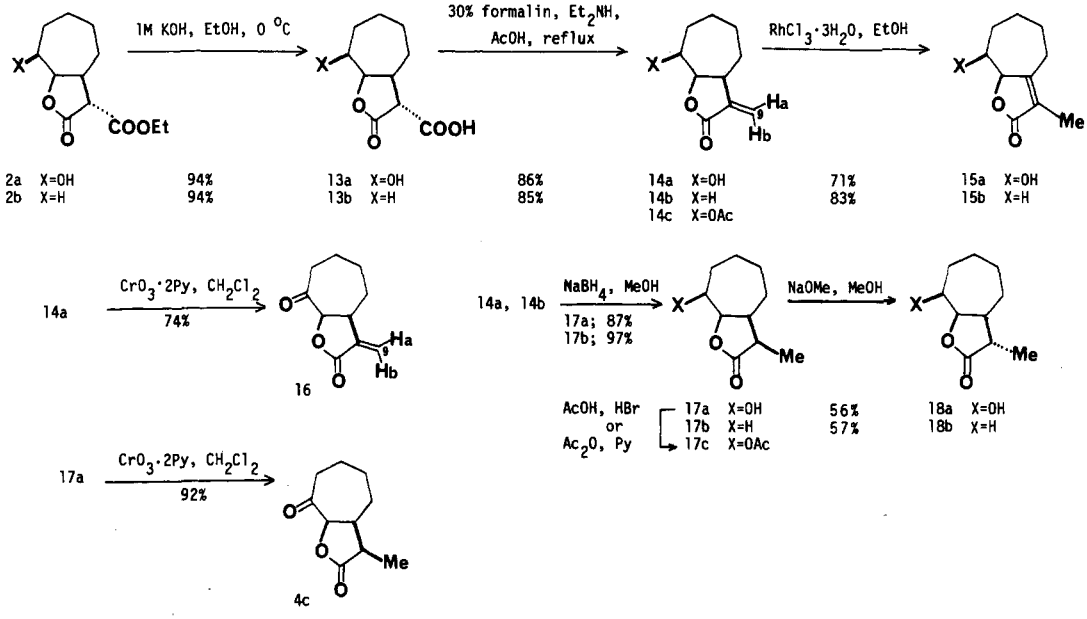


Table II. ^{1}H NMR Spectral Data of Cis-Fused Octahydro-2*H*-cyclohepta[*b*]furan-2-one Derivatives

	chemical shift, δ				*J* value (Hz)			results of NOE experiment			
compd	3H	3aH	8aH	8H	3H,3aH	3aH,8aH	8H,8aH	3H,3aH	3aH,8aH	8H,8aH	others
2a[a,b]	3.62	3.22	4.61	4.37	11.0	8.9	1.7	0%	5%		
2c[c]			4.70	5.25		8.9	1.5			not measured	
2d[a,d]	3.60	3.25	4.55	3.81	11.7	8.8	1.3	0	+		
2b[a,b]	3.32	3.11	4.79		8.0	8.1	10.2 3.8		7%		
2e[c]	3.30	3.08	4.73		7.8	7.8	10.5 3.8			not measured	
6[a,d]	3.30	3.04	4.61	3.86	5.8	8.0	9.0	0	+	0	8H,3H + 8aH,3H$_\alpha$ + 8aH,7H$_\alpha$ +
9[a,d]	2.68 2.44	2.83	4.59	4.31	9.5 9.0	8.5	1.7		+	+ (weak)	8H,7H$_\beta$ + 8H,7H$_\alpha$ +
10[a]	2.93 2.26	2.66	4.48	3.88	10.2 4.2	8.3	9.0			not measured	
17a[a,d]	2.88	2.67	4.69	4.19	9.0	6.8	2.4	+	+	+ (weak)	3aH,C$_3$-Me 0
17b[a,d]	2.86	2.53	4.65	2.25 (8 H$_\alpha$)	9.0	5.8	9.8 5.8		+	+ (8H$_\alpha$,8aH)	8aH,3H +
17c[a,d]	2.83	2.75	4.71	5.20	9.0	6.5	1.7		+		3aH,C$_3$-Me 0
18a[a,d]	2.59	2.38	4.47	4.35	11.0	8.8	1.7	0	+	0	3aH,C$_3$-Me +
18b[a,d]	2.32	2.34	4.58		10.4	8.2	11.0 2.8		+		3aH,C$_3$-Me +
14a[a,d]		3.31	4.71	4.27		9.2	2.0		+	+	
14b[a,d]		3.26	4.74			8.5	10.5 3.8		+		
14c[a,d]		3.38	4.77	5.24		9.2	1.8		+		
16[a]		3.40	5.26			9.3				not measured	
4a[a,d]	3.24	3.30	5.39			8.7			+		
4b[c]			5.25			8.1				not measured	
4c[c]			5.03			6.3				not measured	

[a] 200-MHz ^{1}H NMR data. [b] NOE effect was determined by the conventional method. [c] 90-MHz ^{1}H NMR data. [d] NOE effect was determined by the NOE difference spectra.

14b in the presence of Pt or 10% Pd–C catalysts gave **15b** as a major product. Reduction of **14a** and **14b** with $NaBH_4$ in methanol gave the corresponding 3β-methyl derivatives **17a** and **17b**, respectively. Acetylation of **17a** with acetic anhydride and pyridine in the presence of 4-(dimethylamino)pyridine or acetic acid and concentrated HBr gave the acetate **17c**. The Collins oxidation of **17a** gave the (3aα,8aα)-3β-methyloctahydro-2*H*-cyclohepta[*b*]furan-2,8-dione (**4c**).

Stereochemical Assignment. The stereochemistries of the above-mentioned compounds were determined by the analyses of the ^{1}H NMR spectra as well as some chemical transformations. The results of the analyses of the ^{1}H NMR spectra of cis-fused and trans-fused octahydro-2*H*-cyclohepta[*b*]furan-2-one derivatives shown in this paper are summarized in Tables II and III, respectively.

(1) Stereochemical Assignment at C_{3a} and C_{8a}. The stereochemistries of the ring junction of the compounds shown in Tables II and III were determined by the measurement of the NOE effect between C_{3a}-H and C_{8a}-H in ^{1}H NMR spectra. In the cis-fused derivatives, **2a**, **2b**, **2d**, **6**, **9**, **17a–c**, **18a**, **18b**, **14a–c**, and **4a**, the NOE effect between C_{3a}-H and C_{8a}-H was always observed, on the con-

Table III. ^{1}H NMR Spectral Data of Trans-Fused Octahydro-2*H*-cyclohepta[*b*]furan-2-one Derivatives

	chemical shift, δ				*J* value (Hz)			results of NOE experiment[a]			
compd	3H	3aH	8aH	8H	3H,3aH	3aH,8aH	8H,8aH	3H,3aH	3aH,8aH	8H,8aH	others
7[b]	3.44–3.16		4.25	4.41		10.4	2.5		not measured		
8[b]	3.36	2.70	4.17	3.95	12.0	10.2	8.2	0	0	0	8aH,3H + 8H,3aH +
11[b]	2.70 2.31	2.89	4.27	4.40	12.0	9.8	3.0		0	0	
12[b]		2.35	4.17	3.87		9.8	8.0		0	0	
5a[b]	3.42	2.76	5.00		12.0	11.0			not measured		
5b[b]	3.67	2.56	5.31		9.0	11.2		+	0		
5c[c]			4.95			10.4			not measured		
15a[b]			4.98	4.46			1.5			+	
15b[c]			4.84						not measured		

[a] NOE effect was determined by the NOE difference spectra. [b] 200-MHz ^{1}H NMR data. [c] 90-MHz ^{1}H NMR data.

trary in the trans-fused derivatives, **8**, **11**, **12**, and **5b**, the NOE effect between C_{3a}-H and C_{8a}-H was not observed. The stereochemistries of the ring junction of these compounds were also deduced from the coupling constant between C_{3a}-H and C_{8a}-H. In the cis-fused compounds, **2a–e**, **6**, **9**, **10**, **17a–c**, **18a**, **18b**, **14a–c**, **16**, and **4a–c**, the coupling constant was smaller than 9.3 Hz, on the contrary the trans-fused compounds, **7**, **8**, **11**, **12**, and **5a–c**, showed the corresponding coupling constant to be larger than 9.8 Hz.

(2) Stereochemical Assignment at C_3. The stereochemistries of the substituent at C_3 were determined by the measurement of the NOE effect between C_3-H and C_{3a}-H (see compounds **2a**, **2d**, **6**, **17a**, and **18a** in Table II and compounds **8**, **5b** in Table III) and/or between the C_3-substituent and C_{3a}-H (see compounds **17a**, **17c**, **18a**, **18b** in Table II). The stereochemistry of the substituent at C_3 could not be determined by the coupling constant between C_3-H and C_{3a}-H in the ^{1}H NMR spectra. This value was largely influenced by the kind of substituent at C_8 (see **2a** and **2b** in Table II) and its stereochemistry (see **2a** and **6** in Table II), probably because of the conformational change of the γ-lactone ring by the dipole–dipole interaction between the substituent at C_8 and the oxygen atom of the γ-lactone ring. The stereochemical assignment of the substituent at C_3 was also possible from the value of the chemical shift of C_{3a}-H by the consideration of the shielding or deshielding effect of the substituent at C_3 to C_{3a}-H in the ^{1}H NMR spectra. Thus the resonances of C_{3a}-H of compounds **18a** and **18b**, possessing the methyl group of α-configuration at C_3, appeared at a higher field than those of compounds **17a** and **17b**, possessing the methyl group of β-configuration at C_3, by the shielding effect of the C_3-Me σ bond. On the other hand, the resonances of C_{3a}-H of **5a** possessing the ethoxycarbonyl group of α-configuration at C_3 appeared at a lower field than that of **5b** possessing the ethoxycarbonyl group of β-configuration at C_3.

The stereochemical assignment of the substituent at C_3 based on the analyses of the above-mentioned ^{1}H NMR spectra was further supported by the following evidences. The acid (HBr in acetic acid) or base (NaOEt in ethanol) treatment of **2a** and **2b** gave recovered starting materials. This experimental result strongly suggested that compounds **2a** and **2b** were thermodynamically more stable isomers than the corresponding C_3-epimers. The examination of Dreiding models showed that the compounds possessing the substituent of α-configuration at C_3 were more stable than the corresponding β-epimers which had serious interaction between the C_3-substituent and the C_{3a}–C_4 bond (see Figure 1). On the contrary, the base (NaOMe in methanol) treatment of **17a** and **17b** gave the corresponding C_3-epimers **18a** and **18b** (see Scheme III).

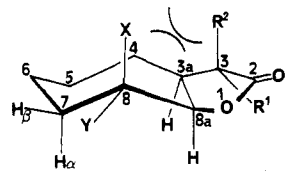


Figure 1.

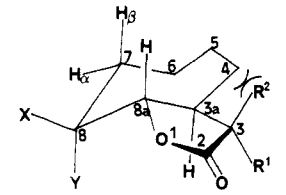


Figure 2.

These experimental results showed that **17a** and **17b** were thermodynamically less stable isomers possessing the β-methyl group at C_3.

(3) Stereochemical Assignment at C_8. The stereochemistries of the substituent at C_8 were deduced from the values of the coupling constant between C_8-H and C_{8a}-H in the ^{1}H NMR spectra. From the examination of the Dreiding models the most stable conformations of cis- and trans-fused octahydro-2*H*-cyclohepta[*b*]furan-2-ones were concluded to be as shown in Figures 1 and 2, respectively. On the basis of the stereostructure shown in Figure 1, the cis-fused compounds, **2a**, **2c**, **2d**, **9**, **17a**, **17c**, **18a**, **14a**, and **14c**, possessing the small coupling constant ($J_{8,8a} \leq 2.4$ Hz), were assigned to be 8β-epimers and the compounds **6** and **10**, possessing the larger coupling constant ($J_{8,8a} = 9.0$ Hz), were assigned to be 8α-isomers. Analogously, on the basis of the stereostructure shown in Figure 2, the trans-fused compounds, **7** and **11**, possessing the small coupling constant ($J_{8,8a} = 2.5$ and 3.0, respectively), were assigned to be 8α-epimers and the compounds **8** and **12**, possessing the larger coupling constant ($J_{8,8a} = 8.2$ and 8.0 Hz, respectively), were assigned to be 8β-isomers. The above-mentioned stereochemical assignment of the C_8-substituent was also supported by the comparison of the resonances of C_8-H in the ^{1}H NMR spectra. Thus the resonances of C_8-H of cis-fused compounds, **2a** and **9**, possessing a β(axial)-substituent at C_8 appeared at a lower field than those of cis-fused compounds, **6** and **10**, possessing an α(equatorial)-substituent at C_8. Analogously, the resonance of C_8-H of trans-fused compounds, **7** and **11**, possessing an α(axial)-substituent at C_8 appeared at a lower field than those of trans-fused compounds, **8** and **12**, possessing a β(equatorial)-substituent at C_8. The resonances of C_{3a}-H of compounds, **7** and **11**, possessing an α(axial)-hydroxyl group at C_8 appeared at a lower field than those of the corresponding β(axial)-isomers, **8** and **12**. The large

Table IV. Control of Crop Diseases by 9, 4b, 14a, 14b, and 14c at 500 ppm

diseases	evaluated values of disease control[e]				
	9	4b	14a	14b	14c
sheath blight of rice[a]	0	0	2	0	1
powdery mildew of wheat[b]	4	2	2	0	1
damping-off of cucumber[c]	0	0	5	0	5
scab of apple[d]	0	0	0	4	0

[a] Caused by *Rhizoctonia solani*. [b] Caused by *Erysiphe graminis*. [c] Caused by *Pythium aphanidermatum*. [d] Caused by *Venturia inaequalis*. [e] This assessment was made by rating disease severity of sheath blight, powdery mildew, and scab or numbering infecting seedling of damping-off, and the indices are expressed as 5 scales (5, 100%; 4, 99–90%; 3, 89–70%; 2, 69–50%; 1, 49–30%; 0, 29–0%).

downfield shift of the resonances of C_{3a}-H of **7** and **11** in ^{1}H NMR spectra was well-explained by the consideration of the deshielding effect of the 8α(axial)-hydroxyl group based on the stereostructure of the trans-fused octahydro-2*H*-cyclohepta[*b*]furan-2-ones shown in Figure 2.

Biological Activities. The compounds **14a** and **14b** showed cell growth inhibitory activity against murine lymphocytic leukemia (P-388) in vitro. The growth inhibitory ratios of **14a** and **14b** are 40% and 76% at the concentration of 1 μg/mL, respectively. The compounds **13b**, **14a**, **14b**, and **14c** showed serious inhibitory activities toward seeds germination, seedling growth, and root growth of *Echinochloa frumentacea* (Japanese name: Shokuryō hie), *Brassica juncea* (Japanese name: Seiyō karashina), and *Cucumis sativus* (Japanese name: Kyūri) at a concentration of 1000 ppm. The compounds **9**, **4b**, **14a**, **14b**, and **14c** showed preventive activities in controlling crop diseases as shown in Table IV. In vitro antimicrobial activities of **14a** and **14c** are also studied and the results are summarized in Table V.

Experimental Section

All melting points are uncorrected. NMR spectra were recorded in $CDCl_3$. Mass spectra were recorded at 25 eV unless otherwise stated. Reactions were run under an atmosphere of nitrogen. Kiesel gel 60 (Merck 70–200 mesh) was employed for column chromatography.

Catalytic Hydrogenation of Ethyl 8-Hydroxy-2-oxo-2*H*-cyclohepta[*b*]furan-3-carboxylate (1a) in Acetic Acid. A mixture of **1a** (1.00 g, 4.27 mmol), acetic acid (60 mL), PtO_2 (102 mg), and activated charcoal powder (397 mg) was shaken under 1 atm of hydrogen. Hydrogen uptake (464 mL) ceased after 6 h and the mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was poured into water (50 mL) and extracted with chloroform (5 × 30 mL). The combined extracts were washed successively with a saturated $NaHCO_3$ aqueous solution (50 mL) and a saturated NaCl aqueous solution (3 × 30 mL), dried (Na_2SO_4), and concentrated to give an oily crude product (951 mg), which was subsequently chromatographed over silica gel (50 g, 3 cm i.d. column).

The fractions eluted with a mixture of ethyl acetate and $CHCl_3$ (1:19, 500 mL) gave spectroscopically pure (3aα,8aα)-ethyl 2-oxooctahydro-2*H*-cyclohepta[*b*]furan-3α-carboxylate (**2b**, 249 mg, 26%) as a colorless oil, which was crystallized from a mixture of ether and hexane to give colorless needles: mp 35 °C; IR (KBr) 1778, 1734 cm^{-1}; ^{1}H NMR (200 MHz) δ 1.33 (3 H, t, J = 7.0 Hz, $CO_2CH_2CH_3$), 1.42–2.18 (10 H, m), 3.11 (1 H, m, C_{3a}-H), 3.32 (1 H, d, J = 8.0 Hz, C_3-H), 4.28 (2 H, q, J = 7.0 Hz, $CO_2CH_2CH_3$), 4.79 (1 H, ddd, J = 10.2, 8.1, 3.8 Hz, C_{8a}-H); ^{13}C NMR (22.5 MHz) δ 14.2 (q), 24.5 (t), 27.0 (t), 30.4 (t), 30.7 (t), 31.0 (t), 43.3 (d), 54.1 (d), 62.1 (t), 83.6 (d), 167.9 (s), 171.4 (s); MS (13.5 eV), m/e (relative intensity) 226 (M^+, 2.5), 198 (30), 181 (20), 152 (95), 136 (24), 112 (100), 108 (30), 95 (44). Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.99; H, 8.19.

The fractions eluted with a mixture of ethyl acetate and $CHCl_3$ (1:4, 400 mL) gave (3aα, 8aα)-ethyl 8β-hydroxy-2-oxooctahydro-2*H*-cyclohepta[*b*]furan-3α-carboxylate (**2a**, 566 mg, 55%) as colorless needles: mp 74–76 °C; IR (KBr) 3460, 1755, 1735 cm^{-1}; ^{1}H NMR (200 MHz) δ 1.31 (3 H, t, J = 7.0 Hz, $CO_2CH_2CH_3$), 1.06–2.18 (8 H, m), 3.22 (1 H, dddd, J = 11.0, 11.0, 8.9, 6.6 Hz, C_{3a}-H), 3.62 (1 H, d, J = 11.0 Hz, C_3-H), 4.27 (2 H, q, J = 7.0 Hz, $CO_2CH_2CH_3$), 4.37 (1 H, ddd, J = 6.7, 1.7, 1.0 Hz, C_8-H), 4.61 (1 H, dd, J = 8.9, 1.7 Hz, C_{8a}-H); ^{13}C NMR (22.5 MHz) δ 14.1 (q), 24.7 (t), 26.0 (t), 30.6 (t), 32.3 (t), 42.0 (d), 54.4 (d), 61.9 (t), 72.4 (d), 85.5 (d), 168.2 (s), 172.7 (s), MS (13.5 eV), m/e (relative intensity) 242 (M^+, 4.5), 214 (22), 196 (23), 178 (43), 170 (20), 157 100), 151 (25), 150 (24), 128 (30), 115 (36), 110 (21). Anal. Calcd for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49. Found: C, 59.63; H, 7.60.

The fractions eluted with ethyl acetate gave monoethyl cycloheptylmalonate (**3a**, 48 mg, 5%), which was treated with diazomethane in ether and subsequently chromatographed over silica gel to give ethyl methyl cycloheptylmalonate (29 mg) as a colorless oil: IR (neat) 1760, 1740 cm^{-1}; ^{1}H NMR (90 MHz) δ 1.25 (3 H, t, J = 7.0 Hz), 1.25–1.85 (12 H, m), 2.26 (1 H, m), 3.24 (1 H, d, J = 8.2 Hz), 3.70 (3 H, s), 4.16 (2 H, q, J = 7.0 Hz); MS 13.5 eV), m/e (relative intensity) 242 (M^+, 1), 147 (100), 146 (98), 119 (35). Anal. Calcd for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.64; H, 9.28.

Catalytic Hydrogenation of 1a in Ethanol. A mixture of **1a** (701 mg, 2.99 mmol), ethanol (40 mL), PtO_2 (71 mg), and activated charcoal powder (282 mg) was shaken under 1 atm of hydrogen. Hydrogen uptake (384 mL) ceased after 4 h and the mixture was filtered. The filtrate was concentrated and the residue was chromatographed over silica gel (34 g, 2.6 cm i.d. column) by the analogous procedure as mentioned above to give **2a** (365 mg, 50%), **2b** (228 mg, 34%), and **3a** (30 mg, 4%).

Catalytic Hydrogenation of Ethyl 8-Acetoxy-2-oxo-2*H*-cyclohepta[*b*]furan-3-carboxylate (1c). A mixture of **1c** (491 mg, 1.86 mmol), acetic acid (20 mL), PtO_2 (50 mg), and activated charcoal powder (200 mg) was shaken under 1 atm of hydrogen. Hydrogen uptake (233 mL) ceased after 1 h 50 min and the mixture was filtered. The filtrate was poured into ethyl acetate (50 mL) and the mixture was washed with a saturated NaCl aqueous solution (50 mL). $NaHCO_3$ (30 g) and water (10 mL) was added into the mixture, and it was stirred for 4 h at 0 °C. Then the organic layer was separated and washed successively with a saturated $NaHCO_3$ aqueous solution (2 × 50 mL) and a saturated NaCl aqueous solution, dried (Na_2SO_4), and concentrated to give an oily crude product (338 mg), which was subsequently chromatographed over silica gel (17 g, 2.1 cm i.d. column).

The fractions eluted with chloroform (400 mL) gave **2b** (188 mg, 45%).

Table V. In Vitro Antimicrobial Spectral Data of 14a and 14c

compd	concn (ppm)	evaluated values of preventive activities[a]				
		Mycosphaerella melonis	*Pyrenophora graminea*	*Alternaria kikuchiana*	*Venturia inaequalis*	*Rhynchosporium secalis*
14a	200	10	5	4	*b*	10
	100	8	0	2	5	6
	50	7	0	0	*b*	3
14c	200	5	0	0	7	5
	100	2	0	0	*b*	3
	50	0	0	0	*b*	1

[a] The preventive activities are expressed as 10 scales (10, 100%; 9, 99–90%; 8, 89–80%; 7, 79–70%; 6, 69–60%; 5, 59–50%; 4, 49–40%; 3, 39–30%; 2, 29–20%; 1, 19–10%; 0, 9–0%). [b] Not determined.

The fractions eluted with a mixture of ethyl acetate and chloroform (1:9, 120 mL) gave (3aα,8aα)-ethyl 8β-acetoxy-2-oxooctahydro-2*H*-cyclohepta[*b*]furan-3α-carboxylate (**2c**, 121 mg, 24%) as colorless needles: mp 61.5–63.0 °C; IR (KBr) 1785, 1735 cm^{-1}; ^1H NMR (90 MHz) δ 1.33 (3 H, t, J = 7.0 Hz, $CO_2CH_2CH_3$), 1.20–1.90 (6 H, m), 2.10 (3 H, s, $OCOCH_3$), 2.00–2.40 (2 H, m, C_7-H), 3.00–3.50 (2 H, m, C_3-H, C_{3a}-H), 4.25 (2 H, q, J = 7.0 Hz, $CO_2CH_2CH_3$), 4.70 (1 H, dd, J = 8.9, 1.5 Hz, C_{8a}-H), 5.25 (1 H, dd, J = 6.9, 1.5 Hz, C_8-H); MS, m/e (relative intensity) 284 (M^+, 4.5), 241 (59), 195 (47), 177 (24), 151 (100), 43 (44). Anal. Calcd for $C_{14}H_{20}O_6$: C, 59.14; H, 7.09. Found: C, 59.13; H, 7.00.

Catalytic Hydrogenation of Ethyl 8-Methoxy-2-oxo-2*H*-cyclohepta[*b*]furan-3-carboxylate (1d). A mixture of **1d** (490 mg, 1.97 mmol), acetic acid (40 mL), PtO_2 (50 mg), and activated charcoal powder (200 mg) was shaken under 1 atm of hydrogen. Hydrogen uptake (247 mL) ceased after 2 h and the mixture was filtered. The filtrate was worked up as mentioned in the previous section and chromatographed over silica gel (25 g, 2.6 cm i.d. column) to give an oily product (409 mg, 81%), which was shown to be a 1:3 mixture of **2b** (t_R 4.6 min) and (3aα,8aα)-ethyl 8β-methoxy-2-oxooctahydro-2*H*-cyclohepta[*b*]furan-3α-carboxylate (**2d**) (t_R 5.0 min) by HPLC analysis [10-μm silica gel (Kyowa gel MIC-SI-10), 25 cm × 4 mm i.d. column, EtOAc–hexane (3:7), flow rate 1.25 mL/min]. **2d** was isolated by HPLC under the same conditions as a colorless crystals: mp 53 °C; IR (KBr) 1780, 1770, 1740 cm^{-1}; ^1H NMR (200 MHz) δ 1.33 (3 H, t, J = 7.2 Hz, $CO_2CH_2CH_3$), 3.08–3.42 (1 H, m, C_{3a}-H), 3.34 (3 H, s, OCH_3), 3.60 (1 H, d, J = 11.7 Hz, C_3-H), 3.81 (1 H, dm, J = 6.7 Hz, C_8-H), 4.28 (2 H, q, J = 7.2 Hz, $CO_2CH_2CH_3$), 4.55 (1 H, dd, J = 8.8, 1.3 Hz, C_{8a}-H). Anal. Calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87. Found: C, 60.62; H, 7.88.

Catalytic Hydrogenation of Ethyl 2-Oxo-2*H*-cyclohepta[*b*]furan-3-carboxylate (1b) in Acetic Acid. A mixture of **1b** (999 mg, 4.58 mmol), acetic acid (30 mL), PtO_2 (99 mg), and activated charcoal powder (402 mg) was shaken under 1 atm of hydrogen. Hydrogen uptake (502 mL) ceased after 1.5 h and the mixture was filtered. The filtrate was worked up as usual to give **2b** (670 mg, 65%).

Catalytic Hydrogenation of 1b in Ethanol. A mixture of **1b** (501 mg, 2.30 mmol), ethanol (120 mL), PtO_2 (50 mg), and activated charcoal powder (200 mg) was shaken under 4 atm of hydrogen in a pressure bottle. Hydrogen uptake was ceased after 7.5 h and the mixture was filtered and concentrated to give an oily crude product (510 mg), which showed two spots on TLC (Merck, silica gel GF_{254}, thickness 0.25 mm, EtOAc–$CHCl_3$ (1:9), R_f values 0.78, 0.00). The crude product was chromatographed over silica gel (15 g, 2 cm i.d. column) and eluted successively with chloroform (400 mL) and ethyl acetate (150 mL).

The fractions eluted with chloroform gave **2b** (383 mg, 74%).

The fraction eluted with ethyl acetate gave **3a** (50 mg, 13%).

Catalytic Hydrogenation of Methyl 2-Oxo-2*H*-cyclohepta[*b*]furan-3-carboxylate (1e) in Acetic Acid. A mixture of **1e** (482 mg, 2.36 mmol), acetic acid (50 mL), PtO_2 (50 mg), and activated charcoal powder (200 mg) was shaken under 1 atm of hydrogen. After hydrogen uptake ceased, the mixture was filtered, concentrated, poured into water (100 mL), and worked up as usual to give an oily crude product, which was chromatographed over silica gel (25 g, 2.6 cm i.d. column) and eluted with a mixture of ethyl acetate and chloroform (1:9) to give (3aα,8aα)-methyl 2-oxooctahydro-2*H*-cyclohepta[*b*]furan-3α-carboxylate (**2e**, 431 mg, 83%) as a colorless oil: IR (neat) 1780, 1743 cm^{-1}; ^1H NMR (90 MHz) δ 1.05–2.20 (10 H, m), 2.90–3.25 (1 H, m, C_{3a}-H), 3.30 (1 H, d, J = 7.8 Hz, C_3-H), 3.79 (3 H, s, CH_3), 4.73 (1 H, ddd, J = 10.5, 7.8, 3.8 Hz, C_{8a}-H); MS, m/e (relative intensity) 212 (M^+, 9), 184 (21), 168 (17), 156 (29), 152 (51), 140 (23), 137 (26), 113 (54), 112 (100), 95 (50), 94 (59), 87 (26), 82 (24), 81 (22), 79 (22), 75 (21), 67 (27), 55 (25). Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.03, H, 7.73.

The fractions eluted with ethyl acetate gave monomethyl cycloheptylmalonate (**3b**, 26 mg, 5%) as a colorless oil.

Acetylation of 2a. To a stirred solution of **2a** (49 mg, 0.20 mmol) in anhydrous pyridine (0.2 mL) was added acetic anhydride (0.1 mL) at room temperature. The mixture was stirred for 20 h at room temperature and poured into a saturated NaCl aqueous solution (30 mL). The mixture was extracted with ethyl acetate (3 × 30 mL). The combined extracts were washed successively with 1 M HCl (2 × 30 mL), a saturated $NaHCO_3$ aqueous solution (3 × 20 mL), and a saturated NaCl aqueous solution (3 × 20 mL), dried (Na_2SO_4), and concentrated to give **2c** (48 mg, 77%) as colorless needles.

(3aα,8aα)-Ethyl 2,8-Dioxooctahydro-2*H*-cyclohepta[*b*]-furan-3α-carboxylate (4a). Chromic anhydride (1.65 g, 16.5 mmol) was added to a mixture of anhydrous methylene chloride (21 mL) and anhydrous pyridine (3.3 mL, 40.9 mmol) at 0 °C, and the mixture was stirred for 15 min. Then **2a** (204 mg, 0.84 mmol) dissolved in methylene chloride (16 mL) was added over 10 min. The mixture was stirred at 0 °C for 4 h, then allowed to stand at room temperature overnight, and filtered through Celite under reduced pressure. The filtrate was washed successively with a saturated $NaHCO_3$ aqueous solution (3 × 50 mL), 2 M HCl (3 × 50 mL), and a saturated NaCl aqueous solution. The mixture was subsequently passed through a short column (2.5 cm i.d. column) of silica gel (5 g) and concentrated to give spectroscopically pure **4a** (169 mg, 84%) as a colorless oil: IR (neat) 1795, 1735 cm^{-1}; ^1H NMR (200 MHz) δ 1.33 (3 H, t, J = 7.2 Hz, $CO_2CH_2CH_3$), 3.24 (1 H, m, C_3-H), 3.30 (1 H, m, C_{3a}-H), 4.29 (2 H, q, J = 7.2 Hz, $CO_2CH_2CH_3$), 5.39 (1 H, d, J = 8.7 Hz, C_{8a}-H); MS, 240 (M^+, 39), 195 (44), 194 (66), 176 (79), 170 (35), 166 (67), 153 (23), 140 (39), 139 (56), 138 (72), 137 (39), 127 (33), 114 (25), 109 (27), 99 (26), 98 (100), 97 (23), 95 (32), 94 (33), 93 (27), 81 (47), 80 (39), 68 (23), 67 (22), 55 (37), 29 (43), 18 (41). Anal. Calcd for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71. Found: C, 59.76; H, 6.86.

Equilibration of 4a and Its Trans Isomer, (3aα,8aβ)-Ethyl 2,8-Dioxooctahydro-2*H*-cyclohepta[*b*]furan-3α-carboxylate (5a). A mixture of **4a** (314 mg, 1.31 mmol), acetic acid (38 mL), and a 48% HBr aqueous solution (251 μL) was stirred for 20 h at room temperature. The mixture was poured into a saturated NaCl aqueous solution (100 mL) and extracted with chloroform (5 × 20 mL). The combined extracts were successively washed with a saturated $NaHCO_3$ solution (4 × 50 mL) and a saturated NaCl aqueous solution (3 × 50 mL), dried (Na_2SO_4), and concentrated to give an oily crude product (293 mg), which was shown to be 6:2:17 mixture of **4a** (t_R 6.9 min), **5b** (t_R 8.7 min), and **5a** (t_R 10.3 min) by HPLC analysis [10-μm silica gel (Kyowa gel MIC-SI-10), 25 cm × 4 mm i.d. column, EtOAc–hexane (3:7), flow rate 3.1 mL]. The crude product was separated by HPLC [10-μm silica gel (Kyowa gel MIC-SI-10), 30 cm × 8 mm i.d. column, EtOAc–hexane (3:7), 30 mg of crude product was injected in each time].

The first peak (t_R 10 min) gave **4a** (71 mg, 22.6%).

The second peak (t_R 12.2 min) gave **5b** (21 mg, 6.7%) as a colorless oil: IR (neat) 1785, 1725 cm^{-1}; ^1H NMR (200 MHz) δ 1.34 (3 H, d, J = 7.2 Hz, $CO_2CH_2CH_3$), 2.56 (1 H, m, C_{3a}-H), 3.67 (1 H, d, J = 9.0 Hz, C_3-H), 4.30 (2 H, q, J = 7.2 Hz, $CO_2CH_2CH_3$), 5.31 (1 H, d, J = 11.2 Hz, C_{8a}-H). Anal. Calcd for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71. Found: C, 60.23, H, 6.83.

The third peak (t_R 15 min) gave **5a** (127 mg, 40.4%) as colorless crystals: mp 74.5 °C; IR (KBr) 1790, 1775 (sh), 1728 cm^{-1}; ^1H NMR (200 MHz) δ 1.33 (3 H, t, J = 7.2 Hz, $CO_2CH_2CH_3$), 2.76 (1 H, m, C_{3a}-H), 3.42 (1 H, d, J = 12.0 Hz, C_3-H), 4.30 (2 H, q, J = 7.2 Hz, $CO_2CH_2CH_3$), 5.00 (1 H, d, J = 11.0 Hz, C_{8a}-H). MS, m/e (relative intensity) 240 (M^+, 29), 195 (36), 194 (100), 176 (87), 170 (32), 167 (47), 166 (67), 149 (28), 139 (31), 138 (87), 137 (30), 127 (26), 111 (34), 109 (36), 98 (59), 94 (28), 81 (39), 80 (30). Anal. Calcd for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71. Found: C, 59.62; H, 6.66.

In another experiment, isolated **5a** (10 mg) was treated with 48% HBr (8 μL) in acetic acid (1.2 μL) for 20 h at room temperature and worked up as usual to give an oily crude product. From HPLC analysis, this crude product was also a 6:2:17 mixture of **4a**, **5b**, and **5a**.

Reduction of 4a. To a stirred solution of **4a** (106 mg, 0.44 mmol) in THF (11 mL) at 0 °C was added lithium tri-*tert*-butoxyaluminum hydride (495 mg, 1.93 mmol). The solution was stirred for 2 h at 0 °C and worked up as usual to give an oily crude product (115 mg), which was subsequently chromatographed over silica gel (5 g, 2 cm i.d. column) and eluted with a mixture of ethyl acetate and chloroform (1:9) to give a colorless oil, 103 mg (96%). This was shown to be a 15:1 mixture of **2a** (t_R 2.8 min) and the corresponding α-alcohol **6** (t_R 4.6 min) by HPLC analysis [10-μm silica gel (Kyowa gel MIC-SI-10), 25 cm × 4 mm i.d. column, EtOAc–hexane (1:1), flow rate 2.2 mL/min]. Pure **6** was isolated by HPLC [10-μm silica gel (Kyowa gel MIC-SI-10), 25 cm × 4

mm i.d. column, EtOAc–hexane (3:7), flow rate 3.1 mL/min] as colorless crystals: mp 55–56 °C; IR (KBr); 3490, 1780, and 1726 cm^{-1}; ^1H NMR (200 MHz) δ 1.33 (3 H, t, J = 7.2 Hz, $CO_2CH_2CH_3$), 2.43 (1 H, br s, O*H*), 3.04 (1 H, m, C_{3a}-H), 3.30 (1 H, d, J = 5.8 Hz, C_3-H), 3.86 (1 H, ddd, J = 10.0, 9.0, 1.5 Hz, C_8-H), 4.29 (2 H, q, J = 7.2 Hz, $CO_2CH_2CH_3$), 4.61 (1 H, dd, J = 9.0, 8.0 Hz, C_{8a}-H). Anal. Calcd for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49. Found: C, 59.31; H, 7.59.

Reduction of 5a. To a stirred solution of **5a** (80 mg, 0.33 mmol) in THF (8.5 mL) at 0 °C was added lithium tri-*tert*-butoxyaluminum hydride (373 mg, 1.46 mmol). The solution was stirred for 2 h at 0 °C and worked up as usual to give an oily crude product (70 mg), which was 14:1 mixture of **7** and **8** by HPLC analysis [10-μm silica gel (Kyowa gel MIC-SI-10, 25 cm × 4 mm i.d. column, EtOAc–hexane (3:7), flow rate 3.1 mL/min].

The first peak (t_R 5.5 min) gave **7** (56 mg, 69.4%) as colorless crystals: mp 104 °C; IR (KBr) 3470, 1770, 1735 cm^{-1}; ^1H NMR (200 MHz) δ 1.33 (3 H, t, J = 7.2 Hz, $CO_2CH_2CH_3$), 2.15 (1 H, d, J = 2.5 Hz, O*H*), 3.44–3.16 (2 H, C_3-H, C_{3a}-H), 4.25 (1 H, dd, J = 10.4, 2.5 Hz, C_{8a}-H), 4.30 (2 H, d, J = 7.2 Hz, $CO_2CH_2CH_3$), 4.41 (1 H, dddd, J = 5.0, 5.0, 2.5, 2.5 Hz, C_8-H). Anal. Calcd for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49. Found: C, 59.77; H, 7.34.

The second peak (t_R 8.6 min) gave **8** (5 mg, 6.2%) as colorless crystals: mp 84 °C; IR (KBr) 3490, 1778, 1745 cm^{-1}; ^1H NMR (200 MHz) δ 1.33 (3 H, t, J = 7.1 Hz, $CO_2CH_2CH_3$), 2.44 (1 H, d, J = 2.4 Hz, O*H*), 2.70 (1 H, m, C_{3a}-H), 3.36 (1 H, d, J = 12.0 Hz, C_3-H), 3.95 (1 H, m, C_8-H), 4.17 (1 H, dd, J = 10.2, 8.2 Hz, C_{8a}-H).

(3aα,8aα)-8β-Hydroxyoctahydro-2*H*-cyclohepta[*b*]furan-2-one (9). A mixture of **2a** (507 mg, 2.1 mmol), dimethyl sulfoxide (5 mL), water (100 μL), and NaCl (200 mg, 3.4 mmol) was heated. The reaction temperature was raised from 140 °C to 180 °C in 40 min and kept at 180 °C for 50 min. The mixture was cooled, poured into a saturated NaCl aqueous solution (100 mL), and extracted with chloroform (5 × 50 mL). The combined extracts were washed with a saturated NaCl aqueous solution (3 × 100 mL), dried (Na_2SO_4), and concentrated under reduced pressure to give an oily crude product (460 mg), which was passed through a short column of silica gel (6 g, 2.5 cm i.d. column) with a mixture of chloroform and ethyl acetate (4:1) and concentrated to give a crystalline material. This was then recrystallized from ether to give **9** (338 mg, 95%) as colorless crystals: mp 82–82.5 °C; IR (KBr) 3400, 1760 cm^{-1}; ^1H NMR (200 MHz) δ 1.49 (1 H, m, C_7-H_α), 2.07 (1 H, m, C_7-H_β), 2.44 (1 H, dd, J = 9.0, 17.3 Hz, C_3-H), 2.46 (1 H, d, J = 5.5 Hz, O*H*), 2.68 (1 H, dd, J = 9.5, 17.3 Hz, C_3-H), 2.94–2.72 (1 H, m, C_{3a}-H), 4.31 (C_8-H, dddd, J = 7.3, 5.5, 1.7, 1.7 Hz, C_8-H), 4.59 (C_{8a}-H, dd, J = 8.5, 1.7 Hz, C_{8a}-H); MS (13.5 eV), m/e (relative intensity) 170 (M^+, 20), 152 (39), 142 (59), 127 (43), 126 (41), 124 (48), 123 (27), 110 (58), 108 (28), 98 (36), 96 (31), 93 (43), 92 (32), 85 (70), 83 (100), 82 (33), 81 (31), 80 (20), 67 (20). Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.75; H, 8.37.

(3aα,8aα)-Octahydro-2*H*-cyclohepta[*b*]furan-2,8-dione (4b). Chromic anhydride (2.3 g, 23.0 mmol) was added to a mixture of anhydrous methylene chloride (29 mL) and anhydrous pyridine (4.7 mL, 58.2 mmol) at 0 °C and the mixture was stirred for 15 min. Then **9** (198 mg, 1.16 mmol) dissolved in methylene chloride (23 mL) was added over 10 min. The mixture was stirred at 0 °C for 6 h, then allowed to stand at room temperature, and worked up as usual to give spectroscopically pure **4b** (186 mg, 95%) as a colorless oil, which was crystallized from the mixture of chloroform and ether (1:1) to give colorless plates: mp 45–46 °C; IR (KBr) 1780, 1722 cm^{-1}; ^1H NMR (90 MHz) δ 1.00–2.10 (6 H, m), 2.00–3.20 (5 H, m), 5.25 (1 H, d, J = 8.1 Hz, C_{8a}-H); MS, m/e (relative intensity) 168 (32), 140 (70), 111 (59), 98 (100), 84 (42), 83 (30), 81 (58), 70 (25), 69 (26), 68 (52), 67 (55), 55 (90), 41 (22). Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.26; H, 7.02.

Equilibration of 4b and Its Trans Isomer, (3aα,8aβ)-Octahydro-2*H*-cyclohepta[*b*]furan-2,8-dione (5c). A mixture of **4b** (40 mg, 0.24 mmol), acetic acid (5 mL), and a 48% HBr aqueous solution (40 μL) was stirred for 20 h at room temperature and worked up as usual to give an oily product, which was shown to be a 2:1 mixture of **5c** (t_R 7.4 min) and **4b** (t_R 8.2 min) by HPLC analysis [10-μm silica gel (Kyowa gel MIC-SI-10), 25 cm × 4 mm i.d. column, EtOAc–hexane (1:1), flow rate 2:1 mL].

The first peak gave 24.4 mg (61%) of **5c** as colorless crystals: mp 108–108.5 °C; IR (KBr) 1800, 1730 cm^{-1}; ^1H NMR (90 MHz) δ 1.10–3.00 (11 H, m), 4.95 (1 H, d, J = 10.4 Hz, C_{8a}-H); MS, m/e (relative intensity) 168 (M^+, 22), 140 (51), 111 (42), 98 (64), 97 (76), 84 (37), 81 (44), 70 (22), 68 (59), 67 (69), 55 (100), 41 (44). Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.19; H, 7.33.

The second peak gave **4b** (11.6 mg, 29%).

Reduction of 4b. To a stirred solution of **4b** (97 mg, 0.58 mmol) in THF (8 mL) at 0 °C was added lithium tri-*tert*-butoxyaluminum hydride (641 mg, 2.50 mmol). The solution was stirred for 2 h at 0 °C and worked up as usual to give an oily crude product, which was separated by HPLC [10-μm silica gel (Kyowa gel MIC-SI-10), 25 cm × 1 cm i.d. column, EtOAc–hexane (1:1), flow rate 2.1 mL/min].

The first peak (t_R 29 min) gave **9** (64 mg, 65%).

The second peak (t_R 53 min) gave (3aα,8aα)-8α-hydroxyoctahydro-2*H*-cyclohepta[*b*]furan-2-one (**10**) (10.7 mg, 11%) as a colorless oil: IR (neat) 3700–3100, 1770 cm^{-1}; ^1H NMR (200 MHz) δ 2.26 (1 H, dd, J = 17.5, 4.2 Hz, C_3-H_α), 2.66 (1 H, m, C_{3a}-H), 2.93 (1 H, dd, J = 17.5, 10.0 Hz, C_3-H_β), 3.88 (1 H, dd, J = 9.0, 9.0 Hz, C_8-H), 4.48 (1 H, dd, J = 9.0, 8.3 Hz, C_{8a}-H); MS, m/e (relative intensity) 170 (M^+, 5), 152 (11), 142 (14), 127 (24), 124 (37), 123 (26), 110 (70), 109 (30), 98 (35), 95 (37), 93 (30), 92 (23), 85 (100), 83 (50), 82 (42), 81 (50), 80 (25), 79 (20), 67 (37), 66 (20), 57 (34), 43 (23).

Reduction of 5c. To a stirred solution of **5c** (11.5 mg, 0.07 mmol) in THF (1.5 mL) at 0 °C was added lithium tri-*tert*-butoxyaluminum hydride (76 mg, 0.30 mmol). The solution was stirred for 2 h at 0 °C and worked up as usual to give an oily crude product, which was separated by HPLC [10-μm silica gel (Kyowa gel MIC-SI-10), 25 cm × 4 mm i.d. column, EtOAc–hexane (1:1), flow rate 1.03 mL/min].

The first peak (t_R 10.8 min) gave (3aα,8aβ)-8α-hydroxyoctahydro-2*H*-cyclohepta[*b*]furan-2-one (**11**, 9.1 mg, 78%) as colorless needles: mp 58 °C; IR (KBr) 3400, 1800 cm^{-1}; ^1H NMR (200 MHz) δ 2.31 (1 H, dd, J = 17.0, 12.0 Hz, C_3-H_β), 2.70 (1 H, ddd, J = 17.0, 8.5, 0.5 Hz, C_3-H_α), 2.89 (1 H, m, C_{3a}-H), 4.27 (1 H, dd, J = 9.8, 3.0 Hz, C_{8a}-H), 4.40 (1 H, ddd, J = 5.5, 5.5, 3.0 Hz, C_8-H); MS, m/e (relative intensity) 170 (M^+, 16), 152 (24), 85 (100). Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.35; H, 8.23.

The second peak (t_R 20 min) gave (3aα,8aβ)-8β-hydroxyoctahydro-2*H*-cyuclohepta[*b*]furan-2-one (**12**) (1 mg, 9%) as a colorless oil, which was crystallized from ether to give colorless prisms: mp 108 °C; IR (KBr) 3510, 1795 cm^{-1}; ^1H NMR (200 MHz) δ 2.35 (1 H, m, C_{3a}-H), 3.87 (1 H, ddd, J = 2.0, 8.0, 12.0 Hz, C_8-H), 4.17 (1 H, dd, J = 8.0, 9.8 Hz, C_{8a}-H). Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.41; H, 8.52.

(3aα,8aα)-8β-Hydroxy-2-oxooctahydro-2*H*-cyclohepta-[*b*]furan-3α-carboxylic Acid (13a). A mixture of **2a** (2.42 g, 10.0 mmol), ethanol (50 mL), and 1 M KOH aqueous solution (20 mL) was stirred for 3 h at 0 °C, poured into a mixture of 2 M HCl (20 mL) and a saturated NaCl aqueous solution (300 mL), and extracted with ethyl acetate (3 × 300 mL). The combined extracts were washed with a saturated NaCl aqueous solution, dried (Na_2SO_4), and concentrated to give a crystalline material, which was recrystallized from a mixture of chloroform and ethyl acetate (1:1) to give **13a** (2.01 g, 94%) as colorless needles: mp 150–151.5 °C: IR (KBr) 3580, 3300–2800 1765, 1720 cm^{-1}; ^1H NMR (90 MHz) δ 0.80–2.20 (8 H, m), 3.13 (1 H, dddd, J = 11.4, 10.8, 8.9, 6.6 Hz, C_{3a}-H), 3.53 (1 H, d, J = 11.4 Hz, C_3-H), 4.25 (1 H, ddd, J = 6.7, 1.7, 1.0 Hz, C_8-H), 4.63 (1 H, dd, J = 8.9, 1.7 Hz, C_{8a}-H), 5.00–6.30 (2 H, br s, O*H*, CO_2H); MS (13.5 eV), m/e (relative intensity) 214 (M^+, 8), 152 (31), 142 (50), 127 (100), 126 (62), 110 (50), 109 (36), 96 (34), 93 (39), 85 (33), 84 (30), 83 (30), 82 (31), 81 (35), 60 (42), 58 (46). Anal. Calcd for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59. Found: C, 55.80; H, 6.41.

(3aα,8aα)-8β-Hydroxy-3-methyleneoctahydro-2*H*-cyclohepta[*b*]furan-2-one (14a). A mixture of **13a** (544 mg, 2.54 mmol), acetic acid (18.4 mL), sodium acetate (470 mg, 5.73 mmol), diethylamine (4.6 mL), and 30% formalin (13.8 mL) was refluxed for 20 min. Then the mixture was cooled, poured into water (100 mL), and extracted with chloroform (5 × 50 mL). The combined extracts were washed successively with 2 M hydrochloric acid, a saturated $NaHCO_3$ aqueous solution (3 × 100 mL), and a saturated NaCl aqueous solution, dried (Na_2SO_4), and concen-

trated to give an oily crude product (585 mg), which was passed through a short column of silica gel [6 g, 2.5 cm i.d. column, $CHCl_3$–EtOAc (4:1)] and subsequently recrystallized from ether to give **14a** (398 mg, 86%) as colorless needles: mp 86.5 °C; IR (KBr) 3450, 1745, 1660 cm^{-1}; ^1H NMR (200 MHz) δ 2.96 (1 H, br s, O*H*), 3.31 (1 H, m, C_{3a}-H), 4.27 (1 H, dm, J = 8.0 Hz, C_8-H), 4.71 (1 H, dd, J = 9.2, 2.0 Hz, C_{8a}-H), 5.54 (1 H, d, J = 3.0 Hz, C_9-H_a), 6.26 (1 H, d, J = 3.3 Hz, C_9-H_b); MS, m/e (relative intensity) 182 (M^+, 1.5), 164 (8), 154 (6), 139 (11), 138 (11), 136 (14), 135 (14), 125 (23), 123 (27), 112 (81), 107 (21), 94 (22), 93 (20), 81 (21), 79 (32), 58 (43), 55 (22), 43 (100). Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.50; H, 7.79.

(3aα,8aα)-8β-Acetoxy-3-methyleneoctahydro-2*H*-cyclohepta[*b*]furan-2-one (14c). A mixture of **14a** (32 mg, 0.18 mmol), (dimethylamino)pyridine (21.5 mg, 0.18 mmol), acetic anhydride (100 μL, 1.06 mmol), and pyridine (1 mL) was stirred for 14 h at room temperature and worked up as usual to give an oily crude product (40 mg), which was chromatographed over silica gel (3 g) and eluted with a mixture of ethyl acetate and chloroform (2:8) to give **14c** (35 mg, 89%) as a colorless oil: IR ($CHCl_3$) 3025, 2940, 2860, 1760, 1742, 1662 cm^{-1}; ^1H NMR (200 MHz) δ 2.04 (3 H, s, COC*H*$_3$), 3.29–3.46 (1 H, m, C_{3a}-H), 4.77 (1 H, dd, J = 9.2, 1.8 Hz, C_{8a}-H), 5.24 (1 H, br d, J = 9.0 Hz, C_8-H), 5.57 (1 H, d, J = 2.8 Hz, C_9-H_a), 6.32 (1 H, d, J = 3.2 Hz, C_9-H_b); MS, m/e (relative intensity) 224 (M^+, 2), 182 (42), 164 (100), 163 (29), 154 (29), 136 (35), 135 (40), 112 (37), 107 (24). Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.00; H, 7.38.

8β-Hydroxy-3-methyl-4,5,6,7,8,8aα-hexahydro-2*H*-cyclohepta[*b*]furan-2-one (15a). A mixture of **14a** (35 mg, 0.19 mmol), degassed ethanol (2 mL), and $RhCl_3 \cdot 3H_2O$ (4 mg) was refluxed for 3 h, cooled, and concentrated. The residue was chromatographed over silica gel (2 g, 1 cm i.d. column) and eluted with a mixture of chloroform and ethyl acetate (4:1). The eluent was concentrated to give **15a** (25 mg, 71%) as colorless needles: mp 70–72 °C; IR (KBr) 3500, 1745, 1670 cm^{-1}; ^1H NMR (200 MHz) δ 1.81 (3 H, C_3-Me), 2.17 (1 H, m, C_7-H_β), 2.30 (1 H, d, J = 3.8 Hz, O*H*), 2.49 (1 H, br dd, J = 19.0, 12.0 Hz, C_4-H_b), 2.77 (1 H, br d, J = 19.0 Hz, C_4-H_α), 4.46 (1 H, m, $W_{h/2}$ = 11 Hz, C_8-H), 4.98 (1 H, m, $W_{h/2}$ = 6.0 Hz, C_{8a}-H); MS, m/e (relative intensity) 182 (M^+, 6), 154 (32), 125 (25), 112 (100). Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.81; H, 7.80.

(3aα,8aα)-8β-Hydroxy-3β-methyloctahydro-2*H*-cyclohepta[*b*]furan-2-one (17a). $NaBH_4$ (67 mg, 1.77 mmol) was added to a solution of **14a** (260 mg, 1.43 mmol) in methanol (5 mL) and the mixture was stirred for 2 h at room temperature, poured into water, and extracted with chloroform (5 × 20 mL). The combined extracts were washed with a saturated NaCl aqueous solution, dried (Na_2SO_4), and concentrated to give an oily crude product (347 mg), which was chromatographed over silica gel (15 g, 2.6 cm i.d. column) and eluted with a mixture of chloroform and ethyl acetate (9:1) to give **17a** (228 mg, 87%) as a colorless oil: IR (neat) 3700–3150, 1760 cm^{-1}; ^1H NMR (200 MHz) δ 1.20 (3 H, d, J = 7.0 Hz, C_3-Me), 2.21 (1 H, d, J = 6.2 Hz, O*H*), 2.67 (1 H, m, C_{3a}-H), 2.88 (1 H, dq, J = 9.0, 7.0 Hz, C_3-H), 4.19 (1 H, dddd, J = 9.5, 6.2, 2.4, 1.8 Hz, C_8-H), 4.69 (1 H, dd, J = 6.8, 2.4 Hz, C_{8a}-H). Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. C, 64.79; H, 8.75.

(3aα,8aα)-8β-Hydroxy-3α-methyloctahydro-2*H*-cyclohepta[*b*]furan-2-one (18a). A mixture of **17a** (12.5 mg, 0.07 mmol) and 1 M NaOMe in methanol (1.5 mL) was allowed to stand at room temperature for 1 h and poured into a saturated NaCl aqueous solution (30 mL). The mixture was worked up as usual to give an oily crude product, which showed a single peak in HPLC [10-μm silica gel (Kyowa gel MIC-SI-10, 25 cm × 4 mm i.d. column, EtOAc–hexane (3:7), flow rate 3.1 mL/min]. Under these conditions the crude product was separated to give **18a** (7 mg, 56%) as colorless crystals: mp 86.5–87 °C; IR (KBr) 3475, 1740 cm^{-1}; IR ($CHCl_3$) 3625, 3450, 1760 cm^{-1}; ^1H NMR (200 MHz) δ 1.22 (3 H, d, J = 7.0 Hz, C_3-Me) 2.20 (1 H, d, J = 5.0 Hz, O*H*), 2.38 (1 H, dddd, J = 11.0, 11.0, 8.8, 6.0 Hz, C_{3a}-H), 2.59 (1 H, dq, J = 11.0, 7.0 Hz, C_3-H), 4.35 (1 H, dddd, J = 6.0, 5.0, 1.7, 1.5 Hz, C_8-H), 4.47 (1 H, dd, J = 8.8, 1.7 Hz, C_{8a}-H); MS (13.5 eV), m/e (relative intensity) 186 (M^+, 1), 185 (2), 157 (8), 129 (6), 126 (7), 113 (11), 112 (7), 111 (6), 100 (100), 99 (6), 96 (4), 84 (5), 82 (5), 70 (2), 68 (6), 58 (11). Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 64.31; H, 8.73.

Attempted Epimerization of 17a in Acetic Acid in the Presence of 48% HBr. Formation of (3aα,8aα)-8β-Acetoxy-3β-methyloctahydro-2*H*-cyclohepta[*b*]furan-2-one (17c). A mixture of **17a** (12.5 mg, 0.07 mmol) and a 48% HBr aqueous solution (20 μL) in acetic acid (2 mL) was allowed to stand at room temperature for 22 h and poured into a saturated NaCl aqueous solution (40 mL). The mixture was worked up as usual to give an oily crude product, which was separated by HPLC [10-μm silica gel (Kyowa gel MIC-SI-10, 25 cm × 4 mm i.d. column, EtOAc–hexane (3:7), flow rate 3.1 mL/min] to give **17c** (t_R 3.8 min, 9.5 mg, 62%) as a colorless oil: IR (neat) 1778, 1742, cm^{-1}; ^1H NMR (200 MHz) δ 1.21 (3 H, d, J = 7.0 Hz, C_3-Me), 2.10 (3 H, s, $COCH_3$), 2.75 (1 H, m, C_{3a}-H), 2.83 (1 H, dq, J = 9.0, 7.0 Hz, C_3-H), 4.71 (1 H, br d, J = 6.5 Hz, C_{8a}-H), 5.20 (1 H, ddd, J = 10.5, 1.7, 1.7 Hz, C_8-H). Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.36; H, 8.05.

Acetylation of 17a with Acetic Anhydride in Pyridine in the Presence of 4-(Dimethylamino)pyridine. A mixture of **17a** (9 mg, 0.05 mmol), acetic anhydride (24 μL, 0.25 mmol), 4-(dimethylamino)pyridine (6 mg, 0.25 mmol), and pyridine (0.3 mL) was allowed to stand at room temperature for 20 h and worked up as usual to give an oily crude product (6.5 mg), which was purified by HPLC [10-μm silica gel (Kyowa gel MIC-SI-10) 25 cm × 4 mm i.d. column, EtOAc–hexane (3:7), flow rate 3.1 mL/min] (t_R = 4 min) to give **17c** (5.5 mg, 50%).

(3aα,8aα)-2-Oxooctahydro-2*H*-cyclohepta[*b*]furan-3α-carboxylic Acid (13b). A mixture of **2b** (2.13 g, 9.4 mmol), ethanol (50 mL), and 1 M KOH aqueous solution (20 mL) was stirred for 3 h at 0 °C, poured into a mixture of 2 M HCl (20 mL) and a saturated NaCl aqueous solution (300 mL), and worked up as usual to give a crude crystalline material, which was recrystallized from a mixture of chloroform and ethyl acetate (1:1) to give **13b** (2.01 g, 94%) as colorless needles: mp 102–103 °C; IR (KBr) 3400–2900, 1775, 1720 cm^{-1}; ^1H NMR (90 MHz) δ 1.00–2.27 (10 H, m), 2.90–3.35 (1 H, dddd, J = 10.0, 8.3, 8.1, 4.5 Hz, C_{3a}-H), 3.35 (1 H, d, J = 8.3 Hz, C_3-H), 4.77 (1 H, ddd, J = 8.1, 8.1, 3.8 Hz, C_{8a}-H), 9.50 (1 H, br s, CO_2H); MS (13.5 eV), m/e (relative intensity) 198 (M^+, 1), 154 (54), 110 (23), 108 (40), 107 (26), 95 (35), 94 (94), 82 (100). Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.09; H, 7.10.

(3aα,8aα)-3-Methyleneoctahydro-2*H*-cyclohepta[*b*]-furan-2-one (14b). A mixture of **13b** (133 mg, 0.67 mmol), acetic acid (4.9 mL), sodium acetate (124 mg, 1.51 mmol), diethylamine (1.2 mL), and 30% formalin (3.7 mL) was gently refluxed (bath temperature 100 °C) for 20 min and worked up as usual to give an oily crude product (145 mg), which was chromatographed over silica gel [6 g, 2 cm i.d. column] and eluted with a mixture of chloroform and ethyl acetate (19:1) to give **14b** (95 mg, 85%) as a colorless oil: IR (neat) 1760, 1660 cm^{-1}; ^1H NMR (200 MHz) δ 3.26 (1 H, m, C_{3a}-H), 4.74 (1 H, ddd, J = 10.5, 8.5, 3.8 Hz, C_{8a}-H), 5.58 (1 H, d, J = 2.8 Hz, C_9-H_a), 6.30 (1 H, d, J = 3.2 Hz, C_9-H_b); MS (13.5 eV), m/e (relative intensity) 167 (M + 1, 25), 166 (M^+, 91), 139 (21), 138 (100), 137 (47), 124 (21), 122 (44), 121 (29), 120 (21), 111 (36), 110 (77), 109 (30), 96 (36), 95 (98), 94 (100), 92 (33), 82 (49), 80 (30). Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.50; H, 8.67.

3-Methyl-4,5,6,7,8,8aα-hexahydro-2*H*-cyclohepta[*b*]-furan-2-one (15b). Method A. A mixture of **14b** (97 mg, 0.58 mmol), acetic acid (3 mL), PtO_2 (10 mg), and activated charcoal (40 mg) was shaken under 1 atm of hydrogen for 2 h and filtered. The filtrate was worked up as usual to give an oily product, which was a 6:1 mixture of **15b** and **17b** (97 mg) ^1H NMR analysis.

Method B. A solution of **14b** (108 mg, 0.65 mmol) in ethyl acetate was shaken in the presence of 10% Pd–C (30 mg) under 1 atm of hydrogen for 2 h and filtered. The filtrate was concentrated to give a 4:1 mixture of **15b** and **17b** (113 mg).

Method C. A mixture of **14b** (88 mg, 0.53 mmol), degassed ethanol (6 mL), and $RhCl_3 \cdot 3H_2O$ (10 mg) was refluxed for 3 h, cooled, and concentrated. The residue was chromatographed over silica gel (5 g, 2 cm i.d. column) and eluted with a mixture of chloroform and ethyl acetate (9:1). The eluent was concentrated to give **15b** (73 mg, 83%) as a colorless oil: IR (neat) 1760, 1675 cm^{-1}; ^1H NMR (90 MHz) δ 1.00–3.00 (10 H, m), 1.79 (3 H, m, $W_{h/2}$ = 5.0 Hz, C_9-H), 4.70–4.97 (1 H, m, C_{8a}-H); MS, m/e (relative intensity) 166 (M^+, 78), 138 (27), 137 (55), 110 (26), 109 (34), 96 (31), 95 (100), 82 (23), 81 (38), 67 (56). Anal. Calcd for $C_{10}H_{14}O_2$:

C, 72.26; H, 8.49. Found: C, 72.08; H, 8.52.

(3aα,8aα)-3β-Methyloctahydro-2*H*-cyclohepta[*b*]furan-2-one (17b). $NaBH_4$ (33 mg, 0.87 mmol) was added to a solution of **14b** (118 mg, 0.71 mmol) in methanol (3 mL) and the mixture was stirred for 2 h at room temperature and worked up as usual to give an oily crude product (135 mg), which was chromatographed over silica gel (6 g, 2 cm i.d. column) and eluted with chloroform to give **17b** (116 mg, 97%) as a colorless oil: IR (neat) 1770 cm^{-1}; ^1H NMR (200 MHz) δ 1.18 (3 H, d, J = 7.0 Hz, C_3-Me), 2.25 (1 H, ddd, J = 13.0, 9.0, 5.8 Hz, C_8-H_α), 2.53 (1 H, dddd, J = 10.5, 9.0, 5.8, 2.0 Hz, C_{3a}-H), 2.86 (1 H, dq, J = 9.0, 7.0 Hz, C_3-H), 4.65 (1 H, ddd, J = 9.8, 5.8, 5.8 Hz, C_{8a}-H); MS, m/e (relative intensity) 168 (M^+, 2), 124 (25), 109 (20), 96 (70), 95 (100), 82 (44), 81 (24), 78 (22), 77 (28). Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.17; H, 9.66.

(3aα,8aα)-3α-Methyloctahydro-2*H*-cyclohepta[*b*]furan-2-one (18b). A mixture of **17b** (23 mg, 0.14 mmol) and 1 M NaOMe in methanol (3 mL) was allowed to stand at room temperature for 2 h and poured into a saturated NaCl aqueous solution (50 mL). The mixture was worked up as usual to give an oily crude product, which was separated by HPLC [10-μm silica gel (Kyowa gel MIC-SI-10, 25 cm × 8 mm i.d. column, EtOAc–hexane (2:8), flow rate 3.1 mL/min] to give **18** b (t_R 7.6 min, 13 mg, 57%) as a colorless oil: IR (neat) 1767 cm^{-1}; ^1H NMR (200 MHz) δ 1.25 (3 H, d, J = 6.5 Hz, C_3-Me), 4.58 (1 H, ddd, J = 11.0, 8.2, 2.8 Hz, C_{8a}-H), 2.32 (1 H, dq, J = 10.4, 6.5 Hz, C_3-H), 2.34 (1 H, m, C_{3a}-H). Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.68; H, 9.73.

Attempted Epimerization of 17b in Acetic Acid in the Presence of 48% HBr. A mixture of **17b** (24 mg, 0.14 mmol) and a 48% HBr aqueous solution (40 μL) in acetic acid (4 mL) was allowed to stand at room temperature for 20 h and poured into a saturated NaCl aqueous solution (60 mL). The mixture was worked up as usual to give an oily product (24 mg), which was recovered **17b** by the analyses of the ^1H NMR spectrum and HPLC.

(3aα,8aα)-3-Methyleneoctahydro-2*H*-cyclohepta[*b*]-furan-2,8-dione (16). Chromic anhydride (1.54 g, 18.3 mmol) was added to a mixture of anhydrous methylene chloride (19.3 mL) and anhydrous pyridine (3.1 mL, 38.4 mmol) at 0 °C, and the mixture was stirred for 15 min. Then **14a** (130 mg, 0.72 mmol) dissolved in methylene chloride (10 mL) was added over 15 min. The mixture was stirred at 0 °C for 4 h and then worked up as usual to give oily crude product, which was chromatographed over silica gel (5 g, 2 cm i.d. column) and eluted with a mixture of chloroform and ethyl acetate (9:1) to give **16** (96 mg, 74%) as a colorless oil: IR (neat) 1775, 1730, 1665 cm^{-1}; ^1H NMR (200 MHz) δ 3.40 (1 H, dddd, J = 10.0, 9.3, 3.0, 2.5 Hz, C_{3a}-H), 5.26 (1 H, d, J = 9.3 Hz, C_{8a}-H), 5.70 (1 H, d, J = 2.5 Hz, C_9-H_a), 6.42 (1 H, d, J = 3.0 Hz, C_9-H_b). Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.85; H, 6.65.

(3aα,8aα)-3β-Methyloctahydro-2*H*-cyclohepta[*b*]furan-2,8-dione (4c). Chromic anhydride (2.0 g, 20 mmol) was added a mixture of anhydrous methylene chloride (20 mL) and pyridine (4.0 mL, 49.6 mmol) at 0 °C, and the mixture was stirred for 15 min. Then **17a** (159 mg, 0.86 mmol) dissolved in methylene chloride (15 mL) was added over 10 min. The mixture was stirred at 0 °C for 6 h and worked up as usual to give an oily crude product (155 mg), which was passed through a short column of silica gel and recrystallized from ether to give **4c** (145 mg, 92%) as colorless needles: mp 105–105.5 °C; IR (KBr) 1780, 1720 cm^{-1}; ^1H NMR (90 MHz) δ 1.20 (3 H, d, J = 6.8 Hz, C_9-H), 1.00–2.10 (6 H, m), 2.33–2.73 (2 H, m, C_7-H), 2.73–3.10 (2 H, m, C_{3a}-H, C_3-H), 5.03 (1 H, d, J = 6.3 Hz, C_{8a}-H); MS, m/e (relative intensity) 182 (M^+, 21), 154 (82), 125 (36), 112 (97), 111 (59), 97 (58), 82 (48), 81 (100), 70 (23), 69 (31), 68 (40), 67 (33), 56 (27), 55 (80). Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.74; H, 7.78.

Acknowledgment. The present work was financially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Japanese Government (No. 59540337).

Cycloshikonin and Its Derivatives.[1] A Synthetic Route of Shikonin

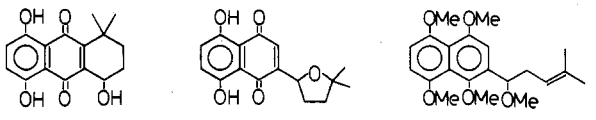
Yasuhiro Tanoue, Akira Terada,* and Yasunari Sugyō

Department of Chemistry, Kyushu Institute of Technology, Tobata, Kitakyushu, Fukuoka 804, Japan

Received August 6, 1986

Intramolecular cyclizations of 5,8-dihydroxy-2-(1,4-dihydroxy-4-methylpentyl)-1,4-naphthoquinone (**4**) and 2-(1-hydroxy-4-methyl-4-pentenyl)-1,4,5,8-tetramethoxynaphthalene (**9**) with *p*-toluenesulfonic acid gave 5,8-dihydroxy-2-(5,5-dimethyl-2-tetrahydrofuranyl)-1,4-naphthoquinone (**2**), and 2-(5,5-dimethyl-2-tetrahydrofuranyl)-1,4,5,8-tetramethoxynaphthalene (**6**), respectively. Demethylation of **6** with CAN and AgO–40% HNO_3 gave **2**. Ring-opening of **2** in acetic anhydride with *p*-toluenesulfonic acid was successful to afford 5,8-diacetoxy-2-(1,4-diacetoxy-4-methylpentyl)-1,4-naphthoquinone (**12**), and the following hydrolysis by alkali produced **4**, which could be derived to (±)-shikonin.

The cyclizations of the side chain of shikonin and alkannin, an enantiomer of shikonin, to form cycloshikonin and cycloalkannin have been well-known by many previous investigators.[3] The structures of cycloshikonin and cycloalkannin had been considered to be a hydroanthraquinone (**1**) up to recently. However, Sankawa et al.[4] have corrected the structure and shown that cycloalkannin was a tetrahydrofuran compound, 5,8-dihydroxy-2-(5,5-dimethyl-2-tetrahydrofuranyl)-1,4-naphthoquinone (**2**).



1 2 3

During our synthetic studies on shikonin and its derivatives, we have found that the 1,4,5,8-tetramethoxynaphthalene compound **3** having a side chain similar to that of shikonin could also cyclize to **2** by Lewis acid.[2b] As cycloshikonin is supposed to be chemically more stable than shikonin itself toward Lewis acid, we expected that

(1) Synthesis on Naphthoquinone Derivatives. 3. For 2, see 2b.
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(4) Sankawa, U.; Otuka, H.; Kataoka, Y.; Iitaka, Y.; Hoshi, A.; Kuretani, K. *Chem. Pharm. Bull.* **1981**, *29*, 116.

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