[Chem. Pharm. Bull.
32(6)2249—2261(1984)]

Syntheses and Anti-histaminic and Anti-allergic Activities of Hexahydro-4-hydroxy-1-benzofuran-2-ones

NAOKI TAKEUCHI,[a] TOSHIO KASAMA,[b] RIKA IKEDA,[a] KAZUE SHIMIZU,[a]
KUMIKO HATAKEYAMA,[a] YOKO AIDA,[b] YOKO KANEKO,[b]
and SEISHO TOBINAGA*,[a]

Showa College of Pharmaceutical Sciences,[a] Tsurumaki, Setagaya-ku, Tokyo 154, Japan and Research Laboratory of Biological Sciences, Kodama Ltd.,[b] Matsudo, Chiba 271, Japan

(Received September 6, 1983)

The hexahydro-4-hydroxy-1-benzofuran-2-ones **3a**, **4a**, and **5a** (related to the 6β-hydroxyeremophilenolides **1** and **2**, which show anti-histaminic and anti-allergic activities) were synthesized from dimedone through the compounds **18a**, **23a**, and **24a**, followed by dehydration reactions. Pharmacological investigations of **3a**, **4a**, **5a**, **18a**, **23a**, and **24a** showed that compounds **4a** and **5a** have anti-histaminic activity and cause marked inhibition in the Schultz–Dale reaction.

Keywords——hexahydro-4-hydroxy-1-benzofuran-2-one; anti-histaminic; anti-allergic; Schultz–Dale reaction

In the previous communication,[1] we reported that the 6β-hydroxyeremophilenolides **1** and **2**, constituents of rhizomes of *Petasites japonicus* MAXIM., have dose-dependent anti-histaminic and significant anti-allergic activities. These activities are of considerable interest in connection with the adverse allergic contact dermatitis activity of isoalantolactone and related compounds, which have an α-methylene-γ-butyrolactone moiety.[2] We were interested in the structural requirements for these interesting pharmacological activities, and thus we synthesized various hydroxy-α,β-unsaturated-γ-butyrolactones such as **3a**, **4a**, and **5a** in order to determine their anti-histaminic and anti-allergic activities.

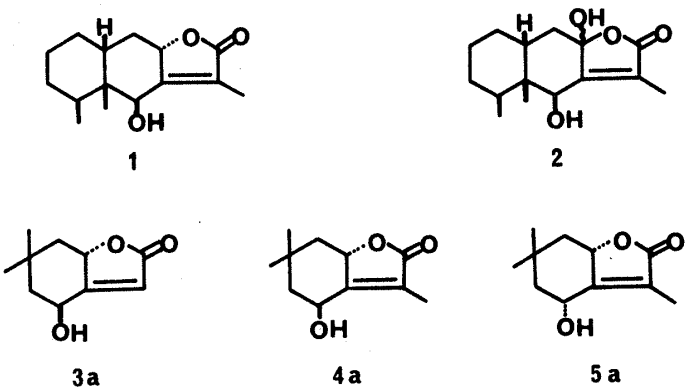

Chart 1

Chemistry

(1) Synthetic Studies on 2,4,5,6,7,7aβ-Hexahydro-4β-hydroxy-6,6-dimethyl-1-benzofuran-2-one (3a)

Though several synthetic methods are available for the title compounds, in particular

from synthetic studies on sesquiterpenoids,[3] the present synthesis proceeded from dimedone to **6a** by alkylation, followed by lactonization and reduction to yield **3a**.

Alkylation of dimedone with ethyl bromoacetate in the presence of 25% KOH in EtOH gave **6a**, mp 100—101 °C (33.9% yield). Several attempts at the lactonization of **6a** were unsuccessful, namely, treatment of **6a** with Ac_2O–AcONa gave the acetate **6b** (oil), treatment with H_2SO_4 in EtOH afforded the ethyl ether **7b** (oil), and treatment with H_2SO_4 in AcOH yielded the carboxylic acid **7a**, mp 201—202 °C. Similar attempts with the acid **7a** were also unsuccessful. Treatment of **7a** with H_2SO_4 in EtOH gave **6a** and **7b**, treatment with Ac_2O–AcONa afforded a neutral compound **8**, mp 164—165 °C, and treatment with DCC in pyridine yielded the enol lactone **9**, mp 92—94 °C. The enol lactone **9** gave a novel reduction product **10** (oil) on reduction with $NaBH_4$ in EtOH.

On the other hand, when crystalline **6a** was allowed to stand for a long period, it afforded an oxygenated compound **11a**, mp 69—70 °C, which was obtained practically by air oxidation of **6a** in chloroform for 4 d. Though reaction of **11a** with AcONa in Ac_2O at 90 °C for 3 h gave the corresponding acetate **11b**, mp 50—51 °C, the same reaction at 115 °C for 12 h afforded the dehydration products, namely, the lactone **13**, mp 100.5—102 °C, and the diacetate **14**

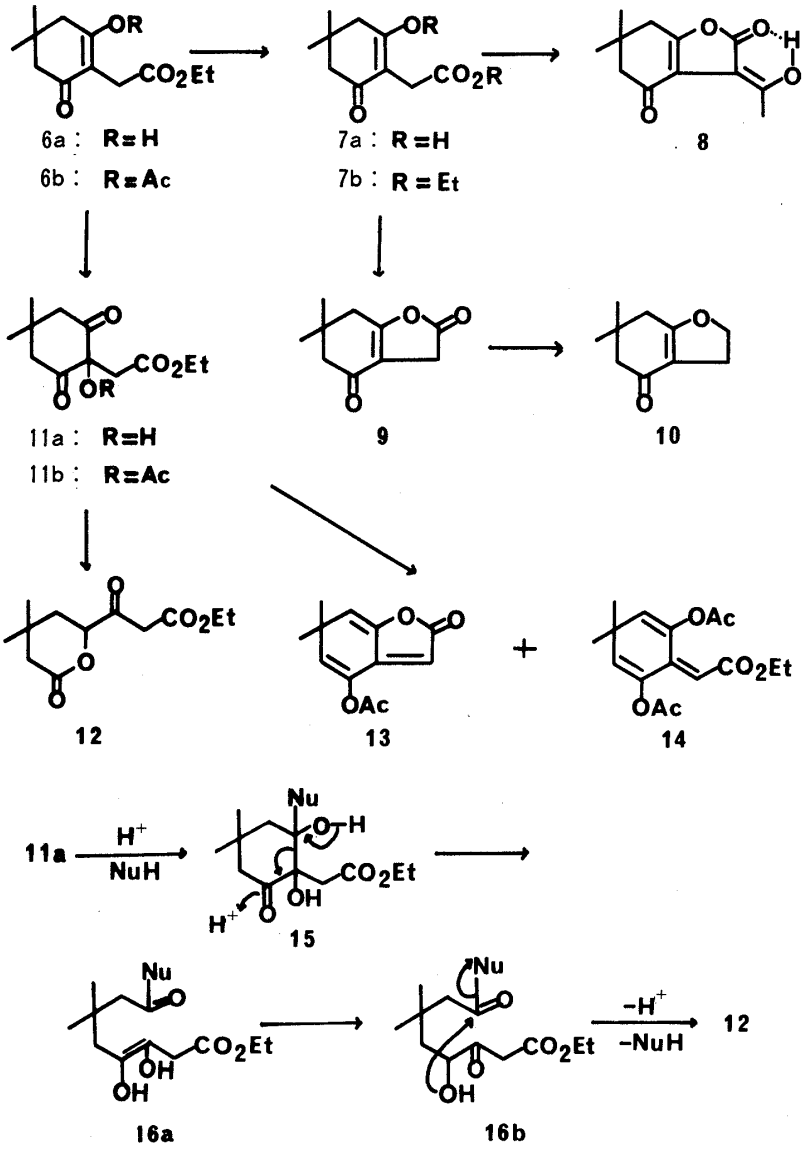

Chart 2

(oil). An alternative reaction of **11a** with conc. H_2SO_4 at room temperature for 2 h yielded a novel rearranged product **12** (oil). The mechanism of this rearrangement of **11a** to **12** may be as follows. First, addition of a nucleophile to the protonated carbonyl group proceeds to give an intermediate **15**, then C–C bond cleavage occurs, followed by substitution and elimination reactions (**15**—**16a**—**16b**—**12**) to yield the lactone **12** as shown in Chart 2.

Reduction of **11a** with $NaBH_4$ in EtOH gave the triol **17a**, mp 139—140 °C, (acetate **17b**, mp 91—92 °C), and the γ-lactone **18a**, mp 95—96 °C, (acetate **18b**, oil, acetylated with AcOH in the presence of $HClO_4$), in yields 9.5% and 35.3%, respectively. Reaction of **18a** with Jones' reagent gave the ketone **20**, mp 119—120.5 °C, and that with acetone in the presence of *p*-TsOH afforded the acetonide **19**, mp 75—77 °C. The desired α,β-unsaturated lactone **3a**, mp 73—74.5 °C, was obtained by the treatment of **18a** with DCC and CuCl in ether. The acetate **3b** (oil) was also obtained by the reaction of **18b** with $SOCl_2$ in pyridine.

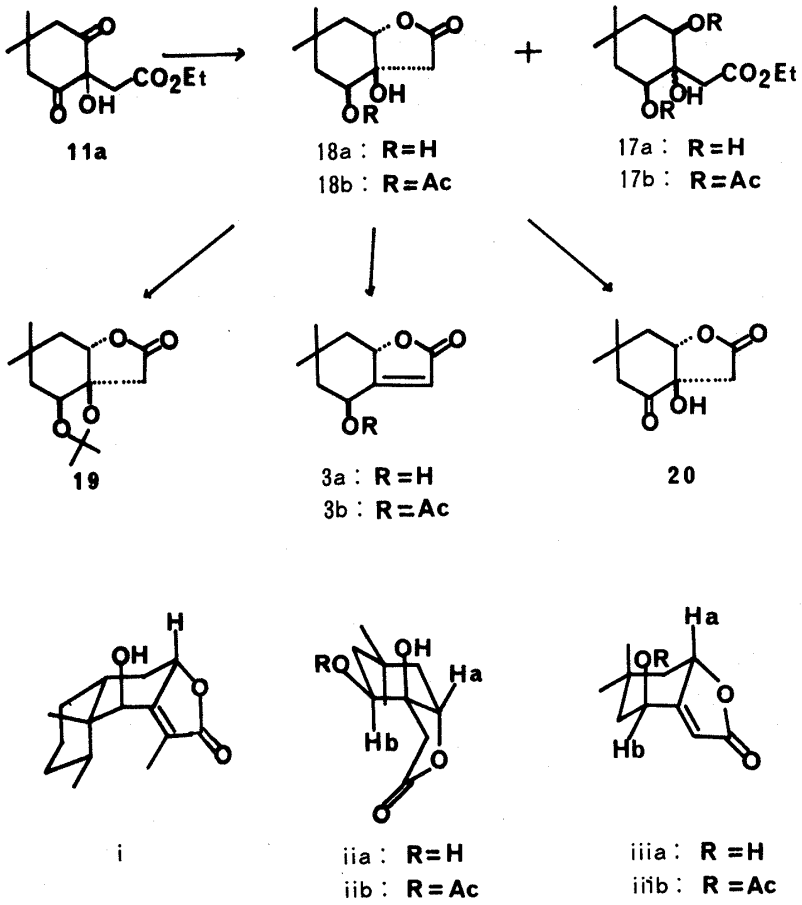

Chart 3

The structure of **18a** (iia) was assigned on the basis of the following evidence: (a) the two hydroxyl groups are *cis* because of the formation of the acetonide **19**, (b) Ha and Hb may be equatorial and axial in view of the proton signals in the nuclear magnetic resonance (NMR) spectrum at δ 4.56 (t, J=4.4 Hz) and 3.84 (dd, J=8.8 and 6.1 Hz); these protons were assigned by comparison with the chemical shifts of the corresponding proton signals of **18b** (iib) at δ 4.52 (t, J=4.9 Hz) and 5.04 (dd, J=8.1 and 6.6 Hz). The structure of **3a** (iiia) was also assigned on the basis of the proton signals of Ha and Hb at δ 5.27 (ddd, J=11.2, 6.1, and 1.2 Hz) and 4.97 (dd, J=3.7 and 2.4 Hz); conformational inversion had taken place. Compound **3a** has a conformation similar to that of the pharmacologically active natural sesquiterpene lactone **1** (i).

(2) Syntheses of 2,4,5,6,7,7aβ-Hexahydro-4-hydroxy-3,6,6-trimethyl-1-benzofuran-2-ones (4a) and (5a)

The target compounds **4a** and **5a** were synthesized in a way similar to that described for **3a**. Although reaction of dimedone with ethyl α-bromopropionate and NaH in DMF did not give the alkylated product, reaction with ethyl α-iodopropionate under the same conditions afforded the alkylated product **21**, mp 114—116 °C, in 34.1% yield. Air oxidation of **21** gave the oxygenated product **22**, mp 100—101 °C, and subsequent reduction of **22** with $NaBH_4$ in EtOH afforded two isomeric γ-lactones **23a**, mp 84—86 °C, (acetate **23b**, oil), and **24a**, mp 143—145 °C, (acetate **24b**, mp 165—166 °C), in yields of 22.9%, and 41.9%, respectively. The lactone **23a** gave the acetonide **25**, mp 136—137 °C, but **24a** did not. Oxidation of **24a** with Jones' reagent gave the compound **26**, mp 138—138.5 °C, and reduction of **26** with $NaBH_4$ afforded **23a** and a trace amount of **24a**.

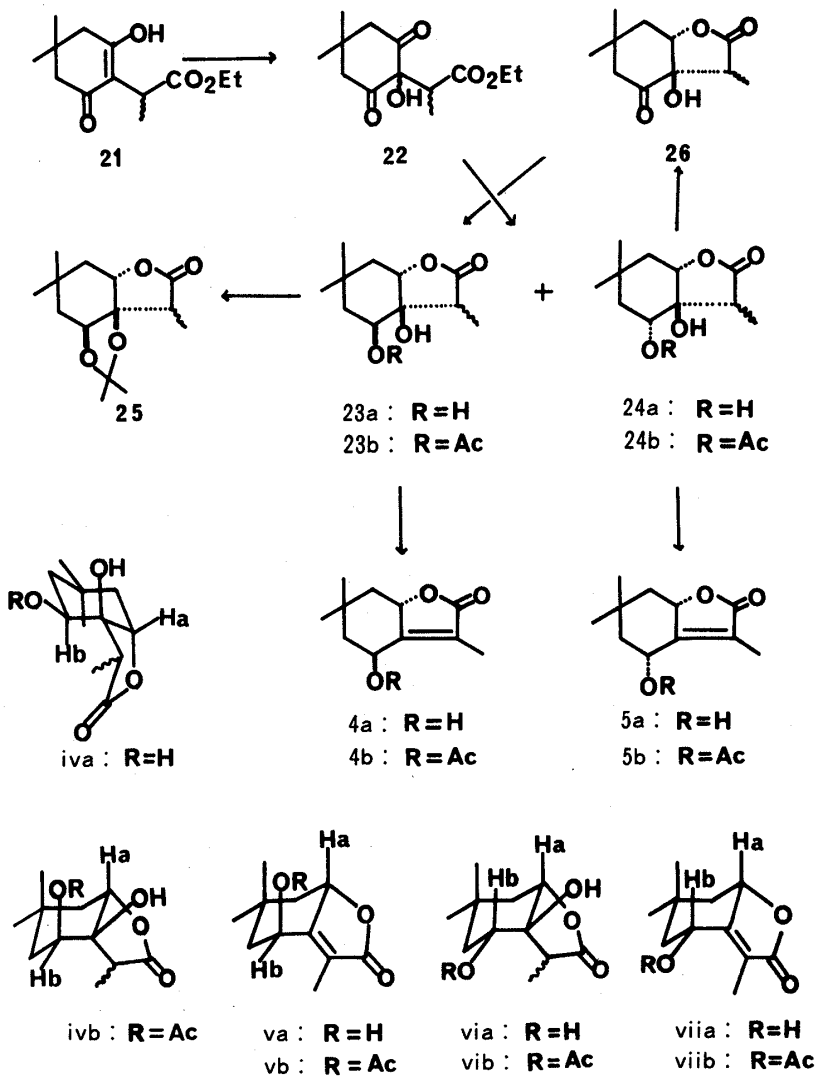

Chart 4

The structures of **23a** (iva) and **24a** (via) were assigned on the basis of the above chemical evidence and the NMR data: (a) **23a** gave the acetonide **25** but **24a** did not, (b) Ha and Hb in **23a** may be equatorial and axial because the corresponding proton signals in the NMR spectrum are observed at δ 4.55 (t, $J=5.5$ Hz) and 3.85 (dd, $J=8.4$ and 4.8 Hz). On the other hand, the proton signals of Ha and Hb in **24a** are observed at δ 4.44 (dd, $J=11.1$ and 6.5 Hz)

and 4.13 (dd, $J=12.2$ and 5.1 Hz). Therefore, Ha and Hb in **24a** may both possess axial configuration. Further, in the acetylation of **23a**, conformational inversion took place to yield **23b** (ivb), but in the conversion of **24a** to **24b** (vib) such inversion did not proceed.

Subsequently, the transformations of **23a** and **24a** to the unsaturated lactones **4a** and **5a** by dehydration were investigated. Although dehydration of **23a** with DCC–CuCl in ether was unsuccessful, the acetate **23b** gave the unsaturated lactone **4b** (oil) with $SOCl_2$ in pyridine and hydrolysis of **4b** with conc. HCl in MeOH afforded the target compound **4a**, mp 106—108 °C. The other target compound **5a**, mp 114—114.5 °C, was obtained similarly by the treatment of **24b** with $SOCl_2$ in pyridine to give **5b** followed by hydrolysis with conc. HCl in MeOH. The structures of **4a** (va) and **5a** (viia) were assigned from the NMR data and those of **4b** and **5b**. Ha and Hb in **4b** (vb) may be assumed to be axial and equatorial since the corresponding proton signals are observed at δ 5.02 (ddd, $J=11.8$, 5.9, and 1.8 Hz) and 5.83 (dd, $J=4.2$ and 2.2 Hz). On the other hand, Ha and Hb in **5b** (viib) may be both axial because the corresponding proton signals are observed at δ 4.80 (ddd, $J=11.4$, 6.4, and 1.5 Hz) and 5.79 (ddd, $J=11.5$, 5.6, and 1.5 Hz). In the transformation of **23a** to **4a**, conformational inversion takes place, but in the case of **24a** to **5a**, it does not. Compound **4a** has essentially the same conformation as the natural sesquiterpene lactone (i).

Among these compounds, **18a**, **3a**, **23a**, **24a**, **4a**, and **5a** were subjected to pharmacological investigations.

Pharmacology

The effects of synthetic γ-butyrolactones on histamine-induced contraction, passive cutaneous anaphylaxis and the Schultz–Dale reaction were studied as follows.

1. Agents

Synthetic γ-butyrolactones **3a**, **4a**, **5a**, **18a**, **23a**, and **24a** were used in this study. They were dissolved in ethanol and diluted with saline for *in vitro* studies and suspended in 0.5% CMC for *in vivo* studies. Other agents used were histamine hydrochloride (Wako), diphenhydramine hydrochloride (Kowa), isoproterenol hydrochloride (Nikken Kagaku), egg albumin (Difco), Evans blue (Wako), anti-egg albumin rabbit serum (rabbit antiserum; produced in our laboratory) and anti-egg albumin mouse serum (mouse antiserum; produced in our laboratory).

2. Animals

Male Hartley strain guinea pigs weighing 250 to 400 g (Japan Medical Science Animal Resources Institute) and male Wistar rats weighing 200 to 300 g (Shizuoka Agricultural Cooperative Association for Laboratory Animals) were used.

3. Methods

1) Effects of γ-Butyrolactones on Histamine-Induced Contraction in Isolated Guinea Pig Ileum——The guinea pig ileum preparation was suspended in a 10 ml organ bath filled with Tyrode's solution, kept at 26 °C and bubbled through with air. Contraction activity was recorded isotonically *via* a transducer (ME-4012, Medical Electronics Co.). Drugs were applied at 5 min before the addition of the agonist.

2) Effects of γ-Butyrolactones on Passive Cutaneous Anaphylaxis (PCA)——i) Heterologous PCA in Guinea Pigs:[4] Rabbit antiserum with a PCA titer of 1 : 5000 was diluted to 1 : 1000 and 1 : 5000 with saline. The diluted rabbit antiserum was given intradermally on one side of the shaved back of normal guinea pigs. The same volume of saline was injected into the other side. After 3 h, the animals were injected intravenously with the challenging antigen, 5.0 ml/kg of the saline solution containing 25 mg of egg albumin and Evans blue.

Thirty min later, the animals were exsanguinated, the back skin of each animal was removed, and the sizes of the blue wheals revealed on the skin were measured. The mean size for each group was calculated, and the inhibition percentages were calculated by means of the following equation:

$$100 \times \frac{A-B}{A}$$

A: mean wheal size of control group
B: mean wheal size of the treated group

γ-Butyrolactones were orally administered at 1 h before the injection of antigen.

ii) Homologous PCA in Rats:[5] Mouse antiserum with a PCA titer of 1 : 250 was diluted to 1 : 100 and 1 : 250 with saline. The diluted mouse antiserum was given intradermally in the shaved back of normal rats. After 48 h, the animals were injected with the antigen intravenously and the wheal sizes were measured in the same manner as mentioned above.

3) Effects of γ-Butyrolactones on the Schultz–Dale Reaction——Guinea pigs were sensitized once a week for 4 weeks by administering egg albumin mixed with complete Freund's adjuvant subcutaneously. Animals were exanguinated on the 8th day after the last sensitization. The ileum was removed. The ileum preparation was suspended in an organ bath and the intensity of contraction was recorded isotonically in the same manner as described in section 3-1. After the contractile response induced by 10^{-7} g/ml of histamine had stabilized, 10^{-4} g/ml of egg albumin (antigen) was added. Drugs were applied at 5 min before the addition of the antigen. The inhibition percentages of drugs were calculated from the following equation:[6]

$$\left(1-\frac{B}{A}\right) \times 100$$

$$A: \frac{\text{antigen-induced contraction}}{\text{histamine-induced contraction}}$$

$$B: \frac{\text{antigen-induced contraction of the drug-treated preparation}}{\text{histamine-induced contraction}}$$

4. Results

1) Effects of γ-Butyrolactones on Histamine-Induced Contraction in Isolated Guinea Pig Ileum——As shown in Fig. 1, a parallel shift to the right was observed in the dose–response curves to histamine of ileum treated with **4a** and **5a**, but **3a** produced only very weak inhibition of the response at low doses of histamine. On the other hand, the histamine-induced contractions were unaffected by **18a**, **23a**, and **24a**.

2) Allergic Effects of γ-Butyrolactones on PCA——The results of heterologous and homologous PCA tests are shown in Tables I and II. Compounds **3a**, **4a**, and **5a** which were inhibitory on histamine-induced contraction, had no effect on these PCA reactions.

3) Effects of γ-Butyrolactones on the Schultz–Dale Reaction——As shown in Table III, **4a** and **5a**, which had competitive antagonistic activity on histamine-induced contraction, markedly inhibited the egg albumin-induced contraction.

5. Discussion

Histamine is thought to be an important mediator in the antigen-antibody reaction and antihistaminergic agents sometimes show an anti-allergic effect. In the light of a previous report that 6β-hydroxyeremophilenolides have competitive antagonistic effects on histamine-induced contraction as well as anti-allergic effects (on the PCA reaction), we newly synthesized six related compounds and tested them for effect on histamine-induced contraction, as well as heterologous PCA in guinea pigs (IgG antibody) and homologous PCA in rats (IgE antibody) in type I allergic reaction.[7,8] In addition, the effects on the Schultz–Dale reaction using sensitized tissue were studied to determine the ability of the compounds

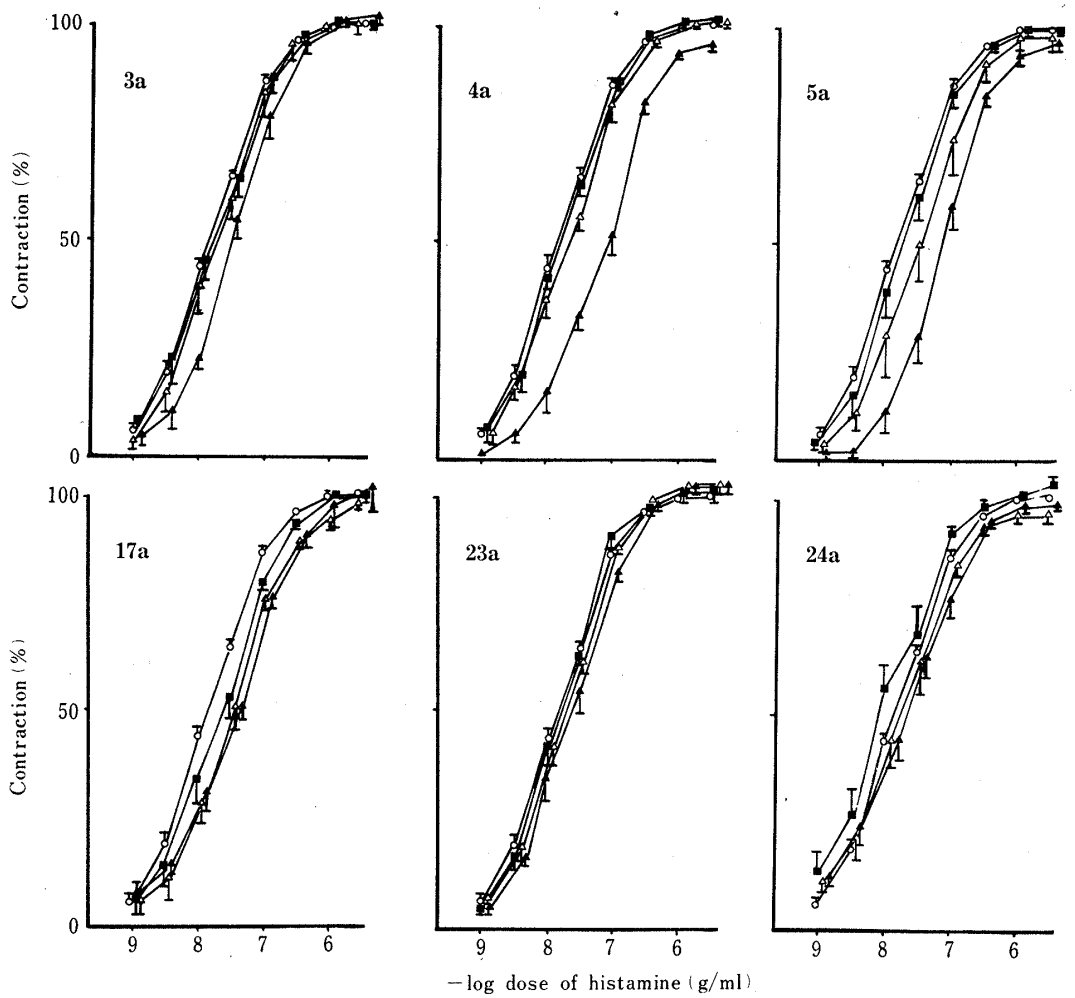

Fig. 1. Effects of γ-Butyrolactones on Histamine-Induced Contraction in the Isolated Guinea Pig Ileum

Each point represents the mean ± S.E. of 5 preparations. ○, control; ■, 10^{-5}; △, 10^{-4}; ▲, 3×10^{-4} g/ml.

TABLE I. Effects of γ-Butyrolactones (**3a**, **4a**, and **5a**) on Heterologous PCA in Guinea Pigs Provoked by Anti-egg Albumin Rabbit Serum

Drug	Dose (mg/kg)	Number	1:1000[a]		1:5000	
			Diameter mean ± S.E.	Inhibition (%)	Diameter mean ± S.E.	Inhibition (%)
Control		5	9.6 ± 0.4		6.2 ± 0.5	
3a	100, *p.o.*	5	9.8 ± 0.3	−2.1	6.4 ± 0.3	−3.2
4a	100, *p.o.*	5	9.5 ± 0.5	1.0	7.1 ± 0.6	−14.5
5a	100, *p.o.*	5	9.7 ± 0.3	−1.0	6.1 ± 0.3	1.0
Isoproterenol	0.5, *i.m.*	5	9.5 ± 0.3	1.0	5.9 ± 0.4	4.8
	0.1, *i.v.*	5	7.1 ± 0.2[b]	26.0	3.8 ± 0.3[b]	38.7

a) Serum dilution. *b*) Significant differences ($p < 0.01$).

to modify the release of histamine, slow reacting substance of anaphylaxis (SRA-A) or other mediators.[9,10]

Compounds **4a** and **5a** produced a parallel shift to the right in the dose–response curves

TABLE II. Effects of γ-Butyrolactones (**3a**, **4a**, and **5a**) on Homologous PCA in Rats Provoked by Anti-egg Albumin Mouse Serum

Drug	Dose (mg/kg)	Number	1:100[a]		1:250	
			Diameter mean ± S.E.	Inhibition (%)	Diameter mean ± S.E.	Inhibition (%)
Control		5	10.2 ± 0.3		6.6 ± 0.6	
3a	100, *p.o.*	5	8.4 ± 0.4	17.6	6.1 ± 0.2	7.6
4a	100, *p.o.*	5	9.5 ± 0.3	6.9	6.8 ± 0.3	−3.0
5a	100, *p.o.*	5	9.9 ± 0.4	2.9	7.3 ± 0.5	−10.6
Isoproterenol	0.5, *i.m.*	5	7.1 ± 0.2[b]	30.4	3.3 ± 0.6[b]	50.0
	0.1, *i.v.*	5	6.9 ± 0.5[b]	32.4	2.2 ± 0.6[b]	66.7

a) Serum dilution. *b*) Significant differences ($p < 0.01$).

TABLE III. Effects of γ-Butyrolactones (**4a** and **5a**) on the Schultz–Dale Reaction in the Isolated Ileum of Guinea Pig Sensitized with Egg Albumin

Drug	Dose (g/ml)	Number of animals	Inhibition (%) (Egg albumin 10^{-4} g/ml)
4a	3×10^{-4}	6	83.7
5a	3×10^{-4}	6	85.0
6-HE	10^{-4}	7	84.5
Isoproterenol	10^{-7}	6	58.9
Diphenhydramine	10^{-7}	6	53.4

6-HE: 6β-hydroxyeremophilenolide.

of the ileum to histamine. In the PCA tests, γ-butyrolactones were orally administrated at 1 h before the injection of the challenging antigen, because these drugs were toxic at the dose of 10 mg/kg when given intravenously. In spite of the administration of large doses of **3a**, **4a**, and **5a**, no inhibitory effect on heterologous or homologous PCA was observed. In the Schultz–Dale reaction, **4a** and **5a** markedly inhibited responses to the addition of challenging antigen. Compound **3a** had an inhibitory effect on histamine-induced contraction at low histamine doses but had no effect on PCA. Other drugs, **18a**, **23a**, and **24a** had no antihistaminergic effect and so the anti-allergic effect was not examined.

The present and previous results suggest that it is necessary to have a hydroxyl group at the C-4 position and that β-OH is better than α-OH in these γ-butyrolactones for antihistaminergic activity. It also appears that an α,β-unsaturated double bond and a methyl group at C-3 contribute to the antihistaminergic activity. Anti-allergic activity may require other substituents which afford a larger molecular weight, as was found in studies of allergic contact dermatitis activity of α-methylene-γ-butyrolactones.[2]

Experimental

All melting points are uncorrected. Infrared (IR) spectra were recorded with a Hitachi 260-10 spectrometer, and NMR spectra with a Varian T-60 or a JEOL JNM-FX100 spectrometer with tetramethylsilane as an internal standard. Elementary analyses were done by Miss. M. Takeda, Kissei Pharmaceutical Company, Ltd., Matsumoto, Japan. Mallinckrodt silica gel (100 mesh) and Merck Kieselgel G nach Stahl were used for column chromatography and thin layer chromatography (TLC), respectively.

Ethyl 6-Hydroxy-4,4-dimethyl-2-oxo-6-cyclohexenylacetate (6a)——A solution of ethyl α-bromoacetate (8.1 g) in ethanol (10 ml) was added to a solution of dimedone (8.4 g) in 25% KOH (13 ml), and the whole was stirred overnight at room temperature. The reaction mixture was made basic with 10% NaOH, and wshed with chloroform. The alkaline layer was acidified with 10% HCl, and extracted with chloroform. The organic layer was washed with water, then dried and concentrated. The residue was subjected to silica gel chromatography. The chloroform eluate gave 4.59 g (33.9%) of **6a** as colorless crystals (ether–hexane), mp 100—101 °C. IR (KBr) cm^{-1}: 1740, 1555. NMR ($CDCl_3$) δ: 1.06 (6H, s, 2×–Me), 1.26 (3H, t, J=7 Hz, –Me), 2.28 (4H, s, 2×–CH_2–), 3.36 (2H, s, –CH_2–), 3.80 (1H, br, –OH), 4.06 (2H, q, J=7 Hz, –OCH_2–). MS (*m/e*), Calcd for $C_{12}H_{18}O_4$ (M^+): 226.1205. Found: 226.1200.

Ethyl 6-Acetoxy-4,4-dimethyl-2-oxo-6-cyclohexenylacetate (6b)——Dry AcONa (10 mg) was added to a solution of **6a** (100 mg) in acetic anhydride (5 ml) and the whole was heated overnight at 80 °C with stirring. The reaction mixture was poured into ice-water and extracted with chloroform. The organic layer was washed with sat. $NaHCO_3$ and H_2O, then dried and concentrated. The residue was subjected to silica gel chromatography. The chloroform eluate gave 95 mg (80.1%) of **6b** as a colorless oil. IR (film) cm^{-1}: 1780, 1740, 1680. NMR ($CDCl_3$) δ: 1.10 (6H, s, 2×–Me), 1.20 (3H, t, J=7 Hz, –Me), 2.20 (3H, s, –Me), 2.36 (2H, s, –CH_2–), 2.52 (2H, s, –CH_2–), 3.23 (2H, s, –CH_2–), 4.09 (2H, q, J=7 Hz, –OCH_2–). MS (*m/e*), Calcd for $C_{14}H_{20}O_5$ (M^+): 268.1310. Found: 268.1315.

6-Hydroxy-4,4-dimethyl-2-oxo-6-cyclohexenylacetic Acid (7a)——Two drops of conc. H_2SO_4 were added to a solution of **6a** (100 mg) in AcOH (3 ml) and the whole was refluxed overnight. The reaction mixture was concentrated under a vacuum and poured into ice-water. The separated crystals were collected, washed with H_2O, and then recrystallized from AcOEt to yield 50.1 mg (57.2%) of **7a** as colorless crystals, mp 201—202 °C. IR (KBr) cm^{-1}: 1710, 1640, 1570. NMR ($CDCl_3$+DMSO-d_6) δ: 1.07 (6H, s, 2×–Me), 2.26 (4H, s, 2×–CH_2–). 3.18 (2H, s, –CH_2–), 5.85 (2H, br, –CO_2H and –OH). MS (*m/e*), Calcd for $C_{10}H_{14}O_4$ (M^+): 198.0893. Found: 198.0895.

Ethyl 6-Ethoxy-4,4-dimethyl-2-oxo-6-cyclohexenylacetate (7b)——A solution of **6a** (100 mg) in EtOH (5 ml) was treated with conc. H_2SO_4 (1 ml), and the whole was allowed to stand overnight at room temperature. The reaction mixture was poured into ice-water and extracted with chloroform. The organic layer was extracted with sat. $NaHCO_3$ and divided into the acidic layer (A) and the neutral layer (B). (A) was acidified with conc. HCl and then extracted with chloroform. The chloroform solution was washed with H_2O, then dried and concentrated. The residue was subjected to silica gel chromatography. The chloroform eluate gave 64 mg (64%) of **6a** as colorless crystals. (B) was washed with H_2O, then dried and concentrated. The residue was subjected to silica gel chromatography. The chloroform eluate gave 22 mg (19.6%) of **7b** as colorless oil. IR (film) cm^{-1}: 1740, 1650, 1633. NMR ($CDCl_3$) δ: 1.22 (6H, s, 2×–Me), 1.33 (3H, t, J=7 Hz, –Me), 1.36 (3H, t, J=7 Hz, –Me), 2.33 (2H, s, –CH_2–), 2.52 (2H, s, –CH_2–), 3.38 (2H, s, –CH_2–), 4.13 (2H, q, J=7 Hz, –OCH_2–), 4.17 (2H, q, J=7 Hz, –OCH_2–). MS (*m/e*), Calcd for $C_{14}H_{22}O_4$ (M^+): 254.1516. Found: 254.1504.

Preparation of 6a and 7b from 7a——Two drops of conc. H_2SO_4 were added to a solution of **7a** (500 mg) in EtOH (6 ml) and the whole was refluxed for 2 h. The reaction mixture was poured into ice-water and extracted with chloroform. The organic layer was extracted with sat. $NaHCO_3$ and separated into the aqueous layer (A) and the organic layer (B). A was acidified with conc. HCl and then extracted with chloroform. From A, 340 mg (59.6%) of **6a** was isolated. B was washed with H_2O, dried and concentrated and the residue was subjected to silica gel chromatography. The chloroform eluate gave 230 mg (32.0%) of **7b** as a colorless oil.

2,3,4,5,6,7-Hexahydro-3-(1-hydroxyethylidene)-6,6-dimethyl-1-benzofuran-2,4-dione (8)——Dry AcONa (20 mg) was added to a solution of **7a** (100 mg) in Ac_2O (2 ml) and the whole was refluxed for 2 h. The reaction mixture was poured into ice-water and extracted with chloroform. The organic layer was washed with sat. $NaHCO_3$ and H_2O, then dried and concentrated. The residue was subjected to silica gel chromatography. The chloroform eluate gave 68 mg (60.7%) of **8** as yellowish crystals (ether–hexane), mp 164—165 °C. IR (nujol) cm^{-1}: 1780, 1635. NMR ($CDCl_3$) δ: 1.18 (6H, s, 2×–Me), 2.43 (5H, s, –CH_2– and –Me), 2.60 (2H, s, –CH_2–), and 13.3 (1H, s, –OH). MS (*m/e*), Calcd for $C_{12}H_{14}O_4$ (M^+): 222.0892. Found: 222.0899. *Anal.* Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 65.01; H, 6.38.

2,3,4,5,6,7-Hexahydro-6,6-dimethyl-1-benzofuran-2,4-dione (9)——DCC (53.5 mg) was added to a solution of **7a** (50 mg) in dry pyridine (5 ml) and the whole was stirred overnight at room temperature. The resulting solid was removed by filtration. The filtrate was diluted with H_2O, acidified with conc. HCl and extracted with chloroform. The organic layer was washed with sat. $NaHCO_3$ and H_2O, then dried and concentrated. The residue was subjected to silica gel chromatography. The chloroform eluate gave 8.5 mg (21%) of **9** as colorless crystals (chloroform–ether), mp 92—94 °C. IR (KBr) cm^{-1}: 1840, 1815, 1650. NMR ($CDCl_3$) δ: 1.16 (6H, s, 2×–Me), 2.33 (2H, s, –CH_2–), 2.53 (2H, t, J=3 Hz, –CH_2–), 3.40 (2H, t, J=3 Hz, –CH_2–). MS (*m/e*), Calcd for $C_{10}H_{12}O_3$ (M^+): 180.0787. Found: 180.0787.

2,3,4,5,6,7-Hexahydro-6,6-dimethyl-1-benzofuran-4-one (10)——$NaBH_4$ (12 mg) was added to a solution of **9** (59 mg) in MeOH (3 ml) and the whole was stirred at room temperature for 2 h. The reaction mixture was acidified with dil. HCl and extracted with chloroform. The organic layer was washed with sat. $NaHCO_3$ and H_2O, then dried and concentrated. The residue was subjected to silica gel chromatography. The chloroform eluate gave 26 mg (47.8%) of **10** as a colorless oil. IR (film) cm^{-1}: 1630. NMR ($CDCl_3$) δ: 1.11 (6H, s, 2×–Me), 2.23 (2H, s, –CH_2–), 2.28 (2H, t, J=1.6 Hz, –CH_2–), 2.80 (2H, br, –CH_2–), 4.58 (2H, t, J=9.2 Hz, –OCH_2–). MS (*m/e*), Calcd for $C_{10}H_{14}O_2$ (M^+): 166.0995. Found: 166.1027.

Ethyl 1-Hydroxy-4,4-dimethyl-2,6-dioxocyclohexylacetate (11a)——A current of air was bubbled into a solution of **6a** (1 g) in chloroform (10 ml) for 4 d. The reaction mixture was dried and concentrated, and the residue was recrystallized from ether–hexane to yield 0.75 g (70.1%) of **11a** as colorless crystals, mp 69—70 °C. IR (KBr) cm^{-1}: 3450, 1740, 1705. NMR ($CDCl_3$) δ: 0.97 (3H, s, –Me), 1.10 (3H, s, –Me), 1.25 (3H, t, J=7 Hz, –Me), 2.77 (4H, s, 2×–CH_2–), 2.90 (2H, s, –CH_2–), 4.16 (2H, q, J=7 Hz, –OCH_2–), 4.65 (1H, s, –OH). MS (*m/e*): 242 (M^+). *Anal.* Calcd for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49. Found: C, 59.39; H, 7.50.

Ethyl 1-Acetoxy-4,4-dimethyl-2,6-dioxocyclohexylacetate (11b)——Dry AcONa (10 mg) was added to a solution of **11a** (50 mg) in Ac_2O (2 ml) and the whole was heated at 90 °C for 3 h. The reaction mixture was poured into ice-water and extracted with chloroform. The organic layer was washed with sat. $NaHCO_3$ and H_2O, then dried and concentrated. The residue was subjected to silica gel chromatography. The chloroform eluate gave 49 mg (84.5%) of **11b** as colorless crystals (ether–hexane), mp 50—51 °C. IR (film) cm^{-1}: 1760, 1740, 1720. NMR ($CDCl_3$) δ: 1.18 (6H, s, 2×–Me), 1.25 (3H, t, J=8 Hz, –Me), 2.17 (3H, s, –OCOMe), 2.73 (4H, m, 2×–CH_2–), 2.92 (2H, s, –CH_2–), 4.17 (2H, q, J=8 Hz, –OCH_2–). CI-MS (*m/e*): 285 (M^++1).

5-Ethoxycarbonylacetyl-3,3-dimethyl-5-pentanolide (12)——A solution of **11a** (50 mg) in conc. H_2SO_4 (1 ml) was stirred at room temperature for 2 h. The reaction mixture was poured into ice-water and extracted with chloroform. The organic layer was washed with H_2O, then dried and concentrated. The residue was subjected to silica gel chromatography. The chloroform eluate gave 14 mg (28%) of **12** as a colorless oil. IR (film) cm^{-1}: 1745, 1720. NMR ($CDCl_3$) δ: 1.10 (6H, s, 2×–Me), 1.26 (3H, t, J=7.4 Hz, –Me), 1.83 (2H, m, –CH_2–), 3.33 (2H, s, –CH_2–), 3.70 (2H, s, –CH_2–), 4.19 (2H, q, J=7.4 Hz, –OCH_2–), 4.85 (2H, dd, J=10.6, 6 Hz, –OCH<). MS (*m/e*), Calcd for $C_{12}H_{18}O_5$ (M^+): 242.1152. Found: 242.1132.

4-Acetoxy-2,6-dihydro-6,6-dimethyl-1-benzofuran-2-one (13) and Ethyl 2,6-Diacetoxy-4,4-dimethyl-2,5-cyclohexadienylideneacetate (14)——A catalytic amount of dry AcONa was added to a solution of **11a** (50 mg) in Ac_2O (5 ml) and the whole was heated at 115 °C for 12 h. The reaction mixture was poured into ice-water and extracted with chloroform. The organic layer was washed with sat. $NaHCO_3$, dil. HCl, and H_2O, then dried and concentrated. The residue was subjected to silica gel chromatography. The first chloroform eluate gave 11 mg (24.2%) of **13** as colorless crystals (ether–hexane), mp 100.5—102 °C. IR (KBr) cm^{-1}: 1770, 1635. NMR ($CDCl_3$) δ: 1.30 (6H, s, 2×–Me), 2.27 (3H, s, –OCOMe), 5.70, (1H, d, J=1.8 Hz, olefinic H), 5.83 (1H, t, J=1.8 Hz, olefinic H), 6.17 (1H, d, J=1.8 Hz, olefinic H). MS (*m/e*), Calcd for $C_{12}H_{12}O_4$ (M^+): 220.0735. Found: 220.0735. The second chloroform eluate gave 18 mg (28.3%) of **14** as a colorless oil. IR (film) cm^{-1}: 1780, 1725, 1630, 1605. NMR ($CDCl_3$) δ: 1.27 (6H, s, 2×–Me), 1.31 (3H, t, J=7.1 Hz, –Me), 2.15 (3H, s, –OCOMe), 2.24 (3H, s, –OCOMe), 4.20 (2H, q, J=7.1 Hz, –OCH_2–), 5.73 (3H, s, 3×olefinic H). MS (*m/e*), Calcd for $C_{16}H_{20}O_6$ (M^+): 308.1258. Found: 308.1230.

Ethyl 1,2β,6β-Trihydroxy-4,4-dimethylcyclohexylacetate (17a) and 2,3,3a,4,5,6,7,7aβ-Octahydro-3aβ,4β-dihydroxy-1-benzofuran-2-one (18a)——$NaBH_4$ (600 mg) was added to a solution of **11a** (1 g) in EtOH (20 ml) and the whole was stirred at 0 °C for 1 h. The reaction mixture was acidified with dil. HCl and extracted with chloroform. The organic layer was washed with sat. NaCl, then dried and concentrated. The residue was subjected to silica gel chromatography. The first chloroform eluate gave 97 mg (9.5%) of **17a** as colorless crystals (ether–hexane), mp 139—140 °C. IR (KBr) cm^{-1}: 3400, 3350, 1690. NMR ($CDCl_3$) δ: 0.93 (3H, s, –Me), 0.98 (3H, s, –Me), 1.25 (3H, t, J=7.5 Hz, –Me), 1.50 (4H, d, J=8.4 Hz, 2×–CH_2–), 2.16 (1H, m, –OH), 2.72 (2H, s, –CH_2–), 3.50 (1H, m, –OH), 3.53 (2H, t, J=8.4 Hz, 2×–OCH<), 4.19 (2H, q, J=7.5 Hz, –OCH_2–), 4.23 (1H, m, –OH), MS (*m/e*): 246 (M^+). *Anal.* Calcd for $C_{12}H_{22}O_5$: C, 58:51; H, 9.00. Found: C, 58.49; H, 9.09. The second chloroform eluate gave 292 mg (35.3%) of **18a** as colorless crystals (ether–hexane), mp 95—96 °C. IR (KBr) cm^{-1}: 3430, 1760. NMR ($CDCl_3$) δ: 1.00 (3H, s, –Me), 1.02 (3H, s, –Me), 1.50—1.73 (4H, m, 2×–CH_2–), 2.60 (1H, d, J=17 Hz, –HCH–), 2.91 (1H, d, J=17 Hz, –HCH–), 3.45 (2H, s, 2×–OH), 3.84 (1H, dd, J=8.8, 6.1 Hz, –OCH<), 4.56 (1H, t, J=4.4 Hz, –OCH<). MS (*m/e*): 200 (M^+). *Anal.* Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 60.13; H, 8.11.

Ethyl 2β,6β-Diacetoxy-1-hydroxy-4,4-dimethylcyclohexylacetate (17b)——Ac_2O (1.5 ml) was added to a solution of **17a** (50 mg) in dry pyridine (0.5 ml) and the whole was allowed to stand overnight at room temperature. The reaction mixture was poured into ice-water and then extracted with ether. The ether layer was washed with sat. $NaHCO_3$, dil. HCl, and H_2O, then dried and concentrated. The residue was recrystallized from ether–hexane to yield 49 mg (73.1%) of **17b** as colorless crystals, mp 91—92 °C. IR (KBr) cm^{-1}: 3450, 1730, 1715. NMR ($CDCl_3$) δ: 1.01 (3H, s, –Me), 1.09 (3H, s, –Me), 1.26 (3H, t, J=7 Hz, –Me), 1.67 (4H, m, 2×–CH_2–), 2.08 (6H, s, 2×–OCOMe), 2.55 (2H, s, –CH_2–), 4.00 (1H, m, –OH), 4.18 (2H, q, J=7 Hz, –OCH_2–), 4.90 (2H, dd, J=11, 5.3 Hz, 2×–OCH<). CI-MS (*m/e*): 331 (M^++1).

4β-Acetoxy-2,3,3a,4,5,6,7,7aβ-octahydro-3aβ-hydroxy-1-benzofuran-2-one (18b)——A 70% $HClO_4$ solution (0.12 ml) was added to a solution of **18a** (100 mg) in AcOH (5 ml) and the whole was heated at 50 °C for 2 h. The reaction mixture was poured into ice-water and then extracted with ether. The ether layer was washed with sat. $NaHCO_3$ and H_2O, then dried and concentrated. The residue was subjected to silica gel chromatography. The chloroform eluate gave 66 mg (54.6%) of **18b** as a colorless oil. IR (film) cm^{-1}: 3450, 1770, 1730. NMR ($CDCl_3$) δ: 1.03 (3H, s, –Me), 1.07 (3H, s, –Me), 1.59—1.76 (4H, m, 2×–CH_2–), 2.13 (3H, s, –OCOMe), 2.65 (1H, d, J=17.1 Hz, –HCH–), 2.75 (1H, d, J=17.1 Hz, –HCH–), 2.82 (1H, m, –OH), 4.52 (1H, t, J=4.9 Hz, –OCH 〉 94 (1H, dd, J=8.1, 6.6 Hz, –OCH<). MS (*m/e*), Calcd for $C_{12}H_{18}O_5$ (M^+): 242.1153. Found: 242.1183.

2,3,3a,4,5,6,7,7aβ-Octahydro-3aβ,4β-isopropylidenedioxy-4,4-dimethyl-1-benzofuran-2-one (19)——Anhydrous $CaCl_2$ (20 mg) and *p*-TsOH (10 mg) were added to a solution of **17a** (15.7 mg) in acetone (1 ml) and the whole was refluxed for 1 h. The resulting solid was removed by filtration. The filtrate was poured into water and extracted with chloroform. The organic layer was washed with sat. $NaHCO_3$, dil. HCl, and H_2O, then dried and concentrated. The residue was subjected to silica gel chromatography. The chloroform eluate gave 13 mg (69.2%) of **19** as colorless crystals (hexane), mp 75—77 °C. IR (nujol) cm^{-1}: 1785. NMR ($CDCl_3$) δ: 1.01 (3H, s, –Me), 1.36 (3H, s, –Me), 1.50 (3H, s, –Me), 1.89 (4H, m, 2×–CH_2–), 2.53 (1H, d, J=17.8 Hz, –HCH–), 2.74 (1H, d, J=17.8 Hz, –HCH–), 4.33 (1H, dd, J=4, 2 Hz, –OCH<), and 4.61 (1H, dd, J=11, 6 Hz, –OCH<). CI-MS (*m/e*): 241 (M^++1).

2,3,3a,4,5,6,7,7aβ-Octahydro-3aβ-hydroxy-6,6-dimethyl-1-benzofuran-2,4-dione (20)——A solution of **18a** (100 mg) in acetone (5 ml) was treated with 0.5 ml of Jones' reagent [obtained by adding 6 ml of H_2O to a mixture of CrO_3 (2.67 g) and conc. H_2SO_4 (2.3 ml)]. The mixture was allowed to stand at room temperature for 5 min, then poured into ice-water and extracted with chloroform. The organic layer was washed with sat. $NaHCO_3$ and H_2O, then dried and concentrated. The residue was recrystallized from ether–hexane to yield 35 mg (35.4%) of **20** as colorless crystals, mp 119—120.5 °C. IR (KBr) cm^{-1}: 3470, 1770, 1720. NMR ($CDCl_3$) δ: 0.90 (3H, s, –Me), 1.15 (3H, s, –Me), 1.47—3.10 (6H, m, 3×–CH_2–), 4.30 (1H, s, –OH), 4.68 (1H, dd, J=12, 7 Hz, –OCH<). MS (*m/e*), Calcd for $C_{10}H_{14}O_4$ (M^+): 198.0893. Found: 198.0896.

2,4,5,6,7,7aβ-Hexahydro-4β-hydroxy-6,6-dimethyl-1-benzofuran-2-one (3a)——DCC (110 mg) and CuCl (40 mg) were added to a solution of **18a** (47.8 mg) in anhydrous ether (3 ml) and the whole was heated overnight at 80 °C in a sealed tube. The resulting solid was removed by filtration. The filtrate was washed with dil. HCl and H_2O, then dried and concentrated. The residue was subjected to silica gel chromatography. The chloroform eluate gave 15.7 mg (36.1%) of **3a** as colorless crystals (ether–hexane), mp 73—74.5 °C. IR (nujol) cm^{-1}: 3410, 1735, 1642. NMR ($CDCl_3$) δ: 1.00 (3H, s, –Me), 1.30 (3H, s, –Me), 1.40—2.44 (4H, m, 2×–CH_2–), 4.97 (1H, dd, J=3.7, 2.4 Hz, –OCH<), 5.27 (1H, ddd, J=11.2, 6.1, 1.2 Hz, –OCH<), 5.85 (1H, d, J=1.5 Hz, olefinic H). MS (*m/e*), Calcd for $C_{10}H_{14}O_3$ (M^+): 182.0943. Found: 182.0964.

4β-Acetoxy-2,4,5,6,7,7aβ-hexahydro-6,6-dimethyl-1-benzofuran-2-one (3b)——Method A: $SOCl_2$ (0.06 ml) was added to a solution of **17b** (60 mg) in dry pyridine (0.5 ml) and the whole was stirred at 0 °C for 30 min. The reaction mixture was poured into ice-water and extracted with chloroform. The organic layer was washed with dil. HCl, sat. $NaHCO_3$, and H_2O, then dried and concentrated. The residue was subjected to silica gel chromatography. The chloroform eluate gave 18.8 mg (33.9%) of **3b** as a colorless oil. IR (film) cm^{-1}: 1750, 1650. NMR ($CDCl_3$) δ: 1.03 (3H, s, –Me), 1.22 (3H, s, –Me), 1.25—2.53 (4H, m, 2×–CH_2–), 2.07 (3H, s, –OCOMe), 5.13 (1H, ddd, J=12, 7, 1.8 Hz, –OCH<), 5.86 (1H, dd, J=4, 2 Hz, –OCH<), 5.98 (1H, d, J=1.8 Hz, olefinic H). MS (*m/e*), Calcd for $C_{12}H_{16}O_4$ (M^+): 224.1047. Found: 224.1040.

Method B: Ac_2O (1.5 ml) was added to a solution of **3a** (20 mg) in dry pyridine (0.5 ml) and the whole was allowed to stand overnight at room temperature. The reaction mixture was poured into ice-water and extracted with ether. The ether layer was washed with sat. $NaHCO_3$, dil. HCl, and H_2O, then dried and concentrated to yield 19 mg (77.2%) of **3b** as a colorless oil.

Ethyl 2-(6-Hydroxy-4,4-dimethyl-2-oxo-6-cyclohexenyl)propionate (21)——A solution of dimedone (1 g) in dry DMF (1 ml) was added to a mixture of NaH (340 mg) and dry DMF (13 ml) and the mixture was stirred at room temperature for 2 h. A solution of ethyl α-iodopropionate (1.9 g) in dry DMF (1 ml) was then added and the whole was stirred overnight at room temperature. The reaction mixture was poured into ice-water, made basic with 10% NaOH and washed with chloroform. The aqueous layer was acidified with conc. HCl and extracted with chloroform. The organic layer was washed with H_2O, then dried and concentrated. The residue was subjected to silica gel chromatography. The chloroform eluate gave 585 mg (34.1%) of **21** as colorless crystals (ether–hexane), mp 114—116 °C. IR (KBr) cm^{-1}: 1730, 1555. NMR ($CDCl_3$) δ: 1.05 (6H, s, 2×–Me), 1.25 (3H, d, J=8 Hz, –Me), 1.32 (3H, t, J=8 Hz, –Me), 2.30 (4H, s, 2×–CH_2–), 4.20 (2H, q, J=8 Hz, –OCH_2–). MS (*m/e*), Calcd for $C_{13}H_{20}O_4$ (M^+): 240.1361. Found: 240.1372.

Ethyl 2-(1-Hydroxy-4,4-dimethyl-2,6-dioxocyclohexyl)propionate (22)——A current of air was bubbled into a solution of **21** (100 mg) in chloroform (20 ml) for 2 d. The reaction mixture was dried and concentrated. The residue was recrystallized from ether–hexane to yield 94 mg (88.1%) of **22** as colorless crystals, mp 100—101 °C. IR (KBr) cm^{-1}: 3400, 1740, 1708. NMR ($CDCl_3$) δ: 0.83 (3H, s, –Me), 1.25 (3H, s, –Me), 1.17 (3H, d, J=7 Hz, –Me), 1.21 (3H, t, J=7 Hz, –Me), 1.50—3.55 (5H, m, 2×–CH_2– and CH<), 4.01 (1H, s, –OH), 4.17 (2H, q, J=7 Hz, –OCH_2–). MS (*m/e*), Calcd for $C_{13}H_{20}O_5$ (M^+): 236.1309. Found: 236.1309. *Anal.* Calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87. Found: C, 60.84; H, 7.94.

2,3,3a,4,5,6,7,7aβ-Octahydro-3aβ,4β-dihydroxy-3,6,6-trimethyl-1-benzofuran-2-one (23a) and 2,3,3a,4,5,6,7,7aβ-Octahydro-3aβ,4α-dihydroxy-3,6,6-trimethyl-1-benzofuran-2-one (24a)——$NaBH_4$ (50 mg) was added to a solution of **22** (100 mg) in EtOH (4 ml) and the whole was stirred at 0 °C for 1 h. The reaction mixture was acidified with dil. HCl and extracted with chloroform. The organic layer was washed with sat. NaCl, then dried and concentrated. The residue was subjected to silica gel chromatography. The first chloroform eluate gave 19 mg (22.9%) of **23a** as colorless crystals (ether–hexane), mp 84—86 °C. IR (KBr) cm^{-1}: 3420, 1745. NMR ($CDCl_3$) δ: 1.00 (3H, s, –Me), 1.06 (3H, s, –Me), 1.24 (3H, d, J=7.4 Hz, –Me), 1.39—1.82 (4H, m, 2×–CH_2–), 2.72 (1H, q, J=7.4 Hz, –CH<), 3.14 (2H, br,

2×–OH), 3.85 (1H, dd, J=8.4, 4.8 Hz, –OCH<), 4.55 (1H, t, J=5.5 Hz, –OCH<). *Anal.* Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.38; H, 8.70. The second chloroform eluate gave 35 mg (41.9%) of **24a** as colorless crystals (ether–hexane), mp 143—145 °C. IR (KBr) cm^{-1}: 3400, 3360, 1750. NMR ($CDCl_3$) δ: 1.03 (6H, s, 2×–Me), 1.33 (3H, d, J=7.1 Hz, –Me), 1.14—2.15 (4H, m, 2×–CH_2–), 1.90 (2H, br, 2×–OH), 2.85 (1H, q, J=7.1 Hz, –CH<), 4.13 (1H, dd, J=12.2, 5.1 Hz, –OCH<), 4.44 (1H, dd, J=11.1, 6.5 Hz, –OCH<). *Anal.* Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.72; H, 8.55.

4β-Acetoxy-2,3,3a,4,5,6,7,7aβ-octahydro-3aβ-hydroxy-3,6,6-trimethyl-1-benzofuran-2-one (23b)——Ac_2O (1.5 ml) was added to a solution of **23a** (200 mg) in dry pyridine (0.5 ml) and the whole was allowed to stand overnight at room temperature. The reaction mixture was poured into ice-water and then extracted with ether. The ether layer was washed with sat. $NaHCO_3$, dil. HCl, and H_2O, then dried and concentrated. The residue was subjected to silica gel chromatography. The chloroform eluate gave 220 mg (92.1%) of **23b** as a colorless oil. IR (film) cm^{-1}: 3460, 1765, 1740. NMR ($CDCl_3$) δ: 1.03 (3H, s, –Me), 1.05 (3H, s, –Me), 1.18 (3H, d, J=7 Hz, –Me), 1.40—1.97 (4H, m, 2×–CH_2–), 2.12 (3H, s, –OCOMe), 2.59 (1H, q, J=7 Hz, –CH<), 2.73 (1H, m, –OH), 4.52 (1H, dd, J=7.6, 5.8 Hz, –OCH<), 5.01 (1H, dd, J=6, 4 Hz, –OCH<). MS (m/e), Calcd for $C_{13}H_{20}O_5$ (M^+): 256.1311. Found: 256.1319.

4α-Acetoxy-2,3,3a,4,5,6,7,7aβ-octahydro-3aβ-hydroxy-3,6,6-trimethyl-1-benzofuran-2-one (24b)——**24a** (200 mg) was added to a solution of 70% $HClO_4$ (0.12 ml) in AcOH (5 ml) and the whole was heated at 50 °C for 2 h. The reaction mixture was poured into ice-water and then extracted with ether. The ether layer was washed with sat. $NaHCO_3$ and H_2O, then dried and concentrated. The residue was recrystallized from ether–hexane to yield 170 mg (83.6%) of **24b** as colorless crystals, mp 165—166 °C. IR (KBr) cm^{-1}: 3400, 1745, 1739, 1723. NMR ($CDCl_3$) δ: 1.10 (6H, s, 2×–Me), 1.32 (3H, d, J=7 Hz, –Me), 1.30—2.00 (4H, m, 2×–CH_2–), 2.17 (3H, s, –Me), 2.83 (1H, q, J=7 Hz, –CH<), 3.75 (1H, s, –OH), 4.52 (1H, dd, J=11.2, 7 Hz, –OCH<), 5.24 (1H, dd, J=11.4, 7 Hz, –OCH<). MS (m/e), Calcd for $C_{13}H_{20}O_5$ (M^+): 256.1309. Found: 256.1294.

2,3,3a,4,5,6,7,7aβ-Octahydro-3aβ,4β-isopropylidenedioxy-3,6,6-trimethyl-1-benzofuran-2-one (25)——*p*-TsOH (10 mg) was added to a solution of **23a** (50 mg) in acetone (1 ml) and the whole was refluxed for 2 h. The reaction mixture was poured into water and extracted with ether. The ether layer was washed with sat. $NaHCO_3$ and H_2O, then dried and concentrated. The residue was recrystallized from ether–hexane to yield 45 mg (75.8%) of **25** as colorless crystals, mp 135—137 °C. IR (KBr) cm^{-1}: 1783. NMR ($CDCl_3$) δ: 1.02 (3H, s, –Me), 1.17 (3H, s, –Me), 1.27 (3H, d, J=7 Hz, –Me), 1.33 (3H, s, –Me), 1.52 (3H, s, –Me), 1.53—2.22 (4H, m, 2×–CH_2–), 2.53 (1H, q, J=7 Hz, –CH<), 4.22 (1H, dd, J=4, 2 Hz, –OCH<), 4.54 (1H, dd, J=12.2, 6.2 Hz, –CH<). CI-MS (m/e): 255 (M^++1).

2,3,3a,4,5,6,7,7aβ-Octahydro-3aβ-hydroxy-3,6,6-trimethyl-1-benzofuran-2,4-dione (26)——Jones' reagent (0.1 ml) was added to a solution of **24a** (50 mg) in acetone (1 ml) and the whole was stirred at 0 °C for 4 min. The reaction mixture was poured into H_2O and extracted with chloroform. The organic layer was washed with sat. $NaHCO_3$ and H_2O, then dried and concentrated. The residue was recrystallized from ether–hexane to yield 32 mg (64.6%) of **26** as colorless crystals, mp 138—138.5 °C. IR ($CHCl_3$) cm^{-1}: 1780, 1715. NMR ($CDCl_3$) δ: 0.90 (3H, s, –Me), 1.06 (3H, d, J=7 Hz, –Me), 1.13 (3H, s, –Me), 1.12—2.53 (4H, m, 2×–CH_2–), 2.82 (1H, q, J=7 Hz, –CH<), 3.98 (1H, s, –OH), 4.55 (1H, dd, J=11, 7 Hz, –OCH<). MS (m/e), Calcd for $C_{11}H_{16}O_4$ (M^+): 212.1049. Found: 212.1049.

Preparation of 23a and 24a from 26——$NaBH_4$ (5.7 mg) was added to a solution of **26** (50 mg) in EtOH (1 ml) and the whole was stirred at 0 °C for 1 h. The reaction mixture was poured into ice-water and extracted with chloroform. The organic layer was washed with sat. NaCl, dried and concentrated. The residue was subjected to silica gel chromatography. The first chloroform eluate gave 23 mg (45.6%) of **23a** as colorless crystals (ether–hexane). The second chloroform eluate gave a trace of **24a** as colorless crystals (ether–hexane).

4β-Acetoxy-2,4,5,6,7,7aβ-hexahydro-3,6,6-trimethyl-1-benzofuran-2-one (4b)——$SOCl_2$ (0.16 ml) was added to a solution of **23b** (200 mg) in dry pyridine (1.3 ml) at 0 °C and the whole was stirred at room temperature for 30 min. The reaction mixture was poured into ice-water and extracted with ether. The ether layer was washed with dil. HCl, sat. $NaHCO_3$, and H_2O, then dried and concentrated. The residue was subjected to silica gel chromatography. The chloroform eluate gave 120 mg (64.5%) of **4b** as a colorless oil. IR (film) cm^{-1}: 1760, 1750. NMR ($CDCl_3$) δ: 1.02 (3H, s, –Me), 1.24 (3H, s, –Me), 1.37 (2H, m, –CH_2–), 2.14 (2H, m, –CH_2–), 1.93 (3H, d, J=1.7 Hz, –Me), 2.07 (3H, s, –Me), 5.02 (1H, ddd, J=11.8, 5.9, 1.8 Hz, –OCH<), 5.83 (1H, dd, J=4.2, 2.2 Hz, –OCH<). MS (m/e), Calcd for $C_{13}H_{18}O_4$ (M^+): 238.1203. Found: 238.1192.

2,4,5,6,7,7aβ-Hexahydro-4β-hydroxy-3,6,6-trimethyl-1-benzofuran-2-one (4a)——Conc. HCl (2 ml) was added to a solution of **4b** (110 mg) in MeOH (10 ml) and the whole was refluxed for 3 h. The reaction mixture was poured into H_2O and extracted with ether. The ether layer was washed with H_2O, then dried and concentrated. The residue was subjected to silica gel chromatography. The chloroform eluate gave 55 mg (60.7%) of **4a** as colorless crystals (ether–hexane), mp 106—108 °C. IR ($CHCl_3$) cm^{-1}: 3450, 1750, 1690. NMR ($CDCl_3$) δ: 0.98 (3H, s, –Me), 1.28 (3H, s, –Me), 1.48—2.52 (4H, m, 2×–CH_2–), 1.82 (3H, d, J=1.8 Hz, –Me), 3.13 (1H, m, –OH), 4.96, (1H, dd, J=4.2, 2 Hz, –OCH<), 5.16 (1H, br, –OCH<). MS (m/e), Calcd for $C_{11}H_{16}O_3$ (M^+): 196.1100. Found: 196.1105. *Anal.* Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.31; H, 8.36.

4α-Acetoxy-2,4,5,6,7,7aβ-hexahydro-3,6,6-trimethyl-1-benzofuran-2-one (5b)——$SOCl_2$ (0.12 ml) was added to a solution of **24b** (150 mg) in dry pyridine (1 ml) at 0 °C and the whole was stirred at room temperature for 30 min.

The reaction mixture was poured into ice-water and extracted with ether. The ether layer was washed with dil. HCl, sat. $NaHCO_3$, and H_2O, then dried and concentrated to yield 120 mg (86.1%) of **5b** as a colorless oil. IR (film) cm^{-1}: 1755, 1740, 1690. NMR ($CDCl_3$) δ: 1.07 (3H, s, –Me), 1.13 (3H, s, –Me), 1.39 (2H, m, $-CH_2-$), 1.92 (3H, t, $J=1.5$ Hz, –Me), 2.07 (2H, m, $-CH_2-$), 2.17 (3H, s, –Me), 4.80 (1H, ddd, $J=11.4$, 6.4, 1.5 Hz, –OCH<), 5.79 (1H, ddd, $J=11.5$, 5.6, 1.5 Hz, –OCH<). MS (*m/e*), Calcd for $C_{13}H_{18}O_4$ (M^+): 238.1203. Found: 238.1183. This product **5b** was used in the next step without further purification.

2,4,5,6,7,7aβ-Hexahydro-4α-hydroxy-3,6,6-trimethyl-1-benzofuran-2-one (5a)——Conc. HCl (5 ml) was added to a solution of **5b** (750 mg) in MeOH (25 ml) and the whole was refluxed overnight. The reaction mixture was poured into H_2O and extracted with ether. The ether layer was washed with sat. $NaHCO_3$ and H_2O, then dried and concentrated. The residue was recrystallized from ether–hexane to yield 400 mg (64.8%) of **5a** as colorless crystals, mp 114—114.5 °C. IR (KBr) cm^{-1}: 3380, 1730, 1680. NMR ($CDCl_3$) δ: 1.02 (6H, s, 2×–Me), 1.40—2.60 (4H, br, 2×$-CH_2-$), 2.03 (3H, t, $J=1.8$ Hz, –Me), 4.75 (2H, br, 2×–OCH<). MS (*m/e*), Calcd for $C_{11}H_{16}O_3$ (M^+): 196.1100. Found: 196.1103. *Anal.* Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.23; H, 8.36.

References and Notes

1) S. Tobinaga, N. Takeuchi, T. Kasama, J. Yamashita, Y. Aida, and Y. Kaneko, *Chem. Pharm. Bull.*, **31**, 745 (1983).
2) G. Schlewer, J-L. Stampf, and C. Benezra, *J. Med. Chem.*, **23**, 1031 (1980), and references cited therein.
3) K. Yamakawa and T. Satoh, *J. Synth. Org. Chem. Jpn.*, **38**, 783 (1980).
4) Z. Ovary, *J. Immunol.*, **71**, 6 (1953).
5) Z. Ovary, S. S. Caiagza, and S. Kojima, *Int. Arch. Allergy Appl. Immunol.*, **48**, 16 (1975).
6) H. Fujimura, K. Turumi, M. Yanagihara, Y. Hiramatsu, Y. Tamura, Y. Shimizu, M. Hojyo, and Y. Yoshida, *Folia Pharmacol. Jpn.*, **78**, 291 (1981).
7) K. Ishizaka, T. Ishizaka, and M. M. Nornbrook, *J. Immunol.*, **97**, 75 (1966).
8) K. Ishizaka and T. Ishizaka, *J. Immunol.*, **99**, 1187 (1967).
9) A. Koda, *Allergy*, **17**, 767 (1968).
10) J. Augstein, J. B. Farmer, T. B. Lee, P. Sheard, and M. L. Tattersall, *Nature New Biology*, **245**, 215 (1973).