Studies on Synthesis and Stereochemistry of 3-Methyloctahydroisocoumarins and 1-Methyloctahydro-3*H*-2-benzopyran-3-ones

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Four stereoisomers of 3-methyloctahydroisocoumarins (4a—d) and two 1-methyloctahydro-3*H*-2-benzopyran-3-ones (10a, b) were synthesized. The stereochemical correlations including the configurations of the ring juncture and the methyl group and also the ring conformations of these six lactones were investigated by chemical means and by nuclear magnetic resonance (NMR) spectrometry, such as two-dimensional(2D) NMR and steady-state ^1H–^1H nuclear Overhauser effect experiments. It was concluded that the lactone ring of 4b, c, and 10a adopts a boat or a slightly distorted boat conformation in solution.

Keywords 3-methyloctahydroisocoumarin; 1-methyloctahydro-3*H*-2-benzopyran-3-one; synthesis; stereochemistry; configuration; ring conformation; 2D INADEQUATE; ^{13}C/^1H COSY; ^1H–^1H NOE

Perhydroisocoumarin derivatives such as the antibiotic actinobolin,[2] the antitumor agent bactobolin,[3] ramulosin[4] and hydroxyramulosin,[5] and perhydro-2-benzopyran-3-one derivatives such as *dl*-pyroangolensolide and their synthetic intermediates[6] have been studied. The structures of their isocoumarin and perhydro-2-benzopyran-3-one derivatives are interesting from the viewpoint of stereochemistry, such as the substituent configurations and ring conformations. For this reason, the present work has been undertaken to study the synthesis and stereochemistry of isomeric 3-methyloctahydroisocoumarins (3-methyloctahydro-1*H*-2-benzopyran-1-ones) and 1-methyl-octahydro-3*H*-2-benzopyran-3-ones.

In the preceding paper,[1] the stereochemistry of four isomeric 3-methylhexahydrophthalides was elucidated by means of proton nuclear magnetic resonance (^1H-NMR) and mass spectroscopy. In this paper, we report the synthesis of 3-methyloctahydro-1*H*-2-benzopyran-1-ones (**4a**—**d**) and 1-methyloctahydro-3*H*-2-benzopyran-3-ones (**10a**, **b**). The stereochemistries of these lactones were studied by means of one- and two-dimensional (1D and 2D[7]) NMR spectroscopy.

Synthesis The synthetic schemes are shown in Charts 1 and 2. The sterically important key intermediate, methyl *cis*-2-(2-oxopropyl)cyclohexane-1-carboxylate (**3**), was prepared by hydrogenation of methyl 2-carboxymethylbenzoate[8] (**1**) under a moderate pressure of hydrogen over platinum oxide as a catalyst in acetic acid (AcOH)

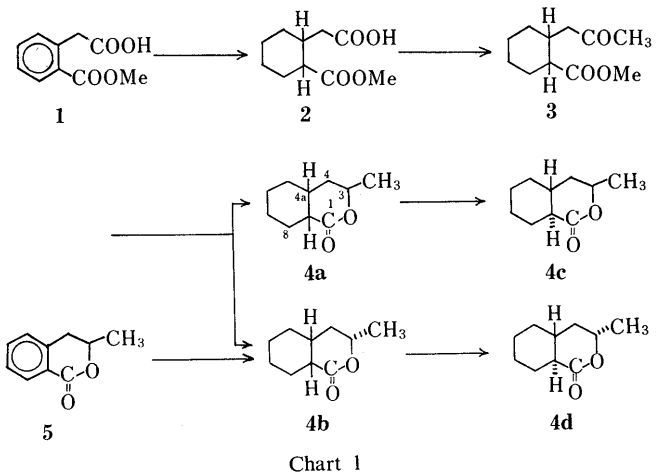

Chart 1

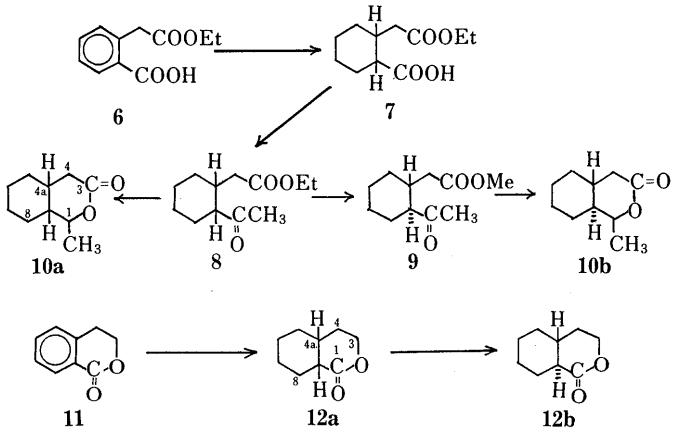

Chart 2

and resulting methyl *cis*-2-carboxymethylcyclohexane-1-carboxylate (**2**) was chlorinated with oxalyl chloride ($(COCl)_2$), followed by treatment with diazomethane (CH_2N_2) and with 57% aqueous hydroiodic acid (HI) to provide **3** as a colorless oil, bp 109 °C/3.5 mmHg, in 77% overall yield.

Reduction of **3** with sodium borohydride ($NaBH_4$) in methanol (MeOH) afforded a mixture of two stereoisomers of 3-methyl-*cis*-octahydro-1*H*-2-benzopyran-1-one in the ratio of **4a**:**4b**=3:4. Separation of the mixture was achieved by use of the difference of the rate of lactone-ring opening between **4a** and **4b** in aqueous 10% sodium carbonate (Na_2CO_3) solution (see Experimental). Consequently, both **4a**[9] and **4b** were obtained as crystalline solids.

Crystalline **4b** was also obtained by catalytic hydrogenation of 3-methyl-3,4-dihydro-1*H*-2-benzopyran-1-one[10] (**5**).

In order to obtain the *trans* ring-fused isomers **4c** and **4d**, inversion reaction with base or acid was carried out. Thus, each of the *cis* lactones **4a** and **4b** was heated under reflux with 10% sodium hydroxide (NaOH) solution or 37% hydrochloric acid (HCl)-ethanol (EtOH) (1:1) to be converted to the corresponding 3-methyl-*trans*-octahydro-1*H*-2-benzopyran-1-one (**4c** or **4d**) with concomitant inversion of the configuration at C(8a). Purification of the *trans* isomer **4c** was effected by converting it into the hydrazide. The lactone **4c** was regenerated in the pure state on hydrolysis of the hydrazide with concentrated HCl. The *trans* lactone **4d** crystallized and so **4d** was purified by

TABLE I. Physical and Spectral Data for 3-Methyloctahydro-1*H*-2-benzopyran-1-ones (**4a—d**), 3-Methyloctahydro-3*H*-2-benzopyran-3-ones (**10a, b**), and Octahydro-1*H*-2-benzopyran-1-ones (**12a, b**)

Compd. No.	bp (°C/mmHg) (mg (°C))	IR ($CHCl_3$) cm^{-1} CO	Formula	Analysis[a] Calcd	Found	MS (*m/z*)
4a (Hydrazide mp 99—100)	— (72)	1715	$C_{10}H_{16}O_2$	168.1151	168.1158	67, 82,[c] 95, 126, 168 (M^+)
4b (Hydrazide mp 129—131)	115/4 (32.5)	1730	$C_{10}H_{16}O_2$	168.1151	168.1175	67, 82,[c] 113, 126, 168 (M^+)
4c (Hydrazide mp 138—139)	135—140[b]/3 (—)	1730	$C_{10}H_{16}O_2$	168.1151	168.1138	67, 82,[c] 95, 124, 168 (M^+)
4d (Hydrazide mp —)	108/3.5 (44—45)	1720	$C_{10}H_{16}O_2$	168.1151	168.1158	67, 82,[c] 95, 124, 168 (M^+)
10a (Hydrazide mp 102—103.5)	125/5 (—)	1715	$C_{10}H_{16}O_2$	168.1151	168.1123	67, 82,[c] 124, 168 (M^+)
10b (Hydrazide mp 137—138)	120/4.5 (—)	1715	$C_{10}H_{16}O_2$	168.1151	168.1140	67, 82,[c] 124, 168 (M^+)
12a (Hydrazide mp 109—110)	118/4.5 (—)	1730	$C_9H_{14}O_2$	154.0994	154.0991	67, 81,[c] 112, 126, 154 (M^+)
12b (Hydrazide mp 123—124)	105/3 (48)	1730	$C_9H_{14}O_2$	154.0994	154.0987	67, 81,[c] 95, 126, 154 (M^+)

a) Determined by high-resolution MS for M^+ (*m/z*). *b*) Bath temperature. *c*) Base peak.

recrystallization (see Experimental).

The lactone formation for **4a—d**, and **10a, b** and **12a, b** (see below) was confirmed by the absence of characteristic COOH and OH absorptions in the infrared (IR) absorption spectra.

As shown in Chart 2, for the synthesis of the 1-methyloctahydro-3*H*-2-benzopyran-3-ones (**10a, b**), the same procedures were applied as described above and elsewhere.[1] Thus, starting from 2-ethoxycarbonylmethylbenzoic acid[11] (**6**) *via* *cis*-2-ethoxycarbonylmethylcyclohexane-1-carboxylic acid (**7**), the acid chloride, and the diazo ketone, the corresponding *cis* methyl ketone **8**, bp 105 °C/5 mmHg was prepared in 53% overall yield. By means of isomerization reaction with base the ketone **8** was readily converted to the *trans* isomer **9**, bp 96 °C/3 mmHg.

Reduction of each of these ketones (**8** and **9**) with $NaBH_4$ in MeOH gave only one lactone isomer in each case; the *cis*- and *trans*-ketone (**8** and **9**) were converted to 1-methyl-*cis*-octahydro-3*H*-2-benzopyran-3-one (**10a**) and the *trans* isomer **10b**, respectively.

The *cis*- and *trans*-octahydro-1*H*-2-benzopyran-1-one (**12a** and **12b**) were also synthesized for comparison of the (^{13}C-NMR) chemical shifts with those of **4a—d**. Thus, **12a** was prepared by catalytic hydrogenation of 3,4-dihydro-1*H*-2-benzopyran-1-one[12] (**11**) and isomerization of **12a** with base gave **12b** (Chart 2). Purification of **12a** and **12b** was effected by converting them into the hydrazides.

The physical, IR absorption, and mass spectral data for these lactones, (**4a—d**, **10a, b**, and **12a, b**) are listed in Table I.

Stereochemistry of Methyloctahydrobenzopyranones (4a—d and 10a, b) by NMR Spectrometry The stereochemistry of these lactones has been studied by measuring ^1H–^1H spin-coupling constants and steady-state ^1H–^1H nuclear Overhauser effects (NOEs) among the protons in the lactones, since vicinal ^1H–^1H spin-coupling constants can give information on dihedral angle between the protons[13] and intramolecular NOE[14] can give information on the conformation and configuration of molecules in solution. In order to apply the parameters of the coupling constants and NOEs between protons to stereochemical analyses, it is essential to determine unambiguous assignments of the objective proton resonances. For this reason, we also performed 2D ^{13}C–^{13}C double quantum spectroscopy[7,15] [2D INADEQUATE (incredible natural abundance double quantum transfer experiment)], ^1H–^1H coupled ^{13}C–^1H heteronuclear chemical shift correlation spectroscopy[7,16] (C/H COSY), and ^1H-decoupled ^1H-NMR (^1H–{^1H} NMR) experiments.

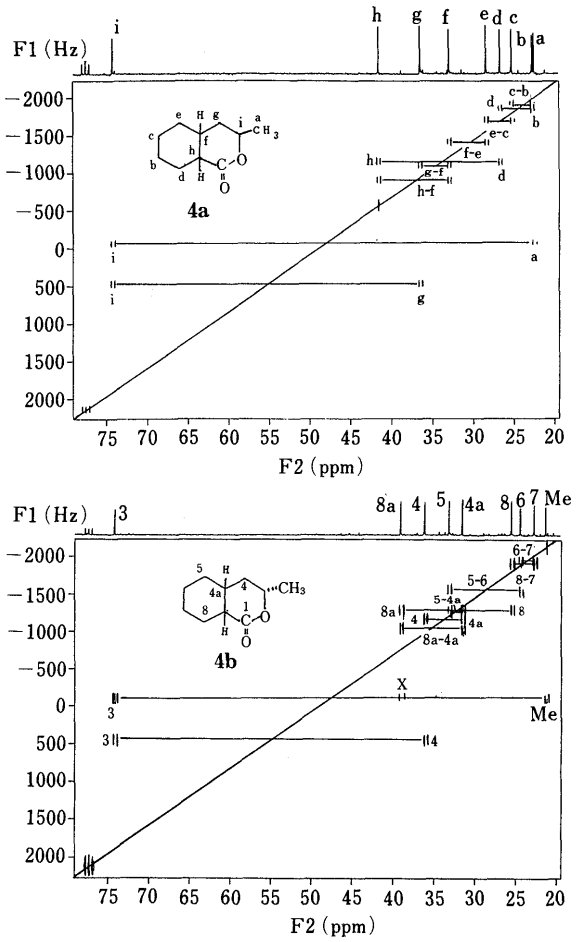

Fig. 1. 2D INADEQUATE Spectra of **4a** and **4b** in $CDCl_3$

X) Folded peaks (see reference 15*b*)). Measurement conditions were as follows: sample solution, 190 mg/0.5 ml (**4a**) or 120 mg/0.5 ml (**4b**); proton broad-band decoupled; spectral width (both dimensions), 4500 Hz; collecting experiments (t_1), 64 (**4a**) or 45 (**4b**); collecting data points, 64 × 4k (**4a**) or 45 × 2k (**4b**); timing of the pulse sequence[15a] (tau), 6.58 ms; preparation delay, 5 s; dummy cycles at the beginning of each phase cycling block, 4; accumulations of each collecting, 640 (**4a**) or 960 (**4b**); exponential line broadening as weighting function, 40 Hz (t_1) and 3 Hz (t_2); real data points, 128 × 1 k.

Assignments of ^{13}C and ^1H Resonances Figure 1 shows the 2D INADEQUATE spectra of **4a** and **4b**. The horizontal (same double quantum frequency) line between a pair of doublets in the contour map indicates a directly coupled

TABLE II. Assigned ^{13}C Signals[a] (δ) for Octahydrobenzopyranones in $CDCl_3$ by 2D INADEQUATE

Carbon[b]	Compound No.							
	12a	**12b**	**4a**	**4b**	**4c**	**4d**	**10a**	**10b**
1	174.66	173.87	173.67	175.28	175.43	173.34	77.71	79.58
3	66.84	67.89	74.22	74.09	72.61	77.35	171.50	171.15
4	28.26	29.79	36.56	36.03	36.21	38.54	34.60	37.04
4a	31.99	36.42	32.99	31.51	34.37	37.25	30.82	30.05
5	31.28	33.65	28.47	33.05	34.54	33.01	28.63	33.34
6	24.63	25.43	25.26	24.29	25.70	25.32	23.58	25.25
7	22.59	25.85	22.74	22.63	25.49	26.15	21.98	25.85
8	25.85	26.86	26.73	25.44	26.71	26.99	26.56	27.70
8a	40.35	45.32	41.62	39.01	43.05	46.19	38.49	41.26
Me			22.54	21.24	21.13	22.33	20.77	16.91

a) Given in ppm relative to internal $^{13}CH_3Si(CH_3)_3$, ± 0.015 ppm. *b*) Numbering as shown in Charts 1 and 2.

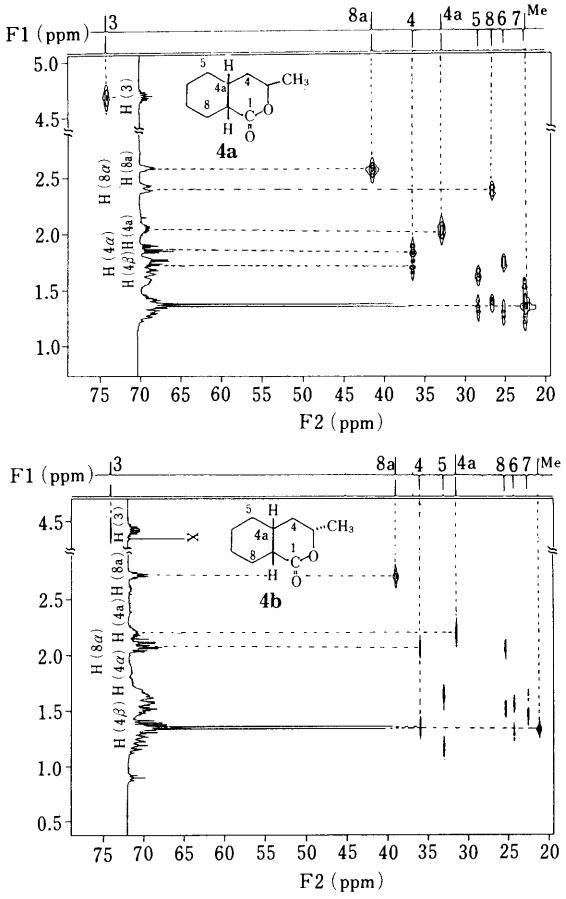

Fig. 2. C/H COSY Spectra of **4a** and **4b** in $CDCl_3$

DEPT Spectra are shown at the top at theta = 90 (under) and 135 (upper).[17] Measurement conditions of the C/H COSY spectra were as follows: sample solution, 60 mg/0.6 ml (**4a**) or 50 mg/0.6 ml (**4b**); spectral width (dimension), 1300 Hz (F_1) and 4500 Hz (F_2) collecting experiments (t_1), 128; collecting data points, 128 × 1 k; preparation delay, 1.5 s; accumulations of each collecting, 32 (**4a**) or 48 (**4b**); exponential line broadening as weighting function, 2 Hz (t_2); real data points, 256 × 1 k.

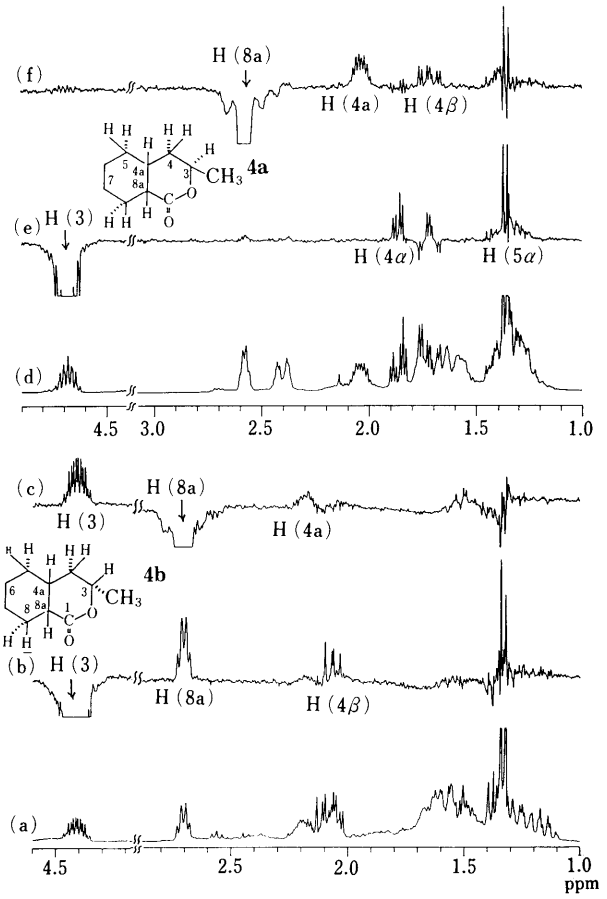

Fig. 3. NOE Difference Spectra of **4a** and **4b** in $CDCl_3$

(a), (d) Off-resonance gated irradiation spectra (control) of **4b** and **4a**, respectively; (b), (c) (**4b**) and (e), (f) (**4a**) NOE difference spectra between on-(shown by arrow) and off-resonance saturated. Saturation and acquisition times were 5 and 3 s. Decoupling power ($\gamma H_2/2\pi$) was 4.0 Hz.

^{13}C–^{13}C pair.[15b,c] Accordingly, the INADEQUATE spectrum of **4a** shows that the carbon labeled i is connected with those labeled g and a, and h with f and d. The connectivity of the carbon labeled h with carbonyl carbon was also determined by 2D INADEQUATE (not shown). Thus, the carbon skeleton of **4a** is as shown in Fig. 1. The chemical shift (δ 74.22) and DEPT[17] (distortionless enhancement by polarization transfer) data (the spectra are shown at the top in Fig. 2) of the carbon labeled i in **4a** are not in conflict with the connection of that i with an oxygen atom. Consequently, the complete connectivity of the full skeleton of **4a** can be deduced. The INADEQUATE spectrum of **4b** was analyzed similarly and the result is shown in Fig. 1. All the ^{13}C assignments for **4a** and **4b** are straightforward, based on the spectra in Fig. 1. The assignments of the ^{13}C resonances of the other lactones (**4c—d**, **10a, b**, and **12a, b**) were also determined by 2D INADEQUATE and are listed

TABLE III. Assigned ^{1}H Signals[a] (δ) and Observed ^{1}H–^{1}H Spin-Coupling Constants[b] (Hz) for Methyloctahydrobenzopyranones in $CDCl_3$

Proton[c] No.	Compound No.					
	4a	**4b**	**4c**	**4d**	**10a**	**10b**
1					4.58 (dq) (7.0, 6.5)	4.58 (dq) (4.7, 6.8)
3	4.68 (ddq) (4.2, 11.3, 6.3)	4.42 (ddq) (3.5, 11.0, 6.2)	4.51 (ddq) (5.0, 10.0, 6.3)	4.47 (ddq) (11.5, 3.5, 6.3)		
4α	1.85 (ddd) (4.1, 4.2, 14.0)	1.35 (ddd) (11.0, 6.5, 14.0)	1.56 (ddd) (5.0, 7.0, 14.0)	1.38 (d, t-like) (13.5, 11.5)	2.43 (dd) (5.6, 18.0)	2.08 (dd) (10.6, 18.2)
4β	1.72 (ddd) (4.0, 11.3, 14.0)	2.07 (ddd) (3.5, 8.5, 14.0)	1.85 (ddd) (10.0, 4.5, 14.0)	1.86 (ddd) (13.5, 3.0, 3.5)	2.56 (dd) (7.0, 18.0)	2.66 (dd) (5.5, 18.2)
4a	2.03 (dddd) (4.0, 4.1, 4.3, 11.5)	2.20 (dddd) (6.5, 8.5, 5.0, 11.0)	1.61 (ddm) (7.0, 4.5)	1.61 (t-, q-like) (3.0, 11.5)	2.14 (dddd) (10.5, 7.0, 5.6, 4.5)	1.78 (m)
5α	1.33 (m)	1.16 (ddt) (12.5, 3.0, 11.0)	1.21 (dd, t-like) (12.5, 3.5, 11.0)	1.06 (dd, t-like) (12.5, 3.0, 11.5)	1.43 (m)	0.99 (dd, t-like) (13.0, 3.5, 11.0)
5β	1.65 (d[d]) (18[d])	1.65 (m)	1.88 (d[d]) (15[d])	1.81 (m)	1.60 (m)	1.84 (m)
6α	1.75 (d[d]) (18[d])	1.59 (m)	1.77 (m)	1.76 (m)	1.63 (m)	1.77 (m)
6β	1.30 (m)	1.27 (m)	1.27 (m)	1.27 (m)	1.44 (m)	1.24 (m)
7α	1.26 (m)	1.47 (m)	1.27 (m)	1.27 (m)	1.45 (m)	1.32 (m)
7β	1.57 (m)	1.65 (m)	1.84 (m)	1.86 (m)	1.66 (m)	1.84 (dm) (13.0)
8α	2.40 (dd, t-like) (13.3, 4.3, 3.5)	2.08 (m)	2.15 (dd, t-like) (12.5, 1.4,[e] 3.5)	2.34 (d, q-like) (12.5, 3.3)	1.65 (m)	1.65 (dm) (12.5)
8β	1.40 (m)	1.56 (m)	1.31 (m)	1.24 (m)	1.57 (m)	1.04 (dd, t-like) (12.5, 3.0, 11.5)
8a	2.58 (q-like) (4.3)	2.71 (d, t-like) (5.0, 4.5)	2.08 (d, t-like) (3.5, 11.3)	1.85 (t-like[d]) (15[d])	1.74 (d, q-like) (7.2, 4.5)	1.67 (t[d]) (15[d])
Me	1.35 (d) (6,3)	1.34 (d) (6.2)	1.35 (d) (6.3)	1.36 (d) (6.3)	1.39 (d) (6.5)	1.29 (d) (6.8)

a) In ppm relative to internal TMS, ±0.01 ppm. *b*) ±0.25 Hz. *c*) Numbering as shown in Charts 1 and 2. *d*) Obtained from the F1 dimension slice plot spectra of C/H COSY, ±5 Hz. *e*) W-coupling. Proton assignments were obtained from C/H COSY spectra and the configurations (α or β) were determined by consideration of the vicinal coupling constants and the NOE data.

in Table II together with those of **4a** and **4b**.

The proton resonances in these lactones (**4a—d** and **10a, b**) were assigned by C/H COSY experiments. The C/H COSY spectra of **4a** and **4b** are shown in Fig. 2. Since correlation signals between ^{1}H and ^{13}C were observed to all proton resonances in the spectra, all the proton resonances in **4a** and **4b** were readily assignable in the ^{1}H dimension to already assigned carbon peaks. The relative configuration (α or β and axial or equatorial) of the ring protons was assigned by considering the vicinal coupling constants which were obtained from ordinary ^{1}H–{^{1}H} NMR spectra or the F1 (^{1}H frequency dimension) slice plot spectra (not shown) to the proton-bearing carbon in C/H COSY, and by considering the results of NOE experiments which will be described later.

Assigned ^{1}H data of these six lactones (**4a—d** and **10a, b**) are listed in Table III.

Stereostructural Determination of 4a—d Methyl configuration and ring conformations of the lactones in solution have been determined by applying the Karplus rule[13] to the magnitude of vicinal coupling constant(s) of these molecules and by considering the results of ^{1}H–^{1}H NOE experiments. The NOE experiments on these lactones (**4a—d** and **10a, b**) were performed at ordinary temperature in chloroform-d_1 ($CDCl_3$) solutions. NOE difference spectra of **4a** and **4b** are shown in Fig. 3. NOE values (%) and vicinal coupling constants of these six lactones employed for stereochemical analyses are shown in Fig. 4.

As shown in Fig. 3, irradiation at the resonance due to

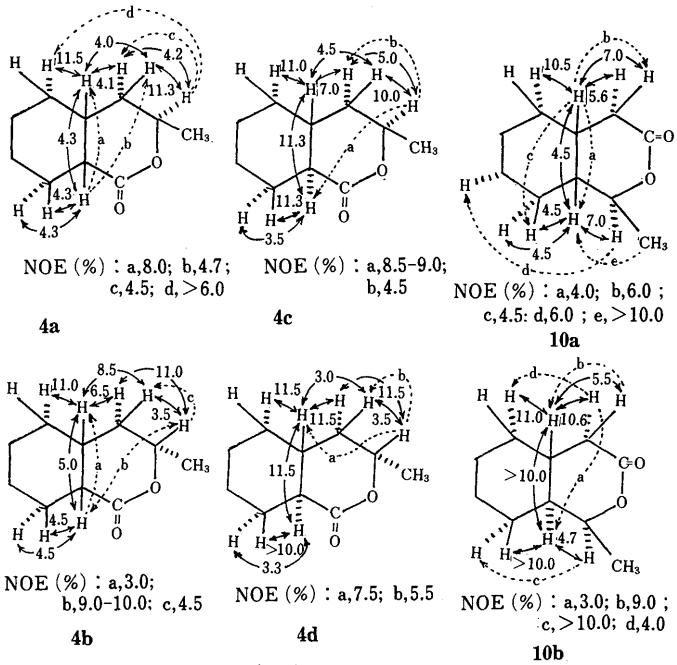

Fig. 4. Observed Vicinal ^{1}H–^{1}H Spin-Coupling Constants (Hz) and NOE Values (%) in Methyloctahydrobenzopyranones

Numbering is shown in Charts 1 and 2. The full lines denote the spin-couplings between protons. Average error of coupling constants, ±0.25 Hz. The dotted lines denote NOEs between protons. Decoupling power ($\gamma H_2/2\pi$) used for NOE experiments, 3.0—4.5 Hz.

H(8a) of **4a** produced NOEs for H(4a) and the proton resonance at δ 1.72 (H(4) or H(6β)) (Fig. 3f). *A priori*, one

might expect that this enhanced signal at δ 1.72 represents an NOE between H(8a) and H(4). However, the coupling pattern of the enhanced signal at δ 1.72 in the difference spectrum clearly shows that it should be assigned to one of H(4) and not to H(6β). In contrast, irradiation at the H(3) resonance produced NOEs for H(4) at δ 1.85, and H(5) at δ 1.34. These results indicate that H(8a), H(4) at δ 1.72 and H(4a) of the lactone ring take a similar arrangement and that it should be β-configuration. On the other hand, H(3), H(4) at δ 1.82 and H(5) at δ 1.34 take α-configuration. Consequently, the methyl group at C(3) takes a β-configuration. On the basis of the NOE between H(3) and H(5α), and of the vicinal coupling constants ($J_{H(4a)-H(5\alpha)}$ = 11.5 Hz, $J_{H(8a)-H(8\alpha \text{ and } 8\beta)}$ = both 4.3 Hz, and $J_{H(4a)-H(8a)}$ = 4.3 Hz), the cyclohexane ring of **4a** can be determined to take a chair conformation. The lactone ring can also be considered to take a chair conformation from the vicinal coupling data between the lactone ring protons ($J_{H(3)-H(4\beta)}$ = 11.3 Hz, $J_{H(3)-H(4\alpha)}$ = 4.2 Hz, $J_{H(4a)-H(4\alpha)}$ = 4.1 Hz, and $J_{H(4a)-H(4\beta)}$ = 4.0 Hz). Therefore, the stereostructure of **4a** should be as shown in Fig. 5.

By a similar analysis of **4b** based on the vicinal coupling constants ($J_{H(4a)-H(5\alpha)}$ = 11.0 Hz, $J_{H(8a)-H(8\alpha \text{ and } 8\beta)}$ = both 4.5 Hz, and $J_{H(4a)-H(8a)}$ = 5.0 Hz) (Fig. 4), the cyclohexane ring can be considered to take the same conformation as in the case of **4a**. However, the conformation of the lactone ring is not the same because a large NOE was observed between H(3) and H(8a). Then, irradiation at the resonance due to H(8a), which resides in a 1,4-relationship with respect to H(3) in **4b**, produced NOEs for H(4a) (3.0%) and H(3) (9.0%). In contrast, irradiation at the H(3) resonance produced NOEs for H(4) at δ 2.07 (4.5%) and H(8a) (10.0%) (Figs. 3 and 4). These results indicate that H(3), H(8a), H(4a), and H(4) at δ 2.07 of the lactone ring take β-configuration, and that the distance between H(3) and H(8a) is very short. Consequently, the methyl group can be considered to take an α-configuration and the lactone ring to take a boat-like conformation. This conclusion is also supported by conformational analysis based on the vicinal coupling constants between H(3) and H(4), and between H(4a) and H(4) ($J_{3-4\alpha}$ = 11.0 Hz, $J_{3-4\beta}$ = 3.5 Hz, $J_{4a-4\alpha}$ = 6.5 Hz, and $J_{4a-4\beta}$ = 8.5 Hz). Therefore, the stereostructure of **4b** should be as shown in Fig. 5.

Now, on the basis of the vicinal couplings between H(8a) and H(8α) (4.3—5.0 Hz) and between H(8a) and H(8β) (4.3—5.0 Hz) in **4a** and **4b**, and **10a**, which will be described later, the cyclohexane ring in the *cis*-isomers at the ring-juncture is in a chair conformation in which H(8a) is equatorial.

Similarly, based on the data in Fig. 4, the stereostructures of **4c** and **4d** can be determined to be as shown in Fig. 5.

The large NOE between H(3α) and H(8a) (8.5%) in **4c** is evidence for the existence of the lactone ring in a boat-like conformation.

Stereostructural Determination of 10a, b In the case of **10a**, since the information from the spin-coupling constants alone in Fig. 4 can not derermine the conformation of **10a**, we have performed ^{1}H–^{1}H NOE experiments in order to elucidate the configuration of the methyl group and the ring conformations.

As can be seen in Fig. 4, various magnitudes of NOEs in **10a** were observed between the following ^{1}H–^{1}H pairs: H(4a)–H(4) at δ 2.56 (6.0%), H(4a)–H(8a) (4.0%), H(4a)–H(8β) ($\sim$4.5%), H(1)–H(7α) (6.0%), and the methyl group–H(8a) (>10%). These results indicate that H(8a), methyl group, and H(4) at δ 2.56 take the same configuration with respect to H(4a) and have β-configuration. Moreover, if we consider the NOEs between H(4a) and H(8β) and between H(1) and H(7α) it seems that the cyclohexane ring takes a chair conformation. Indeed, the vicinal coupling constants between H(4a) and H(5α), between H(4a) and H(8a), and between H(8a) and H(8α and 8β) can be explained reasonably in terms of a chair conformation for the cyclohexane ring of **10a**. Thus, the stereomodel examination of **10a** based on the data mentioned above allows us to conclude that the lactone ring takes a slightly distorted boat conformation which has a β-quasi-axial methyl group. Therefore, the stereostructure of **10a** should be as shown in Fig. 5.

In the case of **10b**, a similar analysis based on the data in Fig. 4 indicated the stereostructure shown in Fig. 5.

From the stereochemical analyses for these six lactones mentioned above, the characteristic features of the stereostructures are summarized in Table IV.

In conclusion, four stereoisomers of 3-methyloctahydroisocoumarins (3-methyloctahydro-1*H*-2-benzopyran-1-ones) (**4a**—**d**) and two 1-methyloctahydro-3*H*-2-benzopyran-3-ones (**10a**, **b**) were synthesized for stereochemical analysis. In the NMR study of these six lactones, unambiguous total proton and carbon signal assignments were obtained, and the methyl configuration and

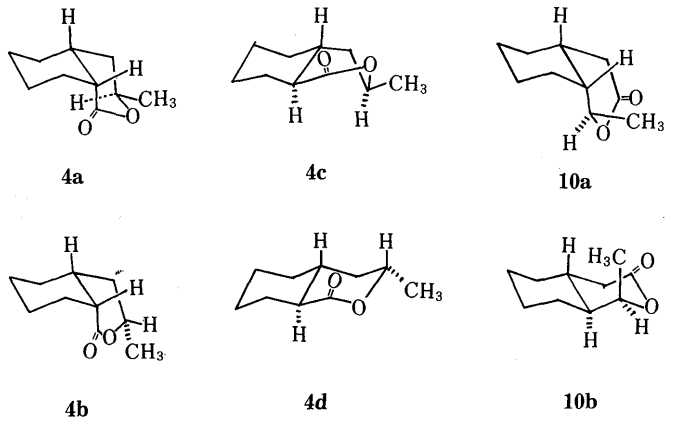

Fig. 5. Plausible Conformations for Methyloctahydrobenzopyranones Based on Vicinal Proton Spin-Coupling Constants and NOE Data

Table IV. Stereostructures of 3-Methyloctahydro-1*H*-2-benzopyran-1-ones (**4a**—**d**) and 3-Methyloctahydro-3*H*-2-benzopyran-3-ones (**10a**, **b**) in $CDCl_3$

Compd. No.	Ring juncture	Methyl[a]	H(8a)[a]	Ring conformation	
				Cyclohexane	Lactone
4a	*cis*	e	e	Chair	Chair-like
4b	*cis*	e	e	Chair	Boat-like
4c	*trans*	e	—	Chair	Boat-like
4d	*trans*	e	—	Chair	Chair-like
10a	*cis*	qa	e	Chair	Slightly distorted boat
10b	*trans*	a	—	Chair	Chair-like

a) Abbreviations: e, equatorial; qa, quasi-axial; a, axial.

ring conformations were determined by using NMR techniques such as 2D INADEQUATE, C/H COSY, ordinary ^1H–{^1H} NMR, and ^1H–^1H NOE measurements. It is clarified that the lactone ring of **4b,c** and **10a** takes a boat-like (**4b,c**) or a slightly distorted boat (**10a**) conformation, and that the cyclohexane ring of **4a,b** and **10a** takes a chair conformation such that H(8a) is equatorial at the cyclohexane ring (see Fig. 5).

Experimental

All melting points were measured with a Yanagimoto micromelting point apparatus and are uncorrected. IR spectra were recorded on a Shimadzu IR-420 spectrophotometer. Mass spectra (MS) were obtained on a Hitachi M-80 mass spectrometer with a direct inlet system operating with an ionization energy of 20 eV.

All the ^{13}C (75.4 MHz) and ^1H (300.0 MHz) NMR spectra were obtained on a Varian XL-300 spectrometer using a 5 mm broad-band probe and operating in a pulse Fourier transform mode with quadrature detection. The software used to obtain 2D NMR spectra was from Varian Instruments, version 5.2 and/or 6.1D. All spectra except 2D INADEQUATE spectra were recorded for 30–60 mg of sample in 0.6 ml of $CDCl_3$, which included tetramethylsilane (TMS) as an internal reference. The 2D INADEQUATE spectra were recorded for 75–200 mg of sample in 0.4–0.5 ml of $CDCl_3$.

The 2D INADEQUATE experiments for the lactones (**4a—d, 10a, b** and **12a, b**) were performed using the same pulse sequence and procedure as described elsewhere.[15c] C/H COSY experiments were performed using the reported pulse sequence[16] and procedure.[15c] The ^1H–^1H NOE experiments in the difference mode were performed at ordinary temperature using the same procedure as described elsewhere.[15c]

Chemical shifts were determined in ppm from TMS as an internal standard. The abbreviations used are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad.

Methyl *cis*-2-Carboxymethylcyclohexane-1-carboxylate (2) A solution of methyl 2-carboxymethylbenzoate[8] (**1**) (5.5 g) in AcOH (80 ml) and water (5 ml) was catalytically hydrogenated over PtO_2 (900 mg) for 2 d at room temperature under 3.75 kg/cm^2 pressure of hydrogen. The amount of H_2 uptake was 2.2 l. After filtration, the filtrate was concentrated *in vacuo* and the residue was dissolved in Et_2O. The ethereal solution was washed with water and dried over Na_2SO_4. After removal of the solvent by evaporation, the residue was distilled *in vacuo* to give 5.5 g of **2** as a colorless liquid, bp 140 °C/3 mmHg. *Anal.* Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 59.51; H, 8.49. ^1H-NMR ($CDCl_3$) δ: 3.67 (3H, s, CH_3), 10.80 (1H, br, COOH).

Methyl *cis*-2-(2-Oxopropyl)cyclohexane-1-carboxylate (3) Oxalyl chloride (2 ml) was added to a solution of **2** (2.0 g) in anhydrous benzene (C_6H_6) (20 ml) at room temperature and the mixture was allowed to stand overnight. After removal of the solvent and excess of the reagent by evaporation *in vacuo* under 40 °C, the slightly yellow residue (acid chloride) was dissolved in anhydrous Et_2O (30 ml). The ethereal solution was treated with an excess of CH_2N_2–Et_2O and was kept standing overnight at room temperature. After evaporation of the solvent, the residue was dissolved in $CHCl_3$ (70 ml). The solution was shaken with 57% aqueous HI (10 ml) for 10 min and separated. The $CHCl_3$ solution was shaken with 5% aqueous $Na_2S_2O_3$, washed with water, and dried over Na_2SO_4. After evaporation of the solvent, the residue was distilled *in vacuo* to give 1.57 g of **3** as a colorless liquid, bp 109 °C/3.5 mmHg. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720 (CO). ^1H-NMR ($CDCl_3$) δ: 2.13 (s, $COCH_3$), 3.65 (3H, s, CH_3).

3-Methyl-*cis*-octahydro-1*H*-2-benzopyran-1-ones (4a and 4b) $NaBH_4$ (650 mg) was added portionwise to a stirred solution of **3** (1.2 g) in MeOH (35 ml) and water (0.5 ml) for 30 min in an ice-bath. The solution was allowed to stand for 1 h under the same conditions, acidified with 20% HCl, and concentrated. The residue was extracted with Et_2O, and the ethereal solution was washed with water and dried over Na_2SO_4. Evaporation of the solvent gave 1.0 g of a colorless liquid (lactone mixture). The liquid was stirred with 50 ml of 10% aqueous Na_2CO_3 solution for 30 min, then extracted with ether and the ethereal solution was treated in a usual manner and evaporated. The residual liquid was stirred with another 50 ml of 10% Na_2CO_3 solution. After three repetitions of this procedure, the ethereal solution was washed with water and dried over Na_2SO_4. Evaporation of the solvent gave a colorless solid. Recrystallization from petroleum ether gave 260 mg of **4a** as colorless prisms, mp 71—72 °C. The hydrazide of **4a** (recrystallized from EtOH–Et_2O), mp 99—100 °C. The aqueous Na_2CO_3 layers were combined, acidified with concentrated HCl, and extracted with Et_2O. The ethereal solution was washed with water, dried over Na_2SO_4, and evaporated. The residual oil was heated to reflux with hydrazine hydrate (300 mg) in a small amount of anhydrous EtOH for 15 min to give 400 mg of another 3-methyl-*cis*-octahydro-1*H*-2-benzopyran-1-one hydrazide as colorless needles (recrystallized from EtOH–Et_2O), mp 129.5—131 °C. *Anal.* Calcd for $C_{10}H_{20}N_2O_2$: C, 59.97; H, 10.07; N, 13.99. Found: C, 59.81; H, 9.85; N, 13.89. The hydrazide (400 mg) was hydrolyzed with 15% HCl (10 ml) in a usual manner to give 300 mg of the lactone **4b** as colorless prisms, bp 115 °C/4 mmHg, mp 32.5 °C.

Reduction of 3-Methyl-3,4-dihydro-1*H*-2-benzopyran-1-one (5) to the Lactone (4b) A solution of **5**[10] (1.1 g) in AcOH (30 ml) was catalytically hydrogenated over PtO_2 (600 mg) for 3 d at room temperature and under atmospheric pressure of hydrogen. The amount of H_2 uptake was 600 ml. The resulting solution was treated in a usual manner to afford 925 mg of **4b** as colorless prisms, bp 115 °C/4 mmHg, mp 32.5 °C.

3α-Methyl-*trans*-octahydro-1*H*-2-benzopyran-1-one (4d) A solution of **4b** (500 mg) in 10% aqueous NaOH (10 ml) was heated to reflux for 90 h. The solution was acidified with concentrated HCl and extracted with Et_2O. The ethereal solution was washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and evaporated. The residual liquid was distilled *in vacuo* to afford 350 mg of a colorless liquid, bp 108 °C/3.5 mmHg, which crystallized in part. Recrystallization from petroleum ether gave 150 mg of **4d** as colorless prisms, mp 44—45 °C.

3β-Methyl-*trans*-octahydro-1*H*-2-benzopyran-1-one (4c) A solution of **4a** (200 mg) in 10% aqueous NaOH (4 ml) was heated to reflux for 50 h. The solution was acidified with concentrated HCl and extracted with Et_2O. The ethereal solution was washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and evaporated. The residual liquid (mixture of **4a** and **4c**) was shaken with 2.5 ml of 1% aqueous NaOH for 5 min and extracted with Et_2O. The ethereal solution was treated in a usual manner and concentrated to give 126 mg of a colorless liquid (mainly **4a**). The aqueous solution was acidified with concentrated HCl and extracted with Et_2O. The ethereal solution was treated in a usual manner and concentrated to give 54 mg of **4c** as a colorless liquid, bp 135—140 °C (bath temperature)/3 mmHg. The hydrazide of **4c** (recrystallized from EtOH–Et_2O): colorless needles, mp 138—139 °C. *Anal.* Calcd for $C_{10}H_{20}N_2O_2$: C, 59.97; H, 10.07; N, 13.99. Found: C, 59.97; H, 10.04; N, 14.23.

Isomerization of 4a with HCl A solution of **4a** (800 mg) in concentrated HCl (35 ml) and EtOH (35 ml) was heated to reflux for 7 h. After removal of a large part of the EtOH by evaporation *in vacuo*, the residue was extracted with Et_2O. The ethereal solution was treated in a usual manner and concentrated to give 750 mg of a colorless liquid (lactone mixture). The liquid was shaken with 9 ml of 1% aqueous NaOH for 5 min and extracted with Et_2O. The ethereal solution was treated in a usual manner and concentrated to give 350 mg of a colorless liquid (mainly **4c**). The liquid was shaken again with 6 ml of 1% aqueous NaOH for 5 min and extracted with Et_2O. Treatment of the ethereal solution in a usual manner gave unchanged **4a** (31 mg) and that of the aqueous solution gave **4c** (245 mg). Thus, the first aqueous solution was acidified with concentrated HCl and extracted with Et_2O. The ethereal solution was treated in a usual manner and concentrated to give 375 mg of a colorless liquid. The liquid was shaken again with 5.5 ml of 1% aqueous NaOH for 5 min and extracted with Et_2O. Treatment of the ethereal solution in a usual manner gave **4c** (135 mg) and the aqueous solution gave a liquid (235 mg). Treatment of the liquid (235 mg) with petroleum ether gave crystalline **4d** (68 mg).

Isomerization of 4b with HCl A solution of **4b** (900 mg) in concentrated HCl (35 ml) and EtOH (35 ml) was heated to reflux for 10 h. After removal of a large part of the EtOH by evaporation *in vacuo*, the residue was extracted with Et_2O. The ethereal solution was treated in a usual manner and concentrated to give 850 mg of a colorless liquid (lactone mixture). The liquid was shaken with 12 ml of 1% aqueous NaOH for 5 min and extracted with Et_2O. The ethereal solution was treated in a usual manner and concentrated to give 300 mg of a colorless liquid (mainly **4c**). The aqueous solution was acidified with concentrated HCl and extracted with Et_2O. The ethereal solution was treated in a usual manner and concentrated to give 525 mg of a colorless liquid (mainly **4d**). Treatment of the liquid with petroleum ether gave crystalline **4d** (285 mg).

***cis*-2-Ethoxycarbonylmethylcyclohexane-1-carboxylic Acid (7)** A solution of 2-ethoxycarbonylmethylbenzoic acid[11] (**6**) (6.0 g) in AcOH (90 ml) and water (6 ml) was catalytically hydrogenated over PtO_2 (1.2 g) for 3 d at room temperature and under 3.67 kg/cm^2 pressure of hydrogen. The

amount of H_2 uptake was 2.4 l. The resulting solution was treated in a usual manner to afford 5.7 g of **7** as a colorless liquid, bp 146—147 °C/3.5 mmHg. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3000—2400 (COOH), 1720, 1710 (CO). ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7.0, CH_3), 4.14 (2H, q, J=7.0, OCH_2–), 10.05 (1H, br, COOH).

The acid was treated with CH_2N_2–Et_2O to give the methylester as a colorless liquid, bp 108 °C/3.5 mmHg. *Anal.* calcd for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83. Found: C, 62.66; H, 8.99. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7.0, CH_3), 3.65 (3H, s, OCH_3), 4.14 (2H, q, J=7.0, OCH_2–).

Ethyl 2-(*cis*-2-Acetylcyclohexyl)acetate (8) Reaction of **7** (2.0 g) with oxalyl chloride (2 ml), followed by treatment with CH_2N_2–Et_2O and 57% HI by the same procedure as in the case of **3** gave 1.14 g of **8** as colorless oil, bp 118 °C/3.5 mmHg. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1725, 1710 (CO). ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J=6.5 Hz, CH_3), 2.15 (3H, s, $COCH_3$), 4.11 (2H, q, J=6.5 Hz, OCH_2–).

Methyl 2-(*trans*-2-Acetylcyclohexyl)acetate (9) A solution of **8** (1.05 g) and 10% KOH–EtOH was heated to reflux for 2 h. After evaporation of the solvent *in vacuo*, the residue was dissolved in a small amount of water. The solution was acidified with concentrated HCl and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and evaporated. The residual viscous liquid was treated with CH_2N_2–Et_2O in a usual manner and the ester was distilled *in vacuo* to afford 890 mg of **9** as a colorless liquid, bp 96 °C/3 mmHg. *Anal.* Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.67; H, 9.47. ^{1}H-NMR ($CDCl_3$) δ: 2.13 (3H, s, $COCH_3$), 3.63 (3H, s, OCH_3).

1β-Methyl-*cis*-octahydro-3*H*-2-benzopyran-3-one (10a) $NaBH_4$ (500 mg) was added portionwise to a stirred solution of **8** (970 mg) in MeOH (30 ml) and water (1.5 ml) for 15 min under ice-cooling. The solution was allowed to stand for 50 min under the same conditions, then acidified with 20% HCl, and concentrated. The residue was dissolved in 10% aqueous NaOH and the solution was washed with Et_2O. The aqueous layer was acidified with concentrated HCl and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with water and dried over Na_2SO_4. After evaporation of the solvent, the residual liquid was treated with hydrazine hydrate in EtOH to gave a colorless solid. Recrystallization of the solid from EtOH–Et_2O gave 475 mg of a hydrazide as colorless prisms, mp 102—103.5 °C. *Anal.* Calcd for $C_{10}H_{20}N_2O_2$: C, 59.97; H, 10.07; N, 13.99. Found: C, 59.79; H, 10.07; N, 13.71. The hydrazide (500 mg) was treated with 15% HCl in a usual manner to give 400 mg of **10a** as a colorless liquid, bp 125 °C/5 mmHg.

1β-Methyl-*trans*-octahydro-3*H*-2-benzopyran-3-one (10b) Compound **9** (750 ml) in EtOH (25 ml) and water (0.5 ml) was reduced with $NaBH_4$ (350 mg), followed by treatment with hydrazine hydrate (350 mg) in EtOH (10 ml) in the same manner as in the case of **8** to give 400 mg of a hydrazide as colorless leaflets (recrystallized from EtOH–Et_2O), mp 137—138 °C. *Anal.* Calcd for $C_{10}H_{20}N_2O_2$: C, 59.97; H, 10.07; N, 13.99. Found: C, 59.79; H, 10.50; N, 13.83. Hydrolysis of the hydrazide with 15% HCl gave the lactone **10b** quantitatively as a colorless oil, bp 120 °C/4.5 mmHg.

***cis*-Octahydro-1*H*-2-benzopyran-1-one (12a)** A solution of 3,4-dihydro-1*H*-2-benzopyran-1-one[12] (**11**) (2.9 g) in AcOH (40 ml) was catalytically hydrogenated over PtO_2 (650 mg) for 2 d at room temperature and under 3.7 kg/cm^2 pressure of hydrogen. The amount of H_2 uptake was 1.7 l. After filtration, the filtrate was concentrated *in vacuo* and the residue was dissolved in Et_2O. The ethereal solution was shaken with 10% aqueous Na_2CO_3, washed with water, and dried over Na_2SO_4. Evaporation of the solvent, followed by distillation *in vacuo* gave 2.15 g of **12a** as a colorless liquid, bp 118 °C/4.5 mmHg. The hydrazide of **12a**, colorless needles (recrystallized from EtOH–Et_2O), mp 109—110 °C. *Anal.* Calcd for $C_9H_{18}N_2O_2$: C, 58.03; H, 9.74; N, 15.04. Found: C, 57.96; H, 9.67; N, 14.88.

***trans*-Octahydro-1*H*-2-benzopyran-1-one (12b)** A mixture of **12a** (1.0 g) and 10% aqueous NaOH (20 ml) was heated to reflux for 90 h. The solution was acidified with concentrated HCl and extracted with Et_2O. The ethereal solution was treated in a usual manner. The resulting liquid (bp 95 °C/2.5 mmHg, 750 mg, **12a** and **12b** mixture) was treated with hydrazine hydrate (300 mg) in EtOH (5 ml) to give a solid. Recrystallization from $CHCl_3$ afford 450 mg of a hydrazide as colorless prisms, mp 123—124 °C. *Anal.* calcd for $C_9H_{18}N_2O_2$: C, 58.03; H, 9.74; N, 15.04. Found: C, 57.80; H, 9.60; N, 14.74. Hydrolysis of the hydrazide (260 mg) with 15% HCl in a usual manner gave the lactone **12b** (190 mg) as colorless prisms, bp 103 °C/3 mmHg, mp 48 °C.

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References and Notes

1) Y. Fujiwara, S. Kimoto and M. Okamoto, *Chem. Pharm. Bull.*, **23**, 1396 (1975).
2) Actinobolin from a *Streptomyces* culture: T. H. Haskell and Q. R. Alfred, *Antibiot. Ann.*, **1958—1959**, 505 (1959). Structure: F. J. Antosz, D. B. Nelson, D. L. Herald, Jr. and M. E. Munk, *J. Am. Chem. Soc.*, **92**, 4933 (1970); D. B. Nelson and M. E. Munk, *J. Org. Chem.*, **35**, 3832 (1970); J. B. Wetherington and J. W. Moncrief, *Acta Crysta.*, **B31**, 501 (1975). Total synthesis: M. Yoshioka, H. Nakai and M. Ohno, *J. Am. Chem. Soc.*, **106**, 1133 (1984); R. S. Garigipati, D. M. Tschaen and S. M. Weinreb, *ibid.*, **107**, 7790 (1985).
3) Bactobolin: S. Kondo, Y. Horiuchi, M. Hamada, T. Takeuchi and H. Umezawa, *J. Antibiot.*, **32**, 1069 (1979).
4) Ramulosin from *Pestolatia ramulosa*: F. Stodola, C. Cabot and C. Benjamin, *Biochem. J.*, **93**, 92 (1964). Total synthesis: R. Cordova and B. B. Snider, *Tetrahedron Lett.*, **25**, 2945 (1984).
5) 6-Hydroxyramulosin: S. W. Tanenbaum and S. C. Agarwal, *Tetrahedron Lett.*, **27**, 2377 (1970).
6) S. E. Drewes, P. A. Grieco and J. C. Huffman, *J. Org. Chem.*, **50**, 1309 (1985).
7) A. Bax, "Two-dimensional NMR in Liquids," D. Reidel Publishing Co., Dordrecht, Holland, 1982.
8) R. Wegscheider and A. Glogau, *Monatsh. Chem.*, **24**, 915 (1905); R. Huisgen and E. Rauenbusch, *Justus Libigs Ann. Chem.*, **641**, 51 (1961).
9) Synthesis of *d,l*-epiramulosin and the configuration of ramulsosin: J. A. Findley, J. M. Matsoukas and J. Krepinsky, *Can. J. Chem.*, **54**, 3419 (1976). The compound assigned the stereostructure of **4a** in the literature is not coincident with our **4a** in physical and spectral data.
10) R. B. Tirodkar and R. N. Usgankar, *J. Ind. Chem. Soc.*, **46**, 935 (1969).
11) J. Wislicenus, *Justus Liebigs Ann. Chem.*, **233**, 105 (1898); T. Kametani and H. Sugahara, *J. Chem. Soc.*, **1964**, 3856 (1964).
12) H. Iida, K. Kawano, T. Kikuchi and F. Yoshimizu, *Yakugaku Zasshi*, **96**, 176 (1976).
13) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).
14) J. H. Noggle and R. E. Schirmer, "The Nuclear Overhauser Effect, Chemical Applications," Academic Press, New York, 1971, Chapter 3.
15) *a*) T. H. Mareci and L. F. Freeman, *J. Magn. Reson.*, **48**, 158 (1982); *b*) W. F. Reynold, J. F. Sawyer, R. G. Enriquez, L. I. Escobar, M. A. Chaves and J. N. Shoolery, *Can J. Chem.*, **64**, 1051 (1985); *c*) M. Okamoto, Y. Fujiwara, T. Oka and Y. Uemura, *Chem. Pharm. Bull.*, **36**, 521 (1988).
16) A. Bax and G. A. Morris, *J. Magn. Reson.*, **42**, 501 (1981); A. Bax, *ibid.*, **53**, 517 (1983).
17) D. M. Doddrell, D. T. Pegg and M. R. Bendall, *J. Magn. Reson.*, **48**, 323 (1982).