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STEREOCONTROLLED SYNTHESIS OF CLERODIN HOMOLOG
— A SYNTHETIC APPROACH TO STRUCTURE-ACTIVITY RELATIONSHIPS[1] —

YASUHIRO KOJIMA and NATSUKI KATO*

Department of Agricultural Chemistry, Nagoya University,
Chikusa-ku, Nagoya 464, Japan

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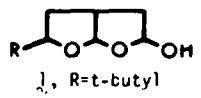
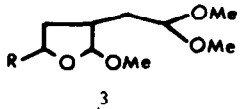
In order to elucidate the structure-activity relationships of the antifeeding diterpenes, clerodin homolog 5 was stereoselectively synthesized through 18 steps via a key intermediate 12. The perhydrofuro[2,3-b]furan ring in the synthesized homolog was less stable than that of the natural product, and its reactivity on methanolysis and potency of the antifeeding activity were almost the same as those of a 2,6-dimethylphenyl derivative 10 which is more sterically restricted than a phenyl derivative 2. The findings supported the hypothesis for the relationships on the structure (stereostructure) and activity of biological active substances. The methodology is conceptually termed "Dynamic structure-activity relationships," and is effective from the standpoint of drug design.

In the course of elucidating the structure-activity relationships of the antifeeding substances[2] having a neo-clerodane skeleton[3a] such as clerodin [3b], clerodendrin A[3c], and caryoptin[3d], we have recently reported both the synthesis of perhydrofuro[2,3-b]furan derivatives (1 and 2)[4,5], which have a partial structure in the natural products. Though it is considered that the perhydrofuro[2,3-b]-furan ring is an active center of the antifeeding activity[2c,d], antifeeding activities of the synthetic derivatives[5] for the larvae of Spodoptera litura F. were only 1/10∼1/20 fold as compared with those of the natural products. As one of the reasons for the latter results, it was assumed that the model compounds, 1 and 2, had a less stable perhydrofuro[2,3-b]furan ring[5] than those of the natural products. Then, we sought to confirm relationships between the potency of the biological activity for the compounds and chemical stability of the active center for some chemical reactions. Quantitative experiments of 1 with MeOH by catalysis of 70% $HClO_4$ gave a tri-MeOH adduct 3 at room temperature, whereas clerodin was only converted into a mono-MeOH adduct 4 under the same condition. It has been concluded that the instability of the model compounds may be attributed to the flexibility and ease of the free-rotation of the perhydrofuro[2,3-b]furan rings as compared with those of the natural products. Thus, it presented a new problem, namely, as to whether the decalin ring portion except for the methyl groups or the C^8 and/or C^9 methyl groups together with it were required for the stabili-



1, R=t-butyl
2, R=phenyl



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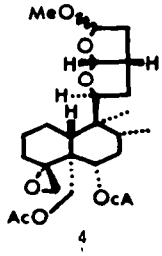

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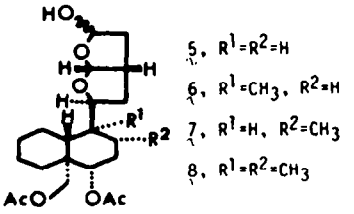
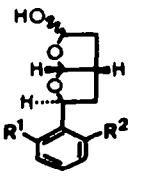
zation of the perhydrofuro[2,3-b]furan ring in the natural products. If the C^8 methyl group is responsible for that, an ortho-dimethylphenyl derivative may be the simplest model system for the stabilization of the furo-furan ring. Then, we planned to synthesize the clerodin homologs (5 ~ 8) and ortho-mono and dimethylphenyl derivatives 9 and 10[6].

In the present study, we describe in detail both a stereocontrolled synthesis of clerodin homolog 5 and the antifeeding activity of 5 and its derivatives for the larvae of S. litura F. Since the transformation of a furan alcohol 11 to 5 could be carried out with a methodology recently reported by us[4,5], an epoxy acetonide 12 was chosen as a key intermediate. However, we supposed that the determination of the relative configuration at a C^{11} position may be accompanied by considerable effort. The trans-decalin ring in 12 would be constructed by a Diels-Alder reaction of butadiene with a carbomethoxyquinone 13, which has the required functional groups at C^5, C^6, and C^9 positions; moreover, an epoxide ring would be synthesized through elongation of a C_2 unit (e.g., ketone → nitrile → vinyl → epoxide) at the C^9 position (Scheme I).

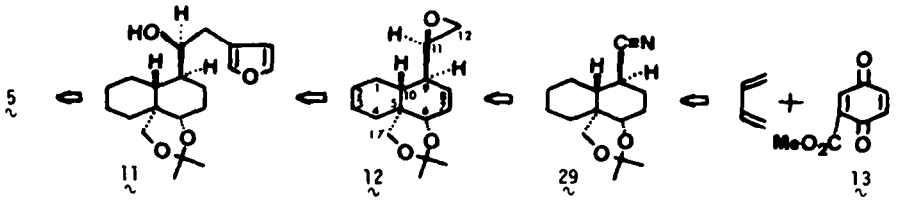


5, $R^1=R^2=H$
6, $R^1=CH_3$, $R^2=H$
7, $R^1=H$, $R^2=CH_3$
8, $R^1=R^2=CH_3$



9, $R^1=H$, $R^2=CH_3$
10, $R^1=R^2=CH_3$

Scheme I



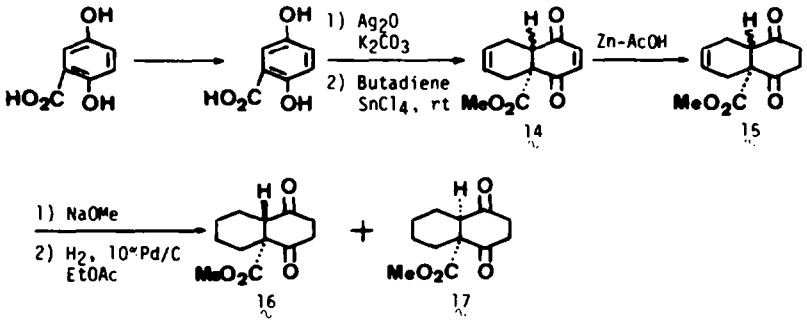
Synthesis of the key intermediate, epoxy acetonide 12.

We commenced a preparation of the key intermediate 12 via a Diels-Alder reaction with methyl gentisate readily obtained by methylation of gentisic acid. The Diels-Alder reaction of a p-quinone 13, prepared by silver oxide oxidation[7] of methyl gentisate, with butadiene ($SnCl_4$, 0°C) gave a desired adduct 14 in 90.8% yield from methyl gentisate. The ^1H NMR spectrum exhibited signals at δ6.58 and 6.80 (ABq, J=10.2 Hz) and δ6.66 (s) with a ratio of 1 : 4. In fact, since the vinyl protons in the related compound with the cis junction appeared as a singlet at δ6.56[8], it was proved that the Diels-Alder adduct 14 consisted trans- and cis-adducts in the ratio of 1 : 4. The adduct 14 was then converted into a dihydro derivative 15 by the reduction with zinc-acetic acid[9] in 97.2% yield. Epimerization of 15 by sodium methoxide in MeOH (-20°C) improved the ratio of the cis- and trans-decalin derivatives to 1 : 3.3. Since the mixture was difficult to separate on TLC, we resorted to the next reaction without separation. Catalytic hydrogenation of the derivatives gave a mixture of a trans-diketo ester 16 and its isomer 17 in 98.8% yield with a ratio of 3 : 1, which was separated by silica gel column chromatography. The reaction rate of the reduction at a trans-dihydro derivative of the epimerized 15 was much faster than that of the corresponding cis derivative. In the case of the reduction of a large amount of the epimerized 15, a trans-diketo ester 16 was purified through a silica gel column chromatography at the stage in which the trans-dihydro derivative alone was reduced and the recovered cis-dihydro derivative was again transformed into 16 through epimerization followed by a catalytic reduction (Scheme II).

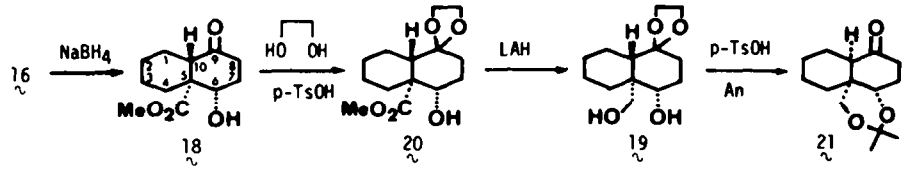
Transformation of 16 into the key intermediate 12 requires both a selective reduction

at the C^6 position and the selective C_2 carbon elongation reaction at the C^9 position. According to expectations based on the prevention by an axial methoxycarbonyl group at the C^5 position, a reducing agent may attack selectively a C^6 carbonyl group from a β-face. In fact, selective reduction of 16 with $NaBH_4$ gave a single product 18, as expected, in 87.8% yield [C^6-H: δ3.96 (1H, dd, J=12.0, 4.0 Hz)]. The alcohol 18 was then transformed into a ketal diol 19 via a ketal alcohol 20 by treatment with ethylene glycol (p-TsOH, reflux, 90.5%) followed by reduction with $LiAlH_4$ (Et_2O, 0°C, 88.0%). Both removal of the protective ketal group and simultaneous protection of dihydroxy groups were achieved by treatment of 19 with acetone in the presence of a catalytic amount of p-TsOH, affording a keto acetonide 21 in 91.0% yield. Its ^1H NMR spectrum showed a broad triplet (J=3.0 Hz) at δ3.74 ascribed to a methine proton at the C^6 position. It was therefore assumed from consideration of the Dreiding model that the obtained compound 21 held a cis ring junction, occurring by epimerization at a C^{10} position (Scheme III).

Scheme II



Scheme III

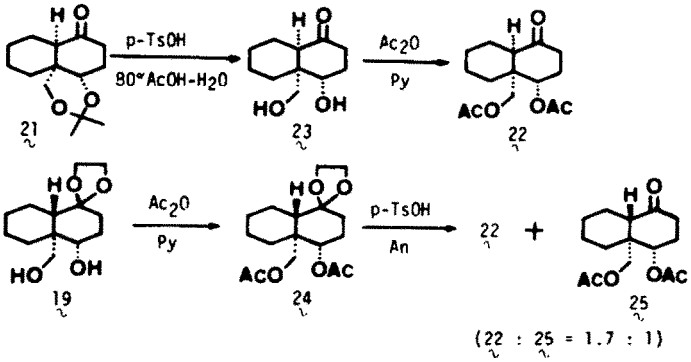


Confirmation of the structure of 21 was achieved by its conversion into a keto diacetate 22 via a keto diol 23 with treatment of 80% AcOH-H_2O in the presence of a catalytic amount of p-TsOH followed by acetylation. Thus, the cis ring junction of the keto acetonide 21 was established since 22 exhibited a triplet (δ5.32, J=5.2 Hz, W1/2=11.4 Hz) attributable to the methine proton at the C^6 position. It was proved which of the reactions, 18 → 20 or 19 → 21, caused the epimerization at the C^{10} position as follows. Acetylation of 19 (Ac_2O, Py, rt) afforded a diacetate 24 [C^6-H: δ5.28 (1H, br.t, J=7.3 Hz, W1/2=16.7 Hz)], which was transformed into a mixture of keto diacetates, 22 and 25 [C^6-H: δ5.08 (1H, t, J=8.2 Hz)], in a ratio of 1.7 : 1. It became apparent from consideration of these results that the epimerization of the trans to cis ring junction occurred in the deketalization step (Scheme IV).

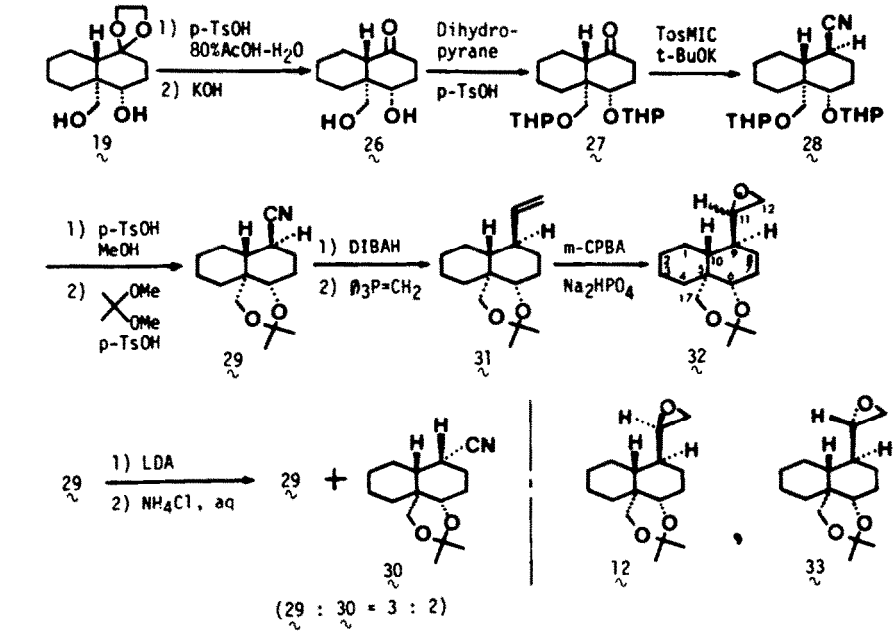
The high yield of 21 is because, if 21 takes the trans ring junction, its acetonide linkage causes serious steric interaction with the decalone ring. This conclusion is also well confirmed by the following equilibrium experiments: the epimerization of 21 by KOH (MeOH, rt or reflux) was unsuccessful, but, under the same condition, 23 was converted into a mixture of a trans-keto diol 26 and 23 in a ratio of 5 : 1. As mentioned so far, because the acetonide protection of the 1,3-diol system caused the epimerization of the trans to cis ring junction under the acidic condition, the further reactions proceeded by using a tetrahydropyranyl group as a protective group.

Treatment of the ketal diol 19 with 80% AcOH-H_2O in the presence of a catalytic amount of p-TsOH followed by KOH work up gave a mixture of a trans-keto diol 26 and a cis-keto diol 23 in a ration of 5 : 1. The former was then transformed, by treatment with dihydro-

Scheme IV

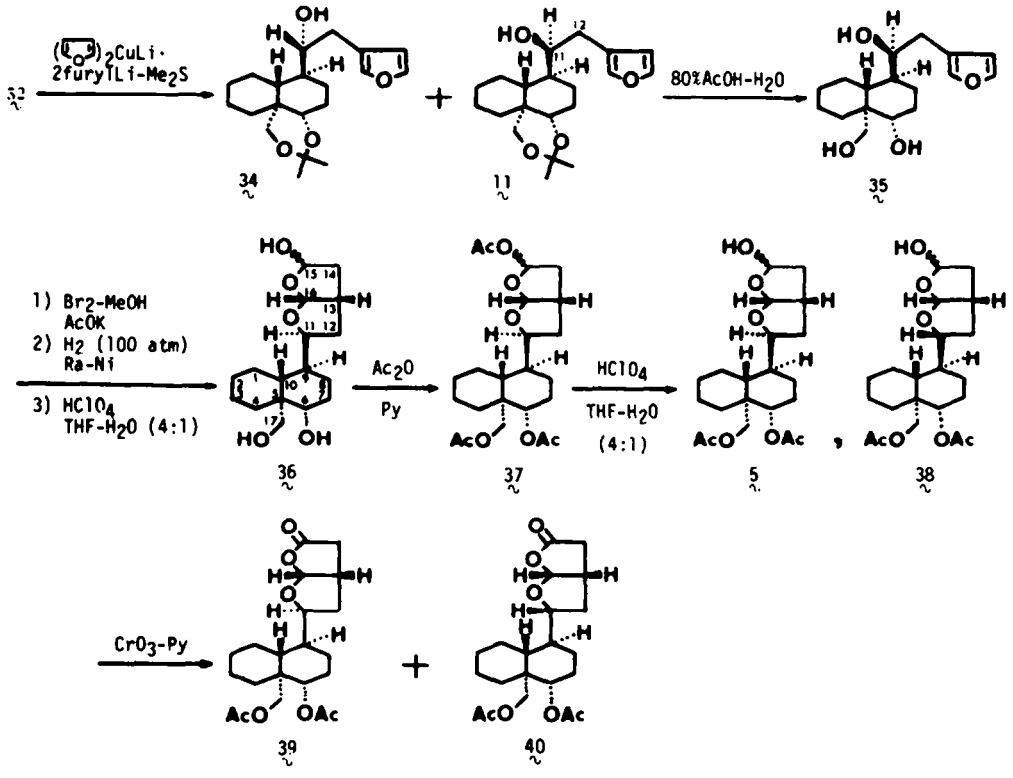


Scheme V



pyrane, into a tetrahydropyranyl ether 27 in 89.0% yield. Elongation of the C_2 unit at the C^9 position in 27 was initiated by transformation of it into a nitrile derivative 28 by using TosMIC[10] (tert-BuOK, DME-tert-BuOH, rt, 74.7%). The nitrile 28 was then converted into a single product, nitrile acetonide 29, by treatment with dimethoxypropane (p-TsOH, acetone, 0°C, 91.0% from 28). The relative configuration with respect to the nitrile group could not be decided by the ^1H NMR spectrum because the signal of the C^9 proton overlapped with other proton signals. Treatment of 29 with LDA followed by quenching with aqueous NH_4Cl afforded a mixture of 29 and its epimer 30 in a ratio of 3 : 2. The C^{17} methylene protons of 29 and 30 appeared as a doublet signal at δ3.68 and 3.80 (J=12.0 Hz), and a double doublet at δ3.86 (J=12.0, 1.0 Hz) and 4.45 (J=12.0, 1.0 Hz), respectively. The low field shift of the latter might be attributed to the alignment of the same side, i.e., α-configuration, of the C^{17} methylene and nitrile groups. Moreover, the signal at the higher field, δ3.86, showed a long range coupling (J= 1 Hz) with the C^6 methine proton and the other signal (δ4.45) coupled with one of methylene protons at the C^4 position. These findings agreed with a consideration of the Dreiding model for 29 and 30. It was therefore concluded that 29 held a desired β-oriented nitrile group. Transformation of the nitrile acetonide 29 into a vinyl acetonide 31 was smoothly achieved by reduction with DIBAH followed by a Wittig reaction with methylene triphenylphosphorane in 75.5% overall yield.

Scheme VI



(39 : 40 = 93 : 7)

Reaction of 31 with mCPBA gave an epoxy acetonide 32 in 81.0% yield, which was a mixture of the key intermediate 12 bearing a desired configuration with respect to the C^{11} position and its epimer 33 in a ratio of 92 : 8 (Scheme V). The relative configuration of the C^{11} position in 32 was determined by applying the combination method of empirical force-field calculation and lanthanide-induced shift experiment.

Derivation of the epoxy acetonide 32 to the clerodin homolog 5.

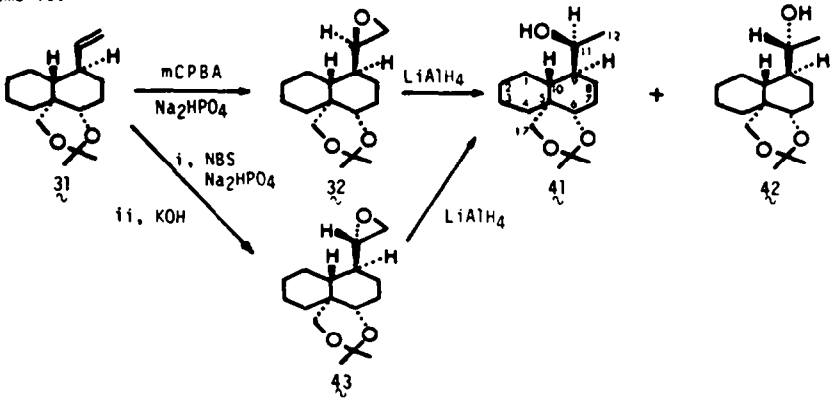
Transformation of the epoxy acetonide 32 into the final product 5 was initiated by its reaction with lithium di(3-furyl)cuprate·2-furyllithium-dimethyl sulfide complex[11], yielding the desired furan alcohol 11 and its C^{11} epimer 34 in a ratio of 92 : 8 (100% yield); 11: δ3.74 (1H, br.dd, J=8.8, 4.4 Hz, >CH-OH), and 34: δ3.88 (1H, overlapping with the C^{17} methylene protons). Treatment of the furan derivative 11 with 80% AcOH-H_2O yielded a furan triol 35, and the crude furan triol was converted into a perhydrofuro[2,3-b]furan derivative 36 having the natural form in 77.0 % yield by a sequence similar to that previously developed for the synthesis of the model compounds, 1 and 2[4,5]. Acetylation of 36 gave a triacetate 37 in a quantitative yield which was an epimeric mixture with respect to a C^{15} position: δ6.24 and 6.26 (each 0.25 and 0.75H, both d, each J=6.0 and 5.0 Hz, C^{15}-H). Acid hydrolysis of 37 smoothly provided the final product 5 in a quantitative yield: δ5.68 and 5.70 (each 0.5H, both d, each J=5.4 and 5.2 Hz, C^{16}-H). The ^{1}H NMR spectrum did not reveal the existence of the diastereomer 38, but oxidation of 5 with CrO_3-Py complex gave a mixture of γ-lactones, 39 and 40, in a ratio of 93 : 7; 39: δ5.93 (0.93H, d, J=5.2 Hz, C^{16}-H) and 40: δ5.80 (0.07H, d, J=5.0 Hz, C^{16}-H). It was therefore concluded that the final product 5 contained about 7 percent of the unnatural form 38 analogous with the model compounds, 1 and 2[5] (Scheme VI).

As mentioned so far, the clerodin homolog 5 was synthesized in 6% overall yield through 18 steps via the key intermediate 12 from gentisic acid. It is remarkable that 5 was not the desired compound which controls the flexibility and free-rotation of the perhydrofuro[2,3-b]furan ring.

Determination of the relative configuration of the key intermediate epoxy acetonide 12 and its epimer[12].

The relative configuration at the C^{11} position of the epoxy acetonide 32, which was the key intermediate for the synthesis of the clerodin homolog 5, was difficult to determine on the NMR spectra, because the epoxy group rotated freely about a C^9-C^{11} axis and the C^{11} methine proton of the acetonide 32 appeared as a broad signal at δca. 2.6 overlapping with signals of methylene protons on a C^{12} position. On the other hand, the epoxy acetonide 32 contained a small amount (ca. 10 %) of an epimer from comparison of peak heights of C^6 carbon atoms on ^{13}C NMR spectrum.

Scheme VII



While the epimers could not be separated from each other on silica gel TLC, it was predicted that their hydroxy derivatives could be separated into the two components. For the above reason and to make sure the binding between the compound and $Eu(fod)_3$, 32 was transformed into hydroxy acetonides, 41 and 42, in a ratio of 92 : 8 by reduction with $LiAlH_4$ (Scheme VII).

The hydroxy acetonides, 41 and 42, which were the epimer with respect to the C^{11} position, could be distinguished by ^1H NMR in the following way: signals of a methine proton at the C^{11} position and a C^{11} methyl group in 41 appeared as a broad quartet signal (J=6.5 Hz) at δ3.88 and a doublet signal (J=6.5 Hz) at δ1.13, respectively, whereas those in 42 emerged at δ3.8 overlapping with C^{17} methylene proton signals and as a doublet (J=6.5 Hz) at δ0.92, respectively. On the other hand, in preparing 43 via a bromohydrin intermediate, the ratio of the hydroxy acetonides, 41 and 42, reversed to 15 : 85 (Scheme VII).

Experimental LIS's for the hydroxy acetonides obtained by addition of $Eu(fod)_3$ were shown in Table 1-(a). The LIS's of six individual protons for both hydroxy acetonides were on straight lines on the correlation diagrams. Even if the lanthanide-induced shift reagent was added to the compounds having many equivalent protons, there were few protons observed as isolated signals with clear linear relationships.

On the other hand, the energy-minimized Cartesian coordinates about whole atoms on the hydroxy acetonides were obtained by using Allinger's force-field (program: MMI. QCPE No. 318)[13]. The fitness of the coordinate for each geometry on the hydroxy acetonides was judged by the agreement between the calculated and observed LIS's. The best fit location of Eu was determined for the respective hydroxy acetonides using the LIS's, and the coordinate system was given by Armitage's method[14]. Calculated LIS's were derived from the McConnell-Robertson equation (Table 1-(a))[15]. The best-fit location was taken as the minimum of the normalized standard deviation [R-factor (%)] between the observed and calculated shifts (Table 2-(a)). The values of their R-factors, 3.6 and 4.5% for 41 and 42, respectively, satisfied sufficiently the suitability of their atomic coordinates[16]. On the other hand, when the LIS's calculated for the hydroxy acetonides in which the coordinates on whole protons were interchanged for each other, their R-factors led to more than 10% (Table 2-(a)). Based on the satisfactory atomic coordinates, their conformational structures are shown in Figure 1.

Furthermore, since links of chain compounds are generally more mobile than those of cyclic compounds, conformation of the chain

Table 1-(a) Obsd. and calcd. LIS values of hydroxy acetonides, 41 & 42

		H^6	$H^{8'}$	H^9	H^{11}	H^{13}	$H^{13'}$
41	Obsd.	3.71	8.56	11.56	23.38	3.38	4.75
	Calcd.	3.51	8.56	10.79	23.82	3.71	4.32
42	Obsd.	4.07	15.00	15.55	24.69	2.09	3.11
	Calcd.	3.67	16.05	14.74	24.59	1.73	3.56

Table 1-(b) Calcd. LIS values of hydroxy acetonides, 41 & 42 rotated about the C^{11}-C^9 axis.

		H^6	$H^{8'}$	H^9	H^{11}	H^{13}	$H^{13'}$
41	θ=-7°	3.43	8.82	11.23	23.50	3.83	4.39
42	θ=-6°	3.50	14.86	15.33	24.97	2.27	3.17

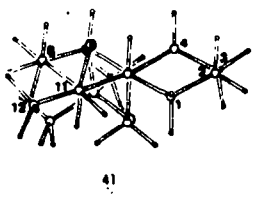
Table 2-(a) R-factors between the calcd. and obsd. LIS values.

	Hydroxy acetonide 41	Hydroxy acetonide 42	[r(Å)	ψ(deg)	φ(deg)]*
Atomic params. of 41	3.6 %	17.8 %	[2.5	150	150]
Atomic params. of 42	18.4 %	4.5 %	[2.5	110	150]

Table 2-(b) R-factors between the calcd. and obsd. LIS values obtained by the coordinates rotating about the C^{11}-C^9 bond axis.

	Hydroxy acetonide 41	Hydroxy acetonide 42	[r(Å)	ψ(deg)	φ(deg)]
Atomic params. of 41	2.7 %	15.9 %	[2.5	150	140]
Atomic params. of 42	15.5 %	2.1 %	[2.5	160	130]

* r: Oxygen-Eu distance. ψ: Angle between the Eu donor bond and the C^{11}-OH bond axes. φ: Azimuthal angle of Eu around the C^{11}-OH bond axis.



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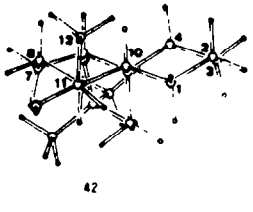

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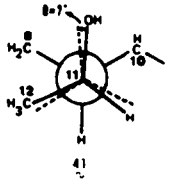
Figure 1. Conformation of hydroxy acetonides viewed by ORTEP through the C^{11}-C^9 axis



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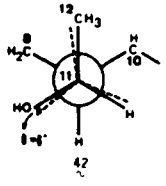

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Figure 2. Newmann projection of hydroxy acetonides viewed through the C^{11}-C^9 axis

ones is relatively alterable with solvents, temperature, contaminants, etc. We assumed that the conformational changes by the rotation of a C^{11}-C^9 single bond in comparison with the bonds of the cyclic structure might easily have occurred because of the coordination of bulky Eu(fod)$_3$ to the C^{11} hydroxyl group. Then, by rotating the C^{11}-C^9 bond only, i.e., by rotating the coordinates of the C^{11} proton, the hydroxyl and the methyl groups around the C^{11}-C^9 bond axis, the best-fit location of Eu was determined as described above. When the axis was turned counterclockwise through 7° and 6° in 41 and 42, respectively (Figure 2), the calculated LIS's approximated more closely the observed ones (Table 1-(b)), and their R-factors showed a higher reliability at 2.7 and 2.1%, respectively (Table 2-(b)). Therefore, these results confirmed that the epoxy acetonide 12 obtained by mCPBA possessed the same configuration as that of the natural product. And the small R-factors may show that the calculated coordinates are most likely in accord with those of the real molecules in the solution[16].

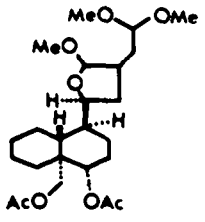
Entomological tests and structure-activity relationships on the antifeeding activity of the clerodin homolog 5 and its analogs.

Clerodin homolog 5 afforded only a ring opening product, tri-MeOH adduct 44, by the reaction with MeOH; 44: δ4.36 (1H, t, J=5.1 Hz, -CH-$(OMe)_2$), m/z 425 (M^+-31). This behavior in 5 was similar to that of the perhydrofuro[2,3-b]furan rings on 1 and 2[5].

It was suggested that C^8 and/or C^9 methyl groups in neo-clerodane diterpenes could assure a very subtle contribution to the stability of the perhydrofuro[2,3-b]furan ring.

The clerodin homolog 5 together with 1 and 2 was used for the test of the antifeeding activity for the larvae of S. litura F. following the known leaf disk method for the entomological tests[2]. As a reference, it showed the results for the methylphenyl derivatives, 9 and 10, were sterically more restricted than 2 about the free rotation and flexibility of their perhydrofuro[2,3-b]furan ring[6]. Since the natural products retained the same potency for their hemiacetal and γ-lactone derivatives on the biological test, the entomological test of the model compounds was also run with the hemiacetal and γ-lactone derivatives.

In a previous study[6], we reported that, as an approach to clarify quantitatively and rapidly structural factors (steric or electronic effects etc.) which were essential for the appearance of biological activity of compounds, a chemical reaction at their active center in the place of their biological reactions at receptor in vivo provided significant information linking the biological activity and the structure of the compounds. We applied this methodology to clarify the chemical reactivity on the active center of the clerodin homolog 5; 5 afforded only the tri-MeOH adduct 44 at room temperature but, at the reaction condition of 2°C, yielded a mono-MeOH adduct 45: δ4.90 and 5.02 (each 0.5H, both d, each J=5.5 Hz and J=5.0 Hz, >CH-OMe), m/z 378 (M^+-32). The proportion and structure of these MeOH adducts were ascertained by gas chromatography (GC) and GC-MS spectrometry. The behavior of 5 was comparable to that of the perhydrofuro[2,3-b]furan ring of the 2,6-



44

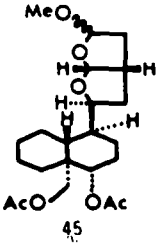


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Table 3

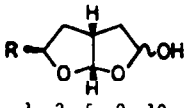
R / Reac. temp.	t-Butyl 1[a]	Phenyl 2[a]	2-Me-phenyl 9[b]	2,6-DiMe-phenyl 10[b]	Clerodin homolog 5
2°C	80	80	90	100	100[c]
10°C	30	30	50	80	80

a): Ref. 5.
b): Ref. 6.
c): mono-MeOH adduct ratios in mono- and tri-methoxy adducts (GC).

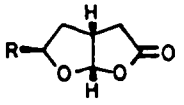
Table 4

R	t-Butyl[a]	Phenyl[a]	2-Me-phenyl[b]	2,6-DiMe-phenyl[b]	Clerodin homolog
Compds. / Conc.(ppm)	1	2	9	10	5
1000	-	-	+ + +	+ + + +	+ + + +
500			+ +	+ + +	+ + +
250			-	+	-
Compds. / Conc.(ppm)	46	47	48	49	39
1000	-	+	+ + +	+ + + +	+ + + +
500			+ +	+ + +	+ + +
250			+	+ +	+ +

a): Ref. 5.
b): Ref. 6.
c): Degrees of antifeeding activity: ++++ (100~95%), +++ (95~75), ++ (75~50), + (50~25%), - (25~0%).



1, 2, 5, 9, 10



39, 46 ~ 49

dimethylphenyl derivative 10; moreover, biological activity of 5 was almost identical with that of 10.

Thus, chemical reactivities at the active center of these model compounds showed a tendency to increase with successive, phenyl deriv. 2 > 2-methylphenyl deriv. 9 > 2,6-dimethylphenyl deriv. 10 ≧ clerodin homolog 5 (>>clerodin hemiacetal[5]) (Table 3). Contrary to the reactivity, their biological activities decreased with successive, phenyl deriv. 2 < 2-methylphenyl deriv. 9 < 2,6-dimethylphenyl deriv. 10 ≧ clerodin homolog 5 (<<clerodin hemiacetal) (Table 4). As predicted before, these results show unequivocally that, as the free-rotation of the perhydrofuro[2,3-b]furan ring is stereocontrolled by substituent groups (methyl group or decalin ring etc.), the ring becomes a more stable system and exhibits more potent activity. Furthermore, it is noteworthy that, despite the enormous difference on the structure of support moieties and, particularly, on stereochemistry, clerodin homolog 5 and 2,6-dimethylphenyl derivative 10 showed a similar potency of the antifeeding activity. These findings clearly corroborate the previous hypothesis[6] for the relationship on the structure and activity of biological active substances; i) for the appearance of the biological activity, a definite steric environment is required around the active center, ii) when the above condition is satisfied, the chemical reactivities on the active center remain constant regardless of the structure of the support moieties, iii) the active center holding a constant reactivity represents a constant biological activity. We would expect that the same hypothesis would apply in the case when electronic effects are operative as a major control factor in the appearance of such activity. This methodology comparing the dynamic changes (reactivity) at the active center and the variation of biological activity accompanied by structural changes may be conceptually termed "Dynamic structure-activity relationships," and is effective on the standpoint of drug design creating new active substances from basic ones by claryfying pertinently and rapidly structural factors for the appearance of the activity.

In order to clarify further the relationship between the antifeeding activity of the model compounds and that of the natural products, we are now carring out the synthesis of the clerodin homologs (6, 7, 8) having the methyl groups at the C^8 and/or C^9 positions, which should stereocontrol the stability of the perhydrofuro[2,3-b]furan ring.

EXPERIMENTAL

NMR spectra were recorded on JEOL FX-100 and MH-100 spectrometers with an internal standard of tetramethylsilane. Mass and GC-MS spectra were recorded on a JEOL D-100 spectrometer. High resolution mass spectra were obtained on a JEOL 01-SG spectrometer. IR spectra were determined on a JASCO A-3 spectrometer. GLC analysis was performed on a JEOL GC-1100 spectrometer with a 3% OV-1 glass column (φ3mm x 1m) at 160°C. Force-field calculation was performed on FACOM M-200 (Computer Center of Nagoya University) and HITAC M-200H (Computer Center of Institute for Molecular Science) computers.

Diels-Alder adduct 14

To a sol of methyl gentisate (800 mg, 4.6 mmol) in 40 ml of dry benzene was added, anhydrous K_2CO_3 (800 mg) and then Ag_2O (2.4 g). The mixture was stirred for 10 min at 50°C and then filtered through celite. The filtrate was evaporated in vacuo in the dark. To a sol of the residue (crude p-quinoe 13) in 20 ml of MeCN was added with stirring at 0°C, butadiene (ca. 2 g) in 40 ml of dry MeCN and then a catalytic amount of $SnCl_4$. After stirring for 30 min at room temperature, the reaction mixture was poured onto ice-water and extracted with EtOAc. Organic layer was washed with sat. $NaHCO_3$, water, and then brine, dried (Na_2SO_4), and evaporated in vacuo. The purification of the residue on silica gel TLC gave 952 mg of the Diels-Alder adduct 14 (90.8%), IR($CHCl_3$): 1735, 1600 cm^{-1}; ^1H NMR ($CDCl_3$): δ2.18∿2.66 (4H, m), 2.92 (0.8 H, m, trans-adduct), 3.56 (0.2H, cis-adduct), 3.66 and 3.78 (each 2.4 and 0.6H, both s), 5.66 (2H, m), 6.62 and 6.82 (0.2H, ABq, J=10.2 Hz), 6.66 (0.8H, s); MS: m/z(%) 188 (M^+-32, 17), 161 (100).

Dihydro derivative 15

A sol of 14 (920 mg, 4.18 mmol) in 40 ml of glacial AcOH was stirred at 60°C for 1hr in the presence of 2.68 g (40.8 mmol) of Zn. After cooling, the excessive Zn and ZnOAc was filtered off through a Buchner funnel. The filtrate was neutralized at 0°C by $NaHCO_3$ and extracted with EtOAc. Organic layer was washed with water and then brine, dried (Na_2SO_4), and evaporated in vacuo. The purification of the residue on silica gel TLC gave 902 mg of the dihydro derivative 15 (97.2%), IR ($CHCl_3$): 1740, 1720 cm^{-1}; ^1H NMR ($CDCl_3$): δ2.10∿3.00 (8H, M), 3.45 (1H, t, J=5.8 Hz), 3.76 (3H, s), 5.60 (2H, br.s); MS: m/z(%) 222 (M^+, 13), 77 (100).

Epimerization of 15 by sodium methoxide

To a sol of 15 (850 mg, 3.83 mmol) in 45 ml of dry MeOH was added with stirring at -20°C, 10 ml of dry MeOH containing 122 mg of $NaOCH_3$. After stirring for 1 hr, the mixture was poured onto ice-water and extracted with EtOAc. The sol was treated in the manner described above to afford 765 mg of the epi-

merized dihydro derivative (90%, trans : cis =3.3 : 1), IR ($CHCl_3$): 1720, 1740 cm^{-1}; ^1H NMR ($CDCl_3$): δ2.0∿3.2 (8H, m), 3.44 (0.7H, t, J=5.6 Hz), 3.62 and 3.72 (each 0.3H and 0.7H, both s), 5.58 (1H, br.s); MS: m/z(%) 222 (M^+, 10), 77 (100).

trans-Diketo ester 16 and cis-diketo ester 17
A sol of the epimerized dihydro derivative (750 mg, 3.39 mmol) in 30 ml of EtOAc was hydrogenated at room temperature overnight in the presence of 30 mg of 10%Pd/C. After removal of the catalyst, EtOAc was evaporated in vacuo. The purification of the residue on silica gel TLC gave 558 mg of the trans-diketo ester 16 (77.4%) accompanied by 186 mg of the cis-diketo ester 17 (24.8%). 16: mp 89.5∿90.0°C (needle); IR $CHCl_3$): 1740, 1720 cm^{-1}; ^1H NMR ($CDCl_3$): δ1.04∿1.86 (8H, m), 2.00 2.80 (5H, m), 3.66 (3H, s); MS: m/z(%) 224 (M^+, 23), 81 (100). 17: mp 86.5∿87°C (prism); IR ($CHCl_3$): 1740, 1720 cm^{-1}; ^1H NMR ($CDCl_3$): δ1.24∿1.80 (8H, m), 2.72 (4H, m), 3.10 (1H, dd, J=8.7, 5.0 Hz), 3.72 (3H, s); MS: m/z(%) 224 (M^+, 36), 81 (100) [Found: C, 64.12; H, 7.25. Calcd. for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19%].

α-Hydroxy derivative 18
To a sol of 16 (500 mg, 2.24 mmol) in 9 ml of dioxane-iso-PrOH-H_2O (2 : 2 : 1) was added dropwise at room temperature, a sol of $NaBH_4$ (42.4 mg, 1.32 mmol) in 1 ml of water. After stirring for 5 min, 1 ml of aq. H_2SO_4 (10%) was added at 0°C to the reaction mixture. The chilled mixture was extracted with EtOAc. The sol was treated in the manner described above to afford 444 mg of the C^6 α-alcohol 18 (87.8%), IR ($CHCl_3$): 3420, 1740, 1720 cm^{-1}; ^1H NMR ($CDCl_3$): δ1.0∿2.6 (13H, m), 3.74 (3H, s), 3.96 (1H, dd, J=12.0, 4.0 Hz); MS: m/z(%) 226 (M^+, 4), 81 (100).

Ketal derivative 20
A sol containing 400 mg (1.76 mmol) of 18 dissolved in 20 ml of dry benzene was refluxed overnight with 0.5 ml of ethylene glycol and a catalytic amount of p-TsOH in a 30 ml flask fitted with a water separater. The chilled benzene sol was treated in the manner described above to afford 452 mg of the ketal 20 (95.0%), mp 120∿121°C (prism); IR ($CHCl_3$): 3530, 1710 cm^{-1}; ^1H NMR ($CDCl_3$): δ1.20∿2.32 (13H, m), 3.35 (1H, m, disappeared with D_2O), 3.72 (3H, s), 3.92 (5H, m); MS: m/z(%) 270 (M^+, 15), 99 (100) [Found: C, 62.00; H, 8.05. Calcd. for $C_{14}H_{22}O_5$: C, 62.20; H, 8.20%].

Ketal diol 19
To a stirred suspension of 112 mg of LAH in 4 ml of dry ether was added at 0°C dropwise during 5 min, a sol of 400 mg (1.48 mmol) of 20 in 5 ml of dry ether. After additional stirring for 1 hr, EtOAc was added to the reaction mixture. And then the mixture was poured onto ice-10%HCl and extracted with EtOAc. The sol was treated in the manner described above to afford 316 mg of the diol 19 (88.0%), IR ($CHCl_3$): 3450 cm^{-1}; ^1H NMR ($CDCl_3$): δ1.02∿2.28 (13H, m), 2.88 (2H, s, disappeared with D_2O), 3.48 (1H, d, J=11.0 Hz); MS: m/z(%) 224 (M^+, 6), 99 (100).

Keto acetonide 21
A catalytic amount of p-TsOH was added at room temperature to a stirred sol of 300 mg (1.24 mmol) of 19 in 5 ml of acetone. After 12 hr, the reaction mixture was poured onto water and extracted with EtOAc. The sol was treated in the manner described above to afford 254 mg of the keto acetonide 21 (91.0%), mp 99∿100°C (prism); IR ($CHCl_3$): 1705 cm^{-1}; ^1H NMR ($CDCl_3$): δ1.20∿1.70 (8H, m), 1.46 (3H, s), 1.52 (3H, s), 1.80∿2.30 (3H, m), 2.70 (1H, m), 3.12 (1H, br.s), 3.56 (1H, d, J=12.0 Hz), 3.74 (1H, t, J=3.0 Hz), 4.06 (1H, d, J=12.0 Hz); MS: m/z (%) 238 (M^+, 2), 85 (100) [Found: C, 70.52; H, 9.30. Calcd. for $C_{14}H_{22}O_3$: C, 70.55; H, 9.31%].

trans-Keto diol 26 and cis-keto diol 23
A sol of 600 mg (2.48 mmol) of 19 in 6 ml of AcOH-H_2O (4 : 1) was stirred overnight at room temperature in the presence of a catalytic amount of p-TsOH. The reaction mixture was added at 0°C to sat. methanolic KOH for quenching AcOH, and extracted with EtOAc. The sol was treated in the manner described above to afford 366 mg of the trans-keto diol 26 and 72 mg of the cis-keto diol 23 (13.2%). 26, IR ($CHCl_3$): 3450, 1710 cm^{-1}; ^1H NMR ($CDCl_3$): δ1.0∿2.2 (13H, m), 2.86 (2H, s, disappeared with D_2O), 3.68 (1H, dd, J=9.0, 4.0 Hz), 3.82 (2H, s), MS: m/z(%) 180 (M^+-18, 6), 139 (100). 23, IR ($CHCl_3$): 3430, 1705 cm^{-1}; ^1H NMR ($CDCl_3$): δ1.0∿2.8 (13H, m), 3.62 (1H, d, J=11.3 Hz), 4.00 (1H, d, J=11.3 Hz), 4.08 (1H, t, J=4.7 Hz); MS: m/z(%) 180 (M^+-18, 7), 139 (100).

Tetrahydropyranyl ether 27
To a sol of 360 mg (1.82 mmol) of 26 in 10 ml of dry CH_2Cl_2 was added at 0°C, 0.42 ml (ca. 2.5 eq.) of dihydropyran and then 3 mg of p-TsOH. After stirring for 3 hr, the reaction mixture was poured onto ice-sat. $NaHCO_3$ and extracted with EtOAc. The sol was treated in the manner described above to afford 549 mg of the pyranyl ether (89.0%), IR (CCl_4): 1715 cm^{-1}; ^1H NMR (CCl_4): δ1.2∿2.6 (23H, m), 3.3∿4.1 (7H, m), 4.50 (2H, m); MS: m/z(%) 281 (M^+-85, 1), 85 (100).

Nitrile derivative 28
To a stirred mixture of 1.75 g of t-BuOK (15.5 mmol) in 20 ml of dry t-BuOH and 569 mg of 26 in 20 ml of dry dimethoxymethane was added at room temperature under argon, dropwise (during 5 min), a sol of 594 mg of TosMIC (3.1 mmol) in 5 ml of dry dimethoxyethane. After 3 hr, the reaction mixture was added to ice-water and extracted with EtOAc. The sol was treated in the manner described above to afford 438 mg of the nitrile derivative 28 (74.7%), IR (CCl_4) : 2250 cm^{-1}; ^1H NMR (CCl_4): δ1.2∿2.4 (26H, m), 3.1∿4.1 (7H, m), 4.60 (2H, m); MS: m/z(%) 292 (M^+-85, 2), 85 (100).

Nitrile acetonide 29
A sol of 400 mg (1.06 mmol) of 28 in 5 ml of MeOH was stirred for 4 hr at room temperature in the presence of 4 mg of p-TsOH. The reaction mixture was then added to sat. $NaHCO_3$ and extracted with EtOAc. The dried organic layer was evaporated in vacuo. To a sol of the residue in 5 ml of acetone was added at 0°C, 1.4 ml of dimethoxy propane and then 5 mg of p-TsOH. After stirring for 7 hr, the reaction mixture was added to sat. $NaHCO_3$ and extracted with EtOAc. The sol was treated in the manner described above to affored 226 mg of the nitrile acetonide 29 (91.0%), mp 101∿101.5°C; IR (CCl_4): 2250 cm^{-1}; ^1H NMR (CCl_4): δ1.38 (3H, s), 1.42 (3H, s), 1.12∿2.60 (14H, m), 3.48 (1H, dd, J=8.0, 5.3 Hz), 3.74 (1H, d, J=12.0 Hz), 3.86 (1H, d, J=12.0 Hz); MS: m/z

(%) 234 (M^+-15, 65), 174 (100), [Found: C, 72.00; H, 9.37; N, 5.56. Calcd. for $C_{15}H_{32}O_2N$; C, 72.25; H, 9.30; N, 5.62%].

Vinyl acetonide 31

To a sol of 200 mg (0.80 mmol) of 29 in 5 ml of dry toluene was added at -78°C under argon, 1.6 ml (ca. 2 eq) of 10%DIBAH (in hexane). After stirring for 1 hr, 1 ml of MeOH and then 0.5 ml of H_2O was added and stirring was continued at -78°C for 10 min and then 0°C for 1 hr. The reaction mixture was passed through neutral alumina (Aluminiumoxid 90, aktive I, Merck) using CH_2Cl_2 as a eluting solvent. The eluate was condensed in vacuo. The crude aldehyde was slowly added at -78°C under argon, to methylene triphenylphosphorane in THF [prepared from 411 mg (1.15 mmol) of methyl triphenylphosphonium bromide and 0.8 ml of 1.4 M n-BuLi (in hexane)]. The reaction mixture was stirred at -78°C for 30 min and then at 0°C for 1 hr, poured onto ice-water, and extracted with EtOAc. The sol was treated in the manner described above to afford 152 mg of the vinyl acetonide 31 (75.5%), IR (CCl_4): 1640 cm^{-1}; ^1H NMR ($CDCl_3$): δ1.0∿2.6 (14H, m), 1.40 (3H, s), 1.46 (3H, s), 3.40 (1H, d, J=11.0, 5.3 Hz), 4.88 (1H, dd, J=15.6, 1.8 Hz), 4.90 (1H, dd, J=11.6, 1.8 Hz0, 5.40 (1H, m); MS: m/z(%) 235 (M^+-15, 36), 95 (100).

Epoxy acetonide 32

To a sol of 200 mg (0.80 mmol) of 31 in 5 ml of CH_2Cl_2 was added at 0°C, 152 mg (1.04 mmol) of sodium phosphate, dibasic, and then 186 mg (1.04 mmol) of mCPBA. After stirring at room temperature overnight, the reaction mixture was poured onto a cold 5% NaOH sol and extracted with EtOAc. The sol was treated in the manner described above to afford 170 mg of the epoxy acetonide 32 (80.0%) as a colorless crystal (recrystallized from n-hexane for elemental analysis). 32, mp 84.5∿85°C; ^1H NMR: δ1.0∿2.6 (17H, m), 1.28 (3H, s), 1.34 (3H, s), 3.30 (1H, dd, J=9.0, 4.3 Hz), 3.68 (2H, s); MS: m/z(%) 251 (M^+-15, 71), 91 (100), [Found: C, 72.49; H, 10.06. Calcd. for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84%].

Furan alcohol 11 and its epimer 34

To a stirred ethereal lithium di(3-furyl)cuprate·2furyllithium-dimethyl sulfide complex [prepared from 1.66 g (11.3 mmol) of 3-bromofuran, 8.0 ml (11.3 mmol) of 1.4M n-BuLi, 538 mg (2.83 mmol) of CuI, and 1.2 ml of $(CH_3)_2S$] was added at 0°C under argon, 150 mg (0.57 mmol) of the epoxy acetonide 32 in 3 ml of dry ether. After 48 hr, the reaction mixture was quenched with sat. aq. NH_4Cl at -78°C, diluted with EtOAc, and filtered to remove suspended solids. The sol was treated in the manner described above to afford 173 mg (92.0 %) of the furan alcohol 11 and 15 mg (8.0%) of its epimer 34 as a colorless crystal. 11: IR (CCl_4): 3450, 870 cm^{-1}; ^1H NMR (CCl_4): δ1.0∿2.2 (14H, m), 2.38 (1H, dd, J=12.8, 4.4 Hz), 2.56 (1H, dd, J=12.8, 8.8 Hz), 3.36 (1H, d, J=5.6, 3.3 Hz), 3.58 (2H, s), 3.74 (1H, br.dd, J=8.8, 4.4 Hz), 6.20 (1H, br.s), 7.22 (1H, br.s), 7.30 (1H, br.s); MS: m/z(%) 319 (M^+-15, 70), 82 (100). 34: mp 148.5∿150°C; IR (CCl_4): 3450, 870 cm^{-1}; ^1H NMR ($CDCl_3$): δ1.0∿2.6 (16H, m), 1.36 (3H, s), 1.41 (3H, s), 3.42 (1H, dd, J=9.2, 5.0 Hz), 3.78 (1H, d, J=12.8 Hz), 3.80 (1H, overlapped with C^{17} methylene signals), 3.94 (1H, d, J=12.8 Hz), 6.28 (1H, br.s), 7.28 (1H, br.s), 7.36 (1H, br.s); MS: m/z(%) 319 (M^+-15, 24), 82 (100), [Found: C, 72.15; H, 8.96. Calcd. for $C_{20}H_{30}O_4$: C, 71.82 ; H, 9.04%].

Conversion of the furan alcohol 11 into the perhydrofuro[2,3-b]furan derivative 36

A sol of 150 mg (0.45 mmol) of 11 in 3 ml of AcOH-H_2O (4 : 1) was stirred at room temperature for 5 hr. The reaction mixture was then poured onto EtOAc. The sol was treated in the manner described above to afford the crude furan-alcohol 35. The crude product 35 (ca. 130 mg) was converted onto 108 mg (77.0%) of the perhydrofuro[2,3-b]furan derivative 36 followed by the method: i) methanolysis of the furan ring, ii) catalytic hydrogenation, iii) acid catalyzed demethylation and epimerization. 36: IR (CCl_4) 3450 cm^{-1}; ^1H NMR ($CDCl_3$): δ1.0∿2.4 (18H, m), 2.08 (2H, br.s, disappeared with D_2O), 2.80 (1H, m), 3.40 (1H, dd, J=9.8 , 5.5 Hz), 3.80 (1H, d, J=11.5 Hz), 3.97 (1H, br.s, disappeared with D_2O), 4.0 (1H, overlapped with C^{17} methylene proton signals), 4.06 (1H, d, J=11.5 Hz), 5.50 (1H, s), 5.68 (and 5.70 (each 0.5H, both d, each J=5.3 Hz and 5.1 Hz); MS: m/z(%) 294 (M^+-18, 3), 111 (100).

Clerodin homolog triacetate 37

A sol of 100 mg (0.32 mmol) of 36 in 3 ml of pyridine was added. The mixture was warmed to room temperature and stirred overnight. The reaction sol was then poured onto ice-5%HCl and extracted with EtOAc. The sol was treated in the manner described above to afford 140 mg (100%) of the triacetate 37 as a colorless oil. 37: IR (CCl_4): 1735 cm^{-1}; ^1H NMR ($CDCl_3$): δ1.2∿2.4 (18H, m), 2.00 (3H, s), 2.02 and 2.04 (3H, each s), 2.06 (3H, s), 2.86 (1H, m), 4.06 (1H, d, J=12.0 Hz), 4.08 (1H, overlapped with C^{17} methylene signals), 4.56 (1H, dd, J= 11.7, 5.7 Hz), 4.60 (1H, d, J=12.0 Hz), 5.60 and 5.70 (each 0.25H and 0.75H, both d, each J=4.8 Hz and J=5.5 Hz), 6.24 and 6.26 (each 0.25H and 0.75H, both br.d, each J=6.0 Hz and J=5.0 Hz); MS: m/z(%) 379 (M^+-60, 5), 111 (100).

Transformation of the triacetate 37 into the final produc 5

A catalytic amount of 70%$HClO_4$ was added at 0°C to a stirred sol of 100 mg (0.23 mmol) of 37 in 3 ml of THF-H_2O (4 : 1). After 1 hr, the reaction mixture was poured onto sat. $NaHCO_3$ and extracted with EtOAc. The sol was treated in the manner described above to afford 90.0 mg (100%) of the final product 5, IR (CCl_4): 3450, 1735 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.0∿2.2 (18H, m), 2.00 (3H, s), 2.06 (3H, s), 2.90 (1H, m), 4.04 (1H, d, J=12.0 Hz), 4.06 (1H, overlapped with C^{17} methylene signals), 4.50 (1H, overlapped with C^{17} methylene signals), 4.60 (1H, d, J=12.0 Hz), 5.50 (1H, m), 5.68 and 5.70 (each 0.5H, both d, each J= 5.4 Hz and J=5.2 Hz); MS: m/z(%) 379 (M^+-18, 2), 111 (100), [High MS, Found: 378.2018. Calcd. for $C_{21}H_{30}O_6$: 378.2040].

Clerodin homolog γ-lactones, 39 and 40

A large excess of CrO_3·2Py was added at 0°C to a stirred sol of 10 mg (0.025 mmol) of 5 in 0.5 ml of dry CH_2Cl_2. The reaction mixture was warmed to room temperature and stirred for additional 2 hr. The mixture was added to a cold aq. 5%HCl and extracted with EtOAc. The sol was treated in the manner described above to afford 10 mg (100%) of a mixture of the γ-lactones, 39 and 40, IR (CCl_4): 1795, 1740 cm^{-1}; ^1H NMR ($CDCl_3$): δ1.2∿2.2 (16H, m), 2.00 (3H, s), 2.06 (3H, s), 2.40 (1H, dd, J=17.7,

3.0 Hz), 2.74 (1H, dd, J=17.7, 9.3 Hz), 3.04 (1H, m), 4.06 (1H, d, J=12.0 Hz), 4.24 (1H, dd, J=9.0, 5.3 Hz), 4.56 (1H, dd, J=11.0, 5.0 Hz), 4.64 (1H, d, J=12.0 Hz), 5.80 and 5.93 (each 0.07H and 0.93H, both d, each J=5.0 Hz and J=5.2 Hz); MS: m/z(%) 335 (M^+-59, 5), 334 (M^+-60, 12), 147 (100), [High MS: Found: 334.1773. Calcd. for $C_{19}H_{26}O_5$; 334.1780].

Clerodin homolog tri-MeOH adduct 44
A catalytic amount of p-TsOH stirred sol of 10 mg (0.025 mmol) of 5 in 3 ml of MeOH. After 3 hr, the reaction mixture was poured onto sat. $NaHCO_3$ and extracted with EtOAc. The sol was treated in the manner described above to afford 10 mg (100%) of the tri-MeOH adduct 44, IR (CCl_4): 1740 cm^{-1}; ^1H NMR ($CDCl_3$): δ1.2~2.1 (19H, m), 2.00 (3H, s), 2.06 (3H, s), 3.31 (9H, br.s), 3.68 (1H, m), 4.11 (1H, d, J=12.3 Hz), 4.36 (1H, t, J=5.1 Hz), 4.64 (1H, d, J=12.3 Hz), 4.66 (2H, overlapped with C^{17} methylene signals); MS: m/z(%) 425 (M^+-31, 2), 157 (100).

Clerodin homolog methyl acetal 45
To a stirred sol of 10 mg (0.025 mmol) of 5 in 1 ml of ether were added at 0°C, 1 ml of MeOH and a catalytic amount of p-TsOH. After 3 hr, the reaction mixture was poured onto sat. $NaHCO_3$ and extracted with EtOAc. The sol was treated in the manner described above to afford 7.2 mg (70.0%) of 45, IR (CCl_4): 1735 cm^{-1}; ^1H NMR ($CDCl_3$): δ1.2~2.2 (18H, m), 2.00 (3H, s), 2.06 (3H, s), 2.80 (1H, m), 3.30 (3H, br.s), 4.06 (1H, d, J=11.5 Hz), 4.08 (1H, overlapped with one of C^{17} methylene signals), 4.62 (1H, d, J=11.5 Hz), ca. 4.62 (1H, overlapped with one of C^{17} methylene signals), 4.90 and 5.02 (each 0.5H, both d, each J=5.5 Hz and J=5.0 Hz), 5.62 and 5.70 (each 0.5H, both d, each J=5.1 Hz and J=5.3 Hz); MS: m/z(%) 378 (M^+-32, 2), 111 (100).

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