Cajucarins A and B, New Clerodane Diterpenes from *Croton cajucara*, and Their Conformations

Hideji ITOKAWA,*[,a] Yoshitatsu ICHIHARA,[a] Masahiro SHIMIZU,[a] Koichi TAKEYA,[a] and Mario MOTIDOME[b]

Department of Pharmacognosy, Tokyo College of Pharmacy,[a] Horinouchi 1432-1, Hachioji, Tokyo 192-03, Japan and Instituto de Quimica, Universidade de São Paulo,[b] São Paulo, SP Brazil. *Received August 1, 1989*

Two new clerodane diterpenes, cajucarins A (1) and B (2), were isolated from the cortices of *Croton cajucara*. The conformations of 1 and 2 were studied by means of spectroscopic methods and molecular orbital calculations.

Keywords *Croton cajucara*; Euphorbiaceae; clerodane diterpene; cajucarin A; cajucarin B; conformational study; molecular orbital calculation

Clerodane diterpenes have attracted interest in connection with their synthesis,[1] stereochemistry,[2-5] and biological activities. We have studied clerodane diterpenes of several plants of the Flacourtiaceae and Menispermaceae families, and reported the isolation of antitumor clerodanes[6] and the determination of the stereochemistry of clerodanes by analysis of the carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectra.[7]

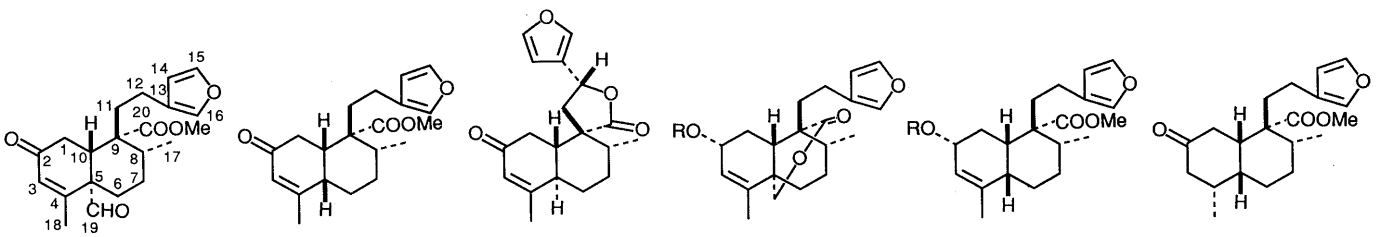
Plants of the genus *Croton* (Euphorbiaceae) are rich sources of clerodanes. From *Croton cajucara* BENTH, a Brazilian medicinal plant known for its antidiabetic and antilipotropic properties, several nor-clerodanes were isolated and their structures were elucidated by Simões *et al.*[8] and our group.[9] In this paper, we describe the structures of two new clerodane diterpenes, cajucarins A (**1**) and B (**2**), isolated from *C. cajucara*, as well as conformational studies of **1** and **2** by means of NMR and circular dichroism (CD) studies and semi-empirical molecular orbital calculations [the complete neglect of differential overlap/2 (CNDO/2) and the modified neglect of diatomic overlap (MNDO)]. These studies revealed the preferred side-chain rotamer for cajucarin A and the non-steroidal and ring B boat conformation for cajucarin B. The result of the MNDO calculation also provided an explanation for the ^{13}C-NMR signals of **1**.

Structures of Cajucarins A and B Compounds **1** and **2** were isolated from a dichloromethane extract of cortices of *Croton cajucara* (commonly called "sacaca" in Brazil) purchased in Belém, Brazil.

Cajucarin A (**1**) was obtained as a colorless oil, whose molecular formula of $C_{21}H_{26}O_5$ was deduced from the mass spectrum (MS) [the chemical ionization mass spectrum (CIMS) 359 $(M+H)^+$] and ^{13}C-NMR [the proton decoupled and the distortionless enhancement by polarization transfer (DEPT)] spectra. Its infrared (IR) spectrum showed the presence of α,β-unsaturated carbonyl (C=O, 1670 cm^{-1}; C=C, 1615 cm^{-1}) and furyl (1505 and 875 cm^{-1}) groups. Analyses of the proton (^{1}H) and ^{13}C-NMR spectra revealed the presence of an allylic methyl group coupled with an olefinic proton [^{1}H-NMR: δ 1.80 (3H, d, J= 0.8 Hz)], a secondary methyl group [^{1}H-NMR: δ 0.93 (3H, d, J=6.7 Hz)], a formyl group [^{1}H-NMR: δ 9.48 (d, J=1.6 Hz), ^{13}C-NMR: δ 191.64 (d)], a methoxycarbonyl group [^{1}H-NMR: δ 3.60 (3H, s), ^{13}C-NMR: δ 51.40 (q) and 174.54 (s)] and a β-substituted furyl group [^{1}H-NMR: δ 6.26 (d, J=1.6 Hz), 7.24 (br s) and 7.34 (d, J=1.6 Hz)].

The spectral characteristics resembled those of *t*-dehydrocrotonin (**3**)[9] (dehydrocrotonin[8]), a 19-nor-clerodane diterpene, previously isolated from the same plant. However, the absence of a γ-lactone moiety and the presence of methoxycarbonyl and formyl groups were indicated as described above. Thus, **1** was revealed to be clerodane with a methoxycarbonyl, a formyl and two methyl groups. The ^{1}H- and ^{13}C-NMR spectra were eventually assigned as shown in Table I by ^{1}H–^{1}H correlated spectroscopy (COSY), ^{1}H–^{13}C COSY, decoupling experiments and comparison with reported ^{13}C-NMR data of other clerodanes.[10]

The relative configurations and the positions of the substituents of **1** were determined as follows. The proton at C-8 was deduced to be axial from the coupling constants (J= 13.7 and 4.0 Hz) with the protons at C-7. And H-8 was coupled to the methyl group at C-8 (J=6.7 Hz). Thus, these observations indicated the equatorial orientation for the methyl group at C-8. The W-type long-range coupling was observed between the aldehyde proton and the axial proton at C-6, and the latter proton showed 7% nuclear Overhauser effect (NOE) enhancement with H-10, indicating that the formyl group was attached to C-5 and had a *trans* relationship with H-10 (Chart 2). Furthermore the NOE experiment showed 7% enhancement between the aldehyde proton and the axial proton at C-1 that has a *trans* diaxial relationship with H-10. Consequently, the methoxycarbonyl group was required to be attached to C-9, which



1 **2** **3** **4**: R=H **5**: R=*p*-bromobenzoyl **6**: R=H **7**: R=*p*-bromobenzoyl **8**

Chart 1

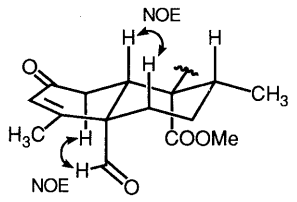


Chart 2

Table I. ^{1}H- and ^{13}C-NMR Data for Cajucarin A (**1**)

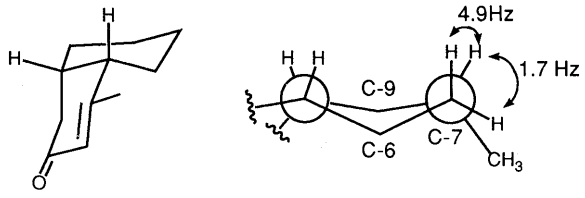
^{1}H		^{13}C	
1	2.81 (dd, 18.2, 14.7 Hz)	1	35.04 (t)
1	2.62 (dd, 18.2, 4.7 Hz)	2	196.69 (s)
3	6.14 (d, 0.7 Hz)	3	130.69 (d)
5	—	4	159.83 (s)
6	2.73 (dt, 13.1, 3.3 Hz)	5	55.46 (s)[a]
6	1.23 (dddd, 13.7, 13.1, 4.0, 1.6 Hz)	6	28.54 (t)
7	1.67 (qd, 13.7, 3.3 Hz)	7	27.46 (t)
7	1.59 (dtd, 13.7, 4.0, 3.3 Hz)	8	35.27 (d)
8	1.76—1.84 (qdd, 6.7, 13.7, 4.0 Hz)	9	52.13 (s)[a]
10	2.48 (dd, 14.7, 4.7 Hz)	10	44.80 (d)
11	1.98 (td, 12.7, 4.4 Hz)	11	30.93 (t)
11	2.17 (ddd, 12.7, 12.5, 4.0 Hz)	12	18.16 (t)
12	2.25 (ddd, 13.3, 12.5, 4.4 Hz)	13	123.93 (s)
12	2.38 (ddd, 13.3, 12.7, 4.0 Hz)	14	110.64 (d)
14	6.26 (d, 1.6 Hz)	15	143.03 (d)
15	7.36 (d, 1.6 Hz)	16	138.67 (d)
16	7.24 (br s)	17	16.96 (q)
17	0.93 (3H, d, 6.7 Hz)	18	19.29 (q)
18	1.80 (3H, d, 0.7 Hz)	19	191.64 (d)
19	9.48 (d, 1.6 Hz)	20	174.54 (s)
OCH_3	3.60 (3H, s)	OCH_3	51.40 (q)

^{1}H- and ^{13}C-NMR spectra were recorded at 400 and 100 MHz in $CDCl_3$. Chemical shifts (δ) are referred to TMS. *a*) These assignments may be interchanged.

Table II. ^{1}H- and ^{13}C-NMR Data for Cajucarin B (**2**) in $CDCl_3$

^{1}H		^{13}C	
1	2.59 (dd, 14.6, 12.2 Hz)	1	36.69 (t)
1	2.65 (dd, 14.6, 3.7 Hz)	2	197.50 (s)
3	5.86 (d, 1.1 Hz)	3	125.18 (d)
5	2.40 (dt, 12.5, 3.7 Hz)	4	164.72 (s)
6	1.61 (dtd, 14.1, 12.5, 3.7 Hz)	5	38.19 (d)
6	1.74 (ddt, 14.1, 4.0, 3.7 Hz)	6	20.27 (t)
7	1.60 (dtd, 14.4, 3.7, 1.7 Hz)	7	26.83 (t)
7	1.90 (dddd, 14.4, 12.5, 4.9, 4.0 Hz)	8	31.19 (d)
8	2.20—2.33 (qdd, 7.2, 4.9, 1.7 Hz)	9	51.75 (s)
10	2.50—2.60 (dt, 12.2, 3.7 Hz)	10	37.74 (d)
11	1.87—2.09[a]	11	36.93 (t)
11	1.87—2.09[a]	12	19.16 (t)
12	2.20—2.33[a]	13	123.69 (s)
12	2.20—2.33[a]	14	110.15 (d)
14	6.23 (d, 1.6 Hz)	15	142.05 (d)
15	7.35 (d, 1.6 Hz)	16	137.95 (d)
16	7.20 (br s)	17	17.54 (q)
17	1.15 (3H, d, 7.2 Hz)	18	21.86 (q)
18	1.99 (3H, d, 1.1 Hz)	19	—
19	—	20	173.90 (s)
OCH_3	3.70 (3H, s)	OCH_3	50.33 (q)

a) Overlapping signals.



non-steroidal boat conformation for ring B

Chart 3. Conformational Properties of Cajucarin B

was supported by the chemical conversion from **1** to δ-lactone **4** as described below. The whole structure of cajucarin A is **1**, as shown in Chart 1.

The absolute configuration of **1** was determined by applying the exciton chirality method[11] to its allylic benzoate derivative **5**. Sodium borohydride reduction of **1** gave the δ-lactone **4** (IR 1733 cm^{-1}) having an allylic alcohol moiety, which was treated with *p*-bromobenzoyl chloride in pyridine to give the allylic benzoate **5**. The benzoyloxy group at C-2 of **5** was equatorial, because the proton at C-2 was deduced to be axial from its coupling constant with the axial H-1 (J=10.4 Hz) and 5.9% NOE enhancement with H-10. The positive CD sign of **5** (245 nm, $\Delta\varepsilon$ +11.8) thus delineated its neo absolute configuration as shown Chart 1.

Cajucarin B (**2**), the molecular formula $C_{20}H_{26}O_4$ from the high-resolution electron impact mass spectrum (HREIMS), was obtained as a colorless oil. The spectral data for **2** were generally similar to those of **1** with the exception of the absence of a formyl group, which suggested that **2** was a 19-nor type of **1**. The coupling constant between H-5 and H-10 (J=3.7 Hz) in the ^{1}H-NMR indicated that **2** had an A/B *cis* ring junction. The ^{1}H- and ^{13}C-NMR data were assigned by applying two-dimensional (2D) NMR and decoupling experiments as shown in Table II.

The absolute configuration of cajucarin B was determined in the same manner as that for cajucarin A. Benzoylation of the allylic alcohol **6**, which was obtained by sodium borohydride reduction of **2**, afforded the *p*-bromobenzoate **7**. The benzoyloxy group of **7** was deduced to be equatorial, because H-2 was assigned as an axial proton from its coupling constants with H_2-1 (J=12.8 and 5.6 Hz) and the 8.3% NOE enhancement with H-10. The positive CD sign (242 nm, $\Delta\varepsilon$ +8.54) of **7** exhibited neo absolute configuration[11] as shown in Chart 1.

The Conformational Studies of Cajucarin B The ^{1}H-NMR spectrum of cajucarin B showed two conformational features. The first is that the non-steroidal conformation was more favored in $CDCl_3$ solution, since H-10 was axial on ring A and H-5 was axial on ring B, as shown by their coupling constants (H-10, J=12.2, 3.7 and 3.7 Hz, H-5, J=12.5, 3.7 and 3.7 Hz) (Chart 3).

The other feature is the conformation of ring B. As shown in Chart 3, the coupling constants of H-8 with H_2-7 were 4.9 and 1.7 Hz, indicating that H-8 deviated from the normal equatorial orientation. This observation suggested a boat conformation for ring B. Although the chair form for ring B requires the bulky side-chain (C-11–C-16) group to be axial, the boat one permits the group to be equatorial. Furthermore this conformation was supported by analyses of the CD spectra of the 3,4-dihydro compound **8** obtained by the catalytic hydrogenation of **2**. Compound **8** also had a non-steroidal conformation in $CDCl_3$ from the coupling constant between H-10 and one of H_2-1 (J=11.0 Hz). An attempt to determine the configuration of C-4 by ^{1}H-NMR

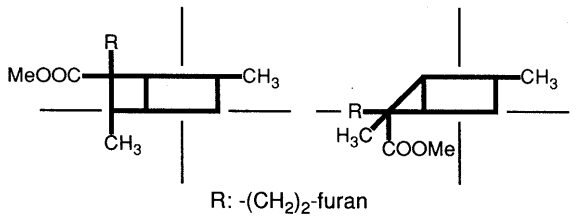


Chart 4

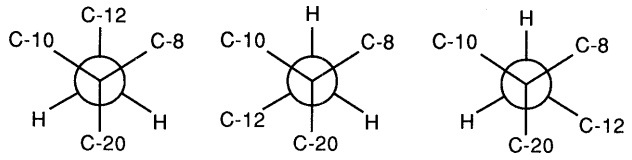


Chart 5. Three Predominant Rotamers of Cajucarin A

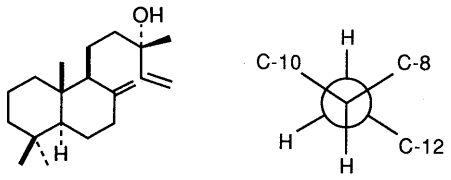


Chart 6. Preferred Rotamer (**10**) of Labdane Diterpene (**11**)[18]

in $CDCl_3$ proved unsuccessful, because of the overlapping of signals. However, ^{1}H-NMR in C_6D_6 showed that H-4 was axial from its coupling constant with H_2-3 (J=13.7 and 4.3 Hz), indicating the equatorial orientation for Me-18. In addition, the coupling constants of H-8 with H_2-7 (4.0 and 2.0 Hz) showed the same deviation as in the case of **2**. The CD spectra of **8** displayed negative Cotton effects [290 nm ($\Delta\varepsilon$ −0.35, EtOH) and 290 nm ($\Delta\varepsilon$ −0.29, $CHCl_3$)] although the absolute configuration of cajucarin B is in the neo-clerodane series, as described above. When the octant rule was applied to the C-2 ketone of **8**, the negative Cotton effect was in good agreement with the boat conformation of ring B (Chart 4).

The Conformational Studies of Cajucarin A Clerodane diterpenes have various side-chains (C-11–C-16), such as furofuran (*e.g.* clerodin[12,13]), γ-lactone and furan (*e.g.* teucvin[14,15]), δ-lactone and furan (*e.g.* columbin[16]) and so on. Cajucarin A possesses a 2-furylethyl group as the side-chain, which can take several possible rotamers with respect to the C-11–C-12 bond orientation: they are an antiperiplanar (**9a**) and two synclinal (**9b** and **9c**) conformations.[17]

Buckwalter and co-workers inferred that the preferred rotamer of the labdane diterpene (**11**) was **10** from ^{13}C-NMR studies as shown in Chart 6.[18] Our investigation of the preferred rotamer of cajucarin A by a series of NOE experiments and molecular orbital calculations showed that the antiperiplanar conformation (**9a**), which differed from that of the labdane diterpene (**11**), was most favorable: the 2D nuclear Overhauser effect spectroscopy (NOESY) spectrum of **1** in $CDCl_3$ indicated that protons of the side-chain were spatially in close proximity to other protons as shown in Chart 7, and this was further supported by NOE

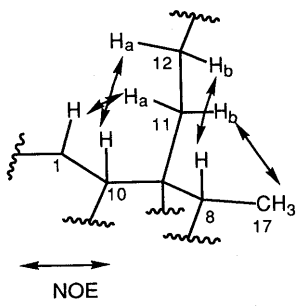


Chart 7

Table III. NOEDS Data for Cajucarin A

Protons correlated	Enhancement (%)
H_a-11, H-1	6.4
H_b-11, Me-17	3.5
H_a-12, H-10	5.3
H_b-12, H-8	8.2

Table IV. Heat of Formation (kcal/mol) and Total Energy (eV) for Three Rotamers (**9a**—**c**)[a]

	Heats of formation	Total energies
9a	−116.92571	−7132.943
9b	−114.84334	−7132.832
9c	−113.88113	−7132.713

a) The heat of formation and total energy were calculated by the MNDO and CNDO/2 methods, respectively.

difference experiments (Table III).

In many cases, semi-empirical molecular orbital calculations have been found to be an effective method for the conformational analysis. We applied the CNDO/2[19] and MNDO[20] methods to predict the relative stabilities of the three predominant rotamers. The total energy and the heat of formation for the optimized structures are recorded in Table IV.[21] The MNDO energy difference between the antiperiplanar conformation and the two synclinal ones indicated that the former was more stable than the latter by about 2.1 and 3.0 kcal/mol. Hence, the NOE results were further supported.

The MNDO results and the conformational studies allowed us to interpret of the ^{13}C-NMR chemical shift of cajucarin A. In the ^{13}C-NMR spectrum, the C-12 methylene carbon adjacent to the furyl group resonated at rather high field (18.2 ppm) in $CDCl_3$. To the best of our knowledge, the chemical shift of this kind of carbon was originally assigned by Wagner and co-workers in comparison with data of other clerodanes.[22]

The ^{13}C-NMR chemical shift correlates with carbon hybridization, electronegativity, steric interactions and so on.[23] The large negative atomic charge (C-12, −1.770)[24] and the *γ-gauche* effects of H-8 and H-10 would be expected to make C-12 resonate at rather high field.

Experimental

Melting points (uncorrected) were determined on a Yanagimoto micro melting point apparatus, optical rotations on a JASCO DIP-4 digital polarimeter, CD spectra on a JASCO J-500C, IR spectra on a Hitachi 260-

30 or a Perkin-Elmer 1710 FTIR spectrometer and ultraviolet (UV) spectra on a Hitachi 557. ^{1}H-NMR (400 MHz) and ^{13}C-NMR (100 MHz) were recorded on a Bruker AM-400 spectrometer with tetramethylsilane (TMS) as an internal standard. Mass spectra were obtained on a Hitachi RMU-7L spectrometer. Thin layer chromatography (TLC) was run on 0.25 mm silica gel (60 F_{254}, Merck) or RP-18 plates (F_{254s}, Merck). Silica gel column chromatography was carried out on Kieselgel 60 (50—100 times the amount of the sample). High performance liquid chromatography (HPLC) for final purification was done on a CIG column system (Kusano Scientific Co., Tokyo) with CPS-000-1 (10 μm silica gel) or CPS-000-20 (20 μm ODS).

Computational chemistry experiments were run on a HITAC M-280H computer at the Computer Centre, the University of Tokyo (MNDO), or on an NEC PC-9801UX (CNDO/2[25]). The MNDO (version 4.0) program was run on MOPAC, distributed by Quantum Chemistry Program Exchange (QCPE).

Extraction and Isolation Dried and finely powdered cortices of *Croton cajucara* were extracted with CH_2Cl_2. The extract (60 g) was chromatographed on a silica gel column and eluted with *n*-hexane–EtOAc (9 : 1, 4 : 1, 1 : 1) and MeOH. This fractionation gave fractions 1—12, combined on the basis of TLC monitoring. Fraction 10, which contained cajucarin A (**1**, 35 mg) and cajucarin B (**2**, 200 mg), was subjected to HPLC (*n*-hexane–EtOAc–MeCN, 7 : 2 : 1 and benzene–EtOAc, 49 : 1). These procedures led to the isolation of compound **1**. Compound **2** was further purified by HPLC: *n*-hexane–EtOAc–MeCN (7.3 : 1.7 : 1) and MeOH–H_2O (8.3 : 1.7, using ODS).

Cajucarin A (1) Colorless oil, $[\alpha]_D^{20}$ −462.0° (c=0.37, $CHCl_3$). CIMS m/z (rel.int.): 359 (M^++1, 12), 330 (47), 299 (33), 269 (47), 248 (100). IR ($CHCl_3$): 2960, 1715, 1670, 1620, 1505, 875 cm^{-1}. UV (MeOH): 218.0 (8200), 238.5 (8600), 299.5 (800) nm (ε).

Cajucarin B (2) Colorless oil, $[\alpha]_D^{20}$ −25.9° (c=6.48, $CHCl_3$). EIMS m/z (rel.int.): 330 (M^+, 18), 271 (6), 248 (27), 236 (29), 176 (48), 134 (47), 121 (74), 81 (100). HRMS: $C_{20}H_{26}O_4$, Calcd 330.1829. Found 330.1809. IR (CCl_4): 2943, 1734, 1676, 1636, 1567, 1503, 875 cm^{-1}. UV (MeOH): 234.0 (10500) nm (ε).

Reduction of 1 A MeOH solution of **1** (10 mg) was treated with an excess of $NaBH_4$. After work-up in the usual way, the product was purified by HPLC (benzene–EtOAc–MeCN, 8 : 1.5 : 0.5) to afford compound **4** (8.5 mg) as a colorless oil: $[\alpha]_D^{20}$ +7.9° (c=0.13, $CHCl_3$). EIMS m/z (rel.int.): 330 (M^+, 7), 312 (5), 284 (8), 267 (10), 231 (13), 218 (28), 105 (100). IR ($CHCl_3$): 3493, 2941, 1733, 1503, 875 cm^{-1}. UV (EtOH): 210.5 (9300) nm (ε). ^{1}H-NMR ($CDCl_3$): δ 0.95 (3H, d, J=6.6 Hz), 1.35 (1H, td, J=13.2, 10.1 Hz), 1.45 (1H, ddd, J=12.5, 4.2, 2.1 Hz), 1.55 (1H, qd, J=13.2, 4.2 Hz), 1.66 (3H, t, J=1.6 Hz), 1.79—1.91 (4H, m), 2.17—2.25 (3H, m), 2.34 (1H, td, J=13.4, 4.7 Hz), 2.43 (1H, td, J=13.4, 4.7 Hz), 4.30 (1H, m), 4.34 (1H, d, J=11.9 Hz), 4.43 (1H, dd, J=11.9, 1.6 Hz), 5.46 (1H, d, J=1.6 Hz), 6.30 (1H, d, J=1.7 Hz), 7.27 (1H, d, J=1.7 Hz), 7.37 (1H, t, J=1.7 Hz).

Benzoylation of 4 Benzoylation of **4** (7.5 mg) with *p*-bromobenzoyl chloride in pyridine (15 min) and work-up in the usual way afforded **5** (7.0 mg) as colorless needles: mp 47.5—49.5 °C, $[\alpha]_D^{20}$ +100.0 (c=0.15, $CHCl_3$). EIMS m/z (rel.int.): 514 (2), 512 (2), 312 (64), 218 (86), 105 (100). IR ($CHCl_3$): 3024, 1718, 1510, 875 cm^{-1}. UV (EtOH): 206.5 (18000), 246.0 (18600) nm (ε). CD (EtOH): 245 nm ($\Delta\varepsilon$ +11.8). ^{1}H-NMR ($CDCl_3$): δ 0.98 (3H, d, J=6.6 Hz), 1.48 (1H, ddd, J=13.7, 4.6, 2.1 Hz), 1.53—1.58 (1H, m), 1.63 (1H, td, J=13.1, 10.4 Hz), 1.70 (3H, t, J=1.6 Hz), 1.75—1.88 (2H, m), 1.92 (1H, m), 2.02 (1H, dd, J=13.1, 2.1 Hz), 2.20—2.50 (4H, m), 2.37 (1H, ddd, J=13.1, 10.2, 2.1 Hz), 4.39 (1H, d, J=11.9 Hz), 4.52 (1H, d, J=11.9, 1.6 Hz), 5.52 (1H, d, J=1.6 Hz), 5.60 (1H, d, J=10.4, 10.2 Hz), 6.31 (1H, dd, J=1.6, 0.8 Hz), 7.29 (1H, dd, J=1.6, 0.8 Hz), 7.36 (1H, t, J=1.6 Hz), 7.58 (2H, d, J=8.6 Hz), 7.89 (2H, d, J=8.6 Hz).

Reduction of 2 A MeOH solution of **2** (20 mg) was treated with an excess of $NaBH_4$. After work-up in the usual way, the product was purified by HPLC (benzene–EtOAc, 8.2 : 1.8) to afford compound **6** (12 mg) as a colorless oil: $[\alpha]_D^{20}$ +4.0° (c=0.20, $CHCl_3$). EIMS m/z (rel.int.): 332 (M^+, 8), 314 (5), 272 (14), 161 (62), 121 (84), 105 (100). IR ($CHCl_3$): 3601, 3024, 1723, 1504, 875 cm^{-1}. UV (EtOH): 215.5 (3900) nm (ε). ^{1}H-NMR (C_6D_6): δ 1.19 (3H, d, J=7.1 Hz), 1.23 (1H, dq, J=13.0, 3.0 Hz), 1.35 (1H, qd, J=13.0, 4.0 Hz), 1.40—1.48 (2H, m), 1.53—1.59 (1H, m), 1.56 (3H, t, J=1.5 Hz), 1.65 (1H, q, J=12.8 Hz), 1.83—1.91 (2H, m), 1.94—2.02 (1H, m), 2.12 (1H, dd, J=12.8, 1.3 Hz), 2.23 (1H, ddd, J=12.8, 5.6, 1.3 Hz), 2.18—2.29 (3H, m), 3.32 (3H, s), 4.22 (1H, br s), 5.39 (1H, d, J=1.5 Hz), 6.02 (1H, d, J=1.6 Hz), 6.99 (1H, d, J=1.6 Hz), 7.10 (1H, t, J=1.6 Hz).

Benzoylation of 6 Benzoylation of **6** (10 mg) with *p*-bromobenzoyl chloride in pyridine (30 min) and work-up in the usual way afforded **7** (9.0 mg) as a colorless oil: $[\alpha]_D^{20}$ +73.2° (c=0.25, $CHCl_3$). EIMS m/z (rel.int.): 516 (1), 514 (1), 314 (6), 271 (14), 183 (100), 105 (89). IR ($CHCl_3$): 2945, 1713, 1505, 875 cm^{-1}. UV (MeOH): 207.0 (14000), 243.5 (17500) nm (ε). CD (MeOH): 242.0 nm ($\Delta\varepsilon$ +8.54). ^{1}H-NMR (C_6D_6): δ 1.17 (3H, d, J=7.1 Hz), 1.19 (1H, dq, J=13.0, 2.8 Hz), 1.36—1.43 (2H, m), 1.49—1.58 (1H, m), 1.53 (3H, t, J=1.5 Hz), 1.82—1.99 (3H, m), 2.02 (1H, td, J=11.1, 10.7 Hz), 2.15—2.28 (4H, m), 2.54 (1H, ddd, J=11.1, 5.3, 1.1 Hz), 3.35 (3H, s), 5.23 (1H, d, J=1.5 Hz), 5.85 (1H, m), 6.05 (1H, d, J=1.6 Hz), 7.01 (1H, d, J=1.6 Hz), 7.13 (1H, t, J=1.6 Hz), 7.15 (2H, d, J=8.6 Hz), 7.82 (2H, d, J=8.6 Hz).

Catalytic Hydrogenation of 2 A solution of **2** (33 mg) in EtOH was hydrogenated over 12 mg of 5% palladium on carbon for 20 min at room temperature. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was purifed by HPLC (benzene–EtOAc, 49 : 1) to afford **8** (20 mg) as a colorless oil: $[\alpha]_D^{20}$ −6.3° (c=0.22, $CHCl_3$). EIMS m/z (rel.int.): 332 (M^+, 3), 301 (1), 273 (1), 238 (36), 206 (80), 149 (65), 95 (100). IR (CCl_4): 2950, 1725, 1505, 1460, 1170, 875 cm^{-1}. UV (EtOH): 212.0 (4700) nm (ε). CD (EtOH): 290 nm ($\Delta\varepsilon$ −0.35), ($CHCl_3$): 290 nm ($\Delta\varepsilon$ −0.29). ^{1}H-NMR ($CDCl_3$): δ 1.04 (3H, d, J=6.5 Hz), 1.16 (3H, d, J=7.2 Hz), 1.50—1.63 (3H, m), 1.84—2.06 (5H, m), 2.15—2.29 (5H, m), 2.32 (1H, ddd, J=11.0, 6.0, 3.4 Hz), 2.55 (1H, dd, J=14.2, 11.0 Hz), 2.59 (1H, dd, J=14.2, 6.0 Hz), 3.70 (3H, s), 6.22 (1H, dd, J=1.6, 1.1 Hz), 7.19 (1H, dd, J=1.6, 1.1 Hz), 7.34 (1H, t, J=1.6 Hz). ^{1}H-NMR (C_6D_6): δ 0.66 (3H, d, J=6.6 Hz), 1.04 (1H, dq, J=13.3, 3.5 Hz), 1.08 (3H, d, J=7.3 Hz), 1.18 (1H, qd, J=13.3, 3.9 Hz), 1.24 (1H, dddd, J=13.8, 3.9, 3.5, 2.0 Hz), 1.50 (1H, dddd, J=13.8, 13.0, 4.9, 3.5 Hz), 1.52—1.58 (2H, m), 1.80 (1H, t, J=13.7 Hz), 1.87—1.92 (2H, m), 2.08 (1H, ddd, J=13.7, 4.7, 1.9 Hz), 2.10—2.14 (1H, m), 2.19—2.27 (3H, m), 2.38 (1H, t, J=13.6 Hz), 2.80 (1H, ddd, J=13.6, 3.4, 1.9 Hz), 3.28 (3H, s), 6.02 (1H, d, J=1.6 Hz), 6.99 (1H, d, J=1.6 Hz), 7.10 (1H, t, J=1.6 Hz).

Acknowledgments We would like to thank Dr. Akiko Itai and Dr. Nobuo Tomioka, Faculty of Pharmaceutical Sciences, The University of Tokyo, for helpful discussions. This work was financially supported by the Ministry of Education, Science, and Culture of Japan.

References and Notes

1) T. Tokoroyama, K. Fujimori, T. Shimizu, Y. Yamagiwa, M. Monden, and H. Iio, *Tetrahedron*, **44**, 6607 (1989), and references cited therein.
2) S. Manabe and C. Nishino, *Tetrahedron*, **42**, 3461 (1986).
3) A. S. Sarma and A. K. Gayen, *Indian J. Chem.*, **24B**, 1208 (1985).
4) M. Martinez-Ripoll, J. Fayos, B. Rodriguez, M. C. Garcia-Alvarez, G. Savona, F. Piozzi, M. Paternostro, and J. R. Hanson, *J. Chem. Soc., Perkin Trans. 1*, **1981**, 1186.
5) M. Morita, Y. Kojima, N. Kato, K. Miwa, I. Tanaka, T. Yamane, and T. Ashida, *Tetrahedron Lett.*, **24**, 5631 (1983).
6) H. Itokawa, N. Totsuka, K. Takeya, K. Watanabe, and E. Obata, *Chem. Pharm. Bull.*, **36**, 1585 (1988).
7) H. Itokawa, K. Mizuno, Y. Ichihara, and K. Takeya, *Planta Med.*, **53**, 271 (1987).
8) J. C. Simões, A. J. Ribeiro da Silva, H. Serruya, and M. Helena da Silva Bentes, *Ciencia Cultura*, **31**, 1140 (1979).
9) H. Itokawa, Y. Ichihara, H. Kojima, K. Watanabe, and K. Takeya, *Phytochemistry*, **28**, 1667 (1989).
10) V. Gambaro, M. C. Chamy, J. A. Garbarino, A. San-Martin, and M. Castillo, *Phytochemistry*, **25**, 2175 (1986), and references cited therein.
11) N. Harada, J. Iwabuchi, Y. Yokota, H. Uda, and K. Nakanishi, *J. Am. Chem. Soc.*, **103**, 5590 (1981).
12) D. H. R. Barton, H. T. Cheung, A. D. Cross, L. M. Jackman, and M. Martin-Smith, *J. Chem. Soc.*, **1961**, 5061.
13) N. Harada and H. Uda, *J. Am. Chem. Soc.*, **100**, 8022 (1978).
14) E. Fujita, I. Uchida, and T. Fujita, *J. Chem. Soc.*, **1973**, 793.
15) E. Fujita, I. Uchida, and T. Fujita, *J. Chem. Soc., Perkin Trans. 1*, **1974**, 1547.
16) D. H. R. Barton and D. Elad, *J. Chem. Soc.*, **1956**, 2085.
17) The sequence rule was applied. C-12 and C-20 are prior to other substituent groups on C-11 and C-9, respectively.
18) B. L. Buckwalter, I. R. Burfitt, A. A. Nagel, E. Wenkert, and F. Naf, *Helv. Chim. Acta*, **58**, 1567 (1975).
19) J. A. Pople and G. A. Segal, *J. Chem. Phys.*, **44**, 3289 (1966).
20) M. J. S. Dewar and W. Thiel, *J. Am. Chem. Soc.*, **99**, 4899 (1977); *Idem, ibid.*, **99**, 4907 (1977).
21) Starting geometries were derived from the optimum conformations

predicted by the Allinger MM2 program which was modified for a microcomputer by E. Osawa. Furan was replaced with cyclohexadiene for the MM2 calculation, because of the lack of available parameters.
22) H. Wagner, R. Seitz, H. Lotter, and W. Herz, *J. Org. Chem.*, **43**, 3339 (1978).
23) E. Breitmaier and W. Voelter, "Carbon-13 NMR Spectroscopy," Third ed., VCH, Weinheim, 1987, pp. 110—119.
24) The atomic charges of other methylene groups are summarized below. C-1, −0.0023; C-6, −0.0446; C-7, −0.0722; C-11, 0.0785.
25) O. Kikuchi, "The Molecular Orbital Method," Kodansha, Tokyo, 1971, pp. 171—193.