

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

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**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; cajucarins A; cajucarins B; conformational study; molecular orbital calculation

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

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.*<sup>8)</sup> and our group.<sup>9)</sup> 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 cajucarins A and the non-steroidal and ring B boat conformation for cajucarins B. The result of the MNDO calculation also provided an explanation for the <sup>13</sup>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.

Cajucarins A (1) was obtained as a colorless oil, whose molecular formula of C<sub>21</sub>H<sub>26</sub>O<sub>5</sub> was deduced from the mass spectrum (MS) [the chemical ionization mass spectrum (CIMS) 359 (M+H)<sup>+</sup>] and <sup>13</sup>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<sup>-1</sup>; C=C, 1615 cm<sup>-1</sup>) and furyl (1505 and

875 cm<sup>-1</sup>) groups. Analyses of the proton (<sup>1</sup>H) and <sup>13</sup>C-NMR spectra revealed the presence of an allylic methyl group coupled with an olefinic proton [<sup>1</sup>H-NMR: δ 1.80 (3H, d, J = 0.8 Hz)], a secondary methyl group [<sup>1</sup>H-NMR: δ 0.93 (3H, d, J = 6.7 Hz)], a formyl group [<sup>1</sup>H-NMR: δ 9.48 (d, J = 1.6 Hz), <sup>13</sup>C-NMR: δ 191.64 (d)], a methoxycarbonyl group [<sup>1</sup>H-NMR: δ 3.60 (3H, s), <sup>13</sup>C-NMR: δ 51.40 (q) and 174.54 (s)] and a β-substituted furyl group [<sup>1</sup>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)<sup>9)</sup> (dehydrocrotonin<sup>8)</sup>), 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 <sup>1</sup>H- and <sup>13</sup>C-NMR spectra were eventually assigned as shown in Table I by <sup>1</sup>H–<sup>1</sup>H correlated spectroscopy (COSY), <sup>1</sup>H–<sup>13</sup>C COSY, decoupling experiments and comparison with reported <sup>13</sup>C-NMR data of other clerodanes.<sup>10)</sup>

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

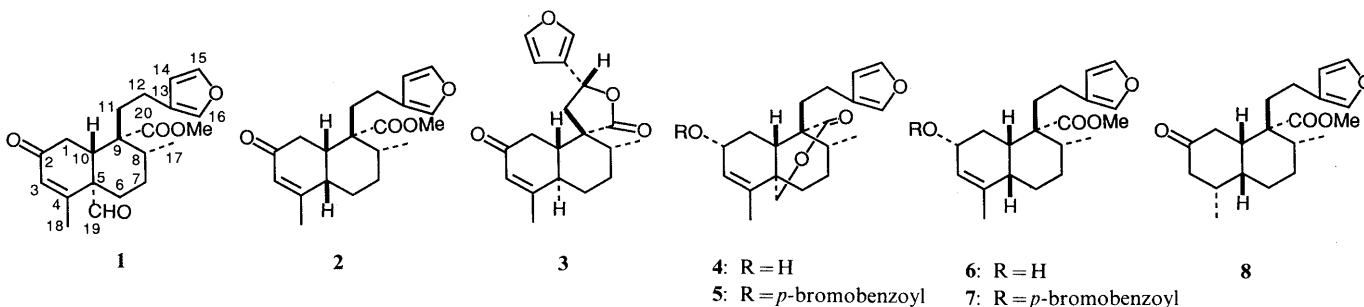
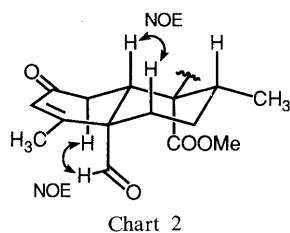


Chart 1

TABLE I.  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR Data for Cajucarín A (1)

$^1\text{H}$		$^{13}\text{C}$	
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) <sup>a)</sup>
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) <sup>a)</sup>
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 <sub>3</sub>	3.60 (3H, s)	OCH <sub>3</sub>	51.40 (q)

$^1\text{H}$ - and  $^{13}\text{C}$ -NMR spectra were recorded at 400 and 100 MHz in  $\text{CDCl}_3$ . Chemical shifts ( $\delta$ ) are referred to TMS. <sup>a)</sup> These assignments may be interchanged.

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

The absolute configuration of **1** was determined by applying the exciton chirality method<sup>(11)</sup> to its allylic benzoate derivative **5**. Sodium borohydride reduction of **1** gave the  $\delta$ -lactone **4** (IR  $1733\text{ cm}^{-1}$ ) having an allylic alcohol moiety, which was treated with *p*-bromobenzoyl chloride in pyridine to give the allylic benzoate **5**. The benzoxyloxy 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 ( $J=10.4\text{ Hz}$ ) and 5.9% NOE enhancement with H-10. The positive CD sign of **5** (245 nm,  $\Delta\epsilon +11.8$ ) thus delineated its neo absolute configuration as shown Chart 1.

Cajucarín B (**2**), the molecular formula  $\text{C}_{20}\text{H}_{26}\text{O}_4$  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 ( $J=3.7\text{ Hz}$ ) in the  $^1\text{H}$ -NMR indicated that **2** had an A/B *cis* ring junction. The  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR data were assigned by applying two-dimensional (2D) NMR and decoupling experiments as shown in Table II.

The absolute configuration of cajucarín B was determined in the same manner as that for cajucarín A. Benzoxylation

TABLE II.  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR Data for Cajucarín B (**2**) in  $\text{CDCl}_3$ 

$^1\text{H}$		$^{13}\text{C}$	
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 <sup>a)</sup>	11	36.93 (t)
11	1.87—2.09 <sup>a)</sup>	12	19.16 (t)
12	2.20—2.33 <sup>a)</sup>	13	123.69 (s)
12	2.20—2.33 <sup>a)</sup>	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 <sub>3</sub>	3.70 (3H, s)	OCH <sub>3</sub>	50.33 (q)

<sup>a)</sup> Overlapping signals.

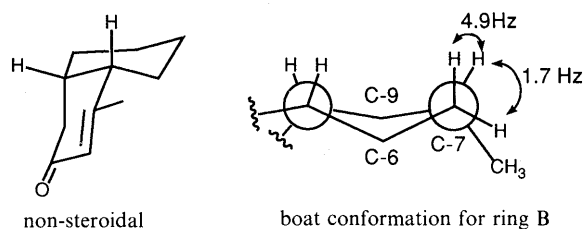


Chart 3. Conformational Properties of Cajucarín B

of the allylic alcohol **6**, which was obtained by sodium borohydride reduction of **2**, afforded the *p*-bromobenzoate **7**. The benzoxyloxy group of **7** was deduced to be equatorial, because H-2 was assigned as an axial proton from its coupling constants with H<sub>2</sub>-1 ( $J=12.8$  and  $5.6\text{ Hz}$ ) and the 8.3% NOE enhancement with H-10. The positive CD sign (242 nm,  $\Delta\epsilon +8.54$ ) of **7** exhibited neo absolute configuration<sup>(11)</sup> as shown in Chart 1.

**The Conformational Studies of Cajucarín B** The  $^1\text{H}$ -NMR spectrum of cajucarín B showed two conformational features. The first is that the non-steroidal conformation was more favored in  $\text{CDCl}_3$  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  $3.7\text{ Hz}$ , H-5,  $J=12.5$ ,  $3.7$  and  $3.7\text{ Hz}$ ) (Chart 3).

The other feature is the conformation of ring B. As shown in Chart 3, the coupling constants of H-8 with H<sub>2</sub>-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  $\text{CDCl}_3$  from the coupling constant between H-10 and one of H<sub>2</sub>-1 ( $J=11.0\text{ Hz}$ ). An attempt to determine the configuration of C-4 by  $^1\text{H}$ -NMR

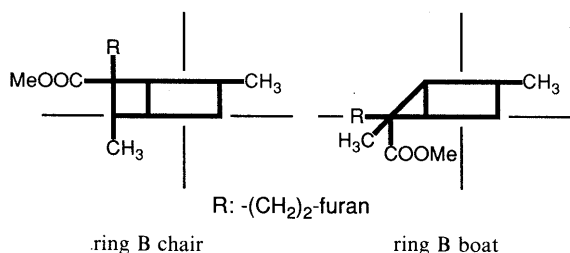


Chart 4

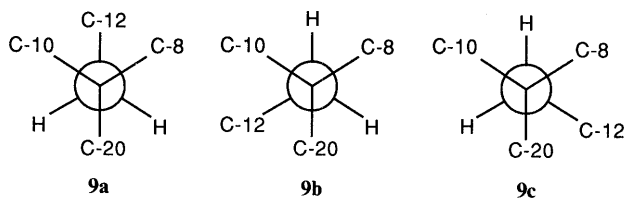
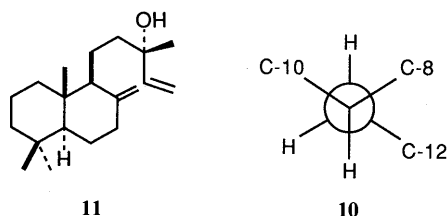


Chart 5. Three Predominant Rotamers of Cajucarín A

Chart 6. Preferred Rotamer (**10**) of Labdane Diterpene (**11**)<sup>18)</sup>

in  $\text{CDCl}_3$  proved unsuccessful, because of the overlapping of signals. However,  $^1\text{H-NMR}$  in  $\text{C}_6\text{D}_6$  showed that H-4 was axial from its coupling constant with  $\text{H}_2\text{-3}$  ( $J=13.7$  and  $4.3\text{ Hz}$ ), indicating the equatorial orientation for Me-18. In addition, the coupling constants of H-8 with  $\text{H}_2\text{-7}$  ( $4.0$  and  $2.0\text{ Hz}$ ) showed the same deviation as in the case of **2**. The CD spectra of **8** displayed negative Cotton effects [ $290\text{ nm}$  ( $\Delta\epsilon -0.35$ , EtOH) and  $290\text{ nm}$  ( $\Delta\epsilon -0.29$ ,  $\text{CHCl}_3$ )] although the absolute configuration of cajucarín 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 Cajucarín A** Clerodane diterpenes have various side-chains (C-11–C-16), such as furofuran (e.g. clerodin<sup>12,13)</sup>),  $\gamma$ -lactone and furan (e.g. teucvin<sup>14,15)</sup>),  $\delta$ -lactone and furan (e.g. columbin<sup>16)</sup>) and so on. Cajucarín 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.<sup>17)</sup>

Buckwalter and co-workers inferred that the preferred rotamer of the labdane diterpene (**11**) was **10** from  $^{13}\text{C-NMR}$  studies as shown in Chart 6.<sup>18)</sup> Our investigation of the preferred rotamer of cajucarín 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  $\text{CDCl}_3$  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

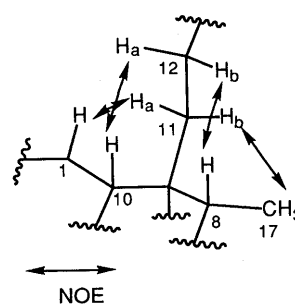


Chart 7

TABLE III. NOEDS Data for Cajucarín A

Protons correlated	Enhancement (%)
$\text{H}_a\text{-11, H-1}$	6.4
$\text{H}_b\text{-11, Me-17}$	3.5
$\text{H}_a\text{-12, H-10}$	5.3
$\text{H}_b\text{-12, H-8}$	8.2

TABLE IV. Heat of Formation (kcal/mol) and Total Energy (eV) for Three Rotamers (**9a–c**)<sup>a)</sup>

	Heats of formation	Total energies
<b>9a</b>	−116.92571	−7132.943
<b>9b</b>	−114.84334	−7132.832
<b>9c</b>	−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<sup>19)</sup> and MNDO<sup>20)</sup> 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.<sup>21)</sup> 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  $^{13}\text{C-NMR}$  chemical shift of cajucarín A. In the  $^{13}\text{C-NMR}$  spectrum, the C-12 methylene carbon adjacent to the furyl group resonated at rather high field (18.2 ppm) in  $\text{CDCl}_3$ . 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.<sup>22)</sup>

The  $^{13}\text{C-NMR}$  chemical shift correlates with carbon hybridization, electronegativity, steric interactions and so on.<sup>23)</sup> The large negative atomic charge (C-12,  $-1.770$ )<sup>24)</sup> and the  $\gamma$ -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.  $^1\text{H-NMR}$  (400 MHz) and  $^{13}\text{C-NMR}$  (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<sub>254</sub>, Merck) or RP-18 plates (F<sub>254</sub>, 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  $\mu\text{m}$  silica gel) or CPS-000-20 (20  $\mu\text{m}$  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<sup>25</sup>). 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  $\text{CH}_2\text{Cl}_2$ . 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 cajucarins A (**1**, 35 mg) and cajucarins 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<sub>2</sub>O (8.3:1.7, using ODS).

**Cajucarins A (1)** Colorless oil,  $[\alpha]_{\text{D}}^{20} -462.0^\circ$  ( $c=0.37$ ,  $\text{CHCl}_3$ ). CIMS  $m/z$  (rel.int.): 359 ( $\text{M}^+ + 1$ , 12), 330 (47), 299 (33), 269 (47), 248 (100). IR ( $\text{CHCl}_3$ ): 2960, 1715, 1670, 1620, 1505, 875  $\text{cm}^{-1}$ . UV (MeOH): 218.0 (8200), 238.5 (8600), 299.5 (800) nm ( $\epsilon$ ).

**Cajucarins B (2)** Colorless oil,  $[\alpha]_{\text{D}}^{20} -25.9^\circ$  ( $c=6.48$ ,  $\text{CHCl}_3$ ). EIMS  $m/z$  (rel.int.): 330 ( $\text{M}^+$ , 18), 271 (6), 248 (27), 236 (29), 176 (48), 134 (47), 121 (74), 81 (100). HRMS:  $\text{C}_{20}\text{H}_{26}\text{O}_4$ , Calcd 330.1829. Found 330.1809. IR ( $\text{CCl}_4$ ): 2943, 1734, 1676, 1636, 1567, 1503, 875  $\text{cm}^{-1}$ . UV (MeOH): 234.0 (10500) nm ( $\epsilon$ ).

**Reduction of 1** A MeOH solution of **1** (10 mg) was treated with an excess of  $\text{NaBH}_4$ . 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:  $[\alpha]_{\text{D}}^{20} +7.9^\circ$  ( $c=0.13$ ,  $\text{CHCl}_3$ ). EIMS  $m/z$  (rel.int.): 330 ( $\text{M}^+$ , 7), 312 (5), 284 (8), 267 (10), 231 (13), 218 (28), 105 (100). IR ( $\text{CHCl}_3$ ): 3493, 2941, 1733, 1503, 875  $\text{cm}^{-1}$ . UV (EtOH): 210.5 (9300) nm ( $\epsilon$ ).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  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  $^\circ\text{C}$ ,  $[\alpha]_{\text{D}}^{20} +100.0^\circ$  ( $c=0.15$ ,  $\text{CHCl}_3$ ). EIMS  $m/z$  (rel.int.): 514 (2), 512 (2), 312 (64), 218 (86), 105 (100). IR ( $\text{CHCl}_3$ ): 3024, 1718, 1510, 875  $\text{cm}^{-1}$ . UV (EtOH): 206.5 (18000), 246.0 (18600) nm ( $\epsilon$ ). CD (EtOH): 245 nm ( $\Delta\epsilon +11.8$ ).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  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  $\text{NaBH}_4$ . 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:  $[\alpha]_{\text{D}}^{20} +4.0^\circ$  ( $c=0.20$ ,  $\text{CHCl}_3$ ). EIMS  $m/z$  (rel.int.): 332 ( $\text{M}^+$ , 8), 314 (5), 272 (14), 161 (62), 121 (84), 105 (100). IR ( $\text{CHCl}_3$ ): 3601, 3024, 1723, 1504, 875  $\text{cm}^{-1}$ . UV (EtOH): 215.5 (3900) nm ( $\epsilon$ ).  $^1\text{H-NMR}$  ( $\text{C}_6\text{D}_6$ ):  $\delta$  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:  $[\alpha]_{\text{D}}^{20} +73.2^\circ$  ( $c=0.25$ ,  $\text{CHCl}_3$ ). EIMS  $m/z$  (rel.int.): 516 (1), 514 (1), 314 (6), 271 (14), 183 (100), 105 (89). IR ( $\text{CHCl}_3$ ): 2945, 1713, 1505, 875  $\text{cm}^{-1}$ . UV (MeOH): 207.0 (14000), 243.5 (17500) nm ( $\epsilon$ ). CD (MeOH): 242.0 nm ( $\Delta\epsilon +8.54$ ).  $^1\text{H-NMR}$  ( $\text{C}_6\text{D}_6$ ):  $\delta$  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 purified by HPLC (benzene–EtOAc, 49:1) to afford **8** (20 mg) as a colorless oil:  $[\alpha]_{\text{D}}^{20} -6.3^\circ$  ( $c=0.22$ ,  $\text{CHCl}_3$ ). EIMS  $m/z$  (rel.int.): 332 ( $\text{M}^+$ , 3), 301 (1), 273 (1), 238 (36), 206 (80), 149 (65), 95 (100). IR ( $\text{CCl}_4$ ): 2950, 1725, 1505, 1460, 1170, 875  $\text{cm}^{-1}$ . UV (EtOH): 212.0 (4700) nm ( $\epsilon$ ). CD (EtOH): 290 nm ( $\Delta\epsilon -0.35$ ), ( $\text{CHCl}_3$ ): 290 nm ( $\Delta\epsilon -0.29$ ).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  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).  $^1\text{H-NMR}$  ( $\text{C}_6\text{D}_6$ ):  $\delta$  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).

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## 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.