Studies on the Constituents of Aceraceae Plants. XIII.[1] Diarylheptanoids and Other Phenolics from *Acer nikoense*

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From a mixture of the bark and twigs of *Acer nikoense* MAXIM. (Aceraceae), nine compounds (1—9) were newly isolated. Compound 1 was identical with acerogenin E, and compounds 8 and 9 were β-orcinol derivatives. Acerogenin K (2), a new diarylheptanoid of the cyclic biphenyl type, yielded acerogenin E on oxidation. Acerogenins F (3) through L (7) are new diarylheptanoids of the cyclic diphenyl ether type, whose skeletons and substituents of the diphenyl ether moieties are the same as those of acerogenin A. Their structures were elucidated on the basis of chemical and spectroscopic evidence.

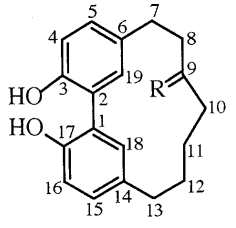
Key words *Acer nikoense*; diarylheptanoid; acerogenin (F, H, I, J, K, L); β-orcinol; diphenyl ether; Aceraceae

The stem bark of *Acer nikoense* MAXIM. (Aceraceae) has been used as a folk medicine in Japan for hepatic disorder and as an eyewash. We have mainly isolated glycosidic diarylheptanoids from the plant so far.[2] We next investigated non-glycosidic compounds in the ether-soluble portion of the same source, and nine compounds **1**—**9** were newly isolated. This paper deals with the identification and the structure determination of **1**—**9**.

Compounds **1**, $C_{19}H_{20}O_3$, mp 229—231 °C, and **2**, $C_{19}H_{22}O_3$, mp 238—240 °C, both optically inactive, exhibited nineteen signals due to two 1,2,4-trisubstituted benzenes, six methylenes, and a carbonyl (**1**) or a hydroxymethine (**2**) in their ^{13}C-NMR spectra. They showed UV absorption maxima at 247 nm (log ε 3.84) and at 251 nm (log ε 3.71), respectively; these maxima are assignable to a biphenyl system.[3] From the above evidence **1** was suggested to be acerogenin E, a diarylheptanoid of cyclic biphenyl type, and **2** was considered to be an alcohol derivative of **1** (racemate). These assignments were confirmed by direct comparison of **1** with an authentic sample of acerogenin E and by Oppenauer oxidation of **2**, yielding acerogenin E.[2a] Acerogenin E is known as the genin of aceroside XI, isolated from *Acer nikoense*. The new compound **2** was designated acerogenin K.

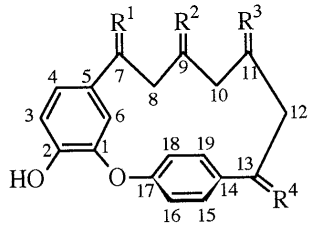
Compounds **3**—**7** ($C_{19}H_{20-22}O_{3-4}$) each showed nineteen carbon signals assignable to diarylheptanoid structures in the ^{13}C-NMR spectra, though no UV absorption maximum (around 250 nm) due to a biphenyl system was observed. In the ^{1}H-NMR spectra of **3**—**7**, aromatic proton signals ascribable to two benzene rings, 1,4-disubstituted and 1,2,4-trisubstituted benzenes, were commonly observed and the 6-H aromatic proton signal resonated at abnormally high magnetic field (δ 5.4—6.1, d, $J \fallingdotseq 2$ Hz). These characteristics indicated that the compounds are diarylheptanoids having the same cyclic diphenyl ether system as acerogenin A, a typical constituent in this plant.[2d] The structural differences among **3**—**7** were in the substituents on the heptane chain. Compounds **3**—**7** were designated acerogenins F (**3**), J (**4**), I (**5**), H (**6**) and L (**7**).

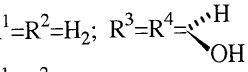
In ^{1}H-NMR spectra, methylene protons at a benzyl position generally resonate at lower magnetic field by about 1.3 ppm than ordinary methylenes. In the case of **3**—**7**, the benzyl protons (7-H_2 and/or 13-H_2) were



1: R=O
2: R=OH, H

Chart 1



3: R^1=R^2=H_2; R^3=R^4=


4: R^1=R^2=H_2;
R^3=

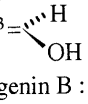
; R^4=

relative configurations

5: R^1=R^3=H_2; R^2=R^4=OH, H

6: R^1=O; R^2=R^4=H_2; R^3=OH, H

7: R^1=R^3=R^4=H_2; R^2=O

acerogenin A: R^1=R^2=R^4=H_2;
R^3=

(*R* configuration)

acerogenin B: R^1=R^3=R^4=H_2;
R^2=OH, H (racemic)

acerogenin C: R^1=R^2=R^4=H_2; R^3=O

Chart 2

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Table 1. ^{1}H-NMR Data for Acerogenins F(**3**), H(**4**), I(**5**), H(**6**) and L(**7**)

No.	**3**[a]	**4**[a]	**5**[b]	**6**[a]	**7**[c]
3	7.24 (d, J=8.1)	7.25 (d, J=8.1)	7.28 (d, J=8.1)	7.32 (d, J=8.3)	6.81 (d, J=8.1)
4	6.76 (dd, J=8.1, 2.0)	6.76 (dd, J=2.0, 8.1)	6.75 (dd, J=2.0, 8.1)	7.86 (br d, J=8.3)	6.59 (dd, J=2.2, 8.1)
6	6.04 (d, J=2.0)	6.07 (d, J=2.0)	5.99 (d, J=2.0)	6.44 (d, J=2.0)	5.41 (d, J=2.2)
7	2.48 (t, J=5.4)[d]	2.50 (t, J=6.0)[d]	Ha 2.70 (br dd, J=15, 6)	—	2.83 (m)[d]
			Hb 3.02 (br dd, J=15, 13)		
8	Ha 1.32 (m)	Ha 1.31 (m)	Ha 1.65 (m)	Ha 2.30 (m)	2.28 (m)[d]
	Hb 1.56 (m)	Hb 1.62 (m)	Hb 1.87 (m)	Hb 2.75 (m)	
9	Ha 0.98 (m)	Ha 1.00 (m)[d]	3.37 (br s)	1.47 (m)[e]	—
	Hb 1.41 (m)[d]	Hb 1.43 (m)[d]			
10	Ha 1.10 (m)	Ha 1.00 (m)[d]	Ha 0.75 (m)	Ha 1.29 (m)	1.75 (m)[d]
	Hb 1.41 (m)[d]	Hb 1.43 (m)[d]	Hb 1.53 (m)	Hb 1.47 (m)[e]	
11	3.47 (br s)	3.96 (br s)	Ha 1.12 (m)	3.46 (br s)	1.55 (m)[d]
			Hb 1.79 (m)		
12	Ha 2.12	Ha 2.06	Ha 1.72 (m)	Ha 1.66 (m)	1.66 (m)[d]
	(ddd, J=5.4, 11.1, 13.1)	(ddd, J=2.0, 6.1, 14.1)			
	Hb 2.82 (dt, J=4.4, 13.1)	Hb 2.60 (dd, J=4.7, 14.1)	Hb 2.40 (m)	Hb 2.09 (m)	
13	5.31 (dd, J=5.4, 10.4)	5.55 (br s)	4.93 (br dd)	Ha 2.87 (dt, J=3.7, 13.0)	2.75 (t, J=6.6)[d]
				Hb 2.95 (dt, J=4.2, 13.0)	
15	8.08 (dd, J=2.0, 8.4)	7.31 (br s)[d]	7.21 (dd, J=8.4, 2.0)	7.36 (dd, J=2.2, 6.6)	7.28 (d, J=8.4)[d]
16	7.44 (dd, J=2.4, 8.4)	7.31 (br s)[d]	6.85 (dd, J=8.4, 2.0)	7.12 (dd, J=3.2, 6.6)	6.97 (d, J=8.4)[d]
18	7.01 (dd, J=2.4, 8.1)	7.16 (d, J=8.4)	7.39 (dd, J=8.4, 2.0)	7.2[g]	6.97 (d, J=8.4)[d]
19	7.34 (dd, J=2.0, 8.1)	8.12 (d, J=8.4)	8.08 (dd, J=8.4, 2.0)	7.38 (dd, J=2.2, 7.0)	7.28 (d, J=8.4)[d]

a) Measured in C_5D_5N. *b*) Measured in $C_5D_5N+D_2O$ (9:1). *c*) Measured in CD_3OD. *d*) Two-proton signal. *e*) Three-proton signal. *f*) Four-proton signal. *g*) The exact chemical shifts and coupling constants could not be determined because of overlapping of the solvent signals.

observed at δ 2.4—3.0, and the signals shifted to δ 4.9—5.6 after hydroxylation at the benzylic position. Furthermore, the signals of 7-H_2 and 13-H_2 were distinguishable from each other, since only 7-H_2 coupled with 6-H by ^4J (about 0.5 Hz). The results of long-range selective proton decoupling (LSPD) experiments among 7-H_2, C-6 and C-4 supported the assignment of 7-H_2.[4] These findings were applied to the signal assignments for **3**—**7**.

Both acerogenins F(**3**), mp 254—255 °C, $[\alpha]_D$ +127° and J(**4**), mp 223—225 °C, $[\alpha]_D$ +65.2°, gave the same molecular formula, $C_{19}H_{22}O_4$. In the ^{1}H-NMR spectra, they exhibited two hydroxymethine proton signals at δ 3.47 (11-H) and 5.31 (13-H) in **3**, and at δ 3.96 (11-H) and 5.55 (13-H) in **4**. Since **3** and **4** showed similar IR and NMR spectra, it was suggested that they were stereoisomers. In the ^{1}H–^{1}H correlation spectroscopy (COSY) of **3**, the following aliphatic chain was found: C-10$_{[\delta 1.10(Ha),1.41(Hb)]}$–C-11$_{[\delta 3.47(H)]}$–C-12$_{[\delta 2.12(Ha),2.82(Hb)]}$–C-13$_{[\delta 5.31(13\text{-}H)]}$. The ^{1}H–^{1}H COSY of **4** gave a similar result for the carbon chain C-10–C-13 (Table 1). These facts indicated that the aliphatic carbons C-11, -12 and -13 form a 1,3-diol system in the two compounds.

For the determination of the configuration of the hydroxyls at C-11 and C-13, nuclear Overhauser effect (NOE) experiments were carried out. In the case of **3**, irradiation of 11-H as well as 13-H caused enhancement of the 19-H signal by 15.4% and 7.4%, respectively. On the other hand, in the case of **4**, irradiation of 11-H and 13-H resulted in increases of the signal intensity of 19-H by 10% and that of 15-H by 7.2%, respectively.[5] Although Dreiding models of **3** and **4**, which are regarded as macrocyclic compounds, showed various possible conformations, the hydroxy group at C-11, a bulkier radical than a hydrogen atom, should be directed away from the inside of the macrocyclic ring. Taking this spatial restriction into account, the results of the NOE experiments described above indicated that 19-H of **3** is sterically close to 11-H as well as 13-H, *i.e.*, the two hydroxyl groups at C-11 and C-13 take the same directions in **3**. In contrast, 11-H and 13-H of **4** are close to 19-H and 15-H, respectively, *i.e.*, the hydroxyls are directed to the opposite sides in **4**. Consequently, the structures of acerogenins F and J were concluded to be rel(11*R*,13*R*)-**3** and rel(11*R*,13*S*)-**4**, respectively, as shown in Chart 2.

Table 2. ^{13}C-NMR Data for Acerogenins F(**3**), J(**4**), I(**5**), H(**6**) and L(**7**)

No.	**3**[a]	**4**[a]	**5**[b]	**6**[a]	**7**[c]
1	150.9	151.0	150.2	150.3	148.6
2	145.6	145.7	144.5	152.5	143.1
3	117.5	117.6	116.8	118.1	115.1
4	123.0	123.0	122.4	122.8	121.9
5	133.0	133.0	132.9	128.4	133.4
6	117.3	117.1	116.1	119.3	113.4
7	32.2	32.1	28.5	198.9	27.3
8	28.5	28.5	36.6	40.5	41.1
9	25.6	25.6	71.0	24.1	209.9
10	40.0	40.3	38.7	40.3	46.2
11	68.6	67.2	20.1	68.7	19.1
12	51.5	49.1	38.5	41.3	27.5
13	72.7	70.9	73.7	32.5	35.4
14	143.7	142.7	141.9	140.8	138.8
15	128.0	127.7	129.4	131.4	131.3
16	124.8	123.5	122.1	123.3	123.2
17	158.1	157.6	157.0	155.9	154.4
18	122.6	123.7	123[d]	124.2	123.2
19	129.4	128.1	127.5	132.1	131.3

a) Measured in C_5D_5N. *b*) Measured in $C_5D_5N+D_2O$ (9:1). *c*) Measured in CD_3OD. *d*) The exact chemical shift could not be determined because of overlapping of the solvent signals.

Acerogenin I(**5**), $C_{19}H_{22}O_4$, mp 214—215 °C, $[\alpha]_D$ −17.2°, has the same molecular formula as **3** and showed two hydroxymethine protons at δ 3.37 (9-H) and 4.93 (benzyl, 13-H) in the ^{1}H-NMR spectrum.[4] The cross peaks observed in the ^{1}H–^{1}H COSY indicated

the following aliphatic chain: C-7$_{[\delta 2.70(Ha),3.02(Hb)]}$–C-8$_{[\delta 1.65(8\text{-}Ha),1.87(Hb)]}$–C-9$_{[\delta 3.37(H)]}$–C-10$_{[\delta 0.75(H),1.53(H)]}$. The above results led to the structure of acerogenin I as **5** (Chart 2).

Acerogenin H (**6**), $C_{19}H_{20}O_4$, mp 245—246 °C, $[\alpha]_D$ −36.4°, showed IR absorption due to a conjugated carbonyl at 1660 cm^{-1}, and carbon signals ascribable to a carbonyl (δ 198.9) and a hydroxymethine (δ 68.7) in the ^{13}C-NMR spectrum. Its UV absorption maxima at 232 (logε 4.11), 279 (3.91), 307 (3.74) and 354 (3.41) nm exhibited bathochromic shifts on addition of sodium acetate, which implied that the carbonyl exists at C-7. The ^{1}H–^{1}H COSY spectrum showed the following carbon chain: C-10$_{[\delta 1.29(Ha),1.47(Hb)]}$–C-11$_{[\delta 3.46(H)]}$–C-12$_{[\delta 1.66(Ha),2.09(Hb)]}$–C-13$_{[\delta 2.87(13\text{-}Ha),2.95(Hb)]}$. The above results led to the structure of acerogenin H as **6**.

Acerogenin L (**7**), $C_{19}H_{20}O_3$, mp 188—190 °C, optically inactive, showed an absorption due to a carbonyl at 1700 cm^{-1} in the IR spectrum and gave signals due to an ethylene adjacent to the carbonyl at δ 2.28 and 2.83 (each 2H, m) in the ^{1}H–^{1}H NMR spectrum. Although the carbonyl position may be at C-9 or at C-11 (corresponding to acerogenin C, mp 116 °C), the structure of acerogenin L was determined as **7**, because hydrogenation of **7** with sodium borohydride afforded acerogenin B. Acerogenins B and C are known as the aglycones of glycosidic constituents of this plant.[2b,c]

Compounds **8**, $C_{10}H_{12}O_4$, mp 145 °C, and **9**, $C_{10}H_{10}O_5$, mp 150—151 °C, were suggested to be β-orcinol derivatives on the basis of their NMR spectra and MS. In fact, they were identical with methyl 2,4-dihydroxy-3,6-dimethylbenzoate (methyl atrarate) and methyl 2,4-dihydroxy-3-formyl-6-methylbenzoate (methyl haematommate) based on a comparison of their physicochemical data with reported values.[6] Most known β-orcinol derivatives are components of lichen, but **8** and **9** have been isolated from the higher plants, such as *Xylosma velutina* (Flacourtiaceae).[6]

In this study, seven diarylheptanoids and two β-orcinol derivatives were newly isolated from *Acer nikoense*. Acerogenins K (**2**), F (**3**), J (**4**), I (**5**), H (**6**), and L (**7**) are new compounds.

Experimental

Details of the instruments and TLC procedures used in this work were essentially the same as described in our previous paper.[1]

Extraction and Isolation The stem bark and twigs (2.7 kg) of *Acer nikoense* were collected in Gumma prefecture, Japan, and were extracted with MeOH (3 l × 3, 3 h) under reflux. The MeOH extract (287 g) was dissolved in water (2 l) and partitioned successively with ether, EtOAc and BuOH. The extracts weighed 56 g, 58 g and 116 g, respectively. The ether extract was chromatographed on silica gel with $CHCl_3$ containing increasing proportions of MeOH (49 : 1→9 : 1). Elution with $CHCl_3$–MeOH yielded **9** (12.1 mg) at 49 : 1, **3** (94.5 mg) and a fraction rich in **5** (fraction 1) at 19 : 1, and **8** (4.6 mg) at 9 : 1. The eluate with 29 : 1 was rechromatographed on silica gel with C_6H_6–EtOAc (9 : 1→0 : 1) to give **1** (32.6 mg) and **7** (11 mg) at 9 : 1, acerogenin A (26.2 mg) and acerogenin B (168.7 mg) at 4 : 1, **2** (14.9 mg) and (−)-centrolobol (10.2 mg) at 2 : 1, **6** (21.8 mg) at 1 : 1, and **4** (33.3 mg) at 0 : 1. Fraction 1 was subjected to repeated preparative HPLC on ODS (YMC-pack octadecyl silica (ODS) AQ. 250 × 10 mm i.d., 33% MeOH) to give **5** (60 mg) and a crystalline compound (4 mg).[7]

Acerogenin E (1) Colorless needles (MeOH), mp 229—231 °C. High MS *m/z*: Calcd for $C_{19}H_{20}O_3$ (M^+) 296.1410. Found 296.1411. UV λ_{max}^{MeOH} nm (logε): 247 (3.84). 299 (3.66). This compound was identical with an authentic sample of acerogenin E on the basis of TLC, IR and NMR comparisons and melting point determination.[2a]

Acerogenin K (2) Colorless needles (MeOH), mp 238—240 °C, $[\alpha]_D^{26}$ 0.0° (*c* = 1.1, EtOH). MS *m/z*: 298 (M^+), 280, 212. High MS *m/z*: Calcd for $C_{19}H_{22}O_3$ (M^+) 298.1570. Found 298.1570. IR ν_{max}^{KBr} cm^{-1}: 3450, 1600, 1495. UV λ_{max}^{MeOH} nm (logε): 210 (4.15, end absorption), 251 (3.71), 300 (3.63). NMR (C_5D_5N) δ_H: 1.42 (m, 11-Ha), 1.75—1.83 (2H, m, 11-Hb, 12-Ha), 1.90 (m, 10-Ha), 1.95—2.1 (3H, m, 8-Ha, 10-Hb, 12-Hb), 2.48 (m, 8-Hb), 2.53 (m, 13-Ha), 2.89 (br t, *J* = 16, 13-Hb), 3.01 (br d, *J* = 15, 7-Ha), 3.32 (br d, *J* = 15, 7-Hb) 4.47 (br t, *J* = 10, 9-H), 7.2 (4H, m, 4-, 5-, 15-, 16-H), 7.47 (br s, 18-H), 7.6 (br s, 19-H). δ_C: 23.5 (C-11), 27.1 (C-12), 27.6 (C-7), 30.4 (C-13), 35.8 (C-8), 40.7 (C-10), 68.1 (C-9), 116.9 (C-4, -16), 127.4 (C-2), 127.5 (C-1), 129.8 (C-15), 130.0 (C-5), 131.1 (C-14), 131.6 (C-6), 134.6 (C-19), 135.1 (C-18), 152.7 (C-3, -17). A solution of **2** (30 mg) in toluene (30 ml) was oxidized with cyclohexanone (1 ml) and aluminum isopropoxide (30 mg) according to the procedure of Eastham and Teranishi (cited in ref. 8). The oxidation product (2 mg), mp 229—230 °C (MeOH), was identical with acerogenin E on the basis of TLC and MS comparisons, and mixed melting point determination.

Acerogenin F (3) Colorless needles (MeOH), mp 254—255 °C, $[\alpha]_D^{21}$ +127° (*c* = 0.5, MeOH). *Anal.* Calcd for $C_{19}H_{22}O_4$: C, 72.61; H 7.01. Found: C, 72.55; H, 7.02. MS *m/z*: 314 (M^+), 296, 227, 132. IR λ_{max}^{KBr} cm^{-1}: 3400 (OH), 1600, 1500 (arm.). UV λ_{max}^{MeOH} nm (logε): 278 (3.40).

Acerogenin J (4) Colorless needles (MeOH), mp 223—225 °C, $[\alpha]_D^{25}$ +65.2° (*c* = 0.5, MeOH). MS *m/z*: 314 (M^+), 296, 253, 240, 227. High MS *m/z*: Calcd for $C_{19}H_{22}O_4$, (M^+) 314.516. Found 314.1514. IR ν_{max}^{KBr} cm^{-1}: 3400, 1590, 1430, 1210. UV λ_{max}^{MeOH} nm (logε): 215 (4.14), 274 (3.43). ^{1}H-NMR (CD_3OD) δ: 3.35 (11-H), 5.10 (13-H), 7.18 (15-H), 7.56 (19-H).

Acerogenin I (5) Colorless needles (MeOH–H_2O), mp 214—215 °C, $[\alpha]_D^{20}$ −17.2° (*c* = 0.6, MeOH). MS *m/z*: 314 (M^+), 296, 241, 227. High MS *m/z*: Calcd for $C_{19}H_{22}O_4$ (M^+) 314.1519. Found 314.1525. IR ν_{max}^{KBr} cm^{-1}: 3300 (OH), 1598, 1500 (arom.). UV λ_{max}^{EtOH} nm (logε): 213 (4.19, sh), 274 (3.40).

Acerogenin H (6) Colorless needles (EtOAc), mp 245—246 °C, $[\alpha]_D^{20}$ −36.4° (*c* = 0.5, MeOH). MS *m/z*: 312 (M^+), 269, 239, 212, 198. High MS *m/z*: Calcd for $C_{19}H_{20}O_4$ (M^+) 312.1362. Found 312.1365. IR ν_{max}^{KBr} cm^{-1}: 3300 (OH), 1660 (C=O). UV λ_{max}^{EtOH} nm (logε): 232 (4.11), 279 (3.91), 307 (3.74), 354 (3.41). UV $\lambda_{max}^{EtOH+AcONa}$ nm: 250, 347.

Acerogenin L (7) Colorless needles ($CHCl_3$–MeOH), mp 188—190 °C, $[\alpha]_D^{26}$ 0.0° (*c* = 0.3, $CHCl_3$). *Anal.* Calcd for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 76.96; H, 6.83. MS *m/z*: 296 (M^+), 249, 225. IR ν_{max}^{KBr} cm^{-1}: 3400, 2930, 1700, 1590, 1510, 1230. UV λ_{max}^{EtOH} nm (logε): 206 (4.45, end absorption), 276 (3.43). A solution of **7** (8 mg) in MeOH (2 ml) was treated with sodium borohydride (10 mg) and the solution was worked up as usual. The hydrogenation product, mp 177 °C (MeOH), was identical with an authentic sample of acerogenin B on the basis of TLC and MS comparisons, and mixed melting point determination.[2d]

Methyl 2,4-Dihydroxy-3,6-dimethylbenzoate (8) Colorless needles, mp 145 °C (lit., mp 140—142 °C).[6] MS *m/z*: 196 (M^+), 164, 136. High MS *m/z*: Calcd for $C_{10}H_{12}O_4$ (M^+) 196.0734. Found 196.0733. ^{13}C-NMR ($CDCl_3$) δ: 7.7 (C-9), 24.2 (C-8), 51.9 (CH_3O–), 105.3 (C-1), 108.6 (C-3), 110.6 (C-5), 140.2 (C-6), 158.1 (C-4), 163.2 (C-2), 172.7 (C-7).

Methyl 2,4-Dihydroxy-3-formyl-6-methylbenzoate (9) Colorless needles (sublimation), mp 150—151 °C (lit., mp 135—136 °C, ($CHCl_3$–MeOH)).[6] MS *m/z*: 210 (M^+), 196, 178, 150, 136. High MS *m/z*: Calcd for $C_{10}H_{10}O_5$ (M^+) 210.0526. Found 210.0523. ^{13}C-NMR ($CDCl_3$) δ: 25.2 (C-8), 52.3 (CH_3O–), 104.0 (C-1), 108.5 (C-3), 112.1 (C-5), 152.3 (C-6), 166.7 (C-4), 168.3 (C-2), 172.0 (C-7), 193.9 (C-9).

References and Notes

1) Part XII: Shiratori S., Nagumo S., Inoue T., Nagai M., Chi H. J., *Chem. Pharm. Bull.*, **42**, 960—962 (1994).
2) *a*) Nagumo S., Kaji N., Inoue N., Nagai M., *Chem. Pharm. Bull.*, **41**, 1255—1257 (1993); *b*) Nagai M., Kubo M., Fujita M., Inoue T., Matsuo M., *ibid.*, **26**, 2805—2810 (1978); *c*) Kubo M., Nagai M., Inoue T., *ibid.*, **31**, 1917—1922 (1983); *d*) Kubo M., Inoue T., Nagai M., *ibid.*, **28**, 1300—1303 (1980).
3) Begley M. I., Cambell R. V. M., Crombie L., Tuck B., Whiting D. A., *J. Chem. Soc.* (*C*), **1971**, 3634—3642.
4) In the proton non-decoupling ^{13}C-NMR spectrum of **3**, the signals of C-4 and C-6 are split into doublets with $^1J_{C-H}$ coupling (each about 158 Hz). These split signals are further divided into double

triplets (about 9.5 Hz for $^3J_{(6\text{-H/C-4})}$ and $^3J_{(4\text{-H/C-6})}$; about 4 Hz for $^3J_{(7\text{-H}_2\text{/C-4})}$ and $^3J_{(7\text{-H}_2\text{/C-6})}$). Irradiation of 7-$H_2$ caused a change in the signal shapes of C-4 and C-6 from two double triplets to two doublets (about 9.5 Hz).

5) The NOE experiments for **4** were carried out in methanol-d_4 solution (see Experimental).
6) Cordell G. A., Chang P. T. O., Fong H. H. S., Farnsworth M. R., *Lloydia*, **40**, 340—343 (1977) and references cited therein.
7) This compound, mp 204—205 °C, $C_{19}H_{22}O_4$ (High MS), was presumed to be a diastereomer of **5**, because its mass fragmentation pattern was superimposable on that of **5**.
8) Nagai M., Matsuda E., Inoue T., Fujita M., Chi H. J., Ando T., *Chem. Pharm. Bull.*, **38**, 1506—1508 (1990).