

Studies on the Constituents of the Seeds of *Hernandia ovigera* L. IX.¹⁾ Identification of Two Dibenzylbutyrolactone-Type Lignans and an Attempt of Conversion into Phenyltetralin-Type Lignan

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Two kinds of lignans were isolated from the seeds of *Hernandia ovigera* L. in addition to the nine lignans previously reported. One was confirmed as (–)-dimethylmatairesinol (11) and the other was identified as 5'-methoxypodorhizol (14) by comparison with the authentic sample. An attempt at the cyclization of 14 afforded two compounds which were determined to be isohernandin (15) and an isomer of 15, 2-hydroxymethyl-5,6-methylenedioxy-7-methoxy-4-(3',4',5'-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthoic acid lactone (16).

Keywords *Hernandia ovigera*; dimethylmatairesinol; 5'-methoxypodorhizol; lignan; isohernandin; phenyltetralin lignan

In the previous series of this study, the authors reported the isolation and structural determination of nine sorts of lignans from the seeds of *Hernandia ovigera* L. collected in Okinawa. Namely, desoxypodophyllotoxin (DPT) (1),²⁾ desoxypicropodophyllin (DPP) (2),²⁾ and hernandin (3)³⁾ as phenyltetralin-type lignans, bursehernin (4),²⁾ podorhizol (5),²⁾ (–)-yatein (6),⁴⁾ and hernolactone (7)⁴⁾ as dibenzylbutyrolactone-type lignans and 1,2,3,4-dehydro-DPT (8)³⁾ and 1,2,3,4-dehydropodophyllotoxin (9)⁴⁾ as phenyl-naphthalene-type lignans were isolated, and their structures were clarified.

This time we reexamined the components of the original seeds and isolated two more known lignans. This paper describes the identification of these two lignans and the chemical transformation of a phenyltetralin-type lignan into one of them.

Compound A was isolated from the mother liquor, from which (–)-yatein (6) was afforded⁴⁾ by using preparative thin layer chromatography (PTLC). It was obtained as colorless needles, mp 123–125 °C, with an optical rotation of $[\alpha]_D -24.8^\circ$ (CHCl₃). A molecular formula of C₂₂H₂₆O₆ and a molecular weight 386.1728 were deduced by means of high resolution mass spectrometry (HI-MS). In the mass spectrum (MS), fragment peaks were seen at 208, 177, 151, and 107. Fragment peak 208 corresponds to fragment ion (10) which is similar to that of 4²⁾ (Fig. 2). In the ultraviolet (UV) spectrum, absorption maxima were observed at 281 and 230 nm. In the infrared (IR) spectrum, the existence of

a carbonyl group was observed at 1770 cm⁻¹. Proton magnetic resonance (¹H-NMR) spectrum revealed the presence of six aromatic protons, two protons of lactone methylene, twelve protons of four methoxy groups, four protons of two benzyl methylenes and two protons of lactone junctions. This physical data coincides with that of (–)-dimethylmatairesinol (11) isolated from *Cinnamomum camphora* SIEB.⁵⁾ Direct comparison with the authentic sample was unavailable; however, additional confirmation was pursued by means of a circular dichroism (CD) spectrum. The CD spectrum showed negative Cotton effects at 233 and 276 nm as in the cases of 4, 5, 7, and analogous compounds,⁶⁾ suggesting that the configurations of C-2 and C-3 are 2*R* and 3*R*. In conclusion, compound A was confirmed as (–)-dimethylmatairesinol (11).

Compound B was isolated from fraction 6-4 described in the previous paper.⁴⁾ Fraction 6-4 was purified by means of PTLC, followed by recrystallization from benzene–hexane. It was obtained as colorless needles, mp 127–129 °C, $[\alpha]_D -49.1^\circ$ (CHCl₃). Its molecular formula of C₂₃H₂₆O₉ and molecular weight of 446.1583 were deduced by means of HI-MS. In the UV spectrum, absorption maxima were seen at 235 and 281 nm. In the IR spectrum, the existence of a hydroxy group, carbonyl group, and methylenedioxy group were seen at 3450, 1760, and 935 cm⁻¹, respectively. ¹H-NMR spectrum showed the presence of four aromatic protons, two methylenedioxy group protons, a proton of the hydroxy group junction, two lactone methylene protons,

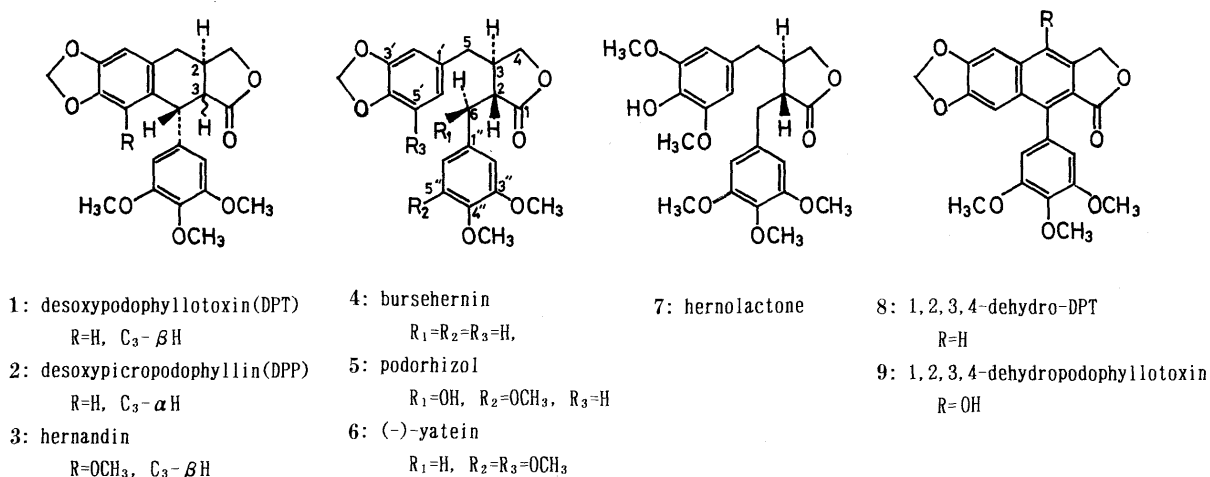


Fig. 1

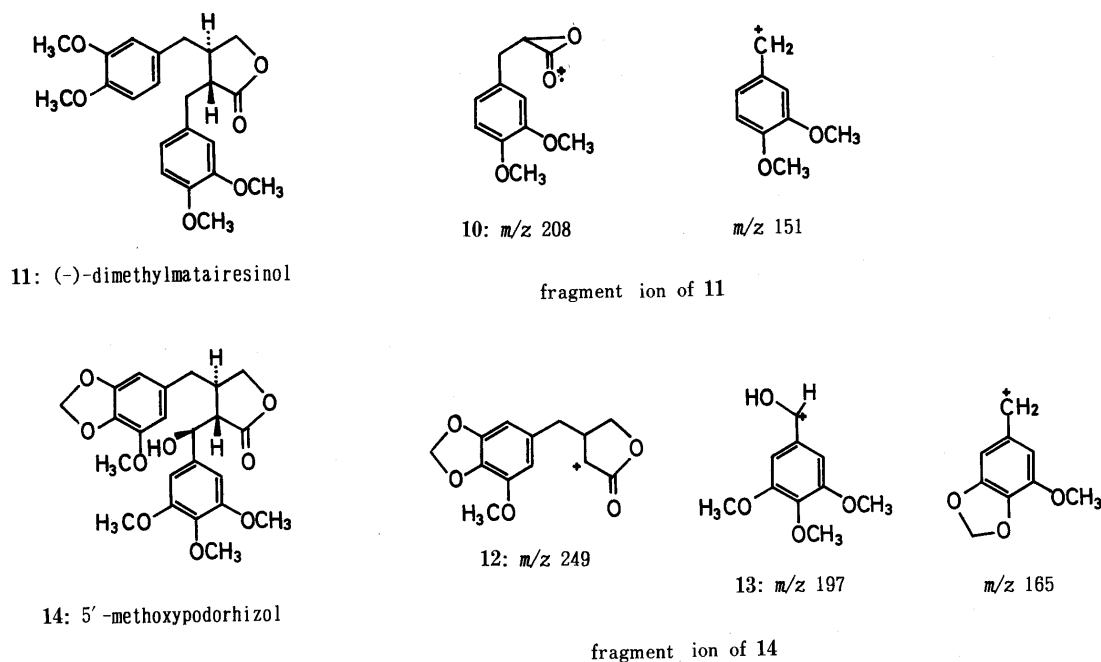


Fig. 2

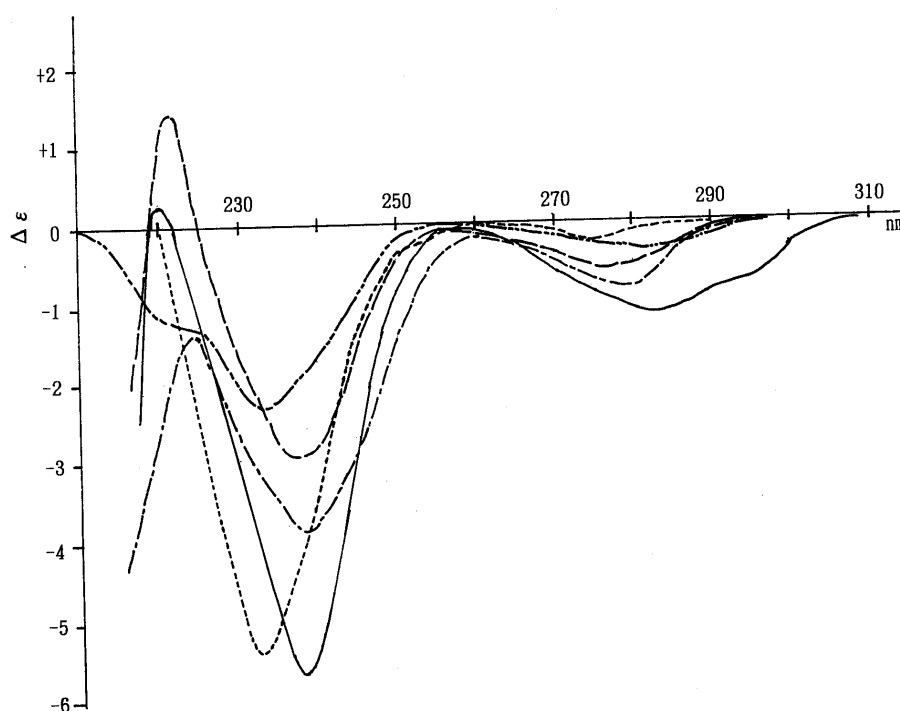


Chart 1. CD Curves of Dibenzylbutyrolactone in EtOH

..... compound A; ——— compound B; — podorhizol (5); - - - bursehernin (4); —·— hernolactone (7).

twelve protons of four methoxy groups, two protons of benzyl methylene, and a hydroxy group which disappeared after the addition of D_2O . In the MS spectrum, ion peaks at 249 and 197 were assigned as fragment ions **12** and **13** (Fig. 2), respectively, revealing that one methoxy group existed in the same benzene nucleus together with the methylenedioxy group. The fact that two aromatic protons which have small J values appear at δ 6.03 (d, $J=1.5$ Hz) and δ 5.97 (d, $J=1.5$ Hz) in the NMR spectrum shows that a methoxy group is situated at the 5' position. The CD

spectrum shows negative Cotton effects at 238 and 280 nm, as in the cases of **4**, **5**, **7** and **11**, revealing that the configurations of C-2 and C-3 are 2*S* and 3*R*. Regarding the configuration of C-6, it was known that a proton of C-6 appeared at δ 5.28 ($J=2.0$ Hz) in **5** (C-6*S*) and δ 4.83 ($J=7.5$ Hz) in epipodorhizol (C-6*R*).⁷⁾ In this compound, a C-6 proton appears at δ 5.28 ($J=3.0$ Hz), revealing that the configuration of C-6 is *S*. From the above results, compound B was determined to be 5'-methoxypodorhizol (**14**) isolated from *Hernandia cordigera*.⁸⁾ However, a small

discrepancy was seen in the physical data of both compounds (lit.⁸) mp 112–113 °C, $[\alpha]_D -20.5^\circ$ (CHCl₃). To clarify this ambiguity, direct comparison with the authentic sample, which was given through the generosity of Dr. P. Richomme, was examined by means of NMR spectra. Although the presented sample was low grade and a few ambiguous signals due to the impurity were observed in the spectrum, all essential absorptions to support the identity of both samples were confirmed.

It was expected that hernandin (**3**), a phenyltetralin-type lignan formerly isolated from the original seeds,³ would be derived from **14** by cyclization. According to the Stevenson's method,⁹ compound **14** was treated with excess trifluoroacetic acid in dichloromethane for 12 h at room temperature. As a result, two compounds, **15** and **16**, which had melting points of 180–182 °C and 204–206 °C respectively, were isolated by means of PTLC using the mixture of benzene, chloroform, and ethyl acetate (2 : 1 : 1). Both compounds showed the same molecular weight of 428 by means of MS spectra. The CD spectra showed a positive Cotton effect at 272 and 286 nm in **15** and 270 and 286 nm in **16**, contrary to that of **3**. In the NMR spectrum of **15**, a methylenedioxy group appeared at δ 5.90 and 5.91, similar to **3** (δ 5.92, 5.94). However, a methoxy group in the tetralin ring which was observed at δ 3.63 in **3** was revealed at a slightly higher magnetic field (δ 3.30), and a proton reduced

to C-4 appeared at a higher magnetic field which had a larger J value (δ 4.33, $J=9.4$ Hz) than that of **3** (δ 4.81, $J=4.8$ Hz¹⁰). In the NMR spectrum of **16**, a proton of C-4 appeared at a higher magnetic field than that of **3**, similar to the case of **15** having a large J value (δ 4.24, $J=10.3$ Hz). However, the aspect of methylenedioxy and methoxy groups in the tetralin ring are different from those of **3** and **15**. Namely, the signal of the methylenedioxy group appeared at a higher magnetic field than those of **3** and **15** (δ 5.77, 5.66), and by contrast, the signal of methoxy group was revealed at a lower magnetic field than those of **3** and **15** (δ 3.91). The above results suggest that the configuration of C-4 of both **15** and **16** is 4 β -aryl. In conclusion, compound **15** is isohernandin, 2-hydroxymethyl-5-methoxy-6,7-methylenedioxy-4-(3',4',5'-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthoic acid lactone, and compound **16** is 2-hydroxymethyl-5,6-methylenedioxy-7-methoxy-4-(3',4',5'-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthoic acid lactone, a positional isomer of **15** in relation to methylenedioxy and methoxy groups. The measurement of specific rotation was unattainable due to their small quantity.

Experimental

All melting points were determined on a Yanaco micro melting point apparatus and are uncorrected. IR spectra were taken with a Jasco infrared spectrometer, model IR-810. ¹H and ¹³C-NMR spectra were measured with Varian XL-300 or with Varian Gemini-200 spectrometers. Chemical shift values are expressed in ppm relative to internal tetramethylsilane. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; m, multiplet. MS spectra were taken with a Hitachi M-80 mass spectrometer. CD spectra were taken with a Jasco J-500 polarimeter. Optical rotations were measured on a Jasco DIP-181 polarimeter. Column chromatography was carried out on Merck silica gel (Kieselgel 60; 70–230 mesh). Precoated silica gel plates used in PTLC were Merck Kieselgel 60 F₂₅₄ of 0.5 mm thickness.

Isolation Compound A was isolated from the mother liquor from which (–)-yatein (**6**) was separated as described in the previous report.⁴ The residue of the mother liquor was subjected to PTLC (solvent; hexane:ethyl acetate=5:1) and rechromatographed on PTLC (solvent; hexane:acetone=3:1) to afford a crystalline material as colorless needles, mp 123–125 °C (from MeOH). Compound B was isolated from fraction 6-4 of the previous report.⁴ Fraction 6-4 was purified by means of PTLC (solvent; hexane:ethyl acetate=1:1) to afford a crystalline material as colorless needles, mp 127–129 °C (from benzene-hexane).

(–)-Dimethylmatairesinol (11) Colorless needles, mp 123–125 °C (from MeOH) (lit.⁵) mp 126–127 °C. $[\alpha]_D -24.8^\circ$ ($c=1.41$, CHCl₃). UV λ_{max}^{MeOH} nm (log ϵ): 230 (4.18), 281 (3.75). IR $\nu_{max}^{CHCl_3}$ cm⁻¹: 1770 (C=O), 1605, 1600, 1520. MS m/z : 386 (M⁺, base peak), 208, 177, 151, 107. ¹H-NMR (CDCl₃) δ : 2.48–2.66 (4H, m), 2.93–2.97 (2H, m), 3.82, 3.84, 3.85, 3.86 (each 3H, s, OCH₃), 3.89 (1H, one of lactone-CH₂), 4.12 (1H, dd, $J=9.2, 6.9$ Hz, one of lactone-CH₂), 6.49–6.79 (6H, m, arom-H). ¹³C-NMR (CDCl₃) δ : 34.5 (C-6), 38.2 (C-5), 41.1 (C-3), 46.6 (C-2), 55.9 (C-3', 3'', 4', 4''), 71.3 (C-4), 111.1 (C-2'), 111.4 (C-5'), 111.9 (C-2''), 112.4 (C-5''), 120.6 (C-6'), 121.4 (C-6''), 130.2 (C-1'), 130.5 (C-1''), 147.9 (C-4'), 148.0 (C-4''), 149.1 (C-3', 3''), 178.7 (C-1). HI-MS Calcd for C₂₂H₂₆O₆ (M⁺): 386.1729. Found: 386.1729.

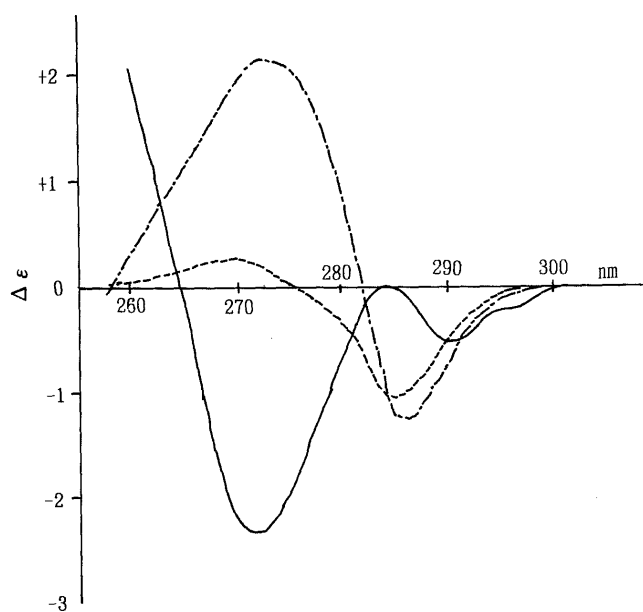


Chart 2. CD Curves of 4-Aryltetralin Lignan in EtOH
—, hernandin (**3**); ----, compound **15**; - · - · -, compound **16**.

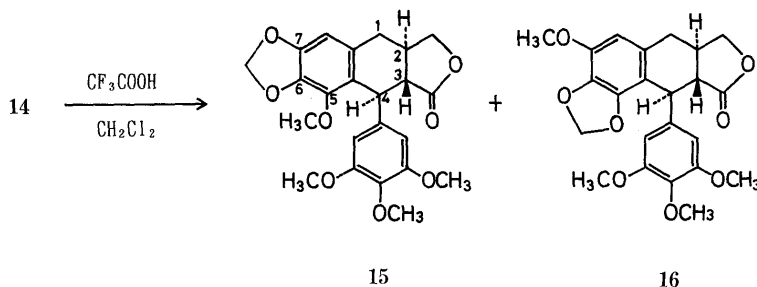


Fig. 3

(-)-5'-Methoxypodorhizol (**14**) mp 127–129 °C (from benzene–hexane) (lit.⁹⁾ 112–113 °C). $[\alpha]_D^{25} -49.1^\circ$ ($c=1.0$, CHCl_3). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (log ϵ): 235 (4.06), 281 (3.19). IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 3600, 3450 (OH), 1760 (C=O), 1635, 1595, 1510, 935 (OCH_2O). MS m/z : 446 (M^+), 249, 197 (base peak), 181, 165, 138, 125. $^1\text{H-NMR}$ (CDCl_3) δ : 2.26 (1H, dd, $J=13.8$, 7.8 Hz, $\text{C}_5\text{-H}$), 2.46 (1H, dd, $J=13.8$, 7.8 Hz, $\text{C}_5\text{-H}$), 2.56 (1H, br s, $\text{C}_6\text{-OH}$, disappeared on addition of D_2O), 2.66 (1H, dd, $J=6.3$, 3.0 Hz, $\text{C}_2\text{-H}$), 2.81 (1H, m, $\text{C}_3\text{-H}$), 3.84 (12H, s, $\text{C}_{5',3'',4'',5''}\text{-OCH}_3$), 3.98 (1H, dd, $J=9.0$, 5.7 Hz, $\text{C}_4\text{-H}$), 4.38 (1H, dd, $J=9.0$, 7.8 Hz, $\text{C}_4\text{-H}$), 5.29 (1H, br s, $\text{C}_6\text{-H}$), 5.92, 5.95 (each 1H, d, $J=1.5$ Hz, OCH_2O), 5.07 (1H, d, $J=1.5$ Hz, $\text{C}_6\text{-H}$), 6.03 (1H, d, $J=1.5$ Hz, $\text{C}_2\text{-H}$), 6.50 (2H, s, $\text{C}_{2'',6''}\text{-H}$).

Cyclization of 14 A solution of compound **14** (54.4 mg, 0.122 mmol) in dichloromethane (4 ml) was added to a stirred solution of trifluoroacetic acid (1 ml) in dichloromethane (5 ml) at room temperature under a nitrogen atmosphere. After stirring for 12 h, the solvent was removed. A residual solid was purified by means of PTLC (solvent; hexane: CHCl_3 : ethyl acetate = 2:1:1) affording two zones ($R_f=0.25$ and 0.16) from which **15** and **16** were respectively isolated.

Isohernandin (15) 35.1 mg, 67%. Colorless needles, mp 180–182 °C (from EtOH). IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 1780 (C=O), 1620, 1595, 1500, 950. MS m/z : 428 (M^+ , base peak), 413, 181, 165, 115. $^1\text{H-NMR}$ (CDCl_3) δ : 2.40 (2H, m, $\text{C}_{2,3}\text{-H}$), 2.86 (2H, m, $\text{C}_1\text{-H}$), 3.30 (3H, s, $\text{C}_5\text{-OCH}_3$), 3.81 (9H, s, $\text{C}_{3',4',5'}\text{-OCH}_3$), 3.92 (1H, dd, $J=10.2$, 8.5 Hz, one of lactone- CH_2), 4.30 (1H, d, $J=9.4$ Hz, $\text{C}_4\text{-H}$), 4.45 (1H, dd, $J=8.5$, 6.0 Hz, one of lactone- CH_2), 5.90, 5.91 (each 1H, d, $J=1.4$ Hz, OCH_2O), 6.40 (1H, s, $\text{C}_8\text{-H}$), 6.47 (2H, br s, $\text{C}_{2',6'}\text{-H}$). Anal. Calcd for $\text{C}_{23}\text{H}_{24}\text{O}_8$: C, 64.48; H, 5.65. Found: C, 64.47; H, 5.64.

2-Hydroxymethyl-5,6-methylenedioxy-7-methoxy-4-(3',4',5'-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthoic Acid Lactone (16) 4.2 mg, 8%. Colorless needles, mp 204–206 °C (from EtOH). IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 1780 (C=O), 1640, 1590, 1500, 940. MS m/z : 428 (M^+), 413, 181 (base peak), 165, 152, 115. $^1\text{H-NMR}$ (CDCl_3) δ : 2.35–2.65 (2H, m, $\text{C}_{2,3}\text{-H}$), 2.80–3.00

(2H, m, $\text{C}_1\text{-H}$), 3.80 (6H, s, $\text{C}_{3',5'}\text{-OCH}_3$), 3.83 (3H, s, $\text{C}_{4'}\text{-OCH}_3$), 3.91 (3H, s, $\text{C}_7\text{-OCH}_3$), 3.95 (1H, dd, $J=11.0$, 8.5 Hz, one of lactone- CH_2), 4.24 (1H, d, $J=10.3$ Hz, $\text{C}_4\text{-H}$), 4.49 (1H, dd, $J=8.5$, 6.4 Hz, one of lactone- CH_2), 5.66, 5.77 (each 1H, d, $J=1.3$ Hz, OCH_2O), 6.36 (1H, s, $\text{C}_8\text{-H}$), 6.51 (2H, s, $\text{C}_{2',6'}\text{-H}$).

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References and Notes

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- 10) In our previous report³⁾ we described this signal as δ 4.84, $J=10$ Hz using a 90 Mc instrument. This time we reexamined it precisely by means of a 300 Mc instrument and confirmed the accurate datum.