Studies on the Constituents of the Seeds of *Hernandia ovigera* L. VIII.[1] Syntheses of (±)-Desoxypodophyllotoxin and (±)-β-Peltatin-A Methyl Ether

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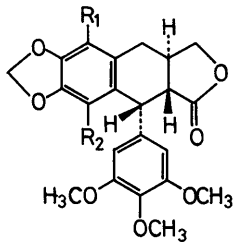
(±)-Desoxypodophyllotoxin (2), a chief component of the seeds of *Hernandia ovigera* L., and (±)-β-peltatin-A methyl ether (3), an analogous phenyltetralin lignan, which have 2,3-*trans*, 3,4-*cis* configuration were synthesized according to the method developed for the synthesis of hernandin (1). The syntheses were pursued using the corresponding 4-phenyl-1,2-dihydronaphthalene lactones (9 and 10) followed by cleavage of the lactone moiety to give the unsaturated hydroxy acids (11 and 12). Subsequent hydrogenation and ring closure by means of *p*-toluenesulfonic acid afforded both 2,3-*trans*, 3,4-*cis* and 2,3-*cis*, 3,4-*cis* lignans (2 and 13 or 3 and 14), which were isolated by preparative thin layer chromatography.

Keywords *Hernandia ovigera*; hernandin; phenyltetralin lignan; desoxypodophyllotoxin; β-peltatin-A methyl ether; intramolecular Diels–Alder reaction

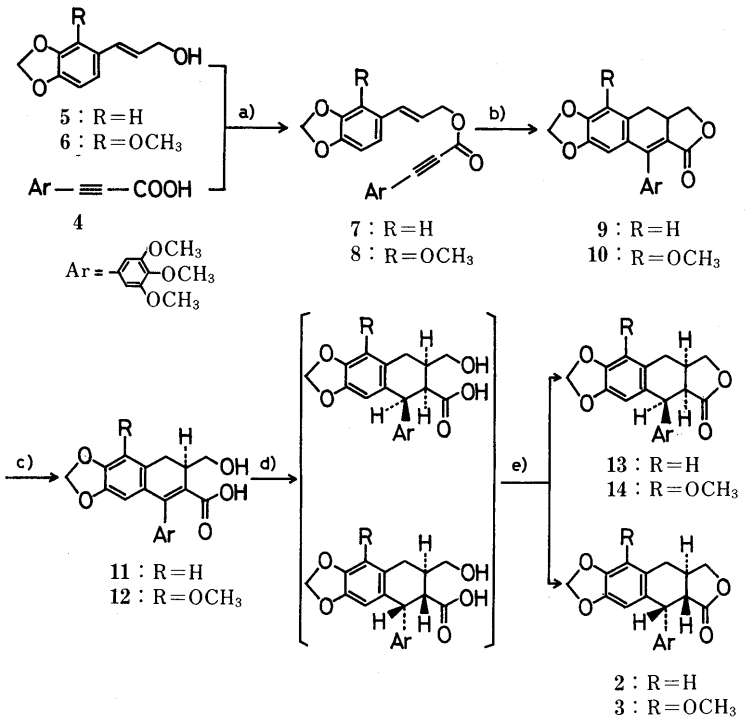
Hernandin (**1**) is a phenyltetralin-type lignan isolated from *Hernandia ovigera* L.[2] In the previous paper of this series,[1] the authors reported the synthesis of (±)-**1** which has 2,3-*trans*, 3,4-*cis* configuration. Most of the synthetic procedure was carried out according to the method developed by Klemm *et al.*[3a–d] and the corresponding 1,2-dihydro-3-naphthoic acid lactone was obtained by means of the intramolecular Diels–Alder reaction[4] of the cinnamyl phenylpropiolate prepared by the condensation of the two phenylpropanoid-type compounds. However, it is known that direct catalytic hydrogenation of 1,2-dihydro-3-naphthoic acid lactone affords only the 2,3-*cis* tetralin-type compound.[3] The key point of our method lies in the cleavage of the lactone moiety of 1,2-dihydro-3-naphthoic acid lactone prior to the catalytic hydrogenation leading to the tetralin-type product. The cleavage of the lactone moiety releases the restriction on the direction of attack by hydrogen in catalytic hydrogenation and makes it possible to obtain both *cis* and *trans* compounds. The unsaturated hydroxy acid obtained by the cleavage of lactone moiety afforded two kinds of hydroxy acids by catalytic hydrogenation on Pd–C, of which one had 2,3-*cis* and the other 2,3-*trans* configuration. The former was more easily lactonized than the latter by hydrochloric acid on account of the proximity of the hydroxy and carboxyl groups.

This time the authors adopted the above method for the syntheses of analogous 4-phenyltetralin-type lignans and succeeded in synthesizing (±)-desoxypodophyllotoxin (**2**) and (±)-β-peltatin-A methyl ether (**3**) (Fig. 1). The syntheses were carried out through the scheme in Chart 1.



1 : R_1=H, R_2=OCH_3
2 : R_1=R_2=H
3 : R_1=OCH_3, R_2=H

Fig. 1



a) DCC b) DMF, Δ c) 7% KOH d) 10% Pd-C, H_2 e) *p*-TsOH, benzene

Chart 1

Concerning the starting materials, 3,4,5-trimethoxyphenylpropiolic acid[3a] (**4**) was prepared according to the method described in our previous paper.[1] *trans*-3,4-Methylenedioxycinnamyl alcohol[3a] (**5**) and *trans*-2-methoxy-3,4-methylenedioxycinnamyl alcohol[3c] (**6**) are known substances, but the method of preparation was improved in detail as described in the experimental section. The condensation of **5** or **6** with **4** gave **7** or **8**, respectively, followed by ring closure to afford **9** or **10**.[5] Compounds **9** and **10** were successively hydrolyzed to give the corresponding unsaturated hydroxy acids **11** and **12**. The next step was slightly modified from the case of the synthesis of **1**. In the former case, the experiment was done in two steps after the hydrogenation of the 1,2-dihydrohydroxy acid to distinguish the objective hydroxy acid (2,3-*trans* type) from another possible lactone (2,3-*cis* type). To improve the yield of the desired 2,3-*trans* lactone, the hydrogenated products were directly treated with *p*-toluenesulfonic acid (*p*-TsOH) without isolating the hydroxy acid and the resultant two sorts of lactones were isolated by preparative thin layer chromatography (PTLC). In the synthesis of **2**, **2** and isopicrodesoxypodophyllotoxin (**13**) were obtained in 35 and 26% yields, respectively, and in the synthesis of **3**, **3** and isopicro-*β*-peltatin methyl ether (**14**) were obtained in 48 and 27% yields, respectively. Recently Achiwa *et al.*[6] reported the synthesis of (−)-**2** from the corresponding 1,2-dihydro-(−)-**9**, which was derived from (+)-podorhizon utilizing our method followed by cyclization. These results showed that this method was advantageous for the syntheses of 4-phenyltetralin-type lignans which have the same configuration as natural products.

Experimental

All melting points were determined on a Yanaco micro melting point apparatus and are uncorrected. The instruments used in this study were as follows: infrared (IR) spectra, Jasco IR-810 spectrometer; mass spectra (MS), Hitachi M-80; nuclear magnetic resonance (NMR) spectra, Varian XL-300 and Gemini-200 instruments (with tetramethylsilane as an internal standard; chemical shifts are recorded in δ values). 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 F_{254}, 0.5 mm thickness.

Starting Materials Substituted cinnamyl alcohols were prepared from the corresponding benzaldehyde *via* substituted ethyl cinnamate by means of the Wittig–Horner reaction and lithium aluminum hydride (LAH) reduction as described in the previous report.[1]

5: ^{1}H-NMR ($CDCl_3$) δ: 1.51 (1H, br s, OH), 4.29 (2H, dd, J=6.0, 1.2 Hz, CH=CHC$\underline{H}_2$O), 5.96 (2H, s, OCH_2O), 6.20 (1H, dt, J=15.6, 6.0 Hz, CH=C$\underline{H}$–CH_2), 6.52 (1H, dt, J=15.6, 1.2 Hz, C$\underline{H}$=CHCH$_2$), 6.76 (1H, d, J=7.8 Hz, C_5-H), 6.82 (1H, dd, J=7.8, 1.5 Hz, C_6-H), 6.93 (1H, d, J=1.5 Hz, C_2-H).

6: ^{1}H-NMR ($CDCl_3$) δ: 1.50 (1H, br s, OH), 3.99 (3H, s, C_2-OCH_3), 4.29 (2H, dd, J=6.0, 1.4 Hz, CH=CHC$\underline{H}_2$O), 5.94 (2H, s, OCH_2O), 6.27 (1H, dt, J=16.0, 6.0 Hz, CH=C$\underline{H}$–CH_2), 6.52 (1H, d, J=8.4 Hz, C_6-H), 6.79 (1H, d, J=16.0 Hz, C$\underline{H}$=CH), 6.95 (1H, d, J=8.4 Hz, C_5-H).

3,4-Methylenedioxycinnamyl 3′,4′,5′-Trimethoxyphenylpropiolate[3a] (7) A dry pyridine solution (5 ml) of **5** (0.18 g, 1.01 mmol), **4** (0.26 g, 1.1 mmol) and *p*-TsOH (9.5 mg) was treated with a dry pyridine solution (3 ml) of 1,3-dicyclohexylcarbodiimide (DCC) (0.25 g, 1.2 mmol). The mixture was stirred at room temperature for 1 h. After the addition of AcOH (2 ml), the reaction mixture was allowed to stand at 0 °C for 4 h. The precipitate was filtered off and washed with cold pyridine. The filtrate was acidified with concentrated HCl and extracted with $CHCl_3$. The extract was washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent, the resulting residue was purified by column chromatography benzene–AcOEt, 20:1) to give **7** (0.25 g, 65%). mp 135—136 °C (from hexane–AcOEt) (lit.[3a] 130—131 °C). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2210 (C≡C), 1705 (C=O), 940 (OCH_2O). MS *m/z*: 396 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 3.86 (6H, s, $C_{3',5'}$-OCH_3), 3.88 (3H, s, $C_{4'}$-OCH_3), 4.86 (2H, dd, J=6.6, 1.2 Hz, CH=CH–C$\underline{H}_2$O), 5.97 (2H, s, OCH_2O), 6.16 (1H, dt, J=15.9, 6.6 Hz, CH=C$\underline{H}$–CH_2), 6.64 (1H, d, J=15.9 Hz, C$\underline{H}$=CH), 6.77 (1H, d, J=8.1 Hz, C_5-H), 6.84 (2H, s, $C_{2',6'}$-H), 6.85 (1H, dd, J=8.1, 1.5 Hz, C_6-H), 6.95 (1H, d, J=1.5 Hz, C_2-H). *Anal.* Calcd for $C_{22}H_{20}O_7$: C, 66.66; H, 5.09. Found: C, 66.54; H, 5.08.

2-Methoxy-3,4-methylenedioxycinnamyl 3′,4′,5′-Trimethoxyphenylpropiolate[3c] (8) This compound was obtained in 85% yield from **6** (418 mg, 2.01 mmol) and **4** (472 mg, 2.00 mmol) by the same procedure as described in the preparation of **7**. mp 101.5—104 °C (from hexane–AcOEt). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2210 (C≡C), 1700 (C=O), 935 (OCH_2O). MS *m/z*: 426 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 3.86 (6H, s, $C_{3',5'}$-OCH_3), 3.88 (3H, s, $C_{4'}$-OCH_3), 4.01 (3H, s, C_2-OCH_3), 4.87 (2H, dd, J=6.6, 1.2 Hz, CH=CH–C$\underline{H}_2$O), 5.95 (2H, s, OCH_2O), 6.24 (1H, dt, J=16.2, 6.6 Hz, CH=C$\underline{H}$–CH_2), 6.53 (1H, d, J=8.4 Hz, C_5-H), 6.84 (2H, s, $C_{2',6'}$-H), 6.91 (1H, d, J=16.2 Hz, C$\underline{H}$=CH), 6.97 (1H, d, J=8.4 Hz, C_6-H). *Anal.* Calcd for $C_{23}H_{22}O_8$: C, 64.78; H, 5.20. Found: C, 64.70; H, 5.21.

(±)-2-Hydroxymethyl-6,7-methylenedioxy-4-(3′,4′,5′-trimethoxyphenyl)-1,2-dihydro-3-naphthoic Acid Lactone[3b] (9) A solution of **7** (103 mg, 0.51 mmol) in dimethylformamide (DMF) (10 ml) was heated under stirring at 145 °C for 1 h. The mixture was poured into water and extracted with $CHCl_3$. The extract was washed with brine and dried over anhydrous Na_2SO_4. The $CHCl_3$ layer was evaporated and the resulting residue was purified by column chromatography with $CHCl_3$. Repeated recrystallization of the crude product from MeOH–CH_2Cl_2 afforded **9** (77.6 mg, 39%). Colorless needles, mp 251—254 °C (lit.[3b] 252—253 °C). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1740 (C=O), 940 (OCH_2O). ^{1}H-NMR ($CDCl_3$) δ: 2.82 (1H, d, J=16.0 Hz, one of C_1-H), 2.94 (1H, dd, J=16.0, 6.6 Hz, one of C_1-H), 3.40 (1H, m, C_2-H), 3.84 (6H, s, $C_{3',5'}$-OCH_3), 3.92 (3H, s, $C_{4'}$-OCH_3), 4.01, 4.70 (each 1H, dd, J=8.8, 8.8 Hz, lactone-CH_2), 5.97 (2H, s, OCH_2O), 6.52 (3H, br s, $C_{5,2',6'}$-H), 6.77 (1H, s, C_8-H). *Anal.* Calcd for $C_{22}H_{20}O_7$: C, 66.66; H, 5.09. Found: C, 66.58; H, 5.00.

(±)-2-Hydroxymethyl-8-methoxy-6,7-methylenedioxy-4-(3′,4′,5′-trimethoxyphenyl)-1,2-dihydro-3-naphthoic Acid Lactone[3c] (10) This compound (as a 9:1 mixture with dehydro-*β*-peltatin methyl ether)[5] was obtained in 46% yield from **8** (550 mg, 1.29 mmol) in DMF (30 ml) by the same procedure as described for the preparation of **9**. ^{1}H-NMR ($CDCl_3$) δ: 2.33 (1H, dd, J=16.0, 16.0 Hz, one of C_1-H), 3.29 (1H, m, C_2-H), 3.45 (1H, dd, J=16.0, 8.8 Hz, one of C_1-H), 3.83 (6H, s, $C_{3',5'}$-OCH_3), 3.92 (3H, s, $C_{4'}$-OCH_3), 4.03, 4.71 (each 1H, dd, J=8.8, 8.8 Hz, lactone-CH_2), 4.04 (3H, s, C_8-OCH_3), 5.95, 5.97 (each 1H, d, J=1.4 Hz, OCH_2O), 6.28 (1H, s, C_5-H), 6.48 (2H, br s, $C_{2',6'}$-H).

(±)-2-Hydroxymethyl-6,7-methylenedioxy-4-(3′,4′,5′-trimethoxyphenyl)-1,2-dihydro-3-naphthoic Acid (11) An MeOH solution (30 ml) of **9** (102 mg, 0.26 mmol) was stirred with KOH (2.1 g) at 50 °C for 3 h. The mixture was poured into water and extracted with $CHCl_3$ to remove neutral material. The aqueous layer was carefully neutralized with 2% HCl solution at 0 °C and extracted with Et_2O. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent, **11** (104 mg, 98%) was obtained as an amorphous powder. Compound **11** was used *in situ* at the next step without purification.

(±)-Desoxypodophyllotoxin (2) and (±)-Isopicrodesoxypodophyllotoxin (13) An EtOH solution (30 ml) of **11** (95 mg, 0.23 mmol) was stirred with 10% Pd–C (95 mg) at 46 °C for 22 h in a stream of hydrogen under elevated pressure (4.7 atm). The catalyst was filtered off, and the filtrate was evaporated. The resulting residue was dissolved in dry benzene (25 ml), and the solution was refluxed with *p*-TsOH (10 mg) and 4 Å molecular sieves (80 mg) for 1 h. The molecular sieves were filtered off, then the filtrate was washed with saturated $NaHCO_3$ solution (2 ml) and brine, and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified by PTLC (*n*-hexane–AcOEt, 3:2) to give **2** (32 mg, 35%) and **13** (24 mg, 26%).

2: Colorless needles, mp 238—241 °C (from EtOH) (lit.[7] 234—236 °C). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1740 (C=O), 945 (OCH_2O). MS *m/z*: 398 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 2.67—2.86 (3H, m, $C_{1,2,3}$-H), 3.02—3.14 (1H, m, C_1-H), 3.76 (6H, s, $C_{3',5'}$-OCH_3), 3.81 (3H, s, $C_{4'}$-OCH_3), 3.92 (1H, dd, J=9.9, 8.7 Hz, one of lactone-CH_2), 4.46 (1H, dd, J=8.7, 6.4 Hz, one of lactone-CH_2), 4.60 (1H, d, J=1.8 Hz, C_4-H), 5.93, 5.95 (each 1H, d, J=1.5 Hz, OCH_2O), 6.35 (2H, s, $C_{2',6'}$-H), 6.53 (1H, s, C_5-H), 6.67 (1H, s, C_8-H). *Anal.* Calcd for $C_{22}H_{22}O_7$: C, 66.32; H, 5.57. Found: C, 66.30; H, 5.57.

13: Colorless needles, mp 208—210 °C (from EtOH) (lit.[3a] 203—204 °C). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1770 (C=O), 940 (OCH_2O). MS *m/z*: 398 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 2.70 (1H, dd, J=15.9, 5.0 Hz, C_3-H), 2.98 (1H, dd, J=15.9, 8.7 Hz, one of C_1-H), 3.10—3.26 (2H, m, one of C_1-H and

C_2-H), 3.50 (1H, dd, J=8.9, 7.8 Hz, one of lactone-CH_2), 3.77 (6H, s, $C_{3',5'}$-OCH_3), 3.83 (3H, s, $C_{4'}$-OCH_3), 4.32—4.50 (2H, m, C_4-H and one of lactone-CH_2), 5.96 (2H, s, OCH_2O), 6.50 (2H, s, $C_{2',6'}$-H), 6.65 (1H, s, C_5-H), 6.74 (1H, s, C_8-H). *Anal.* Calcd for $C_{22}H_{22}O_7$: C, 66.32; H, 5.57. Found: C, 66.19; H, 5.56.

(±)-2-Hydroxymethyl-8-methoxy-6,7-methylenedioxy-4-(3′,4′,5′-trimethoxyphenyl)-1,2-dihydro-3-naphthoic Acid (12) This compound was obtained in 99% yield from crude **10** (103 mg, 0.24 mmol) by the same procedure as described for the preparation of **11**. Compound **12** was used *in situ* at the next step without purification.

(±)-β-Peltatin-A Methyl Ether (3) and (±)-Isopicro-β-peltatin Methyl Ether (14) These compounds were prepared in 48 and 27% yields, respectively, from **12** (46 mg, 0.10 mmol) by the same procedure as used for the preparation of **2** and **13**.

3: Colorless prisms, mp 203—207 °C (from EtOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1775 (C=O), 945 (OCH_2O). MS m/z: 428 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 2.47 (1H, dd, J=16.5, 10.5 Hz, one of C_1-H), 2.58—2.74 (2H, m, one of C_1-H and C_2-H), 3.18 (1H, dd, J=21.3, 4.9 Hz, C_3-H), 3.76 (6H, s, $C_{3',5'}$-OCH_3), 3.81 (3H, s, $C_{4'}$-OCH_3), 3.94 (1H, dd, J=10.5, 8.7 Hz, one of lactone-CH_2), 4.07 (3H, s, C_8-OCH_3), 4.47 (1H, dd, J=8.7, 6.6 Hz, one of lactone-CH_2), 4.58 (1H, d, J=3.9 Hz, C_4-H), 5.91, 5.92 (each 1H, d, J=1.5 Hz, OCH_2O), 6.28 (1H, s, C_5-H), 6.36 (2H, s, $C_{2',6'}$-H). *Anal.* Calcd for $C_{23}H_{24}O_8$: C, 64.48; H, 5.65. Found: C, 64.60; H, 5.66.

14: Colorless needles, mp 189—190.5 °C (from EtOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1765 (C=O), 940 (OCH_2O). MS m/z: 428 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 2.53—2.63 (1H, m, C_1-H), 3.08—3.23 (3H, m, $C_{1,2,3}$-H), 3.52 (1H, dd, J=9.0, 7.2 Hz, one of lactone-CH_2), 3.77 (6H, s, $C_{3',5'}$-OCH_3), 3.83 (3H, s, $C_{4'}$-OCH_3), 4.03 (3H, s, C_8-OCH_3), 4.35—4.44 (2H, m, C_4-H and one of lactone-CH_2), 5.92, 5.93 (each 1H, d, J=1.5 Hz, OCH_2O), 6.38 (1H, s, C_5-H), 6.53 (2H, s, $C_{2',6'}$-H).

References and Notes

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