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SYNTHESIS OF STEREOSPECIFICALLY DEUTERATED MATAIRESINOL, PODORHIZOL, EPIPODORHIZOL, AND YATEIN

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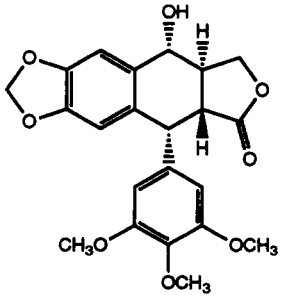
ABSTRACT.—(2,5,6,2′,5′,6′-$^2H_6$)-Matairesinol [**6**], (7′α-$^2H_1$)-yatein [**13**], (7-$^2H_1$)-epipodorhizol [**14**], and (7-$^2H_1$)-podorhizol [**17**] have been prepared as a preliminary to conducting incorporation studies in plants of the *Podophyllum* species in order to further understand the biosynthesis of podophyllotoxin.

Podophyllotoxin [**1**], a lignan isolated from several species of *Podophyllum*, is a potent cytotoxic compound that gave one of the earliest indications of the potential of natural products as anticancer agents (1–3). It has been used as a precursor to the clinical chemotherapeutic agents teniposide and etoposide, which are active against small-cell lung cancer and other tumors (4).

The biosynthesis of podophyllotoxin has been investigated by a number of groups (5–14). It has been proposed that formation of podophyllotoxin begins with the enzyme-mediated coupling of a hydroxycinnamyl alcohol derivative with a substituted hydroxycinnamic acid (7); further biosynthetic modifications of the coupled compound(s) could lead to matairesinol [**2**] and/or yatein [**3**], which have been proposed as potential precursors of podophyllotoxin (9). The initial coupling is however unlikely, because recent work on the formation of matairesinol in *Forsythia* species has shown that coupling occurs between two *E*-coniferyl alcohol moieties to give pinoresinol (15), which is then converted to lariciresinol and secoisolarisiresinol (16–18), and finally to matairesinol (19). The recently demonstrated conversion of matairesinol to podophyllotoxin (14) could proceed through the intermediate compound yatein, but no conclusive evidence of this has been reported. Such a conversion would involve aromatic ring modifications,



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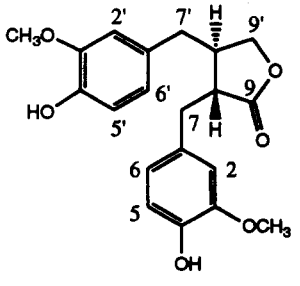

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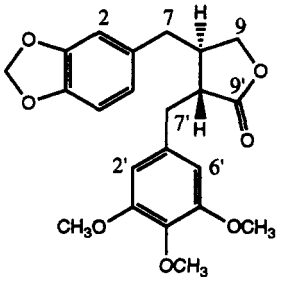

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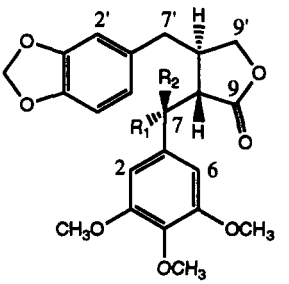


4 R_1=H; R_2=OH
5 R_1=OH; R_2=H

which are common for hydroxycinnamyl lignan monomers but remain to be established at the dimeric level. Kamil and Dewick (9) have demonstrated the in vivo conversion of yatein to podophyllotoxin, with the conversion involving a stereo-controlled cyclization and stereospecific benzylic hydroxylation. The stereochemistry of the cyclization of yatein, in terms of whether the pro-*R* or pro-*S* hydrogen on C-7′ is lost during the process, was not however determined, nor was the stereochemistry of the hydroxylation process. Efforts toward determining the stereochemistry of the latter process have been reported previously (13). It was therefore of interest to us to study the possible conversion of matairesinol to yatein and/or podophyllotoxin, as well as the stereochemistry of the cyclization of yatein during its conversion to podophyllotoxin. Such a study required the preparation of stereospecifically labeled precursors, and this paper reports our efforts at the synthesis of stereospecifically deuterated matairesinol and yatein, as well as podorhizol [**4**] and epipodorhizol [**5**], two naturally occurring compounds that were prepared as their labeled analogs for use as synthetic precursors of yatein.

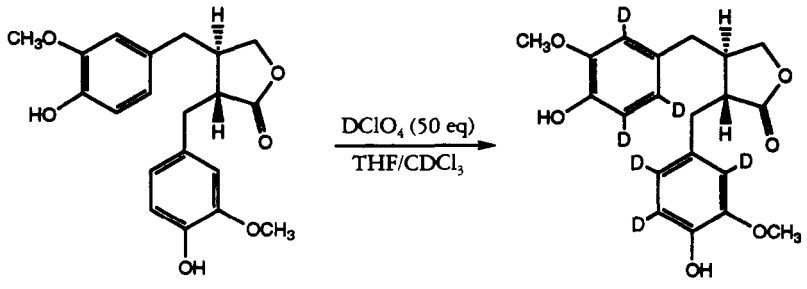
RESULTS AND DISCUSSION

The investigation of the proposed conversion of matairesinol [**2**] to yatein [**3**] and/or podophyllotoxin [**1**] required (2,5,6,2′,5′,6′-$^2H_6$)-matairesinol [**6**]; the conversion of this compound (and the compounds described below) could then be monitored by mass spectrometric analysis of the resultant deuterium-labeled species.

The preparation of the labeled matairesinol followed the method of Brown and Daugan (20,21). Thus, matairesinol [**2**] was prepared and converted to the deuterium-labeled analog **6** by treatment with $DClO_4$ in $THF/CDCl_3$ (see Scheme 1). The hexadeuteromatairesinol **6** was identified on the basis of its ^1H-nmr and mass spectral data.

The preparation of stereospecifically deuterated yatein was initially envisioned to follow the methodology of Kamil and Dewick (9), using as a key intermediate anhydropodorhizol [**7**], which was formed by base-catalyzed condensation of (*R*)-(+)-β-piperonyl-γ-butyrolactone [**8**] and 3,4,5-trimethoxybenzaldehyde [**9**]. According to this methodology, a stereoselective deuteration of compound **7** instead of hydrogenation, followed by epimerization via base treatment would potentially lead to a single deuterium label at the C-7′ position of yatein, i.e., (7′β-$^2H_1$)-yatein [**10**]. Conceivably, the deuterated anhydropodorhizol [**11**], prepared from the deuterated trimethoxybenzaldehyde [**12**], would lead to (7′α-$^2H_1$)-yatein [**13**] via Kamil and Dewick's route.

While Kamil and Dewick (9) reported that anhydropodorhizol [**7**] was produced in reasonable yield, our synthetic efforts yielded no isolable amount of compound **7**, but rather, an approximately 1:1 mixture of the alcohols podorhizol [**4**] and epipodorhizol



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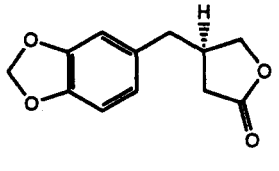
SCHEME 1. Preparation of (2,5,6,2′,5′,6′-$^2H_6$)-Matairesinol [**6**].

[**5**]. Changes in reaction conditions failed to produce any anhydropodorhizol, and in each case yielded only the mixture of alcohols. Attempts to mesylate the mixture of alcohols, with the desire that the mesylates would eliminate to give a mixture of *E*- and *Z*-anhydropodorhizols, proved to be unsuccessful.

Because the podorhizol/epipodorhizol mixture was readily obtainable in good yield, we chose to modify our synthetic strategy and use the alcohols to arrive at the desired labeled yateins. It is known that hydrogenolysis of benzyl alcohols can be achieved by using palladium-on-carbon, Raney nickel, and several other catalysts. In the case of palladium, it has been reported (22, 23, 27–30) that hydrogenolysis proceeds with inversion of configuration of the original benzylic proton; and conversely, when Raney nickel is used as catalyst (22–31) hydrogenolysis proceeds with retention of configuration of the benzylic proton.

To investigate this methodology for our purposes, we first subjected a 1:1 mixture



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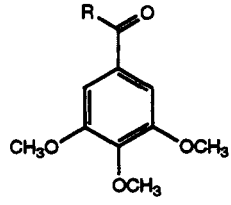
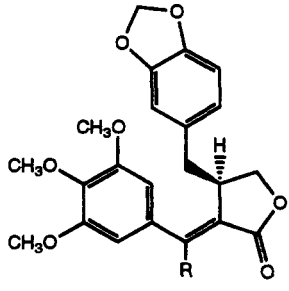
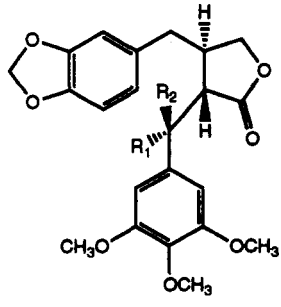


9 R=H
12 R=D



7 R=H
11 R=D



10 R_1=H; R_2=D
13 R_1=D; R_2=H

of podorhizol and epipodorhizol to hydrogenolysis over Pd/C (5%), with a catalytic amount of $HClO_4$. Yatein [**3**] was obtained from the reaction and its identity was confirmed by ^{1}H-nmr and mass spectral analysis, based on comparison to known data (32). Surprisingly, however, only epipodorhizol was converted to yatein, and podorhizol was recovered in nearly quantitative yield from the reaction. To confirm the differential reactivity of podorhizol and epipodorhizol under hydrogenolysis conditions, the individual alcohols were subjected to hydrogenolysis over Pd/C (5%) and a catalytic amount of $HClO_4$. Conversion of epipodorhizol to yatein proceeded smoothly, while no yatein was produced from podorhizol, even under prolonged reaction times.

The difference in reactivity may be explained by examination of Dreiding models or suitable Newman projections, as depicted in Figure 1. The first configuration, **A**, that of epipodorhizol [**5**], shows a situation in which formation of a hydrogen bond between the C-7 hydroxyl group and the lactone carbonyl is possible because there is little steric interaction between the bulky trimethoxyphenyl group and the lactone ring. In the second configuration, **B**, that of podorhizol [**4**], hydrogen bonding between the C-7 hydroxyl group and the lactone carbonyl is unfavorable due to the vicinal interaction of the trimethoxyphenyl and the lactone ring. This interaction results in rotation around the C-7/C-8 bond to the conformer **C**, allowing a lower energy steric arrangement, but creating a situation in which hydrogen bonding is no longer possible. These steric arguments have been reported and are supported by nmr findings (33). Thus, the difference in hydrogen-bonding ability of the two alcohols could account for the significant difference in their reactivities, since it has been well-established, by placing

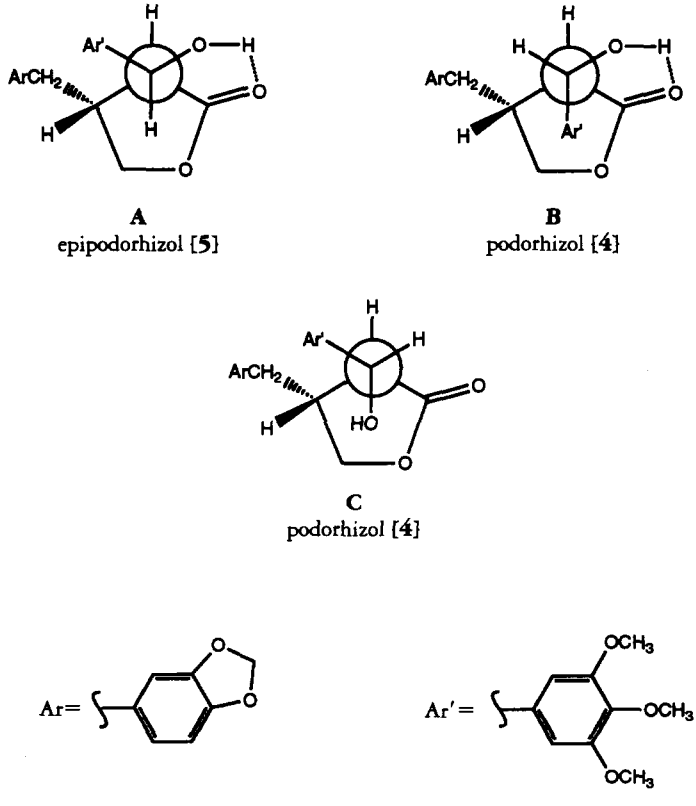
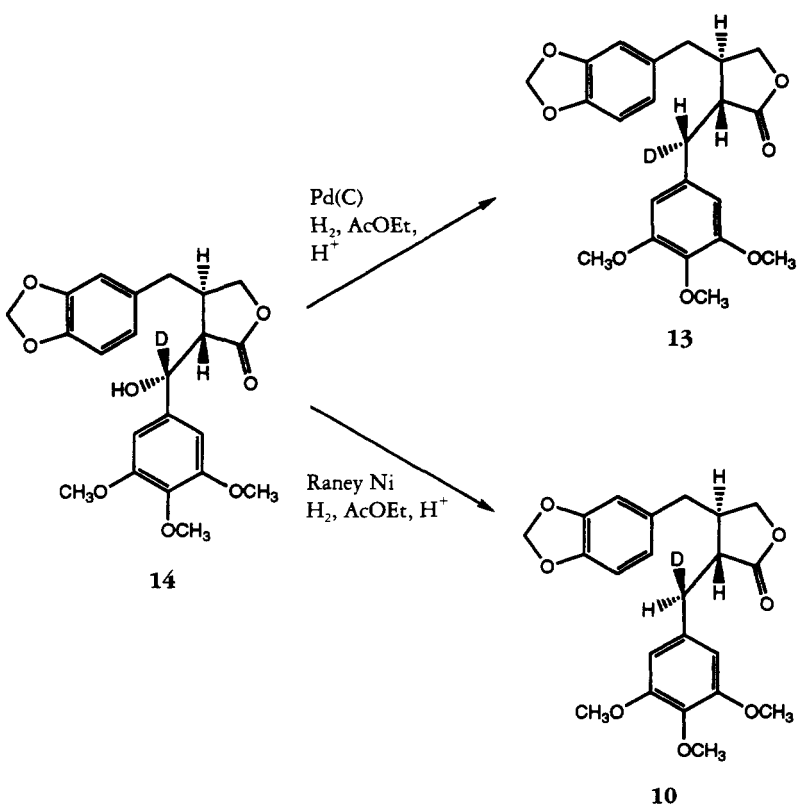


FIGURE 1. Newman Projections Showing Configurations about the C-7/C-8 Bond for Epipodorhizol [**5**] and Podorhizol [**4**].

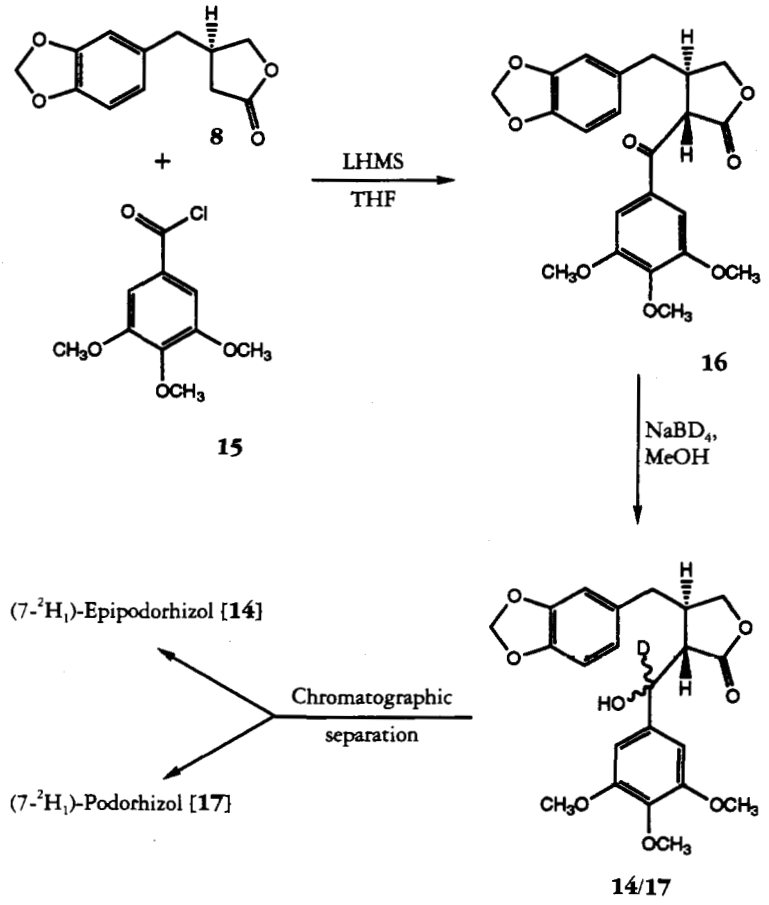
various substituents on the benzylic oxygen, that the relative rate of hydrogenolysis increases in proportion to the leaving group ability of the group at the benzylic position (23, 25–30). Hydrogen bonding in epipodorhizol would presumably cause a slight lengthening of the benzylic carbon-oxygen bond, thereby leading to an enhanced rate of hydrogenolysis. It is of note that Kamil and Dewick reported that hydrogenolysis of either podorhizol or epipodorhizol proved to be completely unsuccessful under a variety of conditions (9).

In an attempt to prepare (7′β-$^2H_1$)-yatein [**10**], epipodorhizol [**5**] was subjected to hydrogenolysis over Pd/C (5%) using deuterium gas and catalytic $DClO_4$. However, under these conditions aromatic ring deuteration occurred, making this route unsuitable for our purposes.

We next sought to prepare (7-$^2H_1$)-epipodorhizol [**14**], because hydrogenolysis of this compound over Pd/C (established as being successful in the synthesis of unlabeled yatein) would lead to (7′α-$^2H_1$)-yatein [**13**], and hydrogenolysis over Raney nickel would potentially lead to (7′β-$^2H_1$)-yatein [**10**], as indicated in Scheme 2. In order to obtain (7-$^2H_1$)-epipodorhizol [**14**], the synthetic route outlined in Scheme 3 was used. The first step involved base-catalyzed condensation of (*R*)-(+)-β-piperonyl-γ-butyrolactone [**8**] with 3,4,5-trimethoxybenzoyl chloride [**15**] to yield the known compound podorhizone [**16**]. This compound was then reduced to the alcohols (7-$^2H_1$)-epipodorhizol [**14**] and (7-$^2H_1$)-podorhizol [**17**], using sodium borodeuteride. Following chromatographic separation of the labeled alcohols, (7-$^2H_1$)-epipodorhizol [**14**] was subjected to hydrogenolysis using hydrogen gas and palladium-on-carbon (5%) with a



SCHEME 2. Proposed Preparation of (7′α-$^2H_1$)-Yatein [**13**] and (7′β-$^2H_1$)-Yatein [**10**] from (7-$^2H_1$)-Epipodorhizol [**14**].



SCHEME 3. Synthesis of (7-$^2H_1$)-Epipodorhizol [**14**] from Podorhizone [**16**].

catalytic amount of $HClO_4$, affording a less polar product. Nmr and mass spectral analyses were carried out and the product was identified as the desired (7′α-$^2H_1$)-yatein [**13**].

(7-$^2H_1$)-Epipodorhizol [**14**] was next subjected to hydrogenolysis over Raney nickel in order to obtain (7′β-$^2H_1$)-yatein [**10**]. Unfortunately, many experiments with varying grades of Raney nickel and differing reaction conditions failed to yield isolable amounts of the desired compound. The lack of product formation could be attributed to the lower reactivity of the nickel catalyst relative to the Pd catalyst, as previously reported (22,23,27,28).

In summary, we have prepared (2,5,6,2′,5′,6′-$^2H_6$)-matairesinol and (7′α-$^2H_1$)-yatein, which can now be used in plant incorporation studies in order to firmly establish the biosynthetic pathway(s) leading to podophyllotoxin. Additionally, the preparation and subsequent use of unlabeled and deuterium-labeled podorhizol and epipodorhizol as synthetic intermediates has afforded more insight into the chemistry and reactivity of these diarylbutyrolactone lignans.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Mps were recorded on a Gallenkamp melting point apparatus and are uncorrected. Optical rotation values were obtained on a Perkin-Elmer 241 polarimeter, using sodium D line illumination, at room temperature, with $CHCl_3$ as solvent. ^1H-, ^2H-, and ^{13}C-nmr spectra were

recorded on Bruker WP 200, WP 270, or Varian Unity 400 MHz spectrometers in $CDCl_3$ as solvent with TMS as the internal standard. Ir spectra were recorded on a Perkin-Elmer 710B spectrophotometer. Low-resolution eims were obtained on a VG Analytical 7070E-HF mass spectrometer. Analytical tlc was performed on E. Merck aluminum-supported Si gel 60 F_{254} (0.2 mm) plates. Prep. tlc was performed on 20 cm×20 cm GF_{254} (0.5 mm) glass-supported plates. Si gel for flash chromatography was E. Merck (230–400 mesh).

(2,5,6,2′,5′,6′-$^2H_6$)-MATAIRESINOL [**6**].—Matairesinol [**2**] (18.7 mg; 0.052 mmol) was dissolved in 3 ml THF/$CDCl_3$ (1:1). To the solution was then added 68% $DClO_4$ in D_2O (0.235 ml; 2.62 mmol; 50 molar equivalent), and the solution was allowed to stir while monitoring aliquots of the reaction by ^1H nmr (i.e., disappearance of aromatic peaks). At 4 h, the exchange appeared to be complete by nmr analysis. To the reaction flask was added 10 ml CH_2Cl_2, and the solution was washed with brine to remove residual acid. After drying and evaporation of the solvent, the residue was purified by prep. tlc to obtain **6** (15.8 mg; 83.5%). The ^1H-nmr spectrum ($CDCl_3$) appeared the same as for unlabeled matairesinol [**2**], with the exception that no aromatic proton peaks were evident. ^1H nmr (270 MHz, $CDCl_3$) δ 5.52 (1H, s, O*H*), 5.50 (1H, s, O*H*), 4.15 (1H, dd, J=9.1 and 7.0 Hz, H-9′β), 3.88 (1H, dd, J=9.1 and 7.0 Hz, H-9′α), 3.82 (6H, s, OCH_3), 2.95 (1H, dd, J=14.2 and 5.5 Hz, H-7α), 2.87 (1H, dd, J=14.2 and 6.8 Hz, H-7β), 2.41–2.63 (4H, m, H-8, H-8′, H-7′α,β); eims *m/z* 364 (M^+, 14), 224 (6), 197 (5), 167 (7), 140 (100), 125 (10), 97 (9), 80 (5), 68 (4).

PODORHIZOL [**4**] AND EPIPODORHIZOL [**5**].—(*R*)-(+)-β-Piperonyl-γ-butyrolactone [**8**] (550 mg; 2.5 mmol) was dissolved with stirring in 10 ml THF (dry, distilled) and cooled to −78°, under N_2 blanket. To the stirring solution was slowly added LDA (3 mmol; 1.2 molar equivalent). The solution was allowed to warm to 0° to ensure enolate formation, then recooled to −78°. After 20 min of additional stirring, 3,4,5-trimethoxybenzaldehyde [**9**] (490.5 mg; 2.5 mmol), dissolved in 5 ml THF, was added dropwise to the enolate solution. The reaction was allowed to proceed for 1.5 h, at which time tlc analysis (CH_2Cl_2-MeOH, 15:1) indicated complete conversion of the lactone **8** to an approximately 1:1 mixture of the alcohols **4** and **5**. The reaction was quenched by the addition of 1N HCl and the solvents were removed by rotary evaporation. The slightly yellow-colored residue was redissolved in Et_2O and the Et_2O layer was washed with brine, dried with anhydrous $MgSO_4$, filtered, and evaporated, leaving the mixture of alcohols **4** and **5** as a colorless oil (841.5 mg; 89%). Alcohols **4** and **5** were separated by flash chromatography (CH_2Cl_2-MeOH, 98:2), with epipodorhizol [**5**] eluting first. Yield of podorhizol [**4**]: 372.3 mg (40.2%); yield of epipodorhizol [**5**]: 397.1 mg (42.9%); 93.4% total recovery after flash chromatography.

Podorhizol [**4**].—Mp 123–125.5° [lit. (9) 124–126°]; ^1H nmr (270 MHz, $CDCl_3$) δ 6.47 (2H, s, H-2, H-6), 6.59 (1H, d, J=7.7 Hz, H-5′), 6.30 (1H, dd, J=7.8 and 1.5 Hz, H-6′), 6.22 (1H, d, J=1.5 Hz, H-2′), 5.92 (2H, dd, J=1.4 and 1.4 Hz, -OCH_2O-), 5.25 (1H, d, J=2.9 Hz, H-7), 4.39 (1H, dd, J=8.7 and 8.0 Hz, H-9′α), 3.97 (1H, dd, J=8.7 and 8.9 Hz, H-9′β), 3.83 (3H, s, 4-OMe), 3.82 (6H, s, 3-, 5-OMe), ca. 2.80 (1H, m, H-8′), 2.61 (1H, dd, J=6.1 and 2.9 Hz, H-8), 2.47 (1H, dd, J=13.7 and 7.7 Hz, H-7′α), 2.25 (1H, dd, J=13.7 and 8.1 Hz, H-7′β); eims *m/z* 416 (M^+, 14), 399 (3), 264 (2), 220 (20), 198 (70), 197 (39), 182 (16), 170 (21), 155 (11), 136 (35), 135 (100), 105 (8), 77 (21).

Epipodorhizol [**5**].—Mp 132–133.5° [lit. (9) 133–134°]; ^1H nmr (270 MHz, $CDCl_3$) δ 6.66 (1H, d, J=8.2 Hz, H-5′), 6.65 (2H, s, H-2, H-6), 6.34 (1H, dd, J=8.2 and 1.7 Hz, H-6′), 6.33 (1H, d, J=1.7 Hz, H-2′), 5.92 (2H, dd, J=1.4 and 1.4 Hz, -OCH_2O-), 4.79 (1H, d, J=7.9 Hz, H-7), 4.18 (1H, dd, J=9.3 and 7.8 Hz, H-9′α), 3.92 (1H, dd, J=9.3 and 8.4 Hz, H-9′β), 3.88 (6H, s, 3-, 5-OMe), 3.83 (3H, s, 4-OMe), 2.62 (1H, dd, J=9.1 and 7.8 Hz, H-8), ca. 2.50 (1H, m, H-8′), 2.20 (1H, dd, J=13.8 and 8.9 Hz, H-7′α), 2.12 (1H, dd, J=13.7 and 5.4 Hz, H-7′β); eims *m/z* 416 (M^+, 13), 399 (3), 264 (2), 220 (20), 198 (63), 197 (38), 182 (18), 170 (21), 155 (9), 136 (31), 135 (100), 105 (9), 85 (7), 77 (9).

YATEIN [**3**].—A 1:1 mixture of the alcohols **4** and **5** (337.1 mg; 0.81 mmol) was dissolved in 16 ml of EtOH-CH_2Cl_2 (1:1) with stirring, in a 25-ml two-neck, septum-sealed round-bottomed flask. To this solution was added Pd/C (5%) (862.2 mg; 0.41 mmol). After 5 to 10 min of stirring, the flask was attached to a hydrogenator with a 50-ml hydrogen gas capacity, and the system was purged of air by vacuum aspiration, and charged with hydrogen gas. After the addition of a few drops of 70% $HClO_4$ via syringe, the reaction was allowed to proceed while monitoring hydrogen uptake and periodically checking by tlc (CH_2Cl_2-MeOH, 15:1). After 8 h tlc analysis showed a non-polar spot at R_f ca. 0.8, in a relative ratio of 1:1:0.1 with podorhizol [**4**] and epipodorhizol [**5**], respectively. At this time the catalyst was removed by filtration, and the solvent removed by rotary evaporation, leaving a pale yellow-green, amorphous solid residue. The residue was subjected to prep. tlc (CH_2Cl_2-MeOH, 98:2; developed twice), and the non-polar band was isolated, affording 87.7 mg (54.1% based on reacted epipodorhizol) of a very pale yellow glassy solid, which was identified by ^1H-nmr analysis as yatein [**3**]. $[\alpha]_D$ −24.7° (c=1.24, $CHCl_3$) [lit. (32) $[\alpha]_D$ −28.4°]; ir (KBr pellet) ν max 2777, 1764, 1243, 1590, 1506, 1489 cm^{-1}; ^1H nmr (270 MHz, $CDCl_3$) δ 6.70 (1H, d,

J=6.8 Hz, H-5), 6.49 (1H, dd, J=6.9 and 1.6 Hz, H-6), 6.46 (1H, d, J=1.6 Hz, H-2), 6.36 (2H, s, H-2′, H-6′), 5.94 (2H, dd, J=2.5 and 1.4 Hz, -OCH_2O-), 4.18 (1H, dd, J=9.3 and 7.1 Hz, H-9α), 3.88 (1H, dd, J=9.3 and 7.5 Hz, H-9β), 3.85 (3H, s, 4′-OMe), 3.83 (6H, s, 3′-, 5′-OMe), 2.94 (1H, m, H-7′α), 2.88 (1H, m, H-7′β), ca. 2.62 (1H, m, H-7β), ca. 2.57 (1H, m, H-8′), ca. 2.51 (1H, m, H-7α), ca. 2.49 (1H, m, H-8); ^{13}C nmr (270 MHz, $CDCl_3$) δ 178.49 (C-9′), 46.49 (C-8′), 41.07 (C-8), 71.18 (C-9), 38.37 (C-7), 35.28 (C-7′), 131.57 (C-1), 108.79 (C-2), 147.97 (C-3), 146.45 (C-4), 108.34 (C-5), 121.57 (C-6), 133.33 (C-1′), 106.35 (C-2′), 153.31 (C-3′), 136.80 (C-4′), 153.31 (C-5′), 106.35 (C-6′), 101.11 (-OCH_2O-), 56.14 (C-3′-OCH_3), 60.87 (C-4′-OCH_3), 56.14 (C-5′-OCH_3); eims m/z 400 (M^+, 54), 264 (3), 251 (4), 238 (3), 219 (4), 181 (100), 167 (13), 151 (16), 135 (52), 105 (12), 84 (26), 77 (28), 65 (9).

YATEIN [**3**] FROM EPIPODORHIZOL [**5**].—Epipodorhizol [**5**] (52 mg; 0.125 mmol) was dissolved with stirring in 7 ml EtOAc in a 15-ml two-neck, septum-sealed round-bottomed flask. To the solution was added Pd/C (5%) (133 mg; 0.0625 mmol) and the suspension was allowed to stir for an additional 5–10 min. The reaction flask was then attached to a hydrogenator with a 50-ml hydrogen gas capacity, and the system was purged of air and charged with hydrogen gas. After the addition of 2 drops 70% $HClO_4$, the reaction was allowed to proceed. At 6 h tlc analysis (CH_2Cl_2-MeOH, 15:1) indicated that the starting material had been converted to a less polar material at R_f ca. 0.8, presumably yatein [**3**]. After work-up to remove residual acid, and prep. tlc purification, 34 mg of yatein [**3**] was isolated (68.0% yield), identical with the material previously described.

ATTEMPTED CONVERSION OF PODORHIZOL [**4**] TO YATEIN [**3**].—To confirm that podorhizol [**4**] is not converted to yatein [**3**] under hydrogenolysis conditions, the preceding experiment was repeated using podorhizol [**4**] (63 mg; 0.151 mmol) in place of epipodorhizol [**5**] (0.076 mmol Pd/C, 5%). Even after 155 h, no reaction had occurred, as noted by tlc analysis.

PODORHIZONE [**16**].—(*R*)-(+)-β-Piperonyl-γ-butyrolactone [**8**] (890 mg; 4.05 mmol) was dissolved with stirring in 15 ml THF (dry, distilled) and cooled to −78°, under N_2 blanket. After 10 min of stirring, LDA (4.65 mmol; 1.15 molar equivalent) was added dropwise to the stirring lactone solution. The reaction flask was allowed to warm to 0° to ensure enolate formation, then recooled to −78°. After 20 min, 3,4,5-trimethoxybenzoyl chloride [**15**] (1.17 g; 5.06 mmol), dissolved in 10 ml THF, was added dropwise to the stirring enolate solution. The reaction was allowed to proceed for 3 h at −78°, then was allowed to warm to room temperature over the next 16 h. At this time, tlc analysis (Et_2O-hexane, 4:1) showed the reaction to be complete, i.e., no remaining lactone. The reaction was quenched with 10 ml saturated NH_4Cl solution, and the product was extracted with Et_2O (3×50 ml). The combined organic portions were washed with 1 N HCl (50 ml) and brine (3×50 ml), then dried with anhydrous $MgSO_4$. After filtering off the drying agent, the solvent was removed by rotary evaporation, leaving an orange-yellow residue. The residue was subjected to flash chromatography (Et_2O-hexane, 4:1). When allowed to stand for a period of time, those fractions containing the product, podorhizone [**16**], as determined by tlc analysis (Et_2O-hexane, 4:1), yielded 473 mg of long, thin, colorless needles (28.2% yield). Mp 131–134° [lit. (34) 129–130°]; [α]D +74.8° (c=0.33, $CHCl_3$) [lit. (34) [α]D +79.6°]; ^{1}H nmr (270 MHz, $CDCl_3$) δ 7.17 (2H, s, H-2, H-6), 6.60–6.70 (3H, m, H-2′, H-5′, H-6′), 5.92 (2H, dd, J=2.5 and 1.3 Hz, -OCH_2O-), 4.54 (1H, dd, J=8.9 and 7.1 Hz, H-9′β), 4.25 (1H, d, J=6.3 Hz, H-8), 4.14 (1H, dd, J=8.9 and 5.9 Hz, H-9′α), 3.93 (3H, s, 4-OMe), 3.89 (6H, s, 3-, 5-OMe), 3.41 (1H, m, H-8′), 2.79 (1H, dd, J=19.0 and 13.8 Hz, H-7′β), 2.76 (1H, dd, J=19.0 and 13.8 Hz, H-7′α); eims m/z 414 (M^+, 25), 279 (9), 195 (64), 161 (100), 131 (48), 77 (16).

(7-$^2H_1$)-EPIPODORHIZOL [**14**] AND (7-$^2H_1$)-PODORHIZOL [**17**].—Podorhizone [**16**] (63.1 mg; 0.152 mmol) was dissolved with stirring in 5 ml 95% EtOH, and cooled to 0°. After stirring for 15 min, sodium borodeuteride (15.9 mg; 0.38 mmol) was added portionwise to the stirring solution over 30 min. The reaction was allowed to proceed for 2 h, at which time tlc analysis (CH_2Cl_2-MeOH, 15:1) indicated that the starting material **16** had been completely converted to a mixture of the deuterated alcohols **14** and **17**. The reaction was quenched by the addition of 5 ml 1N HCl, and the solvents were removed by rotary evaporation. The residue was redissolved in CH_2Cl_2, washed with brine (3×15 ml), dried with $MgSO_4$, filtered, and evaporated, leaving a pale yellow, oily residue. The residue was subjected to prep. tlc (CH_2Cl_2-MeOH, 98:2) and the two major bands, corresponding to the epimeric alcohols **14** and **17**, were isolated. Yield of (7-$^2H_1$)-epipodorhizol [**14**]: 31.7 mg (50.1%); yield of (7-$^2H_1$)-podorhizol [**17**]: 29.3 mg (46.3%); total yield of **14** and **17**: 96%.

(7-$^2H_1$)-Epipodorhizol [**14**].—^{1}H nmr ($CDCl_3$) showed the same spectral data as those in the spectrum for epipodorhizol [**5**], with the following exceptions: missing 4.79 ppm doublet, with the coupling constant, J=7.9 Hz; and the 2.62 ppm doublet of doublets, with the coupling constants, J=9.1 and 7.8 Hz, condensed to a 2.62 ppm doublet, with the coupling constant, J=9.0 Hz; ^{2}H nmr ($CDCl_3$) showed a broad singlet at 4.81 ppm, relative to the $CHCl_3$ peak at 7.25 ppm; eims m/z 417 (M^+, 3), 399 (8), 384 (1), 264 (7), 220 (29), 197 (50), 182 (21), 135 (100), 126 (13), 111 (13), 96 (11), 77 (15).

(7-$^2H_1$)-Podorhizol [**17**].—^{1}H nmr ($CDCl_3$) showed the same spectral data as those in the spectrum for podorhizol [**4**], with the following exceptions: missing 5.25 ppm doublet, with the coupling constant, J=2.9 Hz; and a 2.61 ppm doublet of doublets, with the coupling constants, J=6.1 and 2.9 Hz, condensed to 2.61 ppm doublet, with the coupling constant, J=6.1 Hz; ^{2}H nmr ($CHCl_3$) showed a broad singlet at 5.25 ppm, relative to $CHCl_3$ peak at 7.25 ppm; eims *m/z* 417 (M^+, 3), 399 (1), 264 (1), 220 (21), 197 (38), 182 (21), 170 (7), 135 (100), 126 (12), 111 (12), 96 (10), 77 (24), 66 (11).

(7′α-$^2H_1$)-YATEIN [**13**].—(7-$^2H_1$)-Epipodorhizol [**14**] (75 mg; 0.18 mmol) was dissolved with stirring in 7 ml EtOAc in a 15-ml two-neck, septum-sealed round-bottomed flask. To the solution was added Pd/C (5%) (48 mg; 0.043 mmol) and the suspension was allowed to stir for an additional 5–10 min. The reaction flask was then attached to a hydrogenator with a 50-ml H_2 gas capacity, and the system was purged of air and charged with H_2 gas. After the addition of 3 drops concentrated HCl, the reaction was allowed to proceed, while monitoring H_2 uptake and checking periodically by tlc (CH_2Cl_2-MeOH, 15:1). At 48 h tlc analysis indicated that the starting material had been converted to a less polar material, presumably (7′α-$^2H_1$)-yatein [**13**]. After work-up to remove residual acid, the product was purified by prep. tlc, affording 41.7 mg of (7′α-$^2H_1$)-yatein [**13**], as a colorless, glassy solid (57.7% yield). [α]D −25.6° (c=0.4, $CHCl_3$) [lit. (32) [α]D −28.4°]; ^{1}H nmr ($CDCl_3$) showed the same spectral data as those in the spectrum for yatein [**3**] with the following exception: the ABX multiplet at ca. 2.88–2.94 ppm, integrating for the two protons, H-7′α and H-7′β, condensed to a doublet at 2.88 ppm, with coupling constant, J=6.6 Hz, and integrating for one proton, H-7′β; eims *m/z* 401 (M^+, 52), 385 (18), 265 (4), 252 (5), 239 (3), 182 (100), 135 (46), 77 (18), 55 (17).

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