# An Asymmetric Synthesis of (−)-Deoxypodophyllotoxin

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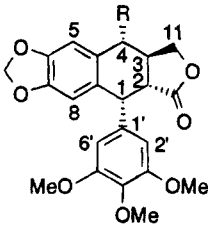
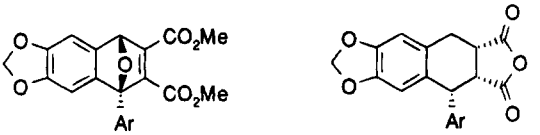
A Diels–Alder cycloaddition between the fumarate of methyl (*S*)-mandelate (**22**) and α-hydroxy-α-aryl-*o*-quinodimethane **21** produces an *endo* cycloadduct (**23**) in 58% yield. The preparation of the precursor to *o*-quinodimethane **21** and the conversion of cycloadduct **23** to optically pure (−)-deoxypodophyllotoxin (**1**) is described.

Deoxypodophyllotoxin (**1**) and podophyllotoxin (**2**) are two well known naturally occurring aryltetralin lignans. Both compounds are cytotoxic,[1] and their derivatives have potential clinical use as antitumor agents. Etoposide[2–6] and teniposide[3,6] are derivatives of podophyllotoxin which are currently being used for treating various types of cancer. Due to their biological activity, the pursuit of methods for the asymmetric synthesis of podophyllotoxin and other aryltetralin lignans has become an interesting challenge.




**1** R = H
**2** R = OH

Many of the published nonasymmetric and asymmetric syntheses of podophyllotoxin and other congeners were cited in our previous paper.[7] While there are a few racemic syntheses of deoxypodophyllotoxin which have been reported,[8–12] only one asymmetric synthesis is known.[13] The racemic syntheses of deoxypodophyllotoxin utilized a Diels–Alder reaction to establish the aryltetralin unit. Rodrigo[8] reacted an isobenzofuran with dimethyl acetylenedicarboxylate to give an aryltetralin cycloadduct (**3**) with a C(2)–C(3) double bond. Selective reduction of the double bond gave a species with the desired 1,2-*cis* stereochemistry but undesired 2,3-*cis* stereochemistry. Regioselective epimerization at C-3 produced an intermediate with the necessary 1,2-*cis* and 2,3-*trans* stereochemistry of deoxypodophyllotoxin. Takano *et al.*[9] generated an *o*-quinodimethane from an [*o*-(hydroxymethyl)benzyl]silane to which was added maleic anhydride resulting in a cycloadduct (**4**) with the all *cis* stereochemistry. Jones *et al.*[10] added dimethyl maleate to a benzopyranone which reacted with concurrent decarboxylation to give an adduct (**5**) with a C(3)–C(4) double bond. The all *cis* stereochemistry was subsequently obtained by selective hydrogenation of the double bond. In both of the Takano *et al.* and Jones *et al.* methods, the intermediates were later epimerized at C-3 to give the desired 1,2-*cis* and 2,3-*trans* stereochemistry. In a different approach, Yamaguchi *et al.*[11] prepared a 1-aryl-3,4-dihydronaphthalene lactone (**6**) via an intramolecular cycloaddition of a cinnamyl phenylpropiolate. After hydrolyzing the lactone, the C(1)–C(2) double bond was hydrogenated to give a mixture of an intermediate with the undesired 2,3-*cis* stereochemistry and an intermediate with the correct 1,2-*cis*-2,3-*trans* stereochemistry thereby avoiding an epimerization step.




Ar = 3,4,5-trimethoxyphenyl

In the asymmetric synthesis of deoxypodophyllotoxin by Achiwa *et al.*,[13] the optical activity was introduced in the first step when α-piperonylidenesuccinic acid half-methyl ester was enantioselectively hydrogenated using a chiral rhodium bis(phosphine) catalyst. The last step of the synthesis involved hydrogenation of the C(1)–C(2) double bond as described by Yamaguchi *et al.*[11] (see above) and unfortunately resulted in a mixture of (+)-isodeoxypicropodophyllin (2,3-*cis*) and (−)-deoxypodophyllotoxin (2,3-*trans*). Deoxypodophyllotoxin can be

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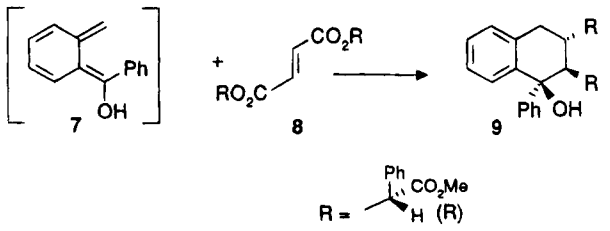
**Scheme 1**



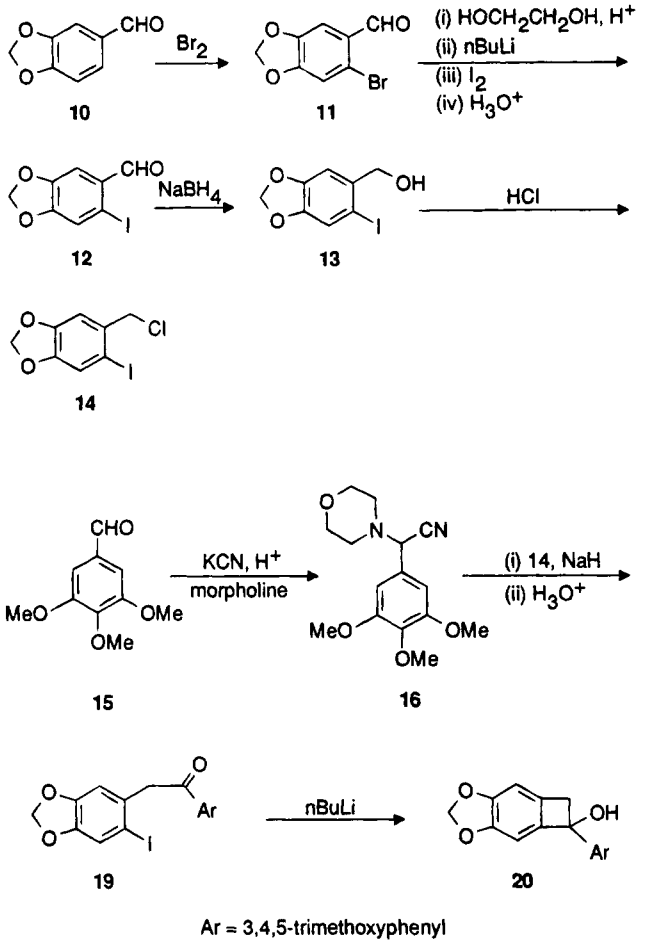

synthesized indirectly from podophyllotoxin[14] via catalytic hydrogenation, and therefore asymmetric syntheses of podophyllotoxin can also be considered as indirect routes to optically active deoxypodophyllotoxin.

In our studies of the asymmetric synthesis of lignans, it has been discovered that the fumarate, maleate, and acrylate of methyl (*S*)-lactate each add to α-hydroxy-*o*-quinodimethane with very high diastereoselectivity.[15] Similar results were obtained when the lactate group was replaced with a mandelate group.[16] Furthermore, it has been observed that the fumarate of methyl (S)-lactate also adds diastereoselectively to α-hydroxy-α′-phenyl-*o*-quinodimethane and yields an *exo* cycloadduct with the correct absolute stereochemistry for the stereogenic centers of podophyllotoxin.[17] This reaction has been used to generate podophyllotoxin analogs,[17] (−)-neopodophyllotoxin,[18] and (−)-α-dimethylretrodendrin and its diastereomers.[7] In our continued search for other diastereoselective methods for preparing aryltetralin lignans it has recently been found that the fumarate of methyl mandelate (**8**) adds in a highly diastereoselective manner to α-hydroxy-α-phenyl-*o*-quinodimethane (**7**) to give an *endo* cycloadduct (**9**) (Scheme 1).[19] We would now like to report a novel asymmetric synthesis of (−)-deoxypodophyllotoxin (**1**) (Schemes 2 and 3) based on this reaction.

## Results and Discussion

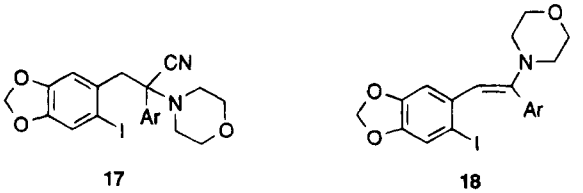
The transient α-hydroxy-α-aryl-*o*-quinodimethane (**21**) (see Scheme 3) was generated by thermally[20] inducing ring opening of benzocyclobutenol **20**. The benzocyclobutenol (**20**) was synthesized according to the pathway shown in Scheme 2 following, in part, the earlier work of Narasimhan *et al.*[21] Piperonal (**10**) was converted to 6-bromopiperonal (**11**) in 98% crude yield by adapting a literature procedure.[22] 6-Bromopiperonal was first protected by forming the ethylene glycol acetal and then the bromine replaced by iodine by treating successively with *n*-butyllithium and iodine. Hydrolysis of the protecting group gave 6-iodopiperonal (**12**)[23,24] in good yield (83%)

**Scheme 2**




Ar = 3,4,5-trimethoxyphenyl

from 6-bromopiperonal. Reduction of aldehyde **12** to 6-iodopiperonyl alcohol (**13**)[23] followed by the treatment with hydrochloric acid afforded benzyl chloride **14** in 69% overall yield from piperonal. Compound **14** has been previously synthesized by an alternative two-step method[25] in which alcohol **13** was an intermediate. While this synthesis was shorter than ours, the yield of benzyl chloride **14** was poorer (60%). In order to prepare compound **16**, a reaction was used based on the Strecker synthesis of α-amino nitriles.[26] 3,4,5-Trimethoxybenzaldehyde (**15**) was treated with potassium cyanide and morpholine under acidic conditions to produce α-aminoacetonitrile **16** in high yield (92%). Compound **16** was treated with strong base to form a resonance stabilized carbanion which then reacted with benzyl chloride **14**. After workup, a mixture of products was observed consisting of cyanomorpholine **17**, enamine **18**, and ketone **19**.




Hydrolysis of this mixture led to the conversion of compounds **17** and **18** to the desired ketone **19**. Cycliza-

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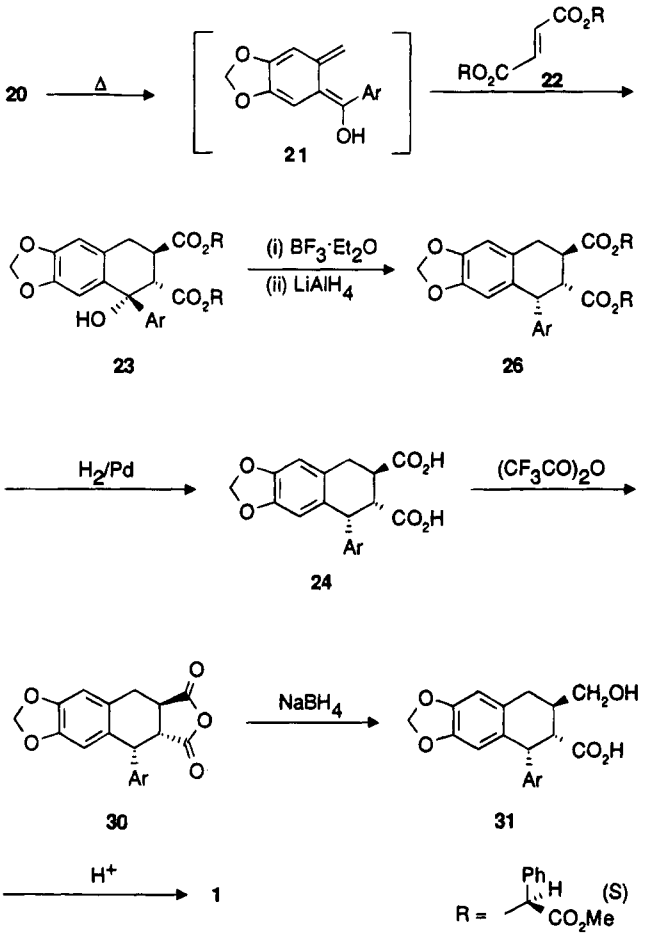
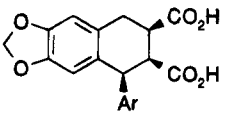
**Scheme 3**




tion of ketone **19** to **20** was accomplished by using *n*-butyllithium. It would seem that this cyclization might also be feasible for the bromo analog of **19** eliminating the need for the earlier bromine–iodine exchange. However, Narasimhan reported that treatment of the bromo analog of **19** with *n*-butyllithium caused reduction of the C–Br bond and addition of the butyl group to the ketone function.[21] These byproducts were not present with the cyclization of the aryl iodide **19**.

The remaining steps for the transformation of benzocyclobutenol **20** to (−)-deoxypodophyllotoxin are shown in Scheme 3. The procedure for the synthesis of cycloadduct **23** was the same as that used in the earlier work on α-hydroxy-α-phenyl-*o*-quinodimethane (**7**).[19] Compound **20** was thermolyzed in refluxing toluene in the presence of the fumarate of methyl (*S*)-mandelate (**22**)[18] resulting in a 58% isolated yield of the major cycloadduct after chromatography. The *o*-quinodimethane **21** is depicted as having the hydroxyl group in the *E* geometry. This geometry is assumed on the basis of our past experience and the torquoselectivity rules presented by Houk *et al.*[27] Analysis of the crude cycloaddition mixture before chromatography by HPLC and $^1$H NMR (300 MHz) indicated the presence of a minor cycloadduct in a ratio of 9:1 (major:minor). The major cycloadduct exhibited a double doublet at 3.14 ppm for H4a with a $J_{4a,3}$ coupling of 11.9 Hz and a doublet at 3.80 ppm for H2 with a $J_{2,3}$ of 11.5 Hz. These coupling constants indicated that protons H2 and H3 were *trans* and diaxial. The major cycloadduct was assigned structure **23** based on previous experience with the cycloaddition of the fumarate of methyl (*R*)-mandelate to α-hydroxy-α-phenyl-*o*-quinodimethane (Scheme 1).[20] The fumarate of methyl (*S*)-lactate might have been used in place of **22**, but using the mandelate derivative allowed for an easy removal of the chiral auxiliary in a later step of the synthesis while avoiding the possibility of epimerizing the C-2 and C-3 centers during an ester hydrolysis or transesterification.

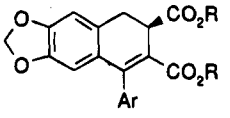
While compound **23** had the required absolute stereochemistry at the C-2 and C-3 centers for the structure of (−)-deoxypodophyllotoxin, the necessary 1,2-*cis* geometry relative to the aryl group was not present. Reduction of the hydroxyl group with concurrent inversion of C-1 proved to be difficult. In an attempt to invert the C-1 center and to remove the mandelate groups at the same time, the cycloadduct was subjected to catalytic hydrogenolysis. Unfortunately, $^1$H NMR analysis of the crude product indicated that the product was a mixture of diacids presumed to be **24** and **25** in a ratio of 1:4 (**24**:**25**).



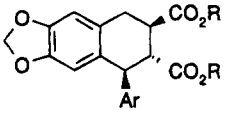

**25**

Obtaining diacid **25** as the major product suggested that the cycloadduct was eliminating across the C(1)–C(2) bond faster than the hydroxyl group could be hydrogenolyzed. This theory was supported by catalytically hydrogenating alkene **27** (see below), produced by acid-catalyzed dehydration of **23**, giving diacids **24** and **25** in a ratio similar to that observed above. To find a more efficient method of synthesizing diacid **24**, a selective ionic reduction of the benzylic alcohol was pursued.

When the cycloadduct was reacted with sodium borohydride in trifluoroacetic acid,[28] a mixture of compounds **26**–**28** was obtained.




**27**




**28**

Optimization of these reduction conditions produced compounds **26**, **27**, and **28** in a ratio of 3.6:1.0:2.4, respectively. Using a different reduction system consisting of triethylsilane and boron trifluoride etherate[29] produced compounds **26**, **27**, and **28** in an optimum ratio of 11.0:1.0:11.1, respectively. Although the $NaBH_4$/TFA system produced the inverted product **26** more selectively than the $Et_3SiH/BF_3{\cdot}OEt_2$ system, relative to the noninverted product **28**, the latter system afforded much less elimination (**27**). Consequently, both reduction systems gave approximately the same yield of the desired **26** (~50%). An excellent procedure for reducing cycloadduct **23** in a very selective manner was discovered after much experimentation. A methylene chloride solution of the cycloadduct was treated with $BF_3{\cdot}OEt_2$ at a low temperature, turning the solution dark blue, and was then decolorized by the addition of $LiAlH_4$. Integration of the

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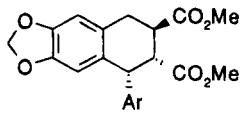
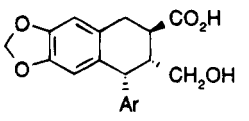
crude $^1$H NMR spectrum revealed a product ratio of 15.0:1.0:2.0 (**26**:**27**:**28**). No precedent has been found for the stereoinversion of a diaryl alcohol by reduction with $BF_3$·$OEt_2$/$LiAlH_4$. The reaction of the Lewis acid with the hydroxyl group likely produced a closely-associated ion pair since the diaryl cation has been observed to be quite stable (blue color has remained for long periods of time at temperatures as high as −5 °C). In this case, the selective addition of hydride to one face of the cation was probably sterically controlled by the adjacent ester group. The desired inverted reduction product **26** could only be isolated in 36% yield by chromatography because of the very similar retention times of the three products. Since the isolation of compound **26** was unnecessary at this stage, the crude reduction product was used to synthesize deoxypodophyllotoxin. The last few steps of the synthesis were straightforward. The mandelate groups were removed from **26** by catalytic hydrogenolysis to give the corresponding diacid **24**. Due to difficulties in purifying the diacid, the compound was characterized by conversion to its dimethyl ester **29**. Refluxing the crude diacid in trifluoroacetic anhydride[30] resulted in a crude product presumed to be the anhydride **30**.[31] Sodium borohydride was then utilized to regioselectively reduce the crude anhydride. The $^1$H NMR spectrum of the crude reduction product was consistent with the presence of isomers **31** and **32** with H-1 protons appearing at $\delta$ 4.39 and 4.48, respectively.[31] The desired $\gamma$-hydroxy acid **31** was favored over its regioisomer (**32**) by a ratio of 3.3:1.0 probably due to the steric hinderence of the aryl group located on C-1. Lactonization of **31** to (−)-deoxypodophyllotoxin (**1**) was effected by refluxing a solution of the crude hydroxy acid in benzene in the presence of a catalytic amount of *p*-toluenesulfonic acid.[7] The crude product was chromatographically separated to give optically pure (−)-deoxypodophyllotoxin[13a,14,32] in 30% yield from cycloadduct **23**.




**29**




**32**

## Conclusion

An asymmetric synthesis of (−)-deoxypodophyllotoxin has been established in a yield of 6% starting from piperonal (**10**). This yield is comparable to the yield obtained in the asymmetric synthesis reported by Achiwa *et al.*[13]

## Experimental Section

The analytical instruments employed have been described in a previous paper.[7]

**6-Iodopiperonal (12).** 6-Bromopiperonal[22] (7.34 g, 32.0 mmol) was dissolved in benzene (200 mL). A catalytic amount of *p*-TsOH (1 mg) and ethylene glycol (3.80 mL, 68.1 mmol) were added to the solution which was then refluxed for 15 h using a Dean−Stark trap to remove water. Most of the benzene was evaporated off to form a concentrated solution, and the solution was filtered through silica gel (40% EtOAc/hexanes) to remove excess ethylene glycol. Evaporation of the solvent gave colorless crystals (acetal) which were dissolved in dry THF (100 mL). The THF solution was cooled to −78 °C under $N_2$ to which was added *n*-BuLi (2.0M in hexanes, 19 mL, 40 mmol). A solution of iodine (9.80 g, 38.6 mmol) in THF (30 mL) was added immediately after the addition of *n*-BuLi. The stirred solution was warmed to room temperature and quenched with saturated aqueous $NH_4Cl$, and $NaHSO_{3(s)}$ was added until the solution was decolorized. The mixture was extracted with EtOAc, dried ($MgSO_4$), and evaporated. The crude product was dissolved in 15% MeOH/benzene (70 mL) and stirred with 20% HCl (50 ml) for 16 h. The mixture was extracted with EtOAc and the solvent evaporated to a concentrated solution. The solution was filtered through silica gel (40% EtOAc/hexanes) and evaporated to give a light yellow solid (7.34 g, 83%). A sample of colorless crystals was obtained by recrystallization from 40% AcOH/$H_2O$: mp 102−104 °C (lit.[24] 108.5−110.5 °C); IR ($CH_2Cl_2$) 1684 (CO) cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 6.08 (s, 2H), 7.34 (s, 1H), 7.37 (s, 1H), 9.89 (s, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 93.2 (C), 102.6 ($CH_2$), 108.9 (CH), 119.4 (CH), 129.6 (C), 149.1 (C), 153.5 (C), 194.3 (CH); mass spectrum *m*/*z* (relative intensity) 276 (M$^+$, 100), 247 (10), 148 (15), 120 (22); HRMS calcd for $C_8H_5O_3I$ 275.9283, found 275.9290.

**6-Iodopiperonyl Alcohol (13).** 6-Iodopiperonal (5.63 g, 20.4 mmol) was refluxed in *i*-PrOH (60 mL) in the presence of $NaBH_4$ (75.3 mg, 2.00 mmol) for 16 h. The solution was cooled to room temperature and quenched with 10% $HCl_{(aq)}$. The solution was extracted with EtOAc, dried ($MgSO_4$), and evaporated to give a yellow solid (5.49 g, 97%). Recrystallization from AcOH gave a sample of colorless crystals: mp 107−108 °C (lit.[23] 106−107 °C); IR ($CH_2Cl_2$) 3605 (OH) cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 1.92 (s, 1H), 4.58 (s, 2H), 5.97 (s, 2H), 6.98 (s, 1H), 7.23 (s, 1H); $^{13}$C ($CDCl_3$) $\delta$ 69.2 ($CH_2$), 85.3 (C), 101.7 ($CH_2$), 109.0 (CH), 118.5 (CH), 136.2 (C), 147.9 (C), 148.6 (C); mass spectrum *m*/*z* (relative intensity) 278 (M$^+$, 100), 261 (13), 149 (17), 122 (14); HRMS calcd for $C_8H_7O_3I$ 277.9440, found 277.9450.

**5-(Chloromethyl)-6-iodo-1,3-benzodioxole (14).** A stirred solution of **13** (3.98 g, 14.3 mmol) in 50% AcOH/$CH_2Cl_2$ (50 mL) was saturated with $HCl_{(g)}$. After 5 h of stirring at room temperature, $H_2O$ was added and the solution extracted with $CH_2Cl_2$. The organic layers were combined and washed with saturated aqueous $NaHCO_3$. The organic layer was dried ($MgSO_4$) and evaporated to give a light brown solid (3.67 g, 87%). Recrystallization from *i*-PrOH afforded an analytical sample of colorless crystals: mp 59−60 °C (lit.[25] 65−66 °C); $^1$H NMR ($CDCl_3$) $\delta$ 4.61 (s, 2H), 5.98 (s, 2H), 6.96 (s, 1H), 7.24 (s, 1H); $^{13}$C ($CDCl_3$) $\delta$ 51.4 ($CH_2$), 88.1 (C), 101.9 ($CH_2$), 110.0 (CH), 118.8 ($CH_2$), 133.1 (C), 148.5 (C), 148.6 (C); mass spectrum *m*/*z* (relative intensity) 296 (M$^+$, 41), 261 (100), 134 (16), 127 (9); HRMS calcd for $C_8H_6O_2I^{35}Cl$ 295.9101, found 295.9110.

**1-(3,4,5-Trimethoxyphenyl)-1-morpholinoacetonitrile (16).** KCN (1.83 g, 28.1 mmol) was added to $H_2O$ (5 mL) at 0 °C followed by the addition of morpholine (2.35 mL, 26.8 mmol). Concentrated HCl (2.34 mL) was added dropwise with stirring and the solution warmed to room temperature. A solution of 3,4,5-trimethoxybenzaldehyde (5.02 g, 25.6 mmol) in MeOH (52 ml) was added to the aqueous solution and the mixture stirred for 5 days (116 h). The resulting colorless precipitate was filtered off. The precipitate was stirred in $CH_2Cl_2$ and $MgSO_4$ added. The insoluble portion of the precipitate and the drying agent were filtered off, and the solvent was evaporated to give a colorless solid (6.84 g, 92%): mp 136−138 °C; IR ($CH_2Cl_2$) 2231 (CN) cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 2.59 (m, 4H), 3.75 (m, 4H), 3.86 (s, 3H), 3.89 (s, 6H), 4.75 (s, 1H), 6.77 (s, 2H); $^{13}$C ($CDCl_3$) $\delta$ 50.0 ($CH_2$), 56.3 ($CH_3$), 60.8 ($CH_3$), 62.5 (CH), 66.7 ($CH_2$), 105.0 (CH), 115.2 (C), 127.9 (C), 138.4 (C), 153.5 (C); mass spectrum *m*/*z* (relative intensity) 292 (M$^+$, 7), 265 (4), 206 (100), 181 (25), 176 (10), 149 (27); HRMS calcd for $C_{15}H_{20}O_4N_2$ 292.1423, found 292.1433.

**Ketone 19.** Compounds **14** (3.6 g, 12 mmol) and **16** (3.96 g, 13.5 mmol) were dissolved in dry DMF (50 mL) and placed under $N_2$. NaH (57% in oil, 4.0 g, 95 mmol) was added to the

(30) Moore, J. A.; Kelly, J. E. *Org. Prep. Proc. Int.* **1974**, *6*, 255−258.

(31) Compounds **30**−**32** were not fully characterized due to difficulty in purifying them by chromatography. Their structural assignments are based on $^1$H NMR spectra of the crude samples.

(32) Brewer, C. F.; Loike, J. D.; Horwitz, S. B. *J. Med. Chem.* **1979**, *22*, 215−221.

solution and the solution warmed to 70 °C. After 1 h of stirring, the solution was cooled to room temperature and quenched with $H_2O$ (25 mL). 10% Aqueous HCl (25 mL) was added to the solution and the solution was stirred at 61 °C for 16 h. The solution was cooled to room temperature, saturated with NaCl, and extracted with $CH_2Cl_2$. The organic layer was dried ($MgSO_4$) and evaporated to give a brown solid. Recrystallization from AcOH gave light yellow crystals (3.7 g, 67%): mp 176–178 °C; IR ($CH_2Cl_2$) 1684 (CO) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 3.92 (s, 9H), 4.33 (s, 2H), 5.96 (s, 2H), 6.75 (s, 1H), 7.27 (s, 2H), 7.28 (s, 1H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 50.2 ($CH_2$), 56.4 ($CH_3$), 60.9 ($CH_3$), 88.9 (C), 101.7 ($CH_2$), 106.0 (CH), 110.2 (CH), 118.6 (CH), 131.6 (C), 142.7 (C), 147.6 (C), 148.6 (C), 153.0 (C), 195.5 (C); mass spectrum $m/z$ (relative intensity) 456 ($M^+$, 1), 329 (17), 278 (52), 261 (10), 230 (9), 195 (95), 181 (43); HRMS calcd for $C_{18}H_{17}O_6I$ 456.0070, found 456.0027.

**α-Hydroxy-α-aryl-benzocyclobutenol 20.** Ketone **19** (1.21 g, 2.65 mmol) was dissolved in dry THF (36 mL), placed under $N_2$, and cooled to −80 °C in a hexanes/liquid $N_2$ bath. *n*-BuLi (2.0M in hexanes, 3.3 mL, 6.6 mmol) was added to the stirred solution followed by quenching with saturated $NH_4Cl_{(aq)}$ after 2 min. The solution was warmed to room temperature, $H_2O$ (25 mL) was added, and the solution was saturated with NaCl. The THF layer was separated and the aqueous layer extracted with EtOAc. The organic layers were combined, dried ($MgSO_4$), and evaporated. The crude product was chromatographed on silica gel (20% EtOAc/hexanes) to give colorless crystals (622 mg, 71%): mp 141–143 °C (lit.[21] 142–144 °C); IR ($CH_2Cl_2$) 3587 (OH) $cm^{-1}$; $^1H$ NMR $\delta$ 2.75 (s, 1H), 3.39 (AB, 2H, $J$ = 13.5, $\Delta\delta$ = 21.4), 3.82 (s, 9H), 5.93 (AB, 2H, $J$ = 1.3, $\Delta\delta$ = 3.9), 6.66 (s, 2H), 6.72 (s, 1H), 6.76 (s, 1H); $^{13}C$ ($CDCl_3$) $\delta$ 48.7 ($CH_2$), 56.1 ($CH_3$), 60.8 ($CH_3$), 79.9 (C), 100.4 ($CH_2$), 102.9 (CH), 103.1 (CH), 105.9 (CH), 134.8 (C), 139.4 (C), 140.8 (C), 147.4 (C), 148.9 (C), 153.0 (C); mass spectrum $m/z$ (relative intensity) 330 ($M^+$, 48), 313 (15), 299 (72), 283 (26), 268 (15), 255 (10), 195 (100); HRMS calcd for $C_{18}H_{18}O_6$ 330.1103, found 330.1135.

**(+)-Endo Cycloadduct 23.** Fumarate **22**[18] (1.42 g, 3.44 mmol) was dissolved in toluene (6 mL), and the solution was slightly warmed. Benzocyclobutenol **20** (567 mg, 1.72 mmol) was dissolved in $CH_2Cl_2$ and added dropwise to the toluene solution. The methylene chloride was allowed to boil off and the solution refluxed for 44 h followed by evaporation. The crude product was chromatographed on silica gel (20–30% EtOAc/hexanes) to give a colorless solid (743 mg, 58%): mp 186–188 °C; $[\alpha]^{25}_D$ +132° (*c* 0.96, $CHCl_3$); IR ($CHCl_3$) 3417 (OH), 1743 (CO) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 3.14 (dd, 1H, $J$ = 11.9, 16.3), 3.41 (dd, 1H, $J$ = 4.5, 16.4), 3.62 (s, 3H), 3.71 (m, 1H), 3.72 (s, 3H), 3.80 (d, 1H, $J$ = 11.5), 3.80 (s, 6H), 3.90 (s, 3H), 3.96 (s, 1H), 5.73 (s, 1H), 5.88 (AB, 2H, $J$ = 1.3, $\Delta\delta$ = 3.0), 5.89 (s, 1H), 6.45 (s, 1H), 6.63 (s, 1H), 6.73 (s, 2H), 6.93 (m, 2H), 7.24 (m, 3H), 7.37 (m, 3H), 7.43 (m, 2H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 32.7 ($CH_2$), 39.7 (CH), 52.6 ($CH_3$), 52.8 ($CH_3$), 54.7 (CH), 56.2 ($CH_3$), 60.9 ($CH_3$), 74.8 (CH), 75.0 (CH), 76.4 (C), 101.1 ($CH_2$), 104.0 (CH), 107.4 (CH), 109.3 (CH), 126.9 (C), 127.0 (CH), 127.6 (CH), 128.5 (CH), 128.7 (CH), 129.1 (CH), 129.3 (CH), 132.7 (C), 133.2 (C), 133.5 (C), 137.0 (C), 142.0 (C), 146.7 (C), 147.3 (C), 152.9 (C), 169.2 (C), 169.6 (C), 171.6 (C), 174.0 (C); mass spectrum $m/z$ (relative intensity) 742 ($M^+$, 3), 530 (18), 365 (18), 339 (52), 324 (13), 308 (17), 149 (70), 121 (25), 107 (100), 91 (23), 79 (58); HRMS calcd for $C_{40}H_{38}O_{14}$ 742.2261, found 742.2268.

**Reduction Products 26–28.** Cycloadduct **23** (155 mg, .209 mmol) was dissolved in $CH_2Cl_2$ (41 mL), placed under $N_2$, and cooled to −20 °C in an acetone/dry ice bath. As $BF_3{\cdot}OEt_2$ (0.15 mL, 1.2 mmol) was added, the stirred solution turned dark blue. The temperature of the cold bath was lowered to −55 °C and $LiAlH_4$ (0.37 M in ether, ~2 mL) was added dropwise until the solution was decolorized. 50% $H_2O$/MeOH (20 mL) was added dropwise, and after stirring for 20 min the solution was warmed to room temperature. 10% $HCl_{(aq)}$ (1 mL) was added, and the $CH_2Cl_2$ layer was separated and washed with 10% $HCl_{(aq)}$ (20 mL). The aqueous layers were combined and extracted with $CH_2Cl_2$, the organic layers combined, dried ($MgSO_4$), and evaporated to give a purple, amorphous solid (145 mg, 96%). $^1H$ NMR integration indicated that compounds **26–28** were present in a ratio of 15.0:1.0:2.0 (**26**:**27**:**28**). Chromatography on silica gel (20% EtOAc/hexanes) gave samples of compounds **26** and **28** as colorless amorphous solids and **27** as colorless crystals: Inverted reduction product **26**. $[\alpha]^{25}_D$ −49.2° (*c* 0.12, $CHCl_3$); IR 1745 (CO) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 3.01 (dd, 1H, $J$ = 13.1, 18.3), 3.39 (m, 2H), 3.53 (dd, 1H, $J$ = 5.7, 11.7), 3.59 (s, 3H), 3.63 (s, 6H), 3.68 (s, 3H), 3.73 (s, 3H), 4.52 (d, 1H, $J$ = 5.6), 5.66 (s, 1H), 5.90 (s, 2H), 6.04 (s, 1H), 6.11 (s, 2H), 6.40 (s, 1H), 6.66 (s, 1H), 7.07 (m, 4H), 7.20 (m, 1H), 7.35 (m, 3H), 7.40 (m, 2H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 32.1 ($CH_2$), 37.3 (CH), 46.5 (CH), 48.0 (CH), 52.5 ($CH_3$), 56.2 ($CH_3$), 60.6 ($CH_3$), 74.1 (CH), 74.7 (CH), 100.9 ($CH_2$), 107.2 (CH), 107.6 (CH), 109.4 (CH), 126.6 (C), 126.9 (CH), 127.9 (CH), 128.4 (CH), 128.7 (CH), 128.8 (CH), 129.2 (CH), 129.5 (C), 133.3 (C), 133.5 (C), 136.9 (C), 137.2 (C), 146.5 (C), 146.8 (C), 152.6 (C), 168.8 (C), 169.4 (C), 171.0 (C), 174.0 (C); mass spectrum $m/z$ (relative intensity) 726 ($M^+$, 35), 532 (13), 499 (22), 411 (73), 384 (14), 365 (42), 339 (66), 324 (14), 308 (19), 283 (11), 149 (100), 121 (100), 107 (31), 91 (58), 77 (41), 57 (27); HRMS calcd for $C_{40}H_{38}O_{13}$ 726.2312, found 726.2324. Eliminated reduction product **27**: mp 184–186 °C; $[\alpha]^{25}_D$ +77.5° (*c* 0.16, $CHCl_3$); IR 1749 (CO) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 3.29 (dd, 1H, $J$ = 7.0, 16.4), 3.36 (dd, 1H, $J$ = 4.7, 16.2), 3.58 (s, 3H), 3.63 (s, 3H), 3.64 (s, 3H), 3.81 (s, 6H), 4.08 (dd, 1H, $J$ = 4.3, 6.8), 5.76 (s, 1H), 5.91 (s, 2H), 5.93 (s, 1H), 6.28 (s, 1H), 6.38 (d, 2H, $J$ = 1.9), 6.74 (s, 1H), 7.03 (dd, 2H, $J$ = 1.3, 8.0), 7.28 (m, 8H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 31.5 ($CH_2$), 41.3 (CH), 52.4 ($CH_3$), 52.5 ($CH_3$), 56.0 ($CH_3$), 60.9 ($CH_3$), 74.6 (CH), 74.9 (CH), 101.3 ($CH_2$), 105.5 (CH), 106.3 (CH), 108.5 (CH), 109.2 (CH), 120.7 (C), 127.3 (CH), 128.4 (CH), 128.6 (CH), 128.9 (CH), 129.8 (C), 133.3 (C), 133.8 (C), 134.0 (C), 137.4 (C), 146.5 (C), 148.5 (C), 149.3 (C), 153.0 (C), 167.2 (C), 168.8 (C), 168.9 (C), 172.0 (C); mass spectrum $m/z$ (relative intensity) 724 ($M^+$, 6), 530 (2), 408 (23), 393 (12), 365 (15), 338 (5), 323 (2), 307 (2), 149 (42), 121 (13), 107 (38), 91 (61), 77 (31), 57 (100); HRMS calcd for $C_{40}H_{36}O_{13}$ 724.2155, found 724.2158. Noninverted reduction product **28**. $[\alpha]^{25}_D$ +77.2° (*c* 0.15, $CHCl_3$); IR 1750 (CO) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 3.16 (dd, 1H, $J$ = 10.3, 15.9), 3.30 (dd, 1H, $J$ = 4.5, 15.9), 3.42 (m, 2H), 3.59 (s, 3H), 3.71 (s, 3H), 3.75 (s, 6H), 3.86 (s, 3H), 4.18 (d, 1H, $J$ = 8.5), 5.71 (s, 1H), 5.84 (s, 1H), 5.88 (s, 2H), 6.28 (s, 1H), 6.39 (s, 2H), 6.64 (s, 1H), 7.15 (d, 1H, $J$ = 2.1), 7.17 (d, 1H, $J$ = 1.5), 7.27 (m, 3H), 7.38 (m, 5H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 32.1 ($CH_2$), 42.9 (CH), 48.8 (CH), 50.1 (CH), 52.4 ($CH_3$), 52.6 ($CH_3$), 56.0 ($CH_3$), 60.8 ($CH_3$), 74.8 (CH), 100.9 ($CH_2$), 106.4 (CH), 107.8 (CH), 109.2 (CH), 126.9 (C), 127.2 (CH), 127.6 (CH), 128.5 (CH), 128.7 (CH), 129.0 (CH), 129.2 (CH), 130.7 (C), 133.2 (C), 133.5 (C), 137.0 (C), 138.7 (C), 146.3 (C), 146.5 (C), 153.2 (C), 168.5 (C), 169.1 (C), 172.8 (C), 173.2 (C); mass spectrum $m/z$ (relative intensity) 726 ($M^+$, 15), 532 (8), 499 (18), 412 (35), 383 (10), 365 (32), 339 (39), 324 (10), 308 (13), 283 (10), 149 (100), 121 (69), 107 (44), 91 (80), 77 (54), 57 (36); HRMS calcd for $C_{40}H_{38}O_{13}$ 726.2312, found 726.2314.

**(−)-Deoxypodophyllotoxin (1).** Crude reduction product **26** (145 mg, 0.200 mmol) was stirred with Pd/C (5% Pd, 36 mg) in 30% MeOH/AcOH (20 mL) under $H_2$ (1 atm, rt) for 4 days (89 h). The solution was filtered and the catalyst washed with EtOAc. The solvent was evaporated to give a light yellow solid which was then dissolved in saturated aqueous $NaHCO_3$. The solution was washed with EtOAc. The organic layers were combined and washed with $NaHCO_{3(aq)}$ and $H_2O$. The aqueous layers were combined, acidified with 10% $HCl_{(aq)}$, saturated with NaCl, and extracted with $CH_2Cl_2$. The $CH_2Cl_2$ layers were combined, dried ($MgSO_4$), and evaporated to give diacid **24** as a light yellow solid (67 mg, 78%): $^1H$ NMR ($CDCl_3$) $\delta$ 2.88 (dd, 1H, $J$ = 11.9, 15.7), 3.08 (m, 1H, $J$ = 5.6, 11.8), 3.22 (dd, 1H, $J$ = 5.5, 16.1), 3.29 (dd, 1H, $J$ = 5.6, 11.8), 3.69 (s, 6H), 3.76 (s, 3H), 4.47 (d, 1H, $J$ = 5.5), 5.90 (s, 2H), 6.15 (s, 2H), 6.41 (s, 1H), 6.61 (s, 1H), 8.14 (s, 2H)). Crude diacid **24** (67 mg, 0.16 mmol) was dissolved and refluxed in trifluoroacetic anhydride (6.5 mL) for 2 h. The solvent was evaporated to give the presumed anhydride **30** as a light brown solid. Crude anhydride **30** was refluxed with $NaBH_4$ (8.0 mg, 0.21 mmol) in *i*-PrOH (7.5 mL) for 15 h, cooled to rt, and acidified with 10% $HCl_{(aq)}$. Most of the *i*-PrOH was evaporated off. EtOAc (5.5 mL) and $H_2O$ (5.5 mL) were added to the product,

the aqueous layer was saturated with NaCl, and the EtOAc layer was separated. The aqueous layer was extracted with $CH_2Cl_2$, and the organic layers were combined, dried ($MgSO_4$), and evaporated to give hydroxy acid **31** as a brown solid. The $^1H$ NMR spectrum displayed two signals at 4.39 and 4.48 ppm in the ratio of 3.3:1.0. Crude hydroxy acid **31** was refluxed in benzene (7.0 mL) with a catalytic amount of *p*-TsOH (1 mg) for 17.5 h and then cooled to rt. $H_2O$ (5 mL) was added and the solution saturated with NaCl. The benzene layer was separated and the aqueous layer extracted with $CH_2Cl_2$. The organic layers were combined, dried ($MgSO_4$), and evaporated to give a brown solid. Chromatography on silica gel (20% EtOAc/hexanes) gave (−)-deoxypodophyllotoxin as a colorless amorphous solid (24.5 mg, 30% from cycloadduct **23**): $[\alpha]^{25}_D$ −112° (*c* 0.05, $CHCl_3$), (lit.[13a] −113.4°); IR ($CH_2Cl_2$) 1781 (CO) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 2.74 (br s, 2H), 2.76 (m, 1H), 3.07 (m, 1H), 3.75 (s, 6H), 3.81 (s, 3H), 3.92 (m, 1H), 4.46 (m, 1H), 4.60 (br s, 1H), 5.94 (AB, 2H, $J$ = 1.3, $\Delta\delta$ = 6.4), 6.35 (s, 2H), 6.52 (s, 1H), 6.67 (s, 1H) ($^1H$ NMR spectral data were in agreement with the literature[14,32]); $^{13}C$ NMR ($CDCl_3$) $\delta$ 32.8 (CH), 33.1 ($CH_2$), 43.7 (CH), 47.5 (CH), 56.2 ($CH_3$), 60.7 ($CH_3$), 72.0 ($CH_2$), 101.2 ($CH_2$), 108.3 (CH), 108.4 (CH), 110.4 (CH), 128.2 (C), 130.6 (C), 136.2 (C), 137.1 (C), 146.7 (C), 147.0 (C), 152.5 (C), 174.8 (C); mass spectrum *m*/*z* (relative intensity) 398 ($M^+$, 40), 244 (8), 181 (10), 173 (9), 129 (8), 86 (68), 84 (100), 57 (12); HRMS calcd for $C_{22}H_{22}O_7$ 398.1380, found 398.1365.

**Dimethyl Ester 29.** Diacid **24** (18 mg, 0.042 mmol) was suspended in ether (0.5 mL) and cooled to 0 °C. A freshly prepared solution of diazomethane in ether was added dropwise until no more gas was evolved, and the solution remained yellow. The solution was stirred for 5 min and warmed to rt, and the ether was evaporated to give a yellow solid. Chromatography on silica gel (15% EtOAc/hexanes) gave **29** as a colorless amorphous solid (14 mg, 73%): $[\alpha]^{25}_D$ −121° (*c* 0.08, $CHCl_3$); IR ($CHCl_3$) 1735 (CO) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 2.85 (dd, 1H, $J$ = 13.4, 17.8), 3.17 (m, 2H), 3.35 (dd, 1H, $J$ = 5.7, 12.0), 3.56 (s, 3H), 3.70 (s, 3H), 3.74 (s, 6H), 3.79 (s, 3H), 4.48 (d, 1H, $J$ = 5.7), 5.90 (AB, 2H, $J$ = 1.3, $\Delta\delta$ = 2.7), 6.10 (s, 2H), 6.41 (s, 1H), 6.60 (s, 1H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 32.4 ($CH_2$), 37.2 (CH), 46.5 (CH), 47.8 (CH), 51.5 ($CH_3$), 52.0 ($CH_3$), 56.1 ($CH_3$), 60.8 ($CH_3$), 101.0 ($CH_2$), 106.7 (CH), 107.5 (CH), 109.5 (CH), 126.7 (C), 129.5 (C), 137.1 (C), 137.3 (C), 146.6 (C), 146.8 (C), 152.8 (C), 172.5 (C), 175.5 (C); mass spectrum *m*/*z* (relative intensity) 458 ($M^+$, 90), 398 (50), 339 (100), 324 (15), 308 (16), 283 (32), 252 (23), 231 (19), 149 (23), 57 (44); HRMS calcd for $C_{24}H_{26}O_9$ 458.1577, found 458.1570.

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**Supplementary Material Available:** Copies of $^1H$ and $^{13}C$ NMR spectra of all compounds (25 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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