Efficient Synthesis of 1-Aryl-3,4-dihydro-4-hydroxynaphthalene: Application to the Stereocontrolled Synthesis of (±)-Isopicropodophyllin and (±)-Isopodophyllotoxin

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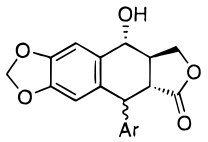
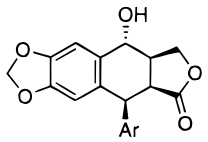
Introduction

The structural complexities and varied biological activities of aryltetralin lignans, as exemplified by the natural product podophyllotoxin (**1**), make them challenging synthetic targets.[1] Several methods have become available for the synthesis of podophyllotoxin (**1**) and its congeners.[2] Rodrigo *et al.* reported the synthesis of (±)-isopicropodophyllin (**2**) and (±)-isopodophyllotoxin (**3**) from piperonal via hydrogenolysis of the Diels−Alder adduct in 22% and 20% overall yields, respectively.[3] They also reported the isolation of the dihydronaphthol **4** (20%) as unexpected byproduct during a hydrogenolysis of the adduct.[3]

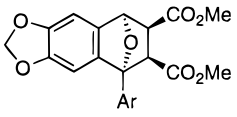


1 : 1α-Ar podophyllotoxin

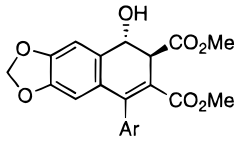


2 isopicropodophyllin

3 : 1β-Ar isopodophyllotoxin



Diels-Alder adduct



4

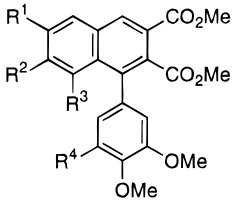
Ar = 3,4,5-trimethoxyphenyl

In the course of synthetic studies searching for biologically active aryltetralin lignan derivatives, the need for a practical synthesis of (±)-isopicropodophyllin (**2**) and (±)-isopodophyllotoxin (**3**) became apparent. We envisioned that the dihydronaphthol **4** could serve as a versatile synthetic intermediate for the synthesis of aryltetralin lignans, provided **4** is readily accessible. The stereocontrolled hydrogenation of **4** should provide precursors of **2** and **3**. Additionally, the α,β-unsaturated ester function of **4** might be suitable for the preparation of C-1 and/or C-2 functionalized aryltetralin lignans. The reaction of **4** with oxidizing agents, for example, might afford the 1,2-epoxy compound. Herein we report an efficient method for synthesizing **4** and its application to the synthesis of **2** and **3**.

Results and Discussion

1-Hydroxy-1,2-dihydronaphthalenes have been shown to undergo ready dehydration to afford naphthalenes under acidic conditions.[4,5] We expected that we should be able to avoid the dehydration by careful selection of acid catalyst and conditions. If this were possible, acid-promoted isomerization of the adduct **10**, generated from the isobenzofuran **9** and dimethyl maleate, could afford the dihydronaphthol **4** (Scheme 1). The isobenzofuran **9** in turn would be generated from the acetoxyaldehyde **8** under acidic conditions.[6] Thus, a single-step conversion of **8** into **4** using dimethyl maleate and acid catalysts could be expected.

The starting acetoxyaldehydes **7** (88%) and **8** (89%) were prepared by a one-pot procedure from corresponding aldehydes **5** and **6**, respectively.[7] Initially, we attempted to synthesize the dihydronaphthol **11** from the acetoxyaldehyde **7** as a model. Treatment of **7** with dimethyl maleate in the presence of a catalytic amount of TFA in toluene at 70 °C led to a formation of a complicated mixture of products containing the dihydronaphthol **11** (10%), the naphthalene **12** (10%), and unidentified byproducts. When this reaction was carried out without added solvent, the desired **11** was obtained in 90% yield with no **12** detected.[8] The *trans* relationship between H_3-H_4 of **11** is consistent with the mode of formation (*vide infra*) and based on the observed large coupling constant ($J_{3,4}$ = 8.0 Hz) in the ^{1}H NMR spectrum. For *cis*-dihydronaphthols, this coupling constant is 4.1−5.0 Hz.[4] The selective formation of the *trans* compound **11** could be explained by acid-catalyzed cleavage of the oxygen bridge



12 : $R^1 = R^2 = R^3 = OMe$, $R^4 = H$

13 : R^1, R^2 = -OCH_2O-, $R^3 = H$, $R^4 = OMe$

(1) (a) Rao, C. B. S. *Chemistry of Lignans*; Andhra Univ. Press: India, 1978. (b) Ayres, D. C.; Loike, J. D. *Lignans*, Cambridge Univ. Press: Cambridge, 1990. (c) Yalowich, J. D. ; Fry, D. W.; Goldman, T. D. *Cancer Res.* **1982**, *42*, 3648 and references cited therein. (d) Kimura, M.; Suzuki, J.; Yamada, T.; Yoshizaki, M.; Kikuchi, T.; Kadota, S.; Matsuda, S. *Planta Med.* **1985**, 291.

(2) (a) Ward, R. S. *Chem. Soc. Rev.* **1982**, *11*, 75. (b) Ward, R. S. *Tetrahedron* **1990**, *46*. 5029. (c) Ogiku, T; Yoshida, S.; Kuroda, T.; Takahashi, M.; Ohmizu, H.; Iwasaki, T. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 3495. (d) Ogiku, T; Yoshida, S.; Kuroda, T.; Ohmizu, H.; Iwasaki, T. *Synlett* **1992**, 651. For a recent review for the synthesis of podophyllotoxin and related compounds, see Ward, R. S. *Synthesis* **1992**, 719.

(3) Forsey, S. P.; Rajapaksa, D.; Taylor, N. J.; Rodrigo, R. *J. Org. Chem.* **1989**, *54*, 4280.

(4) Caple, R.; Chen, G. M.-S.; Nelson J. D. *J. Org. Chem.* **1971**, *36*, 2874.

(5) Wittig, G.; Pohmer, L. *Chem. Ber.* **1956**, *89*, 1334.

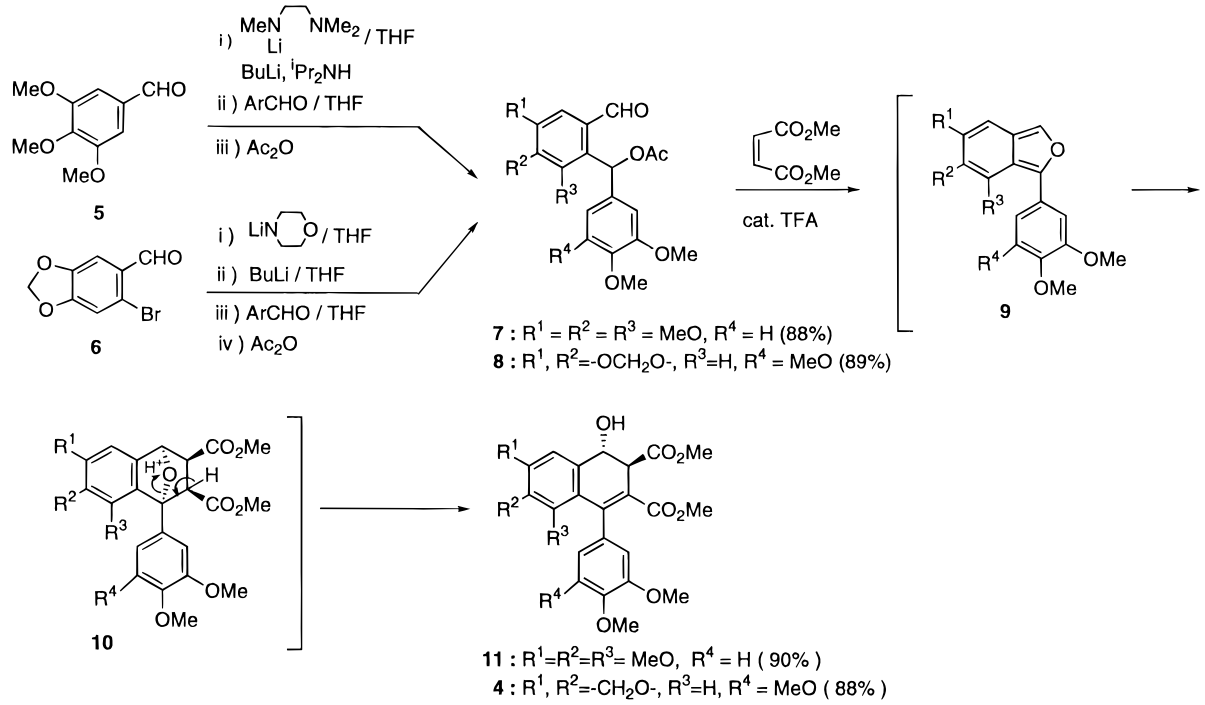
(6) Recently, we have reported the synthesis of heteroaromatic arylnaphthalene lignans from acetoxyaldehydes via heteroaromatic arylisobenzofurans. Kuroda, T.; Takahashi, M.; Ogiku, T.; Ohmizu, H.; Kondo, K.; Iwasaki, T. *J. Chem. Soc., Chem. Commun.* **1991**, 1635. Kuroda, T.; Takahashi, M.; Ogiku, T.; Ohmizu, H.; Nishitani, T.; Kondo, K.; Iwasaki, T. *J. Org. Chem.* **1994**, *59*, 7353.

(7) (a) Comins, D. L.; Brown, J. D. *J. Org. Chem.* **1984**, *49*, 1078. (b) Comins, D. L.; Brown, J. D. *Tetrahedron Lett.* **1981**, *22*, 4213.

(8) The use of *p*-toluenesulfonic acid in lieu of TFA caused a considerable decrease in yield of **11** (38%) with concomitant formation of **12** (9%).

S0022-3263(96)00938-3 CCC: $12.00

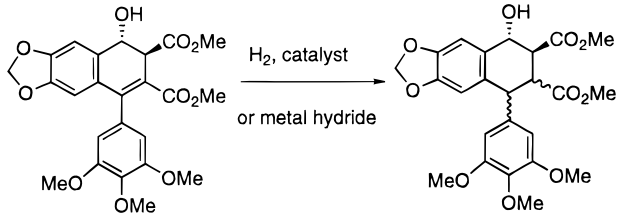
Scheme 1



of the endo adduct **10** followed by deprotonation.[9] The preferential formation of endo adducts has previously been reported in the acid-catalyzed Diels–Alder reaction of isobenzofurans with dimethyl maleate.[10] Similarly, treatment of the acetoxyaldehyde **8** with dimethyl maleate under the same conditions gave the desired dihydronaphthol **4** in 88% yield. In a separate experiment, the dihydronaphthol **11** did aromatize to give naphthalene **12** (82%) by treatment with a catalytic amount of boron trifluoride etherate in the presence of dimethyl maleate at room temperature, as reported in the case of 1-hydroxy-1,2-dihydronaphthalenes.[4] This result clearly demonstrates the importance of carefully selecting the reaction conditions.

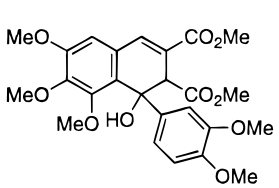
We next attempted to synthesize the tetralins **14** and **16** via stereocontrolled hydrogenation of **4** (Scheme 2, Table 1). Catalytic hydrogenation of **4** was expected to

Scheme 2

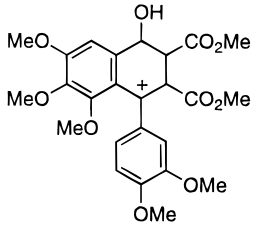


deliver hydrogen preferentially from the same side as hydroxyl group[11] to afford tetralin **14**. Contrary to expectation, hydrogenation of **4** with 10% palladium on charcoal (1 atm H_2, MeOH-EtOAc, 25 °C) gave a mixture of tetralins **14** and **15**[12] (1:2 ratio of **14** and **15**) in 95% yield (Table 1, entry 1). The cationic rhodium complex, [Rh(nbd)(diphos-4)]BF_4,[15] has been employed for directed hydrogenation of cyclic homoallylic alcohols. Coordination of a proximal hydroxy group with the catalyst can lead to the delivery of hydrogen to the unsaturated bond in a syn fashion.[11a] Therefore, this methodology appeared

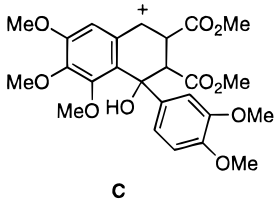
(9) The formation of **11** rather than the 1-hydroxy compound **A** can be attributed to the greater stability of the transient diaryl carbocation **B** compared to the monoaryl one **C**. See, for example : March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley-Interscience: New York, 1992; pp 165–174.



A



B



C

(10) Meegalla, S. K.; Rodrigo, R. *J. Org. Chem.* **1991**, *56*, 1882.

(11) (a) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307. (b) Evans, D. A.; Morrissey, M. M. *J. Am. Chem. Soc.* **1984**, *106*, 3866. (c) Evans, D. A.; Morrissey, M. M.; Dow, R. L. *Tetrahedron Lett.* **1985**, *26*, 6005. (d) Satoh, T.; Suzuki, S.; Suzuki, Y. *Chem. Pharm. Bull.* **1971**, *19*, 817. (e) For the hydroxyl-directed hydrogenation using metal hydrides, see: Iio, H.; Isobe, M.; Kawai, T.; Goto, T. *J. Am. Chem. Soc.* **1979**, *101*, 6076. Salomon, R. G.; Sachinvala, N. D.; Raychaudhuri, S. R.; Miller, D. B. *J. Am. Chem. Soc.* **1984**, *106*, 2211. Hanzawa, Y.; Kawagoe, K.; Kawada, K.; Kobayashi, Y. *Chem. Pharm. Bull.* **1985**, *33*, 2579.

(12) The stereochemistry of **14**–**16** was determined by ^1H NMR spectroscopy. The coupling constants of these compounds compare very well with those of similar tetralins.[3,13,14]

(13) Gupta, A.; Rodrigo, R. *J. Chem. Soc., Chem. Commun.* **1989**, 959.

(14) Maddafold, S. P.; Charlton, J. L. *J. Org. Chem.* **1993**, *58*, 4132.

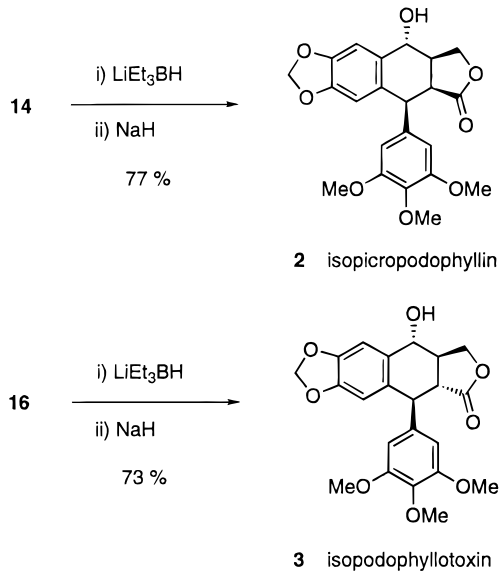
(15) nbd = norbornadiene, diphos-4 = 1,4-bis(diphenylphosphino)-butane. For previous examples of the hydroxyl-directed hydrogenation using [Rh(nbd)(diphos-4)]BF_4, see ref 11a–c.

Table 1. Reduction of Dihydronaphthol 4

entry	reagent	solvent	time (h)	product (yield,[a] %)
1	10% Pd/C	$MeOH-CH_2Cl_2$	1	**14** (32),**15** (63)
2	$[Rh(nbd)(diphos\text{-}4)]BF_4$	CH_2Cl_2	20	**14** (81), **15** (4)[b]
3	$NiCl_2 \cdot 6H_2O/NaBH_4$	MeOH−THF	20	**16** (87)[c]

[a] Isolated yield. [b] Dihydronaphthol **4** was recovered in 5% yield. [c] Naphthalene **13** was obtained in 5% yield.

Scheme 3



to be very attractive for the selective hydrogenation of **4**. As expected, hydrogenation of **4** with $[Rh(nbd)(diphos\text{-}4)]BF_4$ (50 atm H_2, CH_2Cl_2, 25 °C) produced stereoselectively **14** (20:1 ratio of **14** and **15**) in 81% yield (entry 2). When **4** was hydrogenated with $NiCl_2 \cdot 6H_2O-NaBH_4$[16] (MeOH−THF, 25 °C) the epimeric tetralin **16**[12] was obtained in 87% yield along with the aromatized product **13** (5%) (entry 3).[17] No further attempts at optimizing the above hydrogenation conditions were attempted.

The tetralins **14** and **16** thus obtained were converted to (±)-isopicropodophyllin (**2**) and (±)-isopodophyllotoxin (**3**), respectively, upon reaction with $LiEt_3BH$ followed by NaH (Scheme 3).[3] The overall yield of **2** starting with piperonal was 44% and for **3** was 45%.

In summary, we have demonstrated that dihydronaphthols can be obtained in one step and good yields from acetoxyaldehydes. We have also demonstrated the utility of dihydronaphthol **4** in an efficient synthesis of congeners **2** and **3** of podophyllotoxin. Further synthetic uses of the dihydronaphthols made available by this methodology will be reported in future papers.

Experimental Section

General. Melting points were determined on a capillary melting point apparatus and are uncorrected. ^1H NMR spectra were obtained at 200 MHz. Chemical shifts are reported in ppm (δ) using Me_4Si as standard. Elemental analyses were carried out in this laboratory. Column chromatography was performed with silica gel (70−230 mesh). $[Rh(nbd)(diphos\text{-}4)]BF_4$ and $LiEt_3BH$ were purchased from Aldrich Chemical Co. Butyllithium was the 1.6 M solution in hexane supplied by Asia Lithium Co.

2-(α-Acetoxy-3,4-dimethoxybenzyl)-3,4,5-trimethoxybenzaldehyde (7). To a solution of *N,N,N′*-trimethylethylenediamine (4.6 mL, 36 mmol) in THF (100 mL) was added BuLi (20.6 mL, 33 mmol) at −78 °C. After 5 min, 3,4,5-trimethoxybenzaldehyde (**5**) (5.88 g, 30 mmol) in THF (30 mL) was added, and the mixture was stirred at −78 °C for an additional 15 min. Diisopropylamine (4.7 mL, 33 mmol) and BuLi (37.5 mL, 60 mmol) were added, and the flask was sealed and put in a freezer (−20 °C) for 6 h. To this solution was added 3,4-dimethoxybenzaldehyde (4.98 g, 30 mmol) in THF (50 mL) at −78 °C, and the mixture was stirred for an additional 1 h. To this solution was added acetic anhydride (6.12 g, 60 mmol), and the mixture was allowed to warm to room temperature during 1 h. The mixture was poured into vigorously stirred cold water (200 mL) and extracted with EtOAc. The organic extract was washed with brine and dried over $MgSO_4$. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane:EtOAc = 4:1) to give a white solid. Recrystallization from isopropyl ether gave **7** (10.67 g, 88% yield) as colorless crystals. Mp 96−98 °C. IR (Nujol) 1740, 1680 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.15 (s, 3H), 3.83 (s, 3H), 3.85 (s, 3H), 3.93 (s, 3H), 3.94 (s, 3H), 3.99 (s, 3H), 6.64−6.90 (m, 3H), 7.37 (s, 1H), 7.64 (s, 1H), 10.29 (s, 1H). MS (*m*/*z*) 404 (M^+). Anal. Calcd for $C_{21}H_{24}O_8$: C, 62.37; H, 5.98. Found: C, 62.56; H, 5.91.

2-(α-Acetoxy-3,4,5-trimethoxybenzyl)-4,5-(methylenedioxy)benzaldehyde (8). To a solution of morpholine (3.13 g, 36 mmol) in THF (100 mL) was added BuLi (20.6 mL, 33 mmol) at −78 °C. After 5 min, 2-bromo-4,5-(methylenedioxy)benzaldehyde (6.87 g, 30 mmol) in THF (30 mL) was added, and the mixture was stirred at −78 °C for an additional 15 min. To this solution was added BuLi (20.6 mL, 33 mmol) at −78 °C, and the mixture was stirred for an additional 15 min. To this solution was added 3,4,5-trimethoxybenzaldehyde (5.88 g, 30 mmol) in THF (50 mL) at −78 °C, and the mixture was stirred for an additional 1 h. To this solution was added acetic anhydride (6.12 g, 60 mmol), and the mixture was allowed to warm to room temperature during 1 h. The mixture was poured into vigorously stirred cold water (200 mL) and extracted with EtOAc. The organic extract was washed with brine and dried over $MgSO_4$. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane:EtOAc = 4:1) to give a white solid. Recrystallization from isopropyl ether gave **8** (10.35 g, 89% yield) as colorless crystals. Mp 90−92 °C. IR (Nujol) 1740, 1680 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.17 (s, 3H), 3.82 (br s, 9H), 6.09 (s, 2H), 6.54 (s, 2H), 7.06 (s, 1H), 7.33 (s, 1H), 7.57 (s, 1H), 10.13 (s, 1H). MS (*m*/*z*) 388 (M^+). Anal. Calcd for $C_{20}H_{20}O_8$: C, 61.85; H, 5.19. Found: C, 61.76; H, 5.33.

Reactions of Acetoxyaldehydes with Dimethyl Maleate. Reaction of 7 in Toluene. To a solution of acetoxyaldehyde **7** (808 mg, 2 mmol) and dimethyl maleate (1.3 mL, 10 mmol) in toluene (10 mL) was added TFA (10 μL), and the mixture was heated for 2 h at 70 °C. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography [silica gel (230−400 mesh), hexane:EtOAc = 2:1]. Recrystallization from EtOAc−hexane gave the dihydronaphthol **11** (98 mg, 10% yield) and the naphthalene **12** (94 mg, 10% yield) as colorless crystals.

Dimethyl (3,4-*trans*)-4-Hydroxy-6,7,8-trimethoxy-1-(3,4-dimethoxyphenyl)-3,4-dihydronaphthalene-2,3-dicarboxylate (11). Mp 144−145 °C. IR (Nujol) 3420, 1740, 1695 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.16 (s, 3H), 3.30−4.00 (m, 2H), 3.46 (s, 3H), 3.68 (s, 3H), 3.74 (s, 3H), 3.84 (s, 3H), 3.88 (s, 3H), 3.91 (s, 3H),

(16) (a) Satoh, T.; Nanba, K.; Suzuki, S. *Chem. Pharm. Bull.* **1971**, *19*, 817. (b) Abe, N.; Fujisaki, F.; Sumoto, K.; Miyano, S. *Chem. Pharm. Bull.* **1991**, *39*, 1167. (c) Miyano, S.; Abe, N.; Fujisaki, F.; Sumoto, K. *Heterocycles* **1987**, *26*, 1813.

(17) A possible explanation for the formation of **16** involves initial formation of **14** followed by epimerization at C-2 under the reaction conditions. The formation of *cis* hydrogenated products with Ni^{2+}/BH_4^- system[16] and a facile epimerization at C-2[3] have previously been reported.

5.02 (d, J = 8.0 Hz, 1H), 6.70−6.90 (m, 4H). MS (m/z) 488 (M^+). Anal. Calcd for $C_{25}H_{28}O_{10}$: C, 61.47; H, 5.78. Found: C, 61.72; H, 5.56.

Dimethyl 1-(3,4-Dimethoxyphenyl)-6,7,8-trimethoxynaphthalene-2,3-dicarboxylate (12). Mp 215−217 °C. IR (Nujol) 1740, 1695 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.30 (s, 3H), 3.56 (s, 3H), 3.84 (s, 3H), 3.90 (s, 3H), 3.93 (s, 3H), 3.94 (s, 3H), 4.03 (s, 3H), 6.86 (s, 3H), 7.10 (s, 1H), 8.45 (s, 1H). MS (m/z) 470 (M^+). Anal. Calcd for $C_{25}H_{26}O_9$: C, 63.82; H, 5.57. Found: C, 63.72; H, 5.66.

Reaction of 7 without Added Solvent. To a mixture of dimethyl maleate (10 mL) and TFA (5 μL) was added dropwise a solution of acetoxyaldehyde **7** (808 mg, 2 mmol) in dimethyl maleate (5 mL) over a period of 2.5 h at 70 °C. The mixture was then heated for 1.5 h at 70 °C and concentrated under reduced pressure. The residue was purified by flash chromatography [silica gel (230−400 mesh), hexane:EtOAc = 2:1] to give a white solid. Recrystallization from Et_2O gave the dihydronaphthol **11** (878 mg, 90% yield) as colorless crystals.

Reaction of 8. Dimethyl (3,4-*trans*)-4-Hydroxy-6,7-(methylenedioxy)-1-(3′,4′,5′-trimethoxyphenyl)-3,4-dihydronaphthalene 2,3-Dicarboxylate (4). The reaction of **8** with dimethyl maleate was performed as described in the preparation of **11** (without added solvent). The reaction mixture was concentrated, and the mixture was purified by flash chromatography [silica gel (230−400 mesh), hexane:EtOAc = 2:1] to give a white solid. Recrystallization from Et_2O gave the dihydronaphthol **4** (831 mg, 88% yield) as colorless crystals. Mp 172−174 °C (lit.[3] mp 173−175 °C). Anal. Calcd for $C_{24}H_{24}O_{10}$: C, 61.02; H, 5.12. Found: C, 61.12; H, 5.06. The spectral data of this compound were identical in all respects with those described previously.[3]

Reaction of the Dihydronaphthol (11) with Boron Trifluoride Etherate. To a suspension of the dihydronaphthol **11** (140 mg, 0.29 mmol) in dimethyl maleate (10 mL) was added boron trifluoride etherate (47% solution in Et_2O, 10 μL), and the mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel chromatography (hexane:EtOAc = 4:1) to give a white solid. Recrystallization from EtOAc−hexane gave the naphthalene **12** (110 mg, 82% yield) as colorless crystals.

Heterogeneous Catalytic Hydrogenation of 4. A solution of the dihydronaphthol **4** (100 mg, 0.20 mmol) in EtOAc (15 mL) and MeOH (5 mL) was hydrogenated over 10% Pd−C (100 mg) at atmospheric pressure and 25 °C for 5 h. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure. The residual mixture was separated by silica gel column chromatography (hexane:EtOAc = 2:1). Crystallization from hexane gave **14** (32 mg, 32% yield) and **15** (63 mg, 63% yield) as colorless needles.

Dimethyl (1,2-*cis*,2,3-cis,3,4-*trans*)-4-Hydroxy-6,7-(methylenedioxy)-1-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene-2,3-dicarboxylate (14). Mp 173−175 °C (lit.[3] mp 174−175 °C). *Anal.* Calcd for $C_{24}H_{26}O_{10}$: C, 60.75; H, 5.52. Found: C, 60.81; H, 5.55. The spectral data of this compound were identical in all respects with those described previously.[3]

Dimethyl (1,2-*cis*,2,3-*trans*,3,4-*trans*)-4-Hydroxy-6,7-(methylenedioxy)-1-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene-2,3-dicarboxylate (15). Mp 171−173 °C. IR (Nujol) 3420, 1740, 1695 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.86 (d, J = 4.6 Hz, 1H), 3.40 (dd, J = 9.4, 12.5 Hz, 1H), 3.46 (s, 3H), 3.53−3.65 (m, 1H), 3.74 (s, 3H), 3.84 (s, 3H), 3.88 (s, 3H), 3.91 (s, 3H), 4.54 (d, J = 5.7 Hz, 1H), 4.85 (dd, J = 4.6, 9.4 Hz, 1H), 5.93 (br s, 2H), 6.38 (s, 3H), 7.17 (s, 1H). MS (m/z) 474 (M^+). Anal. Calcd for $C_{24}H_{26}O_{10}$: C, 60.76; H, 5.52. Found: C, 60.81; H, 5.55.

Hydrogenation of 4 with a Cationic Rhodium Catalyst. The dihydronaphthol **4** (200 mg, 0.4 mmol) and [Rh(nbd)(diphos-4)]BF_4 (14 mg, 0.02 mmol) were dissolved in CH_2Cl_2 (10 mL) and hydrogenated at the pressure of 50 atm and 25 °C for 5 h. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:EtOAc = 2:1) and crystallized from hexane to give **14** (162 mg, 81% yield) and **15** (8 mg, 4% yield) as colorless needles.

Hydrogenation of 4 with $NiCl_2·6H_2O$−$NaBH_4$. To a stirred solution of the dihydronaphthol (**4**) (100 mg, 0.2 mmol) and $NiCl_2·6H_2O$ (95 mg, 0.4 mmol) in MeOH (1 mL) and THF (5 mL) was added $NaBH_4$ (31 mg, 0.81 mmol) in small portions over a period of 10 min at 0 °C. After addition of $NaBH_4$, the mixture was stirred for 4 h at room temperature. The black precipitate was filtered off and the filtrate was acidified with 10% aqueous HCl. The solvent was removed under reduced pressure, and the residue was diluted with H_2O. After extraction with Et_2O, the organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane:EtOAc = 2:1) to give the tetralin **16** as a white solid (87 mg, 87% yield) along with the aromatized product **13** (5 mg, 5% yield). Recrystallization of **16** from isopropyl ether gave colorless crystals.

Dimethyl (1,2-*trans*,2,3-*trans*,3,4-*trans*)-4-Hydroxy-6,7-(methylenedioxy)-1-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene-2,3-dicarboxylate (16). Mp 174−175 °C. IR (Nujol) 3420, 1740, 1695 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.40 (dd, J = 9.4, 12.5 Hz, 1H), 3.50−3.65 (m, 1H), 3.51 (s, 3H), 3.71 (s, 3H), 3.83 (s, 6H), 3.92 (s, 3H), 4.54 (d, J = 5.7 Hz, 1H), 4.83 (d, J = 2.8 Hz, 1H), 4.99 (dd, J = 2.8, 9.4 Hz, 1H), 5.96 (s, 2H), 6.40 (s, 2H), 6.96 (s, 1H), 7.24 (s, 1H). MS (m/z) 474 (M^+). Anal. Calcd for $C_{24}H_{26}O_{10}$: C, 60.76; H, 5.52. Found: C, 60.59; H, 5.71.

Dimethyl 6,7-(Methylenedioxy)-1-(3,4,5-trimethoxyphenyl)-naphthalene-2,3-dicarboxylate (13). Mp 216−217 °C. IR (Nujol) 1730, 1690 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.66 (s, 3H), 3.83 (s, 6H), 3.94 (s, 6H), 6.08 (s, 2H), 6.55 (s, 2H), 6.93 (s, 1H), 7.23 (s, 1H), 8.40 (s, 1H). MS (m/z) 454 (M^+). Anal. Calcd for $C_{24}H_{22}O_9$: C, 63.43; H, 4.88. Found: C, 63.59; H, 4.71.

(±)-Isopicropodophyllin (2). A solution of **14** (104 mg, 0.22 mmol) in THF (5 mL) was cooled to 0 °C, and $LiEt_3BH$ (1.0 M solution in THF, 0.73 mL) was added. After 1 h, aqueous acetic acid (50%) was added until the yellow color disappeared. Water (10 mL) was then added, and the mixture was extracted with CH_2Cl_2. The organic extract was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was dissolved in MeOH/THF (5 mL, 1:1), and water (1 mL) was added. The mixture was stirred for 12 h. The solvents were largely removed under reduced pressure, and the residue was extracted with EtOAc. The organic extract was washed with water, and the solvent was removed under reduced pressure to give a solid (63.5 mg). To a solution of this solid in THF (25 mL) was added NaH (60%, 18 mg, 0.44 mmol). The mixture was stirred for 1 h at 25 °C. Cold water (15 mL) was added, and the volume was reduced to approximately 15 mL by evaporation. The solution was extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated to dryness under reduced pressure. The residue was recrystallized from CH_2Cl_2−MeOH to give **2** (50 mg, 77% yield). Mp 190−191 °C (lit.[3] mp 191−192 °C). Anal. Calcd for $C_{22}H_{22}O_8$: C, 63.76; H, 5.35. Found: C, 63.59; H, 5.51. The spectral data of this compound were identical in all respects with those described previously.[3]

(±)-Isopodophyllotoxin (3). The tetralin **16** was transformed to **3** by the same method as above (47 mg, 73% yield). Mp 270−272 °C (lit.[3] mp 272−273 °C). Anal. Calcd for $C_{22}H_{22}O_8$: C, 63.76; H, 5.35. Found: C, 63.59; H, 5.51. The spectral data of this compound were identical in all respects with those described previously.[3]

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