# A General Asymmetric Synthesis of (-)-α-Dimethylretrodendrin and Its Diastereomers

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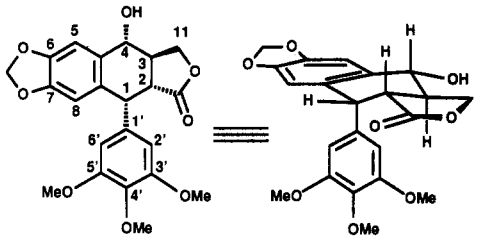
A Diels-Alder cycloaddition between the fumarate of methyl (*R*)-mandelate **14** and α-hydroxy-α'-aryl-*o*-quinodimethane **12** produced an *exo* cycloadduct **15** in 44% yield which was converted to optically pure (-)-α-dimethylretrodendrin(**21**) and three of its diastereomers. The 1,2,3-*cis* diastereomer **19** was found to possess an unexpected conformation as deduced from NOE experiments.

The continued impetus for the development of asymmetric syntheses of aryltetralin lignans stems from the discovery some years ago of two clinically important antitumor drugs derived from podophyllotoxin (**1**), namely Etoposide[1-5] and Teniposide.[2,5] Other congeners of podophyllotoxin also show notable antitumor activity.[1,3,6-10] The common feature of these compounds, associated with their biological activity, is the presence of an axial aryl group on the tetralin ring as shown in **1**.[7,8] Although many




**1** Podophyllotoxin

nonasymmetric syntheses of podophyllotoxin and its analogues have been described,[8-22] relatively fewer asymmetric syntheses are present in the literature.[23-41] A review paper by Ward discusses several asymmetric and nonasymmetric syntheses of aryl tetralin lignans[11] and some of the asymmetric syntheses are discussed below.

One of the first asymmetric syntheses of an aryl tetralin lignan was reported by Koga *et al.* who detailed the synthesis of optically pure (-)-isodeoxypodophyllotoxin from a chiral piperonyl-γ-butyrolactone.[23] Meyers *et al.* applied an asymmetric addition of an aryllithium species to a chiral naphthyloxazoline to produce the requisite intermediate for the synthesis of (+)-phyltetralin.[24] Using an analogous strategy, they also carried out the first asymmetric synthesis of (-)-podophyllotoxin.[25] The final steps of this synthesis produced a structure having the undesirable 1,2-*trans* stereochemistry and unfortunately, generation of the requisite 1,2-*cis* stereochemistry via kinetic protonation of the C-2 anion produced roughly an equal mixture of the starting 1,2-*trans* and the desired 1,2-*cis* products. Given the relative thermodynamic instability of the 1,2-*cis* geometry, as manifest in the facile epimerization of podophyllotoxin to its C-2 epimer, picropodophyllotoxin,[42] a synthetic stratagem which avoids this thermodynamic sink is highly desirable. An asymmetric synthesis of (-)-deoxyisopodophyllotoxin using the addition of a dithiolane to a menthyl-substituted butenolide has been reported by Pelter *et al.*[26] An all-*trans* geometry, corresponding to that of isopodophyllotoxin, resulted from the acid-catalyzed ring closure in the final step. A similar synthetic scheme has been used by Van Speybroeck *et al.* in the total synthesis of (-)-podophyllotoxin.[27] In these cases, the oxygens at positions 4 and 11 were bridged by a silyl group in order to control the 1,2-*cis* stereochemistry introduced during the acid-catalyzed ring closure. Achiwa *et al.* have carried out the syntheses of (+)-collinusin[28] and (-)-deoxypodophyllotoxin.[29] The chirality in this case was introduced via catalytic hydrogenation using a chiral rhodium bis(phosphine) catalyst, but in the synthesis of deoxypodo-

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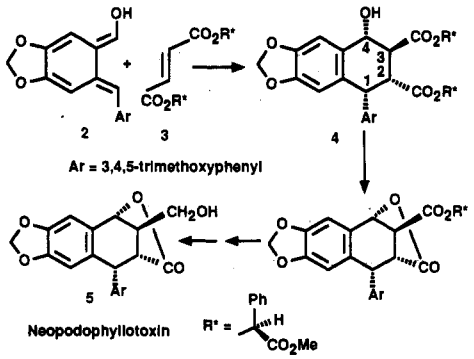
**Scheme I**




phyllotoxin, a mixture of (−)-deoxypodophyllotoxin (1,2-*cis*) and (+)-isodeoxypicropodophyllin (1,2-*trans*) was obtained in the final steps of the synthesis. Choy has carried out a synthesis of (−)-epiisopodophyllotoxin by an anionic Diels–Alder addition of a lithio-α-oxy-α′-aryl-*o*-quinodimethane to a chiral butenolide.[30] The initial cycloadduct had an all-*cis* stereochemistry but was eventually epimerized at C-2 to give the epiisopodophyllotoxin (1,2-*trans*) geometry. This synthesis exemplifies the difficulties in preparing the 1,2-*cis* stereochemistry because of the facile epimerization at C-2. Brown *et al.* have carried out syntheses of a variety of tetralin lignans including (−)-α-conidendrin,[31] (+)-isolariciresinol,[32] (−)-α-dimethylretrodendrin[35] and (+)-isodeoxypodophyllotoxin.[36] All of these syntheses involved optical resolution of racemic intermediates.

While a general nonasymmetgric method for the synthesis of eight podophyllum derivatives was described by Rodrigo *et al.*,[12] a general asymmetric synthesis of aryltetralin lignans, applicable to the synthesis of a variety of relative stereochemistries, has not been reported.

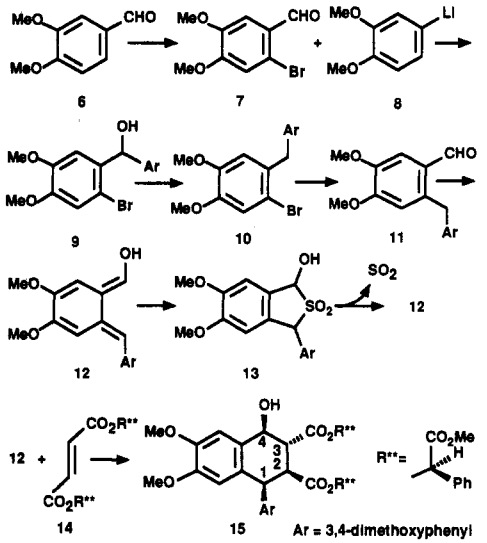
We have reported the highly diastereoselective additions of methyl lactate or methyl mandelate-substituted acrylates and fumarates to α-hydroxy-*o*-quinodimethanes.[43] These reactions furnished cycloadducts with the necessary absolute stereochemistry for the synthesis of neopodophyllotoxin[38] (Scheme I) and two podophyllotoxin analogs.[39] It occurred to us that these same cycloadducts might function as starting materials for a general asymmetric synthesis of aryltetralin lignans.

Using a cycloaddition reaction similar to that shown in Scheme I, we have now carried out a general asymmetric synthesis of (−)-α-dimethylretrodendrin (**21**) and three of its diastereomers starting from a single cycloadduct **15** (Schemes II and III).

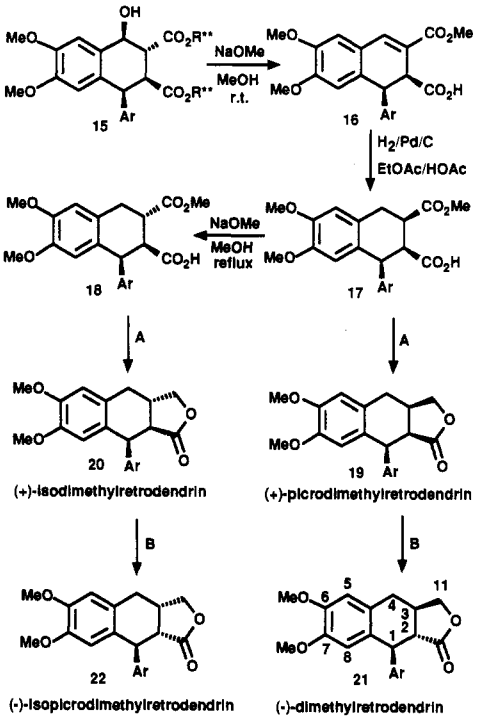
In this paper the three diastereomers of dimethylretrodendrin are named using the nomenclature convention used for podophyllotoxin. The relative stereochemistries at centers 1 and 2 are designated relative to C-3 using the prefixes iso and picro, respectively.

In our previous synthesis of neopodophyllotoxin (Scheme I), generation of the α-aryl-*o*-quinodimethane **2** intermediate was accomplished by irradiation of the corresponding *o*-benzylbenzaldehyde. Direct trapping of the transient **2** with fumarate **3** gave cycloadduct **4**. Problems in this synthesis arose from triplet energy transfer from the excited aldehyde to the fumarate **3** which resulted in substantial isomerization of fumarate to maleate. The same effect was observed in the present case where photolysis of **11** in a benzene solution of fumarate **14** gave the cycloadduct **15** in only moderate yields (Scheme II). It was therefore decided to use the sulfone precursor **13** for the generation of **12** thereby precluding fumarate isomerization.

**Scheme II**




**Scheme III**




The preparation of the aldehyde precursor **11** has been described previously but due to difficulties[37] a new approach was taken in this work (Scheme II). The bromo aldehyde **7** was prepared according to a literature procedure via bromination of **6** in acetic acid.[37] Addition of the aryllithium **8** to **7** at −78 °C afforded the diarylmethanol

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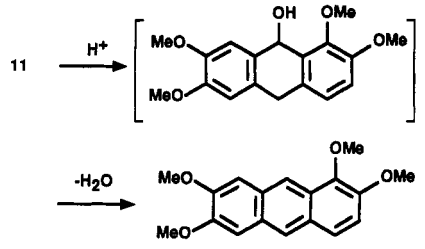
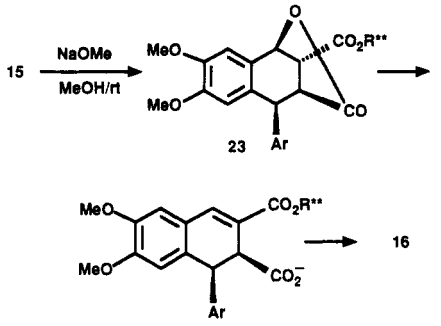
9. The alcohol could be cleanly deoxygenated by the method of ionic reduction of diarylmethanols using a mixture of trifluoroacetic acid (TFA) and $NaBH_4$.[45] In this case, a methylene chloride solution of **9** was added to a solution of TFA and $NaBH_4$ at 0 °C to produce a deep purple solution which rapidly decolorized to give **10** in 97% yield after chromatography. It was also found that the reaction could be carried out using a 50:50 mixture of TFA and glacial acetic acid to give a 95% yield of **10**. It was found that purification of **9** was necessary before the TFA/$NaBH_4$ reduction step as use of the crude addition product gave an intractable mixture of products. Treatment of the bromide **10** with *n*BuLi at −78 °C and quenching with DMF afforded the aldehyde **11** in 94% yield. Sulfone **13** was prepared by trapping of the *o*-quinodimethane **12** with $SO_2$ using the method previously reported.[37] Initial attempts to prepare **13** by irradiation of **11** in the presence of $SO_2$ in anhydrous benzene led to substantial anthracene formation probably due to trace amounts of sulfurous acid which caused intramolecular cyclization of the aldehyde. It was possible




to stop this anthracene formation by the addition of a small amount of pyridine. Irradiation of the aldehyde under a continuous stream of $SO_2$ (saturated solution) resulted in only 50% conversion to a mixture of the *cis*- and *trans*-sulfones ($\delta$: *trans* 5.67, 5.63; *cis* 5.46, 5.32; 1.2:1, *trans*/*cis*) even after 24 h. This suggested that an equilibrium existed between **11** and **13** and that incomplete sulfone formation was due to the high UV absorption of $SO_2$ in benzene between 265 and 360 nm. Slow thermal degradation of the sulfone **13** back to aldehyde **11** completed the equilibrium process. When the $SO_2$ concentration was decreased from saturation to about 4–5 g/100 mL, the reaction went to completion in 6 h with the *cis*-sulfone being the major component as indicated by TLC. At higher concentrations of $SO_2$ the solution becomes more polar and this polar effect may be responsible for the increase in the amount of the *trans*-sulfone, as it has been observed that the *cis*-sulfone isomerizes to the *trans* in polar solvents. Previous experience with the photolysis of *o*-benzylbenzaldehydes and trapping of the transient (*E*,*E*)-$\alpha$-hydroxy-$\alpha'$-phenyl-*o*-quinodimethanes (*o*-QDMs) by $SO_2$ suggests that only the *cis*-sulfone is formed initially.[39]

Using a procedure similar to that used in the synthesis of the two podophyllotoxin analogs,[39] cycloadduct **15** was synthesized in 44% yield (based on **11**; 90:10 ratio of **15** to other diastereomers) by thermolyzing the crude sulfone **13** in refluxing toluene in the presence of the fumarate **14**. The major cycloadduct exhibited a large $J_{3,4}$ coupling of 9.4 Hz indicating a *trans* disposition of the 4-hydroxyl and 3-carboxy groups consonant with our previous findings.[38] The minor cycloadducts (ca. 5%) were not characterized but they exhibited NMR doublets at $\delta$ 5.47 and

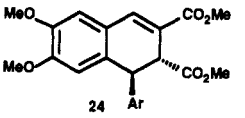
**Scheme IV**




5.18 with couplings of ca. 3 Hz typical of the H4 signals of endo cycloadducts.[46]

The absolute stereochemistry of the cycloadduct is controlled by the absolute stereochemistry of the chiral auxiliary in the dienophile and for the synthesis of (−)-$\alpha$-dimethylretrodendrin, it is necessary to use either methyl (*R*)-lactate or methyl (*R*)-mandelate. Since methyl (*R*)-lactate is not readily available, methyl (*R*)-mandelate[44] was employed to control the absolute stereochemistry.

Synthesis of lignans from cycloadduct **15** requires regiodifferentiation of the C-2 and C-3 esters which can be achieved via the previously reported lactonization method shown in Scheme I. However, disconnection of the C-4 oxy group in the lactone, a requirement for the synthesis of 4-deoxy lignans, via catalytic hydrogenolysis would also cleave the remaining C-3 mandelate group resulting in an undifferentiated 2,3-diacid. As an alternative, it was felt that it might be possible to carry out a tandem lactonization/base-induced elimination. Treatment of the cycloadduct **15** with anhydrous methanol/sodium methoxide at room temperature gave the elimination product **16** in 97% yield. A plausible mechanism may involve initial formation of the 2,4-lactone **23**, followed by elimination and transesterification of the 3-mandelate group (Scheme IV). About 3% of compound **24** was produced during the conversion of **15** to **16**. Compound **24** had spectroscopic properties identical to those previously reported.[37]




It is important to note the 4-fold success of the simple one-step reaction leading to **16**. Firstly, differentiation of the two ester groups has been accomplished with retention of the thermodynamically unfavorable 1,2-*cis* configuration. Secondly, the presence of the 2-acid group precludes base-catalyzed epimerization of the C-2 center as the formation of the carboxylate salt in the presence of base reduces the acidity at the $\alpha$-carbon. Thirdly, deoxygenation and double bond formation allows for manipulation

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(42) Tanford, C. *J. Am. Chem. Soc.* **1962**, *84*, 1748–1749.
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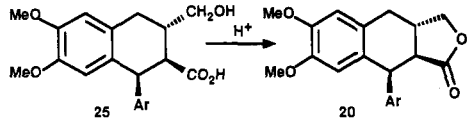
Table I. Chemical Shifts for Lignans 19–22 in $CDCl_3$ (δ)

| compound | H1 | H2 | H3 | $H4_\alpha$ | $H4_\beta$ | H5 | H6′ | H2′ | H8 | H5′ | $H11_\alpha$ | $H11_\beta$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 19 | 4.52 | 3.07 | 3.15 | 2.71 | 2.99 | 6.77 | 6.51 | 6.87 | 6.71 | 6.72 | 3.35 | 4.38 |
| 21 | 4.12 | 2.50 | 2.63 | 2.93 | 3.00 | 6.61 | 6.79 | 6.71 | 6.33 | 6.83 | 3.99 | 4.53 |
| 20 | 4.64 | 2.77 | 3.09 | 2.77 | 2.77 | 6.68 | 6.36 | 6.95 | 6.52 | 6.67 | 3.92 | 4.44 |
| 22 | 4.44 | 3.32 | 3.03 | 2.51 | 2.89 | 6.68 | 6.57 | 6.69 | 6.62 | 6.77 | 3.96 | 3.33 |

of the stereochemistry at the C-3 center. Finally, transesterification of the 3-mandelate group now permits catalytic hydrogenation of the double bond without hydrogenolysis of the ester to the acid as would have occured if the mandelate group were still present. Catalytic hydrogenation of **16** in ethyl acetate/acetic acid over Pd/C gave the all-*cis* compound **17** in 87% yield. It has been reported that the hydrogenation of compound **24** having a 1,2-*trans* geometry gave a saturated lignan having the all-*trans* stereochemistry suggesting that hydrogen addition occurs preferentially to the face opposite the sterically large aryl group.[37] Similarly then, the stereoselective hydrogenation of **16** to give **17** (all-*cis*) can be explained by the preference for addition to the least sterically hindered face.

Intermediate **17** was the thermodynamic summit from which all of the diastereomers of dimethylretrodendrin were synthesized via selective epimerizations at appropriate points. Entry into the all-*cis* configuration was possible by reduction of the 3-ester group of **17** with lithium triethylborohydride (Scheme III). Upon aqueous acid workup of the reduction product, incomplete cyclization to lactone **19** was observed as evident from the $^1$H-NMR of the crude product. The yield of lactone **19** was increased from 78 to 84% by refluxing the crude product in benzene in the presence of *p*-TsOH (*p*-toluenesulfonic acid). Base-catalyzed epimerization of the C-2 carbon of **19** in refluxing *t*-BuOH/NaO*t*Bu/THF gave optically pure (−)-α-dimethylretrodendrin in 94% yield. The spectroscopic properties were identical to those previously reported.[35] Entry into the deoxypodophyllotoxin geometry from **17** was possible using a method similar to that reported by Takano.[20] Compound **17** having the 1,2,3-*cis* geometry was converted to **18** (1,2-*cis*-2,3-*trans*) in 83% yield by refluxing in NaOMe/methanol solution followed by acid workup. Reduction of **18** with lithium triethylborohydride and dilute acid workup gave the open hydroxy acid **25** which could be cyclized by refluxing in benzene with a trace of *p*-TsOH. Alternatively, this intervening step could




25 20

be omitted by slow evaporation of the acidic aqueous workup solution at room temperature which gave **20** directly in 79% yield after purification. As mentioned earlier, it is well known that podophyllotoxin undergoes epimerization at C-2 even in the presence of a trace of base to give picropodophyllotoxin. It was found that **20** could be cleanly converted to the C-2 epimer **22** in 87% yield by refluxing in NaO*t*Bu/*t*BuOH.

The $^1$H NMR chemical shifts and coupling constants for the four lignans (**19–22**) are shown in Table I and Table II, respectively. The geometry of the *trans*-lactones in dimethylretrodendrin(**21**) and isodimethylretrodendrin-(**20**) renders the two molecules conformationally inflexible and hence assignment of coupling constants to a particular

Table II. Observed Coupling Constants for Lignans 19–22

| compound | $J_{1,2}$ | $J_{2,3}$ | $J_{3,4\alpha}$ | $J_{3,4\beta}$ | $J_{11\alpha 11\beta}$ | $J_{11\alpha,3}$ | $J_{11\beta,3}$ | $J_{4\alpha,4\beta}$ |
|---|---|---|---|---|---|---|---|---|
| 19 | 5.5 | 10.1 | 6.1 | 9.0 | 8.5 | 8.5 | 8.5 | 15.8 |
| 21 | 10.9 | 13.5 | ~14 | 5.3 | 8.6 | 10.4 | 6.4 | ~14 |
| 20 | 3.4 | – | – | – | 8.6 | 9.9 | 6.2 | – |
| 22 | 2.8 | 9.6 | 5.1 | 6.5 | 9.1 | 7.4 | 3.4 | 15.4 |

conformation becomes unambiguous. The small $J_{1,2}$ coupling constant of 3.4 Hz for isodimethylretrodendrin (**20**) is similar to the coupling of 1.5 Hz found in deoxypodophyllotoxin[7] suggesting a similar conformation in which the aryl group is in an axial position. The chemical shift of the H1 proton (δ 4.64) also compares well to that in deoxypodophyllotoxin (δ 4.60). The remaining corresponding shifts and couplings between the two compounds also correlate very well.

For dimethylretrodendrin (**21**), the large couplings between H1 and H2 (10.9 Hz) as well as H2 and H3 (13.5 Hz) suggest that the protons lie in a *trans*-diaxial arrangement. It is also interesting to note that H1 for **21** is shifted to substantially higher field than the H1's for the other lactones. This suggests an axial orientation for H1 since it would then lie above the deshielding plane of the tetralin ring. The equatorial nature of the pendant aryl ring is evident from the relative upfield shift of H8, which lies in the shielding region of this ring.

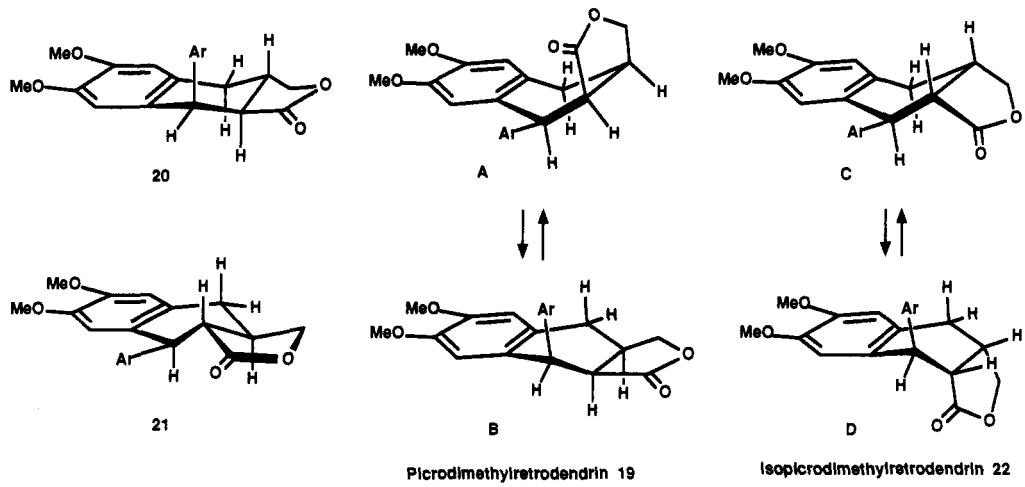
The proposed solution conformations of **20** and **21** are shown in Scheme V.

The remaining two lignans **19** and **22** have the 2,3-*cis*-lactone ring fusion. It has been proposed that lactones bearing the 2,3-*cis* fusion are highly flexible[7,12] and exist in the boat forms A/B and C/D shown in Scheme V.

Rodrigo has proposed that the all-*cis* 4-oxy/deoxygenated lactones preferentially adopt conformation **A** on the basis of the conformation observed for 4-methoxyisopicropodophyllin determined by X-ray analysis.[12] This conclusion is dissonant with our findings. Using NOE-difference spectroscopy, irradiation of the $H4_\alpha$ proton of **19** resulted in observable NOE's of 3.6 and 7.7% to the ortho protons of the C4 aromatic ring (H2′ and H6′, respectively, see Scheme V). NOE's of this magnitude could only arise if conformation **B** is the dominant one in solution. The ortho protons in conformation **A** are too distant from $H4_\alpha$ to give rise to NOE enhancements. Further evidence for conformation **B** comes from the observed chemical shifts of the H11 protons. The $H11_\alpha$ proton is shifted to higher field at 3.35 ppm while $H11_\beta$ is observed at 4.38 ppm. The chemical shifts of these protons can be compared to the 2-methyl derivative of deoxyisopicropodophyllotoxin[8] (3.27 and 4.25 ppm) which was found from X-ray analysis to adopt a conformation similar to **B** in which the aryl group was axially disposed as opposed the equatorial disposition proposed by Rodrigo.[12] We therefore conclude that **19** and probably the other all-*cis*-lactones adopt conformation **B** in solution.

It was shown by Beard *et al.*[8] that the *trans*-lactone ring was not an absolute requirement for antitumor activity as evidenced in the modest activity of the 1,2,3-*cis* derivatives 2-methyldeoxyisopicropodophyllotoxin and

**Scheme V**




2-phenyldeoxyisopicropodophyllotoxin. The observed activity of the former compound is likely attributable to its conformational similarity with deoxypodophyllotoxin whereas a structure–activity disparity exists for the latter compound as it was shown to adopt conformation **A** in solution and in the solid state. Picropodophyllotoxin, the compound obtained by epimerization of the C-2 center in podophyllotoxin, was found to have a preferred conformation analogous to **C**. The small residual antitumor activity of this compound was thought to arise from the minor conformation analogous to **D**.[7] Given the relative uncertainty in the conformational preferences of the *cis*-lactones together with their anomalous antitumor activity, a more rigorous conformational analysis of the various lignan geometries would be valuable.

Our work on the development of efficient general asymmetric methods for the synthesis of tetralin lignans is ongoing. We also envisage exploitation of the discussed methods for the syntheses of the pericarbonyl lignans.

## Experimental Section

$^1$H NMR spectra were recorded on a Bruker AM-300 spectrometer using tetramethylsilane as internal standard. IR spectra were recorded on a Perkin-Elmer 881 spectrometer. Aldrich silica gel (230–400 mesh, 60 Å) was used for all chromatography. Exact mass/mass spectra were obtained on an Analytical VG 7070E-HF instrument. Melting points were measured on a hot stage and are uncorrected. Optical rotations were recorded on a Rudolf Research Autopol III instrument.

**α-(3,4-Dimethoxyphenyl)-6-bromoveratryl Alcohol (9).** 4-Bromoveratrole (1.73 g, 7.97 mmol, 1.11 equiv) was dissolved in THF (10 mL). The solution was cooled to −78 °C under $N_2$ and to this was added *n*-BuLi (1.86 M/hexanes, 4.25 mL, 7.91 mmol) dropwise. After 5 min, 6-bromoveratraldehyde (1.76 g, 7.19 mmol) in THF (35 mL) was added and the solution warmed to room temperature. The orange solution was stirred 17 h, quenched with 5% aqueous sodium bicarbonate (20 mL), saturated with NaCl, and finally extracted with ethyl acetate and the solvent evaporated. The yellow oil (3.35 g) was chromatographed on silica to give the pure product as a yellow oil (2.05 g, 74%): $^1$H NMR ($CDCl_3$) δ 7.08 (s, 1H), 7.00 (s, 1H), 6.97 (d, 1H, $J$ = 1.9), 6.88 (dd, 1H, $J$ = 1.9, 8.3), 6.81 (d, 1H, $J$ = 8.3), 6.08 (s, 1H), 3.86 (s, 6H), 3.85 (s, 3H), 3.84 (s, 3H), 2.35 (bs, OH); $^{13}$C NMR ($CDCl_3$) δ 148.91 (C), 148.69 (C), 148.48 (C), 135.09 (C), 134.75 (C), 118.99 (CH), 115.33 (CH), 112.58 (C), 110.94 (CH), 110.78 (CH), 110.09 (CH), 74.29 (CH), 56.18 ($CH_3$), 56.06 ($CH_3$), 55.88 ($CH_3$); mass spectrum $m/z$ (rel inten) 385 (10), 384 ($M^+$, 52), 383 (12), 382 (53), 271 (16), 245 (31), 243 (28), 165 (43), 139 (100), 138 (46); HRMS calcd for $C_{17}H_{19}O_5Br$ 382.0415, 384.0395; found 382.0395, 384.0429.

**1-(3,4-Dimethoxybenzyl)-6-bromoveratrole (10).** To a solution of glacial acetic acid (15 mL) and trifluoroacetic acid (15 mL) at 0 °C was added $NaBH_4$ (10 equiv, 1.36 g). The alcohol **9** (1.38 g, 3.60 mmol) in $CH_2Cl_2$ (20 mL) was immediately added giving a dark purple solution which was stirred 1 min followed by the rapid addition of 5 equiv more of $NaBH_4$. The solution turned yellow immediately and stirring was continued for another 5 min. The sample was diluted with $H_2O$ (40 mL) and extracted with $CH_2Cl_2$, dried ($MgSO_4$), and evaporated to give a brown oil. The oil was chromatographed on silica (25% ethyl acetate/hexanes) giving an oil (1.25 g, 95%). The sample could be recrystallized from 2-propanol (0.960 g, 73%) giving a colorless solid: mp 72–73 °C; IR ($CH_2Cl_2$) 1509 (vs), 1029 (s); $^1$H NMR ($CDCl_3$) δ 7.04 (s, 1H), 6.80 (d, 1H, $J$ = 8.1), 6.74 (d, 1H, $J$ = 1.44), 6.69 (1H, dd, $J$ = 1.44, 8.1), 6.64 (s, 1H), 3.99 (s, 2H), 3.86 (s, 6H), 3.84 (s, 3H), 3.76 (s, 3H); $^{13}$C NMR ($CDCl_3$) δ 148.91 (C), 148.42 (C), 148.05 (C), 147.46 (C), 132.48 (C), 132.41 (C), 120.66 (CH), 115.52 (CH), 113.54 (CH), 112.11 (CH), 111.20 (CH), 114.42 (C), 56.17 ($CH_3$), 56.00 ($CH_3$), 55.88 ($CH_3$), 55.83 ($CH_3$), 40.84 ($CH_2$); mass spectrum $m/z$ (rel inten) 369 (16), 368 ($M^+$, 85), 367 (17), 366 (84), 288 (8), 287 (38), 257 (31), 256 (100), 241 (36), 229 (24), 225 (11); HRMS calcd for $C_{17}H_{19}O_4Br$ 366.0466, 368.0446; found 366.0459, 368.0456.

**6-(3,4-Dimethoxybenzyl)veratraldehyde (11).** The bromide **10** (2.18 g, 5.93 mmol) was dissolved in THF (50 mL) and cooled to −78 °C under $N_2$. *n*-BuLi (2.5 M/hexanes, 1.2 equiv, 7.12 mmol, 2.85 mL) was added and the solution stirred 1 min followed by addition of DMF (3 equiv, 1.38 mL). The solution was stirred 1 h at −78 °C and then at room temperature for 50 min. The solution was quenched with aqueous 15% ammonium chloride, saturated with NaCl, extracted with $CH_2Cl_2$, dried ($MgSO_4$), and evaporated to give a yellow oil (1.81 g). The product was purified by silica gel chromatography (50% ethyl acetate/hexanes) giving a light yellow oil which crystallized on standing (1.76 g, 94%). The spectroscopic properties were identical to those reported in the literature.[37]

**1-(3,4-Dimethoxyphenyl)-3-hydroxy-5,6-dimethoxy-1,3-dihydrobenzo[c]thiophene 2,2-Dioxide (13).** The aldehyde **11** (1.93 g, 6.11 mmol) was dissolved in dry benzene (distilled from $CaH_2$, 50 mL) and pyridine added (10 μL). Benzene (150 mL) containing dissolved $SO_2$ (13.9 g) was added to the aldehyde solution and irradiated with a water-cooled 450-W Hanovia medium-pressure mercury lamp immersed in the solution for 6 h under a $N_2$ atmosphere. The solvent was evaporated at room temperature and traces of solvent and $SO_2$ removed by evaporation at high vacuum (0.5 mm, 25 °C). The crude glassy yellow product was used immediately in the cycloaddition step without purification.

**(+)-Exo Cycloadduct 15.** A solution of the fumarate of methyl (R)-mandelate[44] (5.87 g, 14.2 mmol) and ZnO (2.0 g) were brought to reflux in toluene (35 mL) under a slight vacuum (210 mm). A solution of the hydroxy sulfone (from previous reaction) in $CH_2Cl_2$/toluene (25 mL/10 mL) was added over a period of 50 min with concomitant evaporation of $SO_2$ and $CH_2Cl_2$. After

complete addition, the solution was refluxed 10 min longer. Filtration and evaporation afforded a brown oil which was chromatographed on silica (40–60% EtOAc/hexanes) giving **6** as the major adduct (1.93 g, 44%, based on starting aldehyde) as an oil: IR ($CH_2Cl_2$) 3495 (br, OH), 1745 (CO) $cm^{-1}$; $[\alpha]^{20}_D$ +51.3° (*c* 1.69, $CH_2Cl_2$); $^1H$ NMR ($CDCl_3$) δ 7.48–7.45 (m, 2H), 7.40–7.37 (m, 3H), 7.30 (s, 1H), 7.19 (t, 1H, *J* = 7.3), 6.98 (t, 2H, *J* = 7.7), 6.89 (d, 2H, *J* = 7.2), 6.51 (d, 1H, *J* = 1.6), 6.42–6.36 (m, 3H), 6.24 (s, 1H), 5.54 (s, 1H), 4.99 (dd, 1H, $J_{4,3}$ = 9.4, $J_{4,OH}$ = 2.8, H4), 4.83 (d, 1H, *J* = 2.8, OH), 4.54 (d, 1H, $J_{1,2}$ = 5.74, H1), 3.93 (s, 3H), 3.79 (s, 3H), 3.71 (s, 3H), 3.69 (s, 3H), 3.66 (s, 3H), 3.61 (s, 3H), 3.61 (m, H2), 3.40 (dd, 1H, $J_{3,4}$ = 9.4, $J_{3,2}$ = 12.5, H3); $^{13}C$ NMR δ 174.10 (CO), 171.63 (CO), 170.23 (CO), 168.52 (CO), 148.78 (C), 148.46 (C), 148.09 (C), 147.81 (C), 133.33 (C), 133.07 (C), 132.82 (C), 129.40 (C), 120.01 (C), 128.81 (2 × CH), 128.68 (CH), 128.30 (C), 128.19 (2 × CH), 128.03 (2 × CH), 126.95 (2 × CH), 121.95 (CH), 112.61 (CH), 111.44 (CH), 110.41 (CH), 108.63 (CH), 74.97 (CH), 74.08 (CH), 71.21 (CH), 55.86 ($CH_3$), 55.80 (2 × $CH_3$), 55.38 ($CH_3$), 53.35 ($CH_3$), 52.45 ($CH_3$), 46.91 (CH), 46.27 (CH), 45.61 (CH); MS *m/z* (rel inten) 728 ($M^+$, 1), 563 (2), 562 (2), 518 (2), 517 (3), 516 (8), 394 (49), 351 (24), 325 (20), 107 (100), 79 (59), 77 (57); HRMS calcd for $C_{40}H_{40}O_{13}$ 728.2469, found 728.2426.

**Elimination Product 16.** The cycloadduct **15** (0.362 g, 0.496 mmol) was stirred in NaOMe/methanol (0.1 M, 40 mL, 8 equiv, dry) at rt for 1 day. The solution was acidified with 20% HCl (pH ca. 1–2), extracted with $CH_2Cl_2$, and dried ($MgSO_4$), and the solvent was evaporated to leave a yellow oil. The sample was chromatographed on silica (45% EtOAc/5% HOAc/hexanes) to give a yellow oil (0.207 g, 97%): $[\alpha]^{20}_D$ −321° (*c* 0.67, $CHCl_3$); IR 1743 (w), 1711 (s) $cm^{-1}$; $^1H$ NMR δ 7.64 (s, 1H, alkene), 6.87–6.84 (m, 4H), 6.59 (s, 1H), 4.51 (d, 1H, $J_{1,2}$ = 7.7, H1), 3.93 (d, 1H, $J_{2,1}$ = 7.7, H2), 3.89 (s, 3H), 3.88 (s, 3H), 3.81 (s, 3H), 3.77 (s, 3H), 3.70 (s, 3H); $^{13}C$ NMR ($CDCl_3$) δ 174.54 (CO), 167.15 (CO), 150.66 (C), 148.85 (C), 148.47 (C), 147.73 (C), 139.27 (CH), 139.03 (CH), 124.49 (C), 123.64 (C), 122.02 (CH), 112.59 (CH), 112.45 (CH), 111.25 (CH), 111.14 (CH), 56.06 ($CH_3$), 55.95 ($CH_3$), 55.83 ($CH_3$), 55.79 ($CH_3$), 52.05 ($CH_3$), 47.55 (CH, C), 46.83 (CH); MS *m/z* (rel inten) 429 (1.5), 428 (6.3, $M^+$), 396 (36.5), 395 (25.7), 394 (100), 382 (42.8), 351 (27.4), 138 (17.6), 60 (9.7); HRMS calcd for $C_{23}H_{24}O_8$ 428.1471, found 428.1475.

**3-Carbomethoxy-6,7-dimethoxy-1-(1,2-*cis*)-(3′,4′-dimethoxyphenyl)-1,2,3,4-tetrahydronapthalene-(2,3-*cis*)-2-carboxylic Acid (17).** The alkene **16** (0.280 g, 0.654 mmol) was dissolved in a mixture of EtOAc (30 mL) and acetic acid (10 mL) and Pd/C (5% Pd, dry, 129 mg) catalyst added. The mixture was stirred under $H_2$ (1 atm, rt) for 24 h followed by filtration through silica (EtOAc eluent) and evaporation to give a beige solid (0.288 g). The solid was recrystallized from $CH_2Cl_2$/hexane to give a colorless solid (242 mg, 86%): mp 195–196 °C; IR ($CH_2Cl_2$) 3057 (COOH), 1734 (vs, CO), 1712 (m, CO) $cm^{-1}$; $[\alpha]^{20}_D$ −88° (*c* 0.284, $CHCl_3$); $^1H$ NMR ($CDCl_3$) δ 6.81 (s, 2H), 6.73 (s, 1H), 6.66 (s, 1H), 6.43 (s, 1H), 4.40 (d, 1H, $J_{1,2}$ = 6.0, H1), 3.87 (s, 6H), 3.74 (s, 3H), 3.70 (s, 3H), 3.61 (s, 3H), 3.51 (m, 2H, H2, H4a), 3.18 (ddd, 1H, $J_{2,3}$ = 3.68, $J_{3,4e}$ = 5.47, $J_{3,4a}$ = 12.17, H3), 3.00 (dd, $J_{4e,4a}$ = 16.35, $J_{4e,3}$ = 5.45, H4e); $^{13}C$ NMR δ 175.69 (CO), 173.25 (CO), 148.61 (C), 148.09 (C), 147.61 (C), 147.12 (C), 133.46 (C), 127.58 (2 × C), 122.18 (CH), 112.79 (CH), 111.88 (CH), 111.14 (CH), 110.92 (CH), 55.92 ($CH_3$), 55.85 ($CH_3$), 55.79 ($CH_3$), 55.74 ($CH_3$), 52.12 ($CH_3$), 47.90 (CH), 47.83 (CH), 42.50 (CH), 28.15 ($CH_2$); MS *m/z* (rel inten) 399 (18), 398 (− $CH_3OH$, 71), 370 (9), 339 (7), 325 (23), 299 (8), 285 (10), 270 (21), 269 (100), 238 (15), 151 (12); HRMS calcd for $C_{23}H_{26}O_8$ 430.1628, found 430.1589; calcd for $C_{22}H_{22}O_7$ (− $CH_3OH$) 398.1365, found 398.1346.

**(+)-Picrodimethylretrodendrin (19).** Acid ester **17** (64.0 mg, 0.149 mmol) was dissolved in THF (15 mL, dried over sodium/benzophenone). A solution of $LiEt_3BH$ (1 M, 5.7 equiv, 0.84 mL) in THF was added at room temperature under a $N_2$ atmosphere. Upon initial addition, the solution effervesced and a slight cloudiness persisted for about 2 min. Stirring at room temperature was continued for 19 h. Amberlite resin (Aldrich, IRC 718, ion-exchange, 1.0 g) was added and the solution diluted with 20% HCl (5 mL). After 2 h the solution was filtered through silica (70–270 mesh, THF eluent), extracted (EtOAc), and dried ($MgSO_4$), and the solvent evaporated to give a yellow oil (0.0848 g). The crude mixture was dissolved in benzene (dry, 25 mL) and refluxed with a trace of *p*-TsOH (1 mg) for 14 h. The solvent was evaporated and the brownish oil chromatographed on silica (40–50% EtOAc/hexanes) giving a clear oil (48.2 mg 84%): $[\alpha]^{20}_D$ +143°; IR ($CH_2Cl_2$) 1768 (lactone CO) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 6.87 (d, 1H, *J* = 2.1, H2′), 6.77 (s, 1H, H5), 6.72 (d, 1H, *J* = 8.3, H5′), 6.71 (s, 1H, H8), 6.51 (dd, 1H, *J* = 2.2, 8.3, H6′), 4.52 (d, 1H, $J_{1,2}$ = 5.53, H1), 4.38 (t, 1H, *J* = 8.5, H11$_\beta$), 3.91 (s, 3H), 3.84 (s, 3H), 3.81 (s, 6H), 3.35 (t, 1H, *J* = 8.5, H11$_\alpha$), 3.15 (m, 1H, H3), 3.07 (dd, 1H, $J_{2,1}$ = 5.53, $J_{2,3}$ = 10.1, H2), 2.99 (dd, 1H, $J_{4\beta,3}$ = 8.96, $J_{4\beta,4\alpha}$ = 15.7, H4$_\beta$), 2.71 (dd, 1H, $J_{4\alpha,3}$ = 6.12, $J_{4\alpha,4\beta}$ = 15.7, H4$_\alpha$); $^{13}C$ NMR ($CDCl_3$) δ 178.04 (CO), 148.77 (C), 148.17 (C), 148.01 (C), 131.00 (C), 130.64 (C), 127.74 (C), 120.78 (CH), 112.64 (CH), 111.77 (CH), 111.53 (CH), 110.90 (CH), 74.23 ($CH_2$), 56.06 ($CH_3$), 55.96 ($CH_3$), 55.86 ($CH_3$), 55.79 ($CH_3$), 46.65 (CH), 44.60 (CH), 34.71 (CH), 29.86 ($CH_2$); MS *m/z* (rel inten) 386 (5), 385 (23), 384 ($M^+$, 100), 353 (19), 325 (18), 312 (15), 299 (16), 270 (15), 269 (74), 151 (13), 84 (13); HRMS calcd for $C_{22}H_{24}O_6$ 384.1573, found 384.1570.

**(−)-α-Dimethylretrodendrin (21).** Picroretrodendrin (**19**) (3.5 mg, 0.009 mmol) was refluxed in sodium *tert*-butoxide/*t*-butyl alcohol solution (0.1 M, 5 mL) under $N_2$ for 24 h. The clear solution was diluted with 20% HCl (10 mL) and extracted with $CH_2Cl_2$ (3 × 10 mL), dried ($MgSO_4$), and evaporated. The product was purified on silica (30–50% EtOAc/hexanes) and recrystallized (EtOAc/hexanes) giving a colorless solid (3.3 mg, 94%): mp 182–183 °C (lit.[35] 188–189 °C); $[\alpha]^{20}_D$ −58°, (lit.[35] −58°); IR ($CH_2Cl_2$) 1780 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 6.83 (d, 1H, *J* = 8.2, H5′), 6.79 (dd, 1H, *J* = 1.7, 8.3, H6′), 6.71 (d, 1H, *J* = 1.6, H2′), 6.61 (s, 1H, H5), 6.33 (s, 1H, H8), 4.53 (dd, 1H, $J_{11\beta,3}$ = 6.4, $J_{11\beta,11\alpha}$ = 8.6, H11$_\beta$), 4.12 (d, 1H, $J_{1,2}$ = 10.9, H1), 3.99 (dd, 1H, $J_{11\alpha,11\beta}$ = 8.6, $J_{11\alpha,3}$ = 10.4, H11α), 3.88 (s, 3H), 3.87 (s, 3H), 3.82 (s, 3H), 3.60 (s, 3H), 3.00 (dd, $J_{4\beta,3}$ = 5.3, $J_{4\beta,4\alpha}$ = 14.8 H4$_\beta$), 2.93 (t, 1H, $J_{4\alpha,4\beta}$ = 14.8, $J_{4\alpha,3}$ = 14), 2.63 (m, 1H, H3), 2.50 (dd, 1H, $J_{2,1}$ = 10.9, $J_{2,3}$ = 13.5, H2); $^{13}C$ NMR ($CDCl_3$) δ 175.51 (CO), 148.77 (C), 147.89 (C), 147.77 (C), 147.67 (C), 135.56 (C), 131.35 (C), 126.77 (C), 121.82 (CH), 112.95 (CH), 112.45 (CH), 111.38 (CH), 110.97 (CH), 70.98 ($CH_2$), 55.96 ($CH_3$), 55.87 ($CH_3$), 55.80 (2 × $CH_3$), 48.91 (CH), 45.77 (CH), 40.15 (CH), 32.61 ($CH_2$); HRMS calcd for $C_{22}H_{24}O_6$ 384.1573, found 384.1577.

**3-Carbomethoxy-6,7-dimethoxy-1-(1,2-*cis*)-(3′,4′-dimethoxyphenyl)-1,2,3,4-tetrahydronapthalene-(2,3-*trans*)-2-carboxylic Acid (18).** The picro-half-ester **17** (0.247 g, 0.574 mmol) was dissolved in NaOMe/methanol (0.1 M, 40 mL, 7 equiv) and refluxed under $N_2$ for 20 h. The solution was acidified (20% HCl) and extracted with $CH_2Cl_2$ (3 × 15 mL). The organic layer was dried ($MgSO_4$) and the solvent evaporated giving a yellow oil (0.25 g). The oil was chromatographed on silica (35% EtOAc/5% HOAc/hexanes) giving a light yellow oil (0.205 g, 83%): IR ($CH_2Cl_2$) 1734 (CO), 1711 (CO) $cm^{-1}$; $[\alpha]^{20}_D$ +163° (*c* 0.278, $CHCl_3$); $^1H$ NMR ($CDCl_3$) δ 6.69 (d, 1H, *J* = 8.34, H5′), 6.66 (s, 1H, H5), 6.58 (d, 1H, *J* = 1.91, H2′), 6.41 (s, 1H, H8), 6.40 (dd, *J* = 8.34, 1.91, H6′), 4.56 (d, 1H, $J_{1,2}$ = 5.4, H1), 3.87 (s, 3H), 3.81 (s, 3H), 3.74 (s, 3H), 3.72 (s, 3H), 3.67 (s, 3H), 3.37 (dd, 1H, $J_{2,1}$ = 5.4, $J_{2,3}$ = 11.7, H2), 3.23 (dd, 1H, $J_{4e,3}$ = 5.7, $J_{4e,4a}$ = 15.8, H4e), 3.11 (dt, 1H, $J_{3,2}$ = 11.8, $J_{3,4e}$ = 5.7, H3), 2.88 (dd, 1H, $J_{4a,3}$ = 11.7, $J_{4a,4e}$ = 15.7, H4a); $^{13}C$ NMR ($CDCl_3$) δ 178.08 (CO), 175.46 (CO), 148.44 (C), 148.11 (C), 147.98 (2 × C), 133.92 (C), 128.68 (C), 125.57 (C), 121.67 (CH), 112.62 (CH), 112.24 (CH), 110.90 (CH), 110.34 (CH), 55.94 ($CH_3$), 55.85 ($CH_3$), 55.80 ($CH_3$), 55.70 ($CH_3$), 52.02 ($CH_3$), 47.79 (CH), 45.51 (CH), 36.94 (CH), 31.99 ($CH_2$); MS *m/z* (rel inten) 399 (26), 398 (− $CH_3OH$, 100), 370 (10), 339 (10), 325 (36), 270 (20), 269 (93), 238 (15), 151 (21); HRMS calcd for $C_{23}H_{26}O_8$ 398.1365 (− $CH_3OH$), found 398.1364.

**2,3-*trans*-Acid Alcohol (25).** The half-ester **18** (80 mg, 0.187 mmol) was dissolved in dry THF (20 mL) and the system placed under $N_2$. $LiHBEt_3$ (10 equiv, 2 mL, 1.0 M, in THF) was added dropwise to the solution with concomitant evolution of gas (orange to yellow color change). The reaction was stirred at rt for 23 h and acidified with dilute HCl (20%, pH 1) followed by the addition of Amberlite resin (Aldrich, IRC 718, 3.2 g). After stirring 3 h, the suspension was filtered (EtOAc eluent) and dried ($MgSO_4$). Evaporation of the solvent gave a yellow oil which was chromatographed on silica (4% AcOH/66% EtOAc/hexanes) to give a colorless oil (57.1 mg, 76%): $[\alpha]^{20}_D$ + 177 (*c* 0.487, $CHCl_3$); IR 1701 (br, CO acid); $^1H$ NMR ($CDCl_3$) δ 6.69 (d, 1H, *J* = 8.3, H5′), 6.65 (s, 1H, H5), 6.59 (bs, 1H, H2′), 6.47 (dd, 1H, *J* = 8.2, ca. 1, H6′), 6.41 (s, 1H, H8), 4.46 (d, 1H, $J_{1,2}$ = 5.3, H1), 4.5 (bs, OH),

3.87 (s, 3H), 3.79 (s, 3H), 3.74 (s, 3H), 3.71 (s, 3H), 3.7 (m, 2H, $CH_2OH$; from COSY 45), 3.02 (m, 2H, $H4_{eq}$, H2), 2.75 (dd, 1H, $J$ = 11.0, 16.8, $H4_{ax}$), 2.34 (br m, 1H, H3); $^{13}C$ NMR ($CDCl_3$) $\delta$ 178.15 (CO), 148.15 (C), 147.91 (C), 147.78 (C), 147.58 (C), 134.66 (C), 129.10 (C), 127.30 (C), 121.82 (CH), 113.02 (CH), 112.07 (CH), 110.77 (2 × CH), 65.34 ($CH_2$), 55.86 ($CH_3$), 55.83 ($CH_3$), 55.81 ($CH_3$), 55.70 ($CH_3$), 46.79 (2 × CH), 32.38 (CH), 31.60 ($CH_2$); MS $m/z$ (rel inten) 403 (2), 402 ($M^+$, 4), 386 (4), 385 (25), 384 (– $H_2O$, 100); 353 (8), 339 (11), 325 (10), 269 (17), 246 (15), 201 (13), 151 (22); HRMS calcd for $C_{22}H_{26}O_7$ 402.1679, found 402.1687; calcd (– $H_2O$) 384.1573, found 384.1576.

**(+)-Isodimethylretrodendrin (20). Method A.** The acid alcohol **25** (11.9 mg, 0.0296 mmol) was refluxed in dry benzene (4 mL) over molecular sieves (0.33 g, 4 Å) in the presence of *p*-TsOH (1.3 mg) for 2.5 h. The solution was filtered through silica (EtOAc eluent) and the solvent evaporated to give a clear oil (6 mg, 53%).

**Method B.** The half-ester **18** (69.6 mg, 0.162 mmol) was dissolved in dry THF (10 mL), and LiHBEt$_3$ (1.0 M/THF, 5 equiv 0.81 mL) was added under an $N_2$ atmosphere. The solution was stirred at room temperature for 15 h followed by addition of Amberlite resin (Aldrich, IRC-718) (evolution of gas). Dilute HCl (20%, 10 mL) was added and the mixture stirred for 7 h. Filtration and evaporation under a slight vacuum (ca. 200 mm) gave a crystalline residue (280 mg) which was dissolved in a mixture of $CH_2Cl_2$ (10 mL), $H_2O$ (10 mL), and methanol (2 mL). The organic fraction was separated and the aqueous layer extracted with $CH_2Cl_2$ (2 × 10 mL). The combined organic extracts were dried ($MgSO_4$), and the solvent was evaporated. The yellow oil was placed under high vacuum (1 mm, 50 °C, 1 h) to give a viscous oil (63.4 mg). Chromatography on silica (30–50% EtOAc/hexanes) afforded the pure product (49.3 mg, 79%): $[\alpha]^{20}_D$ +115° (*c* 0.32, $CHCl_3$); IR ($CH_2Cl_2$) 1779 cm$^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 6.95 (d, 1H, $J$ = 2.0, H2′), 6.68 (s, 1H, H5), 6.67 (d, 1H, $J$ = 8.3, H5′), 6.52 (s, 1H, H8), 6.36 (dd, 1H, $J$ = 2.0, 8.3, H6′), 4.64 (d, 1H, $J_{1,2}$ = 3.4, H1), 4.44 (dd, 1H, $J_{11\beta,3}$ = 6.2, $J_{11\beta,11\alpha}$ = 8.6, $H11_\beta$), 3.92 (t, 1H, $J$ = 9.9, $H11_\alpha$), 3.90 (s, 3H), 3.84 (s, 3H), 3.81 (s, 3H), 3.75 (s, 3H), 3.12–3.06 (m, 1H, H3), 2.83–2.70 (m, 3H, H2, $H4_\alpha$, $H4_\beta$); $^{13}C$ NMR ($CDCl_3$) $\delta$ 175.10 (CO), 148.23 (C), 148.03 (2 × C), 147.87 (C), 133.48 (C), 129.83 (C), 127.07 (C), 122.61 (CH), 114.41 (CH), 113.22 (CH), 111.35 (CH), 110.32 (CH), 72.15 ($CH_2$), 55.90 (3 × $CH_3$), 55.79 ($CH_3$), 47.65 (CH), 42.88 (CH), 32.70 ($CH_2$, CH); MS $m/z$ (rel inten) 385 (26), 384 ($M^+$, 100), 369 (3), 353 (9), 339 (11), 325 (8), 299 (8), 281 (8), 269 (17), 246 (17), 201 (17), 151 (27), 84 (29), 57 (30); HRMS calcd for $C_{22}H_{24}O_6$ 384.1573, found 384.1594.

**(–)-Isopicrodimethylretrodendrin (22).** Isodimethylretrodendrin (**20**) (0.022 g, 0.056 mmol) was refluxed in sodium *tert*-butoxide/*tert*-butanol solution (10 mL, 0.1 M) for 13 h under $N_2$. The cloudy solution was acidified (10% HCl) to produce a homogeneous yellow solution which was extracted with $CH_2Cl_2$ and dried ($MgSO_4$) and the solvent evaporated to give a yellow oil. Chromatography on silica gel (50% EtOAc/hexanes) afforded **22** as a yellow solid (18.9 mg, 87%): $[\alpha]^{20}_D$ = –17.2° (*c* 0.376, $CHCl_3$); IR ($CH_2Cl_2$) 1769, 1514 (s) cm$^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 6.77 (d, 1H, $J$ = 8.3, H5′), 6.69 (d, $J$ = 1.7, H2′), 6.68 (s, 1H, H5), 6.62 (s, 1H, H8), 6.57 (dd, 1H, $J$ = 8.3, 1.7), 4.44 (m, 2H, H1, $H11_\beta$), 3.96 (dd, 1H, $J_{11\alpha,3}$ = 3.4, $J_{11\alpha,11\beta}$ = 9.1, $H11_\alpha$), 3.88 (s, 3H), 3.85 (s, 3H), 3.81 (s, 3H), 3.78 (s, 3H), 3.32, (dd, 1H, $J_{2,1}$ = 2.8, $J_{2,3}$ = 9.6, H2), 3.03 (m, 1H, H3), 2.89 (dd, 1H, $J_{4\beta,3}$ = 6.5, $J_{4\beta,4\alpha}$ = 15.4, $H4_\beta$), 2.51 (dd, 1H, $J_{4\alpha,3}$ = 5.1, $J_{4\alpha,4\beta}$ = 15.4, $H4_\alpha$); $^{13}C$ NMR ($CDCl_3$) $\delta$ 148.48 (CO), 149.10 (C), 148.13 (C), 148.03 (C), 147.73 (C), 135.35 (C), 129.28 (C), 126.90 (C), 119.68 (CH), 112.63 (CH), 111.70 (2 × CH), 111.14 (CH), 72.87 ($CH_2$), 55.94 (2 × $CH_3$), 55.91 (2 × $CH_3$), 46.62 (CH), 44.35 (CH), 32.78 (CH), 31.47 ($CH_2$); mass spectrum (rel inten) 385 (24), 384 ($M^+$, 100), 369 (8), 353 (22), 339 (11), 325 (22), 312 (20), 299 (14), 269 (36), 246 (14); HRMS calcd for $C_{22}H_{24}O_6$ 384.1573, found 384.1580.

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**Supplementary Material Available:** Copies of $^1H$ and $^{13}C$ NMR spectra (22 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 ACS; see any current masthead page for ordering information.