(−)-Arctigenin as a Lead Structure for Inhibitors of Human Immunodeficiency Virus Type-1 Integrase

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The natural dibenzylbutyrolactone type lignanolide (−)-arctigenin (**2**), an inhibitor of human immunodeficiency virus type-1 (HIV-1) replication in infected human cell systems, was found to suppress the integration of proviral DNA into the cellular DNA genome.[11b] In the present study **2** was tested with purified HIV-1 integrase and found to be inactive in the cleavage (3′-processing) and integration (strand transfer) assays. However, the semisynthetic 3-*O*-demethylated congener **9** characterized by a catechol substructure exhibited remarkable activities in both assays. Structure−activity relationship studies with 30 natural (**1**−**6**), semisynthetic (**7**−**21**), and synthetic (**37**−**43**, **45**, **46**) lignans revealed that (1) the lactone moiety is crucial since compounds with a butane-1,4-diol or tetrahydrofuran substructure and also lignanamide analogues lacked activity and (2) the number and arrangement of phenolic hydroxyl groups is important for the activity of lignanolides. The congener with two catechol substructures (**7**) was found to be the most active compound in this study. **7** was also a potent inhibitor of the "disintegration" reaction which models the reversal of the strand transfer reaction. The inhibitory activity of **7** with the core enzyme fragment consisting of amino acids 50−212 suggests that the binding site of **7** resides in the catalytic domain.

Introduction

For years pharmacological antiretroviral research with virally encoded enzymes as targets has focused principally on agents that inhibit human immunodeficiency virus (HIV) reverse transcriptase and HIV protease, respectively.[1] Surprisingly, HIV integrase, the protein mediating integration of HIV DNA into the human genome[2] and therefore also essential to the virus life cycle,[3] has been neglected as a target for quite a long time. Recently the first *in vitro* studies on inhibitors of retroviral integrase were published. Aurintricarboxylic acid and its relatives[4] as well as the polyanionic drug suramin[5] have shown considerable activities. Our first investigation of potential integrase inhibitors focused on DNA binders and topoisomerase-blocking agents.[6] Perhaps due to a nonspecific block of DNA function, certain DNA binders were found to inhibit human immunodeficiency virus type-1 (HIV-1) integrase. Nonintercalative topoisomerase inhibitors, such as camptothecin (type I) and epipodophyllotoxins (type II), respectively, did not inhibit HIV-1 integrase, a fact which independently has been found by two other groups.[7] However, some other compounds that also do not bind DNA exhibited activity, *e.g.*, the flavone quercetin and caffeic acid phenylethyl ester (CAPE).[6] These results prompted us to carry out structure−activity studies on flavones,[8] curcumin,[9a] and cosalane derivatives.[9b] More recently we found that other drug families including copper phenanthroline,[9c] tyrphostins,[9e] and AZT nucleotides inhibited HIV-1 integrase.[9d]

Two naturally occurring lignanolides of the dibenzylbutyrolactone type, (−)-arctigenin (**2**) and (−)-trachelogenin (**3**), apparently implicated in natural plant defenses, have been shown to inhibit replication of HIV-1 in infected human cell systems.[10,11] **2** and **3** were efficient inhibitors of the nuclear matrix-associated DNA topoisomerase II activity, particularly of the enzyme from HIV-1-infected cells. So, we initially assumed that these compounds were active due to prevention of the increase of topoisomerase II activity involved in virus replication after infection of cells with HIV-1.[10] However, using the polymerase chain reaction (PCR) technique to determine the degree of integration of proviral DNA into the cellular DNA genome, it has been found that **2** and **3** strongly suppressed HIV-1 integration. From these results, we concluded that the anti-HIV effect of **2** and **3** is primarily caused by inhibition of the HIV integration reaction rather than by inhibition of DNA topoisomerase II.[11] These observations led us to determine whether **2** and **3** are in fact inhibitors of the HIV-1 integrase and to consider a series of natural, semisynthetic, and synthetic congeners for a structure−activity relationship. Herein we report on their isolation, synthesis, and biological activity.

Chemistry

On the basis of the hypothesis that the natural dibenzylbutyrolactone type lignanolides **2** and **3**, respectively, are HIV-1 integrase inhibitors, it was obvious to assume that (−)-matairesinol (**1**), the 4″-*O*-demethyl derivative of **2** and in addition its biogenetic precursor in plants,[12] might also be active. Ring closure between C-7 and C-6″ leads to cyclolignanolide type compounds like α-peltatin (**4**), *β*-peltatin (**5**), and 4′-*O*-demethylpodophyllotoxin (**6**), well-known from, e.g., *Podophyllum* species. The *O*-demethyl derivatives **7**−**9** containing at least one catechol substructure (**8** and **9**) or even two (**7**) could be of particular interest since it is

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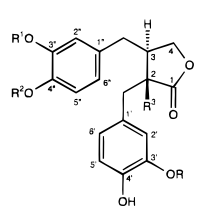
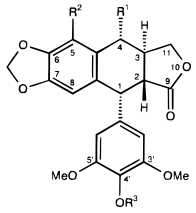
Chart 1



1: (-)-Matairesinol
(R = R^1 = Me; R^2 = R^3 = H)
2: (-)-Arctigenin
(R = R^1 = R^2 = Me; R^3 = H)
3: (-)-Trachelogenin
(R = R^1 = R^2 = Me; R^3 = OH)

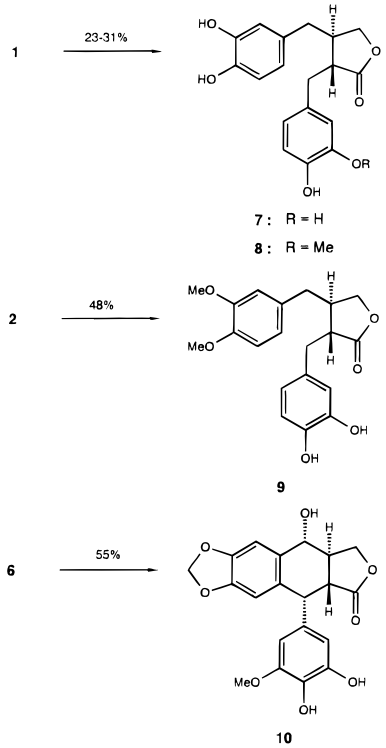


4: α-Peltatin
(R^1 = H; R^2 = OH, R^3 = H)
5: ß-Peltatin
(R^1 = H; R^2 = OH; R^3 = Me)
6: 4'-O-Demethylpodophyllotoxin
(R^1 = OH; R^2 = R^3 = H)

reasonable to assume they could be mammalian metabolites of **1** and **2**. This seems to be the case also for **10** as a potential metabolite of **6**.[13] Since dibenzylbutyrolactone type lignanolides and other lignans derive biogenetically from two molecules of coniferyl alcohol, they are characterized by at least two vicinal oxygen functions in both aromatic moieties at 3,4 positions. Cyclolignanolides, *e.g.*, **4**−**6**, usually possess three vicinal oxygen functions (3,4,5 positions) at one of the aromatic moieties, the so-called pendant ring. However, in all these cases 4-hydroxy-3-methoxyphenyl (including 4-hydroxy-3,5-dimethoxyphenyl, *e.g.*, **6**) substructures or 3,4-dimethoxyphenyl (including 3,4,5-trimethoxyphenyl, *e.g.*, podophyllotoxin) substructures are typical, whereas 3,4-dihydroxyphenyl (catechol) moieties are extremely rare, *e.g.*, thujaplicatin (5′-hydroxymatairesinol, 5′-hydroxy-**1**) from *Thuja plicata* DÜNN., Cupressaceae.[14] This is striking, particularly since the catechol substructure is common in other phenolic secondary metabolite families of the plant kingdom including caffeic acid derivatives (*e.g.*, chlorogenic acids, rosmarinic acid, cynarin) and flavonoids (*e.g.*, quercetin). In order to study the influence of the lactone moiety on the inhibition of HIV-1 integrase, the corresponding 2,3-dibenzylbutane-1,4-diol derivatives of **1** and **2**, (−)-secoisolariciresinol (**11**) and 4-methylsecoisolariciresinol (**12**), could be examined, as well as **11** which is also a natural lignan and, in addition, an early precursor in the biosynthesis of **1** and **2**.[12] Furthermore, it would be useful to study the corresponding 9-deoxo derivatives, the 3,4-dibenzyltetrahydrofurans **14** and **15**, respectively. The 2,3-*cis* isomers of the genuine cyclolignanolides **4**−**6**, α-peltatin B (**17**), *β*-peltatin B (**18**), and 4′-*O*-demethylpicropodophyllotoxin (**19**), are characterized by a less strained and therefore chemically less reactive lactone moiety compared with **4**−**6**. Another interesting structural variation is represented by the arctigenic acid amide **20** and its catechol derivative **21**. Natural lignanamides of this type, the jacpaniculines, have recently been discovered in the seeds of *Jacquemontia paniculata* (BURN. f.) HALLIER f. var. *paniculata*, Convolvulaceae.[15]

Attention could be focused furthermore on certain arctigenin (**2**) derivatives with a diminished or an enhanced number of oxygen functions, *i.e.*, compounds with (a) no substituents at all in the 3′,4′,5′ positions (**37**, **41**), (b) only one hydroxyl group in the 4′ position and no substituents in the 3′,5′ positions (**38**, **42**), (c) only one hydroxyl group in the 3′ position and no substituents in the 4′,5′ positions (**39**, **43**), and (d) three vicinal hydroxyl groups (**40**). Finally, the lactone moiety of **2** and **9**, respectively, could be substituted by a cyclopentanone substructure to give **45** and **46**, respectively. All these variations seemed to be necessary in order to derive crucial information about the structural requirements for a potential HIV-1 integrase inhibitor from lignans.

Scheme 1[a]

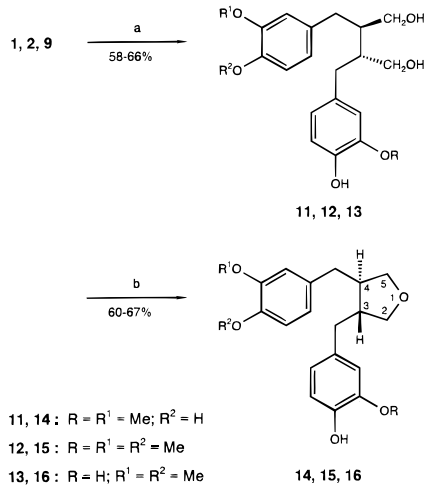


[a] Reagents: $AlCl_3$, pyridine, CH_2Cl_2, reflux, then dilute HCl.

Isolation of Dibenzylbutyrolactone Type Lignanolides and Cyclolignanolides from Plants. The *trans*-dibenzylbutyrolactone type lignanolides **1**−**3** were isolated from the leaves and stems of *Forsythia intermedia* L., Oleaceae (**1**, **2**),[16] and the epigeal part of *Ipomoea cairica* SWEET, Convolvulaceae (**3**).[17] The cyclolignanolide type congeners **4**−**6** were obtained from the rhizoma resin of *Podophyllum peltatum* L. (**4**, **5**) and ***P***. *emodi* L. (**6**), Berberidaceae.[18] Compounds **1**−**6** served as substrates in the enzyme assays and also as starting material for the semisynthetic preparation of O-demethylated derivatives, 2,3-dibenzylbutane-1,4-diols, cyclic ethers (tetrahydrofuranoid lignans), 2,3-dibenzylbutyramides, and 2,3-*cis*-cyclolignanolides, respectively.

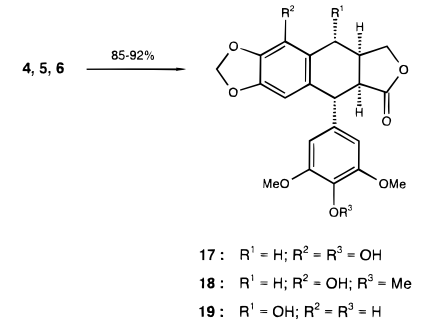
Semisynthetic Natural Lignans and Analogues. Methoxy groups in *ortho* position of phenolic hydroxyls can be demethylated by $AlCl_3$/pyridine in CH_2Cl_2 to furnish the catechol structure.[19] By application of this method, we obtained **7** and **8** from **1**, **9** from **2**, and **10** from **6**, respectively (Scheme 1). Recently, **10** has already been synthesized by another group in a different manner, *i.e.*, from podophyllotoxin *via* its *o*-quinone with subsequent catalytic hydrogenation as a synthetic intermediate of 4*β*-substituted anilino derivatives which turned out to be potent DNA topoisomerase II inhibitors.[20] $LiBH_4$ reduction of **1**, **2**, and **9** in THF afforded diols **11**−**13** (Scheme 2).[21] Closure of the diols **11**−**13** to the corresponding cyclic ethers **14**−**16** was achieved by treatment with *p*-toluenesulfonic acid in CH_2Cl_2 (Scheme 2).[21] Isomerization of the cyclolignanolides **4**−**6** was achieved by treatment with aqueous NH_3 in CH_3OH furnishing the corresponding *cis*-derivatives **17**−**19** (Scheme 3).[18a] Butyramides **20**−**21** were syn-

Scheme 2[a]



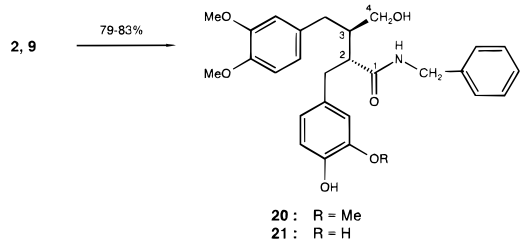
[a] Reagents: (a) $LiBH_4$, THF, reflux, then HCl (5%); (b) *p*-toluenesulfonic acid, CH_2Cl_2, reflux.

Scheme 3[a]



[a] Reagents: NH_3 (20%), MeOH, reflux.

Scheme 4[a]



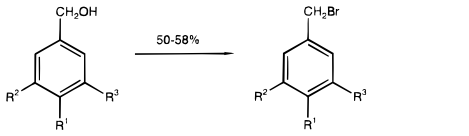
[a] Reagents: benzylamine, CH_2Cl_2, reflux.

thesized by treatment of the corresponding lactones **2** and **9** with benzylamine in CH_2Cl_2 (Scheme 4).

Total Synthesis of Natural Lignans and Analogues. Racemic *trans*-2,3-dibenzylbutyrolactones were synthesized by conjugate addition of acyldithiane anions to butenolide followed by trapping of the enolate anion so generated with the appropriate substituted benzyl bromide, using the original synthetic strategy of Ziegler and Schwartz.[22] The method is characterized by the fact that racemic 2,3-*trans*-configurated compounds are obtained.

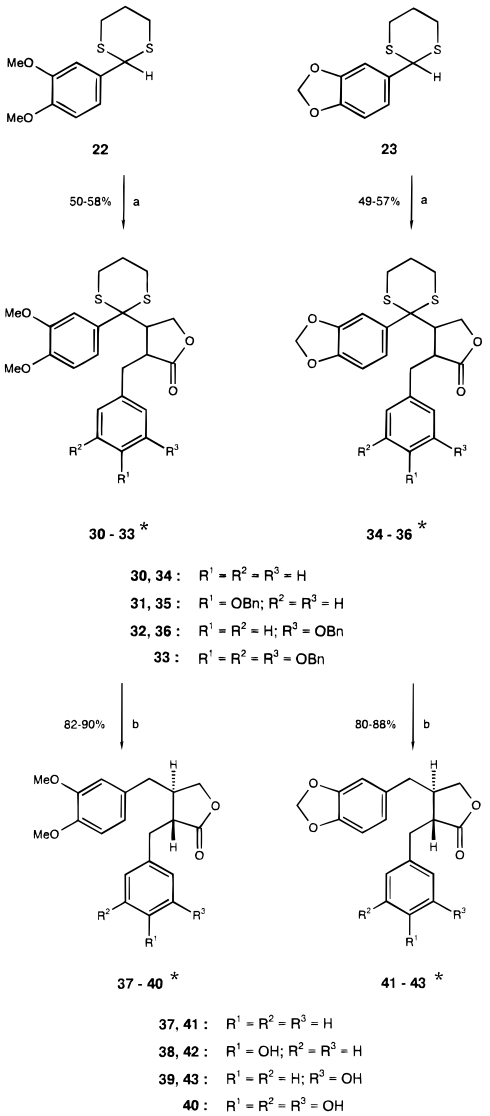
Aryl dithianes **22** and **23** were prepared by the reaction of the corresponding aromatic aldehyde with 1,3-propanedithiol and dry HCl.[23] Treatment of the corresponding benzyl alcohols with triphenylphosphine and bromine in acetonitrile afforded benzyl bromides **26**−**29** (Scheme 5).[24] Dibenzylbutyrolactone dithianes **30**−**36** were prepared from dithianes **22** and **23** by reaction with *n*-butyllithium and 2-butenolide in THF at −78 °C followed by direct alkylation with benzyl bromides **26**−**29** in the presence of HMPA. Simultaneous desulfurization and debenzylation of **30**−**36** and **44** were achieved by treatment with Raney nickel in refluxing ethanol and afforded *trans*-2,3-dibenzylbutyrolactones **37**−**43** (Scheme 6).

Scheme 5[a]



[a] Reagents: triphenylphosphine, acetonitrile, bromine, 0 °C, then appropriate (benzyloxy)benzyl alcohol, acetonitrile, 50 °C.

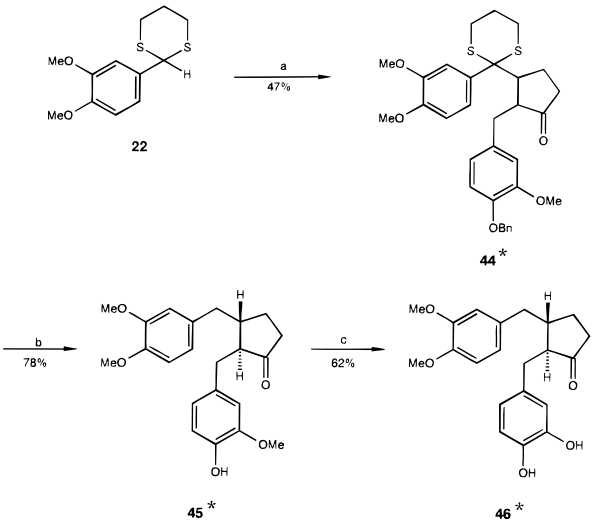
Scheme 6[a]



[a] Reagents: (a) *n*-butyllithium, THF, −78 °C, then 2-butenolide, THF, −78 °C; then benzyl bromide, **26**, **27**, and **29**, respectively, HMPA, THF, −78−20 °C; (b) Raney nickel (W-2), ethanol, reflux. An asterisk indicates (±)-2,3-*trans*-forms.

Exchange of the lactone ring of racemic *trans*-2,3-dibenzylbutyrolactones by a cyclopentanone ring was achieved by modification of the procedure using 2-cyclopentenone instead of 2-butenolide (Scheme 7). The *trans*-configuration of **44**−**46** was assigned on the basis of the ^{13}C-NMR and H,C-COSY spectra. The signals

Scheme 7[a]



[a] Reagents: (a) *n*-butyllithium, THF, −78 °C, then 2-cyclopentanone, THF, −78 °C, then **28**, HMPA, THF, −78−20 °C; (b) Raney nickel (W-2), ethanol, reflux; (c) $AlCl_3$, pyridine, reflux, then dilute HCl. An asterisk indicates (±)-2,3-*trans*-forms.

corresponding to C-2 and C-3 appeared at δ 54.94 and 42.12. This is typical of *trans*-arrangement of the two benzyl substituents on the butyrolactone ring.[25]

Results and Discussion

HIV-1 Integrase Inhibitory Activities. Purified HIV-1 integrase produced *via* an *Escherichia coli* expression vector or by baculovirus-infected insect cells[26] is incubated with a 21-mer oligonucleotide corresponding to the U5 end of the HIV LTR. The initial step involves nucleolytic cleavage of two bases from the 3′ end.[2] Subsequently these recessed 3′ ends are used in a nucleophilic attack on an identical second oligonucleotide, which serves as the target DNA, in a strand transfer reaction. These two steps (3′-processing and strand transfer) were assayed together as described previously.[6,8]

Structure−Activity Relationships. The naturally occurring (−)-arctigenin (**2**) and 27 related lignans as well as two alicyclic analogues (**45**, **46**) were examined for their ability to inhibit 3′-processing and strand transfer by HIV-1 integrase. The phosphorimager picture showing the two activities employed for a subset of compounds is represented in Figure 1. With the exception of **3**, all compounds are listed in Table 1 or 2 together with their chemical structures and activities. Table 1 includes a series of lignanolides of the dibenzylbutyrolactone type. Surprisingly, the anti-HIV active natural compounds **2** and **3** turned out to be inactive against HIV-1 integrase *in vitro*. However, certain closely related derivatives of **2** exhibited activity. The most potent compound, **7**, a lignanolide with two catechol substructures, was characterized by a total inhibition of the 3′-processing step as well as of the strand transfer step at 100 μM and IC_{50} values of 21.4 ± 15.0 and 5.4 ± 4.0 μM, respectively (Figure 2). Next in potency was the corresponding compound with only one pair of adjacent hydroxyls on the phenyl ring at positions 3 and 4, **9**, with inhibition values of about 50% at 100 μM. The 3′,4′-O,O-demethylated arctigenin derivative **8**, however, revealed only a weak inhibition of the strand transfer reaction. The remaining lignanolides of Table 1 and the different lignan types of Table 2 were inactive.

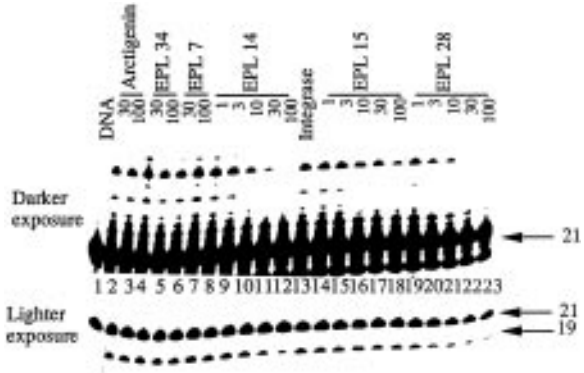
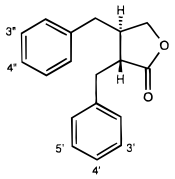


Figure 1. Phosphorimager picture showing inhibition of HIV-1 integrase-catalyzed 3′-processing (cleavage) and strand transfer (integration) by lignans: lane 1, DNA alone; lane 13, + integrase without drug; lanes 2−12 and 14−23, + indicated concentrations of arctigenin (lanes 2−3), EPL 34 = **40** (lanes 4−5), EPL 7 = **1** (lanes 6−7), EPL 14 = **7** (lanes 8−12), EPL 15 = **8** (lanes 14−18), and EPL 28 = **9** (lanes 19−23). The DNA strand transfer (integration) products migrate more slowly than the 21-mer substrate DNA. The 3′-processing product (19-mer, indicated by the lower arrow) and the DNA substrate (21-mer, indicated by the upper arrow) are also shown). The upper panel is a darker exposure of the gel in order to show the integration products, while the lower panel is a lighter exposure in order to show the 3′-processing products.

Although one pair of *o*-hydroxyls appears to be a minimum requirement for remarkable potency of lignanolides, it was not an absolute criterion for activity even in this group of lignans. Somewhat surprisingly, the cyclolignanolide **10**, closely related to the active **9**, was found to be inactive inspite of the fact that a 3,4-catechol substructure is present (Table 2). Furthermore non-lignanolide type derivatives of the active 4′-*O*-demethylarctigenin (**9**) like its butane-1,4-diol analogue **13**, its tetrahydrofuran analogue **16**, and its benzylamide derivative **21**, though all containing a 3,4-catechol moiety, produced only weak or even undetectable inhibitory activity at 100 μM in the 3′-processing as well as in the strand transfer reaction. These findings indicate the importance of the lactone moiety for the potency of lignans. This is also supported by the fact that the alicyclic cyclopentanone analogue **46** revealed no activity in the 3′-processing reaction and only modest activity in the strand transfer step (footnote b in Table 2).

The influence of the number and arrangement of phenolic hydroxyl groups is straightforward. There are similarities with the structure−activity relationship studies of flavones[8] and CAPE derivatives[9f] but also some differences. HIV-1 integrase-inhibiting flavones with certain structural similarities to lignans (two aromatic moieties with oxygen functions) require the presence of at least one *ortho* pair of phenolic groups (catechol substructure) and, in addition, at least one or two extra hydroxyl groups. Potency of active flavones is enhanced by the presence of additional hydroxyl groups. The structure−activity study presented here demonstrated that, for potency of lignans in both assays (3′-processing and strand transfer), a 3′,4′-catechol substructure is sufficient, whereas an *ortho* pair of phenolic hydroxyl groups in the 3″,4″ positions is not, even when an additional hydroxyl in the 4′ position is present (**8**). The correspondingly substituted flavones (3′,4′-dihydroxyflavone and 6,7-dihydroxyflavone, respectively) were found to be inactive.[8] Furthermore,

Table 1. Structure–Activity of Dibenzylbutyrolactone Type Lignanolides against HIV-1 Integrase



compd	substitutions 3′	4′	5′	3″	4″	inhibition at 100 μM[b] (%) cleavage (3′-processing)	integration (strand transfer)
(−)-arctigenin	OMe	OH		OMe	OMe	<5	<5
1	OMe	OH		OMe	OH	<5	<5
8	OMe	OH		OH	OH	<5	41 ± 8
9	OH	OH		OMe	OMe	37 ± 29	52 ± 29
7	OH	OH		OH	OH	92 ± 14	100
40[a]	OH	OH	OH	OMe	OMe	<5	<5
37[a]				OMe	OMe	<5	<5
38[a]		OH		OMe	OMe	<5	<5
39[a]	OH			OMe	OMe	<5	<5
41[a]				dioxymethylene		<5	<5
42[a]		OH		dioxymethylene		<5	<5
43[a]	OH			dioxymethylene		<5	<5

[a] These compounds represent racemates. [b] The inhibition ± SD values ($N \geq 3$) for cleavage and integration reactions are listed.

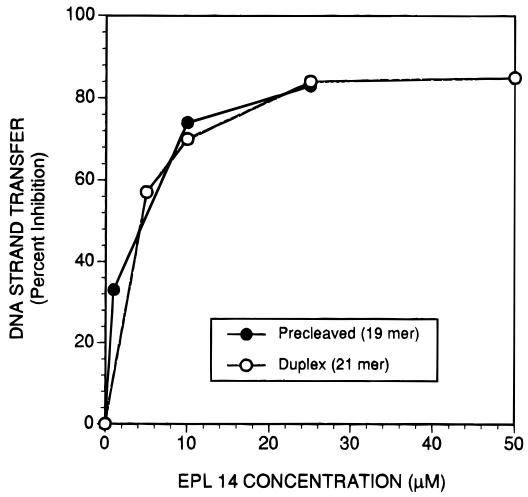
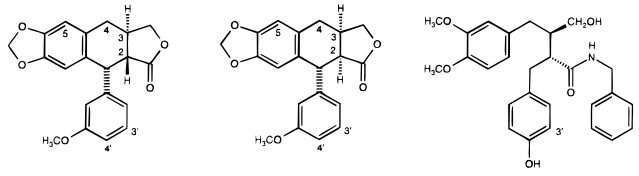
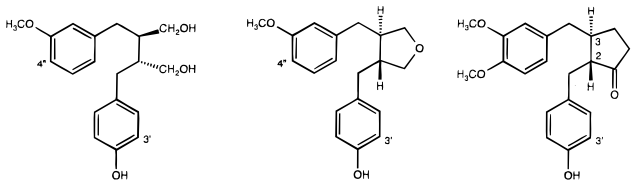


Figure 2. Inhibition of strand transfer by EPL 14 = **7**. The precleaved oligonucleotide (19-mer) corresponds to the HIV terminus after the 3′-processing step (dinucleotide cleavage) of the normal duplex oligonucleotide (21-mer). Inhibition was calculated after phosphorimager quantification of strand transfer reactions in the presence of the indicated drug concentrations.

Table 2. Inactive Lignans against HIV-1 Integrase (Inhibition of 3′-Processing and Strand Transfer Reaction, <5% at 100 μM)



	Substitutions 4	5	3′	4′		Substitutions 4	5	3′	4′		Substitutions 3′	
4		OH	OMe	OH	**17**		OH	OMe	OH	**20**	OMe	
5		OH	OMe	OMe	**18**		OH	OMe	OMe	**21**	OH	
6	OH		OMe	OH	**19**	OH		OMe	OH			
10	OH		OH	OH								



	Substitutions 3′	4″		Substitutions 3′	4″		Substitutions 3′	
11	OMe	OH	**14**	OMe	OH	**45**[a]	OMe	
12	OMe	OMe	**15**	OMe	OMe	**46**[a,b]	OH	
13	OH	OMe	**16**	OH	OMe			

[a] These compounds represent racemates. [b] Inhibition value of the strand transfer reaction at 100 μM: 38%.

inhibitory potency of active lignans, in contrast to the flavones and CAPE derivatives, is not enhanced but eliminated by the presence of adjacent groups of three phenolic hydroxyls (**40**). Thus, the influence of the number of phenolic hydroxyl groups and especially their arrangement is of particular significance for the activity of lignanolides.

The anti-HIV-1 activity of (−)-arctigenin (**2**)[10,11] could be due either to its metabolism to certain O-demethylated congeners with HIV-1 integrase-inhibiting activity, *e.g.*, **8** or even **7**, or to its action on an earlier stage in the viral life cycle. In V79 Chinese hamster cells genetically engineered for stable expression of the rat single cytochrome P450 isoform 2B1, **2** was metabolized to **8**.[27]

Very recently R. L. Lafemina and his group published that α- and β-conidendrol exhibited very strong inhibition of the integrase sequence-specific endonuclease activity (3′-processing) and strand transfer reaction.[28] Like **7** both compounds are lignanolides with biscatechol substructure: **7** is exactly a *seco*-congener of α-conidendrol (Figure 3). Both α- and β-conidendrol as well as the compounds in the present study failed to show anti-HIV activity in cellular assays (unpublished data).

Site of Action. The "disintegration' reaction, an apparent reversal of the natural integration step of the enzyme, offers the advantage of being catalyzed by truncated integrase lacking the N-terminus (zinc finger) and the C-terminus (DNA binding) regions. Like quercetagetin, the most active flavone, and CAPE,[8] the biscatechol **7** was a potent inhibitor of disintegration not

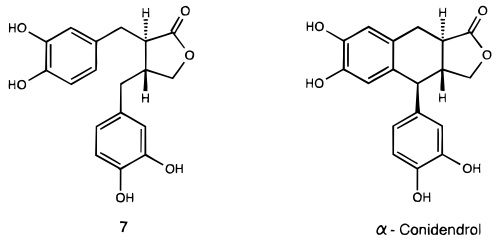


Figure 3. Structure of lignanolide **7** compared with structure of cyclolignanolide α-conidendrol.

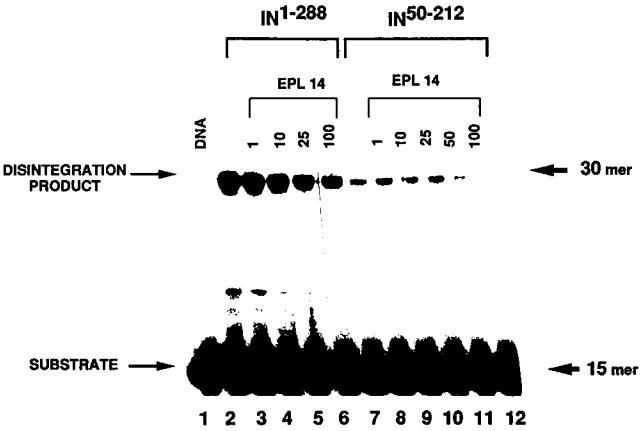


Figure 4. Phosphorimager picture showing the inhibitory effect of EPL 14 = **7** on disintegration catalyzed by the full-size HIV-1 integrase (IN^{1-288}) and the deletion mutant IN^{50-212}: lane 1, DNA alone; lane 2, + IN^{1-288} without drug; lanes 3−6, + IN^{1-288} and EPL 14 = **7**; lane 7, + IN^{50-212} without drug; lanes 8−12, + IN^{50-212} and EPL 14 = **7**. Numbers above lanes correspond to drug concentrations in micromolar.

only of full size HIV-1 integrase (1−288) but also of the core integrase fragment consisting of amino acids 50−212 (Figure 4). This inhibition of the truncated enzyme suggests that the binding site of **7** resides in the catalytic domain of HIV-1 integrase. Hence the core domain of HIV-1 integrase containing the conserved amino acids DD (35) and E[2] represents the common site of action for a variety of drugs.[8,9]

Experimental Section

Biological Methods: Preparation of Radiolabeled DNA Substrates. The following oligonucleotides were purchased from Midland Certified Reagent Co. (Midland, TX): AE118, 5′-GTGTGGAAAATCTCTAGCAGT-3′; AE146, GGACGCCATAGCCCCGGCGCGGTCGCTTTC-3′; AE156, 5′-GTGTGGAAAATCTCTAGCAGGGGCTATGGCGTCC-3′; AE117, 5′-ACTGCTAGAGATTTTCCACAC-3′; AE157, 5′-GAAAGCGACCGCGCC-3′; and AE118S, 5′-GTGTGGAAAATCTCTAGCA-3′. These oligonucleotides were purified by HPLC. The AE117 and AE118 oligonucleotides correspond to the U5 end of the HIV LTR. For the 3′-processing and integration assays, AE118 was 5′-end-labeled using polynucleotide T_4 kinase and [γ-^{32}P]-ATP. The kinase was heat-inactivated, and an equimolar amount of AE117 was added. The mixture was heated at 95 °C and allowed to cool slowly to room temperature. The reaction was then run on a G-25 Sephadex quick spin column (Boehringer Mannheim) to separate annealed double-stranded oligonucleotide from unincorporated label. For integration reactions using the precleaved oligo, AE118S was labeled, annealed, and purified as above.

3′-Processing and Integration Assays. Purified recombinant HIV-1 integrase wild-type (IN^{1-288}) and truncated enzyme (IN^{50-212}) were a generous gift of Dr. R. Craigie, Laboratory of Molecular Biology, NIDDK. The enzyme was preincubated at a final concentration of 0.25 μM at 30 °C with inhibitor in reaction buffer (50 mM NaCl, 1 mM HEPES, 50 μM EDTA, 50 μM dithiothreitol, 10% glycerol (w/v), 7.5 mM $MnCl_2$, 0.1 mg/mL bovine serum albumin, 10 mM 2-mercaptoethanol, 10% dimethyl sulfoxide, and 25 mM MOPS, pH 7.2). After 30 min, 0.3 pmol of the labeled cleavage/integration substrate was added, and the incubation was continued for an additional 60 min at 30 °C. The final reaction volume was 16 μL. The reaction was quenched by the addition of an equal volume of Maxam−Gilbert loading dye.

Disintegration Assays. The disintegration reactions[29] were performed as above with the "Y" oligonucleotide substrate and an integrase deletion mutant, IN^{50-212},[30] which lacks the N-terminal zinc finger and C-terminal DNA-binding domains. For this assay, AE157 was 5′-end-labeled as above. Equimolar amounts of AE117, AE156, and AE146 were added. The mixture was annealed and run on a G-25 Sephadex quick spin column as above.

Gel Electrophoresis and Quantitation. An aliquot from each reaction was electrophoresed on a denaturing 20% polyacrylamide gel. Gels were dried and subjected to autoradiography using Kodak XAR-2 film or exposed in a Molecular Dynamics Phophorimager cassette. Gels were analyzed using a Betascope 603 blot analyzer (Betagen, Waltham, MA). Percent inhibition was calculated as described previously.

Chemical Methods: General Directions. All experiments were monitored by thin layer chromatography using aluminum sheets coated with a 0.2 mm layer of silica gel 60 F_{254} (Merck art. no. 5554). Melting points were taken on a Büchi 530 melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AC 250 or AC 300 spectrometer. Resonances in δ units downfield from internal Me_4Si are noted as singlet (s), doublet (d), triplet (t), multiplet (m), broad signal (br), or doublet of doublets (dd). Coupling constants are in hertz (Hz). ^{13}C NMR spectra were recorded on a Bruker AC 300 spectrometer, operating at 75.50 MHz for compounds **16** and **45**. All compounds displayed NMR spectra fully in agreement with their proposed structures. EIMS and HRMS were obtained using MAT-711 and CH_5DF Finnigan spectrometers. Elemental analyses (C, H, N) were performed for crystal forms and are within ±0.4% of the theoretical values. Purity of gums, oils, and amorphous powders was proved by HRMS and by application of two HPLC systems using a reverse phase Eurospher 100-C18 column; eluent A, MeOH:phosphoric acid, 0.5% (v/v), at 1.5 mL/min (gradient system from 50:50 to 100:0 within 40 min); eluent B, MeCN:phosphoric acid, 0.5% (v/v), at 1 mL/min (gradient system from 40:60 to 100:0 within 40 min). **26**−**28** were only characterized by ^{1}H NMR and HRMS. Intermediate products **22**, **23**, and **32** were used directly without further purification. All commercially available chemicals were used as supplied by the manufacturers.

Isolation of Lignanolides/Cyclolignanolides from Plants. (−)-Matairesinol (**1**) and (−)-arctigenin (**2**) were isolated from the leaf and stem material of *F. intermedia* after acidic hydrolysis of the methanolic extract using modified literature methods.[16] The mixture was partitioned between H_2O and CH_2Cl_2, and the organic layer was fractionated on a silica gel column with CH_2Cl_2:CH_3OH (100:4). (−)-Trachelogenin (**3**) was isolated from epigeal parts of *I. cairica* by silica gel column chromatography of the CH_2Cl_2-soluble plant extract with $CHCl_3$−*n*-hexane and further purified by thin layer chromatography (silica gel 60 PF_{254} with $CaSO_4$, $CHCl_3$−cyclohexane−EtOAc) using the technique of radial development (Chromatotron). Spectral data (^{1}H NMR, MS) and melting point of **3** were previously described.[12] α-Peltatin (**4**) and β-peltatin (**5**) were isolated from the resin of *P. peltatum* and 4′-*O*-demethylpodophyllotoxin (**6**) from the resin of *P. emodi*, respectively, using modified literature methods.[18] The resins were passed down on an Al_2O_3 column (eluant EtOAc) and further purified by fractionation on a silica gel column with $CHCl_3$:CH_3OH (90:10).

(−)-Matairesinol (1): crystals from CH_3OH; mp 85−87 °C; ^{1}H NMR ($CDCl_3$) δ 6.83 (1 H, d, J = 8.0 Hz), 6.80 (1 H, d, J = 8.5 Hz), 6.61 (2 H, m), 6.51 (1 H, dd, J = 8.0, 1.8 Hz), 6.40 (1 H, d, J = 1.8 Hz), 5.57 (1 H, s, O*H*, D_2O exchangeable), 5.55 (1 H, s, O*H*, D_2O exchangeable), 4.15 (1 H, dd, J = 9.0, 7.0 Hz, H-4b), 3.89 (1 H, dd, J = 9.0, 7.0 Hz, H-4a), 3.81 (3 H, s, OCH_3), 3.80 (3 H, s, OCH_3), 2.96 (1 H, dd, J = 14.0, 5.0 Hz, H-7′b), 2.87 (1 H, dd, J = 14.0, 7.0 hz, H-7′a), 2.45−2.65 (4 H,

m, H-2, H-3, H-7″a, H-7″b); HRMS *m/z* calcd for $C_{20}H_{22}O_6$ (M^+) 358.1416, obsd 358.1418; EIMS *m/z* 358 (M^+, 61), 221 (4), 194 (4), 175 (3), 164 (4), 137 ($[C_8H_9O_2]^+$, 100), 131 (6), 122 (13), 107 (5), 94 (9). Anal. ($C_{20}H_{22}O_6 \cdot H_2O$) C, H.

(−)-Arctigenin (2): crystals from CH_3OH; mp 98 °C; ^1H NMR ($CDCl_3$) δ 6.83 (1 H, d, $J = 7.9$ hz), 6.76 (1 H, d, $J = 8.0$ hz), 6.60 (2 H, m), 6.55 (1 H, dd, $J = 8.0$, 1.9 Hz), 6.46 (1 H, d, $J = 1.9$ Hz), 5.57 (1 H, s, O*H*, D_2O exchangeable), 4.14 (1 H, dd, $J = 9.0$, 7.0 Hz, H-4b), 3.89 (1 H, m, overlapping, H-4a), 3.85 (3 H, s, OCH_3), 3.82 (6 H, s, 2 OCH_3), 2.96 (1 H, dd, $J =$ 14.0, 5.4 Hz, H-7′b), 2.89 (1 H, dd, $J = 14.0$, 6.0 hz, H-7′a), 2.61 (2 H, m, H-2, H-7″b), 2.54 (2 H, m, H-3, H-7″a); HRMS *m/z* calcd for $C_{21}H_{24}O_6$ (M^+) 372.1573, obsd 372.1574; EIMS *m/z* 372 (M^+, 82), 235 (3), 221 (2), 194 (3), 177 ($[C_{10}H_9O_3]^+$, 13), 151 ($[C_9H_{11}O_2]^+$, 77), 137 ($[C_8H_9O_2]^+$, 100), 122 (10), 107 (11), 94 (6). Anal. ($C_{21}H_{24}O_6$) C, H.

α-Peltatin (4): crystals from CH_3OH; mp 214−215 °C; ^1H NMR (DMSO-d_6) δ 9.54 (1H, s, O*H*, D_2O exchangeable), 8.26 (1 H, s, O*H*, D_2O exchangeable), 6.25 (2 ArH, s, H-2′, H-6′), 6.10 (1 ArH, s, H-8), 5.93 (2 H, s, OCH_2O), 4.42 (2 H, m), 3.96 (1 H, dd, $J = 10.0$, 8.5 Hz), 3.62 (6 H, s, 2 OCH_3), 3.05 (1 H, dd, $J = 15.5$, 4.5 Hz), 2.87 (1 H, dd, $J = 13.5$, 5.0 Hz), 2.50 (2 H, m); HRMS *m/z* calcd for $C_{21}H_{20}O_8$ (M^+) 400.1158, obsd 400.1153; EIMS *m/z* 400 (M^+, 100), 355 (9), 246 (25), 201 (25), 189 (22), 168 (18), 154 (13), 115 (12). Anal. ($C_{21}H_{20}O_8$) C, H.

***β*-Peltatin (5):** crystals from CH_3OH; mp 220−222 °C; ^1H NMR (DMSO-d_6) δ 9.57 (1 H, s, O*H*, D_2O exchangeable), 6.25 (2 ArH, s, H-2′, H-6′), 6.11 (1 ArH, s, H-8), 5.93 (2 H, s, OCH_2O), 4.44 (2 H, m), 3.97 (1 H, dd, $J = 10.0$, 8.5 Hz), 3.64 (6 H, s, 2 OCH_3), 3.61 (3 H, s, OCH_3), 3.06 (1 H, dd, $J = 15.5$, 4.5 Hz), 2.93 (1 H, dd, $J = 13.5$, 5.0 Hz), 2.50 (2 H, m); HRMS *m/z* calcd for $C_{22}H_{22}O_8$ (M^+) 414.1315, obsd 414.1315; EIMS *m/z* 414 (M^+, 100), 246 (18), 201 (15), 189 (24), 181 (23), 168 (12). Anal. ($C_{22}H_{22}O_8$) C, H.

4′-*O*-Demethylpodophyllotoxin (6): crystals from CH_3OH; mp 236−238 °C; ^1H NMR (DMSO-d_6) δ 8.29 (1 H, s, O$H_{phenolic}$, D_2O exchangeable), 7.10 (1 ArH, s), 6.47 (1 ArH, s), 6.29 (2 ArH, s), 6.00 (1 H, s, OCH_2O), 5.96 (1 H, s, OCH_2O), 5.78 (1 H, d, $J = 7$ Hz, O$H_{alcoholic}$, D_2O exchangeable), 4.60 (1H, dd, $J = 9.4$, 7.4 Hz), 4.46 (2 H, m), 4.08 (1H, dd, $J = 10.3$, 8.6 hz), 3.63 (6 H, s, 2 xOCH_3), 3.09 (1 H, dd, $J = 14.0$, 5.0 Hz), 2.62 (1 H, m); HRMS *m/z* calcd for $C_{21}H_{20}O_8$ (M^+) 400.1158, obsd 400.1151; EIMS *m/z* 400 (M^+, 100), 382 ($M - H_2O$, 3), 201 (15), 154 (41). Anal. ($C_{21}H_{20}O_8$) C, H.

Demethylation of 1, 2, and 6: General Procedure for Ether Cleavage (7−10). (2*R*,3*R*)-2,3-Bis(3,4-dihydroxybenzyl)butyrolactone (7) and (2*R*,3*R*)-2-(4-Hydroxy-3-methoxybenzyl)-3-(3,4-dihydroxybenzyl)butyrolactone (8).[19] In a solution of **1** (1.08 g, 3 mmol) in CH_2Cl_2 (50 mL) was suspended $AlCl_3$ (0.8 g, 6.6 mmol), and pyridine (2.1 mL, 26.4 mmol) was added dropwise under stirring. The mixture was refluxed for 24 h, cooled in ice, and partitioned between diluted HCl and $CHCl_3$:CH_3OH (90:10). The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated to dryness. The residue was fractionated by column chromatography (silica gel, $CHCl_3$:CH_3OH, 90:10) to afford **8** as a gum (0.24 g, 23%). The combined aqueous layers were saturated with NaCl and extracted with methyl ethyl ketone. The organic layer was evaporated and the residue purified by column chromatography (silica gel, $CHCl_3$:CH_3OH, 80:20) to give **7** as a gum (0.31 g, 31%).

(2*R*,3*R*)-2,3-Bis(3,4-dihydroxybenzyl)butyrolactone (7): ^1H NMR (DMSO-d_6) δ 8.83 (1H, s, O*H*, D_2O exchangeable), 8.78 (1 H, s, O*H*, D_2O exchangeable), 8.76 (1 H, s, O*H*, D_2O exchangeable), 8.75 (1 H, s, O*H*, D_2O exchangeable), 6.66 (3 ArH, m), 6.44 (3 ArH, m), 3.96 (1 H, m), 3.80 (1 H, m), 2.70 (2 H, m), 2.28−2.50 (4 H, m); HRMS *m/z* calcd for $C_{18}H_{18}O_6$ (M^+) 330.1103, obsd 330.1100; EIMS *m/z* 330 (M^+, 100), 207 (10), 180 (8), 150 (15), 123 ($[C_7H_7O_2]^+$, 93).

(2*R*,3*R*)-2-(4′-Hydroxy-3′-methoxybenzyl)-3-(3″,4″-dihydroxybenzyl)butyrolactone (8): ^1H NMR (DMSO-d_6) δ 8.83 (1 H, O*H*, D_2O exchangeable), 8.79 (1 H, s, O*H*, D_2O exchangeable), 8.76 (1 H, s, O*H*, D_2O exchangeable), 6.61−6.72 (4 ArH, m), 6.35−6.55 (2 ArH, m), 4.02 (1 H, m), 3.83 (1 H, m), 3.73 (3 H, s, OCH_3), 2.75 (2 H, m), 2.36−2.51 (4 H, m); HRMS *m/z* calcd for $C_{19}H_{20}O_6$ (M^+) 344.1260, obsd 344.1258; EIMS *m/z* 344 (M^+, 100), 221 (4), 194 (7), 164 (6), 137 ($[C_8H_9O_2]^+$, 82), 123 ($[C_7H_7O_2]^+$, 25).

(2*R*,3*R*)-2-(3′,4′-Dihydroxybenzyl)-3-(3″,4″-dimethoxybenzyl)butyrolactone (9). ^1H NMR ($CDCl_3$) δ 6.48−6.79 (6 ArH, m, plus 2 H, 2 O*H*, D_2O exchangeable), 4.12 (1 H, dd, $J = 9.0$, 6.5 Hz, H-4b), 3.88 (1 H, m, overlapping, H-4a), 3.85 (3 H, s, OCH_3), 3.83 (3 H, s, OCH_3), 2.87 (2 H, m), 2.47−2.64 (4 H, m); MS *m/z* calcd for $C_{20}H_{22}O_6$ (M^+) 358.1416, obsd 358.1415; EIMS *m/z* 358 (M^+, 85), 177 (14), 151 ($[C_9H_{11}O_2]^+$, 100), 123 ($[C_7H_7O_2]^+$, 14).

3′,4′-*O*,*O*-Didemethylpodophyllotoxin (10):[20] crystals from CH_3OH; mp 218−220 °C; ^1H NMR (DMSO-d_6) δ 8.68 (1 H, s, O$H_{phenolic}$, D_2O exchangeable), 8.15 (1 H, s, O$H_{phenolic}$, D_2O exchangeable), 7.09 (1 ArH, s), 6.45 (1 ArH, s), 6.34 (1 ArH, s), 5.99 (1 ArH, s), 5.96 (2 H, s, OCH_2O), 5.85 (1 H, d, $J = 6.5$ Hz, O$H_{alcoholic}$, D_2O exchangeable), 4.61 (1 H, dd, $J = 9.5$, 7.0 Hz), 4.46 (1 H, t, $J = 8$ Hz), 4.36 (1 H, d, $J = 5$ Hz), 4.07 (1 H, dd, $J = 10.0$, 9.0 Hz), 3.66 (3 H, OCH_3), 3.06 (1 H, dd, $J =$ 14.0, 5.0 Hz), 2.65 (1 H, m); HRMS *m/z* calcd for $C_{20}H_{18}O_8$ (M^+) 386.1002, obsd 386.1002; EIMS *m/z* 386 (M^+, 100), 368 ($M - H_2O$, 12), 229 (19), 140 (31). Anal. ($C_{20}H_{18}O_8 \cdot H_2O$) C, H.

General Procedure for the Preparation of 2,3-Dibenzylated Butane-1,4-diols 11−13. (2*R*,3*R*)-2-(4′-Hydroxy-3′-methoxybenzyl)-3-(3″,4″-dimethoxybenzyl)-1,4-butanediol (12).[21] To a solution of **2** (0.37 g, 1 mmol) in dry THF (30 mL) was added $LiBH_4$ (44 mg, 20 mmol). The mixture was refluxed for 24 h. After cooling in ice, the mixture was decomposed by the dropwise addition of HCl (5%) and extracted with EtOAc (30 mL). The organic layer was evaporated to dryness and the residue purified by column chromatography (silica gel, $CHCl_3$:CH_3OH, 90:10) to afford **12** as a gum (250 mg, 66%): ^1H NMR (DMSO-d_6) δ 8.65 (1 H, s, O$H_{phenolic}$, D_2O exchangeable), 6.82 (1 ArH, d, $J = 8.0$ Hz), 6.50−6.64 (5 ArH, m), 4.55 (2 H, t, $J = 5$ Hz, 2 CH_2-O*H*, D_2O exchangeable), 3.71 (3 H, s, OCH_3), 3.67 (6 H, s, 2 OCH_3), 3.37 (4 H, m), 2.51 (4 H, m), 1.83 (2 H, m); HRMS *m/z* calcd for $C_{21}H_{28}O_6$ (M^+) 376.1886, obsd 376.1889; EIMS *m/z* 376 (M^+, 25), 358 ($M - H_2O$, 5), 189 (8), 177 (7), 151 ($[C_9H_{11}O_2]^+$, 100), 137 ($[C_8H_9O_2]^+$, 58).

(2*R*,3*R*)-2,3-Bis(4-hydroxy-3-methoxybenzyl)-1,4-butanediol (11): ^1H NMR (DMSO-d_6) δ 8.65 (2 H, s, 2 O$H_{phenolic}$, D_2O exchangeable), 6.64 (4 ArH, m), 6.51 (2 ArH, br d, $J =$ 7.9 Hz), 4.54 (2 H, br t, 2 CH_2-O*H*, D_2O exchangeable), 3.68 (6 H, s, 2 OCH_3), 3.38 (4 H, m), 2.51 (4 H, m), 1.82 (2 H, m); HRMS *m/z* calcd for $C_{20}H_{26}O_6$ (M^+) 362.1729, obsd 362.1722; EIMS *m/z* 362 (M^+, 30) 344 ($M - H_2O$, 7), 137 ($[C_8H_9O_2]^+$, 100). Anal. ($C_{20}H_{26}O_6 \cdot 0.5H_2O$) C, H.

(2*R*,3*R*)-2-(3′,4′-Dihydroxybenzyl)-3-(3″,4″-dimethoxybenzyl)-1,4-butanediol (13): ^1H NMR (DMSO-d_6) δ 8.65 (1 H, s, O$H_{phenolic}$, D_2O exchangeable), 8.57 (1 H, s, O$H_{phenolic}$, D_2O exchangeable), 6.82 (1 ArH, d, $J = 8.0$ Hz), 6.57−6.67 (4 ArH, m), 6.37 (1 ArH, br d, $J = 7.9$ hz), 4.54 (1 H, t, $J = 5$ Hz, CH_2O*H*, D_2O exchangeable), 4.50 (1 H, t, $J = 5$ Hz, CH_2O*H*, D_2O exchangeable), 3.71 (3 H, s, OCH_3), 3.69 (3 H, s, OCH_3), 3.35 (4 H, m), 2.50 (4 H, m), 1.82 (2 H, m); HRMS *m/z* calcd for $C_{20}H_{26}O_6$ (M^+) 362.1729, obsd 362.1720; EIMS *m/z* 362 (M^+, 24), 344 ($M - H_2O$, 5), 151 ($[C_9H_{11}O_2]^+$, 100), 123 ($[C_7H_7O_2]^+$, 20).

General Procedure for the Preparation of 3,4-Dibenzyltetrahydrofurans 14−16. (3*R*,4*R*)-3-(4′-Hydroxy-3′-methoxybenzyl)-4-(3″,4″-dimethoxybenzyl)tetrahydrofuran (15). Diol **12** (0.38 g, 1 mmol) and *p*-toluenesulfonic acid (0.01 g, 0.05 mmol) were dissolved in CH_2Cl_2 (10 mL) and refluxed for 24 h. The mixture was washed with a saturated solution of $NaHCO_3$, and the organic layer was evaporated. The residue was purified by column chromatography (silica gel, $CHCl_3$:cyclohexane, 80:20) to afford **15** as white crystals (0.24 g, 67%, mp 61−63 °C) from CH_3OH: ^1H NMR (DMSO-d_6) δ 8.71 (1 H, s, O*H*, D_2O exchangeable), 6.84 (1 ArH, d, $J =$ 8.0 Hz), 6.54−6.70 (5 ArH, m), 3.71 (9 H, br s, 3 OCH_3), 3.36 (2 H, m), 2.50 (6 H, m, overlapping), 2.12 (2 H, m); HRMS *m/z* calcd for $C_{21}H_{26}O_5$ (M^+) 358.1780, obsd 358.1783; EIMS *m/z* 358 (M^+, 80), 151 ($[C_9H_{11}O_2]^+$, 100), 137 ($[C_8H_9O_2]^+$, 66). Anal. ($C_{21}H_{26}O_5$) C, H.

(3*R*,4*R*)-3,4-Bis(4-hydroxy-3-methoxybenzyl)tetrahydrofuran (14): crystals from CH_3OH; mp 112−114 °C; ^1H

NMR (DMSO-d_6) δ 8.72 (2 H, s, O*H*, D_2O exchangeable), 6.51−6.67 (6 ArH, m), 3.74 (6 H, br s, 2 OCH_3), 3.38 (2 H, m), 2.43 (6 H, m, overlapping), 2.10 (2 H, m); HRMS *m*/*z* calcd for $C_{20}H_{24}O_5$ (M^+) 344.1624, obsd 344.1625; EIMS *m*/*z* 344 (M^+, 46), 137 ($[C_8H_9O_2]^+$, 100). Anal. ($C_{20}H_{24}O_5$) C, H.

(3*R*,4*R*)-3-(3′,4′-Dihydroxybenzyl)-4-(3″,4″-dimethoxybenzyl)tetrahydrofuran (16): ^{1}H NMR (DMSO-d_6) δ 8.73 (1 H, s, O*H*, D_2O exchangeable), 8.67 (1 H, s, O*H*, D_2O exchangeable), 6.84 (1 ArH, d, J = 8.0 hz), 6.61−6.70 (3 ArH, m), 6.54 (1 ArH, br s), 6.39 (1 ArH, br d, J = 7.8 Hz), 3.78 (6 H, br s, 2 OCH_3), 3.33 (2 H, m), 2.51−2.59 (6 H, m, overlapping), 2.05 (2 H, m); ^{13}C NMR (DMSO-d_6, 75.50 MHz) δ 73.28 (C-2), 46.37 (C-3), 46.37 (C-4), 73.29 (C-5), 38.77 (C-7′), 38.49 (C-7″), 132.72 (C-1′), 115.22 (C-2′), 142.35 (C-3′), 143.98 (C-4′), 115.61 (C-5′), 120.70 (C-6′), 132.91 (C-1″), 112.05 (C-2″), 147.38 (C-3″), 148.81 (C-4″), 111.38 (C-5″), 120.70 (C-6″); HRMS *m*/*z* calcd for $C_{20}H_{24}O_5$ (M^+) 344.1624, obsd 344.1625; EIMS *m*/*z* 344 ($C_{20}H_{24}O_5$, M^+, 43), 152 ($[C_9H_{12}O_2]^+$, 100), 151 ($[C_9H_{11}O_2]^+$, 94), 137 ($[C_8H_9O_2]^+$, 19), 124 ($[C_7H_8O_2]^+$, 29), 123 ($[C_7H_7O_2]^+$, 29), 121 (12), 107 (8), 85 (15), 83 (30), 77 (10).

General Procedure for the Preparation of *cis*-Cyclolignanolides 17−19. Isomerization of *trans*-cyclolignanolides to the *cis*-isomers was performed by modification of the method of Hartwell and Detty.[18a]

α-Peltatin-B (17). To a solution of **4** (414 mg, 1 mmol) in CH_3OH (10 mL) was added aqueous NH_3 (20%, 5 mL). The mixture was magnetically stirred and heated until NH_3 was evaporated. Cooling of the mixture to room temperature afforded **17** as crystals which were recrystallized from CH_3OH (364 mg, 91%, mp 267−268 °C): ^{1}H NMR (DMSO-d_6) δ 9.46 (1 H, OH, D_2O exchangeable), 8.26 (1 H, O*H*, D_2O exchangeable), 6.39 (2 ArH, s, H-2′, H-6′), 6.23 (1 ArH, s, H-8), 5.93 (1 H, s, OCH_2O), 5.92 (1 H, s, OCH_2O), 4.43 (1 H, dd, J = 9.0, 7.6 Hz), 4.15 (1 H, d, J = 3.0 Hz), 3.86 (1 H, dd, J = 9.0, 2.7 Hz), 3.68 (6 H, s, 2 OCH_3), 3.52 (1 H, dd, J = 9.5, 3.0 Hz), 3.02 (1 H, m), 2.54−2.62 (2 H, M, overlapping); HRMS *m*/*z* calcd for $C_{21}H_{20}O_8$ (M^+) 400.1158, obsd 400.1157; EIMS *m*/*z* 400 (M^+, 100), 355 (18), 328 (30), 285 (18), 246 (24), 139 (20), 115 (14), 77 (20). Anal. ($C_{21}H_{20}O_8$) C, H.

***β*-Peltatin-B (18):** crystals from CH_3OH; mp 203−205 °C; ^{1}H NMR (DMSO-d_6) δ 9.49 (1 H, s, O*H*, D_2O exchangeable), 6.45 (2 ArH, s, H-2′, H-6′), 6.24 (1 ArH, s, H-8), 5.93 (1 H, s, OCH_2O), 5.92 (1 H, s, OCH_2O), 4.43 (1 H, dd, J = 9.0, 7.5 Hz), 4.20 (1 H, d, J = 3.0 Hz), 3.88 (1 H, dd, J = 9.0, 2.7 Hz), 3.70 (6 H, s, 2 OCH_3), 3.63 (3 H, s, OCH_3), 3.54 (1 H, dd, J = 9.5, 3 Hz), 3.03 (1 H, m), 2.57 (2 H, m); HRMS *m*/*z* calcd for $C_{22}H_{22}O_8$ (M^+) 414.1315, obsd 414.1319; EIMS *m*/*z* 414 (M^+, 100), 383 (25), 369 (17), 355 (17), 339 (12), 299 (12), 246 (22). Anal. ($C_{22}H_{22}O_8$) C, H.

4′-*O*-Demethylpicropodophyllotoxin (19): crystals from CH_3OH; mp 233−234 °C; ^{1}H NMR (DMSO-d_6) δ 8.31 (1 H, s, O$H_{phenolic}$, D_2O exchangeable), 7.05 (1 ArH, s), 6.54 (2 ArH, s), 5.98 (1 ArH, s), 5.96 (1 H, s, O*H*, D_2O exchangeable), 5.92 (1 H, s, OCH_2O), 5.91 (1 H, s, OCH_2O), 4.50 (1 H, d, J = 8.5 Hz), 4.39 (2 H, m), 3.83 (1 H, d, J = 8 Hz), 3.73 (6 H, s, 2 OCH_3), 3.41 (1 H, dd, J = 9.4, 8.2 Hz), 2.50 (1 H, m); HRMS *m*/*z* calcd for $C_{21}H_{20}O_8$ (M^+) 400.1158, obsd 400.1153; EIMS *m*/*z* 400 (M^+, 23), 382 ($M - H_2O$, 45), 298 (100), 283 (63), 154 (40). Anal. ($C_{21}H_{20}O_8 \cdot 0.5H_2O$) C, H.

General Procedure for the Preparation of 2,3-Dibenzyl-4-hydroxy-*N*-benzylbutyramides 20 and 21. (2*R*,3*R*)-2-(4′-Hydroxy-3′-methoxybenzyl)-3-(3″,4″-dimethoxybenzyl)-4-hydroxy-*N*-benzylbutyramide (20). 2 (372 mg, 1 mmol) and benzylamine (130 mg, 1.2 mmol) were dissolved in CH_2Cl_2 (30 mL) and refluxed for 4 h. The mixture was washed with diluted HCl, and the organic layer was evaporated to dryness. The residue was crystallized from CH_3OH to afford **20** (380 mg, 79%, mp 132−134 °C): ^{1}H NMR ($CDCl_3$) δ 6.60−6.99 (11 ArH, m), 5.64 (2 H, O*H*, D_2O exchangeable, plus N*H*), 4.33 (2 H, d, J = 5.5 Hz), 4.13 (1 H, br s, O*H*, D_2O exchangeable), 4.00 (1 H, d, J = 11.8 Hz), 3.78 (3 H, s, OCH_3), 3.77 (6 H, s, 2 OCH_3), 3.57 (1 H, m), 3.05 (1 H, dd, J = 13, 10.5 Hz), 2.82 (2 H, m), 2.66 (1 H, dd, J = 14.0, 7.5 Hz), 2.48 (1 H, m), 2.04 (1 H, m); HRMS *m*/*z* calcd for $C_{28}H_{33}NO_6$ (M^+) 479.2308, obsd 479.2302; EIMS *m*/*z* 479 (M^+, 0.3), 461 ($M - H_2O$, 0.2), 372 ($M - C_6H_5CH_2NH_2$, 2), 285 (0.6), 195 (1), 178 (1), 151 ($[C_9H_{11}O_2]^+$, 2), 137 ($[C_8H_9O_2]^+$, 3), 106 (11). Anal. ($C_{28}H_{33}NO_6$) C, H, N.

(2*R*,3*R*)-2-(3′,4′-Dihydroxybenzyl)-3-(3″,4″-dimethoxybenzyl)-4-hydroxy-*N*-benzylbutyramide (21): crystals from CH_3OH; mp 93−95 °C; ^{1}H NMR (DMSO-d_6) δ 8.66 (2 H, br, 2 O$H_{phenolic}$, D_2O exchangeable), 8.16 (1 H, t, J = 6 Hz, NH), 6.39−7.26 (11 ArH, m), 4.40 (1 H, br s, O$H_{alcoholic}$, D_2O exchangeable), 4.26 (1 H, dd, J = 15.5, 6.0 Hz), 4.10 (1 H, dd, J = 15.5, 5.0 Hz), 3.71 (3 H, s, OCH_3), 3.70 (3 H, s, OCH_3), 3.37 (2 H, m), 2.69 (5 H, m), 1.88 (1 H, m); HRMS *m*/*z* calcd for $C_{27}H_{31}NO_6$ (M^+) 465.2151, obsd 465.2157; EIMS *m*/*z* 465 (M^+, 3), 447 ($M - H_2O$, 5), 388 ($M - C_6H_5$, 12), 358 ($M - C_6H_5CH_2NH_2$, 58), 177 (17), 151 ($[C_9H_{11}O_2]^+$ 100), 123 ($[C_7H_7O_2]^+$, 40), 107 (13). Anal. ($C_{27}H_{31}NO_6 \cdot 0.5H_2O$) C, H, N.

Methyl 3,4,5-Tris(benzyloxy)benzoate (24). Methyl 3,4,5-trihydroxybenzoate (18.4 g, 0.1 mol) was dissolved in methyl ethyl ketone (500 mL) and treated with powdered K_2CO_3 (100 g, 0.72 mol). Benzyl bromide (36 mL, 0.3 mol) was added dropwise, and the reaction mixture was stirred at reflux for 24 h. K_2CO_3 was removed by filtration and the filtrate evaporated to give the crude product which was purified by column chromatography (basic Al_2O_3, EtOAc). The eluate was concentrated and the product crystallized from EtOAc:*n*-hexane (1:1) to give **24** (42 g, 93%, mp 98 °C): ^{1}H NMR (acetone-d_6) δ 7.27−7.48 (15 ArH, m), 6.78 (2 H, s), 5.22 (4 H, s), 5.13 (2 H, s), 3.85 (3 H, s); HRMS *m*/*z* calcd for $C_{29}H_{26}O_5$ (M^+) 454.1780, obsd 454.1783. Anal. ($C_{29}H_{26}O_5$) C, H.

3,4,5-Tris(benzyloxy)benzyl Alcohol (25). A solution of methyl 3,4,5-tris(benzyloxy)benzoate (25 g, 0.055 mol) in dry THF (150 mL) was treated with $LiBH_4$ (6 g, 0.295 mol) and heated at reflux for 24 h. The reaction mixture was treated with HCl (10%), and the solvent was evaporated. The residue was partitioned between EtOAc (500 mL) and H_2O (500 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ solution. After evaporation of the solvent, **25** (21 g, 90%) was obtained as white crystals (mp 105 °C): ^{1}H NMR (DMSO-d_6) δ 7.27−7.48 (15 ArH, m), 6.78 (2 H, s), 5.10 (4 H, s), 4.92 (2 H, s), 4.42 (2 H, s), 3.36 (1 H, br s, O*H*); HRMS *m*/*z* calcd for $C_{28}H_{26}O_4$ (M^+) 426.1831, obsd 426.1834. Anal. ($C_{28}H_{26}O_4$) C, H.

General Procedure for the Preparation of (Benzyloxy)benzyl Bromides 26−29. 3-(Benzyloxy)benzyl Bromide (27). To a suspension of triphenylphosphine (8.2 g, 30.8 mmol) in acetonitrile (7 mL) maintained under argon in an ice bath was added dropwise bromine (1.6 mL, 30.8 mmol) over a period of 20 min. The ice bath was removed, and after the addition of dry pyridine (2.2 mL), a solution of 3-(benzyloxy)-benzyl alcohol (6 g, 28 mmol) in acetonitrile (10 mL) was added in one portion. The reaction mixture was heated to 50 °C for 30 min. The solvent was evaporated, and the resulting triphenylphosphine oxide was removed by column chromatography (silica gel, cyclohexane:EtOAc, 65:35). Evaporation of the eluate afforded (benzyloxy)benzyl bromide **27** as white crystals (4.1 g, 53%, mp 50 °C): ^{1}H NMR (CD_3OD) δ 6.90−7.44 (9 ArH, m), 5.07 (2 H, s, PhCH_2O), 4.51 (2 H, s, PhCH_2-Br); HRMS *m*/*z* calcd for $C_{14}H_{13}O^{79}Br$ (M^+) 276.0150, obsd 276.0147.

4-(Benzyloxy)benzyl bromide (26): mp 80 °C; ^{1}H NMR (DMSO-d_6) δ 6.98−7.44 (9 ArH, m), 5.11 (2 H, s, PhCH_2O), 4.70 (2 H, s, PhCH_2Br); HRMS *m*/*z* calcd for $C_{14}H_{13}O^{79}Br$ (M^+) 276.0150, obsd 276.0147.

4-(Benzyloxy)-3-methoxybenzyl bromide (28): mp 70 °C; ^{1}H NMR (acetone-d_6) δ 6.99−7.50 (8 ArH, m) 5.12 (2 H, s, PhCH_2O), 4.63 (2 H, s, PhCH_2Br), 3.83 (3 H, s, OCH_3); HRMS *m*/*z* calcd for $C_{15}H_{15}O_2{}^{79}Br$ (M^+) 306.0255, obsd 306.0258.

3,4,5-Tris(benzyloxy)benzyl bromide (29): mp 112 °C; ^{1}H NMR (acetone-d_6) δ 7.27−7.60 (15 ArH, m), 6.96 (2 H, s), 5.16 (4 H, s), 5.04 (2 H, s), 4.60 (2 H, s); HRMS *m*/*z* calcd for $C_{28}H_{25}O_3{}^{79}Br$ (M^+) 488.0987, obsd 488.0981. Anal. ($C_{28}H_{25}O_3$-Br) C, H.

General Procedure for the Preparation of [(Benzyloxy)benzyl]butyrolactone Dithianes 30−36. (±)-2-[3′-(Benzyloxy)benzyl]-3-[α,α-(1,3-dithiopropylene)-3″,4″-(methylenedioxy)benzyl]butyrolactone (36). To a stirred solution of **23** (2.4 g, 10 mmol) in dry THF (20 mL) maintained under argon at −78 °C was added a solution of *n*-butyllithium (6.25 mL, 10 mmol, 1.6 M) in *n*-hexane. The resulting solution

was stirred for 0.5 h, and a solution of 2-butenolide (0.71 mL, 10 mmol) dissolved in dry THF (2 mL) was added. The reaction mixture was stirred for a further 2.5 h at −78 °C and then treated dropwise with a solution of 3-(benzyloxy)benzyl bromide (2.8 g, 10 mmol) and HMPA (1.8 mL, 10 mmol) in dry THF (5 mL). The reaction mixture was allowed to warm to room temperature overnight, an then the reaction was quenched with water. The mixture was extracted with EtOAc, and the EtOAc, and the extracts were washed with water and dried over Na_2SO_4. Evaporation of the solvent left a gum which was purified by column chromatography (silica gel, cyclohexane−EtOAc, 95:5) to give **36** as crystals after crystallization from acetone−diisopropyl ether (3.0 g, 58%, mp 125 °C): ^{1}H NMR ($CDCl_3$) δ 6.63−7.46 (12 ArH, m), 6.00 (1 H, s, OCH_2O), 5.98 (1 H, s, OCH_2O), 5.00 (2 H, s, PhCH_2O), 4.58 (1 H, dd, J = 10.0, 5.0 Hz), 3.88 (1 H, dd, J = 10.0, 8.6 Hz), 3.14 (1 H, m), 2.95 (1 H, dd, J = 14.0, 6.0 Hz), 2.60−2.75 (6 H, m), 1.93 (2 H, m); HRMS m/z calcd for $C_{29}H_{28}O_5S_2$ (M^+) 520.1378, obsd 520.1375. Anal. ($C_{29}H_{28}O_5S_2$) C, H.

(±)-2-Benzyl-3-[α,α-(1,3-dithiopropylene)-3,4-dimethoxybenzyl]butyrolactone (30): crystals from acetone; mp 101 °C; ^{1}H NMR ($CDCl_3$) δ 7.49 (1 H, dd, J = 8.5, 2.3 Hz), 7.36 (1 H, d, J = 2.3 Hz), 7.21 (3 H, m), 6.95 (2 H, m), 6.87 (1 H, d, J = 8.5 Hz), 4.59 (1 H, dd, J = 10.0, 5.0 Hz), 3.93 (3 H, s, OCH_3), 3.87 (1 H, t, overlapping), 3.84 (3 H, s, OCH_3), 3.19 (1 H, m), 2.98 (1 H, dd, J = 14.0, 6.0 Hz), 2.61−2.74 (5 H, m), 2.53 (1 H, dd, J = 14.0, 6.0 Hz), 1.92 (2 H, m); HRMS m/z calcd for $C_{23}H_{26}O_4S_2$ (M^+) 430.1273, obsd 430.1272. Anal. ($C_{23}H_{26}O_4S_2$) C, H.

(±)-2-[4′-(Benzyloxy)benzyl]-3-[α,α-(1,3-dithiopropylene)-3″,4″-dimethoxybenzyl]butyrolactone (31): crystals from acetone; mp 68 °C; ^{1}H NMR ($CDCl_3$) δ 6.79−7.50 (12 ArH, m), 5.03 (2 H, s, PhCH_2O), 4.58 (1 H, dd, J = 10.0, 5.0 Hz), 3.92 (3 H, s, OCH_3), 3.87 (1 H, t, overlapping), 3.85 (3 H, s, OCH_3), 3.14 (1 H, m), 2.94 (1 H, dd, J = 14.0, 5.5 Hz), 2.62−2.75 (5 H, m), 2.44 (1 H, dd, J = 14.0, 5.5 Hz), 1.92 (2 H, m); HRMS m/z calcd for $C_{30}H_{32}O_5S_2$ (M^+) 536.1691, obsd 536.1696. Anal. ($C_{30}H_{32}O_5S_2$·0.5H_2O) C, H.

(±)-2-[3′,4′,5-Tris(benzyloxy)benzyl]-3-[α,α-(1,3-dithiopropylene)-3″,4″-dimethoxybenzyl]butyrolactone (33): ^{1}H NMR ($CDCl_3$) δ 7.24−7.45 (17 ArH, m), 6.83 (1 H, d, J = 8.5 Hz), 6.29 (2 H, s), 5.02 (6 H, s, 3 PhCH_2O), 4.53 (1 H, dd, J = 9.8, 5.4 Hz), 3.86 (3 H, s, OCH_3), 3.84 (3 H, s, OCH_3), 3.77 (1 H, t, J = 9.3 Hz), 3.13 (1 H, m), 2.93 (1 H, dd, J = 14.0, 5.0 Hz), 2.67 (5 H, m), 2.39 (1 H, dd, J = 14.0, 5.5 Hz), 1.93 (2 H, m); HRMS m/z calcd for $C_{44}H_{44}O_7S_2$ (M^+) 748.2528, obsd 748.2521. Anal. ($C_{44}H_{44}O_7S_2$) C, H.

(±)-2-Benzyl-3-[α,α-(1,3dithiopropylene)-3,4-(methylenedioxy)benzyl]butyrolactone (34): crystals from acetone; mp 178 °C; ^{1}H NMR ($CDCl_3$) δ 7.44 (1 H, dd, J = 8.2, 2.0 Hz), 7.36 (1 H, d, J = 2.0 Hz), 7.0−7.26 (5 ArH, m), 6.82 (1 H, d, J = 8.2 Hz), 6.02 (2 H, s, OCH_2O), 4.53 (1 H, dd, J = 10.0, 5.0 Hz), 3.82 (1 H, dd, J = 10.0, 9.0 Hz), 3.18 (1 H, m), 3.00 (1 H, dd, J = 14.0, 6.0 Hz), 2.61−2.72 (6 H, m), 1.93 (2 H, m); HRMS m/z calcd for $C_{22}H_{22}O_4S_2$ (M^+) 414.0960, obsd 414.0968. Anal. ($C_{22}H_{22}O_4S_2$) C, H.

(±)-2-[4′-(Benzyloxy)benzyl]-3-[α,α-(1,3-dithiopropylene)-3″,4″-(methylenedioxy)benzyl]butyrolactone (35): crystals froma acetone; mp 132 °C; ^{1}H NMR ($CDCl_3$) δ 6.87−7.43 (12 ArH, m), 6.01 (1 H, s, OCH_2O), 5.98 (1 H, s, OCH_2O), 5.02 (2 H, s, PhCH_2O), 4.56 (1 H, dd, J = 10.0, 5.0 Hz), 3.85 (1 H, t, J = 10.0 Hz), 3.11 (1 H, m), 2.92 (1 H, dd, J = 14.0, 6.0 Hz), 2.54−2.76 (6 H, m), 1.93 (2 H, m); HRMS m/z calcd for $C_{29}H_{28}O_5S_2$ (M^+) 520.1378, obsd 520.1372. Anal. ($C_{29}H_{28}O_5S_2$) C, H.

General Procedure for the Preparation of Hydroxylated *trans*-2,3-Dibenzylbutyrolactones 37−43. (±)-*trans*-2-(3′-Hydroxybenzyl)-3-[3″,4″-(methylenedioxy)benzyl]-butyrolactone (43). 36 (2.5 g, 4.8 mmol) was heated with a suspension of W-2 Raney nickel (25 g) in ethanol for 2 h. The catalyzator was removed by filtration and the solution evaporated to dryness. The crude product was purified by thin-layer chromatography (silica gel 60 PF_{254} with $CaSO_4$, CH_2Cl_2:cyclohexane:CH_3OH, 100:20:2) using the technique of radial development (Chromatotron) to give **43** as a gum (1.41 g, 90%): ^{1}H NMR ($CDCl_3$) δ 7.17 (1 H, t, J = 7.8 Hz), 6.47−6.75 (6 ArH, m), 5.93 (2 H, s, OCH_2O), 5.65 (1 H, s, OH), 4.10 (1 H, dd, J = 9.0, 7.0 Hz, H-4b), 3.85 (1 H, dd, J = 9.0, 7.5 Hz, H-4a), 3.01 (1 H, dd, J = 14.0, 5.0 Hz, H-7′b), 2.89 (1 H, dd, J = 14.0, 7.0 Hz, H-7′a) 2.58 (2 H, m, H-2, H-7″b), 2.47 (2 H, H-3, H-7″a); HRMS m/z calcd for $C_{19}H_{18}O_5$ (M^+) 326.1154, obsd 326.1158.

(±)-*trans*-2-Benzyl-3-(3,4-dimethoxybenzyl)butyrolactone (37): ^{1}H NMR ($CDCl_3$) δ 7.16−7.33 (5 ArH, m), 6.76 (1 H, d, J = 8.0 Hz, H-5″), 6.56 (1 H, dd, J = 8.0, 1.9 Hz, H-6″), 6.44 (1 H, d, J = 1.9 Hz, H-2″), 4.12 (1 H, dd, J = 9.2, 6.8 Hz, H-4b), 3.88 (1 H, m, overlapping, H-4a), 3.86 (3 H, s, OCH_3), 3.81 (3 H, s, OCH_3), 3.09 (1 H, dd, J = 14.0, 5.0 Hz, H-7′b), 2.94 (1 H, dd, J = 14.0, 7.0 Hz, H-7′a), 2.58 (2 H, H-2, H-7″b), 2.49 (2 H, m, H-3, H-7″a); HRMS m/z calcd for $C_{20}H_{22}O_4$ (M^+) 326.1518, obsd 326.1515.

(±)-*trans*-2-(4′-Hydroxybenzyl)-3-(3″,4″-dimethoxybenzyl)butyrolactone (38): ^{1}H NMR ($CDCl_3$) δ 7.01 (2 H, d, J = 8.5 Hz, H-2′, H-6′), 6.78 (1 H, d, J = 8.0 Hz, H-5″), 6.76 (2 H, d, J = 8.5 Hz, H-3′, H-5′), 6.58 (1 H, dd, J = 8.0, 1.9 Hz, H-6″), 6.46 (1 H, d, J = 1.9 Hz, H-2″), 5.22 (1 H, s, OH), 4.13 (1 H, dd, J = 9.0, 7.0 Hz, H-4b), 3.89 (1 H, m, overlapping, H-4a), 3.86 (3 H, s, OCH_3), 3.82 (3 H, s, OCH_3), 2.98 (1 H, dd, J = 14.0, 5.0 Hz, H-7′b), 2.86 (1 H, dd, J = 14.0, 7.0 Hz, H-7′a), 2.59 (2 H, m, H-2, H-7″b), 2.52 (2 H, m, H-3, H-7″a); HRMS m/z calcd for $C_{20}H_{22}O_5$ (M^+) 342.1467, obsd 342.1465.

(±)-*trans*-2-(3′-Hydroxybenzyl)-3-(3″,4″-dimethoxybenzyl)butyrolactone (39): ^{1}H NMR ($CDCl_3$) δ 7.14 (1 H, t, J = 8.0 Hz), 6.64−6.78 (4 ArH, m), 6.56 (1 H, dd, J = 8.0, 1.8 Hz, H-6″), 6.48 (1 H, d, J = 1.8 Hz, H-2″), 5.93 (1 H, s, OH), 4.14 (1 H, dd, J = 9.0, 7.0 Hz, H-4b), 3.88 (1 H, m, overlapping, H-4a), 3.85 (3 H, s, OCH_3), 3.82 (3 H, s, OCH_3), 2.99 (1 H, dd, J = 14.0, 5.0 Hz, H-7′b), 2.90 (1 H, dd, J = 14.0, 7.0 Hz, H-7′a), 2.60 (2 H, m, H-2, H-7″b), 2.50 (2 H, m, H-3, H-7″a); HRMS m/z calcd for $C_{20}H_{22}O_5$ (M^+) 342.1467, obsd 342.1465.

(±)-*trans*-2-(3′,4′,5′-Trihydroxybenzyl)-3-(3″,4″-dimethoxybenzyl)butyrolactone (40): ^{1}H NMR (DMSO-d_6) δ 8.74 (2 H, s, 2 OH), 6.95 (1 H, s, OH), 6.81 (1 H, d, J = 8.0 Hz, H-5″), 6.63 (1 H, br s, H-2″), 6.60 (1 H, d, J = 8.0 Hz, H-6″), 6.15 (2 H, br s, H-2′, H-6′), 4.00 (1 H, m, H-4b), 3.87 (1 H, m, H-4a), 3.72 (3 H, s, OCH_3), 3.70 (3 H, s, OCH_3), 2.66 (2 H, m, H-7′a, H-7′b), 2.55 (2 H, m, H-2, H-7″b), 2.41 (2 H, m, H-3, H-7″a); HRMS m/z calcd for $C_{20}H_{22}O_7$ (M^+) 374.1366, obsd 374.1362.

(±)-*trans*-2-Benzyl-3-[3,3-(methylendioxy)benzyl]butyrolactone (41): ^{1}H NMR ($CDCl_3$) δ 7.30−7.42 (5 ArH, m), 6.77 (1 H, d, J = 8.2 Hz, H-5″), 6.50 (2 ArH, m), 6.77 (1 H, d, J = 8.2 Hz, H-5″), 6.50 (2 ArH, m), 5.93 (2 H, s, OCH_2O), 4.09 (1 H, dd, J = 9.0, 6.85 Hz, H-4b), 3.92 (1 H, dd, J = 9.9, 7.3 Hz, H-4a), 3.20 (1 H, dd, J = 14.0, 5.0 Hz, H-7′b), 2.98 (1 H, dd, J = 14.0, 7.0 Hz, H-7′a), 2.57 (2 H, m, H-2, H-7″b), 2.43 (2 H, m, H-3, H-7″a); HRMS m/z calcd for $C_{19}H_{18}O_4$ (M^+) 310.1205, obsd 310.1205.

(±)-*trans*-2-(4′-Hydroxybenzyl)-3-[3″,4″-(methylendioxy)-benzyl]butyrolactone (42): ^{1}H NMR ($CDCl_3$) δ 7.04 (2 H, d, J = 8.4 Hz, H-2′, H-6′), 6.76 (2 H, d, J = 8.4 Hz, H-3′, H-5′), 6.72 (1 H, d, J = 8.3 Hz, H-5″), 6.48 (2 H, m), 5.94 (2 H, s, OCH_2O), 5.06 (1 H, s, OH), 4.09 (1 H, dd, J = 9.0, 7.0 Hz, H-4b), 3.85 (1 H, dd, J = 7.0 Hz, H-4a), 3.00 (1 H, dd, J = 14.0, 5.0 Hz, H-7′b), 2.89 (1 H, dd, J = 14.0, 7.0 Hz, H-7′a), 2.57 (2 H, m, H-2, H-7″b), 2.45 (2 H, m, H-3, H-7″a): HRMS m/z calcd for $C_{19}H_{18}O_5$ (M^+) 326.1154, obsd 326.1151.

(±)-2-[4′-(Benzyloxy)-3′-methoxybenzyl]-3-[α,α-(1,3-dithiopropylene)-3″,4″-dimethoxybenzyl]cyclopentanone (44). Dithiane **44** was prepared by the method described for compounds **30**−**36** using 2-cyclopentenone instead of 2-butenolide: HRMS m/z calcd for $C_{32}H_{36}O_5S_2$ (M^+) 564.2004, obsd 564.2007.

(±)-*trans*-2-(4′-Hydroxy-3′-methoxybenzyl)-3-(3″,4″-dimethoxybenzyl)cyclopentanone (45). 45 was prepared from **44** by the method described for compounds **37**−**43**: ^{1}H NMR (DMSO-d_6) δ 8.75 (1 H, s, OH, D_2O exchangeable), 6.53−6.84 (6 ArH, m), 3.69 (9 H, br s, 3 OCH_3), 2.76 (2 H, m), 2.67 (1 H, dd, J = 13.0, 4.0 Hz), 2.32 (2 H, m), 2.16 (1 H, m), 1.82−1.97 (3 H, m), 1.44 (1 H, m); ^{13}C NMR (DMSO-d_6, 75.50 MHz) δ 219.38 (C-1), 54.94 (C-2), 42.12 (C-3), 26.20 (C-4), 40.26 (C-5), 37.23 (C-7′), 32.99 (C-7″), 132.49 (C-1′), 112.60 (C-2′), 144.68 (C-3′), 146.97 (C-4′), 115.11 (C-5′), 121.35 (C-6′), 130.09 (C-1″), 113.24 (C-2″), 147.22 (C-3″), 148.41 (C-4″), 111.68 (C-5″), 120.55 (C-6″), 55.24 (OCH_3), 55.39 (OCH_3), 55.42 (OCH_3); HRMS m/z calcd for $C_{22}H_{26}O_5$ (M^+) 370.1780, obsd 370.1786.

(±)-*trans*-2-(3′,4′-Dihydroxybenzyl)-3-(3″,4″-dimethoxybenzyl)cyclopentanone (46). **45** (0.5 g, 1.35 mmol) in CH_2Cl_2 (20 mL) and $AlCl_3$ (0.2 g, 1.5 mmol) were suspended in a solution and then pyridine (0.6 mL, 7.5 mmol) was added dropwise. The mixture was refluxed for 24 h and then partitioned between diluted HCl and $CHCl_3$:CH_3OH, 90:10. The organic layer was dried over Na_2SO_4 and evaporated to dryness. The crude product was purified by column chromatography (silica gel, $CHCl_3$:CH_3OH, 90:10) to afford 20 mg of **46**, 60% yield: ^{1}H NMR (DMSO-d_6) δ 8.76 (1 H, s, O*H*, D_2O exchangeable), 8.67 (1 H, s, O*H*, D_2O exchangeable). 6.82 (1 H, D, J = 8.5 Hz), 6.59−6.67 (4 H, m), 6.41 (1 H, dd, J = 7.9, 1.9 Hz), 3.72 (6 H, s, 2 OCH_3), 2.76 (2 H, m), 2.29 (2 H, m), 1.76−2.01 (6 H, m); HRMS m/z calcd for $C_{21}H_{24}O_5$ (M^+) 356.1624, obsd 356.1631.

Supporting Information Available: Table of HRMS and HPLC data, table of elemental analyses, and additional biological data for compound **7** (no evidence for DNA binding) (3 pages). Ordering information can be found on any current masthead page.

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