5-Alkylresorcinols from *Hakea trifurcata* That Cleave DNA

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Abstract: A dichloromethane extract of *Hakea trifurcata* that mediated relaxation of ϕX174 replicative form DNA at micromolar concentrations in the presence of Cu^{2+} was resolved into six active components by bioassay-guided fractionation. Five of the active principles were characterized structurally and shown to be 5-alkylresorcinol derivatives. These included 1,3-dihydroxy-5-tridecylbenzene (**1**), 1,3-dihydroxy-5-(*cis*-8′-pentadecenyl)benzene (**2**), 1,3-dihydroxy-5-[14′-(3″,5″-dihydroxyphenyl)-*cis*-6′-tetradecenyl]benzene (**3**), 1,3-dihyroxy-5-[14′-(3″,5″-dihydroxyphenyl)tetradecyl]benzene (**4**), and 1,3-dihydroxy-5-[16′-(3″,5″-dihydroxyphenyl)-*cis*-8′-hexadecenyl]benzene (**5**). The structures of these five natural principles were confirmed by total synthesis; compounds **1**−**5** were accessible from 3,5-dimethoxybenzaldehyde in overall yields of 59%, 27%, 15%, 16%, and 13%, respectively.

The potential of natural products as therapeutic agents and as tools for the investigation of biological systems has long been recognized.[1] As physiological processes have become understood in greater detail at the cellular and biochemical levels, in parallel with the pathophysiology associated with certain diseases, strategies for the identification of biological and biochemical mediators have evolved in their sophistication and molecular focus.[2]

Given their abundance as constituents of plants, it is not surprising that phenolic and catecholic compounds are well represented among the natural products whose isolation has been reported,[3] or that they can exhibit potent biological activities such as the skin sensitization characteristic of poison oak and poison ivy,[4] as well as antiviral activity.[5] 1,3-Dihydroxy-5-alkylbenzenes, known as resorcinols, have also been isolated from many plants, including those in the Proteaceae, Anacardiaceae, Ginkogoaceae, and Graminae families.[6] The resorcinols have a wide variety of biological activities, including fungicidal and bacteriocidal activities against numerous pathogens.[7]

Recently, we reported the identification of several resorcinol derivatives from plants in the genus *Hakea*;[8,9] these were isolated by bioassay-guided fractionation of dichloromethane extracts on the basis of their ability to catalyze the relaxation of supercoiled, covalently closed, circular DNA in the presence of Cu(II) and O_2.[10] Although the molecular mechanism of DNA strand scission by these agents has not been reported, it has been shown that the resorcinol OH groups were essential for Cu(II)-mediated cleavage[11] and that poison oak urushiol (a mixture of 3-alk(en)ylcatechol derivatives) could cleave DNA at high concentrations in the presence of $CuCl_2$ and O_2.[12]

Presently, we provide a complete description of the isolation and structural characterization of five 5-alkylresorcinol derivatives from *Hakea trifurcata* (Figure 1). Also described is the chemical synthesis of each derivative, which facilitated a study of the mechanism of DNA strand scission by these compounds.[13]

Results and Discussion

A dichloromethane extract prepared by soaking the roots, twigs, and bark of the dried plant material from *H. trifurcata* was found to be capable of mediating the relaxation of ϕX174 replicative form DNA, a supercoiled, covalently closed, circular DNA, but only when the incubation was carried out in the presence of Cu^{2+}. This is shown in Figure 2, which illustrates that the relaxation of the supercoiled (form I) DNA afforded

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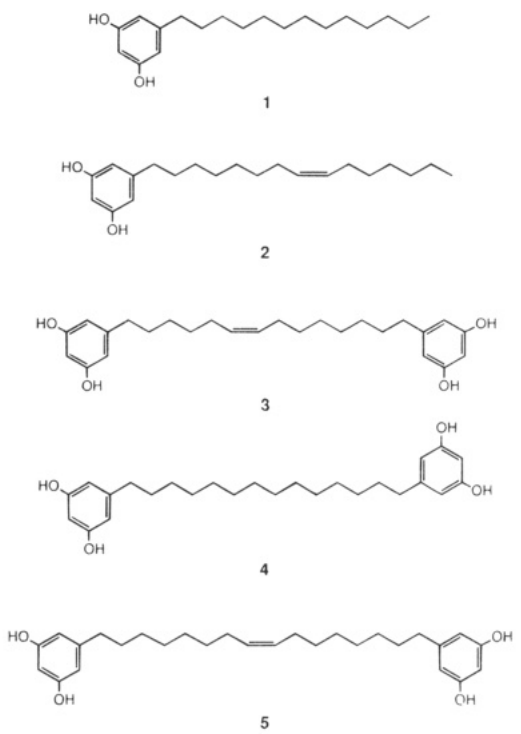

Figure 1. 5-Alkylresorcinol derivatives isolated from *Hakea trifurcata* by bioassay-guided fractionation.

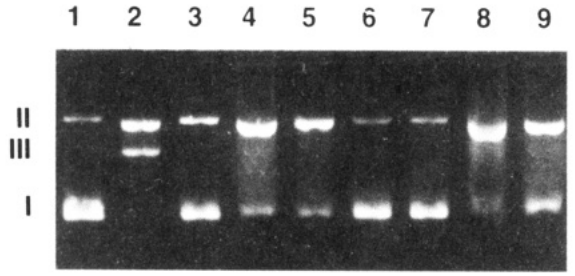

Figure 2. Strand scission of ϕX174 replicative form DNA. DNA samples (180 ng) in 40 μL of H_2O containing 3% dimethoxyethane were treated as indicated below, incubated at 25 °C for 30 min, and then analyzed on a 1.2% agarose gel (40 V, 18 h). Lane 1, DNA alone; lane 2, 10 μM Fe(II) + 0.1% H_2O_2; lane 3, 10 μM Cu(II); lane 4, 20 μg of a CH_2Cl_2 extract of *H. trifurcata* + 10 μM Cu(II); lane 5, 10 μg of extract + 10 μM Cu(II); lane 6, 20 μg of hexane layer + 10 μM Cu(II); lane 7, 10 μg of hexane layer + 10 μM Cu(II); lane 8, 20 μg of aqueous methanol layer + 10 μM Cu(II); lane 9, 10 μg of aqueous methanol layer + 10 μM Cu(II).

exclusively nicked circular (form II) DNA but no linear duplex (form III) DNA. Form III DNA can only be formed, of course, if nicks occur on both DNA strands in relatively close proximity. The absence of form III DNA in the experiment depicted in Figure 2, and also when the extract was employed at higher concentrations (data not shown), indicated that the active principle(s) present in this extract mediated only single-stranded DNA cleavage. Nonetheless, the potency of cleavage mediated by this crude extract was exceptional; the "smearing" of the DNA bands in the gel also suggested that the active principles might bind to DNA avidly. Accordingly, the extract was subjected to fractionation to permit isolation and characterization of the principle(s) responsible for DNA cleavage.

Isolation and Structure Determination. The dichloromethane extract of *H. trifurcata* was partitioned between 20% aqueous methanol and hexane. Bioassay of each of these fractions (Figure 2) indicated that most of the material capable of relaxing supercoiled DNA had partitioned into the aqueous methanol layer. Since only about 60% of the extract by weight was present in this phase, the partition seemed suitable for an initial fractionation step.

Chromatography of the material contained in the aqueous methanol layer was carried out by Sephadex LH-20 chromatography. Washing of the column was carried out with 1:1 $CH_3OH-CHCl_3$; the active fractions were readily detectable by bioassay for DNA relaxation activity (cf. Figure 2). However, in spite of the fact that less than 25% of the original mass of material remained in these active fractions, the partially purified active principle(s) were no more active on a weight basis than the original crude extract. This property of the extract became even more pronounced following fractionation on silica gel by flash chromatography, using 5% CH_3OH in $CHCl_3$ as the eluant. Typically, none of the fractions was active initially, although some activity became apparent when the fractions were reassayed after having been maintained in solution under ambient conditions for some time. It was found subsequently that incubation of the fractions in alkaline solution, especially in the presence of Cu^{2+}, prior to admixture of supercoiled DNA to the assay mixture greatly enhanced DNA cleavage. In addition to facilitating the identification of the active extracts, this observation provided an important mechanistic insight into the nature of DNA cleavage by the natural product(s).[13]

Flash chromatography afforded two active fractions, A and B, each of which constituted about 5% of the weight of the original extract and seemed homogeneous, as judged by silica gel TLC in each of several solvent systems. However, gas chromatographic assay of fraction A, which was the less polar fraction, indicated that it consisted of two components; these were separated and found to be quite similar chemically. On the basis of their chemical and spectral properties, we have previously identified these two species as the 5-alkylresorcinol derivatives 1,3-dihydroxy-5-tridecylbenzene (**1**)[9,14] and 1,3-dihydroxy-5-(*cis*-8′-pentadecenyl)benzene (**2**).[9,15]

Fraction B was thought to be homogeneous and was used in structure elucidation studies that led to the assignment of a structure to this active principle.[9a] Subsequently, fraction B was analyzed by C_{18} reversed-phase HPLC; elution with 3:1 methanol−water indicated that this fraction actually consisted of one major component, having a retention time of 28 min, and three minor components, with retention times of 36, 42, and 53 min (supporting information, Figure 1). These were separated by preparative reversed-phase HPLC; in order of elution, we obtained 2.8, 0.6, 0.8, and 1.4 mg of the four components. Each of these was shown to mediate DNA relaxation in the presence of Cu^{2+}.

The major component, which eluted from the HPLC after 28 min and was denoted **3**, was found to have M_r 412 by chemical ionization mass spectrometry. The ultraviolet spectrum, determined in aqueous solution, had λ_{max} at 280 (ϵ 3100) and 275 nm (ϵ 3000), which is characteristic of alkylresorcinols.[3a] The ^1H NMR spectrum of this compound was found to be quite similar to that of **2**,[16] with the exception that no high-field signal

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(15) This compound has been identified previously. See: (a) Morimoto, H.; Kawamatsu, Y.; Sugihara, H. *Chem. Pharm. Bull.* **1968**, *16*, 2282. (b) Tyman, J. H. P.; Tychopoulos, V.; Colenutt, B. A. *J. Chromatogr.* **1981**, *213*, 287.

(16) Compound **2**: ^1H NMR ($CDCl_3$) δ 0.88 (t, 3 H, J = 7 Hz), 1.30 (m, 16 H), 1.57 (m, 2 H), 2.02 (m, 4 H), 2.48 (t, 2 H, J = 7.5 Hz), 5.35 (m, 2 H), 6.17 (br s, 1 H), 6.24 (br s, 2 H). Compound **3**: ^1H NMR ($CDCl_3$) δ 1.24−1.39 (m, 12 H), 1.51−1.60 (m, 4 H), 1.95−2.06 (m, 4 H), 2.44 (t, 4 H, J = 7.5 Hz), 5.35 (t, 2 H, J = 4.5 Hz), 6.08 (d, 2 H, J = 1.5 Hz), 6.12 (d, 4 H, J = 1.5 Hz).

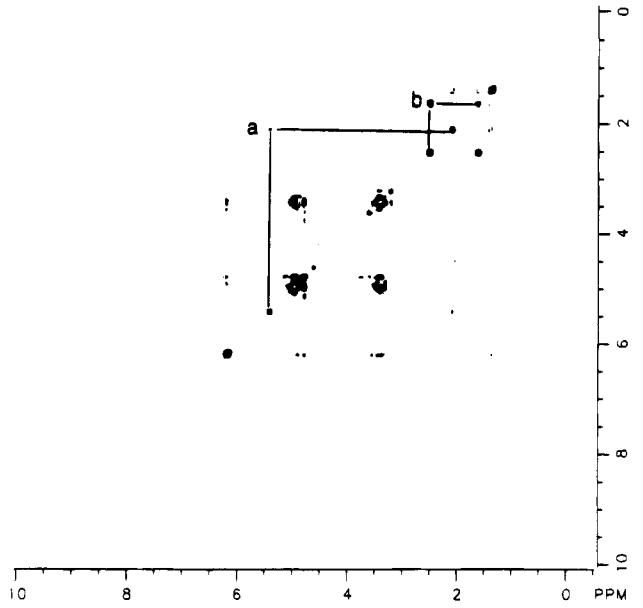


Figure 3. Contour plot of the COSY spectrum of **3** in deuteriomethanol. (a) Coupling of the vinyl protons to the allylic methylene protons. (b) Coupling of the benzylic protons to the homobenzylic protons.

corresponding to a terminal methyl group was present. The UV and NMR spectra alone made it clear that **3** was likely also a 5-alkylresorcinol having a structure similar to that of **2**.

In this regard, a detailed comparison of the ^{1}H NMR spectra of **2** and **3** proved quite illuminating. In particular, the relative intensities of the benzylic and homobenzylic protons in **3** were twice that of the olefinic protons; in **2** the intensities of these signals were equal. This suggested that **3** contained two aromatic moieties for each olefin. A possible structure for **3**, consistent with the absence of a methyl group noted above, was a bis-resorcinol analogue of **2**. In fact, **3** formed a tetra-*O*-acetate upon treatment with acetic anhydride in pyridine (*m/z* 580, chemical ionization mass spectrometry).

The tentative assignment of **3** as a bis-resorcinol derivative was verified by obtaining a homonuclear 2D correlation spectrum (COSY) (Figure 3). The COSY spectrum of **3** was acquired in deuteriomethanol at 361.1 MHz, with a sweep width of 3816.8 Hz. This revealed that the vinyl protons (δ 5.33) were coupled to the allylic methylene groups (δ 2.01) on either side of the olefin and that the allylic groups were further coupled to aliphatic multiplets. Thus, the vinyl protons were attached to an isolated, nonconjugated double bond. Also evident from the COSY spectrum was the coupling of the benzylic triplet (δ 2.44) to a broad multiplet (δ 1.50−1.53) that can be assigned as the homobenzylic protons. Thus, the double bond had to be at least three carbon atoms removed from either resorcinol moiety in order to maintain the aliphatic nature of the homobenzylic protons. The COSY spectrum served to confirm the structure of **3** as a bis(3,5-dihydroxyphenyl)alkene; the molecular weight, determined by mass spectrometry, indicated that the alkene must have a chain length of 14 carbon atoms. Although the exact position of the double bond could not be determined on the basis of the foregoing data, the configuration of the alkene appeared to be *Z*, as evidenced by an olefinic coupling constant of 4.5 Hz.

The exact position of the double bond was established by ozonolysis of the tetra-*O*-acetate of **3**. Following treatment with O_3 in CS_2 at −78 °C, the crude aldehydic product mixture was analyzed by chemical ionization mass spectrometry as described.[17] The mass spectrum so obtained contained strong peaks for aldehydes having M_r values of 320 and 292, thus indicating that oxidative cleavage had occurred between carbons 6 and 7 of the 14-carbon chain. Accordingly, **3** was assigned as 1,3-dihydroxy-5-[14′-(3″,5″-dihydroxyphenyl)-*cis*-6′-tetradecenyl]benzene.[9a,15a] Not surprisingly, given that compound **3** was the major constituent of fraction B, this is the structure originally assigned to fraction B when it was believed to be a single compound.[9a]

The component of fraction B that eluted from the reversed-phase HPLC column at 42 min (supporting information, Figure 1) was denoted **4**. The spectral characteristics of this compound were very similar to those of **3**; these included an ultraviolet spectrum with maxima at 281 and 275 nm. The chemical ionization mass spectrum indicated that the compound had M_r 414, suggesting that it might simply be the saturated analogue of **3**. The ^{1}H NMR spectrum of **4** supported this assignment; it was most similar to that of **3** in that it contained resonances corresponding to aromatic, benzylic, and homobenzylic H's in the same apparent ratio.[18] Also consistent with the proposed structure, the ^{1}H NMR spectrum of **4** lacked the resonances corresponding to olefinic and allylic protons.

The component of fraction B that eluted from reversed-phase HPLC at 53 min (denoted **5**) had M_r 440 and a UV spectrum characteristic of alkyl resorcinols (λ_{max} 281 and 275 nm). To minimize the decomposition that had been noted when the other analogues were handled on a small scale, **5** was converted to its tetra-*O*-acetate by treatment with acetic anhydride in pyridine. The ^{1}H NMR spectrum of the tetra-*O*-acetate indicated the presence of a bis-resorcinol structure.[19] However, both the ^{1}H NMR and mass spectral data suggested that the resorcinol moieties were linked by a 16-carbon chain containing a single double bond. The position of the double bond was again established by ozonolysis and subsequent mass spectrometric analysis of the reaction mixture.[17] A single peak was observed for the formed aldehydes corresponding to M_r 320. This indicated that the olefin in **5** was located between carbon atoms 8 and 9 in the 16-carbon chain; the symmetry of this structure is consistent with the observation of a single aldehyde upon ozonolysis.

The remaining component of fraction B, which eluted from the reversed-phase HPLC after 36 min, was analyzed utilizing the same strategies employed for **1**−**5**. In fact, this compound had the same UV spectrum (λ_{max} 282 and 276 nm) as the other compounds studied. The ^{1}H NMR spectrum of this compound was also similar to those of the other bis-resorcinol derivatives, although a more complicated olefinic region suggested the presence of additional unsaturation.[20] Although mass spectrometric analysis permitted the determination of M_r 438, consistent with a bis-resorcinol linked by a 16-carbon chain containing two olefins, attempts to acetylate the small sample available resulted only in extensive decomposition such that it has not been possible to determine the exact positions of unsaturation.

Synthesis of Resorcinol Derivatives 1−5. The structures assigned to **1**−**5** were confirmed by their total synthesis, which

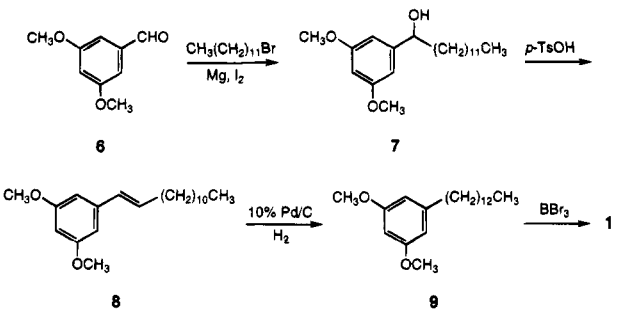
(17) Barr, J. R.; Scannell, R. T.; Yamaguchi, K. *J. Org. Chem.* **1989**, *54*, 494.

(18) Due to the small quantitites of compound, it was not possible to obtain an accurate integration for this sample. Compound **4**: ^{1}H NMR ($CDCl_3$) δ 1.25 (m, aliphatic protons), 1.54 (m, homobenzylic protons), 2.42 (t, J = 7.5 Hz, benzylic protons), 6.05 (br s, aromatic protons), 6.12 (br s, aromatic protons).

(19) Tetra-*O*-acetate of compound **5**: ^{1}H NMR ($CDCl_3$) δ 1.35 (m, 16 H), 1.65 (m, 4 H), 2.00 (m, 4 H), 2.20 (s, 12 H), 2.53 (t, 4 H, J = 7 Hz), 5.38 (t, 2 H, J = 5 Hz), 6.75 (d, 2 H, J = 1.5 Hz), 6.84 (d, 4 H, J = 1.5 Hz).

(20) Due to the small quantities of the compound, it was not possible to obtain an accurate integration for this sample: ^{1}H NMR ($CDCl_3$) δ 1.44 (m, aliphatic protons), 1.68 (m, homobenzylic protons), 2.18 (m, allylic methylene), 2.55 (m, benzylic protons), 2.89 (t, J = 2.0 Hz), 3.54 (br s, phenolic protons), 6.19 (br s, aromatic protons), 6.25 (br s, aromatic protons).

Scheme 1



permitted direct comparison of the naturally derived and synthetic materials.

Compound **1** was prepared starting from commercially available 3,5-dimethoxybenzaldehyde (**6**), as outlined in Scheme 1. Dodecylmagnesium bromide, prepared *in situ*, effected the conversion of **6** to secondary alcohol **7** in 90% yield; heating **7** in benzene in the presence of *p*-toluenesulfonic acid effected its dehydration to provide *trans*-alkene **8** in high yield. Catalytic hydrogenation over 10% palladium-on-carbon converted olefin **8** to saturated dimethoxyresorcinol derivative **9**; the latter was obtained as colorless needles in 89% yield from **8**. The methoxyl protecting groups were then removed via the agency of BBr_3 in CH_2Cl_2, affording resorcinol derivative **1** as colorless microcrystals from hexanes. The overall yield of **1** was 59% for four steps.

Resorcinol derivative **2** was also prepared starting from **6** (Scheme 2). Treatment of **6** with *n*-hexylmagnesium bromide in dry ether afforded secondary alcohol **10** in essentially quantitative yield; dehydration in the presence of *p*-toluenesulfonic acid then afforded conjugated olefin **11**. Alkene **11** was isomerized and oxidized to primary alcohol **12** in 65% yield using a modification of a published procedure[21] to facilitate the rearrangement of a conjugated alkene having a long aliphatic substituent. The borane alkene complex was prepared using boron trifluoride etherate and then isomerized thermally to the borane complex of the terminal alkene, after which treatment with basic H_2O_2 afforded the primary alcohol. Primary alcohol **12** was treated with triphenylphosphine and bromine[22] in an effort to obtain the corresponding bromide. However, this procedure produced di- and tribrominated products bearing halogen on the aromatic nucleus in addition to the primary carbon. The desired primary bromide was prepared successfully at low temperature by using the milder triphenylphosphine–*N*-bromosuccinimide procedure.[23] The remainder of the carbon skeleton was introduced by the alkylation of 1-octyne with bromide **13**, using *n*-butyllithium as the base;[24] 1,3-dimethoxy-5-(8′-pentadecynyl)benzene (**14**) was obtained as a colorless oil in 88% yield. The synthesis of alkylresorcinol derivative **2** was then completed by partial hydrogenation of **14** over 5% palladium-on-calcium carbonate in the presence of quinoline to afford *cis*-alkene **15**.[25] Initial efforts to effect the deprotection of **15** with BBr_3 gave low yields, apparently due to reaction of BBr_3 with the alkene moiety. Therefore, **15** was deprotected using freshly prepared methylmagnesium iodide at 165 °C in the absence of solvent.[26] This procedure afforded **2** as colorless microcrystals in 92% yield following chromatographic purification.

Bis-resorcinol derivatives **3**–**5** were also prepared starting from **6** (Schemes 3–5). Analogous to the initial steps used for the syntheses of **1** and **2**, **6** was treated with *n*-butylmagnesium bromide, and the derived secondary alcohol **16** was dehydrated using *p*-toluenesulfonic acid; the overall yield for both steps was 89%. *trans*-Olefin **17** was converted to primary alcohol **18** in analogy with the conversion **11** → **12**, albeit in somewhat better (78%) yield. Conversion to primary bromide **19** was also carried out using triphenylphosphine–*N*-bromosuccinimide at low temperature. Treatment of bromide **19** with lithium acetylide–ethylenediamine complex at room temperature[27] for 12 h afforded a mixture of the desired alkyne **20** and the isomeric 2-alkyne which could not be separated. The intended transformation was accomplished successfully by carrying the reaction out initially at 10–15 °C and then at room temperature for 1.5 h.[28] Alkyne **20** was obtained as a colorless oil in essentially quantitative yield. The alkyne was then converted to the respective anion with *n*-butyllithium and alkylated with bromide **13** in HMPA,[29] affording the desired product **21** in 53% yield. Completion of the synthesis of **3** was then accomplished by partial hydrogenation of **21** over 5% palladium-on-calcium carbonate in the presence of quinoline and deblocking of *cis*-olefin **22** using freshly prepared methylmagnesium iodide. Bis-resorcinol derivative **3** was obtained as colorless microcrystals, mp 102 °C.

Intermediate **21** was also used for the preparation of bis-resorcinol derivative **4** (Scheme 4). Hydrogenation of the alkyne over 10% palladium-on-carbon in ethyl acetate afforded the fully saturated congener **23** in excellent yield. Demethylation using methylmagnesium iodide at high temperature gave the desired alkylresorcinol derivative **4**. Following chromatographic purification, **4** was isolated as colorless microcrystals.

The final compound, bis-resorcinol **5**, was synthesized as shown in Scheme 5, using intermediates employed for the syntheses of **2** and **3**. Thus, key intermediate **13** was added slowly to a solution containing lithium acetylide–ethylenediamine complex at 10–15 °C; after 20 min, the reaction mixture was allowed to return to room temperature and was stirred at 25 °C for 1.5 h. This procedure afforded alkyne **24** in 89% yield. Alkylation of the anion of **24** with bromide **13** afforded the protected bis-resorcinol intermediate **25**, in analogy with the conversion **20** → **21**. Partial hydrogenation of **25** using Lindlar catalyst provided the requisite *cis*-alkene **26** in 96% yield. Final deprotection of **26** to afford **5** was also accomplished using methylmagnesium iodide at high temperature. In common with **1**–**4**, bis-resorcinol derivative **5** was also isolated as colorless microcrystals.

All of the synthetic intermediates and final products were characterized spectroscopically and by either combustion analysis or high-resolution mass spectrometry. In addition to the identity of their spectral and physical properties with those of the respective natural products, synthetic compounds **1**–**5** were

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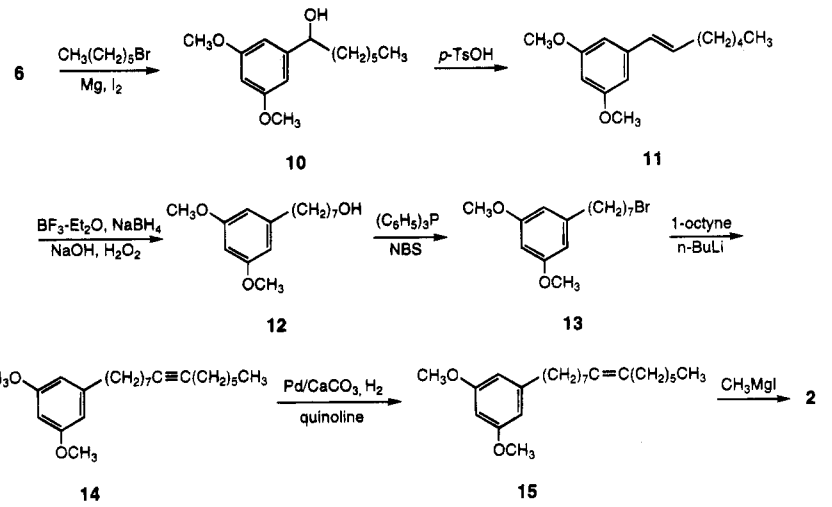
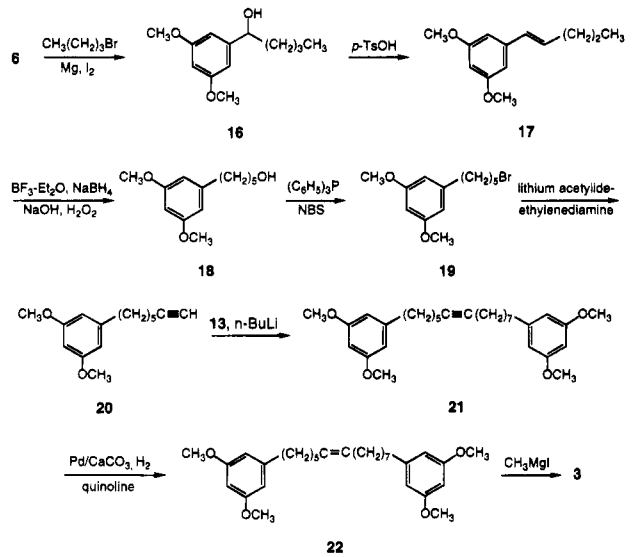
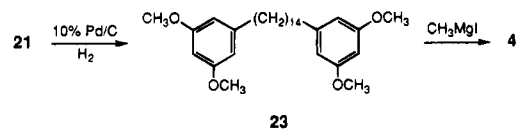
Scheme 2



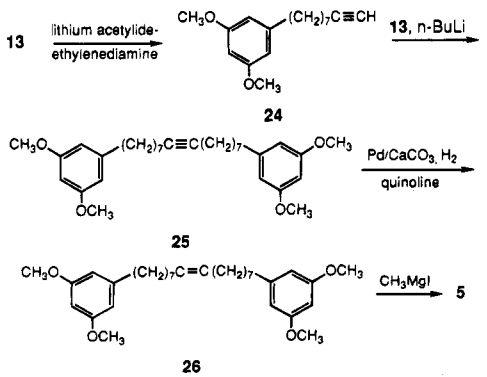
Scheme 3



Scheme 4



Scheme 5



also shown to mediate relaxation of supercoiled DNA in the presence of Cu^{2+}. Representative examples illustrating the extent of cleavage under specific conditions are presented in the following paper in this issue.[13a]

Experimental Section

General Methods. The organic chemical intermediates, reagents, and catalysts used for the synthesis of **1**–**5** were purchased from Aldrich Chemicals, as were all deuterated NMR solvents. The only exception was 3,5-dimethoxybenzaldehyde, which was obtained from Lancaster Synthesis. Sephadex LH-20 was purchased from Sigma Chemicals; ϕX174 replicative form DNA and agarose were from Bethesda Research Laboratories. All solvents were distilled prior to use; diglyme was distilled from calcium hydride. HPLC separations employed a 10-μm Alltech C_{18} reversed-phase column (25 cm × 1.0 cm). Gas chromatographic separations were performed on a Varian Model 3400 gas chromatograph with a J&W Scientific 0.25-μm coated DB1 column (30 m × 0.25 mm), using helium as the carrier gas at a flow rate of 4 mL/min and flame ionization detection. Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. High-field NMR experiments were recorded at 360 MHz on a Nicolet NTC 360 FT-NMR spectrometer or on a GE QE-300 NMR spectrometer. Chemical shift values are expressed relative to added tetramethylsilane. Low-resolution chemical ionization and electron impact mass spectra were recorded on a Finnigan MAT 4600 gas chromatograph/mass spectrometer using a direct exposure probe. Methane was employed as a reagent gas with a source pressure of 0.35 Torr and an electron energy of 100 eV. High-resolution mass spectra were recorded on a VG ZAB-SE mass spectrometer. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA. Ozone was generated using a Welsbach ozonizer.

Isolation of Active Principles. *H. trifurcata* was collected in Western Australia, and a dichloromethane extract was prepared from the roots, twigs, and bark of the dried plant material. The extract was partitioned between aqueous methanol and hexane. The active material in the aqueous methanol layer was then fractionated by successive chromatographies on Sephadex LH-20 and silica gel columns. Because these procedures effected only partial separation of multiple active principles, individual active fractions were fractionated further by either gas chromatography or reversed-phase HPLC. The entire fractionation procedure was guided by a bioassay, in which individual fractions were assayed for their ability to relax supercoiled ϕX174 replicative form DNA.[10]

In a typical series of experiments, 620 mg of extract was dissolved in 80 mL of methanol and treated with 20 mL of water. The resulting dark red solution was extracted with three 100-mL portions of *n*-hexane, and the aqueous methanol phase was concentrated under diminished pressure and then lyophilized. The residue (390 mg) was dissolved in 5 mL of 1:1 methanol–chloroform and applied to a Sephadex LH-20 column (167 cm × 2.2 cm). The column was eluted with 1:1 methanol–chloroform, and the active fractions were combined and concentrated (150 mg). This material was purified further by flash chromatography on a silica gel column (12 cm × 1.5 cm), using 5% methanol in chloroform as the eluant. This procedure afforded two active fractions, denoted A (32 mg) and B (33.5 mg).

Fraction A was purified by gas chromatography on a 0.25-μm coated DB1 column with a temperature program of 70 → 310 °C at a 10 °C/min gradient rate, using He gas at a flow rate of 4 mL/min. Compounds **1** and **2** were isolated, having retention times of 21.0 and 23.0 min, respectively.

Fraction B was purified by reversed-phase HPLC using a 10-μm Alltech C_{18} column (25 cm × 1.0 cm). The column was eluted with 3:1 methanol−water at a flow rate of 1.5 mL/min. Four pure compounds were isolated with retention times of 28, 36, 42, and 53 min in yields of 2.8, 0.6, 0.8, and 1.4 mg, respectively. Three of these compounds (having retention times of 28, 42, and 53 min) were characterized structurally as resorcinol derivatives **3**−**5**, respectively.

DNA Relaxation Assay. In a typical experiment, the extract/fraction was employed in five different amounts (40, 20, 10, 4, and 2 μg), each of which was dissolved in 10 μL of 3.3% dimethoxyethane in water and added to the reaction mixture. The reaction mixture contained 50 μL (total volume) of 25 mM sodium cacodylate, pH 7.4, 175 ng of ϕX174 replicative form DNA, 16 μM $CuCl_2$, and 12 μM 2-mercaptoethanol. The reaction mixture was maintained at 25 °C for 30 min and then treated with 50 μL of loading buffer (40 mM Tris−OAc, pH 7.8, containing 5 mM EDTA, 40% glycerol, 0.4% sodium dodecyl sulfate, and 0.3% bromophenol blue), maintained on ice for 2 min, centrifuged, and applied to a 1.2% agarose slab gel. Horizontal gel electrophoresis was carried out at 40 V for 14.5 h in 300 mL of 40 mM Tris−OAc, pH 7.8, containing 300 μg of ethidium bromide.

Synthesis of Compounds 1−5. The procedures for the syntheses of **2** and **3** are given below. Those for **1**, **4**, and **5** are included with the supporting information for this article.

1,3-Dimethoxy-5-(1′-hydroxyheptyl)benzene (10). An anhydrous solution of 100 mL of ether under argon containing 2.76 g (114 mmol) of magnesium turnings and approximately 10% of a solution of 19.5 g (115 mmol) of 1-bromohexane in 100 mL of dry ether was treated with a small crystal of iodine and two drops of 1,2-dibromoethane. The reaction mixture was warmed to initiate the reaction, and then the remainder of the 1-bromohexane was added at a rate that maintained solvent reflux. The reaction mixture was stirred under reflux for an additional 1 h and then treated dropwise at room temperature with a solution containing 12.0 g (72 mmol) of 3,5-dimethoxybenzaldehyde (**6**) in 80 mL of dry ether. The reaction mixture was heated at reflux for an additional 4 h, and then the cooled reaction mixture was treated cautiously with 15 mL of water and 75 mL of 2.8 N HCl. The layers were separated, and the aqueous layer was extracted with three 60-mL portions of ether. The combined organic extract was washed with two 90-mL portions of water and then with 90 mL of brine. The dried ($MgSO_4$) organic phase was concentrated under diminished pressure, and the residue was purified by flash chromatography on a silica gel column (35 cm × 4 cm). Elution with 10:1 and then 4:1 hexanes−ethyl acetate provided 1,3-dimethoxy-5-(1′-hydroxyheptyl)benzene (**10**) as a colorless oil: yield 17.9 g (98%); silica gel TLC R_f 0.40 (4:1 hexanes−ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 0.87 (t, 3 H, J = 7 Hz), 1.21−1.32 (m, 8 H), 1.58−1.76 (m, 2 H), 2.43 (s, 1 H, ex D_2O), 3.77 (s, 6 H), 4.52 (t, 1 H, J = 7 Hz), 6.35 (t, 1 H, J = 2 Hz), 6.49 (d, 2 H, J = 2 Hz); ^{13}C NMR ($CDCl_3$) δ 14.48, 23.04, 26.23, 29.65, 32.21, 39.45, 55.70, 75.10, 99.65, 104.24, 148.18, 161.17; mass spectrum (chemical ionization) m/z 253 $(M + 1)^+$ and 235; mass spectrum (electron impact) m/z 252.174 $(M)^+$ ($C_{15}H_{24}O_3$ requires 252.173).

1,3-Dimethoxy-5-(*trans*-1′-heptenyl)benzene (11). A solution containing 18.8 g (74.5 mmol) of 1,3-dimethoxy-5-(1′-hydroxyheptyl)-benzene (**10**) and 0.80 g (4.2 mmol) of *p*-toluenesulfonic acid monohydrate in 650 mL of toluene was heated at reflux for 20 h in an apparatus fitted with a Dean−Stark trap. The cooled reaction mixture was washed successively with 150 mL of saturated sodium bicarbonate solution, 150 mL of water, and 150 mL of brine. The organic phase was dried (Na_2SO_4), and the solution was concentrated under diminished pressure. The pale yellow oily residue was purified by flash chromatography on a silica gel column (35 cm × 4 cm). Elution with 30:1 hexanes−ethyl acetate provided 1,3-dimethoxy-5-(*trans*-1′-heptenyl)-benzene (**11**) as a colorless oil: yield 14.9 g (85%); silica gel TLC R_f 0.45 (10:1 hexanes−ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 0.92 (t, 3 H, J = 7 Hz), 1.27−1.40 (m, 4 H), 1.43−1.55 (m, 2 H), 2.20 (q, 2 H, J = 7 Hz), 3.79 (s, 6 H), 6.18−6.32 (m, 2 H), 6.35 (t, 1 H, J = 2 Hz), 6.51 (d, 2 H, J = 2 Hz); ^{13}C NMR ($CDCl_3$) δ 14.51, 23.02, 29.47, 31.91, 33.39, 55.70, 99.56, 104.46, 130.13, 132.25, 140.47, 161.33; mass spectrum (chemical ionization) m/z 235 $(M + 1)^+$; mass spectrum (electron impact) m/z 234.162 $(M)^+$ ($C_{15}H_{22}O_2$ requires 234.162).

1,3-Dimethoxy-5-(7′-hydroxyheptyl)benzene (12). To a solution containing 8.73 g (37.2 mmol) of 1,3-dimethoxy-5-(*trans*-1′-heptenyl)-benzene (**11**) and 0.67 g (13.2 mmol) of sodium borohydride in 75 mL of dry diglyme under N_2 was added 3.3 mL (26.6 mmol) of boron trifluoride etherate. The reaction mixture was stirred at 25 °C for 1 h and then quickly heated to reflux at 160−165 °C for 2.5 h. The cooled reaction mixture was quenched by the addition of 20 mL of water. Aqueous sodium hydroxide solution (5 M, 27 mL) was added, followed by 27 mL of 30% H_2O_2. Stirring was continued at room temperature for 1.5 h. The reaction mixture was treated with 80 mL of ice water and then extracted with three 80-mL portions of ether. The combined organic extract was washed with 80 mL of water and then with 80 mL of brine. The dried ($MgSO_4$) organic phase was concentrated under diminished pressure, and the residue was purified by flash chromatography on a silica gel column (30 cm × 4 cm). Elution with 5:1 and then 3:1 hexanes−ethyl acetate provided 1,3-dimethoxy-5-(7′-hydroxyheptyl)benzene (**12**) as a colorless oil: yield 6.14 g (65%); silica gel TLC R_f 0.35 (3:1 hexanes−ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 1.38−1.48 (m, 6 H), 1.50−1.76 (m, 4 H), 1.82 (br, 1 H, ex D_2O), 2.54 (t, 2 H, J = 7.5 Hz), 3.63 (t, 2 H, J = 7 Hz), 3.77 (s, 6 H), 6.29 (d, 1 H, J = 2 Hz), 6.34 (d, 2 H, J = 2 Hz); ^{13}C NMR ($CDCl_3$) δ 26.12, 29.71, 31.61, 33.17, 36.69, 55.63, 63.31, 97.99, 106.92, 145.69, 161.10; mass spectrum (chemical ionization) m/z 253 $(M + 1)^+$; mass spectrum (electron impact) m/z 252.174 $(M)^+$ ($C_{15}H_{24}O_3$ requires 252.173).

5-(7′-Bromoheptyl)-1,3-dimethoxybenzene (13). A solution containing 6.0 g (23.7 mmol) of 1,3-dimethoxy-5-(7′-hydroxyheptyl)-benzene (**12**) and 6.7 g (25.5 mmol) of triphenylphosphine in 60 mL of DMF and 20 mL of CH_2Cl_2 under N_2 was stirred at 25 °C for 10 min and then cooled to −70 °C. A solution of *N*-bromosuccinimide (4.54 g, 25.5 mmol) in 45 mL of DMF was added dropwise over a period of 2 h. The reaction mixture was allowed to warm to 25 °C and was stirred at 25 °C for an additional 1 h. The reaction mixture was then treated with 250 mL of water and 200 mL of saturated $NaHCO_3$ and then extracted with three 200-mL portions of ether. The combined organic extract was washed with 150 mL of water and then with 150 mL of brine. The dried ($MgSO_4$) organic phase was concentrated under diminished pressure, and the residue was triturated with three 100-mL portions of hexanes containing 5% ethyl acetate. The hexanes extract was concentrated, and the oily residue was purified by flash chromatography on a silica gel column (30 cm × 4 cm). Elution with 80:1 hexanes−ethyl acetate gave 5-(7′-bromoheptyl)-1,3-dimethoxybenzene (**13**) as a colorless oil: yield 5.16 g (70%); silica gel TLC R_f 0.50 (10:1 hexanes−ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 1.30−1.50 (m, 6 H), 1.56−1.68 (m, 2 H), 1.80−1.92 (m, 2 H), 2.55 (t, 2 H, J = 7.5 Hz), 3.41 (t, 2 H, J = 7 Hz), 3.78 (s, 6 H), 6.29 (d, 1 H, J = 2 Hz), 6.33 (d, 2 H, J = 2 Hz); ^{13}C NMR ($CDCl_3$) δ 28.54, 29.08, 29.53, 31.58, 33.25, 34.42, 36.68, 55.66, 98.02, 106.02, 145.59, 161.15; mass spectrum (chemical ionization) m/z 314 $(M)^+$. Anal. Calcd for $C_{15}H_{23}BrO_2$: C, 57.15; H, 7.35; Br, 25.35. Found: C, 57.02; H, 7.28; Br, 25.12.

1,3-Dimethoxy-5-(8′-pentadecynyl)benzene (14). To a stirred solution of 0.2 mL (1.35 mmol) of 1-octyne in 5 mL of dry hexamethylphosphoramide at 0 °C under argon was added 1.1 mL of 1.6 M (1.8 mmol) *n*-butyllithium in hexanes. The combined solution was stirred at 0 °C for 30 min, and then the hexanes were removed under vacuum. The reaction mixture was then cooled to 0 °C and treated with a cold solution containing 339 mg (1.08 mmol) of 5-(7′-bromoheptyl)-1,3-dimethoxybenzene (**13**) in 5 mL of dry THF. The reaction mixture was stirred at room temperature for an additional 12 h and then added to 50 mL of ice water. The mixture was extracted with three 50-mL portions of hexanes. The combined organic phase was washed with 100 mL of water and then with 100 mL of brine. The dried (Na_2SO_4) organic phase was concentrated under diminished pressure, affording a clear oil which was applied to a silica gel column (7 cm × 4 cm). Flash chromatography (1:5 CH_2Cl_2−hexanes) afforded 1,3-dimethoxy-5-(8′-pentadecynyl)benzene (**14**) as a colorless oil: yield 329 mg (88%); silica gel TLC R_f 0.47 (9:1 hexanes−ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3 H, J = 7 Hz), 1.28−1.68 (m, 18 H), 2.15 (t, 4 H, J = 7 Hz), 2.53 (t, 2 H, J = 7 Hz), 3.78 (s, 6 H), 6.31 (d, 1 H,

J = 1.5 Hz), 6.35 (d, 2 H, J = 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 14.50, 19.21, 23.05, 29.00, 29.23, 29.50, 29.61, 29.69, 31.69, 31.85, 36.75, 55.59, 80.57, 80.69, 98.00, 106.90, 145.70, 161.15; mass spectrum (chemical ionization) m/z 345 $(M + 1)^+$; mass spectrum (electron impact) m/z 344.271 $(M)^+$ ($C_{23}H_{36}O_2$ requires 344.271).

1,3-Dimethoxy-5-(*cis*-8′-pentadecenyl)benzene (15). A mixture of 310 mg (0.9 mmol) of 1,3-dimethoxy-5-(8′-pentadecynyl)benzene (**14**), 60 mg of 5% palladium-on-calcium carbonate, and 1.7 mL of quinoline in 15 mL of cyclohexane was stirred under 1 atm H_2 for 1 h. The reaction mixture was filtered through Celite and washed with ethyl acetate. The solution was concentrated under diminished pressure to afford a pale yellow oil. The crude product was purified by flash chromatography on a silica gel column (30 cm × 2 cm). Elution with 1:5 CH_2Cl_2−hexanes afforded 1,3-dimethoxy-5-(*cis*-8′-pentadecenyl)-benzene (**15**) as a colorless oil: yield 270 mg (87%); silica gel TLC R_f 0.44 (1:1 CH_2Cl_2−hexanes); ^{1}H NMR ($CDCl_3$) δ 0.92 (t, 3 H, J = 7 Hz), 1.36−1.45 (m, 16 H), 1.58−1.70 (m, 2 H), 1.97−2.12 (m, 4 H), 2.58 (t, 2 H, J = 7.5 Hz), 3.75 (s, 6 H), 5.33 (t, 2 H, J = 5.0 Hz), 6.33 (d, 1 H, J = 2 Hz), 6.37 (d, 2 H, J = 2 Hz); ^{13}C NMR ($CDCl_3$) δ 14.56, 23.14, 27.67, 29.46, 29.70, 29.80, 29.89, 30.23, 31.74, 32.27, 36.78, 55.59, 98.01, 108.92, 130.26, 130.38, 145.76, 161.17; mass spectrum (chemical ionization) m/z 347 $(M + 1)^+$. Anal. Calcd for $C_{23}H_{38}O_2$; C, 79.71; H, 11.05. Found: C, 79.35; H, 10.71.

1,3-Dihydroxy-5-(*cis*-8′-pentadecenyl)benzene (2). Methyl iodide (0.5 mL, 0.8 mmol) and magnesium (46 mg, 1.89 mmol) were stirred together in 2 mL of dry ether until the initial exothermic reaction had subsided. A solution containing 54 mg (0.156 mmol) of 1,3-dimethoxy-5-(*cis*-8′-pentadecenyl)benzene (**15**) in 2 mL of ether was added dropwise, and then the solution was concentrated under diminished pressure. The residue was heated to 100 °C while still under vacuum (aspirator) and was then heated at 165 °C for 15 min under N_2. The cooled reaction mixture was treated with 20 mL of 10% aqueous NH_4-Cl and then extracted with three 20-mL portions of ether. The combined organic extract was washed with 20 mL of water and 20 mL of brine. The dried organic phase was concentrated under diminished pressure, and the residue was purified by flash chromatography on a silica gel column (15 cm × 2 cm). Elution with 10:1 and then 4:1 hexanes−ethyl acetate afforded 1,3-dihydroxy-5-(*cis*-8′-pentadecenyl)benzene (**2**) as colorless microcrystals: yield 46 mg (92%); mp 31−33 °C; silica gel TLC R_f 0.35 (10:1 CH_2Cl_2−ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3 H, J = 7 Hz), 1.19−1.40 (m, 16 H), 1.48−1.60 (m, 2 H), 1.92−2.08 (m, 4 H), 2.47 (t, 2 H, J = 7.5 Hz), 5.35 (t, 2 H, J = 5 Hz), 5.74 (br, 2 H, ex D_2O), 6.16 (d, 1 H, J = 2 Hz), 6.24 (d, 2 H, J = 2 Hz); ^{13}C NMR ($CDCl_3$) δ 14.54, 23.09, 27.65, 29.42, 29.68, 29.72, 29.84, 30.18, 31.48, 32.22, 36.29, 100.67, 108.44, 130.28, 130.40, 146.52, 157.05; mass spectrum (chemical ionization) m/z 319 $(M + 1)^+$; mass spectrum (electron impact) m/z 318.256 $(M)^+$ ($C_{21}H_{34}O_2$ requires 318.256).

1,3-Dimethoxy-5-(1′-hydroxypentyl)benzene (16). An anhydrous solution of 45 mL of dry ether under argon containing 1.90 g (78.1 mmol) of magnesium turnings and approximately 10% of a solution of 10.73 g (78.3 mmol) of 1-bromobutane in 45 mL of dry ether was treated with a small crystal of iodine and 2 drops of 1,2-dibromoethane. The reaction mixture was warmed to initiate the reaction, and then the remainder of the 1-bromobutane was added at a rate that maintained solvent reflux. The reaction mixture was stirred under reflux for an additional 1 h and then treated dropwise at room temperature with a solution containing 8.31 g (50 mmol) of 3,5-dimethoxybenzaldehyde (**6**) in 50 mL of dry ether. The reaction mixture was heated at reflux for an additional 4 h, and then the cooled reaction mixture was treated cautiously with 12 mL of water and 52 mL of 2.8 N HCl. The layers were separated, and the aqueous layer was extracted with three 30-mL portions of ether. The combined organic extract was washed with two 30-mL portions of water and then with 30 mL of brine. The dried ($MgSO_4$) organic phase was concentrated under diminished pressure, and the residue was purified by flash chromatography on a silica gel column (30 cm × 4 cm). Elution with 10:1 and then 4:1 hexanes−ethyl acetate provided 1,3-dimethoxy-5-(1′-hydroxypentyl)benzene (**16**) as a colorless oil: yield 11.0 g (98%); silica gel TLC R_f 0.41 (4:1 hexanes−ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 0.87 (t, 3 H, J = 7 Hz), 1.20−1.40 (m, 4 H), 1.61−1.81 (m, 2 H), 2.22 (s, 1 H, ex D_2O), 3.76 (s, 6 H), 4.54 (t, 1 H, J = 7 Hz), 6.33 (t, 1 H, J = 2 Hz), 6.47 (d, 2 H, J = 2 Hz); ^{13}C NMR ($CDCl_3$) δ 14.44, 23.04, 28.41, 29.13, 55.71, 75.10, 99.70, 104.24, 148.12, 161.22; mass spectrum (chemical ionization) m/z 225 $(M + 1)^+$ and 207; mass spectrum (electron impact) m/z 224.142 $(M)^+$ ($C_{13}H_{20}O_3$ requires 224.141).

1,3-Dimethoxy-5-(*trans*-1′-pentenyl)benzene (17). A solution containing 11.0 g (49.0 mmol) of 1,3-dimethoxy-5-(1′-hydroxypentyl)-benzene (**16**) and 0.50 g (2.6 mmol) of *p*-toluenesulfonic acid monhydrate in 500 mL of toluene was heated to reflux for 20 h in an apparatus fitted with a Dean−Stark trap. The cooled reaction mixture was washed successively with 120 mL of saturated $NaHCO_3$, 120 mL of water, and 100 mL of brine. The organic phase was dried (Na_2-SO_4), and the solution was concentrated under diminished pressure. The yellow, oily residue was purified by flash chromatography on a silica gel column (35 cm × 4 cm). Elution with 40:1 and then 30:1 hexanes−ethyl acetate provided 1,3-dimethoxy-5-(*trans*-1′-pentenyl)-benzene (**17**) as a colorless oil: yield 9.21 g (91%); silica gel TLC R_f 0.66 (10:1 hexanes−ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 0.98 (t, 3 H, J = 7 Hz), 1.45−1.60 (m, 2 H), 2.22 (q, 2 H, J = 7 Hz), 3.80 (s, 6 H), 6.19−6.33 (m, 2 H), 6.37 (t, 1 H, J = 2 Hz), 6.52 (d, 2 H, J = 2 Hz); ^{13}C NMR ($CDCl_3$) δ 14.19, 22.96, 35.50, 55.66, 99.60, 104.50, 130.38, 131.92, 140.46, 161.35; mass spectrum (chemical ionization) m/z 207 $(M + 1)^+$; mass spectrum (electron impact) m/z 206.130 $(M)^+$ ($C_{13}H_{18}O_2$ requires 206.131).

1,3-Dimethoxy-5-(5′-hydroxypentyl)benzene (18). To a solution containing 5.73 g (27.8 mmol) of 1,3-dimethoxy-5-(*trans*-1′-pentenyl)-benzene (**17**) and 0.44 g (11.6 mmol) of sodium borohydride in 52 mL of dry diglyme under N_2 was added slowly 2.4 mL (19.3 mmol) of boron trifluoride etherate. The reaction mixture was stirred at 25 °C for 1 h and then quickly heated to reflux at 160−165 °C for 2 h. The cooled reaction mixture was quenched by the addition of 10 mL of water. Aqueous sodium hydroxide solution (5 M, 20 mL) was added, followed by 20 mL of 30% H_2O_2. Stirring was continued at room temperature for 1.5 h. The reaction mixture was treated with 40 mL of ice water and then extracted with three 60-mL portions of ether. The combined organic extract was washed with 60 mL of water and then with 60 mL of brine. The dried ($MgSO_4$) organic phase was concentrated under diminished pressure, and the residue was purified by flash chromatography on a silica gel column (35 cm × 4 cm). Elution with 5:1 and then 3:1 hexanes−ethyl acetate gave 1,3-dimethoxy-5-(5′-hydroxypentyl)benzene (**18**) as a colorless oil: yield 4.88 g (78%); silica gel TLC R_f 0.35 (3:1 hexanes−ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 1.33−1.45 (m, 2 H), 1.53−1.69 (m, 4 H), 1.97 (s, 1 H, ex D_2O), 2.56 (t, 2 H, J = 7.5 Hz), 3.63 (t, 2 H, J = 7 Hz), 3.77 (s, 6 H), 6.29 (d, 1 H, J = 2 Hz), 6.34 (d, 2 H, J = 2 Hz); ^{13}C NMR ($CDCl_3$) δ 25.89, 31.48, 33.05, 36.65, 55.64, 63.16, 98.05, 106.94, 145.47, 161.13; mass spectrum (chemical ionization) m/z 225 $(M + 1)^+$; mass spectrum (electron impact) m/z 224.143 $(M)^+$ ($C_{13}H_{20}O_3$ requires 224.141).

5-(5′-Bromopentyl)-1,3-dimethoxybenzene (19). A solution containing 4.70 g (21.0 mmol) of 1,3-dimethoxy-5-(5′-hydroxypentyl)-benzene (**18**) and 5.94 g (22.6 mmol) of triphenylphosphine in 55 mL of DMF and 18 mL of CH_2Cl_2 under argon was stirred at 25 °C for 10 min and then cooled to −70 °C. A solution of *N*-bromosuccinimide (4.02 g, 22.5 mmol) in 40 mL of DMF was added dropwise over a period of 1 h. The reaction mixture was allowed to warm to 25 °C and was stirred at 25 °C for an additional 1 h. The reaction mixture was then treated with 220 mL of water and 180 mL of saturated $NaHCO_3$ and then extracted with three 150-mL portions of ether. The combined organic extract was washed with 100 mL of water and then with 100 mL of brine. The dried ($MgSO_4$) organic phase was concentrated under diminished pressure, and the residue was triturated with three 80-mL portions of hexanes containing 5% ethyl acetate. The hexanes extract was concentrated, and the oily residue was purified by flash chromatography on a silica gel column (30 cm × 4 cm). Elution with 80:1 hexanes−ethyl acetate afforded 5-(5′-bromopentyl)-1,3-dimethoxybenzene (**19**) as a colorless oil: yield 4.02 g (67%); silica gel TLC R_f 0.50 (10:1 hexanes−ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 1.44−1.54 (m, 2 H), 1.58−1.70 (m, 2 H), 1.84−1.93 (m, 2 H), 2.57 (t, 2 H, J = 7.5 Hz), 3.40 (t, 2 H, J = 7 Hz), 3.77 (s, 6 H), 6.30 (d, 1 H, J = 2 Hz), 6.34 (d, 2 H, J = 2 Hz); ^{13}C NMR ($CDCl_3$) δ 28.29, 30.83, 33.17, 34.23, 36.48, 55.66, 98.13, 106.91, 145.15, 161.22; mass spectrum (chemical ionization) m/z 287 $(M + 1)^+$; mass spectrum (electron impact) m/z 286.056 $(M)^+$ ($C_{13}H_{19}O_2Br$ requires 286.057).

1,3-Dimethoxy-5-(6′-heptynyl)benzene (20). To a stirred suspension of 1.24 g (90%, 12 mmol) of lithium acetylide−ethylenediamine complex in 20 mL of dry DMSO under argon was added at 10−15 °C a solution containing 1.15 g (4.0 mmol) of 5-(5′-bromopentyl)-1,3-dimethoxybenzene (**19**) in 16 mL of DMSO over a period of 30 min. The reaction mixture was stirred at 25 °C for 1.5 h and then treated with 120 mL of ice−water. The mixture was extracted with three 60-mL portions of ethyl acetate, and the combined organic extract was washed with two 30-mL portions of water and then with 50 mL of brine. The dried ($MgSO_4$) organic phase was concentrated, and the residual pale yellow oil was applied to a silica gel column (20 cm × 2 cm). Flash chromatography (50:1 hexanes−ethyl acetate) provided 1,3-dimethoxy-5-(6′-heptynyl)benzene (**20**) as a colorless oil: yield 0.89 g (96%); silica gel TLC R_f 0.50 (10:1 hexanes−ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 1.41−1.70 (m, 6 H), 1.94 (t, 1 H, J = 2 Hz), 2.19 (dt, 2 H, J = 7, 2 Hz), 2.56 (t, 2 H, J = 7 Hz), 3.77 (s, 6 H), 6.30 (d, 1 H, J = 1.5 Hz), 6.34 (d, 2 H, J = 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 18.79, 28.82, 28.87, 31.17, 36.56, 55.63, 68.70, 85.02, 98.08, 106.91, 145.42, 161.18; mass spectrum (chemical ionization) m/z 233 $(M + 1)^+$; mass spectrum (electron impact) m/z 232.147 $(M)^+$ ($C_{15}H_{20}O_2$ requires 232.146).

1,3-Dimethoxy-5-[14′-(3″,5″-dimethoxyphenyl)-6′-tetradecynyl]benzene (21). To a stirred solution of 170 mg (0.73 mmol) of 1,3-dimethoxy-5-(6′-heptynyl)benzene (**20**) in 2 mL of dry THF at −30 to −40 °C under argon was added 470 μL of 1.6 M (0.75 mmol) n-butyllithium in hexanes. The cooling bath was removed; after 1.5 h, a cold solution containing 236 mg (0.75 mmol) of 5-(7′-bromoheptyl)-1,3-dimethoxybenzene (**13**) in 3 mL of dry hexamethylphosphoramide was added dropwise at −10 °C. The reaction mixture was stirred at 25 °C for 22 h. The cooled reaction mixture was treated with 40 mL of ice−water and 20 mL of 10% NH_4Cl and then extracted with three 40-mL portions of ether. The combined organic phase was washed with two 30-mL portions of water and then with 30 mL of brine. The dried ($MgSO_4$) organic phase was concentrated under diminished pressure to afford a pale brown oil, which was applied to a silica gel column (30 cm × 2 cm). Flash chromatography (40:1 and then 20:1 hexanes−ethyl acetate) afforded 1,3-dimethoxy-5-[14′-(3″,5″-dimethoxyphenyl)-6′-tetradecynyl]benzene (**21**) as a colorless oil: yield 180 mg (53%); silica gel TLC R_f 0.29 (10:1 hexanes−ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 1.30−1.58 (m, 12 H), 1.59−1.71 (m, 4 H), 2.10−2.18 (m, 4 H), 2.51−2.58 (m, 4 H), 3.77 (s, 12 H), 6.29 (d, 2 H, J = 1.5 Hz), 6.34 (d, 4 H, J = 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 19.20, 29.00, 29.24, 29.50, 29.60, 29.68, 31.23, 31.70, 36.63, 36.73, 55.64, 80.53, 80.75, 98.01, 106.91, 145.58, 145.74, 161.14; mass spectrum (chemical ionization) m/z 467 $(M + 1)^+$; mass spectrum (electron impact) m/z 466.308 $(M)^+$ ($C_{30}H_{42}O_4$ requires 466.308).

1,3-Dimethoxy-5-[14′-(3″,5″-dimethoxyphenyl)-*cis*-6′-tetradecenyl]benzene (22). A mixture of 64 mg (0.137 mmol) of 1,3-dimethoxy-5-[14′-(3″,5″-dimethoxyphenyl)-6′-tetradecynyl]benzene (**21**), 10 mg of 5% palladium-on-calcium carbonate, and 260 μL (2.0 mmol) of quinoline in 2.5 mL of cyclohexane was stirred under 1 atm H_2 for 1 h. The reaction mixture was filtered through Celite and washed with ethyl acetate. The solvent was evaporated under diminished pressure to afford a pale yellow oil. The crude product was purified by flash chromatography on a silica gel column (20 cm × 2 cm). Elution with 15:1 hexanes−ethyl acetate afforded 1,3-dimethoxy-5-[14′-(3″,5″-dimethoxyphenyl)-*cis*-6′-tetradecenyl]benzene (**22**) as a colorless oil: yield 58 mg (91%); silica gel TLC R_f 0.32 (10:1 hexanes−ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 1.23−1.45 (m, 12 H), 1.56−1.69 (m, 4 H), 1.97−2.09 (m, 4 H), 2.54 (t, 4 H, J = 7.5 Hz), 3.77 (s, 12 H), 5.35 (t, 2 H, J = 4.5 Hz), 6.30 (d, 2 H, J = 1.5 Hz), 6.35 (d, 4 H, J = 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 27.61, 27.67, 29.47, 29.70, 29.78, 29.88, 30.08, 30.22, 31.67, 31.72, 36.75, 55.65, 98.02, 106.93, 130.19, 130.42, 145.74, 145.79, 161.14; mass spectrum (chemical ionization) m/z 469 $(M + 1)^+$; mass spectrum (electron impact) m/z 468.324 $(M)^+$ ($C_{30}H_{46}O_4$ requires 468.324).

1,3-Dihydroxy-5-[14′-(3″,5″-dihydroxyphenyl)-*cis*-6′-tetradecenyl]benzene (3). Methyl iodide (0.70 mL, 10.8 mmol) and magnesium (70 mg, 2.88 mmol) were stirred together in 3 mL of dry ether until the initial exothermic reaction had subsided. A solution containing 58 mg (0.123 mmol) of 1,3-dimethoxy-5-[14′-(3″,5″-dimethoxyphenyl)-*cis*-6′-tetradecenyl]benzene (**22**) in 3 mL of dry ether was added dropwise, and then the solution was concentrated under diminished pressure. The residue was heated to 100 °C while still under vacuum (aspirator) and was then heated at 165 °C for 15 min under N_2. The cooled reaction mixture was treated slowly with 20 mL of 10% aqueous NH_4Cl and extracted with three 20-mL portions of ether. The combined organic extract was washed with 20 mL of water and 20 mL of brine. The dried ($MgSO_4$) organic phase was concentrated under diminished pressure. The residue was purified by flash chromatography on a silica gel column (10 cm × 2 cm). Elution with 5:1 and then 2:1 hexanes−ethyl acetate afforded 1,3-dihydroxy-5-[14′-(3″,5″-dihyroxyphenyl)-*cis*-6′-tetradecenyl]benzene (**3**) as colorless microcrystals: yield 35 mg (70%); mp 102 °C; silica gel TLC R_f 0.25 (1:1 hexanes−ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 1.24−1.39 (m, 12 H), 1.51−1.60 (m, 4 H), 1.95−2.06 (t, 4 H, J = 7.5 Hz), 2.44 (t, 4 H, J = 7.5 Hz), 5.03 (s, 4 H, ex D_2O), 5.30 (t, 2 H, J = 4.5 Hz), 6.08 (d, 2 H, J = 1.5 Hz), 6.10 (d, 4 H, J = 1.5 Hz); ^{1}H NMR (acetone-d_6) δ 1.20−1.38 (m, 12 H), 1.45−1.60 (m, 4 H), 1.93−2.06 (m, 4 H), 2.40 (t, 4 H, J = 7.5 Hz), 5.30 (t, 2 H, J = 4.5 Hz), 6.13 (s, 2 H), 6.14 (s, 4 H), 8.10 (s, 4 H, ex D_2O); ^{13}C NMR (acetone-d_6) δ 27.30, 28.68, 29.52, 29.76, 29.99, 30.16, 31.47, 31.56, 36.11, 100.36, 100.37, 107.11, 107.17, 130.02, 130.11, 145.30, 145.34, 158.69, 158.78; mass spectrum (chemical ionization) m/z 413 $(M + 1)^+$; mass spectrum (electron impact) m/z 412.261 $(M)^+$ ($C_{26}H_{36}O_4$ requires 412.261).

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Supporting Information Available: Experimental description of the method for determining double bond position in the 5-alkenylresorcinol substituents; information for the synthesis and characterization of compounds **7**, **8**, **9**, **1**, **23**, **4**, **24**, **25**, **26** and **5**; and a figure illustrating the separation of compounds **3**, **4**, and **5** by reversed-phase HPLC (11 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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