Articles

Shortcut Syntheses of Naturally Occurring 5-Alkylresorcinols with DNA-Cleaving Properties

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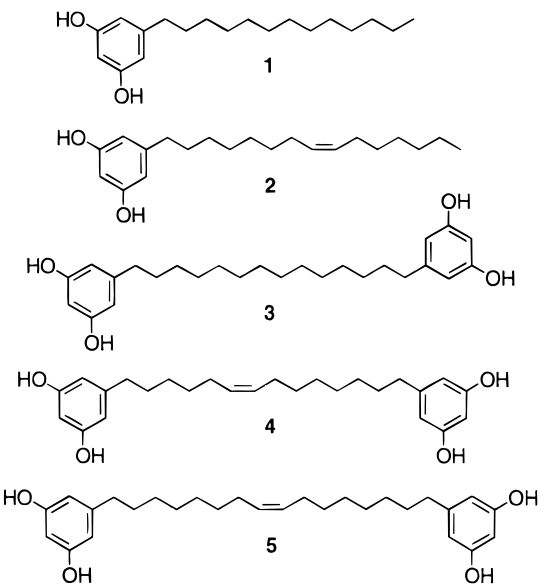
Resorcinols such as **1**−**5** bearing long alkyl- or alkenyl substituents at the C-5 position, including bola-formed bis-resorcinol derivatives, have recently been isolated from natural sources and were shown to exhibit exceptional DNA-cleaving properties under oxidative conditions. Previous synthetic approaches to such compounds seem inappropriately lengthy with regard to their structural simplicity. Disclosed is a very flexible synthesis which assembles these targets from triflate **7** and well accessible alkenes, dienes, enynes, or dienynes, respectively, by means of a boron-mediated reaction manifold. As a typical example, hexadeca-1,15-dien-8-yne **11** is hydroborated with 9-H-9-BBN at all possible sites, the alkenyl borane entity of the resulting tris-borane **12** is selectively cleaved off to afford the desired (*Z*)-alkene group in a stereoselective manner, the remaining two terminal alkylboranes are treated with NaOMe, and the bis-borate complex **13** thus formed is finally used as the nucleophile for a palladium-catalyzed Suzuki cross-coupling reaction with triflate **7**. This sequence is carried out in one pot and provides product **14** in 62% overall yield. Demethylation of **14** (and analogues) can be conveniently achieved by means of 9-iodo-9-BBN to afford the natural product **5**. The efficiency and flexibility of this unprecedented approach which combines different features of classical and modern boron chemistry is further demonstrated by the synthesis of anacardic and ginkgolic acid derivatives.

Recent reports on the exceptional potency of the resorcinols **1**−**5**, isolated from the west Australian shrub *Hakea trifurcata*, to cleave DNA under oxidative conditions [O_2, Cu(II)] denote a highlight in the vast literature on non-isoprenoid phenol lipids.[1] Elegant studies of Hecht et al. brought some insight into the mechanism of action of these metabolites.[2] Thus, DNA cleavage is most likely triggered by copper-assisted oxygenation of their benzene rings and generation of diffusible oxygen radicals which effect the scission of the nucleic acid strand.[2,3] However, the way of binding of these compounds to DNA is still obscure as they lack structural elements that might entail intercalation, groove binding, or electrostatic interaction. A correlation between the length of their aliphatic chain and the biological response has been observed which seems to indicate an essentially hydrophobic interaction.[2]

Subsequent work has demonstrated that various structurally related 3-alk(en)ylcatechols found in poison oak (*Toxicadendron diversilobum*) or poison ivy (*Toxicadendron radicans*) have similar DNA-cleaving properties as



compounds **1**−**5**.[4] Moreover, several other phenolic lipids are well known to exhibit cytotoxic activity.[5] Thus, a further pharmacological evaluation of this class of compounds is promising which requires a straightforward entry into long chain alkylphenols in order to study the structure/activity profile in more detail. Existing methods, however, seem inappropriately lengthy with regard

[⊗] Abstract published in *Advance ACS Abstracts,* April 1, 1997.

(1) Review: Tyman, J. H. P. *Chem. Soc. Rev.* **1979**, 499−537.

(2) (a) Lytollis, W.; Scannell, R. T.; An, H.; Murty, V. S.; Reddy, K. S.; Barr, J. R.; Hecht, S. M. *J. Am. Chem. Soc.* **1995**, *117*, 12683−12690. (b) Singh, U. S.; Scannell, R. T.; An, H.; Carter, B. J.; Hecht, S. M. *J. Am. Chem. Soc.* **1995**, *117*, 12691−12699. (c) Scannell, R. T.; Barr, J. R.; Murty, V. S.; Reddy, K. S.; Hecht, S. M. *J. Am. Chem. Soc.* **1988**, *110*, 3650−3651.

(3) This metal-assisted scenario is reminiscent of the mode of action of metallobleomycins, although the elementary steps of oxygen transfer to the DNA may be different. For reviews see i.a.: (a) Hecht, S. M. *Pure Appl. Chem.* **1989**, *61*, 577−580. (b) Sugiyama, H.; Ehrenfeld, G. M.; Shipley, J. B.; Kilkuskie, R. E.; Chang, L.-H.; Hecht, S. M. *J. Nat. Prod.* **1985**, *48*, 869−877. (c) Stubbe, J.; Kozarich, J. W. *Chem. Rev.* **1987**, *87*, 1107−1136.

(4) Wasser, C.; Silva, F.; Rodriguez, E. *Experientia* **1990**, *46*, 500−502.

(5) (a) Arisawa, M.; Ohmura, K.; Kobayashi, A.; Morita, N. *Chem. Pharm. Bull.* **1989**, *37*, 2431−2434. (b) Itokawa, H.; Totsuka, N.; Nakahara, K.; Takeya, K.; Lepoittevin, J.-P.; Asakawa, Y. *Chem. Pharm. Bull.* **1987**, *35*, 3016−3020.

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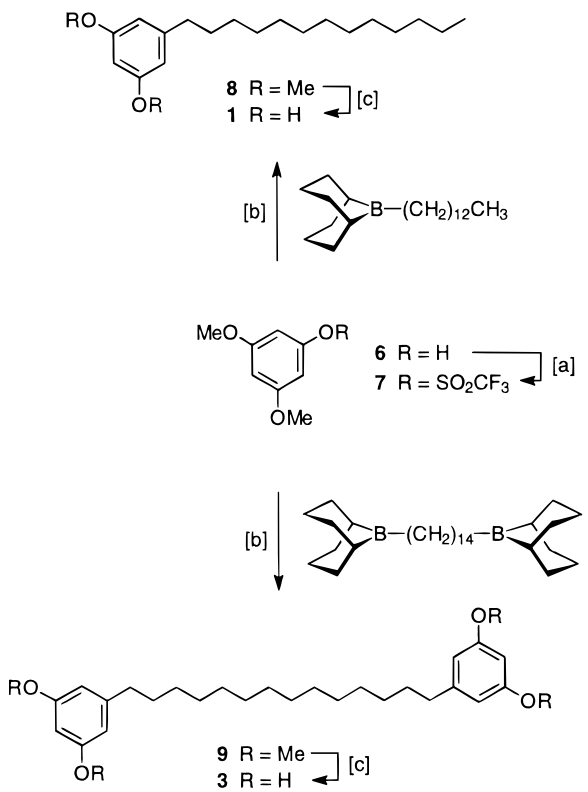
Scheme 1[a]

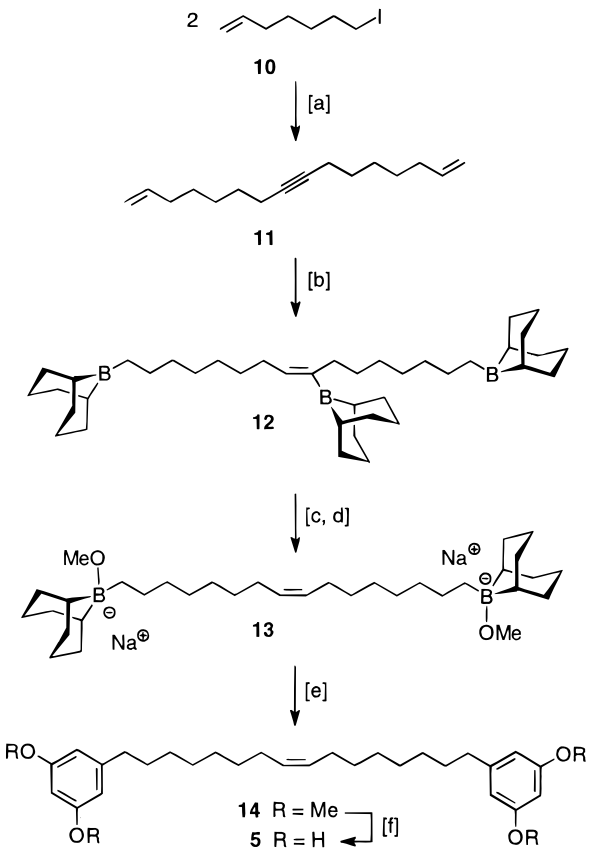


[a] [a] Triflic anhydride, 2,6-lutidine, CH_2Cl_2, 94%; [b] NaOMe, $PdCl_2$(dppf) cat., THF, 88% (**7** → **8**), 87% (**7** → **9**); [c] 9-iodo-9-BBN, hexane, 90% (**8** → **1**), 88% (**9** → **3**).

to the structural simplicity of such targets.[1,2,6] Therefore we were prompted to develop a new approach which requires a minimum number of steps and clearly surpasses the established routes in terms of flexibility and overall yield.

Our synthesis relies on the palladium-catalyzed, base-induced cross-coupling of 9-alkyl-9-BBN derivatives with aryl triflate **7** which is obtained from cheap 3,5-dimethoxyphenol (**6**) and triflic anhydride in the presence of 2,6-lutidine (Scheme 1). In view of the performance of Suzuki reactions in general,[7,8] the 88% isolated yield of **8** on coupling of **7** with 9-tridecyl-9-BBN in the presence of NaOMe and catalytic amounts of $PdCl_2$(dppf)[9] may not be surprising. Subsequent cleavage of the methyl ethers by 9-iodo-9-BBN (see below)[10] affords compound **1** in excellent overall yield. In a similar sequence, bis-hydroboration of 1,13-tetradecadiene with 9-H-9-BBN dimer under standard conditions, followed by a twofold Suzuki reaction of the resulting bis-borane with **7** (2 equiv), and a final cleavage of the OMe groups as described leads to the bola-form resorcinol **3** without incident.

Scheme 2[a]



[a] [a] LiC≡CLi, THF/HMPA, 72%; [b] 9-H-9-BBN (3 equiv), THF; [c] MeOH/HOAc (99:1); [d] NaOMe (2 equiv); [e] **7** (2 equiv), $PdCl_2$(dppf) cat., 62% (over steps [b−e]); [f] 9-iodo-9-BBN, hexane, 98%.

Previous syntheses of phenolic lipids containing (*Z*)-configurated double bonds in the side chain essentially relied on Lindlar hydrogenations of the respective alkyne precursors. However, we encountered problems in effecting such semihydrogenations in a reproducible manner.[11] The formation of minor, but inseparable byproducts, most likely isomers formed by a scrambling of the double bond, could not be suppressed (*cf.* Supporting Information). Therefore we explored an unambiguous alternative route.

A very convenient solution takes advantage of the largely different stabilities of B-C(sp^3) and B-C(sp^2) bonds towards hydrolysis (Scheme 2).[12] Specifically, dilithioacetylene[13] was alkylated with 2 equiv of 7-iodo-1-heptene (**10**) to afford diene-yne **11**. This compound was hydroborated with 9-H-9-BBN dimer at both double bonds as well as at the alkyne site to afford the tris-borane **12**. Addition of MeOH (containing 1% HOAc, w/w) then

(6) See also: (a) Baylis, C. J.; Odle, S. W. D.; Tyman, J. H. P. *J. Chem. Soc., Perkin Trans. 1* **1981**, 132−141. (b) Durrani, A. A.; Tyman, J. H. P. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1658−1666. (c) Alonso, E.; Ramon, D. J.; Yus, M. *J. Org. Chem.* **1997**, *62*, 417−421.

(7) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483. (b) Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314−321. (c) Oh-e, T.; Miyaura, N.; Suzuki, A. *J. Org. Chem.* **1993**, *58*, 2201−2208.

(8) For recent methodological advancements in Suzuki reactions and for applications to the synthesis of physiologically active natural products from our laboratory see: (a) Fürstner, A.; Seidel, G. *Tetrahedron* **1995**, *51*, 11165−11176. (b) Fürstner, A.; Konetzki, I. *Tetrahedron* **1996**, *52*, 15071−15078. (c) Fürstner, A.; Nikolakis, K. *Liebigs Ann.* **1996**, 2107−2113. (d) Fürstner, A.; Seidel, G.; Gabor, B.; Kopiske, C.; Krüger, C.; Mynott, R. *Tetrahedron* **1995**, *51*, 8875−8888.

(9) Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 158−163.

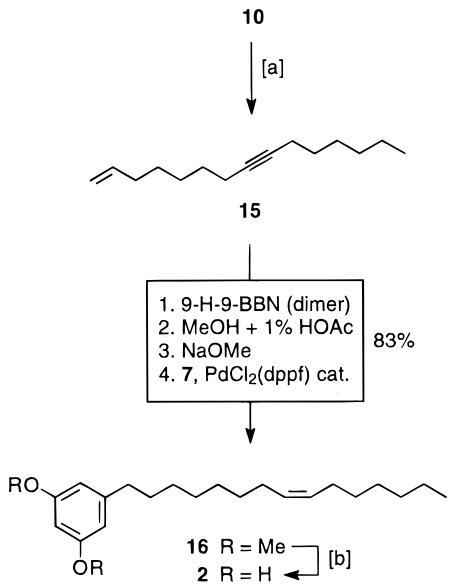
(10) Köster, R.; Seidel, G. In *Organometallic Syntheses*; King, R. B., Eisch, J. J., Eds.; Elsevier: Amsterdam, 1988; Vol. 4, pp 440−442.

(11) Review: Marvell, E. N.; Li, T. *Synthesis* **1973**, 457−468.

(12) (a) Brown, H. C.; Wang, K. K. *J. Org. Chem.* **1986**, *51*, 4514−4517. (b) Brown, H. C.; Scouten, C. G.; Liotta, R. *J. Am. Chem. Soc.* **1979**, *101*, 96−99.

(13) (a) Prepared from n-BuLi and acetylene according to: Brandsma, L. *Preparative Acetylenic Chemistry*, 2nd ed.; Elsevier: Amsterdam, 1988; pp 23−24. (b) For an alternative synthesis from n-BuLi and trichloroethylene see: Sekiguchi, A.; Ichinohe, M.; Kabuto, C.; Sakurai, H. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 2981−2988. Dilithioacetylene prepared according to this latter procedure on alkylation with **10** gave, however, a somewhat lower yield of dienyne **11**.

Scheme 3[a]



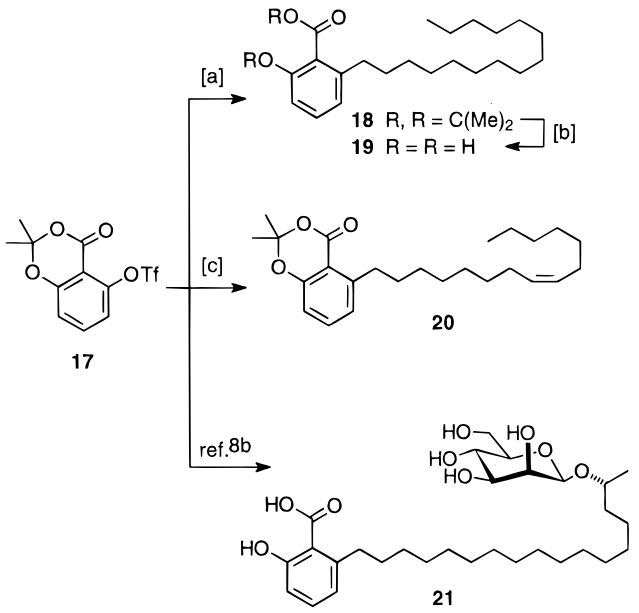
[a] [a] 1-Octynyllithium, THF, 90%; [b] 9-iodo-9-BBN, hexane, 96%.

effects a smooth and regioselective protonolysis of the alkenylborane group without affecting the terminal alkylborane entities. Subsequent treatment with NaOMe leads to the bis-borate complex **13** as the actual nucleophile for the ensuing Suzuki coupling with 2 equiv of triflate **7**. It is worth mentioning that this sequence comprising the triple hydroboration, the selective protonoloysis, the subsequent borate formation, and two final Pd-catalyzed C−C-bond formations is effected in one pot and proceeds with 62% isolated yield overall. Since the hydroboration of internal alkynes is strictly (*Z*)-selective, the formation of any isomeric product is precluded. The same one-pot procedure, when applied to enyne **15** as the substrate, leads in a single operation to product **16** in 83% yield (Scheme 3). From these examples it is obvious that the series of homologues of the resorcinol targets in question can be assembled from triflate **7** and simple alkenes, dienes, enynes, or dienynes, respectively, by highly efficient and routine steps. The reactions can easily be up-scaled and are likely suitable for automatization. This clearly surpasses previous approaches in all preparative respects.

A final issue concerns the cleavage of the methyl ether groups. While BBr_3 works fine for nonolefinic compounds, this reagent is inapplicable to e.g. **14** and **16** due to concomitant haloboration of the double bonds. In these cases, deprotection has previously been achieved by heating the substrates with MeMgI in the solid state at 100−165 °C![2] It is obvious that these rude conditions are inappropriate for the preparation of analogues bearing more sensitive functional groups. A very convenient alternative consists in the use of 9-iodo-9-BBN.[10] This reagent readily cleaves the ether functions without affecting the double bonds. Moreover, the workup of the reaction mixtures is conveniently achieved by adding ethanolamine and filtering off the crystalline 9-BBN adduct thereof.

In summary, the reaction manifold outlined above combines all essential features for preparing series of (more highly functionalized) analogues of these interesting natural products. First results along these lines are

Scheme 4[a]



[a] [a] (i) 1-Pentadecene, 9-H-9-BBN, THF; (ii) NaOMe, $PdCl_2$(dppf) cat. 79%; [b] KOH, H_2O/DMSO, 95%; [c] (i) **15**, 9-H-9-BBN (2 equiv), THF; (ii) MeOH/HOAc (99:1); (iii) NaOMe, $PdCl_2$(dppf) cat., 67%.

the ready syntheses of anacardic acid **19**,[14] the ginkgolic acid derivative **20**,[15] as well as of the β-D-mannosylated compound **21**,[8b,16] which acts as a selective inhibitor of the $GABA_A$/benzodiazepine chloride channel receptor complex (Scheme 4). Future work will concentrate on the synthesis of resorcinol derivatives bearing a DNA sequence specific recognition pattern *e.g.* attached to one of the phenolic OH functions.[17]

Experimental Section

General. For the instrumentation used and the spectral formats see the Supporting Information. Melting points were measured on a Gallenkamp apparatus (uncorrected) or by differential scanning calorimetry (DSC). All hydroboration and cross-coupling reactions have been monitored by ^{11}B NMR by taking aliquots of the crude reaction mixtures and taking spectra relative to $BF_3 \cdot Et_2O$ as external standard; the characteristic shifts (δ, ppm) are reported below. All reactions were carried out under Ar using Schlenk techniques. 9-H-9-BBN[18] dimer and 9-iodo-9-BBN[10] have been prepared according to the procedures cited; 1-tridecene, 1-pentadecene, 1,13-tetradecadiene, and all other reagents have been purchased and used as received. The solvents were dried by distillation over the

(14) (a) For an alternative approach to anacardic acid and related salicylic acid derivatives and for a compilation of the literature see: Zehnter, R.; Gerlach H. *Liebigs Ann*. **1995**, 2209−2220. (b) For a report on the prostaglandin synthetase inhibitory activity of this compound see: Kubo, I.; Kim, M.; Naya, K.; Komatsu, S.; Yamagiwa, Y.; Ohashi, K.; Sakamoto, Y.; Hirakawa, S.; Kamikawa, T. *Chem. Lett*. **1987**, 1101−1104.

(15) For a review on ginkgolic acid see ref 1; it is also the major antitumor principle of the chloroform extracts of *Ginkgo biloba*, cf. ref 5b; for structure elucidation see: Morimoto, H.; Kawamatsu, Y.; Sugihara, H. *Chem. Pharm. Bull*. **1968**, *16*, 2282−2286.

(16) Shan, R.; Anke, H.; Nielsen, M.; Sterner, O.; Witt, M. R. *Nat. Prod. Lett*. **1994**, *4*, 171−178.

(17) For leading references on the design of artificial sequence specific DNA binding/cleaving agents see i.a.: (a) Dervan, P. B. *Science* **1986**, *232*, 464−471. (b) Barton, J. K. *Science* **1986**, *233*, 727−734. (c) Sigman, D. S. *Acc. Chem. Res*. **1986**, *19*, 180−186. (d) Chu, B. C. F.; Orgel, L. E. *Proc. Nat. Acad. Sci. U.S.A*. **1985**, *82*, 963−967 and lit cit.

(18) For a convenient large-scale preparation see: Binger, P.; Köster, R. *Inorg. Synth*. **1974**, *15*, 147−149.

following drying agents prior to use and were transferred under Ar: THF (Mg−anthracene), hexane, Et_2O (Na/K alloy), CH_2Cl_2 (P_4O_{10}), MeOH (Mg). Flash chromatography: Merck silica gel (230−400 mesh) with hexane/ethyl acetate as the eluent in the proportions indicated.

3,5-Dimethoxyphenol Trifluoromethanesulfonate (7). A solution of triflic anhydride (11.4 g, 40 mmol) in CH_2Cl_2 (30 mL) is added over a period of 45 min to a solution of 3,5-dimethoxyphenol (**6**) (5.04 g, 33 mmol) and 2,6-lutidine (4.9 g, 46 mmol) in CH_2Cl_2 (160 mL) at −10 °C. After stirring for 2 h at 0 °C the reaction is quenched with water, the organic layer is separated and dried (Na_2SO_4), the solvent is removed *in vacuo*, and the crude product is purified by distillation (bp = 75−81 °C, 10^{-3} torr) to afford **7** as a colorless syrup (8.79 g, 94%). ^{1}H NMR: δ = 6.45 (t, 1H, J = 1.5), 6.42 (d, 2H), 3.79 (s, 6H). ^{13}C NMR: δ = 161.5, 150.6, 118.5 (q, J_{CF} = 320 Hz), 100.3, 100.0, 55.7. MS, *m*/*z* (rel intensity): 286 (88) [M$^+$], 257 (2), 153 (8), 125 (100), 110 (8), 79 (8), 69 (22).

1,3-Dimethoxy-5-tridecylbenzene (8). A solution of 1-tridecene (474 mg, 2.6 mmol) and 9-BBN (317 mg, 2.6 mmol) in THF (60 mL) is stirred for 2 h at ambient temperature (^{11}B NMR: δ = 82.6). NaOMe (162 mg, 3 mmol) is then added (^{11}B NMR: δ = −2.5), followed by triflate **7** (645 mg, 2.3 mmol) and $PdCl_2$(dppf) (56 mg, 0.07 mmol). The mixture is refluxed for 1 h, the solvent is removed *in vacuo*, the crude product is suspended in CH_2Cl_2, and the insoluble residues are filtered off through a short pad of silica. Evaporation of the solvent and flash chromatography using hexane/EtOAc (15:1) as eluent affords product **8** as colorless crystals (647 mg, 88%). mp = 41−42 °C (lit.[2a] 41−42 °C); ^{1}H NMR: δ = 6.34 (d, 2H, J = 2), 6.29 (t, 1H), 3.77 (s, 6H), 2.54 (vt, 2H), 1.60 (m, 2H), 1.40−1.20 (m, 20H), 0.88 (t, 3H, J = 7).- ^{13}C NMR: δ = 160.7, 145.4, 106.5, 97.6, 55.5, 36.3, 31.9, 31.3, 29.7 (3C), 29.65, 29.60, 29.5, 29.4, 22.7, 14.1. MS, *m*/*z* (rel intensity): 320 (17) [M$^+$], 194 (6), 165 (13), 152 (100).

1,3-Dimethoxy-5-[14′-(3″,5″-dimethoxyphenyl)tetradecyl]benzene (9). A solution of 1,13-tetradecadiene (694 mg, 3.6 mmol) and 9-BBN (878 mg, 7.2 mmol) in THF (80 mL) is stirred for 2 h at ambient temperature (^{11}B NMR: δ = 79.4). NaOMe (507 mg, 9.4 mmol) is added and the solution stirred for another 30 min (^{11}B NMR: δ = −2.1) prior to the addition of triflate **7** (1.79 g, 6.3 mmol) and $PdCl_2$(dppf) (152 mg, 0.19 mmol). Complete conversion of the substrates is reached (^{11}B NMR: δ = 55.9) after refluxing the mixture for 1 h. Workup as described above followed by crystallization of the crude product by slowly cooling a solution in hexane to −80 °C affords the title compound as colorless crystals (1.285 g, 87%). mp = 61−62 °C (lit.[2a] 62.5−63 °C); ^{1}H NMR: δ = 6.34 (d, 4H, J = 2), 6.29 (t, 2H), 3.77 (s, 12H), 2.54 (vt, 4H), 1.59 (m, 4H), 1.40−1.20 (m, 20H). ^{13}C NMR: δ = 160.7, 145.4, 106.5, 97.5, 55.2, 36.3, 31.3, 29.7 (2C), 29.6, 29.5, 29.3.- MS, *m*/*z* (rel intensity): 470 (31) [M$^+$], 194 (5), 165 (15), 152 (100).

1,15-Hexadecadien-8-yne (11). A suspension of dilithium acetylide (104 mg, 2.75 mmol)[13] and iodide **10** (1.12 g, 5 mmol) in THF (20 mL) and HMPA (2 mL) is stirred for 16 h at ambient temperature and 2 h at reflux. The solvent is removed *in vacuo*, the residue is suspended in hexane, and insoluble LiI is filtered off through a short pad of silica which is subsequently washed with hexane/ethyl acetate (20:1) in several portions. The combined filtrates are evaporated affording pure **11** as colorless liquid (393 mg, 72%). ^{1}H NMR: δ = 5.81 (m, 2H), 4.92−5.05 (m, 4H), 2.1 (m, 8H), 1.4 (m, 12H). ^{13}C NMR: δ = 138.9, 114.2, 80.1, 33.7, 29.0, 28.4, 28.3, 18.7. MS, *m*/*z* (rel intensity): 218 (1) [M$^+$], 203 (4), 189 (7), 175 (11), 161 (15), 147 (28), 135 (26), 121 (77), 107 (55), 95 (66), 93 (86), 81 (89), 79 (98), 67 (100), 55 (53), 41 (65), 29 (14). Anal. $C_{16}H_{26}$ (218.4) Calcd: C 88.00, H 12.00. Found: C 87.85, H 12.04.

1,3-Dimethoxy-5-[16′-(3″,5″-dimethoxyphenyl)-8′(*Z*)-hexadecen-1-yl]benzene (14). A solution of dienyne **11** (295 mg, 1.35 mmol) and 9-BBN (537 mg, 4.4 mmol) in THF (60 mL) is stirred at ambient temperature for 8 h. To the resulting triorganoborane **12** (^{11}B NMR: δ = 79.1) is added MeOH (containing 1% HOAc, w/w, 166 mg, 5.2 mmol), and the mixture is stirred for 2.5 h until ^{11}B NMR inspection indicates quantitative cleavage of the alkenylborane group (^{11}B NMR: δ = 70.9, 50.8, rel intensity 2:1). After addition of NaOMe (270 mg, 5 mmol), the reaction is stirred for another 60 min until a clear solution of the respective borate complex **13** has formed (^{11}B NMR: δ = 4.1, −2.7) to which triflate **7** (687 mg, 2.4 mmol) and $PdCl_2$(dppf) (59 mg, 0.07 mmol) are added. The mixture is refluxed for 1 h and worked-up as described above. A final flash chromatography with hexane/ethyl acetate (15:1) as the eluent affords product **14** as a colorless syrup (370 mg, 62%). ^{1}H NMR: δ = 6.34 (d, 4H, J = 2.2), 6.29 (t, 2H, J = 1.5), 5.34 (t, 2H, J = 4.5), 3.77 (s, 12H), 2.54 (vt, 4H), 2.00 (m, 4H), 1.60 (m, 4H), 1.40−1.20 (m, 16H). ^{13}C NMR: δ = 160.6, 145.3, 129.8, 106.4, 97.5, 55.2, 36.3, 31.2, 29.7, 29.4, 29.3, 29.2, 27.2. MS, *m*/*z* (rel intensity): 496 (29) [M$^+$], 400 (4), 345 (1), 233 (5), 219 (5), 194 (5), 165 (16), 152 (100).

1-Pentadecen-8-yne (15). A suspension of 1-octynyllithium (0.70 g, 6 mmol) and iodide **10** (1.20 g, 4.9 mmol) in THF (40 mL) is refluxed for 7.5 h. For workup the solvent is removed *in vacuo*, the residue is suspended in hexane (40 mL), the suspension is stirred for 30 min, insoluble LiI is filtered off through a short pad of silica, and the filtrate is concentrated affording **15** as a colorless liquid (912 mg, 90%). ^{1}H NMR: δ = 5.81 (m, 1H), 4.95−5.05 (m, 2H), 2.14 (m, 2H), 2.04 (m, 2H), 1.60−1.20 (m, 14H), 0.88 (t, 3H, J = 7). ^{13}C NMR: δ = 138.9 (d), 114.2 (t), 80.3 (s), 80.0 (s), 31.4 (t), 29.1 (t), 29.0 (t), 28.5 (t), 28.4 (t), 28.3 (t), 22.6 (t), 18.8 (t), 18.7 (t), 14.0 (q). MS, *m*/*z* (rel intensity): 206 (2) [M$^+$], 191 (3), 177 (11), 163 (24), 149 (17), 136 (55), 121 (100), 107 (66), 95 (63), 93 (79), 81 (87), 79 (69), 67 (86), 55 (39), 41 (38). Anal. $C_{15}H_{26}$ (206.4) Calcd: C 87.31, H 12.69. Found: C 87.64, H 12.36.

1,3-Dimethoxy-5-[8′(*Z*)-pentadecen-1-yl]benzene (16). A solution of substrate **15** (336 mg, 1.6 mmol) and 9-BBN (415 mg, 3.4 mmol) in THF (60 mL) is stirred for 7 h at ambient temperature. To the resulting bis-borane (^{11}B NMR: δ = 79.1) is added MeOH (containing 1% HOAc, w/w, 200 mg, 6.3 mmol), and the mixture is stirred for 2.5 h at that temperature until selective cleavage of the alkenyl borane entity has occurred (^{11}B NMR: δ = 71.1, 55.9; rel intensity 1:1). NaOMe (224 mg, 4.1 mmol) is then introduced, and the mixture is stirred for 1 h until borate formation is complete (^{11}B NMR: δ = 4.2, −2.6). Subsequent addition of triflate **7** (425 mg, 1.5 mmol) and $PdCl_2$(dppf) (41 mg, 0.05 mmol), refluxing of the mixture for 1 h, evaporation of the solvent, partition of the residue between Et_2O and water (30 mL each), drying of the organic layer (Na_2SO_4), evaporation of the solvent, and final flash chromatography of the crude product with hexane/ethyl acetate (20:1) affords compound **16** as a colorless syrup (431 mg, 83%). ^{1}H NMR: δ = 6.34 (d, 2H, J = 2.3), 6.29 (t, 1H, J = 2.3), 5.35 (t, 2H, J = 4.5), 3.77 (s, 6H), 2.54 (vt, 2H), 2.01 (m, 4H), 1.60 (m, 2H), 1.40−1.20 (m, 16H), 0.88 (t, 3H, J = 7). ^{13}C NMR: δ = 160.7, 145.3, 129.9, 129.8, 106.4, 97.5, 55.2, 36.3, 31.8, 31.2, 29.7(2C), 29.4, 29.3, 29.2, 29.0, 27.2, 27.1, 22.6, 14.1. MS, *m*/*z* (rel intensity): 346 (20) [M$^+$], 250 (5), 233 (4), 219 (3), 194 (5), 165 (13), 152 (100).

General Procedure for the Cleavage of the Methyl Ether Groups by 9-Iodo-9-BBN. A mixture of the respective 1-alkyl-3,5-dimethoxybenzene derivative (1 mmol) and 9-iodo-9-BBN (2.1 mmol) in hexane (20 mL) is stirred for 1−4 h at ambient temperature. The volatiles are removed *in vacuo*, the residue is dissolved in Et_2O (10 mL), and a solution of ethanolamine (2.2 mmol) in THF (1 mL) is added causing spontaneous precipitation of the 9-BBN·ethanolamine adduct. After stirring for 3 h, this precipitate is filtered off (mp = 217−218 °C), the filtrate is evaporated, and the crude resorcinols are chromatographed using hexane/ethyl acetate (2:1, 1:1) as eluent. This affords analytically pure compounds, the analytical data of which are compiled below.

1,3-Dihydroxy-5-tridecylbenzene (1): 90%, colorless solid, mp = 83−84 °C (lit.[2a] 83.5−85.4 °C). ^{1}H NMR: δ = 6.23 (d, 2H, J = 2.3), 6.16 (t, 1H), 5.25 (s, 2H, OH), 2.48 (t, 2H, J = 7), 1.56 (m, 2H), 1.30−1.15 (m, 20H), 0.88 (t, 3H, J = 7.5). ^{13}C NMR: δ = 156.7, 146.1, 107.9, 100.1, 35.8, 31.9, 31.0, 29.7 (3C), 29.64, 29.58, 29.50, 29.33, 29.29, 22.7, 14.1. MS, *m*/*z* (rel intensity): 292 (24) [M$^+$], 250 (2), 208 (2), 166 (6), 137 (10), 124 (100).

1,3-Dihydroxy-5-[8′(*Z*)-pentadecen-1-yl]benzene (2): 96%, waxy solid, mp = 32 °C (DSC) (lit.[2a] 31−33 °C). ^{1}H NMR: δ

= 6.25 (d, 2H, J = 2.3), 6.17 (t, 1H), 5.61 (s, 2H, OH), 5.35 (t, 2H, J = 4.5), 2.45 (vt, 2H), 2.01 (m, 4H), 1.53 (m, 2H), 1.40−1.20 (m, 16H), 0.88 (t, 3H, J = 7). ^{13}C NMR: δ = 156.4, 146.2, 130.0, 129.8, 108.1, 100.3, 35.8, 31.8, 31.0, 29.74, 29.71, 29.4, 29.3, 29.2, 29.0, 27.21, 27.18, 22.6, 14.1. MS, *m/z* (rel intensity): 318 (16) [M$^+$], 222 (7), 205 (3), 191 (4), 163 (6), 137 (11), 124 (100).

1,3-Dihydroxy-5-[14′-(3″,5″-dihydroxyphenyl)tetradecyl]benzene (3): 88%, colorless solid, mp = 138 °C dec (DSC) (lit.[2a] 118−120 °C). ^{1}H NMR (THF-d_8): δ = 7.79 (s, 4H, OH), 6.04 (d, 4H, J = 2.3), 5.97 (t, 2H), 2.41 (vt, 4H), 1.55 (m, 4H), 1.28 (m, 20H). ^{13}C NMR (THF-d_8): δ = 159.9, 145.3, 107.3, 100.8, 36.8, 32.2, 30.63 (4C), 30.57, 30.50, 30.2. MS, *m/z* (rel intensity): 414 (25) [M$^+$], 396 (2), 291 (2), 231 (3), 166 (4), 137 (12), 124 (100).

1,3-Dihydroxy-5-[16′-(3″,5″-dihydroxyphenyl)hexadec-8′(*Z*)-en-1-yl]benzene (5): 98%, colorless solid, mp = 53 °C dec (DSC) (lit.[2a] 129−132 °C). There is no obvious explanation for this discrepancy in the melting points. ^{1}H NMR (THF-d_8): δ = 7.78 (bs, 4H, OH), 6.03 (d, 4H, J = 2.3), 5.97 (t, 2H), 5.32 (t, 2H, J = 4.5), 2.41 (vt, 4H), 2.02 (m, 4H), 1.55 (m, 4H), 1.31 (m, 18H). ^{13}C NMR (THF-d_8): δ = 159.5, 145.3, 130.5, 107.3, 100.8, 36.8, 32.2, 30.7, 30.4, 30.2, 28.0. MS, *m/z* (rel intensity): 440 (22) [M$^+$], 422 (1), 344 (4), 317 (2), 205 (4), 191 (4), 163 (17), 137 (14), 124 (100).

5-Pentadecyl-2,2-dimethylbenzo[1,3]dioxin-4-one (18). A solution of 1-pentadecene (884 mg, 4.2 mmol) and 9-H-9-BBN (510 mg, 4.2 mmol) in THF is stirred at ambient temperature for 1 h. The resulting borane (^{11}B NMR: δ = 79.9) is reacted with NaOMe (227 mg, 4.2 mmol) for 30 min (^{11}B NMR: δ = −2.7) prior to the addition of triflate **17** (1.24 g, 3.8 mmol)[8b] and $PdCl_2$(dppf) (93 mg, 0.11 mmol). The reaction mixture is refluxed for 1 h (^{11}B NMR: δ = 55.8), the solvent is evaporated, the residue is partitioned between Et_2O and water (30 mL each), the organic layer is separated and dried (Na_2SO_4), the solvent is removed *in vacuo*, and the crude product is purified by flash chromatography with hexane/ethyl acetate (20/1) as the eluent, thus affording product **18** as colorless crystals (1.17 g, 79%): mp = 60−61 °C. ^{1}H NMR: δ = 7.38 (t, 1H, J = 8), 6.92 (d, 1H, J = 8), 6.79 (d, 1H, J = 8), 3.09 (vt, 2H), 1.69 (s, 6H), 1.58 (m, 2H), 1.40−1.20 (m, 24H), 0.88 (t, 3H, J = 7). ^{13}C NMR: δ = 160.2, 157.1, 148.5, 135.0, 125.0, 115.0, 112.1, 104.9, 34.4, 31.9, 31.2, 29.7 (8C), 29.5, 29.3, 25.6 (2C), 22.7, 14.1. MS, *m/z* (rel intensity): 388 (27) [M$^+$], 330 (100), 312 (20), 287 (12), 273 (12), 185 (10), 161 (34), 147 (29), 55 (11), 43 (10).

Anacardic Acid (19). A solution of substrate **18** (1.09 g, 2.8 mmol) in aqueous KOH (50%, 8 mL) and DMSO (20 mL) is heated at 80 °C for 1 h. The reaction mixture is cooled to ambient temperature and diluted with water (20 mL) and ethyl acetate (50 mL), the organic layer is separated and dried (Na_2SO_4), the solvent is removed *in vacuo*, and the crude product is purified by passing through a short silica gel column with hexane/ethyl acetate/HOAc (66:33:1) as the eluent. This gives the title compound as a colorless solid (924 mg, 95%): mp = 87−88 °C (lit.[14b] 89−89.5 °C). ^{1}H NMR: δ = 9.80 (br. s, 1H), 7.30 (t, 1H, J = 8), 6.82 (d, 1H, J = 8), 6.74 (d, 1H, J = 8), 2.94 (vt, 2H), 1.56 (m, 2H), 1.25 (br. s, 24H), 0.88 (t, 3H, J = 7). ^{13}C NMR: δ = 175.8, 162.9, 147.3, 134.8, 122.6, 115.6, 111.3, 36.2, 32.0, 31.9, 29.8, 29.7, 29.6, 29.5, 29.4, 25.6, 22.7, 14.1. MS, *m/z* (rel intensity): 348 (100) [M$^+$], 330 (60), 312 (23), 304 (15), 301 (13), 287 (16), 273 (14), 259 (10), 175 (13), 161 (41), 152 (28), 147 (32), 134 (25), 108 (43), 55 (16), 43 (26).

5-[8′(*Z*)-Pentadecenyl]-2,2-dimethylbenzo[1,3]dioxin-4-one (20). A solution of compound **15** (454 mg, 2.2 mmol) and 9-H-9-BBN (552 mg, 4.52 mmol) in THF (60 mL) is stirred at ambient temperature for 14 h. The resulting bis-borane (^{11}B NMR: δ = 79.4) is treated with MeOH (containing 1% HOAc, w/w, 158 mg, 4.9 mmol) for 5 h causing selective cleavage of the alkenylborane group (^{11}B NMR: δ = 72.9, 55.9, rel intensity = 1:1). Addition of NaOMe (250 mg, 4.6 mmol) and stirring of the mixture for 30 min leads to the corresponding borate complex (^{11}B NMR: δ = 7.6, −2.4) which is cross coupled with triflate **17** (1.403 g, 4.3 mmol) at reflux temperature for 1 h in the presence of $PdCl_2$(dppf) (106 mg, 0.13 mmol). Workup as described above followed by flash chromatography with hexane/ethyl acetate (15:1) as the solvent affords product **20** as a colorless syrup (574 mg, 67%). ^{1}H NMR: δ = 7.38 (t, 1H, J = 8), 6.92 (d, 1H, J = 8), 6.79 (d, 1H, J = 8), 5.34−5.38 (m, 2H), 3.09 (vt, 2H), 1.99 (m, 4H), 1.69 (s, 6H), 1.60 (m, 4H), 1.40−1.20 (m, 14H), 0.88 (t, 3H, J = 7). ^{13}C NMR: δ = 160.2, 157.1, 148.5, 135.0, 130.3, 129.8, 125.0, 115.0, 104.9, 34.3, 32.6, 31.2, 29.7, 29.6, 29.4, 29.3, 29.2, 29.1, 29.0, 27.2, 25.6 (2C), 22.6, 14.1. MS, *m/z* (rel intensity): 386 (46) [M$^+$], 328 (100), 310 (52), 285 (11), 271 (16), 257 (19), 243 (10), 225 (11), 211 (18), 197 (16), 185 (11), 161 (27), 146 (56), 133 (15), 107 (13), 95 (12), 81 (15), 67 (19), 55 (23), 41 (21).

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Supporting Information Available: Copies of the ^{1}H and ^{13}C NMR spectra of products **1**, **2**, **3**, **5**, **8**, **9**, **14**, **16** and of the DSC curves of products **2**, **3**, and **5**; large scale preparation of 7-iodo-1-heptene (**10**); a scheme depicting an alternative approach to product **14** based on Lindlar semihydrogenation as the key-step; description of the instrumentation used and of the spectra formats (30 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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