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Articles

Design, Synthesis, and Biological Evaluation of Conformationally Constrained *aci*-Reductone Mimics of Arachidonic Acid[1]

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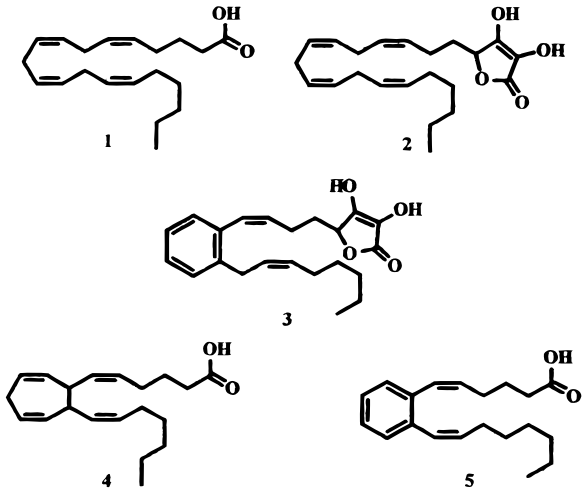
An efficient and convergent synthesis has been developed for the production of 3,4-dihydroxy-5-[4-(2-((2*Z*)-hexenyl)phenyl)-3-(1*Z*)-butenyl]-2(5*H*)-furanone (**12d**). This hydrophobic antioxidant is a stable conformationally constrained mimic of arachidonic acid (AA) (**1**) and its respective *aci*-reductone analogue (**2**). Pd(0)-catalyzed cross-coupling of 5-(3-butynyl)-3,4-dihydroxy-2(5*H*)-furanone (**7**) with 2-((2*Z*)-hexenyl)iodobenzene (**8d**) followed by Lindlar catalyzed hydrogenation produces **12d**. Butynyl intermediate **7** is prepared from 2-(benzyloxy)-5-deoxyascorbic acid (**15**) by iodination (I_2, PPh_3, Imd), iodo substitution with lithium acetylide ethylenediamine complex (LiAEDA, HMPA, −5 °C), and benzyl group cleavage (Ac_2O, Pyr, BCl_3). The utility of this synthetic method was demonstrated by the synthesis of analogues **10e**−**k**. Biological testing revealed that certain of these antioxidants inhibit both cyclooxygenase (COX) and 5-lipoxygenase (5-LO) with comparable efficacy as reported for aspirin and zileuton, respectively. The antioxidant activity of these *aci*-reductones, measured as a function of their inhibitory effect on CCl_4-induced lipid peroxidation of hepatic microsomes, exceeds that produced by α-tocopherol. Synthetic routes and initial structure−activity relationships (SAR) for these novel mixed functioning antioxidants are presented.

Introduction

The development of dual antioxidant arachidonic acid (AA) metabolism inhibitors may provide added benefits over existing drugs for the treatment of diseases associated with oxidative stress and inflammation. Numerous conditions, which are currently treated by the administration of antiinflammatory agents, including asthma, rheumatoid arthritis,[2] irritable bowel disease (IBD),[3,4] adult respiratory distress syndrome (ARDS),[5] atherosclerosis,[6,7] ischemia/reperfusion injury,[8,9] restenosis,[10,11] neurodegenerative disorders,[12−14] and initiation and promotion of carcinogenesis,[15] correlate with abnormally high levels of reactive oxygen species (ROS). Antioxidant-based therapies through the administration of both natural antioxidants (e.g., vitamin E, vitamin C, and superoxide dismutase, SOD) and synthetic antioxidants (e.g., 4-aryl-2-hydroxytetronic acids,[16] 2-*O*-alkylascorbic acids,[17] probucol,[18] and tirilazad mesylate[19]) have been or are currently being investigated for the management of a number of these conditions.

Previously, *S*-AA *aci*-reductone analogue (**2**) (Chart 1) was identified as a stereoselective and potent AA metabolic inhibitor synthesized in our laboratories.[20] This compound inhibits both PGE_2 and LTB_4 production in stimulated macrophages ($IC_{50} = 20\ \mu M$) and blocks AA-induced platelet aggregation (AAIPA) with an $IC_{50} < 10\ \mu M$. Dual cyclooxygenase (COX) and lipoxygenase (LO) activity could be important in preventing substrate shunting in the AA cascade and therefore provide an improved class of antiinflammatory agents. Although **2** demonstrates an encouraging biological profile, both its instability and labored synthesis render this compound less than satisfactory as a pharmaceutical.

Chart 1. Conformationally Constrained Mimics of AA



To provide compounds which retain the biological properties observed in **2**, possess increased stability, and have a simplified synthesis, conformationally constrained analogues of the type **3** (Chart 1) were envisaged. The 2-hydroxytetronic acid moiety is a stable carboxylic acid bioisostere with a redox potential sufficient to protect lipid membranes against oxidative damage. The phenyl ring is proposed to mimic the C8 and C11 cis skipped double bonds of AA (**1**). The ortho

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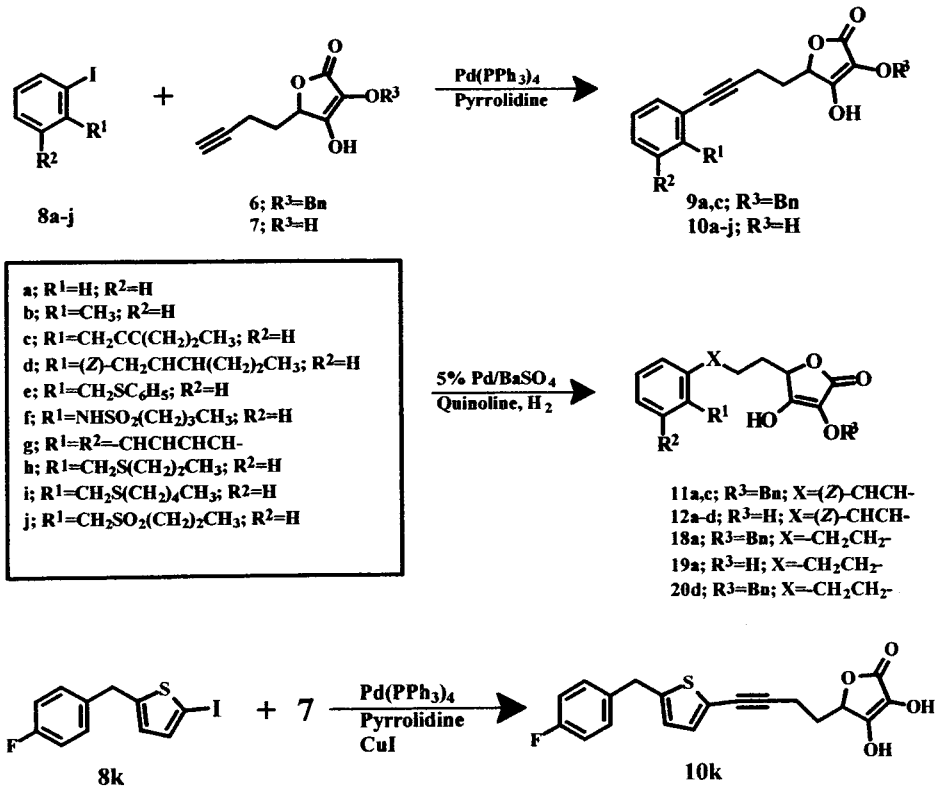
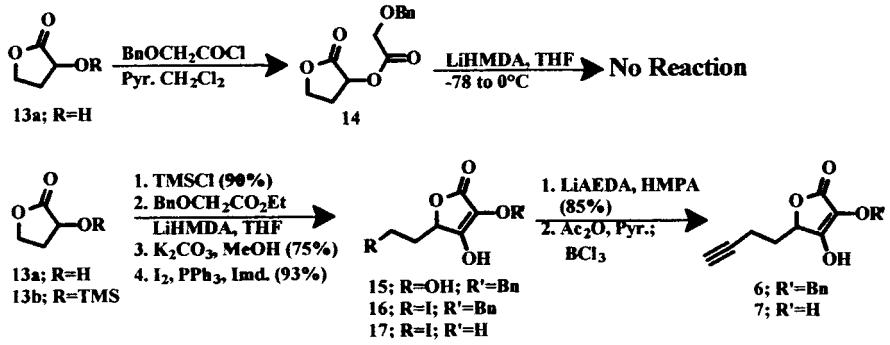
Scheme 1



Scheme 2



substituent, which contains the relative C13 through C20 portion of AA, functions to maintain the suspected COX-bound conformation of the fatty acid. 2-Hexenylbenzene analogue **12d** was identified as the synthetic target in favor of 2-octenyl derivative **3,** because of the lower cost of starting materials.

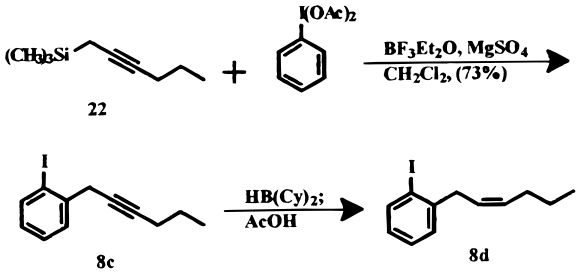
Others have synthesized constrained analogues of AA which display promising biological activities. Nicolaou and Webber[21] prepared cis- and trans-7,13-bridged AA **4**, reported to be potent and selective 5-LO inhibitors. Buckle and Fenwick[22] synthesized ortho-substituted phenyl-5-octenoic acid derivative **5**. This compound has little effect against 5-LO but inhibits phospholipase A_2 by 70% at 20 μM. 2-Hydroxytetronic acid analogue **12d** is ionized at physiological pH and has a biologically relevant redox potential similar to that observed for ascorbic acid.[23] Such a redox function is proposed to interfere with the active site of LO and COX enzymes and to scavenge ROS in lipid membranes. Further, the ortho substituent in **12d** presents a benzylic hydrogen in the same relative position as the C13 *pro-S* hydrogen of AA. This hydrogen is involved in the mechanism by which COX catalyzes the conversion of AA into PGG_2 by way of tyrosyl-385 radical abstraction.[24] Synthetic routes and initial structure−activity relationships (SAR) for these novel mixed functioning AA metabolic inhibitors are discussed.

Results and Discussion

Target compound **12d** and related analogues **10a,b,d−k** were anticipated to be available in a convergent synthesis by coupling 5-(3-butynyl)tetronic acid **6** or **7** with substituted iodobenzenes **8a−k** followed by Lindlar catalyzed hydrogenation (Scheme 1).

Butynyltetronic acid **6** was prepared in four steps from commercially available α-hydroxylactone **13a** by the method of Stork and Rychnovsky (Scheme 2).[25] Intermolecular condensation of the lithium hexamethyldisilazide (LiHMDA)-produced anion of ethyl (benzyloxy)acetate with [(trimethylsilyl)oxy]lactone **13b** followed by treatment with anhydrous K_2CO_3 in MeOH at 0 °C provides 5-deoxyascorbic acid derivative **15** in 75% yield. Initial attempts to synthesize **15** by intramolecular Claisen cyclization[26] of (benzyloxy)acetate

Scheme 3



14 (LiHMDA, THF, −78 → 0 °C) failed; only starting material could be isolated. Iodination (I_2, PPh_3, Imd, 93%) of benzyl-protected tetronic acid **15** provided iodo species **16**, which underwent reaction with 3 equiv of lithium acetylide ethylenediamine (LiAEDA) complex in HMPA at −5 °C to give 2-(benzyloxy)tetronic acid **6** as a yellow solid in 85% crude yield.[27] Benzyl group cleavage[28] to provide intermediate **7** was effected in 80% yield and in one pot by acetylation of the vinylogous acid **6** (Ac_2O, Pyr) followed by treatment of the crude residue with BCl_3. Alternatively, benzyl group cleavage of iodo compound **16** (Ac_2O, Pyr, BCl_3) provides 2-hydroxytetronic acid **17** in 90% yield. However, reaction of **17** with LiAEDA gives **7** in only 30% yield.

In a model study, palladium tetrakis(triphenylphosphine)-catalyzed coupling[29] between 2-(benzyloxy)-tetronic acid **6** and iodobenzene in pyrrolidine at room temperature for 3 h produced benzyl-protected arylethynyl analogue **9a** in 90% isolated yield (Scheme 1). Attempted direct Lindlar catalyzed reduction of intermediate **9a** to the desired 2-hydroxytetronic acid olefin **12a** failed. Saturated compound **18a** formed after 1 h, and after 3 h at atmospheric pressure, debenzylated compound **19a** was isolated. Alternatively, Lindlar reduction of intermediate **9a** (1 equiv of H_2 at 1 atm) to the cis olefin **11a** and benzyl group cleavage (Ac_2O, Pyr, BCl_3) gave the desired cis olefinic 2-hydroxytetronic acid **12a**.

Iodobenzene **8c** was prepared by a BF_3-Et_2O-assisted reductive iodonio-Claisen rearrangement[30] reaction of iodobenzene diacetate with 1-(trimethylsilyl)-2-hexyne[31] **(22)** (Scheme 3). Coupling of (benzyloxy)tetronic acid **6** with iodobenzene **8c** produced diyne **9c** in approximately 50% yield. Lindlar reduction at atmospheric pressure resulted in the formation of monoolefin **11c** after consumption of 1 equiv of H_2. Utilization of a second equivalent of H_2 resulted in reduction of the freshly formed double bond without effecting the triple bond of the hexynyl side chain to produce monoalkyne **20d**. Attempted debenzylation of intermediate **11c** by acetylation and treatment with BCl_3 was unsuccessful and resulted in the isolation of a compound lacking vinyl protons in the ^1H NMR spectrum.[32]

To circumvent problems with benzyl group deprotection and partial alkyne reduction, coupling of 2-((2*Z*)-hexenyl)iodobenzene **(8d)** with 2-hydroxytetronic acid **7** was investigated. Hexenylbenzene **8d** was obtained in 78% yield by dicyclohexylborane reduction of hexyne **8c**. $Pd(PPh_3)_4$-catalyzed coupling in pyrrolidine provided enyne **10d** in better than 70% yield. Lindlar catalyzed reduction yielded target diene **12d**.

This convergent reaction sequence was utilized for the production of compounds **10e**−**k**, which were designed for the exploration of structure−activity relationships. Initial biological screening data against COX-1,[33] COX-2,[33] 5-LO,[34] and LPO[35] for these analogues and related derivatives (**10a**,**b**,**d** and **12d**) are summarized in Table 1. All compounds at a test concentration of 300 μM effectively inhibited CCl_4-induced LPO of polyunsaturated fatty acids from guinea pig liver microsomes as quantified by spectrophotometric analysis of MDA formation, with equivalent or better potency than that produced by α-tocopherol. Generally, poor to modest inhibitory activity against COX-1 and COX-2 was observed by all test compounds. Test compounds were screened at 300 μM against both COX-1, which was isolated from ram seminal vesicle, and COX-2, which was obtained from sheep placenta. COX activity was determined by measuring the formation of thiobarbiturate-reactive substances photospectrometrically at 530 nm. Enyne **10d** and pentylthiomethyl analogue **10i** were the most potent COX inhibitors in this series, with potencies similar to that of aspirin. Precursor enyne **10d** is a slightly more effective inhibitor of COX-1 (55% at 300 μM) than designed AA mimic **12d** (37% at 300 μM). 2-Methylphenyl and phenyl compounds **10a**,**b**, respectively, are ineffective inhibitors of both isoforms of COX. These data suggest that the ortho substituent is important for biological activity.

Table 1. Biological Evaluation of Compounds **10a**−**k** and **12d** for Inhibition of COX-1-, COX-2-, 5-LO-, and CCl_4-Induced LPO of Hepatic Microsomes

compd	COX-1 (300 μM)[a]	COX-2 (300 μM)	5-LO (30 μM)	LPO (300 μM)
10a	5[b]	13	58	62
10b	8	18	43	59
10d	55	28	81, $IC_{50} = 0.4$ μM	72
10e	25	15	100, $IC_{50} = 0.3$ μM	61
10f	8	23	81	75
10g	34	22	97, $IC_{50} = 0.3$ μM	73
10h	38	20	82	72
10i	67	45	90	62
10j	25	12	30	60
10k	NT	NT	100, $IC_{50} = 0.16$ μM	NT
12d	37	28	99	68
α-tocopherol[c]	NT	NT	NT	$IC_{50} = 280$ μM
BW755C[c]	NT	NT	$IC_{50} = 5.6$ μM	NT
aspirin[c]	76, $IC_{50} = 240$ μM	0, $IC_{50} = 660$ μM	0	4
indomethacin[c]	$IC_{50} = 1.7$ μM	$IC_{50} = 2.4$ μM	NT	NT

[a] The test concentrations at which compounds were screened are in parentheses. NT, not tested. [b] Percent inhibition values are provided unless otherwise indicated as an IC_{50} value. All experiments were performed in duplicate by Panlabs, Inc., Bothell, WA. [c] For comparison purposes, data are provided for α-tocopherol, BW755C, aspirin, and indomethacin.

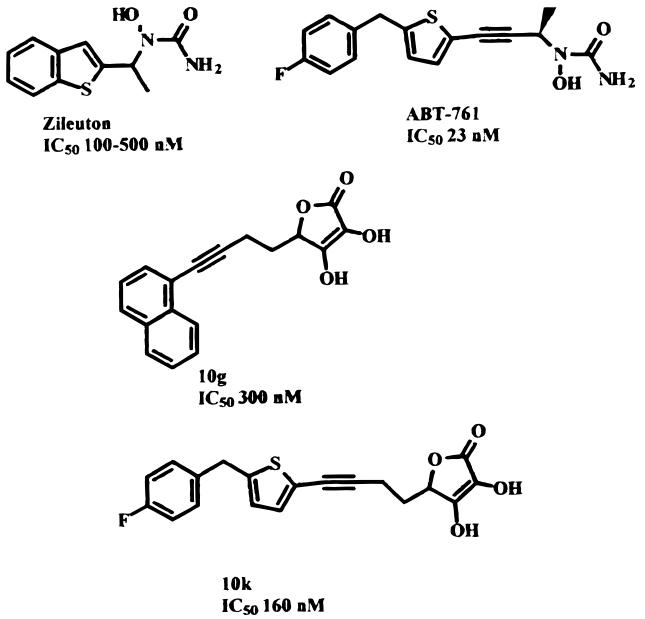


Figure 1. Comparison of the *N*-hydroxyurea 5-LO inhibitors zileuton and ABT-761 with the 2-hydroxytetronic acid analogues **10g**,**k**. The IC_{50} values are for inhibition of 5-LO in the broken RBL-1 cell assay.

Most of the compounds produce greater than 80% inhibition of 5-LO in a crude enzyme preparation from rat basophilic leukemia cells (broken RBL-1) at a test concentration of 30 μM. The observed activity of these agents against 5-LO is likely due primarily to the antioxidant properties associated with the 2-hydroxytetronic acid moiety and, to a lesser degree, the structure of the lipophilic arylbutyne substituent. Not surprisingly, initial studies from our laboratories indicate that removal of the 2-hydroxyl group from the *aci*-reductone ring provides tetronic acids which are devoid of both LPO and 5-LO activity. Note, however, that structural activity relationships for this series of *aci*-reductones exist; the substituents in the aromatic ring influence the inhibitory activity against 5-LO. For example, sulfone **10j** inhibits 5-LO by 30% at 30 μM, while benzenesulfonamide **10f** produces 80% inhibition at 30 μM. IC_{50} values for thiophenol **10e**, enyne **10d**, and naphthylyne derivative **10g** range between 300 and 500 nM, and this is in the range reported for Abbott's 5-LO inhibitor zileuton.[36] The close structural resemblance and similar 5-LO inhibitory activity of the *aci*-reductones **10e**−**j** and the *N*-hydroxyurea class of 5-LO inhibitors suggest that the 2-hydroxytetronic acid functionality may in fact act as a bioisostere for the *N*-hydroxyurea moiety (Figure 1). Interestingly, benzylthiophene derivative **10k**, a close structural analogue of ABT-761, which has an IC_{50} of 23 nM in the broken RBL-1 assay,[36] was the most potent 5-LO inhibitor of this series with an IC_{50} of 160 nM.

ROS are important pathogenic mediators in numerous diseases due to their effect on cellular membranes, which apparently results in the activation of transcription factors such as AP1 and NF-κB.[7] The inflammatory response element NF-κB is upregulated by H_2O_2, oxidatively modified low-density lipoproteins (LDL), lipopolysaccharide (LPS), UV radiation, and certain cytokines in vitro.[37] Antioxidants including pyrrolidinedithiocarbamate (PDTC) and *N*-acetylcysteine block both H_2O_2- and LPS-induced NF-κB nuclear translocation, thus further implicating ROS involvement in the signal transduction pathway which regulates NF-κB activity. Naphthyl-substituted derivative **10g** inhibits LPS-induced NF-κB nuclear translocation by 90% at 30 nM. The potency of this analogue is unprecedented. The internal standards, antioxidant PDTC and glucocorticoid steroid dexamethasone, inhibit NF-κB nuclear translocation by 50% at 10 000 nM and 60% at 1000 nM, respectively. The mechanism of action of naphthyl derivative **10g** is unknown but may be linked to its antioxidant activity. Compounds capable of controlling the production of inflammatory proteins and their products at the gene level are anticipated to lack the undesirable side effects associated with steroids but to produce similar antiinflammatory activity.[38] The mixed functioning antioxidant AA metabolism inhibitors described here may provide superior antiinflammatory activity over conventional therapies in vivo by inhibiting both NF-κB nuclear translocation and inflammatory eicosanoid biosynthesis. Studies designed to determine the mechanisms by which these compounds inhibit 5-LO and NF-κB activation and also to identify important structure−activity relationships are in progress.

Experimental Section

General Methods. Melting points were determined in open capillaries with a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Unless otherwise noted all reagents were purchased from commercial suppliers and used as received. Preparative scale separations were carried out by column chromatography using 70−240 mesh silica gel 60A. ^{1}H and ^{13}C NMR spectra were recorded on either a Bruker AM 300 MHz or Varian 200 MHz spectrometer. Elemental analyses were performed by Quantitative Technologies, Inc., Whitehouse, NJ.

Assay for NF-κB Nuclear Translocation. Experiments were performed with transformed rat alveolar macrophages (NR8383 cells). Cells were treated simultaneously with LPS (1 μg/mL) and the test compounds. Untreated control cells and cells treated with LPS alone were tested in each experiment. Cells were harvested 6 h after treatment, and nuclear proteins were extracted, frozen, and quantified using the Bradford assay. Electrophoretic mobility shift assays (EMSA) were subsequently performed using a radiolabeled NF-κB probe. Following reaction of the nuclear proteins with the radiolabeled probe and separation on a 5% polyacrylamide gel, the bands were assayed by autoradiography. NF-κB binding selectivity was assayed by cold and nonspecific competition using the LPS-treated sample in each experiment. All EMSA were repeated at least once to verify results. Laser densitometry of NF-κB bands was done on autoradiographs to quantify NF-κB binding activity and compare treatment groups

3-(Benzyloxy)-4-hydroxy-5-(2-hydroxyethyl)-2(5*H*)-furanone (15).[25] A solution of 10.0 g (98 mmol) of **13a** in 100 mL of anhydrous THF under argon and with magnetic stirring was cooled to 0−5 °C. Addition of 14 mL (110 mmol) of TMSCl and 16 mL (115 mmol) of TEA immediately produced a white precipitate. The suspension was warmed to room temperature and stirred for 4 h. The suspension was poured into a separatory funnel containing 100 mL of H_2O and 500 mL of ether. The organic layer was washed with 50 mL of H_2O and 50 mL of brine, dried ($MgSO_4$), and concentrated. Purification (Kugelrohr distillation) provided 14.7 g (90%) of the (silyloxy)-lactone **13b**: bp 80−100 °C (8 mmHg).

To a 500-mL two-necked flask, flame-dried under argon and equipped with a magnetic stir bar, were added 200 mL of THF and 18.7 mL (89 mmol) of HMDS. The flask was cooled to −78 °C, and 55.4 mL (89 mmol) of a 1.6 M *n*-BuLi solution in

hexanes was added with stirring over 15 min. The light-yellow solution was stirred for an additional 15 min, and 16.7 g (86 mmol) of ethyl (benzyloxy)acetate was added over 5 min. The solution was stirred for 20 min at −78 °C, and 14.7 g (84.4 mmol) of **13b** was added via syringe. The reaction was quenched after 30 min by pouring into a mixture of 100 mL of 10% concentrated HCl solution and 500 mL of ether. The aqueous layer was separated and washed with 2 × 100 mL of ether. The combined ether extracts were washed with 50 mL of brine, dried ($MgSO_4$), and concentrated.

The yellow oil was dried in vacuo for 15 h and placed under argon, and 400 mL of MeOH was added. The solution was cooled to 0 °C with stirring, and 11.7 g (85 mmol) of anhydrous K_2CO_3 was added. After 30 min, the suspension was concentrated to about 75 mL, diluted with 100 mL of H_2O and 50 mL of saturated bicarbonate solution, and washed with 2 × 100 mL of ether. The aqueous phase was acidified with concentrated HCl to a pH near 1 and extracted with 10 × 150 mL of ether. The combined ether extracts were washed with 100 mL of brine, dried ($MgSO_4$), and concentrated to a yellow oil (18.7 g, 86%) which solidified upon standing. Recrystallization from benzene and hexanes provided 15.8 g (75%) of a white solid: mp 98−99 °C; ^{1}H NMR (acetone-d_6) δ 0.7.46−7.27 (m, 5H), 5.06 (s, 2H), 4.83 (t, J = 6.3 Hz, 1H), 3.85−3.69 (m, 2H), 2.05−1.95 (m, 1H), 1.89−1.76 (m, 1H). Anal. ($C_{13}H_{14}O_5$) C, H.

3-(Benzyloxy)-4-hydroxy-5-(2-iodoethyl)-2(5*H*)-furanone (16).[39] To an oven-dried, 250-mL round-bottom flask flushed with argon were added 5.8 g (22 mmol) of PPh_3, 1.5 g (22 mmol) of imidazole, and 80 mL of Et_2O−CH_3CN (3:1). The mixture was cooled in an ice water bath with magnetic stirring, and 5.6 g (22 mmol) of iodine was added in four equal portions with vigorous stirring. The resulting slurry was warmed at room temperature for 20 min and cooled to 0 °C, 5.0 g (20 mmol) of **15** dissolved in 20 mL of CH_3CN−Et_2O (1:1) was added in one portion, and the remainder was rinsed in with 5 mL of Et_2O. The mixture was stirred at 0 °C for 10 min and then at room temperature for 30 min, and the reaction was quenched by pouring into 150 mL of 10% HCl solution and extracting with 500 mL of Et_2O−hexanes (1:1). The aqueous layer was separated and extracted with 100 mL of Et_2O. The combined organic fractions were washed with 50 mL of H_2O and extracted with 5 × 50 mL of saturated $NaHCO_3$ solution. The combined bicarbonate extracts were washed with 50 mL of Et_2O−hexanes (1:1), acidified to pH below 2, and extracted with 3 × 200 mL of Et_2O. The combined ether extracts were washed with 100 mL of brine, dried ($MgSO_4$), and concentrated to 6.7 g (93%) of a white solid which was not further purified: mp 101−104 °C; ^{1}H NMR ($CDCl_3$) δ 7.40−7.27 (m, 5H), 5.06 (dd, J = 11.4 Hz, 2H), 4.69 (dd, J = 3.4, 8.0 Hz, 1H), 3.06 (t, J = 7.3 Hz, 2H), 2.41−2.29 (m, 1H), 2.02−1.90 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 170.33, 160.61, 136.32, 128.77, 128.69, 128.58, 120.11, 75.76, 73.39, 35.77, −2.03. Anal. ($C_{13}H_{13}O_4I$) Calcd: C, 43.35; H, 3.64. Found: C, 43.94; H, 3.69.

3,4-Dihydroxy-5-(2-iodoethyl)-2(5*H*)-furanone (17). To a dry flask flushed with argon were added 0.72 g (2.0 mmol) of **16** and 10 mL of CH_2Cl_2. The solution was cooled with stirring in an ice−water bath, and 0.38 mL (4.0 mmol) of acetic anhydride and 0.34 mL (4.2 mmol) of pyridine were added. The ice bath was removed, and the solution was stirred for 1 h. All volatile substances were removed in vacuo (2 h at 1 mmHg, 25 °C). Argon was introduced to the reaction flask, the residue was taken up in 20 mL of dry CH_2Cl_2 and cooled to −78 °C, and 5.2 mL (2.6 mmol) of 1.0 M BCl_3 in CH_2Cl_2 was added with stirring. The reaction mixture was kept at −78 °C for 1 h and at room temperature for 30 min. The mixture was poured into 50 mL of brine and extracted with 3 × 30 mL of Et_2O. The combined Et_2O extracts were washed with 5 mL of H_2O and extracted into $NaHCO_3$ (3 × 15 mL). The bicarbonate fractions were pooled and washed with 15 mL of ether, acidified to pH 1 with 25% concentrated HCl solution, and extracted into Et_2O (3 × 30 mL). The Et_2O extracts were washed with 15 mL of brine, dried ($MgSO_4$), and concentrated to 360 mg (67%) of a white crystalline solid: mp 150−151 °C; ^{1}H NMR (acetone-d_6) δ 4.80 (dd, 1H, J = 3.5, 8.0 Hz), 3.50−3.25 (m, 2H), 2.60−2.35 (m, 1H), 2.20−1.95 (m, 1H). Anal. ($C_6H_7O_4I$) C, H.

3-(Benzyloxy)-5-(3-butynyl)-4-hydroxy-2(5*H*)-furanone (6).[27] To a flame-dried, three-necked round-bottom flask with magnetic stir bar, argon inlet, and septum containing 5.7 g (55.8 mmol) of 90% LAEDA complex was added 20 mL of HMPA. The suspension was stirred for 15 min at room temperature and cooled in an ice bath (acetone/CO_2) to between −5 and −10 °C, and 6.7 g (18.6 mmol) of **16** dissolved in 15 mL of HMPA was added over a 2-min period. A dark-brown-orange slurry formed, and the temperature was maintained between 0 and −5 °C for 30 min. The reaction was quenched by the careful addition of 150 mL of 10% concentrated HCl solution, which was immediately extracted with 2 × 200 mL of ether. The combined ether extracts were washed with 2 × 50 mL of 5% aqueous HCl solution and extracted with 4 × 50 mL of $NaHCO_3$ solution. The combined bicarbonate extracts were washed with 50 mL of ether, acidified with 20% concentrated HCl solution to pH 1, and extracted with 3 × 150 mL of Et_2O. The combined Et_2O extracts were washed with 50 mL of brine, dried ($MgSO_4$), and concentrated leaving 4.1 g (85% crude yield) of a yellow solid. This material was used without further purification in subsequent steps: mp 85−88 °C; ^{1}H NMR ($CDCl_3$) δ 7.38−7.26 (m, 5H), 5.06, (q, J_{ab} = 11.6 Hz, 2H), 4.75 (dd, J = 3.5, 8.1 Hz, 1H), 2.27−2.20 (m, 2H), 2.12−2.01 (m, 1H), 1.98 (t, J = 2.6 Hz, 1H), 1.73−1.62 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 169.93, 160.90, 136.39, 128.77, 128.73, 128.64, 120.13, 82.31, 74.30, 73.43, 69.71, 30.78, 13.72.

5-(3-Butynyl)-3,4-dihydroxy-2(5*H*)-furanone (7).[28] An oven-dried, 250-mL one-necked flask equipped with a magnetic stir bar was flushed with argon and attached to an argon inlet, and 2.6 g (10.0 mmol) of **6** and 50 mL of anhydrous CH_2Cl_2 were added. The solution was cooled in an ice bath to 5 °C with magnetic stirring, and 1.9 mL (20.0 mmol) of acetic anhydride was added followed by 1.7 mL (21 mmol) of pyridine. The ice bath was removed after 1 h, and the mixture was concentrated on a rotary evaporator and dried at 0.5 mmHg at room temperature for 12 h. Argon was introduced followed by 100 mL of dry CH_2Cl_2. The solution was cooled to −78 °C with stirring, and 25 mL (25 mmol) of 1.0 M BCl_3 in CH_2Cl_2 was added. The reaction mixture was allowed to gradually warm to 10 °C over about 2 h and maintained at 10 °C for 1 h. The mixture was poured into 50 mL of brine and extracted with 4 × 100 mL of Et_2O. The combined Et_2O fractions were extracted with 3 × 25 mL of saturated $NaHCO_3$ solution. The combined bicarbonate extracts were washed with 25 mL of Et_2O, acidified to pH 1 with concentrated HCl solution, and extracted with 5 × 100 mL of Et_2O. The combined Et_2O washes were dried ($MgSO_4$), filtered through 100 g of silica gel (remove polar impurity), and washed with 1 L of ether. Removal of solvent in vacuo left 1.4 g (80%) of analytically pure off-white solid: mp 124−128 °C dec; ^{1}H NMR (acetone-d_6) δ 4.79 (dd, J = 3.4, 8.3 Hz, 1H) 2.42 (t, J = 2.6 Hz, 1H), 2.37−2.30 (m, 2H), 2.20−2.09 (m, 1H), 1.81−1.67 (m, 1H); ^{13}C NMR (acetone-d_6) δ 170, 153.7, 119, 83.4, 74.7, 70.9, 32.4, 14.4. Anal. ($C_8H_8O_4$) C, H.

2-((2*Z*)-Hexenyl)iodobenzene (8d).[40] A dry, 25-mL two-necked flask equipped with a magnetic stir bar, argon inlet, and septum was cooled to 0 °C, and 3 mL of 1.0 M BH_3 in THF was added. Cyclohexene (607 μL, 6 mmol) was added via syringe, and the suspension stirred at 0−5 °C for 35 min. Iodobenzene **8c**[30] (0.852 g, 3.0 mmol) was added to the reaction mixture dropwise over 5 min. The ice bath was removed, and the yellow reaction mixture stirred at room temperature for 1 h. The solution that formed was cooled in an ice bath, and 1.4 mL (25 mmol) of glacial AcOH was added. The solution stirred at room temperature for 1 h, was poured into 75 mL of H_2O, and was extracted with 3 × 30 mL of hexanes. The combined hexane fractions were washed with 25 mL of H_2O, 25 mL of saturated $NaHCO_3$ solution, 25 mL of H_2O, and 2 × 20 mL of brine, dried ($MgSO_4$), and concentrated to an oil (do not warm above 30 °C to avoid isomerization of the double bond). Purification over 40 g of silica gel using hexanes as

eluant provided 670 mg (78%) of a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.82 (d, J = 7.8 Hz, 1H), 7.30−7.20 (m, 2H), 6.91−6.86 (m, 1H), 5.62−5.46 (m, 2H), 3.47 (d, J = 6.5 Hz, 2H), 2.17−2.10 (m, 2H), 1.49−1.37 (m, 2H), 0.94 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 143.8, 139.3, 131.8, 129.2, 128.3, 127.7, 126.6, 100.8, 38.8, 29.6, 22.7, 13.9. Anal. ($C_{12}H_{15}I$) C, H.

General Procedure for Coupling Reactions.[29] Pd(PPh_3)$_4$ (58 mg, 0.05 mmol), an iodobenzene **8a**−**k** (2.0 mmol), butynyltetronic acid **6** or **7** (1.0 mmol), 2 mL of pyrrolidine, and 19 mg (0.1 mmol) of CuI were added to a flame-dried reaction flask fitted with an argon inlet, septum, and magnetic stir bar. The flask was protected from light (foil), and the yellow mixture was stirred at room temperature until starting material was not visible by TLC analysis ($CHCl_3$−MeOH, 9:1). The reaction mixture was poured into 50 g of ice and 10 mL of concentrated HCl and extracted with 2 × 50 mL of Et_2O. The Et_2O extracts were combined and washed with 2 × 20 mL of 10% HCl solution, 20 mL of H_2O, and 20 mL of brine, dried ($MgSO_4$), and concentrated.

3-(Benzyloxy)-4-hydroxy-5-(4-phenyl-3-butynyl)-2(5*H*)-furanone (9a). This was prepared by coupling **6** with iodobenzene **8a** on a 2.0-mmol scale by the general coupling method described above to yield 600 mg (90%) of **9a**. Purification: The residue was diluted with pentanes and extracted with 5 × 20 mL of $NaHCO_3$ solution. The combined extracts were washed with 25 mL of 1:1 pentane−Et_2O solution, acidified to pH 1 with 20% concentrated HCl solution, and extracted into 2 × 50 mL of Et_2O. The ether extracts were washed with 30 mL of H_2O and 30 mL of brine, dried ($MgSO_4$), and concentrated: ^{1}H NMR ($CDCl_3$) δ 7.38−7.19 (m, 10H), 5.06 (s, 2H), 4.78 (dd, J = 3.5, 8.0 Hz, 1H), 3.75 (dt, J = 3.9, 8.1 Hz, 2H), 2.22−2.12 (m, 1H), 1.81−1.71 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 171.2, 161.7, 136.4, 131.6, 128.6, 128.5, 128.5, 128.3, 127.9, 123.5, 120.0, 87.8, 81.9, 74.9, 73.4, 31.0, 14.7.

3,4-Dihydroxy-5-(4-phenyl-3-butynyl)-2(5*H*)-furanone (10a). Iodobenzene **8a** and 2-hydroxytetronic acid **7** were coupled using the general procedure. Compound **10a** was purified by dissolving in 30 mL of Et_2O and extracting into saturated $NaHCO_3$ solution (3 × 15 mL). The bicarbonate extracts were pooled and washed with 10 mL of Et_2O, acidified to pH 2 with 10% HCl solution, and extracted into Et_2O (2 × 25 mL). The Et_2O extracts were combined and washed with 10 mL of H_2O, 3 mL of 10% saturated $NaHCO_3$ in H_2O (i.e., 1 mL of saturated $NaHCO_3$ solution in 9 mL of H_2O) in order to remove highly polar acidic impurities, 10 mL of H_2O, and 10 mL of brine, dried ($MgSO_4$), and concentrated to a white solid: mp 145−146 °C; ^{1}H NMR (acetone-d_6) δ 7.35−7.15 (m, 5H), 4.75 (dd, J = 3.4, 8.2 Hz, 1H), 2.50−2.40 (m, 2H), 2.20−2.05 (m, 1H), 1.75−1.60 (m, 1H); ^{13}C NMR (acetone-d_6) δ 170.2, 153.8, 132.3, 129.2, 128.7, 124.6, 119.0, 89.3, 82.1, 74.9, 32.4, 15.3.

3,4-Dihydroxy-5-[4-(2-methylphenyl)-3-butynyl]-2(5*H*)-furanone (10b). This was synthesized by coupling 2-hydroxytetronic acid **7** with 2-iodotoluene (**8b**) following the general coupling method above. Purification over silica gel using $CHCl_3$−MeOH (96:4) as eluant provided *aci*-reductone **10b** as a light-yellow solid: mp 111−112 °C; ^{1}H NMR ($CDCl_3$) δ 7.37−7.07 (m, 4H), 5.01 (dd, J = 3.5, 8.5 Hz, 1H), 2.69−2.65 (m, 2H), 2.40 (s, 3H), 2.39−2.27 (m, 1H), 1.97−1.86 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 173.6, 155.8, 140.0, 131.9, 129.3, 127.9, 125.5, 123.1, 117.5, 91.5, 80.9, 76.4, 31.3, 20.7, 15.3. Anal. ($C_{15}H_{14}O_4$) C, H.

3,4-Dihydroxy-5-[4-(2-((2*Z*)-hexenyl)phenyl)-3-butynyl]-2(5*H*)-furanone (10d). This was synthesized by coupling 0.34 g (2.0 mmol) of 2-hydroxytetronic acid **7** with 1.1 g (4.0 mmol) of 2-iodo-1-[(2*Z*)-hexenyl]benzene (**8d**) following the general coupling procedure described above. Purification over silica gel using $CHCl_3$−MeOH (96:4) as eluant provided 100 mg (17%) of a yellow oil, which was dried at 0.05 mmHg at 58 °C for 2 h: ^{1}H NMR (acetone-d_6) δ 7.43−7.15 (m, 4H), 5.70−5.45 (m, 2H), 4.91 (dd, 1H, J = 3.4, 8.3 Hz), 3.57 (d, 2H, J = 5.9 Hz), 2.66 (t, 2H, J = 7.0 Hz), 2.37−2.11 (m, 3H), 2.00−1.85 (m, 1H), 1.48−1.29 (m, 2H), 0.93 (t, 3H, J = 7.3 Hz). Anal. ($C_{20}H_{22}O_4$·0.2H_2O) C, H.

3,4-Dihydroxy-5-[4-(2-((phenylthio)methyl)phenyl)-3-butynyl]-2(5*H*)-furanone (10e). This was synthesized by coupling 350 mg (1.1 mmol) of 2-[(phenylthio)methyl]-1-iodobenzene (**8e**)[41] with 120 mg (0.71 mmol) of 2-hydroxytetronic acid **7** following the general coupling procedure described above. Purification over silica gel using $CHCl_3$−MeOH−AcOH (96:3:1) as eluant provided 180 mg (69%) of a light-yellow oil, which was dried at 0.05 mmHg at 58 °C for 2 h: ^{1}H NMR (acetone-d_6) δ 7.44−7.19 (m, 9H), 4.90 (dd, J = 3.3, 8.3 Hz, 1H), 4.36 (s, 2H), 2.63 (t, J = 7.6 Hz, 2H), 2.28−2.21 (m, 1H), 1.90−1.81 (m, 1H). Anal. ($C_{21}H_{18}O_4S$) C, H.

3,4-Dihydroxy-5-[4-(*N*-butyl-2-benzenesulfonamido)-3-butynyl]-2(5*H*)-furanone (10f). This was synthesized by coupling 400 mg (1.2 mmol) of *N*-butyl-2-iodobenzenesulfonamide (**8f**) with 168 mg (1.0 mmol) of 2-hydroxytetronic acid **7** following the general coupling procedure described above. Purification over silica gel using $CHCl_3$−MeOH−AcOH (500:16:0.5) as eluant provided a light-yellow oil, which was dried at 0.05 mmHg at 58 °C for 2 h: ^{1}H NMR (acetone-d_6) δ 8.00−7.96 (m, 1H), 7.59−7.55 (m, 1H), 7.33−7.24 (m, 2H), 6.66 (s, 1H), 4.82 (dd, J = 3.4, 8.3 Hz, 1H), 3.44−3.36 (m, 2H), 3.23−3.14 (m, 2H), 2.52−2.45 (m, 1H), 2.00−1.94 (m, 1H), 1.69−1.53 (m, 2H), 1.43−1.29 (m, 2H), 0.81 (t, J = 7.2 Hz, 3H); ^{13}C NMR (acetone-d_6) δ 169.8, 153.5, 141.6, 137.6, 130.0, 124.2, 123.8, 120.9, 118.6, 114.4, 108.7, 74.8, 53.6, 32.0, 24.9, 24.1, 20.9, 12.9. Anal. ($C_{18}H_{21}NO_6S$) C, H, N.

3,4-Dihydroxy-5-[4-(2-naphthyl)-3-butynyl]-2(5*H*)-furanone (10g). This was synthesized by coupling 300 μL (2.0 mmol) of 2-iodonaphthalene (**8g**) with 175 mg (1.0 mmol) of 2-hydroxytetronic acid **7** following the general coupling procedure described above. Purification over silica gel using $CHCl_3$−MeOH−AcOH (96:3:1) as eluant provided 230 mg (75%) of a viscous yellow oil, which solidified after drying at 0.05 mmHg at 58 °C for 2 h: ^{1}H NMR (acetone-d_6) δ 8.4−8.3 (m, 1H), 7.96−7.88 (m, 2H), 7.70−7.43 (m, 4H), 4.98 (dd, J = 3.4, 8.3 Hz, 1H), 2.82−2.75 (m, 2H), 2.48−2.29 (m, 1H), 2.00−1.85 (m, 1H). Anal. ($C_{18}H_{14}O_4$·0.5H_2O) C, H.

3,4-Dihydroxy-5-[4-(2-((propylthio)methyl)phenyl)-3-butynyl]-2(5*H*)-furanone (10h). This was synthesized by coupling 440 mg (1.5 mmol) of 2-[(propylthio)methyl]iodobenzene (**8h**) with 170 mg (1.0 mmol) of 2-hydroxytetronic acid **7** following the general coupling procedure described above. Purification over silica gel using $CHCl_3$−MeOH−AcOH (500:16:0.5) as eluant provided 240 mg (72%) of a yellow oil, which was dried at 0.05 mmHg at 58 °C for 2 h: ^{1}H NMR (acetone-d_6) δ 7.44−7.21 (m, 4H), 4.90 (dd, J = 3.4, 8.3 Hz, 1H), 3.89 (s, 2H), 2.70−2.63 (m, 2H), 2.48−2.41 (m, 2H), 2.26−2.21 (m, 1H), 1.90−1.81 (m, 1H), 1.64−1.53 (m, 2H), 0.93 (t, J = 7.3 Hz, 3H). Anal. ($C_{18}H_{20}O_4S$) Calcd: C, 65.05; H, 6.07. Found: C, 64.51; H, 6.28.

3,4-Dihydroxy-5-[4-(2-((pentylthio)methyl)phenyl)-3-butynyl]-2(5*H*)-furanone (10i). This was synthesized by coupling 240 mg (0.75 mmol) of 2-methyl(1-pentyl sulfide)-iodobenzene (**8i**) with 84 mg (0.5 mmol) of 2-hydroxytetronic acid **7** following the general coupling procedure described above. Purification over silica gel using $CHCl_3$−MeOH−AcOH (500:16:0.5) as eluant provided a yellow oil, which was dried at 0.05 mmHg at 58 °C for 2 h: ^{1}H NMR (acetone-d_6) δ 7.43−7.21 (m, 4H), 4.95 (dd, J = 3.4, 8.4 Hz, 1H), 3.89 (s, 2H), 2.70−2.63 (m, 2H), 2.50−2.43 (m, 2H), 2.26−2.21 (m, 1H), 2.00−1.81 (m, 1H), 1.66−1.45 (m, 2H), 1.43−1.20 (m, 4H), 0.87 (t, J = 7.2 Hz, 3H). Anal. ($C_{20}H_{24}O_4S$·0.5H_2O) C, H.

3,4-Dihydroxy-5-[4-(2-((propylsulfonyl)methyl)phenyl)-3-butynyl]-2(5*H*)-furanone (10j). This was synthesized by coupling 600 mg (1.5 mmol) of 2-methyl(1-propyl sulfone)-iodobenzene (**8j**) with 236 mg (1.2 mmol) of 2-hydroxytetronic acid **7** following the general coupling procedure described above. Purification over silica gel using $CHCl_3$−MeOH−AcOH (500:16:0.5) as eluant provided 250 mg (50%) of a light-yellow oil, which was dried at 0.05 mmHg at 58 °C for 2 h: ^{1}H NMR (acetone-d_6) δ 7.56−7.34 (m, 4H), 4.96 (dd, J = 3.4, 8.2 Hz, 1H), 4.57 (s, 2H), 3.03−2.95 (m, 2H), 2.71−2.64 (m, 2H), 2.35−2.26 (m, 1H), 1.94−1.70 (m, 3H), 1.02 (t, J = 7.4 Hz, 3H); ^{13}C NMR (acetone-d_6) δ 169.9, 153.5, 132.9, 132.1, 131.0, 128.9,

128.5, 125.3, 118.6, 94.0, 79.6, 74.4, 57.2, 54.0, 31.5, 15.7, 14.8, 12.7. Anal. ($C_{18}H_{20}O_6S$) Calcd: C, 59.34; H, 5.53. Found: C, 58.93; H, 5.76.

3,4-Dihydroxy-5-[2-(4-((4-fluorophenyl)methyl)thiopheneyl)-3-butynyl]-2(5*H*)-furanone (10k). This was synthesized by coupling 750 mg (4.5 mmol) of **6** with 2.6 g (8.2 mmol) of 4-[(4-fluorophenyl)methyl]-2-iodothiophene[42] following the general coupling procedure described above. The residue was purified over silica gel using $CHCl_3$−MeOH−AcOH (500:15:0.5) as eluant and dried at 0.05 mmHg at 58 °C for 2 h to provide 1.2 g (75% yield) of **10k** as a brown wax: mp 119−121 °C; ^{1}H NMR (acetone-d_6) δ 7.38−7.25 (m, 2H), 7.13−6.99 (m, 3H), 6.78−6.74 (m, 1H), 4.84 (dd, J = 3.3, 8.1 Hz, 1H), 4.14 (s, 2H), 2.59 (t, J = 7.1 Hz, 2H), 2.38−2.14 (m, 1H), 1.90−1.69 (m, 1H); ^{13}C NMR (acetone-d_6) δ 169.19, 164.04, 157.29, 152.78, 145.79, 136.74, 131.80, 130.80, 130.47, 125.54, 122.74, 118.84, 115.89, 115.03, 92.44, 74.90, 74.31, 35.14, 31.84, 15.02. Anal. ($C_{19}H_{15}FO_4S$) C, H.

General Method for Lindlar Hydrogenation. Quinoline (70 μL, 0.6 mmol), 5% Pd/$BaSO_4$ (15 mg), and 0.25 mmol of the acetylene were combined in 20 mL of ethanol and hydrogenated at atmospheric pressure until 6 mL (0.25 mmol) of H_2 was consumed as measured by a H_2O filled buret. The catalyst was removed by filtration through two fluted filter papers, and the solution was concentrated to about 5 mL, taken up in 50 mL of ether, washed with 3 × 15-mL portions of 5% aqueous HCl, 20 mL of H_2O, and 20 mL of brine, dried ($MgSO_4$), and concentrated.

3-(Benzyloxy)-5-(4-phenylbutanyl)-4-hydroxy-2(5*H*)-furanone (18a). Hydrogenation of alkyne **9a** using 50 mg of 5% Pd/$BaSO_4$ and 70 μL of quinoline under a hydrogen-filled balloon for a period of 1 h provided saturated compound **18a**. Workup was performed as described in the general hydrogenation procedure: ^{1}H NMR (acetone-d_6) δ 7.46−7.12 (m, 10H), 5.04 (dd, J_{ab} = 11.4 Hz, 2H), 4.64 (dd, J = 3.5, 7.2 Hz, 1H), 2.58 (t, J = 7.8 Hz, 2H), 2.00−1.89 (m, 1H), 1.66−1.53 (m, 3H), 1.39−1.29 (m, 2H); ^{13}C NMR (acetone-d_6) δ 170.4, 163.8, 143.2, 138.4, 129.1, 129.0, 129.0, 129.0, 128.6, 126.4, 119.8, 76.2, 73.3, 36.2, 32.3, 32.0, 24.2. Anal. ($C_{21}H_{22}O_4$·0.25H_2O) C, H.

3,4-Dihydroxy-5-(4-phenylbutanyl)-2(5*H*)-furanone (19a). Alkyne **9a** was hydrogenated for 3 h as described for saturated compound **18a**. Workup was performed as described in the general hydrogenation procedure: ^{1}H NMR (acetone-d_6) δ 7.28−7.13 (m, 5H), 4.66 (dd, J = 3.4, 7.2 Hz, 1H), 2.62 (t, J = 7.7 Hz, 2H), 2.00−1.93 (m, 1H), 1.69−1.42 (m, 5H); ^{13}C NMR (acetone-d_6) δ 170.7, 154.9, 143.3, 129.2, 129.1, 126.5, 118.6, 76.2, 36.3, 32.7, 32.1, 24.6. Anal. ($C_{14}H_{16}O_4$·0.25H_2O) C, H.

3,4-Dihydroxy-5-(4-phenyl-(3*Z*)-butenyl)-2(5*H*)-furanone (12a). Method A. 3-(Benzyloxy)furanone **11a** (55 mg, 0.17 mmol) in a dry, 10-mL round-bottom flask under argon with a magnetic stir bar was taken up in 2.5 mL of CH_2Cl_2 and cooled to 0 °C, and 31.2 μL (0.33 mmol) of acetic anhydride and 26.1 μL (0.34 mmol) of pyridine were added with stirring. The ice bath was removed, and the solution was stirred at room temperature for 2 h. All volatile materials were removed in vacuo, and the residue was dried at 0.2 mmHg, 25 °C, for 2 h. The residue was placed under argon, dissolved in 1.7 mL of CH_2Cl_2, and cooled to −78 °C with stirring. BCl_3 (1.0 M) in CH_2Cl_2 (0.88 mL, 0.88 mmol) was added, and the mixture stirred while slowly warming to 15 °C over 2 h. The reaction mixture was poured into 25 mL of H_2O and extracted with 2 × 25 mL of Et_2O. The Et_2O extracts were washed with 10 mL of H_2O and extracted with 3 × 15 mL of saturated $NaHCO_3$ solution. The bicarbonate extracts were combined, acidified to pH 2, and extracted with 2 × 25 mL of Et_2O. The Et_2O extracts were combined, washed with 10 mL of H_2O and 10 mL of brine, dried ($MgSO_4$), and concentrated to a light-yellow oil as a 4:1 mixture of unsaturated **12a** and saturated **19a** as estimated by ^{13}C NMR.

Method B. 3,4-Dihydroxyfuranone **10a** was subjected to Lindlar catalyzed hydrogenation by the general method above to give a mixture of alkyne, *cis*-alkene, and alkane as an oil in a ratio of 1:5:0.5 as determined by ^{1}H NMR: ^{1}H NMR ($CDCl_3$) δ 7.34−7.14 (m, 5H), 6.46 (d, J = 11.5 Hz, 1H), 5.65−5.57 (m, 1H), 4.77 (dd, J = 3.5, 8.0 Hz, 1H), 2.49 (dd, J_{ab} = 7.6 Hz, 2H), 2.16−2.09 (m, 1H), 1.80−1.70 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 173.4, 155.9, 137.1, 130.4, 130.3, 128.7, 128.3, 128.3, 126.8, 117.5, 77.2, 31.8, 23.5.

3,4-Dihydroxy-5-[4-(2-methylphenyl)-(3*Z*)-butenyl]-2-(5*H*)-furanone (12b). This was synthesized by Lindlar catalyzed reduction of alkyne **10b** using the general hydrogenation procedure above to produce an oil containing only the cis isomer as observed by ^{1}H NMR spectra: ^{1}H NMR ($CDCl_3$) δ 7.34−7.20 (m, 4H), 6.59 (d, J = 11.4 Hz, 1H), 5.81−5.73 (m, 1H), 4.81 (dd, J = 3.4, 8.2 Hz, 1H), 2.49−2.35 (m, 2H), 2.33 (s, 3H), 2.17−2.13 (m, 1H), 1.81−1.75 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 173.6, 156.0, 136.2, 136.2, 130.2, 129.9, 129.6, 128.8, 127.1, 125.5, 117.4, 77.3, 31.9, 23.4, 19.9.

3,4-Dihydroxy-5-[4-(2-((2*Z*)-hexenyl)phenyl)-(3*Z*)-butenyl]-2(5*H*)-furanone (12d). This was synthesized by Lindlar catalyzed reduction of alkyne **10d** using the general hydrogenation procedure described above to produce an oil containing only the cis isomer as observed by ^{1}H NMR spectra. Less than 5% of starting material remained, which was not separable from the product: ^{1}H NMR (acetone-d_6) δ 7.25−7.15 (m, 4H), 6.59 (d, 1H, J = 11.4 Hz), 5.81−5.76 (m, 1H), 5.51−5.43 (m, 2H), 4.71 (dd, 1H, J = 3.5, 7.6 Hz), 3.44−3.25 (m, 2H), 2.40−1.90 (m, 5H), 1.76−1.58 (m, 1H), 1.50−1.32 (m, 2H), 0.94 (t, 3H, J = 7.3 Hz). Anal. ($C_{20}H_{24}O_4$·0.5H_2O) C, H.

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