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Access to 1,2,3,4-Tetraoxygenated Benzenes via a Double Baeyer–Villiger Reaction of Quinizarin Dimethyl Ether: Application to the Synthesis of Bioactive Natural Products from *Antrodia camphorata*[⊥]

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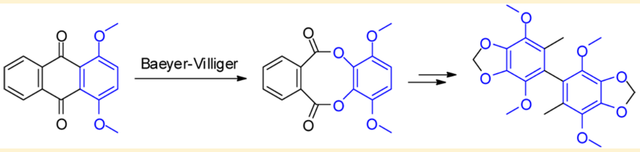
Supporting Information



ABSTRACT: The first systematic investigation into the Baeyer–Villiger reaction of an anthraquinone is presented. The double Baeyer–Villiger reaction of quinizarin dimethyl ether is viable, directly providing the dibenzo[*b*,*f*][1,4]-dioxocin-6,11-dione ring-system, which is otherwise difficult to prepare. This methodology provides rapid access to 1,2,3,4-tetraoxygenated benzenes, and has been exploited by application to the total synthesis of a natural occurring benzodioxole and its biphenyl dimer, which both display noteworthy biological activity. Interestingly, the axially chiral biphenyl was found to be configurationally stable, but the resolved enantiomers exhibit no optical activity at the αD-line.

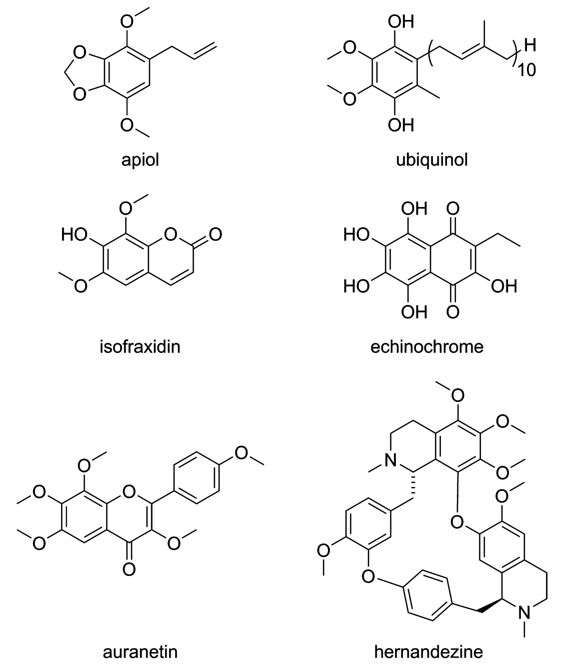
■ INTRODUCTION

The 1,2,3,4-tetraoxygenated benzene moiety is abundant in biologically active natural products spanning several chemotypes, including many food constituents valued for their antioxidant properties. Common and representative examples include apiol (Chart 1), a principal component of the essential oil of parsley;[1] ubiquinol, the reduced form of coenzyme Q_{10}; the cytotoxic coumarin, isofraxidin;[2] the sea urchin-derived, red naphthoquinone pigment, echinochrome;[3] the flavone auranetin, a constituent of orange peel;[4] the bisbenzylisoquinoline alkaloid hernandezine;[5] and tannins such as the oenotheins.[6]

Previous syntheses of 1,2,3,4-tetroxygenated benzenes (Scheme 1) include directed lithiation of 1,2,4-trimethoxybenzene, followed by a low-yielding quench with O_2[7] (eq 1); a directed lithiation/borylation/oxidation sequence, as part of a total synthesis of ecteinascidin 743[8] (eq 2); a three-step biocatalytic synthesis from D-glucose, involving four enzyme-catalyzed reactions and an acid-catalyzed dehydration/aromatization, applied to a synthesis of coenzyme Q_3[9] (eq 3); a three-step procedure from diisopropyl squarate, used in the total synthesis of enchinochrome[10] (eq 4); a peroxyacetic acid-induced Baeyer–Villiger oxidation of 2,6-dimethoxyacetophenone accompanied by electrophilic aromatic hydroxylation[11] (eq 5); and a low-yielding and incompletely regioselective palladium-catalyzed C–H acetoxylation of 1,2,3-trimethoxybenzene[12] (eq 6). The most common approach has been a regioselective Vilsmeier–Haack formylation or Friedel–Crafts acylation of a 1,2,3-tetraalkoxybenzene, followed by Baeyer–Villiger oxidation[13] (eq 7).

Building on our interest in the total synthesis of highly oxygenated benzenoid natural products,[14] we now report a novel and rapid approach to the 1,2,3,4-tetraoxygenated benzene nucleus, particularly suited to symmetrical compounds, involving a double Baeyer–Villiger oxidation of the anthraquinone, quinizarin dimethyl ether (**1**) (Scheme 2). The

Chart 1. Common 1,2,3,4-Tetraoxygenated Benzene-Containing Natural Products



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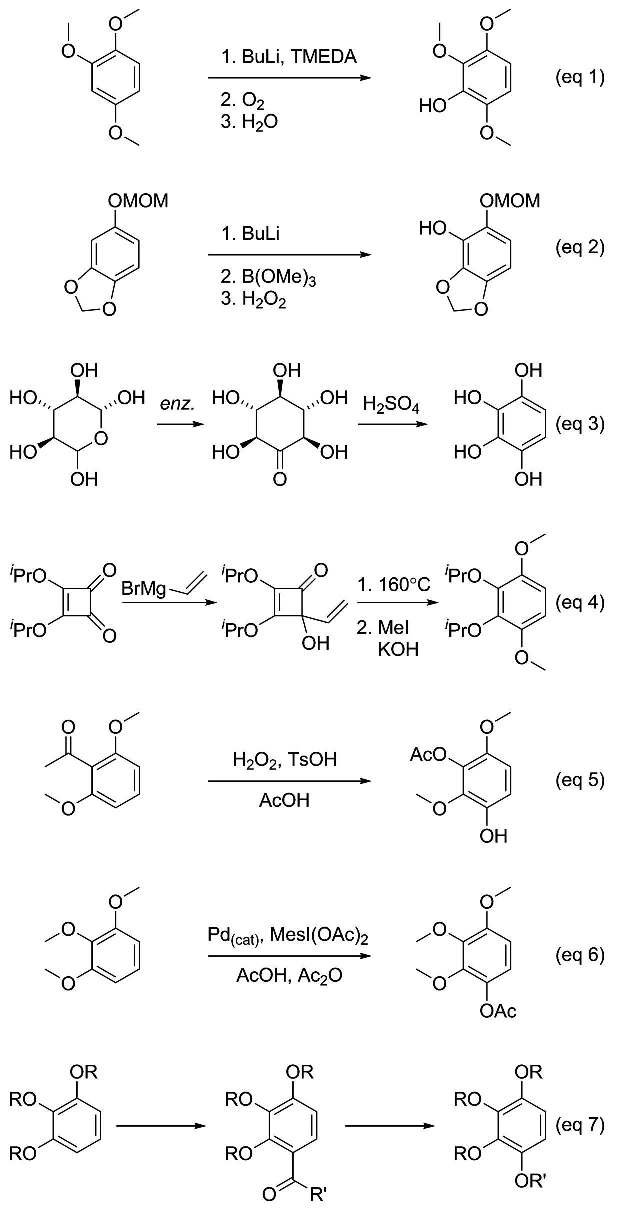
Scheme 1. Examples of Previous Syntheses of 1,2,3,4-Tetraoxygenated Benzenes

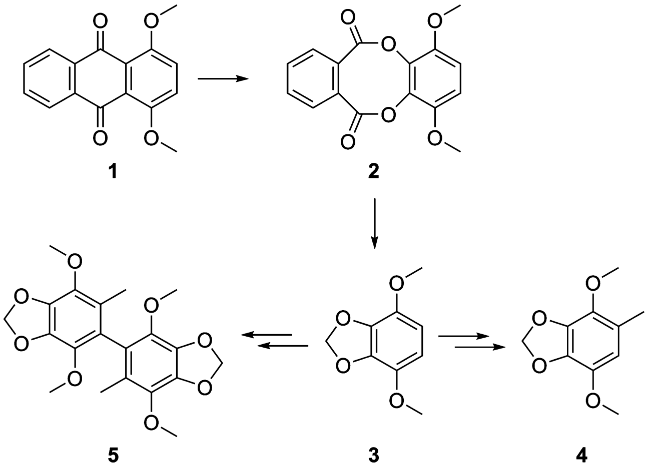


methodology has been applied to the total synthesis of two natural products, **4** and **5** (Scheme 2), which demonstrate biological activity worthy of further investigation.

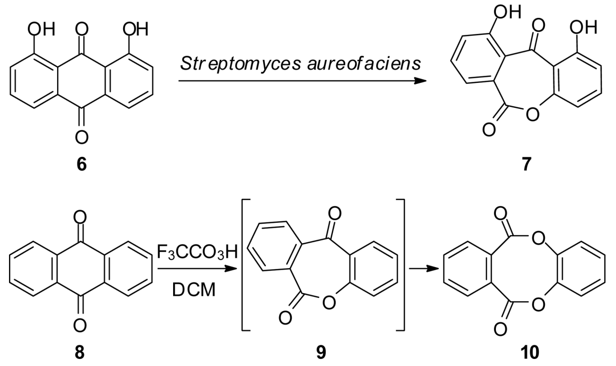
■ RESULTS AND DISCUSSION

To the best of our knowledge, and somewhat surprisingly, there are only two reported examples of Baeyer−Villiger reactions of anthraquinones. Microbial transformation of chrysazin (**6**) gave the oxepine lactone **7** (Scheme 3),[15] a reaction that would be very difficult to replicate through chemical (as opposed to enzymatic) means, since oxygen insertion occurs at the least electron rich site.

Scheme 2. Overview of the Work Described Herein



Scheme 3. Precedents for the Microbial[15] and Chemical[19] Baeyer−Villiger Oxidation of Anthraquinones

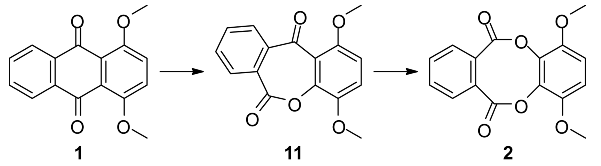


Treatment of anthraquinone (**8**) with peroxytrifluoroacetic acid was reported to give a "very low yield" of dibenzo[*b*,*f*]-[1,4]dioxocine-6,11-dione (**10**).[16] The inefficiency of this reaction was attributed to strain and rigidity in the seven-membered ring of the intermediate oxepine **9**. The ring system present in **10** is quite rare, with the only other reported syntheses involving very low-yielding (3−10%) condensation of phthaloyl chlorides with catechol.[16,17] Our studies suggest that the previous low yields of **10** are, at least in part, due to its instability (see below).

In the Baeyer−Villiger oxidation of quinizarin dimethyl ether (**1**), based on migratory aptitudes,[18] we expected oxygen insertion to occur adjacent to the more electron-rich dimethoxybenzene. Indeed, treatment of **1** with excess *m*-chloroperbenzoic acid (*m*CPBA), alone or with TFA,[19] gave a mixture of the oxepine **11** and dioxocin **2** (Table 1); however, the reaction stalled and could not be pushed to favor the double Baeyer−Villiger product **2**. Thus, alternative oxidants were explored; the more promising results are summarized in Table 1. The reaction of quinizarin dimethyl ether with hydrogen peroxide and sulfuric acid gave only very polar products, perhaps arising from sulfonation. Urea−hydrogen peroxide complex/trifluoroacetic anhydride[20] gave the desired dioxocin in low yield, which was improved with sodium percarbonate in trifluoroacetic acid (TFA).[21] The best yields were obtained with sodium perborate tetrahydrate.[22]

Although a rapid and inexpensive way to access 1,2,3,4-tetraoxygenated benzenes, the Baeyer−Villiger reaction of quinizarin dimethyl ether is somewhat capricious. Yields are very sensitive to reaction time, presumably due to competing transesterification by trifluoroacetic acid (TFA), and/or hydrolysis, and subsequent further oxidation of the electron rich 1,2,3,4-tetraoxygenated benzene. Attempts to minimize the decomposition of **2** by using acetic acid in place of TFA, or

Table 1. Optimization of the Double Baeyer–Villiger Oxidation of Quinizarin Dimethyl Ether (2)



oxidant	equiv (scale)[a]	time (min)	NMR yield[c] (isolated yield) % 2	11	phthalic anhydride
Urea·H_2O_2, TFAA[b]	8, 2.5	135	14	53	13
Na_2CO_3·1.5 H_2O_2	4	120	<50	nd	nd
$NaBO_3$·$4H_2O$	3	120	18	67 (28)	12
$NaBO_3$·$4H_2O$	5	105	58	trace	23
$NaBO_3$·$4H_2O$	5	120	45	–	5
$NaBO_3$·$4H_2O$	6	90	66	–	21
$NaBO_3$·$4H_2O$	6 (2)	90	<66[d] (37)[e]	nd	nd
$NaBO_3$·$4H_2O$	**6 (10)**	**75**[g]	**<70**[d] **(39)**[f]	nd	nd
$NaBO_3$·$4H_2O$	10	30	63 (22)[f]	9	31

[a] All reactions were conducted in TFA on a 1 mmol scale unless indicated. [b] Solvent was DCM. [c] Calculated from the mass and ^1H NMR spectra of crude dioxocin **2** following aqueous workup. [d] Maximum yield based on crude mass. [e] After chromatography. [f] After recrystallization from EtOAc. [g] Water bath used to dissipate initial exotherm. nd = not determined.

DCM with a smaller excess of TFA, were unsuccessful. The reaction with sodium perborate monohydrate was significantly slower than that with the tetrahydrate, with only a small amount of the oxepine **8** present by TLC after 90 min. Similarly, in situ removal of the water by use of TFA/trifluoroacetic anhydride (TFAA) completely shut the Baeyer–Villiger reaction down and resulted in complex mixtures. These results suggest that water facilitates the reaction to some extent. However, deliberate addition of a small amount of water (0.1 mL in 5 mL TFA) led to a decrease in reaction rate. Ultimately, reasonable yields and purities of dioxocin **2** were obtained by increasing the number of equivalents of oxidant, and keeping reaction times short.

It should be noted that sodium perborate tetrahydrate is very cheap (<US $100/kg), safe (used in some teeth bleaching products) and environmentally friendly (hydrolyses to H_2O_2 and boric acid), so its use in stoichiometric excess is not problematic.

Dioxocin **2** is unstable on silica gel, which results in significant losses upon chromatography. The instability of **2** is presumably due to strain in the 8-membered ring, which forces the carbonyl groups out of conjugation with the ring-oxygen lone pair electrons, and the adjacent aromatic ring, as is apparent in the X-ray crystal structure (Figure 1). The latter was obtained after crystallization from EtOAc, the best method of purification if pure dioxocin is required.

An attempt was also made to optimize the yield of the lactone **11**, and while the crude yield could indeed be increased by reducing the number of equivalents of oxidant (up to a ratio of 4:1 of oxepine **11** to dioxocin **2**, based on the ^1H NMR spectrum of the crude product), purification proved difficult; the lactone underwent partial hydrolysis during chromatography. Again, a pure sample of **11** was obtained by crystallization, although the recovery was quite poor (28%).

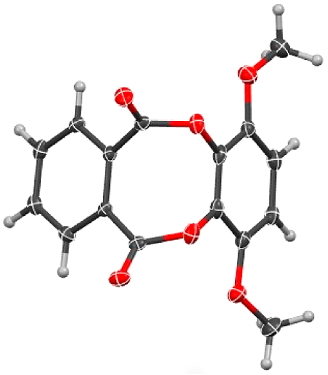
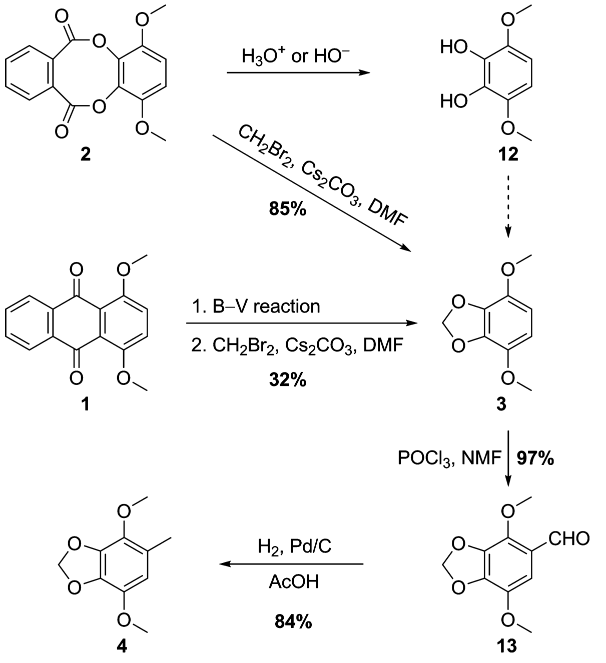


Figure 1. Representation of the crystal structure of dioxocin **2** showing the pronounced buckling of the central ring, which forces the carbonyl groups out of conjugation with the adjacent aromatic ring, and presumably contributes to its hydrolytic instability. Ellipsoids in this and subsequent figures are shown at 50% probability amplitudes with hydrogen atoms assigned arbitrary radii.

The dioxocin **2** was then used in the synthesis of two natural products isolated from the *Antrodia camphorata*[23] (also called *Antrodia cinnamomea*, *Taiwanofungus camphoratus*, *niu-chang-chih* or *jang-jy*), a fungus that grows only on the stout camphor tree, tree *Cinnamomum kanehirae*, in Taiwan, where it is a traditional medicine of great value. The simple benzodioxole **4** exhibits promising in vitro[24] and in vivo[25] anticolon cancer activity, while its dimer, biphenyl **5**, is reported to exhibit antiviral effects against wild-type and lamivudine-resistant hepatitis B virus (HBV).[26]

Initial attempts to cleanly hydrolyze the dioxocin **2** under basic or acidic conditions gave several byproducts in addition to low yields of the desired catechol **12** (Scheme 4). Therefore, we attempted a one-pot, two-step reaction on the predication that

Scheme 4. Synthesis of the Anticancer Natural Product 4[a]

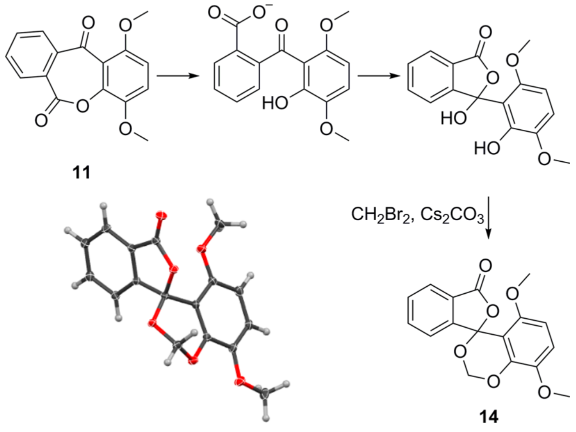


[a] B–V = Baeyer–Villiger, NMF = *N*-methylformanilide.

a mildly nucleophilic base might cleave the rather unstable dioxocin, under conditions that would allow the catechol to be trapped in situ. In practice this worked well, providing the known benzodioxole **3**[14a] in good yield, when undistilled molecular sieve-dried DMF was used as solvent. However, the yield dropped dramatically when freshly distilled, dry DMF was used. We reasoned that adventitious water, or perhaps dimethylamine from partial decomposition of DMF, facilitates the cleavage of the dioxocin. Indeed, when a little water was added to the freshly distilled, dry DMF, yields of the benzodioxole improved.

Given the chromatographic instability of dioxocin **2**, we also attempted the methylenation of the crude product. Although this did provide the easily purified benzodioxole **3**, yields were quite poor (32% from quinizarin dimethyl ether, i.e., over two steps), suggesting that byproducts were interfering with the desired methylenation step. On one occasion, clearly when the double Baeyer–Villiger reaction had not gone to completion, the methylenation of the crude Baeyer–Villiger product gave the unusual spirodioxine **14** as a major product, as confirmed with an X-ray crystal structure. A mechanism explaining its formation is shown in Scheme 5. The ring system present in **14** is unprecedented; discovery of related acetal–lactones lacking the fused benzenes was recently reported,[27] with some derivatives shown to have potent mammalian cytoxicity.[28]

Scheme 5. Representation of the Crystal Structure of 14 and Proposed Mechanism Leading to Its Formation

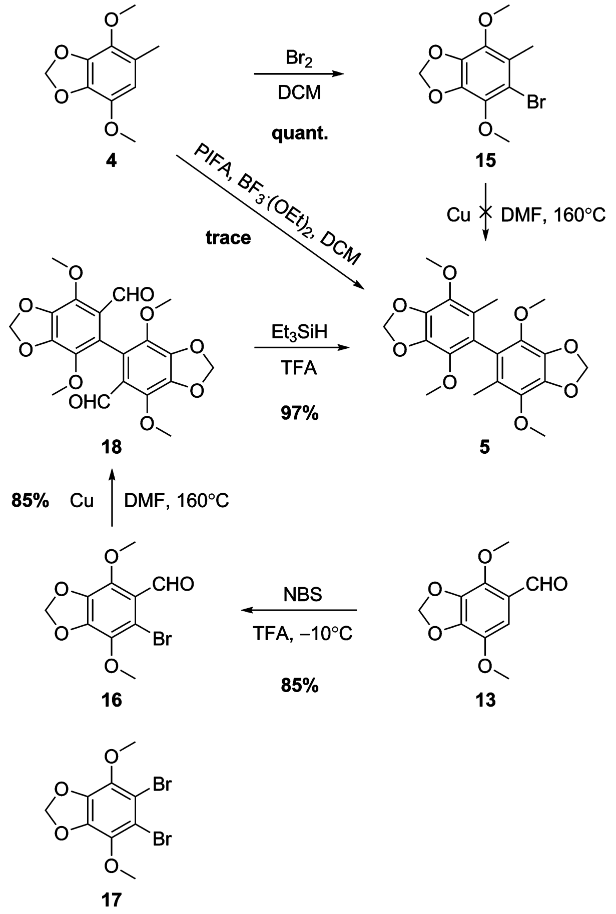


The synthesis of the anticancer natural product **4** (Scheme 4) was completed by Vilsmeier–Haack formylation of **3** to give the benzaldehyde **13**,[29] followed by reductive deoxygenation. Interestingly, the first attempted hydrogenation/hydrogenolysis produced a small amount of the decarbonylation product **3**. There is precedent for decarbonylation of benzaldehydes with Pd/C, but only at high temperatures.[30] On the assumption that the decarbonylation requires "naked" metal sites, the reaction was repeated with Pd/C that was precharged with H_2, and indeed the decarbonylation product was not observed. Synthetic **4** was isolated as a colorless, amorphous solid, while the natural product was reported to be a yellow liquid; however, the NMR spectra for synthetic **4** match the data reported for the natural product.

During the course of our work a synthesis of **4** from 2,3,4,5-teramethoxytoluene was reported.[31]

Our attention then turned to the dimeric antiviral biphenyl **5** (Scheme 6). A single attempt at a PIFA [phenyliodine bis(trifluoroacetate)]-mediated oxidative coupling[32] of **4** gave a complex mixture of products, perhaps containing a trace of the desired biphenyl as judged from the ^{1}H NMR spectrum of the crude material. Therefore, a more conventional approach was investigated. Specifically, we were attracted by the capacity of the Ullmann coupling to deliver sterically congested biaryls.[33]

Scheme 6. Synthesis of the Biphenyl Natural Product 5



Bromination of **4** proceeded smoothly, but the Ullmann coupling of **15** under standard conditions failed (Scheme 6). Similar reactions of 2-halo-3-alkylanisoles and related compounds are known,[34] but the yields are variable and very high temperatures are often required. Copper-mediated Ullmann biaryl coupling is favored by coordinating substituents *ortho* to the halogen,[33] and there are several examples of Ullmann couplings of 2-halo-3-methoxybenzaldehydes,[35] so we chose to explore the reaction of bromobenzaldehyde **16**.

Bromination of **13** with Br_2 was very sluggish, and did not go to completion, even with excess Br_2 and heating. In contrast, NBS in TFA[36] at room temperature led to rapid bromination, but also extensive formation of the dibromide **17**.[37] Fortunately, the bromodecarbonylation was minimal at −10 °C, and **17** was easily separated from the bromobenzaldehyde **16**, which was isolated in excellent yield.

As predicted, the Ullmann coupling of **16** gave an excellent yield of bi(benzaldehyde) **18**, accompanied by a small amount (9%) of the dehalogenation product **13**. In contrast to the hydrogenation/hydrogenolysis of **13**, the analogous deoxygenation of **18** was not a clean reaction. Fortunately, deoxygenation with acidified triethylsilane was rapid and efficient, providing an almost quantitative yield of pure **5**, after a simple aqueous workup. The NMR spectra for synthetic **5** matched the data reported for the natural product.[23]

The natural product **5** was isolated as a racemate, as supported by the lack of optical activity, and confirmed by the centrosymmetric space group of the reported crystal structure.[23] We were interested to ascertain whether this is due to racemic biosynthesis or because the atropisomers are configurationally unstable. Accordingly, the synthetic racemate **5** was subjected to semipreparative normal-phase enantioselective chromatography, affording the two atropisomers in greater than 96% e.r. An X-ray crystal structure of the less mobile enantiomer was obtained, which showed it to be the S-atropisomer **S-5** (Figure 2). To our surprise, the atropisomers exhibit no optical activity at the α-D line in $CHCl_3$ solution. They do, however, give rise to equal and opposite circular dichroism spectra (Figure 3).

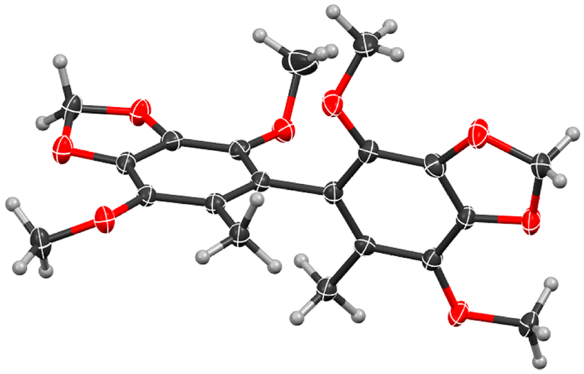


Figure 2. Representation of the crystal structure of the **S** atropisomer of **5**.

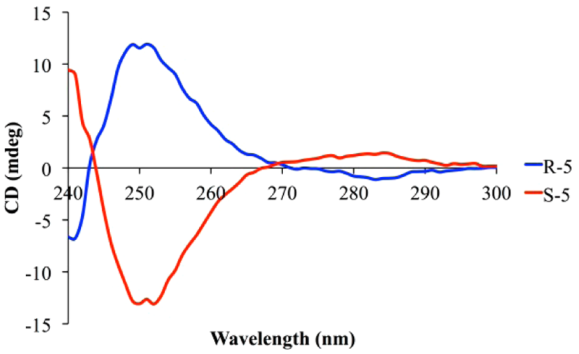


Figure 3. Circular dichroism spectra of **R-5** and **S-5**.

The configurational stability of the atropisomers was assessed by heating a solution of the R-enantiomer in refluxing toluene and monitoring racemisation by analytical enantioselective chromatography over several days. Although some degradation was observed during this period, none of the S-atropisomer was detected (see Supporting Information).

To gain an estimate of the energy barrier to rotation about the biaryl bond, a conformational analysis was undertaken. Using density functional theory, the geometry of the complex was fully optimized and subsequently determined to be a minimum via vibrational frequency analysis. Following on, a relaxed potential energy scan was undertaken along the biaryl dihedral angle coordinate, with the results represented as the torsional potential in Figure 4. All calculations were undertaken at B3LYP/6-31G* using the Gaussian 09 program suite.[38]

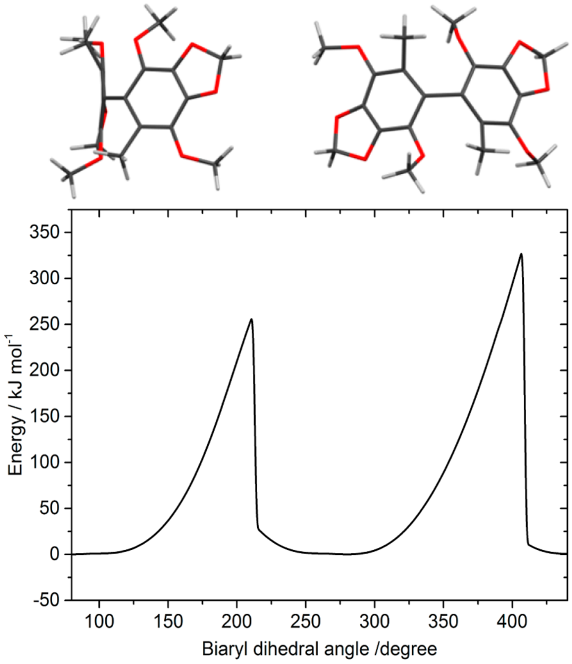


Figure 4. Torsional potential energy scan about the biaryl dihedral angle, produced at the B3LYP/6-31G* level of theory. The structures shown correspond to the tip of the first peak in the plot. The orientation on the left emphasizes the extreme distortion from coplanarity of the biaryl bond/benzene, which results from steric repulsion between the methyl and methoxy groups.

As depicted in Figure 4, the lowest energy pathway, in which the methyls pass by the methoxy groups, involves a highly strained conformation that lies ~250 kJ mol^{-1} above the ground state energy minimum (biaryl dihedral = 80°). Of course, these calculations only give approximate energies for the barriers to rotation as they do not consider the influence of vibrational excitation of specific modes, which could facilitate passage over the barrier. Although the structure of the transition state was not determined, the calculated barriers shown in Figure 4 are on par with those reported in similar work, wherein the half-life was estimated to be greater than 10 years.[39]

The results above suggest that the biosynthesis of **5** is, indeed, racemic. It seems likely that oxidative coupling of a phenolic precursor gives a biphenol, which is not configurationally stable about the biaryl axis, and subsequent *O*-methylation gives ***rac*-5**.

Anti-HCV Activity. The mode of action of biaryl natural product **5** against the DNA encoded wild-type, and lamuvidine-resistant, HBV is not known, but it may be a polymerase inhibitor. Some drugs inhibit both reverse transcriptase and DNA polymerases. For example, lamivudine is approved for the treatment of HIV and chronic hepatitis B.[40] Alternatively, **5** may work through some hepatocyte-specific pathways. Therefore, we were interested to see if the in vitro activity reported for natural product **5** against HBV extended to the RNA encoded hepatitis C virus (HCV), which also has tropism for hepatocytes.

Attempts were made to evaluate the natural product **5** and the dialdehyde precursor **18** in the human hepatoma (Huh7-

J20) cell line, which secretes alkaline phosphatase upon HCV infection.[41] Concomitantly, cell viability (cytotoxicity) was assessed by standard MTT assay. However, the natural product **5** was found to have poor aqueous solubility. At low concentrations **5** was inactive against HCV replication, and the concentrations of DMSO necessary to achieve higher concentrations of **5** (comparable to those reported previously for HBV assays[26]) were cytotoxic. The aldehyde **18** was more water-soluble and had some antiviral activity, with an approximate EC_{50} of 1.7 μM; however, at 10 μM **18** was also cytotoxic, complicating the EC_{50} determination. Thus, at this time, the potential of **5** as an antiviral lead is not particularly encouraging. It remains to be seen if similar activity can be demonstrated in more polar/water-soluble analogues that are less cytotoxic than dialdehyde **18**.

■ CONCLUSION

The first systematic investigation into the Baeyer−Villiger reaction of an anthraquinone has been presented. The double Baeyer−Villiger reaction of quinizarin dimethyl ether with the inexpensive and environmentally benign oxidant sodium perborate tetrahydrate is viable, and provides rapid access to symmetrical 1,2,3,4-tetraoxygenated benzenes. This work has been applied to the first total synthesis of the antiviral biphenyl natural product **5**, which was prepared in five steps and 27% overall yield (3 steps and 70% overall yield from known aldehyde **13**).

■ EXPERIMENTAL SECTION

Materials and Methods. All solvents were distilled prior to use. Anhydrous DMF was obtained by drying over activated 3A molecular sieves for 24 h, followed by distillation under reduced pressure onto activated 3A sieves. "Hexanes" refers to the hydrocarbon fraction distilling from 64−67 °C. All other reagents and materials were purchased from commercial suppliers and used as received.

Temperatures reported for heated reactions refer to bath temperatures unless the reactions were heated under reflux. Organic extracts were dried over anhydrous $MgSO_4$. Solvents were evaporated under reduced pressure at approximately 45 °C, and then traces of solvent were removed under a flow of nitrogen.

Reaction progress was monitored by analytical thin layer chromatography (TLC) using Merck aluminum-backed TLC_{F254} plates. Spots were visualized with a UV lamp (254 nm) and/or by staining with acidified ceric sulfate, or dinitrophenylhydrazine (DNP). Chromatography was performed with either Merck, Silicycle or Davisil silica gel (average particle size: 40−63 μm; average pore size: 60 Å). RSF = rapid silica filtration.[42]

^{1}H and ^{13}C NMR spectra were obtained using 300, 400, 500 or 600 MHz spectrometers, as indicated. Deuterochloroform ($CDCl_3$) was used as the solvent, with residual $CHCl_3$ (^{1}H, δ = 7.26 ppm) or $CDCl_3$ (^{13}C, δ = 77.16 ppm) being used for calibration.

Infrared (IR) spectra were acquired using an ATR attachment. Mass spectra were recorded using fast atom bombardment (FAB+) or electron impact ionization (EI) (both with magnetic sector mass analyzer), or electrospray ionization (ESI+) and quadrupole mass analyzer, as indicated. CD spectra were recorded on acetonitrile solutions (1 mg mL^{-1}). Melting points were determined on a hot stage melting point apparatus.

Synthesis. *1,4-Dimethoxyanthraquinone (Quinizarin Dimethyl Ether) (**1**).* A mixture of quinizarin (12.01 g, 50.00 mmol), anhydrous K_2CO_3 (27.64 g, 200.0 mmol), methyl iodide (7.5 mL, 120 mmol) and DMF (50 mL) was sealed with a septum and stirred at 40 °C overnight. TLC after this time indicated that the reaction was incomplete, so additional methyl iodide (3.75 mL, 60 mmol) was added and the sealed reaction mixture was stirred for a further 24 h at 40 °C. The reaction mixture was diluted with water (500 mL) and 1 M NaOH (100 mL) and extracted with DCM (4 × 100 mL). The extract was washed with 0.2 M NaOH (4 × 100 mL) and the washes were back-extracted with DCM (3 × 100 mL). The combined organic phase was gravity filtered to remove insoluble impurities, then washed with 0.2 M NaOH (4 × 200 mL), brine (200 mL), dried and evaporated to give **1** as an orange solid (12.72 g, 95%), mp 170−174 °C [lit.[43] 170.5−171.5 °C]. R_f = 0.15 (1:1 EtOAc/hexanes); ^{1}H NMR (500 MHz) δ 8.17 (m [AA′ part of AA′XX′], 2H), 7.71 (m [XX′ part of AA′XX′], 2H), 7.35 (s, 2H), 4.00 (s, 6H). The ^{1}H NMR data were identical to those reported.[44]

*1,4-Dimethoxydibenzo[b,f][1,4]-dioxocin-6,11-dione (**2**).* Sodium perborate tetrahydrate (9.23 g, 60.0 mmol) was added to a stirred solution of quinizarin dimethyl ether (**1**) (2.683 g, 10.00 mmol) in TFA (50 mL) under N_2, in a water bath to dissipate the heat generated. After 75 min the reaction mixture was poured onto ice−water (300 mL) and extracted with DCM (3 × 100 mL). The extract was washed with water (100 mL) and brine (100 mL), dried and evaporated to give crude **2** as an orange solid (2.100 g), which crystallized from EtOAc as colorless needles (1.178 g, 39%), mp 211−215 °C. R_f = 0.25 (1:1 EtOAc/hexanes); IR ν (cm^{-1}): 1761 (C═O); ^{1}H NMR (300 MHz) δ 7.52 (AA′BB′ [apparent s], 4H); 6.65 (s, 2H); 3.79 (s, 6H); ^{13}C NMR (75.5 MHz) δ 166.7, 145.7, 135.5, 135.5, 132.4, 127.5, 109.7, 56.7. MS (EI) m/z 300 ($M^{\bullet+}$, 95%), 229 (51), 104 (100), 76 (64), 69 (31). $C_{16}H_{12}O_6$ requires C, 64.0; H, 4.0; found: C, 64.2; H, 4.1%.

*1,4-Dimethoxydibenzo[b,e]oxepine-6,11-dione (**11**).* Sodium perborate tetrahydrate (2.311 g, 15.02 mmol) was added to a stirred solution of **1** (1.341 g, 4.999 mmol) in TFA (20 mL) at 0 °C under argon. After 90 min the ice bath was removed and stirring was continued for 30 min, then poured onto ice−water (200 mL) and extracted with DCM (4 × 50 mL). The extract was washed with water (2 × 50 mL), and brine (50 mL), dried and evaporated to give a brown solid (1.312 g), which was subjected to flash chromatography. Elution with 1:5 EtOAc/hexanes gave **11** as a yellow solid (1.110 g, 73%, containing 5% dioxocin **2** based on the ^{1}H NMR spectrum; Percentages are yields, not proportions). The pure oxepine **11** crystallized from MeOH as pale yellow needles (0.394 g, 28%), mp 162−166 °C. R_f = 0.35 (1:1 EtOAc/hexanes); IR (ATR) ν (cm^{-1}): 1736 (OC═O), 1691 (C═O). ^{1}H NMR (500 MHz) δ 8.17 (ddd, J = 7.7, 1.4, 0.4 Hz, 1H), 7.65−7.76 (m, 3H), 7.01 (d, J = 9.0 Hz, 1H), 6.77 (d, J = 9.0 Hz, 1H), 3.90 (s, 3H), 3.83 (s, 3H). ^{13}C NMR (500 MHz) δ 191.2, 163.1, 150.1, 145.0, 142.6, 139.3, 134.5, 133.3, 132.5, 127.4, 124.8, 124.1, 116.1, 109.5, 57.0, 56.9. MS (ESI+) m/z observed: 285.0748 [M + H$^+$]; $C_{16}H_{13}O_5^+$ requires 285.0763.

*4,7-Dimethoxy-1,3-benzodioxole (**3**). Method A.* A mixture of dibromomethane (0.60 mL, 8.1 mmol), **2** (1.201 g, 4.000 mmol), Cs_2CO_3 (5.22 g, 16 mmol) and 3Å molcular sieve-dried (but not distilled) DMF (40 mL) was stirred at 80 °C under N_2 overnight. The reaction mixture was allowed to cool then diluted with 0.1 M NaOH (400 mL) and extracted with DCM (3 × 100 mL). The extract was washed with water (2 × 100 mL) and brine (100 mL), dried and evaporated to give **3** as a pale yellow crystalline solid (618 mg, 85%), mp 77−79 °C [lit.[29] 76.5−77.5 °C]. ^{1}H NMR (300 MHz) δ 6.45 (s, 2H); 5.99 (s, 2H); 3.86 (s, 6H). The ^{1}H NMR data are identical to those reported.[14a]

Method B. Sodium perborate tetrahydrate (7.69 g, 50.0 mmol) was added to a stirred solution of quinizarin dimethyl ether (1.344 g, 5.010 mmol) in TFA (25 mL) under argon, in a water bath to dissipate any heat generated. After 45 min the reaction mixture was poured into ice−water (350 mL) and extracted with DCM (3 × 150 mL). The extract was washed with water (100 mL) and brine (100 mL), dried and evaporated to give crude an orange solid (1.064 g). The crude dioxocin was dissolved in DMF (20 mL), treated with dibromomethane (0.60 mL, 8.1 mmol) and Cs_2CO_3 (3.58 g, 11.0 mmol), and stirred at 80 °C under argon for 22 h. Water (5 drops) was added and the reaction mixture was stirred at 80 °C for a further 2 h, then cooled, diluted with 0.1 M NaOH (250 mL) and extracted with Et_2O (4 × 100 mL). The extract was washed with water (2 × 100 mL) and brine (100 mL), dried and evaporated to give the an orange solid (0.558 g), which was subjected to flash chromatography. Elution with 1:9 EtOAc/

hexanes gave **3** as white needles (0.294 g, 32% over 2 steps), identical with the material described above.

On one occasion, the attempted methylenation of a crude mixture of **2** and **8** (0.738 g), as described above, gave, after flash chromatography, eluting with 1:5 EtOAc/hexanes, 5,8-dimethoxy-3′*H*-spiro[benzo[*d*][1,3]dioxine-4,1′-isobenzofuran]-3′-one (**14**) as a white solid (0.377 g), which crystallized from DCM as small white rhomboids, mp 188−198; 200−202 °C (there were two crystal types). R_f = 0.50 (1:1 EtOAc/hexanes); IR (ATR) ν (cm^{-1}): 1771 (C═O). ^{1}H NMR (500 MHz) = δ 7.91 (pseudo d, 1H), 7.60 (ddd [app. dt], J_1 = J_2 = 7.5, J_3 = 1.5 Hz, 1H), 7.56 (ddd [app. dt], J_1 = J_2 = 7.5, J_3 = 1.5 Hz, 1H), 7.27 (pseudo d, 1H), 6.88 (d, J = 9.0 Hz, 1H), 6.33 (d, J = 9.0 Hz, 1H), 5.52 (d, J = 5.5 Hz, 1H), 5.49 (d, J = 5.5 Hz, 1H), 3.89 (s, 3H), 3.26 (s, 3H). ^{13}C NMR (500 MHz) = δ 168.3, 150.8, 148.3, 144.3, 142.3, 134.1, 130.3, 128.1, 124.8, 121.9, 113.1, 109.7, 103.6, 101.3, 87.9, 56.6, 55.7. MS (ESI+) *m*/*z* observed: 315.0855 [M + H$^+$]; $C_{17}H_{15}O_6{}^+$ requires 315.0869.

2,5-Dimethoxy-3,4-methylendioxybenzaldehyde (***13***).[29] $POCl_3$ (1.4 mL, 15 mmol) was added slowly to a stirred mixture of **3** (1.822 g, 10.00 mmol) and *N*-methylformanilide (1.49 g, 11.0 mmol) at 0 °C. The suspension was stirred at room temperature for 3 h, then allowed to stand overnight, before being partitioned between EtOAc (50 mL) and cold, saturated $NaHCO_3$ (50 mL). The phases were separated and the aqueous phase was extracted with EtOAc (2 × 20 mL). The combined organic phase was washed with water (30 mL) and brine (30 mL), dried and evaporated to give **13** as a crystalline tan solid (2.04 g, 97%), which crystallized from hexanes to give **13** as tan prisms, mp 99−101 °C [lit.[29] 101.5−102.5 °C]. R_f = 0.65 (1:1 EtOAc/hexanes); ^{1}H NMR (500 MHz) δ 10.23 (s, 1H), 7.08 (s, 1H), 6.09 (s, 2H), 4.05 (s, 3H), 3.89 (s, 3H). The NMR data are slightly different from those reported.[45]

4,7-Dimethoxy-5-methyl-1,3-benzodioxole (***4***). A degassed solution of **13** (211 mg, 1.00 mmol) in AcOH (5 mL) was added to a stirred suspension of 10% Pd/C (0.21 g) in AcOH (5 mL) under a balloon of H_2. After 24 h, TLC showed the reaction to be complete. The suspension was diluted with Et_2O (50 mL), vacuum-filtered through a pad of Celite, and washed through with Et_2O (50 mL). The filtrate was washed with saturated $NaHCO_3$ (4 × 30 mL) [FOAMING], water (30 mL), and brine (30 mL), dried and evaporated to give pink oil, which was subjected to RSF. Elution with 1:99 EtOAc/hexanes gave **4** as a colorless oil that solidified on standing (165 mg, 84%), which precipitated from hexanes as an amorphous solid, mp 39−40 °C (lit.[23] yellow liquid). R_f = 0.35 (1:9 EtOAc/hexanes); ^{1}H NMR (400 MHz) δ 6.30 (br q, J = 0.7 Hz, 1H), 5.93 (s, 2H,), 3.87 (s, 3H), 3.84 (s, 3H), 2.17 (d, J = 0.6 Hz, 3H); ^{13}C NMR (100 MHz) δ 138.8, 138.6, 136.5, 134.6, 123.6, 108.8, 101.4, 59.8, 56.8, 15.8. The NMR data are identical to those reported,[23] except for the fine benzylic coupling in the ^{1}H NMR spectrum.

5-Bromo-4,7-dimethoxy-6-methyl-1,3-benzodioxole (***15***). A solution of Br_2 (25 μL, 0.49 mmol) in DCM (1 mL) was added dropwise to a stirred solution of **4** (87 mg, 0.44 mmol) in DCM (2 mL) at 0 °C. Stirring was continued for 15 min then the resulting solution was poured into 1 M sodium thiosulfate (15 mL). The mixture was extracted with Et_2O (2 × 15 mL) and the extract was washed with water (10 mL) and brine (10 mL), dried and evaporated to give **15** as a crystalline white solid (122 mg, quant.), which crystallized from hexanes as white needles. R_f = 0.35 (1:9 EtOAc/hexanes); ^{1}H NMR (400 MHz) δ 5.94 (s, 2H), 3.93 (s, 3H), 3.88 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (100 MHz) δ 138.3, 137.5, 137.2, 136.3, 124.3, 110.2, 101.6, 60.3, 60.1, 16.0; MS (FAB+) *m*/*z* 276 [M(^{81}Br) + H]$^+$ (97%), 274 [M(^{79}Br) + H]$^+$ (100%), 196 [M − Br + H]$^+$, (16%). $C_{10}H_{11}BrO_4$ requires: C, 43.7; H, 4.0; found: C, 43.5; H, 4.0%.

6-Bromo-2,5-dimethyoxy-3,4-methylendioxybenzaldehyde (***16***). NBS (0.43 g, 2.4 mmol) was added portionwise to a stirred solution of **13** (420 mg, 2.00 mmol) in TFA (10 mL) at −10 °C (ice/MeOH with occasional liquid N_2). Stirring was continued for 90 min, after which time an ^{1}H NMR spectrum of a sample showed the reaction to be complete. The reaction mixture was diluted with ice/water (200 mL) and basified with solid $NaHCO_3$, whereupon a precipitate formed. The suspension was extracted with Et_2O (4 × 50 mL). The extract was washed with 1 M sodium thiosulfate (2 × 50 mL), water (50 mL) and brine (50 mL), dried and evaporated to give a crystalline, pale yellow solid, which was subjected to RSF. Elution with 1:9 EtOAc/hexanes gave 5,6-dibromo-4,7-dimethoxy-1,3-benzodioxole (**17**) as a colorless solid (51 mg, 8%). ^{1}H NMR (300 MHz): 6.01 (s, 2H), 3.94 (s, 6H); ^{13}C NMR (75 MHz): 139.0, 137.4, 111.5, 102.3, 60.5. The ^{1}H NMR data are similar to those reported.[37a]

Further elution with 1:4 EtOAc/hexanes gave **16** as a crystalline yellow solid (489 mg, 85%), which crystallized from DCM/hexanes as pale yellow needles. R_f = 0.20 (1:5 (EtOAc/hexanes); IR ν (cm^{-1}): 1682 (C═O); ^{1}H NMR (300 MHz) δ 10.20 (s, 1H, 6.07 (s, 2H), 3.97 (s, 3H), 3.91 (s, 3H); ^{13}C NMR (75 MHz) δ 189.4, 144.0, 141.5, 138.4, 136.6, 121.1, 112.6, 102.8, 61.0, 60.5 ; MS (FAB+) *m*/*z* 289 [M(^{79}Br) + H]$^+$ (100%), 291 [M(^{81}Br) + H]$^+$ (88%). $C_{10}H_9BrO_5$ requires: C, 41.6; H, 3.1; found: C, 41.4; H, 2.9. The ^{1}H NMR data are similar to those reported.[37a]

Bi-(2,5-dimethoxy-3,4-methylenedioxybenzaldehyde) (***18***). A degassed suspension of activated[46] copper bronze (0.29 g, 4.6 mmol) in a solution of **16** (289 mg, 1.00 mmol) in dry DMF (1 mL) was stirred at 100 °C under a positive pressure of argon for 1.5 d. The reaction mixture was allowed to cool, then diluted with water (100 mL) and extracted with EtOAc (3 × 30 mL). The extract was filtered, washed with water (3 × 30 mL) and brine (30 mL), dried and evaporated to give a yellow solid (200 mg), which was subjected to RSF. Elution with 1:4 EtOAc/hexanes gave **13** (17 mg, 9%). Further elution with 1:1 EtOAc/hexanes gave **18** as a yellow solid (177 mg, 85%), which crystallized from DCM/hexanes as yellow rhomboids, mp 185−188 °C. R_f = 0.34 (1:1 EtOAc/hexanes); IR ν (cm^{-1}): 1681 (C═O); ^{1}H NMR (500 MHz) δ 10.02 (s, 2H), 6.10 (AA′ [app. q, '*J*' = 1.5 Hz], 4H), 4.06 (s, 6H), 3.69 (s, 3H); ^{13}C NMR (75 MHz) δ 188.8, 143.9, 142.3, 137.9, 136.7, 125.9, 121.0, 102.3, 60.7, 60.0 ; MS (FAB+) *m*/*z* 419 [M + H]$^+$, 100%), 389 (36%), 373 (64%). $C_{20}H_{18}O_{10}$ requires: C, 57.4; H, 4.3; O, 38.2; found: C, 57.6; H, 4.1.

Bi-(2,5-dimethoxy-6-methyl-3,4-methylenedioxybenzene) (***5***). Triethylsilane (0.31 mL, 2.0 mmol) was added dropwise to a stirred solution of **18** (21 mg, 0.050 mmol) in TFA (0.5 mL) at 0 °C, whereupon the bright orange solution immediately turned colorless. After 30 min the reaction mixture was poured onto ice and diluted with saturated $NaHCO_3$ (80 mL), then extracted with Et_2O (3 × 20 mL). The extract was washed with brine, dried and evaporated to give **5** as a colorless oil that solidified on standing (19 mg, 97%), which crystallized from MeOH as colorless rhomboids. R_f = 0.35 (1:4 EtOAc/hexanes); ^{1}H NMR (500 MHz) δ 5.95 (s, 4H), 3.92 (s, 6H, 3.73 (s, 3H, 1.78 (s, 6H); ^{13}C NMR (150 MHz) δ 138.0, 137.4, 137.0, 136.6, 123.3*, 101.2, 60.04, 60.00, 12.8. The NMR data were identical with those reported.[23] *Nonidentical carbons are isochronous.

Enantioselective Chromatography. Racemic **5** was resolved into its individual atropisomers using semipreparative HPLC performed on an Astec Cellulose DMP (3,5-dimethylphenyl carbamate-derivatized) HPLC column (250 mm long, 10 mm i.d., 5 μm particle size). Separation was achieved using a flow rate of 2 mL/min with 5% isopropanol/hexanes. Under these conditions the R enantiomer eluted first. Analytical enantioselective HPLC was conducted using an Astec Cellulose DMP HPLC column (250 mm long, 4.6 mm i.d., 5 μm particle size). Separation was achieved using a flow rate of 0.5 mL/min with 5% isopropanol/hexanes.

Kinetic Stability of *R*-Bi(2,5-dimethoxy-6-methyl-3,4-methylenedioxybenzene) (R-5). A solution of the single atropisomer **R-5** (0.5 mg) in toluene (5 mL) was heated under reflux under argon. Samples were taken at regular intervals over the course of 3 d and analyzed by analytical enantioselective HPLC as described above.

Crystallography. Crystallographic data were acquired at 100(2) K Cu Kα (for **S-5**) or Mo Kα (for **2**, **14**) radiation. Following multiscan absorption corrections and solution by direct methods, the structures were refined against F^2 with full-matrix least-squares using the program SHELXL-97.[47] All hydrogen atoms were added at calculated positions and refined by use of riding models with isotropic displacement parameters based on those of the parent atoms. Anisotropic displacement parameters were employed throughout for the non-hydrogen atoms.

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Biological Assays. *Cell Culture.* The human hepatoma reporter cell line, Huh7-J20,[58] kindly provided by Dr A. Patel (University of Glasgow), was grown in RPMI supplemented with 10% fetal bovine serum (FBS) with gentamicin (0.16 mg/mL) and puromycin (8 μg/mL) at 37 °C with 5% CO_2 in a humidified atmosphere. Monolayers were dispersed with trypsin−EDTA to provide single cell suspensions for assays.

Addition of Test Compounds to Tissue Culture. Culture medium (100 μL/well) was removed from 96 well plates and replaced with the test compounds diluted in RPMI/10% FBS to give triplicate wells with the final concentrations: 0.08, 0.16, 0.31, 0.63, 1.30, 2.50, 5.00 μM for natural product **5**; and 0.08, 0.16, 0.25, 0.31, 0.50, 0.63, 0.75, 1.00, 1.25, 1.40, 1.90, 2.50, 3.80, 5.00 μM for **18** and 0.44% (v/v) DMSO. Negative control cultures consisted of medium with 0.44% (v/v) DMSO (final concentration).

MTT Assay for Cell Viability. Cells were incubated overnight at 6×10^4 cells/well in 96 well plates and compounds **5** or **18** were added as described above, and incubated for 3 d. MTT dye (0.5 mg/mL, 20 μL/well) was added and after 4 h, 100 μL/well media was replaced with lysis buffer consisting of 20% sodium dodecyl sulfate in 50% aqueous DMF. Absorbance was read at 540 nm.

Testing Anti-HCV Activity. Cells to be infected were dispensed at 100 μL/well at 6×10^3 cells/well into 96-well plates 5 h prior to infection. HCV strain JFH-1, originally kindly provided by Dr M. Watson (Institute for Immunology and Infectious Diseases, Murdoch University), was added in 100 μL per well and the plates incubated at 37 °C for at least 2 h prior to addition of test compounds. IFNα-2b (10 units/100 μL) was used as an antiviral compound of known activity.

The EC_{50} was calculated using GraphPad Prism 6 software with log concentrations and a 3 parameter dose response curve.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02861.

^{1}H and ^{13}C NMR spectra of all novel compounds, enantioselective HPLC traces, crystallographic parameters. (PDF)

Crystal data, CCDC 1441041 for **2**, 1441042 for **14** and 1441043 for **S-5**. (CIF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

$^\perp$Dedicated to the memory of Professor Emilio Ghisalberti.

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