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Article

Total Synthesis of the Antitumor−Antitubercular 2,6′-Bijuglone Natural Product Diospyrin and Its 3,6′-Isomer

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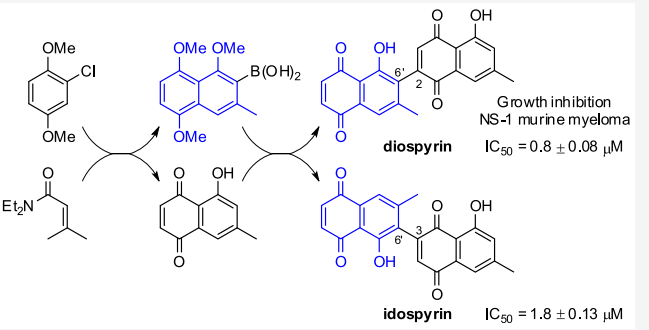
ABSTRACT: The 2,6′-bijuglone natural product diospyrin and its unnatural 3,6′-isomer idospyrin have been synthesized in seven steps each from *N*,*N*-diethylsenecioamide in overall yields of 12% and 13%, respectively. The syntheses diverge from ramentaceone (7-methyljuglone) and include a key Suzuki−Miyaura cross-coupling. Diospyrin, idospyrin, and several synthetic precursors exhibit potent and selective cytotoxicity to the murine myeloma NS-1 cell line over neonatal foreskin cells.



Diospyrin (**1**, Figure 1) is a naturally occurring C-2−C-6′ linked dimer of ramentaceone (7-methyljuglone, **2**). Its structure was established through a series of studies[1] following its first isolation in 1961.[2] Five other C−C linked ramentaceone dimers have since been found in nature,[3] meaning that of the 10 possible dimers, six are confirmed natural products. All six have been the targets of total syntheses,[4] as have two of the "unnatural" ramentaceone dimers,[4f,5] leaving only the C-2−C-8′ and C-3−C-6′ linked dimers, **6** and **7**,[6] respectively (Figure 1), as yet unexplored.

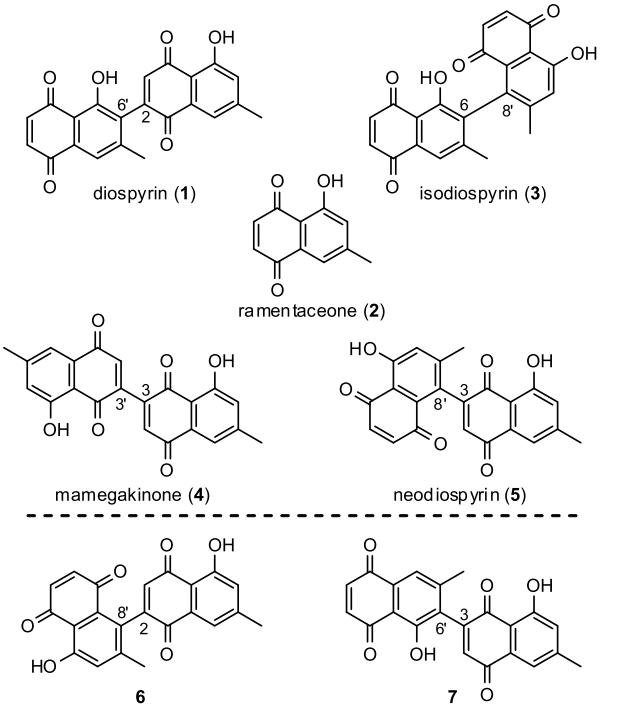


Figure 1. Ramentaceone (**2**), four of its naturally occurring dimers (**1**, **3**−**5**), and the two dimers yet to be characterized (**6**, **7**).

Diospyrin (**1**) has been particularly well studied, perhaps because of its widespread occurrence in Ebenaceae plants.[7] Since its first isolation by Kapil and Dhar from the stem bark of *Diospyros montana* Roxb.,[2] a small tree found throughout India, diospyrin (**1**) has been isolated in numerous investigations of other members of the Ebenaceae family belonging to the genera *Diospyros*[2,8] and *Euclea*.[6a,8c,9] The use of a number of these plants, in particular *D. montana* Roxb.[10] and *E. natalensis* A.DC.,[11] in traditional remedies for an array of ailments has encouraged the assessment of diospyrin (**1**) for various bioactivities.[8g,12] In 1996, derivatives of diospyrin (**1**) were investigated for their antiprotist properties and demonstrated moderate inhibitory activity against the parasites *Leishmania donovani*, *Trypanosoma cruzi*, and *T. brucei brucei*.[13] This finding prompted the first, and previously only, synthesis of diospyrin (**1**) by Yoshida and Mori, who obtained the natural product in nine steps and 9% overall yield.[4h]

More recently, the antitumor potential of diospyrin (**1**) and some of its derivatives has been explored across a number of

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studies from the Hazra group.[14] Diospyrin (**1**) inhibited the growth of the human cancer cell lines A375 (melanoma) and Hep2 (laryngeal carcinoma) at low micromolar concentrations (IC_{50} = 0.8 and 3.6 μM, respectively) and was thus derivatized by first alkylating its phenolic hydroxyls and then modifying one or both of the naphthoquinone units.[14c−e] Further investigation of diospyrin and derivatives was severely limited by the small quantities that could be isolated from *D. montana* Roxb.[14c] Moreover, the influence that the position of the dimeric bond has on the antitumor activity of ramentaceone dimers has not been considered. Indeed, only two other ramentaceone dimers, isodiospyrin (**3**) and mamegakinone (**4**) (Figure 1), have been tested for antitumor activity,[15] and the data from these studies cannot be directly compared with each other nor with data for diospyrin (**1**).

A study by the Maxwell group, examining the inhibition of *Mycobacterium tuberculosis* DNA gyrase by ramentaceone dimers, illustrates that the connectivity of monomeric units can affect the bioactivity of the dimer.[16] Diospyrin (**1**) inhibited the action of *M. tuberculosis* DNA gyrase (IC_{50} = 15 μM) with potency comparable to that of ciprofloxacin (IC_{50} = 10 μM),[16] a fluoroquinolone antibiotic formerly used in tuberculosis treatment.[17] Meanwhile, neodiospyrin (**5**) and isodiospyrin (**3**) showed comparatively poor activity in the same assay (IC_{50} = 50 and 100 μM, respectively).

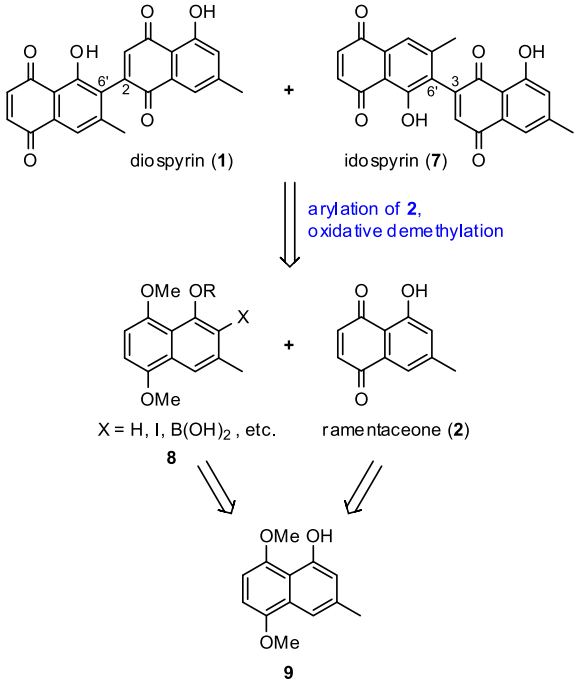
A similar evaluation of the antitumor activity of isomeric ramentaceone dimers may determine whether the position of the isomeric bond is important to their activity. Thus, we elected to pursue the synthesis of diospyrin (**1**) and of one of its unexplored isomers, the 3,6′-dimer, for which we propose the name idospyrin (**7**) (Figure 1). Herein, we describe studies toward the direct arylation of ramentaceone (**2**), eventual success in the total synthesis of diospyrin (**1**) and its unnatural 3,6′-isomer idospyrin (**7**), and a preliminary assessment of mammalian cytotoxicity of these compounds and several precursors.

RESULTS AND DISCUSSION

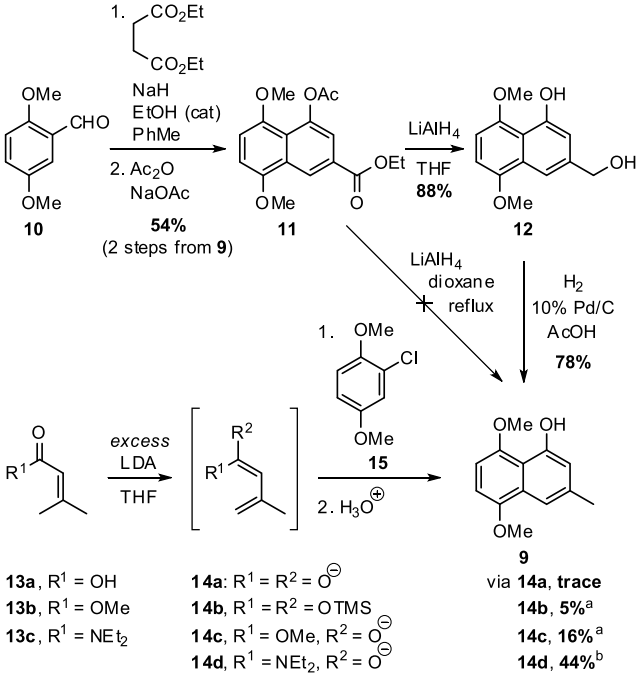
Synthesis. Yoshida and Mori's synthesis of **1** constructs a binaphthyl framework via a key Suzuki−Miyaura coupling, with both coupling partners prepared separately via Diels−Alder reactions of vinyl ketene acetals with benzoquinones.[4h] In light of recent advances in strategies for the arylation of quinones,[18] we proposed a synthesis of diospyrin (**1**) and idospyrin (**7**) via arylation of ramentaceone (**2**) (Scheme 1). This approach was expected to yield both desired C-2−C-6′ and C-3−C-6′ linked naphthylquinones, which could be separated and deprotected to afford diospyrin (**1**) and idospyrin (**7**), respectively. The naphthol **9** was identified as a key precursor from which both ramentaceone (**2**) and a suitable naphthalene coupling partner **8** could be prepared (Scheme 1).

Naphthol **9** has been a synthetic target or used to demonstrate a methodology on a number of occasions,[19] due to its utility as a precursor to ramentaceone (**2**)[19c] and other naturally occurring naphthoquinones.[19e] Most of these routes are surprisingly lengthy,[19a,c,e,f] with the exception of that developed by Sammes[19b] and later improved upon by Watanabe.[19d] This methodology involves the reaction of a dienolate (or equivalent) **14c,d** with the benzyne derived from a halobenzene such as **15** (Scheme 2), delivering naphthol **9** in one step. In the current work, this strategy was modified and applied to cheap and readily available 3,3-dimethylacrylic acid

Scheme 1. Retrosynthetic Identification of Common Precursors to Diospyrin (1) and Idospyrin (7)



Scheme 2. Naphthol 9 Was Prepared by Two Routes: Stobbe Condensation and Dienolate−Aryne Cyclization



[a]Yield determined by ^{1}H NMR spectroscopy. [b]Isolated yield.

(**13a**), though both the derived dienediolate **14a**[20] and the bis(trimethylsilyl) vinyl ketene acetal **14b**[21] furnished only traces of naphthol **9** (Table S1, Supporting Information). Subsequent attempts to improve upon the yield of **9** obtained via ester dienolate **14c** proved fruitless (Table S1, Supporting Information). Conceding, we prepared *N,N*-diethylsenecioamide (**13c**)[22] and followed the precedent set by Watanabe[19d] in which the use of dienolate **14d** significantly increases the

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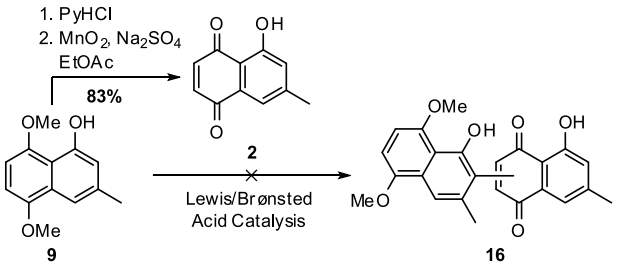
yield of naphthol **9**, a result of the greater stability of amide versus ester enolates.[23]

An alternative route to naphthol **9** was devised and investigated in parallel to the dienolate pathway (Scheme 2). Naphthoate **11** was prepared by a Stobbe condensation between 2,5-dimethoxybenzaldehyde (**10**) and diethyl succinate, followed by intramolecular cyclization of the resultant crude product.[24] Attempts to reduce the diester **11** directly to naphthol **9** with $LiAlH_4$ in refluxing dioxane[25] were unsuccessful, the reduction instead stalling at diol **12**. A more appropriate room-temperature $LiAlH_4$ reduction of **11** was employed to produce **12**, which was converted to naphthol **9** by hydrogenolysis.[19e] This procedure[26] gave **9** in four steps and a 37% overall yield, inferior in both yield and efficiency to the preparation of **9** via senecioamide dienolate **14d** (one step, 44%).

Naphthol **9** and ramentaceone (**2**) were the simplest coupling partners required to trial some strategies for the arylation of naphthoquinones directed at synthesis of diospyrin (**1**). Conversion of naphthol **9** directly to ramentaceone (**2**) is ineffective under standard oxidative demethylation conditions,[19c] which instead result in the formation of the naphthazarin derivative.[27] This transformation, previously carried out over three steps via acetylation of **9**,[19c] was instead performed by demethylating **9** with pyridinium chloride and oxidizing the nascent hydroquinone with MnO_2, the latter step being incorporated into a standard workup (Scheme 3).

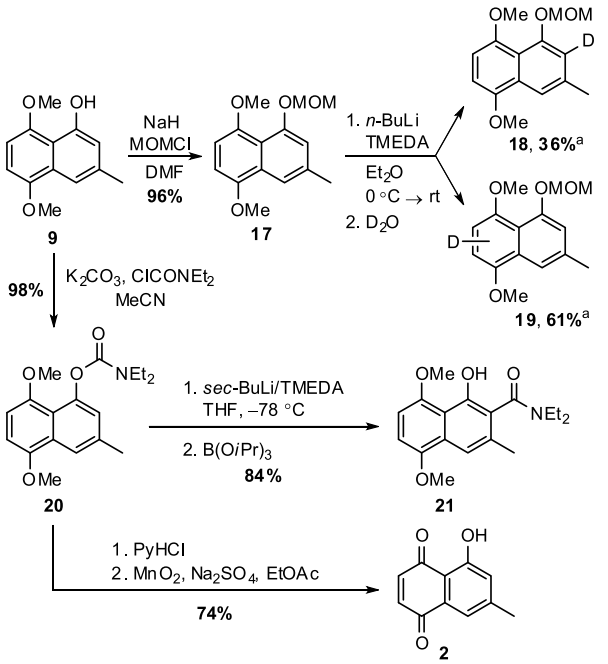
Scheme 3. Preparation of Ramentaceone (2) and Unsuccessful Acid-Catalyzed Conjugate Addition Approach



The addition of electron-rich arenes to naphthoquinones and juglones has been reported under catalysis by Lewis[18a] or Brønsted[18j] acids, and it was predicted that naphthol **9** may be sufficiently activated to show such reactivity; however, all attempts to induce a conjugate addition with **2** were unsuccessful (Scheme 3; Table S2, Supporting Information). No reaction between **9** and either model compound juglone or ramentaceone (**2**) was observed in the presence of $In(OTf)_3$,[18a] $InCl_3$, $Yb(OTf)_3$,[28] or H_2SO_4.[18j] Subsequent control experiments revealed **9** was unlikely to be sufficiently electron rich for this approach to succeed, as it failed to react with naphthoquinone (Table S2, Supporting Information), which is a suitable electrophile for activated arenes under $In(OTf)_3$ catalysis.[18a] Furthermore, ramentaceone (**2**) and its methyl ether also appeared poorly suited to this approach, as both juglones were unreactive toward resorcinol dimethyl ether (Table S3, Supporting Information), which undergoes $In(OTf)_3$-catalyzed conjugate addition to other quinones.[18a] With evidence suggesting the desired electrophilic aromatic substitution was unlikely to be achievable, we looked toward alternative strategies for the construction of the targeted binaphthyl.

Arylboronic acids have recently emerged as effective reagents for the arylation of quinones under mild reaction conditions,[18c,d,29] and methodologies have been developed that tolerate unprotected phenolic hydroxyls in both coupling partners.[18c,d] These reports prompted our pursuit of a suitable naphthylboronic acid, which was initiated with a directed *ortho* metalation (D*o*M)−borylation approach. Naphthol **9** was first fitted with a methoxymethoxy (MOM) directing group (Scheme 4), which was preferred due to ease of cleavage

Scheme 4. Pursuit of a Suitable Naphthylboronic Acid Pronucleophile via D*o*M−Borylation



[a]Deuterium incorporation (not yield) as assessed by integration of the crude ^1H NMR spectrum.

later in the synthesis. Unfortunately, treatment of **17** with *n*-BuLi/*N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) resulted in competing metalation *ortho* to its methoxy groups, as demonstrated by a deuterium quench, which provided **18** and its isomers **19** (Scheme 4). This result was somewhat surprising given that MOM groups have been established as superior directors of *ortho* metalation relative to methoxy groups.[30] In this case we surmise that the combined rate-accelerating inductive effects of the two methoxy substituents[31] and some steric hindrance from the 7-methyl group tip the balance in favor of metalation of the dimethoxy-substituted ring of **17**.

A more powerful directing group was therefore required to execute the desired D*o*M−borylation; thus the *N*,*N*-diethylcarbamate **20** was prepared (Scheme 4). Cleavage of *N*,*N*-dialkylcarbamates is often not trivial, and we expected the reductive[32] and alkaline hydrolysis[33] methods for deprotection to be incompatible with the syntheses of **1** and **7**. Before undertaking further experiments, **20** was subjected to the aforementioned global deprotection/oxidation sequence with pyridinium chloride and MnO_2, which resulted in conversion to ramentaceone (**2**) in good yield.

Having established that the carbamate directing group could likely be cleaved late in the synthesis, **20** was lithiated with *sec*-

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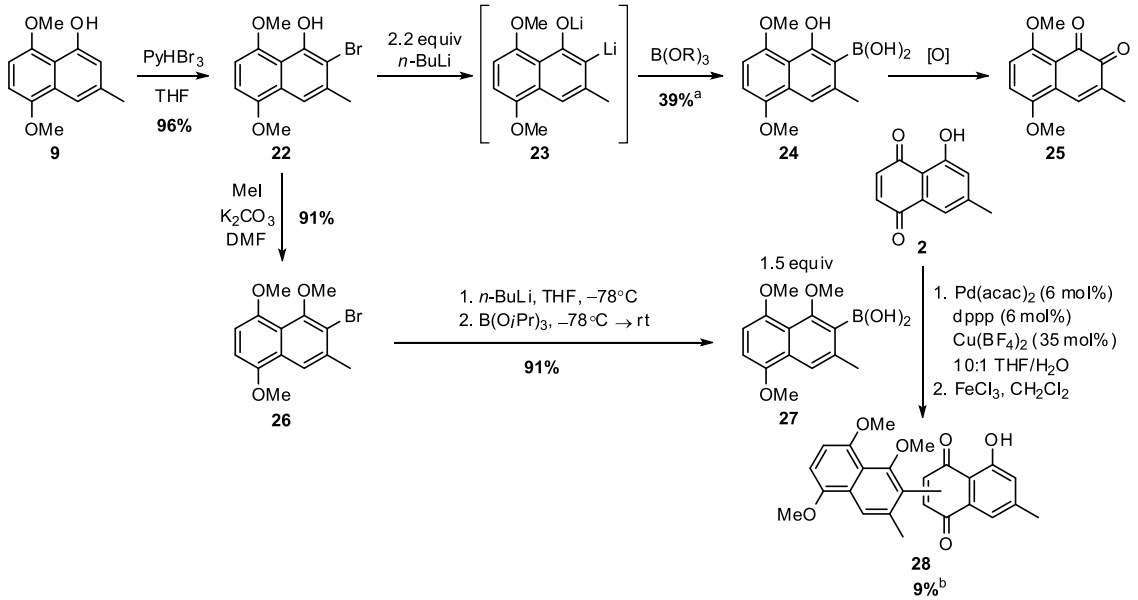
Scheme 5. Lithium−Halogen Exchange/Borylation of Bromides 22 and 26 and Addition of Boronic Acid 27 to Ramentaceone (2)



[a]Conversion determined by ^{1}H NMR spectroscopy. See Table S4, Supporting Information, for detailed reaction conditions and results regarding formation of **24** and **25**. [b]Combined ^{1}H NMR yield. dppp = 1,3-bis(diphenylphosphino)propane.

BuLi/TMEDA[34] and quenched with triisopropyl borate at −78 °C. However, even at this temperature, the intermediate aryllithium underwent anionic Fries rearrangement, outcompeting borylation to cleanly afford the amide **21** (Scheme 4). Repetition of the experiment at −98 °C slowed metalation, but did not stabilize the transient aryllithium, as only amide **21** and the starting carbamate **20** were returned upon workup. Poor solubility of **20** in other solvents precluded lower temperature experiments and eliminated some potential strategies for promoting D*o*M−borylation over the anionic Fries rearrangement.[35] The D*o*M−borylation approach was therefore abandoned in favor of borylation via the corresponding aryl halide.

Iodination of 1-naphthols can be complicated by the formation of dimeric binaphthols;[36] thus **9** was instead smoothly converted to bromonaphthol **22** with pyridinium tribromide[37] (Scheme 5). Borylation of *ortho*-halonaphthols such as **22** via both Miyaura-type chemistry and deprotonation/lithium−halogen exchange is unprecedented, to the best of our knowledge. Of these two strategies, Miyaura borylation of **22** was not pursued due to the reported difficulties borylating the simple substrate *o*-bromophenol,[38] for which deprotonation followed by lithium−bromine exchange successfully delivers 2-hydroxyphenylboronic acid;[39] additionally, the latter strategy has also been successfully applied to *m*- and *p*-halo-1-naphthols.[40]

Initial attempts to generate lithium *ortho*-lithionaphthoxide **23** (Scheme 5) with 2.2 equiv of *n*-BuLi in ether at −78 °C failed to achieve lithium−bromine exchange, returning bromonaphthol **22**. This result was first attributed to the poor solubility of the lithium bromonaphthoxide in ether, reasoning quickly proven incorrect when the result was duplicated upon repetition of the experiment in THF, in which the bromonaphthoxide dissolved completely (Table S4, Supporting Information). Increasing the reaction temperature of the lithium−halogen exchange to 0 °C effected complete conversion of **22** to *o*-lithionaphthoxide **23**, as assessed by deuterium quenching experiments. However, this change did not translate into good yields of boronic acid **24**, as deuterium quenching also showed that **23** was unstable at 0 °C in THF, with a half-life of approximately 90 min (Table S4, Supporting Information). Deprotonation of THF was strongly implicated, as the decomposition of **23** was found to be significantly slower in ether. This finding allowed for the boronic acid **24** to be obtained in 16% conversion following a borate ester quench of **23**, with further tuning of the reaction conditions (Table S4, Supporting Information) improving the conversion to 39%. This already poor result was further diminished by the facile autoxidation of **24** to *ortho*-naphthoquinone **25**.[19d] This autoxidation occurred simply during reaction workup to varying, not-insignificant, degrees and hindered attempts to isolate **24**. This complication, coupled with the poor yields of boronic acid **24**, dictated the protection of bromonaphthol **22** as its methyl ether **26**. Lithium−bromine exchange of **26**[4h] and quenching with triisopropyl borate provided a good yield of **27**, a suitable boronic acid with which to further explore arylation of ramentaceone (**2**).

Of the variety of protocols using arylboronic acids for the arylation of quinones, methodologies that did not require expensive catalysts[18b,29d] or a considerable excess of either the arylboronic acid or the quinone coupling partner[29c,41] were most appealing. The protocols reported by Baran and co-workers[18d] and Csákÿ et al.[18c] were selected, as they meet the above criteria and showed added promise, having succeeded in the arylation of juglone. The work of Baran and co-workers is representative of a strategy that has been employed by a number of different research groups, in which a metal catalyst and persulfate are used to generate aryl radicals from the arylboronic acid, and nucleophilic radical addition to the quinone leads to the desired products.[42] Accordingly, these conditions were tested in attempts to arylate ramentaceone (**2**) with boronic acid **27**; however, there was no evidence that

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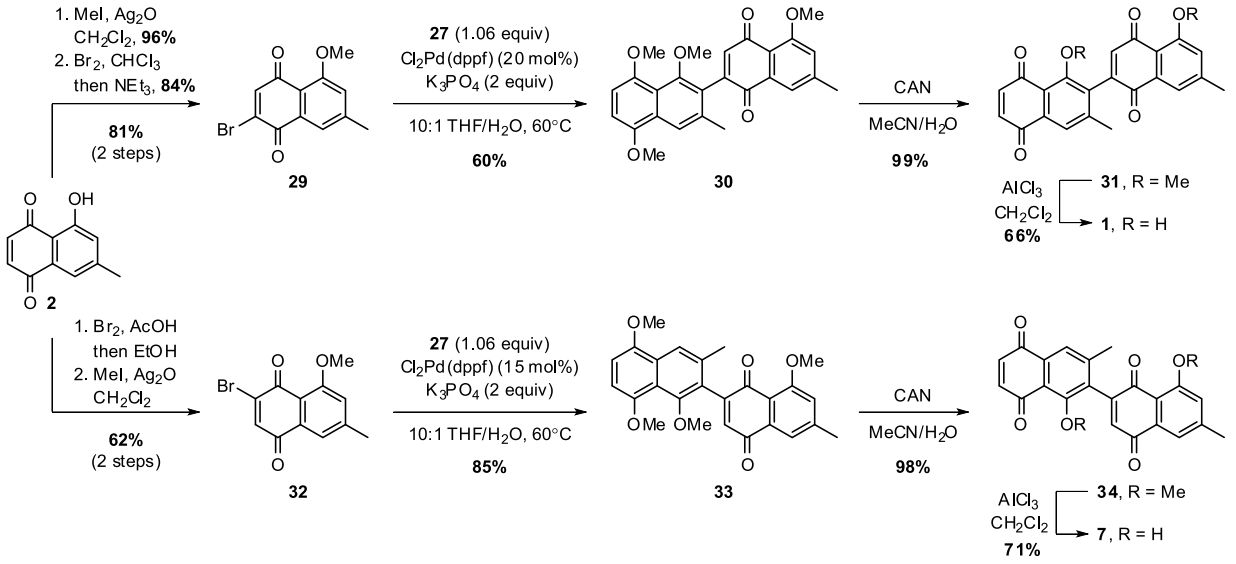
Scheme 6. Synthesis of Diospyrin (1) and Idospyrin (7)



naphthylquinone **28** was produced across a number of experiments (Table S5, Supporting Information).

The work from the Csákÿ group involves arylation of quinones with arylboronic acids under palladium/copper catalysis; that is, conjugate addition, followed by oxidation with $FeCl_3$ to furnish an arylquinone.[18c] Application of this protocol to our system (Scheme 5) resulted in complete deborylation of boronic acid **27** with low conversion of ramentaceone (**2**) and formed both naphthyljuglones **28** in a combined 9% yield. An attempt to improve upon this result by changing the phosphine ligand to 1,1′-bis-(diphenylphosphino)ferrocene (dppf) resulted in no reaction.

Although all avenues for the arylation of ramentaceone (**2**) had not been completely exhausted, the numerous strategies tested (Schemes 3 and 5, Tables S2, S3, and S5, Supporting Information) had failed to provide a promising lead. Thus, our original plan to obtain both of the naphthyljuglones required for synthesis of **1** and **7** from a single arylation experiment was abandoned.

With arylboronic acid **27** in hand, the logical approach to complete the syntheses of diospyrin (**1**) and idospyrin (**7**) was via Suzuki−Miyaura cross-coupling (Scheme 6). For the synthesis of **1**, the required halojuglone coupling partner was prepared by methylation of ramentaceone (**2**)[43] followed by bromination, with regioselective elimination of HBr from the intermediate juglone dibromide[44] furnishing the 2-bromide **29**. Inverting this sequence[45] provided access to 3-bromojuglone **32** as the major regioisomer in 62% yield across two steps from ramentaceone (**2**).

Initially, naphthylboronic acid **27** and 2-bromojuglone **29** were coupled under conditions described by Yoshida and Mori in their synthesis of diospyrin.[4h] In our hands this procedure gave unsatisfactorily low yields of naphthyljuglone **30**, with competing conjugate addition of EtOH to **29** identified as a significant side-reaction. Switching to the conditions of Narayan and Roush in their synthetic studies toward angelmicin B[46] resulted in a significantly improved yield of **30**. These conditions were also effective for the coupling of 3-bromojuglone **32** with **27** to afford the isomeric naphthyljuglone **33**.

The binaphthyl bond of naphthyljuglones **30** and **33**—and of **31**, **34**, diospyrin (**1**), and idospyrin (**7**)—is potentially hindered enough to restrict rotation about its axis.[47] Natural diospyrin is optically inactive,[3a,48] and it remains unclear whether this is because there is unrestricted rotation about the binaphthyl bond of **1**[4h,49] or because natural diospyrin is simply racemic.[47] Thus, we did not attempt to control the stereochemistry of the Suzuki−Miyaura reactions when preparing naphthyljuglones **30** and **33**.

The pyridinium chloride and MnO_2 global deprotection/oxidation sequence that succeeded with naphthalenes **9** and **20** failed when applied to naphthyljuglones **30** and **33**, affording an insoluble black mass in both cases. Instead, oxidative demethylation of **30** yielded diospyrin dimethyl ether (**31**), which was treated with $AlCl_3$[4h] to furnish diospyrin (**1**), for which the physical and spectroscopic data match the literature (Table S6, Supporting Information).[4h] This oxidative demethylation/deprotection sequence was repeated with **33** to give the novel isomer idospyrin (**7**).

Antiproliferative Activity. The activity of diospyrin (**1**), idospyrin (**7**), and precursors was assessed against the murine myeloma-derived NS-1 (ATCC TIB-18) cell line and non-cancerous neonatal foreskin fibroblasts (Nff) (ATCC PCS-201), using a resazurin assay.[50] The results are presented in Table 1. While the resazurin assay determines mitochondrial metabolic activity as a proxy for cell viability, natural diospyrin (**1**) and its semisynthetic diethyl ether have previously been shown to induce apoptosis in a variety of cancer cell lines.[14a]

Diospyrin (**1**) and the two precursors, GAP-R370 (**30**) and diospyrin dimethyl ether (**31**), have similar growth inhibitory activity against the NS-1 cell line and are somewhat selective, with 10−30-fold lower potency against Nff. The biquinone isomer idospyrin (**7**) and its dimethyl ether **34** have similar potency and selectivity to diospyrin (**1**) and its precursors **30** and **31**. The most potent and selective compound in the series is the partially reduced tetramethyl ether GAP-R380 (**33**).

Diospyrin and a number of derivatives have been shown to be cytotoxic to a variety of cancer cell lines, and the subject has been reviewed.[51] The monomer ramentaceone (**2**) and diospyrin isomer isodiospyrin (**3**) have also both been reported to be cytotoxic to human colon carcinoma cells

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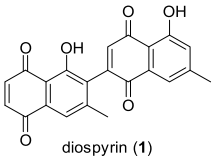
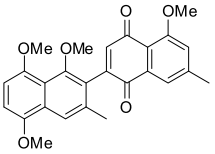
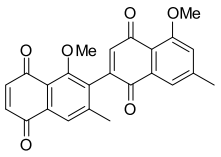
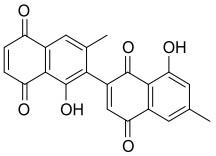
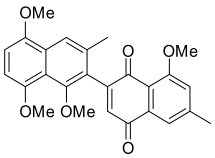
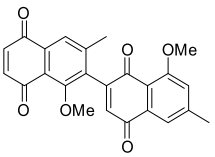
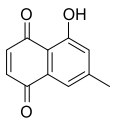
Table 1. Growth Inhibition of NS-1 (Murine Myeloma) and Nff (Neonatal Foreskin Fibroblast) Cells

Compound	IC_{50} (μM)[a] NS-1	Nff	Selectivity Index
 diospyrin (**1**)	0.8 ± 0.08	5.8 ± 0.19	10
 GAP-R370 (**30**)	0.4 ± 0.02	7.6 ± 2.8	19
 diospyrin dimethyl etther (**31**)	0.8 ± 0.05	25.7 ± 2.7	31
 idospyrin (**7**)	1.8 ± 0.13	31.8 ± 3.3	14
 GAP-R380 (**33**)	0.4 ± 0.01	25.4 ± 1.2	181
 idospyrin dimethyl ether (**34**)	2.0 ± 0.07	61.8 ± 4.4	32
 ramentaceone (**2**)	0.5 ± 0.02	7.6 ± 0.80	15
5-fluorouracil	2.8 ± 0.31	13%[b]	>352

[a]All results are the average of three replicates ± the SEM. [b]Percentage growth inhibition at 1 mM.

with similar IC_{50} values (Figure 2).[52] However, isodiospyrin was later found to be inactive against a panel of cell lines, including Col-2, which was derived from a human colon cancer. Ramentaceone (**2**), on the other hand, displayed broad activity against multiple cell lines with low μg/mL IC_{50} values.[53] In a study of the constituents of *Diospyros maritima*, ramentaceone (**2**), the two methoxylated congeners **35** and **36**, the isomer plumbagin (**38**), and the plumbagin dimers maritinone (**39**), chitranone (**40**), and zeylanone (**41**) (Figure 2) were all found to have comparable cytotoxicity to four human cell lines.[54]

Ramentaceone (**2**) was shown to induce apoptosis in the HL-60 (promyelocytic leukemia) cell line, through the generation of reactive oxygen species (ROS).[55] ROS have also been implicated in the antitumor activity of diospyrin (**1**) and its dimethyl and diethyl ethers.[51,56] Indeed, production of ROS is the mode of action most commonly attributed to bioactive quinones, along with conjugation with the sulfhydryl groups of glutathione and the cysteine residues of proteins.[57]

The similar growth inhibitory potency of the compounds presented herein (**1**, **2**, **7**, and **31**−**34**), despite significant structural changes (especially the change of biaryl linkage), is consistent with multiple modes of action involving chemical reactivity, rather than discrete receptor−ligand interactions. That said, diospyrin and its precursors are not indiscriminate cytotoxins; in our hands, none displayed toxicity to *Staph-*

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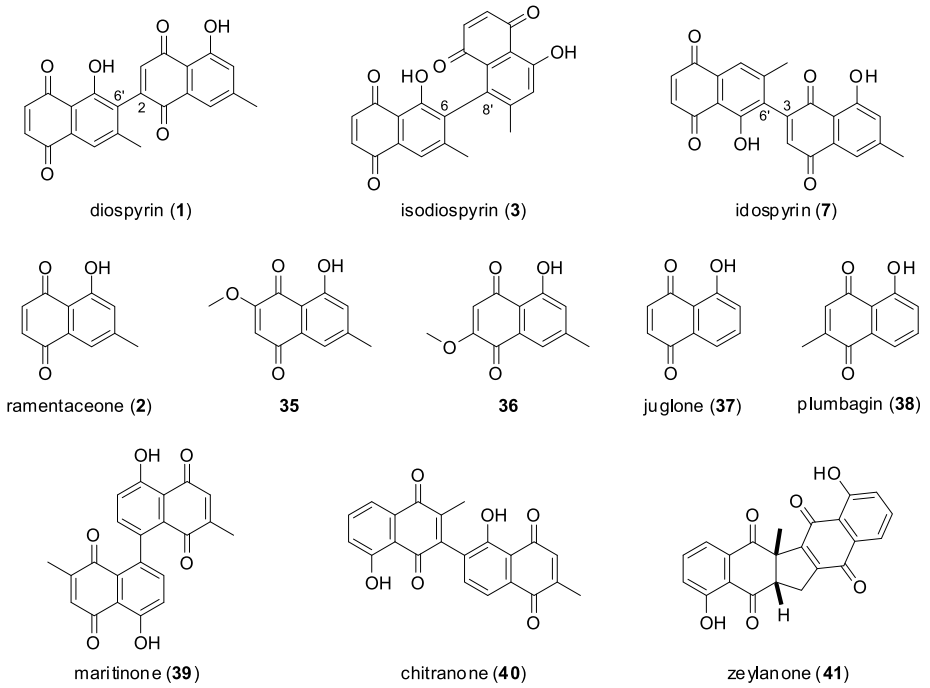

Figure 2. A selection of cytotoxic naphthoquinones and dimers related to diospyrin. Note, natural zeylanone is racemic.[58]

ylococcus aureus, *Candida albicans*, and *Tritrichomonas fetus* at concentrations up to 100 μg/mL.

Dimerization is an efficient way to increase chemical diversity in secondary metabolism; in principle, one monomer can give rise to many different, considerably more complex dimers. Hence, it is not surprising that this biosynthetic device has evolved in all kingdoms of life. Dimerization is particularly effective for quinones, where the inherent chemical reactivity of the monomer is likely to be retained in dimers. However, as previously noted,[56] structural modifications affect physicochemical, pharmacokinetic, and pharmacodynamic properties of quinones. These often subtle changes alter the profile of biomolecules directly or indirectly impacted by quinonoid natural products, thereby modulating their bioactivity. Occasionally this must provide a selective advantage to the producing organism; hence, the biosynthetic machinery is evolutionarily preserved.

In summary, the 2,6′-bijuglone natural product diospyrin (**1**) and its novel 3,6′-isomer idospyrin (**7**) have both been synthesized in seven steps, diverging from senecioamide **13c**, in overall yields of 12% and 13%, respectively. A number of strategies for the arylation of 2,3-unsubstituted naphthoquinones were tested for their application to the syntheses of **1** and **7**, without success. Ultimately, the desired arylation was realized by Suzuki−Miyaura cross-coupling of the isomeric bromojuglones.

Given that six of the possible 10 ramentaceone (**2**) dimers have already been isolated from living organisms, it seems likely that idospyrin (**7**) will eventually be proven a natural product.

While diospyrin (**1**) and idospyrin (**7**) have quite potent cytotoxicity and display some selectivity toward a myeloma cell line over noncancerous cells, the fact that the monomer ramentaceone (**2**) and derivatives/precursors share similar cytotoxicity suggest their activity is not mediated through discrete ligand−receptor interactions. It remains to be established whether the antitubercular activity of diospyrin, through inhibtion of *M. tuberculosis* DNA gyrase, is shared by idospyrin and their precursors and derivatives.

EXPERIMENTAL SECTION

General Experimental Procedures. All solvents were distilled prior to use. THF, pentane, PhMe, and *n*-hexane were obtained from a Pure Solv 5-Mid solvent purification system (Innovative Technology Inc.). "Anhydrous THF" refers to THF freshly distilled from a purple solution containing sodium benzophenone ketyl. "Dry" DMF, MeCN, and CH_2Cl_2 refers to solvents stored over activated type 3A molecular sieves for at least 24 h.[59] "Degassed" solvents refer to solvents that were vigorously stirred while being sparged with N_2 for at least 30 min.

The concentration of solutions of *n*-BuLi and *sec*-BuLi were determined by titration with *N*-benzylbenzamide.[60] TMEDA was dried over and distilled from CaH_2 under N_2 onto fresh KOH pellets and was stored as such under N_2.[59a] Diisopropylamine was dried over and distilled from NaH under N_2 onto fresh KOH pellets and was stored as such under N_2.[59a] *N*,*N*-Diethylsenecioamide (**13c**) was prepared by a known method from 3,3-dimethylacrylic acid and diethylamine.[22] 2-Chloro-1,4-dimethoxybenzene (**15**) was prepared by a known method from 1,4-dimethoxybenzene.[61] A solution of chloromethyl methyl ether in MeOAc was prepared by a known method from dimethoxymethane and acetyl chloride.[62] All other reagents and materials were purchased from commercial suppliers and used as received.

All reactions, except method 1 for the preparation of **2**, were conducted in oven- or flame-dried glassware under an atmosphere of N_2 with the use of syringe and septum-cap techniques. Where indicated, reaction temperatures refer to the temperature of the heating or cooling bath. The temperature −78 °C indicated is approximate and refers to the temperature achieved by a dry ice−acetone bath. All organic extracts were evaporated under reduced pressure at 40−45 °C. Trace residual solvent was removed under a stream of N_2.

Reaction progress was monitored by TLC using Merck aluminum-backed TLC silica gel 60 F_{254} plates, which were also used for preparative TLC. Spots were visualized using ultraviolet light. Flash column chromatography was performed using Davisil chromatographic silica media LC60A 40−63 μm.

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^{1}H and ^{13}C NMR spectra were acquired using Bruker Avance IIIHD (600 MHz for ^{1}H and 150 MHz for ^{13}C) and Bruker Avance IIIHD (500 MHz for ^{1}H and 125 MHz for ^{13}C) spectrometers, as indicated. Spectra were acquired at 25 °C unless otherwise indicated. Spectra were calibrated against $CHCl_3$ (for ^{1}H spectra; δ 7.26) or $CDCl_3$ (for ^{13}C spectra; δ 77.16) peaks. Yields determined by ^{1}H NMR spectroscopy used 1,3,5-trimethoxybenzene as an internal standard. At least 10 mg of internal standard and of analyte were completely dissolved for each determination. A ^{1}H NMR spectrum of the solution was then obtained with a relaxation delay of 30 s, and at least 32 scans were collected.

High-resolution mass spectra were recorded on a Waters Liquid Chromatograph Premier mass spectrometer using ESI and APCI in positive or negative mode, as indicated. IR spectra were recorded on a PerkinElmer Spectrum One FT-IR spectrometer with attenuated total reflectance (ATR) using neat samples. Assignments of IR absorption bands were made with reference to the literature.[63] Melting points were determined using a Reichert hot stage melting point apparatus.

Synthesis. *5,8-Dimethoxy-3-methylnaphthalen-1-ol (**9**). Method 1.* Pd/C (10 wt % Pd, 1.05 g) was added to a solution of hydroxymethylnaphthol **12** (7.71 g, 32.9 mmol) in AcOH (160 mL), and the resulting suspension was degassed before being stirred at room temperature under a balloon of H_2 for 40 h. The reaction mixture was diluted with Et_2O (200 mL) and vacuum filtered through a pad of Celite, washing the filter cake with Et_2O (3 × 50 mL). The filtrate was washed with water (3 × 150 mL), and the aqueous phase was back-extracted with Et_2O (150 mL). The combined organic phases were washed with brine (150 mL), dried over $MgSO_4$, filtered, and evaporated. The tan crude solid was subjected to flash chromatography. Elution with 1:9 EtOAc/hexanes afforded impure **9** as an off-white solid (6.23 g), which recrystallized from hexanes to give **9** (5.59 g, 78%) as colorless needles, identical with the product described below.

Method 2. A stirred solution of *i*Pr_2NH (2.50 mL, 17.7 mmol) in anhydrous THF (30 mL) was cooled to 0 °C, treated dropwise with 2.16 M *n*-BuLi in hexanes (8.20 mL, 17.7 mmol), and stirred at 0 °C for 15 min. The resulting solution of LDA was cooled to −78 °C before being treated dropwise with a solution of *N*,*N*-diethylsenecioamide (**13c**)[22] (0.792 g, 5.10 mmol) in anhydrous THF (20 mL). The solution was stirred at −78 °C for 1 h and warmed to −20 °C over 15 min before a solution of 2-chloro-1,4-dimethoxybenzene (**15**)[61] (1.777 g, 10.29 mmol) in anhydrous THF (10 mL) was added dropwise, causing the reaction solution to turn orange. The solution was allowed to warm to room temperature overnight (16 h) with stirring before being quenched with saturated aqueous NH_4Cl (10 mL), acidified with 1.5 M HCl (40 mL), and extracted with $CHCl_3$ (3 × 40 mL). The extract was dried over Na_2SO_4, filtered, and evaporated. The yellow crude residue was subjected to flash chromatography. Elution with 1:9 EtOAc/hexanes afforded **9** (0.486 g, 44%) as a colorless solid, mp 114−115 °C [lit.[19e] mp 116−117 °C]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.37 (s, 1H), 7.50 (m [pseudo dd], J = 1.6, 0.9 Hz, 1H), 6.77 (d, J = 1.5 Hz, 1H), 6.62 (d [AB], J = 8.4 Hz, 1H), 6.60 (d [AB], J = 8.4 Hz, 1H), 4.00 (s, 3H), 3.94 (s, 3H), 2.44 (s, 3H). The ^{1}H NMR data match those in the literature.[19d,e]

*5-Hydroxy-7-methyl-1,4-naphthoquinone (7-Methyljuglone, Ramentaceone) (**2**). Method 1.* A mixture of naphthol **9** (1.09 g, 5.00 mmol) and pyridinium chloride (6.36 g, 55.0 mmol) was stirred under reflux for 30 min. The reaction mixture was briefly allowed to cool, but while still a liquid, it was diluted with water (40 mL), and the resulting suspension was cooled to room temperature and extracted with EtOAc (4 × 30 mL). The extract was treated with Na_2SO_4 (4.30 g, 30.3 mmol) and MnO_2 (6.52 g, 75.0 mmol), and the resulting brown suspension was stirred at room temperature for 40 min. The reaction mixture was vacuum filtered through a pad of Celite, washing the filter cake with EtOAc (3 × 40 mL) until the washes were colorless. Evaporation of the filtrate gave **2** (0.785 g, 83%) as an orange solid, mp 120−122 °C [lit.[19c] 120.5−122 °C]. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.86 (s, 1H), 7.44 (m [pseudo dd], J = 1.5, 0.3 Hz, 1H), 7.09 (m [pseudo dd], J = 1.5, 0.7 Hz, 1H), 6.918 (d [AB], J = 10.3 Hz, 1H), 6.909 (d [AB], J = 10.3 Hz, 1H), 2.44 (s, 3H). The ^{1}H NMR data match those in the literature.[19c]

Method 2. A mixture of carbamate **20** (0.254 g, 0.802 mmol) and pyridinium chloride (1.75 g, 15.1 mmol) was stirred under reflux for 20 min. The reaction mixture was briefly allowed to cool, but while still a liquid, it was diluted with water (15 mL) and the resulting suspension was cooled to room temperature and extracted with EtOAc (4 × 10 mL). The extract was treated with Na_2SO_4 (0.767 g, 5.40 mmol) and MnO_2 (1.05 g, 12.1 mmol), and the resulting brown suspension was stirred at room temperature for 40 min. The reaction mixture was vacuum filtered through a pad of Celite, washing the filter cake with EtOAc (3 × 30 mL) until the washes were colorless, and the filtrate was evaporated. The dark orange crude solid was subjected to flash chromatography. Elution with 3:7 CH_2Cl_2/hexanes afforded **2** (0.112 g, 74%) as an orange solid, identical with the product described above.

*5,8-Dimethoxy-1-(methoxymethoxy)-3-methylnaphthalene (**17**).* A stirred suspension of NaH (0.592 g, 24.7 mmol; prepared by washing a 60% mineral oil dispersion of NaH (0.986 g) with *n*-hexane (35 mL)) in dry DMF (30 mL) at 0 °C was treated dropwise with a solution of naphthol **9** (1.75 g, 8.00 mmol) in dry DMF (15 mL). The resulting mixture was stirred at 0 °C for 15 min before a *ca.* 6.4 M solution of chloromethyl methyl ether in MeOAc[62] (4.6 mL, *ca.* 29 mmol) was added slowly. The reaction mixture was allowed to warm to room temperature and was stirred for 30 min before being cooled to 0 °C and quenched with saturated NH_4Cl (10 mL). The resulting suspension was diluted with water (150 mL) and extracted with Et_2O (3 × 100 mL). The extract was washed with brine (75 mL), dried over Na_2SO_4, filtered, and evaporated. The off-white crude solid was subjected to flash chromatography. Elution with 1:9 EtOAc/hexanes afforded **17** (2.02 g, 96%) as a colorless solid, mp 63−65 °C. R_f (1:9 EtOAc/hexanes) 0.25; IR (ATR) ν_{max} cm^{-1} 1609, 1511, 1269, 1086, 1048, 846; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (m [pseudo dd], J = 1.6, 0.9 Hz, 1H, H-4), 6.98 (d, J = 1.6 Hz, 1H, H-2), 6.704 (d [AB], J = 8.6 Hz, 1H, H-7), 6.696 (d [AB], J = 8.6 Hz, 1H, H-6), 5.24 (s, 2H, OCH_2O), 3.94 (s, 3H, 5-OCH_3), 3.90 (s, 3H, 8-OCH_3), 3.61 (s, 3H, $CH_2OC\underline{H}_3$), 2,47 (s, 3H, $ArCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.6 (C-1), 150.7 (C-8), 149.4 (C-5), 136.0 (C-3), 129.1 (C-4a), 117.9 (C-8a), 116.9 (C-2), 116.2 (C-4), 106.0 (C-7), 104.2 (C-6), 97.3 (OCH_2O), 57.3 (8-OCH_3), 56.6 ($CH_2O\underline{C}H_3$), 55.9 (5-OCH_3), 22.0 ($ArCH_3$); HRMS (ESI+) m/z $[M + H]^+$ calcd for $C_{15}H_{19}O_4^+$ 263.1278; found, 263.1276. NMR assignments were made with the assistance of COSY, HSQC, and HMBC experiments.

*N,N-Diethyl-O-(5,8-dimethoxy-3-methylnaphthalen-1-yl)-carbamate (**20**).* A stirred suspension of naphthol **9** (0.656 g, 3.01 mmol) and K_2CO_3 (0.630 g, 4.56 mmol) in dry MeCN (20 mL) was treated with $ClCONEt_2$ (0.95 mL, 7.50 mmol) at room temperature. The reaction mixture was stirred under reflux for 30 h before being cooled to room temperature, diluted with water (50 mL), and extracted with Et_2O (3 × 30 mL). The extract was washed with water (20 mL) and brine (20 mL), dried over Na_2SO_4, filtered, and evaporated. The brown crude oil was subjected to flash chromatography. Elution with 1:4 EtOAc/hexanes afforded **20** (0.933 g, 98%) as a colorless oil that crystallized on standing to a colorless solid, mp 118−120 °C. R_f (1:4 EtOAc/hexanes) 0.3; IR (ATR) ν_{max} cm^{-1} 1699 (s, C═O), 1607, 1506, 1364, 1261, 1059, 871, 812; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (m [pseudo dd], J = 1.6, 0.9 Hz, 1H, H-4), 7.00 (d, J = 1.6 Hz, 1H, H-2), 6.67 (d [AB], J = 8.5 Hz, 1H, H-6), 6.63 (d [AB], J = 8.5 Hz, 1H, H-7), 3.93 (s, 3H, 5-OCH_3), 3.82 (s, 3H, 8-OCH_3), 3.55 (q, J = 7.1 Hz, 2H, NCH_2)*, 3.42 (q, J = 7.1 Hz, 2H, NCH_2)^, 2.47 (s, 3H, $ArCH_3$), 1.32 (t, J = 7.1 Hz, 3H, $NCH_2C\underline{H}_3$)*, 1.23 (t, J = 7.1 Hz, 3H, $NCH_2C\underline{H}_3$)^; ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.3 (C═O), 149.7 (C-8), 149.1 (C-5), 147.1 (C-1), 135.8 (C-3), 128.8 (C-4a), 122.7 (C-2), 119.1 (C-4), 118.8 (C-8a), 104.2 (C-6 or C-7), 104.1 (C-6 or C-7), 56.0 (5-OCH_3), 55.8 (8-OCH_3), 42.1 (NCH_2)^, 41.8 (NCH_2)*, 21.6 ($ArCH_3$), 14.2 ($NCH_2\underline{C}H_3$)*, 13.6 ($NCH_2\underline{C}H_3$)^; HRMS (ESI+) m/z $[M + H]^+$ calcd for $C_{18}H_{24}O_4N^+$ 318.1700; found, 318.1700. NMR assignments were made with the assistance of COSY, HSQC, and HMBC experiments. Superscripts (*, ^) denote resonances that belong to the same spin system.

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*N,N-Diethyl-1-hydroxy-5,8-dimethoxy-3-methyl-2-naphthamide (**21**).* TMEDA (40 μL, 0.27 mmol) was added to a solution of carbamate **20** (63 mg, 0.20 mmol) in anhydrous THF (4.0 mL). The resulting solution was cooled to −78 °C over 20 min and stirred as it was slowly treated dropwise with 1.06 M *sec*-BuLi in cyclohexane (0.27 mL, 0.29 mmol). The resulting brown solution was stirred at −78 °C for 20 min before being quenched with triisopropyl borate (0.11 mL, 0.48 mmol), stirred at −78 °C for a further 1 h, and allowed to warm slowly to room temperature overnight (17 h). The reaction mixture was acidified with 0.1 M HCl (7 mL), diluted with water (5 mL), and extracted with EtOAc (3 × 15 mL). The extract was washed with brine (15 mL), dried over Na_2SO_4, filtered, and evaporated. The brown crude oil was subjected to flash chromatography. Elution first with 1:4 EtOAc/hexanes and increasing polarity to 2:3 EtOAc/hexanes afforded **21** (53 mg, 84%) as a colorless residue, which solidified on standing to give an off-white solid, mp 126−127 °C. R_f (2:3 EtOAc/hexanes) 0.2; IR (ATR) ν_{max} cm^{-1} 3356 (m, OH), 1623 (s, C═O), 1606, 1497, 1362, 1246, 1065, 862; ^1H NMR (500 MHz, $CDCl_3$) δ 9.58 (s, 1H, OH), 7.55 (q, J = 0.8 Hz, 1H H-4), 6.64 (AB [app. s], 2H, H-6, H-7), 3.99 (s, 3H, 8-OCH_3), 3.94 (s, 3H, 5-OCH_3), 3.79 (dq [pseudo sextet], J = 14.1, 7.1 Hz, 1H, NCH_2)*, 3.51 (dq [pseudo sextet], J = 14.1, 7.1 Hz, 1H, NCH_2)*, 3.23 (dq [pseudo sextet], J = 14.3, 7.1 Hz, 1H, NCH_2)^, 3.18 (dq [pseudo sextet], J = 14.3, 7.1 Hz, 1H, NCH_2)^, 2.38 (d, J = 0.8 Hz, 3H, $3CH_3$), 1.29 (dd [app. t], J = 7.1 Hz, 3H, $NCH_2C\underline{H}_3$)*, 1.06 (dd [app. t], J = 7.1 Hz, 3H, $NCH_2C\underline{H}_3$)^; ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6 (C═O), 150.4 (C-8), 150.0 (C-1), 149.8 (C-5), 134.1 (C-3), 127.9 (C-4a), 121.5 (C-2), 113.9 (C-8a), 113.6 (C-4), 103.7 (C-6 or C-7), 103.2 (C-6 or C-7), 56.5 (8-OCH_3), 55.9 (5-OCH_3), 42.8 (NCH_2)^, 38.9 (NCH_2)*, 19.6 ($3CH_3$), 14.2 ($NCH_2\underline{C}H_3$)^, 13.0 ($NCH_2\underline{C}H_3$)*; HRMS (ESI+) m/z $[M + H]^+$ calcd for $C_{18}H_{24}O_4N^+$ 318.1700; found, 318.1711. NMR assignments were made with the assistance of COSY, HSQC, and HMBC experiments. Superscripts (*, ^) denote resonances that belong to the same spin system.

*1′,5,5′,8′-Tetramethoxy-3′,7-dimethyl-[2,2′-binaphthalene]-1,4-dione; GAP-R370 (**30**). Method 1.*[4h] A mixture of bromojuglone **29** (0.114 g, 0.404 mmol) and $Pd(PPh_3)_4$ (45 mg, 39 μmol) was stirred in degassed PhMe (5.2 mL) for 15 min and treated with a degassed 2 M aqueous Na_2CO_3 solution (0.33 mL, 0.66 mmol) followed by a solution of boronic acid **27** (0.125 g, 0.453 mmol) in degassed EtOH (1.3 mL). The resulting mixture was stirred under reflux for 6 h before being cooled to room temperature, diluted with water (10 mL), and extracted with $CHCl_3$ (3 × 20 mL). The extract was washed with brine (15 mL), dried over Na_2SO_4, filtered, and evaporated. The green crude residue was subjected to flash chromatography. Elution with CH_2Cl_2 afforded impure **30** as a red film (44 mg), which was again subjected to flash chromatography. Elution with 3:7 EtOAc/hexanes furnished **30** (19 mg) as an orange-red solid. Additionally, impure fractions were subjected to preparative TLC. Development with 2:3 EtOAc/hexanes afforded **30** (11 mg) as a red-orange solid (total 30 mg, 17%), spectroscopically identical with the product described below.

Method 2. A stirred solution of bromojuglone **29** (0.121 g, 0.430 mmol), boronic acid **27** (0.126 g, 0.456 mmol), and $Cl_2Pd(dppf)\cdot CH_2Cl_2$ (72 mg, 88 μmol) in degassed THF (8.6 mL) was treated with 1 M aqueous K_3PO_4 (0.86 mL, 0.86 mmol). The resulting mixture was stirred vigorously at 60 °C for 6 h before being cooled to room temperature, diluted with water (30 mL), and extracted with CH_2Cl_2 (4 × 25 mL). The extract was washed with brine (25 mL), dried over Na_2SO_4, filtered, and evaporated. The red-brown crude residue was subjected to flash chromatography. Elution first with 1:5:44 NEt_3/EtOAc/hexanes and increasing polarity to 1:15:34 NEt_3/EtOAc/hexanes afforded **30** (0.111 g, 60%), which crystallized upon evaporation of relevant fractions as red prisms, mp 202−204 °C [lit.[4h] 195−196 °C]. ^1H NMR (500 MHz, $CDCl_3$) δ 7.94 (q, J = 0.9 Hz, 1H), 7.63 (m [pseudo dd], J = 1.5, 0.6 Hz, 1H), 7.14 (br s, 1H), 6.86 (s, 1H), 6.74 (d [AB], J = 8.5 Hz, 1H), 6.73 (d [AB], J = 8.5 Hz, 1H), 4.04 (s, 3H), 3.96 (s, 3H), 3.92 (s, 3H), 3.64 (s, 3H), 2.50 (s, 3H), 2.28 (d, J = 0.9 Hz, 3H). The ^1H NMR data match those in the literature.[4h]

*1′,5,5′,8′-Tetramethoxy-3′,7-dimethyl-[3,2′-binaphthalene]-1,4-dione; GAP-R380 (**33**).* A stirred solution of bromojuglone **32** (90 mg, 0.32 mmol), boronic acid **27** (93 mg, 0.34 mmol), and $Cl_2Pd(dppf)\cdot CH_2Cl_2$ (40 mg, 49 μmol) in degassed THF (6.4 mL) was treated with 1 M aqueous K_3PO_4 (0.64 mL, 0.64 mmol). The resulting mixture was stirred vigorously at 60 °C for 9 h before being cooled to room temperature, diluted with water (25 mL), and extracted with CH_2Cl_2 (3 × 25 mL). The extract was washed with brine (20 mL), dried over Na_2SO_4, filtered, and evaporated. The red-brown crude residue was subjected to flash chromatography. Elution with 3:7 EtOAc/hexanes, increasing polarity to 7:13 EtOAc/hexanes, afforded **33** (0.118 g, 85%) as an orange-red solid. A sample was recrystallized from Et_2O/hexanes as orange-red granules, mp 159−160 °C. R_f (2:3 EtOAc/hexanes) 0.35; IR (ATR) ν_{max} cm^{-1} 1657 (s, C═O), 1623, 1597, 1258, 1071, 850, 800; ^1H NMR (600 MHz, $CDCl_3$) δ 7.91 (q, J = 0.9 Hz, 1H, H-4′), 7.62 (m [pseudo dd], J = 1.5, 0.6 Hz, 1H, H-8), 7.12 (br s, 1H, H-6), 6.86 (s, 1H, H-2), 6.74 (d [AB], J = 8.5 Hz, 1H, H-6′), 6.72 (d [AB], J = 8.5 Hz, 1H, H-7′), 3.96 (s, 3H, 5′-OCH_3), 3.95 (s, 3H, 5-OCH_3), 3.92 (s, 3H, 8′-OCH_3), 3.65 (s, 3H, 1′-OCH_3), 2.51 (s, 3H, 7-CH_3), 2.29 (d, J = 0.9 Hz, 3H, 3′-CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 185.6 (C-1), 183.5 (C-4), 160.2 (C-5), 153.7 (C-1′), 150.2 (C-3), 150.0 (C-8′), 149.4 (C-5′), 146.4 (C-7), 135.6 (C-2), 134.6 (C-3′), 134.4 (C-8a), 128.9 (C-4a′), 127.9 (C-2′), 119.8 (C-8), 119.0 (C-8a′), 118.5 (C-6), 118.4 (C-4′), 118.3 (C-4a), 105.3 (C-7′), 104.6 (C-6′), 62.9 (1′-OCH_3), 56.6 (8′-OCH_3), 56.5 (5-OCH_3), 56.0 (5′-OCH_3), 22.5 (7-CH_3), 20.7 (3′-CH_3); HRMS (ESI+) m/z $[M + H]^+$ calcd for $C_{26}H_{25}O_6^+$ 433.1646; found, 433.1664. NMR assignments were made with the assistance of COSY, HSQC, and HMBC experiments.

*5,5′-Dimethoxy-7,7′-dimethyl-[3,6′-binaphthalene]-1,1′,4,4′-tetraone; Idospyrin Dimethyl Ether (**34**).* A stirred solution of GAP-R380 (**33**) (78 mg, 0.18 mmol) in 5:2 MeCN/water (7.7 mL) was cooled to 0 °C and treated dropwise with a cold (0 °C) solution of cerium(IV) ammonium nitrate (0.301 g, 0.549 mmol) in 1:1 MeCN/water (6.4 mL) over 10 min. The reaction mixture was stirred at 0 °C for 70 min, forming a yellow suspension, which was diluted with water (20 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The extract was washed with brine (15 mL), dried over Na_2SO_4, filtered, and evaporated to give **34** (71 mg, 98%) as a yellow-orange solid, mp 188−192 °C. R_f (2:3 EtOAc/hexanes) 0.3; IR (ATR) ν_{max} cm^{-1} 1658 (s, C═O), 1598, 1581, 1277, 1263, 1057, 1039; ^1H NMR (500 MHz, $CDCl_3$) δ 7.82 (q, J = 0.6 Hz, 1H, H-8′), 7.63 (m [pseudo dd], J = 1.5, 0.6 Hz, 1H, H-8), 7.14 (br s, 1H, H-6), 6.92 (d [AB], J = 10.3 Hz, 1H, H-2′), 6.88 (d [AB], J = 10.3 Hz, 1H, H-3′), 6.78 (s, 1H, H-2), 3.97 (s, 3H, 5-OCH_3), 3.71 (s, 3H, 5′-OCH_3), 2.52 (s, 3H, 7-CH_3), 2.30 (d, J = 0.6 Hz, 3H, 7′-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.0 (C-1 and C-1′), 183.9 (C-4′), 182.5 (C-4), 160.4 (C-5), 158.1 (C-5′), 148.1 (C-3), 147.0 (C-7), 144.9 (C-7′), 140.7 (C-3′), 137.0 (C-6′), 136.9 (C-2′), 135.5 (C-2), 134.2 (C-8a), 133.7 (C-8a′), 124.4 (C-8′), 121.7 (C-4a′), 120.1 (C-8), 118.7 (C-6), 117.8 (C-4a), 62.7 (5′-OCH_3), 56.6 (5-OCH_3), 22.5 (7-CH_3), 20.9 (7′-CH_3); HRMS (ESI+) m/z $[M + H]^+$ calcd for $C_{24}H_{19}O_6^+$ 403.1176; found, 403.1179. NMR assignments were made with the assistance of COSY, HSQC, and HMBC experiments.

*5,5′-Dihydroxy-7,7′-dimethyl-[3,6′-binaphthalene]-1,1′,4,4′-tetraone; Idospyrin (**7**).* A stirred solution of idospyrin dimethyl ether (**34**) (64 mg, 0.16 mmol) in CH_2Cl_2 (14 mL) was cooled to 0 °C and treated with $AlCl_3$ (0.227 g, 1.70 mmol) added in one portion. The reaction mixture was allowed to warm from 0 °C to room temperature gradually over 12 h. The dark purple reaction mixture was cooled to 0 °C and quenched with water (20 mL), acidified with 10% aqueous citric acid (20 mL), and separated. The aqueous phase was extracted with $CHCl_3$ (3 × 20 mL). The organic phases were combined, washed with brine (20 mL), dried over Na_2SO_4, filtered, and evaporated. The dark red crude residue was subjected to flash chromatography. Elution first with 1:4 $CHCl_3$/PhMe and increasing polarity to 2:3 $CHCl_3$/PhMe afforded impure **7** as a red solid (51 mg). Trituration of this solid with 1:9 CH_2Cl_2/hexanes afforded **7** (42 mg, 71%) as a red powder, mp 217−220 °C. R_f (CH_2Cl_2) 0.5; IR (ATR) ν_{max} cm^{-1} 1664 (s, 1-C═O, 1′-C═O), 1632 (s, 4-C═O, 4′-

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C═O), 1612, 1592, 1379, 1364, 1342, 1259, 1216, 1095, 1052, 847; ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.16 (s, 1H, 5′-OH), 11.84 (s, 1H, 5-OH), 7.58 (br s, 1H, H-8′), 7.52 (m [pseudo dd], J = 1.5, 0.4 Hz, 1H, H-8), 7.12 (m [pseudo dd], J = 1.5, 0.8 Hz, 1H, H-6), 6.97 (AB [app. s], 2H, H-2′ and H-3′), 6.88 (s, 1H, H-2), 2.47 (s, 3H, 7-CH_3), 2.33 (s, 3H, 7′-CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 189.9 (C-4′), 187.8 (C-4), 184.3 (C-1′), 184.1 (C-1), 162.3 (C-5), 159.3 (C-5′), 149.0 (C-7), 146.7 (C-7′), 145.1 (C-3), 139.6 (C-2′ or C-3′), 139.5 (C-2), 138.9 (C-2′ or C-3′), 132.0 (C-8a), 131.6 (C-8a′), 128.5 (C-6′), 124.5 (C-6), 120.9 (C-8′), 120.8 (C-8), 113.2 (C-4a), 113.1 (C-4a′), 22.4 (7-CH_3), 21.3 (7′-CH_3); HRMS (APCI+) m/z [M + H]$^+$ calcd for $C_{22}H_{15}O_6^+$ 375.0863; found, 375.0871. NMR assignments were made with the assistance of COSY, HSQC, and HMBC experiments.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jnatprod.0c00800.

Experimental procedures and characterization data for compounds **1**,[4h] **11**,[24] **12**,[64] **22**,[37] **26**,[4g] **27**,[4h] **29**,[43,44] **31**,[4h] and **32**;[45,65] tables detailing additional experiments and their results; and ^{13}C and ^{1}H NMR spectra of new and known compounds (PDF)

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Notes

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■ REFERENCES

(1) (a) Ganguly, A. K.; Govindachari, T. R. *Tetrahedron Lett.* **1966**, *7*, 3373−3376. (b) Sidhu, G. S.; Pardhasaradhi, M. *Tetrahedron Lett.* **1967**, *8*, 1313−1316. (c) Sidhu, G. S.; Pardhasaradhi, M. *Indian J. Chem.* **1970**, *8*, 569−571.

(2) Kapil, R. S.; Dhar, M. M. *J. Sci. Ind. Res.* **1961**, *20B*, 498−500.

(3) (a) Sidhu, G. S.; Prasad, K. K. *Tetrahedron Lett.* **1967**, *8*, 2905−2910. (b) Krishnamoorthy, V.; Thomson, R. H. *Phytochemistry* **1969**, *8*, 1591−1594. (c) Yoshihira, K.; Tezuka, M.; Natori, S. *Tetrahedron Lett.* **1970**, *11*, 7−10. (d) Yoshihira, K.; Tezuka, M.; Takahashi, C.; Natori, S. *Chem. Pharm. Bull.* **1971**, *19*, 851−854. (e) Van Der Vijver, L. M.; Gerritsma, K. W. *Pharm. Weekbl.* **1976**, *111*, 1273−1285.

(4) (a) Brockmann, H.; Laatsch, H. *Tetrahedron Lett.* **1973**, *14*, 3695−3698. (b) Van Der Vijver, L. M.; Gerritsma, K. W. *J. Chromatogr. A* **1975**, *114*, 443−450. (c) Maiti, B. C.; Musgrave, O. C.; Skoyles, D. *J. Chem. Soc., Chem. Commun.* **1976**, 244−245. (d) Laatsch, H. *Liebigs Ann. Chem.* **1980**, *1980*, 1321−1347. (e) Kumari, L. K.; Babu, M. H.; Pardhasaradhi, M. *Indian J. Chem.* **1982**, *21B*, 619−621. (f) Laatsch, H. *Liebigs Ann. Chem.* **1984**, *1984*, 319−339. (g) Baker, R. W.; Liu, S.; Sargent, M. A. *Aust. J. Chem.* **1998**, *51*, 255−266. (h) Yoshida, M.; Mori, K. *Eur. J. Org. Chem.* **2000**, *2000*, 1313−1317.

(5) Laatsch, H. *Liebigs Ann. Chem.* **1985**, *1985*, 2420−2442.

(6) (a) Ferreira, M. A.; Costa, M. Á. C.; Alves, A. C.; Lopes, M. H. *Phytochemistry* **1974**, *13*, 1587−1589. (b) Ferreira, M. A.; Costa, M. A. C.; Alves, A. C.; Lopes, M. H. *Phytochemistry* **1973**, *12*, 433−435.

(7) Tang, D.; Zhang, Q.; Xu, L.; Guo, D.; Luo, Z. *Hortic. Plant J.* **2019**, *5*, 59−69.

(8) (a) Fallas, A. L.; Thomson, R. H. *J. Chem. Soc. C* **1968**, 2279−2282. (b) Tezuka, M.; Kuroyanagi, M.; Yoshihira, K.; Natori, S. *Chem. Pharm. Bull.* **1972**, *20*, 2029−2035. (c) Van Der Vijver, L. M.; Gerritsma, K. W. *Phytochemistry* **1974**, *13*, 2322−2323. (d) Alves, A. C.; Costa, M. A. C.; Paul, M. I. *Planta Med.* **1983**, *47*, 121−124. (e) Jeffreys, J. A. D.; Bin Zakaria, M.; Waterman, P. G. *Phytochemistry* **1983**, *22*, 1832−1833. (f) Costa, M. A. C.; Alves, A. C.; Seabra, R. M.; Andrade, P. B. *Planta Med.* **1998**, *64*, 391. (g) Adeniyi, B. A.; Fong, H. H. S.; Pezzuto, J. M.; Luyengi, L.; Odelola, H. A. *Phytother. Res.* **2000**, *14*, 112−117. (h) Ganapaty, S.; Thomas, P. S.; Fotso, S.; Laatsch, H. *Phytochemistry* **2004**, *65*, 1265−1271.

(9) Costa, M. Á. C.; Lopes, M. H.; Paul, M. I.; Ferreira, M. A.; Alves, A. C. *Phytochemistry* **1976**, *15*, 829.

(10) (a) Hartwell, J. L. *Lloydia* **1969**, *32*, 153−205. (b) Jain, S. K.; Tarafder, C. R. *Econ. Bot.* **1970**, *24*, 241−278.

(11) Hutchings, A. *Bothalia* **1989**, *19*, 111−123.

(12) (a) Floyd, M. A.; Evans, D. A.; Howse, P. E. *J. Insect Physiol.* **1976**, *22*, 697−701. (b) Hazra, B.; Sur, P.; Roy, D. K.; Sur, B.; Banerjee, A. *Planta Med.* **1984**, *50*, 295−297. (c) Hazra, B.; Saha, A. K.; Ray, R.; Roy, D. K.; Sur, P.; Banerjee, A. *Trans. R. Soc. Trop. Med. Hyg.* **1987**, *81*, 738−741. (d) Likhitwitayawuid, K.; Dej-adisai, S.; Jongbunprasert, V.; Krungkrai, J. *Planta Med.* **1999**, *65*, 754−756. (e) Lall, N.; Meyer, J. J. M. *J. Ethnopharmacol.* **2001**, *78*, 213−216. (f) Hayeshi, R.; Mukanganyama, S.; Hazra, B.; Abegaz, B.; Hasler, J. *Phytother. Res.* **2004**, *18*, 877−883. (g) Pinho, B. R.; Sousa, C.; Valentão, P.; Oliveira, J. M. A.; Andrade, P. B. *PLoS One* **2014**, *9*, e90122. (h) Uddin, G.; Rauf, A.; Siddiqui, B. S.; Muhammad, N.; Khan, A.; Shah, S. U. A. *Phytomedicine* **2014**, *21*, 954−959.

(13) Yardley, V.; Snowdon, D.; Croft, S.; Hazra, B. *Phytother. Res.* **1996**, *10*, 559−562.

(14) (a) Chakrabarty, S.; Roy, M.; Hazra, B.; Bhattacharya, R. K. *Cancer Lett.* **2002**, *188*, 85−93. (b) Hazra, B.; Kumara, B.; Biswas, S.; Pandey, B. N.; Mishra, K. P. *Toxicol. Lett.* **2005**, *157*, 109−117. (c) Sarma, M. D.; Ghosh, R.; Patra, A.; Hazra, B. *Bioorg. Med. Chem.* **2007**, *15*, 3672−3677. (d) Sarma, M. D.; Ghosh, R.; Patra, A.; Chowdhury, R.; Chaudhuri, K.; Hazra, B. *Org. Biomol. Chem.* **2007**, *5*, 3115−3125. (e) Sarma, M. D.; Ghosh, R.; Patra, A.; Hazra, B. *Eur. J. Med. Chem.* **2008**, *43*, 1878−1888.

(15) (a) Kuo, Y.-H.; Chang, C.-l.; Li, S.-Y.; Chou, C.-J.; Chen, C.-F.; Kuo, Y.-H.; Lee, K.-H. *Planta Med.* **1997**, *63*, 363−365. (b) Kayser, O.; Kiderlen, A. F.; Laatsch, H.; Croft, S. L. *Acta Trop.* **2000**, *76*, 131−138. (c) Ting, C.-Y.; Hsu, C.-T.; Hsu, H.-T.; Su, J.-S.; Chen, T.-Y.; Tarn, W.-Y.; Kuo, Y.-H.; Whang-Peng, J.; Liu, L. F.; Hwang, J. *Biochem. Pharmacol.* **2003**, *66*, 1981−1991.

(16) Karkare, S.; Chung, T. T. H.; Collin, F.; Mitchenall, L. A.; McKay, A. R.; Greive, S. J.; Meyer, J. J. M.; Lall, N.; Maxwell, A. *J. Biol. Chem.* **2013**, *288*, 5149−5156.

(17) World Health Organization *Treatments of Tuberculosis: Guidelines*; WHO Press: Geneva, Switzerland, 2010; pp 29−34; 83−91.

(18) (a) Zhang, H.-B.; Liu, L.; Chen, Y.-J.; Wang, D.; Li, C.-J. *Adv. Synth. Catal.* **2006**, *348*, 229−235. (b) Demchuk, O. M.; Pietrusiewicz, K. M. *Synlett* **2009**, *2009*, 1149−1153. (c) Molina, M. T.; Navarro, C.; Moreno, A.; Csákÿ, A. G. *Org. Lett.* **2009**, *11*, 4938−4941. (d) Fujiwara, Y.; Domingo, V.; Seiple, I. B.; Gianatassio, R.; Bel, M. D.; Baran, P. S. *J. Am. Chem. Soc.* **2011**, *133*, 3292−3295. (e) Honraedt, A. l.; Le Callonnec, F.; Le Grognec, E.; Fernandez, V.; Felpin, F.-X. *J. Org. Chem.* **2013**, *78*, 4604−4609. (f) Patil, P.; Nimonkar, A.; Akamanchi, K. G. *J. Org. Chem.* **2014**, *79*, 2331−2336. (g) Wang, D.; Ge, B.; Li, L.; Shan, J.; Ding, Y. *J. Org. Chem.* **2014**, *79*, 8607−8613. (h) Wang, D.; Ge, B.; Yang, S.; Miao, H.; Ding, Y. *Russ. J. Gen. Chem.* **2014**, *84*, 1615−1621. (i) Moon, Y.; Jeong, Y.; Kook, D.; Hong, S. *Org. Biomol. Chem.* **2015**, *13*, 3918−3923. (j) Redaelli, M.; Mucignat-Caretta, C.; Isse, A. A.; Gennaro, A.; Pezzani, R.; Pasquale, R.; Pavan, V.; Crisma, M.; Ribaudo, G.; Zagotto, G. *Eur. J. Med. Chem.* **2015**, *96*, 458−466. (k) Wang, Y.; Zhu, S.; Zou, L.-H. *Eur. J. Org. Chem.* **2019**, *2019*, 2179−2201.

(19) (a) Cooke, R. G.; Dowd, H. *Aust. J. Chem.* **1952**, *5A*, 760−767. (b) Sammes, P. G.; Wallace, T. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1377−1380. (c) Parker, K. A.; Tallman, E. A. *Tetrahedron* **1984**, *40*, 4781−4788. (d) Watanabe, M.; Hisamatsu, S.; Hotokezaka, H.; Furukawa, S. *Chem. Pharm. Bull.* **1986**, *34*, 2810−2820. (e) Rizzacasa, M. A.; Sargent, M. V. *Aust. J. Chem.* **1988**, *41*, 1087−1097. (f) Semmelhack, M. F.; Ho, S.; Cohen, D.; Steigerwald, M.; Lee, M. C.; Lee, G.; Gilbert, A. M.; Wulff, W. D.; Ball, R. G. *J. Am. Chem. Soc.* **1994**, *116*, 7108−7122.

(20) Aurell, M. J.; Gaviña, P.; Mestres, R. *Tetrahedron* **1994**, *50*, 2571−2582.

(21) Matsuda, F.; Kawasaki, M.; Ohsaki, M.; Yamada, K.; Terashima, S. *Tetrahedron* **1988**, *44*, 5745−5759.

(22) Green, J. R.; Alo, B. I.; Majewski, M.; Snieckus, V. *Can. J. Chem.* **2009**, *87*, 745−759.

(23) (a) Sullivan, D. F.; Woodbury, R. P.; Rathke, M. W. *J. Org. Chem.* **1977**, *42*, 2038−2039. (b) Woodbury, R. P.; Rathke, M. W. *J. Org. Chem.* **1977**, *42*, 1688−1690.

(24) Bloomer, J. L.; Stagliano, K. W.; Gazzillo, J. A. *J. Org. Chem.* **1993**, *58*, 7906−7912.

(25) Ji, F.; Huang, H.; Li, M.; Guo, Y.; Song, C.; Chang, J. *Synthesis* **2018**, *50*, 3921−3926.

(26) Jia and co-workers independently employed the same procedure to prepare naphthol **9**, which they published during preparation of this manuscript. Cui, J.; Li, S.; Jia, J. *Nat. Prod. Res.* **2020**, 1.

(27) Laatsch, H. *Liebigs Ann. Chem.* **1986**, *1986*, 1655−1668.

(28) Buccini, M.; Piggott, M. J. *Org. Lett.* **2014**, *16*, 2490−2493.

(29) (a) Wang, J.; Wang, S.; Wang, G.; Zhang, J.; Yu, X.-Q. *Chem. Commun.* **2012**, *48*, 11769−11771. (b) Komeyama, K.; Kashihara, T.; Takaki, K. *Tetrahedron Lett.* **2013**, *54*, 1084−1086. (c) Walker, S. E.; Jordan-Hore, J. A.; Johnson, D. G.; Macgregor, S. A.; Lee, A.-L. *Angew. Chem., Int. Ed.* **2014**, *53*, 13876−13879. (d) Wang, D.; Ge, B.; Du, L.; Miao, H.; Ding, Y. *Synlett* **2014**, *25*, 2895−2898.

(30) (a) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879−933. (b) Bringmann, G.; Gulder, T.; Hertlein, B.; Hemberger, Y.; Meyer, F. *J. Am. Chem. Soc.* **2010**, *132*, 1151−1158.

(31) (a) Maggi, R.; Schlosser, M. *Tetrahedron Lett.* **1999**, *40*, 8797−8800. (b) Chadwick, S. T.; Rennels, R. A.; Rutherford, J. L.; Collum, D. B. *J. Am. Chem. Soc.* **2000**, *122*, 8640−8647.

(32) (a) Sibi, M. P.; Snieckus, V. *J. Org. Chem.* **1983**, *48*, 1937−1938. (b) Morin, J.; Zhao, Y.; Snieckus, V. *Org. Lett.* **2013**, *15*, 4102−4105.

(33) Inoue, M.; Carson, M. W.; Frontier, A. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 1878−1889.

(34) James, C. A.; Snieckus, V. *J. Org. Chem.* **2009**, *74*, 4080−4093.

(35) Singh, K. J.; Collum, D. B. *J. Am. Chem. Soc.* **2006**, *128*, 13753−13760.

(36) Uno, H.; Sakamoto, K.; Honda, E.; Fukuhara, K.; Ono, N.; Tanaka, J.; Sakanaka, M. *J. Chem. Soc., Perkin Trans. 1* **2001**, 229−238.

(37) Deville, J. P.; Behar, V. *Org. Lett.* **2002**, *4*, 1403−1405.

(38) Fang, H.; Kaur, G.; Yan, J.; Wang, B. *Tetrahedron Lett.* **2005**, *46*, 1671−1674.

(39) Gilman, H.; Santucci, L.; Swayampati, D. R.; Ranck, R. O. *J. Am. Chem. Soc.* **1957**, *79*, 3077−3081.

(40) (a) Fukazawa, T.; Ando, Y.; Ohmori, K.; Hayashi, T.; Suzuki, K. *Org. Lett.* **2017**, *19*, 1470−1473. (b) Wilson, C. M.; Ganesh, V.; Noble, A.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2017**, *56*, 16318−16322.

(41) Deb, A.; Manna, S.; Maji, A.; Dutta, U.; Maiti, D. *Eur. J. Org. Chem.* **2013**, *2013*, 5251−5256.

(42) Baxter, R. D.; Liang, Y.; Hong, X.; Brown, T. A.; Zare, R. N.; Houk, K. N.; Baran, P. S.; Blackmond, D. G. *ACS Cent. Sci.* **2015**, *1*, 456−462.

(43) Maiti, B. C.; Musgrave, O. C.; Skoyles, D. *Tetrahedron* **2005**, *61*, 1765−1771.

(44) O'Keefe, B. M.; Mans, D. M.; Kaelin, D. E., Jr.; Martin, S. F. *Tetrahedron* **2011**, *67*, 6524−6538.

(45) Brimble, M. A.; Brenstrum, T. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1612−1623.

(46) Narayan, S.; Roush, W. R. *Org. Lett.* **2004**, *6*, 3789−3792.

(47) Sankaram, A. V. B.; Reddy, V. V. N.; Shoolery, J. N. *Indian J. Chem., Sect B* **1987**, *26*, 41−46.

(48) Lillie, T. J.; Musgrave, O. C.; Skoyles, D. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2155−2161.

(49) Lillie, T. J.; Musgrave, O. C. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1161−1164.

(50) (a) Lacey, H. J.; Vuong, D.; Pitt, J. I.; Lacey, E.; Piggott, A. M. *Aust. J. Chem.* **2016**, *69*, 152−160. (b) Lacey, H. J.; Booth, T. J.; Vuong, D.; Rutledge, P. J.; Lacey, E.; Chooi, Y.-H.; Piggott, A. M. *J. Antibiot.* **2020**, *73*, 756.

(51) Sagar, S.; Kaur, M.; Minneman, K. P.; Bajic, V. B. *Eur. J. Med. Chem.* **2010**, *45*, 3519−3530.

(52) Gafner, F.; Chapuis, J. C.; Msonthi, J. D.; Hostettmann, K. *Phytochemistry* **1987**, *26*, 2501−2503.

(53) Mebe, P. P.; Cordell, G. A.; Pezzuto, J. M. *Phytochemistry* **1998**, *47*, 311−313.

(54) Gu, J.-Q.; Graf, T. N.; Lee, D.; Chai, H.-B.; Mi, Q.; Kardono, L. B. S.; Setyowati, F. M.; Ismail, R.; Riswan, S.; Farnsworth, N. R.; Cordell, G. A.; Pezzuto, J. M.; Swanson, S. M.; Kroll, D. J.; Falkinham, J. O., III; Wall, M. E.; Wani, M. C.; Kinghorn, A. D.; Oberlies, N. H. *J. Nat. Prod.* **2004**, *67*, 1156−1161.

(55) Kawiak, A.; Zawacka-Pankau, J.; Wasilewska, A.; Stasilojc, G.; Bigda, J.; Lojkowska, E. *J. Nat. Prod.* **2012**, *75*, 9−14.

(56) Hazra, B.; Das Sarma, M.; Kumar, B.; Basu, S.; Das, K.; Pandey, B. N.; Mishra, K. P. *Chemotherapy (Basel, Switz.)* **2007**, *53*, 173−176.

(57) (a) El-Najjar, N.; Gali-Muhtasib, H.; Vuorela, P.; Urtti, A.; Vuorela, H. *Handb. Chem. Biol. Plant Anal. Methods* **2014**, *2*, 595−610. (b) Bolton, J. L.; Dunlap, T. *Chem. Res. Toxicol.* **2017**, *30*, 13−37. (c) O'Brien, P. J. *Chem.-Biol. Interact.* **1991**, *80*, 1−41.

(58) Maruo, S.; Nishio, K.; Sasamori, T.; Tokitoh, N.; Kuramochi, K.; Tsubaki, K. *Org. Lett.* **2013**, *15*, 1556−1559.

(59) (a) Armarego, W. L. F.; Chai, C. *Purification of Laboratory Chemicals*, 6th ed.; Butterworth-Heinemann: Oxford, UK, 2009. (b) Williams, D. B. G.; Lawton, M. *J. Org. Chem.* **2010**, *75*, 8351−8354.

(60) Burchat, A. F.; Chong, J. M.; Nielsen, N. *J. Organomet. Chem.* **1997**, *542*, 281−283.

(61) Tanemura, K.; Suzuki, T.; Nishida, Y.; Satsumabayashi, K.; Horaguchi, T. *Chem. Lett.* **2003**, *32*, 932−933.

(62) Berliner, M. A.; Belecki, K. *J. Org. Chem.* **2005**, *70*, 9618−9621.

(63) (a) Bloom, H.; Briggs, L. H.; Cleverley, B. *J. Chem. Soc.* **1959**, 178−185. (b) Colthup, N. B.; Daly, L. H.; Wiberley, S. E. *Introduction to Infrared and Raman Spectroscopy*, 3rd ed.; Academic Press: Boston, 1990. (c) Silverstein, R. M.; Webster, F. X.; Kiemle, D. J. *Spectrometric Identification Of Organic Compounds*, 7th ed.; John Wiley & Sons: Hoboken, NJ, 2005.

(64) Couladouros, E. A.; Strongilos, A. T. *Eur. J. Org. Chem.* **2002**, *2002*, 3341−3350.

https://dx.doi.org/10.1021/acs.jnatprod.0c00800
J. Nat. Prod. XXXX, XXX, XXX−XXX

(65) Bringmann, G.; Gotz, R.; Keller, P. A.; Walter, R.; Boyd, M. R.; Lang, F.; Garcia, A.; Walsh, J. J.; Tellitu, I.; Bhaskar, K. V.; Kelly, T. R. *J. Org. Chem.* **1998**, *63*, 1090−1097.

https://dx.doi.org/10.1021/acs.jnatprod.0c00800
J. Nat. Prod. XXXX, XXX, XXX−XXX