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Note

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Total Synthesis of Avrainvilleol

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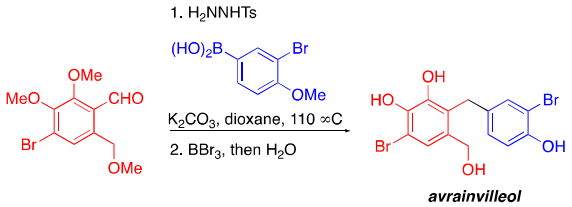


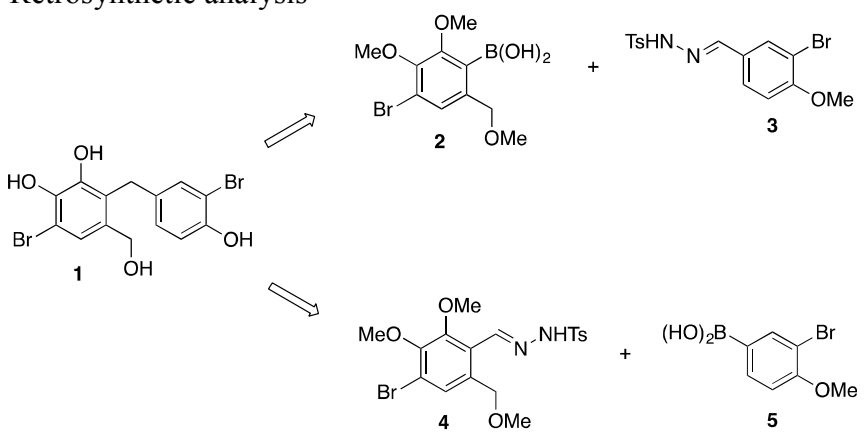
Abstract. The first total synthesis of the marine natural product avrainvilleol is reported. The total synthesis features the first application of the transition metal-free coupling of a tosyl hydrazone and a boronic acid to the preparation of a complex natural product, and the first example of this coupling with a hindered di-ortho substituted hydrazone substrate.

The diarylmethane motif is commonly encountered in a wide array of biologically active molecules.[1] Diarylmethanes have been reported to exhibit HIV reverse transcriptase inhibition,[2] antibacterial activity,[3] HMG-CoA reductase inhibition,[4] antioxidant activity,[5] and cytotoxicity to human cancer cell lines.[6] While there are a myriad of reports on methods to prepare simple diarylmethanes,[1] few of these methods have been utilized in the synthesis of more complex naturally occurring diarylmethanes. One report of the synthesis of several biologically active diarylmethanes includes a Friedel-Crafts alkylation as the key step and a low yielding, late-stage benzylic bromination.[7] Other reports focus on the addition of a benzyllithium nucleophile to a benzaldehyde.[8] However, selective deoxygenation of a secondary benzylic alcohol in the presence of a primary alcohol proved problematic. The condensation of phenols with formaldehyde has been reported, but this approach is limited to coupling electron rich aromatic moieties and is often low yielding.[9]

Avrainvilleol (**1**) is an example of a brominated diarylmethane natural product isolated from red algae in 1983.[10] At that time, biological activities for **1** including antibacterial activity and feeding deterrence were reported. Since then, potent antioxidant activity has also been measured.[11] In addition to avrainvilleol, numerous brominated phenol-containing diarylmethanes with varying substitution patterns have been isolated.[12] Despite the structural diversity of these compounds and the variety of biological activities observed, no unified approach to the synthesis of these halogenated diarylmethanes has been disclosed. This is likely because obvious transition metal catalyzed cross-coupling approaches[13] would require discrimination of a single halogen in one coupling partner in the presence of multiple other halogens present in the reagents. The presence of these halogens would also thwart an approach that relied on lithiation

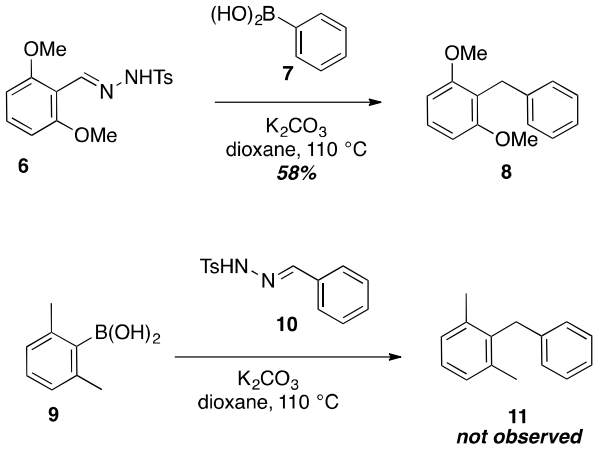
and addition to a suitable electrophile. A search for a high-yielding, scalable, and convergent approach to avrainvilleol that would also be amenable to other brominated phenol-containing diarylmethanes revealed the recent report of a transition metal-free coupling of a tosyl hydrazone with a boronic acid (Scheme 1).[14] This approach would have several advantages. Functional groups like free phenols, methyl ethers, and halogens are well tolerated. If such a key step proved successful, adaptation of the route and altering the substitution pattern of the hydrazone and/or the boronic acid would allow the rapid preparation of other brominated phenol-containing diarylmethanes and libraries of analogues for structure-activity studies. In theory, **1** could arise from two possible unions of a functionalized tosylhydrazone and boronic acid. Reaction of the hydrazone **3** with the diortho-substituted boronic acid **2** could lead to avrainvilleol after removal of the methyl ethers. Alternatively, hydrazone **4** and known boronic acid **5**[15] could be merged to give rise to **1**. Preliminary[14] and subsequent[16] reports of these hydrazone/boronic acid couplings revealed that a single ortho-, meta-, or para-substituent was well tolerated in either the hydrazone or boronic acid coupling partner. However to our knowledge, no one has reported such a coupling with the more sterically demanding diortho-substitution in either substrate.

Scheme 1. Retrosynthetic analysis



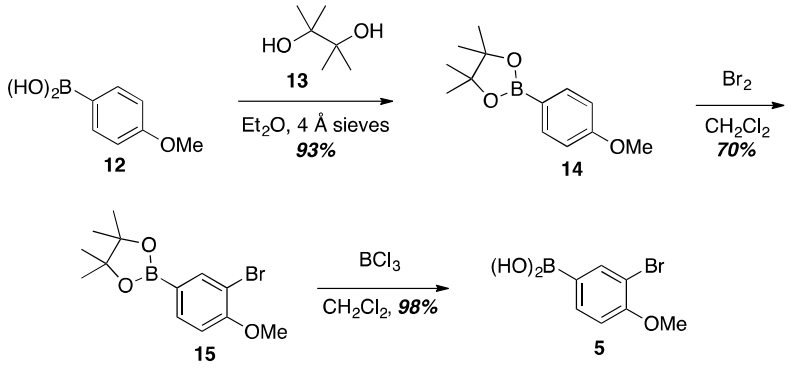
Before embarking on the synthesis of avarinvilleol, the susceptibility of di-ortho substituted substrates, either hydrazones and/or boronic acids, in the coupling reaction would need to be assessed. Initial feasibility studies (Scheme 2) revealed that steric hindrance in the boronic acid coupling partner is deleterious to the efficacy of this coupling reaction. For example, all attempts to couple hydrazone **10** with di-ortho substituted boronic acids such as commercially available **9** returned starting material or products of hydrazone dimerization. In contrast, the 2,6-dimethoxy substituted hydrazone **6** cleanly coupled with phenylboronic acid (**7**) to give the corresponding diarylmethane **8**. Clearly, only the retrosynthesis combining diortho-substituted hydrazone **4** and boronic acid **5** would enable the completion of avrainvilleol.

Scheme 2. Di-ortho substitution in the coupling of tosylhydrazones and boronic acids



Following a known procedure (Scheme 3),[15] the desired boronic acid **5** could be synthesized in three steps from commercially available 4-methoxyphenyl boronic acid. Protection of the boronic acid moiety as the corresponding pinacol ester **14** proceeded uneventfully. Monobromination ortho to the methoxy group followed by deprotection with two equivalents of BCl_3 gave the necessary 3-bromo-4-methoxyphenyl boronic acid (**5**) in high yield.

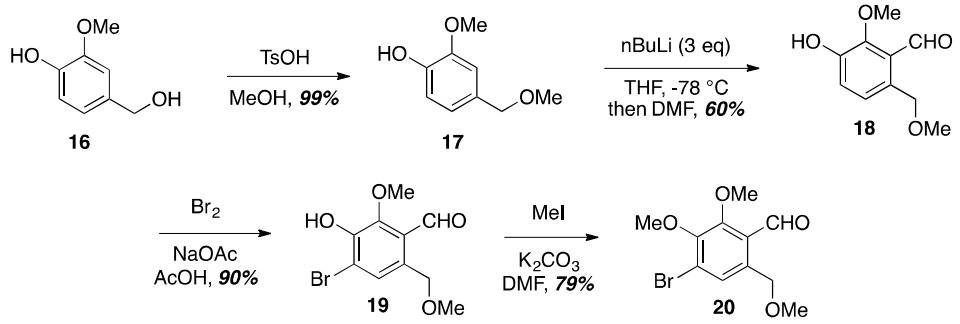
Scheme 3. Synthesis of the boronic acid **5**



Preparation of the hydrazone coupling partner commenced with treatment of vanillyl alcohol (**16**) with acidic methanol to deliver the methoxy ether **17** (Scheme 4). Previous studies indicated that **17** is regioselectively deprotonated with excess of nBuLi at the most sterically hindered position, presumably due to chelation from the two adjacent methyl ethers. Quenching with DMF delivered the known aldehyde **18** as a single regioisomer.[17] While treatment of **18** with Br_2 in various solvents (MeOH, CH_2Cl_2) led to indiscriminate bromination, regioselective monobromination was achieved by the addition of Br_2 to a buffered solution of **18** in acetic acid.[18] It should be noted here that **19** could easily and quantitatively be transformed to the corresponding tosyl hydrazone. But all attempts to couple this hydrazone with boronic acid **5** led to rapid decomposition under the basic conditions, presumably through the intermediacy of

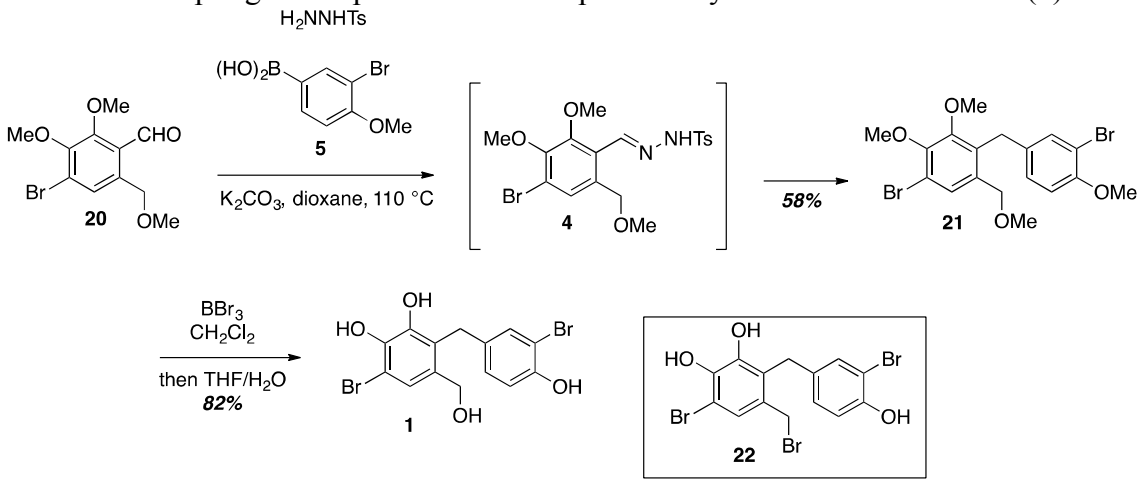
a para quinone methide. Fortunately, straightforward methylation under standard conditions gave **20** in excellent yield.

Scheme 4. Synthesis of the aldehyde **20**



Refluxing aldehyde **20** in the presence of tosylhydrazine, a slight excess of the boronic acid **5**, potassium carbonate led to the tetramethyl avrainvilleol **21**, presumably through the intermediate hydrazone **4** (Scheme 5). However, the deprotection and purification of avrainvilleol proved challenging. Treatment of tetramethyl avrainvilleol with excess BBr_3 led to a single product devoid of methyl ether peaks in the NMR spectrum. But the chemical shift of the two methylenes did not match those reported for avrainvilleol. Based on the upfield shift (4.3 ppm in **22** and 4.5 ppm in **1**) of the singly benzylic methylene, we reasoned that bromination of the highly reactive benzylic alcohol occurred delivering bromo avrainvilleol **22**. Gratifyingly, simply stirring this crude bromide in a THF/H_2O mixture rapidly delivered avrainvilleol. In our hands, synthetic **1** rapidly decomposed in $CDCl_3$ perhaps due to trace amounts of HCl or DCl. One can imagine that **1** might form a highly reactive para-quinone methide under acidic conditions leading to decomposition. Luckily, spectroscopic data of naturally occurring **1** in d_6-acetone has also been reported,[19] and the spectral data for synthetic **1** (^{1}H and ^{13}C NMR) were identical with those previously reported.[10,19]

Scheme 5. Coupling and deprotection to complete the synthesis of avrainvilleol (**1**)



This work shows the promise of the transition-metal free coupling of readily available boronic acids and tosylhydrazones to prepare complex, biologically active

diarylmethanes. Specifically, the synthesis of avrainvilleol was completed in six steps (longest linear sequence) starting with commercially available vanillyl alcohol. Efforts are currently underway to apply this method to other challenging diarylmethane containing natural products. In addition, the convergent nature of this approach lends itself well to the rapid preparation of a library of synthetic analogues. Collaborative efforts to probe the relationship between diarylmethane substitution pattern and biological activity are also underway and will be reported in due course.

Experimental Section

All solvents were degassed with nitrogen and passed through activated molecular sieves prior to use. Reactions involving air or moisture sensitive reagents or intermediates were performed under an inert atmosphere of nitrogen in glassware that had been oven or flame dried. Reagents were used without further purification unless indicated otherwise. The ^{1}H and ^{13}C NMR spectra were obtained on a JEOL ECX-400 spectrometer, operating at 400 and 100 MHz respectively. Unless indicated otherwise, all spectra were run as solutions in $CDCl_3$. The ^{1}H NMR chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) and are, in all cases, referenced to the residual protio-solvent present (δ 7.24 for $CHCl_3$). The ^{13}C NMR chemical shifts are reported in ppm relative to the center line of the multiplet for deuterium solvent peaks (δ 77.0 (t) for $CDCl_3$).

2-benzyl-1,3-dimethoxybenzene (8). A mixture of **6**[20] (167 mg, 0.5 mmol), phenylboronic acid (92 mg, 0.75 mmol), and K_2CO_3 (104 mg, 0.75 mmol) in dioxane (2 mL) was refluxed for 5 h. The mixture was concentrated to remove dioxane and sat. $NaHCO_3$ (5 mL) was added. The mixture was extracted with CH_2Cl_2 (3 x 15 mL) and the organic layers were washed with sat. $NaHCO_3$ (10 mL), brine (10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/hexane (1:19) to give 66 mg (58%) of **8** as a colorless oil that solidified upon standing; ^{1}H NMR (400 MHz) δ 7.32-7.16 (m, 6 H), 6.59 (d, J = 8.2 Hz, 2H), 4.07 (s, 2H), 3.83 (s, 6 H); ^{13}C NMR (100 MHz) δ 158.4, 142.0, 128.7, 128.1, 127.4, 125.5, 117.8, 103.9, 55.8, 28.8; IR (neat) 3028, 2835. 1593, 1493, 1473, 1453, 1280, 1153, 1105, 767, 725; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{17}O_2$ 229.1223; Found 229.1234.

4-bromo-3-hydroxy-2-methoxy-6-(methoxymethyl)benzaldehyde (19). A solution of bromine in AcOH (5.1 mL, 1 M, 5.1 mmol) was added dropwise to a solution of 3-hydroxy-2-methoxy-6-(methoxymethyl)benzaldehyde (**18**)[17] (1.00 g, 5.1 mmol) and NaOAc (450 mg, 5.5 mmol) in AcOH (10 mL). The mixture was stirred 12 h at rt and then poured into H_2O (100 mL). Solid $NaHCO_3$ was added until bubbling ceased. The slurry was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with sat. $NaHCO_3$ (50 mL), brine (50 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/hexane (1:3) to give 1.28 g (91%) of **19** as a pale yellow solid; ^{1}H NMR (400 MHz) δ 10.43 (s, 1H), 7.59 (s, 1H), 5.78 (s, 1H), 4.70 (s, 2H), 3.98 (s, 3H), 3.47 (s, 3H); ^{13}C NMR (100 MHz) δ 191.0, 151.4, 145.8, 133.9, 126.5, 125.8, 116.9, 71.4, 63.4, 58.8;

IR (neat) 3317, 2939, 1682, 1573, 1479, 1389, 1279, 994, 907, 735; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{10}H_{11}BrNaO_4$ 296.9733; Found 296.9737.

4-bromo-2,3-dimethoxy-6-(methoxymethyl)benzaldehyde (20). MeI (2.1 g, 0.918 mL, 14.8 mmol) was added to a mixture of **19** (926 mg, 3.4 mmol) and K_2CO_3 (1.4 g, 10.1 mmol) in DMF (15 mL) and the reaction was stirred for 4 h. H_2O (20 mL) was added and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (25 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/hexane (1:9) to give 0.968 g (99%) of **20** as a white solid; ^{1}H NMR (400 MHz) δ 10.43 (s, 1H), 7.66 (s, 1H), 4.73 (s, 2H), 4.00 (s, 3H), 3.89, (s, 3H), 3.47 (s, 3H); ^{13}C NMR (100 MHz) δ 191.4, 157.8, 149.5, 138.3, 126.5, 126.4, 125.3, 71.5, 62.5, 60.9, 59.0; IR (neat) 2988, 1688, 1553, 1381, 1264, 1121, 1027, 981, 809; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{11}H_{13}BrNaO_4$ 310.9889; Found 310.9863.

1-bromo-4-(3-bromo-4-methoxybenzyl)-2,3-dimethoxy-5-(methoxymethyl)benzene (21). A mixture of aldehyde **20** (106 mg, 0.37 mmol), tosyl hydrazine (69 mg, 0.37 boronic acid **5**[15] (132 mg, 0.571 mmol), and K_2CO_3 (79 mg, 0.571 mmol) in dioxane (1 mL) was refluxed for 4 h. The mixture was cooled to rt and concentrated under reduced pressure. Sat. $NaHCO_3$ (5 mL) was added and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/hexane (1:9) to give 102 mg (58%) of **21** as a colorless oil; ^{1}H NMR (400 MHz) δ 7.34 (s, 1H), 7.29 (s, 1 H), 6.95 (d, J = 6.3 Hz, 1H), 6.76 (d, J = 6.3 Hz), 4.27 (s, 2 H), 3.95 (s, 2 H), 3.86 (s, 3 H), 3.84 (s, 3 H), 3.69 (s, 3 H), 3.34 (s, 3 H); ^{13}C NMR (100 MHz) δ 154.2, 152.7, 150.2, 134.2, 133.9, 133.0, 132.7, 128.4, 128.0, 115.8, 111.9, 111.6, 72.1, 60.9, 60.6, 58.5, 56.3, 30.5; IR (neat) 2930, 1494, 1397, 1281, 1254, 1183, 1150, 1036, 815; HRMS (ESI-TOF) m/z: $[M+NH_4]^+$ Calcd for $C_{18}H_{24}Br_2NO_4$ 476.0067; Found 476.0066.

Avrainvilleol (**1**): A solution of BBr_3 (2 mL, 1 M in CH_2Cl_2, 2 mmol) was added dropwise to a solution of **21** (92 mg, 0.20 mmol) in CH_2Cl_2 (4 mL) at 0 °C. The reaction was allowed to slowly warm to rt and stirred overnight. The mixture was poured into ice water (20 mL) and concentrated to remove CH_2Cl_2. THF (10 mL) and H_2o (2 mL) was added and the mixture was stirred for 1 h. The mixture was extracted with Et_2O (20 mL) and the organic layer was washed with sat. $NaHCO_3$ (2 x 10 mL), brine (10 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with Et_2O/hexane (7:3) to give 66 mg (82%) of **1** as a pale yellow oil; ^{1}H NMR (400 MHz, Me_2CO-d_6) δ 7.30 (d, J = 1.8 Hz, 1 H), 7.13 (s, 1 H), 7.02 (dd, J = 8.2, 1.8 Hz, 1 H), 6.85 (d, J = 8.2 Hz, 1 H), 4.50 (s, 2 H), 3.99 (s, 2H); ^{13}C NMR (100 MHz, Me_2CO-d_6) δ 153.1, 145.8, 142.3, 135.1, 134.1, 133.4, 129.6, 125.9, 122.9, 117.1, 110.3, 108.8, 62.0, 30.4; IR (neat) 3412, 1595, 1573, 1494, 1257, 1094; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{14}H_{12}Br_2NaO_4$ 424.9000; Found 424.8955.

Acknowledgements

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Supplementary Data

Comparison of isolated and synthetic avrainvilleol and copies of NMR spectra of all new compounds associated with this article can be found in the online version at:

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