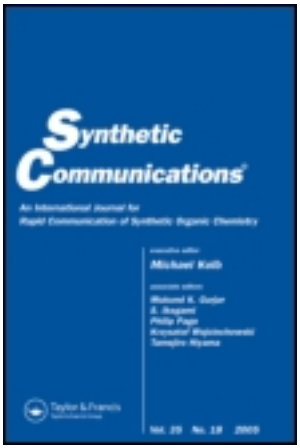

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Improved and Highly Versatile Synthesis of 5-Aryltropones

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Improved and Highly Versatile Synthesis of 5-Aryltropones

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Abstract: The use of 5-iodo-2-methoxytropone in palladium(0)-catalyzed coupling reactions with a variety of arylboronic acids has resulted in significantly improved reaction yields and times for a sterically and electronically diverse series of novel 5-aryltropones. In addition, the required 5-iodo-2-methoxytropone was conveniently synthesized in excellent yield.

Keywords: Antimitotic, arylboronic acids, aryltropones, colchicinoids, palladium coupling

INTRODUCTION

Colchicine **1** (Figure 1) is a highly potent antimitotic agent that binds to the protein tubulin in an irreversible manner.[1] Through this binding at a distinct site, termed the colchicine-binding site, colchicine inhibits microtubule formation and hence exerts its anticancer ability.[2] Structurally, colchicine consists of a three-ringed system: a trimethoxybenzene ring (A ring), a saturated seven-membered ring containing an acetamido group (B ring), and an α-methoxytropone ring (C ring). Besides colchicine, many molecules that bind to the colchicine domain of tubulin have also been highly investigated.[3] One such compound is 2-methoxy-5-(2′,3′,4′-trimethoxyphenyl)

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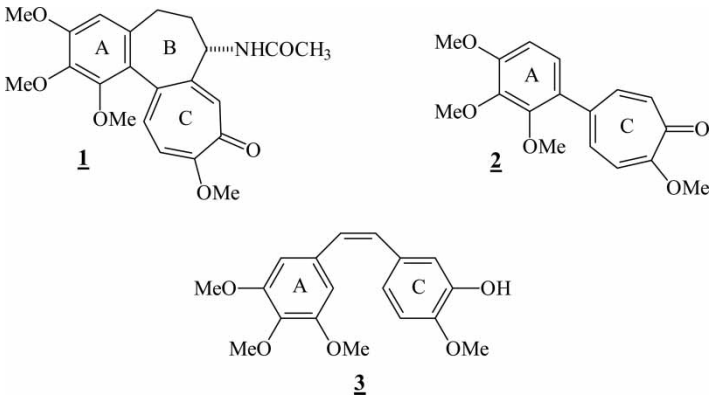


Figure 1. Colchicine and related colchicinoids.

tropone **2** (MTC, Figure 1), a bicyclic colchicinoid that lacks the central B ring of the parent compound, colchicine. The compound MTC is nearly as potent as colchicine and it binds to tubulin at the colchicine-binding site.[4] However, despite this high potency, colchicinoids such as MTC are not yet in standard use as antineoplastic agents.[3]

Attempts to obtain potent colchicine-site analogs have typically focused on using conventional structure–activity relationship (SAR) studies. In addition, many of these SAR studies have also sought to further clarify the mechanistic understanding of the colchicine–tubulin interaction with the hope that this would produce more clinically useful colchicine-site drugs. For example, previous SAR studies of the bicyclic compound MTC have revealed that potent colchicinoids can be achieved through C-ring modification.[5,6] Concerning the A ring, however, nearly all of the previously investigated colchicine and colchicinoid derivatives contain the same trimethoxy-substitution pattern. As a result, little is known concerning the SAR of the A ring; only a single study by Banwell has been reported.[7] Recently, the promise of the antiangeogenic and antivascular bicyclic compound **3**, (combretastatin A-4, Figure 1) a colchicine-site ligand, has sparked renewed interest in colchicine-site drugs as potential anticancer agents.[8] The recent discovery of the first active A-ring modified combretastatin analog (trimethyl substitution)[9] has also raised questions concerning the role of the A ring in the colchicine–tubulin interaction. With this in mind, we sought to further explore the role of the A ring in the colchicine–tubulin binding interaction by synthesizing a diverse series of A-ring modified MTC analogs (5-aryltropones) in a SAR study.

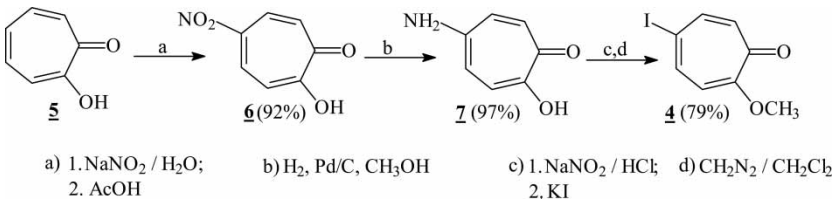
For the synthesis of these 5-aryltropones, we sought an approach that would be both facile and of high yield. In addition, we also desired a methodology that would be applicable to synthesizing a broad range of A-ring modified bicyclic colchicinoids (5-aryltropones). Remarkably, few methods

exist to selectively introduce aryl substitution on the tropone nucleus. The methods that have achieved moderate to good success have used palladium-catalyzed coupling reactions. For example, Nair et al. utilized the palladium-catalyzed reaction of arylboronic acids with 5-bromo-2-methoxytropone to synthesize a series of 5-aryltropones.[10] Also, Keenan et al. used a similar method with arylzinc chlorides and 5-([(trifluoromethyl)sulfonyl]oxy)-2-methoxytropone to produce a similar series of 5-aryltropones.[11] In these studies, however, the scope of compounds that were synthesized was limited and reaction yields tended to decrease as more sterically demanding and electronically diverse arylboronic acids or arylzinc chlorides were used. In addition, the synthesis of the necessary 5-bromo-2-methoxytropone requires multiple steps and was of only moderate yield.[12]

More recently, it was shown that palladium-catalyzed coupling reactions produced some sterically demanding 5-aryltropones in highest yield using arylboronic acids.[7] In addition, recent work has also resulted in a concise synthesis of the compound 5-iodo-2-methoxytropone **4**.[13] Therefore, based on these recent results we sought to synthesize our series of A-ring modified MTC analogs utilizing the palladium-catalyzed reaction (standard Suzuki protocol) of a diverse series of arylboronic acids with 5-iodo-2-methoxytropone **4**.

RESULTS AND DISCUSSION

At the start of our synthesis we first sought to optimize the yield of **4**. In the article concerning the synthesis of **4** the authors did not report any detailed reaction conditions. In addition, although the synthesis of this compound was concise, the overall yield of **4** was very low (27%). Our synthesis of **4** is shown in Scheme 1. The key step in optimizing the overall reaction yield lies in the diazotization of **7**. We found that slow addition of sodium nitrite as well as careful control of the reaction temperature significantly improved diazonium salt formation. More important, we also discovered that the reaction time and temperature involved in the reaction of the diazonium salt with potassium iodide was crucial. We found that reaction times longer than 1 h and at a temperature greater than 55°C resulted in more than a twofold

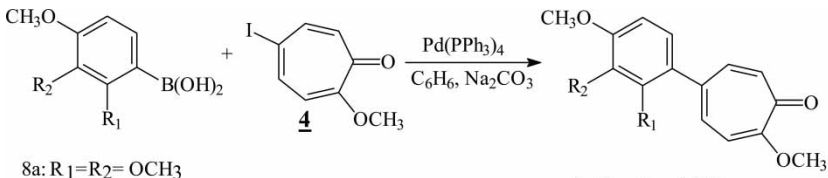


Scheme 1.

decrease in reaction yield for this step. The optimized overall reaction yield for **4** was 70% and the procedure for its formation is later described in detail.

In the preparation of our diverse series of arylboronic acid derivatives, **8a–i**,[14] significant improvement in reaction yields was achieved through a series of modifications.[15] First, preparation of the required aryl-lithium from the corresponding aryl bromide necessitated lowering the reaction temperature to −95°C. It was also found that optimal halogen–lithium exchange occurred with t-butyl lithium in a solvent of ether rather than the standard THF. Most important, a switch in alkyl borate reagents from tributyl borate to triisopropyl borate resulted in significant reaction yield improvements. By utilizing these modifications we were able to synthesize our series of arylboronic acid derivatives **8a–i** in overall excellent yield (72–90%). (Arylboronic acids (**8a–i**) were prepared by reaction of the corresponding aryl bromide with 2.0 equiv. of t-butyllithium in diethyl ether at −95°C for 30 min. To this solution was added 1.5 equiv. of triisopropyl borate and the resulting solution was stirred at −95°C for 20 min. The reaction was cooled to room temperature and the solvent was evaporated under vacuum. The resulting oil was then hydrolyzed and purified utilizing acidic silica-gel and radial chromatography to afford the pure arylboronic acids in excellent yield.)

The arylboronic acids **8a–i** were then coupled to **4** utilizing the palladium-catalyzed method of Nair et al.[10] to yield novel MTC analogs **9a–h** (Scheme 2). All reactions were run at room temperature in benzene, and were complete in 3–5 h (Table 1). In contrast, previous palladium-catalyzed coupling reactions of less sterically and electronically demanding arylboronic acids with 5-bromo-2-methoxytropone required refluxing in benzene and much longer reaction times of 16–20 h.[10] Thus, it appears that a switch in halotropones from bromo to iodo not only lessens the required reaction time but also the harshness of the conditions required



8a: R_1=R_2= OCH_3
8b: R_1= OCH_3; R_2= OTBDMS
8c: R_1= OCH_3; R_2= OH
8d: R_1= OCH_3; R_2= NO_2
8e: R_1= OCH_3; R_2= CH_3
8f: R_1= OTBDMS; R_2= OCH_3
8g: R_1= OH; R_2= OCH_3
8h: R_1= CH_3; R_2= OCH_3
8i: R_1= CH_3; R_2= CH_3

2: R_1=R_2= OCH_3
9a: R_1= OCH_3; R_2= OTBDMS
9b: R_1= OCH_3; R_2= OH
9c: R_1= OCH_3; R_2= NO_2
9d: R_1= OCH_3; R_2= CH_3
9e: R_1= OTBDMS; R_2= OCH_3
9f: R_1= OH; R_2= OCH_3
9g: R_1= CH_3; R_2= OCH_3
9h: R_1= CH_3; R_2= CH_3

Scheme 2.

Table 1. Coupling of arylboronic acids with 5-iodo-2-methoxytropone **4**

Arylboronic acids				
R1	R2	Product[a]	Reaction time (h)	% Yield[b]
8a OCH_3	OCH_3	2	3	93
8b OCH_3	OTBDMS	9a	4	91
8c OCH_3	OH	9b	3	94
8d OCH_3	NO_2	9c	4	88
8e OCH_3	CH_3	9d	3	95
8f OTBDMS	OCH_3	9e	5	88
8g OH	OCH_3	9f	4	87
8h CH_3	OCH_3	9g	3	93
8i CH_3	CH_3	9h	3	90

[a]Novel compounds 9a–h were characterized by ^1H and ^{13}C NMR, IR, and GC-MS.
[b]All yields are for pure isolated product.
Note: TBDMS is an abbreviation for tetrabutyldimethylsilyloxy.

for complete reaction. It can also be seen in Table 1 that the MTC analogs **9a–h** (5-aryltropones) were all prepared in excellent yield regardless of the steric and electronic nature of the arylboronic acid. This is significant, because in previous work yields of 5-aryltropones were lower and seemed to be more influenced by the nature of the arylboronic acid.[10,11] Therefore, our work appears to demonstrate that in the palladium-catalyzed coupling of arylboronic acids with halotropones, optimal yields of 5-aryltropones are achieved using 5-iodo-2-methoxytropone as compared with the corresponding 5-bromo-2-methoxytropone.

In summary, compared with previous studies, the work presented here demonstrates some significant improvements in the palladium-catalyzed synthesis of bicyclic aryltropones. First, our methodology results in higher yields of both the arylboronic acid and halotropone that are required in these coupling reactions. The high yield and facile synthesis of the necessary 5-iodo-2-methoxytropone **4** is most notable. Previous palladium-catalyzed coupling reactions have utilized the corresponding 5-bromo-2-methoxytropone,[12] of which the synthesis is more complex and of lower overall yield as compared with **4**. In our palladium-catalyzed coupling reactions, the use of **4** as the halotropone instead of the corresponding bromo adduct resulted in much faster reaction times, milder reaction conditions, and higher reaction yields of a more diverse series of 5-aryltropones (Table 1). Significantly, these novel A-ring modified colchicinoids (5-aryltropones) spanned a wide range of steric and electronic properties. Thus, the future use of this protocol should give direct access to a broad range of A-ring substitution patterns in bicyclic colchicinoids. This high yield production of diverse bicyclic colchicinoids will in turn help facilitate SAR studies concerning

the A ring of colchicine and related colchicinoids. Because of the structural similarity that these 5-aryltropones share with the combretastatins, use of this methodology may also generate new leads in cancer chemotherapy.

EXPERIMENTAL

All NMR spectra were recorded on a Varian 300 spectrometer. Infrared spectra were measured in spectroscopic-grade chloroform on a Perkin Elmer 1600 series FTIR. GC-MS were obtained using a Shimadzu QP-5000 GC-MS. Melting points were obtained using a electrothermal open-capillary melting point apparatus and are uncorrected. All reagents were obtained from Aldrich Chemical Corporation unless otherwise noted. Column chromatography was performed using Baker silica gel 60–200 mesh or 200–400 mesh. A chromatatron (Harrison Research) was used for radial chromatography. Separations that were performed on the chromatatron were accomplished under an atmosphere of nitrogen. The plates used in the chromatatron were 1 mm silica gel PF-254 with $CaSO_4$ 1/2 H_2O. Thin-layer chromatography (TLC) was performed using a variety of solvents on Merck 0.25-mm plates.

Procedure for the Formation of 5-Iodo-2-methoxytropone 4

To a stirred solution of tropolone **5** (0.650 g, 5.31 mmol) in 15 mL of warm water was added dropwise 12 mL of an aqueous sodium nitrite solution (0.74 g, 10.7 mmol). The resulting solution was stirred at room temperature for 30 min. To this solution was added 1.2 mL of glacial acetic acid and the reaction was then stirred for an additional 30 min. A tan precipitate formed, which was vacuum filtered and allowed to dry under an atmosphere of nitrogen yielding 0.82 g (92%) of pure 5-nitrotropolone **6**.

Compound **6** (0.75 g, 4.5 mmol) was placed in a pressure bottle along with 15 mol% of 10% Pd/carbon. To the solid was added 15 mL of dry methanol. The bottle was charged with hydrogen to 14.5 psi on a Parr hydrogenator and allowed to shake for 2 h. The reaction mixture was filtered and evaporated to yield 0.59 g (97%) of pure 5-aminotropolone **7**. No further purification was necessary.

To 5-aminotropolone **7** (0.255 g, 1.9 mmol) was added 3.2 mL of concentrated HCl along with 5.2 mL of distilled water. The resulting solution was cooled to $-20^{\circ}C$ and a 1.1 equiv. sodium nitrite (0.141 g, 2.0 mmol) solution (4.5 mL H_2O) was slowly added over a 30-min time period. After an additional 15 min of stirring, potassium iodide (0.371 g, 2.2 mmol) in 4.5 mL of H_2O was added to the reaction over a 20-min time period. The cooling bath was then removed and the resulting solution was heated at 50–55°C for 45 min. The solution was cooled to room temperature and extracted three times with methylene chloride. The aqueous layer was neutralized with 3 N NaOH and

then extracted one additional time with methylene chloride. The organic extracts were combined and washed once with 10% sodium bisulfite and then with brine, dried over sodium sulfate, and evaporated to yield crude 5-iodotropolone. Purification of this compound was then accomplished utilizing radial chromatography and a solvent system of 60:40 hexane–acetone to yield 0.364 g (79%) of pure 5-iodotropolone. Methylation was then carried out in quantitative yield using diazomethane, resulting in 0.384 g of **4** in an overall yield of 70%. Mp: 121–123°C; ^{1}H NMR ($CDCl_3$) δ 7.61 (d, 1H, $J = 10.5$ Hz); 7.55 (d, 1H, $J = 12.7$ Hz); 6.78 (d, 1H, $J = 12.8$ Hz); 6.30 (d, 1H, $J = 10.5$ Hz); 3.97 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 179.87, 165.44, 145.22, 141.62, 136.01, 112.39, 95.08, 56.45; IR 3084, 2984, 1630, 1575, 1280 cm^{-1}; GC: $t_R = 27.94$ min, purity $> 99\%$ (only one peak was observed); MS m/z (intensity %): 262 (100), 244 (15), 233 (66), 219 (41), 204 (18), 191 (32), 165 (5), 135 (44), 127 (18), 107 (45).

General Procedure for Preparation of Arylboronic Acids (8a–i)

Arylboronic acids (**8a**–**i**) were prepared by reaction of the corresponding aryl bromide with 2.0 equiv. of t-butyllithium in diethyl ether at −95°C for 30 min. To this solution was added 1.5 equiv. of triisopropyl borate and the resulting solution was stirred at −95°C for 20 min. The reaction was cooled to room temperature and the solvent was evaporated under vacuum. The resulting oil was then hydrolyzed utilizing acidic silica gel and radial chromatography to afford the arylboronic acids (characterization follows).

2,3,4-Trimethoxyphenylboronic acid 8a: mp: 71–73°C; ^{1}H NMR ($CDCl_3$) δ 7.50 (d, 1H, $J = 8.7$ Hz); 6.77 (d, 1H, $J = 8.7$ Hz); 6.27 (bs, 2H); 3.99 (s, 3H); 3.91 (s, 3H); 3.83 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 158.12, 156.24, 141.32, 130.82, 128.76, 107.08, 60.98, 60.56, 56.65; IR 3346, 1590, 1458, 1340, 1278, 1220, 1085 cm^{-1}; GC: $t_R = 20.10$ min, purity $> 99\%$ (only one peak was observed); MS m/z: 212 (M^+).

3-t-Butyldimethylsilyloxy-2,4-dimethoxyphenylboronic acid 8b: mp: 96–97°C; ^{1}H NMR ($CDCl_3$) δ 7.42 (d, 1H, $J = 9.0$ Hz); 6.71 (d, 1H, $J = 9.0$ Hz); 6.52 (bs, 2H); 3.89 (s, 3H); 3.83 (s, 3H); 1.03 (s, 9H); 0.18 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 157.42, 155.13, 152.06, 137.40, 128.89, 107.88, 61.04, 58.38, 26.10, 18.94, −4.11; IR 3340, 1594, 1466, 1354, 1270, 1096 cm^{-1}; GC: $t_R = 22.03$ min, purity $> 99\%$ (only one peak was observed); MS m/z: 312 (M^+).

3-Hydroxy-2,4-dimethoxyphenylboronic acid 8c: ^{1}H NMR ($CDCl_3$) δ 7.39 (d, 1H, $J = 8.6$ Hz); 6.80 (d, 1H, $J = 8.6$ Hz); 6.32 (bs, 2H); 6.08 (s, 1H); 3.92 (s, 3H); 3.85 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 158.30, 152.81, 144.78, 133.10, 127.02, 108.20, 60.92, 58.74; IR 3344–3250, 1602, 1470, 1346, 1288,

$1092\,cm^{-1}$; GC: $t_R = 28.80$ min, purity $> 99\%$ (only one peak was observed); MS m/z: 198 (M^+).

2,4-Dimethoxy-3-nitrophenylboronic acid 8d: ^1H NMR ($CDCl_3$) δ 7.97 (d, 1H, $J = 8.5$ Hz); 6.84 (d, 1H, $J = 8.5$ Hz); 5.82 (bs, 2H); 3.92 (s, 3H); 3.90 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 157.31, 154.36, 141.88, 138.78, 117.21, 108.25, 63.99, 57.10; IR 3336, 1593, 1479, 1281, 1224, $1097\,cm^{-1}$; GC: $t_R = 27.68$ min, purity $> 99\%$ (only one peak was observed); MS m/z: 227 (M^+).

2,4-Dimethoxy-3-methylphenylboronic acid 8e: mp: 179–182°C; ^1H NMR ($CDCl_3$) δ 7.54 (d, 1H, $J = 8.7$ Hz); 6.71 (d, 1H, $J = 8.7$ Hz); 6.18 (bs, 2H); 3.93 (s, 3H); 3.82 (s, 3H); 2.28 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 159.22, 147.31, 139.20, 137.64, 125.43, 107.69, 61.23, 59.79, 18.91; IR 3341, 2964, 1597, 1486, 1290, 1220, $1095\,cm^{-1}$; GC: $t_R = 26.19$ min, purity $> 99\%$ (only one peak was observed); MS m/z: 196 (M^+).

2-t-Butyldimethylsilyloxy-3,4-dimethoxyphenylboronic acid 8f: mp: 83–84°C; ^1H NMR ($CDCl_3$) δ 7.49 (d, 1H, $J = 8.5$ Hz); 6.64 (d, 1H, $J = 8.5$ Hz); 5.66 (bs, 2H); 3.89 (s, 3H); 3.74 (s, 3H); 1.05 (s, 9H); 0.25 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 157.40, 154.52, 139.83, 134.95, 131.19, 106.12, 60.90, 56.13, 26.31, 18.86, −4.32; IR 3350, 1599, 1480, 1281, 1230, $1082\,cm^{-1}$; GC: $t_R = 21.43$ min, purity $> 99\%$ (only one peak was observed); MS m/z: 312 (M^+).

2-Hydroxy-3,4-dimethoxyphenylboronic acid 8g: ^1H NMR ($CDCl_3$) δ 7.54 (d, 1H, $J = 8.9$ Hz); 6.87 (d, 1H, $J = 8.9$ Hz); 6.13 (bs, 2H); 6.06 (bs, 1H); 3.90 (s, 3H); 3.78 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 158.21, 153.76, 141.52, 136.89, 129.80, 107.91, 60.68, 57.07; IR 3502–3312, 1602, 1481, 1277, 1231, $1097\,cm^{-1}$; GC: $t_R = 28.43$ min, purity $> 99\%$ (only one peak was observed); MS m/z: 198 (M^+).

3,4-Dimethoxy-2-methylphenylboronic acid 8h: mp: 166–168°C; ^1H NMR ($CDCl_3$) δ 7.97 (d, 1H, $J = 8.7$ Hz); 6.89 (d, 1H, $J = 8.7$ Hz); 5.87 (bs, 2H); 3.93 (s, 3H); 3.82 (s, 3H); 2.68 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 156.08, 147.26, 140.30, 134.71, 122.85, 109.13, 60.41, 56.02, 15.11; IR 3329, 2980, 1588, 1478, 1299, 1214, $1095\,cm^{-1}$; GC: $t_R = 25.31$ min, purity $> 99\%$ (only one peak was observed); MS m/z: 196 (M^+).

4-Methoxy-2,3-dimethylphenylboronic acid 8i: mp: 232–235°C; ^1H NMR ($CDCl_3$) δ 8.14 (d, 1H, $J = 9.0$ Hz); 6.86 (d, 1H, $J = 9.0$ Hz); 5.52 (bs, 2H); 3.89 (s, 3H); 2.72 (s, 3H); 2.24 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 160.52, 146.44, 137.28, 136.04, 125.62, 107.48, 56.15, 18.38, 14.86; IR 3346, 2970–2950, 1590, 1493, 1275, 1208, $1090\,cm^{-1}$; GC: $t_R = 26.79$ min, purity $> 99\%$ (only one peak was observed); MS m/z: 180 (M^+).

General Palladium-Catalyzed Coupling Procedure for the Formation of 5-Aryltropones (2 and 9a–h)

The coupling reaction was accomplished according to a procedure modified from Nair et al.[10] To a stirred solution of 5-iodo-2-methoxytropone **4** (0.310 g, 1.2 mmol) in benzene (10 mL) was added tetrakis(triphenyl-phosphine) palladium (0.068 g, 0.059 mmol) along with 1.2 mL of 2M Na_2CO_3. The resulting solution was stirred for 10 min. To this solution was added 1.1 equiv. of arylboronic acid (**8a–i**) in ethanol (1 mL) and the reaction was allowed to stir at room temperature for the time indicated in Table 1. Two drops of 30% hydrogen peroxide were added to the reaction flask and the resulting solution was stirred for an additional half hour. The reaction was diluted with water and extracted three times with methylene chloride. The organic portions were combined, dried with sodium sulfate, and evaporated to yield the crude 5-aryltropone. Purification using radial chromatography and a solvent system of 60:40 hexane–acetone yielded pure 5-aryltropone as shown in Table 1 (characterization follows).

2-Methoxy-5-(2′,3′,4′-trimethoxyphenyl)tropone 2: mp: 118–119°C; ^{1}H NMR ($CDCl_3$) δ 7.45 (dd, 1H, $J = 12.7$, $J = 1.8$ Hz); 7.27 (d, 1H, $J = 12.7$ Hz); 7.17 (dd, 1H, $J = 10.5$, $J = 1.8$ Hz); 6.95 (d, 1H, $J = 8.3$ Hz); 6.80 (d, 1H, $J = 10.5$ Hz); 6.71 (d, 1H, $J = 8.3$ Hz); 3.98 (s, 3H); 3.92 (s, 3H); 3.90 (s, 3H); 3.72 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 180.04, 164.65, 152.86, 151.31, 142.43, 139.82, 138.67, 135.32, 131.98, 129.24, 124.56, 112.77, 108.22, 60.89, 56.30, 56.12, 56.02; IR 2930, 1625, 1578, 1480, 1442, 1250, 1085 cm^{-1}; GC: $t_R = 46.80$ min, purity $> 99\%$ (only one peak was observed); MS m/z (intensity %): 302 (85), 274 (100), 259 (36), 228 (54), 216 (30), 201 (22), 145 (45), 114 (18).

2-Methoxy-5-(3′-t-butyldimethylsilyloxy-2′,4′-dimethoxyphenyl)tropone 9a: clear oil/film; ^{1}H NMR ($CDCl_3$) δ 7.48 (d, 1H, $J = 12.4$ Hz); 7.26 (d, 1H, $J = 12.3$ Hz); 7.20 (d, 1H, $J = 10.2$ Hz); 6.83 (d, 1H, $J = 10.2$ Hz); 6.79 (d, 1H, $J = 8.7$ Hz); 6.69 (d, 1H, $J = 8.7$ Hz); 3.98 (s, 3H); 3.84 (s, 3H); 3.56 (s, 3H); 1.04 (s, 9H); 0.22 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 180.62, 164.79, 153.91, 149.95, 140.24, 139.10, 137.98, 136.15, 132.85, 129.74, 122.07, 113.13, 107.68, 60.62, 56.45, 55.72, 25.80, 18.82, −4.22; IR 3050, 2987–2930, 1626, 1579, 1490, 1446, 1286, 1232, 1082 cm^{-1}; GC: $t_R = 51.42$ min, purity $> 99\%$ (only one peak was observed); MS m/z (intensity %): 402 (8), 387 (6), 345 (100), 330 (12), 314 (40), 302 (34), 287 (22), 259 (10), 244 (14), 165 (16), 150 (18), 114 (10).

2-Methoxy-5-(3′-hydroxy-2′,4′-dimethoxyphenyl)tropone 9b: mp: 181–182°C; ^{1}H NMR ($CDCl_3$) δ 7.50 (dd, 1H, $J = 12.6$, $J = 2.0$ Hz); 7.29 (d, 1H, $J = 12.6$ Hz); 7.23 (dd, 1H, $J = 10.3$, $J = 2.0$ Hz); 6.83 (d, 1H, $J = 10.3$ Hz); 6.76 (d, 1H, $J = 8.0$ Hz); 6.70 (d, 1H, $J = 8.0$ Hz); 6.05

(bs, 1H); 3.99 (s, 3H); 3.93 (s, 3H); 3.65 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 180.30, 164.25, 148.04, 144.58, 139.72, 138.86, 138.92, 136.34, 132.61, 129.11, 120.42, 112.88, 106.90, 61.08, 56.62, 56.58; IR 3540–3210 (broad), 3036, 2980–2920, 1632, 1582, 1476, 1432, 1278, 1090 cm^{-1}; GC: $t_R = 48.86$ min, purity > 99% (only one peak was observed); MS m/z (intensity %): 288 (100), 260 (76), 245 (48), 227 (12), 213 (23), 199 (25), 185 (50), 183 (17), 159 (9), 145 (11), 128 (26), 115 (28).

2-Methoxy-5-(2′4′-dimethoxy-3′-nitrophenyl)tropone 9c: mp: 171–172°C; ^{1}H NMR ($CDCl_3$) δ 7.41 (d, 1H, $J = 12.7$ Hz); 7.32 (d, 1H, $J = 8.8$ Hz); 7.23 (d, 1H, $J = 12.7$ Hz); 7.20 (d, 1H, $J = 10.5$ Hz); 6.84 (d, 1H, $J = 8.8$ Hz); 6.79 (d, 1H, $J = 10.5$ Hz); 3.97 (s, 3H); 3.91 (s, 3H); 3.57 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 179.83, 164.88, 151.39, 149.72, 147.62, 138.20, 136.29, 132.76, 132.19, 131.92, 130.11, 111.89, 107.97, 62.34, 56.64, 56.38; IR 3080, 2982–2890, 1628, 1592, 1496, 1422, 1376, 1242 cm^{-1}; GC: $t_R = 47.13$ min, purity > 99% (only one peak was observed); MS m/z (intensity %): 317 (10), 289 (100), 274 (42), 256 (22), 242 (37), 228 (62), 216 (10), 201 (18), 145 (49), 115 (31).

2-Methoxy-5-(2′,4′-dimethoxy-3′-methylphenyl)tropone 9d: mp: 142–143°C; ^{1}H NMR ($CDCl_3$) δ 7.39 (d, 1H, $J = 12.3$ Hz); 7.28 (d, 1H, $J = 12.3$ Hz); 7.19 (d, 1H, $J = 10.2$ Hz); 6.99 (d, 1H, $J = 8.3$ Hz); 6.82 (d, 1H $J = 10.2$ Hz); 6.74 (d, 1H, $J = 8.3$ Hz); 3.98 (s, 3H); 3.90 (s, 3H); 3.61 (s, 3H); 2.20 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 180.24, 164.92, 152.02, 149.33, 143.88, 140.21, 138.44, 137.61, 131.45, 130.14, 125.70, 111.88, 108.82, 60.90, 56.93, 56.10, 29.20; IR 3050, 2984–2882, 1627, 1588, 1498, 1425, 1270, 1096 cm^{-1}; GC: $t_R = 45.68$ min, purity > 99% (only one peak was observed); MS m/z (intensity %): 286 (100), 258 (72), 243 (29), 227 (4), 215 (33), 200 (16), 185 (11), 152 (8), 128 (53), 115 (14).

2-Methoxy-5-(2′-t-butyldimethylsilyloxy-3′,4′-dimethoxyphenyl)tropone 9e: mp: 152–153°C; ^{1}H NMR ($CDCl_3$) δ 7.48 (dd, 1H, $J = 12.6$, $J = 2.2$ Hz); 7.26 (d, 1H, $J = 12.7$ Hz); 7.16 (dd, 1H, $J = 10.9$, $J = 2.2$ Hz); 6.93 (d, 1H, $J = 9.6$ Hz); 6.78 (d, 1H, $J = 11.0$ Hz); 6.63 (d, 1H, $J = 9.6$ Hz); 3.99 (s, 3H); 3.90 (s, 3H); 3.82 (s, 3H); 0.79 (s, 9H); 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 180.24, 164.66, 153.92, 147.10, 140.92, 140.27, 136.22, 134.80, 133.10, 128.78, 124.74, 112.96, 105.52, 60.82, 56.58, 56.20, 25.60, 18.72, −4.08; IR 3040, 2976–2928, 1632, 1570, 1496, 1446, 1284, 1222, 1082 cm^{-1}; GC: $t_R = 51.22$ min, purity > 99% (only one peak was observed); MS m/z (intensity %): 402 (6), 387 (9), 345 (100), 330 (18), 314 (36), 302 (39), 287 (20), 259 (16), 244 (12), 165 (19), 150 (11), 114 (10).

2-Methoxy-5-(2′-hydroxy-3′,4′-dimethoxyphenyl)tropone 9f: mp: 167–168°C; ^{1}H NMR ($CDCl_3$) δ 7.53 (dd, 1H, $J = 12.4$, $J = 1.8$ Hz); 7.29 (d, 1H, $J = 12.4$ Hz); 7.23 (dd, 1H, $J = 10.2$, $J = 1.8$ Hz); 6.95 (d, 1H,

$J = 8.5$ Hz); 6.82 (d, 1H, $J = 10.2$ Hz); 6.56 (d, 1H, $J = 8.5$ Hz); 6.15 (bs, 1H); 3.97 (s, 3H); 3.95 (s, 3H); 3.90 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 180.68, 164.69, 153.26, 147.30, 139.96, 138.40, 136.14, 135.98, 133.56, 125.04, 123.88, 113.08, 104.23, 61.18, 56.66, 56.14; IR 3550–3190 (broad), 3042, 2980–2930, 1630, 1578, 1474, 1430, 1278, 1094 cm^{-1}; GC: $t_R = 49.18$ min, purity $> 99\%$ (only one peak was observed); MS m/z (intensity %): 288 (100), 260 (70), 245 (41), 227 (9), 213 (42), 199 (20), 185 (48), 183 (21), 159 (9), 145 (11), 128 (19), 115 (18).

2-Methoxy-5-(3′,4′-dimethoxy-2′-methylphenyl)tropone 9 g: mp:159–160°C; ^{1}H NMR ($CDCl_3$) δ 7.27 (d, 1H, $J = 12.2$ Hz); 7.23 (d, 1H, $J = 12.1$ Hz); 7.01 (d, 1H, $J = 10.5$ Hz); 6.92 (d, 1H, $J = 8.1$ Hz); 6.81 (d, 1H, $J = 7.9$ Hz); 6.79 (d, 1H, $J = 10.6$ Hz); 3.98 (s, 3H); 3.90 (s, 3H); 3.84 (s, 3H); 2.17 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 181.40, 164.83, 153.10, 142.22, 140.08, 136.17, 132.85, 130.20, 130.02, 124.78, 112.79, 109.68, 60.42, 56.57, 56.14, 28.32; IR 3020, 2980–2912, 1636, 1564, 1490, 1428, 1278, 1226 cm^{-1}; GC: $t_R = 45.81$ min, purity > 99 % (only one peak was observed); MS m/z (intensity %): 286 (100), 258 (80), 243 (23), 228 (4), 215 (30), 200 (14), 185 (11), 152 (6), 128 (57), 115 (17).

2-Methoxy-5-(4′-methoxy-2′,3′-dimethylphenyl)tropone 9 h: mp: 148–149°C; ^{1}H NMR ($CDCl_3$) δ 7.28 (d, 1H, $J = 11.7$ Hz); 7.23 (d, 1H, $J = 11.7$ Hz); 7.03 (d, 1H, $J = 10.4$ Hz); 7.00 (d, 1H, $J = 8.5$ Hz); 6.80 (d, 1H, $J = 10.4$ Hz); 6.76 (d, 1H, $J = 8.5$ Hz); 3.98 (s, 3H); 3.86 (s, 3H); 2.21 (s, 3H); 2.15 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 179.86, 164.20, 154.23, 144.12, 141.32, 137.15, 132.73, 131.10, 130.52, 123.79, 113.08, 109.81, 60.22, 56.30, 28.22, 27.10; IR 3028, 2978–2894, 1630, 1558, 1494, 1432, 1268, 1220 cm^{-1}; GC: $t_R = 45.43$ min, purity $> 99\%$ (only one peak was observed); MS m/z (intensity %): 270 (100), 258 (71), 243 (28), 228 (9), 213 (23), 199 (14), 185 (39), 152 (11), 128 (61), 115 (24).

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