Nucleophilic Acylations of Quinone Methides: An Umpolung Approach to α -Aryl Ketones and Benzofurans

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Supporting Information

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General Methods

Dichloromethane was purified by passage through a bed of activated alumina. Purification of reaction products was carried out by flash chromatography using EM Reagent silica gel 60 (230-400 mesh). Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light and ceric ammonium molybdate (CAM) stain. Melting points (**mp**) were obtained on a Thomas Hoover Capillary Melting Point Apparatus and are uncorrected. Infrared spectra (**IR**) were obtained on a Bio-Rad FTS-40 FTIR spectrophotometer. Infrared spectra were obtained as a thin film on a NaCl disk or as a KBr disk. Proton nuclear magnetic resonances (**¹H NMR**) were recorded in deuterated solvents on a Varian Inova 500 (500 MHz) spectrometer. Chemical shifts are reported in parts per million (ppm, δ) relative to the residual protio solvent (CDCl_3 , δ 7.27; D_2O , δ 4.80; DMSO, δ 2.50, CD_3OD , δ 3.31). ¹H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q), or septet (sep). Splitting patterns that could not be interpreted or easily visualized are designated as multiplet (m) or broad (br). Coupling constants are reported in Hertz (Hz). Proton-decoupled (**¹³C-NMR**) spectra were recorded on a Varian Inova 500 (125 MHz) or a Varian Inova 400 (100 MHz) spectrometer and are reported in ppm using the solvent as an internal standard (CDCl_3 , δ 77.0; DMSO, δ 39.5, CD_3OD , δ 49.15). Electrospray mass spectra (**ESI-MS**) were obtained using a Micromass Quattro II Triple Quadrupole HPLC/MS/MS Mass Spectrometer. Unless otherwise noted, all other commercially available reagents and solvents were purchased from Aldrich and used without further purification.

Protected thiazolium carbinols were prepared according to previously published procedures.¹ Quinone methide precursors were prepared according to the general procedure reported by Heslin and Moody.²

Typical Procedure for the Nucleophilic Acylation of *o*-Quinone Methides

A dry 10 mL round bottom flask was charged with the protected thiazolium carbinol (0.620 mmol) and fitted with a septa in a nitrogen-filled drybox. Also in the box, a separate vial was charged with tetramethylammonium fluoride ($\text{Me}_4\text{N}\cdot\text{F}$, 96 mg, 1.03 mmol). Both reagents were removed from the box and the carbinol was placed under a positive pressure of nitrogen. The quinone methide precursor (0.413 mmol) dissolved in CH_2Cl_2 (3 mL) was added to the flask containing the carbinol. The resulting yellow solution was immediately cooled to -78°C . Last, the $\text{Me}_4\text{N}\cdot\text{F}$ suspended in CH_2Cl_2 (1.7 mL) was added dropwise to the reaction. Upon $\text{Me}_4\text{N}\cdot\text{F}$ addition, the reaction turned dark green or red depending on the substrates. After 24 h at -78°C the reaction was allowed to attain room temperature and stirred for an additional hour at 23°C . At this time, a TLC showed all of the quinone methide precursor had been consumed. The reaction was diluted with saturated NaCl and CH_2Cl_2 . The layers were separated and the aqueous layer was extracted two additional times with CH_2Cl_2 . The organic layers were combined, dried over Na_2SO_4 , filtered and concentrated. The resulting residue was purified by flash column chromatography on silica gel.

¹ Mattson, A. E.; Zuhl, A. M.; Reynolds, T. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 4932-4933.

² Heslin, J. C.; Moody, C. J. *J. Chem. Soc., Perkins Trans. 1* **1988**, 1417-1423.

Characterization of α -Aryl Ketones

1-(4-chlorophenyl)-2-(2-hydroxyphenyl)ethanone (3): Purified with 5 to 40% ether/hexanes, yielding 46 mg (72%) of **3** as a white solid. $R_f = 0.37$ (40/60 ether/hexanes); Mp: 134-135 °C; IR (film) 3418.0; 3028.5, 2959.2, 1673.9, 747.8 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.03-8.01 (m, 2H); 7.48-7.45 (m, 2H); 7.31 (s, 1H); 7.19-7.15 (m, 2H); 6.94-6.86 (m, 2H); 4.25 (s, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 199.8, 155.5, 140.9, 134.4, 131.2, 130.6, 129.4, 129.4, 121.2, 121.0, 117.8, 41.1; LRMS (electrospray): Mass calculated for $\text{C}_{14}\text{H}_{11}\text{ClO}_2$ $[2\text{M}]^+$, 492.1. Found 492.8.

2-(2-hydroxyphenyl)-1-(naphthalen-2-yl)ethanone (4): Purified with 4 to 35% ether/hexanes, yielding 66 mg (66%) of **4** as a white solid. $R_f = 0.28$ (40/60 ether/hexanes); Mp: 144-145 °C; IR (film) 3415.6, 3059.3, 2912.7, 1676.1, 1175.9, 747.2 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.69 (s, 1H); 8.13-8.11 (m, 1H); 8.05-8.03 (m, 1H); 7.95-7.90 (m, 2H); 7.86 (s, 1H); 7.68-7.65 (m, 1H); 7.63-7.60 (m, 1H); 7.28 (s, 1H); 7.22-7.19 (m, 1H); 7.01-7.00 (m, 1H); 6.93-6.90 (m, 1H); 4.44 (s, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 201.4, 156.0, 136.3, 133.3, 132.7, 131.7, 131.6, 131.3, 130.1, 129.4, 129.1, 128.1, 127.3, 124.4, 121.4, 121.1, 118.1, 41.4; LRMS (electrospray): Mass calculated for $\text{C}_{18}\text{H}_{14}\text{O}_2$, $[\text{M}+23]^+$, 285.1. Found 285.3.

2-(2-hydroxyphenyl)-1-(3-methoxyphenyl)ethanone (5): Purified with 4 to 30% ether/hexanes, yielding 70 mg (70%) of **5** as a white solid. $R_f = 0.24$ (40/60 ether/hexanes); Mp: 108-109 °C; IR (film) 3411.6; 3005.3; 2920.4; 1675.2; 1260.2; 753.2 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.74-7.72 (m, 2H); 7.61 (s, 1H); 7.45-7.41 (m, 1H); 7.20-7.17 (m, 3H); 6.97-6.96 (m, 1H); 6.91-6.88 (m, 1H); 4.30 (s, 2H); 3.87 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 201.2, 160.2, 155.7, 137.4, 131.3, 130.1, 129.3, 122.0, 121.3, 121.1, 120.9, 117.8, 113.4, 55.7, 41.3; LRMS (electrospray):

Mass calculated for $\text{C}_{15}\text{H}_{14}\text{O}_3$, $[2\text{M}]^+$, 484.2. Found 484.4.

(E)-1-(2-hydroxyphenyl)-4-phenylbut-3-en-2-one (6): Purified with 4 to 30% ether/hexanes, yielding 17 mg (53%) of **6** as a yellow solid. $R_f = 0.29$ (40/60 ether/hexanes); Mp: 61-63 °C; IR (film) 3357.6, 3029.5, 2924.5, 1681.9, 1600.9, 1454.7, 752.0 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.90 (s, 1H); 7.79-7.76 (m, 1H); 7.61-7.59 (m, 2H); 7.44-7.43 (m, 3H); 7.22-7.16 (m, 2H); 7.00-6.98 (m, 1H); 6.92-6.86 (m, 2H); 4.01 (s, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 201.1, 156.0, 146.3, 134.2, 131.5, 131.1, 129.4, 129.3, 129.0, 125.4, 121.4, 121.0, 118.1, 44.0; LRMS (electrospray): Mass

calculated for $\text{C}_{16}\text{H}_{14}\text{O}_2$ $[2\text{M}]^+$, 476.2. Found 476.5.

1-(4-chlorophenyl)-2-(2-hydroxyphenyl)propan-1-one (7): Purified with 4 to 22% ether/hexanes, yielding 41 mg (60%) of **7** as a white solid. $R_f = 0.40$ (40/60 ether/hexanes); Mp: 115-116 °C; IR (film) 3391, 2931.1, 1667.8, 1589, 1453.3, 1093.1, 754.0 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.01-8.00 (m, 2H); 7.41-7.39 (m, 2H); 7.15-7.11 (m, 2H); 6.88-6.85 (m, 2H); 6.83 (s, 1H); 4.95 (q, $J = 7.0$ Hz, 1H); 1.57 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 202.4, 153.8, 140.1, 134.5, 130.5, 129.6, 129.2,

128.9, 126.8, 121.5, 117.3, 43.4, 17.5; LRMS (electrospray): Mass calculated for $C_{15}H_{13}ClO_2$ $[2M+23]^+$, 543.1. Found 544.5.

1-(4-chlorophenyl)-2-(2-hydroxyphenyl)-2-phenylethanone (8): Purified with 8 to 40% ether/hexanes, yielding 68 mg (68%) of **8** as a yellow solid. R_f = 0.28 (40/60 ether/hexanes); Mp: 93.5-95 °C; IR (film) 3407.6, 3030.3, 2925.7, 1673.2, 1587.6, 1455.6, 1093.0, 751.0 cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$) δ 8.03-8.01 (m, 2H); 7.43-7.25 (m, 7H); 7.18-7.16 (m, 1H); 7.05-7.04 (m, 1H); 6.91-6.89 (m, 1H), 6.84-6.82 (m, 1H), 6.28 (s, 1H), 6.23 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.6, 153.9, 140.2, 137.4, 135.2, 130.7, 130.0, 129.3, 129.3, 129.1, 128.8, 127.7, 125.5, 121.2, 116.9, 54.8; LRMS (electrospray): Mass calculated for $C_{20}H_{15}ClO_2$ $[2M+23]^+$, 667.2. Found 668.4.

1-(4-chlorophenyl)-2-(2-hydroxy-3-methoxyphenyl)ethanone (9): Purified with 4 to 25% ether/hexanes, yielding 67 mg (67%) of **9** as a white solid. R_f = 0.23 (40/60 ether/hexanes); Mp: 104-106 °C; IR (film) 3437.8, 2939.6, 2840.9, 1688.0, 1479.8, 1272.7, 1076.3, 762.7 cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$) δ 8.03-8.02 (m, 2H); 7.44-7.42 (m, 2H); 6.83-6.80 (m, 3H); 5.92 (s, 1H); 4.28 (s, 2H); 3.90 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.0, 146.9, 143.7, 139.7, 135.2, 130.3, 129.1, 123.1, 120.7, 120.0, 109.8, 56.2, 39.6; LRMS (electrospray): Mass calculated for $C_{15}H_{13}ClO_3$ $[M+23]^+$, 299.7. Found 299.8.

1-(4-chlorophenyl)-2-(2-hydroxy-4-methoxyphenyl)ethanone (10): Purified with 5 to 33% ether/hexanes, yielding 54 mg (75%) of **10** as a white solid. R_f = 0.23 (40/60 ether/hexanes); Mp: 107.5-109 °C; IR (film) 3419.8, 2956.3, 2836.8, 1675.3, 1619.2, 1589.3, 1207.9, 1093.9, 819.0 cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$) δ 8.04-8.03 (m, 2H); 7.62 (s, 1H); 7.49-7.47 (m, 2H); 7.07-7.05 (m, 1H); 6.53 (m, 1H); 6.48-6.45 (m, 1H); 4.20 (s, 2H); 3.76 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.3, 160.7, 156.7, 140.9, 134.3, 131.6, 130.7, 129.4, 113.0, 107.1, 103.5, 55.6, 40.5; LRMS (electrospray): $C_{15}H_{13}ClO_3$ $[M]^+$, 276.1. Found 278.4.

1-(4-chlorophenyl)-2-(1H-indol-3-yl)ethanone (12): Purified with 4 to 40% ether/hexanes, yielding 49 mg (70%) of **12** as a white solid. R_f = 0.25 (40/60 ether/hexanes); Mp: 158.5-159 °C; IR (film) 3352.6, 3080.1, 2917.4, 1681.5, 742.0 cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$) δ 8.17 (bs, 1H); 8.01-8.00 (m, 2H); 7.63-7.61 (m, 1H); 7.43-7.41 (m, 2H); 7.37-7.35 (m, 1H); 7.24-7.21 (m, 1H); 7.18-7.15 (m, 1H); 7.08 (s, 1H); 4.39 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.0, 139.7, 163.4, 135.1, 130.3, 129.2, 127.4, 123.5, 122.6, 120.1, 118.9, 111.6, 108.8, 35.9; LRMS (electrospray): $C_{16}H_{12}ClNO$ $[M]^+$, 269.1. Found 270.4.

Synthesis of Protected Thiazolium Carbinol **13**

2-bromo-3,5-dimethoxybenzaldehyde (17):

2,3-dimethoxybenzaldehyde (1g, 6.02 mmol) was added to a 25 mL round bottom flask and dissolved in acetic acid (5 mL). The resulting colorless solution was briefly cooled in an ice bath. A solution of bromine (320 μ L, 6.25 mmol) in acetic acid (2 mL) was added dropwise to the cool reaction mixture. Once the addition was complete the ice bath was removed. After approximately 5 min the reaction had solidified and water (10 mL) was added. The solid was collected by vacuum filtration and rinsed with water. The solid was then dissolved in CH_2Cl_2 and washed with saturated NaHCO_3 . The layers were separated and the aqueous layer was extracted two additional times with CH_2Cl_2 . The combined organic layers were dried with sodium sulfate and then filtered through a plug of silica gel using CH_2Cl_2 as the eluent. The filtrate was concentrated to afford a white solid consisting of both mono and dibrominated aldehydes. A small amount of ethyl acetate was added to the solid. After standing at 5 $^\circ\text{C}$, a white solid (the dibrominated aldehyde) had precipitated. The solid was separated from the liquid by vacuum filtration and the filtrate was concentrated to yield the monobrominated aldehyde (1.02 g, 4.16 mmol, 69%) as a white solid. ^1H NMR (500 MHz, CDCl_3) δ 10.43 (s, 1H); 7.06 (d, 1H, $J = 2.7$ Hz); 6.73 (d, 1H, $J = 2.7$ Hz); 3.93 (s, 3H); 3.87 (s, 3H). Spectral data matched the reported data.³

(2-bromo-3,5-dimethoxyphenyl)(4,5-dimethylthiazol-2-yl)methanol

(18): To a flame-dried 100 mL round bottom flask under positive nitrogen pressure was added 4,5-dimethylthiazole (432 μ L, 4.08 mmol) and THF (20 mL). The resulting solution was cooled to -78 $^\circ\text{C}$. $n\text{BuLi}$ (2.1 mL, 4.08 mmol) was added dropwise to the cold reaction causing it to turn into pink solution that was stirred at -78 $^\circ\text{C}$ for 45 min. At this time, the aldehyde (**17**, 2 g, 8.16 mmol) was added in one portion. Upon addition, the reaction turned yellow. After stirring at -78 $^\circ\text{C}$ for an hour, the dry ice/acetone bath was removed and the reaction warmed to 23 $^\circ\text{C}$. After 3 h at room temperature the reaction was diluted with water and extracted three times with ethyl acetate. The combined organics were dried over sodium sulfate, filtered and concentrated. Recrystallization from ethyl acetate yielded the desired carbinol as a white solid (1.35 g, 3.77 mmol, 92%). ^1H NMR (500 MHz, CDCl_3) δ 6.85 (s, 1H); 6.49 (d, 1H, $J = 2.7$ Hz); 6.38 (d, 1H, $J = 2.7$ Hz); 3.90 (s, 3H); 3.82 (s, 3H); 2.32 (s, 3H); 2.29 (s, 3H)

TES-protected thiazolium carbinol (13): A dry 100 mL round bottom flask was charged with carbinol **18** (1.35 g, 3.77 mmol) and placed under positive nitrogen pressure. CH_2Cl_2 (30 mL) was added and the carbinol was

³ Merlic, C. A.; Aldrich, C. C.; Albaneze-Walker, J.; Saghatelian, A.; Mammen, J. *J. Org. Chem.* **2001**, 66, 1297-1309.

completely dissolved. Triethylsilylchloride (1 mL, 5.66 mmoles) was then added followed by imidazole (308 mg, 4.52 mmoles). The resulting suspension was stirred at 23 °C overnight. After 15 h the reaction was diluted with water and CH₂Cl₂. The layers were separated and the organic layer was washed two additional times with water. The combined aqueous layers were extracted one time with CH₂Cl₂. The combined organic layers were dried over sodium sulfate, filtered and concentrated to yield the silyl protected carbinol as a pale yellow oil that was used in the next step without further purification. The TES-protected carbinol was dissolved in iodomethane (5 mL). The resulting pale yellow solution was heated to 80 °C for 20 h. After cooling to room temperature, any remaining iodomethane was removed *in vacuo* to yield a yellow residue. Diethyl ether was added to the residue causing the protected thiazolium carbinol to precipitate as pale yellow solid. The solid was isolated by vacuum filtration and dried under vacuum (1.79 g, 77% over the two steps). ¹H NMR (500 MHz, CDCl₃) δ 6.82 (s, 1H); 6.63 (s, 1H); 6.54 (s, 1H); 3.91 (s, 3H); 3.86 (s, 6H); 2.54 (s, 6H); 0.92-0.87 (m, 9H); 0.71-0.60 (m, 6H) ¹³C NMR (125 MHz, CDCl₃) δ 175.9, 160.9, 157.3, 144.6, 137.5, 131.1, 107.0, 104.0, 101.3, 73.0, 56.8, 56.5, 40.1, 14.0, 13.2, 6.93, 5.04.

Synthesis of Quinone Methide Precursor 2f

2-hydroxy-4-methoxybenzaldehyde (19): K₂CO₃ (4 g, 28.9 mmoles) and acetone (16 mL) were added to a dry 50 mL round bottom flask under a positive nitrogen pressure. 2,4-Dihydroxybenzaldehyde (2 g, 14.5 mmoles) was added to the reaction mixture to create a light peach suspension. 18-Crown-6 (383 mg, 1.45 mmoles) was added in one portion and last the iodomethane (0.9 mL, 14.5 mmoles) was added dropwise by syringe. The resulting reaction mixture was stirred at 23 °C overnight. After 18 h the reaction was complete by TLC (40% ether/hexanes). CH₂Cl₂ was added and the organic layer was washed with water. The aqueous layer was extracted with CH₂Cl₂ and the combined organic layers were dried with sodium sulfate, filtered and concentrated to yield a brown oil. The crude oil was purified by flash column chromatography on silica gel using a 20% to 50% ether/hexanes gradient as eluent. Two spots were isolated. The desired aldehyde was isolated as a white solid (*R_f* in 40% ether/hexanes = 0.55, 1.17 g, 53%). ¹H NMR (500 MHz, CDCl₃) δ 11.5 (s, 1H); 9.74 (s, 1H); 7.45 (m, 1H); 6.57-6.55 (m, 1H); 6.45 (m, 1H); 3.89 (s, 3H). Data matched that of commercially available aldehyde. The second compound isolated was the dialkylated aldehyde, also a white solid (*R_f* in 40% ether/hexanes = 0.32, 383 mg). ¹H NMR (500 MHz, CDCl₃) δ 10.3(s, 1H); 7.84 (m, 1H); 6.58-6.55 (m, 1H); 6.45 (m, 1H); 3.92 (s, 3H); 3.89 (s, 3H). Data matched that of commercially available aldehyde.

2-(tert-butyldimethylsilyloxy)-4-methoxybenzaldehyde (20): To a dry 50 mL round bottom flask under a positive nitrogen flow containing 2-hydroxy-4-methoxybenzaldehyde (1.17g, 7.69 mmoles) was added DMF (2.6 mL). Next, *t*-

butyldimethylsilylchloride (2.4 g, 15.9 mmol) was added followed by imidazole (1.3 g, 19.1 mmol). After stirring at room temperature for 1 h the reaction was complete by TLC (40% ether/hexanes). The reaction was diluted with ether and water. The layers were separated and the organic layer was washed two additional times with water. The substrate is acid sensitive so it is important to use neutral conditions during workup. The organic layer was washed with saturated NaCl then dried with magnesium sulfate, filtered and concentrated to a pale yellow oil. The crude oil was purified by bulb to bulb distillation using a Kugelrohr apparatus. At 0.1 torr, the desired product came over between 150-175 °C as a clear, colorless oil (1.02g, 50%). R_f =0.56 (40/60 ether/hexanes); IR (film) 2933.1, 2854.6, 1681.6, 1061.9, 1255.8, 1206.8, 1168.5, 845.9 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 10.3(s, 1H); 7.80 (m, 1H); 6.62-6.60 (m, 1H); 6.36 (m, 1H); 3.86 (s, 3H); 1.04 (s, 9H); 0.30 (s, 6H). ^{13}C NMR (125 MHz, CDCl_3) δ 188.7, 165.9, 151.0, 130.3, 121.6, 108.1, 105.4, 55.8, 25.9, 25.8, 18.6.

(2-(*tert*-butyldimethylsilyloxy)-4-methoxyphenyl)methanol (21): To a 50 mL round bottom flask containing **20** (1.02g, 3.82 mmol) was added methanol (19 mL). The reaction was cooled 0 °C. NaBH_4 (178 mg, 4.71 mmol) was cautiously added to the aldehyde solution. After addition was complete the reaction was allowed to slowly attain room temperature. After 2 h the reaction was complete by TLC (40% ether/hexanes). The reaction was quenched with saturated NaCl and concentrated to remove the methanol. The aqueous layer was then extracted three times with ether. The combined organic layers were dried over magnesium sulfate, filtered and concentrated to afford a clear, colorless oil (700 mg, 68%) that was pure by ^1H NMR. R_f =0.38 (40/60 ether/hexanes); IR (film) 3356.5, 2954.3, 2932.1, 2858.5, 1611.3, 1504.6, 1162.7, 844.2 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.20 (d, 1H, J = 8.2 Hz); 6.51 (dd, 1H, J = 8.4 and 2.0 Hz); 6.40 (d, 1H, J = 2.0 Hz); 4.61 (s, 2H); 3.78 (s, 3H); 1.03 (s, 9H); 0.28 (s, 6H). ^{13}C NMR (125 MHz, CDCl_3) δ 160.4, 154.8, 130.1, 124.4, 105.9, 105.8, 61.8, 55.6, 26.0, 25.9, 18.4.

***tert*-butyl(2-(chloromethyl)-5-methoxyphenoxy)dimethylsilane (2f):** To a dry 100 mL round bottom flask under nitrogen, containing **21** (700 mg, 2.61 mmol) was added toluene (26 mL). The reaction was cooled to 0 °C then freshly distilled thionyl chloride (552 μL , 7.57 mmol) was added. Almost immediately, the reaction turned pink. Allowed to slowly attain room temperature and stirred overnight. After 18 h the reaction was poured into 20% KOH (4 g of KOH in 20 mL of H_2O). The layers were separated and the aqueous layer was extracted three times with CH_2Cl_2 . The combined organics were dried with sodium sulfate, filtered and concentrated to yield **2e** as a yellow oil (705 mg, 94%) that was pure by ^1H NMR. It was used in the next step without further purification. **2e** is acid sensitive and decomposes on the SiO_2 TLC plates. IR (film) 2955.8, 2932.3, 2858.4, 1610.5, 1504.5, 1260.1, 1202.1, 1165.7, 846.6 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.26-7.25 (m, 1H); 6.52-6.50 (m, 1H); 6.39 (m, 1H); 4.60 (s, 2H); 3.79 (s, 3H); 1.05 (s, 9H); 0.29 (s, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 161.2, 155.2, 131.8, 121.1, 106.4, 105.6, 55.6, 42.3, 26.0, 25.9, 18.5.

1-(2-bromo-3,5-dimethoxyphenyl)-2-(2-hydroxy-4-methoxyphenyl)ethanone (14): A 25 mL round bottom flask was charged with the protected thiazolium carbinol **13** (289 mg, 0.471 mmol) and fitted with a septa in a nitrogen-filled drybox. Also in the box, a

separate vial was charged with tetramethylammonium fluoride ($\text{Me}_4\text{N}\cdot\text{F}$, 73 mg, 0.784 mmol). Both reagents were removed from the box and the carbinol was placed under a positive pressure of nitrogen. The quinone methide precursor **2f** (90 mg, 0.314 mmol) dissolved in CH_2Cl_2 (6 mL) was added to the flask containing the carbinol. The resulting yellow solution was immediately cooled to -78°C . Last, the $\text{Me}_4\text{N}\cdot\text{F}$ suspended in CH_2Cl_2 (1 mL) was added dropwise to the reaction. Upon $\text{Me}_4\text{N}\cdot\text{F}$ addition, the reaction turned orange. After 24 h at -78°C the reaction was allowed to attain room temperature and stirred for an additional hour at 23°C . The reaction was diluted with saturated NaCl and CH_2Cl_2 . The layers were separated and the aqueous layer was extracted two additional times with CH_2Cl_2 . The organic layers were combined, dried over Na_2SO_4 , filtered and concentrated. The resulting residue was purified by flash column chromatography on silica gel. Purified with 50-80% ether/hexanes, yielding 74 mg (62%) of **13** as an orange oil. This substrate is sensitive to silica gel so the purification was done quickly using a relatively small amount of silica gel. $R_f = 0.19$ (60/40 ether/hexanes); IR (film) 3393.3, 3005.3, 2939.7, 1619.4, 736.5 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.38 (bs, 1H) 6.99-6.97 (m, 1H); 6.54-6.52 (m, 2H); 6.44-6.45 (m, 2H); 4.17 (s, 2H); 3.89 (s, 3H); 3.76 (s, 3H); 3.75 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 206.7, 160.7, 160.3, 157.1, 156.5, 143.5, 132.1, 113.4, 106.9, 104.5, 103.4, 101.8, 99.3, 56.8, 56.0, 55.6, 45.4; LRMS (electrospray): Mass calculated for $\text{C}_{17}\text{H}_{17}\text{BrO}_5$ $[\text{2M}]^+$, 760.1. Found 762.1.

2-(2-bromo-3,5-dimethoxyphenyl)-6-methoxybenzofuran (15): To a 10 mL round bottom flask under nitrogen containing **14** (71 mg, 0.186 mmoles) was added CH_2Cl_2 (1 mL). Amberlyst 15 resin (260 mg) added and freshly dried, powered 4Å MS (200 mg). Stirred at 0°C for 10 h then kept in a 4°C fridge overnight. A TLC (60% ether/hexanes) at this time showed the reaction was complete. The reaction was filtered through a plug of silica gel using 5% to 15% ether/hexanes as eluent, yielding 50 mg (74%) of **15** as a clear, colorless oil that turned into a white solid upon standing. $R_f = 0.61$ (60/40 ether/hexanes); Mp: $98-99^\circ\text{C}$; IR (film) 3001.3, 2939.2, 1621.6, 1585.1, 824.9 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.56 (s, 1H); 7.52-7.51 (m, 1H); 7.13-7.12 (m, 1H); 7.09 (s, 1H); 6.93-6.91 (m, 1H) 6.52-6.51 (m, 1H); 3.94 (s, 3H); 3.91 (s, 3H); 3.90 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 159.8; 158.8; 157.5; 155.4; 152.7; 132.9; 122.4; 121.9; 112.5; 107.9; 105.5; 102.0; 99.9; 95.8; 56.8; 56.0; 55.9; LRMS (electrospray): Mass calculated for $\text{C}_{17}\text{H}_{15}\text{BrO}_4$ $[\text{M}]^+$, 362.0. Found 365.2

2-(3,5-dimethoxy-2-(3-methylbut-2-enyl)phenyl)-6-methoxybenzofuran: To a flame-dried 10 mL round bottom flask under nitrogen was added benzofuran **15** (18 mg, 0.0496 mmoles) and $\text{PdCl}_2(\text{dppf})$ (10 mg, 0.0122 mmoles). DMF (0.25 mL) was added to create a red suspension. Last, prenyl tributyltin (50 μL , 0.148 mmoles) was added in one portion by syringe. The reaction was heated to 100°C . TLC (40% ether/hexanes) indicated all of the starting material had been consumed after 5 h. The reaction was cooled to room temperature and 1 mL of ether was added along with a spatula tip of KF and the mixture was stirred for 15 min. The mixture was then purified using a small silica gel column with 5% ether/hexanes as eluent. The product was isolated as a colorless oil (13 mg, 76%). $R_f = 0.76$ (60/40 ether/hexanes); IR (film) 2956.6, 2925.9, 2854.8, 1612.4, 1588.4, 1505.4, 1461.4, 1207.8, 1155.8, 1040.4 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.48-7.46 (m, 1H); 7.09 (s, 1H); 6.92-6.88 (m, 2H); 6.80 (s, 1H); 6.54-6.53 (m, 1H); 5.20 (m, 1H); 3.90 (s, 3H); 3.88

(s, 3H); 3.87 (s, 3H); 3.52 (d, 2H, $J = 6.1$ Hz); 1.73 (s, 6H) ^{13}C NMR (125 MHz, CDCl_3) δ 159.2, 158.8, 158.2, 155.8, 154.8, 131.8, 131.7, 123.9, 122.7, 121.5, 121.3, 112.1, 105.5, 104.3, 99.5, 96.0, 56.0, 55.7, 26.2, 26.1, 18.3; LRMS (electrospray): Mass calculated for $\text{C}_{22}\text{H}_{24}\text{O}_4$ $[2\text{M}]^+$,

Demethylmoracin I (16): To a flame-dried 25 mL round bottom flask under positive nitrogen pressure was added diphenylphosphine (93 μL , 0.536 mmoles) and THF (1 mL). The solution was cooled to 0 $^\circ\text{C}$. $n\text{BuLi}$ (300 μL , 0.536 mmoles) was added to the cool reaction and immediately a bright orange solution was formed. Stirring was continued for 1 h at 0 $^\circ\text{C}$.

In a separate flame-dried 10 mL round bottom flask was prepared a solution of benzofuran **15** (21 mg, 0.0596 mmoles) in THF (0.4 mL). This solution was added to the freshly prepared lithium diphenylphosphanide dropwise by cannula. After the addition was complete the reaction was first warmed to room temperature then heated to 70 $^\circ\text{C}$ for 20 h. At this time the reaction, now a brown solution, was cooled to room temperature. Ether and 1M NaOH were added and the mixture was stirred until the reaction became homogenous. The reaction was poured into a separatory funnel and acidified to pH 4 with 1M HCl. The layers were separated and the aqueous layer was extracted two additional times with ether. The combined organic layers were dried over magnesium sulfate, filtered and concentrated to afford a brown oil. The crude oil was purified by flash column chromatography on silica gel using 5% MeOH/ CH_2Cl_2 as eluent to afford 11 mg (61%) of demethylmoracin I as a brown solid that was recrystallized from ether/hexanes to yield white crystals. $R_f = 0.45$ (8:1 CH_2Cl_2 :MeOH); IR (KBr) 3351.0, 2917.6, 1625.1, 1490.0, 1155.9 cm^{-1} ; Mp: recrystallized white solid 170-171 $^\circ\text{C}$; ^{13}C NMR (125 MHz, CDCl_3) δ 158.0, 157.2, 157.0, 156.7, 156.4, 133.2, 131.5, 125.8, 123.2, 122.0, 119.4, 113.2, 107.8, 105.7, 103.9, 98.5, 26.7, 26.1, 18.2 HREIMS m/z 310.1197, calculated for $\text{C}_{19}\text{H}_{18}\text{O}_4$, 310.1205.

Reported ^1H NMR Data for Demethylmoracin I (CD_3OD) ⁴	Actual ^1H NMR Data Found (CD_3OD)
1.64 (6H, s)	1.65 (6H, s)
3.42 (2H, d, $J = 6.3$ Hz)	3.44 (2H, d, $J = 6.0$ Hz)
5.13 (1H, m)	5.14 (1H, m)
6.33 (1H, d, $J = 2.5$ Hz)	6.35 (1H, d, $J = 2.4$ Hz)
6.61 (1H, d, $J = 2.5$ Hz)	6.62 (1H, d, $J = 2.4$ Hz)
6.66 (1H, s)	6.68 (1H, s)
6.72 (1H, dd, $J = 2.2$ and 8.4 Hz)	6.74 (1H, dd, $J = 2.0, 8.4$ Hz)
6.87 (1H, d, $J = 2.1$ Hz)	6.88 (1H, d, $J = 1.5$ Hz)
7.33 (1H, d, $J = 8.4$ Hz)	7.35 (1H, d, $J = 8.4$ Hz)

⁴ Lee, D.; Bhat, K. P. L.; Fong, H. H. S.; Farnsworth, N. R.; Pezzuto, J. M.; Kinghorn, A. D. *J. Nat. Prod.* **2001**, 64, 1286-1293.

Competition Experiment

To a flame dried 10 mL round bottom flask was added the protected thiazolium carbinol **1a** (100 mg, 0.196 mmoles). The flask was fitted with a septa and put under a positive pressure of nitrogen. CH_2Cl_2 was added next (0.5 mL) and the reaction was cooled to $-78\text{ }^\circ\text{C}$ in a dry ice and acetone bath. The methoxybenzyl bromide **22** (39 mg, 0.196 mmoles) was added in CH_2Cl_2 (0.5 mL) then the siloxybenzyl bromide **2a** (59 mg, 0.196 mmoles) was added in CH_2Cl_2 (0.5 mL). Stirred for 5 min to ensure the reaction was cooled to $-78\text{ }^\circ\text{C}$. Last, $\text{Me}_4\text{N}\cdot\text{F}$ (37 mg, 0.392 mmoles) was added in CH_2Cl_2 (0.5 mL) and the reaction immediately turned green. Stirred at $-78\text{ }^\circ\text{C}$ for 6.5 h then kept in a $-78\text{ }^\circ\text{C}$ freezer overnight. After 23 h total, the reaction was warmed to $23\text{ }^\circ\text{C}$ and stirred for an additional hour. The reaction was then diluted with brine and CH_2Cl_2 . The layers were separated and the aqueous layer was extracted two additional times with CH_2Cl_2 . The combined organic layers were dried over sodium sulfate, filtered and concentrated. 108 mg of an unpurified orange residue was isolated. The ^1H NMR of the unpurified reaction mixture showed mainly **3** and **22** with no sign of the methoxy α -aryl ketone **23** when compared to the ^1H NMR of an authentic sample. Purified by flash column chromatography on silica gel using 5% to 35% ether/hexanes as the eluent. The α -aryl ketone **3** was isolated (21 mg, 44%).

Preparation of an Authentic Sample of 23

To a reaction vial containing the α -aryl ketone (6 mg, 0.024 mmoles) was added methanol (0.3 mL). Fitted with cap and septa and put under positive nitrogen pressure. Trimethylsilyl diazomethane (0.2 mL, 2M solution in hexanes) was added slowly to the reaction mixture. Stirred at room temperature overnight. At this time the reaction appeared complete by TLC and was concentrated. Purified by prep TLC using 40% ether/hexanes as eluent. The product was isolated as a pale yellow oil. ; ^1H NMR (500 MHz, CDCl_3) δ 8.00-7.98 (m, 2H); 7.45-7.43 (m, 2H); 7.19-7.17 (m, 2H); 6.95-6.89 (m, 2H); 4.25 (s, 2H); 3.80 (s, 3H).

500 MHz ^1H NMR Spectrum of Unpurified Competition Experiment 500 MHz ^1H NMR Spectrum of Methoxy Ether

Select NMR Spectra