

Use of the *vicinal* Element Effect for Regiochemical Control of Quinone Substitutions and its Implication for Convergent Mitomycin Construction

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Supporting Information

Flame-dried (under vacuum) glassware was used for all non-aqueous reactions. All reagents and solvents were commercial grade and purified prior to use when necessary. Diethyl ether (Et₂O), tetrahydrofuran (THF), dichloromethane (CH₂Cl₂), and benzene (C₆H₆) were dried by passage through a column of activated alumina as described by Grubbs.¹ Benzene was additionally passed through a column containing activated Q-5 reactant. Solvents other than benzene were degassed using the freeze-pump-thaw method when necessary. All additional solvents were dried by distillation from calcium hydride when necessary. Molecular sieves (spheres, 4Å) were calcined at 400 °C and stored at room temperature in an air-tight container. 2,3-Dibromo-5-methoxy-6-methylbenzoquinone was prepared according to the procedure described by Rapoport.¹ The preparation of stannyleneamine **4** will be described later.

Thin layer chromatography (TLC) was performed using glass-backed silica gel (250 μ) plates and flash chromatography utilized 230–400 mesh silica gel from Scientific Adsorbents. Neutral Alumina was used as received from Scientific Adsorbents for chromatography of acid-sensitive intermediates or products. Products were visualized by UV light, iodine, and/or the use of ceric ammonium molybdate, potassium permanganate, ninhydrin, *p*-anisaldehyde, and potassium iodoplatinate solutions.

IR spectra were recorded on a Nicolet Avatar 360 spectrophotometer. Liquids and oils were analyzed as neat films on a salt plate (transmission), whereas solids were applied to a diamond plate (ATR). Nuclear magnetic resonance spectra (NMR) were acquired on either a Varian Inova-400 or VXR-400 instrument. Chemical shifts are measured relative to tetramethylsilane, as judged

¹ Luly, J. R.; Rapoport, H. J. Am. Chem. Soc. 1983, 105, 2859-2866.

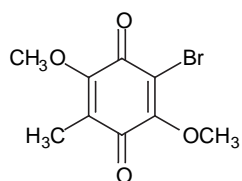
by the residual partially deuterated solvent peak. Mass spectra were obtained using a Kratos MS-80 spectrometer using the ionization technique indicated. Combustion analyses were performed by Atlantic Microlabs, Norcross, GA.

Ratios of diastereomers and isomeric products were measured directly from integration of ^1H NMR absorptions of protons common to the components. Precision was checked by varying the relaxation delay for measurements on the same compound. Ratios reported generally represent a lower limit defined by multiple runs.

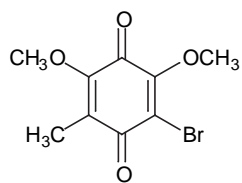
Calculations were performed on minimized structures using PC Model (Serena Software) and the MOPAC suite (both PM3 and AM1).

General Procedure for Methanol Additions

A methanol solution of quinone **1** (0.01 M) at rt was treated with sodium methoxide in a single portion. The reaction was followed by TLC to completion and the solvent was removed under reduced pressure. The crude mixture was dissolved in EtOAc, washed with water, and dried (Na_2SO_4) prior to chromatographic purification.

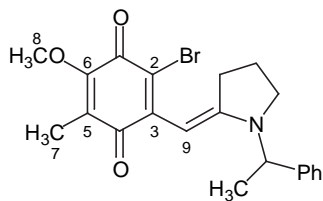


2-Bromo-3,6-dimethoxy-4-methyl *p*-benzoquinone (6). A small amount of the corresponding hydroquinones, produced in the same ratio as the quinones, was typically observed. Therefore, the crude mixture was treated with 10% Pd/C in ethyl acetate and stirred open to the air for 2 h. The mixture was filtered through Celite and silica gel, washing well with EtOAc. Purification over silica gel (1-3% ether in hexanes) gave an orange solid, mp 107-108.5 °C; $R_f=0.12$ (2% Et_2O /hexanes - SiO_2); IR (ATR) 1666, 1653, 1590 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 4.19 (s, 3H), 4.04 (s, 3H), 1.93 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) ppm 182.0, 176.8, 156.9, 155.3, 126.4, 115.1, 61.9, 61.4, 8.8; HRMS (CI): Exact mass calcd for $\text{C}_9\text{H}_9\text{BrO}_4$ $[\text{M}]^+$, 259.9684. Found 259.9696.



2-Bromo-3,5-dimethoxy-6-methyl *p*-benzoquinone (7).

Purification over silica gel (1-3% ether in hexanes) or recrystallization from ether gave an orange solid, mp 136.5-138 °C. $R_f=0.09$ (2% Et_2O /hexanes - SiO_2); IR (ATR) 1665, 1651, 1640 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 4.14 (s, 3H), 3.97 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) ppm 180.9, 177.1, 155.7, 154.4, 129.1, 118.9, 61.6, 61.1, 9.9; HRMS (CI): Exact mass calcd for $\text{C}_9\text{H}_9\text{BrO}_4$ $[\text{M}]^+$, 259.9684. Found 259.9673.

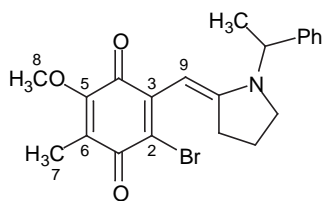


Quinone adduct 5. A cold (0 °C) THF solution of quinone **6** was treated with a THF solution of enamine **4**, resulting in an immediate color change from orange to blue. Following a period of stirring (30 min), the solvent was removed and replaced with Et₂O/aq KF solution.

After a white solid had formed, the layers were separated, the aqueous layer was further extracted with ether, and the combined organic layers were dried (Na₂SO₄). Filtration, concentration in vacuo, and chromatography using a jacketed column cooled with ice-water (alumina, 0-5-10% ethyl acetate in hexanes) furnished the unstable quinone (40% yield) as a blue oil. *R*_f=0.22 (20% EtOAc/hexanes - SiO₂); IR (film) 1653, 1648, 1540 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.39-7.26 (m, 5H), 5.46 (s, 1H), 5.14 (q, *J* = 7.0 Hz, 1H), 4.02 (s, 3H), 3.51-3.44 (m, 1H), 3.31-3.25 (m, 1H), 2.91-2.83 (m, 1H), 2.74-2.67 (m, 1H), 1.99-1.81 (m, 2H), 1.92 (s, 3H), 1.65 (d, *J*=7.0 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) ppm 187.1, 174.4, 163.5, 156.5, 147.8, 140.2, 129.1, 129.1, 128.0, 126.7, 126.7, 126.7, 116.3, 92.0, 61.3, 54.3, 48.6, 34.8, 22.5, 17.8, 9.4; HRMS (EI): Exact mass calcd for C₂₁H₂₂BrNO₃ [M]⁺, 415.0783. Found 415.0790.

5 Could also be generated in 21% yield by addition of **4** to **1** in cold (-78 °C) THF, followed by work-up as described above.

Structural assignment. (400 MHz, Varian I400) An HMBC experiment (Figure S1) revealed ³*J*_{HC} crosspeaks for H7→C1, H9→C1, and H9→C2, consistent with the regiochemistry depicted. NOE measurements revealed an enhancement (22%) of CH₃CHN(Ph) upon irradiation of H9.



Quinone adduct 10. In a manner analogous to the synthesis of **5**, the unstable blue quinone **10** was prepared from **7** in 38% isolated yield after chromatography using a jacketed column cooled with ice-water (alumina, 0-10-30% Et₂O/hexanes). *R*_f=0.07 (20%

EtOAc/hexanes - SiO₂); IR (film) 1663, 1636, 1560 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.40-7.27 (m, 5H), 5.39 (s, 1H), 5.11 (q, *J*=7.0 Hz, 1H), 3.91 (s, 3H), 3.51-3.45 (m, 1H), 3.32-

3.27 (m, 1H), 2.88-2.80 (m, 1H), 2.68-2.62 (m, 1H), 1.99 (s, 3H), 1.97-1.83 (m, 2H), 1.66 (d, $J=7.0$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) ppm 181.7, 179.4, 161.4, 155.5, 146.0, 140.4, 129.0, 128.9, 128.9, 127.8, 126.6, 126.6, 118.9, 90.3, 60.2, 54.1, 48.2, 34.5, 22.4, 17.7, 9.9.

Structural assignment. (400 MHz, Varian I400) An HMBC experiment (Figure S2) revealed $^3J_{\text{HC}}$ crosspeaks for $\text{H7} \rightarrow \text{C1}$, $\text{H9} \rightarrow \text{C4}$, and $\text{H9} \rightarrow \text{C2}$, consistent with the regiochemistry depicted. NOE measurements revealed an enhancement (25%) of $\text{CH}_3\text{CHN}(\text{Ph})$ upon irradiation of H9.

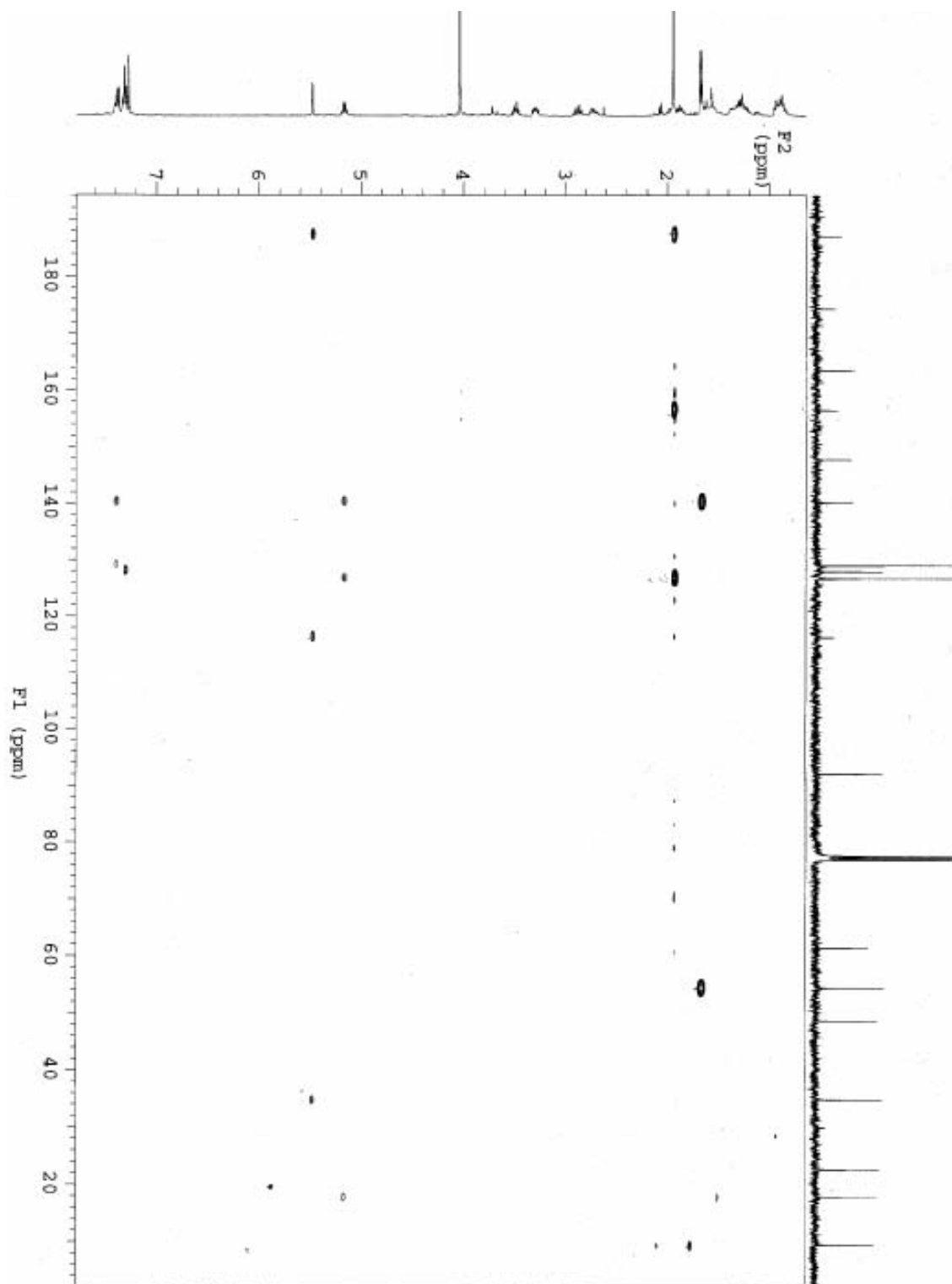


Figure S1. HMBC Plot (400 MHz) of quinone adduct **5**.

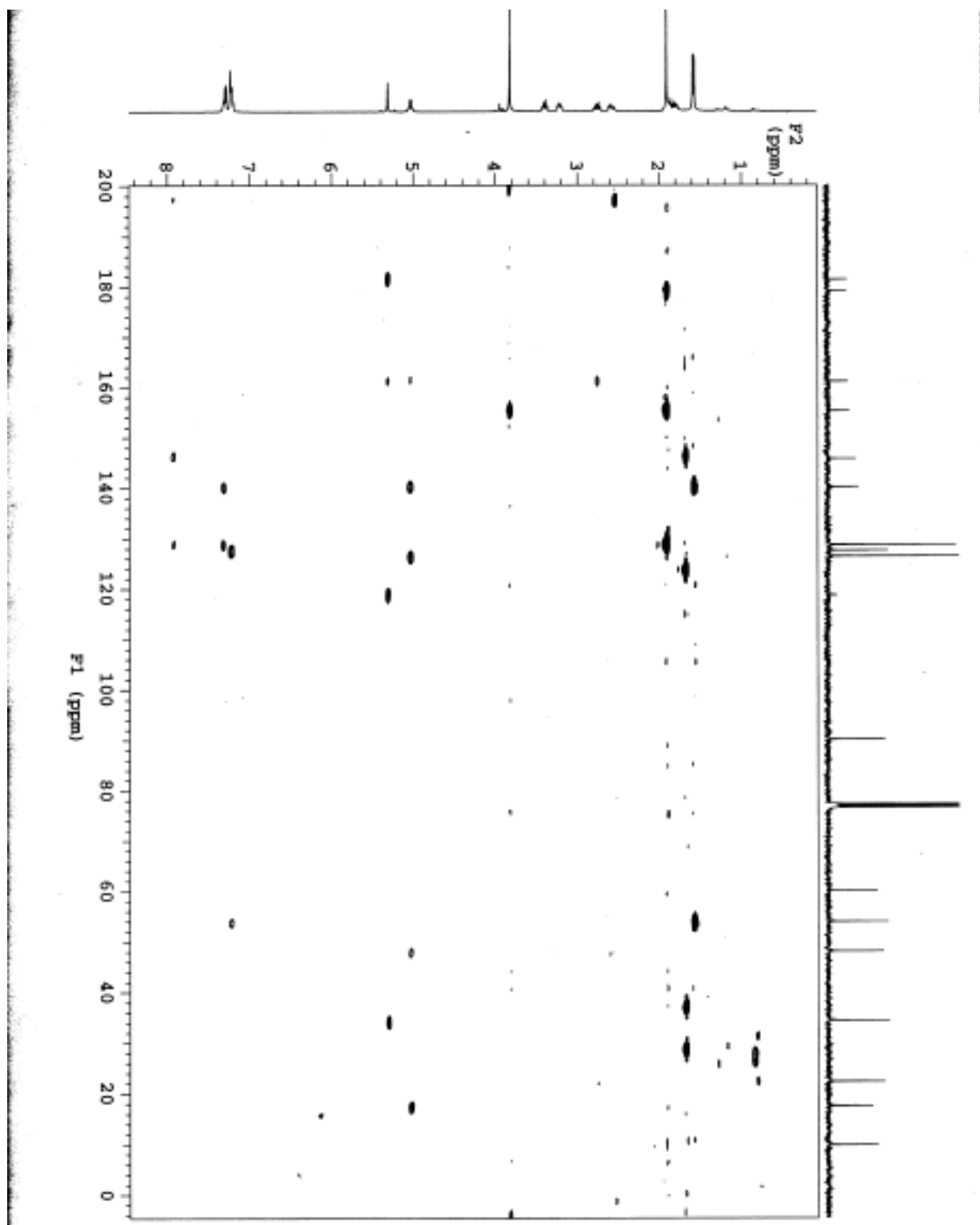


Figure S2. HMBC Plot (400 MHz) of quinone adduct **10**.

¹ Pangborn, A.B.; Giardello, M.A.; Grubbs, R.H.; Rosen, R.K.; Timmers, F.J. *Organometallics* **1996**, *15*, 1518–1520.