Regiochemical Control by Remote Substituents – A Selective Synthesis of Angularly Fused Ring Systems

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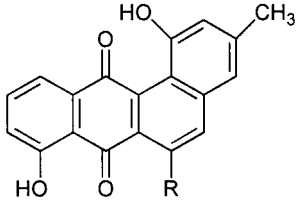
Keywords: Diels–Alder / Quinones / Regiocontrol / Regioselectivity

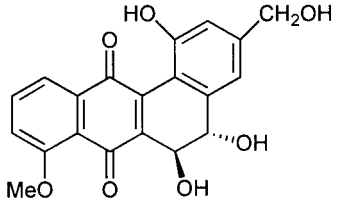
Diels–Alder reactions of quinones **4**, **7**, and **15** exhibit remarkable regioselectivity. In contrast, the Diels–Alder reaction of quinone **12** showed no regioselectivity, indicating that the regioselectivities are due to electronic interactions. The selectivity is nicely explained using molecular electrostatic potentials.

Introduction

Natural products researchers have identified a number of tetracyclic and hexacyclic aromatic compounds that are angularly fused. Some of these compounds such as tetrangulol (**1**), 6-hydroxytetrangulol (**2**), and PD116740 (**3**) exhibit significant biological activity.[1] Recently, 6-hydroxy tetrangulol was reported to be a CPP32 protease inducer.[2] These compounds present significant challenges for the control of regiochemistry on carbons that are distant from one another, a challenge similar to that encountered in linearly fused anthracyclines. However, the presence of the angular fusion might confer opportunities for selectivity not available in linear systems. In our approach, the angularly fused ring system is regioselectively assembled by a strategy that takes advantage of the *proximity* of functional groups enforced by the angular fusion. This permits a strategy that is direct and significantly different from the previously reported approaches to these compounds.[3,4]

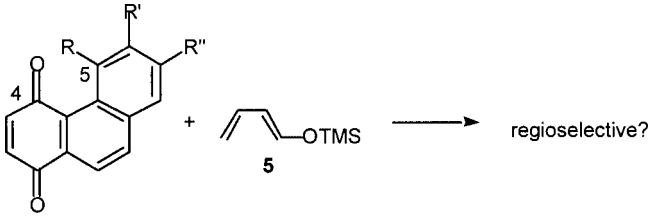


1: R = H
2: R = OH

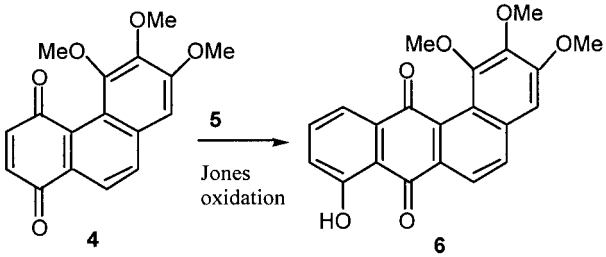


3

The key question in our approach to this system was whether the substituent at C-5 of a 1,4-phenanthrenequinone would, either by a steric or electronic effect, attenuate the directing effect of the carbonyl group at C-4.



In order to test this hypothesis, quinone **4** was synthesized. The synthesis of **4** was accomplished using an intramolecular $SnCl_4$-mediated cyclization of a hydroxy benzoquinone.[5] The Diels–Alder adduct was produced by the addition of two equivalents of 1-trimethylsilyloxybutadiene (**5**) to quinone **4** at –78 °C followed by warming to ambient temperature. The solvent was removed, and the residue was oxidized using the Jones reagent.[6] The product **6** was purified by silica gel flash column chromatography. No other quinone-containing products were detected. The regiochemistry of **6** was confirmed by an X-ray structure determination.[7] This result provides a novel approach to the problem of regiochemical communication in benzanthracene quinones.



4 **6**

In order to better understand the scope of this interesting reaction, we decided to determine which substituents at C-

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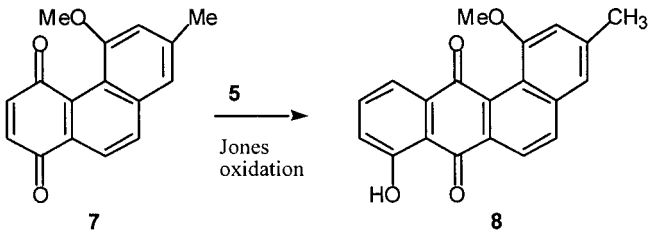
 DOI: 10.1002/ejoc.200500202

5 would allow a regioselective Diels–Alder reaction. Compound **7**[8] reacted with diene **5** at –78 °C in dichloromethane to produce quinone **8** in 78% isolated yield as the only isomer. The regiochemistry was confirmed by the transformation of **8** into tetrangulol (**1**) using iodotrimethylsilane.



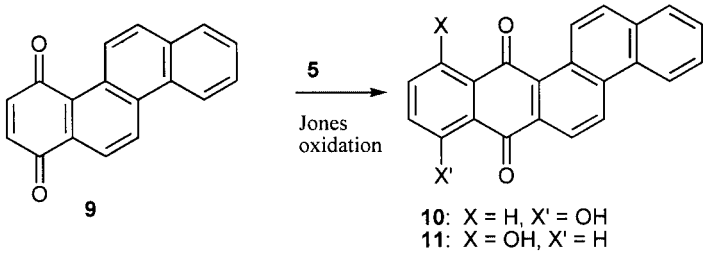
7 **8**

Commercially available chrysenequinone **9** was treated with diene **5** followed by Jones oxidation.[9] In this case there is no substituent at C-5 to influence the carbonyl group at C-4. We were not surprised to isolate a 1:1 mixture of regioisomeric quinones **10** and **11** in a combined yield of 64%.

Quinone **12** was prepared from 3,5-dimethylanisole.[8,9] The methyl group at C-5 allows us to assess the importance of steric attenuation of the carbonyl group at C-4. When treated with diene **5**, a 1:1 mixture of quinones **13** and **14** was produced. This result suggests that the high regioselectivities observed with quinones **4** and **7** were primarily due to electronic interactions.

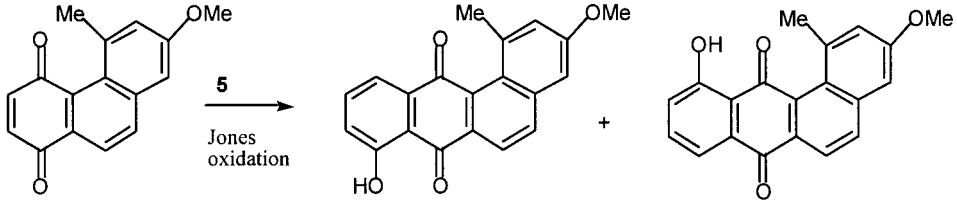
Quinone **15** was then synthesized by the reaction of 2,4-hexadienal with excess benzoquinone at 90 °C for 20 hours.[10] It reacted with **5** to produce a 8:1 ratio of two anthraquinones. The major isomer was treated with hydrazine to produce compound **18** in quantitative yield. HMBC spectroscopy revealed a three-bond coupling between the carbonyl group and the hydrogen atom *peri* to the carbonyl group, thereby defining the structure as **18** and the major isomer as anthraquinone **17**.

In our synthesis of frenolicin B, a rigid pyranolactone subunit was proposed to be responsible for the highly regioselective Diels–Alder reaction.[6] In this work we demonstrate that substituents such as the carboxaldehyde, which are conformationally flexible, can also exert a strong directing effect.

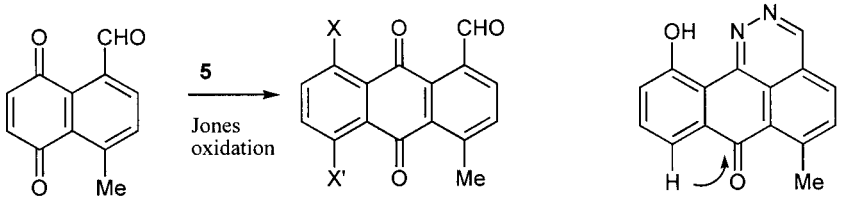


9

10: X = H, X' = OH
11: X = OH, X' = H



12 **13** **14**



15

16: X = H, X' = OH
17: X = OH, X' = H

18

Theoretical Analysis

The geometry of **4** was fully optimized at the RHF/6-31G(d)[11] level of theory and verified as a minimum by an analytical Hessian calculation, using the quantum chemistry program GAMESS.[12] The calculated geometry shows that the quinone is significantly distorted from planarity (Figure 1b) to minimize the repulsive interaction with the C-5 methoxyl group. To gauge the effect of this distortion on the regioselectivity, molecular electrostatic potential (MEP) maps were evaluated 2 Å above and below the dienophile (DP) plane.[13] The terms "above" and "below" are defined in Figure 1.

Our calculations suggest that the regiocontrol is due to relatively long range electrostatic interactions between the substituents rather than through HOMO–LUMO interactions. We undertook these calculations precisely because the regiocontrol is not readily explainable in terms of traditional HOMO–LUMO arguments. The MEP maps (Figure 1a and 1c) show the molecular potential felt by a positive test charge and identify relative positive (solid contours) and negative parts (dotted contours) of the molecule. Both MEPs show a positive center region and negative regions at either side. The MEP 2 Å below the DP plane (Figure 1c) shows an almost equal negative charge distribution on either side due to the quinone oxygens. The MEP 2 Å above the DP plane (Figure 1a) shows more concentrated negative charge on the C-4 side of the ring due mostly to the C-5 methoxyl oxygen, and only little negative charge on the C-1 side. Thus, these MEP maps indicate that an incoming 1-trimethylsilyloxybutadiene should attack **4** from above with the OTMS group away from the C-5 methoxyl group. A MEP of 1-trimethylsilyloxybutadiene has been

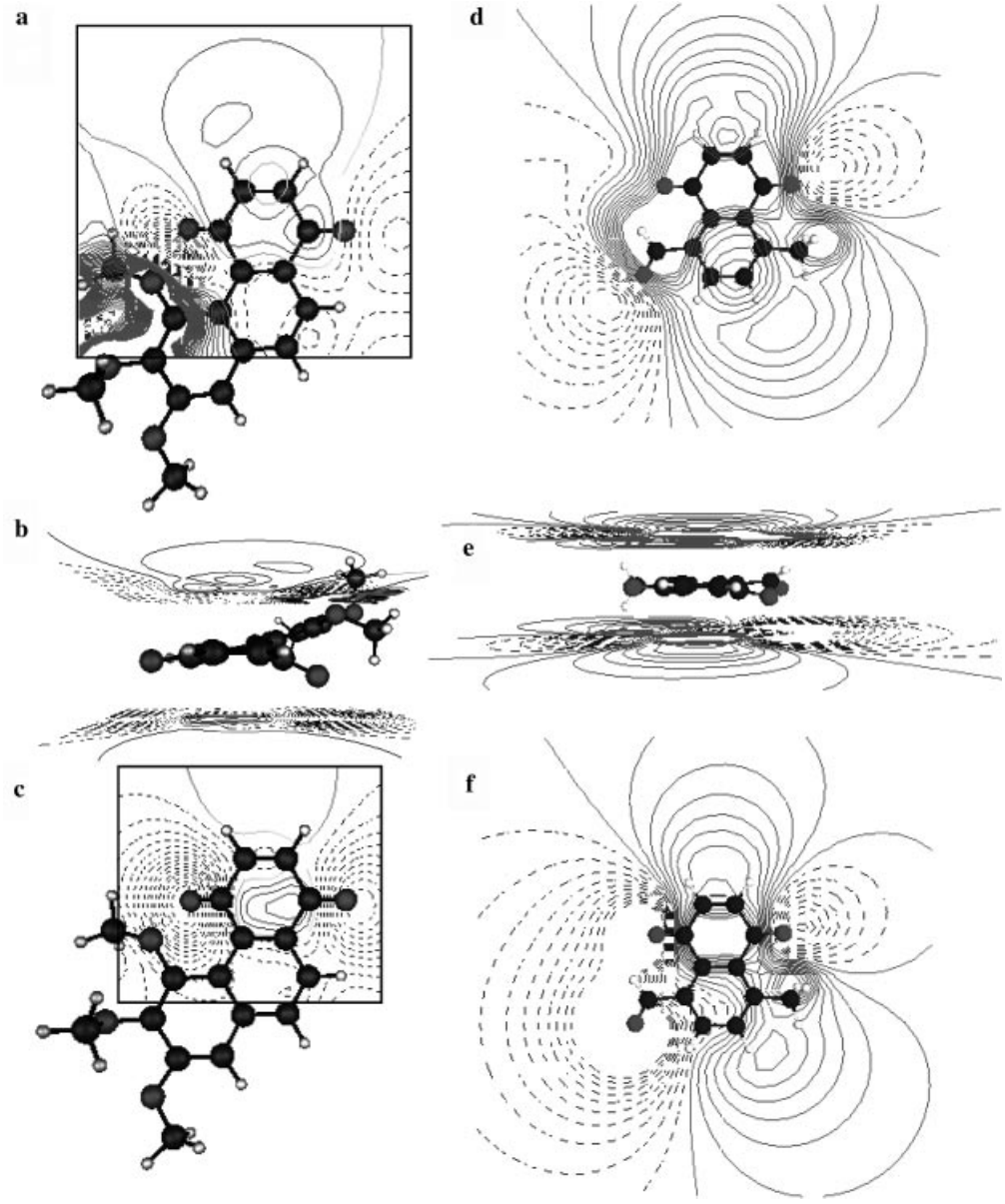


Figure 1. MEPs of **4** evaluated in planes 2 Å above (a) and below (c) the plane of the site of dienophile attack (defined in b), and similarly for **15** (d–f).

published as Figure 2 in ref.[6b]. The reaction is not likely to modify the partial charges of the substituents controlling regioslectivity because they are remote from the region that undergoes chemical change.

A similar analysis of the MEP of **15** also explains the observed selectivity. The aldehyde group is shown to distort the quinone group, though to a lesser extent than for **4** (compare Figure 1b and Figure 1e). Thus, the aldehyde group and neighboring quinone oxygen protrude from opposite sides of the quinone ring. As a result, the least negative region of the dienophile, and hence the preferred location of the OTMS group upon attack, is on the "aldehyde side" of the ring and adjacent to the aldehyde. Thus, **17** is predicted to be the preferred product in agreement with our experimental findings.

Experimental Section

General Procedure for the Diels–Alder/Oxidation: To a solution of the 1,4-phenanthrenequinone (0.2 mmol) in dry CH_2Cl_2 (2 mL) was added dropwise 1-(trimethylsilyloxy)-1,3-butadiene (**5**) (0.07 mL, 0.4 mmol) at –78 °C under argon. The resulting solution was allowed to slowly warm to room temp. overnight. After removal of the solvent in vacuo, the residue was dissolved in acetone (5 mL) and was treated with Jones reagent (2.7 M, 0.163 mL, 0.44 mmol) at 0 °C. The resulting red mixture was allowed to warm to room temp. and after 1 h was quenched with excess 2-propanol. After stirring for an additional 5 min, the mixture was concentrated in vacuo. The residue was partitioned between CH_2Cl_2 and saturated NH_4Cl. The solvent was removed, and the residue was purified by silica gel flash chromatography (sgc).

8-Hydroxy-1,2,3-trimethoxybenz[*a*]anthracene-7,12-dione (6): Purified by sgc (H/EA, 4:1) to give 61 mg (84%) of **6** as a red solid; m.p. 232 °C. ^{1}H NMR ($CDCl_3$): δ = 3.98 (s, 1 H), 4.03 (s, 6 H), 6.99 (s, 1 H), 7.23 (dd, J = 1.8, 7.2 Hz, 1 H), 7.58–7.66 (m, 2 H), 7.90 (d, J = 8.7 Hz, 1 H), 8.16 (d, J = 8.7 Hz, 1 H), 12.24 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 56.2, 61.1, 61.3, 102.9, 115.6, 118.2, 120.8, 121.5, 122.7, 131.8, 132.1, 135.2, 136.6, 136.7, 137.1, 143.9, 150.7, 156.2, 161.6, 185.9, 188.3 ppm. IR (KBr): $\tilde{\nu}$ = 2945, 1681, 1632, 1600 cm^{-1}. HRMS: *m*/*z* calcd. 364.0947, found 364.0949.

8-Hydroxy-1-methoxy-3-methylbenz[*a*]anthracene-7,12-dione (8): Purified by sgc (60:1 H/EA) to give 49.6 g (78%) as a red solid. m.p. 211–212 °C. ^{1}H NMR ($CDCl_3$): δ = 12.2 (s, 1 H), 8.22–8.19 (d, 1 H, J = 8.4 Hz), 7.96–7.93 (d, 1 H, J = 8.4 Hz), 7.64–7.59 (m, 2 H), 7.28 (s, 1 H), 7.24–7.21 (dd, 1 H, J = 8.4 Hz, 1.6 Hz), 6.91 (s, 1 H), 3.98 (s, 3 H), 2.54 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 188.3, 185.5, 161.4, 157.3, 141.1, 138.4, 137.1, 137.1, 136.5, 132.6, 132.5, 122.5, 121.8, 120.0, 119.7, 118.2, 115.4, 111.4, 56.0, 22.2 ppm. IR (KBr): $\tilde{\nu}$ = 1673, 1633 cm^{-1}. MS: *m*/*z* = 318 [M$^+$, base peak], 301 [M – OH$^+$]. HRMS: *m*/*z* calcd. 318.2559, found 318.2563.

8-Hydroxybenzo[*b*]chrysene-7,12-dione (10) and 11-Hydroxybenzo[*b*]chrysene-7,12-dione (11): Purified by sgc (H/EA, 4:1) and recrystallization with H/EA (1:1) to give 39 mg (yield: 64%) orange crystals as 1:1 ratio. ^{1}HNMR ($CDCl_3$): δ = 7.28–7.36 (m, 1 H), 7.64–7.75 (m, 3 H), 7.82–7.86 (m, 1 H), 7.95–7.97 (m, 1 H), 8.00–8.05 (m, 1 H), 8.57–8.60 (m, 1 H), 8.73–8.76 (m, 1 H), 9.11–9.16 (m, 1 H), 9.58 and 9.69 (d, J = 9.9 Hz, 1 H), 12.45 and 12.87 (s, 1 H) ppm. MS: *m*/*z* 324, 277, 239, 201, 169, 120. HRMS: *m*/*z* for $C_{22}H_{12}O_3$ calcd. 324.0786, measured 324.0793. TLC (H/EA = 2:1) R_f = 0.65.

8-Hydroxy-3-methoxy-1-methylbenz[*a*]anthracene-7,12-dione (13) and 11-Hydroxy-3-methoxy-1-methylbenz[*a*]anthracene-7,12-dione (14): Purified by sgc (H/EA, 10:1) to give a colored liquid. ^{1}H NMR ($CDCl_3$): δ = 2.50 and 2.54(s, 3 H), 3.95 and 3.97 (s, 3 H), 6.99–7.80 (m, 4 H), 7.95–8.07 (m, 2 H), 8.23 and 8.25 (d, J = 6.6 Hz, 1 H), 11.83 and 12.29 (s, 1 H) ppm.

1-Formyl-5-hydroxy-4-methyl-9,10-anthraquinone (16): Purified by sgc (H/EA, 10:1) to give an orange solid. **16**: ^{1}HNMR (300 MHz): δ = 2.95 (s, 3 H), 7.32 (dd, J = 5.1, 1.5 Hz, 1 H), 7.69–7.87 (m, 4 H), 10.50 (s, 1 H), 12.03 (s, 1 H) ppm. MS: *m*/*z* 266, 237, 181, 152. HRMS: *m*/*z* for $C_{16}H_{10}O_4$ calcd. 266.0579, measured 266.0583. TLC (H/EA = 4:1) R_f = 0.40.

1-Formyl-8-hydroxy-4-methyl-9,10-anthraquinone (17): Purified by sgc (H/EA, 10:1) to give an orange solid. ^{1}H NMR (300 MHz): δ = 2.91 (s, 3 H), 7.32 (dd, J = 5.1, 1.5 Hz, 1 H), 7.69–7.87 (m, 4 H), 10.63 (s, 1 H), 12.03 (s, 1 H) ppm. ^{13}C NMR (100 MHz): δ = 24.1, 115.6, 119.7, 123.9, 131.9, 132.6, 134.1, 134.3, 137.5, 138.5, 138.9, 146.6, 162.0, 183.8, 189.8, 192.4 ppm. MS: *m*/*z* 266, 237, 181, 152. HRMS: *m*/*z* for $C_{16}H_{10}O_4$ calcd. 266.0579, measured 266.0583. TLC (H/EA = 4:1) R_f = 0.40.

11-Hydroxy-6-methyldibenzo[*de*,*h*]cinnoline-1,7-dione (18): Purified by sgc (H/EA, 3:1) to give an orange solid. ^{1}H NMR (400 MHz): δ = 3.08(s, 3 H), 7.38 (d, J = 8.0 Hz, 1 H), 7.59 (t, J = 7.6 Hz, 1 H), 7.94(m, 2 H), 8.13 (d, J = 8.4 Hz, 1 H), 9.46 (s, 1 H) ppm. ^{13}C NMR (100 MHz): δ = 24.9, 115.4, 119.7, 123.0, 123.5, 124.2, 125.0, 131.7, 133.1, 134.1, 138.9, 149.7, 151.5, 152.9, 160.0, 183.6 ppm. MS: *m*/*z* 262, 234, 151. HRMS: *m*/*z* for $C_{16}H_{10}N_2O_2$ calcd. 262.0742, measured 262.0747. TLC (H/EA = 3:1) R_f = 0.25.

5-Formyl-8-methyl-1,4-naphthoquinone (15): To a 50-mL, round-bottom flask were added 2,4-hexadienal (0.5 g, 0.50 mmol), 1,4-benzoquinone (2.1 g, 20 mmol), and toluene (6 mL). The mixture was heated at 90 °C for 20 h. The solvent was removed under reduced pressure. Purification by sgc (H/EA, 10:1) afforded quinone **15** (0.14 g, 14% yield). ^{1}HNMR (300 MHz): δ = 2.83 (s, 3 H), 6.99 (d, J = 0.9 Hz, 2 H), 7.66 (d, J = 8.1 Hz, 1 H), 7.90 (d, J = 8.1 Hz, 1 H), 10.53 (s, 1 H) ppm. ^{13}C NMR (75 MHz): δ = 23.5, 130.1, 132.5, 133.6, 137.3, 137.4, 138.2, 140.3, 146.3, 186.3, 187.0, 192.4 ppm. MS: *m*/*z* 200, 115, 57. HRMS: *m*/*z* for $C_{12}H_8O_3$ calcd. 200.0473, measured 200.0476. TLC (H/EA) R_f = 0.30.

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Received: March 17, 2005

