The Formal Oxidative Addition of Electron-Rich Transoid Dienes to Bromonaphthoquinones

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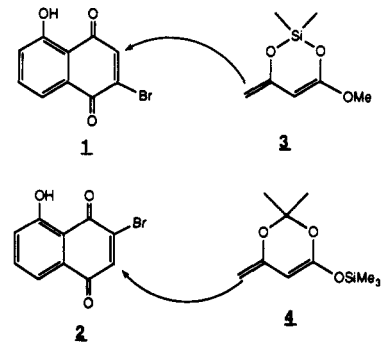
Received March 27, 1990

This work established the idea that a halogen atom, such as bromine, will act as a control element in the regiospecific formation of a new carbon–carbon bond. The addition of the electron-rich end of a transoid diene to a bromojuglone derivative occurred exclusively at the unsubstituted carbon of the quinone. Thus, 2,2-dimethyl-4-methoxy-6-methylene-1,3-dioxa-2-sila-4-cyclohexene (**3**) and either 2- or 3-bromo-5-hydroxy-1,4-naphthoquinone (**1** or **2**) afforded the adducts **19** or **20** in 57% or 71% yield. Similarly, 2,2-dimethyl-6-methylene-4-(trimethylsiloxy)-1,3-diox-4-ene (**4**) and **1** gave **21** in 77% yield.

As part of a program directed toward the synthesis of pyranonaphthoquinones,[1] we report the highly regiospecific synthesis of certain bromonaphthoquinones and the formal oxidative addition of selected electron-rich dienes to 2- and 3-bromo-5-hydroxy-1,4-naphthoquinones, **1** and **2**, respectively. Since these bromojuglone derivatives were readily accessible in high yield,[2] we investigated the possibility that a halogen atom might act as a control element in the regiospecific creation of a new carbon–carbon bond. However, the exclusive addition of the nucleophilic end of an electron-rich diene to the unsubstituted carbon of the bromojuglone was not assured. For the purposes of the synthesis of pyranonaphthoquinones, it was also highly desirable to avoid Diels–Alder adducts, especially with the addition to 3-bromojuglone **2**. In order to circumvent this potential eventuality, we synthesized two electron-rich dienes **3** and **4**, which were locked in a transoid conformation (Scheme I).

Scheme I

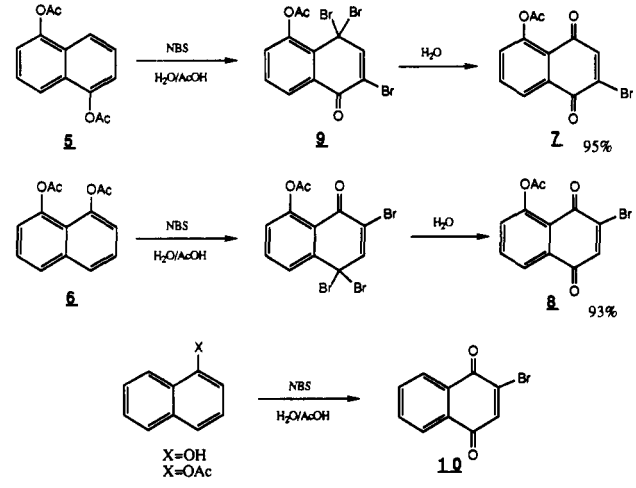


1 **3** **2** **4**

Results

We and others[2,3] have reported the highly regiospecific conversion of 1,5- and 1,8-diacetoxynaphthalene, **5** and **6**, to 2-bromo- and 3-bromo-5-acetoxy-1,4-naphthoquinone, **7** and **8**. When **5** or **6** was allowed to stir at 65 °C for 1 h in the presence of 4 equiv of *N*-bromosuccinimide dissolved in aqueous acetic acid, **7** or **8** was afforded in greater than 90% yield. In each case, one regioisomer was produced without any of the other isomer as shown by HPLC. The reaction proceeded via a tribromonaphthalenone intermediate **9**, which was subsequently hydrolyzed to a bromoquinone. The intermediate **9** has been isolated,[3] characterized, and shown to hydrolyze under the reaction conditions of the bromination of **5** to produce **7** (Scheme II).

Scheme II



5 **9** **7** **6** **8** **10**

The introduction of the bromine atom in the final product was controlled by the relative position of the acetoxy group of the brominated ring since bromination is ortho and para. Thus, 1,6- and 1,7-diacetoxynaphthalene gave 2-bromo-6-acetoxy-1,4-naphthoquinone and 3-bromo-6-acetoxy-1,4-naphthoquinone in 70% and 55%, respectively. Furthermore, when 2-ethyl-1-naphthol was subjected to NBS in aqueous acetic acid, a 90% yield of 2-ethyl-1,4-naphthoquinone was obtained. The lack of halogen in the final product was a result of the ethyl substituent blocking bromination of the ortho position. However, the bromination of 1,4-diacetoxy-2-methylnaphthalene formed 2-bromo-3-methyl-1,4-naphthoquinone in a modest 24% yield.

The bromojuglone acetates **7** and **8** were readily hydrolyzed to the corresponding 5-hydroxy-1,4-naphthoquinones **1** and **2** in high yield with ethanolic aqueous sulfuric acid. The melting points of **1** and **2** were identical with values reported previously.[4]

Given the ready accessibility of **1** and **2**, it was feasible to consider these compounds as potential intermediates for the synthesis of pyranonaphthoquinones. In order to introduce the four-carbon unit containing the carboxyl moiety, we opted to investigate the addition of electron-rich dienes to **1** and **2**. The synthesis of pyranonaphthoquinones from juglone derivatives requires regiospecific carbon–carbon bond formation. Thus, it is essential that the bromine atom function as a regiochemical control el-

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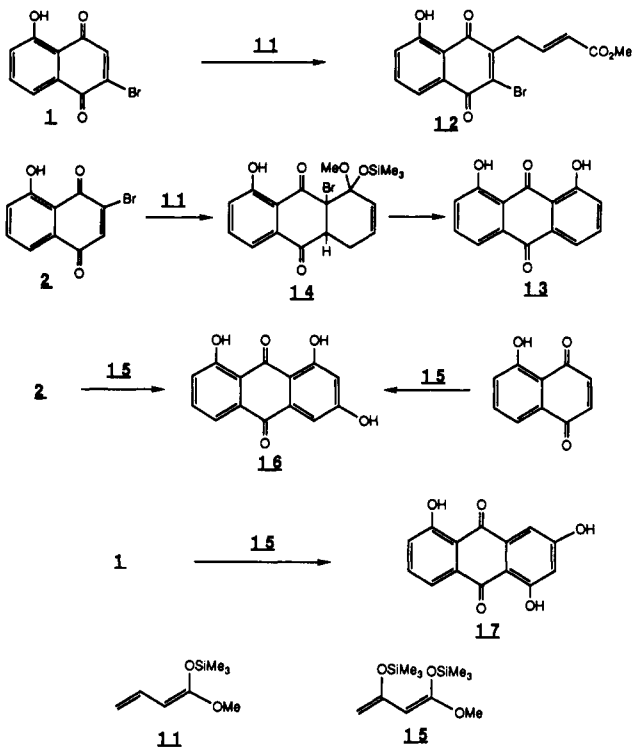
Scheme III



ement directing carbon–carbon bond formation.

It was not at all obvious which carbon, C-2 or C-3, of a bromojuglone will be preferentially attacked by a nucleophilic diene. The nucleophilic end of the electron-rich dienes was known to add preferentially to the C-2 position in juglone as inferred from the structure of a number of Diels–Alder reaction products derived from juglone. Ab initio calculations[5] at the STO-3G level performed for juglone shows a coefficient for the LUMO at the C-2 position to be only slightly greater than the C-3 position. We performed MINDO calculations on **1** and **2** and found the carbon not substituted with bromine to have a larger coefficient than the substituted carbon in the LUMO. Nevertheless, the difference in the absolute value of the numbers is so small as to be as meaningless as the STO-3G results for juglone in terms of predicting the site of nucleophilic attack. However, there was precedent in the literature for nucleophilic attack at the unsubstituted carbon of **2** as shown by Kishi.[6]

Juglone proved unreactive toward the dienes **3**, **4**, and **11**. Thus we turned to bromojuglone derivatives because these compounds are better oxidizing agents (more electron deficient) than juglone and should be more reactive toward the dienes.

The addition of the diene **11** to **1** was carried out at −78 °C in THF for 6 h followed by the addition of 6 N hydrochloric acid at −78 °C. Upon flash chromatography of the residue isolated from the reaction mixture, a 70% yield of the adduct **12** was obtained (Scheme III). The NMR data did not allow one to distinguish between the structure shown for **12** and a structure in which the double bond was conjugated to the naphthoquinone ring. Hence, the final structure for **12** was determined by X-ray crystallography.

The result of this reaction showed that bromine would exert a powerful directing effect for nucleophilic attack by steering the diene to the unsubstituted carbon of the quinone, despite the directing effect of the 5-hydroxy group. However, when the quinone **2** was allowed to react with **11**, instead of oxidative addition, only the Diels–Alder product **13** was observed (61% yield). The reaction and product isolation were conducted under the same conditions of time, temperature, and solvent as for the addition of **11** to **1**. In view of this undesirable Diels–Alder reaction, we sought a way to foil it by locking the diene in a *transoid* conformation. Thus, we synthesized the dienes **3** and **4**.

The ultimate formation of the anthraquinone **13** suggests the structure for the initial Diels–Alder product was **14**. No attempt was made to observe **14** directly but presumably under our reaction conditions **14** did not ring open in a fashion analogous to the Diels-Alder adduct proposed by Kraus[7,8] as an intermediate in the formal oxidative addition of a diene similar to **11** to a 3-acyljuglone. However, our reaction conditions do not mimic Kraus's. Specifically, we did not use fluoride ion to decompose the silylated adduct. In view of our success with **3** and **4** in formal oxidative addition reactions (vide infra), it is quite clear that a Diels–Alder adduct is not necessarily a precursor for the oxidative addition of dienes to bromojuglone derivatives.

The ready accessibility of the diene **15**, which was easily prepared from methyl acetoacetate in two steps,[9] allowed us to investigate the reactions of **15** with **1**, **2**, and juglone. Thus, juglone and **2** gave the same Diels–Alder adduct **16** in 69% and 73% yield, respectively, while **1** and **15** gave the opposite regioisomer **17** in 69% yield.[10] These reactions confirm the notion that the nucleophilic end of an electron-rich diene will add to the unsubstituted carbon. Once again, no formal oxidative addition was observed.

The syntheses of the dienes **3**, **4**, **11**, and **15** are convenient, but not always straight forward. All dienes require LDA to remove a proton (in one case two protons) from the precursor dissolved in THF at −78 °C. The dienes **3**, **11**, and **15** also require HMPA as a cosolvent to prevent conjugate addition of LDA in the case of **11** and to prevent C-silation in all cases except **4**. With **4**, HMPA appears to be unnecessary to circumvent the previously mentioned problem. By far, diene **4** is the easiest to prepare and is the most stable. For example, **3** rearranged to the C-silated isomer **18** on standing several days in the refrigerator (Scheme IV). However, this problem was alleviated by storing **3** as a solid in the freezing compartment.

When **3** was added to **1** or **2** dissolved in THF at −78 °C for several hours followed by the addition of 6 N HCl also at −78 °C and liquid chromatography, the adducts **19** and **20** were afforded in 57% and 71% yield, respectively. Under similar conditions **1** or **10** and **4** gave **21** or **22** in 77% or 72% yield.

In order to avoid the extra step involved in making the trimethylsilyl ether **4**, the addition of the dienolate anion[11] **23** to **1** and **10** gave **21** and **22** in 68% and 59%, respectively. These yields are generally lower than the yields obtained for the addition of silyl ether diene **4**. When the dianion **24** was added to **1**, the product **25** was clearly derived from the addition of the middle carbon to the anion of **1**. The anion was formed by proton transfer from **1** to the terminal carbon of the dianion.

In summary, the formal oxidative addition of the transoid dienes to **2** afforded products, particularly **20**, which

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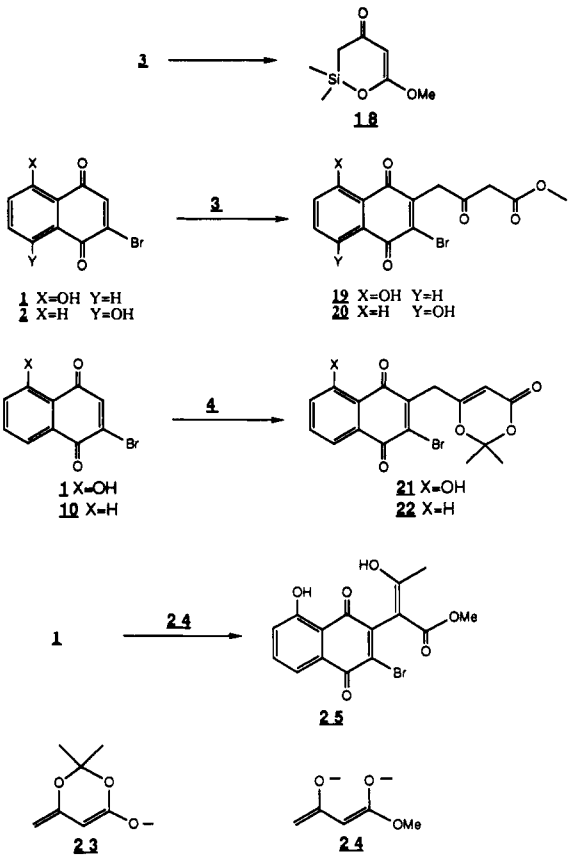
Scheme IV



we are currently attempting to convert to pyranonaphthoquinones.

Experimental Section

General. All melting points and boiling points are uncorrected. Unless otherwise specified, all nuclear magnetic resonance spectra were recorded with a Bruker WH-90 spectrometer using $CDCl_3$ as a solvent. All chemical shifts are reported in parts per million downfield from internal tetramethylsilane; coupling constants (J) are given in hertz. Infrared spectra were determined on a Bio-Rad FJS-7. Mass spectra were recorded on a Hewlett-Packard Model 5993 at an ionization voltage of 70 eV. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. Tetrahydrofuran and diisopropylamine were distilled under nitrogen from CaH_2 and BaO, respectively. All other reagents were obtained from Aldrich Chemical Company.

General Procedure for Synthesizing Bromonaphthoquinones. A warm solution of substrate (10 mmol) dissolved in acetic acid (100 mL) was added over a period of 20 min, with stirring, to a solution of NBS (7.2 g, 40 mmol) dissolved in acetic acid (100 mL) and water (200 mL). The solution of NBS was heated to 65 °C prior to the addition of the substrate and kept at 65 °C during the addition. The reaction mixture was stirred at 65 °C for 45 min following the addition and then poured into water (200 mL). The aqueous suspension was extracted with chloroform (4 × 50 mL). The combined extracts were washed with water (4 × 200 mL) and dried over $MgSO_4$, and the solvent was evaporated to give the quinone.

2-Bromo-5-acetoxy-1,4-naphthoquinone (7). Following the general procedure, the reaction between 1,5-diacetoxynaphthalene (5) (2.4 g, 10 mmol) and NBS (7.2 g, 40 mmol) afforded 7 as a yellow solid (2.8 g, 95%); the ^1H NMR spectrum of the product before recrystallization from ethanol was identical with the spectrum of the recrystallized bromoquinone 7: mp 155–156 °C (lit.[4] mp 158 °C); IR 1790, 1690, 1680, 1600 cm^{-1}; ^1H NMR 8.11 (dd, J = 7, 1.5, 1 H), 7.73 (t, J = 7, 1 H), 7.35 (dd, J = 7, 1.5, 1 H), 7.27 (s, 1 H), 2.45 (s, 3 H); ^{13}C NMR 180.9 (s), 177.5 (s), 169.2 (s), 149.9 (s), 141.5 (d), 138.5 (s), 134.9 (d), 132.7 (s), 130.4 (d), 126.4 (d), 123.3 (s), 20.9 (q).

3-Bromo-5-acetoxy-1,4-naphthoquinone (8). Following the general procedure, the reaction between 1,8-diacetoxynaphthalene (6) (2.4 g, 10 mmol) and NBS (7.2 g, 40 mmol) afforded 8 as a yellow solid (2.7 g, 93%); the ^1H NMR spectrum of the product before recrystallization from ethyl acetate was identical with the spectrum of recrystallized bromoquinone 8: mp 149–150 °C (lit.[4] mp 151.5 °C); IR 1770, 1675, 1660, 1595 cm^{-1}; ^1H NMR 8.01 (dd, J = 8, 1.5, 1 H), 7.75 (t, J = 8, 1 H), 7.53 (s, 1 H), 7.42 (dd, J = 8, 1.5, 1 H), 2.45 (s, 3 H); ^{13}C NMR 181.6 (s), 176.3 (s), 169.3 (s), 150.9 (s), 141.2 (s), 139.5 (d), 135.7 (d), 133.9 (s), 130.3 (d), 125.4 (d), 122.9 (s), 20.9 (q).

2-Bromo-6-acetoxy-1,4-naphthoquinone. Following the general procedure, the reaction between 1,6-diacetoxynaphthalene (2.4 g, 10 mmol) and NBS (7.2 g, 40 mmol) afforded the bromoquinone which upon recrystallization from acetone gave a yellow solid (2.0 g, 70%): mp 152–153 °C; IR 1751, 1677, 1657, 1592 cm^{-1}; ^1H NMR 8.59–7.81 (m, 4 H), 2.47 (s, 3 H). Anal. Calcd for $C_{12}H_7O_4Br$: C, 48.84; H, 2.40. Found: C, 48.76; H, 2.46.

3-Bromo-6-acetoxy-1,4-naphthoquinone. Following the general procedure, the reaction between 1,7-diacetoxynaphthalene (2.4 g, 10 mmol) and NBS (7.2 g, 40 mmol) afforded the bromoquinone which upon recrystallization from ethyl acetate gave a yellow solid (1.6 g, 55%): mp 134–136 °C; IR 1770, 1690, 1670, 1605 cm^{-1}; ^1H NMR 8.13–7.40 (m, 4 H), 2.33 (s, 3 H). Anal. Calcd for $C_{12}H_7O_4Br$: C, 48.84; H, 2.40. Found: C, 48.61; H, 2.46.

2-Ethyl-1,4-naphthoquinone. Following the general procedure, the reaction between 2-ethyl-1-hydroxynaphthalene (0.5 g, 3 mmol) and NBS (2.1 g, 12 mmol) yielded 2-ethyl-1,4-naphthoquinone (0.5 g, 90%); the ^1H NMR spectrum of the product before recrystallization from ethanol was identical with the spectrum of the recrystallized product: mp 83–84 °C (lit.[12] mp 87 °C); the spectra of the product were identical with the published spectra.

2-Bromo-3-methyl-1,4-naphthoquinone. Following the general procedure, the reaction between 1,4-diacetoxy-2-methyl-1,4-naphthalene (2.6 g, 10 mmol) and NBS (7.2 g, 40 mmol) afforded a yellow solid which upon recrystallization from ethanol gave the bromoquinone (0.6 g, 24%): mp 157–158 °C (lit.[13] mp 156–158 °C); MS m/e 252 (M + 2), 250 (M), 172, 116.

2-Bromo-1,4-naphthoquinone (10). Following the general procedure, the reaction between 1-hydroxynaphthalene (2.9 g, 20 mmol) (purified by vacuum distillation) and NBS (14.2 g, 80 mmol) yielded 10 as a yellow solid after recrystallization from ethanol (4.0 g, 84%): mp 131–132 °C (lit.[14] mp 132 °C); IR 1680, 1665, 1600, 1575 cm^{-1}; ^1H NMR 8.30–7.95 (m, 2 H), 7.81–7.63 (m, 2 H), 7.45 (s, 1 H). Note: It is important that the solution of naphthol be added slowly. Fast addition gave a brown precipitate.

2-Bromo-5-hydroxy-1,4-naphthoquinone (1). The bromoquinone 7 (9.0 g, 30 mmol) was refluxed, with stirring, for 90 min in a solution of ethanol (360 mL), water (90 mL), and concentrated sulfuric acid (18 mL). Then most of the ethanol was evaporated under reduced pressure. The brown precipitate was collected by suction filtration yielding 1 (7.0 g, 92%); the ^1H NMR spectrum of the product before recrystallization from acetone was identical with the spectrum of recrystallized 1: mp 135–136 °C (lit.[4] mp 136 °C); IR 1680, 1640, 1590 cm^{-1}; ^1H NMR 11.53 (s, 1 H), 7.80–7.69 (m, 2 H), 7.58 (s, 1 H), 7.43–7.27 (m, 1 H); ^{13}C NMR 187.5 (s), 176.0 (s), 161.8 (s), 140.9 (s), 140.3 (d), 136.5 (d), 130.8 (s), 125.2 (d), 120.9 (d), 114.7 (s).

3-Bromo-5-hydroxy-1,4-naphthoquinone (2). Following the procedure for synthesizing 1, bromoquinone 8 (1.3 g, 4.4 mmol) was hydrolyzed in a refluxing solution of ethanol (52 mL), water (18 mL), and concentrated sulfuric acid (2 mL) to yield 2 as a brown solid (1.0 g, 90%); the ^1H NMR spectrum of the product before recrystallization from acetone was identical with the spectrum of recrystallized 2: mp 170–172 °C (lit.[4] mp 172 °C); ^1H NMR 11.70 (s, 1 H), 7.81–7.60 (m, 2 H), 7.50 (s, 1 H), 7.42–7.22 (m, 1 H); ^{13}C NMR 183.1 (s), 181.7 (s), 162.2 (s), 142.4 (s), 141.5

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(d), 137.3 (d), 131.9 (s), 124.6 (d), 119.8 (d), 114.2 (s).

2,2-Dimethyl-4-methoxy-6-methylene-1,3-dioxa-2-sila-4-cyclohexene (3). In a 500-mL 3-necked round-bottom flask were placed THF (100 mL) and diisopropylamine (25.2 mL, 180 mmol) under nitrogen, cooled to −78 °C, and maintained throughout the reaction. Added dropwise to this solution were 72 mL of 2.5 M *n*-butyllithium (180 mmol). The reaction mixture was allowed to stir for 15 min. HMPA (32 mL, 184 mmol) was added to the solution and allowed to stir for 10 min. Methyl acetoacetate (9.3 mL, 86 mmol) was added via syringe dropwise and stirred for 20 min. Dichlorodimethylsilane (10.9 mL, 90 mmol) was added to above mixture during which the solution turned a deep red color. After an additional 20 min, the solution was allowed to warm to room temperature and the solvent was removed under reduced pressure. The residue was distilled at 0.1 mm and collected between 54 and 60 °C (54%): ^{1}H NMR 4.50 (1 H, s), 4.02 (1 H, s), 3.89 (1 H, s), 3.64 (3 H, s), 0.37 (6 H, s); ^{13}C NMR 156.7 (s), 152.0 (s), 86.4 (t), 74.7 (d), 54.7 (q), 1.9 (q). Anal. Calcd for $C_7H_{12}O_3Si$: C, 48.81; H, 7.02. Found: C, 48.98; H, 7.46.

2,2-Dimethyl-6-methylene-4-(trimethylsiloxy)-1,3-diox-4-ene (4). In a 250-mL 3-necked round-bottom flask were placed THF (75 mL) and diisopropylamine (10.5 mL, 75 mmol) under nitrogen. The solution was cooled to −78 °C, and maintained at that temperature throughout the reaction. Added dropwise to this solution were 30 mL of 2.5 M *n*-butyllithium (75 mmol). The solution was allowed to stir for 20 min. 2,2,6-Trimethyl-1,3-dioxen-4-one (9.2 mL, 70 mmol) was added dropwise and allowed to stir for 45 min. Trimethylsilyl chloride (9.3 mL, 73 mmol) was added to the resulting solution, which was allowed to stir for 40 min. The reaction mixture was permitted to warm to room temperature, and the solvent was removed under reduced pressure. The residue was distilled at 0.1 mm and collected between 30 and 38 °C (9.3 g, 62%): ^{1}H NMR 4.75 (1 H, s), 4.16 (1 H, s), 3.96 (1 H, s), 1.52 (6 H, s), 0.30 (9 H, s); ^{13}C NMR 158.1, 150.9, 95.2, 92.4, 79.1, 20.1, 0.5. Anal. Calcd for $C_{10}H_{18}O_3Si$: C, 56.03; H, 8.46. Found: C, 56.02; H, 8.39.

1-Methoxy-1-(trimethylsiloxy)-1,3-butadiene (11). In a 250-mL 3-necked round-bottom flask were placed THF (75 mL) and diisopropylamine (14 mL, 100 mmol) under nitrogen. The solution was cooled to −78 °C and maintained at that temperature throughout the reaction. Added dropwise to this solution were 40 mL of 2.5 M *n*-butyllithium (100 mmol). The reaction mixture was allowed to stir for 15 min. HMPA (21 mL, 120 mmol) was added to the solution, which was allowed to stir for 10 min. Methyl crotonate (10.6 mL, 100 mmol) was added via syringe dropwise. The resulting solution was stirred for 30 min. Trimethylsilyl chloride (20 mL, 157 mmol) was added to the reaction mixture with additional stirring for 20 min. The reaction mixture was allowed to warm to room temperature and stirred for an additional 2 h. The solvent was removed under reduced pressure, and the residue was diluted with 250 mL of pentane and filtered to remove LiCl salts. The filtrate was washed with water (3 × 70 mL) and dried over $MgSO_4$. Pentane was removed under reduced pressure, and the residue was distilled at 24 mm and collected between 83 and 89 °C (7.2 g, 42%): ^{1}H NMR 6.49 (1 H, dt, J = 10, 18), 4.80 (1 H, dd, J = 2, 18), 4.58 (1 H, dd, J = 2.10), 4.47 (1 H, d, J = 10), 3.58 (3 H, s), 0.21 (9 H, s): ^{13}C NMR 158.7 (s), 132.5 (d), 106.9 (t), 80.7 (d), 54.8 (q), 0.3 (m); MS *m/e* 172, 157, 141, 89, 73.

4-(2-Bromo-5-hydroxy-1,4-dioxonaphth-3-yl)-*trans*-2-butenoate, Methyl Ester (12). Naphthoquinone 1 (1.0 g, 4 mmol) was dissolved in THF (75 mL) and placed under nitrogen at −78 °C. The diene 11 (2.1 g, 12 mmol) was added via syringe dropwise, and the mixture was allowed to stir for 6 h. To effect desilylation, 6 N HCl (10 mL) was added to the solution at −78 °C, at which point the solution was exposed to air and allowed to warm slowly to room temperature with stirring for 2 h. The solvent was removed under reduced pressure and then diluted with dichloromethane (100 mL). The solution was washed with water (3 × 30 mL), and the filtrate was dried over $MgSO_4$. The solvent was removed under reduced pressure. Flash chromatography (hexane–ethyl acetate, 10:1) afforded 0.98 g (70%) of **12**: 112–114 °C; ^{1}H NMR 11.85 (1 H, s), 7.78–7.27 (3 H, m), 7.03–6.78 (1 H, m), 6.01 (1 H, d, J = 15), 3.79–3.61 (5 H, m); ^{13}C NMR 186.3 (s), 176.8 (s), 166.4 (s), 162.2 (s), 147.2 (s), 141.5 (s), 141.1 (d), 131.2 (s), 136.7 (d), 125.2 (d), 124.3 (d), 120.9 (d), 114.4 (s), 51.6 (q), 33.3 (t); IR 1721, 1675, 1638, 1591 cm^{-1}. Anal. Calcd for $C_{15}H_{11}O_5Br$: C, 51.30; H, 3.16; Br, 22.76. Found: C, 51.40; H, 3.16; Br, 22.69.

X-ray Crystallography. A clear orange-red crystal of **12** which gave sharp optical extinction under crossed polarizers was selected from a batch crystallized from ethanol. Unit cell dimensions and an orientation matrix for data collection were determined from 25 centered reflections using Mo Kα radiation, λ = 0.71069 Å, on an Enraf-Nonius CAD-4 X-ray diffractometer at 293 ± 1 K. Crystal data: $C_{15}H_{11}O_5Br$, MW = 351.2 g/mol, triclinic, space group $P\bar{1}$, a = 5.428 (1) Å, b = 10.991 (2) Å, c = 11.862 (2) Å, α = 74.81 (1)°, β = 79.94 (2)°, γ = 85.81 (2)°, Z = 2, ρ = 1.73 g/cm^3. Total number of unique reflections measured out to sin θ/λ = 0.5947 Å^{-1} was 2368. Of these, 1857 had $F_o > \sigma(F_o)$ and were used in the structure solution and refinement. Empirical absorption corrections from ψ scans were applied. The structure was solved using a combination of direct and difference Fourier methods and refined by a full-matrix least-squares procedure using established programs.[15] Hydrogen atom parameters were not refined. Anisotropic refinement (on F) of all nonhydrogen atoms (190 variable parameters) converged to R = 0.053, R_w = 0.043 and GOF = 1.13. Maximum shift/esd for any parameter in the final least-squares refinement was 0.01. A final difference Fourier synthesis showed no significant residual electron density.

1,8-Dihydroxy-9,10-anthraquinone (13). Naphthoquinone 2 was subjected to the same experimental procedure as described for **12**. This afforded **13** (0.59 g, 61%): mp 190–191 °C; ^{1}H NMR 11.81 (1 H, s), 7.92–7.60 (2 H, m), 7.41–7.22 (1 H, m) (lit.[10] mp 190–192 °C); ^{1}H NMR 11.92 (1 H, s), 7.73 (2 H, m), 7.30 (1 H, m).

1,3,8-Trihydroxy-9,10-anthraquinone (16). In a 100-mL round-bottom flask 2 (1.0 g, 4 mmol) was dissolved in THF (50 mL), placed under nitrogen, and cooled to −78 °C. The diene **15** (2.1 g, 8 mmol) was added and stirred for 1 h. To effect desilylation 6 N HCl (10 mL) was added and stirred for 1 h. Most of the solvent was removed under reduced pressure and then diluted with chloroform (125 mL). The solution was washed with water (2 × 30 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure. Flash chromatography (hexane–ethyl acetate, 10:1) afforded **16** (0.75 g, 73%): mp 285 °C dec; ^{1}H NMR 11.74 (1 H, s), 11.68 (2 H, s), 7.95–7.59 (3 H, m), 7.43 (1, H, d, J = 2.5), 7.20 (1 H, d, J = 1.5) (lit.[10] mp 287 °C dec; ^{1}H NMR 11.96 (2 H, s), 7.90–7.20 (3 H, m), 7.09 (1 H, d, J = 2), 6.55 (1 H, d, J = 2).

1,3,5-Trihydroxy-9,10-anthraquinone (17). Naphthoquinone 1 was subjected to the same procedure and workup as described for **16**, affording **17** (0.71 g, 69%): mp 320 °C; ^{1}H NMR (CD_3–OD) 7.78–7.25 (3 H, m), 6.98 (1 H, J = 1.5), 6.65 (1 H, d, J = 2) (lit.[10] mp 320–322 °C dec); ^{1}H NMR 12.64 (1 H, s), 12.28 (1 H, s), 7.90–7.17 (3 H, m), 7.06 (1 H,d, J = 2), 6.52 (1 H, d, J = 2).

2-Bromo-3-(2,4-dioxo-4-methoxybutyl)-5-hydroxy-1,4-naphthoquinone (19). In a 250-mL 2-necked round-bottom flask, naphthoquinone 1 (1.0 g, 4 mmol) was dissolved in THF (75 mL), placed under nitrogen, and cooled to −78 °C. The diene **3** (2.1 g, 12 mmol) was added via syringe and allowed to stir for 5 h. To effect desilylation, 6 N HCl (10 mL) was added to −78 °C. The reaction mixture was stirred for 1 h while allowing the solution to warm to room temperature. The solvent was removed under reduced pressure, and the residue was diluted with dichloromethane (125 mL). The solution was washed with water (3 × 50 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure. Flash chromatography (hexane–ethyl acetate, 10:1) afforded **19** (0.84 g, 57%): mp 141 °C; ^{1}H NMR 11.70 (1 H, s), 7.71–7.20 (3 H, m), 4.20 (2 H, s), 3.80 (3 H, s), 3.68 (2 H, s); IR 1750, 1704, 1680, 1669 cm^{-1}; ^{13}C 196.7 (s), 186.2 (s), 176.3 (s), 167.1 (s), 164.8 (s), 144.2 (s), 142.2 (s), 136.4 (d), 134.1 (s), 125.0 (d), 121.1 (d), 114.2 (s), 52.1 (q), 49.5 (t), 44.5 (t). Anal. Calcd for $C_{15}H_{11}O_6Br$: C, 49.07; H, 3.02; Br, 21.76. Found: C, 49.20; H, 3.08; Br, 21.54.

3-Bromo-2-(2,4-dioxo-4-methoxybutyl)-5-hydroxy-1,4-naphthoquinone (20). Naphthoquinone 2 was subjected to the same experimental procedure as described for **19**. Flash chromatography (hexane–acetone, 5:1) afforded **20** (1.0 g, 71%): mp 130 °C; IR 1748, 1703, 1679, 1667 cm^{-1}; ^{1}H NMR 11.66 (1 H, s), 7.60–7.54 (2 H, m), 7.20–7.17 (1 H, m), 4.10 (2 H, s), 3.72 (3 H, s), 3.60 (2 H, s); ^{13}C NMR 201.6 (s), 171.6 (s), 167.3 (s), 153.1 (s), 150.5 (s), 144.9 (s), 144.0 (s), 140.9 (d), 134.9 (s), 128.3 (d), 123.9

(d), 111.8 (s), 54.1 (q), 50.77 (t), 46.6 (t). Anal. Calcd for $C_{15}H_{11}O_6Br$: C, 49.07; H, 3.02; Br, 21.76. Found: C, 49.35; H, 3.14; Br, 22.27.

2,2-Dimethyl-6-[(2-bromo-5-hydroxy-1,4-dioxonaphth-3-yl)methyl]-1,3-dioxen-4-one (21). Method A. In a 250-mL 3-necked round-bottom flask, naphthoquinone **1** (1.0 g, 4 mmol) was dissolved in THF (75 mL), placed under nitrogen, and cooled to −78 °C. The diene **4** (2.6 g, 12 mmol) was added via syringe, and the reaction mixture was allowed to stir for 12 h. To effect desilylation, 6 N HCl (10 mL) was added at −78 °C and stirred for 2 h while allowing the solution to warm to room temperature. The solvent was removed under reduced pressure, and the residue was diluted with dichloromethane (125 mL). The solution was washed with water (3 × 50 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure. Flash chromatography (hexane–acetone, 5:1) afforded **21** (1.2 g, 77%) **Method B.** In a 250-mL round-bottom flask were placed THF (50 mL) and diisopropylamine (1.7 mL, 12 mmol) under nitrogen. The solution was cooled to −78 °C, and maintained at that temperature throughout the reaction. Added dropwise to this solution was 4.75 mL of *n*-butyllithium (12 mmol). The solution was allowed to stir for 10 min. 2,2,6-Trimethyl-1,3-dioxen-4-one (1.6 mL, 12 mmol) was added via syringe, and the solution was allowed to stir for 1 h. Naphthoquinone **1** (1.0 g, 4 mmol) dissolved in THF (40 mL) was added slowly through a dropping funnel. The reaction mixture was allowed to stir for 4 h and was treated with 6 N HCl (15 mL) at −78 °C followed by stirring for 2 h while allowing the solution to warm to room temperature. The reaction was subjected to the same procedure as described in method A, affording **21** (1.0 g, 68%): mp 115 °C; ^1H NMR 11.77 (1 H, s), 7.74–7.38 (3 H, m), 5.30 (1 H, s), 3.86 (2 H, s), 1.69 (6 H, s); IR 1710, 1690, 1640, 1580 cm^{-1}; ^{13}C NMR 185.3, 176.4, 171.5, 165.2, 158.1, 144.0, 141.9, 137.2, 135.0, 125.2, 121.7, 114.3, 98.2, 92.5, 47.8, 19.1. Anal. Calcd for $C_{17}H_{13}O_6Br$: C, 51.93; H, 3.33; Br, 20.32. Found: C, 51.45; H, 3.54; Br, 20.01.

2-Bromo-5-hydroxy-3-[2-hydroxy-1-(methoxycarbonyl)-1-propenyl]-1,4-naphthoquinone (25). In a 250-mL 3-necked round-bottom flask were placed THF (30 mL) and NaH (0.6 g, 10 mmol) under nitrogen. The solution was cooled to −78 °C and maintained at that temperature throughout the reaction. Methyl acetoacetate (1.1 mL, 10 mmol) was added via syringe, and resulting solution was allowed to stir for 10 min. Added dropwise to this solution was 4.2 mL of *n*-butyllithium (11 mmol), and the mixture was allowed to stir for 10 min. Naphthoquinone **1** (2.0 g, 8 mmol) dissolved in THF (50 mL) was added via a dropping funnel, and the reaction mixture was allowed to stir for 30 min. The solution was permitted to warm to room temperature and stirred for an additional 15 min. The mixture was cooled to −78 °C and 6 N HCl (7 mL) was added and stirred for 5 min. The reaction mixture was allowed to warm to room temperature, and the solvent was removed under reduced pressure. The residue was diluted with dichloromethane (125 mL), washed with water (2 × 50 mL), and dried over $MgSO_4$. Flash chromatography (hexane–ethyl acetate, 10:1) afforded **25** (2.6 g, 88%): mp 134–135 °C; IR 1678, 1656, 1636 cm^{-1}; ^1H NMR 13.06 (1 H, s), 11.93 (1 H, s), 7.76–7.27 (3 H, m), 3.72 (3 H, s), 1.93 (3 H, s); ^{13}C NMR 186.5 (s), 175.3 (s), 170.1 (s), 162.1 (s), 145.7 (s), 143.7 (s), 140.1 (s), 136.6 (d), 129.0 (s), 125.1 (d), 120.8 (d), 118.5 (s), 98.3 (s), 52.2 (q), 20.1 (q). Anal. Calcd for $C_{15}H_{11}O_6Br$: C, 49.07; H, 3.02; Br, 21.76. Found: C, 48.91; H, 3.15; Br, 21.65.

Acknowledgment. We are grateful to the National Science Foundation for a Grant (CHE-8418897) (A.K.) used to purchase the CAD-4 X-ray diffractometer system.

Registry No. **1**, 69008-03-3; **2**, 52431-65-9; **3**, 130573-42-1; **4**, 130573-43-2; **5**, 605-89-0; **6**, 6566-25-2; **7**, 77189-69-6; **8**, 77197-58-1; **10**, 2065-37-4; **11**, 110362-29-3; **12**, 130573-44-3; **13**, 117-10-2; **15**, 74590-73-1; **16**, 52431-74-0; **17**, 52431-73-9; **18**, 130573-45-4; **19**, 130573-46-5; **20**, 130573-47-6; **21**, 130573-48-7; **25**, 130573-49-8; $MeCOCH_2CO_2Me$, 105-45-3; Cl_2SiMe_2, 75-78-5; MeCH/dbdCHCO$_2$Me, 18707-60-3; 1,6-diacetoxynaphthalene, 59335-81-8; 2-bromo-6-acetoxy-1,4-naphthoquinone, 130573-50-1; 1,7-diacetoxynaphthalene, 51850-49-8; 3-bromo-6-acetoxy-1,4-naphthoquinone, 130573-51-2; 2-ethyl-1-hydroxynaphthalene, 30159-69-4; 2-ethyl-1,4-naphoquinone, 5409-32-5; 1,4-diacetoxy-2-methylnaphthalene, 573-20-6; 2-bromo-3-methyl-1,4-naphthoquinone, 3129-39-3; 1-hydroxynaphthalene, 90-15-3; 2,2,6-trimethyl-1,3-dioxen-4-one, 5394-63-8.

Supplementary Material Available: Tables of final atomic fractional coordinates, anisotropic displacement parameters, and selected bond distances and angles and an ORTEP diagram for **12** (4 pages); observed and calculated structure factors (9 pages). Ordering information is given on any current masthead page.

Radical Cyclization of *N*-(Cyclohex-2-enyl)-α,α-dichloroacetamides. Stereoselective Syntheses of (±)-Mesembranol and (±)-Elwesine

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Received March 28, 1990 (Revised Manuscript Received July 17, 1990)

Stereoselective syntheses of the *Sceletium* alkaloid (±)-mesembranol (**2**) and the *Amaryllidaceae* alkaloid (±)-elwesine (**3**) have been achieved. A key step in the syntheses involves the Bu_3SnH-mediated radical cyclization of the dichloroacetamides **34** and **46**, which provides the *cis*-3a-aryloctahydroindolones **36** and **47**, respectively. The amides **34** and **46** were prepared in a highly stereocontrolled manner from the corresponding 1-arylcyclohexenes **29** and **41** along the lines: **29** → **30a** → **31** → **32** → **33** → **34** and **41** → **42a** → **44a** → **45a** → **46**. Transformation of **36** into (±)-mesembranol was readily accomplished by reduction with diborane and subsequent removal of the *O*-benzyl protecting group by hydrogenolysis over Pd/C. On the other hand, debenzylation of **36** with Raney Ni afforded a mixture of the 6α- and 6β-alcohols **39a** and **39b**, which was then reduced by alane to give a separable mixture of (±)-mesembranol and (±)-6-epimesembranol (**40**). Reduction of **47** with diborane followed by catalytic hydrogenolysis over Pd/C afforded the amino alcohol **50**, which has already been converted into (±)-elwesine by Pictet–Spengler cyclization.

Sceletium alkaloids such as mesembrine (**1**) and mesembranol (**2**), which possess a *cis*-3a-arylhydroindole nucleus as the basic structural element, have remained attractive target molecules for total synthesis.[1] This may

0022-3263/91/1956-0095$02.50/0