# A Powerful *o*-Quinone Dimethide Strategy for Intermolecular Diels−Alder Cycloadditions

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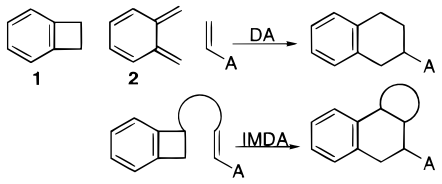
**Abstract:** Conrotatory thermal fragmentation of *trans*-1,2-disilyloxybenzocyclobutenes generates *o*-quinone dimethides at remarkably low temperatures. Smooth stereoselective Diels−Alder cycloaddition with a range of dienophiles provides hydronaphthalene derivatives in excellent yield. Direct oxidative desilylation of the adducts affords the corresponding naphthoquinones. Substitution of the benzene nucleus with an electron-releasing methoxyl group directs the cycloaddition to give good control of regioselectivity in the expected direction. A short synthesis of the aglycon of the anticancer antibiotic idarubicin is presented.

The influence of the Diels−Alder reaction in classical and contemporary organic synthesis can hardly be overstated.[1] For many years, our laboratory has been interested in highly functionalized dienes, capable of imparting to their cycloaddition products functionality implements, which would facilitate progression to complex targets.[2] An already well recognized opportunity in this regard is represented by *o*-quinone dimethides of the type **2** (Scheme 1).[3] Cycloaddition of **2** with dienophiles creates tetrahydro- or dihydronaphthalenes. Novel sequences based on 1,4-elimination of complementary bis(benzyl) substituents,[4] cheleotropic eliminations,[5] or photoenolizations[6] have been used to generate *o*-quinone dimethides. However, the most widely practiced method for reaching **2** has been via fragmentation of benzocyclobutenes (cf. **1**).[7]

While there certainly are ample instances of intermolecular Diels−Alder (DA) reactions based on the use of type **1** systems as precursors of type **2** dienes,[8] the bulk of the important teachings in this regard arise from intramolecular Diels−Alder (IMDA) reactions of **1**, generated from analogues of **2** bearing a pendant site of dienophilicity. We note that the widely practiced IMDA reactions of **2** have been directed to the synthesis of constellations associated with hydrophenanthroid targets (cf. steroids, diterpenes, alkaloids).[9]

**Scheme 1**




The purposes of our research can be summarized along the following lines. We wished to develop quinodimethide precursor types that would give rise to type **2** systems under conditions that are sufficiently general to permit classical intermolecular Diels−Alder reactions with a range of dienophiles. We wanted the type **2** structure, so generated, to be capable of incorporating an oxygen-based functionality at both of its termini (see structure **3,** Scheme 2). Furthermore, we hoped to create protocols such that the benzylic oxygens in adduct **4** could be exploited via oxidation (cf. **5**). To be particularly valuable, the oxidation when needed would have to take clear precedence over elimination reactions leading to aromatization (cf. **6**). For certain targets, protocols for clean elimination would be desirable. Our orienting

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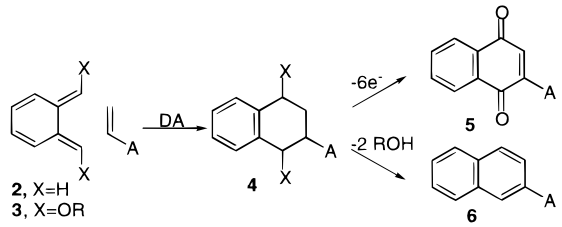
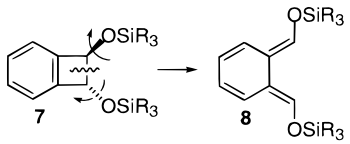
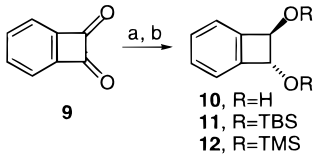
**Scheme 2**




**Scheme 3**




**Scheme 4**[a]



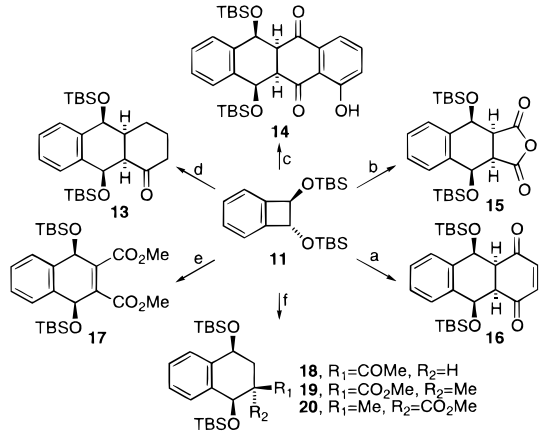

[a] (a) $NaBH_4$, MeOH; (b) TMSCl, HMDS or TBSOTf, $Et_3N$ (50−70%, two steps).

target structures for this opening phase of the inquiry would be anthracycline-based systems of high biological interest.

It seemed that a benzocyclobutene of type **7** (Scheme 3), with two trans-disposed silyloxy functions could be of considerable value in reaching our goals. Following the calculations and chemistry of Houk,[10] we expected the two $\beta$-donating $OSiR_3$ groups to facilitate conrotatory ring opening of the cyclobutene thereby generating the (*E*,*E*)-quinone dimethide (see torquoisomer **8**).[11] Remarkably, while diacyloxy[12] and dimethoxy[13] versions of **3** had been prepared and evaluated, the bis(silyloxy) compounds were unknown. Such compounds were foreseen to have several potential advantages, particularly as regards the projected post-Diels−Alder phase of the sequence.

The known[14] dione **9** (Scheme 4), upon reduction with sodium borohydride in methanol afforded **10** as the major product (trans:

**Scheme 5**[a]




[a] All reactions (90−95%) performed in benzene at 40 °C, 1−2 h with: (a) benzo-1,4-quinone; (b) maleic anhydride; (c) 5-hydroxynaphtho-1,4-quinone; (d) cyclohexen-2-one; (e) dimethylacetylene dicarboxylate; (f) for **18**, methyl vinyl ketone; for **19** and **20**, methyl methacrylate at 50 °C (**19**:**20** = 9:1).

cis = 6:1).[15] Interestingly, the trans diol had not been known. This mixture was silylated, as shown, to generate **11** or **12**. Although *trans*-**11** could be purified, **12** was used as a mixture of trans and nonreactive cis isomers. Reactions of either **11** or **12** were carried out with various potential dienophiles in benzene-$d_6$ or toluene-$d_8$. *Uncatalyzed cycloadditions occurred under remarkably mild conditions.* A particularly impressive case is seen in the formation of **13** (Scheme 5). Although cyclohexen-2-one is a notoriously sluggish dienophile in noncatalyzed Diels−Alder reactions,[16] **13** is formed in near-quantitative yield at 40°!

Given the reasonable assumption that conrotatory opening of **11** produces, torquospecifically,[11] the outside−outside dienes, all cycloadditions would have occurred in a highly endo-selective fashion.[17] In fact, of the group of dienophiles surveyed to date with the diene derived from **11**, the sole exo product we have observed has been **20**, which is the minor product (∼1:9) accompanying **19**.

We next turned to the matter of post-Diels−Alder survival of the adducts and their amenability to oxidative desilylation. For this purpose we utilized the bis(trimethylsilyloxy) system **12** as the *o*-quinone dimethide precursor. Our focus at this stage was on direct oxidation−desilylation, a reaction type earlier described by Jung.[18] While we have not studied the scope of this reaction in detail, we have found that, at least in simple cases, dicyanodichlorobenzoquinone[19] (DDQ) accomplishes direct oxidation smoothly (see products **21**, **22**, and **23**; Scheme 6).

(10) (a) Dolbier, W. R.; Koroniak, H.; Houk, K. N.; Sheu, C. *Acc. Chem. Res.* **1996**, *29*, 471. (b) KirMSe, W.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1984**, *106*, 7989. (c) Niwayama, S.; Kallel, E. A.; Sheu, C.; Houk, K. M. *J. Org. Chem.* **1996**, *61*, 2517. (d) Niwayama, S.; Kallel, E. A.; Spellmeyer, D. C.; Sheu, C.; Houk, K. M. *J. Org. Chem.* **1996**, *61*, 2813.

(11) (a) Rudolf, K.; Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 3708. (b) Houk, K. N.; Spellmeyer, D. C.; Jefford, C. W.; Rimbault, C. G.; Wang, Y.; Miller, R. D. *J. Org. Chem.* **1988**, *53*, 2125. (c) Nakamura, K.; Houk, K. N. *J. Org. Chem.* **1995**, *60*, 686.

(12) *trans*-Diacyloxy-substituted benzocyclobutenes of type **3** give Diels−Alder products with **42** at 80 °C. Elaboration into the naphthoquinone was not possible, and in practice, thermal elimination of the diacetoxy groups gave the corresponding anthracene: (a) Hassall, C. H.; Broadhurst, M. J.; Thomas, G. J. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2239. (b) Broadhurst, M. J.; Hassall, C. H.; Thomas, G. J. *Tetrahedron* **1984**, *40*, 4649.

(13) *trans*-Dimethoxybenzocyclobutenes of type **3** give Diels−Alder products with maleic anhydride: Arnold, B. J.; Sammes, P. G.; Wallace, T. W. *J. Chem. Soc., Perkin Trans. 1* **1974**, 415.

(14) (a) Liebeskind, L. S.; Lescosky, L. J.; McSwain, C. M., Jr. *J. Org. Chem.* **1989**, *54*, 1435. (b) Dürr, H.; Nickels, H. *J. Org. Chem.* **1980**, *45*, 973. (c) Abou-Teim, O.; Goodland, M. C.; McOmie, F. W. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2659. (d) Liebeskind, L. S.; South, M. S. *J. Org. Chem.* **1982**, *47*, 3815. Silyloxy-substituted benzocyclobutenes have also been prepared by Suzuki: (e) Hosoya, T.; Hasegawa, T.; Kuriyama, Y.; Suzuki, K. *Tetrahedron Lett.* **1995**, *36*, 3377. (f) Hosoya, T.; Hasegawa, T.; Kuriyama, Y.; Matsumoto, T.; Suzuki, K. *Synlett* **1995**, 177. (g) Matsumoto, T.; Hamura, T.; Kuriyama, Y.; Suzuki, K. *Tetrahedron Lett.* **1997**, *38*, 8985.

(15) Bis(trimethylsilyloxy) derivatives **11** and **33** were obtained in 4:1−6:1 trans/cis ratios. The bis(*tert*-butyldimethylsilyloxy) derivatives **12** and **27** were obtained in 6:1−9:1 trans/cis ratios. The difference was possibly due to partial decompostion of the trans isomer during preparation of **11** and **33**.

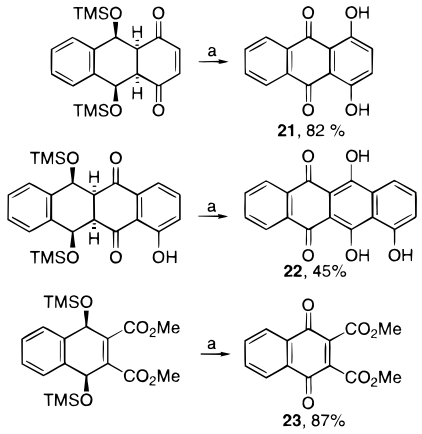
(16) (a) Fringuelli, F.; Taticchi, A.; Wenkert, E. *Org. Prep. Proc. Int.* **1990**, *22*, 131. (b) Bartlett, P. D.; Woods, G. F. *J. Am. Chem. Soc.* **1940**, *62*, 2933. (c) Friguelli, F.; Pizzo, F.; Taticchi, A.; Halls, T. D. J.; Wenkert, E. *J. Org. Chem.* **1982**, *47*, 5057.

(17) Relative configuration of the adducts were determined by 2-D and NOE NMR experiments. All product ratios were determined by integration in the NMR spectra.

(18) Using $TrBF_4$: (a) Jung, M. E. *J. Org. Chem.* **1976**, *41*, 1479. See also: (b) Muzart, J. *Synthesis* **1993**, 11.

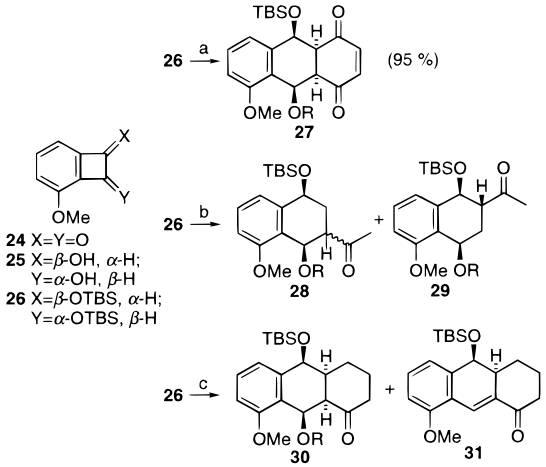
(19) (a) Paterson, I.; Cowden, C. J.; Rahn, V.; Woodrow, M. D. *Synlett* **1998**, 915. (b) Piva, O.; Amougay, A.; Pete, J. *Tetrahedron Lett.* **1991**, *32*, 3993. (c) Jung, M. E.; Pan, Y.-G.; Rathke, M. W.; Sullivan, D. F.; Woodbury, R. P. *J. Org. Chem.* **1977**, *42*, 3961.

**Scheme 6**[a]




[a] (a) DDQ, THF, 22 °C, 12 h.

**Scheme 7**[a]

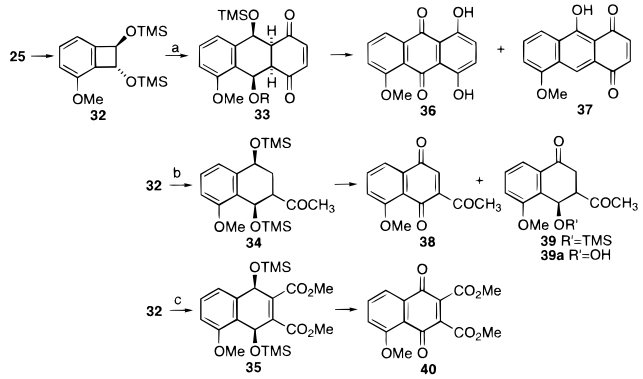



[a] R = TBS; (a) benzo-1,4-quinone, 80 °C, 3 h (95%); (b) methyl vinyl ketone, 120 °C, 4 h (**28**[20]:**29** = 7:1, 95%); (c) cyclohexen-2-one, 120 °C, 24 h (**30**:**31** = 1:6, 70%).

We next probed the adaptability of the reaction to ortho-substituted versions of *trans*-disilyloxybenzocyclobutenes. Of particular interest was the question of the degree of regiochemical control exercised by a "peri" methoxyl group in cycloadditions with biased dienophiles. Reduction of diketone **24** (Scheme 7) as before afforded a mixture of *trans*- (**25**) and *cis*-diols with the former being predominant (∼8:1). Silylation of **25** provided **26**. It was soon found that **26** was much less reactive than the desmethoxyl analogue **11** vis à vis cycloaddition. This large difference presumably reflects the relative facility of cyclobutene fragmentation. It might have been expected that the methoxyl function would stabilize the radicaloid character of the fragmenting bis(silyloxy) $\delta$-bond en route to the quinone dimethide.[10] In retrospect, overall loss of reactivity of **26** relative to **11** may well be a consequence of serious hindrance imposed by the *peri*-methoxyl group to conrotatory opening in the preferred "outside−outside" torquo mode.[11] Thus, it was found that Diels−Alder reaction of **26** with 1,4-benzoquinone required temperatures of ∼80 °C to occur at a reasonable rate. Compound **27** was obtained in 95% yield.

We investigated the case of methyl vinyl ketone to probe issues of regiochemistry in *o*-quinone dimethides where the perturbing element is in the "benzo" section. In this reaction, compounds **28**[20] and **29** were obtained in a 7:1 ratio as shown. Cycloaddition with cyclohexen-2-one required temperatures of 120 °C and was conducted over 24 h. At the end of this period, there were isolated two products, **30** and **31**, in a ratio of 1:6, each corresponding to the expected regiochemical outcome. The reasons for apparent regiospecificity when cyclohexen-2-one was the dienophile as opposed to methyl vinyl ketone are not yet known. Interestingly, in the cyclohexen-2-one case, the major product **31** apparently arose from position-specific elimination of the silyloxy group peri to the methoxyl function. The $\beta$-elimination of this particular silyloxy function can readily be rationalized by steric and electronic effects exerted by the methoxyl.

**Scheme 8**[a]




[a] R = TMS; (a) benzo-1,4-quinone, 80 °C, 3 h, and then DDQ, THF, 22 °C, 12 h (**36**:**37** = 7:1, 80%); (b) methyl vinyl ketone 120 °C, 4 h and then DDQ, THF, 22 °C, 12 h (**38**:**39:39a** = 1:1:1, 80%); (c) dimethylacetylene dicarboxylate 120 °C, 3 h and then DDQ, THF, 22 °C, 4 h (92%).

We have investigated, though not in great detail, the oxidation of the Diels−Alder product in the *peri*-methoxyl series. For this purpose, as above, we turned to the bis(trimethylsilyloxy) benzocyclobutene derivative, **32** (Scheme 8), readily synthesized from **24**. Oxidations of the Diels−Alder adducts **33**, **34**, and **35** were again conducted with DDQ. With **33**, the major product was **36**;[21] however, this compound was accompanied by 15% of **37**. Again regioselective elimination of the silyloxy group peri to the methoxyl had occurred to a small extent competitively with oxidation. With adduct **34**, treatment with DDQ provided **38**[22] and the product of only partial oxidation, **39**. Its recovery was complicated by hydrolysis of the silyl group (see **39a**). Oxidation of **35** occurred smoothly to produce **40**. Thus with our present protocols, the *peri*-methoxyl does tend to complicate the ready exploitation of the silyloxy groups for structural development through oxidation. It clearly facilitates elimination of its peri silyloxy group, and perhaps hinders its oxidation. However, the basic capability has been demonstrated.

A pleasing application of this Diels−Alder strategy described herein was accomplished in the context of a highly concise and efficient total synthesis of the important anthracycline drug precursor idarubicinone (**43**).[23] Cycloaddition of **12** and **41**[12] occurred smoothly to produce the endo-adduct **42** (Scheme 9).

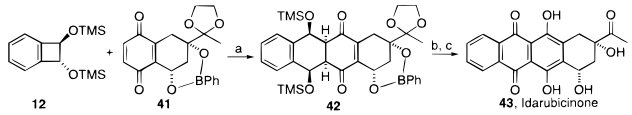
(20) Compound **28** was obtained as a 4:3 mixture of endo and exo diastereomers.

(21) (a) Bosshard, D.; Fumagalli, S.; Good, R.; Treub, W.; Philipsborn, W. V.; Eugster, C. H. *Helv. Chim. Acta* **1964**, *47*, 769. (b) Uno, H. *J. Org. Chem.* **1986**, *51*, 350.

(22) Kessler, H.; Müller, A. *Liebigs Ann. Chem.* **1986**, 1687.

(23) Idarubicin (Idamycin) was approved in 1990 for use in the United States for treatment of acute nonlymphocytic and lymphoblastic leukemia. It has been shown to have superior therapeutic efficacy and reduced cardiotoxicity and to provide longer duration of survival compared to Daunorubicin: (a) Hollingshead, L. M.; Faulds, D. *Drugs* **1991**, *42*, 690. (b) Cersosimo, R. J. *Clin. Pharm.* **1992**, *11*, 152. Idarubicin is produced, with some difficulty, by semisynthesis from Daunomycin: Penco, S. *Chim. Ind. Milan* **1993**, *75*, 369; EP 0 337 665 B1.

**Scheme 9**[a]




[a] (a) 50 °C, 2 h and then DDQ, THF 22 °C, 10 h; (b) $H_2O_2$, NaOH, THF; (c) TsOH, acetone; 65% three steps.

Oxidative desilylation of **42** followed by sequential cleavage of the borate and ketal blocking groups delivered idarubicinone (**43**). The overall yield for the four-step total synthesis of **43** was 65%. This sequence attempted with methoxyl-substituted benzocyclobutene **32** resulted in a 1:1 mixture of regioisomers due to the low polarization of dienophile **41**.

In summary, the major goals of the project have been realized, though some difficulties can arise in the oxidative desilylation step, particularly in the case of the Diels−Alder adducts bearing a *peri*-methoxyl function. Obviously these interesting results raise issues of mechanism, scope, possibilities for catalysis, and feasibility in attaining enantiocontrol in the cycloaddition step. Such matters are under current investigation and will be disclosed in due course.

## Experimental Section[24]

***trans*-Bis(*tert*-butyldimethylsilyloxy)benzocyclobutene (11).** Sodium borohydride (125 mg, 3.29 mmol) was added to a 0 °C solution of benzocyclobutenedione **9**[14] (400 mg, 3.28 mmol) dissolved in methanol (16 mL). The resulting solution was stirred for 30 min or until TLC showed complete consumption of starting material, at which time excess borohydride was quenched with acetone (1 mL). The solvent was removed at 0 °C via rotary evaporation and the residue passed through a plug of silica gel and rinsed with ethyl acetate. The filtrate was concentrated at 0 °C, redissolved in $CH_2Cl_2$ (20 mL), and cooled to −78 °C. To the solution was added TBSOTf (0.90 mL, 3.94 mmol) and $NEt_3$ (0.68 mL, 4.92 mmol), and the resulting solution stirred for 1.5 h at which time it was diluted with $Et_2O$ (20 mL), washed once each with water and brine, and then dried over $MgSO_4$. Purification by column chromatography (97:3 hexanes/ethyl acetate) gave pure trans **11** (675 mg, 58%): FTIR (film) 2955, 2929, 2857, 1256, 1114, 835, 777 $cm^{-1}$, $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.02−7.14 (m, 4H), 4.73 (s, 2H), 0.77 (s, 18H), 0.02 (s, 12H), 0.01 (s, 12H); $^{13}C$ (100 MHz, $CDCl_3$) $\delta$ 144.3, 129.4, 122.8, 79.6, 25.7, 17.7, −4.8 (2); MS for $[C_{20}H_{36}O_2Si_2 + Na]^+$, *m*/*z* 387.

**General Procedure for the Diels−Alder Reaction with 11.** Dienophile (2.0 equiv) and disilyloxybenzocyclobutene **11** were combined in benzene-$d_6$ and heated at 45 °C until quantitative conversion was observed by $^1H$ NMR (typically 1.5−2.5 h). Removal of the solvent followed by column chromatography yielded compounds **13**−**20**.

**Cyclohexenone Diels−Alder Adduct 13.** Colorless oil after chromatography (93%): FTIR (film) 2929, 2856, 1677, 1604, 1254, 836, 775 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.36 (d, $J$ = 6.9 Hz, 1H), 7.29 (d, $J$ = 6.8 Hz, 1H), 7.18 (m, 2H), 4.57 (d, $J$ = 10.4 Hz, 1H), 4.48 (d, $J$ = 4.2 Hz, 1H), 3.05 (app t, $J$ = 7.8 Hz, 1H), 2.26 (m, 1H), 2.09 (m, 1H), 1.95 (ddd, $J$ = 5.9, 7.1, 12.9 Hz, 1H), 1.50 (m, 2H), 1.29 (m, 1H), 0.85 (s, 9H), 0.78 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H), −0.03 (s, 3H), −0.06 (s, 3H); $^{13}C$ (100 MHz, $CDCl_3$) $\delta$ 212.0, 139.2, 138.0, 127.3, 127.1, 124.9, 124.5, 71.3, 65.6, 54.1, 44.0, 42.6, 26.3, 24.7, 21.9, 18.7, 18.5, −4.2 (2), −4.5, −4.6; HRMS (FAB) for $[C_{26}H_{44}O_3Si_2 + Na]^+$, *m*/*z* calcd 483.2727, found 483.2727.

**General Procedure for Jung-Type Oxidation of the Diels−Alder Adducts from 12.** Dienophile (2.0 equiv) and disilyloxybenzocyclobutene **12** were combined in benzene-$d_6$ and heated at 45 °C until quantitative conversion was observed by $^1H$ NMR (typically 1.5−2.5 h). The solvent was removed via rotary evaporation and the residue dissolved in THF ([0.2M]) without further purification. DDQ was added (2.1 equiv) as a solid at 25 °C, and the resulting solution stirred for an additional 12 h, at which point it was diluted with a 2-fold excess of methylene chloride and washed twice with saturated $NaHCO_3$ solution. After drying over $MgSO_4$ the material was purified by column chromatography (80:20 hexanes/ethyl acetate) to give pure compound.

**Naphthoquinone 21.** Red solid (mp 187−188 °C) after chromatography (82%): FTIR (film) 1627, 1585, 1454, 1226 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 12.94 (s, 2H, exch. with $D_2O$), 8.41 (m, 2H), 7.91 (m, 2H), 7.27 (s, 2H); $^{13}C$ (100 MHz, $CDCl_3$) $\delta$ 187.0, 157.8, 134.5, 133.5, 129.4, 127.1, 112.8; HRMS (DEI) for $[C_{14}H_8O_4]^+$, *m*/*z* calcd 240.0423, found 240.0423.

***trans*-Bis(*tert*-butyldimethylsilyloxy)-3-methoxybenzocyclobutene (26).** 3-Methoxybenzocyclobutendione (200 mg, 1.23 mmol) was dissolved in methanol (10 mL), cooled to 0 °C, and sodium borohydride (33 mg, 0.87 mmol) was added. After 1 h, the solvent was removed at 0 °C, the residue was passed through a plug of silica with cold ethyl acetate, and the filtrate was concentrated. The residue was dissolved with $CH_2Cl_2$ (10 mL), the mixture cooled to −78 °C, and TBSOTf (1.13 mL, 4.92 mmol) and $Et_3N$ (0.68 mL, 4.92 mmol) were added. After 2 h, methanol (1 mL) was added. The organic solution was washed with $NH_4Cl_{(aq)}$ and $NaCl_{(aq)}$, dried ($MgSO_4$), and evaporated. Purification by column chromatography (hexanes → 95:5 hexanes/EtOAc) gave pure *trans*-**26** (338 mg, 70%) as a colorless oil: FTIR (film) 2927, 2855, 1606, 1584, 1482 $cm^{-1}$; $^1H$ (400 MHz, toluene-$d_8$) $\delta$ 7.24 (dd, $J$ = 7.70 Hz, 1H), 6.95 (d, $J$ = 7.17 Hz, 1H), 6.87 (d, $J$ = 8.25 Hz, 1H), 5.18 (s, 1H), 5.09 (s, 1H), 3.78 (s, 1H), 1.15 (s, 9H), 1.11 (s, 9H), 0.38 (s, 3H), 0.32 (s, 3H), 0.30 (s, 3H), 0.26 (s, 3H); $^{13}C$ (100 MHz, $CDCl_3$) $\delta$ 155.6, 145.9, 131.0, 127.6, 115.2, 115.1, 79.3, 79.0, 56.9, 25.8, 18.0, −3.9, −4.5, −4.7, −5.1; HRMS ($NH_3$/CI) for $[C_{21}H_{38}O_3Si_2]^+$, *m*/*z* calcd 394.2359, found 394.2346.

**Benzoquinone Diels−Alder Adduct 27.** Benzo-1,4-quinone (8 mg, 74 $\mu$mol) was heated in toluene-$d_8$ (1 mL) with **26** (15 mg, 38 $\mu$mol) at 80 °C 3 h, when quantitative conversion was observed by $^1H$. Attempted purification by column chromatography caused partial enolization of the adduct. Pure **27** was obtained as a colorless oil: FTIR (film) 2928, 2855, 1674, 1472, 1253 $cm^{-1}$; $^1H$ (400 MHz, toluene-$d_8$) $\delta$ 7.02 (dd, $J$ = 7.93 Hz, 1H), 6.87 (d, $J$ = 7.48 Hz, 1H), 6.39 (d, $J$ = 7.56 Hz, 1H), 6.27 (s, 2H), 5.85 (d, $J$ = 5.40 Hz, 1H), 5.12 (d, $J$ = 5.39 Hz), 3.31 (s, 3H), 2.67 (dd, $J$ = 5.36 Hz, 9.98 Hz, 1H), 2.55 (dd, $J$ = 5.03 Hz, 10.0 Hz, 1H), 0.89 (s, 9H), 0.84 (s, 9H), 0.22 (s, 3H), 0.14 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H); $^{13}C$ (100 MHz, toluene-$d_8$) $\delta$ 197.6, 196.7, 156.4, 141.5, 141.0, 140.1, 135.6, 126.6, 121.0, 110.1, 71.4, 64.0, 54.2, 49.4, 48.6, 26.7, 26.6, −4.1, −4.2, −4.4, −4.6; HRMS (DCI) for $[C_{27}H_{43}O_5Si_2]^+$, *m*/*z* calcd 503.2649, found 503.2634.

***trans*-Bis(trimethylsilyloxy)-3-methoxybenzocyclobutene (32).** 3-Methoxybenzocyclobutendione (500 mg, 3.09 mmol) was dissolved in methanol (18 mL), cooled to 0 °C, and sodium borohydride (81 mg, 2.16 mmol) was added. After 1 h, the solvent was removed at 0 °C, the residue was passed through a plug of silica with cold ethyl acetate, and the filtrate was concentrated. The residue was dissolved with $CH_2Cl_2$ (10 mL), the mixture cooled to 0 °C, and HMDS (3.90 mL, 12.4 mmol) and TMSCl (2.35 mL, 12.4 mmol) were added. After 12 h, volatiles were evaporated and the residue was passed with *n*-pentane through Celite, and the filtrate was evaporated to give 6:1 mixture of *trans*- and *cis*-**32** (0.68 g, 60%) as a colorless oil: FTIR (film) 2957, 2897, 1606, 1586, 1482, 1252 $cm^{-1}$; $^1H$ (400 MHz, $CDCl_3$) $\delta$ 7.24 (dd, $J$ = 7.68 Hz, 1H), 6.80 (d, $J$ = 7.30 Hz, 1H), 6.76 (d, $J$ = 8.36 Hz, 1H), 5.02 (s, 1H), 4.86 (s, 1H), 3.78 (s, 3H), 0.20 (s, 9H), 0.19 (s, 9H); MS for $[C_{15}H_{24}O_3Si_2 + Na]^+$, *m*/*z* 310. Evidence for *cis*-**33** was as follows: $^1H$ (400 MHz, $CDCl_3$) $\delta$ 5.53 (d, $J$ = 3.84 Hz, 1H), 5.30 (d, $J$ = 3.80 Hz, 1H), 3.93 (s, 3H).

**Naphthacene 37 and Naphthoquinone 36.** Benzo-1,4-quinone (31 mg, 0.28 mmol) was heated with bis(trimethylsilyloxy)benzocyclobutene **32** (50 mg, 0.14 mmol) in toluene-$d_8$ (1 mL) at 80 °C 3 h, when conversion was observed to be complete by $^1H$ NMR. The solvent was evaporated and the residue taken up in THF (4 mL), and DDQ (60 mg, mmol) was added at 0 °C. After being stirred 12 h at 22 °C, the mixture was poured into a $NaHCO_3$ solution. The organic layer was washed with ice cold 1 N HCl, dried ($MgSO_4$), and evaporated. Column chromatography on silica gel (95:5 → 9:1 toluene/acetone) gave first pure **37** (3.6 mg, 10%) as a red amorphous solid: FTIR (film)

(24) Please see Supporting Information for General Methods section.

2920, 2849, 1720, 1664, 1480, 1261 $cm^{-1}$; $^1H$ (400 MHz, $CDCl_3$) $\delta$ 13.76 (s, 1H), 8.57 (s, 1H), 8.05 (d, $J = 8.30$ Hz, 1H), 7.63 (dd, $J = 8.07$ Hz, 1H), 7.09 (d, $J = 7.87$ Hz, 1H), 7.05 (s, 2H), 4.04 (s, 3H); $^{13}C$ (100 MHz, CDCl3) $\delta$ 189.4, 184.0, 162.2, 157.5, 141.0, 139.6, 129.9, 128.8, 127.6, 126.3, 116.8, 116.5, 109.8, 55.9; HRMS (DEI) for $[C_{15}H_{10}O_4]^+$, *m/z* calcd 254.0579, found 254.0579. Further elution (9:1 toluene/acetone → 9:1 $CH_2Cl_2$/MeOH) gave **36** (26 mg, 70%) as a dark orange solid (mp 240.0−240.8 °C, hexanes/ether): FTIR ($CCl_4$) 2927, 1623, 1588, 1281 $cm^{-1}$; $^1H$ (400 MHz, $CDCl_3$) $\delta$ 13.26 (s, 1H), 12.88 (s, 1H), 8.04 (d, $J = 8.04$ Hz, 1H), 7.78 (dd, $J = 8.26$ Hz, 1H), 7.39 (d, $J = 8.43$ Hz, 1H), 7.30−7.20 (m, 2H), 4.08 (s, 3H); $^{13}C$ (100 MHz, $CDCl_3$) $\delta$ 187.2, 186.7, 161.0, 157.4, 157.3, 135.6, 135.5, 129.9, 128.0, 119.7, 118.3, 113.5, 56.6; HRMS (DEI) for $[C_{15}H_{10}O_5]^+$, *m/z* calcd 270.0528, found 270.0530.

**Idarubicinone (43). Crude cyclic boronate 41** (73 mg, 0.20 mmol) was combined with disilyloxybenzocylcobutene **12** in toluene-$d_8$ (1 mL) and heated at 45 °C for 7 h, at which time $^1H$ NMR indicated that the reaction was complete. The solvent was removed and the residue taken up in THF (1 mL), and to the resulting orange solution was added solid DDQ (4 equiv). After stirring for 12 h at 25 °C, the solution was diluted with $CH_2Cl_2$ (5 mL), washed twice with saturated $NaHCO_3$ solution, and dried over $Na_2SO_4$. After removal of the solvent via rotary evaporation, the reddish solid was dissolved in THF (1.5 mL) and cooled to 0 °C. With rapid stirring, 30% $H_2O_2$ (1 mL) was added followed by 1 N NaOH solution (1 mL). The resulting turbid violet mixture was stirred for an additional 15 min, at which time the reaction was considered complete by TLC ($R_f$ 0.2, 1:1 hexanes/ethyl acetate). The reaction was quenched at 0 °C by the addition of 1 mL of saturated $NaHSO_3$ solution, diluted with 10 mL of $Et_2O$, and washed with brine. The aqueous layer was washed twice with dichloromethane, and the combined organic layers were dried over $Na_2SO_4$ and concentrated. The reddish gum was purified by column chromatography (65:35 hexanes/ethyl acetate) to give (***cis*-3-[1-(1,1-ethylenedioxy)ethyl]-1,2,3,4,6,11-hexahydro-5,12-dihydroxy-6,11-dioxonaphthacene** as a red solid (46 mg, 55%): $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 13.59 (s, 1H), 13.38 (s, 1H), 8.31 (m, 2H) 7.78 (m, 2H), 5.25 (br s, 1H), 4.02 (s, 4H), 3.71 (br s, 1H), 3.19 (dd, $J = 18.2$ Hz, 1H), 2.75 (d, $J = 18.5$ Hz, 1H), 2.37 (m, 1H), 1.95 (dd, $J = 5.0, 9.3$ Hz, 1H), 1.44 (s, 3H); MS for $[C_{22}H_{20}O_8 + Na]^+$, *m/z* 435. This compound was dissolved in acetone (5 mL) and stirred in the presence of catalytic *p*-toluenesulfonic acid at 25 °C for 8 h, at which point TLC indicated the reaction complete. The solvent was removed via rotary evaporation and the residue dissolved in 1:1 THF/diethyl ether and washed once with brine. The organic layer was dried over $Na_2SO_4$, concentrated, and then recrystallized from $CH_2Cl_2$ and $Et_2O$ to give idarubicinone **43** as a red solid (12 mg 83%): mp 176−178 °C (lit.,[12a] 174−178 °C); FTIR (film) 3416, 1713, 1623, 1587, 1415, 1374, 1236 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 13.52 (s, 1H, exchange with $D_2O$), 13.26 (s, 1H, exchange with $D_2O$), 8.28 (m, 2H), 7.79 (m, 2H), 5.27 (br s, 1H), 4.58 (br s, 1H, exchange with $D_2O$), 3.80 (br s, 1H, exchange with $D_2O$), 3.20 (dd, 2.0, 18.6 Hz, 1H), 2.91 d, $J = 18.7$ Hz, 1H), 2.47 (s, 3H), 2.36 (m, 1H), 2.20 (dd, $J = 5.0, 9.5$ Hz, 1H); $^{13}C$ (100 MHz, THF) $\delta$ 210.3, 186.1, 185.9, 156.1, 155.9, 136.2, 135.1, 133.7, 133.0, 132.9, 126.0, 125.9, 110.3, 109.8, 76.1, 60.5, 35.0, 32.6, 22.8; MS for $[C_{20}H_{16}O_7 + Na]^+$, *m/z* 391. Idarubicinone was also produced in improved yield by the preceding procedure with chromatography steps omitted. Thus, **41** (128 mg, 0.31 mmol) condensed with **12** (106 mg, 0.38 mol) yielded **43** (75 mg, 65%), which was purified by crystallization.

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**Supporting Information Available:** Characterization data and representative spectra of **13**, **14**, **15**, **16**, **17**, **18**, **19**, **20**, **22**, **23**, **26**, **27**, **28**, **29**, **30**, **31**, **32**, **36**, **37**, **38**, **39**, **40**, and **43** (print/PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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