Diels–Alder Reactions of Cyclopropenone Ketals: A Concise Tropolone Annulation Applicable to Rubrolone C Ring Introduction

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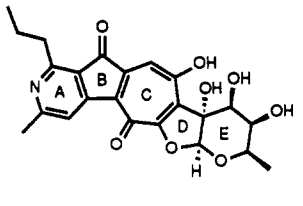
A concise tropolone annulation applicable to rubrolone C ring introduction is detailed based on the room-temperature [4 + 2] cycloaddition reaction of the cyclopropenone ketal **10** with the oxygenated diene **9**. Conversion of the sensitive [4 + 2] cycloadduct **11** to the norcaradiene **18**, low temperature electrocyclic rearrangement to a cycloheptatrienone ketal, and tautomerization to **12** provided a fully oxygenated tropolone analogous to that found in rubrolone.

Rubrolone (**1**),[1] a red tropoloalkaloid isolated from *Streptomyces enchinoruber*, was identified in a single-crystal X-ray structure determination and shown to possess the unique azuleno[2,3-*c*]pyridine-2,5,13-trione aglycon **2** characteristic of a class of structurally related agents.[2-4] In conjunction with a continued examination of the



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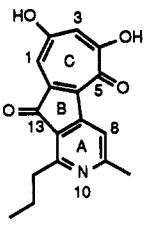

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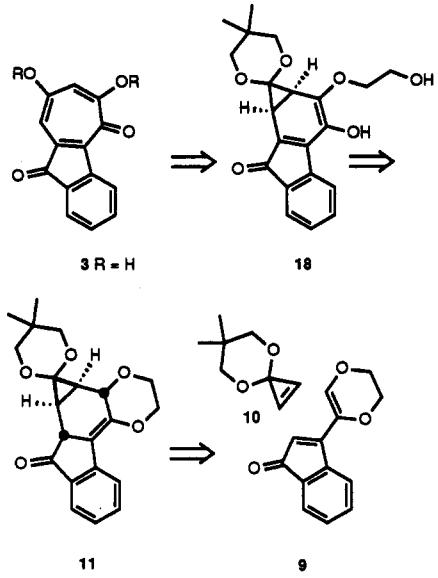
thermal cycloaddition reactions of cyclopropenone ketals,[5-12] herein we detail a concise synthesis of **3** based on the development of a tropolone annulation[5-8] applicable to rubrolone C ring introduction. Key to the implementation of the approach was the Diels–Alder reaction of the cyclopropenone ketal **10** with the highly oxygenated diene **9** and subsequent conversion of the sensitive [4 + 2] cycloadduct **11** to the norcaradiene **18** (Scheme 1). In situ low temperature electrocyclic rearrangement to a cycloheptatrienone ketal and tautomerization to **12** was anticipated to provide a fully oxygenated and suitably protected tropolone analogous to that found in rubrolone. Inherent in the design of the tropolone annulation was the incorporation of three oxygen substituents in the diene–dienophile reaction partners permitting the direct preparation of a 2,4-dihydroxycycloheptatrienone in a process complementary to those detailed based on the [4 + 2] and [3 + 4] cycoaddition reactions of cyclopropenone ketals.[5-8]

Scheme 1



The required diene **9** was conveniently prepared in two steps from 2-bromoinden-1-one (**6**) which in turn was derived by elimination of HBr (1.1 equiv, Et_3N, CH_2Cl_2, 40 °C, 6 h, 71%) from 2,2-dibromo-1-indanone (**5**),[13] Scheme 2. Conjugate addition of the higher order cyanocuprate **7**[14] prepared from 2-lithio-1,4-dioxene cleanly provided the 1,4-addition product **8** (THF, −40 to −15 °C, 63%). The addition product **8**, which proved to be surprisingly stable and was purified by standard chromatography techniques (SiO_2), was treated with DBU (1.2 equiv, CH_2Cl_2, 25 °C, 30 min, 72%) to provide the reactive diene **9** through elimination of HBr. Notably, the 2-bromo substituent in **6** served to permit the direct reintroduction of the indenone unsaturation required for the diene preparation and served, by virtue of its size, to stabilize the inherently reactive indenone structure of **6**.

The key Diels–Alder reaction of **9** with the cyclopropenone ketal **10**[15] was conducted at *room temperature and was complete within 15 min.* This exceptionally rapid

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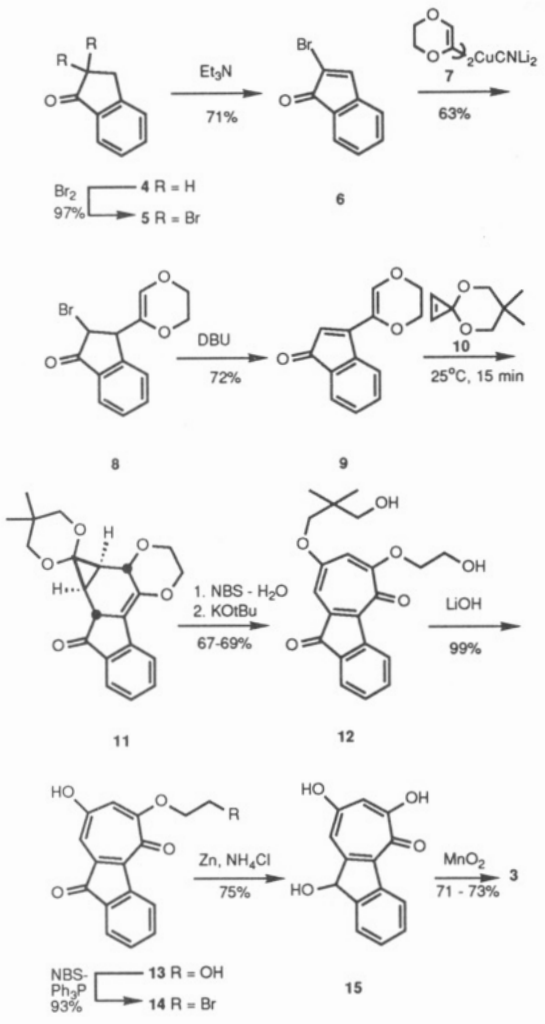
Scheme 2



[4 + 2] cycloaddition reaction may be attributed to the use of a diene incorporating an exceptionally reactive indenone substructure and the strained dienophile **10**. The sensitive and strained [4 + 2] cycloadduct **11** which proved to be clean isolated directly from the crude reaction mixture was not stable to standard workup conditions or purification by conventional chromatographic techniques but could be isolated in a pure state with a significant loss of material by trituration (hexane, 44% isolated) and characterized. A single diastereomer of the [4 + 2] cycloadduct was observed which was predictably derived from cycloaddition through the less sterically encumbered exo transition state,[7,8] Figure 1. Confirmation that cycloaddition through an exo transition state to provide **11** was observed was derived from the 2D ^{1}H–^{1}H NMR spectrum with observation of diagnostic NOE cross peaks including C19-H/C3-H$_\alpha$ accessible only to the exo adduct. The deliberate isolation and purification of the adduct **11** was accompanied by a loss of product and consequently was more effectively carried into the subsequent transformations without isolation or characterization.

Low temperature and sequential treatment of pure **11** with H_2O (3.0 equiv), *N*-bromosuccinimide (3.0 equiv, THF, −10 °C), and potassium *tert*-butoxide (3.0 equiv) or DBU (3.0 equiv) provided **12** directly in good conversions (67–69%). The low temperature treatment of **11** with *N*-bromosuccinimide–H_2O provides the intermediate bromohydrin **16** and attempts to isolate the sensitive product or its keto isomer were not successful. Moreover, much

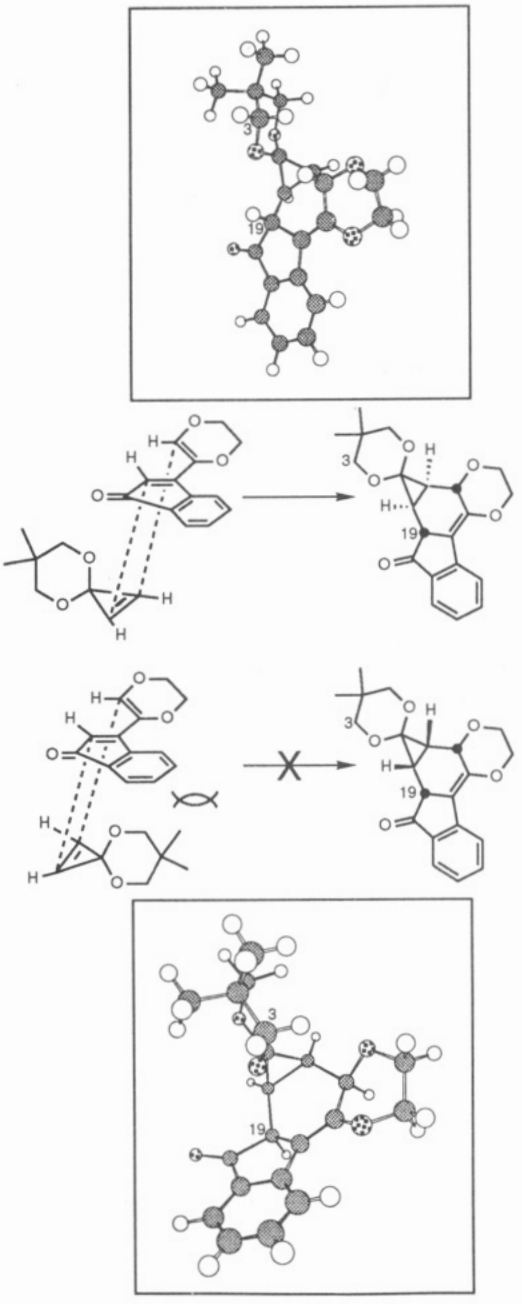


Figure 1.

lower yields of **12** were obtained if the mild NBS–H_2O treatment of **11** was conducted for an extended period of time (30 min vs 2–5 min, −10 °C) prior to addition of base (3.0 equiv of DBU). Subsequent treatment of in situ generated **16** with DBU or potassium *tert*-butoxide resulted in elimination of HBr, enolization of **17** with intermediate generation of norcaradiene **18**, low temperature (<0 °C) electrocyclic rearrangement[16] to the cycloheptatrienone ketal **19**, and tautomerization to the cycloheptatrienone **12** (Scheme 3). Because of the sensitivity of **11** to isolation and purification, crude **11** was generally subjected to the sequential treatment with NBS–H_2O (THF, −10 °C) and potassium *tert*-butoxide and provided **12** in 40–45% overall yield from **9**. Diagnostic differences in the ^{1}H NMR chemical shifts of ketal methylene signals

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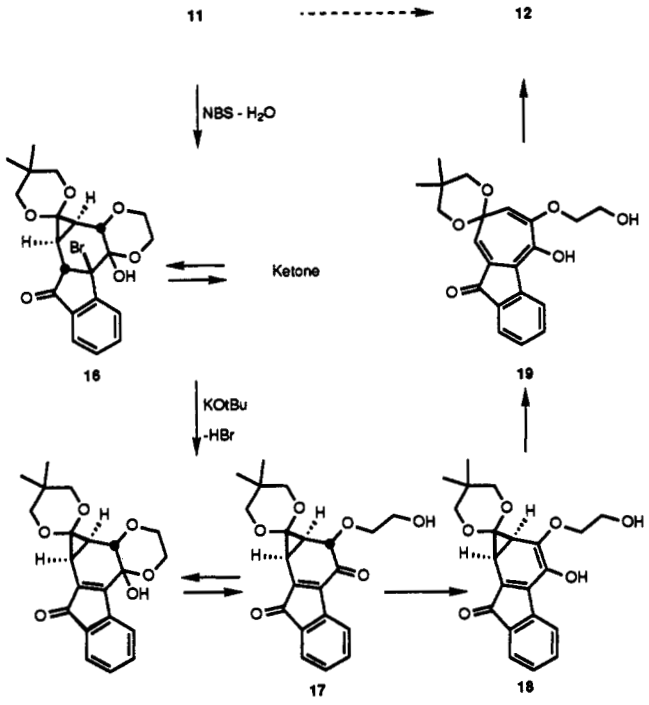
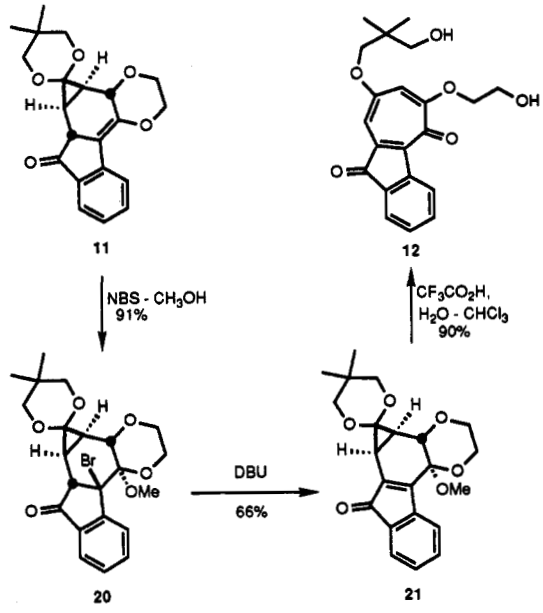
Scheme 3



Scheme 4



which were simplified to two singlets and two simple triplets and the collapse of the diastereotopic propylene ketal methyl signals to a clean singlet (6H) upon conversion to **12** served to confirm its structure. Characteristic of aryl ethers or vinylogous esters, the methylenes directly adjacent to the ether oxygens exhibited diagnostic downfield shifts relative to the methylenes bearing the free hydroxyl groups and the ^{13}C NMR spectrum of **12** exhibited two diagnostic carbonyl signals, confirming that the structure and tautomer **12** accurately reflects the product structure.[17]

That the conversion may proceed as illustrated in Scheme 3 was established upon stepwise conversion of **11** to **12** following a comparable sequence (Scheme 4). Treatment of **11** with NBS–CH_3OH (1.1 equiv, CH_3OH, 0 °C, 5 min, 91%) provided **20**[18] as a single diastereomer. Elimination of HBr from **20** was effected upon mild treatment with DBU (1.1 equiv, CH_2Cl_2, 0 °C, 10 min, 66%) to cleanly provide **21**.[19] Finally, acid-catalyzed hydrolysis of the mixed ketal (5% aqueous CF_3CO_2H, $CHCl_3$, 0 °C, 1 h, 90%) provided **12** in a surprisingly clean reaction in light of the number of potentially competitive reactions. Presumably the reaction proceeds by mixed ketal hydrolysis, enolization with norcaradiene generation, electrocyclic rearrangement to the cycloheptatrienone ketal, and tautomerization to **12**.

Tropolone **12** proved surprisingly resistant to exhaustive hydrolysis to provide **3** directly. Although this was not investigated in detail, subjection of **12** to standard hydrolysis conditions[20] (5 equiv of LiOH, THF–CH_3OH–H_2O 3:1:1, 60 °C, 12 h) led to clean monohydrolysis and selective generation of **13** (Scheme 2). Exposure of **12** or **13** to more vigorous hydrolysis conditions[20] did not lead to further hydrolysis to provide **3**. Similarly, exposure of **12** or **13** to HBr–HOAc (1:1–1:5, reflux, 6–12 h), 10% aqueous HCl–dioxane (100 °C, 12 h), BBr_3 (CH_2Cl_2, −78 to −5 °C), $AlCl_3$–EtSH (CH_2Cl_2, 25 °C), or Me_3SiI ($CHCl_3$, 50 °C) failed to remove both tropolone ethers. We suspected that the slow or problematic hydrolysis of the 2-hydroxyethyl ether may be due to the free hydroxy group which may preclude intermolecular hydrolysis by intramolecular addition to the C4 center with hemiketal formation. Consequently, the methyl ether **22**[21] was prepared by treatment of **12** with Ag_2O–CH_3I (3.0 and 5.0 equiv, CH_3CN, 25 °C, 12 h, 89%) with surprisingly clean and selective formation of the mono methyl ether presumably resulting from selective alkylation of the sterically more accessible alcohol (Scheme 5). Subjection of **22** to hydrolysis under a variety of vigorous conditions[22] did not lead to exhaustive hydrolysis with generation of **3** but

(17) Treatment of **12** with $LiBH_4$ (THF, 0 °C, 30 min, 84%) led to reduction of the C13 ketone and provided a product which still incorporated the 2,2-dimethylpropane-1,3-diol substituent [^1H NMR ($CDCl_3$, 400 MHz) δ 8.00 (d, 1H, J = 1.0 Hz), 7.89 (s, 1H), 7.60 (d, 1H, J = 7.4 Hz), 7.55 (s, 1H), 7.40 (t, 1H, J = 7.4 Hz), 7.30 (dt, 1H, J = 1.0, 7.4 Hz), 5.57 (s, 1H), 4.30 (t, 2H, J = 5.0 Hz), 4.16 (d, 2H, J = 6.5 Hz), 4.10 (t, 2H, J = 5.0 Hz), 3.39 (s, 2H), 0.98 (s, 6H); FABHRMS (NBA–NaI) m/e 395.1470 (M + Na^+, $C_{21}H_{24}O_6$ requires 395.1471)]. Notably, this firmly established that **12** did not contain a 2,2-dimethyl-3-hydroxylpropyl ester characteristic of benzoate rearrangement products and that the tropolone ring system was intact.

(18) For **20**: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.98 (d, 1H, J = 7.6 Hz), 7.78 (d, 1H, J = 7.6 Hz), 7.66 (dt, 1H, J = 1.0, 7.6 Hz), 7.50 (dt, 1H, J = 1.0, 7.6 Hz), 4.26 (d, 1H, J = 6.4 Hz), 3.94–4.00 (m, 1H), 3.85 (d, 1H, J = 12.9 Hz), 3.78 (d, 1H, J = 6.4 Hz), 3.66–3.52 (m, 4H), 3.34 (d, 1H, J = 1.7 Hz), 2.27 (s, 1H), 2.09 (dd, 1H, J = 1.7, 11.0 Hz), 1.46 (dd, 1H, J = 6.4, 11.0 Hz), 1.09 (s, 3H), 1.02 (s, 3H); FABHRMS (NBA) m/e 465.0920 (M + H^+, $C_{22}H_{25}BrO_6$ requires 465.0913).

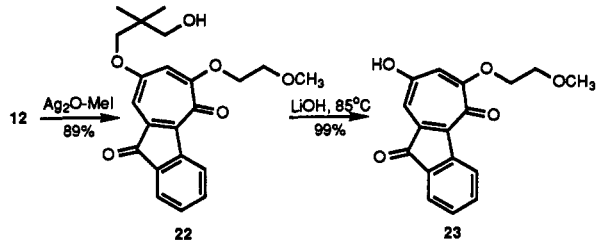
(19) For **21**: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.48 (d, 1H, J = 7.4 Hz), 7.38 (d, 1H, J = 7.4 Hz), 7.30 (dt, 1H, J = 1.0, 7.4 Hz), 7.17 (dt, 1H, J = 1.0, 7.4 Hz), 4.27 (dt, 1H, J = 4.8, 11.4 Hz), 3.95 (dt, 1H, J = 3.0, 11.4 Hz), 3.92 (d, 1H, J = 3.8 Hz), 3.79 (d, 1H, J = 11 Hz), 3.78 (d, 1H, J = 5.7 Hz), 3.66 (dd, 1H, J = 3.0, 12.4 Hz), 3.57 (dd, 1H, J = 1.9, 11.4 Hz), 3.42 (d, 1H, J = 11.4 Hz), 3.40 (d, 1H, J = 6.7 Hz), 3.38 (s, 3H), 1.99 (d, 1H, J = 9.6 Hz), 1.92 (dd, 1H, J = 6.4, 9.6 Hz), 1.16 (s, 3H), 0.84 (s, 3H); FABHRMS (NBA–CsI) m/e 517.0627 (M + Cs^+, $C_{12}H_{24}O_6$ requires 517.0627).

(20) Other conditions examined include NaOH (5.0 equiv, EtOH–H_2O, 100 °C, 24 h), t-BuOK–H_2O (9 and 3 equiv, THF, 25–55 °C, 24 h), LiOH (5.0 equiv, DMSO, 110 °C, 6–12 h), and KOH (5.0 equiv, EtOH–H_2O, 25–100 °C, 6 h).

(21) For **22**: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.92 (d, 1H, J = 7.4 Hz), 7.91 (d, 1H, J = 1.0 Hz), 7.78 (d, 1H, J = 1.0 Hz), 7.67 (d, 1H, J = 7.4 Hz), 7.51 (dt, 1H, J = 1.0, 7.4 Hz), 7.31 (dt, 1H, J = 1.0, 7.4 Hz), 4.35 (t, 2H, J = 4.6 Hz), 4.20 (s, 2H), 3.88 (t, 2H, J = 4.6 Hz), 3.50 (s, 3H), 3.39 (d, 2H, J = 6.0 Hz), 1.01 (s, 6H).

(22) The conditions examined include LiOH (5.0 equiv, THF–CH_3OH–H_2O 3:1:1, 85 °C, 12 h, 99% **23**) and KOH (10 equiv, EtOH, 110 °C, 48 h, only **23**).

Scheme 5



provided the monohydrolysis product **23**[23] instead. Presumably the C2 ether of **12** or **22** undergoes initial hydrolysis and the resulting tropolone anion is no longer sufficiently reactive to permit a second ether hydrolysis requiring hydroxide nucleophilic addition to C4.

Consequently, the remaining C4 ether of tropolone **13** was removed in a two-step sequence involving conversion to the primary bromide **14** (5.0 equiv of NBS, 4.0 equiv of Ph_3P, DMF, 25 °C, 12 h, 95–99%)[24] followed by reductive cleavage of the 2-bromoethyl ether (2.6 equiv of Zn, 2.6 equiv of NH_4Cl, EtOH, 65–70°C, 75%). Under the conditions of the reaction, the benzylic ketone was reduced to the corresponding alcohol[25] more rapidly than ether cleavage, leading to the clean generation of **15** (Scheme 2). Although the conversion of **14** to **15** was not examined in detail, zinc reduction of **14** in HOAc (25 °C, 1 h) or dioxane (100 °C, 6 h) also provided **15**, while attempts to conduct the reaction in EtOH (NH_4Cl, 12 h) at 25 °C or in H_2O (100 °C, 12 h) provided recovered starting material. Simple oxidation of **15** with MnO_2 provided **3** (71–73%) in excellent yield.

In Schemes 1–2 and 4–5, **3** and **13** and related agents have been represented in the 5-keto tautomeric form. However, like rubrolone itself which may be methylated with CH_2N_2 to provide a mixture of the two accessible 2-keto and 5-keto methyl ethers, **3** and **13** may exist in three and two tautomeric forms, respectively, Figure 2. Although no unambiguous experimental evidence was secured that would distinguish between the tautomeric forms of **3** and **13**, we do wish to note that one might expect the 2-keto tautomer of **13** to effectively undergo competitive intramolecular alkylation of the C5 alkoxide upon phosphonium salt activation of the primary alcohol rather than conversion to **14**. Although hemiketal formation involving reaction of the free alcohol with the 5-keto group of **13** was not observed which could suggest that **13** may preferentially exist in the 2-keto tautomeric form, the fact that **12** does not exhibit evidence of hemiketal formation suggests its formation would not be expected even with the 5-keto tautomer.

In the course of this work a substantial number of alternative and unsuccessful approaches to the introduction of an indenone C3 functionalized side chain capable of conversion to a diene structurally related to **9** were

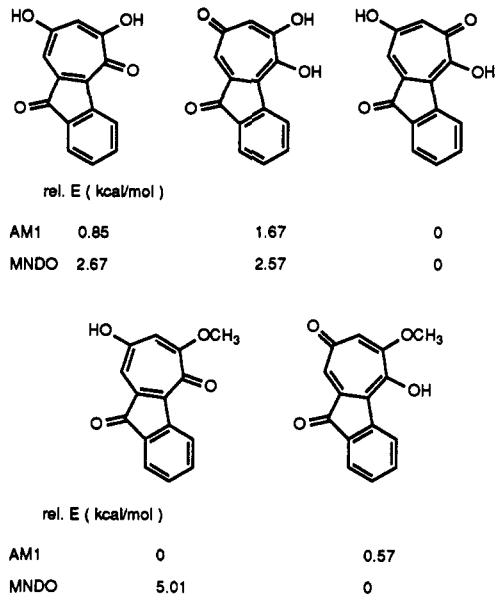
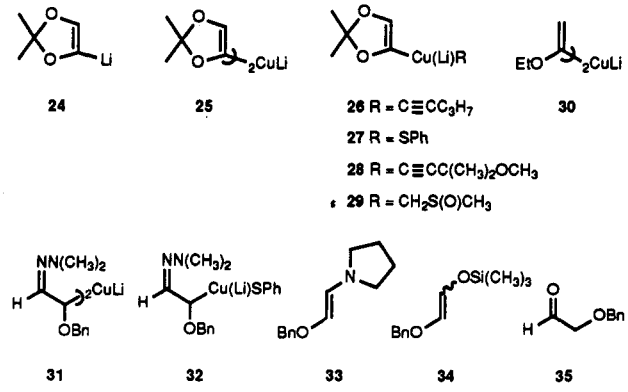


Figure 2.

examined. The lithium reagent **24**[26] underwent clean 1,2-addition with **6** (–78 °C, 5 min, 31% unoptimized)[27] and the cuprates **25–29** failed to provide isolable 1,4-adducts upon reaction with **6**. Conjugate addition of cuprate **30**[28] (–45 °C, 5 min) provided 3-acetylinden-1-one (30% unoptimized)[29] upon conventional aqueous workup through enol ether hydrolysis and subsequent elimination of HBr. Initial attempts to oxidize the enol ether of the crude conjugate addition product to the corresponding α-hydroxy ketone by treatment with *m*-CPBA were not promising. Since it appeared unlikely that this approach would compete with the successful addition of **7**, it was not pursued further. Similarly, the cuprates **31–32**, the enamine **33**, the trimethylsilyl enol ether **34**, and the thiazolium-catalyzed[30] or photochemically-initiated[31] addition of **35** with **6** failed to provide the corresponding 1,4-addition products although these were not investigated in detail.



Application of this work in the total synthesis of rubrolone is in progress and will be reported in due course.[32]

(23) For **23**: ^1H NMR ($CDCl_3$, 400 MHz) δ 8.00 (d, 1H, J = 1.0 Hz), 7.93 (d, 1H, J = 7.4 Hz), 7.80 (d, 1H, J = 1.0 Hz), 7.67 (d, 1H, J = 7.4 Hz), 7.50 (dt, 1H, J = 1.0, 7.4 Hz), 7.31 (dt, 1H, J = 1.0, 7.4 Hz), 4.37 (t, 2H, J = 4.6 Hz), 3.90 (t, 2H, J = 4.6 Hz), 3.51 (s, 3H).

(24) Bates, H. A.; Farina, J.; Tong, M. *J. Org. Chem.* **1986**, *51*, 2637. Treatment of **13** with Ph_3P–CBr_4 (py, 25 °C, 12 h) failed to provide **14** and its reaction with TMSCl–LiBr (CH_3CN, reflux, 2 d 14%, 6 d 63%) proved much less convenient.

(25) For 4-[(2-bromoethyl)oxy]-2,13-dihydroxybenz[*b*]azulen-5-one: ^1H NMR (CD_3OD, 400 MHz) δ 8.14 (d, 1H, J = 7.4 Hz), 7.87 (s, 1H), 7.60 (s, 1H), 7.58 (d, 1H, J = 7.4 Hz), 7.35 (t, 1H, J = 7.4 Hz), 7.29 (t, 1H, J = 7.4 Hz), 5.54 (s, 1H), 4.54 (t, 2H, J = 5.4 Hz), 3.88 (t, 2H, J = 5.4 Hz).

(26) Flynn, D. L.; Mitscher, L. A.; Veysoglu, T.; Wielogorski, Z. *Heterocycles* **1982**, *18*, 83.

(27) For the 1,2-adduct: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.48 (d, 1H, J = 7.4 Hz), 7.23 (d, 1H, J = 7.4 Hz), 7.22 (t, 1H, J = 7.4 Hz), 7.17 (t, 1H, J = 7.4 Hz), 6.82 (s 1H), 6.19 (s, 1H), 2.58 (s, 1H), 1.50 (s, 6H).

(28) Chavdarian, C. G.; Heathcock, C. H. *J. Am. Chem. Soc.* **1975**, *97*, 3822.

Experimental Section

2,2-Dibromo-1-indanone (5). A solution of 1-indanone (4, 5.0 g, 37.9 mmol) in HOAc (200 mL) was treated dropwise with Br_2 (12.7 g, 4.1 mL, 79.5 mmol, 2.1 equiv) at 100 °C over 20 min. The resulting reaction mixture was stirred at 100 °C for an additional 45 min before being cooled to room temperature. The mixture was poured into a solution of H_2O (100 mL) and CH_2Cl_2 (100 mL). The resulting aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic solutions were washed with H_2O (3 × 150 mL), saturated aqueous $NaHCO_3$ (100 mL), and saturated aqueous NaCl (100 mL). The organic solution was dried (Na_2SO_4) and concentrated under vacuum. The crude solid was recrystallized from EtOH to afford 2,2-dibromo-1-indanone[13] (5, 10.64 g, 10.98 g theoretical, 97%) as white cubes: mp 133–134 °C (EtOH, white cubes), lit.[13] mp 133–134 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.87 (d, 1H, J = 7.7 Hz), 7.70 (t, 1H, J = 7.7 Hz), 7.45 (t, 1H, J = 7.7 Hz), 7.38 (d, 1H, J = 7.7 Hz), 4.24 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 192.5, 147.0, 136.8, 128.9, 128.8, 126.4, 126.0, 59.9, 52.1; IR (KBr) ν_{max} 3061, 1719, 1605, 1463, 1425, 1325, 1299, 1272, 1213, 1106, 1050, 977, 944, 873, 846, 808, 769, 745, 681 cm^{-1}; FABHRMS (NBA–NaI) m/e 288.8870 (M + H$^+$, $C_9H_6Br_2O$ requires 288.8864).

Anal. Calcd for $C_9H_6Br_2O$: C, 34.83; H, 1.94. Found: C, 34.60; H, 1.82.

2-Bromoinden-1-one (6). A solution of 2,2-dibromo-1-indanone (5, 412 mg, 1.42 mmol) in CH_2Cl_2 (10 mL) was treated with Et_3N (173 mg, 0.24 mL, 1.71 mmol, 1.2 equiv), and the reaction mixture was stirred at 40 °C for 6 h. The precipitate was removed by filtration and the filtrate was concentrated under vacuum to provide a thick oil. Chromatography (SiO_2, 2 × 25 cm, 10% EtOAc–hexane) afforded 6 (210 mg, 297 mg theoretical, 71%) as a light brown-orange oil which solidified to a low melting solid upon standing: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.58 (d, 1H, J = 1.0 Hz), 7.43 (dd, 1H, J = 1.0, 7.1 Hz), 7.32 (dt, 1H, J = 1.0, 7.1 Hz), 7.18 (dt, 1H, J = 1.0, 7.1 Hz), 7.00 (d, 1H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 189.8, 147.2, 143.6, 139.1, 137.4, 134.4, 128.7, 123.8, 121.8; IR (neat) ν_{max} 3069, 1732, 1601, 1547, 1456, 1359, 1288, 1250, 1217, 1076, 1048, 945, 895, 860, 791, 747 cm^{-1}; FABHRMS (NBA–NaI) m/e 207.9515 (M$^+$, C_9H_5BrO requires 207.9524).

Anal. Calcd for C_9H_5BrO: C, 51.67; H, 2.39. Found: C, 51.76; H, 2.33.

2-Bromo-3-(1,4-dioxen-2-yl)-1-indanone (8). A cooled sample of neat 1,4-dioxene (1.5 g, 17.4 mmol) was treated dropwise with t-BuLi (9.0 mL of 1.7 M in pentane, 15.3 mmol) at −45 °C.[14] The resulting slurry was stirred at −15 °C for 1 h before it was diluted with THF (20 mL). The resulting cooled solution of 2-lithio-1,4-dioxene (−15 °C) was transferred by cannula into a solution of CuCN (685 mg, 7.65 mmol) and LiCl (324 mg, 7.65 mmol) in THF (10 mL) at −15 °C. The resulting reaction mixture was stirred at −15 to 0 °C for 10 min or until a homogeneous solution was obtained. The solution was recooled to −40 °C and a solution of 6 (801 mg, 3.83 mmol) in THF (5 mL) was added. The reaction mixture was allowed to warm to −15 °C over 5–15 min, and then the reaction was quenched with the addition of 5% NH_4OH in saturated aqueous NH_4Cl (30 mL). The mixture was stirred at 25 °C for 30 min before it was extracted with Et_2O (3 × 150 mL). The combined Et_2O solutions were dried ($MgSO_4$) and concentrated under vacuum. Chromatography (SiO_2, 3 × 25 cm, 10% EtOA–hexane) afforded 8 (710 mg, 1.13 g theoretical, 63%) as a thick colorless oil which solidified upon standing to a low melting solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.80 (d, 1H, J = 7.6 Hz), 7.68 (dt, 1H, J = 1.0, 7.6 Hz), 7.49 (dd, 1H, J = 1.0, 7.6 Hz), 7.45 (t, 1H, J = 7.6 Hz), 6.15 (s, 1H), 4.71 (d, 1H, J = 4.4 Hz), 4.08–3.99 (m, 4H), 3.88 (d, 1H, J = 4.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 197.8, 151.2, 135.9, 133.9, 133.7, 128.9, 125.3, 125.2, 124.5, 64.7, 64.1, 51.9, 49.0; IR (neat) ν_{max} 3065, 2933, 2876, 1726, 1683, 1603, 1464, 1384, 1318, 1286, 1246, 1207, 1150, 1087, 1026, 932, 900, 859, 819, 751, 724 cm^{-1}; FABHRMS (NBA–CsI) m/e 426.8946 (M + Cs$^+$, $C_{13}H_{11}BrO_3$ requires 426.8946).

Anal. Calcd for $C_{13}H_{11}BrO_3$: C, 52.88; H, 3.73. Found: C, 52.67; H, 3.42.

3-(1,4-Dioxen-2-yl)-inden-1-one (9). A solution of 8 (150 mg, 0.51 mmol) in CH_2Cl_2 (2 mL) was treated with DBU (95 mg, 94 μL, 0.61 mmol, 1.2 equiv) at 25 °C. The reaction mixture was stirred at 25 °C for 30 min before the solvent was removed under vacuum. Chromatography (SiO_2, 2.5 × 15 cm, 20% EtOAc–hexane) afforded 9 (78 mg, 109 mg theoretical, 72%) as a thick orange oil which solidified upon standing to a low melting orange solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.47 (dd, 1H, J = 1.0, 7.6 Hz), 7.34 (dt, 1H, J = 1.0, 7.6 Hz), 7.29 (d, 1H, J = 7.6 Hz), 7.27 (t, 1H, J = 7.6 Hz), 7.16 (s, 1H), 5.98 (s, 1H), 4.27 (s, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 196.1, 154.2, 141.4, 134.7, 133.1, 133.0, 132.4, 129.0, 122.1, 121.6, 118.5, 65.2, 63.8; IR (neat) ν_{max} 3056, 2964, 2923, 2872, 1713, 1600, 1544, 1462, 1395, 1369, 1277, 1241, 1210, 1154, 1082, 1056, 908, 759 cm^{-1}; FABHRMS (NBA–NaI) m/e 215.0711 (M + H$^+$, $C_{13}H_{10}O_3$ requires 215.0708).

2-[(2,2-Dimethyl-3-hydroxypropyl)oxy]-4-[(2-hydroxyethyl)oxy]benz[*b*]azulene-5,13-dione (12). From 9. The diene 9 (59 mg, 0.28 mmol) was treated with 10[15] (102 mg, 0.73 mmol, 2.6 equiv) at 25 °C. The reaction mixture was stirred at 25 °C for 15 min and diluted with THF (5 mL), and the solution was cooled to −10 °C. The solution containing 11 was treated sequentially with H_2O (15.1 mg, 15 μL, 0.84 mmol, 3.0 equiv), NBS (150.0 mg, 0.84 mmol, 3.0 equiv), and t-BuOK (0.84 mL of 1.0 M in t-BuOH, 0.84 mmol, 3.0 equiv). The resulting reaction mixture was allowed to warm to 0 °C and stirred for 2 h before the reaction was quenched by adding 10 mL of pH 7 Na_2HPO_4–NaH_2PO_4 buffer. The mixture was extracted with $CHCl_3$ (3 × 70 mL), and the combined organic solutions were dried ($MgSO_4$) and concentrated. Chromatography (SiO_2, 1.5 × 15 cm, CH_3OH–EtOAc–hexane, 1:5:4) followed by recrystallization of the yellow solid from $CHCl_3$–CH_3OH provided 12 (42 mg, 102 mg theoretical, 41%): mp 204–205 °C ($CHCl_3$–CH_3OH, yellow powder); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.90 (d, 1H, J = 1.1 Hz), 7.87 (d, 1H, J = 7.4 Hz), 7.76 (d, 1H, J = 1.1 Hz), 7.67 (d, 1H, J = 7.4 Hz), 7.51 (dt, 1H, J = 1.1, 7.4 Hz), 7.31 (dt, 1H, J = 1.1, 7.4 Hz), 4.34 (t, 2H, J = 4.6 Hz), 4.19 (s, 2H), 4.13 (t, 2H, J = 4.6 Hz), 3.40 (s, 2H), 1.01 (s, 6H); ^{13}C NMR (CD_3OD–$CDCl_3$, 100 MHz) δ 192.8, 165.1, 154.0, 142.0, 135.0, 134.9, 134.6, 133.2, 131.8, 128.5, 124.7, 123.2, 119.2, 116.4, 69.5, 69.3, 67.2, 59.8, 35.6, 20.4; IR (KBr) ν_{max} 3482, 2961, 2888, 1712, 1698, 1616, 1602, 1477, 1420, 1401, 1371, 1314, 1286, 1246, 1199, 1177, 1061, 1009, 976, 907, 883 cm^{-1}; FABHRMS (NBA–CsI) m/e 503.0489 (M + Cs$^+$, $C_{21}H_{22}O_6$ requires 503.0471).

From 11. The sensitive [4 + 2] cycloadduct 11 was isolated in pure form (44%) from a similar reaction (2.6 equiv of 10, 25 °C, 15 min) by trituration with hexane: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.93 (d, 1H, J = 7.6 Hz), 7.74 (dt, 1H, J = 1.0, 7.6 Hz), 7.57 (dt, 1H, J = 1.0, 7.6 Hz), 7.29 (dt, 1H, J = 1.0, 7.6 Hz), 4.25 (dd, 1H, J = 1.8, 3.1 Hz), 4.17 (t, 1H, J = 2.6 Hz), 4.16 (t, 1H, J = 3.2 Hz), 4.0–3.9 (m, 2H), 3.71 (d, 1H, J = 11.0 Hz), 3.58 (dd, 1H, J = 1.0, 11.0 Hz), 3.55 (s, 2H), 2.87 (dd, 1H, J = 1.8, 4.8 Hz), 1.76 (dd, 1H, J = 4.8, 10.9 Hz), 1.73 (dd, 1H, J = 3.1, 10.9 Hz), 1.14 (s, 3H), 0.97 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 203.7, 146.5, 146.2, 134.9, 134.7, 127.1, 125.1, 123.5, 110.6, 87.7, 77.2, 75.6, 75.3, 66.3, 66.2, 65.0, 43.7, 38.0, 29.8, 22.3, 22.0; IR (KBr) ν_{max} 3055, 2962, 2908, 2868, 1712, 1675, 1601, 1470, 1454, 1431, 1395, 1370, 1306, 1286, 1205, 1145, 1110, 1079, 1043, 981, 914, 761, 733 cm^{-1}; FABHRMS (NBA) m/e 355.1540 (M + H$^+$, $C_{21}H_{22}O_5$ requires 355.1545). The 2D ^{1}H–^{1}H NOESY NMR spectrum of 11 ($CDCl_3$, 400 MHz) displayed diagnostic NOE cross peaks for C^{16}-H/C^{15}-H, C^{13}-H/C^{14}-H, C^{14}-H/C^{15}-H, C^7-H/C^6-H, C^7-H/C^{19}-H, C^7-H/C^9-H$_\beta$, C^8-H$_\beta$/C^8-H$_\alpha$, C^8-H$_\beta$/C^9-H$_\beta$, C^8-H$_\beta$/C^9-H$_\alpha$, C^8-H$_\beta$/C^6-H, C^8-H$_\alpha$/C^9-H$_\beta$, C^8-H$_\alpha$/C^9-H$_\alpha$, C^8-H$_\alpha$/C^6-H, C^5-H$_\alpha$/C^5-H$_\beta$, C^5-H$_\alpha$/C^3-H$_\alpha$, C^5-H$_\alpha$/C^1-H, C^3-H$_\alpha$/C^3-H$_\beta$, C^3-H$_\alpha$/C^1-H, C^3-H$_\alpha$/C^{19}-H, C^{19}-H/C^1-H, C^1-H/C^6-H.

A cooled solution (0 °C) of purified 11 (35.5 mg, 0.10 mmol) in THF (1.0 mL) was treated with H_2O (3.6 mg, 3.6 μL, 0.20 mmol), NBS (24.9 mg, 0.14 mmol), and DBU (11.2 mg, 11.0 mg, 0.12 mmol). The mixture was stirred at 0 °C for an additional 1 h and diluted with $CHCl_3$ (100 mL). The organic solution was washed with pH 7 Na_2HPO_4–NaH_2PO_4 buffer (20 mL) and H_2O

(29) For 3-acetylinden-1-one: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.89 (d, 1H, J = 7.6 Hz), 7.53 (d, 1H, J = 7.6 Hz), 7.40 (t, 1H, J = 7.6 Hz), 7.30 (t, 1H, J = 7.6), 6.37 (s, 1H), 2.55 (s, 3H).

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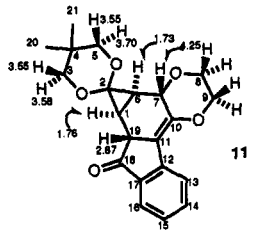
(32) In vitro cytotoxic assay (L1210) of 3, 15, and 14 revealed IC_{50} values of >50, >50, and 10 μg/mL, respectively.



11

(20 mL), dried ($MgSO_4$), and concentrated under vacuum. Chromatography (SiO_2, 2.0 × 15 cm, CH_3OH–EtOAc–hexane, 1:5:4) followed by recrystallization of the yellow solid from $CHCl_3$–CH_3OH provided **12** (25 mg, 36 mg theoretical, 69%).

2-Hydroxy-4-[(2-hydroxyethyl)oxy]benz[*b*]azulene-5,13-dione (13). A solution of **12** (37 mg, 0.10 mmol) in THF–CH_3OH–H_2O (3:1:1, 1.0 mL) was treated with LiOH–H_2O (21 mg, 0.50 mmol, 5.0 equiv), and the reaction mixture was stirred at 60 °C for 12 h. The solvents were removed under vacuum, and the residue was treated with 1.0 mL of 1 N aqueous HCl. The aqueous solution was extracted exhaustively with $CHCl_3$ (5 × 30 mL), and the combined organic solutions were dried ($MgSO_4$) and concentrated. The resulting yellow solid was recrystallized from CH_3OH–$CHCl_3$ to afford **13** (28 mg, 28.4 mg theoretical, 99%) as yellow powder: mp > 280 °C (CH_3O–$CHCl_3$); ^1H NMR (CD_3OD–$CDCl_3$, 400 MHz) δ 8.00 (d, 1H, *J* = 7.4 Hz), 7.83 (d, 1H, *J* = 1.0 Hz), 7.82 (d, 1H, *J* = 1.0 Hz), 7.58 (d, 1H, *J* = 7.4 Hz), 7.52 (dt, 1H, *J* = 1.0, 7.4 Hz), 7.28 (dt, 1H, *J* = 1.0, 7.4 Hz), 4.30 (t, 2H, *J* = 4.9 Hz), 4.02 (t, 2H, *J* = 4.9 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 193.6, 167.9, 154.0, 144.5, 143.2, 135.2, 134.0, 133.5, 130.3, 128.3, 124.3, 123.5, 120.2, 117.0, 70.0, 59.7; IR (KBr) ν_{max} 3441, 2928, 2856, 1621, 1568, 1472, 1456, 1416, 1361, 1257, 1123, 1094, 990, 881, 836, 778, 732, 697 cm^{-1}; FABHRMS (NBA) *m/e* 285.0749 (M + H^+, $C_{16}H_{12}O_5$ requires 285.0762).

4-[(2-Bromoethyl)oxy]-2-hydroxybenz[*b*]azulene-5,13-dione (14). A solution of **13** (5.2 mg, 0.081 mmol) in DMF (0.5 mL) was treated with Ph_3P (19.0 mg, 0.072 mmol, 4.0 equiv) followed by NBS (13.0 mg, 0.072 mmol, 5.0 equiv). The resulting reaction mixture was stirred at 25 °C for 12 h before it was diluted with $CHCl_3$ (30 mL). The solution was washed with H_2O (5 mL) and saturated aqueous NaCl (2 × 10 mL), dried ($MgSO_4$), and concentrated under vacuum. Chromatography (SiO_2, 1 × 5 cm, CH_3OH–EtOAc–hexane, 10:45:45) afforded **14** as a yellow powder (6.1 mg, 6.4 mg theoretical, 95%): mp > 280 °C ($CHCl_3$–CH_3OH, 3:7); ^1H NMR (DMSO-d_6, 400 MHz) δ 7.95 (d, 1H, *J* = 7.4 Hz), 7.76 (s, 1H), 7.71 (s, 1H), 7.60 (t, 1H, *J* = 7.4 Hz), 7.59 (d, 1H, *J* = 7.4 Hz), 7.33 (t, 1H, *J* = 7.4 Hz), 4.53 (t, 2H, *J* = 5.0 Hz), 3.95 (t, 2H, *J* = 5.0 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 193.3, 167.5, 153.2, 143.8, 142.9, 135.3, 134.2, 133.5, 130.6, 128.5, 124.2, 123.7, 120.1, 117.3, 68.1, 31.9; IR (KBr) ν_{max} 3410, 3061, 2926, 1716, 1595, 1483, 1382, 1275, 1225, 1198, 1172, 1111, 1073, 1024, 990, 906, 809, 772, 735, 679, 638 cm^{-1}; FABHRMS (NBA) *m/e* 346.9930 (M + H^+, $C_6H_{11}BrO_4$ requires 346.9919).

2,4,13-Trihydroxybenz[*b*]azulen-5-one (15). A solution of **14** (15.0 mg, 0.043 mmol) in EtOH (0.5 mL) was treated with zinc dust (7.0 mg, 0.11 mmol, 2.6 equiv) and NH_4Cl (5.9 mg, 0.11 mmol, 2.6 equiv), and the resulting mixture was stirred at 65 °C for 20 min. The mixture was cooled to 25 °C, the solid residue was removed by filtration, and the filtrate was concentrated under vacuum. Chromatography (SiO_2, 1 × 5 cm, CH_3OH–EtOAc–hexane, 10:45:45) afforded **15** (7.8 mg, 10.5 mg theoretical, 75%) as a white solid: mp > 280 °C (CH_3OH); ^1H NMR (CD_3OD, 400 MHz) δ 7.99 (d, 1H, *J* = 7.4 Hz), 7.70 (d, 1H, *J* = 1.0 Hz), 7.55 (d, 1H, *J* = 7.4 Hz), 7.42 (d, 1H, *J* = 1.0 Hz), 7.33 (t, 1H, *J* = 7.4 Hz), 7.23 (t, 1H, *J* = 7.4 Hz), 5.50 (s, 1H); ^{13}C NMR (CD_3OD, 100 MHz) δ 171.3, 154.3, 149.3, 147.5, 140.0, 132.9, 131.9, 129.7, 128.3, 125.6, 125.2, 118.6, 118.1, 75.5; IR (neat) ν_{max} 3521, 3436, 2954, 1699, 1623, 1590, 1559, 1423, 1308, 1280, 1098, 1019, 895, 774, 746 cm^{-1}; FABHRMS (NBA–NaI) *m/e* 242.0575 (M^+, $C_{14}H_{10}O_4$ requires 242.0579).

2,4-Dihydroxybenz[*b*]azulene-5,13-dione (3). A solution of **15** (2.0 mg, 0.008 mmol) in CH_3OH (0.5 mL) was added to a suspension of MnO_2 (10 mg, 5 wt equiv) in 0.5 mL of CH_3OH. The reaction mixture was stirred at 25 °C for 1 h before the solid residue was removed by filtration through a plug of Celite. The filtrate was concentrated under vacuum. Chromatography (SiO_2, 1 × 3 cm, CH_3OH–EtOAc–hexane, 1:4.5:4.5) afforded **3** (1.4 mg, 1.98 mg theoretical, 71%; typically 71–73%) as an orange solid: mp > 280 °C (CH_3OH); ^1H NMR (CD_3OD, 400 MHz) δ 7.90 (d, 1H, *J* = 7.4 Hz), 7.64 (d, 1H, *J* = 1.1 Hz), 7.59 (d, 1H, *J* = 1.1 Hz), 7.54 (d, 1H, *J* = 7.4 Hz), 7.48 (dt, 1H, *J* = 1.1, 7.4 Hz), 7.21 (dt, 1H, *J* = 1.1, 7.4 Hz); ^{13}C NMR (CD_3OD, 100 MHz) δ 195.9, 180.0, 154.5, 145.4, 130.6, 136.2, 135.3, 131.8, 129.1, 125.5, 125.4, 124.7, 121.2, 117.5; IR (KBr) ν_{max} 3424, 2995, 1574, 1415, 1344, 1277, 1046, 1010, 923, 728, 651, 621 cm^{-1}; UV (CH_3OH) λ_{max} (ε) 210 (17 600), 258 (20 100), 298 (2300), 308 (1700) nm; FABHRMS (NBA) *m/e* 239.0340 (M – H^+, $C_{14}H_8O_4$ requires 239.0344).

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Supplementary Material Available: Copies of ^1H NMR spectra of **9**, **11**–**15**, and **3** (7 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.