Squaric Acid Ester-Based Total Synthesis of Echinochrome A

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Abstract: The total synthesis of echinochrome A is described. Both key intermediates **5** and **8** were efficiently prepared from diisopropyl squarate **7**. Nucleophilic addition of aryllithium **8** to **5**, followed by thermal ring-expansion/cyclization of the 1,2-adduct **4**, furnished hydroquinone **3**. Oxidation and full deprotection of **3** gave the title compound.

Echinochrome A **1** (Figure 1) is a highly oxygenated component of the pigments derived from sea urchins. It was first unambiguously identified by Moore and coworkers[1] in a mixture of ca. 30 compounds obtained from calcareous fragments of two *Echinothrix* species, i.e., *E. diadema* Linn and *E. calamaris* Pallis.

Echinochrome A possesses antibacterial properties against both Gram-positive and Gram-negative marine bacteria, particularly *Pseudomonas* strain No. 111 and *Vibrio fisheri* (NCMB 1281).[2] Echinochrome A was first synthesized by Wallenfels and Gauhe in 1943, albeit in very low overall yield (1.5−2%).[3] Herein is reported a successful total synthesis of the title compound utilizing the chemistry of squaric acid developed by Moore and Liebeskind.[4]

The total synthesis of echinochrome A was conceived as depicted in Scheme 1. The main feature of the proposed retrosynthetic analysis relies on the fact that both intermediates **5** and **8** can be synthesized from diisopropylsquarate **7**, a common and readily available starting material.

The synthesis was begun with the preparation of 4-ethyl-3-isopropoxycyclobutene-1,2-dione **5** by a previously developed method (Scheme 2).[5] Diisopropylsquarate **7** was treated with EtMgBr at −78 °C and then quenched at low temperature to give the corresponding 1,2-adduct

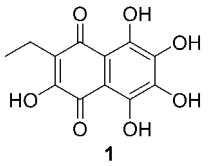

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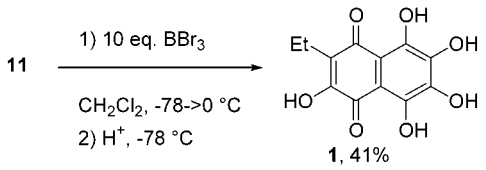
Figure 1. Structure of echinochrome A.

6. The crude material smoothly rearranged to **5** in 66% overall yield upon treatment with a catalytic amount of concentrated HCl at 25 °C.

Vinyl-substituted cyclobutenone **10**, the precursor of aryllithium **8**, was prepared in 64% yield by addition of vinylmagnesium bromide to **7** followed by an aqueous NH_4Cl quench (Scheme 3). Compound **10** was then thermolyzed to produce the corresponding hydroquinone which, due to its high tendency to oxidize in air, was directly methylated with MeI/KOH in DMSO[6] to give **9** in 87% overall yield from **10**.

Aryllithium **8** was generated from **9** with *s*-BuLi in the presence of TMEDA; 1,2-addition at the more electrophilic carbonyl group of **5**[3] took place uneventfully to produce adduct **4** in 59% overall yield (Scheme 4). Adduct **4** thermally rearranged at 160 °C to produce hydroquinone **3**. The crude hydroquinone was immediately oxidized with ceric ammonium nitrate in ether/water to naphthoquinone **2**, which, on exposure to air, hydrolyzed to naphthoquinone **11** in 95% yield from **4**. This observations did not affect the synthetic plan since the last step involved the complete deprotection of the hydroxyl groups.

Toward this end, exposure of **11** to an excess of TMSI[7] in either CCl_4 or HBr[8] in acetic acid only gave mixtures of partially demethylated products. We then attempted to achieve the deprotection using BBr_3 in dichloromethane.[9] Full deprotection took place in 41% yield only when an excess of BBr_3 (10-fold) was used (eq 1). If a lesser amount of BBr_3 was used, a complex mixture of partially demethylated products was observed.



In conclusion, a simple and efficient convergent total synthesis of echinochrome A starting from squaric acid esters was achieved.

Experimental Section

General Methods. ^1H NMR spectra were recorded on a Varian Gemini 200 (200 MHz) spectrometer in deuteriochloroform ($CDCl_3$) with either tetramethylsilane (TMS) (0.0 ppm) or chloroform (7.26 ppm) as internal reference unless otherwise indicated. Data are reported in the following order: chemical shift in ppm (δ), multiplicities (br (broadened), s (singlet), d

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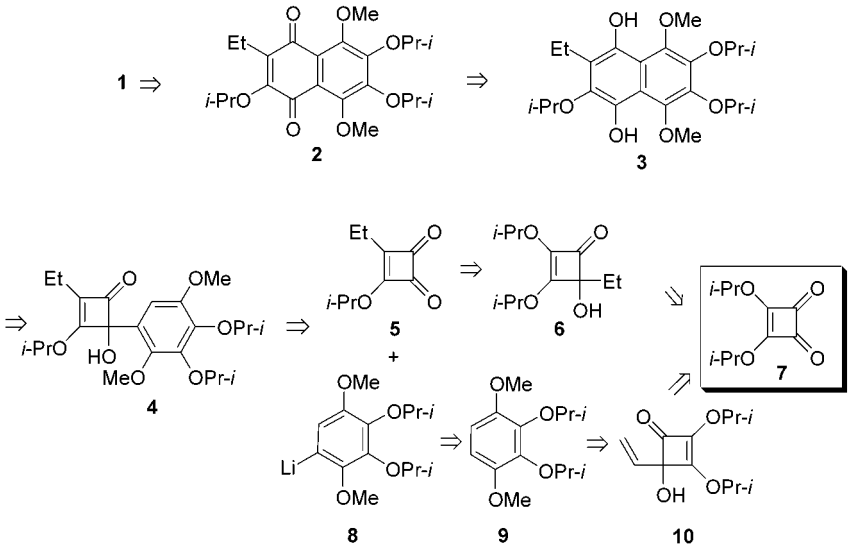
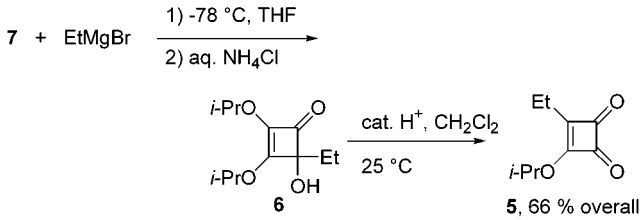
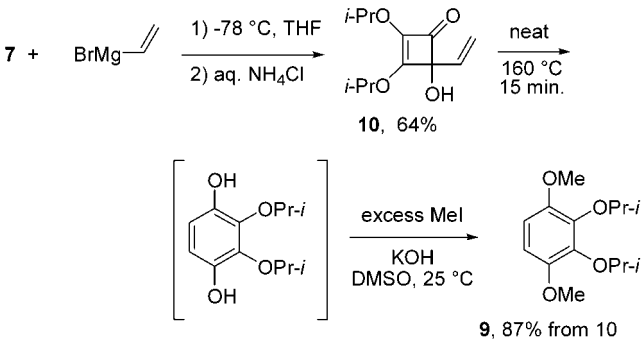
Scheme 1



Scheme 2



Scheme 3



(doublet), t (triplet), q (quartet), sex (sextet), hep (heptet), m (multiplet), exch (exchangeable), app (apparent)), coupling constants, *J* (Hz), and integration. Infrared spectra were recorded on a Perkin-Elmer FTIR 1600 series spectrophotometer. Peaks are reported (cm^{-1}) with the following relative intensities: s (strong, 67−100%), m (medium 40−67%), and w (weak 20−40%).

Analytical thin-layer chromatography was performed on Merck silica gel plates with F-254 indicator. Acid-pretreated silica gel plates were used to monitor the final deprotection of **2**. Visualization was accomplished by UV light, iodine, or *p*-anisaldehyde solution. Medium-pressure liquid chromatography (MPLC) was performed as described by Baeckström et al.[10] using gradient solutions with the indicated solvent systems. Purification of **1** was carried out using acid-pretreated silica gel. THF was dried over activated 4 Å molecular sieves. TMEDA was distilled from sodium and stored over activated 4 Å molecular sieves. All reactions were performed under a dry N_2 atmosphere in oven- and or flame-dried glassware.

Commercial Chemicals. The following materials were obtained from commercial sources: *s*-BuLi, EtMgBr, MeI, ceric ammonium nitrate, TMSI, HBr in acetic acid, and BBr_3.

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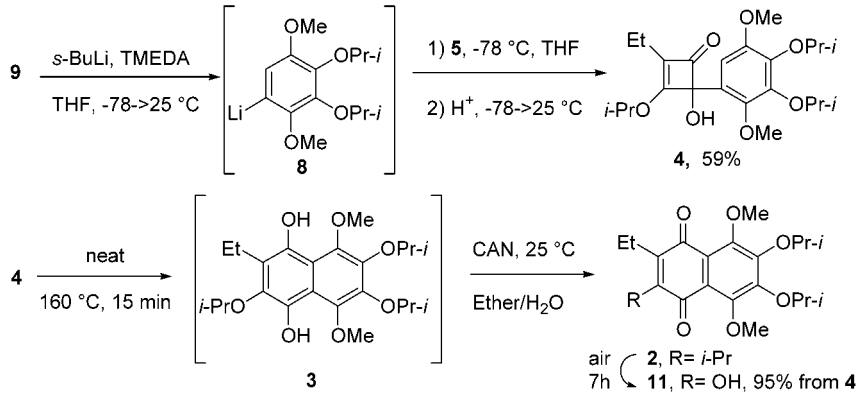
Experimental Procedures. 3-Ethyl-4-isopropoxycyclobuten-1,2-dione (5). Ethylmagnesium bromide (5.60 mL, 3.00 M, 16.800 mmol, 1.11 equiv) was added via syringe to a cold (−78 °C) THF (40 mL) solution of 2,3-diisopropyl squarate (3.00 g, 15.14 mmol, 1.00 equiv). The reaction mixture was slowly allowed to reach 25 °C, and then it was stirred for 8 h at that temperature. After that period of time, the dark solution was cooled to −78 °C and quenched with a saturated NH_4Cl solution. After the mixture warmed to 25 °C, it was extracted with ether (3 × 20 mL), and the organic extracts were combined and dried over anhyd $MgSO_4$. The mixture was filtered, and the solvent was removed under reduced pressure to give a yellow oil. The oil was taken up in dichloromethane (20 mL) and treated with 4 drops of concentrated HCl. After ca. 4 h, all of the starting material had reacted. The dark solution was washed with water (1 × 20 mL), dried over anhyd $MgSO_4$, and filtered. The solvent was removed under reduced pressure to give a yellow oil (1.4 g, 8.30 mmol, 55%). TLC (silica gel, 20% ethyl acetate/hexanes, R_f = 0.36); chromatographic purification (Baeckström column, silica gel, 1.5 × 10 cm, ethyl acetate/hexanes gradient); IR (CH_2Cl_2, KCl, cm^{-1}) 2986 (m), 2940 (m), 1792 (s), 1759 (s), 1593 (s); ^1H NMR ($CDCl_3$, 300 MHz) δ 5.28 (sept, J = 6.2 Hz, 1 H), 2.51 (q, J = 7.6 Hz, 2 H), 1.34 (d, J = 6.1 Hz, 6 H), 1.17 (t, J = 7.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 197.6, 195.0, 194.1, 185.0, 78.7, 22.4, 18.3, 9.7; HRMS(EI) calcd for $C_9H_{12}O_4$ 168.0786, found 168.0771.

1,2-Diisopropyl-3-hydroxy-3-vinylcyclobutenone (10). To a cold (−78 °C, dry ice/acetone) THF (20 mL) solution of diisopropylsquarate (3.0 g, 15.10 mmol) was added vinylmagnesium bromide (18.74 mmol, 15.6 mL, 1.00 M) dropwise. After 4 h, the reaction was quenched at −78 °C with aq NH_4Cl (20 mL). The crude mixture was allowed to reach 25 °C and then extracted with ether (3 × 20 mL), and the organic extracts were combined and dried over anhyd $MgSO_4$. The mixture was filtered, and the solvent was removed under reduced pressure. The product (2.20 g, 64%) was obtained as a yellow oil. TLC (silica gel, 20% ethyl acetate/hexanes, R_f = 0.26); chromatographic purification (Baeckström column, silica gel, 1.5 × 10 cm, ethyl acetate/hexanes gradient); IR (NaCl, cm^{-1}) 3384 (s), 2975 (s), 2935 (s), 2875 (m), 1650 (s), 1540 (m); ^1H NMR ($CDCl_3$, 200 MHz) δ 5.95 (dd, J = 17.3, 10.6 Hz, 1 H), 5.50 (dd, J = 17.3, 1.0 Hz, 1 H), 5.31 (dd, J = 10.6, 1.0 Hz, 1 H), 4.85 (two overlapping multiplets, J = 6.2 Hz, 2 H), 3.37 (bs, 1 H), 1.39 (d, J = 6.2 Hz, 3 H), 1.36 (d, J = 6.2 Hz, 3 H), 1.29 (d, J = 6.1 Hz, 3 H), 1.26 (d, J = 6.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 184.2, 166.1, 134.6, 132.4, 118.0, 86.6, 77.3, 73.6, 22.7, 22.5, 22.4; HRMS (EI) calcd for $C_{12}H_8O_4$ 226.1205, found 226.1196.

1,4-Dimethoxy-2,3-diisopropoxybenzene (9). Cyclobutenone **10** (2.26 g, 10.0 mmol) was immersed into a preheated oil bath at 160 °C for 15 min. The hydroquinone thus formed (R_f = 0.5, 20% EtOAc/hexanes) was taken up in DMSO (10 mL), and ground KOH (4.56 g, 80 mmol) was added followed by MeI (2.84

Scheme 4



g, 20 mmol). After 2 h, the mixture was poured into water (100 mL). The mixture was extracted with ether (3 × 10 mL), and the organic extracts were combined and dried over anhyd $MgSO_4$. The mixture was filtered, and the solvent was removed under reduced pressure. The product (2.20 g, 87%) was obtained as a yellow oil after purification: TLC (silica gel, 20% ethyl acetate/hexanes, $R_f = 0.8$); chromatographic purification (Baeckström column, silica gel, 1.5 cm × 10 cm, ethyl acetate/hexanes gradient); IR (NaCl, cm^{-1}) 3512 (w), 2975 (s), 2973 (s), 2931 (s), 1594 (w), 1488 (s); ^1H NMR ($CDCl_3$, 300 MHz) δ 6.55 (s, 2 H), 4.47 (m, $J = 6.2$ Hz, 2 H), 3.78 (s, 6 H), 1.29 (d, $J = 6.1$, 12 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 148.4, 141.7, 105.6, 75.1, 55.9, 22.4; HRMS (EI) calcd for $C_{14}H_{22}O_4$ 254.1518, found 254.1530.

2-Ethyl-3-isopropoxy-4-hydroxy-4-(2′,5′-dimethoxy-3′,4′-diisopropoxyphenyl)-2-cyclobuten-1-one (4). To a cold (−78 °C) mixture of TMEDA (0.23 g, 1.97 mmol) and *sec*-butyllithium (1.5 mL, 1.3 M, 1.97 mmol) was added dropwise a THF (5 mL) solution of 1,4-dimethoxy-2,3-diisopropoxybenzene **9** (0.5 g, 1.97 mmol) via cannula. At this point, the solution turned bright yellow. The mixture was stirred at −78 °C for 2 h and at 25 °C for 1 h. It was then cooled to −78 °C and cannulated into a cold (−78 °C) THF (7 mL) solution of 3-ethyl-4-isopropoxycyclobuten-1,2-dione **5** (0.3 g, 1.97 mmol). After 2 h, the reaction was quenched at −78 °C with water. The mixture was warmed to 25 °C and extracted with ether (3 × 20 mL). The organic extracts were combined and dried over anhyd $MgSO_4$. The mixture was filtered, and the solvent was removed under reduced pressure to give a yellow oil (0.49 g, 59%): TLC (silica gel, 20% ethyl acetate/hexanes, $R_f = 0.16$); chromatographic purification (Baeckström column, silica gel, 1.5 × 10 cm, ethyl acetate/hexanes gradient); IR (KCl, cm^{-1}) 3387 (w), 2975 (w), 2931 (w), 1791 (s), 1748 (s), 1617 (s); ^1H NMR ($CDCl_3$, 200 MHz) δ 6.45 (s, 1 H), 5.26 (br s, 1 H), 4.79 (m, $J = 6.2$ Hz, 1 H), 4.50 (m, $J = 6.2$ Hz, 1H), 4.41 (m, $J = 6.0$ Hz, 1H), 3.99 (s, 3 H), 3.76 (s, 3 H), 2.23 (q, $J = 7.5$ Hz, 2 H), 1.44 (d, $J = 6.3$ Hz, 3 H), 1.36 (d, $J = 6.3$ Hz, 3 H), 1.3−1.2 (m, 6H), 1.18 (t, $J = 7.6$ Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 190.4, 178.8, 150.1, 146.3, 145.8, 141.8, 129.0, 123.8, 104.2, 93.4, 77.2 (s), 77.3, 60.8 (s), 75.6, 75.4, 62.2, 55.9, 22.7, 22.5, 22.4, 22.3, 15.9, 11.9; HRMS (FAB+) calcd for $C_{23}H_{34}O_7$ 422.2305, found 422.2313.

2-Ethyl-3-hydroxy-6,7-diisopropoxy-5,8-dimethoxy-1,4-naphthoquinone (11). Cyclobutenone **4** (0.43 g, 1.0 mmol) was placed into a round-bottomed flask fitted with a condenser. The system was purged several times with nitrogen and then immersed into an oil bath at 150 °C. After 20 min, the reaction had gone to completion as indicated by TLC (silica gel, 20% ethyl acetate/hexanes, $R_f = 0.67$). The yellow oil was taken up in ether (5 mL), and water (3 mL) was added. To this mixture was gradually added solid ceric ammonium nitrate until the hydroquinone was completely oxidized to the naphthoquinone **2**. The organic phase was then separated, and the aqueous phase was extracted with ether (3 × 10 mL). The organic extracts were combined and dried over anhyd $MgSO_4$. The mixture was filtered, and the solvent was removed under reduced pressure to give a bright red oil (silica gel, 20% ethyl acetate/hexanes, $R_f = 0.68$), which on 7 h exposure to air hydrolyzed to hydroxynaphthoquinone **11** (0.35 g, 91%); TLC (silica gel, 20% ethyl acetate/hexanes, $R_f = 0.40$); chromatographic purification (Baeckström column, silica gel, 1.5 × 10 cm, ethyl acetate/hexanes gradient); IR (neat, cm^{-1}) 3350 (m), 2975 (s), 2935 (s), 2875 (m), 1650 (s), 1540 (m); ^1H NMR ($CDCl_3$, 200 MHz) δ 7.45 (bs, 1 H), 4.72 (m, $J = 6.1$ Hz, 1 H), 4.68 (m, $J = 6.1$ Hz, 1 H), 3.91 (s, 3 H), 3.89 (s, 3 H), 2.53 (q, $J = 7.5$ Hz, 2 H), 1.33 (d, $J = 6.2$ Hz, 6 H), 1.15 (t, $J = 7.5$ Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 183.8, 179.8, 153.8, 152.7, 152.3, 151.8, 150.5, 125.0, 121.8, 118.2, 76.9, 76.6, 61.2, 22.7, 22.6, 16.7, 12.6; HRMS (FAB+) calcd for $C_{20}H_{26}O_7$ 379.1757, found 379.1746.

Echinochrome A. To a cold (−78 °C) dichloromethane (3 mL) solution of naphthoquinone **11** (230 mg, 0.6 mmol) was added dropwise a dichloromethane solution of BBr_3 (6.1 mL, 1.00 M, 6.1 mmol, 10 equiv). The initially pale yellow solution turned red as the addition proceeds. After the addition was complete, the cooling bath was removed and the mixture was stirred at 25 °C for 24 h. After that time, the reaction was quenched with water (30 mL) at −78 °C. The mixture was warmed to 25 °C and stirred at that temperature for 24 h to ensure a complete hydrolysis. The organic phase was then separated, and the aqueous phase was extracted with ethyl acetate (4 × 15 mL). The organic extracts were combined and dried over anhyd $MgSO_4$. The mixture was filtered, and the solvent was removed under reduced pressure to give a bright red solid. The product (65 mg, 41%) was obtained as a bright-red solid after chromatography purification): TLC (H^+-pretreated silica gel, 40% ethyl acetate/hexanes, $R_f = 0.34$); chromatographic purification (Baeckström column, H^+-pretreated silica gel, 1.5 × 10 cm, ethyl acetate/hexanes); mp 215−216 °C (lit.[1] mp 222−223 from chloroform) (ethyl acetate/hexanes, 1:4); IR (KBr pellet, cm^{-1}) 3308 (s), 2975 (m), 2930 (m), 2880 (m), 1584 (s), 1465 (m), 1422 (s), 1280 (s); ^1H NMR (300 MHz) δ 2.74 (q, $J = 7.5$ Hz, 2 H), 1.17 (t, $J = 7.6$ Hz, 3 H); ^{13}C NMR (75.5 MHz) δ 179.6, 177.9, 165.1, 163.5, 155.0, 143.1, 140.9, 126.8, 108.3, 103.7, 17.4, 13.3; HRMS (EI) calcd for $C_{12}H_{10}O_7$ 266.0427, found 266.0430.

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Supporting Information Available: NMR spectra for obtained compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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