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A Facile Synthesis of Stentorin, the Photoreceptor of *Stentor coeruleus*

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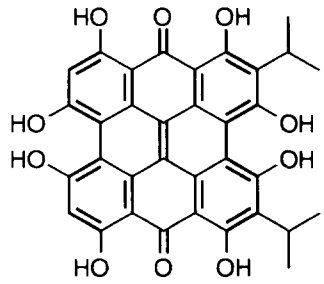
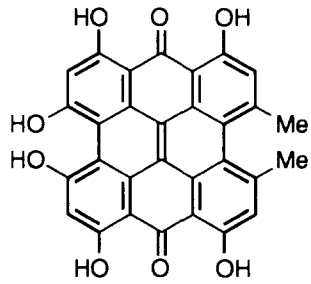
Abstract: Stentorin, a protozoan photoreceptor, was effectively synthesized via the Ullmann coupling reaction of 5-bromo-2-isopropyl-1,3,6,8-tetramethoxyanthraquinone, which was prepared from 3-isopropyl-2,4-dimethoxy-6-(3,5-dimethoxybenzyl)benzoic acid via intramolecular Friedel-Crafts reaction and regioselective bromination.

Studies on the pigments of protozoan ciliate *Stentor* and *Blepharisma* began in the 1870's, and their gross structures have been believed to be hypericin-like.[1] In 1993, Song et al. proposed the molecular structure of stentorin as **1** or its regio isomer with respect to the isopropyl groups,[2] which was distinctively different from that of hypericin (**2**).[3] Very recently, Cameron and Riches have synthesized both of the compounds suggested for stentorin, concluding that the real structure of stentorin was **1**.[4] We have been interested in the structure and biological functions of protozoan pigments. In this paper, we would like to communicate our facile synthesis of stentorin (**1**), which is completely different from that reported by Cameron and Riches.



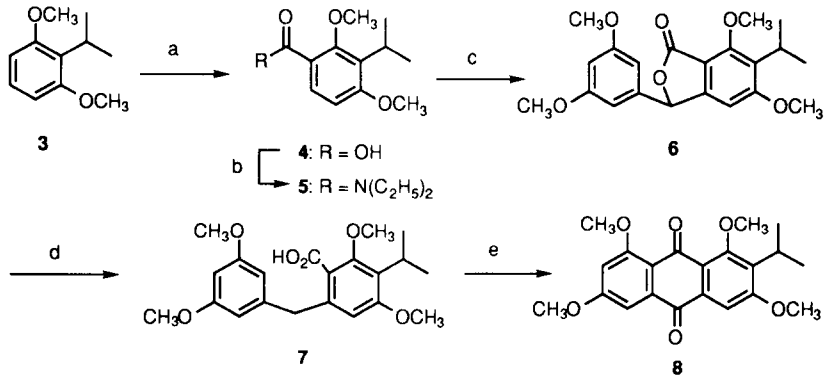
Stentorin (**1**)



Hypericin (**2**)

Following a survey of the literature on the synthesis of hypericin (**2**),[5-7] we chose the Friedel-Crafts strategy to synthesize the anthraquinone derivative required for the synthesis of stentorin. We first converted symmetrical 2-isopropyl-1,3-dimethoxybenzene (**3**), which was easily synthesized from 1,3-dimethoxybenzene according to the Engler's method,[8] to 2,4-dimethoxy-3-isopropylbenzonitrile by the reaction with chloro-

sulfonyl isocyanate followed by the treatment with dimethylformamide.[9] The nitrile was hydrolyzed with NaOH to afford 2,4-dimethoxy-3-isopropylbenzoic acid (**4**) in 86% overall yield. The product **4** was converted ($SOCl_2$, then Et_2NH) to diethylamide **5** in order to condense with 3,5-dimethoxybenzaldehyde. Reaction with the *ortho*-lithiated derivative of **5** prepared by directed metalation using *sec*-butyllithium[10] gave the adduct, which was treated with *p*-toluensulfonic acid to afford lactone **6** in 65% overall yield.[11] Hydrogenolysis of **6** proceeded smoothly to afford **7** [mp 133-4℃] in 98% yield. The carboxylic acid **7** was subjected to the intramolecular Friedel-Crafts reaction by use of trifluoroacetic anhydride in CH_2Cl_2 to give the unstable cyclized derivative,[12] which, without isolation, was treated with oxygen in methanol of the intermediate to afford 1,3,6,8-tetramethoxy-2-isopropylanthraquinone (**8**) in 75% yield.[13] The intramolecular Friedel-Crafts reaction of 3,5-dimethoxy-2-(3'-isopropyl-2',4'-dimethoxybenzyl)-benzoic acid using a variety of acids proved unsuccessful.



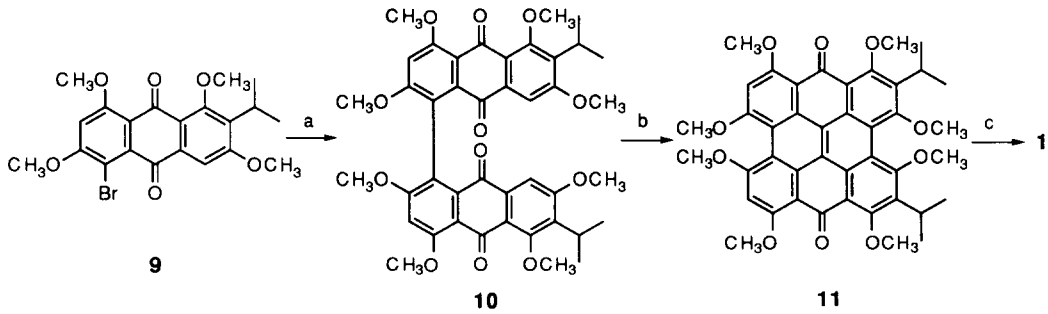
Scheme 1 (a) 1) $ClSO_2NCO$, then DMF. 2) NaOH/EtOH. (b) 1)$SOCl_2$, then Et_2NH. (c) 1) *sec*-BuLi/THF, -78℃, then 3,5-dimethoxybenzaldehyde. 2) *p*-TsOH. (d) H_2/10% Pd-C/AcOEt. (e) $(CF_3CO)_2O/CH_2Cl_2$, 0℃, then O_2/MeOH.

Treatment of **8** with *N*-bromosuccinimide (4 equiv) in the presence of $FeCl_3$ (1.2 equiv) in THF afforded the monobrominated product **9** [mp 207-8℃. ^1H NMR ($CDCl_3$) δ 1.30 (d, *J* = 7.0 Hz, 6H), 3.63 (septet, *J* = 7.0 Hz, 1H), 3.87 (s, 3H), 3.93 (s, 3H), 3.99 (s, 6H), 6.73 (s, 1H), 7.35 (s, 1H)] in 93% yield. Without the Lewis acid, the reaction was impracticably slow. The bromination occurred regioselectively at the 5 position. This position is sterically less hindered than the 4 position because the bulky isopropyl group of **8** would force the methoxy group at the 3 position to impede the 4 position.

The Ullmann reaction[5,14] of **9** under heating at 240℃ in the presence of copper in naphthalene for 2 h effectively produced the coupling product **10** [m/z (EI) 738 (M^+). ^1H NMR ($CDCl_3$) δ 1,27 (d, *J* = 7.0 Hz, 6H), 1,28 (d, *J* = 7.0 Hz, 6H), 3.64 (septet, *J* = 7.0 Hz, 2H), 3.71 (s, 6H), 3.77 (s, 6H), 3.90 (s, 6H), 4.06 (s, 6H), 6.82 (s, 2H), 7.10 (s, 2H)] in 83% yield. Subsequent treatment of **10** with Cu in acetic acid formed 9,14-diisopropyl-1,3,4,6,8,10,13,15-octamethoxyhelianthrone [mp 192℃. m/z (EI) 706 (M^+). ^1H NMR ($CDCl_3$) δ 1.24 (d, *J* = 7.0 Hz, 6H), 1.29 (d, *J* = 7.0 Hz, 6H), 3.33 (s, 6H), 3.65 (septet, *J* = 7.0 Hz, 2H), 3.94 (s, 6H), 4.09, (s, 6H), 4.14 (s, 6H), 6.86 (s, 2H), 6.94 (s, 2H)], which was finally subjected to

exposure to light (500 W tungsten lamp, 12 h)[5] to afford octamethoxystentorin (**11**)[15] in 25% overall yield from **10**. Demethylation of **11** with KI in 85% aq phosphoric acid under the Falk's protocol[7] deposited crude **1**, which was purified by silica gel chromatography (acetone/hexane = 2/1) to afford a dark solid in 80% yield. This compound was identical with an authentic sample, kindly provided by Prof. Cameron, in UV-visible spectrum and Rf values on silica gel TLC (acetone/hexane = 2/1 and 20% MeOH/CH_2Cl_2). The chemical shifts of stentorin in ^1H NMR highly depend on the concentration. Especially, the phenolic OH and aromatic protons shifted from the reported value.[16] By adjusting the concentration, the spectrum of our synthetic stentorin was proved to be superimposable on that reported in the literature.[2]

In summary, we completed a facile synthesis of stentorin (**1**), by which we are able to supply stentorin in a quantity for further studies on its biological functions and molecular mechanism as a photoreceptor.



Scheme 2 (a) Cu/Naphthalene, 240℃. (b) 1) Cu/HCl/AcOH, (2) hν. c) KI/85% H_3PO_4.

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11. **6:** mp 144℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (d, *J* = 7.0 Hz, 3H), 1.29 (d, *J* = 7.0 Hz, 3H), 3.62 (septet, *J* = 7.0 Hz, 1H), 3.78 (s, 6H), 3.81 (s, 3H), 4.08 (s, 3H), 6.11 (s, 1H), 6.44 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 20.87, 20.91, 24.72, 55.52, 55.94, 62.87, 81.31, 100.03, 100.79, 105.07, 109.78, 130.46, 139.41, 151.35, 158.03, 161.33, 164.91, 168.19. IR (Nujol) 1749, 1595, 1316, 1294, 1232, 1204, 1185, 1160, 1132, 1120, 1074, 1015, 940, 832, 720 cm^{-1}.
12. This unstable cyclized product was assigned to be 2-isopropyl-1,3,6,8-tetramethoxy-10-trifluoroacetyl-antracene-9-ol.[6]
13. **8:** m/z (EI) 370 (M^+). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (d, *J* = 7.0 Hz, 6H), 3.66 (septet, *J* = 7.0 Hz, 1H), 3.88 (s, 3H), 3.92 (s, 3H), 3.94 (s, 6H), 6.74 (d, *J* = 2.5 Hz, 1H), 7.29 (d, *J* = 2.5 Hz, 1H), 7.46 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 20.52, 25.23, 45.84, 55.71, 55.84, 56.58, 62.73, 102.13, 104.67, 105.28, 118.28, 122.07, 133.40, 136.45, 138.05, 159.35, 161.77, 162.56, 163.65, 181.27, 183.81. IR (Nujol) 1664, 1596, 1577, 1322, 1265, 1235, 1213, 1190, 1164, 1144, 1115, 1086, 1060, 1044, 1018, 986, 945, 925, 874, 853, 765, 725 cm^{-1}.
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15. **11:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (d, *J* = 7.0 Hz, 6H), 1.60 (d, *J* = 7.0 Hz, 6H), 3.36 (s, 6H), 3.96 (septet, *J* = 7.0 Hz, 2H), 4.12 (s, 6H), 4.14 (s, 6H), 4.20 (s, 6H), 6.97 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 21.35, 21.96, 25.60, 56.12, 56.82, 61.15, 63.15, 95.84, 111.14, 112.16, 115.09, 118.71, 122.63, 127.89, 129.18, 135.51, 160.38, 161.52, 161.74, 162.07, 182.27.
16. Professor P.-S. Song also observed the same concentration dependence of chemical shifts in ^{1}H NMR on natural stentorin (private communication).

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