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Model studies toward the total synthesis of halenaquinol and halenaquinone

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Abstract—A strategy for the synthesis of the furan-fused tetracyclic core of halenaquinol and halenaquinone was explored through a model study. The synthesis involved the intramolecular [4+2] cycloaddition reaction of the *o*-quinodimethane, generated from benzocyclobutene as the key step.

1. Introduction

The furan-fused polycyclic structure core of halenaquinol and halenaquinone has been found in natural products, and many of them show significant biological activities. For example, halenaquinol **1** and halenaquinone **2** are pentacyclic polyketides isolated from marine sponges,[1] and possess antibiotic, cardiotonic, and protein tyrosine kinase inhibitory activities.[2] In addition, sodium salt of halenaquinol monosulfate **3** also showed interesting anti-viral activity. The unique furan-fused polycyclic structure associated with above natural products together with their intriguing biological activities has inspired the synthesis of these natural products[3] (Fig. 1).

Here, we disclose short-step approach to the furan-fused tetracyclic core structure **4** using the intramolecular [4+2] cycloaddition reaction of the *o*-quinodimethane as the key step,[4] and a full account of the experiments investigated.[5]

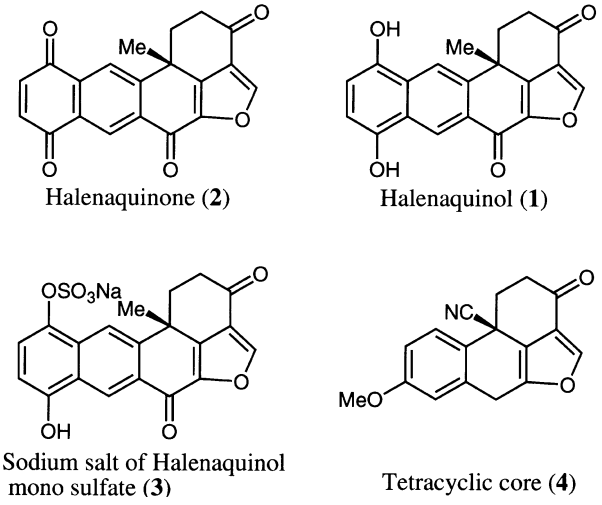

Figure 1.

2. Results and discussion

The alcohol **5**[6] was converted to bromide **6**, which was used for the alkylation of benzocyclobutene **7**[7] to afford the alkylated product **8**. With the requisite benzocyclobutene **8** in hand, we examined the key intramolecular [4+2] cycloaddition reaction. Thus thermal reaction of **8** in refluxing *o*-dichlorobenzene proceeded to give rise to the cycloadduct **9** as a single isomer in good yield (Fig. 2, Scheme 1). The stereochemistry of **9** was determined to be *cis* form by X-ray diffraction analysis as shown in Fig. 3.

The stereoselectivity of the above reverse electron demand Diels–Alder type of [4+2] cycloaddition reaction can be rationalized as shown below. Of the two transition states, the secondary orbital interaction between electron-rich furan and electron-deficient diene system, generated from the thermal treatment of **8**, would stabilize the *endo*-transition state.[4] Consequently the reaction proceeds via *endo*-transition state to provide the *cis* adduct, exclusively.

We next focused our attention on the conversion of dihydrofuran moiety in **9** to furan ring. First, we explored the acid-catalyzed ring opening of the dihydrofuran ring followed by oxidation of the resulting alcohol as shown in Scheme 2. Treatment of **9** with ethyleneglycol in the presence of catalytic amounts of *p*-TsOH in benzene afforded an alcohol. Swern oxidation of this alcohol gave

Keywords: halenaquinol; halenaquinone; [4+2] cycloaddition.

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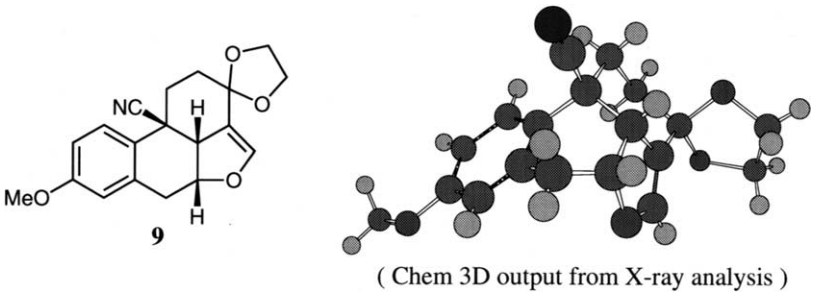
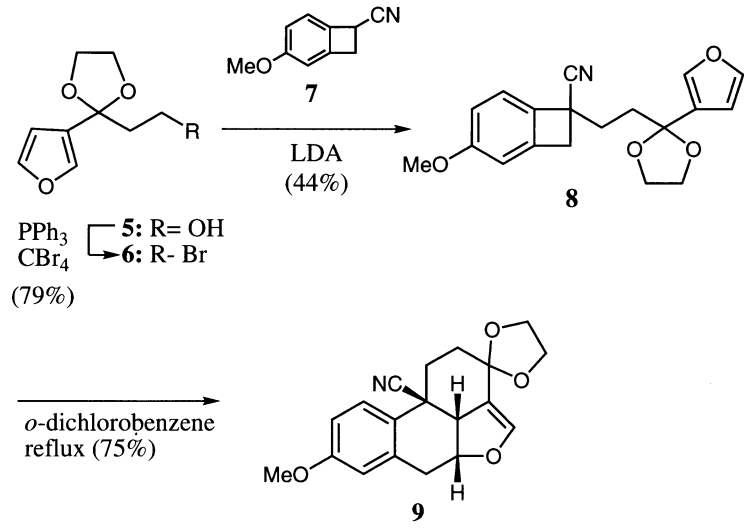


Figure 2.



Scheme 1.

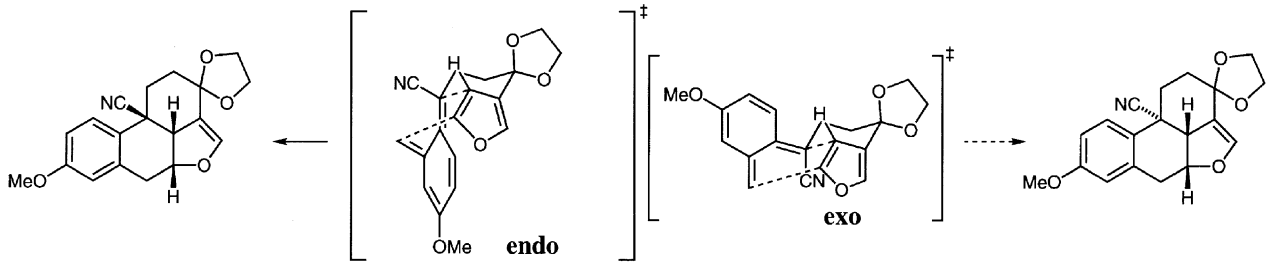


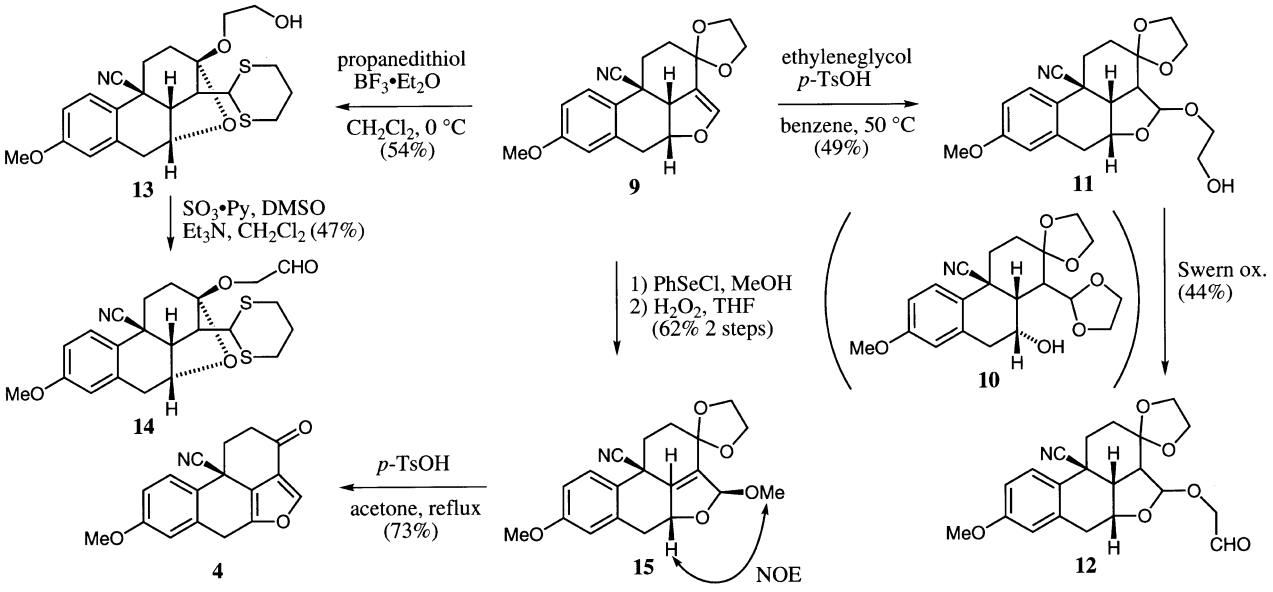
Figure 3.

an aldehyde **12**. Consequently, the structure of the alcohol obtained above was not desired alcohol **10**, but the tetrahydrofuran acetal **11**. The use of 1,3-propanethiol and $BF_3{\cdot}Et_2O$ in CH_2Cl_2 instead of ethyleneglycol and *p*-TsOH in CH_2Cl_2 resulted in the formation of the bridged acetal **13**. The structure of **13** was confirmed by the fact that the oxidation of **13** with $SO_3{\cdot}Py$ provided the aldehyde **14**. Thus, we were forced to develop an alternative route to **4**.

Treatment of **9** with PhSeCl in MeOH gave phenylseleno derivative, which was oxidized with H_2O_2 to afford the dihydrofuran **15**. The stereochemistry of methoxy group on the dihydrofuran ring in **15** was confirmed by the NOE experiment as shown in Scheme 2. Finally, acid-catalyzed removal of MeOH furnished the desired tetracyclic core **4**. In the ^1H NMR spectrum of **4**, disappearance of the methoxy group at δ 3.46 on the dihydrofuran ring and the appearance of the signal at δ 7.97 showed the formation of the furan ring system.

3. Conclusion

We have demonstrated the facile synthesis of the tetracyclic core **4** of the pentacyclic polyketides of halenaquinol **1** and halenaquinone **2** using an intramolecular [4+2] cycloaddition reaction of *o*-quinodimethane generated from pertinent benzocyclobutene **8** as the crucial step. This short step access to the furan-fused tetracyclic compound **4** would provide us with promising entry to the pentacyclic polyketides of **1** and **2**.



Scheme 2.

4. Experimental

4.1. General

Melting points were determined with a Yanaco micro melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were taken on a Varian Gemini 300 or Unity Plus 500 spectrometer. ^{1}H NMR spectra were recorded at the indicated field strength as solutions in $CDCl_3$ unless otherwise indicated. Chemical shifts are given in parts per million (ppm, δ) downfield from TMS and are referenced to $CHCl_3$ (7.26 ppm) as internal standard. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. ^{13}C NMR spectra were recorded at the indicated field strength as solutions in $CDCl_3$ unless otherwise indicated. Chemical shifts are given in parts per million (ppm, δ) downfield from TMS and are referenced to the center line of $CDCl_3$ (77.0 ppm) as internal standard. Carbon signals were assigned by a DEPT pulse sequence, q=methyl, t=methylene, d=methyne, and s=quaternary carbons. Infrared spectra (IR) were measured with a Perkin–Elmer 1600 series FT-IR spectrophotometer. Mass spectra (MS) and high-resolution mass spectra (HRMS) were measured on a JEOL JMS-AX505HAD mass spectrometer. Column chromatography was performed on Merck silica gel 60 (No 7734-5B) or (No 9385).

4.1.1. 2-[3-(Furyl)-2-(2-bromoethyl)]-1,3-dioxolane (6). CBr_4 (1.26 g, 3.80 mmol) and Ph_3P (998 mg, 3.80 mmol) were added to a stirred solution of **5** (500 mg, 2.72 mmol) in CH_2Cl_2 (10 mL) at room temperature, and the reaction mixture stirred at room temperature for 0.5 h. The reaction was quenched with satd. NH_4Cl (aq), and the organic layer separated. The organic layer was dried, and evaporated to give colorless semisolid, which was chromatographed on SiO_2 (20 g, hexane/acetone=50:1) to afford **6** (563 mg, 84%) as colorless oil. This bromide **6** was unstable and used immediately in the next step. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.47–2.55 (2H, m), 3.35–3.43 (2H, m), 3.87–4.05 (4H, m), 6.34 (1H, s), 7.39–7.44 (2H, m).

4.1.2. 7-{2-[1-(3-Furyl)-2,5-dioxolanyl]ethyl}-3-methoxybicyclo[4.2.0]-octa-1(2),3,5-triene-7-carbonitrile (8). A solution of **7** (159 mg, 1.08 mmol) in THF (5 mL) at −78°C was added to a stirred solution of LDA (0.6 M in THF, 2.2 mL), and the resulting mixture stirred at −78°C for 0.5 h. A solution of **6** (268 mg, 1.08 mmol) in THF (5 mL) at −78°C was added to the reaction mixture at −78°C, and then stirred at −78°C–0°C for 3 h. The reaction was quenched with satd. NaCl (aq), and the aqueous mixture extracted with Et_2O (10 mL×4). The extracts were combined, dried, and evaporated to give pale yellow oil, which was chromatographed on SiO_2 (15 g, hexane/acetone=30:1) to afford **8** (142 mg, 42%) as colorless oil.

IR (neat) 2957, 2231, 1592, 1372, 1326 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ; 1.99–2.08 (2H, m), 2.13–2.25 (2H, m), 3.19 (1H, d, J=14.1 Hz), 3.64 (1H, d, J=14.1 Hz), 3.78 (3H, s), 3.89–3.90 (2H, m), 3.95–3.98 (2H, m), 6.33 (1H, t, J=0.9 Hz), 6.7 (1H, d, J=2.1 Hz), 6.79–6.82 (1H, dd, J=2.4, 8.3 Hz), 7.09 (1H, d, J=8.5 Hz), 7.36 (1H, t, J=1.7 Hz), 7.39 (1H, t, J=0.9 Hz); ^{13}C NMR (75 MHz) δ: 31.85 (t), 36.33 (t), 41.73 (s), 42.38 (t), 55.68 (q), 65.00 (t), 106.89 (s), 108.60 (d), 109.37 (d), 115.01 (d), 121.86 (s), 122.92 (d), 127.31 (s), 135.19 (s), 140.09 (d), 142.03 (s), 143.55 (d), 161.13 (s); MS m/z 325 (M^+); HRMS calcd for $C_{19}H_{19}NO_4$: 325.1314, Found 325.1393.

4.1.3. 9-Methoxy-4,16,19-trioxapentacyclo[14.1.4.1⟨2,5⟩.0⟨7,12⟩.0⟨13,20⟩]-icosa-2(3),7(8),9,11-tetraene-13-carbonitrile (9). A stirred solution of **8** (100 mg, 0.31 mmol) in *o*-dichlorobenzene (6 mL) was heated at reflux for 2 h. After cooling, the solvent was evaporated to give pale yellow oil, which was chromatographed on SiO_2 (10 g, hexane/acetone=30:1) to afford **9** (85 mg, 85%) as colorless solid (mp 154–157°C from i-Pr_2O).

IR (KBr) 2932, 2230, 1671, 1616, 1580, 1500, 1462, 1312, 1169 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 1.83–1.89 (2H, m), 2.52 (1H, dt, J=4, 15 Hz), 2.86 (1H, td, J=3, 15 Hz), 3.11 (1H, dd, J=1.5, 16 Hz), 3.27 (1H, dd, J=3, 16 Hz), 3.79 (3H, s), 3.83–3.92 (4H, m), 3.98–4.00 (1H, m), 5.29 (1H, d, J=10.5 Hz), 6.02 (1H, s), 6.81 (1H, d, J=8 Hz), 6.83 (1H, s), 7.22 (1H, d, J=8 Hz); ^{13}C NMR (75 MHz) δ: 29.59 (t), 31.20 (t), 34.04 (t), 35.13 (s), 51.03 (d), 55.18 (q), 63.60 (t), 65.20 (t), 79.62 (d), 104.53 (s), 110.29 (s), 112.66 (d), 115.72 (d), 122.23 (s), 122.63 (s), 126.74 (d), 136.76 (s), 142.95 (d), 159.50 (s); MS m/z 325 (M^+); HRMS calcd for $C_{19}H_{19}NO_4$: 325.1314, Found 325.1343.

Crystallographic data for **9**: monoclinic, space group $P21$, with a=6.456(1) Å, b=35.490(3) Å, c=7.039(1) Å, β=95.72(1)°, V=1604.8(4) $Å^3$, and Z=4 (D_{calcd}=1.347 g/cm^3, μ(MoKα)=0.95 cm^{-1}, absorption corrected by ω scans; 3628 unique reflections; 3006 with $I > 2.00\sigma(I)$ were used in refinement; $R1$=4.1%, $wR2$=6.0%.

4.1.4. 3-(2-Hydroxyethoxy)-9-methoxy-4,16,19-trioxapentacyclo[14.-1.4.1⟨2,5⟩,0⟨7,12⟩.0⟨13,20⟩]icosa-7(12),8,10-triene-13-carbonitrile (11). p-TsOH·H_2O (20.5 mg, 0.11 mmol) and ethyleneglycol (0.036 mL, 0.65 mmol) were added to a stirred solution of **9** (175 mg, 0.54 mmol) in benzene (12 mL), and the resulting mixture heated at 50°C for 9 h. After cooling the reaction was quenched with satd. $NaHCO_3$ (aq), and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (10 mL×3). The organic layer and extracts were combined, dried, and evaporated to give colorless oil, which was chromatographed on SiO_2 (25 g, hexane/acetone=5:1) to afford **11** (103 mg, 49%) as colorless solid (mp 75∽78°C).

IR (KBr) 3492, 2949, 2239, 1613, 1155 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 1.70 (1H, br s), 1.82–1.86 (2H, m), 2.08–2.11 (2H, m), 2.78 (1H, dd, J=2, 9 Hz), 2.99–3.07 (2H, m), 3.40 (1H, t, J=9 Hz), 3.57–3.61 (1H, m), 3.63–3.66 (2H, m), 3.70–3.74 (1H, m), 3.81 (3H, s), 3.94–4.09 (4H, m), 4.45–4.50 (1H, m), 4.95 (1H, br s), 6.76 (1H, br s), 6.80 (1H, dd, J=2.6, 8.5 Hz), 7.47 (1H, d, J=8.5 Hz); ^{13}C NMR (75 MHz) δ: 29.61 (t), 33.62 (t), 34.31 (t), 43.96 (d), 50.04 (d), 55.33 (q), 62.12 (t), 64.01 (t), 65.08 (t), 70.18 (t), 76.74 (d), 100.66 (s), 105.45 (d), 106.43 (s), 112.51 (d), 115.67 (d), 123.13 (s), 126.38 (d), 135.85 (s), 159.54 (s); MS m/z 387 (M^+); HRMS calcd for $C_{21}H_{25}NO_6$: 387.1680, Found 387.1687.

4.1.5. 3-(2-Formylmethoxy)-9-methoxy-4,16,19-trioxapentacyclo[14.-1.4.1⟨2,5⟩,0⟨7,12⟩.0⟨13,20⟩]icosa-7(12),8,10-triene-13-carbonitrile (12). To a stirred solution of $(COCl)_2$ (0.1 mL, 1.15 mmol) in CH_2Cl_2 (2 mL) was added DMSO (0.16 mL, 2.29 mmol) at −78°C, and the reaction mixture was stirred at −78°C for 5 min. To the reaction mixture was added a solution of **11** (69 mg, 0.18 mmol) in CH_2Cl_2 (2 mL) at −78°C, and the resulting mixture was stirred at −78°C for 30 min. Triethylamine (0.48 mL, 3.44 mmol) was added to the reaction mixture, and the mixture was stirred at −78°C∽0°C for 1 h. The reaction was quenched with H_2O, and the aqueous mixture was extracted with Et_2O (10 mL×3). The organic extracts were combined, washed with H_2O and brine, successively, then dried and evaporated to give a pale yellow oil, which was chromatographed on SiO_2 (8 g, hexane/acetone=15:1–4:1) to afford **12** (30 mg, 44%) as colorless oil.

IR (neat) 2948, 2228, 1758 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 1.80 (2H, m), 2.01 (1H, m), 2.82 (1H, d, J=9 Hz), 2.93 (1H, br), 2.99 (1H, d, J=9 Hz), 3.50 (1H, t, J=9 Hz), 3.83 (3H, s), 4.03 (5H, m), 4.21 (2H, s), 4.82 (1H, q-like, J=9 Hz), 5.22 (1H, s), 6.78 (1H, br s), 6.81 (1H, d, J=8.5 Hz), 7.45 (1H, d, J=8.5 Hz), 9.41 (1H, s); MS m/z 385 (M^+); HRMS calcd for $C_{21}H_{23}NO_6$: 385.1524, Found 385.1547.

4.1.6. 13-(2,6-Dithianyl)-12-(2-hydroxyethoxy)-5-methoxy-15-oxatetracyclo[10.2.1.0⟨3,8⟩.0⟨9,14⟩]pentadeca-3(8),4,6-triene-9-carbonitrile (13). 1,3-Propanethiol (0.037 mL, 0.37 mmol) and BF_3·Et_2O (0.047 mL, 0.37 mmol)) at 0°C were added to a stirred solution of **9** (100 mg, 0.31 mmol) in CH_2Cl_2 (5 mL), and the reaction mixture stirred at 0°C for 1 h. The reaction was quenched with satd. $NaHCO_3$ (aq), and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (5 mL×3) and the organic layer and extracts were combined, dried, and evaporated to give pale yellow oil, which was chromatographed on SiO_2 (10 g, hexane/acetone=10:1∽5:1) to afford **13** (72 mg, 54%) as colorless solid (mp 193∽196°C).

IR (KBr) 3460, 2940, 2237, 1611, 1252 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 1.84–1.92 (2H, m), 2.04 (1H, td, J=6.4, 14 Hz), 2.13 (1H, dd, J=1.3, 14 Hz), 2.24–2.29 (2H, m), 2.61 (1H, br s), 2.76–2.85 (4H, m), 3.00–3.15 (3H, m), 3.30 (1H, dd, J=9, 19 Hz), 3.68–3.86 (7H, br m), 4.61–4.64 (1H, m), 5.15 (1H, d, J=12 Hz), 6.67 (1H, br s), 6.76 (1H, dd, J=1.7, 9 Hz), 7.58 (1H, d, J=9 Hz); ^{13}C NMR (75 MHz) δ: 25.44 (t), 29.65 (t), 30.48 (t), 30.55 (t), 33.51 (t), 35.41 (t), 37.58 (s), 44.78 (d), 45.82 (d), 48.54 (d), 55.27 (q), 61.77 (t), 63.88 (t), 73.76 (d), 106.93 (s), 111.81 (d), 114.49 (d), 123.14 (s), 126.68 (d), 128.23 (s), 133.21 (s), 159.43 (s); MS m/z 433 (M^+); HRMS calcd for $C_{22}H_{27}NO_4S_2$: 433.5861, Found 433.5833.

4.1.7. 13-(2,6-Dithianyl)-12-(2-formylmethoxy)-5-methoxy-15-oxatetracyclo[10.2.1.0⟨3,8⟩.0⟨9,14⟩]pentadeca-3(8),4,6-triene-9-carbonitrile (14). To a stirred solution of **13** (81 mg, 0.187 mmol) in CH_2Cl_2 (2 mL) were added Et_3N (0.13 mL, 0.94 mmol), and a solution of SO_3·Py (149 mg, 0.94 mmol), in DMSO (1.4 mL) at 0°C, and the reaction mixture was stirred at room temperature for 2 h. The reaction was quenched with 10% citric acid (aq), and the aqueous mixture was extracted with Et_2O (10 mL×3). The organic extracts were combined, washed with satd. $NaHCO_3$ (aq), dried, and evaporated to give pale yellow oil, which was chromatographed on SiO_2 (8 g, hexane/acetone=15:1–8:1) to afford **14** (38 mg, 47%) as colorless oil.

IR (neat) 2934, 2233, 1729 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 1.81–1.99 (2H, m), 2.04–2.21 (2H, m), 2.23–2.43 (2H, m), 2.76–2.91 (4H, m), 3.02–3.20 (3H, m), 3.30 (1H, m), 3.80 (3H, s), 4.21 (2H, ABq, J=15 Hz), 4.57 (1H, br), 5.19 (1H, d, J=12 Hz), 6.69 (1H, br s), 6.79 (1H, d, J=8 Hz), 7.61 (1H, d, J=8 Hz), 9.73 (1H, s); MS m/z 431 (M^+); HRMS calcd for $C_{22}H_{25}NO_4S_2$: 431.1224, Found 431.1201.

4.1.8. 3,9-Dimethoxy4,16,19-trioxapentacyclo[14,-1.4.1⟨2,5⟩.0⟨7,12⟩.0⟨13,20⟩]icosa-2(20),7(12),8,10-tetraene-13-carbonitrile (15). PhSeCl (27.9 mg, 0.154 mmol) at 0°C was added to a stirred solution of **9** (50 mg, 0.154 mmol) in MeOH (3.5 mL, and the resulting solution stirred at 0°C for 1 h, then at room temperature for 2.5 h. Additional PhSeCl (8.9 mg, 0.046 mmol), was added to the reaction mixture and the stirring continued at room temperature for 0.5 h. The reaction mixture was diluted with EtOAc (15 mL), and the organic mixture washed with satd. $NaHCO_3$ (aq) and brine successively, then dried, and evaporated to give colorless oil, which was used directly in the next step.

A solution of H_2O_2 (31% in H_2O, 0.071 mL) at 0°C was added to a stirred solution of the above oil in THF (6.5 mL), and the reaction mixture stirred at 0°C for 14 h. The reaction was quenched with H_2O, and the aqueous mixture extracted with EtOAc (5 mL×3). The organic extracts were combined, washed with satd. $NaHCO_3$ (aq), dried, and evaporated to give colorless oil, which was chromatographed on SiO_2 (6 g, hexane/acetone=15:1) to afford **15** (34 mg, 62%) as colorless solid (mp 160–163°C).

IR (KBr) 2961, 2233, 1702, 1610 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 2.11 (1H, dm, J=12 Hz), 2.16 (1H, dm, J=16 Hz), 2.34 (1H, t-like, J=15 Hz), 2.72 (1H, dm, J=12 Hz), 2.92 (1H, dd, J=10, 15 Hz), 3.36–3.40 (1H, m), 3.46 (3H, s), 3.79 (3H, s), 3.81–4.12 (4H, br m), 5.03 (1H, dd, J=7, 10 Hz), 5.95 (1H, br s), 6.60 (1H, br s), 6.86 (1H, dd, J=2.6, 8.7 Hz), 7.33 (1H, d, J=8.7 Hz); ^{13}C NMR (75 MHz) δ: 33.92 (t), 35.39 (t), 37.28 (s), 40.29 (t), 54.86 (q), 55.29 (q), 65.22 (t), 66.21 (t), 77.99 (d), 103.66 (s), 108.70 (d), 114.35 (d), 114.66 (d), 120.36 (s), 125.48 (s), 127.93 (d), 132.95 (s), 134.54 (s), 142.50 (s), 159.59 (s); MS m/z 355 (M^+), 207 (100); HRMS calcd for $C_{20}H_{21}NO_5$: 355.1420, Found 355.1420.

4.1.9. 8-Methoxy-3-oxo-1,2,6-trihydro-5-oxaacephenanthrylene-10b-carbonitrile (4). A solution of p-TsOH·H_2O (8 mg) in acetone (0.8 mL) was added to a stirred solution of **15** (30 mg, 0.085 mmol) in acetone (1 mL) and the reaction mixture heated at reflux for 16 h. After cooling, the reaction was quenched with satd. $NaHCO_3$ (aq), and the aqueous mixture extracted with CH_2Cl_2 (5 mL×3). The organic extracts were combined, dried, and evaporated to give colorless oil, which was chromatographed on SiO_2 (3 g, hexane/acetone=20:1) to afford **4** (19 mg, 80%) as colorless solid (mp 181∽184°C).

IR (KBr) 2935, 2226, 1695, 1673 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 2.18 (1H, td, J=3.4, 13 Hz), 2.83 (1H, dt, J=3,18 Hz), 3.01 (1H, ddd, J=2.6, 4.3, 13 Hz), 3.15 (1H, ddd, J=4.3, 14, 18 Hz), 3.85 (3H, s), 4.00 (1H, d, J=20 Hz), 4.18 (1H, d, J=20 Hz), 6.88 (1H, br s), 6.95 (1H, dd, J=2.6, 8.5 Hz), 7.50 (1H, d, J=8.5 Hz), 7.97 (1H, br s); ^{13}C NMR (75 MHz) δ: 28.76 (t), 35.31 (s), 35.58 (t), 37.97 (t), 55.44 (q), 113.87 (d), 115.27 (d), 118.47 (s), 120.36 (s), 120.87 (s), 124.91 (s), 127.65 (d), 135.06 (s), 143.32 (d), 148.90 (s), 159.74 (s), 191.43 (s); MS m/z 279 (M^+), 223 (100); HRMS calcd for $C_{17}H_{13}NO_3$: 279.0895., Found 279.0902.

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