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General.

All reactions were carried out under a nitrogen atmosphere. Common solvents were purified before use. Tetrahydrofuran (THF) and diethyl ether (Et₂O) were purified by distillation from sodium-benzophenone ketyl. Dichloromethane (CH₂Cl₂), N,N-dimethylformamide (DMF), acetonitrile (MeCN) and benzene were distilled from calcium hydride. Methanol (MeOH) was distilled from magnesium. All reagents used were reagent grade and purified where necessary. Reactions were monitored by thin layer chromatography (TLC) using 250 μ m Baker precoated silica gel (230-400 mesh). Carbon and proton NMR spectra were recorded on 400 MHz spectrometer. ¹H NMR chemical shifts are reported as δ values (ppm) relative to internal tetramethylsilane or residual CHCl₃ (7.26) in CDCl₃. ¹³C NMR chemical shifts are reported as δ values (ppm) relative to residual CHCl₃ (77.0) in CDCl₃. Peak multiplicities in ¹H NMR are abbreviated as s (singlet), d (doublet), m (multiplet), sep (septet), td (triplet of doublets) and/or br (broad). Infrared spectra (IR) were recorded in reciprocal centimeters (cm⁻¹).

3-Chloromethyl-5,8-dimethoxy-naphthalen-1-ol (6).

To a solution of triphenylphosphine (2.1 g, 8 mmol) in 10 mL THF was added 3 mL of CCl_4 . The reaction mixture was stirred for 10 min and alcohol **5** (930 mg, 4 mmol) was introduced as a solid. The resulting solution was refluxed for 2 h, then diluted with water (50 mL). The product was extracted with EtOAc and washed twice with water. The combined aqueous layers were back extracted once with EtOAc and the combined organics were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by pre-absorbed silica gel chromatography (4:1 hexanes:EtOAc) yielded 950 mg (95 %) of **6** as

Kozhinov, Behar; "Extension of the Tandem Conjugate Addition-Dieckmann Condensation: The Formal Synthesis of Tetracenomycin A₂" (JO035341K) a white solid; mp= 136-137 °C. ¹H NMR (400 MHz, CDCl₃) δ 9.48 (s, 1H), 7.71 (s, 1H), 6.95 (s, 1H), 6.69 (d, J = 8 Hz, 1H), 6.66 (d, J = 8 Hz, 1H), 4.67 (s, 2H), 4.01 (s, 3H), 3.94 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 155, 150.2, 149.9, 136.4, 128.1, 115.4, 112.9, 111.3, 104.1, 103.7, 56.3, 55.7, 46.8. IR (thin film) 3360, 1617, 1519, 1455, 1390, 1287, 1251, 1183, 1096, 1054, 809, 707, 605 cm⁻¹. LRMS (EI) calcd for C₁₃H₁₃³⁵ClO₃ (M⁺): 252, found: 252. Anal. Calcd. for C₁₃H₁₃ClO₃: C, 61.79; H, 5.19. Found: C, 61.67; H, 5.18.

(4-Hydroxy-5,8-dimethoxy-naphthalen-2-yl)-acetic acid methyl ester (7).

A flask, containing benzyl chloride **6** (923 mg, 3.65 mmol), $PdCl_2(PPh_3)_2$ (130 mg, 0.18 mmol) and potassium carbonate (530 mg, 3.83 mmol) was evacuated and then filled with carbon monoxide. By means of syringe MeOH (5mL) and THF (10mL) were added and the mixture was stirred under carbon monoxide for 24 h. Then the reaction mixture was diluted with H₂O (50 mL). The product was extracted with EtOAc and washed twice with water. The aqueous layers were extracted once with EtOAc and the combined organics were dried over Na₂SO₄ and concentrated *in vacuo*. Purification by preabsorbed silica gel chromatography (4:1 hexanes:EtOAc) yielded 870 mg (87 %) of **7** as a yellow solid; mp= 91-92 °C. ¹H NMR (400 MHz, CDCl₃) δ 9. 44 (s, 1H), 7.60 (s, 1H), 6.86 (s, 1H), 6.64 (s, 2H), 3.99 (s, 3H), 3.92 (s, 3H), 3.71 (s, 2H), 3.69 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 171.7, 154.5, 149.7, 133, 128, 114.4, 113.2, 112.2, 103.2, 103.1, 55.9, 55.4, 51.8, 41.4. IR (thin film) 3376, 2950, 2841, 1738, 1637, 1615, 1519, 1454, 1393, 1336, 1305, 1250, 1180, 1157, 1126, 1091, 1055, 1016, 971, 801, 726 cm⁻¹.

Kozhinov, Behar; "Extension of the Tandem Conjugate Addition-Dieckmann Condensation: The Formal Synthesis of Tetracenomycin A_2 " (JO035341K) LRMS (EI) calcd for $C_{15}H_{16}O_5$ (M⁺): 276, found: 276. Anal. Calcd. for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84. Found: C, 65.08; H, 5.78.

(4-Hydroxy-3-iodo-5,8-dimethoxy-naphthalen-2-yl)-acetic acid methyl ester (8).

To a solution of ester 7 (860 mg, 3.11 mmol) in CH₂Cl₂ (125 mL) at room temperature was added iodine (1.58 g, 6.23 mmol) followed by morpholine (760 mg, 9.33 mmol). The reaction mixture was stirred for 15 min and then quenched with 10% Na₂S₂O₃ solution. Organic layer was separated and washed once with water. The aqueous layers were extracted once with EtOAc and the combined organics were dried over Na₂SO₄ and concentrated *in vacuo*. Purification by pre-absorbed silica gel chromatography (4:1 hexanes:EtOAc) gave 950 mg (76 %) **8** as a yellow solid; mp= 147-148 °C. ¹H NMR (400 MHz, CDCl₃) δ 10.55 (s, 1H), 7.68 (s, 1H), 6.70 (d, *J* = 8 Hz, 1H), 6.66 (d, *J* = 8 Hz, 1H), 4.00 (s, 3H), 3.98 (s, 2H), 3.92 (s, 3H), 3.72 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 171.6, 153.9, 150.3, 148.8, 136.3, 127.7, 115.3, 114.3, 87.1, 57.0, 56.0, 52.6, 47.2. IR (thin film) 3313, 2948, 2839, 1738, 1605, 1486, 1451, 1433, 1409, 1367, 1252, 1198, 1165, 1132, 1093, 1059, 726 cm⁻¹. LRMS (EI) calcd for C₁₅H₁₅IO₅ (M⁺): 401, found: 401. Anal. Calcd. for C₁₅H₁₅IO₅: C, 44.80; H, 3.76. Found: C, 45.66; H, 3.80.

(4-Acetoxy-3-iodo-5,8-dimethoxy-naphthalen-2-yl)-acetic acid methyl ester (9).

To a stirred solution of iodoester **8** (500 mg, 1.24 mmol) and N,N-dimethylaminopyridine (30 mg, 0.24 mmol) in pyridine (2 mL) was added acetic anhydride (150 mg, 1.47 mmol) at room temperature. The reaction mixture was stirred for 15 h and then diluted with 10 % HCl (20 mL). The product was extracted with EtOAc and washed twice with water.

Kozhinov, Behar; "Extension of the Tandem Conjugate Addition-Dieckmann Condensation: The Formal Synthesis of Tetracenomycin A₂" (JO035341K) The aqueous layers were extracted once with EtOAc and the combined organics were dried over Na₂SO₄ and concentrated *in vacuo*. Purified by silica gel chromatography (4:1 hexanes:EtOAc) gave 520 mg (95 %) of **9** as a yellow solid; m.p. 114-115 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.07 (s, 1H), 6.70 (d, *J* = 7 Hz, 1H), 6.67 (d, *J* = 7 Hz, 1H), 4.00 (s, 2H), 3.87 (s, 3H), 3.81 (s, 3H), 3.69 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 170.9, 168.9,149.2, 147.9, 146.9, 134.9, 131.5, 127.6, 121.8, 119.2, 107.0, 106.1, 105.0, 98.5, 56.7, 55.8, 52.3, 46.9, 21.1. IR (thin film) 2998, 2950, 2837, 1768, 1734, 1621, 1589, 1458, 14.33, 1411, 1368, 1344, 1301, 1264, 1192, 1135, 1096, 1054, 1010, 977, 911, 872, 807, 781, 729 cm⁻¹. LRMS (EI) calcd for C₁₇H₁₇IO₆ (M⁺): 444, found: 443. Anal. Calcd. for C₁₇H₁₇IO₅: C, 45.96; H, 3.86. Found: C, 47.40; H, 4.10.

3-(1-Acetoxy-5,8-dimethoxy-3-methoxycarbonylmethyl-naphthalen-2-yl)-propynoic acid methyl ester (11).

To a solution of acetyl iodoester **9** (200 mg, 0.45 mmol) in acetonitrile (2 mL) and triethylamine (2 mL) was added $PdCl_2(PPh_3)_2$ (31 mg, 0.045 mmol) and CuI (26 mg, 0.135mmol). 3,3,3-triethoxy-1-propyne (**10**) (93 mg, 0.54 mmol) was added and the mixture was heated to reflux. After refluxing for 14 hours, the reaction mixture was diluted with EtOAc and washed twice with H₂O. The aqueous layers were extracted once with EtOAc. The combined organics were dried over Na₂SO₄ and concentrated *in vacuo*. The crude material was then dissolved in 2 mL of MeOH and p-toluenesulfonic acid (170 mg, 0.9 mmol) was added. After stirring for twenty-four hours at room temperature, the reaction mixture was diluted with EtOAc and washed twice and washed twice with H₂O. The aqueous layers were dried over Na₂SO₄ and concentrated *in vacuo*.

Kozhinov, Behar; "Extension of the Tandem Conjugate Addition-Dieckmann Condensation: The Formal Synthesis of Tetracenomycin A₂" (JO035341K) Na₂SO₄. Concentration *in vacuo*, followed by silica gel chromatography (4:1 hexanes:EtOAc) gave 110 mg (61 %) of diester **11** as a solid; mp=141-142 °C . ¹H NMR (400 MHz, CDCl₃) δ 8.03 (s, 1H), 7.72 (d, *J* = 8 Hz, 1H), 6.68 (d, *J* = 8 Hz, 1H), 3.94 (br. s, 2H), 3.86 (s, 3H), 3.81 (s, 3H), 3,71 (s, 3H), 2.41 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 171.3, 169.6, 154.5, 151.7, 149.5, 133.4, 128.7, 121.7, 119.0, 113.3, 107.2, 89.0, 80.8, 56.9, 56.2, 53.1, 52.6, 40.1, 21.0. IR (thin film) 3000, 2953, 2840, 2216, 1770, 1738, 1712, 1602, 1463, 1355, 1265, 1206, 1110, 1055 cm⁻¹. LRMS (EI) calcd for C₂₁H₂₀O₈ (M⁺): 400, found: 400. Anal. Calcd. for C₂₁H₂₀O₈: C, 63.00; H, 5.03. Found: C, 62.72; H, 5.06.

9-Acetoxy-3,5,8-trimethoxy-1-methyl-anthracene-2-carboxylic acid methyl ester (12).

To a ice-cooled stirred suspension of CuI (119 mg, 0.627 mmol) in THF (2 mL) was added 1.6 M ether solution of MeLi (0.78 mL, 1.255 mmol). This was stirred for 10 min, then solution of diester **11** (200 mg, 0.502 mmol) in THF (4 mL) was introduced via cannulation. The reaction mixture was allowed to warm up to room temperature and then stirred overnight. Then it was quenched with 10 % HCl and the product was extracted with EtOAc. Organic layer was washed twice with water and aqueous solutions were extracted once more with EtOAc. The combined organics were dried over Na₂SO₄ and concentrated *in vacuo*. The crude yellow product (160 mg, 84 % crude yield) was used in the next step without purification. To a solution of crude phenol (160 mg, 0.41 mmol) in 2 mL DMF at room temperature was added K_2CO_3 (160 mg, 1.16 mmol) followed by MeI (0.05 mL, 0.8 mmol). Resulting suspension was stirred overnight, then was diluted

Kozhinov, Behar; "Extension of the Tandem Conjugate Addition-Dieckmann Condensation: The Formal Synthesis of Tetracenomycin A₂" (JO035341K) with water and the product was extracted with EtOAc and washed twice with water. The aqueous layers were extracted once with EtOAc and the combined organics were dried over Na₂SO₄ and concentrated *in vacuo*. Silica gel chromatography (CH₂Cl₂) yielded 120 mg (60 % two steps) of **12** as a yellow solid; mp= 227-228 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.55 (s, 1H), 7.11 (s, 1H), 6.60 (d, *J* = 8 Hz, 1H), 6.56 (d, *J* = 8 Hz, 1H), 4.08 (s, 3H), 3.97 (s, 3H), 3.95 (s, 3H), 3.90 (s, 3H), 2.92 (s, 3H), 2.45 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 170.2, 168.8, 153.3, 149.2, 148.9, 138.4, 130.6, 127.4, 121.3, 118.1, 117.1, 115.5, 104.0, 102.1, 56.9, 56.4, 55.8, 52.7, 25.9, 21.8. IR (thin film) cm⁻¹ 2950, 1760, 1728, 1661, 1611, 1456, 1350, 1322, 1261, 1199, 1020. LRMS (EI) calcd for C₂₂H₂₂O₇ (M⁺): 398, found: 398. Anal. Calcd. for C₂₂H₂₂O₇: C, 66.32; H, 5.57. Found: C, 63.83; H, 5.52.

9-Acetoxy-3-methoxy-1-methyl-5,8-dioxo-5,8-dihydro-anthracene-2-carboxylic acid methyl ester (13).

A solution of ceric ammonium nitrate (83 mg, 0.15 mmol) in 0.5 mL of water was added, with a vigorous stirring to a solution of **12** (30 mg, 0.075 mmol) in 2 mL of acetonitrile over a period of 5 min. A transient blue-black color was observed after each addition. The mixture was stirred overnight and then diluted with water (20 mL). The product was extracted with EtOAc and washed twice with water. The aqueous layers were extracted once with EtOAc and the combined organics were dried over Na₂SO₄ and concentrated *in vacuo*. Purification by silica gel chromatography (4:1 hexanes:EtOAc) gave 17 mg (63 %) of acetyl quinone as a yellow solid; mp= 223-224 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.35 (s, 1H), 7.21 (s, 1H), 6.97 (d, *J* = 10 Hz, 1H), 6.89 (d, *J* = 10 Hz, 1H), 4.10 (s, 3H), Kozhinov, Behar; "Extension of the Tandem Conjugate Addition-Dieckmann Condensation: The Formal Synthesis of Tetracenomycin A₂" (JO035341K) 4.00 (s, 3H), 2.90 (s, 3H), 2.56 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 183.9, 183.3, 169.5, 167.2, 156.7, 150, 142.1, 141.5, 138.2, 135.4, 129.5, 124.3, 123.8, 119.8, 119, 117, 56.7, 53.1, 25.3, 22.1. IR (thin film) 2953, 2854, 1767, 1732, 1678, 1663, 1589, 1413, 1278, 1256, 1220, 1177, 1128, 1103, 1084, 1012, 862 cm⁻¹. LRMS (EI) calcd for C₂₀H₁₆O₇ (M⁺): 368, found: 368. Anal. Calcd. for C₂₀H₁₆O₇: C, 65.22; H, 4.38. Found: C, 65.74; H, 4.02.

9-Hydroxy-3-methoxy-1-methyl-5,8-dioxo-5,8-dihydro-anthracene-2-carboxylic acid methyl ester (14).

A solution of acetyl quinone **13** (8 mg, 0.021 mmol) in 2 mL of acetone and 2 mL of 3M HCl was refluxed for 1 h. The reaction mixture was then diluted with water and the product was extracted with EtOAc and washed twice with water. The aqueous layers were extracted once with EtOAc and the combined organics were dried over Na₂SO₄ and concentrated *in vacuo*. Purification by silica gel chromatography (4:1 hexanes:EtOAc) yielded 5 mg (70 %) of **13** as a red solid; mp= 207-208. ¹H NMR (400 MHz, CDCl₃) δ 14.88 (s, 1H), 7.85 (s, 1H), 7.07 (d, *J* = 10 Hz, 1H), 6.94 (d, *J* = 10 Hz, 1H), 4.05 (s, 3H), 3.99 (s, 3H), 3.03 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 188.4, 184.0, 167.5, 167.0, 157.8, 145.1, 140.5, 140.2, 136.2, 128.4, 121.0, 119.8, 118.6, 117.5, 108.1, 56.5, 53.1, 25.9. IR (thin film) 3335, 2922, 2850, 1732, 1667, 1589, 1463, 1357, 1341, 1260, 1215, 1100, 805 cm⁻¹. LRMS (EI) calcd for C₁₈H₁₄O₆ (M⁺): 326, found: 326. Anal. Calcd. for C₁₈H₁₄O₆: C, 66.26; H, 4.32;. Found: C, 59.35; H, 6.50.











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10 N CX F1P F2P F2 F2

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NMR plot

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3.9246

- 3.7204

- 1.5830

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