Synthesis of 1,2,3,12a,12b-Hexahydrocyclopropa-[1,2-*d*]benzo[*f*]pyrrolo[1,2-*b*]isoquinolin-5,7-dione Related to Duocarmycins and Anthramycin

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Structural features of the Duocarmycins and Anthramycin were incorporated into 1,2,3,12a,12b-hexahydro-cyclopropa[1,2-*d*]benzo[*f*]pyrrolo[1,2-*b*]isoquinolin-5,7-dione. The synthesis of the *cis* and *trans* diastereomers was accomplished using a benzyne Diels-Alder reaction and an imine-anhydride cyclization as key steps.

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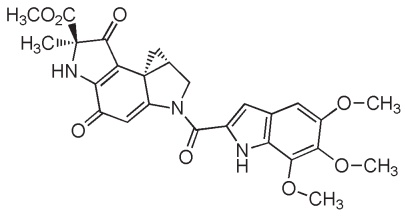
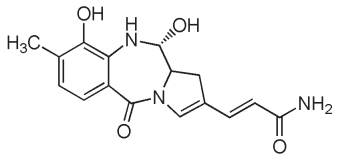
The anti-tumor agent (+)-CC-1065 was first isolated in 1978 and structure elucidation revealed a complex molecule composed of 3 pyrrolo-indole subunits that are capable of alkylating DNA [1-5]. While (+)-CC-1065 proved to be active against a variety of cancers, *in vivo* studies revealed intolerable hepatic toxicity [6]. Subsequent efforts led to the duocarmycins and related compounds that have shown high levels of cytotoxicity and have been of interest as antineoplastic agents (Figure I) [7-9]. The mechanism of cytotoxicity has been shown to involve site specific binding within the minor groove of DNA followed by alkylation involving nucleophilic attack on the cyclopropyl ring with resulting aromatization of the cyclohexadienone system to give the phenol [3]. The property of site specific alkylation offers the potential to target specific oncogenes and possibly reduce the indiscriminate toxicity associated with traditional alkylating agents. Duocarmycins and (+)-CC-1065 analogs are generally specific for A-T rich sequences of DNA. This has been related to hydrophobic bonding within the minor groove and the complementary shape of the compound and receptor [3-5].



(+)Duocarmycin A



Anthramycin

Figure 1

Anthramycin was first isolated in the 1950's by Tendler and subsequently purified and crystallized by Leimgruber in 1965 [10,11]. *In vivo* testing revealed antibacterial and antitumor properties that were mediated by the ability of the compound to alkylyate DNA within the minor groove [12]. Sequence selectivity for G-C rich regions of DNA was demonstrated with alkylation occurring as a result of nucleophilic attack of the 2-amino group of guanine at the carbinolamine carbon (C11) as the carbinolamine, imine or as a ring opened aldehyde [13,14].

Given the sequence selective alkylation of these two groups of compounds albeit at different sites and different sequences within the minor groove of DNA, it was of interest to combine several of the structural features. With this in mind, the synthesis of Compound **1** was undertaken (Figure 2). Compound **1** incorporated the cyclopropyl spiro-fused cyclohexadienone system of the duocarmycins amide linked to the pyrrolidine ring system, which would approximate the pyrroline ring of anthramycin. It was believed that the amide linkage would stabilize the cyclohexadienone and give a less reactive and more selective agent. To the contrary however; Compound **1** could be synthesized but was too unstable to completely characterize. Therefore Compound **2** was targeted since it was known that in the duocarmycins that fusion of the cyclohexadienone system with an aromatic ring increased stability.

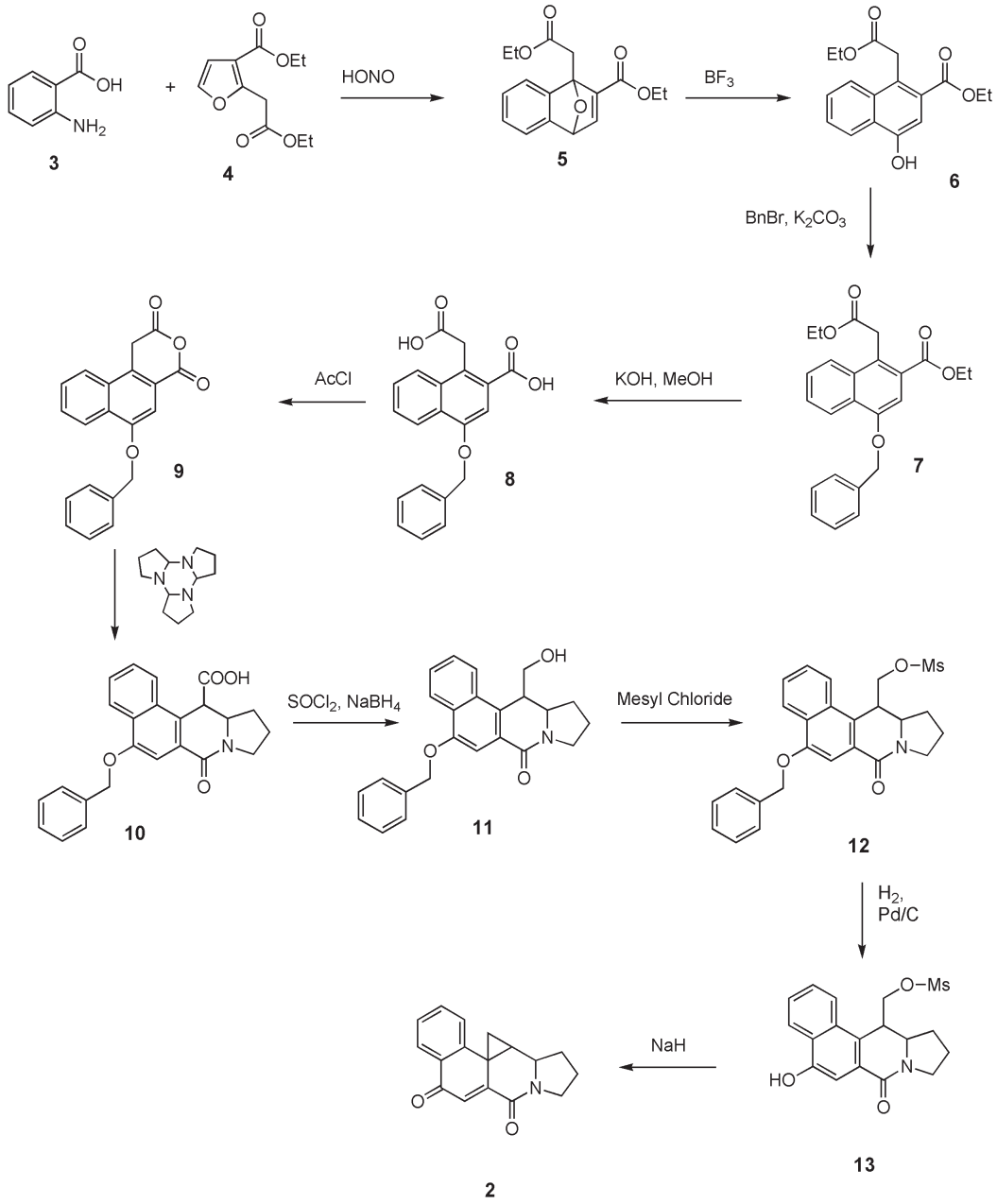
The synthesis begins with the generation of benzyne by the nitrosation of anthranilic acid and subsequent Diels-Alder reaction with the previously prepared furan **4** (Scheme 1) [15-16]. This gave the unstable diester **5** in 50% yield which was immediately purified by flash chromatography and allowed to react with BF_3 to give the phenol **6** in

1 2

Figure 2

quantitative yield. Benzylation was accomplished under standard conditions followed by hydrolysis to give the diacid **8** and conversion to the anhydride **9** was accomplished by refluxing in acetyl chloride [17-20]. Condensation of the anhydride with the 1-pyrroline trimer gave **10** in quantitative yield as a 50:50 mixture of *cis* and *trans* isomers [21,22]. The diastereomers were identified on the basis of their respective ^{1}H and ^{13}C-NMR spectra. In the case of the *cis* isomer, the C-12 proton appeared at δ 4.48 with $J_{12\text{-}12a}$ = 5.0 Hz. The *trans* isomer C-12 proton

Scheme 1



appeared at δ 4.12 with $J_{12\text{-}12a}$ = 11.8 Hz. The diastereomers could be separated by fractional recrystallization however the recovery was low and it was found to be more efficient to separate after the following step. Reduction of the acid to the alcohol could be accomplished with diborane. This worked well in the case of the *cis* isomer; however in the case of the *trans* isomer the acid reduction was slow and amide reduction began to compete significantly lowering the yield. In order to gain entry into the *trans* compound, the acid as a mixture of *cis* and *trans* isomers was converted to the acid chloride. The acid chlorides were then reduced with $NaBH_4$ to give the alcohols, which could be separated by spinning band chromatography [22]. In the conversion of the acids to the acid chlorides, some epimerization occurred so that the *trans* alcohol was the predominant product (60/40: *trans*/*cis*). Mesylation of the alcohols occurred under standard conditions. The benzyl protecting group was then removed *via* hydrogenolysis in THF to give the unstable phenol-mesylate **13**. Cyclization to give the cyclopropyl ring was accomplished under basic conditions (NaH) in dry THF to give a clean product which was extracted and recrystallized from ether to give the final compounds.

EXPERIMENTAL

Melting points were determined in open capillary tubes with a Thomas-Hoover melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker (250 and 400 MHz) NMR spectrometer unless otherwise indicated with tetramethysilane as an internal standard. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, Georgia and are within ± 0.4 of the theoretical percentages. Common reagent grade chemicals were purchased from Aldrich Chemical Company. All the reactions were carried out under a nitrogen atmosphere. High-resolution mass specta were obtained on a 7070 Micromass magnetic sector mass spectrometer.

Ethyl 2-Ethoxycarbonylmethylfuran-3-carboxylate (**4**).

A suspension of diethyl 1,3-acetonedicarboxylate (1 g, 4.9 mmol) in 3 mL of 3 *N* Na_2CO_3 was cooled in an ice bath and treated with 50% chloroacetaldehyde (0.38 g, 4.9 mmol) over a period of 1 hour. The mixture was stirred at room temperature for 6 hours. The solution was acidified and extracted with chloroform (3 X 10 mL) washed with water, dried and concentrated under vacuum. The resulting oily material in 2 mL of dioxane was treated with 0.1 mL of concentrated HCl and stirred at room termperature for 2 hours. The reaction mixture was diluted with water and extracted with chloroform. The organic layer was washed with water, dried and concentrated under vacuum. Chromatography (silica gel, 66% pet ether-ether) afforded pure **4** (550 mg, 50%) as an oil. bp 148-150 °C at 1.0 Torr (bp 86-90 °C at 0.2 Torr) [15]; ^1H NMR ($CDC1_3$): δ 7.32 (d, 1H, J = 1.9 Hz), 6.69 (d, 1H, J = 1.9 Hz), 4.28 (q, 2H), 4.16 (q, 2H), 4.05, (s, 2H), 1.33 (t, 3H), 1.25 (t, 3H); ^{13}C NMR: δ 168.2, 163.0, 153.9, 141.4, 115.4, 110.5, 60.9, 60.0, 33.5, 13.9, 13.7; IR (film): ν 3130, 2983, 1742, 1707, 1614, 1517, 1307, 1261, 1182 cm^{-1}; MS (EI): 226 (m/z), 181, 153, 125, 108.

1-Carboxymethyl-2-carboxy-1,4-dihydro-1,4-epoxynaphthalene Diethylester (**5**).

A solution of **4** (3 g, 13.27 mmol) and isoamyl nitrite (1.95 g, 16.6 mmol) in 10 mL of dry THF was treated dropwise with anthranilic acid (1.82 g, 13.27 mmol) in 25 mL of dry THF over a period of 45 minutes while heating at reflux. After the addition was complete, the reaction mixture was stirred at reflux for 45 minutes. The THF was removed under vacuum. Chromatography (silica gel 66% pet ether-ether) afforded pure **5** (2 g, 50%) as an oil which was used immediately in the subsequent reaction; ^1H NMR ($CDC1_3$): δ 7.6 (s, 1H), 7.26 (m, 2H), 7.03 (m, 2H), 5.7 (d, 1H, J=1.9Hz), 4.15 (dq, 4H), 3.9 (d, 2H, J=16.3Hz), 3.25 (dd, 1H, J=16.5, 0.78Hz), 1.25 (dt, 6H); MS (EI): 302 (m/z), 257, 228, 204, 200, 172, 155, 131.

3-Carboxy-4-carboxymethyl-l-naphthol diethylester (**6**).

A solution of **5** (3.5 g, 11.6 mmol) in 25 mL of chloroform was treated with boron trifluoride etherate (6.5 g, 45.7 mmol) and stirred for 30 minutes at room temperature. The reaction mixture was washed with water, dried and concentrated under reduced pressure to give pure **6** (3.45 g, 100%) as an oil which solidified upon standing and recrystallized from ether-pet ether; mp 105-107 °C; ir: (KBr) 3396, 3074, 2989, 1739, 1679, 1599, 1478, 1433, 1385, 1335, 1259 cm^{-1}; ^1H NMR ($CDC1_3$): δ 7.95 (m, 2H), 7.5 (m, 2H), 6.9 (s, 1H), 4.46 (s, 2H), 4.3 (dq, 4H) , 1.3 (dt, 6H); ^{13}C NMR: δ 172.9, 167.8, 151.2, 133.6, 128.3, 127.2, 126.6, 126.4, 124.5, 124.41, 122.6, 108.7, 61.2 (2 C) , 34.3, 14.2, 14.1; MS (EI): 302 (m/z), 256, 228, 201, 157, 127, 115.

Anal. Calcd. for $C_{17}H_{18}O_5$: C, 67.54; H, 5.96. Found: C, 67.33; H, 6.00.

1-Benzyloxy-3-carboxy-4-carboxymethyl Naphthalene Diethylester (**7**).

A solution of **6** (2.0 g, 6.6 mmol) in 25 mL of acetone was treated with anhydrous K_2CO_3 (0.92 g, 6.6 mmol) and benzyl bromide (1.24 g, 7.2 mmol). The resulting mixture was stirred at reflux for 24 hours. The K_2CO_3 was removed by filtration. Acetone was removed under reduced pressure and the resulting oily material was crystallized from ether/pet ether to give pure **7** (2.5 g, 98%). mp 80-81 °C; ir (KBr): ν 3436, 2986, 1731, 1708, 1596, 1369, 1242, 1199 cm^{-1}; ^1H NMR ($CDC1_3$): δ 8.37 (m, 1H), 8.02 (m, 1H), 7.55 (m, 4H), 7.37 (m, 4H), 5.23 (s, 2H), 4.46 (s, 2H), 4.39 (q, 2H), 4.15 (q, 2H), 1.4 (t, 3H), 1.21 (t, 3H); ^{13}C NMR ($CDC1_3$): δ 171.3, 167.8, 153.4, 136.6, 133.5, 128.4 (2 C), 128.3 (2 C), 127.9 (2 C), 127.4 (2 C), 126.8, 125.8, 124.6, 122.5, 105.1, 79.1, 61.1, 60.6, 34.3, 14.1, 14.0; MS (EI): 392 (m/z), 347, 319, 255, 200, 155, 127, 91.

Anal. Calcd. for $C_{24}H_{24}O_5$: C, 73.46; H, 6.12. Found: C, 73.33; H, 6.19.

1-Benzyloxy-3-carboxy-4-carboxymethyl Naphthalene (**8**).

A solution of **7** (2.5 g, 6.3 mmol) in 25 mL of 3 *N* methanolic KOH was heated at reflux for 6 hours. The methanol was removed *in vacuo*. The residue was dissolved in 10 mL of water, washed with ether, and acidified with HCl. The resulting precipitate was filtered, washed with water and dried to give **8** which was recrystallized from ethanol/ether (2 g, 95% yield), mp 191-193 °C ; ir (KBr): ν 2953, 2625, 1713, 1679, 1596, 1513, 1411, 1367, 1259, 1096 cm^{-1}; ^1H NMR ($CDC1_3$/DMSO): δ 8.17 (m, 1H), 7.94 (m, 1H), 7.41 (m, 4H), 7.26 (s, 1H), 7.2 (m, 3H), 5.08 (s, 2H), 4.3 (s, 2H); ^{13}C NMR: δ 172.7 , 169.8, 152.6,

136.0, 133.0, 128.4 (2 C), 127.9 (2 C), 127.3 (2 C), 126.8, 126.7, 126.2, 125.5, 124.4, 121.8, 104.8, 69.4, 34.0; MS (EI): 336 (m/z), 318, 274, 155, 127, 91.

Anal. Calcd for $C_{20}H_{16}O_5$: C, 71:43; H, 4.76. Found: C, 71.21; H, 4.92.

9-Benzyloxybenzo[*f*]isochroman-1,3-dione (**9**).

A solution of acid **8** (2.5 g, 7.4 mmol) in 45 mL of acetyl chloride was heated at reflux for 12 hours. Acetyl chloride was removed under reduced pressure and the residue was recrystallized from benzene/pet ether to give **9** as a light green precipitate (2.1 g, 89%) which was used immediately in the subsquent reaction, mp 204-206°C; IR (KBr) 3456, 3107, 1784, 1738, 1659, 1594, 1374 cm^{-1}; ^1H NMR ($CDC1_3$): δ 8.41 (m, 1H), 7.99 (m, 1H), 7.76 (m, 2H), 7.37-7.57 (m, 7H) 5.34 (s, 2H), 4.50 (s, 2H).

1,2,3,12,12a-Tetrahydro-12-carboxy-7-benzyloxybenzo[*f*]-pyrrolo[1,2-*b*]isoquinoline-5-one (**10**).

A solution of **9** (2.0 g, 6.3 mmol) in 20 mL of dry CH_2Cl_2 was treated with 1-pyrroline trimer (0.48 g, 2.3 mmol) dissolved in 5 mL of CH_2Cl_2 [21]. The resulting solution was stirred at reflux for 1 hour during which time a precipitate formed. Stirring was continued for an additional 2 hours at room temperature. The reaction mixture was diluted with ether, cooled and filtered to give 2.4 g (100%) of acid **10** as an equal mixture of *cis* and *trans* isomers. *Cis* isomer: ^1H NMR($CDC1_3$/DMSO): δ 8.4 (m, 1H), 8.16 (m, 1H), 7.6 (s, 1H), 7.56 (m, 4H), 7.42 (m, 3H), 5.20-5.23 (m, 2H), 4.48 (d, 1H, J=5.0 Hz), 4.17 (m, 1H) , 3.88 (m, 1H), 3.62 (m, 1H), 2.33 (m, 1H), 2.15 (m, 2H), 1.95 (m, 1H); ^{13}C NMR: δ 170.8 161.6, 153.0, 135.7, 130.3, 127.6, 127.5, 126.9, 126.57, 126.4, 126.1, 125.7, 124.8, 123.1, 121.6, 101.9, 69.0, 56.4, 44.0, 42.8, 39.9,, 39.6, 39.2, 38.9, 38.6, 38.2, 29.0, 22.0. *Trans* isomer: ^1H NMR($CDC1_3$/DMSO): δ 8.33 (m, 1H), 7.95 (m, 1H), 7.55 (s, 1H), 7.52 (m, 4H), 7.34 (m, 3H), 5.30-5.33 (m, 2H), 4.12 (d, 1H, J=11.8 Hz), 4.02 (m, 1H), 3.77 (m, 1H), 3.54 (m, 1H), 2.32 (m, 1H), 2.0 (m, 3H); ^{13}C NMR: δ 173.8, 160.5, 152.0, 135.0, 129.7 (2 C), 126.8, 126.7, 126.2 (2 C), 125.7, 125.6, 125.3, 125.0, 124.6, 122.6, 120.9, 101.0, 68.2, 57.6, 48.8, 43.2, 30.6, 20.6; MS (EI): 343 (387-COOH), 274, 252, 155, 127, 91; MS (CI, NH_3): 344 (m/z), 238, 183, 137.

Anal. Calcd. for $C_{24}H_{21}NO_4$ (+ 3/4 H_2O) : C, 71.9; H, 5.6; N, 3.5. Found: C, 72.1; H, 5.37; N, 3.5.

1,2,3,12,12a-Tetrahydro-7-benzyloxy-12-hydroxymethyl-benzo-[*f*]pyrrolo[1,2-*b*]isoquinoline-5-one **(11)**.

A solution of **10** (500 mg, 1.29 mmol) in 20 mL of benzene was treated with thionyl chloride (10.0 mL) and the solution was stirred at reflux for 1 hour. The resulting orange-brown solution was evaporated to dryness to remove excess thionyl chloride. An addditional 10 ml of benzene was added and the solution again evaporated to dryness. The residue was then dissolved in 30 mL of dry THF and sodium borohydride (782 mg, 20.6 mmol) was added. The mixture was stirred at room temperature overnight after which time 25 mL of H_2O was added and the product extracted into ethyl acetate (100 mL). The organic layer was separated, dried and evaporated. The crude product was purified by spinning band chromotography (silica gel 9% ethanol-ether) to give the *cis* (124 mg, 26%) and *trans* (185 mg, 38%) isomers initially as oils however both solidified upon the addition of ether. *Cis* isomer: mp

190-191 °C ; ^1H NMR ($CDC1_3$): δ 8.37 (m, 1H), 8.09 (m, 1H), 7.51 (m, 5H), 7.38 (m, 3H), 5.21 (s, 2H), 4.04 (m, 1H), 3.83 (m, 3H), 3.68 (m, 1H), 3.5 (m, 1H), 2.75 (br s, 1H), 2.38 (m, 1H), 2.18 (m, 1H) , 2.05 (m, 1H) , 1. 8 (m, 1H); ^{13}C NMR: δ 163.4, 153.8, 136.8, 131.1, 129.0, 128.5, 127.8 (2 C), 127.6, 127.5 (2 C), 127.3 (2 C), 126.6, 124.0, 123.0, 102.4, 70.1, 61.3, 58.7, 45.2, 39.0, 29.1, 23.3; EIHRMS: m/z 373.1679 ($C_{24}H_{23}NO_3$ requires 373.1678).

Anal. Calcd. for $C_{24}H_{23}NO_3$ (1/10 H_2O): C, 76.70; H, 6.18; N, 3.73. Found: C, 76.77; H, 6.19; N, 3.62.

Trans isomer: mp 200-201 °C ^1H NMR ($CDC1_3$/DMSO): δ 8.4 (m, 1H), 8.15 (m, 1H), 7.74 (s, 1H), 7.55 (m, 4H), 7.37 (m, 3H), 5.29 (s, 2H), 4.24 (m, 1H), 4.05 (m, 1H), 3.9 (m, 2H), 3.68 (m, 1H), 3.35 (m, 1H), 2.5 (br s, 1H), 2.08 (m, 1H), 1.9 (m, 2H), 1.52 (m, 1H); ^{13}C NMR: δ 163.7, 158.7, 153.4, 136.6, 131.5, 128.3 (2 C), 127.7, 127.3 (2 C), 126.7, 126.5, 126.3, 126.2, 123.9, 122.7, 102.5, 69.9, 65.9, 58.3, 44.5, 39.0, 30.8, 21.5; EIHRMS: m/z 373.1686 ($C_{24}H_{23}NO_3$ requires 373.1678).

Anal. Calcd. for $C_{24}H_{23}NO_3$ (1/10 H_2O): C, 76.70; H, 6.18; N, 3.73. Found: C, 76.66; H, 6.24; N, 3.59.

1,2,3,12,12a-Tetrahydro-7-benzyloxy-12-(methanesulfonyloxy-methyl)benzo[*f*]pyrrolo[1,2-*b*]isoquinoline-5-one (**12**).

A solution of *cis* alcohol **11** (150 mg, 0.4 mmol) and triethylamine (82 mg, 0.8 mmol) in 15 mL of dry CH_2C1_2 was treated with methanesulfonyl chloride (69 mg, 0.6 mmol). The resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was diluted with CH_2C1_2, washed with 1 *N* HC1, saturated $NaHCO_3$ solution, water, dried and concentrated under reduced pressure. Chromatography (silica gel, 9% ethanol-ether) afforded the pure mesylate **12** as a solid (170 mg, 95%); ^1H NMR ($CDC1_3$): δ 8.42 (m, 1H), 8.1 (m, 1H), 7.6 (m, 5H), 7.36 (m, 3H), 5.25-5.28 (m, 2H), 4.37 (dd, 1H, J=10.8, 7.3 HZ), 4.26 (dd, 1H, J=10.8, 3.3 HZ), 4.07 (m, 2H), 3.88 (m, 1H), 3.62 (m, 1H), 2.79 (s, 3H), 2.25 (m, 1H), 2.13 (m, 1H), 1.84 (m, 1H); ^{13}C NMR: δ 162.8, 154.4, 136.5 (2C), 130.7, 128.5 (2C), 128.4, 127.9, 127.8, 127.6 (2C), 127.4, 126.9, 126.0, 123.4, 123.1, 102.4, 70.1, 66.7, 58.1, 45.1, 37.1, 36.4, 29.1, 23.2.

Anal. Calcd. for $C_{25}H_{25}NO_5S$: C, 66.50; H, 5.58; N, 3.10. Found: C, 66.32; H, 5.54; N, 3.07.

Simarily prepared was the *trans* isomer. ^1H NMR ($CDC1_3$): δ 8.43 (m, 1H), 8.09 (m, 1H), 7.75 (s, 1H), 7.6 (m, 4H), 7.39 (m, 3H), 5.30 (s, 2H), 4.58 (m, 1H), 4.28 (m, 3H), 3.915 (m, 1H), 3.35 (m, 1H), 2.92 (s, 3H), 2.1 (m, 2H), 1.9 (m, 2H); ^{13}C NMR: δ 163.7, 154.5, 137.0, 136.6, 131.3, 128.3, 127.8, 127.7, 127.3 (2 C), 126.9, 126.8 (2 C), 123.1, 123.0, 122.9, 102.9, 71.8, 70.3, 58.2, 44.9, 37.4, 36.5, 30.5, 21.7; EIHRMS: m/z 451.1448 ($C_{25}H_{25}NO_5S$ requires 451.1453).

Anal. Calcd. for $C_{25}H_{25}NO_5S$: C, 66.50; H, 5.58; N, 3.10. Found: C, 66.40; H, 5.37; N, 2.99.

1,2,3,12,12a-Tetrahydro-7-hydroxy-12-(methanesulfonyloxy-methyl)benzo[*f*]pyrrolo[1,2-*b*]isoquinoline-5-one (**13**).

A mixture of *cis*-**12** (160 mg, 0.35 mmol) and 10% Pd/C (90 mg) in THF (10 mL) was shaken under H_2 for 10 hours. The mixture was filtered and concentrated under reduced pressure. The product was crystallized upon addition of ether to give pure phenol **13** (113 mg, 90%) which was used immediately in the subsquent reaction. *Cis* isomer: ^1H NMR ($CDC1_3$): δ 9.8 (s, 1H), 8.38 (d, 1H, J=8.29Hz), 8.07 (d, 1H, J=8.4Hz), 7.6 (s, 1H), 7.58

(m, 2H), 4.4 (dd, 1H, J=7.7, 10.7Hz), 4.27 (dd, 1H, J=3.2, 10.7Hz), 4.11 (m, 2H), 3.88 (m, 1H), 3.6 (m, 1H), 2.82 (s, 3H), 2.28 (m, 2H), 2.19 (m, 1H), 1.89 (m, 1H); CIHRMS (CH_4): m/z 362.10635 ($C_{18}H_{20}NO_5S$ requires 362.1062).

Similarily prepared was the *trans* isomer which was used immediately in the subsequent reaction. ^{1}H NMR ($CDC1_3$): δ 8.89 (br s, 1H), 8.4 (m, 1H), 8.2 (s, 1H), 8.0 (m, 1H), 7.6 (m, 2H), 4.58 (m, 1H), 4.28 (m, 3H), 3.97 (m, 1H), 3.45 (m, 1H), 2.9 (s, 3H), 2.2 (m, 1H), 1.9 (m, 2H), 1.6 (m, 1H); ^{13}C NMR: δ 163.6, 153.1, 131.1, 127.1, 126.0, 125.0, 123.2, 123.1, 120.8, 117.1, 105.2, 71.8, 67.4, 58.1, 44.6, 37.8, 29.3, 21.5.

1,2,3,12a,12b-Hexahydro-cyclopropa[1,2-*d*]benzo[*f*]pyrrolo-[1,2-*b*]isoquinolin-5,7-dione (**2**).

Sodium hydride (13 mg of 60% in mineral oil, 0.32 mmol) was washed with petroleum ether (3 X 1 mL) and suspended in 2 mL of dry THF. A solution of *cis* **13** (90 mg, 0.25 mmol) in 1 mL of THF and 0.1 mL of DMF was added to the suspension of sodium hydride and the resulting solution protected from light was stirred for 30 minutes at room temperature. A solution of phosphate buffer (pH 7, 5 mL) was added. The mixture was extracted with ethyl acetate (3 X 5 mL). The combined organic layers were dried and concentrated under reduced pressure. The resulting oily material was crystallized from ether to give pure **2** (61 mg, 92%) as off white plates. *Cis* Isomer: mp 160-162 °C ; ^{1}H NMR ($CDC1_3$): δ 8.22 (dd, 1H, J= 1.0, 7.8 Hz), 7.58 (m, 1H), 7.40 (m, 1H), 7.2 (s, 1H) , 7.01 (d, 1H, J= 8.0 Hz), 4.05 (m, 1H), 3.65 (m, 1H), 3.49 (m, 1H), 2.71 (m, 1H), 2.33 (m, 1H), 2.08 (m, 1H), 1.92 (m, 4H); ^{13}C NMR ($CDC1_3$): δ 184.7, 161.5, 149.0, 143.2, 132.9, 132.0, 129.0, 126.6, 126.5, 121.1, 55.5 , 45.4, 32.3, 31.0, 27.4, 23.3, 22.4; EIHRMS: m/z 265.1095 ($C_{17}H_{15}NO_2$ requires 265.1103).

Anal. Calcd. for $C_{17}H_{15}NO_2$ (+ 1/3 H_2O) : C, 75.00; H, 5.75; N, 5.14. Found: C, 74.85; H, 5.88; N, 5.08.

The *trans* isomer was prepared in a similar manner; ^{1}H NMR ($CDC1_3$): δ 8.25 (d, 1H, J= 8.0 Hz), 7.61 (m, 1H), 7.49 (m, 1H), 7.28 (s, 1H) , 7.01 (d, 1H, J= 8.0 Hz), 4.19-4.30 (m, 1H), 3.81-3.97 (m, 1H), 3.11-3.28 (m, 1H), 2.81-2.88 (m, 1H), 0.81-2.15 (m, 5H), 1.40-1.50(m, 1H); ^{13}C NMR ($CDC1_3$): δ 185.2, 160.9, 146.8, 144.0, 133.2, 132.7, 130.4, 126.8 (2 C) 120.8, 58.8, 44.4, 31.1, 29.0, 27.9, 27.3, 22.0.

Anal. Calcd. for $C_{17}H_{15}NO_2$ (+ 2/3 H_2O): C, 73.64; H, 5.88; N, 5.05. Found: C, 73.50; H, 5.70; N, 5.05.

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