GENERAL SYNTHETIC PATHWAY TO OXYGENATED 3-METHYLBENZ[*g*]ISOQUINOLINE-5,10-DIONES

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Abstract - The synthesis of naturally occurring dioxygenated and trioxygenated 3-methylbenz[*g*]isoquinoline-5,10-diones has been accomplished. The critical step involved regioselective additions of di- or trifluorobenzylzinc bromides to activated methyl 6-methylnicotinate. Aromatizations of the resultant dihydropyridines followed by hydrolysis led to the corresponding benzylpyridinecarboxylic acids which on annulative-oxidations led to the respective difluoro- or trifluorobenz[*g*]isoquinoline-5,10-diones. Displacements of fluorides by methoxide led to the di- or trimethoxy analogues which on selective demethylations led to bostrycoidin, 8-*O*-methyl-bostrycoidin, tolypocladin, 5-deoxybostrycoidin or 5-deoxy-6-*O*-methyl-bostrycoidin. The synthesis of isobostrycoidin and isotolypocladin has also been accomplished.

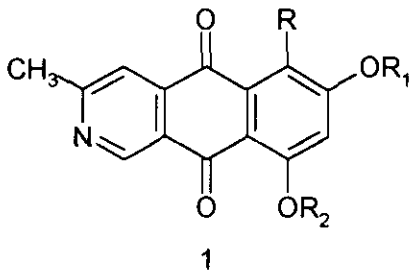
Many products with anthracene-9,10-dione (anthraquinone) chromophores have been isolated from natural sources.[1-3] On the other hand, 2-azaanthraquinones (benz[*g*]isoquinoline-5,10-diones) are rare. Benz[*g*]isoquinoline-5,10-dione has been isolated from the woody parts of the plant *Psychotria camponutans* found in Panama.[4] It is of interest to note that this dione has been reported to exhibit growth inhibition against methicillin-resistant *Staphylococcus aureus*[5] and also acts as an insect teratogen.[6]

Five members of oxygenated 3-methylbenz[*g*]isoquinoline-5,10-diones have thus far been isolated and characterized from fungal sources. Three of these aza analogues (using the names proposed in the literature) hold three oxygenated substituents (hydroxy or methoxy) . Bostrycoidin (**1a**) was first isolated from *Fusarium bostrycoides* in 1954[7] and the structure assigned by Arsenault in 1965.[8] It was subsequently isolated from *Fusarium solani* found on the roots of diseased citrus trees[9,10] and *Fusarium solani* D_2 purple cultures.[11] Bostrycoidin has been synthesized using potential biochemical pathways [12,13] and in two other multi-step pathways.[14-16]

The dione, 8-*O*-methylbostrycoidin (**1b**), was isolated from the toxinogenic strain of *Fusarium moniliforme* from moldy corn ears grown in the Transkei.[17] A synthetic pathway to **1b** has been reported.[14] Tolypocladin (**1c**) [18] has been isolated from the mycelium of the cyclosporin producing fungus *Tolypocladium inflatum* and a synthesis was subsequently reported.[19]

Only two aza dioxygenated analogues have been isolated which are 5-deoxybostrycoidin (**1d**)[20] and 5-deoxy-6-*O*-demethylbostrycoidin (**1e**)[21] (Figure 1). Compound (**1d**) was isolated from a 169 mutant of *Nectria*

haematococca which was grown in a culture enriched with asparagine (some bostrycoidin was also isolated). Compound (**1e**) was obtained from cultures of *Nectria haematococca* grown in a similar medium.



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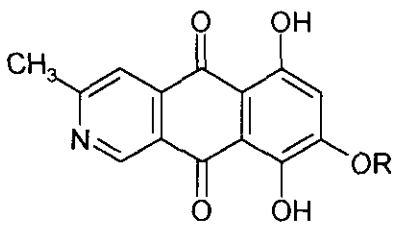
a, R=OH, R_1=CH_3, R_2=H
b, R=OH, R_1=R_2=CH_3
c, R=OH, R_1=R_2=H
d, R=R_2=H, R_1=CH_3
e, R=R_1=R_2=H

Figure 1. Naturally occurring 3-methylbenz[*g*]isoquinoline-5,10-diones

Our interest in the development of novel antitumor agents with benz[*g*]isoquinoline-5,10-dione chromophores [22] prompted us to investigate regioselective pathways which have culminated in the total synthesis of **1a-e.** In addition, the pathway has also been utilized to synthesize isobostrycoidin (**2a**), isotolypocladin (**2b**) and iso-5-deoxybostrycoidin (**3**) (Figure 2).



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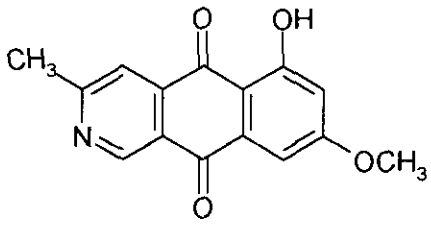

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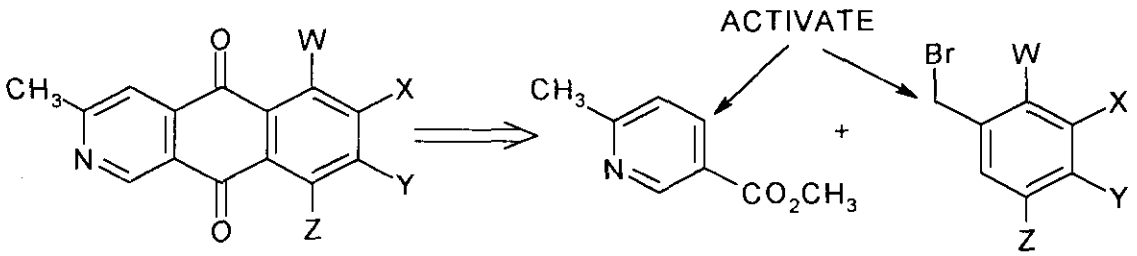
Figure 2. Isobostrycoidin (**2a,** R = CH_3), Isotolypocladin (**2b**, R = H) and Iso-5-deoxybostrycoidin (**3**)

RESULTS AND DISCUSSION

The retrosynthetic analysis leading to these molecules is illustrated in Scheme 1.

Scheme 1



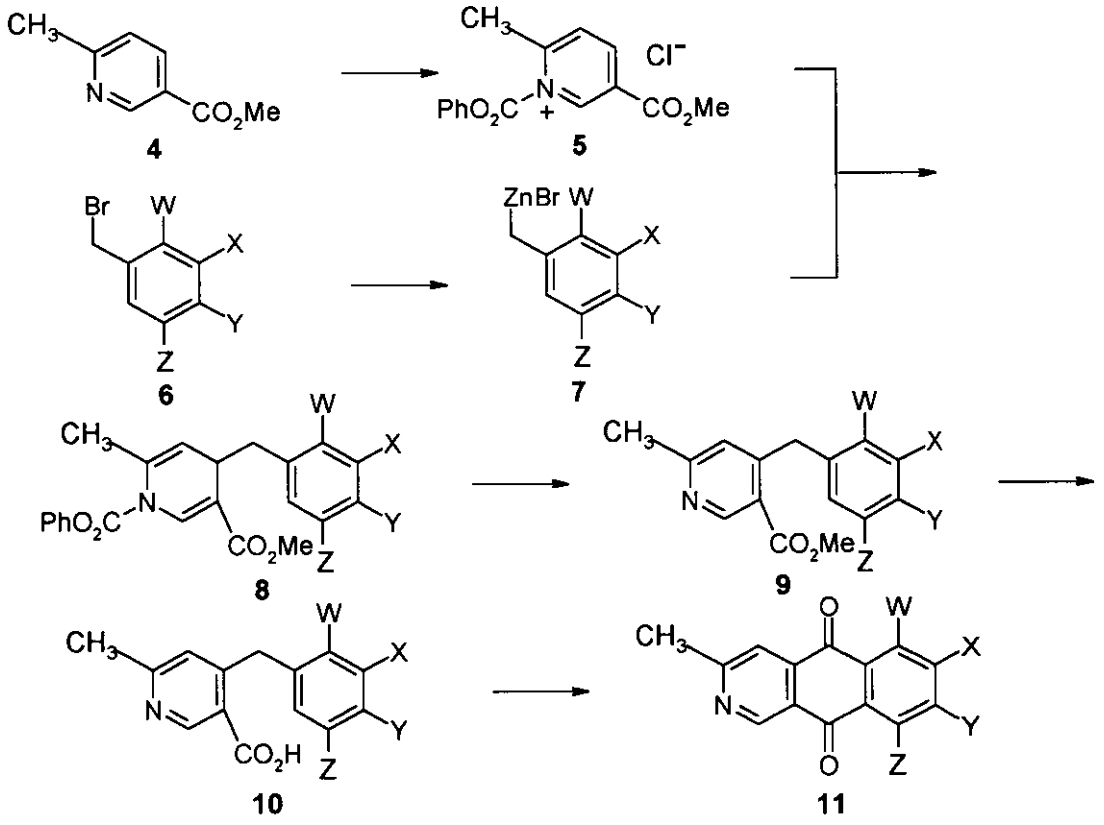
The crucial step involved regioselective addition of the appropriate di- or trifluorobenzylzinc bromides, easily

obtained by treatment of the corresponding regioisomeric di- or trifluorobenzyl bromides with zinc metal in tetrahydrofuran, to the pyridinium salt formed from methyl 6-methylnicotinate by treatment with phenyl chloroformate. [23] Aromatizations of these intermediates followed by hydrolysis and cyclizations of the acids with concomitant oxidation would lead to the desired fluoro intermediates. Displacement of the fluorides (S_NAr) by sodium methoxide or benzyltrimethylammonium methoxide followed by selective dealkylations of the ethers would lead to the natural products and related isomeric analogues.

Synthesis of the Di- and Trifluorobenz[*g*]isoquinoline-5,10-diones

The general synthetic pathway to these fluoro analogues is oulined in Scheme 2.

Scheme 2



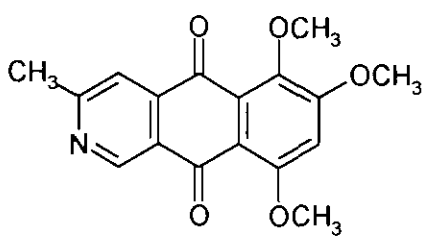
Trifluoro- and Difluorobenz[*g*]isoquinoline-5,10-diones

11	W	X	Y	Z
a	F	F	H	F
b	F	H	F	F
c	H	F	H	F
d	F	H	F	H

The synthesis of all the fluoro analogues commenced with the readily available methyl 6-methylnicotinate (**4**). Treatment of **4** with phenyl chloroformate in THF at 0°C led to the pyridinium chloride (**5**). The regioisomeric trifluoro (**6a** and **6b**) and difluorobenzyl bromides **6c** and **6d**) were treated with zinc dust in THF at room temperature to yield the corresponding benzylzinc bromides (**7a-d**). Addition of the THF solutions of (**7a-d**) to the pyridinium chloride (**5**) led to the dihydropyridines (**8a-d**) in good yields. Aromatizations of esters (**8a-d**) with sulfur in refluxing decalin led to the pyridines (**9a-d**) which on saponification and acidification led the the acids (**10a-d**). Cyclizations of these acids with fuming sulfuric acid led to the desired fluoro-substituted benz[*g*]isoquinoline-5,10-diones (**11a-d**).

Trioxygenated Products

Treatment of **11a** with sodium methoxide in methanol (or benzyltrimethylammonium methoxide in methanol) led to the trimethoxy analogue (**12**). Selective demethylation of **12** with boron tribromide in dichloromethane led to bostrycoidin (**1a**). [14] Spectroscopic comparisons (^{1}H NMR, IR) with the literature data confirmed the identity of this product. [14] Upon heating **12** in concentrated sulfuric acid, complete demethylation occurred to produce tolypocladin (**1c**) whose ^{1}H NMR spectrum was identical in all respects to that of an authentic sample. [24] Treatment of **11b** with benzyltrimethylammonium methoxide in methanol led to regioisomer (**13**). The synthesis of isobostrycoidin (**2a**) or isotolypocladin (**2b**) [24] could readily be accomplished by treatment of **13** with boron tribromide-dichloromethane or concentrated sulfuric acid, respectively.



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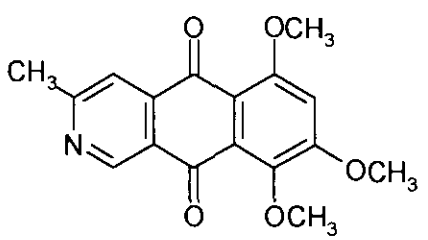

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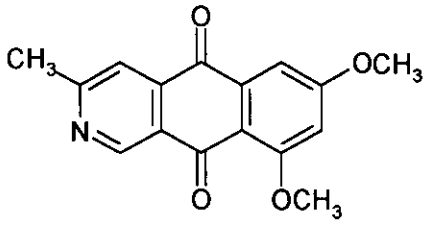
Dioxygenated Derivatives

Treatment of **11c** or **11d** with sodium methoxide in methanol (or benzyltrimethylammonium methoxide in methanol) led to the corresponding dimethoxy analogues (**14**) and (**15**), both of which have been previously prepared. [14]

Selective demethylation of **14** with boron tribromide in dichloromethane led to 5-deoxybostrycoidin (**1d**) identical in all respects (^{1}H NMR and IR) to the reported data. [20] Attempts to convert **14** to **1e** were fraught with difficulties. Treatment of **14** with boron tribromide in dichloromethane at room or elevated temperature did not effect complete demethylation. Heating **14** in concentrated sulfuric acid led to some of the desired product but was accompanied by considerable decomposition. On the other hand, the demethylation of **1d**



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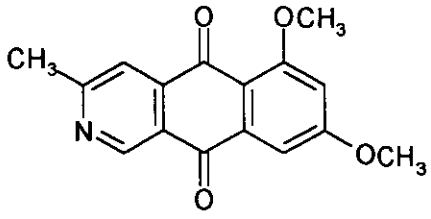

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to afford **1e** was readily accomplished by aluminum chloride in refluxing dichloromethane. The demethylation of **15** with boron tribromide in dichloromethane led to **3**, quite different in its ^{1}H NMR spectrum to that of **1d**. Following the procedure described by Cameron, [14] photolysis of **14** in acetonitrile-water led to 8-*O*-methylbostrycoidin (**1b**).

CONCLUSIONS

The sequence of reactions which is described should prove quite useful in the synthesis of other related oxygenated analogues and also for the preparation of other substituted benz[*g*]isoquinoline analogues which could be formed *via* S_NAr displacements of the fluorides.

EXPERIMENTAL

Melting points were determined on a Thomas Hoover capillary melting point apparatus or a Fisher-Johns apparatus. NMR were recorded on a Bruker ARM-500 MHZ instrument and the IR data were taken on a Perkin-Elmer system 2000 FT-IR. MS were recorded on a Finnigan automated gas chromatograph/EI-CI mass spectrometer system. The benzyl bromides were purchased from Aldrich or Oakwood except 2,3,5-trifluorobenzyl bromide which was prepared from 2,3,5-trifluorobenzoic acid (Oakwood product). The zinc powder (Aldrich 32,493-O) was used as received. Microanalysis were performed by Robertson Microlit Laboratories, Inc., Madison, NJ.

The steps involved in the total synthesis of tolypocladin (**1c**) will be described as a typical procedure. The synthesis of the related analogues followed a similar pathway.

2,3,5-Trifluorobenzyl alcohol

A solution of 2,3,5-trifluorobenzoic acid (0.51 g, 2.7 mmol) in ether (5 mL) was added dropwise to a suspension of lithium aluminum hydride (0.19 g, 5.0 mmol) in ether (18 mL) which was kept in an ice bath under an atmosphere of nitrogen. After stirring for 1 h, ice water (10 mL) was carefully added dropwise, followed by dilute sulfuric acid (10 mL, 5%) and the mixture was allowed to stir for 1 h. The layers were separated and the aqueous phase extracted with ether (3 x 8 mL). The combined extracts were dried over magnesium sulfate and concentrated to yield the product (0.34 g, 78%) as a clear oil; ^{1}H NMR ($CDCl_3$) δ 6.98

(m, 1H), 6.85 (m, 1H), 4.78 (s, 2H).

***2,3,5-Trifluorobenzyl bromide* (6a)**

A solution of 2,3,5-triflurobenzyl alcohol (0.34 g, 2.1 mmol) in dichloromethane (5 mL) was treated with N-bromosuccinimide (0.62 g, 3.5 mmol) and triphenylphosphine (0.68 g, 2.6 mmol). The resultant yellow solution was purged with nitrogen and the exothermic reaction was allowed to stir for 2.5 h at rt. The solvent was removed by rotary evaporation and the mixture was subjected to column chromatograpy over silica gel using chloroform:hexane (3:1) as the eluent to yield **6a** (0.34 g, 72%) as a viscous oil; ^{1}H NMR ($CDCl_3$) δ 6.90 (m, 2H), 4.45 (s, 2H).

***Methyl 6-methyl-1-phenoxycarbonyl-4-(2,3,5-trifluorobenzyl)-1,4-dihydronicotinate* (8a)**

A solution of 2,3,5-trifluorobenzyl bromide (**6a**, 2.5 g, 11 mmol) in THF (8 mL, freshly distilled from sodium metal) was added dropwise to a suspension of zinc dust (0.98 g, 15 mmol) in THF (15 mL). The mixture was immersed in a water bath and stirred at rt for 4 h. Phenyl chloroformate (1.4 mL, 11 mmol) was added dropwise to a solution of methyl 6-methyl nicotinate (**4**, 2.25 g, 15 mmol) in THF (15 mL) held in an ice bath and the mixture was stirred for 45 min. The solution of 2,3,5-trifluorobenzyl zinc bromide (**7a**, with traces of unreacted zinc) was cooled in an ice bath and added to the phenoxycarbonylpyridinium chloride solution **5** over a 15 min period *via* a cannula and the resultant mixture was stirred in the ice bath for 50 min. The mixture was allowed to warm to rt and then quenched into aqueous ammonium chloride (20 mL, 20%). The product was extracted with ethyl acetate (2 x 50 mL) and the extracts washed with sodium bicarbonate (15 mL, 10%), water (25 mL), ammonium chloride (15 mL, 20%) and again with water (25 mL). The extract was dried over sodium sulfate, decanted from the drying agent and concentrated by rotary evaporation to afford a yellow oil. Purification by colum chromatography over silca gel using chloroform:hexane (3:1) as eluent led to **8a** (2.6 g, 56%) as a white solid; mp 72-73°C; ^{1}H NMR ($CDCl_3$) δ 8.11 (s, 1H), 7.41 (m, 2H), 7.27 (m, 1H), 7.10 (d, J = 8.1 Hz, 2H), 6.77 (m, 1H), 6.65 (m, 1H), 5.00 (d, J = 6.00 Hz, 1H), 3.79 (s, 3H), 3.62 (m, 1H), 2.85 (d, J = 5.4 Hz, 2H), 2.18 (s, 3H). Anal. Calcd for $C_{22}H_{18}NO_4F_3$: C, 63.31; H, 4.35; N, 3.36. Found. C, 63.26; H, 4.43; N, 3.20.

***Methyl 6-methyl-4-(2,3,5-trifluorobenzyl)nicotinate* (9a)**

A mixture of **8a** (2.2 g, 5.3 mmol) and sulfur (0.22 g, 6.9 mmol) in decalin (13 mL) was heated in an oil bath at 190-195°C for 5.5 h. Water was added to the cooled mixture and the decalin was removed by steam distillation. The residual aqueous material was extracted with dichloromethane (2 x 50 mL) and the extracts dried over sodium sulfate. Concentration under reduced pressure led to a dark, partially solid product. This material was purified by column chromatography over silca gel using hexane:ethyl acetate (2:1) as the eluent to afford **9a** (1.2 g, 77%); mp 87-88°C; ^{1}H NMR ($CDCl_3$) δ 9.05 (s, 1H), 6.95 (s, 1H), 6.82 (m, 1H), 6.58 (d, J = 2.7 Hz, 1H), 4.41 (s, 2H), 3.90 (s, 3H), 2.56 (s, 3H). Anal. Calcd for $C_{15}H_{12}NO_2F_3$: C, 61.02; H, 4.10; N,

4.74. Found: C, 61.09; H, 4.00; N, 4.67.

***6-methyl-4-(2,3,5-trifluorobenzyl)nicotinic acid* (10a)**

Sodium hydroxide (0.38 g, 9.5 mmol) in water (2 mL) was added to the methyl ester (**9a**) (0.74 g, 2.5 mmol) in methanol (14 mL). The mixture was refluxed for 2.5 h., cooled and acidified with conc hydrochloric acid. The solid was collected by filtration and dried to yield **10a** (0.69 g, 98%); mp 227-230°C; the analytical sample was obtained by recrystallization from methanol; ^{1}H NMR (DMSO-d_6) δ 13.27 (br s, 1H), 8.87 (s, 1H), 7.40 (m, 1H), 7.10 (s, 1H), 6.81 (m, 1H), 4.41 (s, 2H), 2.51 (s, 3H). Anal. Calcd for $C_{14}H_{10}NO_2F_3$: C, 59.79; H, 3.58; N, 4.98. Found: C, 59.46; H, 3.61; N, 4.85.

***3-Methyl-6,7,9-trifluorobenz[g]isoquinoline-5,10-dione* (11a)**

A mixture of acid (**10a**) (14 mg, 0.05 mmol) in fuming sulfuric acid (0.2 mL, 20% free sulfur trioxide) was heated at in an oil bath held at 120-130°C for 15 min. The resultant dark solution was poured over ice (2.0 g) and the product extracted into dichloromethane (2 x 20 mL). The aqueous layer was neutralized by the addition of solid sodium bicarbonate and extracted with dichloromethane (20 mL). The combined extracts were dried over sodium sulfate and concentrated under reduced pressure to yield **11a** (13 mg, 93%) as an orange solid); mp 180-181°C; the analytical sample was purified by sublimation; ^{1}H NMR ($CDCl_3$) δ 9.41 (s, 1H), 7.85 (s, 1H), 7.40 (m, 1H), 2.79 (s, 3H); MS, M^+ 277: m/z (CI, methane) M + H^+ (278, 100%). Anal. Calcd for $C_{14}H_6NO_2F_3$: C, 60.66; H, 2.18; N, 5.05. Found: C, 60.51; H, 2.15; N, 4.92.

***3-Methyl-6,7,9-trimethoxybenz[g]isoquinoline-5,10-dione* (12)**

a) Procedure A: Benzyltrimethylammonium methoxide (3.0 g, 6.7 mmol, 40% in methanol) was added dropwise to a suspension of **11a** (64 mg, 0.23 mmol) in methanol (20 mL). The resultant suspension was purged with nitrogen and heated in an oil bath held at 50°C for 18 h. The brown solution was cooled and the methanol allowed to evaporate in the hood. Water (15 mL) was added to the residue and the mixture was extracted with dichloromethane (4 x 40 mL). The combined extracts were dried over sodium sulfate and concentrated to yield a yellow solid. Purification by flash chromatography over silica gel using dichloromethane:ethyl acetate (2:1) as eluent led to pure **12** (58 mg, 81%) as a bright yellow solid; mp 210-211°C (recrystallized from methanol); lit., mp[14] 210-211°C; ^{1}H NMR ($CDCl_3$) δ 9.34 (s, 1H), 7.75 (s, 1H), 6.85 (s, 1H), 4.04 (s, 3H), 4.02 (s, 3H), 3.94 (s, 3H), 2.72 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 183.2, 180.7, 163.9, 159.9, 158.8, 149.2, 144.0, 139.2, 128.0, 125.4, 117.4, 114.3, 102.5, 61.5, 56.9, 56.3, 25.1; IR (KBr disc) ν_{max} (cm^{-1}) 1680, 1658, 1591; MS , M^+, 313 , m/z (CI, methane) 314(M + H^+, 100%) .

b) Procedure B: Commercial sodium methoxide (Aldrich, 150 mg, 2.8 mmol) was added to a mixture of **11a** (42 mg, 0.15 mmol) in methanol (7 mL). The mixture was purged with nitrogen and heated in an oil bath at 55°C for 45 min. The brown suspension was cooled, quenched into water (6 mL) and extracted with dichloromethane (3 x 10 mL). The combined extracts were dried over sodium sulfate and concentrated under

reduced pressure. Purification by flash chromatography as in procedure A led to **12** (25 mg, 53%).

3-Methyl-6,9-dihydroxy-7-methoxybenz[g]isoquinoline-5,10-dione* (1a , *bostrycoidin)

Boron tribromide (1M solution in dichloromethane, 1.2 mL, 1.2 mmol) was added dropwise to a solution of **12** (25 mg, 0.08 mmol) in dichloromethane (40 mL) which was being cooled in an dry ice-acetone bath under an atmosphere of nitrogen. After 15 min, the dark purple solution was allowed to warm to rt and then the mixture was partially concentrated under a slow nitrogen stream. Water (40 mL) was added and the mixture was continuously extracted with dichloromethane. Concentration of the extracts led to a red solid which was purified by flash chromatography over silica gel using dichloromethane:ethyl acetate (4:1) to give **1a** (19 mg, 83%) as an orange solid; mp 239-240°C (decomp) lit., mp [14] 237-239°C (decomp) ^{1}H NMR ($CDCl_3$) δ 13.46 (s, 1H), 13.17 (s, 1H), 9.47 (s, 1H), 7.93 (s, 1H), 6.73 (s, 1H), 4.00 (s, 3H), 2.71 (s, 3H); IR (KBr disc) ν_{max} (cm^{-1}) 1627, 1615, 1589; MS, M^+ 285, m/z (CI, methane) M + H^+ (286, 100%).

3-Methyl-6,7,9-trihydroxybenz[g]isoquinoline-5,10-dione* (1c, *tolypocladin)

Dione (**12**) (0.026 g, 0.083 mmol) was treated with concentrated sulfuric acid (1.2 mL) and the mixture was heated in an oil bath at 120-130°C for 21 h. The dark solution was cooled and quenched over ice (9 g). The pH was adjusted to 5 by addition of sodium hydroxide (2M) and sodium acetate. The resultant mixture was continuously extracted with chloroform. Concentration of the extracts led to pure **1c** (0.012 g, 53%) as a red solid; mp > 300°C; lit., mp [18] >320°C; ^{1}H NMR (DMSO-d_6) δ 13.42 (s, 1H), 12.50 (brs, 1H), 11.50 (br s, 1H), 9.28 (s, 1H), 7.93 (s, 1H), 6.68 (s, 1H), 2.71 (s, 3H); IR (KBr disc) ν_{max} (cm^{-1}) 1629, 1589, 1464, 1415, 1302; MS, M^+ 271: m/z (CI, methane) M + H^+ (272, 100%).

***Methyl 6-methyl-1-phenoxycarbonyl-4-(2,4,5-trifluorobenzyl)-1,4-dihydronicotinate* (8b)**

Prepared from 2,4,5-trifluorobenzyl bromide (**6b**) and **5** after purification of the crude material by column chromatography over silica gel using chloroform as the eluent; 61% yield; mp 80-81°C; ^{1}H NMR ($CDCl_3$) δ 8.08 (s, 1H), 7.40 (m, 2H), 7.26 (m, 1H), 7.07 (m, 2H), 6.94 (m, 1H), 6.87 (m, 1H), 5.00 (d, J = 5.5 Hz, 1H), 3.78 (s, 3H), 3.60 (m, 1H), 2.77 (m, 2H), 2.18 (s, 3H). Anal. Calcd for $C_{22}H_{18}NO_4F_3$: C, 63.31; H, 4.35; N, 3.36. Found: C, 63.26; H, 4.44; N, 3.14.

***Methyl 6-methyl-4-(2,4,5-trifluorobenzyl)nicotinate* (9b)**

Prepared and purified as in the typical aromatization procedure from **8b** in 71% yield; mp 92-93.5°C; ^{1}H NMR ($CDCl_3$) δ 9.03 (s, 1H), 6.93 (m, 3H), 4.33 (s, 2H), 3.90 (s, 3H), 2.55 (s, 3H). Anal. Calcd for $C_{15}H_{12}NO_2F_3$: C, 61.02; H, 4.10; N, 4.74, Found: C, 61.05; H, 4.00; N, 4.74.

***6-Methyl-4-(2,4,5-trifluorobenzyl)nicotinic acid* (10b)**

Prepared from **9b** following the typical procedure in 94% yield; mp > 300°C (decomp); ^{1}H NMR δ (DMSO-d_6) 8.85 (s, 1H), 7.50 (m, 1H), 7.26 (m, 1H), 4.31 (s, 2H), 2.48 (s, 3H). This material was not further purified and used directly in the next step.

***3-Methyl-6,8,9-trifluorobenz[g]isoquinoline-5,10-dione* (11b)**

Prepared from acid (**10b**) in 76% yield; mp 191-193°C (decomp), purified by sublimation; ^{1}H NMR ($CDCl_3$) δ 9.41 (s, 1H), 7.86 (s, 1H), 7.38 (m, 1H), 2.79 (s, 3H); MS, M^+, 277; m/z (CI, methane) M + H^+ (278, 100%). Anal. Calcd for $C_{14}H_6NO_2F_3$: C, 60.66; H, 2.18; N, 5.05. Found: C, 60.26; H, 2.06; N, 4.70.

***3-Methyl-6,8,9-trimethoxybenz[g]isoquinoline-5,10-dione* (13)**

Prepared as in procedure A from **11b** with purification by column chromatography over silica gel using gradient elution with chloroform:ethyl acetate (4:1) followed by ethyl acetate after a first yellow band had eluted led to **13** (65%) as a bright yellow solid; mp 206-209°C (decomp); lit., mp [14] 214-216 °C; ^{1}H NMR ($CDCl_3$) δ 9.25 (s, 1H), 7.75 (s, 1H), 6.78 (s, 1H), 4.00 (s, 3H), 3.99 (s, 3H), 3.91 (s, 3H), 2.69 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 182.7, 180.6, 164.7, 160.6, 159.0, 148.7, 143.9, 140.0, 127.9, 125.1, 117.9, 114.5, 101.6, 61.5, 56.8, 55.3, 25.2; IR (KBr disc) ν_{max} (cm^{-1}) 1669, 1581, 1550; MS, M^+ 313; m/z , (EI mild) M^+ (313, 100%).

***3-Methyl-6,9-dihydroxy-8-methoxybenz[g]isoquinoline-5,10-dione* (2a, *isobostrycoidin*)**

A solution of **13** (8 mg, 0.026 mmol) in dichloromethane (10 mL) was cooled in a dry ice-acetone bath while being held under a nitrogen blanket. Boron tribromide (1.0 M solution in dichloromethane, 0.3 mL, 0.3 mmol) was added dropwise. After 15 min, the purple solution was allowed to warm to room temperature and the excess boron tribromide was removed under a slow stream of nitrogen. Water (8 mL) was added slowly, the layers separated and the aqueous layer extracted with dichloromethane (25 mL). The combined extracts were dried over sodium sulfate and concentrated under reduced pressure to afford a red solid. Purification by column chromatography over silica gel using dichlromethane: methanol (99:1) yielded **2** (5.5 mg, 73%) as a red solid, mp 274-277°C (decomp); ^{1}H NMR ($CDCl_3$) δ 13.42 (s, 1H), 13.37 (s, 1H), 9.48 (s, 1H), 7.97 (s, 1H), 6.71 (s, 1H), 4.03 (s, 3H), 2.79 (s, 3H); IR (KBr disc) ν_{max} (cm^{-1}) 1617, 1584; MS, M^+ 285; m/z (CI, methane) M + H^+ (286, 100%). Anal. Calcd for $C_{15}H_{11}NO_5$: C, 63.16, H, 3.89, N, 4.91. Found: C, 62.99; H, 4.18; N, 4.80.

***3-Methyl-6,8,9-trihydroxybenz[g]isoquinoline-5,10-dione* (2b, *isotolypocladin*)**

A mixture of **13** (0.011 g, 0.035 mmol) and concentrated sulfuric acid (0.5 mL) was heated in an oil bath held at 120-130°C for 27 hr. The resultant dark red solution was quenched over ice (4.5 g) and the pH adjusted to 5 using sodium hydroxide (2M) and sodium acetate. The mixture was continuously extracted with chloroform and the extract concentrated to yield **3** (6.6 mg, 69%) as a red solid; mp 300-305°C(decomp), lit., mp [19] 317°C (decomp); ^{1}H NMR (DMSO-d_6) δ 13.30 (s, 2H), 9.33 (s, 1H); 7.97 (s, 1H), 6.51 (s, 1H), 2.77 (s, 3H); IR (KBr disc) ν_{max} (cm^{-1}) 1653, 1590; MS, M^+ 271; m/z (CI, methane) M + H^+ (272, 100%).

***Methyl 6-methyl-1-phenoxycarbonyl-4-(3,5-difluorobenzyl)-1,4-dihydronicotinate* (8c)**

A solution of 3,5-difluorobenzyl bromide (**6c**, 3.02 g, 14.6 mmol) in THF (18 mL) was added dropwise over

a period of 5 min to zinc dust (1.07 g, 16.3 mmol) in THF(8 mL). The mixture was kept in a water bath at rt and allowed to stir for 4 h. Phenyl chloroformate (1.6 mL, 13 mmol) was added dropwise over a period of 5 min to a solution of methyl 6-methylnicotinate (2.01 g, 13.3 mmol) in THF (25 mL) held in an ice bath. The mixture was stirred for 1 h in an ice bath. The organozinc bromide was added to the cold phenoxycarbonylpyridinium chloride solution *via* a cannula over a 10 min period and the mixture was stirred for 1 h. The mixture was allowed to warm to rt and quenched into an aqueous ammonium chloride solution (20%, 30 mL). The product was extracted into ethyl acetate (2 x 50 mL), the extract washed with aqueous sodium bicarbonate (10%, 20 mL), water (40 mL), aqueous ammonium chloride (20%, 20 mL) and water (40 mL). The extracts were dried over magnesium sulfate and concentrated by rotary evaporation to yield a viscous oil. This oil was chromatographed over silica gel (3:1 chloroform:hexane) to yield **8c** (3.22 g, 60%) as a solid; mp 73-74°C; ^{1}H NMR ($CDCl_3$) δ 8.11 (s, 1H), 7.40 (m, 2H), 7.27 (d, 1H), 7.12 (m, 2H), 6.67 (m, 3H), 4.95 (m, 1H), 3.80 (s, 3H), 3.53 (m, 1H), 2.88 (m, 1H), 2.86 (m, 1H), 2.20 (s, 3H). Anal. Calcd for $C_{21}H_{19}NO_4F_2$: C, 66.16; H, 4.79; N, 3.51. Found: C, 66.00, H, 4.81, N, 3.38.

***Methyl 6-methyl-4-(3,5-difluorobenzyl)nicotinate* (9c)**

A mixture of (**8c**) (0.41 g, 1.02 mmol) and sulfur (0.05 g, 1.56 mmol) in decalin (3 mL) was heated in an oil bath at 190-195°C for 4 h. The mixture was cooled to rt and residual sulfur was removed by filtration. Water (25 mL) was added and the mixture was steam distilled to remove the decalin. The residual aqueous portion was extracted with dichloromethane (3 x 15 mL) and the combined extracts were dried over sodium sulfate. Concentration of the extracts under reduced pressure led to a dark, partially solid product (0.27 g) . This material was purified by column chromatography over silica gel (3:1 hexane: ethyl acetate) to yield **9c** (0.17 g, 61%); mp 70-71°C; ^{1}H NMR ($CDCl_3$) δ 9.01 (s, 1H), 6.94 (s, 1H), 6.66 (m, 3H), 4.32 (s, 2H), 3.86 (s, 3H), 2.55 (s, 3H). Anal. Calcd for $C_{15}H_{13}NO_2F_2$: C, 64.98; H, 4.73; N, 5.05. Found: C, 64.89; H, 4.70; N, 5.06.

***6-Methyl-4-(3,5-difluorobenzyl)nicotinic acid* (10c)**

Ester (**9c**) was hydrolyzed following the typical procedure to yield **10c** (87%); mp > 300°C; ^{1}H NMR (DMSO-d_6) δ 13.25 (s, 1H), 8.86 (s, 1H), 7.21 (s, 1H), 6.92 (s, 1H), 6.91 (s, 1H), 4.35 (s, 2H), 2.46 (s, 3H). Anal. Calcd for $C_{14}H_{11}NO_2F_2$: C, 63.88; H, 4.21; N, 5.32. Found: C, 63.67; H, 4.17; N, 5.18.

***3-Methyl-7,9-difluorobenz[g]isoquinoline-5,10-dione* (11c)**

A mixture of acid (**10c**) (0.10 g, 0. 38 mmol) in fuming sulfuric acid (0.8 mL, 33% free SO_3) was heated at 130-135°C in an oil bath for 45 min. The dark red solution was quenched over ice (3.0 g) and the product extracted with dichloromethane (3 x 50 mL). The aqueous layer was neutralized with solid sodium bicarbonate and extracted with dichloromethane (20 mL). The combined extracts were dried over potassium carbonate and the solvent was removed by rotary evaporation to yield **11c** (0.051g, 52%) as a light brown solid. An

analytically pure sample was prepared by chromatography over silica gel (2:1 dichloromethane: ethyl acetate); mp 180-182°C; sample darkens on standing; ^{1}H NMR ($CDCl_3$) δ 9.44 (s, 1H), 7.6 (m, 2H), 7.26 (m, 1H), 2.78 (s, 3H). Anal. Calcd for $C_{14}H_7NO_2F_2$: C, 64.87; H, 2.72; N, 5.40 : Found: C, 64.53; H, 2.40; N, 5.03.

***3-Methyl-7,9-Dimethoxybenz[g]isoquinoline-5,10-dione* (14)**

Procedure A: Following this procedure and purification by flash chromatography over silica gel (2:1 dichloromethane: ethyl acetate) afforded **14** (98%) as a yellow solid.

Procedure B. Sodium methoxide (0.91 g, 1.7 mmol) was added to **11c** (0.02 g, 0.08 mmol) in methanol (1 mL). The mixture was heated in an oil bath held at 55°C for 1 h. The dark green mixture was allowed to cool to rt and quenched into ice water. The product was extracted into dichloromethane (7 x 10 mL) and the extracts were dried over sodium sulfate. Concentration under rotary evaporation led to a yellow solid (0.025 g). This material was purified by column chromatography over silica gel (4:1 chloroform: ethyl acetate) to afford **14** (0.018 g , 78%); mp 214-215°C; lit., mp [14] 214-215°C; ^{1}H NMR ($CDCl_3$) δ 9.41 (s, 1H); 7.80 (s, 1H), 7.43 (d, J = 2.4 Hz, 1H), 6.84 (d, J = 2.4 Hz, 1H), 4.02 (s, 3H), 3.99 (s, 3H), 2.74 (s, 3H); IR (KBr disc) ν_{max} (cm^{-1}) 1677, 1659, 1596; MS, M^+ 283, m/z (CI, methane) M + H^+ (284, 100%).

3-Methyl-7-methoxy-9-hydroxybenz[g]isoquinoline-5,10-dione* (1d, *5-deoxybostrycoidin)

Dione (**14**) (25 mg, 0.088 mmol) in dichloromethane (40 mL) was treated dropwise with boron tribromide (1 M solution in dichloromethane , 1 mL, 1 mmol) while being cooled in an dry ice-acetone bath. After 15 min., the reddish solution was allowed to warm to rt and the mixture was partially concentrated under a slow stream of nitrogen. Water (40 mL) was added slowly and the resultant mixture was continuously extracted with dichloromethane. The yellow solid obtained upon concentration was purified by column chromatography using dichloromethane:methanol (99:1) as the eluent to give **1d** (17 mg, 71%) as a bright yellow solid; mp 193-194°C; lit., mp [20] 195-196°C; ^{1}H NMR ($CDCl_3$) δ 12.76 (s, 1H), 9.43 (s, 1H), 7.87 (s, 1H), 7.36 (d, J = 2.5 Hz, 1H), 6.76 (d, J = 2.5 Hz, 1H), 3.95 (s, 3H), 2.77 (s, 3H); IR (KBr disc) ν_{max} (cm^{-1}) 1675, 1635 and 1588.

***3-Methyl-7,9-dihydroxybenz[g]isoquinoline-5,10-dione* (1e)**

Aluminum trichloride (0.0254 g, 0.188 mmol) was added in small portions to **1d** (0.012 g, 0.045 mmol) in dichloromethane (2 mL). The resultant bright red mixture was purged with nitrogen and refluxed for 75 min. The cooled mixture was concentrated and hydrochloric acid (6M, 2 mL) was added to the residue. The mixture was refluxed for 3 h, cooled and adjusted to pH 4 with sodium hydroxide (2M) and sodium acetate. The mixture was continuously extracted with dichloromethane. Concentration of the extracts led to **1e** (0.010 g, 87%); mp 288-290°C (decomp); lit., mp [21] 300-305°C (decomp); ^{1}H NMR (DMSO-d_6) δ 12.69 (s, 1H), 9.24 (s, 1H), 7.84 (s, 1H), 7.09 (d, J = 2.1 Hz, 1H), 6.57 (d, J = 2.2 Hz, 1H), 2.69 (s, 3H).

6-Hydroxy-7,9-dimethoxy-3-methylbenz[g]isoquinoline-5,10-dione*(1b, *8-O-methylbostrycoidin)

Water (13 mL) was added to a solution of **14** (7 mg, 0.025 mmol) in acetonitrile (9 mL). The resultant suspension was placed in a pyrex cold finger apparatus under a nitrogen atmosphere and irradiated with a GE sunlamp (275 W, 110-125V, AC) for 10 h. The orange solution was concentrated to yield a red solid (7 mg) which was purified by flash chromatography using dichloromethane: ethyl acetate (4:1) as eluent to afford **1b** (4.1 mg, 55%) as a red solid; mp 210-212°C; lit., mp[14] 214-216°C; ^{1}H NMR δ ($CDCl_3$) δ 13.3 (s, 1H), 9.46 (s, 1H), 7.87 (s, 1H), 6.89 (s, 6H), 4.06 (s, 6H), 2.76 (s, 3H).

***Methyl 6-methyl-1-phenoxycarbonyl-4-(2,4-difluorobenzyl)-1,4-dihydronicotinate* (8d)**

Prepared from **6d** and **5** following the typical procedure in 76% yield; mp 56-58°C; ^{1}H NMR δ 8.05 (s, 1H), 7.39 (m, 2H), 7.26 (m, 1H), 7.05 (m, 3H), 6.78 (m, 2H), 5.01 (d, J = 6.2 Hz, 1H), 3.78 (s, 3H), 3.60 (m, 1H), 2.84 (m, 1H), 2.75 (m, 1H), 2.16 (s, 3H). Anal. Calcd for $C_{22}H_{19}NO_4F_2$: C, 66.16, H, 4.79, N, 3.51. Found: C, 66.16; H, 4.68, N, 3.38.

***Methyl 6-methyl-4-(2,4-difluorobenzyl)nicotinate* (9d)**

Dihydropyridine (**8d**) was aromatized following the typical procedure and purified by column chromatography over silica gel using hexane: ethyl acetate as the eluent (2:1) to afford **9d** in 72% yield; mp 50-51°C; ^{1} H NMR ($CDCl_3$) δ 9.01 (s, 1H), 7.07 (m, 1H), 6.92 (s, 1H), 6.82 (m, 2H), 4.36 (s, 2H), 3.89 (s, 3H), 2.53 (s, 3H). Anal. Calcd for $C_{15}H_{13}NO_2F_2$: C, 64.98. H, 4.73; N, 5.05. Found: C, 64.96; H, 4.57; N, 4.90.

***4-(2,4-Difluorobenzyl)nicotinic acid* (10c)**

Ester (**9c**) was hydrolyzed following the typical procedure to afford **10c** (87%); mp > 300°C; ^{1}H NMR (DMSO-d_6) δ 13.10 (br s, 1H), 8.86 (s, 1H), 7.20 (m, 2H), 7.15 (d, 2H), 4.33 (s, 2H), 2.45 (s, 3H). The crude acid was utilized in the next step.

***3-Methyl-6,8-difluorobenz[g]isoquinoline-5,10-dione* (11d)**

Prepared from **10d** following the typical procedure with purification by elution with ethyl acetate over silica gel as a yellow solid (23%); mp 180-182°C (decomp) which darkens on standing; ^{1}H NMR ($CDCl_3$) δ 9.43 (s, 1H), 7.90 (m, 2H), 7.24 (s, 1H), 2.80 (s, 3H).

***3-Methyl-6,8-dimethoxybenz[g]isoquinoline-5,10-dione* (15)**

Prepared from **11d** following procedure A (61%); mp 206-208°C; lit., mp[14] 216.5-217°C; purification was accomplished by column chromatography over silica gel using dichloromethane: ethyl acetate 2:1 as eluent; ^{1}H NMR ($CDCl_3$) δ 9.34 (s, 1H), 7.88 (s, 1H), 7.47 (d, J = 2.2 Hz, 1H), 6.81 (d, J = 2.2 Hz, 1H), 4.02 (s, 3H), 4.01 (s, 3H), 2.75 (s, 3H); MS, M^+ 283; m/z (Cl methane) M + H^+ (284, 100%)

***3-Methyl-6-hydroxy-8-methoxybenz[g]isquinoline-5,10-dione* (3, *iso-5-deoxybostrycoidin*)**

Boron tribromide (1.0 M in dichloromethane, 0.03 mL, 0.03 mmol) was added to a solution of **15** (0.007 g, 0.025 mmol) in dichloromethane (10 mL) which was being cooled in a dry-ice acetone bath. After 15 min, the

bright red solution was allowed to warm to rt and stirring was continued for 20 min. Water (10 mL) was added slowly, the layers were separated and the aqueous portion was extracted with dichloromethane (2 x 25 mL). The combined extracts were dried over sodium sulfate and concentrated to yield **3** (0.003 g, 45%) as a yellow solid; mp 150-153°C (decomp) ; ^{1}H NMR ($CDCl_3$) δ 12.57 (s, 1H), 9.41 (s, 1H), 7.99 (s, 1H), 7.41 (d, J = 2.4 Hz, 1H), 6.75 (d, J = 2.4 Hz, 1H), 3.97 (s, 3H), 2.84 (s, 2H).

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