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Concise and Efficient Synthesis of Calothrixin B

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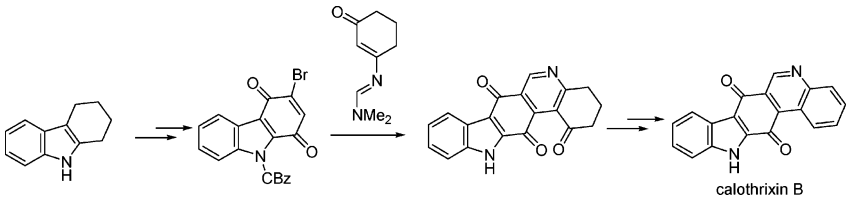

A convergent synthesis of the naturally occurring alkaloid Calothrixin B is presented, which used a regioselective hetero-Diels−Alder reaction between a "push−pull" 2-aza-diene and a *N*-protected 3-bromo-9*H*-carbazole-1,4-dione to construct the five-ring skeleton of the molecule. Protection of the indole motif with a benzyl group was unattractive for delivery of sufficient target material because the removal of the protecting group had not been high yielding. We therefore elected to temporarily protect the indole motif with a more labile benzyloxycarbonyl group. Accordingly, the synthesis of calothrixin B proceeded in 17% overall yield over 9 steps from the commercially available 1,2,3,9-tetrahydro-4*H*-carbazol-4-one.

Introduction

In 1999, Rickards, Smith, and co-workers[1] reported the discovery of two new carbazole alkaloids named calothrixins A (**1a**) and B (**1b**) from cell extracts of cyanobacterial *Calothrix* species. These natural compounds, which display a unique indolo[3,2-*j*]phenanthridine ring system,[2] exert in vitro growth-inhibitory effects in antiplasmodial and anticancer assays at nanomolar concentrations. The mechanism by which these compounds exert their cytotoxic activity is still largely unknown.[3]The structural novelty and the significant biological properties of the calothrixins render these molecules attractive targets for chemical synthesis and several groups, including ours, have achieved their preparation. Kelly et al. reported the first synthesis of the calothrixins based on ortho-lithiation reactions to create the $C_{6a}-C_7$ and $C_{12a}-C_{13}$ bonds.[4] Chai et al. prepared the calothrixins using a Friedel−Crafts reaction and a lithiation−cyclization reaction to create the C_7-C_{7a} and $C_{12a}-C_{13}$ bonds, respectively.[5] An allene-mediated electrocyclic reaction with creation of the $C_{6a}-C_{13a}$ bond was the key feature of the synthesis reported by Hibino et al.[6] The synthesis of calothrixin B reported by Bennasar et al. is characterized by a regioselective cyclization of an acyl radical with concomitant formation of the $C_{13}-C_{13a}$ bond.[7] A strategy different from those reported previously was followed by our group in 2005 to reach calothrixin B whose basic five-ring structure was forged in one single operation by recourse to a hetero-Diels−Alder reaction (simultaneous creation of the C_6-C_{6a} and $C_{13a}-C_{13b}$ bonds).[8]

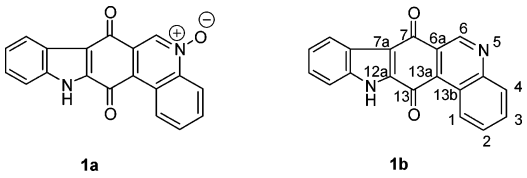

FIGURE 1. Structures of calothrixin A (**1a**) and calothrixin B (**1b**).

(1) Rickards, R. W.; Rothschild, J. M.; Willis, A. C.; de Chazal, N. M.; Kirk, K.; Saliba, K. J.; Smith, G. D. *Tetrahedron* **1999**, *55*, 13513.

(2) For a preparation of the 12*H*-indolo[3,2-*j*]phenanthridine skeleton prior to the discovery of the calothrixins, see: (a) Elango, S.; Srinivasan, P. C. *Tetrahedron Lett.* **1993**, *34*, 1347. (b) Mohanakrishnan, A. Z.; Srinivasan, P. C. *J. Org. Chem.* **1995**, *60*, 1939.

(3) (a) Doan, N. T.; Rickards, R. W.; Rothschild, J. M.; Smith, G. D. *J. Appl. Phycol.* **2000**, *12*, 409. (b) Chen, X.; Smith, G. D.; Waring, P. *J. Appl. Phycol.* **2003**, *15*, 269.

(4) Kelly, T. R.; Zhao, Y.; Cavero, M.; Torneiro, M. *Org. Lett.* **2000**, *2*, 3735.

(5) (a) Bernardo, P. H.; Chai, C. L. L.; Elix, J. A. *Tetrahedron Lett.* **2002**, *43*, 2939. (b) Bernardo, P. H.; Chai, C. L. L. *J. Org. Chem.* **2003**, *68*, 8906.

(6) Tohyama, S.; Tominari, C.; Matsumoto, K.; Yamabuki, A.; Ikegata, K.; Nobuhiro, J.; Hibino, S. *Tetrahedron Lett.* **2005**, *46*, 5263.

(7) Bennasar, M. L.; Roca, T.; Ferrando, F. *Org. Lett.* **2006**, *8*, 561.

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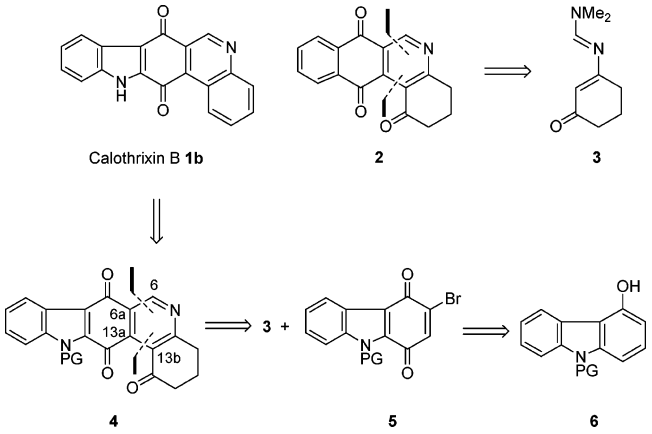
SCHEME 1. Retrosynthetic Analysis of Calothrixin B



Herein, we report full details of our total synthesis of calothrixin B from the commercially available 2,3,4,9-tetrahydro-1*H*-carbazole. Note that oxidation of calothrixin B to calothrixin A was previously reported[4] so that a synthesis of **1b** also constitutes a formal synthesis of **1a**.

Results and Discussion

We, recently, reported a synthesis of 5-aza-analogues of angucyclinones, e.g., **2**, based on a heterocyclic Diels−Alder reaction and featuring the novel "push−pull" diene **3**.[9] Considering the structural similarities displayed by calothrixin B **1b** and compound **2**, we thought that an identical cycloaddition strategy could well be applied to assemble the core structure of **1b** in one single operation. From a retrosynthetic perspective (Scheme 1), trione **4** appears as a possible key precursor to calothrixin B. The forward sequence from **4** to calothrixin B would involve a dehydrogenation step to form the fully aromatized A ring and subsequent excision of oxygen at carbon C-1. Trione **4** could be disconnected at the $C_{13a}-C_{13b}$ and C_6-C_{6a} linkages to give two fragments, diene **3** and dienophile **5**. Dienophile **5** could be derived from an *N*-protected 9*H*-carbazol-4-ol **6**, the synthesis of which could be envisaged from the commercially available 2,3,4,9-tetrahydro-1*H*-carbazole (Scheme 2). Due to its high convergency, this approach appears well suited to prepare analogues of the calothrixins in useful quantities so that structure−activity relationships can be explored.

At the outset of our work we noted that, in the two previous syntheses known at that time,[4,5] the MOM protecting group had been chosen to temporarily mask the indole nitrogen atom and that its removal could be effected only in relatively harsh conditions and in fair chemical yield. Our intention was thus to choose a protecting group that could be more easily and efficiently removed and started from the premise that a benzyloxycarbonyl (Cbz) group or, optionally, a benzyl (Bn) group should meet these requirements. According to the plan laid out earlier this proposed strategy thus required the formation of the *N*-protected 9*H*-carbazol-4-ol **10** and **14** prior to the preparation of key dienophiles **12** and **16**, respectively.

The synthesis of dienophile **12** was accomplished as depicted in Scheme 2. Dehydrogenation of 1,2,3,9-tetrahydro-4*H*-carbazol-4-one **7**[10] on Pd/C afforded 9*H*-carbazol-4-ol **8**,[11] which was subjected to conditions for bis-protection with the Cbz-group, using benzyl chloroformate (NaH, Cbz-Cl). Isolated **9** was chemoselectively monodeprotected by treatment with aqueous sodium hydroxyde to furnish the *N*-Cbz-protected 9*H*-carbazol-4-ol **10**. Conversion of **10** to the 3-bromo-9*H*-carbazol-4-ol **11** was accomplished in excellent yield by exposure to 1 equiv of NBS in acetonitrile. Oxidation of **11** with diacetoxyiodobenzene under acidic conditions completed the synthesis of the desired dienophile **12**. The optimized synthesis of the *N*-Bn-protected analogue **16**[8] was achieved following a somewhat different route. Thus, 1,2,3,9-tetrahydro-4*H*-carbazol-4-one **7** was first transformed into its *N*-benzyl derivative **13**, and this later was dehydrogenated via a two-step procedure to give the 9-benzyl-9*H*-carbazol-4-ol **14**. This compound was next smoothly and selectively brominated by treatment with less than 1 equiv of NBS (0.5 to 0.75 equiv)[12,13] in acetonitrile to give the 9-benzyl-3-bromo-9*H*-carbazol-4-ol **15** in 90% yield (based on reacting **14**). Subsequent oxidation of **15** with diacetoxyiodobenzene provided the desired dienophile **16** in excellent chemical yield.

With dienophile **12** in hand, we were thus in a position to effect the key [4+2] cycloaddition (Scheme 3). As anticipated on the basis of our earlier studies,[9] this reaction was smoothly effected by admixture of **12** with a slight excess of diene **3** in acetonitrile and subsequent heating at 40 °C for 4 h. Surprisingly, the major compound formed was not the expected adduct **17** but its deprotected derivative **18**. Moreover, we also observed that the ratio between **17** and **18** could be greatly improved in favor of **18** (80% isolated yield) after 48 h of heating in acetonitrile at 40 °C. Because **18** was isolated along with benzyl dimethylcarbamate, we assumed that the easy cleavage of the *N*-Cbz group took place under the action of in situ liberated dimethylamine hydrobromide. Similarly, dienophile **16** reacted with diene **3** to give the expected adduct **19** in 80% isolated yield. At this stage, it is worth mentioning that the change in the nature of the indole protective group resulted in a dramatic change of the velocity of the cycloaddition reaction which, in the same conditions, was complete after 4 h for dienophile **12** instead of 48 h for dienophile **16**. This different behavior undoubtedly reflects the electron-acceptor nature of the Cbz protecting group which, in lowering the electron density in the quinone unit of **12**, favors its cycloaddition reaction with the electron-rich diene **3**.

With the cycloaddition reaction accomplished, transformation of compound **18** into calothrixin B could be completed in a few additional steps, e.g., triflation, dehydrogenation of ring A, and excision of the superfluous oxygen at C_1 (Scheme 4). Thus, deprotonation of **18** followed by triflation afforded a mixture of enol triflate **20** and aryl triflate **21** which, without separation, were subsequently heated in dioxane in the presence of DDQ to give the sole triflate **21**. Subjection of **21** to conditions for reduction (Pd(0), formic acid) completed the synthesis of calothrixin B. It is worth noting that this transfor-

(8) Sissouma, D.; Collet, S.; Guingant, A. *Synlett* **2004**, 2612.

(9) (a) Collet, S.; Rémi, J. F.; Cariou, C.; Laïb, S.; Guingant, A.; Vu, N. Q.; Dujardin, G. *Tetrahedron Lett.* **2004**, *45*, 4911. (b) Vu, N. Q.; Dujardin, G.; Collet, S.; Raiber, E.-A.; Guingant, A.; Evain, M. *Tetrahedron Lett.* **2005**, *46*, 7669.

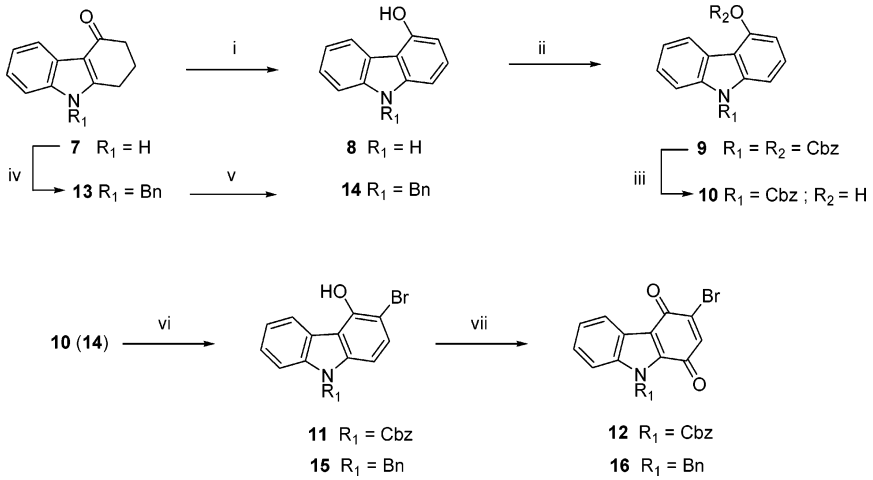
(10) 1,2,3,9-Tetrahydro-4*H*-carbazol-4-one **7** was prepared by oxidation of the commercially available 2,3,4,9-tetrahydro-1*H*-carbazole following an already reported procedure. See: Oikawa, K.; Yonemitsu, O. *J. Org. Chem.* **1977**, *42*, 1213.

(11) 1,2,3,9-Tetrahydro-4*H*-carbazol-4-one and 9*H*-carbazol-4-ol are both commercially available.

(12) Use of 1 equiv of NBS led to the formation of a secondary compound resulting from over-bromination of **15**.

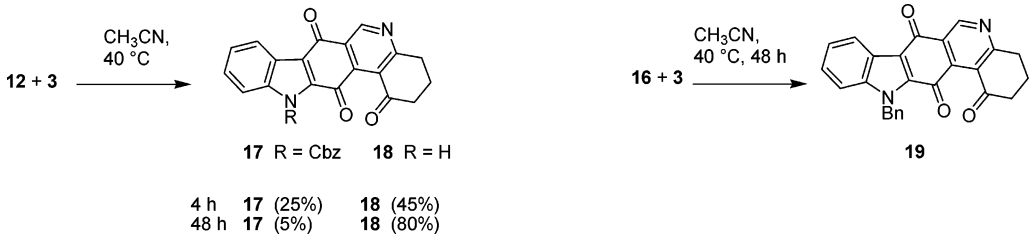
(13) Poumaroux, A.; Bouaziz, Z.; Domard, M.; Fillion, H. *Heterocycles* **1997**, *43*, 585.

SCHEME 2. Synthesis of Dienophiles 12 and 16[a]

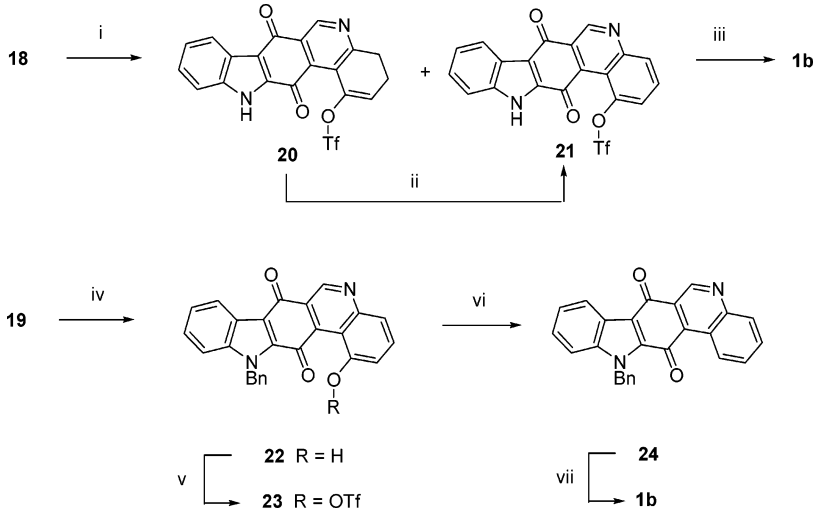


[a] Reagents and conditions: (i) **7**, 10% Pd/C, 10:1 PhOPh:1,2,5-trimethylbenzene, 250 °C, 18 h, 90%; (ii) NaH (2.3 equiv), $BnCO_2Cl$ (2.3 equiv), rt, 1 h, 91%; (iii) NaOH, 3:1 dioxane:water, 40 °C, 3 h, 90%; (iv) NaH, DMF, BnBr, 0−20 °C, 2 h, 95%; (v) **13**, NaH, THF, $PhSO_2Me$, 20 °C then reflux, 2 h, 94%; (vi) preparation of **11**:**10**, NBS (1 equiv), CH_3CN, rt, 0.5 h, 94%; preparation of **15**:**14**, NBS (0.5 to 0.75 equiv), CH_3CN, 20 °C, 0.5 h, 90%; (vii) preparation of **12**:**11**, $PhI(OAc)_2$, 2:3 AcOH:TFA, rt, 0.5 h, 83%; preparation of **16**:**15**, $PhI(OAc)_2$, 2:3 AcOH:TFA, 20−50 °C, 0.5 h, 96%.

SCHEME 3. The Key Cycloaddition Reaction



SCHEME 4. Completion of the Synthesis[a]



[a] Reagents and conditions: (i) LiHMDS, 3:2 THF:HMPA, −78 °C then $PhNTf_2$ in THF, 1 h; (ii) DDQ, dioxane, reflux, 2 h, 51% over two steps; (iii) $Pd(PPh_3)_4$, NEt_3, HCO_2H, dioxane, reflux, 4 h, 75%; (iv) 10% Pd−C, PhOPh, 250 °C, 15 min, 73%; (v) TfOTf, NEt_3, CH_2Cl_2, −78 to 20 °C, 2 h, 94%; (vi) $Pd(PPh_3)_4$, NEt_3, HCO_2H, dioxane, reflux, 20 min, 95%; (vii) $AlCl_3$ (5 equiv), benzene, reflux, 2 h, 57%.

mation could be effected without the need for indole nitrogen atom reprotection.

As shown in Scheme 4, calothrixin B could also be reached from the *N*-benzyl protected adduct **19**, although in a less efficient manner. Transformation of adduct **19** toward *N*-Bn protected calothrixin B **24** was achieved without incident. However, the removal of the *N*-benzyl protecting group to give calothrixin B turned out to be far from routine and could be effected only in a fair yield of 57% by subjection of **24** to an excess of $AlCl_3$ in benzene at reflux.

Conclusion

In conclusion, we have described an approach for the preparation of calothrixin B exploiting a regioselective hetero-

Diels−Alder cycloaddition to assemble the core structure of the molecule. It was shown that the electronic nature of the indole moiety *N*-protecting group (i.e., Cbz vs Bn) influenced the reactivity significantly. On the whole, the route with a *N*-Cbz protective group was more rewarding since this group, in addition to accelerating the cycloaddition process, was easily removed in the course of the reaction under the action of the liberated dimethylamine hydrobromide. Also of particular note is the fact that recourse to reprotection of the indole nitrogen atom was unnecessary to achieve the transformation of the Diels−Alder adduct toward calothrixin B, which was constructed in a total of 9 steps, in 17% overall yield from commercially available 1,2,3,9-tetrahydro-4*H*-carbazol-4-one **7**.

Experimental Section

(*E*,*E*)-*N*,*N*-Dimethyl-*N*′-(3-oxocyclohex-1-en-1-yl)imidoformamide (3). A solution of 3-aminocyclohex-2-ene-1-one[14] (1.59 g, 14.32 mmol) and dimethylformamide dimethylacetal (3.8 mL, 28.42 mmol) was heated in THF (30 mL) at 80 °C for 4 h. After being cooled to room temperature the solution was concentrated in vacuo. Purification of the residue by column chromatography on silica gel (9:1 EtOAc:MeOH containing 2% Et_3N) afforded 2.19 g (13.19 mmol, 92%) of diene **3** as a 3:1 mixture of *E*,*E* and *Z*,*E* isomers. The mixture of dienes was next heated in refluxing toluene for 1.5 h then concentrated to give diene **3** as the single *E*,*E*-isomer. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.95−2.04 (m, 2H), 2.32 (t, J = 6.5 Hz, 2H), 2.46 (t, J = 6.3 Hz, 2H), 3.03 and 3.06 (2s, 6H), 5.43 (s, 1H), 7.62 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.1, 30.5, 34.4, 36.8, 40.4, 110.7, 152.0, 172.5, 199.9. FT-IR (liquid film, cm^{-1}) 2939, 2815, 1615, 1557. MS (EI, 70 eV) *m*/*z* (rel intensity) 166 (M^+, 91), 138 (18), 123 (46), 109 (32), 71 (27), 44 (100), 28 (9). HRMS (EI) calcd for $C_9H_{14}N_2O$ 166.1106, found 166.110 [M^+].

9*H*-carbazol-4-ol (8).[11,15] To a stirred solution of 1,2,3,9-tetrahydro-4*H*-carbazol-4-one **7** (1 g, 5.41 mmol) in a 10:1 mixture of Ph_2O and 1,2,5-trimethylbenzene (55 mL) at room temperature was added 10% Pd/C (810 mg, 0.75 mmol). The mixture was heated for 18 h at 250 °C under an inert atmosphere of N_2 then cooled to room temperature. The catalyst was removed by filtration on Celite and the filter cake was rinsed several times with EtOAc. Volatiles were removed under reduce pressure and the resulting mixture was loaded onto a silica gel column. Elution of the column with hexanes (removal of Ph_2O) then with CH_2Cl_2 provided 890 mg of **8** (4.86 mmol, 90%) as a pale brown solid: mp 173 °C (AcOEt:hexanes). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.30 (s, 1H), 6.58 (d, J = 7.8 Hz, 1H), 7.02 (d, J = 7.8 Hz, 1H), 7.21−7.27 (m, 3H), 7.37−7.43 (m, 2H), 8.07 (br s, 1H), 8.27 (d, J = 7.7 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 103.3, 105.2, 110.0, 111.8, 119.7, 122.3, 122.8, 125.1, 126.6, 138.8, 141.4, 151.9. FT-IR (KBr, cm^{-1}) 3399, 3260, 1638, 1609, 1586, 1450. MS (EI, 70 eV) *m*/*z* (rel intensity) 183 (M^+, 100), 155 (31), 154 (55),127 (15).

Benzyl 4-{[(Benzyloxy)carbonyl]oxy}-9*H*-carbazole-9-carboxylate (9). To a solution of 9*H*-carbazol-4-ol **8** (1 g, 5.46 mmol) in dry DMF (15 mL) at 0 °C was added NaH (60% dispersion in mineral oil, 500 mg, 12.6 mmol). The mixture was stirred for 1 h at 0 °C and allowed to warm to room temperature. Benzyl chloroformate (1.8 mL, 12.6 mmol) was then added and the mixture was stirred for an additional 1 h. After it was quenched with water (100 mL), the mixture was extracted several times with CH_2Cl_2 and the combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (4:1 CH_2Cl_2:hexanes) to give 2.24 g of **9** (4.97 mmol, 91%) as a pale brown solid: mp 104 °C (CH_2Cl_2:hexanes). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.27 (s, 2H), 5.49 (s, 2H), 7.16−7.21 (m, 2H), 7.31−47 (m, 12H), 7.87 (d, J = 7.8 Hz, 1H), 8.14 (d, J = 7.8 Hz, 1H), 8.22 (d, J = 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 68.5, 70.3, 113.9, 115.8 (2C), 117.9, 122.0, 123.2, 123.4, 127.1, 127.15, 128.0, 128.3, 128.35, 128.4, 128.5, 134.6, 134.8, 137.8, 139.3, 145.5, 151.6, 153.0 (NB: 23 out of 28 resonance peaks were observed). FT-IR (KBr, cm^{-1}) 2924, 1752, 1724, 1591. MS (EI, 70 eV) *m*/*z* (rel intensity) 451 (M^+, 3), 407 (5), 272 (11), 91 (100). HRMS (EI) calcd for $C_{28}H_{21}NO_5$ 451.1420, found 451.143 [M^+].

Benzyl 4-Hydroxy-9*H*-carbazole-9-carboxylate (10). To a stirred solution of **9** (2 g, 4.43 mmol) in a 3:1 mixture of dioxane and water (80 mL) at 40 °C was added sodium hydroxide (350 mg, 8.86 mmol). After it was stirred for 3 h, the reaction mixture was quenched with water (50 mL) and neutralized with aqueous saturated NH_4Cl. The mixture was extracted several times with CH_2Cl_2 and the combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Purification of the residue by column chromatography on silica gel (4:1 CH_2Cl_2:hexanes) provided 1.26 g of **10** (3.97 mmol, 90%) as a pale brown solid: mp 159 °C (AcOEt:hexanes). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.41 (s, 1H), 5.57 (s, 2H), 6.72 (d, J = 7.8 Hz, 1H), 7.24−7.30 (m, 2H), 7.34−7.46 (m, 5H), 7.46−7.56 (m, 2H), 7.91 (d, J = 8.4 Hz, 1H), 8.28 (d, J = 7.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 68.7, 109.1, 109.5, 114.2, 115.8, 122.9, 123.6, 125.1, 126.5, 127.7, 128.6 (2C), 128.7 (2C), 128.8, 135.2, 137.7, 140.0, 151.3, 152.4. FT-IR (KBr, cm^{-1}) 3315, 3036, 1694, 1629, 1593. MS (EI, 70 eV) *m*/*z* (rel intensity) 317 (M^+, 16), 273 (14), 272 (11), 182 (4), 91 (100). HRMS (EI) calcd for $C_{20}H_{15}NO_3$ 317.1052, found 317.106 [M^+].

Benzyl 3-Bromo-4-hydroxy-9*H*-carbazole-9-carboxylate (11). To a solution of **10** (1.0 g, 3.15 mmol) in dry CH_3CN (50 mL) at room temperature was added freshly recrystallized NBS (560 mg, 3.15 mmol). After it was strirred for 30 min, the solution was concentrated and the residue was purified by column chromatography on silica gel (1:1 CH_2Cl_2:hexanes) to give 1.17 g of **11** (2.95 mmol, 94%) as a white solid: mp 130 °C (AcOEt:hexanes). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.55 (s, 2H), 6.06 (s, 1H), 7.33−7.48 (m, 6H), 7.53−7.56 (m, 2H), 7.60 (d, J = 9.0 Hz, 1H), 8.22−8.25 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 68.9, 103.8, 109.9, 114.6, 115.8, 123.0, 123.7, 124.3, 127.0, 128.6 (2C), 128.8 (3C), 129.4, 135.0, 137.7, 139.0, 147.4, 152.0. FT-IR (KBr, cm^{-1}) 3405, 1733, 1588, 1461. MS (EI, 70 eV) *m*/*z* (rel intensity) 397 (M^+, ^{81}Br, 3), 397 (M^+, ^{79}Br, 4), 353 (3), 153 (5), 91 (100). HRMS (EI) calcd for $C_{20}H_{14}NO_3{}^{79}Br$ 395.0157, found 395.017 [M^+].

Benzyl 3-Bromo-1,4-dioxo-1,4-dihydro-9*H*-carbazole-9-carboxylate (12). To a solution of **11** (1.0 g, 2.53 mmol) in a 2:3 mixture of AcOH and TFA (25 mL) at room temperature was successively added a few drops of water and diacetoxy iodobenzene (2.45 g, 7.6 mmol). After the mixture was stirred for 30 min at 40 °C, it was cooled to room temperature, MeOH (75 mL) was added, and stirring was continued for an additional 30 min. The mixture was extracted with CH_2Cl_2 several times and the combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Purification of the residue by column chromatography on silica gel (1:1 CH_2Cl_2:hexanes) afforded 860 mg (2.10 mmol, 83%) of **12** as a red solid: mp 175 °C (AcOEt:hexanes). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.51 (s, 2H), 7.22 (s, 1H), 7.39−7.52 (m, 7H), 7.99 (d, J = 8.4 Hz, 1H), 8.29 (d, J = 8.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 71.0, 114.6, 121.3, 123.2, 123.8, 126.1, 128.8 (3C), 129.2 (2C), 129.4, 133.7, 134.9, 137.3, 138.0, 138.3, 149.8, 174.7, 175.9. FT-IR (KBr, cm^{-1}) 3441, 1756, 1668, 1593, 1531. MS (EI, 70 eV) *m*/*z* (rel intensity) 411 (M^+, ^{81}Br, 1), 409 (M^+, ^{79}Br, 1), 367 (5), 91 (100). HRMS (EI) calcd for $C_{20}H_{12}NO_4{}^{79}Br$ 408.9950, found 408.997 [M^+].

9-Benzyl-1,2,3,9-tetrahydro-4*H*-carbazol-4-one (13). To a solution of 1,2,3,9-tetrahydro-4*H*-tetrahydrocarbazol-4-one **7**[10,11] (4.0 g, 21.6 mmol) in dry DMF (50 mL) at 0 °C was added sodium

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hydride (60% dispersion in mineral oil, 990 mg, 24.7 mmol) in small portions. After the mixture was stirred for 2 h at 0 °C it was allowed to warm to room temperature and benzyl bromide (2.9 mL, 24.7 mmol) was added dropwise. The reaction mixture was then stirred at room temperature for an additional 2 h and quenched with water (50 mL). The precipitate that formed was filtered and washed with pentane to provide 5.6 g (20.3 mmol, 95%) of **13** as a pale brown solid that was used without further purification. An analytically pure sample of **13** was obtained by crystallization from EtOAc: mp 148 °C (AcOEt). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.22 (qt, J = 6.0 Hz, 2H), 2.58 (t, J = 6.0 Hz, 2H), 2.86 (t, J = 6.0 Hz, 2H), 5.32 (s, 2H), 7.00−7.03 (m, 2H), 7.18−7.32 (m, 6H), 8.30 (d, J = 6.9 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.3, 23.4, 37.9, 47.0, 109.6, 113.1, 121.7, 122.7, 123.2, 124.9, 126.1 (2C), 127.9, 129.0 (2C), 136.0, 137.1, 151.8, 193.9. FT-IR (KBr, cm^{-1}) 3080, 2941, 1641, 1631, 1612, 1531. MS (EI, 70 eV) *m*/*z* (rel intensity) 275 (M^+, 52), 247 (22), 91 (100), 65 (20). Anal. Calcd for $C_{19}H_{17}NO$: C, 82.88; H, 6.22; N, 5.09. Found: C, 82.72; H, 6.29; N, 4.97.

9-Benzyl-9*H*-carbazol-4-ol (14). To a stirred solution of **13** (2.0 g, 7.27 mmol) in dry THF (20 mL) at room temperature was added sodium hydride (60% dispersion in mineral oil, 670 mg, 16.7 mmol) in small portions. After the solution was stirred for 2 h, methylbenzene sulfinate (1.23 mL, 9.36 mmol) was added dropwise. The mixture was then refluxed for 2 h and subsequently quenched with water (20 mL) and aqueous saturated NH_4Cl (10 mL) at room temperature. The mixture was extracted several times with EtOAc and the combined organic layers were dried over anhydrous $MgSO_4$ and concentrated. The residue was taken up in dioxane (20 mL) and the resulting solution was refluxed for 15 h. After it was cooled to room temperature, the solution was concentrated and the residue was purified by column chromatography on silica gel (8:2 CH_2Cl_2:hexanes) to afford 1.86 g (6.81 mmol, 94%) of **14** as a pale brown solid: mp 172 °C (AcOEt:hexanes). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.39 (s, 1H), 5.50 (s, 2H), 6.60 (d, J = 7.8 Hz, 1H), 6.97 (d, J = 8.1 Hz,1H), 7.12−7.15 (m, 2H), 7.24−7.29 (m, 5H), 7.33−7.41 (m, 2H), 8.33 (d, J = 7.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 46.7, 101.8, 105.2, 108.5, 111.3, 119.6, 122.1, 122.9, 125.1, 126.5 (2C), 126.6, 127.5, 128.8 (2C), 137.2, 140.1, 142.7, 152.0. FT-IR (KBr, cm^{-1}) 3345, 3020, 1636, 1603, 1585. MS (EI, 70 eV) *m*/*z* (rel intensity) 273 (M^+,25), 91 (100), 65 (14). HRMS (EI) calcd for $C_{19}H_{15}NO$ 273.1154, found 273.116 [M^+].

9-Benzyl-3-bromo-9*H*-carbazol-4-ol (15). To a stirred solution of **14** (1.8 g, 6.59 mmol) in dry CH_3CN (70 mL) at room temperature was added freshly recrystallized NBS (880 mg, 4.95 mmol). After being stirred for 30 min, the solution was concentrated in vacuo and the residue purified by column chromatography on silica gel (1:1 CH_2Cl_2:hexanes) to provide 1.57 g (4.46 mmol, 90%) of **15** as a white solid: mp 175 °C (AcOEt:hexanes). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.29 (s, 2H), 6.12 (s, 1H), 6.84 (d, J = 8.7 Hz, 1H), 7.08−7.11 (m, 2H), 7.22−7.35 (m, 5H), 7.40−7.46 (m, 2H), 8.36 (d, J = 7.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 46.7, 99.2, 102.7, 108.6, 111.6, 119.9, 121.7, 123.3, 125.7, 126.3 (2C), 127.6, 128.4, 128.8 (2C), 136.8, 140.2, 141.6, 148.1. FT-IR (KBr, cm^{-1}) 3394, 3050, 1597, 1484. MS (EI, 70 eV) *m*/*z* (rel intensity) 353 (M^+, ^{81}Br, 8), 351 (M^+, ^{79}Br, 8), 91 (100), 65 (12). HRMS (EI) calcd for $C_{19}H_{14}NO^{79}Br$ 351.0259, found 351.025 [M^+].

9-Benzyl-3-bromo-1*H*-carbazole-1,4(9*H*)-dione (16). To a stirred solution of **15** (1.22 g, 3.46 mmol) in a 2:3 mixture of AcOH and TFA (25 mL) containing a few drops of water was added diacetoxy iodobenzene (3.34 g, 10.38 mmol). The solution was stirred for 30 min at 50 °C then MeOH (75 mL) was added and stirring was continued for an additional 30 min. The solution was extracted several times with CH_2Cl_2 and the combined organic layers were dried over anhydrous $MgSO_4$ and concentrated. Purification of the residue by column chromatography on silica gel (1:1 CH_2Cl_2:hexanes) afforded 1.21 g (3.30 mmol, 96%) of **16** as red needles: mp 208 °C (AcOEt). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.84 (s, 2H), 7.12 (s, 1H), 7.15 (d, J = 8.0 Hz, 2H), 7.25−7.30 (m, 3H), 7.37−7.51 (m, 3H), 8.31 (d, J = 7.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 48.4, 111.8, 116.4, 123.4, 124.4, 125.3, 126.9 (2C), 127.7, 128.2, 129.0 (2C), 133.3, 136.0, 137.4, 139.3, 140.4, 175.2, 178.2. FT-IR (KBr, cm^{-1}) 3380, 3036, 1663, 1646, 1583, 1518. MS (EI, 70 eV) *m*/*z* (rel intensity) 367 (M^+, ^{81}Br, 11), 365 (M^+, ^{79}Br, 11), 91 (100), 65 (11). HRMS (EI) calcd for $C_{19}H_{12}NO_2{}^{79}Br$ 365.0051, found 365.006 [M^+].

3,4-Dihydro-1*H*-indolo[3,2-*j*]phenanthridine-1,7,13(2*H*,12*H*)-trione (18). To a stirred solution of diene **3** (520 mg, 3.13 mmol) in dry CH_3CN (15 mL) at room temperature was added a solution of dienophile **12** (850 mg, 2.07 mmol) in dry CH_3CN (15 mL). After the mixture was heated for 18 h at 40 °C, it was cooled to room temperature and concentrated in vacuo. The residue was purified by column chromatography on silica gel (elution with 1:1 EtOAc:hexanes then with pure EtOAc) to give 520 mg of cycloadduct **18** (1.64 mmol, 79%) as a red solid: mp >300 °C dec ($CHCl_3$:hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.20 (qt, J = 6.6 Hz, 2H), 2.90 (t, J = 6.6 Hz, 2H), 3.14 (t, J = 6.6 Hz, 2H), 7.40 (t, J = 7.2 Hz, 1H), 7.50 (t, J = 7.2 Hz, 1H), 7.62 (m, 1H), 8.17 (d, J = 8.1 Hz, 1H), 9.22 (s, 1H), 13.21 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.0, 32.5, 38.7, 113.9, 116.6, 122.3, 123.4, 124.3, 126.9, 127.4, 128.2, 137.4, 138.5, 138.9, 149.3, 168.1, 176.0, 178.8, 197.6. FT-IR (KBr, cm^{-1}) 3289, 1701, 1657, 1570, 1523. MS (EI, 70 eV) *m*/*z* (rel intensity) 316 (M^+, 56), 288 (100), 260 (24), 232 (10). HRMS (EI) calcd for $C_{19}H_{12}N_2O_3$ 316.0848, found 316.084 [M^+].

12-Benzyl-3,4-dihydro-1*H*-indolo[3,2-*j*]phenanthridine-1,7,-13(2*H*,12*H*)-trione (19). To a stirred solution of diene **3** (100 mg, 0.60 mmol) in dry CH_3CN (4 mL) at room temperature was added a solution of dienophile **16** (200 mg, 0.55 mmol) in dry CH_3CN (4 mL). The reaction mixture was heated for 48 h at 40 °C, cooled to room temperature, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (95:5 CH_2Cl_2:EtOAc) to give 180 mg of cycloadduct **19** (0.44 mmol, 80%) as an orange solid: mp 118 °C ($CHCl_3$:hexanes). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.27 (qt, J = 6.6 Hz, 2H), 2.93 (t, J = 6.6 Hz, 2H), 3.18 (t, J = 6.6 Hz, 2H), 5.89 (s, 2H), 7.20−7.32 (m, 5H), 7.40−7.47 (m, 3H), 8.43 (d, J = 7.8 Hz, 1H), 9.42 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.4, 33.1, 39.2, 48.6, 111.7, 118.4, 123.6, 123.9, 125.1, 126.8, 127.0 (2C), 128.0, 128.1, 128.2, 128.9 (2C), 135.6, 136.0, 140.0, 140.7, 150.3, 168.2, 177.5, 179.3, 198.3. FT-IR (KBr, cm^{-1}) 3409, 3041, 2958, 1702, 1666, 1569, 1509. MS (EI, 70 eV) *m*/*z* (rel intensity) 406 (M^+, 100), 378 (21), 315 (6), 91 (93), 65 (11). HRMS (EI) calcd for $C_{26}H_{18}N_2O_3$ 406.1317, found 406.133 [M^+].

7,13-Dioxo-12,13-dihydro-7*H*-indolo[3,2-*j*]phenanthridin-1-yl Trifluoromethanesulfonate (21). To a solution of **18** (150 mg, 0.47 mmol) in THF (3 mL) at −78 °C were added HMPA (2 mL) and LiHMDS (1 M solution in THF, 1.2 mL, 1.2 mmol). After the solution was stirred for 1 h at −78 °C, a solution of $PhNTf_2$ (254 mg, 0.71 mmol) in THF (1 mL) was added via cannula. The reaction mixture was stirred for an additional 1 h at −78 °C, quenched with water (5 mL), and neutralized with aqueous 1 M HCl. The mixture was then extracted with EtOAc and the combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (1:1 EtOAc/hexanes) to afford a mixture of **20** and **21**. To this mixture, dissolved in dioxane (2 mL), was added DDQ (160 mg, 0.70 mmol) in one portion. After the solution was refluxed for 2 h, it was cooled to room temperature and concentrated under reduced pressure. The residue was taken up in EtOAc and the resulting solution was filtered through a short plug of neutral alumina to give 107 mg of **21** (0.24 mmol, 51%) as a red solid: mp 276 °C ($CHCl_3$). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.42 (dd, J = 7.2 and 7.9 Hz, 1H), 7.50 (dd, J = 6.5 and 7.9 Hz, 1H), 7.63 (d, J = 8.1 Hz, 1H), 8.06−8.20 (m, 3H), 8.35 (d, J = 8.1 Hz, 1H), 9.66 (s, 1H), 13.43 (s, 1H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 114.0, 114.8, 115.9, 117.9 (CF_3, J = 319 Hz), 122.2, 123.2, 124.1, 124.6, 126.9, 127.4, 131.1, 131.8, 136.5, 137.5, 138.6, 143.6, 148.8, 151.4, 177.5, 178.7. FT-IR (KBr,

cm^{-1}) 3391, 3281, 1673, 1653, 1616, 1555, 1529. MS (EI, 70 eV) *m*/*z* (rel intensity) 446 (M^+, 62), 314 (56), 297 (42), 285 (100), 269 (2), 257 (54). HRMS (EI) calcd for $C_{20}H_9N_2O_5F_3S$ 446.0184, found 446.021 [M^+].

Removal of the Trifluoromethanesulfonyloxy Group of 21: Obtention of 1b. To a stirred solution of **21** (100 mg, 0.22 mmol) in dioxane (5 mL) at room temperature were added NEt_3 (0.125 mL, 0.88 mmol), $Pd(PPh_3)_4$ (12 mg, 4 mol %), and formic acid (0.030 mL, 0.59 mmol). The mixture was refluxed for 4 h under an inert atmosphere of N_2 then cooled to room temperature. The precipitate was collected by filtration, washed with EtOAc, then crystallized from acetone to give 50 mg (0.17 mmol, 75%) of **1b** as a red solid: mp >300 °C dec (acetone). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.39−7.52 (m, 2H), 7.63−7.66 (m, 1H), 7.89−8.01 (m, 2H), 8.18−8.21 (m, 2H), 9.60 (d, J = 8.4 Hz, 1H), 9.64 (s, 1H), 13.20 (br s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 113.9, 115.5, 122.2, 122.5, 123.3, 124.3, 124.8, 127.1, 129.8, 130.2, 131.4, 131.5, 132.5, 137.9, 138.4, 147.5, 151.2, 180.3, 180.8. FT-IR (KBr, cm^{-1}) 3292, 2921, 1653,1558, 1532. MS (EI, 70 eV) *m*/*z* (rel intensity) 298 (M^+, 100), 270 (52), 242 (14), 121 (67). HRMS (EI) calcd for $C_{19}H_{10}N_2O_2$ 298.0742, found 298.074 [M^+].

12-Benzyl-1-hydroxy-7*H*-indolo[3,2-*j*]phenanthridine-7,13-(12*H*)-dione (22). To a stirred solution of **19** (150 mg, 0.37 mmol) in Ph_2O (4 mL) was added 10% Pd/C (97 mg, 0.09 mmol). The mixture was heated for 1 h at 250 °C under an inert atmosphere of N_2. After the mixture was cooled to room temperature, the catalyst was removed by filtration on Celite and the filter cake was rinsed several times with EtOAc. Volatiles were removed under reduced pressure and the resulting mixture was loaded onto a silica gel column. Elution of the column with hexanes (removal of Ph_2O) and then with CH_2Cl_2 provided 110 mg of **22** (0.27 mmol, 73%) as a brown solid: mp 245 °C ($CHCl_3$:hexanes). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 5.93 (s, 2H), 7.11 (d, J = 7.5 Hz, 1H), 7.24−7.50 (m, 7H), 7.59 (d, J = 7.8 Hz, 1H), 7.72−7.79 (m, 2H), 8.21 (d, J = 7.8 Hz, 1H), 9.43 (s, 1H), 10.92 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 49.1, 111.7, 114.2, 117.3, 118.3, 123.0, 123.1, 124.2, 124.5, 125.8, 126.6 (2C), 128.1, 129.0 (2C), 129.2, 133.2, 135.8, 136.9, 141.5, 147.6, 153.6, 154.4, 180.1, 185.0 (NB: 25 out of 26 resonance peaks were observed). FT-IR (KBr, cm^{-1}) 3420, 3080, 1651, 1646, 1608, 1552. MS (EI, 70 eV) *m*/*z* (rel intensity) 404 (M^+, 53), 313 (3), 91 (100), 65 (11). HRMS (EI) calcd for $C_{26}H_{16}N_2O_3$ 404.1161, found 404.118 [M^+].

12-Benzyl-7,13-dioxo-12,13-dihydro-7*H*-indolo[3,2-*j*]phenanthridin-1-yl Trifluoromethanesulfonate (23). To a solution of **22** (100 mg, 0.25 mmol) in CH_2Cl_2 (5 mL) maintained at −78 °C under a nitrogen atmosphere were added Et_3N (0.174 mL, 1.25 mmol) and Tf_2O (0.084 mL, 0.5 mmol). The mixture was stirred for 2 h at −78 °C, allowed to warm to room temperature, and quenched by the addition of water. It was then extracted with CH_2Cl_2 and the combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Purification of the residue by column chromatography on silica gel (eluent: CH_2Cl_2) afforded 126 mg (0.23 mmol, 94%) of **23** as a red solid: mp 220 °C ($CHCl_3$: hexanes). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.92 (s, 2H), 7.23−7.34 (m, 4H), 7.42−7.46 (m, 2H), 7.65 (d, J = 7.8 Hz, 1H), 7.90 (t, J = 8.1 Hz, 1H), 8.29 (d, J = 8.2 Hz, 1H), 8.42−8.46 (m, 1H), 9.83 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 48.9, 112.1, 116.3, 117.5, 118.5 (CF_3, J = 322 Hz), 123.0, 123.7, 125.2, 126.4, 126.7 (2C), 127.8, 128.8 (2C), 130.9, 131.3, 135.9, 136.4, 138.2, 140.1, 144.4, 149.2, 152.3, 178.9, 179.2 (NB: 25 out of 27 resonance peaks were observed). FT-IR (KBr, cm^{-1}) 3430, 2933, 1657, 1655, 1615, 1517. MS (EI, 70 eV) *m*/*z* (rel intensity) 536 (M^+, 5), 404 (33), 91 (100), 65 (17). HRMS (EI) calcd for $C_{26}H_{15}N_2O_3$ 403.1083, found 403.109 [$M - SO_2CF_3$]$^+$.

12-Benzyl-7*H*-indolo[3,2-*j*]phenanthridine-7,13(12*H*)-dione (*N*-Benzyl Calothrixin B)(24). To a stirred solution of **23** (70 mg, 0.13 mmol) in dioxane (4 mL) at room temperature were added NEt_3 (0.073 mL, 0.52 mmol), $Pd(PPh_3)_4$ (6 mg, 4 mol %), and formic acid (0.014 mL, 0.35 mmol). The mixture was refluxed for 20 min under an inert atmosphere of N_2. After it was cooled to room temperature the mixture was quenched with brine and extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (2:98 EtOAc: CH_2Cl_2) to provide 48 mg (0.12 mmol, 95%) of **24** as a red solid: mp 264 °C ($CHCl_3$:hexanes). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.03 (s, 2H), 7.21−7.34 (m, 5H), 7.44−7.49 (m, 3H), 7.74 (t, J = 7.2 Hz, 1H), 7.84 (t, J = 6.9 Hz, 1H), 8.20 (d, J = 8.4 Hz, 1H), 8.47−8.49 (m, 1H), 9.56 (d, J = 8.1 Hz, 1H), 9.81 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 48.5, 111.6, 117.7, 123.1, 123.3, 123.9, 124.5, 125.1, 126.6 (2C), 127.7, 127.9, 128.0, 128.9 (2C), 130.1, 130.3, 131.4, 133.3, 135.1, 136.2, 140.1, 147.9, 152.2, 181.0, 182.0. FT-IR (KBr, cm^{-1}) 3058, 1651, 1612, 1568, 1523. MS (EI, 70 eV) *m*/*z* (rel intensity) 388 (M^+, 64), 149 (18), 91 (100), 65 (17). HRMS (EI) calcd for $C_{26}H_{16}N_2O_2$ 388.1212, found 388.119 [M^+].

7*H*-Indolo[3,2-*j*]phenanthridine-7,13(12*H*)-dione (Calothrixin B) (1b). To a stirred solution of **24** (70 mg, 0.18 mmol) in benzene (7 mL) was added $AlCl_3$ (120 mg, 0.9 mmol) in one portion. The mixture was refluxed for 2 h and subsequently quenched at room temperature by the addition of water (10 mL). It was then extracted with CH_2Cl_2 and the combined organic layers were dried over anhydrous $MgSO_4$. Volatiles were removed in vacuo. Purification of the residue by column chromatography on silica gel (1:3 EtOAc: hexanes) afforded 31 mg (0.10 mmol, 57%) of **1b** as a red solid.

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Supporting Information Available: General experimental details and copies of ^{1}H and ^{13}C NMR spectra for compounds **1b**, **3**, **8**, **9**−**16**, **18**, **19**, and **21**−**24**. This material is available free of charge via the Internet at http://pubs.acs.org.

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