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# Synthetic Approaches to Indolo[2,3-*a*]carbazole Alkaloids. Syntheses of Arcyriaflavin A and AT2433-B Aglycone

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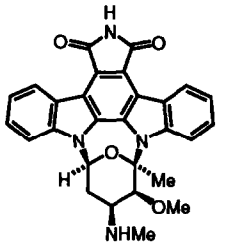
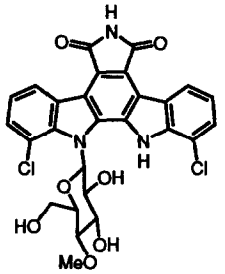
*Key Words:* Indolo[2,3-*a*]carbazole, arcyriaflavin, AT2433-B, Fischer indole synthesis

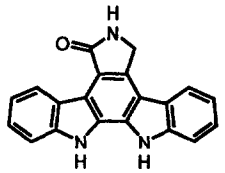
***Abstract***: Ozonolysis of tetrahydrophthalimides **17** and **18** or cyclohexene diester **25** and treatment of the intermediate dialdehydes (**19**,**20**,**26**) with an arylhydrazine affords the corresponding *bis*-arylhydrazones (**21**-**24**,**27**,**28**). Exposure of **21** and **23** to PPSE in $CH_3NO_2$ gives the indolo[2,3-*a*]carbazole alkaloids arcyriaflavin A (**8**) and AT2433-B aglycone (**29**) in low yield. *bis*-Phenylhydrazones (osazones) (**33**,**34**,**42**,**44**) of cyclohexandiones were synthesized by *m*-CPBA oxidation of 4,5-*bis*(trimethylsilyloxy)tetrahydrophthalimides followed by treatment of the presumed intermediate 1,2-cyclohexanediones with an arylhydrazine. These osazones were cyclized to the corresponding indolo[2,3-*a*]carbazoles with PPSE.

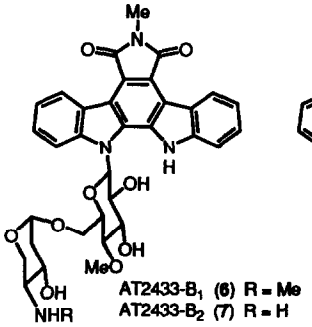
## Introduction

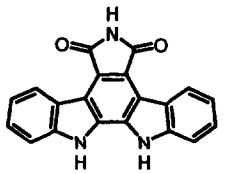
Indolo[2,3-*a*]carbazole alkaloids and the biogenetically related *bis*-indolylmaleimides constitute a rapidly growing family of natural products possessing diverse and, in some cases, extraordinary biological activity.[1,2] During the past fifteen years, about sixty natural products that incorporate the indolo[2,3-*a*]carbazole ring system[3] have been isolated from soil organisms, blue-green algae, and slime molds. In addition, myriad more synthetic analogues have been described in the patent literature,[4] as a result of the unique, powerful, and selec-

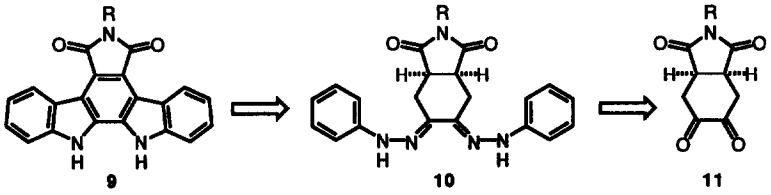



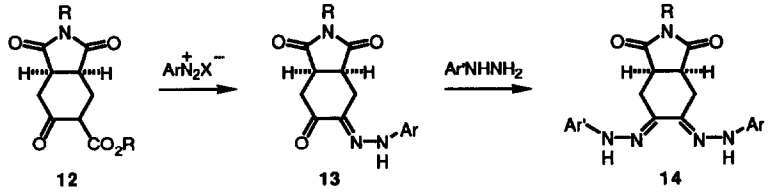
tive inhibitory effects these compounds have on protein kinases.[1e] Representative examples of these natural products are staurosporine (**1**),[5] TAN-999 (**2**),[6] Bmy-41950 (**3**),[7] rebeccamycin (**4**),[8] K-252c (**5**),[9] AT2433-$B_1$ (**6**),[10] AT2433-$B_2$ (**7**),[10] and arcyriaflavin A (**8**).[1c] Many of these compounds show promising antitumor, antibiotic, antihypertensive, and antiinflammatory activity.

An obvious approach to the indolo[2,3-*a*]carbazole ring system **9** is via a *bis*-Fischer indole synthesis (Scheme 1),[11] and, during the course of our studies, this method was successfully employed by Bergman and Pelcman to construct arcyriaflavin A (**8**) and rebeccamycin aglycone.[12] More recently, Bonjouklian, Moore and coworkers have utilized a *bis*-Fischer indolization to synthesize tjipanazole D and E.[2b]



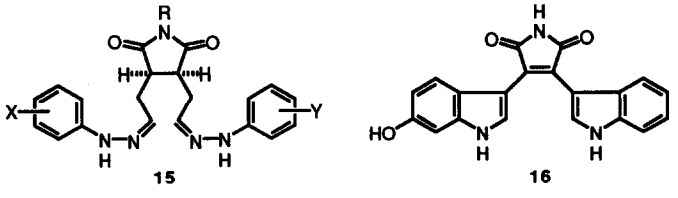
**Scheme 1**

Our approach to this problem differed from that of Bergman and Pelcman in that we desired to adapt the *bis*-Fischer indolization to the synthesis of *unsymmetrical* indolo[2,3-*a*]carbazoles via unsymmetrical *bis*-phenylhydrazones (osazones) **14**, prepared either from dione **11** or via a Japp-Klingeman reaction on a suitable substrate **12** (Scheme 2).



**Scheme 2**

Furthermore, we felt that appropriate modification of this strategy could be used to synthesize *bis*-indolylmaleimides, such as arcyriarubin B (**16**)[13] via the open-chain *bis*-phenylhydrazone analogue **15**.

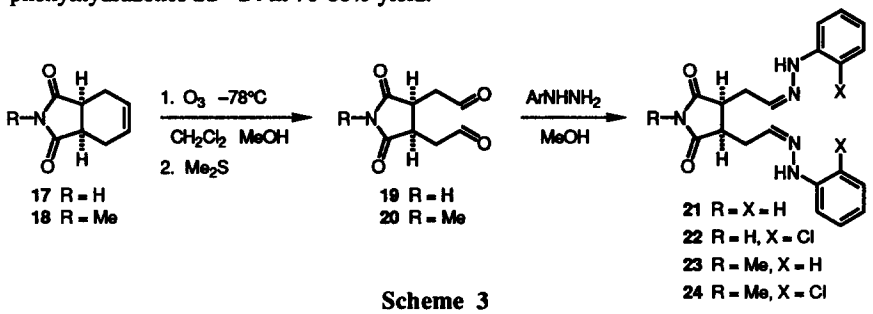


We now wish to describe our initial work towards the realization of these goals.[14]

## Results and Discussion

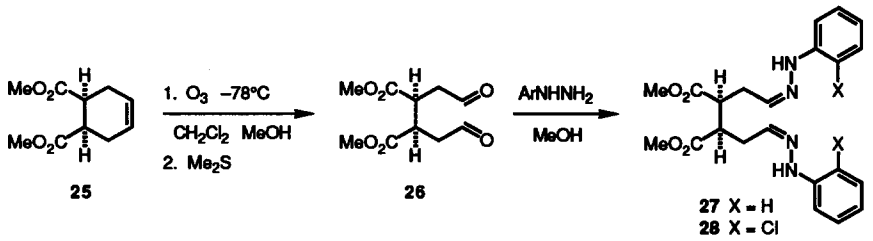
The synthesis of open-chain *bis*-phenylhydrazones was achieved as summarized in Scheme 3. Thus, the readily available tetrahydrophthalimides **17** and **18** were ozonized at –78 °C, followed by treatment with

dimethyl sulfide,[15] to give the labile dialdehydes **19** and **20**, which polymerized on attempted isolation. Therefore, treatment of the crude ozonolysis reaction mixture with an arylhydrazine (2 equiv) afforded the desired *bis*-phenylhydrazones **21** - **24** in 70-80% yield.



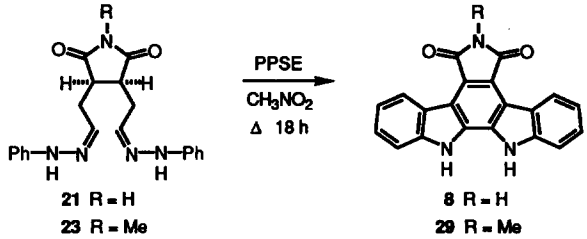

**Scheme 3**

The diester series, prepared from cyclohexene diester **25**, proved to be far more stable than those compounds derived from imides **17** and **18** (Scheme 4).



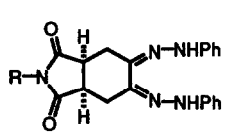

**Scheme 4**

Unfortunately, these *bis*-phenylhydrazones proved more fragile than we had anticipated, and conventional Fischer-indole acidic catalysts decomposed them. The mild catalyst polyphosphoric acid trimethylsilyl ester (PPSE)[16] has been successfully used for Fischer indole cyclizations.[12,16b] However, much to our surprise, when *bis*-phenylhydrazones **21** and **23** were treated with PPSE in $CH_3NO_2$ at reflux, the fully aromatized indolo[2,3-*a*]carbazoles arcyriaflavin A (**8**) and AT2433-$B_1$ and $B_2$ aglycone (**29**) were produced, respectively, in 10-12% yield after chromatography. The *bis*-indolylmaleimides (or succinimides) could not be detected. Unfortunately, similar cyclization attempts with *bis*-phenylhydrazones **22**, **24**, **27**, and **28** with PPSE in a variety of solvents only served to decompose these compounds.

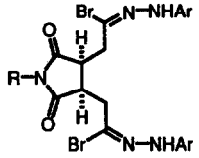



In an effort to prevent this premature cyclization of *bis*-phenylhydrazones to the presumed intermediate osazones **30** (i.e., **21** → **30** → **8**), we attempted to block the reactive centers with a suitable group. Thus, treatment of *bis*-*o*-chlorophenylhydrazones **22** and **24** with *N*-bromosuccimide (NBS) at room temperature

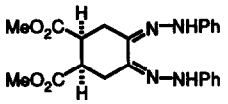
(THF) gave the corresponding *bis*-hydrazonyl bromides **31** and **32** in good yields. However, attempts either to cyclize these compounds to *bis*-indolylmaleimides or to displace the bromides with cyanide led to decomposition.




**30** R = H
**33** R = Me




**31** R = H
**32** R = Me
(Ar = 2-Cl-$C_6H_5$

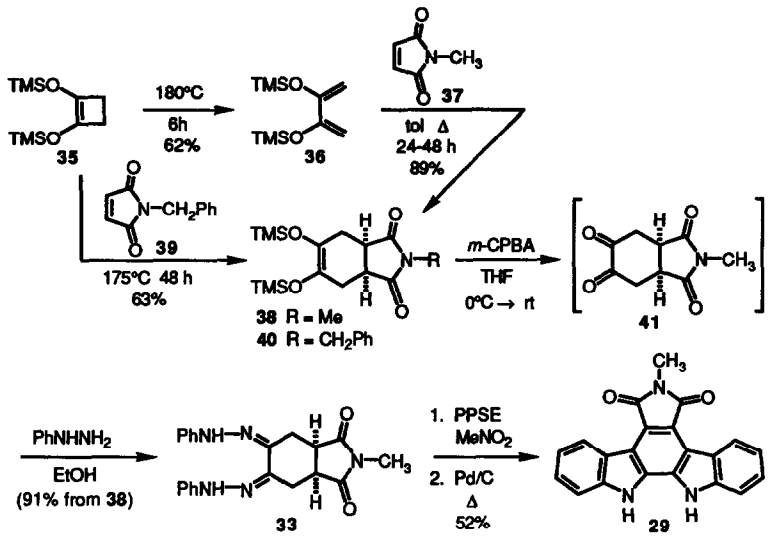



**34**

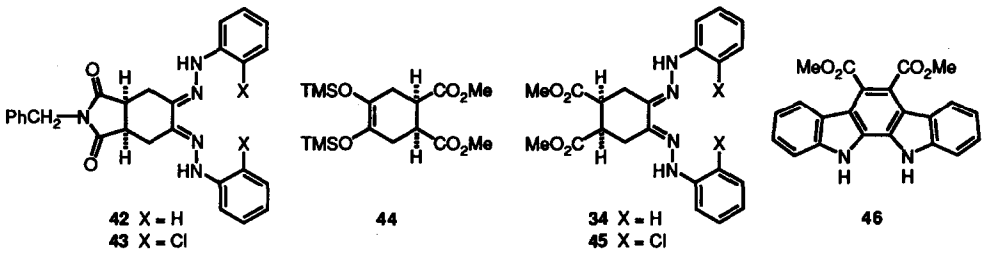
In contrast to **22** and **24**, when identical bromination conditions were applied to *bis*-phenylhydrazones **21**, **23** or **27**, an exothermic reaction immediately took place yielding a dark, complex mixture. When this bromination reaction was performed on **23** and **27** at −10 °C (THF, pyridine), the ring-closed osazones **33** and **34** were obtained in 53-66% yields after chromatography. This new reaction potentially represents an excellent route to cyclic osazones, and provides access to unsymmetrical *bis*-phenylhydrazones, which can be synthesized via the ozonolysis path shown in Scheme 3, utilizing, for example, an aldehyde ester ozonolysis product.[17]

This unexpected ring closure in both the twin-Fischer indole cyclizations of *bis*-phenylhydrazones **21** and **23** and the NBS bromination of **23** and **27** has precedent in the cyclization of adipaldehyde *bis*-phenylhydrazone by heating in air in various solvents.[18] It is conceivable that the formation of indolocarbazoles **8** and **29** from *bis*-phenylhydrazones **21** and **23**, respectively, involves Fischer indolization prior to oxidative ring closure of the resulting *bis*-indolylsuccinimide, since precedents also exist both for the oxidation of *bis*-indolylsuccinimides to *bis*-indolylmaleimides[1c] and for the oxidative ring closure of the latter to indolo[2,3-*a*]carbazoles.[19]

Our synthesis of the requisite diones **11** and osazones **10**, as proposed in Scheme 1, is summarized in Scheme 5. Cycloaddition of 2,3-*bis*(trimethylsilyloxy)-1,3-butadiene (**36**) (commercially available or prepared from **35**)[20] with *N*-methylmaleimide (**37**) gave the expected Diels-Alder adduct **38**.[20] Interestingly, we found that cyclobutene **35**, our precursor to diene **36**, reacts with *N*-benzylmaleimide (**39**) to give adduct **40** directly. In a variation of the Rubottom-Brook-Hassner oxidation of silyl enol ethers,[21] treatment of **38** with *m*-chloroperbenzoic acid (*m*-CPBA) followed by the addition of two equiv of phenylhydrazine to the presumed dione **41** intermediate gave the desired *bis*-phenylhydrazone (osazone) **33**. Although we had independently discovered the utility of PPSE in the subsequent twin Fischer indole cyclization, we had not uncovered the importance of $CH_3NO_2$ as the solvent in this reaction, until it was communicated to us by Professor Bergman.[22] Thus, following Bergman's conditions,[12] osazone **33** was smoothly converted into *N*-methylarcyriaflavin A (**29**), the aglycone of AT2433-$B_1$ and $B_2$. The *N*-benzylmaleimide adduct **40** was similarly converted into **42** and **43**, upon oxidation with *m*-CPBA and treatment with phenylhydrazine and *o*-chlorophenylhydrazine, respectively. Likewise, the Diels-Alder dimethyl maleate cycloadduct **44** underwent oxidation with *m*-CPBA to give, after treatment with the appropriate arylhydrazine, osazones **34** and **45**. Osazone **34** was converted under the Bergman-Pelcman conditions to indolo[2,3-*a*]carbazole in 63% yield. As Bergman and Pelcman found, some dihydro product is normally isolated with the fully aromatic indolo[2,3-*a*]carbazole **46**. Refluxing this mixture with 10% Pd/C in diglyme converted the dihydro compound into **46**.



Scheme 5



## Summary

Two key findings emerge from the present study. *Bis*-phenylhydrazones **21** and **23**, readily prepared in two steps from tetrahydrophthalimides **17** and **18**, are converted in low yield with the Bergman-Pelcman conditions (PPSE/$MeNO_2$) to arcyriaflavin A (**8**) and AT2433-B aglycone (**29**). Secondly, in a variation of the Rubottom-Brook-Hassner oxidation of silyl enol ethers, peracid treatment of *bis*(trimethylsilyloxy)tetrahydrophthalimides **38** and **40** affords osazones **33**, **42**, and **43** following treatment of the presumed intermediate dione (e.g., **41**) with an arylhydrazine. Also discovered in this research is the facile cyclization of *bis*-phenylhydrazones **23** and **27** to osazones **33** and **34** with NBS. This reaction potentially offers a route to unsymmetrical osazones and, hence, to unsymmetrical indolo[2,3-*a*]carbazole alkaloids.

## Experimental

Melting points were determined on a Büchi 510 melting point apparatus and are uncorrected. Ultraviolet spectra (UV) were recorded on a Hewlett Packard 8451A Diode Array spectrophotometer. Infrared spectra (IR) were recorded on a Perkin-Elmer 599 spectrophotometer or a BioRad Digilab Division FTS-40 spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian EM-360A spectrometer or Varian XL-300 Fourier transform spectrometer. Low resolution mass spectra were obtained on a Finnigan 4023

GC/MS system. Elemental analyses were performed by Atlantic Microlab Inc., Norcross, GA. Ozonolysis was performed in a three-neck flask fitted with an ozone inlet tube that extended below the solvent surface, a -100 °C thermometer and a $CaCl_2$ drying tube. Ozone in oxygen was produced using a Welsbach model T-408 ozonator set at 100 volts A.C. and oxygen pressure at 6-7 p.s.i. Hydrocarbon-free oxygen, Air Products zero grade or equivalent (< 2 ppm hydrocarbon), was passed through a cold trap (dry ice/isopropanol) to insure the absence of hydrocarbons. *N*-Benzylmaleimide (**39**) and 1,2-*bis*(trimethylsilyloxy)cyclobutene (**35**) were prepared by literature methods.

**Maleimide *bis*-Phenylhydrazones 21-24. General procedure**: A pre-dried stream of ozone in oxygen was passed through a solution of the appropriate *cis*-$\Delta^4$-tetrahydrophthalimide derivative **17** or **18** (0.01-0.0375 mol) in 1:5 MeOH/$CH_2Cl_2$ (75-150 mL) at –78 °C, until the solution developed a pale blue color. Nitrogen was then bubbled through the solution until the blue coloration disappeared. The cooling bath was removed and DMS (3-6 mL, 0.0375-0.075 mol) was added quickly via syringe, and the resulting solution allowed to warm to rt over 2 h. The solution was re-cooled to 0 °C and a solution of the appropriate arylhydrazine (2 equiv) in MeOH (10-25 mL) was added dropwise over 30 min. The resulting solution was allowed to come to rt overnight, during which time an off white to yellow precipitate usually formed. The precipitate was isolated by filtration, washed with MeOH and dried.

**Adipaldehyde-3,4-dicarboximide *bis*(Phenylhydrazone) (21)**. In this case, no precipitate was ever observed. The yellow-orange reaction mixture was concentrated in vacuo to give a stiff red glass in quantitative crude yield. Since attempts to purify this compound by chromatography or crystallization invariably led to decomposition, it was used immediately in the next reaction: $^1$H NMR (300 MHz, DMSO-$d_6$) δ 11.40-11.05 (b, 1 H), 9.81 (bs, 2 H), 7.59-6.50 (m, 12 H), 3.75-2.00 (m, 6 H).

**Adipaldehyde-3,4-dicarboximide *bis*(2-Chlorophenylhydrazone) (22)**. This compound was isolated in 67% yield. Recrystallization from $CH_2Cl_2$/hexane gave the analytical sample; mp 164-165 °C: IR (KBr) 3370, 3310, 3200, 3080, 2900, 1780, 1710, 1602, 1520, 1450, 1460, 1370, 1350, 1340, 1310, 1300, 1250, 1220, 1200, 1165 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$) δ 11.27 (s, 1 H), 9.41 (s, 2 H), 7.66 (t, J = 4.0 Hz, 2 H), 7.32 (d, J = 8.3 Hz, 2 H), 7.27 (d, J = 7.9 Hz, 2 H), 7.15 (t, J = 7.7 Hz, 2 H), 6.72 (t, J = 7.6 Hz, 2 H), 3.39 (bs, 3 H), 2.68 (bs, 3 H); $^{13}$C NMR (300 MHz, DMSO-$d_6$) δ 180.4, 141.9, 141.8, 129.2, 127.9, 118.9, 115.6, 113.6, 41.5, 28.9; MS *m/e* 435, 433, 431, 293, 292, 291, 290, 263, 151, 142, 139, 128, 127, 126, 111, 99, 91, 84, 80, 77, 69, 65, 55, 44 (100); UV (EtOH) $\lambda_{max}$ 280, 308 nm. Anal. Calcd for $C_{20}H_{19}N_5O_2Cl_2$: C, 55.57; H, 4.43; N, 16.24. Found: C, 55.17; H, 4.43; N, 15.98.

***N*-Methyladipaldehyde-3,4-dicarboximide *bis*(Phenylhydrazone) (23)**. This compound was isolated in 51% yield. Attempts to purify this compound were unsuccessful; crude mp 123-125 °C (dec): IR (KBr) 3310, 3045, 2960, 2940, 2910, 1775, 1695, 1610, 1540, 1510, 1501, 1450, 1390, 1355, 1310, 1270, 1120, 1050 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$) δ 9.77 (s, 2 H), 7.26 (bs, 2 H), 7.13 (t, J = 7.5 Hz, 4 H), 6.85 (d, J = 8.4 Hz, 4 H), 6.66 (t, J = 7.2 Hz, 2 H), 3.38 (s, 3 H), 2.86 (bs, 3 H), 2.60 (bs, 3 H); $^{13}$C NMR (300 MHz, DMSO-$d_6$) δ 179.2, 145.8, 137.8, 128.9, 118.0, 111.5, 40.5, 28.8, 24.4; UV (EtOH) $\lambda_{max}$ 242, 278, 308 nm.

***N*-Methyladipaldehyde-3,4-dicarboximide *bis*(2-Chlorophenylhydrazone) (24)**. This compound was isolated in 84% yield. Recrystallization from $CH_2Cl_2$/hexane gave the analytical sample; mp 168-170 °C: IR (KBr) 3320, 1778, 1705, 1600, 1525, 1445, 1385, 1315, 1290, 1250, 1100, 1035, 870, 750 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$) δ 10.16 (s, 2 H), 8.41 (t, J = 4.0 Hz, 2 H), 8.03-7.87 (m, 6 H), 7.47 (t, J = 7.5 Hz, 2 H), 4.18 (m, J = 4.1 Hz, 2 H), 3.62 (s, 3 H), 3.48 (bs, 4 H); $^{13}$C NMR (300 MHz, DMSO-$d_6$) δ 179.1, 141.9, 141.7, 129.2, 127.8, 118.9, 115.6, 113.5, 40.2, 28.9, 24.5; MS *m/e* 445, 306, 304, 268, 192,

179, 142, 139, 129, 128, 127 (100), 126, 111, 101, 99, 94, 92, 90, 80, 77, 67, 65; UV (EtOH) $\lambda_{max}$ 278, 309 nm. Anal. Calcd for $C_{21}H_{21}N_5O_2Cl_2$: C, 56.62; H, 4.75; N, 15.73; Cl, 15.71. Found: C, 56.37; H, 4.77; N, 15.56; Cl, 15.80.

**3,4-Dicarbomethoxyadipaldehyde (26).** A pre-dried stream of ozone in oxygen was passed through a mixture of **25** (3.71 g, 0.019 mol), and $NaHCO_3$ (0.54 g) in 1:5 MeOH/$CH_2Cl_2$ (62.5 mL) at -78 °C, until the solution developed a pale blue color. Nitrogen was then bubbled through the solution until the blue coloration disappeared. The cooling bath was removed and DMS (3 mL, 0.038 mol) was added quickly via syringe, and the resulting solution allowed to warm to rt overnight. The solution was concentrated in vacuo, and the residue redissolved in $CH_2Cl_2$ (50 mL). The solution was washed with $H_2O$ (50 mL) and the aqueous phase extracted with $CH_2Cl_2$ (2x50 mL). The organic layers were combined, washed successively with $H_2O$ (1x100 mL), brine (1x100 mL) and dried with $MgSO_4$. The mixture was filtered and concentrated in vacuo to give 3.14 g (73%) of a clear oil. Kugelrohr distillation gave the analytical sample; bp 200 °C / 0.2 Torr): IR (neat) 3450, 3200, 2970, 2920, 2860, 2750, 1740, 1445, 1390, 1335, 1230, 1050 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 9.73 (bs, 2 H), 3.69 (s, 6 H), 3.37 (bs, 2 H), 3.00-2.94 (m, 2 H), 2.61 (bs, 1 H), 2.55 (bs, 1 H); $^{13}C$ NMR (300 MHz, $CDCl_3$) δ 198.9, 172.0, 51.8, 41.9, 39.3; MS *m/e* 230, 198, 181, 167, 139, 116, 111, 93, 87, 83, 71, 65, 59, 55 (100), 53, 45. Anal. Calcd for $C_{10}H_{14}O_6$: C, 52.17; H, 6.13. Found: C, 52.06; H, 5.40.

**3,4-Dicarbomethoxyadipaldehyde *bis*(Arylhydrazones) (27, 28). General procedure**: To a solution of **26** (2.30 g, 0.01 mol) in MeOH (20 mL) was added the appropriate arylhydrazine (2 equiv) and the resulting solution stirred was overnight, during which time a precipitate formed and was isolated by filtration.

**3,4-Dicarbomethoxyadipaldehyde *bis*(Phenylhydrazone) (27).** This compound was isolated as an off-white solid in 78% yield. Recrystallization from $CH_2Cl_2$/hexane gave the analytical sample; mp 129-131.5 °C: IR (KBr) 3310, 3040, 3005, 2960, 2910, 1950, 1735, 1600, 1512, 1490, 1445, 1420, 1345, 1310, 1260, 1200, 1165, 1100, 1005 $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$) δ 10.50 (s, 2 H), 7.89-7.84 (m, 6 H), 7.59 (d, J = 7.9 Hz, 4 H), 7.39 (t, J = 7.3 Hz, 2 H), 4.34 (s, 6 H), 4.07 (bs, 1 H), 3.81-3.78 (m, 1 H), 3.38-3.10 (m, 4 H); $^{13}C$ NMR (300 MHz, DMSO-$d_6$) δ 173.2, 145.9, 136.7, 136.6, 129.0, 118.1, 111.5, 51.7, 51.6, 44.4, 31.8; MS *m/e* 410, 303, 183, 158, 145, 119, 108, 105, 93, 92, 77 (100), 66, 65, 59, 51; UV (EtOH) $\lambda_{max}$ 244, 280, 310 nm. Anal. Calcd for $C_{22}H_{26}N_4O_4$: C, 64.36; H, 6.39; N, 13.66. Found: C, 63.83; H, 6.43; N, 13.54.

**3,4-Dicarbomethoxyadipaldehyde *bis*(2-Chlorophenylhydrazone) (28).** This compound was isolated as a yellow solid in 83% yield; mp 144-145 °C: IR (KBr) 3345, 2950, 2900, 1740, 1600, 1510, 1460, 1445, 1420, 1345, 1310, 1255, 1190, 1150, 1040, 1030 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.76 (bs, 2 H), 7.42-737 (m, 2 H), 7.27-7.13 (m, 4 H), 6.78-6.71 (m, 2 H), 3.71 (s, 6 H), 3.34-3.21 (m, 2 H), 2.83-2.71 (m, 2 H), 2.58-2.49 (m, 2 H); $^{13}C$ NMR ($CDCl_3$) δ 173.4, 140.8, 138.9, 129.0, 127.8, 119.6, 116.4, 113.8, 52.0, 44.5, 32.0; MS *m/e* calcd for $C_{22}H_{25}N_4O_4Cl_2$: 479.1253; found: 479.1238; 479, 460, 387, 369, 353, 337 (100), 277, 261, 239, 220, 212, 183, 165; UV (EtOH) $\lambda_{max}$ 245, 276, 307 nm. Anal. Calcd for $C_{22}H_{24}N_4O_4Cl_2$: C, 55.12; H, 5.05; N, 11.69; Cl, 14.79. Found: C, 54.61; H, 5.07; N, 11.35; Cl, 15.46.

**Polyphosphoric Acid Silyl Ester (PPSE).**[16] A solution of $P_4O_{10}$ (1.42 g, 0.01 mol), hexamethyldisiloxane (2.56 g, 0.016 mol) in $CH_2Cl_2$ (5 mL) was heated to reflux for 30 min under nitrogen. The solvent and low boiling reaction products were removed by distillation, and the clear residue was heated to 180 °C for 5-10 min. The resulting pale yellow oil was cooled and used immediately.

**AT-2433 B Aglycone (29) from 23.** To a solution of freshly prepared PPSE (1 mmol based on $P_4O_{10}$) and HgO (65 mg, 0.3 mol) in $CH_3NO_2$ (5 mL) was added **23** (100 mg, 0.3 mmol) and the resulting

mixture was stirred at rt overnight. The mixture was then heated to reflux for 6 h, cooled and then poured into $H_2O$. The mixture was filtered with difficulty to give a mustard yellow solid which was air dried. The solid was continuously extracted with EtOAc in a Soxhlet device. The extract was concentrated in vacuo, and the residue purified by preparative thin layer chromatography (6:4 EtOAc/hexane) to give a bright yellow solid (11 mg) in 12% yield, mp >325 °C: IR (KBr) 3350, 2940, 1750, 1680, 1570, 1475, 1460, 1435, 1400, 1380, 1325, 1265, 1250, 1060 $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$) δ 11.56 (s, 2 H), 8.91 (d, J = 7.9 Hz, 2 H), 7.72 (d, J = 8.2 Hz, 2 H), 7.50 (t, J = 7.3 Hz, 2 H), 7.30 (t, J = 7.5 Hz, 2 H), 3.05 (s, 3 H); $^{13}C$ NMR (300 MHz, DMSO-$d_6$) δ 169.8, 140.3, 128.8, 126.7, 124.2, 121.5, 120.1, 118.8, 115.6, 111.9, 40.3; MS *m/e* 340, 339, 295, 294, 281, 280, 255, 254, 253, 227, 155, 127, 100, 86 (100), 83, 74; UV (EtOH) $\lambda_{max}$ 238, 275, 284, 308, 318, 402 nm; HRMS calcd for $C_{21}H_{13}N_3O_2$: 339.1008, found 339.1008. The spectral data for **29** agreed with that reported.[10]

**Arcyriaflavin A (8) from 21.** To a solution of freshly prepared PPSE (~0.01 mol based on $P_4O_{10}$) in $CH_3NO_2$ (10 mL) was added **21** (1.64 g, 0.0038 mol), and the resulting red solution was heated to reflux overnight. The dark reaction mixture was poured into ice water (30 mL) and stirred for 1 h. The brown mixture was filtered with great difficulty to give a mustard colored powder (1.29 g). This solid was absorbed on to silica (2 g) and eluted through a pad with an EtOAc/$CH_2Cl_2$ gradient to give an orange solid (0.116 g) in 10% yield, mp >325 °C: IR (FTIR (THF)) 3580, 3509, 3217, 1752, 1724, 1710, 1405, 1366, 1330, 1318 $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$) δ 11.76 (s, 2 H), 10.98 (s, 1 H), 8.99 (d, J = 8.1 Hz, 2 H), 7.80 (d, J = 8.4 Hz, 2 H), 7.55 (t, J = 7.5 Hz, 2 H), 7.35 (t, J = 7.5 Hz, 2 H); MS *m/e* 325, 207, 194, 193, 149, 129, 117, 115, 105, 104, 103, 97, 95, 92, 91 (100), 84, 78, 73, 69, 65, 60, 57, 55, 51; UV (EtOH) $\lambda_{max}$ 236, 258, 270, 282, 300, 314, 400 nm. The spectral data for **8** agreed with that reported.[1c,12]

**Adipaldehyde-3,4-dicarboximide *bis*(2-Chlorophenylhydrazonyl Bromides) (31-32). General procedure:** To a mixture of **22** or **24** (0.0011-0.0023 mol) and NBS (2 equiv) was added THF (10-25 mL) and the resulting solution stirred for 2-24 h at room-temperature, during which time the solution developed a orange-brown color. The solvent was evaporated in vacuo, and the dark residues were purified by either chromatography or extraction.

**Adipaldehyde-3,4-dicarboximide *bis*(2-Chlorophenylhydrazonyl Bromide) (31).** This compound was purified by vacuum chromatography through a silica pad (1:1 EtOAc/hexane) to give a red sweet smelling solid in 84% yield, mp 175-177 °C (dec): IR (KBr) 3320, 3200, 3080, 1799, 1720, 1635, 1601, 1510, 1445, 1370, 1350, 1301, 1250, 1160, 1085, 1050, 1040 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 8.79 (s, 1 H), 8.18 (s, 2 H), 7.36-7.13 (m, 6 H), 6.92-6.78 (m, 2 H), 3.75-3.19 (m, 6 H); $^{13}C$ NMR (300 MHz, $CDCl_3$) δ 177.6, 138.8, 129.4, 128.0, 121.2, 120.4, 117.7, 114.5; MS *m/e* 591, 589, 510, 429, 384, 370, 302, 295, 288, 230, 205, 167, 142, 139, 126, 111, 99, 92, 80 (100), 65; UV (EtOH) $\lambda_{max}$ 276, 300, 384 nm. A satisfactory analysis could not be obtained for this compound.

***N*-Methyladipaldehyde-3,4-dicarboximide *bis*(2-Chlorophenylhydrazonyl Bromide) (32).** This compound was purified by treating the crude reaction residue with EtOAc (30 mL) and washing the resulting solution successively with $H_2O$ (3x30 mL), and brine (1x30 mL) and drying over $MgSO_4$. The mixture was filtered, and evaporated in vacuo to give a red oil which when triturated with EtOAc/hexanes solidified. The product was isolated by filtration, and dried giving a red-brown sweet smelling solid in 57% yield; mp 148-149 °C: IR (KBr) 3320, 2920, 1780, 1699, 1648, 1600, 1405, 1340, 1285, 1260, 1185, 1145, 1050 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 8.17 (s, 2 H), 7.29-7.14 (m, 6 H), 6.86-6.80 (m, 2 H), 3.64-3.62 (m, 2 H), 3.44-3.37 (m, 2 H), 3.28-3.20 (m, 2 H), 3.03 (s, 3 H); $^{13}C$ NMR (300 MHz, $CDCl_3$) δ 177.5, 138.8, 129.3, 127.9, 121.2, 120.7, 117.7, 114.4, 41.1, 38.5, 25.2; MS *m/e* 605, 521, 441, 406, 396, 382, 316, 295, 230,

127 (100), 111, 99, 92, 82, 80, 75, 65, 63; UV (EtOH) $\lambda_{max}$ 274, 306, 382 nm. Anal. Calcd for $C_{21}H_{19}N_5O_2Br_2Cl_2$: C, 41.75; H, 3.17; N, 11.59. Found: C, 41.42; H, 3.12; N, 11.27.

**Osazones 33 and 34 from *bis*-Phenylhydrazones 23 and 27.** These compounds were also prepared by the following procedure. To a solution of **23** or **27** (0.7 mmol) and pyridine (71 mg, 0.9 mmol) in THF (5 mL) at -10 °C was added a solution of NBS (158 mg, 0.9 mmol) in THF (7 mL) dropwise. The resulting solution was allowed to warm to rt overnight during which time it developed a dark red color. The solution was heated to reflux for 4 h, cooled and the solvent concentrated in vacuo. The dark solid residue was triturated with 9:1 hexane/$CH_2Cl_2$ and filtered to give a orange yellow powder. The solid was further purified by vacuum chromatography on a silica pad ($CH_2Cl_2$) to give **33** or **34** as bright yellow solids in 53-66% yield which were identical to samples prepared later.

**Cycloadditions with 2,3-*bis*(trimethylsilyloxy)butadiene (36) and Maleic Acid Derivatives. General procedure:** 2,3-*bis*(trimethylsilyloxy)butadiene (**36**) (1-19 mmol) and 0.9-1.5 equiv of the appropriate maleic acid derivative (**37**, **39**, or dimethyl maleate) were dissolved in dry toluene (10-25 mL) and the resulting solution heated to reflux for 24-48 h. The solvent was removed in vacuo to give viscous oils which often solidified upon refrigeration. The residues were purified by either bulb to bulb Kugelrohr distillation, or recrystallization from $Et_2O$/hexanes to yield gummy white solids.

***N*-Methyl-4,5-*bis*(trimethylsilyloxy)-*cis*-$\Delta^4$-tetrahydrophthalimide (38).** This was isolated in 89% yield: mp 78-80 °C; IR (neat) 2960, 2900, 2850, 1775, 1695, 1440, 1385, 1350, 1325, 1250, 1180, 1150, 1090 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 3.06 (m, 2 H), 2.98 (s, 3 H), 2.53 (m, 4 H), 0.13 (s, 18 H); $^{13}C$ NMR ($CDCl_3$) δ 179.6, 129.4, 39.8, 29.1, 25.1, 0.48; MS *m/e* 342, 341, 326, 298, 270, 253, 133, 127, 73 (100). Anal. Calcd for $C_{15}H_{27}NO_4Si_2$: C, 52.75; H, 7.97; N, 4.10. Found: C, 51.85; H, 7.50; N, 4.32.

***N*-Benzyl-4,5-*bis*(trimethylsilyloxy)-*cis*-$\Delta^4$-tetrahydrophthalimide (40).** This was isolated in 79% yield; bp 250 °C / 0.15 Torr (lit.[17] bp 170 °C / 0.04 mbar): $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.31 (m, 5 H), 4.63 (s, 2 H), 3.04 (bs, 2 H), 2.52 (bs, 4 H), 0.10 (s, 18 H); $^{13}C$ NMR (300 MHz, $CDCl_3$) δ 179.2, 135.6, 129.3, 128.8, 128.6, 127.9, 42.7, 39.7, 28.9, 0.37; MS *m/e* 418, 417, 374, 346, 274, 260, 167, 147, 91, 73 (100). Alternatively, **40** was prepared by degassing and sealing a solution of **35** (0.61 g, 2.7 mmol) and **39** (0.50 g, 2.7 mmol) in 1,2-dichlorobenzene (2.5 mL) in a heavy walled tube. The tube was heated to 120 °C in a pipe heater for 12 h, then at 175 °C for an additional 48 h. The solvent was removed by distillation, and the residue was distilled (bulb to bulb) (260 °C / 0.15 Torr) to give **40** (63%) as a white solid.

**Dimethyl 4,5-*bis*(Trimethylsilyloxy)-*cis*-$\Delta^4$-tetrahydrophthalate (44).** This was isolated in 62% yield; bp 250 °C / 0.25 Torr: IR (neat) 2950, 1746, 1695, 1430, 1385, 1340, 1300, 1250, 1200, 1165, 1100, 1040, 1020 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 3.69 (s, 6 H), 3.04 (bs, 2 H), 2.60 (bs, 2 H), 2.41 (bs, 2 H), 0.17 (s, 18 H); $^{13}C$ NMR (300 MHz, $CDCl_3$) δ 172.7, 130.3, 51.7, 51.6, 40.3, 29.4, 0.53; MS *m/e* 374, 245, 229, 226, 213, 195, 184 (100), 169, 153, 139, 125, 114, 97, 81, 71, 69, 55. A satisfactory analysis could not be obtained for this compound.

**Synthesis of Osazones. General procedure:** To a solution of *m*-CPBA (1.2 equiv) in dry THF (20 mL) at 0 °C was added a solution of 4,5-*bis*(trimethylsilyloxy)tetrahydrophthalimide (0.9-1.5 mmol) in THF (10 mL) dropwise via syringe. The solution was allowed to warm to rt over 90 min, and then re-cooled to 0 °C before a solution of 2 equiv of the appropriate phenylhydrazine in EtOH (10 mL) was added dropwise over 10 min. The resulting solution (bright yellow color) was allowed to warm to rt overnight. Concentration in vacuo gave mustard yellow powders, which could be purified by recrystallization from hexane/$CH_2Cl_2$ or flash chromatography ($CH_2Cl_2$/1%MeOH, 50 g silica) to give the corresponding osazones as bright yellow solids.

***N*-Benzyl-*cis*-1,2-cyclohexanedione-4,5-dicarboximide Phenylosazone (42).** This was isolated in 68% yield as an orange oil: IR (KBr) 3295, 3150, 2925, 1780, 1700, 1605, 1585, 1500, 1430, 1405, 1345, 1255, 1170 $cm^{-1}$; $^1H$ NMR (60 MHz, $CDCl_3$) δ 7.4-6.9 (m, 15 H), 4.7 (s, 2 H), 3.3-2.8 (m, 6 H); MS *m/e* 451, 449, 431, 359, 358, 354, 336, 325, 299, 285, 267, 262, 245, 223, 196, 167, 149, 105, 91 (100), 77, 66, 65; UV (EtOH) $\lambda_{max}$ 260, 310, 392 nm. A satisfactory analysis could not be obtained. The difficulty in purifying these osazones for acceptable elemental analyses has been encountered by Bergman.[12]

***N*-Benzyl-*cis*-1,2-cyclohexanedione-4,5-dicarboximide 2-Chlorophenylosazone (43).** This was isolated in 80% yield; mp 166-167 °C: IR (FT-IR, $CH_2Cl_2$) 3375, 1708, 1587, 1581, 1528, 1517, 1515, 1513, 1505, 1498, 1398, 1346, 1166, 1050, 1033 $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$) δ 8.75 (s, 1 H), 7.32-6.58 (m, 14 H), 4.25 (AB q, J = 15.9 Hz, 2 H), 3.25-3.10 (m, 3 H), 2.80-2.50 (m, 3 H); $^{13}C$ NMR (300 MHz, $CDCl_3$) δ 178.0, 177.9, 140.9, 138.9, 135.1, 130.3, 129.0, 128.9, 127.7, 127.6, 127.4, 121.7, 121.2, 118.5, 117.5, 115.2, 114.9, 42.5, 39.3, 37.9, 32.9, 23.2; MS *m/e* 521, 393, 267, 251, 232, 230, 191, 149, 139, 127, 111, 99, 91 (100); UV (EtOH) $\lambda_{max}$ 254, 306, 384 nm. Anal. Calcd for $C_{27}H_{23}N_5O_2Cl_2$: C, 62.31; H, 4.45; N, 13.46. Found: C, 62.20; H, 4.47; N, 13.38.

***N*-Methyl-*cis*-1,2-cyclohexanedione-4,5-dicarboximide Phenylosazone (33).** This was isolated in 91% yield; mp 234-235 °C (dec): IR (KBr) 3440, 3320, 1775, 1700, 1600, 1580, 1320, 1305, 1435, 1380, 1285, 1250 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 12.60 (s, 1 H), 9.64 (s, 1 H), 7.27-7.02 (m, 8 H), 6.82 (t, J = 7.3 Hz, 1 H), 6.75 (t, J = 7.2 Hz, 1 H), 3.16-2.75 (m, 6 H), 2.82 (s, 3 H); $^{13}C$ NMR (300 MHz, $CDCl_3$/DMSO-$d_6$) δ 177.4, 143.4, 137.8, 131.3, 129.4, 128.6, 128.3, 128.2, 128.0, 127.9, 119.3, 119.0, 111.9, 111.7, 42.0, 36.9, 31.1, 22.5; MS *m/e* 376, 375, 358, 283 (100), 268, 196, 181, 172, 167, 158, 144, 128, 112, 105, 92 (100); UV (MeOH) $\lambda_{max}$ 232, 258, 312, 390 nm. Anal. Calcd for $C_{21}H_{21}N_5O_2$: C, 67.18; H, 5.64; N, 18.65. Found: C, 67.09; H, 5.65; N, 18.58.

***cis*-4,5-Dicarbomethoxy-1,2-cyclohexanedione Phenylosazone (34).** This was isolated in 82% yield; mp 168-170 °C: IR (KBr) 3340, 2950, 1740, 1720, 1600, 1560, 1505, 1475, 1440, 1360, 1250, 1200, 1180, 1010 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 12.94 (s, 2 H), 7.59 (s, 2 H), 7.35 (m, 2 H), 7.26 (m, 2 H), 7.16 (d, J = 7.9 Hz, 2 H), 7.10 (d, J = 7.8 Hz, 2 H), 6.97 (t, J = 7.2 Hz, 1 H), 6.86 (t, J = 7.1 Hz, 1 H), 3.75 (s, 3 H), 3.72 (bs, 1 H), 3.67 (s, 3 H), 3.43 (m, 1 H), 3.17-2.81 (m, 4 H); $^{13}C$ NMR (300 MHz, $CDCl_3$) δ 172.71, 172.65, 144.7, 143.8, 139.5, 129.5, 129.3, 129.2, 127.9, 121.4, 120.4, 113.3, 52.2, 52.1, 40.8, 39.8, 34.3, 24.7; MS *m/e* 408, 316, 284, 256, 243, 224, 210, 196 (100), 183, 167, 152, 143, 130, 120, 105, 92, 77; UV (EtOH) $\lambda_{max}$ 231, 260, 310, 390 nm. A satisfactory analysis could not be obtained.

***cis*-4,5-Dicarbomethoxy-1,2-cyclohexanedione 2-Chlorophenylosazone (45).** This was isolated in 84% yield; mp 147-148 °C: IR (KBr) 3380, 3250, 2955, 1745, 1600, 1580, 1500, 1475, 1440, 1380, 1285, 1201, 1035 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 12.38 (s, 1 H), 7.96 (s, 1 H), 7.81 (d, J = 7.8 Hz, 1 H), 7.68 (d, J = 7.7 Hz, 1 H), 7.32 (d, J = 8.0 Hz, 1 H), 7.26-7.19 (m, 3 H), 6.88 (t, J = 7.7 Hz, 1 H), 6.80 (t, J = 7.6 Hz, 1 H), 3.77 (s, 3 H), 3.73 (m, 1 H), 3.70 (s, 3 H), 3.42-3.37 (m, 1 H), 3.18-3.07 (m, 2 H), 2.96-2.89 (m, 2 H); $^{13}C$ NMR (300 MHz, $CDCl_3$) δ 1.72.5, 172.3, 141.41, 141.36, 139.1, 130.5, 129.1, 129.0, 127.7, 121.7, 120.9, 118.6, 117.6, 115.2, 114.7, 52.2, 52.1, 40.9, 39.9, 34.4, 25.2; MS *m/e* 478, 349, 318, 289, 230 (100), 167, 127, 111, 99, 92, 65; UV (EtOH) $\lambda_{max}$ 234, 256, 305, 384 nm. Anal. Calcd for $C_{22}H_{24}N_4O_4Cl_2$: C, 55.12; H, 5.05; N, 11.69. Found: C, 55.41; H, 4.65; N, 11.71.

**5,6-Dihydro-5,6-dicarbomethoxyindolo[2,3-*a*]carbazole and 5,6-Dicarbomethoxyindolo-[2,3-*a*]carbazole (46).** To a solution of PPSE (0.25 mmol based on $P_2O_5$) in $CH_3NO_2$ (5 mL) was added **34** (204 mg, 0.5 mmol) and the resulting solution was heated to reflux for 12 h. The resulting dark solution

was cooled and poured into $H_2O$ (~100-200 mL). The mixture was filtered with difficulty to give a mustard yellow solid which was continuously extracted in a Soxhlet device with EtOAc (250 mL). Alternatively, the mixture was extracted directly with EtOAc (3x100 mL), and the organic phase dried over $MgSO_4$ and filtered. In either case, the EtOAc solution obtained was concentrated in vacuo to give a brown residue (98-130 mg) comprised of two highly fluorescent compounds. The mixture was separated by preparative TLC (1:1 EtOAc/hexane) to give 5,6-dihydro-5,6-dicarbomethoxyindolo[2,3-*a*]carbazole (high $R_f$, 24 mg) and 5,6-dicarbomethoxyindolo[2,3-*a*]carbazole (**46**) (low $R_f$, 18 mg) as yellow solids in 13 and 10% yields, respectively. Alternatively, the brown residue was redissolved in diglyme (10 mL) and Pd/C (10%, 30 mg) was added and the resulting mixture heated to reflux overnight. The mixture was filtered through Celite, the resulting dark yellow solution poured into $H_2O$ (100 mL) and the resulting cloudy mixture and extracted with EtOAc (3x150 mL). The EtOAc extracts were combined, dried over $MgSO_4$, filtered and the filtrate concentrated in vacuo to give a brown residue. The residue was purified by preparative TLC (1:1 EtOAc/hexane) to give **46** as a yellow solid (117 mg) in 63% yield, mp 269-271 °C (dec).

**5,6-Dihydro-5,6-dicarbomethoxyindolo[2,3-*a*]carbazole**: IR (KBr) 3400, 3350, 3060, 2960, 1732, 1600, 1435, 1335, 1260, 1205, 1180, 1010 $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$/$CDCl_3$) δ10.90 (s, 2 H), 7.45-7.41 (m, 4 H), 7.11-6.99 (m, 4 H), 4.63 (bs, 2 H), 3.67 (s, 6 H); $^{13}C$ NMR (300 MHz, DMSO-$d_6$/$CDCl_3$) δ 171.6, 136.2, 127.7, 126.1, 121.0, 119.5, 119.4, 118.5, 111.3, 105.4, 51.3, 42.7; UV (MeOH) $\lambda_{max}$ 232, 254, 296, 316, 345, 360, 376 nm.

**5,6-Dicarbomethoxyindolo[2,3-*a*]carbazole (46)**: IR (KBr) 3500, 3280, 2910, 1720, 1685, 1545, 1495, 1460, 1445, 1400, 1340, 1275, 1245, 1230, 1150, 1020, 1000 $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$/$CDCl_3$) δ 11.61 (s, 2 H), 8.10 (d, J = 8.0 Hz, 2 H), 7.78 (d, J = 8.1 Hz, 2 H), 7.48 (t, J = 7.6 Hz, 2 H), 7.24 (t, J = 7.6 Hz, 2 H), 4.01 (s, 6 H); $^{13}C$ NMR (300 MHz, DMSO-$d_6$/$CDCl_3$) δ 168.3, 138.9, 126.2, 124.8, 121.5, 121.4, 118.8, 117.7, 115.6, 110.4, 51.5; MS *m/e* 372, 341, 254, 242, 227, 214, 201, 186, 171, 163, 142, 135, 127, 121, 114, 100, 95, 84, 77, 73, 69; UV (MeOH) $\lambda_{max}$ 255, 296, 330, 342, 360 nm; HRMS calcd for $C_{22}H_{16}N_2O_4$: 372.1110, found 372.1110.

**AT-2433 B Aglycone (29) from 33**. A solution of **33** (263 mg, 0.7 mmol) in $CH_3NO_2$ (5 mL) was added to freshly prepared PPSE (5 mmol based on $P_4O_{10}$) at 100 °C, and the resulting solution was heated to reflux for 1 h. The cooled solution was poured into $H_2O$ (75 mL) and the resulting mixture was extracted with EtOAc (3x50 mL). The extracts were combined, washed successively with $H_2O$ (1x100 mL), brine (1x100 mL) and then dried over $MgSO_4$. The solution was concentrated in vacuo to give 224 mg of a yellow foam which was dried overnight in vacuo. The yellow foam and Pd/C (10%, 30 mg) were dissolved in diglyme (15 mL) and the resulting mixture was heated to reflux for 14 h. The hot reaction mixture was filtered through Celite, washed with EtOAc and the combined filtrate was concentrated in vacuo. The residue was treated with $H_2O$ (50 mL) after which a fine yellow precipitate formed which could be isolated by filtration and dried in a rotary vacuum oven at 200 °C (109 mg). Extraction of this filtrate with EtOAc gave an additional 15 mg of product; 52% total yield. This material was identical to that prepared from **23**.

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## References and Notes


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22. Professor Jan Bergman, private communication. We thank Professor Bergman for communicating his results prior to publication and for sending us a copy of Dr. Benjamin Pelcman's doctoral thesis.