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Approaches to the Synthesis of Indolo[2,3-*a*]quinolizidine-2,6-dione

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Dedicated with admiration to Professor R. Alan Aitken

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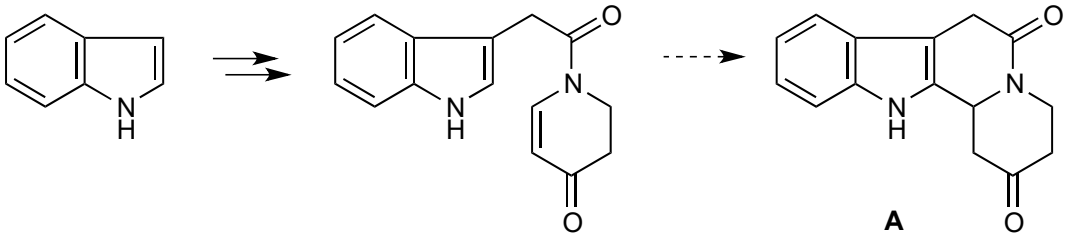
Abstract

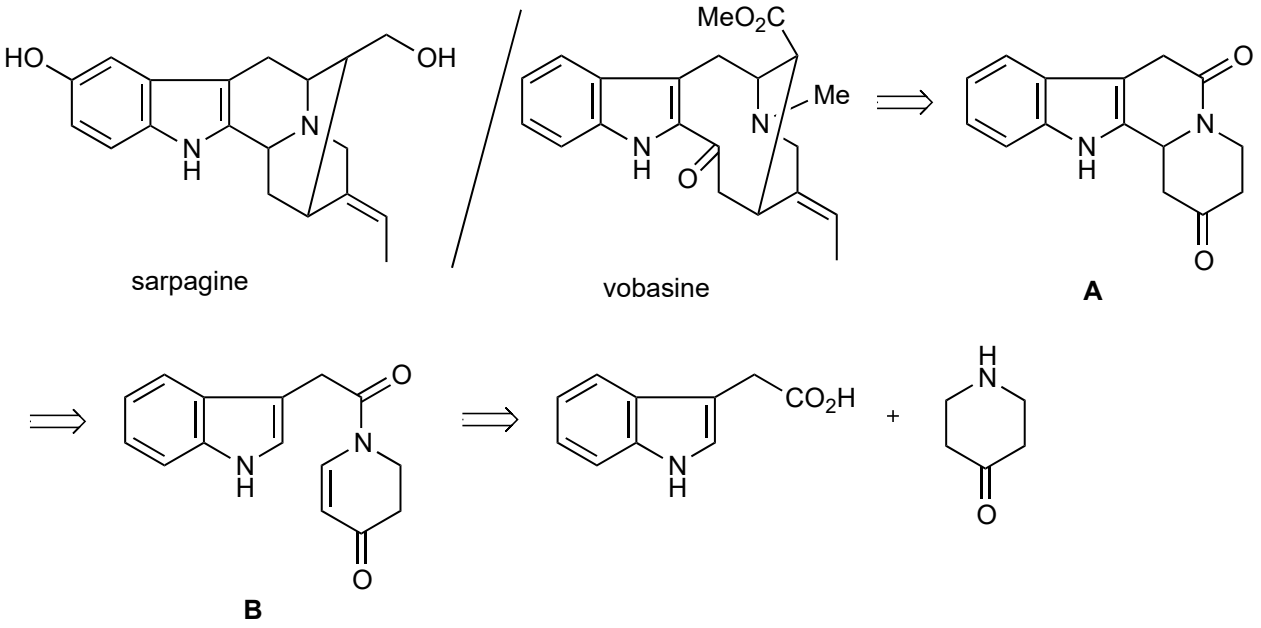
We describe the synthesis of several new potential precursors for the novel 1,3,4,7,12,12*b*-hexahydroindolo[2,3-*a*]quinolizine-2,6-dione (**A**), which we envisaged as being an ideally functionalized entry point into the sarpagine-vobasine class of indole alkaloids.



Keywords: Indole, 4-piperidone, indolo[2,3-*a*]quinolizine, vinylogous imide

Introduction

In our approach to this class of compounds and in continuation of our interest in the synthesis and chemistry of indolo[2,3-a]quinolizidines,[1–4] we envisaged 1,3,4,7,12,12*b*-hexahydroindolo[2,3-*a*]quinolizine-2,6-dione (**A**) as a potential stepping stone to alkaloids of the sarpagine-vobasine group of indole alkaloids (Scheme 1).[5–7] In our approach, the target molecule **A** would be accessible from vinylogous imide **B**, which we would obtain from indole-3-acetic acid and a suitable piperidone.



Scheme 1. Projected approach to the sarpagine-vobasine class of indole alkaloids.

Our rationale for the proposed cyclization of vinylogous imide **B** is based on the successful vinylogous cyclizations reported by Wenkert and Büchi and referenced below. The related cyclization of a vinylogous amide by Winterfeldt also portends success. These three precedents are summarized in Figure 1.[8–10]

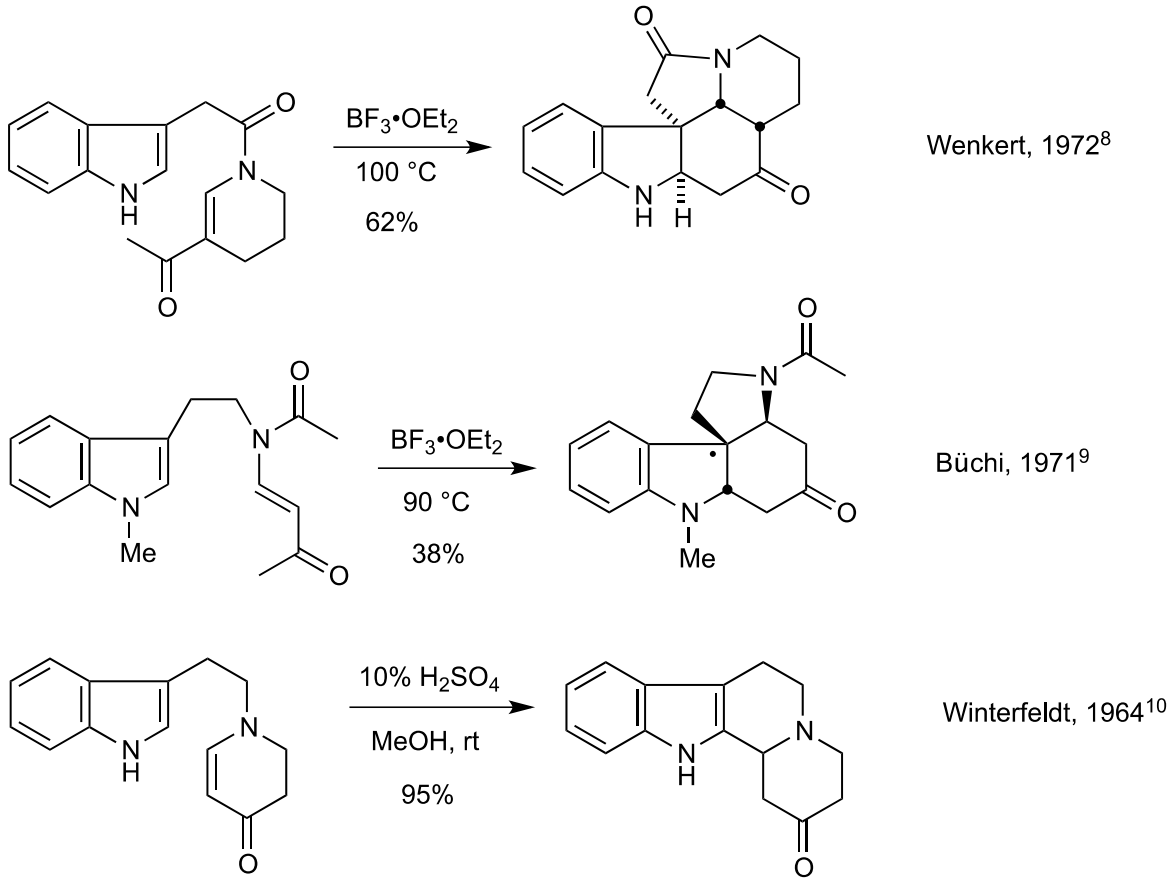
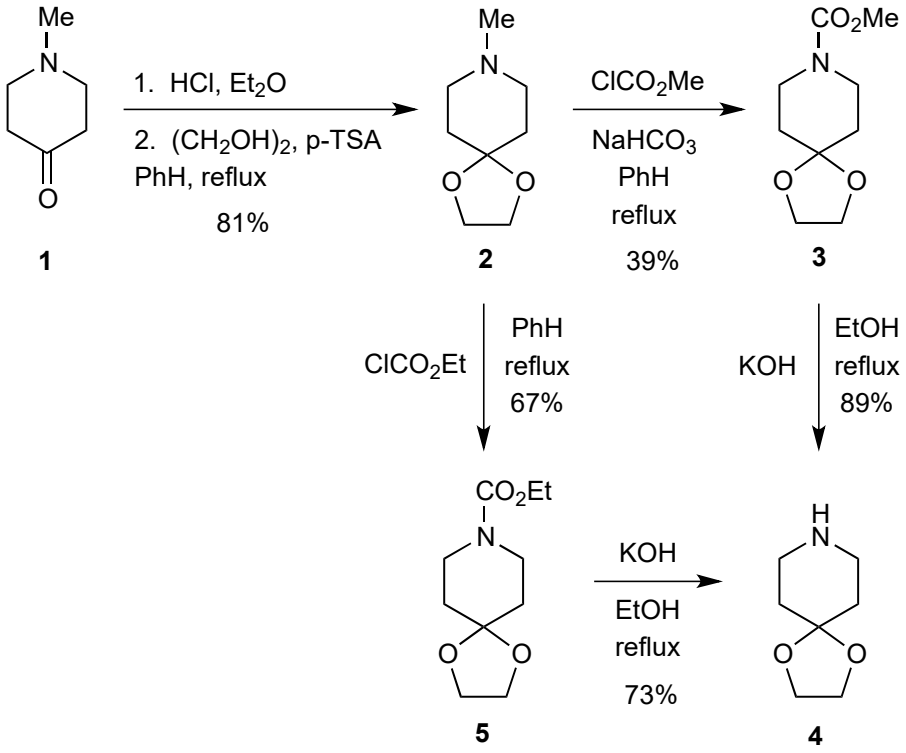


Figure 1

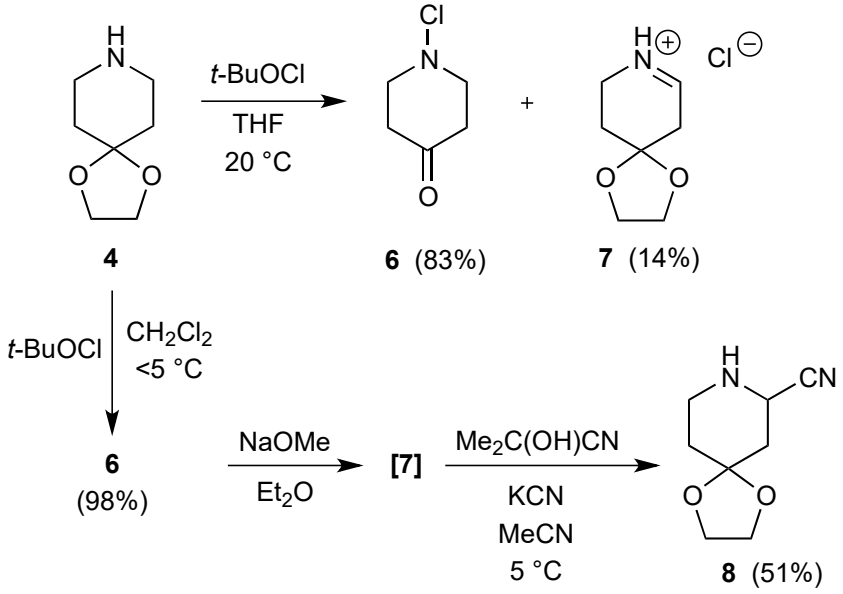
Results and Discussion

Our initial goal was to prepare 4-piperidones that would be suitable for coupling with indole-3-acetic acid *en route* to **B**. Although several of these piperidones are known, we decided to report full analytical data for these compounds. Our efforts are described in the following schemes 2–4.

1-Methyl-4-piperidone (**1**) was converted to ketal **2**, which was transformed into methyl carbamate **3**.[11] Hydrolysis of **3** afforded 1,4-dioxa-8-azaspiro[4.5]decane (**4**) in high yield. Interestingly, the overall yield of **4** was slightly higher using the ethyl carbamate **5**[12,13] (40% vs. 28%) (Scheme 2). We believe that the lower yield of **3** was likely due to sodium bicarbonate being mistakenly used in the reaction instead of in the workup, which was avoided in the preparation of **5**. *N*-Chlorination of **4** to give **6** using t-butyl hypochlorite[14] proceeded very well and we were able to isolate the dehydropyridine hydrochloride **7** when the *N*-chlorination was carried out in THF at 20 °C. An efficient synthetic protocol for the desired cyanoamine **8** (Scheme 3) involved chlorination of **4** in dichloromethane at lower temperature (<5 °C) to give **6** in 98% yield. Treatment of **6** with base to provide intermediate **7** followed by *in situ* cyanation afforded **8** in 51% yield over two steps.

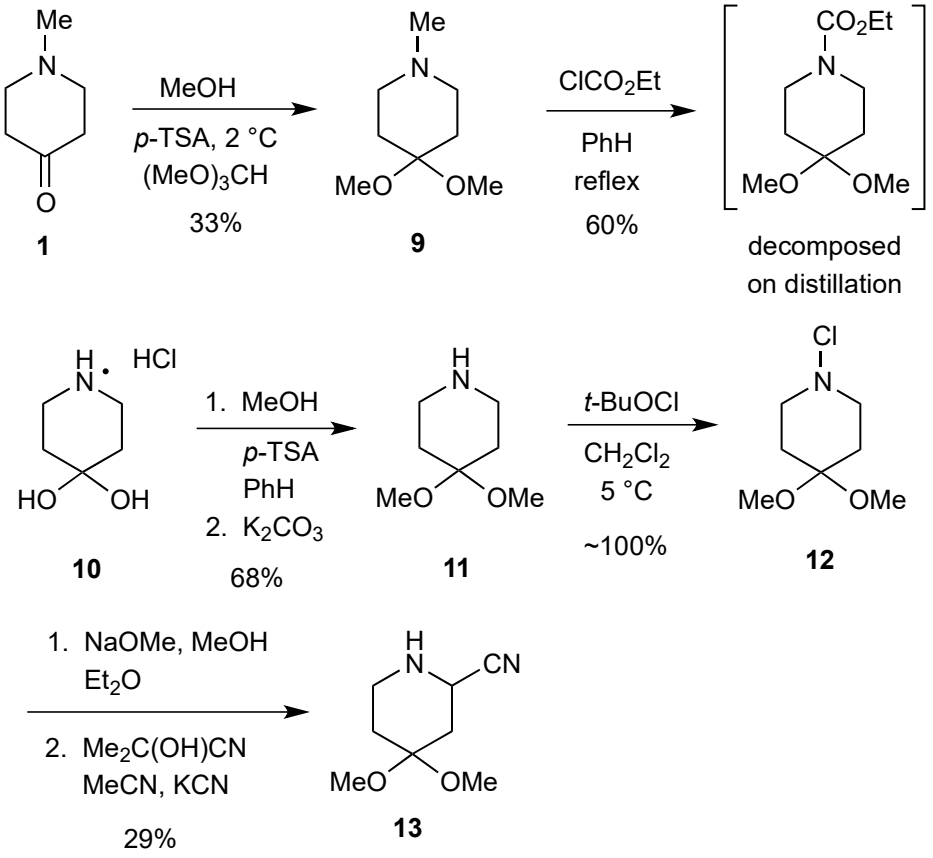


Scheme 2. Synthesis of 1,4-dioxa-8-azaspiro[4,5]decane (**4**).



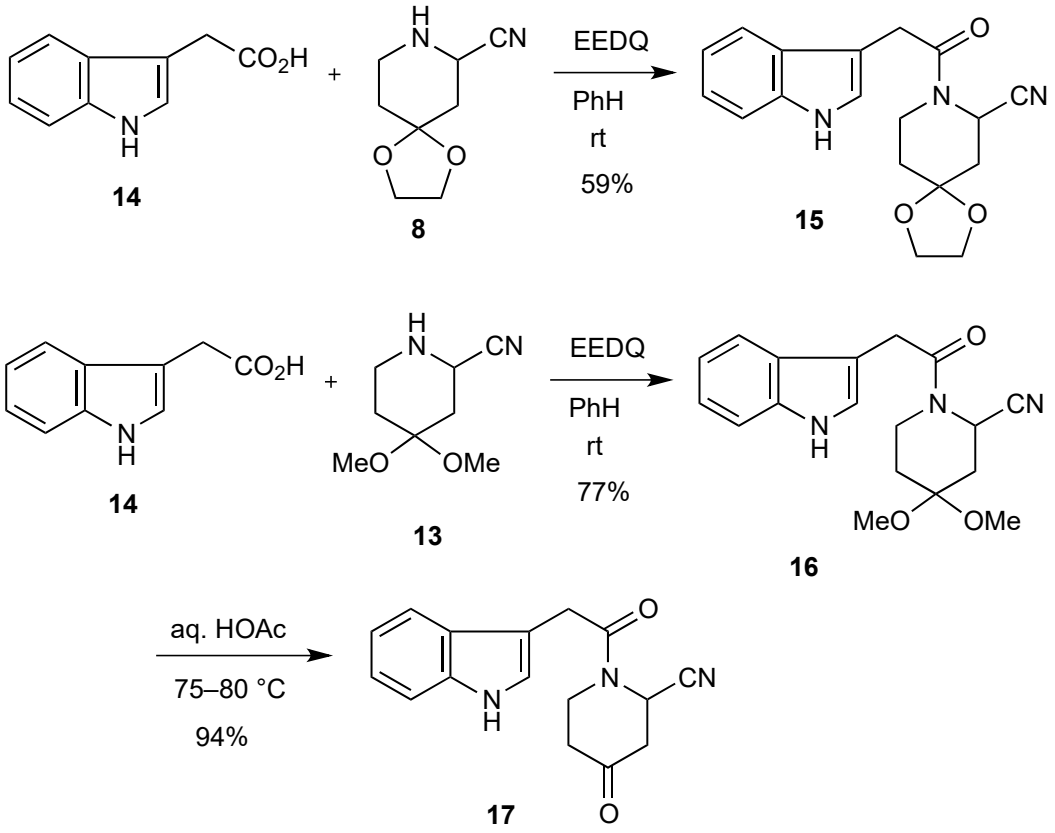
Scheme 3. Synthesis of 7-cyano-1,4-dioxa-8-azaspiro[4,5]decane (**8**).

We next considered the preparation of the new compound 2-cyano-4,4-dimethoxypiperidine (**13**) (Scheme 4). Initially, we prepared the new 1-methyl-4,4-dimethoxypiperidine (**9**), but the presumed *N*-carboethoxy analogue was not stable and decomposed during attempted distillation. However, commercially available 4-piperidone hydrate hydrochloride (**10**) was converted to 4,4-dimethoxypiperidine (**11**),[15] which was transformed in two steps to the desired 2-cyano-4,4-dimethoxypiperidine (**13**) (Scheme 4).



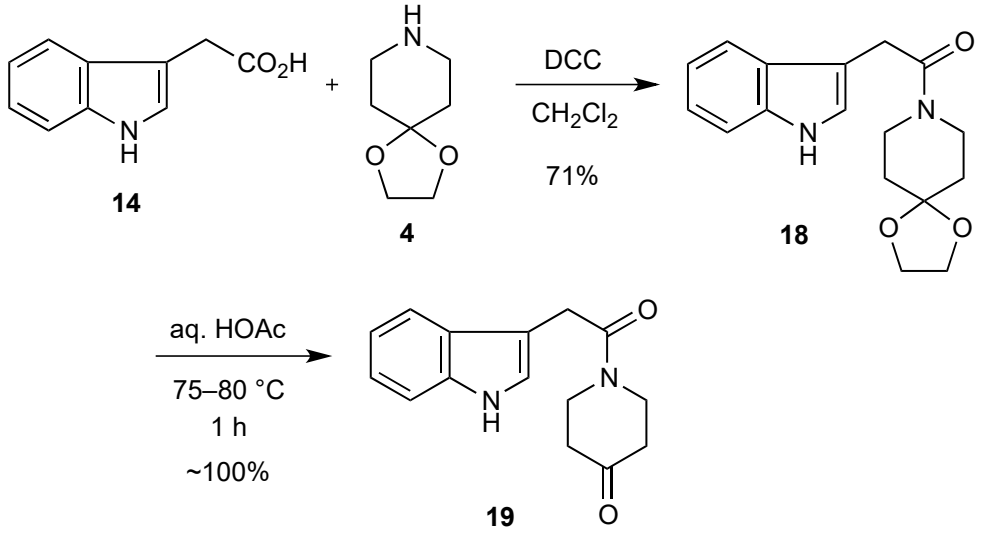
Scheme 4. Synthesis of 2-cyano-4,4-dimethoxypiperidine (**13**).

The coupling of the aforementioned 4-piperidone ketals **8** and **13** with indole-3-acetic acid (**14**) and the subsequent hydrolysis of **16** to **17** is presented in Scheme 5. Cyanoketal **15** was not pursued because the yield of **16** is higher and we felt that the latter would be more amenable to ketal hydrolysis. Moreover, deprotection of ketal **15** in 50% HOAc gave side products that lowered the yield of **17**. Unfortunately, our attempts to eliminate HCN from **17** to the desired vinylogous imide **B** have been unsuccessful, under basic conditions (DBU; pyridine/$AgNO_2$; LiCl; LDA; *t*-OBu) or via an enamine formed *in situ* from **17**.



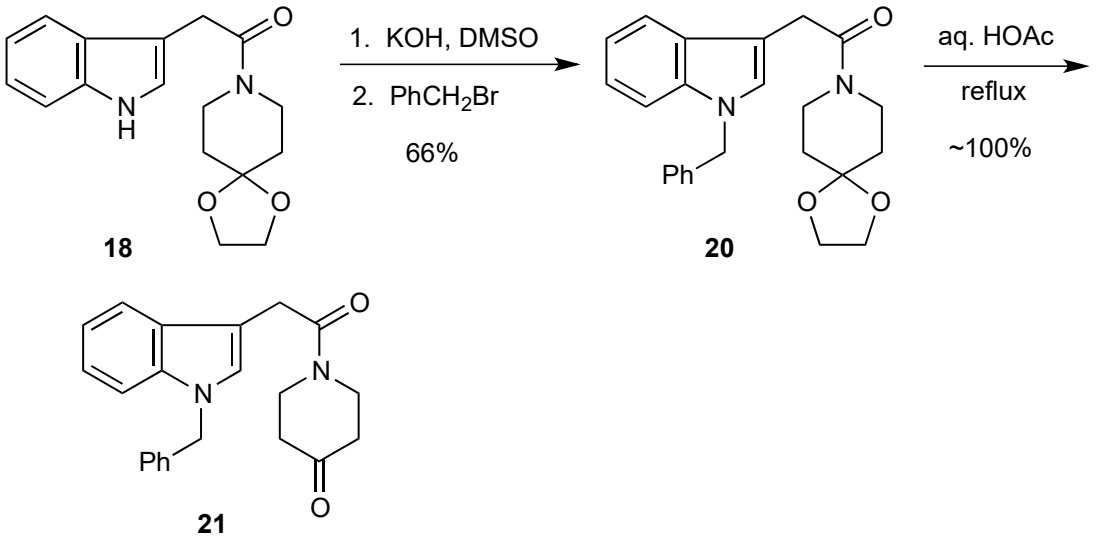
Scheme 5. Synthesis of ketals **15** and **16** and hydrolysis of **16** to cyanoamide **17**.

We then turned our attention to the synthesis of the simple ketoamide **19**,[16] which was accomplished in high yield from indole-3-acetic acid (**14**) and piperidine ketal **4** (Scheme 6).



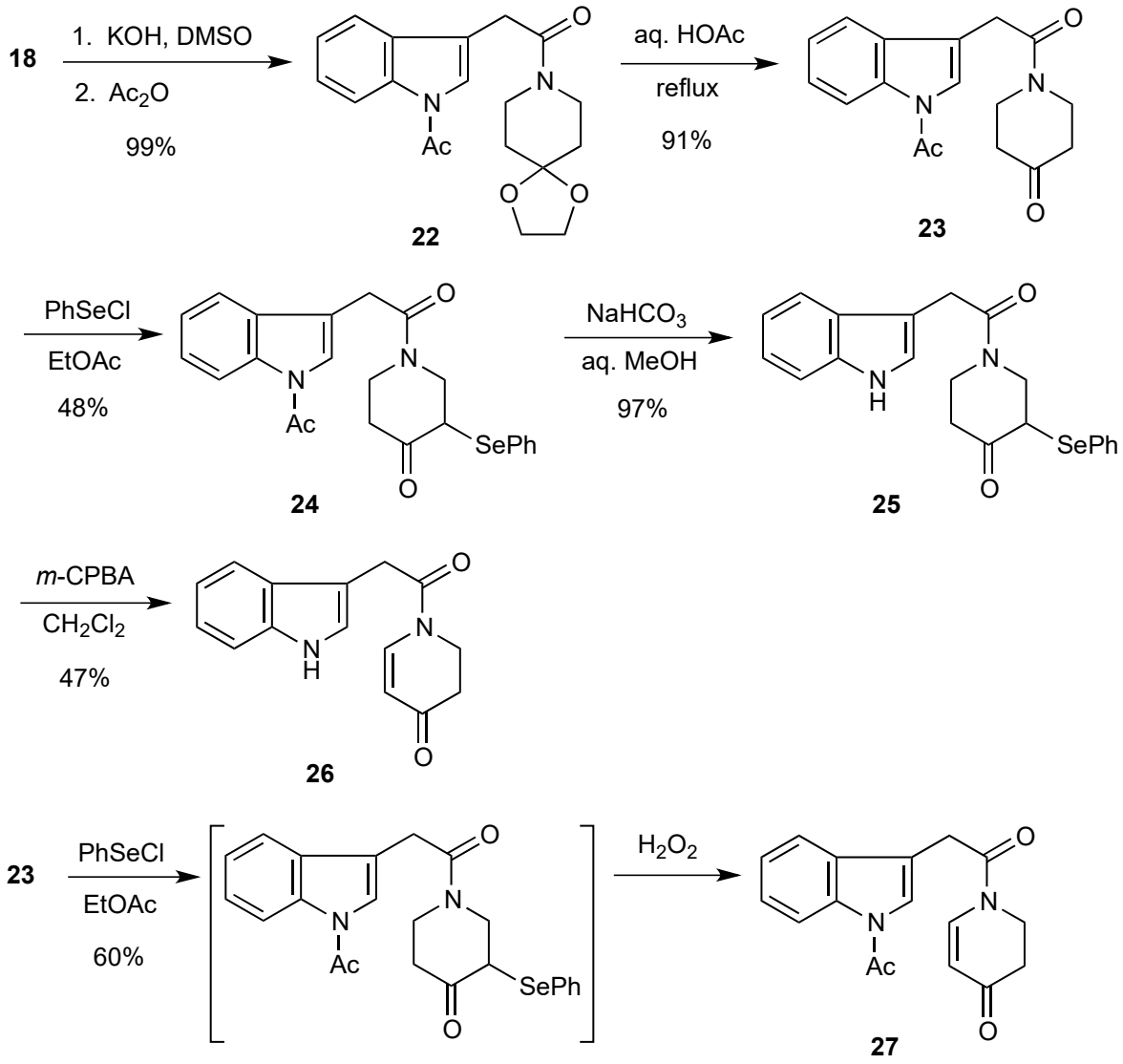
Scheme 6. Synthesis of ketoamide **19**.

However, attempts to introduce the requisite double bond in the piperidone ring of **19** proved difficult (e.g., α-bromination of the ketone or of the derived enamine, and catalytic $PdCl_2$ were unsuccessful), so we switched our attention to the presumed more robust *N*-protected analogues. We prepared the *N*-benzyl analogue **21** (Scheme 7), but subsequent debenzylation with, for example, HBr or catalytic hydrogenation failed, which led us to the *N*-acetyl and *N*-phenylsulfonyl groups (Schemes 8 and 9).



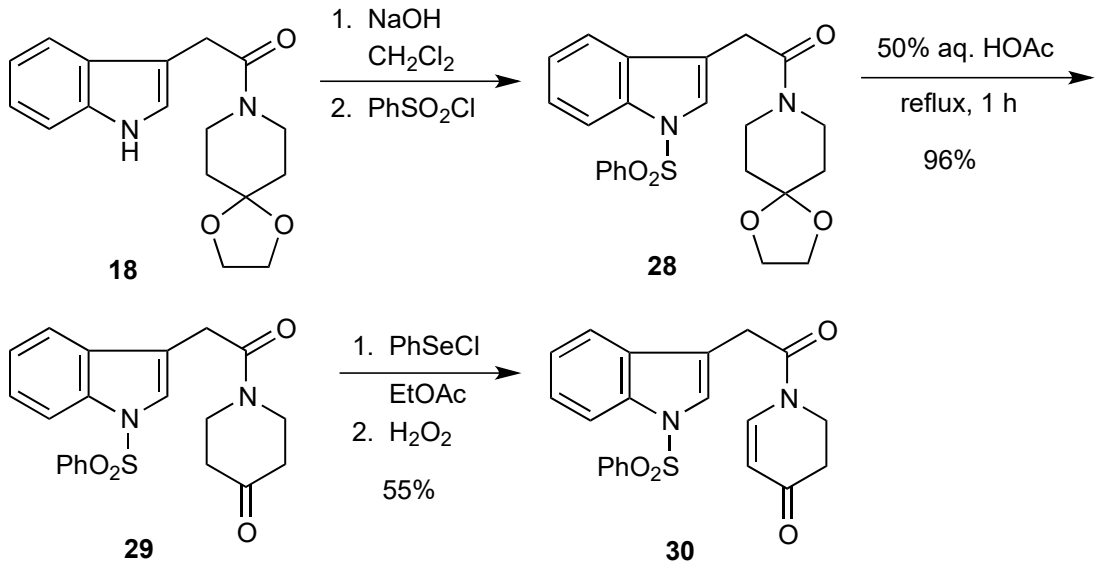
Scheme 7. Synthesis of *N*-benzylindole derivative **21**.

The syntheses of the vinylogous imide **26** and the *N*-acetyl derivative **27** are depicted in Scheme 8. The introduction of the double bond via phenylselenyl chloride proceeded well.



Scheme 8. The synthesis of vinylogous imides **26** and **27**.

Likewise, this method worked well to transform ketal **18** to *N*-phenylsulfonyl vinylogous imide **30** (Scheme 9).



Scheme 9. The synthesis of vinylogous imide **30**.

With vinylogous imides **26**, **27**, and **30** now available to us, we examined cyclization routes to the target **A** (1,3,4,7,12,12*b*-hexahydroindolo[2,3-*a*]quinolizine-2,6-dione). Unfortunately, attempts to cyclize **26**, **27**, and **30** under numerous conditions (10% H_2SO_4; $AlCl_3$; BF_3; TFA; HCO_2H; $TiCl_4$; $SnCl_4$; TMSOTf; $POCl_3$; $NaBH_4$; HCl; P_2S_5; $HgCl_2$; LDA) led to either no reaction, decomposition, or complex mixtures. It is important to note that Wenkert's successful cyclization (Figure 1) involves an amide whereas the present case involves a more labile vinylogous imide. Thus, attempted deacetylation of **27** with 5% aqueous K_2CO_3 resulted in the formation of methyl 3-indolylacetate and 4-oxo-1,2,3,4-tetrahydropyridine from cleavage of both the *N*-acetyl group and the vinylogous imide. This side reaction doomed other reaction conditions. Future work towards the synthesis of **A** will include radical cyclization protocols,[16] as we have prepared several suitable precursors **B** (**26**, **27**, and **30**). We will report this new research in due course.

Conclusion

We have described the synthesis of three novel vinylogous imides, **26**, **27**, and **30**. But, unlike the corresponding vinylogous amides, such as Winterfeldt's compound (Figure 1), these vinylogous imides are prone to undergo amide-bond cleavage to afford indole-3-acetic acid and the corresponding pyridine.

Experimental Section

General. Analytical thin layer chromatography (TLC) was done on silica gel 60 F-254 precoated sheets (EM reagents), layer thickness 0.2 mm, with visualization by using 254 nm UV light and/or with ceric ammonium sulphate (CAS) in 5% sulfuric acid (H_2SO_4), 2,4-dinitrophenylhydrazine, anisaldehyde-sulfuric acid, fluorescein-bromine, or van Urk's reagent. All compounds were uniform by TLC (one spot) unless otherwise indicated. The column chromatography was performed by using the flash chromatography technique on silica gel 60 (VWR) 230-400 mesh. Radial chromatography employed a Harrison Chromatotron. Melting points were determined in open glass capillaries using a Büchi 510 melting point apparatus. All melting points and boiling points are uncorrected. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Varian

EM360A (60 MHz) spectrometer or on a Varian XL-300 (300 MHz) spectrometer using either $CDCl_3$, DMSO-d_6, or acetone-d_6 as solvents as indicated. Chemical shifts are reported in δ (parts per million) downfield from tetramethylsilane (δ 0.00) as an internal standard. Data for proton NMR will be presented as follows: δ (multiplicity, number of protons, coupling constants). All coupling constants are reported in Hertz. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded at 75.4 MHz with proton decoupling on a Varian XL-300 (300 MHz) spectrometer in $CDCl_3$: 77.0; DMSO-d_6: 39.5; or acetone-d_6: 29.8, as indicated. Chemical shifts are reported in δ (parts per million) downfield from tetramethylsilane. Infrared (IR) spectra were obtained on a Perkin-Elmer 599 spectrophotometer as a neat film, a KBr pellet (2%), or in a $CHCl_3$ solution as indicated, were calibrated with the 1601 cm^{-1} absorption of polystyrene and are reported in wavenumbers. Mass spectra (MS) were obtained on a Finnigan 4023 GC/EI-CI mass spectrometer using electron impact at 70 eV. High resolution mass spectra (HRMS) were obtained from Rockefeller University using electron impact or chemical ionization (CI) with methane (CH_4) as the carrier gas. Ultraviolet (UV) spectra were recorded on a Hewlett Packard 84.51A diode array spectrophotometer using 95% EtOH as the solvent. Elemental analyses were obtained by Atlantic Microlab, Inc. DMSO was dried by stirring over CaH_2 overnight and then distilling prior to use. Ethyl acetate was dried by stirring over K_2CO_3 overnight. Methylene chloride was distilled from P_4O_{10} and stored over 3 Å sieves. Tetrahydrofuran was distilled from Na/benzophenone. Removal of solvent from samples was accomplished on a rotary evaporator at aspirator pressure (15-20 Torr). All chemicals were commercially available except those whose synthesis is described or referenced.

8-Methyl-1,4-dioxa-8-azaspiro[4.5]decane (2). 1-Methyl-4-piperidone (**1**) (32.0 g, 0.283 mol) was dissolved in cold (0 °C) anhydrous Et_2O (600 mL) in a 1 L three-neck round bottom flask. HCl gas was bubbled through a $CaCl_2$ drying tube into a trap then through a gas dispersion tube into the flask until the Et_2O was saturated. The outlet for the gas led into an empty trap then into a solution of aqueous NaOH. After saturation, the Et_2O was removed by decantation. The ice bath was removed and replaced with a heating mantle, and benzene (spectrometric grade, stored over 3 Å sieves, 350 mL) was added to the white solid salt followed by ethylene glycol (47 mL, 0.85 mol) and *p*-TsOH (0.6 g, 3 mmol). The three-neck flask was fitted with a reflux condenser and a Dean-Stark trap. The solution was heated to reflux for 18 h. The clear benzene layer was separated from the orange lower layer which was then basified with an aqueous KOH solution until it was pH 12. The aqueous layer was extracted with CH_2Cl_2; the organic layers were combined, dried (K_2CO_3), and concentrated in vacuo to give an amber oil. The amber oil was distilled under reduced pressure to give ketal **2** (36.0 g, 81%) as a colorless liquid; bp 45–47 °C, 0.23 Torr; IR (neat) 2910, 2795, 1470, 1360, 1310, 1240, 1160, 1090, 1040, 915 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.90 (s, 4H), 2.90 (t, 4H, J = 3 Hz), 2.26 (s, 3H), 1.69 (t, 4H, J = 3 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 106.2, 63.6, 53.0, 45.4, 34.5.

8-Methoxycarbonyl-1,4-dioxa-8-azaspiro[4.5]decane (3).[11] Methyl chloroformate (28.36 g, 0.30 mol) was added dropwise to a refluxing magnetically stirred solution of **2** (15.62 g, 0.099 mol) and $NaHCO_3$ (21.5 g, 0.26 mol) in benzene (150 mL). The mixture was heated to reflux for 18 h, then cooled and filtered. The benzene filtrate was washed with saturated aqueous $NaHCO_3$ solution and brine, then concentrated in vacuo to give a cloudy yellow liquid which was distilled under reduced pressure to give **3** (7.79 g, 39%) as a colorless liquid; bp 55–60 °C, 0.35 Torr; IR (neat) 2950, 2900, 1760, 1475, 1450, 1365, 1300, 1240, 1160, 1100 cm^{-1}. This compound was first reported in a 2007 patent but without experimental details.[11]

1,4-Dioxa-8-azaspiro[4.5]decane (4). A solution of ketal **3** (6.88 g, 0.034 mol), KOH (9.50 g, 0.17 mol) and 95% EtOH (35 mL) was heated to reflux for 4 h, then cooled and filtered. The resulting solid was dissolved in H_2O and combined with the organic filtrate. The layers were separated and the organic layer was extracted with benzene. The organic layers were combined, dried over $MgSO_4$, concentrated in vacuo, then distilled under

reduced pressure to give **4** (4.32 g, 89%) as a colorless liquid; bp 106–108 °C/15–25 Torr (lit.[12] bp 108–110 °C/26 Torr); IR (neat) 3300, 2950, 2880, 2830, 1470, 1440, 1420, 1360, 1330, 1320 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.95 (s, 4H), 2.95 (s, 1H), 2.60 (t, 4H, J = 5.8 Hz), 1.73 (t, 4H, J = 5.8 Hz).

A mixture of *N*-ethoxycarbonyl-4-piperidone ethylene ketal (**5**) (4.00 g, 0.018 mol), KOH (5.23 g; 0.093 mol), and EtOH (25 mL) was heated to reflux for 4 h under N_2. The mixture was diluted with H_2O (15 mL), extracted with benzene, and dried ($MgSO_4$). The benzene phase was concentrated in vacuo and the product was vacuum distilled at 95-95 °C/20 Torr affording **4** (1.78 g, 73%) identical to that prepared from **3**.

8-Ethoxycarbonyl-1,4-dioxa-8-azaspiro[4.5]decane (5).[12,13] A solution of 8-methyl-1,4-dioxa-8-azaspiro[4.5]decane (**2**) (21.49 g, 0.137 mol) in dry benzene (150 mL) was heated to reflux under N_2. To the refluxing solution was added dropwise over 1 h ethyl chloroformate (30 mL, 34.0 g, 0.31 mol). Vigorous gas evolution (CH_3Cl) occurred during the addition. After the addition was complete, the solution was heated to reflux for an additional 4 h. The heat was removed and the solution was stirred at room temperature for 12 h and then filtered. The precipitate (3.09 g) is presumed to be the hydrochloride salt of **2**. The filtrate was washed successively with 2 N HCl, saturated aqueous $NaHCO_3$, and brine. It was then dried (Na_2SO_4) and concentrated to give 25.13 g of a cloudy liquid which was distilled at 92–110 °C (0.13 Torr) (lit.[13] bp 98–102 °C/0.5 Torr) to give **5** (19.76 g, 67%) as a colorless liquid; IR (neat film) 2941, 1695, 1420, 1224 and 1110 cm^{-1}; NMR ($CDCl_3$) δ 4.3 (m, 2H), 4.1 (s, 4H), 3.1 (m, 4H), 1.7 (m, 4H), and 1.3 (m, 3H) ppm.

8-Chloro-1,4-dioxa-8-azaspiro[4.5]decane (6). To a solution of ketal **4** (4.00 g, 28.0 mmol) in CH_2Cl_2 (40 mL) kept in dimmed light, at 0–5 °C was added dropwise a solution of *tert*-butyl hypochlorite[14] (3.04 g, 28.0 mmol) in CH_2Cl_2 (10 mL). The drop rate was adjusted to keep the temperature of the solution below 5 °C. After the addition was complete, the solution was stirred at 2 °C for 1 h. The lights were turned back on and the reaction mixture was then washed with H_2O. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with H_2O, dried (K_2CO_3), and concentrated to give **6** (4.83 g, 98%) as a pale yellow oil which was used in subsequent steps with no further purification; IR (neat film) 2980, 1210, 1140, 1110 and 1030 cm^{-1}.

Another preparation afforded **6** along with 1,2-dehydro **7**. A solution of **4** (2.68 g, 0.019 mol) in anhydrous THF (125 mL) at room temperature (20 °C) was treated in the dark with *t*-BuOCl (2.19 g, 0.020 mol). After 24 h, a white solid was filtered from the solution, washed with THF, and dried to give the HCl salt (0.47 g, 14%) of 1,2-dehydro-4-piperidone ethylene ketal (**7**); IR (nujol) 2780–2500 (broad H bonded salt), 1600 (C=N), 1126, 1028 and 1109 (ketal) cm^{-1}; UV max (95% EtOH) 205 nm (log ε 0.14), 270 nm (log ε 0.07); MS (70 eV) m/e (rel intensity) 100 (27), 86 (100). *Anal.* HRMS *m/z* Calcd for $C_7H_{11}NO_2$: 141.0790. Found: 141.0791. The filtrate was concentrated in vacuo and yielded **6** (2.78 g, 83%) as a pale green liquid; IR (neat) 2980 and 2870 (C-H), and 1100 (ketal) cm^{-1}; NMR ($CDCl_3$) δ 4.0 (s, 4H), 3.2–3.4 (broad t, 4H), 1.7–2.0 (broad t, 4H).

7-Cyano-1,4-dioxa-8-azaspiro[4.5]decane (8). To a solution of chloramine **6** (4.83 g, 27.2 mmol) in anhydrous Et_2O (30 mL) was added freshly prepared NaOMe solution (20 mL) (prepared by adding Na (0.78 g, 34 mg-atoms) to dry MeOH (20 mL)). The mixture was heated to reflux for 3 h until a drop of the mixture on damp acidified (with dilute HOAc) starch-iodide paper produced very little purple color. To the mixture was added dry CH_3CN (120 mL). The mixture was then cooled to 5 °C with an ice bath and acetone cyanohydrin (2.55 g, 30.0 mmol) was added in one portion. To the mixture was added KCN (0.044 g, 0.68 mmol). The mixture was stirred for 12 h (the ice was allowed to melt). The mixture was concentrated in vacuo and the residue was partitioned between saturated aqueous $NaHCO_3$ and CH_2Cl_2. The layers were separated and the aqueous layer was extracted with fresh CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to yield a yellow oil (3.35 g) which was dissolved in Et_2O and chromatographed (neutral Al_2O_3) using Et_2O/hexane (1:1) as eluent. This yielded a colorless oil **8** (2.35 g, 51%); IR (neat) 3350, 2980, 2242,

2222, 1360, 1135, and 1085 cm^{-1}; NMR ($CDCl_3$) δ 3.98 (m, 5H), 2.99 (m, 2H), 2.31 (br s, 1H); 1.9 (m, 2H), and 1.67 (t, 2H) ppm.

1-Methyl-4,4-dimethoxypiperidine (9). To a solution of *p*-TsOH (11.8 g, 62.0 mmol) in dry MeOH (140 mL) at 2 °C was added 1-methyl-4-piperidone (**1**) (5.00 g, 44.0 mmol) and trimethyl orthoformate (69 mL, 66.9 g, 631 mmol). The yellow solution was stirred for 20 h with the temperature warming to room temperature as the ice melted. Solid $NaHCO_3$ was added to the solution followed by H_2O (250 mL). Gas evolution was observed. The mixture was stirred for 15 min then diluted with more H_2O and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and concentrated to yield an oil, which was distilled (short path) to yield **9** (2.33 g, 33%) as a colorless oil, bp 70 °C/aspirator vacuum; IR (neat film) 2960, 2844, 2815, 1360, 1302, 1265, 1155, 1112, 1090, 1052, and 898 cm^{-1}. *Anal.* HRMS *m/z* Calcd for $C_8H_{17}NO_2$: 159.1259. Found: 159.1251. This compound was not characterized further because it decomposed upon attempted demethylation with ethyl chloroformate.

4,4-Dimethoxypiperidine (11). A mixture of 4-piperidone hydrate hydrochloride (**10**) (10.0 g, 59.0 mmol), *p*-TsOH (0.33 g, 1.70 mmol), MeOH (30 mL) and benzene (150 mL) was heated to reflux for 22 h using a Dean-Stark trap to remove H_2O. At this point the Dean-Stark trap was replaced with a Soxhlet filled with activated 3 Å molecular sieves (Linde). After an additional 30 h of reflux, the mixture was allowed to cool to room temperature and the supernatant liquid was decanted and saved. The solid residue was dissolved in 50% aqueous K_2CO_3 solution (40 mL) and extracted with $CHCl_3$ (120 mL). The organic layer was dried and concentrated to give a yellow oil (7.58 g) which was distilled to yield **11** (3.37 g, 39%) as a colorless oil, bp 72–74 °C/aspirator vacuum (lit.[15] bp 75 °C/10 Torr). The previously decanted liquid was rotovaped to dryness and the residue rinsed with benzene then dissolved in 50% aqueous K_2CO_3 (30 mL). The solution was extracted with $CHCl_3$ (60 mL) and the organic layer was dried (K_2CO_3) and concentrated to give a yellow oil (6.04 g). Distillation afforded additional **11** (2.46 g, 29%) for a combined yield of 68%; IR (neat film) 3340, 2965, 2842, 1355, 1260, 1145, 1135, 1110 and 1050 cm^{-1}; NMR ($CDCl_3$) δ 3.15 (s, 6H), 2.81 (t, 4H), 1.68 (t, 4H), and 1.36 (s, 1H) ppm. *Anal.* HRMS *m/z* Calcd for $C_7H_{15}NO_2$: 145.1103. Found: 145.1110.

1-Chloro-4,4-dimethoxypiperidine (12). To a stirred solution of **11** (5.00 g, 34.4 mmol) in CH_2Cl_2 (50 mL) at 2 °C was added dropwise a solution of *t*-BuOCl (3.74 g, 34.4 mmol) in CH_2Cl_2 (15 mL). The drop rate was adjusted to keep the reaction temperature below 5 °C. The solution was stirred at 2 °C for 1 h after the addition was complete. The mixture was then washed with H_2O. The organic layer was separated and the aqueous layer was reextracted with additional CH_2Cl_2. The combined organic layers were washed with H_2O, dried (K_2CO_3) and concentrated in vacuo to give crude **12** (6.61 g) as a yellow oil which was used in the next step without further purification.

2-Cyano-4,4-dimethoxypiperidine (13). To a solution of chloramine **12** (6.61 g, 34.4 mmol) in anhydrous Et_2O (40 mL) was added freshly prepared NaOMe solution (20 mL) (prepared by adding Na (1.00 g, 43.5 mg-atoms) to dry MeOH (20 mL). The mixture was heated to reflux for 5 h until a drop of the mixture on damp acidified (with dilute HOAc) starch-iodide paper produced very little purple color. To the mixture was added dry CH_3CN (150 mL). The mixture was cooled to 5 °C with an ice bath and acetone cyanohydrin (3.23 g, 38.0 mmol) was added in one portion. To the mixture was then added a spatula tip full of KCN. The mixture was stirred for 15 h (the ice was allowed to melt). The mixture was concentrated in vacuo and the residue partitioned between saturated aqueous $NaHCO_3$ and CH_2Cl_2. The layers were separated and the aqueous layer was extracted with fresh CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to yield crude product (4.49 g) as a brown viscous oil. The oil was dissolved in Et_2O and chromatographed (neutral Al_2O_3) using Et_2O/hexane (1:1) as eluent. After a forerun, **13** (1.70 g, 29%) as a colorless oil was collected; IR

(neat film) 3350, 2980, 2855, 1467, 1360, 1130, 1092, and 1045 cm^{-1}. *Anal.* HRMS *m/z* Calcd for $C_8H_{13}N_2O_2$: 169.0977. Found: 169.0976.

1-[2-(3-Indolyl)-1-oxoethyl]-2-cyano-4-piperidone ethylene ketal (15). To a mixture of indole-3-acetic acid (**14**) (0.507 g, 2.89 mmol), **8** (0.499 g, 2.97 mmol) and dry benzene (25 mL) was added EEDQ (0.795 g, 3.21 mmol). The mixture was stirred for 23 h. Filtration afforded **15** (0.556 g, 59%) as a white solid, mp 158–161 °C. Several recrystallizations from CH_2Cl_2/pentane gave the analytical sample: mp 160–161 °C; IR (KBr) 3380, 3280, 2950, 2900, 2870, 1690, 1460, 1420, 1340, 1240 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.35 (bs, 1H), 7.70–7.00 (m, 5H), 5.96 (m, 1H), 4.00 (s, 4H), 3.93 (m, 4H), 1.93 (d, 2H, J = 6.0 Hz), 1.73–1.35 (m, 2H). *Anal.* HRMS *m/z* Calcd for $C_{18}H_{19}N_3O_3$: 325.1417. Found: 325.1426. *Anal.* Calcd for $C_{18}H_{19}N_3O_3$: C, 66.40; H, 5.89; N, 12.91. Found: C, 66.26; H, 5.89; N, 12.90.

1-[2-(3-Indolyl)-1-oxoethyl]-2-cyano-4,4-dimethoxypiperidine (16). To a stirred mixture of cyanoamine (**13**) (0.76 g, 4.47 mmol) and indole-3-acetic acid (**14**) (0.78 g, 4.47 mmol) in dry benzene (40 mL) was added in one portion *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) (1.21 g, 4.89 mmol). The mixture was stirred at room temperature for 15 h. The precipitate was filtered to yield **16** (0.38 g, 26%) as a tan solid mp 194–196.5 °C which was sufficiently pure to use without purification. Additional **16** (0.75 g, 51%) was obtained by cooling the filtrate at 2 °C overnight and filtering and collecting the precipitate; IR ($CHCl_3$) 3510, 1658, 1458, 1415, 1130, and 1088 cm^{-1}; UV (95% EtOH) λ^{max} 227, 274, 281, and 290 nm. *Anal.* HRMS *m/z* Calcd for $C_{18}H_{21}N_3O_3$: 327.1583. Found: 327.1604.

1-[2-(3-Indolyl)-1-oxoethyl]-2-cyano-4-piperidone (17). A mixture of cyano ketal **16** (0.150 g, 0.458 mmol) and 50% aqueous HOAc (15 mL) was heated with stirring at 75–80 °C for 1 h. The solid dissolved at this temperature. The solution was cooled with an ice bath and basified with 7 N NH_4OH (15 mL). The resulting mixture was extracted twice with CH_2Cl_2. The combined organic fractions were dried (K_2CO_3) and concentrated to yield **17** (0.121 g, 94%) as a light tan foam which was used without purification; IR ($CHCl_3$) 3505, 1740, 1665, 1415, and 1262 cm^{-1}; NMR ($CDCl_3$) δ 8.45 (broad s, 1H), 6.9–7.6 (m, 5H), 5.9 (broad s, 1H), 3.9 (s, 2H), 3.7 (broad s, 2H), and 2.0–2.6 (m, 4H) ppm. *Anal.* HRMS *m/z* Calcd for $C_{16}H_{15}N_3O_2$: 281.1168. Found: 281.1164.

1-[2-(3-Indolyl)-1-oxoethyl]-4-piperidone ethylene ketal (18). A solution of indole-3-acetic acid (**14**) (5.54 g, 0.032 mol) in anhydrous CH_2Cl_2 (100 mL) was mixed at room temperature with diisopropylcarbodiimide (3.72 g, 0.031 mol) under N_2. After ca. 15 min a flocculent ppt appeared and 4-piperidone ethylene ketal (**4**) (4.54 g, 0.032 mol) was added. The mixture was stirred for 12 h and filtered. The filtrate was washed with H_2O, dried (K_2CO_3), and concentrated in vacuo to 8.46 g of a white foam. Trituration of the foam with Et_2O gave **18** (6.64 g, 71%) as off-white needles, mp 144–146 °C; IR (nujol) 3270 (N-H), 1639 (C=O), 1100 (ketal) cm^{-1}; UV max (95% EtOH) 228 nm (log ε 3.88), 275 nm (log ε 3.72), 282 nm (log ε 3.75), 291 nm (log ε 3.69); NMR ($CDCl_3$) δ 8.7 (broad s 1H), 6.9–7.8 (m, 5H), 3.3–4.1 (m, 10H), 1.3–1.8 (m, 4H); MS (70 eV) m/e (rel intensity) 300, 170, 157, 142, 130. The analytical sample was recrystallized five times from THF/Et_2O to give pale colorless cubes, mp 163.5–164 °C. *Anal.* Calcd for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71; N, 9.33. Found: C, 67.97; H, 6.80; N, 9.29.

1-[2-(3-Indolyl)-1-oxoethyl]-4-piperidone (19). A mixture of 1-[2-(3-indolyl)-1-oxoethyl]-4-piperidone ethylene ketal (**18**) (2.11 g, 7.01 mmol) and 50% aqueous HOAc (50 mL) was heated to reflux for 1 h. The solids dissolved upon heating. The solution was cooled to 2 °C and was basified by the slow addition of 7 N NH_4OH (35 mL). The resultant mixture was extracted with CH_2Cl_2 (2x) and the combined organic extracts were dried (K_2CO_3) and concentrated to give crude **19** (2.35 g, 100%) as a tan solid which could be recrystallized from THF but was sufficiently pure to use in further reactions. The recrystallized material had mp 175–177 °C; IR (neat) 3300 (broad N-H), 1720 (C=O, ketone), 1639 (C=O amide) cm^{-1}; UV max (95% EtOH) 228 nm (log ε

3.89), 273 nm (log ε 3.68), 280 nm (log ε 3.71), 290 nm (log ε 3.67); NMR ($CDCl_3$) δ 9.0 (broad s, N-H), 6.8–7.7 (m, 5H), 3.4–4.0 (m, 6H), 1.8–2.5 (m, 4H); MS (70 eV) m/e (rel intensity) 256, 130 (100). *Anal.* HRMS *m/z* Calcd for $C_{15}H_{16}N_2O_2$: 256.1212. Found: 256.1207; *Anal.* Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found C, 70.31; H, 6.30; N, 10.91. This compound was described in the *Supporting Information* of reference 16 as an unrecrystallized yellow solid having melting point of 45–46 °C, although the reported elemental analysis is correct.

1-(2-(3-(1-Benzyl)-indolyl)-1-oxoethyl)-4-piperidone ethylene ketal (20). To dry DMSO (35 mL) at room temperature under nitrogen was added powdered KOH (0.97 g, 0.017 mol). The mixture was mechanically stirred for 5 min and to it was added 1-(2-(3-indolyl)-1-oxoethyl)-4-piperidone ketal (**18**) (2.50 g, 0.0083 mol) in one portion. The mixture was stirred for an additional 5 min and then $PhCH_2Br$ (2.02 mL, 0.017 mol) was added in one portion. The resulting viscous solution was stirred for an additional 30 min at room temperature. The reaction was worked up by pouring onto ice-H_2O, extracting with Et_2O (3x), washing the Et_2O extract with H_2O (5x) and then brine (1x), drying (Na_2SO_4) and concentrating in vacuo to afford crude **20** as a white solid. Recrystallization from 95% EtOH gave **20** (2.0 g, 66%) as white crystals; mp 119–120 °C; IR (KBr) 1620 (amide C=O), 1100 cm^{-1} (ketal), no N-H absorption; NMR ($CDCl_3$) δ 7.0–7.7 (m, 10H), 5.2 (s, 2H), 3.9 (s, 4H), 3.8 (s, 2H), 3.4–3.7 (m, 4H), and 1.1–1.85 ppm (m, 4H). *Anal.* Calcd for $C_{24}H_{26}N_2O_3$: C, 73.82; H, 6.71; N, 7.18. Found: C, 73.39; H, 6.73; N, 7.32.

1-(2-(3-(1-Benzyl)-indolyl)-1-oxoethyl)-4-piperidone (21). To 1-(2-(3-*N*-benzylindolyl)-1-oxoethyl)-4-piperidone ketal (**20**) (1.30 g, 0.0033 mol) was added 50% aqueous HOAc (100 mL). The reaction mixture was heated to reflux under N_2 for 1 h. The reaction mixture was allowed to cool, then was neutralized with conc. NH_4OH and extracted with CH_2Cl_2. The organic phase was dried (K_2CO_3) and concentrated in vacuo to afford **21** (1.19 g, 100%) as a yellow oil. Thin layer chromatography (EtOAc:NEt_3, 95:5) revealed a single spot with a lower R_f value than the starting material (R_f **20** = 0.50; R_f **21** = 0.38); IR ($CHCl_3$) 1715 (C=O), 1640 cm^{-1} (amide C=O), no N-H or ketal absorption; NMR ($CDCl_3$) δ 6.7–7.7 (m, 10H), 5.15 (s, 2H), 3.82 (s, 2H), 3.4–3.75 (m, 4H) and 1.7–2.4 ppm (m, 4H). *Anal.* HRMS *m/z* Calcd for M^+ m/e 346.1681; found 346.1697.

1-(2-(3-(1-Acetyl)-indolyl)-1-oxoethyl)-4-piperidone ethylene ketal (22). To dry DMSO (20 mL) at room temperature under nitrogen was added powdered KOH (0.28 g, 0.005 mol). The mixture was mechanically stirred for 5 min and to it was added 1-(2-(3-indolyl)-1-oxoethyl)-4-piperidone ketal (**18**) (0.75 g, 0.0025 mol) in one portion. The mixture was stirred an additional 5 min and then Ac_2O (0.50 mL, 0.005 mol) was added in one portion. The resulting viscous solution was stirred for an additional 30 min at room temperature. The reaction mixture was poured into ice-water, and the whole was extracted with Et_2O (3x). The extract was washed sequentially with H_2O (5x), and brine (1x), dried (Na_2SO_4) and concentrated in vacuo to afford **22** as an off white solid (0.83 g, 97%). Recrystallization from 95% EtOH gave, in three crops, compound **22** (0.56 g, 66%) as white needles; yield: mp 187–188.5 °C; IR (KBr) 3110, 2960, 2930, 2890, 1715, 1650, 1455, 1410, 1390, 1380 cm^{-1}; IR ($CHCl_3$) 1700 (indole amide C=O), 1640 (pip. amide C=O), 1100 cm^{-1} (ketal), no N-H absorption; UV (95% EtOH) λ_{max} = 218, 238, 261, 290 and 300 nm; ^1H NMR ($CDCl_3$) δ 8.44–7.21 (m, 5H), 3.73 (s, 4H), 3.76 (s, 2H), 3.73 (t, 2H, J = 5.9 Hz), 3.56 (t, 2H), J = 5.9 Hz), 2.55 (s, 3H), 1.66 (t, 2H, J = 5.9 Hz), 1.58 (t, 2H, J = 5.9 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 168.3, 168.3, 135.3, 129.9, 125.3, 123.5, 123.1, 118.6, 116.3, 106.5, 64.3, 41.1, 40.0, 35.4, 34.6, 30.3, 23.9. *Anal.* Calcd for $C_{19}H_{22}N_2O_4$: C, 66.64; H, 6.43; N, 8.18. Found: C, 66.22; H, 6.49; N, 8.02.

1-(2-(3-(1-Acetyl)-indolyl)-1-oxoethyl)-4-piperidone (23). A solution of ketal **22** (13.5 g, 39.2 mmol) in 50% aqueous HOAc (600 mL) was heated to reflux under N_2 for 1.5 h, then cooled in ice, and neutralized with concentrated NH_4OH (300 mL). The mixture was extracted with CH_2Cl_2, and the extract was washed with H_2O and brine, and dried (Na_2SO_4). Concentration of the CH_2Cl_2 extract afforded crude **23** (10.18 g, 86%) as a

yellow-white solid. Recrystallization from CH_2Cl_2/Et_2O gave tiny colorless needles, mp 151–152 °C; IR (KBr) 1700 (C=O), 1640 cm^{-1} (amide C=O), no N–H or ketal absorption; UV (95% EtOH) λ_{max} = 212, 128, 161, 290 and 300 nm; NMR ($CDCl_3$) δ 6.8–7.7 (m, 5H), 3.3–4.0 (m, 6H), 2.6 (s, 3H), and 2.0–2.4 ppm (m, 4H). *Anal.* Calcd for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.39; H, 6.16; N, 9.32. *Anal.* HRMS *m/z* Calcd for $C_{17}H_{18}N_2O_3$: 298.13174; Found: 298.13169.

1-(2-(3-(1-Acetyl)-indolyl)-1-oxoethyl)-3-phenylselenenyl-4-piperidone (24). Phenylselenyl chloride (0.66 g, 3.4 mmol) was added to a solution of 1-(2-(3-*N*-acetylindolyl)-1-oxoethyl)-4-piperidone (**23**) (1.00 g, 3.35 mmol) in dry EtOAc (5 mL) under N_2, and the dark red solution was stirred overnight. Flash chromatography (EtOAc/hexane, 8:2) gave **24** (0.61 g, 48%), which crystallized from hexane/EtOAc as a pale yellow solid; mp 108–110 °C; IR ($CHCl_3$) 3020, 2980, 1720, 1660, 1490, 1460, 1440 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.3–8.5 (m, 1H), 7.1–7.7 (m, 9H), 3.6–4.0 (m, 6H), 2.6–3.5 (m, 3H), 2.5 (s, 3H). Several recrystallizations from EtOAc/hexane gave the analytical sample as a white solid. *Anal.* Calcd for $C_{22}H_{22}N_2O_3Se$: C, 60.92; H, 4.89; N, 6.18. Found C, 60.93; H, 4.92; N, 6.13.

1-(2-(3-Indolyl)-1-oxoethyl)-3-phenylselenenyl-4-piperidone (25). Piperidone **24** (0.04 g, 0.08 mmol) was dissolved in MeOH (40 mL) and H_2O (10 mL) with some heating. After cooling to room temperature, a solution of 10% $NaHCO_3$ (10 mL) was added. The mixture was stirred for 1.5 h and then extracted with CH_2Cl_2 (5 x 50 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated in vacuo to give **25** (0.03 g, 97%) as a yellow solid: mp 57–58 °C; IR ($CHCl_3$) 3500, 3010, 2940, 1720, 1650, 1490, 1470, 1450 cm^{-1}; UV (95% EtOH) λ_{max} = 291, 282, 275, 220 nm; ^1H NMR ($CDCl_3$) δ 8.3–8.7 (m, 1H), 7.0–7.8 (m, 10H), 3.6–4.1 (m, 6H), 2.5–3.3 (m, 3H). This was used directly as described in the next step.

1-(2-(3-Indolyl)-1-oxoethyl)-2,3-dihydro-4-pyridone (26). Phenyl selenenyl ketone **25** (0.035 g, 0.086 mmol) was dissolved in CH_2Cl_2 (5 mL). *m*-CPBA (85%, 0.015 g, 0.072 mmol) was added in small portions, while keeping the temperature of the solution under 30 °C. After 20 min, the reaction mixture was poured into a solution of aqueous 10% $NaHCO_3$ (2 mL) and CH_2Cl_2 (5 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated in vacuo. Radial chromatography (EtOAc/hexane; 8:2) gave **26** (0.0086 g, 47%) as a yellow oil; IR ($CHCl_3$) 3500, 3010, 2980, 1665, 1600, 1455, 1410 cm^{-1}; UV (95% EtOH) λ_{max} = 220, 285, 290 nm; MS *m/e*, mass/intensity: M^+ 254 (12%), M^{+1} 255, 131, 130, 129, 128, 103, 102, 96, 77 ^1H NMR ($CDCl_3$) δ 8.4–8.8 (m, 1H), 7.9 (d, 1H, J = 8 Hz), 7.0–7.7 (m, 5H), 5.3 (d, 1H, J = 8 Hz), 4.0–4.3 (m, 4H), 2.4–2.7 (m, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 193.5, 170.0, 142.9, 136.2, 126.6, 122.7, 122.6, 120.0, 119.9, 118.4, 111.4, 107.3, 35.7, 31.5, 31.4. *Anal.* HRMS *m/z* Calcd for $C_{15}H_{14}N_2O_2$: 254.1055; Found: 254.1052.

1-(2-(3-*N*-Acetylindolyl)-1-oxoethyl)-2,3-dihydro-4-pyridone (27). To a solution of 1-(2-(3-*N*-acetylindolyl)-1-oxoethyl)-4-piperidone (**23**) (5.61 g, 0.0188 mol) in EtOAc (475 mL) was added all at once PhSeCl (3.85 g, 0.0201 mol). The resulting red solution was stirred under nitrogen at room temperature for 12 h (the solution went from red to orange-yellow). To the reaction mixture was added H_2O (400 mL), THF (400 mL), and then 30% H_2O_2 (6.27 mL, 0.055 mol) was added dropwise while keeping the temperature of the reaction mixture below 35 °C. The reaction mixture was stirred for an additional hour, then washed with H_2O, 10% Na_2CO_3, dried (K_2CO_3) and concentrated in vacuo to afford a yellow solid (4.0 g; 72%). Recrystallization (4x) from CH_2Cl_2/Et_2O gave the analytical sample as tiny colorless crystals, mp 152–154 °C; IR ($CHCl_3$) 1710, 1675 and 1600 cm^{-1}; NMR ($CDCl_3$) δ 8.3–8.5 (m, 1H), 7.8–8.0 (d, 1H), 7.1–7.65 (m, 4H), 5.3–5.5 (d, 1H), 3.7–4.3 (m, 4H), and 2.4–2.8 ppm (m, 5H); MS 296 (M^+) (3.5%), 254 (1.1%), 172 (3.8 %), 157 (3.9%), 130 (100%), and 96 (6%). *Anal.* Calcd for $C_{17}H_{16}N_2O_3$: C, 68.91; H, 5.44; N, 9.45. Found: C, 68.80; H, 5.53; N, 9.41.

1-[2-(3-1-(Phenylsulfonyl)indolyl)-1-oxoethyl]-4-piperidone ethylene ketal (28). Indole **18** (7.65 g, 0.025 mol) was added all at once to a cold (0 °C) suspension of NaOH (3.05 g, 0.076 mol) and Bu_4NHSO_4 (0.31 g, 0.89

mmol) in CH_2Cl_2. After 15 min, a solution of $PhSO_2Cl$ (3.5 mL, 0.025 mol) in CH_2Cl_2 (20 mL) was added dropwise over 40 min. The mixture was allowed to warm to room temperature, stirred for 2 h, and poured over a mixture of ice (100 g) and saturated aqueous NH_4Cl (100 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 75 mL). The organic layers were combined and washed with brine, then dried ($MgSO_4$), and concentrated in vacuo to give **28** (12.8 g) which was used in the next reaction. TLC (EtOAc/hexane, 4:1) showed no starting material; IR ($CHCl_3$) 1640 (amide C=O), 1380, 1280, 1170 and 1120 cm^{-1} (SO_2), no N-H absorption; NMR ($CDCl_3$) δ 6.9–8.1 (m, 10H), 3.3–4.1 (m, 10H), and 1.1–1.8 ppm (m, 4H). This was hydrolyzed directly as described in the next step.

1-[2-(3-1-(Phenylsulfonyl)indolyl)-1-oxoethyl]-4-piperidone (29). A solution of crude piperidone ketal **28** (12.8 g) in 50% HOAc (180 mL) was heated to reflux for 3 h. The solution was cooled and neutralized with a mixture of NH_4OH (100 mL) and ice (100 g). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (5 x 100 mL). The organic layers were combined and washed with brine, then dried ($MgSO_4$), and concentrated in vacuo to give **29** (9.46 g, 96%) from unprotected ketal as a yellow solid. An analytical sample was recrystallized from EtOAc to give **29** as a white solid: mp 165–166 °C; ^{1}H NMR ($CDCl_3$) δ 8.18–7.21 (m, 10H), 3.88 (t, 2H, J = 6.4 Hz), 3.83 (s, 2H), 3.60 (t, 2H, J = 6.4 Hz), 2.40 (t, 2H, J = 6.4 Hz), 2.12 (t, 2H, J = 6.4 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 206.2, 168.5, 138.0, 135.1, 134.0, 130.1, 129.3, 126.6, 125.3, 123.8, 123.5, 119.6, 116.0, 113.7, 44.6, 40.6, 31.2. *Anal.* HRMS *m/z* Calcd for 396.1143; found 396.1141. *Anal.* Calcd for $C_{21}H_{20}N_2O_4S$: C, 63.72; H, 5.08; N, 7.07; S, 8.09. Found: C, 63.43; H, 5.12; N, 6.99; S, 8.00.

1-[2-(1-(Phenylsulfonyl)-3-indolyl)-1-oxoethyl]-2,3-dihydro-4-pyridone (30). A solution of PhSeCl (11.6 g, 8.4 mmol) in EtOAc (50 mL) was added to a solution of piperidone **29** (3.00 g, 7.6 mmol) in EtOAc (300 mL). The solution was stirred at room temperature under Ar for 15 h. Water (100 mL) was added and the layers were separated. Tetrahydrofuran (100 mL) was added to the organic phase which was then cooled to 0 °C. H_2O_2 (30%, 2.15 mL, 19 mmol) was added dropwise while the temperature was kept below 30 °C. The solution was stirred for 1.5 h, washed successively with H_2O, aqueous $NaHCO_3$, and brine. The organic layer was dried ($MgSO_4$) and concentrated in vacuo to give a yellow oil. Flash chromatography (EtOAc/hexane, 4:1) gave vinylogous imide **30** (1.67 g, 55%) as a yellow solid. The analytical sample was recrystallized from CH_2Cl_2/hexane to give **30** as pale yellow needles: mp 134–138 °C; IR ($CHCl_3$) 3020, 2940, 1700, 1680, 1605, 1455, 1420, 1380, 1355, 1310 cm^{-1}; UV (95% EtOH) λ_{max} = 206, 256, 292 nm; ^{1}H NMR ($CDCl_3$) δ 8.49–6.98 (m, 11H), 5.23 (d, 1H, J = 8.0 Hz), 3.96 (s, 2H), 3.93 (t, 2H, J = 7.0 Hz), 2.40 (t, 2H, J = 7.0 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 193.0, 168.2, 142.1, 137.8, 135.0, 134.0, 129.9, 129.3, 126.6, 125.3, 124.4, 124.4, 123.6, 119.4, 114.5, 113.7, 47.3, 35.6, 30.8; MS *m/e* (relative intensity) M^+ 394 (28), M^{+1} 395, M^{+2} 396, 270 (100), 156, 141, 130, 129, 96, 77. *Anal.* HRMS *m/z* Calcd for $C_{21}H_{18}N_2O_4S$: C, 63.95; H, 4.60; N, 7.10; S, 8.13. Found: C, 63.83; H, 4.60; N, 7.08; S, 8.03.

***t*-Butyl hypochlorite.** The procedure of Mintz and Walling[14] was followed. A mixture of glacial HOAc (24.5 mL, 0.43 mol) and *t*-BuOH (37 mL, 0.39 mol) was added to cold (0–10 °C) NaOCl (500 mL, bleach, 5.25%, Sure Fine) in the dark and stirred for 3 min. The layers were separated and the yellow organic layer was washed with 10% aqueous Na_2CO_3, H_2O, dried ($CaCl_2$), and filtered to give 20.3 g (48%) of the hypochlorite as a yellow liquid. It was stored over anhydrous $CaCl_2$ in a freezer in an amber bottle wrapped in foil.

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