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A Novel Method for Suppression of the Abnormal Fischer Indole Synthesis†

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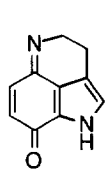
Abstract: A method is described for the use of the Fischer indole synthesis to prepare 7-hydroxyindoles in good yield. The method involves the construction of a 4-aminobenzoxazine and removal of the N-O tether after the indole has been formed. © 1997 Elsevier Science Ltd.

The pyrrolo[2,3,4-*d,e*]quinoline unit **1** is a structural element found in a number of natural products including the discorhabdin alkaloids,[1,2,3,4,5,6] the isobatzellines,[7] and batzellines,[7b,8] wakayin,[9] the makaluvamines,[10,11,12] damirones A and B,[13,14] and terrestrially-derived haematopodin.[14b] In the course of our work towards the synthesis of this unit, we developed a novel solution to the problem of the abnormal Fischer indole synthesis for *ortho*-substituted phenylhydrazones.[15]



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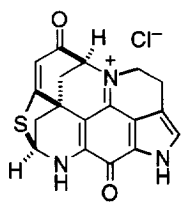

discorhabdin D

Our first attempt to prepare a 4,7-substituted indole began with the synthesis of an appropriately substituted phenylhydrazine. Commercially-available 2-methoxy-5-nitroaniline (**2**) was diazotized and the diazonium salt was reduced with tin(II) chloride to give 2-methoxy-5-nitrophenylhydrazine (**3**) in 60% yield (Scheme 1). Acid-catalyzed addition of hydrazine **3** to 2,3-dihydrofuran (**4**) gave the corresponding hydrazone of 4-hydroxybutanal (**5**) in almost quantitative

† This article was submitted in honor of Professor Samuel Danishefsky, a longtime friend and colleague, and a worthy recipient of the 1996 Tetrahedron Award.

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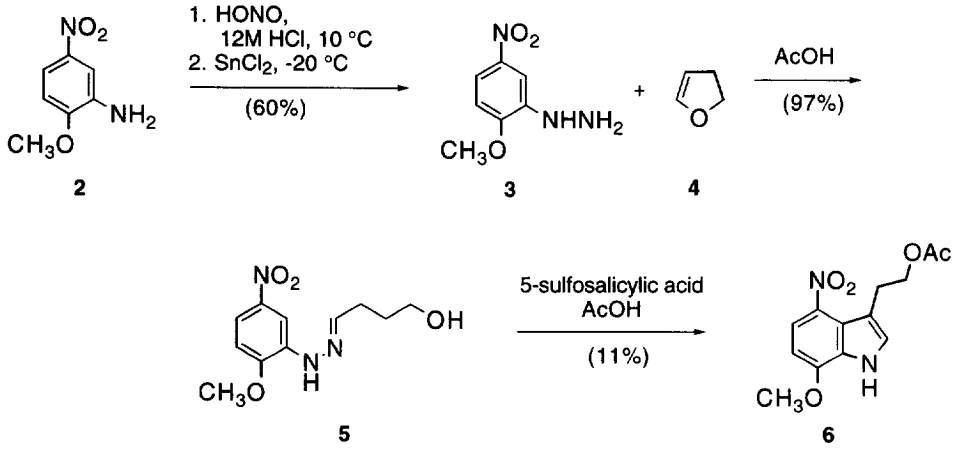
yield, as an approximate 3:1 mixture of geometric isomers about the C=N bond. Although we have no direct information about which ismoer predominates, it is most reasonable to assume that the *E* isomer predominates. Unfortunately, hydrazone **5** proved to be a poor substrate for the Fischer indole synthesis, giving indole **6** in only 11% yield upon treatment with 5-sulfosalicyclic acid in acetic acid solution.[16]

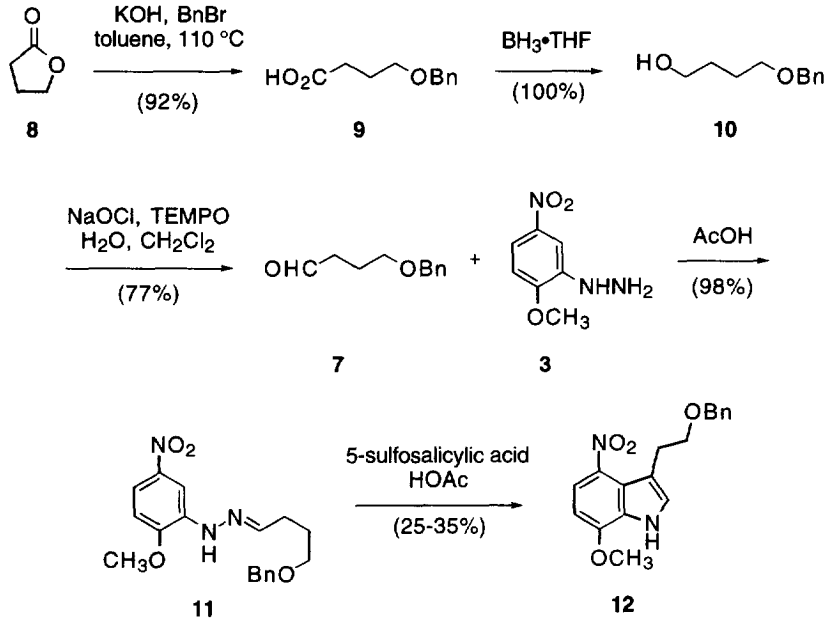
Scheme 1



Since it was possible that the free hydroxy group present in hydrazone **5** might interfere with the Fischer indole synthesis, we sought to prepare a hydrazone bearing an ether instead of an alcohol at the 4-alkyl position. To this end, 4-benzyloxybutanal (**7**) was prepared (Scheme 2). γ-Butyrolactone (**8**) was heated with KOH and benzyl bromide to provide 4-benzyloxybutyric acid (**9**) in 92% yield.[17] Reduction to alcohol **10** proceeded quantitatively with borane.[18] TEMPO oxidation then gave 4-benzyloxybutanal (**7**) in 77% yield.[19] Condensation of the aldehyde with hydrazine **3** afforded hydrazone **11** in nearly quantitative yield. Hydrazone **11** was isolated as an inseparable mixture of *E* and *Z* isomers, in this case in an approximate ratio of 2:1. When hydrazone **11** was dissolved in acetic acid and treated with a slight excess of 5-sulfosalicylic acid, indole **12** was isolated in about 30% yield Separation of the product from the crude reaction mixture was tedious, but mass recoveries were consistently on the order of about 90%. The mixture appeared to contain many indole products in addition to the major product, indole **12** (many small proton NMR resonances in the general area

where the indole resonances of **12** occur). This offered an explanation for the difficulties in separating indole **12** from the product mixture. It also raised the question of what was responsible for the formation of the other indole products.

Scheme 2

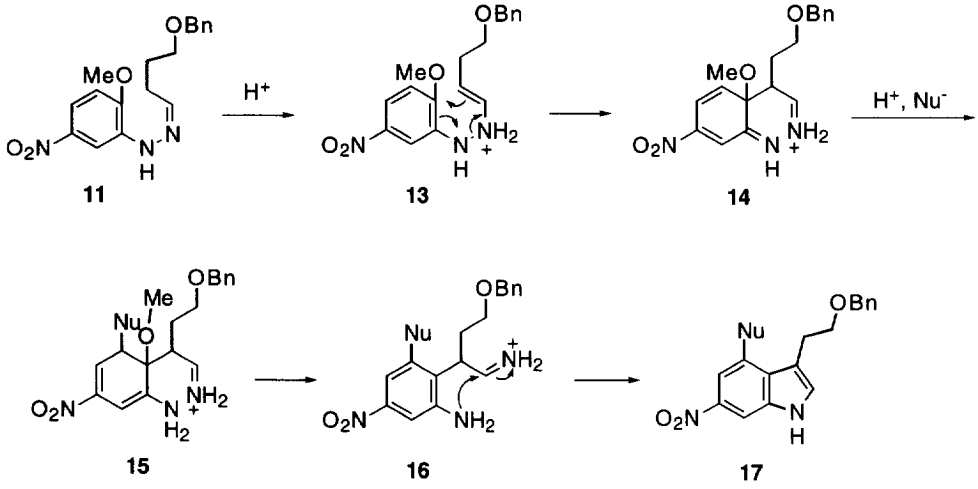


8 **9** **10** **7** **3** **11** **12**

The origin of the contaminating indole products obtained along with indole **12** is rooted in the mechanism of the Fischer indole synthesis. The key step in the mechanism is a [3,3]sigmatropic rearrangement. When the rearrangement occurs to the unsubstituted ortho position, the "normal" product, indole **12**, is produced. However, the rearrangement can follow another course, as shown in Scheme 3.[20] In this alternative pathway, ene-hydrazine **13** undergoes sigmatropic rearrangement to the ortho position bearing the methoxy group, giving tertiary ether **14**. Tertiary ether **14** can not easily rearomatize, so it undergoes side reactions which ultimately lead to several indole products. One possible fate of tertiary ether **14** is nucleophilic attack at the δ position of the conjugated imine. Any adventitious nucleophile present in the reaction mixture may add to the conjugated imine, and this would lead to dienamine **15**. Loss of

methanol from dienamine **15** then follows, restoring aromaticity to the benzene ring and giving aniline **16**. Closure and aromatization of the pyrrole ring then proceeds as with the normal Fischer indole synthesis, producing indoles such as **17**.[21]

Scheme 3

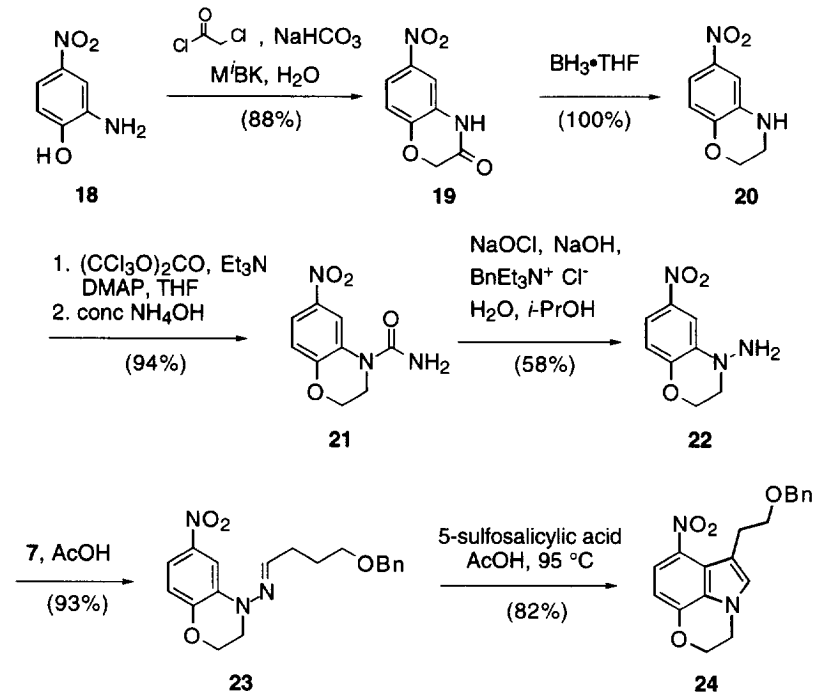


The abnormal Fischer indole synthesis is a general problem when an *ortho* substituent is present on the phenylhydrazone. Mixtures of indole products are always obtained, and yields of the desired indole are generally poor. We thought we might avoid this problem if we could temporarily constrain the hydrazone so that it could only undergo electrocyclization in the desired direction. Such a constraint would result if the nitrogen and oxygen atoms could be linked by a short tether. To this end, we investigated the preparation and use of a suitably-functionalized benzoxazine.

The required phenylhydrazine was synthesized in four steps from 2-amino-4-nitrophenol (**18**) (Scheme 4). Aminophenol **18** was annulated with chloroacetyl chloride, giving benzoxazone **19** as previously reported.[22] The amide was reduced with borane, providing benzoxazine **20** in quantitative yield.[23] Carbamoylation of the amine was accomplished by succesive treatment of benzoxazine **20** with triphosgene and ammonia.[24] This afforded urea **21** in 94% yield. Subjection of the urea to the conditions of the Hoffmann rearrangement

gave phenylhydrazine **22** in about 60% yield.[25] Condensation with 4-benzyloxybutanal (**7**) then provided hydrazone **23** in 93% yield. Hydrazone **23** showed no *E-Z* isomerism in its ^{1}H NMR spectrum. Once again, we have no direct evidence as to which stereoisomer predominates. However, it is most likely that the *E* isomer predominates for thermodymanic reasons. Using the same conditions employed for the preparation of indole **12**, hydrazone **23** was heated in acetic acid, along with a slight excess of 5-sulfosalicylic acid (Scheme 4). A single product, indole **24**, was obtained in 82% yield. Thus, by rigidly defining the geometry of an *ortho*-substituted phenylhydrazone, the abnormal Fischer indole synthesis can be completely suppressed.[26]

Scheme 4

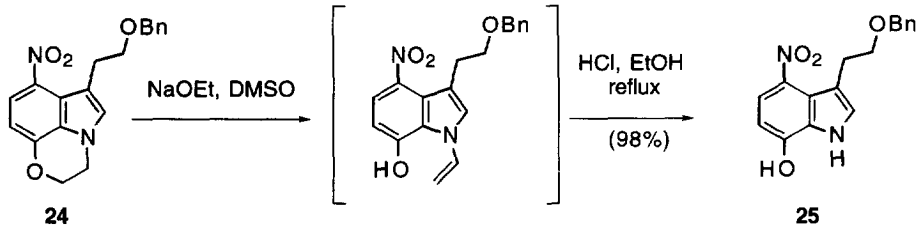


There are some previously known examples of using hydrazones of 4-aminobenzoxazines similar to hydrazone **23** in the Fischer indole synthesis.[27] In each of these cases, the two carbon tether was a necessary structural element in the target molecule. What we desired was to use the tether to suppress the

abnormal Fischer indole synthesis, then remove it once the indole had been prepared. With indole **24** in hand, we turned our attention to removal of the tether.

Indole **24** was dissolved in anhydrous DMSO and treated with sodium ethoxide at room temperature, opening the oxazine by E_2 elimination of *p*-nitrophenoxide (Scheme 5). After extractive removal of the DMSO and treatment of the crude product with acid, 7-hydroxy-4-nitroindole (**25**) was isolated in 98% yield. The same strategy was used to prepare other indoles bearing various substituents on the benzene ring. In each case, no evidence of contaminating indole products was seen. Since the dimethylene chain is readily introduced and then cleaved, this "tether" strategy may prove to be an attractive method for suppressing the abnormal Fischer indole synthesis.

Scheme 5



24 **25**

In conclusion, we have designed a method that allowed for the use of the Fischer indole synthesis to prepare a 7-substituted indole in high yield. The new methodology should allow for convenient access to the pyrrolo[2,3,4-*d*,*e*]quinoline nucleus, and eventually may be applicable to other indole alkaloids as well.

Experimental Section

General: Unless otherwise noted, reactions were dried over $MgSO_4$ or Na_2SO_4, filtered through a fritted glass funnel or a plug of cotton, and concentrated with a rotary evaporator at aspirator pressure (*ca.* 30 mm Hg), warming when necessary. Also unless otherwise noted, thin layer chromatography (TLC) solvent systems were the same as those used for column chromatography with $R_f \approx 0.3$. Thin layer chromatography was performed using Merck F-254 silica gel plates. Column chromatography was performed using ICI Sili Tech 32-63 δ A

silica gel, or Merck 60 (230-400 mesh) silica gel according to the procedure of Still.[28]

Starting materials were obtained from commercial suppliers and used without further purification. Tetrahydrofuran (THF) was distilled under N_2 from sodium-benzophenone immediately prior to use. Triethylamine were distilled under N_2 from CaH_2 immediately prior to use. Dimethyl sulfoxide (DMSO) was distilled from CaH_2 and stored over 4 Å molecular sieves. The molarity of solutions containing NaOCl was determined by iodometric titration.[29]

Melting points were measured in capillary tubes and are uncorrected. ^1H NMR spectra were recorded using a Bruker AMX-300, AM-400, or AM-500 spectrometer. ^{13}C NMR spectra were recorded using a Bruker AM-400 or AM-500 spectrometer at 100 or 125 MHz respectively. Chemical shifts are referenced to internal $CHCl_3$ (^1H 7.26 ppm, ^{13}C 77.0 ppm), DMSO (^1H 2.49 ppm, ^{13}C 39.5 ppm), CHD_2CN (^1H 1.93 ppm, ^{13}C 1.3 ppm), CD_2HOD (^1H 3.30 ppm, ^{13}C 49.0 ppm) or tetramethylsilane (0.00 ppm). ^1H NMR data are tabulated in order: multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet; b, broad), number of protons, and coupling constants in Hertz. For mixtures of stereoisomers, the ^1H resonances of the major stereoisomer are reported, unless otherwise indicated. In these cases, however, ^{13}C resonances from the minor isomers may be included. Infrared spectra were recorded with a Perkin-Elmer Model 1420 Ratio Recording spectrophotometer, a Perkin-Elmer 1600 FTIR, or an ATI Mattson Gemini FTIR. Samples were prepared as a thin film on NaCl plates (film), as a KBr window (KBr), or in solution as indicated ($CDCl_3$, CH_2Cl_2 or $CHCl_3$). Elemental analyses were performed by the Microanalytical Laboratory operated by the College of Chemistry, University of California at Berkeley. Mass spectra were recorded by the Mass Spectroscopy Facility operated by the University of California at Berkeley.

2-Methoxy-5-nitrophenylhydrazine (3).[16] To 170 mL of 12 M HCl was added 10.00 g (59.47 mmol) of 2-methoxy-5-nitrophenylaniline. The suspension turned pinkish-gray over about 5 min. The reaction mixture was cooled with an ice bath, then a solution of 4.51 g (65.4 mmol) of $NaNO_2$ in 25 mL of water was added *via* pipette, expelling the nitrite solution below the surface of the reaction mixture, and keeping the internal temperature below 10 °C. The reaction was complete when a positive test on starch-KI paper was obtained, indicating an

excess of NO_2^- ion was present. (Additional $NaNO_2$ was added if the starch-KI test was negative.)[30]

The solution of the diazonium salt was cooled to –25 °C, and a solution of 30.03 g (133.1 mmol) of $SnCl_2 \bullet 2H_2O$ in 30 mL of 12 M HCl was gradually added by pipette, keeping the internal temperature below –20 °C. An additional 50 mL of 12 M HCl was added during the addition of the $SnCl_2$ solution to ensure adequate stirring of the reaction mixture. After addition was complete, stirring was continued for 25 min, then the yellow precipitate was filtered and stirred into 200 mL of 25% KOH solution. The orange precipitate was collected and taken up in 200 mL of ethyl acetate. The aqueous layer was drained, then the organic layer was washed with 50 mL of brine, dried and concentrated to an orange solid. Recrystallization from 160 mL of methanol gave 6.49 g (60%) of orange needles, mp 126-127 °C. (TLC 1:1 hexanes:EtOAc, streaks above the product). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.59 (bs, 2), 3.92 (s, 3), 5.80 (bs, 1), 6.75 (d, 1, J = 8.8), 7.67 (dd, 1, J = 2.7, 8.8), 7.82 (d, 1, J = 2.7); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.00, 104.97, 108.25, 114.76, 140.99, 142.34, 150.92; IR (CH_2Cl_2) 905, 1275, 1430, 2328, 3000, 3068 cm^{-1}.

4-Hydroxybutanal, 2-methoxy-5-nitrophenylhydrazone (5). To 20 mL of glacial acetic acid was added 2.00 g (10.9 mmol) of hydrazine **3**. The mixture was warmed to 40 °C to aid dissolution, then to the warm solution was added 1.1 mL (14.5 mmol) of 2,3-dihydrofuran (**4**). The reaction mixture was stirred without additional heating for 20 min, then poured into 200 mL of H_2O and extracted with EtOAc (4 x 50 mL). The combined EtOAc layers were back extracted with saturated aqueous $NaHCO_3$ solution (3 x 50 mL), then brine (1 x 50 mL), then dried and concentrated to a red oil. This was triturated with diethyl ether and pumped under high vacuum to remove any remaining EtOAc. The product gradually solidified to give 2.70 g (97%) of an analytically pure red glass. Recrystallization attempts were unsuccessful. ^{1}H NMR (500 MHz, $CDCl_3$) mixture of E and Z isomers δ 1.85 (m, 2), 2.37-2.41 (m, 2 [minor]), 2.43-2.47 (m, 2 [major]), 3.74 (m, 2), 3.93 (s, 3 [major]), 3.95 (s, 3 [minor]), 6.67 (t, 1 J = 5.3 [minor]), 6.78 (d, 1, J = 8.9 [overlapping major and minor]), 7.27 (t, 1, J = 5.2 [major]), 7.67 (dd, 1, J = 2.7, 8.8 [major]), 7.68 (m, 1 [minor]), 7.76 (bs, 1 [major]), 7.94 (bs, 1 [minor]), 8.09 (d, 1, J = 2.7 [major]), 8.15 (d, 1, J = 2.5[minor]); ^{13}C NMR (125 MHz, $CDCl_3$) mixture of E and Z isomers δ 22.70, 28.68, 28.73, 29.47, 55.98, 56.07, 61.35, 61.97, 106.57, 107.01, 108.71, 108.82, 114.76, 115.26, 135.03, 142.36, 143.26, 143.99, 149.50, 150.02; IR (CH_2Cl_2) 1350,

1532, 1599, 1622, 2958, 3620, 3690 cm^{-1}. Anal Calcd for $C_{11}H_{15}N_3O$: C, 52.17, H, 5.97, N, 16.59. Found: C, 52.47, H, 5.96, N, 16.26.

3-(2-Acetoxy)ethyl-7-methoxy-4-nitroindole (6). To a solution of 49 mg (0.22 mmol) of hydrazone **5** in 0.5 mL of glacial acetic acid was added 50 mg of 5-sulfosalicylic acid•$2H_2O$. The mixture was heated at reflux for five min, then poured into 5 mL of H_2O. The aqueous suspension was extracted with EtOAc (2 x 5 mL), then the combined EtOAc layers were back extracted with saturated aqueous $NaHCO_3$ solution (2 x 5 mL), dried, and concentrated to a red oil. This was partially purified *via* chromatography (99:1 $CHCl_3$: methanol) to give 7 mg (11%) of impure (acetoxy)ethylindole. ^1H NMR (500 MHz, $CDCl_3$) δ 2.01 (s, 3), 3.28 (t, 2, J = 6.7), 4.02 (s, 3), 4.26 (t, 2, J = 6.7), 6.60 (d, 1, J = 8.7), 7.21 (d, 1, J = 2.7), 7.99 (d, 1, J = 8.7), 8.85 (bs, 1); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.01, 55.99, 65.65, 100.42, 113.07, 120.71, 120.99, 126.79, 128.31, 136.67, 150.69; IR (KBr) 1254, 1296, 1317, 1501, 1570, 1736, 3350, 3406 cm^{-1}.

4-Benzyloxybutanal (7). To a solution of 1.08 g (6.00 mmol) of 4-benzyloxy-1-butanol (**10**) in 18 mL of CH_2Cl_2 was added 9.6 mL (13 mmol) of saturated aqueous $NaHCO_3$ solution, 72 mg (0.60 mmol) of KBr, 72 mg (0.32 mmol) of benzyltriethylammonium chloride, and 18 mg (0.12 mmol, 2 mol%) of TEMPO.[19] To the ice-cooled mixture was added a solution of 9.6 mL (7.2 mmol) of 5% aqueous NaOCl solution, 6 mL of saturated aqueous $NaHCO_3$ solution, 6 mL of brine, and 216 mg (3.70 mmol) of NaCl, over 10 min, with vigorous stirring. After 45 min, the layers were separated, and the aqueous layer was extracted with additional CH_2Cl_2 (3 x 20 mL). The combined CH_2Cl_2 layers were back extracted with saturated aqueous $NaHCO_3$ solution (1 x 20 mL), and brine (1 x 20 mL), then dried and concentrated to an oil. This was purified via chromatography (4:1 hexanes: EtOAc) to give 824 mg (77%) of the aldehyde as a colorless oil. Spectral data were in agreement with those previously reported.[31]

4-Benzyloxybutyric acid (9).[17] To a solution of 83 mL (0.70 mol) of benzyl bromide and 15.0 g (0.174 mol) of g-butyrolactone (**8**) in 300 mL of toluene was added 49.2 g (0.745 mol) of freshly crushed 85% KOH. The mixture was stirred at reflux, under N_2, for three days, then partitioned between 300 mL of H_2O and 150 mL of diethyl ether. The layers were separated, and the aqueous layer was

extracted with additional ether (2 x 150 mL). The ether/toluene layers were set aside, and the aqueous layer was cooled with an ice bath, then acidified with 150 mL of 3 M H_2SO_4 solution. The acidic suspension was then extracted with CH_2Cl_2 (3 x 150 mL). The combined CH_2Cl_2 layers were dried and concentrated to 8.85 g (26.2%) of a colorless oil.

The ether/toluene layer was concentrated to remove most of the diethyl ether, and the residue was heated at reflux with 80 mL of H_2O and 16 g of NaOH for 20 h. The layers were separated, then the aqueous layer was diluted to 200 mL. This was extracted with ether (3 x 50 mL). The aqueous layer was treated with a slurry of 20 mL H_2SO_4 in 100 mL of ice. The acidic suspension was then extracted with CH_2Cl_2 (3 x 100 mL). The combined CH_2Cl_2 layers were dried and concentrated to 22.44 g (66%) of additional product for a total yield of 31.29 g (92%). This acid was used without purification in the next step. ^1H NMR and IR spectral data were in agreement with those previously reported.[32] ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.70, 30.90, 68.94, 72.84, 127.57, 128.34, 138.17, 179.68.

4-Benzyloxybutan-1-ol (10). To a solution of 17.11 g (88.1 mmol) of 4-benzyloxybutanoic acid (**9**) in 35 mL of THF was added 94 mL (94 mmol) of 1 M BH_3•THF, while cooling the solution with an ice bath. The mixture was stirred for 1 h at 25 °C, then quenched by slowly adding 36 mL of 1:1 (*v/v*) THF-H_2O. The quenched mixture was stirred for 1 h, then solid K_2CO_3 was added until the solid appeared to be free flowing. The reaction mixture was filtered through celite, the salts were washed with diethyl ether, then the combined filtrate and washings were concentrated to 15.59 g (98%) of a slightly yellow oil. This was used without purification in the following step. (TLC 3:1 Hexanes: EtOAc, R_f = 0.1) ^1H NMR and IR spectral data were in agreement with those previously reported.[32] ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.61 (CH_2), 30.03 (CH_2), 62.61 (CH_2), 70.28 (CH_2), 73.00 (CH_2), 127.61 (CH), 127.67 (CH), 128.37 (CH), 138.09 (C).

4-Benzyloxybutanal, 2-methoxy-5-nitrophenylhydrazone (11). To a solution of 615 mg (3.36 mmol) of 2-methoxy-5-nitrophenylhydrazine (**3**) in 5 mL of glacial acetic acid was added 598 mg (3.36 mmol) of 4-benzyloxybutanal (**7**), washing in the last traces of the aldehyde with 1 mL of acetic acid. The reaction was instantaneous. The solution was poured into 60 mL of water and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were back extracted

with saturated aqueous $NaHCO_3$ solution (2 x 50 mL), and brine (1 x 50 mL), dried and concentrated to 1129 mg (98%) of a red oil. An analytical sample was prepared by chromatography (3:2 hexanes: EtOAc, two overlapping spots, minor isomer slightly higher R_f than major isomer.) ^1H NMR (400 MHz, $CDCl_3$, 73:27 ratio of *E* and *Z* isomers) δ 1.87 (m, 2), 2.35 (m, 2 [minor]), 2.42 (m, 2 [major]), 3.54 (m, 2), 3.83 (s, 3, [minor]), 3.88 (s, 3, [major]), 4.49 (s, 2), 6.64 (t, 1, *J* = 5.4 [minor]), 6.73 (d, 1, *J* = 8.9 [major]), 6.75 (d, 1, *J* = 8.9 [minor]), 7.18 (t, 1, *J* = 5.3 [major]), 7.22-7.35 (m, 5), 7.63 (dd, 1, *J* = 2.8, 8.8 [major]), 7.67 (dd, 1, *J* = 2.8, 8.9 [minor]), 7.72 (bs, 1 [major]), 7.85 (bs, 1 [minor]), 8.12 (d, 1, *J* = 2.8 [major]), 8.17 (d, 1, *J* = 2.8 [minor]); ^{13}C NMR (100 MHz, mixture of *E* and *Z* isomers) δ 22.92 (CH_2), 26.04 (CH_2), 26.80 (CH_2), 29.90 (CH_2), 55.82 (CH_3), 55.85 (CH_3), 68.74 (CH_2), 69.36 (CH_2), 72.70 (CH_2), 106.37 (CH), 106.82 (CH), 108.56 (CH), 108.68 (CH), 114.46 (CH), 115.06 (CH), 127.28 (CH), 127.32 (CH), 127.40 (CH), 128.12 (CH), 128.16 (CH), 134.94 (C), 135.02 (C), 138.07 (C), 138.30 (C), 142.25 (C), 143.02 (CH), 143.79 (CH), 149.35 (C), 149.85 (C); IR (film) 1266, 1343, 1531, 1590, 1615, 2857, 2941, 3337 cm^{-1}. Anal Calcd for $C_{18}H_{21}N_3O_4$: C, 62.96, H, 6.16, N, 12.24. Found: C, 62.74, H, 6.18, N, 12.31.

3-(2-Benzyloxy)ethyl-7-methoxy-4-nitroindole (12). To a solution of 840 mg (2.45 mmol) of hydrazone **11** in 8.4 mL of glacial acetic acid was added 840 mg (3.30 mmol) of 5-sulfosalicylic acid•$2H_2O$. The acid was partially dissolved, and the solution was heated to 115 °C for 10 min. The reaction mixture was poured into a two-phase mixture of 25 mL of EtOAc and 50 mL of H_2O, then the mixture was shaken and separated. The aqueous phase was extracted with additional EtOAc (2 x 25 mL), then the combined organic layers were back extracted with saturated aqueous $NaHCO_3$ solution (3 x 25 mL), and brine (1 x 25 mL), then dried and concentrated to a brown oil. This was partially purified via chromatography (2:1 hexanes: EtOAc). Concentration of the product containing fractions was followed by recrystallization from $CHCl_3$: hexanes, giving 228 mg (29%) of the indole as a bright yellow solid, mp 107-108 °C. Variable amounts of additional product (<10%) could be obtained after repeated chromatography and recrystallization of the supernatant mixture. ^1H NMR (400 MHz, $CDCl_3$) δ 3.23 (2, t, *J* = 6.2), 3.72 (2, t, *J* = 6.2), 3.93 (3, s), 4.54 (2, s), 6.45 (1, d, *J* = 8.7), 7.02 (1, d, *J* = 2.6), 7.27 (5, m), 7.90 (1, d, *J* = 8.7), 8.84 (1, bs); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.18 (CH_2), 55.83 (CH_3), 71.30 (CH_2), 72.75 (CH_2), 100.08 (CH), 113.65 (C), 120.46 (C), 120.58 (CH), 127.27 (CH), 127.49 (CH), 127.70 (CH), 128.22 (C), 128.27 (CH), 136.56 (C), 138.34 (C),

150.46 (C); IR ($CDCl_3$) 1280, 1320, 1510, 1565, 1630, 2870, 2950, 3480 cm^{-1}; UV (λ_{max}, ε(mol•cm•L^{-1}), THF) 249 (8620), 390 (6570). Anal Calcd for $C_{18}H_{18}N_2O_4$: C, 66.25, H, 5.56, N, 8.58. Found: C, 65.98, H, 5.65, N, 8.66.

2,3-Dihydro-6-nitro-1,4-benzoxazine (20).[33] To a suspension of 5.56 g (28.6 mmol) of 2(*H*)-6-nitro-1,4-benzoxazin-3-one (**19**)[22] in 40 mL of THF was added 43 mL of 1.0 M borane in THF.[23] After 40 min, the reaction mixture was cooled for 10 min, then quenched by slowly adding 25 mL of 3.2 M HCl and warming back to a gentle reflux for 10 min. The reaction mixture was again cooled, then poured into 400 mL of H_2O and extracted with EtOAc (4 x 100 mL). The combined EtOAc layers were back extracted with brine (1 x 50 mL), dried, and concentrated to 5.18 g (100%) of an orange solid, mp 115-116 °C. This was homogeneous by ^1H NMR spectroscopy. (TLC 3:1 hexanes: EtOAc, 2 elutions) ^1H NMR (500 MHz, $CDCl_3$) δ 3.47 (m, 2), 4.10 (bs, 1), 4.33 (m, 2), 6.81 (d, 1, J = 8.8), 7.47 (d, 1, J = 2.6), 7.57 (dd, 1, J = 2.6, 8.8); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.97, 65.54, 110.03, 114.70, 116.38, 133.80, 141.79, 149.34; IR (KBr) 1333, 1514, 1588, 3423 cm^{-1}.

4-(*N*)-Aminocarbonyl-6-nitro-2,3-dihydro-1,4-benzoxazine (21). To a solution of 4.63 g (25.7 mmol) of benzoxazine **20** in 100 mL of THF was added 5 mL (36 mmol) of triethylamine, and 50 mg (0.41 mmol) of 4-dimethylaminopyridine. The solution was cooled with an ice bath, then 3.05 g (10.3 mmol) of triphosgene was added in one portion.[31] After stirring for 30 min, the reaction mixture was poured into 100 mL of 27% aqueous NH_3, swirled, then partitioned between 500 mL of H_2O and 100 mL of EtOAc. The mixture was shaken and separated, then the aqueous phase was extracted with additional EtOAc (2 x 100 mL). The combined EtOAc layers were back extracted with brine (1 x 50 mL), dried, and concentrated to 5.53 g (96%) of a yellow solid. Recrystallization from EtOH gave an analytical sample, mp 188-190 °C. TLC 3:1 EtOAc- hexanes. ^1H NMR (400 MHz, d_6-DMSO) δ 3.76 (t, 2, J = 4.5), 4.31 (t, 2, J = 4.5), 6.77 (bs, 2), 7.03 (d, 1, J = 9.0), 7.79 (dd, 1, J = 2.8, 9.0), 8.76 (d, 1, J = 2.8); ^{13}C NMR (100 MHz, d_6-DMSO) δ 42.08 (CH_2), 65.76 (CH_2), 117.17 (CH), 118.28 (CH), 118.51 (CH), 127.51 (C), 140.24 (C), 151.02 (C), 155.89 (C); IR (KBr) 1331, 1508, 1578, 1601, 1661, 3401, 3472 cm^{-1}. Anal Calcd for $C_9H_9N_3O_4$: C, 48.44, H, 4.06, N, 18.83. Found: C, 48.64, H, 4.11, N, 18.64.

4-Amino-2,3-dihydro-6-nitro-1,4-benzoxazine (22). A suspension of 2.50

g (11.2 mmol) of urea **21** in 125 mL of abs EtOH was heated to reflux, during which time the urea dissolved. To the hot solution was added 32 mL of an aqueous solution of 0.50 M NaOCl (16 mmol), and 2.5 M NaOH (80 mmol).[25] After 40 min, an additional 8 mL of the NaOCl (4.0 mmol) and NaOH (20 mmol) solution was added. The reaction mixture was concentrated to remove most of the EtOH, then poured into 200 mL of H_2O and extracted with EtOAc (3 x 70 mL) to remove most of the impurities. The aqueous layer was acidified with 3.2 M HCl, then extracted with EtOAc (3 x 70 mL). The second set of EtOAc layers was combined, back extracted with brine (1 x 70 mL), dried, and concentrated to 2.1 g of crude hydrazine as an orange solid, still containing some EtOAc. After further drying, yields of 55-60% could be obtained. This material could be taken on without purification to the next step, or it could be purified by recrystallization from absolute EtOH to give analytically pure material, mp 90-91 °C. (TLC 1:1 hexanes: EtOAc) ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.42 (m, 2), 3.74 (bs, 2), 4.40 (m, 2), 6.71 (d, 1, J = 8.8), 7.54 (dd, 1, J = 2.7, 8.8), 7.98 (d, 1, J = 2.7); ^{13}C NMR (100 MHz, $CDCl_3$) δ 51.66 (CH_2), 65.84 (CH_2), 109.08 (CH), 115.56 (CH), 115.96 (CH), 138.45 (C), 141.88 (C), 149.75 (C); IR (KBr) 1327, 1490, 1578, 1625, 3319 cm^{-1}. Anal Calcd for $C_8H_9N_3O_3$: C, 49.23, H, 4.65, N, 21.53. Found: C, 49.38, H, 4.63, N, 21.13.

4-Benzyloxybutanal, 4-amino-2,3-dihydro-6-nitro-1,4-benzoxazine hydrazone (23). To 81 mg (0.42 mmol) of hydrazine **22** was added a solution of 70 mg (0.39 mmol) of 4-benzyloxybutanal (**7**) in 1 mL of glacial AcOH. Upon dissolution of the hydrazine, the reaction was complete. The reaction mixture was poured into 10 mL of H_2O and extracted with EtOAc (2 x 5 mL). The combined EtOAc layers were back extracted with saturated aqueous $NaHCO_3$ solution (2 x 5 mL), and brine (1 x 2.5 mL), then dried and concentrated to an oil. This was purified *via* chromatography (2:1 hexanes–EtOAc) to give an orange oil which crystallized upon trituration with diethyl ether. In this manner, 132 mg (89%) of orange crystals, mp 68-69 °C was obtained. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.92 (m, 2), 2.53 (dt, 2, J = 5.3, 7.3), 3.50 (t, 2, J = 4.8), 3.59 (t, 2, J = 6.2), 4.37 (t, 2, J = 4.8), 4.52 (s, 2), 6.85 (d, 1, J = 8.8), 6.96 (t, 1, J = 5.2), 7.25-7.35 (m, 5), 7.62 (dd, 1, J = 2.7, 8.8), 8.39 (d, 1, J = 2.7); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.31 (CH_2), 29.92 (CH_2), 41.26 (CH_2), 63.88 (CH_2), 69.62 (CH_2), 72.93 (CH_2), 109.51 (CH), 115.30 (CH), 116.44 (CH), 127.51 (CH), 127.64 (CH), 128.31 (CH), 133.44 (C), 138.42 (C), 139.02 (CH), 142.93 (C), 147.80 (C); IR (KBr) 1330, 1516, 1579, 1613, 2856, 2951 cm^{-1}. Anal Calcd for $C_{19}H_{21}N_3O_4$: C, 64.21,

H, 5.96, N, 11.82. Found: C, 64.00, H, 5.96, N, 11.74.

6-(2-Benzyloxy)ethyl-7-nitro-2,3-dihydropyrrolo[1,2,3-*d*,*e*]benzoxazine (24). To a solution of 2.1 g (10 mmol, crude) of hydrazine **22** in 20 mL of glacial acetic acid was added 1.50 g (8.42 mmol) of aldehyde **7**. After stirring at 25 °C for 10 min, 2.10 g (8.26 mmol) of 5-sulfosalicylic acid•$2H_2O$ was added. The mixture was heated to 97 °C for 10 min, then poured into 200 mL of H_2O. The suspension was extracted with EtOAc (3 x 70 mL), then the combined EtOAc layers were back extracted with saturated $NaHCO_3$ solution (2 x 70 mL) and brine (1 x 70 mL), dried, and concentrated to an oil. This was purified by chromatography (3:2 hexanes: EtOAc) to give 1.92 g (51% for two steps) of a waxy yellow solid, mp 72-78 °C. When hydrazine **22** was purified, the yield for the hyrazone formation-Fischer indole synthesis sequence was 76%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.30 (t, 2, J = 6.4), 3.72 (t, 2, J = 6.4), 4.25 (t, 2, J = 4.8), 4.53 (s, 2), 4.56 (t, 2, J = 4.8), 6.62 (d, 1, J = 8.6), 7.16 (s, 1), 7.29 (m, 5), 8.01 (d, 1, J = 8.6); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.09 (CH_2), 42.96 (CH_2),65.54 (CH_2), 71.28 (CH_2), 72.67 (CH_2),104.61 (CH), 114.28 (C), 120.18 (C), 121.28 (CH), 126.41 (C), 127.31 (CH), 127.52 (CH), 128.15 (CH), 128.70 (CH), 136.14 (C), 138.51 (C), 148.29 (C); IR (KBr) 1243, 1296, 1390, 1502, 1572, 1625, 2849, 2931 cm^{-1}. Anal Calcd for $C_{19}H_{18}N_2O_4$: C, 67.45, H, 5.36, N, 8.28. Found: C, 67.34, H, 5.50, N, 8.25.

3-(2-Benzyloxy)ethyl-7-hydroxy-4-nitroindole (25). To a solution of 338 mg (1.00 mmol) of indole **24** in 5 mL of DMSO was added 204 mg (3.00 mmol) of NaOEt. The reaction was monitored by TLC (1:1 hexanes: EtOAc) as indole **24** (R_f 0.39) was converted into a less polar intermediate (R_f 0.54), adding more NaOEt if necessary. After 20 min, the reaction mixture was poured into 45 mL of H_2O and to this was added 5 mL of 1 M HCl. The aqueous suspension was extracted with diethyl ether (3 x 15 mL), then the combined organic layers were back extracted with H_2O (2 x 15 mL), and brine (1 x 15 mL), dried, and concentrated to a red residue. This was taken up in 5 mL of EtOH, and to this was added 1 mL of 3.2 M HCl. The mixture was stirred at 70 °C for 1 h, then poured into 25 mL of H_2O and extracted with EtOAc (3 x 5 mL). The combined EtOAc layers were back extracted with brine (1 x 5 mL), dried, and concentrated to an oil. Trituration with CH_2Cl_2 or $CHCl_3$ gave 307 mg (98%) of a yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO) δ 3.12 (t, 2, J = 6.9), 3.52, (t, 2, J = 6.9), 4.43 (s, 2), 6.60 (d, 1, J = 8.6), 7.23 (m, 5), 7.40 (d, 1, J =

2.6), 7.84 (d, 1, J = 8.6), 11.22 (s, 1), 11.69 (s, 1); ^{13}C NMR (100 MHz, d_6-DMSO) δ 28.08 (CH_2), 71.46 (CH_2), 71.89 (CH_2), 104.51 (CH), 112.00 (C), 121.19 (CH), 121.33 (C), 127.40 (CH), 127.46 (CH), 127.81 (C), 128.32 (CH), 129.02 (CH), 134.54 (C), 138.88 (C), 150.39 (C); IR (KBr) 1246, 1259, 1483, 1567, 1637, 3237, 3341 cm^{-1}. Anal Calcd for $C_{17}H_{16}N_2O_4$: C, 65.38, H, 5.16, N, 8.97. Found: C, 65.23, H, 5.16, N, 8.63.

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26. A reviewer has suggested that the successful cyclization of **23**, compared to **5** and **11**, might be due to the fact that **23** is a single stereoisomer, whereas **5** and **11** are mixtures of *E* and *Z* isomers about the C=N bond. We cannot rule out this possibility, and indeed, the yield of indole in the case of **5**, **11**, and **23** (11%, 30%, 82%) might correlate with the observed diastereomeric ratios of 3:1, 2:1, >20:1, if one assumes the minor isomers in the case of **5** and **11** have the same configuration as the sole observed isomer of **23**. However, this rationale is not in accord with the generally accepted mechanism of the Fischer indole reaction, which is believed to involve tautomerization to the diprotonated enamine. In other words, both *E* and Z

hydrazones would give the same diprotonated enamine. For this reason, we think it unlikely that the differences observed are due to the differences in diastereomeric ratios observed with the different hydrazones.

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