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A FACILE CONSTRUCTION OF THE BENZ[*c*,*d*]INDOLE FRAMEWORK

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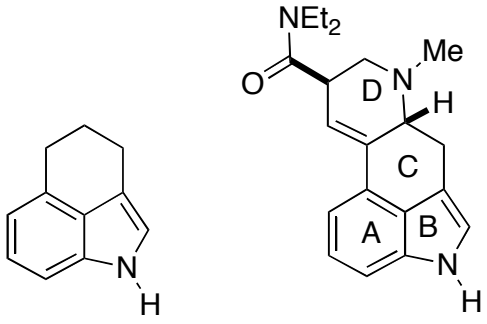
Abstract – The Bradsher cycloaddition of isoquinolinium salts has been applied to 5-acetaminoisoquinoline. In 3 simple steps: (i) quaternization of isoquinoline N (ii) cycloaddition with electron-rich dienophile (iii) dehydration, the benz[*c*,*d*]-indole framework is formed.

The indole ring system has been at the top of the list of privileged substructures in medicinal chemistry.[1] The same can be said for the benz[*c*,*d*]indole framework **1** exemplified by lysergic acid diethylamide (**2**).[2] In the new era of synthesis where a premium is placed on diversity-oriented programs (as compared to target-oriented approaches), indoles are no exception.[3,4] In this report, we describe the first steps in the development of a benz[*c,d*]indole synthesis via Bradsher cycloaddition chemistry that has the potential for diversity.



1 **2**

In the 1980's and 90's, the Falck group at Texas Southwestern Medical School and our group at Hunter/CUNY exploited the Bradsher cycloaddition of isoquinolinium salts as a method for natural products synthesis. Thus, as summarized in Scheme 1, inverse-electron-demand cycloaddition of an

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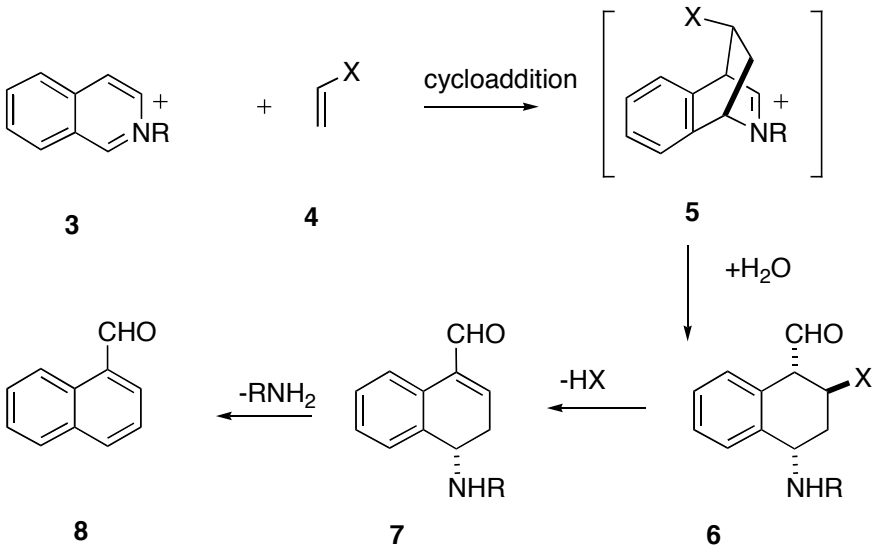
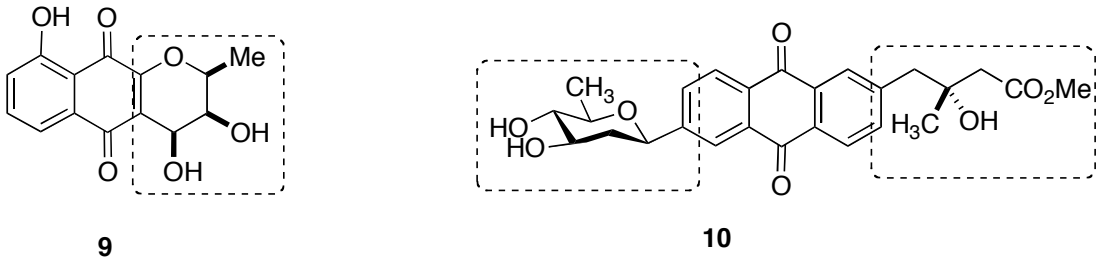
This paper is dedicated to Prof. Steven M. Weinreb on the occasion of his 65th birthday.

isoquinolinium salt (**3**) with an electron-rich dienophile (**4**) affords a tricyclic intermediate (**5**) which is then processed to afford materials such as **6-8**. Further chemistry culminated in syntheses of natural products such as cryptosporin (**9**)[5] and vineomycinone B2 methyl ester (**10**)[6], (the boxed sections show atoms that derive from dienophiles and the unboxed atoms derive from isoquinoline). The latter synthesis



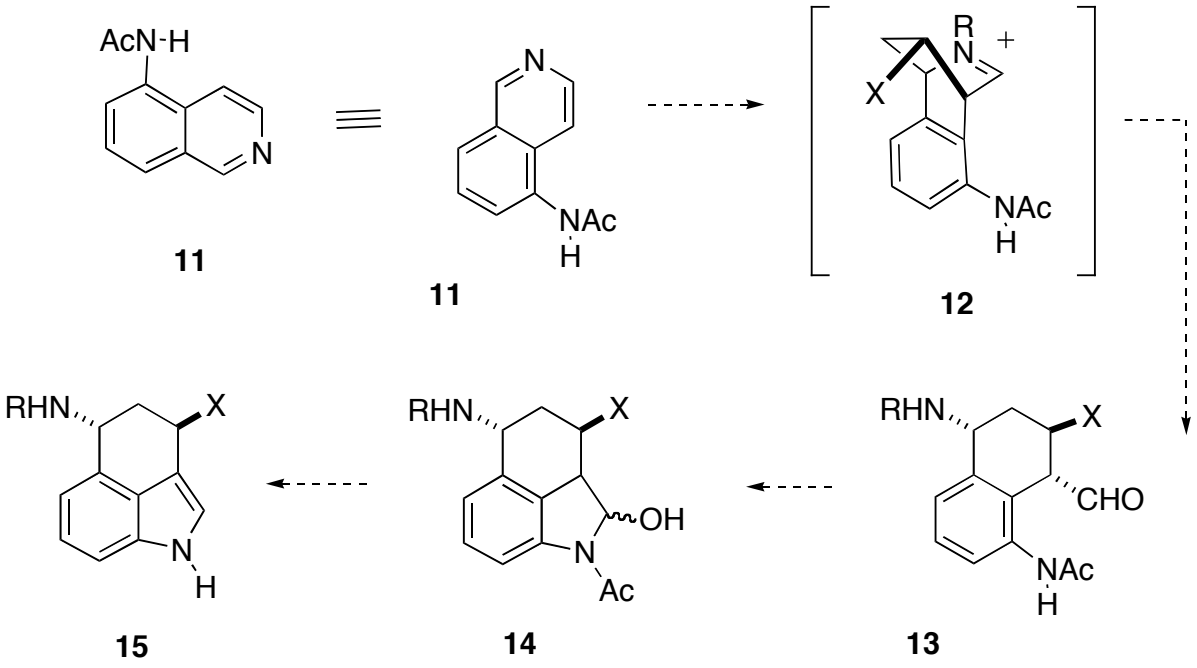
Scheme 1 Generalized reaction sequence for the Bradsher cycloaddition

is a tour de force using two Bradsher cycloadditions with a pyridoisoquinoline core. A wide range of electron-rich dienophiles [7,8,9] were shown to be suitable as were various substituted isoquinolines; thus in the present "diversity" era, this transformation could be considered as candidate for membership in the new armamentarium.



9 **10**

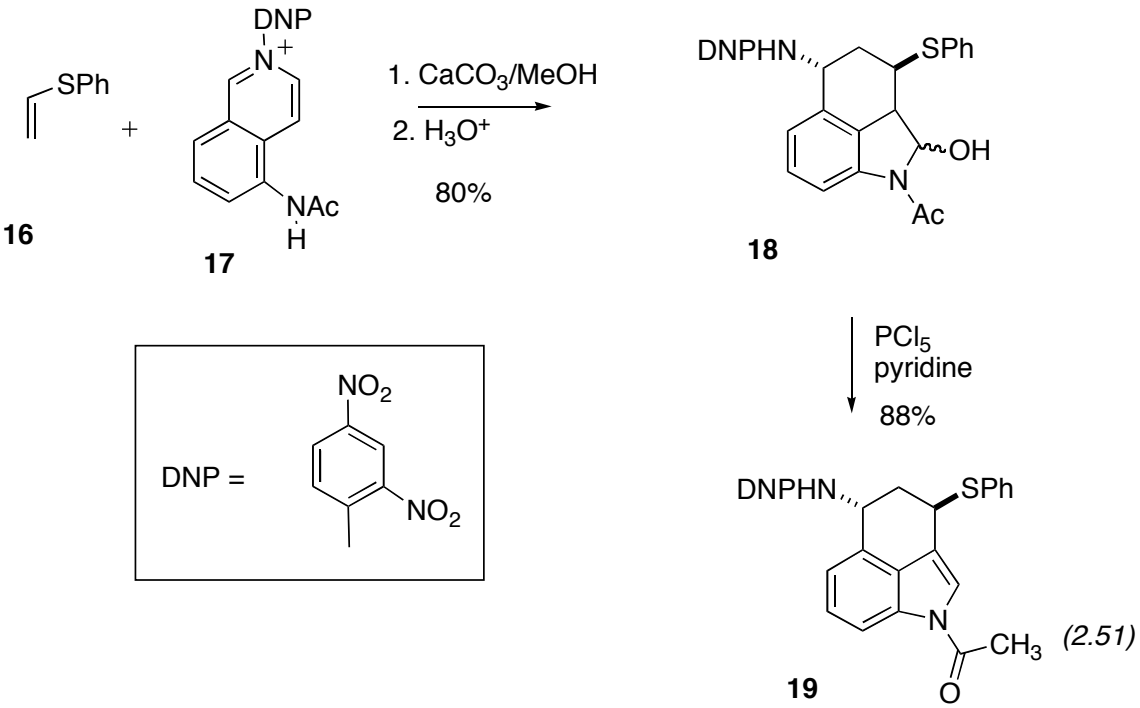
In our plans for developing the Bradsher chemistry, we recognized that the aldehyde (**13**) generated by cleavage of the intermediate iminium salt (**12**), itself derived from the acetamide of 5-aminoisoquinoline (**11**) should be captured intramolecularly to afford a benz[c,d]indole framework (**14**) which should be convertible to **15** (Scheme 2).



Scheme 2 Isoquinoline to benz[*c,d*]indole transformation *via* Bradsher cycloaddition

Thus, the known acetylaminoisoquinoline (**11**)(derived from commercially available 5-nitroisoquinoline)[10] was quaternized with 2,4-dinitrochlorobenzene to afford inverse-electron-demand diene (**17**). This was followed by the application of a Bradsher protocol: the dienophile phenyl vinyl sulfide (**16**) was mixed with salt (**17**) in anhydrous methanol in the presence of excess calcium carbonate and a clean reaction took place. After removal of the solid calcium carbonate and methanol, the residue was dissolved in THF and was treated with aqueous acid. The major product, precipitated by addition of water and isolated in 80% yield was the desired benz[*c.d*]indole (**18**), obtained as a mixture of epimers at the indoline carbon. The relative configuration of the other groups is based on the precedent of our similar chemistry with the parent isoquinoline.[11] A variety of approaches were studied to accomplish the dehydration of the hydroxyindoline to the indole. The best method in this system was the treatment of **18** with PCl_5 in pyridine solvent. This led to benz[*c,d*]indole (**19**) in 88% yield. Although our nmr and analytical data for both **18** and **19** were consistent with the structures as drawn, we confirmed their assignments by an X-Ray determination of **19** (Figure 1).[12]

At this point, we were able to re-evaluate earlier work by Sammes.[13] He described the intramolecular cycloaddition of pentenylisoquinolinium salt (**20**). Using the same Bradsher mechanisms outlined above, the Sammes group concluded that their intermediate (**21**) unraveled to **22** and thence cyclized to oxazepine (**23**). We thought it might be possible, based on the conclusive structure assignment via X-Ray in our series, that **23** should be re-assigned the indole structure (**24**). To test this speculation, the observed proton chemical shifts of the methyl groups in **23** and **24** were calculated using the ACD/NMR Predictor



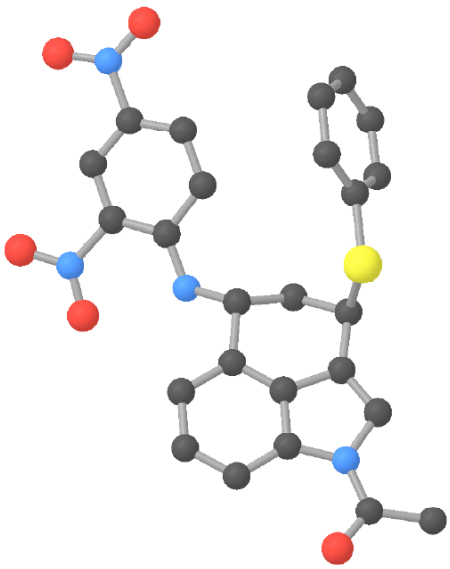
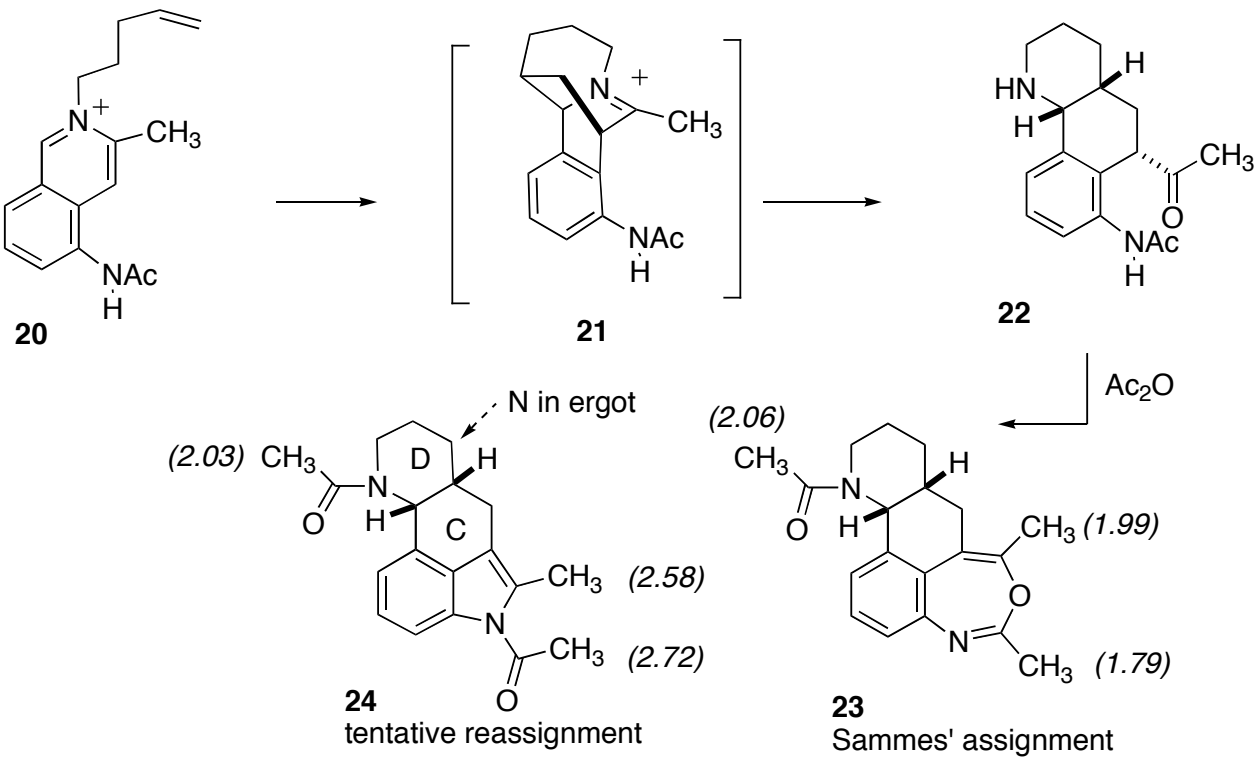


Figure 1 X-Ray crystal structure of benz[*c*,*d*]indole (**19**)

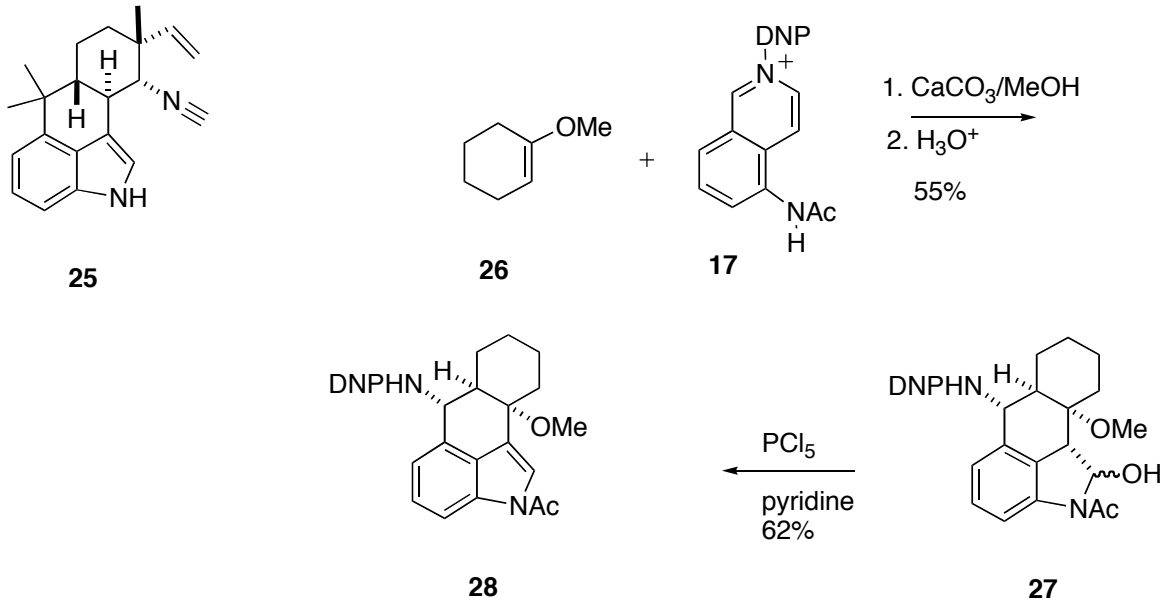
version 8.09. These calculated values are shown adjacent to the corresponding methyl for **23** and **24** as well as for **19**. For the known structure (**19**), the computed shift of δ2.51 is in good agreement with the observed value of 2.60. The observed shifts for the Sammes material, δ 2.31, 2.59, 2.76 are in better agreement with the indole assignment. Interestingly, indole (**24**) has an ergot-like skeleton with the nitrogen interchanged with the indicated carbon in ring D.



Scheme 3 Sammes' intramolecular Bradsher cycloaddition

Another natural product family with an embedded benz[*c*,*d*]indole is that of the hapalindoles,[14] exemplified by hapalindole J (**25**). Cycloaddition of methoxycyclohexene (**26**) with isoquinoline salt (**17**) in MeOH in the presence of $CaCO_3$ took place quite slowly. After 3 days, the $CaCO_3$ was removed and, after removal of MeOH, the residue was treated with THF/H_2O/.01 M HCl. This sequence afforded the simple analog (**27**) of hapalindole in 55% yield. As in the simpler example described above, the material existed as a mixture of epimers at the indoline carbon. The remaining stereochemistry is assigned using our earlier results as precedent. It should be noted that the cis fusion of the C and D rings does not correspond to the natural stereochemistry. This material could similarly be dehydrated with PCl_5 to afford tetracyclic indole (**28**).

In conclusion, this brief exploration extends the scope of the Bradsher cycloaddition of isoquinoline salts to a very simple and mild preparation of the privileged benz[*c*,*d*]indole framework.



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EXPERIMENTAL SECTION

5-Acetylaminoisoquinoline (11): A solution of 5-nitroisoquinoline 21.8 g. (125 mm) dissolved in 350 mL of ethanol(abs) was placed in a 500 mL Parr hydrogenation bottle. To this solution was added 1.11 g of 10% palladium on carbon. The bottle was attached to the Parr hydrogenator, evacuated, flushed with hydrogen and then shaking begun. The reaction mixture was allowed to shake overnight after which time no more hydrogen uptake was observed. The catalyst was removed by filtration through celite followed by repeated washings with ethanol. The reaction mixture was concentrated to approximately 250 mL followed by addition of 1 g of activated charcoal and then heated for 1 h. Filtration through celite followed by concentration in vacuo yielded 5-aminoisoquinoline as a light tan solid. The crude 5-aminoisoquinoline was dissolved in 80 mL of acetic acid (anhydrous) and acetic anhydride 18.0 mL (190 mmol) was added. The mixture was stirred overnight. Water, 70 mL was added to the solution which was then heated to 90 °C for 2 h in order to decompose any remaining acetic anhydride. The solution was poured into a 600 mL beaker and cooled in an ice bath. Neutralization of the reaction mixture by addition

of concentrated ammonium hydroxide caused the product to precipitate. Filtration followed by washing with 2 x 50 mL of water and 2 x 50 mL of petroleum ether then drying, yielded 20.9 g (89.7%) of the product **11** as a light tan solid: mp 162-164 °C (lit., 166 °C). NMR (^{1}H 400 MHz $CDCl_3$) δ 9.14 (s, 1H, Ar-H), 8.39 (d, 1H, J=5.5 Hz, Ar-H), 8.25 (s, 1H, Ar-H), 7.95 (d, 1H, J=7.9 Hz, Ar-H), 7.70 (d, 1H, J=7.9 Hz, Ar-H), 7.57 (d, 1H, J=5.5 Hz, Ar-H), 7.47 (dd, 1H, J=7.3, 7.9 Hz Ar-H), 2.24 (s, 3H, Acetyl-CH_3).

2-(2,4-Dinitrophenyl)-5-acetylaminoisoquinolinium chloride (17): 5-Acetylaminoisoquinoline (**11**) 370 mg (1.99 mmol) was dissolved in 2.5 mL acetonitrile (anhydrous) and then 2,4-dinitrochlorobenzene, 445 mg (2.20 mmol) was added. The reaction mixture was refluxed for 8 h in an oil bath. The reaction mixture was concentrated and the remaining acetonitrile removed by hi-vac. The product was washed with 3 x 2 mL portions of CH_2Cl_2 to yield 727 mg (94.0%) of the salt as an orange solid; mp 128-133 °C (decomp). NMR (^{1}H 400 MHz DMSO-d^6) δ 9.2 (s, 1 H, Ar-H), 8-9 (m, 9H, Ar-H), 2.38 (s, 3H, Acetyl-CH_3).

2-Hydroxy-1,2,2a,3,4,5-octahydro-3-thiophenyl-5-(2,4-dinitrophenyl)aminobenz[*c*,*d*]indole (18): In a dry 50 ml 2-neck round bottom flask fitted with a stopper, magnetic bar, condenser, and nitrogen adapter were added 180 mg (0.463 mm) of the isoquinolinium salt (**17**) followed by addition of 2 mL of anhydrous methanol. The salt was dissolved in the methanol by stirring for a few minutes. To the solution was added 302 mg (3.0 mm) of freshly dried $CaCO_3$. To the stirred suspension was added 90 mL (0.69 mm) of phenyl vinyl sulfide (**16**). The reaction mixture was stirred at 40 °C for 48 h. The reaction mixture was filtered through celite and washed with a mixture of CH_2Cl_2/MeOH (4:1) followed by THF. After concentration under vacuum, the crude product was treated with 7 mL of THF followed by addition of 3 mL of 0.01 N HCI. The reaction mixture was stirred under an argon atmosphere for 24 h. To the reaction mixture was added 10 mL of H_2O to yield an orange colored precipitate. The precipitate was filtered on a Buchner funnel and after drying, the product was a yellow colored solid weighing 147 mg (63% yield): mp 205-207 °C. When the reaction was run on a larger scale (approximately 20 g) the yield was higher (80%), probably due to better recovery of the finely powdered product. NMR (^{1}H 300 MHz DMSO-d^6) δ 8.8 (d, 1H, J=2.7 Hz, Ar-H-between NO_2 groups), 8.3 (d, 1H, J=7.7 Hz, Ar-H), 8.27 (dd, 1H, J=2.6, 9.5 Hz, C-5-Ar-H on DNP), 7.44 (d, 1H, J=9.8 Hz, Ar-H), 7.33 (m, 2H, Ar- H), 7.1-7.25 (m, 4H), 7.01 (d, 1H, J=7.7 Hz, Ar-H), 6.93 (d, 1H, J=8.8 Hz, AcN-CH-OH), 5.95 (m, 1H,C2a-H), 5.31 (m, 1H, C5-H), 3.6 (m, 1H, 1⁄2-CH_2), 3.25 (m, 1H, C3-H), 2.34 (s, 3H, acetyl-CH3), 2.30 (s, 1H, OH), 2.15 (m, 1H, 1⁄2-CH_2). ^{13}C NMR (75 MHz, DMSO-d_6) δ 169.5, 146.5, 140.4, 135.4, 132.5, 132.4, 131.7, 131.1, 130.3, 130.2, 130.0, 129.0, 128.8, 127.2, 123.6, 122.4, 115.5, 115.2, 85.9, 49.2, 46.4, 37.0, 36.4, 23.1 pm. Anal. Calcd for $C_{25}H_{22}N_4O_6S$, C, 59.28; H, 4.38; N, 11 .06; S, 6.33. Found C, 59.37; H, 4.49; N, 10.94; S, 6.32; MS found no molecular ion peak.

1-Acetyl-3-thiophenyl-5-(2,4-dinitrophenyl)aminobenz[*c*,*d*]indole (19): In a 100 mL. 2-necked r.b. flask were dissolved 200 mg (0.40 mmol) of the hydroxyindolene (**18**) in 6 mL of pyridine. To the solution was added 169 mg of phosphorous pentachloride (0.81 mmol) and the reaction stirred for 10-1 5 min. The brown reaction mixture was poured into 50 mL of water and extracted with 5 x 25 mL portions of CH_2Cl_2. The organic layers were combined and washed with 25 mL of brine. The organic layer was dried with $MgSO_4$ and concentrated in vacuo. The resulting product was washed with 2 x 5 mL portions of benzene followed by concentration to remove the remaining pyridine. Column chromatography of the crude product using CH_2Cl_2 as the eluent gave 171 mg (88.4 %) of the indole as a bright yellow solid: mp 218-219 °C. The reaction can be done on a large scale (approximately 15 g) and the product precipitated by addition of water. The product is then washed with cold methanol to yield a useable product in slightly lower yield of 80%. NMR (^{1}H 300 MHz $CDCl_3$) δ 9.2 (d, 1H, J=2.6 Hz), 8.95 (d, 1H, J=8.2 Hz, Ar-N-H), 8.25 (dd, 2H, J = 2.5 Hz, 9.4 + m, 1H, Ar-H), 7.4-7.6 (m, 6H, Ar-H), 7.3 (m, 1H), 7.1 (bs, 1H, indole-H), 7.0 (d, 1H, J=9.6 Hz), 5.6 (m, 1H, benzylic next to Ar-N-H), 4.95 (m, 1H, next to S-Ph), 2.7 (m, 1H, 1⁄2-CH_2), 2.6 (s, 3H, N-Ac), 2.35 (m, 1H, 1⁄2-CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3, 148.0, 136.5, 134.0, 133.7, 133.1, 131.1, 130.7, 129.5, 129.2, 128.4, 127.7, 126.6, 124.4, 120.7, 118.3, 117.4, 116.3, 114.2, 48.5, 38.9, 35.5, 23.8. HRMS (CI) calcd for $C_{25}H_{20}N_4O_5S$ 488.1154, found 488.1197. Anal. Calcd for $C_{25}H_{20}N_4O_5S$, C, 61.47; H, 4.13; N, 11.47. Found C, 61.38; H, 4.04; N, 11.36.

1-Acetyl-2-hydroxy-6-(2,4-dinitrophenyl)amino-10a-methoxy-2,2,2a,6,6a,7,8,9,10,10-decahydro-napth[1,2,3-*c*,*d*]indole (27): In a dry 100 mL 2-neck round bottom flask fitted with a magnetic bar, stopper, condenser, and argon inlet was dissolved 390 mg (1.00 mmol) of 2-(2,4-dinitrophenyl)-5-acetylaminoisoquinolinium chloride (**17**) in 3 mL of anhydrous methanol. To the solution was added 700 mg (6.99 mmol) of freshly flame dried $CaCO_3$. To the stirred suspension was added 190 mg (1.69 mmol) of methoxycyclohexene. The reaction mixture was stirred at 40 °C under an argon atmosphere. Over a three day period two more additions of 190 mg (1.69 mmol) of methoxycyclohexene were added to the reaction mixture until the isoquinolinium salt was consumed. To the reaction mixture was added 10 mL of CH_2Cl_2 and the reaction mixture was filtered through a sintered funnel to remove the $CaCO_3$. The filter pad was washed with 4 x 10 mL of dimethoxyethane: CH_2Cl_2 (1:1) and the reaction mixture concentrated in vacuo. The reaction mixture was dissolved in a mixture if THF / H_20 (10 :1) and 2 ml of 0.01 N HCl added. The reaction mixture was stirred at rt for 24 hours under an argon atmosphere. The hydroxyindoline was precipitated by addition of cold water and isolation was accomplished by filtration. The product was washed with 2 x 3 mL of cold methanol followed by 2 x 5 mL of petroleum ether. After drying 265 mg (54.9 %) of the indoline (**27**) was obtained as a bright yellow solid. NMR (^{1}H 300 MHz DMSO-d_6) showed the presence of two diastereomers in approximately 5:1 ratio. Selected NMR data are

as follows: Major isomer: δ 8.45 (d, 1H, J = 8.6 Hz, N-H, 3.68 (d, 1H, J=6.9 Hz, C2a-H), 2.89 (s, 3H, OCH_3), 2.18 (s, 3H, Acetyl- CH_3) Minor Isomer: δ 8.56 (d, 1H, J=8.6 Hz, N-H), 3.78 (m, 1H, C2a-H), 2.93 (s, 3H, O CH_3), 2.22 (s, 3H, Acetyl- CH_3). MS found no molecular ion.

1-Acetyl-6-(2,4-dinitrophenyl)amino-10a-methoxy-2,6,6a,7,8,9,10,10a-octahydronapth[1,2,3-*c*,*d*]-indole (28): In a dry 100 mL 2-neck round bottom flask fitted with a magnetic bar, stopper, and argon inlet were dissolved 242 mg (0.502 mmol) of the indoline (**27**) in 10 mL of pyridine. To the solution were added 108 mg of phosphorus pentachloride. The reaction mixture was stirred for 1.5 h at rt under an argon atmosphere. The reaction mixture was poured into a 250 mL separatory funnel containing 50 mL of water. The aqueous layer was extracted with 1 x 75 mL and 2 x 50 mL portions of CH_2Cl_2. The organic layers were combined, washed with 1 x 50 mL of water, and 2 x 50 mL of brine. The organic layer was dried and concentrated to give a yellow-brown oil. The oil was azeotroped with 3 successive portions of toluene in order to remove the residual pyridine. Radial chromatography (silica gel) with chloroform provided 152 mg (62%) of the indole as a bright yellow solid: mp 183-185 °C. NMR (^{1}H 300 MHz $CDCl_3$) δ 10.46 (bs, 1H, N-H), 9.07 (d, 1H, J = 2.8 Hz, Ar-H), 8.28 (dd, 1H, J = 2.6, 9.6 Hz, Ar-H), 8.13 (bs, 1H, Ar-H), 7.47 (bs, 1H, Ar-H), 7.40 (d, 1H, J = 9.7 Hz, Ar-H), 7.25-7.38 (m, 2H, Ar-H), 4.89 (d, 1H, J =8.8 Hz, C5-H), 3.23 (s, 3H, OCH_3), 2.67 (s, 3H, Acetyl- CH_3), 2.65 (m, 1H, 1/2-C10CH_2), 2.46 (m, 1H, 1/2-C6CH_2), 1.78 (m, 1 H, 1/2-C9CH_2), 1.5-1.7 (m, 3H, 1/2-C7CH_2, 1/2-C8CH_2, 1/2-C10CH_2), 1.3-1.38 (m, 1H, 1/2-C8CH_2), 1.13-1.23 (m, 1H, 1/2-C9CH_2), 0.78-0.93 (m, 1H, 1/2-C7CH_2). NMR (^{13}C 75 MHz $CDCl_3$) δ 168.4, 146.6, 135.1, 130.2, 130.0, 128.2, 126.5, 125.0, 122.3, 121.6, 116.0-116.5 (appears to be 3 quaternary carbons-not well separated), 113.2, 76.1, 54.8, 48.8, 48.0, 31.8, 29.2, 25.0, 24.0, 23.2 pm. HRMS (CI) calcd for $C_{24}H_{24}N_4O_6$ 464.1696, found 464.1685.

REFERENCES

1. D. A. Horton, G. T. Bourne, and M. L. Smythe, *Chem. Rev,* 2003, **103**, 893.
2. A. Padwa, S. K. Bur, and H. Zhang, *J. Org. Chem.,* 2005, **70**, 6833.
3. C. M. Coleman and D. F. O'Shea, *J. Am. Chem. Soc.,* 2003, **125**, 4054.
4. H. Oguri and S. L. Schreiber, *Org. Lett.,* 2005, **7**, 47.
5. R. B. Gupta and R. W. Franck, *J. Am. Chem. Soc.,* 1989, **111**, 7668.
6. V. Bolitt, C. Mioskowski, R. O. Kollah, S. Manna, D. Rajapaksa, and J. R. Falck, *J. Am. Chem. Soc.*, 1991, **113**, 6320.
7. R.W. Franck and R. B. Gupta, *Tetrahedron Lett.*, 1985, **26**, 293.
8. R. B. Gupta and R.W. Franck, *J. Am. Chem. Soc.*, 1987, **109**, 5393.
9. H. Yin, R. W. Franck, S-l. Chen, G. J. Quigley, and L. Todaro, *J. Org. Chem.*, 1992, **57**, 644.

10. J. J. Craig and W. E. Cass, *J. Am. Chem. Soc.*, 1942, **64**, 783.

11. R. B. Gupta, R. W. Franck, K. D. Onan, and C. E. Soll, *J. Org. Chem.,* 1989, **54**, 1097.

12. Clifford E. Soll Cycloadditions of isoquinolinium salts: a new route to benz[*c*,*d*]indoles. City Univ. New York, New York, NY, USA. *Diss. Abstr. Int. B* **1991**, *52*846, CAN 116:41276

13. G. P. Gisby, P. G. Sammes, and R. A. Watt, *J. Chem. Soc., Perkin Ttrans. 1*, 1982, 249.

14. H. Muratake and M. Natsume, *Tetrahedron,* 1990, **46**, 6331 and following papers from the Natsume lab.