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Spiroquinazoline support studies: methods for the preparation of imidazoloindolines from oxindoles

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Abstract—Two methods for the annulation of glycine to the 1 and 2 positions of oxindoles are described. The first method involves introduction of an α-azidoacetyl group on the oxindole nitrogen followed by an intramolecular Staudinger reaction to complete the annulation. The second method involves acylation of the oxindole nitrogen with an *N*-Cbz–glycine derivative followed by reduction of the oxindole carbonyl group and subsequent cyclization to provide an imidazoloindoline.

1. Introduction

Imidazoloindolines appear as a substructure in a variety of alkaloids including the tryptoquivalines,[1] asperlicins,[2] and fumiquinazolines.[3] Several years ago we hoped to accomplish the synthesis of structurally unique alkaloid spiroquinazoline (**2**)[4] from the spirooxindole alkaloid alantrypinone (**1**) via reductive annulation of a glycine residue to the 1 and 2 positions of an oxindole (Fig. 1).[5,6] In support of this idea we developed several methods for accomplishing this task. This paper describes the results of these studies and introduces *p*-nitrophenyl 2-azidoacetate as a new reagent for the N-acylation of amides.

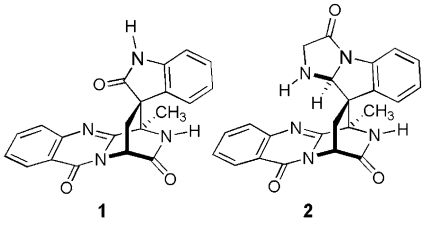

Figure 1. Alantrypinone (**1**) and Spiroquinazoline (**2**).

2. Results and discussion

Our initial studies focused on the transformation of 3,3-dimethyloxindole (**3**) to imidazoloindoline **7** and involved an intramolecular Staudinger reaction largely developed by Eguchi for use in heterocycle synthesis (Scheme 1).[6,7] Thus, the anion derived from deprotonation of known oxindole **3**[8] was acylated using α-chloroacetyl chloride to provide **4** in 90% yield. Treatment of **4** with sodium azide in DMSO gave **5** in 70% yield along with 10% of oxindole **3**. Thus imide N-deacylation is a minor problem in this reaction. Treatment of **5** with triphenylphosphine provided the expected intramolecular Staudinger product **6** in 92% yield. Borch reduction of **6** with sodium cyanoborohydride completed the desired four-step annulation and provided **7** in quantitative yield.[9]

An alternative method for converting **3** into **7** involved initial acylation of the anion derived from **3** with *p*-nitrophenyl *N*-Cbz–glycinate[10] to provide imide **8** in 88% yield. It is notable that in structurally related *N*-acyl oxindoles with *gem*-dimethyl substitution at C_α, the *N*-Cbz group readily adds to the oxindole carbonyl group.[11] Compound **8** exists entirely in the acyclic form as shown in Scheme 1. It was speculated that treatment of **8** with triethylsilane in the presence of an appropriate acid might effect sequential cyclization of the glycine derived nitrogen onto the oxindole carbonyl group, ionization of the resulting carbinol, and reduction of the resulting *N*-acyliminium ion to provide **7**.[10] In reality, treatment of **8** with triethylsilane (4 equiv) in dichloromethane/trifluoroacetic acid (10:1) provided only deacylation product **3**. Treatment of **8** with boron trifluoride etherate (8 equiv) and triethylsilane (2 equiv) in dichloromethane at room temperature returned only the starting imide. On the other hand, saturation of a dichloromethane solution of **8** with BF_3 gas at −78 °C in the presence of triethylsilane (2 equiv), followed by gradual addition of another 4 equiv of triethylsilane and an aqueous workup, gave carbinol **9** in 79% yield. Treatment of **9** with *p*-toluenesulfonic acid in benzene provided **10** and hydrogenolysis of the *N*-Cbz group provided **7** in 98% overall yield.

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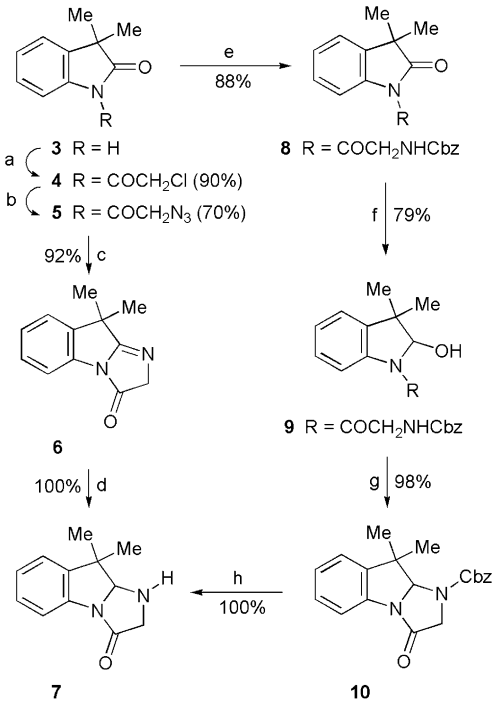
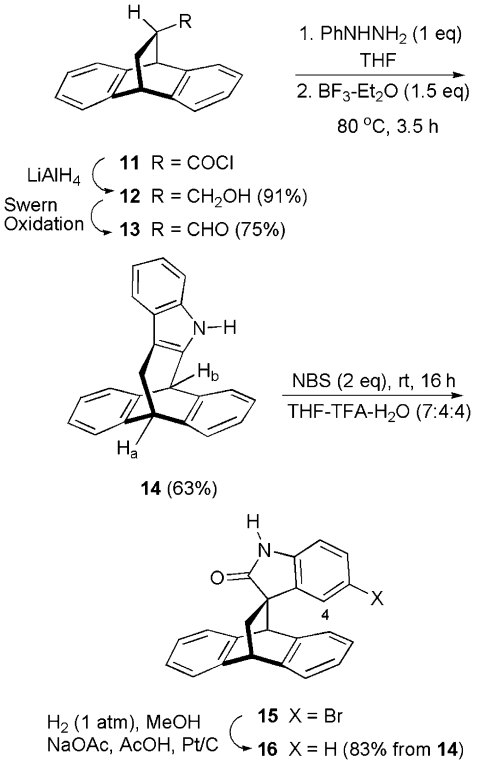


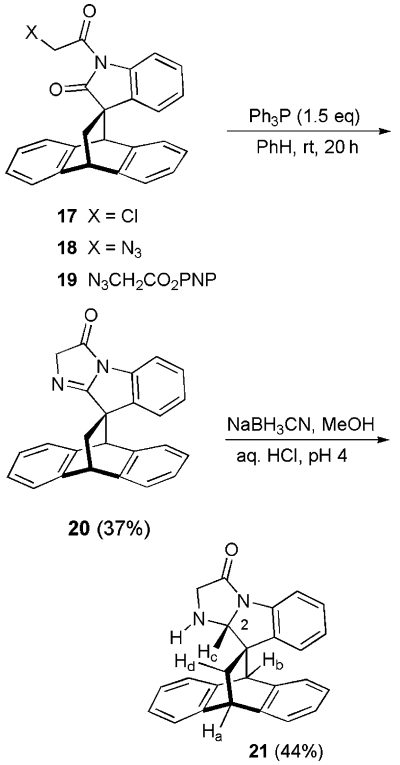
Scheme 1. Two methods for preparing **7** from oxindole **3**: (a) *n*-BuLi, THF, −78 °C; $ClCH_2COCl$ (5 equiv), −78 °C; (b) NaN_3 (4 equiv), DMSO, rt, 20 min; (c) Ph_3P (1.1 equiv), PhH, rt, 2 h; (d) $NaBH_3CN$, MeOH, aq HCl, pH 4, rt; (e) *n*-BuLi, THF, −78 °C; $CbzNHCH_2CO_2PNP$ (1.5 equiv), −78 °C; (f) Et_3SiH (6 equiv), BF_3 (excess), CH_2Cl_2, −78 °C; (g) *p*-TsOH monohydrate, PhH, 80 °C, 30 min and (h) H_2 (1 atm), 10% Pd/C, EtOAc, 3 h.

Our next studies focused on a substrate more closely related to alantrypinone. Thus oxindole **16** was prepared as shown in Scheme 2.[6] The Diels–Alder reaction between acryloyl chloride and anthracene provided acid chloride **11**. Reduction of **11** with lithium aluminum hydride provided alcohol **12** in 91% overall yield from anthracene.[12] Swern oxidation of **12** provided **13** in 75% yield,[13,14] and treatment of **13** with phenylhydrazine in the presence of boron trifluoride etherate gave indole **14** in 63% yield.[15] The regiochemistry of the indole was established using difference NOE experiments. For example irradiation of H_a led to enhancement of the signal for the adjacent methylene and irradiation of H_b led to enhancement of the indole NH. Ring contraction of **14** to oxindole **16** was accomplished using a standard procedure followed by reduction of the intermediate aryl bromide **15** using platinum on carbon.[5,16] It is notable that H_4 of the oxindole aromatic ring in **15** appeared as an upfield singlet (δ 5.0), as one would expect based on its position relative to the dihydroanthracene substructure, and as observed for the analogous proton in 21-*epi*-alantrypinone.[5] The chemical shift of this proton served as an analytical landmark through the remainder of the chemistry described in this paper.

We next examined the intramolecular Staudinger annulation protocol as described in Scheme 3.[6] Acylation of the anion derived from **16** with chloroacetyl chloride provided imide **17** in 40% yield. Treatment of **17** with sodium azide in DMSO, however, failed to provide the desired azide **18**. Only oxindole **16** was obtained in 66% yield. Thus N-deacylation was more problematic with **17** than with substrate **4** (Scheme 1). Introduction of the azido group in the acylating agent circumvented this problem. Rather than using the well known, but hazardous, azidoacetyl chloride as an acylating agent,[17] we decided to examine *p*-nitrophenyl azidoacetate (**19**) as an acylating agent. This new crystalline reagent was prepared by DCC coupling of azidoacetic acid[18] with *p*-nitrophenol in 64% yield. Sequential treatment of



Scheme 2. Preparation of oxindole **16**.



Scheme 3. Preparation of **21**.

oxindole **16** with *n*-BuLi and **19** provided **18** in 40% yield. Treatment of **18** with a slight excess of triphenylphosphine in benzene at room temperature gave a 37% yield of crystalline cyclization product **20** along with 11% of oxindole **16**. Thus, imide deacylation, as with **4** and **17**, was once again a problem. It is also notable that **20** underwent nearly complete conversion to anthracene upon standing in $CDCl_3$ for 2 h. Nonetheless, reduction of **20** using the Borch conditions provided **21** and the corresponding C_2 epimer in 78% yield as a 5:1 mixture, respectively.[9] Pure **21** (43%) and its epimer (4%) were isolated and difference NOE experiments were used to assign stereochemistry at C_2. For example, irradiation of H_c in **21** showed an enhancement of 3.7% at H_d and of 2.5% at the NH. On the other hand, irradiation of H_c in the C_2 diastereomer of **21** showed an enhancement of 3.3% at H_b and of 2.0% at the NH.

Attempts to apply the annulation methods described above for the conversion of alantrypinone to spiroquinazoline have thus far met with failure. For example, the method that relies on the regioselective reduction of imide **8** provides a complex mixture of unidentifiable products when applied to an appropriate alantrypinone derivative. Perhaps this is not surprising given the presence of numerous Lewis basic sites present in such derivatives. Although we were able to prepare appropriate cyclization substrates from alantrypinone, we were not able to accomplish the key aza-Wittig reaction. Instead, the deacylation reaction mentioned above became dominant reaction pathway.

In spite of this disappointment, the research described herein does provide two routes to analogs of spiroquinazoline. The stereochemical course of the reduction of **20** is also notable and suggests that stereochemical problems may accompany attempts to access spiroquinazoline via reduction of an acylimine. In addition, it was found that compound **10** was a weak inhibitor of Substance-P binding to the human NK-1 receptor, the biological activity that has (in part) rendered spiroquinazoline an interesting target for total synthesis.[19] Nonetheless, the quest for other methods (and variations of the methods described herein) for converting alantrypinone to spiroquinazoline and related alkaloids[20] continues in our laboratories.

3. Experimental

3.1. General

All compounds were prepared as racemic mixtures. Melting points are uncorrected. Solvents were dried using standard protocols. All carbon multiplicities (s=C, d=CH, t=CH_2, and q=CH_3) were determined using DEPT techniques. COSY and NOE experiments were used to support NMR peak assignments. Mass spectra were recorded using EI (electron impact) or ESI (electrospray ionization) techniques as indicated.

3.1.1. 1-(Chloroacetyl)-3,3-dimethyl-2-indolinone (4). To a stirred solution of 310 mg (1.90 mmol) of oxindole **3**[8] in 12 mL of dry THF, cooled to −78 °C, was added dropwise 1.66 mL (2.66 mmol) of a 1.6 M solution of *n*-BuLi in hexanes over a period of 3 min. After 10 min at −78 °C, 757 μL (9.50 mmol) of freshly distilled chloroacetyl chloride was added in one portion. The reaction mixture was stirred at −78 °C for 1 h, and then partitioned between 120 mL of ethyl acetate and 30 mL of water. The organic layer was sequentially washed with two 40-mL portions of saturated aqueous $NaHCO_3$, 30 mL of water, dried ($MgSO_4$), and concentrated in vacuo. The residue was recrystallized from a mixture of CH_2Cl_2 and hexanes to give 260 mg (58%) of **4** as a white crystalline solid. The mother liquor was concentrated and the residue was flash chromatographed over 10 g of silica gel (EtOAc/hexanes, 1:3) to give additional 140 mg (32%) of **4**: mp 139.0–140.0 °C (recrystallized from CH_2Cl_2/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.46 (s, 6H, $2CH_3$), 4.86 (s, 2H, CH_2Cl), 7.23–7.26 (m, 2H, ArH), 7.28–7.37 (m, 1H, ArH), 8.24 (ddd, J=8.1, 0.9, 0.9 Hz, 1H, H7).

3.1.2. 1-(Azidoacetyl)-3,3-dimethyl-2-indolinone (5). To a vigorously stirred solution of 435 mg (1.68 mmol) of **4** in 8 mL of DMSO was added 438 mg (6.73 mmol) of NaN_3 in one portion. The reaction mixture was stirred at room temperature for 20 min, then poured into 30 mL of water, and extracted with 150 mL of ethyl acetate. The organic solution was washed with four 30-mL portions of water, dried ($MgSO_4$), and concentrated in vacuo to give an orange liquid, which solidified under high vacuum (1 mm of Hg). The solid was flash chromatographed over 15 g of silica gel (Et_2O/hexanes, 1:3, then 1:2) to provide 380 mg (85%) of azide **5** as a white solid in addition to 43 mg (10%) of oxindole **3**. An analytically pure sample of **5** as a white crystalline solid (300 mg or about 80% recovery) was obtained by recrystallization from a mixture of Et_2O and hexanes: mp 101–102 °C; IR (KBr) 2172, 2110, 1757, 1712, 1606 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.45 (s, 6H, $2CH_3$), 4.62 (s, 2H, $COCH_2$), 7.23–7.27 (m, 2H, ArH), 7.28–7.38 (m, 1H, ArH), 8.28 (ddd, J=8.1, 0.9, 0.9 Hz, 1H, H7); ^{13}C NMR (acetone-d_6, 75.5 MHz) δ 25.5 (q), 45.2 (s), 55.1 (t), 117.0 (d), 123.5 (d), 126.5 (d), 128.9 (d), 136.5 (s), 139.4 (s), 170.1 (s), 182.7 (s); mass-spectrum (EI), *m*/*z* (relative intensity) 244 (M^+, 16), 161 (100); Anal. calcd for $C_{12}H_{12}N_4O_2$: C, 59.05; H, 4.96. Found: C, 59.18; H, 4.90.

3.1.3. 2,9-Dihydro-9,9-dimethyl-3*H*-imidazo[1,2-*a*]-indole-3-one (6). To a stirred solution of 220 mg (0.90 mmol) of azide **5** in 6 mL of benzene was added 260 mg (0.99 mmol) of solid triphenylphosphine in one portion. The reaction mixture was stirred at room temperature for 2 h, after which time TLC (silica gel, EtOAc/hexanes, 1:1) indicated complete consumption of starting material. The reaction mixture was concentrated in vacuo and the residue was flash chromatographed over 50 g of silica gel (EtOAc/hexanes, 2:1) to give 165 mg (92%) of imidazoline **6** as a white solid. Sublimation at 1 mm of Hg and 100 °C provided an analytically pure sample of **6** as a white crystalline solid: mp 138–139 °C (sublimed); IR (KBr) 1731, 1673, 1665, 1610 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.56 (s, 6H, $2CH_3$), 4.53 (s, 2H, $COCH_2$), 7.19 (ddd, J=7.5, 7.5, 1.2 Hz, 1H, ArH), 7.29 (ddd, J=7.5, 1.2, 0.6 Hz, 1H, ArH), 7.31 (ddd, J=7.5, 7.5, 1.4 Hz, 1H, ArH), 7.60 (dm, J=7.8 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 26.3 (q), 40.6 (s), 66.2 (t), 112.8 (d), 123.4 (d), 125.6 (d), 128.5 (d), 134.3 (s), 140.9 (s), 174.8 (s), 176.7 (s); mass-spectrum (EI), *m*/*z* (relative intensity) 200 (M^+, 44), 172 (100); Anal.

calcd for $C_{12}H_{12}N_2O$: C, 72.03; H, 6.05. Found: C, 72.12; H, 6.29.

3.1.4. 1,2,9,9a-Tetrahydro-9,9-dimethyl-3*H*-imidazo[1,2-*a*]indole-3-one (7). From **6**: to a stirred solution of 145 mg (0.725 mmol) of imidazoline **6**, a tiny amount of bromocresol green (just to get a green solution), and 45 mg (0.750 mmol) of $NaBH_3CN$ (addition of hydride changes green solution color to blue) in 10 mL of MeOH was added dropwise 1 N aqueous HCl until the solution became yellow (4–5 drops). Addition of HCl was continued whenever the yellow solution turned blue. The reaction mixture was stirred for 1 h at room temperature, after which time TLC (silica gel, Et_2O/Et_3N, 95:5) still showed the presence of starting material. Additional $NaBH_3CN$ (45 mg, 0.75 mmol) was added until starting material was completely consumed. The reaction mixture was partitioned between 150 mL of EtOAc and 20 mL of saturated aqueous $NaHCO_3$. The organic layer was washed with 15 mL of water, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over 14 g of flash silica gel (Et_2O/Et_3N, 95:5) to give 146 mg (100%) of **7** as a white solid. From **10**: to a solution of 18 mg (0.054 mmol) of **10** in 5 mL of ethyl acetate was added 20 mg of 10% Pd/C. The mixture was stirred at room temperature under 1 atm of H_2 for 3 h. Then the reaction mixture was passed through a 1-cm pad of Celite and concentrated in vacuo to give 11 mg (100%) of amine **7** as a white solid. The hydrochloride of **7** was readily obtained as a white crystalline solid by passing dry HCl through a solution of **7** in ether. Hydrochloride: mp 203–204 °C (dec) (Et_2O). Free base: mp 91.5–92.5 °C; IR (KBr) 3304, 3253, 1708, 1693, 1604 cm^{-1}; ^1H NMR (MeCN-d_3, 300 MHz) δ 1.02 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 2.71 (br s, 1H, NH), 3.55 (d, J=15.7 Hz, 1H, CHH), 3.94 (d, J=15.7 Hz, 1H, CHH), 5.21 (s, 1H, NHCH), 7.12 (tm, J=7.8 Hz, 1H, ArH), 7.2–7.26 (m, 2H, ArH), 7.38 (d, J=7.8 Hz, 1H, ArH); ^{13}C NMR (C_6D_6, 75.5 MHz) δ 23.7 (q), 24.9 (q), 44.6 (s), 54.5 (t), 88.5 (d), 116.2 (d), 123.4 (d), 125.4 (d), 128.4 (d), 138.0 (s), 143.6 (s), 170.9 (s); mass-spectrum (EI), m/z (relative intensity) 202 (M^+, 100); Anal. calcd for $C_{12}H_{15}ClN_2O$ (hydrochloride): C, 60.54; H, 6.35. Found: C, 60.30; H, 6.26.

3.1.5. Benzyl [[(3,3-dimethyl-2-oxo-1-indolinyl)carbonyl]-methyl]carbamate (8). To a stirred solution of 175 mg (1.09 mmol) of oxindole **3** in 5 mL of dry THF, cooled to −78 °C, was added dropwise 885 μL of a 1.6 M solution of *n*-BuLi in hexanes over a period of 2 min. After 10 min at −78 °C, a solution of 538 mg (1.63 mmol) of *p*-nitrophenyl *N*-Cbz–glycinate (**10**) in 3 mL of THF was added by cannula. The reaction mixture was stirred at −78 °C for 20 min, and then left to warm to room temperature. After 4 h at room temperature, the reaction mixture was dissolved in 150 mL of ethyl acetate and washed with two 20-mL portions of 1 M aqueous sodium carbonate. The organic layer was dried ($MgSO_4$), concentrated in vacuo, and the residue was flash chromatographed over 14 g of silica gel (EtOAc/hexanes, 1:3, then 1:2) to give 336 mg (88%) of imide **8** as a white crystalline solid: mp 118.5–119.0 °C; IR (KBr) 3434, 1756, 1724, 1699 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.45 (s, 6H, $2CH_3$), 4.70 (d, J=5.6 Hz, 2H, CH_2NH), 5.17 (s, 2H, OCH_2), 5.52 (br s, 1H, NH), 7.23–7.26 (m, 2H, ArH), 7.27–7.38 (m, 6H, ArH), 8.23 (ddd, J=8.1, 0.9, 0.9 Hz, 1H, H7); ^{13}C NMR (DMSO-d_6, 75.5 MHz) δ 25.4 (q), 44.7 (s), 47.4 (t), 67.2 (t), 116.7 (d), 122.3 (d), 125.8 (d), 128.2 (d), 128.4 (d), 128.6 (d), 135.2 (s), 136.5 (s), 138.2 (s), 156.6 (s), 170.4 (s), 182.1 (s) (one doublet was not seen due to overlap with other peaks); mass-spectrum (EI), m/z (relative intensity) 352 (M^+, 0.15), 161 (100); Anal. calcd for $C_{20}H_{20}N_2O_4$: C, 68.22; H, 5.72. Found: C, 68.05; H, 5.71.

3.1.6. Benzyl [[(2-hydroxy-3,3-dimethyl-1-indolinyl)carbonyl]-methyl]carbamate (9). A solution of 81 mg (0.23 mmol) of imide **8** and 80 μL (0.49 mmol) of Et_3SiH in 8 mL of CH_2Cl_2, cooled to −78 °C, was saturated with gaseous BF_3. The resulting mixture was stirred at −78 °C for 2 h. TLC (EtOAc/hexanes, 1:1) indicated the presence of starting material. Two 20-μL (0.12 mmol) portions of Et_3SiH were added over a period of 1 h to achieve complete consumption of starting material. The reaction mixture was poured into 100 mL of EtOAc and washed with two 30-mL portions of saturated aqueous $NaHCO_3$. The organic layer was dried ($MgSO_4$) and concentrated in vacuo to give 85 mg of colorless amorphous residue. The residue was flash chromatographed over 12 g of silica gel (EtOAc/hexanes, 1:2, then 1:1) to give 65 mg (79%) of **9** as a white solid (**9** solidifies very slowly): mp 136–137 °C: IR (KBr) 3395, 3385, 1699, 1673, 1598 cm^{-1}; ^1H NMR (Me_2CO-d_6, 300 MHz) δ 1.21 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 4.36 (dd, J=17.1, 5.6 Hz, 1H, COCHNH), 4.44 (dd, J=17.1, 5.6 Hz, 1H, COCHHNH), 5.12 (s, 2H, OCH_2), 5.50 (d, J=8.3 Hz, 1H, CHOH, exchangeable), 5.56 (d, J=8.3 Hz, 1H, CHOH), 6.46 (dt, J=5.6 Hz, 1H, NH), 7.06 (ddd, J=7.4, 7.4, 1.1 Hz, 1H, ArH), 7.19 (ddd, J=7.7, 7.7, 1.4 Hz, 1H, ArH), 7.23 (dm, J=7.4 Hz, 1H, ArH), 7.27–7.42 (m, 5H, ArH), 8.08 (br d, J=7.2 Hz, 1H, ArH); ^{13}C NMR (Me_2CO-d_6, 75.5 MHz) δ 20.0 (q), 29.8 (q), 44.4 (t), 45.8 (s), 66.9 (t), 91.9 (d), 117.1 (d), 123.2 (d), 124.9 (d), 128.2 (d), 128.7 (d), 129.2 (d), 138.2 (s), 140.1 (s), 141.2 (s), 157.6 (s), 169.4 (s), one doublet was not seen due to overlap with other signals; mass-spectrum (EI), m/z (relative intensity) 354 (M^+, 3.5), 91 (100); Anal. calcd for $C_{20}H_{22}N_2O_4$: C, 67.83; H, 6.26. Found: C, 67.57; H, 6.37.

3.1.7. Benzyl 2,3,9,9a-tetrahydro-9,9-dimethyl-3-oxo-1*H*-imidazo[1,2-*a*]indole-3-carboxylate (10). To a solution of 194 mg (0.54 mmol) of **9** in 30 mL of benzene was added 10 mg (10 mol %) of *p*-toluenesulfonic acid monohydrate. The resulting mixture was refluxed for 30 min after which time TLC (EtOAc/hexanes, 1:1) indicated complete consumption of starting material. The reaction mixture was cooled to room temperature, passed through a 1-cm pad of basic alumina (Brockman activity II), and concentrated in vacuo to give 180 mg (98%) of imidazolidine **10** as a thick colorless liquid slowly solidifying into a white solid: mp 67–68 °C; IR (KBr) 1725, 1712, 1604 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, 60 °C) δ 1.02 (s, 3H, CH_3), 1.58 (br s, 3H, CH_3), 4.18 (dd, J=16.4, 1.8 Hz, 1H, COCHNH), 4.45 (d, J=16.4 Hz, 1H, COCHHN), 5.22 (1/2 of AB quartet, J=12.2 Hz, 1H, OCHH), 5.27 (1/2 of AB quartet, J=12.2 Hz, 1H, OCHH), 5.62 (d, J=1.8 Hz, 1H, NCHN), 7.14–7.20 (m, 2H, ArH), 7.26 (ddd, J=7.6, 5.5, 3.6 Hz, 1H, ArH), 7.34–7.41 (m, 5H, ArH), 7.51 (ddd, J=7.6, 0.9, 0.9 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 75.5 MHz, 60 °C) δ 23.3 (q), 24.5 (q), 45.9 (s), 52.9 (t), 68.1 (t), 87.1 (d), 116.7 (d),

123.2 (d), 126.3 (d), 128.1 (d), 128.4 (d), 128.7 (d), 128.8 (d), 136.1 (s), 136.5 (s), 142.8 (s), 154.5 (s), 167.3 (s); mass-spectrum (EI), *m/z* (relative intensity) 336 (M^+, 7), 91 (100); Anal. calcd for $C_{20}H_{20}N_2O_3$: C, 71.46; H, 6.00. Found: C, 71.27; H, 5.99.

3.1.8. Indole 14. To a stirred solution of 9.0 g (38.5 mmol) of aldehyde **13** in 100 mL of tetrahydrofuran was added 3.78 mL (4.16 g, 38.5 mmol) of phenylhydrazine. The reaction mixture was stirred for 10 min after which 6.82 mL (7.64 g, 53.85 mmol) of $BF_3 \cdot Et_2O$ was added dropwise over a period of 10 min. The reaction mixture was heated at 80 °C with stirring for 3.5 h. The reaction mixture was partitioned between 150 mL of chloroform and 35 mL of saturated aqueous sodium bicarbonate. The organic layer was washed with two 50-mL portions of saturated aqueous sodium bicarbonate and two 50-mL portions of water. The combined aqueous layers were extracted with 70 mL of chloroform. The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure to afford 11 g of a dark orange solid. This solid was purified by column chromatography over 400 g of silica gel (sample loaded in CH_2Cl_2 and eluted with hexanes/CH_2Cl_2, 99:1; then hexanes/CH_2Cl_2, 2:1; then EtOAc) to give 7.44 g (63%) of indole **14** as a white solid: mp 295–296.5 °C; IR (KBr) 3388 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.22 (d, J=3.7 Hz, 2H, CH_2), 4.47 (t, J=3.6 Hz, 1H, $CHCH_2$), 4.78 (s, 1H, CH), 6.98 (t, J=9.0 Hz, 1H, ArH), 7.05 (t, J=9.0 Hz, 1H, ArH), 7.13 (t, J=8 Hz, 2H, ArH), 7.15 (t, J=8.5 Hz, 2H, ArH), 7.21 (d, J=7 Hz, 1H, ArH), 7.28 (m, 3H, ArH), 7.46 (d, J=6 Hz, 2H, ArH), 7.96 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 31.1 (t), 46.4 (d), 47.4 (d), 104.4 (s), 111.0 (d), 117.8 (d), 119.9 (d), 121.6 (d), 124.4 (d), 126.5 (d), 127.0 (d), 127.2 (d), 130.1 (s), 134.5 (s), 136.5 (s), 141.6 (s), 144.7 (s); exact mass (ESI) calcd for $C_{23}H_{17}NNa^+$: *m/z* 330.1259, observed: *m/z* 330.1253. Anal. calcd for $C_{23}H_{17}N$: C, 89.86; H, 5.58; N, 4.56. Found: C, 89.71; H, 5.82; N, 4.61.

3.1.9. Bromooxindole 15. To a stirred solution of 107.5 mg (0.35 mmol) of indole **14** in 15 mL of a mixture of THF/TFA/H_2O (7:4:4) cooled to 3 °C was added 62 mg (0.35 mmol) of *N*-bromosuccinimide. The reaction was allowed to stir for 1.5 h at 2–3 °C after which another 62 mg (0.35 mmol) of *N*-bromosuccinimide was added. The reaction was allowed to stir for a total of 7.5 h at 2–3 °C. The reaction mixture was partitioned between 50 mL of saturated aqueous sodium bicarbonate and 200 mL of ethyl acetate. The organic layer was washed with two 50-mL portions of water, dried ($MgSO_4$), and concentrated under reduced pressure to afford 121 mg of a beige solid. This material was normally used in subsequent reactions without further purification. For characterization purposes this solid was purified by column chromatography over 15 g of flash silica (eluted with hexanes/ethyl acetate 9:1, then 4:1) to give 57 mg (53%) of bromospirooxindole **15** as a white solid: mp 208–211 °C; IR (KBr) 1716, 1614 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 1.84 (dd, J=11.2, 3.0 Hz, 1H, CH_2), 2.03 (dd, J=11.2, 3.0 Hz, 1H, CH_2), 4.08 (s, 1H, CH), 4.60 (t, J=8.2 Hz, 1H, $CHCH_2$), 5.01 (d, J=2.1 Hz, 1H, ArH), 6.75 (d, J=8.1 Hz, 1H, ArH), 7.08 (m, 4H, ArH), 7.19 (dd, J=10.2, 2.0 Hz, 1H, ArH), 7.25 (m, 2H, ArH), 7.34 (d, J=1.2 Hz, 1H, ArH), 7.50 (d, J=7.0 Hz, 1H, ArH), 10.4 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 62 MHz) δ 39.9 (t), 43.5 (d), 51.8 (s), 52.0 (d), 111.1 (d), 112.7 (s), 123.0 (d), 123.9 (d), 125.41 (d), 125.49 (d), 126.0 (d), 126.5 (d), 126.8 (d), 127.1 (d), 130.5 (d), 136.6 (s), 139.6 (s), 141.14 (s), 141.16 (s), 144.1 (s), 144.2 (s), 179.2 (s) (one aromatic CH obscured by solvent); exact mass (ESI) calcd for $C_{23}H_{16}N^{79}BrNa^+$: *m/z* 424.0307, observed; *m/z* 424.0329.

3.1.10. Oxindole 16. To a stirred solution of 1.0 g (3.26 mmol) of indole **14** in 100 mL of a mixture of THF/TFA/H_2O (60:20:20) cooled to 3 °C was added 1.16 g (6.51 mmol) of *N*-bromosuccinimide. The reaction was allowed to reach room temperature and stirred for 16 h after which it was filtered. The filtrate was partitioned between 150 mL of saturated aqueous sodium bicarbonate and 200 mL of ethyl acetate. The organic layer was washed with two 50-mL portions of saturated aqueous sodium bicarbonate and two 40-mL portions of water, dried ($MgSO_4$), and concentrated under reduced pressure to afford 1.17 g of bromooxindole **15** as a beige solid. To a stirred solution of 1.15 g (2.71 mmol) of bromooxindole **15** in 770 mL of methanol was added 4.64 g (56.6 mmol) sodium acetate, 9.3 mL (9.76 g, 162.6 mmol) of acetic acid and 0.9 g of 5% platinum on carbon. The system was placed under a hydrogen atmosphere for 72 h. The reaction mixture was filtered through a short pad of Celite 545 and the filtrate was concentrated to give a white solid. The solid was partitioned between 200 mL of ethyl acetate and 50 mL of water. The organic layer was washed with five 40-mL portions of water, dried ($MgSO_4$) and concentrated under reduced pressure to afford 0.99 g (83%) of oxindole **16** as a white solid: mp 215–216 °C; IR (KBr) 3231, 1718 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 1.83 (dd, J=13.1, 2.0 Hz, 1H, CH_2), 2.05 (dd, J=13.1, 2.0 Hz, 1H, CH_2), 4.04 (s, 1H, CH), 4.58 (t, J=5.2 Hz, 1H, $CHCH_2$), 5.05 (d, J=8.0 Hz, 1H, ArH), 6.55 (t, J=7.0 Hz, 1H, ArH), 6.78 (d, J=7.8 Hz, 1H, ArH), 6.98 (d, J=7.0 Hz, 1H, ArH), 7.08 (m, 4H, ArH), 7.18 (d, J=6.0 Hz, 1H, ArH), 7.23 (td, J=8.1, 1.0 Hz, 1H, ArH), 7.33 (d, J=6.0 Hz, 1H, ArH), 7.48 (d, J=8.0 Hz, 1H, ArH), 10.25 (br s, 1H, ArH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 39.6 (t), 43.3 (d), 51.0 (s), 51.8 (d), 108.9 (d), 120.4 (d), 122.6 (d), 123.3 (d), 123.6 (d), 124.9 (d), 125.0 (d), 125.5 (d), 126.0 (d), 126.2 (d), 126.3 (d), 127.5 (d), 133.9 (s), 139.7 (s), 141.0 (s), 141.4 (s), 143.8 (s), 144.0 (s), 179.4 (s); exact mass (ESI) calcd for $C_{23}H_{17}NONa^+$: *m/z* 346.1202, found: *m/z* 346.1200.

3.1.11. *p*-Nitrophenyl α-azidoacetate (19). To a solution of 0.92 g (9.12 mmol) of azidoacetic acid in 10 mL of dichloromethane was added 1.15 g (8.29 mmol) of *p*-nitrophenol and 50 mg (0.415 mmol) of 4-dimethylaminopyridine. The solution was stirred for 5 min and 1.80 g (9.12 mmol) of DCC in 5 mL of dichloromethane was added dropwise over a period of 30 min. The mixture was stirred for 2 h at room temperature. The resulting mixture was filtered and the filtrate was concentrated to give a yellow solid. The residue was purified by recrystallization from 90 mL of hexanes/ether (2:1) to give 1.17 g (64%) of *p*-nitrophenyl α-azidoacetate (**19**) as a white solid: mp 81–82.5 °C; IR (KBr) 3111, 2115, 1763, 1616 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.19 (s, 2H, $COCH_2$), 7.33–7.38 (m, 2H, ArH), 8.27–8.33 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 50.4 (t), 122.3 (d), 125.4 (d), 145.8 (s), 154.7 (s), 166.3 (s); mass-spectrum

(EI), *m*/*z* (relative intensity) 222 (M^+, 2), 109 (100); Anal. calcd for $C_8H_6N_4O_4$: C, 43.28; H, 2.72. Found: C, 43.37; H, 2.69.

3.1.12. Imide 18. To a stirred solution of 76 mg (0.24 mmol) of spirooxindole **16** in 4 mL of tetrahydrofuran cooled to −70 °C was added 195 μL (0.27 mmol) of *n*-butyllithium (1.3 M in hexanes). The solution was stirred for 20 min and then 68 mg (0.31 mmol) of *p*-nitrophenyl α-azidoacetate (**19**) in 2 mL of tetrahydrofuran was added. The reaction mixture was stirred at −70 °C for 30 min, then at room temperature for 2 h. The reaction mixture was partitioned between 60 mL of ethyl acetate and 20 mL of water. The organic layer was washed with three 20-mL portions of water, dried ($MgSO_4$), and concentrated under reduced pressure to afford 150 mg of solid. This solid was purified by column chromatography over 5 g of silica (eluted with EtOAc/hexanes, 1:8, then 1:4) to give 33 mg (40%) of imide **18** as a white solid: mp 169–171 °C (dec); IR (KBr) 2120, 1753, 1716 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.94 (dd, J=12.6, 2.8 Hz, 1H, CH_2), 2.26 (dd, J=12.6, 2.8 Hz, 1H, CH_2), 3.96 (s, 1H, $CHAr_2$), 4.39 (s, 2H, CH_2N_3), 4.47 (t, J=2.3 Hz, 1H, $CHCH_2$), 5.25 (d, J=7.6 Hz, 1H, ArH), 6.78 (d, J=7.3 Hz, 1H, ArH), 6.85 (d, J=8.3 Hz, 1H, ArH), 7.12 (m, 6H, ArH), 7.35 (m, 2H, ArH), 8.13 (d, J=8.1 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 62 MHz) δ 41.1 (t), 44.2 (d), 52.4 (s), 53.9 (d), 54.6 (t), 115.8 (d), 123.1 (d), 123.5 (d), 124.0 (d), 125.0 (d), 125.7 (d), 125.9 (d), 126.8 (d), 126.9 (d), 127.1 (d), 128.3 (d), 132.7 (s), 138.1 (s), 138.4 (s), 139.1 (s), 143.3 (s), 143.8 (s), 168.4 (s), 179.2 (s) (one aromatic CH obscured by solvent); exact mass (ESI) calcd for $C_{25}H_{18}N_4O_2Na^+$: *m*/*z* 429.1321, found: *m*/*z* 429.1302.

3.1.13. *N*-Acylamidine 20. To a stirred solution of 129 mg (0.32 mmol) of azide **18** in 4 mL of benzene was added 127 mg (0.47 mmol) of triphenylphosphine in 2 mL of benzene. The mixture was stirred for 20 h. The resulting precipitate was collected by suction filtration to give 35 mg (32%) of imidazolinone **20** as a white solid. The filtrate was concentrated in vacuo to give a mixture of oxindole **16**, triphenylphosphine oxide and *N*-acylamidine **20**. The mixture was purified by column chromatography over 10 g of silica (eluted with EtOAc/Hexanes, 1:2) to give 13 mg (11%) of oxindole **16** and 5.9 mg (5%) of *N*-acylamidine **20** as a white solid: mp 202–203 °C (dec); IR (KBr) 1737, 1654 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 1.85 (dd, J=12.6, 2.8 Hz, 1H, CH_2CH), 2.32 (dd, J=12.6, 2.8 Hz, 1H, CH_2CH), 3.60 (s, 1H, $CHAr_2$), 3.92 (d, J=22 Hz, 1H, $CH_2C{=}O$), 4.05 (d, J=22 Hz, 1H, $CH_2C{=}O$), 4.13 (t, J=2.6 Hz, 1H, $CHCH_2$), 5.44 (d, J=8.1 Hz, 1H, ArH), 6.62 (d, J=7.3 Hz, 1H, ArH), 6.83 (d, J=8.1 Hz, 1H, ArH), 6.97 (m, 2H, ArH), 7.08 (m, 4H, ArH), 7.17 (s, 1H, ArH), 7.76 (d, J=7.8 Hz, 1H, ArH), the remaining ArH was obscured by the benzene; ^{13}C NMR (C_6D_6, 125 MHz) δ 42.9 (t), 44.7 (d), 48.0 (s), 53.6 (d), 65.7 (t), 112.1 (d), 123.4 (d), 123.6 (d), 124.2 (d), 125.2 (d), 125.7 (d), 125.8 (d), 126.7 (d), 127.0 (d), 126.98 (d), 135.7 (s), 138.8 (s), 139.4 (s), 140.5 (s), 143.9 (s), 144.5 (s), 172.3 (s), 174.5 (s), the remaining two aromatic carbons (CH) were obscured by the benzene; exact mass (ESI) calcd for $C_{25}H_{18}N_2O^+$: *m*/*z* 362.1413, found: *m*/*z* 362.1445.

3.1.14. Imidazoloindolines 21 and 2-*epi*-21. To a stirred solution of 57 mg (157 μmol) of imidazolinone **20** in 22 mL of methanol, was added four drops of bromocresol green indicator solution (0.04 g of the indicator in 100 mL of 95% EtOH and 0.1 M aqueous NaOH until blue) and 21 mg (315 μmol) of sodium cyanoborohydride. The reaction was kept at pH 4, maintaining the yellow color by the dropwise addition of 3 N aqueous hydrochloric acid. The reaction was stirred at room temperature for 5.5 h. The reaction mixture was partitioned between 200 mL of ethyl acetate and 60 mL of saturated aqueous sodium bicarbonate. The organic layer was washed with two 50-mL portions of saturated aqueous sodium bicarbonate and 30 mL of water, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed over 30 g of silica (loaded in EtOAc and eluted with EtOAc/hexanes, 1:3) to give 24.8 mg (43%) of imidazoloindoline **21** as a white solid, 18.2 mg of a 7:4:1 mixture of imidazoloindoline **21**, the C_2 epimers of **21** and oxindole **16**, respectively, and 2 mg (4%) of the C_2 epimer of **21** as a white solid. Imidazoloindoline **21**: mp 259.5–260 °C (dec); IR 3432, 1708 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 0.43 (br s, 1H, NH), 1.70 (dd, J=12.9, 2.1 Hz, 1H, CH_2), 2.10 (dd, J=12.9, 2.1 Hz, 1H, CH_2), 3.13 (d, J=14.3 Hz, 1H, CH_2N), 3.41 (d, J=14.3 Hz, 1H, CH_2N), 4.01 (t, J=2.3 Hz, 1H, $CHCH_2$), 4.14 (s, 1H, $CHAr_2$), 4.52 (s, 1H, CHNH), 5.22 (d, J=7.5 Hz, 1H, ArH), 6.53 (td, J=7.7, 0.8 Hz, 1H, ArH), 6.62 (d, J=7.3 Hz, 1H, ArH), 6.88 (t, J=7.8 Hz, 1H, ArH), 6.95 (m, 5H, ArH), 7.09 (d, J=7.2 Hz, 2H, ArH), 7.87 (d, J=7.7 Hz, 1H, ArH); ^{13}C NMR (C_6D_6, 125 MHz) δ 45.0 (d), 45.8 (t), 50.3 (d), 52.3 (s), 54.2 (t), 88.6 (d), 114.3 (d), 122.9 (d), 123.3 (d), 123.7 (d), 125.2 (d), 125.5 (d), 125.6 (d), 125.8 (d), 126.3 (d), 127.2 (d), 137.5 (s), 141.3 (s), 142.0 (s), 142.5 (s), 145.1 (s), 145.6 (s), 168.5 (s), the remaining two aromatic carbons (CH) were obscured by the benzene; exact mass (ESI) calcd for $C_{25}H_{20}N_2ONa^+$: *m*/*z* 387.1473, found: *m*/*z* 387.1547. Anal. calcd for $C_{25}H_{20}N_2O$: C, 82.38; H, 5.54; N, 7.69. Found: C, 82.32; H, 5.82; N, 7.67. C_2 epimer of **21**: mp 265–267 °C (dec); ^1H NMR (C_6D_6, 400 MHz) δ 0.40 (br s, 1H, NH), 1.24 (dd, J=12.5, 2.2 Hz, 1H, CH_2), 2.98 (dd, J=12.5, 3.2 Hz, 1H, CH_2), 3.06 (d, J=1.2 Hz, 2H, CH_2), 3.75 (s, 1H, CH), 3.94 (t, J=2.6 Hz, 1H, $CHCH_2$), 4.82 (br s, 1H, CHNH), 6.13 (d, J=7.6 Hz, 1H, ArH), 6.65 (td, J=7.6, 1.1 Hz, 1H, ArH), 6.80 (m, 2H, ArH), 6.93 (m, 2H, ArH), 7.05 (m, 5H, ArH), 7.85 (d, J=8.0 Hz, 1H, ArH); ^{13}C NMR (C_6D_6, 125 MHz) δ 39.4 (t), 44.9 (d), 52.9 (t), 53.2 (s), 54.5 (d), 85.3 (d), 114.9 (d), 123.2 (d), 124.3 (d), 124.8 (d), 125.0 (d), 125.5 (d), 125.7 (d), 126.3 (d), 126.5 (d), 126.7 (d), 127.5 (d), 138.4 (s), 140.4 (s), 140.9 (s), 141.2 (s), 144.7 (s), 146.3 (s), 168.6 (s), the remaining aromatic carbon was obscured by the benzene; exact mass (ESI) calcd for $C_{25}H_{20}N_2ONa^+$: *m*/*z* 387.1473, found: *m*/*z* 387.1461.

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Supplementary data

Experimental procedures for the preparation of **12** and **13**, and ^1H and ^{13}C NMR spectra of most compounds are

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