1,2,3,9-Tetrahydro-4*H*-carbazol-4-one and 8,9-Dihydropyrido-[1,2-*a*]indol-6(7*H*)-one from 1*H*-Indole-2-butanoic Acid

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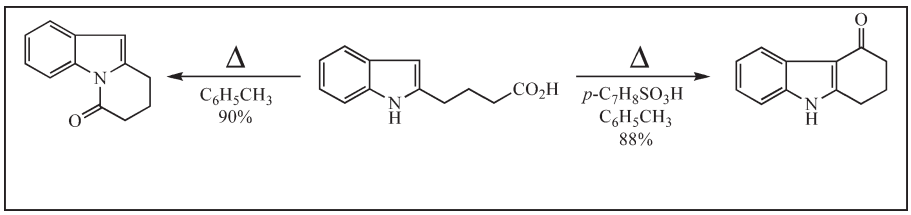

Efficient syntheses of the title ring systems have been developed from 1*H*-indole-2-butanoic acid, which was easily prepared from 2-fluoro-1-nitrobenzene in four steps. Heating 1*H*-indole-2-butanoic acid in toluene containing *p*-toluenesulfonic acid at 110°C furnished 1,2,3,9-tetrahydro-4*H*-carbazol-4-one in 88% yield. Heating this same acid in toluene with no added acid gave 8,9-dihydropyrido[1,2-*a*]-indol-6(7*H*)-one in 90% yield. The tetrahydro-4*H*-carbazol-4-one was also prepared directly in 92% yield from methyl 6-(2-nitrophenyl)-5-oxohexanoate by a tandem reduction—cycloaromatization—acylation reaction with iron in concentrated hydrochloric acid at 110°C. Application of this approach to the closure of five- and seven-membered rings was also successful.

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INTRODUCTION

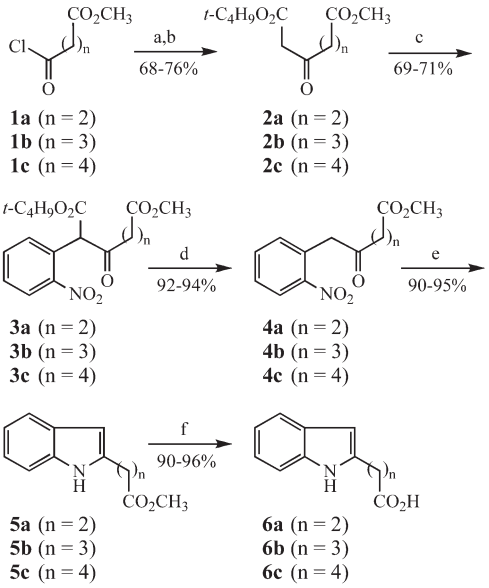
Earlier studies from this laboratory [1] and by others [2] described the synthesis of substituted indoles from 2-nitrobenzyl ketones based on a tandem reduction—cycloaromatization reaction. Our recent work has sought to assemble more complex structures using this strategy. In this study, we have developed a route to synthesize 1,2,3,9-tetrahydro-4*H*-carbazol-4-one and 8,9-dihydropyrido[1,2-*a*]indol-6(7*H*)-one from 1*H*-indole-2-butanoic acid. In the course of this study, we also discovered that the tetrahydro-4*H*-carbazol-4-one could be prepared from methyl 6-(2-nitrophenyl)-5-oxohexanoate in one step by a tandem reduction—cycloaromatization—acylation sequence. Tetrahydro-4*H*-carbazol-4-one is an important building block for the synthesis of alkaloids [3] as well as the core ring structure in current drugs used for the treatment of cancer [4], HIV [5], congestive heart failure [6], and emesis resulting from chemotherapy [7]; 8,9-dihydropyrido[1,2-*a*]indol-6(7*H*)-ones have been studied for the treatment of ischemic disorders [8] and vomiting caused by cancer treatment [9].

Several other approaches have been reported for the tetrahydro-4*H*-carbazol-4-one system. The Fischer indole synthesis between phenylhydrazine and 1,3-cyclohexanedione is the simplest, but only provides a 50% yield [10]. Other routes include C4 oxidation of tetrahydrocarbazole [11]; base-promoted cyclization of 2-(2-trifluoroacetamidophenyl)-2-cyclohexen-1-one [12]; copper(I)-mediated [13] or photochemical [14] arylation of *N*-substituted enaminones; and a number of palladium-catalyzed coupling reactions [15]. Our synthesis requires several steps, but permits the preparation of two pharmacologically valuable compounds without excessively hazardous reagents or expensive catalysts. We have also found that other saturated ring homologues of the title compounds are available using this strategy.

RESULTS AND DISCUSSION

Our cyclization studies required access to a series of 1*H*-indole-2-alkanecarboxylic acids. To this end, a synthesis of these precursors was devised and carried out from Meldrum's acid [16] and commercially available (ω-chlorocarbonyl)alkanoic esters **1a–c** (Scheme 1). Acylation of Meldrum's acid with **1a–c** in the presence of pyridine followed by refluxing in *tert*-butyl alcohol gave the *tert*-butyl methyl 3-oxoalkanedicarboxylic esters **2a-c** in 68–76% yields [17]. Deprotonation of **2a–c** with sodium hydride in anhydrous *N*,*N*-dimethylformamide and reaction with 2-fluoro-1-nitrobenzene at 55–60°C afforded the nucleophilic aromatic substitution products **3a–c** in yields ranging from 69 to 71% [1,2]. Subsequent exposure of **3a–c** to trifluoroacetic acid in the presence of triethylsilane [18] resulted in *tert*-butyl ester cleavage and decarboxylation to provide nitro ketoesters **4a–c** in 92–94% yields. Treatment of **4a-c** with iron powder in acetic acid then initiated a tandem reduction—cycloaromatization reaction to furnish 1*H*-indole-2-alkanecarboxylic esters **5a–c** in 90–95% yields [1]. Finally, basic hydrolysis of **5a–c** provided acids **6a–c** in 90–96% yields.

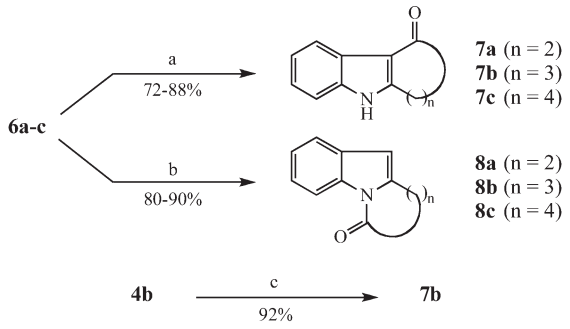
Scheme 1 [a]



[a] Key: (a) Meldrum's acid, pyridine, CH_2Cl_2, 0–22°C; (b) *t*-C_4H_9OH, reflux; (c) NaH, dimethylformamide; 2-fluoro-1-nitrobenzene, 55–60 °C, 48 h; (d) CF_3CO_2H, $(C_2H_5)_3SiH$, CH_2Cl_2, 22°C, 1 h; (e) Fe (>100 mesh), CH_3CO_2H, 115°C, 30 min; (f) 1*M* aqueous NaOH, dioxane, 22°C, 1 h.

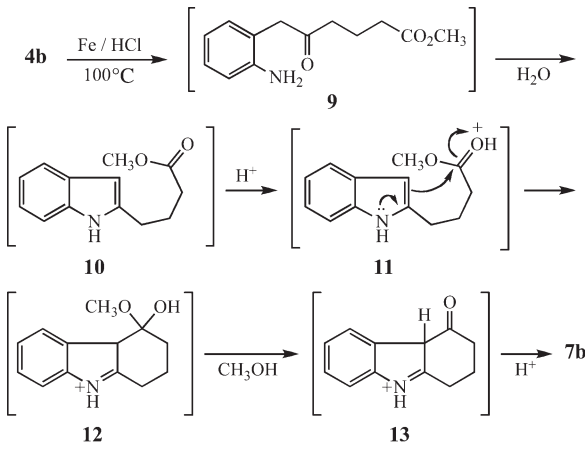
The results of our cyclization studies are summarized in Scheme 2. Treatment of **6a–c** with 2.0–6.0 equivalents of *p*-toluenesulfonic acid in refluxing toluene resulted in a Friedel-Crafts-like ring closure of the acid to C3 of the indole moiety to yield **7a–c** in 72–88% yields. Refluxing **6b** in toluene without the added *p*-toluenesulfonic acid resulted in closure to lactam **8b** (90%); acids **6a** and **6c** did not cyclize under these conditions reflecting stereoelectronic problems in closing the five- and seven-membered rings. Lactamization of **6a** and **6c** was possible in

Scheme 2 [a]



[a] Key: (a) *p*-$C_7H_8SO_3H$, $PhCH_3$, 110°C; (b) for **6a** and **6c**, *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride, 4-(dimethylamino)pyridine, CH_2Cl_2, 22°C; for **6b**, $PhCH_3$, 110°C; (c) Fe (>100 mesh), concentrated HCl, 110°C, 20 min.

Scheme 3



≥80% yields, however, using *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride [19] in the presence of 1.6 equivalents of 4-(dimethylamino)pyridine [20]. Numerous other ring-closing regimes [21] failed to give the desired lactams. This seems to be the first report describing the use of *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide with 4-(dimethylamino)pyridine for lactam closures. The function of the base in this reaction is two-fold, neutralizing the hydrochloride salt of the carbodiimide and scavenging a proton from the cyclized amide.

Remarkably, it was found that treatment of **4b** with iron in concentrated hydrochloric acid yielded **7b** in 92% yield by a tandem process involving a reduction—cycloaromatization—acylation sequence. Attempts to cyclize **6a** and **6c** under the same conditions afforded significantly lower yields and the product mixtures were more complex. The one-step conversion of **4b** to **7b** represents a new tandem reaction sequence.

Mechanistically, reduction of the aromatic nitro group is followed by cycloaromatization to the indole system as previously observed [1,2]. Under strong acid conditions, however, the methyl ester is cyclized onto the C3 position of indole. This most likely occurs by protonation of the ester carbonyl, addition of the electron-rich indole double bond to the carbonyl carbon, loss of methanol and rearomatization (Scheme 3). The closure of acids **6a** and **6c**–**7a** and **7c** should be analogous to the conversion of **10** to **7b** with loss of water in the penultimate step. Finally, the lactamization reactions proceed *via* the expected cyclocondensation mechanisms, with and without added carbodiimide.

CONCLUSION

We have developed a new approach to the synthesis of the title compounds using 1*H*-indole-2-butanoic acid (**6b**) as a common intermediate. Heating this acid in refluxing

toluene containing *p*-toluenesulfonic acid affords 1,2,3,9-tetrahydro-4*H*-carbazol-4-one (**7b**), while heating in toluene with no added acid yields 8,9-dihydropyrido[1,2-*a*]indol-6(7*H*)-one (**8b**). A high yield of **7b** can also be achieved directly from **4b** *via* a tandem reduction—cycloaromatization—acylation reaction promoted by iron in concentrated hydrochloric acid. Homologues **7a** and **7c** can also be prepared by heating **6a** and **6c** in toluene with *p*-toluenesulfonic acid, but direct conversion from **4a** and **4c** with iron in concentrated hydrochloric acid was unsuccessful. Lactamization of **6a** and **6c** requires treatment with *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride in the presence of excess 4-(dimethylamino)pyridine. The synthesis requires several steps, but provides a number of pharmacologically useful compounds in high yield without excessively hazardous or expensive reagents.

EXPERIMENTAL

The commercial acid chlorides were used as received. *N*,*N*-Dimethylformamide, from a freshly opened bottle, was dried over 4 Å molecular sieves under nitrogen and transferred by syringe into reactions where it was used. The hydrochloric acid (1*M*, 2*M*, and 6*M*), sodium hydroxide (1*M*), ammonium chloride (saturated), sodium bicarbonate (saturated), and sodium chloride (saturated) employed in various procedures refer to aqueous solutions. All reactions were run under N_2 in oven-dried glassware. Reactions were monitored by thin layer chromatography on silica gel GF plates (Analtech 21521). Preparative separations were performed using flash column chromatography [22] on silica gel (grade 62, 60–200 mesh) mixed with ultraviolet-active phosphor (Sorbent Technologies UV-5) or thin layer chromatography on 20 cm x 20 cm silica gel GF plates (Analtech 02015). Band elution, for both methods, was monitored using a hand-held ultraviolet lamp. Hexanes used in chromatography had a boiling range of 65–70°C. Melting points were uncorrected. Infrared spectra were run as thin films on sodium chloride disks and were referenced to polystyrene. Unless otherwise indicated, ^{1}H and ^{13}C nuclear magnetic resonance spectra were measured in chloroform-d_1 at 300 MHz and 75 MHz, respectively, and were referenced to internal tetramethylsilane; coupling constants (*J*) are reported in Hertz. Low-resolution mass spectra (electron impact/direct probe) were run at 70 electron volts.

Representative procedure for the preparation of *tert*-butyl methyl 3-oxoalkanedicarboxylic esters: *tert*-butyl methyl 3-oxohexanedioate (2a). The procedure of Yonemitsu and coworkers was used [18]. To a stirred solution of 7.00 g (48.6 mmoles) of Meldrum's acid and 7.68 g (97.2 mmoles) of pyridine in 50 mL of dichloromethane at 0°C was added a solution of 7.68 g (51.0 mmoles) of **1a** in 10 mL of dichloromethane. Stirring was continued at 0°C for 30 min and at 22°C for 1 h. The crude reaction mixture was washed with 2*M* hydrochloric acid (three times) to remove the excess pyridine and the solution was dried (magnesium sulfate) and concentrated under vacuum. The resulting oil was dissolved in 50 mL of *tert*-butyl alcohol and refluxed for 3 h. The crude reaction mixture was cooled, concentrated under vacuum and distilled under high vacuum to give 8.20 g (73%) of keto diester **2a** containing some enol as a colorless oil, bp 85–110°C (0.5 mmHg). IR: 1737, 1717 cm^{-1}; ^{1}H NMR: δ 3.68 (s, 3H), 3.41 (s, 2H), 2.87 (t, 2H, J = 6.6), 2.62 (t, 2H, J = 6.6), 1.47 (s, 9H); ^{13}C NMR: δ 201.4, 172.8, 166.2, 81.9, 51.7, 50.4, 37.2, 27.8 (3C), 27.5.

***tert*-Butyl methyl 3-oxoheptanedioate (2b).** This compound (9.00 g, 76% containing some enol) was isolated as a colorless oil, bp 110–130°C (0.5 mmHg). IR: 1738, 1716 cm^{-1}; ^{1}H NMR: δ 3.67 (s, 3H), 3.35 (s, 2H), 2.62 (t, 2H, J = 7.0), 2.36 (t, 2H, J = 7.2), 1.92 (quintet, 2H, J = 7.1), 1.47 (s, 9H); ^{13}C NMR: δ 202.5, 173.5, 166.4, 82.0, 51.5, 50.5, 41.6, 32.7, 27.9 (3C), 18.5.

***tert*-Butyl methyl 3-oxooctanedioate (2c).** This compound (8.50 g, 68% containing some enol) was isolated as a colorless oil, bp 125–140°C (0.5 mmHg). IR: 1735, 1716 cm^{-1}; ^{1}H NMR: δ 3.67 (s, 3H), 3.35 (s, 2H), 2.56 (distorted t, 2H, J = 6.7), 2.33 (distorted t, 2H, J = 6.7), 1.63 (m, 4H), 1.47 (s, 9H); ^{13}C NMR: δ 202.8, 173.7, 166.4, 81.9, 51.5, 50.5, 42.3, 33.7, 27.9 (3C), 24.2, 22.7.

Representative procedure for nucleophilic aromatic substitution: *tert*-butyl methyl 2-(2-nitrophenyl)-3-oxohexanedioate (3a). A modification of the procedure described by Bunce *et al*. was used [1]. To a suspension of 1.36 g (56.7 mmoles) of oil-free sodium hydride in 20 mL of dry *N*,*N*-dimethylformamide was added 4.00 g (28.4 mmoles) of 2-fluoro-1-nitrobenzene in 25 mL of dimethylformamide. Stirring was initiated and a solution of 6.35 g (29.7 mmoles) of **2a** in 5 mL of dimethylformamide was added. The reaction mixture was heated to 55–60°C and stirred for 48 h, then cooled, added to 50 mL of saturated ammonium chloride and extracted with ether (three times). The combined organic extracts were washed with saturated sodium chloride (one time), dried (magnesium sulfate) and concentrated under vacuum. The crude product was purified by flash chromatography on a 50 cm × 2 cm silica gel column using 10% ether in hexanes to give 6.65 g (69%) of keto diester **3a** containing some enol as a yellow oil. IR: 1736, 1640, 1613, 1520, 1351 cm^{-1}; ^{1}H NMR: δ 7.98 (dd, 1H, J = 8.0, 1.2), 7.58 (td, 1H, J = 7.6, 1.4), 7.46 (td, 1H, J = 7.9, 1.6), 7.33 (dd, 1H, J = 7.6, 1.4), 5.28 (s, 1H), 3.64 (s, 3H), 2.50 (m, 4H), 1.32 (s, 9H); ^{13}C NMR: δ 200.4, 172.7, 170.6, 149.7, 133.7, 132.6, 130.1, 128.3, 124.5, 82.6, 61.3, 51.7, 37.4, 29.8, 27.8 (3C).

***tert*-Butyl methyl 2-(2-nitrophenyl)-3-oxoheptanedioate (3b).** This compound (6.00 g, 69% containing some enol) was isolated as a yellow oil. IR: 1738, 1645, 1526, 1394, 1352 cm^{-1}; ^{1}H NMR: δ 7.98 (dd, 1H, J = 8.0, 1.2), 7.57 (td, 1H, J = 7.6, 1.4), 7.45 (td, 1H, J = 7.9, 1.4), 7.25 (dd, 1H, J = 7.6, 1.4), 5.25 (s, 1H), 3.57 (s, 3H), 2.25 (m, 4H), 1.88 (m, 2H), 1.33 (s, 9H); ^{13}C NMR: δ 200.8, 172.7, 170.7, 149.7, 133.7, 132.8, 130.1, 128.4, 124.3, 82.6, 61.3, 51.8, 37.4, 29.9, 28.0, 27.8 (3C).

***tert*-Butyl methyl 2-(2-nitrophenyl)-3-oxooctanedioate (3c).** This compound (4.20 g, 71% containing some enol) was isolated as a yellow oil. IR: 1735, 1643, 1615, 1524, 1352 cm^{-1}; ^{1}H NMR: δ 7.98 (dd, 1H, J = 8.0, 1.3), 7.56 (td, 1H, J = 7.5, 1.4), 7.45 (td, 1H, J = 7.9, 1.6). 7.25 (dd, 1H, J = 7.7. 1.4), 5.26 (s, 1H), 3.63 (s, 3H), 2.21 (m, 2H), 2,12 (m, 2H), 1.57 (m, 4H), 1.24 (s, 9H); ^{13}C NMR: δ 201.8, 173.7, 170.7, 149.7, 133.7, 132.5, 130.5, 128.8, 124.3, 82.4, 61.0, 51.5, 33.6, 32.5, 27.8 (3C), 25.7, 24.3.

Representative procedure for *tert*-butyl ester cleavage and decarboxylation: methyl 5-(2-nitrophenyl)-4-oxopentanoate (4a). The procedure of Mehta *et al*. [17] was used. To a solution of 5.20 g (14.8 mmoles) of **3a** in 50 mL of dichloromethane were added 27.6 g (18.0 mL, 242 mmoles) of

trifluoroacetic acid and 4.88 g (6.70 mL, 42.0 mmoles) of triethylsilane. The mixture was stirred at 22°C for 1 h and then concentrated under vacuum to give 3.50 g (94%) of **4a** as a light yellow oil, which was used without further purification. IR: 1735, 1722, 1525, 1351 cm^{-1}; ^1H NMR: δ 8.11 (dd, 1H, J = 8.0, 1.1), 7.60 (td, 1H, J = 7.7, 1.3), 7.46 (td, 1H, J = 7.9, 1.5), 7.31 (dd, 1H, J = 7.7, 1.1), 4.16 (s, 2H), 3.67 (s, 3H), 2.93 (t, 2H, J = 6.5), 2.65 (t, 2H, J = 6.5); ^{13}C NMR: δ 204.0, 173.1, 148.5, 133.7, 133.6, 130.1, 128.5, 125.2, 51.8, 47.8, 37.1, 27.8; ms: m/z 251 (M^+). *Anal*. Calcd. for $C_{12}H_{13}NO_5$: C, 57.37; H, 5.18; N, 5.58. Found: C, 57.41; H, 5.21; N, 5.53.

Methyl 6-(2-nitrophenyl)-5-oxohexanoate (4b). This compound (3.46 g, 92%) was isolated as a light yellow oil and used without further purification. IR: 1729, 1525, 1346 cm^{-1}; ^1H NMR: δ 8.11 (dd, 1H, J = 8.0, 1.1), 7.59 (td, 1H, J = 7.7, 1.5), 7.46 (td, 1H, J = 7.9, 1.5), 7.28 (dd, 1H, J = 7.7, 1.1), 4.09 (s, 2H), 3.68 (s, 3H), 2.70 (t, 2H, J = 7.1), 2.38 (t, 2H, J = 7.1), 1.96 (quintet, 2H, J = 7.1); ^{13}C NMR: δ 204.9, 173.6, 148.6, 133.6 (2C), 130.2, 128.4, 125.2, 51.6, 47.9, 41.4, 32.9, 18.7; ms: m/z 265 (M^+). *Anal*. Calcd. for $C_{13}H_{15}NO_5$: C, 58.87; H, 5.66; N, 5.28. Found: C, 59.00: H, 5.58; N, 5.23.

Methyl 7-(2-nitrophenyl)-6-oxoheptanoate (4c). This compound (1.45 g, 92%) was isolated as a light yellow oil and used without further purification. IR: 1727, 1528, 1352 cm^{-1}; ^1H NMR: δ 8.10 (dd, 1H, J = 8.2, 1.3), 7.59 (td, 1H, J = 7.5, 1.3), 7.46 (td, 1H, J = 8.1, 1.5), 7.27 (dd, 1H, J = 7.6, 1.1), 4.10 (s, 2H), 3.67 (s, 3H), 2.62 (distorted t, 2H, J = 6.8), 2.34 (distorted t, 2H, J = 6.8), 1.67 (m, 4H); ^{13}C NMR: δ 205.2, 173.8, 148.6, 133.5 (2C), 130.3, 128.3, 125.2, 51.5, 47.8, 42.2, 33.7, 24.3, 22.9; ms: m/z 279 (M^+). *Anal*. Calcd. for $C_{14}H_{17}NO_5$: C, 60.22; H, 6.09; N, 5.02. Found: C, 60.24; H, 6.10; N, 4.98.

Representative procedure for reductive cyclization to the 1*H*-indoles: methyl 1*H*-indole-2-propanoate (5a). The procedure of Bunce *et al*. [1] was used. A mixture of 1.50 g (5.98 mmoles) of **4a**, 25 mL of acetic acid and 2.00 g (35.9 mmoles, 6.0 eq) of iron powder (>100 mesh) was heated with stirring at 115°C (oil bath) until thin layer chromatography indicated complete consumption of starting material (*ca* 30 min). The crude reaction was cooled, transferred to a separatory funnel containing 50 mL of water and extracted with ether (three times). The combined ether layers were washed with water (one time), saturated sodium bicarbonate (three times), saturated sodium chloride (one time), then dried (magnesium sulfate) and concentrated under vacuum to give a brown solid. Recrystallization from hexanes gave 1.10 g (91%) of **5a** as a tan solid, mp 97–98°C (lit [23] mp 97–98°C, hexane). IR: 3357, 1720 cm^{-1}; ^1H NMR: δ 8.47 (br s, 1H), 7.52 (dd, 1H, J = 7.9, 0.6), 7.31 (dq, 1H, J = 8.0, 0.9), 7.12 (td, 1H, J = 7.9, 1.3), 7.06 (td, 1H, J = 7.9, 1.1), 6.24 (dd, 1H, J = 2.0, 0.9), 3.72 (s, 3H), 3.08 (t, 2H, J = 6.7), 2.73 (t, 2H, J = 6.7); ^{13}C NMR: δ 174.3, 138.1, 136.0, 128.4, 121.3, 119.9, 119.6, 110.5, 99.8, 51.9, 33.9, 23.1; ms: m/z 203 (M^+). *Anal*. Calcd. for $C_{12}H_{13}NO_2$: C, 70.94; H, 6.40; N, 6.90. Found: C, 70.92; H, 6.39; N, 6.92.

Methyl 1*H*-indole-2-butanoate (5b). This compound (1.15 g, 95%) was isolated as a tan solid, mp 69–71°C. IR: 3392, 1718 cm^{-1}; ^1H NMR: 8.06 (br s, 1H), 7.52 (d, 1H, J = 7.6 Hz), 7.30 (d, 1H, J = 6.0 Hz), 7.08 (m, 2H), 6.25 (s, 1H), 3.66 (s, 3H), 2.81 (t, 2H, J = 7.2 Hz), 2.40 (t, 2H, J = 7.2 Hz), 2.04 (m, 2H); ^{13}C NMR: δ 173.9, 138.4, 128.8, 121.1, 119.8, 119.6, 110.3, 100.0, 51.6, 33.1, 30.0, 27.3, 24.5; ms: m/z 217 (M^+). *Anal*. Calcd. for $C_{13}H_{15}NO_2$: C, 71.89; H, 6.91; N, 6.45. Found: C, 71.85; H, 6.92; N, 6.43.

Methyl 1*H*-indole-2-pentanoate (5c). This compound (1.10 g, 90%) was isolated as a tan solid, mp 121–124°C. IR: 3353, 1719 cm^{-1}; ^1H NMR: δ 7.98 (br s, 1H), 7.52 (d, 1H, J = 6.8 Hz), 7.28 (d, 1H, J = 8.0 Hz), 7.08 (m, 2H), 6.24 (s, 1H), 3.67 (s, 3H), 2.76 (t, 2H, J = 7.2 Hz), 2.37 (t, 2H, J = 3.6 Hz), 1.76 (m, 4H); ^{13}C NMR: δ 174.2, 139.3, 136.0, 128.9, 121.2, 119.6, 119.8, 110.5, 99.8, 51.7, 33.9, 28.7, 28.0, 24.6; ms: m/z 231 (M^+). *Anal*. Calcd. for $C_{14}H_{17}NO_2$: C, 72.73; H, 7.36; N, 6.06. Found: C, 72.70; H, 7.33; N, 6.10.

Representative procedure for the ester hydrolysis: 1*H*-indole-2-propanoic acid (6a). A mixture of 1.00 g (4.93 mmoles) of **5a** in 20 mL of dioxane and 15 mL of 1*M* sodium hydroxide was stirred at 22°C for 1 h. The solution was concentrated to one-half volume under vacuum, acidified with 3*M* hydrochloric acid and extracted with ether (three times). The combined ether layers were washed with saturated sodium chloride (one time), then dried (magnesium sulfate) and concentrated under vacuum. The crude product was purified by flash chromatography on a 15 cm × 2 cm silica gel column using 50% ether in hexanes to give 0.85 g (91%) of **6a** as a white solid, mp 165–167°C (lit [24] mp 167°C). IR: 3462–2300, 3392, 1701 cm^{-1}; ^1H NMR: δ 9.87 (br s, 1H), 8.26 (br s, 1H), 7.52 (dd, 1H, J = 7.7, 0.7), 7.30 (dd, 1H, J = 8.0, 0.9), 7.13 (td, 1H, J = 7.7, 1.3), 7.07 (td, 1H, J = 7.9, 1.1), 6.26 (dd, 1H, J = 1.9, 0.8), 3.08 (t, 2H, J = 6.8), 2.81 (t, 2H, J = 6.8); ^{13}C NMR: δ 178.4, 137.6, 135.5, 128.4, 121.4, 119.9, 119.7, 110.5, 99.9, 33.6, 22.9; ms: m/z 189 (M^+). *Anal*. Calcd. for $C_{11}H_{11}NO_2$: C, 69.84; H, 5.82; N, 7.41. Found: C, 69.88; H, 5.85; N, 7.37.

1*H*-Indole-2-butanoic acid (6b). This compound (0.33 g, 90%) was isolated as a white solid, mp 114–115°C. IR: 3252–2348, 3386, 1700 cm^{-1}; ^1H NMR: 10.85 (br s, 1H), 7.95 (br s, 1H), 7.52 (dd, 1H, J = 7.7, 0.7), 7.29 (dd, 1H, J = 8.0, 0.9), 7.12 (td, 1H, 7.9, 1.3), 7.07 (td, 1H, J = 7.7, 1.1), 6.27 (dd, 1H, J = 2.0, 0.8), 2.83 (t, 2H, J = 7.3), 2.45 (t, 2H, J = 7.3), 2.06 (quintet, 2H, J = 7.3); ^{13}C NMR: δ 179.2, 138.1, 135.9, 128.7, 121.2, 119.9, 119.7, 110.4, 100.1, 33.0, 27.3, 24.2; ms: m/z 203 (M^+). *Anal*. Calcd. for $C_{12}H_{13}NO_2$: C, 70.94; H, 6.40; N, 6.90. Found: C, 70.98; H, 6.41; N, 6.85.

1*H*-Indole-2-pentanoic acid (6c).. This compound (0.90 g, 96%) was isolated as a white solid, mp 145–147°C. IR: 3425–2350, 3384, 1700 cm^{-1}; ^1H NMR: δ 10.50 (s, 1H), 7.92 (br s, 1H), 7.52 (d, 1H, J = 6.8 Hz), 7.30 (d, 1H, J = 8.0 Hz), 7.10 (m, 2H), 6.24 (s, 1H), 2.80 (t, 2H, J = 6.8 Hz), 2.42 (t, 2H, J = 7.2 Hz), 1.76 (m, 4H); ^{13}C NMR: δ 178.4, 138.9, 135.7, 128.7, 121.0, 119.7, 119.6, 110.2, 99.7, 33.4, 28.4, 27.8, 24.1; ms: m/z 217 (M^+). *Anal*. Calcd. for $C_{13}H_{15}NO_2$: C, 71.89; H, 6.91; N, 6.45. Found: C, 71.88; H, 6.86; N, 6.47.

Representative procedure for indole acylation: 3,4-dihydrocyclopent[*b*]indol-1(2*H*)-one (7a). A solution of 200 mg (1.06 mmoles) of **6a** in 10 mL of toluene was heated to reflux and 200 mg of *p*-toluenesulfonic acid monohydrate was slowly added through the top of the condenser. After 1 h at reflux, a second 200-mg portion of *p*-toluenesulfonic acid (total 400 mg, 2.10 mmoles, 2.0 eq) was added and refluxing was continued for a total of 12 h. The resulting solution was cooled, added to water and extracted with ether. The ether layer was washed

with saturated sodium bicarbonate (three times) and saturated sodium chloride (one time), then dried (magnesium sulfate) and concentrated under vacuum. The crude product was purified by flash chromatography on a 20 cm × 2 cm silica gel column using increasing concentrations of ether in hexanes to give 136 mg (75%) of **7a** as an off-white solid, mp 250–252°C (lit [11] mp 252–253°C). IR: 3371, 1648 cm^{-1}; ^1H NMR (dimethyl sulfoxide-d_6): δ 12.0 (br s, 1H), 7.67 (d, 1H, J = 7.5), 7.45 (d, 1H, J = 8.0), 7.22 (td, 1H, J = 7.7, 1.3), 7.16 (td, 1H, J = 7.7, 1.3), 3.08 (m, 2H), 2.82 (m, 2H); ^{13}C NMR (dimethyl sulfoxide-d_6): δ 194.7, 167.7, 142.2, 129.8, 127.6, 122.9, 121.5, 119.4, 112.6, 40.6, 21.0; ms: m/z 171 (M^+). *Anal*. Calcd. for $C_{11}H_9NO$: C, 77.19; H, 5.26; N, 8.19. Found: C, 76.94; H, 5.20; N, 8.23.

1,2,3,9-Tetrahydro-4H-carbazol-4-one (7b). This compound was prepared from 150 mg (0.74 mmoles) of **6b** using a modified procedure. In this case, 844 mg (4.44 mmoles, 6.0 eq) of *p*-toluenesulfonic acid monohydrate was required and this was added in 2.0-eq portions at 1-h intervals during the first 3 h of the 12-h reflux period. Product **7b** (120 mg, 88%) was isolated as an off-white solid, mp 225–228°C (dec) (lit [11] mp 219–221°C). IR: 3368, 1588, 1566 cm^{-1}; ^1H NMR (dimethyl sulfoxide-d_6): δ 11.7 (br s, 1H), 7.99 (d, 1H, J = 7.5), 7.46 (dd, 1H, J = 7.8, 1.1), 7.25 (td, 1H, J = 7.7, 1.2), 7.19 (td, 1H, J = 7.7, 1.2), 2.99 (t, 2H, J = 6.3), 2.42 (t, 2H, J = 6.4), 2.13 (quintet, 2H, J = 6.4); ^{13}C NMR (dimethyl sulfoxide-d_6): δ 192.1, 148.4, 134.1, 122.7, 122.2, 120.5, 120.2, 108.8, 106.5, 37.7, 22.9, 20.4; ms: m/z 185 (M^+). *Anal*. Calcd. for $C_{12}H_{11}NO$: C, 77.84; H, 5.95; N, 7.57. Found: C, 77.78; H, 5.94; N, 7.60.

6,7,8,9-Tetrahydrocyclohept[b]indol-10(5H)-one (7c). This compound was prepared as described for **7b** using 203 mg (0.93 mmoles) of **6c** to give 133 mg (72%) of **7c** as a tan solid, mp 217–218 °C (lit [11] mp 220–221°C). IR: 3365, 1718 cm^{-1}; ^1H NMR (dimethyl sulfoxide-d_6): δ 11.7 (br s, 1H), 8.14 (dd, 1H, J = 7.4, 1.4), 7.34 (dd, 1H, J = 7.9, 1.3), 7.12 (m, 2H), 3.10 (t, 2H, J = 6.3), 2.64 (m, 2H), 1.93 (quintet, 2H, J = 6.4), 1.83 (m, 2H); ^{13}C NMR (dimethyl sulfoxide-d_6): δ 196.4, 149.0, 135.0, 127.3, 122.2, 121.2, 120.9, 113.7, 110.9, 42.7, 27.0, 24.3, 21.8; ms: m/z 199 (M^+). *Anal*. Calcd. for $C_{13}H_{13}NO$: C, 78.39; H, 6.53; N, 7.04. Found: C, 78.19; H, 6.48; N, 7.05.

Direct preparation of 7b from 4b. A 100-mL single-necked round-bottomed flask equipped with a reflux condenser (N_2 inlet) and a magnetic stir bar was charged with 200 mg (0.75 mmoles) of **4b** and 8 mL of concentrated hydrochloric acid. The mixture was heated to 80°C (oil bath) and 126 mg (2.25 mmoles, 3.0 eq) of iron powder (>100 mesh) was added (*Caution!* This addition is sufficiently exothermic to boil the mixture). The reaction is contained by using a large flask and immediately replacing the condenser after adding the iron). The reaction was refluxed at 110°C until thin layer chromatography indicated complete consumption of starting material (*ca* 20 min), then cooled, added to 15 mL of water and extracted with ether (three times). The combined ether layers were washed with saturated sodium chloride (one time), dried (magnesium sulfate) and concentrated under vacuum. The resulting solid was flash chromatographed on a 20 cm × 2 cm silica gel column eluted with increasing concentrations of ether in hexanes to give 128 mg (92%) of **7b**. The physical properties and spectral data matched those reported above.

Representative procedures for lactam formation: 1,2-dihydro-3*H*-pyrrolo[1,2-*a*]indol-3-one (8a). To a suspension of 100 mg (0.53 mmoles) of **6a** in 5 mL of dichloromethane was added 103 mg (0.85 mmoles, 1.6 eq) of 4-(dimethylamino)pyridine. The mixture was stirred for 10 min to give a clear light brown solution. To this solution was added 101 mg (0.53 mmoles) of *N*-(3-dimethylaminopropyl-*N*′-ethylcarbodiimide hydrochloride and the reaction mixture was stirred at 22°C for 24 h. The crude reaction mixture was washed with water, 1*M* hydrochloric acid, saturated sodium bicarbonate and saturated sodium chloride, then dried (magnesium sulfate) and concentrated under vacuum. The resulting oil was purified by preparative thin layer chromatography using 60% ether in hexanes to give 72 mg (80%) of the lactam as a white solid, mp 149–151°C (lit [25] mp 151–153°C). IR: 1731 cm^{-1}; ^1H NMR: δ 8.07 (m, 1H), 7.48 (m, 1H), 7.25 (m, 2H), 6.27 (s, 1H), 3.14 (A of ABm, 2H), 3.08 (B of ABm, 2H); ^{13}C NMR: δ 171.6, 143.6, 135.3, 130.4, 124.0, 123.2, 120.5, 113.5, 100.3, 34.9, 19.6; ms: m/z 171 (M^+). *Anal*. Calcd. for $C_{11}H_9NO$: C, 77.19; H, 5.26; N, 8.19. Found: C, 77.14; H, 5.24; N, 8.21.

8,9-Dihydropyrido[1,2-a]indol-6(7H)-one (8b). This compound was prepared by dissolving 100 mg (0.49 mmoles) of **6b** in 15 mL of dry toluene and refluxing for 36 h. The reaction mixture was cooled and the solvent was evaporated to dryness under vacuum. The crude product was purified by preparative thin layer chromatography using 50% ether in hexanes to give 82 mg (90%) of **8b** as a white solid, mp 78–79°C (lit [25] mp 79–81°C). IR: 1690, cm^{-1}; ^1H NMR: δ 8.44 (dd, 1H, J = 8.1, 0.9), 7.45 (dd, 1H, J = 6.8, 1.6), 7.25 (m, 2H), 6.31 (s, 1H), 2.97 (td, 2H, J = 6.8, 1.2), 2.78 (t, 2H, J = 6.4), 2.07 (quintet, 2H, J = 6.4); ^{13}C NMR: δ 169.4, 138.1, 134.8, 129.7, 124.0, 123.9, 119.6, 116.3, 104.8, 34.4, 23.8, 21.4; ms: m/z 185 (M^+). *Anal*. Calcd. for $C_{12}H_{11}NO$: C, 77.84; H, 5.95; N, 7.57. Found: C, 77.76; H, 5.93; N, 7.59.

7,8,9,10-Tetrahydro-6H-azepino[1,2-a]indol-6-one (8c). This compound was prepared as described for **8a** on an 80 mg (0.37 mmole) scale to give 60 mg (81%) of the lactam as a white solid, mp 172–175°C. IR: 1692 cm^{-1}; ^1H NMR: δ 8.42 (dm, 1H, J = 7.9), 7.46 (dm, 1H, J = 7.3), 7.32–7.20 (complex, 2H), 6.36 (s, 1H), 3.06 (t, 2H, J = 5.9), 2.94 (distorted t, 2H, J = 5.8), 1.94 (m, 4H); ^{13}C NMR: δ 173.8, 139.5, 136.9, 129.6, 124.1, 123.5, 119.5, 116.3, 107.9, 35.9, 25.8, 23.7, 20.8; ms: m/z 199 (M^+). *Anal*. Calcd. for $C_{13}H_{13}NO$: C, 78.39; H, 6.53; N, 7.04. Found: C, 78.35; H, 6.54; N, 7.06.

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[20] The use of a larger excess of 4-(dimethylamino)pyridine promotes side reactions that generate more complex product mixtures.

[21] (a) Several other reagent combinations did not afford satisfactory results for the lactamization. All conditions listed below were run in dichloromethane and each was tried with added triethylamine and/or 4-(dimethylamino)pyridine; (b) *N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide alone: see ref. 19b; (c) *N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide with 1-hydroxybenzotriazole: Harigawa, D.; Neya, M.; Miyazaki, Y.; Hemmi, K.; Hashimoto, M. J Chem Soc Chem Commun 1984, 1676; (d) Polymer-bound *N*-benzyl-*N*′-cyclohexylcarbodiimide: LeBas, M.-D. H.; McKinley, N. F.; Hogan, A.-M. L.; O'Shea, D. F. J Comb Chem 2005, 7, 503; (e) *N*,*N*′-Dicyclohexylcarbodiimide appeared to promote lactam formation, but *N*,*N*′-dicyclohexylurea and excess carbodiimide could not be removed from the product.

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