Syntheses of 2-Spiroindoles and Pyrrolo[1,2-*a*]indoles

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C-alkylated products obtained from methyl 3-hydroxyindole-2-carboxylate afford either spiro compounds, such as an indolic analogue of nitramine, or tricyclic products with a pyrrolo[1,2-*a*]indole framework. Di-*C*-alkylated derivatives give access to tetracyclic compounds.

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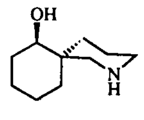
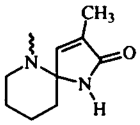
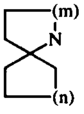
Spirocyclic piperidine alkaloids, such as nitramine **1** have been isolated from plants of the genus *Nitraria.* These alkaloids have received considerable synthetic attention [1-3] as their unusual 2-azaspiro[5.5]undecane skeleton resembles the neurotoxic histrionicotoxin [4]. Other representative examples of [4.5]spirolactam are derivatives of pandamarine **2** that mimic some secondary structural features of peptides namely the II β–turn type [5].



Nitramine **1**



Pandamarine **2**



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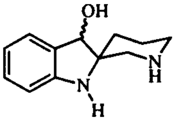

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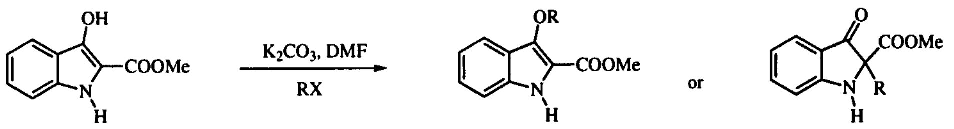
Type **3** spiroamines are usually considered as key sub-units of several natural products [6]. We wanted to extend the study of these biologically active structures to indole derivatives of type **4**. Few 2-spiroindoxyl derivatives has been described; we can mention the *Aristotelia* alkaloids [7], the mitragynine alkaloids [8] and tetrahydrocarbazole compound, pseudoindoxyl [9]. Since we are involved in the synthesis of 2-spiroindoxyl derivatives from 1-acetyl-1*H*-indol-3(2*H*)-ones [10,11], we wanted to explore the reactivity of methyl 3-hydroxy-1*H*-indole-2-carboxylate **5**.

Compound **5** is an interesting synthon for the syntheses of many bioactive compounds such as anti-allergic products, [12-14] or in the duocarmycin synthesis [15]. Compound **5** possesses three potential sites of alkylation, due in part to the existence of tautomeric equilibrium. Thus, treating compound **5** with an electrophile (RX) in the presence of a base can give access to three (*O*,*C*,*N*)-monoalkylated products. Products from *N*,*O*-dialkylation or *N*,*C*-dialkylation can also be obtained. The outcome of the alkylation reactions depends on the experimental conditions [18-22], solvent, nature of the base, structure of the electrophile, *etc.*). Unangst *et al* [12-16] have already observed that *O*-alkylation reactions are more frequently encountered than *N*- or *C*-alkylation reactions [21,22]. We have also observed such behavior [23] for the alkylation of **5**. *C*-alkylation was, for example, reported for allyl halides by Houghton *et al* [24]. In a preliminary study, we implemented some alkylation reactions with different functionalized halides (Scheme 1), and we always observed the formation of only one product, either the *O*- or *C*-alkylated derivative. *C*-alkylated compounds **8** and **9** were obtained from 3-bromopropanenitrile and benzyl 3-bromopropanoate. It is postulated that alkylation reactions proceed *via* a Michael addition of **5** with acrylonitrile or benzyl acrylate, generated from the corresponding halide in the basic media.

Mono *C*-alkylated compounds **8** or **9** are pivotal intermediates in the formation of spiro compounds by further reaction with the ester group in the 2-position; they can also provide a route to pyrrolo[1,2-*a*]indole by reaction of the *C*-chain with the indole nitrogen atom. We first examined the formation of spiro derivatives from compound **8** or **9**.

Hydrogenation of the nitrile function in compound **8** was performed; we tried some standard hydrogenation methods such as H_2/Raney nickel or H_2/palladium on carbon which left **8** unchanged. Only the use of Adams' catalyst (platinum oxide) allowed us to reduce the nitrile (Scheme 2). The product of the reduction was not the free amine, but rather the spirolactam **10** in 90% yield from the reaction of the amine function, formed *in situ*, with the ester group at the C-2 position of the indole ring. This behavior was also described in the synthesis of nitramine [25]. It is noteworthy that the nucleophilic attack of the amine generated did not involve the C-3 keto group. No δ-carboline precursor was formed. We also observed that when the indole nitrogen atom was substituted with a methyl group such as can be found in compound **12** [26], the nitrile reduction with platinum oxide did not occur and **12** remained unchanged.

Scheme 1



5

6 R = $(CH_2)_3CN$

7 R = CH_2COOBn

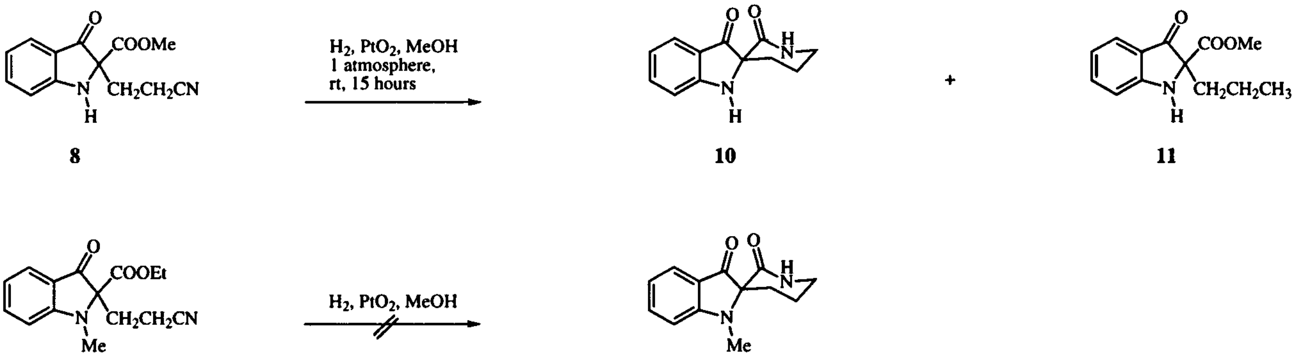
8 R = $(CH_2)_2CN$

9 R = $(CH_2)_2COOBn$

Table

RX	Temperature °	Time	Compounds	% Yield
$Br(CH_2)_3CN$	60	24 hours	6	78
$ClCH_2COOBn$	60	1.5 hours	7	67
$Br(CH_2)_2CN$	90	1 hour	8	85
$Br(CH_2)_2COOBn$	90	1.5 hours	9	70

Scheme 2



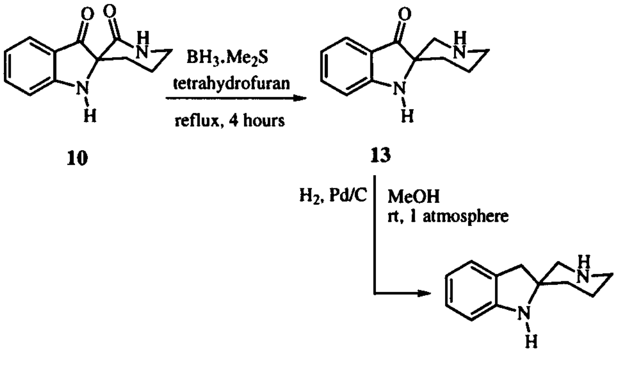
8 **10** **11**

12

Surprisingly in the reduction step of compound **8**, we isolated compound **11** in low yield (10%). Compound **11** resulted from the transformation of a nitrile into a methyl group. There is precedent for such results, however the experimental conditions usually are more severe [27]. The structure of compound **11** was confirmed by an independent synthesis consisting of hydrogenation of methyl 2-allyl-3-oxo-2,3-dihydro-1*H*-indole-2-carboxylate.

To obtain the indole analogue of nitramine from compound **10**, the lactam function and the keto function require reduction. De Kimpe *et al* described a synthesis of nitramine [28] using lithium aluminium hydride as the reducing agent for the lactam, but in our case we only observed degradation of compound **10**. The borane-methyl sulfide complex reduced the lactam to give compound **13** in 45% yield. Then we had to perform the reduction of the keto function in the 3-position in order to achieve the synthesis. Sodium borohydride did not afford the expected product. We only observed degradation of the starting material. Catalytic hydrogenation of the keto group of **13** gave compound **14** (71% yield) which possesses an indoline structure (Scheme 3).

Scheme 3



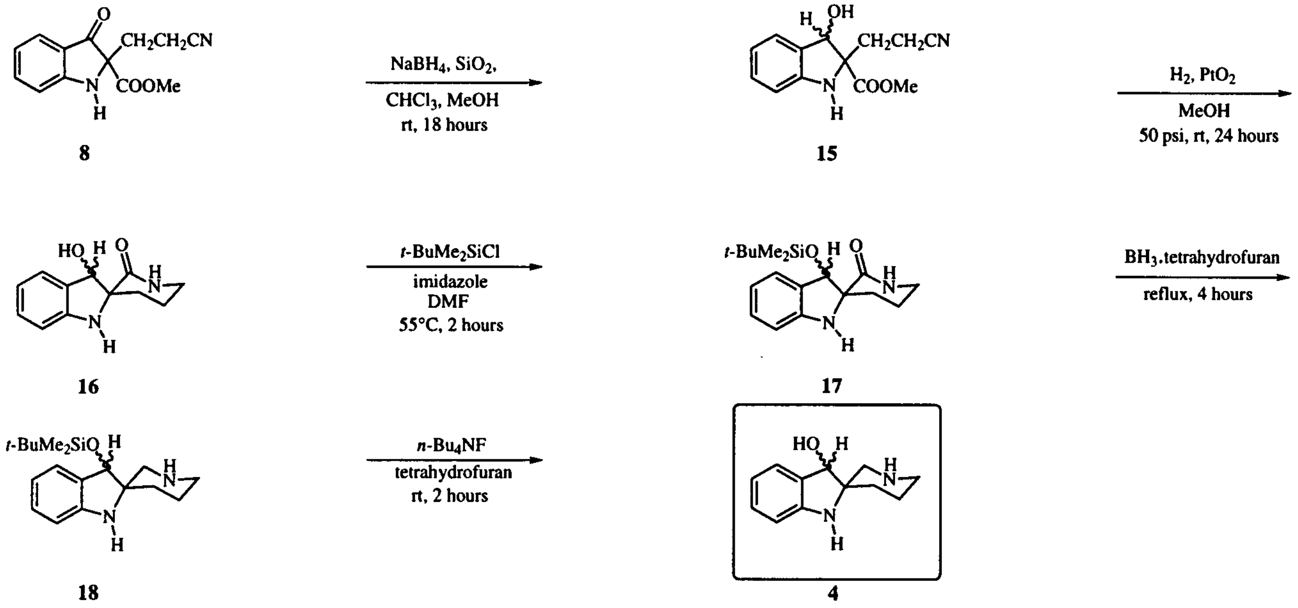
10 **13**

14

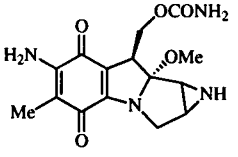
Therefore it was necessary to consider another pathway. Sodium borohydride reduction of the keto function at 3-position of compound **8** generated an alcohol **15** in 54%

yield, as a single diastereoisomer, which was, after the cyclization step (57% yield), protected as the *t*-butyldimethylsilyl ether **17** (95% yield). Reduction of the lactam with borane-tetrahydrofuran complex afforded **18** in 57% yield, which was then deprotected to give **4** in good yield (82%) (Scheme 4).

Scheme 4



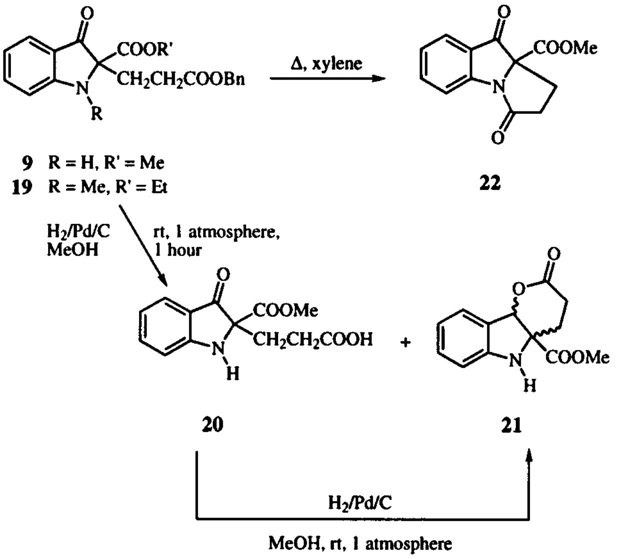
Since we had examined the reactivity of *C*-alkylated product **8** which allowed us to obtain spiro structure **4**, we wanted to use a *C*-alkylated compound such as **9** which could give access to pyrrolo[1,2-*a*]indole derivatives possessing the framework of mitomycin. This aim is connected to one of our research programs on antitumor agents.



Mitomycin C

The generated amino group from compound **8** preferred to react with the ester function in the 2-position rather than with the 3-keto group to give **10** (Scheme 2). By contrast the hydrogenolysis of the benzyl group in compound **9** afforded a mixture of keto acid **20** and lactone **21** in 55% and 45% yields respectively. Hydrogenation of the keto group of **20** directly afforded **21** in 80% yield, which demonstrates a better affinity of the COOH group for the OH in 3-position than for the indole NH group. Nevertheless heating **9** in xylene afforded the pyrrolo[1,2-*a*]indole structure **22** in a good yield (90%) [22] (Scheme 5).

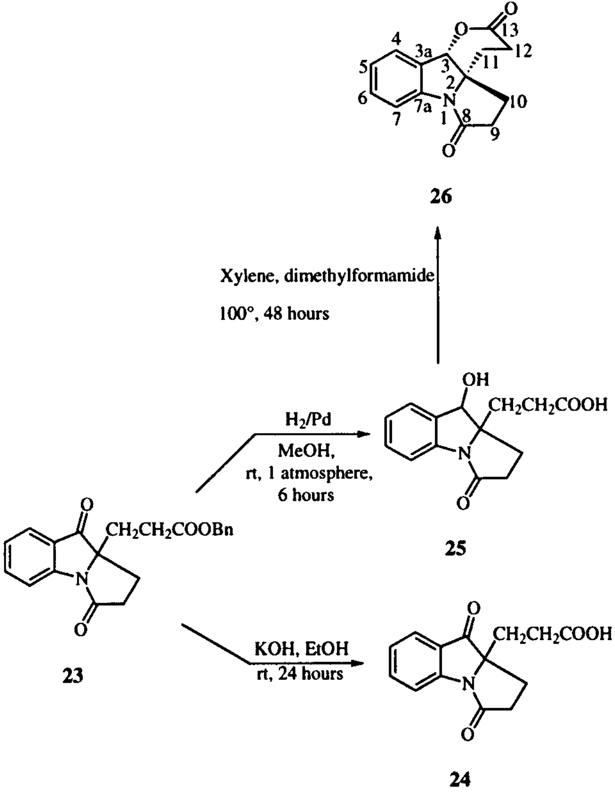
Scheme 5



During the synthesis of **9** from **5** we observed the direct formation of the pyrrolo[1,2-*a*]indole **23** in low yield

(10-15%). This yield can be increased to 50% by using 2 equivalents of the alkylating agent. The formation of **23** may result from a demethoxycarboxylation of **22** in basic medium followed by alkylation with a second equivalent of benzyl 3-bromopropanoate. Since ethyl 3-hydroxy-1-methylindole-2-carboxylate gives only mono *C*-alkylated compound **19**, we propose that the formation of the pyrrolo framework occurred before the decarboxylation step.

Scheme 6



Compound **23** was stirred at room temperature for six hours under an atmosphere of hydrogen to give hydroxy acid **25** in 88% yield, as a single diastereoisomer. Saponification of **23** gave keto acid **24** in 90% yield. Heating hydroxy acid **25** in xylene/dimethylformamide at 100° afforded the tetracyclic lactone **26** in high yield (90%) (Scheme 6). A nmr study of compound **26** 2D COSY, NOESY and HMQC experiments [29] allowed us to propose the reported structure; for example 2D NOESY experiments show connectivities between H_3, H_{10} and H_{11ax} protons.

We recently demonstrated [23] the potential of *O*-alkylated derivatives of methyl 3-hydroxy-1*H*-indole-2-carboxylate **5**. In this paper, we have explored *C*-alkylated products of methyl 3-hydroxy-1*H*-indole-2-carboxylate **5** with functional derivatives such as a β-bromoester or a nitrile. The *C*-alkylated products are precursors to spiro and pyrrolo[1,2-*a*]indole structures. These *C*-alkylated compounds are promising synthetic intermediates for the synthesis of natural products.

EXPERIMENTAL

Chromatography was carried out with Merck silica gel (230-400 mesh) and tlc with Merck silica gel $60F_{254}$ tlc plates (200 μ). The ^1H nmr spectra were recorded on a Bruker AM 300 WB spectrometer and ^{13}C nmr spectra were recorded on a Bruker Avance 250 DPX spectrometer. The chemical shifts are reported in parts per million, downfield from tetramethylsilane which was used as the internal standard. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. The ir spectra were obtained with a Perkin Elmer 1320 spectrophotometer. Mass spectra were recorded on a R-10-10-C Nermag apparatus, and chemical ionizations were accomplished with ammonia.

Spiro[3-hydroxy-2*H*-indole-2,3'-piperidine] (**4**).

Compound **18** (204 mg, 0.64 mmole) was dissolved in tetrahydrofuran (10 ml) and tetrabutylammonium fluoride (1*M* solution in tetrahydrofuran, 1.2 ml, 1.28 mmoles) was added dropwise at 0° under argon. The solution was stirred for 2 hours at room temperature. The solvent was removed *in vacuo* and the residue obtained was purified on a silica gel column (eluent:dichloromethane:methanol:concentrated ammonium hydroxide, 100:20:4) to give a white solid, 110 mg (84%), mp 180-182° (dichloromethane); ir (potassium bromide): ν 3313, 3055 cm^{-1}, ^1H nmr (dimethyl sulfoxide-d_6): δ 1.41-1.48 (m, 3H, CH_2), 1.72-1.75 (m, 1H, CH_2), 2.18-2.22 (m, 2H, CH_2), 2.74-2.79 (m, 2H, CH_2), 4.53 (d, 1H, *H*-3, J = 7.8 Hz), 4.88 (d, 1H, O*H*, J = 7.8 Hz), 5.61 (br s, 1H, N*H*), 6.43-6.51 (m, 2H, H_{arom}), 6.92 (t, 1H, $1H_{arom}$, J = 7.8 Hz), 7.08 (d, 1H, H_{arom}, J = 7.8 Hz); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 23.2 (CH_2), 29.0 (CH_2), 45.3 (CH_2), 54.4 (CH_2), 62.8 (C-2), 74.4 (CH-3), 108.3 (CH), 115.9 (CH), 125.3 (CH), 128.0 (CH), 129.8 (C), 149.8 (C); ms: (m/z, NH_3) 205 (M^++1).

Anal. Calcd. for $C_{12}H_{16}N_2O$: C, 70.58; H, 7.90; N, 13.72. Found: C, 70.49; H, 7.83; N, 13.50.

Syntheses of Compounds **6**, **7**, **8** and **9**.

General Procedure.

Methyl 3-hydroxy-1*H*-indole-2-carboxylate (**5**) (250 mg, 1.30 mmoles) was dissolved in dry dimethylformamide (5 ml), potassium carbonate (233 mg, 1.69 mmoles) and the halide derivative (1.3 equivalents) was added. The mixture was heated at 60° or 90° (as indicated in the Table) for 1.5 hours. Dimethylformamide was removed under reduced pressure, then water was added to the residue (10 ml). The aqueous layer was neutralized with a 10% aqueous hydrochloric acid solution and the product was extracted twice with 10 ml of diethyl ether. The organic layers were dried (magnesium sulfate). After filtration, the solvent was removed *in vacuo* and the residue obtained was chromatographed on a silica gel column using dicholoromethane as the eluent.

Methyl 3-(3-Cyanopropoxy)-1*H*-indole-2-carboxylate (**6**) [22].

Methyl 3-(Benzyloxycarbonylmethoxy)-1*H*-indole-2-carboxylate (**7**).

This compound was obtained as a solid, 325 mg (74%), mp 160° (ethanol); ir (potassium bromide): ν 3340, 1750, 1700 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 3.92 (s, 3H, O*Me*), 4.76 (s, 2H, OCH_2), 5.25 (s, 2H, CH_2Ø), 7.01 (t, 1H, H_{arom}, J = 8.1 Hz), 7.16 (d, 1H, H_{arom}, J = 8.1), 7.22-7.34 (m, 6H, H_{arom}), 7.79 (d, 1H, H_{arom}, J = 7.3 Hz), 8.41 (br s, 1H, N*H*).

Anal. Calcd. for $C_{19}H_{17}NO_5$: C, 67.25; H, 5.05; N, 4.13. Found: C, 67.10; H, 4.90; N, 4.35.

Methyl 2-(2-Cyanoethyl)-3-oxo-2,3-dihydro-1*H*-indole-2-carboxylate (**8**).

This compound was obtained as an oil, 200 mg (63%); ir (film): ν 3340, 2220, 1700 (br) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.35-2.49 (m, 4H, CH_2CH_2CN), 3.81 (s, 3H, O*Me*), 5.25 (s, 1H, N*H*), 6.96 (t, 1H, H_{arom}, J = 8.1 Hz), 7.04 (d, 1H, H_{arom}, J = 8.1 Hz), 7.55 (t, 1H, H_{arom}, J = 8.1 Hz), 7.62 (d, 1H, H_{arom}, J = 8.1 Hz).

Anal. Calcd. for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.47. Found: C, 63.67; H, 4.90; N, 11.30.

Methyl 2-(2-Benzyloxycarbonylethyl)-3-oxo-2,3-dihydro-1*H*-indole-2-carboxylate (**9**).

This compound was obtained as an oil, 350 mg (70%); ir (film): ν 3370, 1700 (broad) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.21-2.60 (m, 4H, CH_2CH_2COO), 3.76 (s, 3H, OCH_3), 5.01 (s, 2H, CH_2Ø), 5.32 (br s, 1H, N*H*), 6.88 (d, 1H, H_{arom}, J = 8.1 Hz), 7.31-7.37 (m, 5H, H_{arom}), 7.47 (m, 1H, H_{arom}), 7.58 (d, 1H, H_{arom}, J = 8.1 Hz), 7.72 (m, 1H, H_{arom}); uv (methanol): λ_{max} 232.4 nm; ms: (IE) m/z 353 (M^+).

Anal. Calcd. for $C_{20}H_{19}NO_5$: C, 67.98; H, 5.42; N, 3.97. Found: C, 68.08; H, 5.50; N, 3.85.

Spiro[3-oxo-2*H*-indole-2,3'-(2'-oxopiperidine)] (**10**).

Compound **8** (100 mg, 0.4 mmole) was dissolved in 5 ml of dry methanol. Platinum oxide (10 mg) was added and the solution was stirred under one atmosphere of hydrogen during 15 hours. The catalyst reagent was filtered and the solvent was removed under reduced pressure to afford yellow crystals which were chromatographed on a silica gel column using dichloromethane:methanol, 95:5 as eluent. Product **10** was obtained as yellow crystals, 78 mg (90%), mp 209° (methanol); ir (potassium bromide): ν 3330, 1670, 1640 cm^{-1}, ^{1}H nmr (dimethyl sulfoxide-d_6): δ 1.65-2.20 (m, 4H, $CH_2CH_2CH_2NH$), 3.60 (d, 2H, CH_2NH, J = 7.3 Hz), 6.70 (t, 1H, H_{arom}, J = 8.1 Hz), 6.82 (d, 1H, H_{arom}, J = 8.1 Hz), 7.30 (t, 1H, H_{arom}, J = 8.1 Hz), 7.45 (d, 1H, H_{arom}, J = 8.1 Hz), 7.84 (br s, 1H, N*H*), 7.90 (br s, 1H, N*H*); ms: (m/z, NH_3): 217 (M^++1).

Anal. Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.66; H, 5.59; N, 12.95. Found: C, 66.86; H, 5.35; N, 12.84.

Methyl 2-Propyl-3-oxo-2,3-dihydro-1*H*-indole-2-carboxylate (**11**).

Compound **11** was isolated as an oil along with compound **10**, 10 mg (10%); ir (film): ν 3340, 1730, 1680 cm^{-1}; ^{1}H nmr, (deuteriochloroform): δ 0.92 (t, 3H, $CH_2CH_2CH_3$, J = 7.3 Hz), 1.33 (m, 2H, $CH_2CH_2CH_3$), 1.90 (m, 1H, $CH_2CH_2CH_3$), 2.15 (m, 1H, $CH_2CH_2CH_3$), 3.78 (s, 3H, O*Me*), 5.19 (s, 1H, N*H*), 6.88 (t, 1H, H_{arom}, J = 8.1 Hz), 6.97 (d, 1H, H_{arom}, J = 8.1 Hz), 7.48 (t, 1H, H_{arom}, J = 8.1 Hz), 7.59 (d, 1H, H_{arom}, J = 8.1 Hz).

Anal. Calcd. for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.80; H, 6.70; N, 6.15.

Spiro[3-oxo-2*H*-indole-2,3'-piperidine] (**13**).

Compound **10** (200 mg, 0.93 mmole) was dissolved in dry tetrahydrofuran (10 ml), and then borane-methyl sulfide complex (0.93 ml, 1.86 mmoles) was added dropwise under argon and the solution was stirred under reflux 4 hours. The mixture was then allowed to cool to room temperature and a 4*N* aqueous hydrochloric acid solution (1.4 ml, 5.55 mmoles) was added, followed by addition of methanol (1.4 ml). The solution was refluxed for 1.5 hours and then water was added (10 ml). The aqueous layer was basified and the product was extracted twice with ethyl acetate (10 ml). The organic layer was dried over magnesium sulfate. After filtration, the solvent was evaporated and the residue was purified on a silica gel column (eluent:dichloromethane:methanol, 97:3) to give the expected product as an oil, 85 mg (45%); ir (film): ν 3325; 1680 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.64-1.82 (m, 4H, CH_2), 2.65 (br s, 1H, N*H*), 2.81-2.98 (m, 4H, CH_2), 3.80 (br s, 1H, N*H*), 6.62 (t, 1H, H_{arom}, J = 8.2 Hz), 6.67 (d, 1H, H_{arom}, J = 8.2 Hz), 6.96-7.26 (m, 2H, H_{arom}).

Anal. Calcd. for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.19; H, 6.82; N, 13.78.

Spiro[2,3-dihydro-2*H*-indole-2,3'-piperidine] (**14**).

Compound **13** (50 mg, 0.25 mmole) was dissolved in dry methanol (5 ml) and 10% palladium on carbon (10 mg) was added. The solution was stirred for 3 hours under an hydrogen atmosphere. The catalyst was then filtered and the solvent was evaporated *in vacuo*. The residue obtained was then chromatographed on a silica gel column (eluent:dichloromethane:methanol, 95:5) to give an oily product, 35 mg (71%); ir (film): ν 3311 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.66-2.07 (m, 4H, CH_2), 2.85-2.95 (m, 4H, CH_2), 3.14-3.28 (m, 2H, CH_2), 5.32 (br s, 1H, N*H*), 5.92 (m, 1H, N*H*), 6.65 (m, 2H, H_{arom}), 6.97-7.07 (m, 2H, H_{arom}); ^{13}C nmr (deuteriochloroform): δ 19.4 (CH_2), 28.7 (CH_2), 33.9 (CH_2), 40.2 (CH_2), 43.4 (CH_2), 59.9 (C-2), 108.6 (CH_{arom}), 117.6 (CH_{arom}), 123.9 (CH_{arom}), 125.1 (C), 126.7 (CH_{arom}), 148.2 (C); ms: (m/z, NH_3) 189 (M^++1).

Anal. Calcd. for $C_{12}H_{16}N_2$: C, 76.56; H, 8.57; N, 14.88. Found: C, 76.40; H, 8.50; N, 14.70.

Methyl 2-(2-Cyanoethyl)-3-hydroxy-2,3-dihydro-1*H*-indole-2-carboxylate (**15**).

Compound **8** (3.7 g, 15 mmoles) was dissolved in chloroform (90 ml) and methanol (30 ml). Silica gel (7.5 g) and then sodium borohydride (1.43 g, 37 mmoles) were added to the solution at 0°. The mixture was then stirred at room temperature overnight. Silica gel was filtered and the solvents were removed under reduced pressure. Water (30 ml) was added to the residue and the products were extracted twice with ethyl acetate (40 ml). The organic layers were dried over magnesium sulfate. After filtration the solvent was removed *in vacuo* and the residue obtained was purified on a silica gel column using dichloromethane:methanol, 99/1 as eluent to afford compound **15** as a white solid, 2 g (54%), mp 218-220° (dichloromethane); ir (potassium bromide): ν 3260, 2253, 1724 cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 2.06-2.20 (m, 2H, CH_2), 2.48-2.61

(m, 2H, C*H*$_2$), 3.62 (s, 3H, OC*H*$_3$), 5.05 (d, *H*-3, J = 7.8 Hz), 5.74 (d, 1H, O*H*, J = 7.8 Hz), 6.37 (br s, 1H, N*H*), 6.54-6.62 (m, 2H$_{arom}$), 6.99 (t, 1H$_{arom}$, J = 8.2 Hz), 7.10 (d, 1H$_{arom}$, J = 8.2 Hz); ^{13}C nmr (dimethyl sulfoxide-d$_6$): δ 12.9 (CH$_2$), 29.2 (CH$_2$CN), 53.0 (CH$_3$), 72.5 (C-2), 76.5 (CH), 109.6 (CH), 118.3 (CH), 121.0 (CN), 126.0 (CH), 129.2 (C), 129.9 (CH), 150.7 (C), 175.2 (CO); ms: (m/z, NH$_3$) 247 (M$^+$+1).

Anal. Calcd. for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.55; H, 5.63; N, 11.15.

Spiro[3-hydroxy-2*H*-indole-2,3'-(2'-oxopiperidine)] (**16**).

The procedure was the same as for the hydrogenation of compound **8** under 3 atmospheres of hydrogen with a reaction time of 24 hours, (57%), mp 174-176° (ethanol); ir (potassium bromide): ν 3320, 3200, 1675 cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d$_6$): δ 1.54-1.62 (m, 1H, C*H*$_2$), 1.72-1.82 (m, 2H, C*H*$_2$), 2.02-2.12 (m, 1H, CH$_2$), 3.12-3.16 (m, 2H, C*H*$_2$NH), 5.10 (d, 1H, *H*-3, J = 7.8 Hz), 5.38 (d, 1H, O*H*, J = 7.8 Hz), 6.39 (d, 1H, H$_{arom}$, J = 7.5 Hz), 6.52 (t, 1H, H$_{arom}$, J = 7.5 Hz), 6.94 (t, 1H, H$_{arom}$, J = 7.5 Hz), 7.04 (d, 1H, H$_{arom}$, J = 7.5 Hz), 7.44 (br s, 1H, N*H*); ^{13}C nmr (dimethyl sulfoxide-d$_6$): δ 23.3 (CH$_2$), 28.6 (CH$_2$), 42.1 (CH$_2$), 68.1 (C-2), 76.4 (CH-3), 108.8 (CH), 117.2 (CH), 125.6 (CH), 129.2 (C), 131.0 (CH), 151.4 (C), 174.1 (CO).

Anal. Calcd. for $C_{12}H_{14}N_2O_2$: C, 66.05; H, 6.47; N, 12.84. Found: C, 66.21; H, 6.38; N, 12.75.

Spiro[3-*t*-butyldimethylsilyloxy-2*H*-indole-2,3'-(2'-oxopiperidine)] (**17**).

Compound **16** (750 mg, 3.44 mmoles) was dissolved in dry dimethylformamide (35 ml). Imidazole (470 mg, 6.88 mmoles) and *t*-butyldimethylsilyl chloride (1 g, 6.88 mmoles) were added and the solution was stirred for 2 hours at 55°. The dimethylformamide solution was concentrated under reduced pressure to 5 ml. Then water (30 ml) was added and a white precipitate appeared. After filtration, the solid was washed with ethanol and dried *in vacuo*, 1.1 g, (95%), mp 210-212° (ethanol); ir (potassium bromide): ν 3291, 3202, 1654 cm^{-1}, ^{1}H nmr (deuteriochloroform): δ 0.11 (s, 3H, SiC*H*$_3$), 0.15 (s, 3H, SiC*H*$_3$), 0.93 (s, 9H, *t*-Bu), 1.70-1.80 (m, 2H, C*H*$_2$); 1.90-1.92 (m, 1H, C*H*$_2$); 2.19-2.25 (m, 1H, C*H*$_2$), 3.24-3.29 (m, 2H, C*H*$_2$NH), 4.33 (s, 1H, N*H*), 5.78 (s, 1H, *H*-3), 6.60 (d, 1H, H$_{arom}$, J = 7.8 Hz), 6.77 (t, 1H, H$_{arom}$, J = 7.8 Hz), 6.91 (br s, 1H, N*H*), 7.04-7.15 (m, 2H, H$_{arom}$); ^{13}C nmr (deuteriochloroform): δ -2.4 (CH$_3$), 20.1 (CH$_2$), 21.5 (*C*(CH$_3$)$_3$), 27.8 (CH$_3$), 29.5 (CH$_2$), 44.4 (CH$_2$), 71.7 (C-2), 79.9 (CH-3), 112.7 (CH), 121.6 (CH), 126.6 (CH), 130.9 (CH), 131.9 (C), 150.1 (C), 176.0 (CO).

Anal. Calcd. for $C_{18}H_{28}N_2O_2Si$: C, 65.02; H, 8.49; N, 9.62. Found: C, 65.32; H, 8.70; N, 9.33.

Spiro[3-*t*-butyldimethylsilyloxy-2*H*-indole-2,3'-piperidine] (**18**).

Compound **17** (250 mg, 0.75 mmole) was dissolved in dry tetrahydrofuran (10 ml) and boran-tetrahydrofuran complex (1*M* solution in tetrahydrofuran, 4.4 ml, 4.38 mmoles) was added and the solution was heated 4 hours under reflux. After cooling the solvent was removed under reduced pressure. Water (5 ml) was added to the residue and the aqueous layer was basified with a 5% sodium hydroxide solution to *p*H 12. The product was then extracted twice with ethyl acetate (10 ml). The organic layer was then dried over magnesium sulfate. After filtration, the solvent was removed *in vacuo* and the residue was purified on a silica gel column (eluent:dichloromethane:methanol, 97:3) to afford a white solid, 125 mg (52%), mp 132-134° (ethanol); ir (potassium bromide): ν 3345 cm^{-1}, ^{1}H nmr (dimethyl sulfoxide-d$_6$): δ 0.01 (s, 3H, SiC*H*$_3$), 0.12 (s, 3H, SiC*H*$_3$), 0.80 (s, 9H, *t*-Bu), 1.63-1.72 (m, 4H, C*H*$_2$), 2.58-2.71 (m, 4H, CH$_2$), 3.20 (br s, 1H, N*H*), 4.73 (s, 1H, NH), 5.78 (s, 1H, *H*-3), 6.49-6.57 (m, 2H, H$_{arom}$), 6.97 (t, 1H, H$_{arom}$, J = 7.8 Hz), 7.08 (d, 1H, H$_{arom}$, J = 7.8 Hz).

Anal. Calcd. for $C_{18}H_{30}N_2OSi$: C, 67.87; H, 9.49; N, 8.79. Found: C, 67.52; H, 9.20; N, 8.45.

Ethyl 2-(2-Benzyloxycarbonylethyl)-3-oxo-2,3-dihydro-1-methylindole-2-carboxylate (**19**).

The same procedure was used as for compound **9** to furnish an oil, 65%; ir (film): ν 1720 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.20 (t, 3H, OCH$_2$C*H*$_3$, J = 7.0 Hz), 2.01-2.25 (m, 2H, C*H*$_2$), 2.42-2.52 (m, 1H, C*H*$_2$), 2.66-2.76 (m, 1H, C*H*$_2$), 2.90 (s, 3H, N*Me*), 4.11-4.19 (m, 2H, OC*H*$_2$CH$_3$), 5.03 (s, 2H, C*H*$_2$Ø), 6.76 (t, 1H, H$_{arom}$, J = 8.1 Hz), 7.26-7.33 (m, 6H, H$_{arom}$), 7.47 (d, 1H, H$_{arom}$, J = 8.1 Hz), 7.56 (d, 1H, H$_{arom}$, J = 8.1 Hz); ^{13}C nmr (deuteriochloroform): δ 14.1 (CH$_3$), 26.3 (CH$_2$), 28.0 (CH$_2$), 29.2 (CH$_3$), 62.2 (CH$_2$), 66.4 (CH$_2$), 79.3 (C-2), 108.8 (CH), 118.1 (CH), 119.6 (C), 125.1 (CH), 126.9 (CH), 128.6 (CH), 135.6 (C), 138.1 (CH), 162.0 (C), 166.7 (CO), 172.3 (CO), 195.4 (CO).

Anal. Calcd. for $C_{22}H_{23}NO_5$: C, 69.27; H, 6.08; N, 3.67. Found: C, 69.51; H, 5.88; N, 3.60.

3-[2-(Methoxycarbonyl)-3-oxo-2,3-dihydro-1*H*-2-indolyl]propanoic Acid (**20**).

Compound **9** (200 mg, 0.56 mmole) was dissolved in dry methanol (5 ml) and 10% palladium on carbon (25 mg) was added. The solution was stirred for 1 hour at room temperature under one atmosphere of hydrogen, then palladium on carbon was filtered and the solvent was removed *in vacuo*. Water (10 ml) was added, and the aqueous layer was made basic (*p*H = 10-11) with 5% sodium hydroxide solution. The aqueous layer was twice treated with ethyl acetate (10 ml) and then acidified to *p*H 1 with a 10% hydrochloric acid solution. Extraction twice with ethyl acetate (10 ml), drying (magnesium sulfate) and evaporation *in vacuo* give **20** as an oil, 70 mg (47%); ir (film): ν 3330, 1740, 1680 cm^{-1}; ^{1}H nmr (methanol): δ 2.10-2.30 (m, 2H, C*H*$_2$COOH), 2.38-2.45 (m, 2H, C*H*$_2$CH$_2$COOH), 3.70 (s, 3H, OMe), 5.49 (br s, 1H, NH), 6.79 (t, 1H, H$_{arom}$, J = 8.1 Hz), 6.95 (m, 1H, H$_{arom}$), 7.92-7.98 (m, 1H, H$_{arom}$), 7.52 (d, 1H, H$_{arom}$, J = 8.1 Hz); ms: (IE) m/z 263 (M$^+$).

Anal. Calcd. for $C_{13}H_{13}NO_5$: C, 59.31; H, 4.98; N, 5.32. Found: C, 59.45; H, 4.82; N, 5.45.

Methyl 2-Oxo-2,3,4,4a,5,9b-hexahydropyrano[3,2-*b*]indole-4a-carboxylate (**21**).

Compound **21** was isolated along with compound **20** during the hydrogenolysis of compound **9** as an oily product, 62 mg (45%); ir (film): ν 3300, 1730, 1690 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.20-2.31 (m, 1H, C*H*COO), 2.55-2.63 (m, 1H, C*H*COO), 2.82-2.95 (m, 1H, C*H*CH$_2$COO), 3.00-3.07 (m, 1H, CHCH$_2$COO), 3.77 (s, 3H, O*Me*), 5.51 (s, 1H, C*H*OCO), 5.54 (s, 1H, N*H*), 7.14-7.19 (t, 1H, H$_{arom}$, J = 8.1 Hz); 7.32-7.34 (m, 2H, H$_{arom}$), 7.62 (d, 1H, H$_{arom}$, J = 8.1 Hz); ms: (m/z, NH$_3$): 248 (M$^+$+1).

Anal. Calcd. for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67. Found: C, 63.39; H, 5.05; N, 5.55.

Benzyl 3-(3,9-Dioxo-2,3,9,9a-tetrahydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)propanoate (**23**).

The procedure was the same as for compound **9** by using 2 equivalents of benzyl 3-bromopropionate to give an oil, 250 mg (50%); ir (film): ν 1720 (broad) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.18-2.52 (m, 6H, CH_2); 2.54-2.64 (m, 1H, $NCOCH_2CH_2$), 2.99-3.54 (m, 1H, $NCOCH_2CH_2$), 5.08 (m, 2H CH_2Ø), 7.20-7.44 (m, 7H, H_{arom}), 7.14 (d, 1H, H_{arom}, J = 8.1 Hz), 7.39 (d, 1H, H_{arom}, J = 8.1 Hz); ms: (m/z, NH_3): 350 (M^++1).

Anal. Calcd. for $C_{21}H_{19}NO_4$: C, 72.19; H, 5.48; N, 4.01. Found: C, 72.45; H, 5.30; N, 4.15.

3-(3-Oxo-2,3-9,9a-tetrahydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)propanoic Acid (**24**).

Compound **23** (0.2 g, 0.6 mmole) was dissolved in ethanol (5 ml). Potassium hydroxide (50 mg, 0.89 mmole) was added and the mixture was stirred at room temperature for 24 hours. After evaporation of ethanol, water (10 ml) was added and the solution was basified to *p*H 10-11 with a 5% sodium hydroxide solution and non acidic products were extracted twice with ethyl acetate (10 ml). Then the aqueous layer was acidified to *p*H 1 with a 10% hydrochloric acid solution and the acidic compounds were extracted with ethyl acetate (10 ml). The organic layer was dried (magnesium sulfate). After filtration, the solvent was removed under reduced pressure to give an oil, 130 mg, (87%); ir (film): ν 3350, 1740, 1690 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 1.60-2.22 (m, 8H, CH_2); 6.72 (t, 1H, H_{arom}, J = 8.2 Hz), 7.82 (d, 1H, H_{arom}, J = 8.2 Hz), 7.27-7.48 (m, 2H, H_{arom}); ms: (m/z, NH_3) 260 (M^++1).

Anal. Calcd. for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40. Found: C, 64.58; H, 5.15; N, 5.52.

3-(9-Hydroxy-3-oxo-2,3,9,9a-tetrahydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)propanoic Acid (**25**).

Compound **23** (0.2 g, 0.6 mmole) was dissolved in dry methanol (8 ml) and 10% palladium on carbon (20 mg) was added. The mixture was stirred for 6 hours under one atmosphere of hydrogen. Palladium on carbon was filtered and methanol was removed *in vacuo*. Water (10 ml) was added and the solution was basified to *p*H 10-11 with a 5% sodium hydroxide solution and non acidic products were extracted twice with ethyl acetate (10 ml). Then the aqueous layer was acidified to *p*H 1 with a 10% hydrochloric acid solution and the acidic compounds were extracted with ethyl acetate (10 ml). The organic layer was dried (magnesium sulfate). After filtration, the solvent was removed under reduced pressure to give an oil, 130 mg (88%); ir (film): ν 3450, 1650 (large) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 1.86-2.30 (m, 6H, CH_2), 2.36-3.04 (m, 1H, $NCOCH_2CH_2$), 3.24-3.30 (m, 1H, $NCOCH_2CH_2$), 5.22 (s, 1H, $CHOH$), 7.05 (t, 1H, H_{arom}, J = 8.1 Hz), 7.14-7.30 (m, 3H, H_{arom}); ms: (m/z, NH_3) 243 (M-18).

Anal. Calcd. for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.78; N, 5.36. Found: C, 64.45; H, 5.60; N, 5.19.

3,4,6,7-Tetrahydro-2*H*,5*H*,12b*H*-pyrano[3,2-*b*]pyrrolo[1,2-*a*]indole-2.7-dione (**26**).

Compound **25** (130 mg, 0.5 mmole) was dissolved in a mixture of xylene (5 ml) and dimethylformamide (1 ml) and the solution was heated at 100° for 48 hours. The solvent was removed under reduced pressure and the obtained residue was directly purified on a silica gel chromatography (eluent:dichloromethane:methanol, 99:1) to give an oil, 100 mg (83%); ir (film): ν 1740, 1690 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.08 (ddd, 1H, *H*-11β, J = 12.0, 11.6, 3.5), 2.29 (ddd, 1H, H-12β, J = 16.8, 11.6, 3.8), 2.38 (m, 3H, *H*-10α,β, *H*-11α), 2.52 (ddd, 1H, H-12β, J = 16.6 Hz, 5.9 Hz, 3.6 Hz), 2.60 (ddd, 1H, *H*-9, J = 17.0 Hz, 8.0 Hz, 1.1 Hz), 2.94 (ddd, *H*-9, J = 17.1 Hz, 12.5 Hz, 8.0 Hz), 5.92 (s, *H*-3), 7.17 (t, 1H, *H*-5, J = 7.8 Hz), 7.34 (t, 1H, *H*-6, J = 7.8 Hz), 7.37 (d, 1H, *H*-4, J = 7.8 Hz), 7.59 (d, 1H, *H*-7, J = 8.0 Hz); ^{13}C nmr (deuteriochloroform): 28.1 (CH_2COO), 30.8 (CH_2CH_2COO), 34.2 (CH_2CO), 34.3 (CH_2), 69.1 (C-2), 86.3 (C*H*-3), 115.15 (CH_{arom}-7), 125.5 (CH_{arom}-5), 125.7 (CH_{arom}-4), 130.9 (CH_{arom}-6), 131.0 (C_{arom}-3a), 139.7 (C_{arom}-7a), 170.8 (C=O, lactone), 172.4 (C=O, lactam); ms: (m/z, NH_3) 244 (M^++1).

Anal. Calcd. for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 68.92; H, 5.16; N, 5.65.

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[26] Compound **12** was obtained in 80% yield by reacting ethyl 3-hydroxy-1-methylindole-2-carboxylate with 3-bromopropanenitrile as for compound **8**.

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[29] The numbering of atoms in compound **26** in Scheme 6 refer to the nmr data.