SYNTHESIS OF THE ABCD RING SYSTEM OF *VINCA* ALKALOIDS USING TANDEM INTRAMOLECULAR [2+2]-PHOTOCYCLOADDITION-RETRO-MANNICH FRAGMENTATION[1]

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Abstract – Irradiation of 3-alkyl indole **20** gave spiropyrroline **22** via [2+2]-photocycloaddition and subsequent *in situ* retro-Mannich fragmentation of fused cyclobutane **21**. *N*-Alkylation of **22** followed by treatment of the resulting pyrrolinium salt with sodium hydride and lithium diisopropylamide generated a dienolate dianion, e.g. **24**, which underwent cyclization to afford tetracyclic products **25**, **27** and **30**. The configuration of **25** was proven by a series of NMR experiments which established that ring C in the major stereoisomer resides in a boat conformation. Tetracycles **25**, **27**, and **30** contain structural features including the ABCD ring system and substituents found in certain alkaloids of the *Vinca* family.

Indole alkaloids of the tropical periwinkle (*Vinca rosea*) have attracted interest from natural product chemists for more than a half century, in large part due to the unique pharmacological properties that certain members of the class exhibit.[2] Prominent within this family are the naturally occurring bisindole alkaloids vinblastine (**1**) and vincristine (**2**), two of today's most widely used drugs for the treatment of cancer (Figure 1).[3] Recognition of the pentacyclic alkaloid vindoline (**3**) as a structural component of **1** and **2** brought attention to **3**, as well as its desmethoxy analog vindorosine (**4**), that has led to a large number of synthetic strategies for accessing these complex structures.[4,5] Success in these endeavors along with methodology for coupling **3** with its catharanthine partner has resulted in practical routes to totally synthetic vinblastine and vincristine for their use in medicine.[6]
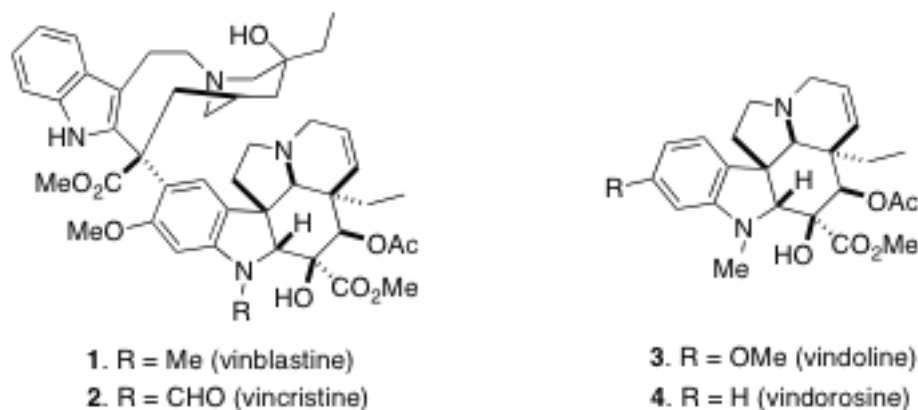
Figure 1. Structures of indole alkaloids vinblastine, vincristine, vindoline and vindorosine

The first synthesis of **3** was completed in 1975 by Büchi[4a] and proceeded via tetracyclic ketone **5** comprising rings A, B, C and D of the vindoline skeleton (Scheme 1). Annulation of ring E on to **5** led to pentacycle **6** which was advanced in four steps to (±)-**3**. Ketone **5** ("Büchi's ketone") and closely related compounds have been used in several routes to **3**,[4a,c,d] making this tetracyclic scaffold a key component of pathways to members of this alkaloid class. More recent studies have explored varied and in some cases highly innovative strategies for acquiring **3**.[7] These include several syntheses which produce natural (-)-vindoline in enantio-enriched form.[7,8] Nevertheless, the case for a utilitarian precursor similar to ketone **5** as a gateway to vindoline and related alkaloids remains compelling.
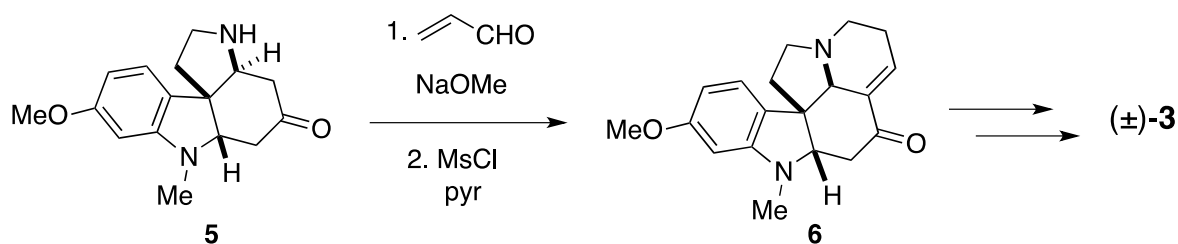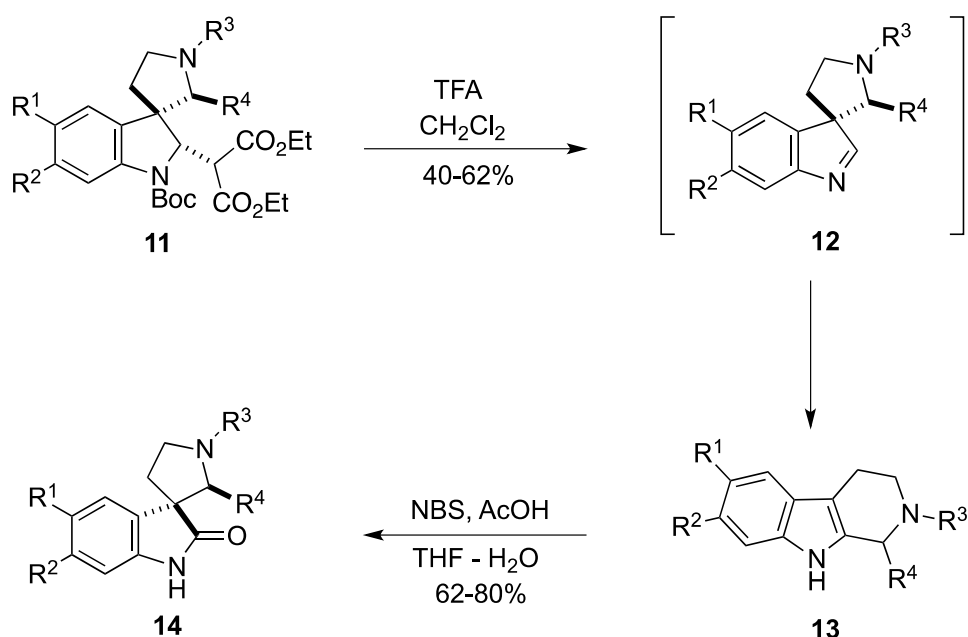

Scheme 1

As part of a broad study on the use of cyclobutanes in natural product synthesis,[9] we devised several new synthetic strategies based upon directed fragmentation of a strained cyclobutane ring.[10] The concept has been demonstrated in the construction of both carbocyclic[11] and heterocyclic[12] systems present in a variety of natural products. In 2006, we reported a novel route to the spiro[indolopyrrolidine] system **7** from tryptamine derivative **8** using tandem intramolecular [2+2]-photocycloaddition of a 3-substituted indole followed by retro-Mannich fragmentation of photoadduct **9** to give **10** (Scheme 2).[13] We also showed that this methodology (abbreviated TIPCARM) could be employed in construction of the tricyclic core of the *Gelsemium* alkaloid koumine.
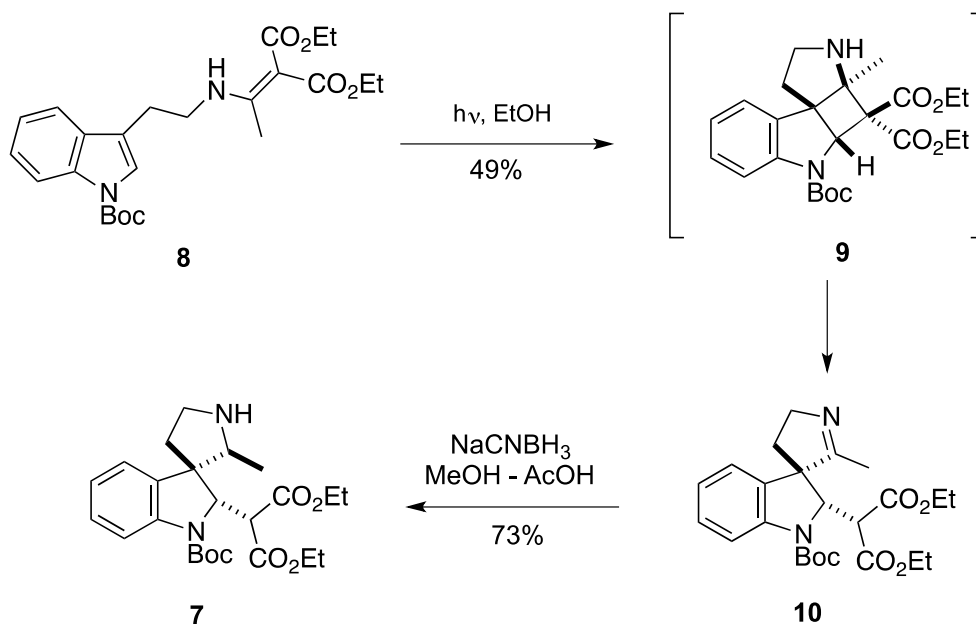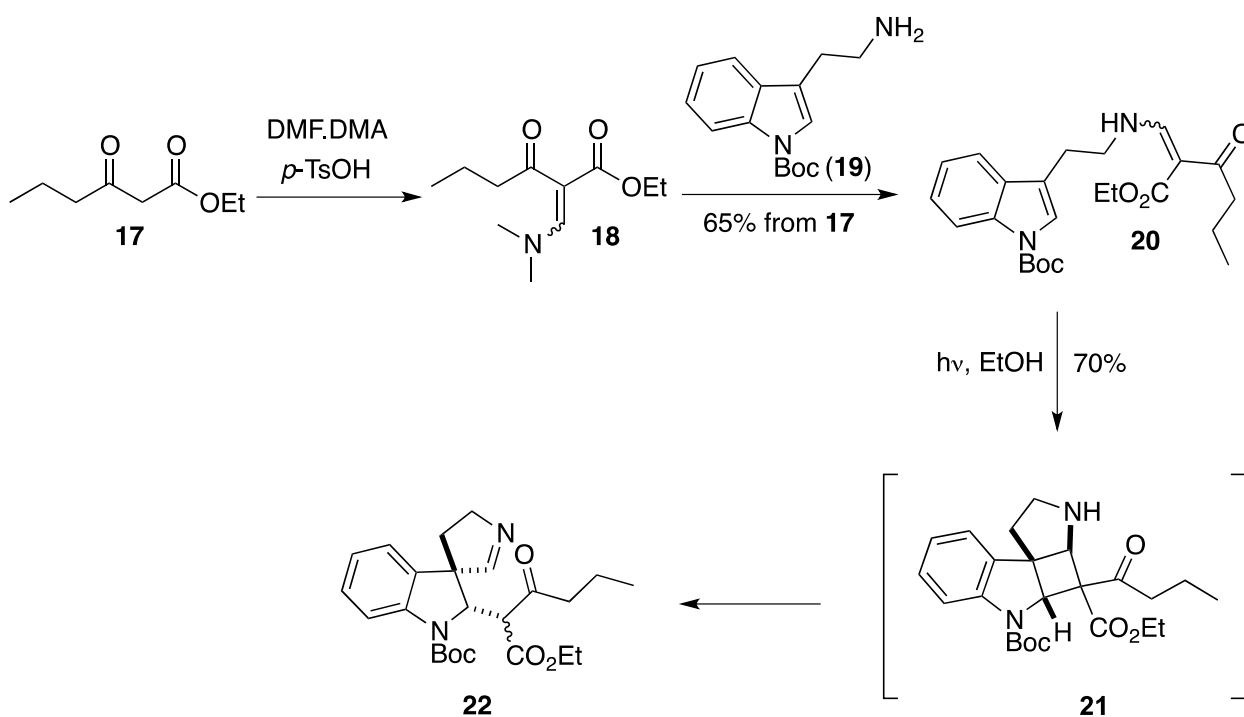
Scheme 2

An extension of this method in which a second retro-Mannich fragmentation was introduced in order to expel the malonate residue from C2 of **7**, [TIPCA(RM)$_2$], resulted in conversion of **11** to indolenine **12** which underwent subsequent rearrangement to β-carboline **13**.[14] Further rearrangement of **13** via brominative oxidation led to efficient syntheses of the oxindole alkaloids (±)-coerulescine (**14**), (±)-horsfiline (**15**),[15] and (±)-elacomine (**16**)[16] (Scheme 3). It was apparent in the course of these studies that TIPCARM represents a powerful approach to building heterocyclic frameworks common to a wide variety of indole alkaloids, including members of the *Strychnos* and *Vinca* families. We now describe a further extrapolation of TIPCARM which assembles the tetracyclic core comprising rings A, B, C, and D of vindorosine (**4**) and which thereby affords a platform for accessing an array of *Vinca* alkaloids.
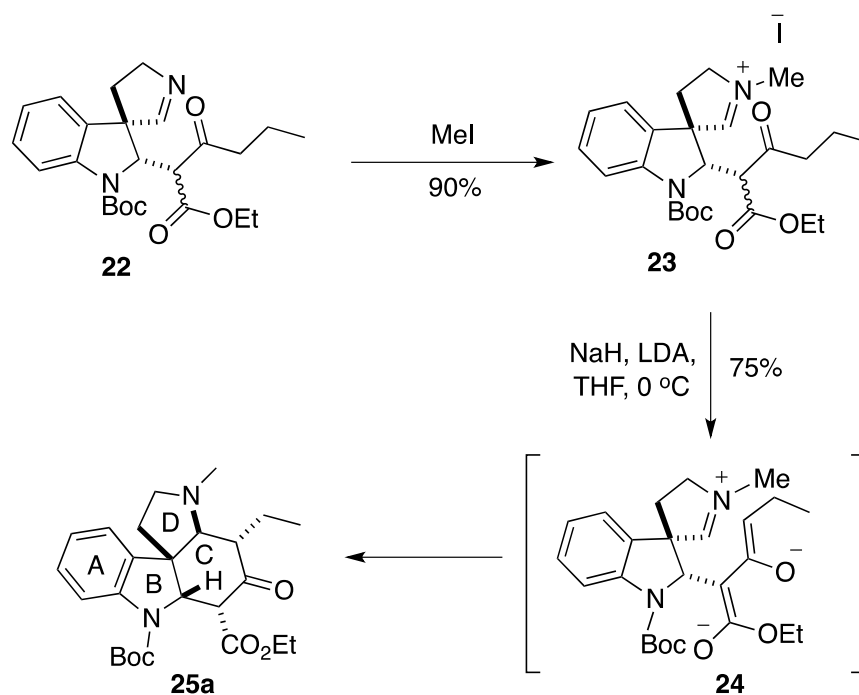

Scheme 3

A photo substrate analogous to **8** that would include all of the carbons needed to assemble an ABCD tetracycle analogous to Buchi's ketone **5** would ideally embody both the angular ethyl group and the ring C carboxylic ester present in a *Vinca* alkaloid such as **3**.   This led to commercially available ethyl 3-oxohexanoate (**17**) as the starting point for our approach to **3** and/or **4**. Condensation of **17** with *N,N*-dimethylformamide dimethyl acetal in the presence of *p*-toluenesulfonic acid gave enamine **18** which was coupled with *N*-Boc tryptamine **19**[14] to afford photo substrate **20** as a *ca*. 1:1 mixture of (*E*) and (*Z*) stereoisomers (Scheme 4). Irradiation of **20** in ethanol through Corex glass produced transiently fused cyclobutane **21** which fragmented *in situ* via retro-Mannich scission to yield spiropyrroline **22**. Although the configuration of the ester substituent in **22** remained undefined, the relative orientation of substituents around the indoline nucleus was fixed by virtue of their derivation from *cis*-fused cyclobutane **21**.

Scheme 4

Spiropyrroline **22** was unstable and attempts to fabricate ring C of a tetracyclic species from this imine were unsuccessful. However, **22** formed a stable methiodide **23** upon exposure to neat methyl iodide, and when **23** was reacted with sodium hydride and lithium diisopropylamide in THF in order to generate dianion **24**, tetracyclic ketone **25** was formed in good yield as a 2:1 mixture of stereoisomers at the carboxylic ester (Scheme 5).

Scheme 5

The relative configuration of major isomer **25a** was established by a series of NMR experiments which included NOESY correlations between protons on rings C and D. Thus, a strong NOESY correlation between H-3 and H-10b confirmed that ring C in **25a** adopts a boat conformation and places H-3 on the endo face of the fused C/D system (Figure 2). The ^{1}H NMR spectrum of **25a** displays a singlet for H-2 at δ 5.02 indicating that this proton is cis and nearly orthogonal to H-3 at δ 3.28. A strong NOESY correlation between H-6 and methyl protons H-23 at δ 0.9 proved that H-6 and the ethyl substituent on ring C are cis and therefore that H-5 and H-6 are trans. The latter assignment is consistent with the signal for H-5 at δ 2.43 which appears as a doublet of triplets with coupling constants of 8.4 and 1.1 Hz. The small coupling constant between H-5 and H-6 is in accord with their trans orientation in a ring C boat conformation where the dihedral between these protons is close to 90°.
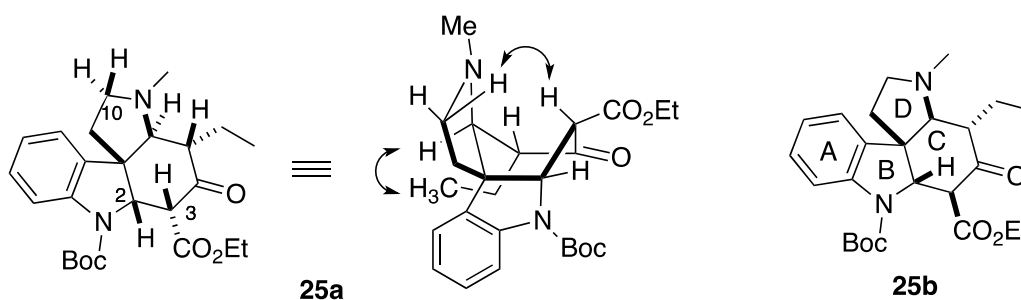

Figure 2

The minor isomer **25b** from **23** showed H-3 as a doublet at δ 3.68. The larger coupling (7.9 Hz) of this proton with H-2 implies a trans diaxial relationship and suggests that ring C in this stereoisomer adopts a chair conformation. This is consistent with the absence of a NOESY correlation between H-3 and H-10b in this stereoisomer.

The finding that methiodide **23** could be transformed via its dienolate into tetracyclic keto ester **25** raised the possibility that an extension of this strategy could be used to fabricate the entire pentacyclic skeleton of a *Vinca* alkaloid such as **4** from **22**.   In this plan, the pyrroline nitrogen of **22** would be quaternized with an alkyl group which, after cyclization of the corresponding dienolate to give the tetracyclic counterpart of **25**, would be functionalized in a manner that could lead directly to ring E.   To this end, **22** was reacted with allyl iodide and the resulting pyrrolinium salt **26** was treated with sodium hydride and lithium diisopropylamide in THF (Scheme 6). Tetracyclic keto ester **27** was produced in good overall yield from these two reactions but attempts to selectively oxidize the terminal olefin of **27** in the presence of the tertiary amine were unsuccessful.
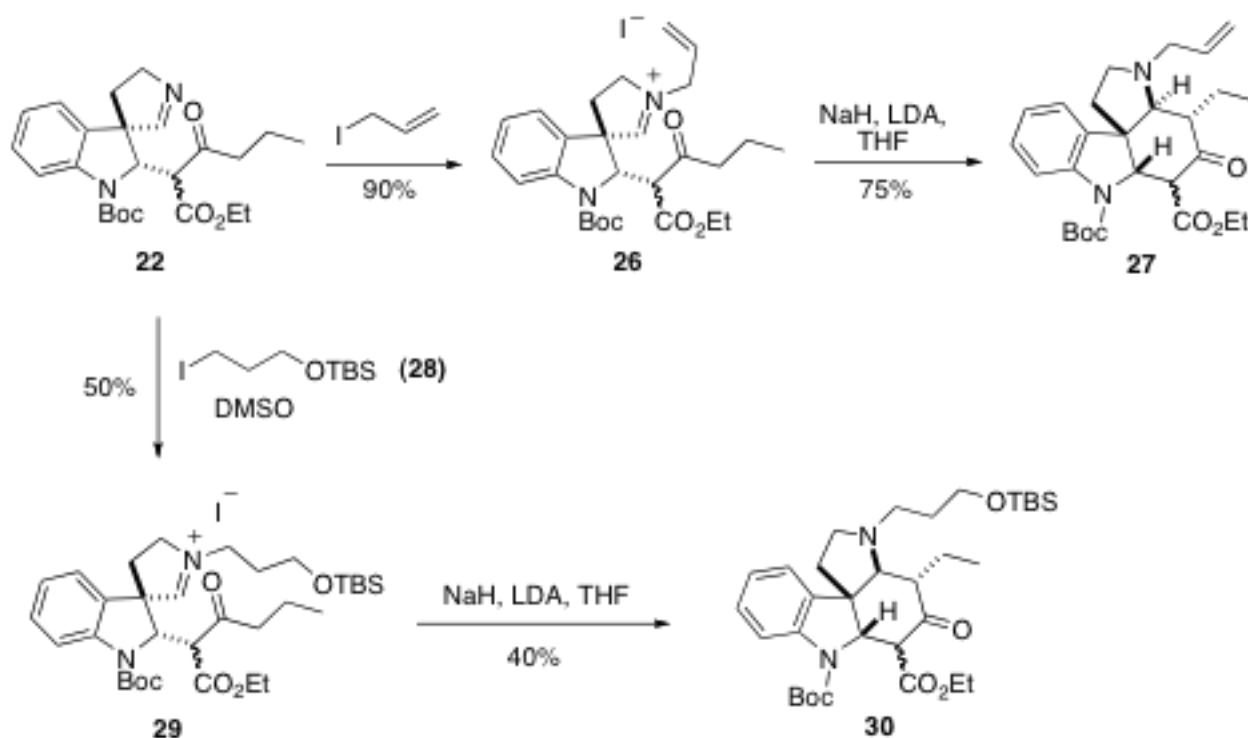
Scheme 6

An alternative sequence designed to accomplish annulation of ring E employed iodo ether **28**[17] for alkylation of **22** (Scheme 6). This gave iodide **29** but cyclization of this substrate via its dienolate produced tetracyclic keto ester **30** in only 20% overall yield from **22**. Although the *tert*-butyldimethylsilyl ether of **30** could be cleaved with tetra-*n*-butylammonium fluoride, oxidation of the resulting primary

alcohol to an aldehyde resulted in spontaneous retro-aza-Michael fragmentation that returned acrolein.   It is clear from these experiments that while spiropyrroline **22** offers an attractive platform for erecting the full pentacyclic scaffold of *Vinca* alkaloids, a judicious selection of the alkylating agent employed for quaternizing the pyrroline nitrogen must be made if the plan is to be successful.[18]

In summary, an approach based on tandem intramolecular photocycloaddition-retro-Mannich fragmentation of a C-3 substituted indole has been extended via cyclization of the resulting 2-alkyl 3,3'-spiropyrroline product to afford a functionalized tetracyclic keto ester resembling "Büchi's ketone" **5**. Further efforts will be focused on completion of a generic pentacyclic *Vinca* alkaloid precursor by annulating the final E ring of the alkaloid skeleton on to the tetracyclic nucleus of **22**.

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18. Experimental Section:

General. Infrared spectra were recorded neat unless otherwise indicated and are reported in cm^{-1}. ^{1}H NMR spectra were recorded in deuterated solvents, are reported in ppm relative to tetramethylsilane and are referenced internally to the residual protonated solvent. ^{13}C NMR spectra were recorded in deuterated solvents, are reported in ppm relative to tetramethylsilane and are referenced internally to the residual protonated solvent. Routine monitoring of reactions was performed using silica gel on aluminum-backed TLC plates. Flash chromatography was performed with the indicated eluents on 230-400 mesh silica gel. Air and/or moisture sensitive reactions were performed under inert atmosphere conditions. Reactions requiring rigorously anhydrous conditions were performed under an argon atmosphere in glassware dried in an oven at 150 °C or by flame and then cooled under argon. Dry THF and dichloromethane were obtained from a commercial solvent purification system. All other solvents and commercially available reagents were either purified via literature procedures or used without purification.

(2*S*,3*S*)-2-(1-*tert*-Butoxycarbonyl-2'-methyl-1,2,4',5'-tetrahydrospiro[indole-3,3'-pyrrol]-2-yl)-malonic acid diethyl ester (10). A degassed solution of **8** (100 mg, 225 µmol) in EtOH (100 mL) was irradiated with a Hanovia 450W medium pressure mercury lamp through a Corex filter for 4 h. The solution was concentrated under vacuum and the resulting yellow oil was purified by flash chromatography (hexanes:EtOAc 1:1) to afford **10** as a pale yellow oil (49 mg, 49%, 4:1 mixture of rotamers): IR (neat) 2979, 2934, 2863, 1752, 1733, 1706, 1603, 1483, 1372, 1308, 1283, 1253, 1165, 1028, 867, 755 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) for major rotamer δ 1.23 (t, *J* = 7.2 Hz, 3H), 1.25 (t, *J* = 7.2 Hz), 1.53 (s, 9H), 1.90 (ddd, *J* = 12.8, 10.4, 8.4 Hz, 1H), 2.03 (s, 3H), 2.41 (dd, *J* = 12.8, 6.0 Hz, 1H), 3.59 (d, *J* = 9.6 Hz, 1H), 3.76-3.84 (m, 1H), 3.95 (dd, *J* = 8.0, 7.2 Hz, 1H), 4.04-4.30 (m, 4H), 5.17 (d, *J* = 9.6 Hz, 1H), 6.93 (t, *J* = 7.6 Hz, 1H), 7.03 (t, *J* = 7.6 Hz, 1H), 7.25 (t, *J* = 8.0 Hz, 1H), 7.55 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 13.8 (x 2), 13.9, 14.0, 14.2, 17.7, 19.3, 21.0, 28.2 (x 2), 29.6, 38.1, 44.3, 53.0, 54.4, 57.4, 58.8, 61.7, 61.8 (x 2), 62.1, 65.5, 65.6, 67.5, 82.1, 109.9, 116.5, 119.9, 123.0, 123.7, 128.5, 133.0, 134.7, 149.2, 152.2, 166.4, 166.7, 166.8, 168.3, 173.3, 173.8; MS (CI) 446 (44), 445 (100), 417 (22), 399 (25), 389 (85), 346 (33), 345 (99), 344 (22), 343 (41), 299 (24); HRMS (CI) calcd for C$_{24}$H$_{33}$N$_2$O$_6$ *m/z* +*1* 445.2339, found 445.2345.

***tert*-Butyl 3-(2-((2-(ethoxycarbonyl)-3-oxohex-1-en-1-yl)amino)ethyl)-1*H*-indole-1-carboxylate (20).** A mixture of **17** (0.50 mL, 4.00 mmol), *N,N*-dimethylformamide dimethyl acetal (600 mg, 3.80 mmol) and *p*-TsOH (50 mg, 0.26 mmol) was stirred for 20 min, after which **19** (1.00 g, 3.80 mmol) was added in one portion. The mixture was stirred for 3 h, then was poured into H$_2$O (10 mL) and extracted with EtOAc (3 x 50 mL). The combined extracts were washed with brine and dried (Na$_2$SO$_4$) and the solvent was removed under vacuum. The residue was purified by flash

chromatography (hexanes:EtOAc 10:1) to give **20** as a colorless oil (1.10 g, 65%): IR (neat) 2976, 1732, 1694, 1634, 1453, 1379, 1255, 1158, 1092, 768, 746 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.97 (t, J = 7.3 Hz, 3H), 1.22 (t, J = 6.8 Hz, 3H), 1.64 (m, 2H), 1.68 (s, 9H), 2.87 (t, J = 7.3 Hz, 2H), 3.02 (t, J = 7.0 Hz, 2H), 3.65 (tt, J = 6.9, 6.9 Hz), 4.15 (tt, J = 6.9, 6.1 Hz, 2H), 7.27 (m, 1H), 7.35 (t, J = 7.4 Hz, 1H), 7.42 (s, 1H), 7.49 (d, J = 7.4 Hz, 1H), 8.16 (d, J = 13.0 Hz, 1H), 11.17 (bs, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 14.1, 14.5, 18.5, 26.7, 28.2, 44.0, 49.7, 59.4, 83.3, 99.9, 115.5, 116.1, 118.5, 122.5, 123.7, 124.7, 129.5, 135.0, 149.8, 160.1, 165.5, 202.1; HRMS (CI) calcd for C$_{24}$H$_{33}$N$_2$O$_5$ m/z+1 429.2311, found 429.2561.

(2S,3S)-*tert*-Butyl   2-((R)-1-ethoxy-1,3-dioxohexan-2-yl)-4',5'-dihydrospiro-[indoline-3,3'-pyrrole]-1-carboxylate (22). A degassed solution of **20** (500 mg, 1.20 mmol) in EtOH (100 mL) was irradiated with a Hanovia 450W medium pressure mercury lamp through a Corex filter for 40 h. The solution was concentrated under vacuum, and the resulting yellow oil was purified by chromatography on silica gel (hexanes:EtOAc 5:1) to afford **22** as a pale yellow oil (355 mg, 70%): IR (neat) 2972, 2932, 1709, 1481, 1382, 1251, 1166, 1055, 752, 733 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.83 (t, J = 7.9 Hz, 1H), 0.98 (t, J = 7.9 Hz, 2H), 1.11 (t, J = 7.1 Hz, 1H), 1.21 (t, J = 7.1 Hz, 2H), 1.51 (m, 2H), 1.60 (s, 9H), 2.00 (m, 1H), 2.06 (d, J = 4.6 Hz, 1H), 2.36 (m, 2H), 2.60 (m, 1H), 3.90 (m, 1H), 4.00 (m, 2H), 4.11 (m, 2H), 5.05 (t, J = 7.0 Hz, 1H), 6.84 (t, J = 9.6 Hz, 1H), 6.90 (m, 1H), 7.23 (tt, J = 6.9, 6.9 Hz, 1H), 7.64 (d, J = 11.7 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 13.4, 13.8, 14.1, 16.8, 25.9, 28.3, 41.6, 46.3, 59.5, 60.2, 61.8, 67.7, 82.3, 115.9, 122.8, 123.6, 128.7, 166.1, 166.8, 167.5; HRMS calcd for C$_{24}$H$_{32}$N$_2$O$_5$ m/z 428.2311, found 428.2322.

(2S,3S)-1-(*tert*-Butoxycarbonyl)-2-((R)-1-ethoxy-1,3-dioxohexan-2-yl)-1'-methyl-4',5'-dihydrospiro-[indoline-3,3'-pyrrol]-1'-ium iodide (23). Methyl iodide (2.2 mL, 4.0 mmol) was added to **22** (430 mg, 1.00 mmol), the reaction vessel was sealed, and the contents were stirred for 4 h. The pale yellow solution was concentrated under vacuum and the resulting solid was dried under high vacuum to afford **23** as a yellow solid (510 mg, 90%). This material was used for the next step without purification.

(3aR,6R,6aS,11bR)-7-*tert*-Butyl 6-ethyl 4-ethyl-3-methyl-5-oxo-3,3a,4,5,6,6a-hexahydro-1H-pyrrolo[2,3-d]carbazole-6,7(2H)-dicarboxylate (25). To a suspension of NaH (2.10 mg, 0.06 mmol) in THF under Ar at 0 °C was added **23** (30 mg, 0.04 mmol). After 20 min, LDA (0.06 mL, 1M in THF) was added to the suspension and the mixture was stirred for 4 h. Aqueous NH$_4$Cl was added, the mixture was extracted with EtOAc (3 x 5 mL) and the combined extracts were washed with brine, dried (Na$_2$SO$_4$) and filtered. The filtrate was concentrated under vacuum and the residue was purified by chromatography on silica gel (hexanes:EtOAc 4:1) to afford **25** as a

colorless oil (23 mg, 75%, 2:1 mixture of isomers). Data for major isomer **25a**: IR (neat) 2970, 1709, 1614, 1479, 1367, 1251, 1165, 1101, 1049 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.86 (t, J = 7.7 Hz, 3H), 1.34 (t, J = 7.1 Hz, 3H), 1.50 (s, 9H), 1.66 (m, 2H), 1.89 (m, 1H), 2.09 (m, 1H), 2.29 (m, 2H), 2.37 (s, 3H), 2.43 (t, J = 7.7 Hz, 1H), 2.53 (m, 1H), 3.15 (dd, J = 9.2, 9.2 Hz, 1H), 3.3 (dd, J = 7.9, 7.9 Hz, 1H), 3.72 (d, J = 2.5 Hz, 1H), 4.24 (m, 2H), 5.00 (d, J = 2.6 Hz, 1H), 7.00 (dd, J = 10.0, 7.4 Hz, 1H), 7.15 (d, J = 7.1 Hz, 1H), 7.21 (m, 1H), 7.74 (d, J = 5.5 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 13.9, 14.3, 20.9, 28.4, 31.5, 34.9, 36.2, 51.2, 51.5, 59.9, 61.6, 81.3, 97.2, 100.4, 115.3, 122.6, 123.2, 128.2, 136.1, 142.0, 152.6, 166.4, 168.7; HRMS (CI) calcd for C$_{25}$H$_{34}$N$_2$O$_5$ $m/z+1$ 443.2546, found 443.2557.

(2S,3S)-1'-Allyl-1-(*tert*-butoxycarbonyl)-2-(1-ethoxy-1,3-dioxohexan-2-yl)-4',5'-dihydrospiro-[indoline-3,3'-pyrrol]-1'-ium iodide (26). Allyl iodide (678 mg, 4.00 mmol) was added to **22** (430 mg, 1.00 mmol), the reaction vessel was sealed, and the mixture was stirred for 4 h. The pale yellow solution was concentrated under vacuum to remove excess allyl iodide and the resulting solid was dried under high vacuum to afford **26** as yellow solid (540 mg, 90%). This material was used for the next step without purification.

(3aS,4S,6aS,11a1R)-7-*tert*-Butyl 6-ethyl 3-allyl-4-ethyl-5-oxo-3,3a,4,5,6,6a-hexahydro-1H-pyrrolo[2,3-d]carbazole-6,7(2H)-dicarboxylate (27). To a suspension of NaH (2.1 mg, 0.06 mmol) in THF under Ar at 0 ^{o}C was added **26** (24 mg, 0.04 mmol). After 20 min, LDA (0.06 mL, 1M in THF) was added to the suspension and the mixture was stirred for 4 h. Aqueous NH$_4$Cl was added to the mixture which was extracted with EtOAc (3 x 5 mL). The combined extracts were washed with brine, dried (Na$_2$SO$_4$) and filtered, and the filtrate was concentrated under vacuum. Purification of the residue by chromatography on silica gel (hexanes:EtOAc 5:1) afforded **27** as a colorless oil (19 mg, 75%): IR (neat) 2975, 2931, 1711, 1479, 1367, 1251, 1103, 1063, 836 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.85 (t, J = 7.1 Hz, 3H), 1.32 (t, J = 7.1 Hz, 3H), 1.44 (s, 9H), 1.63 (m, 2H), 2.25 (m, 1H), 2.54 (m, 1H), 2.76 (m, 1H), 2.89 (m, 1H), 3.18 (tt, J = 5.4, 4.9, Hz, 1H), 3.36 (dd, J = 5.9, 13.0 Hz, 1H), 3.48 (dd, J = 13.0, 6.4 Hz, 1H), 4.25 (m, 2H), 4.99 (s, 1H), 5.16 (d, J = 9.9 Hz, 1H), 5.22 (d, J = 17.0 Hz, 1H), 5.86 (m, 1H), 7.00 (t, J = 7.2 Hz, 1H), 7.20 (m, 2H), 7.62 (d, J = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 13.9, 14.3, 21.0, 28.2, 30.7, 34.9, 48.8, 50.9, 52.0, 59.9, 61.5, 81.3, 94.8, 99.8, 106.8, 115.2, 117.1, 122.4, 123.4, 128.2, 136.1, 141.9, 152.6, 166.1, 168.8; HRMS (CI) calcd for C$_{28}$H$_{37}$N$_2$O$_5$ $m/z+1$ 469.2678, found 469.2682.

(2S,3S)-1-(*tert*-Butoxycarbonyl)-1'-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-2-((R)-1-ethoxy-1,3-dioxohexan-2-yl)-4',5'-dihydrospiro[indoline-3,3'-pyrrol]-1'-ium iodide (29). To a solution of **22** (78 mg, 0.18 mmol) in DMSO (2 mL) at room temperature was added **28** (550 mg, 1.80 mmol),

the reaction vessel was sealed, and the mixture was stirred for 4 h. The solution was diluted with CH$_2$Cl$_2$ (15 mL), washed with brine (6 x 5 mL) and dried (Na$_2$SO$_4$). The solvent was removed under vacuum to give **29** as a yellow oil (54 mg, 50%) which was used for the next step without further purification.

7-*tert*-Butyl   6-ethyl   3-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-4-ethyl-5-oxo-3,3a,4,5,6,6a-hexahydro-1*H*-pyrrolo[2,3-*d*]carbazole-6,7(2*H*)-dicarboxylate (30). To a suspension of NaH (2.10 mg, 0.06 mmol) in THF under Ar at 0 $^{\circ}$C was added **29** (30 mg, 0.04 mmol). After 20 min, LDA (0.06 mL, 1M in THF) was added to the suspension and the mixture was stirred for 4 h. Aqueous NH$_4$Cl was added to the mixture which was extracted with EtOAc (3 x 5 mL). The combined extracts were washed with brine, dried (Na$_2$SO$_4$) and filtered, and the filtrate was concentrated under vacuum. Purification of the residue by chromatography on silica gel (hexanes:EtOAc 5:1) afforded **30** as a colorless oil (12 mg, 40%): IR (neat) 2930, 2856, 1711, 1479, 1367, 1252, 1185, 1097, 836 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.09 (d, J = 7.5 Hz, 6H), 0.88 (s, 9H), 0.95 (t, J = 7.4 Hz, 3H), 1.31 (t, J = 7.2 Hz, 3H), 1.53 (s, 9H), 1.65 (m, 2H), 1.98 (m, 1H), 2.60 (m, 1H), 2.80 (m, 4H), 3.24 (m, 1H), 3.60 (tt, J = 6.3, 4.1 Hz, 2H), 3.85 (m, 1H), 4.08 (t, J = 7.2 Hz, 2H), 5.11 (d, J = 10.9 Hz, 1H), 7.00 (t J = 7.2 Hz, 1H), 7.20 (m, 2H), 7.62 (d, J = 8.1 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ -5.3, 13.9, 14.3, 18.3, 21.0, 25.9, 28.3, 28.5, 30.3, 31.1, 34.9, 45.3, 49.1, 50.6, 59.9, 61.0, 61.5, 81.3, 94.6, 99.2, 115.2, 122.4, 123.4, 128.2, 136.2, 141.8, 152.6, 166.2, 168.9; HRMS (CI) calcd for C$_{33}$H$_{52}$N$_2$O$_6$Si *m/z+1* 601.3673, found 601.3701.