Synthesis of some Fused β-Carbolines Including the First Example of the Pyrrolo[3,2-*c*]-β-carboline System

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Condensation of 1-methyl-β-carboline-3-carbaldehyde with ethyl azidoacetate and subsequent thermolysis of the resulting azidopropenoate was used to [*c*] annulate a pyrrole ring onto the β-carboline moiety, thus producing the first example of the pyrrolo[3,2-*c*]-β-carboline ring system. The latter ring system results from cyclization at the C-4 carbon, whereas cyclization at the N-2 nitrogen atom also occurs to form a pyrazolo[3,2-*c*]-β-carboline ring system. Condensation of β-carboline-1-carbaldehyde with ethyl azidoacetate produced a non-isolable intermediate, which immediately underwent cyclization, however in this case cyclization occurred *via* attack at the ester and the azide remained intact. The resulting 5-azidocanthin-6-one was transformed to the first examples of 5-aminocanthin-6-ones. β-Carboline-1,3-dicarbaldehyde failed to give an acceptable reaction with ethyl azidoacetate, but did undergo selective condensation with dimethyl acetylene dicarboxylate at the C-1 carbaldehyde with concomitant cyclization to form a highly functionalized 2-formyl-canthine derivative.

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Introduction.

The potential DNA-intercalating ability of polycyclic *N*-heteroaromatic compounds has spurred much interest in this area in recent years [1], exemplified by ellipticine (**1**) [2] and syntheses directed towards the preparation of ellipticine analogues [1c]. We are interested in annulated β-carbolines, particularly those bearing extended [a], [b] and [c] annulated heteroarene rings (Figures 1 and 2) since they have potential as DNA intercalators.

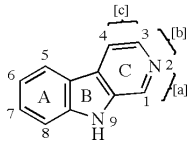
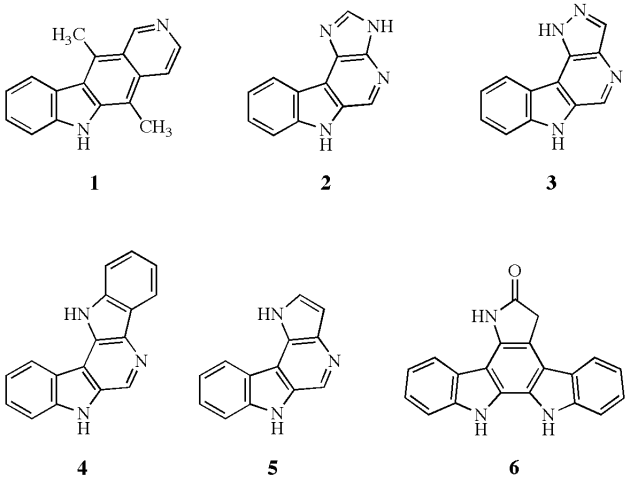


Figure 1

The preparations of new tetrahydro-β-carboline-containing ring systems bearing further rings fused at either the [a], or [b] position, or at both of these positions, have recently been disclosed by Nefzi and co-workers [3]. However, as planarity seems to be an important requirement towards DNA intercalation, our interests lies primarily in fully aromatic annulated β-carbolines and we note the recent first syntheses of such compounds as indazolo-[3,2-*a*]-β-carbolines and benzo[4',5'][1,2,3]triazino[6,1-*a*]-β-carbolines [1d], imidazo[4,5-*c*]-β-carbolines (**2**) [4], and pyrazolo[4,3-*c*]-β-carbolines (**3**) [5]. A whole series of compounds based on 7,12-dihydropyrido[3,2-□:5,4-□']diindole (**4**) have been synthesized and employed as probes, "molecular yardsticks" to define the spatial dimensions of the lipophilic regions of the benzodiazepine receptor binding cleft [6], whilst the parent pyrrolo[3,2-*c*]-β-carboline (**5**) itself remained unknown. We note the structural similarity between **5** and the staurosporine aglycone (**6**) [7], particularly with respect to the position of the new pyrrolo nitrogen. We envisioned the synthesis of **5** from a β-carboline-3-carbaldehyde, *via* Hemetsberger methodology [8]. Here we report a brief study of the condensation of β-carboline-carbaldehydes with ethyl azidoacetate towards the formation of new ring systems.



1 **2** **3**

4 **5** **6**

Figure 2

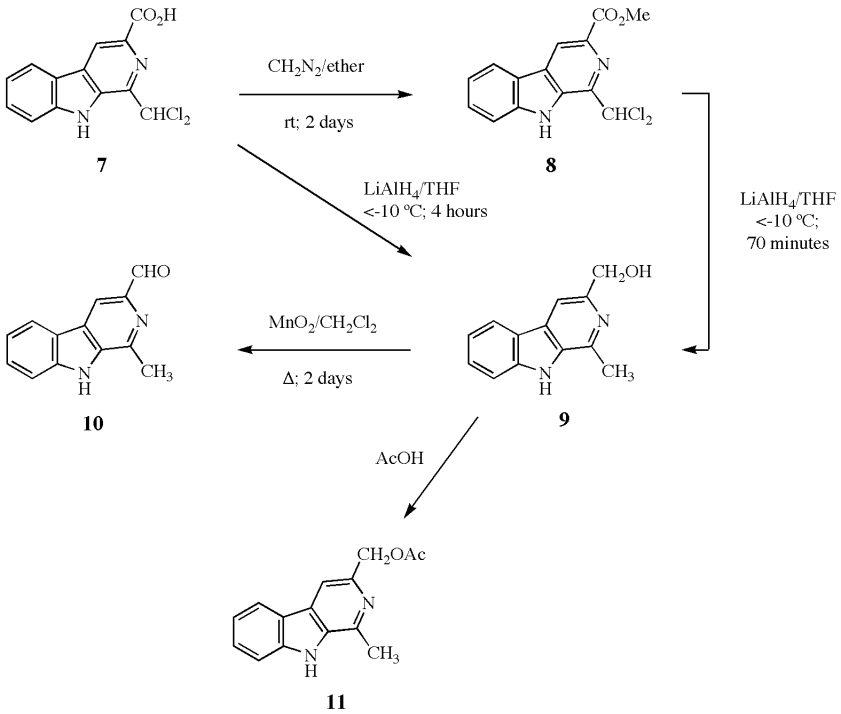
Results and Discussion.

1. Reactions of β-Carboline-3-carbaldehydes with Ethyl azidoacetate.

Our previous report concerning the synthesis of canthine and canthinone derivatives utilized 1-dichloromethyl-β-carboline-3-carboxylate (**7**), which is readily available from L-tryptophan in two steps *via* a convenient and high

yielding synthesis that requires no purification [9]. In that work, 1-dichloromethyl-β-carboline-3-carboxylate (**7**) was converted to the corresponding ester **8** in quantitative yield using ethereal diazomethane. Reduction of the ester using lithium aluminium hydride proceeded cleanly and gave the known alcohol, 3-hydroxymethylharmane [10] (**9**) in 86% yield. Alternatively, reduction of the free acid **7** with lithium aluminium hydride proceeded in essentially quantitative yield. Shorter reaction times during the latter reduction led to an incomplete conversion as evident by the isolation, in up to 8% yield, of aldehyde **10**. Oxidation of alcohol **9** proceeded in a very sluggish manner using "very active manganese dioxide", [11] however aldehyde **10** was consistently prepared in 87% yield (Scheme 1).

Scheme 1

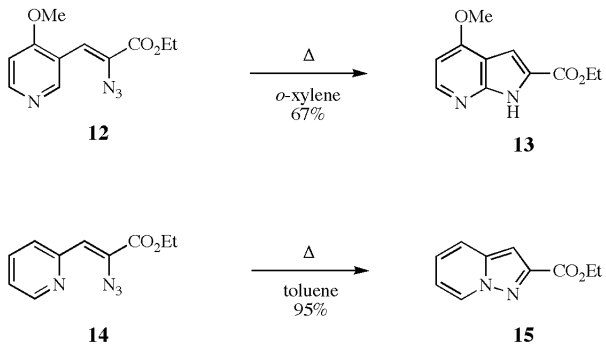


Heating 3-hydroxymethyl-β-carboline (**9**) in glacial acetic acid simply resulted in the formation of acetoxy derivative **11**, which clearly shows the behavioural differences between the less reactive pyridine ring and that of indole, since in the case of a hydroxymethylindole, a diindolylmethane will often form *via* intramolecular substitution by the nucleophilic indole [12].

A search through the literature revealed no reference to either a β-carboline-3-carbaldehyde or 1-carbaldehyde having been condensed with an alkyl azidoacetate, and hence further ring formation from such an intermediate has not been described. The corresponding condensation with pyridines substituted with an aldehyde at either C-2 [13-15], C-3 [15-17], or C-4 [15-16] have been described, generally occurring in low to moderate yields. The subsequent thermal decomposition of the resulting vinyl azides has received little attention, a 4-substituted 3-pyridyl vinyl azide (**12**) gave a good yield of the expected 7-azaindole **13** (Scheme 2) [17], however thermolysis of ethyl 2-azido-3-(2-pyridyl)propenoate (**14**) gave a very high yield of a pyrazolopyridine **15** resulting from cyclization of the vinylnitrene intermediate onto the pyridine nitrogen (Scheme 2) [14], and not a pyrrolopyridine which would result from cyclization onto the pyridine C-3 position.

Condensation of aldehyde **10** with a ten times excess of ethyl azidoacetate proceeded very slowly at –15 ºC, while

Scheme 2



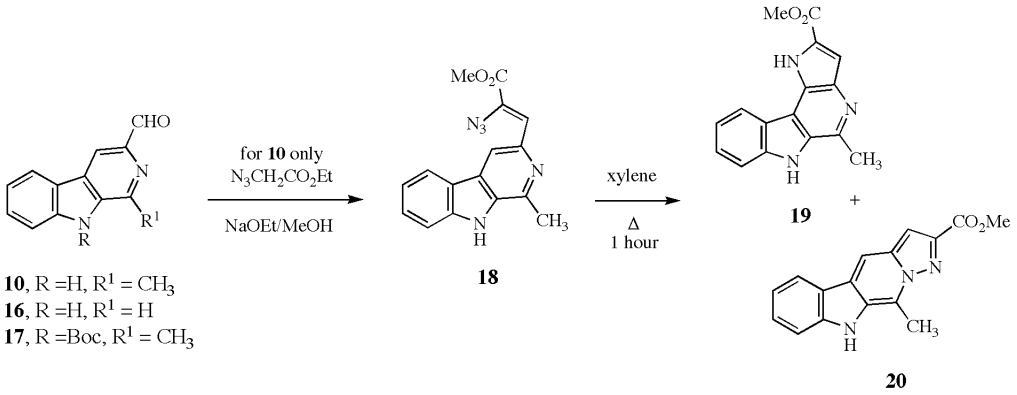
allowing the temperature to rise above 0 ºC incurred visible decomposition of the azide. Non-dehydrated alcoholic intermediates were sometimes observed by ^{1}H NMR analysis during the reaction and it was deemed necessary to allow the reaction to warm to room temperature to effect complete dehydration to form the unsaturated azide (**18**). Perhaps consequently, full conversion of the aldehyde was not achieved, 44% of the starting material was recovered, and with consideration of the 56% conversion of the starting material, the crude 2-azidopropenoate **18** was recovered in a modest 55% yield after deduction of the recovered starting material (31% yield without this deduction). Thermolysis of 2-azidopropenoate **18** produced two products which were easily separated by chromatography and thus the pyrrolo[4',5':5,6]pyrido[3,4-*b*]indole derivative (**19**) and its structural isomer pyrazolo[1',5':1,6]pyrido-[3,4-*b*]indole derivative (**20**) were each recovered in 41% yield (Scheme 3). The ^{1}H NMR spectrum of the pyrrolo-[3,2-*c*]-β-carboline (**19**) exhibited two NH resonances, both of which underwent exchange with D_2O, while the absence of a signal assignable to a β-carboline H4 proton, indicates that substitution has occurred at C-4. A singlet appearing at 7.47 ppm was assigned to H3. Conversely, the ^{1}H NMR spectrum of the pyrazolo[3,2-*c*]-β-carboline (**20**) exhibited a single NH resonance, while a singlet assigned to the H4 proton coincides with that expected for the β-carboline H4 proton. A singlet appearing at 7.26 was assigned to H3.

Initially we looked favourably upon the methyl substituent at C-1 of aldehyde **10**, since the compounds formed from **10** would be derivatives of harmane (1-methyl-β-carboline) [19], but furthermore, the position of the methyl group bears some resemblance to the corresponding substituent in ellipticine (**1**). However, its presence might have caused some steric hindrance about the pyridine nitrogen, hindering attack at this position during the thermolysis of **18**. Furthermore, the acidic nature of this group may have interfered with the condensation of **10** with ethyl azidoacetate and therefore the parent aldehyde [20] (**16**) was employed, but condensation of **16** with ethyl azidoacetate failed to provide the corresponding 2-azidopropenoate. The *N*-protected aldehyde (**17**), which contains a less activated β-carboline ring system and therefore more reactive aldehyde group, similarly failed. In both of these cases little reaction was observed, whilst any product formed could not be separated from the starting material.

2. Reaction of 1-Formyl-β-carboline with Ethyl azidoacetate.

We have previously reported the preparation of aldehyde **21** from the 1-dichloromethyl-β-carboline [9] (**7**), indeed the aldehyde **21** was prepared in four steps from readily available tryptophan in 54% overall yield. Condensation of aldehyde **21** with ethyl azidoacetate gave the 5-azidocanthin-6-one derivative (**24**) directly and in good yield (Scheme 4).

Scheme 3

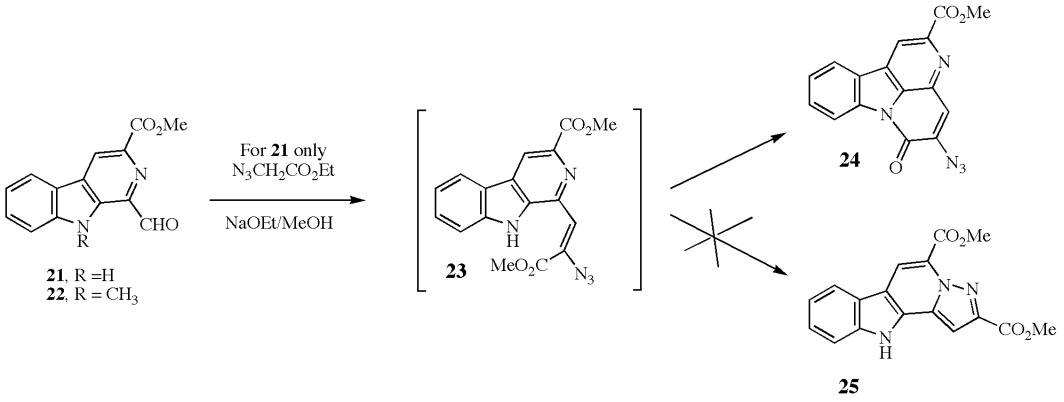


The pyrazolo[1',5':1,6]pyrido[3,4-*b*]indole ring system is rare; there are only a few reports dealing with the reduced 9,10-dihydro system, which have been reported to exhibit pepsin-inhibiting and anti-ulcerogenic properties [18], whilst the fully unsaturated pyrazolo[1',5':1,6]pyrido-[3,4-*b*]indole is hitherto unknown. The presumed planarity, as well as the potential bridgehead quarternary nitrogen, ought to make product **20** a possible candidate for DNA intercalating studies.

Presumably, the *cis*-isomer **23** (*cis* with respect to the ester) is formed preferentially and undergoes spontaneous cyclization. ^{1}H NMR analysis revealed that the reaction proceeds in a very clean manner and only signals attributed to the starting material (**21**) and product **24** were observed.

The alternative product **25** shown in Scheme 4, resulting from decomposition of azide **23** and the subsequent cyclization of the presumed nitrene intermediate onto the

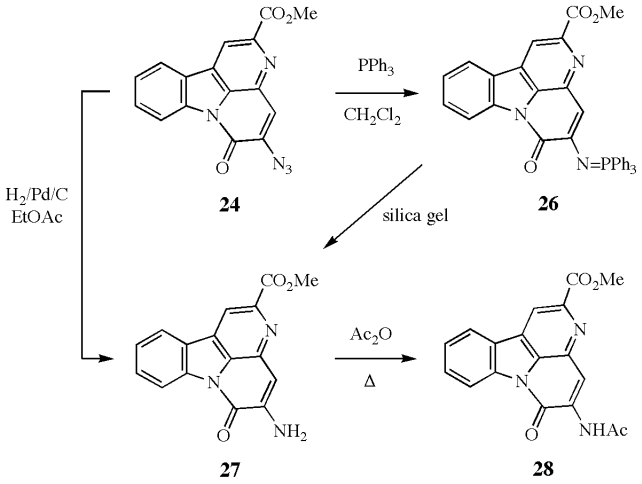
Scheme 4



pyridine nitrogen, *i.e.* at *N*-2, analogous to the formation of **15** from **14** (Scheme 2), was not expected to form under the mild conditions employed for the condensation of aldehyde **21** and ethyl azidoacetate. However, whilst we were unable to isolate the presumed non-cyclized intermediate **23** (or the corresponding *trans* isomer), we were interested in examining the thermal decomposition of such a compound as the resulting pyrazolo[1,5-a]-β-carboline structure (**25**) is unknown. The [a] benzo-annulated ring system of **25** has only recently been synthesized for the first time [1d] and its intercalation ability has been examined [1c]. Our strategy was to block the indole nitrogen *N*-9 with a methyl substituent, however the resulting aldehyde **22** failed to condense with ethyl azidoacetate. This failure could in part be due to steric hindrance in the proximity of the aldehyde caused by the *N*-substituent, conversely, we feel that the ready condensation of aldehyde **21** with ethyl azidoacetate was facilitated by the subsequent intramolecular cyclization, which would reduce the steric hindrance of the azidopropenoate substituent at C-1 of the presumed intermediate **23**.

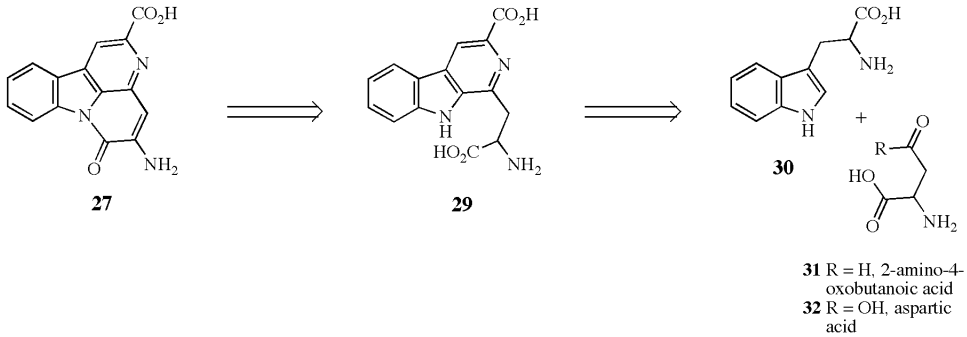
The reduction of azide **24** to the corresponding amino derivative **27** was achieved in high yield using palladium-catalyzed hydrogenation. An alternate two-step reduction [21] involving an initial reaction with triphenylphosphine,

Scheme 5



gave the expected phosphine imine **26**, contaminated with triphenylphosphine oxide, in low yield after chromatography on silica gel, whilst the major product isolated was the amine **27**. Presumably, hydrolysis of **26** occurs in the presence of silica gel and unfortunately the resulting amine **27** has an undesirable affinity for silica gel. Fortunately, partial precipitation of phosphine imine **26** usually occurs

Scheme 6



during the reaction and **26** was collected in an analytically pure state and fully characterized. Amine **27** was found to be relatively insoluble and consequently the more soluble acetyl derivative **28** was prepared and fully characterized.

It is worth noting that the 5-aminocanthin-6-ones (**24**-**28**) are the first examples of canthin-6-ones or indeed canthine derivatives possessing a nitrogen substituent at the C-5 position. The only other heteroatom substituent observed at the C-5 position of canthin-6-one or canthine derivatives described previously have been hydroxy or alkoxy substituents [22] and we anticipate the future isolation of canthine derived natural products containing a C-5 nitrogen substituent. It is also interesting to note the potential biosynthetic pathway to the formation of 5-aminocanthin-6-ones (Scheme 6).

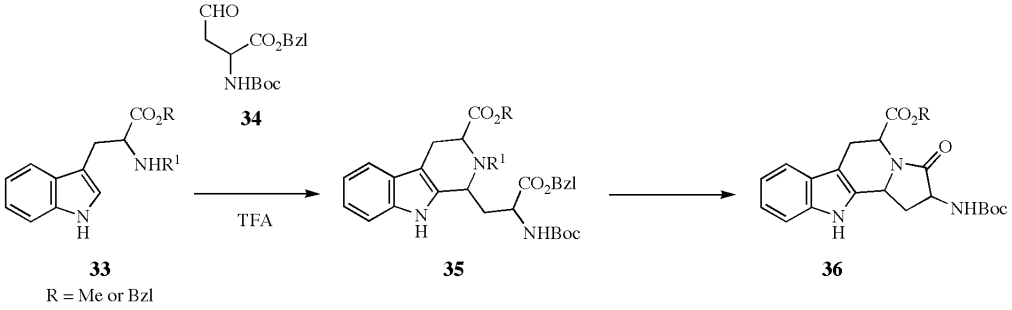
Thus 5-aminocanthin-6-one **27** could result from the oxidation of the product formed from the favoured intramolecular cyclization of β-(β-carboline)alanine (**29**). The latter product could result from oxidation of the product formed from the biosynthetic Pictet Spengler-type [23] condensation of tryptophan (**30**) with 2-amino-4-oxobutanoic acid (**31**) or aspartic acid (**32**). However, the reaction of tryptophan methyl and benzyl esters (**33**) with aldehyde **34** has been conducted under Pictet-Spengler conditions by De la Figuera *et. al.* to provide tetrahydro-β-carbolines **35** [24], which, not surprisingly, underwent cyclization to the hexahydroindolizino[8,7-*b*]indole derivatives (**36**) (Scheme 7).

3. Reaction of 1,3-β-Carbolinedicarbaldehyde with Ethyl Azidoacetate and other Activated Methylene Compounds.

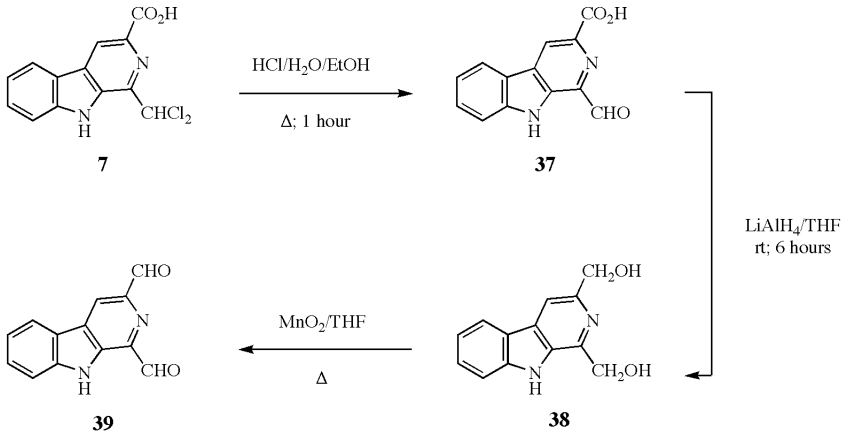
We have previously described the high yielding conversion of 1-dichloromethyl-β-carboline (**7**) to 1-formyl-β-carboline [9] (**37**), conducted under acidic conditions. Reduction of **37** with lithium aluminium hydride gave the diol **38** in moderate yield, whilst the subsequent oxidation with "very active manganese dioxide" consistently gave **39**, but in only 58% yield.

The double condensation of dialdehyde **39** with ethyl azidoacetate did not give any reasonable product, however regioselective condensation of dialdehyde **39** with dimethyl acetylene dicarboxylate (DMAD) in the presence of triphenylphosphine gave a high yield of the canthine derivative (**41**). The mechanism is assumed to be analogous to that proposed by Yavari and co-workers for similar condensations of DMAD in the presence of triphenyl phosphine with aldehydes and leading to the preparation of various heterocycles [25]. Hence, a 1:1 adduct is formed between triphenylphosphine and DMAD, which deprotonates the β-carboline and the latter species subsequently

Scheme 7

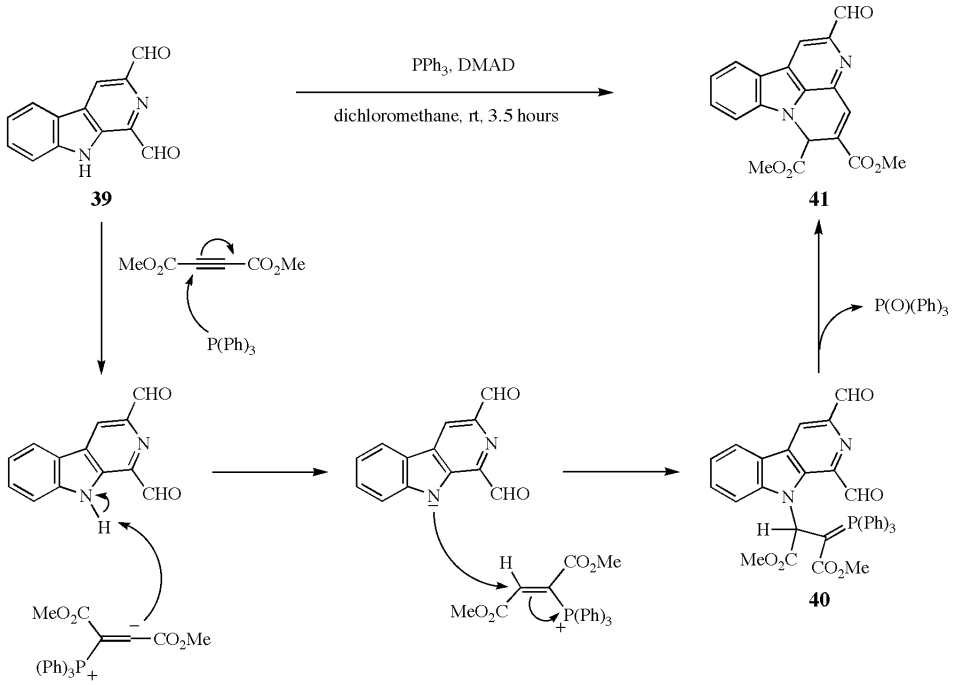


Scheme 8



attacks the 1:1 adduct to form phosphorane **40**, and cyclization is accomplished *via* an intramolecular Wittig reaction to give the functionalized unsaturated canthine derivative (**41**) (Scheme 9). The formation of the phosphorane *via* substitution onto the β-carboline N9 consequently allows for the regioselective Wittig reaction to occur exclusively at the aldehyde substituent at C1.

Scheme 9



We have previously described the reaction of the less reactive aldehyde **21** under similar conditions [9], which gave a high yield of the corresponding canthine derivative containing an ester at C-2, but took 20 hours.

Having regioselectively reacted the C-1 aldehyde of dialdehyde **39** we next looked at the reactivity of the remaining aldehyde of product **41**, however attempted condensation with ethyl azidoacetate gave a complex mixture, which is not entirely surprising given that the highly functionalized canthine (**41**) ought to be susceptible to Michael addition at C-4.

EXPERIMENTAL

NMR spectra were recorded on a Bruker DPX 300 spectrometer, at 300 MHz for ^{1}H and 75.4 MHz for ^{13}C. Chemical shifts were recorded as δ values in parts per million (ppm). Protons attached to heteroatoms were confirmed using D_2O exchange experiments. Infrared spectra were recorded on a Thermo Nicolet® Avatar® 330 Fourier Transform Infrared Spectrophotometer as neat samples. Mass spectra (ESI) were obtained using a Perkin-Elmer API 150 EX spectrometer. Elemental analyses were performed by H. Kolbe Mikroanalytisches Laboratorium, Mulheim an der Ruhr, Germany. Melting points were measured on a Buchi B-545 apparatus and are uncorrected. Chromatography was performed using Merck Silica Gel 60. All solvents were purified by distillation or otherwise were analytical grade and used as received. Tetrahydrofuran was distilled from sodium and benzophenone.

3-Hydroxymethyl-1-methylpyrido[3,4-*b*]indole (**9**).

Method A.

A suspension of $LiAlH_4$ (0.16 g, 4.2 mmol) in anhydrous THF (10 mL) was stirred and cooled in a salt-ice slurry, under nitrogen. A solution of methyl 1-dichloromethyl-β-carboline-3-carboxylate [9] (**8**) (0.250 g, 0.809 mmol) in anhydrous THF (20 mL) was added dropwise, over 14 minutes, and stirring was continued for 70 minutes with cooling and under argon. Water (0.23 mL) was cautiously added dropwise, followed by 2 *M* NaOH (1.7 mL), and finally further water (1.7 mL). The resulting precipitate was filtered and washed with ethyl acetate. The combined filtrate was washed with brine twice, dried ($MgSO_4$), and evaporated *in vacuo* and the remaining residue was purified *via* column chromatography (alumina-5% MeOH/CH_2Cl_2) to give the title compound (0.148 g, 86%) as a colourless powder, mp 192–194 °C (lit. [10] 196–197 °C).

Method B.

Following Method A, but with β-carboline **7** (0.250 g, 0.847 mmol) and a duration of 4 hours, gave the title compound (0.178 g, 99%) as a white powder.

1-Methylpyrido[3,4-*b*]indole-3-carbaldehyde (**10**).

3-Hydroxymethyl-β-carboline (**9**) (0.100 g, 0.446 mmol) and manganese dioxide [11] (0.388 g, 4.46 mmol) were heated at reflux together in dry dichloromethane (35 mL) for two days. The resulting mixture was passed through a short column of silica, topped with a thin layer of celite, initially using dichloromethane, and then 5% MeOH/CH_2Cl_2 to give the title compound (86 mg, 87%) as an off-white powder, mp 208–209 ºC; R_f (5% MeOH/CH_2Cl_2) 0.33; ir: 3279, 2825, 1681, 1591, 1571, 1503, 1370, 1343, 1249, 844, 740 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 12.12 (s, 1H, NH), 10.06 (s, 1H, CHO), 8.65 (s, 1H, H4), 8.36 (d, J = 7.9 Hz, 1H, aryl CH), 7.67 (d, J = 8.1 Hz, 1H, aryl CH), 7.60 (t, J = 8.1 Hz, 1H, aryl CH), 7.32 (t, J = 7.9 Hz, 1H, aryl CH), 2.85 (s, 3H, CH_3); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 192.83 (CHO), 142.75 (2 C, aryl C), 140.82, 136.94 (aryl C), 128.52 (aryl CH), 126.81 (aryl C), 122.18 (aryl CH), 121.53 (aryl C), 120.33, 113.36, 112.41 (aryl CH), 20.27 (CH_3); ms: m/z = 211 $[M+H]^+$, 209 $[M-H]^+$.

Anal. Calcd. for $C_{13}H_{10}N_2O$: C, 74.27; H, 4.79; N, 13.33. Found: C, 74.16; H, 4.73; N, 13.24.

3-Acetoxymethyl-1-methylpyrido[3,4-*b*]indole (**11**).

3-Hydroxymethyl-β-carboline (**9**) (0.183 g, 0.862 mmol) was stirred in glacial acetic acid at room temperature for 5 days, followed by heating at reflux for 14 hours. The resulting dark solution was evaporated *in vacuo* and the remaining residue purified *via* column chromatography (silica gel-ethyl acetate) to give the title compound (0.133 g, 61%) as a pale yellow powder, mp 125–127 ºC; R_f (10% MeOH/CH_2Cl_2) 0.39; ir: 3340, 1705, 1626, 1564, 1501, 1455, 1360, 1263, 1249, 1234, 1026, 954, 879, 745 cm^{-1}; ^1H nmr (deuteriochloroform): δ 10.17 (bs, 1H, NH), 8.07 (d, J = 7.9 Hz, 1H, aryl CH), 7.91 (s, 1H, H4), 7.52–7.43 (m, 2H, aryl CH), 7.26 (t, J = 8.0 Hz, 1H, aryl CH), 5.41 (s, 2H, CH_2), 2.75 (s, 3H, CH_3), 2.06 (s, 3H, $COCH_3$); ^{13}C NMR (deuteriochloroform): δ 170.78 ($COCH_3$), 142.92, 141.44, 140.38, 133.92, 128.36 (aryl C), 127.83, 121.29 (aryl CH), 121.21 (aryl C), 119.53, 112.21, 111.27 (aryl CH), 67.49 (CH_2), 20.58, 19.51 ($COCH_3$ and CH_3); ms: m/z = 253 $[M-H]^+$.

Anal. Calcd. for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.69; H, 5.48; N, 10.92.

9-*tert*-Butyloxycarbonyl-1-methylpyrido[3,4-*b*]indole-3-carbaldehyde (**17**).

A suspension of β-carboline **10** (0.116 g, 0.55 mmol) and di-*tert*-butyldicarbonate (0.249 g, 1.14 mmol) in anhydrous acetonitrile (25 mL), containing a catalytic quantity of *N,N*-dimethylaminopyridine, was stirred at room temperature, under nitrogen, for 50 minutes. The solvent was then evaporated *in vacuo* and the remaining residue purified *via* column chromatography (silica gel-chloroform) to give the title compound (0.117 g, 68%) as a white powder, mp 144–145 ºC (decomp.); R_f (10% MeOH/CH_2Cl_2) 0.52; ir: 2856, 1738, 1689, 1569, 1440, 1369, 1343, 1284, 1228, 1150, 1110, 916, 836, 766, 742 cm^{-1}; ^1H nmr (deuteriochloroform): δ 10.15 (s, 1H, CHO), 8.37 (s, 1H, H4), 8.05 (d, J = 8.5 Hz, 1H, aryl CH), 8.01 (d, J = 7.7 Hz, 1H, aryl CH), 7.59 (t, J = 8.4 Hz, 1H, aryl CH), 7.40 (t, J = 7.5 Hz, 1H, aryl CH), 2.85 (s, 3H, CH_3), 1.73 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (dimethyl sulfoxide-d_6): δ 193.01 (CHO), 149.55 (CO), 146.87 (aryl C), 146.71 (2 C, aryl C), 140.45, 136.50, 133.23 (aryl C), 129.92, 123.68, 121.26, 115.22, 110.95 (aryl CH), 85.44 ($C(CH_3)_3$), 28.04 ($C(CH_3)_3$), 24.83 (CH_3); ms: m/z = 311 $[M+H]^+$.

Anal. Calcd. for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.58; H, 5.74; N, 8.86.

Methyl 2-Azido-3-(1-methylpyrido[3,4-*b*]indol-3-yl)-2-propenoic Acid (**18**).

Sodium (0.10 g, 4.4 mmol) was dissolved in methanol (4.0 ml) and the stirred solution was cooled in a salt-ice slurry, under argon. A solution containing β-carboline-3-carbaldehyde (**10**) (0.100 g, 0.476 mmol) and ethyl azidoacetate (0.625 g, 4.8 mmol) in methanol (8.0 mL) was added dropwise, over 28 minutes, to the methoxide solution and the resulting bright yellow solution was stirred further with cooling for 4 hours. The cooling bath was then removed and the solution was stirred at ambient temperature for 22 hours before it was poured onto ice and allowed to sit overnight. The resulting precipitate was collected by filtration, washed with water, and dried to give the title compound (45 mg, 31%). The mother liquor was extracted with ethyl acetate and the organic extract was washed with brine, dried ($MgSO_4$), and evaporated *in vacuo* to give starting material (44 mg). The yield of the title compound was 55%, taking into account the recovered starting material, obtained as a pale orange powder, mp 164 ºC (decomp.); R_f (2.5% MeOH/CH_2Cl_2) 0.18; ir: 2119, 1719, 1693, 1624, 1500, 1342, 1297, 1233, 1209, 1080, 904, 825, 742 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 11.85 (s, 1H, NH), 8.87 (s, 1H, H4'), 8.31 (d, J = 7.8 Hz, 1H, aryl CH), 7.63-7.53 (m, 2H, aryl CH), 7.27 (t, J = 7.0 Hz, 1H, aryl CH), 7.18 (s, 1H, H3), 3.87 (s, 3H, OCH_3), 2.76 (s, 3H, CH_3); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 164.56 (CO_2CH_3), 143.18, 141.64, 141.06, 134.92 (aryl C), 129.02, 128.20 (aryl CH), 127.89, 124.30 (aryl C), 122.81 (aryl CH), 122.18 (aryl C), 120.68, 116.28, 113.11 (aryl CH and C-3), 53.89 (CO_2CH_3), 21.30 (CH_3); ms: m/z = 306 $[M-H]^+$.

Anal. Calcd. for $C_{16}H_{13}N_5O_2$: C, 62.53; H, 4.26; N, 22.79. Found: C, 62.44; H, 4.33; N, 22.68.

Thermolysis of Methyl 2-Azido-3-(1-methylpyrido[3,4-*b*]indol-3-yl)-2-propenoic Acid (**10**).

A solution of the azidopropenoate **10** (32 mg, 0.10 mmol) in 25% dichloromethane/xylene (40 mL) was added dropwise, over 13 minutes, to a vigorously stirred and rapidly refluxing solution of xylene (10 mL), at such a rate as to allow the dichloromethane to be rapidly distilled off. A reflux condenser was then installed and heating at reflux was continued for one hour. The solution was then allowed to cool, evaporated *in vacuo*, and the remaining residue was purified *via* column chromatography (silica gel-ethyl acetate) to give two products;

Methyl 1,6-Dihydro-5-methylpyrrolo[4',5':5,6]pyrido[3,4-*b*]indole-2-carboxylate (**19**).

The title compound (12 mg, 41%) was recovered as a pale yellow powder, mp 265 ºC (decomp.); R_f (2.5% MeOH/CH_2Cl_2) 0.06; ir: 3314, 1676, 1529, 1353, 1289, 1272, 1207, 1168, 1101, 1006, 827, 760, 736 cm^{-1}; ^1H nmr (deuteriochloroform): δ 9.44 and 8.83 (each bs, 1H, NH), 8.19 (d, J = 7.8 Hz, 1H, aryl CH), 7.61-7.52 (m, 2H, aryl CH), 7.47 (s, 1H, H3), 7.37 (t, J = 7.2 Hz, 1H, aryl CH), 3.99 (s, 3H, OCH_3), 2.87 (s, 3H, CH_3); ^{13}C NMR (deuteriochloroform): δ 162.59 (CO_2CH_3), 139.74, 138.83, 136.82, 132.61 (aryl C), 127.15 (aryl CH), 125.77, 124.34 (aryl C), 122.15, 120.68 (aryl CH), 120.26, 112.61 (aryl C), 111.89 (aryl CH), 109.50 (C-3), 52.05 (CO_2CH_3), 20.39 (CH_3); ms: m/z = 280 $[M+H]^+$, 278 $[M-H]^+$.

Anal. Calcd. for $C_{16}H_{13}N_3O_2$: C, 68.81; H, 4.69; N, 15.05. Found: C, 68.68; H, 4.74; N, 15.15.

Methyl 10-Methylpyrazolo[1',5':1,6]pyrido[3,4-*b*]indole (**20**).

The title compound (12 mg, 41%) was recovered as a pale yellow powder, mp 260 ºC (decomp.); R_f (2% MeOH/CH_2Cl_2) 0.35; ir: 3325, 1712, 1616, 1538, 1495, 1482, 1466, 1390, 1311, 1216, 1183, 1007, 841, 765, 745, 689 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 11.04 (bs, 1H, NH), 8.39 (s, 1H, H4), 8.17 (d, J = 6.7 Hz, 1H, aryl CH), 7.49-7.40 (m, 2H, aryl CH), 7.26 (s, 1H, H3), 7.15 (t, J = 6.7 Hz, 1H, aryl CH), 3.89 (s, 3H, OCH_3), 2.95 (s, 3H, CH_3); ^{13}C (dimethyl sulfoxide-d_6): δ 163.91 (CO_2CH_3), 145.08, 143.03, 138.19, 131.96 (aryl C), 129.74 (aryl CH), 126.71 (aryl C), 122.76 (aryl CH), 122.01 (aryl C), 119.82 (aryl CH), 119.47 (aryl C), 111.62, 105.84, 100.02 (aryl CH), 52.53 (CO_2CH_3), 13.86 (CH_3); ms: m/z = 280 $[M+H]^+$, 278 $[M-H]^+$.

Anal. Calcd. for $C_{16}H_{13}N_3O_2$: C, 68.81; H, 4.69; N, 15.05. Found: C, 69.00; H, 4.61; N, 15.11.

Methyl 5-Azido-6-oxoindolo[3,2,1-*de*][1,5]naphthyridine-2-carboxylate (**24**).

A solution of aldehyde [9] **21** (0.273 g, 1.07 mmol) and ethyl azidoacetate (1.385 g, 10.7 mmol) in methanol (40 mL) was added dropwise over 38 minutes, under argon, to a stirred solution of sodium ethoxide (0.657 g, 9.66 mmol) in methanol (10 mL), cooled *via* an ice-salt slurry. Stirring was continued with cooling *via* an iced water bath for 24 hours before the mixture was poured onto crushed ice. The resulting precipitate was collected and washed with water, then with 1:1 methanol/water (2 mL), and dried to give the title compound (0.262 g, 76%) as a pale orange powder, mp 200 ºC (darkens), 209 ºC (decomp.); R_f (2.5% MeOH/CH_2Cl_2) 0.73; ir: 2139, 1710, 1673, 1451, 1438, 1375, 1328, 1301, 1285, 1263, 1225, 1143, 1119, 879, 792, 757, 738 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.76 (s, 1H, H1), 8.63 (d, J = 8.2 Hz, 1H, aryl CH), 8.15 (d, J = 7.7 Hz, 1H, aryl CH), 7.75 (t, J = 7.5 Hz, 1H, aryl CH), 7.67 (s, 1H, H4), 7.60 (t, J = 7.5 Hz, 1H, aryl CH), 4.12 (s, 3H, OCH_3); ^{13}C nmr (deuteriochloroform): δ 165.07 (CO_2CH_3), 155.15, 144.47, 139.01, 137.50, 135.00 (aryl C and C-6), 130.88 (aryl CH), 130.19, 129.96 (aryl C), 126.08 (aryl CH), 124.25 (aryl C), 122.61, 121.67, 116.90, 116.70 (aryl CH), 52.84 (CO_2CH_3); ms: m/z = 320 $[M+H]^+$.

Anal. Calcd. for $C_{16}H_9N_5O_3$: C, 60.19; H, 2.84; N, 21.94. Found: C, 60.25; H, 2.96; N, 21.85.

Methyl 1-Formyl-9-methylpyrido[3,4-*b*]indole-3-carboxylate (**22**).

Sodium hydride (60% in mineral oil, 45 mg, 1.1 mmol) was added all at once to a stirred suspension of aldehyde [9] **21** (0.250 g, 0.983 mmol) and methyl iodide (0.16 g, 1.1 mmol) in DMF (2.0 mL) and stirring was continued under argon at room temperature overnight. The resulting suspension was poured onto ice and the resulting precipitate was collected by filtration, washed with water, and dried to give the title compound (0.238 g, 90%) as a bright yellow powder, mp 177–179 ºC (ethanol/water); R_f (2.5% MeOH/CH_2Cl_2) 0.43; ir: 2833, 1699, 1468, 1446, 1370, 1318, 1261, 1192, 1133, 1123, 1056, 981, 936, 833, 785, 748, 730, 717 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 10.12 (s, 1H, CHO), 8.95 (s, 1H, H4), 8.36 (d, J = 7.8 Hz, 1H, aryl CH), 7.69 (m, 2H, aryl CH), 7.36 (t, J = 7.5 Hz, 1H, aryl CH), 4.06 and 3.95 (each s, 3H, OCH_3 and CH_3); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 192.27 (CHO), 164.89 (CO_2CH_3), 142.88, 136.92, 135.89, 135.72, 131.74 (aryl C), 129.70, 121.95, 121.38, 120.32 (aryl CH), 120.17 (aryl C), 110.97 (aryl CH), 52.23 (CO_2CH_3), 34.13 (CH_3); ms: m/z = 269 $[M+H]^+$.

Anal. Calcd. for $C_{15}H_{12}N_2O_3$: C, 67.16; H, 4.51; N, 10.44. Found: C, 67.04; H, 4.60; N, 10.33.

5-(Triphenylphosphoranylidene)amino-6-oxoindolo[3,2,1-*de*]-[1,5]naphthyridine-2-carboxylate (**26**).

A suspension of azide **24** (101 mg, 0.32 mmol) and triphenylphosphine (83 mg, 0.32 mmol) in dichloromethane (5 mL) was stirred at room temperature for 2 hours. The resulting precipitate was collected by filtration and washed with a little dichloromethane and dried to give the title compound (63 mg, 36%) as a bright yellow powder, mp 276 ºC (decomp.); R_f (2.5% MeOH/CH_2Cl_2) 0.48; ir: 1658, 1533, 1486, 1453, 1431, 1308, 1292, 1280, 1246, 1223, 1102, 983, 856, 791, 744, 712, 690 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.70 (d, J = 8.2 Hz, 1H, aryl CH), 8.54 (s, 1H, H1), 8.09 (d, J = 7.7 Hz, 1H, aryl CH), 7.94-7.87 (m, 6H, aryl CH), 7.64 (t, J = 7.3 Hz, 1H, aryl CH), 7.59-7.47 (m, 10H, aryl CH), 7.06 (s, 1H, H4), 4.05 (s, 3H, OCH_3); ^{13}C nmr (deuteriochloroform) [26]: δ 166.61 (CO_2CH_3), 159.91 ($^3J_{p\text{-}c}$ = 23.5 Hz, C-6), 149.45, 143.26 (aryl C), 140.02 ($^2J_{p\text{-}c}$ = 8.8 Hz, C-5), 132.68 ($^2J_{p\text{-}c}$ = 10.0 Hz, C_o), 132.07 ($^4J_{p\text{-}c}$ = 2.8 Hz, C_p), 130.01 (aryl CH), 129.68 (q, $^1J_{p\text{-}c}$ = 102.0 Hz, C_i), 129.21 ($^3J_{p\text{-}c}$ = 12.3 Hz, C_m), 128.19, 125.37 (aryl C), 125.25, 122.35, 117.34 (aryl CH), 114.79 ($^3J_{p\text{-}c}$ = 14.4 Hz, C-4), 113.54 (aryl CH), 52.96 (CO_2CH_3); ms: m/z = 554 $[M+H]^+$.

Anal. Calcd. for $C_{34}H_{24}N_3O_3P.2(H_2O)$: C, 69.26; H, 4.79; N, 7.13. Found: C, 69.51; H, 4.68; N, 7.13.

Methyl 5-Amino-6-oxoindolo[3,2,1-*de*][1,5]naphthyridine-2-carboxylate (**27**).

Method A.

A fine suspension of azide **24** (74 mg, 0.23 mmol) and a catalytic quantity of 5% Pd/C in ethyl acetate (185 mL) was stirred at room temperature, under 14 atmospheres of hydrogen, for 17 hours. The resulting suspension was filtered through celite and the filtrate evaporated *in vacuo* to give the title compound (61 mg, 90%) as a bright yellow powder, mp 259–262 ºC; R_f (2.5% MeOH/CH_2Cl_2) 0.20; ir: 3459, 3307, 1745, 1679, 1602, 1578, 1438, 1364, 1302, 1255, 1223, 1110, 1001, 968, 827, 788, 741 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.69-8.67 (m, 2H, H1 and aryl CH), 8.16 (d, J = 7.6 Hz, 1H, aryl CH), 7.74 and 7.58 (each t, J = 7.6 Hz, 1H, H8 and H9), 7.16 (s, 1H, H4), 5.02 (bs, 2H, NH_2), 4.11 (s, 3H, OCH_3); ^{13}C nmr (tetrahydrofuran-d_8): δ 166.25 (CO_2CH_3), 156.60, 144.93, 144.80, 139.76, 139.54 (aryl C and C-6), 130.16 (aryl CH), 129.76, 128.74, 126.22 (aryl C), 125.88, 123.10, 117.02, 113.34, 104.08 (aryl CH), 51.70 (CO_2CH_3); ms: m/z = 294 $[M+H]^+$, 292 $[M-H]^+$.

Anal. Calcd. for $C_{16}H_{11}N_3O_3$: C, 65.53; H, 3.78; N, 14.33. Found: C, 65.46; H, 3.84; N, 14.30.

Method B.

Following the procedure for the formation of phosphine amide **26** from azide **24** (100 mg, 0.31 mmol), the whole crude reaction mixture, including the precipitate, was chromatographed on silica gel initially using dichloromethane and then 10% MeOH/CH_2Cl_2 to give the title compound (54 mg, 59%) as a bright yellow powder.

Methyl 5-Acetylamino-6-oxoindolo[3,2,1-*de*][1,5]naphthyridine-2-carboxylate (**28**).

A suspension of the amine **27** (0.100 g, 0.34 mmol) in acetic anhydride (5.0 mL) was heated at reflux for 30 minutes and then allowed to cool to room temperature. A precipitate formed and was collected, washed with water, and dried to give the title compound (82 mg, 72%) as a cream coloured powder, mp 294–295 ºC (decomp.); R_f (ethyl acetate) 0.38; ir: 3374, 1715, 1693, 1657, 1633, 1504, 1453, 1429, 1372, 1357, 1338, 1309, 1285, 1269, 1219, 1194, 1139, 1111, 879, 796, 756, 743 cm^{-1}; ^1H nmr (deuteriochloroform): δ 9.22 and 8.79 (each s, 1H, H4 and H1), 8.63 (d, J = 8.3 Hz, 1H, aryl CH), 8.60 (bs, 1H, NH), 8.18 (d, J = 7.8 Hz, 1H, aryl CH), 7.77 (t, J = 7.8 Hz, 1H, aryl CH), 7.61 (t, J = 7.6 Hz, 1H, aryl CH), 4.14 (s, 3H, OCH_3), 2.35 (s, 3H, CH_3); ^{13}C nmr (deuteriochloroform): δ 169.31, 166.26 ($COCH_3$ and CO_2CH_3), 155.97, 145.52, 139.69, 137.18, 134.70 (aryl C and C-6), 131.53 (aryl CH), 130.80, 129.37 (aryl C), 126.97 (aryl CH), 125.34 (aryl C), 123.46, 119.51, 117.63, 117.08 (aryl CH), 53.73 (CO_2CH_3), 25.34 ($COCH_3$); ms: m/z = 336 $[M+H]^+$, 334 $[M-H]^+$.

Anal. Calcd. for $C_{18}H_{13}N_3O_4$: C, 64.47; H, 3.91; N, 12.53. Found: C, 64.55; H, 3.85; N, 12.41.

1,3-Di(hydroxymethyl)pyrido[3,4-*b*]indole (**38**).

A solution of 1-formyl-β-carboline-3-carboxylate [9] (**37**) (0.142 g, 0.591 mmol) in THF (30 mL) was added dropwise, over 30 minutes, to a stirred suspension of $LiAlH_4$ (0.226 g, 5.96 mmol) in anhydrous THF (10 mL), with cooling *via* an iced water bath and under argon. Stirring was continued at ambient temperature for 5 hours under argon. Water (0.33 mL) was cautiously added, followed by 5 *M* NaOH (0.98 mL), and finally further water (0.98 mL). The resulting precipitate was filtered through celite and washed with ethyl acetate. The combined filtrate was washed with brine twice, dried ($MgSO_4$), and evaporated *in vacuo* to give the title compound (66 mg, 49%) as a yellow powder, mp 171–174 ºC; R_f (20% MeOH/$CHCl_3$) 0.13; ir: 3213, 3136, 1407, 1311, 1259, 1210, 1031, 1009, 961, 902, 869, 828, 736 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 11.26 (s, 1H, NH), 8.21 (d, J = 7.8 Hz, 1H, aryl CH), 8.04 (s, 1H, H4), 7.64 (d, J = 8.2 Hz, 1H, aryl CH), 7.51 (t, J = 7.6 Hz, 1H, aryl CH), 7.20 (t, J = 7.5 Hz, 1H, aryl CH), 5.49 and 5.32 (each t, J = 5.7 Hz, 1H, OH), 4.94 and 4.70 (each d, J = 5.6 Hz, 2H, CH_2); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 150.07, 144.46, 141.76, 133.29, 129.67 (aryl C), 128.62, 122.29 (aryl CH), 121.53 (aryl C), 119.84, 113.06, 110.78 (aryl CH), 65.38, 64.30 (CH_2); ms: m/z = 229 $[M+H]^+$, 227 $[M-H]^+$.

Anal. Calcd. for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.34; H, 5.33; N, 12.19.

Pyrido[3,4-*b*]indole-1,3-dicarbaldehyde (**39**).

A mixture of the 1,3-di(hydroxymethyl)-β-carboline (**38**) (100 mg, 0.438 mmol) and manganese dioxide (0.761 g, 8.75 mmol) in anhydrous THF (25 mL) was heated at reflux for 3.5 hours. After cooling, the mixture was filtered through celite and the celite was washed with ethyl acetate. The combined filtrate was evaporated *in vacuo* to give a motley yellow solid, which was purified *via* column chromatography (silica gel-ethyl acetate) to give the title compound (57 mg, 58%) as a bright yellow powder, mp 266–269 ºC; R_f (ethyl acetate) 0.87; ir: 3352, 2812, 1674, 1587, 1500, 1458, 1356, 1285, 1212, 1100, 963, 836, 760, 749, 727, 693, 676 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 12.57 (s, 1H, NH), 10.33 and 10.20 (each s, 1H, CHO), 9.09 (s, 1H, H4), 8.51 (d, J = 7.7 Hz, 1H, aryl CH), 7.86 (d, J = 8.2 Hz, 1H, aryl CH), 7.68 (t, J = 7.6 Hz, 1H, aryl CH), 7.41 (t, J = 7.4 Hz, 1H, aryl CH); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 193.97, 192.19 (CHO), 143.09, 142.56, 135.63, 135.52, 131.65 (aryl C), 129.80, 122.53, 121.50 (aryl CH), 120.39 (aryl C), 118.25, 113.56 (aryl CH); ms: m/z = 225 $[M+H]^+$, 223 $[M-H]^+$.

Anal. Calcd. for $C_{13}H_8N_2O_2$: C, 69.64; H, 3.60; N, 12.49. Found: C, 69.69; H, 3.54; N, 12.36.

Dimethyl 2-Formyl-6*H*-indolo[3,2,1-*de*][1,5]naphthyridine-5,6-dicarboxylic acid (**41**).

To a stirred suspension of dialdehyde **39** (46 mg, 0.21 mmol) and triphenylphosphine (54 mg, 0.21 mmol) in dichloromethane (8 mL), cooled *via* an iced brine bath (–5 ºC) and under argon, was added a solution of dimethyl acetylene dicarboxylate (29 mg, 0.21 mmol), over 4 minutes. Stirring was continued at ambient temperature for 3.5 hours before the solvent was evaporated *in vacuo* and the remaining yellow solid was purified *via* column chromatography (silica gel-50% ethyl acetate/*n*-hexane) to give the title compound (0.68 mg, 95%) as a bright yellow powder, mp 217 ºC (decomp.); R_f (50% ethyl acetate/*n*-hexane) 0.50; ir: 2820, 1732, 1693, 1629, 1559, 1438, 1373, 1360, 1324, 1279, 1237, 1204, 1176, 1140, 1086, 1057, 980, 950, 887, 778, 738, 727, 705 cm^{-1}; ^1H nmr (deuteriochloroform): δ 10.19 (s, 1H, CHO), 8.60 (s, 1H, H1), 8.21 (d, J = 7.9 Hz, 1H, aryl CH), 8.14 (s, 1H, H4), 7.75-7.67 (m, 2H, aryl CH), 7.47 (t, J = 7.9 Hz, 1H, aryl CH), 6.43 (s, 1H, H6), 3.98 and 3.73 (each s, 3H, CH_3); ^{13}C NMR (deuteriochloroform): δ 192.98 (CHO), 167.56, 165.31 (CO_2CH_3), 146.40, 141.52, 136.75, 136.68 (aryl C), 135.65, 129.93 (aryl CH and C-4), 128.42, 126.51 (aryl C), 123.46 (aryl CH), 123.00 (aryl C), 122.83, 117.29, 112.00 (aryl CH), 57.63 (C-6), 53.73, 53.30 (CO_2CH_3); ms: m/z = 351 $[M+H]^+$, 349 $[M-H]^+$.

Anal. Calcd. for $C_{20}H_{16}N_2O_6$: C, 65.14; H, 4.03; N, 8.00. Found: C, 65.19; H, 4.07; N, 7.89.

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