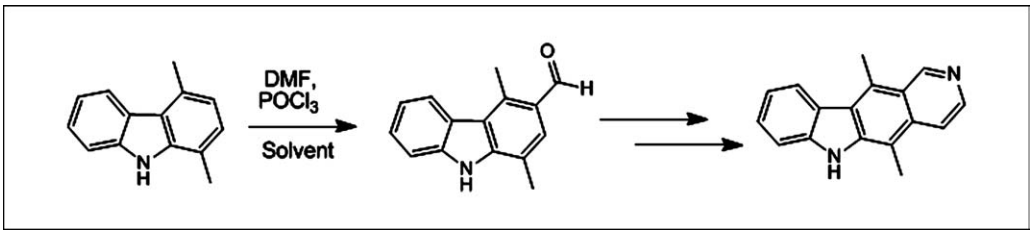
Modifications to the Vilsmeier-Haack Formylation of 1,4-Dimethylcarbazole and Its Application to the Synthesis of Ellipticines

Fiona M. Deane, Charlotte M. Miller, Anita R. Maguire, and Florence O. McCarthy*

Department of Chemistry, School of Pharmacy and Analytical and Biological Chemistry Research Facility, University College Cork, Cork, Ireland
*E-mail: f.mccarthy@ucc.ie

Received May 24, 2010
DOI 10.1002/jhet.598
Published online 12 April 2011 in Wiley Online Library (wileyonlinelibrary.com).



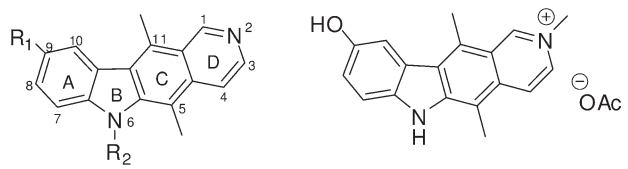
An improved method for the preparation of 3-formyl-1,4-dimethylcarbazole, a key intermediate in the synthesis of ellipticine, is presented. Conditions of the Vilsmeier-Haack reaction have been modified to facilitate the production of 3-formyl-1,4-dimethylcarbazole as a major product leading to an overall improvement in yield of ellipticine from 3% to 14%. This approach was also applied to the synthesis of 6-methylellipticine and 9-methoxyellipticine.

J. Heterocyclic Chem., **48**, 814 (2011).

INTRODUCTION

Since the 1950s, the natural product ellipticine (5,11-dimethyl-6*H*-pyrido[4,3-*b*]carbazole, **1**; Figure 1) has engendered interest due to its antineoplastic properties and limited side effects [1]. The synthetic drug Celiptium **2** has been used clinically as an anti-cancer drug, including treatment of breast cancer, myeloblastic leukemia, and solid tumors [2]. More recently, studies have also indicated activity against HIV [3]. Ellipticine is seen to display its activity *via* a multimodal mechanism of action of which DNA intercalation, inhibition of topoisomerase II, oxidative bioactivation, and inhibition of p53 phosphorylation and c-kit kinase have all been implicated [4–6].

Synthetic strategies leading to ellipticine are usually classified according to the construction of the last ring as B, C, D, and B + C types [7–10]. One of the most versatile ''D-type'' routes to ellipticine starting from appropriately substituted indoles or carbazoles is due to Cranwell and Saxton [11], and subsequently, a number of important modifications have increased the utility of this route further [12–14]. Although these modifications have decreased the difficulty and length of the original synthesis, one main disadvantage still exists. The problematic Vilsmeier-Haack formylation of 1,4-dimethylcarbazole **5** typically affords the desired 3-formyl-1,4-dimethylcarbazole **6** in low yields (<30%) along with unwanted side products. The formylation reaction is a critical step as the success of the Cranwell–Saxton route depends on the efficient introduction of a suitable substituent at the 3-position of 1,4-dimethylcarbazole **5** (which then permits the construction of pyridine ring D). This article describes a simple modification of the Vilsmeier-Haack reaction, which increases the yield of 3-formyl-1,4-dimethylcarbazole **6** dramatically leading to an increased overall yield of ellipticine (14%) by this route.



2

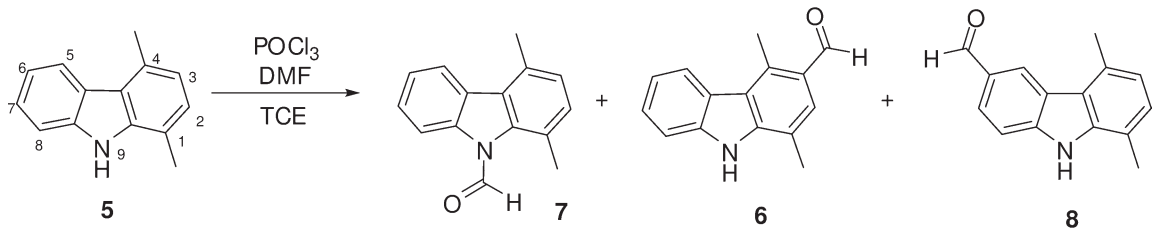
R_1,R_2 = H, **1**
R_1 = H,R_2 = CH_3, **3**
R_1 = OMe,R_2 = H, **4**

Figure 1. Structures of ellipticine and Celiptium.

RESULTS AND DISCUSSION

Formylation of 1,4-dimethylcarbazole 5. As part of an ongoing research program in our laboratory, a modified Cranwell–Saxton route was investigated toward the synthesis of ellipticine **1** [15,16]. From our experience of the Dalton method of formylation, the reaction afforded low

Scheme 1



yields of 3-formyl-1,4-dimethylcarbazole **6** but the major product was shown to be undesired 9-formyl-1,4-dimethylcarbazole **7** with typical yields of >50% (Scheme 1 and Table 1), which was previously unreported. ^{1}H-NMR spectroscopic analysis after column chromatography determined that 3-formyl-1,4-dimethylcarbazole **6** was contaminated with 6-formyl-1,4-dimethylcarbazole **8**, which could not be separated from the desired product by chromatography (Scheme 1). It was observed that multiple recrystallizations of the isomeric mixture greatly reduced the amount of the 6-formyl derivative **8** present; however, it also led to decreased overall yields of 3-formyl-1,4-dimethylcarbazole **6** with consequent effects on the route to ellipticine **1**. Although other groups have investigated the formylation reaction with substituents blocking the 6- and 9-positions of the carbazole, the formylation of 1,4-dimethylcarbazole **5** has remained essentially unchanged from Daltons original paper [10]. The Vilsmeier-Haack reaction was subsequently studied comprehensively using 1,4-dimethylcarbazole **5** as the initial substrate. Initially, the reaction was undertaken using various molar ratios of $POCl_3$ and DMF, and reaction times (Table 1).

Using 1 equiv of $POCl_3$ and 1 equiv of DMF afforded 9-formyl-1,4-dimethylcarbazole **7** as a major product (66% yield) with only a minor amount of the isomeric mixture of **6** and **8** formed (10%) (Entry 1, Table 1). Use of less than 1 equiv of $POCl_3$ afforded 9-formyl-1,4-dimethylcarbazole **7** as a sole product with very poor yields (Entry 2, Table 1). The reaction time was lengthened to improve the yield of 3-formyl-1,4-dimethylcarbazole **6**; however, no appreciable difference was observed (Entry 3). It is clear that increasing the equivalents of $POCl_3$ and DMF was seen to increase the yield of **6** (entries 4 and 5) with the most significant yield observed for entry 5. Regarding entry 5, the reaction was initiated with 1 equiv of $POCl_3$ and 1 equiv of DMF. TLC analysis of the reaction mixture after 3.5 h showed that only trace amounts of **6** and **8** (identical R_f value) had formed. At this stage, a further 0.2 equiv of each reagent was added, and the heating of the reaction was increased to afford a more vigorous reflux.

Because of the high yield of **6** obtained using method C, it appeared that prolonged heating was an important parameter of the reaction. Further evidence of this was seen in a ^{1}H-NMR spectroscopic study at elevated temperature. Starting with **7** in d_6-DMSO, the temperature was increased in 10°C increments and the formyl peak at 10.46 ppm was monitored. This peak diminished gradually until the temperature reached 110°C where it disappeared completely. Further testament to the lability of the amide bond of compound **7** was observed by the ease in which the compound could by recycled back to

Table 1

Effect of varying the stoichiometry of reagents and conditions on the formation of **6** and **8** from 1,4-dimethylcarbazole **5** in trichloroethylene.

	Reaction conditions					% Yield		
Entry	$POCl_3$[a]	DMF[a]	Time	Temperature (°C)	Method	**6** and **8**[b]	**7**	Ratio of **6** and **8**[c]
1	1 equiv	1 equiv	3.5 h	87.5	A	10	66	1.00:0.23
2	0.66 equiv	1 equiv	3.5 h	87.5	A	0	8	–
3	1 equiv	1 equiv	6 h	87.5	B	12	44	1.00:0.17
4	4.5 equiv	4.5 equiv	3.5 h	87.5	A	30	51	1.00:0.23
5	1.2 equiv	1.2 equiv	6.5 h	87.5	C	51	8	1.00:0.19

Reaction conditions: See Experimental for conditions A–C. A, heat under gentle reflux for 3.5 h; B, heat under gentle reflux for 6 h; C, heat under vigorous reflux for 3.5 h, extra equivalents of $POCl_3$ and DMF are added and the reaction mixture is heated under reflux for a further 3 h. Initial experiments using the original Cranwell–Saxton conditions (*o*-dichlorobenzene as solvent) yielded no improvement in yield of compound **6**.

[a] Equivalents of DMF and $POCl_3$ are relative to 1 equiv of starting material 1,4-dimethylcarbazole **5**.

[b] The "combined yield" of **6** and **8** refers to an isolated yield of 3-formyl-1,4-dimethylcarbazole and 6-formyl-1,4-dimethylcarbazole after chromatography.

[c] Determined from ^{1}H-NMR spectroscopic analysis of the singlet peaks corresponding to the formyl protons at 10.10–10.50 ppm.

1,4-dimethylcarbazole **5** *via* mild hydrolysis conditions (See Experimental section). Therefore, it was decided to use a higher boiling point solvent in the reaction to exploit the lability of the C—N amide bond of **7** leading to the production of greater yields of **6** (Table 2).

A panel of solvents including DMF, toluene, nitrobenzene, and chlorobenzene were used to test this effect. The initial reaction involving DMF was heated to 70°C for 2 h to determine if the choice of solvent would affect the production of formylated products at temperatures below reflux. At this temperature, the reaction did not go to completion as starting material **5** (24%) was isolated from the reaction following column chromatography along with undesired **7** as the sole product (Entry 1, Table 2). Increasing the temperature of DMF (Entry 2, Table 2) led to an increased yield of **7**; however, no formation of isomers **6** and **8** was observed. Starting material **5** (31%) was also isolated from the reaction following chromatography. Encouraging results were seen when toluene was used as solvent for the formylation reaction (Entry 3, Table 2), as formation of **7** was not detected, however, yields of desired **6** were still low. Use of nitrobenzene as solvent again demonstrated the lability of the amide bond at higher temperature as none of the 9-formyl derivative **7** was isolated from the reaction mixture (Entry 4, Table 2). However, the reaction led to the production of poor yields of compound **6** along with the formation of a blue polymeric side product. As a consequence of this, we next looked at chlorobenzene as another high-boiling point solvent.

Initial results were promising as work up of the reaction after 3.5 h afforded compounds **6–8** with no trace of the polymeric impurity (Entry 5, Table 2). However, after 3.5 h a substantial amount of undesired *N*-formyl derivative **7** had formed. We found that far greater yields of **6** were obtained using longer reflux times (6.5 h) and increased equivalents of $POCl_3$ and DMF (entries 6 and 7, Table 2). Regarding entries 6–8, the reactions were initiated using 1 equiv of $POCl_3$ and 1 equiv of DMF; however, after 3.5 h, addition of extra equivalents of $POCl_3$ and DMF was seen to produce improved yields of **6** and **8**.

Finally, a large scale synthetic batch using method C with just 1.01 equiv of $POCl_3$ and DMF was undertaken leading to the formation of **6** and **8** with a yield of 64%. This result shows prolonged heating together with a second addition of $POCl_3$ and DMF after 3.5 h to be the key criteria in the reaction with significantly improved yields and product ratio (<10% of undesired **8** in product mixture). This improvement in selectivity has evident synthetic advantages.

Another method of formylation explored was the Duff reaction, which was shown by Plug et al. to regiospecifically formylate at position 9 of ellipticine **1** [17]. Using this protocol on 1,4-dimethylcarbazole **5**, only starting material **5** and polyformylated carbazoles were obtained.

Formylation of 1,4,9-trimethylcarbazole 9. Given the success of our modified formylation conditions with **6**, we trialed a series of reaction conditions on the formylation of 1,4,9-trimethylcarbazole **9** toward the synthesis of 6-methylellipticine **3**. Because of the protection of the indole nitrogen by a methyl group, formylation at position 9 would not be an issue in this case with the synthetic challenge to affect selective formylation at C3 rather than C6 Scheme 2 [18]. Given the effect of increased equivalents of phosphorus oxychloride in the formylation of 1,4-dimethylcarbazole **5**, 2 equiv were used toward the formylation of **9** as standard conditions.

Table 2

Effect of varying solvents on the formation of **6** and **8** from 1,4-dimethylcarbazole **5**.

	Reaction conditions						% Yield[a]			
Entry	$POCl_3$[b]	DMF[b]	Solvent	Time	Temperature (°C)	Method	**5**	**6** and **8**	**7**	Ratio of **6** ans **8**[c]
1	1 equiv	–	DMF	2 h	70	D	24	0	32	0
2	1.01 equiv	–	DMF	6.5 h	153	C	31	0	54	0
3	1.01 equiv	1.01 equiv	$C_6H_5CH_3$	6.5 h	111	C	0	26	0	1.00:0.12
4	1 equiv	1 equiv	$C_6H_5NO_2$	6 h	150	B	23	18	0	1.00:0.14
5	1 equiv	1 equiv	C_6H_5Cl	3.5 h	131	A	0	12	33	1.00:0.21
6	1.5 equiv	1.5 equiv	C_6H_5Cl	6.5 h	131	C	0	52	4	1.00:0.09
7	1.15 equiv	1.15 equiv	C_6H_5Cl	6.5 h	131	C	0	54	3	1.00:0.08
8	1.01 equiv	1.01 equiv	C_6H_5Cl	6.5 h	131	C	0	64	6	1.00:0.09

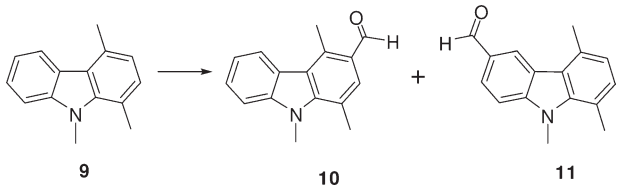
Reaction conditions: See Experimental for conditions A–D. A, heat under reflux for 3.5 h; B, heat under gentle reflux for 6 h; C, heat under reflux for 3.5 h, extra equivalents of $POCl_3$ and DMF are added and the reaction mixture is heated under reflux for a further 3 h; D, heat to 70°C for 2 h.

[a] The "combined yield" of **6** and **8** refers to an isolated yield of 3-formyl-1,4-dimethylcarbazole and 6-formyl-1,4-dimethylcarbazole after chromatography.

[b] Equivalents of DMF and $POCl_3$ are relative to 1 equiv of starting material 1,4-dimethylcarbazole **5**.

[c] Determined from ^{1}H-NMR spectroscopic analysis from the singlet peaks corresponding to the formyl proton at 10.10–10.50 ppm.

Scheme 2



Once again, it could be seen that reaction solvents greatly altered the yield of products formed. Similar to its unmethylated derivative **5**, use of higher boiling point solvents were seen to lead to improved yields of products. In this case, however, no reaction occurred using the lower boiling point solvent trichloroethylene (Entry 1, Table 3) with the greatest yields obtained using DMF as solvent (Entry 3, Table 3). Moderate yields were also obtained using chlorobenzene as solvent. Disappointingly, the regioselectivity was lower for the *N*-methyl carbazole derivative **10** than with the *N*—H carbazole **6** with 20–30% of the undesired 6-formyl regioisomer present in this instance.

Formylation of 6-methoxy-1,4-dimethylcarbazole 12. Because of high yields obtained for 3-formyl-1,4-dimethylcarbazole **6** from use of chlorobenzene as solvent and modified reaction conditions (Entry 8, Table 2), it was decided that this protocol should be implemented to the formylation of 6-methoxy-1,4-dimethylcarbazole **12**, a key precursor for 9-methoxyellipticine **4** and 9-hydroxyellipticine. As reaction at C-6 was blocked in this case, the Vilsmeier Haack reaction of **12** was previously shown to formylate at position 3 with yields of 60% [15]. Interestingly, conducting the Vilsmeier-Haack reaction in chlorobenzene with the more activated carbazole **12** leads to lower yields of the desired 3-formylcarbazole **13** (22%) than seen with the less activated carbazoles. However, formation of the 7- and 8-formyl derivatives, **14** and **15**, offer potentially useful synthetic intermediates for further investigation (Scheme 3), in particular the new one-step synthesis of **15** [19]. The formation of these side products can be rationalized by the activating effect of the methoxy group on the A ring.

The desired 3-formyl derivative **13** could efficiently be separated from the 7-formyl and 8-formyl isomers, **14** and **15**, by column chromatography and carried through a modified Cranwell–Saxton route to afford 9-methoxyellipticine **4** with an overall yield of 13% [14,16]. It is worth noting that using the Dracínský modification of the Cranwell–Saxton route (in which a benzene sulfonamide **16** replaces a toluene sulfonamide as the precursor to **4**) would lead to a more efficient production of **4** (Scheme 3) [14].

Synthesis of ellipticine 1. On implementation of our modified Vilsmeier-Haack conditions into ellipticine **1** synthesis, the overall yield from indole improved from 3% to 14% (Scheme 4). It was observed that the highest overall yields were obtained when the isomeric mixture of 3-formyl and 6-formyl carbazoles was carried through the synthesis following the published routes until formation of the *N*-tosyl derivative, where purification by recrystallization was seen to yield the 3-isomer as the sole product.

The 3-formyl derivatives, **6** and **8**, were treated with aminoacetaldehyde diethyl acetal in solvent free conditions to afford the desired imine **17** and **18** in quantitative yields. Platinium(IV) oxide-catalyed hydrogenation of **17** and **18** in ethanol furnished the corresponding amines **19** and **20** (98%) (3-isomer:6-isomer, 1.00:0.07). The 6-isomer of the imine and the amine, **18** and **20**, have not been reported previously. Treatment of **19** and **20** with tosyl chloride in pyridine afforded the *N*-tosyl derivative **21**, which was recyrstallized with dichloromethane and hexane to afford **21** as the sole product (68%). Finally, cyclization to ellipticine **1** was achieved by treatment of the pure *N*-tosyl derivative **21** with concentrated hydrochloric acid in dioxane (58%). Starting from indole, the overall yield of **1** was calculated to be 14%.

Table 3

The effect of varying solvents on the formation of **10** and **11**.

	Reaction conditions						% Yield	
Entry	$POCl_3$[a]	DMF[a]	Time	Temperature (°C)	Solvent	Method	**10** and **11**[b]	Ratio of **10** and **11**[c]
1	2 equiv	1 equiv	6 h	87.5	TCE	B	0	–
2	2 equiv	–	2 h	153	DMF	D	35	1.00:0.23
3	2 equiv	–	6 h	153	DMF	B	68	1.00:0.20
5	2 equiv	1 equiv	6 h	131	C_6H_5Cl	B	53	1.00:0.36

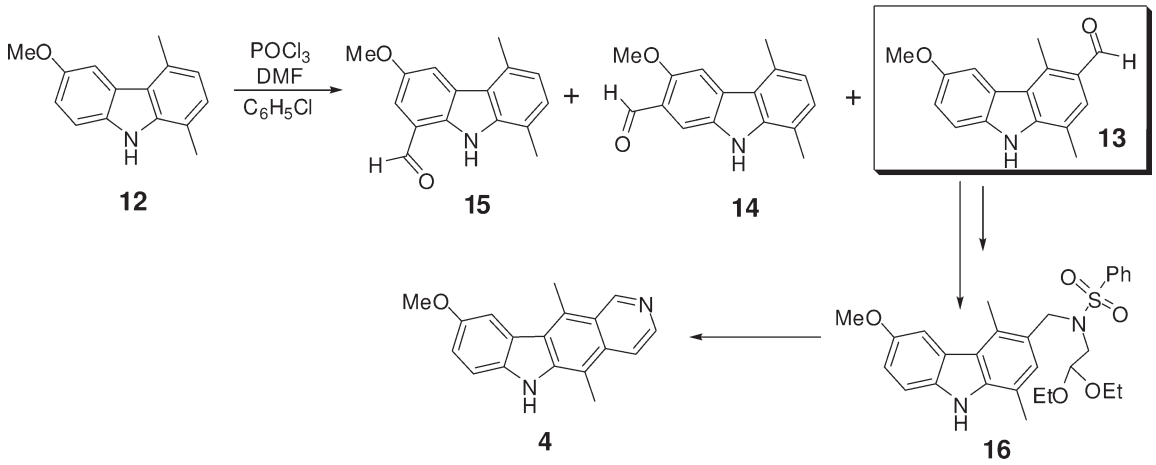
Reaction conditions: See Experimental. B, heat under reflux for 6 h; D, heat to 70°C for 2 h.

[a] Equivalents of DMF and $POCl_3$ are relative to 1 equiv of starting material 1,4,9-trimethylcarbazole **9**.

[b] The "combined yield" of **10** and **11** refers to an isolated yield of 3-formyl-1,4,9-trimethylcarbazole and 6-formyl-1,4,9-trimethylcarbazole after column chromatography.

[c] Determined from NMR analysis from the singlet peaks corresponding to the formyl proton at 10.10–10.50 ppm.

Scheme 3



Synthesis of 6-methylellipticine 3. Similar to the synthesis of ellipticine **1**, the isomeric mixture of 3-formyl- and 6-formyl-1,4,9-trimethylcarbazole, **10** and **11**, was carried through a modified Cranwell–Saxton route where purification by recrystallization was achieved at the *N*-tosyl derivative **26** (Scheme 4). Regarding the synthesis of amines, **24** and **25**, and the *N*-tosyl amide **26**, reaction conditions differed from those described for ellipticine **1**.

Through use of sodium borohydride in methanol, reduction of imines **22** and **23** to the corresponding amines **24** and **25** was found to be more efficient and higher yielding than the hydrogenation reaction described for **22** and **23**. Dalton reported the formation of **23**, whereas compound **25** or **26** has not been reported previously [12]. The tosylation reaction was found to proceed with greater efficiency through use of potassium carbonate, tosyl chloride in a solvent mixture of THF and water, although the yield was slightly lower than that observed for the formation of **21**. Cyclization to 6-methylellipticine **3** was achieved in similar conditions to those quoted for ellipticine **1** with good yields (55%). The overall yield of 6-methylellipticine **3**, starting from 1,4-dimethylcarbazole **5**, was calculated to be 15%.

CONCLUSIONS

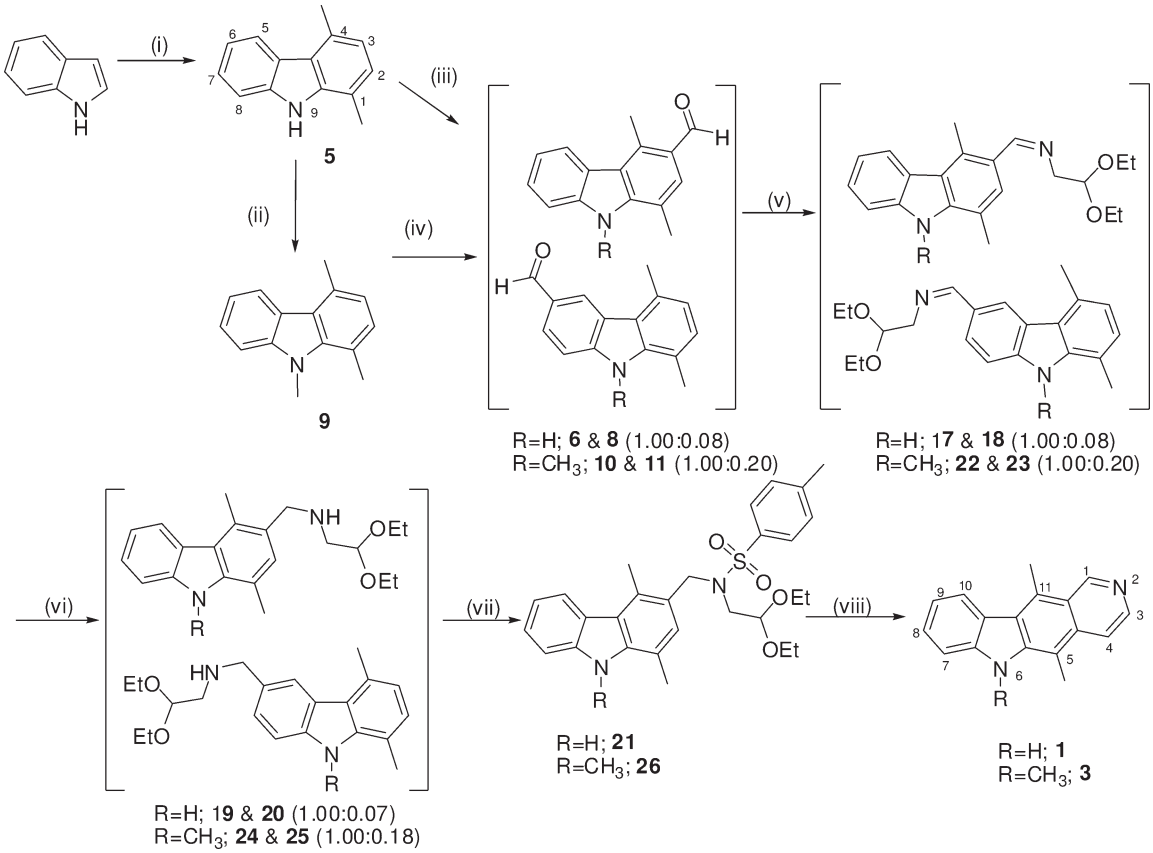
We have successfully devised a route to the key intermediate 3-formyl-1,4-dimethylcarbazole **6** with a significant improvement in yields compared with previously published procedures through use of chlorobenzene as solvent. Applying this method to the modified Cranwell–Saxton route, the overall yield of ellipticine **1** (from starting material indole) increased from 3% to 14%. In contrast, treatment of 1,4,9-trimethylcarbazole **9** under the same conditions did not lead to an improvement relative to reaction in DMF. Interestingly, formylation of 6-methoxy-1,4-dimethylcarbazole **12** following newly our newly developed chlorobenzene protocol led to new formylated intermediates **14** and **15,** which have clear synthetic potential while use of the Dalton method proved most effective for the synthesis of the 3-formyl derivative **13** [12]. Overall, it is clear that as formylations of the carbazole nucleus are complex, selective formylation to the desired C3 formyl derivative can be achieved by careful optimization of reaction conditions.

EXPERIMENTAL

General procedures. Melting points were measured on a Uni-Melt Thomas Hoover Capillary Melting Point apparatus and are uncorrected. Low-resolution mass spectra were recorded on a Waters Micromass Quattro Micro mass spectrometer (Instrument number QAA1202) in electrospray ionization (ESI) positive and negative modes and a Waters Micromass LCT Premier (Instrument number KD160) was used for high-resolution acquisitions. Infrared (IR) spectra were recorded as potassium bromide (KBr) disks on a Perkin-Elmer FT-IR Paragon 1000 or a Spectrum One FT-IR spectrophotometer. ^{1}H (300 MHz) and ^{13}C-NMR (75 MHz) NMR were recorded on a Bruker Avance 300 NMR spectrometer. All spectra were recorded at 20°C in deuterated chloroform ($CDCl_3$) with tetramethylsilane (TMS) as an internal standard unless otherwise stated. Chemical shifts (δ_H and δ_C) are reported in parts per million (ppm), relative to TMS and coupling constants are expressed in Hertz (Hz). Splitting patterns in ^{1}H-NMR spectra are designated as s (singlet), br s (broad singlet), d (doublet), dd (doublet of doublets), ddd (doublet of doublet of doublets), dt (doublet of triplets), t (triplet), q (quartet), and m (multiplet). Thin-layer chromatography (TLC) was carried out on precoated silica gel plates (Merck 60 PF_{254}). Visualization was achieved by UV light (254 nm), vanillin or potassium permanganate staining. Column chromatography was carried out using Kieselgel 60, 0.040–0.063 nm (Merck).

Synthesis of ellipticine 1. ***1,4-Dimethylcarbazole 5.*** Indole (30.002 g, 0.256 mol), hexane-2,5-dione (66 mL, 0.530 mol)

Scheme 4. Reagents and conditions: (i) hexane-2,5-dione, *p*-TsOH, EtOH, reflux for 2 h, **5** = 57%; (ii) NaH, MeI DMF, r.t. overnight, **9** = 94%; (iii) $POCl_3$, DMF, chlorobenzene, reflux for 6.5 h, **6** and **8** = 64%; (iv) $POCl_3$, DMF, reflux for 6 h, **10** and **11** = 68% (v) aminoacetaldehyde diethylacetal, 110°C for 2 h, **17** and **18** = 100%, **22** and **23** = 95%; (vi) PtO_2, H_2, EtOH, r.t. at 50 psi for 3 d, **19** and **20** = 98%, or $NaBH_4$, MeOH, r.t. for 2 h, **24** and **25** = 92%; (vii) *p*-TsCl, pyridine, r.t. for 3 d, **21** = 68% or *p*-TsCl, K_2CO_3, THF, H_2O (1:2), r.t. for 1.5 h, **26** = 55%; and (viii) HCl, dioxane, reflux for 6 h, **1** = 58%, **3** = 55%.*Attempts to isolate 7-formyl-6-methoxy-1,4-dimethylcarbazole **14** from the mixture were unsuccessful.



and a catalytic amount of *p*-toluenesulfonic acid were dissolved in ethanol (300 mL) and heated under reflux for 2 h. After this time, the reaction mixture was cooled to room temperature, evaporated under reduced pressure, and the resulting purple solid was purified by flash chromatography eluting with hexane-ethyl acetate (9:1) to afford an off-white solid. Subsequent recrystallization from ethyl acetate and hexane produced 1,4-dimethylcarbazole **5** (28.425 g, 57%) as white crystals: m.p. 94–95°C (ref. 12, 92–93°C); ν_{max} (cm^{-1}) (KBr) 3417, 2919, 1455, 728; δ_H (300 MHz) 2.52 [3H, s, C(1)CH_3], 2.85 [3H, s, C(4)CH_3], 6.93 [1H, d, J = 7.3, C(3)H], 7.12 [1H, d, J = 7.3, C(2)H], 7.24 [1H, overlapping ddd, J = 8.0, 6.8, 1.2, C(6)H], 7.40 [1H, overlapping ddd, J = 8.0, 6.9, 0.9, C(7)H], 7.46 [1H, d, J = 7.8, C(8)H], 7.97 (1H, br s, NH), 8.17 [1H, d, J = 7.9, C(5)H]; *m/z* (ES+) 196 $[M + H]^+$ (20%), 119 (7), 84 (5).

Formylation of 1,4-dimethylcarbazole 5.

Method A. $POCl_3$ was added, dropwise, to an ice-cold solution of 1,4-dimethylcarbazole **5** (3.515 g, 0.018 mol) and DMF (1.4 mL, 0.018 mol) in solvent (50 mL) (see Tables 1–3) over the course of 10 min. The reaction mixture was heated under reflux for 3.5 h, cooled, poured into a solution of sodium acetate (20 mL, 25% w/w), and evaporated under reduced pressure to afford a brown solid, which was diluted with ethyl acetate (50 mL), washed with water (4 × 20 mL), brine (10 mL), dried, and evaporated under reduced pressure. The resulting brown solid was purified by column chromatography (hexane-ethyl acetate, 100:0 to 90:10).

Method B. Method B is initially the same as method A. After dropwise addition of $POCl_3$, the reaction was heated under reflux for 6 h. Workup of the reaction mixture proceeded *via* the same reaction conditions as method A.

Method C. Method C is initially the same as method A. After dropwise addition of $POCl_3$, the reaction was heated under vigorous reflux for 3.5 h. After this time, further equivalents of $POCl_3$ and DMF (see Tables 1–3) were added and the reaction mixture was heated under reflux for a further 3 h. Workup of the reaction mixture proceeded *via* the same reaction conditions as method A.

Method D. Method D is initially the same as method A. After dropwise addition of $POCl_3$, the reaction was heated to 70°C for 2 h after which time workup of the reaction mixture proceeded *via* the same reaction conditions as method A.

9-Formyl-1,4-dimethylcarbazole 7. M.p. 145-146°C; ν_{max} (cm^{-1}) (KBr) 3017, 2918, 1679, 1589; δ_H (300 MHz) 2.64 [3H, s,

C(1)CH_3], 2.73 [3H, s, C(4)CH_3], 7.02 [1H, d, J = 7.6, C(3)H], 7.11 [1H, d, J = 7.6, C(2)H], 7.36 [1H, overlapping ddd, J = 7.7, 7.5, 1.3, C(6)H], 7.44 [1H, overlapping ddd, J = 8.0, 7.4, 1.5, C(7)H], 8.02 [1H, d, J = 8.1, C(8)H], 8.64 [1H, d, J = 7.8, C(5)H], 9.90 (1H, s, N—CHO); δ_C (75 MHz) 20.6 [CH_3, C(1)CH_3], 22.5 [CH_3, C(4)CH_3], 110.4 (C, aromatic C), 117.3 (CH, aromatic CH), 119.5 (C, aromatic C), 122.1 (CH, aromatic CH), 124.5 (CH, aromatic CH), 125.9 (CH, aromatic CH), 126.9 (CH, aromatic CH), 127.2 (C, aromatic C), 130.4 (CH, aromatic CH), 131.5 (C, aromatic C), 136.5 (C, aromatic C), 137.7 (C, aromatic C), 160.2 (C, C=O); *m/z* (ES+) 224 $[M + H]^+$ (6%), 151 (2), 101 (100). HRMS Found: $[M + H]^+$, 224.1077. Calc. for $C_{15}H_{14}NO$: $[M + H]^+$, 224.1075; Found C, 80.51; H, 5.90; N, 6.42. $C_{15}H_{13}NO$ requires C, 80.69; H, 5.87; N, 6.27.

3- and 6-Formyl-1,4-dimethylcarbazole, 6 and 8. ν_{max} (cm^{-1}) (KBr) 3238, 2920, 2850, 1646, 1585, 734; δ_H (300 MHz) (for the minor isomer 6-formyl-1,4-dimethylcarbazole **8** one proton equates to 0.08H) 2.57 [0.24H, s, C(1)CH_3 of **8**], 2.58 [3H, s, C(1)CH_3 of **6**], 2.9 [0.24H, s, C(4)CH_3 of **8**], 3.2 [3H, s, C(4)CH_3 of **6**], 7.03 [0.08H, d, J = 7.4, C(3)H of **8**], 7.21 [0.08H, d, J = 7.6, C(2)H of **8**], 7.33 [1H, ddd, J = 8.1, 7.0, 1.4, C(6)H of **6**], 7.48 [1H, overlapping ddd, J = 8.1, 7.0, 1.1, C(7)H of **6**], 7.54 [1.08H, d, J = 7.9, C(8)H of **6**, C(8)H of **8**], 7.77 [1H, s, C(2)H of **6**], 7.98 [0.08H, dd, J = 8.4, 1.5, C(7)H of **8**], 8.28 [1H, d, J = 8.0, C(5)H of **6**], 8.36 (1H, br s, NH of **6**), 8.41 (0.8H, br s, NH of **8**), 8.66 [0.08H, br s, C(5)H of **8**], 10.11 (0.08H, s, CHO of **8**), 10.46 (1H, s, CHO of **6**); *m/z* (ES+) 224 $[M + H]^+$ (34%), 146 (2), 118 (6).

Typical procedure for hydrolysis of 9-formyl-1,4-dimethylcarbazole 7. A solution of **7** (4.870 g, 21.8 mmol) in dichloromethane (250 mL) was stirred with silica (25 g) and 1*M* sulphuric acid (2 drops) for 5 days. The reaction mixture was filtered, dried (magnesium sulfate), and evaporated under reduced pressure to afford 1,4-dimethylcarbazole **5** (4.254 g, 100%) as a white solid with identical characteristics to those above.

3-(2,2-Diethoxyethyliminomethyl)-1,4-dimethylcarbazole 17 and 6-(2,2-diethoxyethyliminomethyl)-1,4-dimethylcarbazole 18. A mixture of 3- and 6-formyl-1,4-dimethylcarbazole, **6** and **8**, (1.00:0.08) (20.013 g, 0.089 mol) and amino-acetaldehyde diethyl acetal (12.9 mL, 0.089 mol) was heated at 110°C as stirring for 4 h. After this time, the reaction mixture was allowed to cool, diluted with toluene (50 mL), and evaporated under reduced pressure to produce a mixture of 3- and 6-(2,2-diethoxyethyliminomethyl)-1,4-dimethylcarbazole, **17** and **18**, (1.00:0.08) as a yellow/orange oil, which was used without further purification (30.325 g, 100%): ν_{max} (cm^{-1}) (film) 3159, 2974, 2890, 1636, 1588, 1500, 1116, 1066, 746; δ_H (300 MHz) (for the minor isomer, 6-(2,2-diethoxyethyliminomethyl)-1,4-dimethylcarbazole **18** one proton equates to 0.08H) 1.18–1.27 (6.48H, m, 2× OCH_2CH_3 of **17**, 2× OCH_2CH_3 of **18**), 2.43 [3H, s, C(1)CH_3 of **17**], 2.48 [0.24H, s, C(1)CH_3 of **18**], 2.80 [3H, s, C(4)CH_3 of **17**], 2.82 [0.24H, s, C(4)CH_3 of **18**], 3.46–3.81 [4.32H, m, 2× OCH_2CH_3 of **17**, 2× OCH_2CH_3 of **18**], 3.85 [2.16H, d, J = 4.8, NCH_2CH of **17**, NCH_2CH of **18**], 4.89 [1.08H, t, J = 5.4, $CH(OEt)_2$ of **17**, $CH(OEt)_2$ of **18**], 6.88 [0.08H, d, J = 7.7, C(3)H of **18**], 7.08 [0.08H, d, J = 7.7, C(2)H of **18**], 7.22 [1H, ddd, J = 8.1, 7.2, 1.1, C(6)H of **17**], 7.33–7.42 {1.08H, m, including 7.37 [1H, ddd, J = 8.1, 7.1, 1.0, C(7)H of **17**], C(8)H of **18**}, 7.47 [1H, d, J = 7.9, C(8)H of **17**], 7.79–7.85 {1.08H, m, including 7.81 [1H, s, C(2)H of **17**], C(7)H of **18**}, 8.14 [1H, d, J = 7.9, C(5)H of **17**], 8.36 [0.08H, d, J = 1.1, C(5)H of **18**], 8.41 (0.08H, s, ArCHN of **18**), 8.74 (1H, s, ArCHN of **17**), 9.18 (1H, br s, NH of **17**), 9.23 (0.08H, br s, NH of **18**); *m/z* (ES+) 339 $[M + H]^+$ (100%), 250 (4), 175 (4).

3-(2,2-Diethoxyethylaminomethyl)-1,4-dimethylcarbazole 19 and 6-(2,2-diethoxyethylaminomethyl)-1,4-dimethylcarbazole 20. A mixture of 3- and 6-(2,2-diethoxyethyliminomethyl)-1,4-dimethylcarbazole, **17** and **18** (1.00:0.08) (14.215 g, 0.042 mol) was dissolved in absolute ethanol (50 mL) and transferred to a hydrogenation vessel. Platinum oxide (0.142 g, 0.63 mmol) was added, and the reaction mixture was shaken under an atmosphere of hydrogen at 50 psi for 3 days after which time the solution was filtered over celite and concentrated under reduced pressure to produce a mixture of 3- and 6-(2,2-diethoxyethylaminomethyl)-1,4-dimethylcarbazole, **19** and **20**, (1.00:0.07) as green/brown oil (14.071 g, 98%), which was used without further purification: ν_{max} (cm^{-1}) (film) 3525, 3316, 3153, 2975, 2921, 1598, 1457, 1116, 1053, 753; δ_H (300 MHz) (for the minor isomer, 6-(2,2–diethoxyethylaminomethyl)-1,4-dimethylcarbazole **20** one proton equates to 0.07H) 1.17–1.24 (6.42H, m, 2× OCH_2CH_3 of **19**, 2× OCH_2CH_3 of **20**) 1.94 (1.07H, br s, $ArCH_2NH$ of **19**, $ArCH_2NH$ of **20**), 2.45 [3H, s, C(1)CH_3 of **19**], 2.50 [0.21H, s, C(1)CH_3 of **20**], 2.84 [3H, s, C(4)CH_3 of **19**], 2.86 [0.21H, s, C(4)CH_3 of **20**], 3.47–3.73 (6.42H, m, 2× OCH_2CH_3 of **19**, 2× OCH_2CH_3 of **20**, $NHCH_2CH$ of **19**, $NHCH_2CH$ of **20**), 3.96 (2H, s, $ArCH_2NH$ of **19**), 3.98 (0.14H, s, $ArCH_2NH$ of **20**), 4.41 [0.07H, t, J = 5.1, $CH(OEt)_2$ of **20**], 4.66 [1H, t, J = 5.6, $CH(OEt)_2$ of **19**], 6.91 [0.07H, d, J = 7.5, C(3)H of **20**], 7.10 [0.07H, d, J = 7.5, C(2)H of **20**], 7.14 [1H, s, C(2)H of **19**], 7.19–7.25 {1.07H, m, including 7.22 [1H, ddd, J = 8.1, 7.0, 1.3, C(6)H of **19**], C(7)H of **20**}, 7.35–7.41 {1.07H, m, including 7.38 [1H, overlapping ddd, J = 8.1, 7.0, 1.1, C(7)H of **19**], C(8)H of **20**}, 7.44 [1H, d, J = 7.6, C(8)H of **19**], 8.07 [0.07H, br s, C(5)H of **20**], 8.21 [1H, d, J = 7.9, C(5)H of **19**], 8.36 (1.07H, s, NH of **19**, NH of **20**); *m/z* (ES+) 341 $[M + H]^+$ (100%), 244 (12), 208 (8).

N-tosyl-3-(2,2-diethoxyethylaminomethyl)-1,4-dimethyl-carbazole 21. To a solution of 3- and 6-(2,2-diethoxyethylaminomethyl)-1,4-dimethylcarbazole, **19** and **20**, (1:0.07) (14.071 g, 0.041 mol) in pyridine (200 mL) was added *p*-toluenesulfonyl chloride (11.820 g, 0.062 mol) and the reaction mixture was stirred at room temperature for 3 days. After this time, the reaction mixture was poured into water (200 mL) and extracted with ether (3 × 100 mL). The organic layer was subsequently washed with hydrochloric acid (1*M*, 3 × 100 mL), brine (100 mL), water (100 mL), dried, and evaporated under reduced pressure to yield a brown solid, which was purified by recrystallization (dichloromethane-hexane) to afford the single isomer of *N*-tosyl-3-(2,2-diethoxyethylaminomethyl)-1,4-dimethyl-carbazole **21** as an off-white solid (13.771 g, 68%): m.p. 177–179°C (ref. 18, 183.5–185°C); ν_{max} (cm^{-1}) (KBr) 3370, 2975, 2914, 2869, 1596, 1455, 1349, 1172, 1167, 1113, 736; δ_H (300 MHz) 1.07 (6H, t, J = 7.0, 2× OCH_2CH_3), 2.39 [3H, s, C(1)CH_3], 2.42 [3H, s, C(4′)CH_3], 2.81 [3H, s, C(4)CH_3], 3.19 (2H, d, J = 5.5, NCH_2CH), 3.25–3.57 (4H, m, 2× OCH_2CH_3), 4.13 [1H, t, J = 5.4, $CH(OEt)_2$], 4.66 (2H, s, $ArCH_2N$), 6.96 [1H, s, C(2)H], 7.21–7.28 [3H, m, C(3′)H, C(5′)H, C(6)H], 7.41 [1H, overlapping ddd, J = 8.1, 7.0, 1.0, C(7)H], 7.47 [1H, d, J = 7.6, C(8)H], 7.73 [2H, d, J = 8.3, C(2′)H, C(6′)H], 7.99 (1H, br s, NH), 8.20 [1H, d, J = 7.8, C(5)H]; *m/z* (ES+) 403 $[M + H—C_6H_4CH_3]^+$ (34%), 341 $[M—SO_2C_6H_4CH_3]^+$ (20).

Ellipticine (5,11-dimethyl-6H-pyrido[4,3-b]carbazole) 1. To a stirring solution of *N*-tosyl-3-(2,2-diethoxyethylaminomethyl)-1,4-dimethylcarbazole **21** (13.778 g, 0.028 mol) in

1,4-dioxane (150 mL), hydrochloric acid (6*M*, 30 mL) was added and the reaction mixture was heated under reflux for 6 h. After this time, the solution was cooled, poured into water (200 mL), made alkaline with potassium carbonate solution (10% v/v), and extracted with chloroform (3 × 100 mL). The organic layer was washed with brine (100 mL), water (100 mL), dried, and evaporated under reduced pressure to produce a green solid, which was further purified by chromatography (dichloromethane–methanol, 100:0 to 80:20) to afford ellipticine **2** as an orange solid (3.983 g, 58%): m.p. 315–316°C (ref. 12, 315–317°C): ν_{max} (cm^{-1}) (KBr) 3369, 3138, 2860, 1617, 1589, 1413, 737; δ_H (300 MHz, d_6-DMSO) 2.72 [3H, s, C(5)CH_3], 3.19 [3H, s, C(11)CH_3], 7.18 [1H, ddd, J = 8.0, 6.7, 1.5, C(9)H], 7.45 [1H, overlapping ddd, J = 8.1, 6.7, 1.0, C(8)H], 7.49 [1H, dd, J = 8.1, 1.0, C(7)H], 7.86 [1H, d, J = 6.1, C(4)H], 8.31 [1H, d, J = 7.9, C(10)H], 8.35 [1H, d, J = 6.1, C(3)H], 9.62 [1H, s, C(1)H], 11.33 (1H, s, NH); *m/z* (ES+) 247 $[M + H]^+$ (84%), 169 (100), 148 (12).

Synthesis of 6-methylellipticine 3. ***1,4,9-Trimethylcarbazole 9.*** 1,4-Dimethylcarbazole **5** (35.555 g, 0.182 mol) was dissolved in anhydrous DMF (150 mL) and stirred at 0°C under nitrogen for 10 min. Sodium hydride (60% dispersion in mineral oil, 8.750 g, 0.365 mol) was added portion wise to the reaction mixture over a period of 5 min and the mixture was stirred for a further 10 min. Methyl iodide (23 mL, 0.365 mol) was added in one portion, and the reaction mixture was allowed to warm to room temperature and stirred overnight. Water (100 mL) was added resulting in the formation of a white precipitate and the whole mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with water (2× 50 mL), brine (2× 50 mL), dried, and concentrated under reduced pressure to afford 1,4,9-trimethylcarbazole **9** as an off-white solid (35.756 g, 94%): m.p. 128–129°C (ref. 12, 131–132°C); ν_{max} (cm^{-1}) (KBr) 3038, 3010, 2922, 1469, 744; δ_H (300 MHz) 2.84 [6H, s, C(1)CH_3, C(4)CH_3], 4.11 [3H, s, N(9)CH_3], 6.88 [1H, d, J = 7.3, C(3)H], 7.07 [1H, d, J = 7.2, C(2)H], 7.23 [1H, ddd, J = 8.0, 7.0, 1.1, C(6)H], 7.39 [1H, d, J = 8.0, C(8)H], 7.47 [1H, ddd, J = 8.1, 7.0, 1.1, C(7)H], 8.18 [1H, d, J = 7.9, C(5)H]; *m/z* (ES+) 210 $[M + H]^+$ (24%), 147 (10), 115 (100).

3-Formyl-1,4,9-trimethylcarbazole 10 and 6-formyl-1,4,9-trimethylcarbazole 11. Starting materials used were 1,4,9-trimethylcarbazole **9** (11.510 g, 0.055 mol), $POCl_3$ (10.1 mL, 0.0110 mol) and DMF (200 mL).The reaction was initiated using the same procedure as described for the formylation of 1,4-dimethylcarbazole **5**. Workup for this reaction differed from that of 3-formyl-1,4-dimethylcarbazole **6**. After the initial reaction (*via* conditions B or D, see Table 3), the reaction mixture was cooled to room temperature and poured into water. Using potassium carbonate solution (10% w/v), the reaction mixture was basified and then extracted with chloroform. The organic layer was washed successively with saturated aqueous sodium bicarbonate, brine, dried over magnesium sulfate, and evaporated under reduced pressure to afford a brown oil. This was purified using column chromatography eluting with hexane-ethyl acetate (100:0 to 80:20) to give a single band consisting of a mixture (which could not be separated) of 3-formyl- and 6-formyl-1,4,9-trimethylcarbazole, **10** and **11**, (1.00:0.20) (8.830 g, 68%) as an off-white solid: ν_{max} (cm^{-1}) (KBr) 2926, 2694, 1678, 1588, 1560, 744, 727; δ_H (300 MHz) (for the minor isomer, 6-formyl-1,4,9-trimethylcarbazole **11** one proton equates to 0.2H) 2.85 [0.6H, s, C(1)CH_3 of **11**], 2.87 [3H, s, C(1)CH_3 of **10**], 2.88 [0.6H, s, C(4)CH_3 of **11**], 3.17 [3H, s, C(4)CH_3 of **10**], 4.14 [3H, s, N(9)CH_3 of **10**], 4.16 [0.6H, s, N(9)CH_3 of **11**], 6.98 [0.2H, d, J = 7.4, C(3)H of **11**], 7.15 [0.2H, d, J = 7.4, C(2)H of **11**], 7.32 [1H, ddd, J = 8.1, 7.1, 1.1, C(6)H of **10**], 7.45 [1.2H, d, J = 8.1, C(8)H of **10**, C(8)H of **11**] 7.54 [1H, ddd, J = 8.2, 7.1, 1.1, C(7)H of **10**], 7.69 [1H, s, C(2)H of **10**], 8.00 [0.2H, dd, J = 8.6, 1.5, C(7)H of **11**], 8.28 [1H, d, J = 8.0, C(5)H of **10**], 8.63 [0.2H, d, J = 1.4, C(5)H of **11**], 10.09 (0.2H, s, CHO of **11**), 10.43 (1H, s, CHO of **10**); *m/z* (ES+) 238 $[M + H]^+$ (88%), 142 (4), 119 (10).

3-(2,2-Diethoxyethyliminomethyl)-1,4,9-trimethylcarbazole 22 and 6-(2,2-diethoxyethyliminomethyl)-1,4,9-trimethyl-carbazole 23. Using the same procedure as described for the synthesis of **17** and **18**, and starting from **10** and **11** (8.830 g, 0.037 mol), 3- and 6-(2,2-diethoxyethyliminomethyl)-1,4,9-trimethylcarbazole, **22** and **23** (1.00:0.20) was afforded as an orange solid, which was used without further purification (12.457 g, 95%): ν_{max} (cm^{-1}) (KBr) 2976, 2914, 2870, 1665, 1596, 1455, 1168, 1090, 737; δ_H (300 MHz) (for the minor isomer, 6-(2,2-diethoxyethyliminomethyl)-1,4-dimethylcarbazole **23** one proton equates to 0.20H) 1.21 (7.2H, t, J = 7.0, 2× OCH_2CH_3 of **22**, 2× OCH_2CH_3 of **23**), 2.82 [0.6H, s, C(1)CH_3 of **23**], 2.83 [3H, s, C(1)CH_3 of **22**], 2.86 [0.6H, s, C(4)CH_3 of **23**], 2.97 [3H, s, C(4)CH_3 of **22**], 3.57–3.82 (4.8H, m, 2× OCH_2CH_3 of **22**, 2× OCH_2CH_3 of **23**), 3.83–3.86 (2.4H, m, NCH_2CH of **22**, NCH_2CH of **23**), 4.09 [3H, s, N(9)CH_3 of **22**], 4.10 [0.6H, s, N(9)CH_3 of **23**], 4.85 [1.2H, t, J = 5.4, $CH(OEt)_2$ of **22**, $CH(OEt)_2$ of **23**], 6.91 [0.2H, d, J = 7.4, C(3)H of **23**], 7.08 [0.2H, d, J = 7.4, C(2)H of **23**], 7.26 [1H, ddd, J = 8.0, 7.0, 1.2, C(6)H of **22**], 7.38 [0.2H, d, J = 8.6, C(8)H of **23**], 7.40 [1H, d, J = 8.0, C(8)H of **22**], 7.48 [1H, ddd, J = 8.1, 7.1, 1.1, C(7)H of **22**], 7.82 [1H, s, C(2)H of **22**], 7.95 [0.2H, dd, J = 8.6, 1.5, C(7)H of **23**], 8.24 [1H, d, J = 7.9, C(5)H of **22**], 8.43 [0.2H, d, J = 1.3, C(5)H of **23**], 8.45 (0.2H, s, ArCHN of **23**), 8.83 (1H, s, ArCHN of **22**); *m/z* (ES+) 353 $[M + H]^+$ (100%), 247 (2), 175 (4).

3-(2,2-Diethoxyethylaminomethyl)-1,4,9-trimethylcarbazole 24 and 6-(2,2-diethoxyethylaminomethyl)-1,4,9-trimethy-lcarbazole 25. To a stirring mixture of 3- and 6-(2,2-diethoxyiminomethyl)-1,4,9-trimethylcarbazole, **22** and **23**, (1.00:0.20) (12.457 g, 0.035 mol) in methanol (300 mL) at 0°C was added sodium borohydride (13.392 g, 0.354 mol) in portions over a period of 30 min. Once addition was complete, the mixture was stirred at room temperature for a further 2 h. After this time, the reaction mixture was evaporated under reduced pressure to afford a white residue, which was acidified to pH 1 using hydrochloric acid (1*M*), basified using sodium hydroxide (30%), and extracted with toluene (3 × 100 mL). The organic layer was washed with brine (2× 50 mL), dried, and evaporated under reduced pressure to afford a mixture of 6- and 3-(2,2-diethoxyethylaminomethyl)-1,4,9-trimethylcarbazole, **24** and **25**, (1.00:0.18) as brown oil, which was used without further purification (11.529 g, 92%): ν_{max} (cm^{-1}) (film) 3334, 2973, 2926, 1467, 1129, 1061, 748; δ_H (300 MHz) (for the minor isomer, 6-(2,2-diethoxyethylaminomethyl)-1,4-dimethylcarbazole **25** one proton equates to 0.18H) 1.20 (7.08H, t, J = 7.0, 2× OCH_2CH_3 of **24**, 2× OCH_2CH_3 of **25**), 1.52 (1.18H, br s, NH of **24**, NH of **25**), 2.81 [0.54H, s, C(1)CH_3 of **25**], 2.82 [3H, s, C(1)CH_3 of **24**], 2.84 [3.54H, s, C(4)CH_3 of **25**, C(4)CH_3 of **24**], 3.45–3.73 (7.08H, m, 2× OCH_2CH_3 of **24**,

2× OCH_2CH_3 of **25**, NCH_2CH of **24**, NCH_2CH of **25**), 3.94 (2H, s, $ArCH_2NH$ of **24**), 3.99 (0.36H, s, $ArCH_2NH$ of **25**), 4.08 [3H, s, $N(9)CH_3$ of **24**], 4.09 [0.54H, s, $N(9)CH_3$ of **25**], 4.65 [1H, t, J = 5.6, $CH(OEt)_2$ of **24**], 4.67 [0.18H, t, J = 5.5, $CH(OEt)_2$ of **25**], 6.86 [0.18H, d, J = 7.3, C(3)H of **25**], 7.05 [0.18H, d, J = 7.3, C(2)H of **25**], 7.12 [1H, s, C(2)H of **24**], 7.16–7.26 {1.18H, m, including 7.21 [1H, ddd, J = 8.0, 6.9, 1.1, C(6)H of **24**], C(8)H of **25**}, 7.37 [1H, d, J = 8.1, C(8)H of **24**], 7.40–7.49 {1.18H, m, including 7.45 [1H, ddd, J = 8.1, 7.1, 1.0, C(7)H of **24**], C(7)H of **25**}, 8.09 [0.18H, br s, C(5)H of **25**], 8.24 [1H, d, J = 7.9, C(5)H of **24**]; *m/z* (ES+) 355 $[M + H]^+$ (100%), 251 (16), 222 (45).

N-tosyl-3-(2,2-diethoxyethylaminomethyl)-1,4,9-trimethyl-carbazole 26. Potassium carbonate (6.754 g, 0.049 mol) was added to a solution containing a mixture of 3- and 6-(2,2-diethoxyethylaminomethyl)-1,4-dimethylcarbazole, **24** and **25**, (1:0.18) (11.529 g, 0.033 mol) and *p*-toluenesulfonyl chloride (9.323 g, 0.049 mol) in THF and water (1:2, 150 mL) and the mixture was stirred for 1.5 h. After this time, the reaction was poured into water (100 mL), and extracted with chloroform (2× 100mL). The organic layer was washed with brine (2 × 50 mL), dried, and evaporated under reduced pressure resulting in a brown solid, which was recrystallized (dichloromethane-hexane) to afford the single isomer *N*-tosyl-3-(2,2-diethoxyethylaminomethyl)-1,4-trimethylcarbazole **26** as an off-white solid (9.222 g, 55%): 156–157°C; ν_{max} (cm^{-1}) (KBr) 2975, 2928, 1470, 1340, 1156, 1119, 1094, 746; δ_H (300 MHz) 1.07 (6H, t, J = 7.0, 2× OCH_2CH_3), 2.39 [3H, s, $C(4')CH_3$], 2.71 [3H, s, $C(1)CH_3$], 2.80 [3H, s, $C(4)CH_3$], 3.18 (2H, d, J = 5.5, NCH_2CH), 3.28–3.55 (4H, m, 2× OCH_2CH_3), 4.08 [3H, s, $N(9)CH_3$], 4.19 [1H, t, J = 5.4, $CH(OEt)_2$], 4.65 (2H, s, $ArCH_2N$), 6.88 [1H, s, C(2)H], 7.23 [1H, ddd, J = 8.1, 7.0, 1.2, C(6)H] 7.28 [2H, d, J = 8.4, C(3′)H, C(5′)H], 7.38 [1H, d, J = 8.0, C(8)H], 7.47 [1H, ddd, J = 8.1, 7.0, 1.0, C(7)H], 7.74 [2H, d, J = 8.3, C(2′)H, C(6′)H], 8.21 [1H, d, J = 7.9, C(5)H]; δ_C 15.7 (2× CH_3), 16.5 (CH_3), 20.6 (CH_3), 21.8 (CH_3), 32.6 (CH_3), 49.8 (CH_2), 51.0 (CH_2), 63.4 (CH_2), 102.4 (CH_2), 108.7 (CH), 117.6 (quat.), 119.3 (2× CH), 123.1 (quat.), 123.2 (quat.), 124.0 (CH), 124.2 (quat.), 125.3 (CH), 127.8 (2× CH), 129.9 (2× CH), 131.4 (quat.), 131.8 (CH), 138.0 (quat.), 139.9 (quat.), 142.5 (quat.), 143.4 (quat.); *m/z* (ES+) 531 $[M + Na]^+$ (2%), 417 $[M—C_6H_4CH_3]^+$ (90), 354 $[M + H—SO_2C_6H_4CH_3]^+$ (30); HRMS Found: $[M + Na]^+$, 531.2291. Calc. for $C_{29}H_{36}N_2O_4NaS$: $[M + Na]^+$, 531.2295.

6-Methylellipticine (5,6,11-trimethyl-6H-pyrido[4,3-b]carbazole) 3. To a stirring solution of *N*-tosyl-3-(2,2-diethoxyethylaminomethyl)-1,4,9-trimethylcarbazole **26** (9.222 g, 0.018 mol) in 1,4-dioxane (100 mL) was added hydrochloric acid (6*M*, 20 mL) and the reaction mixture was heated under reflux for 6 h. After this time, the solution was cooled, poured into aqueous potassium carbonate solution (5% w/v, 100 mL) and extracted with chloroform (3 × 50 mL). The organic layer was washed with brine (50 mL), water (50 mL), dried, and evaporated under reduced pressure resulting in a brown solid, which was further purified by column chromatography (ethyl acetate-methanol, 95:5) to afford 6-methylellipticine **3** as a golden solid (2.602 g, 55%): m.p. 202–204°C (ref. 12, 209–211°C); ν_{max} (cm^{-1}) (KBr), 2922, 1590, 1478, 1387, 738; δ_H (300 MHz) 3.06 [3H, s, $C(5)CH_3$], 3.26 [3H, s, $C(11)CH_3$], 4.14 [3H, s, $N(6)CH_3$], 7.32 [1H, ddd, J = 8.1, 7.1, 1.0, C(9)H], 7.41 [1H, d, J = 8.2, C(7)H], 7.59 [1H, ddd, J = 8.3, 7.3, 1.1, C(8)H], 7.90 [1H, d, J = 6.2, C(4)H], 8.36 [1H, d, J = 7.9, C(10)H], 8.50 [1H, d, J = 6.2, C(3)H], 9.70 [1H, s, C(1)H]; *m/z* (ES+) 261 $[M + H]^+$ (100%), 115 (40), 74 (18).

Formylation of 6-methoxy-1,4-dimethylcarbazole 12. Under general conditions method C above, a solution of 6-methoxy-1,4-dimethylcarbazole **12** (7.292 g, 0.0324 mol), DMF and phosphorous oxychloride in chlorobenzene (200 mL) was reacted. After workup, this resulted in a brown solid, which was purified by column chromatography eluting with hexane-ethyl acetate (100:0 to 80:20) to afford three bands; a yellow solid consisting of 8-formyl-6-methoxy-1,4-dimethylcarbazole **15** (0.487 g, 6%), a yellow solid consisting of a mixture of 7-formyl-6-methoxy-1,4-dimethylcarbazole **14** and 8-formyl-6-methoxy-1,4-dimethylcarbazole **15** (0.023 g)* (0.7:1), and a cream solid containing 3-formyl-6-methoxy-1,4-dimethylcarbazole **13** (2.62 g, 22%).

3-Formyl-6-methoxy-1,4-dimethylcarbazole 13. M.p. 206-207°C (ref. 12, 206°C); ν_{max} (cm^{-1}) (KBr) 3305, 2832, 1656, 1579, 1222; δ_H (300 MHz) 2.55 [3H, s, $C(1)CH_3$], 3.17 [3H, s, $C(4)CH_3$], 3.95 (3H, s, OCH_3), 7.12 [1H, dd, J = 8.8, 2.4, C(7)H], 7.43 [1H, d, J = 8.8, C(8)H], 7.74 [1H, s, C(2)H], 7.76 [1H, d, J = 2.4, C(5)H], 8.25 (1H, br s, NH), 10.44 (1H, s, CHO); *m/z* (ES+) 254 $[M + H]^+$ (32%), 119 (2), 105 (6).

7-Formyl-6-methoxy-1,4-dimethylcarbazole 14. δ_H (300 MHz) 2.52 [3H, s, $C(1)CH_3$], 2.85 [3H, s, $C(4)CH_3$], 4.04 (1H, s, OCH_3), 6.92 [1H, d, J = 7.2, C(3)H], 7.18 [1H, d, J = 7.3, C(2)H], 7.66 [1H, s, C(8)H], 8.06 [1H, s, C(5)H], 8.06 (1H, br s, NH), 10.59 (1H, s, CHO).

8-Formyl-6-methoxy-1,4-dimethylcarbazole 15. M.p. 154–156°C (ref. 19, 161°C); ν_{max} (cm^{-1}) (KBr) 3350, 2956, 1672, 1479, 1230, 802; δ_H (300 MHz) 2.56 [3H, s, $C(1)CH_3$], 2.81 [3H, s, $C(4)CH_3$], 3.98 (1H, s, OCH_3), 6.97 [1H, d, J = 7.3, C(3)H], 7.19 [1H, d, J = 7.3, C(2)H], 7.43 [1H, d, J = 2.4, C(7)H], 8.00 [1H, d, J = 2.4, C(5)H], 9.96 (1H, br s, NH), 10.17 (1H, s, CHO); *m/z* (ES+) 254 $[M + H]^+$ (50%), 105 (4), 101 (100).

Acknowledgments. We are grateful to Waters, Enterprise Ireland, Cancer Research Ireland and Cork County council higher education grant for their financial support.

REFERENCES AND NOTES

[1] Garbett, N. C.; Graves, D. E. Curr Med Chem Anticancer Agents 2004, 4, 149.

[2] Stiborová, M.; Bieler, C. A.; Wiessler, M.; Frei, E. Biochem Pharmacol 2001, 62, 1675.

[3] Stiborová, M.; Breuer, A.; Aimová, D.; Stiborová-Rupertová, M.; Wiessler, M.; Frei, E. Int J Cancer 2003, 107, 885.

[4] Auclair, C. Arch Biochem Biophys 1987, 259, 1.

[5] Vendôme, J.; Letard, S.; Martin, F.; Svinarchuk, F.; Dubreuil, P.; Auclair, C.; Le Bret, M. J Med Chem 2005, 48, 6194.

[6] Thompson, D.; Miller, C.; McCarthy, F. O. Biochemistry 2008, 47, 10333.

[7] Hewlins, M. J. E.; Oliveira-Campos, A. M.; Shannon, P. V. R. Synthesis 1984, 4, 289.

[8] Gribble, G. W.; Saulnier, M. G. Heterocycles 1985, 23, 1277.

[9] Sainsbury, M. Synthesis 1977, 437.

[10] Gribble, G. W. The Alkaloids 1990, 39, 239.

[11] Cranwell, P. A.; Saxton, J. E. J Chem Soc 1962, 3482.

[12] Dalton, L. K.; Demerac, S.; Elmes, B. C.; Loder, J. W.; Swan, J. M.; Teitei, T. Aust J Chem 1967, 20, 2715.

[13] Guthrie, R. W.; Brossi, A.; Mennona, F. A.; Mullin, J. G.; Kierstead, R. W.; Grunberg, E. J Med Chem 1975, 18, 755.

[14] Dracínský, M.; Sejbal, J.; Rygerová, B.; Stiborová, M. Tetrahedron Lett 2007, 48, 6893.

[15] Dalton, L. K.; Demerac, S.; Teitei, T. Aust J Chem 1969, 22, 185.

[16] Jackson, A. H.; Jenkins, P. R.; Shannon, P.; V. R. J Chem Soc Perkin Trans 1 1977, 14, 1698.

[17] Plug, J. P. M.; Koomen, G.-J.; Pandit, U. K. Synthesis 1992, 1221.

[18] Yokoyama, Y.; Okuyama, N.; Iwadate, S.; Momoi, T.; Murakami, Y. J Chem Soc Perkin Trans 1 1990, 1319.

[19] Sainsbury, M.; Smith, A. D.; Vong, K. K.; Scopes, D. I. J Chem Soc Perkin Trans 1 1988, 2945.