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REVIEW

Isolation, biological activity and synthesis of the natural product ellipticine and related pyridocarbazoles

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The tetracyclic natural product ellipticine (5,11-dimethyl-6*H*-pyrido[4,3-*b*]carbazole) was first isolated from the plant material of *Ochrosia elliptica* Labill in 1959. Woodward *et al.* reported the first synthesis of ellipticine later the same year, and this was followed by many different synthetic strategies in subsequent decades. Investigation of the biological activity of ellipticines uncovered potent *anti*-cancer properties and several ellipticine derivatives have been the subject of clinical trials. The ellipticine family of compounds exert their biological activity *via* several modes of action, the most well established of which are intercalation with DNA and topoisomerase II inhibition. In recent times other modes of action have been revealed, including kinase inhibition, interaction with p53 transcription factor, bio-oxidation and adduct formation. The scope of this review covers key features of the biological activity of ellipticine, with emphasis on new modes of action, followed by synthetic routes to ellipticine, including key early syntheses of pyrido[4,3-*b*]carbazoles and comprehensive coverage of the literature since the late 1980s, along with more recent syntheses of ellipticine analogues and substituted ellipticines.

1. Introduction

The tetracyclic natural product ellipticine **1** (5,11-dimethyl-6*H*-pyrido[4,3-*b*]carbazole, Fig. 1) was isolated in 1959.[1] Woodward *et al.*[2] reported the first synthesis of ellipticine later the same year, and this was followed by many different synthetic strategies in subsequent decades. Naturally the initial goal was an efficient synthesis of ellipticine itself, however substitution at C-9 was soon found to significantly increase the cytotoxic activity of ellipticine and as a result, 9-hydroxy and 9-methoxy ellipticines became attractive targets.

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2. Isolation and biological activity

Ellipticine **1** was first isolated from the leaf material of *Ochrosia elliptica* Labill by Goodwin *et al.* in 1959.[1] This small tropical evergreen tree belonging to the *Apocynaceae* family also



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Charlotte Miller obtained her Bachelor of Science degree (Hons) in Chemistry at University College Cork, Ireland being awarded the title of College Scholar. In 2012, she was awarded a Ph.D. in organic and medicinal chemistry, in the Department of Chemistry and Analytical and Biological Chemistry Research Facility (ABCRF) at UCC, for her work on the synthesis and evaluation of novel ellipticine derivatives and analogues as anti-cancer agents.



Florence O. McCarthy

Florence McCarthy graduated from the School of Pharmacy, University of Sunderland, UK winning the Pfizer prize for Excellence in Medicinal Chemistry and continued to PhD studies in anticancer research with Prof. Paul Groundwater. He subsequently joined Prof. Bill Denny at the ACSRC, University of Auckland, New Zealand in conjunction with Pfizer Global R&D working on a series of kinase inhibition programmes. He joined the Department of Chemistry at University College Cork in 2005 and currently leads a team of researchers in medicinal and pharmaceutical chemistry investigating the synthesis and evaluation of diverse bioactive molecules from steroids to complex heterocycles.

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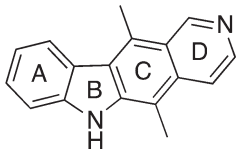


Fig. 1 Ellipticine **1**.

contained several other alkaloids, including 9-methoxyellipticine. Ellipticine has since been isolated from several other plants of the *Apocynaceae* family (*Ochrosia vieillardii*, *Ochrosia acuminate* and *Ochrosia moorei*)[3–5] and from *Strychnos dinkagei* of the *Loganiaceae* family.[6,7]

2.1 Intercalation

The first reported mechanism of action of ellipticine was intercalation with DNA, several early studies used UV absorption and circular dichroism to study the interaction of DNA and ellipticine.[8–12] Most studies proposed a binding mode parallel to the base pairs of ellipticine with strong DNA binding constants. Dodin *et al.* reported DNA affinity constants of 8.3×10^5 M^{-1} and 3.3×10^5 M^{-1} at pH 5 & 9 respectively.[9] The same group later used fluorescence spectroscopy in deuterated buffer solutions to study interactions of *N*-methylellipticinium **2** and 9-hydroxy-*N*-methylellipticinium **3** with DNA (Fig. 2).[10] *N*-Methylellipticinium **2** showed no preference for intercalation sites, while **3** was found to interact with a site containing at least one G–C base pair, inferring that the 9-hydroxy group confers G–C preference.

In 2005, Canals *et al.* published a crystal structure determination of ellipticine in complex with a six base-pair oligionucleotide–d$(CGATCG)_2$, with 1.5 Å resolution.[13] This showed ellipticine aligned with the major axis, parallel to the hydrogen bonds of the base pairs. The d$(CGATCG)_2$ hexanucleotide was intercalated by two ellipticine molecules, with the pyridine nitrogen orientated towards the major groove in both cases. A preference for G–C base pairs was also evident, since the AT–TA site remained empty. Overall, there was good correlation with an earlier dinucleotide structure published by Jain *et al.*[14] An unwinding angle of 14° with respect to standard B–DNA was observed for each intercalation site. Both intercalation sites were separated by 6.9 Å, compared to 3.3 Å for normal base pairs.

2.2 Topoisomerase II inhibition

Ross and Bradley were the first researchers to associate ellipticine induced DNA strand breaks with topoisomerase II inhibition.[15] Ellipticine was found to induce strand breaks in DNA from L1210 cells, in concentrations of 1.25–5.0 μg mL^{-1} and the authors proposed that the strand breaks were due to topoisomerase II activity.

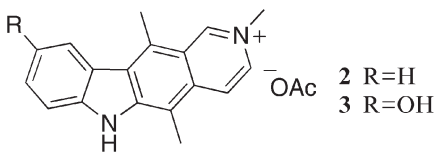


Fig. 2

Froelich–Ammon *et al.* published a major study of ellipticine-topoisomerase activity in 1995, identifying topoisomerase II as the primary cellular target of the drug.[16] This was determined by employing yeast cells with a temperature sensitive strain of topo II (at 25 °C enzyme activity is 100% and at 30 °C activity decreases to 10%). At 25 °C, 90% of the cell culture was killed by a 200 μg dose of ellipticine, while at 30 °C, no cell death was observed at any concentration of ellipticine used. In a second experiment, a 10 μg dose of ellipticine induced a 6-fold increase in topoisomerase II-mediated strand breakage, but the same concentration of ellipticine had no effect on the rate of religation. Thus, ellipticine may be considered to be a catalytic inhibitor of topo II as opposed to a topo II poison, *i.e.* ellipticine acts primarily by increasing the forward rate of cleavage of DNA.

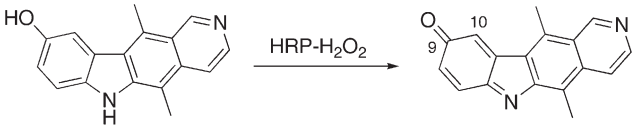
Fluorescence spectroscopy was then used to study interaction of ellipticine with DNA, topo II and the DNA-topo II complex. It was established that protonated ellipticine binds to DNA, whereas deprotonated ellipticine binds to topoisomerase II and is also the major species present in the ternary complex. Thus the enzyme determines the protonation state of ellipticine in the ternary complex. Formation of this ternary complex results in increased levels of covalently bound topoisomerase II-DNA cleavage complex.

2.3 Bio-oxidation and adduct formation

The bio-oxidation pathway was originally proposed by Auclair and Paoletti, who postulated that ellipticine could serve as a substrate for peroxidises *in vivo*.[17] They employed a horse radish peroxidise (HRP)–hydrogen peroxide oxidizing system as a model of bio-oxidation and studied the ability of various ellipticines to undergo oxidation. Under these conditions, 9-hydroxyellipticine **4** was oxidised to the quinone imine **5** (Scheme 1). The quinone imine **5** was shown to be a strong electrophile, oxidizing NADH to NAD^+. It is also highly susceptible to nucleophilic attack at the C-10 position, and bound irreversibly to bovine serum albumin.[17]

In the last decade, Stiborová *et al.* have extensively studied the bio-oxidation and adduct formation pathways of ellipticine *in vitro* and *in vivo*. The group began by investigating the potential of ellipticine to form DNA adducts after activation by cytochrome P450 (CYP) and have isolated and identified several metabolites formed by human cytochrome P450 enzymes (Scheme 2).[18] 13-Hydroxyellipticine and the ellipticine *N*-oxide were identified as the metabolites responsible for two DNA-ellipticine adducts.

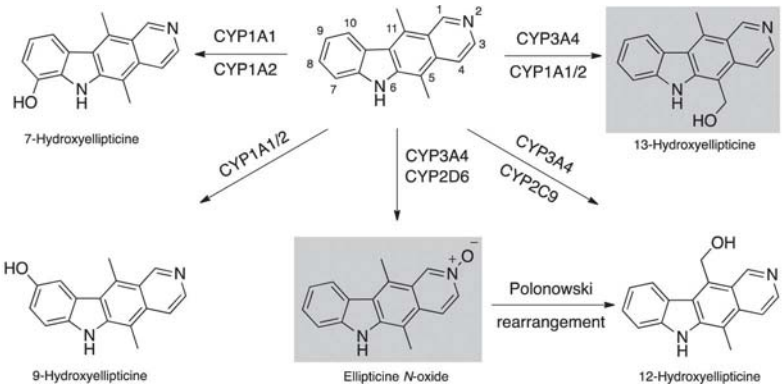
The group have also studied peroxidase-mediated oxidation of ellipticine and performed experiments with peroxidases (human myeloperoxidase, human and ovine cyclooxygenases, bovine lactoperoxidase and horseradish peroxidase).[19] In this case, four DNA adducts were formed, two major and two minor. The two



4 **5**

Scheme 1

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Scheme 2 Ellipticine metabolites formed by human cytochrome P450 enzymes.[18]

major adducts corresponded to those previously identified from CYP-mediated oxidation, derived from 13-hydroxyellipticine and ellipticine *N*-oxide. The same adducts were formed in leukemia HL-60 and CCRF-CEM cells and a good correlation between cytotoxicity and the levels of DNA adducts was observed.[20]

The key on-going question in this area is whether adduct formation is responsible for the cytotoxicity of ellipticines. A recent publication by Stiborová *et al.* sought to evaluate the contribution of DNA adduct formation to cytotoxicity and found plausible correlation in six out of seven cancer cell lines tested.[21] However, further work is required in this area in order to conclusively understand this mechanism and its overall contribution to ellipticine cytotoxicity.

2.4 Kinase inhibition

In the last decade, ellipticine interactions with several enzymes have been studied, including inhibition of c-Kit kinase and AKT.

c-Kit kinase is a type III receptor tyrosine kinase (RTK), a class of enzymes which regulate signalling pathways that control cell growth and proliferation. c-Kit plays a key role in mast cell survival, differentiation, maturation and function.[22] It is expressed by and critical for the development and growth of mast cells, melanocytes, hematopoetic stem cells and the interstitial cells of Cajal.[23] Mutations in the gene encoding for c-Kit kinase are associated with some highly malignant cancers and therefore both wild-type and mutated c-Kit are viable drug targets in anticancer chemotherapy.[24]

The most common enzymatic pocket mutation in c-Kit kinase is the D816V point mutation, which is associated with germ cell tumours, adult mastocytosis and a small proportion of atypical paediatric mastocytosis.[25,26] In 2005, Vendome *et al.* reported that several ellipticine derivatives exhibited c-Kit kinase inhibition.[27] A range of derivatives significantly inhibited both wild type and D816V mutated c-Kit kinase (Table 1), with Imatinib **6** as a reference compound.

9-Hydroxyellipticine **4** and 9-hydroxy-*N*-methylellipticinium **3**, were the most active of the series, with equal inhibition of wild type and D816V mutated c-Kit. These were closely followed by the *N*-alkylamino-9-hydroxyellipticinium **10** which showed a slight preference for D816V mutated c-Kit. Of the rest of the series, compounds which were unsubstituted at C-9 were generally inactive and those with a C-9 methoxy group were only moderately active. Salt formation at the N-2 position did not seem to affect the c-Kit inhibitory activity, suggesting that the N-2 position is not directly involved in binding to c-Kit. Finally, addition of bulky alkylamino side chains at C-1 was significantly unfavourable for activity.

Molecular mechanics simulations were employed in order to identify possible binding sites, with docking studies carried out using the GOLD program. It was found that all the active compounds docked similarly in part of the ATP binding pocket, which is made favourable by three hydrogen bonding interactions. The docked position of the most active compounds is shown in Fig. 3, along with hydrogen bonding interactions for 9-hydroxyellipticine **4**.[27]

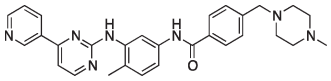
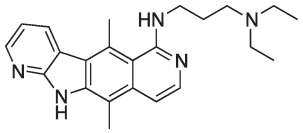
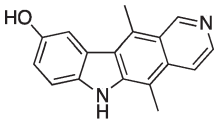
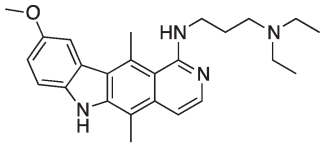
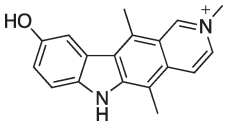
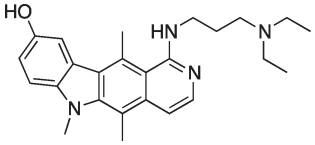
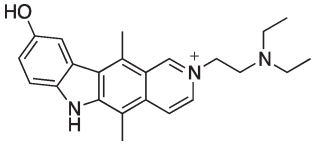
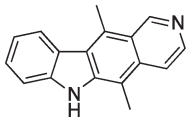
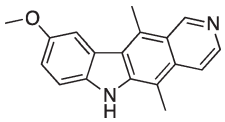
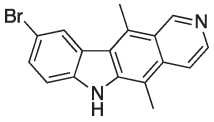
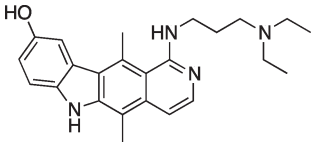
In our research group, extensive molecular dynamics simulations of five different binding modes for 9-hydroxyellipticine **4** suggested a different binding mode to that proposed by Vendome *et al.*[27,28] Initially, Poisson–Boltzmann/Linear Response Approximation pK_a calculations indicated a strong preference for protonation at N-2. The CHARMM force field was used for protein, ADP and Mg^{2+}, while new force field parameters were developed for 9-hydroxyellipticine and two nanoseconds of molecular dynamics were performed for each of five different c-Kit-ellipticine complexes.

The preferred binding mode for 9-hydroxyellipticine **4** (Fig. 4) involves two key hydrogen bonding interactions, C(9)OH–Glu671 and N(2)H–Glu640, with the C(11) methyl group facing the protein backbone and the C(5) methyl group exposed to solvent. Poisson–Boltzmann Free Energy (PBFE) calculations indicated that this binding mode was preferred across a diverse range of substituted ellipticines.

In 2004, Jin *et al.* reported the inhibition of AKT by 9-methoxy-*N*-methylellipticinium acetate **14**.[29] AKT is a serine/threonine kinase (*i.e.* it phosphorylates the hydroxyl group of serine and threonine residues of other proteins), which is activated in response to growth factors or cytokines by a mechanism involving PI3-K (phosphoinoside 3-kinase).[30,31] It provides a survival signal that protects cells from apoptosis induced by various stresses.

In 40–50% of endometrial cancers, AKT is overexpressed due to mutation of tumour suppressor PTEN (phosphatase and tensin homolog). 9-Methoxy-*N*-methylellipticinium acetate **14** (Fig. 5) was tested against four endometrial cancer cell lines in a 12 μM or 24 μM single dose. Inhibition of AKT kinase activity

Table 1 Inhibition of wild type and D816V mutated c-Kit kinase by ellipticine derivatives[27]

Compound	IC_{50} WT μM	IC_{50} D816V μM	Compound	IC_{50} WT μM	IC_{50} D816V μM
 **6**	0.1	10	 **7**	2.3	1.9
 **4**	0.4	0.4	 **8**	2.5	2.0
 **3**	0.4	0.4	 **9**	2.5	3.6
 **10**	0.45	0.3	 **1**	> 10	> 10
 **11**	0.8	0.6	 **12**	> 10	> 10
 **13**	1.4	1.2			

and apoptosis was observed in the two cell lines with high AKT levels (RL95-2 and Ishikawa cells) but not in the cell lines with normal AKT activity. Further investigation suggested direct inhibition of AKT and not upstream kinases that phosphorylate AKT.

Later, Tang *et al.* found that the same compound (9-methoxy-*N*-methylellipticinium acetate **14**) inhibited AKT kinase activity in ovarian cancer cell lines with overactivation of AKT.[32] In this case, 9-methoxy-*N*-methylellipticinium acetate **14** appeared to prevent phosphorylation of AKT at Ser473, so it is possible that inhibition of an upstream kinase such as PDK2 may be involved. Overall the compound selectively induced apoptosis in ovarian cancer cell lines with overactivation of AKT but had minimal effect on normal cells.

In 2009, Fang *et al.* reported that growth of non-small cell lung cancer (NSCLC) epithelial cells A549 was inhibited by ellipticine **1**.[33] They proposed that ellipticine induced cytotoxicity by modulating the signalling pathways and subcellular redistribution of AKT and p53.

2.5 Interaction with p53 tumour suppressor

Known as the 'guardian of the genome', p53 is the key transcription factor which orchestrates coordinated changes in proliferation and apoptosis. On activation, it increases transcription of genes involved in inhibition of DNA replication *e.g.* p21 and Gadd45, but has opposing effects on BAX and Bcl2 which help regulate apoptosis.[34] In the last twenty years, the pivotal role of p53 in cancer has been elucidated. The gene TP53, encoding p53 protein, is mutated or deleted in approximately 55% of human cancers, mainly by point mutations in the core DNA binding domain.[35,36]

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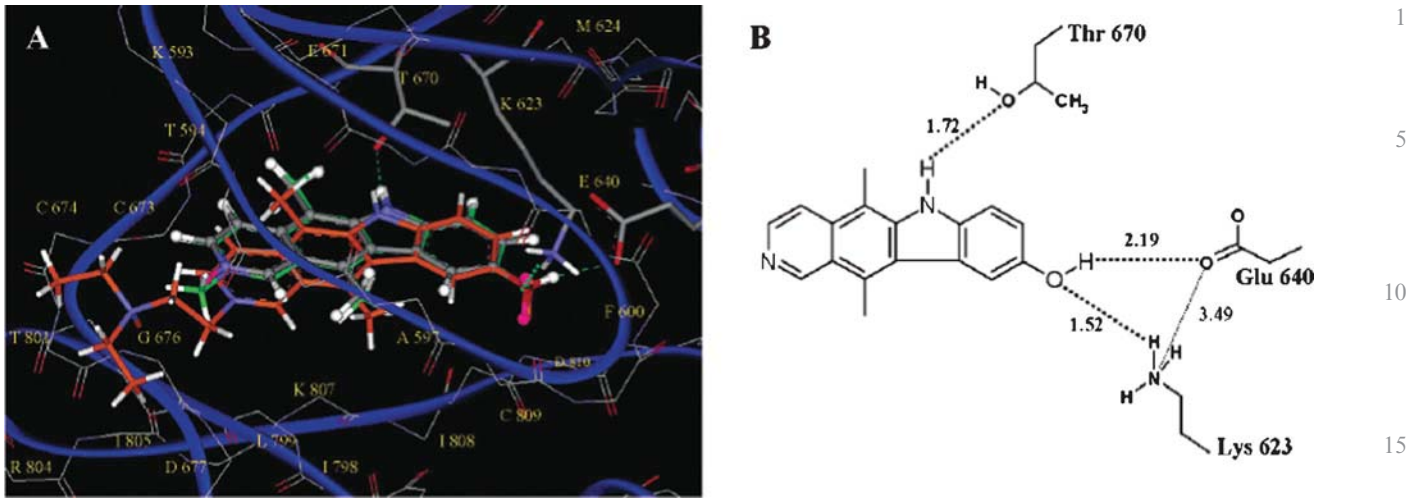


Fig. 3 (A) Detail of the docked position of the most active compounds (9-hydroxyellipticine **4** is shown in gray, 9-hydroxy-*N*-methylellipticinium **3** in green, and *N*-alkylamino-9-hydroxyellipticinium **10** in orange). Conserved interactions are represented by dashed lines. (B) Map of the main interactions for 9-hydroxyellipticine **4**.[27]

In 1998, Shi *et al.* performed cluster analysis of 112 ellipticines from the NCI 60-cell line screen and found that the ellipticinium salts, but not the ellipticines, were more potent on average against p53 mutant cell lines over wild type p53 lines.[37] This analysis opened up a new area of ellipticine research in the last decade. Sugikawa *et al.* found that 9-hydroxyellipticine **4** induced apoptosis in the G1 phase of the cell cycle of mutant p53 cells and suggested that this activity may be *via* restoration of wild type p53 function.[38] Mizumoto *et al.* then examined the impact of 9-hydroxyellipticine **4** on the cellular responses to various antineoplastic agents in pancreatic cancer cells.[39] Exposure of mutant p53 expressing cells to 1 μM of 9-hydroxyellipticine resulted in restoration to wild type p53 activity without producing apoptosis. This pre-treatment with 9-hydroxyellipticine sensitised cells to treatment with cisplatin and mitomycin C, but not 5-fluorouracil, etoposide or vincristine. The effect was limited to cells expressing mutant p53.

In 2003, Peng *et al.* definitively showed that ellipticine and several derivatives can activate the transcription function of p53, increasing the function of some mutant p53 types by 5–6 fold.[40] In mutant p53-transfected H1299 cells, ellipticine induced MDM2 and p21 expression indicated activation of p53 function at an optimal dose of 8 μM. Immunoprecipitation experiments

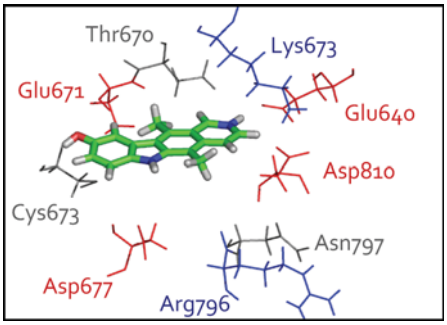


Fig. 4 Proposed binding mode of protonated 9-hydroxyellipticine **4** in the c-Kit kinase active site, determined from molecular dynamics simulations.[28]

demonstrated that treatment with ellipticine induced a shift of mutant p53 conformation towards that of wild type p53, thus restoring function.

Kuo *et al.*[41] studied the molecular mechanism of ellipticine activity in human breast MCF-7 cancer cells and showed that induction of p53, Fas/Fas ligand death receptor activation and the mitochondrial proapoptotic pathway were all involved in ellipticine action on these cells. An IC_{50} value of 1.52 μM was recorded, with cell cycle arrest at the G2/M phase. Upregulation of p53, KIPI/p27 was observed, along with increased expression of the Fas ligands, mFasL and sFasL. In the mitochondrial proapoptotic pathway, increased expression of BAX and decreased Bcl2 and Bcl-X_L induced the release of cytochrome C from mitochondria to cytoplasm, which then activated caspase-9. The same group carried out a similar study on ellipticine action in hepatocellular carcinoma (HCC) cells.[42] On treatment with ellipticine (IC_{50} = 4.1 μM), p53 levels increased in a dose dependent manner and reached maximum levels at 12 h.

In 2008, Xu *et al.* developed a high-content screen for compounds which increase localisation of p53 to the nucleus of cytoplasm.[43] Ellipticine was among several hits resulting from this screen and was subjected to further testing. In HCT116 colon cancer cells expressing wild type p53, ellipticine was found to increase overall levels of p53 and induce localisation in the nucleus, resulting in increased p21 expression. This result was in contrast to previous work, which reported that ellipticine had no effect of cells expressing wild type p53.[38,40] It was also shown that p53 localisation was unrelated to ellipticine action on DNA or topoisomerase II, since p53 localisation in the nucleus was

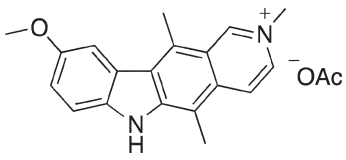


Fig. 5 9-Methoxy-*N*-methylellipticinium acetate **14**.

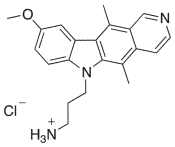


Fig. 6 3-(9-Methoxy-5,11-dimethyl-6*H*-pyrido[4,3-*b*]carbazol-6-yl)propan-1-aminium chloride **15**.

observed within one hour, whereas DNA damage was not observed until 16 hours after treatment.

Lu *et al.*[44] identified the ellipticine derivative, 3-(9-methoxy-5,11-dimethyl-6*H*-pyrido[4,3-*b*]carbazol-6-yl)propan-1-aminium chloride **15** (Fig. 6) as a potential lead compound for p53 activation and studied its effects on three cancer cell lines. HCT116, a wild type p53 line; SW620 with mutant p53 and HCT116 $p53^{-/-}$, a p53 deficient cell line were treated with **15**, with GI_{50} values between 0.5 and 1 μM. Induction of p53 activity was observed in all three cell lines, but was highest (7.5 fold activity) in HCT116 and much less in SW620 (1.5 fold). Two p53 target proteins, p21 and DR5 were also upregulated in all three cell lines. Another transcription factor p73, with similar function to p53, was also found to be critical in the *anti*-tumour effects of the derivative **15**.

Recent studies have focused on combination treatments of ellipticine with existing well known anti-cancer agents. Huang *et al.*[45] found that combined treatment of DLD1 cancer cells with 5-fluorouracil and ellipticine resulted in increased cell death compared to treatment with either agent alone. Wang *et al.*[46] recently reported that ellipticine alone did not alter p53 expression levels in mutant p53 Raji cells. However, in chemo-resistant mutant p53 Ramos cells, ellipticine treatment sensitised cells towards doxorubicin induced apoptosis.

2.6 Clinical use of ellipticine derivatives

An early clinical trial of 9-hydroxyellipticine **4** was terminated due to solubility problems (Fig. 7),[47] however, in 1994 it was used against metastatic breast cancer in combination with etoposide, methotrexate and chlorambucil, producing 48% partial response (PR) and 1.8% complete response (CR).[48]

Clinical trials of 9-hydroxy-*N*-methylellipticinium acetate (Celiptium®) **16** began in 1977 and no favourable therapeutic response was observed in patients with advanced stages of gastric adenocarcinoma, lung carcinoma, metastatic soft tissue carcinoma, lymphoma or ovarian cancer. When administered to patients suffering from advanced metastatic breast cancer (refractory to all other treatment), 9-hydroxy-*N*-methylellipticinium acetate **16** induced objective remissions in 25% of patients, lasting up to 18 months.[47] The dosage was 80–100 mg m^{-2}/week, *via* 1 h i.v. infusion, for 4 weeks. The treatment was particularly effective in patients with oesteolytic breast cancer metastasis. 9-Hydroxy-*N*-methylellipticinium acetate **16** also gave 1 CR, 2 PR and 7 stabilisations out of 22 metastatic renal cancers.[48] In another phase II study of 9-hydroxy-*N*-methylellipticinium acetate **16** (100 mg m^{-2}/week) in advanced breast cancer, an objective response rate (CR & PR) of 19% was observed out of 79 patients (30% in soft tissue metastases).[49]

The clinical success of Celiptium® prompted extensive studies into the synthesis of ellipticinium analogues and several of these progressed to clinical trials. In 1992, 2-(diethylamino-2-ethyl)-9-hydroxyellipticinium chloride (Datelliptium) **17** was found to be active in previously treated metastatic breast cancer and devoid of the toxicities reported with 9-hydroxy-*N*-methylellipticinium acetate **16**. Dosage was 150 mg m^{-2} day^{-1} i.v. for 5 days, every 3 weeks, and the responses were 1 CR, 4 PR in 30 patients.[48] The toxicity of datelliptium was mainly hepatic, and it induced rare and mild leukopenia and severe fatigue.

In recent years, patent applications for ellipticine based cancer treatments have continued, along with patents in new areas such as treatments for genetic diseases and obesity.[50–55]

2.7 Summary of Biological Activity

Since its discovery, several key mechanisms of action have been found to contribute to ellipticine anticancer activity. These include DNA intercalation and topoisomerase II inhibition, two closely related mechanisms which have been well established in the literature. More recent investigations have shown that ellipticines induce multifaceted biological responses, including interaction with kinases, p53 tumour suppressors and the mitochondrial apoptotic pathway. The relative contributions of these interactions towards the overall bioactivity of ellipticines require further research, however it seems clear that the ellipticine family of compounds are truly multi-modal anticancer agents.

While ellipticine and 9-hydroxyellipticine exhibit potent anticancer activity, properties such as low solubility and bioavailability have impeded their use in a clinical setting. To this end, a vast range of ellipticine derivatives have been prepared and evaluated for potential improvement in cytotoxicity, including ellipticinium salts,[56–60] ellipticine glycosides,[61–63] dimers,[64] hybrids[65–68] and conjugates.[69–72]

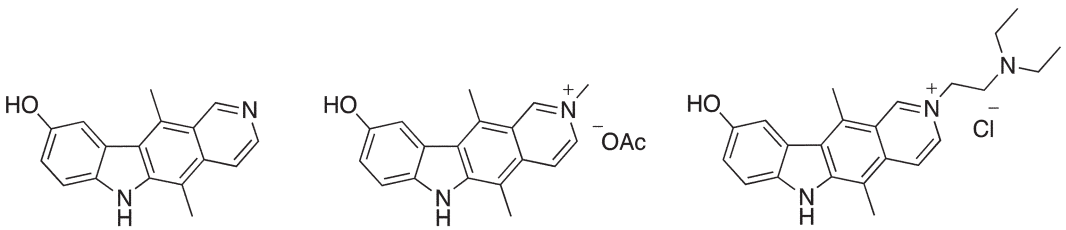
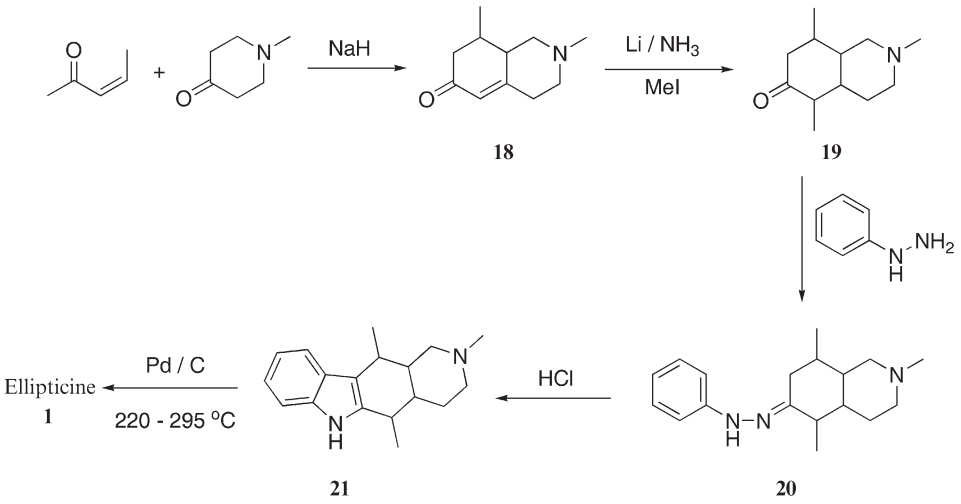


Fig. 7 Ellipticine derivatives used in clinical trials.

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Scheme 3

3. Classification of synthetic routes

There have been several reviews on the synthesis of ellipticine: Sainsbury[73] (1977), Hewlins *et al.*[74] (1984), Gribble and Saulnier[75] (1985), Kansal *et al.*[76] (1986), Álvarez *et al.*[77] (2001), and finally, Knölker and Reddy[78] (2002). Of these, Sainsbury, Hewlins and Gribble comprehensively reviewed the literature published to date and in particular, Gribble and Saulnier's review was extensive and detailed. Kansal focused on selected key syntheses to date, along with proposed biogenetic pathways to ellipticine and Álvarez covered a range of related alkaloids in a relatively short review. Knölker and Reddy's comprehensive review of biologically active carbazole alkaloids included a section on the synthesis of pyrido[4,3-*b*]carbazoles.

The early reviews categorised the syntheses of ellipticine by the last ring to be cyclised (B, C or D–Fig. 1), giving three subgroups: B-type, C-type and D-type.[73,74] Gribble and Saulnier opted for a more detailed system based on the last bond to be formed, resulting in eight different categories.[75] Kansal *et al.* used the earlier, ring-based system, adding a new B+C type category for syntheses in which the B and C rings are formed simultaneously.[76] Finally, Knölker and Reddy categorised by the key reactions in the route (*e.g.* palladium catalysed, condensation, Diels–Alder, cycloaddition *etc.*).[78]

In this review, the ring-based system is used, giving four main categories: B-type, C-type, D-type and B+C type. Within these sections, the syntheses are generally grouped by the key reaction type. The scope of this review covers key early syntheses of pyrido[4,3-*b*]carbazoles (pre-1985), followed by comprehensive coverage of the literature since the late 1980s, along with more recent synthesis of ellipticine analogues and substituted ellipticines.

4. B-type syntheses

B-type syntheses may be categorised by the key B-ring forming reaction, which has been accomplished by, a) Fisher indolization, b) triazole formation, c) nitrene insertion and d) other B-type cyclisations.

4.1 Fischer indolization reactions

The first B-type synthesis was developed by Stillwell and Woodward with the key B-ring formation *via* Fischer indolization (Scheme 3).[79,73] Condensation of (Z)-pent-3-en-2-one and 1-methyl-4-piperidone in the presence of sodium hydride gave **18**. This was converted to 2,5,8-trimethyloctahydroisoquinolin-6(2*H*)-one **19** *via* reductive Stork alkylation using methyl iodide in the presence of lithium and liquid ammonia. The phenylhydrazone derivative **20** was formed and then subjected to Fischer indolisation to afford 2-methyl-1,2,3,4,5,5a,11,11a-octahydroellipticine **21** (82%). Finally, dehydrogenation with palladium on carbon gave ellipticine **1** in a very low yield of 0.3%

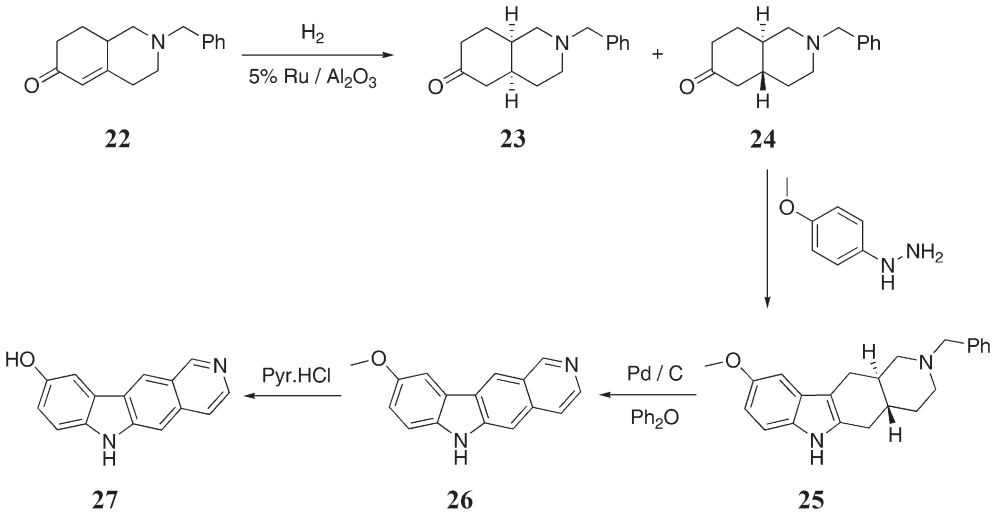
Archer *et al.* utilized a similar strategy in their synthesis of 5,11-demethylellipticines (Scheme 4).[80] Catalytic hydrogenation of hexahydroisoquinolin-6-one **22** gave the *cis* and *trans* isomers **23** and **24**, which were easily separable by chromatography. The *trans* isomer **24** was subjected to Fischer indolization with *para*-methoxyphenylhydrazine to give octahydro-1*H*-pyrido[4,3-*b*]carbazole **25** in 61% yield. The *cis* isomer **23** gave a mixture of **25** and a non linear isomer, which were readily separated. Debenzylation and dehydrogenation were effected with palladium on charcoal to give 9-methoxy-6*H*-pyrido[4,3-*b*]carbazole **26** (73%). This was converted to 6*H*-pyrido[4,3-*b*]carbazol-9-ol **27** with pyridine hydrochloride in 52% yield.

4.2 Triazole formation

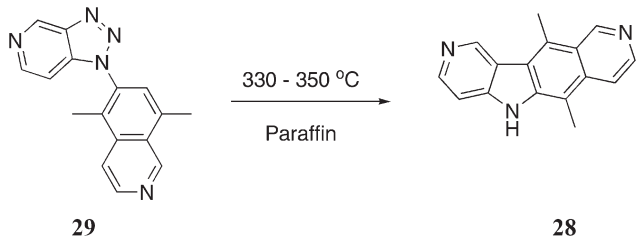
Bisagni *et al.* were the first to use a triazole intermediate in their synthesis of the ellipticine analogue, 9-azaellipticine **28** (Scheme 5).[81] The intermediate **29** cyclised under thermal conditions to give **28** in 41% yield.

When this reaction was applied to the synthesis of 1-chloro-9-azaellipticines, only a trace of the desired product was detected. The route was successfully adapted by changing the triazole intermediate[82–84] and this area is extensively reviewed by Gribble *et al.*[75]

In 1980, Miller *et al.* published a route involving Goldberg coupling of an acetanilide with an isoquinoline, followed by B-ring cyclisation with palladium acetate.[85] Unfortunately this



Scheme 4

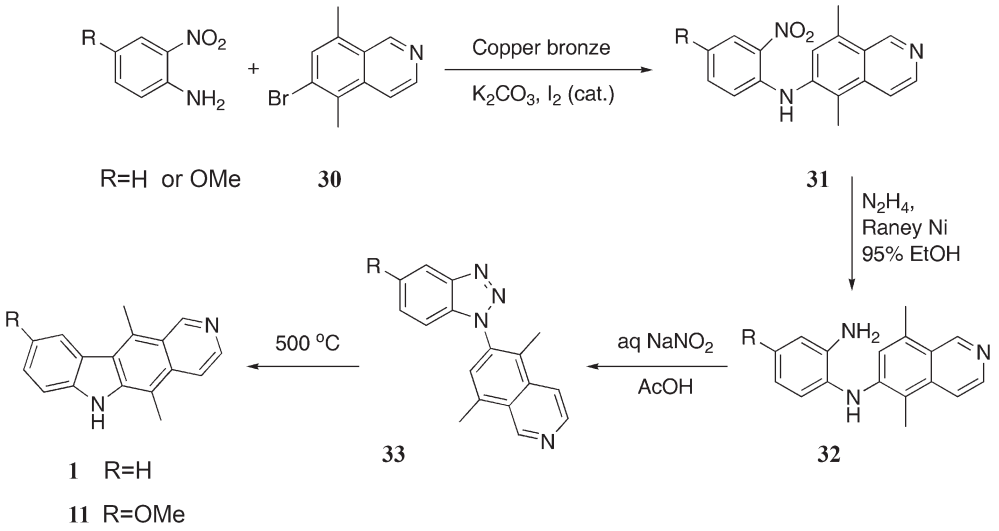


Scheme 5

final cyclisation step cyclisation was rather low yielding (15–25%). As a result, a triazole intermediate was incorporated into the synthesis, providing a much more attractive route (Scheme 6).[86] Goldberg coupling of *o*-nitroaniline or 4-methoxy-2-nitroaniline with 6-bromo-5,8-dimethylisoquinoline **30** gave the diarylamines **31** in good yields (54% and 53%). Reduction of the nitro group gave the diamines **32**, which were diazotized without purification to benzotriazoles **33** (97% and 94%). After studying several methods of triazole decomposition, pyrolysis at 500 °C gave ellipticine **1** (69%) and 9-methoxyellipticine **11** (62%).

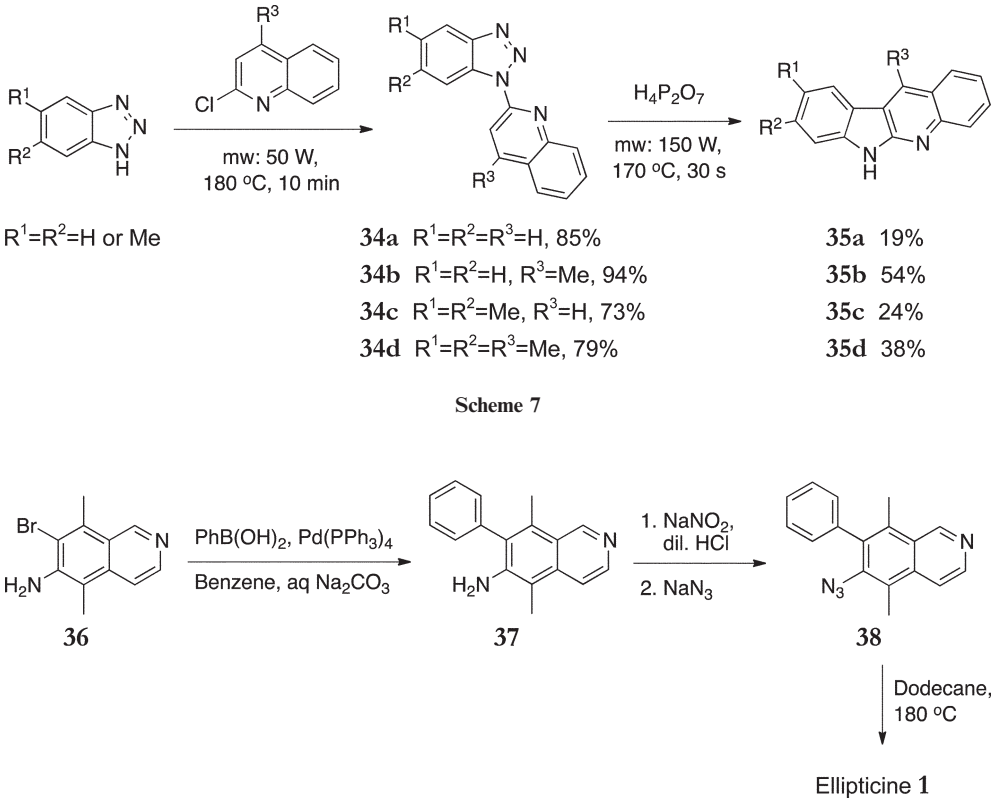
While the inclusion of a triazole intermediate significantly improved the overall yield of the route, a four step synthesis of 6-bromo-5,8-dimethylisoquinoline **30** was also required, with overall yields of 30–35%. Any alteration of the C and D rings would require adaptation of this route and, as Bisagni *et al.* previously discovered with 1-chloro-9-azaellipticines, could pose problems in the thermal cyclization step.[82–84]

In a modern application of triazole intermediates, Vera-Luque *et al.* prepared the 5-aza-2-deazaellipticine analogues (α-carbolines), under microwave conditions (Scheme 7).[87] Commercially available benzotriazoles were reacted with 2-chloroquinoline or 2-chloro-4-methylquinoline under optimized microwave



Scheme 6

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Scheme 7

Scheme 8

conditions to give the pyridylbenzotriazoles **34a–d** in yields of 73–94%. Cyclization was carried out under microwave conditions in the presence of pyrophosphoric acid to give 5-aza-2-deazaellipticines **35a–d** (19–54%).

4.3 Nitrene insertion

In 1989, Miller *et al.* published the first synthesis to utilise nitrene insertion as the B-ring forming reaction (Scheme 8).[88] 7-Bromo-5,8-dimethylisoquinolin-6-amine **36** was prepared in four steps from *N*-(2,5-dimethylphenyl)acetamide in 50% overall yield. This was subjected to Suzuki coupling with phenylboronic acid to give the amine **37** in 99% yield, followed by conversion to the azide **38** (85%). Finally the azide was heated in dodecane to give ellipticine **1** in 96% yield after preparative thin layer chromatography.

The overall yield of ellipticine, including the four step synthesis of isoquinoline **36**, was 40% which is comparable with most of the highest yielding routes. Any variation in the C and D rings would require a separate synthesis of the isoquinoline, which lessens its attractiveness in this area. Nevertheless, the route would be amenable to the synthesis of A-ring substituted elllipicines or A-ring analogues due to the availability of a wide range of arylboronic acids.

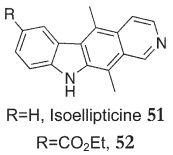
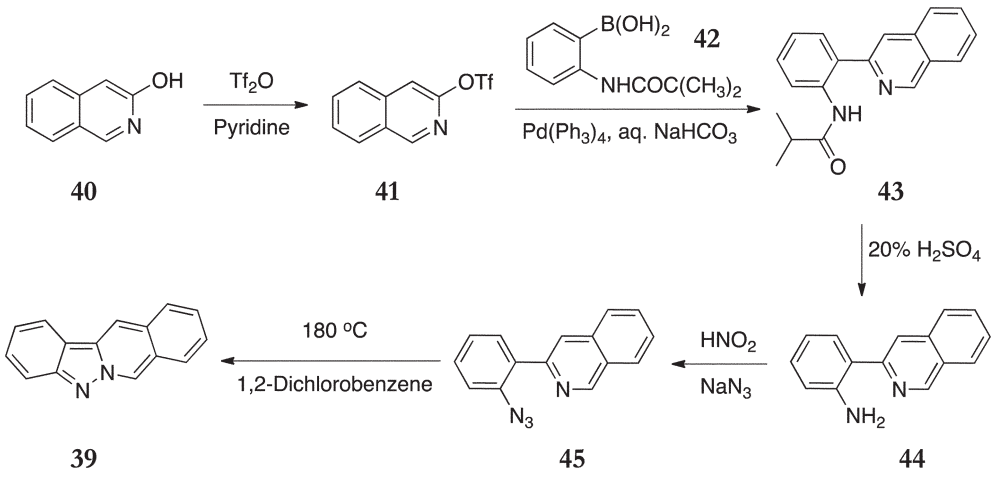


Fig. 8

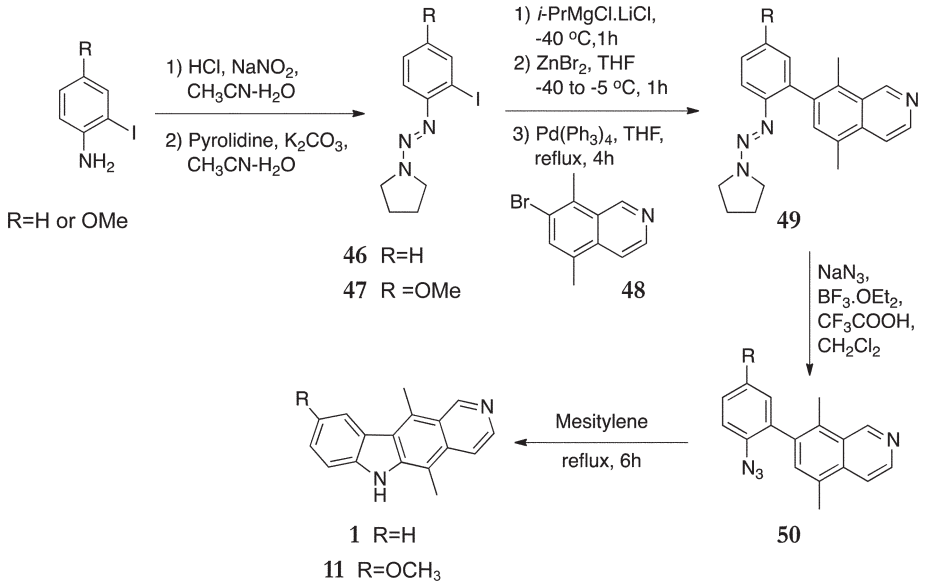
In their recent synthesis of the ellipticine analogue, indazolo[2,3-*b*]isoquinoline **39**, Timári *et al.* applied similar chemistry, including Suzuki coupling and nitrene insertion (Scheme 9).[89] 3-Hydroxyisoquinoline **40** was converted to its triflate **41** (90%) and coupled with the boronic acid **42** under Suzuki conditions to give **43** (94%). Hydrolysis to the free amine **44** and conversion to the azide **45** proceeded smoothly and in good yields (89% and 90% respectively). Ring closure was effected by heating the azide in 1,2-dichlorobenzene to give indazolo[2,3-*b*]isoquinoline **39** in 66% yield.

Liu and Knochel published an alternative nitrene insertion synthesis in 2007.[90] Attracted by the convenient conversion of aryl triazines to azides under mild conditions, they first optimised the preparation of a wide variety of polyfunctional aryl triazines. Triazines **46** and **47** were prepared from 2-iodoaniline and 2-iodo-4-methoxyaniline in excellent yields (92% and 94% respectively, Scheme 10). Negishi coupling with 7-bromo-5,8-dimethylisoquinoline **48** gave the aryl triazines **49** (75% and 63%). Conversion to the azides **50** (78% & 94%), followed by refluxing in mesitylene gave ellipticine **1** (57%) and 9-methoxyellipticine **11** (68%).

Overall yields for ellipticine and 9-methoxyellipticine were 31% and 38%. 7-Bromo-5,8-dimethylisoquinoline **48** was prepared from 1,4-dibromo-2,5-dimethylbenzene in eight steps, with an overall yield of 43%. Isoellipticine **51** and ethyl 5,11-dimethyl-10*H*-pyrido[3,4-*b*]carbazole-7-carboxylate **52** (Fig. 8) were prepared *via* the same route from 6-bromo-5,8-dimethylisoquinoline **30**, in similar yields.



Scheme 9



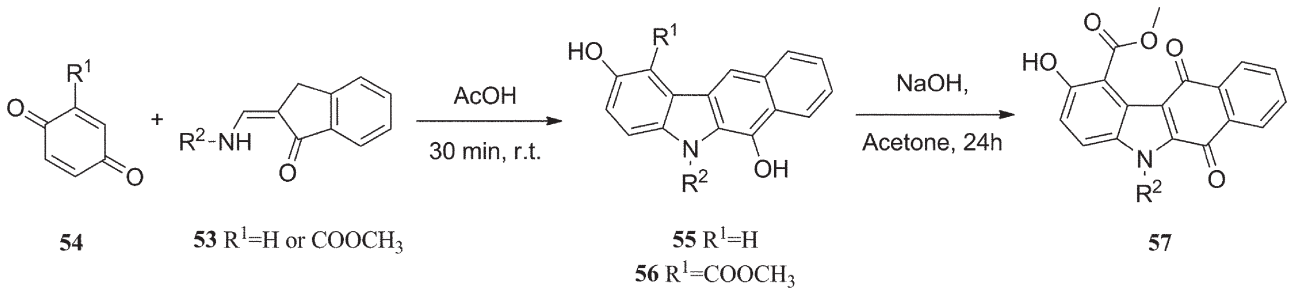
Scheme 10

4.4 Other applications of B-type routes

Asche *et al.* utilized a modified Nenitzescu reaction in their synthesis of the ellipticine analogues, 5*H*-benzo[b]carbazoles and their corresponding quinones (Scheme 11).[91] 2-Aminomethylene-1-indanones **53** were prepared in two steps from 1-indanone with twenty different R^2 groups (yields varying from 49% to 98%). Reaction with benzoquinones **54** in glacial acetic acid for 30 min gave 5*H*-benzo[b]carbazoles **55** (50%) and **56** (60–70%). The 1-substituted compounds **56**, readily oxidised to the corresponding quinones **57** in 70–90% yields. The synthesis was limited to 2-aminomethylene-1-indanones **53** bearing electron donating substituents. When electron withdrawing substituents were present the reaction did not proceed at room temperature and heating resulted in the formation of spirocyclic benzofuran derivatives.

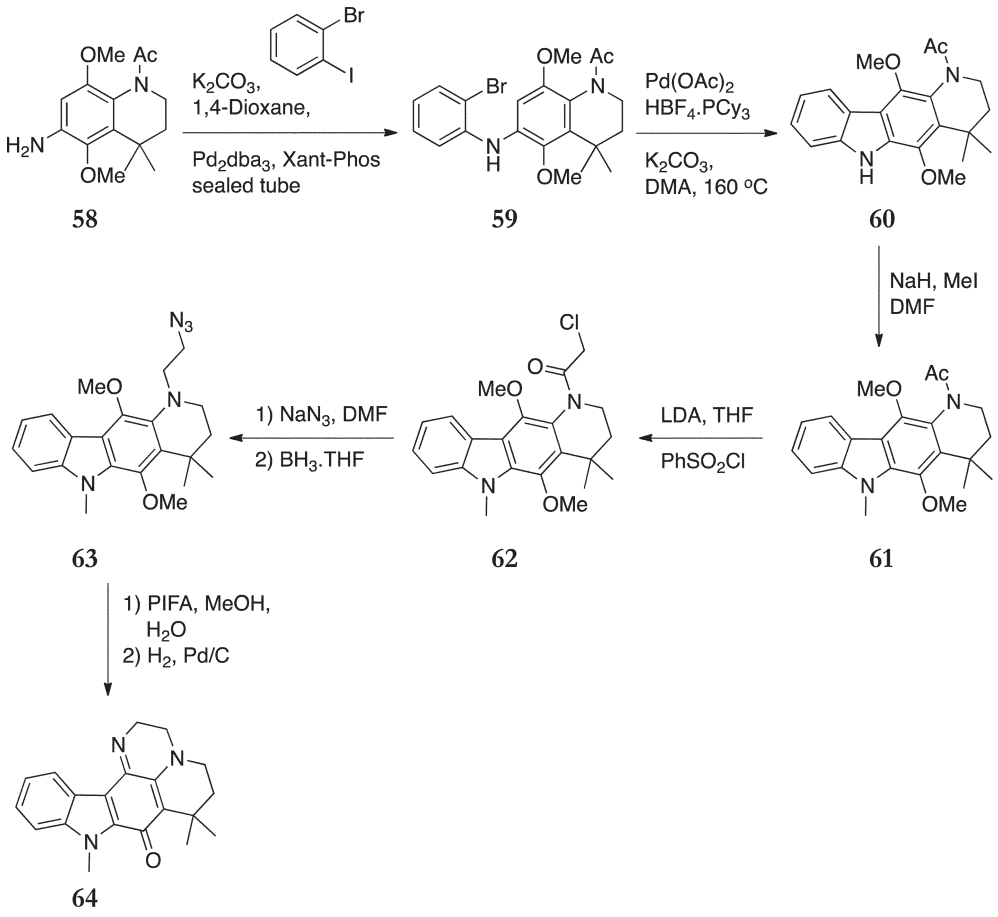
Recently, Bouclé and Guillard published their synthesis of a new pyrido[3,2-*b*]carbazole as an ellipticine–makaluvamine hybrid.[92] The synthesis features a Hartwig–Buchwald coupling followed by a Heck reaction to form the carbazole ring system (Scheme 12). The aminotetrahydroquinoline **58** was prepared in five steps from 2,5-dimethoxyaniline in 48% yield. Pd-catalyzed Hartwig–Buchwald coupling of **58** with 2-bromoiodobenzene gave the diarylamine **59** (74%), which was cyclised to the corresponding carbazole **60** under Heck conditions (80%). Methylation of the indole nitrogen was achieved under standard conditions to give **61** in quantitative yield. Treatment of **61** with LDA followed by quenching the resulting enolate with benzenesulfonyl chloride afforded the chloroamide **62** (40%). This was treated with sodium azide followed by reduction of the amide to give **63** (62% over 2 steps). Finally, oxidation with PIFA gave the quinone, the azide was reduced by catalytic hydrogenation and cyclised to give the imine target compound **64** in 35% yield.

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54 **53** R^1=H or $COOCH_3$ **55** R^1=H **56** R^1=$COOCH_3$ **57**

Scheme 11



58 **59** **60** **61** **62** **63** **64**

Scheme 12

5. C-type syntheses

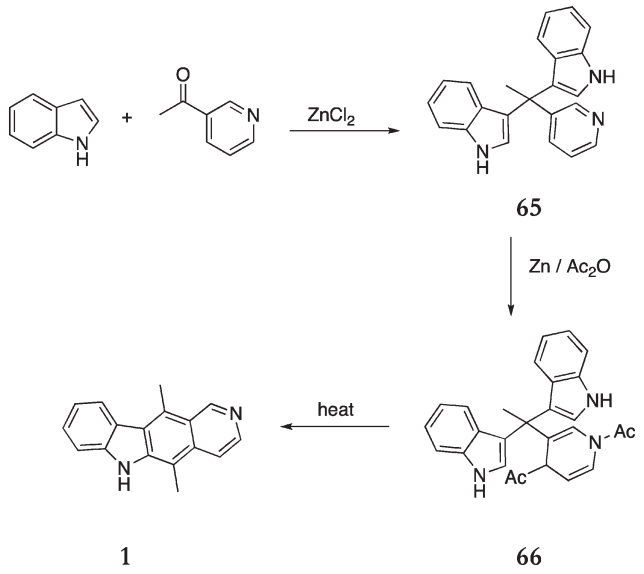
C-Type syntheses are some of the most versatile and highly exploited routes to ellipticine, typically involving coupling of indole and pyridine subunits. In this section, the syntheses are categorised based on the coupling reaction: C-3 coupling of indoles with substituted pyridines, C-2 coupling of indoles with substituted pyridines and cycloaddition reactions.

5.1 C-3 coupling of indoles with substituted pyridines

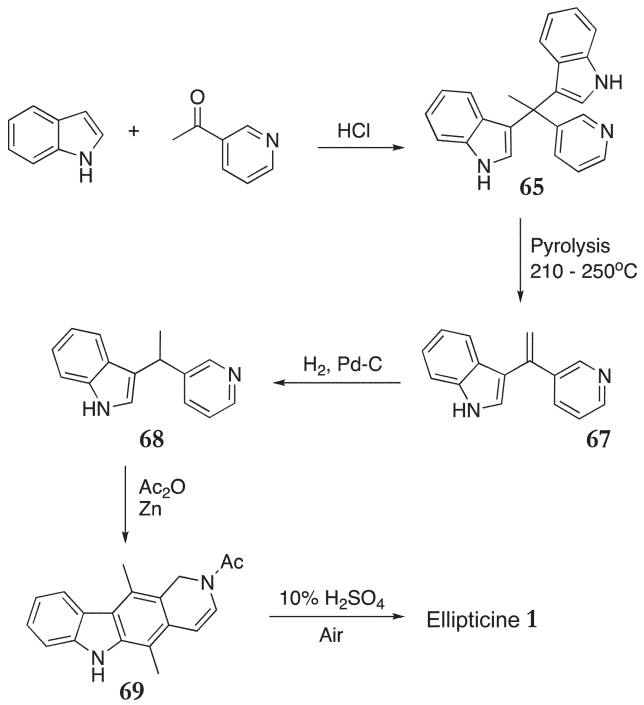
The first synthesis of ellipticine **1** was published by Woodward *et al.* in 1959 along with their elucidation of the structure (Scheme 13).[2] Condensation of indole with 3-acetylpyridine gave the bis-indoyl derivative **65**, which was reduced with zinc and acetic anhydride to the *N*,γ-diacetyldihydropyridine derivative **66**. This was subjected to pyrolysis to give ellipticine **1**.

Despite being attractively simple, this route had little practical value as the overall yield was minute. The bulky bis-indoyl derivative **65** was a poor substrate for the reduction step and the final oxidative cyclisation required severe pyrolytic conditions, resulting in an overall yield of 2%.

Zee and Su were attracted by the simplicity of Woodward's original route and attempted to adapt the route to overcome the problematic reactions and low yields (Scheme 14).[93] The initial condensation of indole and 3-acetylpyridine was catalysed by HCl instead of zinc chloride, which improved the yield of bis-indoyl derivative **65** (81%). Vacuum pyrolysis of **65** gave **67**



Scheme 13



Scheme 14

(50%), which was hydrogenated to give the key intermediate **68** (90%). When reductive acetylation was carried out, the expected product (1,4 acetylation of the pyridine ring) was not isolated, as intramolecular condensation at C-2 had occurred simultaneously to give 2-acetyl-1,2-dihydroellipticine **69** in 48% yield. This was hydrolysed and aromatised by refluxing with 10% sulfuric acid in an oxygen rich environment to produce ellipticine **1** in 68% yield.

The overall yield of ellipticine from indole was 12%, a significant improvement on that of Woodward *et al.* (2% overall). However, two additional steps were required and the problematic pyrolysis step was still low yielding. Although this route has not been used to synthesise any substituted ellipticines, it is feasible that substitution on the indole would be tolerated.

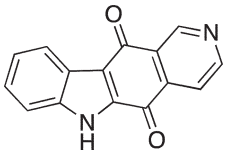


Fig. 9 Ellipticine quinone **70**.

In the course of their work on Friedel–Crafts acylation of *N*-protected indoles, Ketcha and Gribble developed a novel route to the ellipticine quinone **70** (Fig. 9).[94] First reported in 1979 by Talyor and Joule, the ellipticine quinone has proved a popular and convenient ellipticine precursor.[95] Treatment of **70** with two equivalents of methyllithium, followed by sodium borohydride, affords ellipticine in yields of over 90% and it is a key intermediate in a variety of C-type routes.

In the Gribble route, 3,4-pyridinedicarboxylic anhydride **71** was converted to the monomethylester **72** (73%), followed by conversion to the acid chloride **73** with thionyl chloride in 78% yield.[94] Friedel–Crafts acylation of 1-phenylsulfonylindole with **73** gave the keto ester **74** (50%), which was cyclised employing Comins' methodology to the ellipticine quinone **70** (47%) (Scheme 15).

The analogous quinones **75**, **76** (Fig. 10) were also synthesised *via* this route. The deazaellipticine quinone **75** was synthesised in three steps from phthalic anhydride (21% overall). The isoellipticine quinone **76** was accessible *via* direct reaction of 3,4-pyridinedicarboxylic anhydride **71** with 1-phenylsulfonylindole (19% over three steps).

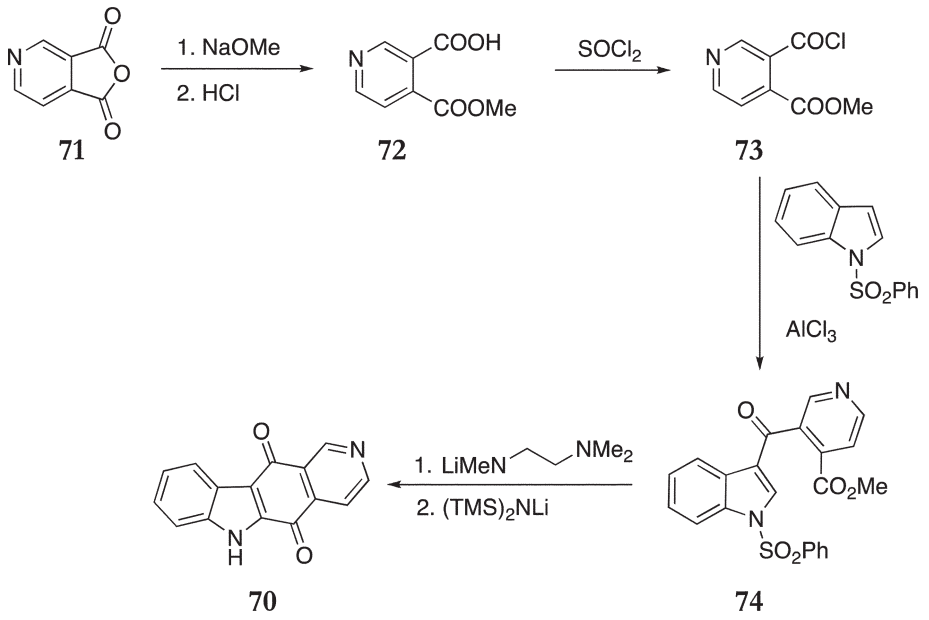
While not the best yielding route to ellipticine (13% overall yield for the ellipticine quinone **70**), this route does provide access to a variety of ellipticine analogues.

In 2005, Bennasar *et al.* published a radical cascade route to the ellipticine quinone (Scheme 16).[96] Reaction of the *N*-benzyl-2,3-disubstituted indole **77** with 3-pyridylmagnesium bromide gave the coupled product **78**, which was reduced with triethylsilane to the methyl ester **79** (55% from **77**). Hydrolysis followed by phenylselenation of the carboxylic acid yielded the acyl selenide **80** in 76% yield. The key cyclisation step was carried out with irradiation and hexabutylditin, affording the *N*-benzylellipticine quinone **81** in a 42% yield.

The *N*-benzylellipticine quinone **81** may be converted to ellipticine in two steps; treatment with methyllithium followed by sodium borohydride would give N-benzylellipticine. However, subsequent removal of the benzyl group has been shown to be problematic, Birch reduction effects deprotection but also reduces the pyridine ring which must then be re-aromatised with 10% palladium on carbon and decalin.[97] These additional steps significantly reduce the overall yields for the route and impact on its versatility. Other indole protecting groups (Me, MOM) were used, but with little success.

In their synthesis of 1-fluoroellipticine **82**, Marsais *et al.* prepared a tri-functional pyridine for C-3 coupling with an indole (Scheme 17).[98] Initially 2-fluoropyridine was brominated to give 3-bromo-2-fluoropyridine **83** in 75% yield. This was lithiated and isomerised by LDA to give 4-bromo-2-fluoro-3-lithiopyridine, followed by treatment with acetaldehyde to give

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Scheme 15

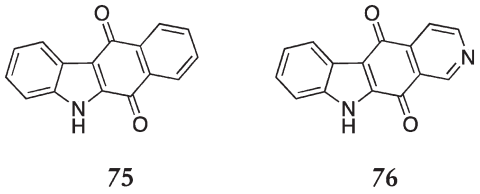
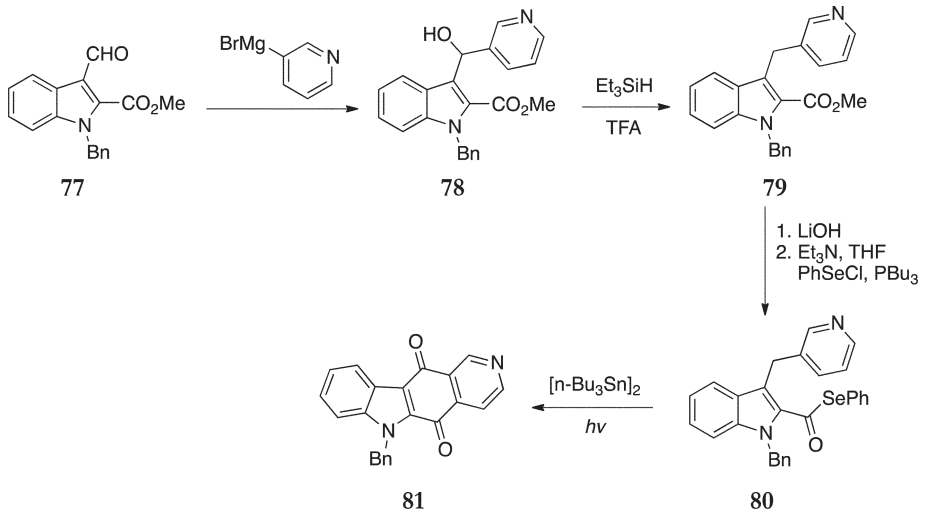


Fig. 10

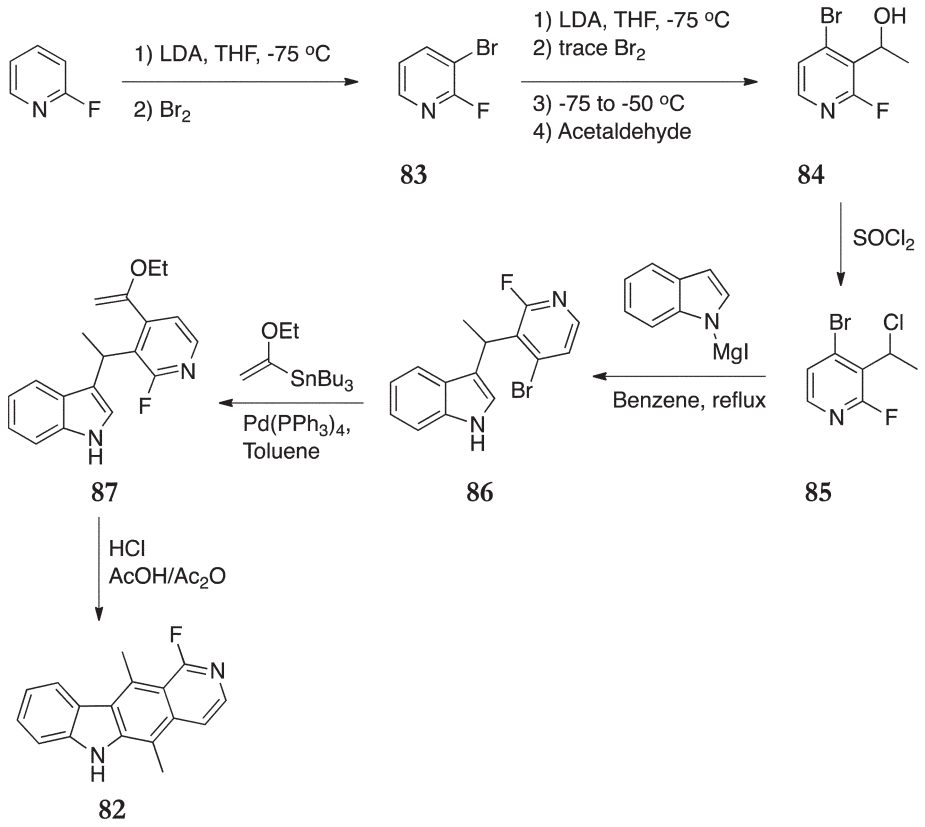
the tri-substituted pyridine **84** (75%). The acetaldehyde had to be added quickly, with efficient reaction cooling in order to avoid forming an isomeric side product. The chloro derivative **85** was prepared by treatment with thionyl chloride (95%) and reacted with 1-indolylmagnesium iodide to give **86** in 65% yield. Next, lithium–bromine exchange followed by treatment with acetaldehyde was attempted but the lithio derivative of **86** did not react with acetaldehyde and gave the debrominated product. However, reaction with a tributylvinylstannane gave the vinyl compound **87** (95%), which readily cyclized under acidic conditions to afford 1-fluoroellipticine **82** in 54% yield.

5.2 C-2 coupling of indoles with substituted pyridines

In 1992, Gribble *et al.* published full detail of their general and versatile C-type route (Scheme 18).[99,100] Initially, indole was protected to give *N*-phenylsulfonylindole **88** in 91% yield. Regiospecific C-2 lithiation with lithium diisopropylamide followed by addition of 3,4-pyridinedicarboxylic anhydride **71** gave a mixture of protected ketoacids **89** & **90** (79%). Ring opening of the anhydride was regioselective for the desired product **89**, and the regioisomers were separated by fractional crystallisation from acetone. The minor isomer was insoluble in acetone and the ratio of **89** to **90** was found to be 92 : 8.



Scheme 16



Scheme 17

Deprotection of the indole was achieved with potassium carbonate in methanol to give ketoacid **91** in quantitative yield. At this point, Sauliner and Gribble had envisaged cyclisation to the ellipticine quinone **70**, however, after several unsuccessful attempts to cyclise the ketoacid **91**, it was found that heating in acetic anhydride affected cyclisation to the ketolactam **92** (100%). This ketolactam was smoothly converted to ellipticine **1** in 82% yield by treatment with two equivalents of methyllithium followed by refluxing with sodium borohydride in ethanol.

This synthesis has been successfully utilised to produce a wide variety of substituted ellipticines and ellipticine analogues. 9-Methoxyellipticine **11** was synthesised starting from 5-methoxyindole in an overall yield of 47%, subsequent demethylation gave 9-hydroxyellipticine **4** (93%) (Fig. 11).[100] Various 5,11-disubstituted ellipticines were also synthesised *via* sequential regioselective alkylations of ketolactam **92** giving 5-*n*-butyl-11-methyl-6*H*-pyrido[4,3-*b*]carbazole **93** (70%), the 5,11-di-*n*-butyl derivative **94** (18%) and 11-demethylellipticine **95** (57%). 11-Demethylellipticine **95** had previously been converted to the natural product olivacine **96** by treatment with methyllithium followed by oxidation of a dihydropyridine intermediate with iodine (54%).[101]

13-Oxoellipticine **97**, an alkaloid isolated from the African tree *Strychnos dinklagei* was also synthesised *via* this route (Scheme 19).[102,103] Ketolactam **92** was treated with vinyllithium followed by methyllithium to give **98**, which was oxidatively cleaved with chromic acid to give 13-oxoellipticine **97** (58% from **92**).

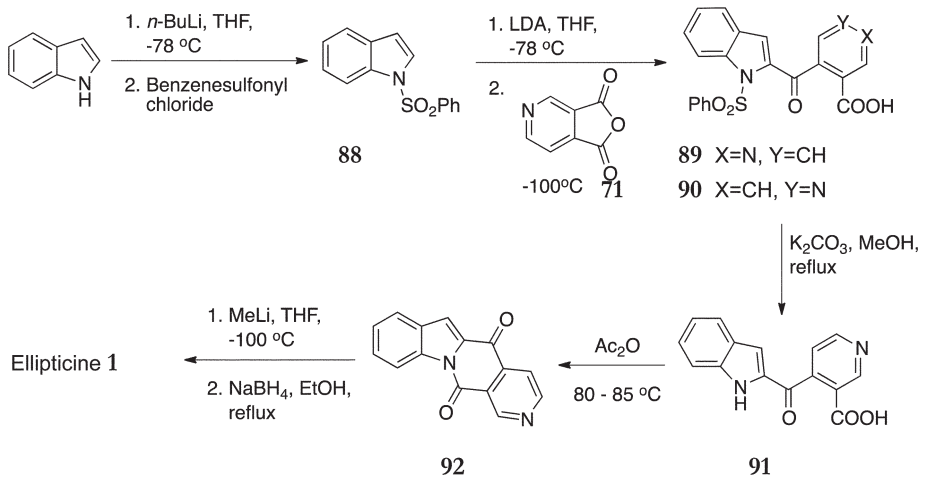
Several ellipticine analogues were accessible *via* this route by varying the anhydride used (Fig. 12), including isoellipticine[104] (5,11-dimethyl-10*H*-pyrido[3,4-*b*]carbazole) **51** (85% from the minor isomer of the coupling reaction **90**), 5,11-dimethyl-10*H*-pyrido[2,3-*b*]carbazole[105] **99** (60% overall) and deazaellipticine[106] (5,11-dimethyl-5*H*-benzo[*b*]carbazole) **100** (61% overall).

Modi *et al.* developed a route for the synthesis of C-11 substituted ellipticines from Gribble's ketolactam **92** (Scheme 20).[107,108] Treatment of the ketolactam **92** with one equivalent of methyllithium gave the lactone **101** in 62% yield. This was converted to the bisulfide **102** (45%) and then 12-oxoellipticine **103** (85%). Finally, the formyl group was reduced to the alcohol 5-methyl-11-methanol-6*H*-pyrido[4,3-*b*]carbazole **104** in 89% yield.

Overall, Saulnier and Gribble's synthesis is one of the highest yielding and most versatile routes to ellipticine and its analogues. C-5 and C-11 substituents may be introduced *via* sequential regioselective alkylation of the ketolactam intermediate. A-Ring substituents may be varied using substituted indoles, and D-ring ellipticine analogues (C-1 to C-4) are accessible by variation of the anhydride used.

In 1990, Hibino and Sugino published a route based on thermal electrocyclic reaction of a 2-alkenylindole intermediate (Scheme 21).[109] Initially 3-ethylpyridine **105** was converted to the *N*-oxide **106** in 81% yield. This was converted to 3-ethyl-4-cyanopyridine followed by treatment with methyllithium to give 3-ethyl-4-acetylpyridine **107** (39%). Reaction of **107** with 2-lithiophenylsulfonylindole afforded the key 2-alkenylinole intermediate **108** in 21% yield. Thermal cyclisation to ellipticine **1** (30%)

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Scheme 18

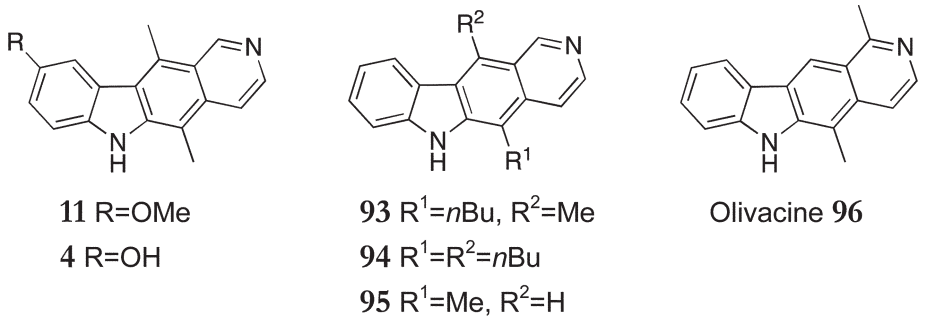
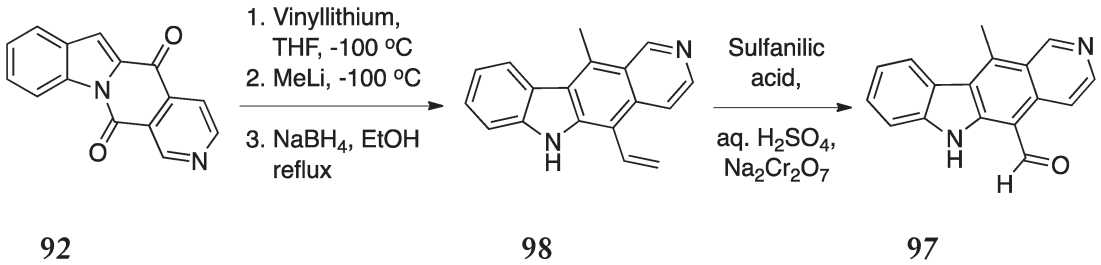


Fig. 11



Scheme 19

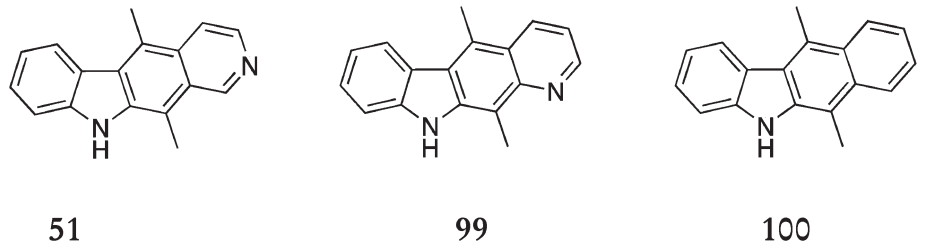


Fig. 12

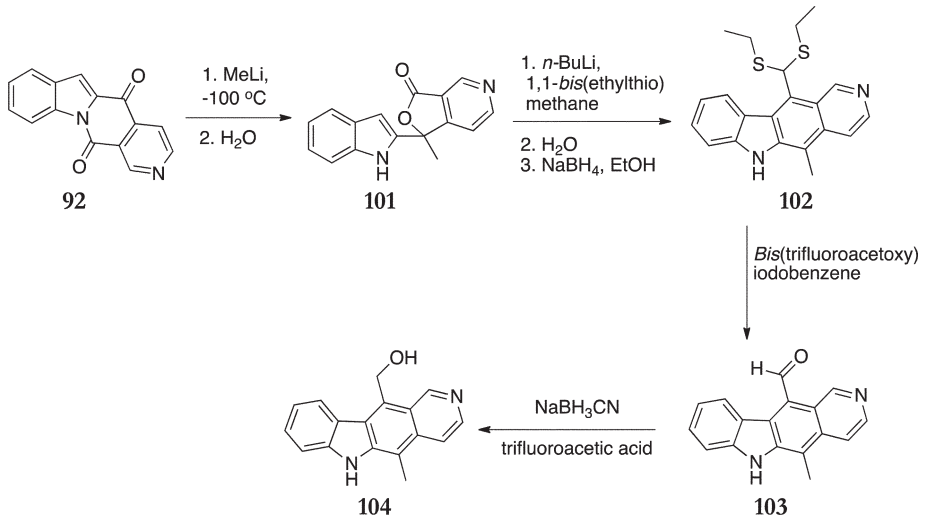
was only partially successful, as it was accompanied by 11-demethylellipticine **95** (43%).

This route suffered from low yields in both the coupling and cyclisation steps along with the problem of demethylation during thermal cyclisation, resulting in an overall yield of 2% for ellipticine. The thermal cyclisation step may be amenable towards synthesis of 11-demethylellipticine analogues, however, the synthesis of olivacine **96** (Fig. 11) resulted in an overall yield of just 0.3% due to poor yields in the preceding steps.

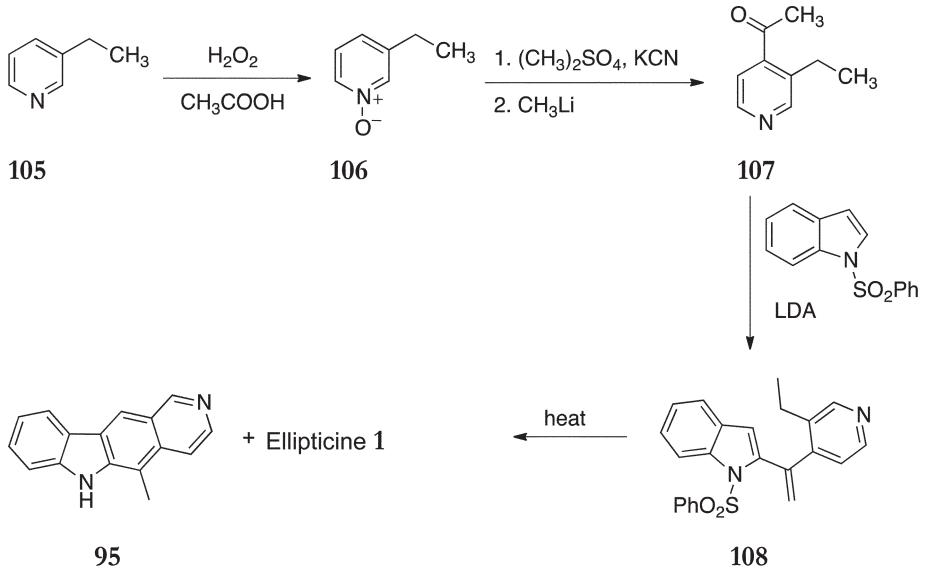
In parallel with their work on the synthesis of 1-aminoellipticines, Bisagni *et al.* synthesised a range of 11-aminoellipticines **109** *via* a novel C-2 coupling route (Scheme 22).[110] 5-Methoxy-1-(phenylsulfonyl)-1*H*-indole **110** was lithiated at C-2 and reacted with 4-acetyl-*N*,*N*-diisopropylnicotinamide **111** to give the coupled product **112** in 62% yield. This was converted to the lactone **113** (80%) and reduced with activated zinc powder in acetic acid followed by hydrochloric acid to give carboxylic acid **114** (62%). Conversion to the amide derivatives **115** was achieved *via* acylimidazole intermediates in yields of 55–80%. Finally, cyclization in phosphorus oxychloride and removal of the protecting group with RANEY® nickel gave the 11-aminoellipticines **109a–c** (23–32%).

Bisagni *et al.* also adapted this route for synthesis of the 9-azaellipticine analogues **116** (Fig. 13).[111]

Miki *et al.* developed a route *via* coupling of an N-protected indole-2,3-dicarboxylic anhydride with a substituted pyridine.[112,113] 1-(4-Methoxybenzyl)indole-2,3-dicarboxylic anhydride **117** was reacted with (3-bromo-4-pyridyl)triisopropoxytitanium **118** at low temperature to give the coupled product **119** (61%). Removal of both the *para*-methoxybenzyl (PMB) and carboxy groups was effected with 20% perchloric acid to give **120** in 81% yield. (In the initial publication,[112] **117** was protected with a benzyl group, however, low yields for deprotection resulted in a change to the *para*-methoxybenzyl group).[113] A Wittig reaction furnished **121**

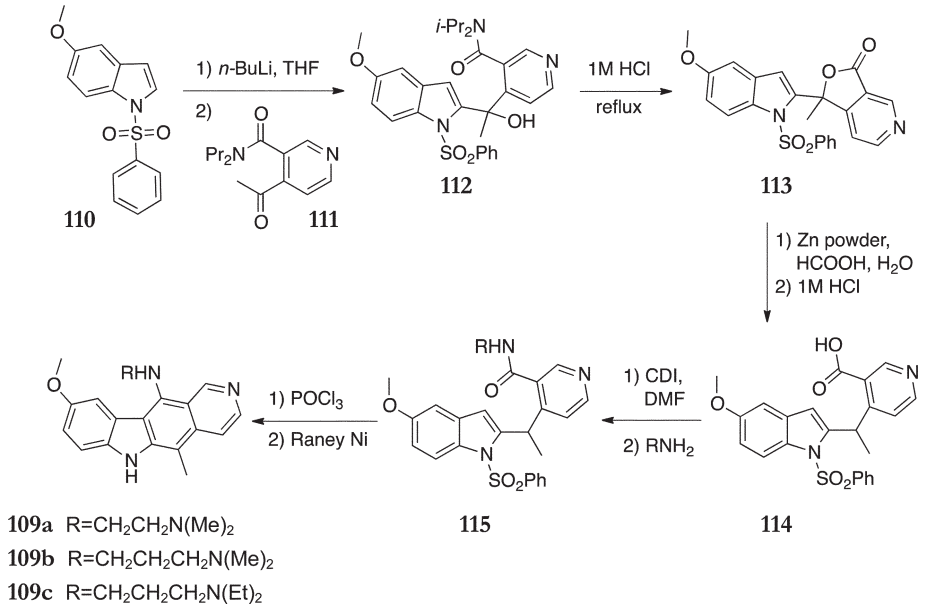


Scheme 20



Scheme 21

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Scheme 22

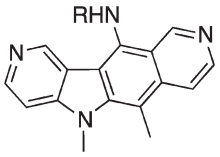
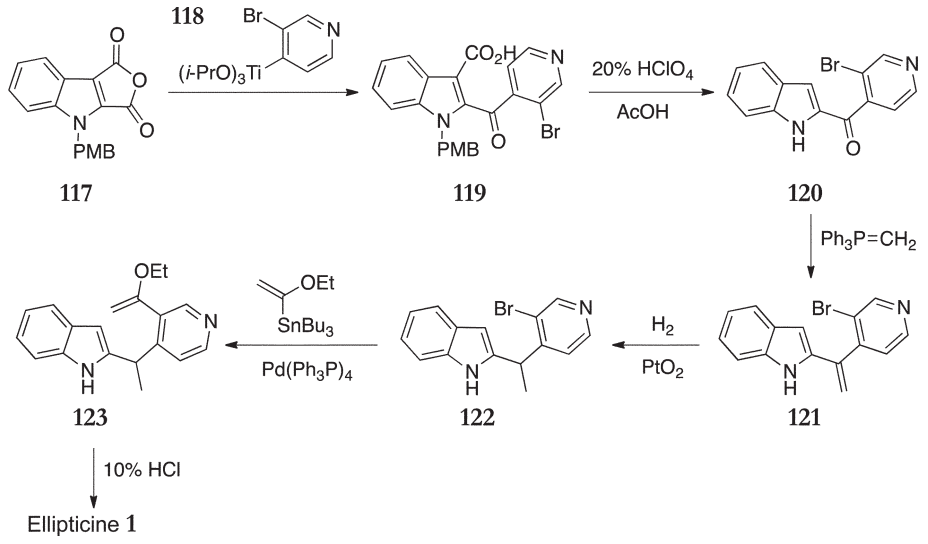


Fig. 13 9-Azaellipticine analogues **116**.

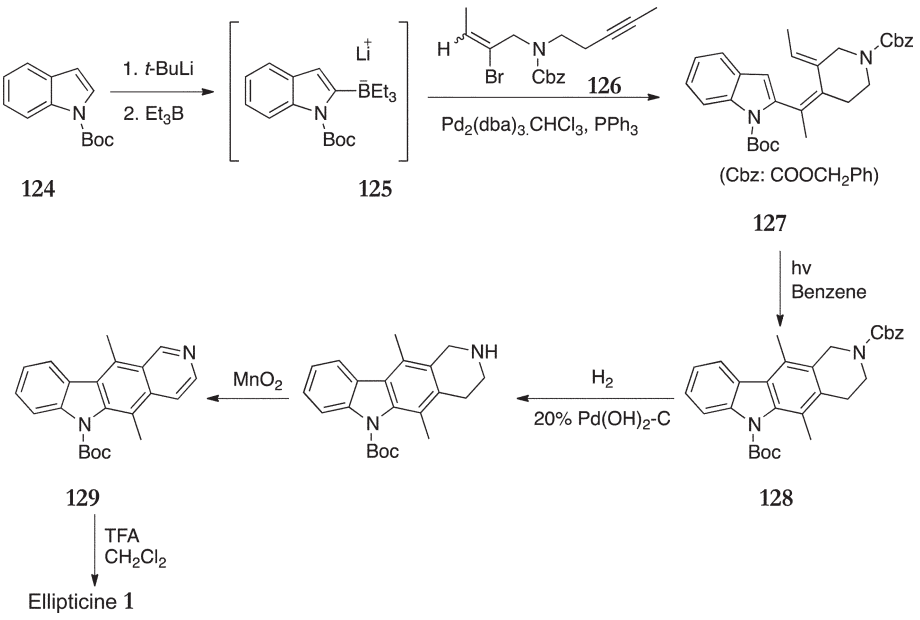
(63%), which was then hydrogenated to **122** in 73% yield. Treatment of **122** with (ethoxyvinyl)tributyltin in the presence of tetrakis(triphenylphosphine)palladium(0) gave the corresponding ethoxyvinyl derivative **123**. This was converted to ellipticine by treatment with 10% hydrochloric acid (87%) (Scheme 23).

A novel route published in 2000 by Ishikura *et al.* utilised palladium catalysed tandem cyclisation–cross-coupling of an indolylborate and vinyl bromide (Scheme 24).[114] 1-(*t*-Butyloxycarbonyl)indole **124** was converted to the indolylborate **125**, which was reacted *in situ* with vinyl bromide **126** using a 1 : 4 ratio of $Pd_2(dba)_3{\cdot}CHCl_3$ and Ph_3P to give the hexatriene **127** (64%). Irradiation of **127** with a high pressure mercury lamp yielded the tetrahydropyridocarbazole **128** in 41% yield. Deprotection of the carboxybenzyl (Cbz) group was achieved by hydrogenation and oxidation with manganese dioxide afforded the Boc-protected ellipticine **129**. Finally, the Boc group was removed with trifluoroacetic acid to give ellipticine in 84% yield.

This synthesis is a novel strategy towards ellipticine, however, disadvantages include a three step synthesis of the vinyl bromide **126** and a moderate overall yield of 14%. The route may be amenable to synthesis of A-ring substituted ellipticines and variation of the vinyl bromide could be used to produce C or D-ring substituents.



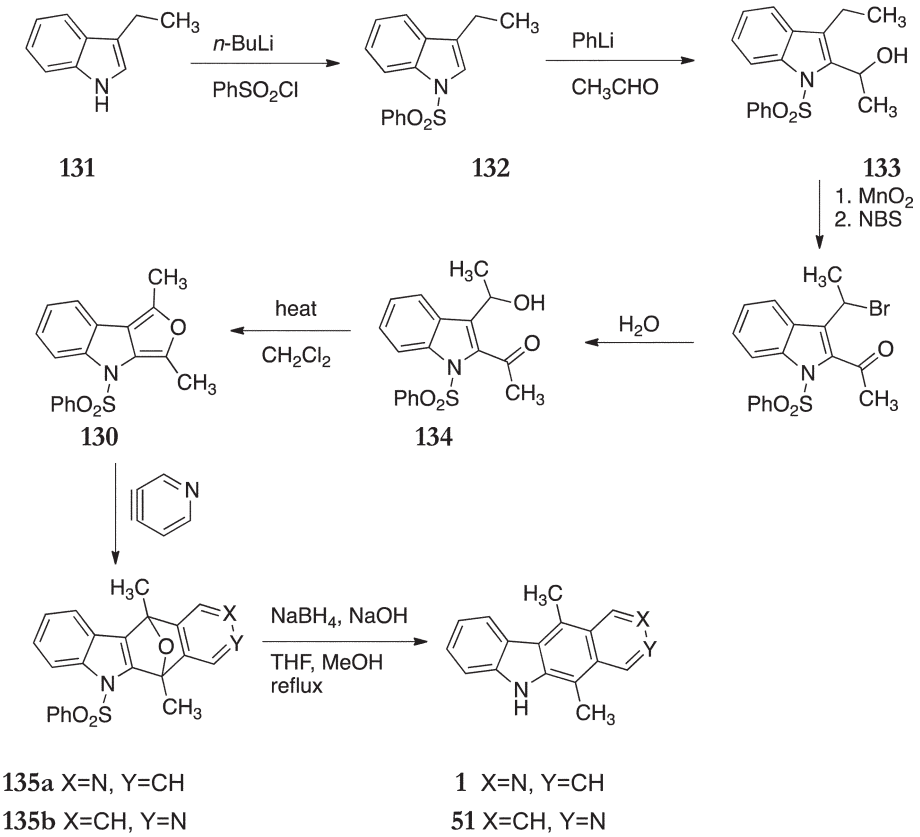
Scheme 23



Scheme 24

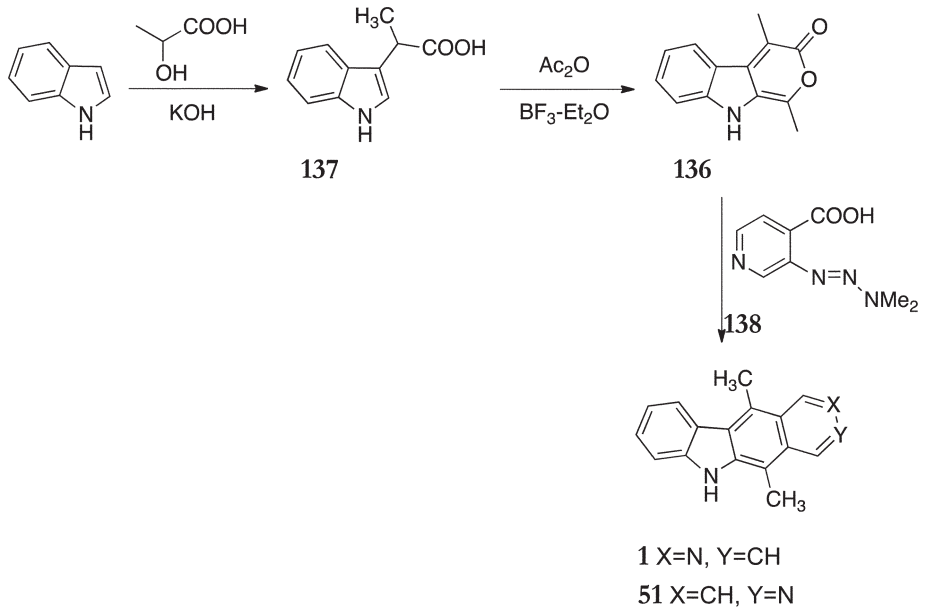
5.3 Cycloaddition reactions

The first route to utilise a cycloaddition as the C-ring forming reaction was published in 1984 by Gribble *et al.*[115] The key step involved a Diels–Alder reaction of furo[3,4-*b*]indole **130** and 3,4-pyridyne (Scheme 25). 3-Ethylindole **131** was protected with a benzenesulfonyl group to give **132** (74%), followed by C-2 lithiation and quenching with acetaldehyde which furnished the desired alcohol **133** (73%). Oxidation, bromination and hydrolysis gave the hydroxy ketone **134** in 86% yield from **133**. This conveniently cyclised to the furo[3,4-*b*]indole **130** during attempted recrystallisation from dichloromethane in quantitative yield.



Scheme 25

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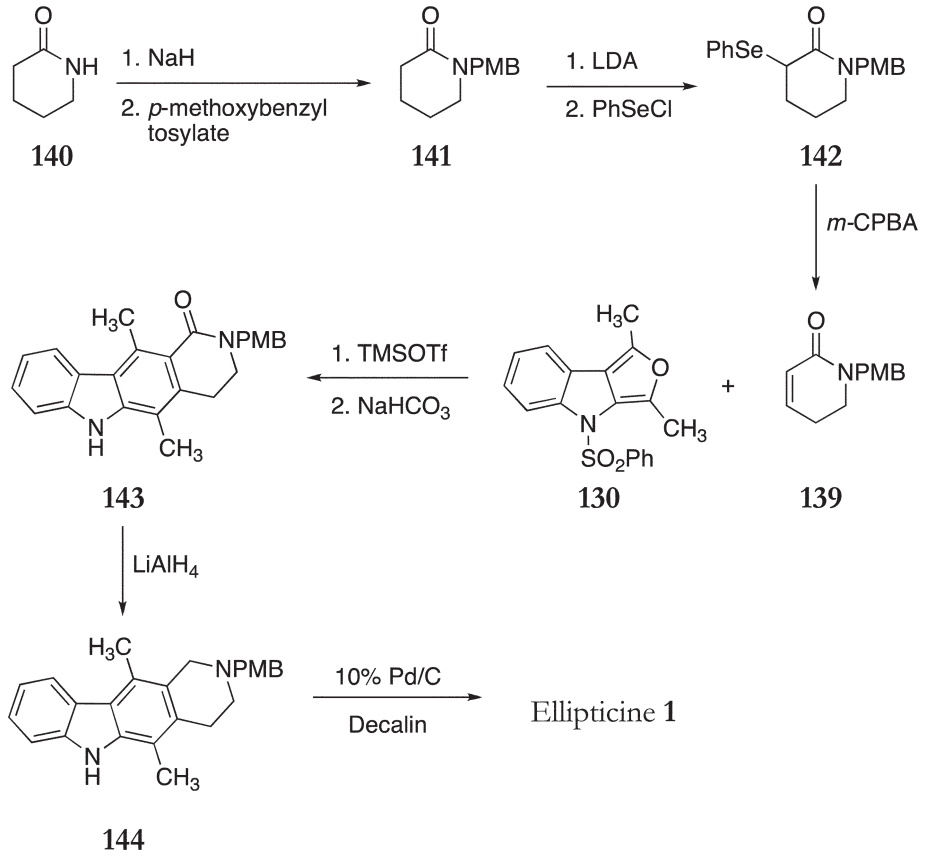


Scheme 26

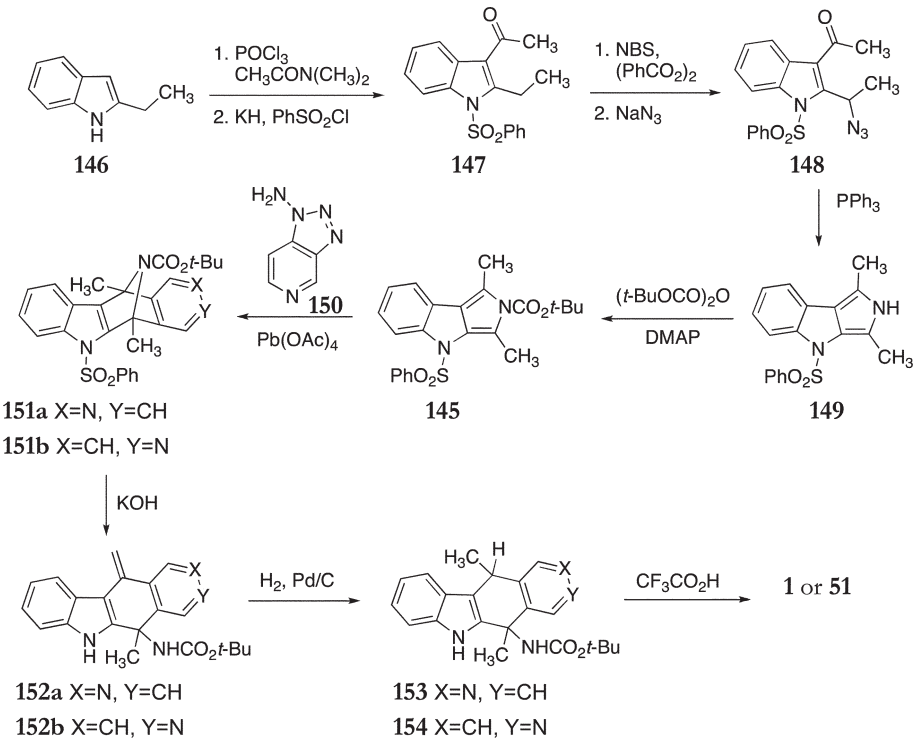
Furo[3,4-*b*]indole **130** was also synthesised from indole-3-carboxaldehyde in a yield of 21% over 5 steps in the same publication.

In the cycloaddition reaction, 3,4-pyridyne was generated *in situ* from reaction of 1-aminotriazolo[4,5-*c*]pyridine and lead tetraacetate, to which **130** was added to give a mixture of the isomeric cycloadducts **135a+b** (38%). Treatment with sodium borohydride and sodium hydroxide effected both desulfonylation and oxygen-bridge extrusion to afford an approximately 1 : 1 mixture of ellipticine **1** and isoellipticine **51** , which were separated by column chromatography (23% and 29% respectively).

The two main disadvantages of this route were the lengthy synthesis of the furo[3,4-*b*]indole **130** and the lack of regioselec-

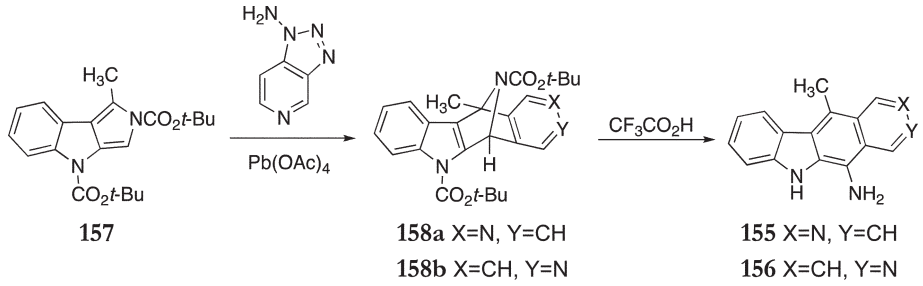


Scheme 27



146 147 148 149 145 150 151a X=N, Y=CH 151b X=CH, Y=N 152a X=N, Y=CH 152b X=CH, Y=N 153 X=N, Y=CH 154 X=CH, Y=N

Scheme 28



157 158a X=N, Y=CH 158b X=CH, Y=N 155 X=N, Y=CH 156 X=CH, Y=N

Scheme 29

tivity in the cycloaddition step resulting in a 1 : 1 mixture of ellipticine and isoellipticine.

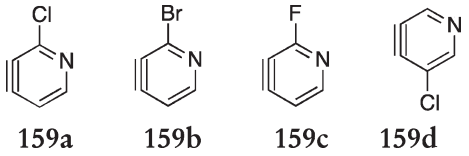
A somewhat similar route was published by May and Moody around the same time as that of Gribble *et al.* above and was based on Diels–Alder reaction of the pyranoindolone **136** and pyridyne (Scheme 26).[116,117] Indole was first converted to 2-(1*H*-indol-3-yl)propanoic acid **137** (32%) by treatment with lactic acid and base, followed by reaction with boron trifluoride in acetic anhydride to give the pyranoindolone **136** (43%). The pyridyltriazene **138** was synthesised in a one pot procedure by diazotisation of 3-aminopyridine-4-carboxylic acid followed by coupling with dimethylamine (73%). Heating pyranoindolone **136** with excess pyridyltriazene **138** in acetonitrile gave a 1 : 1 mixture of ellipticine **1** and isoellipticine **51** (40%).

While this route was significantly shorter than the previous route and did not require protection of the indole nitrogen, the lack of regioselectivity in the cycloaddition step still remained a major drawback.

Gribble *et al.* sought to overcome the problem of regioselectivity by changing the dienophile in their route.[118] In preliminary investigations they found that the key intermediate furo[3,4-*b*]indole **130** reacted completely regioselectively with ethyl acrylate in the presence of aluminium chloride. Thus, they choose 5,6-dihydropyridone **139** as a new dienophile for the route (Scheme 27). Sequential treatment of lactam **140** with sodium hydride and *p*-methoxybenzyl tosylate gave the *N*-protected lactam **141** in 68% yield. This was lithiated with lithium diisopropylamide and then quenched with phenylselenenyl chloride to yield **142** (94%), followed by oxidative elimination to give 5,6-dihydropyridone **139** (78%).

The Diels–Alder reaction between furo[3,4-*b*]indole **130** (synthesis in Scheme 25 above) and 5,6-dihydropyridone **139** successfully produced a single regioisomer **143** in 40% yield. This was converted to ellipticine in two steps *via* reduction of the carbonyl to give **144**, followed by *N*-deprotection and aromatization to give ellipticine (20%). No isoellipticine was detected

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159a **159b** **159c** **159d**

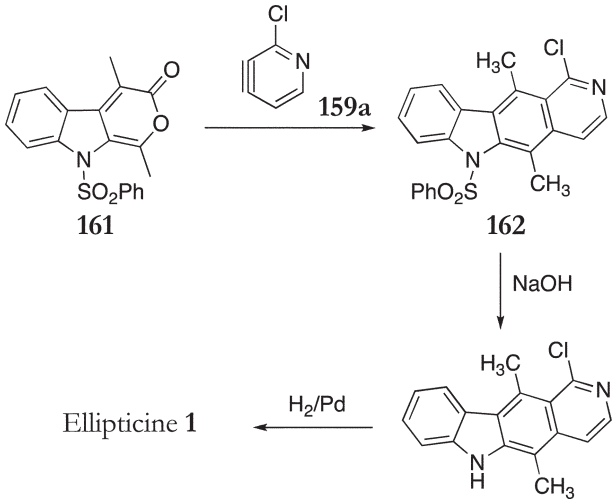
Fig. 14

and, as such this was the first regioselective Diels–Alder synthesis of ellipticine.

In 1992, Sha and Yang published a synthesis of ellipticine based on a Diels–Alder reaction between 2,4-dihydro-1,3-dimethylpyrrolo[3,4-*b*]indole **145** and 3,4-pyridyne (Scheme 28).[119] This route is a variation on the first Diels–Alder route published by Gribble *et al.*[115] in 1984. Acetylation of 2-ethylindole **146** followed by *N*-protection of the indole gave **147** in 68% yield. This was brominated and reacted with sodium azide to give the azido derivative **148** (78%). A Staudinger reaction of **148** with triphenylphosphine produced dihydropyrolo[3,4-*b*]indole **149** (90%) which was reacted with Boc anhydride and 4-dimethylaminopyridine to give the key intermediate 2,4-dihydropyrrolo[3,4-*b*]indole **145** (90%). 3,4-Pyridyne was generated *in situ* from 1-aminotriazolo[4,5-*c*]pyridine **150** and reacted with **145** to give the cycloadducts **151a & b** (62% yield, ratio 55 : 45). Treatment of this mixture with base gave **152a** (35%) and **152b** (39%) which were separated by column chromatography. Both compounds were separately hydrogenated to give **153** (80%) and **154** (83%) followed by conversion to ellipticine **1** (85%) and isoellipticine **51** (78%).

This approach was also used to synthesise new 5-aminoellipticines **155** & **156**, with **157** as the key intermediate (Scheme 29). The Diels–Alder reaction gave cycloadducts **158a** & **b** (65%), which were treated with trifluoroacetic acid to give 5-aminoellipticine **155** and 11-aminoisoellipticine **156** (60% combined yield).

Diaz *et al.* investigated the regioselective effect of substituents on the pyridyne in the Diels–Alder reactions, focusing on two previously published routes[115,117] (Scheme 25–Gribble & Scheme 26–Moody).[120] They synthesised four substituted pyridynes **159a–d** (Fig. 14), selected for the ease of introduction and removal of the halogen and to allow modulation of polarisation and steric hindrance.

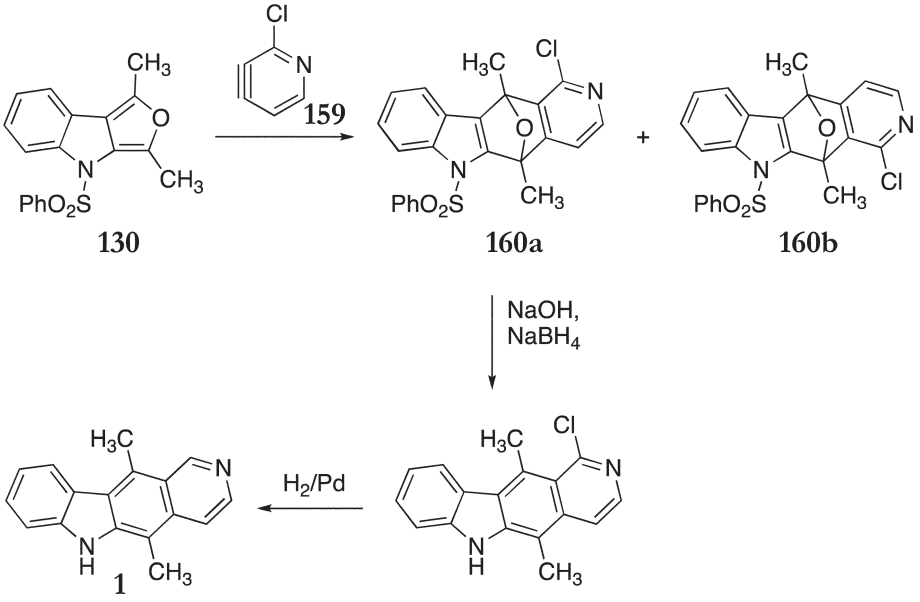


161 **162**

Scheme 31

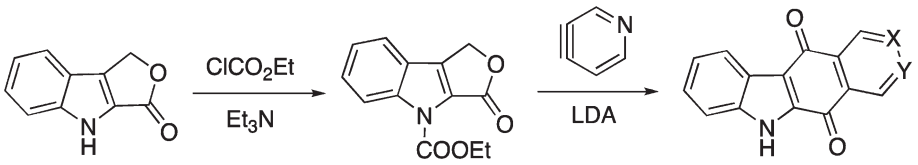
Reactions of pyridynes **159b–d** with Gribble's furo[3,4-*b*]indole **130** showed no regioselectivity, all gave 1 : 1 mixtures of cycloadducts. However, pyridyne **159a** afforded modest regioselectivity towards the ellipticine cycloadduct **160a** over the isoellipticine cycloadduct **160b**, with a ratio of 2.4 : 1 (88%) (Scheme 30). The cycloadducts were separated and **160a** was converted to ellipticine in two steps (88%).

When Moody's pyranoindole **136** (see Scheme 26 above) was reacted with pyridynes **159a–d** no regioselectivity was observed. In an attempt to make Moody's diene more similar to Gribble's, a benzenesulfonyl group was introduced on the indole nitrogen to give **161** in a 78% yield. This pyranoindole reacted regioselectively with pyridyne **159a** to give the cycloadduct **162** as



130 **160a** **160b** **1**

Scheme 30



Scheme 32

the sole product (20%) (Scheme 31). *N*-Deprotection and hydrogenation gave ellipticine in 46% yield.

Mal *et al.* devised an anionic [4+2] cycloaddition strategy towards the ellipticine quinone and related carbazole quinones.[121,122] Indolofuranone **163** was treated with triethylamine and ethylchloroformate to give the *N*-ethoxycarbonyl derivative **164** in 92% yield (Scheme 32). Reaction of **164** with 3,4-pyridyne (prepared *in situ* from 3-bromopyridine) in the presence of lithium diisopropylamide gave an inseparable mixture of the ellipticine and isoellipticine quinones **70** & **76** (45%).

6. D-type syntheses

To date the vast majority of D-type syntheses have been based on an early route published by Cranwell and Saxton in 1962.[123] A wide range of modifications and improvements have been published since, mainly focusing on improvement of carbazole formation or D-ring cyclisation. Two other D-type syntheses, not based on the Cranwell–Saxton route, are discussed under other D-type routes.

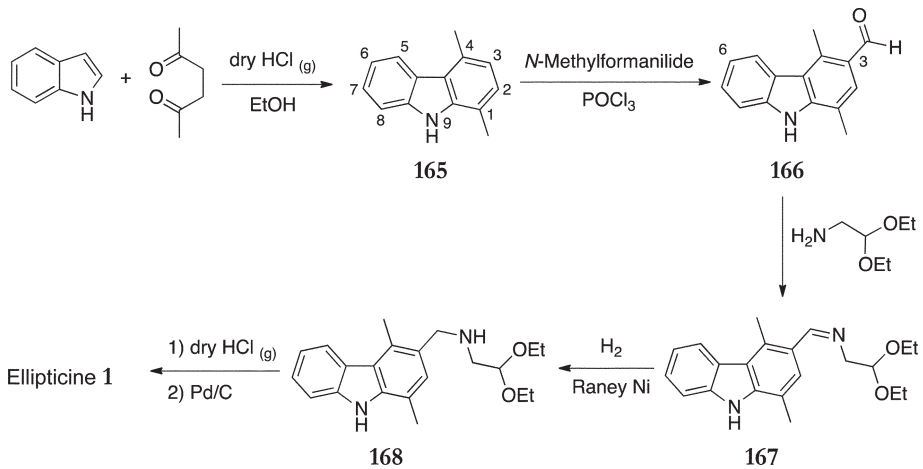
6.1 Cranwell–Saxton based approaches

Cranwell and Saxton published their D-type route in 1962 and numerous modifications and adaptations have been published since.[123] In the original route, 1,4-dimethylcarbazole **165** was prepared from indole and hexane-2,5-dione under acidic conditions in 36% yield (Scheme 33). Vilsmeier–Haack formylation furnished 3-formyl-1,4-dimethylcarbazole **166** along with the expected side product 3,6-diformyl-1,4-dimethylcarbazole and these were separated by chromatography to give **166** in 40% yield. Condensation with 2,2-diethoxyethylamine gave the imine **167** (85%) and attempts to convert this directly to ellipticine *via* Pomeranz–Fritsch synthesis were unsuccessful, so **167** was hydrogenated to produce the amine **168** (71%). Cyclisation was achieved on treatment with dry hydrogen chloride in ethanol, followed by dehydrogenation with palladium on carbon to furnish ellipticine **1** in a yield of 9.6% over two steps.

With an overall yield of just 0.8%, this route was even lower yielding than Woodwards first synthesis in 1959.[2] The low yielding carbazole formation, lack of specificity in the Vilsmeier–Haack formylation and the poor yielding cyclisation–aromatisation reaction were the most problematic steps. However, the chemistry was attractively robust and these problematic reactions offered ample opportunity for optimisation, resulting in numerous publications in subsequent years.

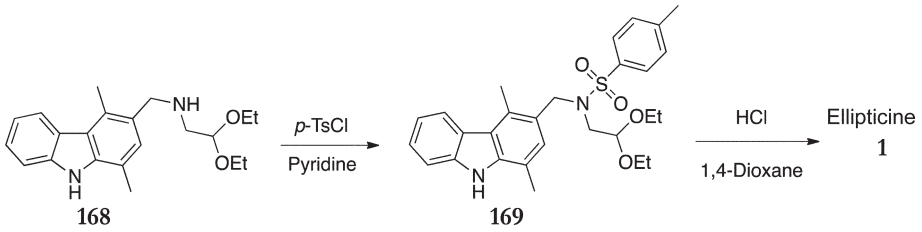
Based on their studies of Pomeranz–Fritsch isoquinoline synthesis,[124] Jackson *et al.* published the first and most significant modification of the Cranwell–Saxton route, dramatically improving the yield of the final cyclisation step (Scheme 34).[125] Conversion of amine **168** to its corresponding tosylate **169** (93%), followed by cyclisation in 1,4-dioxane and dilute hydrochloric acid, gave ellipticine in 90% yield (84% over the two steps).

Later, the same group applied this strategy in their synthesis of 8,9,10-trimethoxyellipticine.[126] Gruthrie *et al.* also utilised this modified Cranwell–Saxton route in their synthesis of 8,9-dimethoxyellipticine **170**, starting from the 5,6-dimethoxyindole **171** (Scheme 35).[127]



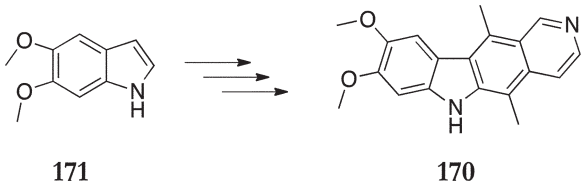
Scheme 33

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Scheme 34

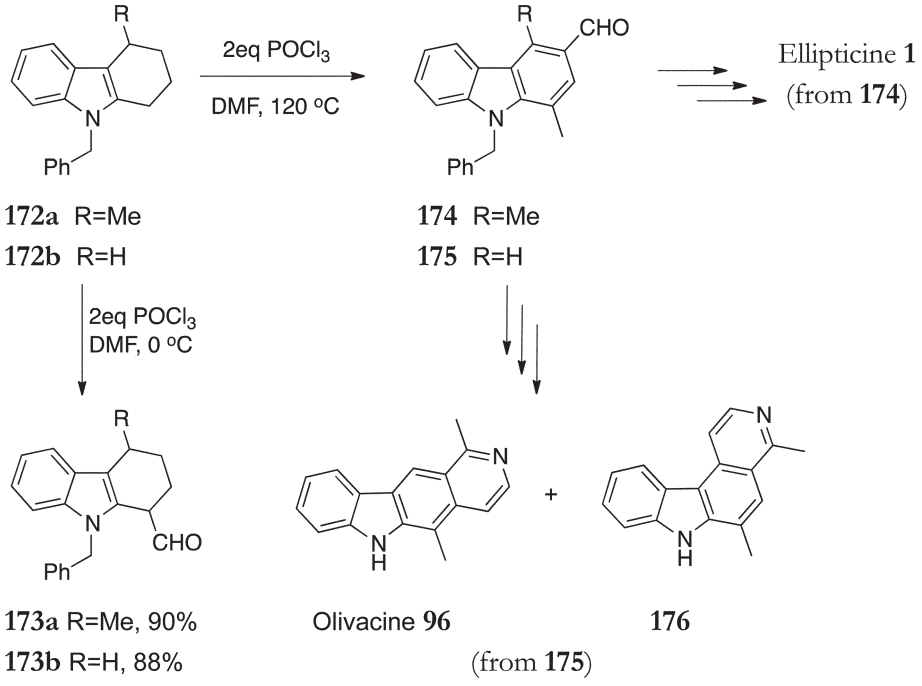
In 1970, Bruck reported an unusual product of a Vilsmeier–Haack reaction with *N*-methyl-1,2,3,4-tetrahydrocarbazole.[128] Later, Murakami *et al.* investigated this reaction and subsequently applied it to the synthesis of ellipticine and olivacine (Scheme 36).[97,129] When 9-benzyl-1,2,3,4-tetrahydrocarbazoles **172a** & **b** were treated with two equivalents of phosphorous oxychloride in dimethylformamide at 0 °C, 9-benzyl-1-formyl-1,2,3,4-tetrahydrocarbazoles **173** were isolated in good yields. However, when the same reaction was carried out at 120 °C, the unexpected 1-methyl-3-formylcarbazole products **174** & **175** were formed. 9-Benzyl-1,4-dimethyl-9*H*-carbazole-3-carbaldehyde **174** was converted to ellipticine *via* the modified Cranwell–Saxton route. The imine intermediate was subjected to Birch reduction to effect simultaneous debenzylation and reduction to the amine. This gave ellipticine in an overall yield of 22% from 9-benzyl-1,2,3,4-tetrahydrocarbazole **172**. 9-Benzyl-1-methyl-9*H*-carbazole-3-carbaldehyde **175** was converted to olivacine **96** *via* treatment with methyllithium and Jones reagent to give the methyl ketone, followed by the usual D-ring steps. This route was less attractive as the final cyclisation gave a 1.2 : 1 mixture of olivacine **96** and its non-linear isomer **176**.



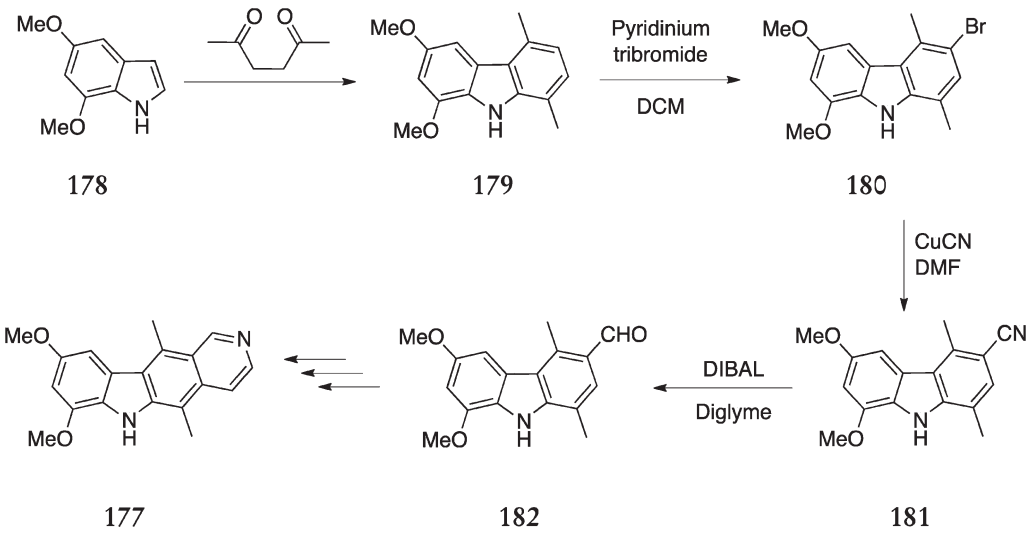
Scheme 35

During the 1990s, Shannon's group focused on the synthesis of A-ring substituted ellipticines *via* the Cranwell–Saxton route. The main obstacle to overcome was lack of regioselectivity in the Vilsmeier–Haack reaction of A-ring (hydroxy or methoxy) substituted carbazoles. The group published several different strategies, the first of which involved selective bromination of the required carbazole and conversion to a key nitrile intermediate (Scheme 37).[130] This strategy was similar to that developed by Hogan *et al.* in the late 1980s for the synthesis olivacine **96**.[131,132]

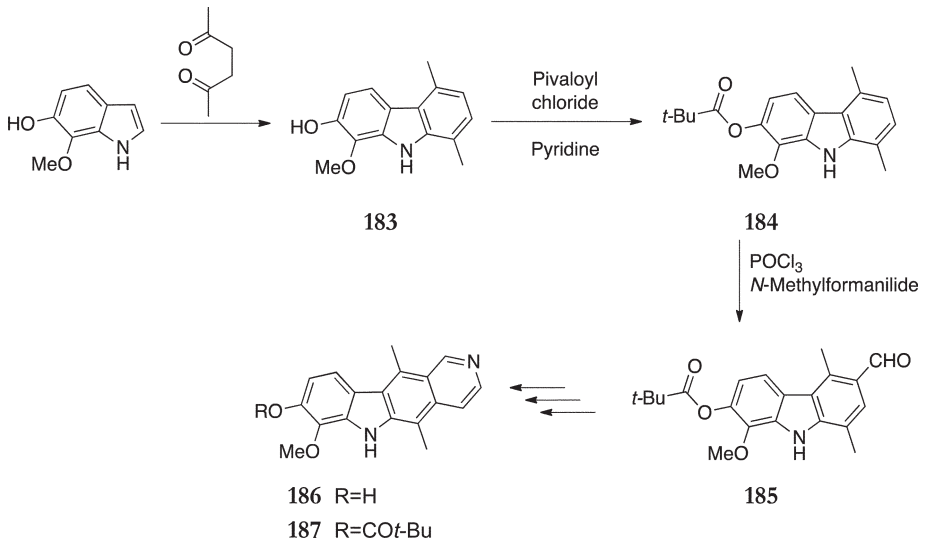
In Shannon's route to 7,9-dimethoxyellipticine **177**, 5,7-dimethoxyindole **178** was condensed with hexane-2,5,-dione to give 6,8-dimethoxy-1,4-dimethyl-9*H*-carbazole **179** in 72% yield. Vilsmeier–Haack reaction of this compound resulted in formylation at the C-5 position rather than the desired C-3 position. When the solvent was changed to dimethylformamide, formylation occurred at both C-5 and C-3. As a result, selective



Scheme 36



Scheme 37



Scheme 38

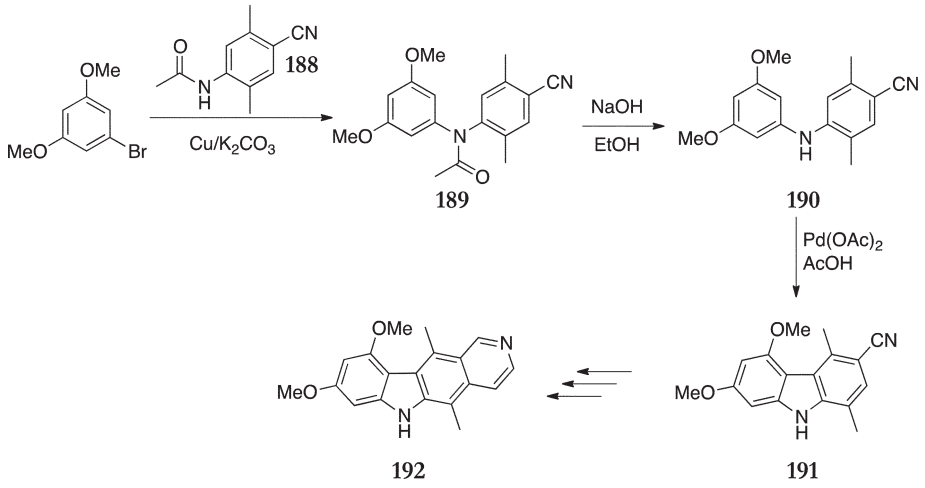
bromination at C-3 was investigated, and treatment of carbazole **179** with pyridinium tribromide in dichloromethane, gave 3-bromo-6,8-dimethoxy-1,4-dimethyl-9*H*-carbazole **180** (72%). Conversion to the nitrile **181** was carried out with copper (I)cyanide (52%) and DIBAL reduction gave the desired 3-formyl-6,8-dimethoxy-1,4-dimethylcarbazole **182** (66%). This was converted to 7,9-dimethoxyellipticine **177** in three steps *via* Jackson's route[125] (53%), with an overall yield of 9% from 5, 7-dimethoxyindole **178**.

In an alternative route to A-ring substituted ellipticines, Shannon's group also used a *t*-butylester as protecting group to direct selective Vilsmeier–Haack formylation (Scheme 38).[133] 6-Hydroxy-7-methoxyindole was converted to the corresponding carbazole **183** and as expected, the Vilsmeier–Haack reaction resulted in formylation at C-6. The group next used an acetate group to protect the alcohol and then successfully formylated at C-3, however the acetate group caused problems later in the synthesis. Finally the *t*-butylester **184** was formed in 81% yield and subjected to Vilsmeier–Haack conditions to give the 3-formyl product **185** (78%). This was converted to the corresponding ellipticine *via* Jackson's route,[125] with the final cyclisation step yielding a mixture of 8-hydroxy-7-methoxyellipticine **186** (44%) and the *t*-butylester **187** (27%).

Later, the same group published the synthesis of 10-hydroxyellipticine *via* the above protection strategy.[134]

Finally, in a third route to A-ring substituted ellipticines, Shannon *et al.* circumvented the problematic Vilsmeier–Haack reaction by using substituted diphenylamines as intermediates (Scheme 39).[134,135] Goldberg coupling of 1-bromo-3,5-dimethoxybenzene with the amide **188** gave **189** (72%), which was hydrolysed to give the diphenylamine **190** in 98% yield. Cyclisation with palladium acetate afforded the carbazole **191**

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Scheme 39

in a disappointing yield of 32%. DIBAL reduction followed once again by Jackson's modified Cranwell–Saxton route[125] gave 8,10-dimethoxyellipticine **192**.

While overall yields were relatively low, this route was used to synthesise a variety of A-ring mono and disubstituted ellipticines.[134,135] Groundwater and Lewis also used a similar strategy in their synthesis of 7-fluoroelliptcine in 1995.[136]

Mustafin *et al.* also published an alternative route towards carbazoles for use in the Cranwell–Saxton route (Scheme 40).[137–139] Reaction of 2,5-dimethylaniline and 3-chlorocyclohexene gave the tetrahydrocarbazole **193** *via* Claisen rearrangement of the initial *N*-alkenylamine followed by intramolecular cyclisation (61%). Dehydrogenation with palladium on carbon gave 1,4-dimethylcarbazole **165** in 87% yield.

While 1,4-dimethylcarbazole **165** was formed in two steps rather than one in the Cranwell–Saxton method, the yield is higher (53% *versus* 36%). The group also prepared 1-methylcarbazole and 1-methoxycarbazole from the appropriate anilines in yields of 64–78%.

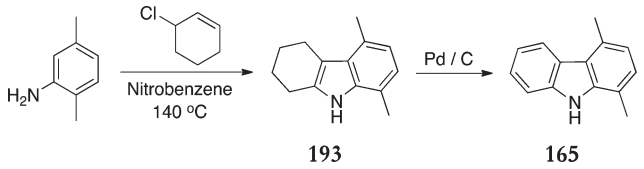
In 2007, Dračínský *et al.* reported a further improvement of the final cyclisation step.[140] Use of a benzenesulfonyl group instead of Jackson's *para*-toluenesulfonyl group improved both yield and reaction time (Scheme 41). Thus, the benzenesylfonyl amine **194** was refluxed with hydrochloric acid in 1,4-dioxane for just 20 min (previously 6 hours) to give a 97% yield of ellipticine **1** (previously 90%). In addition to this, the product crystallised directly from the reaction mixture and no further purification was required.

Recently, Lee *et al.* investigated the use of microwave reaction conditions on the Cranwell–Saxton route, resulting in improved yields and reaction times (Scheme 42).[141] The initial cycloaddition proceeded in 75% yield in the microwave, followed by the conventional Vilsmeier–Haack reaction (55%). Next, a one-pot reaction sequence formed the tosylated amine **169** in 68% yield and the final cyclization step to ellipticine proceeded in 76% yield.

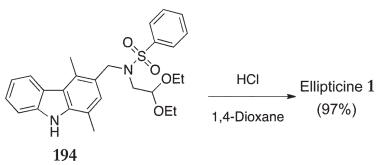
The incorporation of microwave heating in this route resulted in an overall yield of 21%, which compares very favourably with the original route (0.8%) and also Jackson's modification (7%). Reaction times are also dramatically reduced. Other ellipticines prepared under these conditions include 9-bromoellipticine (17% from 5-bromoindole) and 9-nitroellipticine (7% from 1,4-dimethyl-3-formylcarbazole **166**).

Like Shannon[130,133–135] and Mustafin,[137–139] Konakahara *et al.* have continued the focus on improved preparation of carbazoles. Their recently published strategy employs Suzuki–Miyaura coupling to give a biphenyl compound, followed by a double *N*-arylation to form the required carbazole (Scheme 43).[142] First, the polyfunctional aryl halide **195** was prepared in two steps from 2,5-dimethylphenol *via* formylation (70%) and iodination (73%). This was subjected to Suzuki–Miyaura coupling conditions with (2-hydroxyphenyl)boronic acid to give the biphenyl compound **196** in 69% yield. This reaction required optimisation of reaction conditions and solvent and eventually copper acetate was found to significantly decrease the quantities of side products formed. Next, **196** was converted to the ditriflate **197** (92%) and subjected to double *N*-arylation with O-*tert*-butyl carbamate to give 1,4-dimethyl-3-formylcarbazole **166** (62%). The final steps were carried out as previously described,[125] in yields of 67% and 79%, except that a nosyl group was used instead of tosyl.

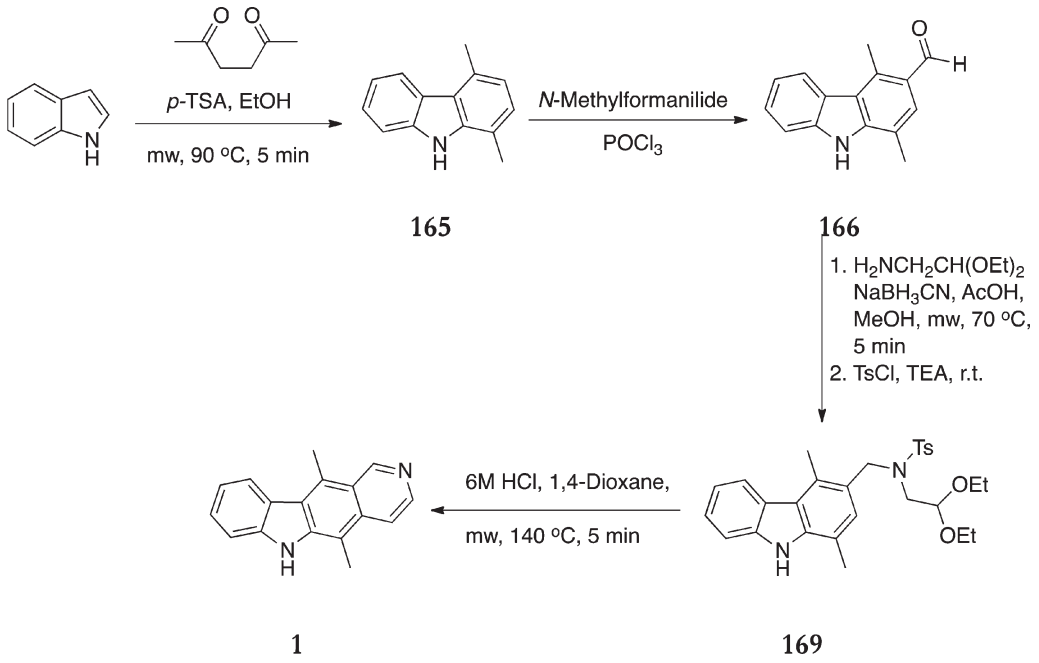
The overall yield of ellipticine was 10.6% from 2,5-dimethylphenol, thus the improvement in yield is not dramatic, and the number of steps involved is increased compared to earlier routes.



Scheme 40

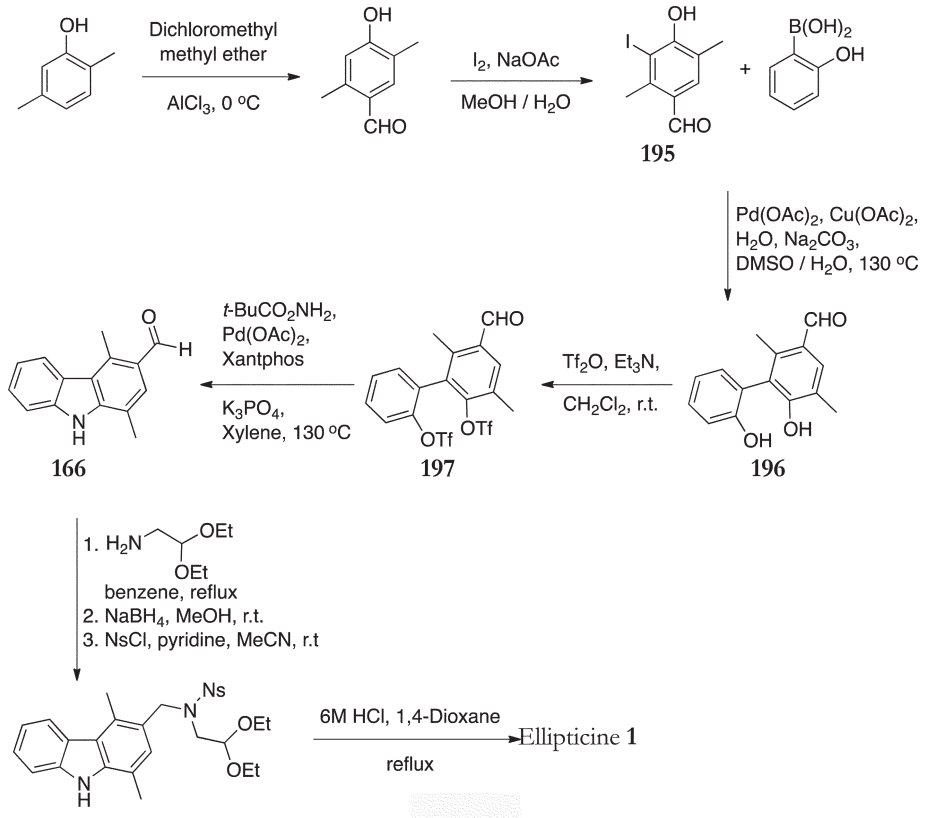


Scheme 41



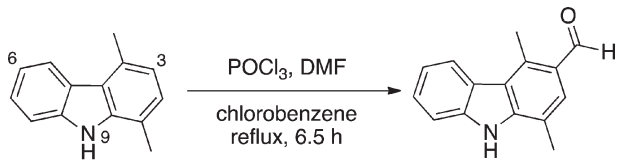
Scheme 42

In our own research group, Deane *et al.* carried out significant optimisation of the Vilsmeier–Haack formylation of 1,4-dimethylcarbazole **165**.[143] Solvent, reaction time and reagent equivalents were investigated, resulting in improved yield and selectivity of 1,4-dimethyl-3-formylcarbazole **166** (Scheme 44). The optimum conditions were 1.01 equivalents of both phosphorous oxychloride and dimethylformamide refluxing in chlorobenzene for 6.5 h, resulting in a 64% yield of 1,4-dimethyl-3-formylcarbazole **166**. The high boiling point solvent and long reaction time were the key factors in the improved yield.



Scheme 43

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165 166

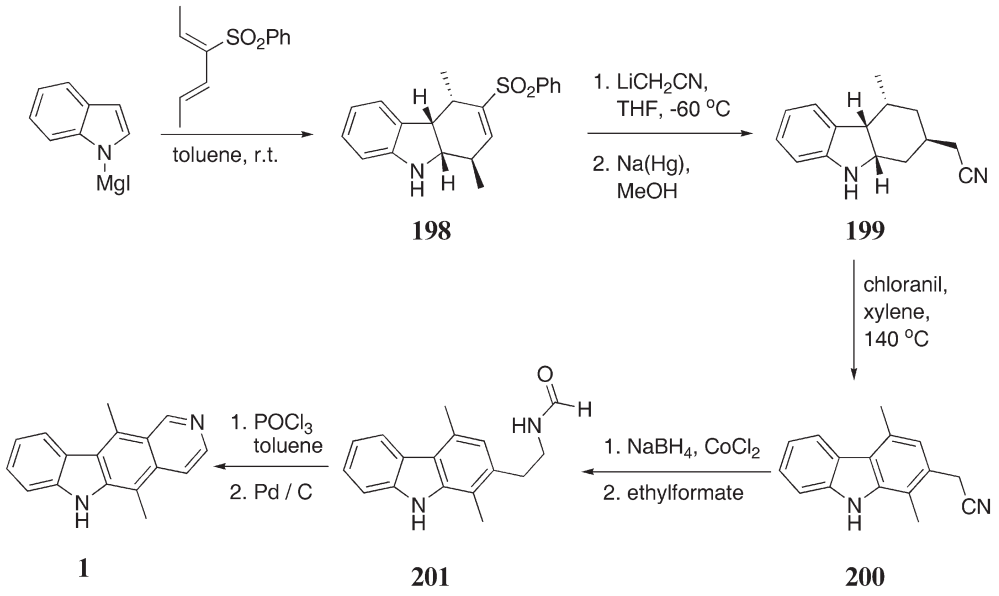
Scheme 44

The Cranwell–Saxton route is by far the most widely investigated and modified synthesis of ellipticine. This has resulted in improved overall yields and preparation of a variety of substituted ellipticines, particularly A-ring substituents.

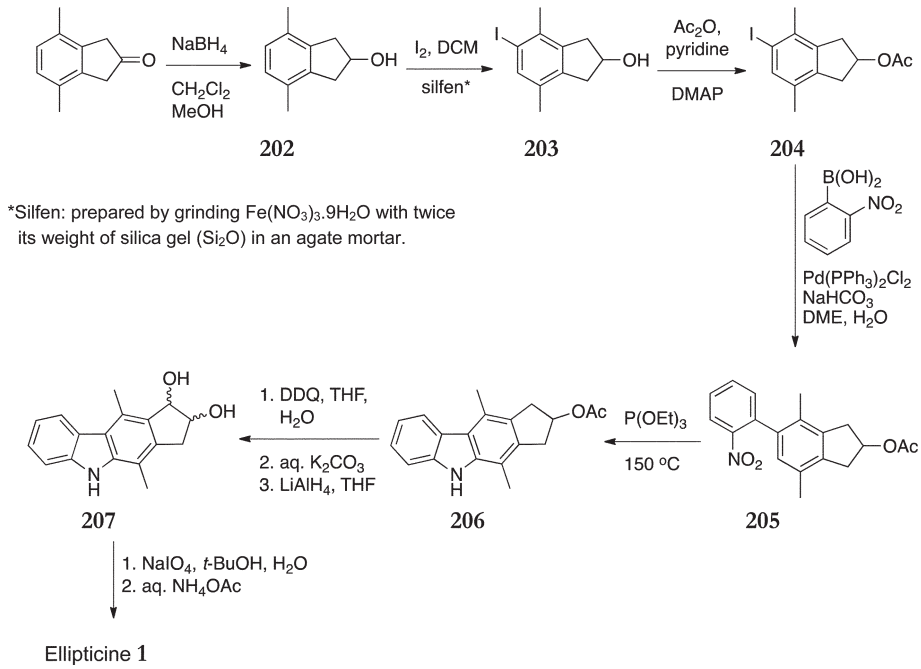
6.2 Other D-type routes

There have been few D-type syntheses of ellipticine which were not related to the Cranwell–Saxton route. One early route published by Bisagni and co-wokers[144] in 1979, towards 1-chloroellipticines was extensively reviewed by Gribble.[75]

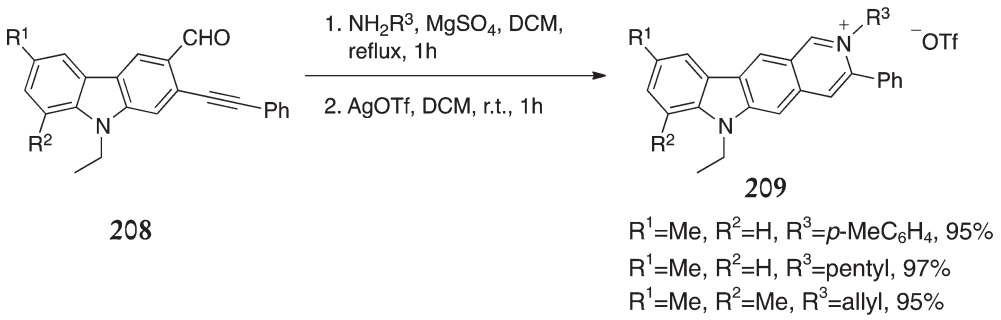
In 1990, Bäckvall and Plobeck published a route to ellipticine and olivacine *via* cycloaddition of 2-phenylsulfonyl-1,3-dienes



Scheme 45



Scheme 46

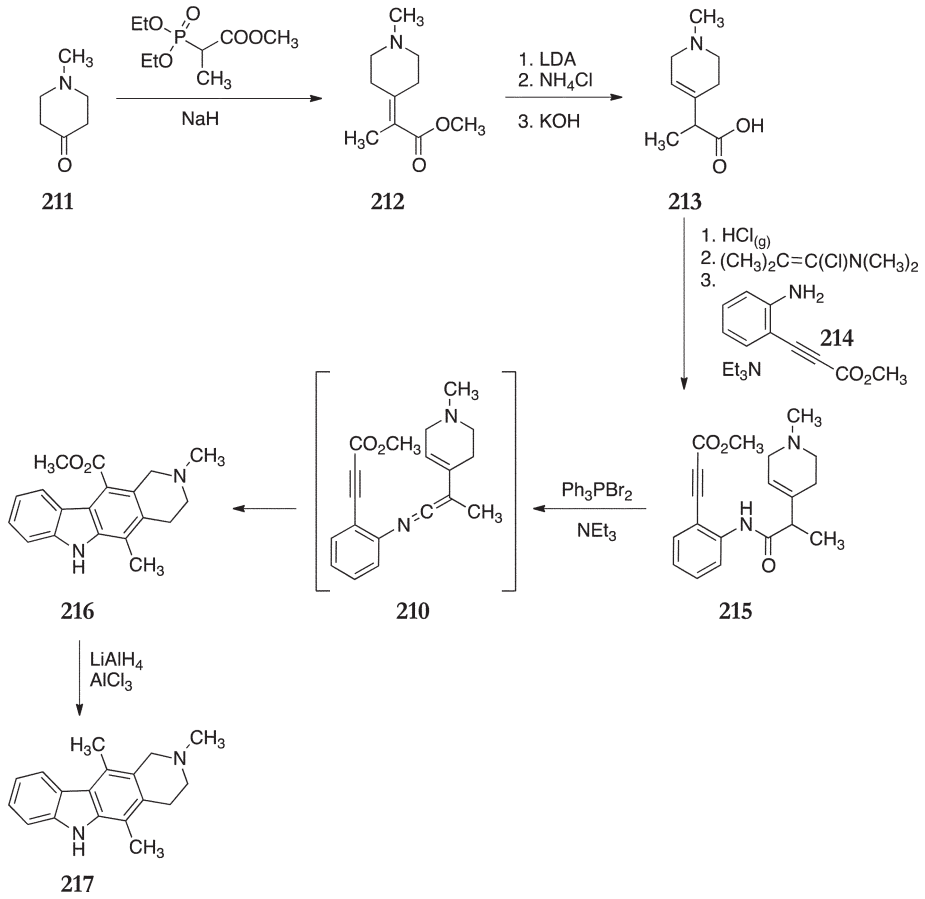


Scheme 47

with indoles (Scheme 45).[145] Reaction of indolylmagnesium iodide and 3-(phenylsulfonyl)-2,4-hexandiene gave the tetrahydrocarbazole **198** in 73% yield as a 7 : 1 mixture of diastereoisomers (major diastereoisomer shown). Michael addition of the lithium salt of acetonitrile, followed by elimination of the sulfone with sodium amalgam gave **199** (92% over two steps). Aromatisation of **199** was attempted by several methods and chloranil in xylene was found to be most successful, affording the carbazole **200** in 64% yield. Reduction and formylation gave the previously known compound **201** (68%), which had been synthesised in 1976 by Oikawa and Yonemitsu[146] *via* a different route and converted to ellipticine by a Bischler–Napieralski cyclisation followed by aromatisation (89%). The overall yield of ellipticine was 26%.

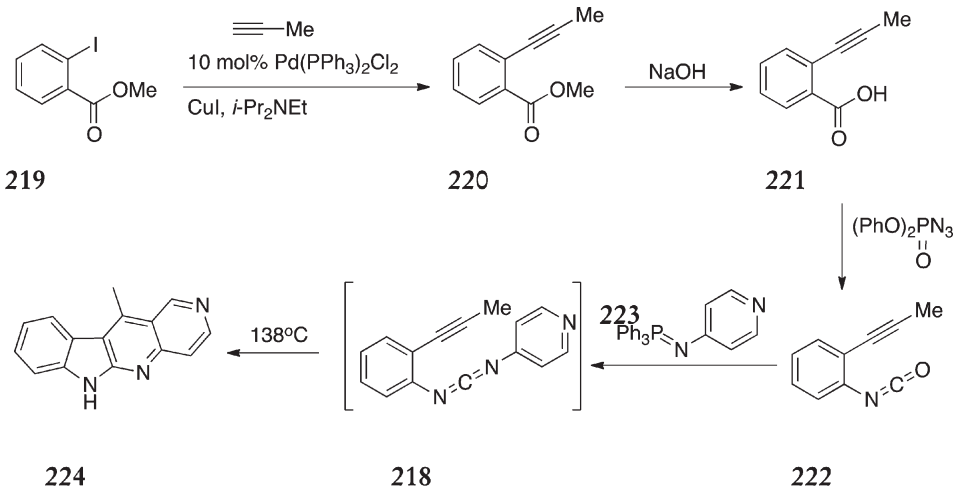
The route was also used to prepare olivacine **96** in 18% overall yield by reacting with acetic anhydride instead of ethylformate in the penultimate step. Again, the olivacine precursor had previously been prepared by Naito *et al.* in 1981 *via* a different route.[147]

More recently, in 2006, Ho and Hsieh reported a synthesis of ellipticine from 4,7-dimethylindene (Scheme 46).[148] Reduction of 4,7-dimethylindene gave the alcohol **202** (99%), which was iodinated to give **203** in 82% yield. Esterification with acetic anhydride gave **204** (99%) and Suzuki coupling of this with (2-nitrophenyl)boronic acid gave the diaryl compound **205** (79%). This was cyclised with triethylphosphite to give **206** in 73% yield. DDQ oxidation of **206** followed by *in situ* reduction with lithium aluminium hydride gave a mixture of *cis* and *trans* diols **207** (68%), which was directly converted to ellipticine in 87% yield.

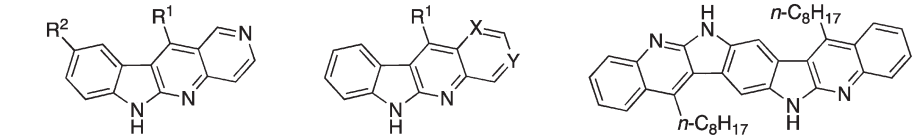


Scheme 48

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Scheme 49



225

a R^1=1-Cyclohexyl, R^2=H

b R^1=Ph R^2=H

cR^1=Me R^2=OMe

226

a X=N, Y=CH

b X=CH, Y=N

227

Fig. 15

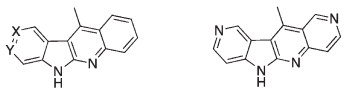
In 2011 Chaitanya and Nagarajan published a new D-type route *via* electrophilic cyclisation of 2-alkynyl-3-carbazolylaldimines **208**.[149] A range of functionalised ellipticinium salts **209** were prepared in > 90% yields by reaction with an amine followed by cyclisation of the resulting imine intermediate with silver trifluoromethanesulfonate (Scheme 47). Unfortunately preparation of the 2-alkynyl-3-carbazolylaldimines **208** was somewhat complicated due to the lack of regioselectivity of the Vilsmeier–Haack formylation previously described in the Cranwell–Saxton series.

7. B+C type syntheses

B+C Type syntheses involve simultaneous cyclisation of the B and C rings of ellipticine, this has generally been accomplished by intramolecular cyclisation *via* radical mechanisms.

In the course of their work on intramolecular Diels–Alder cycloaddition reactions for the formation of carbazoles, Differding and Ghosez developed the first B+C type route to ellipticine.[150] The key step involved Diels–Alder cycloaddition of acetylenic vinylketenimines **210**. *N*-Methylpiperidone **211** was converted to the conjugated ester **212** *via* a Wittig–Horner reaction (75%). This was treated with lithium diisopropylamide followed by quenching with ammonium chloride to give a β, γ unsaturated ester, which was directly hydrolysed to the acid **213** (75%). Carboxylic acid **213** was converted to an acid chloride with hydrogen chloride and Ghosez's reagent and then coupled with the aniline derivative **214** to give anilide **215** (75%). The vinylketenimine **210** was successfully generated and underwent intramolecular cycloaddition *in situ* to give **216** (50%). Finally, reduction gave *N*-methyl-tetrahydroellipticine **217** (71%) (Scheme 48) which had previously been converted to ellipticine.[151]

In 2000, a new B+C type route was published by Zhang *et al.* towards the synthesis of 5-aza analogues of ellipticine (Scheme 49).[152] The key step involved generation of benzoenynyl carbodiimides **218** and thermolysis to give the 6*H*-indolo[2,3-*b*][1,6]naphthyridines. Initially, methyl-2-iodobenzoate **219** underwent Pd-catalysed cross-coupling to give the alkyne derivative **220** in 98% yield. This was hydrolysed with base to give the corresponding acid **221** (61%), followed by treatment with diphenyl phosphorazidate to give **222** *via* a modified Curtius rearrangement. The aza-Wittig reaction of **222** and iminophosphorane **223** produced the benzoenynyl carbodiimides **218** *in situ* which were submitted to thermolysis to give the 6*H*-indolo[2,3-*b*][1,6]naphthyridine **224** in 49% yield.

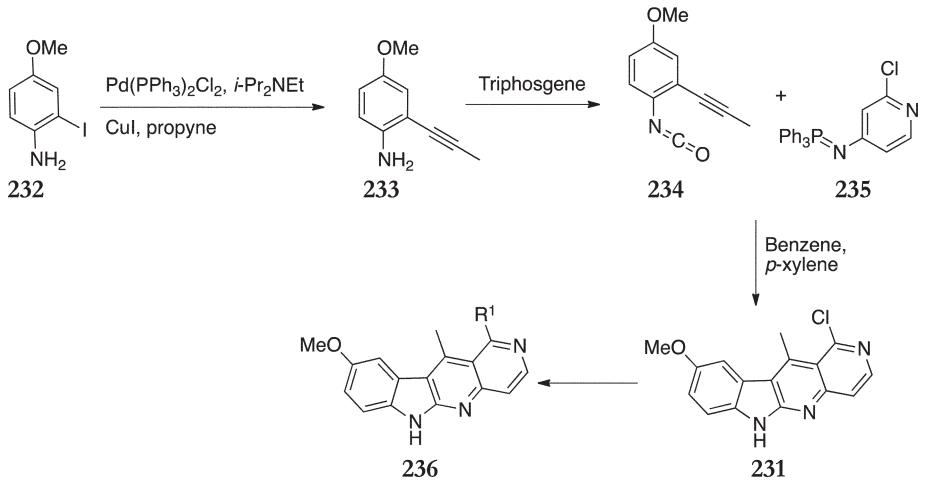


228 X=N, Y=CH

229 X=CH, Y=N

230

Fig. 16



Scheme 50

Table 2

236	R^1
a	$NH(CH_2)_3N(CH_3)(CH_2)_3NH_2$
b	$NH(CH_2)_3NH(CH_2)_3NH_2$
c	$HN(H_2C)_3-N\langle\rangle N-(CH_2)_3NH_2$

This route was used to synthesise a range of substituted 6*H*-indolo[2,3-*b*][1,6]naphthyridines **225a–c**, D-ring analogues **226a** & **b**, and a dimer with two linearly fused indoloquinoline units **227** (Fig. 15).

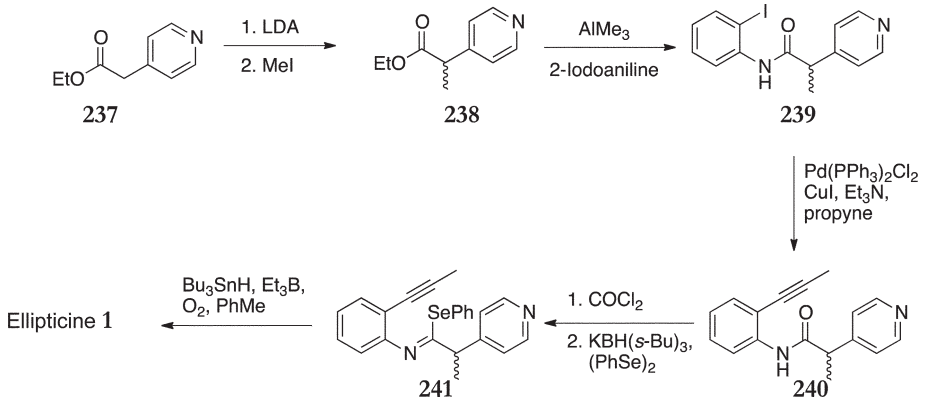
Subsequently, the same group published work on A-ring analogues *via* the same route, starting from a substituted pyridine in place of methyl-2-iodobenzoate **219**.[153] This gave compounds **228**, **229** & **230** in good to moderate yields (Fig. 16).

Moody *et al.* modified this route to produce 5-aza-1-chloro-9-methoxyellipticine **231** (Scheme 50 & Table 2).[154] 2-Iodo-4-methoxyaniline **232** was subjected to Sonogashira coupling to give the alkyne derivative **233** (86%), which was converted to the isocyanate **234** in 96% yield using triphosgene. The aza-Wittig reaction and radical cycloaddition was accomplished in one pot by heating **234** with the phosphorane **235** to give 5-aza-1-chloro-9-methoxyellipticine **231** in 17% yield. The chlorine at position 1 was then readily replaced with amine side chains to give **236a–c**.

Pederson *et al.* developed a radical cascade route to ellipticine from ethyl-2-(4-pyridyl)acetate **237** (Scheme 51).[155] Methylation was effected with lithium diisopropylamide followed by methyliodide to give **238** in 93% yield. Amide coupling with trimethylaluminium and 2-indoaniline yielded the amide **239** (81%). Sonogashira coupling conditions were utilised to introduce the alkyne **240** (88%), which was then converted to the imidoyl selanide **241** (48%). The final radical cyclisation step was accomplished with triethylboron, oxygen gas and tributyltin hydride to give ellipticine in 61% yield.

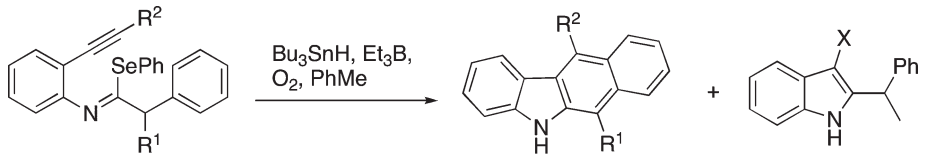
The utility of this route was demonstrated by synthesis of a range of substituted benzo[*b*]carbazoles (Scheme 52 & Table 3). Variation of the alkyne used in the Sonogashira coupling reaction gave a range of imidoyl selanides **242a–f**, which underwent radical cyclisation to benzo[*b*]carbazoles **243a–f**. In the case of benzo[*b*]carbazoles **243 e & f**, indole side products **244 e & f** were also isolated.

The overall yield of ellipticine from this route was 19%. In an effort to make the route more attractive on a large scale, the toxic tributyltin hydride in the final step was replaced with



Scheme 51

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242a-f 243a-f 244

Scheme 52

Table 3 Yields of substituted benzo[*b*]carbazoles prepared by Pederson *et al.*[155]

	R^1	R^2	% Yield 243	**244**
a	H	Ph	33	—
b	CH_3	Ph	55	—
c	CH_3	CH_2OAc	40	—
d	CH_3	H	18	—
e	CH_3	$SiMe_3$	0	X=CHO, 33%
f	CH_3	CO_2Me	19	X=CH_2CO_2Me, 29%

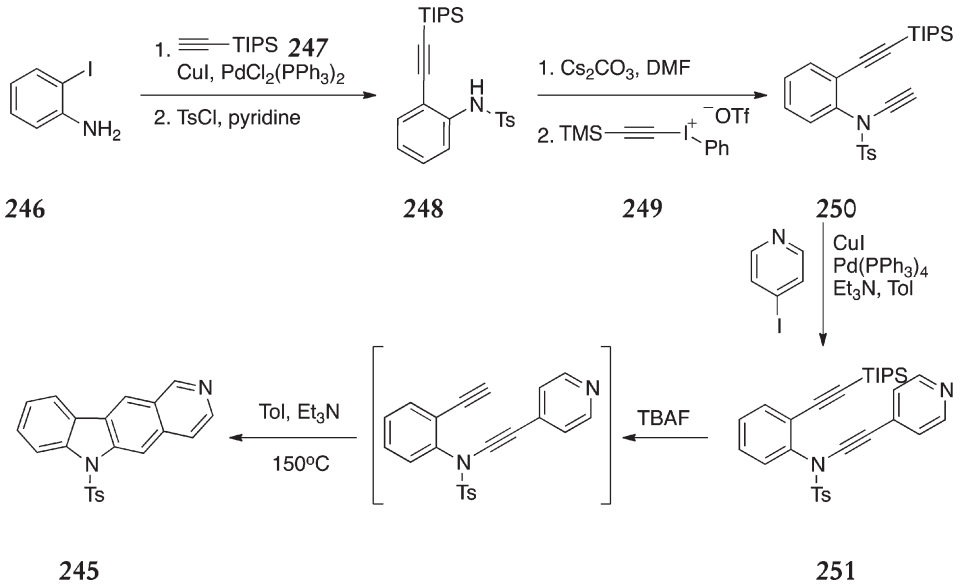
tributylgermanium hydride (Bu_3GeH), which resulted in a 49% yield (*versus* 61% with tributyltin hydride). The main advantage of this route lies in the scope for variation at C-5 and C-11. The initial alkylation could be carried out with a variety of alkylating agents and, along with use of different alkynes in the Sonogashira step, there is scope for a wide range of substituted ellipticines.

In the course of their work on intramolecular dehydro Diels–Alder reactions of *N*-(*o*-ethynyl)arylamides, Martínez–Esperón *et al.* developed a new route to the demethylated ellipticine derivative **245** (Scheme 53).[156] Sonogashira coupling of *o*-iodoaniline **246** and the alkyne **247**, followed by *N*-tosylation gave **248** in 78% yield. This was treated with the (trimethylsilyl)ethynyliodonium salt **249** to give **250** in 85% yield. A second Sonogashira coupling with 4-iodopyridine gave the arylamide **251**, which was not isolated but treated *in situ* with tributylammonium fluoride, followed by heating, to give the demethylated ellipticine derivative **245** (21%).

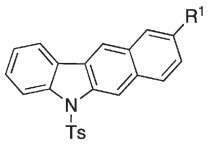
A variety of substituted benzo[*b*]carbazoles **252** were prepared in a similar fashion in moderate to good yields from the corresponding arylamides (Fig. 17).

8. Summary

While the Cranwell–Saxton route is clearly the most widely investigated and modified synthesis of ellipticine, it is not the highest yielding or most versatile route.[123] Jackson's modification improved the overall yield from 0.8% to 8% and Lee's incorporation of microwave heating gave further improvement to 21%.[125,141] Of the B-type routes, Miller's nitrene insertion gave a 40% yield of ellipticine over seven steps and was applied to the synthesis of the analogue, indazolo[2,3-*b*]isoquinoline.[88] In a similar vein, Liu and Knochel's nitrene route offered yields of 31–40% over five steps, but with greater variation of substituents.[90] In the C-type category, the early routes employed harsh conditions and were low yielding.[2,93] Gribble's ketolactam route was the most important progression in this area and easily stands out as the highest yielding synthesis of ellipticine overall (59% over five steps).[100] It has also been shown to be versatile for preparation of both substituted ellipticines and analogues.[102–106,108] Several of the C-type cycloaddition routes may be useful if both ellipticine and isoellipticine are required, however the issue of regioselectivity still remains problematic, and those routes which are regioselective suffer from much lower yields.[118,120] Finally, B+C type routes have primarily been used



Scheme 53



252a R^1=NO_2, 60%
252b R^1=OMe, 50%
252c R^1=Cl, 82%
252d R^1=F, 73%

Fig. 17 Substituted benzo[*b*]carbazoles.

for the synthesis of ellipticine analogues, in particular, Zhang's route offers an attractive preparation of 5-azaellipticines and was also modified by Moody.[152,154] Overall, the interest in ellipticines and related pyridocarbazoles is set to expand given the diversity of structure and emerging bioactivity inherent in this compound class.

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