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Recent syntheses of ellipticine and its derivatives

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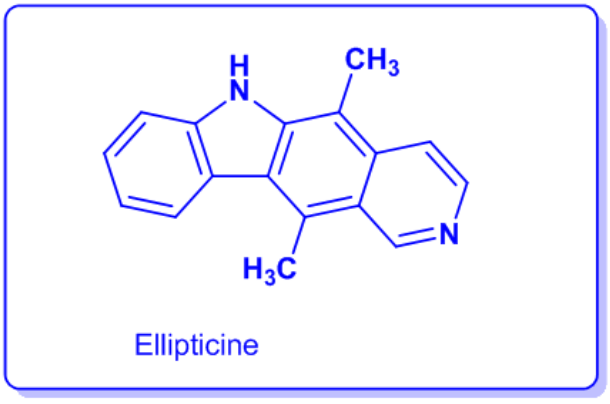
Abstract

The pyrido[4,3-b]carbazole alkaloid, ellipticine, was attracting considerable interest for many years due to its pronounced antitumor activity. We review the most important achievements in the field of ellipticine synthesis and its derivatives since 2012.



Keywords: Ellipticine, ellipticine derivatives, alkaloids, synthesis

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1. Introduction

The natural plant product ellipticine[1-7] was isolated in 1959 from the Australian evergreen tree, Ochrosia elliptica, of the Apocynaccae Apocynaceae. This compound was found to be a promising anticancer drug. So, the syntheses of ellipticine and its derivatives have been reported by many groups.[8-27]

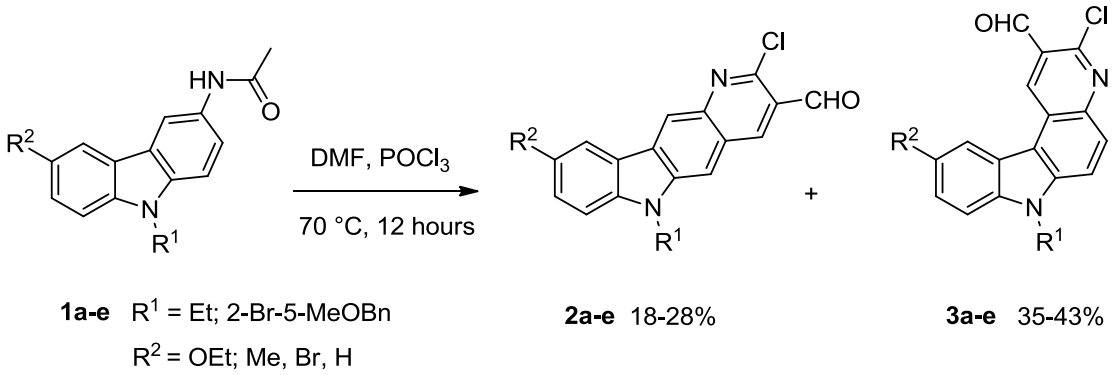
The planar polycyclic structure was found to interact with DNA through intercalation, exhibiting a high DNA binding affinity (10^6 M^{-1}). The presence of protonatable ring nitrogens distinguished ellipticine from other simple intercalators. Both monocationic and uncharged species were found to be present under physiological conditions. The position charge stabilized the binding of ellipticine to nucleic acids, while the more lipophilic uncharged compound was shown to readily penetrate membrane barriers. The structural nature of these compounds offers a plausible basis for the implication of multiple modes of action, including DNA binding, interactions with membrane barriers, oxidative bioactivation and modification of enzyme function; most notably that of topoisomerase II and telomerase. Pharmaceutically, a number of toxic side effects have been shown to be problematic, but the amenability of ellipticine towards systematic structural modification has permitted the extensive application of rational drug design. A number of successful ellipticine analogs have been designed and synthesized with improved toxicities and anticancer activities.[28-29] More recently the synthetic focus has broadened to include the design of hybrid compounds, as well as drug delivery conjugates. Considerable research efforts have been directed towards gaining a greater understanding of the mechanism of action of these drugs that will aid further in the optimization of drug design.

This article provide an overview of the various syntheses of ellipticine from the years 2013 to 2017. Although a previous review by McCarthy *et al*. has appeared in 2012,[30] some reports were missing from their compilation. Thus, we have chosen to cover the literature under one section up to December 2017, omitting those works which have already been reported in the previous review.

2. Synthesis of Ellipticine and Derivatives

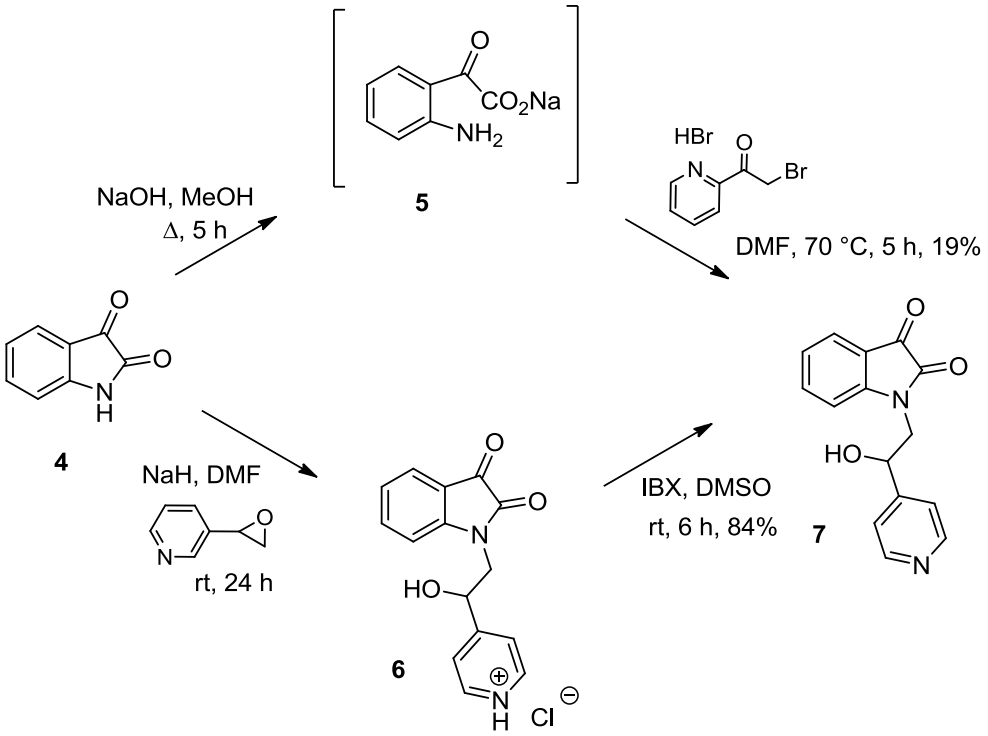
In 2014, Meesala et al.[31] have developed a simple and an efficient method to synthesize a new series of ellipticine analogues using the Vilsmeier–Haack reagent (Scheme 1). They described the synthesis of pyrido[3,2-*b*]carbazoles and pyrido[2,3-*c*]carbazoles by treating *N*-(carbazol-3-yl)acetamides **1a-e** with DMF (2.5 equiv) and $POCl_3$ (10.0 equiv) at 70 °C for 12 hours. The reaction works well with different types of *N*-(carbazol-3-yl)acetamide derivatives and provides the corresponding linear and angular products. The angular products were obtained as the major isomers compared to the linear products.

Since the pyridocarbazoles contain the reactive substituents chlorine and aldehyde, these can be utilized for further heteroannulations to develop novel pyridocarbazole-based heterocyclic systems which may exhibit interesting biological properties.



Scheme 1. Synthesis of pyridocarbazoles **2** and **3**.

Nagarajan et al.[32] reported a simple and efficient route to the synthesis of ellipticine quinone **12** (Scheme 3) from isatin **4**. The first key step is the synthesis of **7** from isatin using various alkylating reagents (Scheme 2). They performed reaction between sodium 2-(2-aminophenyl)-2-oxoacetate **5** and 2-bromo-1-(pyridin-4-yl)ethanone hydrobromide in DMF at 70 °C for 5 h affording **7** in 17% yield. The next step is the rearrangement of **7** to carboxylic acid **9**. Hydrolysis of compound **7** afforded **9** through an intermediate **8** along with easily separable decarboxilated product **10** in 76% and 24% yield respectively (Scheme 3).

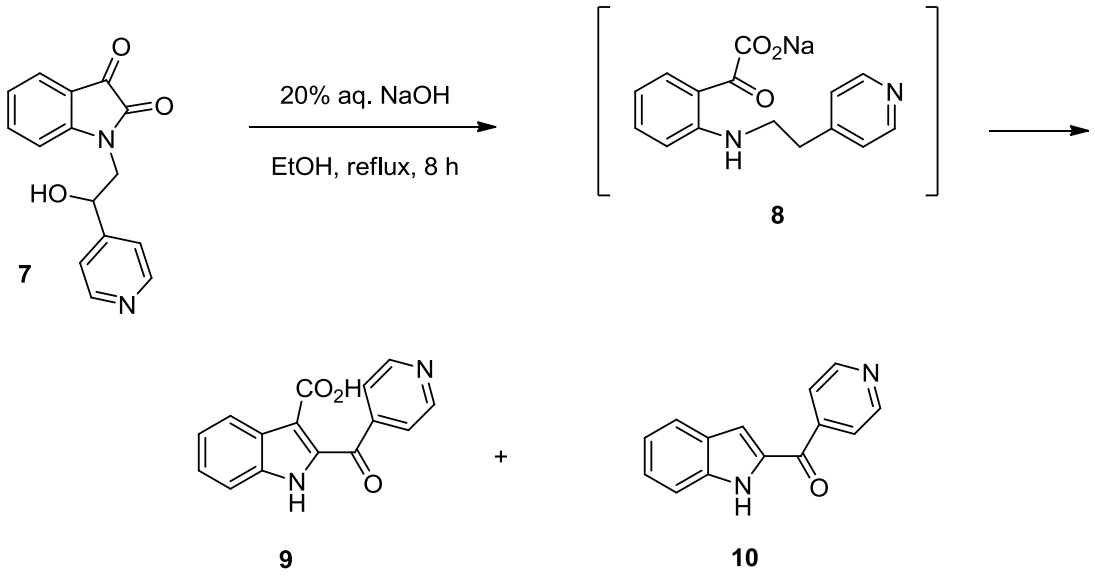


Scheme 2. Synthesis of **7**.

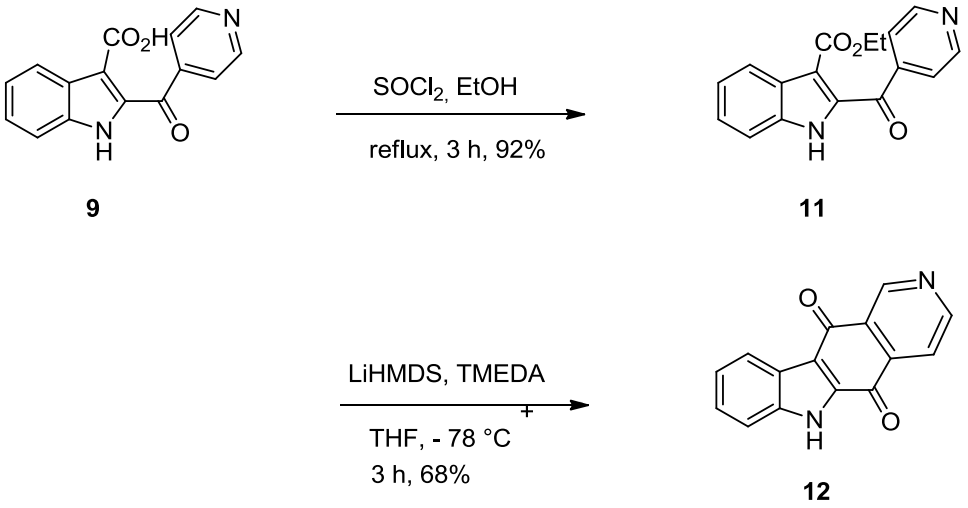
The key intermediate **9** was subjected to esterification with ethanol to give corresponding ester **11** in 92% yield. The ortho-lithiation of **11** by utilizing of LiHMDS/TMEDA produced the target ellipticine quinone **12** in good yield (Scheme 4).

In 2014, Nagarajan et al.[33] reported an expedient synthesis of the pyrido[4,3-*b*]carbazole alkaloids, ellipticine **29** and 9-methoxyellipticine **30** (Scheme 7) over seven steps from known 1,4-dimethylcarbazoles **13**

and **14** with 23% and 25% overall yields, respectively. For the first time, they have utilized the H_3PO_4-mediated Friedel–Crafts cyclodehydration as a key step to construct these pyrido[4,3-*b*]carbazole alkaloids.

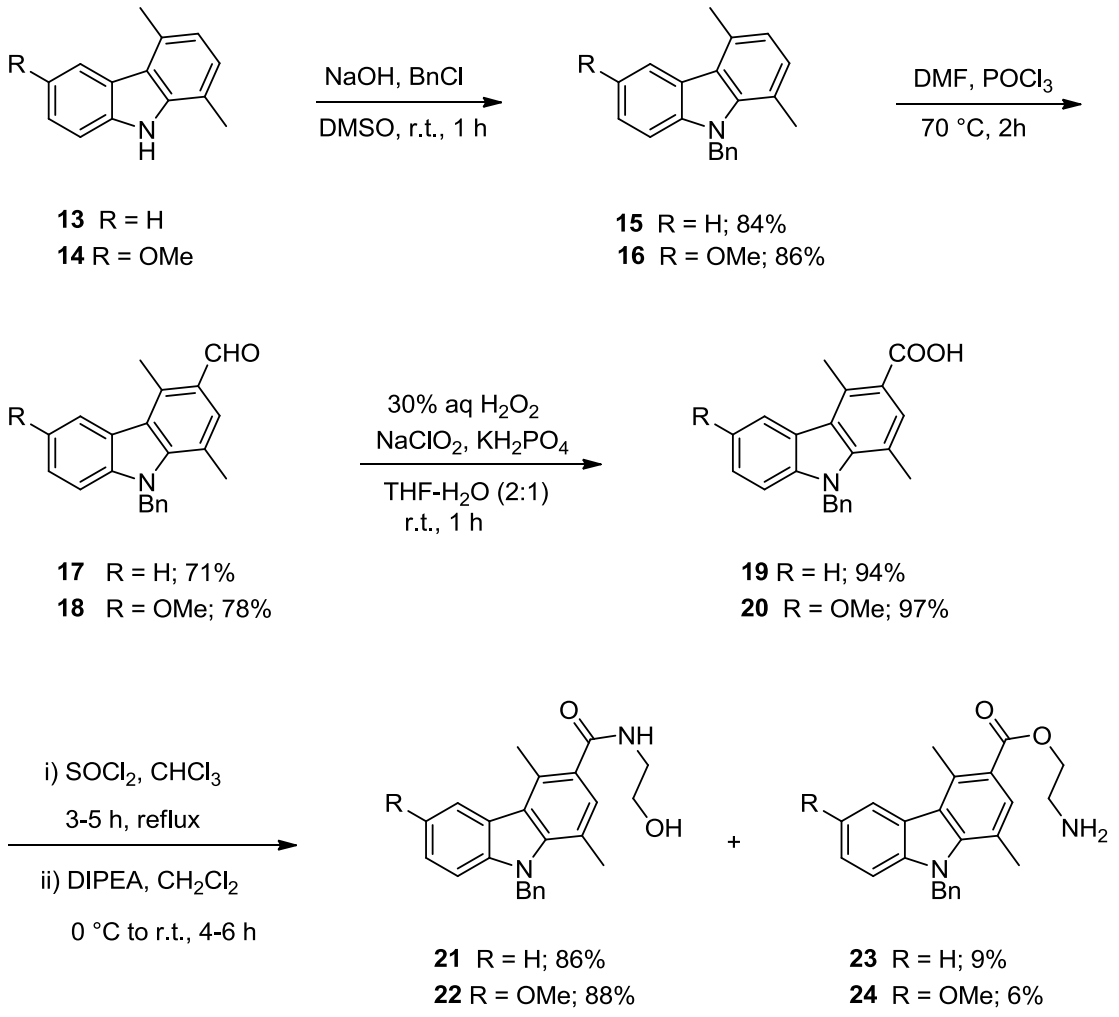


Scheme 3. Indoledione-indole rearrangement of **7** to carboxylic acid **9**.



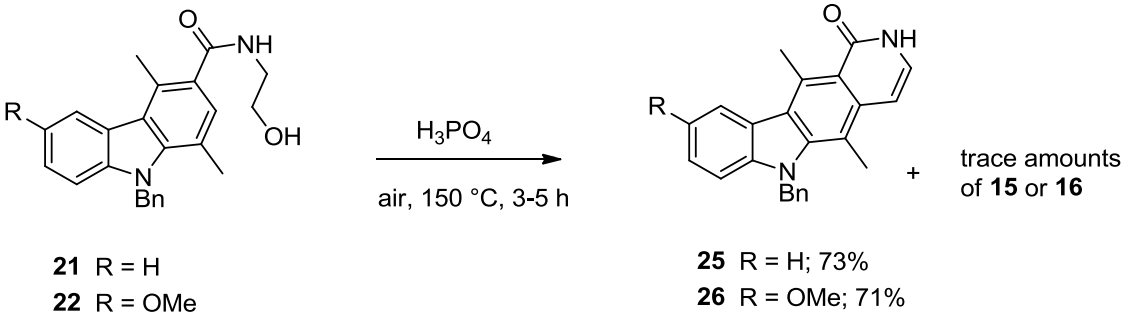
Scheme 4. Synthesis of ellipticine quinone **12**.

Their synthesis commenced with the preparation of 9-benzyl-1,4-dimethylcarbazoles **15** and **16** from the corresponding 1,4-dimethylcarbazoles, which can be readily prepared by literature methods (Scheme 5). N-Benzylation of **13** and **14** afforded **15** and **16** in excellent yields. Next, Vilsmeier– Haack formylation of **15** and **16** with DMF and $POCl_3$ at 70 °C furnished aldehydes **17** and **18**. Subsequent Pinnick oxidation, using 30% aqueous H_2O_2, $NaClO_2$, and KH_2PO_4 in THF–H_2O (2:1), transformed **17** and **18** into acids **19** and **20** in 94% and 97% yields, respectively. Acids **19** and **20** were converted into the corresponding acid chlorides using $SOCl_2$, followed by amidation with 2-aminoethanol afforded the desired amides **21** and **22** along with esters **23** and **24** in smaller amounts (Scheme 5).



Scheme 5. Synthesis of 9-benzyl-*N*-(2-hydroxyethyl)-1,4-dimethyl-9*H*-carbazole-3-carboxamides **21** and **22.**

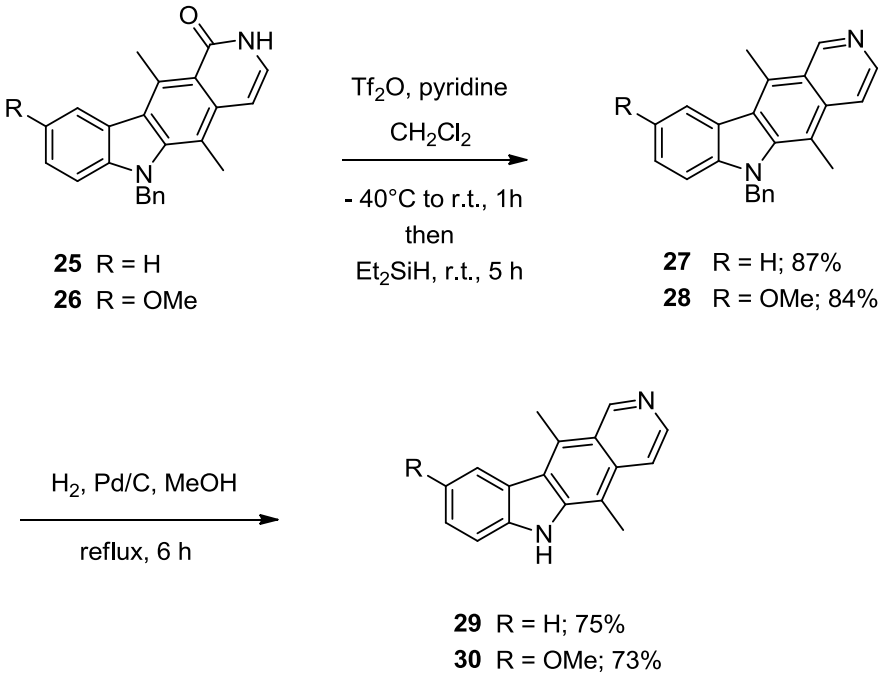
Treatment of **21** or **22** with H_3PO_4 in air at 150 °C furnished dihydropyridocarbazolones **25** and **26** in 73% and 71% yields, respectively. Under these rather forcing conditions, they also observed the formation of the oxidative cleavage products **15** or **16** in trace amounts (Scheme 6).



Scheme 6. The key H_3PO_4-mediated Friedel-Crafts cyclodehydration.

Having assembled the tetracyclic scaffold of the natural products, two simple transformations remained in order to access ellipticine **29** and 9-methoxyellipticine **30**. This would involve conversion of the amide group

into an imine followed by the cleavage of the *N*-benzyl group in the intermediates **25** and **26**. As shown in Scheme 7, the first of these challenges was achieved by reductive amination using mild reagents Tf_2O and Et_3SiH. This generated *N*-benzylellipticines **27** and **28** in good yields. Next, the N-benzyl group was removed from **27** and **28** by using 10% palladium on carbon to furnish ellipticines **29** and **30**.



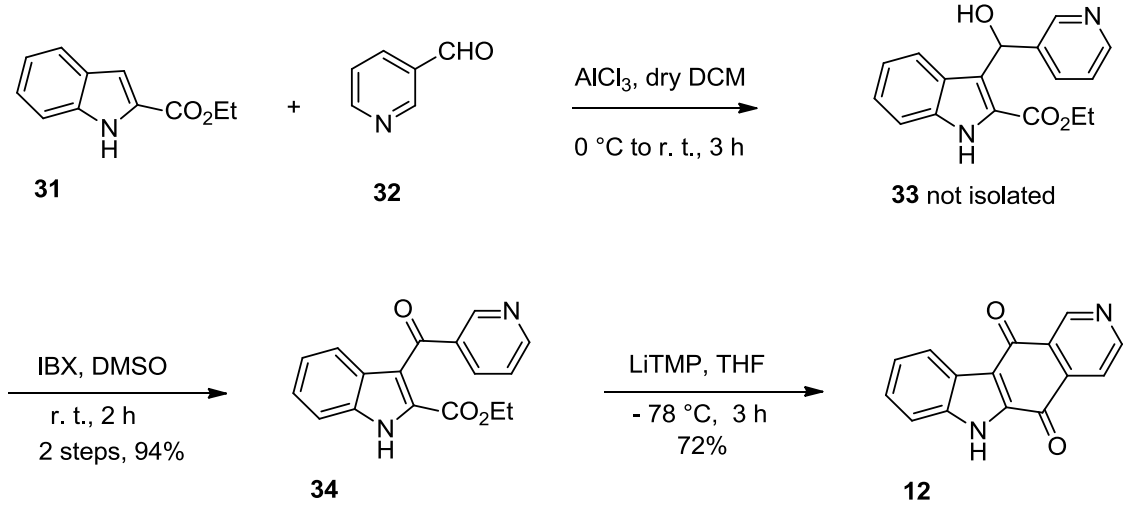
25 R = H
26 R = OMe

27 R = H; 87%
28 R = OMe; 84%

29 R = H; 75%
30 R = OMe; 73%

Scheme 7. Synthesis of ellipticine **29** and 9-methoxyellipticine **30**.

The same authors reported[34] later a novel and concise total synthesis of biologically important ellipticine quinone and calothrixin B in three-step sequences of 67% and 38% good overall yields, respectively. They have also extended this route to the synthesis of olivacine in 16% overall yield over 6 steps. Their synthetic approach for these compounds is superior to that of previously reported methods in terms of availability of starting materials, overall yields, and the number of steps used.



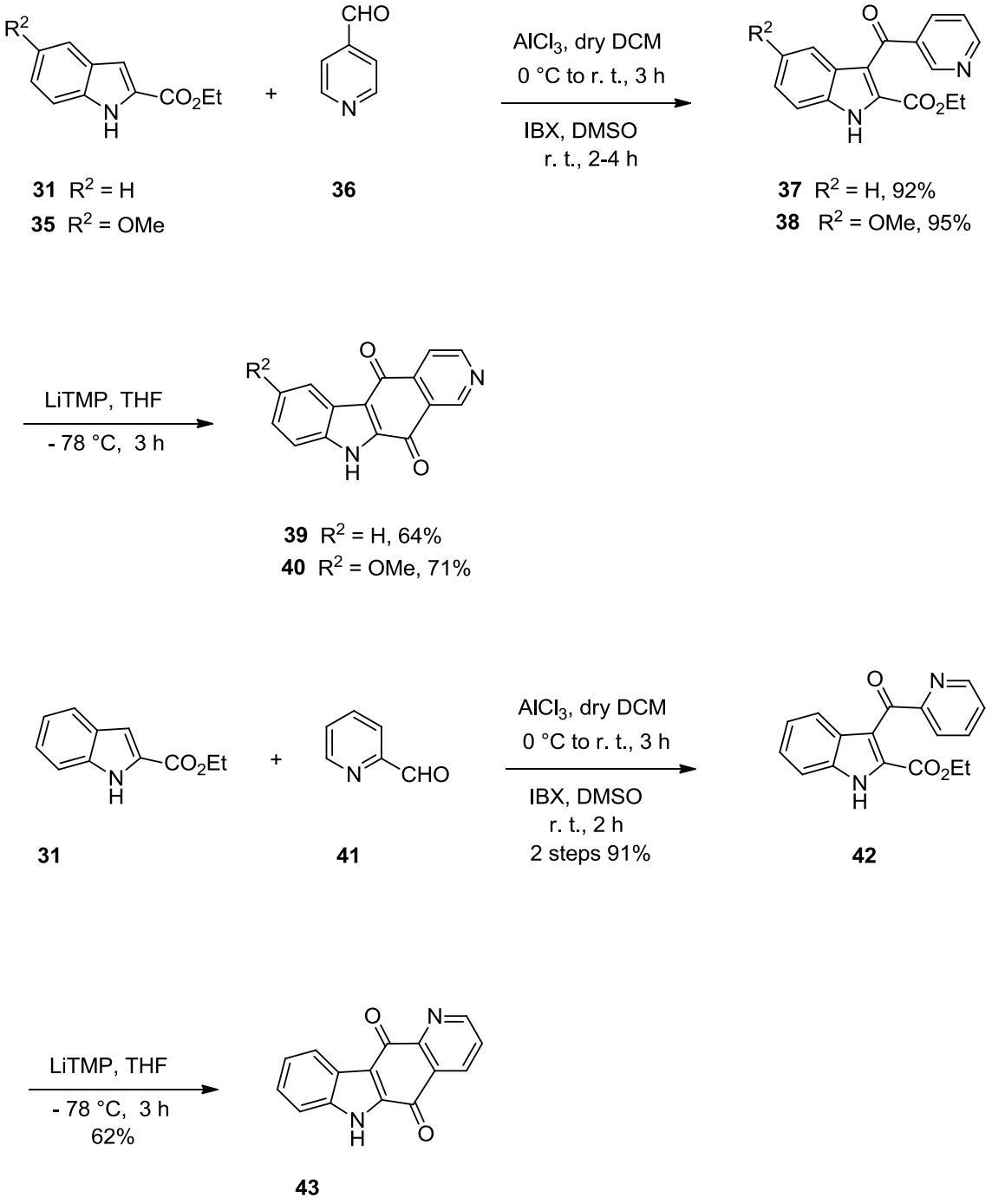
31 **32** **33** not isolated

34 **12**

Scheme 8. Synthesis of ellipticine quinone.

They treated commercially available ethyl 1H-indole-2-carboxylate **31** with pyridine-3-carboxaldehyde **32** in presence of $AlCl_3$ followed by oxidation using IBX in DMSO, giving ketone **34** in 94% yield. The carbinol formed **33** was not isolated from the reaction mixture, and subsequently they carried out oxidation after the reaction work up. The ketone **34** was then subjected to directed o-lithiation reaction using LiTMP (lithium tetramethylpiperidide) as a base to afford a single regioisomer **12** in 72% yield. Thus, ellipticine quinone **12** was obtained in 3 steps and 67.6% overall yield (Scheme 8).

Similarly, isoellipticine quinones **39** and **40** can be obtained by varying pyridine part **36** as shown in Scheme 9. Also the other isomer of ellipticine quinone **43** was synthesized by using pyridine-2-carboxaldehyde **41**.



31 R^2 = H
35 R^2 = OMe

36

37 R^2 = H, 92%
38 R^2 = OMe, 95%

39 R^2 = H, 64%
40 R^2 = OMe, 71%

31

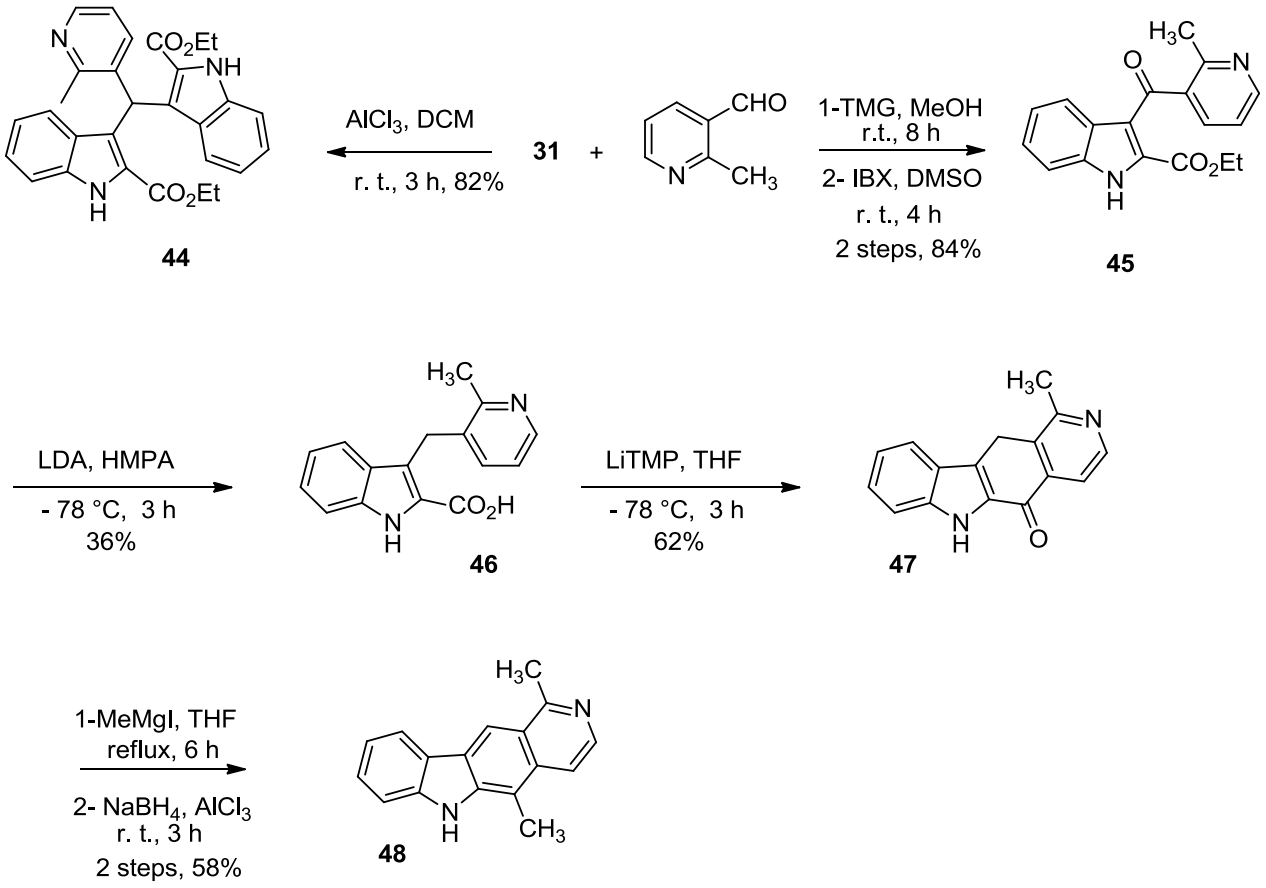
41

42

43

Scheme 9. Synthesis of isomeric ellipticine quinones.

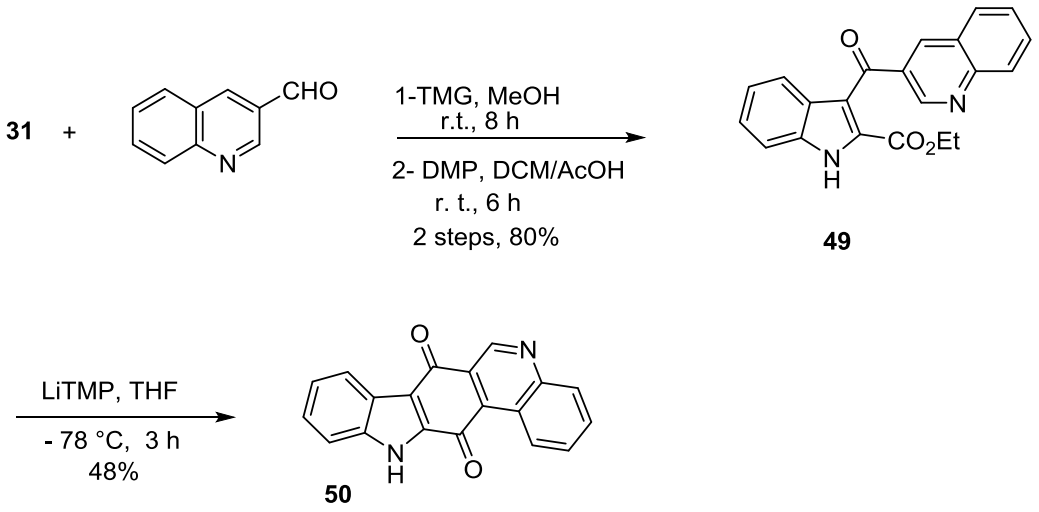
They have successfully applied their synthetic route to the synthesis of olivacine **48** and calothrixin B **51**. Treatment of **31** with 2-methylnicotinaldehyde in the presence of 1,1,3,3-tetramethylguanidine (TMG) in MeOH at room temperature followed by oxidation using IBX afforded the ketone **45** in 84% yield. Wolff−Kishner reduction of the ketone **45** gave reduced compound **46**. The cyclized compound **47** was obtained by treating **46** with LDA/HMPA at −78 °C. Finally, the addition of MeMgI into **47** followed by treatment upon $NaBH_4/AlCl_3$ (3:1) in dry THF at room temperature produced **48** in 58% yield. Thus, olivacine **48** was obtained in 6 steps and 15.6% overall yield as shown in Scheme 10.



Scheme 10. Synthesis of olivacine **48**

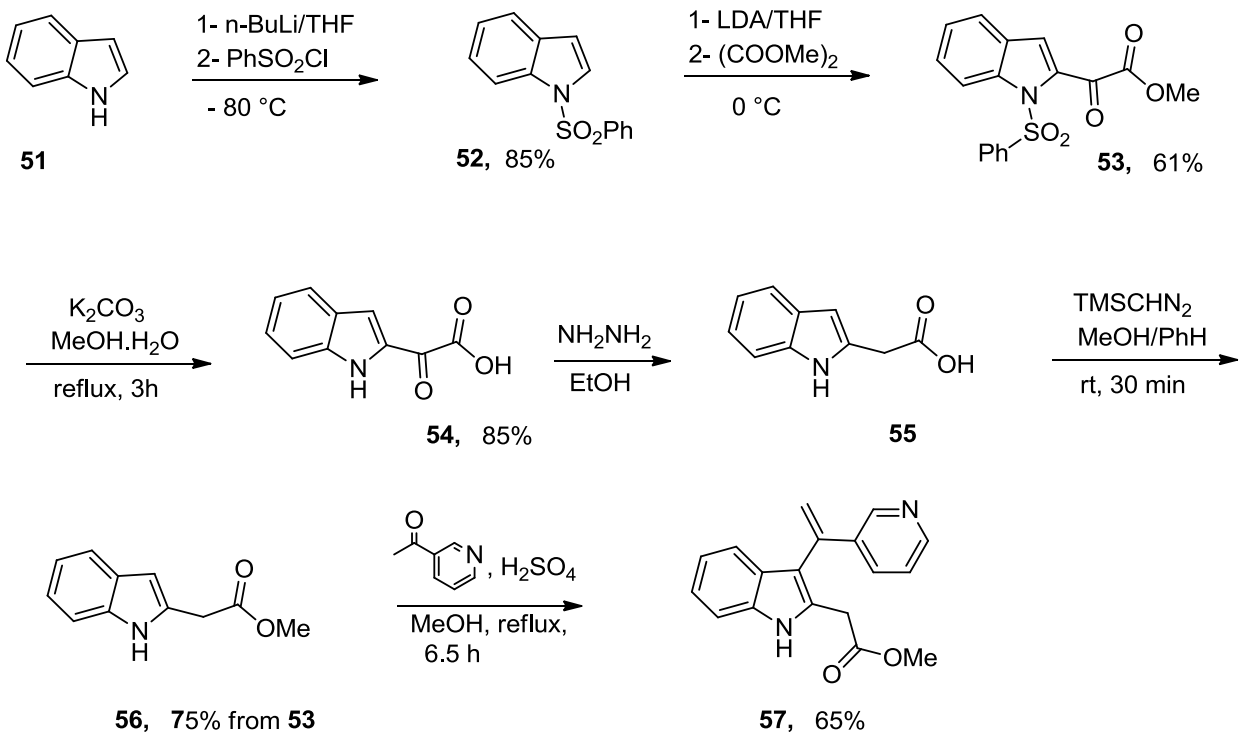
The synthesis of calothrixin B **50** is outlined in Scheme 11. The reaction of **31** with quinoline-3-carboxaldehyde in the presence of TMG in MeOH followed by oxidation with Dess−Martin periodinane (DMP) in DCM/ AcOH (9:1) at room temperature gave the ketone **49** in 80% yield. Then intramolecular directed *o*-lithiation reaction of **49** in the presence of LiTMP afforded **50** in 48% yield. Thus, calothrixin B **50** was obtained in three steps and 38.4% overall yield.

In 2014, Konakahara et al.[35] developed a simple and efficient synthetic method of novel four ellipticine derivatives in good to high yields. Moreover three kinds of novel pyridocarbazole-5-carboxylate derivatives were synthesized. All these new compounds exhibited higher solubility in water than ellipticine itself.



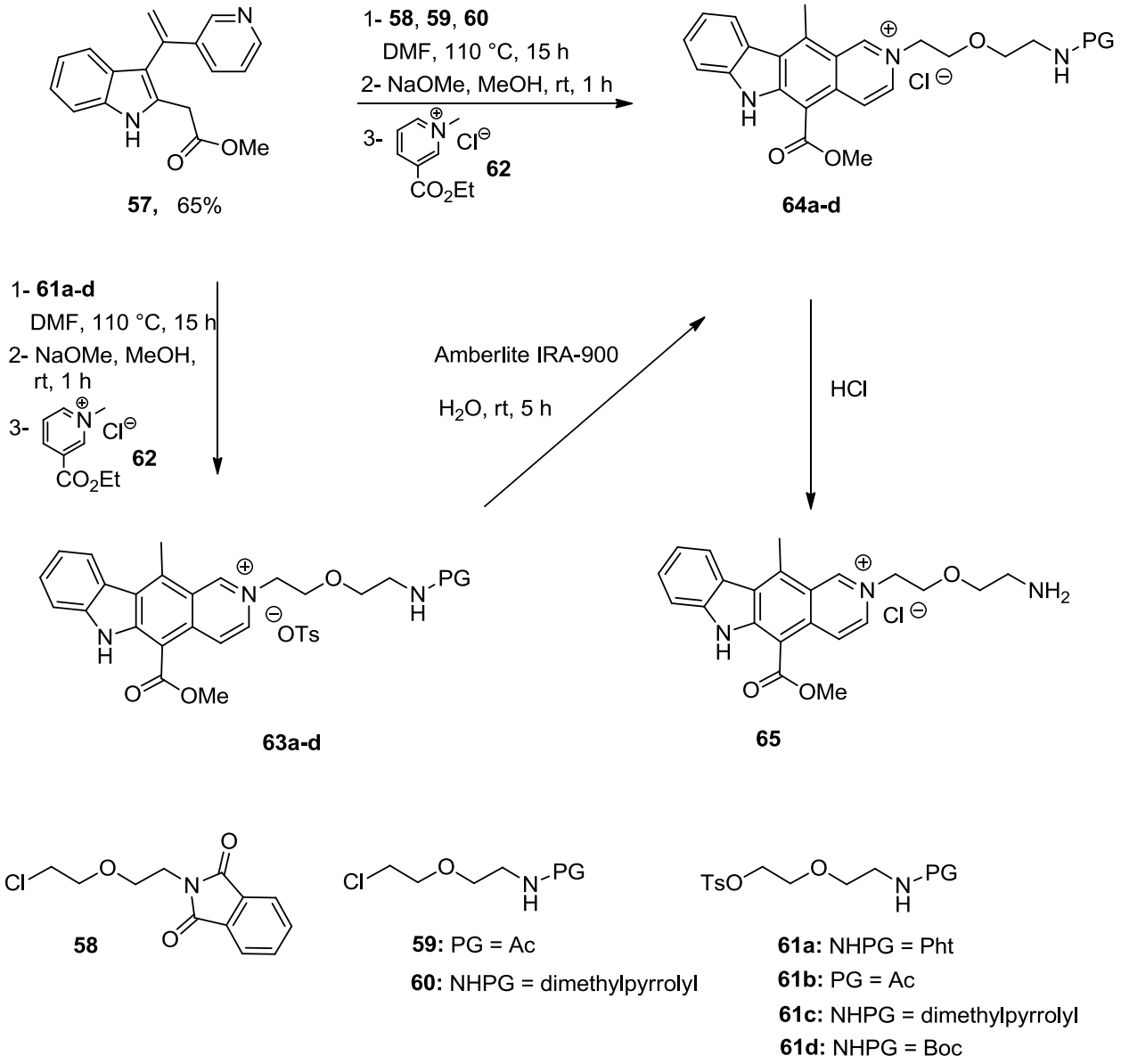
Scheme 11. Synthesis of Calothrixin B **50**.

2-alkyl-5-methoxycarbonyl-11-methyl-*6H*-pyrido[4,3-*b*]carbazol-2-ium chloride derivatives were prepared from indole **51**. First, the NH group of **51** was protected with benzensulfonyl group to give **52** which was oxalylated on the C-2 atom to give compound **53** in a 61% yield. Removal of benzene sulfonyl protecting group and hydrolysis of the ester group of **53** give the corresponding carboxylic acid **54** in an 85% yield. The carbonyl group of **54** was reduced with hydrazine leading to the formation of 2-indolylacetic acid **55**. The crude product was treated with trimethylsilyldiazomethane to give the corresponding methyl ester **56**. Finally, a mixture of **56** and 3-acetylpyridine was heated in the presence of concentrated sulfuric acid leading to methyl 2-(3-(1-(pyridin-yl)vinyl)-1*H*-indol-2-yl)acetate **57** in 65% yield (Scheme 12).



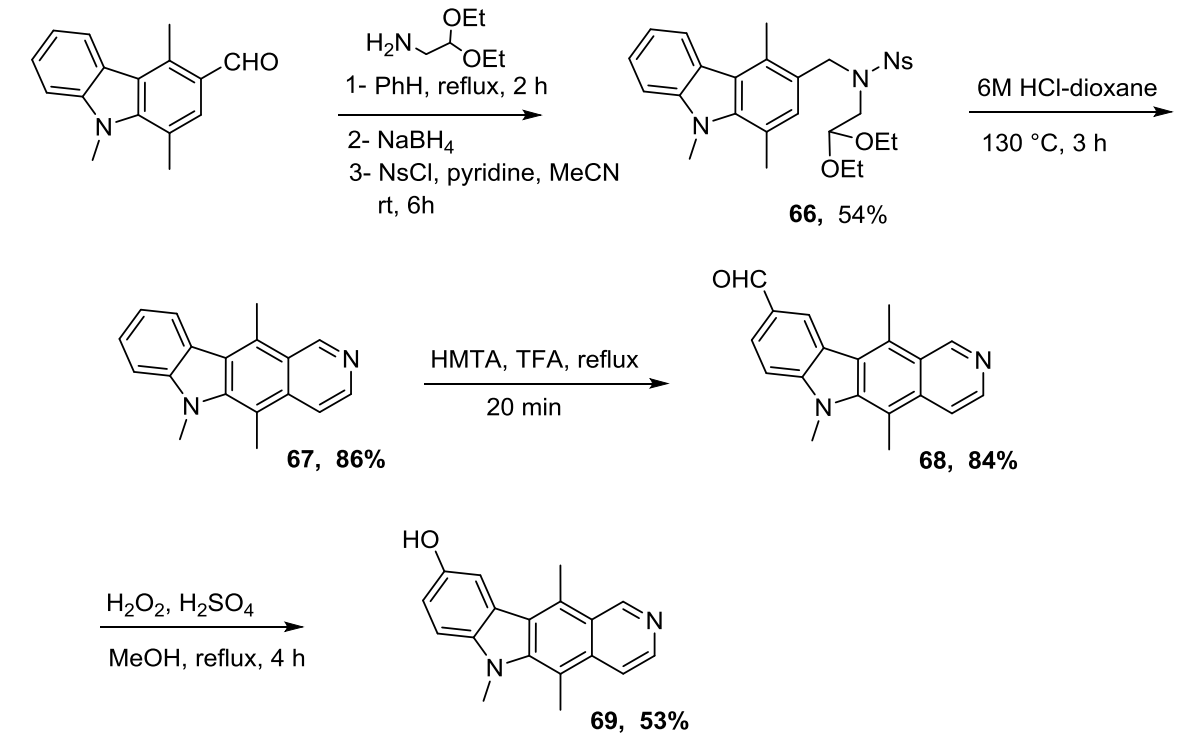
Scheme 12. Synthesis of **57**.

To construct a pyridocarbazole ring, the compound **57** was treated with **58** and **59** in the presence of 3-ethoxycarbonyl-1-methylpyridinium chloride **62** leading to 2-alkylpyridocarbazolium derivatives **64a**,**b** in a yield of 10% (Scheme 13). Alternatively, the 2-alkylpyridocarbazolium derivatives **64a**, **64b** and **64d** were prepared in good yields in two steps via treatment of **57** with **61a**, **61b** and **61d** respectively, in the presence of NaOMe and **62** followed by the action of Amberlite IRA-900 (Scheme 13). The stability of the quaternary salts of these molecules increases by converting them into the corresponding tosylate and chloride salts.

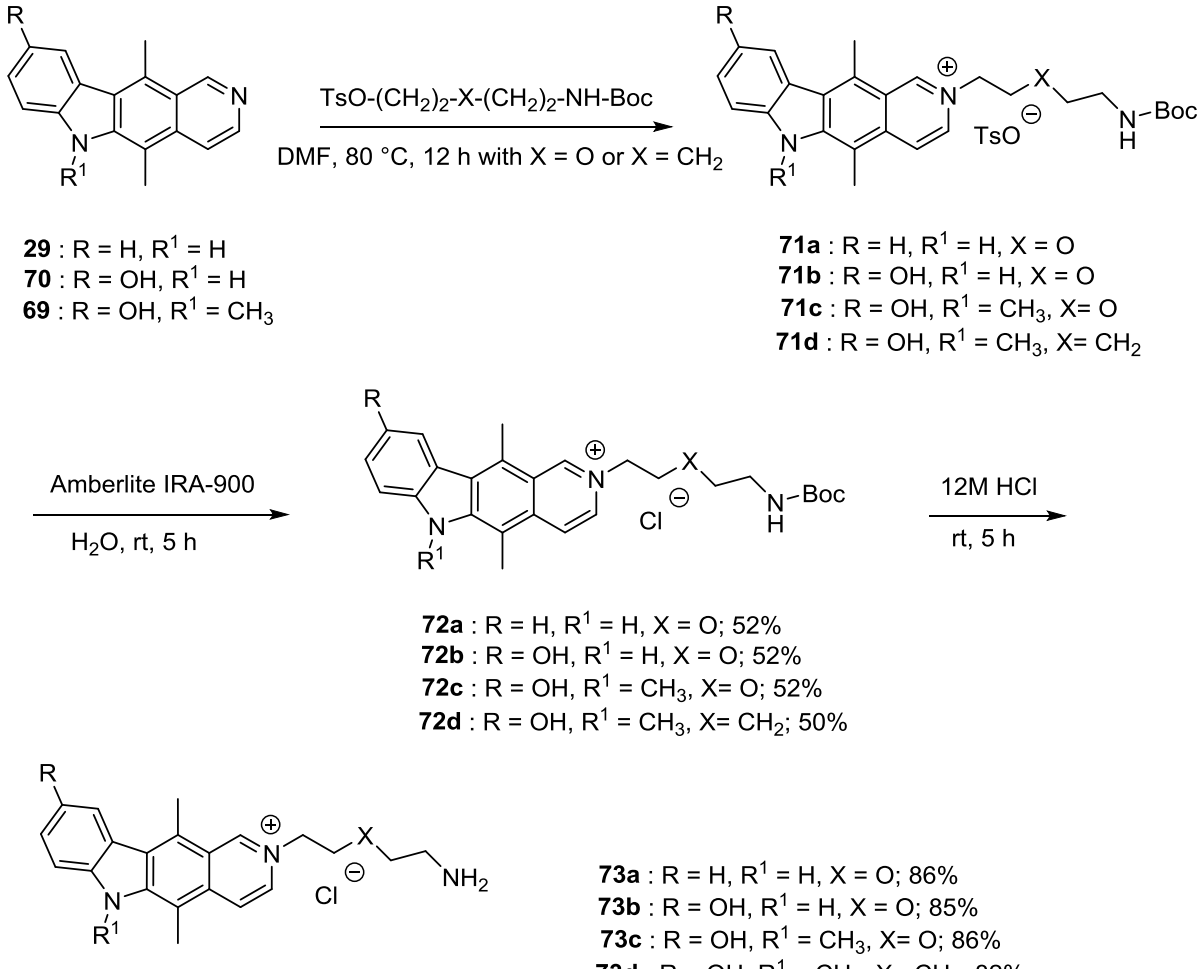


Scheme 13. Synthesis of 2-alkylellipticinium analogue **65**.

Ellipticine **29**, hydroxyellipticine **70**, 6-methylellipticine **67** and 9-hydroxy-6-methylellipticine **69** were prepared via a modification of a previously reported method,[36] as shown in Scheme 14 for **67** and **69** and followed by Dakin oxidation leading to the formation of 9-hydroxyellipticine **70** in 55% yield.



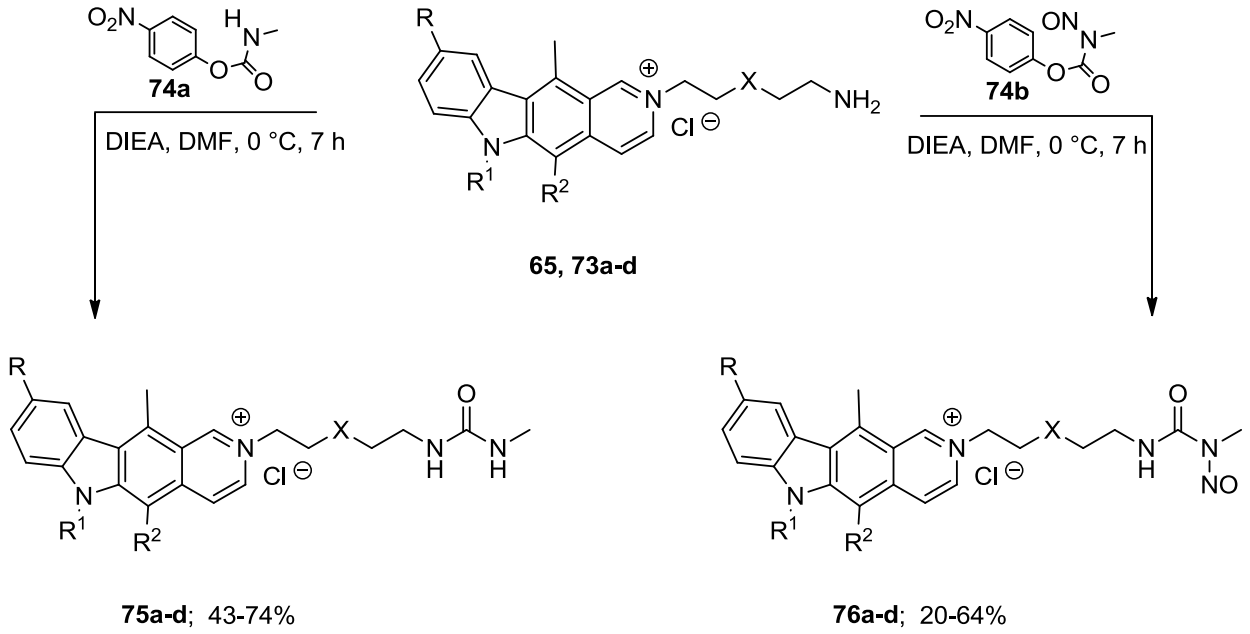
Scheme 14. Synthesis of 6-methylellipticine **67** and 9-hydroxy-6-methylellipticine **69.**



Scheme 15. Synthesis of 2-alkyl analogues of ellipticine **73a-d.**

Ellipticine **29**, 9-hydroxyellipticine **70**, and 9-hydroxy-6-methylellipticine **69** were treated with **61d** to form the corresponding ellipticinium tosylate quaternary salts **71a-c** (Scheme 15). In a similar manner, tosylate salts **71a-d** were then treated with Amberlite IRA-900 to give the corresponding chloride salts **72a-d**. These chloride salts were then refluxed in HCl (12M) to give the 2-alkyellipticinium analogues **73a-d** in good yields.

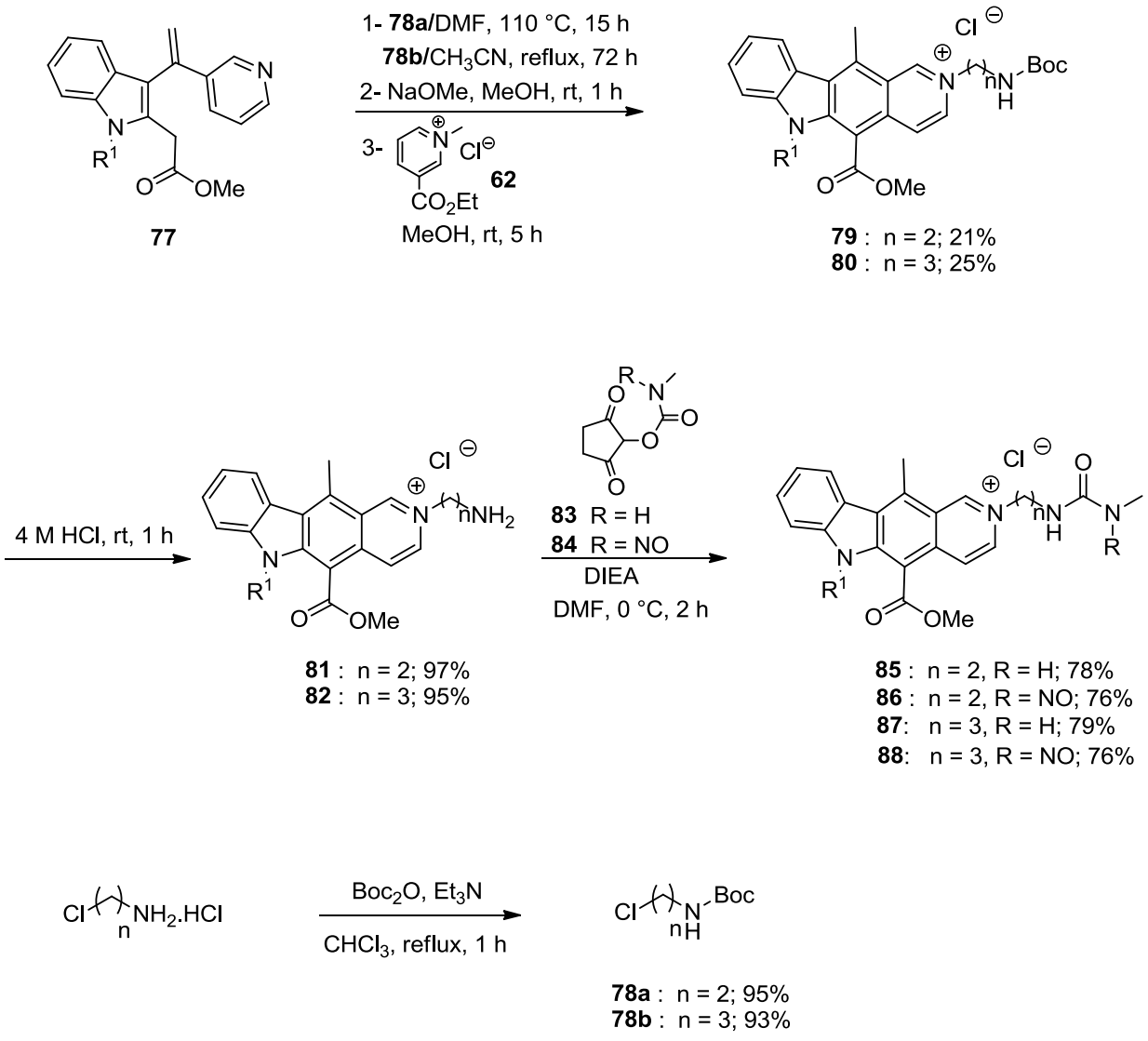
The obtained 2-(2-aminoethoxy)ethoxy)ethyl-5-methoxycarbonyl-11-methyl-6*H*-[4,3-*b*]carbazol-2-ium chloride **65** and its analogues **73a**-**d** were treated with *p*-nitrophenyl *N*-methylcarbamate **74a** and its *N*-nitroso derivative **74b** to get the corresponding urea derivatives **75a**-**e** and *N*-nitrosourea derivatives **76a**-**e** (Scheme 16).



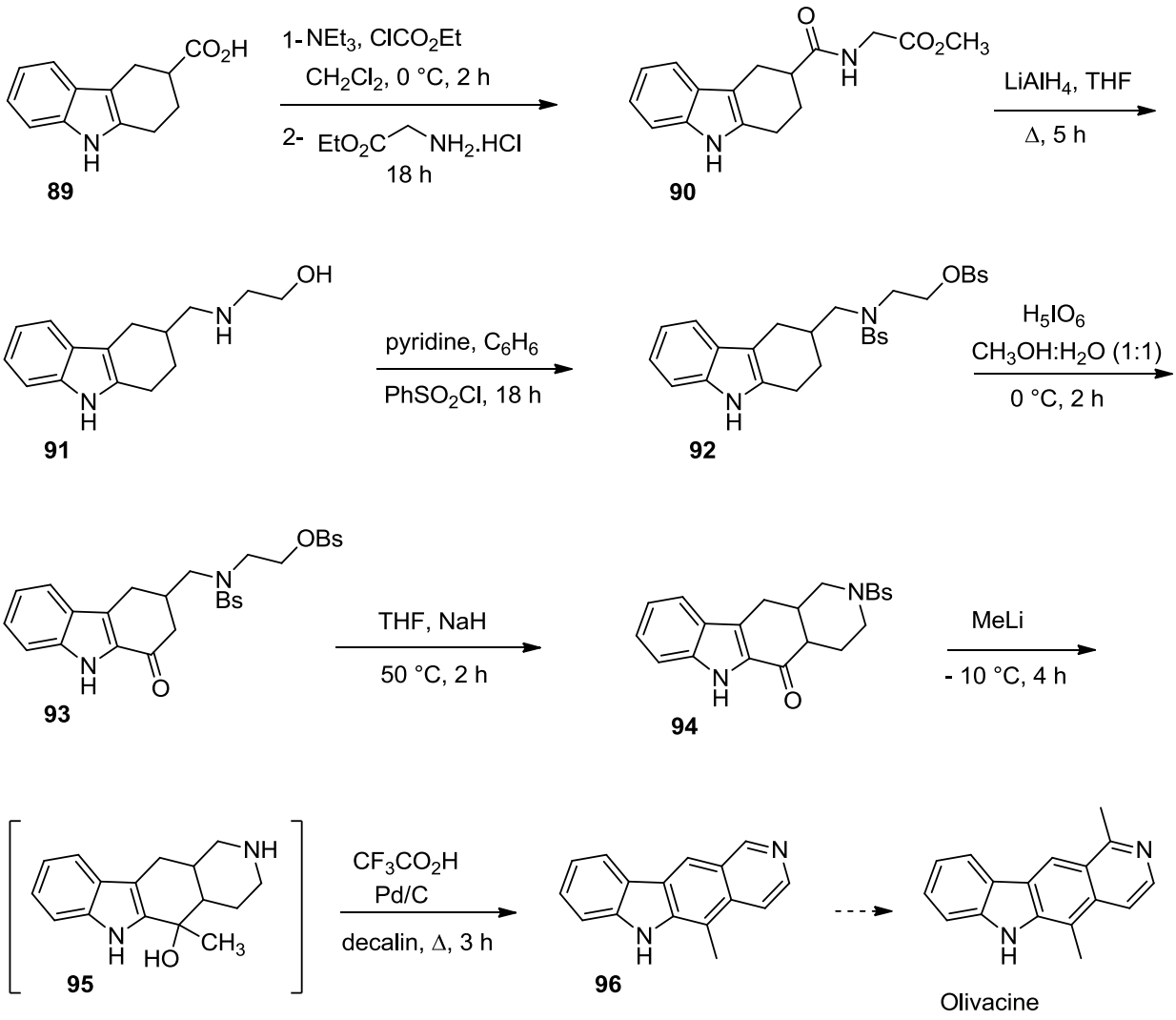
Scheme 16. Synthesis of urea and nitrosourea analogues of ellipticine derivatives **75a-e**, **76a-e.**

Finally, 2-(2-aminoethyl)- and 2-(3-aminopropyl)-pyridocarbazol-2-ium chlorides **81**-**88** were synthesized by a method analogous to the synthesis of **75e** and **76e** in poor to high yields (Scheme 17).

In 2016, Ergün et al.[37] reported a new synthetic route for the synthesis of 5-methyl-6*H*-pyrido[4,3-*b*]carbazole **96**, so called 11-demethylellipticine (Scheme 18). They have used tetrahydrocarbazole acid **89** as a starting material and synthesized according to the literature.[38] Then, acid **89** was converted to glycine **90** derivative using ethyl chloroformate and methyl glycinate. The reduction of glycine **90** with lithium aluminium hydride gave amine alcohol **91**. Amine alcohol **91** was reacted with benzene sulfonyl chloride and gave protected compound **92**. The oxidation of the compound **92** at position 1 with periodic acid yielded tetrahydrocarbazolone **93.** Then, reaction of **93** in the presence of sodium hydride led to the tetracyclic structure **94**. Finally, pyridocarbazole **96** was synthesized by aromatization of compound **95**, which was obtained from reaction between compound **94** and methyl lithium. One of the syntheses of pyridocarbazole alkaloid olivacine had been achieved via the reaction between pyridocarbazole **96** and methyl lithium in the literature previously.[39] Tetracyclic structure **94** can also allow the synthesis of several ellipticine derivatives.



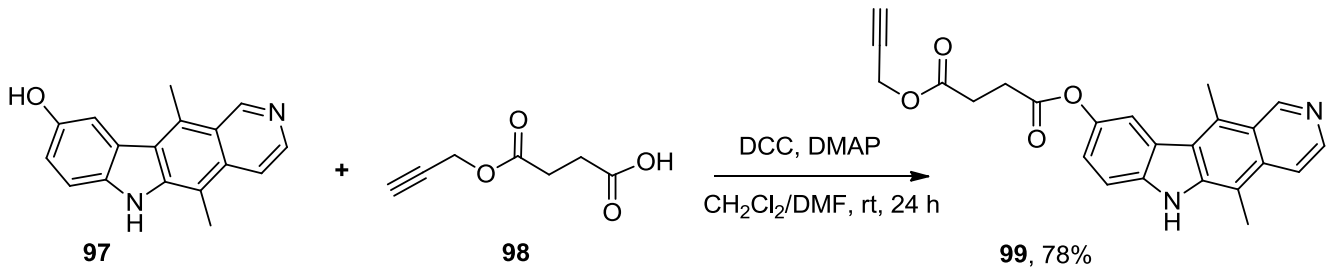
Scheme 17. Synthesis of urea and nitrosourea derivatives of pyridocarbazole-5-carboxylates **85-88.**



Scheme 18. Synthesis of 11-demethylellipticine **96**.

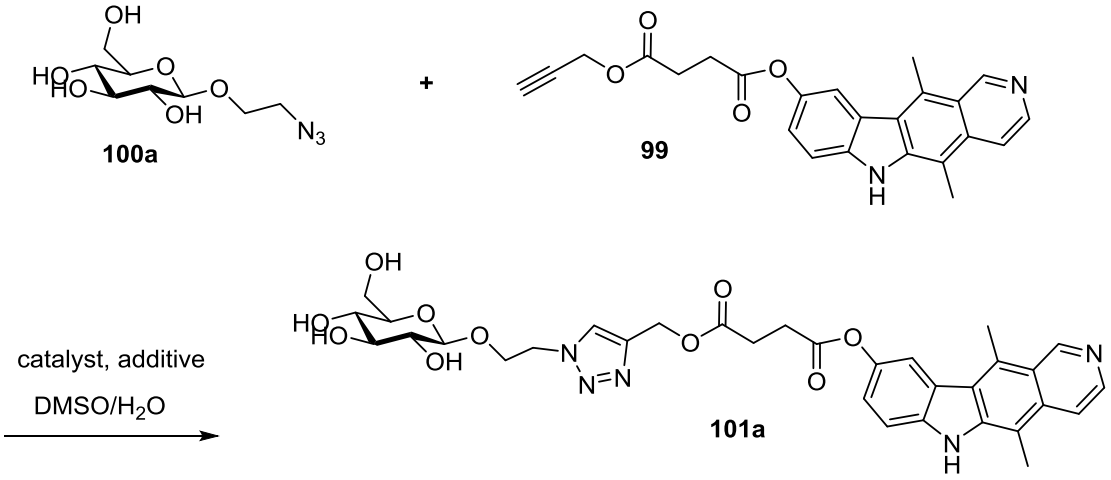
The same year Konakahara and al.[40] succeeded in developing the simple and efficient synthesis of three novel 9-hydroxyellipticine derivatives linked with a glucose moiety by a triazole ring-succinate tether at the position 9 of an ellipticine nucleus (Scheme 19).

9-Hydroxysuccinate **97** was synthesized by a previously reported method,[41] and then treated with monopropargyl succinate **98** leading to the formation of ellipticin-9-yl propargyl succinate **99** in a 78% yield.



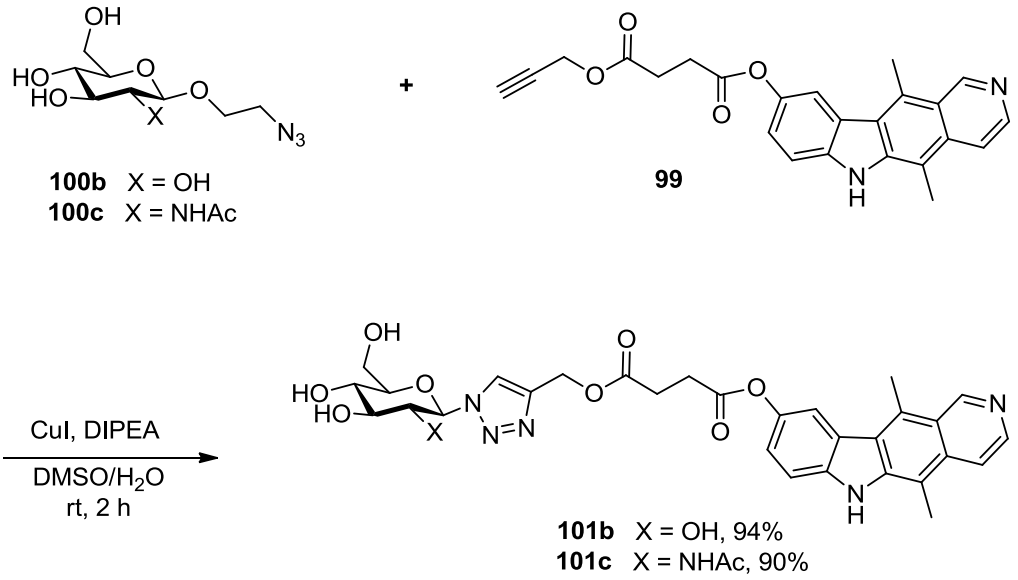
Scheme 19. Synthesis of ellipticin-9-yl propargyl succinate **99**.

Reaction of ellipticin-9-yl propargyl succinate **99** and 2-azidoethyl β-D-glucopyranoside **100a** was performed and the best yields were obtained using CuI as catalyst in the presence of diisopropylethylamine (DIPEA) (Scheme 20).



Scheme 20. Huisgen reaction of 2-azidoethyl β-D-glucopyranoside **100a** and ellipticin-9-yl propargyl succinate **99**.

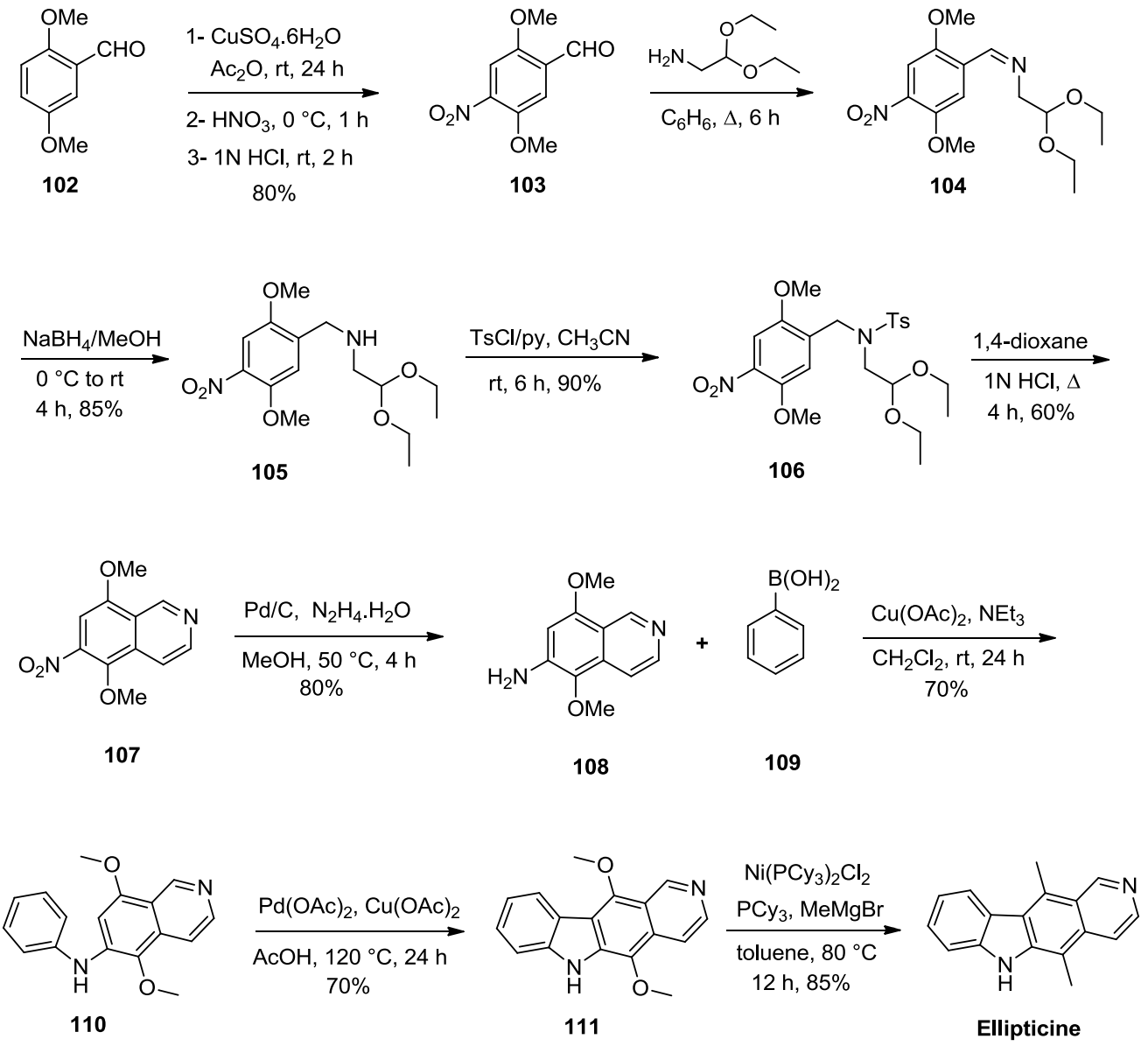
The reaction of **99** with β-D-glucopyranosyl azide **100b** and 2-acetamido-2-deoxy-β-D-glucopyranosyl azide **100c** gave the corresponding products **101b-c**, in 94 and 90% yields, respectively (Scheme 21).



Scheme 21. Huisgen reaction of 2-azidoethyl β-D-glucopyranoside **101b-c** and ellipticin-9-yl propargyl succinate **100**.

These compounds exhibited potent antitumor activity. The introduction of glucose conjugaison at the 9-position enhanced its solubility in water compared with those of ellipticine alone. This is the first report of the synthesis and evaluation of the antitumor activity of the uncharged glucose-conjugates of 9-hydroxyellipticine with increased water solubility.

An efficient and simple Ni-catalyzed C(aryl)-OMe bond cleavage and subsequent C(aryl)-Me bond formation by treating carbazoles with MeMgBr has been developed in 2016 by Das et al.[42] This protocol was successfully applied to the synthesis of the natural product ellipticine from readily available starting materials.



Scheme 22. Total synthesis of ellipticine.

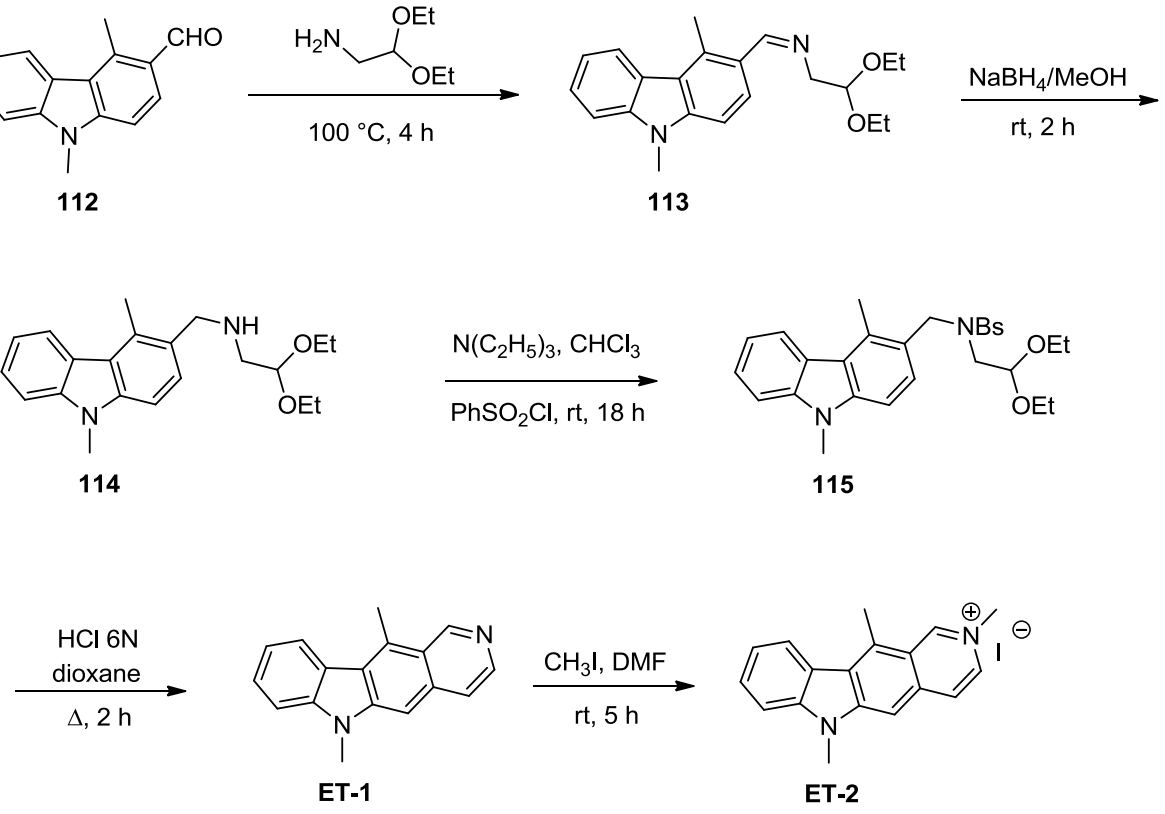
They used commercially available 2,5-dimethoxybenzaldehyde **102** as the starting material and introduced the methyl group through a Ni-catalyzed Kumada-type coupling reactions at a late stage of the synthesis. They began the synthesis with the nitration reaction ($CuSO_4 \cdot 6H_2O/HNO_3$) of 2,5-dimethoxybenzaldehyde **102** to afford nitration product **103** in 80% yield (Scheme 22). The condensation reaction of **103** with aminoacetaldehydediethyl acetal in dry benzene gave imine product **104**. The subsequent reduction of **104** with sodiumborohydride in methanol afforded amine **105** in 85% yield. The protection of amine **105** with a tosyl group gave protected compound **106**, which underwent cyclization in an acidic medium to furnish isoquinoline **107** in 54% yield (two steps). In the next step, the reduction of the nitro group was achieved by using Pd/C in methanol, and amine **108** was isolated in 80% yield. This product was then subjected to a Cu-

catalyzed Chan–Lam-type coupling with phenylboronic acid **109** to afford N-arylated product **110**.[43] Subsequently, the preparation of carbazole **111** was achieved in 70% yield by using a Pd-catalyzed cross-dehydrogenative (CDC) coupling reaction. Finally, they applied their optimized Ni-catalyzed protocol to replace the methoxy with a methyl group to afford ellipticine in 85% yield.

This protocol demonstrates that the lipophilicity of bioactive carbazoles can be easily modified by replacing a methoxy with a methyl group, which is important in the regulation of drug properties such as bioavailability and metabolic stability.

Topcu et al.[44] synthesized in 2016 two novel ellipticine derivatives, *N*-methyl-5-demethyl ellipticine (ET-1) and 2-methyl-*N*-methyl-5-demethyl ellipticinium iodide (ET-2), via a novel pathway shown in Scheme 23.

ET-1 and **ET-2** were generated using a nine-step synthetic pathway with a 12% overall yield. First, 4,9-dimethyl-9*H*-carbazole-3-carbaldehyde **112**[45] was treated with aminoacetaldehyde diethylacetal to yield imine **113**. The imine was reduced with sodium borohydride to produce amine **114**, which was treated with benzene sulfonyl chloride to produce sulfonamide **115**. Finally, cyclization of **ET-1** was achieved by treating sulfonamide **115** with hydrochloric acid. **ET-2** was obtained by treating **ET-1** with iodomethane in DMF. **ET-1** and **ET-2** were more soluble than ellipticine.

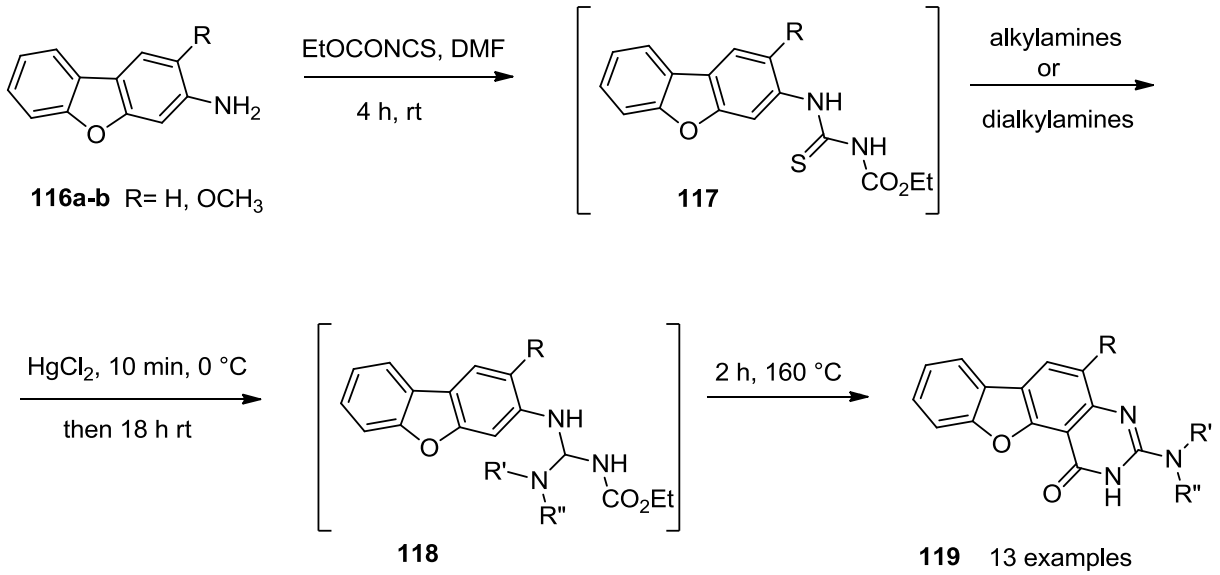


Scheme 23. Synthetic pathway of novel ellipticine derivatives.

A series of 3-(alkyl)(dialkyl)amino)benzofuro[2,3-*f*]quinazolin-1(2*H*)-ones **119** has been synthesized as new ellipticine analogs by Ando and al.[46] in 2016.

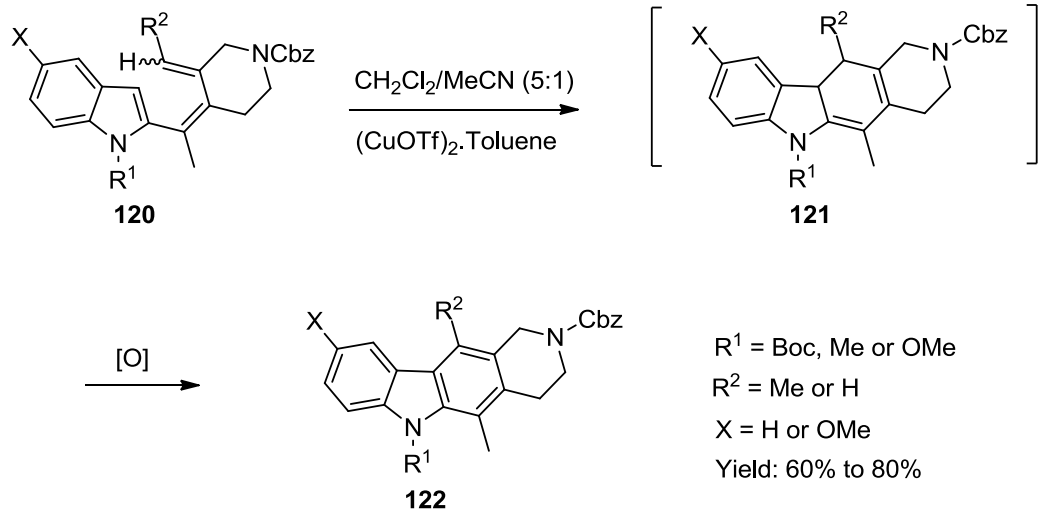
3-Aminodibenzofurans **116a-b** were used as starting materials (Scheme 24). The amino derivatives **116a-b** were reacted with ethoxycarbonylisothiocyanate to give the thiourea intermediates **117**, followed by the addition of the appropriate alkylamine or dialkylamine and $HgCl_2$ to give the ethoxycarbonylguanidine

intermediates **118**. The latter intermediates were subjected to thermal cyclization followed by filtration of the HgS-by-product to give the 3-(alkyl)(dialkyl)amino)benzofuro[2,3-*f*]quinazolin-1(2*H*)-ones **119**, respectively.



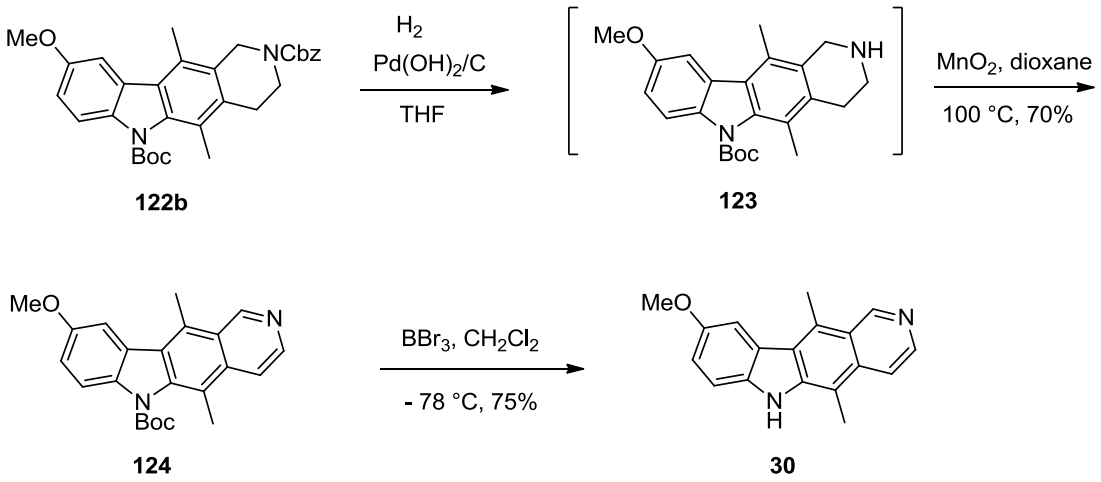
Scheme 24. Synthesis of 3-(alkyl)(dialkyl)amino)benzofuro[2,3-f]quinazolin-1(*2H*)-ones **119**.

Ishikura et al.[47] reported the total syntheses of 9-methoxyellipticine **30**, 3,4-dihydroellipticine **128**, 1,2,3,4-tetrahydroellipticine **129**, 2-methyl1,2,3,4-tetrahydroellipticine **131**, olivacine **142**, 3,4-dihydroolivacine **141**, (±)-janetine **138**, and (±)-guatambuine **136** using triene **120** as a key intermediate. The cyclization of triene **120** to pyridocarbazole **122** was successfully performed by taking advantage of Cu-mediated 6π-electrocyclization, enabling a gram-scale reaction (Scheme25).



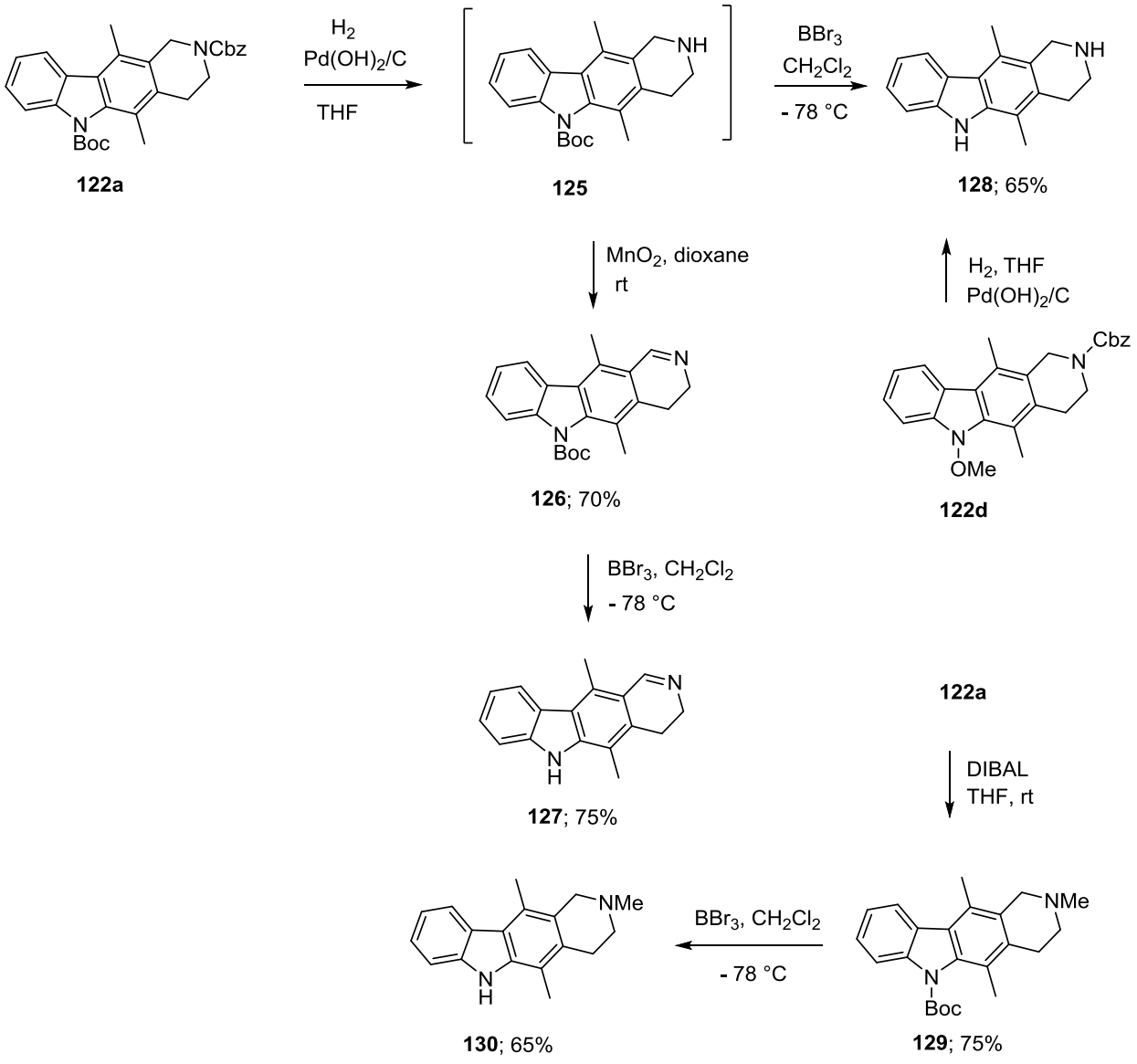
Scheme 25. Cu-mediated cyclization of indole **120**.

9-methoxyellipticine **30** was synthesized starting from carbazole **122b** (Scheme 26). The *N*-Cbz group was removed by catalytic hydrogenation, and resulting amine **123** was subjected, without further purification, to oxidation with MnO_2 in dioxane at 100 °C, to afford **124** in 70% yield. Removal of the *N*-Boc group with BBr_3 afforded **30** in 75% yield.



122b **123** **124** **30**

Scheme 26. Synthesis of 9-methoxyellipticine **30**.

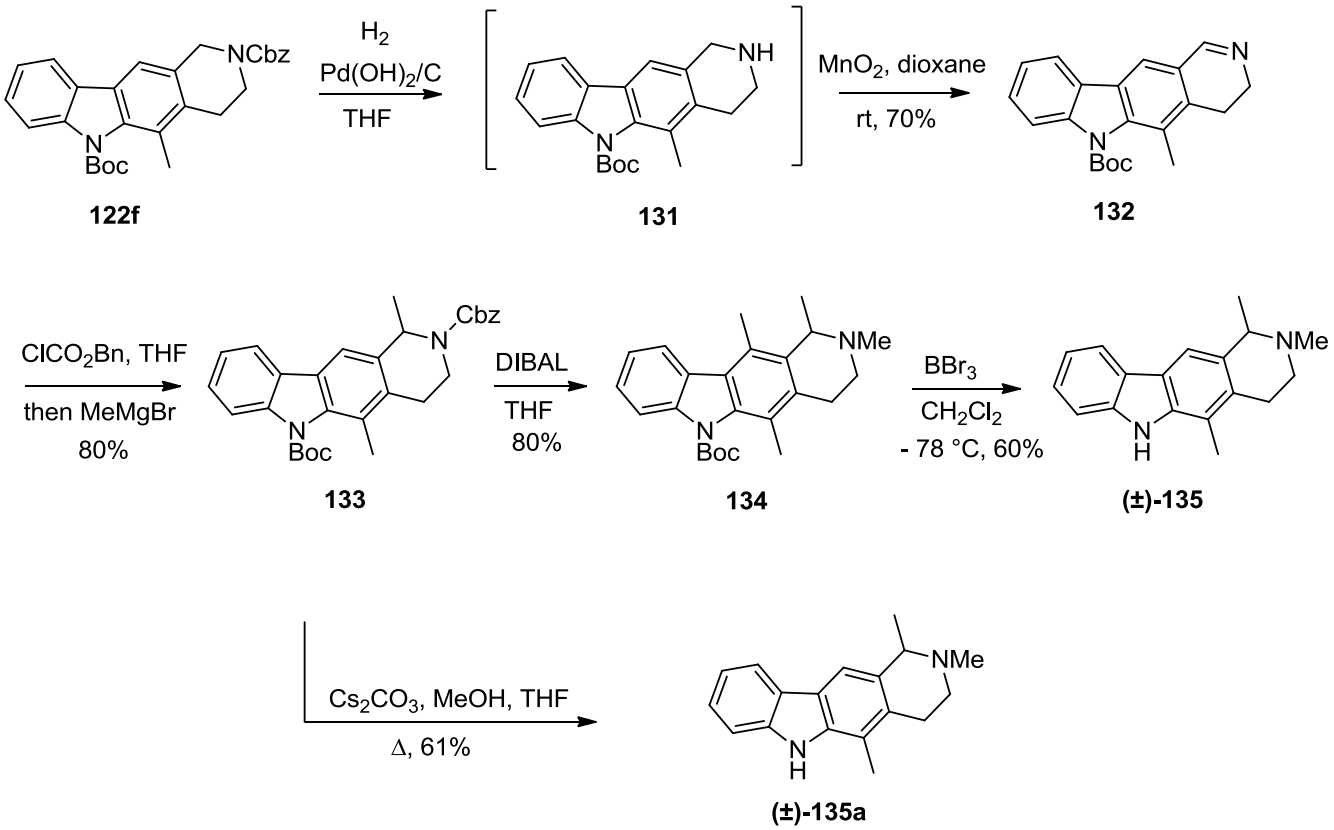


122a **125** **128**; 65% **126**; 70% **122d** **127**; 75% **122a** **130**; 65% **129**; 75%

Scheme 27. Synthesis of **128** and **130**.

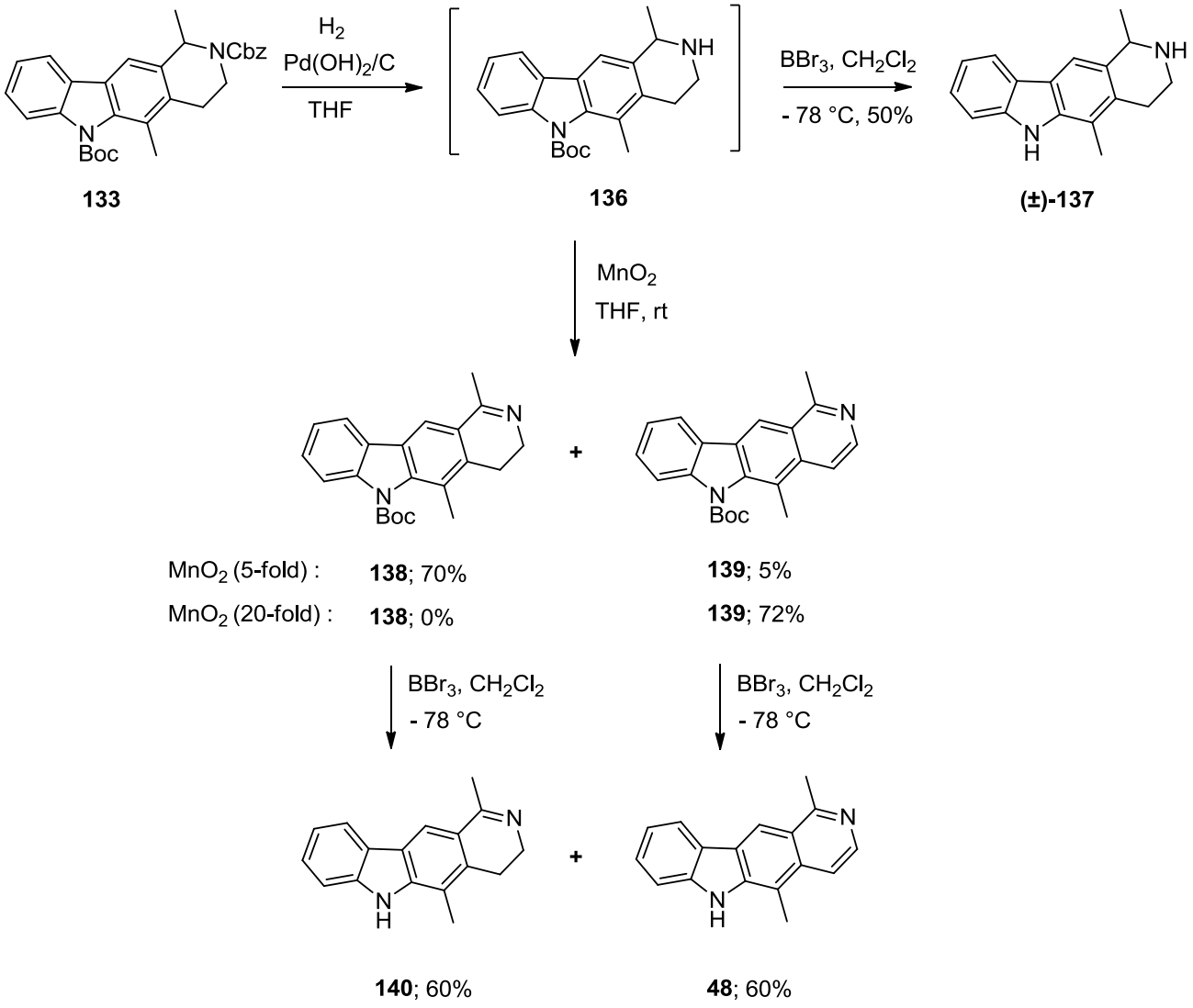
Next, carbazole **122a** was converted to 3,4-dihydroellipticine (μ-alkaloid D) **127**, 1,2,3,4-tetrahydroellipticine **128** and 2-methyl-1,2,3,4-tetrahydroellipticine **130** (Scheme 27). Removal of the *N*-Cbz group of **122a** by catalytic hydrogenation provided amine **125**, which was then treated with BBr_3. This sequence of transformations gave 1,2,3,4-tetrahydroellipticine **129** in 65% yield from **122a**. Moreover, catalytic reduction of carbazole **122d** produced **129** in a one-pot reaction. Additionally, amine **125** was oxidized with MnO_2 to give imine **126**. Treatment of **126** with BBr_3 provided 3,4-dihydroellipticine **127** in 75% yield. The *N*-Cbz group of **122a** was readily reduced to the *N*-Me group with DIBAL in THF at room temperature, leading to compound **129** in 75% yield. The *N*-Boc group was then removed with BBr_3 to give 2-methyl-1,2,3,4-tetrahydroellipticine **130**.

The total syntheses of olivacine **48**, 3,4-dihydroolivacine **140**, (±)-janetine **137** and (±)-gutambuine **135** were undertaken starting from carbazole **122f**. To transform **122f** into carbazole **133**, the *N*-Cbz group of **122f** was removed by catalytic hydrogenation, and resulting amine **131** was subjected, without purification, to oxidation with MnO_2 to yield **132** in 70% yield from **122f**. Next, the Me group was introduced into the C-1 position of **132**. Treatment of **132** with $ClCO_2Bn$ in THF at room temperature, followed by the addition of MeMgBr, readily provided **133** in 80% yield. Conversion of **133** to (±)-guatambuine **135** was carried out (Scheme 28) by first converting the *N*-Cbz group of **133** to its NMe congener with DIBAL; **134** was generated in 80% yield. Removal of the *N*-Boc group in **134** was effected with BBr_3 to provide (±)-guatambuine **135** in 60% yield. Additionally, the *N*-Boc group in **133** was cleaved by treatment with Cs_2CO_3 in refluxing MeOH/THF to render **135a**. A conformational inversion of the D-ring, accompanied by inversion of the nitrogen at the 2-position was observed.



Scheme 28. Synthesis of (±)-**135**.

Next, **133** was converted to (±)-janetine **137** (Scheme 29) by removal of the *N*-Cbz group using catalytic hydrogenation. Resulting amine **136** was subjected, without purification, to reaction with BBr_3 to produce (±)-janetine **137** in 50% yield. Additionally, amine **136** was oxidized with a fivefold excess of MnO_2. This oxidation provided imine **138** in 70% yield and **139** in 5% yield from **133**. A 20-fold excess of MnO_2 and prolonged reaction time (7 d) sufficed for the oxidation of **136** at room temperature, affording **139** in 72% yield from **133**. Removal of the *N*-Boc group in **139** with BBr_3 provided olivacine **48** in 60% yield. On the other hand, 3,4-dihydroolivacine **140** was generated by treatment of **138** with BBr_3.

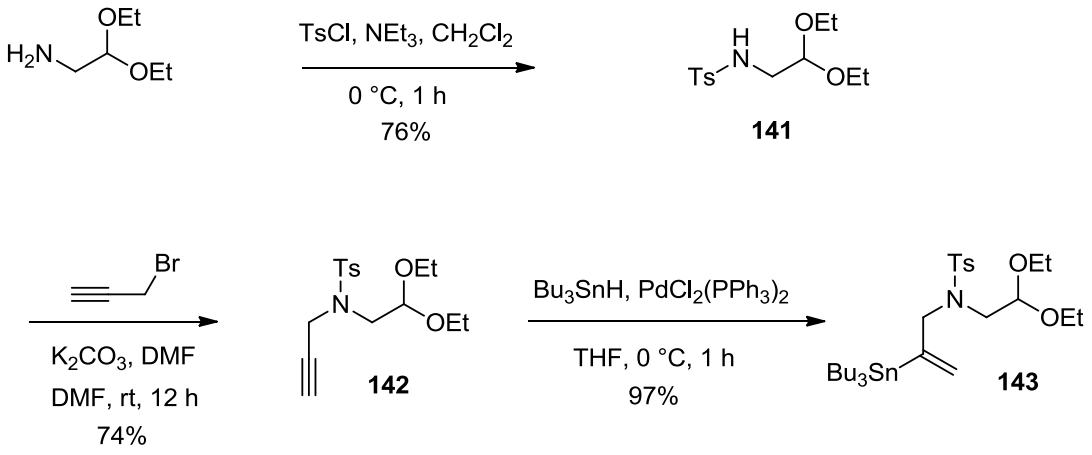


133 136 (±)-137

Scheme 29. Synthesis of **140**, **48** and (±)-**137**.

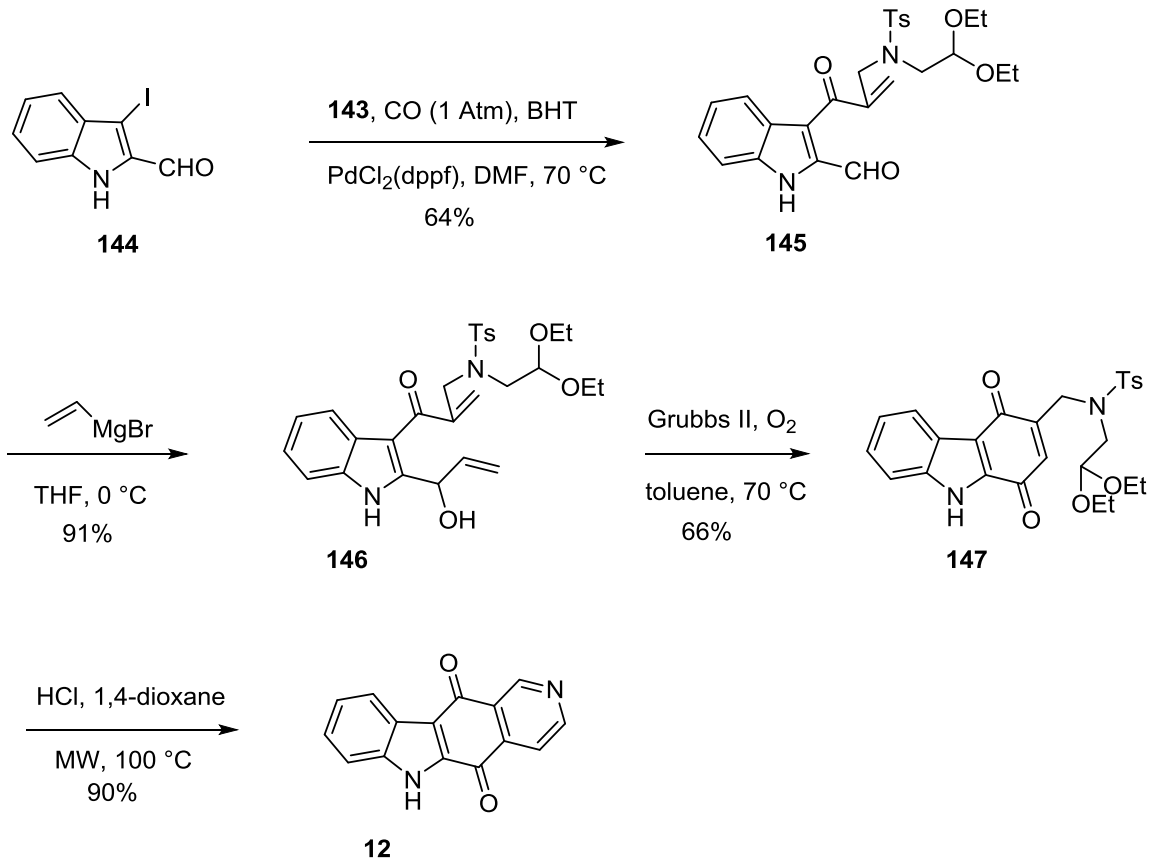
In 2017, Hatae et al.[48] developed a concise protocol for the synthesis of ellipticine quinone as outlined in scheme 31. The three-component Pd-catalyzed cross-coupling reaction between 3-iodoindole-2-carbaldehyde **144** and alkenyl tributyltin **143** under CO (1 atm) atmosphere was conducted in DMF at 70 °C to provide 3-acryloylindole **145** in 64% yield. The alkenyl tributyltin required **143** is obtained by treatment of aminoacetaldehyde diethyl acetal with *p*-toluenesulfonyl chloride and NEt_3 leading to the *p*-toluenesulfonamide **141** in 76% yield. This latter was subjected to alkylation with propargyl bromide to give

the propargylamine **142** in 74% yield. Subsequently, **142** was subjected to Pd-catalyzed hydrostannylation with tributyltin hydride to afford the desired alkenyl tributyltin **143** in 97% yield (Scheme 30).



Scheme 30. Synthesis of alkenyl tributyltin.

The Grignard reaction of **145** with vinylmagnesium bromide afforded the allyl alcohol **146**. Treatment of **146** with grubbs 2nd generation catalyst directly afforded the carbazole-1,4-quinone **147** in 66% yield. Finally, compound **147** was subjected to cyclization with 6M HCl by conventional heating. The desired ellipticine quinone **12** was obtained in 35% yield. Under microwave irradiation, the yield improved and **12** was obtained in 67% yield. Furthermore, cyclization of **147** with 6M HCl under microwave irradiation gave ellipticine quinone **12** as the sole product in 90% yield. Thus, the synthesis of ellipticine quinone **12** was achieved in 34.6% overall yield in four steps (Scheme 31).

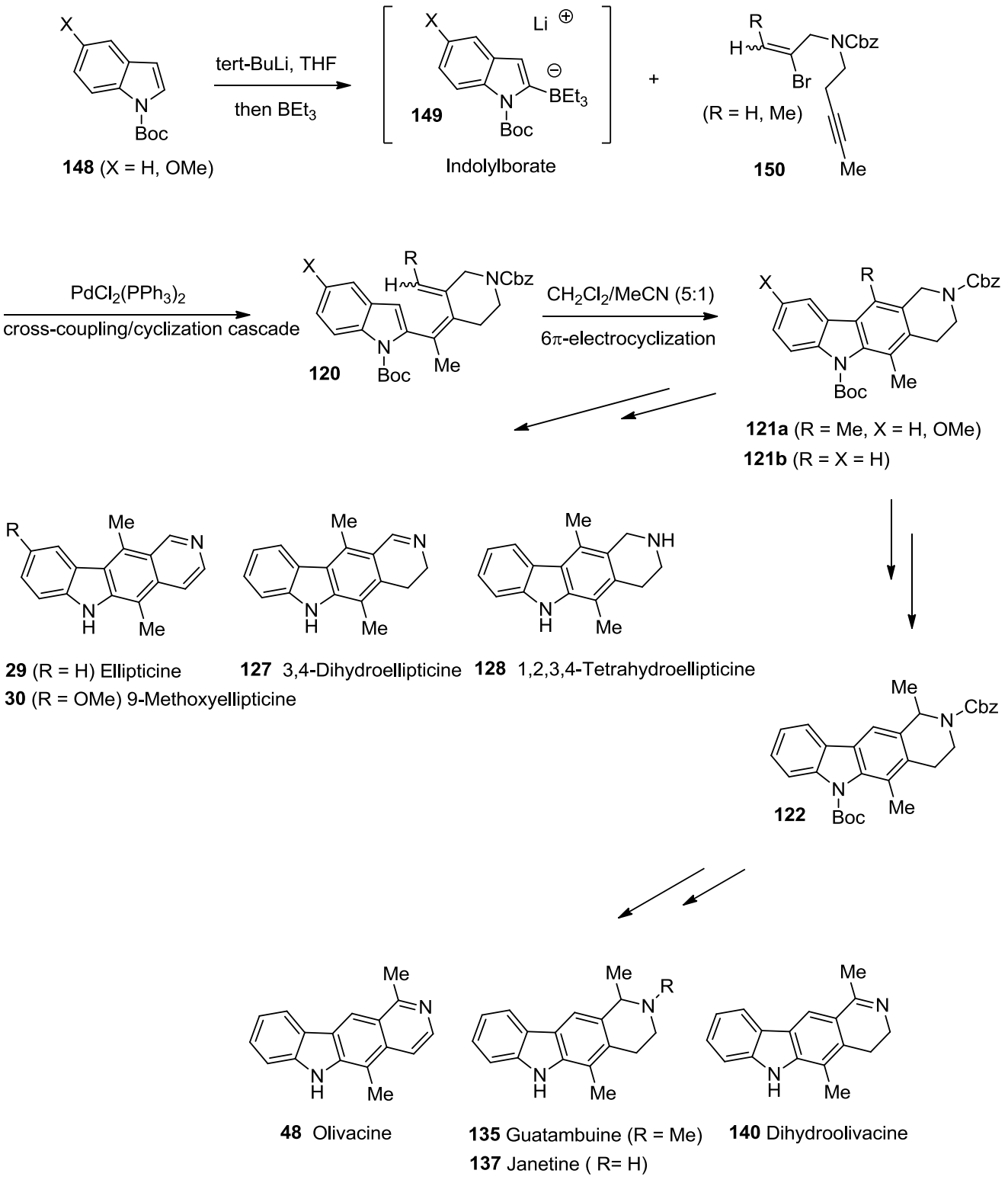


Scheme 31. Synthesis of ellipticine quinone.

Recently, in 2017, ellipticine, olivacine and their five reduced natural variants were synthesized via a palladium-catalyzed tandem cyclization/cross-coupling reaction as the key step by Ishikura et al.[49]

The syntheses of pyridocarbazole alkaloids **29, 30, 48, 122, 127-128, 135, 137, 140** were reported by the one-pot tandem cyclization/cross-coupling reaction of bromide **150** with indolylborate **149**, which was generated *in situ* from indole **148**, to produce hexatriene intermediate **120**. This was followed by 6π-electrocyclization of **120** to produce pyridocarbazole core **121**. Carbazole intermediates **121a** were transformed into ellipticine **29**, 9-methoxyellipticine **30**, 3,4-dihydroellipticine **127**, and 1,2,3,4-tetrahydroellipticine **128**. Olivacine **48**, (±)-guatambuine **135**, (±)-janetine **137**, and 3,4-dihydroolivacine **140** were synthesized from common intermediate **122** derived from **121b** (Scheme 32).

The cytotoxicities of the synthetic alkaloids and their derivatives against HCT-116 and HL-60 cells were determined. Structural properties, such as the aromaticity of the D ring and the presence of a Me group at the *N*(6)- and C(11)-positions, affected the activities of the compounds.



Scheme 32. Synthetic scheme for pyrido[4,3-*b*]carbazole alkaloids.

3. Conclusions

The present review offers an up-to-date literature on the latest syntheses of ellipticine and ellipticine derivatives reported during the last years. Several of these syntheses may be useful, and in particular Hatae et

al.[48] offers an attractive, short and efficient preparation of ellipticine quinone and its analogs. Overall, the interest in ellipticines and related pyridocarbazoles continue to expand given the diversity of structure and emerging bioactivity inherent in this compound class.

4. Acknowledgements

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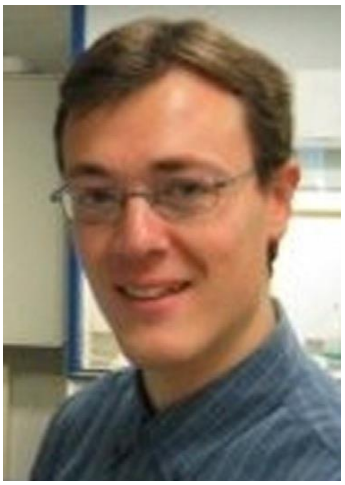
Authors' Biographies

Malika Ibrahim-Ouali carried out her PhD under the supervision of Professor Gramain in Clermont-Ferrand (France) in 1996. The work was focused on the synthesis of alkaloids. She was a postdoctoral fellow with Prof. Knochel in 1996

where she got her first training in organometallic chemistry. In 1997, she joined Professor H. P Husson's group at the ICSN (Paris) as a postdoctoral researcher. Since 1998, she is currently an assistant professor at Aix-Marseille University and her field of interest remains the total synthesis of natural compounds.



Frédéric Dumur received his PhD in chemistry in 2002 from the University of Angers (France) under the supervision of Professor Pietrick Hudhomme. After Post-Doctoral studies at the University of Groningen (The Netherlands), Reims Champagne-Ardennes (France) and Versailles Saint-Quentin-en-Yvelines (France), he joined the Faculty of Sciences at Aix-Marseille University in 2008, where he is currently working as an Associate Professor. His research interests include the synthesis of phosphorescent dopants for OLEDs and photoinitiators of polymerization. He co-authored about 160 publications and 5 book chapters.

