

Review

Recent Advances in the Synthesis of β -Carboline Alkaloids

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Abstract: β -Carboline alkaloids are a remarkable family of natural and synthetic indole-containing heterocyclic compounds and they are widely distributed in nature. Recently, these alkaloids have been in the focus of interest, thanks to their diverse biological activities. Their pharmacological activity makes them desirable as sedative, anxiolytic, hypnotic, anticonvulsant, antitumor, antiviral, antiparasitic or antimicrobial drug candidates. The growing potential inherent in them encourages many researchers to address the challenges of the synthesis of natural products containing complex β -carboline frameworks. In this review, we describe the recent developments in the synthesis of β -carboline alkaloids and closely related derivatives through selected examples from the last 5 years. The focus is on the key steps with improved procedures and synthetic approaches. Furthermore the pharmacological potential of the alkaloids is also highlighted.

Keywords: β -carboline; natural products; total synthesis; bioactive molecules



Citation: Szabó, T.; Volk, B.; Milen, M. Recent Advances in the Synthesis of β -Carboline Alkaloids. *Molecules* **2021**, *26*, 663. <https://doi.org/10.3390/molecules26030663>

Academic Editors: György Szöllösi and Eva Frank

Received: 13 November 2020

Accepted: 21 January 2021

Published: 27 January 2021

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1. Introduction

Carbolines are a remarkable family of heterocyclic natural products, with outstanding pharmacological potential. They are determined by their tricyclic, pyridine-fused indole framework (where the rings are identified as A, B and C), and classified according to the degree of saturation (fully saturated: 1,2,3,4-tetrahydro; partially saturated: 3,4-dihydro; and unsaturated β -carbolines) and the position of the N-atom in the C-ring as α -, β -, γ - or δ -carbolines (Figure 1) [1,2]. β -Carboline alkaloids are widely distributed in nature including various plants, foodstuffs, marine creatures, insects, mammals as well as human tissues and body fluids. Numerous representatives of this family show various biological activities [3–5]. The fascinating diversity of structures and medicinal potential [6] inherent in them encourage several researchers to deal with the synthesis of β -carboline containing natural products and their synthetic derivatives [2,4,7–9]. Several commercial drugs or drug candidates such as vinpocetine, brovincamine, abecarnil, cipargamin, tadalafil, reserpine and lurbinedin contain this unique framework (Figure 1).

This review focuses on the field of β -carboline research through selected examples from the last 5 years, where the key information on natural occurrence, structural diversity and biological activities is highlighted (Table 1). The comprehensive demonstration of recent advances in the synthesis of naturally occurring β -carbolines, including both simple β -carbolines (Section 2 of this review) and fused ring systems containing this framework (see Figure 1 and Section 3 of this review), is discussed with a special emphasis on the innovative framework construction steps.

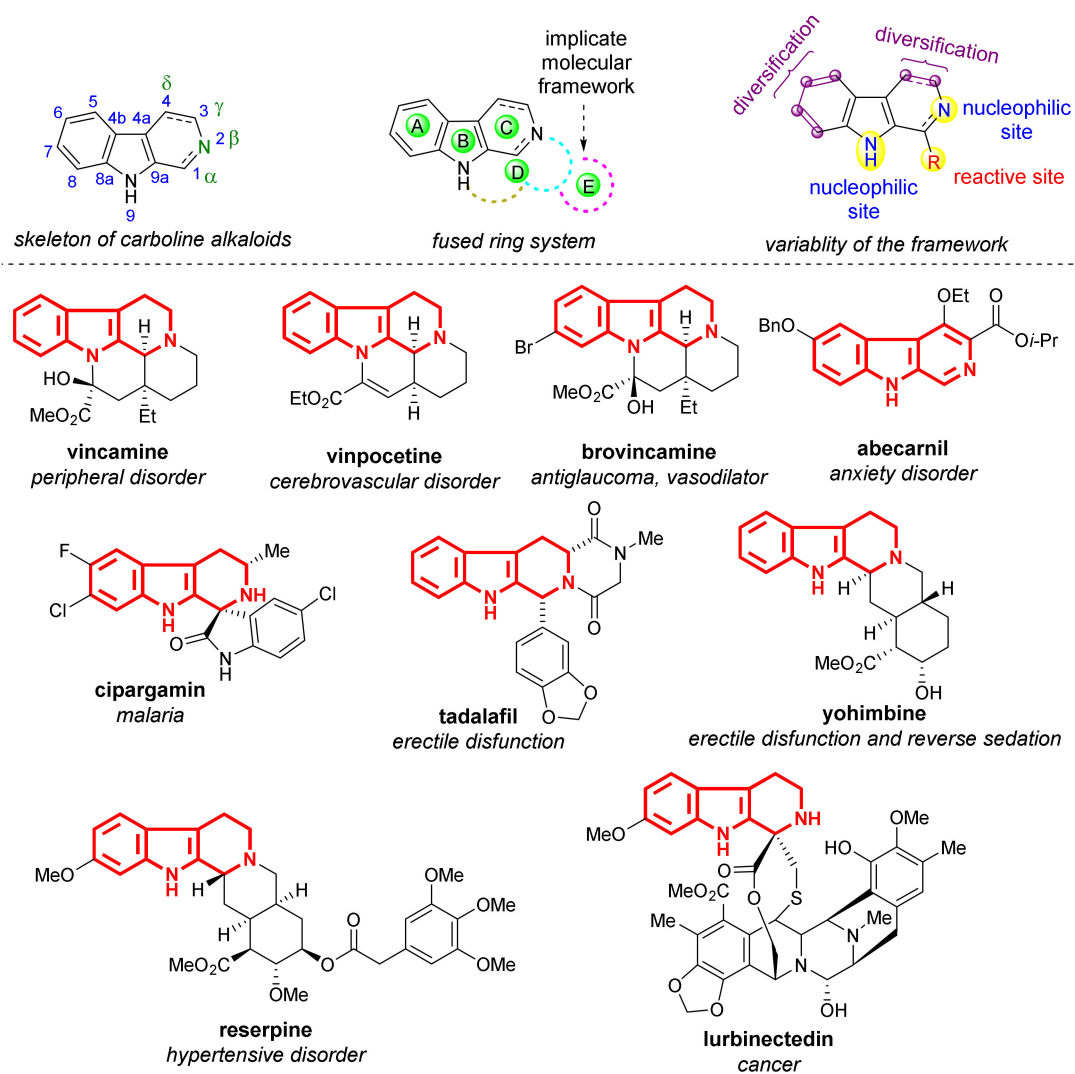


Figure 1. Structure of carboline skeleton and drugs containing a β -carboline framework.

Table 1. Synthesized β -carbolines with their natural occurrence and bioactivity.

| ID | Name | Structure | Occurrence | Bioactivity |
|----|---|-----------|---|---|
| 1 | norharman(β -carboline) | | <i>Noctiluca milaris</i> [10] <i>Strychnos johnsonii</i> [11] <i>Lycoris longituba</i> [12] <i>Selaginella delicatula</i> [13] <i>Trichosanthes kirilowii Maxim</i> [14] <i>Rauwolfia affra</i> [15] <i>Didemnum sp.</i> [16] | MAO-B inhibitor [11] |
| 2 | (-)-tetrahydroharman/ (S)-eleagnine | | 2: $R^1, R^3 = H, R^2 = Me$; 3: $R^1, R^3 = H, R^2 = Pr$; 4: $R^1, R^2 = Me, R^3 = H$; 5: $R^1 = Me, R^2 = Et, R^3 = H$; 6: $R^1 = H, R^2 = Pr, R^3 = Ac$; | not reported |
| 3 | (-)-komaroidine | | | |
| 4 | N-(+)-methyltetrahydro-harman | | | |
| 5 | (+)-1-ethyl-9-methyl-tetrahydro- β -carboline | | | |
| 6 | (+)-N-acetyl-komarodine | | | |
| 7 | stolonine C | | | |
| 8 | eudistomin I | | 8: $R^1 = H, R^2 = 3,4\text{-dihydropyrrol-2-yl}$ 9: $R^1 = Br, R^2 = H$ 10: $R^1 = H, R^2 = \text{indole-3-yl}$ 11: $R^1 = H, R^2 = -C(O)Bn$ 12: $R^1 = H, R^2 = \text{indole-3-yl}; C\text{-ring: dihydro}$ | 8: antibacterial effect [25] 9: antiviral, antibacterial and antifungal activity [26] 11: antibiotic activity [27] |
| 9 | eudistomin N | | | |
| 10 | eudistomin U | | | |
| 11 | eudistomin T | | | |
| 12 | isoeudistomin U | | | |
| 13 | harmalan | | 13: $R = Me$; C-ring: dihydro 14: $R = \text{pyrrol-2-yl}$; C-ring: dihydro 15: $R = CH_3$ 16: $R = CHO$ | 13: anti-neuroinflammatory activities [28] 14: n.a. 15: vasorelaxant effect [31] binding affinity to imidazoline I_{2B} receptors [32] 16: cytotoxic activity [33] AMP phosphodiesterase inhibitor [34] anti-inflammatory agent [35,36] |
| 14 | isoeudistomin M | | | |
| 15 | harman | | | |
| 16 | kumujian C | | | |

Table 1. Cont.

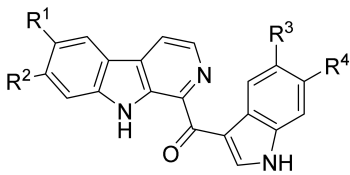
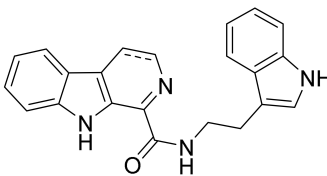
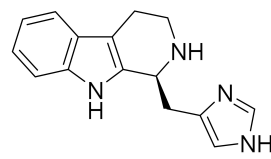
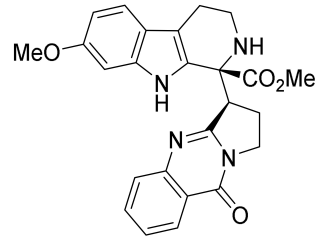
| ID | Name | Structure | Occurrence | Bioactivity |
|----------------------------|---|---|---|--|
| 17 18 19 20 21 | trigonostemine A trigonostemine B trigonostemine G pityriacitrin hyrtiosulawesine |  <p>17: R¹, R³, R⁴ = OMe, R² = H 18: R¹, R³ = H, R², R⁴ = OMe 19: R¹, R⁴ = H, R² = OMe, R³ = OH 20: R¹, R², R³, R⁴ = H 21: R¹, R³ = OH, R², R⁴ = H</p> | <p>17, 18: <i>Trigonostemone lii</i> [37] 17, 18, 19: <i>Trigonostemone filipes</i> [38] 20: <i>Malassezia furfur</i> [39] <i>Paracoccus marine bacteria</i> [40] <i>Dichotomomyces ceipii</i> [41] 21: <i>Hyrtio erectus</i> [42] <i>Alocasia macrorrhiza</i> [43]</p> | <p>17, 18, 19: cytotoxic activity [44] 20: antiproliferative activity [45] anticancer activity [46,47] 21: antiproliferative activity [48,49] antimalarial activity [46] antiphospholipase A2 [50] and antioxidant activity [46]</p> |
| 22 23 | alangiobussine alangiobussinine |  <p>22: C-ring: dihydro 23: C-ring: unsaturated</p> | <i>Alangium bussyanum</i> [51] | not reported |
| 24 | haploscleridamine |  | <i>Sponge of the order Haplosclerida</i> [52] | inhibitor of cathepsin K [52] |
| 25 | (±)-peharmaline A |  | <i>Peganum harmala</i> [53] | cytotoxic activity (HL-60, PC-3, SGC-7901) [54] |

Table 1. Cont.

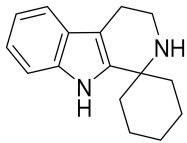
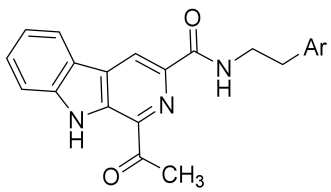
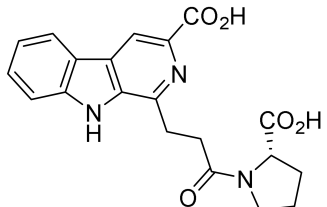
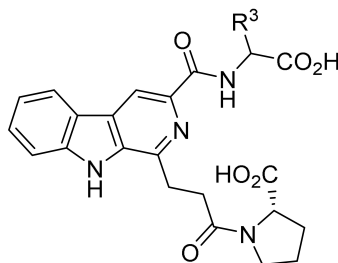
| ID | Name | Structure | Occurrence | Bioactivity |
|----------------------|--|--|---|--|
| 26 | komavine |  | <i>Nitraria komarorii</i> [55] <i>Nitraria schoberi</i> [55] | not reported |
| 27 28 29 30 | marinacarboline A marinacarboline B marinacarboline C marinacarboline D |  27: Ar = C ₆ H ₅ 28: Ar = 4-MeOC ₆ H ₄ 29: Ar = 4-HO-C ₆ H ₄ 30: Ar = 3-indolyl | <i>Marinactinospora thermotolerans</i> SCSIO 00652 [56] | antiplasmodial activity [56] cytotoxic activity [57] |
| 31 | metatacarboline A |  | <i>Mycena metata</i> [58] | not reported |
| 32 33 34 35 | metatacarboline C metatacarboline D metatacarboline E metatacarboline F |  32: R ₃ = CH ₂ OH 33: R ₃ = CH(CH ₃)OH 34: R ₃ = CH ₃ 35: R ₃ = CH(CH ₃) ₂ | <i>Mycena metata</i> [58] | 32, 34: antiproliferative activity, proapoptotic effect [59] |

Table 1. Cont.

| ID | Name | Structure | Occurrence | Bioactivity |
|----|-----------------------------|-----------|--|---|
| 36 | 6-hydroxy-metatacarboline D | | <i>Mycena metata</i> [58] | not reported |
| 37 | shishijimicin A | | <i>Didemnum proliferum</i> [60] | antitumor activity (P388 leukemia cells) [60] |
| 38 | canthine | | basic framework of canthin-6-ones, which are widely distributed in nature [61] | not reported |
| 39 | harmicine | | <i>Kopsia griffithii</i> [62] | not reported |

Table 1. Cont.

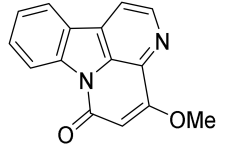
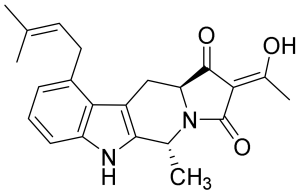
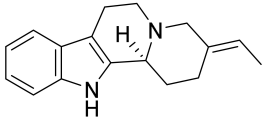
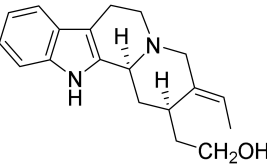
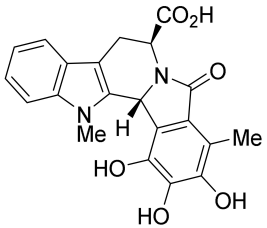
| ID | Name | Structure | Occurrence | Bioactivity |
|----|-------------------|--|--|-----------------------------|
| 40 | cordatanine |  | <i>Drymaria cordata</i> [63] <i>Drymaria diandra</i> [64,65] | anti-HIV activity [64] |
| 41 | griseofamine A |  | <i>Penicillium griseofulvum</i> [66] | antibacterial activity [67] |
| 42 | (+)–deplancheine |  | <i>Alstonia deplanchei</i> [68] | not reported |
| 43 | (–)–geissoschizol |  | <i>Tabernaemontana bufalina</i> [69] <i>Hunteria zeylanica</i> [70] | not reported |
| 44 | chaetogline E |  | <i>modified Epinephelus drummondhayi with a silent fungal gene from Chaetomium globosum</i> [71] | not reported |

Table 1. Cont.

| ID | Name | Structure | Occurrence | Bioactivity |
|----|------------------|-----------|--|--|
| 45 | chaetogline F | | <i>modified Epinephelus drummondhayi with a silent fungal gene from Chaetomium globosum</i> [71] | antibacterial activity [71] |
| 46 | 6-oxofascaplysin | | <i>Hyrtios</i> sp. [72] | weak cytotoxic activity [73] |
| 47 | fascaplysin | | <i>Fascaplysinopsis</i> sp [74] | anticancer activity [73,75] |
| 48 | evodiamine | | <i>Evodia rutaecarpa</i> [76] | anticancer anti-inflammatory antimicrobial and many others [77] |

Table 1. Cont.

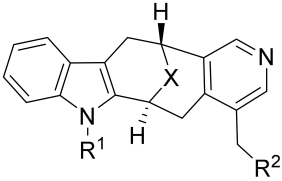
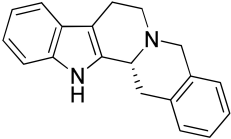
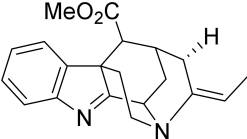
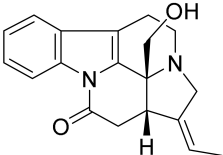
| ID | Name | Structure | Occurrence | Bioactivity |
|----------------|---|---|---|---|
| 49 50 51 | norsuaveoline suaveoline marcophylline |  <p>49: R¹ = H, R² = CH₂, X = NH 50: R¹ = Me, R² = CH₂, X = NH 51: R¹ = H, R² = CH₂OH, X = NMe</p> | 49: <i>Rauwolfia caffra</i> [78] 50: <i>Rauwolfia suaveolens</i> S. Moore (apocynaceae) [79] 51: <i>Rauwolfia macrophylla</i> [80] | 49: not reported 50: acetylcholinesterase inhibitor [81] 51: not reported |
| 52 | (S)-(–)-decarbo-methoxy-dihydro-gambirtannine |  | enantiomer of 52 was isolated from <i>Hunteria zeylanica</i> [82] | not reported |
| 53 | (+)-strictamine |  | <i>Alstonia scholaris</i> <i>Rhazya strictu</i> [83,84] | antitumor, antiviral anti-inflammatory antibiosis activities [83–85] |
| 54 | (±)-arbornamine |  | <i>Kopsia arborea</i> [86] | not reported |

Table 1. Cont.

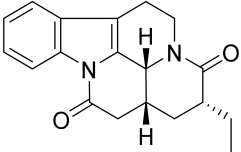
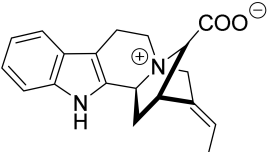
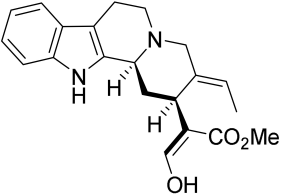
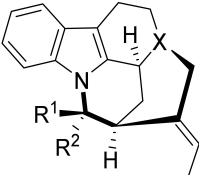
| ID | Name | Structure | Occurrence | Bioactivity | |
|----|-------------------------------------|--|---|---|---|
| 55 | (+)-tacamonine |  | <i>Tabernaemontana eglandulosa</i> [87] | not reported | |
| 56 | (-)-17-nor-excelisidine |  | <i>Alstonia scholaris</i> [85] | antiviral activity [85] | |
| 57 | (+)-geissoschizine |  | <i>Rhazya stricta</i> [88] | not reported | |
| 58 | (+)-16-epi-pleiocarpamine |  | 58: $R^1 = H, R^2 = CO_2Me, X = N$ | 58: <i>Ervatamia cumingiana</i> [89] | 61, 58: anticholinergic activity [96] 59: cytotoxic activity [91] 60: not reported 62: antibacterial activity [94] 63: not reported |
| 59 | (+)-taberdivarine H | | 59: $R^1 = H, R^2 = COO^-, X = N^+Me$ | <i>Pleiocarpa pycnantha</i> [90] | |
| 60 | (+)-16-hydroxymethyl-pleiocarpamine | | 60: $R^1 = CO_2Me, R^2 = CH_2OH, X = N$ | 59: <i>Tabernaemontana officinalis</i> [91] | |
| 61 | (+)-pleiocarpamine | | 61: $R^1 = CO_2Me, R^2 = H, X = N$ | 60: <i>Kopsia singaporensis</i> [92] | |
| 62 | (±)-normavacurine | | 62: $R^1 = H, R^2 = CH_2OH, X = N$ | 60: <i>Kopsia teoi</i> [93] | |
| 63 | (±)-C-mavacurine | 63: $R^1 = H, R^2 = COOH, X = N^+Me$ | 62: <i>Alstonia scholaris</i> [94] | | |
| | | | 63: <i>Strychnos guianensis</i> [95] | | |

Table 1. Cont.

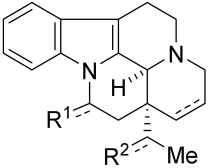
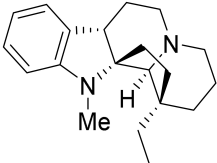
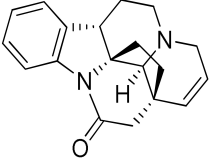
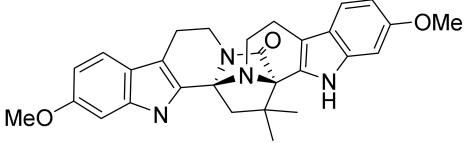
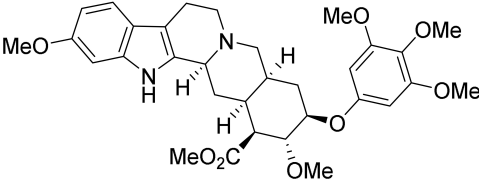
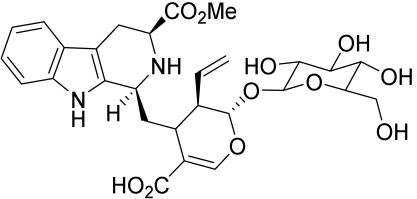
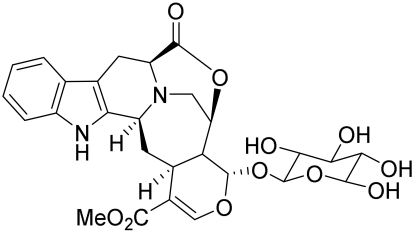
| ID | Name | Structure | Occurrence | Bioactivity |
|----|--|--|--|--|
| 64 | (+) -19-oxoeburnamine |  <p data-bbox="954 368 1167 387">64: R¹ = OH, R² = O</p> <p data-bbox="954 400 1178 419">65: R¹ = OH, R² = OH</p> <p data-bbox="954 432 1211 451">66: R¹ = O, R² = OH, Δ¹⁴</p> <p data-bbox="954 464 1167 483">67: R¹ = O, R² = OH</p> | <i>Kopsia jasminiflora</i> [97] <i>Kopsia pauciflora</i> [98] | not reported closely related analogues show antitumor activity |
| 65 | (+) -19-OH-eburnamine | | | |
| 66 | 19-(S)-hydroxy-Δ ¹⁴ -vincamone | | | |
| 67 | (−)-19-hydroxy-Δ ¹⁴ -eburnamonine | | | |
| 68 | (+) -vallesamidine |  | <i>Vallesia dichotoma</i> [99] | not reported |
| 69 | (+) -14,15-dehydro-strepeliopine |  | <i>Schizozygia caffaeoides</i> [100] | not reported |
| 70 | (+) -peganumine A |  | <i>Peganum harmala</i> L. [101] | cytotoxic activity (MCF-70, PC-3, HepG2, HL-60) [101] |

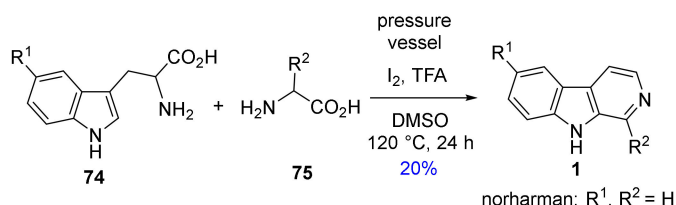
Table 1. Cont.

| ID | Name | Structure | Occurrence | Bioactivity |
|----|----------------------------|---|--|--|
| 71 | reserpine |  | <i>Rauwolfia serpentina</i> [102] | Commercially available drug for the treatment of high blood pressure [103] |
| 72 | (–)-5-carboxystrictosidine |  | <i>Rhazya orientalis</i> [104] <i>Guenttarda platypoda</i> [105] <i>Uncaria tomentosa</i> [106] <i>Ophiorrhiza nutans</i> [107] | not reported |
| 73 | (–)-rubenine |  | <i>Adina rubescens</i> [108] | not reported |

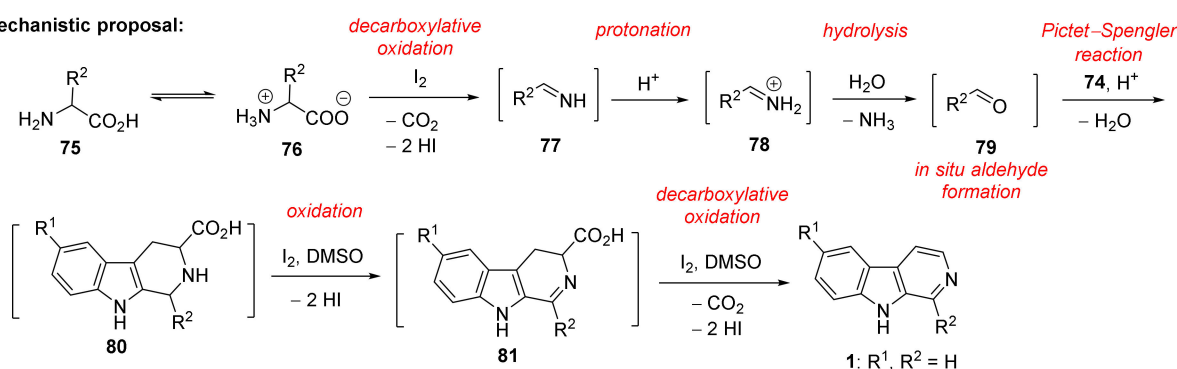
2. Natural Products Containing a Simple β -Carboline Skeleton

A novel one-pot synthesis of norharman (**1**) and 1- or 6-substituted β -carbolines have been achieved by Wang and co-workers (Scheme 1) [109]. The designed synthesis starting from racemic tryptophan (**74**) and various amino acids (**75**) proceeds through sequential steps, driven by a reaction with I_2 and TFA, followed by decarboxylation, deamination, Pictet–Spengler reaction and oxidation. By using various amino acids, further alkaloids and synthetic analogues were also obtained.

Wang et al. 2018

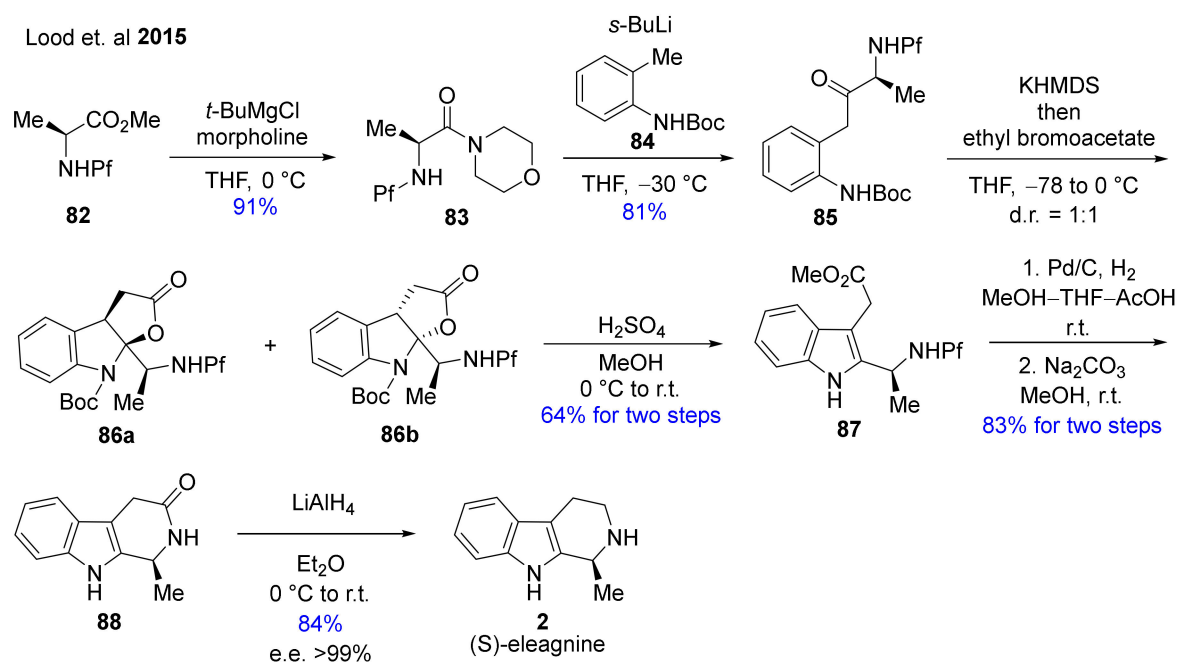


Mechanistic proposal:



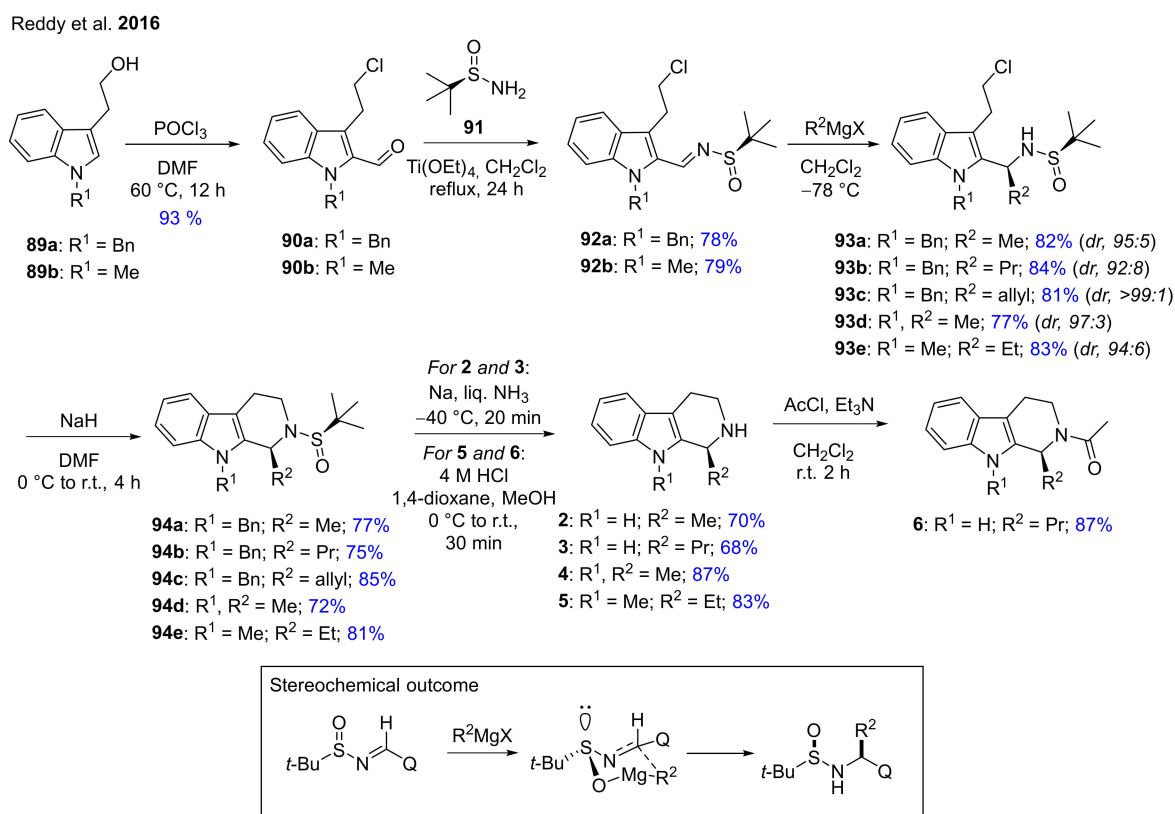
Scheme 1. One-pot synthesis of natural product norharman (**1**) and further β -carboline derivatives.

In 2015, Lood et al. reported the new enantiospecific gram-scale synthesis of (*S*)-eleganine/(*-*)-tetrahydroharmane (**2**) (Scheme 2) [110]. Their synthesis started from the previously modified amino acid methyl ester **82**, which included the appropriate chirality. The treatment of **82** with morpholine in the presence of *t*-BuMgCl resulted in morpholine amide **83**. Amide **83** went through a subsequent lateral lithiation, which was followed by the addition of Boc-protected *o*-toluidine (**84**) to furnish ketone **85** in gram scale. After that, ketone **85** was treated with KHMDS, then the potassium enolate formed was quenched with ethyl bromoacetate, which resulted in a diastereomeric mixture of indoline γ -lactones (**86a** and **86b**). Treating this diastereomeric mixture with sulfuric acid in MeOH facilitated a sequential lactone ring opening and Boc-cleavage to form indole **87**. Hydrogenolysis of Pf-protecting group and treatment of the free amine with Na_2CO_3 base led to lactam **88**. As a final step, $LiAlH_4$ reducing agent was applied on **88** to provide (*S*)-eleganine (**2**) in a gram-scale synthesis with an enantiomeric excess (e.e.) >99%.



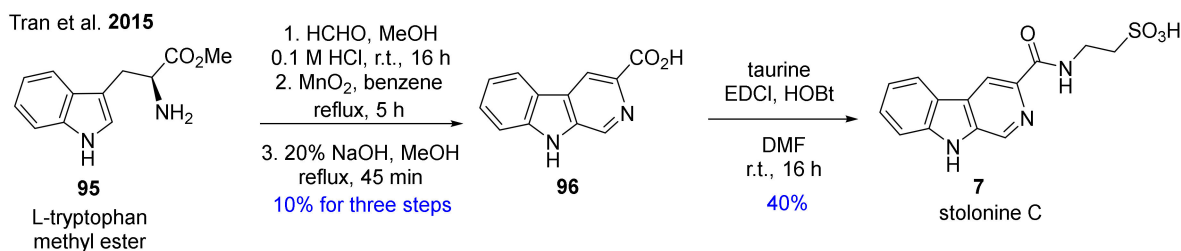
Scheme 2. Enantioselective synthesis of (S)-eleagnine (2).

Reddy et al. have accomplished the stereoselective synthesis of natural compounds (–)-tetrahydroharman (2), (–)-komaroidine (3), *N*-tetrahydroharman (4), (+)-1-ethyl-9-methyltetrahydro- β -carboline (5) and (+)-*N*-acetylkomaroidine (6) using Ellman’s sulfinamide [(*R*)-*tert*-butanesulfinamide, 91] [111] as a chiral auxiliary generally used for the preparation of chiral amines (Scheme 3) [112]. The use of this readily available reagent as the source of asymmetric induction to establish the stereochemical configuration of these alkaloids makes this approach convenient and practical. *N*-Sulfinylimines 92 were prepared with the reaction of 90 and (*R*)-*tert*-butanesulfinamide (91) in the presence of $\text{Ti}(\text{OEt})_4$. The addition of alkyl-Grignard reagent to 92 led to the corresponding sulfinamides 93 with the expected stereochemical outcome and with high diastereoselectivity. In this reaction, the occupation of the less hindered equatorial position in the six-membered transitional state resulted in a favorable attack from the same face (Scheme 3). The synthesis was continued with a reductive or acidic removal of both the benzyl group and the sulfinyl auxiliary to afford products 2–5. A final classical acetylation on the piperidine nitrogen atom was needed to prepare target molecule 6.



Scheme 3. Synthesis of (–)-tetrahydroharman (2), (–)-komaroidine (3), *N*-(+)-methyltetrahydroharman (4), (+)-1-ethyl-9-methyltetrahydro- β -carboline (5) and (+)-*N*-acetylkomaroidine (6).

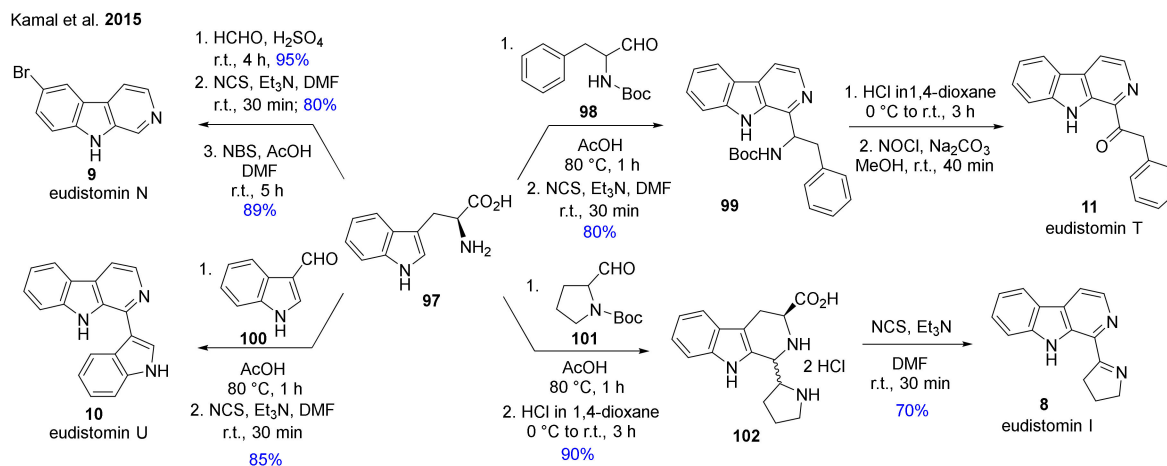
The chemical study on the marine tunicate *Cnemidocarpa stolonifera* contributed to the discovery and synthesis of 3 new alkaloids, including a β -carboline alkaloid called stolonine C (7, Scheme 4) [20]. The synthesis starts from L-tryptophan methyl ester (95) via Pictet–Spengler reaction with formaldehyde followed by dehydrogenation of the C-ring and hydrolysis of the ester group. Intermediate 96 was transformed into an amide with taurine resulting in final product 7.



Scheme 4. Synthesis of stolonine C (7).

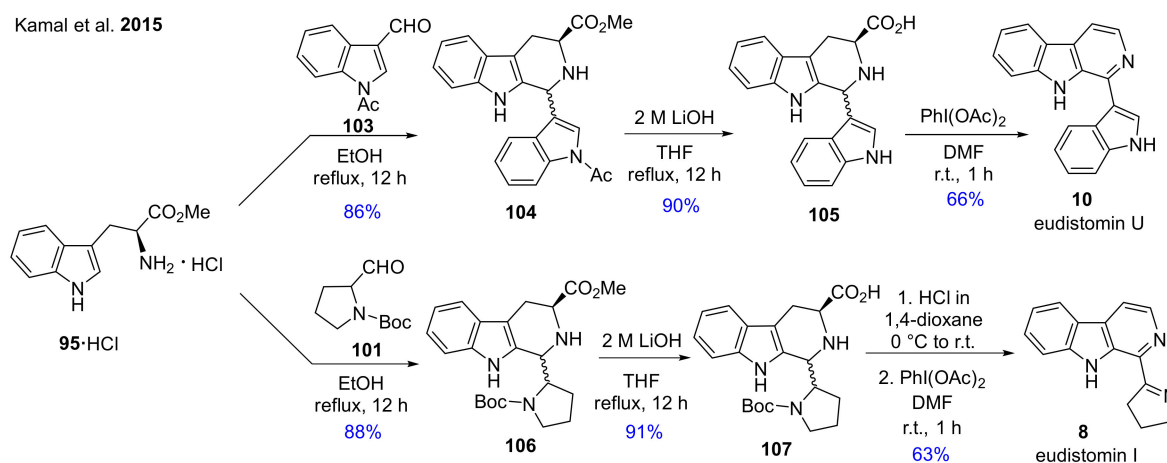
Eudistomins are important natural products belonging to the family of β -carboline alkaloids, and show a wide variety of biological activities [26,113–115]. Kamal et al. have developed an efficient method for the synthesis of diverse β -carboline derivatives and naturally occurring alkaloids such as eudistomins I, N, T and U (8, 9, 10 and 11, respectively) [116] which are isolated from ascidians (Scheme 5) [23,24,27,116,117]. The protocol is based on the Pictet–Spengler reaction of L-tryptophan (97) and the corresponding aldehydes, subsequent decarboxylative aromatization of the C-ring employing NCS and variation of classical synthesis methods in the final steps, providing an easier and more convenient pathway compared to the previously reported methods. In addition, the most efficient synthesis of 10 has been described using a one-pot approach.

It is worth mentioning that the NBS-promoted oxidative dehydrogenation of the C-ring has also been devised and has become very popular recently [118]. The method also provides access to a variety of β -carboline and can be applied effectively in generating molecule libraries.



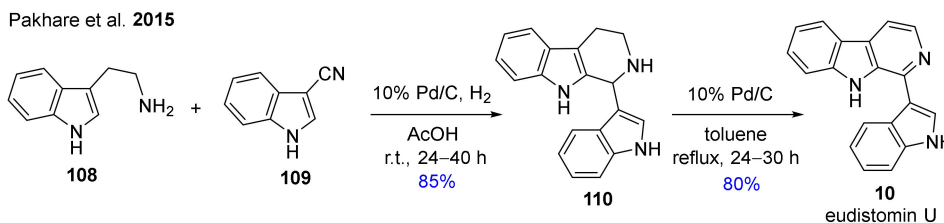
Scheme 5. Kamal's improved synthesis of eudistomins I (8), N (9), T (10) and U (11).

The beneficial pharmacological efficacy of eudistomins has prompted other researchers to further improve their total synthesis [115]. In 2015, also Kamal et al. reported a three-step synthesis of eudistomin U (10) starting from L-tryptophan methyl ester (95 · HCl), which underwent a Pictet–Spengler condensation with *N*-acetylindole-3-carboxaldehyde (103) to form TH β C ester 104 (Scheme 6). Ester hydrolysis and loss of the *N*-acetyl group of intermediate 104 provided carboxylic acid 105. Compound 105 went through an iodobenzene diacetate-mediated oxidative decarboxylation to afford 10 in 51% overall yield (Scheme 5) [119]. Using this method, the authors also developed the synthesis of eudistomin I (8) [119], where iodobenzene diacetate mediates not only decarboxylation and aromatization of the TH β C ring, but also the partial dehydrogenation of the pyrrolidine ring in a one-pot operation.



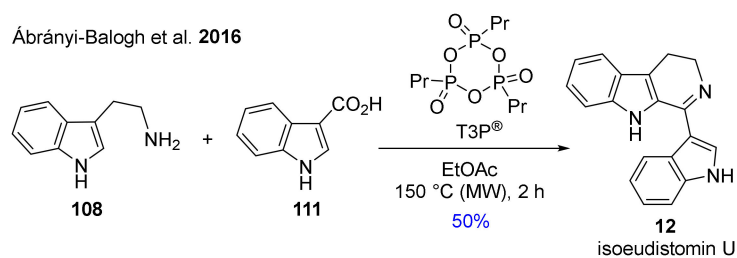
Scheme 6. Kamal's synthesis of eudistomins U (10) and I (8).

An alternative synthesis of **10** through the reaction of tryptamine (**108**) and indole-3-carbonitrile (**109**) followed by dehydrogenation of intermediate **110** with palladium on carbon was described in two steps with 68% overall yield (Scheme 7) [120].



Scheme 7. Synthesis of eudistomin U (**10**).

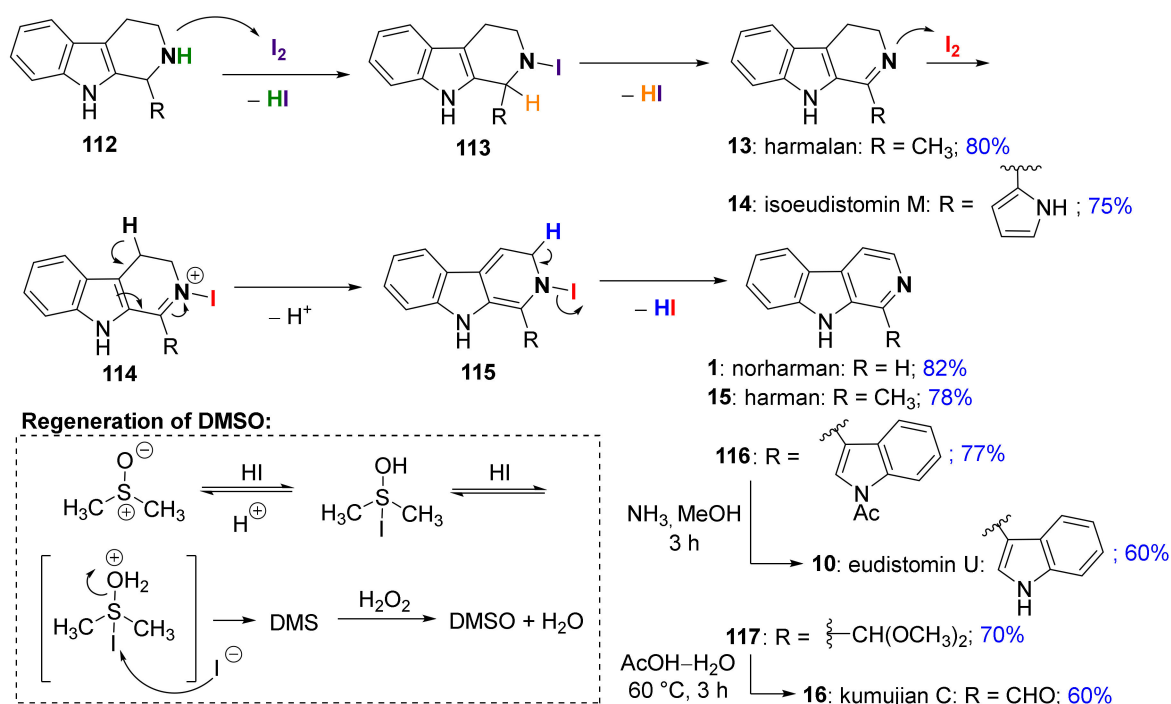
In 2016, Ábrányi-Balogh and co-workers developed a microwave-assisted one-pot protocol in the presence of T3P[®] for the preparation of substituted 3,4-dihydro- β -carbolines (DH β Cs). The new method was also applied for the synthesis of isoeudistomin U alkaloid (**12**) starting from tryptamine (**108**) and indole-3-carboxylic acid (**111**) with 50% yield (Scheme 8) [121].



Scheme 8. Ábrányi-Balogh's synthesis of isoeudistomin U (**12**).

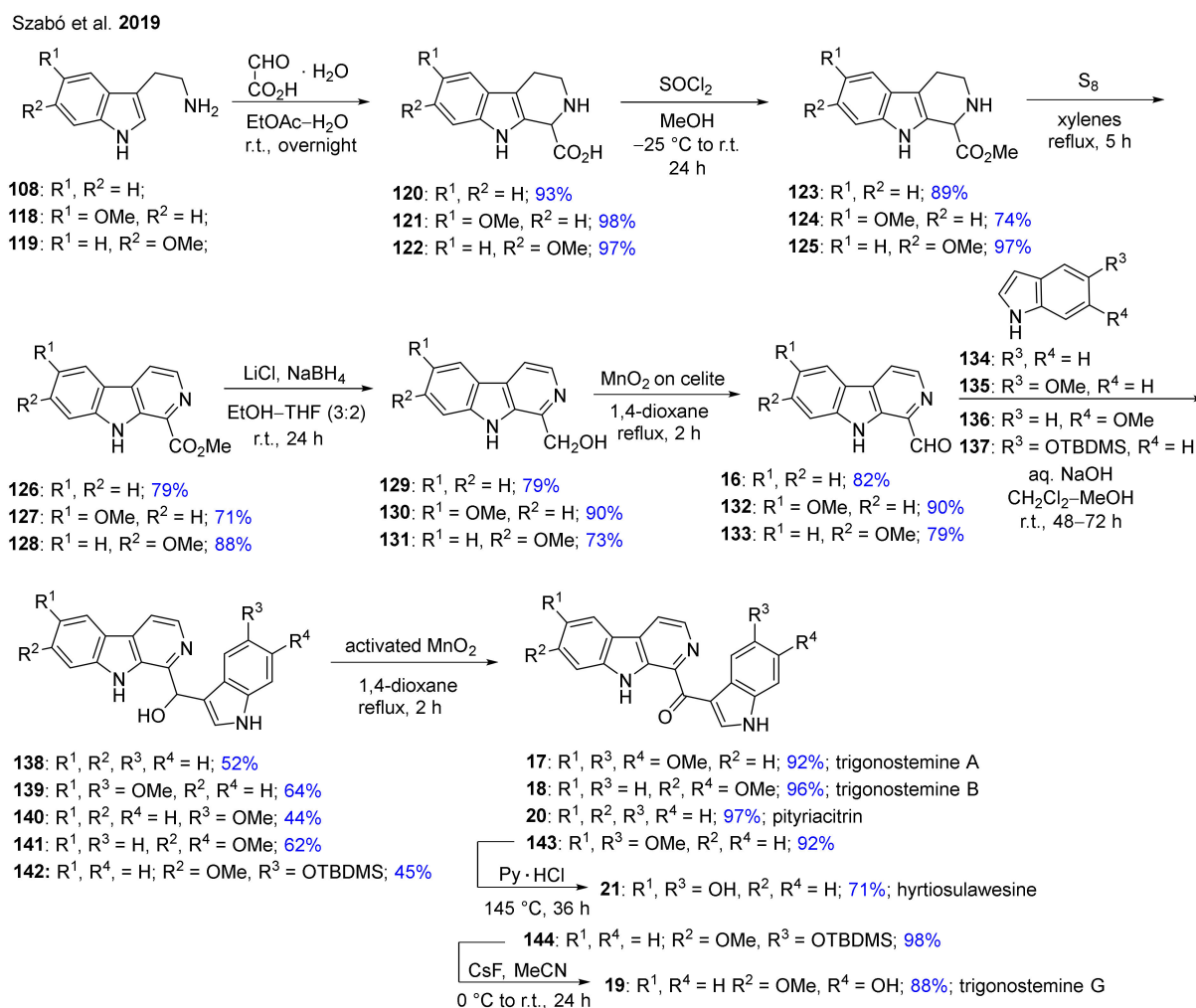
Gaikwad et al. have developed an iodine-mediated metal-free protocol for the chemoselective dehydrogenation and aromatization of TH β Cs into DH β Cs and β -carbolines in the presence of H₂O₂ as the oxidant in DMSO (Scheme 9) [122]. The method was applicable not only for the preparation of variously substituted β -carbolines but also for that of bioactive natural products eudistomin U (**10**), harmalan (**13**), isoeudistomin M (**14**), norharman (**1**), harman (**15**) and kumujian C (**16**). The plausible reaction mechanism of the dearomatization protocol was also presented, which starts with a *N*-iodination followed by an *N*-dehydroiodination of TH β Cs **112** and **113**, respectively. These two steps result in the imine (**13** or **14**), which is then further transformed into an ammonium intermediate (**114**) by an additional *N*-iodination. After deprotonation and dehydro-iodination, the corresponding β -carboline (**1**, **15**, **116** or **117**) is formed. The generated HI reacts with DMSO to give molecular iodine and dimethyl sulfide (DMS). The role of H₂O₂ is to speed up the reaction by the oxidation of DMS back into DMSO. Intermediates **116** and **117** could then be transformed into eudistomin U (**10**) or kumujian C (**16**) in the final step.

Gaikwad et al. 2018

Reaction conditions: I₂, DMSO, H₂O₂, 60–100 °C, 1–12 h

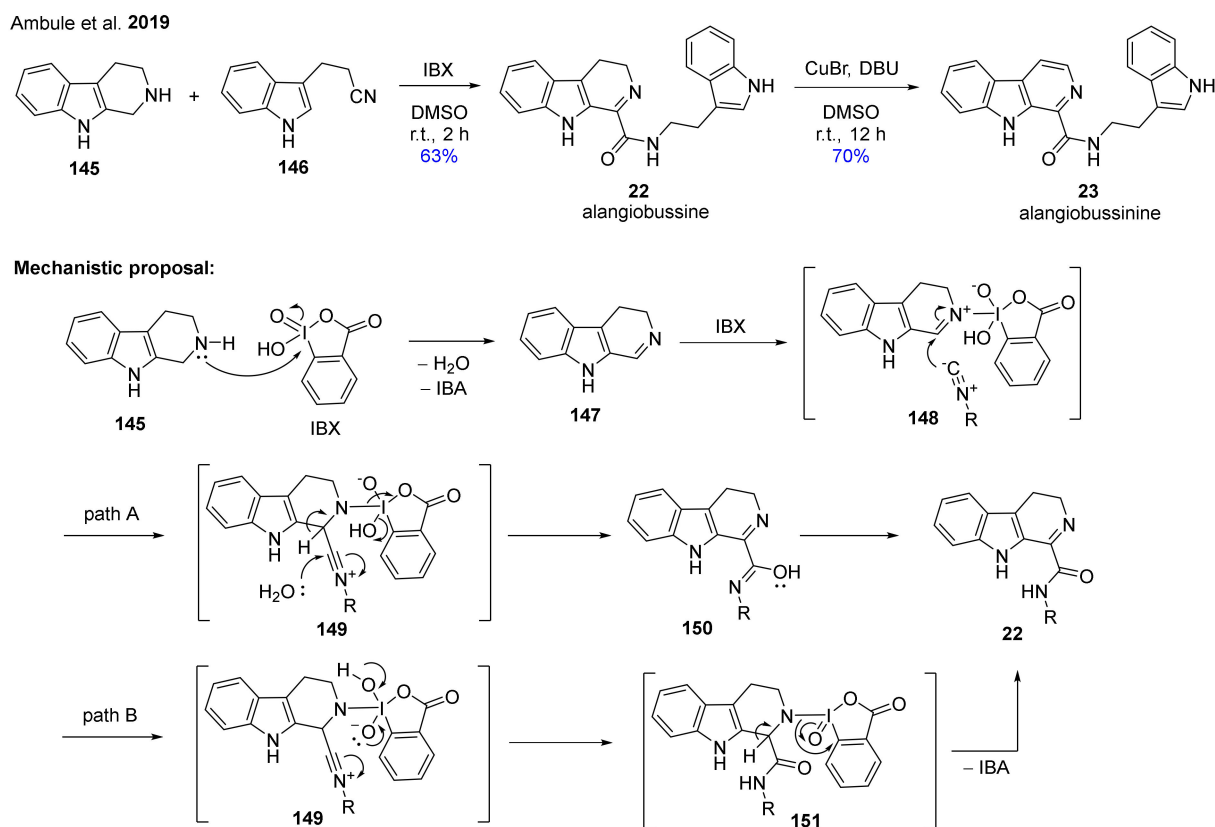
Scheme 9. Synthesis of harmalan (13), isoeudistomin M (14), norharman (1), harman (15), eudistomin U (10) and kumujian C (16) via iodine-mediated dehydrogenation.

Szabó et al. have recently published the first total synthesis of alkaloids trigonostemine A, B and G (17–19) and the preparation of pityriacitrin (20) and hyrtiosulawesine (21) (Scheme 10) [123,124]. The appropriate key intermediates kumujian C (16) and its derivatives (132, 133) were prepared via a novel and practical synthesis route. In the first step, the Pictet–Spengler reaction of tryptamines (108, 118, 119) and glyoxylic acid mono-hydrate gave TH β C carboxylic acids (120–122). This was followed by the esterification of compounds 120–122. Aromatization of the C-ring was carried out in the presence of elemental sulfur. Afterwards the ester group of 126–128 was reduced to give alcohols. Finally, oxidation of the hydroxy group in alcohols 129–131 was achieved using MnO₂ on Celite[®], and aldehydes 16, 132, 133 were isolated in good yields. The synthesis of alkaloids 17–21 was then performed from these building blocks (16, 132, 133), which were reacted with indoles (134–137) to afford secondary alcohols and then oxidized with active MnO₂ to provide the first total synthesis of trigonostemines A (17) and B (18), carried out in 7 steps. At the same time, this pathway represents a new synthetic method for the preparation of pityriacitrin (20). An additional step was needed to produce hyrtiosulawesine (21), where the target compound was obtained by O-demethylation of derivative 143 in pyridine hydrochloride. The first total synthesis of trigonostemine G (19) was performed in 8 steps analogously to the above method. The sensitive OH moiety of the indole was protected by a TBDMS group, which was removed under mild conditions in the final step with CsF (Scheme 10).



Scheme 10. Total synthesis of trigonostemines A (17), B (18) and G (19) and a novel synthetic route for the preparation of pityriacitrin (20) and hyrtiosulawesine (21).

The IBX-mediated total synthesis of alangiobussine (22) and alangiobussinine (23) was achieved through the oxidative addition of isocyanide **146** to tryptoline (**145**) [125]. The general method (Scheme 11) represents an efficient preparation for imino-carboxamides, where tetrahydroisoquinolines and tryptolines were reacted with isocyanides. The IBX-mediated oxidative addition protocol was successfully applied for the gram-scale synthesis of natural product alangiobussine (22), which was further transformed to alangiobussinine (23) through the dehydrogenation of the C-ring in the presence of CuBr and DBU. The plausible reaction mechanism was also investigated by isotopic labeling and real-time NMR experiments, which made two pathways probable.

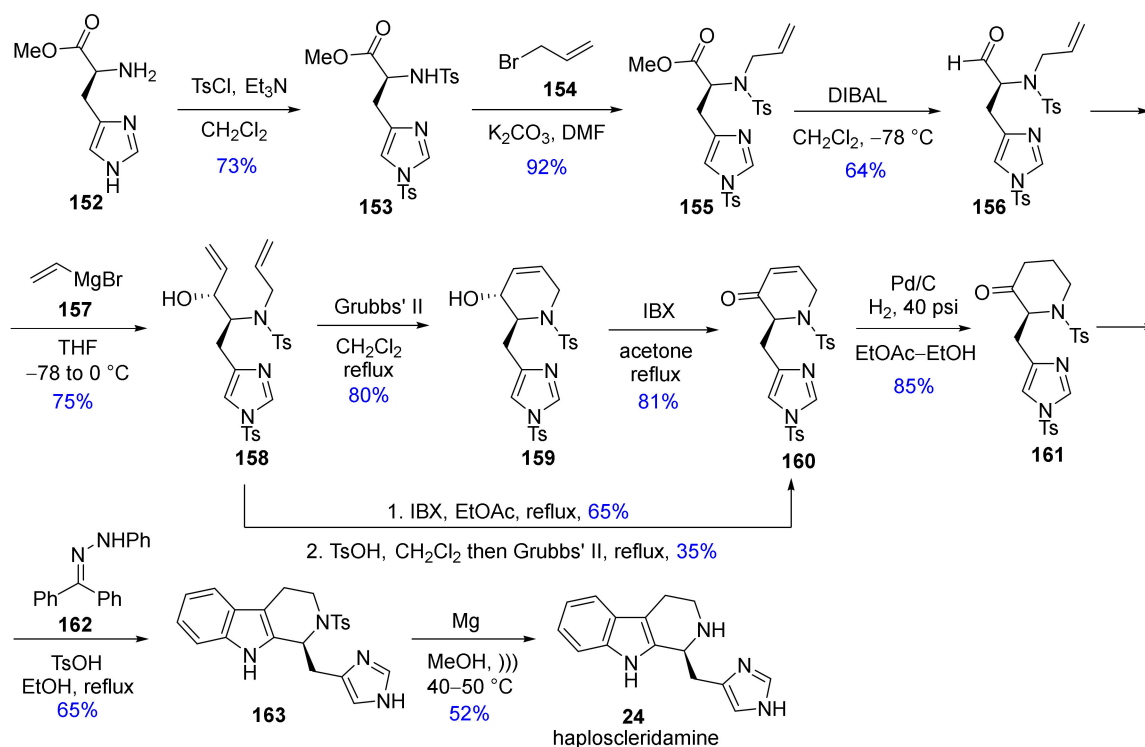


Scheme 11. Synthesis of alangiobussine (**22**) and alangiobussinine (**23**).

The first asymmetric total synthesis of haploscleridamine (**24**) was accomplished from histidine (Scheme 12) [126]. The synthesis starts with the tosylation of histidine methyl ester (**152**), then *N*-allylation with allyl bromide (**154**) was applied on intermediate **153** leading to compound **155**, followed by a partial ester reduction to afford aldehyde **156**. After Grignard reaction with vinylmagnesium bromide (**159**), alcohol **158** was formed, which was transformed into tetrahydropyridine congener **159** via ring-closing metathesis. After oxidation of alcohol to ketone **160**, and reduction C=C double bond to intermediate **161**, indole formation took place via Buchwald modification of the classical Fischer indole synthesis to obtain **163**. Finally, **24** was synthesized by the reductive deprotection of **163** with Mg under ultrasonication conditions.

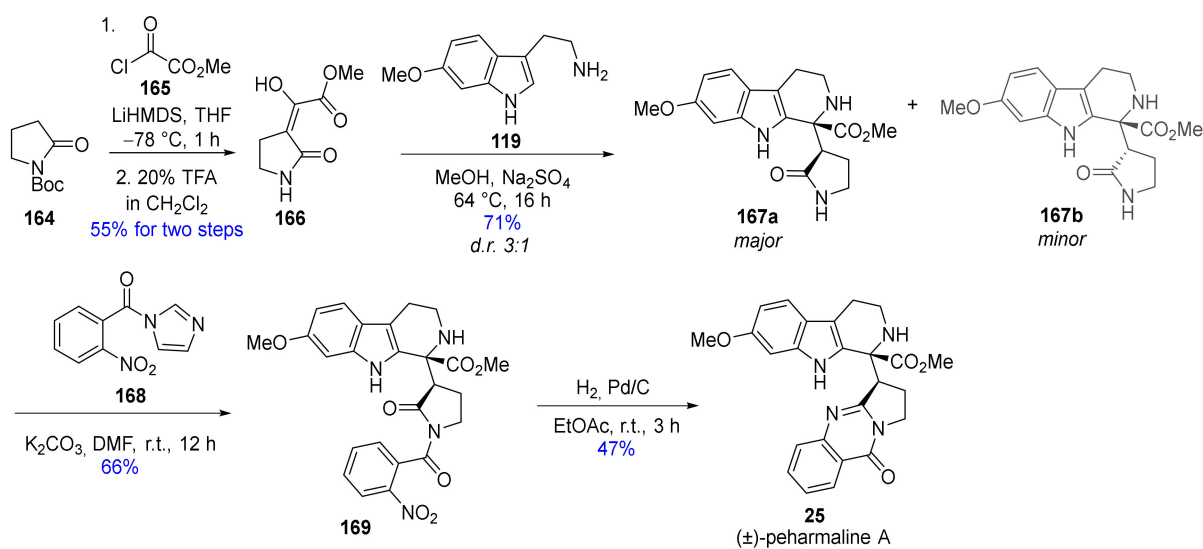
The first total synthesis of the potential anticancer agent, the β -carboline-vasicinone hybrid alkaloid (\pm)-peharmaline A (**25**) was accomplished in a short sequence starting from readily available starting materials (Scheme 13) [127]. Boc-protected pyrrolidone **164** was reacted with acyl chloride **165** in the presence of LiHMDS. After treatment with TFA, the compound thus formed (**166**) was reacted with 6-methoxytryptamine (**119**). The Pictet–Spengler reaction did not take place in a stereoselective manner: besides major diastereomer **167a**, minor product **167b** was also obtained. However, the inversion of the chiral center was observed in the minor diastereomer **167b** during the next step. Natural product **25** was synthesized by *N*-acylation of the mixture of compounds **167a** and **167b** with reagent **168** and subsequent catalytic hydrogenation of nitro derivative **169**.

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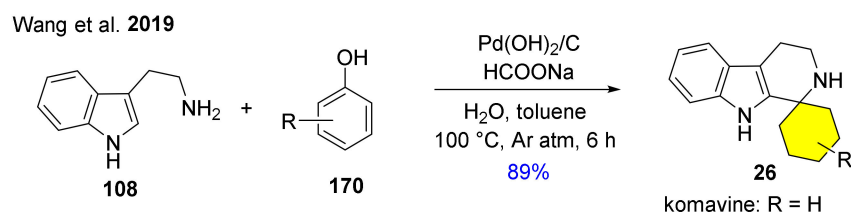
Scheme 12. Synthesis of haploscleridamine (24).

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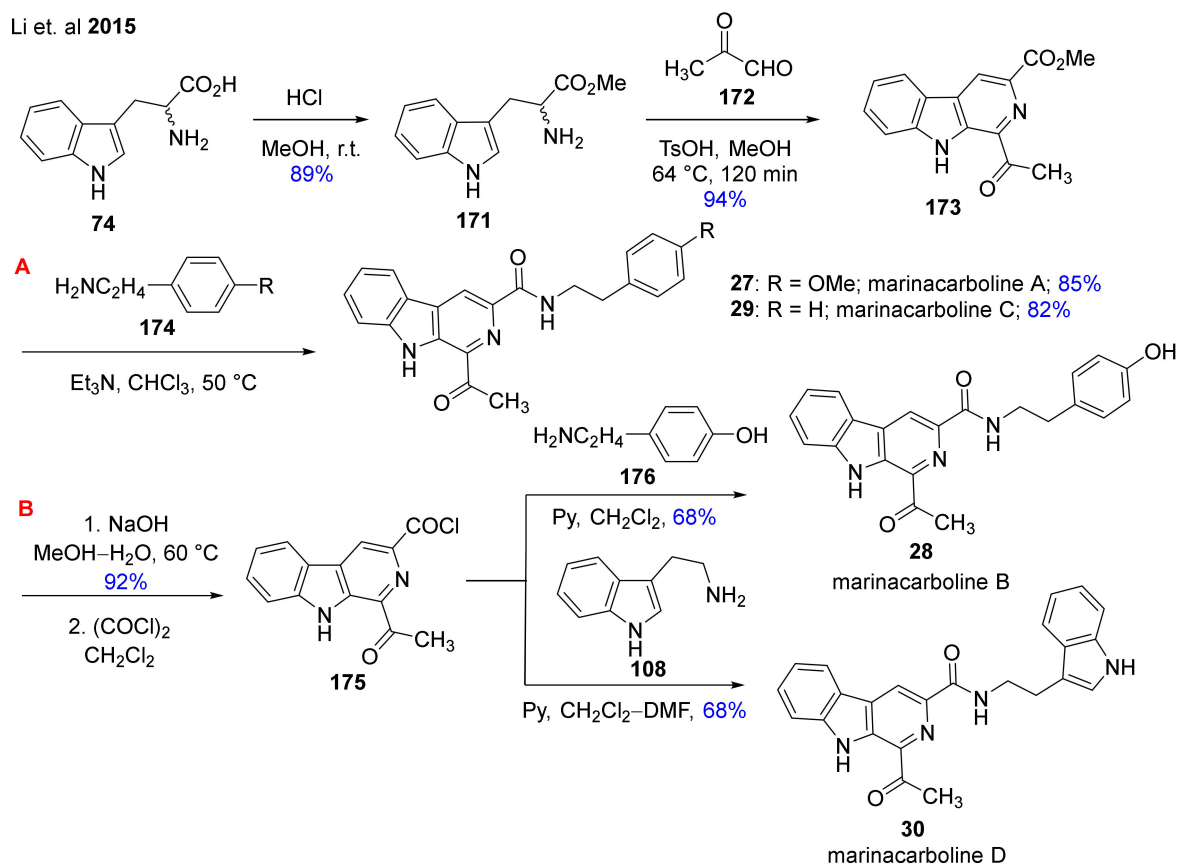
Scheme 13. Synthesis of (±)-peharmaline A (25).

Recently, Wang et al. [128] developed a new synthesis of komavine (**26**), a spiro-TH β C derivative, and several analogous compounds via Pd-catalyzed cross-annulation of phenols (**170**) and tryptamine (**108**) with good functional group tolerance (Scheme 14). With this alternative protocol, TH β C derivatives were synthesized with moderate to excellent yield through the C–O bond cleavage of phenols, C–H bond activation of tryptamines and C–N/C–C bond formation. The presented work offers an efficient protocol for converting phenolic lignin model monomers into valuable compounds.



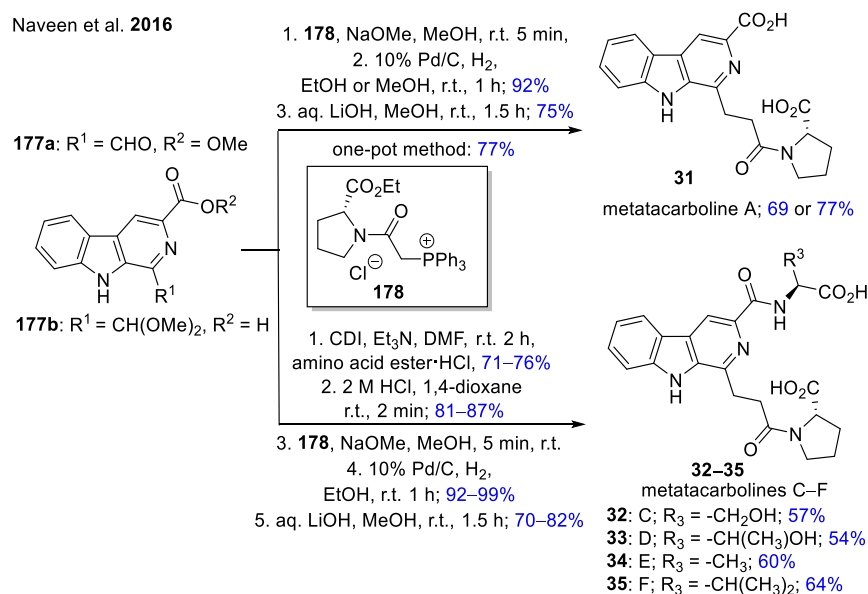
Scheme 14. Pd-catalyzed cross-annulation of phenols (**170**) and tryptamines (**118**).

A series of marine β -carboline alkaloids marinacarboline A–D (**27–30**) was achieved by Li et al. (Scheme 15) [57]. Their strategy applies classical synthetic methods starting from racemic tryptophan (**74**). First, esterification of **74** was implemented, then a Pictet–Spengler reaction was performed to construct the β -carboline skeleton and the key intermediate (**173**) of the synthetic route. Amidation of **173** with the appropriate amines (**174**) resulted in marinacarboline A (**27**) and C (**29**). For the synthesis of the other two marinacarboline (**28** and **30**), the ester group of the key intermediate **173** was hydrolyzed, then transformed into an acid chloride (**175**), which was reacted with tyramine (**176**) or tryptamine (**108**) to achieve the synthesis of marinacarboline B (**28**) and D (**30**).



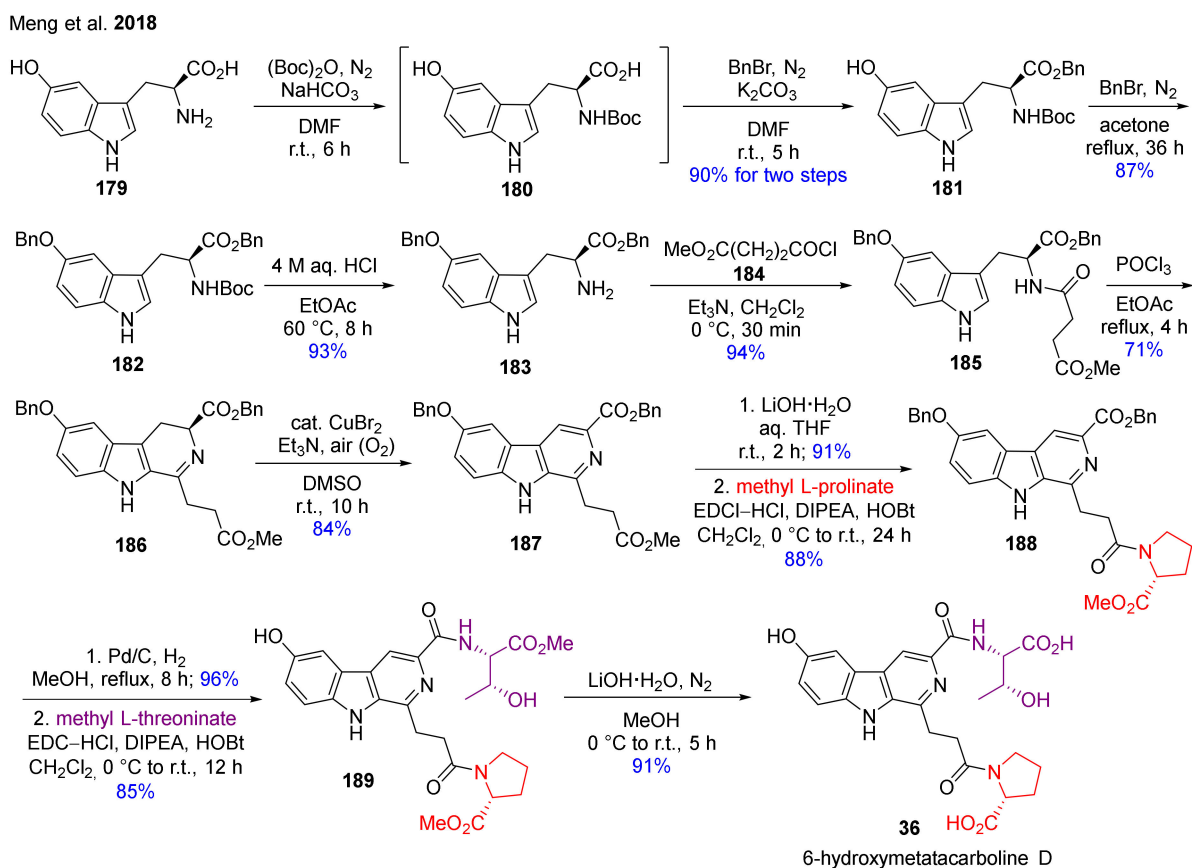
Scheme 15. Synthesis of alkaloids marinacarboline A–D (**27–30**).

The simple total synthesis of water-soluble metatacarbolines A (**31**) and C–F (**32–35**) has been accomplished starting from β -carboline building blocks **177** [59]. Metatacarboline A was prepared in 3 steps by applying the Wittig reaction of aldehyde **177a** with **178**, followed by the catalytic reduction of the previously formed double bond and hydrolysis of ester groups to afford the desired product **31** (Scheme 16). Metatacarbolines C–F were produced in 5 steps starting from the protected aldehyde precursor **177b**. First, the coupling of **177b** with various amino acid esters was performed, then a formyl moiety was formed via acidic treatment of the acetal, followed by the same three steps described previously to form the other four metatacarbolines (**32–35**).



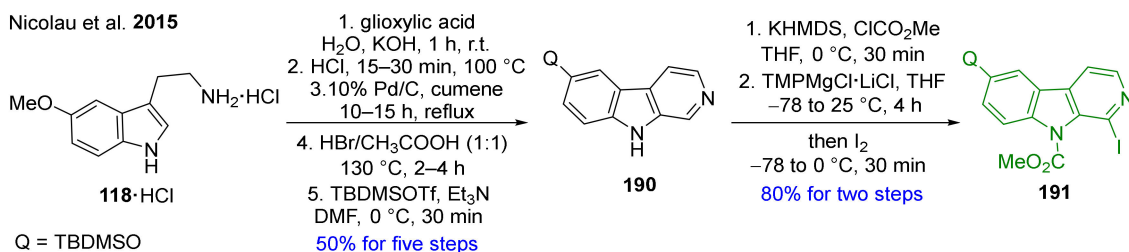
Scheme 16. Total synthesis of metatacarbolines A, C, D, E and F (**31–35**).

The first total synthesis of 6-hydroxymetatacarboline D (**36**) has been developed in 12 steps by Meng et al. via CuBr_2 -catalyzed mild oxidation method by the dehydrogenation of the $\text{DH}\beta\text{C}$'s C-ring (Scheme 17) [129]. The synthesis starts from 5-hydroxytryptophan (**179**), which was converted into Boc- and benzyl-protected compound **182** by applying protecting group chemistry. Compound **185** was obtained through deprotection and acylation. The β -carboline skeleton of **186** was formed via Bischler–Napieralski reaction, which was followed by the mild CuBr_2 -catalyzed conversion of $\text{DH}\beta\text{C} **186** into β -carboline **187**. The hydrolysis of ester **187** and the reaction with methyl L-prolinate followed by a catalytic debenzoylation and amide formation with methyl L-threoninate led to the formation of **189**. After all, double ester hydrolysis resulted in final product **36**.$



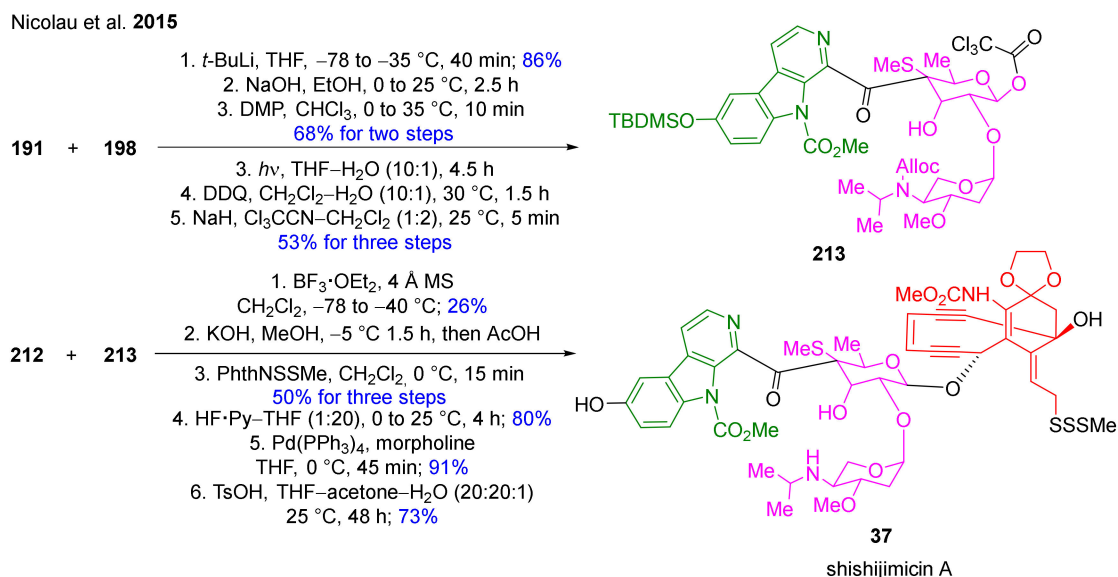
Scheme 17. Synthesis of 6-hydroxymetatacarboline D (36).

The total synthesis of shishijimicin A (37, Table 1), a marine natural product with remarkable antitumor activity has been described by Nicolau et al. in 48 steps (Schemes 18–21) [130]. Their method separates the natural product into three key intermediates. One of them, the β -carboline framework (191, Scheme 18) has been constructed in 8 steps by applying methods known from the literature [131] and functional group transformations to prepare the protected and in position 1 iodine-functionalized key intermediate (191).

Scheme 18. Total synthesis of shishijimicin A (37)—Part 1: Synthesis of β -carboline framework 191.

idation of oxime **199** with *t*-BuOCl resulted in a spontaneous [3+2] dipolar cycloaddition, which led to **200**. This step was followed by a smooth deprotection and oxidation, then the key enediyne fragment **202** was added to the molecule. Removal of the MEM group followed by Swern oxidation and a further oxidation step furnished ketone **204**. Horner–Wadsworth–Emmons olefination was performed, then intermediate **207** bearing a terminal acetylene bond was prepared through a sequence involving removal of the acetate group, cleavage of the TIPS moiety and silylation. Opening of the isoxazole ring was followed by the direct and stereoselective cyclization of **208** into **209** with the inversion of the configuration. The *N*-phthalide moiety was then converted to a methyl carbamate group in two steps to afford enediyne lactone **210**. Reductive cleavage of the lactone function resulted in diol **211**. Subsequent bis-silylation, selective cleavage of the primary OTMS moiety, Mitsunobu reaction, thioacetate formation and cleavage of the secondary OTMS group led to target molecule **212**.

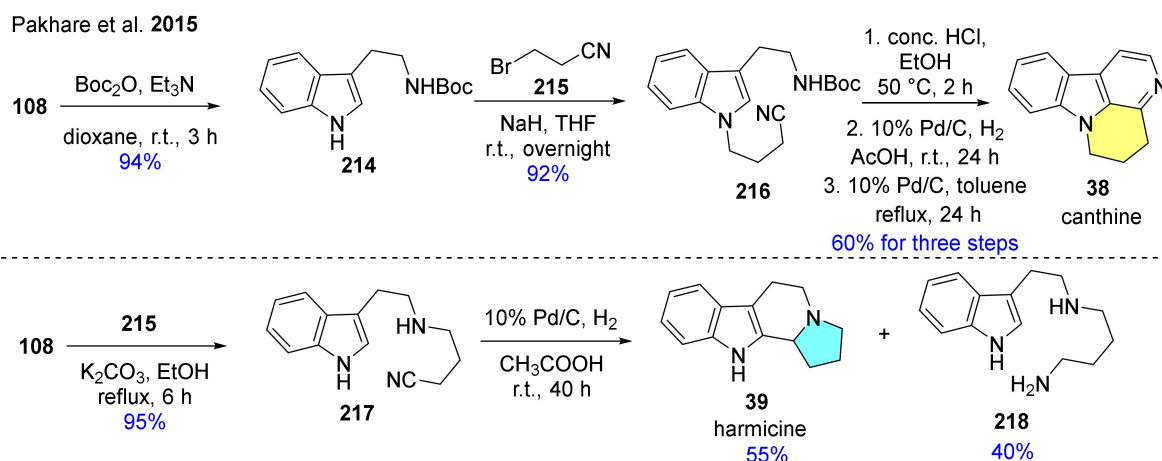
In the final steps, the β -carboline skeleton **131** was connected to the disaccharide **198**, then various transformations were carried out to achieve intermediate **213** (Scheme 21). Finally, enediyne **212** and **213** were combined to complete the synthesis of shishijimicin A (**37**).



Scheme 21. Total synthesis of shishijimicin A (**37**).

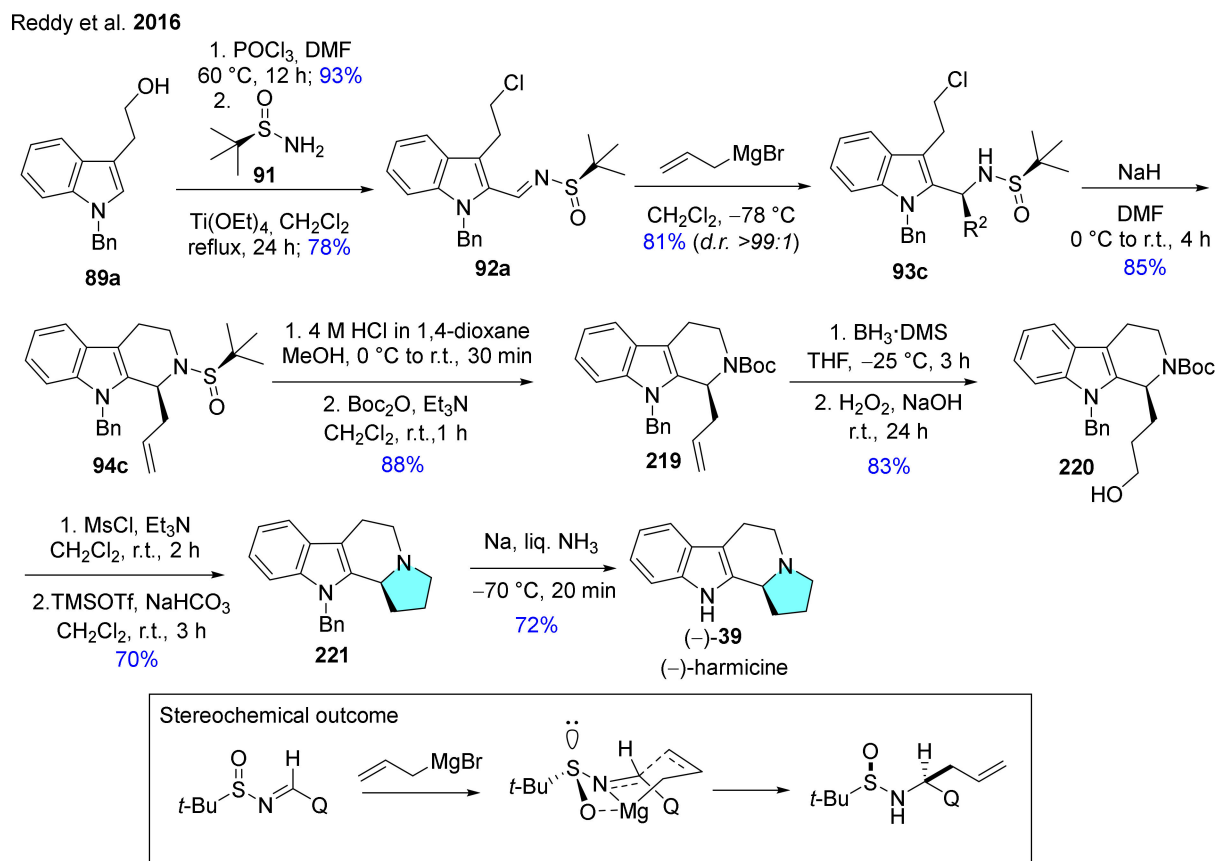
3. Fused Ring Systems Bearing a β -Carboline Skeleton

The reductive Pictet–Spengler reaction has been applied successfully for the preparation of canthine (**38**), the framework of biologically active canthine-6-ones, and harmicine (**39**) (Scheme 22) [120]. Instead of the commonly used aldehydes, nitriles (**216**, **217**) were applied in the reductive intramolecular cyclization protocol, which was carried out with 10% Pd/C and H₂. An additional dehydrogenation of the C-ring in the presence of 10% Pd/C catalyst was needed to form **38**.



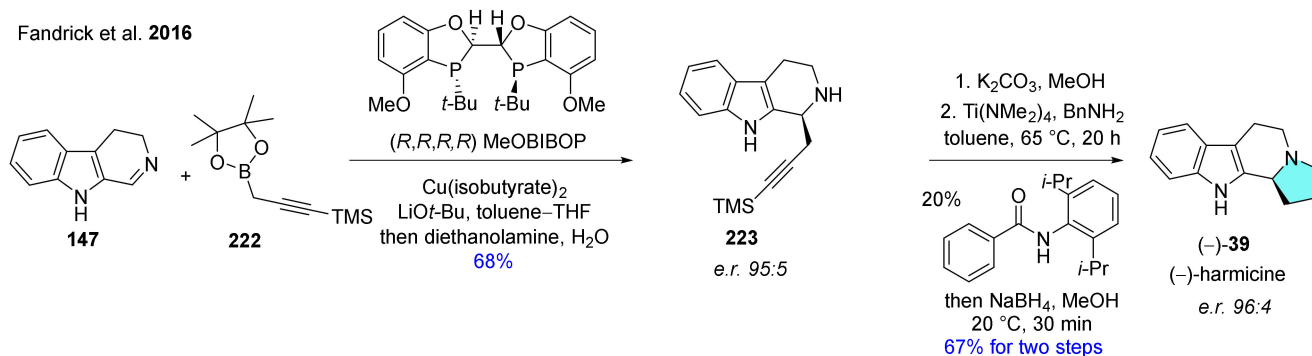
Scheme 22. Synthesis of canthine (**32**) and harmicine (**33**) via reductive Pictet–Spengler cyclization.

The synthetic route of (–)-harmicine ((–)-**39**) was performed as previously mentioned in part in Scheme 2, however with some differences (Scheme 23) [112]. *N*-Sulfinylimine was reacted with allylmagnesium bromide to afford the homoallylic sulfonamide with >99:1 ratio of diastereomers. In this reaction, a six-membered transition state also occurred, providing a high level of stereocontrol [132–134]. Compound **94c** was prepared via base-catalyzed cyclization, then deprotection of the sulfinyl group and protection of the free amine with Boc_2O furnished **219**. Hydroboration of **219** resulted in alcohol **220**, which was converted in the next step into its mesylate. Then deprotection of the Boc group and $\text{S}_{\text{N}}2$ substitution of mesylate with a secondary amine took place. In the final step, debenzoylation of compound **221** led to (–)-**39**.



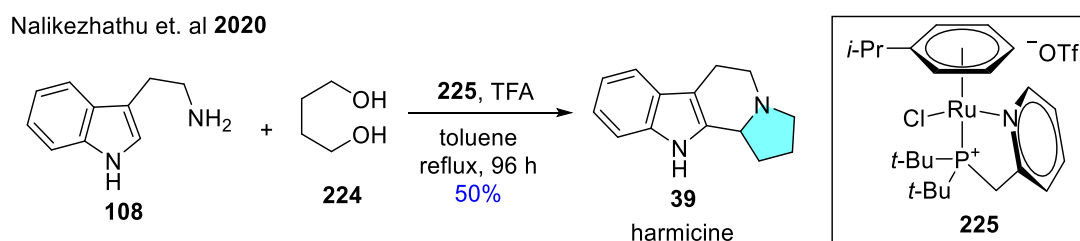
Scheme 23. Synthesis of (–)-harmicine ((–)-**39**).

The copper-catalyzed propargylation of cyclic aldimines was developed by Fandrick et al. (Scheme 24) [135]. By applying this procedure, (–)-(*S*)-harmicine ((–)-**39**) was synthesized from DHβC (**147**), using coupling agent **222**, copper(II)isobutyrate and a chiral ligand to give intermediate **223**, which was deprotected and transformed into (–)-**39** in a titanium-catalyzed ring closure and subsequent C=N bond reduction with good yield and excellent stereoselectivity.



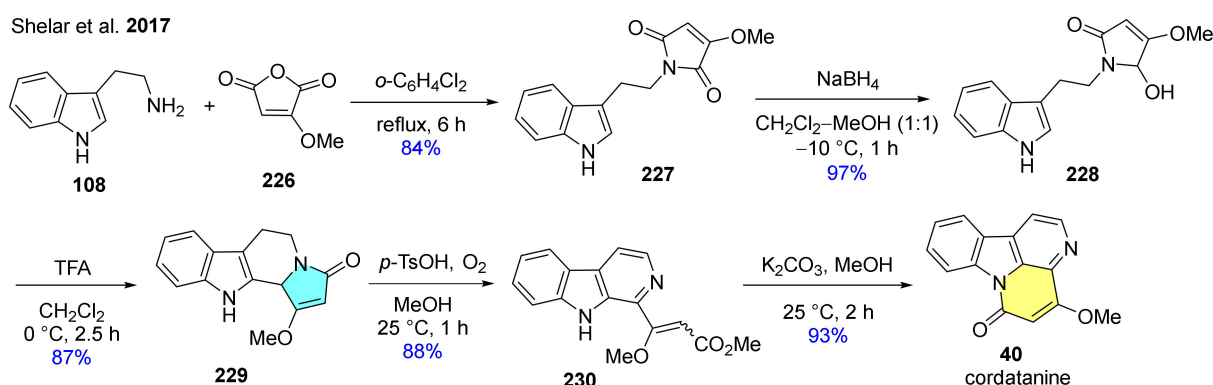
Scheme 24. Synthesis of (–)-harmicine ((–)-**39**).

The one-step synthesis of racemic harmicine (**39**) has been recently reported by Nalikezhathu et al. (Scheme 25) [136]. The new method is based on the pyridyl-phosphine ruthenium(II)-catalyzed tandem Pictet-Spengler reaction through the amination of alcohols. The β -carboline skeleton was effectively constructed providing several synthetic analogues. The subsequent cycloamination was also successfully applied for the synthesis of carbolines including harmicine **39**, where its tetracyclic structure was built up in only one step from tryptamine (**108**) and 1,4-butanediol (**224**), in the presence of trifluoroacetic acid and Ru-catalyst (**225**).



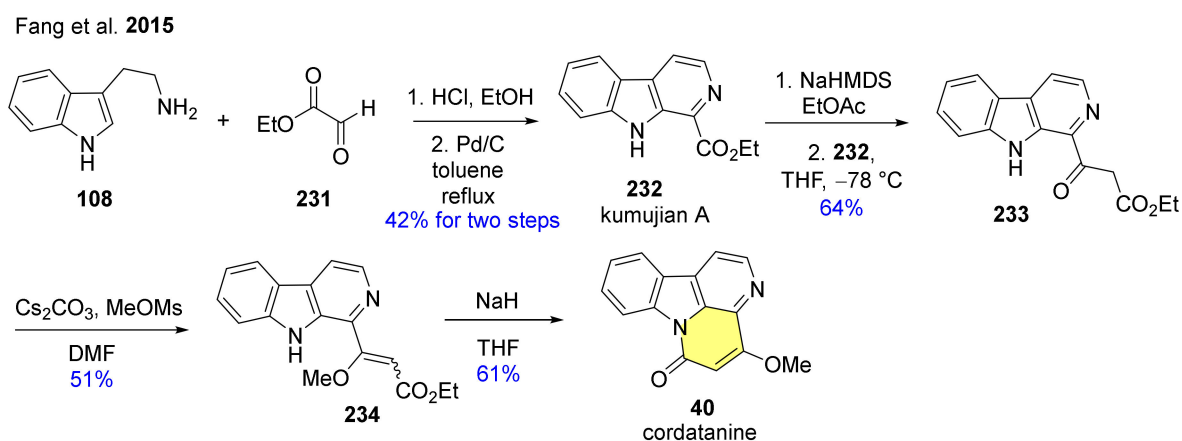
Scheme 25. One-step synthesis of racemic harmicine (**39**).

The practical total synthesis of canthine derivative cordatanine (**40**) has also been accomplished (Scheme 26) [137] starting from tryptamine (**108**) and methoxymaleic anhydride (**226**), and by subsequent regioselective reduction of methoxymaleimide intermediate **227** into hydroxy derivative **228**. Acid-catalyzed intramolecular dehydrative cyclization of **228** furnished compound **229**. The methanolysis of lactam to ester and double oxidative aromatization of the C-ring took place in a one-pot reaction to give **230**. The intramolecular cyclization in the presence of K_2CO_3 in MeOH led finally to cordatanine (**40**).



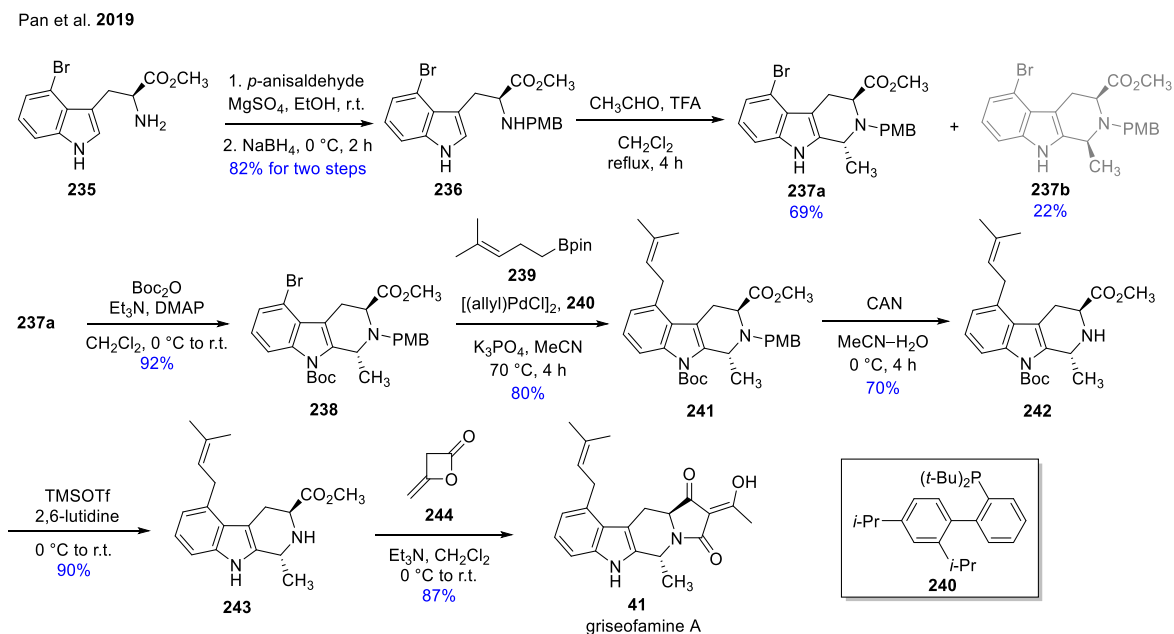
Scheme 26. Five-step synthesis of cordatanine (40).

An alternate synthesis of cordatanine (40) has also been developed (Scheme 27) [138]. Tryptamine (108) was used again as the starting material which underwent a Pictet–Spengler reaction with ethyl glyoxalate (231), followed by direct oxidative aromatization catalyzed by Pd/C to give the synthetic intermediate kumujian A (232). Intermediate 232 was transformed into 233 via Claisen condensation. *O*-Methylation of 233 with methyl methanesulfonate in the presence of cesium carbonate resulted in a cis-trans mixture of 234. The final ring closure reaction was achieved by intramolecular amidation using NaH to obtain target molecule 40.



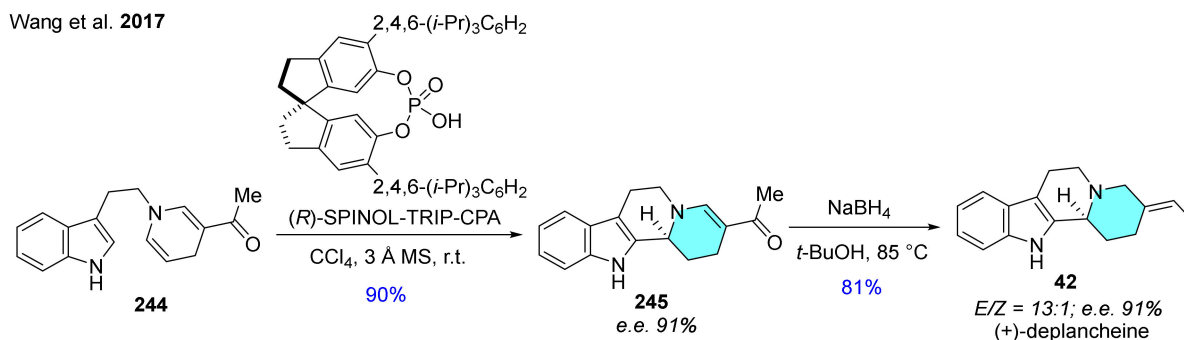
Scheme 27. Alternate synthesis of cordatanine (40).

The first total synthesis of natural product griseofamine A (41) together with its diastereomer 16-epi-griseofamine A was described by Pan et al. (Scheme 28) [67]. The synthesis commences with the introduction of PMB group to commercially available 235 via reductive amination step to prepare 236. Then, a stereoselective Pictet–Spengler reaction was performed with the appropriate acetaldehyde for the construction of β -carboline skeleton. The reaction resulted in a mixture of diastereomers which were separated by column chromatography. The synthesis continued with the major diastereomer 237a. First, the Boc-protection took place to afford intermediate 238, which was further transformed with reagent 239 in a Suzuki–Miyaura cross-coupling reaction using Buchwald’s protocol with ligand 240. The linear prenylated product 241 went through multiple deprotection protocol (from 241 to 242). Finally, the tandem acylation/Lecay–Dieckmann condensation was performed avoiding the commonly used strong bases to achieve the first synthesis of 41. The diastereomer of 41, i.e., 16-epi-griseofamine A was prepared on the same reaction pathway with the slight difference that 237b was applied instead of 237a.



Scheme 28. Total synthesis of griseofamine A (41).

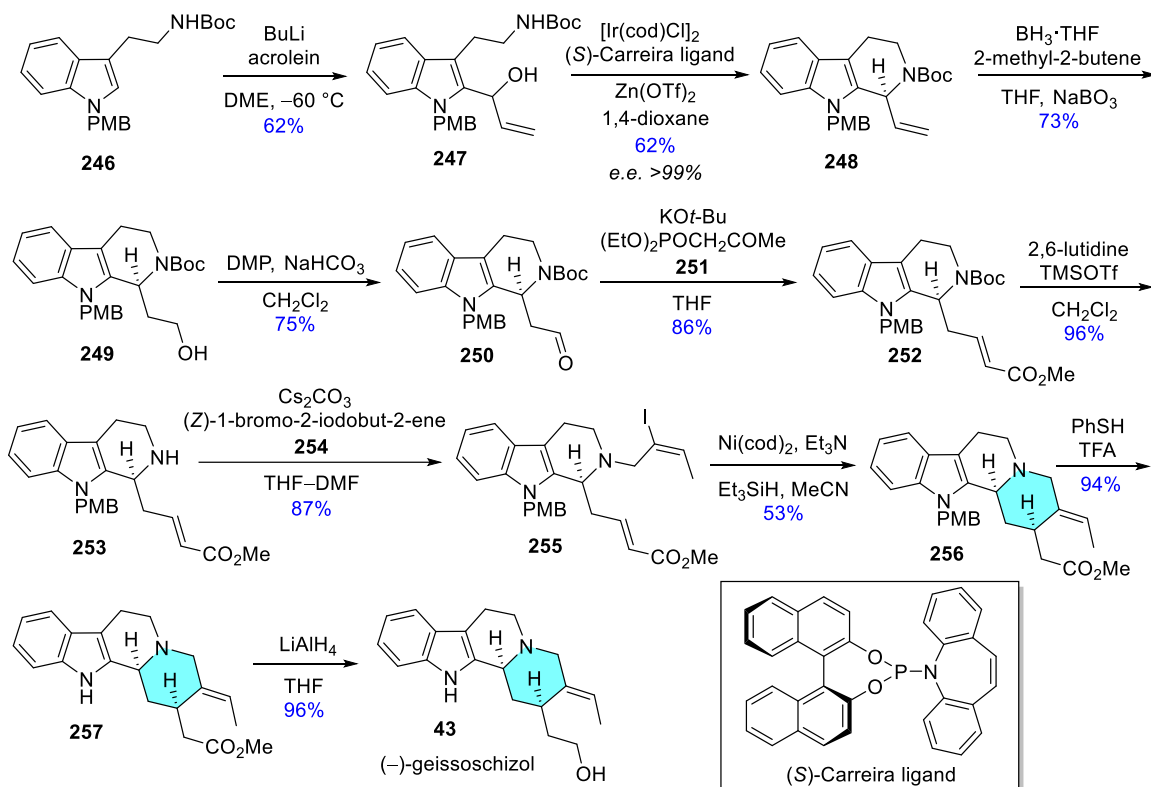
The construction of chiral β -carboline alkaloid (+)-deplancheine (42) has been achieved via (*R*)-SPINOL-TRIP-CPA-catalyzed asymmetric Pictet–Spengler reaction of indolyl dihydropyridine derivative 244 in two steps (Scheme 29) [54]. Intermediate 245 obtained with good enantiomeric excess was reduced with NaBH₄ to obtain the desired product 42.



Scheme 29. Total synthesis of (+)-deplancheine (42).

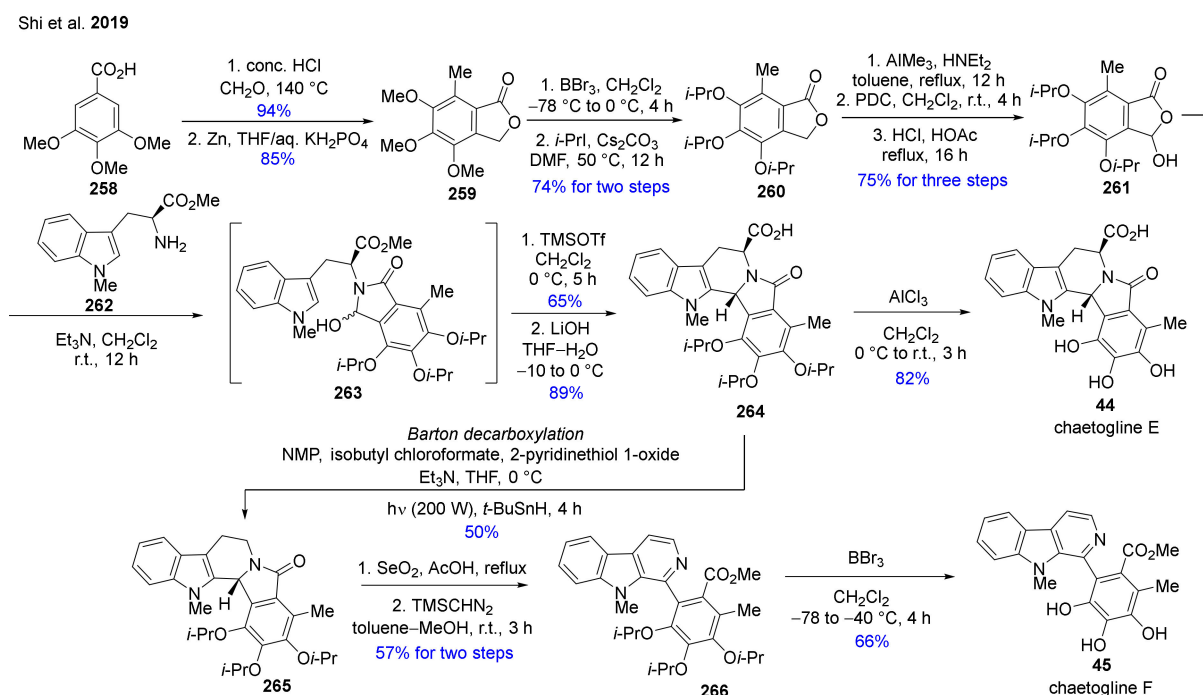
The enantioselective synthesis of (–)-geissoschizol (43) through Ir-catalyzed intramolecular ring closure as the key step has been accomplished by Zheng et al. (Scheme 30) [139]. The secondary allylic alcohol 247 was prepared from the reaction of protected tryptamine 246 and BuLi in the presence of acrolein. With key intermediate 247 in hand, the authors have attained a cyclization to forge the β -carboline skeleton. Intermediate 248 was prepared with Ir-catalyst in the presence of Zn(OTf)₂ promoter and (*S*)-Carreira ligand in 62% yield with excellent e.e. The synthesis was continued with functional group transformations, aiming at the preparation of the corresponding aldehyde 250. Then, a Wittig reaction was performed to give 252, followed by deprotection and *N*-alkylation (from 253 to 255). The formation of D-ring has been implemented via Ni-catalyzed cyclization to form intermediate 255. Finally, deprotection of the indole nitrogen and reduction of the ester group of 257 resulted in target molecule 43.

Zheng et al. 2017



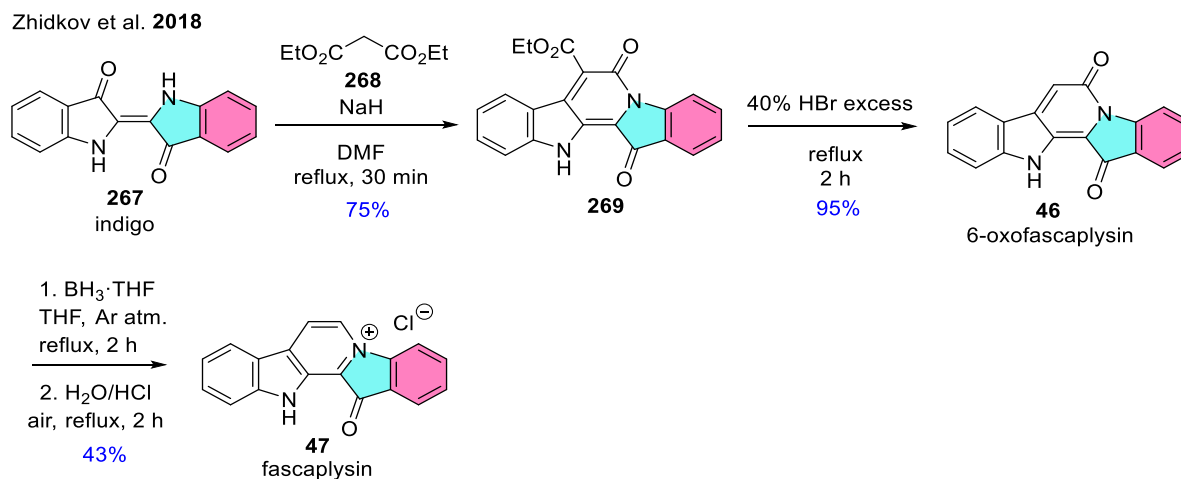
Scheme 30. Synthesis of (–)-geissoschizol (43).

The silent fungal Pictet–Spenglerase gene of *Chaetomium globosum* 1C51 residing in *Epinephelus drummondhayi* guts has been described to enable Pictet–Spengler reaction between 1-methyltryptophane and flavipin to give unnatural products containing novel skeletons in a natural way. Chaetogline alkaloids are representative compounds of this gene-implied strategy as a biosynthetic machinery to produce bioactive compounds [71]. Lei et al. have recently described the first total synthesis of alkaloids chaetogline C–F, among which chaetogline E (44) and F (45) are β -carboline, derived from the genetically modified fungus via a divergent synthesis way (Scheme 31) [140]. The synthesis began with the commercially available 3,4,5-trimethoxybenzoic acid (258) to produce previously described lactone 259. After protecting group transformations, 260 was formed, which was transformed into 261 through aminolysis, oxidation and hydrolysis to achieve spontaneous cyclization. Condensation of 261 with 262 resulted the intermediate 263, which went through a Pictet–Spengler reaction and hydrolysis to give key intermediate 264 with the desired β -carboline skeleton. Further transformation of 264 led to chaetogline E (44) via global deprotection with AlCl_3 . For the synthesis of caethogline F (45), Barton decarboxylation was used to eliminate the carboxyl group and to provide 265. After that, 265 was oxidized, hydrolyzed and methylated to afford 266, which was deprotected with BBr_3 and formed the desired product 45.



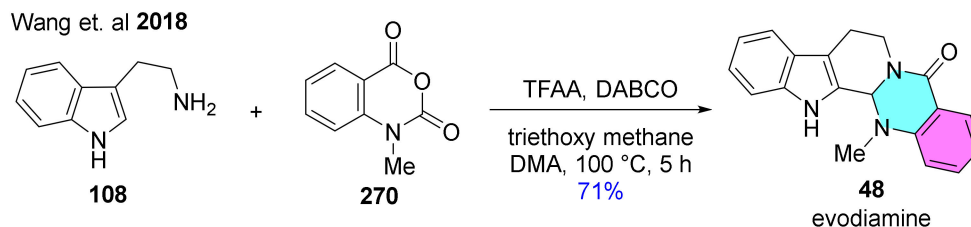
Scheme 31. Synthesis of chaetoglines E (44) and F (45).

Natural products containing a 12*H*-pyrido-[1,2-*a*:3,4-*b'*]diindole framework like 6-oxofascaplysin (46) and fascaplysin (47) show a broad range of bioactivities. In 2018, Zhidkov et al. reported the new synthesis of 47 and the first preparation of 46 (Scheme 32) [141]. Their protocol starts with the reaction of unsubstituted indigo (267) and diethyl malonate (268) in the presence of NaH to give pentacycle 269. The subsequent hydrolysis and decarboxylation were carried out under reflux conditions in an excess of 40% hydrobromic acid to furnish 46 with 70% overall yield. Reduction of the keto moiety with BH₃·THF complex, followed by hydrolysis and oxidation with air gave 47 in 43% isolated yield.



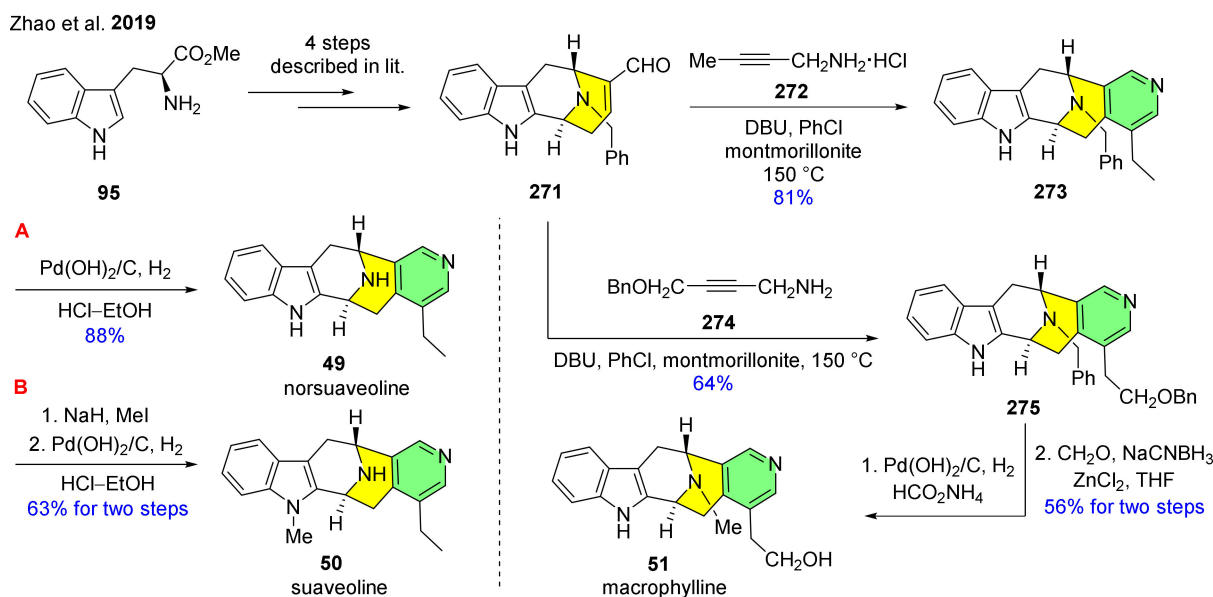
Scheme 32. First synthesis of 6-oxofascaplysin (46) and a new synthetic route for the preparation of fascaplysin (47).

The one-pot synthesis of natural product evodiamine (**48**) and a variety of its closely related derivatives was achieved using a three-component bicyclization reaction (Scheme 33) [142]. The synthesis applied readily available substrates such as tryptamine (**108**) and *N*-methylisatoic anhydride (**270**) in the presence of TFAA and DABCO. With this method, a variety of polycyclic β -carboline scaffold-containing substrates has been synthesized, however as a limitation, a few products were only obtained in poor yield.



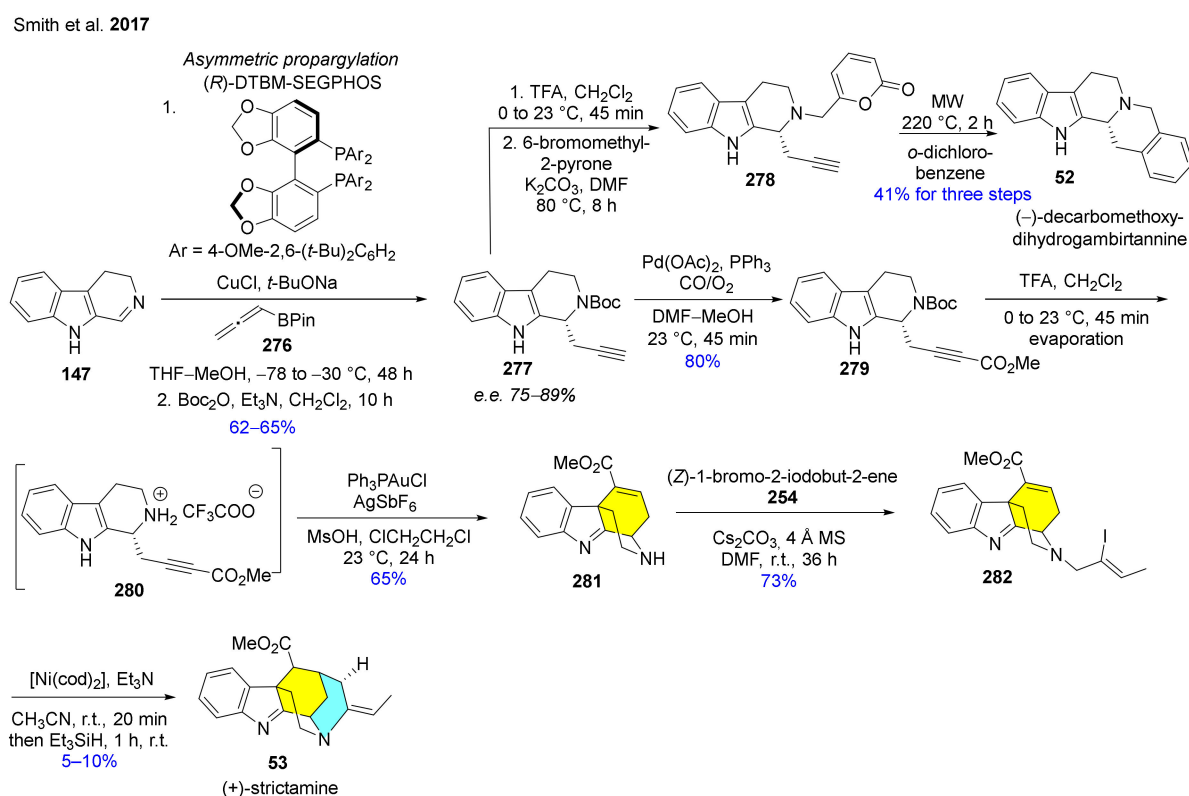
Scheme 33. One-step synthesis of evodiamine (**48**).

The novel synthesis of suaveoline alkaloids (**49–51**) was described by Zhao et al. applying a new method for pyridine incorporation starting from propargyl amines and unsaturated carbonyl compounds through a tandem reaction including condensation–alkyne isomerization– 6π 3-azatriene electrocyclic sequence at the late stage of the synthesis (Scheme 34) [143]. The synthesis started from the readily available L-tryptophan methyl ester (**95**), which was converted into **271** according to previously described methods [144,145]. Next, aldehyde **271** was transformed with propargyl amine hydrochloride (**272**) into the desired pentacycle **273**, including formation of a pyridine ring. This was followed by the cleavage of the benzyl group leading to norsuaveoline (**49**). An additional methylation step was performed on indole nitrogen of **273** before *N*-debenzylation to form the other target alkaloid suaveoline (**50**). To demonstrate the flexibility of the late-stage pyridine incorporation, the authors made a reaction with **271** using another propargyl amine counterpart (**274**). The desired product **275** was further converted into macrophylline (**51**) through a Pd(OH)₂-catalyzed debenzylation and methylation of the piperidine nitrogen atom.



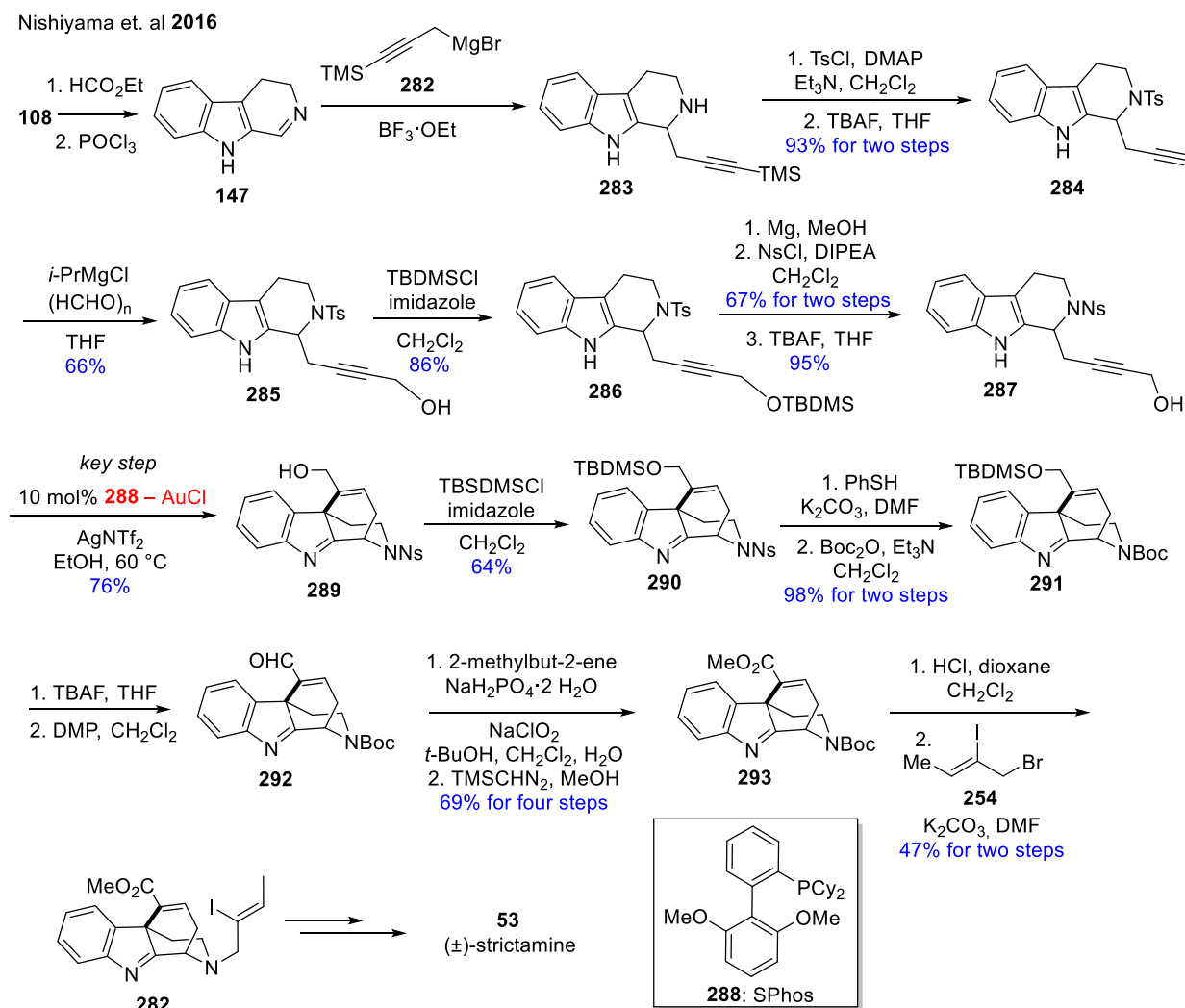
Scheme 34. Synthesis of norsuaveoline (**49**), suaveoline (**50**) and macrophylline (**51**).

Smith et al. elaborated a novel asymmetric propargylation as a new approach for the preparation of β -carboline alkaloids, highlighted by the formal synthesis of (–)-decarbomethoxy-dihydrogambirtannine (**52**) and (+)-strictamine (**53**) (Scheme 35) [146]. Starting from DH β C (**147**), the propargylation was accomplished with allenylboronic acid pinacol ester (**276**) under asymmetric conditions to form **277**. To obtain **278**, **277** was reacted with TFA and 6-bromomethyl-2-pyrone. Finally, an MW-assisted cyclization was performed to complete the synthesis of target molecule **52**. For the synthesis of **53**, **277** went through further transformations and an Au(I)/Ag(I)-based 6-endo-dig cyclization to afford the core framework in compound **281**. According to previously described transformations by Zhu and co-workers [147], alkylation and Ni-promoted cyclization in the presence of Et₃SiH led to **53** with poor yield.



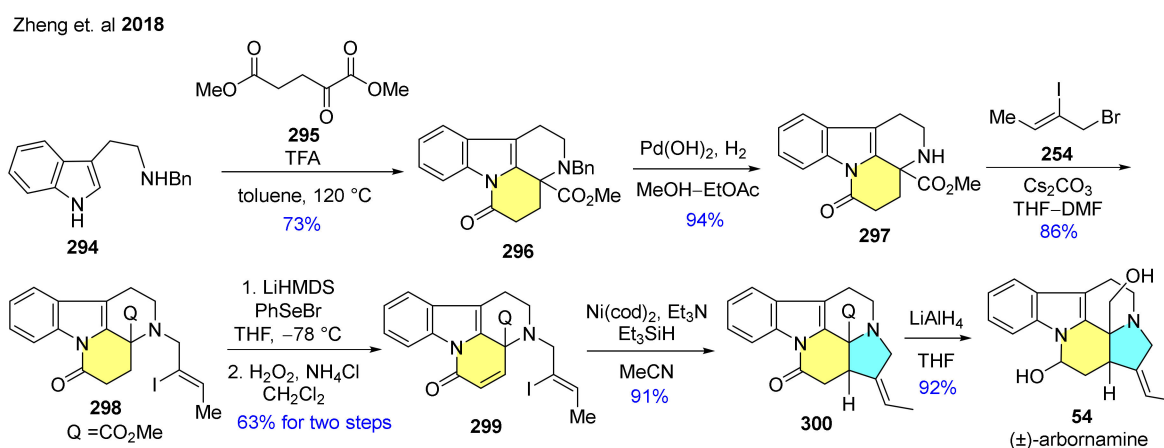
Scheme 35. Synthesis of (S)-(–)-decarbomethoxy-dihydrogambirtannine (**52**) and formal synthesis of (+)-strictamine (**53**).

Formal total synthesis of (±)-strictamine (**53**) based on gold-catalyzed cyclization was developed by a Japanese research group (Scheme 36) [148]. Starting from readily available tryptamine (**108**), a formylation with HCO₂Et and cyclization with POCl₃ was performed to give DH β C (**147**), followed by Grignard reactions and protecting group chemistry to afford **287** [149]. The key intermediate tetracyclic indolenine **289** was formed via SPhosAuCl (**288**)-promoted cyclization to construct the A–D ring system of akuammiline alkaloids. Functional group modifications on **289** operating with a Boc protecting group and ester group formation followed by an *N*-alkylation led to key intermediate **282**. After that, it is possible to prepare **53**, based on a previous publication [147].

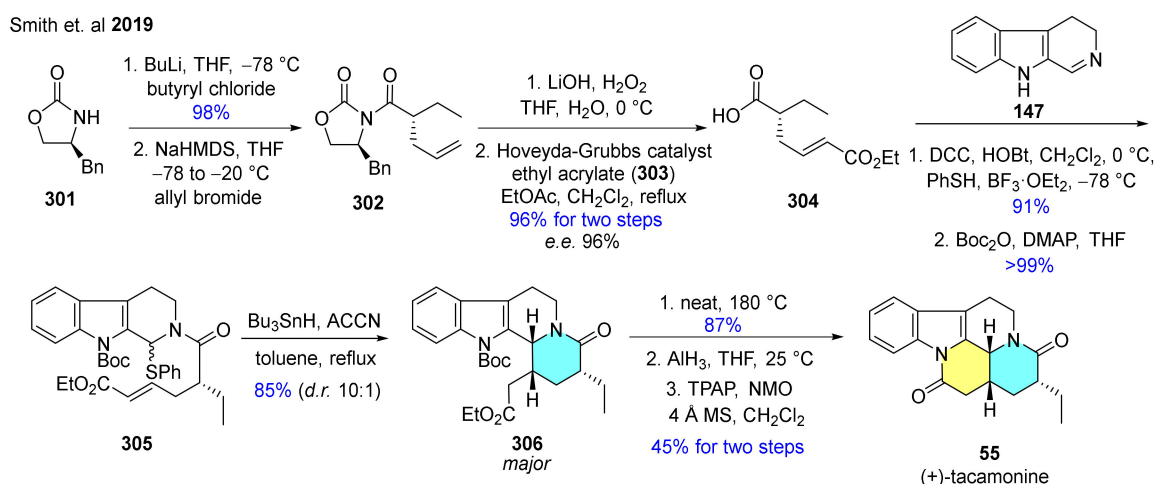


Scheme 36. Formal total synthesis of (±)-strictamine (53).

The synthesis of monoterpene indole alkaloid (±)-arbornamine (54) was described in only 6 steps (Scheme 37) [150]. First, benzyl-protected tryptamine 294 was reacted with dimethyl ester 295, resulting in intermediate 298. Debonylation was carried out under catalytic hydrogenation conditions to afford 297, which was further transformed into 298 with (*Z*)-1-bromo-2-iodobut-2-ene (254). A general selenylation-elimination protocol resulted in the δ -lactam containing product 299. The closure of the final ring was achieved via reductive Heck cyclization promoted by Ni(cod)₂, leading to the appropriate pentacyclic product 300. In the final stage, reduction of the ester moiety of 300 provided the desired alkaloid 54.

Scheme 37. Synthesis of (\pm)-arbornamine (54).

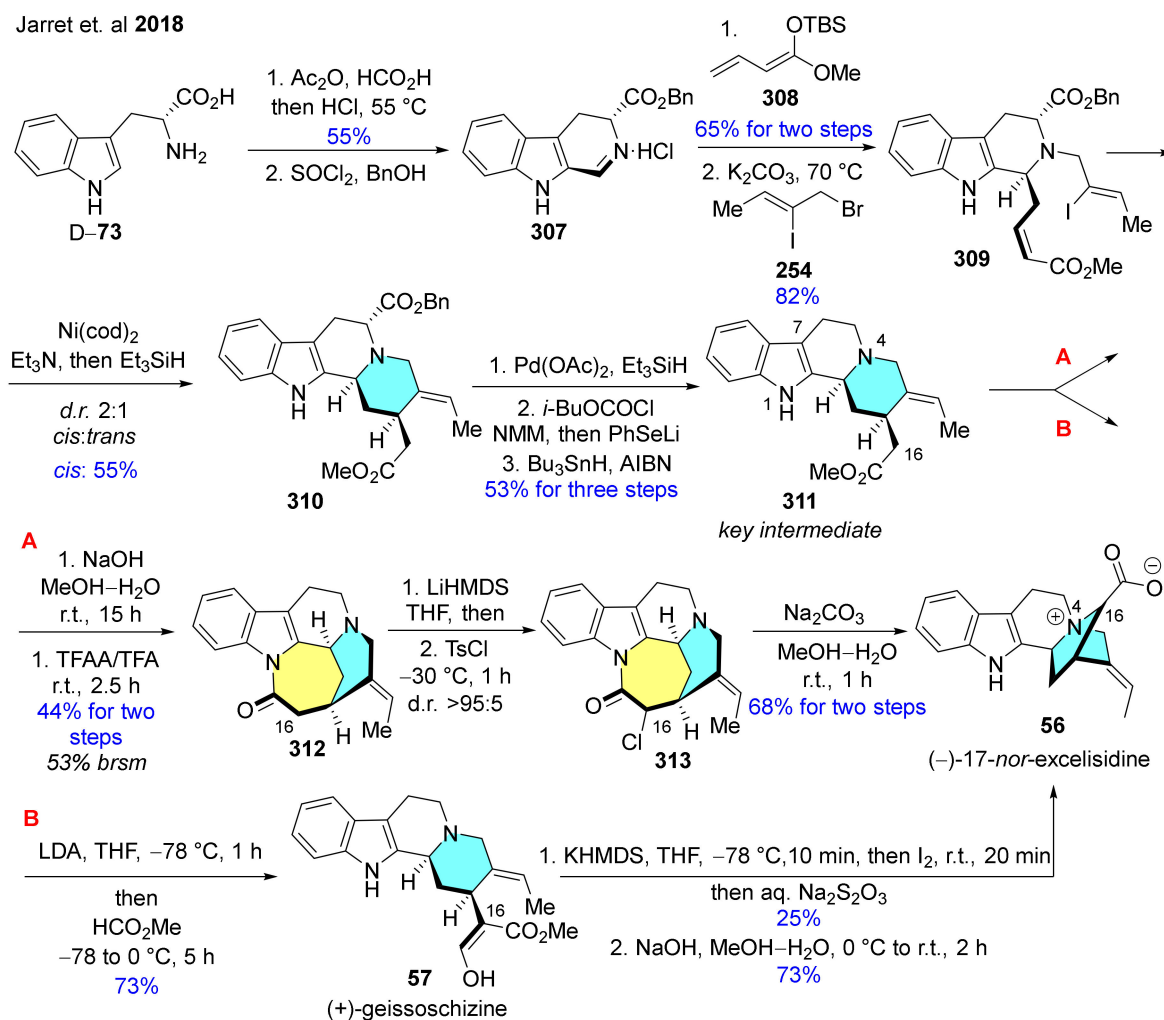
(+)-Tacamonine (55), containing a pentacyclic framework, as well as its closely related bioactive derivatives like eburnamine [151] or vincamine [152] are considered as pharmacologically promising molecules. The first synthesis of (\pm)-tacamonine containing 3 stereocenters has been achieved by Massiot and co-workers [153]. Recently, the asymmetric synthesis of (+)-tacamonine (55) has been reported involving a stereoselective radical cyclization as the key step (Scheme 38) [154]. The synthesis starts from a commercially available oxazolidinone auxiliary (301) through an acylation followed by an allylation to form intermediate 302. After that, 302 was modified with the removal of oxazolidinone part followed by a cross-metathesis with ethyl acrylate (303) resulting in chiral acid 304. Next, intermediate 304 was reacted with DH β C (147) using DCC and HOBt, followed by the reaction with PhSH in the presence of BF $_3$ ·OEt $_2$ to afford α -phenylsulfanyl amide. The precursor for radical cyclization was provided by Boc-protection of the indole nitrogen atom. Then, 305 was treated with Bu $_3$ SnH and ACCN to form 306 which went through the thermolytic removal of the Boc group, then the reduction of the ester followed by an oxidation step with concomitant cyclization to provide 55.



Scheme 38. Synthesis of (+)-tacamonine (55).

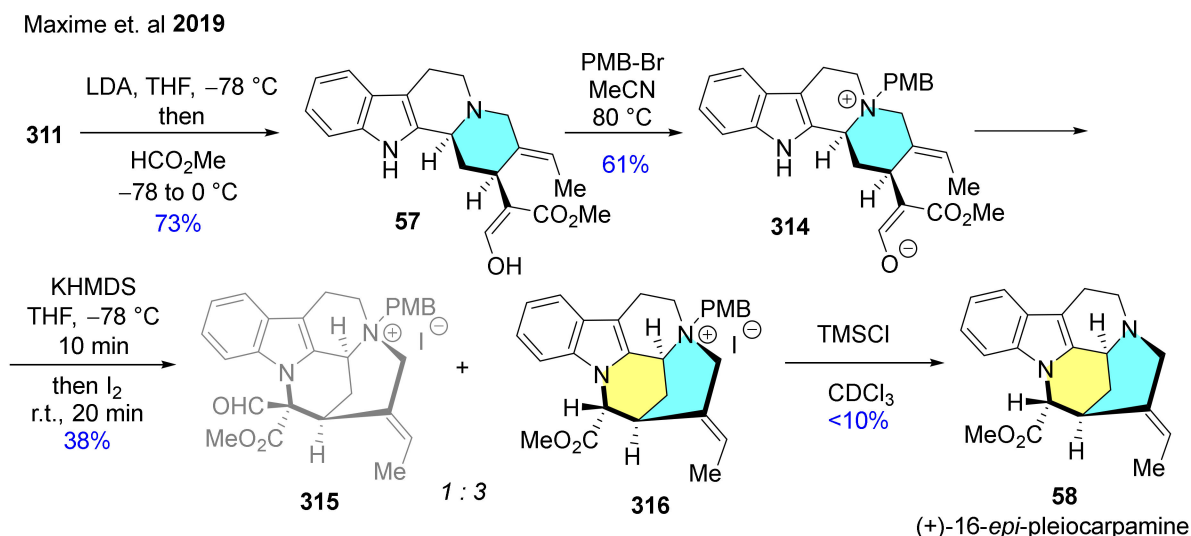
In 2018, alkaloids containing the complete geissoschizine skeleton were synthesized via bioinspired oxidative cyclization, which led to the selective formation of the N4-C16 bond [155]. In this research, (−)-17-nor-excelsinidine (56) was synthesized (Scheme 39), including an α -electrophilic chlorination of a 7-membered-ring lactam and its ring rearrangement via nucleophilic substitution. Two oxidative cyclization strategies were developed to construct (−)-17-nor-excelsinidine starting from enantiopure D-tryptophan (D-73), which

was transformed into **307** via Pictet–Spengler reaction followed by a protecting maneuver. After this, Mannich addition with **308** and *N*-alkylation with 1-bromo-2-iodobut-2-ene (**254**) were accomplished to give **309**. In the presence of $\text{Ni}(\text{cod})_2$, radical cyclization of **309** occurred, then removal of the benzyl ester resulted in key intermediate **311** containing the required scaffold. Next, the oxidative cyclization took place which was achieved on two alternative pathways (Scheme 39A,B) to produce alkaloid **56**. Following the reaction pathway A, the indole nitrogen and the carbonyl of the ester of **311** were connected by forming 7-membered-lactam **312**. The oxidative process was accomplished in two stages. First, the C16-carbon was subjected to umpolung by diastereoselective chlorination to obtain **313**. This was followed by the addition of sodium carbonate in aqueous methanol was induced the nucleophilic substitution of the chlorine by the N4-nitrogen and the cleavage of the lactam to form enantiopure (–)-**56**. Choosing another synthetic route B, **311** was transformed into (+)-geissoschizine (**57**) through a formylation step. After that, **57** was deprotonated with KHMDS and the resulted dianion was then submitted to oxidation with iodine leading to (–)-**56** methyl ester, which was then saponified to **56**.



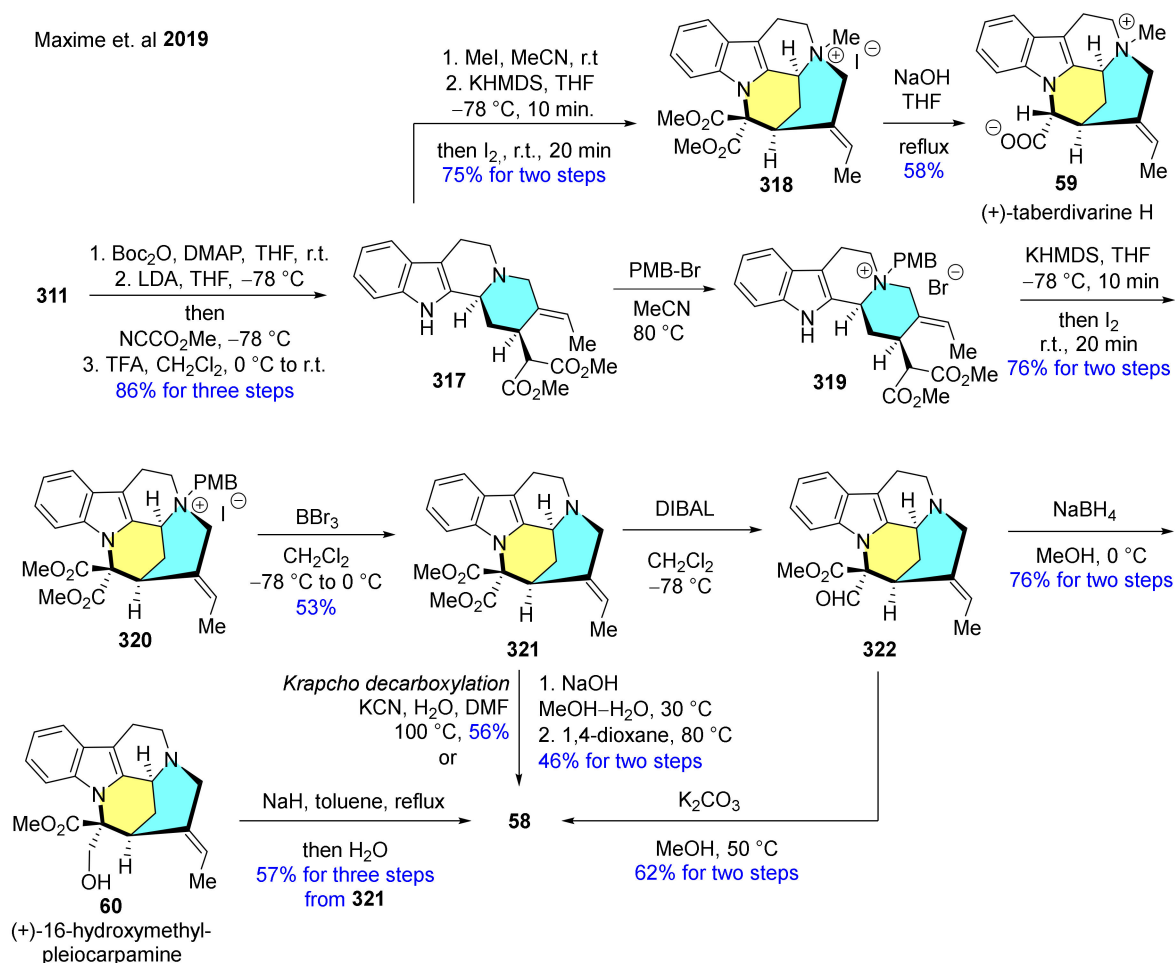
Scheme 39. Total synthesis of (–)-17-nor-excelisidine (**56**) and (+)-geissoschizine (**57**) by applying direct oxidative cyclization.

The same authors reported the total synthesis of further 3 closely related mavacuran alkaloids: (+)-16-*epi*-pleiocarpamine (**58**), (+)-taberdivarine H (**59**) and (+)-16-hydroxymethylpleiocarpamine (**60**) by applying their method described above for the construction of geissoschizine skeleton (Schemes 40 and 41) [156]. The synthesis of **58** starts with the formylation step of **311** leading to the formation of **57**. Heating of **57** with PMB-Br in MeCN resulted in quaternary ammonium compound **314**. In the following reaction step, deprotonation of the indole NH of **314** followed by the addition of I₂ gave a mixture of **315** and **316** containing the desired mavacuran skeleton. Finally, dequaternization of **316** with TMSCl furnished the target molecule **58**, although with a poor yield (Scheme 40).



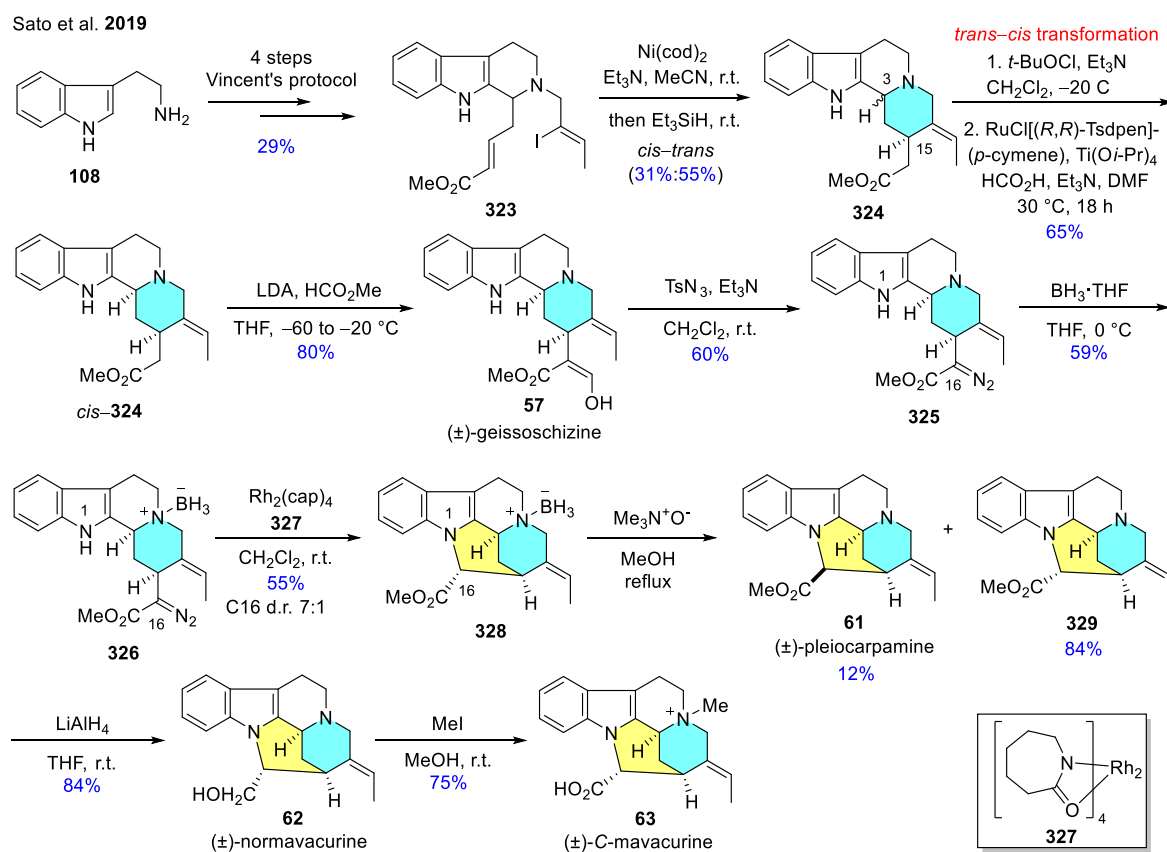
Scheme 40. Synthesis of (+)-16-*epi*-pleiocarpamine (**58**).

Similarly to the method described above, the basic framework of the target molecules was built by applying the key oxidative coupling induced by KHMDS in the presence of I₂ as this latter masks the nucleophilicity of the aliphatic nitrogen center and locks it in the suitable *cis* configuration leading to intermediates **318** and **319** (Scheme 41). (+)-Taberdivarine H (**59**) was synthesized by quaternization of the tertiary nitrogen atom of **317** with MeI followed by an oxidative coupling to give **318**, and subsequent ester hydrolysis and selective decarboxylation. The synthesis continued with the oxidative coupling of **319** and deprotection of **320** with BBr₃. Selective Krapcho decarboxylation of diester **321** occurred to form compound **58**. Selective reduction of key intermediate **321** with DIBAL resulted in the desymmetrized product **322**, followed by a deformylation step in the presence of NaBH₄ to accomplish the synthesis of **60**. Compound **60** was transformed into **58** with NaH in boiling toluene and by subsequent addition of water.



Scheme 41. Synthesis of (+)-16-epi-pleiocarpamine (58), (+)-taberdivarine H (59) and (+)-16-hydroxymethyl-pleiocarpamine (60).

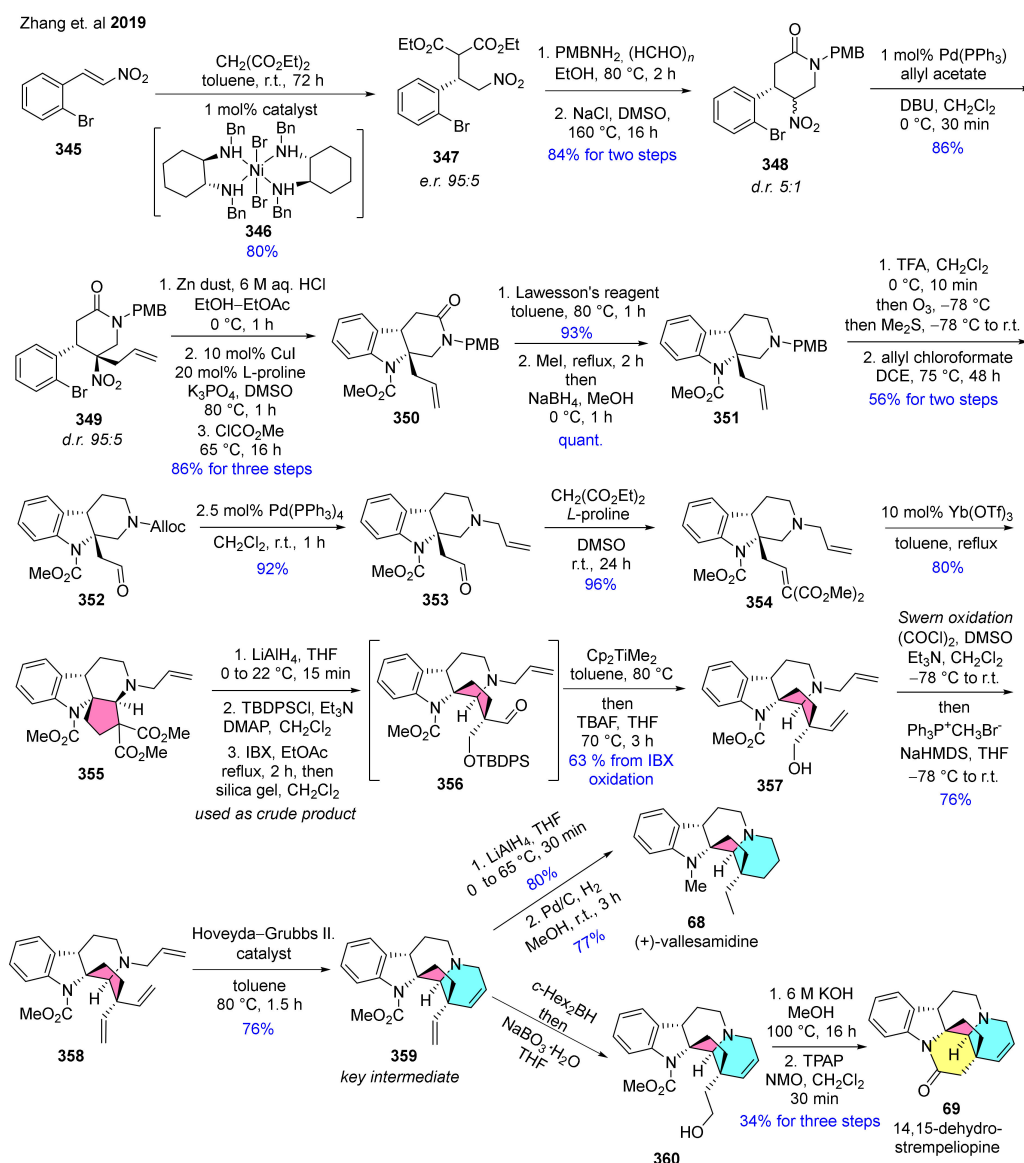
The total synthesis of C-mavacurine alkaloids (±)-pleiocarpamine (61), (±)-normavacurine (62) and (±)-C-mavacurine (63) was accomplished by Sato et al. (Scheme 42) [157]. The innovative key step of the synthesis is a metal carbenoid cyclization by an N-H insertion within a Corynanthe-type compound bearing a diazo function, where the molecular conformation is fixed by an amine-borane complex. The synthesis starts with the preparation of α,β -unsaturated ester 323 from tryptamine (108), applying the previously reported protocol by Vincent and co-workers [155]. This was followed by the Ni(cod)₂-mediated reductive cyclization to afford a mixture of *trans*-324 and the desired *cis*-324. After that, *trans*-324 was treated with *t*-BuOCl, then with HCl in MeOH to form an iminium intermediate, which was effectively transformed into *cis*-324 in the presence of Noyori-type catalyst, formic acid and Et₃N in DMF solvent. Next, *cis*-324 was treated with LDA and methyl formate to obtain the D-ring containing (±)-geissoschizine (57). Natural product 57 was converted into the key intermediate of the reaction, diazo compound 325 using tosyl azide in the presence of Et₃N. As an essential compound for the further steps, 325, was transformed into borane-complex 326 with BH₃·THF to fix the appropriate conformation for the next steps. The cyclization precursor 326 underwent a carbene-generated cyclization with catalyst 327 to form the E-ring containing derivative 328. The amine-borane bond was easily cleaved by heating in the presence of trimethylamine oxide to obtain (±)-pleiocarpamine (61) and intermediate 329. For the synthesis of (±)-normavacurine (62), 329 was used in a reduction step carried out with LiAlH₄ and further transformation into (±)-C-mavacurine (63) by treatment with an excess of MeI.



Scheme 42. Total synthesis of C-mavacurine-type alkaloids (61–63).

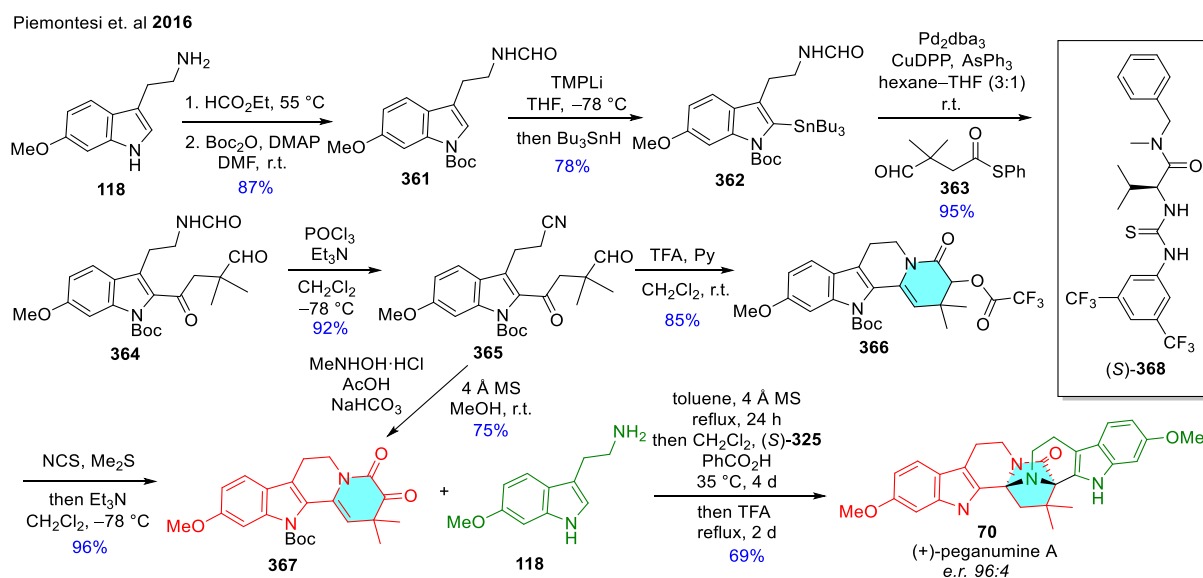
The C19-oxo-functionalized eburnane alkaloids (64–67) were synthesized by Trost et al. (Scheme 43) [158]. The synthesis involves a Pd-catalyzed asymmetric allylic alkylation step of an *N*-alkyl- α,β -unsaturated lactam as a key step for the further ring system construction. Using Corey and Baran's method [159], Boc-protected tryptamine (330) and aldehyde 331 were transformed into tryptamine derivative 332. After that, amine 332 was reacted with *tert*-butyl malonate (333) in the presence of Mukaiyama's reagent (334) to perform an amidation reaction. The formed intermediate 335 was treated with FeCl_3 on silica via ketal cleavage and cyclization to provide the α,β -unsaturated lactam 336. The reaction of intermediate 336 with nucleophile 337, i.e., the key step of the synthesis was accomplished applying $\text{CpPd}(\text{cinnamoyl})$ as a catalyst, Trost ligand (338) and Barton's base as an additive, giving 75% yield with e.e., 90%. The key intermediate 339 thus obtained underwent a desilylation in the presence of TBAF, followed by a simultaneous Boc-group removal and transesterification to afford 340. In the next step, the formation of the C-ring was accomplished through a Bischler-Napieralski reaction using Movassaghi's protocol to prepare 341 [160]. The exposure of 341 to excess of MeLi led to the corresponding ketone 342, where no by-product was observed because of the intramolecular chelate formation. This was followed by the chemoselective dihydroxylation of terminal olefin bond in the presence of OsO_4 and NMO, then by the reaction with NaIO_4 on silica leading to an aldehyde intermediate, which directly cyclized to give pentacycle 343. From this point, the synthesis was continued via divergent routes to the target molecules. First, hydrogenation took place, where the saturation of the double bond of the tetrahydropyridine ring and concomitant partial reduction of the C19 carbonyl group resulted in a mixture of (+)-19-oxoeburnamine (64) and 19-hydroxyeburnamine (65). Focusing on the other two target molecules, a Ley-Griffith oxidation was performed on 343, which led to compound 344. The selective reduction of C19-ketone 344 was performed in the presence of *L*-selectride to

the sequential addition of Lawesson's reagent, MeI and NaBH₄. Protonation of the basic piperidine nitrogen with trifluoroacetic acid and ozonolysis gave the aldehyde, which was treated with allyl chloroformate to obtain **352**. Subsequent treatment of allyl carbamate **352** with catalytic Pd(PPh₃)₄ induced the decarboxylative allylation to give **353**. This was followed by the Knoevenagel condensation of **353** with dimethyl malonate to afford the α,β -unsaturated malonate **354**. Using precursor **354** in the reaction with Yb(OTf)₃, a Lewis acid-catalyzed [1,4]-hydride transfer and Mannich-type cascade cyclization was performed, which resulted in compound **355** containing the appropriate E-ring. The D-ring with the C14=C15 double bond was installed via alkene formation through diastereoselective ring-closing metathesis (from **355** to **358**). To form the metathesis precursor from **355**, the reduction of this malonate to the corresponding diol was carried out. The diol was selectively protected, then the oxidation of the other OH-group was performed, which was followed by an olefination and the removal of the protecting group. After that, Swern oxidation and Wittig reaction took place to furnish the appropriate trialkene. **358**. Then **358** was introduced to the Hoveyda–Grubbs catalyst and the subsequent metathesis reaction occurred to afford key intermediate **359**. From intermediate **359**, the target molecules were formed via two different pathways: **68** was obtained after simple functional group transformations, while **69** was formed by further functionalization and ring closure reaction of **360**.



Scheme 44. Synthesis of (+)-vallesamidine (**68**) and (+)-14,15-dehydrostrepeliopine (**69**) via key intermediate **359**.

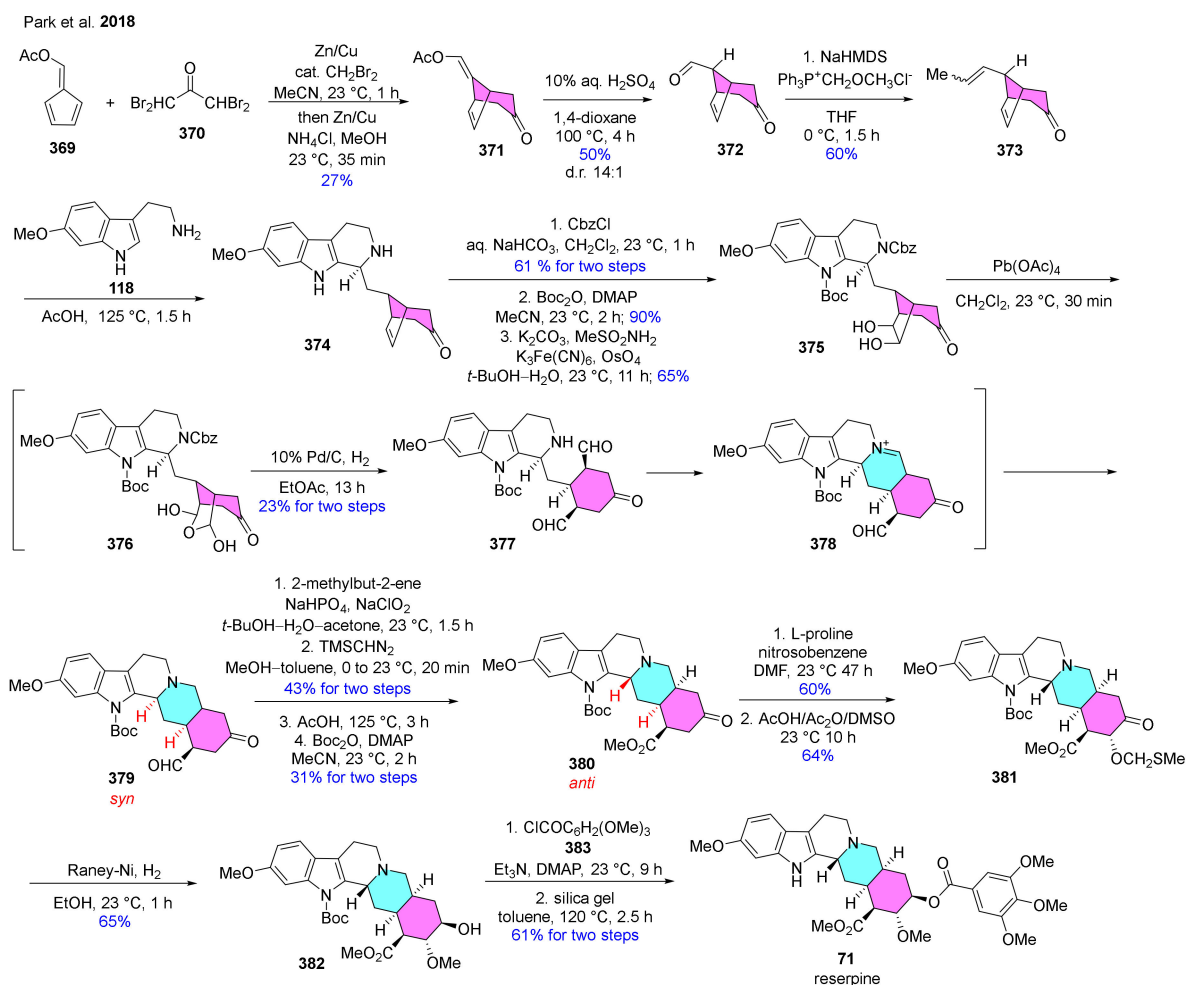
The enantioselective total synthesis of (+)-peganumine A (**70**) was achieved by Zhu and co-workers in 7 steps by applying multiple bond formation methods (Scheme 45) [163]. The synthesis of the octacyclic complex natural product starts from readily available 6-methoxytryptamine (**118**). By combining functional group transformation and a Liebeskind-Srogl cross-coupling (**361** into **364**), this starting material was transformed into advanced intermediate **365**. Further reactions from **365** led to the construction of tetracyclic intermediate **367** via one-pot C–C bond forming lactamization and transannular condensation. Finally, a one-pot chiral (*S*)-**368** thiourea/benzoic acid-catalyzed domino reaction merged the two achiral building blocks (**118**, **367**) into the octacyclic compound (**70**) via enantioselective Pictet-Spengler reaction followed by TFA-catalyzed transannular cyclization.



Scheme 45. First total synthesis of (+)-peganumine A (**70**).

Reserpine (**71**) is a well-known drug for the treatment of high blood pressure. From the first total synthesis of **71** reported by Woodward and co-workers, [164] numerous synthetic approaches have been reported [165]. Recently, a new total synthesis of reserpine (**71**) has been accomplished using a desymmetrization protocol, which applied a simplified non-stereogenic E-ring precursor [166]. The developed strategy constitutes an unconventional form of remote stereoreinduction. Late-stage functionalization of the reserpine E-ring, including a contra-steric C17 oxygenation and a stereoselective C18 ketone reduction, also played pivotal roles in completing the synthesis. As shown in Scheme 46, the synthesis began with the preparation of the bicyclic ketoaldehyde (**372**) through a reductive [4+3] cycloaddition between acetoxyfulvene (**369**) and 1,1,3,3-tetrabromoacetone (**370**) affording bicyclic enolacetate **371**, followed by an enolacetate hydrolysis with aldehyde epimerization. One-carbon homologation of **372** was performed by engaging its aldehyde functionality resulting in the methyl enol ether mixture of geometrical isomers (**373**) as an E-ring precursor. This was followed by an improved Pictet–Spengler protocol in the reaction with tryptamine derivative **118** to construct the TH β C skeleton-containing compound **374**. The N atoms of **374** were protected with Cbz and Boc. At this stage, a desymmetrization protocol was performed starting with an OsO_4 -catalyzed alkene dihydroxylation in the presence of $\text{K}_3\text{Fe}(\text{CN})_6$ to afford diol **375**. Intermediate **375** was then treated with $\text{Pb}(\text{OAc})_4$ to form a mixture where the bis-hemiacetal **376** was the predominant compound instead of its parent dialdehyde. This mixture went through a Pd/C-mediated hydrogenation, and Cbz group removal where the only detectable product was dialdehyde **377**. Next, an intramolecular iminium formation took place induced by an in-situ hydrogenation resulted **378**. After that, the irreversible dehydrogenation and the single stereoisomer suggested the iminium formation took place by selectively engaging one of the two diastereotopic aldehyde *sin*-**379**. Intermediate

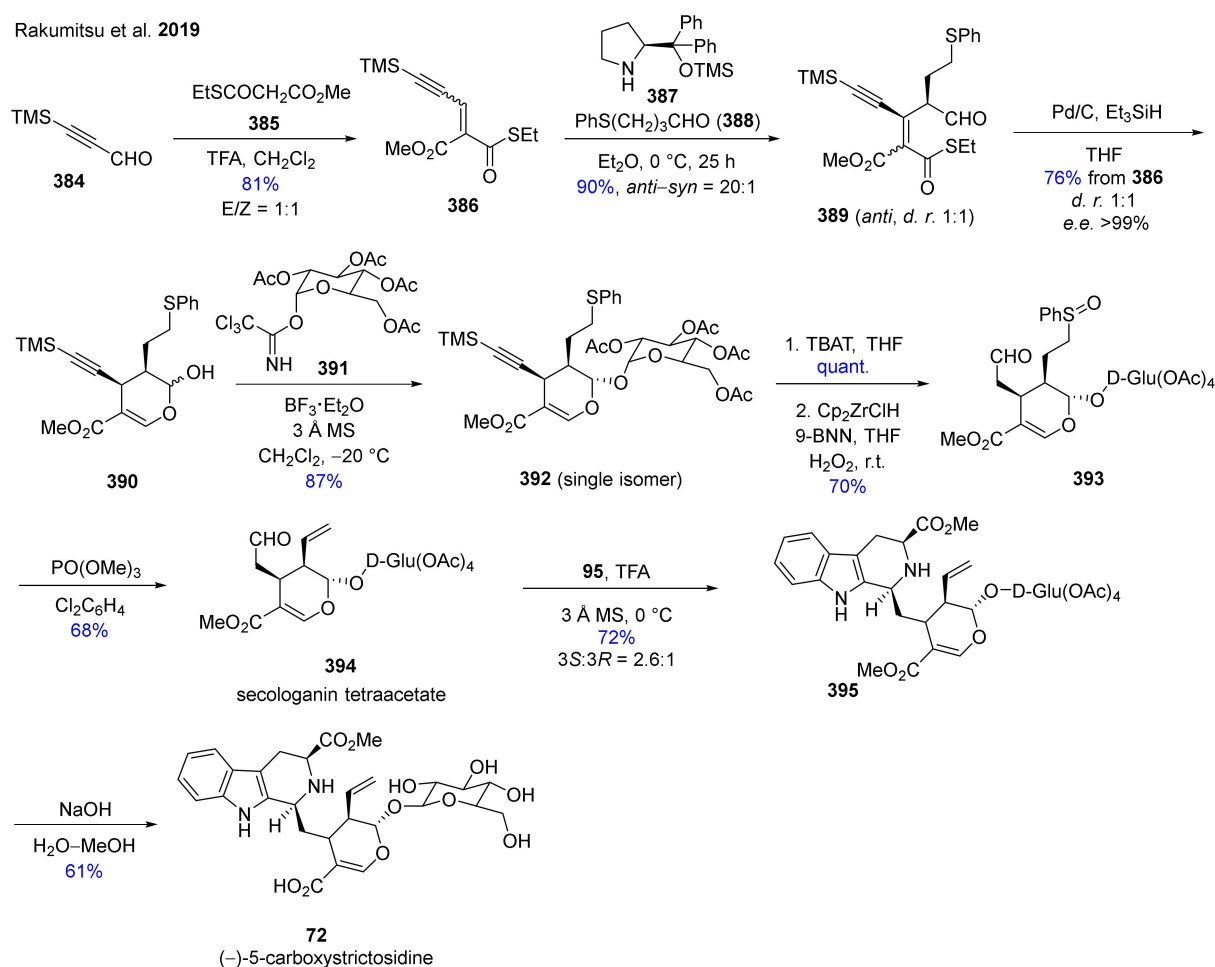
379 went through various transformations including Pinnick oxidation and esterification, HOAc catalyzed epimerization and re-protecting with Boc_2O , resulting in **380**, which was followed by a regio- and stereoselective C17 oxygenation with *L*-proline/nitrosobenzene to complete the substitution pattern required for the E-ring. Pummerer-type conditions (DMSO , Ac_2O) were applied to furnish methylthio methyl ether intermediate **381**, which underwent a reductive desulfurization to prepare the oxygen methylated alcohol **382**. To complete the synthesis, **382** was reacted with 3,4,5-trimethoxybenzoyl chloride (**383**) and removal of the Boc-carbamate by heating in the presence of silica gel to achieve the target molecule reserpine (**71**).



Scheme 46. Synthesis of reserpine (**71**).

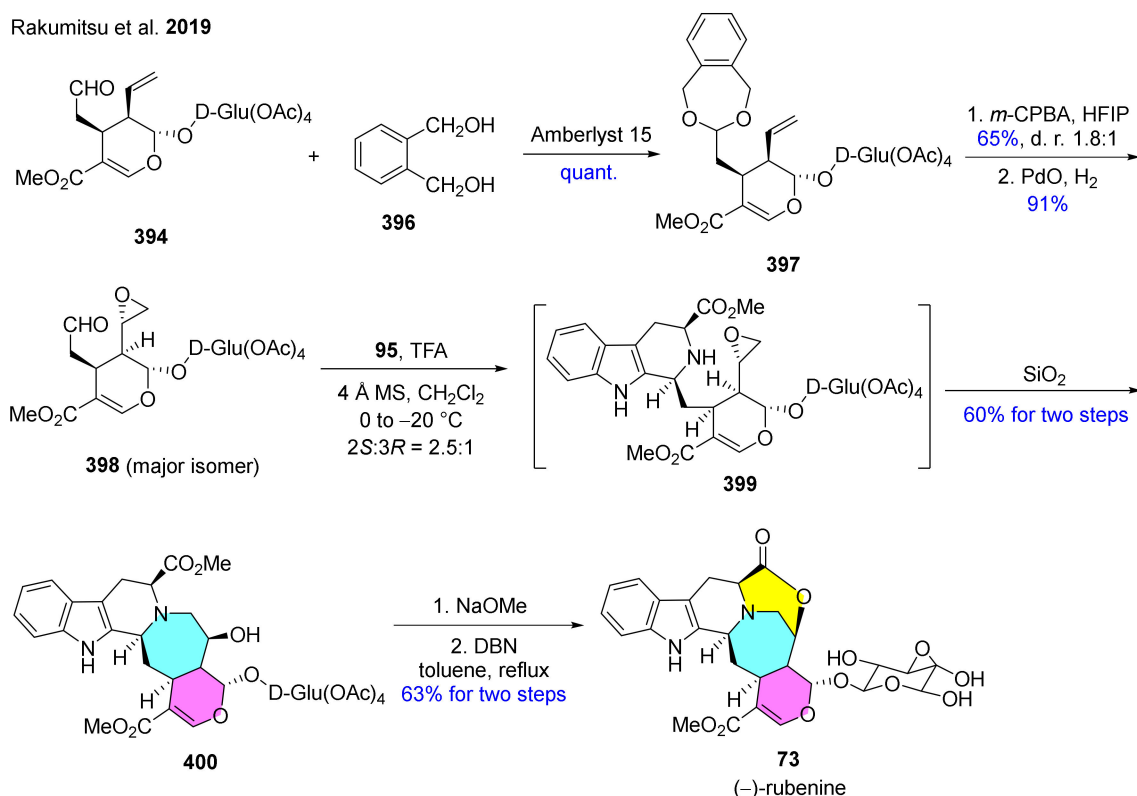
The first enantioselective synthesis of glycosylated monoterpene alkaloids (–)-5-carboxystrictosidine (**72**, Scheme 47) and (–)-rubenine (**73**, Scheme 48) was accomplished by Rakamitsu et. al. [167]. The innovative part of this publication is a sequential anti-selective organocatalytic Michael reaction continued with a Fukuyama reduction and finished by a cyclization to form an optically active dihydropyran ring. The first stage of the synthesis targeted the preparation of hemiacetal **390**. First, thioester derivative **386** was prepared by Knoevenagel condensation from the readily available 3-trimethylsilylpropanal (**384**) and reagent **385**, applying a known literature method [168]. This was followed by the innovative key step, the anti-selective Michael reaction, which was finally performed with organocatalyst **387** and thioaldehyde **388** in Et_2O solvent. The formation of the appropriate dihydropyran ring-containing key intermediate **390** was finally achieved applying Fukuyama's protocol with Pd/C and Et_3SiH , followed by a spontaneous cyclization. Next the glycosylation of hemiacetal diastereomeric mixture **390** was examined through the

reaction with imidate **391**. The key issue of this step was to prepare **392** with controlled stereoselectivity. The silyl group removal was accomplished with TBAT, thereafter the hydroboration/oxidation was performed with Schwartz's reagent (Cp_2ZrClH) in the presence of 9-BNN. In this reaction the thioether was also oxidized to sulfoxide **393**, which was essential for the next sulfoxide elimination reaction. To prepare the terminal olefin bond containing moiety in **394**, Tietze's sulfoxide elimination protocol [169] was used which resulted in another key molecule of the synthesis route called secologanin tetraacetate (**394**). To complete the total synthesis of **72**, a diastereoselective Pictet-Spengler reaction was performed [170] with **95**. Finally, hydrolysis of the acetate groups of **395** led to target molecule **72**.



Scheme 47. Total synthesis of (-)-5-carboxystrictosidine (**72**).

In the same publication, the authors used key intermediate **394** also for the first total synthesis of (-)-rubenine (**73**, Scheme 48). Initially, aldehyde **394** was converted into cyclic acetal **397** upon reaction with 1,2-phenylenedimethanol (**396**). Then, the diastereoselective epoxidation and acetal removal of **397** was accomplished in the reaction with *m*-CPBA in HFIP solvent to obtain intermediate **398**. Next, the Pictet-Spengler reaction of **395** with **95** generated the desired 3*S*-isomer **399**. The E-ring formation was induced by the direct loading of the diastereomeric mixture on silica gel to obtain intermediate **400**. The synthesis of (-)-rubenine (**73**) was completed by the removal of the acetate moieties by methanolysis, followed by the highly strained D-ring formation upon basic lactonization reaction.



Scheme 48. Total synthesis of (–)-rubenine (73).

4. Conclusions

This review summarizes the recently reported syntheses of naturally occurring β -carboline and closely related synthetic derivatives through the selected examples of 73 natural products. It is evident that over the last 5 years this field of alkaloid chemistry has experienced many new and novel synthetic routes, including innovative strategies for the construction of the title framework. Not only the applied methods and synthesized products are interesting for organic chemists, but they also represent a remarkable pharmacological potential. The urgent need for new drug candidates is the driving force of the development highlighted in this review. We believe that the presented synthetic methods give a valuable insight into β -carboline chemistry, while providing inspiration and encouraging further explorations in this family of compounds.

Author Contributions: Conceptualization, T.S., B.V., M.M.; literature search, T.S.; writing—original draft preparation, T.S.; writing—review and editing, B.V., M.M. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

List of Abbreviations and Named reagents.

| | |
|-----------------------------------|---|
| 9-BNN | 9-borabicyclo[3.3.1]nonane |
| Å | angstrom |
| Ac | acetyl |
| ACCN | 1,1'-azobis(cyclohexanecarbo-nitrile) |
| AIBN | azobisisobutyronitrile |
| Alloc | allyloxycarbonyl |
| aq | aqueous |
| Barton's base | 2- <i>tert</i> -butyl-1,1,3,3-tetra-methylguanidine |
| Bn | benzyl |
| Boc | <i>tert</i> -butyloxycarbonyl |
| brsm | yield based on recovered starting material |
| BuLi | <i>n</i> -butyllithium |
| Bz | benzoyl |
| CAN | cerium ammonium nitrate |
| cap | caprolactamate |
| CDI | carbonyldiimidazole |
| <i>c</i> -Hex ₂ BH | dicyclohexylborane |
| cod | cyclooctadiene |
| conc. | concentrated |
| Cp ₂ TiMe ₂ | bis(η ⁵ -cyclopentadienyl)-dimethyl-titanium |
| CuDPP | copper(I)-diphenyl phosphinate |
| d | day |
| d.r. | diastereomeric ratio |
| DABCO | 1,4-diazabicyclo[2.2.2]octane |
| dba | dibenzylideneacetone |
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| DBN | 1,5-diazabicyclo[4.3.0]non-5-ene |
| DCC | <i>N,N'</i> -dicyclohexylcarbodiimide |
| DDQ | 2,3-dichloro-5,6-dicyano-1,4-benzoquinone |
| DEAD | diethyl azodicarboxylate |
| DHβC | 3,4-dihydro-β-carboline |
| DIBAL | diisobutylaluminum hydride |
| DIPEA | <i>N,N</i> -diisopropylethylamine |
| DMAP | 4-dimethylaminopyridine |
| DME | 1,2-dimethoxyethane |
| DMF | dimethylformamide |
| DMP | Dess–Martin periodinane |
| DMS | dimethyl sulfide |
| DMSO | dimethyl sulfoxide |
| e.e. | enantiomeric excess |
| e.r. | enantiomeric ratio |
| EDCI | 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide |
| Et | ethyl |
| h | hour |
| HFIP | 1,1,1,3,3,3-hexafluoroisopropyl alcohol |
| HOBt | 1-hydroxybenzotriazole |
| IBA | 2-iodosobenzoic acid |
| IBX | 2-iodoxybenzoic acid |
| KHMDS | potassium bis(trimethylsilyl)-amide |
| Lawesson's reagent | 2,4-bis(4-methoxy-phenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide |
| LDA | lithium diisopropylamide |
| LiHMDS | lithium bis(trimethylsilyl)amide |
| <i>L</i> -selectride | lithium tri- <i>sec</i> -butyl(hydrido)-borate |
| <i>m</i> -CPBA | <i>meta</i> -chloroperbenzoic acid |

| | |
|--------------------|--|
| Me | methyl |
| MEM | 2-methoxyethoxymethyl ether |
| min. | minute |
| MS | molecular sieve |
| MW | microwave |
| Nap | 2-naphthylmethyl ether |
| NB | 2-nitrobenzyl |
| NBS | <i>N</i> -bromosuccinimide |
| NCS | <i>N</i> -chlorosuccinimide |
| NMM | <i>N</i> -methylmorpholine |
| NMO | 4-methylmorpholine <i>N</i> -oxide |
| NMP | <i>N</i> -methyl-2-pyrrolidone |
| Ns | 2-nitrobenzenesulfonyl |
| <i>o</i> -NBOH | <i>o</i> -nitrobenzylalcohol |
| Oxone [®] | 2 KHSO ₅ ·KHSO ₄ ·K ₂ SO ₄ |
| PDC | pyridinium dichromate |
| Pf | phenylfluorenyl |
| Phth | phthaloyl |
| pin | pinacolato |
| PMB | <i>p</i> -methoxybenzyl |
| Pr | propyl |
| psi | pound-force per square inch |
| Py | pyridine |
| r.t. | room temperature |
| Schwartz's reagent | chloridobis(η ⁵ -cyclo-pentadienyl)hydrido-zirconium |
| T3P [®] | propylphosphonic anhydride |
| TBAF | tetrabutylammonium fluoride |
| TBAT | tetrabutylammonium difluoro-triphenylsilicate |
| TBDPS | <i>tert</i> -butyldiphenylsilyl |
| TBDMS | <i>tert</i> -butyldimethylsilyl |
| <i>t</i> -Bu | <i>tert</i> -butyl |
| TES | triethylsilane |
| TMG | tetramethylguanidine |
| Tf | trifluoromethanesulfonyl |
| TFA | trifluoroacetic acid |
| TFAA | trifluoroacetic anhydride |
| THF | tetrahydrofuran |
| THβC | 1,2,3,4-tetrahydro-β-carboline |
| TIPS | triisopropylsilyl |
| TMG | 1,1,3,3-tetramethylguanidine |
| TMP | 2,2,6,6-tetramethylpiperidine |
| TMS | trimethylsilyl |
| TPAP | tetrapropylammonium perruthenate |
| Ts | <i>p</i> -toluenesulfonyl (tosyl) |
| Tsdpn | <i>N</i> -tosyl-1,2-diphenylethylene-1,2-diamine |

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