DOI 10.1007/s10593-021-03036-9
Chemistry of Heterocyclic Compounds **2021**, *57*(12), 1155–1163

Methods for the synthesis of 3*H*-pyrrolo[2,3-*c*]quinolines

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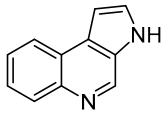
Translated from Khimiya Geterotsiklicheskikh Soedinenii, 2021, *57*(12), 1155–1163

Submitted November 9, 2021
Accepted after revision December 2, 2021



The review examines methods for the preparation of compounds containing the 3*H*-pyrrolo[2,3-*c*]quinoline fragment, which have been published mainly over the past 10–15 years.

Keywords: marinoquinoline, pyrrolo[2,3-*c*]quinoline, heterocycles, natural compounds.

Heterocyclic compounds containing the 3*H*-pyrrolo-[2,3-*c*]quinoline tricyclic system, for example, marinoquinolines **1**–**11**, are attracting considerable attention due to the wide spectrum of biological activity shown.[1–5]

A significant amount of data on the synthesis and use of such compounds exists. Marinoquinolines are reported to possess antibacterial, antifungal, and moderate antineoplastic properties.[1] These compounds are noted to be effective against malaria,[2,3] and are also capable of inhibiting acetylcholinesterase in the human CNS.[4,5] Some compounds containing such fragments can be used to detect Zn^{2+} ions in the presence of various other cations,[6,7] including Cd^{2+} and Hg^{2+}, as well as for selective detection of water[8] and fluoride ions.[9] In general, these compounds are attracting attention not only because of their potential applications in medicine, but also because of their successful use in analytical chemistry. This review discusses contemporary methods for the preparation of such heterocycles published over the past 10–15 years.

The methods for the synthesis of 3*H*-pyrrolo[2,3-*c*]-quinolines can be roughly divided into three categories, depending on the ring closed in the final step.

Annulation of the benzene ring

A sole example of the formation of the benzene ring as the last step in the preparation of such compounds can be found. According to this method, the intramolecular Diels–Alder reaction[10] of a 5-amino-4-methyloxazole derivative containing a propargyl fragment is employed to construct the condensed pyrrolo[2,3-*c*]pyridine fragment (Scheme 1).

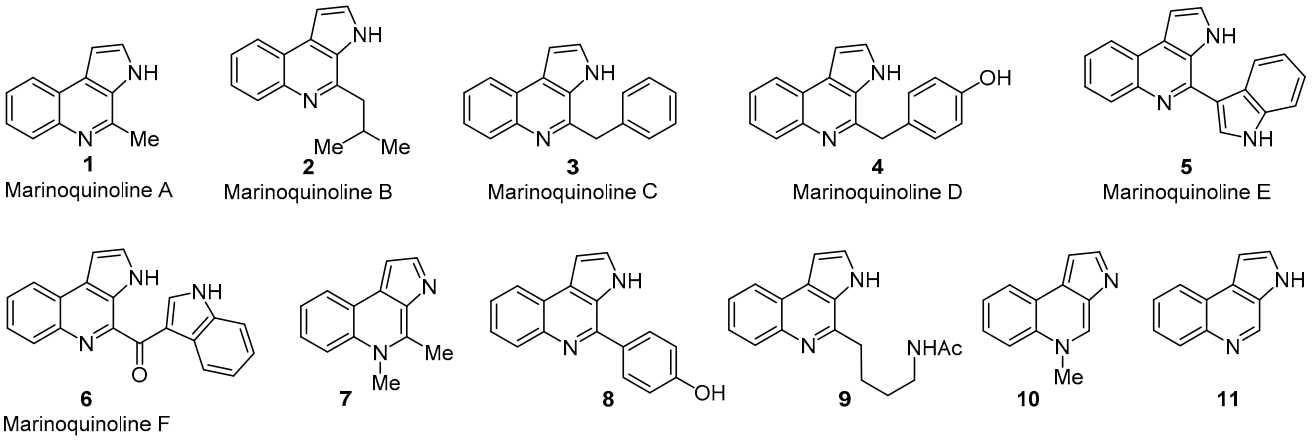
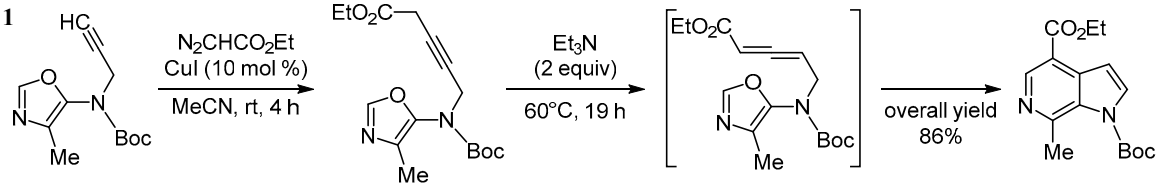
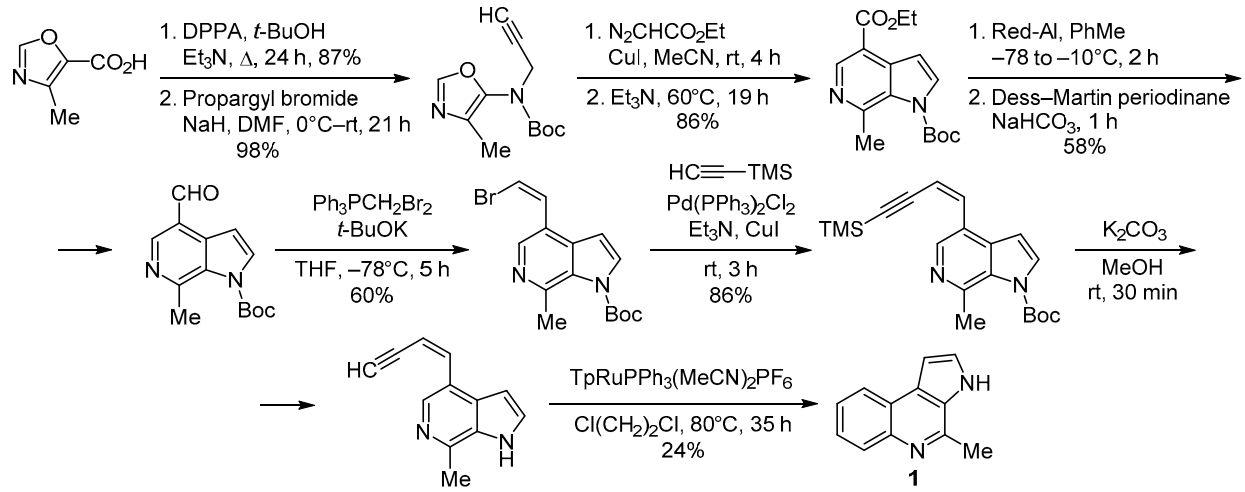


Figure 1. Alkaloids of the marinoquinoline group.

Scheme 1



Scheme 2



Marinoquinoline A (**1**) is formed in the final step as a result of the closure of the benzene ring in a Ru-catalyzed transformation (Scheme 2).

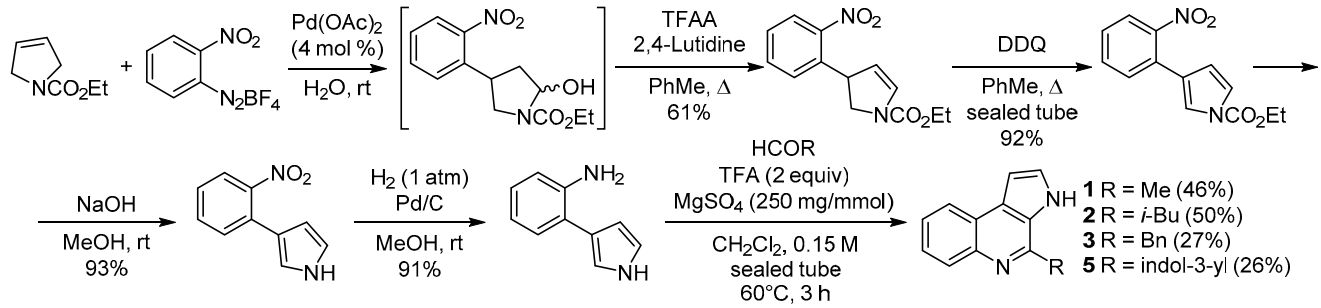
Annulation of the pyridine ring

Most of the studies describing the preparation of pyrrolo-[2,3-*c*]quinolines and published in recent years present synthetic routes involving annulation of the pyridine ring in the final step of the synthesis. In particular, the synthesis of marinoquinolines[1–3,5] was carried out using the Pictet–Spengler reaction accompanied by cyclization and oxidation in the final step (Scheme 3).[11]

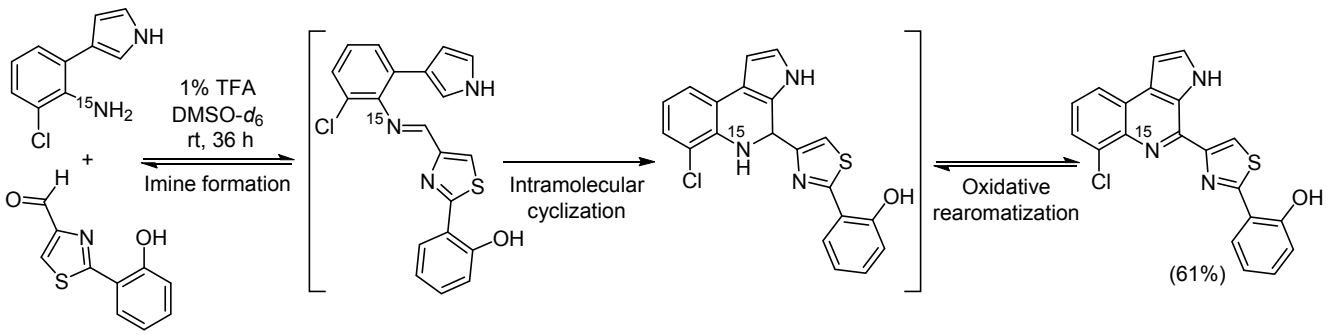
Similar transformations were carried out in the synthesis of substituted (for example, with a halogen atom) marinoquinolines[2] and pyonitrins[12] labeled with the ^{15}N isotope in the quinoline fragment (Scheme 4).

A method for the synthesis of such compounds was also described involving a Pd-catalyzed reaction of *o*-bromonitrobenzene with 3-iodopyrrole-2-carbaldehyde (Scheme 5).[13]

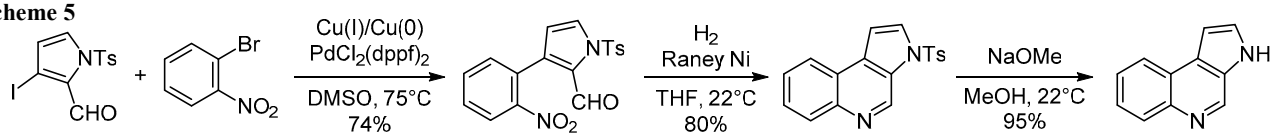
Scheme 3



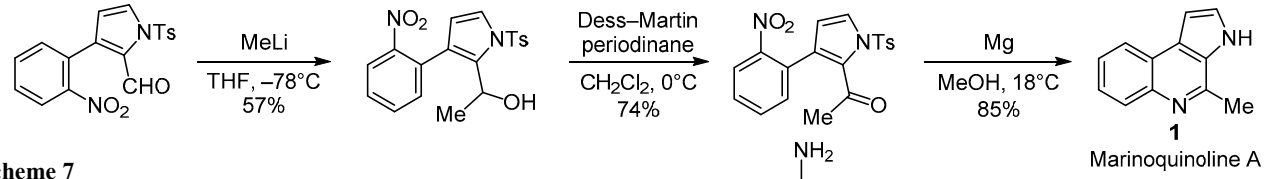
Scheme 4



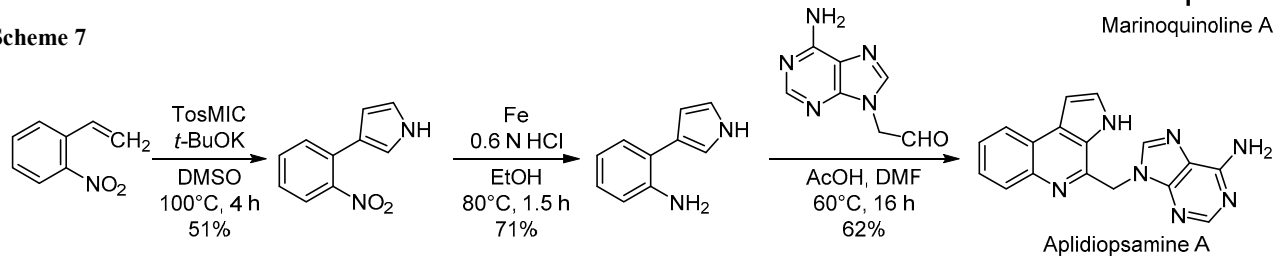
Scheme 5



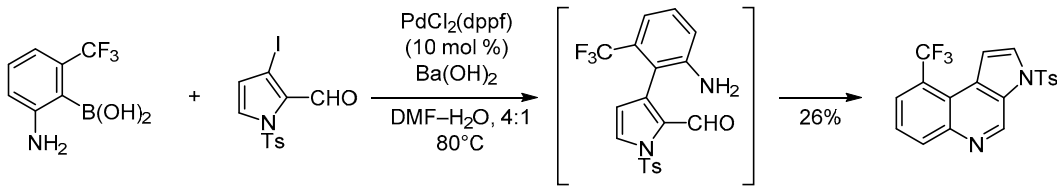
Scheme 6



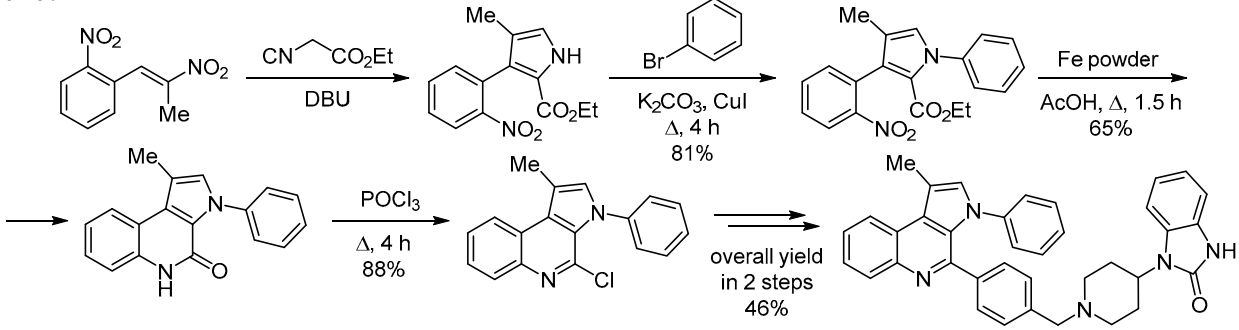
Scheme 7



Scheme 8



Scheme 9



The cyclization of nitrophenylpyrrolecarbaldehyde was also successfully used for the synthesis of marinoquinoline A (**1**) (Scheme 6).[14]

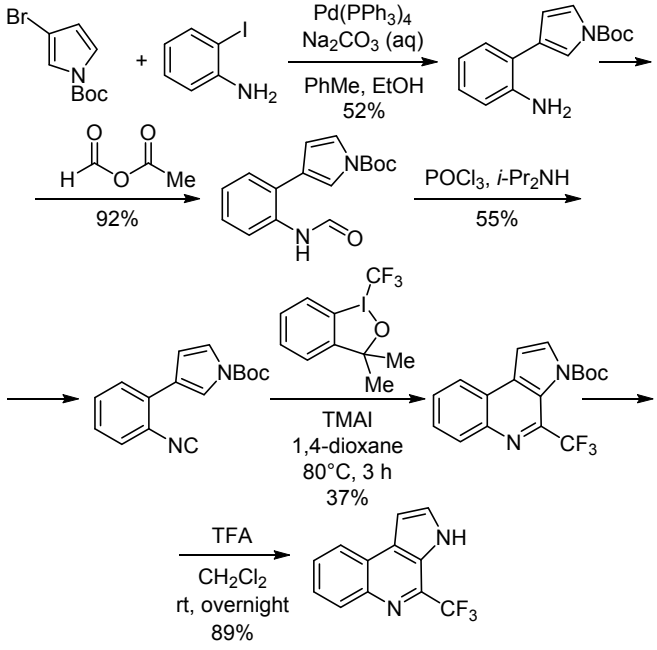
o-Nitrostyrene and toluenesulfonylmethyl isocyanide (TosMIC) were used as starting compounds for the synthesis of aplidiopsamine A.[15] The resulting 3-(*o*-nitrophenyl)pyrrole was reduced to *o*-aminophenylpyrrole and introduced into a reaction with the corresponding carbonyl compound (Scheme 7).

Pyrrolo[2,3-*c*]quinoline structures can also be obtained using the Suzuki cross coupling (Scheme 8).[16]

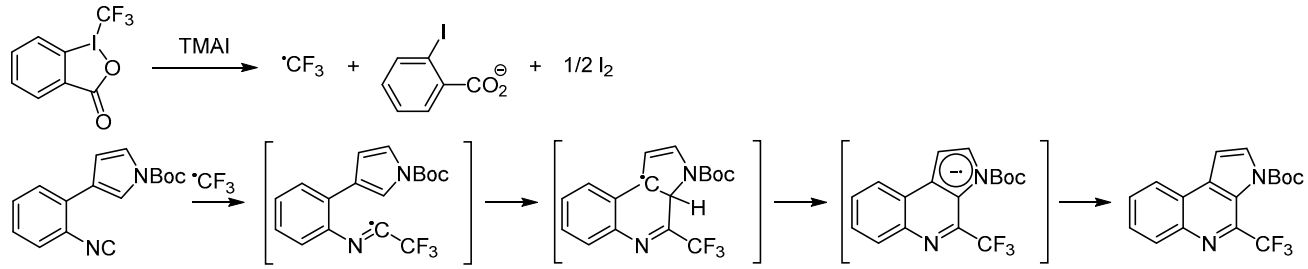
The Barton–Zard reaction was successfully used to form the pyrrole fragment in the preparation of 2-chloro-5-methyl-3-phenyl-3*H*-pyrrolo[2,3-*c*]quinoline (Scheme 9).[17] The mechanism of the Barton–Zard reaction was discussed in detail elsewhere.[18]

A radical method of pyridine ring closure using Togni reagent (1-trifluoromethyl-1,2-benziodoxol-3(1*H*)-one) in the presence of tetramethylammonium iodide (TMAI) is also known (Scheme 10).[19] The mechanism proposed for this cyclization is shown in Scheme 11.

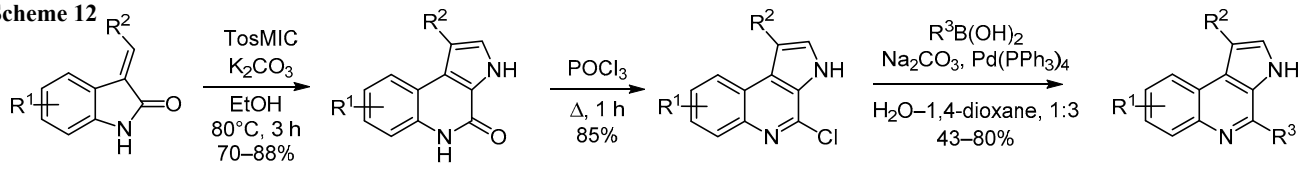
Scheme 10



Scheme 11



Scheme 12

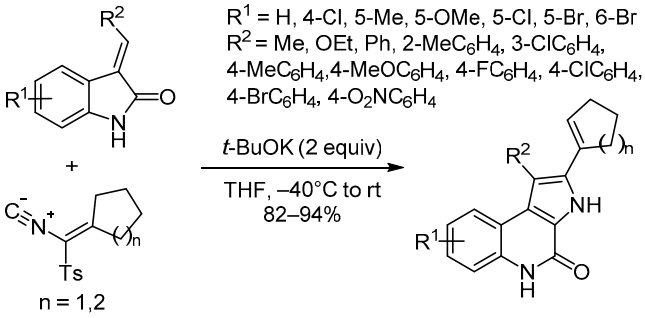


R^1 = H, Me, OMe, F, Cl, Br, NO_2; R^2 = CO_2Me, CO_2Et, Ar, COAr; R^3 = Ar

Marinoquinolines were synthesized on the basis of an oxindole derivative using TosMIC (Scheme 12).[20,21] Experiments have shown that cyclization occurs with both electron donor and electron acceptor substituents R^1 (the yields varied within 70–88%). Various substituents at the olefinic position of oxindole (R^2 = CO_2Et, CO_2Me, substituted aryl and phenacyl) led to target products with yields in the range from 43 to 80%.

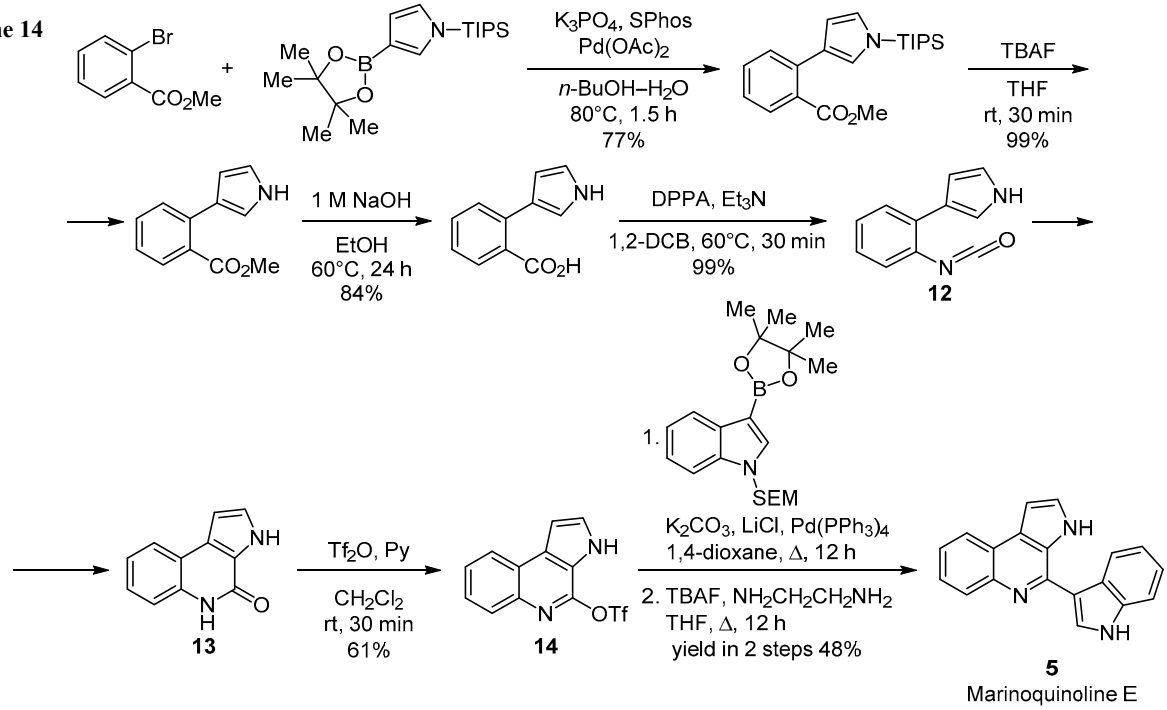
When isocyanates containing a cycloalkylidene substituent were used, the corresponding 4-substituted derivatives of 3*H*-pyrrolo[2,3-*c*]quinolin-4(5*H*)-one were formed in high yields (Scheme 13).[22]

Scheme 13

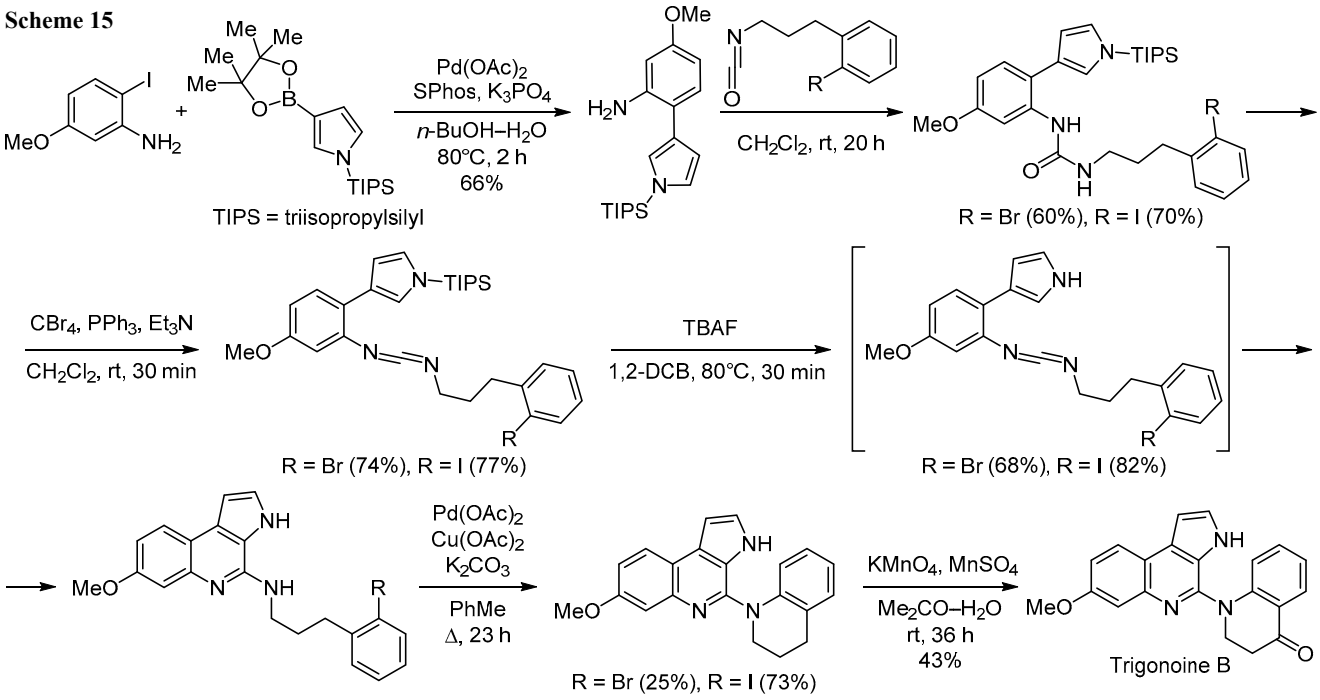


In order to access marinoquinoline E (**5**), the synthesis of the pyrrolo[2,3-*c*]quinoline skeleton was proposed using thermal electrocyclization (Scheme 14).[23] On its implementation, the sequence of the Suzuki–Miyaura reaction, deprotection of the nitrogen atom, hydrolysis of the ester with the formation of 2-(1*H*-pyrrol-3-yl)benzoic acid was carried out. A further attempt to synthesize isocyanate **12** by the Curtius rearrangement was accompanied by tandem electrocyclization proceeding at the same temperature and leading to the formation of product **13**, which was then transformed into triflate **14** to obtain the target marinoquinoline E (**5**).

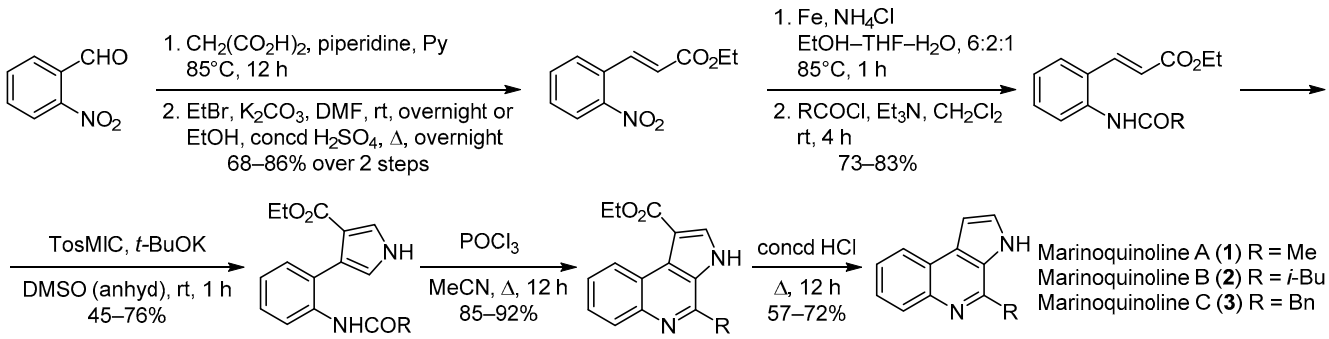
Scheme 14



Scheme 15



Scheme 16



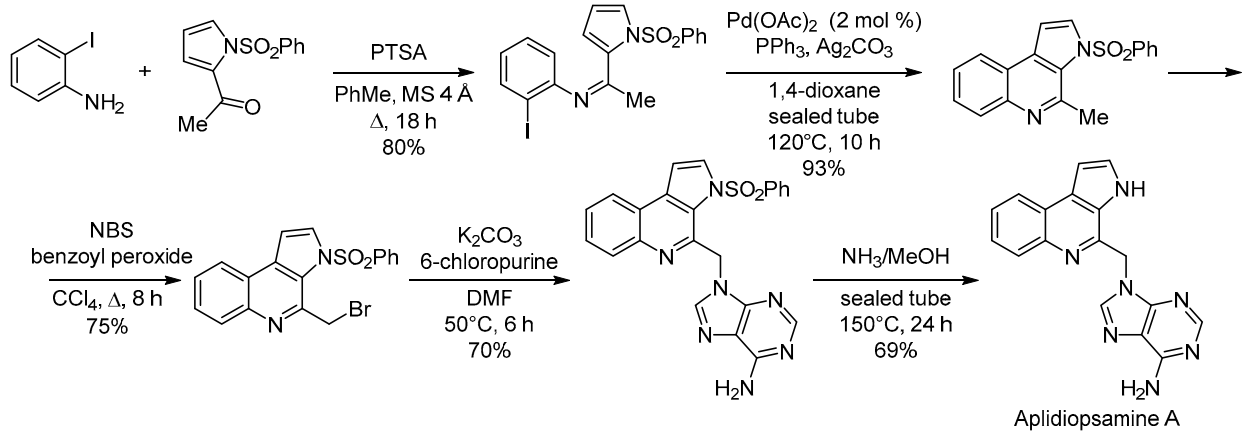
Experiments have shown that it is not possible to attain the replacement of the triflate in compound **14** with 2,3-dihydro-1*H*-quinolin-4-one. Therefore, for the synthesis of trigonoine B, a similar synthesis was carried out where the fragments of the required substituent were present already before electrocyclization (Scheme 15).[24]

A method was developed for the preparation of marinoquinolines A–C from commercially available starting compounds by closing the pyridine ring by the Bischler–Napieralski reaction (Scheme 16).[25]

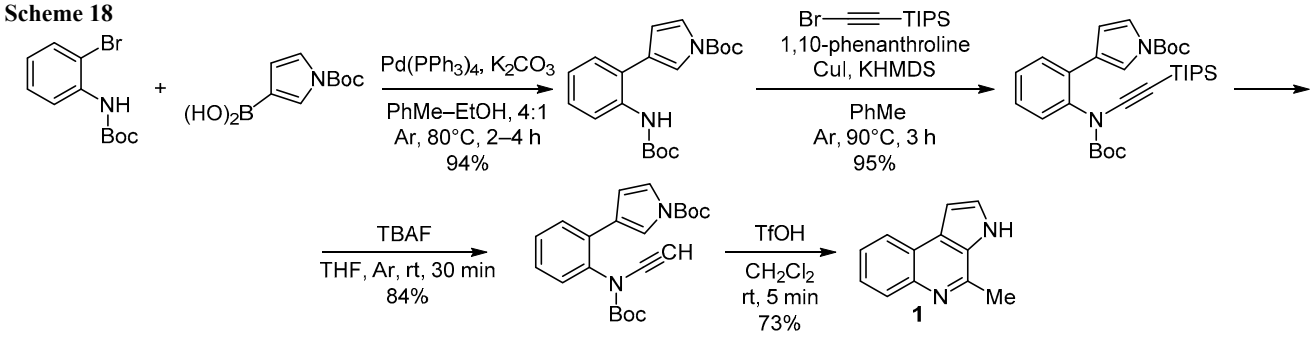
The alkaloid aplidiopsamine A was synthesized as a result of the formation of a pyrrolo[2,3-*c*]quinoline fragment *via* pyridine ring closure employing a Pd-containing catalyst (Scheme 17).[26]

Marinoquinoline A (**1**) was also synthesized by acid-catalyzed cyclization of an *N*-ethynyl-substituted arene derivative (Scheme 18).[27]

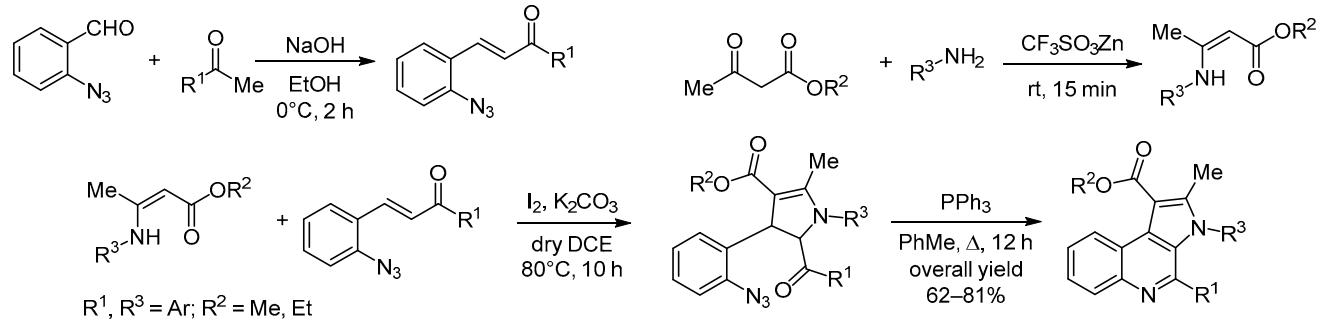
Scheme 17



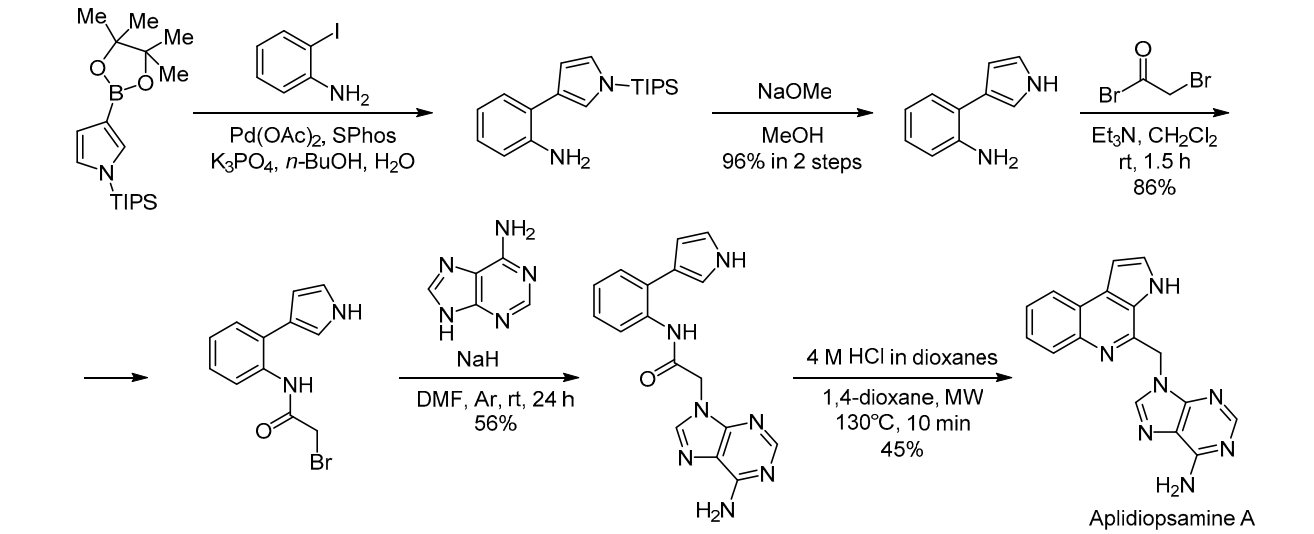
Scheme 18



Scheme 19



Scheme 20



The I_2-catalyzed cyclization of β-enaminoesters with *o*-azidochalcones[28] obtained by the condensation of *o*-azidobenzaldehyde with the corresponding acetyl(het)-arenes (Scheme 19) present another method for the preparation of such heterocycles.

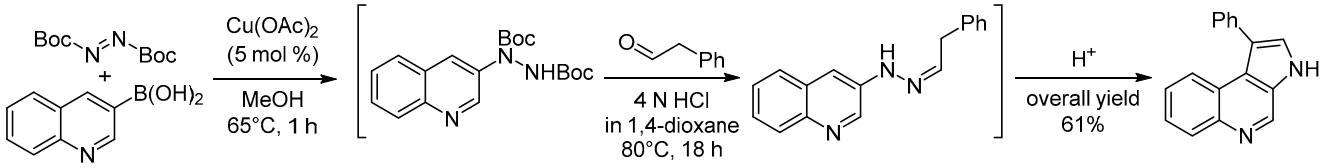
In order to obtain the alkaloid aplidiopsamine A, the biomimetic synthesis of the 3*H*-pyrrolo[2,3-*c*]quinoline fragment was carried out in five steps (Scheme 20).[29] The total yield of the target alkaloid was 21%.

Annulation of the pyrrole ring

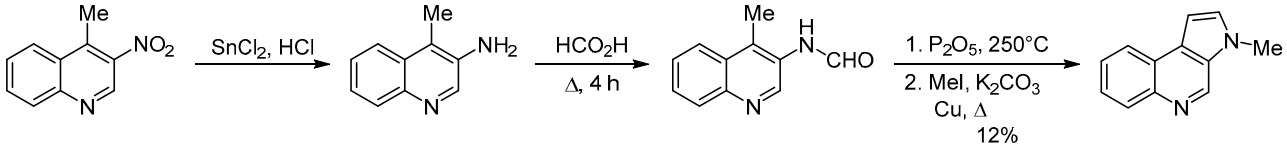
Only a small number of publications can be found on the formation of the pyrrole ring at the final step of the synthesis of the pyrrolo[2,3-*c*]quinoline skeleton. One of the methods for the preparation of such compounds is the Fischer reaction (Scheme 21).[30,31]

The synthesis of similar structures based on 3-formyl-amino-4-methylquinoline (Scheme 22), which is of

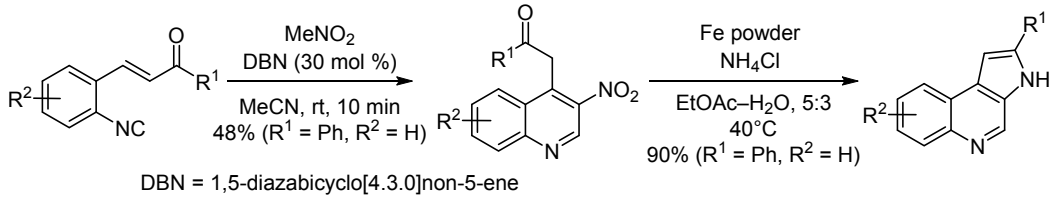
Scheme 21



Scheme 22

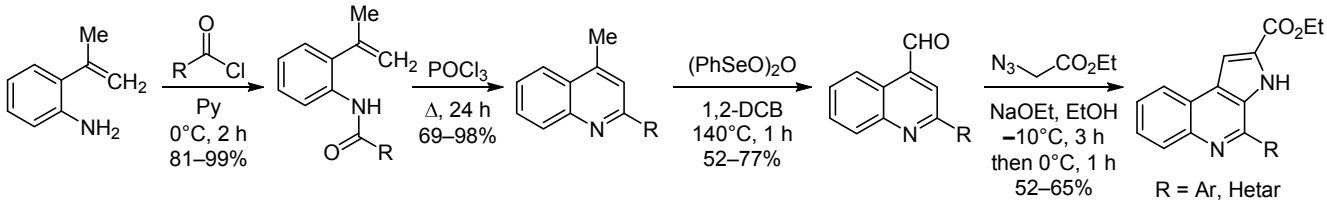


Scheme 23



DBN = 1,5-diazabicyclo[4.3.0]non-5-ene

Scheme 24



R = Ar, Hetar

exclusively historical interest and has no preparative value, has also been reported.[32]

Pyrrolo[2,3-*c*]quinolines can be obtained by reductive cyclization of 3-nitro-4-oxomethyl-substituted quinolines (Scheme 23).[33]

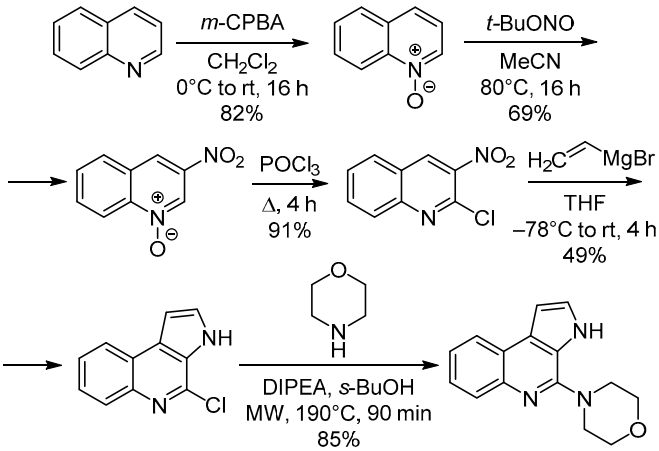
An approach (Scheme 24) to the synthesis of pyrrolo-[2,3-*c*]quinolines based on the Hemetsberger–Knittel reaction (thermal decomposition of α-azidoacrylates) was also developed and described.[34]

3*H*-Pyrrolo[2,3-*c*]quinolin-4(5*H*)-ones were obtained in high yields using Pd-catalyzed cross coupling and subsequent cyclization as a result of transformations given in Scheme 25.[35]

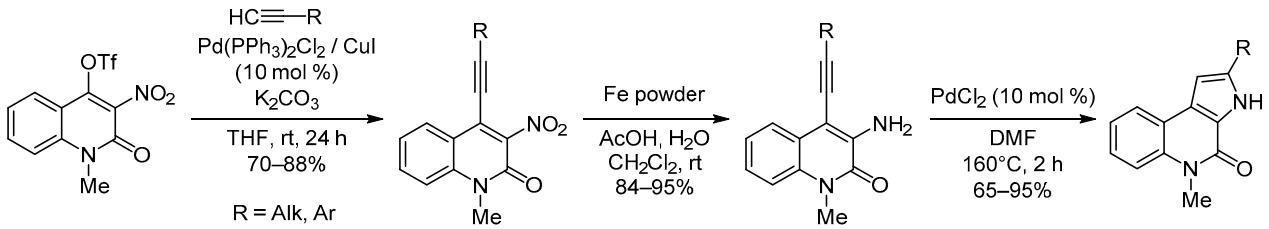
An alternative approach to the synthesis of such compounds is based on a cascade process encompassing Pd-catalyzed *N*-arylation and subsequent cyclization (Scheme 26) leading to 3-substituted 3*H*-pyrrolo[2,3-*c*]-quinolin-4(5*H*)-ones.[36]

An approach to the preparation of pyrrolo[2,3-*c*]-quinolines employing the Bartoli indole synthesis was described (Scheme 27).[37]

Scheme 27

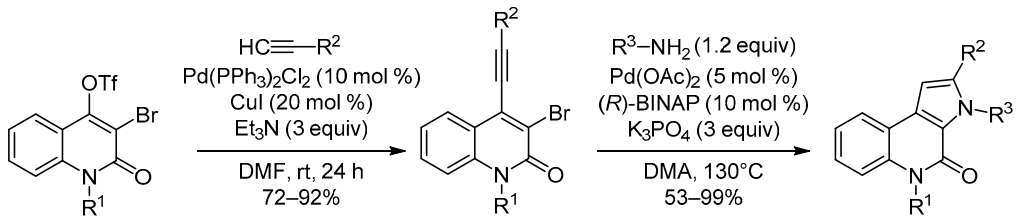


Scheme 25



R = Alk, Ar

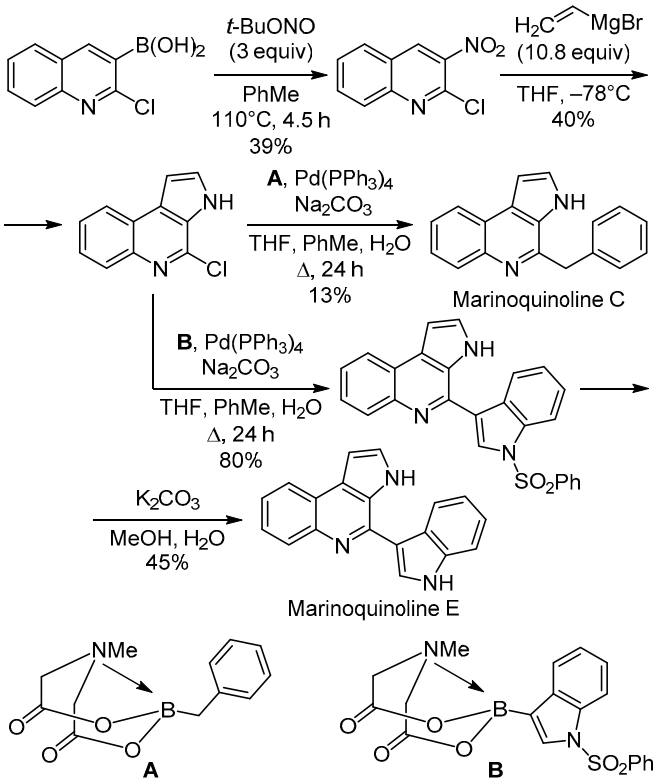
Scheme 26



R1 = Me, Ph; R2 = Ar; R3 = Ph, Bn, Ar

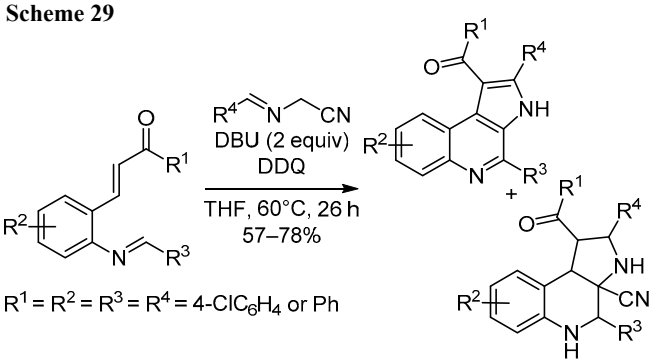
Similar transformations[38] were involved in the preparation of marinoquinolines C and E (Scheme 28).

Scheme 28



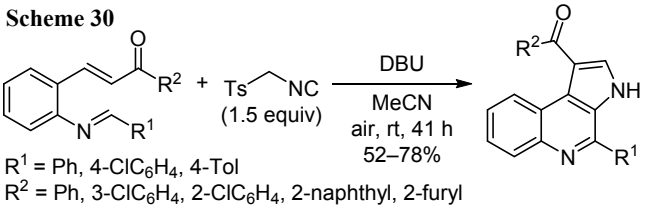
Pyrrolo[2,3-*c*]quinolines with aryl substituents were also obtained in high yields (57–78%) by tandem bicyclization with the participation of azomethine ylides and methylene-aminochalcones (Scheme 29).[39]

Scheme 29



A similar tandem cyclization was also carried out using TosMIC (Scheme 30).[40] In this case, position 4 of the pyrrolo[2,3-*c*]quinoline fragment is unsubstituted. Depending on the substituent R^2, the yields of the target pyrroloquinoline varied from 52 to 78%.

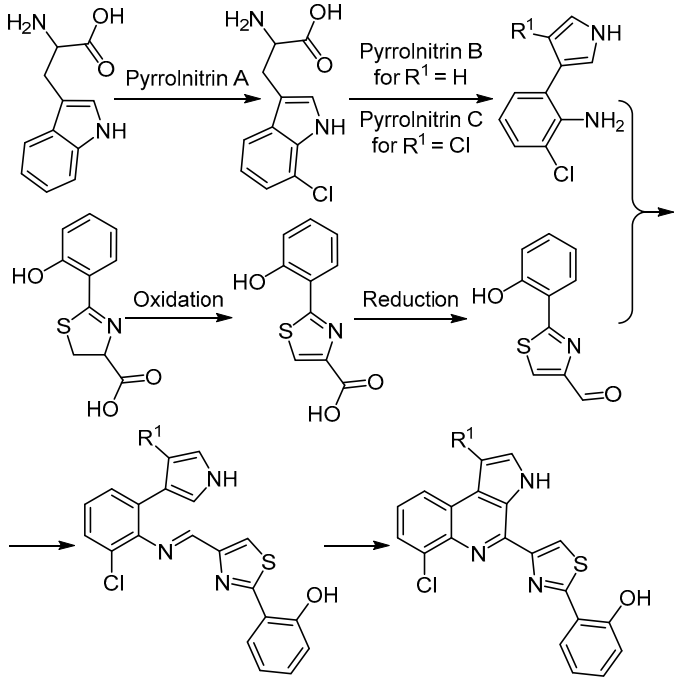
Scheme 30



Nonsynthetic methods of preparation

The literature also describes nonsynthetic methods for the preparation and isolation of such heterocycles, for example, from bacteria or their metabolic products.[1,41–43] Thus, marinoquinolines A–K, pyonitrins A–D were obtained from bacteria *Mooreia alkaloidigena*, *Cytophagales*, *Pseudomonas protegens*, *Ohtaekwangia kribbensis*. Experiments were also carried out to establish the route of biosynthesis. For example, the biosynthesis route proposed for *Pseudomonas protegens* is shown in Scheme 31.

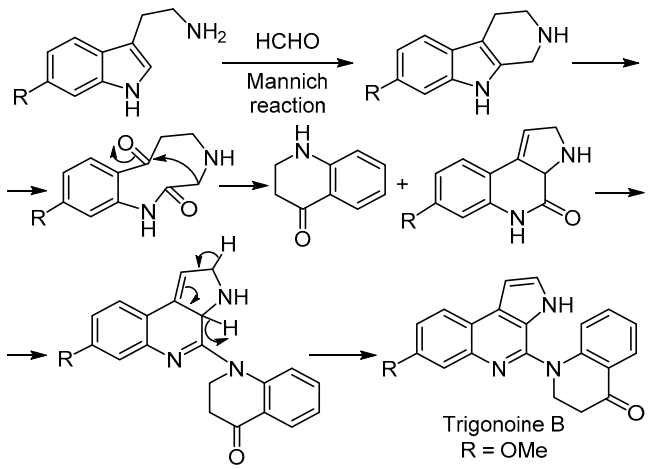
Scheme 31



The alkaloid aplidiopsamine A was isolated from the Australian ascidian *Aplidiopsis confluata*.[44] Experiments showed that it has antimalarial activity.

The alkaloid trigonoine B was isolated from the leaves of *Trigonostemon lii*.[45] The probable biogenetic route of synthesis is given in Scheme 32.

Scheme 32



To conclude, the plethora of synthetic approaches to the preparation of pyrrolo[2,3-*c*]quinolines developed over the past decade indicates a significantly increased interest in this potential pharmacophore fragment in the search for new medicinal compounds. Generally, approaches with the closure of the pyridine ring dominate among the methods for the synthesis of these structures; however, annulation of the pyrrole ring is also of considerable interest. Simultaneously with the preparation of this review, a review article was published devoted to the methods of synthesis of marinoquinoline alkaloids, as well as their biological properties,[46] but it considers the synthesis methods in the chronological order of their appearance in the literature, whereas in this review the classification is carried out according to the method of forming the ring which is closed in the final step of the formation of the 3*H*-pyrrolo[2,3-*c*]quinoline tricyclic system.

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