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Synthesis of Polyheterocyclic Nitrogen-Containing Marine Natural Products[#]

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Summary. The synthetic routes used for the preparation of marine alkaloids variolin B and lamellarins are described.

Keywords. Marine alkaloids; Cross-coupling reactions; Solid-phase synthesis; Heterocycles; Libraries; Combinatorial Chemistry.

Introduction

Our planet offers an incredible diversity of organic life with a huge number of animal and plant species that have adapted to their individual environments throughout evolutionary time. Many of today's medicines have been derived from 'natural products' – extracts from plants and other organisms, which have proved to be highly useful in combating diseases.

Natural products have been extensively used to elucidate complex cellular mechanisms leading to the identification of new targets for therapeutic applications. This shows the importance of developing small molecule libraries based on natural products. Solid-phase combinatorial synthesis is one of the most useful techniques for the preparation of small libraries. It provides a fast access to larger

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collections of products that may possess great diversity and may incorporate optimized physical and pharmacological properties into their structures.

Marine organisms have developed complex biological mechanisms for survival, such as production of potent natural chemicals that may be used in their defense. The sea, with its immense biological diversity, offers a rich hunting ground for the identification of chemical compounds for the effective treatment of cancer among other diseases [1].

Our work in this area is focused on developing new synthetic strategies for the preparation of active polyheterocyclic nitrogen-containing marine natural products. The synthetic route should be versatile for the preparation of derivatives for pharmacological evaluation.

Our first syntheses [2–5] of marine natural products were devoted to the marine alkaloids batzellines [6], isobatzellines [7], makaluvamines [8–10], and discorhabdines [11–13]. These alkaloids are small molecules with a common pyrrolo[4,3,2-*de*]quinoline nucleus and a high degree of functionalization. We evolved a synthetic strategy based on the construction of such molecules starting from a simple quinoline [14].

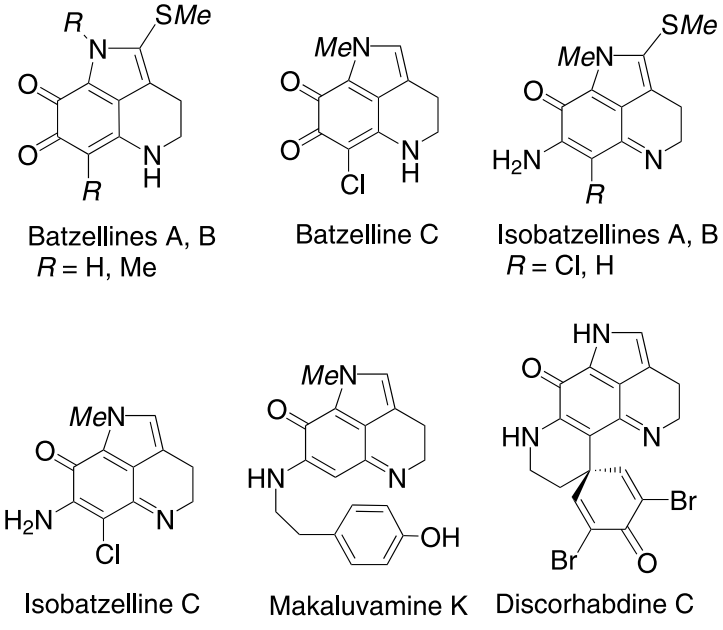


Fig. 1. Structures of batzellines, isobatzellines, makaluvamines and discorhabdines

The second family of marine alkaloids studied was the pyridoacridine group. They show important activity as inhibitors of tumor cells. We developed a new synthesis for ascididemin and its regioisomer isoascididemin [15–17]. The activities of the synthetic natural product as well as of several intermediates were evaluated and some of the synthetic intermediates as well as derivatives had comparable activities to the natural products.

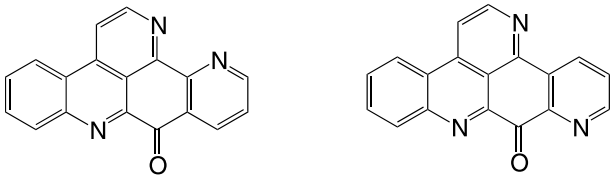


Fig. 2. Structures of ascididemine and isoascididemine

Herein, we describe our progress in the synthesis of variolin B as well as our preliminary results in the solid-phase synthesis of lamellarins.

Variolin B and Derivatives

Variolins were isolated by Munro *et al.* from the red sponge *Kirkpatrickiav variolosa* collected in Antarctic waters [18, 19]. They possess an absolutely new structure without precedents in natural or synthetic compounds. Structurally the four compounds have a common pyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine system and the differences between them lie in the substituent at position 5. This substituent can be an aminopyrimidine ring as in variolin B, an oxidized or reduced form of aminopyrimidine as in variolin A or in *N*(3′)-methyltetrahydrovariolin B and also a non heterocyclic substituent as a methoxycarbonyl group present in variolin D.

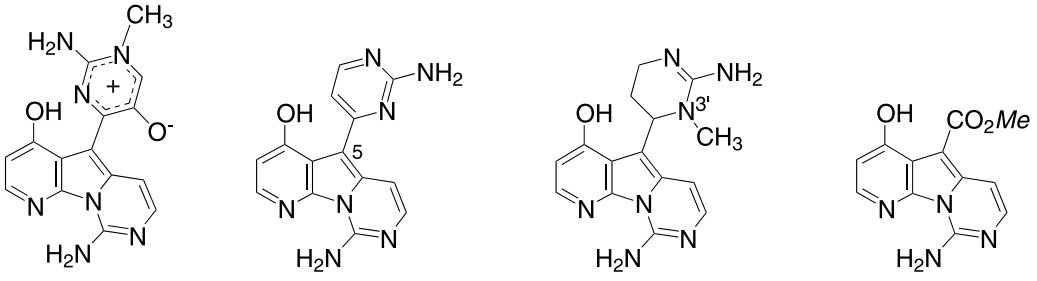


Fig. 3. Structures and activities of variolins

Variolin B is the most active of the group. Thus, it shows an important inhibition of the growth of the P388 tumor cell line and is also active against *Herpes simplex* and polio virus. Variolin A and the methyltetrahydrovariolin B were less active against P388 but the latter showed important activity against the HCT-116 human colon tumor cell line and against *Saccharomyces cersevisae*. Variolin D was inactive in all the tests. The different activities of these compounds show the

importance of the aminopyrimidine aromatic ring attached to position 5 of the tricyclic system.

Our purpose in this field was to develop a total synthesis for the most active compound of the group, variolin B. This synthesis should be flexible to facilitate the preparation of analogues, which will differ in substituents on the A, C, and D rings. During the course of our work two total synthesis of variolin B and several routes to the deoxyvariolin B were published [20–21]. In parallel, we decided to carry out the synthesis of simplified analogs without rings C or A to test if the activity remained in smaller molecules such as 3-aryl- or 3-heteroaryl-7-azaindoles and in 5-aryl- or 5-heteroaryl-1,2-dihydropyrrolo[1,2-*c*]pyrimidin-1-ones. The carbonyl group in the pyrimidone was to be the precursor of the amino group.

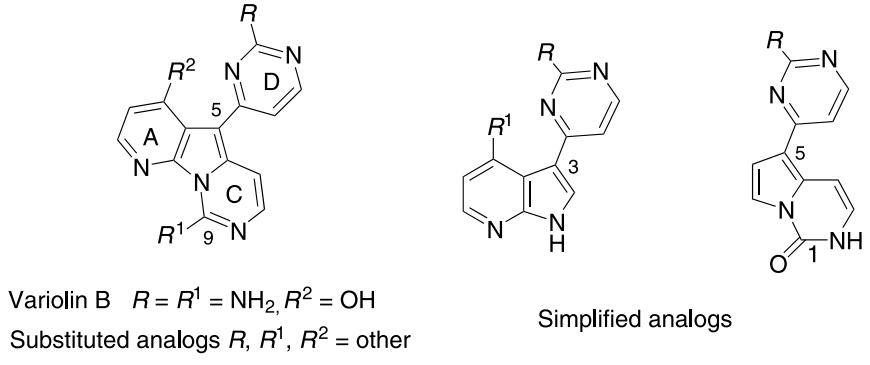


Fig. 4. Substituted and simplified analogs of variolins

The key process involved in the synthesis of this bis-heteroaryl systems was a Pd-catalysed cross-coupling reaction between a substituted 7-azaindole, a pyrrolo[1,2-*c*]pyrimidin-1-one, or a pyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidin-1-one and the appropriate aryl- or heteroaryl-substituted compound.

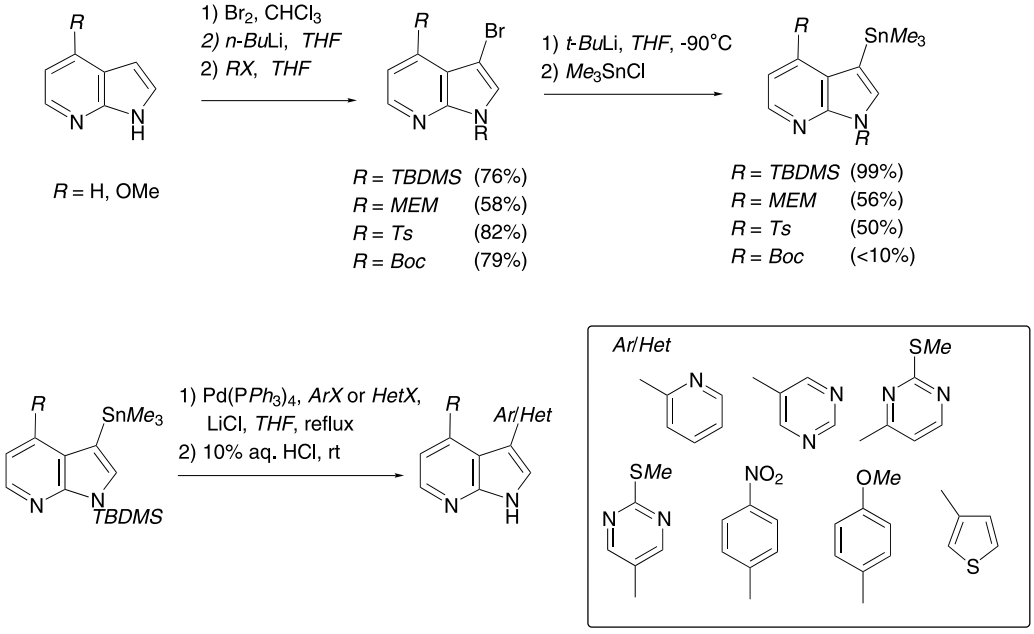
Synthesis of Aryl or Heteroaryl-7-azaindoles

In our hands, *Stille* reaction between a tin derivative of 7-azaindole and the aryl or heteroaryl halide proved to be more useful than *Suzuki*, *Negishi*, or other Pd-catalysed cross-coupling reactions for the formation of aryl or heteroaryl-7-azaindoles.

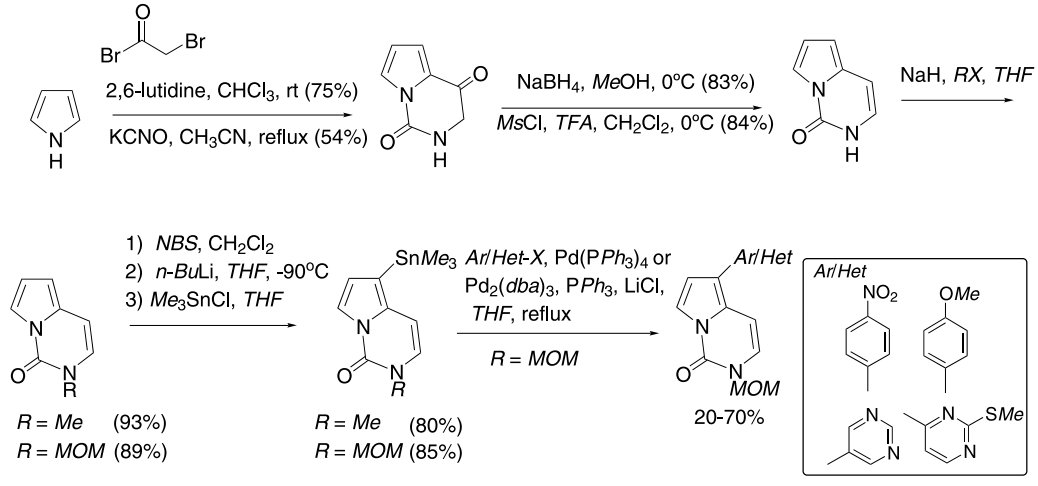
Thus, we studied the effect of *N*(1)-protecting groups in the preparation of tin derivatives of 7-azaindole finding the *t*-butyldimethylsilyl (*TBDMS*) protecting group to be the most effective. We also established the best reaction conditions by modifying the solvent, the catalyst, and the temperature of the reaction, and the ligands. The best results for that coupling reaction were obtained using tetrakis(triphenylphosphine)palladium(0) and LiCl in THF at reflux, giving, after hydrolysis, the arylazaindoles with moderate to good yields [22].

1,2-Dihydropyrrolo[1,2-c]pyrimidin-1-ones

The synthesis of 1,2-dihydropyrrolo[1,2-*c*]pyrimidin-1-one was achieved by a four-step procedure from pyrrole as shown in Scheme 2. *N*-Acetylation of pyrrole with bromoacetyl bromide and lutidine as base in chloroform followed by reaction with



Scheme 1. Synthesis of 5-aryl- or 5-heteroaryl-7-azaindoles



Scheme 2. Synthesis of 5-aryl- or 5-heteroaryl-1,2-dihydropyrrolo[1,2-*c*]pyrimidin-1-ones

potassium cyanate in refluxing acetonitrile gave the bicyclic system of tetrahydropyrrolo[1,2-*c*]pyrimidin-1,4-dione. Reduction of the carbonyl group followed by formation of the mesylate and *in situ* elimination afforded the pyrrolopyrimidone. The tin derivative of pyrrolopyrimidone was prepared by a route similar to that described for 7-azaindoles. *N*-Protection, bromination, interchange of halogen by lithium, and quenching the lithio-derivative with Me_3SnCl afforded in a good overall yield the 5-stannyl-derivative of the pyrrolopyrimidone [23, 24].

The coupling reactions between this new tin derivative and several aryl or heteroaryl halides were tested using the best conditions found for the 7-azaindole.

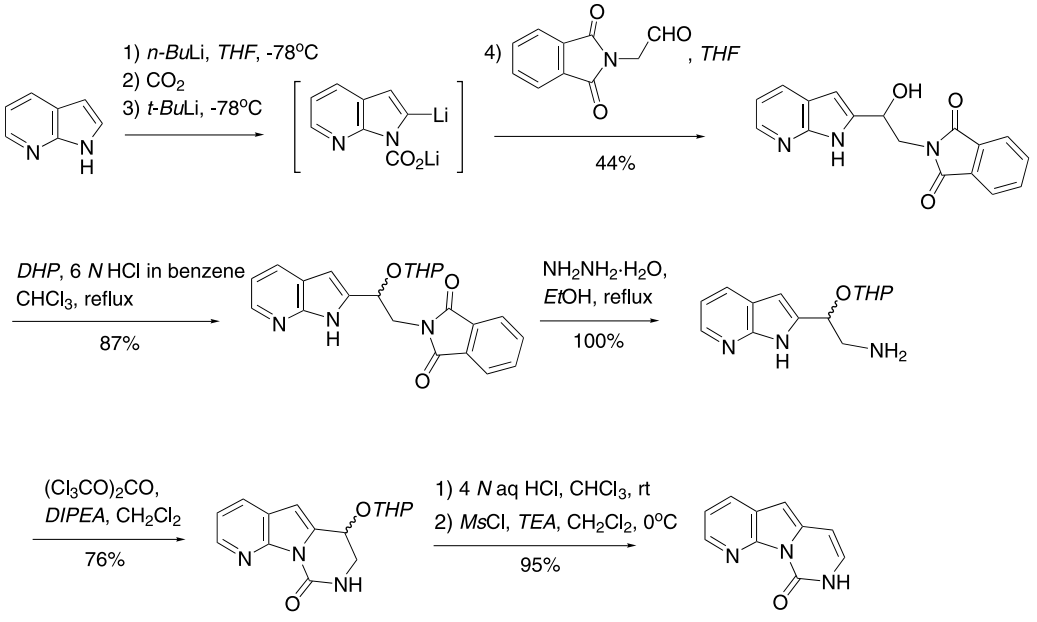
Again, the best yields were achieved for the reaction with π-deficient halides such as 4- and 5-bromopyrimidines or 4-bromonitrobenzene, while for electron-rich aromatic halides such as 4-bromoanisole the yields were lower.

None of the new simplified analogs of variolin B showed significant activity against the different tumor cell lines tested. This result demonstrates the importance of the three heterocyclic ring core systems for the pharmacological activity of this family of compounds.

Pyrido[3′,2′:4,5]pyrrolo[1,2-c]pyrimidin-9-ones

The tricyclic pyridopyrrolopyrimidone system was obtained by a six-step synthetic route from 7-azaindole with good overall yield [25]. The introduction of a functionalised two carbon atom chain at position 2 of 7-azaindole was achieved by reaction of the *N*-protected phthalimidoacetaldehyde [26] with 2-lithio-7-azaindole. A lithium-carboxylate was used as *N*-protecting and *ortho*-directing substituent for the preparation of the 2-lithio-7-azaindole as described by *Katritzky* for indole 2-lithiation [27]. Reaction of 7-azaindole with *n-Bu*Li at low temperature followed by addition of dry CO_2 gave the lithium *N*-carboxylate which could be *C*-metalated with *t-Bu*Li. The addition of the protected aminoaldehyde at low temperature with stirring for a couple of hours at room temperature gave only 44% of alcohol, but the process was very clean and the unreacted 7-azaindole could be recovered.

Protection of the alcohol as a tetrahydropyranyl acetal followed by deprotection of the amino group by reaction with hydrazine yielded the aminoethylazaindole precursor, which was converted into the tricyclic system by reaction with triphosgene and diisopropylethylamine (*DIPEA*) in CH_2Cl_2. Deprotection of the alcohol followed by elimination of its mesylate gave the pyridopyrrolopyrimidone.

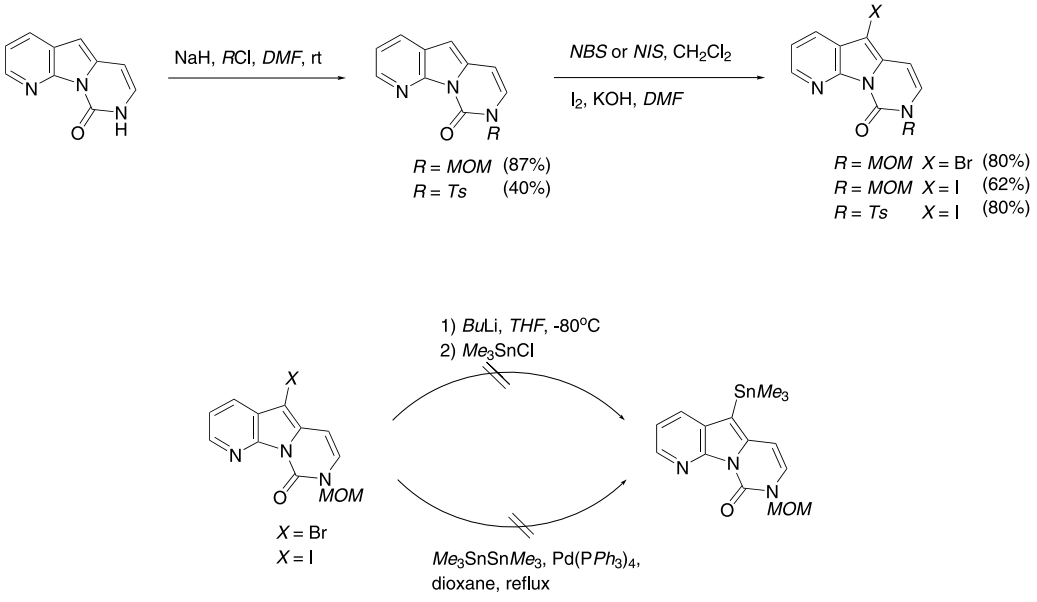


Scheme 3. Synthesis of pyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidone

Synthesis of Deoxyvariolin B

From the tricyclic system of pyridopyrrolopyrimidone the functionalization at position 5 for the introduction of a heteroaryl ring required a sequence of *N*(8)-protection and regioselective halogenation. We used *MOM* or *Ts* as protecting groups and bromide or iodide as halides.

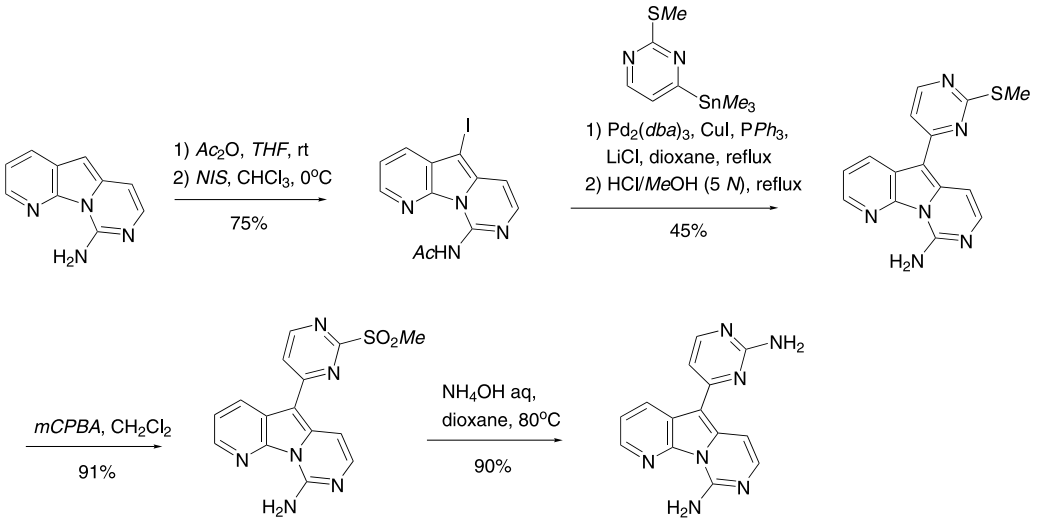
Preparation of tin derivatives by halogen-metal interchange with *n-Bu*Li and quenching with Me_3SnCl in a way similar to that used for the bicyclic systems did not allow us to isolate the organometallic compounds. The bromine-tin interchange process catalysed by Pd using hexamethylditin neither was a synthetically useful process for the preparation of the 5-tin derivative of protected pyridopyrrolopyrimidones (Scheme 4).



Scheme 4. Tin derivatives of pyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidone

These results forced a change in our strategy. We decided to use the halo-derivatives of the tricyclic system with the tin derivative of the aryl or heteroarylcompounds. Thus, 2-methanesulfanyl-4-trimethylstannylpyrimidine was prepared by halogen-metal interchange from the 2-methanesulfanyl-4-iodopyrimidine following the conditions described by *Majeed* [28]. We improved that procedure using hexamethylditin catalysed by Pd(O*Ac*)$_2$ and P*Ph*$_3$ instead of the more expensive Pd(O*Ac*)$_2$(P*Ph*$_3$)$_2$ and reduced the reaction time to 1.5 h and the amount of *TBAF* to 1 eq. However, none of the cross-coupling reactions between the 2-methanesulfanyl-4-trimethylstannyl pyrimidine and the *N-MOM* or *N-Ts* protected 5-iodo or 5-bromopyridopyrrolopyrimidone gave good synthetic results using a wide variety of catalysts, solvents, and reaction conditions. Again, a new strategy was adopted for the coupling reaction. 9-Amino-functionalised tricyclic compounds were used instead of the pyrimidone.

The 9-aminopyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine was obtained by *O*-silylation followed by reaction with ammonia at 150°C and 60 psi in a *Parr* reactor

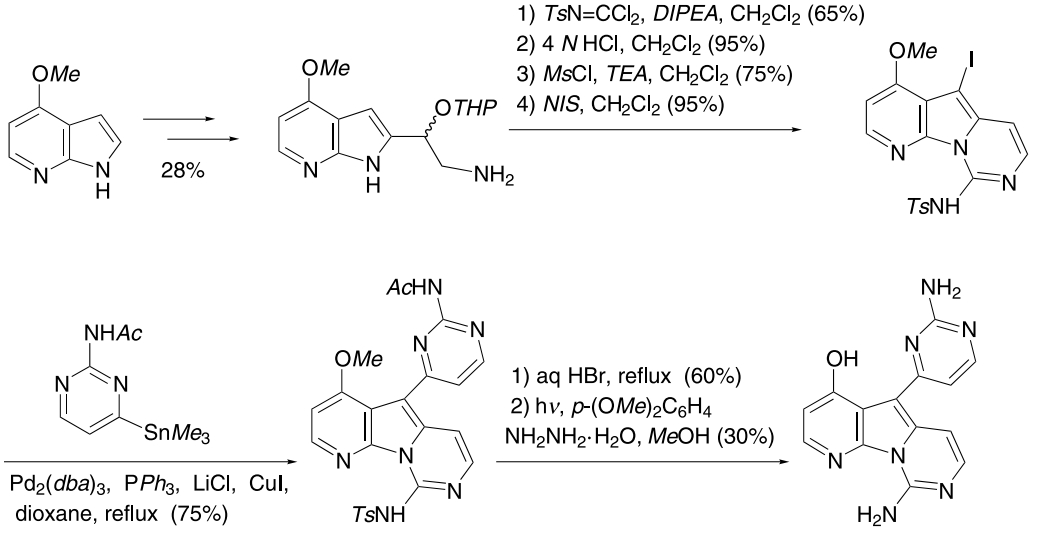


Scheme 5. Synthesis of deoxyvariolin B

following a procedure reported by *Vorbrüggen* for the preparation of 4-amino-2-pyrimidinones [29–30]. Amino protection followed by regioselective iodination and coupling gave the tetracyclic system in which only the transformation of S*Me* into the amino group was required to obtain deoxyvariolin B. This functional group transformation was achieved by oxidation of the S*Me* with *m*-chloroperbenzoic acid followed by substitution with ammonia [32].

Synthesis of Variolin B

For the total synthesis of variolin B [31] we followed the methodology developed for the deoxyvariolin B but with fine-tuning two synthetic steps.



Scheme 6. Synthesis of variolin B

To avoid the transformation of pyrimidone C ring To aminopyrimidine we used the direct introduction of the amino group during the cyclization using instead of triphosgene a synthetic equivalent of phosgene as a protected dichloroimine. As protecting groups we tested tosyl, nosyl, trityl, and chloroacetyl. The tosyl protecting group was the synthetically most useful.

To make the process shorter, avoiding after the coupling process the two steps for the functional transformation of ring D (S*Me* into the NH_2), we prepared 2-acetylamino-4-trimethylstannylpyrimidine.

The total synthesis of variolin B from a 4-methoxy-7-azaindole [30] is shown in Scheme 6. The procedure should allow an easy preparation of derivatives, which differs not only in the substituents of rings A, C, and D but also in the nature of ring D. The pharmacological evaluation of the synthesized compounds is in progress.

Solid-Phase Synthesis of Lamellarins

From marine invertebrates such as sponges, tunicates, and mollusks more than 40 different lamellarins have been isolated since 1985 [33]. At that time, *Faulkner* isolated the first lamellarins from a prosobranch mollusk *Lamellaria sp.* [34].

Two different structural types have been found amongst the lamellarins. Compounds such as lamellarins A, L, and M possess a pentacyclic system consisting of a benzopyrano[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinolin-6-one bound to an additional phenyl ring. This is the most important group and the main differences between compounds of this group are in the number and position of hydroxyl or methoxyl groups on the benzene rings. The other important difference is the oxidation level of ring D.

The second group of lamellarins is represented by lamellarin O. Structurally it is a pyrrole-2-carboxylate substituted by two aryl groups at positions 3 and 4 of the pyrrole ring and by a functionalised phenethyl group at the nitrogen.

A wide array of interesting and significant biological activities of some of the lamellarins has been found including cell division inhibition, HIV-1 integrasa inhibition, cytotoxicity against several cell lines, and imunomodulatory activity.

Several syntheses have been developed for each group of lamellarins [35–42] but none of them on solid-phase. Our purpose was to develop a solid-phase synthesis for each of these two structural different lamellarins. At the same time the synthesis had to be useful for the preparation of related compound libraries in which diversity could be introduced. Our diversity elements are focused on the three different aromatic groups, in which not only the substitution of the benzene rings but also the nature of these aromatic rings could be changed.

Solid-Phase Synthesis of Lamellarins U and L

The synthesis of pentacyclic lamellarins is based on a 1,3-dipolar cycloaddition, as in *Banwell's* solution procedure [38], with the formation of the two heterocyclic rings – pyrone and pyrrole – in a single step from an open-chain compound which contains the three diversity elements [43].

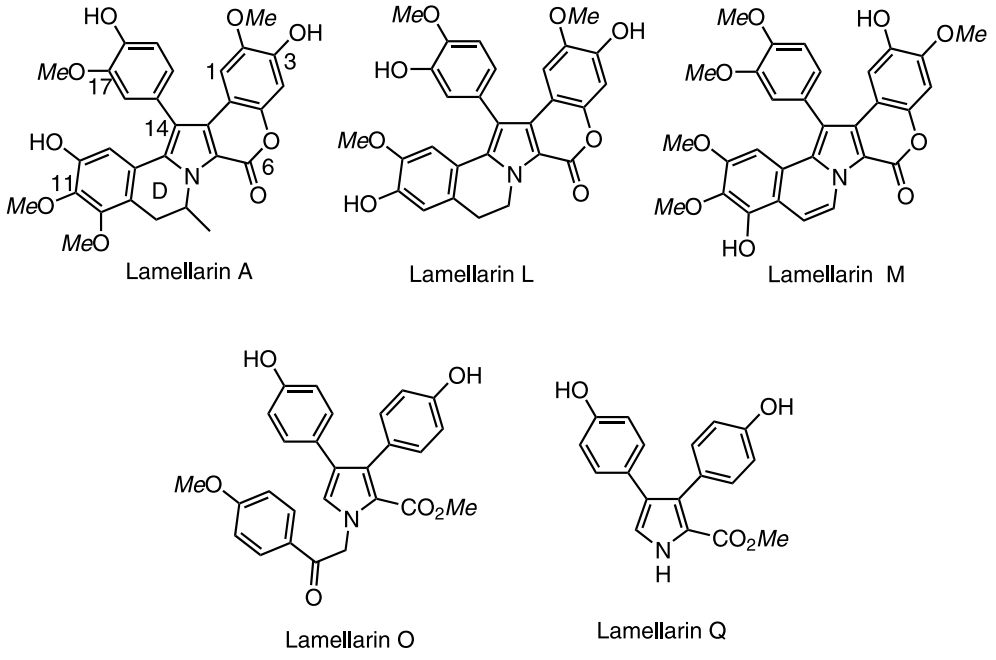
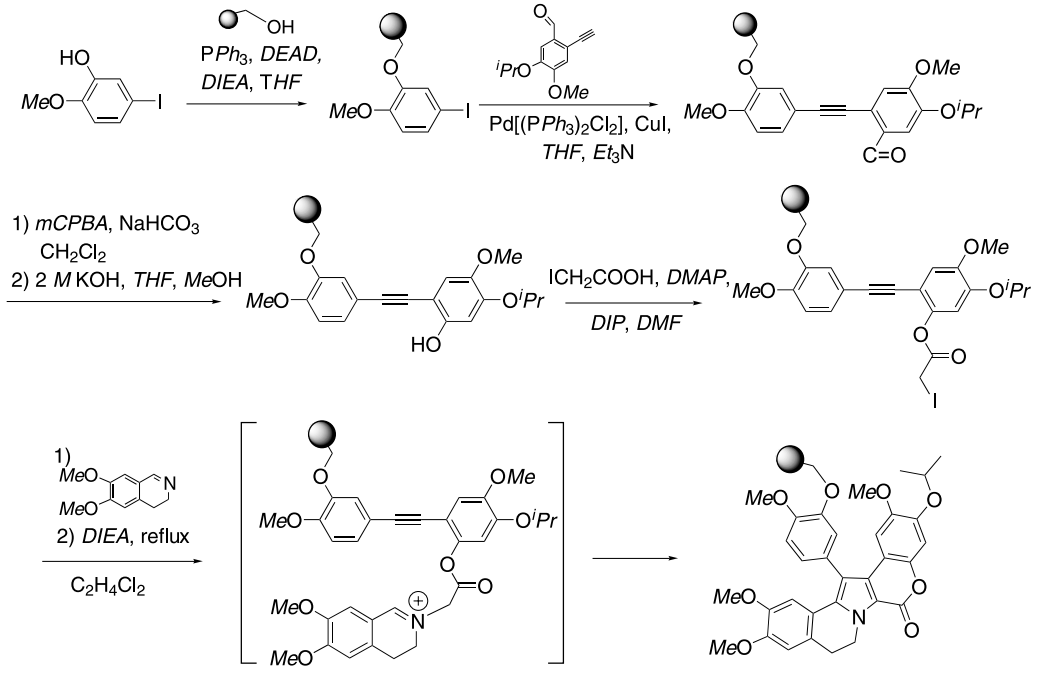


Fig. 5. Structure of lamellarins



Scheme 7. Solid-phase synthesis of pentacyclic lamellarins

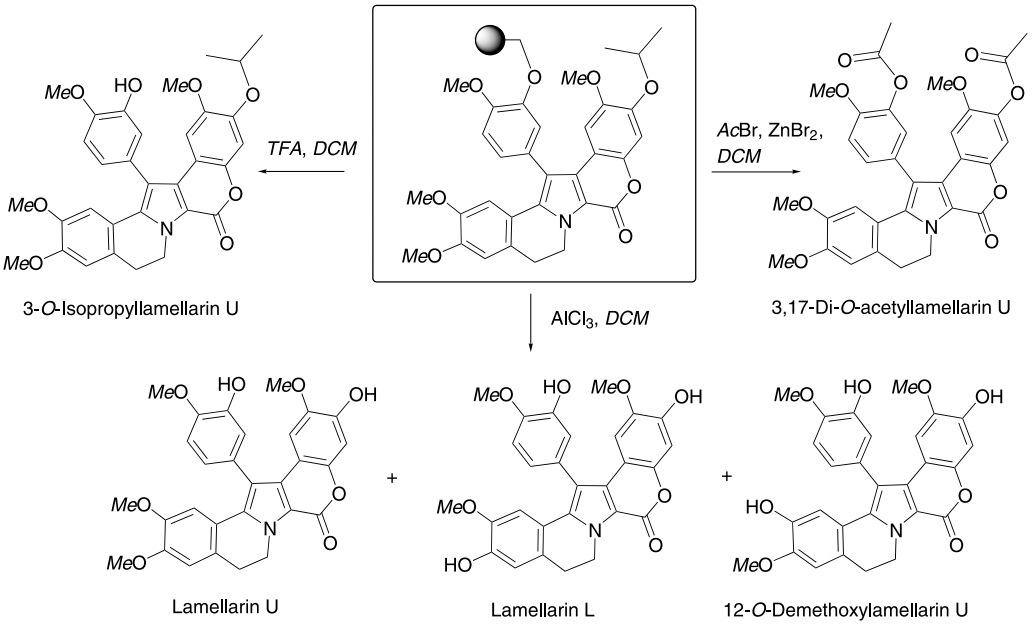
For that, 5-iodo-2-methoxyphenol was anchored to the resin. A *Sonogashira* cross-coupling reaction with a properly substituted arylacetylene afforded an anchored diarylacetylene in which two diversity elements had been introduced.

The use of an aldehyde as a masked phenol group required its transformation into the phenol group. This functional group transformation was performed by oxidation under *Baeyer-Villiger* conditions followed by saponification of the resulting formate. Esterification of the phenol with iodoacetic acid followed by *N*-alkylation with the properly substituted 3,4-dihydroisoquinoline afforded the precursor of the pentacyclic compound which was transformed *in situ* into the pentacyclic system.

Several important questions needed to be answered during the development of the synthesis. The first was related to the resin. We tested *Merrifield* resin functionalised as chloride or hydroxyl and also the hydroxyl-*Wang* resin. The anchorage of the 5-iodo-2-methoxyphenol under basic conditions in *DMF* for the Cl-*Merrifield* resin or *Mitsunobu* conditions for the HO-*Merrifield* resin were both successful. However, the HO-*Merrifield* was chosen because it was easier to follow the end of the reaction by IR-spectroscopy and also because of a higher yield, although just a single treatment was necessary for the Cl-*Merrifield* resin, while a double reaction was needed for the hydroxy version. For anchoring to the HO-*Wang* resin we used the *Mitsunobu* conditions, also with good results.

The second very important question was how to follow the reactions on solid-phase. IR Spectroscopy for functional group interconversions as well as proton and carbon ^{1}H and ^{13}C gel phase NMR or magic angle spin NMR and HPLC-MS analyses of the cleavage compounds have been the most useful methods to check the success of the different transformations.

The appropriate choice of the cleavage reaction conditions permits the introduction of an extra degree of diversity. The *Merrifield* anchored pentacyclic compound cleaved with acetyl bromide and zinc bromide afforded 3,17-di-*O*-acetyllamellarin U. The same *Merrifield* resin cleaved with aluminum chloride gave three compounds: lamellarin U, lamellarin L, and 12-*O*-demethoxylamellarin



Scheme 8. Cleavage of pentacyclic lamellarins

U. All of these possess the 17-hydroxy group coming from the cleavage, a 3-hydroxy from deprotection of the isopropyl ether, and the difference between them remains in *Me*O/OH groups in positions 11 and 12 from the demethylation of one or the other methoxy groups at these positions. A convenient and easy method based on ^{1}H NMR spectroscopy with both external and internal standards has recently been described for the quantification of members of libraries [44].

Finally the Wang anchored pentacyclic compound cleaved with *TFA* afforded the 3-protected lamellarin U.

Solid-Phase Synthesis of Lamellarins O and Q

An *N*-protected methyl dibromopyrrole-2-carboxylate was used as a building block for the synthesis of lamellarins O and Q. Two successive and selective cross-coupling reactions followed by *N*-deprotection, *N*-alkylation, and cleavage was used as synthetic strategy.

p-Iodophenol was anchored on the Cl-*Merrifield* resin in the presence of sodium methoxide. The introduction of the building block onto the resin was achieved by a Pd cross-coupling reaction of its zinc derivative under *Negishi* conditions. The selectivity in the halogen-metal interchange process for this organometallic preparation was derived from the *ortho*-directing effect of the methoxycarbonyl group. The zinc derivative was prepared by reaction of protected methyl 3,4-dibromopyrrole-2-carboxylate with *n-Bu*Li at low temperature followed by $ZnCl_2$ addition. The second Pd-catalysed cross-coupling reaction of the anchored bromide and a boronic acid derivative afforded the anchored bisphenylpyrrole derivative. Cleavage of this triaryl compound from the resin with $AlCl_3$ afforded lamellarin Q. *N*-Desilylation of the anchored triaryl species followed by *N*-alkylation and cleavage with $AlCl_3$ should give *O*-methyllamellarin O using a methoxyphenylboronic acid or lamellarin O using *iso*-propoxyphenylboronic acid for the second coupling reaction [45].

In conclusion we have developed synthetic procedures useful for the total synthesis of variolin B and derivatives and also the first solid-phase synthesis for several lamellarins.

Acknowledgements

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