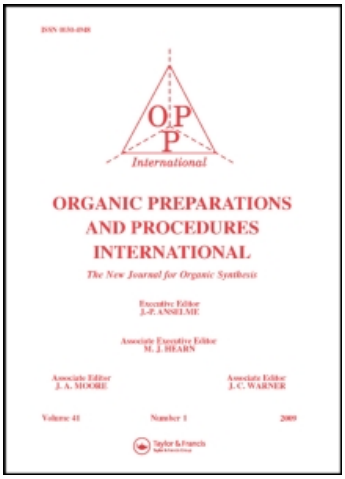

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APPROACHES TO THE SYNTHESIS OF THE LAMELLARINS AND RELATED NATURAL PRODUCTS. A REVIEW

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APPROACHES TO THE SYNTHESIS OF THE LAMELLARINS AND RELATED NATURAL PRODUCTS. A REVIEW

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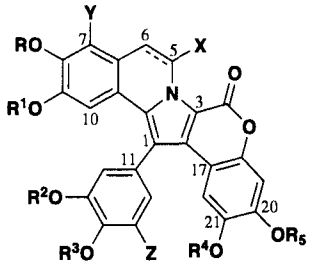
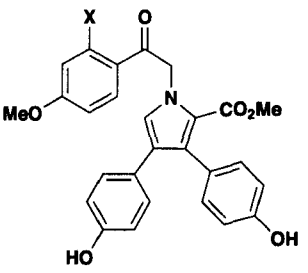
INTRODUCTION AND ISOLATION

The lamellarins are a growing family of marine natural products. First isolated in 1985 by Clardy and co-workers,[1] over 30 different members of this family have been isolated to date. The original source of the lamellarins was from a pseudobranch mollusc, but subsequent isolation efforts have focused on various ascidians. As a result, it has been hypothesized that the presence of lamellarins in molluscs is either due to dietary consumption of the ascidians or perhaps *via* a symbiotic organism present in both species.[2] In terms of the biosynthesis, virtually all of the lamellarins are presumed to originate from three molecules of tyrosine (or DOPA, which is derived from tyrosine),[3] with the possible exception of lamellarin R.[4] More specific studies have not been conducted.

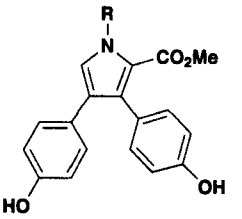
The structure of all lamellarins isolated to date are shown in *Table 1*. The vast majority feature a pentacyclic core, with the basic structural variation coming from hydroxy and methoxy substitution of the aryl rings and in the presence or absence of a $\Delta^{5,6}$ alkene or a C5 carbinolamine.[5] In some cases, one of the phenol OHs is sulfated, resulting in interesting materials with relatively limited stability. There is one other very interesting structural feature in these natural products – the aryl ring at C1. Rotation about this biaryl bond is highly restricted. Clardy reported a calculated barrier to rotation of >600 kcal/mol.[1] Subsequent experimental work has indicated that the actual barrier is lower (*vide infra*) and our own reexamination of this barrier indicates a value closer to 60 kcal/mol. As a result of this restricted rotation, the lamellarins can exist as atropisomers and thus can exist in two enantiomeric forms. Interestingly, only one lamellarin, lamellarin S, has been isolated in optically active form.[6] This general absence of optical

Table 1. Lamellarins Isolated To Date





Lamellarin O, X = H
Lamellarin P, X = OH



Lamellarin Q, R = H
Lamellarin R, R = p-HOC_6H_4

Name	$\Delta^{5,6}$	X	Y	R	R^1	R^2	R^3	R^4	R^5	Z	Citation
A	Single	OH	OMe	Me	Me	H	Me	Me	H	H	1
B	Double	H	OMe	Me	Me	H	Me	Me	H	H	1
B sulfate	Double	H	OMe	Me	Me	H	Me	Me	SO_3Na	H	7
C	Single	H	OMe	Me	Me	H	Me	Me	H	H	1
C sulfate	Single	H	OMe	Me	Me	H	Me	Me	SO_3Na	H	8
D	Double	H	OMe	H	Me	H	Me	Me	H	H	1
E	Single	H	OH	Me	Me	Me	H	Me	H	H	2
F	Single	H	H	Me	Me	Me	Me	Me	H	H	2
G	Single	H	H	H	Me	Me	H	H	Me	H	2
G sulfate	Single	H	SO_3Na	H	Me	Me	H	H	Me	H	8
H	Double	H	H	H	H	H	H	H	H	H	2
I	Single	H	OMe	Me	Me	Me	Me	Me	H	H	3
J	Single	H	H	H	Me	Me	Me	Me	H	H	3
K	Single	H	OH	Me	Me	H	Me	Me	H	H	3
L	Single	H	H	H	Me	Me	H	Me	H	H	3
L sulfate	Single	H	H	H	Me	Me	H	Me	SO_3Na	H	8
M	Double	H	OH	Me	Me	H	Me	Me	H	H	3
N	Double	H	H	H	Me	Me	H	Me	H	H	3
S	Single	H	H	H	Me	H	H	H	H	H	6
T	Single	H	OMe	Me	Me	Me	H	Me	H	H	8
T sulfate	Single	H	OMe	Me	Me	Me	H	Me	SO_3Na	H	8
U	Single	H	H	Me	Me	Me	H	Me	H	H	7
U sulfate	Single	H	H	Me	Me	Me	H	Me	SO_3Na	H	8
V	Single	OH	OMe	Me	Me	Me	H	Me	H	H	7
V sulfate	Single	OH	OMe	Me	Me	Me	H	Me	SO_3Na	H	8
W	Double	H	OMe	Me	Me	Me	H	Me	H	H	7
X	Double	H	OH	Me	Me	Me	H	Me	H	H	7
Y	Single	H	H	Me	H	Me	H	Me	H	H	7
Y sulfate	Single	H	H	Me	H	Me	H	Me	SO_3Na	H	8
Z	Single	H	H	H	Me	H	H	H	Me	H	8
γ	Single	H	OH	Me	Me	H	Me	Me	H	OMe	9
α	Double	H	H	Me	Me	H	Me	Me	H	H	9
ε	Double	H	OH	Me	Me	Me	Me	Me	H	H	9
α sulfate	Double	H	H	Me	Me	Me	H	Me	SO_3Na	H	15

activity may be the result of a late closure of the N4-C5 bond along the biosynthetic pathway, since Clardy and co-workers determined *via* calculations that the open pyrrole/aldehyde form of lamellarin A has little barrier to rotation about the C1-C11 biaryl bond, while the closed carbinolamine form (or the dehydrated or deoxygenated forms) all have substantial barriers to rotation.[1] Still, the observation of slow loss of optical activity for lamellarin S, and the long storage times reported for many of the lamellarin materials prior to isolation, may mean that more members of this family could be optically active initially and simply racemize during the collection, storage, and isolation stages.

As is typical during natural product isolation, structural elucidation was found to be a significant challenge. Three lamellarins have been crystalized and had x-ray structures determined (lamellarin A, E, and K triacetate). The other structures have all been determined by the use of extensive NMR spectroscopy, including numerous heteronuclear methods. Particularly valuable are HMBC methods. HMBC has the drawback that it results in both 2 and 3 bond correlations and these two cannot be differentiated. In conjunction with Fenical's isolation work, Kock and Griesinger have reported the application of a new 1,1-ADEQUATE experiment that yields only two bond correlations, thereby enabling the differentiation of two and three-bond correlations.[10]

I. BIOLOGICAL ACTIVITIES

Beyond their unusual structure, the lamellarins have attracted attention due to their range of interesting and potentially useful biological activities. The first of these activities noted was the cytotoxicity of the lamellarins to a number of cancer cell lines. Following the initial report of the cytotoxicity of lamellarins I, K, and L toward P388 and A549 cell lines,[3] a much more extensive study was undertaken by Quesada and co-workers.[11] They examined 13 different lamellarins against a panel of cancer cell lines, including multidrug resistant (MDR) variants (*Table 2*). Similar levels of cytoxicity were observed against normal and MDR cell lines, with lamellarin D triacetate, K, K triacetate, and M exhibiting the best activity. Of even greater interest was their observation that all of these lamellarins exhibited the ability to reverse the MDR effect *via* inhibition of the P-glycoprotein responsible for this effect. More thorough studies were performed using Lamellarin I and demonstrated that sensitivity of MDR cell lines to doxorubicin, daunorubicin, and vinblastine was restored at concentrations in the 1 μM range.

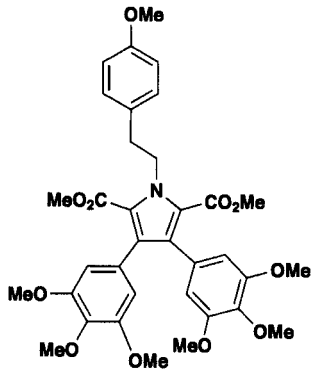
On the basis of this MDR reversing activity, Boger has undertaken a brief SAR effort of lamellarin-like products.[12] The most effective compounds were those related to storniamide A, including permethyl storniamide A and synthetic derivative **1** (*Fig. 1*). Thus, permethyl storniamide A and analog **1** both exhibited a 250% gain in sensitivity when given at a 7.5 μM concentration along with 0.0008 μM vinblastine, which is better than the results obtained with the known MDR reversing agent verapamil.

Returning to the concept of cytotoxicity, Ishibashi has undertaken some SAR work to identify the features critical for cytotoxicity (*Table 3*).[13] From these efforts, it has been hypothe-

Table 2. Cancer Cell Line Studies

Lamellarin	P388	Schabel	Auxb1	Cchrc5	A549	Ht29	Ml28
A	0.89	0.91	0.36	0.71	0.90	2.1	0.93
B	10.1	10.4	5.5	18.0	5.2	>10	10.1
D triacetate	0.11	0.14	0.05	0.06	0.008	0.80	0.16
I	4.9	4.8	0.38	2.0	5.0	4.7	5.0
I acetate	9.0	9.2	4.1	9.0	9.3	>10	9.1
J	2.9	3.9	0.58	1.2	0.60	5.8	2.9
K	0.19	0.017	0.19	0.75	0.18	0.38	0.40
K triacetate	0.09	0.16	0.15	0.16	0.005	0.47	0.93
L	1.2	1.4	0.80	1.3	0.60	6.0	1.2
L triacetate	2.4	2.4	2.2	2.5	1.1	>3	2.3
M	0.15	0.17	0.07	0.17	0.06	0.56	0.54
M triacetate	0.91	1.1	0.76	3.1	0.22	>1	0.90
N triacetate	0.32	0.30	0.10	0.16	0.02	3.2	1.6

sized that the hydroxyls at C8 and C20 are the most critical for activity, while those (hydroxy or methoxy) at C14, 13, and 21 are not as important. Still, it is also obvious from these efforts that a mixture of hydroxy and methoxy groups are necessary for activity.



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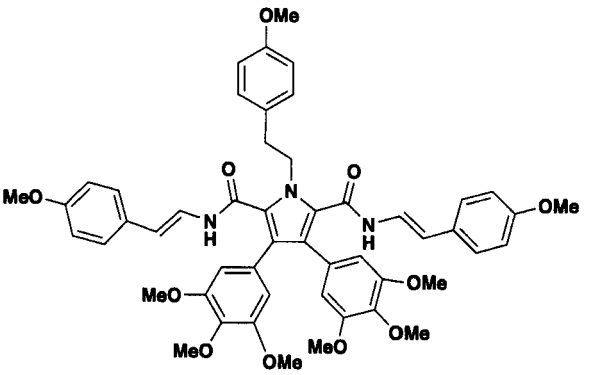


permethyl Storniamide A

Fig. 1

Table 3. SAR Results for Cytotoxicity

Structure	R	R^1	R^2	R^3	R^4	R^5	IC50 (HeLa)
1	OH	OMe	OMe	OH	OMe	OH	0.0105
2	OH	OH	OH	OH	OH	OH	>100
3	OH	OMe	OMe	OH	H	OH	0.0395
4	OH	OMe	OMe	OH	OMe	H	0.8500
5	OMe	OMe	OMe	OMe	OMe	OH	2.5
6	OH	OMe	H	OH	OMe	OH	0.0380
7	OH	OMe	OMe	H	OMe	OH	0.0700
8	OH	OMe	OMe	OH	H	H	4
9	OH	OH	OH	OH	H	H	1.1
10	OAc	OAc	OAc	OAc	OAc	OAc	11
11	OMe	OMe	OMe	OMe	H	H	5.7
12	OMe	OMe	OMe	OMe	diox		>100

Most recently, Bailly and co-workers have investigated more carefully the source of the cytotoxicity of the lamellarins.[14] Through a careful series of studies, they have determined that the most likely cellular target is topoisomerase I. The C_{50} value for DNA cleavage was determined to be 0.42 μM for lamellarin D, compared to 0.087 μM for camptothecin, the most famous topoisomerase I inhibitor. Several similarities with camptothecin were observed, including some common sites of cleavage and poor activity against camptothecin resistant cell lines. On a more fundamental level, it was determined that the presence of the $\Delta^{5,6}$ alkene is critical for the observed inhibition. Further, docking studies indicated that the C8 and C20 hydroxyl groups both make specific contacts with specific residues in topoisomerase I, further validation of the observations of Ishibashi that these two residues are important for activity.[13] In an intriguing follow-up study, the PharmaMar group has shown that the hydroxyl groups of lamellarin D can be capped with amino acids such as alanine, valine, proline, and isoleucine to afford highly active compounds.[15] The presence of a cationic group appears to be important, since the BOC-protected analogs are inactive and poorly cytotoxic. Also of interest is the observation that the stereochemistry of the amino acid has no effect on the biological activity of these compounds.

Finally, Venkateswarlu and co-workers have reported several new lamellarin natural products and attempted to correlate their cytotoxicity with anti-oxidant properties.[9] In a standard DPPH scavenging assay, all of the isolated compounds exhibited very poor anti-oxidant activity (low mM), so it is difficult to attribute much of their anti-cancer potential to anti-oxidant activity.

A different activity of the lamellarins is their ability to inhibit HIV integrase.[16] Integrase is a critical enzyme in the life cycle of HIV and carries out the integration of the viral genetic material into the cellular genetic material. As a result of this unusual function, integrase is a promising target for new chemotherapies for the treatment of AIDS. In this study, Bushman noted that all six of the lamellarins reported were capable of inhibiting HIV integrase, including three non-sulfated compounds. The target for most of the study was lamellarin α 20-sulfate, which inhibited both the terminal cleavage and strand transfer activities (16 and 22 μM respectively). Importantly, this compound also was effective both against preintegration complexes (PICs) and in the live virus. Interestingly, this activity was also only partially localized in the core domain, since the values for inhibition of a recombinant core domain were 62 μM, much higher than that displayed by the intact integrase enzyme. In a subsequent study, it was noted that a disulfated analog of lamellarin α was a slightly less potent HIV integrase inhibitor, but was also quite non-selective, since it inhibited MCV topoisomerase with almost equal potency.[17] Finally, a non-sulfated lamellarin, lamellarin H, was a very potent inhibitor of HIV integrase, but was even more active against MCV topoisomerase and quite cytotoxic as well.

II. TOTAL SYNTHESES

The wide range of intriguing biological activities and the interesting pentacyclic ring system with the pyrrole core of the lamellarins have attracted considerable interest from the synthetic community. Many different syntheses have been reported since the first synthesis of a member of this family - lamellarin O - in 1995. These syntheses can be divided into two main categories based upon the synthetic approach. The first category, adopted in most of the syntheses, involves the formation of pyrrole core at a very late stage of the synthesis, presumably due to the difficulty in functionalizing pyrrole in a regio-controlled manner (*Fig. 2*). The second, less explored, category instead elaborates an intact pyrrole core.

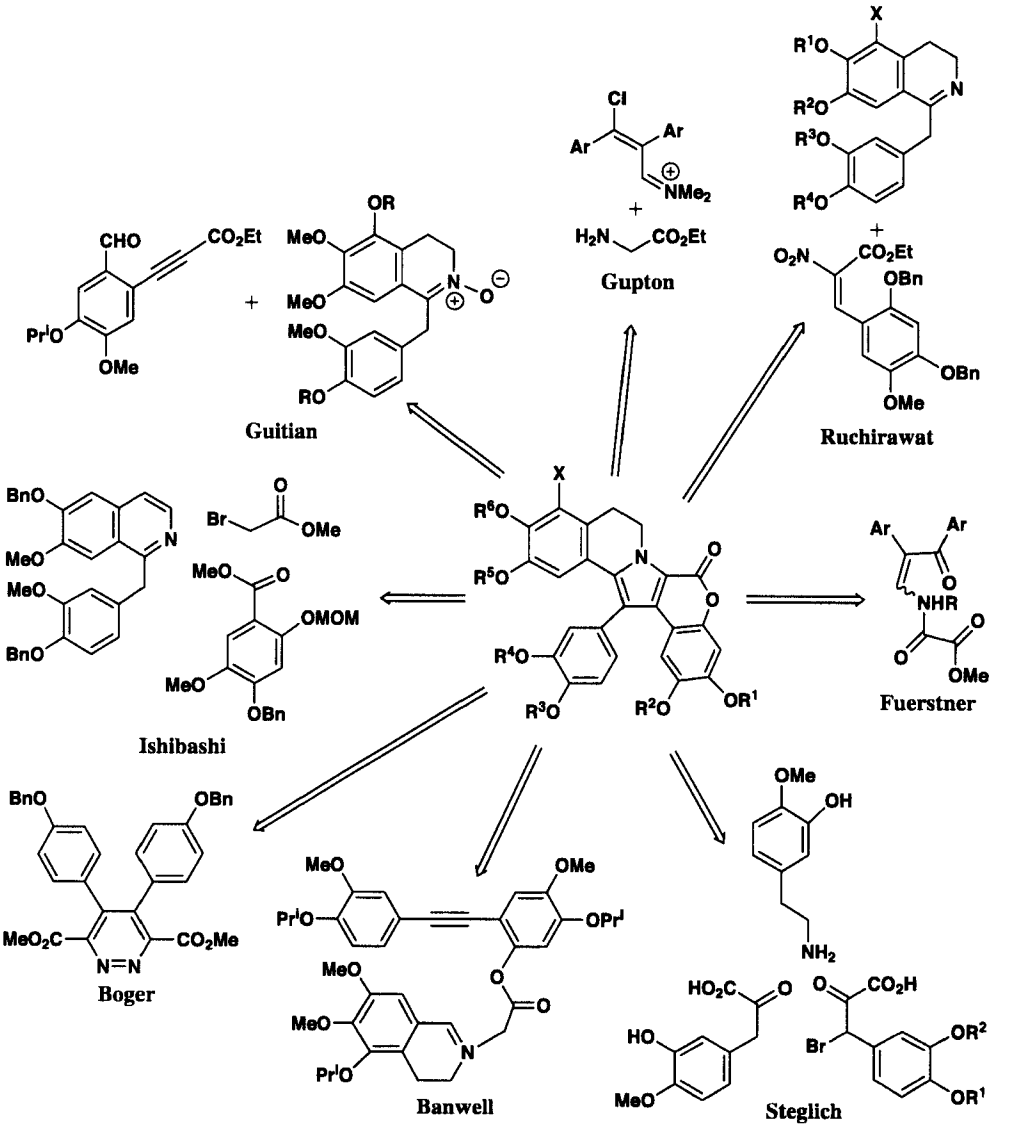
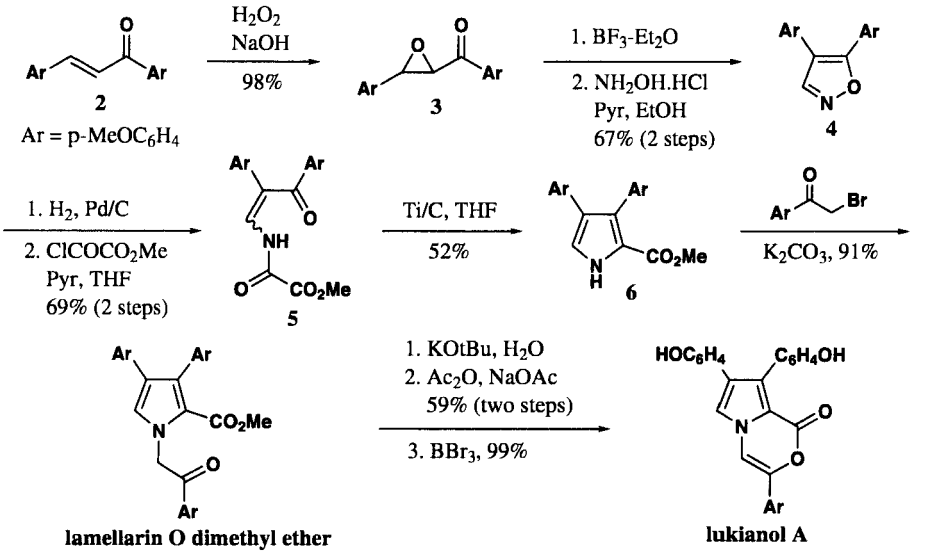


Fig. 2

1. via Late-stage Pyrrole Formation

a) Titanium-Mediated Pyrrole Formation (*Fürstner*)

In 1995, Fürstner and co-workers reported the first synthesis of a lamellarin - lamellarin O dimethyl ether, along with a related alkaloid, lukianol A (*Scheme 1*).[18] The key feature of the synthesis is their previously reported titanium-mediated cyclization of amido-enones to form substituted pyrroles. Thus, treatment of commercially available 4,4'-dimethoxychalcone **2** with H_2O_2/NaOH gave the epoxy ketone **3** in almost quantitative yield. Isoxazole **4** can be readily prepared from **3** through a two-step sequence: pinacol/pinacolone rearrangement using BF_3•Et_2O and trapping the 1,3-keto-aldehyde thus formed with hydroxylamine.



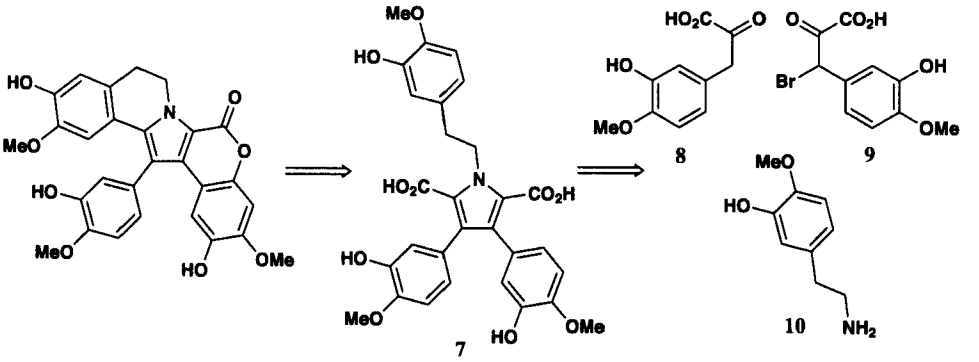
Fürstner's Synthesis of Lamellarin O and Lukianol A

Scheme 1

Reductive cleavage of the N-O bond afforded the ketoenamine as a 1:1 mixture of the (E)- and (Z)- isomers, which were acylated to give the coupling precursor **5**. The isomeric ratio was 2.5:1 instead of 1:1, indicating the low stability of these 3-unsubstituted keto-enamine derivatives. The (Z) isomer was separated by flash chromatography and submitted to the titanium-induced ring closure. The chemo- and regioselective oxo-amide coupling reaction of (Z)-**5** proceeded smoothly upon treatment with Ti-graphite with pyrrole formation in 54% yield. N-alkylation of **6** with 4-methoxyphenacyl bromide afforded lamellarin O dimthyl ether in 91% yield. Lamellarin O dimethyl ether can be converted into Lukianol A by saponification of the methyl ester, enol-lactonization, and deprotection of the methyl ethers.

b) Biomimetic Synthesis (*Steglich*)

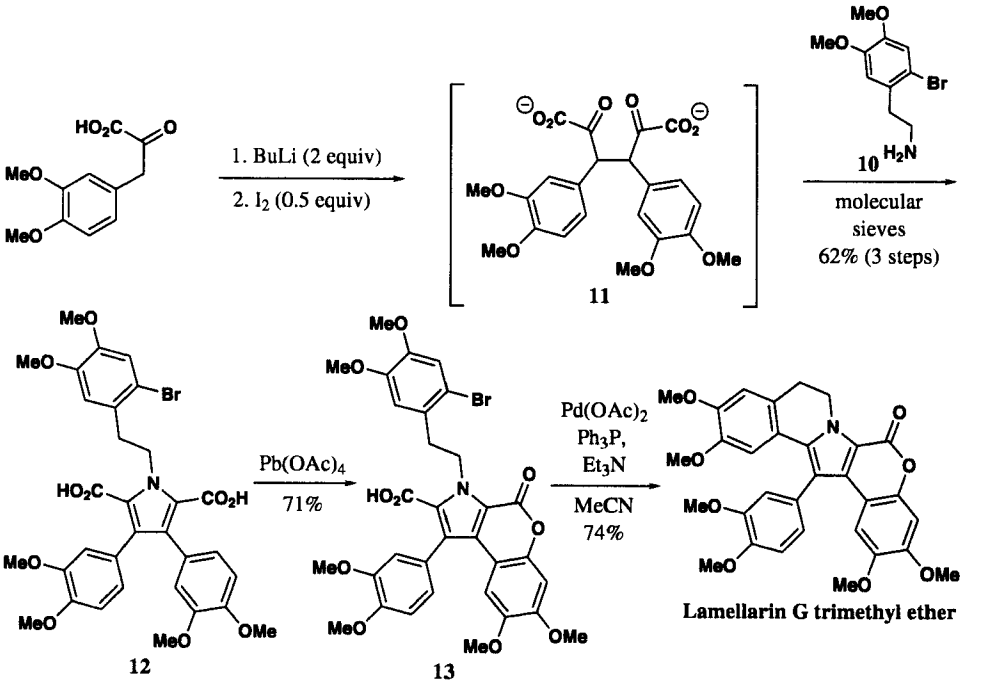
The first biomimetic synthesis of the lamellarins was accomplished by Steglich and co-workers in early 1997.[19] They envisioned that these compounds could be derived biogenetically from 3,4-diarylpyrrole dicarboxylic acids by two consecutive oxidative reactions, the first an oxidative coupling of two 3-(3,4-diaryl)pyruvic acids **8** and **9**, and the second a lactone formation between an aryl ring and a carboxylic acid (as in **7**) (*Scheme 2*).



Steglich's General Biomimetic Approach

Scheme 2

For the synthesis of lamellarins with symmetrical substitution, such as lamellarin G trimethyl ether where all the substitutes are methoxy groups, the preparation can start from 3-(3,4-dimethoxyphenyl)pyruvic acid (*Scheme 3*). The key step, to couple two units of this acid

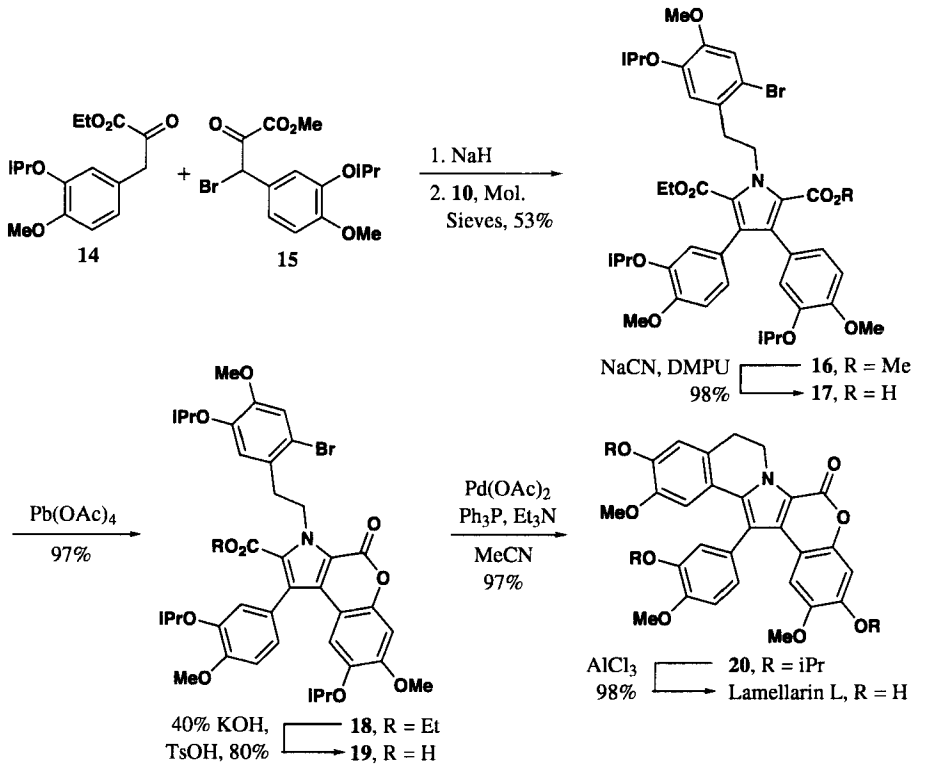


Synthesis of "Symmetric" Lamellarins (Lamellarin G trimethyl ether)

Scheme 3

together, can be performed by treating the pyruvic acid with *n*-butyllithium followed by addition of iodine to furnish the 1,4-diketone **11**, which is subjected to the next condensation step without isolation to form the pyrrole dicarboxylic acid **12** in 62% yield. Oxidative cyclization leading to the lactone was achieved by treating **12** with $Pb(OAc)_4$ in refluxing ethyl acetate. Only one regioisomer was formed by attack of the carboxy radical at the *ortho* position with no adjacent methoxy substituents. Once the first lactone is formed, the neighboring aromatic ring is constrained to be orthogonal relative to the plane of the pyrrole, thereby preventing further cyclizations to give a second lactone. An intramolecular Heck reaction was employed for the formation of the dihydroisoquinoline tether. Treatment of **13** with $Pd(OAc)_2$ and PPh_3 in the presence NEt_3 afforded lamellarin G trimethyl ether in 74% yield. In this step, the Pd(II) intermediate resulting from oxidative insertion into the C-Br bond, fragments to eliminate CO_2. Surprisingly, a better yield is obtained by this method than by the conventional Heck reaction on the free pyrrole without the carboxyl group. The overall yield for this concise sequence is 33%.

When this strategy is applied to nonsymmetrical molecules, where the substituents at C-14/C-20 and C-15/C-21 are different, such as in lamellarin L, two different arylpyruvic acid units (**14** and **15**) have to be coupled (*Scheme 4*).[20] This necessitates both the prior formation of one of



Synthesis of "Non-symmetric" Lamellarins (Lamellarin L)

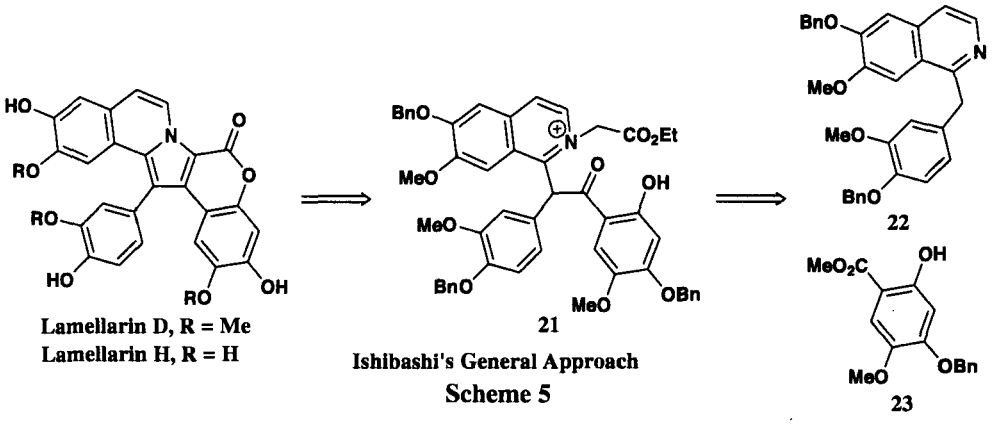
Scheme 4

the two arylpyruvic acid units as the α-halo compound and the ability to selectively cleave one of the two esters. In this case, ester differentiation is accomplished by using methyl and ethyl esters. Both starting materials **14** and **15** can be readily prepared by standard methods from isovanillin.

The enolate of ethyl ester **14** was coupled with the bromide **15** and the resulting 1,4-diketo compound directly reacted with the isopropyl protected form of amine **10** to form pyrrole **16** in 53%. The methyl ester group was selectively cleaved by heating it with NaCN in 1,3-dimethyl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one (DMPU) to afford the monocarboxylic acid **17** in almost quantitative yield. Upon treatment with $Pb(OAc)_4$, the carboxylic acid regioselectively cyclized to form the lactone **18**. The ethyl ester was removed by heating with 40% KOH and distilling off the ethanol. Under these conditions, the lactone ring was also opened, but was reinstalled by treatment with a catalytic amount of *p*-TsOH. Subsequent Heck reaction and deprotection afforded Lamellarin L in excellent overall yield.

c) N-ylide-mediated Pyrrole Formation (*Ishibashi/Ruchirawat*)

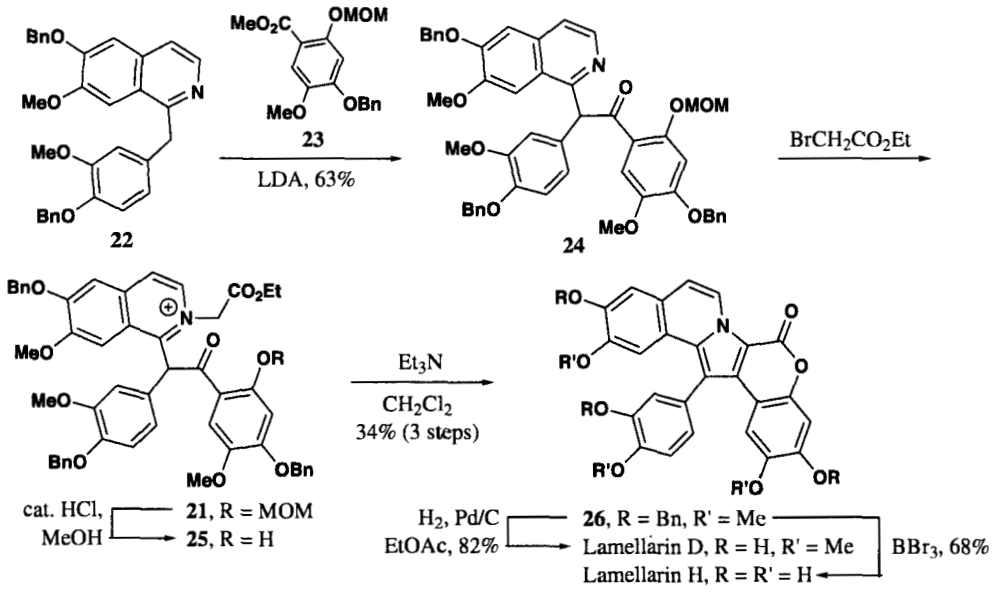
Ishibashi and Iwao described their total synthesis of lamellarin D and H in 1997.[21] Their approach involves the N-ylide-mediated pyrrole formation of a quaternary ammonium salt such as **21**, followed by lactonization (*Scheme 5*). Benzylisoquinoline **22** was made from benzylvanillin in four steps. The other starting material, methyl ester **23**, was also readily obtained in four steps.



Scheme 5

Coupling the benzyl anion of benzylisoquinoline **22** with methyl benzoate **23** gave the acylated product **24** as a mixture of two tautomers (*Scheme 6*). The optimal result was obtained when using 1.1 equivalent LDA as the base to generate the benzyl anion. Quaternization of this mixture was achieved by treating it with methyl bromoacetate. Exposure of **21** to catalytic HCl was sufficient to remove the MOM protecting group. Pyrrole formation and lactonization were accomplished by treatment of **25** with Et_3N. The quaternization, removal of the MOM protecting group, and pyrrole formation can be accomplished in a one-pot procedure. However, decomposition was observed when elevated temperatures or prolonged reaction times were employed. The

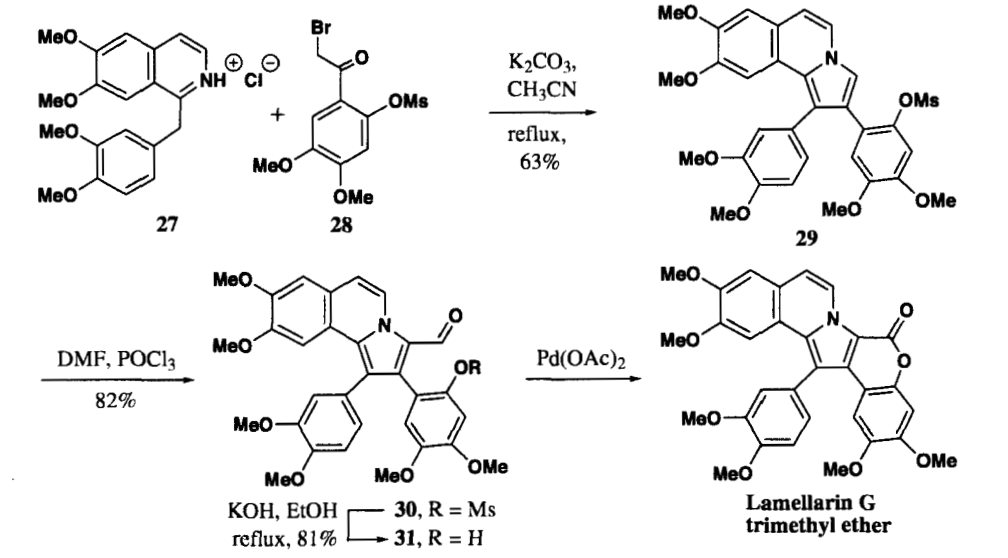
optimal yield (34%) was achieved when a large excess (20 equivalents) of ethyl bromoacetate was used.



Ishibashi's Synthesis of Lamellarins D and H

Scheme 6

Ruchirawat and co-workers adopted a very similar condensation strategy involving only two components - isoquinoline **27** and α-bromoketone **28** (*Scheme 7*).[22] Pyrrole formation by the condensation of isoquinoline **27** and phenylacyl bromide **28** was accomplished in 63% yield. The

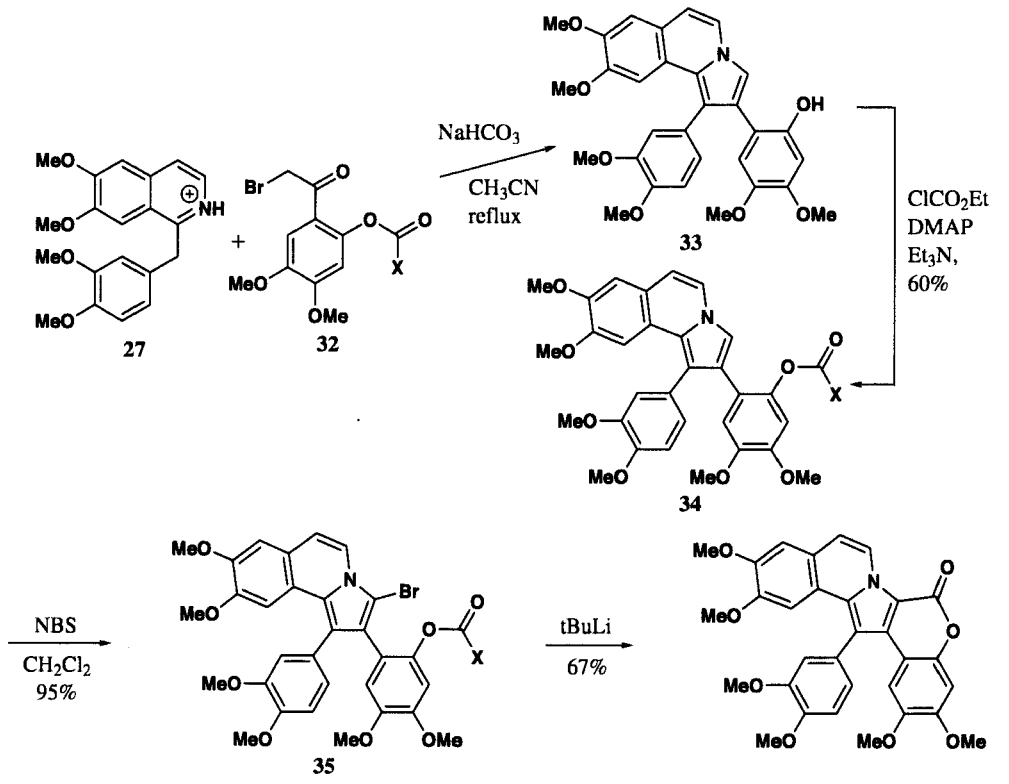


Ruchirawat First Generation Synthesis

Scheme 7

reaction presumably involves quaternization of the isoquinoline and subsequent intramolecular condensation of the N-ylide and the ketone. A Vilsmeier-Haack reaction was used to introduce the formyl group, followed by removal of the mesyl group. Oxidation with $Pd(OAc)_2$ afforded Lamellarin G trimethyl ether in 80% yield, presumably *via* the hemiacetal intermediate.

The Ruchirawat group later developed an improved synthesis *via* direct halogen-metal exchange (*Scheme 8*).[23] They utilized a carbonate or a carbamate protecting group in place of the mesyl group. Conveniently, the carbonate or carbamate protecting groups can also serve as the

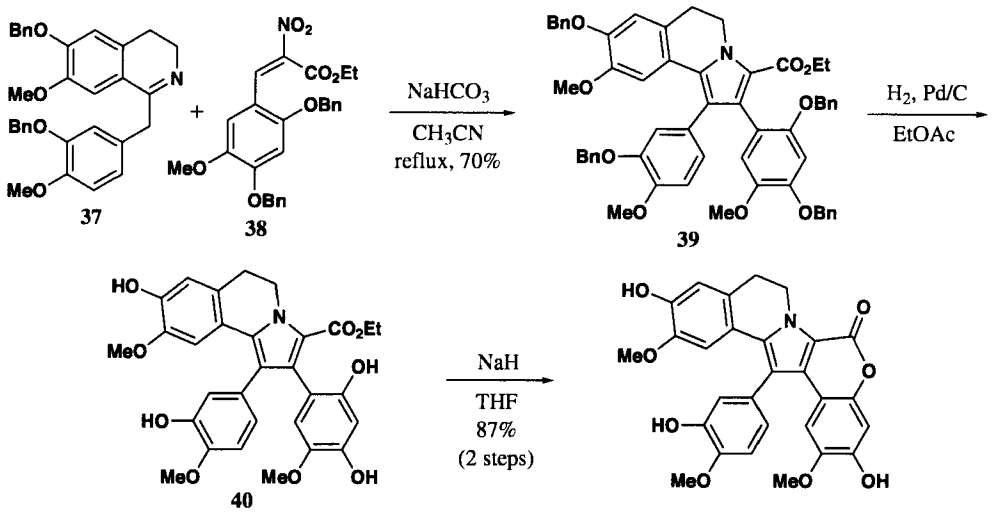


Ruchirawat Second Generation Synthesis

Scheme 8

source of the lactone carbon. During the condensation of **27** and **32**, the carbonate protecting group was partially cleaved, but was reinstalled to afford **34**. Bromination proceeded cleanly to give the bromide **35** in almost quantitative yield. Lithium-halogen exchange afforded lamellarin G trimethyl ether in 67% yield. When the carbamate was chosen as the protecting group, however, pyrrole formation could not be achieved.

More recently, the Ruchirawat group reported a new condensation pathway (*Scheme 9*).[24] They envisioned that condensation of benzyldihydroisoquinoline **37** with a Michael acceptor would lead to the lamellarin skeleton. In the first attempt, the entire lactone portion of the molecule was preformed, as in lactone **36**, which would render this approach highly convergent

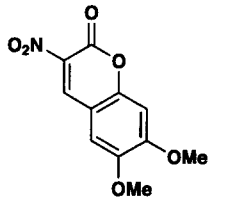


Ruchirawat Michael Addition Synthesis

Scheme 9

(*Fig. 3*). Unfortunately, the reaction afforded the desired lamellarins in only 5-6% yield.

This led their attention to another Michael addition acceptor - an acyclic ester nitrostyrene such as **38**. Both of the starting materials **37** and **38** were readily prepared according to standard methods. Refluxing imine **37** and ester styrene **38** in anhydrous acetonitrile in the presence of $NaHCO_3$ afforded the desired pyrrole **39**. Removal of the benzyl protecting groups was achieved by hydrogenolysis. Subsequent lactonization with sodium hydride gave the target lamellarins in good overall yield.

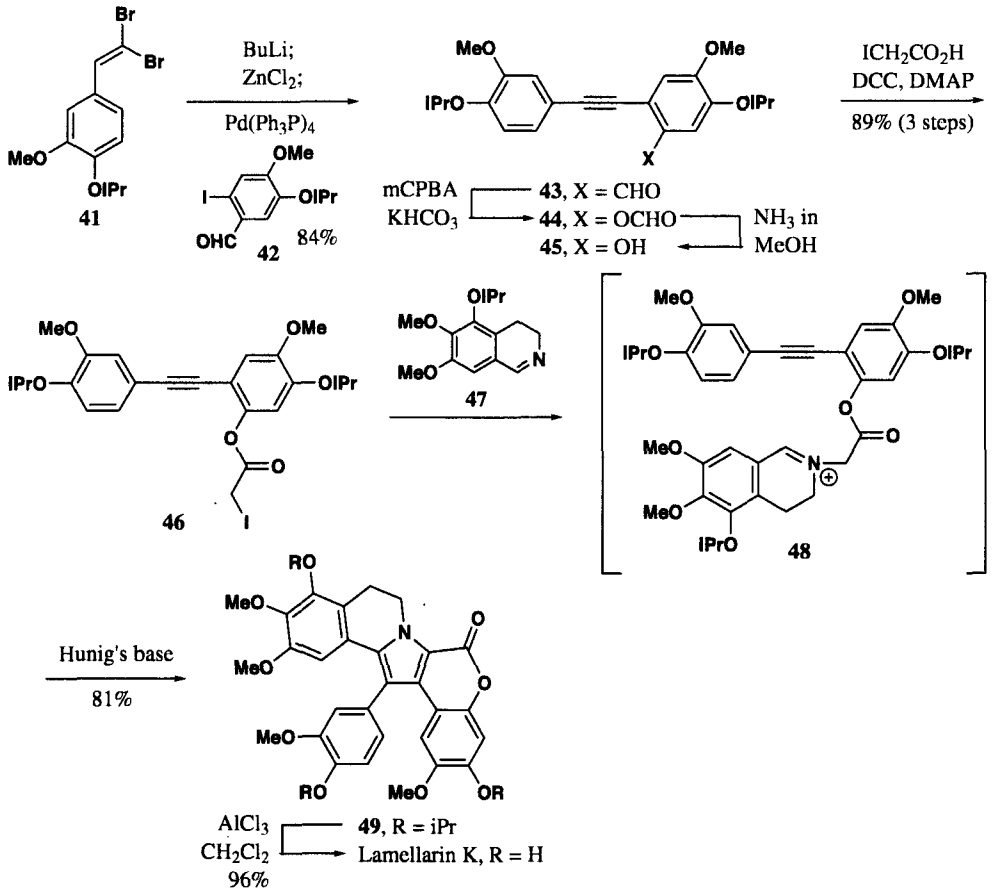


36

Fig. 3

d) Intramolecular [3+2] Cycloaddition Pathway (*Banwell/Alvarez/Guitian*)

In 1997, Banwell and co-workers developed an intramolecular 1,3-dipolar cycloaddition synthesis of lamellarins (*Scheme 10*).[25] The starting materials were readily prepared from commercially available vanillin and isovanillin, respectively. The dibromostyrene **41** was treated with *n*-butyllithium, followed by zinc(II) chloride to give the alkynylzinc chloride, which was subjected to a palladium-mediated cross-coupling reaction with aryl iodide **42**, yielding stilbene **43**. Baeyer-Villiger reaction and the subsequent hydrolysis afforded the corresponded phenol **45**. This phenol was submitted to a DCC-mediated condensation with α-iodoacetic acid to give the ester **46**. Reaction of this iodide with 3,4-dihydro-6,7-dimethoxy-5-isopropoxyisoquinoline **47** yielded the ammonium salt **48**, which was immediately subjected to the treatment with Hunig's base and refluxed in 1,2-dichloroethane, effecting cyclization to give lamellarin K triisopropyl ether **49**. Deprotection of the isopropyl ethers provided the lamellarin K in excellent yield.



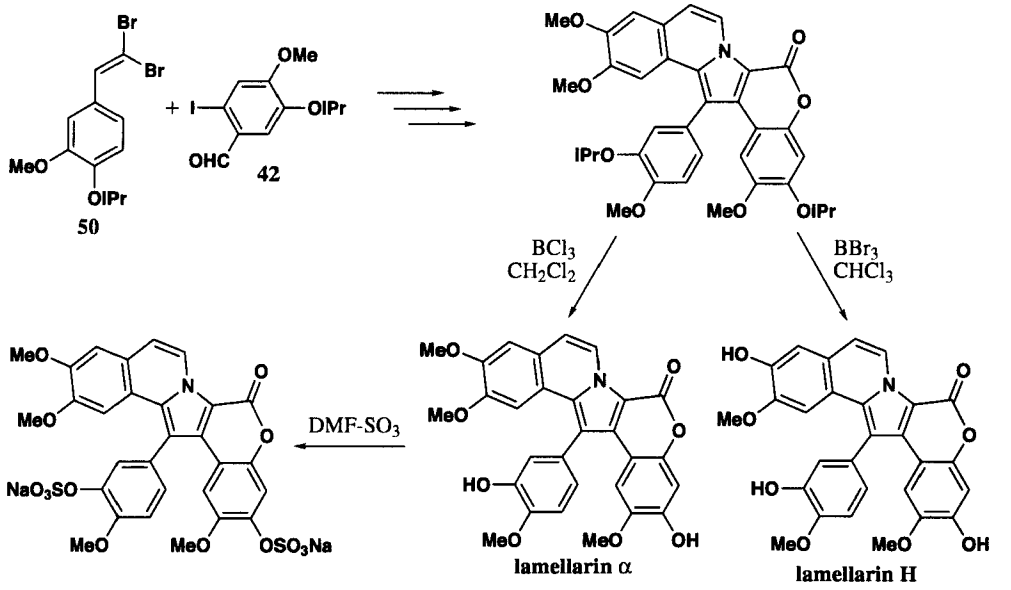
Banwell Cycloaddition Pathway to Lamellarin K

Scheme 10

A slightly modified Banwell strategy was adapted to the total synthesis of lamellarin α 20-sulfate analogues by Faulkner and co-workers (*Scheme 11*).[17] Dibromide **50** was employed instead of **41** and the double bond between C5-C6 was introduced by DDQ oxidation after the formation of the pyrrole core. Deprotection of the isopropyl ethers with BCl_3 gave the target non-sulfated lamellarin in 15% overall yield, which can be turned into the 13,20-disulfate when reacted with the DMF complex of sulfur trioxide. When BBr_3 was employed as the deprotecting agent, lamellarin H was afforded in 15% overall yield. The attempts to turn lamellarin α into its 13 or 20-monosulfate failed, presumably due to the activation of the second sulfation by the presence of the first sulfate group.

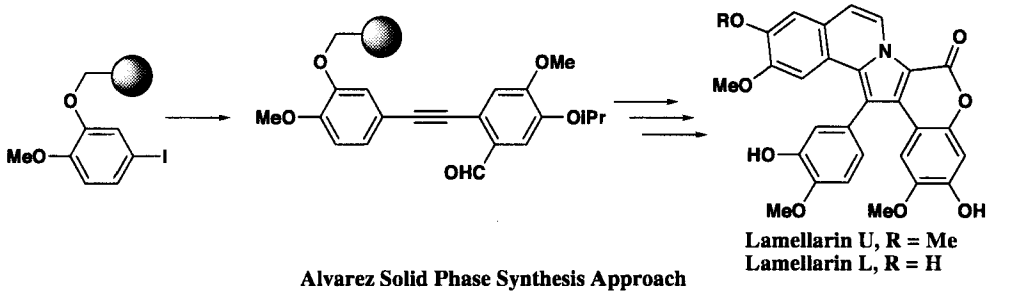
In 2003, Albericio and Álvarez adapted the Banwell synthesis to the solid-phase and successfully prepared lamellarins U and L (*Scheme 12*).[26] The preparation started with a Mitsunobu reaction to attach 5-iodo-2-methoxyphenol on a hydroxymethyl modified Merrifield resin. IR spectroscopy and ^{13}C MAS NMR were the major characterization methods during the

sequence. Cleavage of the final products from the resin with $AlCl_3$ in dry CH_2Cl_2 afforded two major compounds: lamellarin U (in 10% overall yield) and lamellarin L (in 4% overall yield).



Faulkner Synthesis of Lamellarin Sulfates

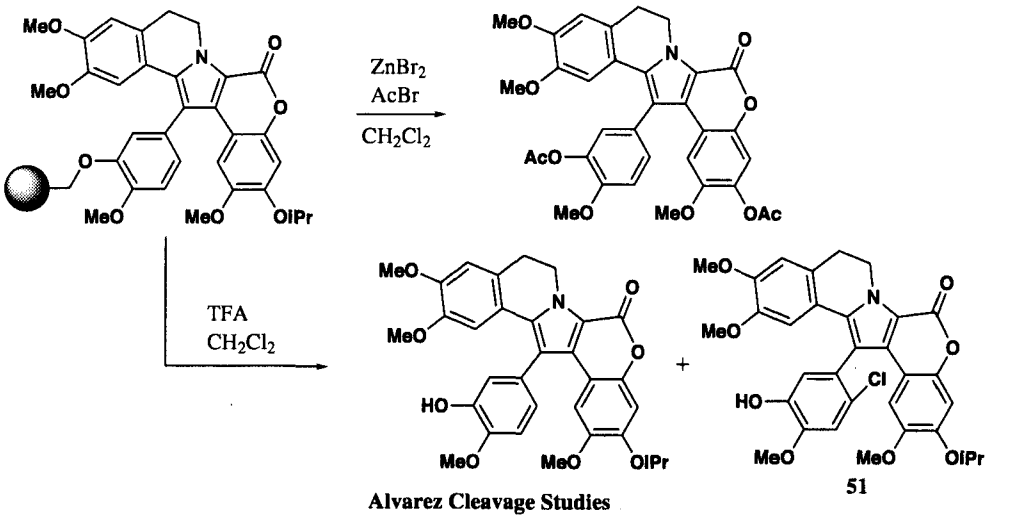
Scheme 11



Alvarez Solid Phase Synthesis Approach

Scheme 12

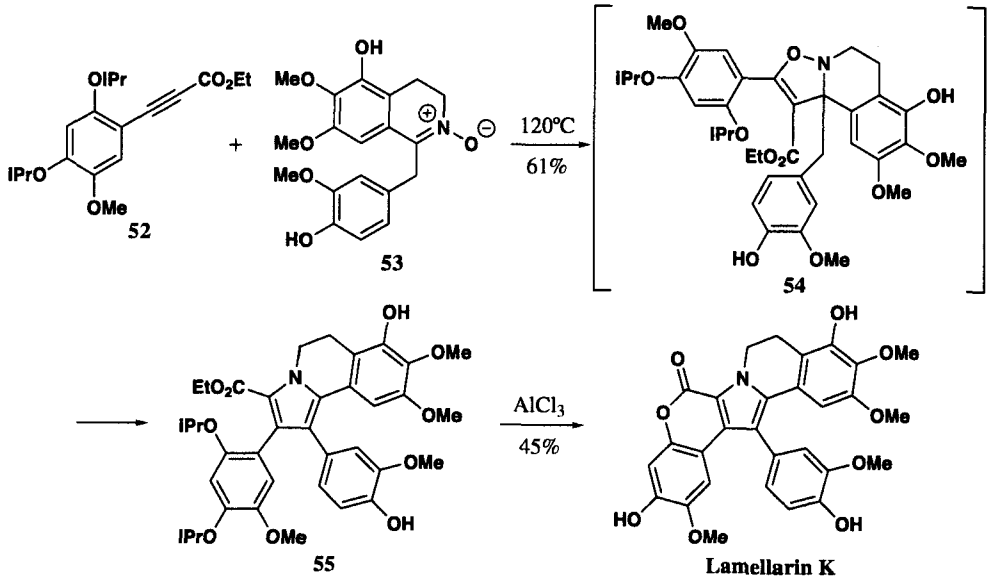
Albericio and Álvarez also discovered that the choice of Lewis acids could influence the proportion of the cleaved products (*Scheme 13*).[27] Although $AlCl_3$ yielded lamellarin U as the major product, there was a significant amount of lamellarin L, as well as some 12-O-demethyl-lamellarin U. When $ZnBr_2$ was chosen as the Lewis acid in the presence of acetyl bromide, di-O-acetyllamellarin U was obtained as the only product. TFA appeared as the appropriate reagent for Wang's resin, with some unexpected Cl-containing byproduct **51** also being formed.



Alvarez Cleavage Studies

Scheme 13

In a related approach, Guitián and co-workers employed a 1,3-dipolar cycloaddition between an alkyne **52** and a dihydroisoquinoline N-oxide **53** (*Scheme 14*).[28] The alkyne was prepared using standard methods from isovanillin. The N-oxide **53** was readily obtained by reduction of the corresponding imine and oxidation with sodium tungstate.



Guitian Synthesis of Lamellarin I and K

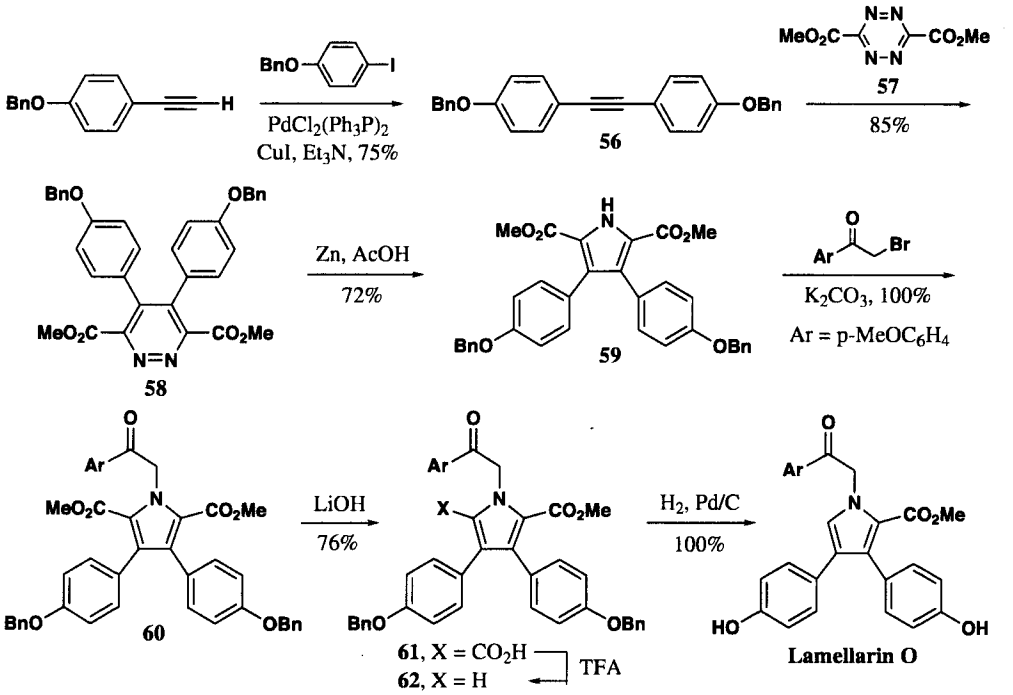
Scheme 14

The key cycloaddition step was achieved by heating a mixture of the N-oxide and alkyne at 120°C in a sealed tube. The isoxazoline intermediate **54** rearranged to give the pyrrole

compound **55** in modest yields. $AlCl_3$ mediated deprotection then yielded lamellarins I and K respectively.

e) Diels-Alder Reaction/Ring Contraction Pathway (*Boger*)

Boger and co-workers employed a somewhat unusual strategy, beginning with a heteroaromatic azadiene Diels-Alder reaction to assemble a six-membered 1,2-diazine core, which then is contracted to afford the pyrrole (*Scheme 15*).[12] The starting alkyne **56** was prepared



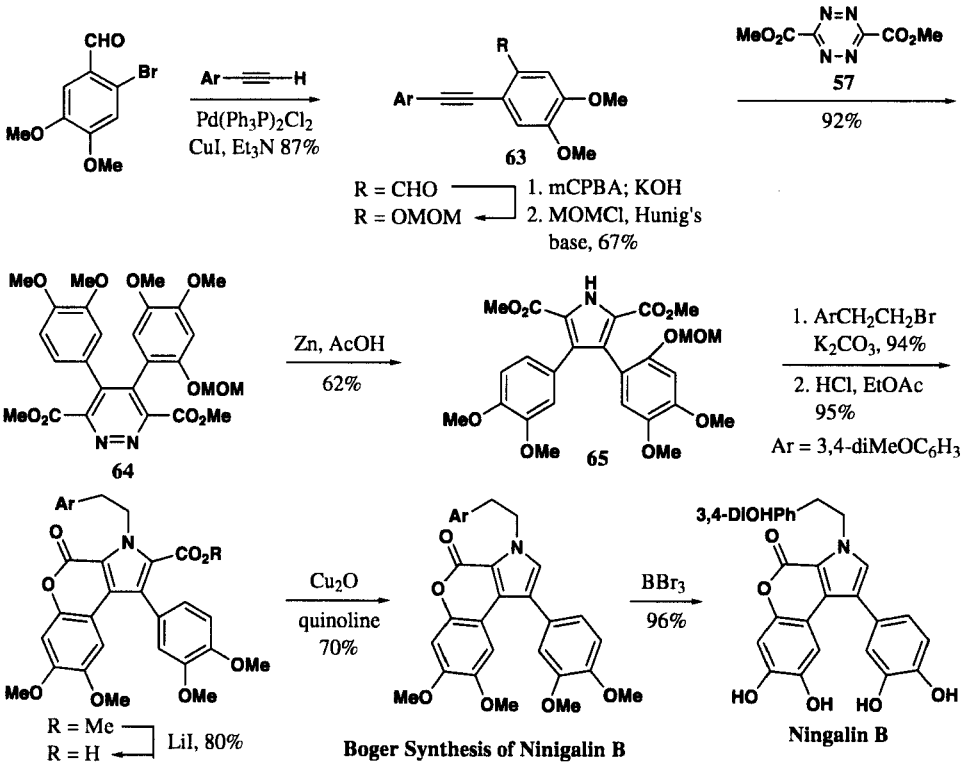
Boger Synthesis of Lamellarin O

Scheme 15

using a Sonogashira coupling. In this coupling, slow addition of the acetylene is required to avoid self-coupling of the acetylene. Reaction between acetylene **56** and tetrazine **57** yielded the 1,2-diazine **58** in 85% yield, which underwent ring contraction upon treatment with Zn, to provide pyrrole **59** in 72% yield. Alkylation with 2-bromo-4'-methoxyacetophenone yielded the pyrrole **60**. Monoacid **61** was obtained by selective hydrolysis with LiOH, which was decarboxylated to give the monomethyl ester **62**. Catalytic hydrogenation removed the benzyl protecting groups and afforded lamellarin O in quantitative yield. Compound **62** can also be converted to lukianol A, as demonstrated in Fürstner's synthesis, by saponification, lactone formation, and removal of the benzyl protecting group.

The same strategy was adapted to the preparation of another related alkaloid - Ningalin B (*Scheme 16*).[29] Disubstituted alkyne **63** was prepared by a Sonogashira cross-coupling. The

MOM-protected hydroxyl was obtained by Baeyer-Villiger oxidation, hydrolysis, and protection. The hetero-Diels-Alder reaction afforded diazine **64**, which yielded pyrrole **65** upon treatment with Zn. N-alkylation, lactone formation, selective hydrolysis of the methyl ester, decarboxylation, and finally deprotection yielded Ningalin B in good yield.

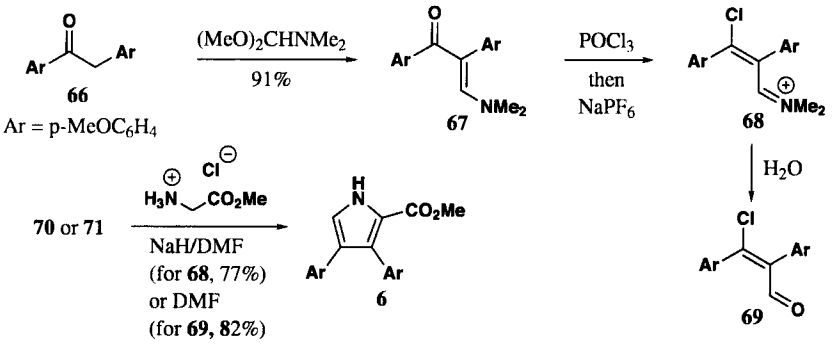


Boger Synthesis of Ninigalin B

Scheme 16

f) Vinylogous Iminium Chemistry (*Gupton*)

Another variation on the preparation of the lamellarin family of natural products employing a late-stage formation of the pyrrole core is the vinylogous iminium ion chemistry developed by Gupton and co-workers.[30] Their formal synthesis of lamellarin O dimethyl ether and lukianol A intercepts the Fürstner intermediate in just three steps from commercially available ketone **66** (*Scheme 17*).[31] Conversion of this ketone to β-chloroenal **69** proceeded *via* formation of vinylogous amide **67**, which was then transformed into chloropropeniminium salt **68** by treatment with phosphorus oxychloride and directly hydrolyzed. Treatment of **69** with methyl glycinate hydrochloride in DMF directly afforded Fürstner's intermediate **6** in 82% yield. Interestingly, compound **68** could also be converted into intermediate **6** using sodium hydride in DMF in 77% yield. In either case, a very short and efficient route to lamellarin-type natural products was developed.



Gupton Synthesis of Lamellarin O

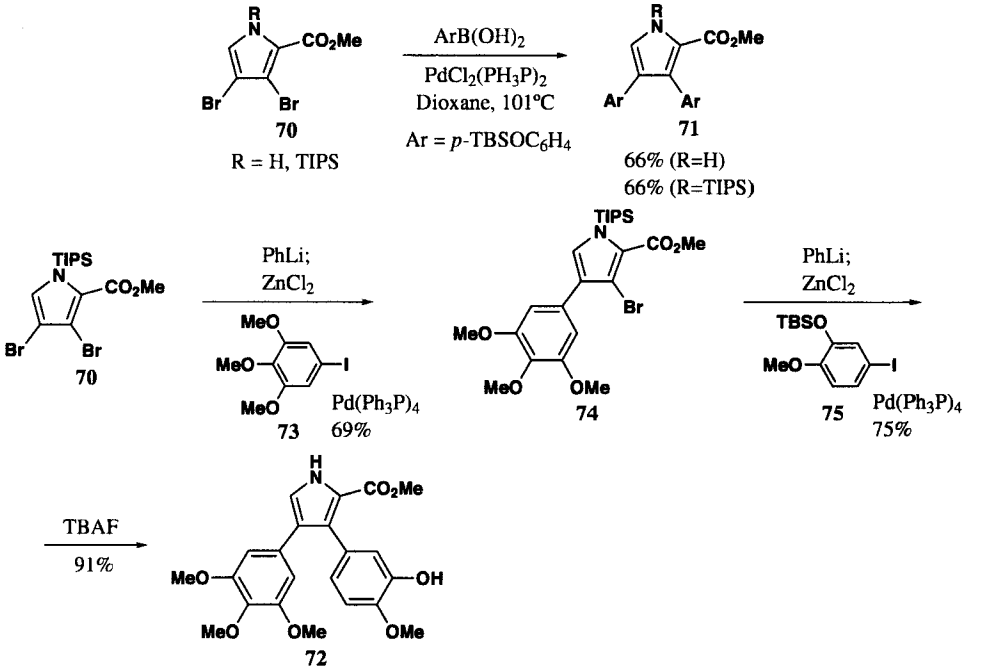
Scheme 17

2. via Preformed Pyrrole Rings

The second main option for synthesizing the lamellarin framework is to begin with an intact pyrrole and then functionalize it. A major part of the challenge in this approach is in establishing reliable methods for regioselectively functionalizing pyrrole. The most common method has been the application of cross-coupling chemistry on halogenated pyrroles, as will be seen in the following sections.

a) Double-cross Couplings (*Banwell/Wong/Iwao*)

The first cross-coupling approach was that of Banwell and co-workers (*Scheme 18*).[32]

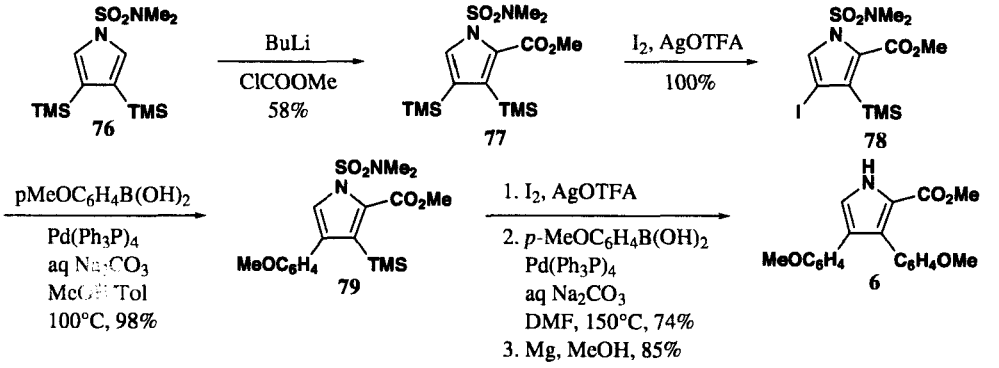


Banwell Cross-Coupling Studies

Scheme 18

These efforts targeted simple lamellarins such as lamellarin O and Q as well as lukianol A. The key starting material was pyrrole **70**, which could be prepared in three steps from pyrrole. Stille couplings on this material, either before or after removal of the TIPS group afforded symmetrically arylated product **71**, which could be readily converted into lamellarin O or Q. Differentially arylated compounds, such as **72**, could be accessed from pyrrole **70** by regioselective halogen-metal exchange, followed by conversion to the corresponding organozinc reagent and Negishi coupling with iodide **73**. A second halogen-metal exchange and coupling, followed by deprotection, then afforded compound **72**. This was the first solution developed to the problem of how to prepare non-symmetrically arylated pyrroles using a cross-coupling approach.

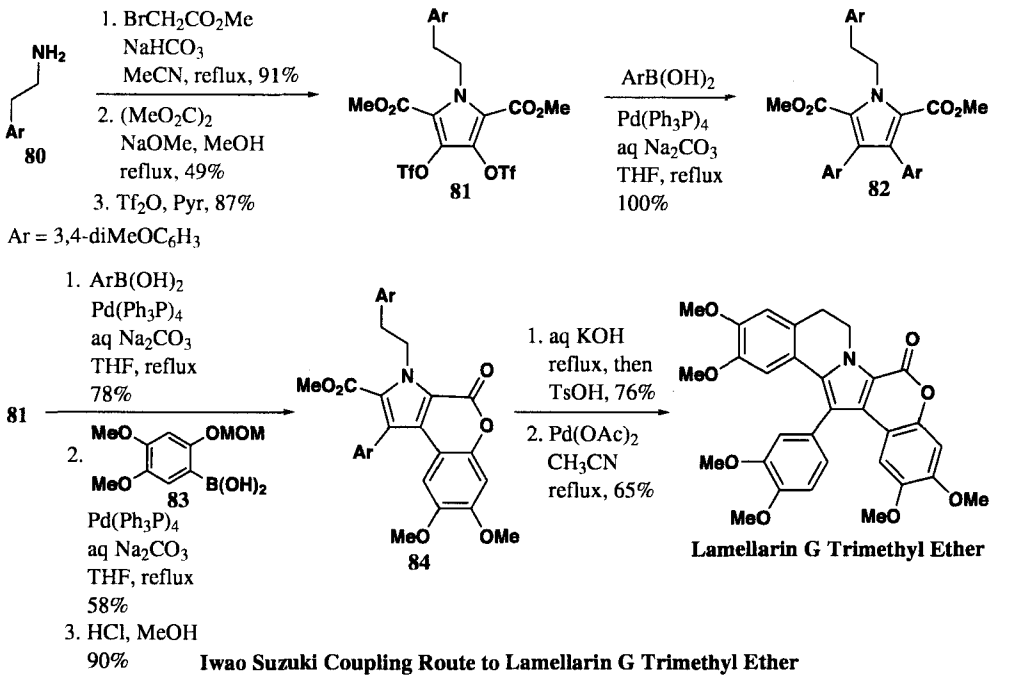
Wong and co-workers adopted a related approach for the synthesis of lukianol A (*Scheme 19*).[33] Starting with disilylated pyrrole **76**, metallation and trapping afforded ester **77** in modest yield. Regioselective iododesilylation occurred at the 4 position to afford iodide **78**. At this point, coupling afforded the monoarylated product. A second iododesilylation/coupling sequence, followed by deprotection of the pyrrole nitrogen, afforded Fürstner's intermediate **6**. Although this route is also capable of affording differentially arylated lamellarin-type molecules, only variations using Heck couplings or Sonogashira couplings were reported. Further, the added steps required for the preparation of silylated precursor **76** and in the regioselective iododesilylation render this approach less than optimal.



Wong Cross-Coupling Route to Lamellarin O

Scheme 19

A more recent variation on this theme comes from the Iwao group (*Scheme 20*).[34] In their approach, bistriflate **81** is prepared in three steps from amine **80** (overall yield 39%). At this point, a double Suzuki coupling with a boronic acid such as 3,4-dimethoxyphenylboronic acid affords product **82** in quantitative yield. However, a monocoupling with this same boronic acid effectively desymmetrizes the molecule and sets the stage for a second Suzuki coupling with boronic acid **83**. At this point, lactonization of one methyl ester and a decarboxylative oxidative coupling of the other with the pendent aryl ring completes the synthesis of lamellarin G trimethyl ether.

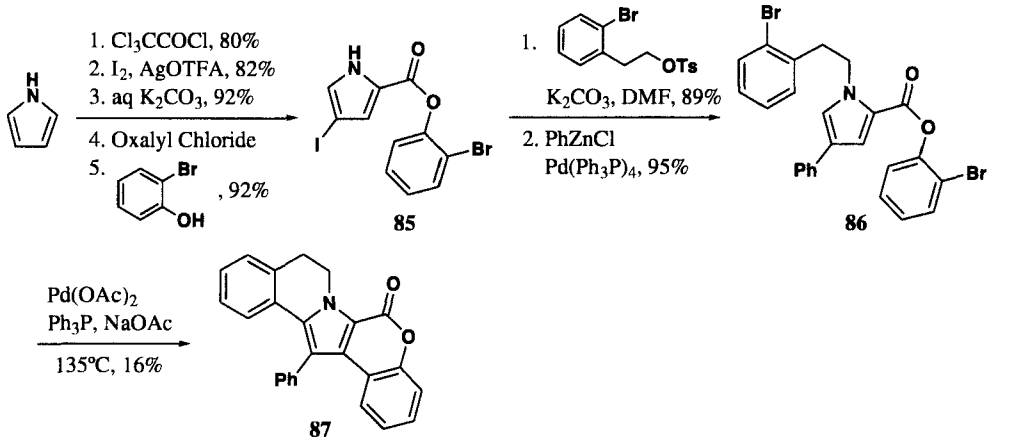


Iwao Suzuki Coupling Route to Lamellarin G Trimethyl Ether

Scheme 20

b) Tandem Heck Coupling (*Banwell*)

A very unusual approach featuring the functionalization of an intact pyrrole was the double-barrelled Heck cyclization reported by Banwell and co-workers (*Scheme 21*).[35] The key reaction is the double Heck cyclization of compound **86** to directly form the intact lamellarin skeleton **87**. The yield is quite modest (16%) and an attempt to employ the more reactive



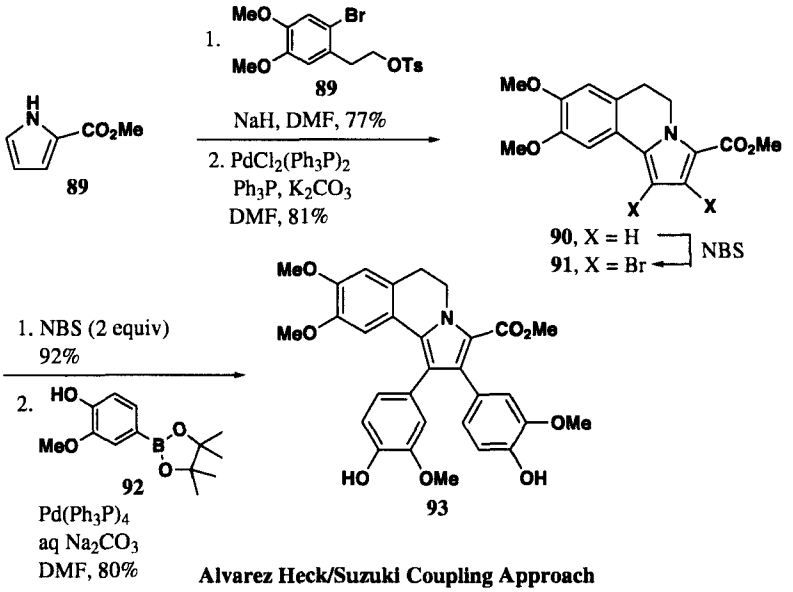
Banwell Double Heck Approach

Scheme 21

Herrmann-Beller catalyst resulted only in loss of the ester functionality and the *o*-bromophenol moiety. Further, the preparation of compound **86** required 7 steps starting from pyrrole. As a result, there is little practical advantage to this route over other options. Nevertheless, the double Heck reaction is a very audacious approach and quite impressive in that it works at all. Further, the Heck cyclization work set the stage for future approaches employing Heck cyclizations, such as that of Alvarez.

c) Heck/Suzuki Couplings (*Alvarez*)

Another Heck coupling approach is that of Alvarez and co-workers (*Scheme 22*).[36] Alkylation of pyrrole ester **88** with tosylate **89** affords the key Heck precursor. The Heck reaction proceeds well to afford dihydroisoquinoline **90**, which can then be mono or dibrominated.



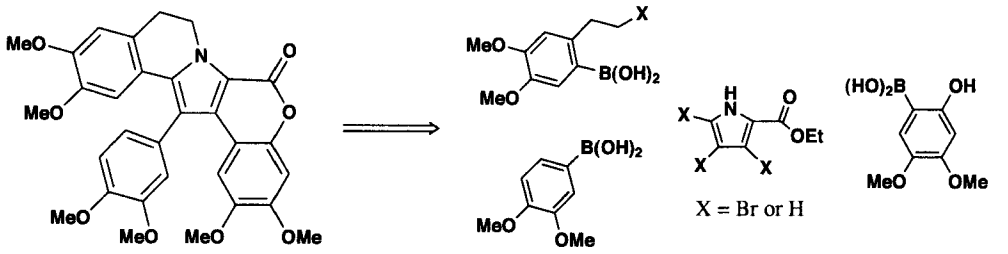
Alvarez Heck/Suzuki Coupling Approach

Scheme 22

Coupling of **91** with **92** then affords dicoupled product **93** which is closely related to the lamellarin skeleton and could, in theory, be transformed into the intact skeleton based on the work of Steglich. When coupled with our recent efforts regarding regioselective couplings, this may be the most versatile and flexible approach to the lamellarins and lamellarin analogs (*vide infra*). Further, it was also noted that monobromination of **90** cleanly afforded the C4-bromo compound, which could then be coupled with good efficiency to afford another class of lamellarin analogs.

d) Triple Suzuki Coupling (*Handy*)

One approach that directly targets the challenge of regioselectively installing the three different aryl substituents found in most members of the lamellarin family of natural products directly on a pyrrole is that of Handy and co-workers (*Scheme 23*).[37] Our approach employs a



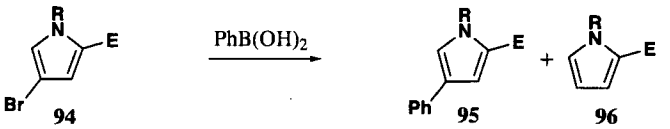
Handy Suzuki Coupling Approach

Scheme 23

series of halogenation/coupling reactions to sequentially install each of the required aryl subunits on a pyrrole ester. In such a way, the maximum degree of flexibility in terms of analog preparation (variation of the aryl substituents, presence or absence of tethers or entire aryl rings) is available for future SAR work.

The synthesis itself begins with pyrrole ester **94**, prepared in three steps from pyrrole (*Table 4*). Initial attempts at performing a Suzuki coupling with this unprotected pyrrole led to mixtures of coupled product and dehalogenated pyrrole ester.[38] Similar problems where encountered with the corresponding Stille or siloxane type couplings as well. Fortunately, by protecting

Table 4. Preparation of the Monoarylated Intermediate



R = CO_2Et

Entry	R[a]	**95/96**[b]
1	TIPS	48%/35%[c]
2	Me	75%/----
3	Bn	72%/----
4	BOC	68%/5%[c]
5	BOC	72%/4%[c,d]

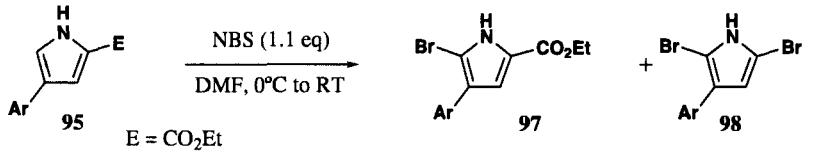
a) $Pd(Ph_3P)_4$ (2 mol%), aq Na_2CO_3/DMF, 110°C. b) Isolated yield. c) Protecting group lost, R = H in product. d) Boronic acid was 3,4-dimethoxyphenyl.

the pyrrole nitrogen, this dehalogenation could be avoided. Further, by employing a BOC protecting group, a separate deprotection step could also be avoided, since the BOC group was slowly cleaved under the coupling conditions (*Entries 4 and 5*). As a result, monoarylated product **95** was prepared in good yield.

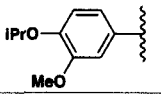
Approaching the construction of the lamellarin skeleton in this fashion requires the ability to regioselectively halogenate the pyrrole core. Early model studies were not particularly

promising, since simple phenyl substituted pyrrole ester **95** afforded equimolar mixtures of the C5 bromo and C3,5 dibromo products, even after extensive optimization of the reaction conditions (*Table 5, entry 1*). Interestingly, the regioselectivity proved to be highly dependent upon the nature of the aryl ring at C4. A moderately electron rich aryl ring, such as a *para*-methoxyphenyl group, at C4 led predominantly to formation of the 5-bromo product with little dibromination (*Table 5, entry 5*). Even more electron rich rings led to complete selectivity for bromination at C5 and even a highly activated ring, such as the 2,3,4-trimethoxyphenyl group, still resulted in bromination of the pyrrole with no competing bromination of the pendant aryl group (*Table 5, entry 2*).

Table 5. Regioselective Halogenation results



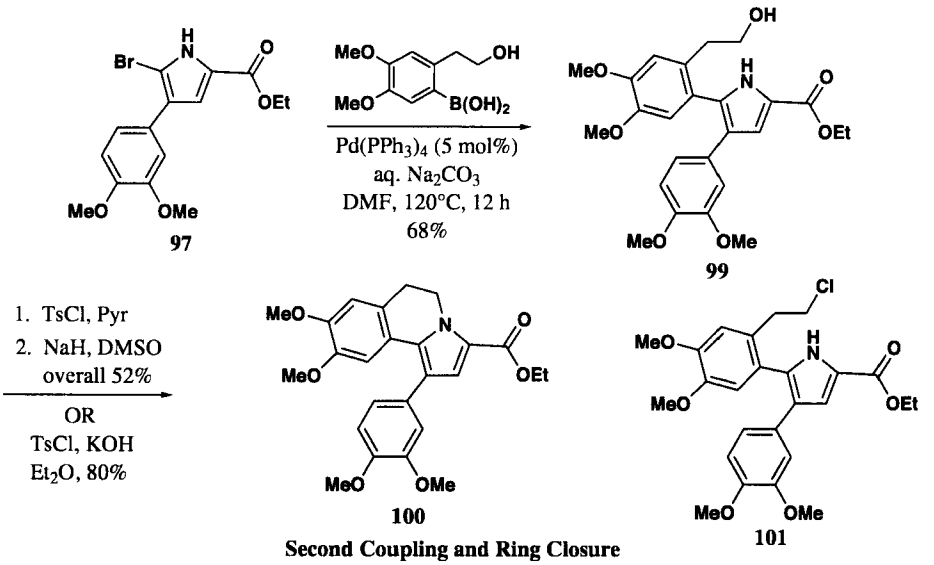
E = CO_2Et

Entry	Aryl Ring	Yield (%)
1	Ph	35%[a]
2	2,3,4-trimethoxyphenyl	75%
3	2,3,4-trimethoxyphenyl	80%
4	3,4-dimethoxyphenyl	92%
5	4-methoxyphenyl	82%[b]
6		89%

a) 40% of the 3,5-dibromo product also isolated. b) 8% of the 3,5-dibromo product also isolated.

With the bromination issues resolved, the second Suzuki coupling proceeded well, as did ring closure to afford dihydroisoquinoline **100** (*Scheme 24*). The one problem that was encountered with this ring closure was the formation of significant amounts of chloride **101** during the tosylate formation step. This chloride proved to be resistant to nucleophilic displacement, even in the presence of tetrabutylammonium iodide, instead affording recovered starting material or, under more forcing conditions, the elimination product. In a more recent observation, it has been noted that this ring closure can be accomplished in a single step by treatment with tosyl chloride and potassium hydroxide in ether. This affords compound **100** in 80% yield.

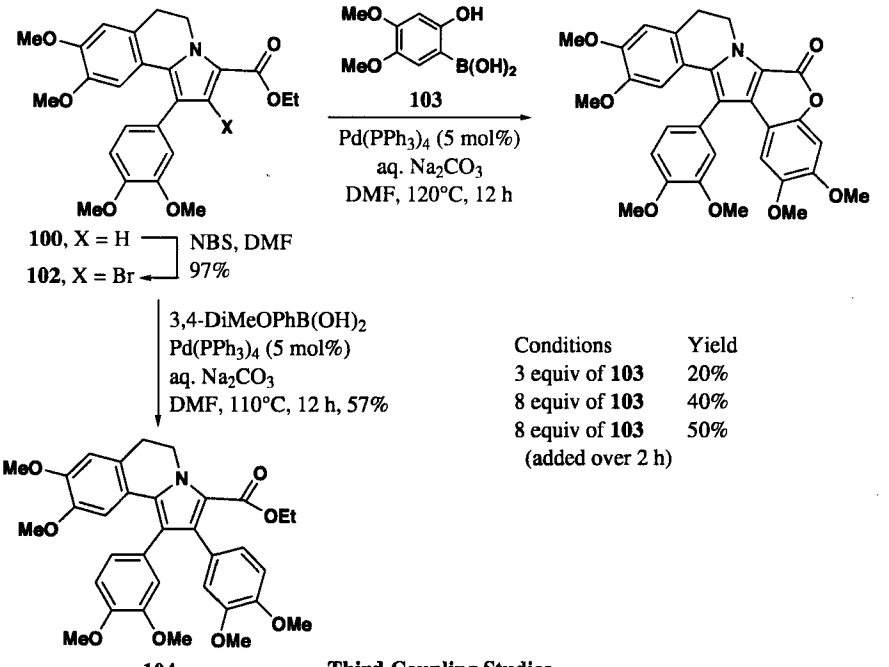
The final halogenation proceeded as planned, but the final coupling reaction proved to be a significant challenge (*Scheme 25*). The major issue was the limited thermal stability of boronic acid **103** with the free ortho phenol moiety. Even room temperature storage overnight was sufficient to result in significant decomposition of the boronic acid. Two methods were



Second Coupling and Ring Closure

Scheme 24

employed to overcome this limited thermal stability: the use of a large excess of the boronic acid or the addition of an excess of the boronic acid over time. Of these, the second option proved to be the more satisfactory, resulting in a 50% yield of lamellarin G trimethyl ether, along with a nearly 50% recovery of dehalogenated starting material **100**.



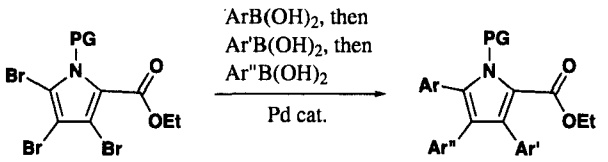
Third Coupling Studies

Scheme 25

Since it was suspected that the free *ortho* phenol was the source of the thermal instability, attempts were made to couple protected versions of this compound. Unfortunately, neither the benzyl, BOM, or MOM protected compounds resulted in any coupled product, though they are much more thermally stable. Presumably this is due to the greater steric hindrance in the coupling of these protected boronic acids. As a possible alternative, it was noted that 3,4-dimethoxyphenylboronic acid will couple in 57% yield to afford compound **104**. From this material, hydrolysis of the ester and oxidative lactonization according to the method of Steglich would afford another route to the lamellarin framework.

e) Regioselective Polycouplings (*Handy*)

More recently, we have been pursuing an even shorter version of the Suzuki coupling approach to the lamellarins that retains the flexibility of the sequential route. As seen in *Scheme 26*, this route involves the use of regioselective coupling reactions on a polyhalopyrrole core. Further, the concept would also be to perform more than one coupling in the same pot, thereby reducing the number of steps required by up to 4 compared to the existing route.



The Regioselectivity Polycoupling Approach

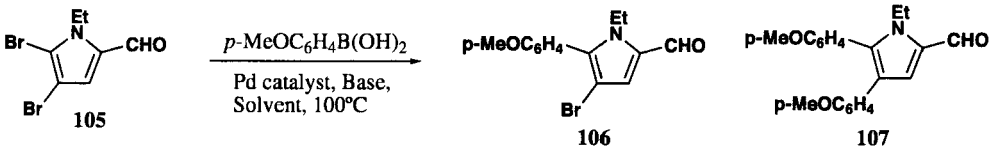
Scheme 26

Although a number of regioselective couplings of polyhaloheteroaromatic systems have been reported, there was no existing work on the pyrrole system prior to our efforts.[39] In general, the regioselectivity in such couplings closely parallels the order of electron deficiency of the halogenated centers, with the most electron-deficient site undergoing coupling first.[40] The most encouraging precedent for our studies was the observation by Bach and co-workers that 4,5-dibromofuran-2-carboxylates and 4,5-dibromofuran-2-carboxaldehydes underwent highly regioselective coupling first at C5, the more electron deficient center.[41]

Given the similarities between pyrrole and furan, we anticipated that the regioselectivity in the coupling of a 4,5-dibromopyrrole ester or aldehyde would be the same as that observed by Bach. However, the intrinsic electronic difference between the 4 and 5 positions is less in the case of pyrroles than for furans. In an effort to maximize the likelyhood of obtaining good regioselectivity in the pyrrole case, we undertook the study of pyrrole aldehyde **105**, since the electronic difference between the 4 and 5 positions is greater in the aldehyde than in the corresponding ester. Using our standard Suzuki coupling conditions on this substrate, a mixture of mono and diarylated products **106** and **107** were obtained (*Table 6*). The only monoarylated product was **106**, in which reaction had occurred first at C5, in keeping with Bach's observations

in the furan series.[41] Still, the ability to stop the reaction after one coupling was far from satisfactory. Simple variation of the reaction temperature did not result in any appreciable improvement. Fortunately, a more thorough study of the reaction conditions (catalyst, base, and solvent) eventually led to the discovery of conditions that resulted exclusively in regioselective coupling at C5 and no appreciable coupling at C4 (*Entry 4*). Indeed, no coupling at C4 occurred when **106** was resubmitted to the same palladium acetate reaction conditions. Quite surprisingly, the choice of base (potassium carbonate) and solvent (DMF) played the major role in enabling this highly regioselective coupling. The difference between catalysts (palladium acetate and tetrakistriphenylphosphine palladium) is much less significant (*Entries 2 and 4*).

Table 6. Regioselectivity Studies on Pyrrole Aldehyde 105



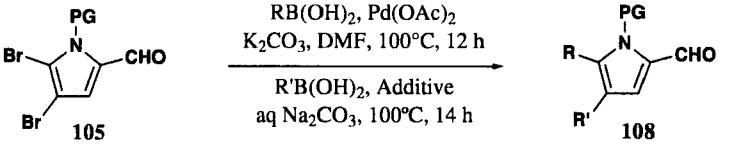
Entry	Catalyst	Base	Solvent	Yield[a]
1	$Pd(Ph_3P)_4$	Na_2CO_3	DMF	32% (29%)
2	$Pd(Ph_3P)_4$	K_2CO_3	DMF	42% (5%)
3	$Pd(OAc)_2$	Na_2CO_3	DMF	45% (18%)
4	$Pd(OAc)_2$	K_2CO_3	DMF	56% (<5%)
5	$Pd(OAc)_2$	K_3PO_4	DMF	28% (7%)
6	$Pd(OAc)_2$	Cs_2CO_3	DMF	31% (5%)
7	$Pd(OAc)_2$	$Ba(OH)_2$	DMF	complex mix
8	$Pd(OAc)_2$	K_2CO_3	Dioxane	48% (8%)
9	$Pd(OAc)_2$	K_2CO_3	H_2O/Acetone	complex mix

a) yield of dicoupled in parentheses.

With these conditions in hand, the stage was set for attempting a one-pot, double coupling of aldehyde **105** (*Table 7*). Since it was known that tetrakis(triphenylphosphine) palladium(0) was capable of catalyzing the second coupling at C4, while the palladium(II) acetate catalyst was not, the first coupling was run under the optimal palladium(II) acetate conditions and, once starting material was consumed by TLC, the second boronic acid, tetrakis(triphenylphosphine) palladium(0), and aqueous sodium carbonate were added. Once the reaction was complete, it was worked up and purified to afford the dicoupled product **108** in 44% yield.

Armed with this promising start, we sought to avoid the addition of a second palladium source by instead generating a phosphine-modified palladium catalyst *in situ* (*Table 7, entry 2*). Rather conveniently, the addition of 2 equivalents of triphenylphosphine (relative to the amount of palladium(II) acetate used) for the second step worked equally well. Even better results were obtained by the use of the more donating tri-*t*-butylphosphine (as its stable tetrafluoroborate salt)

Table 7. One-pot Double Couplings



Entry	PG	R	R'	Additive	Yield
1	Et	p-MeOPh	p-FPh	$Pd(Ph_3P)_4$	44%
2	Et	p-MeOPh	p-FPh	Ph_3P	48%
3	Et	p-MeOPh	p-FPh	tBu_3P/HBF_4	58%
4	MEM	p-MeOPh	p-FPh	tBu_3P/HBF_4	54%
5	MEM	p-FPh	styrenyl	tBu_3P/HBF_4	51%
6	MEM	styrenyl	p-MeOPh	tBu_3P/HBF_4	56%

(*Table 7, entries 3-6*).[42] In the end, a number of dicoupled pyrrole aldehydes could be readily prepared in 50-60% yield from aldehyde **105**. Further, other alkyl protecting groups (such as a MEM group) could be used in place of the ethyl group on the pyrrole nitrogen (*Table 7, entries 4-6*). Unfortunately, other groups, particularly benzyl and allyl, were not compatible with these coupling conditions and afforded complex mixtures of products.

Even more disheartening were attempts to directly translate these reaction conditions to carbamate protected pyrrole aldehydes or esters, such as **109** or **110** (*Fig. 4*). For any of these carbamate protected substrates, the palladium(II) acetate conditions resulted only in recovered

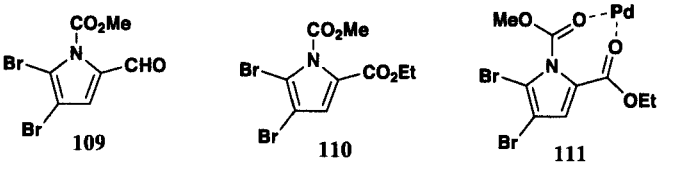
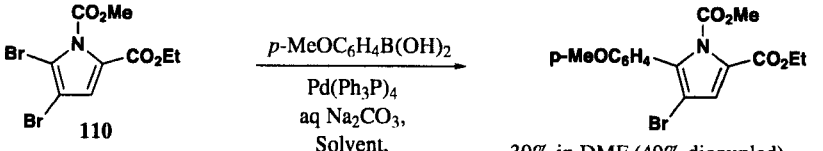


Fig. 4

starting material. We suspect that this may be due to the carbamate protected compounds acting as a bidentate ligand for palladium (as in compound **111**), which then renders it incapable of catalyzing the coupling reaction. This hypothesis is currently under investigation. Fortunately, it was noted that, by returning to the tetrakis(triphenylphosphine) palladium(0) catalyst, coupling would occur (*Scheme 27*). Further optimization noted that an alcohol/aromatic solvent mixture

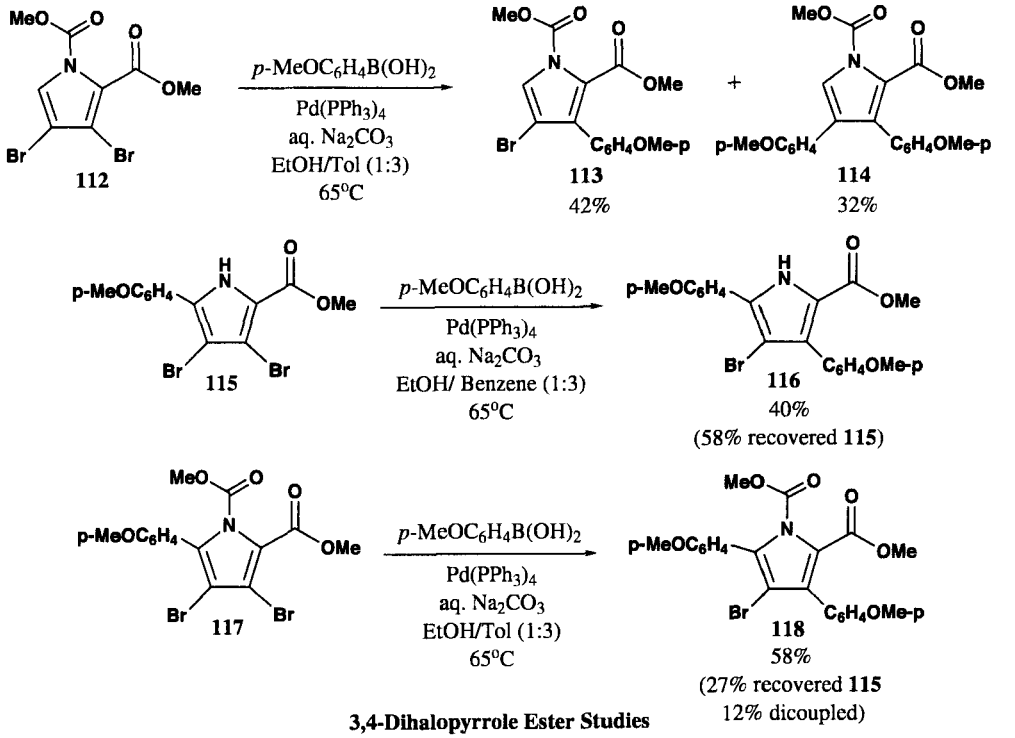


Regioselective Coupling of Pyrrole Ester 110

Scheme 27

(ethanol or methanol with benzene or toluene in a 1:3 ratio) proved to greatly enhance regioselectivity.

The results with this solvent/catalyst combination prompted a study of the regioselective coupling of different dihalopyrrole esters (*Scheme 28*). Simple 3,4-dibromopyrrole ester **112** did afford regioselectivity, with the initial coupling occurring at C3. Again, this is the more electron deficient site. Unfortunately, the rate of the second coupling was quite similar, so that nearly equimolar amounts of the mono-coupled and di-coupled products **113** and **114** were formed, even under partially optimized conditions.



3,4-Dihalopyrrole Ester Studies

Scheme 28

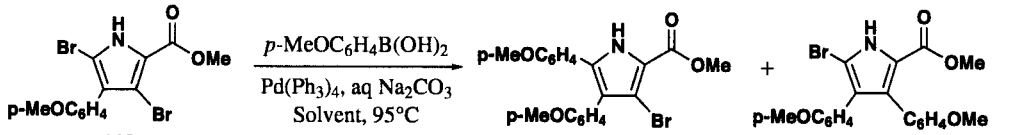
Going to pyrrole ester **115**, a considerable improvement with respect to avoiding dicoupling was noted. In this case, similar reaction conditions afforded monocoupled product **116** in 40% yield, with the remainder of the material being unreacted starting material. Attempts to push this reaction to completion began to result in the formation of greater amounts of dicoupled product. However, by protecting the pyrrole nitrogen as a carbamate, better results could be obtained. Indeed, by carefully controlling the temperature, up to a 58% yield of product **118** could be obtained, along with smaller amounts of starting material and dicoupled product.

The other main dihalopyrrole ester that was studied was 3,5-dibromopyrrole ester **119** (*Table 8*). In this case, the ethanol/toluene conditions proceeded quite well to afford monocoupled product **120** in 70% yield, with the remainder being unreacted starting material. This

worked for a range of arylboronic acids, providing generally good yields and no double coupling under these conditions.

Much to our surprise, an attempt at coupling ester **119** under the same conditions, but using DMF as the solvent, resulted in the formation of a different monocoupled product **121** as the major product, along with a significant amount of dicoupled product. This reversal of regioselectivity is the first observation made of such an effect and efforts are underway to clarify its origin. What is clear at this point, is that the use of highly polar, aprotic solvents (DMF, DMSO, NMP) affords the C3-coupled product **121** as the major product, while the combination of aromatic and low molecular weight alcohols affords the C5-coupled product **120** as the major product. Moderately polar, aprotic solvents (dioxane or acetonitrile) afford roughly equimolar mixtures of **121** and **120**. This effect holds true for esters related to **119**, but with electron deficient aryl rings.

Table 8. 3,5-Dibromopyrrole Ester Studies



119 **120** **121**

Entry	Solvent	Yield (**119/120/121**)
1	Tol/EtOH	---- / 67% /3%
2	DMF	---- / 14% / 39%[a]
3	MeCN	30% / 15% / 30%[b]
4	Dioxane	60% / 13% / 18%[c]
5	DMSO	37% / 10% / 40%[d]
6[e]	Tol/EtOH	---- / 51% / 1%
7[f]	Tol/EtOH	39% / 51% / 1%
8[f]	DMSO	---- / 13% / 42%[g]

a) 33% dicoupled product. b) 17% dicoupled product. c) 6% dicoupled product. d) 10% dicoupled product. e) Boronic acid is p-acetylphenyl. f) C4 aryl is 3,4-difluorophenyl, Boronic acid is o-methoxyphenyl. g) 29% dicoupled product.

III. CONCLUSION

In short, the aromatic skeleton of the lamellarin family of natural products has attracted a great deal of synthetic interest, in part due to their unusual framework and in part due to their intriguing biological activities. Although all of the routes have the advantage of being reasonably short (none are greater than 15 steps in length), the advances in the cross-coupling routes and their greater flexibility with respect to SAR studies appear to give them a practical advantage. Our regioselective polycoupling approach retains this advantage and will further shorten the

synthesis of the lamellarins and related molecules, although additional work is clearly merited in order to achieve better yields and selectivities. Ultimately, the lessons learned from these efforts can ideally be extended to other non-pyrrole-based aromatic products and greatly increase the utility of the regioselective polycoupling approach in natural products and pharmaceutical synthesis.

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