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Solid-Phase Total Synthesis of the Pentacyclic System Lamellarins U and L†

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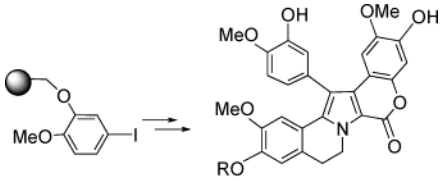
ABSTRACT



Lamellarin U R = Me
Lamellarin L R = H

A total solid-phase synthesis of lamellarins U and L has been achieved. The conversion of an aldehyde group into a formate by a Baeyer–Villiger reaction and a intramolecular [3 + 2] cycloaddition of a 3,4-dihydroisoquinolinium salt over a triple bond comprise the key steps of the process. Each transformation has been controlled with the proper spectroscopic and analytical methods.

The most recent advances in genomic and proteomic research are bringing about important changes in the drug discovery process.[1] For example, the understanding of detailed molecular biology mechanisms is fueling research into a broad spectrum of diseases. These developments are also allowing the development of efficient, automatic, and rapid screening test systems ["high-throughput screening" (HTS)] based on the novel therapeutic targets identified.[2] HTS requires a large number of diverse substances, which are synthesized simultaneously or in parallel mode ["high-throughput organic synthesis"(HTOS)].[3]

Natural products are perhaps the most important source of biologically active compounds and constitute a unique platform for obtaining chemical diversity.[4] Therefore, there is a need for the development of efficient synthetic methods for interesting natural products, which can subsequently be applied to the construction of libraries of compounds that can be fed into HTS systems.[5]

Isolated for the first time in 1985 by Faulkner and coworkers,[6] the lamellarin alkaloids are a group of approximately 35 compounds from the marine prosobranch mollusc *Lamellaria* sp., the marine ascidian *Didemnum* sp., and the sponge *Dendrilla cactos.* These compounds show an interesting range of pharmacological activities, including antitumor and anti-HIV-1 properties, reversal of multidrug

† Dedicated to the memory of Professor D. John Faulkner (1942−2003).
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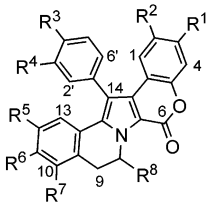
resistance (MDR), and immunomodulatory activity, properties that make these compounds particularly important targets.[7]

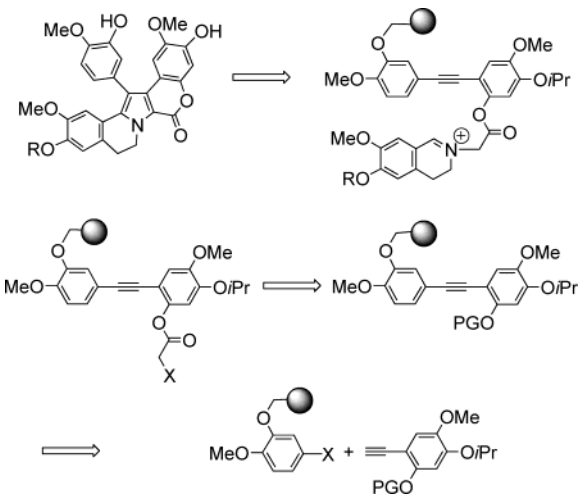
Scheme 1. General Structure of Lamellarins



Although HTOS may be conducted in solution,[8] the solid-phase mode is often the method of choice.[3] Several syntheses in solution have been reported.[9] Herein, the first total solid-phase synthesis of lamellarins is described, which should greatly accelerate the preparation of this class of molecules.

As shown in Scheme 2, a retrosynthetic analysis of the lamellarins highlights a series of different transformations that are needed for the synthesis of these compounds.

Scheme 2. Solid-Phase Analysis of Lamellarins



A hydroxymethyl polystyrene (Merrifield) resin was used as the starting solid support because of its stability and ease of use,[10] both of which ensure that the product remains intact until the final stage of the synthesis.

It is well-known that one of the drawbacks of the solid-phase methodology is the lack of control of the reactions taking place on the support. However, our approach is based on maximal control of the course of these reactions in order to minimize the amounts of byproducts formed. For this reason, each solid-phase reaction was followed by MAS NMR, gel-phase NMR, IR, and a colorimetric test where appropriate. In addition, a small aliquot of each reaction mixture was cleaved and the product characterized by HPLC-MS analysis.

The first step of the synthesis involved anchoring 5-iodo-2-methoxyphenol (**1**) (Scheme 3) onto the hydroxymethyl (Merrifield) resin by a Mitsunobu reaction.[11]

Colorimetric testing and IR spectroscopy were used to follow the reaction in the solid phase until completion, which was seen by the disappearance of the purple color obtained in the TosCl-*p*-nitrobenzylpyridine test[12] or by the disappearance of the OH stretching vibrations at 3450 and 3580 cm^{-1} (characteristic of the resin). The phenoxy resin was characterized by ^{13}C MAS NMR. Preparation of the bisaryl-acetylene-containing resin **4** was achieved by a Sonogashira cross-coupling reaction[13] between the anchored iodophenoxy resin (swelled in THF/Et_3N) and 2-ethynyl-5-isopropoxy-4-methoxybenzaldehyde (**3**).[14]

The reaction was catalyzed by Pd[$(PPh_3)_2Cl_2$] and CuI at rt. Two intense signals at 1680 and 2200 cm^{-1} in the IR spectrum revealed the presence of aldehyde and acetylene functional groups, respectively, on the resin. Intermediate **4** was characterized by ^{13}C MAS NMR.

A key step in this approach was the Baeyer−Villiger reaction on the solid phase,[15] which converted the aldehyde group into the formate **5**. This reaction was carried out by swelling resin **4** in CH_2Cl_2, adding solid $NaHCO_3$ in one portion and finally *m*CPBA in three portions for 3 h. Successful synthesis of the formate was indicated by the strong IR absorption at 1730 cm^{-1}. Hydrolysis of the formate group gave phenol **6**, which was produced by treatment of the resin with a 2 M solution of KOH in MeOH/THF at rt for 5 h. A strong absorption at 3417 cm^{-1} (OH stretching)

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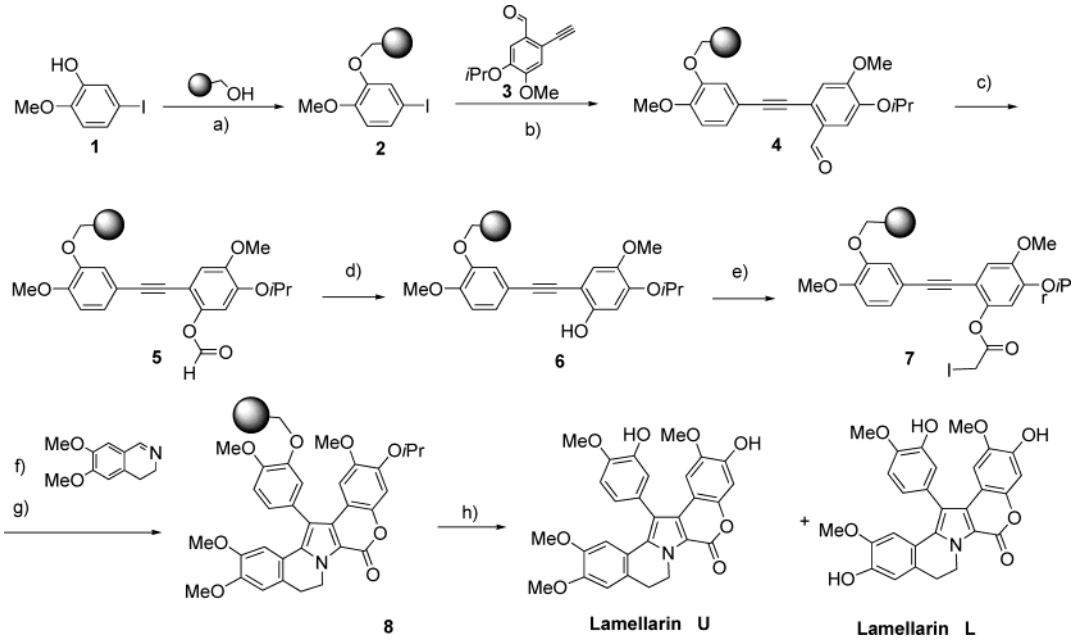
Scheme 3 [a]



[a] Reaction conditions: (a) DEAD, PPh_3, DIEA, THF, 0 °C 10 min, rt, 3 h, loading of Merrifield resin: 0.68 mmol/g; (b) 2-ethynyl-5-isopropoxy-4-methoxy-benzaldehyde (3 equiv), CuI (0.6 equiv), $Pd[(Ph_3)_2Cl_2]$ (0.3 equiv), THF−Et_3N (3:1), N_2, 20 h; (c) *m*CPBA (6 equiv), $NaHCO_3$ (12 equiv), CH_2Cl_2, 0 to 20 °C, 15 h; (d) 2 M KOH, THF−MeOH, rt, 5 h; (e) ICH_2CO_2H (10 equiv), DMAP (15%), DIP (10 equiv), DMF, rt, 12 h; (f) 3,4-dihydro-6,7-dimethoxyisoquinoline (6 equiv), CH_2ClCH_2Cl, rt, 24 h; (g) DIEA (7 equiv), 83 °C, 24 h; (h) $AlCl_3$ (15 equiv), CH_2Cl_2, rt, 12 h.

and the disappearance of the signal at 1730 cm^{-1} were the more relevant features indicating that the reaction had taken place.

The iodoacetate derivative **7** was prepared by reaction of acetylene-phenol derivative **6** with iodoacetic acid using the standard conditions for ester bond formation; i.e., a polar solvent such as DMF, DIP as the activating agent, and DMAP as a catalyst. The purity of the material was assessed by ^{13}C MAS NMR, and this provided evidence of quantitative conversion.

Finally, the pentacyclic system of **8** was obtained by N-alkylation of **7** with 3,4-dihydro-6,7-dimethoxyisoquinoline followed by a [3 + 2] cycloaddition. Treatment of **7** with isoquinoline in dry 1,2-dichloroethane at rt for 24 h was followed by the addition of DIEA in the same pot and heating at 83 °C for an additional 48 h to afford **8**.

Although the classical method for cleaving compounds from a Merrifield-type resin involves the use of HF, it was thought that such conditions could be too harsh for the target compound and inconvenient in a parallel synthesis format. As an alternative, methods based on the use of Lewis acids were assayed as these can be more convenient for heterocyclic molecules. Cleavage of **8** with $AlCl_3$ in dry CH_2Cl_2[16] gave a crude product that was shown by HPLC-MS to consist of two major compounds: lamellarins U and L. These were purified by semipreparative HPLC to give the desired natural products[17,18] lamellarin U (in 10% overall yield) and lamellarin L (in 4% overall yield) after eight-step solid-supported synthesis. The beauty of the present process is emphasized by the cleavage of **8** with another Lewis acid $ZnBr_2$/AcBr in CH_2Cl_2,[19] which rendered mainly 3,17-di-*O*-acetyllamellarin U (in 9% overall yield).[17] The excellent purity of this crude product shown by HPLC (Figure 1) confirms the high content of the target lamellarin in the final product.

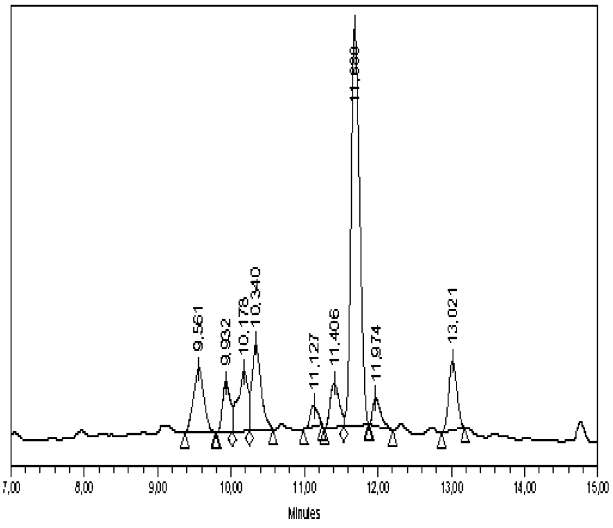


Figure 1. HPLC of the crude material after cleavage with $ZnBr_2$/AcBr.

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A total solid-phase synthesis has been developed for the preparation of several lamellarins. The key steps of this process are the solid-phase conversion of an aldehyde group into a formate by a Baeyer−Villiger reaction and the dipolar [3 + 2] cycloaddition in which a pyrrole and a lactone ring are formed simultaneously. Finally, the use of Merrifield resin could allow an easy and convenient preparation of several analogues just by modulating the cleavage conditions.

In conclusion, the solid-phase synthesis strategy reported here represents a neat synthesis of lamellarins. An additional advantage of this approach is based on the possibility of the introduction of diversity at different stages, including the cleavage. This fact should enable the construction of compound libraries for biological evaluation. Furthermore, the strategy can be extended to encompass other natural and nonnatural products.

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Supporting Information Available: Characterization data for compounds **2**, **4**, **6**, **7**, Lamellarins U and L, and 3,3′-di-*O*-acetyllamellarin U. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Structure assignment was done by mono and bidimensional NMR experiments.

(18) Yields were calculated on the basis of starting Merrifield resin, taking into account the nominal loading quoted by the supplier.

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