TOTAL SYNTHESIS OF LAMELLARIN D AND ANALOGS LIBRARY

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Lamellarins are a group of marine natural products isolated from the prosobranch molluse Lamellaria sp, the ascidian Didemnum sp, and the sponge Dendrilla Cactus. Several of them exhibit interesting biological activities,1 Natural as well as synthetic lamellarins should be excellent candidates for the development of new drugs due to their unique skeletal structure and their important biological activities especially as antitumor agents.2 Lamellarin D has been recently characterized as a topoisomerase I-targeted antitumor agent.3 A variety of synthetic approaches have been developed for this family of alkaloids.1 Herein we describe a new route to the synthesis of Lamellarin D, from a methyl 2-pyrolecarboxylate. Transformation of the starting material into the scaffold, a substituted 5,6-dihydropyrrrole[2,1-al]isoquinoline (5,6-DHPI), was afforded by N-alkylation followed by intramolecular Heck cyclization.4 From this scaffold the synthetic strategy is based on two sequential regioselective bromination/Suzuki cross-coupling reactions which permitted the introduction of differently substituted aryl groups on positions 1 and 2 followed by oxidation, deprotection, and lactonization.

Furthermore, this method has been applied to the preparation of a library of open chain lamellarin analogs (OCLA) used for in vitro antitumor evaluation. The structural differences between the library components remain in:

- The number of aryl groups on the scaffold, may be monoaryl- or diaryl-5,6-DHPI
- The symmetry or not of bisaryl derivatives, refers to the number and nature of aryl-substituents
- The oxidation degree on the position 5
