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Visible-Light-Promoted and Yb(OTf)$_3$-Catalyzed Constructions of Coumarin-Pyrrole-(Iso)quinoline-Fused Pentacycles: Synthesis of Lamellarin Core, Lamellarin D Trimethyl Ether, and Lamellarin H

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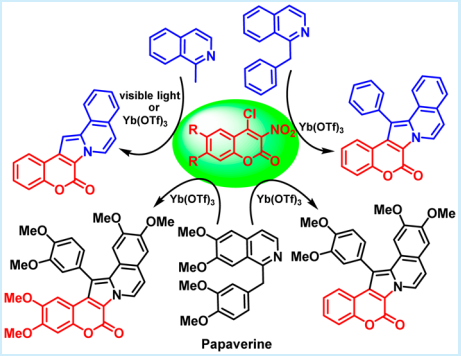
Supporting Information

ABSTRACT: The efficient construction of a coumarin-pyrrole-isoquinoline-fused pentacycle via the visible-light-promoted cyclization of 4-(isoquinolin-1-ylmethyl)-3-nitrocoumarin or Yb(OTf)$_3$-catalyzed coupling of 4-chloro-3-nitrocoumarin and 1-methylisoquinoline is reported. This methodology has further led to the development of the concise synthesis of the lamellarin core in one, two, and three steps, as well as of lamellarin D trimethyl ether in three steps.



Pyrrolo[2,1-*a*]isoquinoline- and coumarin-fused pentacycles constitute the molecular skeleton of the natural products lamellarin alkaloids such as lamellarins D, H, M, N, and α-20-sulfate (Figure 1). These lamellarin alkaloids exhibit a variety of

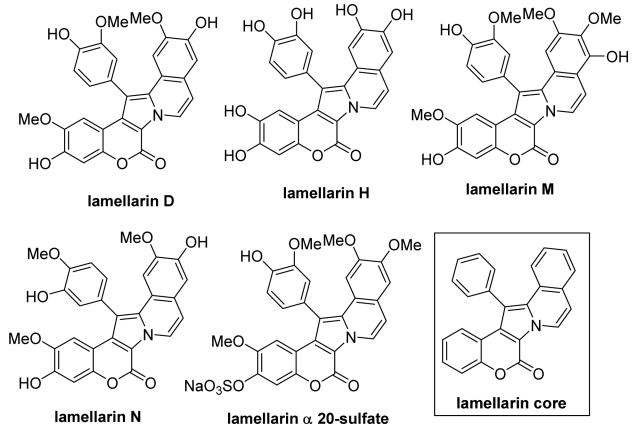
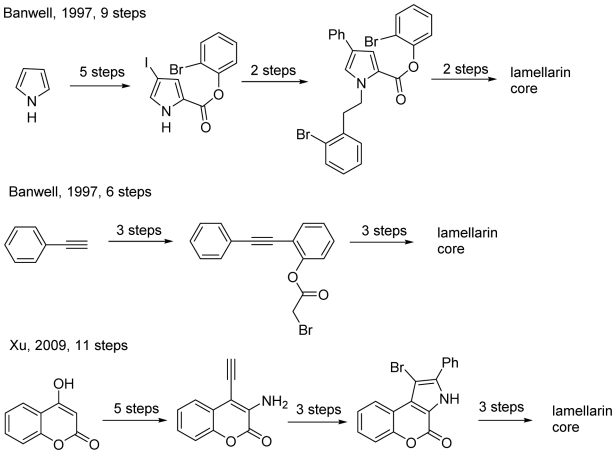


Figure 1. Molecular structures of lamellarins D, H, M, N, and α-20-sulfate.

biological activities.[1] For instance, lamellarin D not only displays strong cytotoxic activity against tumor cell lines[2] but also serves as a potent topoisomerase I inhibitor.[3] Lamellarin H is an effective antiviral agent against the *Molluscum contagiosum* virus.[4] Lamellarin N shows potent inhibition activities against protein kinases,[5] and lamellarin α-20-sulfate is a potent HIV integrase inhibitor.[4,6] In light of their novel structures and intriguing biological properties, the synthesis of the coumarin-pyrrole-isoquinoline-fused pentacycle has become an important and attractive goal for organic chemists. Previous pentacycle syntheses were generally accomplished in two stages by building the pyrrolo[2,1-*a*]isoquinoline core and installing the coumarin moiety onto it (Scheme 1).[7] Direct preparation of the coumarin-pyrrole-isoquinoline-fused pentacyclic system using pre-existing coumarin derivatives, however, has been rarely reported.[8] As a part of our ongoing research on the development of photosensitizer-free, visible-light-mediated

Scheme 1. Previous Synthesis of Lamellarin Core



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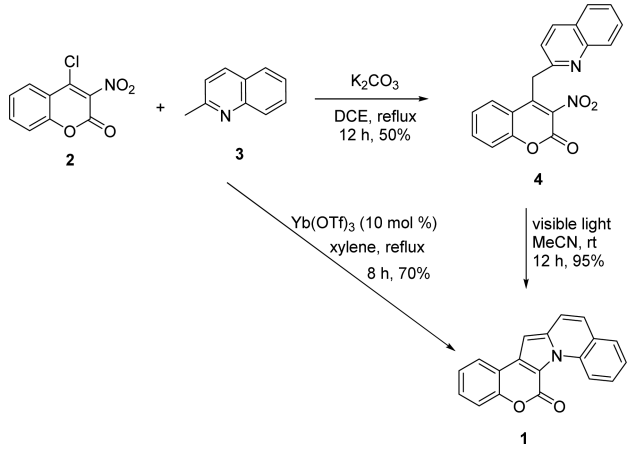
organic reactions,[9] we herein present the synthesis of a coumarin-pyrrole-isoquinoline-fused pentacycle through the cyclization of 4-(isoquinolin-1-ylmethyl)-3-nitrocoumarin under the influence of visible light irradiation or $Yb(OTf)_3$-catalyzed coupling of 4-chloro-3-nitrocoumarin and 1-methylisoquinoline. Further application of this methodology to the synthesis of the lamellarin core, lamellarin D trimethyl ether, and lamellarin H was also explored.

We initiated our study by choosing a coumarin-pyrrole-quinoline-fused pentacycle **1** as the first target (Scheme 2). The

Scheme 2. Synthesis of Compound 1



synthesis of **1** involved K_2CO_3-mediated coupling of commercially available 4-chloro-3-nitrocoumarin (**2**) and 2-methylquinoline (**3**) in 1,2-dichloroethane under reflux conditions to give 3-nitro-4-(quinolin-2-ylmethyl)coumarin (**4**) in 50% yield. During purification of the compound **4**, a new and fluorescent spot on the TLC plate was invariably detected. This observation implied that compound **4** was light-sensitive and slowly converted into a new product under the influence of light. Upon exposure to visible light (23 W fluorescent light bulb or blue LEDs), the compound **4** indeed was found to undergo intramolecular cyclization reaction at room temperature to give the pentacycle **1**, quantitatively. No formation of **1** was observed when the reaction was carried out in the dark. This result confirmed that the cyclization of **4** to **1** was promoted by visible light. As for the solvent effect, among several solvents investigated, acetonitrile gave higher conversion in a shortest time interval. Hence, acetonitrile was used as the solvent for all subsequent visible-light-mediated reactions. The molecular structures of **4** and **1** were confirmed by single-crystal X-ray diffraction analysis as presented in Figure 2.[10] The X-ray crystal structures revealed that the quinoline moiety of **4** is almost orthogonal to the coumarin with the quinoline nitrogen

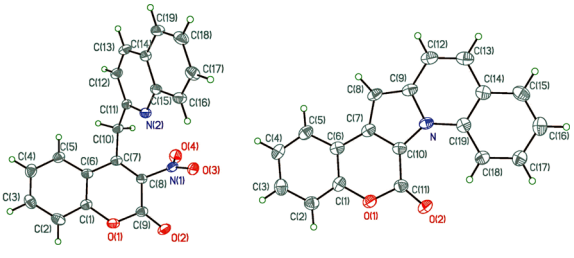


Figure 2. X-ray crystal structures of **4** (left) and **1** (right).

atom pointing toward the nitro group, and the pentacycle **1**, as expected, is virtually planar.

To gain more insight into the mechanism of this visible-light-promoted cyclization, nitrocoumarin **4** was subjected to the EPR measurements. Figure 3 depicts the EPR spectra of **4**

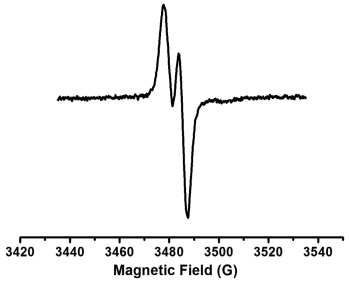
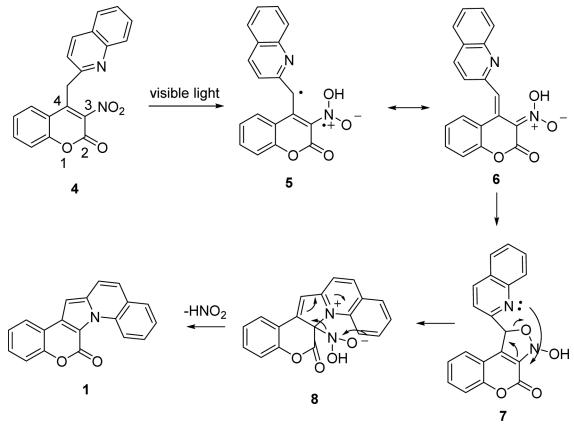


Figure 3. EPR spectra of **4** recorded in degassed CH_3CN solution at room temperature after exposed to visible light.

recorded in degassed CH_3CN solution under visible light irradiation at room temperature. Upon exposure to visible light, strong splitting EPR signals were clearly observed at around 3482−3492 G. This observation provided strong evidence to support that the photochemical reaction of **4** involves, at least in part, a radical species as a transient intermediate.

Based on the EPR experimental results, a plausible mechanism for the formation of **1** from **4** via visible light irradiation is proposed in Scheme 3. Presumably, the

Scheme 3. Proposed Mechanism for the Formation of 1 from 4



photoreaction involves a visible-light-mediated intramolecular hydrogen transfer from the methylene group to the nearby nitro group oxygen to give the biradical species **5**[11] which can delocalize to the 2-oxochroman-3-ylideneazinic acid **6**. The intramolecular cyclization of **6** generates the isoxazol-2(5*H*)-ol derivative **7**. The nucleophilic addition of quinoline nitrogen to the C-3 position of the coumarin ring forms the key carbon−nitrogen bond and subsequently leads to the formation of the quinolinium **8**. Final elimination of nitrous acid from **8** and intermittent aromatization of the pyrrole ring afford the photogenerated pentacycle **1**.

After the synthesis of pentacycle **1** has been successfully realized, we then turned our attention to the preparation of the coumarin-pyrrole-isoquinoline-fused pentacycle **12** and lamellarin core **9** as shown in Scheme 4. The synthesis started with K_2CO_3-mediated coupling of **2** with 1-methylisoquinoline (**10**)

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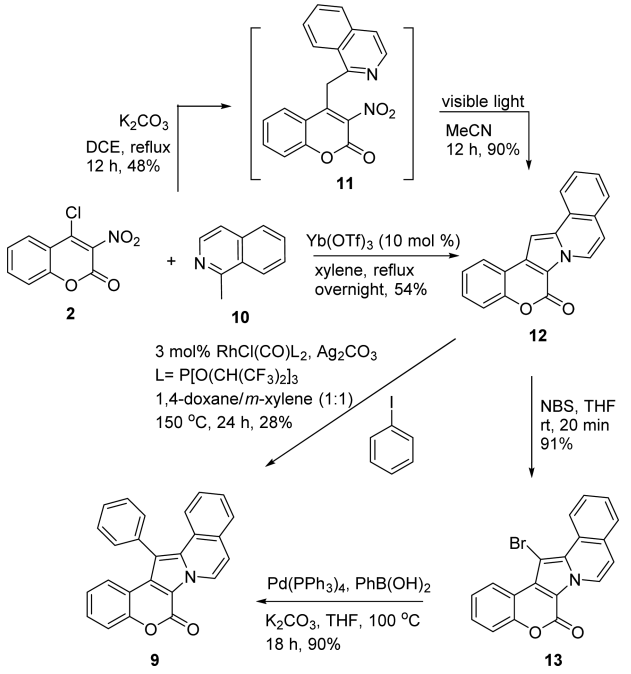
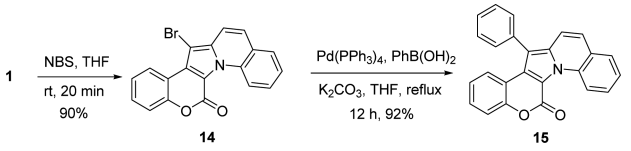
Scheme 4. Synthesis of Compound 12 and Lamellarin Core 9



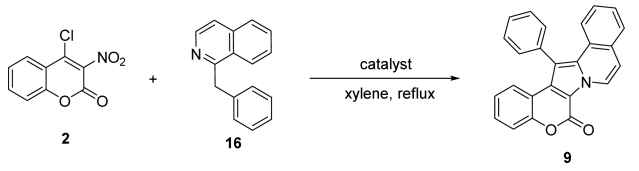
in 1,2-dichloroethane to give 4-(isoquinolin-1-ylmethyl)-3-nitro-2*H*-chromen-2-one (**11**) in 48% yield. Similar to that of **4**, compound **11** was found to be highly sensitive to light and readily undergo intramolecular cyclization reaction which made the isolation of **11** in its pure form difficult. Thus, without further characterization, compound **11** was subjected to visible-light-promoted cyclization in acetonitrile to afford compound **12** in 90% yield. The subsequent Rh-catalyzed coupling[12] of **12** with iodobenzene in 1,4-dioxane/*m*-xylene generated lamellarin core **9** in 28% yield. Alternatively, compound **9** can also be prepared by bromination of **12** with NBS at room temperature to afford **13** and followed by Suzuki coupling of **13** with phenylboronic acid in THF.[7i,8] Similarly, lamellarin core analogue **15** was synthesized from compound **1** to demonstrate the generality of this methodology (Scheme 5). Again, the molecular structures of both **9** and **15**[10] were confirmed by the single-crystal X-ray diffraction analysis (see the Supporting Information).

Scheme 5. Synthesis of Compound 15



In an effort to further shorten the synthetic steps of **9** shown in Scheme 4, we replaced 1-methylisoquinoline (**10**) with 1-benzylisoquinoline (**16**) in which the preinstalled phenyl group on the isoquinoline moiety would be directly introduced to lamellarin core **9**, so that the final metal-catalyzed coupling reaction can be omitted. Unfortunately, all attempts to prepare **9** by reacting **2** with **16** under various basic conditions failed to give the desired product, presumably due to the intrinsic steric hindrance caused by the bulky phenyl group on **16**. Further study, to our delight, indicates that the lamellarin core **9** can be synthesized in one step through Lewis acid catalyzed coupling of **2** and **16** in xylene under reflux conditions. Table 1

Table 1. Optimization of Reaction Parameters for Synthesis of Lamellarin Core 9



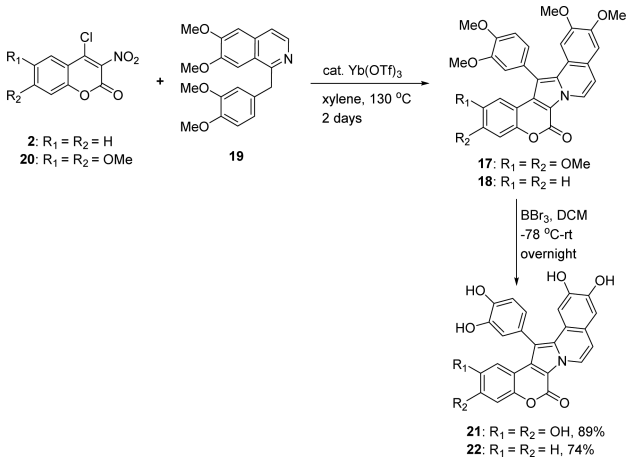
entry	catalyst (10 mol %)	time (h)	yield[a] (%)
1	$AlCl_3$	36	15
2	$FeCl_3$	72	trace
3	$NiNO_3$	72	nr[b]
4	BF_3OEt_2	72	nr
5	$Yb(OTf)_3$	36	17
6	$Sc(OTf)_3$	72	6
7	$Ga(OTf)_3$	72	trace
8	$Bi(OTf)_3$	72	trace

[a]Isolated yield. [b]No reaction.

summarizes the optimization of reaction parameters for the one-step synthesis of lamellarin core **9** from **2** and **16**. According to Table 1, ytterbium triflate was found to be the best Lewis acid with a yield of 17% (entry 5).

The methodology was further utilized in the preparation of lamellarin D trimethyl ether (**17**), its analogue **18**, and lamellarin H as shown in Scheme 6. The $Yb(OTf)_3$-catalyzed

Scheme 6. Preparation of Compounds 17, 18, 21, and 22



coupling of **2** with commercially available papaverine (**19**) in xylene under reflux conditions furnished lamellarin D trimethyl ether analogue **18** in 14% yield. Similarly, lamellarin D trimethyl ether (**17**) was synthesized by coupling 4-chloro-6,7-dimethoxy-3-nitrocoumarin (**20**, prepared from 4-hydroxy-6,7-dimethoxycoumarin in two steps; see the Supporting Information) with **19** in 10% yield (overall yield of 8% in three steps). Subsequent exhaustive demethylation of **17** and **18** using boron tribromide afforded the natural product lamellarin H (**21**) and its analogue **22**. Even though the yield of the coupling step is relatively low, this concise synthesis provides a quick access to the biologically important coumarin-pyrrole-isoquinoline-fused pentacycles and lamellarin D trimethyl ether from commercially available starting materials

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and represents the shortest route to the construction of lamellarin core,[7a,8] lamellarin D trimethyl ether, and lamellarin H[7g,13] ever reported in literature.

This one-step, sequential coupling−cyclization reaction was also utilized to improve the preparation of pentacycles **1** and **12** by reacting **2** directly with **3** and **10** in the presence of a catalytic amount of $Yb(OTf)_3$ in xylene under reflux conditions in 70% and 54% yield, respectively (Schemes 2 and 4). We assumed that the mechanism for the formation of **1** via $Yb(OTf)_3$-catalyzed reaction involves the Lewis acid promoted intramolecular proton transfer (rather than light-promoted hydrogen atom transfer) from the 4-methylene carbon of **4** to the nearby 3-nitro oxygen atom to afford **6**. The remaining mechanistic steps are similar to those of the visible-light-promoted reaction as shown in Scheme 3. Compared to the visible-light-promoted reaction, the $Yb(OTf)_3$-catalyzed route has the advantages of higher overall yield, one less step, and being scalable. Nevertheless, the visible-light-promoted cyclization is more sustainable and environmentally benign and holds the potential for efficient preparation of novel heterocyclic aromatic compounds.

In summary, we have demonstrated that coumarin-pyrrole-isoquinoline-fused pentacycle **12** can be prepared via either visible-light-promoted cyclization of 4-(isoquinolin-1-ylmethyl)-3-nitrocoumarin (**11**) or $Yb(OTf)_3$-catalyzed coupling of 4-chloro-3-nitrocoumarin (**2**) and 1-methylisoquinoline (**10**). The methodology was extended to the one-, two-, and three-step syntheses of lamellarin core **9** with overall yields of 17%, 15%, and 44%, respectively. Moreover, we have successfully implemented this method in the synthesis of lamellarin D trimethyl ether in three steps with an overall yield of 8% and lamellarin H in four steps.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03524.

Synthesis of compounds **1**, **4**, **9**, **11**−**15**, **17**, **18**, and **20**−**22**; experimental details; additional spectra (PDF)
X-ray crystal structure details for **1** (CIF)
X-ray crystal structure details for **4** (CIF)
X-ray crystal structure details for **9** (CIF)
X-ray crystal structure details for **15** (CIF)

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Notes

The authors declare no competing financial interest.

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(10) Crystallographic data (excluding structure factors) for **1**, **4**, and **15** have been deposited with the Cambridge Crystallographic Data Centre as Supplementary Publication Numbers CCDC-1427920, -1427919, and -1436089, respectively. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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