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The application of Morita-Baylis-Hillman reaction: Synthetic studies on perophoramidine

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ABSTRACT

A new concise methodology was developed for the synthesis of the two vicinal quaternary centers of the natural product perophoramidine. Key steps involved the Morita–Baylis–Hillman reaction, reductive cyclization and allylic alkylation. Moreover, most conditions are simple and convenient with good yields.

1. Introduction

In 2002, Ireland and co-workers reported the isolation of perophoramidine from the Philippine ascidian organism Perophoranamei, and this architecturally intriguing natural product possesses cytotoxicity toward HCT116 colon carcinoma cells ($IC_{50} = 60\ \mu M$).[1] With use of multidimensional NMR techniques, the striking molecular structure of perophoramidine is characterized by its complex densely functionalized hexacyclic system with two crucial vicinal all-carbon quaternary stereocenters, the skeletal connectivity of which is related to the Penicillium derived communesin alkaloids (Fig. 1).[2]

By virtue of the appealing biological activities and challenging structures, perophoramidine has attracted an attention of synthetic organic chemists in recent years.[3–8] The first total synthesis of (±)-perophoramidine was reported by Funk, which employed hetero Diels–Alder reaction as a key step.[3] Rainier developed a new spiro cyclization reaction to generate (±)-dehaloperophoramidine.[4] Subsequently, the asymmetric biomimetic Diels–Alder reaction has been used by Qin to first total synthesis of (+)-perophoramidine.[5] Recently, Wang achieved the total synthesis of (+)-perophoramidine using a nickel(II)-catalyzed asymmetric alkylation reaction.[6] Trost utilized a molyndenum-catalyzed asymmetric allylic alkylation to crate (−)-perophoramidine.[7]

Recently, Morita–Baylis–Hillman (MBH) reaction has emerged as a very versatile tool to deliver multifunctional compounds.[9] Toward a unique synthetic strategy distinct from the reported strategies, we envisioned our efforts towards the synthesis of perophoramidine core structure via a key MBH reaction as the starting response, which might construct the pivotal quaternary center at the first step.

As depicted in Fig. 2, we expected that the target perophoramidine could be synthesized from the azide compound **A** via formation of the A ring. The compound **A** could be generated from spiro lactam intermediate **C** via arylation reaction and condensation. Reductive cyclization of aldehyde compound **D** could deliver the lactam compound **C**. The requisite aldehyde compound **D** could be obtained from the isatin via Morita-Baylis-Hillman reaction.

2. Results and discussion

Firstly, we set out to investigate whether the key intermediate quaternary carbon compound **3** could be built via MBH reaction (Scheme 1). It was found that MBH reaction as a means could really proceed well to afford the tertiary alcohol **1** from commercially available isatin, which then followed by Boc protection and nucleophilic elimination reaction providing product **2**. Subsequently, **2** went through decarboxylation to give the desired

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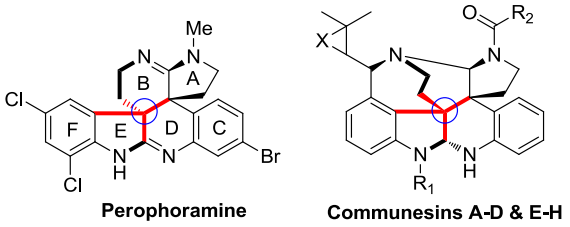


Fig. 1. Structures of perophoramidine and communesins.

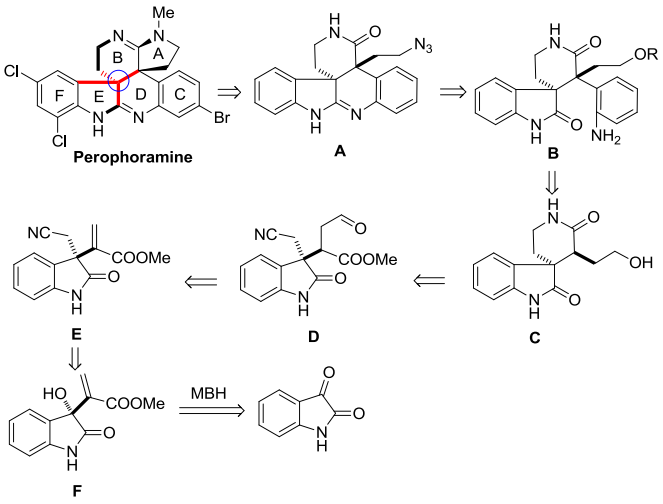
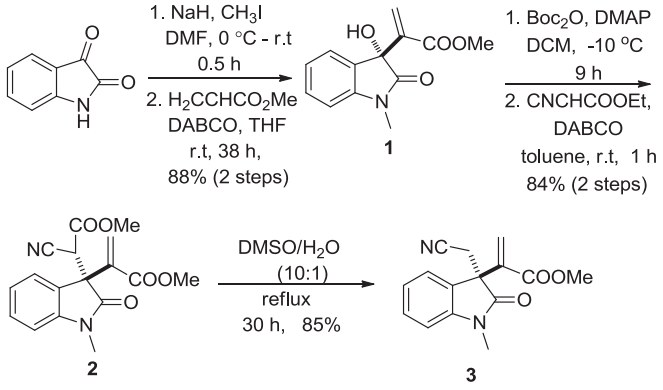


Fig. 2. Retrosynthetic synthesis of Perophoramidine.

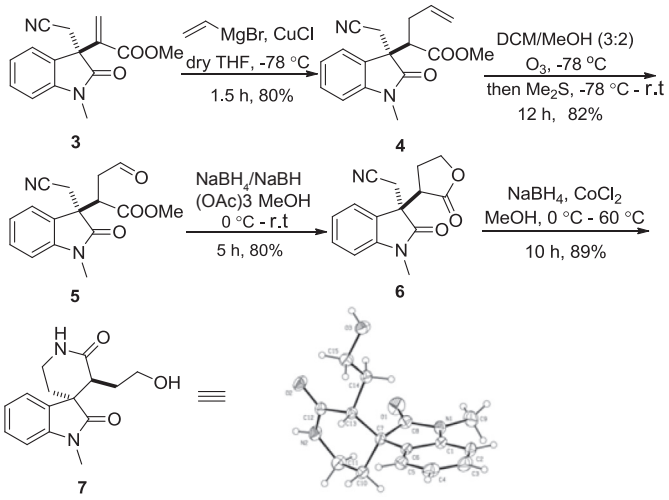


Scheme 1. Synthesis of cyano compound 3 via MBH reaction.

quaternary center intermediate **3**. It is worth noting that the nitrogen in isatin had to be protected first with methyl group, otherwise key intermediate **3** can't be obtained.

As we expected, 1,4-addition of **3** worked smoothly with vinyl Grignard reagent under the established reaction conditions, generating terminal alkenyl **4** in 80% yield. After oxidation of alkenyl group by O_3 and then reduction in the presence of $NaBH_4$, the resultant alcohol underwent intramolecular ester exchange to yield lactone compound **6**, which was subjected to reduction and subsequent amine ester exchange to deliver important spiro-fused oxoindolin **7**, whose structure was established by X-ray analysis (Scheme 2).[10]

With **7** in hand, we next examined the construction of the D ring. To achieve this goal, we settled upon various arylation reactions to establish the second quaternary carbon center.[11]



Scheme 2. Synthesis of the spiro-fused oxoindolin **7**.

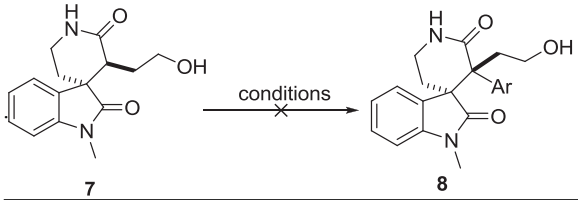
Unfortunately, the approaches using 2-iodoaniline or 1-bromo-2-iodobenzene as the source of aromatic groups were all failed (Table 1).

In view of above result, we decided to change the target and keep on studying the analogue of perophoramidine skeleton. Therefore, we then speculated to build the second quaternary center via allylation reactions (Scheme 3). To our surprise, only benzoyl chloride as a protecting agent could protect the amide, giving the Bz protection of the lactam **9** together with O-protection product **9′** in good yield.[11] Allylation of Bz protection product **9** gave a single alkylation product **10** and less amount of **10′**. The desired oxidation product **11** was performed through ozonation sequence from alkenyl compound **10**.

At this stage, we tried to convert the aldehyde group into an amine, and further synthesizing the D ring.[11] However, after a lot of experiments, we couldn't get the desired aminated product **12** (Table 2). Unfortunately, these conditions were also no working to obtain hydroxylamine product **13**.

After that, we wanted to convert the aldehyde group to the amide and then to synthesize the D ring by using the Zhou's conditions.[12] In this instance, on exposure to potassium carbonate and NIS, aldehyde **11** underwent oxidation to furnish esterification product **14**, which could be involved in the similar amine ester exchange process to lead the amide products **15** and **16** (Scheme 4).

Table 1
The exploration of arylation reaction to form **8**.[a]



Entry	Aryl halide	Base	Ligand	Solvent	Result
1	2-iodoaniline	KHMDS	–	THF	Mess[b]
2	2-iodoaniline	LiHMDS	dppf	THF	Mess[b]
3	1-bromo-2-iodobenzene	KHMDS	–	MeCN	Mess[b]
4	1-bromo-2-iodobenzene	LiHMDS	dppf	MeCN	Mess[b]

[a] All reaction conditions unless otherwise specified: 0.1 mmol of **7**, 0.15 mmol of aryl halide, 0.3 mmol of base, 5 mol % of $Pd(dba)_2$, 0.2 mmol of $ZnCl_2$, 1 mL of solvent, reflux, 36 h, under argon atmosphere.

[b] Aryl halide was homocoupling and **7** was decomposed.