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Concise Syntheses of Meridianins and Meriolins Using a Catalytic Domino Amino-Palladation Reaction

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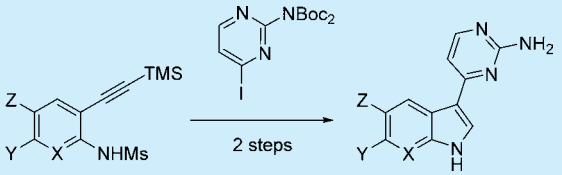
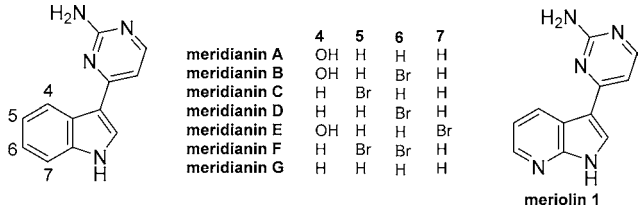
Supporting Information

ABSTRACT: A synthesis of natural and synthetic members of the meridianin family of kinase inhibitory natural products has been developed. The sequence utilizes a variation of the Cacchi palladium-catalyzed domino reaction to efficiently construct the heterocyclic framework of the meridianins and meriolins from monocyclic precursors.



The meridianins are a small family of marine alkaloids isolated from the marine tunicate *Aplidium meridianum*.[1,2] Structurally, they are indole derivatives, with a pendant 2-aminopyrimidine at the C3 position (Scheme 1). They have attracted a great deal of interest as they have been found to have a range of biological activity, with the most notable being their ability to inhibit a range of protein kinases.[3,4] In particular, they exhibit significant activity against the Clks and Dyrk kinase families, which are emerging as medicinally relevant targets due to their involvement in cancer and Alzheimer's disease respectively.[5] More recently, they have also been found to have activity against the parasites responsible for malaria and leishmania.[6]

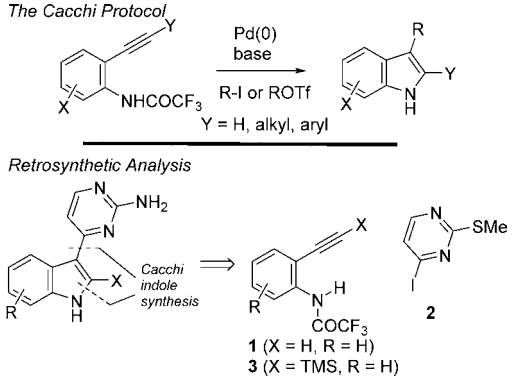
Scheme 1



Furthermore, Meijer and co-workers have found that the azaindole analogs of the meridianins, referred to as meriolins, are potent CDK9 inhibitors.[7] This potent activity, coupled with their antiproliferative properties, has established the meriolins as significant new leads for cancer therapeutics.

As the activity of the individual members of the meridianins is dependent on the substitution pattern on the indole ring,[3] investigation of new substituents may lead to compounds with improved potency and selectivity. While a number of methods[8] are available for the construction of indoles, the majority of syntheses[9] reported for the meridianins and meriolins have focused on the annulation of the pendant pyrimidine moiety onto a preformed indole.[10] While effective, this strategy limits the generation of new analogs by requiring access to the preformed indoles. With these limitations in mind, we have focused on the development of a synthetic strategy that can provide rapid access to the meridianins and the meriolins from readily available monocyclic precursors. The Cacchi indole synthesis involves the reaction of 2-alkynyltrifluoroacetanilides with either aryl halides or vinyl triflates and generates indoles in a very concise fashion (Scheme 2).[11] It allows the simultaneous incorporation of a 3-substituent onto the newly formed indole system in a palladium-catalyzed domino process. The Cacchi protocol has mostly been used to form 2,3-disubstituted indoles, but Cacchi has also reported the use of *o*-ethynyltrifluoroacetanilide (**1**) to form 3-substituted indoles.[12]

Scheme 2



Thus, our proposed retrosynthesis of the meridianins is summarized in Scheme 2. Unfortunately, our attempts to couple *o*-ethynyltrifluoroacetanilide (**1**)[13] with 4-iodo-2-methylthiopyrimidine (**2**),[14] using the reported Cacchi protocol, were unsuccessful. These attempts lead to a complex mixture of products, from which none of the desired indole could be isolated. It was speculated that side reactions arising

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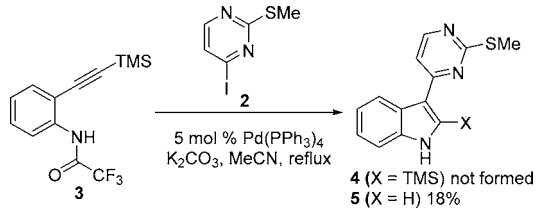
from the monosubstituted alkyne (such as Sonogashira coupling) were complicating matters. As silylalkyne **3** lacks the terminal alkyne hydrogen atom, it should not undergo such side reactions. To our surprise, there has been just one report of a silylalkyne being used in a Cacchi indole synthesis.[13b]

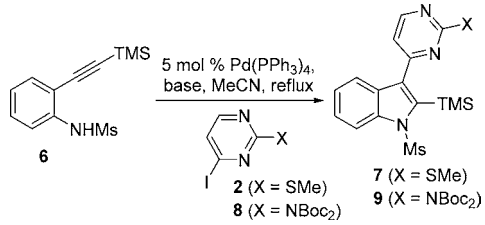
Subjecting silylalkyne **3**[13] to the Cacchi reaction conditions, using **2** as the coupling partner, led to none of the expected 2-silylindole **4**, instead giving a complex mixture of products from which the desired desilylated indole **5** was isolated in just 18% yield (Scheme 3).

Scheme 3



The low reactivity of silylalkyne **3** compared to other alkynes used in the Cacchi protocol necessitated longer reaction times than the original protocol, which we suspected caused the TFA group to be prematurely cleaved giving rise to the complex mixtures of products observed. In order to circumvent this problem, the methanesulfonamide group was investigated as an alternative activating group. In addition to activating the amine group, we reasoned the sulfonamide group should be more stable to the reaction conditions and limit undesired side reactions. Treatment of the known sulfonamide **6**[15] under the original conditions of the Cacchi reaction, using 3 equiv of **2** as the coupling partner with potassium carbonate as the base, produced only a trace of the desired 3-pyrimidoindole system **7** (Table 1, entry 1). Encouragingly, changing the base to cesium carbonate generated **7** in 25% yield (entry 2). A short series of reactions, described in Table 1, gave insight into the factors affecting the reaction.

Table 1. Optimization of the Domino Amino-Palladation Reaction[a]



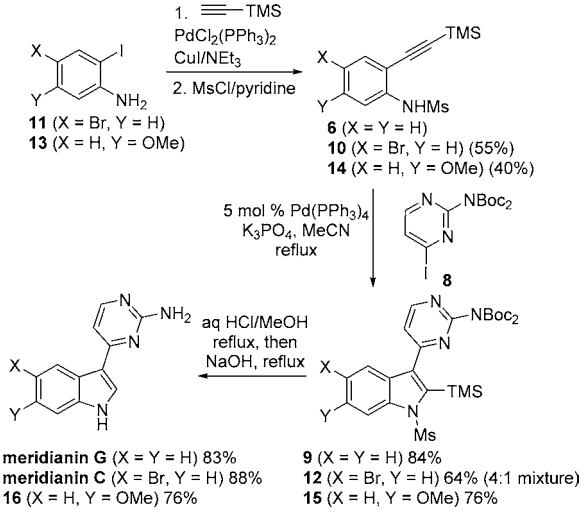
entry	aryl iodide, equiv	base	reaction time (h)	% yield
1	**2**, 3	K_2CO_3	18	trace
2	**2**, 3	Cs_2CO_3	4	25
3	**2**, 3	Cs_2CO_3	18	0
4	**2**, 3	Cs_2CO_3	2	52
5	**2**, 1.5	Cs_2CO_3	2	41
6	**2**, 1.5	K_3PO_4	2	59
7	**8**, 1.5	Cs_2CO_3	1.5	74[b]
8	**8**, 1.5	K_3PO_4	1.5	84[b]

[a]The sulfonamide (0.1 mmol), the indicated amount of iodopyrimidine, and base were treated with 5 mol % $Pd(PPh_3)_4$ in acetonitrile at reflux for the time indicated. All yields refer to isolated products. [b]Reaction conducted on a 1 mmol scale.

Extended reaction times gave little or none of the expected product (entry 3), while shorter reaction times gave more of the desired product (entry 4, 52%). Reducing the number of equivalents of iodide led to a lowering of yield (entry 5). However, by changing the base to tripotassium phosphate a significant increase in yield (entry 6, 59%) could be achieved using just 1.5 equiv of iodide.

While 2-thiomethyl pyrimidines can be converted to 2-aminopyrimidines,[14,16] it was felt that direct introduction of a protected aminopyrimidine would allow a more rapid preparation of the meridianins. Accordingly, protected aminopyrimidine **8** (X = $NBoc_2$) was prepared,[17] and the Cacchi-type reaction further optimized with this substrate (Table 1, entries 7 and 8). Again, the choice of base played a crucial role, with initial investigations revealing that carbonate bases were effective when coupling **6** with iodide **8**, but partial demesylation of the indole product was observed. However, using tripotassium phosphate as the base suppressed this, giving solely the desired silylated indole sulfonamide **9** in 84% yield (Table 1, entry 8 and Scheme 4). Global deprotection of the

Scheme 4



protected meridianin **9** was achieved in a one-pot acid/base process and cleanly delivered the natural product meridianin G in 83% yield without chromatography.

This four step synthesis proceeded in 45% overall yield from commercially available 2-iodoaniline. Moreover, the generation of the 2-silylmeridianin analog **9** provides a highly functionalized indole nucleus that could be further elaborated using chemistry reported by Larock.[18]

This sequence was further investigated by preparing other members of the meridianin family. Sulfonamide **10** was prepared in 55% overall yield from iodide **11**[19] by first coupling with TMS-acetylene using a Sonogashira reaction (TMS acetylene, CuI, $PdCl_2(PPh_3)_2$, NEt_3) and then a reaction with mesyl chloride and pyridine. The reaction of sulfonamide **10** proved to be faster than the one involving sulfonamide **6**, presumably due to thhe inductive effects of the bromine substituent. Carrying out the reaction for 30 min gave the protected meridianin **12**, albeit as a 4:1 mixture of *N*-sulfonyl and N−H indoles. In this case, the demesylation could not be suppressed; however, this was immaterial as the mixture was deprotected using the one-pot acid/base process to afford the

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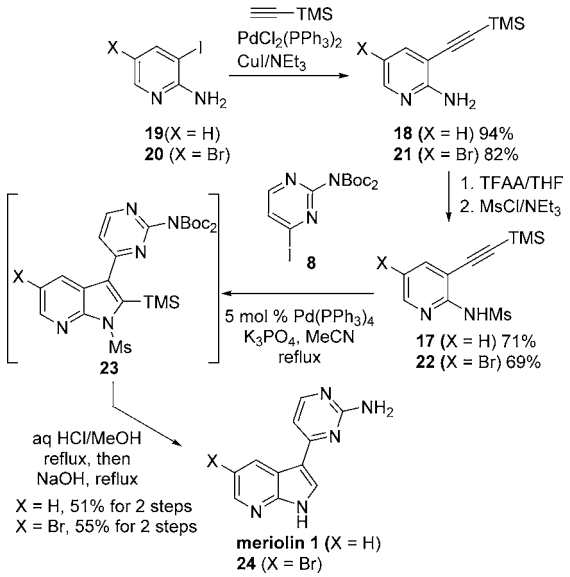
natural product meridianin C in 88% yield without the need for chromatography.

In addition to preparing natural members of the meridianin family, the Cacchi-type domino process can also be used to prepare novel analogs of the natural meridianins. Sonagashira coupling of readily available iodide **13**[20] with TMS-acetylene, followed by mesylation, gave sulfonamide **14**. Coupling of sulfonamide **14** with pyrimidine **8** under the conditions developed gave protected meridianin **15** in 76% yield. Global deprotection of **15** gave the non-natural 6-methoxymeridianin G **16** in 76% yield.

While our method was successful at producing members of the meridianin class of natural products, extension of this protocol to the synthesis of the meriolins initially hit a stumbling block, as it was not possible to prepare the monomesylated aminopyridine starting material **17** by the reaction of aminopyridine **18**[21] with mesyl chloride and pyridine. Despite numerous attempts, the only product isolated was the dimesylated material and efforts to remove one of the mesyl groups and/or utilize the dimesyl compound in the domino amino-palladation protocol failed to yield any of the desired products. This issue was eventually resolved by first acylating aminopyridine **18** with trifluoroacetyl anhydride to yield the monotrifluoroacetamide, followed by a reaction with mesyl chloride and NEt_3 (Scheme 5). Upon workup of this

Scheme 5



reaction, the TFA group was cleaved affording the monomesylated pyridine **19** in 71% yield over two steps. The reaction of **19** with iodide **8** using our optimized conditions (5 mol % $Pd(PPh_3)_4$, K_3PO_4, MeCN) gave the desired azaindole **23**, which was immediately globally deprotected using the one-pot acid/base process to generate meriolin **1** in 51% yield for the two steps. To further illustrate the utility of the protocol, 5-bromomeriolin **1** was synthesized from bromide **20**.[22] The sulfonamide **22** was prepared in 56% overall yield by first introducing the silylalkyne by a Sonogashira coupling (TMS acetylene, CuI, $PdCl_2(PPh_3)_2$, NEt_3) on bromide **21**, followed by the two step sequence (TFAA, THF; then MsCl, NEt_3, THF) to selectively introduce a single methanesulfonamide group onto the amino group. The reaction of sulfonamide **22** with iodide **8** using the optimized conditions (5 mol % $Pd(PPh_3)_4$, K_3PO_4, MeCN) generated the desired azaindole system, which was immediately deprotected by the one-pot acid/base procedure described above to generate the 5-bromo analog **24** in 55% yield over two steps.

In conclusion, a new approach to the meridianins and meriolins utilizing the Cacchi indole synthesis has been developed and can be used to provide rapid access to natural and synthetic members of the meridianin family of natural products. It is anticipated that this method will be of use in the synthesis of further analogs of meridianins and meriolins and allow further studies of the biological properties of these families of compounds.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization for compounds are available with copies of ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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(22) This compound is commercially available but is readily prepared from 3-iodo-2-aminopyridine. Full details are in the Supporting Information.