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Total synthesis of sparstolonin B via a palladium-catalyzed aldehyde α-arylation

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ABSTRACT

A concise and convergent total synthesis of sparstolonin B was developed. A palladium-catalyzed aldehyde α-arylation was utilized to construct the carbon skeleton of the natural product. A subsequent simple one-pot procedure effected global deprotection and closure of the final two rings via an unusual autoredox mechanism for the conversion of a bis-hydroquinone intermediate to the natural product. The 6 step synthetic sequence was realized in 18% overall yield.

1. Introduction

Transition metal catalysis has fundamentally transformed the total synthesis of biologically active natural products.[1] Palladium-catalyzed cross-coupling chemistry is especially useful for the formation of carbon-carbon bonds in complex molecular settings.[2] We became interested in the synthesis of the natural product sparstolonin B because of its unique biological profile and the potential to assemble its carbon skeleton via palladium-catalyzed carbon-carbon bond forming chemistry.

Since the isolation of sparstolonin B in 2011 from the Chinese herb *Sparganium stoloniferum*,[3] the polyphenolic isocoumarin has been shown to demonstrate a diverse array of biological activities.[3,4] The natural product's earliest recognized biological activity was selective antagonism of toll-like receptors (TLRs) 2 and 4.[3] Given the crucial role of TLRs in innate immunity,[4a] antagonists of these proteins are attractive candidates for the treatment of chronic inflammatory diseases,[4b] as well as severe sepsis.[4c] Protective effects of sparstolonin B have already been demonstrated in septic mice.[4d] Sparstolonin B has also been shown to attenuate early liver inflammation in a mouse model of non-alcoholic steatohepatitis.[4e] More recently, sparstolonin B was shown to inhibit HIV-1 transcription by a novel mechanism[4f] and induce apoptosis in neuroblastoma cells.[4g] These diverse and valuable biological activities have rendered sparstolonin B an attractive synthetic target.[5,6]

The first total synthesis of sparstolonin B was reported by Wang and co-workers in 2015.[5] Tang et al. reported an alternative synthesis in 2017 featuring milder reaction conditions.[6] We were interested in devising a concise and convergent total synthesis of sparstolonin B that would facilitate the preparation of analogs for medicinal chemistry studies to optimize the various biological activities of the natural product. We envisioned the use of a palladium-catalyzed carbon-carbon bond forming reaction to facilitate the efficient assembly of the core structure of the natural product.

Herein, we describe an efficient and convergent total synthesis of sparstolonin B that features a palladium-catalyzed aldehyde α-arylation to construct the carbon skeleton of the natural product. A one-pot procedure was devised to effect global deprotection and dual cyclization to yield sparstolonin B. Total synthesis of the natural product was achieved in 18% overall yield in 6 steps from inexpensive and commercially available 2,5-dimethoxybenzoic acid.

2. Results

Our retrosynthetic analysis of sparstolonin B (**1**) commenced with a disconnection of the diaryl ether to furnish hydroquinone **2**, which could readily be prepared by global demethylation of **3**

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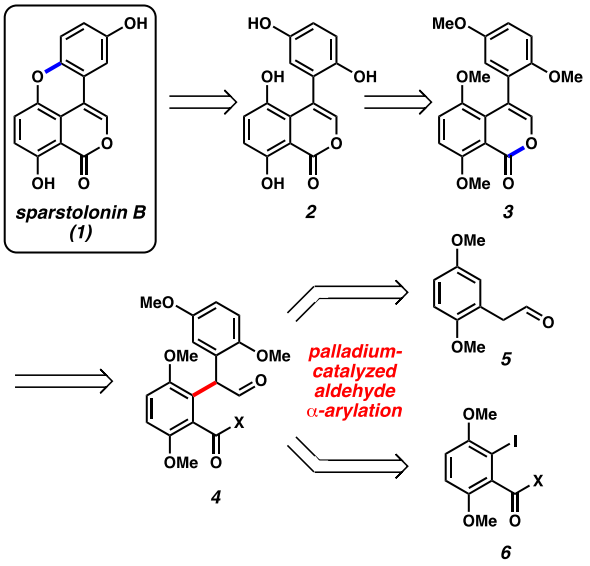


Fig. 1. Retrosynthetic analysis of sparstolonin B (**1**).

(Fig. 1). We hypothesized that 4-arylisocoumarin **3** could be derived from the key α-arylation of aldehyde **5** with aryl iodide **6**. Fragments **5** and **6** could in turn be accessed from commercially available starting materials.

The synthesis of aldehyde **5** is depicted in Fig. 2. Commercial (2,5-dimethoxy)phenylacetic acid (**7**) was quantitatively reduced to aryl alcohol **8** by an excess of lithium aluminum hydride in THF at 0 °C. Treatment of the resultant alcohol with Dess-Martin periodinane[7] in CH_2Cl_2 yielded the desired aldehyde **5** in 83% yield.

The proposed palladium-catalyzed α-arylation of aldehyde **5** with aryl iodide **6** is the key transformation in our synthesis of sparstolonin B, effectively assembling the carbon backbone of the natural product. Traditionally, the α-arylation of aldehydes has been a challenging transformation due to competing aldol reactions under basic conditions. An efficient protocol for the palladium-catalyzed α-arylation of aldehydes was reported by Terao in 2002 (Fig. 3).[8] Various aldehydes **9** were coupled with bromobenzene **10** to furnish α-arylated aldehydes **11**. Soon thereafter, a similar procedure was developed by Lessi for the direct synthesis of 4-arylisocoumarins **16** from 2-arylacetaldehydes such as **12** and methyl 2-halobenzoates such as **13**.[9] This transformation presumably proceeds through a tandem α-arylation/enol lactonization (**12** + **13** → **14** → **15** → **16**).

Before attempting the palladium-catalyzed α-arylation of aldehyde **5** with aryl iodide **6**, we devised model substrate 2-halobenzoate **17** to test the viability of the proposed key reaction

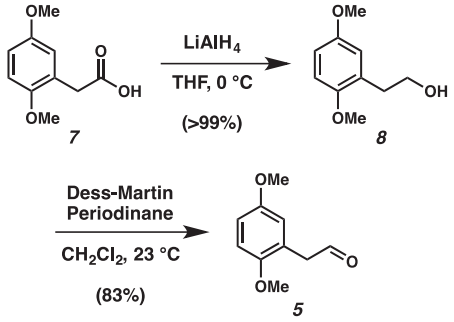


Fig. 2. Syntheses of aldehyde **5**.

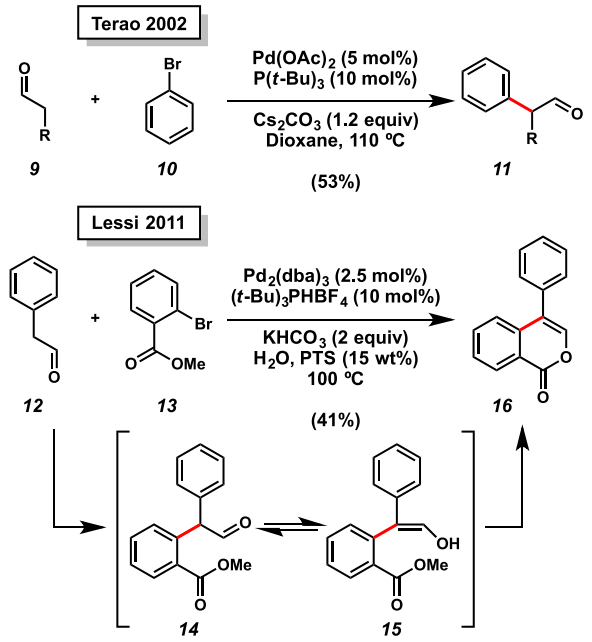


Fig. 3. Previous protocols for α-arylation of aldehydes.

(Table 1). We examined a series of reaction conditions, with various solvents, bases, palladium sources, and ligands. To our delight, we obtained the desired 4-arylisocoumarin **20** in 65% yield in the presence of Cs_2CO_3 as the base, $Pd(OAc)_2$ as the palladium source, *t*-Bu_3PHBF_4 as the ligand precursor, and dioxane as the reaction medium. This reaction proceeds through initial formation of α-arylation product **18**, followed by enolization to ester **19** and subsequent cyclization to 4-arylisocoumarin **20**.

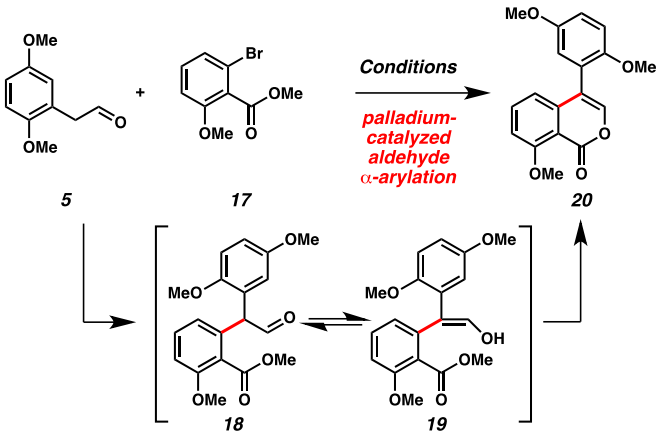
With the generation of model 4-arylisocoumarin **20** in hand, we pursued the synthesis of 2-iodobenzoate **6** for the total synthesis of sparstolonin B (Fig. 4). Commercially available 2,5-dimethoxybenzoic acid (**21**) was converted to benzamide **22** to facilitate installation of the iodide by directed *ortho* metalation.[10] Refluxing benzoic acid **21** in thionyl chloride yielded the corresponding acid chloride, which upon exposure to diethylamine rendered benzamide **22** in 88% overall yield. Directed *ortho* lithiation followed by exposure to 1,2-diiodoethane yielded iodobenzamide **6** in 70% yield.

Next, we attempted the key palladium-catalyzed aldehyde α-arylation and subsequent cyclization. Gratifyingly, the coupling of aldehyde **5** and 2-iodobenzamide **6** yielded an equilibrating mixture of α-arylated aldehyde **23** and enol **24**. While these intermediates did not undergo spontaneous cyclization under the palladium-catalyzed conditions, treatment with refluxing glacial acetic acid generated the desired 4-arylisocoumarin **3** in 78% yield.

We attempted to perform a global removal of the four methyl protecting groups of tricycle **3** with refluxing HBr and glacial acetic acid under an atmosphere of oxygen. Surprisingly, these acidic conditions resulted in the formation of the desired natural product sparstolonin B (**1**).

To account for the conversion of 4-arylisocoumarin **3** to sparstolonin B (**1**), we propose the following mechanism (Fig. 5). Initial global deprotection of the four methoxy groups results in the formation of bis-hydroquinone **2**. Mono-oxidation in the presence of oxygen yields the mixed hydroquinone-quinone intermediate **25**. Nucelophilic attack of the hydroquinone to the electrophilic quinone forms tetracycle **26**, and dehydration furnishes oxocarbenium ion **27**. Reduction of intermediate **27** with concomitant

Table 1
Optimization of tandem palladium-catalyzed aldehyde α-arylation/coumarin formation. PTS = Polyoxyethylene-α-Tocopheryl Sebacate.



Solvent	Base	Pd Source (5 mol%)	Ligand (5 mol%)	Temp	Yield
H_2O/PTS	$KHCO_3$	$Pd_2(dba)_3$	*t*-Bu_3PHBF_4	110 °C	< 5%
Dioxane/H_2O	$KHCO_3$	$Pd_2(dba)_3$·$CHCl_3$	*t*-Bu_3PHBF_4	80 °C	29%
Dioxane	Cs_2CO_3	$Pd(OAc)_2$	*rac*-BINAP	80 °C	< 5%
Dioxane	Cs_2CO_3	$[PdCl(C_3H_5)]_2$	DPPF	80 °C	< 5%
Dioxane	Cs_2CO_3	$Pd(OAc)_2$	*t*-Bu_3PHBF_4	80 °C	65%

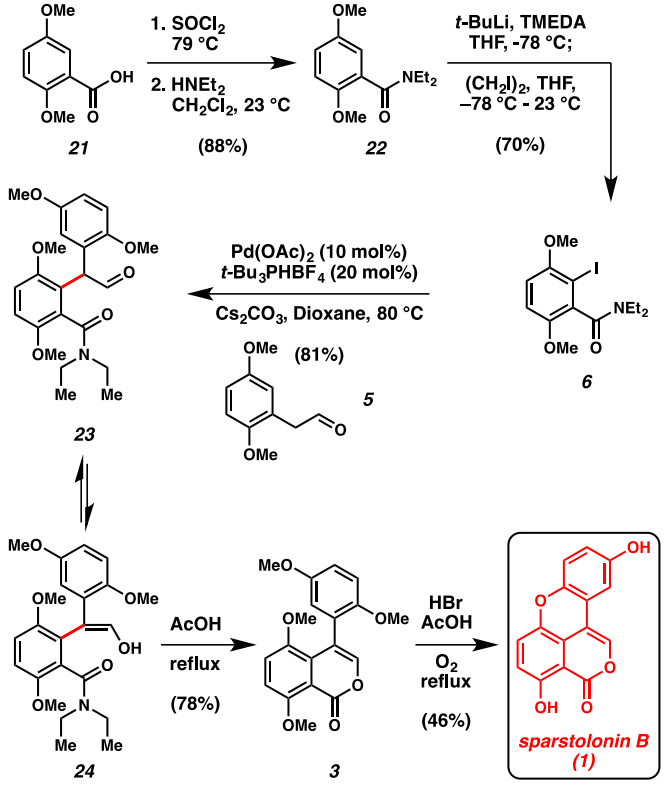


Fig. 4. Completion of total synthesis of sparstolonin B.

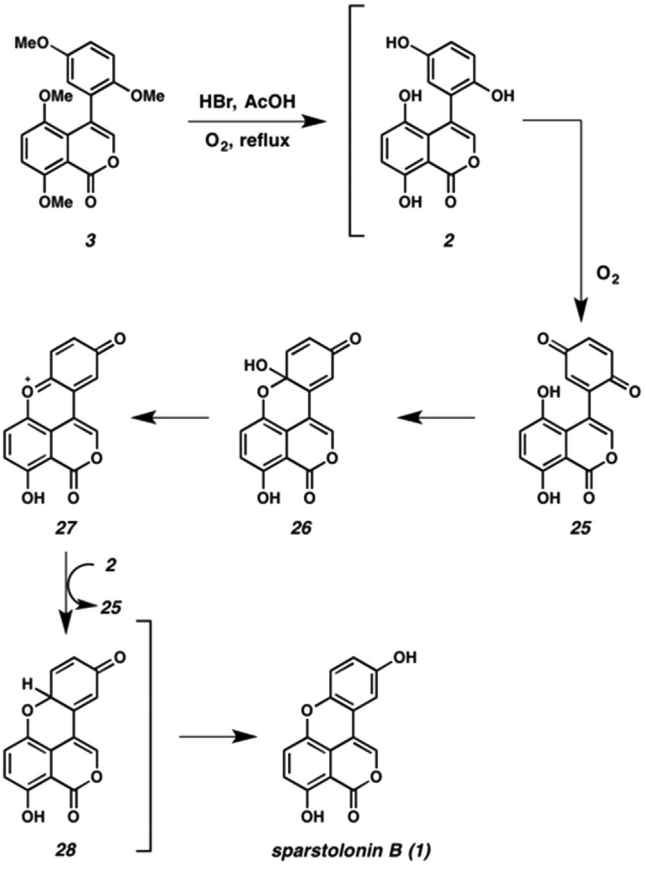


Fig. 5. Proposed mechanism for the conversion of tricycle **3** to sparstolonin B (**1**).

oxidation of another equivalent of **2** to **25** generates tetracycle **28** in an autoredox process.[11] Subsequent tautomerization of intermediate **28** leads to the formation of sparstolonin B (**1**).

In conclusion, we have developed a 6 step synthesis of sparstolonin B from commercially available 2,5-dimethoxybenzoic acid (**21**) in 18% overall yield. Key steps in our approach include a palladium-catalyzed aldehyde α-arylation to assemble the core structure **3** and an unusual autoredox mechanism for the conversion of bis-hydroquinone **2** to the natural product. The application of this flexible synthetic strategy to the synthesis of unnatural analogs of sparstolonin B and the exploration of biological activity for these structures are on-going interests in our group.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.tet.2018.05.012.

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