VIP Natural Products

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# Sequential $C_{sp^3}$–H Arylation and Olefination: Total Synthesis of the Proposed Structure of Pipercyclobutanamide A**

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Our laboratory recently reported the synthesis of the pseudodimeric cyclobutane natural products piperarborenine B (**1**; Figure 1a) and piperarborenine D (proposed structure, **2**) through a sequential cyclobutane C–H arylation strategy.[1,2] This approach led to both the concise preparation of these molecules (6–7 steps) and the structural reassignment of piperarborenine D (revised structure, **3**). While the piperarborenines are the simplest examples of heterodimeric cyclobutane natural products isolated from pepper plants, a number of other heterodimers have been isolated, and they all arise from a formal [2+2] cycloaddition of piperine-like monomers (**4**) having varying oxidation states and chain lengths.[3] Looking to extend our C–H functionalization strategy to more complex members of the family, our attention turned to the pipercyclobutanamides (**5** and **6**).

The pipercyclobutanamides were first isolated by Fujiwara and co-workers in 2001 from the fruits of the black pepper plant, *Piper nigrum*, though no biological activity was reported at that time.[3a] In 2006, Tezuka and co-workers reisolated pipercyclobutanamide A (**5**) and demonstrated a selective inhibition of cytochrome P450 2D6 (CYP2D6).[3c] These heterodimers represent a greater synthetic challenge than the piperarborenines (**1**,**3**) because of the presence of four different substituents on the cyclobutane ring. Both of these natural products contain an unusual *cis* unsaturated amide, and pipercyclobutanamides A (**5**) and B (**6**) contain styrene and styryl diene motifs, respectively. Viewing these molecules as an opportunity to develop cyclobutane C–H olefination chemistry, a synthetic strategy was devised and the retrosynthetic analysis of pipercyclobutanamide A (**5**) is shown in Figure 1b. First, the *cis* alkene is transformed into an aldehyde through a stereocontrolled olefination reaction. The aldehyde could then be deconstructed to a directing group (DG) and the amide into a methyl ester using standard functional group manipulations to provide intermediate **7**. Applying the strategy developed for the piperarborenines, this intermediate could be prepared through a series of epimerizations and $C_{sp^3}$–H functionalizations on the desymmetrized cyclobutane dicarboxylate **8**.

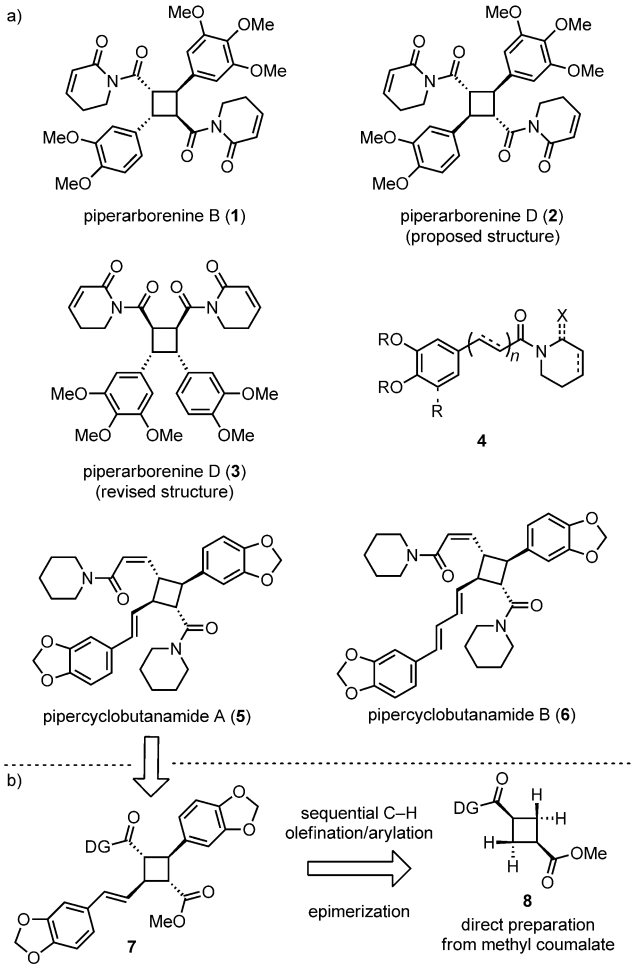


***Figure 1.*** a) Selected heterodimeric cyclobutane natural products. b) Retrosynthesis of pipercyclobutanamide A (**5**).

The direct olefination of $C_{sp^2}$–H bonds has been known since the seminal work of Fujiwara and Moritani in the late 1960s,[4] but few examples exist for the direct olefination of unactivated $C_{sp^3}$–H bonds.[5] During a study towards the teleocidin natural products, Sames and co-workers coupled an unactivated methyl group with a vinyl boronic acid, though the sequence proceeded through a discretely isolated palladacycle.[5e] The first catalytic example was reported in 2010 by Yu and co-workers.[5a] A highly electron-deficient anilide directing group was employed to couple acrylate derivatives directly to unactivated methyl and cyclopropyl C–H bonds. Chen and co-workers later reported the coupling of cyclic vinyl iodides with methylene C–H bonds using Daugulis' picolinamide directing group under palladium catalysis.[5d]

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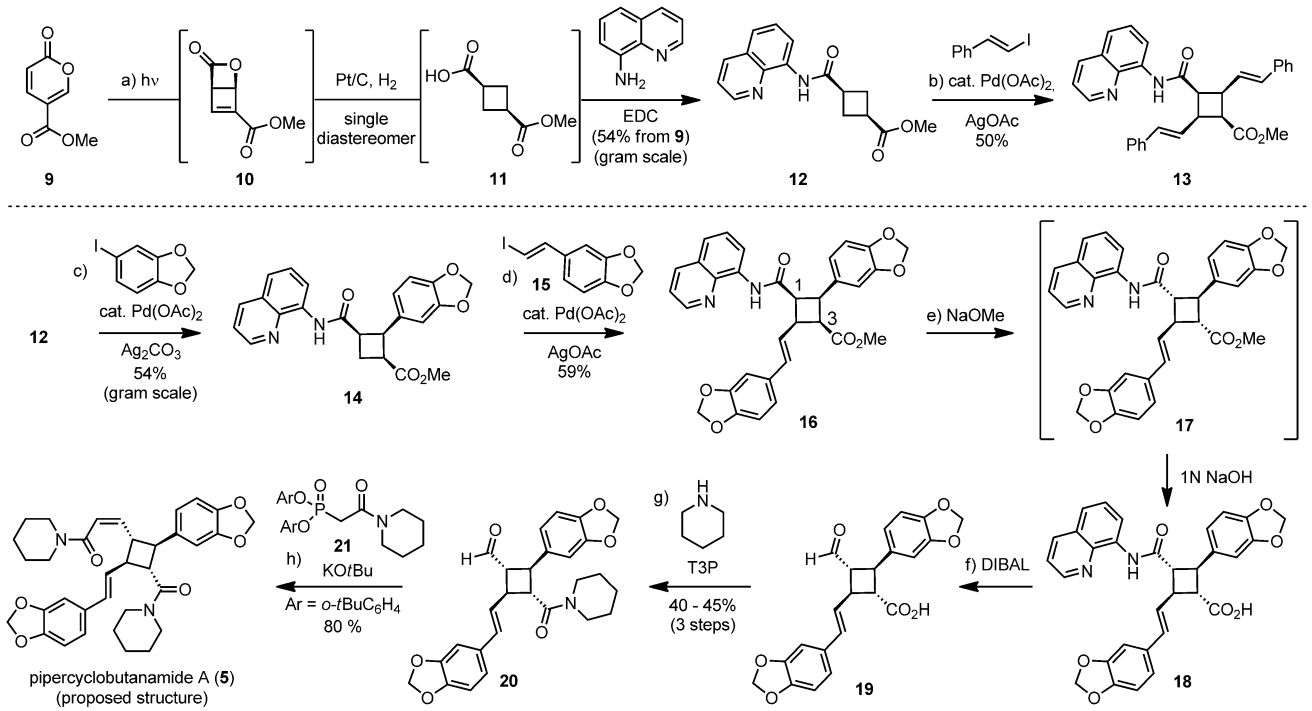
Encouraged by this result in particular, a styrenyl iodide was chosen as the first coupling partner to examine for the synthesis of pipercyclobutanamide A (**5**).[6]

Investigations started with the preparation of the requisite cyclobutane starting material **12** (Scheme 1). By applying the methodology developed previously for the piperarborenine natural products, methyl coumalate (**9**) underwent a photochemical 4π electrocyclization at reduced temperature to give the photopyrone **10**.[7] This unstable intermediate was immediately hydrogenated and coupled to 8-aminoquinoline[8] in a single operation to give the desired C–H olefination precursor **12** in 54% overall yield. The olefination reaction was initially studied with (2-iodovinyl)benzene as a model coupling partner. The use of reaction conditions originally developed for monoarylation [with hexafluoroisopropanol (HFIP) as the solvent and pivalic acid] resulted in low conversion and significant amounts of decomposition. Switching the solvent to toluene improved the reaction considerably to give the bis(olefinated) cyclobutane **13** as the major product in 50% yield. This result is in contrast to our previous work on the piperarborenines in which an epimerization event was required to allow an efficient second C–H functionalization on the cyclobutane ring. The reason for this direct bis(olefination) is unclear, but it may simply be that the vinyl iodide is smaller than the aryl iodide, thereby leading to a more facile second reaction. Furthermore, **13** is an all-*cis* cyclobutane that is quite strained and, to our knowledge, there are no other general methods for the controlled construction of this stereochemical array on a cyclobutane.

Given the modularity of this sequential C–H functionalization strategy, a monoarylation reaction could take place with a subsequent olefination reaction to reach the end goal. When the standard monoarylation conditions were applied to the reaction of cyclobutane **12** with 1-iodo-3,4-methylenedioxybenzene, poor conversion was observed as a result of the methylenedioxy ring (3,4-dimethoxyiodobenzene as a coupling partner performed well). Pivalic acid proved to be an effective additive, and when the reaction was performed in *t*BuOH at high concentration, an acceptable yield of **14** was obtained (54%, 1.00 g scale). Because of the facile double olefination observed in the preparation of **13**, the monoarylated **14** was directly subjected to the C–H olefination reaction with the styrenyl iodide **15**. Optimizing the reaction was straightforward, thus employing catalytic $Pd(OAc)_2$ in the presence of 1.5 equivalents of AgOAc with toluene as the solvent gave the all-*cis* cyclobutane **16** in 59% yield (480 mg scale). Pivalic acid as an additive retarded the reaction rate, and protic solvents such as *t*BuOH and HFIP were inferior, thereby giving low conversion and substantial decomposition, respectively.

With the sequential functionalization product **16** in hand, the relative stereochemistry needed to be altered to the all-




***Scheme 1.*** Total synthesis of the proposed structure of pipercyclobutanamide A (**5**). Reagents and conditions: a) 450-W Hanovia lamp, Pyrex filter, $CH_2Cl_2$, 15 °C, 96 h; then $H_2$, Pt/C, 4 h; then 8-aminoquinoline (1.2 equiv), EDC (1.2 equiv), 0 to 23 °C, 3 h, 54%. b) (2-iodovinyl)benzene (3.0 equiv), $Pd(OAc)_2$ (0.15 equiv), AgOAc (3.0 equiv), PhMe, 80 °C, 12 h, 50%. c) $Pd(OAc)_2$ (0.15 equiv), $Ag_2CO_3$ (1.0 equiv), PivOH (1.0 equiv), 1-iodo-3,4-methylenedioxybenzene (2.0 equiv), *t*BuOH, 85 °C, 15 h, 54%. d) **15** (2 equiv), $Pd(OAc)_2$ (0.15 equiv), AgOAc (1.5 equiv), PhMe, 80 °C, 10 h, 59%. e) NaOMe (2.0 equiv), MeOH/THF (1:4), 45 °C, 2 h, then 1 N NaOH, 1 h. f) DIBAL (3.5 equiv), THF, −78 °C, 0.5 h. g) piperidine (3.0 equiv), T3P (1.5 equiv), $CH_2Cl_2$, 23 °C, 15 min, 40–45% (3 steps). h) **21** (1.5 equiv), KO*t*Bu (1.5 equiv), THF, −78 °C to 0 °C, 2 h, 80%. DIBAL = diisobutylaluminium hydride, EDC = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, T3P = propylphosphonic anhydride, THF = tetrahydrofuran.

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*trans* configuration found in the natural product. This was anticipated to be a facile process given the strained nature of the all-*cis* stereochemistry and the thermodynamically downhill path to the desired all-*trans* product. Experimentally, this was verified through the use of two equivalents of sodium methoxide with C1 epimerization occurring rapidly at room temperature (< 1 min). Upon warming the reaction mixture to 45 °C, the methyl ester (C3) epimerizes over two hours and fully hydrolyzes after the addition of aqueous sodium hydroxide to give acid **18**. Without further purification, **18** was treated with excess DIBAL to transform the aminoquinoline directing group directly into an aldehyde. By employing the free carboxylic acid in this reaction, the correct oxidation state found in the natural product is maintained with the carboxylate anion acting as an innate protecting group.[9] Additionally, the direct reduction of secondary amides to aldehydes with DIBAL has limited precedent, and the success of this reaction is likely the result of the chelating nature of the aminoquinoline motif.[10] Furthermore, this presents a new method for the cleavage of this amide directing group and avoids the extremes of pH and heat, thus expanding the synthetic utility of the Daugulis methodology[6, 8a] if found to be general. Moving forward with the crude aldehyde **19**, piperidine was used as both a base and a coupling partner in the reaction with T3P to provide amide **20** in 40–45% yield upon isolation after three steps (114–386 mg scale).

To complete the synthesis of pipercyclobutanamide A (**5**), only an olefination reaction remained. This transformation was accomplished through the use of Ando's methodology for *cis*-selective unsaturated amide synthesis.[11] Treatment of the aldehyde **20** with the Ando phosphonate (**21**) in the presence of *t*BuOK resulted in an approximately 5:1 *cis*/*trans* mixture of easily separable olefin isomers, thus giving the desired pipercyclobutanamide A (**5**) in 80% yield upon isolation (100 mg scale). Unfortunately, the $^{1}H$ and $^{13}C$ NMR data did not match the spectrum reported for the natural product.[12]

The concise synthesis of the proposed structure of pipercyclobutanamide A (**5**) further demonstrates the power of C–H functionalization logic in synthesis to provide substantial amounts of complex cyclobutanes (7 steps, 5 chromatographic purifications, 5% overall yield, > 100 mg prepared). The sequence features mostly skeleton-forming transformations, is protecting-group-free,[13] and has only one concession step (DIBAL reduction) leading to an ideality of 85%.[14] Salient features of the synthesis include: 1) the first example of C–H olefination on an unactivated cyclobutane ring; 2) stereocontrolled access to highly strained all-*cis* cyclobutanes; 3) direct conversion of aminoquinoline amides directly to aldehydes; and 4) the use of a carboxylate anion as an innate protecting group in an amide reduction.

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# Communications

## Natural Products

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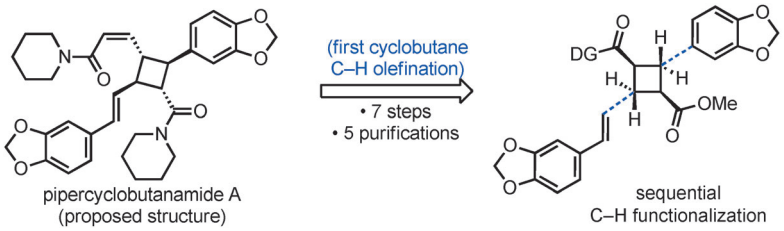
Sequential $C_{sp^3}$–H Arylation and Olefination: Total Synthesis of the Proposed Structure of Pipercyclobutanamide A




**Hip to be square**: A strategy for assembling tetrasubstituted cyclobutanes is reported in the context of a short, protecting-group-free synthesis of the proposed structure of pipercyclobutanamide A. The route features sequential C–H functionalizations on an unactivated cyclobutane wherein C–C bonds to aryl and styrenyl groups are made one by one in a stereocontrolled fashion. DG = directing group.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