Total Synthesis

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Total Synthesis and Structural Revision of the Piperarborenines: When Photochemistry Meets C–H Activation**

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C–H activation · cyclobutanes · photochemistry · piperarborenines · total synthesis

The piperarborenines, isolated from the stems of the creeping shrub *Piper arborescens*,[1] are members of a class of quasi-dimeric monoterpene alkaloids characterized by a tetrasubstituted cyclobutane ring. Closely related to the piperarborenines, but structurally more complex, is the incarvillateine family of natural products,[2] in which the dihydropyridone is replaced by an elaborate bicyclic piperidine moiety containing five contiguous stereocenters (Figure 1). Interestingly, structure–activity relationship studies performed on **3** and derivatives thereof suggest that the cyclobutyl moiety plays a crucial role in the expression of biological activity.[3]

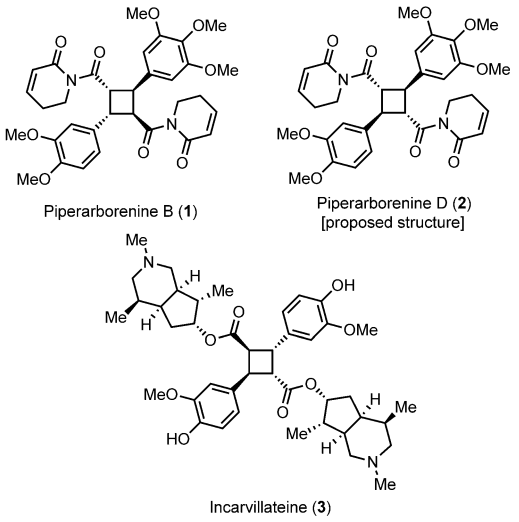
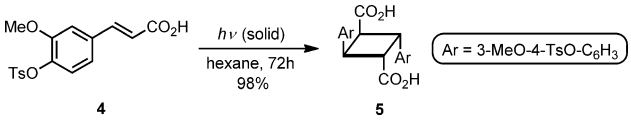


Figure 1. Structures of the piperarborenines and incarvillateine.

In 2004, Kibayashi et al. described the first enantioselective total synthesis of (−)-incarvillateine (**3**).[4] A few years later, Bergman and Ellman,[5] as well as Jia and co-workers,[6] reported independent total syntheses using a similar approach to construct the cyclobutane core. The synthetic focus of these different strategies was placed on the assembly of the bicyclic alkaloid moiety, whilst the construction of the tetrasubstituted cyclobutane ring relied on Kibayashi's elegant topochemical [2+2] photodimerization of the ferulic acid derivative **4** (Scheme 1).[4] Key to the success of this strategy was the realization that subtle structural factors, at loci as remote from the reactive center as the oxygen substituents in the aryl moiety of **4** (cf. tosyl substituent), can have a dramatic impact on the crystal packing arrangement and thus on the outcome of the photodimerization process.[4]



Scheme 1. Kibayashi's topochemical [2+2] photodimerization of ferulic acid derivative **4**.[4]

While this topochemical [2+2] photodimerization approach is a very powerful tool for the synthesis of symmetrical cyclobutanes such as incarvillateine (**3**), several issues arise when two distinct olefins are brought together, including homodimerization, orientation (head-to-head versus head-to-tail) and double-bond isomerization.[7] Nonsymmetrical targets, such as the piperarborenines, thus pose significant hurdles to such a strategy. In spite of remarkable advances in crystal engineering and solid-state photochemistry, which have provided elegant routes towards stereodefined cyclobutanes,[8] photo-heterodimerizations of alkenes are still rare.[9]

Recently Baran et al. described a strategy to circumvent those limitations and access unsymmetrical cyclobutane natural products, based on an innovative metal-catalyzed C(sp^3)–H functionalization of cyclobutanes.[10] The state-of-the-art work of Daugulis and co-workers in the cross-coupling reaction of C(sp^3)–H bonds with aryl iodides[11] inspired Baran and Gutekunst to prepare the piperarborenines by

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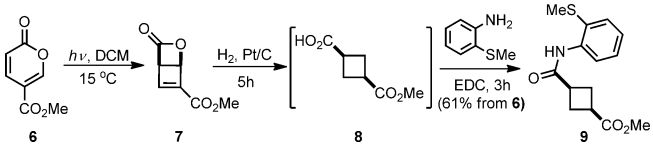
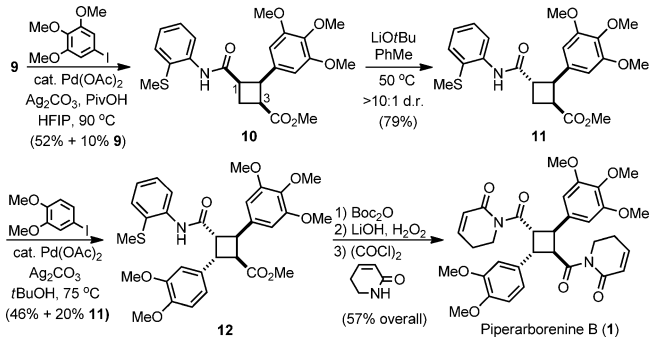
means of two sequential, unprecedented cyclobutane C–H arylations directed by suitable pre-existing carboxylate functionality.

The synthetic pathway to the 1,3-dicarboxylate cyclobutane **8** exploited commercially available methyl coumalate **6** and required only two steps to reach the desired intermediate as a single diastereoisomer (Scheme 2). This expeditious one-pot sequence involves a photochemical 4π-electrocyclization of **6** to give the bicyclic lactone **7**,[12] followed by two successive reductions by hydrogenolysis. Subsequent introduction of a directing group, 2-aminothioanisole, set the stage for C–H activations of cyclobutane **9**. This directing group has comparable efficiency to the most widely employed 8-aminoquinoline, whilst being easier to hydrolyze.[11b] After extensive optimization of the reaction conditions, 3,4,5-trimethoxyiodobenzene was coupled with a C–H bond of amide **9** in the presence of a catalytic amount of palladium(II)acetate to give the trisubstituted cyclobutane **10** in moderate yield (Scheme 3). The all-*syn* selectivity that results from the stereodirecting effect of the aromatic amide as well as the almost complete absence of overarylation products are distinctive features of this impressive transformation.



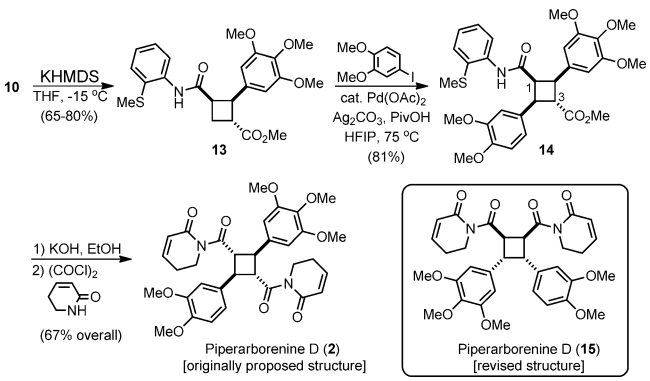
Scheme 2. Synthesis of cyclobutane precursor **9** for C–H activations. DCM = dichloromethane, EDC = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide.



Scheme 3. Total synthesis of piperarborenine B (**1**). Boc = *tert*-butyloxycarbonyl.

The addition of both hexafluoroisopropanol (HFIP) and pivalic acid was found to play a crucial role in the course of the reaction.[13] Selective epimerization of **10** at C-1 using LiO*t*Bu in toluene gave predominantly the desired cyclobutane **11**, which was further arylated with 3,4-dimethoxyiodobenzene under conditions similar to those previously employed (interestingly, HFIP and PivOH no longer provided any beneficial effects for this C–H arylation). The total synthesis of piperarborenine B (**1**) was completed after three further steps, including simultaneous amide and ester hydrolysis,[14] followed by conversion of the resulting dicarboxylic acid to the diimide.

In a similar fashion, the route to piperarborenine D (**2**) began with selective epimerization at C-3 of the common intermediate **10** using KMHDS as a base (Scheme 4). The remarkable selectivity afforded by diverse bases for the epimerization of different acidic stereocenters is noteworthy and probably results from the ability propensity (or not) of each base to generate an amide N-bound anion. The resulting diastereomerically pure cyclobutane **13** underwent a second C–H arylation with 3,4-dimethoxyiodobenzene, and again HFIP and PivOH were found to be critical additives. Treatment of **14** with KOH in refluxing EtOH effected complete epimerization at C-1 as well as full hydrolysis to the dicarboxylic acid, which was then converted to the originally proposed structure of piperarborenine D (**2**) by coupling with dihydropyridone.

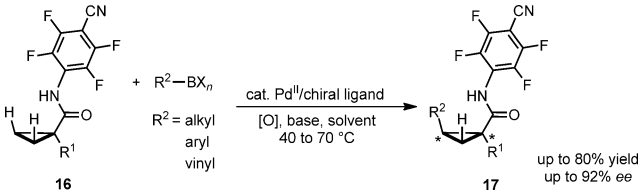


Scheme 4. Total synthesis and structural revision of piperarborenine D (**15**). KHMDS = potassium hexamethyldisilazide.

Owing to inconsistencies between the ^{1}H and ^{13}C NMR spectra of synthetic piperarborenine D (**2**) and the literature data,[1a] the authors proposed a revised unsymmetrical head-to-head type dimer structure for this natural product (**15**). This newly proposed structure was confirmed by chemical synthesis, which was achieved through intramolecular [2+2] photocycloaddition of a mixed cinnamic anhydride. Cyclobutane **15** displayed spectroscopic properties fully in accord with those published.

The first pivotal operation in Baran's total synthesis of the piperarborenines is the very concise access to 1,3-dicarboxylate cyclobutane **8**, showcasing the power of pyrone photochemistry to deliver four-membered-ring products in stereodefined and atom-economical fashion. The innovative use of sequential, programmed cyclobutane C–H activations is the crux of this synthetic approach. Various aspects of these C–H functionalization steps merit further comment. First: the ability of the directing group (combined with additives) to activate exclusively one methylene group during the first arylation reaction and the preference for C–H insertion into the methylene group over the tertiary benzylic C–H bond in the second C–H arylation, which are both striking. Second: the particularly high yield of the coupling giving **14** (compare with the analogous preparation of **10** and **12**), which is

probably a consequence of stereoelectronically unfavorable effects by the β-disposed C-3 ester moiety. Third: the synthetically useful yields achieved in those C–H arylations which, though perhaps modest (ca. 50 % in two cases) from an absolute point of view, accompany spectacular increases in complexity en route to the natural product targets. It is the latter point which perhaps best defines the promise and challenge of C–H functionalization methodologies, which are clearly at a stage ripe for synthetic applications, but still allowing room for further development and discovery. In particular, the achievement of the Baran group along with another recent report by Yu et al. suggest that the use of a cyclic rigid template, in the form of a cyclopropane (Scheme 5)[15] or cyclobutane ring, to enforce selective C–H manipulation is a strategy with considerable potential in synthesis.



Scheme 5. Yu's C–H activation of cyclopropanes.[15]

This remarkable sequential C(sp^3)–H arylation approach to cyclobutane natural products certainly paves the way for future exploitation and raises the exciting possibility of the modular assembly of diverse analogues for biological testing.

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