Concise Synthesis of Piperarborenine B

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This article is in honor of Professor Herbert Waldmann on the occasion of his retirement and for his outstanding contributions in chemistry and biology.

A concise synthesis of piperarborenine B is reported. Organocatalytic electrophilic amination of pyrrolidines, stereospecific oxidative ring contraction and an original diastereoselective Krapcho dealkoxycarbonylation/ transmethylation contribute to a novel synthetic strategy to the preparation of a non-symmetrical cyclobutane core. Being transition-metal-free, directing-group-free and protecting-group-free, a five-step synthesis of piperarborenine B was accomplished.

Number of natural products containing cyclobutane have been isolated and identified as bioactive[1-3]. The synthesis of these bioactive compounds has become an active research area,[4-9] which could provide materials for biological investigation (**Figure 1A**). Recently, novel and elegant synthetic methods have been developed enabling the efficient synthesis of cyclobutanes with different substitution patterns under stereocontrol.[10-13] For instance, intermolecular [2+2] cycloadditions provide numerous non-symmetrical cyclobutane scaffolds,[14, 15] which are prevalent in natural products. Alternatively, the non-symmetrical cyclobutane core of natural products could be prepared by synthetic methods such as radical cyclization[16-18] and 1,2-rearrangment reactions[5, 6, 19, 20].

Piperarborenine B (**6**) is a cytotoxic natural product isolated from *Piper arborescens* and exhibits *in vitro* cytotoxicity against P-388, HT-29, and A549 cancer cell lines (IC_{50} < 4 μg/mL).[21] Structurally, piperarborenine B (**6**) possesses a non-symmetrical truxillate core, which is likely to be a result of head-to-tail hetero-[2+2] cycloaddition *via* bio-inspired synthesis[22, 23] (**Figure 1B**). However, the direct synthesis of piperarborenenine B (**6**) making use of intermolecular hetero-[2+2]-cycloaddition of substrate **4** and piperlongumine (**5**) remains elusive. Meanwhile, several elegant protocols for the preparation of piperarborenine B (**6**) were disclosed, concomitantly featuring the palladium-catalyzed secondary C(sp^3)-H arylation as a synthetic key step for the installation of aryl substituents[24-26] (**Figure 1C**). Noteworthy, the facial selectivity of the arylation is determined by the stereochemistry of the directing group and thus gives a *cis*- product. [24-29] Recently, the non-symmetrical truxillate core of piperarborenine B (**6**) was prepared by our group using stereoselective ring contraction of pyrrolidine[30] (**Figure 1D**). The relatively low yield (24%) of the ring contraction of pyrrolidine containing electron-rich arene subsitutent(s) prompted us to develop an improved protocol, enabling a concise synthesis of piperaborenine B (**6**) and its congeners for further biological investigation. In this work, we report a concise, protecting-group-free synthesis of piperaborenine B (**6**) from known pyrrolidine **7**.[30] A two-step ring contraction procedure to synthesize the multi-substituted cyclobutane, featuring an unprecedented organocatalytic electrophilic amination of pyrrolidine followed by oxidative C-C bond formation *via* nitrogen extrusion, was reported. More importantly, an original diastereoselective Krapcho dealkoxycarbonylation/transmethylation assisted by carboxylic acid was investigated. The resultant *trans*-1,3-*di*-carboxylate attributes to the non-symmetrical cyclobutane core, that is present as key structural feature in many bioactive cyclobutane natural products.

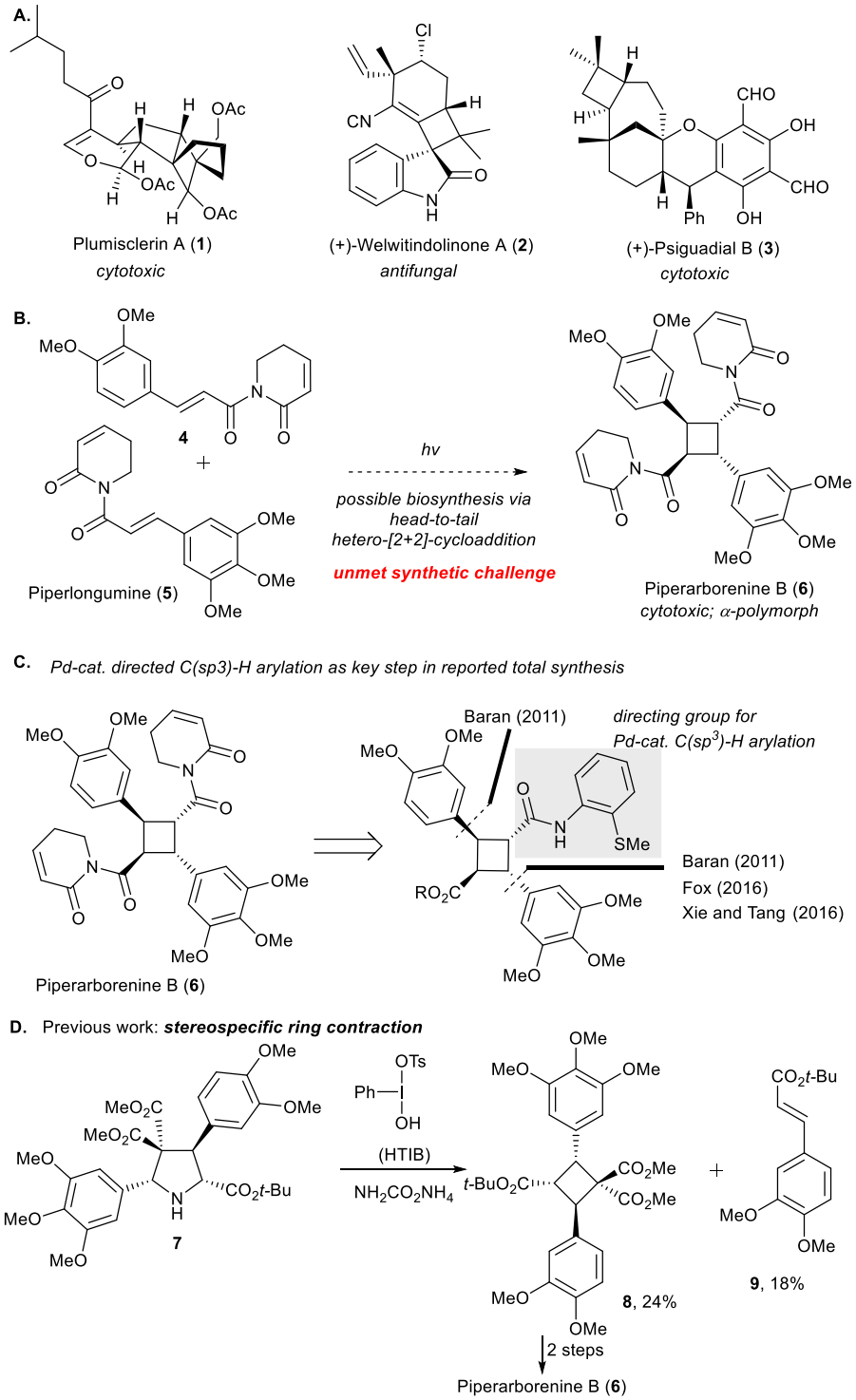
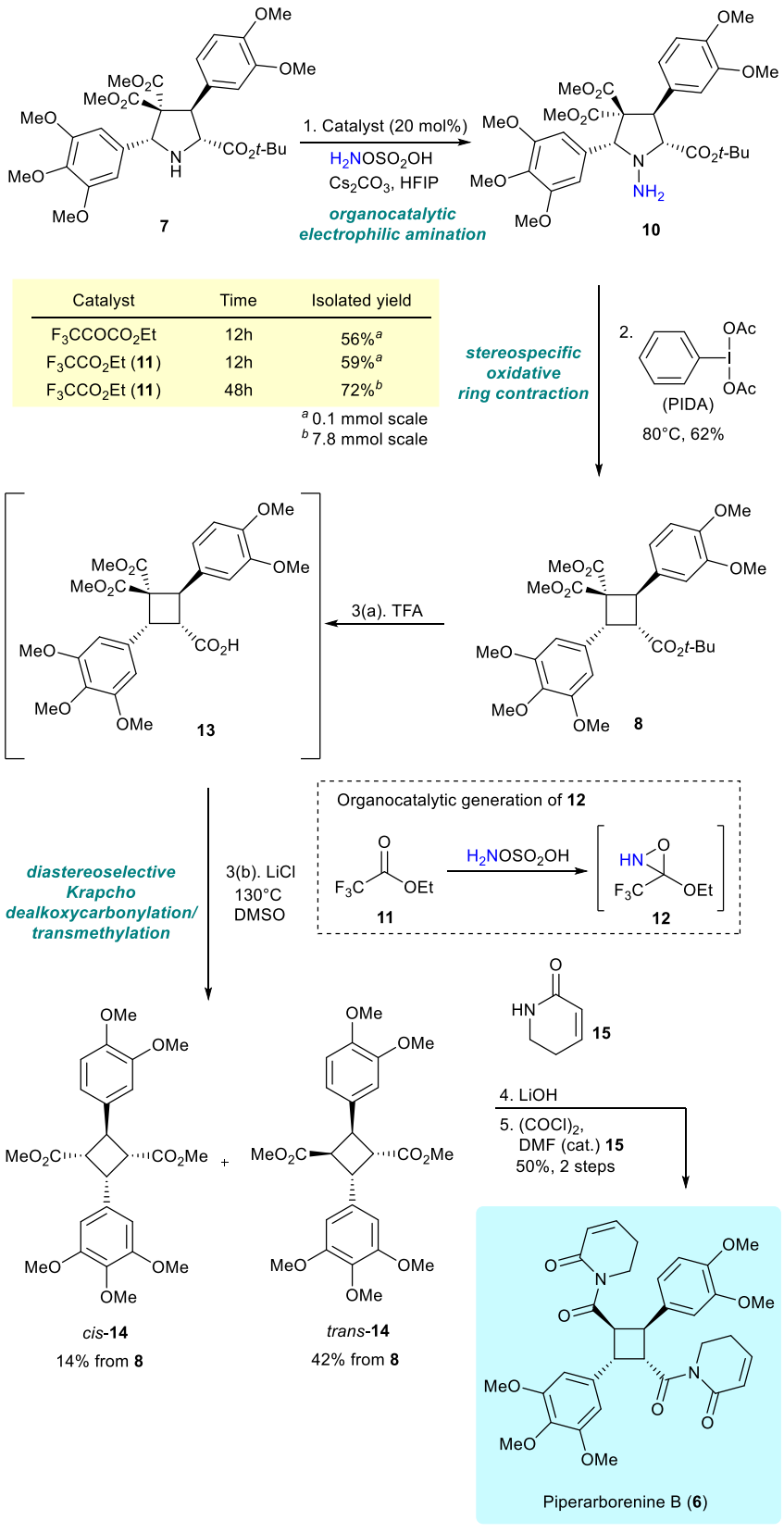


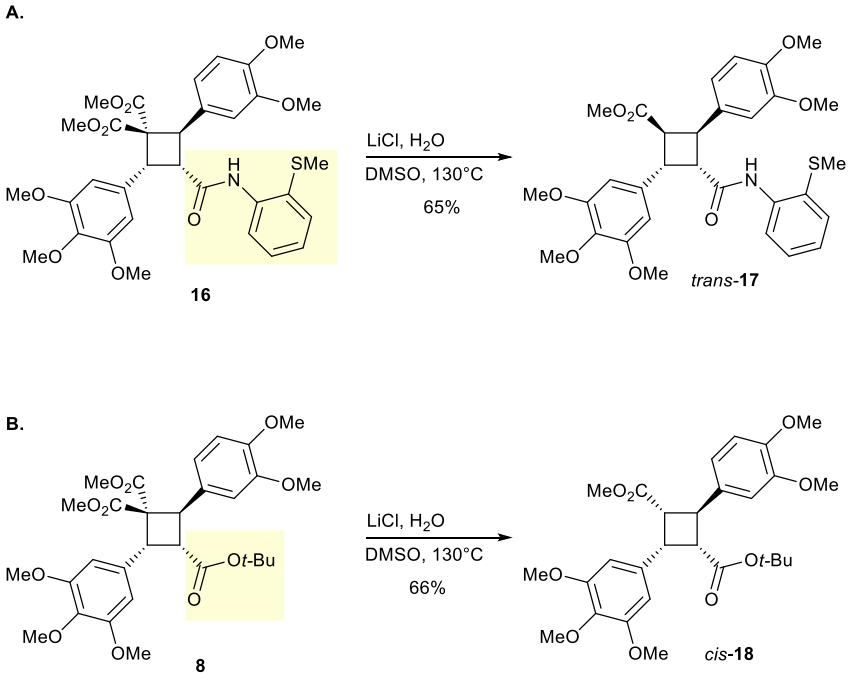
Figure 1. (A) Bioactive natural products containing non-symmetric cylcobutane core. (B) Proposed biosynthesis of piperarborenine B (**6**). (C) Reported total syntheses of piperarborenine B (**6**) featuring Pd(II)-cat. secondary C(sp^3)-H arylation as key reaction. (D) Previous work on stereoselective ring contraction.

Our concise synthesis of piperarborenine B (**6**) is illustrated (**Scheme 1**) and based on the application of the known[31], by [2+3]-cycloaddition straightforwardly accessible pyrrolidine **7**. Inspired by the seminal report of organocatalytic nitrogen transfer to unactivated olefins by Kürti and co-workers,[32] we conceptualized that electrophilic amination[33] of pyrrolidine could be realized by the Kürti's chemistry. Gratifyingly, using Kürti's optimized conditions for electrophilic amination of olefin with 20 mol% of ethyl trifluoropyruvate as catalyst[32] facilitated the electrophilic amination of pyrrolidine **7** to give *N*-aminopyrrolidine **10** in 56% yield. When the more routine reagent ethyl trifluoroacetate (**11**) was used as catalyst, *N*-aminopyrrolidine **10** was formed in comparable yield (i.e. 59%). Scaling up from 0.1 mmol to 7.8 mmol, the yield was improved to 72% when increasing the reaction time to 48h. Compared to the traditional *N*-nitrosylation/reduction protocol of electrophilic amination of pyrrolidines using stoichiometric amounts of zinc as reductant, this method not only circumvents the use of metal but also prevents the over-reduction of the *N*-nitroso group by zinc.[34] Next, treatment of *N*-aminopyrrolidine **10** with PIDA resulted in a stereospecific oxidative ring contraction to give cyclobutane **8** in 62% yield. This organocatalytic electrophilic amination/stereospecific oxidative ring contraction sequence showed a significant improvement of yield from pyrrolidine **7** to cyclobutane **8**, which complements well with the one-step protocol for contractive synthesis for cyclobutanes from electron-rich substituent-containing pyrrolidines.



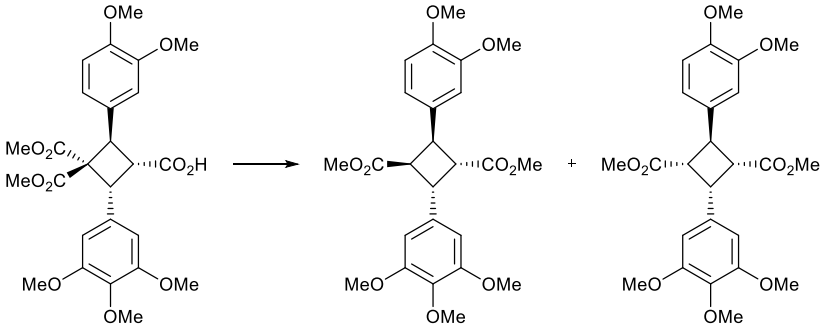
Scheme 1. Concise synthesis of piperarborenine B (**6**)

After the cleavage of the *tert*-butyl group of **8** by TFA, the carboxylic acid **13** formed was subjected to a novel carboxylic acid-assisted diastereoselective Krapcho dealkoxycarbonylation/transmethylation which provided *trans*-**14** and *cis*-**14** in 42% yield and 14% yield, respectively (**Scheme 1**). The symmetrical *cis*-**14** resulted in a single peak for the two methyl ester group (3.42 ppm (s, 6H)) in the ^{1}H NMR. On the other hand, the unsymmetrical *trans*-**14** showed two different chemical shift of the two methyl ester groups with 3.40 and 3.36 ppm. This is the first report of a carboxylic acid assisted selective decarboxylation followed by transmethylation leading to the formation of a non-symmetrical cyclobutane core. However, the product of diastereoselective Krapcho dealkoxycarbonylation of **13** without transmethylation was not identified. Despite the moderate yield, the resultant diester *trans*-**14** could be hydrolyzed to give the corresponding dicarboxylic acid for the synthesis of piperarborenenine B (**6**) without extra step. A detailed investigation of this unprecedented synthetic transformation was carried out (**Scheme 2** and **Table 1**). Diastereoselective Krapcho dealkoxycarbonylation of **16** to give non-symmetrical cyclobutane *trans*-**17** was reported by Xie, Tang and coauthors in 2016,[26] in which the (2-thiomethyl)anilide group acts as a directing group in the prior step of palladium-catalyzed secondary C(sp^3)-H arylation reaction (**Scheme 2A**). Our studies applied the same strategy to construct the *trans*-isomer.[30] Replacing the (2-thiomethyl)anilide group on **16** with *tert*-butyl ester **8** gave the undesired *cis*-1,3-carboxylate (*cis*-**18)** in 66% yield as exclusive product (**Scheme 2B**). This observation is aligned with our proposal that (2-thiomethyl)anilide group acts as a proton donor leading to the formation of the desired *trans*-**17** *via* intramolecular proton transfer.



Scheme 2 (A) Reported diastereoselective Krapcho dealkoxycarbonylation affording *trans*-1,3-dicarboxylate using (2-thiomethyl)anilide as proton donor. (B) *tert*-Butyl ester providing *cis*-1,3-dicarboxylate as exclusive Krapcho dealkoxycarbonylation product.

A systematic optimization to improve the selectivity of Krapcho dealkoxycarbonylation/transmethylation was conducted (**Table 1**). Applying the standard conditions of Krapcho dealkoxycarbonylation (i.e. 10 equiv. of LiCl, 10 equiv. of H_2O in DMSO, 130^{O}C)[26] to carboxylic acid **13** gave a 1:1 mixture *trans*-**14** and *cis*-**14** in 39% yield (entry 1). Meanwhile, an earlier report of carboxylic acid-assisted diastereoselective Krapcho dealkoxycarbonylation of tetrahydrofuran by Johnson and co-workers used potassium acetate as base, generating a 1,2-*trans* carboxylic acid-methyl carboxylate in the synthesis of (+)-virgatusin.[35] Enlightened by this protocol, the same conditions were applied but no product was formed while starting material was almost recovered (entry 2). Next, the variation of the base used for Krapcho dealkoxycarbonylation did not give the desired product (entries 3-4). The above experiments showed that the chloride ion may play a crucial role in the process of dealkoxycarbonylation.[36] We wondered about the potential outcome when hydrogen chloride was used instead of chloride salt. Unfortunately, the use of 37% hydrochloric acid solution without addition of water led to decomposition of the starting material (entry 5).



Entry	Condition	Product/SM recovered[c]
1	LiCl (10 eq.), H_2O (10 eq.), DMSO, 130°C, 12h[a]	*trans*-**14** + *cis*-**14** (39%, 1:1) / n.d.
2	KOAc (2 eq.), DMSO:H_2O (20:1 v:v), 100°C, 16h[b]	n.d. / 95%
3	NaCN (10 eq.), H_2O (10 eq.), DMSO, 130°C, 12h[a]	n.d. / n.d [d]
4	LiF (10 eq.), H_2O (10 eq.), DMSO, 130°C, 12h[a]	n.d./ 66%
5	37% HCl (10 eq.), DMSO, 130°C, 12h[a]	n.d./n.d [d]
6	LiCl (10 eq.), DMSO, 130°C, 8h[b]	*trans*-**14**, 42%, + *cis*-**14**, 14% / n.d.

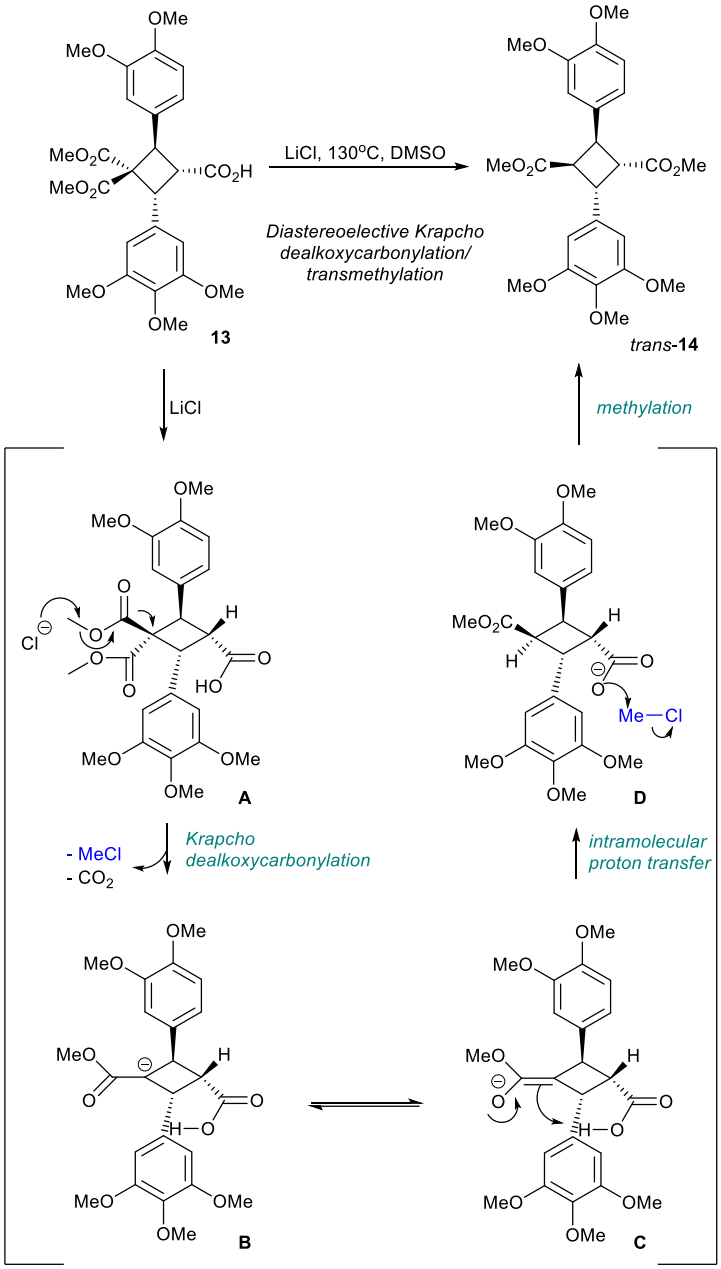
Table 1. Optimization of the diastereoselective Krapcho dealkoxycarbonylation/transmethylation reaction. [a]0.1 mmol scale. [b]0.2 mmol scale. [c]isolated yield. [d]Decomposition. n.d. denotes not detected.

Typically, water protonates the anionic intermediate formed from Krapcho dealkoxycarbonylation to complete the reaction. Diastereoselective Krapcho dealkoxycarbonylation could be the result of intramolecular proton transfer from the sterically bulk (2-thiomethyl)anilide group as proton donor in the presence of water to give *trans*-**17** as exclusive product (*see* **Scheme 2A**). Considering the relatively less bulky carboxylic acid group, we hypothesized that the formation of the undesired *cis*-**14** is due to the protonation of water, that is, intermolecular protonation of the generated anion by protonated solvent (i.e. water) competes with the intramolecular protonation by the proton donating group. Moreover, the good atom economy[37] of this transformation, only with the loss of a CO_2, hints that an external proton donor (i.e. water) may not be necessary. To validate this hypothesis, no water was added and the *trans*-**14** and *cis*-**14** was isolated in 42% and 14%, respectively (entry 6). The significant improvement of product ratio of *trans*-**14** to *cis*-**14** from 1:1 to 3:1 (entry 1 versus entry 6) reveals that excessive amount of water led to the formation of *cis*-**14** as a result of intermolecular protonation. However, we cannot exclude the possibility that *trans*-**14** could be formed in this process. Regarding the process of methylation of carboxylic acid

to give *trans*-**14**, the methyl esters on **13** appear to be the only source of methyl groups. The direct transmethylation from the methyl ester group to the carboxylic acid on **13** is ruled out because *cis*-**18** product formed exclusively without the presence of carboxylic acid as intramolecular proton donor (*see* **Scheme 2B**).

A possible reaction mechanism is proposed (**Scheme 3**). Since *trans*-**14** is the major product, the sequence of events could be carboxylic acid-assisted Krapcho dealkoxycarbonylation of **13** to give **A**, intramolecular proton transfer (i.e. **B** to **D**) and subsequent methylation of the resultant carboxylate **D** by methyl chloride affords *trans*-**14** as product. Successive hydrolysis of ester groups on *trans*-**14** to the corresponding dicarboxylic acid, conversion to acyl chloride and amidation with fragment **15** afforded piperarborenin B (**6**) in 50% yield over two steps (**Scheme 1**).

In summary, a concise synthesis of piperarborenine B (**6**) was accomplished featuring an unprecedented organocatalytic electrophilic amination of pyrrolidine/stereospecific oxidative ring contraction as synthetic key step to prepare multi-substituted cyclobutanes. Moreover, a novel diastereoselective Krapcho dealkoxycarbonylation/transmethylation provides non-symmetrical cyclobutane *trans*-**14** possessing the desired stereochemistry. Furthermore, abstention from the use of directing group[38, 39] and protecting group chemistry[40, 41], which are neither economical nor biomimetic, greatly improved the overall efficiency of the synthesis. Our synthetic strategy enables the efficient assembly of the unsymmetrical cyclobutane core of piperarborenine B, enlightening the preparation of cyclobutane natural products with relevant stereochemistry. We envision that the synthetic strategy reported here could inspire the future preparation of non-symmetrical cyclobutane natural productsand its analogues, thus offers the opportunity to access new libraries of chemical space for drug development.



Scheme 3. Proposed mechanism of diastereoselective Krapcho dealkoxycarbonylation/ transmethylation

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Conflicts of interest

There are no conflicts to declare.

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