

Stereoselective Preparation of Cyclobutanes with Four Different Substituents: Total Synthesis and Structural Revision of Pipericyclobutanamide A and Piperchabamide G**

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Four-membered rings are important structural motifs frequently present in bioactive natural products and pharmaceutical agents.^[1] Pipericyclobutanamides, piperchabamides, nigramides, and dipiperamides (Figure 1) are tetrasubstituted cyclobutanes isolated from *Piper nigrum* and *Piper chaba*, the source of white and black pepper and components of traditional medicines.^[2–7] Isolation of various polyene precursors and stereoisomeric cyclobutanes from these *Pipers* suggested that the four-membered rings might be derived from non-selective photolytic [2+2] cycloaddition of alkenes. Cyclobutanes isolated from *Piper nigrum* and *Piper chaba* have broad pharmacological activities.^[5–7] For example, pipericyclobutanamide A (**1**) and dipiperamide E (**6**) are selective inhibitors for CYP2D6 and CYP3A4, respectively, the two main P450s responsible for drug metabolism.^[4,7] Piperchabamide G, isolated in 2009, inhibits D-GalN/tumor necrosis factor- α -induced death of hepatocytes and has hepatoprotective effect.^[6]

Among dozens of pipericyclobutanamides, piperchabamides, nigramides, and dipiperamides, only the symmetric achiral dipiperamide A (**5**) has been synthesized.^[8,9] The originally proposed structure **4** for dipiperamide A^[3] was revised to **5** after the synthesis reported by Kibayashi and co-workers.^[9] A solid-state [2+2] photolytic homodimerization was employed by Kibayashi to construct the four-membered ring with center symmetry. Extensive optimization was conducted for the crystallization of ferulic acid derivatives to obtain the α -form crystal,^[8] which was required for the regio- and diastereoselective photolytic homodimerization. Bergman and Ellman, and Zhang and Jia used the same protocol to prepare the symmetric cyclobutane core of

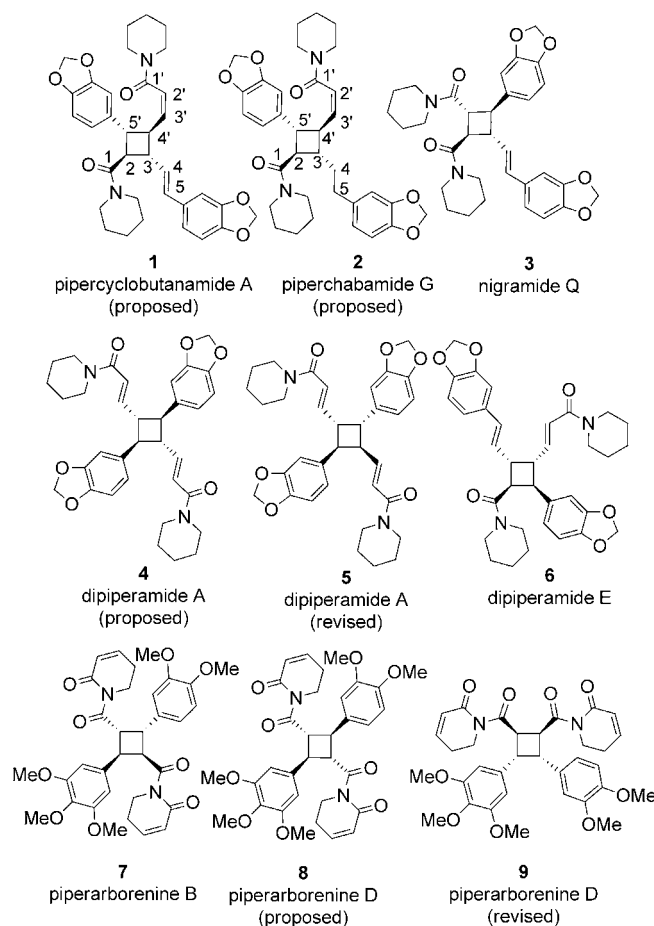


Figure 1. Selected four-membered ring natural products.

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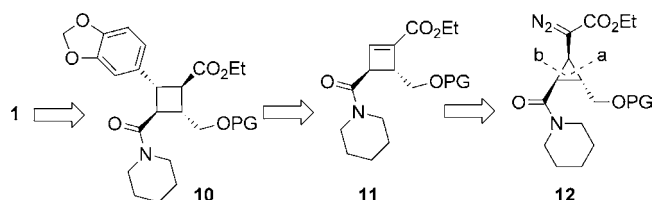
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incarvillateine.^[10] The [2+2] cycloaddition has been the main strategy for the synthesis of four-membered ring natural products^[11] with a few exceptions.^[12] However, it remains a demanding synthetic challenge to prepare unsymmetrical cyclobutanes from heterodimerization of two olefins with high chemo-, regio-, diastereo-, and enantioselectivity.^[13]

Recently, an elegant sequential cyclobutane C–H arylation strategy was developed by Gutekunst and Baran for the diastereoselective synthesis of pseudosymmetric cyclobutanes such as piperarborenine B (**7**) and the proposed structure of piperarborenine D (**8**).^[14] The originally proposed structure **8**^[5] for piperarborenine D was revised to structure **9** after the synthesis from Gutekunst and Baran. Herein we report our strategy for diastereo- and enantioselective introduction of

four different substituents onto cyclobutanes in the context of the total synthesis of the proposed structures of pipericyclobutanamide **1** and piperchabamide **2**. We also propose revised structures for these two natural products.^[15]

We envisioned that both pipericyclobutanamide **1** and piperchabamide **2** could be derived from tetrasubstituted cyclobutane **10** (Scheme 1). The ester and protected primary hydroxy group in intermediate **10** would serve as aldehyde precursors which could be unmasked at different stages for

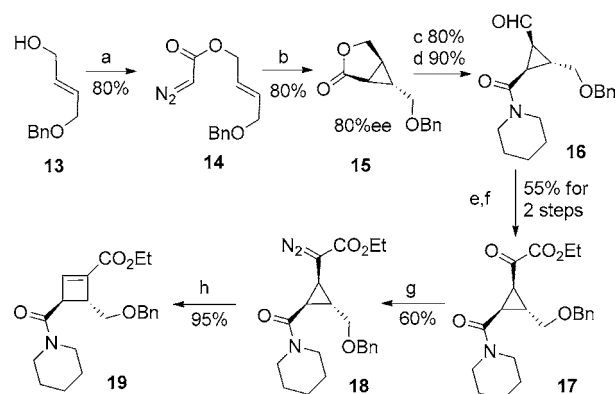


Scheme 1. Proposed strategy for stereoselective synthesis of pipericyclobutanamide **1** and piperchabamide **2**. PG = protecting group.

olefination. Conjugate addition of an aryl group to the cyclobutenolate **11** may provide the tetrasubstituted cyclobutane **10**. The aryl group should approach the four-membered ring from the α face to avoid steric interactions with the adjacent amide substituent. The cyclobutenolate **11** could be prepared from cyclopropane **12** according to a ring expansion method we recently developed.^[16,17] This reaction involved a cyclopropyl metal carbene intermediate derived from the transition-metal-catalyzed decomposition of diazo compounds. We have demonstrated that the ring expansion is stereospecific and regioselective. The regioselectivity is dependent on the substituents of the cyclopropane ring and the choice of catalysts. The cyclopropane C–C bond that is adjacent to the electron-donating group or away from the electron-withdrawing group could be selectively cleaved when a silver(I) catalyst was employed.^[16a] In the case of cyclopropane **12**, we expected that bond **a** would be selectively cleaved over bond **b**. This proposal represents a general and unique strategy for the diastereo- and enantioselective synthesis of unsymmetrical cyclobutanes having four different substituents.

Our synthesis began with the preparation of the diazo compound **14** from the monoprotected diol **13** (Scheme 2).^[18] The bicyclic lactone **15** was obtained by diastereo- and enantioselective intramolecular cyclopropanation of a *trans*-olefin using the chiral $[\text{Rh}_2(5\text{S-MEPY})_4]$ catalyst.^[19] Opening of the lactone with piperidine and subsequent oxidation afforded the trisubstituted cyclopropane **16**, which was then converted into the diazo compound **18** through ketoester intermediate **17** in three steps according to procedures we have previously established.^[16a] Treatment of **18** with a catalytic amount of AgOTf indeed yielded the cyclobutenolate **19** as a single isomer.

With cyclobutenolate **19** in hand, we then turned our attention to the conjugate addition of an aryl nucleophile to this enolate. Under various reaction conditions, we were not able to add an aryl cuprate reagent to **19**. We were pleased to find that the tetrasubstituted cyclobutanes **20** and **21** could be



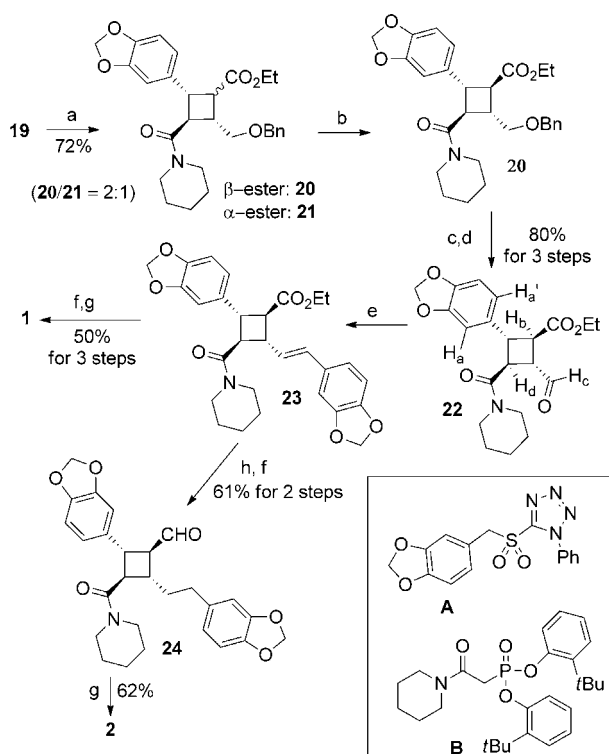
Scheme 2. Stereoselective synthesis of cyclobutenolate. Reagents and conditions: a) Bromoacetyl bromide then TsNHNHTs, DBU. b) 1.0 mol % $[\text{Rh}_2(5\text{S-MEPY})_4]$, CH_2Cl_2 , reflux. c) piperidine, AlMe_3 , CH_2Cl_2 , 0°C to RT, 20 h. d) DMSO, $(\text{COCl})_2$, Et_3N , –78°C, 2 h. e) NaCN, HOAc, MeOH then EtOH/HCl (4 M in 1,4-dioxane) (1:1), 0°C, 2 days. f) Dess–Martin periodinane, CH_2Cl_2 , RT, 2 h. g) TsNHNHTs, toluene, 80°C, then DBU, RT, 12 h. h) 10 mol % AgOTf, CH_2Cl_2 , RT, 2 h. Bn = benzyl, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, MEPY = methyl-2-pyrrolidone-5S-carboxylate.

prepared by a rhodium(I)-catalyzed addition of arylboronic acid to this enolate (Scheme 3).^[20] Indeed, the aryl group approached the cyclobutene ring selectively from the face away from the amide substituent. The stereoselectivity for the protonation step, however, was low and a diastereomeric ratio of 2:1 favoring the isomer **20** was obtained. Simple treatment of this mixture with NaOEt afforded the thermodynamically more stable product **20** as a single stereoisomer. Removal of the benzyl group and subsequent oxidation provided the aldehyde **22**. The stereochemistry of compounds **20** and **22** was confirmed by nOe analysis.^[21] For example, a nOe was observed between H_a/H_a' and H_b , between H_a/H_a' and H_d , between H_b and H_c , and between H_c and H_d of **22**.

After successfully preparing the tetrasubstituted cyclobutane **22** stereoselectively, we then installed the *E* olefin in pipericyclobutanamide **1** using a Julia–Kocienski olefination (Scheme 3).^[22] Compound **23** was obtained as a single olefin isomer, but was contaminated with a by-product derived from reagent **A**. Both polar solvents DMF and HMPA were necessary as lower *E/Z* ratios were observed in either THF or in DMF without HMPA.^[23] Using Ando's reagent **B**, the *Z* olefin of pipericyclobutanamide **1** was prepared from the olefination of an aldehyde intermediate, which was derived from DIBALH reduction (*Z/E* > 20:1).^[24] A *Z/E* ratio of 2:1 was obtained when the Still–Gennari olefination protocol was employed.^[25]

Our spectra (^1H and ^{13}C NMR) for product **1**, however, did not match the data reported in literature for pipericyclobutanamide **1**.^[2] We additionally characterized our synthetic compound **1** by COSY, HMBC, HSQC, ROESY, and HRMS analyses.^[21] All of our spectral data were consistent with the proposed structure **1**.

One of the most significant discrepancies between our data and that from literature for pipericyclobutanamide **1** was the chemical shift of the β -styrene hydrogen H_4 (Table 1).^[2] We did not observe any signal between $\delta = 5.0$ and 5.5 ppm in



Scheme 3. Stereoselective synthesis of proposed structures of piper-cyclobutanamide A and piperchabamide G. Reagents and conditions: a) 5.0 mol % $[\text{Rh}(\text{cod})\text{Cl}]_2$, 1,4-dioxane/ H_2O (10:1), 3,4-(methylenedioxy)phenylboronic acid, RT, 20 h. b) EtONa , EtOH , RT, 10 h. c) Pd/C , H_2 , EtOH , RT, 15 h. d) Dess–Martin periodinane, CH_2Cl_2 , RT, 2 h. e) KHMDS, reagent A, DMF/HMPA (3:1), -35°C to RT, 6 h. f) DIBALH, toluene, -78°C , 30 min. g) KHMDS, reagent B, THF -78°C to 0°C , 2 h. h) Pd/C , H_2 , MeOH , RT, 15 h. cod = 1,5-cyclo-octadiene, DIBALH = diisobutylaluminum hydride, DMF = *N,N'*-dimethylformamide, HMPA = hexamethylphosphoramide, KHMDS = potassium hexamethyldisilazide.

the ^1H NMR spectrum of synthetic compound **1**. After analyzing similar natural products in the literature, we found that chemical shifts for this type of β -styrene hydrogen ranged from $\delta = 6.10$ to 6.29 ppm.^[21] For example, chemical shifts of the β -styrene hydrogen in nigramide Q (**3**)^[5] and dipiperamide E (**6**)^[4] are $\delta = 6.14$ and 6.29 ppm, respectively.

We then prepared piperchabamide G (**2**),^[6] which did not have the styrene olefin. Hydrogenation of the intermediate **23** with subsequent DIBALH reduction and olefination with Ando's reagent B afforded product **2** (*Z/E* > 20:1) as shown in Scheme 3. We were surprised that our spectral data (^1H and ^{13}C NMR) for product **2**, again did not match the data reported in literature for natural product piperchabamide G (Table 1).^[6] All of our spectral data (COSY, HMBC, HSQC, ROESY, and HRMS) were consistent with the proposed structure **2**.^[21]

After failing to find cyclobutane isomers that could match the spectral data of natural products piper-cyclobutanamide A and piperchabamide G, we then carefully analyzed all spectroscopic differences between our synthetic compounds and natural products. We found that ^{13}C chemical shifts of $\delta = 172.2$ and 171.1 ppm were assigned to the two carbonyl

Table 1: Selected ^1H and ^{13}C NMR spectral data ($\delta\text{H}/\delta\text{C}$ in ppm) for compounds **1**, **2**, **25**, and **26**.^[a]

Position	1 (synthetic)	1 (literature) ^[2]	25 (literature) ^[26]
1	−/170.2	−/172.2	−/172.2
4	6.16/128.6	5.21/128.0	5.19/128.1
1'	−/165.8	−/171.1	−/171.1
2'	6.03/120.4	5.75/125.5	5.73/125.5
3'	5.92/140.5	5.86/130.3	5.84/130.3
Position	2 (synthetic)	2 (literature) ^[6]	26 (literature) ^[5]
1	−/170.9	−/173.2	−/173.2
1'	−/165.9	−/170.4	−/170.4
2'	5.98/123.1	5.84/134.0	5.85/134.1
3'	5.93/142.0	5.71/123.2	5.71/123.2

[a] See Tables S1–S6 in the Supporting Information for all data.

carbon atoms in natural product piper-cyclobutanamide A.^[2] We observed ^{13}C chemical shifts of $\delta = 170.2$ and 165.8 ppm for carbonyl carbon atoms C1 and C1', respectively, in our synthetic compound **1**. Our observation is consistent with other closely related natural products.^[21] It appeared that the two carbonyl groups in the natural product piper-cyclobutanamide A were both nonconjugated. Furthermore, the comparison of ^{13}C chemical shifts of the *cis*-alkene in the natural product piper-cyclobutanamide A, our synthetic compound **1**, and related natural products^[21] suggested that the *cis* alkene in natural product piper-cyclobutanamide A was likely not conjugated to a carbonyl group. Similar conclusions could also be made for natural product piperchabamide G.

The ring expansion of vinylcyclobutane **1** through the cleavage of the C4'–C5' bond would produce a hypothetical cyclohexene isomer, which contains a nonconjugated *cis* alkene and a nonconjugated carbonyl group. Numerous six-membered cyclohexenes have been isolated from *Piper nigrum* and *Piper chaba*.^[5,26] It was proposed that they were derived from Diels–Alder cycloaddition of their polyene precursors.

Based on the above analysis, we turned our attention to the six-membered ring isomers of structures **1** and **2**. After examining all known six-membered ring natural products isolated from *Piper nigrum* and *Piper chaba*,^[5,26] we were pleased to find that spectral data (^1H NMR and ^{13}C NMR) of natural product chabamide (**25**) was identical to that of natural product piper-cyclobutanamide A, within experimental error.^[26,27] The unusual $\delta = 5.2$ ppm chemical shift of the β -styrene hydrogen H4 in compound **25** was presumably due to the shielding effect of the adjacent *cis*-aryl group. We also found that spectral data (^1H NMR and ^{13}C NMR) of natural product nigramide F (**26**) was identical to that of natural product piperchabamide G, within experimental error.^[21]

In summary, we have developed a new general strategy for the diastereo- and enantioselective introduction of four different substituents to a cyclobutane ring. The ring expansion of a cyclopropylsilver(I) carbene derived from the diazo compound **18** occurred regioselectively and stereospecifically to afford the cyclobutenone **19**. A rhodium(I)-catalyzed conjugate addition of aryl boronic acid to this cyclobutenone provided the fourth substituent diastereoselectively. Stereoselective synthesis of the *trans* and *cis* alkenes in the proposed structure of pipericyclobutanamide **A** was realized by judicious selection of reaction conditions. After the proposed structures for pipericyclobutanamide **A** (**1**) and piperchabamide **G** (**2**) were synthesized, these two natural products were revised to their six-membered ring isomers chabamide (**25**) and nigramide **F** (**26**), respectively. These structural revisions are important for future studies of the biological activities of the ingredients in white and black peppers, and drug–herb interactions.

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