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

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Abstract

A general strategy was developed for the diastereo- and enantioselective synthesis of cyclobutanes with four different substituents. It consists of three transition metal-catalyzed reactions — a Rh^{II}-catalyzed cyclopropanation, a Ag^I-catalyzed regioselective and stereospecific ring expansion, and a Rh^I-catalyzed addition reaction. Structures of pipericyclobutanamide A and piperchabamide G were synthesized and revised.

Keywords

cyclobutane; pipericyclobutanamide; piperchabamide; chabamide; nigramide

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 component of traditional medicine.^[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, 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 Kibayashi's synthesis.^[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. Research groups of Bergman, Ellman, and Jia used the same protocol to prepare the symmetric cyclobutane core of incarvillateine.^[10] The [2+2] cycloaddition has been the main strategy for the synthesis of

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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 Baran's group for the diastereoselective synthesis of pseudosymmetric cyclobutanes such as piperarborenine **7** and the proposed structure of piperarborenine **D** (**8**).^[14] The originally proposed structure **8**^[3] for piperarborenine **D** was revised to structure **9** after Baran's synthesis. We herein report our strategy for diastereo- and enantioselective introduction of four different substituents to cyclobutanes in the context of total synthesis of proposed structures of pipericyclobutanamide **A** (**1**) and piperchabamide **G** (**2**). We also proposed revised structures for these two natural products.^[15]

We envisioned that both pipericyclobutanamide **A** (**1**) and piperchabamide **G** (**2**) could be derived from tetrasubstituted cyclobutane **10** (Scheme 1). The ester and protected primary hydroxyl group in intermediate **10** would serve as aldehyde precursors that could be unmasked at different stages for olefinations. Conjugate addition of an aryl group to 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. 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 transition metal-catalyzed decomposition of diazo compounds. We have demonstrated that the ring expansion was stereospecific and regioselective. The regioselectivity was dependent on the substituents of the cyclopropane ring and the choice of catalysts. The cyclopropane C-C bond that was adjacent to the electron-donating group or away from the electron-withdrawing group could be selectively cleaved when a Ag^I catalyst was employed.^[16] In the case of cyclopropane **12**, we expected that bond-**a** would be selectively cleaved over bond-**b**. This represents a general and unique strategy for the diastereo- and enantioselective synthesis of unsymmetrical cyclobutanes with four different substituents.

Our synthesis began with the preparation of diazo compound **14** from mono-protected diol **13** (Scheme 2).^[18] Bicyclic lactone **15** was obtained via diastereo- and enantioselective intramolecular cyclopropanation of a *trans*-olefin using chiral Rh₂(5S-MEPY)₄ catalyst.^[19] Opening of the lactone with piperidine followed by oxidation afforded trisubstituted cyclopropane **16**, which was then converted to diazo compound **18** through ketoester intermediate **17** in three steps according to procedures we have established previously.^[16] Treatment of diazo compound **18** with a catalytic amount of AgOTf indeed yielded 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 conditions, we were not able to add an aryl cuprate reagent to enolate **19**. We were pleased to find that tetrasubstituted cyclobutanes **20** and **21** could be prepared by a Rh^I-catalyzed addition of arylboronic acid to this enolate (Scheme 3).^[20] The aryl group indeed 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 isomer **20** was obtained. Simply treating this mixture with NaOEt afforded the thermodynamically more stable product **20** as a single stereoisomer. Removal of the benzyl group followed by oxidation provided aldehyde **22**. The stereochemistry of compounds **20** and **22** was confirmed by nOe analysis.^[21] For example, nOe was observed between Ha/Ha' and Hb, between Ha/Ha' and Hd, between Hb and Hc, and between Hc and Hd of product **22**.

After successfully preparing tetrasubstituted cyclobutane **22** stereoselectively, we then installed the *E*-olefin in pipericyclobutanamide **A** by Julia-Kocienski olefination (Scheme 3).^[22] Compound **23** was obtained as a single olefin isomer but contaminated with byproduct derived from reagent **A**. Both polar solvent DMF and HMPA additive were necessary as lower *E/Z* ratios were observed in THF or in DMF without HMPA.^[23] Using Ando's reagent **B**, the *Z*-olefin of pipericyclobutanamide **A** (**1**) was prepared from the olefination of an aldehyde intermediate, 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 ¹³C NMR) for product **1**, however, did not match the data reported in literature for pipericyclobutanamide **A**.^[2] We then further characterized our synthetic compound **1** by COSY, HMBC, HSQC, ROESY, and HRMS.^[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 **A** was the chemical shift of the β-styrene hydrogen H4 (Table 1).^[2] We did not observe any signal between 5.0 ppm and 5.5 ppm in the ¹H NMR 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 6.10 to 6.29 ppm.^[21] For example, chemical shifts of β-styrene hydrogen in nigramide **Q** (**3**)^[5] and dipiperamide **E** (**6**)^[4] are 6.14 and 6.29 ppm, respectively.

We then prepared piperchabamide **G** (**2**),^[6] which did not have the styrene olefin. Hydrogenation of intermediate **23** followed by DIBALH reduction and olefination with Ando's reagent **B** then afforded product **2** (*Z/E*>20:1) as shown in Scheme 3. We were surprised that our spectral data (¹H NMR and ¹³C 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 pipericyclobutanamide **A** and piperchabamide **G**, we then carefully analyzed all spectroscopic differences between our synthetic compounds and natural products. We found that ¹³C chemical shifts of 172.2 and 171.1 ppm were assigned to the two carbonyl carbons in natural product pipericyclobutanamide **A**.^[2] We observed ¹³C chemical shifts of 170.2 and 165.8 ppm for carbonyl carbons 1 and 1', 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 natural product pipericyclobutanamide **A** were both non-conjugated. Furthermore, the comparison of ¹³C chemical shifts of the *cis*-alkene in natural product pipericyclobutanamide **A**, our synthetic compound **1**, and related natural products^[21] suggested that the *cis*-alkene in natural product pipericyclobutanamide **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 C4'-C5' bond would produce a hypothetical cyclohexene isomer, which contains a non-conjugated *cis*-alkene and a non-conjugated 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 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 pipericyclobutanamide A, within experimental error.^[26, 27] The unusual 5.2 ppm chemical shift of 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 cyclopropyl Ag^{I} carbene derived from diazo compound **18** occurred regioselectively and stereospecifically to afford cyclobutenolate **19**. A Rh^{I} -catalyzed conjugate addition of aryl boronic acid to this cyclobutenolate 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 further studies of biological activities of ingredients in white and black peppers and drug-herb interactions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Selected Four-membered Ring Natural Products

Scheme 1.

Proposed Strategy for Stereoselective Synthesis of Pipericyclobutanamide A and Piperchabamide G

Scheme 2.**Stereoselective Synthesis of Cyclobutenone**

Conditions: a) bromoacetyl bromide then TsNHNHTs, DBU; b) 1.0 mol % $\text{Rh}_2(5\text{-MEPY})_4$, CH_2Cl_2 , reflux; c) piperidine, AlMe_3 , CH_2Cl_2 ; d) DMSO, $(\text{COCl})_2$, Et_3N ; e) NaCN , HOAc , MeOH then EtOH/HCl , 0°C 2 days; f) Dess Martin periodinane; g) TsNHNH_2 , toluene, 80°C , then DBU, rt; h) 10 mol % AgOTf , CH_2Cl_2

Scheme 3.

Stereoselective Synthesis of Proposed Structures of Pipericyclobutanamide A and Piperchabamide G

Conditions: a) 5.0 mol % $[\text{Rh}(\text{COD})\text{Cl}]_2$, dioxane/ H_2O (10:1), 3,4-(methylenedioxy) phenylboronic acid; b) EtONa , EtOH ; c) Pd/C , H_2 , EtOH ; d) Dess Martin periodinane; e) KHMDS , reagent **A**, DMF/HMPA ; f) DIBALH , Tol ; g) KHMDS , reagent **B**, THF ; h) Pd/C , H_2 , MeOH .

Table 1Selected ^1H NMR and ^{13}C NMR Spectral Data for Compounds **1**, **2**, **25**, and **26**^[a]

Position	6H/6C Data		
	synthetic 1	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
	synthetic 2	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 Table S1–S6 in the Supporting Information for all data.