Natural Products

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Structural Revisions of a Class of Natural Products: Scaffolds of Aglycon Analogues of Fusicoccins and Cotylenins Isolated from Fungi

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Abstract: *The reisolation and structural revision of brassicicene D is described, and inspired us to reassign the core skeletons of brassicicenes C–H, J and K, ranging from dicyclopenta[a,d]cyclooctane to tricyclo[9.2.1.0^{3,7}]tetradecane using quantum-chemical predictions and experimental validation strategies. Three novel, highly modified fusicoccanes, brassicicenes L–N, were also isolated from the fungus Alternaria brassicicola, and their structures were unequivocally established by spectroscopic data, ECD calculations, and crystallography. The reassigned structures represent the first class of bridgehead double-bond-containing natural products with a bicyclo[6.2.1]undecane carbon skeleton. Furthermore, their stabilities were first predicted with olefin strain energy calculations. Collectively, these findings extend our view of the application of computational predictions and biosynthetic logic-based structure elucidation to address problems related to the structure and stability of natural products.*

Structurally unexpected and diverse natural products (NPs) isolated from microorganisms and plants have been historically applied to ameliorate human conditions.[1] Several of these NPs have not only inspired the development of new classes of therapeutic agents but also function as versatile tools in plant and animal biology.[2] A promising but insufficiently explored family of terpenoids is the fusicoccane family, which are characterized by a fused 5-8-5 carbocyclic (dicyclopenta[*a*,*d*]cyclooctane) ring system.[3] Among these compounds, fusicoccins (FCs), cotylenins (CNs), and brassicicenes (BCs) are examples of diterpenoids, whereas ophiobolins and ceroplastols are sesterterpenes.[4] Organic molecules sharing this 5-8-5 tricyclic scaffold have been isolated from a variety of sources, including fungi, insects, bacteria, liverworts, algae, and more recently, higher plants.[2c,5]

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Two well-known compounds, fusicoccin A (**1**) and cotylenin A (**2**), are structurally related diterpene glucosides produced by pathogenic fungi (Figure 1).[2c] Both compounds exhibit significant phytohormone-like activities resulting from interactions with plant 14-3-3 proteins.[6] Because the

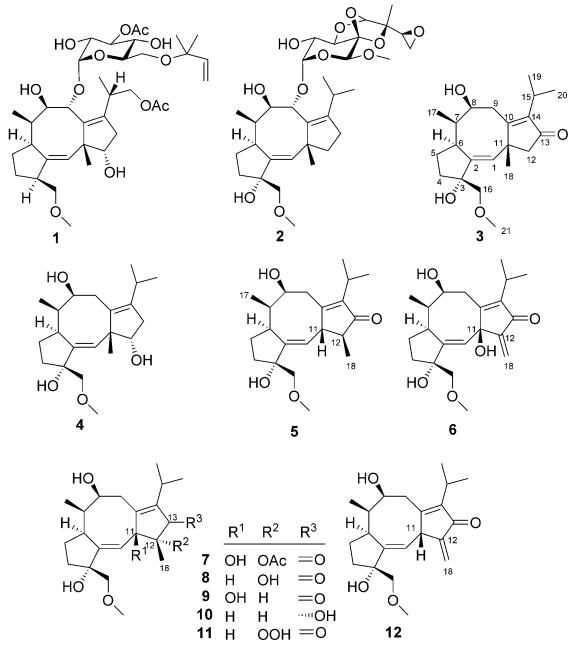


Figure 1. Structures of fusicoccin A (**1**), cotylenin A (**2**), brassicicenes A and B (**3** and **4**), and the original structures of brassicicenes C–H (**5**–**10**), J (**11**), and K (**12**).

14-3-3 protein family is highly conserved in eukaryotes and plays a crucial role in the activation of serine/threonine kinase-dependent signaling pathways by protein–protein interactions (PPIs) with multiple phosphorylated ligands,[7] fusicoccanes are believed to demonstrate biological effects on animal cells. For examples, **2** can potently induce the differentiation of human myeloid leukemia cells,[8] **1** and **2** act synergistically with IFN-α or rapamycin to induce apoptosis in a wide array of cancer cells,[9] and **1** has been shown to induce randomization of left–right patterning during amphibian embryogenesis through an interaction with 14-3-3ε,[10] and to promote platelet aggregation by interactions with 14-3-3-glycoprotein Ib-IX-V.[11] Therefore, the fascinating structures of fusicoccanes and their versatile biological activities have attracted broad interest from the scientific community over the past decades, and a large number of natural and synthetic

fusicoccane derivatives have been reported.[12] For instance, the FC derivative ISIR-042 has been developed for use as an antitumor agent,[13] and brachialactone has been shown to be a highly effective nitrification inhibitor.[14] Recently, remarkable studies have focused on tailoring FC/CN/BC scaffolds by synthetic and biosynthetic methods and have identified targets related to their mechanisms of action.[15]

Intrigued by the structural units of fusicoccanes, we initiated a program of quantum-chemical predictions to verify their reported connectivities in preparation for studying the biogenesis and chemical diversity of these NPs. As described below, these powerful computational calculation methods guided us to successive structural revisions of a class of NPs belonging to the BC-C class, and they were verified with experimental validation methods.

Since 1999, a series of fusicoccane diterpenes (**3**–**12**; Figure 1) which share a universal C3 hydroxy functionality similar to **2**, have been isolated from *Alternaria brassicicola*, a phytopathogenic fungus which causes one of the most important diseases associated with the *Brassica* species. Since then, additional studies have been undertaken to discover more brassicicene C (**5**) analogues and identify the biosynthetic gene cluster.[16] However, when we examined the reasoning underlying the structural elucidation of **5**/**6**, we questioned the original structures not only because of the absence of a reported heteronuclear multiple-bond correlation (HMBC) between H18 and C13 (see Figure S3 in the Supporting Information), but also because of the apparently incompatible nuclear Overhauser effect (NOE) correlation between H17 and H18, a correlation which was observed through the molecular modeling of **6** (Figure 2). As shown in

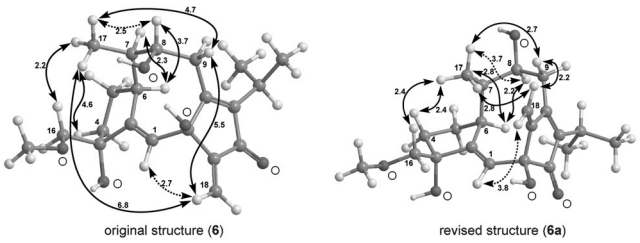


Figure 2. Observed NOESY correlations overlaid on the computed geometries for **6** and **6a**. Each arrow is labeled with a value indicating the distance between the two atoms (in Å). Dashed arrows indicate selected distances for which no NOESY correlation was observed.

Table 1, many of the computed ^{13}C NMR chemical shifts for **5**/**6** were inconsistent with previously reported data.[16b] For example, the C10, C13, and C18 atoms in **6** exhibited notable deviations that were greater than 10 ppm. Herein, our high-accuracy ^{13}C NMR calculations, assisted by a reexamination of the structural elucidation process, indicate that the previously proposed structures for **5** and **6** are incorrect.

We then focused on the experimental data for **5**, **6**, and their analogues, brassicicenes E–H, J, and K (**7**–**12**), which were reported by the group of MacKinnon and others.[16] These authors proposed the carbon framework of **5**–**12** differed from **3** and **4** because of the unusual C12−C18 bonds in **5**–**12**. Their proposed structures were largely based

Table 1: Comparison of the experimental and computed ^{13}C NMR chemical shifts for BC-C and BC-D (in ppm).

No.[a]	BC-C Exptl.[b]	**5**[c]	**5a**[c]	BC-D Exptl.[b]	**6**[c]	**6a**[c]
1	127.7	126.8	132.6	132.2	132.3	135.7
2	147.7	153.8	147.6	146.6	147.1	147.2
3	84.1	82.2	83.7	83.0	82.2	83.2
4	36.6	39.1	38.6	36.3	36.6	36.5
5	38.0	32.6	37.9	35.0	25.4	37.2
6	47.9	50.8	48.1	45.3	39.9	45.3
7	50.9	40.0	53.7	48.3	43.3	50.3
8	75.5	75.3	76.1	74.5	76.6	74.7
9	30.6	34.9	28.9	30.3	35.4	28.4
10	176.7	176.8	180.8	161.1	176.0	164.6
11	44.8	53.6	46.4	153.4	149.9	153.3
12	58.8	52.0	59.9	82.1	81.2	84.1
13	207.4	209.7	203.9	202.3	190.5	197.4
14	151.2	144.4	146.8	147.3	147.0	146.8
15	28.9	30.5	30.4	27.2	25.9	28.5
16	79.5	82.9	79.0	78.4	77.6	80.0
17	12.3	10.4	12.1	10.3	13.6	9.8
18	13.0	15.1	11.5	103.2	114.5	100.4
19	19.0	20.3	17.0	18.8	20.4	16.6
20	22.0	21.8	20.3	21.1	21.4	19.3
21	59.6	59.2	57.0	58.9	58.7	56.3
	AveDev	3.4	1.8	AveDev	3.8	1.7
	MaxDev	10.9	4.9	MaxDev	14.9	4.9
	R^2	0.9935	0.9983	R^2	0.9891	0.9985

[a] For numbering, see Figure 1. [b] Data in CD_3OD taken from Ref. [16b]. [c] Data computed for structures **5**, **5a**, **6**, and **6a** (**5a**, **6a** = revised structures).

on homonuclear and heteronuclear two-dimensional (2D) NMR experiments. In fact, organic substances can possess a variety of unusual four-bond and five-bond ^{1}H–^{1}H couplings, such as allylic, homoallylic, and W couplings.[17] These couplings may introduce ambiguities into their spectral interpretations, thus leading to a panel of architectural possibilities and even resulting in a number of incorrect structural assignments.[17,18]

Although the original structures of **5**/**6** appear to be consistent with the reported experimental data, other structural possibilities can also fit these data (see Figure S4). Therefore, we wondered whether additional spectroscopic evidence could further support our hypothetical structural reassignments. We thus decided to reisolate **5** or **6**, and other compounds that could serve as a biogenetic precursor leading to the brassicicene C (BC-C) class. A culture broth of *A. brassicicola* was chemically investigated by our group, and resulted in the isolation of **3** and four related compounds (**6a** and **13**–**15**; Figure 3). Among these compounds, the analysis of a small quantity (3.8 mg) of **6a** resulted in an $[M+Na]^+$ ion at *m*/*z* 385.1986 (calcd 385.1985) in an HRESI(+)MS experiment. The IR spectrum (3421, 1707, and 1643 cm^{-1}), optical rotation value [−139.6, (*c* 0.08, MeOH)], and ^{1}H and ^{13}C NMR data for the isolate were highly consistent with the experimental data of BC-D. These data suggested that **6a** was the same substance isolated by MacKinnon and coworkers.[16b]

We subsequently performed 2D NMR experiments on the isolate. The HMBC data with regards to C1, C11, C12, and

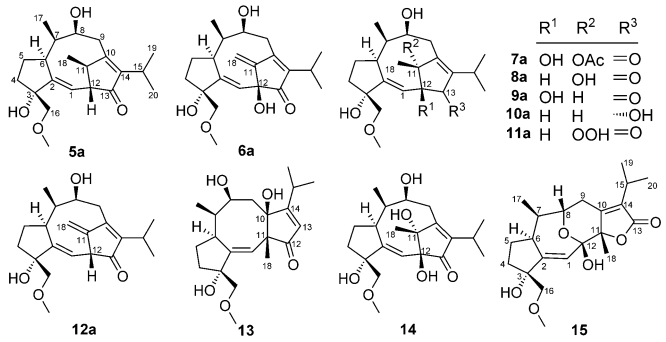
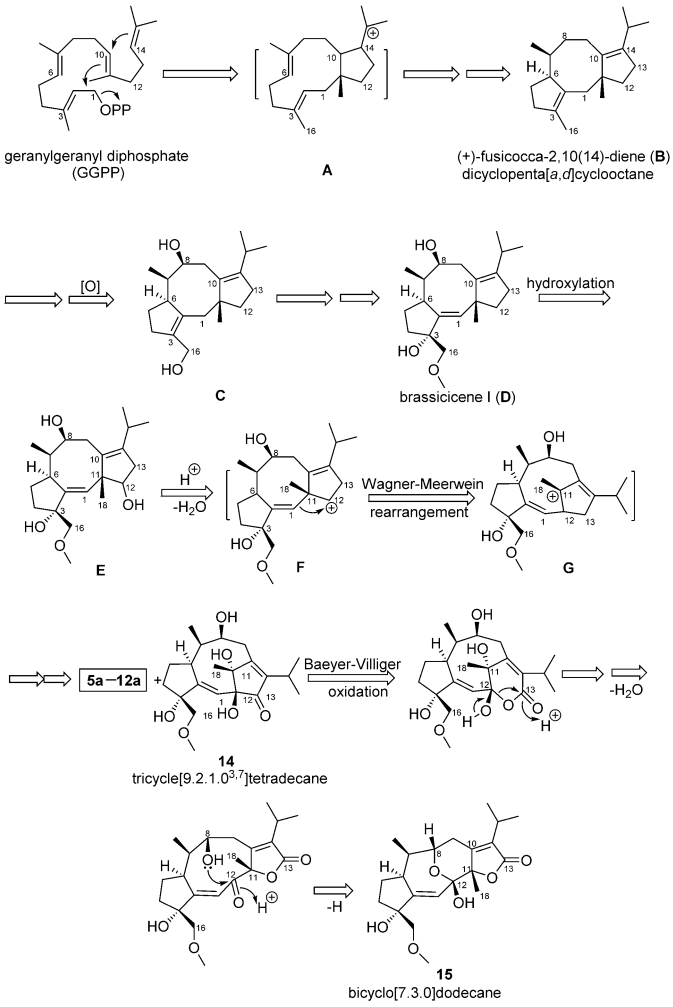


Figure 3. Structures of brassicicenes L (**13**), M (**14**), and N (**15**) and the revised structures of the BC-C class (**5a**–**12a**).

H18 were inconclusive. The HMBC interactions of H1 with C13 and H18 with C10 initially appeared to be at odds with **6**, and instead, they were more compatible with **6a**. In contrast, the NOESY experimental data were more conclusive. We observed almost the same correlations as those that were previously reported.[16b] However, the NOESY interactions of H6/H8 and H17/H18 were more compatible with the structure of **6a** than with **6**. In addition, correlations of H9β with H17 and H18 were disclosed, and thus further supported the revised structure because the distances among these three protons were computed to be less than 2.8 Å in **6a** but greater than 4.7 Å in **6** (Figure 2). Thus, the revised structure (**6a**) was clearly more consistent with the observed correlations, in which the longest NOESY distance was 2.8 Å in **6a** compared to 6.8 Å in the original structure **6**. The absolute configuration of **6a** was subsequently elucidated using a time-dependent density-functional theory (TD-DFT) method and was confirmed using X-ray crystallography after exhaustive attempts.[19] These results unambiguously clarified the structural revision proposed for **6**. Subsequently, the structures of the co-isolated compounds **13**–**15** were also elucidated by extensive spectroscopic analyses, ECD calculations, and validated by X-ray crystallography (see the Supporting Information for details). Notably, **6a** and **14** feature a unique tricyclo[9.2.1.$0^{3,7}$]tetradecane core skeleton which contains a bridgehead double bond, whereas **15** possesses a unique tetracyclic diterpene skeleton bearing an oxabicyclo[4.3.1]nonane moiety.

The putative biogenesis of the 5-8-5 carbocyclic core of fusicoccanes, for example, **1** and **2**, has been proposed to proceed through an initial π-cation cyclization reaction of geranylgeranyl pyrophosphate (GGPP) to form an eleven-membered ring. Then, additional transannular events from a bicyclo[9.3.0]cyclotetradecane precursor could lead to the 5-8-5 ring system.[4,16a] We therefore reasonably predicted that the tricyclic carbon skeletons of BC-C and BC-D could also be generated from the dolabellane nucleus. Although the origins of **5a** and **6a** are uncertain, biogenetically, the formation of the tricyclo[9.2.1.$0^{3,7}$]tetradecane core in **5a** and **6a** can be plausibly traced back to GGPP through a key intermediate, (+)-fusicocca-2,10(14)-diene (**B**; Scheme 1), a tricyclic hydrocarbon precursor which can generate FCs through an unusual chimera diterpene synthase, *P. amygdale* fusicoccadiene synthase (PaFS).[6a] Oxidation of **B** can produce the intermediate fusicocca-2,10(14)-diene-8β,16-diol (**C**). The 3-hydroxylation reaction of **C**, catalyzed by the brassicicene dioxygenase,[16a] and subsequent methoxylation of the product fusicocca-1,10(14)-diene-3,8β,16-triol at position C16 can give rise to another intermediate (**D**) called brassicicene I.[16c] The hydroxylation derivative of **D** then reacts by protonation and loss of water from C12 to form a carbocation intermediate (**F**). The cationic product **F** can generate the 5-9-5 ring system of the carbocation intermediate **G**, which contains a tertiary cation at C11, by a Wagner–Meerwein rearrangement. The newly generated tertiary cation could be quenched either by attack of water to form the hydroxy group at C11, or by deprotonation of a methyl group at C18 to give a terminal double bond located at C18, thus resulting in the formation of the unusual tricyclo[9.2.1.$0^{3,7}$]tetradecane derivatives **5a**–**12a** and **14** (Figure 3). Furthermore, the formation of **15** can be traced back to **14**, involving Baeyer–Villiger oxidation, ester hydrolysis, and ring cleavage, with subsequent intramolecular aldol



Scheme 1. Plausible biosynthetic pathway of **5a**–**12a**, **14**, and **15**.

condensation and dehydration. Such considerations produced various diastereomeric structures of BC-C, which were ascribed to four possible configurations (**5a–d**; see Figure S4) with respect to C11 and C12 of the molecules. The QCP results were subsequently evaluated in terms of their R^2 coefficients, maximum absolute deviations (MaxDev), and average absolute deviations (AveDev; Table 1). The computed carbon NMR chemical shifts for **5a** and **6a** (Table 1) corresponded well with the observed experimental chemical shifts.[16b] Although the structure of **6a** does not consist of a dicyclopenta[*a*,*d*]cyclooctane core, its 5-9-5 ring system (tricyclo[9.2.1.$0^{3,7}$]tetradecane) is unusual. All molecules of the BC-C class (**5a–12a** and **14**; Figure 3) were isolated from the same species (*Alternaria brassicicola*) by independent research groups, thus supporting the proposed biosynthetic pathway (Scheme 1). Taken together, these results challenge the accuracy of the previously proposed structures for the BCs **7–12**.

As a consequence, we successively reassigned the originally proposed architectures **7–12** to the correct ones **7a–12a** (Figure 3) by employing a DFT method to calculate the ^{13}C NMR properties in the same manner as those of **5a** and **6a** were calculated (see the Supporting Information for details). Accordingly, comprehensive analyses of the statistical parameters for all diastereomeric structures of the BCs congeners (see Table S3) enabled us to conclude that the 5-9-5 tricyclic core was preferred in the BC-C class over the longstanding incorrect 5-8-5 ring system.

Structurally, the fusicoccanes **5a–12a** and **14** feature a unique tricyclo[9.2.1.$0^{3,7}$]tetradecane core skeleton containing a bridgehead double-bond system that has been found to be a naturally occurring violation of Bredt's rule, which states that "the terminus of a double bond cannot exist at the bridgehead position of a caged bicyclic system".[21] However, **5a–12a** and **14** could not be arbitrarily deemed anti-Bredt NPs because of the uncertainty with respect to the anti-Bredt classification.[21] The olefin strain (OS) energy is defined as the difference between the strain energy of an olefin and that of its parent hydrocarbon. In the early 1980s, Schleyer and coworkers reported a force-field-based method for predicting the stabilities of bridgehead alkenes.[22] This method resulted in the determination of a correlation between the OS energies of these alkenes and their experimentally observed behaviors, and it enabled alkenes to be classified into three groups: "isolable" ($OS \leq 17$ kcal mol^{-1}), "observable" ($17 \leq OS \leq 21$ kcal mol^{-1}), and "unstable" ($OS \geq 21$ kcal mol^{-1}).[21,22] Most recently, Krenske and Williams demonstrated that this OS energy strategy could be applied to complex NPs.[23] In this case, the stability and classification of these bridgehead-olefinic systems containing bicyclo[6.2.1]undecane NPs were quantitatively determined using OS calculations (see Table S2), and the results demonstrated that all the OS energies of the bridgehead double-bond-containing structures **5a–12a** and **14** fell within the isolable range.

Finally, although CNs have been reported to exert apoptotic and antitumor effects on mammalian cells, none of the isolates (**3**, **6a**, and **13–15**) were observed to be cytotoxic principles against A-549, HL-60, MCF-7, SMMC-7721, and SW-480 human cancer cell lines by using the MTT method.[24] The results indicate that the presence of the glycoside-moiety at C9 of the tricyclic core is important for cytotoxicity.

Bridged polycyclic structures have attracted extensive attention over the past decade as potential drug scaffolds.[21,25] Recently, bridgehead double-bond-containing NPs have represented an active research area.[21] Interestingly, the BC-C class (**5a–12a** and **14**) represents the first class of bridgehead double-bond-containing NPs with a bicyclo[6.2.1]undecane carbon skeleton. And **15** features a precedented carbon backbone in which an oxabicyclo[4.3.1]nonane is incorporated into a bicyclo[7.3.0]dodecane ring system. The bicyclo[6.2.1]undecane ring system is also known to be a precursor of taxanes.[26] In addition, the bicyclo[7.3.0]dodecane substructure in BC-N (**15**) has been observed in other well-known NPs, such as kedarcidin and neocarzinostatin chromophores, which have promising pharmacological effects.[27] Taken together, this work brings new insights into the chemical diversity and biosynthesis of bridgehead double-bond-containing NPs and their modes of action.

Moreover, the impact of the remarkable structural diversity of NPs on the drug discovery process and molecular biology continues to be expanded by advances in analytical technologies. Nevertheless, much progress is necessary before NPs identification can be considered a process devoid of errors, and it is desirable to devise new avenues which can help elucidate candidate structures. These findings will aid organic chemists by adding NMR computations and biosynthetic logic to the library of methodologies used for the structural elucidation of compounds.

Experimental Section

Experimental procedures, 1D and 2D NMR spectroscopy, and MS, UV, and IR analyses, and detailed calculations are provided in the Supporting Information. X-ray crystallographic data of **3**, **6a**, and **13–15** in CIF format is also provided.

Acknowledgements

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