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Discovery and Biomimetic Synthesis of a Phloroglucinol-Terpene Adduct Collection from *Baeckea frutescens* and Its Biogenetic Origin Insight

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Abstract: A phloroglucinol-terpene adduct (PTA) collection consisting of twenty-four molecules featuring three skeletons was discovered from *Baeckea frutescens*. Inspired by its biosynthetic hypothesis, we synthesized this PTA collection by reductive activation of stable phloroglucinol precursors into highly reactive *ortho*-quinone methide (*o*-QM) intermediates and subsequently Diels-Alder cycloaddition. We also demonstrated for the first time the generation process of the active *o*-QM by performing dynamic nuclear magnetic resonance (NMR) and HPLC-MS monitoring experiments. Moreover, the PTA collection showed significant antifeedant effect toward the *Plutella xylostella* larvae.

Introduction

The diverse specialized metabolites generated by plants are probably the consequence of adaptive evolution to allow plants to protect themselves against herbivory, pathogenic microbes, and various abiotic stresses.[1,2] The phloroglucinol-terpene adducts (PTAs) are a class of hybrid natural products with structural features that phloroglucinol derivatives incorporated mono- or sesqui-terpenoid units via various coupling patterns.[3] So far, over 300 PTAs have been discovered from natural sources, most of which came from the plants belonging to families Myrtaceae and Guttiferae.[3–5] Due to their intriguing chemical structures and remarkably biological activities, PTAs have received increasing attention from both chemical and biological communities in recent years.[3–5]

Biogenetically, PTAs are commonly hypothesized to form via a crucial Diels-Alder cycloaddition between terpene precursors and putative *ortho*-quinone methide (*o*-QM) intermediates.[3b,4] Recently, several biomimetic approaches involving Diels-Alder cycloaddition have been reported for the synthesis of a series of PTAs, employing *in situ*-generated *o*-QMs as key intermediates.[4a,4c,4e,6–8] In those reported synthetic strategies, the desired *o*-QM intermediates were commonly generated through oxidative activation of the benzyl sites of phloroglucinol precursors or Knoevenagel condensation between aldehydes and phloroglucinols. However, the generation process of *o*-QMs

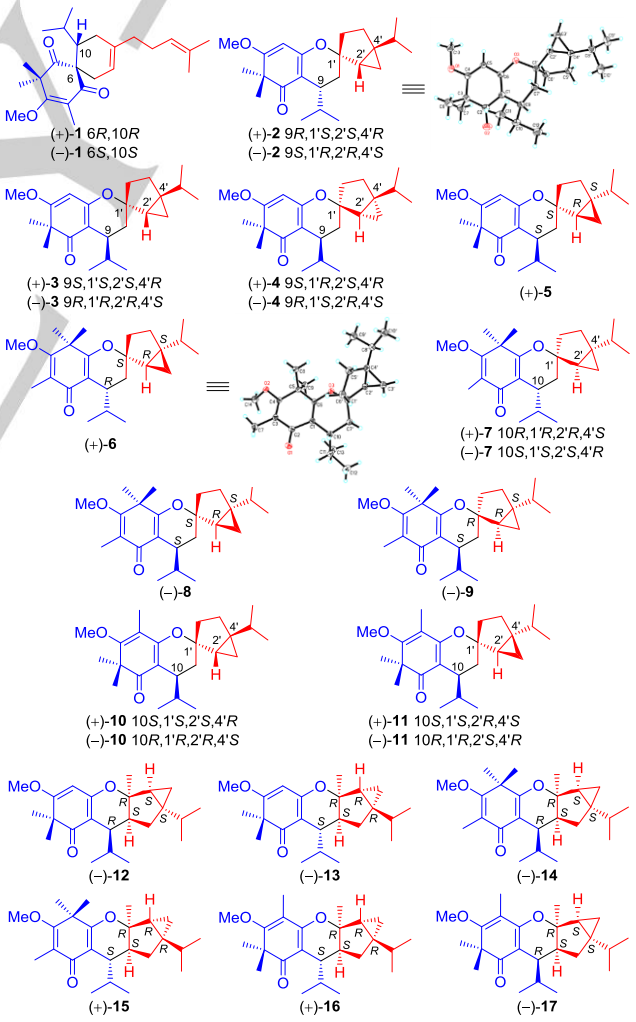


Figure 1. Chemical structures of PTAs from *B. frutescens*.

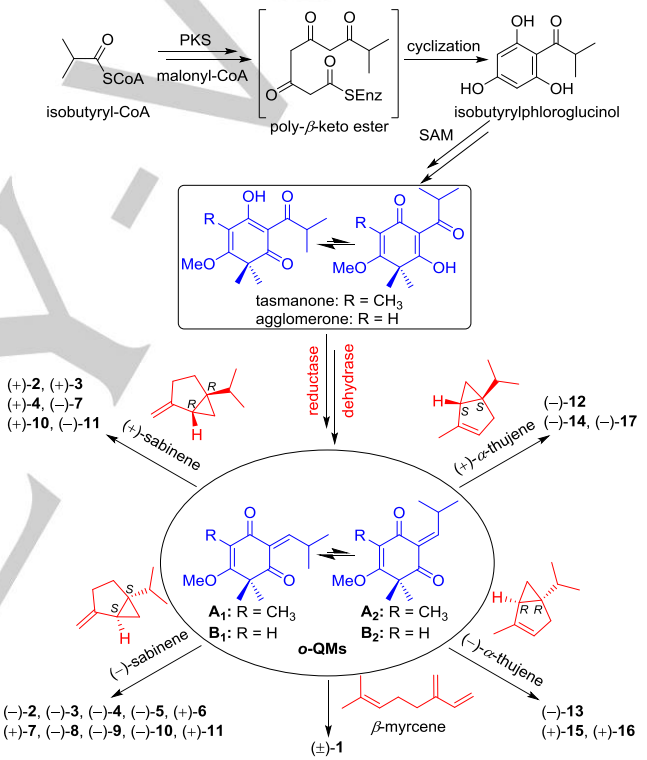
in plants has received much less attention, to the best of our knowledge, no experimental evidence was reported to explain how stable phloroglucinol precursors convert into highly reactive *o*-QM intermediates. Actually, little progress was made in understanding the underlying biosynthesis mechanism of this intriguing group of natural products. Further work is needed to demonstrate how, and perhaps why, plants apply combinatorial strategy to create those diverse PTAs.

In our current study, a PTA collection consisting of twenty-four molecules featuring three skeletons, including twelve new ones, was obtained from the leaves and twigs of *Baeckea frutescens* L. (Myrtaceae). Based on the identification of key phloroglucinol and terpene precursors in the same plant material, a plausible biogenetic route for the PTA collection was proposed. Inspired by this hypothetical biogenetic pathway, we designed a biomimetic synthesis strategy for the PTA collection involving the *in situ* generation of active *o*-QM intermediates via the reductive activation of coexisting phloroglucinol precursors and subsequent Diels-Alder cycloaddition with corresponding monoterpenes. The activation process for conversion of stable phloroglucinol precursors into reactive *o*-QM intermediates was revealed for the first time by using dynamic ^{1}H NMR and HPLC-MS monitoring experiments. Moreover, the quantum chemical calculation of the Diels-Alder cycloaddition and the antifeedant property of the PTA collection toward larvae of *Plutella xylostella* were studied. Herein, we report the discovery, plausible biogenetic pathway, biomimetic synthesis, generation mechanism, and feeding deterrent activity of the PTA collection.

Results and Discussion

The PTA-containing extract of *B. frutescens* was obtained and further fractionated following our early procedure.[5] The PTA-rich fraction was then selected based on the result of HPLC-MS analysis, which revealed typical UV profiles and ion peaks for PTAs. Further UV-guided chiral chromatography isolation was performed to obtain twenty-four optically pure compounds, (+)-frutescone Q (**1**),[4f] (−)-frutescone Q (**1**),[4f] (+)-(**2**), (−)-baeckfrutone Q (**2**),[9b] (+)-**3**, (−)-**3**, (+)-baeckfrutone I (**4**),[9a] (−)-baeckfrutone I (**4**),[9a] (+)-**5**, (+)-baeckfrutone B (**6**),[9a] (+)-baeckfrutone C (**7**),[9a] (−)-baeckfrutone C (**7**),[9a] (−)-baeckfrutone D (**8**),[9a] (−)-baeckfrutone N (**9**),[9a] (+)-**10**, (−)-**10**, (+)-baeckfrutone J (**11**),[9a] (−)-**11**, (−)-**12**, (−)-**13**, (−)-**14**, (+)-baeckfrutone M (**15**),[9a] (+)-**16**, and (−)-**17** (Figure 1). Their structures with absolute configurations were elucidated on the basis of comprehensive spectroscopic and single crystal X-ray diffraction analyses, as well as computational calculations. Among them, (+)-**2**, (+)-**3**, (−)-**3**, (+)-**5**, (+)-**10**, (−)-**10**, (−)-**11**, (−)-**12**, (−)-**13**, (−)-**14**, (+)-**16**, and (−)-**17** are twelve new structures. These molecules constituted a PTA collection comprising three types of carbon skeletons: (A) **1** contains a spiro[5.5]undecane ring system; (B) **2**–**11** possess a polymethylated chroman-spiro-bicyclo[3.1.0]hexane backbone structure; (C) **12**–**17** bear a polymethylated chroman-fused-bicyclo[3.1.0]hexane skeleton. Among these isolates, (+/−)-**1**, (+/−)-**2**, (+/−)-**3**, (+/−)-**4**, (+/−)-**7**, (+/−)-**10**, and (+/−)-**11** are seven pairs of enantiomers. Interestingly, chiral HPLC analysis showed that **1** occurs as a racemic mixture, **2**–**4**, **7**, **10**, and **11** exist as scalemic mixtures, and other PTAs (**5**, **6**, **8**, **9**, and **12**–**17**) present as optically pure compounds in plant (see the Supporting Information for details).

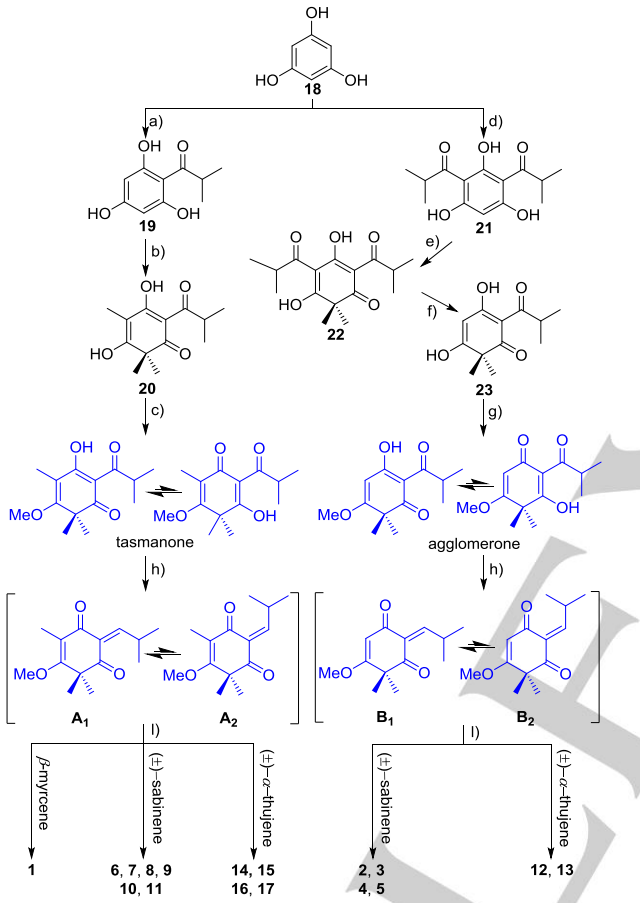
Based on the structural features of these PTAs, a hypothetical biogenetic pathway for the PTA collection is predicted in Scheme 1. First, the construction of the phloroglucinol moiety involved a polyketide pathway utilizing isobutyryl-CoA as the starting unit. Subsequent carbon chain extension, cyclization, and methylation modification led to the generation of two pairs of acylphloroglucinol tautomerisms, tasmanone and agglomerone. The phloroglucinol precursors were further reduced and dehydrated to generate the active *o*-QM intermediates, $\mathbf{A_1}$/$\mathbf{A_2}$ and $\mathbf{B_1}$/$\mathbf{B_2}$. As enophiles, both $\mathbf{A_1}$/$\mathbf{A_2}$ and $\mathbf{B_1}$/$\mathbf{B_2}$ could incorporate different monoterpene precursors [(+)/(−)-sabinene and (+)/(−)-*α*-thujene] through hetero-Diels-Alder cycloaddition to generate **2**–**17** featuring a heterocyclic chroman ring system. Meanwhile, $\mathbf{A_1}$/$\mathbf{A_2}$ could also act as dienophiles to couple with *β*-myrcene via Diels-Alder cycloaddition to form (+)/(−)-**1**, which have a rare all-carbon spirocyclic ring system. Meanwhile, all proposed phloroglucinol and monoterpene precursors were detected in the crude extract of title plant (Figures S17–S19).



Scheme 1. Hypothetical biogenetic pathway of the PTA collection.

To support our biosynthetic hypothesis, we designed a biomimetic synthesis approach to create the PTA collection. Following the similar strategy to those employed by our recent work,[10] we firstly synthesized tasmanone and agglomerone in gram quantities via the concise routes shown in Scheme 2. With the acylphloroglucinol precursors in hand, we then turned our attention to conversion of them into reactive *o*-QMs. After screening various reductants, diisobutylaluminium hydride (DIBAL-H) was proved to be the best option because it could efficiently and chemoselectively reduce the exocyclic carbonyl group in tasmanone and agglomerone. However, the expected alcohol products were too unstable to separate, and would spontaneously dehydrate to afford the desired *o*-QMs. Thus, PTAs were then formed via direct cycloaddition between the reductive products, without further purification, and the

corresponding monoterpenes (commercial availability) through Diels-Alder cycloaddition. Actually, the *o*-QMs (**A_1**/**A_2** and **B_1**/**B_2**) were so highly reactive that the cycloaddition could proceed even at room temperature without any catalyst. Nevertheless, the yield could be improved by enhancing the reaction temperature. HPLC-MS analyses of the synthetic compounds and natural products indicated that we obtained not only all the desired natural PTAs in the collection but also some pseudo-natural stereoisomers (Figures S4–S5 and Table S1). The structures of synthetic compounds were further confirmed by comparing their NMR data with those of natural products (Tables S2–S5).



Scheme 2. Biomimetic synthesis of PTAs. a) $ClCOCH(CH_3)_2$ (1.1 equiv.), $AlCl_3$ (3.0 equiv.), $PhNO_2$, 65 ºC, 82%; b) MeI (3.1 equiv.), NaOMe (4 equiv.), MeOH, 55 ºC, 63%; c) CH_2N_2 (2.5 equiv.), AcOEt-MeOH (5:1), −78 ºC, 91%; d) $ClCOCH(CH_3)_2$ (2.1 equiv.), $AlCl_3$ (4.0 equiv.), $PhNO_2$, 65 ºC,76%; e) MeI (2.0 equiv.), NaOMe (2.0 equiv.), MeOH, 55 ºC, 91%; f) conc. H_2SO_4, 70 ºC, 70%; g) CH_2N_2 (3.0 equiv.), AcOEt-MeOH (5:1), −78 ºC, 95%; h) Diisobutylaluminium hydride (2.0 equiv.),THF, −78 ºC; l) Toluene, 110 °C.

Due to the rapid reactivity of the *o*-QMs, we failed to identify these proposed intermediates in plants. To gain insight into the biogenetic process of reactive *o*-QMs via reductive activation of the stable acylphloroglucinol precursors, we designed an *in vitro* experiment to monitor the dynamic process of the reductive products of tasmanone by using ^{1}H NMR and HPLC-MS. ^{1}H NMR spectra of the reductive products revealed the presence of six characteristic proton signals (H_{a1}, H_{a2}, H_{b1}, H_{b2}, H_c, and H_d; Figures 2 and S20), which were used as the probes to monitor different compounds. The changing trend indicated the sequential generation of four compounds (**24**, **25**, **A_1**, and **A_2**) with the corresponding H_{a1}, H_{a2}, H_{b1}, and H_{b2} signals, followed by their conversion into **26** with H_c, which finally yielded the stable product **27** with H_d. Compound **27** was further isolated and elucidated as a known naturally occurring endoperoxide, which had been isolated from the same plant species by other groups[11,12] and us in the present study. HPLC-MS analysis of the reductive products provided supplementary evidence to support aforementioned dynamic processes (Figures S21–S22). Notably, the above findings provided the first experimental evidence for revealing the dynamic generation process of how the stable acylphloroglucinol precursors converted into reactive *o*-QMs via reductive activation. Thus, the reductive activation and cycloaddition processes are illustrated in Figure 2B. The selective reduction of the exocyclic carbonyl group of tasmanone resulted in the ready formation of the corresponding alcohols **24** and **25**, which in turn spontaneously dehydrated to afford the *o*-QMs **A_1**/**A_2**. Next, combinatorial cycloaddition between *o*-QMs **A_1**/**A_2** and monoterpenes could efficiently result in the creation of PTA collection. Meanwhile, *o*-QMs **A_1**/**A_2** could also undergo an isomerization process to generate the corresponding stable compound **26**, which was spontaneously oxidized to form the endoperoxide **27** by trapping oxygen from environment. Because all putative biogenetic precursors (tasmanone, agglomerone, and monoterpenes) and final stable products (PTAs and **27**) were present in the original plant, the entire chemical synthetic route was highly in line with the plausible biosynthetic pathway.

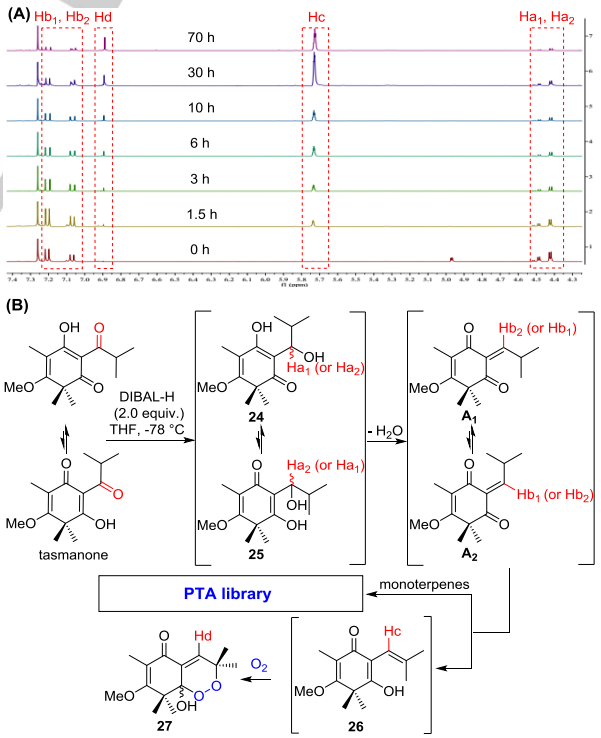


Figure 2. A) Dynamic ^{1}H NMR spectra of the reductive products of tasmanone. B) Generation process for **A_1**/**A_2**, **27**, and PTAs.

Considering the fact that the *o*-QMs and terpene precursors could hybridize spontaneously without any catalyst *in vitro*, we wonder whether the Diels-Alder cycloaddition involved in PTA

biosynthesis is a non-enzyme-mediated process in plants. With this question, we investigated the reactivity of this process computationally by employing PWPB95-D3(BJ)/def2-QZVPP model chemistry. Because all these PTAs were generated in a similar manner, the Diels-Alder cycloadditions between **A_1**/**A_2** and (+)/(−)-sabinene were selected as the studying model. All twenty-four plausible transition structures (TSs) and twelve possible products (nine of which were isolated as natural products in this study, see the Supporting Information for details) of the cycloaddition reactions were located using toluene as the solvent condition. The computed free-energy profile of (+)-**6** is shown in Figure 3, and those of other products are shown in Figure S41. As results, the activation energies of all favoured TSs ($\Delta G^{\ddagger}$) were estimated ranging 21–29 kcal/mol, and the heats of reaction (ΔG) for all cycloaddition reactions were computed to be 4.5–13.5 kcal/mol, indicating that the cycloaddition processes between *o*-QMs and terpenes were exergonic reactions in toluene. The above data indicated that the Diels-Alder cycloaddition could proceed entirely and irreversibly in toluene, even at room temperature without enzymatic assistance, which was consistent with the result of biomimetic synthesis. Interestingly, the activation energies of all preferred TSs in water were predicted to be much lower than those in toluene ($\Delta\Delta G^{\ddagger}$ = 3–13 kcal/mol), suggesting that these Diels-Alder cycloadditions might proceed more easily and rapidly in plants.

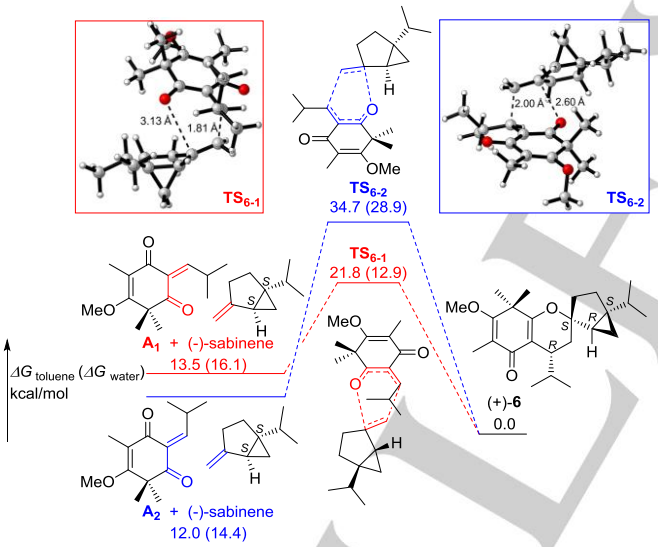


Figure 3. DFT-simulated process for the Diels-Alder cycloaddition of (+)-**6**.

PTAs are highly frequent occurrence in Myrtaceae species, however, the role of these specialized metabolites in plants remains unclear. To probe the potential ecological function of the PTAs, the antifeedant activities of the natural PTA collection as well as several selected PTAs [(±)-**1**, (−)-**4**, (+)-**6**, (+)-**7**, (−)-**10**, (+)-**11**, and (−)-**17**] against third-instar larvae of *Plutella xylostella* (Linnaeus) were tested by using leaf disc no-choice method.[13] As shown in Table S25, the natural PTA collection showed comparable feeding deterrent effect (AFC_{50} = 50.23 ± 7.19 μg/g) to that of the positive control azadirachtin A (AFC_{50} = 43.69 ± 5.91 μg/g), while most of the individual PTAs only displayed moderate to modest antifeedant activities. The above data suggested that the PTA collection likely play an important role in plant defense.

Conclusions

Phytochemical investigation of *B. frutescens* led to the discovery of a PTA collection comprising of twenty-four molecules featuring three skeletons. Inspired by the proposed biosynthetic pathway, we successfully generated highly reactive *o*-QM intermediates by reducing the corresponding stable phloroglucinol precursors and completed the biomimetic synthesis of the PTA collection. Further investigation of the reductive activation of the phloroglucinol precursor revealed the *o*-QMs generation process. Computational studies of the Diels-Alder cycloaddition between *o*-QMs and monoterpenes indicated the combinatorial cycloaddition process could spontaneously proceed in the absence of catalyst. The PTA collection showed significant feeding deterrent effect toward the larvae of *Plutella xylostella*.

Throughout the present study, we proved that reductive activation could convert stable biogenetic phloroglucinol precursors into highly reactive *o*-QMs using only a chemical reductant, implying endogenous reductases may perform this key transformation step during PTA collection biosynthesis in plants. Interestingly, plant aldo-keto reductases (a protein superfamily of NAD[P]H-dependent oxidoreductases) were reported to play a crucial role in diverse plant metabolic processes and biotic/abiotic stress defense.[14] An attractive idea was raised that attacked by potential enemies may induce the enhancement of activities of aldo-keto reductases in plants, which in turn trigger the formation of active *o*-QMs. The resulting PTA collection is believed to play an important defensive role against insect herbivores toward plants.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: biosynthetic pathways • phloroglucinol-terpene adduct • biomimetic synthesis • natural products • *Baeckea frutescens L.*

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Insight of Nature: A phloroglucinol-terpene adduct (PTA) collection was discovered from *Baeckea frutescens*. The plausible biogenetic pathway, biomimetic synthesis, generation mechanism, and feeding deterrent activity of the PTA collection were also investigated. The current study first provided experimental evidences to explain how, and perhaps why, plants apply combinatorial strategy to create the PTA collection.