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Stereodivergent Strategy in Structural Determination: Asymmetric Total Synthesis of Garcinol, Cambogin, and Related Analogues

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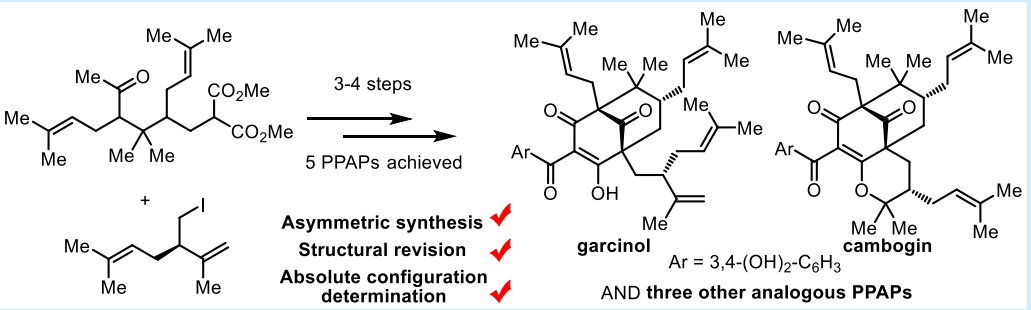

ABSTRACT: The asymmetric total synthesis of five biologically significant polycyclic polyprenylated acylphloroglucinols (PPAPs), including garcinol and cambogin, was achieved through a highly diastereoselective and stereodivergent strategy. Along the way, an efficient cascade Dieckmann cyclization was employed to construct the bicyclo[3.3.1]nonane core in one step. The synthesis provided a general approach toward the chiral *endo*-type B PPAPs and their C-30 diastereomers in a single sequence, which resolved the challenges of the absolute configuration determination/structural revision of PPAPs bearing exocyclic stereocenters.

Garcinol (**1**) and cambogin (or isogarcinol, **2**) are important polycyclic polyprenylated acylphloroglucinols (PPAPs)[1] that exert excellent remedial qualities against many human diseases and ailments.[2] These PPAPs feature a stereocenter at C-30, which is a challenge for chemical synthesis and absolute configuration determination. The total synthesis and absolute configuration determination of **1** and **2** were accomplished by Plietker and coworkers;[3] however, there is still a great number of PPAPs that were isolated with undefined absolute configurations or misassigned structures due to their complex architectures and the limitations of the current analytic methods (Scheme 1A and Figures S1−S4).[1] These structural problems have significantly impeded medicinal studies and caused confusion in the research related to isolation, structure determination, naming, and biological investigation.

Although remarkable rules for the determination of the relative configuration at C-7 have been developed by Grossman, Jacobs, and Rastrelli,[4] the full structure and absolute configuration determination of PPAPs, including the exocyclic stereocenters, still rely on asymmetric synthesis. During the last several decades, great achievements in the synthesis of PPAPs have been made by the groups of Shibasaki,[5] Danishefsky,[6] Plietker,[7] Porco,[8] Shair,[9] Barriault,[10] Maimone,[11] and others.[12] In 2019, our group also developed a Me_2AlSEt-promoted domino Dieckmann cyclization approach for the synthesis of *endo*-type B PPAPs.[13]

However, the asymmetric strategy for the synthesis of PPAPs bearing exocyclic stereocenters is still very limited.[14] With respect to the medicinal significance of **1** and **2**, the synthesis and structural determination of these PPAPs are greatly emphasized.[15] Guttiferone F (**4**) and 30-*epi*-cambogin (**5**),[16] originally assigned as the 30-epimers of **1** and **2**, were isolated by a number of research groups and revealed diverse biological activities such as cytoprotection against HIV-1[16] and cytotoxic effects (Scheme 1A).[17] Previously, their structures and relative configuration were identified by comparing the spectroscopic data with those of **1**. Recently, it was found that their structures were misassigned, and they were revised by our group via spectroscopic analysis.[18] Because considerable research has been conducted based on **4** and **5**, their structures should be further confirmed by synthesis before related research can be accordingly corrected. The other two PPAPs, garcimultiflorone K[19] (**3**) and 13,14-didehydroxyisogarcinol (**6**, 13,14-DDHIG),[20] which demonstrated antiangiogenic activity[19,21] and anti-inflammatory activity,[20] respectively

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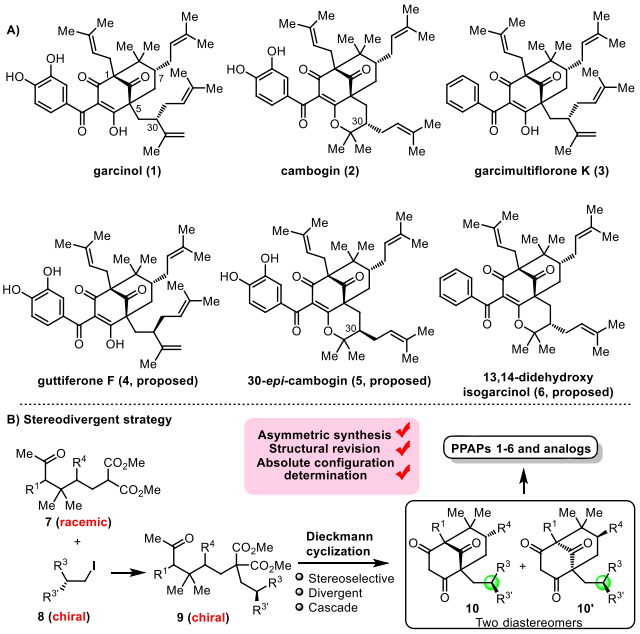
Scheme 1. Bioactive PPAPs and Stereodivergent Strategy for Synthesis and Structural Determination



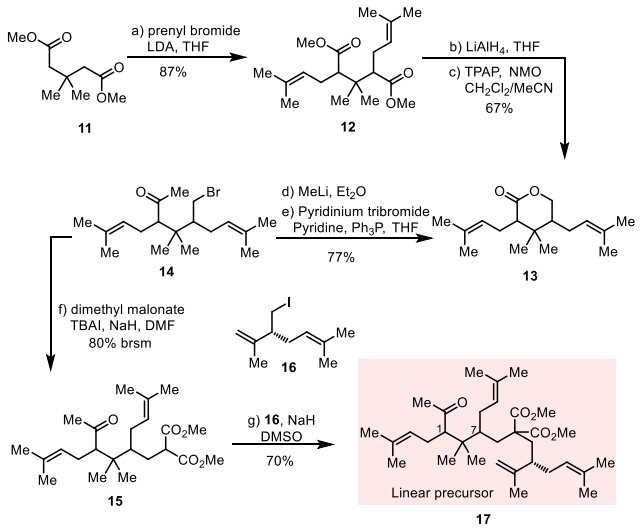
(Scheme 1A), were configurationally identified by electronic circular dichroism (ECD). Because chiroptical methods require the existence of UV−Vis-active chromophores close to the stereocenter,[22] the structural determination of side chains must be carefully interpreted.[23]

On the basis of the above challenges and concerns, we devised a stereodivergent strategy for the synthesis of **1** and its analogues. This would establish a general method for the structure/absolute configuration elucidation of these PPAPs and provide inspiration for future structural determination (Scheme 1B). In particular, an approach to construct the core structure (via **7**) and introduce the molecular chirality (via **8**) in a divergent way was envisioned. Then, with the highly diastereoselective cascade Dieckmann cyclization developed by our group,[13] this approach would be amenable for the synthesis of the natural 7-*endo* PPAPs along with their C-30 diastereomers and provide a conclusive way to determine the structure and absolute configuration of the PPAPs bearing exocyclic chiral centers (**1**−**6** and Figures S1−S4).

Toward this end, we began with the synthesis of racemic compound **15** in six steps under modified conditions according to our previous studies.[13] The enantioenriched **16** was easily prepared in four steps from commercially available building blocks using similar conditions reported in the literature.[24] The coupling of **15** and **16** afforded the linear precursor **17** bearing a bulky lavandulyl group in 70% yield as a mixture of C-1 and C-7 diastereoisomers (Scheme 2). It is worth mentioning that the stereochemistry at C-1 was going to disappear during the following cyclization. Therefore, the ratio of the diastereomers in the mixture was not going to make any difference to the results, and they were not intended to be separated.

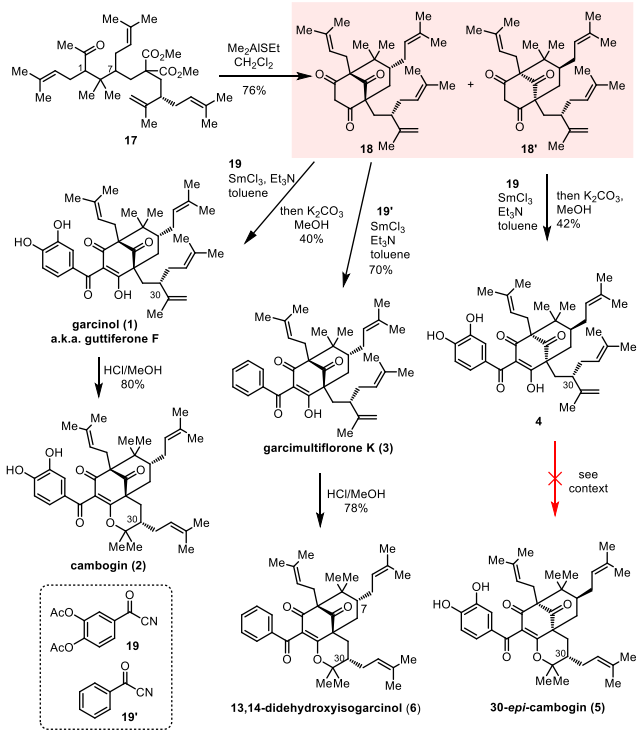
As anticipated, the domino Dieckmann cyclization proceeded efficiently to give two diastereomers **18** and **18′** (1:1 dr), which were separated by column chromatography. The acylation of **18** with **19** or **19′** in the presence of $SmCl_3$ accomplished the first asymmetric synthesis of **1** and **3** in 40 and 70% yield, respectively. The following *O*-cyclization of **1** and **3** was then performed with HCl in MeOH to smoothly

Scheme 2. Synthesis of the Linear Precursor



afford the biologically significant **2** as well as the proposed **6** in 80 and 78% yield (Scheme 3). However, when we verified the

Scheme 3. Total Synthesis of Garcinol and Related PPAPs



synthesis of natural 13,14-DDHIG by comparing the nuclear magnetic resonance (NMR) spectra of **6** to the reported data, major differences were observed. The results suggested that the determination of the structure of the natural product originally identified as 13,14-DDHIG might be incorrect.

The Porco group has already achieved the C7- (**20**), C30- (**21**), and C7,C30-epimers (**22**) of **6** through a cationic oxycyclization strategy (Scheme 4A).[14] We then subjected these epimers and the natural product to a thorough NMR comparison. The NMR data and specific rotation of **20** from the Porco group were found to be in excellent agreement with those of natural 13,14-DDHIG. As a result, we concluded that

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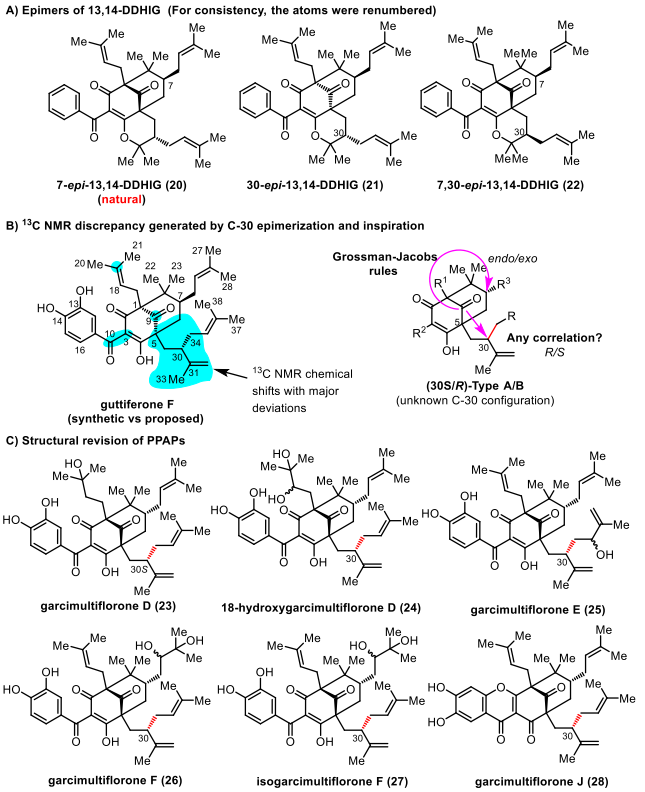
Scheme 4. Structural Determination of PPAPs with Exocyclic Chiral Centers



the natural product whose structure was originally proposed to be 13,14-DDHIG had been misidentified and that it was actually 7-*epi*-13,14-DDHIG (**20**) (Scheme 4A). It should be noted that the relative/absolute configuration of natural **20** was determined by nuclear Overhauser effect (NOE) spectroscopy and ECD, which were shown in this study to be unreliable methods for determining the configuration of PPAP side chains. With the synthesis of **6** completed, the difficulties in accessing all of the epimers of **20** were overcome by combining the work of the Porco group.[14]

Next, the acylation of **18′** with **19** in the presence of $SmCl_3$ resulted in the asymmetric synthesis of **4** in 42% yield. The NMR spectra and specific rotation of **4** differed significantly from those reported for the natural guttiferone F, confirming the misassignment of its original structure.[16,18] The chemical shifts in ^{13}C NMR with major deviations ($\Delta\delta > 0.3$) between the proposed guttiferone F and **4** were calculated. As shown in Scheme 4B, these carbons are mostly around the C-30 stereocenter (see Table S3′ for details), which implied that the stereochemistry of C-30 in the proposed guttiferone F was incorrect. Inspired by the Grossman−Jacobs rule for determining the *exo*/*endo* configuration,[4] a significant chemical shift variance of ^{13}C NMR at C-9 between **4** and **1** ($\Delta\delta = 1.6$) indicated that a correlative rule to determine the configuration of C30 (R/S) based on the chemical shift of the bridged carbonyl carbon could be inferred after further study (Scheme 4B).

Consequently, a large number of misled studies over the last two decades should be clarified with the revision of the proposed guttiferone F to **1** via asymmetric synthesis. These studies include the alleged isolation of **4**, structural determination based on **4**, and biological studies.[25] The structures of six PPAPs (garcimultiflorones D−F, 18-hydroxygarcimultiflorone D, isogarcimultiflorone F, and garcimultiflorone J, **23**−**28**), which were previously determined by NMR analysis and comparing NMR with the proposed guttiferone F, are now structurally corrected to be 30*S* (Scheme 4C).[26] Specifically, we now know that the cyclization of the natural product previously identified as guttiferone F (but now known to be garcinol) led to cambogin, not 30-*epi*-cambogin as reported.[16] After these revisions, all (30*R*)-*endo*-type B PPAPs with a lavandulyl group at C-5 are corrected to be (30*S*)-*endo*-type B PPAPs.[27] Despite the fact that there is still a number of PPAPs with unknown C-30 configurations (Figures S1−S4), we may tentatively infer that the natural PPAPs are most likely to have an (*S*)-lavandulyl group at C-5. This bias can be used as a valuable reference for determining the structure of unknown PPAPs and as an inspiration for preferred biosynthetic pathways.

With the synthetic **4**, the originally assigned structure of guttiferone F, in hand, we then attempted *O*-cyclization to afford **5**. Surprisingly, none of the desired **5** was observed when we treated **4** with acidic conditions such as HCl/MeOH, HCl(aq)/toluene, and *p*-TsOH/toluene (Scheme 3). The unexpected results prompted us to conduct additional experiments to determine the difference in cyclization between **4** and **1** with respect to the C-30 configuration. As we know, a large number of PPAPs bearing a C-30 stereocenter similar to **2** have been assigned structures without determination of the C-30 configuration. Further study of the *O*-cyclization of these compounds may provide evidence that allows us to determine the configurations of their C-30 stereocenters.

First, with Me_2AlSEt as the promoter, we envisioned that the *O*-cyclization might happen after the domino Dieckmann cyclization of **17** to afford the tricyclic products **29** and **29′**. However, only the cyclized product **29** from **18** was isolated after an extended reaction time, along with the unreacted **18**/**18′** in a total yield of 43% (Scheme 5A). The purified compounds **18** and **18′** were then subjected to *O*-cyclization in the presence of HCl/MeOH, respectively. The reaction with **18** proceeded smoothly to give the desired product **29** in 86% yield, whereas the reaction with **18′** gave a mixture of MeOH adducts of the alkenes. These results suggested that PPAPs such as **4** and **18′** were more reluctant to undergo the *O*-cyclization under acidic conditions (Scheme 5B). In contrast with the possible transition state of **18** (I), the prenyl group in the transition state of **18′** (II) was in an axial position, which prevented the reaction from proceeding due to steric hindrance (Scheme 5B).

To get more insight into the cyclization, we conducted a conformational analysis of **18**/**18′**, which also supported the hypothesis on the reaction differentiation. For **18**, the lowest energy conformation has the propenyl group in close proximity to the enol group for cyclization. We speculate that the activation energy of the reaction is mostly from enolization of the diketone. Subsequent cationic cyclization is facile because it has no energy barrier. For **18′**, in addition to enolization, there is a conformational energy cost to bring the propenyl group and the enol close enough for cyclization. This increases the activation energy of the desired cyclization, reduces the "effective concentration" of the enol, and enables the competitive formation of MeOH adducts (Scheme 5C).

Interestingly, when we collected all of the natural PPAPs bearing an *O*-cyclized lavandulyl group (Figures S1−S4), we found the biogenetic *O*-cyclization of PPAPs, including types A

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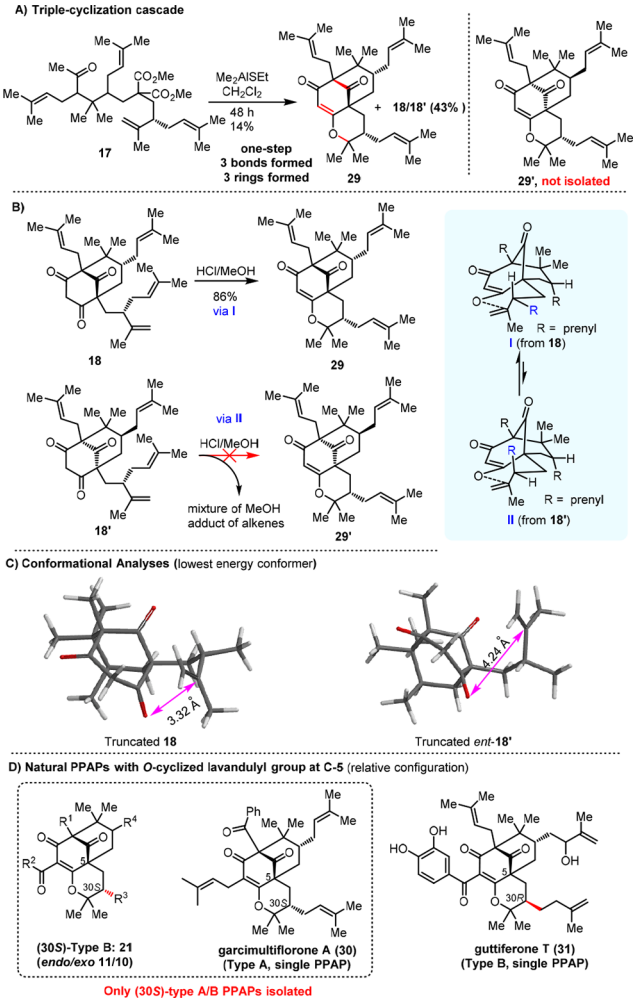
Scheme 5. Control Experiments for *O*-Cyclization and Conformational Analysis



and B, is highly consistent with the observation in this synthesis. So far, no (30*R*)-type A/B PPAPs have been isolated from natural sources (Scheme 5D). These observations not only provide evidence of the study of biosynthetic selectivity but also provide a useful reference for configurational determination. Nevertheless, there is still a single (30*R*)-type B PPAP, named guttiferone T (**31**),[28] bearing an *O*-cyclized *ω*-lavandulyl group. Its structure was elucidated by comparison with 30-*epi*-cambogin and isoxanthochymol, which definitely should be further verified according to our observations (Scheme 5D).

In conclusion, we have developed a general approach for the asymmetric synthesis of *endo*-type B PPAPs bearing exocyclic stereocenters. By employing cascade Dieckmann cyclization as the key step to construct bicyclo[3.3.1]nonane cores, this efficient method has led to the asymmetric synthesis of garcinol, cambogin, and other analogues for the first time. Specifically, with a stereodivergent strategy, both the natural PPAPs and their C-30 epimers could be obtained in a single synthetic sequence, which provided an efficient and conclusive way to resolve the challenges in the structure and absolute configuration determination of PPAPs. Significantly, essential rules for determining the structure of PPAPs with lavandulyl groups were established based on the structural revision and *O*-cyclization investigation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01139.

Detailed experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra of all products (PDF)

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Notes

The authors declare no competing financial interest.

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