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Me_2AlSEt-Promoted Domino Dieckmann Cyclization Enables the Total Synthesis of Polycyclic Polyprenylated Acylphloroglucinols

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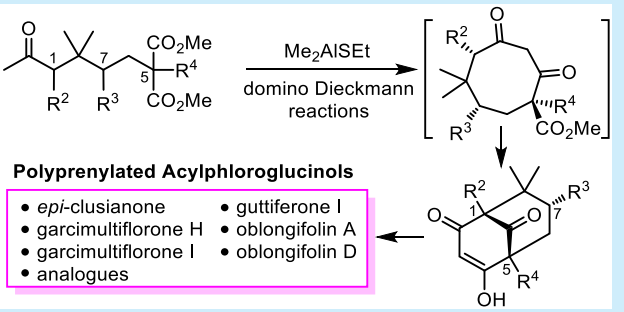
Supporting Information

ABSTRACT: A bioinspired, Me_2AlSEt-promoted domino Dieckmann cyclization via an 8-membered ring intermediate to construct bicyclo[3.3.1]nonanes was developed, and the divergent syntheses of nine complex polycyclic polyprenylated acylphloroglucinols were achieved. This novel domino cyclization tolerates a series of congested substrates, providing a very efficient way to construct diverse polycyclic structures. The selectivity and the advantages of the domino cyclization were studied. Moreover, the structure−activity relationship study leads to the identification of three simplified potent antitumor agents.



Polycyclic polyprenylated acylphloroglucinols (PPAPs), which are generally characterized by highly oxygenated bicyclo[3.3.1] nonane-2,4,9-trione cores that are densely substituted with prenyl and geranyl groups, have been isolated from plants of the Guttiferae (Clusiaceae) family.[1] So far, hundreds of natural PPAPs with diverse skeletons have been identified. The promising bioactivities[2] and synthetic challenges of the PPAPs have initiated a significant interest to synthetic chemists,[3,4] with the molecules such as clusianone,[5] hyperforin,[6] and garcinol[7] achieved from several research groups.[8]

The use of domino reaction sequences has emerged as a particularly attractive avenue in total synthesis for the diastereoselective formation of multiple carbon−carbon bonds.[9] Studies into the biosynthesis of PPAPs describe the efficient construction of 1,3-polyketides by enzyme-promoted cascading Dieckmann reactions and further affording the acylphloroglucinols (Scheme 1, a).[1] When these cascade sequences are incorporated into organic synthesis, powerful strategies for the one-pot production of bicyclo[3.3.1]nonanes **I** may be achieved with the linear precursor **II**, which can be prepared from the easily accessible starting materials. In order to verify this bioinspired strategy, a series of bioactive PPAPs as well as their analogues diversely decorated with prenyl and geranyl groups[10] are set as the targets and their total syntheses are investigated. The PPAPs *epi*-clusianone (**1**) and garcimultiflorones H and I (**2** and **3**),[11] all bearing three prenyl groups, are differentiated with acyl groups at C3 and C2, while guttiferone I (**4**)[12] and oblongifolins A (**5**) and D (**7**)[13] and their unnatural analogues (**6**, **8**) feature different substituents at C1, C5, and C7 (Scheme 1, b).

The synthesis was started with the diesters **9**, which underwent a sequence of transformations such as alkylation, reduction, and oxidation to afford the linear precursors **14a** in gram scale as an inseparable mixture of *cis*- and *trans*-isomers (3:1) in seven steps (Scheme 2). The crucial intramolecular domino Dieckmann cyclization was then investigated with **14a** (Table 1). Although the Dieckmann reaction is well established and has been widely used for preparing 1,3-dicarbonyl compounds, we are not aware of examples of its use in cascades to construct complex molecules. Evaluation of the commonly used basic conditions, such as those involving *t*-BuOK, NaH, and LiHMDS,[14] at room temperature gave no reactions (see the Supporting Information for details). However, under heating, the reaction with LiHMDS generated two products, **16** and **17** (3:1), which featured a rare 8-membered ring structure (entries 1−3). Further attempts to obtain bicyclo[3.3.1]nonanes **15a** or promote the transannular cyclization of **16**/**17** under basic conditions failed. At this point, we assumed that the domino Dieckmann cyclization might be hindered by the methoxy groups, which are poor leaving groups, and thus this group was changed to SEt to facilitate the cyclization. In the following transthioesterification of **14a** under Me_3Al/EtSH conditions, we surprisingly found

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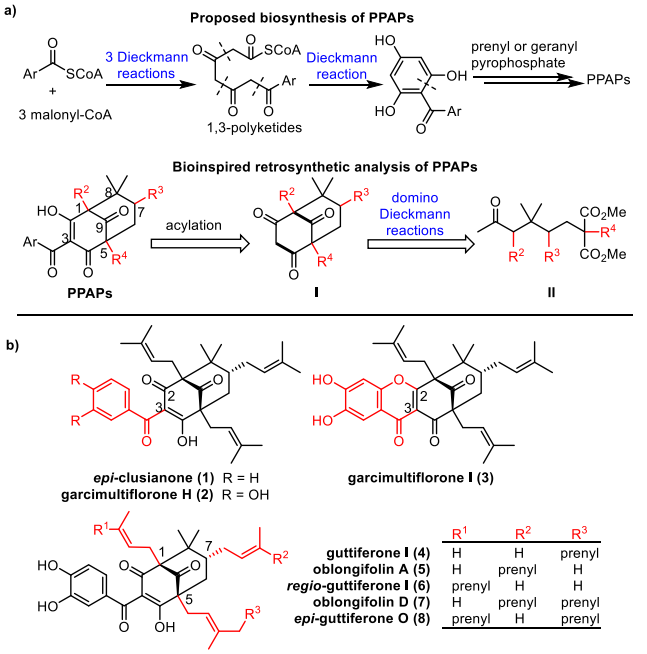
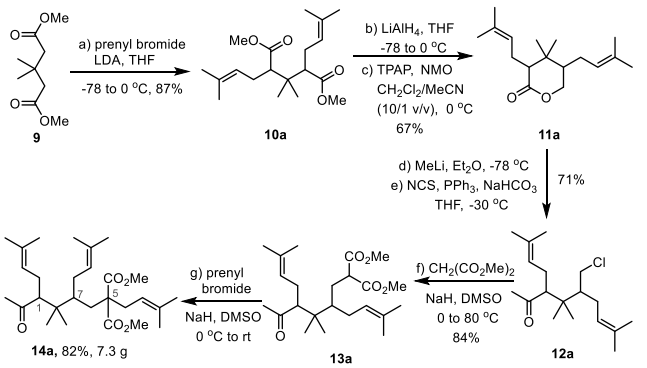
Scheme 1. Bioinspired Strategies for Synthesis of PPAPs and Their Analogues with Diverse Side Chains



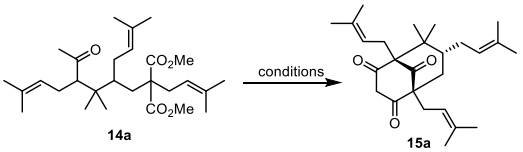
Scheme 2. Synthesis of Congested Linear Precursors



the previous 8-membered ring products (**16** and **17**, 6:1) were obtained instead of the predicted products **18** (entry 4). As we know, the combination of Me_3Al and EtSH generates Me_2AlSEt in situ and has never been used as a Lewis acid promoter in the reactions before.[15] These unexpected results prompted us to further investigate these conditions, and after optimization, we obtained the desired [3.3.1] bicyclic product **15a** in 75% yield. Notably, the ratio of CH_2Cl_2 and heptane in the reaction is crucial for obtaining good results. The cyclization was more successful in CH_2Cl_2/heptane (10/1), and 5 equiv of Me_3Al/EtSH were needed (entries 5−6). Under the optimal conditions, the domino reaction of **14a** has been run in 0.5 mmol scale (0.23 g) to afford **15a** in 72% yield. Other Lewis acids that have been reported to promote Dieckmann reactions were also evaluated. However, no positive effects on the reaction outcomes were observed (entries 7−8).

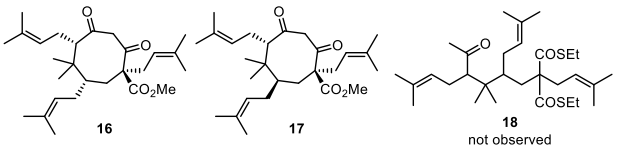
The regioselectivity of the cyclization from **14a** to **16** and **17** rather than the transthioesterification could be attributed to the presence of a methyl ketone, which is more active than the ester, and the loss of EtSH is more favorable than the loss of Me_2AlOMe (Scheme 3). Apparently, the cyclization went

Table 1. Conditions for the Domino Dieckmann Cyclizations[a]

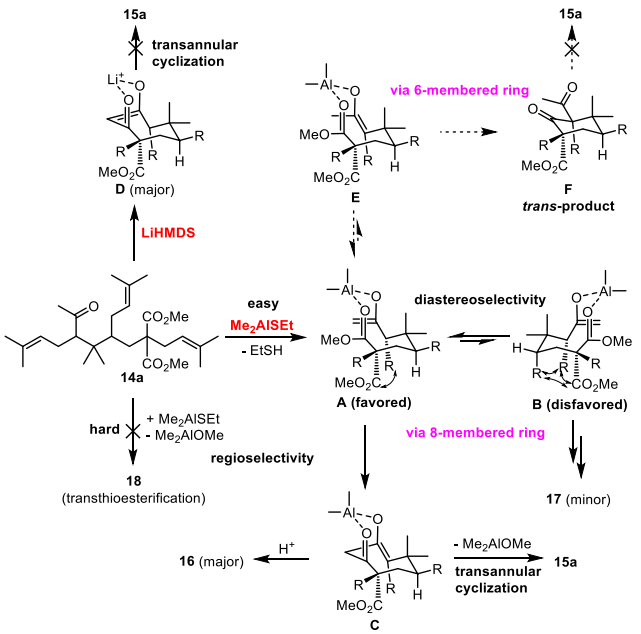


entry	conditions	results
1	*t*-BuOK, THF, reflux	no reaction
2	NaH, toluene, reflux	no reaction
3	LiHMDS, toluene, reflux	**16**/**17** (48%, 3:1)
4[b]	$Al(Me)_3$/EtSH, DCM/heptane, rt	**16**/**17** (73%, 6:1)
5[b]	$Al(Me)_3$/EtSH, DCM/heptane, reflux	**15a** (60%)
6[c]	$Al(Me)_3$/EtSH, DCM/heptane, reflux	**15a** (75%)
7	$TiCl_4/Et_3N$, $Cl(CH_2)_2Cl$, reflux	no reaction
8	*p*-TsOH, toluene, reflux	decomposition

[a]For reaction details, please see the Supporting Information. [b]CH_2Cl_2/heptane = 1:1 (v/v). [c]CH_2Cl_2/heptane = 10:1 (v/v).



Scheme 3. Selectivity and Advantages of the Domino Cyclization toward 15a



through an 8-membered ring intermediate (**A** and **B**), the diastereoselectivity of which was controlled by steric repulsion between the ester and prenyl groups to give **16** as the major product. For the second transannular cyclization, a Lewis acid as the promoter (**C** to **15a**) is crucial to its proceeding, as the enolization under base is more likely to occur at C3, which hampers further conversion to **15a** (**D** to **15a**). The advantages of the domino Dieckmann condensation were also demonstrated by its unusual cyclization pathway. With the diastereoselectivity controlled by the steric hindrance, the cyclization via the 8-membered ring with the favored intermediate could successfully give desired bicyclo[3.3.1]

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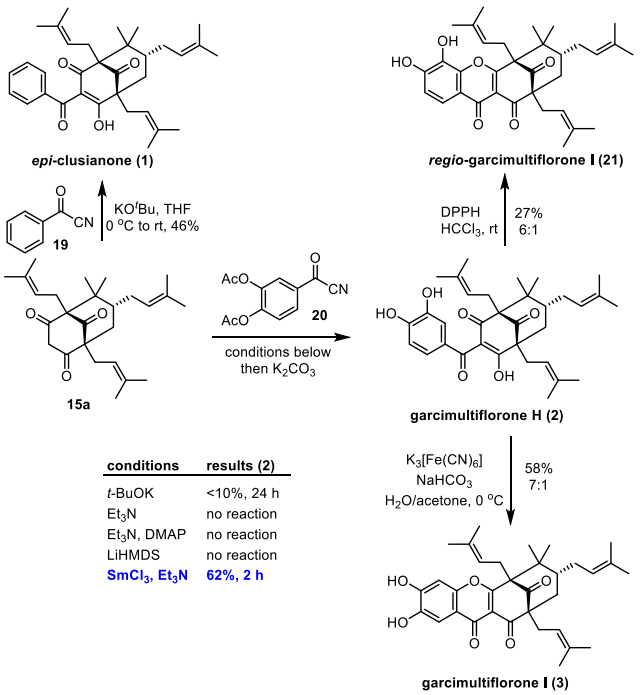
nonanes **15a**, while the cyclization via the 6-membered ring gave a *trans*-intermediate that could not be converted to **15a** (**E** to **15a**).

The total synthesis was then continued by treating **15a** with benzoyl cyanide in the presence of *t*-BuOK, which proceeded smoothly to give *epi*-clusianone (**1**) in 46% yield (Scheme 4).

Scheme 4. Completion of the Synthesis of *epi*-Clusianone (1) and Garcimultiflorones H and I (2 and 3)

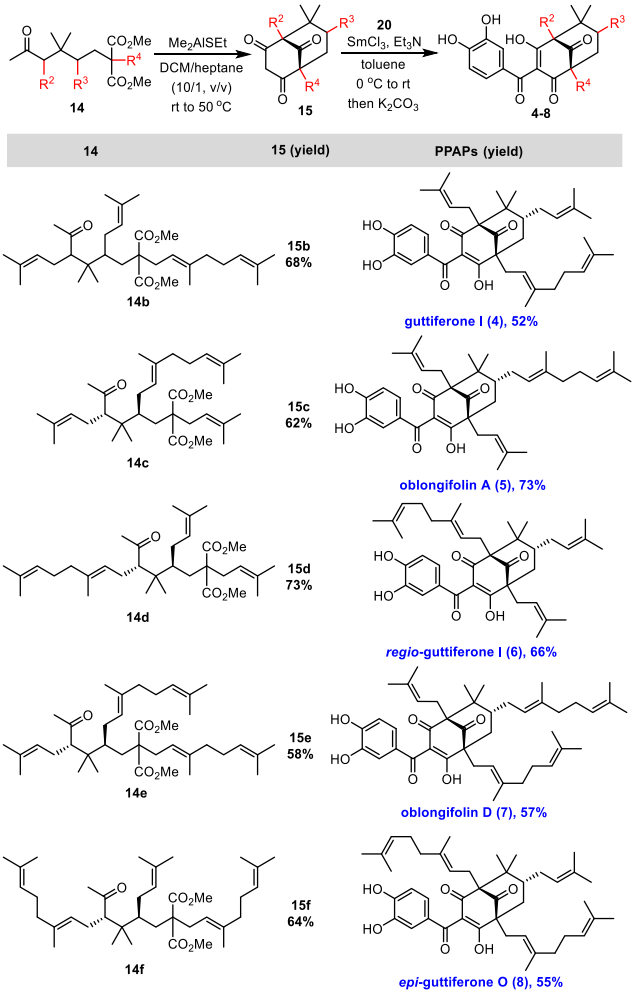


conditions	results (2)
t-BuOK	<10%, 24 h
Et_3N	no reaction
Et_3N, DMAP	no reaction
LiHMDS	no reaction
$SmCl_3$, Et_3N	62%, 2 h

However, when the reaction was run with bulky 4-(cyanocarbonyl)-1,2-phenylene diacetate (**20**), only a trace amount of the *C*-acylated product was observed. Other reagents, such as Et_3N and LiHMDS, did not afford the desired products. Fortunately, we found that the acylation could be smoothly promoted by the Lewis acid $SmCl_3$ under modified conditions reported by Zhou,[16] which afforded garcimultiflorone H (**2**) in 62% yield after quenching with K_2CO_3. The Lewis acid $SmCl_3$ has indeed substantially promoted the reaction not only with benzoyl chloride but also with benzoyl cyanide. Under the current set of conditions, the reactions with the cyclic sterically hindered substrates proceeded very smoothly and were complete in 2 h. The subsequent oxidative cyclization was then conducted with high regioselectivity under different oxidative conditions to give garcimultiflorone I (**3**) in 58% yield[17] and *regio*-garcimultiflorone I (**21**) in 27% yield.[18]

With the novel Me_2AlSEt-promoted domino Dieckmann cyclization and $SmCl_3$-promoted *C*-acylation well established, the scope of the domino Dieckmann cyclization was then demonstrated in the total synthesis of complex PPAPs with a series of congested linear precursors. As indicated in Table 2, the cyclization precursor **14b** (5.9 g) was prepared in one step from **13a** as a mixture (*cis*:*trans* = 3:1), while precursors **14c**–**14f** (1.5–6.2 g) were prepared as *cis*-isomers in a similar sequence to **14a** (see Supporting Information for details). These linear precursors bearing bulky geranyl groups and prenyl groups at either C1, C5, or C7 feature diverse substituents, and herein their successful cyclization provides

Table 2. Domino Dieckmann Cyclization in the Total Synthesis of PPAPs 4–8 Bearing Diverse Substituents



general strategy for the synthesis of PPAPs with various substituents. Under the standard conditions, bicyclo[3.3.1]-nonanes **15b**, **15c**, **15d**, **15e**, and **15f** were obtained via the domino cyclization in good yields from 58% to 73% at about 0.1 g scale. Following *C*-acylation and subsequent treatment with K_2CO_3, the natural products guttiferone I, oblongifolin A, oblongifolin D, and their analogues *regio*-guttiferone I and *epi*-guttiferone O (**4**–**8**) were obtained in a very divergent and efficient way (Table 2). It should be noted that the 8-membered ring intermediates could also be detected during the reactions. When these reactions are conducted at room temperature, a high yield of 8-membered ring intermediate such as **16′** from **14f** can be isolated in 73% yield. Apparently from these examples, the newly developed domino Dieckmann cyclization has demonstrated its significant application with the sterically hindered substrates for the synthesis of complex polycyclic molecules.

Although many PPAPs have been reported to exhibit cytotoxicity against cancer cell lines, limited studies have been performed to elucidate their SARs.[19] Following the synthesis, the cytotoxicities of the synthesized PPAPs (**1**–**8** and **21**) and bicyclo[3.3.1]nonanes **15** against the HeLa (cervical cancer), SGC7901 (gastric cancer), and HCT116 (colorectal carcinoma) cell lines were studied (Figure 1, see Supporting Information for the cytotoxicity data). The

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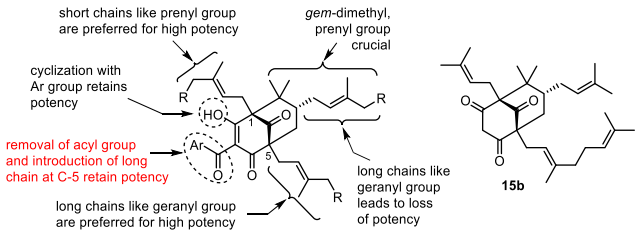

Figure 1. SARs study against three tested cell lines.

biological evaluation revealed a set of structure−activity relationships that could facilitate further optimization. The most notable results were provided by bicyclo[3.3.1]nonanes **15b**, **15e**, and **15f**, which were synthesized for the first time in this study and possess geranyl group at C5. These three simplified compounds showed activity profiles similar to those of PPAPs. The capacity to delete the large acyl group, which is supposed to be crucial to the activity,[20] is both intriguing and unexpected.

In summary, a bioinspired, Me_2AlSEt-promoted domino Dieckmann cyclization via an 8-membered ring was developed in the total synthesis of nine PPAPs. Most of these PPAPs are decorated with the less explored geranyl groups and are synthesized herein for the first time in short steps. The reactions can be run on large scales to give several PPAPs in one sequence. Significantly, both the domino Dieckmann reactions and the *C*-acylation reactions are applicable to the sterically hindered substrates, providing novel strategies for the synthesis of complex molecules. The selectivity and the advantages of the domino cyclization were also studied. Moreover, biological evaluation of the synthesized compounds against three cancer cell lines led to the identification of simplified potent antitumor agents (**15b**, **15e**, and **15f**) from PPAPs for the first time, and a set of SARs that could facilitate further optimization studies was identified.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03078.

Full experimental procedures, characterization data, copies of the NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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