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The Total Syntheses of Guttiferone A and 6-*epi*-Guttiferone A

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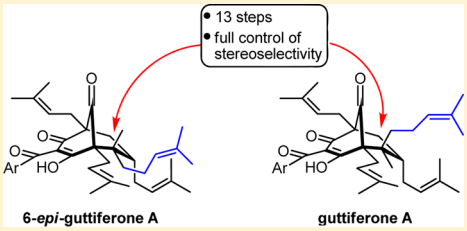
Supporting Information

ABSTRACT: Polyprenylated polycyclic acylphloroglucinols (PPAP) are a constantly growing class of natural products that exhibit a common bicyclo[3.3.1]nonatrione core and consist of currently more than 200 members. A subclassification among the various natural products of this class includes the position of the exocyclic acyl group, the prenylation grade of the core, and the relative configuration at C-7 within the core. About 10% of the reported structures, however, possess an additional chiral center at C-6. Herein we describe a straightforward access to guttiferone A and *epi*-guttiferone A, in which full control of stereoselectivity is achieved via conformational control, and a strict separation of framework decorating from framework constructing operations sets the stage for a short 13-step synthesis.



INTRODUCTION

Within the past 15 years a variety of phloroglucinol-derived natural products with a common bicyclo[3.3.1]nonatrione core have been isolated. The complex bicyclic structure and the high prenylation degree plus the particular placement of the exocyclic acyl group within the core warrant the unusual broad range of bioactivities found in this class of natural products.[1,2] In about 90% of all PPAP structures three endocyclic stereocenters located at C-1, C-5, and C-7 are found. Whereas the former two are connected via the carbonyl bridge, the relative configuration at C-7 relative to C-1/C-5 determines whether the PPAP is considered to be endo- or exo-oriented (Figure 1). The position of the exocyclic acyl group within the core and the C-7 configuration are the two major means that allow a subclassification of the numerous PPAPs into endo- or exo-types A, B, or C (Figure 1). However, in about 10% of the reported PPAPs the C-6-atom is also a stereogenic center, in which a prenyl-type substituent is bound in a trans-configuration relative to the C-7-prenyl-group.[3−5]

The groups of Shibasaki[6] and most recently Shair[7] managed to accomplish elegant total syntheses of hyperforin **1**, an exo-type A PPAP possessing an additional C-6-stereocenter. Herein we describe a concise, highly diastereoselective 10-step total synthesis of guttiferone A **2**, a member of the endo-type B PPAPs. The control of all stereocenters was possible by controlling conformational effects in order to accumulate the substrate induction. Guttiferone A is an active ingredient of different *Garcinia* species, i.e., *Garcinia livingstonei*, *G. macrophylla*, *G. intermedia*, and showed a broad spectrum of bioactivities, i.e. activity against human colon cancer cells (HCT-116, HT-29, SW-480), human ovarian cancer cells (A 2780), protection against Fe-induced neuronal cell damage, and antimicrobial activities.[8−11]

The interesting biological activities and the challenging diastereoselective introduction of the C-6-side chain represent the major sources of inspiration for us to tackle the total synthesis of endo-type B PPAPs possessing an additional stereocenter at C-6 of the bicyclo[3.3.1]nonatrione core.

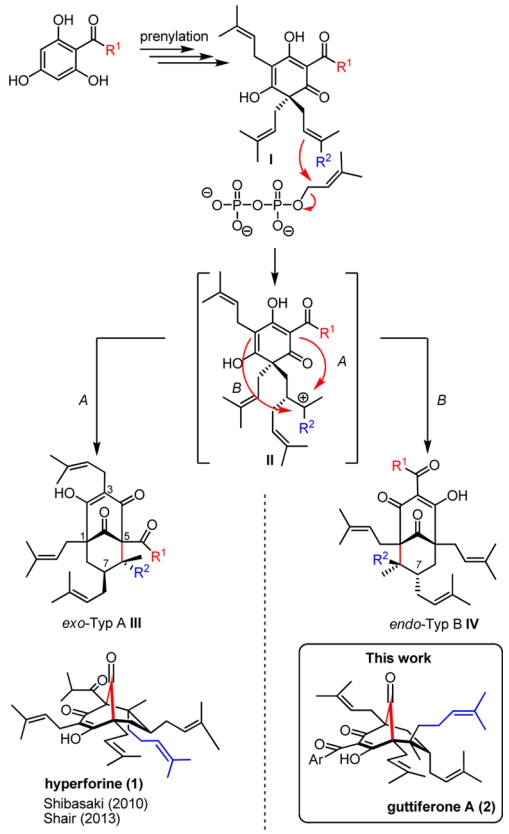


Figure 1. Biosynthesis and molecular structures of hyperforin and guttiferone A.

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Recently, we showed that separating framework-constructing steps from framework-decorating steps allows the efficient construction of various *endo*-type B PPAPs within just 7 steps in a parallel manner.[12] On the basis of these results we wondered whether the 1,4-addition of an alkyl copper reagent could be used to establish the new stereocenter at C-6 within the bicyclic core. Although this step appears to be only a minor modification to the original protocol, the fact that a stereoquartet in **4** has to be established with full control on relative configuration could be troublesome (Figure 2).

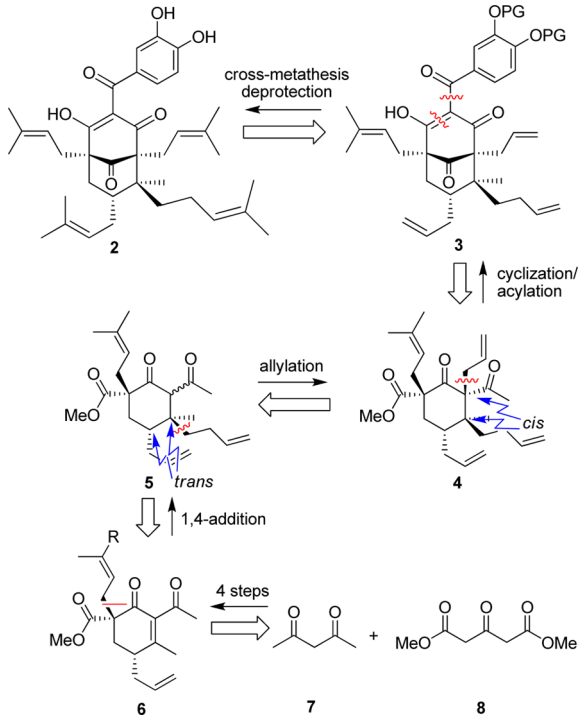

Figure 2. Retrosynthetic analysis.

RESULTS AND DISCUSSION

Total Synthesis of *epi*-Guttiferone A. As shown in Figure 2 the synthesis began using acetylacetone **7** as starting material (Scheme 1). Initial allylation and deacylating aldol condensation[13] furnished the corresponding methylvinylketone **9** in good yield. The subsequent base-mediated tandem Michael-addition−Knoevenagel condensation using dimethyl acetonedicarboxylate **8** led to cyclohexenone **10**, which was directly subjected to a base-mediated regioselective 1,2-addition.[14] Further treatment with isoprenyl bromide led to the diastereoselective formation of cyclohexenone **11**, in which the allyl- and *iso*-prenyl-groups are oriented trans to each other. Having established the first two stereocenters, we performed the 1,4-addition of butenyl-Cu using the modified Yamamoto conditions.[12,15] The reaction exhibited a high degree of diastereoselectivity, but we were surprised to find that the organocopper reagent approached the double bond in **11** cis toward the adjacent allyl group likely due to a nonobvious conformational directing neighbor group effect to give the undesired stereoisomer, **13**. Although not the anticipated diastereomer, we set out to analyze the stereochemical course of the final C-5 allylation (guttiferone numeration). Preliminary studies indicated the Fe-catalyzed allylic substitution[16] that proved previously to be successful for the introduction of an isoprenyl group was not the method of choice. Detailed investigations revealed the Pd-catalyzed decarboxylative allylation[17−19] of **13**-derived allylvinylcarbonates, **15** and **16**, are better suited to obtain good yields and almost perfect stereoselectivity in favor of the cyclohexanone **19**. The new allyl group in **19** was oriented trans to the adjacent C-6 homoallyl group. The subsequent base-mediated cyclization−acylation furnished the fully substituted bicyclo[3.3.1]nonatrione core in **20**, which was concomittantly transferred into 6-*epi*-guttiferone A via cross-metathesis using 2-methyl-2-butene[20] and basic workup (Scheme 1).

Total Synthesis of Guttiferone A: The "Frustrating" Approach. The unexpected stereochemical course of the organocopper 1,4-addition in **11** forced us to change the strategy and to introduce the homoallyl side chain in the beginning of our synthesis (Scheme 2). Hence, benzoylation of ketone **21**[21] and methylenation gave the desired Michael acceptor **22** in good overall yield. Subsequent treatment of **22** with **8** under previously established conditions[12] led to the formation of the corresponding cyclohexenone **23**. Fortunately, the 1,2-addition and isoprenylation gave the desired cyclohexenone **24** in good yield with almost perfect diastereoselectivity. We were pleased to find that the addition of MeCu under Yamamoto conditions proceeded in good yield to give the expected product **25** with exclusive stereoselectivity with regard to the quarternary stereocenter. As observed above, the addition of the MeCu reagent occurred selectively cis to the adjacent allyl group and hence established the correct relative configuration at C-1, C-6, and C-7 (guttiferone numeration). With this compound in hand we investigated the stereochemical course of the Pd-catalyzed decarboxylative allylation and were frustrated to find the C-5−C-6−C-7-configured stereoisomer **31** to be the main product (Scheme 2).

The previously dominating steric influence of the C-7-prenyl group seems to be overruled by the amplifying steric interaction of both the C-6-homoallyl and the C-1-prenyl-group, which results in the formation of cyclohexenone **32** possessing the wrong relative configuration of the two exocyclic carbonyl groups for the attempted intramolecular Claisen condensation.

Total Synthesis of Guttiferone A: The "Successful" Approach. Since in our previous studies the steric demand of the C-7-group was mainly responsible for the diastereoselective course of the C-5-allylation,[12] we were wondering whether the incorporation of the two unsaturated side chains at C-6 and C-7 in **25** into a cyclic structure such as **32** could retard the amplification and might give the desired stereoisomer. Indeed, this assumption proved to be correct (Scheme 3). Hence, the 1,4-addition product **25** was subjected to ring-closing metathesis conditions and gave the anticipated bicyclic product **32** in good yields. Formation of the alloc ethers **33**/**34** and subsequent treatment with $Pd_2(dba)_3$-catalyst under decarboxylative allylation conditions led to the formation of the desired diastereoisomer **38** in good yields and high diastereoselectivity.

The subsequent base-mediated Claisen-condensation led to tricycle **39** possessing the central bicyclo[3.3.1]nonatrione core in good yields. The ring-opening cross-metathesis of **39** proved to be a reliable way to build up three trisubstituted double bonds within one synthetic operation (Scheme 3). After acylation and deprotection, guttiferone A **2** was obtained in 13 steps starting from ketone **21** in a total yield of 13.4% (Scheme 3).

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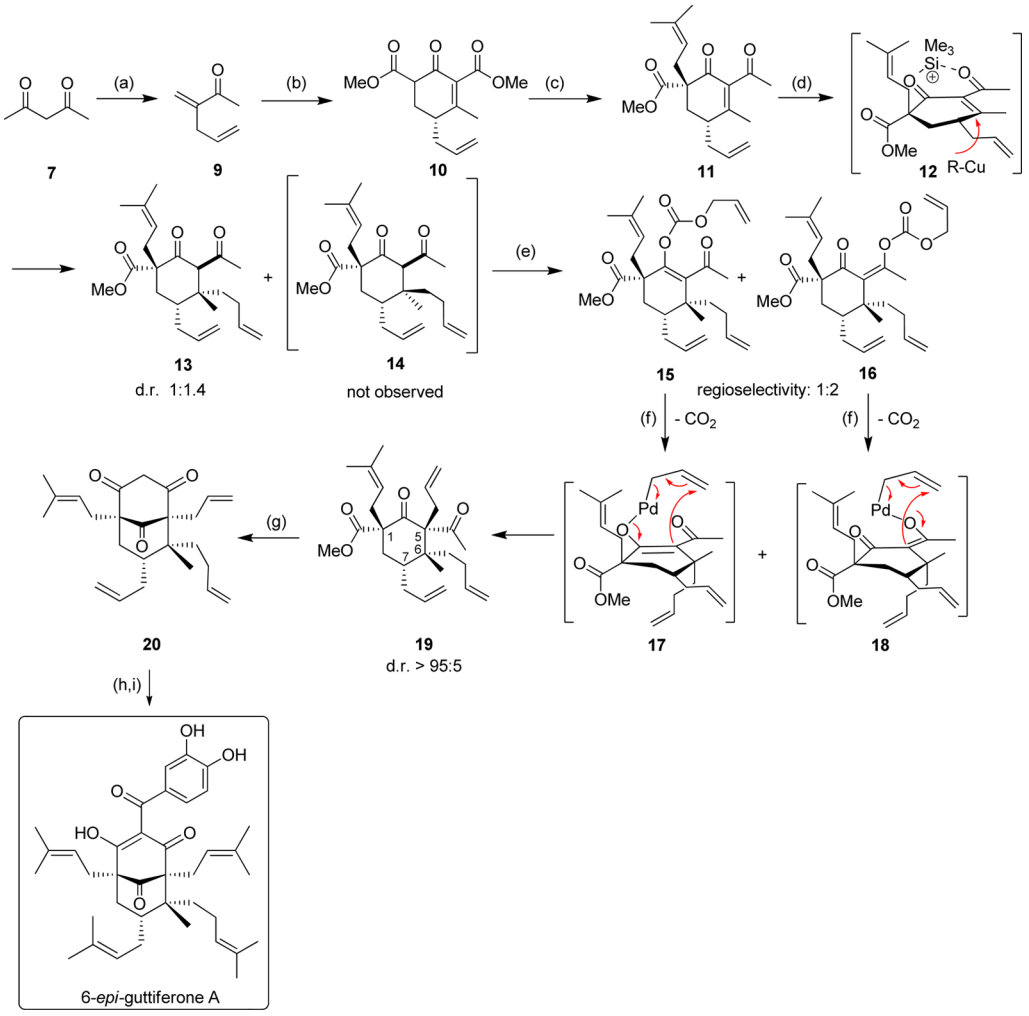
Scheme 1. Total Synthesis of *6-epi*-Guttiferone A[a]



[a]Conditions: (a) NaH (1 equiv), allylbromide (1.2 equiv), then K_2CO_3, $CH_2O_{(aq.)}$, ethanol, 0 °C to rt, 47% (two steps); (b) MeMgCl (2.0 equiv), dimethyl-1,3-acetonedicarboxylate (1.0 equiv), methanol, 0−60 °C, 18 h, 84%; (c) (i) NaH (1.1 equiv), MeLi (2.3 equiv), THF, 0 °C, then (ii) NaH (1.1 equiv), isoprenylbromide (1.5 equiv), THF, 0 °C to rt, 52% (two steps); (d) LiCl (2.0 equiv), CuI (2.0 equiv), TMSCl (2.0 equiv), $CH_2{=}CHCH_2CH_2MgCl$ (2.0 equiv), THF, −78 °C, 4 h, 90%; (e) NaH (1.1 equiv), allylchloroformate (1.5 equiv), DMF, 0 °C − rt, 18 h, 94%; (f) $Pd_2(dba)_3CHCl_3$ (5 mol %), *p*-Tol_3P (12 mol %), 1,4-dioxane, 60 °C, 1 h, 90%; (g) KO*t*Bu (2.0 equiv), quant; (h) Grubbs-II (1 mol %), 2-methyl-2-butene (100 equiv), CH_2Cl_2, 45 °C, 2 h, 96%; (i) KO*t*Bu (5.0 equiv), 3,4-bis-acetoxybenzoyl cyanide (12.5 equiv), THF, K_2CO_3, methanol, 0 °C to rt, 48 h, 58%.

CONCLUSION

In the present contribution we report the 10-step total synthesis of two endo-type B PPAPs, i.e. 6-*epi*-guttiferone A and guttiferone A. The full control of four adjacent stereocenters within a central cyclohexanone motif turned out to be a synthetic challenge. We developed a synthetic algorithm that allows the full control of the diastereoselective course and that could build the base for further total syntheses of higher prenylated PPAPs. In the endo-type-B PPAP synthesis the stereochemical course of every newly formed stereocenter was shown to be directed by only one out of different substituents within the core (Figure 3).

Hence, the trans-stereochemistry at C1 (PPAP-numeration) is mainly directed by the C7-substituent. The addition of the organo copper reagent at C6 occurs cis with respect to the C7-substituent. The sterically more demanding substituent at C6 directs the final allylation at C5 into the trans position (left side, Figure 3). This stereochemical course is not applicable for an endo-type-PPAP synthesis, and we were able to show that a ring-closing metathesis and the resulting conformational change result in a full inversion of the C6-stereochemistry using a Pd-catalyzed decarboxylative Tsuji−Trost allylation.

In order to expand the scope of our synthetic algorithm, future work will concentrate on an extension into the exo-type-PPAP-natural product class. The inversion of the C1-allylation is the crucial step and needs to be developed. If it would be possible to invert the stereochemical course of the C1-allylation and to conserve the stereochemical course of the formation of the C5/C6 stereocenters, the subsequent introduction of all other stereocenters would result in a cyclohexanone that could allow the total synthesis of various exo-type-PPAPs. Synthetic work along these lines is currently being carried out in our laboratories.

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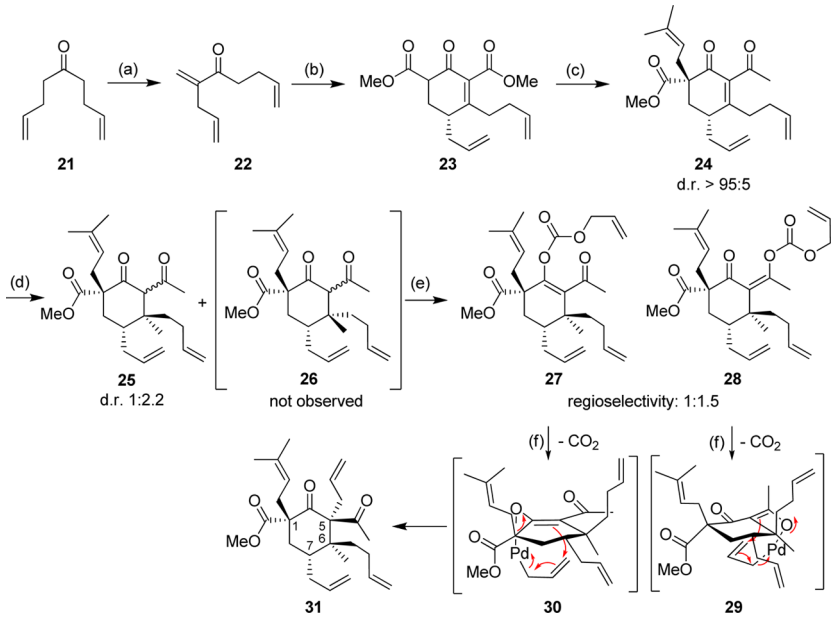
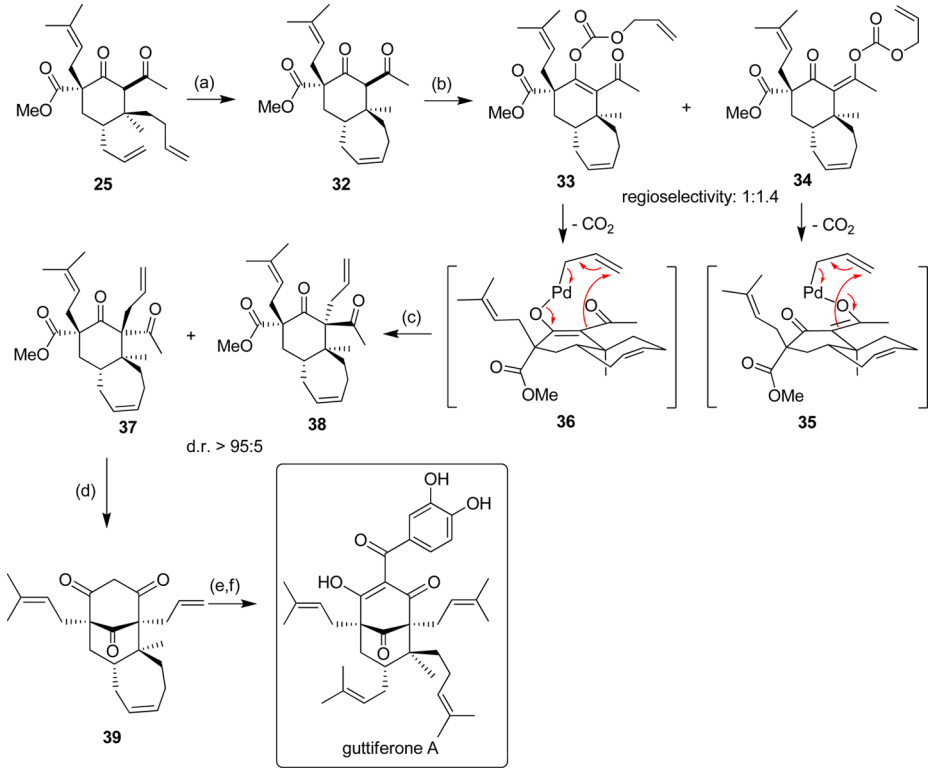
Scheme 2. Total Synthesis of Guttiferone A: "The Frustrating Approach"[a]



[a]Reagents and conditions: (a) LiHMDS (1.2 equiv), benzoyl cyanide (1.5 equiv), THF, −78 °C − rt, 18 h, then K_2CO_3, CH_2O (aq), ethanol, rt, 18 h, 78% (two steps); (b) MeMgCl (2.0 equiv), dimethyl-1,3-acetonedicarboxylate (1.0 equiv), methanol, 0−60 °C, 18 h, 89%; (c) NaH (1.1 equiv), MeLi (2.3 equiv), then NaH (1.1 equiv), prenyl bromide (1.5 equiv), THF, 0 °C to rt, 18 h, 48% (over 2 steps); (d) LiCl (2.0 equiv), CuI (2.0 equiv), MeMgBr (2.0 equiv), Me_3SiCl (2.0 equiv), THF, −78 °C, 4 h, 89%; (e) NaH (1.1 equiv), allyl chloroformate (1.5 equiv), DMF, 0 °C to rt, 18 h, 98%; (f) [Pd_2dba_3] (5 mol %), *p*-Tol_3P (12 mol %), 1,4-dioxane, 60 °C, 1 h, 92%.

Scheme 3. Total Synthesis of Guttiferone A: "The Successful Approach"[a]



[a]Reagents and conditions: (a) Grubbs-II (1 mol %), CH_2Cl_2, 45 °C, 2 h, 94%; (b) NaH (1.1 equiv), allyl chloroformate (1.5 equiv); DMF, 0 °C to rt, 18 h, 98%; (c) [Pd_2dba_3] (5 mol %), *p*-Tol_3P (12 mol %), 1,4-dioxane, 60 °C, 1 h, 94%; (d) KO*t*Bu (2.0 equiv), THF, 0 °C, 15 min, 90%; (e) Grubbs-II (1 mol %), 2-methyl-2-butene (100 equiv), CH_2Cl_2, 45 °C, 2 h, 96%; (f) KO*t*Bu (5.0 equiv.), 3,4-bis-acetoxybenzoyl cyanide (12.5 equiv), then K_2CO_3, methanol, THF, 0 °C to rt, 48 h, 58%.

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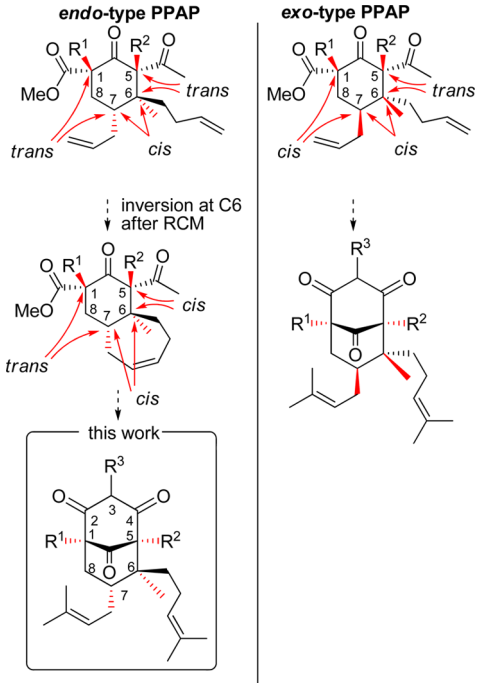

Figure 3. Control of C6-stereochemistry for the total synthesis of endo- or exo-type PPAPs.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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