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A new approach for the construction of a highly congested bicyclic system in polycyclic polyprenylated acylphloroglucinols (PPAPs)

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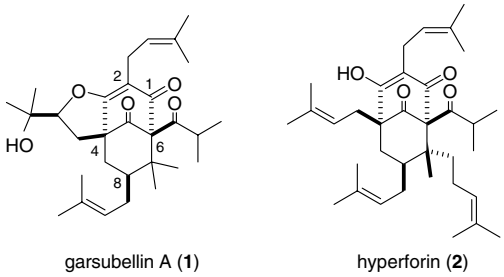
Abstract—A highly congested bicyclo[3.3.1]nonanone core of polycyclic polyprenylated acylphloroglucinols was constructed using a stereoselective Claisen rearrangement and an intramolecular aldol reaction as the key steps. The stereochemistry of C-4 appeared to control the ground state conformation of the cyclohexenone core, which determined the diastereoselectivity in the Claisen rearrangement.

The polycyclic polyprenylated acylphloroglucinols (PPAPs) are a group of naturally occurring secondary metabolites. The isolation and structural determination of PPAPs have been studied intensively. Attention to PPAPs as pharmaceutical leads has recently increased due to their interesting biologic activities. In addition, many PPAPs contain attractive chemical structures from a synthetic viewpoint.[1]

We are especially interested in two compounds in this group, garsubellin A (**1**) and hyperforin (**2**). Garsubellin A was isolated from *Garcinia subelliptica,* and its structure was determined by Fukuyama et al.[2] Garsubellin A potently induces choline acetyltransferase (154% at 10 μM compared to negative control), and it is this property that has led to the consideration of garsubellin A as a pharmaceutical lead for the treatment of Alzheimer's disease. Hyperforin is extracted from St. John's wort, *Hypericum perforatum*.[3] This Western herb inhibits serotonin uptake and has mild antidepressant activity. In vitro biologic studies suggest that hyperforin is responsible for this activity.[4] Other noteworthy properties of hyperforin are its antibacterial activity[5] and its ability to repress the effectiveness of other drugs through drug–drug interactions[6] (Fig. 1).



garsubellin A (**1**) hyperforin (**2**)

Figure 1.

Due to their high structural complexity, however, chemical synthesis of PPAPs is extremely challenging. One of the most difficult steps is the construction of the highly congested bicyclo[3.3.1]nonanone system containing two bridgehead quaternary carbons.[7–9] We achieved the first total synthesis of (±)-garsubellin A in 2005.[10a] In that synthesis, we constructed the bicyclic skeleton through stereoselective Claisen rearrangement, ring-closing metathesis, and allylic oxidation as the key steps (Scheme 1). Although excellent diastereoselectivity was produced in the Claisen rearrangement, the origin of the stereoselectivity in this key reaction was not clear. Moreover, the realization that this approach was not applicable to hyperforin synthesis due to the existence

Keywords: Polycyclic polyprenylated acylphloroglucinols (PPAPs); Garsubellin A; Hyperforin; Bicyclo[3.3.1]nonanone core; Claisen rearrangement; Intramolecular aldol reaction.

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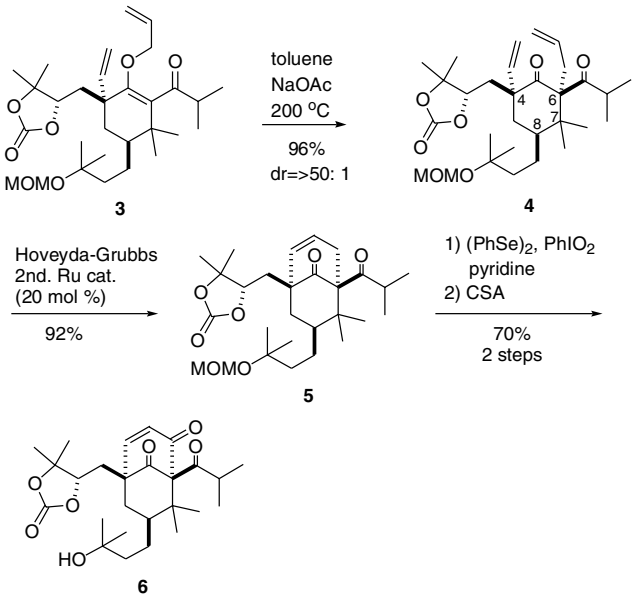
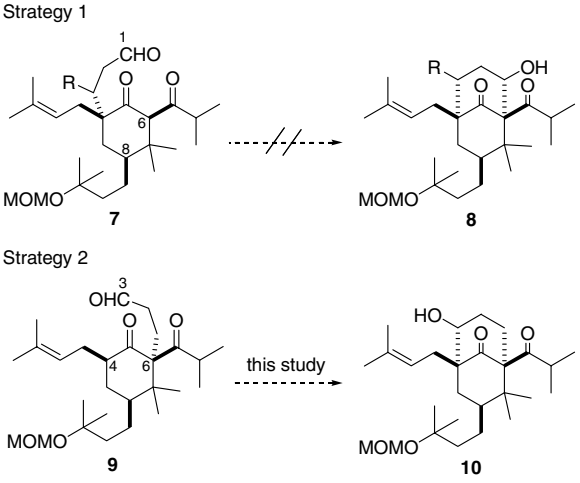


Scheme 1. Construction of bicyclo[3.3.1] system in garsubellin A synthesis (Ref. 10a).

of multiple prenyl groups in the metathesis step[11] forced us to change our synthetic strategy. In this Letter, we describe an alternative method for constructing bicyclo[3.3.1]nonanone with double bridgehead quaternary centers, which is also applicable for the synthesis of a hyperforin system containing free prenyl groups. The origin of the stereoselectivity in the key Claisen rearrangement is also proposed.

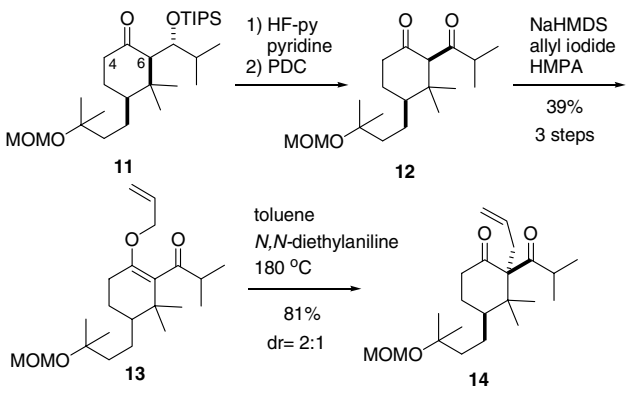
As a 'metathesis-free' strategy for constructing the bicyclic skeleton, we focused on an intramolecular aldol-type reaction (Scheme 2). The prenyl groups should be tolerated in this strategy. In addition, an oxygen functionality can be installed at an appropriate position on the bicyclic system through carbon–carbon bond formation. Indeed, we used this strategy in the synthesis of 8-deprenyl garsubellin A;[8d,e] the bicyclic system was constructed through an aldol-type reaction between C-6 and C-1 (Strategy 1 in Scheme 2). This type of intramolecular aldol reaction, however, did not proceed in the synthesis of garsubellin A, probably due to the higher congestion at the C-6 nucleophilic center in actual substrate **7** compared to the model substrate without a C-8 substituent. In addition, this aldol-type reaction between an aldehyde and a β-diketone is thermodynamically unfavorable. Therefore, a slight change in the cyclohexanone conformation caused by the C-8 substituent could destabilize the product. Based on these results, we selected Strategy 2, which involved an aldol reaction between C-4 and C-3. Claisen rearrangement should reliably provide the ethylformyl group at C-6 of **9**.



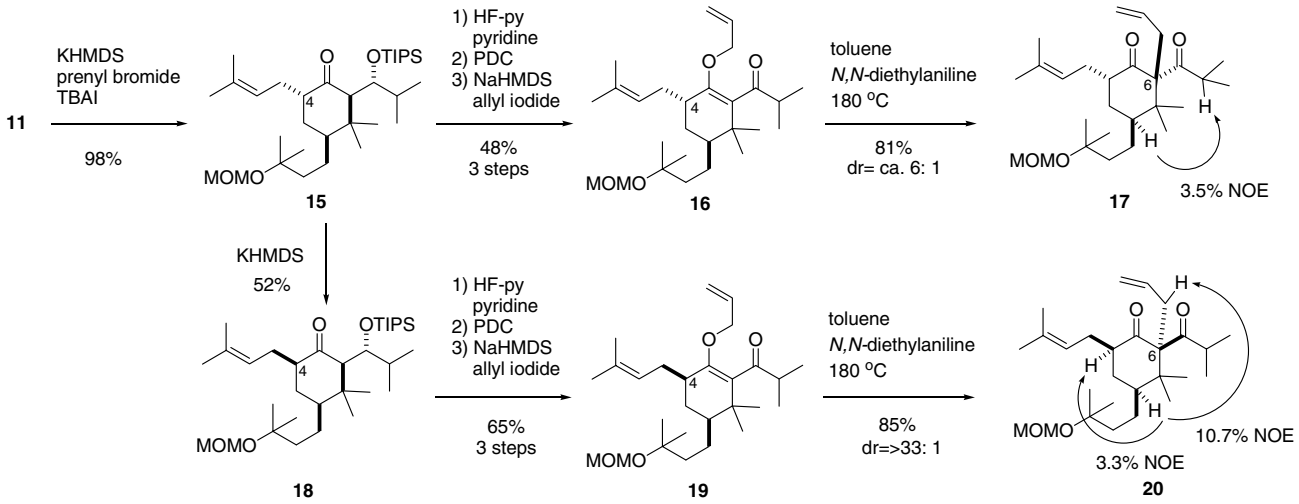
Scheme 2. Intramolecular aldol strategy to construct the bicyclo[3.3.1] system.

Based on these considerations, we began our studies of the Claisen rearrangement with a simple substrate **13**, containing a garsubellin A substitution pattern and without a substituent at C-4. Synthesis of **13** was achieved through three steps from the known compound **11**.[10a,12] Thus, treatment of **11** with HF-py afforded the corresponding secondary alcohol, which was oxidized with PDC at 50 °C. The resulting β-diketone **12** was subjected to selective O-allylation, giving **13** in reasonable yield. The Claisen rearrangement of **13** proceeded by heating a toluene solution of **13** in a sealed tube at 180 °C in the presence of *N*,*N*-diethylaniline.[13] The C-6 quaternary center was constructed in this step in high yield. In contrast to (±)-garsubellin A synthesis (from **3** to **4** in Scheme 1 in which only one isomer was detected); the diastereoselectivity of the Claisen rearrangement was disappointingly low (dr = 2:1).

To clarify the reason for this unexpected outcome, the effect of the substituent (prenyl group) at C-4 on the stereoselectivity of the Claisen rearrangement was investigated. Two precursors, **16** and **19**, were synthesized as shown in Scheme 4. The potassium enolate derived from **11** was prenylated from the α-side (axial attack) stereoselectively, producing **15** as a single isomer. β-Prenylated compound **18** was synthesized through epimerization at C-4 from **15** under basic conditions. Subsequent desilylation, oxidation, and O-allylation from **15** and **18** following the same procedure as described in Scheme 3



Scheme 3. Claisen rearrangement of simple substrate.

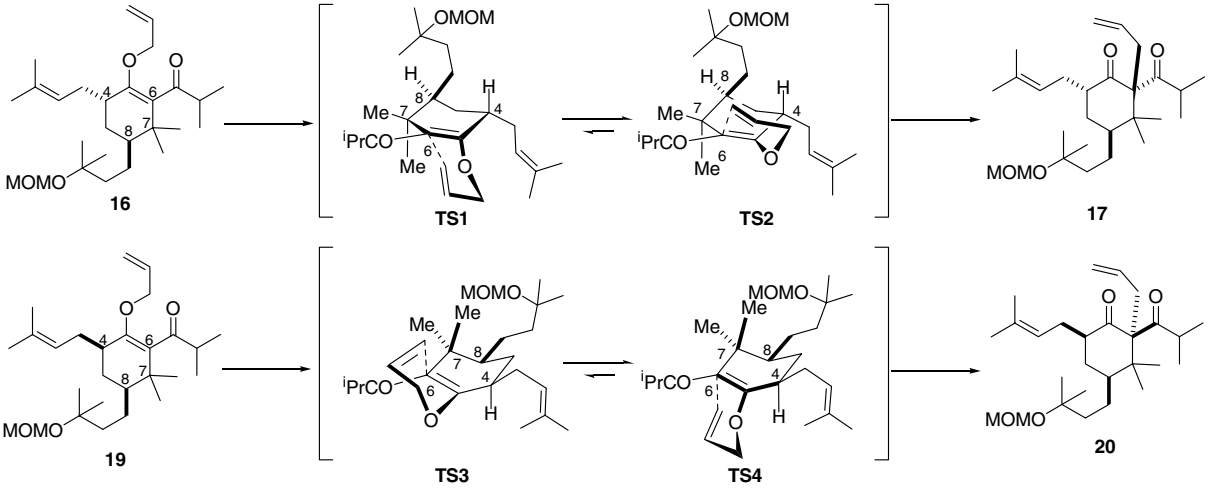


Scheme 4. Effect of C-4 prenyl side chain on diastereoselectivity of the Claisen rearrangement.

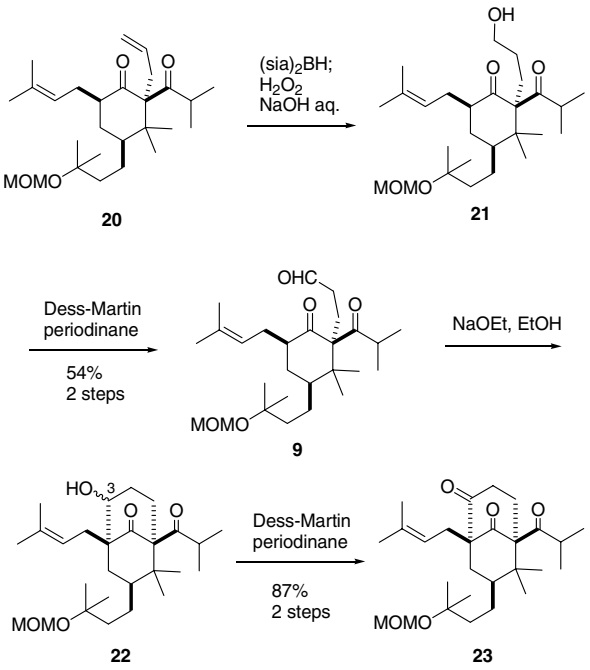
gave Claisen rearrangement precursors **16** and **19**, respectively. The Claisen rearrangement proceeded with high yield for both substrates. The allyl group rearranged with β-selectivity (ca. 6:1) when using **16**, whereas with predominant α-selectivity (>33:1) when using **19**.[14] Therefore, the rearrangement occurred from the opposite side to the prenyl group at C-4 in both cases. These results demonstrated that the stereochemistry at C-4 determines the diastereoselectivity of the Claisen rearrangement, that is, the stereochemistry of the quaternary carbon at C-6.

This stereoselectivity can be explained as follows (Scheme 5). Based on molecular modeling studies,[15] the most stable ground state conformation of **16** is a half-chair with the C-4 prenyl group at the equatorial position. Based on this ground state conformation, Claisen rearrangement should proceed from the β-face of C-6 (**TS2**) to avoid steric repulsion between the C-7 axial methyl and reacting allyl groups. A similar approach might be applicable for the stereoselectivity of the conversion from **19** to **20**. Precursor **19** also prefers the half-chair conformation with the C-4 prenyl group and the C-8 substituent both at equatorial positions. The allyl group should enter C-6 from the α-face (**TS4**), avoiding the C-7 axial methyl group. These results suggest that the C-4 prenyl group, rather than the C-8 substituent, determines the conformation of the cyclohexene core, leading to the fixation of the dimethyl groups' positions at C-7. The allyl group rearranges to C-6 from the opposite side to the axial methyl at C-7.[16] This stereochemical model also explains the stereochemistry of the Claisen rearrangement in the synthesis of garsubellin A (**3** to **4**, Scheme 1).

Further conversion of **20** to a bicyclo[3.3.1]nonanone core of PPAPs was conducted. Terminal olefin-selective hydroboration was accomplished using disiamylborane followed by oxidative workup. Subsequent oxidation of the resulting primary alcohol **21** with Dess–Martin periodinane produced aldehyde **9**. The second key conversion, an intramolecular aldol reaction, proceeded under basic conditions in the presence of NaOEt, providing the bicyclic compound **22** as a diastereomix-



Scheme 5. Proposed model for stereochemical course of the Claisen rearrangement.



Scheme 6. Successful construction of bicyclo[3.3.1]nonanone core.

ture at C-3.[17] The subsequent Dess–Martin oxidation produced the important synthetic intermediate **23**. Thus, a highly congested bicyclic core of PPAPs was constructed and the prenyl group was tolerated (Scheme 6).

In summary, we developed a new approach for constructing the bicyclo[3.3.1]nonanone core of PPAPs using a Claisen rearrangement and an intramolecular aldol reaction as the key steps. The stereochemical course of the Claisen rearrangement of the three compounds (**13**, **16**, **19**) revealed that the diastereoselectivity was dependent on the conformation of the core six-membered ring, which was controlled by the stereochemistry at C-4. Using an intramolecular aldol reaction, the bicyclic system was constructed while maintaining the prenyl group, which was problematic in the former metathesis approach. The two findings should be useful for developing an improved synthetic route for garsubellin A, as well as for the total synthesis of hyperforin.[18] These studies are ongoing.

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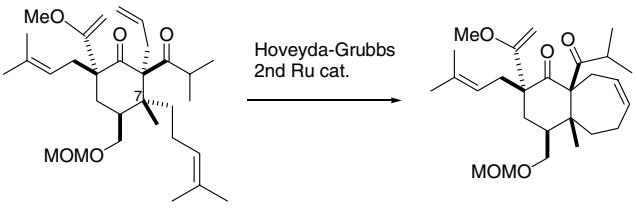
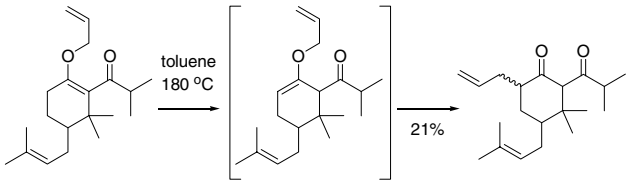
11. In the presence of a prenyl group at C-7 in the hyperforin system, ring-closing metathesis proceeded between the terminal vinyl group and the prenyl group (for a representative result, see Scheme 7), and the desired bicyclo[3.3.1] formation did not proceed at all. In addition, attempts to protect the prenyl group through Mukaiyama hydration, which was used in our garsubellin A synthesis, failed.



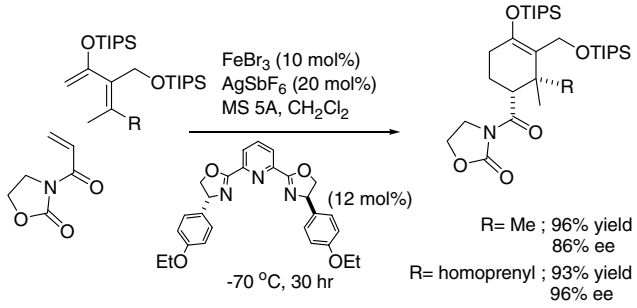
Scheme 7.

12. All studies described in this paper were conducted using racemic compounds.
13. In the absence of *N*,*N*-diethylaniline, double bond isomerization proceeded before Claisen rearrangement (see Scheme 8 for a representative result).



Scheme 8.

14. Relative configurations were determined by NOE analysis.
15. A preliminary conformation search was conducted by CONFLEX5 using an MMFF force field.
16. The model in Scheme 5 also explains the extent of stereoselectivity (ca. 6:1 from **16** vs >33:1 from **19**). There is 1,3-diaxial repulsion between the C-8 substituent and reacting allyl group in **TS2**. No such TS-destabilizing interaction exists, however, in **TS4**.
17. Spiro bicyclic products via intramolecular aldol reaction with the *iso*-propyl ketone were not detected.
18. We developed a catalytic asymmetric Diels–Alder reaction aiming at asymmetric total synthesis of PPAPs: Usuda, H.; Kuramochi, A.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2004**, *6*, 4387. Recent improved results were shown in Scheme 9.



Scheme 9.