Communication

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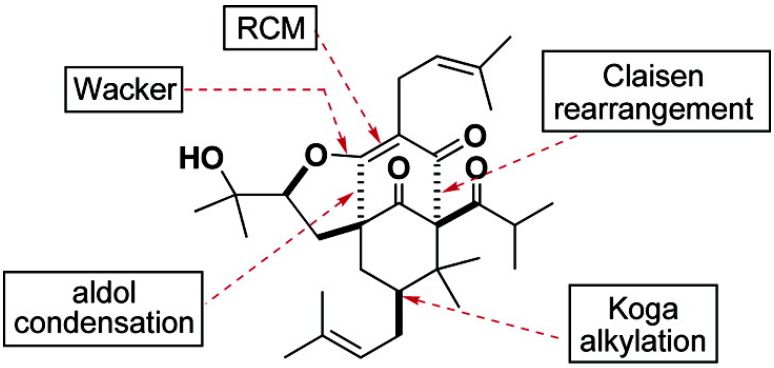

garsubellin A

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Total Synthesis of (±)-Garsubellin A

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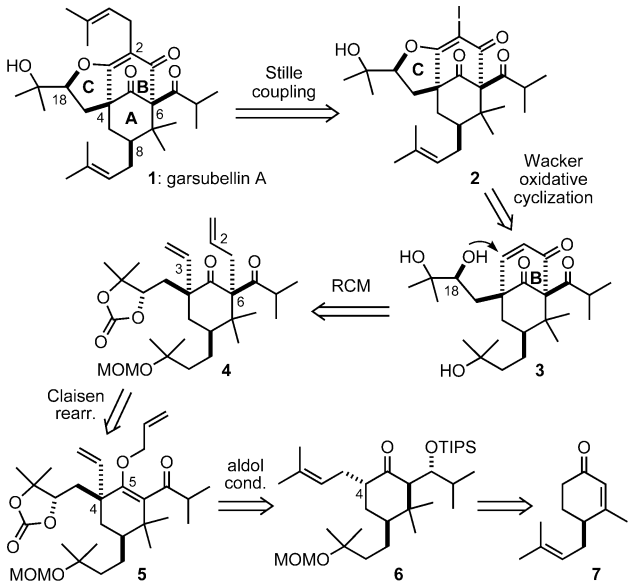
Garsubellin A (**1**) was isolated from *Garcinia subelliptica* by Fukuyama et al., and its structure was determined through intensive NMR studies.[1] Structurally, garsubellin A is a polyprenylated phloroglucin derivative that contains a characteristic highly congested bicyclo[3.3.1]nonane-1,3,5-trione core fused to a tetrahydrofuran ring. Garsubellin A has potent neurotrophic activity by inducing choline acetyltransferase, a key enzyme for physiologic acetylcholine synthesis in the nervous system. Due to its significant biological activity and challenging structure, garsubellin A is an attractive synthetic target.[2] In this communication, we report the first total synthesis of garsubellin A.

The most difficult step in the synthesis of **1** was anticipated to be the construction of the extremely congested quaternary carbon, C-6. Our previous studies targeting 8-deprenyl garsubellin A[2e] demonstrated that the B-ring could be constructed via an intramolecular aldol-type reaction between C-1 and C-6 (Scheme 2; R = H). When this strategy was applied to the real system (R = prenyl, Scheme 2), however, the desired cyclization did not proceed, possibly due to the destabilization of the reactive conformation for this cyclization by the prenyl group.

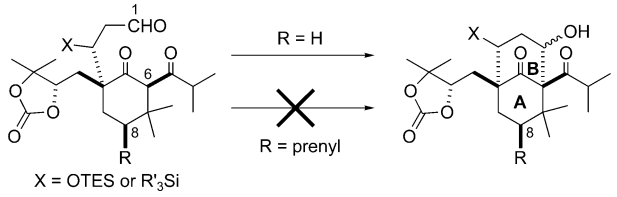
On the basis of these preliminary results, we developed a new synthetic plan, as shown in Scheme 1. The prenyl group at C-2 would be introduced at the last stage through Stille coupling between a prenyl tin reagent and vinyl iodide **2**. The C-ring in **2** would be constructed via a Wacker-type oxidative cyclization of hydroxyenone **3**. For the key B-ring formation, we planned to apply ring-closing metathesis (RCM) to diene **4**, which would be produced via Claisen rearrangement of allyl ether **5**. The precursor ketone for **5** would be produced through a stereoselective aldol condensation at C-4 followed by dihydroxylation from **6**, which can be rapidly assembled from enone **7**. The advantages of this new strategy for B-ring formation, compared to the previous intramolecular aldol strategy, include the following: (1) irreversibility and robustness of RCM in six-membered ring formation; (2) the connection at the C-2−C-3 bond is entropically more favorable than the previous C-1−C-6 connection. We expected that the two alkenes at C-4 and C-6 should be introduced in a cis fashion, which is an essential requirement for RCM, based on the following considerations: (1) Claisen rearrangement of **5** will produce the desired α-allylated product **4** stereoselectively via a six-membered chair transition state; (2) intermolecular aldol reaction at C-4 will proceed from the α-face through an axial attack.

We began our synthesis with enone **7** prepared from commercially available **8** via prenylation followed by methylation and acid hydrolysis of the vinyl ether. Cu-catalyzed conjugate addition of the methyl group and an in situ trapping of the resulting magnesium enolate by isobutyraldehyde gave the *anti*-aldol product as a major isomer (*anti*:*syn* = >50:1, 4:1 of two possible *anti*-isomers), which was protected by a TIPS group to give **9**. After protecting the prenyl group using Mukaiyama hydration,[3] a second prenyl group was introduced to C-4 predominantly (>30:1) at the axial position to give **6**. Because C-6 is significantly more crowded than C-4, selective deprotonation occurred at C-4 to produce Δ(4,5)-enolate when **6** was treated with base.[4] Thus, aldol reaction with acetaldehyde proceeded selectively (>50:1) at C-4 from the α-side (axial attack). Dehydration of this aldol to **10** was conducted using Martin sulfurane. Chemoselective dihydroxylation of the prenyl group was possible at this stage using AD-mix-α (diastereoselectivity = 1:1), giving diol **11**.[5] Protection of the diol as its carbonate, followed by desilylation and oxidation, produced diketone **12**.

Scheme 1. Synthetic Plan for Garsubellin A



Scheme 2. Intramolecular Aldol Strategy (from ref 2e)



The crucial B-ring formation was accomplished in three straightforward steps from **12**: O-allylation,[6] stereoselective Claisen rearrangement through a hypothetical transition state **13** (>50:1), and ring-closing metathesis using the Hoveyda−Grubbs catalyst **14**.[7] Allylic oxidation of **15** under Barton's conditions[8] produced the corresponding enone in excellent yield. The order of the following conversions was crucial for the success of the total synthesis. First, the MOM ether was cleaved using CSA to give the tertiary alcohol **16**. Next, hydrolysis of the carbonate (giving **3**) followed by Wacker oxidative cyclization produced **17**. Then, iodination and dehydration under acidic conditions to regenerate the prenyl group at C-8 produced vinyl iodide **2**. Finally, Stille coupling of **2** with tributyl prenyl tin completed the total synthesis

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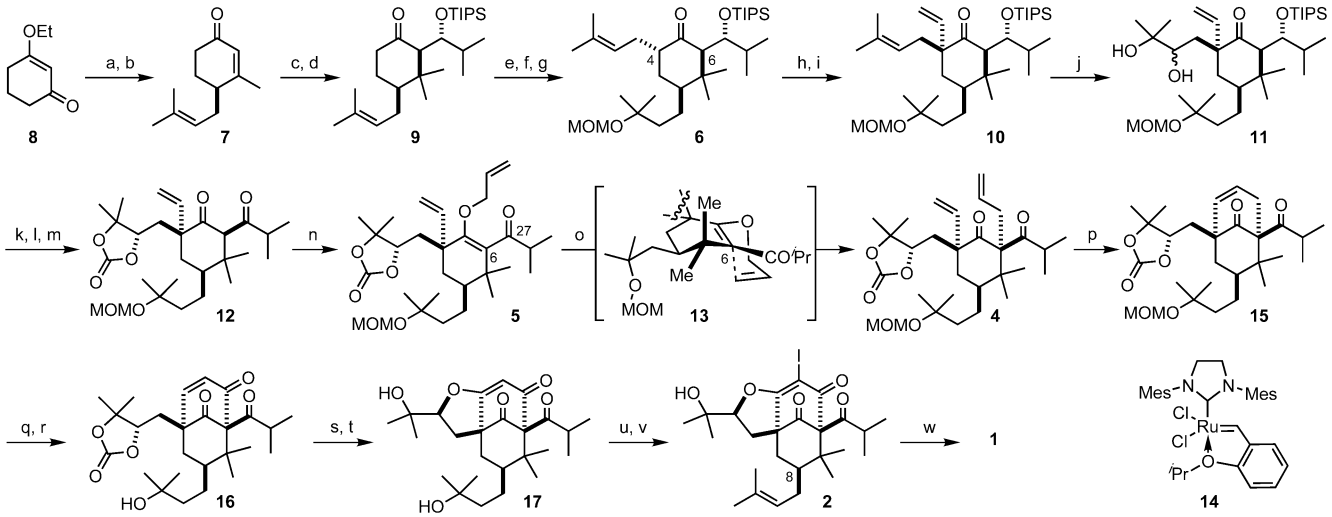
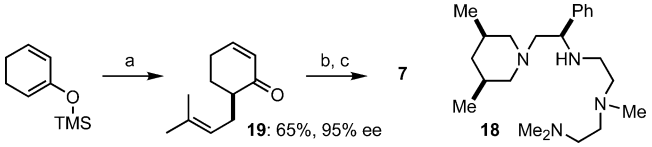
Scheme 3. Total Synthesis of (±)-Garsubellin A[a]



[a] Conditions: (a) LDA; prenyl bromide, Bu_4NI. (b) MeLi·LiBr; HCl, 100% (two steps). (c) MeMgBr, CuI (22 mol %); ^{i}PrCHO, 61%. (d) TIPSOTf, 2,6-lutidine, 92%. (e) $PhSiH_3$, $Co(acac)_2$ (20 mol %), O_2, 73%. (f) MOMCl, $^i Pr_2NEt$, Bu_4NI, 96%. (g) KHMDS, prenyl bromide, Bu_4NI, 98%. (h) LDA, TMEDA; CH_3CHO, 94%. (i) Martin sulfurane, 98%. (j) AD-mix-α (0.4 mol % of Os), $CH_3SO_2NH_2$. (k) Triphosgene, pyridine; separation, 30% (two steps). (l) HF·pyridine. (m) PDC, Celite, 70% (two steps). (n) NaHMDS, MS4A, ethylene carbonate; allyl iodide, 82%. (o) NaOAc, 200 °C, 96%. (p) **14** (20 mol %), 92%. (q) $(PhSe)_2$, $PhIO_2$, pyridine. (r) CSA, 70% (two steps). (s) LiOH. (t) Na_2PdCl_4, TBHP, 71% (two steps). (u) I_2, CAN. (v) *p*-TsOH·H_2O, 80% (two steps). (w) $PdCl_2$·dppf, tributyl prenyl tin, 20%.

Scheme 4. Application of Koga Alkylation to Asymmetric Synthesis of Garsubellin A[a]



[a] Conditions: (a) MeLi·LiBr, **18** (5 mol %), $Me_2N(CH_2)_3NMe_2$, prenyl bromide. (b) MeLi; (c) PCC, 93% (two steps).

of (±)-garsubellin A. Spectroscopic data (^{1}H NMR, IR, MS, HRMS) of synthetic **1** were completely identical to the isolated garsubellin A.

This synthesis can be extended to an asymmetric synthesis of garsubellin A using the catalytic enantioselective alkylation method developed by Koga[9] (Scheme 4). Koga alkylation of the lithium enolate derived from 2-cyclohexenone produced the prenylated product **19** with 95% ee in the presence of chiral amine **18** (5 mol %). **19** was converted to enone **7** (enantioenriched form), an early-stage intermediate in our synthesis, via the addition of MeLi to the ketone followed by allylic rearrangement using PCC.

In conclusion, we have achieved the first total synthesis of garsubellin A. The keys for success are (1) the stereo- and regioselective introduction of the vinyl group at C-4 via aldol condensation, (2) the stereoselective allylation at C-6 via Claisen rearrangement, and (3) ring-closing metathesis for construction of the sterically congested B-ring. On the basis of these results, catalytic asymmetric synthesis of garsubellin A and studies of its biological activity are currently ongoing.

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Supporting Information Available: Experimental procedures and characterization of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(4) Attempted alkylation of the enolate failed on substrates in which the prenyl group had been dihydroxylated.

(5) Using AD-mix-β retarded the reaction without changing the selectivity. Prenyl group-selective dihydroxylation was not possible after cleavage of the TIPS group.

(6) (a) Ethylene carbonate was added to prevent undesired carbonate hydrolysis. (b) Although the regioselectivity of this enolization/O-allylation was not rigorously determined, either of the two possible products (**5** or C-27 allyl ether) can stereoselectively give **4** via Claisen rearrangement.

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