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# Studies toward the total synthesis of garsubellin A: synthesis of 8-deprenyl-garsubellin A

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**Abstract**—During studies directed toward the total synthesis of garsubellin A, synthesis of 8-deprenyl-garsubellin A, containing three (of four in the natural product) stereocenters with the proper configurations, was achieved. Key steps are a one-pot lactone formation, a formal migration to the bicyclo[3.3.1]nonane-1,3,5-trione, and an intramolecular Wacker-type tetrahydrofuran formation. 

Garsubellin A (**1**, Fig. 1), isolated from *Garcinia subelliptica* by Fukuyama et al., is a potent inducer of choline acetyltransferase and might thus be a promising pharmaceutical agent for treating Alzheimer disease.[1] Structurally, garsubellin A is a polyprenylated phloroglucin derivative characterized by a highly oxygenated and densely substituted bicyclo[3.3.1]nonane-1,3,5-trione core fused to a tetrahydrofuran ring and appended by a prenyl side chain. The structural complexity and the biologic activity of garsubellin A prompted us[2] and the Nicolaou group[3] to investigate its total synthesis. We recently reported a concise synthesis of the most advanced tricyclic core in a model system **3**. The obtained stereoisomer, however, contained an unnatural configuration at C-18 resulting from the key one-pot lactone formation (from **11a**/**12a** to **13**, see below). We report herein a synthesis of 8-deprenyl-garsubellin A (**2**) in which all the stereocenters match the natural configurations.

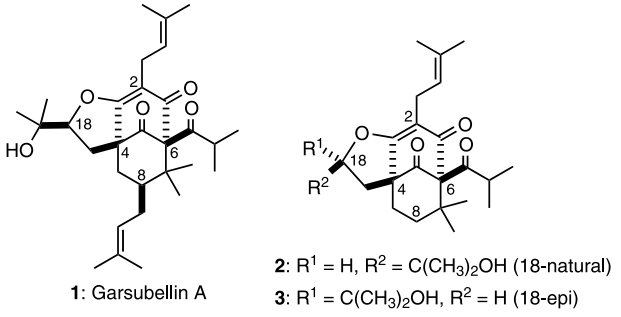
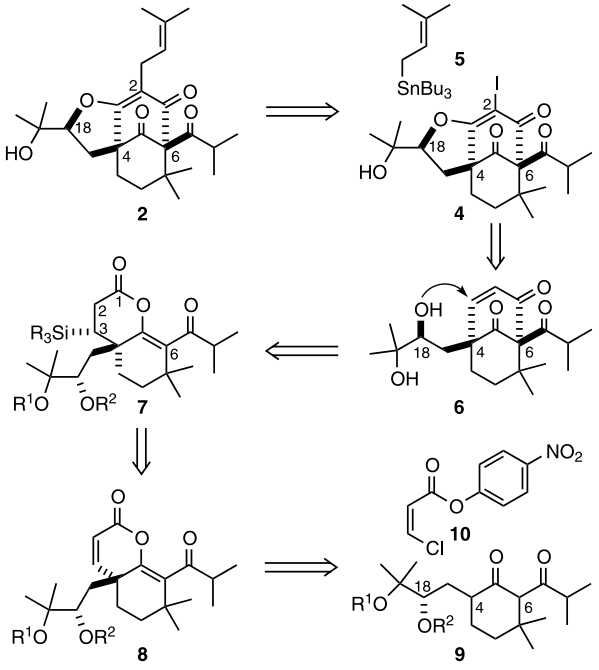



**Figure 1.**

Our retrosynthetic analysis guided by previous studies for the synthesis of **3** is shown in Scheme 1. The prenyl group at the C-2 position should be introduced at the last stage via Stille coupling between tributylprenyltin




**Scheme 1.** Retrosynthetic analysis.

*Keywords*: garsubellin A; cyclic carbonate; one-pot reaction; Tamao oxidation; Wacker-type reaction; Stille coupling.

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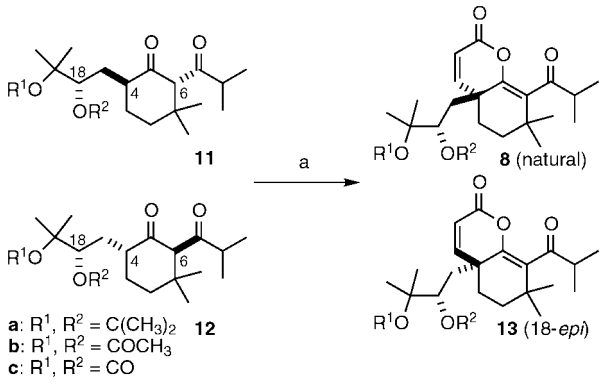
(**5**) and vinyl iodide **4**. The tetrahydrofuran ring of **4** should be constructed via an intramolecular Wacker-type reaction of enone **6**. The bicyclo[3.3.1]nonane-1,3,5-trione core of **6** should be constructed through a formal migration of lactone **7**. In this transformation, the silyl group should act as a scaffold to produce the enone olefin, as well as increase the flexibility of the attached carbon chain (C-1–C-3) for the C-1 electrophilic carbon to reach the C-6 nucleophilic carbon. Compound **7** should be synthesized through a conjugate addition of a silyl group to lactone **8**, which should be synthesized by a one-pot lactone formation from **9** and **10**. There are two major concerns in the present synthesis. (1) How is the stereoselectivity of the key lactone formation reversed? (2) Is the synthetic sequence developed for the *epi*-form (**3**) applicable to the isomer containing the natural configurations?

We started our investigations on point (1). Previously, we developed a one-pot lactone formation from **11a**/**12a** and **10** to **13a** (18-*epi* ) (Scheme 2).[2] The overall reaction proceeded through a regioselective potassium enolate formation at C-4 of **11a**/**12a**, transmetalation to the corresponding lithium enolate, Michael addition to **10**, followed by an elimination of the chloride, enolate formation at C-6, and lactonization. The stereoselectivity of this reaction was high (5:1–25:1), giving unnatural **13a** as the major isomer, irrespective of the configuration at C-6 (Scheme 2, entries 1–3). Therefore, the selectivity was mainly determined by the stereochemistry at C-18. Because it was impossible to invert the configuration of C-18 at a later stage of the synthesis,[4] we attempted to reverse the stereoselectivity of this key lactone formation. The detailed structure of the corresponding lithium enolate derived from **11a**/**12a** was not clear, however, we hypothesized that the high stereoselectivity of the lactone formation could be attributed to the coordination of the oxygen atom at C-18 to the lithium atom of the lithium enolate. Based on this hypothesis, we expected that the stereoselectivity would change if the coordination of the C-18 hydroxyl group was reduced by choosing the appropriate protecting group. Thus, we synthesized **12b** and **11c**/**12c** containing acetyl groups and a cyclic carbonate, respectively, from the previously reported intermediate.[5]

Results of the lactone formation from **12b** and **11c**/**12c** are summarized in Scheme 2 (entries 4–7).[6] Although the reaction from acetyl-protected **12b** gave a low yield of the target lactone (entry 4), the cyclic carbonate-protected **11c** gave **8c** containing the natural configurations as the major isomer (4:1, entry 5). On the other hand, the other diastereomer **12c** gave the 18-*epi* form **13c** as the major isomer with a reduced selectivity (1:2.6, entry 6). These results indicated that in sharp contrast to the acetonide-protected **11a**/**12a**, the direction of the electrophile entry was mainly determined by the configuration at the C-6 carbon in the case of **11c**/**12c**.[7] The dependency of the stereoselectivity on the different stereocenters of the substrates (C-18 in the case of acetonide **11a**/**12a** versus C-6 in the case of cyclic carbonate **11c**/**12c**) might be explained by the difference in the coordination ability of the oxygen atom on C-18




| entry | 11/12 | 8 + 13/% (8 : 13) |
|---|---|---|
| 1 | **11a** | 76 (1:25) |
| 2 | **12a** | 63 (1:5) |
| 3 | **11a** + **12a** | 71 (1:11) |
| 4 | **12b** | < 10 |
| 5 | **11c** | 70 (4:1) |
| 6 | **12c** | 50 (1:2.6) |
| 7 | **11c** + **12c** | 60 (1.2:1) |

**Scheme 2.** Key step one-pot lactone formation. *Reagents and conditions*: (a) 1. KO$^t$Bu (3 equiv.), −78°C, 100 min; 2. $LiClO_4$ (4.5 equiv.), −78°C, 50 min; 3. **10** (2 equiv.), −78°C, 5.5 h; 4. DMAP (5 equiv.), 12-crown-4 (6 equiv.), −78°C to rt, 30 h.

to the lithium atom of the intermediate lithium enolate. In the case of acetonide **11a**/**12a**, the oxygen atom on C-18 strongly coordinates to the lithium, which constrains the bulky acetal moiety at the position to block the electrophile entry from the α-side of the electrophile (Fig. 2). On the other hand, in the case of cyclic carbonate **11c**/**12c**, the electrophile should react through the axial attack to the enolate in the most probable conformation.[8] Because the stereochemistry of C-4 and C-6 disappears in this one-pot lactone formation, we performed the reaction with a mixture of diastereomers **11c** and **12c** (1:1.3) to produce **8c** and **13c** in a ratio of 1.2:1 (60% yield, Scheme 2, entry 7). This procedure could greatly simplify the overall synthetic route. These isomers were easily separable by silica gel column chromatography.

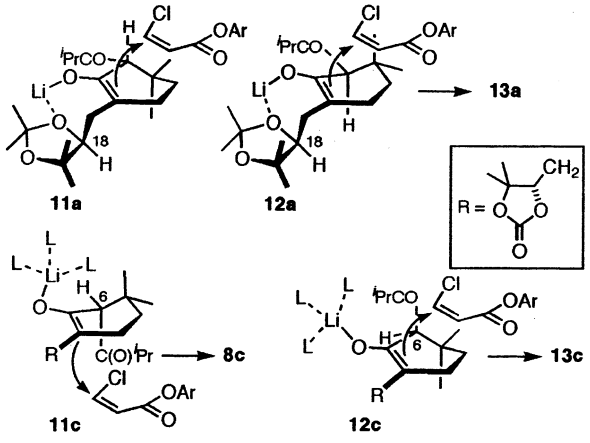
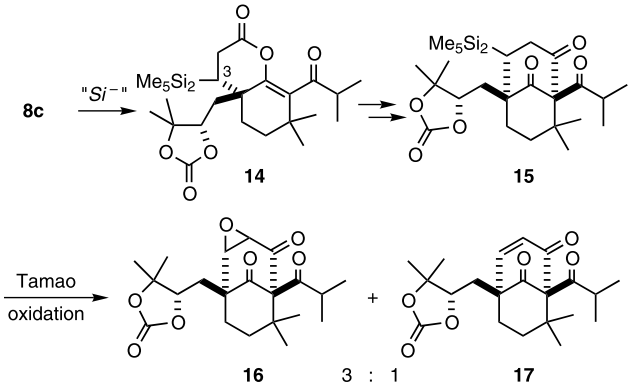



**Figure 2.** Working model to explain the stereoselectivity.

Once the key intermediate lactone **8c** was produced, the next set of tasks were to introduce a silicon at C-3, formal migration to the bicyclo[3.3.1] system, and re-generation of the olefin through Tamao oxidation[9] and β-elimination to give enone **17**. In previous studies, the pentamethyldisilyl group[10] was optimal for our purpose in terms of its stability during the several conversions and susceptibility to Tamao oxidation, when necessary. In the present case (Scheme 3), however, although the conjugate addition of a silylcuprate and the following migration to the bicyclo[3.3.1] system **15** were successful, Tamao oxidation using *m*CPBA and TBAF gave epoxide **16** as the major product. Compound **16** was produced through epoxidation of the concomitant enone **17** that resulted from β-elimination of the target alcohol under basic conditions of Tamao oxidation.

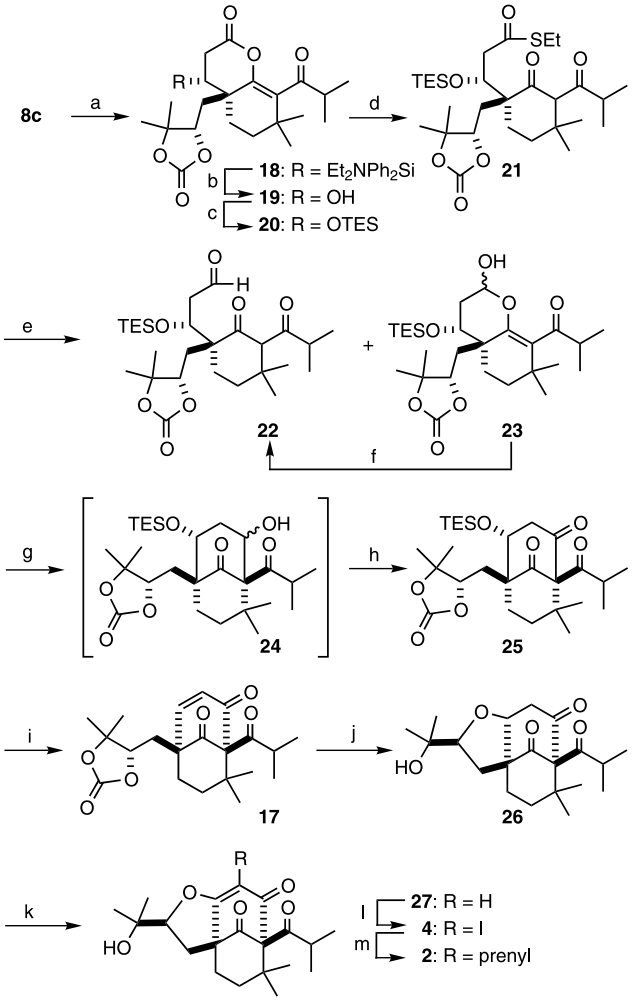



**Scheme 3.** Initial investigations.

Therefore, we conducted Tamao oxidation at the early stage of lactone **7** (Scheme 1), in which β-elimination of the resulting alcohol should be less probable compared to the corresponding β-hydroxy ketone derived from **15**. In this new strategy, we expected that the β-hydroxyl group would remain intact during the formation of the bicyclo[3.3.1] system, and then re-generate the olefin by treatment with a base. To avoid β-elimination in the Tamao oxidation step, a labile $Et_2NPh_2Si$ group[11] that can be converted to the alcohol under neutral conditions[12] should be used. Thus, the synthesis of 8-deprenyl- garsubellin A (**2**) was achieved, as shown in Scheme 4.

$Et_2NPh_2Si$ group[13] was introduced through a conjugate addition of a silylcuprate prepared from CuCN and $Et_2NPh_2SiLi$ in a ratio of 1:3[14] to give **18**. Because this silicon was unstable, crude **18** was directly subjected to Tamao oxidation conditions, and the following protection with a TES group gave **20** in 33% yield (three steps from **8c**). Lactone **20** was then treated with $Me_2AlSEt$ to give thioester **21**, which was converted under Fukuyama conditions[15] to a mixture of aldehyde **22** and lactol **23**.[16] Treatment of the mixture with 0.2 M HCl in THF converted **23** to **22**, and crude **22** was successfully converted to the desired bicyclo[3.3.1] system **24** by treatment with $Al_2O_3$.[17] Oxidation of the secondary alcohol of **24** with Dess–Martin periodinane gave trione **25**, which was converted to enone **17** through β-elimination of TESOH by DBU. Basic hydrolysis of the cyclic carbonate using LiOH resulted in the deprotection and subsequent tetrahydrofuran formation to give **26**. Compound **26** was then subjected to Wacker oxidation conditions and **27** was obtained in 54% yield (two steps from **17**). Iodination followed by Stille coupling with tributylprenyltin[18] completed the synthesis of 8-deprenyl-garsubellin A (**2**).[19]

In summary, we achieved synthesis of 8-deprenyl-garsubellin A (**2**), a model compound that contains proper stereocenters. Key findings in the present study are as follows. (1) The stereochemical course of the key one-pot lactone formation was changed using a cyclic carbonate as a protecting group of the diol. (2) Mild Tamao oxidation at the lactone stage was essential to avoid β-elimination of the resulting hydroxyl group. (3)




**Scheme 4.** *Reagents and conditions*: (a) $CuCN/Et_2NPh_2SiLi = 1/3$, THF; (b) *m*CPBA, KF, DMF; (c) TESOTf, 2,6-lutidine, $CH_2Cl_2$, 33% (three steps); (d) $Me_2AlSEt$, $CH_2Cl_2$, 89%; (e) $Et_3SiH$, Pd/C, $CH_2Cl_2$; (f) 0.2 M HCl, THF; (g) $Al_2O_3$, toluene; (h) Dess–Martin periodinane, $CH_2Cl_2$, 54% (four steps); (i) DBU, $CH_2Cl_2$, 92%; (j) 0.1 M LiOH aq., THF; (k) $Na_2PdCl_4$, TBHP, AcOH–$H_2O$, 54% (two steps); (l) $I_2$, CAN, $CH_3CN$, 100%; (m) $PdCl_2$(dppf), tributylprenyltin, DMF, 25% (+13% from second cycle starting with recovered **27** (50%)).

The β-hydroxyl group could be used to facilitate the formal migration of the lactone to the bicyclo[3.3.1] system and to re-generate the enone at the appropriate stage. Based on these studies, efforts toward a total synthesis of garsubellin A are currently in progress.

## Acknowledgements

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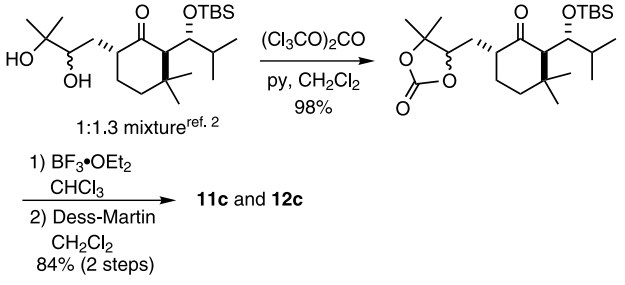
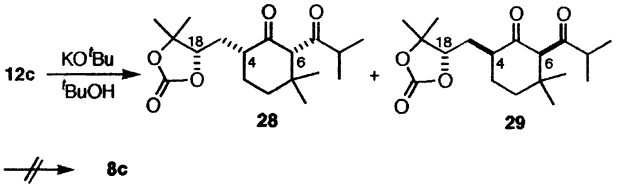
4. Deprotection of the acetonide was only possible at the enone stage (acetonide-protected 18-*epi*-**6**). The free 18-OH form (18-*epi*-**6**), however, could not be isolated due to the rapid intramolecular conjugate addition to the enone.
5. For example, **11c** and **12c** were prepared as follows:




6. The relative configurations of lactones **8c** and **13c** were determined by converting to **27** (and the epimer) and comparing the NMR data with the compound obtained in the previous studies. Previously, the relative configuration of the compound was unequivocally determined based on X-ray crystallography.
7. To produce the desired product **8c** as the major isomer from **12c**, we planned to first epimerize C-6 to di-equatorial isomers **28** and **29**. Although epimerization was successful using KO$^t$Bu in $^t$BuOH at 30°C, the one-pot lactone formation did not proceed from the di-equatorial-isomers. A possible reason might be that the deprotonation in the first step of the lactone formation occurred at C-6 due to the higher acidity of the proton in the axial position, and the resulting anion was not sufficiently reactive for a conjugate addition to **10**. The kinetically formed *trans* isomers **11c** and **12c** appeared to contain a conformation in which the C-6 proton existed in the equatorial position, based on $^1$H NMR chemical shifts [*cis* (di-equatorial) isomers (**28** and **29**): 3.14 and 3.20 ppm; *trans* isomers: 3.51 (**11c**) and 3.49 ppm (**12c**)].




8. **11c** and **12c** should contain axial $^t$PrCO groups to avoid the repulsion between the solvated lithium atom of the enolate.
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11. The formation of the bicyclo[3.3.1] system in the presence of this silyl group was impossible due to the instability of the silicon.
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14. Using $Et_2NPh_2SiLi$ as a nucleophile did not produce any product, and $(Et_2NPh_2Si)_2CuLi{\cdot}LiCN$ gave unpredictable results.
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16. In the previous synthesis of 18-*epi* form, formation of the lactol corresponding to **23** was not significant.
17. β-Elimination of TESOH did not occur during these transformations. Previously, the formation of the bicyclo[3.3.1] system was performed using $K_2CO_3$ as a base. In this case, however, these conditions gave a complex mixture of products.
18. Undesired reduction of the vinyl iodide occurred in this step and **27** was obtained in 50% yield, which was then recycled to give an additional 13% of **2**.
19. Data of **2**: $^1$H NMR (500 MHz, $C_6D_6$) $\delta$ 5.42 (dd, $J$=7.5, 7.5 Hz, 1H), 3.88 (dd, $J$=5.8, 11.0 Hz, 1H), 3.38 (dd, $J$=7.5, 14.3 Hz, 1H), 3.24 (dd, $J$=7.5, 14.3 Hz, 1H), 2.62 (dd, $J$=11.0, 12.9 Hz, 1H), 2.25 (m, 1H), 1.73 (s, 3H), 1.61 (s, 3H), 1.51–1.57 (m, 1H), 1.34–1.38 (m, 1H), 1.37 (s, 3H), 1.34 (d, $J$=6.4 Hz, 3H), 1.29 (d, $J$=6.4 Hz, 3H), 1.26 (s, 3H), 1.17–1.23 (m, 2H), 1.00 (s, 3H), 0.79–0.83 (m, 1H), 0.80 (s, 3H); $^{13}$C NMR (125 MHz, $C_6D_6$) $\delta$ 208.4, 204.5, 192.7, 172.4, 132.4, 122.0, 116.7, 90.1, 82.3, 70.3, 59.5, 43.2, 42.3, 35.9, 32.1, 30.4, 30.2, 26.3, 25.7, 24.4, 22.7, 22.1, 21.7, 20.7, 17.9; IR (neat, cm$^{-1}$): 3471, 1731, 1625; EI-MS $m/z$ 416 ($M^+$); EI-HRMS calcd for $C_{25}H_{36}O_5$ ($M^+$): 416.2563, found: 416.2568.