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Total Synthesis of Garsubellin A

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Our laboratory has recently directed considerable attention to natural products with properties that might be exploitable in the treatment of neurodegenerative diseases. We view such natural products, obtained via total synthesis, as particularly valuable lead structures around which to organize discovery research efforts with a view to enhancing and optimizing biological function.

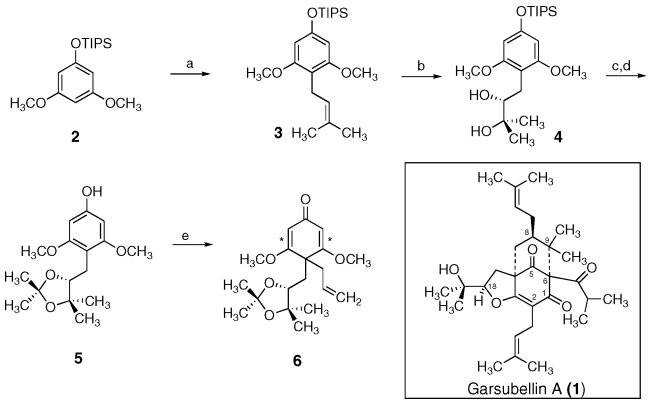
In this connection, the triterpene garsubellin A (**1**), first isolated by Fukuyama and colleagues from the wood of *Garcinia subelliptica* (used as a windbreak on the island of Okinawa), has emerged as a fascinating target for interactive chemical and biological investigations.[1] Garsubellin A enhances choline acetyltransferase (ChAT) activity by 154% in P10 rat septal neurons relative to a control.[1] In principle, a "small molecule" enhancer of ChAT could trigger enhanced cerebral acetylcholine levels in a clinical setting. Recalling that Alzheimer's disease is associated with a significant loss (60−90%) of ChAT activity in the hippocampus, the potential of a small molecule enhancer of this enzyme warrants further study.[3] We note in passing that most of the "anti-Alzheimer" drugs in use today are dedicated to the proposition of enhancing acetylcholine levels by inhibiting the enzyme cholinesterase, thereby attenuating dissipation of the ester bond.

From a strictly chemical perspective, garsubellin A mobilizes formidable structural defenses against prospective total syntheses. Even upon cursory inspection, one notes its trioxygenated bicyclo[3.3.1]nonane skeleton, bearing a gem dimethyl group at C9, two prenyl functions at C2 and C8, a fused tetrahydrofuran function with its own stereogenic issues at C18 and, finally, an isobutyryl function at the bridgehead C6 (comprising a β,β'-bis-1,3-diketo network with C1 and C5).

Not surprisingly, the goal of a garsubellin total synthesis has caught the fancy of many research groups.[4] Indeed several components of the garsubellin problem had already been solved by rather ingenious chemistry.[4] However, as is often the case with difficult puzzles, the complexity of the complete garsubellin problem transcends the sum of the challenges provided by its local sectors. Recently, Shibasaki and co-workers described the first total synthesis of garsubellin A.[5] Below we describe our total synthesis of garsubellin A.[6] While we report here the synthesis of the racemate, as will be seen, the charted pathway enables a reagent-controlled total synthesis of the natural antipode of **1**.

Though the total synthesis described herein was not intended as an exercise in biosimulation, we did take note that, hypothetically, dearomatization of a substituted phloroglucinol matrix (vide infra) could, with proper orchestration, serve to provide a pathway allowing for rapid progress toward our goal. Assembly of phenol **5** was accomplished in a four-step sequence, as shown (Scheme 1). Thus, selective prenylation of the differentially protected phloroglucinol derivative **2** was accomplished by ortho-metalation between the methoxy groups, followed by alkylation with prenyl-bromide.[7] Dihydroxylation of the newly installed prenyl group[8]

Scheme 1[a]



[a] Key: (a) *n*-BuLi, Et_2O, 0 °C then prenylbromide; (b) $K_2OsO_4 \cdot 2H_2O$, K_2CO_3, $K_3Fe(CN)_6$, $CH_3SO_2NH_2$, *t*-BuOH−H_2O, 23 °C; (c) TsOH·H_2O, 2,2-dimethoxypropane, acetone, 23 °C; (d) TBAF, THF, 23 °C (70% from **2**); (e) $Pd(OAc)_2$, PPh_3, $Ti(i\text{-}PrO)_4$, allyl methyl carbonate, C_6H_6, 80 °C, 62%.

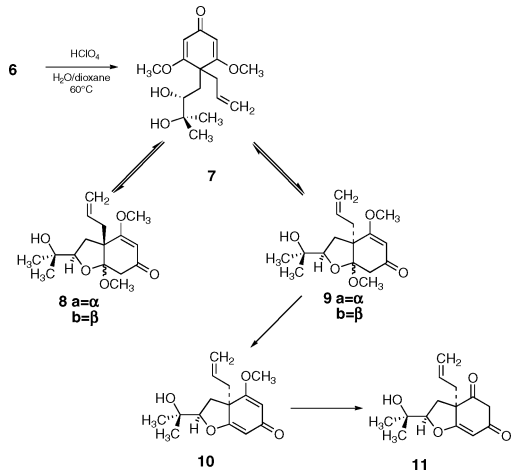
followed by acetonide formation and TBAF desilylation provided the required phenol **5** in 70% yield over the four-step sequence as a crystalline solid (144 °C).

The next major challenge in our approach entailed generating a formal para-aromatic Claisen product, or an equivalent dearomatized system from phenol **5**. This important goal was accomplished by allylation of **5** at the para position, as shown (see compound **6**).[9] The driving force for this transformation likely lies in the stability imparted by the doubly vinylogous carbonate moiety (see asterisks). The most obvious pathway for this transformation would involve direct allylation at the para carbon. An alternative pathway would consist of O-allylation, soon followed in sequence by rapid *o*-Claisen and Cope-like rearrangements to reach **6**.[10] The operative route in the case at hand remains to be rigorously demonstrated.

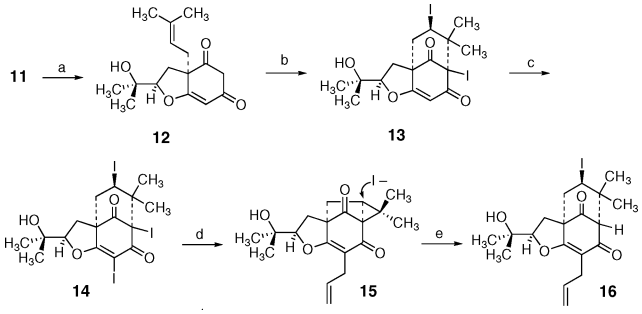
In practice, treatment of acetonide **6** with perchloric acid in a water−dioxane mixture at elevated temperature presumably led to diol **7**, which was, in fact, not isolated (Scheme 2). The first detectable kinetic event was the formation of a mixture of Michael-like cyclization products, **8a**, **8b** and **9a**, **9b**, which are equilibrating during the experiment. A key finding was the discovery that after extended time the **8**, **9** mixture progressed to a single compound, **10**. It seems reasonable that the positioning of the allyl and 2-propanol appendages on opposite faces of the tetrahydrofuran ring (see compounds **9**) would facilitate the β-elimination of methanol providing **10**,[11] thereby driving the diastereoselective cyclization process. Following prolonged reaction as shown, **10** underwent cleavage of the vinylogous methyl carbonate, yielding **11** in 71% yield. The first step in the fashioning of the bicyclo[3.3.1]-bridged ring system was accomplished by conversion of **11** to **12** via olefin cross metathesis (Scheme 3).[4d,12] Iodocarbocyclization of **12** provided **13** using standard iodolactonization conditions

10.1021/ja057418n CCC: $33.50

Scheme 2

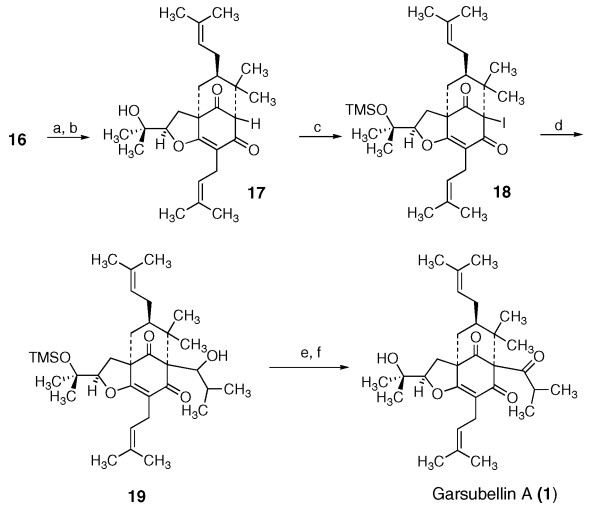


Scheme 3[a]



[a] Key: (a) Grubb's 2nd generation catalyst, CH_2Cl_2/2-methyl-2-butene, 40 °C, 68%; (b) I_2, KI, $KHCO_3$, THF−H_2O, 85%; (c) I_2, CAN, CH_3CN, 50 °C, 77%; (d) *i*-PrMgCl then Li_2CuCl_4, allyl bromide, THF, −78 to 0 °C, 67%; (e) TMSI then 1 N HCl, 0 °C CH_2Cl_2, 98%.

Scheme 4[a]



[a] Key: (a) AIBN, allyltributyltin-C_6H_6, 80 °C, 82%; (b) Grubb's 2nd generation catalyst, CH_2Cl_2/2-methyl-2-butene, 40 °C, 73%; (c) LDA, TMSCl then I_2, THF, −78 to 0 °C, 25−36%; (d) *i*-PrMgCl then isobutyraldehyde, THF, −78 to 0 °C, 72%; (e) DMP, CH_2Cl_2, 23 °C; (f) $Et_3N(HF)_3$, THF, 23 °C, 88%, two steps.

following helpful precedents of Nicolaou and co-workers.[4a,b] Using the iodine/CAN system, a second iodination event was accomplished, this time at the vinylic position of **13**, generating **14**.[5,13] Magnesium−iodine exchange using excess isopropylmagnesium chloride triggered two sequential reactions.[14] A transannular Wurtz cyclopropanation reaction occurred at −78 °C. Upon warming, a second exchange with the vinyl iodide produced the corresponding vinyl Grignard intermediate, which, in a second allylation, led to **15**.[15] Treatment of **15** with TMSI generated **16**. Keck radical allylation of the secondary iodide of **16** cleanly installed the prerequisite allyl group of the required relative configuration (Scheme 4).[16] A second olefin cross metathesis converted both allyl groups to prenyl moieties, yielding deisobutyryl garsubellin A (**17**) in 73% yield.[4d,12] Treatment of **17** with LDA and TMSCl followed by iodination provided **18** in variable yields. A second magnesium−iodine exchange[14] cleanly generated the bridgehead nucleophile, which upon treatment with isobutyraldehyde provided the aldol-type adduct **19** as a mixture of isomers. Dess−Martin oxidation[17] followed by cleavage of the TMS ether provided garsubellin A, matching the reported spectra.[1] With a practical route to garsubellin A in hand, studies are underway to help identify the therapeutically pertinent mode of action of this prospective agent. Similarly, analogues of garsubellin A will be prepared in efforts to improve biological performance.

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Note Added after ASAP Publication. The uncorrected proof version of this paper was inadvertently published on the ASAP Web site on December 30, 2005. The corrected final version was published on January 5, 2006.

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

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