Synthesis of the Fully Functionalized Bicyclic Core of Garsubellin A

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In 1997, Fukuyama et al. disclosed the structure of garsubellin A (**1**, Figure 1), a polyisoprenylated phloroglucinol isolated from *Garcinia subelliptica* found on the Okinawa Islands of Japan.[1a] Structurally, **1** is 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 with lipophilic side chains. Preliminary biological investigations revealed **1** to be a potent inducer of choline acetyltransferase (ChAT), the enzyme responsible for the biosynthesis of the neurotransmitter acetylcholine (ACh) and a biomarker for cholinergic neuron function. It was reported that **1** could increase in vitro ChAT activity by 154% at 10 μM in cultures of P10 rat septal neurons.[1a] Since the dementia associated with neurodegenerative diseases such as Alzheimer's has been partially attributed to an atrophy of cholinergic neurons and corresponding deficiencies in ACh levels, the use of protein neurotrophic factors or neurotrophic mimics (such as garsubellin A) which are capable of increasing neurotransmitter biosynthesis and possibly supporting the survival of cholinergic neurons holds therapeutic potential.[2] Herein, we report the construction of a fully functionalized [3.3.1] bicyclic system **2** which contains the key structural features of garsubellin's framework.

As shown in Figure 1, initial retrosynthetic inspection of the targeted system **2** reveals the lactone fused at C-1 and C-2 as a retron for a selective Baeyer−Villiger oxidation[3] between C-1 and C-23, giving rise to fused cyclobutanone **3**, which can be further disconnected via the intermediacy of an enone to intermediate **4**. The realization that the C-8 appendage might be installed via an intramolecular radical cyclization reveals selenide **5** as the retron for a selenium-induced electrophilic cyclization[4] of prenylated β-ketoester **6** to rapidly establish the bicyclic skeleton through construction of the sterically demanding C-6 to C-9 bond with concomitant installation of the requisite radical precursor functionality at C-8.

Initial synthetic efforts, as illustrated in Scheme 1, focused on effecting the anticipated electrophilic cyclization. Readily available cyclohexadione **7**[5] was *C*-alkylated using the Fuji[6] conditions to give diketone **8** in 80% yield, which was stereoselectively reduced with LiAlH(O-*t*-Bu)$_3$ to dihydroxy-ester **9**. After hydrolysis of the ethyl ester of diol **9** to give carboxylic acid **10**, lactonization was accomplished by treatment with DCC and

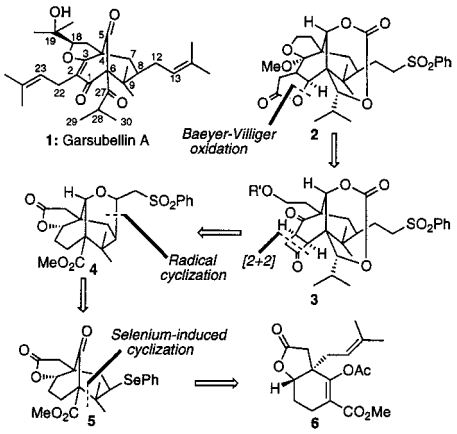
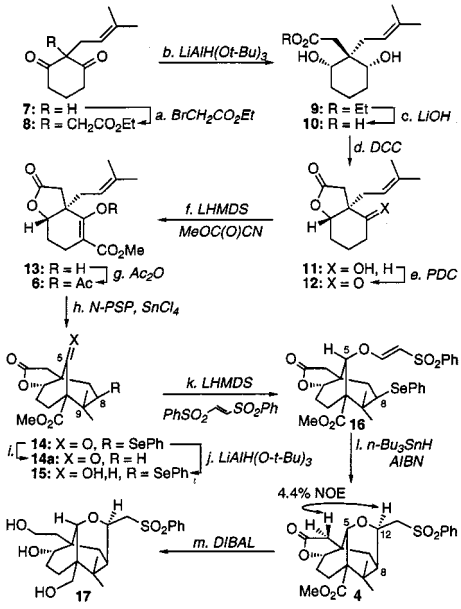


Figure 1. Structure and retrosynthetic analysis of garsubellin A (**1**).

Scheme 1. Assembly of Bicyclic Skeleton of Garsubellin A[a]



[a] (a) 2.0 equiv of $BrCH_2CO_2Et$, 1.2 equiv of DBU, 1.2 equiv of LiI, THF, 65 °C, 24 h, 80%; (b) 2.5 equiv of LiAlH(O-*t*-Bu)$_3$, THF, 0 °C, 2.5 h; (c) 1.3 equiv of LiOH, THF:H_2O (4:1), 25 °C, 30 min; (d) 1.2 equiv of DCC, 0.2 equiv of 4-DMAP, CH_2Cl_2, 25 °C, 30 min, 73% over three steps; (e) 1.3 equiv of PDC, Celite, CH_2Cl_2, 25 °C, 6 h, 77%; (f) 1.2 equiv of LHMDS, 1.2 equiv of HMPA, 1.5 equiv of $CNCO_2Me$, THF, −78 °C, 30 min; (g) 0.5 equiv of DMAP, Ac_2O, 70 °C, 1 h, 75% over two steps; (h) 1.1 equiv of *N*-PSP, 1.0 equiv of $SnCl_4$, CH_2Cl_2, −23 °C, 15 min, 95%; (i) 2.0 equiv of *n*-Bu_3SnH, 0.1 equiv of AlBN, $CH_3C_6H_6$, 80 °C, 2 h, 89%; (j) 1.3 equiv of LiAlH(O-*t*-Bu)$_3$, THF, 0 °C → 25 °C, 2.5 h, 95%; (k) 1.1 equiv of LHMDS, 1.1 equiv of *trans*-$PhSO_2CH{=}CHSO_2Ph$, THF, 0 °C → 25 °C, 2.5 h, 82%; (l) 1.5 equiv of *n*-Bu_3SnH, 0.3 equiv of AlBN, C_6H_6, 80 °C, 12 h, 93%; (m) 6.0 equiv of DIBAL, CH_2Cl_2, −78 °C → 25 °C, 12 h, 80%. AlBN = 2,2′-azobisisobutyronitrile, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DCC = 1,3-dicyclohexylcarbodiimide, DIBAL = diisobutylaluminum hydride, HMPA = hexamethylphosphoramide, LHMDS = lithium bis(trimethylsilyl)amide, *N*-PSP = *N*-(phenylseleno)phthalimide, PDC = pyridinium dichromate.

4-DMAP to provide lactone **11** (73% yield over three steps), which was subsequently oxidized with PDC to keto-lactone **12** in 77% yield. Construction of the requisite β-ketoester moiety was accomplished by acylation of the enolate, generated from ketone **12**, with methyl cyanoformate[7] to give **13** as a tautomeric

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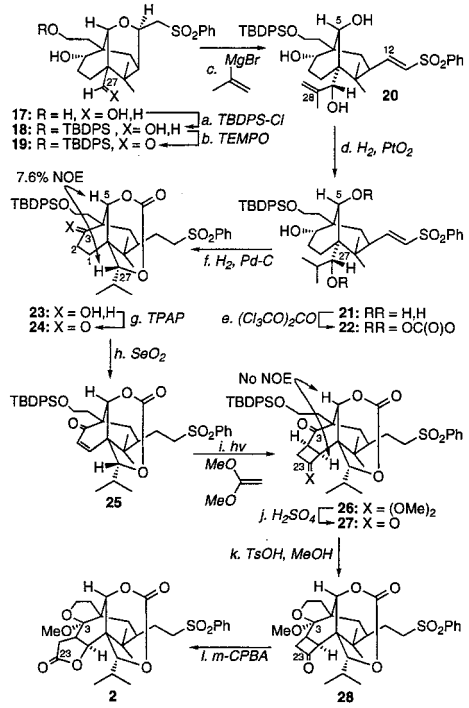
keto−enol mixture. The latter compound (**13**) was acetylated to enol acetate **6** in 75% yield over two steps. With the requisite precursor in hand, the selenium-mediated cyclization[4] was attempted by treating a solution of **6** and *N*-(phenylseleno)phthalimide[8] with $SnCl_4$ at −23 °C. Gratifyingly, substrate **6** underwent facile and remarkably clean conversion to the desired carbocycle **14** in 95% yield. The structure of **14** was confirmed by conversion (*n*-Bu_3SnH, AIBN, 89% yield) to crystalline **14a** which was subjected to X-ray analysis (see Supporting Information).

According to the retrosynthetic planning, the next stage of the synthesis was to convert the phenylselenide at C-8 of **14**, via a radical, to a two-carbon sulfone-terminated side chain. Tethering of the intramolecular radical acceptor was accomplished by initial reduction of the C-5 ketone of **14** to afford a single compound **15** in 95% yield, with reduction occurring exclusively from the opposite side of the *gem*-dimethyl group at C-9. The required vinylogous sulfonate **16** was then constructed in 82% yield by treatment of alcohol **15** with LHMDS at 0 °C, followed by addition of *trans*-1,2-bis(phenylsulfonyl)ethylene.[9] Syringe-pump addition of *n*-Bu_3SnH and AIBN to a refluxing solution of **16** provided tetracycle **4** as the sole product in 93% yield, with the stereochemistry at C-12 shown as suggested by NOE experiments. Experimentation revealed that the new tetrahydropyran ring would undergo facile opening via β-elimination upon treatment with base, thereby releasing the C-8 substituent; it was decided, however, to postpone such release and use the embedded ring as a temporary protecting group for the C-5 alcohol. Continuing toward the desired bicyclic core **2**, tetracycle **4** was exhaustively reduced with DIBAL to give triol **17** in 80% yield.

Selective protection (Scheme 2) of the least hindered primary alcohol with TBDPS-Cl afforded diol **18** (89% yield), which was selectively oxidized with TEMPO to the corresponding aldehyde **19**.[10] Initial attempts to effect the addition of isopropylmagnesium bromide to aldehyde **19** met with failure, as the severe steric hindrance around the C-27 aldehyde resulted in reduction, presumably through β-hydride elimination of the Grignard reagent as previously reported.[11] Fortunately, the use of isopropenylmagnesium bromide effected the desired addition to C-27 with concomitant β-elimination of the sulfone side chain to give **20** in 57% yield (two steps) as a single stereoisomeric compound with the illustrated stereochemistry as determined by NOE studies of a subsequent intermediate (**23**). Since hydrogenation conditions to simultaneously reduce both the C-12 and C-28 olefins could not be defined, the one at C-28 was reduced first by treatment of **20** with H_2/PtO_2 to give **21** in 73%. Subsequently, the free hydroxyls at C-5 and C-27 were selectively protected as a cyclic carbonate by exposure of **21** to triphosgene and pyridine[12] to afford **22** in 86% yield, which then was treated with H_2/Pd-C to give **23** in 88% yield. The free hydroxyl at C-3 was then oxidized with TPAP-NMO[13] to the corresponding ketone **24** in 87% yield. Conversion of **24** to the requisite enone **25** proved more difficult than anticipated, as all attempts to effect olefination by generation, oxidation, and elimination of an α-phenylselenide at C-2 failed, such that **25** could only be obtained by treatment of ketone **24** with SeO_2 in AcOH at 110 °C (60% yield).

With enone **25** at hand, the stage was set for completion of the bicyclic core. The anticipated [2 + 2] cycloaddition occurred regio- and stereoselectively from the *exo*-face of the molecule upon irradiation of a solution of **25** and dimethoxyethylene,[14] albeit in only modest yield (44%) to give the protected cyclobutanone adduct **26**. In preparation for the anticipated Baeyer−Villiger oxidation, the dimethoxyketal at C-23 was hydrolyzed with H_2SO_4 in Et_2O to give cyclobutanone **27**. Before the Baeyer−Villiger oxidation could be performed, however, the carbonyl at C-3 had to be protected by conversion to the mixed ketal **28** via exposure of **27** to TsOH in MeOH (86% yield). Earlier attempts to effect the Baeyer−Villiger oxidation without this carbonyl protection resulted in the formation of a highly unstable lactone that underwent facile β-elimination to give the free acid at C-23. After protection, however, treatment of cyclobutanone **28** with excess *m*-CPBA[6] resulted in clean conversion to the now robust lactone **2**, in 85% yield, completing the construction of the fully functionalized bicyclic core **2** of garsubellin A (**1**).

Scheme 2. Completion of Bicyclic Core of Garsubellin A[a]



[a] (a) 1.5 equiv of TBDPS-Cl, 0.5 equiv of 4-DMAP, pyridine, 25 °C, 12 h, 89%; (b) 0.2 equiv of TEMPO, 1.2 equiv of $PhI(OAc)_2$, CH_2Cl_2, 25 °C, 5 h; (c) 10 equiv of isopropenyl MgBr, THF, −78 °C → 25 °C, 12 h, 57% over two steps; (d) 0.1 equiv of PtO_2, H_2, EtOH, 25 °C, 72 h, 73%; (e) 2.0 equiv of triphosgene, 25 equiv of pyridine, CH_2Cl_2, −78 °C → 25 °C, 30 min, 86%; (f) 0.1 equiv of Pd-C, H_2, EtOH, 25 °C, 24 h, 88%; (g) 0.05 equiv of TPAP, 2.0 equiv of NMO, 4 Å MS, CH_2Cl_2, 25 °C, 12 h, 87%; (h) 4.0 equiv of SeO_2, AcOH, 110 °C, 1 h, 60%; (i) 20 equiv of $(MeO)_2{=}CH_2$, *hν*, C_6H_6, 25 °C, 8 h, 44%; (j) 3.0 equiv of H_2SO_4, Et_2O, 25 °C, 12 h, 82%; (k) 2.0 equiv of TsOH, MeOH, 25 °C, 86%; (l) 10 equiv of *m*-CPBA, 20 equiv of $NaHCO_3$, CH_2Cl_2 25 °C, 85%. 4-DMAP = 4-(dimethylamino)pyridine, *m*-CBPA = 3-chloroperoxybenzoic acid, NMO = 4-methylmorpholine *N*-oxide, TBDPS-Cl = *tert*-butylchlorodiphenylsilane, TPAP = tetrapropylammonium perruthenate, TsOH = *p*-toluenesulfonic acid.

The chemistry described is expected to facilitate the total synthesis of garsubellin A as well as other natural[1b] and designed members of this class of compounds for biological studies.

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Supporting Information Available: Data and procedures for all compounds as well as selected spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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