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Progress toward the Synthesis of Garsubellin A and Related Phloroglucins: The Direct Diastereoselective Synthesis of the Bicyclo[3.3.1]nonane Core†

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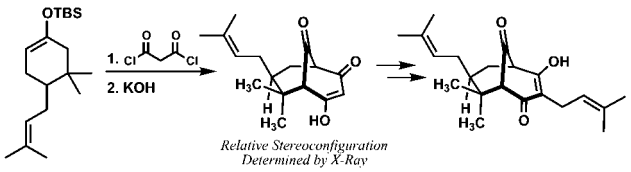
ABSTRACT



A highly diastereoselective single-step cyclization reaction provides access to the bicyclo[3.3.1]nonane core of the polyprenylated phloroglucin natural product garsubellin A. Further elaboration to a more functionalized analogue involves a sequential Claisen rearrangement/Grubbs olefin cross-metathesis strategy. Additionally, this strategy was extended to the preparation of the bis-quaternary carbon array found at the bridgehead positions of the phloroglucin natural products.

Alzheimer's disease affects approximately 4 million Americans and is the most common form of dementia.[1] It afflicts 47% of people over the age of 85, currently the fastest growing group with respect to the rest of the population. These statistics necessitate the expedient development of effective therapeutic agents. Neurodegenerative diseases such as Alzheimer's have been attributed to deficiencies in levels of the neurotransmitter acetylcholine (ACh).[2] Thus, inducers of the enzyme choline acetyltransferase (ChAT), which is responsible for the biosynthesis of ACh, are potential Alzheimer's therapeutics.[3] One such biologically active molecule is garsubellin A (**1**, Figure 1), a polyprenylated phloroglucin isolated from the wood of *Garcinia subelliptica*.[4] Preliminary studies have shown that garsubellin A increases in vitro ChAT activity in rat septal neurons by 154% at a 10 μM concentration.[4]

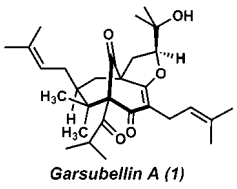


Figure 1. Structure of garsubellin A (**1**).

Structurally, garsubellin A is characterized primarily by a highly oxygenated and densely functionalized bicyclo[3.3.1]-nonane-1,3,5-trione core. Critical to our retrosynthetic plan-

† This paper is dedicated to our colleague Professor Robert H. Grubbs on the occasion of his 60th birthday.

(1) Alzheimer's Association. Alzheimer's Vital Statistics. (http://www.alz.org/research/current/stats.htm).

(2) *Fundamental Neuroscience*; Zigmond, M. J., Bloom, F. E., Landis, S. C., Roberts, J. L., Squire, L. R., Eds.; Academic Press: San Diego, 1999; pp 216−219.

(3) Auld, D. S.; Mennicken, F.; Day, J. C.; Quirion, R. *J. Neurochemistry* **2001**, *77*, 253.

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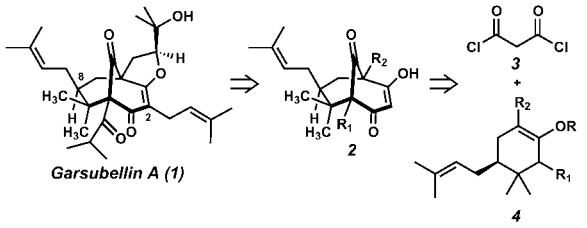
ning was the implementation of a concise and stereocontrolled transformation to construct this core system. Two previous synthetic efforts toward garsubellin A have also focused on the core: one route utilizes a selenium-mediated cyclization,[5] the second employs a more traditional Michael/aldol sequence.[6] Described herein is an approach to garsubellin A featuring the construction of the highly oxygenated [3.3.1] bicyclic core in a single, diastereoselective cyclization reaction.

Our retrosynthetic analysis for garsubellin A is outlined in Scheme 1. It was envisioned that the C(2) prenyl moiety

Scheme 1



could be introduced by either a direct C-alkylation or a late-stage thermal Claisen rearrangement, followed by an olefin cross-metathesis reaction. The functionalized bicyclo[3.3.1]-nonane-1,3,5-trione core (**2**) could arise from a variety of two-bond disconnections; however, we reasoned that a suitably functionalized cyclohexanone enol ether (**4**) and malonyl dichloride (**3**) would be the most direct coupling partners for a single-step construction of the desired ring system. This approach was based on the anticipation that the relative stereochemistry about the core ring structure would arise via remote induction from the C(8) stereocenter, thus allowing for an eventual asymmetric synthesis from a single stereogenic center.[7] For the purposes of preliminary studies, it was expected that readily available racemic enol ethers of the type **4** would reveal the diastereomeric bias of such cyclizations.

Interestingly, garsubellin A is a member of a larger family of biologically relevant prenylated phloroglucin natural products, all of which possess a similar bicyclo[3.3.1]nonane core structure (Figure 2).[8] Therefore, the development of a facile route to the core structure present in garsubellin A

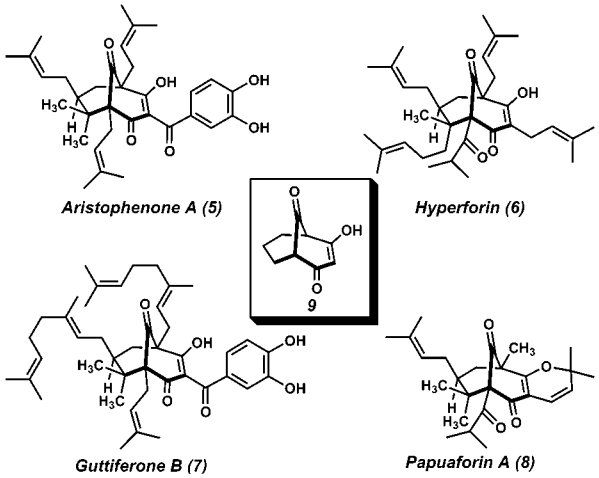


Figure 2. Some bicyclic phloroglucin natural products.

should have broad implications for the preparation of several bicyclic phloroglucin natural products and synthetic analogues.

In 1984, Effenberger reported the reaction between 1-methoxy-1-cyclohexene and malonyl dichloride to give the parent bicyclo[3.3.1]nonane system (**9**) such as the one found in garsubellin A.[9] While this reaction was attractive in that it provided an effective route to the core framework, it required that a 4-fold excess of enol ether be employed, which was to be the more complex subunit in our synthesis. Furthermore, the cyclization reaction has not appeared in the subsequent literature and remains a singular example.[10] Owing to the potential utility of this cyclization in the context of the phloroglucin [3.3.1] bicyclic natural products, we chose to investigate the efficiency and diastereoselectivity of such cyclizations in a more complex arena. We were particularly interested in the resulting relative stereochemical relationship between substitution at C(8) and the malonyl subunit. Additionally, a more versatile enol ether (i.e., trialkylsilyl compared to methyl) would provide a more convenient entry into the complex systems needed for the phloroglucins. Therefore, silyl enol ether **14** was targeted as a reasonable model system for cyclization to the phloroglucin ring system.

The synthesis of silyl enol ether **14** (Scheme 2) commenced with readily available vinylogous ester **10**,[11] which was enolized by LDA and alkylated with prenyl bromide to give **11**.[12] Treatment of **11** with methyllithium followed by aqueous acid furnished enone **12**.[13] Conjugate addition with

(4) Fukuyama, Y.; Kuwayama, A.; Minami, H. *Chem. Pharm. Bull*. **1997**, *45*, 947.

(5) Nicolaou, K. C.; Pfefferkorn, J. A.; Kim, S.; Wei, H. X. *J. Am. Chem. Soc*. **1999**, *121*, 4724.

(6) Usuda, H.; Kanai, M.; Shibasaki, M. *Org. Lett*. **2002**, *4*, 859.

(7) For general reviews on remote diastereoselective induction in alkylations of enolate derivatives see: (a) Caine, D. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 3, Chapter 1.1, pp 1−63. (b) Evans, D. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, Chapter 1, p 1.

(8) For references dealing with the isolation of the compounds **5**−**8** shown in Figure 2, see: (a) Cuesta-Rubio, O.; Padron, A.; Castro, H. V.; Pizza, C.; Rastrelli, L. *J. Nat. Prod.* **2001**, *64*, 973. (b) Gurevich, A. I.; Dobrynin, V. N.; Kolosov, M. N.; Popravko, S. A.; Ryabova, I. D.; Chernov, B. K.; Derbentseva, N. A.; Aizenman, B. E.; Garagulya, A. D. *Antibiotiki (Moscow)* **1971**, *16*, 510. (c) Gustafson, K. R.; Blunt, J. W.; Munro, M. H. G.; Fuller, R. W.; McKee, T. C.; Cardellina, J. H., II.; McMahon, J. B.; Cragg, G. M.; Boyd, M. R. *Tetrahedron* **1992**, *48*, 10093. (d) Winkelmann, K.; Heilmann, J.; Zerbe, O.; Rali, T.; Sticher, O. *J. Nat. Prod.* **2001**, *64*, 701.

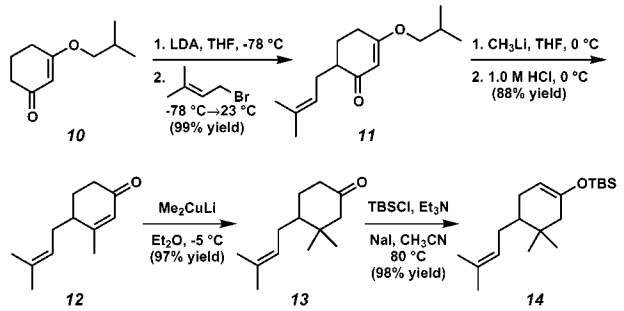
(9) Schönwälder, K.-H.; Kollat, P.; Stezowski, J. J.; Effenberger, F. *Chem. Ber*. **1984**, *117*, 3280.

(10) To our knowledge, there are no related cyclizations of more densely functionalized substrates that utilize a bis-acyl bond construction.

(11) Hara, R.; Furukawa, T.; Kashima, H.; Kusama, H.; Horiguchi, Y.; Kuwajima, I. *J. Am. Chem. Soc*. **1999**, *121*, 3072.

(12) Stork, G.; Danheiser, R. L. *J. Org. Chem*. **1973**, *38*, 1775.

Scheme 2

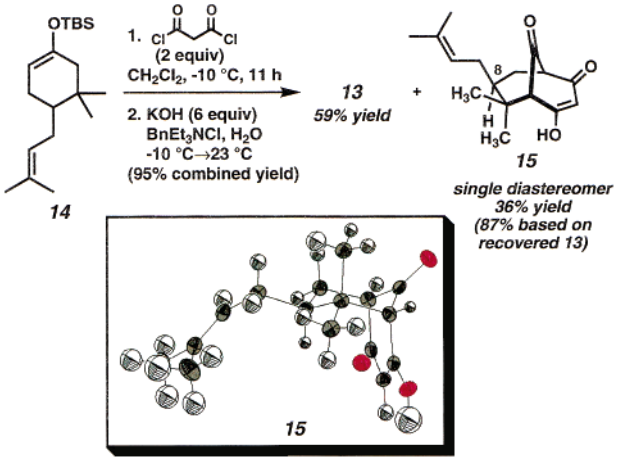


Me_2CuLi and subsequent silyl enol ether formation provided **14** in 84% overall yield.[14,15]

With multigram quantities of **14** readily available, we began to investigate the critical cyclization chemistry with malonyl dichloride. Following substantial experimentation, it was found that the ratio of enol ether to acid chloride could be reversed relative to the Effenberger study[9] and that indeed a TBS enol ether could be employed instead of a methyl enol ether. Both modifications resulted in considerably cleaner cyclizations. Under our carefully optimized conditions, treatment of silyl enol ether **14** with 2 equiv of malonyl dichloride in CH_2Cl_2 at −10 °C, followed by addition of aqueous KOH under phase transfer catalysis (−10 → 23 °C), produced a 36% yield of desired bicycle **15**.[16] Although the isolated yields were modest, unreacted enol ether could be recovered as ketone **13**, providing an overall yield of 95%. Conversion of the recovered ketone to the silyl enol ether, followed by cyclization, gave a 55% combined yield of trione **15** over the 2 cycles. Gratifyingly, the cyclization of **14** to **15** proceeded with complete diastereoselectivity to produce the desired *anti* isomer with respect to the malonyl subunit and the remote prenyl substitution at C(8). The relative stereochemistry in **15** was unambiguously confirmed by single-crystal X-ray diffraction (Scheme 3).[17]

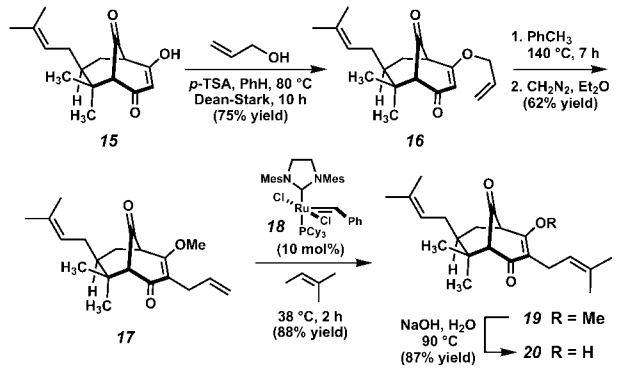
With a rapid synthesis of bicycle **15** in hand, we turned our attention to the installation of the C(2) prenyl group (Scheme 4). While a variety of traditional methods proved unsatisfactory (e.g., direct C-alkylation, Pd-mediated couplings, etc.), a more stepwise route emerged as the most effective method. Condensation of bicycle **15** with allyl alcohol[18] followed by a thermal Claisen rearrangement[19] and treatment with diazomethane produced the allylated bicycle

Scheme 3



17.[20,21] Completion of the prenyl installation was accomplished by an olefin cross-metathesis using the Grubbs ruthenium catalyst **18** in the presence of 2-methyl-2-butene to furnish **19** in 88% yield.[22] Finally, saponification of vinylogous ester **19** proceeded in good yield to provide the semifunctionalized garsubellin A core system **20**.[16] Overall, the sequence produced the bis-prenylated bicyclic core of garsubellin A in just 10 steps.

Scheme 4

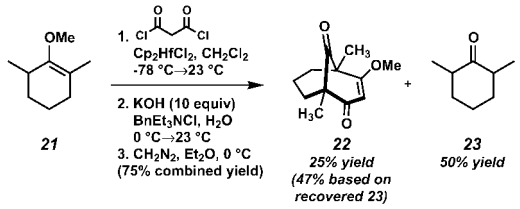


In an attempt to extend this methodology to substrates that are more relevant to the bicyclic phloroglucins (i.e., direct cyclizations that produce the bis-quaternary carbon array), it was found that substituents at the α-positions of the enol ether greatly affect the reactivity of this system. For example, under our standard cyclization conditions, the TBS enol ether derived from 2,6-dimethylcyclohexanone produced virtually none of the desired cyclized product **22**, even with prolonged reaction times and elevated temperatures. After considerable optimization, however, bicycle **22** was obtained in 25% yield

(13) Johnson, W. S.; McCarry, B. E.; Markezich, R. L.; Boots, S. G. *J. Am. Chem. Soc*. **1980**, *102*, 352.
(14) Laval, G.; Audran, G.; Galano, J.-M.; Monti, H. *J. Org. Chem*. **2000**, *65*, 3551.
(15) Duhamel, P.; Hennequin, L.; Poirier, J. M.; Tavel, G.; Vottero, C. *Tetrahedron* **1986**, *42*, 4777.
(16) Obtained as a 1:1 mixture of equilibrating enol isomers.
(17) Crystallographic data have been deposited at the Cambridge Crystallographic Data Center under deposition number 173065.
(18) Allyl ether **16** was obtained as a single enol ether isomer represented by the structure shown in Scheme 4 (by NOE analysis).
(19) (a) Wipf, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, Chapter 7.2, pp 827−873. (b) Blechert, S. *Synthesis* **1989**, 71. (c) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423. (d) Ireland, R. E. *Aldrichimica Acta* **1988**, *21*, 59.
(20) Obtained as a 1:1 mixture of separable enol ether isomers.
(21) Isolated in addition to 30% yield of recovered enol ether **16**.
(22) See the preceding article in this issue: Chatterjee, A. K.; Sanders, D. P.; Grubbs, R. H. *Org. Lett.* **2002**, *4*, 1939.

(47% yield based on recovered ketone **23**) by employing the methyl enol ether **21** and bis(cyclopentadienyl)hafnium dichloride as a Lewis acid mediator followed by standard workup and treatment of the crude reaction mixture with diazomethane (Scheme 5). Although bicycle **22** is obtained

Scheme 5



in modest yield, the direct cyclization to produce the two bridgehead quaternary carbons present in the phloroglucins compares well with lengthier procedures to form similarly substituted systems.[23] These results establish the feasibility of a single-step strategy toward the synthesis of the bicyclic phloroglucins.

In summary, we have developed a highly diastereoselective direct cyclization reaction that delivers the bicyclo[3.3.1]-nonane-1,3,5-trione core of the phloroglucin natural products in a single step. Successful elaboration of ketone **15** (Scheme 4) establishes a viable end-game strategy for the introduction of the final prenyl group at C(2). We have also demonstrated the feasibility of this strategy toward the preparation of the bis-quaternary carbon array found at the bridgehead positions of the phloroglucin natural products (see Figure 2). Current efforts are focused on further optimizing this cyclization, as well as expanding the substrate scope to include fully elaborated systems relevant to the synthesis of garsubellin A and related compounds.

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Supporting Information Available: Experimental details and characterization data for all new compounds including X-ray data for **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) For a recent review on the synthesis of [3.3.1] bicyclic compounds, see: Butkus, E. *Synlett* **2001**, *12*, 1827.