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Total Synthesis of the Proposed Structure of Briarellin J

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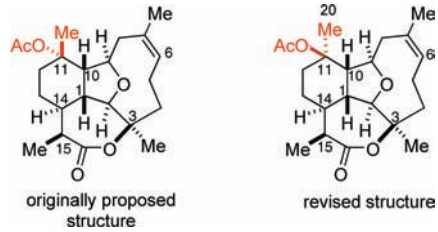
ABSTRACT



The total synthesis of the originally proposed structure of briarellin J is reported in 15 steps from a known compound and in 23 steps from readily available materials. Key reactions include an *exo*-selective intramolecular Diels−Alder and a substrate-controlled hydroboration. Discrepancies in the spectroscopic data of the synthetic and natural material led to a revision of the assigned structure.

The eunicellins, briarellins, asbestinins, and sarcodyctins are related subclasses of the C2−C11 cyclized cembranoid diterpenes isolated as secondary metabolites of alcyonarians (octocoral) found in the Caribbean and Pacific Ocean.[1] Intense synthetic efforts over the past decade have resulted in numerous total syntheses of members of the various subclasses.[2] While the natural role of these diterpenes is proposed to involve predation deterrence,[3] the briarellin diterpenes also exhibit activity against the malaria parasite *Plasmodium falciparum*.[4] The presence of all four subclasses in the same organism provides evidence for the biosynthetic proposal advanced by Faulkner in which a cembrane skeleton serves as the precursor to each subclass.[5] Notably, a suprafacial 1,2-methyl shift from C11 to C12 would be required to transform the briarellins into the asbestinins (Figure 1).

Briarellin J, like almost all briarellins,[6] was isolated by Rodríguez and co-workers from the gorgonian octocoral *Briareum polyanthes*.[4] The carbon framework and relative stereochemistry of briarellin J were assigned on the basis of NMR studies and comparison of the NOESY spectrum to that of the previously isolated and assigned briarellin D. Interestingly, briarellins A−D[7] and J−P[4] have been assigned C11 configurations opposite to those assigned for briarellins E−I[8] (Figure 2). The assigned C11 configuration for briarellins A−D and J−P was based on the absence of an NOE

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(1) For reviews, see: (a) Rodríguez, A. D. *Tetrahedron* **1995**, *51*, 4571–4618. (b) Bernardelli, P.; Paquette, L. A. *Heterocycles* **1998**, *49*, 531–556. (c) Sung, P.-S.; Chen, M.-C. *Heterocycles* **2002**, *57*, 1705–1715.

(2) For a review, see: Ellis, J. M.; Crimmins, M. T. *Chem. Rev.* **2008**, *108*, 5278–5298.

(3) (a) Maia, L. F.; de, A.; Epifanio, R.; Eve, T.; Fenical, W. *J. Nat. Prod.* **1999**, *62*, 1322–1324. (b) Harvell, C. D.; West, J. M.; Griggs, C. C. *Invertebr. Reprod. Dev.* **1996**, *30*, 239–247. (c) Harvell, C. D.; Fenical, W.; Roussis, V.; Ruesink, J. L.; Griggs, C. C.; Greene, C. H. *Mar. Ecol.: Prog. Ser.* **1993**, *93*, 165–173.

(4) Ospina, C. A.; Rodríguez, A. D.; Ortega-Barria, E.; Capson, T. L. *J. Nat. Prod.* **2003**, *66*, 357–363.

(5) Stierle, D. B.; Carte, B.; Faulkner, D. J.; Tagle, B.; Clardy, J. *J. Am. Chem. Soc.* **1980**, *102*, 5088–5092.

(6) The only exceptions are the pachyclavulariaenones; see: (a) Wang, G.-H.; Sheu, J.-H.; Duh, C.-Y.; Chiang, M. Y. *J. Nat. Prod.* **2002**, *65*, 1475–1478. (b) Wang, G.-H.; Sheu, J.-H.; Chiang, M. Y.; Lee, T.-J. *Tetrahedron Lett.* **2001**, *42*, 2333–2336. (c) Sheu, J.-H.; Wang, G.-H.; Sung, P.-J.; Duh, C.-Y.; Chiang, M. Y. *Tetrahedron* **2001**, *57*, 7639–7648.

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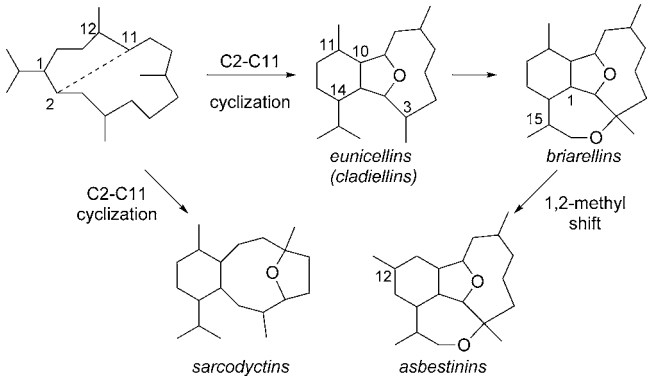


Figure 1. Proposed biosynthesis of the briarellins.

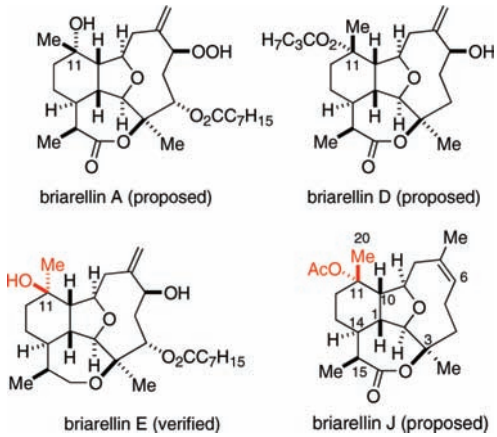


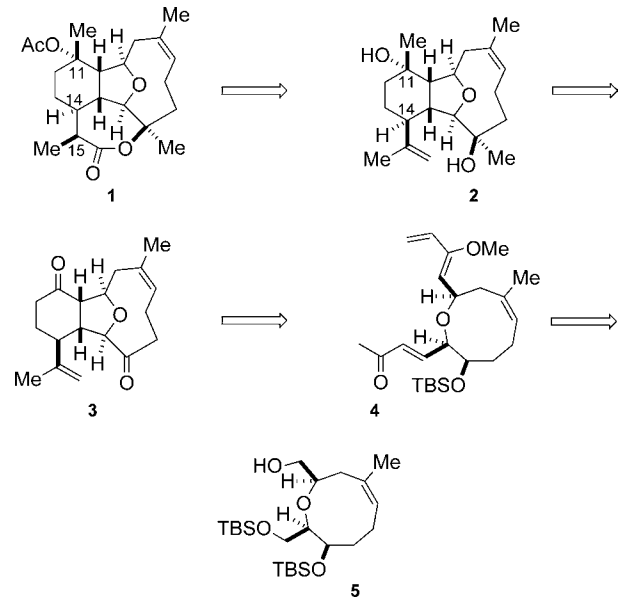
Figure 2. Reported structures of briarellins.

correlation between the C11 methyl and the α C14 methine, whereas this correlation is clearly present in briarellins E−I. The proposed β C11 methyl in briarellins A−D and J−P conflicts with Faulkner's biosynthetic proposal since a very unlikely 1,2-antarafacial methyl shift would be required to generate an asbestinin (Figure 1).[1b]

Although the relative and absolute stereochemistry of briarellins E and F have been established via total synthesis[9] by the Overman group, no synthetic efforts toward briarellins A−D or J−P have been reported to date.

We previously reported the enantioselective preparation of medium ring ethers[10] via a glycolate aldol/ring-closing metathesis strategy and have applied this method to the synthesis of members of the eunicellin[11] and asbestinin classes.[12] Due to the interesting inconsistency with Faulkner's proposed biosynthesis and our experience in the synthesis of C2−C11 cyclized cembranoid diterpenes, we chose briarellin J as a prime target for total synthesis. Retrosynthetically (Scheme 1), the proposed structure of briarellin J (**1**) was envisioned to arise from a late stage substrate-controlled hydroboration of hexahydroisobenzofuran **2** to install the C15 stereocenter, followed by oxidative lactonization to install the ε-lactone and final acetylation of the C11 hydroxyl. Hexahydroisobenzofuran **2** would be derived from methyllithium addition to diketone **3**. Diketone **3** would ultimately result from an intramolecular Diels−Alder reaction of triene **4**. Triene **4** would be readily available from oxonene **5**,[12a] previously prepared in our laboratories in eight steps from (*R*)-benzylglycidyl ether.

Scheme 1. Retrosynthetic Analysis of the Proposed Structure of Briarellin J



The synthesis of diketone **3** (Scheme 2) began from known oxonene **5**, prepared via our glycolate aldol/ring-closing metathesis strategy. Swern oxidation[13] of the primary alcohol and Wittig olefination[14] of the resultant aldehyde afforded (*Z*)-unsaturated ester **6** in good yield. A sequence of reduction of ester **6** to the allylic alcohol, manganese dioxide oxidation to the aldehyde, and a methylene Wittig olefination was performed with only a single final chromatographic purifica-

(8) Rodríguez, A. D.; Cobar, O. M. *Chem. Pharm. Bull.* **1995**, *43*, 1853–1858.

(9) (a) Corminboeuf, O.; Overman, L. E.; Pennington, L. D. *J. Am. Chem. Soc.* **2003**, *125*, 6650–6652. (b) Corminboeuf, O.; Overman, L. E.; Pennington, L. D. *J. Org. Chem.* **2009**, *74*, 5458–5470.

(10) (a) Crimmins, M. T.; Emmitte, K. A. *Org. Lett.* **1999**, *1*, 2029–2032. (b) Crimmins, M. T.; Choy, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 5653–5660. (c) Crimmins, M. T.; Tabet, E. A. *J. Am. Chem. Soc.* **2000**, *122*, 5473–5476. (d) Crimmins, M. T.; Emmitte, K. A. *Synthesis* **2000**, *6*, 899–903. (e) Crimmins, M. T.; Emmitte, K. A. *J. Am. Chem. Soc.* **2001**, *123*, 1533–1534. (f) Crimmins, M. T.; Emmitte, K. A.; Choy, A. L. *Tetrahedron* **2002**, *58*, 1817–1834. (g) Crimmins, M. T.; DeBaillie, A. C. *Org. Lett.* **2003**, *5*, 3009–3011. (h) Crimmins, M. T.; Cleary, P. A. *Heterocycles* **2003**, *61*, 87–92. (i) Crimmins, M. T.; Powell, M. T. *J. Am. Chem. Soc.* **2003**, *125*, 7592–7595.

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(12) (a) Crimmins, M. T.; Ellis, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 17200–17201. (b) Crimmins, M. T.; Ellis, J. M. *J. Org. Chem.* **2008**, *73*, 1649–1660.

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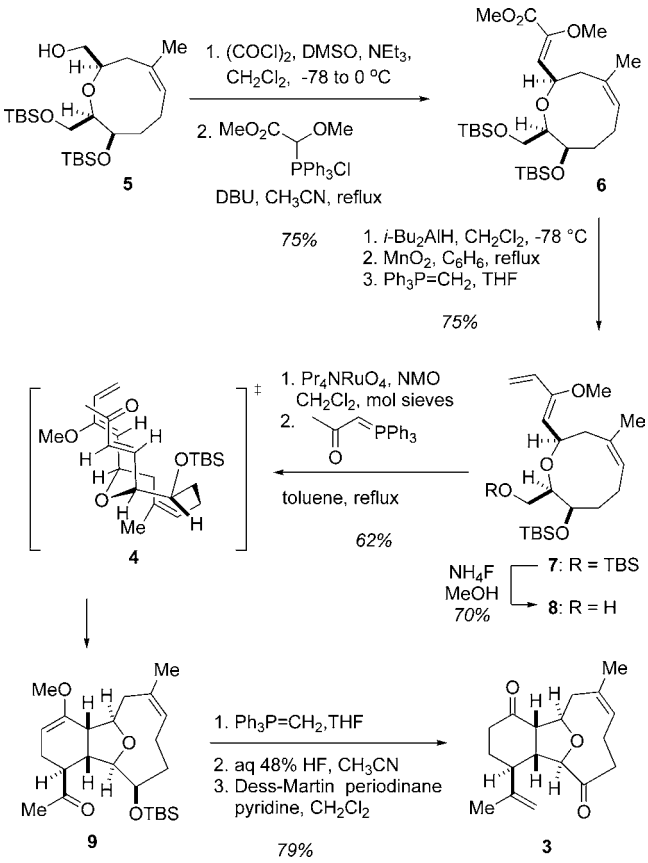
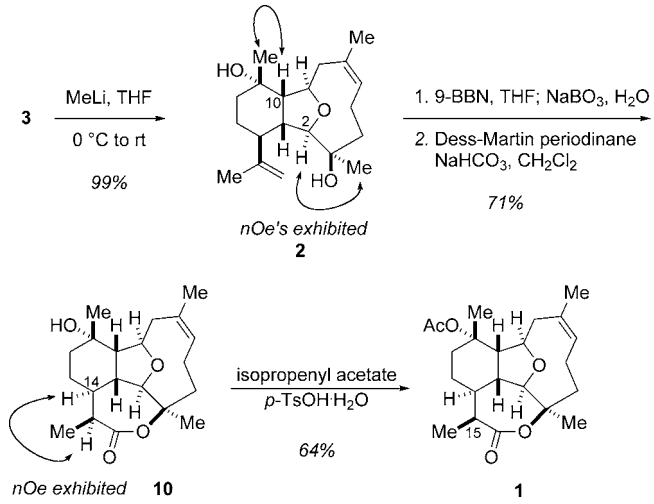
(14) Seneci, P.; Leger, I.; Souchet, M.; Nadler, G. *Tetrahedron* **1997**, *53*, 17097–17114.

Scheme 2. Synthesis of Diketone **3**



Scheme 3. Completion of **1**



tion to construct the requisite diene **7**. Selective cleavage of the primary TBS ether was achieved with ammonium fluoride[15] to afford alcohol **8**. Due to the acid-sensitive nature of the enol ether, alcohol **8** was subjected to a TPAP/NMO[16] oxidation followed immediately by a solvent switch to toluene and exposure of the aldehyde to (acetylmethylene)triphenylphosphorane[17] at 100 °C. Tricycle **9** was produced in 62% yield via an olefination and spontaneous *exo*-selective Diels−Alder reaction.

The observed *exo* selectivity in the Diels−Alder cycloaddition is rationalized by transition state **4** wherein potential nonboding interactions are minimized between the C3 TBS ether and the α hydrogen of the enone. The Diels−Alder adduct **9** was transformed to diketone **3** in three steps. Wittig olefination of ketone **9** generated a functional handle for future elaboration into the ε-lactone; subsequent exposure to aqueous hydrofluoric acid cleaved the secondary TBS ether and hydrolyzed the enol ether to afford a keto-alcohol. Oxidation of the keto-alcohol with Dess−Martin periodinane[18] furnished diketone **3** and unveiled the hexahydroisobenzofuran core.

To complete the synthesis of **1** (Scheme 3), diketone **3** was subjected to a large excess of methyllithium to afford diol **2** as a single diastereomer in 99% yield. NOESY data of **2** indicate a clear correlation between the C11 methyl and the C10 methine hydrogen and also a correlation between the C3 methyl and the C2 oxymethine hydrogen, confirming that addition to the C3 ketone occurs from the convex α face of the nine-membered ring while addition to the C11 ketone occurs from the convex *β* face of the cyclohexanone. Although previous syntheses of C2−C11 cyclized cembranoids in our laboratories required the use of a chiral hydroborating reagent to selectively install the C15 stereocenter,[12] treatment of **2** with 9-BBN followed by oxidative cyclization with Dess−Martin periodinane produced lactone **10** in 71% yield as a single diastereomer exhibiting a clear NOESY correlation between the C14 and C15 methine hydrogens. To account for the exquisite selectivity observed in the substrate-controlled hydroboration, it is proposed that the isopropylidene rests orthogonal to the carbon framework of the cyclohexane ring such that the *Si* face is readily accessible while the *Re* face is blocked by the tertiary alcohol at C3. Although all attempts to acetylate the remaining tertiary alcohol with Ac_2O/DMAP/NEt_3, AcCl/DMAP/NEt_3, or Ac_2O/$Bi(OTf)_3$ failed to produce any desired product, acetate **1** was produced in 64% yield upon treatment of **10** with isopropenyl acetate and *p*-TsOH,[19] thus completing the synthesis of the proposed structure of briarellin J in 15 linear steps from known oxonene **5**.

The ^1H and ^{13}C NMR spectra of synthetic **1** are perceptively different from the data for the natural sample. Fortunately, lactone **10**, with all the requisite stereocenters of the proposed structure installed, is beautifully crystalline, and suitable crystals were obtained and subjected to X-ray

(15) Schinzer, D.; Bohm, O. M.; Altmann, K.-H.; Wartmann, M. *Synlett* **2004**, 1375–1378.

(16) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639–666.

(17) Kuroda, H.; Hanaki, E.; Izawa, H.; Kano, M.; Itahashi, H. *Tetrahedron* **2004**, *60*, 1913–1920.

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(19) Magnus, P.; Giles, M.; Bonnert, R.; Johnson, G.; McQuire, L.; Deluca, M.; Merritt, A.; Kim, C. S.; Vicker, N. *J. Am. Chem. Soc.* **1993**, *115*, 8116–8129.

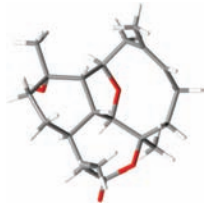
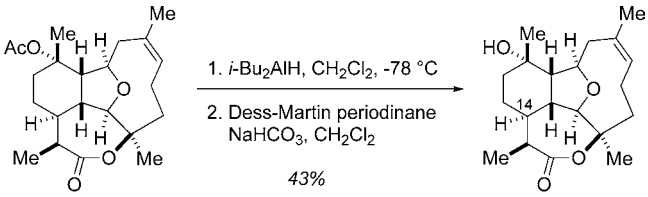


Figure 3. X-ray stucture of lactone **10**.

analysis (Figure 3), verifying the assigned stereochemistry. Although ionization and epimerization of **10** could be problematic under the acidic acetylation conditions, degradation experiments (Scheme 4) show that there is no loss of

Scheme 4. Degradation Study of Acetate **1**



stereochemical integrity upon conversion of lactone **10** into acetate **1**. Reduction of synthetically derived acetate **1** with excess diisobutylaluminum hydride generated a triol which was then oxidatively lactonized with Dess−Martin periodinane.[18] The resultant lactone was identical in all aspects to the previously synthesized lactone **10**, confirming the successful synthesis of the proposed structure of briarellin J.

Our synthesis, combined with the Overman synthesis of briarellins E and F, Faulkner's biosynthetic proposal, and reexamination of the original isolation data, suggests that the true structure of briarellin J contains the opposite stereochemistry at C11 from that originally reported (Figure 2). Careful examination of the original spectra of briarllein J indicates some important NOESY correlations that should be considered in the structure assignment.[4] Specifically, a correlation between the acetate methyl group and the C19 methyl group as well as the correlation between the acetate methyl with the C1 methine provide important insights. The original structural assignment was based on the assumption that the cyclohexane ring of C2−C11 cyclized cembranoids must be locked into a boat conformation.[7,20] However, if true, then the observed acetate methyl NOEs are inconsistent with an α C11 flagpole acetate. More consistent with the observed NOESY data is a chair cyclohexane in which the C11 acetate resides on the β face and the C20 methyl is equatorial. Not only does this revised assignment (Figure 4)

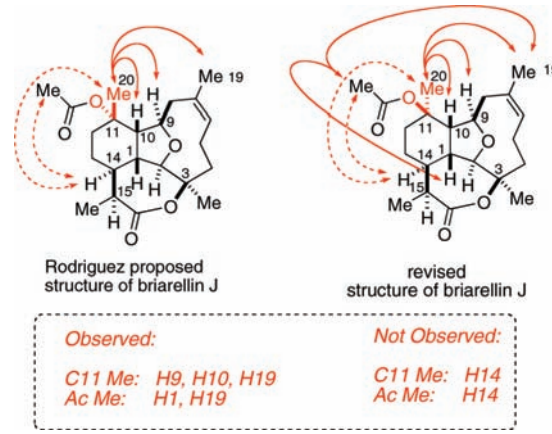


Figure 4. Original and revised structures of briarellin J.

account for all of the observed NOEs, but also the chair conformation with an equatorial C20 methyl would account for the lack of an NOE between the C20 and C14 protons that was originally used to argue for β-stereochemistry of the C11 methyl. Furthermore, since the structural assignments of briarellins B−D and J−P were ultimately based from analogy to briarellin A,[21] it is possible that their C11 stereocenters should be reassigned as well. This structural reassignment would be consistent with the proven structures of briarellin E and F as well as with the proposed biosynthesis.

In summary, the enantioselective total synthesis of the structure previously assigned as briarellin J has been achieved in 15 linear steps from previously prepared oxonene **5**. A revised structure of briarellin J has been advanced in which the C11 methyl is α and the acetate is β. In addition, this work suggests a possible stereochemical reassignment at C11 for briarellins A−D and K−P.

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

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(20) Rodríguez, A. D. *Magn. Reson. Chem.* **1992**, *30*, 977–986.

(21) Assignments of relative stereochemistry for briarellins J, K, L, M, N, O, and P were based off of comparison to briarellin D (see ref 4). Assignments of relative stereochemistry for briarellins B, C, and D were assisted by comparison to briarellin A (see ref 7).