ORGANIC LETTERS

2006
Vol. 8, No. 3
543−545

Total Synthesis of (±)-Bipinnatin J

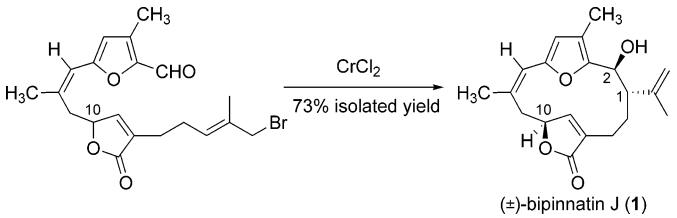
Qinhua Huang and Viresh H. Rawal*

Department of Chemistry, The University of Chicago, 5735 South Ellis Avenue, Chicago, Illinois 60637

vrawal@uchicago.edu

Received December 16, 2005

ABSTRACT



The total synthesis of (±)-bipinnatin J was achieved through a concise route that features the use of a silver ion promoted S_N1-type γ-alkylation of a siloxyfuran and a diastereoselective Cr(II)-mediated macrocyclization to provide bipinnatin J (1), wherein the remote furanone stereocenter at C10 induced the relative stereochemistry of the two additional stereocenters.

Marine invertebrates have yielded a plethora of structurally diverse natural products possessing a range of interesting biological activities.[1] In particular, gorgonian octocorals of the genus *Pseudopterogorgia* have proven to be particularly fertile producers of diterpenes having the cembrane or pseudopterane skeleta. Members of the first group are characterized by the presence of a 14-membered ring carbon framework and include compounds such as lophotoxin and bipinnatin B, whereas the latter group has a contracted, 12-membered ring framework, as seen in kallolide A and pinnatin A (Figure 1).[2] Several of these secondary metabolites exhibit promising pharmacological properties.[1−3] For example, bipinnatins A, B, and D display in vitro activity against the P388 murine tumor cell line, with IC_{50}'s of 0.9, 3.2, and 1.5 μg/mL, respectively.[2f] Additionally, lophotoxin and bipinnatin B are potent neurotoxins that irreversibly block nicotinic acetylcholine receptors.[3f] Bipinatin I possesses strong cytotoxic action, eliciting significant differential responses at the GI_{50} level for all colon and melanoma cancer cell lines at concentrations of 10^{-6} M.[2h]

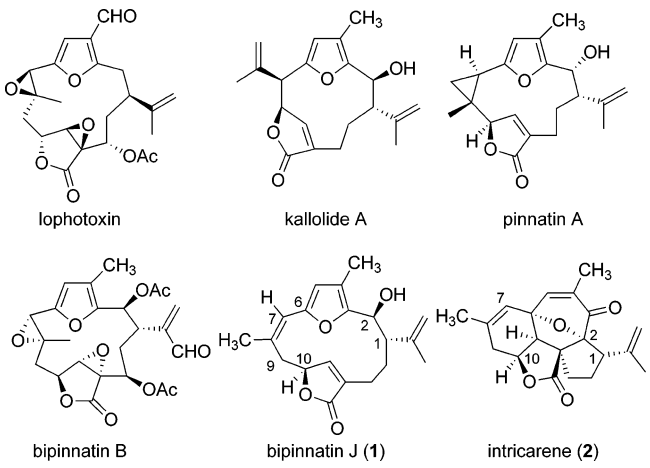


Figure 1. Structures of *Pseudopterogorgia* metabolites.

(1) Faulkner, D. J. *Nat. Prod. Rep.* **2002**, *19*, 1−48 and references therein.

(2) For isolation and bioactivities, see. *Lophotoxin*: (a) Fenical, W.; Okuda, R. K.; Bandurraga, M. M.; Culver, P.; Jacobs, R. S. *Science* **1981**, *212*, 1512−1514. *Kallolides*: (b) Look, S. A.; Burch, M. T.; Fenical, W.; Zheng, Q.; Clardy, J. *J. Org. Chem.* **1985**, *50*, 5741−5746. (c) Rodríguez, A. D.; Shi, J.-G.; Shi, Y.-P. *J. Org. Chem.* **2000**, *65*, 3192−3199. *Pinnatins*: (d) Rodríguez, A. D.; Shi, J.-G.; Huang, S. D. *J. Org. Chem.* **1998**, *63*, 4425−4432. (e) Rodríguez, A. D.; Shi, J.-G. *Org. Lett.* **1999**, *1*, 337−340. *Bipinnatins*: (f) Wright, A. E.; Burres, N. S.; Schulte, G. K. *Tetrahedron Lett.* **1989**, *30*, 3491−3494. (g) Rodríguez, A. D.; Shi, J.-G. *J. Org. Chem.* **1998**, *63*, 420−421. (h) Rodríguez, A. D.; Shi, J.-G.; Huang, S. D. *J. Nat. Prod.* **1999**, *62*, 1228−1237. (i) Rodrguez, A. D.; Shi, Y.-P. *J. Nat. Prod.* **2000**, *63*, 1548−1550.

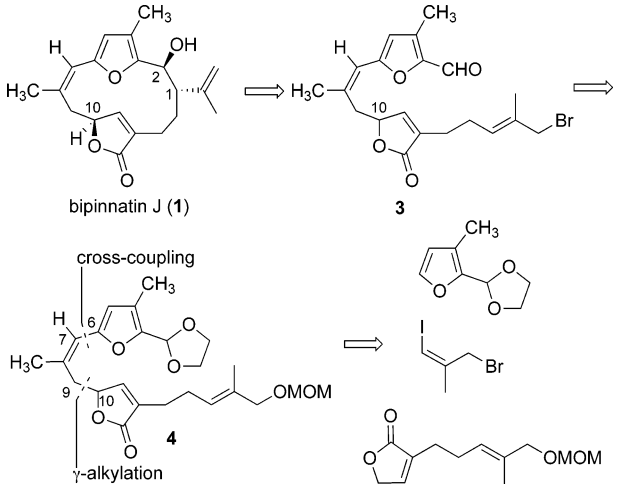
(3) (a) Culver, P.; Jacobs, R. S. *Toxicon* **1981**, *19*, 825−830. (b) Langdon, R. B.; Jacobs, R. S. *Life Sci.* **1983**, *32*, 1223−1228. (c) Sorenson, E. M.; Culver, P.; Chiappinelli, V. A. *Neuroscience* **1987**, *20*, 875−884. (d) Groebe, D. R.; Abramson, S. N. *J. Biol. Chem.* **1995**, *270*, 281−286. (e) Hyde, E. G.; Boyer, A.; Tang, P.; Xu, Y.; Abramson, S. N. *J. Med. Chem.* **1995**, *38*, 2231−2238. (f) Tornoe, C.; Holden-Dye, L.; Garland, C.; Abramson, S. N.; Fleming, J. T.; Sattelle, D. B. *J. Exp. Biol.* **1996**, *199*, 2161−2168.

10.1021/ol053054s CCC: $33.50
Published on Web 01/13/2006

In connection with our interest in the secondary metabolites of gorgonian corals, and their biosynthetic interrelationships,[4] we became interested in the furanocembrane bipinnatin J (**1**).[5−9] Possessing the less common *Z*-olefin in its macrocyclic ring, this compound may well be a precursor to several more oxidized congeners of the *Pseudopterogorgia*-derived cembranes. Of special interest is the structural relationship between bipinnatin J and the recently reported pentacyclic diterpene intricarene (**2**).[10] Isolated from *Pseudopterogorgia kallos*, this aptly named compound may very well arise from bipinnatin J, through oxidation of the furan moiety followed by an oxydopyrylium ion based transannular [5+2] cycloaddition reaction.[11] In this letter, we report a simple, convergent route to furanocembranes culminating in the total synthesis of bipinnatin J (**1**).

Our strategy to bipinnatin J (**1**) can be seen through the retrosynthetic analysis presented in Scheme 1. The plan was

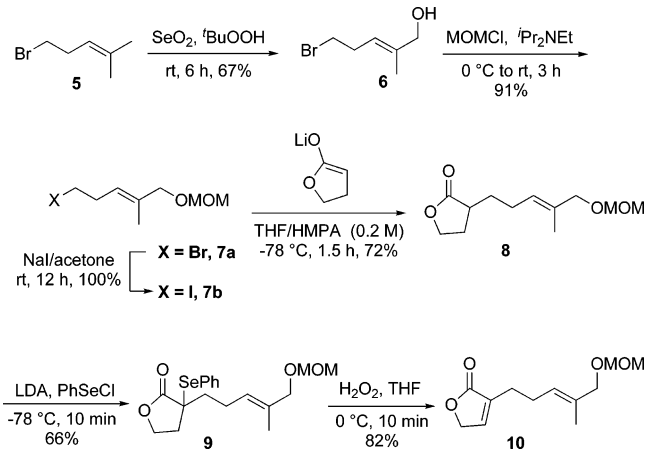
Scheme 1. Retrosynthetic Analysis of Bipinnatin J (**1**)



to construct the 14-membered carbon core of **1** through a metal-promoted macrocyclization of intermediate **3**. An analysis of molecular models indicated that the relative stereochemistry at C1 and C2 would be controlled by the sole stereocenter in the furanone unit, located five carbons away. A highly convergent route was devised for the synthesis of the macrocyclization precursor.

The synthesis of bipinnatin J commenced with the preparation of the substituted butyrolactone unit (Scheme 2).

Scheme 2. Synthesis of Fragment **10**

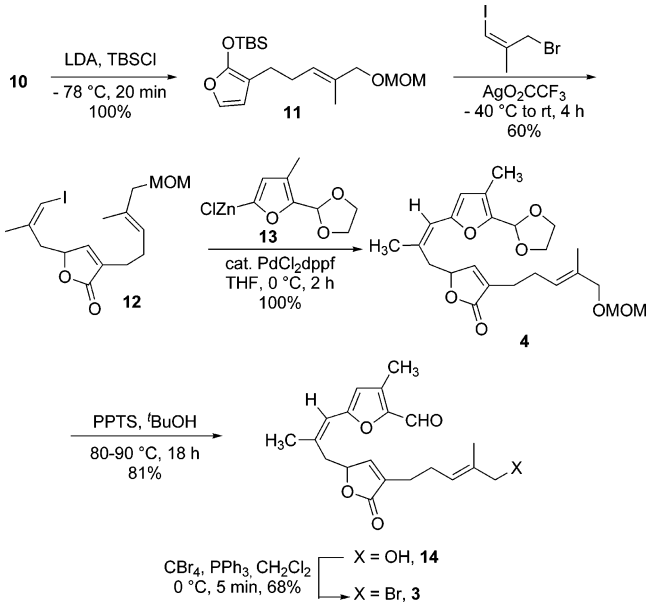


Allylic oxidation of commercially available 5-bromo-2-methylpent-2-ene (**5**) with SeO_2 and *t*-BuOOH proceeded regioselectively to afford *trans*-allylic alcohol **6** in 67% isolated yield.[12] The hydroxyl group was protected as the MOM ether to afford compound **7a** in 91% yield. The cross-coupling of **7a** with 3-bromofuran-2(5*H*)-one to yield the desired alkylated furanone (**10**) proved low yielding, so a less direct route was utilized. The reaction of γ-butyrolactone enolate with bromide **7a** gave the desired alkylation product (**8**), but in a low yield. The major product was a conjugated diene, presumably arising from E2 elimination of **7a**. To favor alkylation over elimination, the bromide was exchanged for an iodide. The modified alkylating agent performed as desired and provided the alkylated γ-butyrolactone (**8**) in 72% yield, along with ~10% of the diene side-product. The required olefin was introduced through a two-step, phenylselenation/selenoxide elimination sequence. The selenoxide elimination proceeded with good regioselectivity and yielded primarily the endocyclic olefin-containing product, **10** (17:1 ratio).

The elaboration of compound **10** to the desired cyclization precursor, **3**, necessitated alkylation at the γ-position of the unsaturated lactone. This transform was achieved through the intermediacy of the corresponding siloxyfuran **11**, prepared in quantitative yield by silation of the enolate of **10** (Scheme 3). The desired γ-alkylation was accomplished under S_N1 conditions. Treatment of siloxyfuran **11** with the requisite allylic bromide in the presence of $Ag(OCOCF_3)_2$

(4) Waizumi, N.; Stankovic, A. R.; Rawal, V. H. *J. Am. Chem. Soc.* **2003**, *125*, 13022−13023.
(5) For isolation of bipinnatin J, see ref 2g.
(6) For the synthetic studies toward bipinnatin J, see: Tsubuki, M.; Takahashi, K.; Sakata, K.; Honda, T. *Heterocycles* **2005**, *65*, 531−540. While this manuscript was being readied for publication, we became aware of a completed synthesis of bipinnatin J: Trauner, D., private communication. See: Roethle, P. A.; Trauner, D. *Org. Lett.* **2006**, *8*, 345−348.
(7) For total synthesis of furanocembranolides, see for example: (a) Rayner, C. M.; Astles, P. C.; Paquette, L. A. *J. Am. Chem. Soc.* **1992**, *114*, 3926−3936. (b) Paquette, L. A.; Astles, P. C. *J. Org. Chem.* **1993**, *58*, 165−169.
(8) For total synthesis of pseudopterolides, see: (a) Marshall, J. A.; Bartley, G. S.; Wallace, E. M. *J. Org. Chem.* **1996**, *61*, 5729−5735. (b) Marshall, J. A.; Liao, J. *J. Org. Chem.* **1998**, *63*, 5962−5970. (c) Marshall, J. A.; Van Devender, E. A. *J. Org. Chem.* **2001**, *66*, 8037−8041.
(9) Other synthetic studies: (a) Marshall, J. A.; Wang, X.-J. *J. Org. Chem.* **1992**, *57*, 3387−3396. (b) Marshall, J. A.; McNulty, L. M.; Zou, D. *J. Org. Chem.* **1999**, *64*, 5193−5200. (c) Tsubuki, M.; Takahashi, K.; Honda, T. *J. Org. Chem.* **2003**, *68*, 10183−10186.
(10) For isolation, see: Marrero, J.; Rodríguez, A. D.; Barnes, C. L. *Org. Lett.* **2005**, *7*, 1877−1880.
(11) Reviews of [5+2] cycloaddition: (a) Mascarenas, J. L. *Adv. Cycloaddit.* **1999**, *6*, 1−54. (b) Harmata, M.; Rashatasakhon, P. *Tetrahedron* **2003**, *59*, 2371−2395.
(12) Andresen, G.; Eriksen, A.; Dalhus, A. B.; Gundersen, L.-L.; Rise, F. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1662−1672.

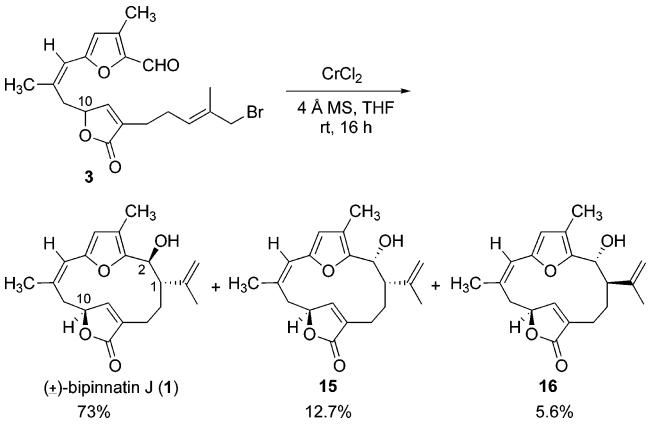
Scheme 3. Synthesis of the Macrocyclization Precursor, **3**



afforded the desired alkylation product (**12**) in 60% yield.[13,14] The required 3-methylfurfural piece was then appended through the Negishi cross-coupling protocol. The reaction of iodide **12** and organozinc compound **13**, which was generated in situ by treatment of dioxolane protected 3-methylfurfural with 1.0 equiv of *t*-BuLi and 1.2 equiv of $ZnCl_2$ in THF at −78 °C, was catalyzed with $PdCl_2$dppf and yielded the coupled product (**4**) in quantitative yield. Treatment of compound **4** with PPTS in refluxing *t*-BuOH removed the dioxolane and MOM ether protecting groups to provide aldehyde **14** in 81% isolated yield. It is noteworthy that the same reaction when carried out in MeOH or ^{i}PrOH led to decomposition of the starting material, with only trace amounts of the desired product present by ^{1}H NMR. The direct, palladium-mediated reductive cyclization of allylic alcohol **14** was examined, but without success.[15]

The Nozaki−Hiyama reaction presented a good alternative for the desired reductive cyclization.[16−18] In preparation for this reaction, the hydroxyl group was converted to the bromide with use of PPh_3 and CBr_4. The Nozaki−Hiyama macrocyclization of bromide **3** was carried out under dilute reaction conditions (0.429 mmol of **3**, 20.6 equiv of $CrCl_2$, 2.0 g of activated, powdered 4 Å molecular sieves, 300 mL of THF) to minimize intermolecular reactions. The reaction went to completion after 16 h and, to our delight, gave bipinnatin J (**1**), a white solid (mp 176−178 °C, lit.[2g] mp 141−142 °C dec), as the major product in 73% isolated yield. The ^{1}H and ^{13}C NMR spectra of the synthetic sample are identical with that reported for the natural product.[2g] Also isolated from the macrocyclization reaction were two diastereoisomeric cyclization products, **15** and **16**, in 12.7% and 5.6% yields, respectively. The structures assigned to these minor products are based on the NMR data and are considered tentative. We are examining the effect of reaction parameters on the diastereoselectivity of the cyclization reaction. The high diastereoselectivity observed in the macrocyclization can be understood by considering the likely transition state for the Nozaki−Hiyama reaction,[7,16−18] wherein the remote furanone stereocenter at C10 induces relative stereochemistry of the two new stereocenters. In

Scheme 4. Macrocyclization to Yield Bipinnatin J (**1**)



summary, we have completed an efficient, convergent total synthesis of bipinnatin J. The longest linear sequence requires 12 steps from the commercially available 5-bromo-2-methylpent-2-ene. The synthesis features the use of a silver ion promoted S_N1-type γ-alkylation of a siloxyfuran and a diastereoselective Cr(II)-mediated macrocyclization, which provides bipinnatin J as the major product. Current efforts are directed toward the asymmetric synthesis of bipinnatin J as well as the biomimetic tranformation of this compound to other *Pseudopterogorgia*-derived diterpenes, including intricarene (**2**).

Acknowledgment. We are grateful to the National Institutes of Health (R01 GM69990) for financial support of this work.

Supporting Information Available: General experimental procedures and characterization data for all key intermediates and bipinnatin J. This material is available free of charge via the Internet at http://pubs.acs.org.

OL053054S

(13) Jefford, C. W.; Sledeski, A. W.; Boukouvalas, J. *J. Chem. Soc., Chem. Commun.* **1988**, 364−365.

(14) Preparation of 3-bromo-1-iodo-2-methylpropene: Larock, R. C.; Han, X. *J. Org. Chem.* **1999**, *64*, 1875−1887.

(15) For examples of palladium promoted reductive coupling of allylic alcohols with aldehydes, see: (a) Takahara, J. P.; Masuyama, Y.; Kurusu, Y. *J. Am. Chem. Soc.* **1992**, *114*, 2577−2586. (b) Kimura, M.; Tomizawa, T.; Horino, Y.; Tanaka, S.; Tamaru, Y. *Tetrahedron Lett.* **2000**, *41*, 3627−3629.

(16) Fürstner, A. *Chem. Rev.* **1999**, *99*, 991−1045.

(17) For the Cr-promoted macrocyclization of allylic bromides, see: (a) Still W. C.; Mobilio, D. *J. Org. Chem.* **1983**, *48*, 4785−4786. (b) Wender, P. A.; Mckinney, J. A.; Muka, C. *J. Am. Chem. Soc.* **1990**, *112*, 5369−5370. (c) Wender, P. A.; Grissom, J. W.; Hoffmann, U.; Mah, R. *Tetrahedron Lett.* **1990**, *31*, 6605−6608;

(18) In Paquette's synthesis of gorgiacerone, the Nozaki−Hiyama reaction was utilized to produce the pseudopterane skeleton (25% yield, see ref 7a). Paquette has also utilized this process for construction of the furanocembrane skeleton (20% yield, see ref 7b).