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Expedient Synthesis of (±)-Bipinnatin J

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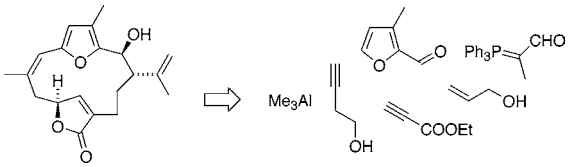
ABSTRACT



A nine-step, stereoselective synthesis of bipinnatin J is described, which features a ruthenium-catalyzed Alder-ene reaction, a Stille cross coupling, and an intramolecular Nozaki–Hiyama–Kishi allylation as key steps. The biosynthetic relationship between bipinnatin J and complex polycyclic diterpenes isolated from gorgonian corals is discussed.

Gorgonian corals have yielded a wide range of furanocembranoids and related diterpenes with attractive architectural and biological features (Scheme 1). Simpler members of this family, such as rubifolide (**1**) and bipinnatin J (**4**) were first isolated from *Gersemia rubiformis* and *Pseudopterogorgia bipinnata*, respectively.[1,2] The more highly oxidized furanocembranoid lophotoxin (**2**) was found in various corals of the genus *Lophogorgia*.[3] Kallolide A (**5**) was isolated from *Pseudopterogorgia kallos*.[2] More recently, Rodríguez reported the isolation of the structurally intriguing diterpenes providencin (**3**), intricarene (**6**), and bielschowskysin (**7**) from this rich source.[4−6]

Some of these natural products have shown significant biological activities. Lophotoxin was found to be an irreversible inhibitor of the nicotinic acetylcholine receptor.[7] Bielschowskysin exhibits strong activity against certain human cancer cell lines and is also effective against *Plasmodium falciparum*, the cause of malaria.[5] Providencin has also shown moderate anticancer activity against three cancer cell lines.[4] Intricarene, the most recently isolated of the family, has thus far displayed weak biological activity. However, lack of material has prevented comprehensive biological evaluation of this compound.[6]

Furanocembranoids have long been popular targets for total synthesis. For instance, Marshall reported syntheses of both rubifolide and kallolide A.[8] Paquette was an early pioneer of the furanocembranoids with work that included syntheses of acersolide and gorgiacerone.[9] Pattenden completed a synthesis of bis-deoxylophotoxin, which is a potential precursor to lophotoxin.[10] Synthetic approaches toward bipinnatin J and pukalide have also been reported.[11]

The possibility to explore biosynthetic relationships and thus develop a unified synthetic approach adds to the attractiveness of the natural products shown in Scheme 1.

(1) Williams, D.; Andersen, R. J.; VanDuyne, G. D.; Clardy, J. *J. Org. Chem.* **1987**, *52*, 332−335.
(2) Rodríguez, A. D.; Shi, J.-G. *J. Org. Chem.* **1998**, *63*, 420−421.
(3) Fenical, W.; Okuda, R. K.; Bandurraga, M. M.; Culver, P.; Jacobs, R. S. *Science* **1981**, *212*, 1512−1514.
(4) Marrero, J.; Rodríguez, A. D.; Baran, P.; Raptis, R. G. *Org. Lett.* **2003**, *5*, 2551−2554.
(5) Marrero, J.; Rodríguez, A. D.; Baran, P.; Raptis, R. G.; Sánchez, J. A.; Ortega-Barria, E.; Capson, T. L. *Org. Lett.* **2004**, *6*, 1661−1664.
(6) Marrero, J.; Rodríguez, A. D.; Barnes, C. L. *Org. Lett.* **2005**, *7*, 1877−1880.
(7) Culver, P.; Fenical, W.; Taylor, P. *J. Biol. Chem.* **1984**, *259*, 3763−3770.
(8) (a) Marshall, J. A.; Liao, J. *J. Org. Chem.* **1998**, *63*, 5962−5970. (b) Marshall, J. A.; Sehon, C. A. *J. Org. Chem.* **1997**, *62*, 4313−4320.
(9) (a) Paquette, L. A.; Astles, P. C. *J. Org. Chem.* **1993**, *58*, 165−169. (b) Rayner, C. M.; Astles, P. C.; Paquette, L. A. *J. Am. Chem. Soc.* **1992**, *114*, 3926−3936.
(10) Cases, M.; Gonzalez-Lopez de Turiso, F.; Hadjisoteriou, M. S.; Pattenden, G. *Org. Biomol. Chem.* **2005**, *3*, 2786−2804.
(11) (a) Stock, C.; Höfer, F.; Bach, T. *Synlett* **2005**, 511−513. (b) Tsubuki, M.; Takahashi, K.; Sakata, K.; Honda, T. *Heterocycles* **2005**, *65*, 531−540. (c) Wipf, P.; Soth, M. J. *Org. Lett.* **2002**, *4*, 1787−1790. (d) Marshall, J. A.; Van Devender, E. A. *J. Org. Chem.* **2001**, *66*, 8037−8041. (e) Paterson, I.; Brown, R. E.; Urch, C. J. *Tetrahedron Lett.* **1999**, *40*, 5807−5810. (f) Tius, M. A. *Chem. Rev.* **1988**, *88*, 719−732.

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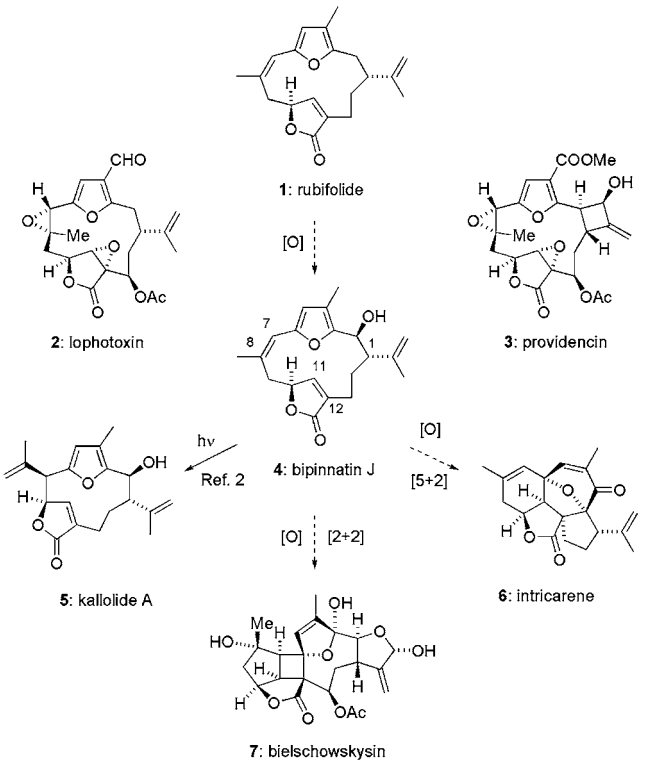
Scheme 1. Gorgonian Furanocembranoids and Their Derivatives



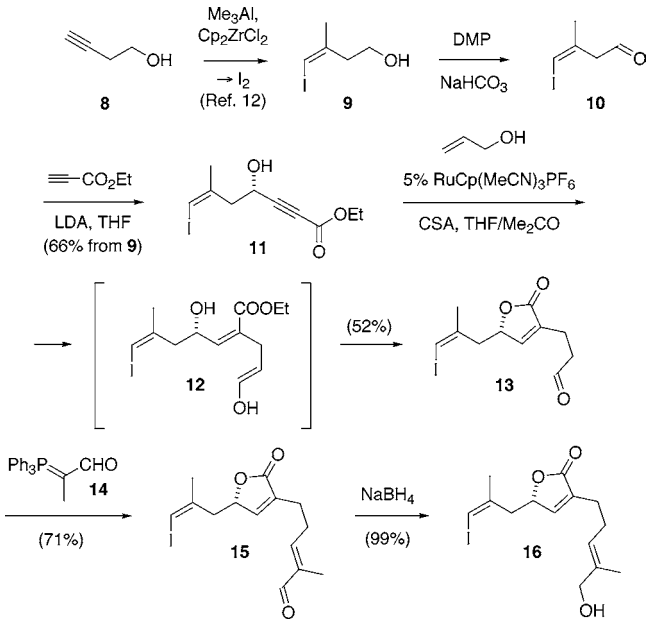
Indeed, Rodríguez has demonstrated that photolysis of bipinnatin J yields kallolide A, presumably through a [1,3]-sigmatropic rearrangement.[2] Intriguingly, Achmatowicz-type oxidation of bipinnatin J, followed by dehydration and transannular 1,3-dipolar cycloaddition of the resulting oxidopyrylium species, could afford intricarene. Similarly, epoxidation of the $\Delta^{7,8}$ double bond, followed by the addition of water and (formal) 2+2 cycloaddition, could convert the bipinnatin J core into the beguiling ring system of bielschowskysin.

We now wish to report the first total synthesis of (±)-bipinnatin J, the prototypical gorgonian furanocembranoid. Our synthesis starts with commercially available 3-butynol (**8**), which was converted into the known (*Z*)-vinyl iodide **9** through zirconium-mediated carboalumination, followed by isomerization and iodination (Scheme 2).[12] Dess−Martin oxidation of this material gave the sensitive aldehyde **10**, which was carried into the next step without further purification. Addition of lithiated ethyl propiolate to **10** afforded propargylic alcohol **11** as a racemate.

In one of the key steps of our synthesis, a ruthenium(II)-catalyzed Trost enyne reaction of **11** with a slight excess of allyl alcohol gave aldehyde **13** as a 7:1 mixture with its regioisomer (not shown).[13] This reaction presumably proceeded through enol **12**, which underwent tautomerization and intramolecular transesterification under these conditions. Overall, this atom-economical transformation not only

(12) Ma, S.; Negishi, E. *J. Org. Chem.* **1997**, *62*, 784−785.
(13) Trost, B. M.; Toste, F. D. *Tetrahedron Lett.* **1999**, *40*, 7739−7743.

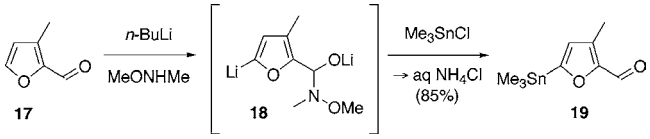
Scheme 2. Preparation of Building Block **15**



provided a functional handle for the elongation of the carbon chain but also efficiently installed a butenolide moiety in a manner not previously used in a furanocembranoid synthesis. Reaction of **13** with a stabilized Wittig reagent **14**, followed by chemoselective reduction of the resulting aldehyde **15**, then gave primary allylic alcohol **16**.

A second building block **19**, representing the furan moiety of the natural product, was prepared in a single step from known 3-methylfurfural (**17**) (Scheme 3).[14] *In situ* protection

Scheme 3. Preparation of Building Block **17**

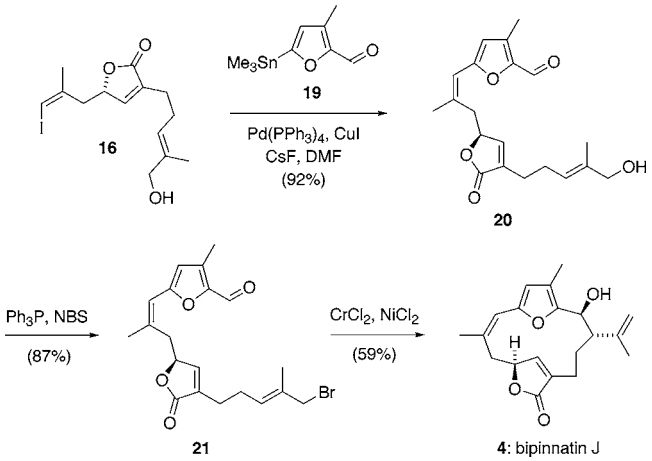


of the aldehyde as the lithio-hemiaminal adduct, followed by deprotonation of the furan nucleus gave intermediate **18**. Lithium-tin exchange cleanly afforded stannyl furfural **19**.[15]

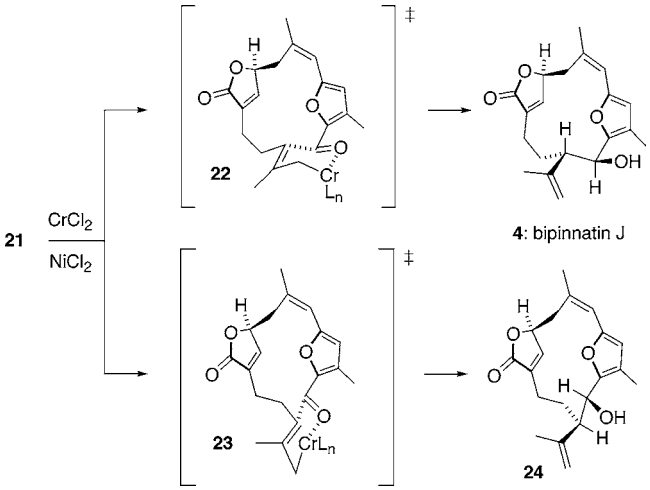
With vinyl iodide **16** and furyl stannane **19** in hand, the stage was set for the combination of the two components and the formation of the macrocyclic ring (Scheme 4). Stille coupling of **16** and **19** gave **20** in excellent yield, which contains all 20 carbons of the target molecule. Conversion of allylic alcohol **20** into the allylic bromide **21** proceeded without incident using PPh_3 and NBS.

(14) Klein, L. L. *J. Org. Chem.* **1985**, *50*, 1770−1773.
(15) Roschangar, F.; Brown, J. C.; Cooley, B. E.; Sharp, M. J.; Matsuoka, R. T. *Tetrahedron* **2002**, *58*, 1657−1666.
(16) (a) Fürstner, A. *Chem. Rev.* **1999**, *99*, 991−1045. (b) Still, W. C.; Mobilio, D. *J. Org. Chem.* **1983**, *48*, 4785−4786. (c) The Nozaki−Hiyama−Kishi reaction has been used by Paquette to close the 13-membered ring of gorgiacerone along the C1−C12 bond. See ref 9b.

Scheme 4. Total Synthesis of (±)-Bipinnatin J



Scheme 5. Diastereoselectivity of the Macrocyclization



In another key step of the synthesis, **21** was subjected to Nozaki−Hiyama−Kishi conditions,[16] which resulted in the formation of bipinnatin J (**4**) *almost as a single diastereomer* (d.r. > 9:1). The smooth and highly diastereoselective formation of the 13-membered ring reflects the conformational rigidity of the precursor **21**, which contains a *cis* double bond and two 1,3-disubstituted five-membered rings of little flexibility. The simple diastereoselectivity of this reaction presumably results from a chair-shaped transition state **22** and reflects the stereochemistry of the allylic bromide (Scheme 5). By contrast, the high 1,6-diastereoselectivity induced by the sole remote stereocenter is more difficult to explain. Molecular mechanics calculations[17] suggest that the other diastereomer of bipinnatin J bearing an *anti* relationship between the secondary alcohol and the isopropenyl group, compound **24**, is considerably higher in energy (E_{rel} = 2.65 kcal mol^{-1}). This could be reflected in the relative energy of the chair-shaped transition state **23** that would lead to its formation.

(17) These calculations were performed with Macromodel version 8.1 (Schroedinger, LLC). Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskcamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440−467.

In summary, we have reported the first total synthesis of the diterpene (±)-bipinnatin J. Our highly stereoselective synthesis is exceptionally short and virtually void of protecting group manipulations due to of the remarkable chemoselectivity of modern transition metal-catalyzed reactions. It comprises nine linear steps starting from commercially available 3-butynol and yields sufficient quantities of material to thoroughly explore the biosynthetic relations indicated in Scheme 1. The asymmetric synthesis of bipinnatin J and its conversion into intricarene and analogues of bielschowskysin are under active investigation. Results from these studies will be reported in due course.

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Supporting Information Available: Spectroscopic and analytical data and experimental procedures for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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