

Exploring Biosynthetic Relationships among Furanocembranoids: Synthesis of (–)-Bipinnatin J, (+)-Intricarene, (+)-Rubifolide, and (+)-Isoepilophodione B

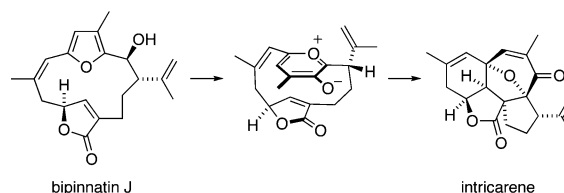
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ABSTRACT



The asymmetric total synthesis of (–)-bipinnatin J and its conversion into (+)-intricarene through a transannular 1,3-dipolar cycloaddition is described. In addition, the conversion of (–)-bipinnatin J into (+)-rubifolide and (+)-isoepilophodione B is reported. Biosynthetic relationships among furanocembranoids and the possible role of 1,3-dipolar cycloadditions in biosynthesis are discussed.

Cycloadditions are now firmly established in the canon of biosynthetic reactions.¹ It is therefore surprising that an important subclass of these reactions, namely 1,3-dipolar cycloadditions, appear to play a very minor role in biosynthesis.² Despite the fact that several 1,3-dipoles have been identified as natural products,³ their participation in a cycloaddition has not been demonstrated. Numerous naturally occurring nitrones, for instance, have been isolated but only one isoxazolidine has been suspected to arise through a biosynthetic [3+2]-cycloaddition.⁴ Similarly, diazo com-

pounds are known as natural products, but pyrazolidines have not been isolated.^{3a} Azomethine ylides could be readily formed from α -amino acid derivatives, yet no genuine example of a biosynthetic cycloaddition involving these interesting 1,3-dipoles appears to have been reported.

In light of this apparent lack of biosynthetic 1,3-dipolar cycloadditions, we became very interested in the recently disclosed natural product intricarene (**5**).^{5a} Intricarene is one of a series of furanocembranoid diterpenes isolated from Caribbean gorgonian corals, mostly by Rodríguez and co-workers (Figure 1).⁵ The simpler members of this series, rubifolide (**1**) and bipinnatin J (**2**), show the traditional macrocyclic make-up of the furanocembranoid family. Kallolide

(1) Stocking, E. M.; Williams, R. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 3078–3115.

(2) (a) Padwa, A.; Schoffshall, A. M. *Adv. Cycloadd.* **1990**, *2*, 1–89. (b) Padwa, A.; Pearson, W. H., Eds. *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Wiley: Hoboken, NJ, 2003. (c) Mulzer, J. *Org. Synth. Highlights* 1991, 77–95.

(3) (a) He, H.; Ding, W.-D.; Bernan, V. S.; Richardson, A. D.; Ireland, C. M.; Greenstein, M.; Ellestad, G. A.; Carter, G. T. *J. Am. Chem. Soc.* **2001**, *123*, 5362–5363. (b) Qian-Cutrone, J.; Huang, S.; Shu, Y.-Z.; Vyas, D.; Fairchild, C.; Menendez, A.; Krampitz, K.; Dalterio, R.; Kloor, S. E.; Gao, Q. *J. Am. Chem. Soc.* **2002**, *124*, 14556–14557. (c) Fenical, W.; Jensen, P. R.; Cheng, X. C. Avrainvillamide, a Cytotoxic Marine Natural Product, and Derivatives thereof. U.S. Patent 6,066,635, 2000.

(4) Irlapati, N. R.; Baldwin, J. E.; Adlington, R. M.; Pritchard, G. J.; Cowley, A. R. *Tetrahedron* **2005**, *61*, 1773–1784.

(5) (a) Marrero, J.; Rodríguez, A. D.; Barnes, C. L. *Org. Lett.* **2005**, *7*, 1877–1880. (b) Rodríguez, A. D.; Shi, J.-G.; Huang, S. D. *J. Org. Chem.* **1998**, *63*, 4425–4432. (c) 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. (d) Rodríguez, A. D.; Shi, Y.-P. *J. Org. Chem.* **2000**, *65*, 5839–5842. (e) Williams, D.; Andersen, R. J.; Van Duyne, G. D.; Clardy, J. *J. Org. Chem.* **1987**, *52*, 332–335.

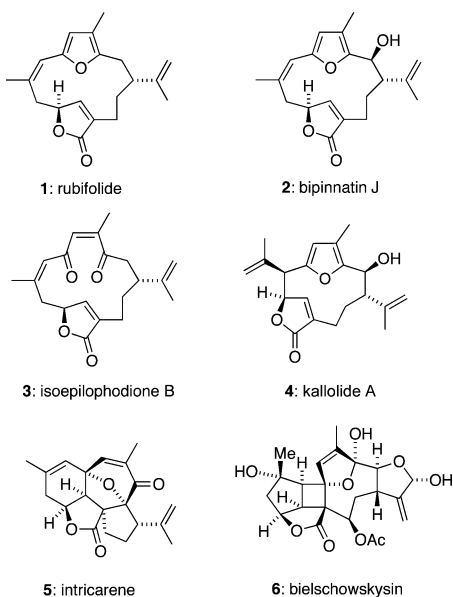


Figure 1. Furanocembranoids isolated from Gorgonian corals.

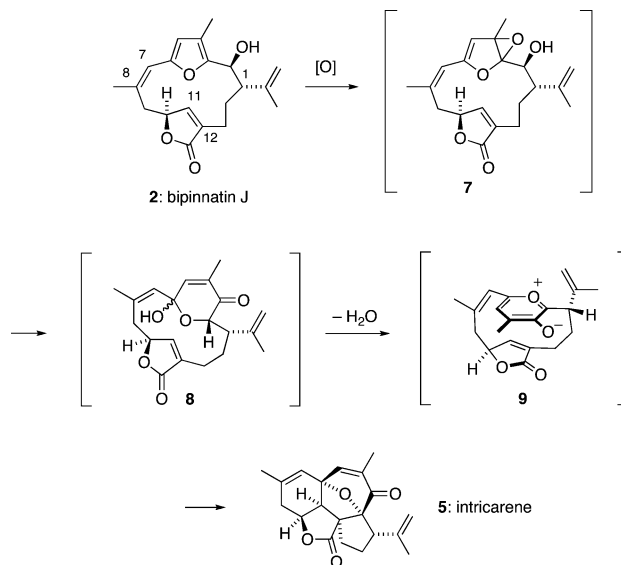
A (**4**) is a photochemically rearranged derivative of **2**, which still retains its furan moiety. By contrast, only remnants of this ring can be found in isoepilophodione B (**3**), intricarene (**5**), and bielschowskysin (**6**). The unique frameworks of **5** and **6** are distinguished from the furanocembranoid skeleton through additional, transannular C,C-bonds.

Apart from their intriguing structural characteristics, many of the furanocembranoids exhibit promising biological activities. Bielschowskysin stands out due to its strong antimalarial activity and significant cytotoxicity against lung and renal cancer cell lines.^{5c} With too little material in hand to comprehensively evaluate the compound, intricarene has thus far only shown modest biological activities.^{5a}

Retrosynthetic analysis of intricarene (**5**) suggests that it could be formed from bipinnatin J (**2**) through a 1,3-dipolar cycloaddition of possible biosynthetic relevance (Scheme 1). Epoxidation of the furan moiety, for instance by a monooxygenase, could afford an unstable spiroepoxide (**7**) whose rearrangement affords hydroxypyranone **8**. Overall, this transformation would correspond to the well-known Achmatowicz oxidation of hydroxyfurans.⁶ Subsequent 1,3-elimination of water yields an oxidopyrylium species **9**, which undergoes a transannular 1,3-dipolar cycloaddition to yield intricarene. Achmatowicz oxidations and subsequent 1,3-dipolar cycloadditions of oxidopyrylium dipoles have been employed in the total synthesis of natural products, but never in a biomimetic context.⁷

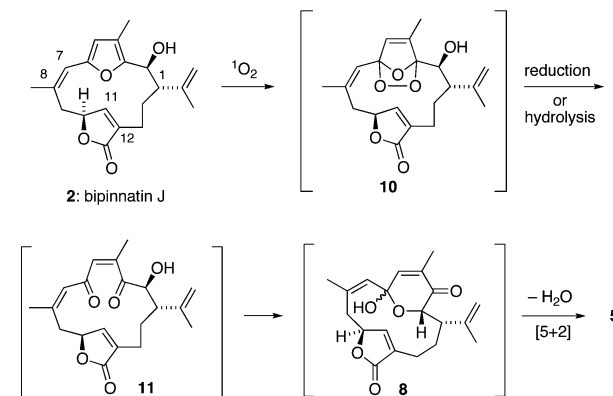
In an alternative pathway, the hydroxypyranone intermediate **8** could be formed through [4+2]-cycloaddition of singlet

Scheme 1. Proposed Biosynthetic Origin of Intricarene



oxygen across the furan to yield ozonide **10**, followed by reduction or hydrolysis to yield dienedione **11** (Scheme 2).

Scheme 2. Formation of Intricarene through Singlet-Oxygen Addition



Rearrangement of this compound would again afford hydroxypyranone **8**. This second entry to oxidopyrylium species has indeed been utilized in synthesis.^{7b,c}

Intrigued by these possible biosynthetic relationships, several laboratories have undertaken the challenge of synthesizing bipinnatin J and converting it into intricarene, including Rawal's⁸ and Pattenden's.⁹ We have previously reported a very efficient, 9-step synthesis of racemic bipinnatin J, which put us in a position to thoroughly investigate biosynthetic relationships between the furanocembranoids.¹⁰

In parallel to our racemic synthesis, we have developed an asymmetric approach to (–)-bipinnatin J (Scheme 3). It

(6) Szechner, B.; Achmatowicz, O. *Pol. J. Chem.* **1994**, *68*, 1149–1160.

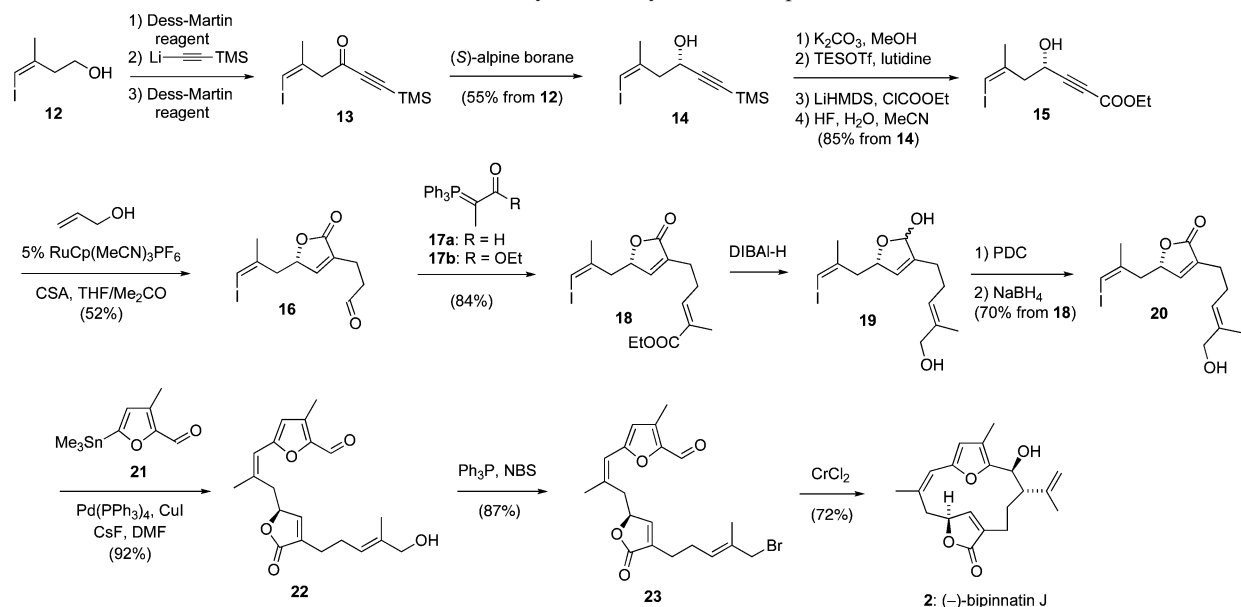
(7) (a) Wender, P. A.; Rice, K. D.; Schnute, M. E. *J. Am. Chem. Soc.* **1997**, *119*, 7897–7898. (b) Magnus, P.; Shen, L. *Tetrahedron* **1999**, *55*, 3553–3560. (c) Bauta, W. E.; Booth, J.; Bos, M. E.; DeLuca, M.; Diorazio, L.; Donohoe, T. J.; Frost, C.; Magnus, N.; Magnus, P.; Mendoza, J.; Pye, P.; Tarrant, J. G.; Thom, S.; Ujjainwalla, F. *Tetrahedron* **1996**, *52*, 14081–14102. (d) Lee, H.-Y.; Sohn, J.-H.; Kim, H. Y. *Tetrahedron Lett.* **2001**, *42*, 1695–1698.

(8) Huang, Q.; Rawal, V. H. *Org. Lett.* **2006**, *8*, 543–545.

(9) Tang, B.; Bray, C. D.; Pattenden, G. *Tetrahedron Lett.* **2006**, *47*, 6401–6404.

(10) Roethle, P. A.; Trauner, D. *Org. Lett.* **2006**, *8*, 345–347.

Scheme 3. Asymmetric Synthesis of Bipinnatin J



starts with oxidation of alcohol **12**,¹¹ followed by addition of lithiated TMS-acetylene and reoxidation. Asymmetric reduction of the resulting ynone **13** with Midland's (*S*)-Alpine borane¹² gave propargylic alcohol **14** in 92% ee. A series of high-yielding standard transformations was used to convert this material into enantiomerically enriched propargylic alcohol **15**, which had been used in racemic form in our previous synthesis. Unfortunately, we were unable to obtain (*S*)-**15** directly by enantioselective reduction of the corresponding ynone or asymmetric propargylate additions to the aldehyde obtained from **12**.

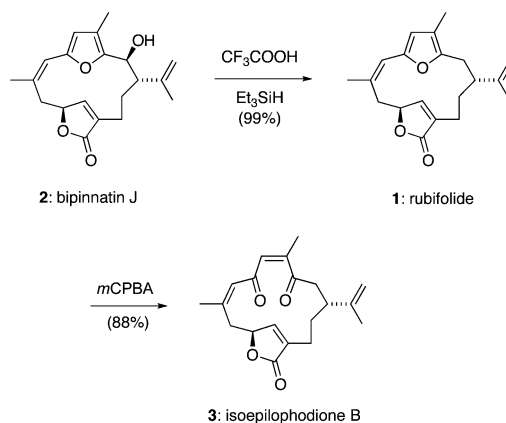
The remainder of our asymmetric synthesis closely follows the racemic one, keeping in mind that only one stereocenter, which is at risk to be racemized, is present until bipinnatin J is reached. Gratifyingly, the ruthenium-catalyzed Alder ene reaction proceeded without incident, as reported by Trost,¹³ to afford **16** in 92% ee. In the subsequent Wittig olefination step, however, we had to divert from our previous synthesis,¹⁰ since reaction of **16** with Ph₃P=C(Me)CHO (**17a**) resulted in complete racemization. Use of the more reactive reagent Ph₃P=C(Me)COOEt (**17b**) largely retained the stereochemical integrity of the olefination product **18** (88% ee) but required two extra steps to distinguish between the ester and butenolide moiety. Careful reduction of **18** with DIBAL-H gave a very sensitive lactol **19**. Oxidation with PDC, followed by chemoselective reduction with sodium borohydride gave allylic alcohol **20**. Stille-coupling with stannane **21** afforded allylic alcohol **22**, which was converted into allylic bromide **23** through Appel reaction.¹⁴ A highly diastereoselective Nozaki-Hiyama-Kishi (NHK)¹⁵ macrocyclization then gave

enantiomerically enriched (-)-bipinnatin J (**2**) in good yield. Chiral HPLC showed that our optically active material had retained 88% ee (see the Supporting Information). Therefore, the Stille-coupling as well as the Appel and NHK reactions proceeded without further racemization.

With ample supplies of racemic and enantiomerically pure bipinnatin J in hand, we were in a good position to explore synthetic and biosynthetic relationships among furanocembranoids.

Rubifolide was obtained from **2** through S_N1-deoxygenation (Scheme 4). Treatment of bipinnatin J with triethylsi-

Scheme 4. Synthesis of (+)-Rubifolide and (+)-Isoepilophodione B



lane and trifluoroacetic acid gave (+)-rubifolide (**1**) in essentially quantitative yield.^{16,17} Oxidation of this natural product with *m*CPBA cleaved the furan nucleus to yield

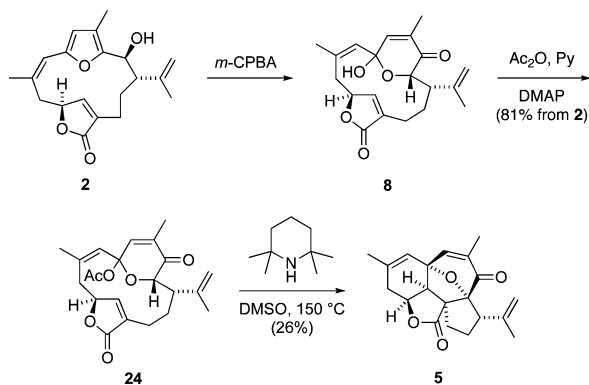
(11) Ma, S.; Negishi, E. *J. Org. Chem.* **1997**, *62*, 784–785.
 (12) Midland, M. M.; Tramontano, A.; Kazubski, A.; Graham, R. S.; Tsai, D. J. S.; Cardin, D. B. *Tetrahedron* **1984**, *40*, 1371–1380.
 (13) Trost, B. M.; Müller, T. J. J.; Martinez, J. *J. Am. Chem. Soc.* **1995**, *117*, 1888–1899.
 (14) Appel, R. *Angew. Chem., Int. Ed.* **1975**, *14*, 801–811.

(15) Fürstner, A. *Chem. Rev.* **1999**, *99*, 991–1045.

(+)-isoepiplophodione **3** in 88% yield. Selective addition of singlet oxygen to the furan moiety of **1**, followed by reduction also gave **3**, shedding light on the potential biosynthetic origin of this natural product (see the Supporting Information).

While these synthetic studies were ongoing, we also investigated the crucial biomimetic conversion of bipinnatin J to intricarene. Both the Achmatowicz strategy shown in Scheme 1 and the singlet-oxygen route shown in Scheme 2 were explored. Oxidation of bipinnatin J with *m*CPBA proved to be most favorable and proceeded cleanly to afford the sensitive hydroxypyranone **8**, apparently as a single stereoisomer (Scheme 5). Acetylation gave acetate **24**, which

Scheme 5. Conversion of Bipinnatin J into Intricarene



exists at room temperature as a mixture of isomers. Variable-temperature NMR spectroscopy showed that these isomers were not two diastereomers with respect to the newly formed acetal stereocenter but two conformers, whose NMR-spectra coalesce above 10 °C (see the Supporting Information).

The elimination of water from **8** or acetic acid from **24** followed by 1,3-dipolar cycloaddition, however, turned out to be a surprisingly difficult task. For instance, treatment of hydroxypyranone **8** with a wide array of acids or dehydrating agents gave little if any intricarene. 1,3-Elimination of acetic acid from **24** under standard conditions, e.g., Et₃N or DBU in MeCN, gave **5** in very low yields (see the Supporting Information for an extensive list of conditions tried).¹⁸

(16) McCombie, S. W.; Shankar, B. B.; Ganguly, A. K. *Tetrahedron Lett.* **1987**, 28, 4123–4126.

(17) For previous synthesis of (–)-rubifolide see: Marshall, J. A.; Sehon, C. A. *J. Org. Chem.* **1997**, 62, 4313–4320.

After expending ca. 1 g of synthetic bipinnatin J, we finally found conditions that reliably yielded intricarene. Dissolution of **24** in DMSO, followed by addition of 2,2,6,6-tetramethylpiperidine (TMP) and heating to 150 °C in a sealed tube afforded intricarene in 26% yield. Thus it appears that the combination of a very hindered secondary amine base with high temperatures and a polar solvent is most effective in achieving the desired conversion. The oxidative transformation starting from (–)-bipinnatin J, which resulted in an asymmetric total synthesis of (+)-intricarene, gave spectra, optical rotation, and MS data that matched the published data.

It is interesting to speculate how relevant our work is for establishing the biosynthetic relationship between bipinnatin J and intricarene. Temperatures in excess of 150 °C certainly cannot be deemed “biomimetic”. On the other hand, the requirement for high temperatures opens the fascinating possibility that, in Nature, an enzyme could mediate the reaction. This enzyme, possibly the very monooxygenase that performs the initial oxidation, could catalyze the formation of the high-energy species **9** or conformationally preorganize **9** toward the cycloaddition. It could also stabilize **9** against nonproductive pathways such as dimerization. In light of our results it seems unlikely that the formation of intricarene proceeds spontaneously from an oxidation product of bipinnatin J (e.g., compound **8**).

Future investigations will be directed at exploring other connections between bipinnatin J and its furanocembranoid congeners, e.g., bielschowskysin. With significant quantities of several furanocembranoids, including intricarene, in hand, we intend to fully evaluate their biological activities. Results of these screenings will be reported in due course.

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Supporting Information Available: Spectroscopic 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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(18) In Pattenden’s work (ref 9), intricarene was obtained from **24** in 10% yield under the DBU/MeCN conditions. However, this was not optimized due to the relative dearth of bipinnatin J available.