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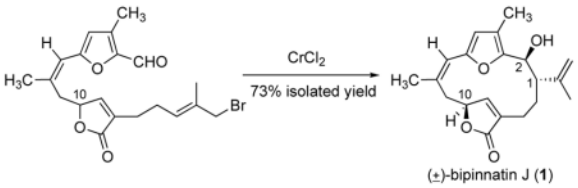
Total Synthesis of (±)-Bipinnatin J

Qinhua Huang and **Viresh H. Rawal***
Department of Chemistry, The University of Chicago, 5735 South Ellis Avenue Chicago, Illinois 60637

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 new 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 GI_{50} level for all colon and melanoma cancer cell lines at concentrations of 10^{-6} M.[2h]

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] cycloadddion 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 to construct the 14-membered carbon core of 1 through a metal-

vrawal@uchicago.edu.

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 six 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). 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**. In order 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 regioselectively 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 y-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 $Ag(OCOCF_3)_2$ 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 using PPh_3 and CBr_4. The Nozaki-Hiyama macrocyclization of bromide **3** was carried out under dilute reaction conditions (0.429 mmol **3**, 20.6 eq $CrCl_2$, 2.0 g activated, powdered 4Å molecular sieves, 300 mL 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] = dec. at 141–142 °C), as the major product in 73% isolated yield. The ^{1}H and ^{13}C NMR spectra of the synthetic sample are identical to that reported for the natural product.[2g] Also isolated from the macrocyclization reaction were two disasteroisomeric 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 CIO induces relative stereochemistry of the two new sterocenters.

In 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-methylpeten-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**).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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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]).

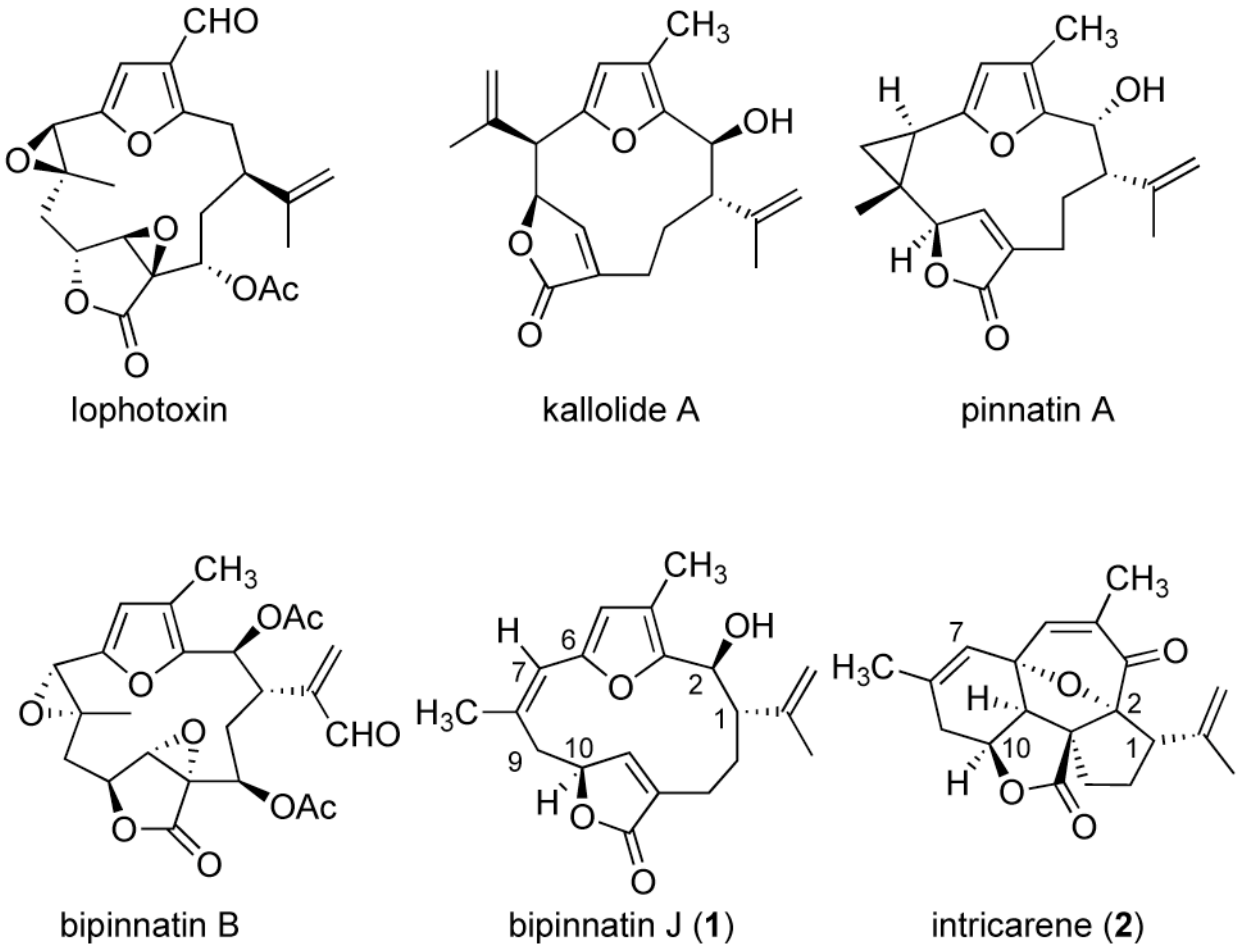
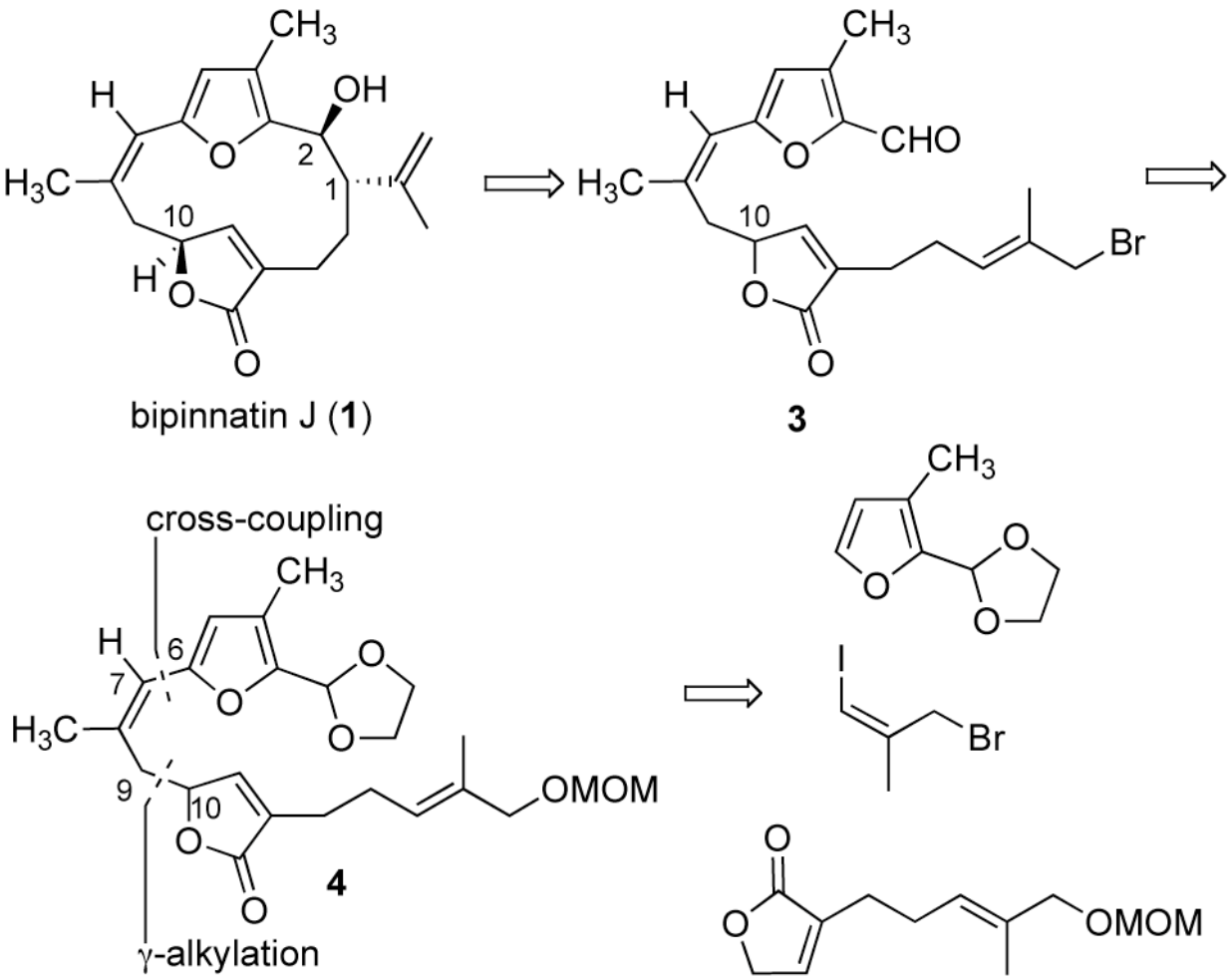
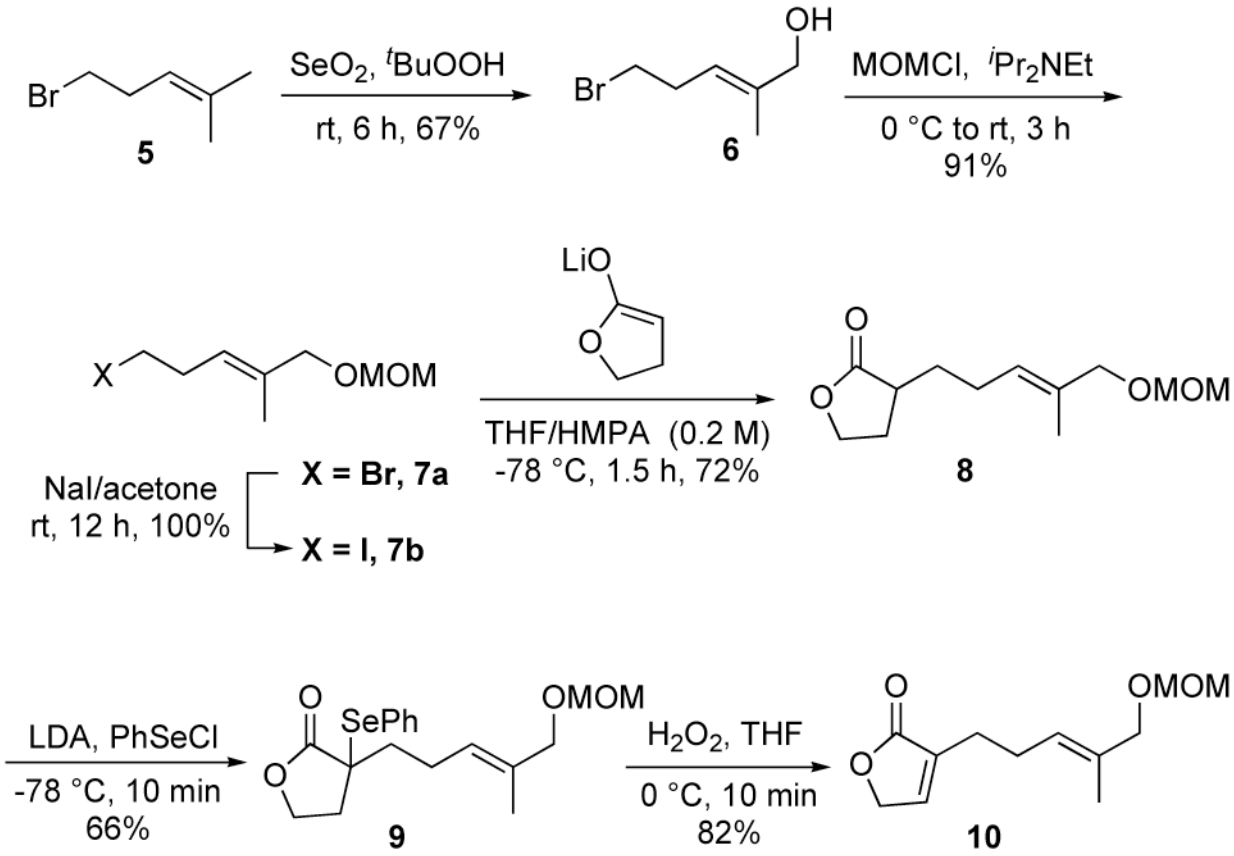


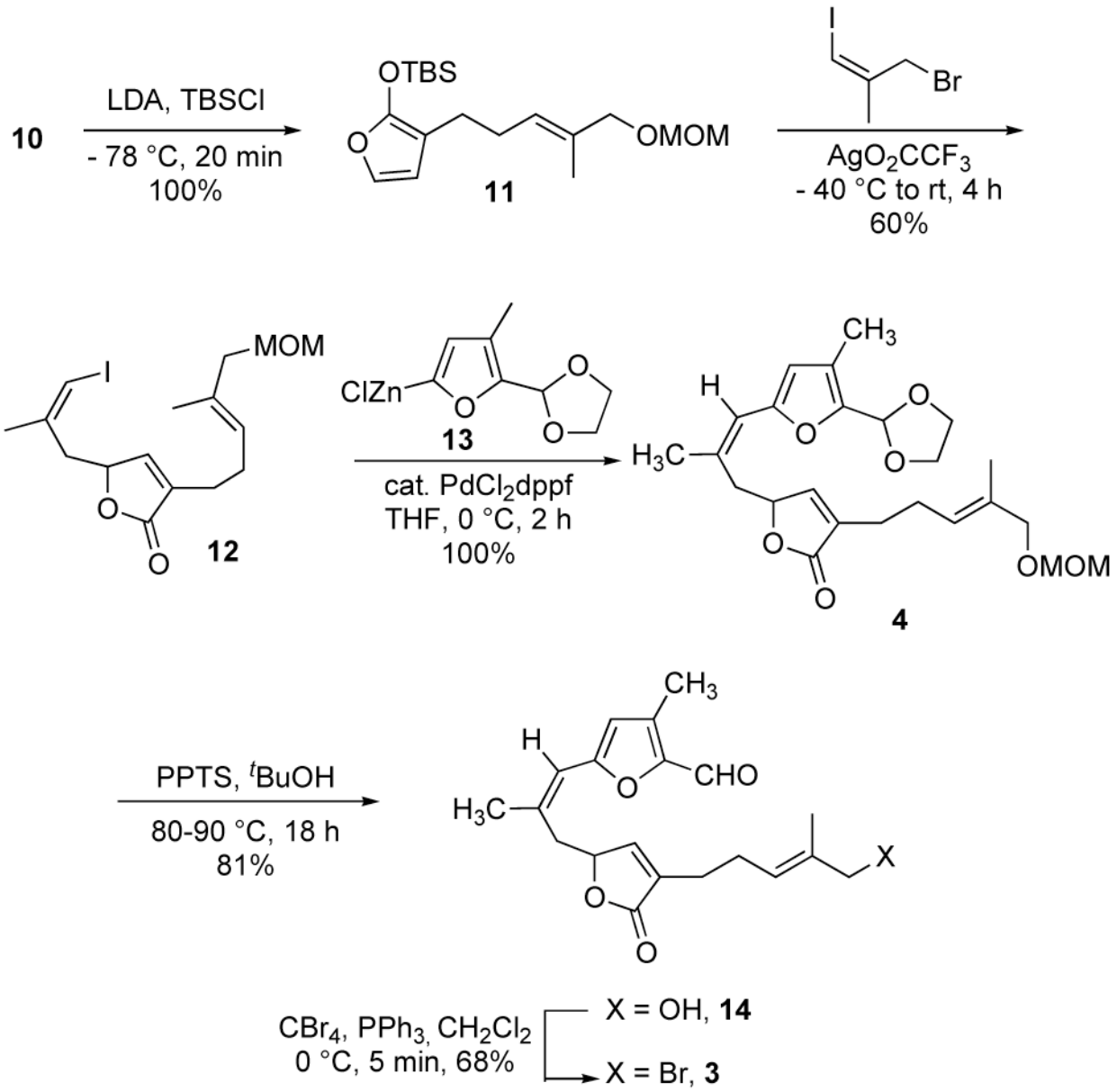
Figure 1.
Structures *of Pseudopterogorgia* Metabolites



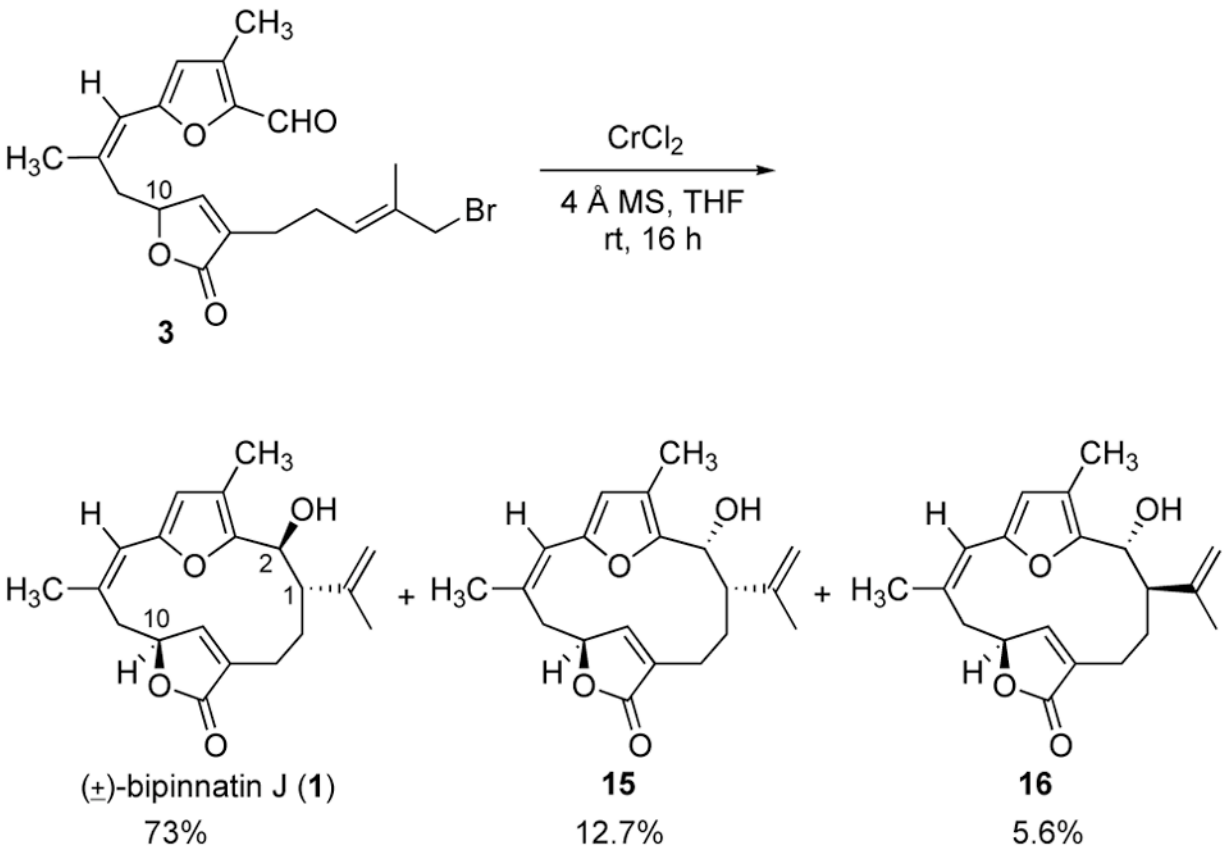
Scheme 1.
Retrosynthetic Analysis of Bipinnatin J (**1**)



Scheme 2.
Synthesis of Fragment **10**



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



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