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A biomimetic total synthesis of (+)-intricarene

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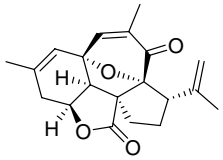
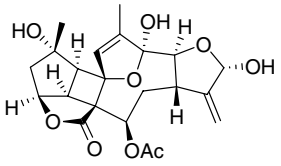
Abstract—An asymmetric synthesis of the furanocembrane (−)-bipinnatin J (**3a**) found in gorgonian corals is described. Treatment of **3a** with $VO(acac)_2$-^{t}BuOOH, followed by acetylation, gave acetoxypyranone **15**. When **15** was heated in the presence of DBU, it underwent a transannular oxidopyrylium-alkene [5+2] cycloaddition producing the polycyclic diterpene (+)-intricarene **1**, isolated from the coral *Pseudopterogorgia kallos*. The total synthesis of intricarene **1** mimics its most likely biosynthesis via oxidation of bipinnatin J (**3a**) in vivo.

Intricarene **1** and bielschowskysin **2** are two structurally intriguing polycyclic diterpenes which have recently been isolated from the coral *Pseudopterogorgia kallos* by Rodriguez et al.[1,2] Bielschowskysin **2** has been shown to display specific in vivo cytotoxicity against cell lung and renal cancer in the NCI antitumor screen; however, due to the dearth of material, a detailed biological evaluation of intricarene **1** has not been possible at this time. Diterpenes **1** and **2** are related as significantly rearranged furanocembrane natural products, which we believe have their origins in the furanobutenolide structure **3**.[3] In the case of intricarene **1**, the most plausible biogenetic precursor is **3a**, which is a natural product, known as bipinnatin J, found in *P. bipinnata*.[4] Thus, oxidation of **3a** in vivo[5] would be expected to lead to a precursor, *viz* **4**, to oxidopyrylium ion **5** which by way of transannular [5+2] cycloaddition[6] with the butenolide double bond should produce intricarene **1** (Scheme 1). In this letter, we describe an asymmetric synthesis of (−)-bipinnatin J (**3a**) followed by its conversion into (+)-intricarene **1** based on this biosynthesis speculation.

In contemporaneous investigations, Trauner and Rawal, and their respective collaborators, have independently drawn attention to the biosynthetic interrelationships between furanobutenolide cembranes and the polycyclic diterpenes **1** and **2**, and both research groups have recently reported a total synthesis of racemic bipinnatin J (**3a**).[7,8] Our asymmetric synthesis of (−)-bipinnatin J (**3a**), presented here, has features in common with the strategies described by Trauner and by Rawal, and uses a similar combination of Pd(0)-mediated cross coupling and Cr(II)-catalysed macrocyclisation protocols from the central intermediate **13**. Our synthesis of enantiomerically pure **13** started from (+)-glycidol **6**, however, and was based on the chemistry we had earlier developed in our synthesis of the furanocembrane bisdeoxylophotoxin.[9]



Intricarene **1**



Bielschowskysin **2**

Thus, conversion of (+)-glycidol into the known alkynediol **7**,[10] followed by carbometallation, isomerisation and iodination, using the conditions described by Negishi et al.[11] first gave the *Z*-iodoalkene **8**, which was next transformed into the corresponding epoxide **9** in two straightforward steps (Scheme 2). Epoxide **9** was now added to a solution of the anion derived from the α-selenylester **10** (NaHMDS, −78 °C),[12] in the presence of $BF_3{\cdot}OEt_2$, which led to a 3:2 mixture of diastereoiso-

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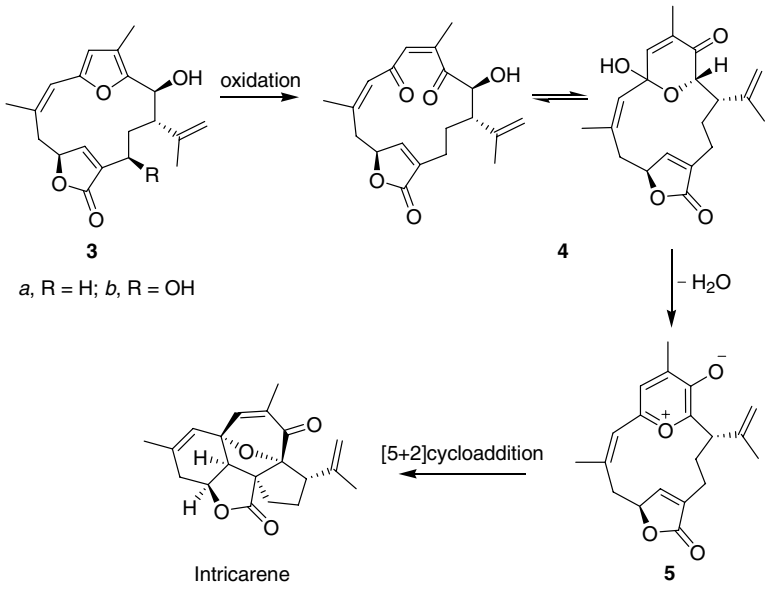
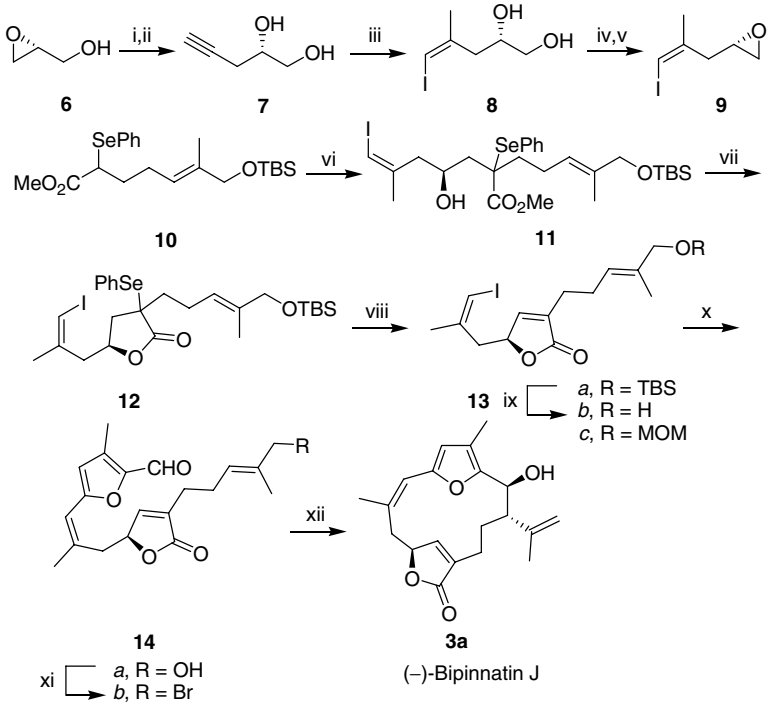
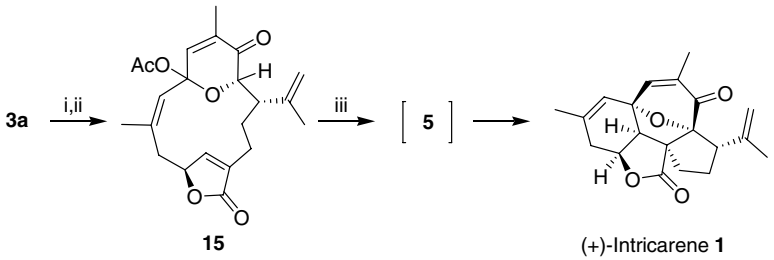


Scheme 1. Speculative biosynthetic route to intricarene **1** from bipinnatin J (**3a**).



Scheme 2. Reagents and conditions: (i) TMS-acetylene, ^{n}BuLi, $BF_3{\cdot}OEt_2$, −78 °C to −30 °C, 97%; (ii) K_2CO_3, MeOH/THF, rt, 92%; (iii) Cp_2ZrCl_2, $AlMe_3$, $(CH_2Cl)_2$ rt, then reflux three days, then I_2, THF, −30 °C to 0 °C; (iv) TsCl, C_5H_5N, 0–3 °C, 48% over two steps; (v) K_2CO_3, MeOH, 73%; (vi) NaHMDS, THF, −78 °C, then **9**, $BF_3{\cdot}OEt_2$, −78 °C to rt, 60%; (vii) *p*-TSA, CH_2Cl_2, rt; (viii) H_2O_2, THF, 0 °C to rt; (ix) PPTS (cat.), CH_2Cl_2/MeOH, 62% over three steps; (x) 3-methyl-5-trimethylstannylfurfural, $Pd(PPh_3)_4$, CuI, CsF, DMF; (xi) Ph_3P, NBS, 72% over two steps; (xii) $CrCl_2$, 4 Å MS, THF, 70%.

mers of adduct **11** in 60% yield. Treatment of **11** with *p*-TSA next gave γ-lactone **12** which, following oxidative elimination of PhSeOH, produced the corresponding butenolide **13a**.[9] Deprotection of the TBS group in **13a** then gave the enantiomerically pure alcohol-vinyl iodide intermediate **13b**. Racemic alcohol **13b** and its MOM ether **13c** were prepared by different routes by Trauner[7] and Rawal[8], respectively. These research groups converted intermediate **13** into (±)-bipinnatin J using essentially the same synthetic steps which we have followed here. Thus, a Pd(0)-catalysed coupling reaction between the vinyl iodide **13b** and 3-methyl-5-trimethylstannylfurfural first gave the enantiomerically pure furanobutenolide **14a**.[7] Bromination of **14a** using NBS/PPh_3 next led to bromide **14b**, which then underwent a smooth diastereoselective intramolecular cyclisation in the presence of $CrCl_2$ producing (−)-bipinnatin J (**3a**) in 70% yield.[13,14] The furanobutenolide **3a** was obtained as



Scheme 3. Reagents and conditions: (i), $VO(acac)_2$, ^tBuOOH, DCM, −20 °C; (ii), Ac_2O, Et_3N, DMAP(cat.), DCM, rt, 30% over two steps; (iii) DBU, CH_3CN, reflux, 1 h, 10%.

colourless crystals, mp 144–147 °C, $[\alpha]_D^{23}$ −103.3 (*c* 0.91, $CHCl_3$); Lit mp 141–142 °C, $[\alpha]_D^{24}$ −125.4 (*c* 1.65, $CHCl_3$), and the ^1H and ^{13}C NMR spectra were superimposable on those reported for natural (−)-bipinnatin J isolated from *P. bipinnata*.

We were now in the position to investigate the proposed biogenetically patterned conversion of our (−)-bipinnatin J (**3a**) into intricarene **1**, implicating a transannular [5+2] cycloaddition reaction from the oxidopyrylium ion-alkene species **5** (Scheme 1).[6] Thus, treatment of (−)-bipinnatin J (**3a**) with $VO(acac)_2$ and ^tBuOOH resulted in oxidative ring expansion of the furan moiety in **3a** and the formation of a mixture of tautomers of the presumed enedione-hydroxypyrone **4**, which could not be purified and adequately characterised. Instead, the product from oxidation was acetylated, using Ac_2O–Et_3N in DCM at room temperature leading to 6-acetoxypyranone **15** (Scheme 3) as a 5:1 mixture of C-6 epimers. When a solution of acetoxypyranone **15** in acetonitrile was heated under reflux in the presence of DBU, the anticipated transannular [5+2] cycloaddition involving the oxidopyrylium ion **5** took place giving (+)-intricarene **1** in an unoptimised 10% yield.[15] The synthetic (+)-intricarene was obtained as colourless crystals, $[\alpha]_D^{24}$ +52.9 (*c* 0.136, $CHCl_3$); Lit $[\alpha]_D^{20}$ +50.0 (*c* 0.7, $CHCl_3$) whose infrared, and ^1H and ^{13}C NMR spectra were superimposable on those recorded for the natural product isolated from *P. kallos*.

In summary, we have achieved an asymmetric synthesis of the furanobutenolide cembrane (−)-bipinnatin J (**3a**) and demonstrated that it can be converted into the intriguing pentacyclic natural product (+)-intricarene **1**, following oxidation to **4** and transannular oxidopyrylium-alkene [5+2] cycloaddition involving species **5**. We believe that our synthesis of intricarene demonstrates a clear biosynthetic relationship with bipinnatin J, and is therefore biomimetic. Further biomimetic studies are now in progress to probe links between other families of structurally intriguing and biologically important natural products isolated recently from corals, including bielschowskysin **2**.

Acknowledgements

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References and notes

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12. α-Selenylester **10** was prepared from the corresponding, known, methyl *E*-7-hydroxy-6-methylhept-5-enoate (Phoenix, S.; Bourque, E.; Deslongchamps, P. *Org. Lett.* **2000**, *2*, 4149–4152.) by (i) protection of the alcohol as its TBS ether (TBSCl, imidazole, DMF, 0 °C, 90%), followed by (ii) phenylselenylation using LDA, THF, TMSCl, PhSeBr, −78 °C to 20 °C, 97%.
13. The diastereoselectivity in the formation of (−)-bipinnatin J using the procedure of Rawal [8] was >80%, and the minor diastereoisomers were eliminated by routine chromatography. Trauner[7] used the Nozaki-Hiyama-Kishi conditions, that is, $CrCl_2$/$NiCl_2$, and obtained a diastereoselectivity of approx. 90%.
14. (a) This $CrCl_2$-mediated macrocyclisation protocol was used earlier by Paquette et al. in their synthesis of the furanobutenolide cembrane acerosolide (Paquette, L. A.; Astles, P. C. *J. Org. Chem.* **1993**, *58*, 165–169.) and other cembranes; For a recent review, see: (b) Fürstner, A. *Chem. Rev.* **1999**, *99*, 991–1046.

15. The yield of intricarene **1** was not optimised due to the relative dearth of (−)-bipinnatin J (**3a**) available. An analysis of molecular models demonstrates a demanding *endo* transition state for the transannular [5+2] cycloaddition of **5**. It is likely therefore that dimerisation of the oxidopyrylium species **5**, for example, competes with the cycloaddition under unfavourable reaction conditions, and this feature requires further investigation.

Following the completion of this manuscript for publication, we were informed that Professor D. Trauner had also completed the synthesis of intricarene from bipinnatin J, using similar chemistry and with a similar outcome; private communication from Professor Trauner.