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Total synthesis of (+)-intricarene using a biogenetically patterned pathway from (−)-bipinnatin J, involving a novel transannular [5+2] (1,3-dipolar) cycloaddition†

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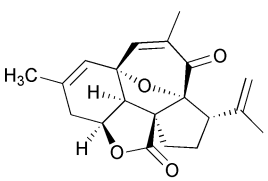
An asymmetric synthesis of the furanobutenolide-based macrocyclic diterpene (−)-bipinnatin J (**4a**) isolated from the gorgonian octocoral *Pseudopterogorgonia bipinnata* is described. The synthesis is based on elaboration of the chiral lactone-substituted vinyl iodide **26b** from (+)-glycidol, followed by an intermolecular Stille coupling reaction with the stannylfurfural **27**, leading to **28a**, and then an intramolecular Nozaki–Hiyama–Kishi allylation reaction, **28b** → **4a**. Treatment of (−)-bipinnatin J (**4a**) with $VO(acac)_2$–$tBuO_2H$ followed by acetylation of the tautomeric hydroxypyranone product **7**/**8**, next gave the acetoxypyrone **30**. When the acetoxypyranone **30** was heated in acetonitrile in the presence of DBU, it gave (+)-intricarene **1**, which is found in *P. kallos*, *via* a novel transannular [5+2] (or 1,3-dipolar) cycloaddition involving the butenolide-oxidopyrylium ion intermediate **31**. We believe that this total synthesis of (+)-intricarene **1** mimics its most likely origin in nature *via* oxidation of (−)-bipinnatin J (**4a**), presumably involving photochemically generated singlet oxygen or possibly a P450 monooxygenase enzyme system.

Introduction

Intricarene **1** is a novel polycyclic diterpene isolated from the Caribbean gorgonian octocoral *Pseudopterogorgia kallos*.[1] The equally unusual diterpene bielschowskysin **2** co-occurs with intricarene in *P. kallos*,[2] together with providencin **3**,[3] another cyclobutane ring-containing diterpene. Apart from their unusual and interesting structures, the natural products **1**–**3** show some useful and promising biological activities. Thus, bielschowskysin **2** displays significant cytotoxicity against lung and renal cancer cell lines, in addition to strong antimalarial activity. Providencin **3** exhibits modest anti-cancer activity against human breast, lung and CNS cancer cell lines. Intricarene **1** shows mild cytotoxicity, but the dearth of natural product has not yet permitted a thorough analysis of its biological properties.

It seems likely that intricarene **1** and bielschowskysin **2** are related biogenetically as products of oxidation and transannular ring-forming processes from more simple furanobutenolide-containing macrocyclic diterpenes, *e.g.* **4a** and **4b**, which have also been isolated from Caribbean gorgonian corals in recent years. Thus, we[4] and others[5,6] have surmised that the most plausible biogenetic precursor to intricarene **1** is the furanobutenolide-based natural product bipinnatin J (**4a**), found in *P. bipinnata*.[7] We envisage that oxidation of the furan ring in **4a** in the marine milieu would most likely involve [4+2] cycloaddition of photochemically generated singlet oxygen, leading to the labile peroxide intermediate **5** (Scheme 1). Hydrolysis of **5** would next give the enedione **7** which would exist in tautomeric equilibrium with the hydroxypyranone **8**. The same hydroxypyranone **8** could also originate from the spiroepoxide intermediate **6** produced from bipinnatin J *via* a monooxygenase. Whatever happens, elimination of water from the hydroxypyranone **8** would next lead to the oxidopyrylium ion species **9**, which we envisage would then undergo a transannular [5+2] (or 1,3-dipolar) cycloaddition[8–10] with the butenolide alkene bond, leading to intricarene **1**. In this paper we first describe a total synthesis of (−)-bipinnatin J (**4a**), and then its conversion into (+)-intricarene **1** based on the aforementioned biosynthesis speculation.[4] In contemporaneous studies Trauner and Roethle,[5] and Rawal and Huang[6] reported



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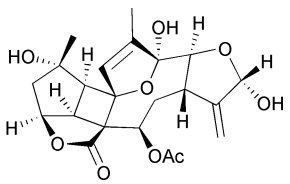

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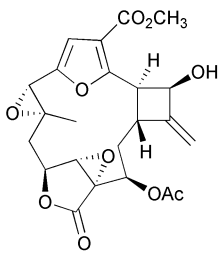

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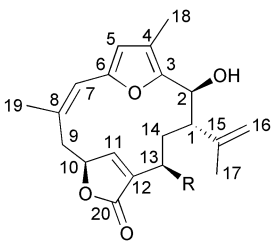

4
a, R = H
b, R = OH

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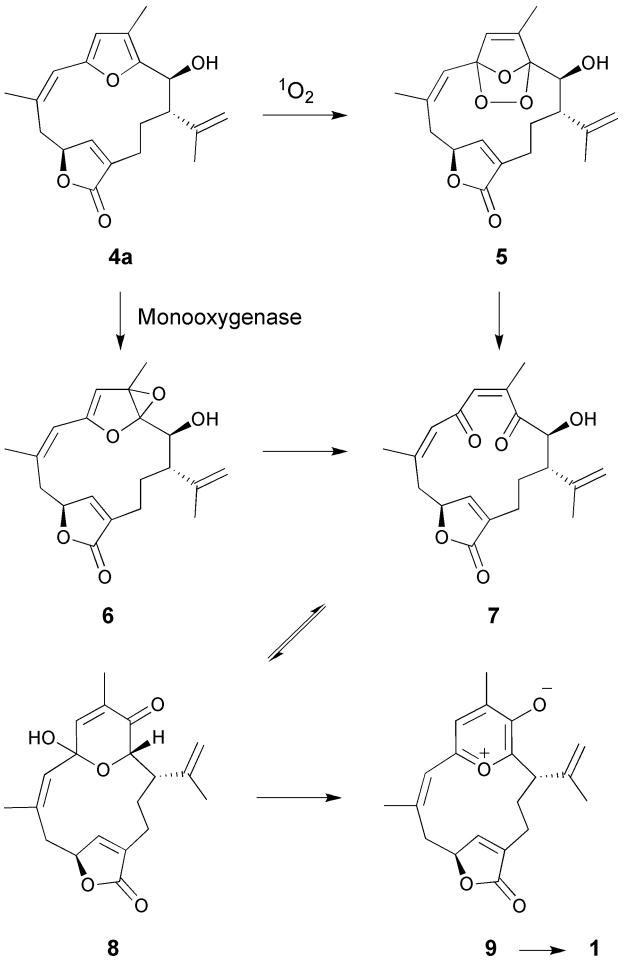
† Electronic supplementary information (ESI) available: Experimental procedures and data for compounds **15b**, **16**, **18**, **10**, **20**, **21a** and **21b**; copies of ^1H and ^{13}C NMR spectra for compounds **28a**, **28b**, **4a** and **1**. See DOI: 10.1039/b910572g



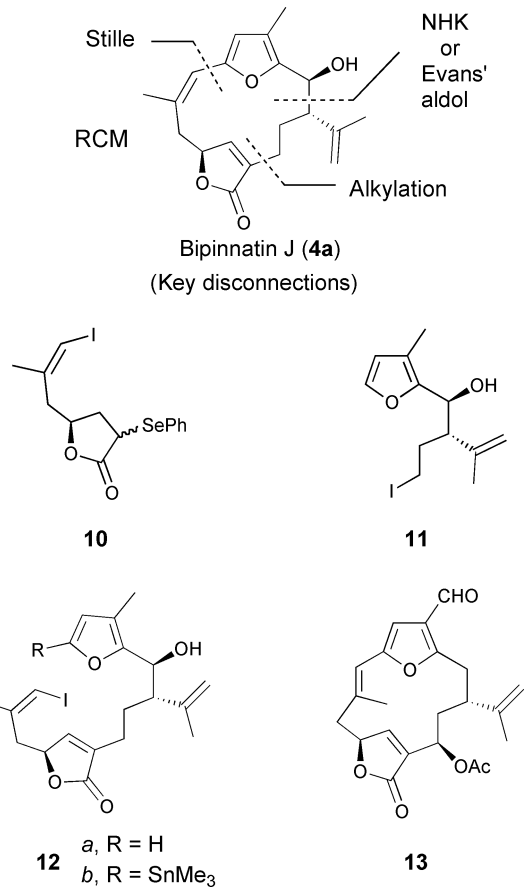
Scheme 1 Proposal for the origin of intricarene **1** from bipinnatin J (**4a**) *in vivo*.

syntheses of racemic bipinnatin J and later, Trauner *et al*[11] developed an alternative synthesis of (–)-bipinnatin J and also described its biomimetic conversion into (+)-intricarene.

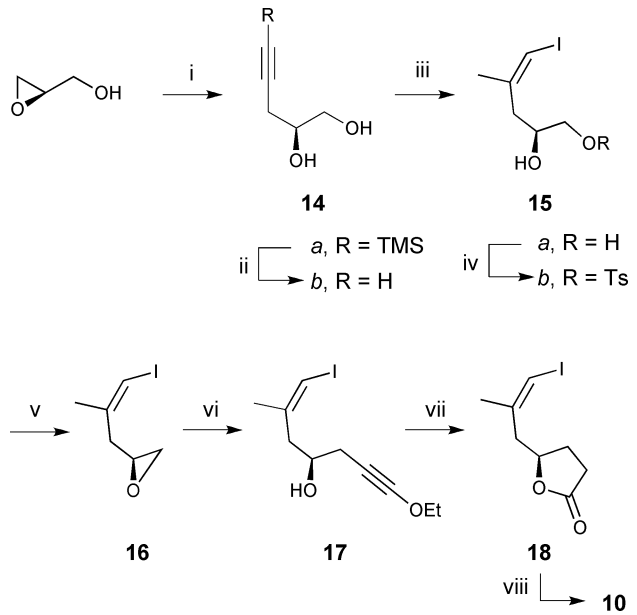
Total synthesis of (–)-bipinnatin J (4a)

A wide variety of synthetic approaches towards the furanobutenolide-based family of cembranoids, exemplified by **3** and **4a**, have been described. These approaches differ largely according to whether the precursors already contain a substituted furan or butenolide prior to a macrocyclisation event, or whether the furan and/or butenolide units are elaborated from macrocyclic precursors.[12] In addition, a significant number of protocols have been developed to achieve macrocyclisations of precursors to the cembranoids. These have included intramolecular Stille coupling[13] and Nozaki–Hiyama–Kishi reactions; intramolecular Wadsworth–Emmons olefinations and metathesis reactions;[14] intramolecular 2,3-Wittig rearrangements;[15] intramolecular alkylation reactions involving β-keto esters and propargylic iodides; and intramolecular radical cyclisations.[16]

The bipinnatin J structure, *i.e.* **4a**, accommodates a vinylfuran unit associated with a *Z*-trisubstituted alkene bond, together with a chiral furanmethanol unit, where the alcohol group is also part of a homoallylic alcohol. These structural features in bipinnatin J suggested a Stille coupling[17] involving a *Z*-iodoalkene and a stannylfuran to elaborate the *Z*-vinylfuran unit, and either an NHK reaction[18] or an Evans alkylation sequence using a furfural and an appropriate allylic species to introduce the chiral furanmethanol functionality in **4a**. Furthermore, both of these synthetic approaches could be executed in both inter- and intramolecular fashion, thereby adding a further level of flexibility to the overall synthetic strategy.



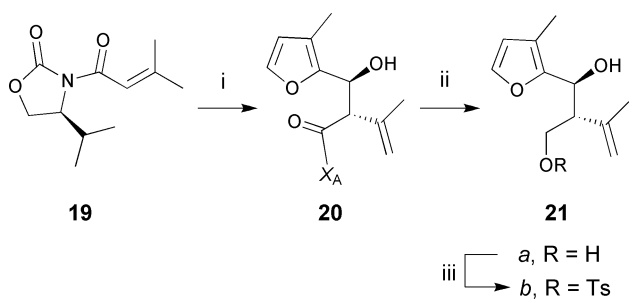
In our first synthetic approach to bipinnatin J, we examined syntheses of the lactone substituted iodoalkene **10** and the chiral allylic alcohol **11**, with the intention of coupling these two fragments *via* an alkylation reaction of the carbanion derived from **10** with **11**, leading to **12a**. The vinyl iodide stannylfuran **12b** would then be converted into **4a** *via* an intramolecular Stille reaction. This overall strategy had already been used by us in an earlier synthesis of *bis*-deoxylophotoxin **13**.[13a] Thus, the lactone substituted iodoalkene **10** was prepared starting with the known alkyne diol **14b**[19] produced in two steps from glycidol (Scheme 2). The alkyne diol **14b** was next treated with Cp_2ZrCl_2–Me_3Al, and then with iodine, following the conditions developed by Negishi and Ma,[20] leading to the *Z*-iodoalkene **15a**. The 1,2-diol functionality in **15a** was converted into the corresponding epoxide **16**. The epoxide **16** was now treated with the lithium salt of ethoxyacetylene leading to **17**, which was immediately hydrolysed with PTSA producing the lactone **18**. Finally, deprotonation of **18** using LiHMDS at –78 °C, followed by quenching of the resulting carbanion with phenylselenium bromide gave the substituted lactone **10**. The *E*-alkene isomer corresponding to **10**



Scheme 2 *Reagents and conditions*: (i) TMS-acetylene, ^{n}BuLi, $BF_3{\cdot}Et_2O$, −78 to −30 °C, 2 h, then −30 °C, 19 h, 98%; (ii) K_2CO_3, MeOH/THF (10:1), r.t., 14 h, 62–92%; (iii) a, Cp_2ZrCl_2, $AlMe_3$, $(CH_2Cl)_2$, r.t. 19 h, then reflux for 3 days; b, I_2, THF, −30 °C to r.t., 2 h; (iv) TsCl, Py, 4 °C, 28 h, 48% over two steps; (v) K_2CO_3, MeOH, r.t. 1.5 h, 73%; (vi) 1-ethoxyacetylene, ^{n}BuLi, $BF_3{\cdot}Et_2O$, −78 °C, 2 h; (vii) PTSA, EtOH, r.t., 2 h, then $CHCl_3$, reflux, 16 h, 81% for two steps; (viii) LiHMDS, THF, −78 °C, 15 min, TMSCl, −78 °C, 30 min, PhSeBr, −78 °C to r.t., 1 h, 83%.

was known from our earlier studies and was used in a synthesis of *bis*-deoxylophotoxin **13**.[13a]

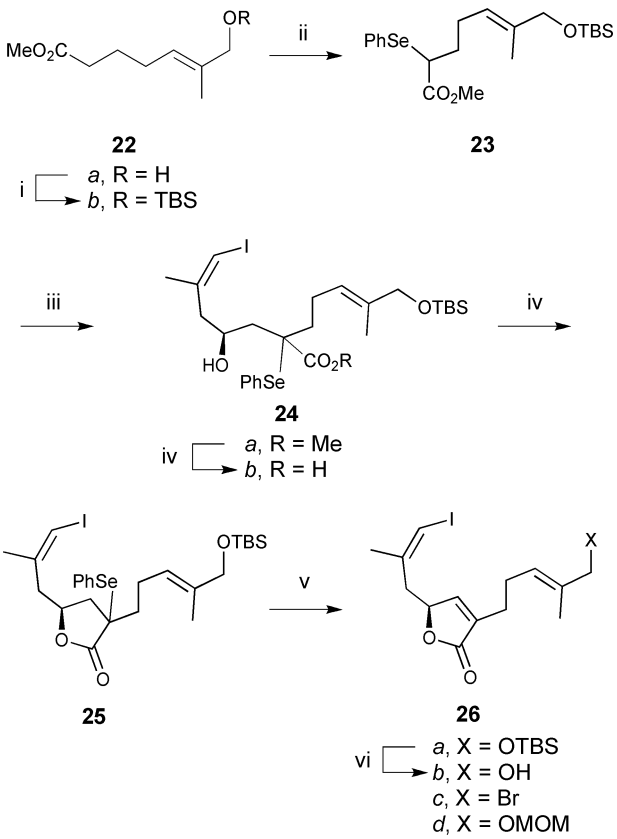
We next examined a synthesis of the substituted alkyl iodide **11** in readiness for the proposed alkylation reaction with the phenylselanyl lactone **10**, leading to **12a**. Thus, deprotonation of the known Evans' chiral oxazolidinone **19**[21] derived from 3-methylbut-2-enoic acid, using Bu_2BOTf–Et_3N at −78 °C, followed by addition of 3-methylfurfural[22] resulted in deconjugative alkylation with the formation of a single diastereoisomer of the homoallylic alcohol **20** (Scheme 3), whose absolute stereochemistry was confirmed by X-ray crystallography.[13a] Reduction of the amide **20**, using $LiBH_4$–MeOH, next led to the alcohol **21a** which was then converted into the corresponding tosylate **21b**. Our next plan was to convert the tosylate **21b** into the homologous iodide **11**, and then couple this iodide to the phenylselanyl lactone **10**. However, we were frustrated



Scheme 3 *Reagents and conditions*: (i) Bu_2BOTf, DCM, −78 °C, 5 min, then Et_3N, −78 °C, 1 h, 0 °C, 15 min, then 3-methylfurfural, −78 °C, 1 h, 0 °C, 1 h, 61%; (ii) $LiBH_4$, MeOH, THF, 0 °C–r.t. overnight, 42%; (iii) Et_3N, DMAP, TsCl, DCM, r.t. 27 h, 49%.

to find that the synthesis of the key homoallylic alcohol **20** was not amenable to large scale operation, due to competing retro-aldolisation and other features, and we were not able therefore to take this sequence further.

We therefore changed our approach, and decided to synthesise the butenolide **26c** which was substituted at C5 with a terminal *Z*-iodoalkene, and also at C3 with a terminal allyl bromide unit. These functionalities would then be reacted, in sequence, with the stannane-substituted furfural **27**, to elaborate bipinnatin J using sequential Stille cross coupling and NHK reactions. Thus, the α-phenylselanyl ester **23** was first prepared from the known allyl alcohol **22a**,[23] following protection as the TBS ether **22b** and phenylselanylation[24] of the carbanion derived from **22b**. Further deprotonation of **23**, using NaHMDS at −78 °C, followed by quenching the resulting carbanion with the epoxide **16** in the presence of $BF_3{\cdot}OEt_2$ next gave the adduct **24a** as a mixture of diastereoisomers in 72% yield (Scheme 4). Hydrolysis of the methyl ester group in **24a** was followed by lactonisation, leading to the phenylselanyl-substituted lactone **25**. Oxidation of **25** and *in situ* elimination of the elements of phenylseleninic acid then gave the substituted butenolide **26a**. Deprotection of the TBS group in **26a** finally gave the enantiomerically pure alcohol **26b**.[25] In contemporaneous studies Trauner and Roethle[5] described a synthetic route to the racemic alcohol **26b**, and Rawal and Huang[6]



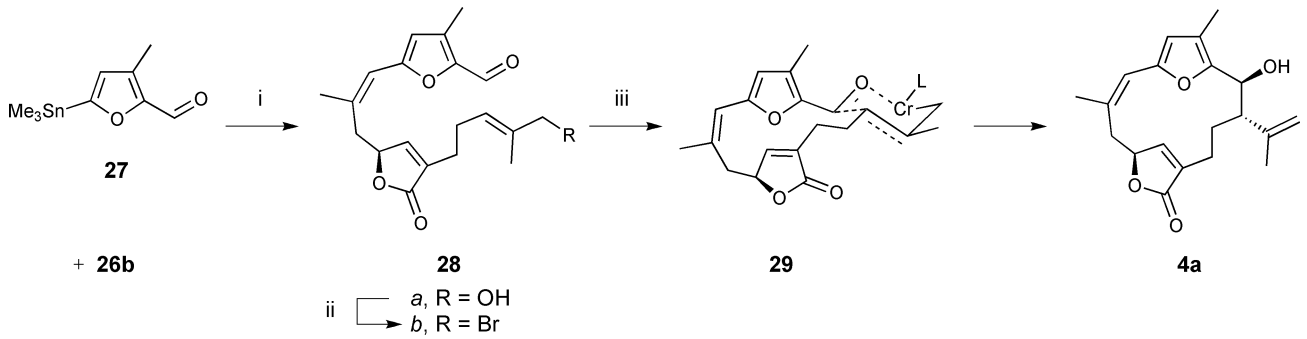
Scheme 4 *Reagents and conditions*: (i) TBSCl, Imidazole, DMF, 0 °C, 10 min, 90%; (ii) a, LDA, THF, −78 °C, 45 min; b, TMSCl, −78 °C, 30 min; c, PhSeBr, THF, −78 °C to r.t., 1 h, 73%; (iii) NaHMDS, THF, −78 °C, 0.5 h, then **16**, $BF_3{\cdot}Et_2O$, −78 °C to r.t. overnight, 72%; (iv) PTSA (0.1 eq), DCM, r.t., 3 h; (v) H_2O_2, THF, 0 °C to r.t., 2 h; (vi) PPTS (0.2 eq), DCM/MeOH (1:1), r.t., 24 h, 62% for 3 steps.

presented an alternative route to the MOM ether **26d** of racemic **26b**. Furthermore, both Trauner and Rawal and their respective collaborators converted their racemic butenolides **26b** and **26d** into (±)-bipinnatin J, using essentially the same synthetic steps that we have used in converting our enantiomerically pure (+)-alcohol **26b** into chiral (–)-bipinnatin J (**4a**).

A Stille coupling reaction between the enantiomerically pure vinyl iodide **26b** and 5-trimethylstannylfurfural **27**,[5,26] using $Pd(PPh_3)_4$ and CuI in the presence of CsF at room temperature gave the *Z*-vinylfuran **28a** in an excellent 90% yield (Scheme 5). Bromination of the alcohol **28a**, using NBS and PPh_3, next gave the corresponding allyl bromide **28b** which underwent a smooth diastereoselective intramolecular NHK reaction in the presence of $CrCl_2$, leading to (–)-bipinnatin J (**4a**), obtained as colourless crystals, mp 144–7 °C, in 70% yield. We found that the conditions used by Rawal and Huang[6] (*i.e.* $CrCl_2$ in the presence of 4 Å molecular sieves) in the aforementioned NHK cyclisation led to a diastereoselectivity >80%. For the same NHK reaction, Trauner and Roethle[5] used $CrCl_2$–$NiCl_2$ and recorded a diastereoselectivity of approx. 90%. The high diastereoselectivity found in the NHK reaction **28b** → **4a** no doubt reflects the important role that the *Z*-double bond in the precursor plays, allowing a favourable chair transition state, *i.e.* **29**, in the cyclisation. The relative stereochemistry of the two new chiral centres resulting from the NHK reaction, is no doubt determined by the remote asymmetric centre on the butenolide ring in the starting material. The synthetic (–)-bipinnatin J displayed ^{1}H and ^{13}C NMR spectroscopic data (Table 1) that were superimposable on those recorded for the natural product isolated from *P. bipinnata*.[7]

Biomimetic synthesis of (+)-intricarene 1 from (–)-bipinnatin J (4a)

Following the successful synthesis of (–)-bipinnatin J (**4a**), we now proceeded to examine its conversion into the polycyclic diterpene intricarene **1** *via* the proposed transannular [5 + 2] cycloaddition



Scheme 5 *Reagents and conditions*: (i) $Pd(PPh_3)_4$, CuI, CsF, DMF, r.t., 20 min, 90%; (ii) Ph_3P, NBS, DCM, –5 °C to 0 °C, 20 min, 80%; (iii) $CrCl_2$, 4 Å MS, THF, r.t., 16 h, 70%.

Table 1 NMR spectroscopic data for synthetic and natural (–)-bipinnatin J

	Synthetic (–)-bipinnatin J		Natural (–)-bipinnatin J[7]	
Position	^{1}H, NMR	^{13}C, NMR	^{1}H, NMR	^{13}C, NMR
1	2.46–2.35, m	51.3, d	2.35, dd (10.8, 10.8)	51.1, d
2	4.51, dd (2.9, 10.9)	65.1, d	4.49, br d (10.8)	65.0, d
3		149.3, s		149.3, s
4		121.2, s		121.0, s
5	6.04, s	114.0, d	6.02, s	113.8, d
6		151.1, s		151.0, s
7	6.12, br s	117.5, d	6.09, br s	117.3, d
8		129.2, s		128.9, s
9α	2.74, dd (4.4, 11.8)	39.8, t	2.71, dd (4.5, 12.0)	39.7, t
9β	3.21, t (11.8)		3.18, dd (11.7, 12.0))	
10	5.02–4.99, m	78.8, d	4.96, m	78.6, d
11	6.86, t (1.6)	152.4, d	6.83, br s	152.2, d
12		132.7, s		132.6, s
13α	2.13–2.07, m	19.8, t	2.07, m	19.6, t
13β	2.46–2.35, m		2.38, ddd (3.0, 14.2, 14.2)	
14α	0.91, dt (3.8, 13.8)	30.2, t	0.88, ddd (3.3, 13.8, 13.8)	30.1, t
14β	1.68, tdd (3.3, 11.1, 13.8)		1.68, dddd (3.3, 3.3, 10.8, 13.8)	
15		142.2, s		142.2, s
16α	5.07, s	118.9, t	5.03, br s	118.4, t
16β	5.18, br s		5.14, br s	
17	1.81, br s	17.6, q	1.78, br s	17.6, q
18	2.06, s	9.6, q	2.03, s	9.4, q
19	2.01, br s	26.0, q	1.98, br s	25.7, q
20		174.4, s		174.2, s
OH	1.86, d (2.9)		1.92, br s	

Table 2 NMR spectroscopic data for synthetic and natural (+)-intricarene

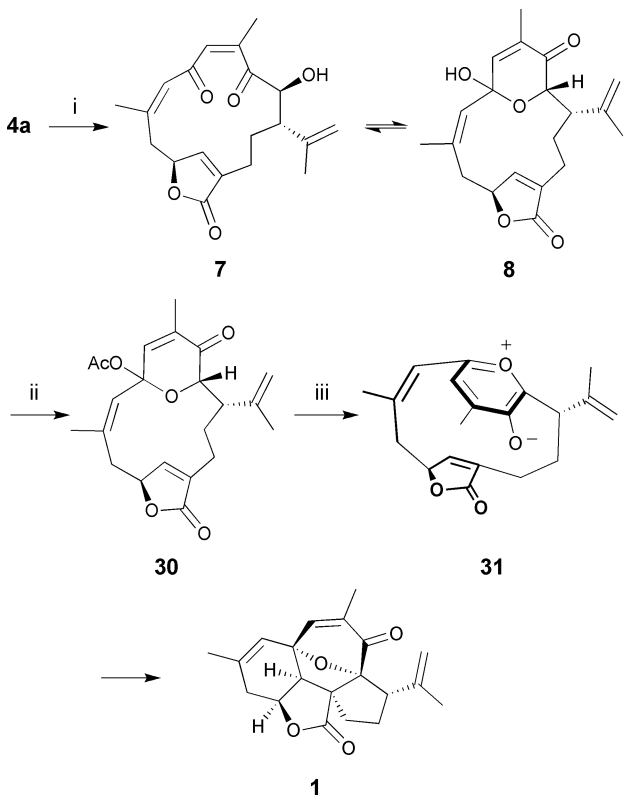
	Synthetic (+)-intricarene		Natural (+)-intricarene[1]	
Position	^{1}H NMR	^{13}C NMR	^{1}H NMR	^{13}C NMR
1	3.39, dd (5.8, 11.9)	46.3, d	3.38, dd (5.7, 11.9)	46.4, d
2		102.8, s		102.8, s
3		193.0, s		193.0, s
4		137.2, s		137.2, s
5	6.28, q (1.6)	147.3, d	6.27, q (1.6)	147.3, d
6		84.6, s		84.6, s
7	6.43–6.41, m	128.0, d	6.41, q (1.6)	128.1, d
8		135.2, s		135.2, s
9α	2.84, dd (8.6, 18.6)	35.6, t	2.82, dd (8.6, 18.6)	35.7, t
9β	2.42, br d (18.6)		2.41, br d (18.6)	
10	4.78, ddd (2.6, 5.3, 8.6)	70.7, d	4.77, ddd (2.6, 5.3, 8.6)	70.7, d
11	2.55, d (5.3)	58.0, d	2.54, d (5.3)	58.0, d
12		64.1, s		64.2, s
13α	2.03–1.98, m	29.3, t	2.01, m	29.3, t
13β	1.97–1.90, m		1.92, m	
14α	2.14–2.09, m	28.5, t	2.11, m	28.5, t
14β	1.97–1.90, m		1.91, m	
15		141.7, s		141.8, s
16α	4.93, q (1.3)	113.3, t	4.92, q (1.3)	113.3, t
16β	4.88, br s		4.86, br s	
17	1.76, br s	23.2, q	1.75, br s	23.1, q
18	1.77, d (1.6)	14.4, q	1.76, d (1.6)	14.4, q
19	1.85, t (1.4)	23.1, q	1.84, t (1.2)	23.0, q
20		178.0, s		177.9, s

from the oxidopyrylium ion intermediate **9**, described earlier (Scheme 1).

Thus, oxidation of the furan ring in (–)-bipinnatin J (**4a**), using $VO(acac)_2$ and $tBuO_2H$, followed by *in situ* rearrangement and tautomerisation, led to a mixture of isomers of presumably the enedione **7** and the hydroxypyranone **8** (Scheme 6). Unfortunately the hydroxypyranone **8** could not be easily purified and properly characterised. It was therefore acetylated, using Ac_2O–Et_3N, leading to the corresponding acetoxypyranone **30** which was obtained as a relatively stable oil. When a solution of the acetoxypyranone **30** in acetonitrile was heated under reflux in the presence of diazobicycloundecane it underwent the anticipated transannular [5 + 2] cycloaddition, *via* the presumed oxidopyrylium ion **31** (*cf* **9**), leading to (+)-intricarene **1** in an unoptimised yield of 10%. The synthetic intricarene displayed ^{1}H and ^{13}C NMR spectroscopic data that were superimposable on those recorded for the natural product isolated from *P. kallos*[1] (Table 2).

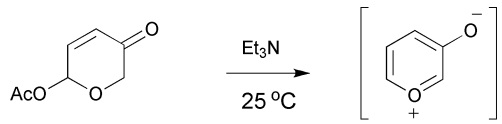
In contemporaneous studies Trauner *et al.*[11] also converted their synthetic bipinnatin J into intricarene using similar conditions to our own. However, with a more plentiful amount of bipinnatin J than we had been able to amass at the time, Trauner *et al.* were able to achieve upwards of 26% yield in the conversion of the acetoxypyrone **30** into intricarene under the optimum conditions of heating **30** in DMSO at 150 °C in the presence of tetramethylpiperidine.

The transannular cyclisation of **30** leading to the pentacyclic system in intricarene occurred with *endo* selectivity. It is likely that the crowded nature of this *endo* transition state, *viz* **31**, and the strain inherent in the pentacycle **1** could conspire to allow competing dimerisations of the oxidopyrylium ion intermediate **31** to take place, thus accounting for the disappointing yield in the overall conversion of **30** into **1**. Unfortunately, the dearth of materials did not allow us to characterise any "dimers" unambiguously. However, it is significant that Hendrickson and Farina[27] established many years ago that when simple oxidopyrylium ions

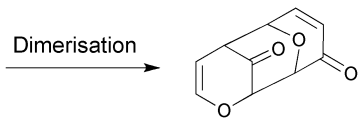


Scheme 6 *Reagents and conditions*: (i) $VO(acac)_2$, $tBuOOH$, DCM, –20 °C, 4 h; (ii) Ac_2O, Et_3N, DMAP (cat.), DCM, 0 °C– r.t., 2.5 h, 30% over two steps; (iii) DBU, CH_3CN, reflux, 1.2 h, 10%.

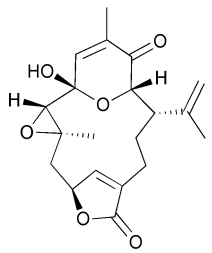
are produced in the absence of a dipolarophile they are indeed prone to undergo dimerisation, *viz* **32** → **33**.



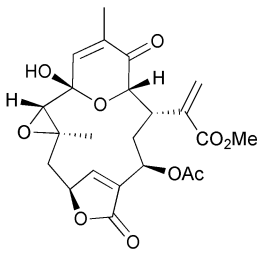
32



33



34



35

Following the publication of our synthesis of intricarene **1** from bipinnatin J (**4a**) *via* the intermediate **8**, Rodríguez and his colleagues[28] reported the presence of the hydroxypyranones **34** and **35** in *Pseudopterogorgia kallos*. The structural relationship between the hydroxypyrananes **34** ("bipinnatin N") and **8** is uncanny and provides considerable credence to our speculated biosynthetic route to intricarene in *P. kallos*, *i.e.* **4a** → **8** → **1**. In passing, it may be significant that bipinnatin N (**34**) is the oxy analogue of the hydroxypyranone **8**, but where the epoxide is derived from a $\Delta^{7,8}$ double bond precursor with the *E*-configuration; *cf* the *Z*-configured $\Delta^{7,8}$ double bond in **8**.

Conclusions

In summary, a total synthesis of the novel pentacyclic diterpene intricarene has been achieved, based on biomimetic speculation that the natural product is derived *in vivo* from the furanobutenolide-based natural product bipinnatin J (**4a**), involving oxidation to **8**, followed by an unprecedented transannular dipolar cycloaddition, *viz* **31** → **1**. Following publication of our work in preliminary form,[4] Wang and Tantillo[29] examined the dipolar cycloaddition reaction **31** → **1** using quantum chemical calculations. These authors concluded that although an enzyme is probably needed to generate and organise the oxidopyrylium species **31**, the subsequent transannular cycloaddition reaction leading to **1** has a sufficiently low activation barrier, *i.e.* approximately 20 kcal/mol, that an enzyme is unlikely to be involved in this part of the conversion. It is probable that other polycyclic diterpenes found in gorgonian octocals, *e.g.* bielschowskysin **2**, also have their origin in related furanobutenolide-based macrocyclic diterpenes, and involve related oxidative transformations and intramolecular pericyclic and other cyclisations in their biosynthesis. Investigations are in progress in our laboratory to probe some of these related biogenetic interconnections, through synthesis, and will be described in due course.

Experimental

General details

All melting points were determined using a Kofler hot-stage or Bibby Stuart Scientific SMP3 apparatus, and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer 1600 series FTIR instrument as liquid films or as dilute solutions in spectroscopic grade chloroform. The abbreviation 'br' refers to a broad absorption. Optical rotations were recorded on a JASCO DIP 370 polarimeter. Proton NMR spectra were recorded on a Bruker DPX360 (360 MHz), Bruker AM 400 (400 MHz) or Bruker DRX 500 (500 MHz) spectrometer as dilute solutions in deuteriochloroform at ambient temperature, unless stated otherwise. The chemical shifts are quoted in parts per million (ppm) relative to residual solvent peaks, and the multiplicity of each signal is designated by the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), br (broad), m (multiplet) and app (apparent). All coupling constants are quoted in Hertz. Assignments were made on the basis of chemical shift, COSY and HMQC experiments recorded on a Bruker AM 400 (400 MHz) instrument and standard Bruker software with no modifications. Carbon-13 NMR spectra were recorded using a Bruker DPX360 (90 MHz), Bruker AM 400 (101 MHz) or Bruker DRX500 (126 MHz) instrument as dilute solutions in deuteriochloroform, unless stated otherwise. Chemical shifts are quoted in parts per million (ppm) downfield of tetramethylsilane, spectra being referenced to residual protonated solvent (δ_H = 77.0 p.p.m. for $CDCl_3$). Assignments were made on the basis of chemical shift using the DEPT sequence. Abbreviations used in the description of resonances are: s (singlet, quaternary), d (doublet, CH), t (triplet, CH_2), q (quartet CH_3). Mass spectra were recorded on either a VG Autospec, an MM-701CF, a VG Micromass 7070E or a Micromass LCT spectrometer, using electron ionisation (EI), electrospray (ESI) or fast atom bombardment (FAB) techniques. High-resolution mass spectrometry data are calculated from the molecular formula corresponding to the observed signal using the most abundant isotopes of each element, to four decimal places.

Microanalytical data were obtained on a Perkin-Elmer 240B elemental analyser. Flash chromatography was performed using Merck silica gel 60 (230–400 mesh ASTM) as the stationary phase, and the solvents employed were of analytical grade; the "petrol" used in chromatography refers to light petroleum, bp 40–60 °C. All reactions were monitored by thin layer chromatography (TLC) using aluminium plates precoated with Merck silica gel 60 F_{254}, which were visualised with ultraviolet light (λ_{max} = 254 nm), and then with either acidic alcoholic vanillin solution, phosphomolybdic acid solution, basic potassium permanganate solution, or acidic anisaldehyde solution. Unless stated otherwise, reactions requiring anhydrous conditions were conducted in an inert atmosphere of nitrogen in flame-dried or oven-dried apparatus. Molecular sieves were stored in a hot oven before use. Dry organic solvents were routinely stored under a nitrogen atmosphere and/or dried over sodium wire. Dichloromethane, triethylamine and pyridine were distilled from calcium hydride. Dry tetrahydrofuran and benzene were distilled from sodium and benzophenone. Methanol and ethanol were distilled from magnesium methoxide and magnesium ethoxide respectively. Anhydrous dimethylformamide and dimethyl sulfoxide were obtained from Aldrich. Solvents were

removed *in vacuo* at approx. 20 mm Hg using a Büchi rotary evaporator.

The NMR spectroscopic data for compounds **1**, **4a** and **28**, are assigned using the conventional numbering pattern for the cembranes and their relatives shown on structure **4**.

(*E*)-7-(*tert*-Butyl-dimethyl-silanyloxy)-6-methyl-hept-5-enoic acid methyl ester 22b. *t*-Butyldimethylsilyl chloride (576 mg, 3.84 mmol) and imidazole (285 mg, 4.19 mmol) were added in one portion to a stirred solution of the alcohol **22a**[23] (600 mg, 3.49 mmol) in DMF (1.8 ml) at 0 °C. The mixture was stirred at 0 °C for 10 mins and then diluted with ether. The ether solution mixture was washed with water (10 ml) and brine (5 ml), then dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by chromatography on silica, eluting with light petroleum-diethyl ether (30: 1), to give the *silyl ether* (897 mg, 90%) as colourless oil. (Found: C, 62.9; H, 10.6. $C_{15}H_{30}O_3Si$ requires C, 62.9; H, 10.5%); ν_{max} (film)/cm^{-1} 1741; δ_H (360 MHz; $CDCl_3$) 5.39–5.35 (1 H, m, =C*H*), 4.01 (2 H, br s, TBSOC*H*$_2$), 3.68 (3 H, s, C*H*$_3$O), 2.32 (2 H, t, *J* 7.5, O=CC*H*$_2$), 2.07 (2 H, app. q, *J* 7.5, C*H*$_2$CH=), 1.70 (2 H, p, *J* 7.5, C*H*$_2$CH$_2$CH=), 1.59 (3 H, s, =CC*H*$_3$), 0.91 (9 H, s, TBS), 0.07 (6 H, s, TBS); δ_C (90 MHz, $CDCl_3$) 174.1 (s), 135.4 (s), 123.2 (d), 68.4 (t), 51.4 (q), 33.5 (t), 26.8 (t), 25.9 (3 × q), 24.7 (t), 18.4 (s), 13.4 (q), −5.3 (2 × q). HRMS (ESI) 309.1851 (M + Na$^+$, $C_{15}H_{30}O_3SiNa$ requires 309.1862).

(*E*)-7-(*tert*-Butyl-dimethyl-silanyloxy)-6-methyl-2-phenylselanyl-hept-5-enoic acid methyl ester 23. A solution of ^{n}BuLi (2.5 M) in hexane (8.0 ml, 20 mmol) was added dropwise over 5 mins to a stirred solution of diisopropylamine (2.02 g, 2.8 ml, 20 mmol) in anhydrous THF (9.19 ml) at 0 °C under a nitrogen atmosphere. The mixture was stirred at 0 °C for 0.5 hr and then kept at 0 °C to use in the next step as a 1.0 M solution of LDA in THF.

As described by Chu *et al.*,[24] a solution of freshly prepared LDA (14.4 ml, 14.4 mmol, 1.0 M) in THF was added dropwise over 5 mins to a stirred solution of the ester **22b** (3.74 g, 13.1 mmol) in anhydrous THF (52 ml) at −78 °C under a nitrogen atmosphere. The mixture was stirred at −78 °C for 45 mins and then TMSCl (1.56 g, 1.8 ml, 14.4 mmol) was added dropwise over 1 min. The mixture was stirred at −78 °C for 0.5 hr, and then a solution of PhSeBr (3.39 g, 14.4 mmol) in anhydrous THF (21 ml) was added dropwise over 10 mins. The mixture was stirred at −78 °C for 0.5 hr, and then allowed to warm to room temperature over 0.5 hr. The mixture was quenched with a saturated solution of aqueous NH_4Cl (130 ml), then diluted with water (150 ml) and Et_2O (300 ml). The separated aqueous layer was extracted with Et_2O (3 × 80 ml) and the combined organic extracts were then dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by chromatography on silica, eluting with light petroleum-diethyl ether (30:1), to give the *α-selanyl ester* (4.20 g, 73%) as a yellow oil (Found: C, 57.5; H, 7.8. $C_{21}H_{34}O_3SeSi$ requires C, 57.1; H, 7.7%); ν_{max} (film)/cm^{-1} 1732; δ_H (400 MHz; $CDCl_3$) 7.61–7.58 (2 H, m, Ph*H*), 7.32–7.29 (3 H, m, Ph*H*), 5.33 (1 H, m, =C*H*), 3.99 (2 H, s, TBSOC*H*$_2$), 3.64 (3 H, s, C*H*$_3$O), 3.67–3.61 (1 H, m, (PhSe)C*H*), 2.18–2.10 (2 H, m, CH$_2$C*H*$_2$C=), 2.05–1.94 (1 H, m, (PhSe)CHC*H*H), 1.86–1.77 (1 H, m, (PhSe)CHCH*H*), 1.57 (3 H, s, =CC*H*$_3$), 0.91 (9 H, s, TBS), 0.06 (6 H, s, TBS); δ_C (90 MHz; $CDCl_3$) 173.4 (s), 136.0 (s), 135.6 (2 × d), 129.0 (2 × d), 128.5 (d), 127.7 (s), 122.2 (d), 68.3 (t), 52.0 (q), 42.8 (d), 31.5 (t), 25.9 (3 × q), 25.9 (t), 18.4 (s), 13.4 (q), −5.3 (2 × q); HRMS (ESI) 465.1335 (M + Na$^+$, $C_{21}H_{34}O_3SeSiNa$ requires 465.1340).

Acetic acid (*E*)-6-(*tert*-butyl-dimethyl-silanyloxy)-1-((*Z*)-(*S*)-2-hydroxy-5-iodo-4-methyl-pent-4-enyl)-5-methyl-1-phenylselanyl-hex-4-enyl ester 24a. A solution of NaHMDS (2.0 M) in THF (1.50 ml, 3.0 mmol) was added dropwise *via* a syringe over 5 mins to a stirred solution of the selanyl ester **23** (1.30 g, 2.94 mmol) in anhydrous THF (20 ml) at −78 °C under a nitrogen atmosphere. The mixture was stirred at −78 °C for 0.5 hr, and then a solution of the oxirane **16** (453 mg, 2.02 mmol) in anhydrous THF (10 ml) was added dropwise *via* a cannula over 3 mins, followed by the addition of $BF_3{\cdot}OEt_2$ (287 mg, 2.02 mmol) dropwise *via* a syringe over 5 mins. The stirred mixture was allowed to warm to room temperature overnight and then it was quenched with a saturated solution of aqueous NH_4Cl (15 ml). The resulting solution was diluted with water (30 ml) and Et_2O (100 ml) and the separated aqueous layer was then extracted with Et_2O (3 × 30 ml). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by chromatography on silica, eluting with light petroleum-diethyl ether (5:1), to give a mixture of diastereoisomer of the *β-hydroxy ester* (964 mg, 72%) as a yellow oil, which was used in the next step.

For characterization purposes, the diastereoisomers were separated by flash chromatography on silica, eluting with light petroleum-diethyl ether (10:1), to give: i) a less polar diastereoisomer (Found: C, 49.1; H, 6.5. $C_{27}H_{43}IO_4SeSi$ requires C, 48.7; H, 6.5%): $[\alpha]_D^{25}$ −12.4 (*c* 1.0, $CHCl_3$); ν_{max} (film)/cm^{-1} 3509, 1724, 837; δ_H (400 MHz; $CDCl_3$) 7.60–7.58 (2 H, m, Ph*H*), 7.41–7.38 (1 H, m, Ph*H*), 7.33–7.27 (2 H, m, Ph*H*), 6.02 (1 H, br s, IC*H*=), 5.31 (1 H, t, *J* 6.7, CH$_2$C*H*=), 4.39–4.38 (1 H, m, C*H*OH), 3.98 (2 H, br s, C*H*$_2$OTBS), 3.65 (3 H, s, OC*H*$_3$), 2.71 (1 H, d, *J* 4.1, O*H*), 2.47 (1 H, dd, *J* 8.1 and 13.3, =C(CH$_3$)C*H*HCHOH), 2.36 (1 H, dd, *J* 5.1 and 13.3, =C(CH$_3$)CH*H*CHOH), 2.31–2.22 (1 H, m, =CHC*H*HCH$_2$), 2.17–2.07 (2 H, m, =CHCH*H*CH$_2$ and CH(OH)C*H*H), 1.99–1.98 (3 H, m, ICH =C(C*H*$_3$)), 1.90–1.80 (3 H, m, CH(OH)CH*H* and =CHCH$_2$C*H*$_2$), 1.60 (3 H, s, =C(C*H*$_3$)), 0.91 (9 H, s, TBS), 0.06 (6 H, s, TBS); δ_C (100 MHZ; $CDCl_3$) 174.3 (s), 144.8 (s), 138.0 (2 × d), 135.3 (s), 129.3 (d), 128.8 (2 × d), 126.6 (s), 122.7 (d), 76.8 (d), 68.3 (t), 68.2 (d), 55.9 (s), 52.2 (q), 46.7 (t), 42.8 (t), 36.6 (t), 25.9 (3 × q), 24.8 (q), 23.8 (t), 18.4 (s), 13.5 (q), −5.3 (2 × q); HRMS (ESI) 689.1024 (M + Na$^+$, $C_{27}H_{43}IO_4SeSiNa$ requires 689.1038), and ii) a more polar diastereoisomer (Found: C, 49.3; H, 6.4. $C_{27}H_{43}IO_4SeSi$ requires C, 48.7; H, 6.5%). $[\alpha]_D^{22}$ −3.76 (*c* 1.22, $CHCl_3$); ν_{max} (film)/cm^{-1} 3492, 1723, 837; δ_H (400 MHz; $CDCl_3$) 7.59–7.57 (2 H, m, Ph*H*), 7.42–7.38 (1 H, m, Ph*H*), 7.34–7.30 (2 H, m, Ph*H*), 6.01 (1 H, br s, IC*H*=), 5.36 (1 H, t, *J* 6.9, CH$_2$C*H*=), 4.10–4.04 (1 H, m, C*H*OH), 4.00 (2 H, br s, C*H*$_2$OTBS), 3.63 (3 H, s, OC*H*$_3$), 2.45–2.33 (3 H, m, =C(CH$_3$)C*H*$_2$CHOH and =CHC*H*HCH$_2$), 2.29–2.22 (1 H, m, CH(OH)C*H*H), 2.19–2.07 (2 H, m, =CHCH*H*CH$_2$ and O*H*), 2.04–1.86 (3 H, m, CH(OH)CH*H* and =CHCH$_2$C*H*$_2$), 1.95 (3 H, br s, ICH=C(C*H*$_3$)), 1.63 (3 H, s, =C(C*H*$_3$)), 0.92 (9 H, s, TBS), 0.07 (6 H, s, TBS); δ_C (100 MHz; $CDCl_3$) 174.8 (s), 144.6 (s), 137.9 (2 × d), 135.2 (s), 129.4 (d), 128.8 (2 × d), 126.6 (s), 123.0 (d), 76.9 (d), 68.4 (t), 68.0 (d), 54.4 (s), 52.2 (q), 47.2 (t), 41.6 (t), 33.3 (t), 25.9 (3 × q), 24.8 (q), 23.5 (t), 18.4 (s), 13.6 (q), −5.3 (2 × q); HRMS (ESI) 689.0999 (M + Na$^+$, $C_{27}H_{43}IO_4SeSiNa$ requires 689.1038).

(*S*)-3-[(*E*)-5-(*tert*-Butyl-dimethyl-silanyloxy)-4-methyl-pent-3-enyl]-5-((*Z*)-3-iodo-2-methyl-allyl)-3-phenylselanyl-dihydro-furan-2-one 25. *p*-Toluenesulfonic acid monohydrate (92.7 mg, 0.487 mmol) was added in one portion to a stirred solution of a mixture of diastereoisomers of the β-hydroxyester **24a** (3.24 g, 4.87 mmol) in DCM (487 ml) at room temperature. The mixture was stirred at room temperature for 3 hrs, and then quenched with a saturated solution of aqueous $NaHCO_3$ (30 ml). The resulting solution was diluted with water (30 ml) and DCM (100 ml), and the separated aqueous layer was then extracted with DCM (3 × 30 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave a mixture of diastereoisomers of the *γ-lactone* (3.09 g, 95%) as a yellow oil which was used in the next step without further purification.

(*S*)-3-[(*E*)-5-(*tert*-Butyl-dimethyl-silanyloxy)-4-methyl-pent-3-enyl]-5-((*Z*)-3-iodo-2-methyl-allyl)-5*H*-furan-2-one 26a. Aqueous H_2O_2 (30% w/w in water, 1.49 ml, 14.6 mmol) was added dropwise over 5 mins to a stirred solution of the selanyl γ-lactone **25** (3.1 g, 4.9 mmol) in THF (70 ml) at 0 °C. The mixture was stirred at 0 °C for 5 mins and then at room temperature for 2 hrs. The reaction was quenched with a saturated solution of aqueous $NaHCO_3$ (15 ml) and then diluted with Et_2O (100 ml). The separated organic extract was washed with H_2O (2 × 10 ml) and brine (5 ml), then dried ($MgSO_4$) and concentrated *in vacuo* to leave the *furanone* (2.25 g, 97%) as yellow oil, which was used without further purification. (Found: C, 50.3; H, 7.0. $C_{20}H_{33}IO_3Si$ requires C, 50.4; H, 7.0%). $[\alpha]_D^{25}$ +29.0 (*c* 1.20, $CHCl_3$); ν_{max} (film)/cm^{-1} 1759; δ_H (400 MHz; $CDCl_3$) 7.09 (1 H, br s, CHC*H*=), 6.12 (1 H, br s, IC*H*=), 5.40–5.37 (1 H, m, =C*H*CH$_2$), 5.06–5.02 (1 H, m, C*H*CH=), 4.01 (2 H, s, C*H*$_2$OTBS), 2.67 (1 H, dd, *J* 5.9 and 13.7, ICH=C(CH$_3$)C*H*H), 2.53 (1 H, dd, *J* 7.6 and 13.7, ICH=C(CH$_3$)CH*H*), 2.38–2.31 (4 H, m, =CHC*H*$_2$ and =CHCH$_2$C*H*$_2$), 2.00 (3 H, d, *J* 1.3, ICH=C(C*H*$_3$)), 1.61 (3 H, s, =C(C*H*$_3$)), 0.91 (9 H, s, TBS), 0.06 (6 H, s, TBS); δ_C (100 MHz; $CDCl_3$) 173.3 (s), 147.6 (d), 142.4 (s), 135.9 (s), 134.1 (s), 122.4 (d), 79.4 (d), 78.4 (d), 68.2 (t), 42.5 (t), 25.9 (3 × q), 25.2 (t), 25.2 (t), 24.8 (q), 18.4 (s), 13.5 (q), −5.3 (2 × q); HRMS (ESI) 499.1141 (M + Na$^+$, $C_{20}H_{33}IO_3SiNa$ requires 499.1141).

(*S*)-3-((*E*)-5-Hydroxy-4-methyl-pent-3-enyl)-5-((*Z*)-3-iodo-2-methyl-allyl)-5*H*-furan-2-one 26b. Pyridinium *p*-toluenesulfonate (245 mg, 0.95 mmol) was added in one portion to a solution of the TBS ether **26a** (2.25 g, 4.72 mmol) in DCM (140 ml) and MeOH (140 ml) and the mixture was stirred at room temperature for 24 hrs and then concentrated *in vacuo*. The residue was purified by chromatography on silica, eluting with light petroleum (bp 40–60 °C)-ethyl acetate (1:2), to give the *alcohol* (1.10 g, 62% over 3 steps) as an almost colourless viscous oil (Found: C, 46.8; H, 5.3. $C_{14}H_{19}IO_3$ requires C, 46.4; H, 5.3%); $[\alpha]_D^{23}$ +43.7 (*c* 1.27, $CHCl_3$); ν_{max} (film)/cm^{-1} 3416, 1746; δ_H (360 MHz; $CDCl_3$) 7.12 (1 H, q, *J* 1.5, CHC*H*=), 6.13 (1 H, q, *J* 1.5, IC*H*=), 5.44–5.40 (1 H, m, =C*H*CH$_2$), 5.07 (1 H, ddd, *J* 1.5, 6.0 and 7.4, C*H*CH=), 4.02 (2 H, d, *J* 6.1, C*H*$_2$OH), 2.68 (1 H, dd, *J* 6.0 and 13.6, ICH=C(CH$_3$)C*H*H), 2.56 (1 H, dd, *J* 7.4 and 13.6, ICH=C(CH$_3$)CH*H*), 2.43–2.33 (4 H, m, =CHC*H*$_2$ and =CHCH$_2$C*H*$_2$), 2.00 (3 H, d, *J* 1.5, ICH=C(C*H*$_3$)), 1.68 (3 H, s, =C(C*H*$_3$)), 1.34 (1 H, t, *J* 6.1, O*H*); δ_C (90 MHz; $CDCl_3$) 173.3 (s), 147.7 (d), 142.2 (s), 136.1 (s), 133.7 (s), 123.5 (d), 79.3 (d), 78.4 (d), 68.2 (t), 42.3 (t), 25.2 (t), 25.0 (t), 24.6 (q), 13.6 (q); HRMS (ESI) 385.0274 (M + Na$^+$, $C_{14}H_{19}IO_3Na$ requires 385.0276).

5-{(*Z*)-3-[(*S*)-4-((*E*)-5-Hydroxy-4-methyl-pent-3-enyl)-5-oxo-2,5-dihydro-furan-2-yl]-2-methyl-propenyl}-3-methyl-furan-2-carbaldehyde 28a. Solutions of the (+)-vinyl iodide **26b** (500 mg, 1.38 mmol) in DMF (5 ml), and the furanylstannane **27**[5,26] (489 mg, 1.79 mmol) in DMF (4 ml) were degassed separately for 0.5 hr with argon before they were added successively *via* cannula to a stirred mixture of $Pd(PPh_3)_4$ (64 mg, 0.06 mmol), CuI (21 mg, 0.11 mmol) and CsF (419 mg, 2.8 mmol) at room temperature. The resulting yellow mixture was stirred at room temperature for 20 mins, whereupon the colour of the mixture changed to brown, first, then black. The mixture was poured into a mixture of a saturated solution of aqueous NH_4Cl (30 ml) and Et_2O (30 ml) and the separated aqueous layer was then extracted with Et_2O (1 × 30 ml). The combined organic extracts were washed with brine (20 ml), then dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by flash chromatography on silica, eluting with light petroleum (bp 40–60 °C)-ethyl acetate (1:1), to give the *furanobutenolide* (427 mg, 90%) as a yellow viscous oil. $[\alpha]_D^{25}$ +56.4 (*c* 1.0, $CHCl_3$); ν_{max} (sol $CHCl_3$)/cm^{-1} 3478, 1746, 1658; δ_H (360 MHz; $CDCl_3$) 9.60 (1 H, s, H-2), 7.32 (1 H, br s, H-11), 6.18 (1 H, s, H-5), 6.17 (1 H, br s, H-7), 5.41–5.38 (1 H, m, H-1), 5.13–5.08 (1 H, m, H-10), 3.99 (2 H, s, H-16), 3.21 (1 H, d, *J* 13.0, H-9α), 2.48–2.28 (5 H, m, H-9β, H-13 and H-14), 2.34 (3 H, s, Me-18), 2.18 (1 H, br s, OH), 2.05 (3 H, d, *J* 1.3, Me-19), 1.64 (3 H, s, Me-17); δ_C (100 MHZ; $CDCl_3$) 175.5 (s), 173.8 (d), 156.9 (s), 149.1 (d), 147.4 (s), 141.9 (s), 136.5 (2 × s), 133.4 (s), 123.8 (d), 115.3 (d), 113.9 (d), 81.5 (d), 68.4 (t), 38.2 (t), 26.7 (q), 25.3 (t), 24.8 (t), 13.7 (q), 10.0 (q); HRMS (ESI) 367.1516 (M + Na$^+$, $C_{20}H_{24}O_5Na$ requires 367.1521). The IR, ^{1}H NMR, ^{13}C NMR and HRMS data were identical with those presented contemporaneously in the literature for racemic material.[5]

5-{(*Z*)-3-[(*S*)-4-((*E*)-5-Bromo-4-methyl-pent-3-enyl)-5-oxo-2,5-dihydro-furan-2-yl]-2-methyl-propenyl}-3-methyl-furan-2-carbaldehyde 28b. Triphenylphosphine (419 mg, 1.59 mmol) and *N*-bromosuccinimide (284 mg, 1.59 mmol) were added to a stirred solution of the (+)-alcohol **28a** (427 mg, 1.24 mmol) in DCM (30 ml) at −5 °C. The mixture was stirred at 0 °C for 20 mins, and then poured into water (10 ml). The separated aqueous layer was extracted with DCM (2 × 30 ml), and the combined organic extracts were then dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash chromatography on silica, eluting with light petroleum (bp 40–60 °C)-ethyl acetate (4:1), to give the *allyl bromide* (400 mg, 80%) as a pale yellow oil. $[\alpha]_D^{27}$ +59.8 (*c* 1.01, $CHCl_3$); ν_{max} (sol $CHCl_3$)/cm^{-1} 1754, 1660; δ_H (360 MHz; $CDCl_3$) 9.65 (1 H, s, H-2), 7.26 (1 H, br s, H-11), 6.19 (1 H, s, H-5), 6.18 (1 H, br s, H-7), 5.55 (1 H, t, *J* 6.5, H-1), 5.15–5.11 (1 H, m, H-10), 3.93 (2 H, s, H-16), 3.17 (1 H, dd, *J* 3.8 and 13.4, H-9α), 2.55 (1 H, dd, *J* 8.5 and 13.4, H-9β), 2.38–2.35 (2 H, m, H-13α,β), 2.35 (3 H, s, Me-18), 2.31–2.28 (2 H, m, H-14α,β), 2.04 (3 H, d, *J* 1.3, Me-19), 1.74 (3 H, s, Me-17); δ_C (90 MHz; $CDCl_3$) 175.5 (s), 173.3 (d), 156.5 (s), 148.9 (d), 147.3 (s), 140.8 (s), 135.7 (s), 133.3 (s), 132.9 (s), 129.2 (d), 115.5 (d), 113.9 (d), 81.0 (d), 41.0 (t), 38.0 (t), 26.5 (t), 25.8 (t), 24.4 (q), 14.5 (q), 10.0 (q); HRMS (ESI) 429.0672 (M + Na$^+$, $C_{20}H_{23}BrO_4Na$ requires 429.0676).

(–)-Bipinnatin J (4a). A solution of the (+)-allylbromoaldehyde **28b** (220 mg, 0.54 mmol) in anhydrous THF (377 ml) was degassed with nitrogen for 1 hr at room temperature, and then it was added *via* a cannula to a mixture of 4 Å MS (activated powder, 2.51 g) and anhydrous $CrCl_2$ (1.37 g, 11.1 mmol) at room temperature under an argon atmosphere. The resulting green-coloured mixture was stirred at 25 °C for 16 hrs and then filtered through celite. The filtrate was concentrated *in vacuo* and the residue was diluted with Et_2O (150 ml) and then washed with water (2 × 20 ml) and brine (10 ml). The separated organic extract was dried (Na_2SO_4) and concentrated *in vacuo* to leave a residue which was purified by chromatography on silica, eluting with light petroleum-ethyl acetate (6:1), to give (–)-*bipinnatin J* (124 mg, 70%) as a colourless solid. mp 144–147 °C (EtOAc-petroleum), Lit. mp 141–142 °C; $[\alpha]_D^{27}$ –129.9 (*c* 1.77, $CHCl_3$), Lit $[\alpha]_D^{24}$ –125.4 (*c* 1.65, $CHCl_3$);[7] ν_{max} (sol $CHCl_3$)/cm^{-1} 3541, 1746; δ_H (360 MHz; $CDCl_3$) 6.86 (1 H, t, *J* 1.6, H-11), 6.12 (1 H, br s, H-7), 6.04 (1 H, s, H-5), 5.18 (1 H, br s, H-16β), 5.07 (1 H, s, H-16α), 5.02–4.99 (1 H, m, H-10), 4.51 (1 H, dd, *J* 2.9 and 10.9, H-2), 3.21 (1 H, t, *J* 11.8, H-9β), 2.74 (1 H, dd, *J* 4.4, 11.8, H-9α), 2.46–2.35 (2 H, m, H-13β and H-1), 2.13–2.07 (1 H, m, H-13α), 2.06 (3 H, s, Me-18), 2.01 (3 H, br s, Me-19), 1.86 (1 H, d, *J* 2.9, OH), 1.81 (3 H, br s, Me-17), 1.68 (1 H, tdd, *J* 3.3, 11.1 and 13.8, H-14β), 0.91 (1 H, dt, *J* 3.8, 13.8, H-14α); δ_C (90 MHz; $CDCl_3$) 174.4 (s, C-20), 152.4 (d, C-11), 151.1 (s, C-6), 149.3 (s, C-3), 142.2 (s, C-15), 132.7 (s, C-12), 129.2 (s, C-8), 121.2 (s, C-4), 118.9 (t, C-16), 117.5 (d, C-7), 114.0 (d, C-5), 78.8 (d, C-10), 65.1 (d, C-2), 51.3 (d, C-1), 39.8 (t, C-9), 30.2 (t, C-14), 26.0 (q, C-19), 19.8 (t, C-13), 17.6 (q, C-17), 9.6 (q, C-18); HRMS (ESI) 351.1578 (M + Na^+, $C_{20}H_{24}O_4Na$ requires 351.1572). The $[\alpha]_D$, IR, ^{1}H NMR, ^{13}C NMR and HRMS data were identical with those presented in the literature for naturally-derived material.[7]

The 6-acetoxypyranone 30. Vanadyl(acetylacetate) (0.74 mg, 0.27 µmol) was added to a solution of synthetic (–)-bipinnatin J (**4a**) (56 mg, 0.17 mmol) in anhydrous DCM (8 ml) at –20 °C under a nitrogen atmosphere, followed by the addition of ^{t}BuOOH (77.5 µl, 0.43 mmol, 5.5 M in decane). The mixture was stirred at –20 °C for 4 hrs, and then poured into a mixture of DCM (20 ml) and H_2O (5 ml) at 0 °C. The two phase mixture was stirred at 0 °C for 5 mins and the separated aqueous layer was then extracted with DCM (pre-cooled to 5–10 °C, 2 × 15 ml). The combined organic extracts were washed with H_2O (2 × 4 ml) and brine (2 × 4 ml), then dried (Na_2SO_4), and concentrated *in vacuo* to leave a yellow residue. The oil, which we believe consisted of a mixture of tautomers of the cyclic hemiketal **8** was used immediately without further purification. ν_{max} (sol $CHCl_3$)/cm^{-1} 3534, 1754, 1671, 1626; HRMS (ESI) 345.1697 (M + H^+, $C_{20}H_{25}O_5$ requires 345.1702), 367.1516 (M + Na^+, $C_{20}H_{24}O_5Na$ requires 367.1521).

Triethylamine (172 mg, 236 µl, 1.7 mmol), acetic anhydride (70 mg, 64 µl, 0.7 mmol) and DMAP (8.3 mg, 0.07 mmol) were added to a solution of the crude cyclic hemiketal in anhydrous DCM (8 ml) at 0 °C. The mixture was allowed to warm to room temperature and stirred over 2.5 hrs, and then diluted with DCM (50 ml). The solution was washed with H_2O (3 × 5 ml) and brine (2 × 3 ml), then dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by chromatography on silica, eluting with light petroleum-ethyl acetate (5:1) to give *6-acetoxypyranone* (20 mg, 30% over two steps) as a yellow oil. ν_{max} (sol $CHCl_3$)/cm^{-1} 1754, 1710, 1677, 1613; δ_H (360 MHz; $CDCl_3$) 7.16 (1 H, br, H-11), 6.42 (1 H, s, H-5), 6.31 (1 H, s, H-7), 5.80 (1 H, br s, H-2), 5.30 (1 H, d, *J* 10, H-10), 4.92–4.88 (1 H, m, H-16α), 4.65 (1 H, br s, H-16β), 3.76 (1 H, d, *J* 14.6, H-9α), 3.23 (1 H, d, *J* 14.6, H-9β), 2.11 (3 H, s, OAc), 2.11 (3 H, s, Me-19), 2.01 (3 H, s, Me-18), 1.68 (3 H, s, Me-17); HRMS (ESI) 387.1802 (M + H^+, $C_{22}H_{27}O_6$ requires 387.1808), 409.1622 (M + Na^+, $C_{22}H_{26}O_6Na$ requires 409.1627).

(+)-Intricarene 1. A solution of DBU (8.67 mg, 0.057 mmol) in degassed anhydrous CH_3CN (60 ml) was added to the 6-acetoxypyranone **30** (20 mg, 0.052 mmol) at room temperature under an atmosphere of argon. The mixture was stirred and heated under reflux for 1.2 hrs under an argon atmosphere, then cooled to room temperature and concentrated *in vacuo*. The residue was purified by chromatography on silica, eluting with light petroleum-diethyl ether (1:1), to give (+)-intricarene (1.7 mg, 10%) as colourless crystals. A satisfactory melting point could not be obtained as the crystals sublimed during heating. $[\alpha]_D^{24}$ +52.9 (*c* 0.14 $CHCl_3$), Lit.[1] $[\alpha]_D^{20}$ +50.0 (*c* 0.7, $CHCl_3$); ν_{max} (sol $CHCl_3$)/cm^{-1} 1769, 1702; δ_H (500 MHz; $CDCl_3$) 6.43–6.41 (1 H, m, H-7), 6.28 (1 H, q, *J* 1.6, H-5), 4.93 (1 H, q, *J* 1.3, H-16α), 4.88 (1 H, br s, H-16β), 4.78 (1 H, ddd, *J* 2.6, 5.3 and 8.6, H-10), 3.39 (1 H, dd, *J* 5.8 and 11.9, H-1), 2.84 (1 H, dd, *J* 8.6 and 18.6, H-9α), 2.55 (1 H, d, *J* 5.3, H-11), 2.42 (1 H, br d, *J* 18.6, H-9β), 2.14–2.09 (1 H, m, H-14α), 2.03–1.98 (1 H, m, H-13α), 1.97–1.90 (2 H, m, H-13β and H-14β), 1.85 (3 H, t, *J* 1.4, Me-19), 1.77 (3 H, d, *J* 1.6, Me-18), 1.76 (3 H, br s, Me-17); δ_C (125 MHZ; $CDCl_3$) 193.0 (s), 178.0 (s), 147.3 (d), 141.7 (s), 137.2 (s), 135.2 (s), 128.0 (d), 113.3 (t), 102.8 (s), 84.6 (s), 70.7 (d), 64.1 (s), 58.0 (d), 46.3 (d), 35.6 (t), 29.3 (t), 28.5 (t), 23.2 (q), 23.1 (q), 14.4 (q); HRMS (ESI) 349.1410 (M + Na^+, $C_{20}H_{22}O_4Na$ requires 349.1416). The IR, ^{1}H NMR, ^{13}C NMR and HRMS were identical to those presented in the literature for natural intricarene. Two additional compounds (0.6 mg and 1.0 mg respectively) were also isolated but neither was characterised. The HRMS (ESI) for the minor (0.6 mg) unknown product showed: 387.1795 (M + H^+, $C_{22}H_{27}O_6$ requires 387.1808), 409.1610 (M + Na^+, $C_{22}H_{26}O_6Na$ requires 409.1627), 404.2062 (M + NH_4^+ requires 404.2073); and the HRMS (ESI) for the major (1 mg) unknown product: 387.1792 (M + H^+, $C_{22}H_{27}O_6$ requires 387.1808), 409.1610 (M + Na^+, $C_{22}H_{26}O_6Na$ requires 409.1627), 404.2051 (M + NH_4^+ requires 404.2073).

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