

# Natural Product Reports

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## Pacific Rim Sesterterpenoids

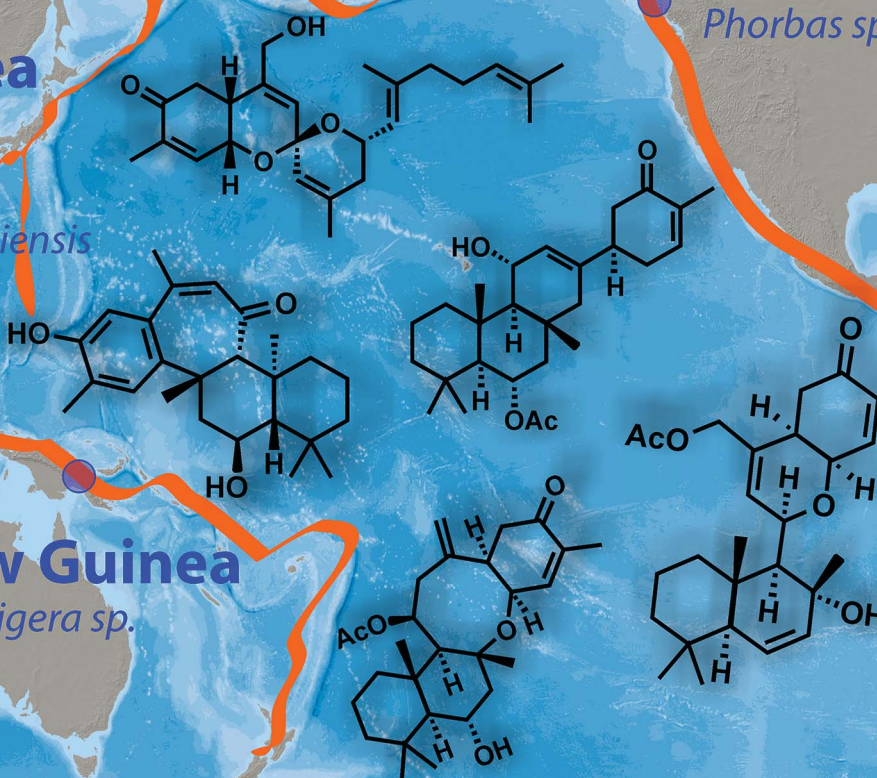
### South Korea

*Monanchora* sp.  
*Phorbas* sp.  
*Clathria gombawuiensis*

Canada  
*Phorbas* sp.

### Papua New Guinea

*Hamigera* sp.



ISSN 0265-0568



#### HIGHLIGHT

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A new family of sesterterpenoids isolated around the Pacific Rim



Cite this: *Nat. Prod. Rep.*, 2018, 35, 210

## A new family of sesterterpenoids isolated around the Pacific Rim

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Covering: 2009 up to the end of 2017

Received 24th October 2017

DOI: 10.1039/c7np00049a

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There has been a recent eruption in the number of known marine sesterterpenoids which have been isolated from Pacific Rim marine organisms. These compounds have novel and unusual structures that exhibit incredibly potent and varied bioactivities. This review details the isolation, biological testing and prospects for this exciting new family with discussion of their potential biogenetic origins.

### 1. Introduction

Isoprenoids have given the world some of the most important classes of drugs and bioactive molecules including taxanes, steroids, tocopherols, artemisinins, ingenanes and cannabinoids (Fig. 1).<sup>1</sup>

This is hardly surprising given that isoprenoids are the largest class of natural products, with estimates of >70 000 distinct compounds providing a vast pool of complexity that can interact with biological targets in a huge variety of different ways.<sup>2</sup> More generally, natural products play a key role in the drug discovery/ pharmaceutical industries. More than half of small molecule

drugs can trace their roots back to natural products since they occupy the vastness of chemical space far better than the more focussed areas that traditional medicinal chemistry is able to populate.<sup>1a</sup> The ongoing discovery of architecturally complex and beguiling natural products also inspires the development of new chemical methodologies which feeds back into the pharmaceutical chemistry arena. The importance of natural products to the pharmaceutical industry and in turn to the wider public has therefore never been more apparent.

### 2. Pacific Rim sesterterpenoids

Of all the isoprenoids, sesterterpenoids are amongst the rarest with little more than 1000 compounds known.<sup>1</sup> Nevertheless, even this small family provides sufficient diversity to serve as a useful mine for bioprospecting.<sup>3</sup> Manoalide is a potent inhibitor of phospholipase A<sub>2</sub> that reached phase II clinical trials in the 1980's as a topical anti-inflammatory. Although it failed to reach market due to supply issues, it is still used as a standard biochemical tool to block calcium channels. More recently marine sesterterpenoids have shown promise as exciting new anti-cancer drug leads.<sup>4,5</sup>

Biogenetically, sesterterpenoids are derived from five dimethylallyl pyrophosphate (DMAPP) monomers that form the C<sub>25</sub> geranylgeranyl pyrophosphate (GFPP) backbone (Scheme 1). Cyclisation of GFPP is catalysed by sesterterpene synthases (STSSs), the dearth of which explains the overall scarcity of sesterterpenoids.<sup>6</sup> This landscape has changed significantly over the past 8 years as an entire new subset of sesterterpenoids has been isolated from marine organisms located around the Pacific Rim swelling their numbers considerably. Eight novel skeletal classes: alotane (1), ansellane (2), secoansellane (3), phorbassane (4), isophorbassane (5), phorane (6), gombane (7) and anvilane (8) have been isolated from marine organisms collected in South Korean, Papua New Guinean and Canadian



Fig. 1 Isoprenoid drugs and bioactive molecules.

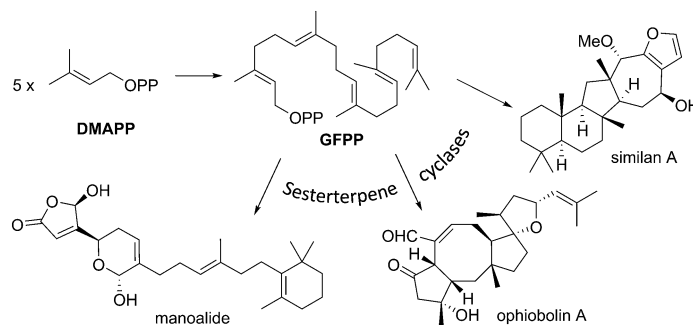
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Scheme 1 Biogenesis of sesterterpenoids.

waters (Fig. 2). These alotane and alotane-derived natural products have attracted considerable attention from biologists and synthetic chemists due to their diverse and often potent biological activities, in addition to their elaborate organic

frameworks. This review compiles details of the isolation and biological testing of this new family of sesterterpenoids. We highlight previously suggested biogeneses and also introduce a few of our own proposals.



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*in Chemistry (2015) and L'Oreal-UNESCO Women in Science laureate for Asia-Pacific, and conferred the Queen's Honour CNZM. She is President of IUPAC Organic and Biomolecular Division III, co-Founder cancer vaccine company SapVax, Associate Editor for Organic and Biomolecular Chemistry, and Past-President of the International Society of Heterocyclic Chemistry.*



*Megan Jamieson completed her BSc Hons at the University of Auckland in 2015, and is currently undertaking a PhD with the supervision of Distinguished Professor Margaret Brimble and Dr Daniel Furkert. Megan's PhD research includes work towards the total synthesis of marine derived sesterterpenoids, and mechanistic elucidation of a recently discovered cobalt catalysed olefination reaction.*



*Christopher Bray was a doctoral student at the University of Oxford before undertaking post-doctoral studies with Prof Gerry Pattenden at the University of Nottingham on the biogenetically patterned synthesis of the furanocembrane family of natural products. He is currently a Lecturer in Synthetic Organic Chemistry in the Department of Chemistry at Queen Mary, University of London. His*

*research interests include the development of new synthetic methodology to access small rings and the total synthesis of bioactive natural products.*



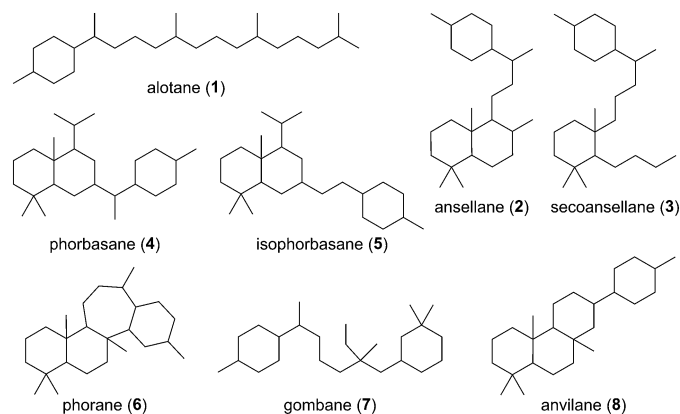


Fig. 2 Alotane (1) and its proposed sesterterpenoid skeletal derivatives.

## 2.1 Alotane sesterterpenoids

This field began in 2009 when Andersen and co-workers isolated alotaketals A and B (**9** and **10**) from a sample of the marine sponge *Hamigera* sp. collected off the coast of Papua New Guinea (Fig. 3).<sup>7</sup>

The alotane framework contains novel tricyclic spiroketal and hydrobenzopyran moieties, unprecedented at the time among known natural products. Alotaketals A and B (**9** and **10**) were found to be potent activators of the secondary messenger cyclic adenosine monophosphate (cAMP) signalling pathway. Treatment of HEK293 cells with alotaketals A or B (**9** or **10**) resulted in activation of the signalling pathway, and the concentration of cAMP in the cells was greatly increased. Most strikingly, alotaketal A (**9**) promoted cAMP activation at nanomolar concentrations (EC<sub>50</sub> 18 nM). In fact, alotaketal A is one of the most potent activators of the cAMP pathway ever to be discovered, being 167 times more potent than forskolin (EC<sub>50</sub> 3 μM), the standard small molecule adjuvant relied upon for biological investigations of cAMP activation. This startling activity prompted a flurry of efforts from the synthetic community which resulted in a number of impressive total syntheses.<sup>8</sup> Soon after the original discovery of the alotaketals, the closely related sesterterpenoids

phorbaketals A–C (**11**–**13**) (Fig. 3), were isolated from a specimen of the marine sponge *Phorbas* sp. collected near Gageo Island, South Korea by Rho *et al.*<sup>9</sup> The similarity between these new natural products is particularly striking given they were isolated over 5000 kilometres apart. Rho *et al.* reported that phorbaketal A (**11**) could be extracted from a cultivated microbial specimen collected from a homogenized sponge specimen, which might suggest that **11**–**13** are originated from symbionts inhabiting the sponge, however this is yet to be confirmed and further work is required to identify the true origin of these metabolites. Alotaketal A (**9**) and phorbaketal A (**11**) are regioisomers differentiated by alkenes positioned at C11 and C19. The epimeric phorbaketals B and C (**12** and **13**) were proposed to originate from **11** by reduction at C4. The discovery of numerous other alotaketals and phorbaketals followed between the years 2013–16. Phorbaketals D–K (**17**–**26**) were isolated by Kang *et al.* off the coast of South Korea from the marine sponge *Monanchora* sp. (Fig. 4).<sup>10</sup> This was followed by isolation of phorbaketals L–N (**27**–**29**) again from the marine sponge *Phorbas* sp. from South Korean waters.<sup>11</sup> Andersen and co-workers further reported the isolation of alotaketal C (**16**)<sup>12</sup> and later D and E (**17** and **18**).<sup>13</sup> These recently discovered alotanes differ by oxidative modification of the tricyclic core or the geranyl side chain, with phorbaketal N (**29**) notably being brominated at C14.

Biogenesis of the alotane carbon skeleton is proposed to proceed by partial cyclization of geranylgeranyl pyrophosphate (GGPP) (Scheme 2).<sup>14</sup> An allylic cation would be generated by dissociation of pyrophosphate, prior to attack from the proximal alkene to form a new 6-membered ring. This generates the alotane skeleton which is proposed to be the progenitor to the alotaketals and phorbaketals. Oxidation of alotane (**1**) at C1, C4 and C9 gives phorbin A (**14**). This natural product was isolated alongside phorbaketals D–K in 2013<sup>10</sup> and is currently the least elaborated and hence biogenetically the earliest of the known alotane sesterterpenoids. A possible pathway to the common spiroketal-hydrobenzopyran framework may involve epoxidation/rearrangement about C7 and further oxidation of the unsaturated skeleton to form hydroxy ketones (e.g. **15** or similar) prior to spiroketalization. Further modification

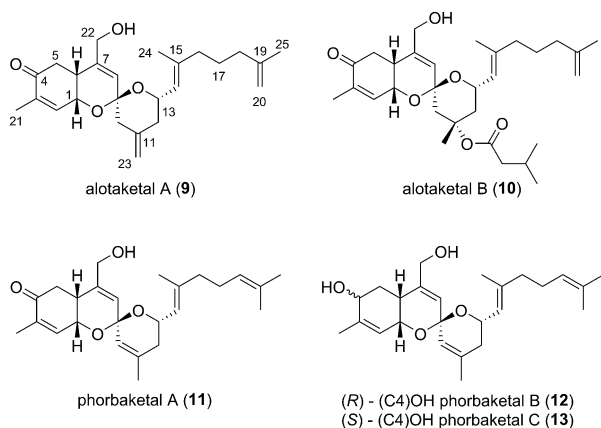


Fig. 3 First alotane natural products.



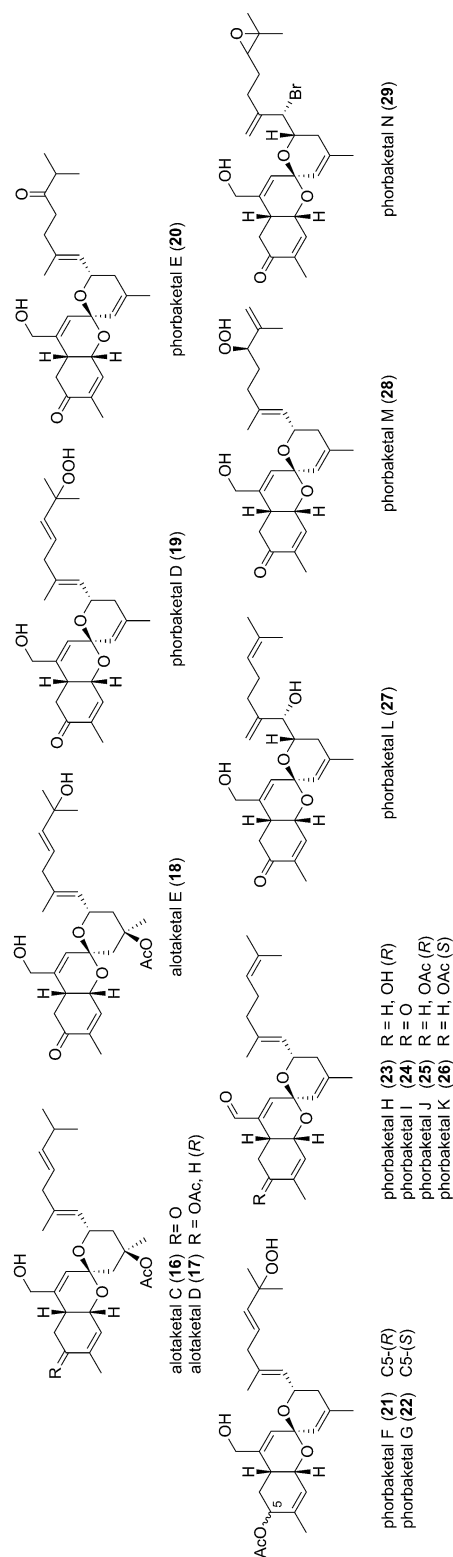


Fig. 4 The alotane family of natural products.

through alkene migrations and/or oxidation of the geranyl side chain or the tricyclic core would lead to other phorbaketal and alotaketal natural products (Fig. 4).

## 2.2 Ansellanes and secoansellane

The first of the ansellanes was reported in 2010 by Andersen *et al.*<sup>15</sup> Ansellone A (30) was isolated from the marine sponge *Phorbasp* sp. and from the nudibranch *Cadlina luteomarginata* observed feeding on the sponge at the time of collection in British Columbia, Canada (Fig. 5). This was the first example of the novel tricyclic ansellane carbon skeleton (2) in a natural product. A few years later Kang and co-workers reported the isolation of ansellone B (37) from a specimen of *Phorbasp* sp. collected from south-western Korean waters. Ansellone B (37) bears an atypical aromatized C ring, absent in all other ansellones isolated subsequently, which instead possess a common benzohydropyran moiety (Fig. 5).<sup>14</sup> A number of further ansellones have since been identified from *Phorbasp* sp. including ansellone B1 (38),<sup>12,16</sup> phorbadiolone (35),<sup>12</sup> and ansellone C (40).<sup>18</sup> All these additional natural products share the hallmark hydrobenzopyran motifs and are differentiated only by the varied oxidation state of the drimane-type *trans*-decalin skeleton. Secoepoxyansellone A (36) is the first example of the degraded secoansellane carbon skeleton (3), being devoid of the parent ansellane C10–C11 junction (Fig. 5).<sup>12</sup> Of the known ansellane natural products these can be split into three sub-categories: pyran-type, aromatic and oxocane-type. Variations within the individual ansellane sub-categories then involve oxidative modification of the drimane-type *trans*-decalin skeleton (Fig. 5).

The ansellane carbon skeleton may be biogenetically derived from cyclization of the pendant oxygenated farnesyl chain of the alotane skeleton starting from 13-hydroxyphorbaspin 41 to form the drimane-type *trans*-decalin ring system (in accord with the Stork–Eschenmoser hypothesis) (Scheme 3).<sup>19</sup> Oxocane-type ansellones B1 (38), C, and C1 (39 and 40) and pyran-type ansellones A (30) and D–G (31–34) may be derived from common intermediate 42, where the C4 alcohol may substitute alcohols (or similar) at either C11 or C9, respectively. Alternatively, aromatization of ring C in intermediate 42 would lead to ansellone B (37). We now propose that degradation of the ansellane skeleton to the secoansellane skeleton possessed by secoepoxyansellone A (36) may occur *via* lactolisation of an intermediate such as 43 at C9, before oxocarbenium generation and a retro-Aldol process (Scheme 3).

In 2017, the total syntheses of ansellones A (30), B1 (38) and phorbadiolone (33) were reported by Tong *et al.* which they suggest will enable future structure–activity relationship studies of ansellane analogues to be carried out.<sup>20</sup>

## 2.3 Phorbasones and isophorbasones

Phorbasones A (44) and B (45) were reported by Rho and co-workers from a *Phorbasp* sp. Sponge found in South Korean waters.<sup>21</sup> The following year Kang *et al.* isolated isophorbasones





Scheme 2 Proposed biogenesis of phorbin A and other alotane natural products.

A (46) also from a Korean specimen of *Phorbas* sp. (Fig. 6).<sup>14</sup> The phorbasane (4) and isophorbasane (5) skeletons are tricyclic and are related through isomerisation around C11. They are thought to be derived from the alotane skeleton through a series of sequential cyclisations starting from the alotane 47 (Scheme 4), which bears remarkable similarity to phorbin A (14) and 13-hydroxyphorbin 41, the respective progenitors to the alotaketals, phorbaketals and ansellanes.

The phorbasane skeleton (4) could be generated by polyene cyclization to give an ansellane type cationic intermediate (48) (Scheme 4)<sup>14,21</sup> which closes to an intermediate [2.2.2] fused bicyclic system (49). Proton migration would then give 50, Grob-like elimination of which gives phorbasane A (44). Dihydroxylation of 44 gives phorbasane B (46) before pinacol rearrangement/aromatization leads to isophorbasane A (46).<sup>14</sup>

## 2.4 Phoranes

Phorone A (51) was isolated in 2012 in South Korea by Kang *et al.* from a specimen of the marine sponge *Phorbas* sp.

(Fig. 7).<sup>14</sup> More recently in 2015, the isolation of phorone B (52) in the same country was reported by Shin *et al.* from the marine sponge *Clathria gombawuiensis*.<sup>18</sup> Phorones A and B (51 and 52) are regioisomers due to their aromatic oxidation pattern and are the only known natural products possessing the tetracyclic phorane skeleton (6), which is related to the ansellane skeleton by way of an additional C8–C19 junction.

The proposed biogenesis of the phorones suggests a key electrophilic aromatic substitution process to join the parent ansellane ring B to ring C (Scheme 5). Aromatisation of an alotane derivative would give phenol 53. The phorones then likely share a biogenesis similar to that seen with the ansellanes. Cyclisation would give drimane like cation 54 trapping of which by exogenous acetate leads to ansellone B (37). Alternatively the cation could be intramolecularly trapped *via* electrophilic aromatic substitution at either C19 or C15 leading to phorone A (52) and B (53) respectively. An alternative, and synthetically much more enticing pathway to the phorones might involve a polyene

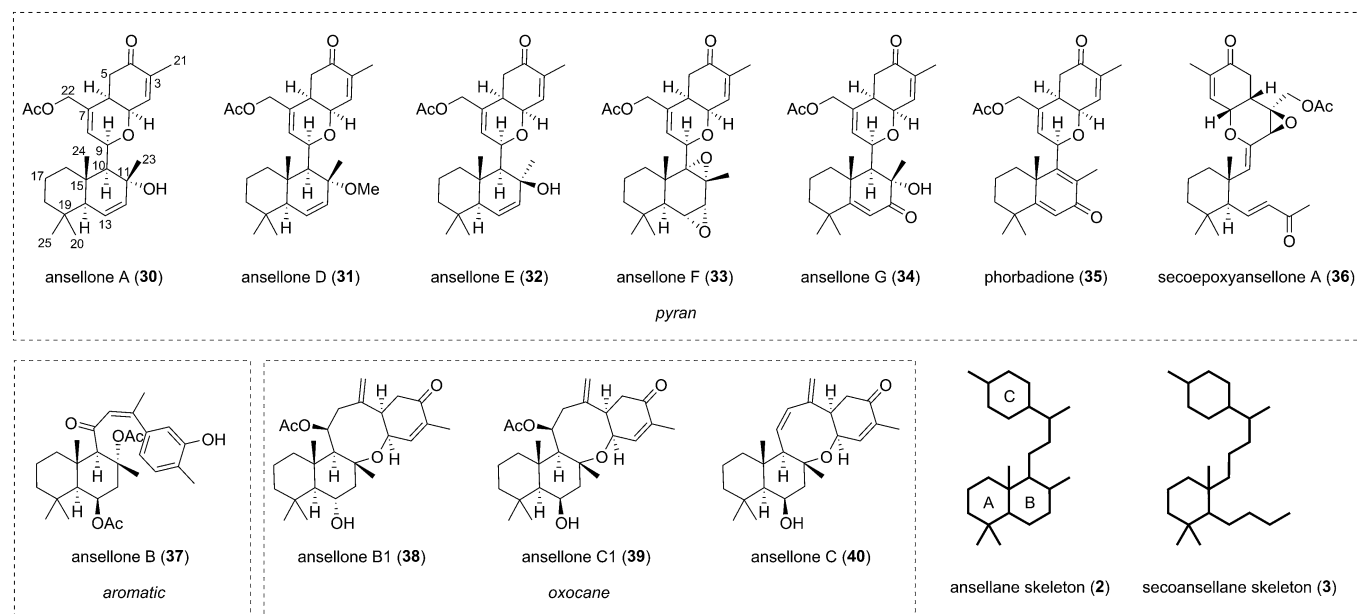
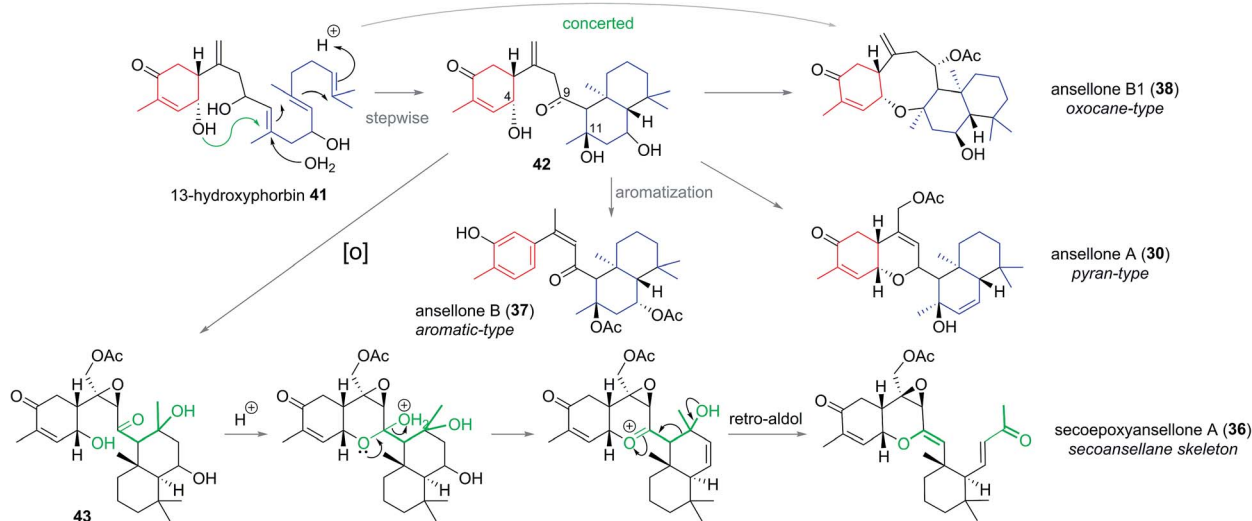


Fig. 5 The ansellane natural products.





Scheme 3 Proposed biogenesis of the ansellane and secoansellane family of natural product.

cyclisation<sup>22</sup> directly from 55 thereby avoiding intermediates such as 54.

## 2.5 Gombanes

In 2014 Shin *et al.* isolated gombaspiroketal A–C (56–58) from the marine sponge *Clathria gombawuiensis* (Fig. 8). These are the first and only examples of the bicyclic gombane carbon skeleton (7).<sup>23</sup> Being structurally analogous to the phorbaketals and alotaketals, gombaspiroketal A–C (56–58) share their common spiroketal and hydrobenzopyran moieties, but feature a novel, rearranged cyclohexenyl substituent attached at the C13 quaternary centre. Gombaspiroketal A and B (56 and 57) feature an unusual spiroketal-methoxy acetal, and are epimers at C13. Gombaspiroketal C (58) is the analogous spiroketal-hemiacetal of gombaspiroketal A. It is possible that the true natural products possess spiroketal-hemiacetal motifs, since methanolysis may have plausibly occurred during the methanolic sponge extraction procedure.

The gombaspiroketal likely share a very close biogenesis to the phorbaketals and alotaketals (whose biogenetic proposal has previously been discussed). The novel dimethylcyclohexenyl methylene motif is proposed to arise from cyclization and migration of the geranyl side chain of

phorbaketals A (11) or similar, from C16 to C13 (Scheme 6).<sup>18</sup> The resulting carbocation 59 would facilitate formation of the spiroketal-methoxy acetal *via* oxocarbenium ion 60. This rearrangement could plausibly occur at an earlier stage in their biogenesis *i.e.* before spiroketalization. The C16 acetal or hemiacetal group resides in the equatorial position, presumably to avoid 1,3-diaxial interactions with groups on the pyran ring.

## 2.6 Anvilanes

The *Phorbasp.* sp. of sponge continues to be a rich source of new sesterterpenoids. Andersen and co-workers isolated anvilones A (61) and B (62) in 2016, from a sample collected in British Columbian waters (Fig. 9). They were isolated alongside eight previously identified natural products of the alotane, ansellane, and secoansellane skeletons. These anvilones are the only isolated natural products of the anvilane skeleton, which features a fused *trans,trans*-6,6,6-tricycle. Anvilone B (61) is distinguished from anvilone A (62) by oxidation and acetylation at C1.<sup>13</sup>

The anvilane skeleton likely originates from polyene cyclization of an alotane (63). This cascade would install the tricyclic core of the anvilones with further modification through

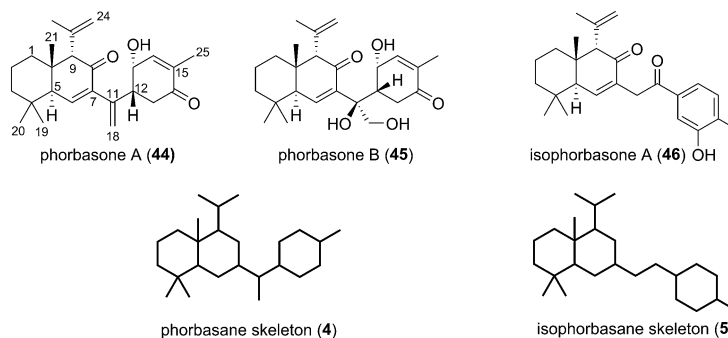
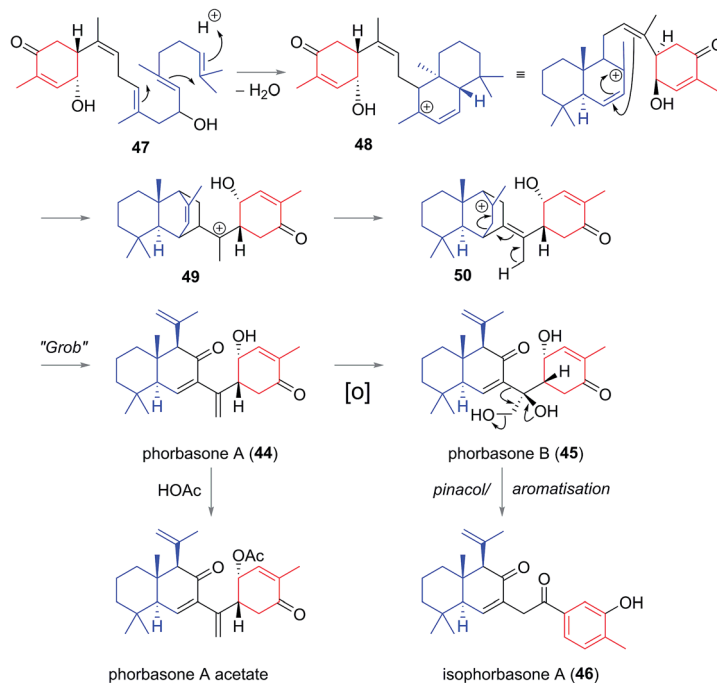


Fig. 6 The phorbasones and isophorbasones natural products.







Scheme 4 Proposed biogenesis of the phorbasanes and isophorbasanes.

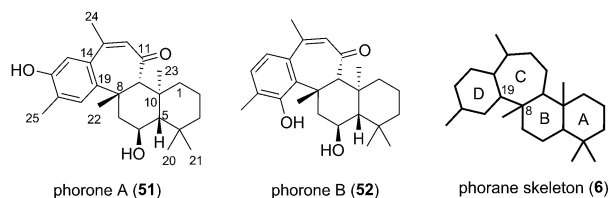


Fig. 7 The phorane duo of natural products.

oxidations and/or acetalisations leading to anvilones A or B (**61** or **62**) (Scheme 7).

### 3. Biological testing

Various biological investigations have revealed the remarkably diverse and potent bioactivities exhibited by the alotane family

of sesterterpenoids. Successful syntheses of alotaketal A (**9**),<sup>8</sup> phorbin A (**14**),<sup>24</sup> ansellones A (**30**), B1 (**38**), phorbadiene (**35**)<sup>20</sup> and phorbaketal A (**11**)<sup>8d,25</sup> (as well as approaches to its framework<sup>26</sup>) open up the possibility of future structure–activity relationship studies to explore the properties of alotane analogues.

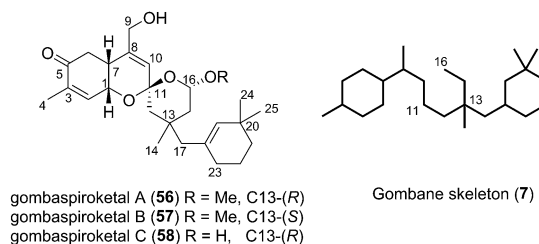


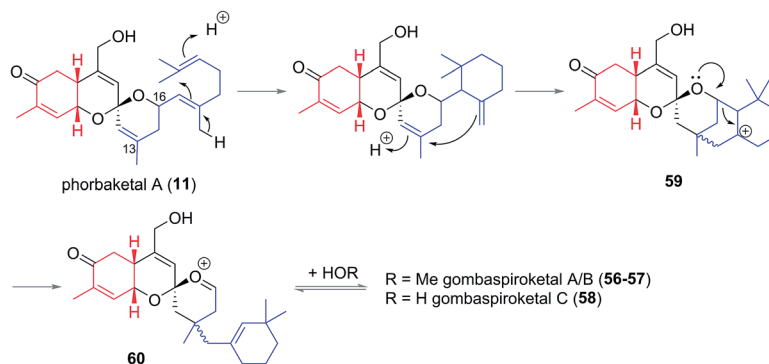
Fig. 8 The gombane natural products.



Scheme 5 Proposed biogenesis of the phorane natural products.







Scheme 6 Proposed biogenesis of the gombane natural products.

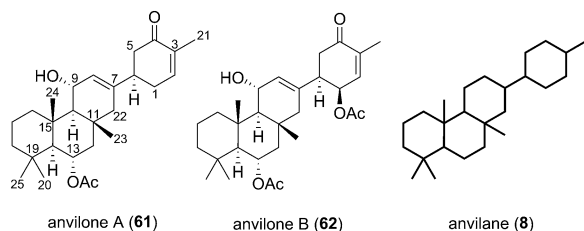


Fig. 9 The anvilane natural products.

### 3.1 cAMP activation

In addition to the cAMP activating ability of alotaketals A (9) and B (10), Andersen *et al.* also found that ansellone A (30) displayed comparable cAMP activation ( $EC_{50}$  14  $\mu\text{M}$ ) to that of forskolin in a HEK293 cell-based assay, however alotaketals A (9) remains the most potent modulator to be identified.<sup>15</sup> Modulation of the cAMP signalling pathway is used in stem cell techniques and is important for the development of treatments for several diseases including heart failure, cancer, and neurodegenerative diseases. As such, the development of new modulators of this pathway is potentially of high medicinal value (Scheme 2).<sup>27</sup>

### 3.2 Cytotoxicity

Cytotoxicity screening of phorbaketals A–C (11–13) by Rho *et al.* against human colorectal cancer HT-29, hepatoma cancer HepG2, and lung cancer A549 cell lines showed phorbaketals A (11) to have mild activity ( $IC_{50}$  11–12  $\mu\text{g mL}^{-1}$ ) towards all three cell lines, while phorbaketals B and C (12 and 13) were moderately active ( $IC_{50}$  12–460  $\mu\text{g mL}^{-1}$ ).<sup>9</sup>

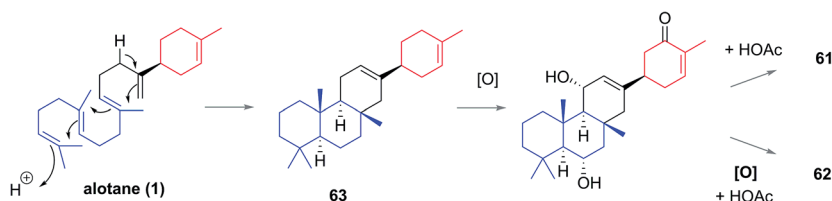
During screening of phorbaketals D–K (17–26) against four cancer cell lines, phorbaketals H and I (23 and 24) were active

against the A498 human renal cancer cell line ( $IC_{50}$  9.8 and 9.0  $\mu\text{M}$  respectively).<sup>10</sup> When considering structure–activity relationships Kang *et al.* noted that a hydroperoxy group on the side chain may be detrimental to cytotoxicity, as 21, 22, and 28 were inactive. This is supported by the observation that phorbaketals A–C (11–13) were cytotoxic towards all three human cancer cell lines.<sup>9</sup>

In a similar fashion, phorbaketals L–N (27–29) were screened for cytotoxicity and phorbaketals N (29) exhibited potent activity.<sup>11</sup> Phorbaketals N (29) displayed cytotoxicity against human pancreatic cancer cell line PANC-1 ( $IC_{50}$  11.4  $\mu\text{M}$ ), and the renal cancer cell lines A498 ( $IC_{50}$  18.7  $\mu\text{M}$ ) and ACHN ( $LC_{50}$  24.4  $\mu\text{M}$ ). It should be noted that phorbaketals N (29) was more cytotoxic than the FDA approved anti-cancer drug fluorouracil<sup>28</sup> against PANC-1 and thus could provide a useful novel drug lead for the treatment of human pancreatic cancers.

Despite its relatively simple framework, phorbin A (14) displayed micromolar cytotoxicity against MIA-paca ( $IC_{50}$  5.2  $\mu\text{M}$ ) and PANC-1 ( $IC_{50}$  7.8  $\mu\text{M}$ ) human pancreatic cancer cell lines as well as renal cancer cell lines A498 ( $IC_{50}$  4.9  $\mu\text{M}$ ) and ACHN ( $IC_{50}$  10.0  $\mu\text{M}$ ).<sup>10,29</sup> In terms of structure–activity relationship, this observed potency implies that the spiroketal moiety possessed by the phorbaketals may not be an important feature for anti-cancer activity.

Gombaspiroketal A–C (56–58) also exhibited moderate cytotoxicity in the A549 and K562 cell lines ( $LC_{50}$  0.85–2.02  $\mu\text{M}$  and  $LC_{50}$  0.77–4.65  $\mu\text{M}$ ), comparable to that of doxorubicin ( $LC_{50}$  0.79 and 0.70  $\mu\text{M}$  respectively).<sup>23</sup> Phorone B (53) and ansellone C (40) were also both found to be moderately cytotoxic towards AK549 and K562 cancer cell lines.<sup>18</sup>



Scheme 7 Proposed biogenesis of the anvilane natural products.



### 3.3 Effects on stem cell differentiation

Biological studies by Hong *et al.* have revealed that phorbaketal A (**11**) can promote osteogenic differentiation of human mesenchymal stem cells. In the presence of phorbaketal A (**11**), mesenchymal stem cells exhibited increased levels of differentiation markers such as osteocalcin, Dlx5, ALP, Runx2, and TAZ. These markers are associated with differentiation into the osteoblast lineage, which is important for bone reformation processes. Thus phorbaketal A (**11**) is potentially useful for research into anabolic therapeutics in bone diseases such as osteoporosis.<sup>30</sup>

Similarly to phorbaketal A (**11**), phorbasonone A (**44**) exhibited a distinct effect on bone reformation processes in a study by Rho *et al.*<sup>21</sup> In mesenchymal stem cells phorbasonone A (**44**) increased calcium deposition activity *via* upregulated gene expression of a range of osteoblast differentiation markers. Phorbasonone B (**45**) showed comparably low activity in these assays, indicating that the 1,2-diol motif disrupts interaction with the target.

Phorbaketal A (**11**) was also shown by Hong *et al.* to inhibit differentiation of mesenchymal stem cells into adipocytes. Similar to its effect on osteogenic differentiation, this activity arises from upregulation of markers which inhibit gene transcription required for differentiation into the adipogenic lineage. This activity indicates phorbaketal A (**11**) may be a useful lead for research into therapeutics to treat obesity.<sup>31</sup>

### 3.4 Anti-HIV activity

In 2016 Andersen *et al.* investigated *Phorbas* sp. metabolites as therapeutic leads towards the promising 'shock and kill' approach to a sterilizing HIV-1 cure.<sup>13</sup> The study found that alotaketals C and D (**16** and **17**), ansellone A (**30**) and anvilone A (**61**) activate latent proviral HIV-1 gene expression. Alotaketals C (**25**) showed latency reversal activity (LRA) (*ca.* 14% at 30  $\mu$ M) approximately 2.1-fold more potent than the control compound prostratin at the same concentration. Prostratin is now entering phase I trials as a potential HIV cure. It was also found that alotaketals D (**26**), ansellone A (**30**), and anvilone A (**61**) have LRA profiles comparable to that of the control prostratin. The alotaketals, ansellones, and anvilones, represent a new set of scaffolds that are promising leads for structure activity relationship development of LRA biological tools and drug candidates.

## 4. Summary and outlook

In this review we have presented a remarkable new family of biogenetically related sesterterpenoids isolated from a variety of marine sponges around the Pacific Rim. These have proven to be a rich source of structurally, biogenetically and biologically intriguing new compounds that are based on previously unseen carbon skeletons.

This new family of sesterterpenoids have novel scaffolds which exhibit diverse and potent bioactivities. Notably, alotaketals A (**9**) has multiple biological activities including potent activation of the cAMP signalling pathway. Other important

biological activity discovered includes cytotoxicity, various effects on stem cell differentiation and latent HIV-1 reactivation. Therefore the alotane and alotane derived natural products have potential use as drug leads in the treatment of multiple diseases including cancer, heart disease, obesity, osteoporosis and HIV.

The alotane skeleton is thought to be biogenetically derived from geranylarnesyl pyrophosphate (GFPP) and we have summarized its proposed biogenetic derivations to related sesterterpenoid skeletons as well as introduced our own biogenetic proposals. Identification of the organism(s) generating these secondary metabolites is yet to be conclusively determined, so far with suggestions by Rho *et al.* of a microbiological origin. We anticipate that the biogenetic proposals presented will inspire future total synthesis endeavours towards these natural products.

## 5. Conflicts of interest

There are no conflicts to declare.

## 6. Acknowledgements

We thank the University of Auckland for the award of a Doctoral Scholarship (MJ), Queen Mary University of London and the Engineering & Physical Sciences Research Council (EP/J50029X/1) for a DTA studentship and the Royal Society of New Zealand Marsden Fund (both to HS).

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