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A biomimetic approach towards phorone sesterterpenoids†

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We report an investigation towards a unified total synthesis of the Korean sponge derived sesterterpenoids, phorones A (1) and B (2), *via* a biomimetic strategy. This work has established a new synthetic strategy to the parent ansellane sesterterpenoid skeleton with unanticipated diversion to a biogenetically related pathway.

Introduction

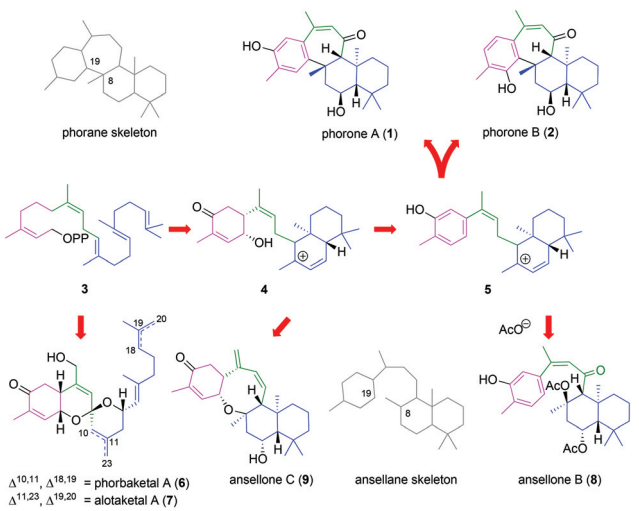
Phorones A (**1**) and B (**2**) are isoprenoid natural products and constitutional isomers which bear the unprecedented tetracyclic phorane carbon skeleton. Phorone A (**1**) was extracted from a sample of the marine sponge *Phorbas* sp. collected off the coast of Korea, and reported in 2012 by Nam, Kang and their co-workers.[1] More recently, the isolation of phorone B (**2**), which exhibits anti-cancer activity, was reported in 2015 by Woo *et al.*[2] from the Korean marine sponge *Clathria gombawuiensis*. While isolated from two distinct genera of sponge, the phorones are likely derived from a common biogenesis related to that of a large family of bioactive sesterterpenoids: encompassing the phorbaketals (**6**),[3] alotaketals (**7**)[4] and ansellones (**8**, **9**)[5] (Scheme 1) as well as the gombaspiroketals,[6] phorbasones[7] and isophorbasones[1] whose isolations have spawned multiple total synthesis efforts over recent years.[8]

A key proposed biogenetic step in the formation of the phorane skeleton from geranylfarnesyl pyrophosphate (**3**) involves intramolecular cyclization of the ansellane tertiary carbocation **5** *via* electrophilic aromatic substitution of the tethered phenol to give *para*- and *ortho*-adducts, as **1** and **2** respectively. Of note is the resulting stereochemical relationship between the seven-membered ring and drimane bicycle, since *cis*-annulation has not previously been reported. The isolation and structural assignments of ansellones B (**8**) and C (**9**) further signifies trapping of the putative tertiary carbocation with either a γ-hydroxycyclohexenone or exogenous acetate. The parent ansellane skeleton is devoid of the C8-19 bridge and so alternative nomenclature for the phorane skeleton is 8β-19-cycloansellane.

In the present work we have investigated a biomimetic synthesis of the phorone isoprenoids in order to elucidate key events in their biogenesis, confirm their assigned relative stereochemistry and assist future structure–activity relationship studies.

Results and discussion

In light of their proposed biogeneses, our retrosynthetic analysis of phorones A (**1**) and B (**2**) (Scheme 2) began with disconnection of the key C8–C19 bond bridging the decalin and aromatic systems.



Scheme 1 Proposed biogeneses of phorones and ansellones (OPP = pyrophosphate).

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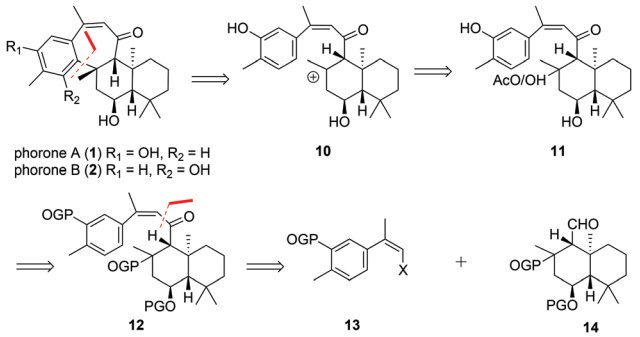


Scheme 2 Retrosynthetic analysis of phorones A (**1**) and B (**2**).

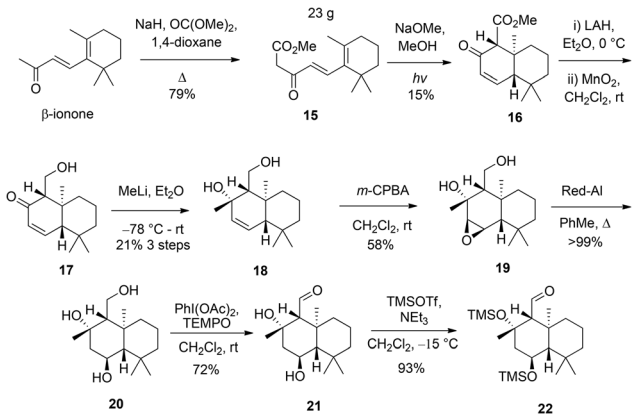
This gave synthon **10** which would enable trapping of the tertiary carbocation *via* electrophilic aromatic substitution of the phenol at the *ortho*- or *para*-positions to give **1** or **2** respectively. We anticipated that a mixture of regioisomers may form from this step. The formation of such a carbocation intermediate **10** could be achieved by treatment of a tertiary alcohol or acetate **11** with Lewis- or Brønsted acid. Construction of the ansellane skeleton **12** was planned to proceed *via* coupling of the (*Z*)-haloalkene **13** with the drimane aldehyde **14** by way of a halogen-metal exchange/electrophile trapping process.[9] The (*Z*)-haloalkene **13** would in turn be accessed by halo-olefination of a suitable acetophenone.

The synthesis of a drimane aldehyde such as **14** commenced by treatment of commercially available β-ionone with NaH in the presence of dimethylcarbonate to give the ester **15**, which could be accessed in >20 g. Photochemically-mediated cyclisation of the ester **15** gave enone **16** (Scheme 3).[10]

Enone **16** was then readily converted to the diol **18** in three steps by reduction with $LiAlH_4$, allylic alcohol oxidation and then nucleophilic addition using an excess MeLi.[9] Diol **18** was then oxidised with *m*-CPBA to give the epoxide **19** as a single diastereomer. The stereochemistry of the epoxide **19** was confirmed by X-ray crystallographic analysis (see ESI†). The observed non-chelation controlled diastereofacial selectivity *anti* to the pendant tertiary alcohol may be a consequence of unfavourable steric interactions between the axial methyl groups and the peracid. Following this, the epoxide **19** was reductively ring-opened using Red-Al in refluxing PhMe, to allow regiospecific formation of the desired 1,3-diol in quantitative yield (1,2-diol product was not observed) to give the triol **20**. The primary alcohol of triol **20** was selectively oxidised, in preference to the secondary and tertiary alcohols, using PhI$(OAc)_2$ with catalytic TEMPO, to the aldehyde **21**. The structure of the aldehyde **21** was confirmed by X-ray crystallographic analysis (Fig. 1, see ESI†) revealing the *syn*-relationship between the tertiary alchohol and the potentially epimerizable aldehyde, with the remaining secondary alcohol on the opposite face of the decalin system.

Following 8 synthetic steps without the need for protecting groups, silylation of the secondary and tertiary alcohols using standard silyl chloride and base combinations returned starting material only, perhaps reflective of a sterically demanding environment. However, rapid trimethylsilylation of both alcohols was achieved using TMSOTf to give the aldehyde **22** (*cf.* **14**) which was used to probe the envisaged coupling with the appropriate vinyl metal species.

The synthesis of a (*Z*)-haloalkene fragment such as **13** began with aromatic nitration of commercially purchased 4-methylacetophenone using HNO_3/H_2SO_4 to nitro compound **23** and hydrogenolysis of the nitro group to an aniline intermediate, before diazotisation and *in situ* hydrolysis finally gave phenol **24**.[11] O-Protection of **24** as the *tert*-butyldimethlsilyl ether using TBSCl in the presence of imidazole gave the siloxyacetophenone **25** (Scheme 4). There are scarcely any methods for the halo-olefination of acetophenones. Indeed, the use of standard halogenated Wittig and Horner–Wadsworth–Emmons reagents in combination with a range of bases was initially investigated but this resulted in either the return of starting materials or the observed formation of only traces of suspected alkenes. Of the few known methods for such a transformation we investigated a three-step process firstly reported by Barluenga[12] and later modified by Ando.[13] Treatment of acetophenone **25** with dibromomethyl lithium, formed through deprotonation of CH_2Br_2 with LiNi-Pr_2, facilitated conversion to alcohol **26**. The tertiary alcohol of **26** was then protected as the trimethylsilyl ether using TMSCl in the presence



Scheme 3 Synthesis of drimane aldehyde **21**.

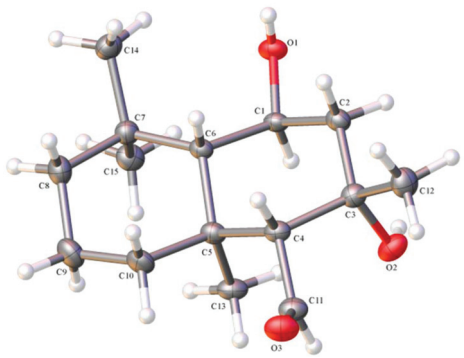


Fig. 1 ORTEP image of aldehyde **21**.

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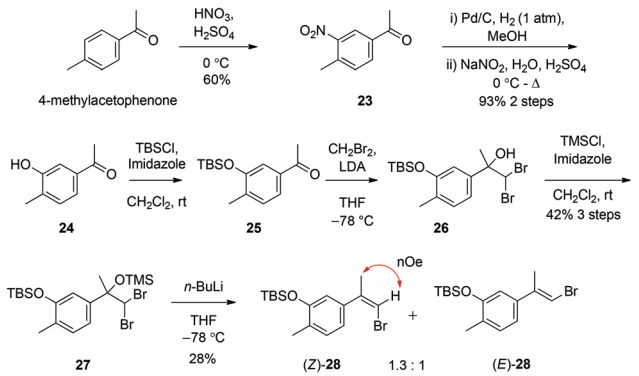
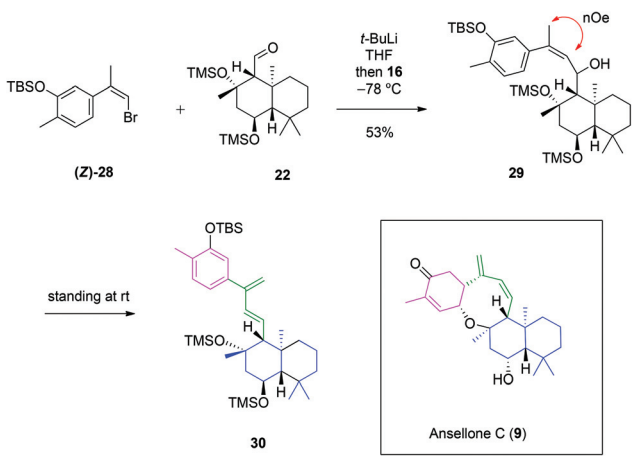


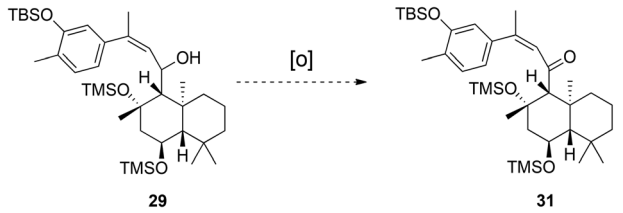
Scheme 4 Synthesis of (*Z*)-bromoalkene **28**.

of imidazole, to give *gem*-dibromide **27**. Finally, treatment of **27** with *n*-BuLi gave an isomeric mixture of bromoalkenes (*Z*) and (*E*)-**28** in a 1.3 : 1.0 ratio respectively. These apolar bromoalkenes were separated by careful column chromatography on standard silica gel, although this essential separation (which could not be achieved using basic alumina or other non-acidic stationary phases) resulted in apparent loss of large amounts of material through degradation during elution. The stereochemistry of each isolated alkene isomer was determined by NOESY experiments (see ESI†).

Having achieved the synthesis of drimane aldehyde **22** and (*Z*)-bromoalkene **28**, work was focused upon their convergence (Scheme 5). Treatment of (*Z*)-**28** with *t*-BuLi at −78 °C caused bromine–lithium exchange to form an organolithium species, to which drimane aldehyde **22** was added. The ansellane alcohol **29** was isolated as a single diastereomer. The stereochemistry of the secondary alcohol was not determined as it would be oxidised to a ketone in the next step. Retention of the crucial *Z*-alkene was confirmed through a NOESY experiment (see ESI†). This point denotes a new chemical synthesis of the novel ansellane skeleton. Following storage at room



Scheme 5 Synthesis of ansellane alcohol **29** and diene **30**.



Scheme 6 Attempted oxidation of allylic alcohol **29**.

temp for 72 hours we observed that alcohol **29** degraded to a complex mixture. Isolation of the major degradation product was achieved and after thorough spectroscopic analysis identified as ansellane diene **30**, bearing a 1,3-diene motif. This seemingly labile transformation involved elimination of the secondary alcohol. It was suggested that this process may reflect a sterically demanding environment of the alcohol, whose elimination is thermodynamically favoured, furthermore with extended π-conjugation. It was interesting to observe a similar 1,3-diene moiety in the biosynthetically related ansellone C (**9**) (which was reported five months after our synthesis of **30**). We hypothesise that the 1,3-diene moiety may be acquired in nature through an analogous deoxygenative elimination process.

After this set-back, storage of the ansellane alcohol in a −30 °C freezer and using within 3/4 days allowed a short interval for probing of oxidation of the allylic alcohol **29** to enone **31**. To our surprise the oxidation of the secondary alcohol could not be achieved using any conventional methods (Dess-Martin's periodinane, MnO_2, IBX and $PhI(OAc)_2$/TEMPO), returning starting material only. It was found that Swern oxidation assisted degradation to a mixture of products of a virtually identical composition to that previously observed upon storage of **29** at room temperature (Scheme 6).

Conclusions

These synthetic accomplishments leading to ansellane alcohol **29** and ansellane diene **30** provide novel chemical syntheses of the important ansellane sesterterpenoid skeleton. Key steps include diastereofacial selective epoxide installation to **19** and subsequent reductive epoxide opening to **20**, before *t*-BuLi-mediated addition of (*Z*)-bromoalkene **28** to aldehyde **22**. This work will provide valuable guidance for future total synthesis endeavours of phorone, ansellone and related natural products, in which we anticipate sustained interest. The labile transformation of ansellane alcohol **29** into ansellane diene **30** has shed some light on the biogenesis of this family of sesterterpenoids, and may provide guidance to related future synthetic endeavours.

Conflicts of interest

The authors have no conflicts to declare.

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