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Biomimetic syntheses of ineleganolide and sinulochmodin C from 5-episinuleptolide via sequences of transannular Michael reactions

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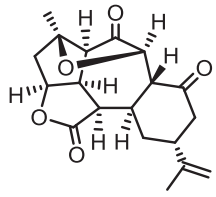
ABSTRACT

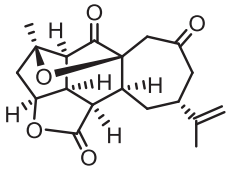
Treatment of a solution of the macrocyclic norcembranoid **7** with lithium hexamethyldisilazide in THF at −78 °C to 0 °C, leads to the polycyclic norcembranoids ineleganolide **1** and sinulochmodin C (**2**) (65%), which are found in the corals *Sinularia inelegans* and *Sinularia lochmodes*, respectively. The conversions are believed to be biomimetic, and occur by successive transannular Michael reactions in **7**. Under different temperature conditions the novel polycycle **30** is the main product, alongside small quantities of **1** and **2**. The polycycle **30** is possibly produced from ineleganolide **1**, following a reverse oxy-Michael reaction and two successive aldol reactions. The significance of the synthesis of ineleganolide **1**, sinulochmodin C (**2**) and the structure **30** from 5-episinuleptolide **7**, to the likely biosynthesis of the related norcembranoids scabrolide A (**3**), scabrolide B (**4**) and horiolide **31** found in *Sinularia* sp. is discussed.

1. Introduction

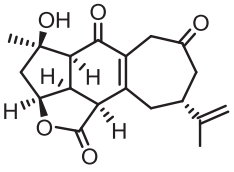
Ineleganolide **1** and sinulochmodin C (**2**) are members of a group of novel polycyclic norcembranoids, which are found exclusively in soft corals of the genus *Sinularia*. Ineleganolide **1** was first reported in 1999 and was isolated from the Taiwanese coral *Sinularia inelegans*.[1] It was later found alongside scabrolide A (**3**) and scabrolide B (**4**) in *Sinularia scabra*,[2] also from Taiwan.[3] Sinculochmodin C (**2**) was reported more recently, in 2005, from *Sinularia lochmodes*, collected off the southernmost tip of Taiwan.[4] Sinulochmodin C (**2**) and the scabrolides **3** and **4** have structures, which are based on the linear fusion of five-, six- and seven-membered carbocyclic rings linked to a five-ring lactone. By contrast, ineleganolide **1** has an angular fusion of five-, seven- and six-membered carbocyclic rings, linked to the same five-ring lactone. However, both ineleganolide **1** and sinulochmodin C (**2**) also feature an interesting five-ring ether bridge linking two of the carbocyclic rings in their structures, which is not found in the scabrolides **3** and **4**.[5] The norcembranoids **1**, **2**, **3** and **4** have a number of structural features in common with the perhaps better-known C_{20}-polycyclic cembranoid diterpenes mandapamate **5**[6] and rameswaralide **6**,[7] which are also found in *Sinularia* sp.



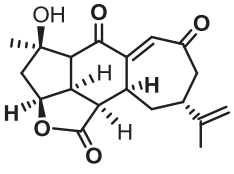
1, Ineleganolide



2, Sinulochmodin C



3, Scabrolide A



4, Scabrolide B

Soft corals dominate the biomass in coral reef environments, and *Sinularia* sp. are particularly abundant in Indo Pacific reefs. Many cembranoid metabolites isolated from *Sinularia* sp., including the metabolites **1**–**6**, have been found to exhibit a wide range of biological activities, e.g., antimicrobial, anti-inflammatory and cytotoxicity. Indeed, these features have been a significant motivation for studies of their synthesis, as possible leads for new therapeutic agents.[8] It is surprising, therefore, that no synthetic studies directed towards the polycyclic norcembranoids **1**–**4** and other members of this intriguing group of biologically active compounds have been forthcoming. By contrast, synthetic investigations towards the polycyclic cembranoid rameswaralide **6**[9] and its relatives,[10] some of which have been based on biosynthesis speculation, have been

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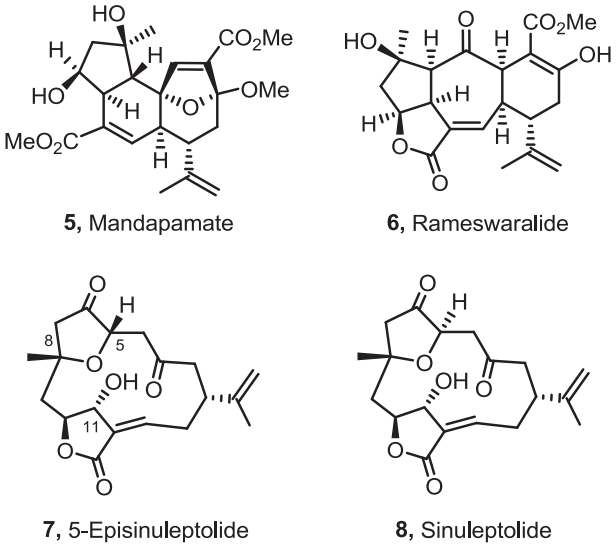
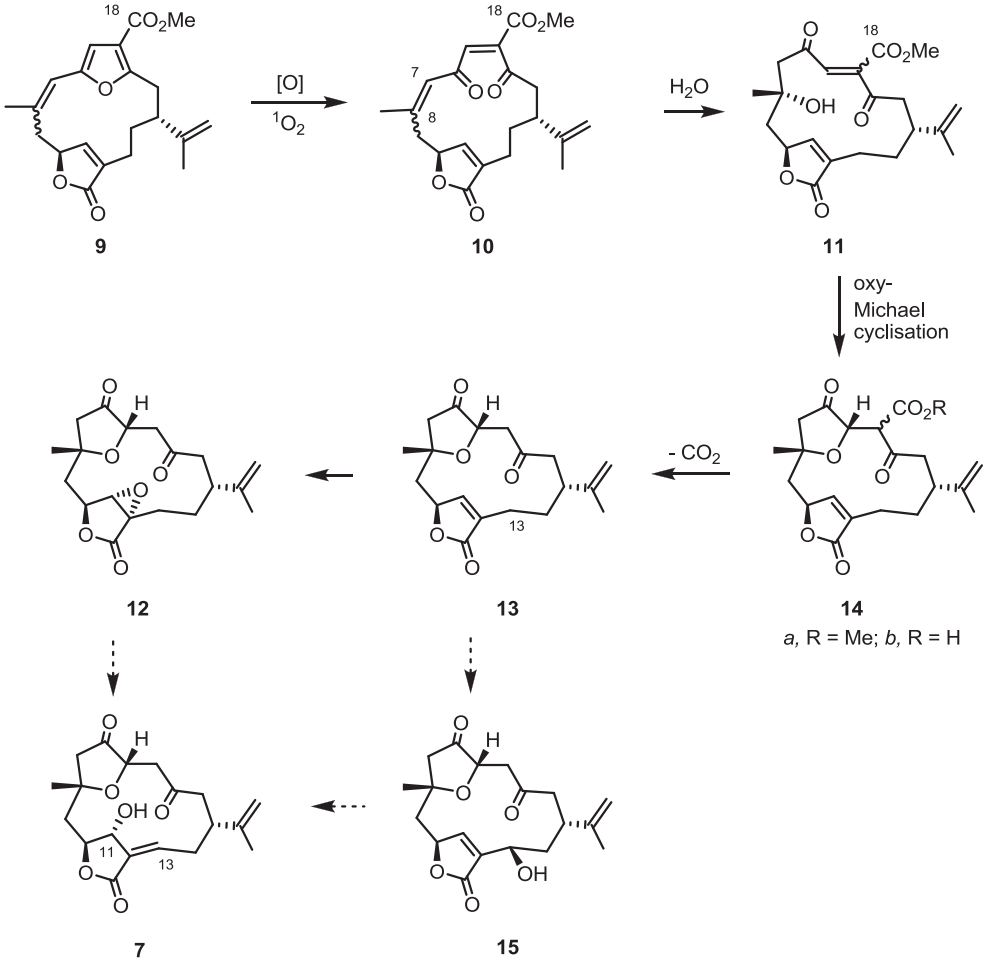
published in the recent literature.[11] In this paper, we describe concise syntheses of ineleganolide **1** and sinulochmodin C (**2**), based on our proposal that they are both biosynthesised in *Sinularia* sp., from a common 14-membered macrocyclic norcembranoid congener, by unique sequences of transannular anionic carbon-to-carbon bond forming reactions.

2. Biosynthesis speculation and retrosynthetic analysis

Ineleganolide **1**, sinulochmodin C (**2**) and the scabrolides **3** and **4** co-occur with some macrocyclic 3(2*H*)-furanone-based norcembranoids in *Sinularia* sp., the most prominent of which is 5-episinuleptolide **7**. 5-Episinuleptolide **7** was the first norcembranoid to be identified in nature, and was isolated from *Sinularia leptoclados* collected off the coast of Magnetic Island, Australia by Bowden et al. in 1978.[12] In more recent years a number of diastereoisomers of **7**, i.e., epimers at C5, C8 or C11, e.g., 'sinuleptolide' **8**,[13] have also been found in several different species of *Sinularia*.[14,15]

5-Episinuleptolide **7**, and its naturally occurring diastereoisomers, are related biogenetically to the ubiquitous C_{20}-macrocyclic cembranoid diterpenes present in corals, by lacking the C18 carbon substituent (cembranoid numbering) in the latter structures. By far the largest group of C_{20}-macrocyclic cembranoids to be characterised are furanobutenolide-based compounds,[16,17] e.g., deoxypukalide **9**,[18] and these metabolites would seem to be the most obvious precursors to the 3(2*H*)-furanone-based macrocyclic norcembranoids, viz. **7**, in vivo. We have proposed that the loss of the C18 carbon substituent in the C_{20}-furanocembranoids, viz. **9**, leading to macrocyclic norcembranoids in *Sinularia*, originates from initial oxidation and hydrolysis of the alkenylfuran unit in **9**, triggered by sunlight—generated singlet oxygen (Scheme 1).[19] Thus, in one process oxidative cleavage of the furan ring in **9**, followed by facial-selective hydration of the C7—C8 alkene bond in the resulting dienedione **10** would first lead to the hydroxyl-substituted enedione **11**. An intramolecular oxy-Michael type cyclisation within **11** would next lead to formation of





Scheme 1. Proposal for the origin of 5-episinuleptolide **7** from the furanobutenolide-based cembranoid **9** involving loss of the C18 CO_2Me substituent in the 3(2*H*)-furanone intermediate **14a**, followed by oxidation of the resulting metabolite **13** (to **12** and/or **15**) and rearrangement.