Tetrahedron 67 (2011) 10045–10052

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

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

Yi Li, Gerald Pattenden *

School of Chemistry, University of Nottingham, University Park, Nottingham NG7 2RD, UK

ARTICLE INFO

Article history:
Received 29 July 2011
Received in revised form 11 September 2011
Accepted 12 September 2011
Available online 1 October 2011

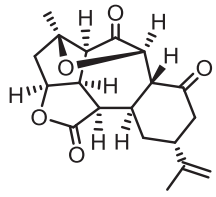
Keywords:
Norcembranoid
Biomimetic synthesis
Transannular cyclisation
Ineleganolide
Sinulochmodin C

ABSTRACT

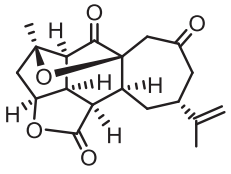
Treatment of a solution of the macrocyclic norcembranoid **7** with lithium hexamethyldisilazide in THF at −78 °C to 0 °C, leads to the polycyclic norcembranoids ineleganolide **1** and sinulochmodin C (**2**) (65%), which are found in the corals *Sinularia inelegans* and *Sinularia lochmodes*, respectively. 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

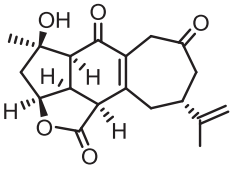
Ineleganolide **1** and sinulochmodin C (**2**) are members of a group of novel polycyclic norcembranoids, which are found exclusively in soft corals of the genus *Sinularia*. Ineleganolide **1** was first reported in 1999 and was isolated from the Taiwanese coral *Sinularia inelegans*.[1] It was later 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.



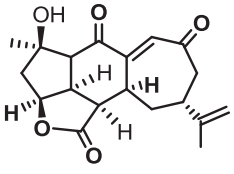
1, Ineleganolide



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

* Corresponding author. Tel.: +44 115 951 3530; e-mail address: gp@nottingham.ac.uk (G. Pattenden).

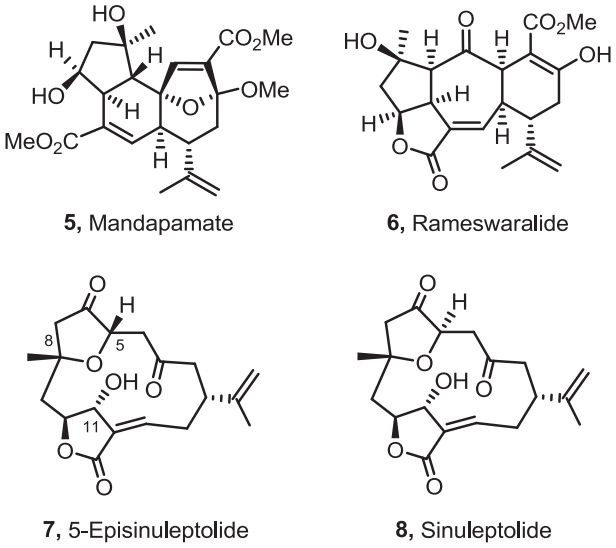
0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.09.040

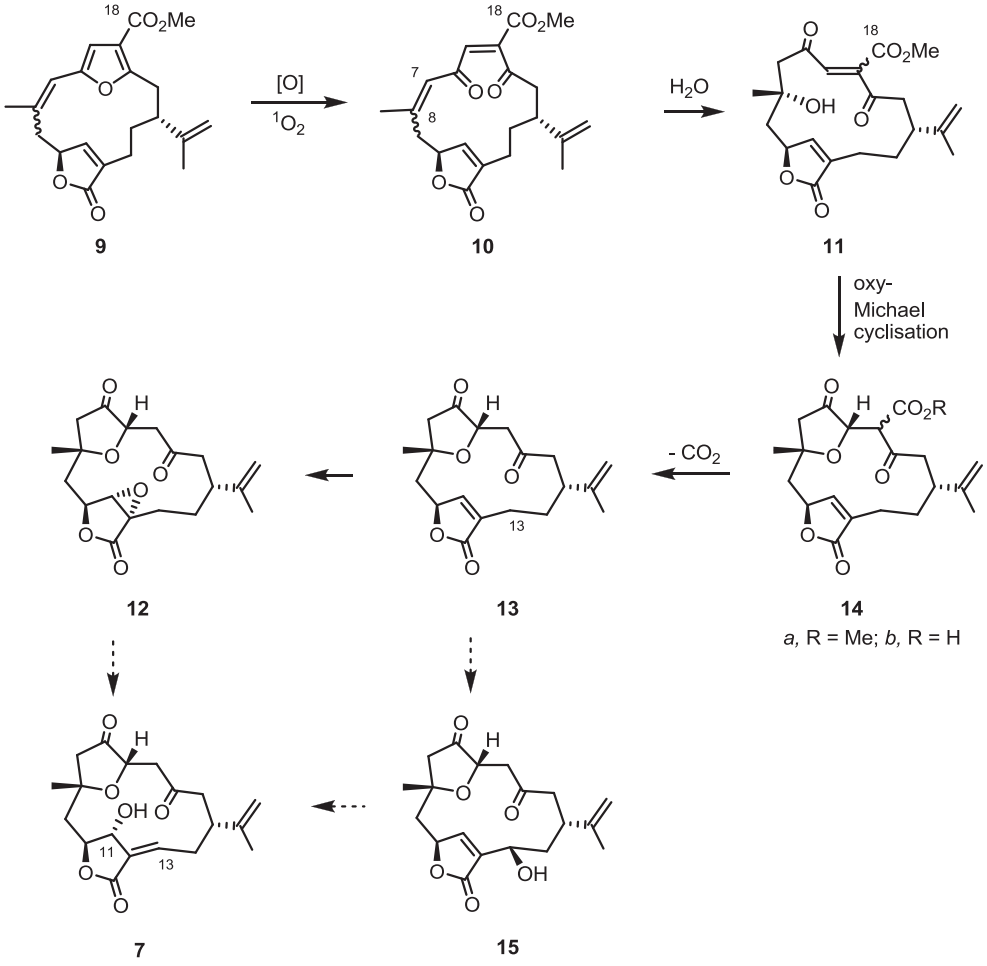
published in the recent literature.[11] In this paper, we describe concise syntheses of ineleganolide **1** and sinulochmodin C (**2**), based on our proposal that they are both biosynthesised in *Sinularia* sp., from a common 14-membered macrocyclic norcembranoid congener, by unique sequences of transannular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

the 3(2*H*)-furanone intermediate **14a**. Hydrolysis of the methyl ester group in **14a** in vivo, followed by decarboxylation of the resulting β-keto acid **14b** with an appropriate decarboxylase, would then produce the macrocyclic norcembranoid **13**.

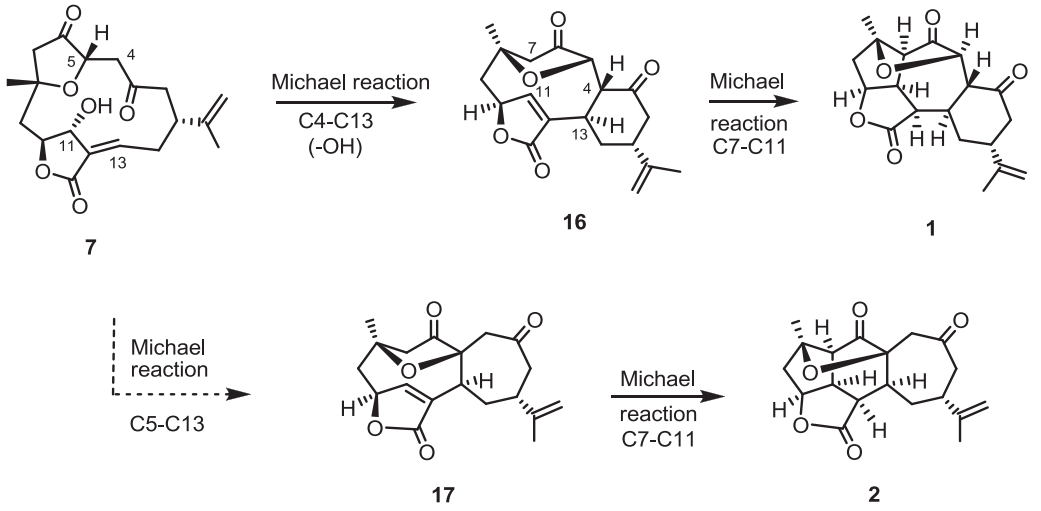
Interestingly, the macrocyclic norcembranoid **13** has been isolated from *Sinularia numerosa* collected in Palau (Belau) in the Western Caroline Islands, alongside the sinuleptolides **7** and **8**, and the C11,C12 epoxide **12** corresponding to **13**.[14a] It seems possible therefore that the allyl alcohol functionality between C11 and C13 in 5-episinuleptolide **7** has its origins in a base-catalysed opening of the epoxide ring in **12**. Alternatively, the same functionality could arise from the butenolide-based metabolite **13**, after enzymatic hydroxylation at C13 and allylic transposition of the resulting allyl alcohol **15** (Scheme 1).[19,20]

With the co-occurrence of ineleganolide **1** and sinulochmodin C (**2**) with 5-episinuleptolide **7** in *Sinularia*, it seems likely that both of the polycyclic metabolites **1** and **2** have their origins in **7** in vivo by successive transannular Michael reactions involving the nucleophilic centres at C4, C5 and C7 and the electrophilic centres at C11 and C13 in the macrocycle **7**. Thus, for example, a transannular Michael reaction between C4 and C13 in 5-episinuleptolide **7**, accompanied by displacement of the oxy group at C11, might first lead to the cyclohexanone intermediate **16** (Scheme 2). A second transannular Michael reaction between C7 and C11 in **16** would then

3. Results and discussion

We obtained a sample (~10 mg) of 5-episinuleptolide **7**, isolated from *Sinularia* sp., through the generosity of Professor J.-H. Sheu (Taiwan). Since we found that 5-episinuleptolide itself was recovered unchanged on treatment with bases, we attempted to prepare its mesylate derivative by treating **7** with methanesulfonyl chloride and triethylamine in THF at −20 °C. To our surprise however, we instead obtained a low yield of the novel enol lactone structure **18**, as a labile oil. The enol lactone **18** is presumably derived from **7** after formation of the corresponding mesylate, followed by in situ deprotonation at C10 and elimination of methanesulfonic acid. In passing, this outcome was interesting in the context of the possible origin of the unusual keto ester-containing norcembranoid **19**, which has been isolated alongside 5-episinuleptolide **7**, as a minor metabolite from some species of *Sinularia*.[14a] Thus, we surmise that the keto ester-containing norcembranoid **19** is derived from 5-episinuleptolide **7** in vivo by methanolysis, accompanied by opening of the lactone ring in the enol lactone intermediate **18**. Unfortunately, the dearth of material did not allow us to thoroughly examine this proposition in any detail in vitro.

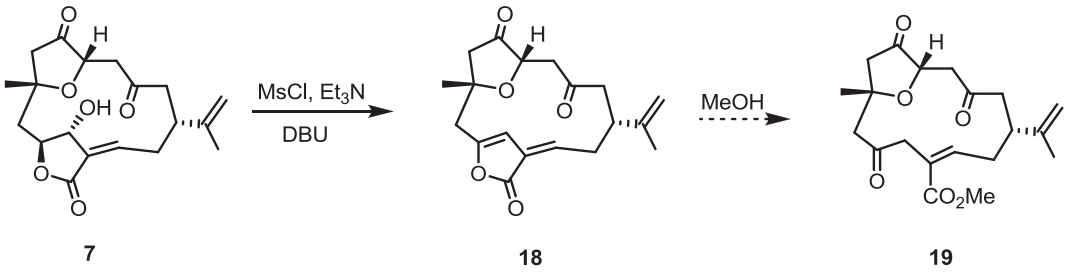
We next decided to prepare the acetate **20** of 5-episinuleptolide, which, by contrast, was smoothly accomplished, in excellent yield, by straightforward treatment of a solution of **7** in DCM with acetic an-

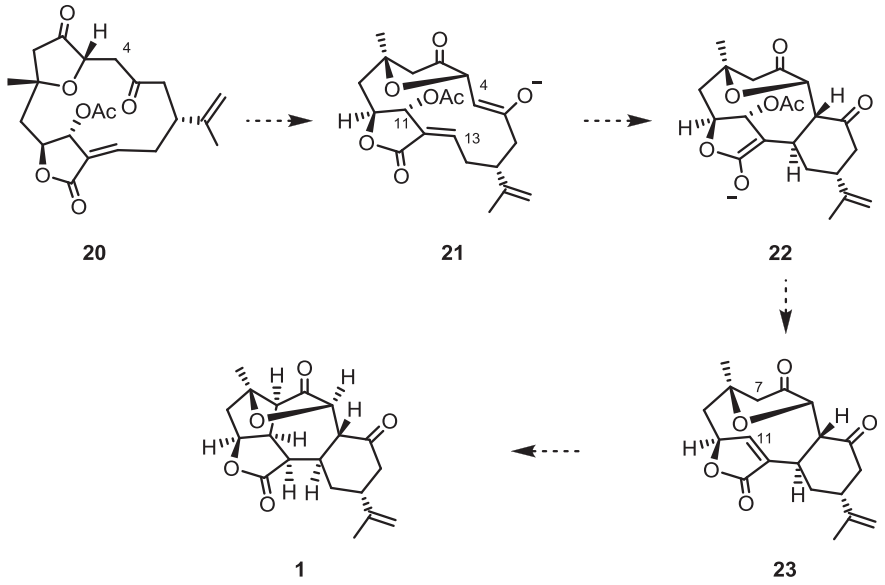


Scheme 2. Proposals for the origin of ineleganolide **1** and sinulochmodin C (**2**) from 5-episinuleptolide **7** in *Sinularia*.

complete the tricyclic ring system in ineleganolide **1**. In a similar manner, a transannular Michael reaction between C5 and C13 in **7** could first lead to the cycloheptanone intermediate **17**, which, in a second transannular Michael reaction involving C7 and C11 would produce sinulochmodin C (**2**). Although there is little way of predicting, a priori, the selectivity and chronology of these anionic processes in vivo, we now describe some studies of the reactions of 5-episinuleptolide **7**, in basic media, which have given credence to the aforementioned biosynthesis speculations to **1** and **2**.

hydride in the presence of triethylamine. Much to our satisfaction, when we treated a solution of the acetate **20** in THF at −78 °C with lithium hexamethyldisilazide (LiHMDS, 5 equiv), and allowed the mixture to warm-up to 0 °C and then left it at 0 °C for 7 h, work-up and chromatographic analysis showed the presence of essentially one major product. Furthermore, this product co-chromatographed with, and exhibited the same MS data as a sample of authentic, naturally derived ineleganolide **1** in HPLC–MS analysis. In addition, the ^{1}H NMR spectrum of the crude product displayed many

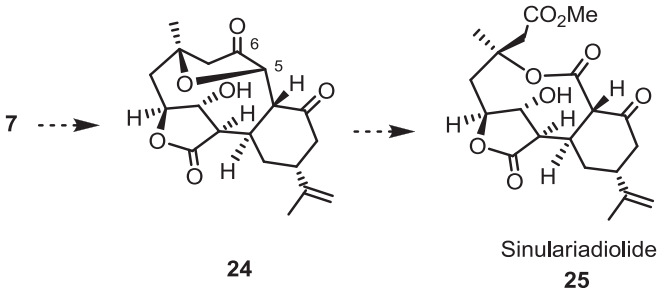




Scheme 3. Conversion of 5-episinuleptolide acetate **20** into ineleganolide **1** in the presence of LiHMDS.

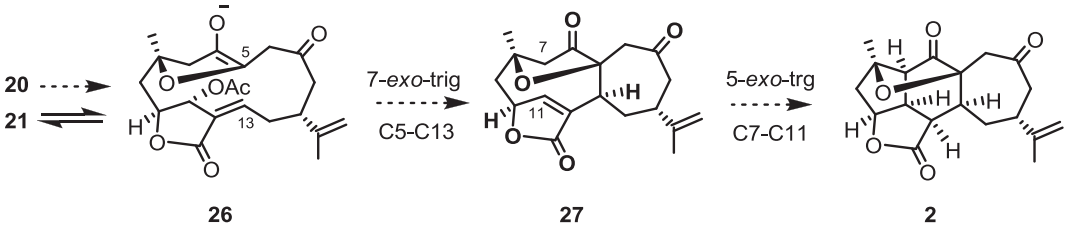
absorptions, which were superimposable on the same resonances in the spectrum of natural ineleganolide **1**. Nevertheless, the synthetic ineleganolide was not pure and closer analysis of the ^{1}H NMR spectrum showed some additional resonances, which were coincident with those reported for natural sinulochmodin C (**2**). The crude product was therefore subjected to further careful chromatography, which gave ineleganolide **1** as the main product and sinulochmodin C (**2**) as the minor product. The synthetic compounds displayed relevant ^{1}H and ^{13}C NMR spectroscopic data, which were identical with those reported for the natural products isolated from *Sinularia* sp.

The seemingly straightforward one-pot conversion of 5-episinuleptolide acetate **20** into ineleganolide **1** and sinulochmodin C (**2**) in the presence of LiHMDS, is really quite remarkable. The conversions also provide convincing support for our proposed biosynthetic routes to **1** and **2** from 5-episinuleptolide **7** in *Sinularia*. Thus, we believe that the conversion of the acetate **20** of 5-episinuleptolide into ineleganolide **1**, for example, is triggered by deprotonation at the sterically more assessable C4 centre in **20**, and that the resulting enolate **21** next undergoes a transannular 6-*exo-trig* (Michael) reaction into C13 leading to the new enolate **22** (Scheme 3). Displacement of the acetoxy group at C11 in **22**, would then produce the substituted cyclohexanone **23** as the most likely central intermediate. Deprotonation at C7 in **23**, followed by a second transannular 5-*exo-trig* (Michael) cyclisation into C11 would then lead to ineleganolide **1** (Scheme 3). Interestingly, prior to the discovery of ineleganolide **1**, the unusual cyclohexanone-containing metabolite sinulariadiolide **25** was reported alongside 5-episinuleptolide **7** in an Okinawa *Sinularia* species.[21] Furthermore, it was suggested that the metabolite could arise via oxidative cleavage of the C5–C6 bond in the intermediate **24** in vivo, which has structural features in common with **23**.

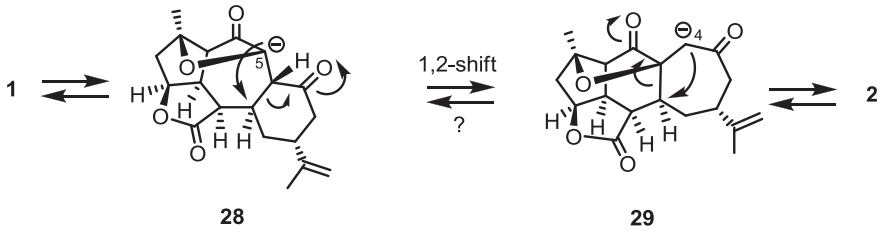


It seems reasonable to presume that sinulochmodin C (**2**) is derived from 5-episinuleptolide acetate **20** in a similar sequence to that of ineleganolide, but involving the enolate **26** arising from equilibration of **21** or direct deprotonation at C5 in **20**, followed by sequential 7-*exo-trig* transannulation linking C5–C13 (to give **27**) and 5-*exo-trig* transannulation involving C7 and C11 (Scheme 4). This may not be the complete picture however since there is a possibility that ineleganolide **1** could act as precursor to sinulochmodin C (**2**) by, for example, carbanion formation at C5, i.e., **28**, followed by 1,2-shift and expansion/contraction of its 6,7-ring system. Likewise, sinulochmodin C (**2**) could be formed first from the acetate **20**, and its carbanion at C4, i.e., **29**, might then undergo a similar 1,2-shift and contraction/expansion of its 7,6-ring system, leading to ineleganolide **1**.

Further insight into the remarkable chemistry of 5-episinuleptolide acetate **20** in the presence of base was obtained when it was treated with NaHMDS instead of LiHMDS and under different temperature conditions. Thus, when a solution of the acetate **20** in THF at −40 °C (rather than −78 °C) was treated with NaHMDS, and the mixture was allowed to warm-up to −10 °C it became dark yellow in colour. After work-up at −10 °C (rather than



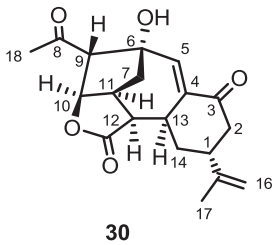
Scheme 4. Proposed origin of sinulochmodin C (**2**) from **20** in the presence of LiHMDS.

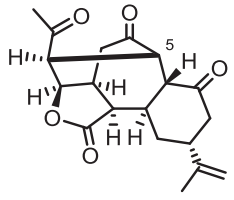


0 °C) followed by chromatography, a new polycyclic norcembranoid was isolated as a colourless gum in 75% yield; only very small amounts of ineleganolide and sinulochmodin C were detected amongst the crude reaction products.

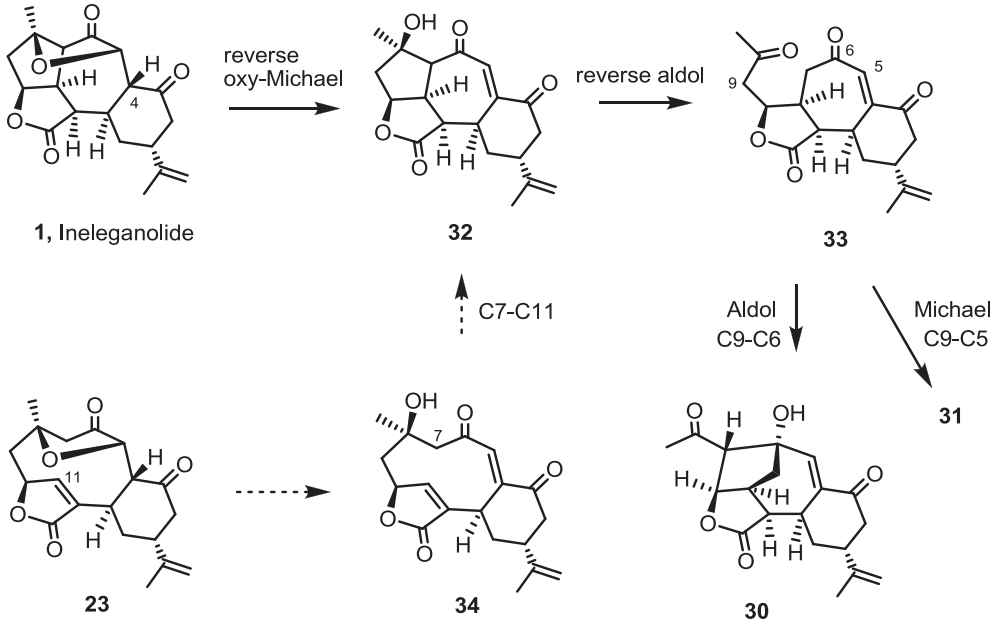
The new polycyclic norcembranoid exhibited a molecular ion at *m*/*z* 353.1362 $[M+Na]^+$ in its high resolution MS, corresponding to the molecular formula $C_{19}H_{22}O_5$. The ^{13}C NMR spectrum showed signals for 19 carbon atoms, and the DEPT spectra revealed the presence of 2 methyls, 4 methylenes, 7 methines and 6 quaternary carbons. The ^{13}C NMR signals at δ 207.9, 197.8, and 177.7 were attributable to carbonyl groups associated with a saturated ketone, an α,β-conjugated ketone, and a lactone, respectively. The resonance at δ 82.0 (s) was associated with a quaternary carbon centre attached to oxygen, and the sp^2 carbon signals at δ 145.5 (s), 112.4(t), associated with ^1H NMR resonances at δ 4.90, 4.50 (olefinics) and δ 1.81 (quaternary Me), established the presence of an isopropenyl group in the new structure; these assignments were confirmed by $^1H-^1H$ COSY and HMQC correlations. The second quaternary methyl group absorbed at δ 2.31 in the proton spectrum, and correlated with a methyl ketone group. A broad signal at δ 2.39 showed strong NOESY correlations with H_2O in $CDCl_3$, which supported the presence of a hydroxyl group. The bowl-shaped polycyclic structure **30** followed for the new compound on the basis of the above observations, and careful examinations of 2D NMR spectra and $^1H-^1H$ COSY and HMBC correlations (see Supplementary data).

The relative stereochemistries of the seven chiral centres in **30** followed from analysis of the NOE correlations observed in the NOESY spectrum in association with studies of molecular models. The NOE interactions between H10 and H11, H11 and H12, H12 and H13 indicated that the protons associated with C10, C11, C12 and C13 should all be *syn* to each other. The proton resonance at C9 appeared as a singlet and exhibited only a weak correlation with H10, implying that these protons were *anti* to each other.





This new, and intriguing structure **30** has not been reported in *Sinularia*, but it shares some structural features with the polycyclic norcembranoid known as horiolide **31**, which was isolated from *Sinularia* species collected off the coasts of the Andaman and Nicobar Islands in the Indian Ocean.[22] We suggest that the structure **30** could have its origins in ineleganolide **1** or perhaps in the substituted cyclohexanone intermediate **23**, which we have implicated in its biosynthesis (see Scheme 3). Thus, deprotonation at C4 in ineleganolide **1**, followed by a reverse oxy-Michael (ElCB) reaction would first produce the enedione-containing intermediate **32** (Scheme 5). A reverse aldol reaction in **32** would next produce the trione **33**, which could then undergo aldolisation involving C6 and C9 leading to the polycycle **30**. Correspondingly, a competitive 6-*exo*-*trig* Michael reaction involving C5 and C9 in **33** would lead to horiolide **31**. It is also conceivable that the enedione-containing structure **32** could have its origins in compound **34** resulting from a reverse oxy-Michael reaction in the purported cyclohexanone intermediate **23** between 5-episinuleptolide acetate and ineleganolide (cf. Scheme 3). This process would require a perhaps



Scheme 5. Proposal for the formation of the polycylic norcembranoid **30** from ineleganolide **1**.

difficult transannular Michael reaction between C7 and C11 in **34**. The proposed reverse oxy-Michael reaction from ineleganolide **1** leading to **32**, would also explain the likely origin of scabrolide B (**4**) from a similar reverse oxy-Michael reaction in sinulochmodin C (**2**) in vivo. Subsequent isomerisation of the alkene bond in **4** would then produce scabrolide A (**3**).

4. Conclusions and comment

The subtleness and balance of the competing ionic reactions in the different reaction conditions leading to ineleganolide **1**, to sinulochmodin C (**2**) or to the structure **30** from 5-episinuleptolide acetate **20** beggers belief somewhat. The outcomes reinforce however what we already know, in the annals of carbanion chemistry, concerning the importance of substrate structure, reaction media, temperature, kinetics, and the nature of the base used, in determining the destinations of competing, and reversible, aldol and Michael reactions in synthesis. Clearly, more studies are required with the sinuleptolides **7** and **8** before we can acquire a deeper understanding of the complexities of the anion chemistry associated with these metabolites in vivo. These studies can only be made however when further quantities of these macrocyclic norcembranoids become available to us.

The origin of sinulochmodin C (**2**) in vivo is perhaps especially interesting, since this metabolite occurs alongside 5-episinuleptolide **7**, and the novel isocembranoid **35** and the dimeric norcembranoid **36** in *S. lochmodes*.[4] This interesting coincidence supports the notion that a radical centre at C5 in 5-episinuleptolide, i.e., **37**, possibly derived from **35**, is the likely precursor to the dimer **36** and, by inference, possibly to sinulochmodin C (**2**) in *S. lochmodes*.[19] The carbon radical centre at C5 in **37** would be stabilised by the captodative effect and, as such, would be prone to dimerisation (to **36**).[23] In addition, the same radical centre could take part in a transannular 7-*exo*-*trig* cyclisation with C13 accompanied by displacement of the oxy centre at C11 in **37** leading to the cycloheptanone **17**. A second (radical or carbanion) transannular reaction between C7 and C11 in **17** would then deliver sinulochmodin C (**2**) (Scheme 6).

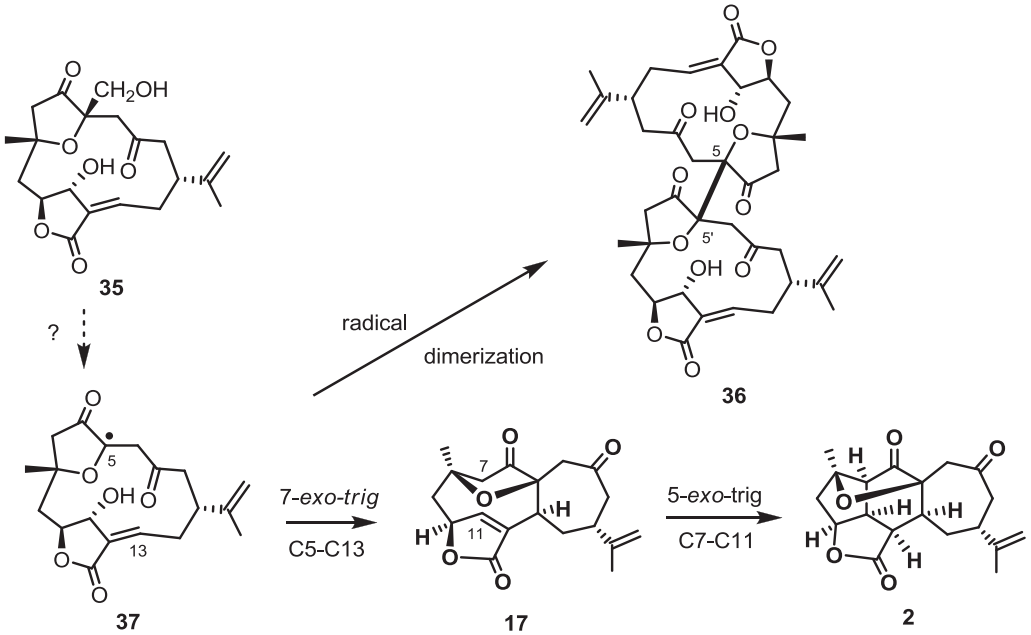
Carbon-centred radical intermediates have been implicated in other biosynthetic pathways, which lead to cembranoids,[17] and can be produced by a variety of processes, including photochemical excitation, electron transfer and oxidation processes. We now plan to study the radical chemistry of the macrocyclic sinuleptolides **7** and **8** in order to clarify whether radical intermediates could be implicated in the biosynthesis of sinulochmodin C (**2**). These investigations, alongside further studies of the anion chemistry of **7** and **8**, will be reported in due course.

5. Experimental

5.1. General details

Proton NMR spectra were recorded on a Bruker AV 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 DRX 500 (500 MHz) instrument and standard Bruker software with no modifications. Carbon-13 NMR spectra were recorded using a Bruker AV 400 (101 MHz) or Bruker DRX 500 (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 ppm 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 a Bruker MicroTOF system, using electrospray (ESI) techniques.

The analyses of reaction products were carried out on an HPLC/MS system (Varian HPLC with Pursuit 5 μ, C18, 250 mm×4.6 m I.D. column, Varian 310 TQ Mass Spectrometer). Flash chromatography was performed using Merck silica gel 60 (230–400 mesh ASTM) as



Scheme 6. Possible radical intermediates and pathways in the formation of sinulochmodin C (**2**) in *Sinularia*.

the stationary phase, and the solvents employed were of analytical grade; the petroleum ether 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 $60F_{254}$, 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. 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. Solvents were removed in vacuo at approx. 20 mmHg using a Büchi rotary evaporator.

5.2. Authentic 5-episinuleptolide 7

A sample of 5-episinuleptolide **7** (~10 mg), which had been isolated from *S. scabra*,[2] was used in all these studies. The sample displayed ^{1}H and ^{13}C NMR spectroscopic data, which were identical to those described in the literature.

5.3. Treatment of 5-episinuleptolide 7 with mesyl chloride/Et_3N/DBU

Mesyl chloride (30 μl) and triethylamine (0.1 ml) were added to a stirred solution of 5-episinuleptolide **7** (1.1 mg) in dry tetrahydrofuran (0.3 ml) at −20 °C. The mixture was stirred at −20 °C for 1 h, then treated with 1,8-diazabicycloundec-7-ene (20 μl), and kept at this temperature for a further 1 h. The mixture was diluted with ethyl acetate (3 ml) and the organic extract was washed with saline, dried over $MgSO_4$ and then evaporated to dryness in vacuo to leave the crude enol lactone (~0.3 mg) **18** as a labile oil. Relevant absorptions in the ^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 6.51 (1H, dd, *J*, 3.2, 6.0, C13–H), 5.96 (1H, s, C11–H), 4.82 (1H, br s, C16–H), 4.27 (1H, app t, *J* 8.0, C5–H), 3.53 (1H, br m, C14–H), 2.90–2.10 (~10H, m), 1.79 (3H, s, C17–Me), 1.40 (3H, s, C18–Me); *m*/*z* (ESI) 353.1336 ($C_{19}H_{22}O_5Na^+$ requires 353.1365). When the crude enol lactone **18** was warmed with Et_3N in MeOH for 5 h and the solution was evaporated to dryness, the residue showed ^{1}H NMR and MS data indicating the presence of the keto ester **19**, albeit quite crude: δ_H (400 MHz, $CDCl_3$) 6.80 (1H, m, C13–H), 4.95 (1H, s, C16–H), 4.72 (1H, s, C16–H′), 4.40 (1H, m, C5–H), 3.72 (3H, s, CO_2*Me*), 3.65 (1H, d, *J*~18, C11–H), similar to corresponding resonances for the natural product;[14a] *m*/*z* (ESI) 385.1606 ($C_{20}H_{26}O_6Na^+$ requires 385.1627).

5.4. 5-Episinuleptolide acetate 20

Acetic anhydride (0.1 ml) was added to a solution of 5-episinuleptolide **7** (4.5 mg, 0.013 mmol) and triethylamine (0.2 ml) in dichloromethane (2.0 ml) and the mixture was stirred at room temperature for 2 h. The solution was evaporated to dryness in vacuo, and the residue was then purified by chromatography on silica, using ethyl acetate/petroleum ether (3:1) as eluent, to give the *acetate* (4.6 mg, 92%) as a viscous oil: δ_H (400 MHz, $CDCl_3$) 6.47 (1H, ddd, *J* 1.1, 4.1, 11.1, C13–H), 5.49 (1H, br s, C11–H), 4.88 (1H, s, C16–H), 4.81 (1H, s, C16–H′), 4.53 (1H, app. dt, *J* 6.6, 2.0, C10–H), 4.28 (1H, dd, *J* 2.8, 8.8, C5–H), 3.80 (1H, ddd, *J* 6.3, 11.1, 15.2, C14–H), 3.06–2.99 (1H, m, C1–H), 2.85 (1H, dd, *J* 2.8, 16.4, C4–H), 2.65–2.55 (2H, m, C2–H), 2.60–2.46 (2H, m, C7–H), 2.57 (1H, dd, *J* 8.9, 16.4, C4–H′), 2.51–2.36 (2H, m, C9–H), 2.23 (1H, ddd, *J* 4.1, 4.3, 15.1, C14–H′), 2.10 (3H, s, OAc), 1.82 (3H, s, C17–Me), 1.44 (3H, s, C18–Me); δ_C (125 MHz, $CDCl_3$) 214.6 (C), 205.3 (C), 171.3 (C), 167.7 (C), 147.3 (CH), 147.0 (C), 127.6 (C), 110.5 (CH_2), 80.9 (CH), 79.1 (C), 76.4 (CH), 75.0 (CH), 51.2 (CH_2), 46.0 (CH_2), 43.1 (CH_2), 41.8 (CH_2), 39.6 (CH), 28.4 (CH_2), 26.6 (CH_3), 21.7 (CH_3), 21.0 (CH_3); *m*/*z* (ESI) 413.1566 ($C_{21}H_{26}O_7Na^+$ requires 413.1576).

5.5. Ineleganolide 1 and sinulochmodin C (2)

A solution of lithium hexamethyldisilazide in tetrahydrofuran (1 M, 30 μl, 0.029 mmol) was added to a stirred solution of the 5-episinuleptolide acetate **20** (2.3 mg, 0.0058 mmol) in dry tetrahydrofuran (0.3 ml) at −78 °C. The stirred solution was allowed to warm to 0 °C over 2 h, and was then kept at this temperature for a further 7 h. The mixture was quenched with aqueous ammonium chloride and then diluted with ethyl acetate (5 ml). The separated organic solution was washed with saline, dried over $MgSO_4$ and then evaporated to dryness in vacuo to leave an oil (1.9 mg). HPLC–MS analysis showed one principal product whose retention time and MS data were identical with those recorded for authentic ineleganolide **1** isolated from *S. scabra*. Other, minor products were also detected by HPLC–MS and these all had the same molecular ion as ineleganolide in their mass spectra, i.e., *m*/*z* 353 (M+Na). Further chromatography on silica, using ethyl acetate/petroleum ether (3:1) as eluent gave (i) ineleganolide **1** (0.5 mg) as a colourless powder: δ_H (400 MHz, $CDCl_3$) 5.12 (1H, app. t, *J* 7.1, C10–H), 5.07 (1H, s, C5–H), 4.94 (1H, s, C16–H), 4.62 (1H, s, C16–H′), 3.41 (1H, ddd, *J* 12.3, 9.3, 7.2, C11–H), 3.08 (1H, dd, *J* 12.3, 2.5, C12–H), 3.00 (1H, m, C14–H), 2.78 (1H, br s, C1–H), 2.70 (1H, d, *J* 13, C4–H), 2.63 (1H, m, C2–H), 2.59 (1H, d, *J* 9.3, C7–H), 2.51 (1H, d, *J* 15.6, C9–H), 2.24 (1H, m, C13–H), 2.10 (1H, dd, *J* 15.6, 7.2, C9–H′), 1.79 (1H, ddd, *J* 2.9, 5.4, 13.3, C14–H), 1.71 (3H, s, C17–Me), 1.28 (3H, s, C18–Me); δ_C (125 MHz, $CDCl_3$) 212.0 (C6), 206.3 (C3), 175.9 (C19), 145.8 (C15), 113.7 (C17), 91.0 (C8), 83.0 (C10), 77.4 (C5), 62.3 (C7), 49.7 (C4), 46.9 (C12), 45.3 (C9), 44.3 (C2), 43.6 (C11), 40.2 (C1), 33.1 (C13), 32.5 (C14), 22.6 (C18), 20.1 (C17); *m*/*z* (ESI) 353.1370 ($C_{19}H_{22}O_5Na^+$ requires 353.1365), and (ii) sinulochmodin C (**2**) (0.2 mg), as a viscous oil: δ_H (400 MHz, $CDCl_3$) 5.16 (1H, app. t, *J* 8.0, C10–H), 4.83 (1H, br s, C16–H), 4.75 (1H, s, C16–H′), 3.76 (1H, app. dt, *J* 10.5, 8.0, C11–H), 2.99 (1H, d, *J* 14.0, C14–H), 2.94 (1H, dd, *J* 11.0, 4.5, C13–H), 2.83 (1H, dd, *J* 10.5, 10.0, C12–H), 2.67 (1H, d, *J* 8.0, C7–H), 2.64 (1H, d, *J* 7.8, C4–H), 2.58 (1H, m, C1–H), 2.58 (1H, d, *J* 7.8, C4–H′), 2.56 (1H, d, *J* 7.5, C9–H′), 2.55 (1H, dd, *J* 15.0, 7.5, C9–H), 2.45–2.3 (2H, m, C2–H, C2–H′), 2.21 (1H, dd, *J* 15.0, 7.5, C9–H′), 1.75 (3H, s, C17–Me), 1.27 (3H, s, C18–Me); δ_C (125 MHz, $CDCl_3$) 213.4 (C6), 206.8 (C3), 176.1 (C19), 147.9 (C15), 111.0 (C16), 89.8 (C8), 83.3 (C10), 80.0 (C5), 57.8 (C7), 51.9 (C13), 51.5 (C11), 50.3 (C4), 46.6 (C9), 46.5 (C14), 38.4 (C12), 37.4 (C1), 31.9 (C2), 22.8 (C18 Me), 20.7 (C17 Me); *m*/*z* (ESI) 353.1359 ($C_{19}H_{22}O_5Na^+$ requires 353.1365).

5.6. Polycyclic norcembranoid 30

A solution of sodium hexamethyldisilazide (1 M, 25 μl, 0.0025 mmol) in THF was added to a stirred solution of the 5-episinuleptolide acetate **20** (2.0 mg, 0.0051 mmol) in dry THF (0.3 ml) at −40 °C. The solution was allowed to warm to −10 °C when it had become dark yellow in colour. The mixture was quenched at −10 °C with aqueous ammonium chloride, and then diluted with ethyl acetate (3 ml). The separated organic solution was washed with saline, dried over $MgSO_4$ and evaporated to dryness in vacuo to leave an oil, which was essentially homogenous in chromatographic analysis. The oil was purified by chromatography on silica, using ethyl acetate/petroleum ether (3:1) as eluent, to give the *polycycle* (1.3 mg, 75%) as a colourless gum: δ_H (500 MHz, $CDCl_3$) 7.08 (1H, app. t, *J* 2.6 Hz, H-5), 5.14 (1H, d, *J* 8.5 Hz, H-10), 4.90 (1H, s, H-16), 4.52 (1H, s, H-16), 3.34 (1H, ddd, *J* 6.9, 8.3, 11.8 Hz, H-11), 3.25 (1H, s, H-9), 3.15 (1H, ddd, *J* 2.9, 6.2, 9.5, H-13), 2.83 (1H, dd, *J* 2.9, 11.8, H-12), 2.78 (1H, m, H-14β), 2.76 (2H, m, H-2β and H-1), 2.60 (1H, dd, *J* 6.1, 18.7, H-2α), 2.39 (1H, br s, OH), 2.38–2.26 (2H, m, H-7), 2.31 (3H, s, Me-18), 2.10 (1H, ddd, *J* 2.9, 6.2,

9.9, H-14α), 1.81 (3H, s, Me-17); δ_C (125 MHz, $CDCl_3$) 207.9 (C), 197.8 (C), 177.7 (C), 145.5 (C), 142.9 (CH), 133.5 (C), 112.4 (CH_2), 82.7 (CH), 82.0 (C), 65.1 (CH), 46.3 (CH), 42.6 (CH_2), 38.3 (CH), 37.1 (CH), 35.8 (CH_2), 33.1 (CH_3), 32.1 (CH), 28.6 (CH_2), 22.2 (CH_3); *m*/*z* (ESI) 353.1362 ($C_{19}H_{22}O_5Na^+$ requires 353.1365).

Acknowledgements

We are grateful to Professor J.-H. Sheu (National Sun Yat-sen University, Taiwan) for his kindness in providing samples of naturally derived 5-episinuleptolide and ineleganolide, used in these studies. We also thank the University of Nottingham for financial support.

G.P. thanks Gilbert Stork for being a constant source of inspiration to him in organic synthesis over many decades, and for being an outstanding human being. What Federer has been to tennis for ten years, Stork has been to organic synthesis forever!

Supplementary data

Supplementary data associated with this article can be found in online version, at doi:10.1016/j.tet.2011.09.040.

References and notes

1. Duh, C.-Y.; Wang, S.-K.; Chia, M.-C.; Chiang, M. Y. *Tetrahedron Lett.* **1999**, *40*, 6033–6035 The structure drawn in this paper for ineleganolide is misleading and indicates that the configuration at C5 is opposite to that established by the crystal structure.
2. Sheu, J.-H.; Ahmed, A. F.; Shiue, R.-T.; Dai, C.-F.; Kuo, Y.-H. *J. Nat. Prod.* **2002**, *65*, 1904–1908.
3. Ineleganolide has also been isolated from *Sinularia leptoclados* and *S. parva*; see Ahmed, A. F.; Shiue, R.-T.; Wang, G.-H.; Dai, C.-F.; Kuo, Y.-H.; Sheu, J.-H. *Tetrahedron* **2003**, *59*, 7337–7344.
4. Tseng, Y.-J.; Ahmed, A. F.; Dai, C.-F.; Chiang, M. Y.; Sheu, J.-H. *Org. Lett.* **2005**, *7*, 3813–3816.
5. Other polycyclic norcembranoids found in *Sinularia* sp. include: Dissectolide: Kobayashi, M.; Appa Rao, K. M. Ch.; Krishna, M. M.; Anjaneyulu, V. *J. Chem. Res., Synop.* **1995**, 188–189; and Yonarolide: Iguchi, K.; Kajiyama, K.; Yamada, Y. *Tetrahedron Lett.* **1995**, *36*, 8807–8808.
6. Venkateswarlu, Y.; Farooq Biabani, M. A.; Venkata Rami Reddy, M.; Prabhakar Rao, T.; Kunwar, A. C.; Faulkner, D. J. *Tetrahedron Lett.* **1994**, *35*, 2249–2252.
7. Ramesh, P.; Reddy, N. S.; Venkateswarlu, Y.; Venkata Rami Reddy, M.; Faulkner, D. J. *Tetrahedron Lett.* **1998**, *39*, 8217–8220.
8. For a review, which includes the pharmacological significance of cembranoids from the soft coral genus *Sinularia*, see: Kamel, H. N.; Slattery, M. *Pharm. Biol.* **2005**, *43*, 253–269.
9. Pattenden, G.; Winne, J. M. *Tetrahedron Lett.* **2009**, *50*, 7310–7313.
10. Li, Y.; Pattenden, G. *Tetrahedron Lett.* **2011**, *52*, 2088–2092.
11. For other synthetic studies towards rameswaralide, see: Srikrishna, A.; Dethe, D. H. *Org. Lett.* **2004**, *6*, 165–168; Mehta, G.; Lakshminath, S. *Tetrahedron Lett.* **2006**, *47*, 327–330; Trost, B. M.; Nguyen, H. M.; Koradin, C. *Tetrahedron Lett.* **2010**, *51*, 6232–6235.
12. Bowden, B. F.; Coll, J. C.; Mitchell, S. J.; Mulder, J.; Stokie, G. J. *Aust. J. Chem.* **1978**, *31*, 2049–2056.
13. Shoji, N.; Umeyama, A.; Arihara, S. *J. Nat. Prod.* **1993**, *56*, 1651–1653.
14. (a) Sato, A.; Fenical, W.; Zheng, Q.; Clardy, J. *Tetrahedron* **1985**, *19*, 4303–4308; (b) Ramesh, P.; Venkateswarlu, Y. *J. Chem. Res., Synop.* **2000**, 48–50.
15. See under Ref. 4.
16. Roethle, P. A.; Trauner, D. *Nat. Prod. Rep.* **2008**, *25*, 298–317.
17. Li, Y.; Pattenden, G. *Nat. Prod. Rep.* **2011**, *28*, 1269–1310.
18. Both the *Z*- and *E*-isomers of deoxypukalide **9** have recently been found in the octocoral *Leptogorgia* sp., see Dorta, E.; Diáz-Marrero, A. R.; Brito, I.; Cueto, M.; D'Croz, L.; Darias, J. *Tetrahedron* **2007**, *63*, 9057–9062.
19. For further discussion see: Li, Y.; Pattenden, G. *Nat. Prod. Rep.* **2011**, *28*, 429–440.
20. The β-epoxide corresponding to **12** and its C5 epimer, together with C13-oxy substituted metabolites corresponding to **12** and **13** have been reported in *Sinularia* sp. See Ref. 2 and also Ahmed, A. F.; Su, J.-H.; Kuo, Y.-H.; Sheu, J.-H. *J. Nat. Prod.* **2004**, *67*, 2079–2082.
21. Iguchi, K.; Kajiyama, K.; Miyaoka, H.; Yamada, Y. *J. Org. Chem.* **1996**, *61*, 5998–6000.
22. Radhika, P.; Rao, P. V. S.; Anjaneyula, V.; Asolkar, R. N.; Laatsch, H. *J. Nat. Prod.* **2002**, *65*, 737–739.
23. Beckwith et al. have calculated that the captodative carbon radical centre at C2 in 3(2*H*)-furanone itself is more stable than the corresponding carbon radical centre at C4 by 7.03 kcal/mol (relative to the C–H bond in *n*-propane). See: Beckwith, A. L. J.; Zavitsas, A. A. *J. Am. Chem. Soc.* **1995**, *117*, 607–614.