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Synthesis of *E*-deoxypukalide, and its biomimetic conversion into deoxypseudopterolide by photochemical ring contraction involving a 1,3-allylic shift

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ABSTRACT

Irradiation of a solution of synthetic *Z*-deoxypukalide **10** in acetonitrile (Pyrex; 400 W Hg lamp) resulted in isomerisation, leading to *E*-deoxypukalide **12**, which was isolated recently from the octocoral *Leptogorgia spp*. Further irradiation of **12**, or prolonged irradiation of **10**, then gave the ring-contracted product, deoxypseudopterolide **1** (>90%) found in octocorals of the genera *Pseudopterogorgia* and *Leptogorgia*. The contraction of the 14-membered rings in **10** and **12** to the 12-membered ring as **1**, occurs by way of photochemical [1,3]-sigmatropic rearrangement.

1. Introduction

Deoxypseudopterolide **1** is the parent member of a group of 12-membered furanobutenolide-based macrocyclic diterpenes isolated from gorgonian corals of the genus *Pseudopterogorgia*[1] and *Leptogorgia*.[2] Other members include the oxidised derivatives **2**[3] and **3**,[4] and the novel dimethyamino derivative **4**.[1,5] These 12-membered ring compounds co-occur with the more common 14-membered cembranes, e.g., acerosolide **5**[1,6] and pukalide **6**,[7] in corals, and there is ground for believing that the former are derived from the latter in vivo, by a ring contraction mechanism. Thus, Rodríguez et al.[8] have recently demonstrated that when a solution of bipinnatin J (**8**), isolated from *Pseudopterogorgia bipinnata*[9] is irradiated in vitro with ultraviolet light, it is isomerised to kallolide A (**9**), a co-metabolite in the coral, in high yield.

Although deoxypseudopterolide **1** and acerosolide **5** were reported as co-metabolites in *Pseudopterogorgia* corals some years ago,[1,3] the presence of **1** alongside pukalide **6** and other 14-membered cembranoids in corals of the general *Leptogorgia* was only described in 2005.[2] Likewise, although pukalide **6** was the very first furanobutenolide-based cembranoid ever to be reported, in 1975,[7] it was not until 2007 that its presumed precursor, deoxypukalide **7** was found in *Leptogorgia spp*.; significantly, both *Z*- and *E*-isomers of **7** were isolated in this study.[10] The co-occurrence of deoxypseudopterolide **1** and deoxypukalide **7** in *Leptogorgia* is surely no co-incidence, and suggests that, like bipinnatin J (**8**) and kallolide A (**9**), they are related biogenetically as cycloisomers, with the 12-membered ring in **1** resulting from ring contraction of the 14-membered ring in **7**. Although total syntheses of kallolide A (**9**) and the 12-keto derivative of **1**, gorgiacerone, have been described,[11] a corresponding biomimetic synthesis of deoxypseudopterolide **1** has not been investigated. In contemporaneous studies, we have developed a total synthesis of *Z*-(+)-deoxypukalide **10**, which was shown to be identical in every respect with the natural product isolated from *Leptogorgia spp*.[12] We now report the outcome of a study of the photochemistry of this 14-membered ring cembranoid.

2. Results and discussion

A solution of *Z*-(+)-deoxypukalide **10** in deoxygenated acetonitrile, was irradiated through Pyrex using a water-cooled 400 W Hg lamp. The disappearance of the starting material was monitored by TLC analysis and ^{1}H NMR spectroscopy, and after 1.5 h when no starting material remained, the solution was evaporated to dryness. The residue was purified by chromatography to give a viscous oil in high yield (90%) whose mass spectrum showed that it had the same mass as the starting *Z*-deoxypukalide. Analysis and comparison of its

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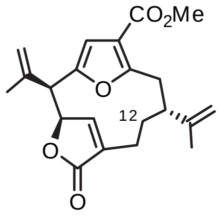

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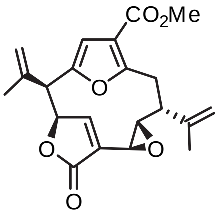

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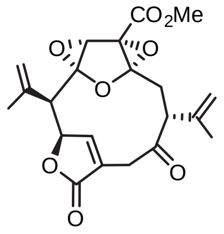

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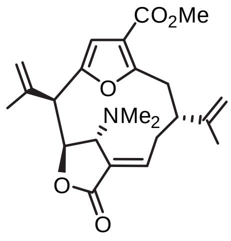

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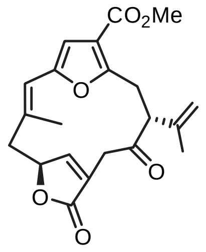

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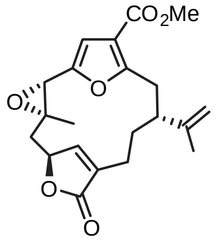

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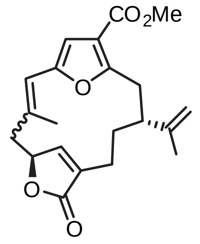

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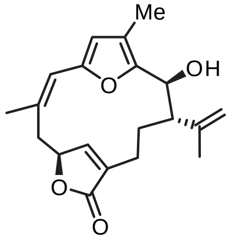

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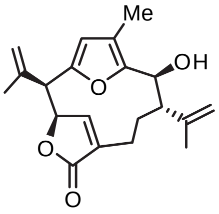

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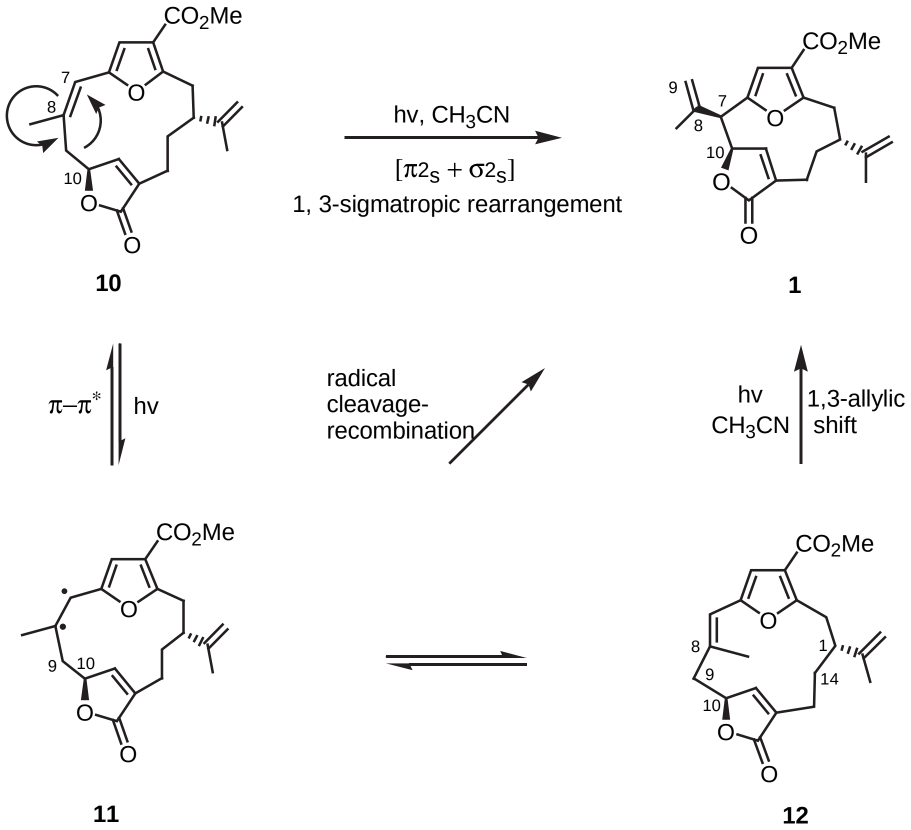
^{1}H NMR and ^{13}C NMR spectroscopic data with those reported for the 12-membered ring compound deoxypseudopterolide **1** isolated from *Pseudopterogorgia acerosa* showed that they were identical.[1] A crystalline sample showed a similar melting point, and their optical rotation data were also closely similar.

The high yielding photochemical rearrangement of *Z*-deoxypukalide **10** into deoxypseudopterolide **1** is a stereospecific [1,3]-sigmatropic reaction with the C10 stereocentre in **10** migrating suprafacially across the C7–C8 alkene bond with retention of its configuration (Scheme 1). The process is allowed photochemically according to orbital symmetry rules, and can be represented as a $[\sigma 2_s + \pi 2_s]$ cycloaddition reaction.[8,13]

To investigate the rearrangement of *Z*-deoxypukalide **10** to **1** in more detail, we interrupted the photo-irradiation after short periods of time and, with re-cycling of **10**, we were able to isolate a new product, as an unstable oil, in approximately 60% yield. Mass spectrometry demonstrated that the oil had the same mass as the starting *Z*-deoxypukalide **10** and as deoxypseudopterolide **1**. The new compound also displayed absorptions in its ^{1}H and ^{13}C NMR spectra, which were similar to many of those found for *Z*-deoxypukalide, but interestingly some of the proton resonances were broader and less-resolved than those recorded for **10**. When the NMR spectra of the photochemical product were recorded at slightly elevated temperature (50 °C), the proton resonances became much sharper. Furthermore, the ^{1}H and ^{13}C NMR spectroscopic data now corresponded closely to those reported for natural *E*-deoxypukalide **12** found in *Leptogorgia spp*.[10]

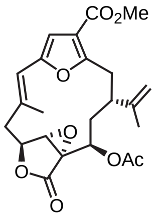
The *E*-deoxypukalide **12** is produced from the corresponding *Z*-isomer **10** by photochemical π–π^* excitation of the C7–C8 alkene bond, involving a 1,2-biradical intermediate, viz. **11** (Scheme 1). Whether or not this same biradical species is involved in the rearrangement of *Z*-(or *E*)-deoxypukalide to deoxypseudopterolide **1**, i.e., by cleavage of the C9–C10 sigma bond in **11** and radical recombination, is not clear, but it is a possibility.

Interestingly, *E*-deoxypukalide **12** is one of the only three furanocembranes found in corals to have a $\Delta^{7,8}$-double bond with the *E*-configuration;[10] the other two are acerosolide **5**[1] and isopukalide **13**.[10] By contrast, there are several examples of naturally occurring 14-membered furanocembranes having a *Z*-configuration at the same $\Delta^{7,8}$-double bond.[14] Perhaps even more interesting, all of the furanocembrane C7–C8 epoxides that have been characterised in nature, e.g., pukalide **6**,[7] lophotoxin **14**,[15] providencin **15**,[16] and bipinnatin D (**16**)[17] appear to originate from $\Delta^{7,8}$-double bonds with an *E*-configuration. This observation may indicate that furanocembrane epoxides produced from *Z*-$\Delta^{7,8}$-double bonds in vivo are inherently labile in the presence of their adjacent furan rings, and rapidly become involved in further interesting biosynthetic processes.[18] It is also apparent that the synthesis of furanobutenolide cembranes having a $\Delta^{7,8}$-double bond with the *E*-configuration is



Scheme 1. The photochemical rearrangement of *Z*- and *E*-deoxypukalide, **10** and **12**, respectively, into deoxypseudopterolide **1**.

problematic. Only two successful approaches have been reported so far.[11a,19] The ease with which the *Z*-$\Delta^{7,8}$-double bond in **10** is isomerised photochemically, leading to *E*-deoxypukalide **12** constitutes a new, third approach to these demanding targets.[20]



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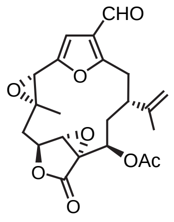

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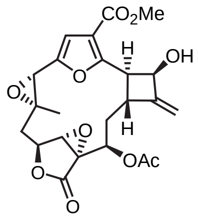

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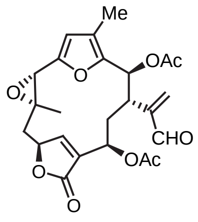

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Significantly, when the synthetic *E*-deoxypukalide **12** was irradiated under the same conditions that had been used with the *Z*-isomer **10**, it was converted directly into deoxypseudopterolide **1** in >90% yield, with no evidence of concurrent isomerisation to *Z*-deoxypukalide **10**. This observation would suggest that the conversion of *Z*-deoxypukalide **10** into **1** proceeds via the corresponding *E*-isomer **12**. However, we cannot eliminate the possibility that both the *Z*- and *E*-isomers of deoxypukalide, **10** and **12**, respectively, together with the common bi-radical intermediate **11**, are all implicated in the overall ring contraction process leading to deoxypseudopterolide **1**. Furthermore, more than one, concerted and/or non-concerted, mechanism could be operating.[13]

3. Conclusion

The photochemical rearrangement of the deoxypukalides **10** and **12**, leading to deoxypseudopterolide **1** is the second example of this novel 14- to 12-membered ring contraction process to be uncovered within the furanobutenolide-based family of cembranoids found in corals.[21] The ease with which the photo-induced 1,3-allylic shift process takes place in vitro is quite remarkable, and it is probable that the ring contraction mimics the biosynthesis of deoxypseudopterolide from deoxypukalide in octocorals, i.e., using sunlight.

4. Experimental

4.1. General details

For general experimental details see Ref. 12.

*4.1.1. (+)-Z-Deoxypukalide (**10**).* The deoxypukalide was synthesised as described previously in our laboratory.[12] It was obtained as colourless crystals, mp 152.5–153.5 °C (from ethyl acetate–light petroleum), $[\alpha]_D^{22}$ +19.9 (*c* 1.15, $CHCl_3$). Naturally derived *Z*-deoxypukalide was described as an oil with $[\alpha]_D^{20}$ +11 (*c* 0.37, $CHCl_3$).[10] The synthetic *Z*-deoxypukalide had ^1H and ^{13}C NMR spectroscopic properties, together with mass spectrometry data, which were identical with those reported earlier,[12] and for the natural product.[10]

*4.1.2. (+)-Deoxypseudopterolide (**1**). 4.1.2.1. (a) From (+)-Z-Deoxypukalide (**10**).* A solution of (+)-*Z*-deoxypukalide **10** (5.0 mg) in acetonitrile (4.0 ml) was deoxygenated with dry nitrogen gas and then irradiated through Pyrex using light from a water-cooled 400 W Hg lamp. The reaction was monitored by TLC analysis, and the irradiation was stopped when no more starting material was detected. The solution was evaporated in vacuo, and the residue was then purified by chromatography on silica using 1:5 ethyl acetate–petroleum ether as eluent to give deoxypseudopterolide **1** (4.5 mg, 90%) as a viscous oil. Crystallisation gave crystals, mp 167–169 °C (from acetone–light petroleum), $[\alpha]_D^{22}$ +45.7 (*c* 0.5, $CHCl_3$). δ_H (400 MHz, $CDCl_3$) 0.87 (1H, app. dt, *J* 14 and 3 Hz, H-12), 1.77–2.3 (1H, obs m, H-12), 1.81 (3H, s, C-13–Me), 2.0 (3H, s, C-17–Me), 2.22 (1H, app. dt, *J* 14 and 3 Hz, H-11), 2.44 (1H, app. dt, *J* 14 and 3 Hz, H-11), 2.74 (1H, dd, *J* 16 and 4 Hz, H-2), 2.77 (1H, app. ddd, *J* 12, 5 and 3 Hz, H-1), 3.32 (1H, dd, *J* 16 and 12 Hz, H-2), 3.8 (1H, obs d, *J* 4 Hz, H-7), 3.82 (3H, s, OMe), 4.81 (1H, s, H-18), 4.86 (1H, s, H-18), 5.05 (1H, s, H-14), 5.06 (1H, s, H-14), 5.43 (1H, d, *J* 4 Hz, H-8), 6.40 (1H, s, H-5), 6.73 (1H, s, H-9); δ_C (100 MHz, $CDCl_3$) 19.3 (q), 21.7 (q), 22.9 (t), 31.6 (t), 35.2 (t), 41.7 (d), 48.6 (d), 51.4 (q), 80.6 (d), 109.9 (d), 114.4 (t), 115.0 (t), 115.4 (s), 137.4 (s), 141.4 (s), 146.7 (d), 147.3 (s), 150.5 (s), 161.8 (s), 164.2 (s), 175.2 (s); HRMS (ESI) 379.1520 ($M+Na^+$, $C_{21}H_{24}O_5Na$ requires 379.1521). Naturally derived deoxypseudopterolide was obtained as colourless prisms, mp 139–140 °C, $[\alpha]_D$ +62 (*c* 0.23, $CHCl_3$).[1]

*4.1.2.2. (b) From (+)-E-Deoxypukalide (**12**).* A solution of synthetic (+)-*E*-deoxypukalide **12** (2.0 mg) in acetonitrile (2.0 ml) was irradiated in an identical manner to that described for the *Z*-isomer. Work up and chromatography gave deoxypseudopterolide **1** (1.8 mg, 90%), which had identical NMR spectroscopic, mass spectrometry, and chiroptical data to those presented under (a).

*4.1.3. (+)-E-Deoxypukalide (**12**).* A solution of synthetic (+)-*Z*-deoxypukalide **10** (5.0 mg) in acetonitrile (4.0 ml) was irradiated in an identical manner to that described for the *Z*-isomer. After 20 min the solution was evaporated in vacuo. The residue was chromatographed on silica using 1:5 ethyl acetate–petroleum ether as eluent to give (+)-*E*-deoxypukalide **12** (1.0 mg) as a viscous oil, and recovered starting material **10** (3.5 mg). The recovered starting material was irradiated again for 20 min giving more *E*-deoxypukalide, and the process was repeated twice more. The combined samples were purified by chromatography to give *E*-deoxypukalide (3 mg, 60%) as an unstable colourless oil. $[\alpha]_D^{23}$ +145.9 (*c* 1.05, $CHCl_3$), (lit.,[10] $[\alpha]_D^{20}$ +79.3 (*c* 0.63, $CHCl_3$)); δ_H (400 MHz, $CDCl_3$): 1.30 (1H, obs m, H-14), 1.7 (1H, obs m, H-14′), 1.79 (3H, s, C-15–Me), 1.79 (3H, s, C-8–Me), 2.25 (1H, app. dd, *J* ~ 14 and 5 Hz, H-13), 2.43 (1H, app. t, *J* 12 Hz, H-13′), 2.61 (1H, dm, *J* ~ 12 Hz, H-9), 2.98 (1H, m, H-1), 3.01 (1H, m, H-9′), 2.92–3.02 (2H, obs m, H-2 and H-2′), 3.82 (3H, s, OMe), 4.95 (1H, br s, H-16), 5.11 (1H, br s, H-16), 5.22 (1H, br s, H-10), 6.0 (1H, s, H-7), 6.4 (1H, s, H-5), 6.95 (1H, s, H-11); δ_C (100 MHz, $CDCl_3$): 19.2, 21.6, 22.5, 32.4, 32.6, 41.3, 42.7, 51.1, 79.9, 108.3, 112.6, 114.9, 119.5, 137.4, 141.4, 145.7, 146.6, 149.3, 160.3, 164.3, 174.3; HRMS (ESI) 379.1509 ($M+Na^+$, $C_{21}H_{24}O_5Na$ requires 379.1521).

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.04.001.

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