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A biogenetically patterned synthetic approach to the unusual furan methylenecyclobutanol moiety in providencin

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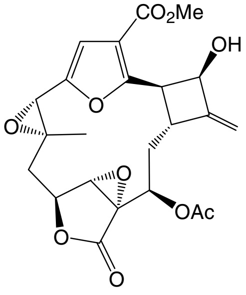
Abstract—Irradiation of a solution of α,β-unsaturated aldehyde **10** in benzene leads to the methylenecyclobutanol **11** by way of a novel intramolecular C–H insertion reaction. The conversion of **10** into **11** has relevance to the possible origin of the cyclobutane ring-based furanocembrane providencin **1** found in gorgonian octocorals.

The Caribbean gorgonian octocorals of the genus *Pseudopterogorgia* are an unbelievably rich source of biologically active and structurally novel cembrane diterpenoid-derived polycyclic natural products.[1] In recent years, two particularly unusual members containing cyclobutane rings, that is, providencin **1**[2] and bielschowskysin **2**,[3] were isolated and characterised from the coral *P. kallos*. It seems likely that these metabolites have their origins in the more familiar furanobutenolide-based cembranes, bipinnatin E (**3a**) and oxygenated derivatives of bipinnatin J (**4**), respectively, which are also found in *Pseudopterogorgia*.[4]



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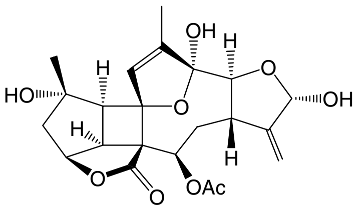

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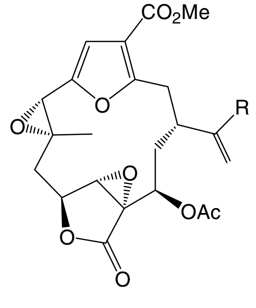
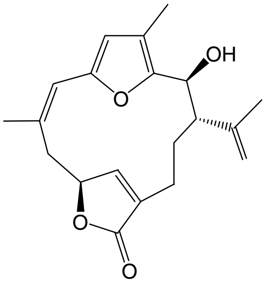


3
a, R = CHO
b, R = Me



4

Although cyclobutane-containing natural terpenes are not overly rare,[5] providencin **1** and bielschowskysin **2** represent the first of their number to be described within the furanobutenolide family of natural cembranes. Their isolation has stimulated us to evaluate strategies to their synthesis based on what we believe to be their most likely origins in Nature, that is, from more simple furanocembranes akin to **3a** and **4**.[6] In this letter, we describe a concise synthesis of the furan methylenecyclobutanol moiety **6** in providencin **1** based on a photochemically mediated intramolecular C–H insertion reaction from the α,β-unsaturated aldehyde precursor **5**, cf. bipinnatin E (**3a**).

The appropriately substituted furan α,β-unsaturated aldehyde **10** was synthesised in four straightforward steps, starting from 2-methyl-3-furoic acid **7a** (Scheme 1). Thus, the furoic acid was first converted into the corresponding *tert*-butyl ester **7b**, which was then brominated using *N*-bromosuccinimide in refluxing CCl_4 in the presence of AIBN, leading to the furanmethyl bromide **8**. Deprotonation of methyl 3-methylbut-2-enoate, using LDA in THF at −78 °C, followed by alkylation of the

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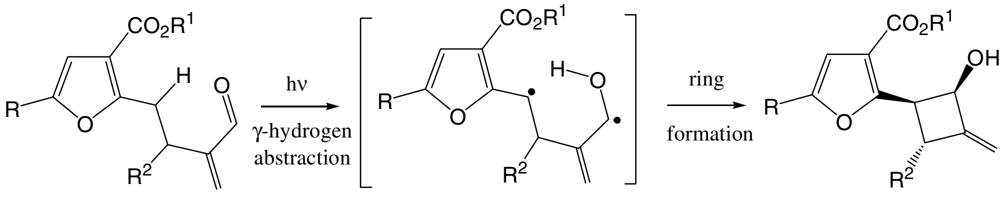
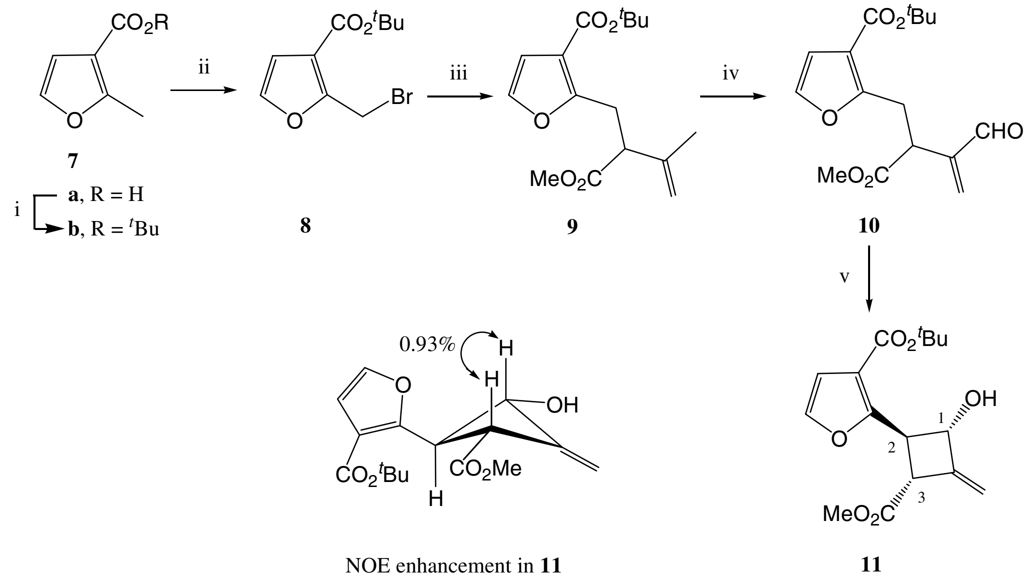


5

6

resulting α-organolithium species with **8** next gave the β,γ-unsaturated ester **9** exclusively.[7] Finally, oxidation of the substrate **9**, using selenium dioxide in refluxing dioxane gave the α,β-unsaturated aldehyde **10** in 36% yield. This allylic oxidation mirrors the likely final biosynthetic step to bipinnatin E (**3a**), since the corresponding furanocembrane (**3b**) bearing an unoxidised isopropenyl appendage, that is, 13-acetoxy-11β,12β-epoxypukalide, is also found in Nature.[8] Irradiation of a dilute solution of **10** in benzene in a pyrex photoreactor using light from a 400 W medium pressure Hg lamp, with regular monitoring by ^{1}H NMR spectroscopy, led to a single photoproduct isolated in 19% yield. The photoproduct displayed all the characteristics of cyclobutanol **11** in its ^{1}H and ^{13}C NMR spectra, and it was obtained as almost a single diastereomer (d.r. > 25:1). The *trans*-1,2-*trans*-2,3-relationship around the cyclobutane ring in **11** was assigned following NOE experiments, where a reciprocal enhancement was observed between the allylic carbinol proton at δ 4.80 ppm and the proton α- to the ester group at δ 3.87 ppm, clearly indicating a *cis*-arrangement. In addition, irradiation of the furanyl methine proton at δ 4.20 ppm did not reveal any NOE enhancements, indicating its *trans*-relationship with respect to the other substituents on the cyclobutane ring. We anticipate that the conformational bias imposed by the macrocyclic ring of a corresponding furanocembrane precursor, viz **3a**, will promote the formation primarily of the desired cyclobutane diastereomer in the product (i.e., *cis*-1,2-*trans*-2,3; cf. **1**), following a photochemical C–H insertion reaction similar to the conversion of **10** into **11**.

Photochemical hydrogen-atom abstraction is one of the oldest and most extensively studied photochemical reactions. The photochemically mediated cyclobutanol formation, illustrated in the conversion **10**→**11**, is known as the Norrish type II or Norrish–Yang reaction.[9,10] Remote functionalisations, that is, hydrogen-atom abstractions over long distances, involving photoactivated carbonyl groups are also well documented.[11] To our knowledge, the only example of a Norrish-type II reaction in the elaboration of a natural product is the synthesis of (−)-punctatin A, involving the irradiation of an α-isobutyl substituted cyclohexanone, described by Sugimura and Paquette in 1987.[12] We believe that our study of the photoinduced intramolecular C–H insertion reaction, from α,β-unsaturated aldehyde **10** leading to the cyclobutanol **11**, is unprecedented. The relevance of the conversion **10**→**11** to the possible origin of providencin **1** from bipinnatin E (**3a**) is evident. We are now directing our efforts towards the total synthesis of **3a**, and hence **1**, by developing the principles established here and in our earlier work.[7]



Scheme 1. Reagents and conditions: (i) 2-methylpropene, CH_2Cl_2, cat. H_2SO_4, rt, 24 h, 68%; (ii) NBS (1.05 equiv), CCl_4, AIBN (5 mol%), Δ, 30 min, 84%; (iii) methyl 3-methylbut-2-enoate, LDA (1.05 equiv), THF, −78 °C, 1 h then **8** (1.0 equiv), 1 h, 70%; (iv) SeO_2 (2.05 equiv), 1,4-dioxane, Δ, 20 min, 36%; (v) hν, PhH (1.26 mM), 19%.

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