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Elaboration of the carbocyclic ring systems in plumarellide and rameswaralide using a coordinated intramolecular cycloaddition approach, based on a common biosynthesis model

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ABSTRACT

Treatment of the furanbutenolide **18a** with trifluoroacetic acid in dichloromethane results in hydrolysis and rearrangement leading to the cycloheptene ring-containing system **19a** found in rameswaralide (**5**). Similar treatment of the diastereoisomeric furanbutenolide **17** produces the cyclohexene ring-containing system **23** present in plumarellide (**1**), together with the C-7 epimer **24** of **19a**. The acid-catalysed conversions **18a** → **19a** and **17** → **23** are rationalised implicating [6+4] and [4+2] cycloaddition pathways and/or two-step carbocation cyclisation sequences.

Plumarellide (**1**), together with the plumarellate (**2**),[1] the mandapamates **3** and **4**,[2] rameswaralide (**5**) [3], and dissectolide (**6**)[4] are amongst some of the more novel and structurally interesting polycyclic diterpenes to have been isolated from corals in recent years. Although plumarellide and its derivative **2** have only been reported so far in the gorgonian octocoral *Plumarella* sp., the other metabolites **3**–**6** have all been isolated from soft corals of the genus *Sinularia*. Indeed, the mandapamate **4**, rameswaralide (**5**) and the norditerpene dissectolide (**6**) co-occur in *S. dissecta*, signalling that they may be related biosynthetically.

The structural feature that the plumarellides **1** and **2** and the mandapamates **3** and **4** have in common is a central cyclohexene ring which is conjoint with a substituted cyclopentane and an oxa-bridged cycloheptene. Dissectolide (**6**) also accommodates a fused cyclohexene–cyclopentane ring system in its structure, but the oxa bridge present in the metabolites **1**–**4** is absent. By contrast, the rameswaralide structure **5** features a central cycloheptenone which is flanked by substituted cyclopentane and cyclohexene rings. Interestingly, the polycyclic structures **1**–**6** are also distinguished by the differing stereochemistries they display at the C7 and C8 centres in their cyclopentane rings. Thus, the secondary OH groups at C8 in the metabolites **3**–**6** are orientated β-, whereas the same OH groups in the plumarellides **1** and **2** have the corresponding α-orientation. In addition, the H-centres at C7 in the metabolites **1**, **2**, **5** and **6** are all on the same α-face of their structures, with *cis*-stereochemistries between their cyclopentane

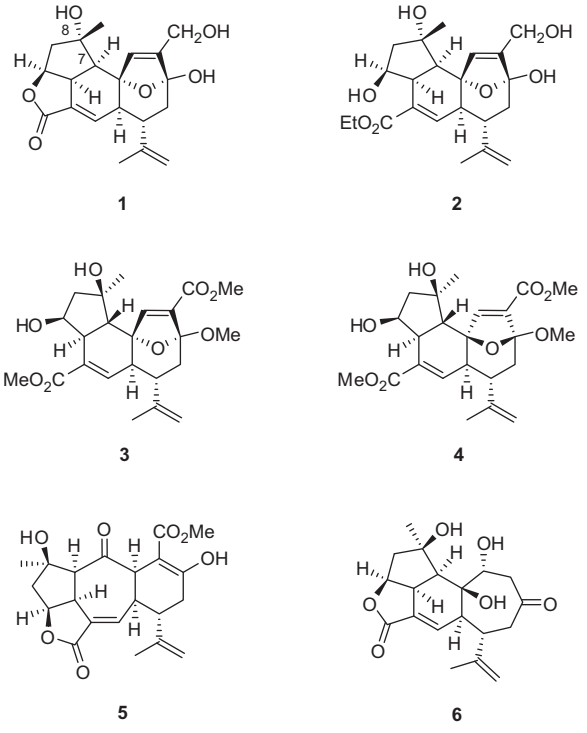

Figure 1.

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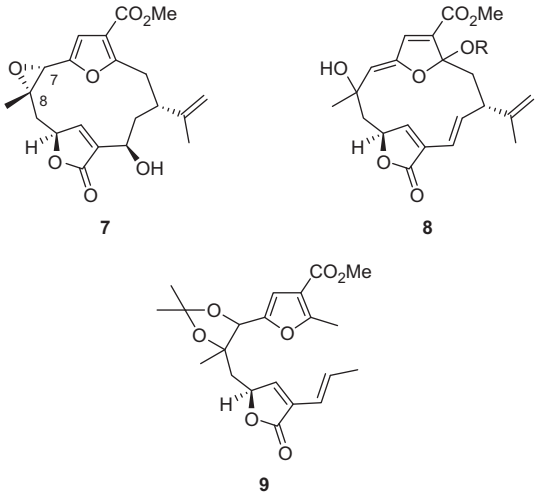

Figure 2.

and cyclohexene-cycloheptenone rings, whereas the mandapamates **3** and **4** have the opposite β-H stereochemistry at their C7 centres, and hence *trans*-stereochemistries between their fused cyclopentane and cyclohexene rings (see Fig. 1).

In previous publications we have drawn attention to the likelihood that the metabolites **1**–**6** are interrelated biosynthetically, and that they have their origins in interesting oxidation processes and transannular cyclisation reactions from furanbutenolide precursors, viz **7**.[5] Thus, it seems probable that the cyclohexene rings in the metabolites **1**–**4** are derived in vivo by way of intramolecular (4+2) type cyclisations involving the alkene unit of an enol ether with a conjugated 1,3-diene unit which is associated with a butenolide moiety accommodated in the same furanbutenolide precursor; see structure **8**. Indeed cembranoid structures containing the unusual enol ether functionality in the structure **8** have been characterised in corals,[6] together with their likely C7–C8 vicinal diol and/or C7–C8 epoxide precursors, cf. **7** (see Fig. 2). However, 14-membered cembranoids containing conjugated 1,3-diene (i.e., vinylbutenolide) units, cf. structure **8**, have not yet been isolated and characterised from marine sources. Lastly, it has also been suggested that a cyclohexene ring-containing structure related to mandapamate **3** could be implicated in the biosynthesis of rameswaralide (**5**) in *S. dissecta*, involving expansion of the 6-ring in the mandapamate to the 7-ring in rameswaralide using a vinylogous α-ketol rearrangement.[3,7] Just as likely however, is that the cycloheptene ring in rameswaralide (**5**) has its origins in a precursor similar in constitution to **8** by way of a competing (4+3) type intramolecular cycloaddition process.[5] In the absence of any defining biosynthesis studies, we have sought to provide credence to some of these biosynthesis speculations by studying transannular cyclisation reactions within synthetically accessible furanobutenolide structures akin to **8**.[8,9] In this Letter we describe concise syntheses of diastereoisomers of the vicinal diol-based furanovinylbutenolide structure **9** and demonstrate that under acid-catalysed conditions they can be converted separately into the cyclohexene and cycloheptene ring-containing systems present in plumarellide (**1**) and rameswaralide (**5**) respectively.

The diastereoisomeric vicinal diol acetonides **17** and **18** (cf. **9**) were smoothly synthesised in seven linear steps starting from the substituted *Z*-vinyl iodide **10b**, produced from the known alcohol **10a** (Scheme 1).[10] Thus, the vinyl iodide **10b** was first coupled to the furylboronic acid **11b**[11] in the presence of Pd^0, leading to the vinylfuran **12** (40% yield based on the furyl bromide precursor **11a** to **11b**). Stereoselective vicinal bis-hydroxylation of **12**, using AD-mix-α,[12] followed by protection of the resulting vicinal diol next gave the acetonide derivative **13**.[13] Removal of the silyl protecting group in **13**, and oxidation of the resulting primary alcohol group then led to the aldehyde **14**, which was obtained as a labile oil. Addition of the lithium salt of ethyl propynoate to the aldehyde **14** in THF at −42 to −78 °C, as expected, led to a mixture of diastereoisomers of the resulting substituted secondary alcohol **15** in 62–74% yield (ratio 1:1 at −42 °C and 3:1 at −78 °C), which were not separated at this stage. A solution of the mixture of diastereoisomers of **15** in acetonitrile was next treated with Bu_3SnH in the presence of $Pd(PPh_3)_4$ leading to the stannane substituted butenolide **16**. Although the stannane **16** could be isolated at this point, for reasons of expediency, we instead diluted the solution containing the stannane with degassed DMF and then treated the resulting solution with *E*-1-bromopropene in the presence of CuI and CsF. Using this 'one-pot' butenolide cyclisation/sp^2–sp^2 coupling procedure,[14] we produced an approx. 3:7 mixture of β- and α-diastereoisomers of the target vinylbutenolide/diol acetonides, **17** and **18a,** respectively, (where α and β refer to the orientation of the acetonide units) in a combined yield of 50% over the two steps.[13] These diastereoisomers were separated by routine chromatography and were clearly distinguished by analysis of their NMR spectroscopic data and comparison of these data with those of similar structures we had synthesised earlier.[8,9] In particular the β-diastereoisomer **17** displayed diagnostic signals at δ 2.01 (dd, *J* 14.6 and 6.0 Hz, H9) and δ 4.79–4.75 (m, H10), whereas the α-diastereoisomer **18a** instead showed corresponding signals at δ 1.93 (dd, *J* 14.6 and 4.6 Hz) and δ 5.17 (app. t, *J* ~6.0 Hz) respectively, for the same protons in their ^{1}H NMR spectra.[15]

When a solution of the α-diastereoisomer **18a** in 1:1 dichloromethane (DCM) and trifluoroacetic acid (TFA) was stirred at room temperature for 15 minutes and then evaporated to dryness, analysis of the residue by NMR spectroscopy showed that only one polycyclic product had been produced, whose data were consistent with the structure **19a** containing the 5,7-bicyclic ring system embedded in rameswaralide (**5**) (Scheme 2). Routine chromatography then gave a pure sample of **19a** as a viscous oil in approx. 60% yield. The same polycycle was also obtained, albeit in lower yields (30–50%), when the acetonide **18a** was treated at room temperature for 18 h with 1:1 DCM–TFA in the presence of one small drop of water, or with TFA and one small drop of water. Lastly, when a solution of **18a** in 1:1 DCM–TFA containing 20% methanol was stirred at room temperature for 18 h, a 1:1 mixture of **19a** and the polycyclic product **20** corresponding to dehydration of **19a** was produced in >65% yield.

The overall structure of the polycycle **19a** followed from detailed analysis of its 1D and 2D proton and carbon NMR spectroscopic data, that is COSY, HMQC and HMBC.[15] Furthermore, examination of the NOESY spectra established the *trans*-fusion of the cyclopentane ring with the cycloheptane ring, and the *cis*-fusion of the cyclopentane ring with the adjacent 5-ring lactone. In some earlier studies we had prepared the constitutionally identical polycyclic structure **19b** in excellent yield by treatment of the analogous acetonide **18b** (as its ethyl ester) with TFA containing a few drops of water.[8,16] At that time, we rationalised the acid-catalysed conversion of **18b** into **19b** occurring by several possible mechanistic pathways, including one involving an intramolecular concerted [6π+4π] cycloaddition reaction from a furanoxonium ion intermediate, that is **21** → **22**, (Scheme 2).

To our initial surprise, but also to our satisfaction, when the β-diastereoisomer **17** corresponding to **18a** was treated in a similar manner with TFA–DCM (in the presence or absence of water or methanol) for 15 minutes at room temperature, chromatography separated the novel polycycle **23**, incorporating the cyclohexene ring and 5,5,6-tricyclic ring system found in plumarellide (**1**), as