Biomimetic synthesis of (±)-9,10-deoxytridachione†

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A tandem Suzuki-coupling/electrocyclisation reaction sequence was employed for the biomimetic synthesis of (±)-9,10-deoxytridachione.

Pyrone containing compounds are characteristically produced by a restricted group of marine molluscs of the order Sacoglossa.[1] These compounds, which are formally derived from a polyketide pathway, have been associated with specific ecophysiological functions of the molluscs, since they may act as mediators in tissue regeneration and chemical defence.[2]

Investigations by John Faulkner and co-workers in the late 70's resulted in the isolation of the novel pyrone containing secondary metabolites tridachione (**1**), and 9,10-deoxytridachione (**2**), from the ether-soluble oil of the ascoglossan mollusc *Tridachiella diomedea* (Mexican dancer) (Fig. 1).[3,4] *In vitro* experiments by Ireland and Faulkner[4] and *in vivo* experiments by Ireland and Scheuer[5] demonstrated that the cyclohexadiene ring system of **2** was converted photochemically to the bicyclo[3.1.0]hexene ring system of 9,10-photodeoxytridachione (**3**).

This interesting chemical relationship has been proposed to proceed through a concerted $[{}_{\sigma}2_{a} + {}_{\pi}2_{a}]$ pericyclic pathway, since retention of optical activity during photolysis was observed.[4] The intriguing chemical behaviour and unique molecular structures associated with such marine polypropionates have led us,[6] and others[7] to initiate a programme of research dedicated to the synthesis of such novel metabolites. We have previously reported our model studies on related polyenes[6,8] and have proposed a general biosynthetic rationale to explain the origins of these highly unsaturated natural products, through cascade isomerisation/electrocyclisation processes of polyene precursors.[9] We now wish to report our studies on the biomimetic total synthesis of (±)-9,10-deoxytridachione.

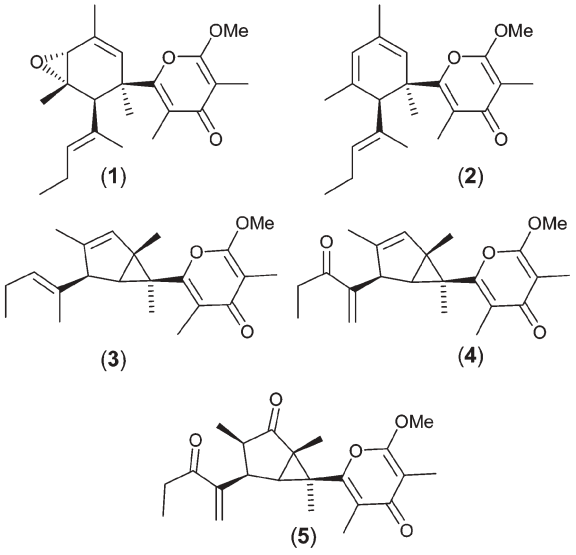
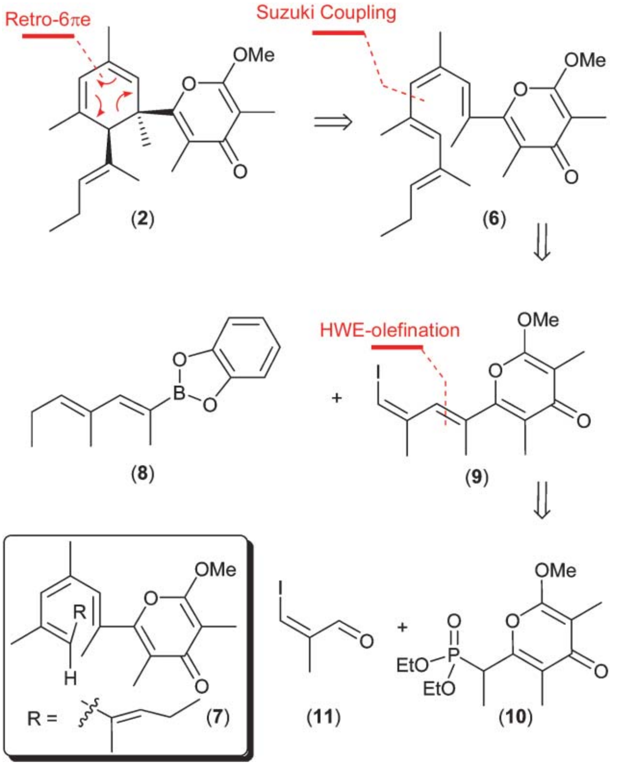


Fig. 1 γ-Pyrone containing marine polypropionates.

Compound **2** was selected as a suitable candidate for our continuing studies, since we envisaged that further chemical manipulation may allow access to a range of analogous natural products including **1**, **3**, and the related tridachiapyrones E (**4**) and F (**5**) (Fig. 1).[10]

Scheme 1 depicts diagrammatically a retrosynthetic rationale towards (±)-9,10-deoxytridachione (**2**). Thus, a retro thermal 6πe-disrotatory electrocyclisation reveals the (*E*,*Z*,*E*,*E*)-conjugated γ-pyrone-tetraene (**6**), which we, and Ireland and Faulkner,[4] have considered a possible biosynthetic precursor to **2**. However, we also appreciated that **2** may be biosynthetically derived through a photochemical 6πe-conrotatory electrocyclisation process[8] of the corresponding (*E*,*Z*,*Z*,*E*)-tetraene **7**, considering the known



Scheme 1 Biomimetic retrosynthetic analysis of **2**.

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photochemical relationship between **2** and **3**.[4,5] Although both thermal and photochemically induced 6πe-electrocyclisation processes have been reported with related polyene systems,[9] to our knowledge, such transformations have not yet been demonstrated with a conjugated γ-pyrone containing polyene.

Further disconnection of **6** revealed the known conjugated (*E*,*E*)-vinyl boronic ester (**8**)[11] and vinyl iodide (**9**), which we believed would be ideal partners for a Suzuki coupling reaction.[12] Further analysis of fragment **9** revealed the Horner–Wadsworth–Emmons olefination reagent **10**, which we had previously developed for the synthesis of cyercene A, a related γ-pyrone diene,[13] and the known aldehyde **11**.[14]

Our synthesis of (±)-(**2**) commenced with condensation of the known aldehyde **11**[14] with the lithium salt of **10**[13] at −78 to 20 °C in THF, to give the conjugated vinyl iodide **9** as the major diastereoisomer [$E : Z \geqslant 6 : 1$] in an unoptimised 40% yield. Suzuki coupling of **9** and boronic ester **8** was performed using standard conditions at 80 °C.[15] The insoluble palladium salts were removed from the reaction mixture by filtration, and ^{1}H NMR analysis of the crude reaction mixture was performed. The presence of four new alkenyl signals in the NMR spectra [δ_H ($CDCl_3$) 5.39, 5.85, 5.98, 6.42 ppm] characteristic of a conjugated tetraene,[6–9] led us to conclude the major constituent of the crude mixture to be compound **6**. Without further purification crude **6** was taken in a sealed tube and heated in benzene at 120 °C for one hour in the absence of light. A mixture of compounds was obtained, which we were unable to separate by conventional flash silica gel chromatography. However, purification of the crude mixture by reverse phase C-18 HPLC [$CH_3CN : H_2O$, 6 : 4] gratifyingly yielded known (±)-**2** in a reasonable 31% yield from **9**, along with a second cyclohexadiene (±)-**12** in 15% yield (Scheme 2).[16] The *exo*-structure for compound **12** was confirmed by nOe measurements (1D and 2D NOESY) (Fig. 2) and ^{1}H and ^{13}C NMR data, which was identical to that recently reported for the *endo*-structure **14** by Manzo *et al.*[17] However, **14** itself was assigned indirectly from diagnostic nOe measurements of the related oxygen adduct **15**.[17] We are confident of our own assignment of structure **12**. Interestingly, compound **12** also bears the same bicyclo[4.2.0]octadiene core as the natural products SNF4435C and SNF4435D,[18,19] and is formally derived from isomerisation of (*E*,*Z*,*E*,*E*)-**6** to (*E*,*Z*,*Z*,*E*)-**13**, followed by thermally allowed consecutive 8πe conrotatory and sterically favoured 6πe-disrotatory electrocyclisations.

In conclusion, we have achieved the first total synthesis of (±)-9,10-deoxytridachione (**2**) in biomimetic fashion, demonstrating experimentally for the first time a chemical relationship between a fully conjugated polyene–γ-pyrone and a complex natural product.[20] The results from this study strengthen our general biosynthetic proposal that compounds of these classes are most likely derived through pericyclic processes of linear polyene precursors. The conversion of γ-pyrone **6** into **12** through successive pericyclic reactions is also a noteworthy transformation.

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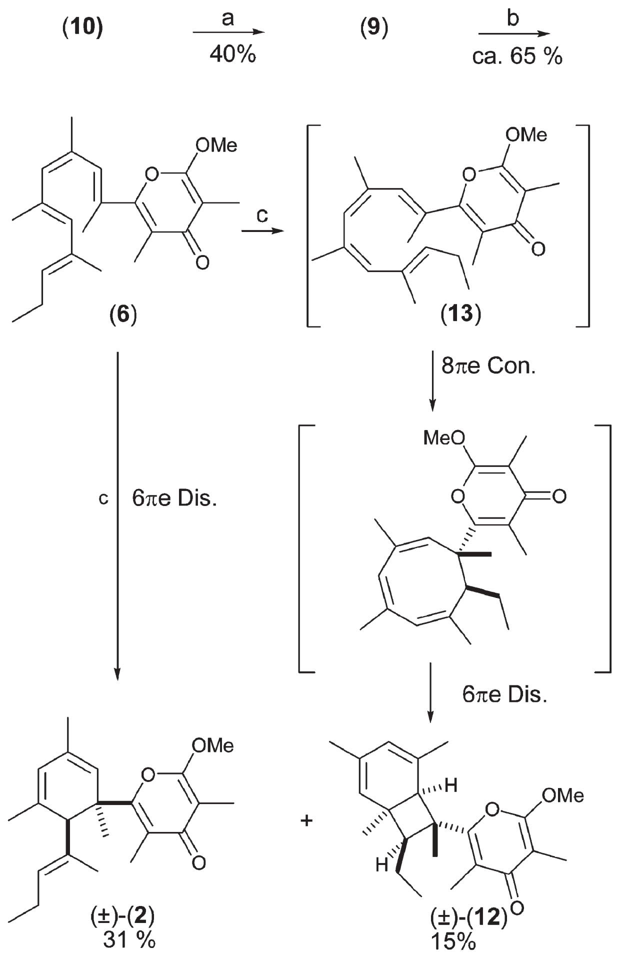

Scheme 2 Synthesis of (±)-9,10-deoxytridachione (**2**). *Reagents and conditions:* (a) LHMDS, THF, −78 °C, 30 min, **11**, −78 to 20 °C, 1 h; (b) 5 mol % $Pd(PPh_3)_4$, THF, KOH, **8**, 80 °C, 2 h; (c) PhH, 120 °C, 1 h.

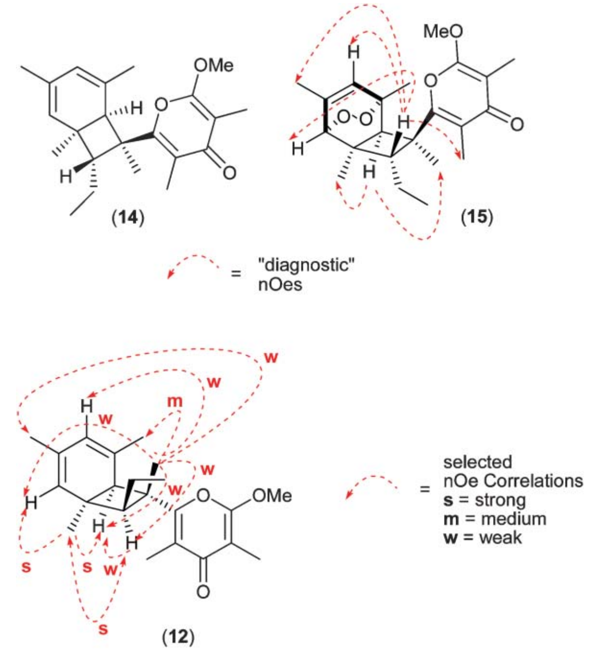

Fig. 2

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16 ^{2}H NMR of the crude reaction mixture before HPLC indicated that the ratio of compounds [**2** : **12**] was approximately [1 : 1]. Compound **2** was identical by ^{1}H NMR to that previously reported (reference 4).

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