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An efficient synthesis of cyercene A

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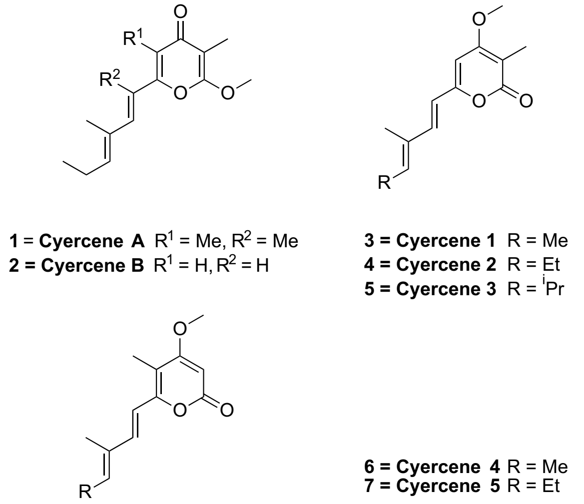
Abstract—An efficient approach to the total synthesis of the marine derived polypropionate cyercene A is described. A key feature of the synthesis is the development of methodology for the diastereoselective Wadsworth–Emmons type condensation of a functionalised γ-pyrone unit.

1. Introduction

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, are associated with specific ecophysiological functions of the molluscs, since they may act as mediators in tissue regeneration and chemical defence.[2]

Cyerce cristallina is an ascoglossan species whose body volume is mainly due to the presence of dorsal appendages aposematically coloured in white and red. When attacked by predators this mollusc secretes a presumably toxic mucus and, if molested further, it detaches its cerata, which then exhibit prolonged contractions and carry on secreting large amounts of mucus. After the occurrence of the autonomic process, the mollusc provides a striking example of regeneration by completely reproducing the cerata within only 7–10 days.

Intrigued by the unusual display of tissue regeneration for such a complex organism, Marzo and co-workers undertook a program of research, aimed at characterising some of the chemical signals involved in the chemical defence and regenerative processes of *C. cristallina.* Analysis of the molluscs cerata resulted in the isolation and characterisation of seven novel pyrone containing compounds, named the cyercenes (Fig. 1).[3]



1 = Cyercene A R^1 = Me, R^2 = Me
2 = Cyercene B R^1 = H, R^2 = H

3 = Cyercene 1 R = Me
4 = Cyercene 2 R = Et
5 = Cyercene 3 R = ^{i}Pr

6 = Cyercene 4 R = Me
7 = Cyercene 5 R = Et

Figure 1.

Of the seven compounds isolated, cyercene A **1** was found to be central to the signalling process responsible for controlling the amazing regenerative properties of the mollusc.[3,4] The unusual biological activity attributed to **1**, along with its interesting structural features make cyercene A **1** a worthy synthetic target.

As part of our continuing efforts directed towards understanding the origins of complex γ-pyrone-containing natural products,[5] we became interested in developing a synthetic route to cyercene A **1**, which could serve as a model for more complex systems.

Keywords: Pyrone; Propionate; Wadworth–Emmons.

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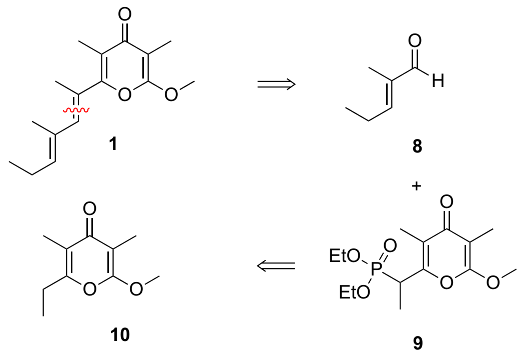
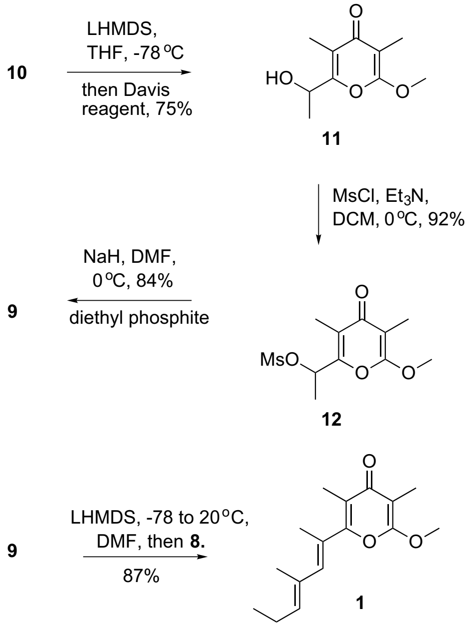


Scheme 1.

Scheme 1 depicts diagrammatically our retrosynthetic approach towards cyercene A **1**. Thus, disconnection of the indicated double bond reveals the commercially available aldehyde **8**, and the phosphono-γ-α-pyrone unit **9**, which we believed could be coupled in a diastereoselective manner to furnish the target compound.[6] Structurally related nonmethylated phosphono-pyrones have been reported by Koster and Hoffmann, however there are no reports of their use in Wadsworth–Emmons olefinations.[7] Further disconnection of the functionalised pyrone unit gives rise to the known pyrone **10**.

Our desire to utilise a Wadsworth–Emmons type approach for the coupling was based upon the well known ability of such reagents to generate *E*-trisubstituted olefins diastereoselectively.[8] It was also desirable to install the double bond in one step, thus avoiding additional dehydration protocols necessary in existing aldol-type methodology utilised in related studies with α-pyrones.[9]



Scheme 2.

Our synthesis of **1** commenced with the readily available 2-ethyl-6-methoxy-3,5-dimethylpyran-4-one **10**.[7,9] Deprotonation of **10** with lithium hexamethyldisilazide at −78 °C in tetrahydrofuran (THF), followed by quenching of the resulting anion with Davis oxaziridine,[10] gave hydroxypyrone **11** in good yield. Compound **11** was smoothly converted into its mesylate in excellent yield, which could be easily purified by flash silica gel chromatography to yield **12** as a white solid. Treatment of **12** with the sodium salt of diethyl phosphite in DMF at 0 °C, successfully generated the desired Wadsworth–Emmons reagent **9** in good yield. Finally, treatment of aldehyde **8** with the lithium salt of **9** at −78 °C to 20 °C in DMF, successfully yielded cyercene A **1** as the major diastereoisomer [E:$Z \geqslant 16{:}1$] in excellent yield (Scheme 2). All spectral data were in agreement with those of the natural compound.[3]

2. Conclusion

We have successfully achieved an efficient first total synthesis of cyercene A, employing a novel γ-pyrone-Wadsworth–Emmons reagent. We believe this type of approach represents useful methodology for the synthesis of this class of compounds.

Acknowledgements

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