

Total Synthesis of the Putative Structure of Tridachiahdropyrone

A thesis submitted for fulfilment of the degree of

Doctor of Philosophy

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March 2005

For Ella Paige



Tridachia crispata

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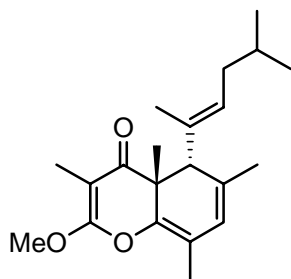
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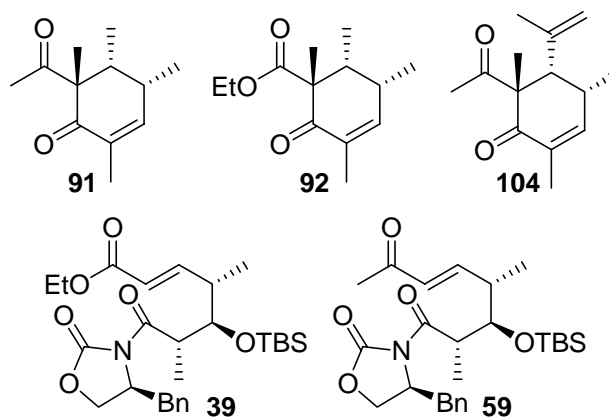
Abstract

Polypropionate marine natural products have emerged as a class of compounds that display a high degree of structural diversity. Specifically, metabolites such as that reported as tridachiahydropyrone (**7**), isolated from sacoglossan molluscs, display novel ring systems. The introductory chapter gives some background on tridachione marine natural products and outlines the isolation of metabolites from several species of sacoglossan mollusc. Chapter One also gives examples of the utility of the tandem conjugate addition-Dieckmann condensation approach being applied to the synthesis of these compounds.

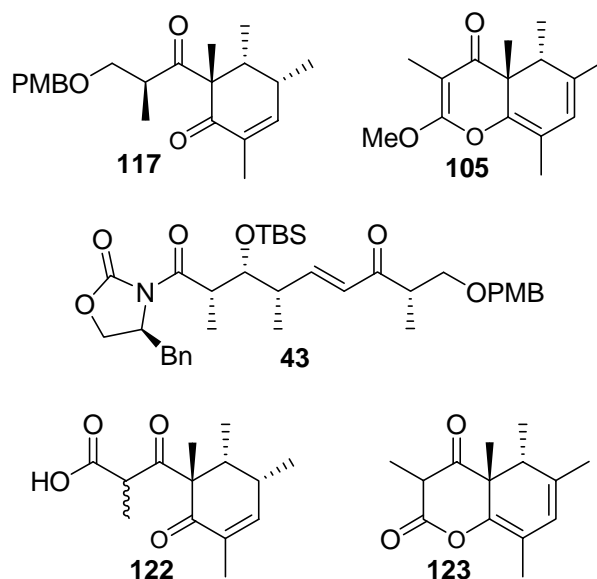


Tridachiahydropyrone (**7**)

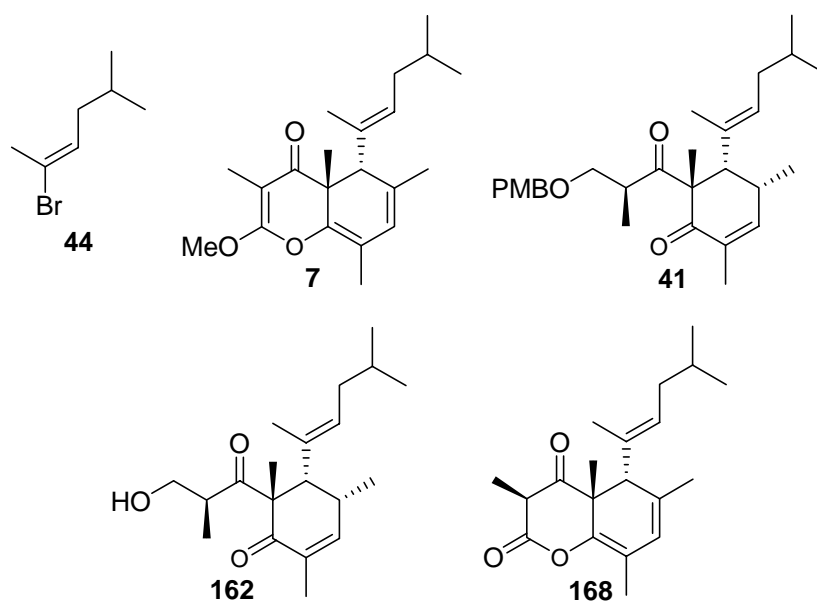
Chapter Two describes the development of the tandem conjugate addition-Dieckmann condensation and subsequent *trans* methylation approach to cyclohexenone rings. The synthetic strategy utilised chiral, functionalised cyclohexenone rings as synthons in the formation of bicyclic ring systems, so development of the carbocyclic ring formation was of vital importance to the overall strategy. Examples are given which confirm the viability of the proposed synthetic route to cyclohexenones such as **91**, **92** and **104** from the reaction of α,β -unsaturated carbonyl compounds **39** and **59** with dialkyl and dialkenyl Gilman cuprates.



Chapter Three describes the incorporation of chiral cyclohexenone **117** into the bicyclic framework of model compound **105**, analogous to the marine natural product reported as tridachiahydropyrone (**7**). The chapter explores the use of cyclohexenone precursor **43** that contained the total carbon framework of the bicyclic core of the desired pyrone. Once again, a tandem conjugate addition-cyclisation reaction was employed using a dialkyl Gilman cuprate, followed by *trans* methylation to give the requisite cyclohexenone synthon **117**. A novel Eaton's reagent-promoted intramolecular cyclisation of acid **122** to pyrone **123** was then effected. Subsequent *O*-methylation afforded α -methoxy- β -methyl- γ -pyrone **105** as a single enantiomer, which had the identical core structure to the natural product. The structure, including relative stereochemistry of **105**, was confirmed by single crystal X-ray analysis.



Chapter Four builds on the previous two chapters and describes the conjugate addition-cyclisation with a higher order Gilman cuprate derived from vinyl bromide **44**, which would deliver the vinyl side-chain required for the synthesis of reported natural product **7**. The same acyclic precursor **43** as used in Chapter Three was cyclised and methylated to yield yet another cyclohexenone synthon **41**. A single crystal X-ray analysis of related alcohol **162** confirmed the relative stereochemistry and structure. Another novel P_2O_5 -mediated intramolecular cyclisation was achieved to give pyrone **168** and *O*-methylation provided a compound with the reported structure of natural product **7** as a single enantiomer. The structure of synthetic **7** was established unequivocally through extensive NMR studies. Comparisons of spectral data confirmed that natural tridachiahdropyrone was not the same as synthetic compound **7**, so revision of the assigned natural product structure is warranted. Several other analogues were also synthesised using this methodology, highlighting the versatility of the method under development.



Declaration

'I certify that this thesis does not incorporate without acknowledgment any material previously submitted for a degree or diploma in any university; and that to the best of my knowledge and belief it does not contain any material previously published or written by another person except where due reference is made in the text.'

David W. Jeffery

18 March 2005

Acknowledgments

I would like to thank my supervisor, Dr. Michael Perkins, for his guidance and wisdom during my years of research. Dr. Perkins was always willing to listen and offer suggestions about my research project. He showed enthusiasm towards my research and encouraged and supported my endeavours. I also appreciated Dr. Perkins' good sense of humour and enjoyed the lunches and leisure activities that he organised.

I am grateful to all of the academic and research staff in the Department of Chemistry. In particular, I would like to express my gratitude to Prof. Rolf Prager, Dr. Martin Johnston, Dr. Gordon Elsey and Dr. Neil Trout, who were always willing to help in any way possible. I appreciate the support provided by the technical and office staff and the use of the chemistry department's ample facilities. I also wish to thank Assoc. Prof. Jonathan White, from the University of Melbourne, for his single crystal X-ray analysis work.

I would like to acknowledge my fellow students over the years spent at Flinders University. Many thanks to Troy Lister, Marc Grabowski, Saba Jahangiri, Milena Kasprzyk, Dani Lyons, Rebecca and John Joannou, Merran Daniel, Simon Mathew and many others for making those years even more enjoyable.

I extend my gratitude to overseas researchers Dr. Robert Walkup, Dr. Chris Adams, Prof. Shigeru Nishiyama and Prof. Kaori Ando, who were only too willing to answer my queries, and Dr. Margherita Gavagnin for her correspondence and copies of natural product spectra.

I wish to acknowledge the financial support of the MF & MH Joyner Scholarship in Science for my PhD scholarship and Flinders University and the Australian Research Council for various project funding.

I thank my family for their support and understanding, which has allowed me to pursue my dreams. I am eternally grateful for the love, encouragement and support shown by my wife Simone during this long haul and for the love of my precious daughter Ella. Time spent with my wife and daughter was the perfect remedy to the long hours spent undertaking my research.

Publications and Presentations

The following is a list of publications that have resulted from research outlined in this thesis and presentations that were delivered at various symposia.

Publications[☞]

1. Formation of Highly Substituted Chiral Cyclohexanone Derivatives Using a Tandem Conjugate Addition/Cyclisation
Jeffery, D.W.; Perkins, M.V. *Tetrahedron Lett.* **2004**, 45, 8667-8671.
2. Synthesis of an Analogue of the Marine Polypropionate Tridachiahdropyrone
Jeffery, D.W.; Perkins, M.V.; White, J.M. *Org. Lett.* **2005**, 7, 407-409.
3. Synthesis of the Putative Structure of Tridachiahdropyrone
Jeffery, D.W.; Perkins, M.V.; White, J.M. *Org. Lett.* **2005**, accepted.

Presentations

Synthetic Studies Directed Toward the Tridachione Family of Marine Natural Products.
Poster presentation delivered at the 19th RACI Organic Conference, Lorne, VIC, July 2003.

Synthetic Studies Directed Toward the Tridachione Family of Marine Natural Products.
Oral presentation delivered at the Adelaide Organic Synthesis Symposium, Adelaide, SA, December 2003.

Towards the Total Synthesis of the Marine Natural Product Tridachiahdropyrone.
Oral presentation delivered at the 15th Southern Highlands Conference on Heterocyclic Chemistry, Moss Vale, NSW, September 2004.

[☞] Reprints (and/or preprints) are contained within Appendix A.