UNIVERSITY OF CALIFORNIA

SANTA CRUZ

NMR AND COMPUTER ASSISTED MOLECULAR MODELING IN MARINE NATURAL PRODUCTS CHEMISTRY

A Dissertation submitted in partial satisfaction of the requirements for the degree of

DOCTOR OF PHILOSOPHY

in

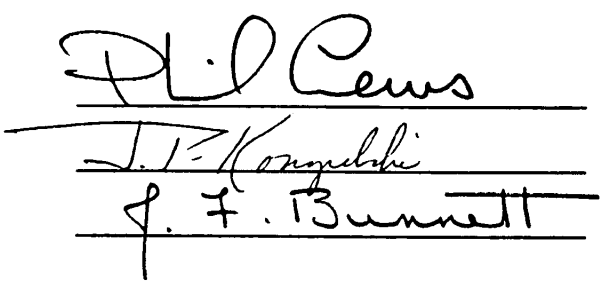
CHEMISTRY

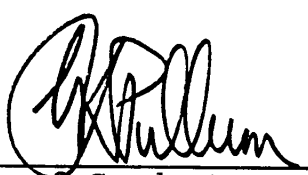
by

WAYNE DeWALD INMAN

JUNE 1989

The dissertation of
Wayne D. Inman is
approved by:



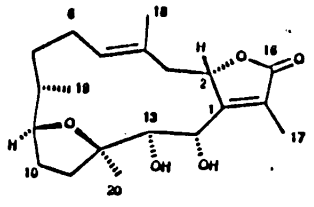


Dean of Graduate Studies and Research

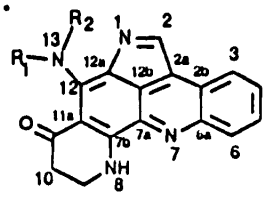
NMR and Computer Assisted Molecular Modeling in Marine Natural Products Chemistry.

by Wayne D. Inman

The research results reported in this thesis demonstrate the effective combination of nuclear magnetic resonance (NMR) spectroscopy and computer assisted molecular modeling in structure determination and conformational analysis of marine natural products. Chapter II describes the structure determination of pachyclavularolide (i) ($C_{20}H_{30}O_5$), a cembrane diterpene, by extensive 2D NMR experiments. The relative stereochemistry at each of six chiral sites was assigned $2S^*$, $8R^*$, $9S^*$, $12R^*$, $13S^*$, $14R^*$. Relative stereochemical assignments were based on ROESY correlations, ^3J coupling constants, and molecular mechanics calculations. Results from the conformational analysis of pachyclavularolide indicated that one major conformation exists in solution. This report represents the first detailed solution conformational analysis of a cembrane macrocycle. The structure and dynamic properties of novel pentacyclic aromatic alkaloids, plakinidine A (ii) and B (iii), and their biological activities are described in chapter III. The skeleton of the fused aromatic rings in plakinidine A and B, a pyrrolo[2,3,4-kl]acridine, represents a structural variation not previously found in aromatic alkaloids of marine or terrestrial organisms. A conformational analysis of a novel macrocyclic ketide-depsipeptide, jasplakinolide (iv), was completed using NMR data, molecular mechanics and dynamics calculations and is reported in chapter IV. A unique structural feature in jasplakinolide resides in the β-tyrosine, where flexibility in the backbone results in two major backbone conformations. The C1-C2-C3-N torsion angle adopts the g^- and g^+ conformations in solution and provides two different orientations of the β-tyrosine phenol side chain. Cooperative aromatic ring side chain coplanar orientations, a molecular tweezer and face-face stacking, were also investigated. Finally, the lithium complexation of jasplakinolide is discussed in chapter V. Only the g^+ C1-C2-C3-N backbone conformation of jasplakinolide weakly binds to Li^+ ($K = 60\ M^{-1}/CD_3CN$).

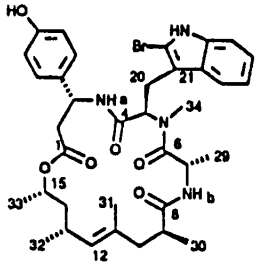


i



$R_1 = H, R_2 = CH_3$: ii

$R_1 = CH_3, R_2 = CH_3$: iii



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Acknowledgements

I would like to acknowledge the valuable contributions made by the following people to my graduate career. First, I would like to thank my mentor, Phil Crews, who has offered support, encouragement, and friendship throughout my stay at UC, Santa Cruz. Special thanks go to Dr. Robert McDowell (Genetech) for introducing me to the world of molecular modeling and assisting with the beginning implementation of the modeling programs at UC, Santa Cruz. I would like to also thank Dr. Clark Still (Columbia University) and Molecular Design, Ltd. for providing the computer programs Macromodel (V1.5) and Chemlab, respectively, and Dr. T. Wipke for the use of the Molecular Engineering Laboratory at UC, Santa Cruz. The molecular modeling work reported in this thesis was made possible by a grant from NSF DMB-8521802 for the purchase of the Evans and Sutherland PS-330 graphics terminal.

This research was supported by a grant to P. Crews from NOAA, National Sea Grant College Program, Department of Commerce, University of California project number R/MP-41. I would like to thank National Sea Grant College Program for a UC Sea Grant Trainee Fellowship, 1986-1988, and the Institute of Marine Resources for a Institute of Marine Sciences Dissertation Year Fellowship, 1988-1989.

"I held them in every light.
I turned them in every attitude.
I surveyed their characteristics.
I dwelt upon their peculiarities.
I pondered upon their conformation.
I mused upon the alteration in their nature."

Edgar Allan Poe
("Berenice", 1835).