



## Copyright Statement

The digital copy of this thesis is protected by the Copyright Act 1994 (New Zealand). This thesis may be consulted by you, provided you comply with the provisions of the Act and the following conditions of use:

- Any use you make of these documents or images must be for research or private study purposes only, and you may not make them available to any other person.
- Authors control the copyright of their thesis. You will recognise the author's right to be identified as the author of this thesis, and due acknowledgement will be made to the author where appropriate.
- You will obtain the author's permission before publishing any material from their thesis.

To request permissions please use the Feedback form on our webpage.  
<http://researchspace.auckland.ac.nz/feedback>

## General copyright and disclaimer

In addition to the above conditions, authors give their consent for the digital copy of their work to be used subject to the conditions specified on the Library [Thesis Consent Form](#)

# Studies in Marine Natural Product Synthesis, Isolation and Ecology

*A Thesis Presented to the University of Auckland for the Degree of*

**Doctor of Philosophy**

*by*

**Brent Steven Lindsay**



UNIVERSITY OF AUCKLAND  
-- SEP 1002  
LIBRARY

*For Murray, Kath, Jan and Karen*

## Abstract

Previous studies indicated the marine pyridoacridone alkaloid ascididemin possessed a unique biological profile. Investigation of synthetic routes to ascididemin led to the discovery that ascididemin precursors possessed a wide range of biological activities. One precursor possessed hollow fiber *in vivo* antitumoral activity and continuing *in vivo* studies at the NCI, using subcutaneous xenograft assays, are in progress. A crystal structure of a precursor indicates that these tetracyclic heterocycles are planar, suggesting intercalation as a mechanism of antitumoral action. Ascididemin was synthesized by two novel ring E forming reactions. The superior methodology was also useful in the preparation of analogues, such as kuanoniamine A. Ascididemin possessed promising hollow fiber *in vivo* antitumoral activity but was poorly active in a subcutaneous xenograft study. Ascididemin was incapable of exerting antitumoral activity at a distance and further analogues were prepared to address this problem. Ten analogues were prepared, with all the non-bromine containing analogues selected for *in vivo* evaluation at the NCI. Two ring A analogues were prepared by a then-new synthetic route, including the antiviral natural product 11-hydroxyascididemin. 11-Methoxyascididemin was selected for hollow fiber evaluation. Two bromine containing ring D analogues were prepared, including the antifungal natural product 2-bromoleptoclinidinone. A crystal structure on 2-bromoleptoclinidinone was the first determined on a pyridoacridone alkaloid and the molecule was planar, further supporting an intercalative mechanism of action. Due to non-selective antitumoral cytotoxicity, ring D analogues are not useful antitumoral agents. Six carbon-based ring E analogues were prepared by novel methodology. All 6-substituted analogues assessed were selected for *in vivo* antitumoral evaluation. Hollow fiber antitumoral activity decreased with bulk of the substituent. 6-Methylascididemin has been selected for subcutaneous xenograft studies. The 5-substituted analogue prepared gave the best *in vitro* antitumoral profile of all alkaloids in this study and has been selected for *in vivo* evaluation. Ring E substituted N-8-deaza-ascididemin analogues possessed no antitumoral activity, highlighting the importance of the 1,10-phenanthroline-like bay region of ascididemin in antitumoral activity. Another four structurally novel, quinoid containing alkaloids have been selected for *in vivo* evaluation. While ascididemin was the only compound capable of topoisomerase II $\alpha$  cleavable complex stabilization, related alkaloids possessed a similar level of inhibitory action against this enzyme. This further supports intercalation as the dominant mechanism of action for pyridoacridone alkaloids.

Ecological roles of four natural pyridoacridone alkaloids were assessed. Alkaloids were species specific antifeedant agents against important consumers. These alkaloids may have a long term detrimental effect on predator physiology, due to the well established ability of these alkaloids to interfere with cell proliferation. Ascididemin elicited avoidance responses in numerous marine species. Ascididemin has no antifouling activity against macrofoulers. Microbiological assessment of

ascididemin, 11-hydroxyascididemin and 2-bromoleptoclinidinone indicated that modification of the ascididemin chromophore leads to the directing of antimicrobial activity towards a different phyla of parasites. Pyridoacridone alkaloids may be part of a non-antibody based immune system. All studies point to pyridoacridone alkaloids enhancing the eventual reproductive success of the organism.

Biological and chemical evaluation of 29 New Zealand ascidians has been performed. Significant biological activity was detected in ten ascidians. Novel metabolites isolated were 2-(3'-bromo-4'-hydroxyphenyl)ethanamine (*Cnemidocarpa bicornuta*) and 1,3-dimethylguanine (unidentified ascidian). Known metabolites isolated were 1,3-dimethylisoguanine (*Cnemidocarpa bicornuta*) and rubrolides A, B and C (unidentified ascidian). The survey highlighted the importance of overexpressed purine bases in ascidian metabolism. No physiological roles for these overexpressed purines are as yet apparent. Our study of NZ ascidians has led to the isolation of many compounds previously isolated from sponges. The widespread distribution of such metabolites gives credence to the theory that common metabolite-generating genes are present in both phyla, due to the evolutionary success of these genes.

Two optically active 9-(5-S-methyl-5-sulfinyl-lyxofuranosyl)-9H-purin-6-amine (lyxosyl-MTAS) nucleosides were isolated from the nudibranch *Doriopsis flabellifera*. This is the first report of any lyxosyl-MTAS nucleoside as either a natural or synthetic product.

# Table of Contents

<b>Abstract</b>	i
Table of Contents	iii
List of Figures	vi
List of Tables	vi
List of Schemes	ix
List of Mechanisms	x
List of Bar Charts	xi
<b>Chapter 1 General Introduction</b>	
1.1 Marine Natural Product Chemistry and Biology	2
1.2 Pyridoacridine Alkaloids	4
<b>Chapter 2 Synthetic Studies on the Ascididemin Pharmacophore</b>	
2.1 Synthesis and Biology of Ascididemin	
2.1.1 Background	10
2.1.2 Synthesis of Ascididemin	11
2.1.3 Bracher's Methodology	13
2.1.3.1 Biology of the Enamine	18
2.1.4 Preparation of 11-Substituted Pyridoacridiones	23
2.1.4.1 Biology of 11-[2'-(Dialkylamino)ethyl]pyrido[2,3- <i>b</i> ]acridine-5,12-diones	28
2.1.5 Alternate Ascididemin Ring E Formations	32
2.1.5.1 Biology of Ascididemin	36
2.1.6 Ring E Formation on Related Substrates	40
2.1.7 Quaternization of N-7 of Ascididemin	45
Summary of Section 2.1: Synthesis and Biology of Ascididemin	50
Experimental for Work Described in Section 2.1	51
Appendix 1. X-ray Diffraction Methods and Data for 11-Methylpyrido[2,3- <i>b</i> ]acridine-5,12-dione	59
Appendix 2. Preliminary Bioactivity Screen/Topoisomerase II $\alpha$ Assays	65
2.2 Synthesis of Substituted Ascididemin Analogues	
2.2.1 Introduction	67
2.2.2 Functionalization of Ascididemin Ring A	
2.2.2.1 Literature Preparations of 11-Substituted Ascididemins	67
2.2.2.1.1 Preparation of 11-Methoxyascididemin	69
2.2.2.1.1.1 Biology of 11-Methoxyascididemin	74

2.2.2.1.2	Preparation of 11-Hydroxyascididemin	76
2.2.2.1.2.1	Biology of 11-Hydroxyascididemin	78
2.2.3	Functionalization of Ascidiemin Ring D	
2.2.3.1	Direct Functionalization of Ascidiemin; Bromination	79
2.2.3.1.1	Biology of 3-Bromoascididemin	81
2.2.3.3	Preparation of 2-Bromoleptoclinidinone	84
2.2.3.3.1	Biology of 2-Bromoascididemin	90
2.2.4	Functionalization of Ascidiemin Ring E	
2.2.4.1	Preparation and Biology of 6-Substituted Ascidiemin Analogues	91
2.2.4.1.1	Preparation, Biology and Chemistry of 6-Methylascididemin	92
2.2.4.1.2	Preparation and Biology of 6-Phenylascididemin	87
2.2.4.1.3	Preparation and Biology of 6-Cinnamylascididemin	102
2.2.4.1.4	Preparation and Biology of 6- <sup>n</sup> Alkylascididemins	106
2.2.4.1.5	Preparation of 6-Substituted Benzo[4,5]sampangines	111
2.2.4.1.5.1	Biology of 6-Substituted Benzo[4,5]sampangines	116
2.2.4.2	Preparation and Biology of 5-Substituted Ascidiemins	120
2.2.4.2.1	Preparation and Biology of the Model System 5-Methyleneacetate-N-8-deaza-ascididemin	121
2.2.4.2.2	Preparation and Biology of 5-Methyleneacetate-ascididemin	127
2.2.4.2.3	Preparation and Biology of Alkenal Precursors	131
2.2.4.2.4	Preparation and Biology of Pseudo-dimeric Moieties	136
	Summary of Section 2.2: Synthesis and Biology of Substituted Ascidiemin Analogues	150
	Experimental for Work Described in Section 2.2	152
	Appendix 3. X-ray Diffraction Methods and Data for 2-Bromoleptoclinidinone	172
2.3	References for Chapter 2	178

### **Chapter 3 Ecological Studies on Pyridoacridone Alkaloids**

3.1	Why do Natural Products Exist?	181
3.2	Potential Ecological Roles of Pyridoacridine Alkaloids	183
3.2.1	External Chemical Defense Roles of Selected Pyridoacridone Alkaloids	184
3.2.1.1	Non-ecologically Relevant Trials	184
3.2.1.2	Ecologically Relevant Trials	186
3.2.1.2.1	Antifeedant Trials	187
3.2.1.2.2	Surface Avoidance Trials	196
3.2.1.2.3	Antifouling Trials	198
3.3	Conclusions	207
3.4	Speculations	207



**Chapter 4 Chemical Investigations of New Zealand Marine Organisms**

## 4.1 Investigations of the Chemical Diversity of New Zealand Ascidiaceans

4.1.1 Background	210
4.1.2 Previous Work on New Zealand Ascidiaceans	211
4.1.3 Survey of 29 Ascidiaceans	212
4.1.3.1 96TC1-6	217
4.1.3.2 97MO1-4	219
4.1.3.3 97MO1-1	223
4.1.3.3 Z8581	226
4.1.3.5 96TA1-8	228
4.1.3.6 96CP1-16	229
4.1.3.7 96ChR1-18	229
4.1.3.8 96ChR1-1	229
4.1.3.9 96BR2-1	229
4.1.3.10 96CZ1-5	230

Summary of Section 4.1: Investigations of the Chemical Diversity of New Zealand Ascidiaceans	232
--	-----

## 4.2 Chemical Studies of Common Auckland Intertidal Invertebrates

4.2.1 Introduction	233
4.2.2 Invertebrate Studies	234
4.2.2.1 <i>Doriopsis flabellifera</i>	234
4.2.2.2 <i>Cliona celata</i>	242
4.2.2.3 <i>Cryptoconchus porosus</i>	243
4.2.2.4 <i>Onchidella nigricans</i>	243
4.2.2.5 <i>Pleurobranchea novaezealandiae</i>	243
4.2.2.6 <i>Lamellaria ophione</i>	244
4.2.2.7 Miscellaneous Observations	244

Summary of Section 4.2: Chemical Studies of Common Auckland Intertidal Invertebrates	246
--	-----

Experimental for Work Described in Section 2.2	247
--	-----

Appendix 4. $^1\text{H}$ and $^{13}\text{C}$ NMR Spectra of Selected Natural Products	255
---	-----

4.3 References for Chapter 4	263
------------------------------	-----

## Acknowledgments

## List of Figures

- 1 Pyridoacridine and pyridoacridone alkaloids.
- 2 The mechanism of the strand passing reaction.
- 3 Retrosynthetic analysis of published ascididemin syntheses.
- 4 Crystal structure of 11-methylpyrido[2,3-*b*]acridine-5,12-dione (**10**).
- 5 Observed 200 MHz <sup>1</sup>H-NMR spectra for methylene protons of **26**.
- 6 Cycloaddition approaches to ring A ascididemin analogues.
- 7 Retrosynthetic analysis of Kubo's synthesis of 11-hydroxyascididemin (**9**).
- 8 Retrosynthetic analysis of Kashman's synthesis of 11-methoxyascididemin (**40**).
- 9 Retrosynthetic analysis of Bracher's synthesis of 2-bromoleptoclinidinone (**8**).
- 10 Crystal structure of 2-bromoleptoclinidinone.
- 12 Chemical shifts for 11-(2'-acrolein)benz[*b*]acridine-5,12-dione, (**83**).
- 13 Synthetic ascididemin analogues with no *P. regularis* outright antifeedant activity.
- 14 Temporal structure of settlement and industrial antifouling agent intervention.
- 15 Schematic layout of antifouling trial in a flow through aquaria.
- 16 β-Carboline and related compounds from *Ritterella sigillinoides*.
- 17 Further metabolites from New Zealand ascidians.
- 18 Analytical HPLC trace of *Hipsistozoa* sp.
- 19 Potential fragmentations of 1,3-dimethylisoguanine and 1,3-dimethylguanaine.
- 20 Chemical shifts and observed HMBC correlations for 2-(3'-bromo-4'-hydroxyphenyl)ethanamine (**91**).
- 21 Halogenated phenethylamine derivatives from ascidians.
- 22 Examples of sponge metabolites containing the monobrominated tyramine moiety.
- 23 Potential fragmentation of 1,3-dimethylguanaine, 1,7-dimethylguanaine and 1,9-dimethylguanaine.
- 24 Rubrolides isolated from the ascidian coded Z8581.
- 25 One potential tautomer of 1,3-dimethylisoguanaine.
- 26 Metabolites of *Doris verrucosa*.
- 27 HMBC and COSY derived NMR assignments of unknown *Doriopsis* nucleoside B.
- 28 Selected NOESY correlations of unknown *Doriopsis* nucleoside B.

## List of Tables

- 1 NMR data for 11-methylpyrido[2,3-*b*]acridine-5,12-dione (**10**).
- 2 NMR data for 11-[2'-(dimethylamino)vinyl]pyrido[2,3-*b*]acridine-5,12-dione (**20**).
- 3 Bioactivity screen for enamine **20** and comparative values for 11-methylpyrido[2,3-*b*]acridine-5,12-dione (**10**)<sup>4</sup>, cleistopholine enamine (**18**)<sup>29</sup> and N-1-deaza-enamine (**19**)<sup>5</sup>.
- 4 Hollow fiber *in vivo* results for enamine **20**.

- 5 NMR data for 11-[2'-(dimethylamino)ethyl]pyrido[2,3-*b*]acridine-5,12-dione, **26**.
- 6 Bioactivity screen for 11-[2'-(dialkylamino)ethyl]pyrido[2,3-*b*]acridine-5,12-diones **26** and **27** with comparative values for 11-methylpyrido[2,3-*b*]acridine-5,12-dione (**10**),<sup>4</sup> 11-[2'-(dimethylamino)ethyl]benz[*b*]acridine-5,12-dione (**25**)<sup>5</sup> and 11-[2'-(diethylamino)ethyl]-benzo[2,3]cleistopholine, (deazadiethylamine).<sup>31</sup>
- 7 Hollow fiber *in vivo* results for 11-[2'-(dimethylamino)ethyl]pyrido[2,3-*b*]acridine-5,12-dione (**26**).
- 8 Bioactivity screen for ascididemin (**6**)<sup>4</sup> with comparative values for 11-methylpyrido[2,3-*b*]acridine-5,12-dione (**10**),<sup>4</sup> 11-[2'-(dimethylamino)vinyl]pyrido[2,3-*b*]acridine-5,12-dione (**20**) and 11-[2'-(dimethylamino)ethyl]pyrido[2,3-*b*]acridine-5,12-dione (**26**).
- 9 Hollow fiber *in vivo* results for ascididemin, **6**.
- 10 Early stage subcutaneous tumor model xenograft *in vivo* results for ascididemin, **6**.
- 11 NMR data for 4-phenylthiobenzo[*de*][3,6]phenanthroline-6(*6H*)-one, **31**.
- 12 NMR data for 4-methoxy-11-methylpyrido[2,3-*b*]acridine-5,12-dione, **45** and 11-methylpyrido[2,3-*b*]acridine-5,12-dione, **10**.
- 13 Comparison of <sup>13</sup>C-NMR data for 11-hydroxyascididemin (**9**, as recorded by Schmitz,<sup>13</sup> Kubo,<sup>42</sup> and Lindsay) and 11-methoxyascididemin (**40**, as recorded by Kashman<sup>20</sup> and Lindsay).
- 14 Bioactivity screen for 11-methoxyascididemin (**40**) with comparative values for ascididemin (**6**).<sup>4</sup>
- 15 Bioactivity screen for 11-hydroxyascididemin (**9**) with comparative values for 11-methoxyascididemin (**40**), ascididemin (**6**)<sup>4</sup> and N-8-deaza-ascididemin (**7**).<sup>4, 5</sup>
- 16 Comparison of <sup>13</sup>C-NMR data for ascididemin (**6**), 2-Bromoascididemin (**8**) and 3-bromoascididemin (**50**).
- 17 Bioactivity screen for 3-bromoascididemin (**50**) with comparative values for ascididemin (**6**)<sup>4</sup> and benzo[4,5]sampangine (**7**).<sup>4, 5</sup>
- 18 Comparison of NCI principal response parameters for ascididemin and 3-bromoascididemin.
- 19 Comparison of NCI principal response parameters for 2-bromoascididemin, 3-bromoascididemin and ascididemin.
- 20 Bioactivity screen for 2-bromoascididemin (**8**) with comparative values for 3-bromoascididemin (**38**), ascididemin (**6**)<sup>4</sup> and 11-hydroxyascididemin (**9**).
- 21 Bioactivity screen for 6-methylascididemin (**63**) with comparative values for ascididemin (**6**).<sup>4</sup>
- 22 Hollow fiber *in vivo* results for 6-methylascididemin, **63**.
- 23 Bioactivity screen for 6-phenylascididemin (**67**) with comparative values for 6-methylascididemin (**63**) and ascididemin (**6**).<sup>4</sup>
- 24 Hollow fiber *in vivo* results for 6-phenylascididemin (**67**, NSC 686553).

- 25 Comparison of  $^{13}\text{C}$ -NMR data for ascididemin (**6**), 6-methylascididemin (**63**), 6-phenylascididemin (**67**) and 6-phenyl-8-deaza-ascididemin (**68**).
- 26 Bioactivity screen for 6-cinnamylascididemin (**69**) with comparative values for 6-methylascididemin (**63**) and 6-phenylascididemin (**67**).
- 27 Comparison of  $^{13}\text{C}$ -NMR data for ascididemin (**6**), 6-cinnamylascididemin (**69**) and 6-phenylascididemin (**67**).
- 28 Hollow fiber *in vivo* results for 6-cinnamylascididemin.
- 29 Comparison of  $^1\text{H}$ -NMR data for benzo[4,5]sampangine (**7**), 6-phenylbenzo[4,5]sampangine (**68**), 6-methylbenzo[4,5]sampangine (**73**) and 6-cinnamylbenzo[4,5]sampangine (**74**).
- 30 NMR data for 6-phenylbenzo[4,5]sampangine, (**68**).
- 31 Comparison of  $^{13}\text{C}$ -NMR data for benzo[4,5]sampangine (**7**), 6-phenylbenzo[4,5]sampangine (**68**), 6-methylbenzo[4,5]sampangine (**73**) and 6-cinnamylbenzo[4,5]sampangine (**74**).
- 32 Bioactivity screen for 6-methylbenzo[4,5]sampangine (**73**) and 6-phenylbenzo[4,5]sampangine (**68**) with comparative values for benzo[4,5]sampangine (**7**).<sup>4, 5</sup>
- 33 Comparison of  $^{13}\text{C}$ -NMR data for 5-methyleneacetate-benzo[4,5]sampangine (**78**), benzo[4,5]sampangine (**7**)<sup>21</sup> and 5-methyleneacetate-ascididemin (**79**).
- 34 Bioactivity screen for 5-methyleneacetate-benzo[4,5]sampangine (**78**) with comparative values for benzo[4,5]sampangine (**7**).<sup>4</sup>
- 35 NMR data for 5-methyleneacetate-ascididemin (**79**).
- 36 Bioactivity screen for 5-methyleneacetate-ascididemin (**79**) with comparative values for ascididemin (**6**),<sup>4</sup> and 6-methylascididemin (**63**).
- 37 NMR data for 3',5'-di(11-pyrido[2,3-*b*]acridine-5,12-dione)pyridine (**84**).
- 38 Bioactivity screen for 3',5'-di(11-pyrido[2,3-*b*]acridine-5,12-dione)pyridine (**84**) and comparative values for enamine **20** and 11-methylpyrido[2,3-*b*]acridine-5,12-dione (**10**).<sup>4</sup>
- 39 Bioactivity screen for 3',5'-di(11-benz[*b*]acridine-5,12-dione)pyridine (**86**) and comparative values for 3',5'-di(11-pyrido[2,3-*b*]acridine-5,12-dione)pyridine (**84**).
- 40 Bioactivity screen for 7-deaza-7-(11-pyrido[2,3-*b*]acridine-5,12-dione)ascididemin (**85**) and comparative values for ascididemin (**6**) and 11-methylpyrido[2,3-*b*]acridine-5,12-dione (**10**).<sup>4</sup>
- 41 NMR data for 7-deaza-7-(11-pyrido[2,3-*b*]acridine-5,12-dione)ascididemin (**85**).
- 42 Crystal data and structure refinement for 2-bromoleptoclinidinone (**8**).
- 43 Atomic coordinates and equivalent isotropic displacement parameters for 2-bromoleptoclinidinone (**8**).
- 44 Bond lengths [ Å ] for 2-bromoleptoclinidinone (**8**).
- 45 Bond Angles [ ° ] for 2-bromoleptoclinidinone (**8**).
- 46 Anisotropic displacement parameters (Å<sup>2</sup>) for 2-bromoleptoclinidinone (**8**).
- 47 Hydrogen coordinates and isotropic displacement parameters (Å<sup>2</sup>) for 2-bromoleptoclinidinone (**8**).

- 48 Maximum permissible solvent level for the brine shrimp assay.
- 49 Antifeedant activity of pyridoacridones toward *Patiriella regularis*.
- 50 Antifeedant activity of pyridoacridones toward *Stegnaster inflatus*.
- 51 Antifeedant activity of pyridoacridones toward *Forsterygion varium*.
- 52 Antimicrobial activity of pyridoacridone alkaloids.
- 53 Antimicrobial activity of ascididemin and synthetic analogues.
- 54 Retention and activity of ascididemin in various gels.
- 55 Composition of gels used in an oceanic antifouling trial.
- 56 Antifouling activity of ascididemin in doped polyethylene.
- 57 Biological evaluation of ascidian crude extracts.
- 58 Chemical evaluation of ascidian crude extracts.
- 59 Comparison of chemical shifts of dimethylated purines.
- 60 Comparison of chemical shifts of sulfur containing nudibranch nucleosides.
- 61 Comparison of chemical shifts of sulfoxide containing nucleosides.

## List of Schemes

- 1 Bracher's Synthesis of Sampangine
- 2 Bracher's Synthesis of Ascididemin
- 3 Syntheses of Benzo[4,5]sampangine
- 4 Preparation of Mannich Base **26**
- 5 Preparation of Mannich Base **27**
- 6 Mannich Base Cyclization to Ascididemin
- 7 Ascididemin Ring E Formation Via Amine **27**
- 8 One Pot Formation of Ascididemin
- 9 One Pot Formation of Benzo[4,5]sampangine
- 10 One Pot Formation of 4-Phenylthiobenzo[de][3,6]phenanthroline-6(6H)-one
- 11 One Pot Formation of Kuanoniamine A
- 12 Attempted One Pot Formation of Sampangine
- 13 Attempted Formation of 4-Phenylaminobenzo[de][3,6]phenanthroline-6(6H)-one
- 14 N-7-Methylascididemin Formation, Route A
- 15 N-7-Methylascididemin Formation, Route B
- 16 Potential Demethylation Pathways
- 17 Unexpected Formation of Benzo[4,5]sampangine
- 18 Reductive Amination/Demethylation
- 19 Reductive Amination/Demethylation Pathways
- 20 Withopf and Lackner's Synthesis of 4-Methoxyquinoline-5,8-quinone
- 21 Preparation of the Key Intermediate, Quinone **45**

- 22 Attempted Syntheses of 11-Methoxyascididemin
- 23 Cleavage of the Methyl Ether
- 24 Bromination of Ascidiidemin
- 25 Knovendi and Kircz's Preparation of 2-Nitro-4-bromo-acetophenone
- 26 Alternate Synthetic Route
- 27 Routes to 4-Bromo-2-amino-acetophenone
- 28 Bracher's Synthesis of 2-Bromoleptoclinidinone
- 29 Preparation of 6-Substituted Ascidiidemins
- 30 Chemistry of 6-Methylascidiidemin
- 31 Preparation of 6-Heptylascidiidemin
- 32 Preparation of 6-Substituted Benzo[4,5]sampangines
- 33 Peterson's Preparation of 5-Substituted Sampangines
- 34 Attempted Preparation of 5-Bromobenzo[4,5]sampangines
- 35 Potential Enamine Products
- 36 Attempted Methoxide Exchange
- 37 Potential Route to 5-Substituted Alkaloids
- 38 Potential Products From Cyclization
- 39 The Alkenal Equivalent
- 40 Preparation of 5-Methyleneacetate-benzo[4,5]sampangine
- 41 Alternate Preparation of 5-Methyleneacetate-benzo[4,5]sampangine
- 42 Preparation of 5-Methyleneacetate-ascidiidemin
- 43 Preparation of Alkenal **82**
- 44 Alternate Preparation of 5-methyleneacetate-benzo[4,5]sampangine
- 45 Preparation of 3',5'-di(11-pyrido[2,3-*b*]acridine-5,12-dione)pyridine
- 46 Preparation of 3',5'-di(11-benz[*b*]acridine-5,12-dione)pyridine
- 47 Preparation of 7-deaza-7-(11-pyrido[2,3-*b*]acridine-5,12-dione)ascidiidemin
- 48 Bromination of Tyramine hydrochloride

## List of Mechanisms

- 1 Bracher's Acetal Condensation-Cyclization Annulation
- 2 Reactivity of Enamine **20**
- 3 Ascidiidemin Ring E Formation from Amine **26**
- 4 Dimer and Trimer Formation
- 5 Proposed Mechanisms for the One Pot Reaction
- 6 Isoxazole Formation
- 7 Reductive Annulation
- 8 Formation of 5-Methyleneacetate-benzo[4,5]sampangine

- 9 Formation of Pyridine Bridged Dimer
- 10 The Reverse Mannich Reaction in Action
- 11 Alternative Formation of Pyridine Bridged Dimer

### List of Bar Charts

- 1 NCI Mean Graphs for 11-[2'-(Dimethylamino)vinyl]pyrido[2,3-*b*]acridine-5,12-dione, **20**.
- 2 NCI Mean Graphs for 11-[2'-(Dimethylamino)ethyl]pyrido[2,3-*b*]acridine-5,12-dione, **26**.
- 3 NCI Mean Graphs for Ascidiemin, **6**.
- 4 NCI Mean Graphs for 11-Methoxyascidiemin, **40**.
- 5 NCI Mean Graphs for 3-Bromoascidiemin, **50**.
- 6 NCI Mean Graphs for 6-Methylascidiemin, **63**.
- 7 NCI Mean Graphs for 6-Phenylascidiemin, **67**.
- 8 NCI Mean Graphs for 6-Cinnamylascidiemin, **69**.
- 9 NCI Mean Graphs for 6-Heptylascidiemin, **70**.
- 10 NCI Mean Graphs for 6-Methylbenzo[4,5]sampangine, **73**.
- 11 NCI Mean Graphs for 6-Phenylbenzo[4,5]sampangine, **68**.
- 12 NCI Mean Graphs for 6-Cinnamylbenzo[4,5]sampangine, **74**.
- 13 NCI Mean Graphs for 5-Methyleneacetate-ascidiemin, **79**.
- 14 NCI Mean Graphs for 11-(2'-Acrolein)benz[*b*]acridine-5,12-dione, **83**.
- 15 NCI Mean Graphs for 3',5'-di(11-pyrido[2,3-*b*]acridine-5,12-dione)pyridine, **84**.
- 16 NCI Mean Graphs for 3',5'-di(11-benz[*b*]acridine-5,12-dione)pyridine, **86**.
- 17 NCI Mean Graphs for 7-deaza-7-(11-pyrido[2,3-*b*]acridine-5,12-dione)ascidiemin, **85**.