*To my family*

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# ABSTRACT

The propellane alkaloids comprise a large class of natural products that possess varying degrees of structural complexity and biological activity. The earliest of these to be isolated was acutumine, a chlorinated alkaloid that has been shown to exhibit selective T-cell cytotoxicity and antiamnesic properties. Alternatively, the hasubanan family of natural products has garnered considerable attention from the synthetic community in part due to its structural similarities to morphine. While these alkaloids have been the subject of numerous synthetic studies over the last forty years, very few enantioselective total syntheses have been reported to date.

As part of a research program directed towards the synthesis of various alkaloid natural products, we have developed a unified strategy for the preparation of the hasubanan and acutumine alkaloids. Specifically, a highly diastereoselective 1,2-addition of organometallic reagents to benzoquinone-derived *tert*-butanesulfinimines was established, which provides access to enantioenriched 4-aminocyclohexadienone products. This methodology enabled the enantioselective construction of functionalized dihydroindolones, which were found to undergo intramolecular Friedel-Crafts conjugate additions to furnish the propellane cores of several hasubanan alkaloids. As a result of these studies, the first enantioselective total syntheses of 8-demethoxyrunanine and cepharatines A, C, and D were accomplished in 9-11 steps from commercially available starting materials.

More recent efforts have focused on applying the sulfinimine methodology to the synthesis of a more structurally complex propellane alkaloid, acutumine. Extensive studies have determined that a properly functionalized dihydroindolone undergoes a

photochemical [2+2] cycloaddition followed by a lactone fragmentation/Dieckmann cyclization to establish the carbocyclic framework of the natural product. The preparation of more appropriately oxidized propellane intermediates is currently under investigation, and is anticipated to facilitate our synthetic endeavors toward acutumine.

# TABLE OF CONTENTS

## CHAPTER 1 1

An Introduction to the Hasubanan Alkaloids

## CHAPTER 2 22

Development of a Diastereoselective 1,2-Addition to Sulfinyl Imines: Application to the Hasubanan Alkaloids

**APPENDIX 1** **88**

Spectra Relevant to Chapter 2

**APPENDIX 2** **215**

X-Ray Crystallography Reports Relevant to Chapter 2

**CHAPTER 3** **229**

An Introduction to Acutumine

**CHAPTER 4** **243**

Progress Toward the Total Synthesis of Acutumine

# LIST OF ABBREVIATIONS

| | |
|---|---|
| $[\alpha]_D$ | angle of optical rotation of plane-polarized light |
| Å | angstrom(s) |
| Ac | acetyl |
| AIBN | azobisisobutyronitrile |
| app | apparent |
| aq | aqueous |
| Ar | aryl group |
| atm | atmosphere(s) |
| Bn | benzyl |
| Boc | *tert*-butoxycarbonyl |
| bp | boiling point |
| br | broad |
| Bu | butyl |
| *n*-Bu | butyl or *norm*-butyl |
| *t*-Bu | *tert*-butyl |
| $c$ | concentration of sample for measurement of optical rotation |
| $^{13}C$ | carbon-13 isotope |
| $^{14}C$ | carbon-14 isotope |
| /C | supported on activated carbon charcoal |
| °C | degrees Celcius |
| calc'd | calculated |
| CBS | Corey-Bakshi-Shibata |

| | |
|---|---|
| Cbz | benzyloxycarbonyl |
| $cm^{-1}$ | wavenumber(s) |
| CN | nitrile |
| conc. | concentrated |
| Cy | cyclohexyl |
| d | doublet |
| *d* | dextrorotatory |
| D | deuterium |
| dba | dibenzylideneacetone |
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| DHP | dihydropyran |
| DIBAL | diisobutylaluminum hydride |
| DMAP | 4-dimethylaminopyridine |
| DME | 1,2-dimethoxyethane |
| DMF | *N*,*N*-dimethylformamide |
| DMP | Dess–Martin periodinane |
| DMSO | dimethylsulfoxide |
| dppp | 1,3-bis(diphenylphosphino)propane |
| dr | diastereomeric ratio |
| *ee* | enantiomeric excess |
| $E^+$ | electrophile |
| *E* | trans (entgegen) olefin geometry |
| EDC | *N*-ethyl-*N*’-(3-dimethylaminopropyl)carbodiimide |

| | |
|---|---|
| e.g. | for example (Latin: *exempli gratia*) |
| eq | equation |
| ESI | electrospray ionization |
| Et | ethyl |
| *et al*. | and others (Latin: *et alii*) |
| FAB | fast atom bombardment |
| g | gram(s) |
| h | hour(s) |
| $^1H$ | proton |
| $^2H$ | deuterium |
| $^3H$ | tritium |
| H-G II | Hoveyda-Grubbs, 2nd generation |
| HMDS | hexamethyldisilamide or hexamethyldisilazide |
| HMPA | hexamethylphosphoramide |
| $h\nu$ | light |
| HPLC | high performance liquid chromatography |
| HRMS | high resolution mass spectrometry |
| Hz | hertz |
| i.e. | that is (Latin: *id est*) |
| IR | infrared spectroscopy |
| $J$ | coupling constant |
| $k$ | rate constant |
| kcal | kilocalorie(s) |

| | |
|---|---|
| kg | kilogram(s) |
| L | liter or neutral ligand |
| *l* | levorotatory |
| LA | Lewis acid |
| LAH | lithium aluminum hydride |
| LDA | lithium diisopropylamide |
| m | multiplet or meter(s) |
| M | molar or molecular ion |
| *m* | meta |
| μ | micro |
| *m*-CPBA | *meta*-chloroperbenzoic acid |
| Me | methyl |
| mg | milligram(s) |
| MHz | megahertz |
| min | minute(s) |
| mL | milliliter(s) |
| mol | mole(s) |
| MOM | methoxymethyl |
| mp | melting point |
| Ms | methanesulfonyl (mesyl) |
| *m/z* | mass-to-charge ratio |
| N | normal or molar |
| NBS | *N*-bromosuccinimide |

| | |
|---|---|
| NIS | *N*-iodosuccinimide |
| nm | nanometer(s) |
| NMO | *N*-methylmorpholine-*N*-oxide |
| NMR | nuclear magnetic resonance |
| NOE | nuclear Overhauser effect |
| NOESY | nuclear Overhauser enhancement spectroscopy |
| $Nu^-$ | nucleophile |
| *o* | ortho |
| *p* | para |
| Ph | phenyl |
| pH | hydrogen ion concentration in aqueous solution |
| $pK_a$ | acid dissociation constant |
| PMB | *para*-methoxybenzyl |
| PMHS | polymethylhydrosiloxane |
| ppm | parts per million |
| Pr | propyl |
| *i*-Pr | isopropyl |
| *n*-Pr | propyl or *norm*-propyl |
| psi | pounds per square inch |
| pyr | pyridine |
| q | quartet |
| R | alkyl group |
| *R* | rectus |

| | |
|---|---|
| ref | reference |
| $R_f$ | retention factor |
| s | singlet or seconds |
| *S* | sinister |
| t | triplet |
| TBAF | tetra-*n*-butylammonium fluoride |
| TBHP | *tert*-butyl hydroperoxide |
| TBS | *tert*-butyldimethylsilyl |
| Tf | trifluoromethanesulfonyl |
| TFA | trifluoroacetic acid |
| TFAA | trifluoracetic anhydride |
| THF | tetrahydrofuran |
| TLC | thin layer chromatography |
| TMS | trimethylsilyl |
| TMSE | 2-(trimethylsilyl)ethyl |
| TOF | time-of-flight |
| tol | tolyl |
| Ts | *para*-toluenesulfonyl (tosyl) |
| UV | ultraviolet |
| w/v | weight per volume |
| v/v | volume per volume |
| X | anionic ligand or halide |
| *Z* | cis (zusammen) olefin geometry |