Second Generation Synthesis of UCS1025A.

Synthetic Efforts Toward Total Syntheses of

CJ-16,264 and Phomopsichalasin.

A THESIS SUBMITTED TO THE FACULTY OF
THE GRADUATE SCHOOL OF THE UNIVERSITY OF MINNESOTA

By

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IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

Thomas R. Hoye, Adviser

June 2009
Acknowledgements

I would like to express my gratitude to the following people for their help and input during my doctoral studies at the University of Minnesota:

Professor Thomas R. Hoye for his teaching and guidance. Thank you, Tom, very much for teaching me the skills and beauty of organic synthesis and its multiple applications. Thank you for allowing me to be a part of “Organic Synthesis” and “Advanced Organic Chemistry Laboratory” courses, to break and fix LC/MS, and to supervise undergraduate researchers.

Hoye group members: Dr. Vadims Dvornikovs, Dorian Nelson, Mandy Schmit, Susie Emond, Dr. Gregory Hanson, Aaron Burns, Junha Jeon, Lucas Kopel, and Cagri Enver Izgu for fruitful collaborations and helpful discussions on various topics of organic chemistry.

Professors Wayland E. Noland and Richard P. Hsung for allowing me to get earlier exposure to organic chemistry by allowing me to work in their research groups.

Professors Christopher J. Douglas and Andrew M. Harned for exciting discussions during numerous synthesis lunches.

Professors T. A. Taton, C. J. Forsyth, S. R. Kass, L. Que, and J. Gao for their teaching graduate courses, from which I learned a lot.

I would like to remember and thank my family, my mother Olga, my father Pavel, my grandmother Argira, my sister Liza, my brother Andrei, and, especially, my husband Alexander for their continuous love and support throughout the entire graduate school educational process.
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<tbody>
<tr>
<td>Ac</td>
<td>Acetyl</td>
</tr>
<tr>
<td>AcCl</td>
<td>Acetyl Chloride</td>
</tr>
<tr>
<td>Alloc</td>
<td>Allyloxy carbonyl</td>
</tr>
<tr>
<td>Ar</td>
<td>Aryl</td>
</tr>
<tr>
<td>ATA</td>
<td>Acyltetramic Acid</td>
</tr>
<tr>
<td>9-BBN</td>
<td>9-Borabicyclo[3.3.1]nonane</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl (\text{C}_6\text{H}_5\text{CH}_2\text{-})</td>
</tr>
<tr>
<td>BHT</td>
<td>2,6-Di-tert-Butyl-4-methylphenol/ Butylated Hydroxytoluene</td>
</tr>
<tr>
<td>°C</td>
<td>Degrees Celsius</td>
</tr>
<tr>
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<td>Calculated</td>
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<td>COSY</td>
<td>Correlated Spectroscopy</td>
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<td>CYP</td>
<td>Cytochrome P450</td>
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<tr>
<td>DBU</td>
<td>1,8-Diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DCM</td>
<td>Dichloromethane</td>
</tr>
<tr>
<td>DEPT</td>
<td>Distortionless Enhancement Polarization Transfer</td>
</tr>
<tr>
<td>DHP</td>
<td>3,4-Dihydro-2(H)-pyrane</td>
</tr>
<tr>
<td>DIBALH</td>
<td>Diisobutylaluminum Hydride</td>
</tr>
<tr>
<td>DIPEA</td>
<td>Hünig’s Base, Diisopropylethylamine</td>
</tr>
<tr>
<td>DMB</td>
<td>2,4-Dimethoxybenzyl</td>
</tr>
<tr>
<td>DMF</td>
<td>Dimethylformamide</td>
</tr>
<tr>
<td>DMP</td>
<td>Dess-Martin Periodinate</td>
</tr>
<tr>
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<td>Dimethylsulfoxide</td>
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<tr>
<td>Dppf</td>
<td>1,1’-Bis(diphenylphosphino)ferrocene</td>
</tr>
<tr>
<td>dr</td>
<td>Diastereomeric Ratio</td>
</tr>
<tr>
<td>E</td>
<td>Electrophile</td>
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</table>
EDC 1-Ethyl-3-[3-dimethylaminopropyl]carbodiimide Hydrochloride
EE Ethoxyethyl
$ee$ Enantiomeric excess
equiv Equivalent
Et$_2$O Diethyl Ether
Et$_3$N or TEA Triethylamine
EtOAc Ethyl Acetate
GC-MS or GC/MS Capillary Gas Chromatography-Mass Spectrometry
HMBC Hetero-Nuclear Multiple Bond Correlation
HMPA Hexamethylphosphoramide
HMOC Heteronuclear Multiple Quantum Correlation
HRMS High Resolution Mass Spectrometry
HSQC Heteronuclear Spin Quantum Correlation
IC$_{50}$ 50% of the concentration for complete inhibition of cellular viability
IMDA Intra-Molecular Diels-Alder
IR Infrared
$J$ Coupling constant (NMR)
LC-MS or LC/MS Liquid Chromatography-Mass Spectrometry
LHMDS Lithium Hexamethyldisilazide
LRMS Low-Resolution Mass Spectrum
MDR Multi-Drug Resistant
Me Methyl
MeI Methyl Iodide
MeOH Methanol
MIC Minimum Inhibitory Concentration
mp Melting Point
MPLC Medium Pressure Liquid Chromatography
<table>
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<th>Description</th>
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<tr>
<td>4Å MS</td>
<td>4-Angstrom Molecular Sieves</td>
</tr>
<tr>
<td>NBS</td>
<td>N-Bromosuccinimide</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>nOe</td>
<td>Nuclear Overhauser Effect/Enhancement</td>
</tr>
<tr>
<td>NOESY</td>
<td>Nuclear Overhauser Effect/Enhancement Spectroscopy</td>
</tr>
<tr>
<td>PCC</td>
<td>Pyridinium Chlorochromate</td>
</tr>
<tr>
<td>PMB</td>
<td>$p$-Methoxybenzyl</td>
</tr>
<tr>
<td>PPh$_3$</td>
<td>Triphenylphosphine</td>
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<tr>
<td>PPTS</td>
<td>Pyridinium $p$-Toluenesulfonate</td>
</tr>
<tr>
<td>$i$-Pr or $^i$Pr</td>
<td>Isopropyl</td>
</tr>
<tr>
<td>$R_f$</td>
<td>Ratio to Front</td>
</tr>
<tr>
<td>RT or rt</td>
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</tr>
<tr>
<td>SEM</td>
<td>Trimethylsilylethoxyethylmethyl</td>
</tr>
<tr>
<td>SKA</td>
<td>Silyl Ketene Acetal</td>
</tr>
<tr>
<td>$t_{1/2}$</td>
<td>Half-Life Time</td>
</tr>
<tr>
<td>TBAF</td>
<td>Tetrabutyl Ammonium Fluoride</td>
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<td>$tertiary$-Butyldiphenylsilyl</td>
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<tr>
<td>TBSCI</td>
<td>$tertiary$-Butyldimethylsilyl Chloride</td>
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<td>$tertiary$-Butyldimethylsilyl Triflate</td>
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<tr>
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</tr>
<tr>
<td>TFA</td>
<td>Trifluoroacetic Acid</td>
</tr>
<tr>
<td>TIPS</td>
<td>Triisopropylsilyl</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin Layer Chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>Trimethylsilyl</td>
</tr>
<tr>
<td>$t_R$</td>
<td>Retention Time</td>
</tr>
<tr>
<td>TRAP</td>
<td>Telomere Repeat Amplification Protocol</td>
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Abstract

The present work consists primarily of the four projects. The first is methodology for silyl triflate-mediated Dieckmann-like cyclization between esters and imides. The second project is the second generation synthesis of a natural product UCS1025A, which included optimization of the synthesis of the triene precursor of UCS1025A and exploration of its biomimetic Intra-Molecular Diels-Alder (IMDA) cycloaddition. A more efficient way to synthesize the corresponding triene via the MeMgBr-mediated addition of the corresponding vinyl iodide to the enal and optimization of the diastereoselectivity of the final Diels-Alder-cycloaddition to produce UCS1025A are described.

The third project, described in Chapter II, is synthetic efforts toward total synthesis of the related natural product CJ-16,264. We have studied the diastereoselective IMDA cycloaddition of the corresponding chiral aldehyde precursor in the presence of MacMillan catalyst followed by BEt₃–promoted Reformatski-coupling with iodolactones in the synthesis of various diastereomeric analogs of CJ-16,264.

The final project, described in Chapter III, is the synthetic efforts total synthesis of the natural products phomopsichalasin and diaporthichalasin, which we envision to be biosynthesized via a series of two sequential and spontaneous IMDA cycloadditions. Several approaches to the heterocyclic portion of the natural products and their tetraene precursor are described.
Chapter I. Second Generation Synthesis of UCS1025A

A. Introduction and Background

“Biomimetic syntheses are often more efficient due to the tactics that nature employs, namely rapid assembly of skeletal complexity, a linear increase of oxidation state, use of mild and simple reagents, and the ability to control chemoselectivity (lack of protecting groups). Despite their inherent advantages, biomimetic syntheses can be exceedingly difficult, due to the inability of chemists to attain the chemo-, regio-, and stereocontrol characterizing most enzymatic processes. The careful practitioner can make use of many abiotic tools in solving these problems; however, these methods usually demand significant departure from the ideal biomimetic route. In light of these difficulties, it is certainly possible, and perhaps prudent, to find the appropriate balance when designing a retrosynthesis. An ideal synthesis might entail the use of powerful synthetic methods, coupled with a flexible adherence to the general synthetic blueprint provided by nature.”

1. Isolation of UCS1025A

UCS1025A (1) (Figure 1) was isolated from the fermentation broth of the Acremonium sp. KY4917 fungus in 2000 by Yamashita and coworkers. In addition to 1, UCS1025B (2) (Figure 1), a C7-hydroxylated analog of 1, was isolated from the same broth. Fungal strain KY4917 was grown on malt extract agar medium and then fermented on glucose and dried mashed potatoes medium. The 30 liters of culture broth afforded 131 mg of UCS1025A (1) and 4.8 mg of UCS1025B (2) after crude extract separation and final purification by silica gel chromatography. The structure and relative configuration of 1 was determined using extensive nuclear magnetic resonance (NMR) studies (1H NMR, 13C NMR, DEPT, HSQC, COSY, NOESY, and HMBC) and X-ray crystallographic analysis in 2002 by Agatsuma and coworkers.3

The interesting structural features of a novel pentacyclic polyketide-derived natural product UCS1025A 1 include: 8 stereogenic centers, an unprecedented furopyrrrolizidine tricyclic core, and a trans-fused octalin moiety. Most intriguing is that in solution,
depending on the nature of the solvent and its pH, \( 1 \) can exist in \( 1a \) (keto-form), \( 1b \) (enol-form), \( 1c \) (open-form as a carboxylate), or as various equilibrium mixtures (Figure 1). In the same work Agatsuma and coworkers have also illustrated that UCS1025B (2) could be derived from UCS1025A upon treatment with mCPBA.

Figure 1. UCS1025A and UCS1025B Natural Products

![Figure 1](image_url)

2. Biological activity of UCS1025A

UCS1025 A (1) was subjected to an initial screening for antibiotic activity. It was found to exhibit antimicrobial activity against the Gram-positive bacteria, *Staphylococcus aureus* (MIC 1.3 µg/mL), *Bacillus subtilis* (MIC 1.3 µg/mL), and *Enterococcus hirae* (MIC 1.3 µg/mL) and the Gram-negative bacterium *Proteus vulgaris* with MIC values in 1.3 - 5.2 µg/mL range. In contrast, UCS1025B (2) showed a weak antimicrobial activity against the same bacteria with MIC values that ranged from 42 to 83 µg/mL, which suggest about importance of the other isomeric forms of \( 1 \) in solution.

UCS1025A (1) was also identified as a novel telomerase inhibitor. This type of biological activity is of special interest and deserves to be described in more detail (Figure 2).
Telomeres are nucleoprotein structures highly conserved in organisms ranging from yeasts to mammals, and they are essential for preventing abnormal recombination and protection against DNA degradation. Telomerase is a ribonucleoprotein enzyme complex that maintains the telomeric structures at the chromosomal termini by adding the strand of telomere repeats. Telomerase activity usually declines as a natural part of aging, and normal human cells either do not express telomerase or express very low levels of it, and, thus, telomeres progressively shorten with each cell division due to incomplete replication of lagging strand DNA synthesis. Loss of telomeres to below a threshold value is believed to induce cell apoptosis.

Figure 2. Telomerase Expression in Stem Cells

Telomerase reactivates in cancer cells and maintains telomere length, allowing them to continue dividing. Thus, telomerase activation is assumed to be the main pathway by
which cancer cells become immortal. These properties predict a substantial therapeutic window between cancer and normal cells, and they make telomerase a potentially universal and relatively safe anticancer target for drug discovery.

As demonstrated in Figure 2, embryonic stem cells are usually characterized by relatively long telomere chains. These telomeres are reconstructed with the help of the telomerase enzyme as shown on the right side of Figure 2. Then, over time, expression of the telomerase enzyme becomes less significant and shortening of the telomeres occurs in adult stem cells (Figure 2), which leads to chromosomal instability and hence, to the onset of cell apoptosis as described above.

A number of small-molecule telomerase inhibitors have been reported. Most were identified by random biochemical screening to measure human telomerase inhibitory activity.\textsuperscript{10} UCS1025A was identified as a telomerase inhibitor during screening of a yeast-based cellular assay by Yamashita and coworkers.\textsuperscript{3,6} During their screening, the unrelated antibiotics chrolactomycin and radicicol (Figure 3) along with 1 were identified as a new class of telomerase inhibitors that exhibited selective inhibitory activity against the telomere-shortened yeast strain. Using a TRAP (telomere repeat amplification protocol) assay with crude cellular extracts from A431 human tumor cells as a source of telomerase, it was demonstrated that UCS1025A and chrolactomycin are direct inhibitors of human telomerase in a dose-dependent manner with an IC\textsubscript{50} of 1.3 \textmu M and 0.5 \textmu M respectively.\textsuperscript{6}

\textbf{Figure 3.} UCS1025A, Chrolactomycin and Radicicol, Examples of a Novel Class of Telomerase Inhibitors
B. Synthetic Strategies Toward UCS1025A

1. Total Syntheses of UCS1025A

i. Danishefsky’s Total Synthesis of UCS1025A

The first total synthesis of UCS1025A (1) was reported in early 2006 by Lambert and Danishefsky at the Sloan-Kettering Institute for Cancer Research/Columbia University, New York.\(^{11}\) Compelled by the telomerase inhibitory activity and the compact structure of 1, they decided to undertake its total synthesis. Their synthetic efforts provided the natural enantiomer of UCS1025A.

Their original synthetic plan involved an aldol or Claisen condensation-like coupling of pyrroliizidine 2 with the fragment 3 to afford the corresponding 1,3-diketone 4 and then to further convert 4 into 5 through a series of oxidations (Scheme I-1).

**Scheme I-1.** Danishefsky’s Original Synthetic Strategy Toward UCS1025A

They prepared the core pyrrolizidine fragment 6, but unfortunately all attempts to introduce functionality at C7 of compound 6 were unsuccessful (Scheme I-2). As an explanation of this result Lambert and Danishefsky suggested that there is a severe steric interaction between the silyloxy-methyl substituent and the \textit{endo} C7a proton. They further explained that trigonalization of C7, a consequence of enolization, would result in an increase in the bicyclic cup angle and thus an amplification of that unfavorable
interaction (cf. 8, Scheme 1-2). In support of this hypothesis they also prepared a pyrrolizidine C2a diastereomer 9, which would not suffer from such an interaction, and have illustrated that 9 does undergo LiHMDS-induced enolization.

**Scheme 1-2.** Danishefsky’s Attempted Functionalization of Core Fragment 2

Disappointed by the remarkable resistance of 6 to enolization Lambert and Danishefsky revised their synthetic strategy to UCS1025A as summarized in Scheme 1-3. Encouraged by the Hoye group report of a mild enolization-cyclization method to access UCS1025A-like structures, as further developed by us and discussed in Chapter I-D-1 part of this thesis, they synthesized pyrrolizidine core 10a. This racemic sample could be separated by HPLC on an enantioselective column. They took advantage of the previously disclosed organocatalytic synthesis of the octalin aldehyde 11 by the MacMillan group. They found that treatment of 10a and 2 equiv of 11 with triethylborane in toluene at –78 °C effected a rapid, quantitative, and completely diastereoselective Reformatsky-type aldol coupling to provide 12 with the full skeleton of the natural product (Scheme 1-3). This remarkable process produced no β-elimination product and an excess of aldehyde 11 could be recovered intact. Deprotection of a TBS group with TBAF followed by Dess-Martin periodinate oxidation provided UCS1025A (1).
Although this synthesis is very convergent and utilizes an efficient coupling of two complex fragments, it does not allow study of the role of the pyrrolizidine core in the biosynthesis of 1.

**Scheme I-3.** Danishefsky’s Revised Total Synthesis of UCS1025A

**ii. Christmann Total Synthesis of UCS1025A and Its Analogs**

The second total synthesis of UCS1025A (1) was reported by our research group in the first half of 2006\(^{17}\) shortly after the Lambert and Danishefsky publication. This work is discussed in Chapter I-C-2.

A third total synthesis of UCS1025A was published by Christmann and co-workers in 2007.\(^{18}\) Although their effort utilized the same end-game strategy as in the Danishefsky’s synthesis described above (*i.e.*, Reformatsky coupling of 10a and 11, TBS deprotection with TBAF, and Dess-Martin oxidation to provide 1), these authors developed a kinetic resolution of carboxylic acid 13a to access iodolactone 10a of high enantiomeric purity from racemic starting materials.

During their synthesis, Christmann *et al.* first tried to utilize a modification of our methodology\(^{13}\) in a one-pot synthesis of acid 13a from amine 14 and maleic anhydride (15) by treating their mixture with TBSOTf and Et\(_3\)N, quenching with 1 N HCl, and neutralizing with K\(_2\)CO\(_3\)/MeOH (Scheme I-4). However, to their surprise they observed formation of the undesired *cis*-isomer 17 with high diastereoselectivity. The authors suggested that this result could be explained by reaction not proceeding via a maleimide intermediate.
They then used our soft-enolization/cyclization methodology to access acid 13a from maleimide 18a. Following the seminal work of Wynberg and Hiemstra, they studied a kinetic resolution of acid (±)-13a via cinchona alkaloids-catalyzed hetero-Michael addition. For example, they showed that the kinetic lactonization of acid (±)-13a in the presence of 0.5 equiv of quinine yielded acid (+)-13a (53% yield, 51% ee) and lactone (−)-20a (47% yield, 62% ee). The kinetic lactonization of acid (±)-13a in the presence of 0.5 equiv of quinidine yielded lactone (+)-20a (23% yield, 47% ee) and acid (−)-13a in 77% yield and 14% ee. Since (−)-13a was the required enantiomer for the synthesis of UCS1025A and resolution with quinine was more selective than with quinidine, acid (−)-13a was obtained by selective conversion to lactone (−)-20a using quinine, and reconversion of isolated (−)-20a to acid (−)-13a (40% ee) by elimination with DBU.

Encouraged by the fact that selective dissolution of the major enantiomer of scalemic mixtures of less than 100% enantiopurity has been used to upgrade the %ee of such mixtures, the authors found that when a weakly enriched scalemic mixture of 13a was triturated in hot n-pentane, acid (−)-13a was preferentially dissolved, while (±)-13a remained as a solid residue (Scheme I-5). They explained this phenomenon by the fact that homochiral and heterochiral compounds have different solubility properties. As shown in Scheme I-5, Christmann et al. converted (−)-13a into UCS1025A (1) using the endgame strategy developed by Danishefsky (vide supra).

In addition to accomplishing a total synthesis of UCS1025A (1), the Christmann research group also described the optimized synthesis of some starting materials and analogs of 1.
Scheme I-5. Christmann’s Resolution of Pyrrolizidines for the Synthesis of UCS1025A (see Scheme I-13 for the structures of the “b” series: 10b, 13b, and 18b-20b)

They developed an efficient synthesis of aldehyde 11 (Scheme I-6),\(^{21,22}\) using a Wittig reaction of aldehyde \(21\)\(^{23}\) and the ylide formed from commercially available phosphonium salt \(22\) to produce trienal \(23\) in 91% yield, which then was converted into \(11\) by an organocatalytic Diels-Alder reaction with MacMillan’s catalyst \(24a\).\(^{15}\)

The authors were able to halve the catalyst loading to 10 mol% by using nitromethane as the solvent and to receive the Diels-Alder adduct \(11\) in 74% yield and 84% ee. The ee of \(11\) was upgraded to >99% by recrystallization of the corresponding alcohol \(25\) and its reoxidation to aldehyde \(11\) with PCC.

Christmann also published a scalable synthesis of maleimidobutyric acid (18a).\(^{24}\) They developed a one-step procedure of heating amine \(14\) and maleic anhydride (15) in acetic acid for only 90 min to avoid 1,4-addition of acetic acid to the Michael acceptor. Instead of chromatographic purification, the authors obtained pure acid 18a by partitioning the reaction mixture in ethyl acetate/water and either recrystallization of the
crude product from fairly concentrated ethyl acetate solution or Kugelrohr distillation (Scheme I-6).

**Scheme I-6.** Christmann’s Optimized Synthesis of Aldehyde 11 and Acid 18a

The latest contribution by this research group was the synthesis of malimide analogs of UCS1025A (Scheme I-7).²¹ Being aware of obstacles encountered by Lambert and Danishefsky during reaction of pyrrolizidine 6 with electrophiles (*vide supra*), they developed an aldol reaction of malimide 26 with various aldehydes. To avoid β-elimination of the hydroxyl group in 26 they generated dianion 27, which was added to aldehydes to produce diols 28. As reported by Procter *et al.* for a similar substrate,²⁵ the ring hydroxyl group was protected selectively over the side-chain hydroxyl group (imidazole, TBSCl), and the remaining secondary alcohol was oxidized to a ketone with DMP or PCC to provide β-ketoimides 29.

Interestingly, when the authors tried to subject compound 29b to various IMDA conditions, they observed only decomposition of starting materials or a complex mixture
of products. They speculated that the reason behind the decomposition was the facile β-elimination of TBS-OH under the reaction conditions. The elimination gave rise to a highly reactive dienophile, which could be trapped by Diels-Alder reaction with cyclopentadiene (not shown).

**Scheme I-7.** Christmann’s Synthesis of Malimide Analogs 29a-c of UCS1025A

2. **Synthetic Efforts Toward UCS1025A**

i. **Snider’s Synthetic Efforts Toward UCS1025A**

The first synthetic efforts toward UCS1025A (1) and its analogs were reported by Snider and Neubert in 2004.26 They described a concise synthesis of the tricyclic compound 34, having the pyrrolizidine core of UCS1025A (Scheme I-8).

**Scheme I-8.** Snyder’s Synthetic Efforts Toward UCS1025A Analog 34
They started by adding prolinol (29) to the ketene generated from 30\textsuperscript{27} upon heating in toluene. Modified Moffat oxidation with EDC/DMSO and aldol condensation gave enol 32. The latter was subjected to oxidation with DMDO at –40 °C to provide alcohol 34 by way of epoxide 33, followed by spontaneous opening into pyrrolidinone 34, which is a quite reactive compound and would be hard to access otherwise. This oxidation represents a possible biomimetic route to pyrrolidinones like 34.

ii. Shirai’s Synthetic Efforts Toward UCS1025A

Shirai et al. reported a completely different approach to the synthesis of 2,4-dialkyl-3-hydroxybutanolides with three successive stereogenic centers (e.g., Scheme I-9, lactone 35), by an acid-catalyzed ring-switch reaction of the 2-(2-hydroxyalkyl)lactams 36.\textsuperscript{28}

Scheme I-9. Shirai’s Retrosynthesis of UCS1025A

As illustrated in Scheme I-10, they started with the diastereoselective aldol reaction of N-Boc-butyrolactam (37) with (S)-4-(tert-butyldiphenylsiloxy)-2-triethylsiloxybutanal (38),\textsuperscript{29} which afforded aldol adducts as a mixture of four diastereomers (39, 40, 41, and 42, the latter two of the four were inseparable). Treatment of aldol adducts 39 and 40 with TsOH at rt for 3 h resulted in TES-group removal with production of the corresponding diols, which were further in situ converted into the corresponding chiral butanolides 35 and 43 via a ring-switch lactonization. The relative configurations of 35 and 43 were determined by NOE-difference experiments.

iii. Other Approaches to the Synthesis of UCS1025A

Several other research groups reported their interest in the synthesis of UCS1025A (1), although this work has not been explicitly published in scientific literature. For
example, Denmark et al. at the University of Illinois, Urbana-Champaign reported some efforts on inter-[4+2]/intra-[3+2] cycloadditions of nitroalkenes approach to synthesis of UCS1025A (1). DeBoef et al. at the University of Rhode Island reported efforts on rhodium-catalyzed C-H-activation and hydroalkylation of allylic C-H bonds and its application to synthesis of pyrrolizidinone natural products like UCS1025A (1).

**Scheme I-10.** Shirai’s Synthesis of Hydroxybutanolide 35

1. Hoye Group’s Hypothesis on Biosynthesis of UCS1025A

   Our research group initiated studies on a total synthesis of UCS1025A (1) in 2003, shortly after the publication of the isolation and structure elucidation of 1. In contrast to all other reported efforts on the synthesis of UCS1025A, our group was interested in the biosynthetic origin of UCS1025A. We were intrigued by the following question: does the octalin moiety of this natural product come from an enzymatically catalyzed IMDA cycloaddition of a triene precursor like 45, or does this cycloaddition occur **spontaneously** under biologically relevant conditions? (Scheme I-11).

   While there has been long standing interest in the idea that Diels-Alderases can promote [4+2] cycloadditions, the fact is that very few actual examples of such processes exist. Requirement for enzymatic catalysis is nearly always evolutionarily disadvantageous, and in cases like 45 some of such cycloadditions might occur spontaneously on the organism’s time-scale. We further hypothesized that the
heterocyclic pyrrolizidine moiety of 45 serves a dual role: i) that of “super-dienophile”, 
<i.e.,</i> a dienophile, containing activating 1,3-dicarbonyl group that, when protonated or 
complexed to metal ions ubiquitous under biosynthetic conditions in an aqueous medium, 
promotes ambient temperature cyclization, and ii) that of a chiral auxiliary to induce the 
correct relative configuration of newly formed stereocenters in the octalin.

**Scheme I-11.** Hoye Group’s Hypothesis on Biosynthesis of UCS1025A (1)

This hypothesis was also supported by a considerable number of isolated natural 
products containing both an octalin and an acyltetramic acid (ATA) unit as in the 
generalized structure 46. ATAs of Types 1-3 are depicted in Figures 1, 4, and 5 (<i.e.,</i> Type 1 in UCS1025A open-form (1c) in Figures 1 and 4 and CJ-16,367 (301) in Figure 6).

2. Dvornikovs’ 1st Generation Total Synthesis of UCS1025A

To explore the hypothesis on biosynthesis of UCS1025A (1), one would have to 
answer the following questions: 1) would the nonenzymatic reaction be fast enough to be 
the natural event? 2) If so, would the chiral heterocyclic moiety in 45 induce a 
sufficiently high level of diastereocontrol that none of <i>tetraepi</i>-UCS10125A (55) would 
have been observed during the isolation of UCS1025A? These questions become more 
fascinating to consider in light of the facile interconversions among isomeric species 1a
(keto-form), 1b (enol-form), 1c (open-form) that were observed during the original isolation studies of UCS1025A.\textsuperscript{3} It was fully reasonable to think that the substrate 45 would also access the analogous isomeric species. This further added to the intrigue of the Diels-Alder event, since keto-, enol-, and open forms of the triene each possesses different dienophilic character, and the IMDA rate and diastereoselectivity would be unique to each.

**Figure 4.** Types of Octalinoyl Acyltetramic Acid Natural Products

The initial retrosynthetic analysis proposed by Hoye and Dvornikovs is shown in Scheme I-12. Biomimetic endo-selective IMDA of 45 would be used to form the octalin moiety and to install four final stereocenters of 1. The desired triene 45 would be assembled via Grignard coupling of Weinreb amide 47 and alkenyl iodide 48b. The latter could be accessed via silylative Dieckmann-like cyclization of methyl maleimidobutyrate (18b),\textsuperscript{34} developed in our laboratory.\textsuperscript{13}
Scheme I-12. Hoye and Dvornikovs: Initial Retrosynthesis of UCS1025A (1)

The concise construction of the alkenyl iodide 48b is depicted in Scheme I-13. Dvornikovs started with development of an intramolecular Dieckmann-like condensation, in which the α-carbon of a butyrate ester side chain added (via its generated in situ ketene acetal) to one of the imide carbonyl groups of 18b (presumably activated by in situ silylation).

Methyl ester 49b was formed with a very high level of diastereoccontrol (dr > 30:1). Lithium hydroxide enabled hydrolysis of 49b gave the acid 13b. The latter could be isolated and handled, but over time it cyclized to a tricyclic lactone 20b (this lactonization was especially fast, when acid 13b was heated in organic solvent). Acid 13b smoothly underwent sequential iodolactonization into 10b and silylative ring-opening to the TIPS ether/TIPS-ester alkenyl iodide 48b.

Iodine-magnesium exchange between 48b and i-PrMgCl, followed by addition of Weinreb amide 47 gave 50b, a bis-TIPS analogue of 45, in 35% yield. This coupling was the most problematic step in the Dvornikovs synthesis, since it gave variable yields varying from 0% to 35%. Bis-TIPS-triene 50b underwent IMDA cycloaddition with a $t_{1/2}$ of ca. 6 days at room temperature and 3 h at 65 °C in CDCl$_3$ to provide, predominantly, a ca. 4:3 ratio of two isomeric adducts 51b and 52b, each resulting from an endo mode of addition (Scheme I-14). These two compounds were not amenable to separation by either normal or reversed-phase chromatography. This sense of diastereoselectivity, as well as the rate of the IMDA reaction, is to be contrasted with the thermal IMDA reaction of the Weinreb amide 47 itself, which required 5-6 days at 165 °C and proceeded with 1:3 endo:exo selectivity.$^{35}$ The substrate control expressed in the IMDA addition of 50b favors the endo addition, but the facial selectivity for the approach of the diene to the dienophile was almost nonexistent. Hoye and Dvornikovs speculated that such selectivity was likely a reflection of the remote nature of the existing stereocenters in 50b.$^{17}$ The TIPS ester of 50b was selectively cleaved with KF/MeOH to provide a new Diels-Alder substrate, the tricyclic lactone 53b, which exists only in its enol tautomeric form by $^1$H NMR spectroscopy. Hoye and Dvornikovs explained such tautomeric preference by suggesting that the hydroxyl group of the free carbinol amide, which in 1 plays an important role in stabilizing the keto-form by way of an internal hydrogen bond, is absent in 53b (cf. 45 in Scheme I-11). No Diels-Alder cyclization of 53b was observed over several days at room temperature, and even at 65 °C in CDCl$_3$, the $t_{1/2}$ for formation of 54b and 55b (dr 1:2) was ca. 20 h. Enols 54b and 55b that could also be formed from
51b and 52b respectively by analogous selective cleavage of TIPS-esters were not separable by chromatography in the authors’ hands.

Scheme I-14. Dvornikovs: Synthetic Efforts Toward UCS1025A (1)

As shown in Scheme I-15, both TIPS groups of 50b were removed with HF•pyridine to provide the desired biomimetic Diels-Alder substrate 45 in its keto-form 45a (CDCl₃), which was consistent with the role of the internal hydrogen bond (vide supra). Triene 45 underwent very clean [4 + 2] cycloaddition at room temperature in CDCl₃ with a t₁/₂ of ca. 26 h yielding UCS1025A (1) and unnatural 9,10,15,18-tetraepi-UCS1025A (56) in a 1:3 ratio. Most intriguing of all, when 45 was dissolved in phosphate buffer (pH 7.2, D₂O, 0.1 M), it immediately converted into carboxylate 45c (¹H NMR data), which rapidly cyclized into a nearly 1:1 mixture of 1c and 56c with a t₁/₂ of 10 min!

Unfortunately, facile keto-enol tautomerization of 1 and 56 conspired to make separation of these isomers frustratingly challenging. Researchers were able to get a pure sample of 1 by multiple HPLC purifications and recrystallization of its 1b enol-isomer, which tautomerized into 1a upon standing in CDCl₃.

Nevertheless, the remarkably fast IMDA cycloaddition under biologically relevant conditions set the time-limits, within which enzyme catalysis would need to function, if it takes place in the biosynthesis of 1. The observed rate of IMDA transformation of carboxylate 45c is sufficiently fast to be easily compatible with the hypothesis that 1 is formed in vivo by a nonenzymatic event. However, the lack of diastereoselectivity of this cycloaddition (1c and 56c were formed in a 1:1 ratio) would suggest the opposite.

As mentioned earlier to support the hypothesis on the biosynthesis of UCS1025A (1), one would need positive answers to both questions: 1) would the nonenzymatic reaction be fast enough to be the natural event? 2) If so, would the chiral heterocyclic moiety in 45 induce a sufficiently high level of diastereocontrol that none of tetraepi-UCS10125A (56) would have been observed during the isolation of UCS1025A? To answer the second question we decided to study the IMDA cycloaddition of 45 in full detail and to have an access to sufficient quantities of triene 45, which was not as straightforward as it seems.
To assemble the full carbon framework of 45 Dvornikovs used the coupling of iodide 18b and Weinreb amide 47, which resulted in variable yields of 50b (0-35%). The major side-product of this reaction was ester 19b, a product of protonation of initially formed magnesium anion of 48b. He spent quite a bit of time fruitlessly trying to optimize this coupling as well as seeing an alternative strategy to 50b. As depicted in Scheme I-16, he tried to couple the anion, generated via iodine-magnesium exchange, with acid chloride 57, but the only isolated product of this reaction was 19b. Vadims was also able to do a lithium-iodine exchange of 48b with n-BuLi, followed by addition of aldehyde 23. The corresponding alcohol 58b was consistently produced in 20-35% yield, and, additionally, extensive formation of a protonated by-product 19b and decomposition of 48b were observed. However, all subsequent attempts to convert 58b to 50b under various oxidative conditions (e.g., Swern, IBX, TPAP/NMO) failed; Dvornikovs observed only decomposition of the starting material 58b and/or of the product 50b.


D. New Progress Toward UCS1025A. Second Generation Total Synthesis of UCS1025A

1. Silylative Dieckmann-like Cyclizations of Ester-Imides
i. Introduction and Background

Upon contemplating modes of construction of the heterocyclic core of the telomerase inhibitor UCS1025A (1), Hoye and Dvornikovs considered the cyclization of an ester enolate equivalent with an imide carbonyl group as in 18b. The base sensitivity of 18b quickly revealed itself; no trace of the corresponding aldol adduct was ever observed under basic reaction conditions. This turned their attention to a cationic process involving the silyl ketene acetal (SKA) 60 derived from the enolizable ester 59 (as in 18b). One of the most common methods to generate SKA 60 is the reaction of the acyclic carboxylic acid ester 59 with trialkyl silyl triflates (R₃SiOTf) in the presence of an amine base (e.g., Et₃N) (Scheme I-17). However, under these conditions depending on the structure of the acyl and alkoxy groups in 59, SKA 60 may reversibly rearrange into the frequently thermodynamically more stable α-trialkylsilylcarboxylates 61 (Scheme I-17). Silylation at the carbonyl oxygen atom of 62 is always the first step of the reaction. The resulting equilibrium ratio of 60 : 61 depends upon the resonance stabilization in the ester group. With increasing resonance stabilization, α-silylated product 61 is formed preferentially.

Scheme I-17. In Situ Generation of SKA 60 and Trapping with an Electrophile

Bulky R₃Si-groups slow down the rearrangement of 60 to 61. Under thermodynamic control, the reactions of carboxylic acid esters 59, SKAs 60, and esters 61 with R₃SiOTf afford identical distributions of products, irrespective of the starting material used. SKA 60 can be trapped by either inter- or intramolecular processes with another more reactive electrophile (e.g., the Lewis acid activated carbonyl group in 63) with formation
of the aldol adduct 64. This siphoning of the reactive SKA 60 eventually leads to complete conversion to the thermodynamically most stable aldol product 64. SKAs serve as nucleophiles in various addition reactions to C=X containing electrophiles, including aldehydes/ketones, imines, enones, and acyl halides to provide β-hydroxyesters, β-aminoesters, δ-ketoesters, and β-ketoesters respectively.39

Hoye and Dvornikovs first demonstrated12 that this approach is very effective for generating species like 49b essentially as a single diastereomer (cf. Scheme I-13), a key-intermediate in the synthesis of the natural product UCS1025A (1). Prior to these studies, we were not aware of an imide functional group serving the role of acceptor. Considering the vast array of possible substrates 18 for this cyclization, this methodology represented a highly convergent strategy for the synthesis of compounds with a pyrrolizidone skeleton or their analogs 49 (Scheme I-18).

**Scheme I-18. Silylative Dieckmann-like Cyclizations of Ester-Imides 18**

We wanted to develop a diastereoselective version of such a cyclization to study effects from changing the ring size in the imide 18, the ring size of the newly formed carbocycle 49, the nature of the carbonyl acceptor, and the impact of different substituent(s) R1 and R2 in imide 18. The results of these studies were published in 2006.13

**ii. Silylative Dieckmann-like Cyclization of Methyl Maleimidobutyrate (18b)**

The synthesis of ester-imide 18b can be achieved in 3-4 steps from readily available starting materials (Schemes I-19). Esterification of commercially available 4-aminobutyric acid (14) occurred uneventfully. The resulting aminoester 65 reacted with maleic acid anhydride (15) giving acid 66 in 100% yield. Cyclization of the acid 66 in the
presence of Ac₂O/NaOAc gave ester-imide 18b in only 54% yield. The major by-product of the reaction was imide 67, the product of 1,4-addition of AcOH to 18b. To improve the overall yield of the synthesis, I tried to find conditions for the elimination of AcOH in 67. This elimination is certainly possible under forcing conditions. However, after several unsuccessful attempts I decided it would be easier to find different conditions for 18b synthesis. Reflux of acid 66 in AcCl for 10 h yielded a mixture of the desired ester-imide 18b and the 2-chlorosuccinimide 68 in total yield of 80%. Elimination of HCl with Et₃N in 68 gave ester-imide 18b in 89% yield.

Scheme I-19. Synthesis of Methyl Butyromaleimide 18b

When ester-imide 18b was treated with TMSOTf and TEA in chlorocarbon solvents (CH₂Cl₂ or CDCl₃), the bicyclic lactam 49c was produced in high yield and diastereomeric ratio (dr) (Scheme I-20). The endo-orientation of the carbomethoxy group in the predominant product—a fortunate outcome vis-à-vis synthesis of 1—was established on the basis of a single crystal x-ray analysis and eventual elaboration into UCS1025A.¹⁷ The sense of diastereoselectivity of this reaction is consistent with C-C bond formation through an open transition state geometry for the addition of the SKA to an O-silylated imide carbonyl as suggested in 71-endο (as opposed to the synclinal geometry of 71-exο). This reaction could be extended to higher trialkysilyl triflates. TBSOTf and TIPSOTf gave products 49a and 49b, respectively, with comparable
outcomes; the only difference was a progressively slower overall reaction rate \( t_{1/2} \approx 15 \text{ min, 49a; 7 h, 49b; and 6 min, 49c at [18b] = 0.3 \text{ M in CDCl}_3 \text{ and 1.5 equiv of R}_3\text{SiOTf).} \\
In addition, I observed a low, steady state level of each of the intermediate SKAs 69 by \(^1\text{H NMR spectroscopy.}^{40} \) When the reaction mixture was undercharged with TMSOTf, major product 49c was accompanied by a small amount of \( \alpha \)-silylated ester 70. This suggested that the SKA 69 was competitively and, perhaps, reversibly silylated at the \( C^* \) vs. \( O^* \) atoms in 69. Indeed, resubjection of isolated 70 to TMSOTf/Et\(_3\)N in CDCl\(_3\) resulted in its clean conversion to lactam 19b (Scheme I-20).

**Scheme I-20.** Silylative Dieckmann-like Cyclizations of Methyl Maleimidobutyrate (18b)

Knowing that similar cyclizations can be applied to the total synthesis of complex molecules, I investigated deprotection conditions for 49c and the stability of the resulting alcohol 72 (Scheme I-21). I found that the TMS-group could be removed with HF/pyridine, buffered with pyridine, or DBU (cat) in MeOH in high yield. The resulting hydroxyl-group in 72 can be reprotected with TESCl or any \( R_3\text{SiOTf.} \) However, under more strongly acidic conditions (non-buffered HF/Py, Amberlyst\(^{\circledast} \) 21), I observed slow dehydration of 72 with formation of enamide 74 (probably via unfavorable formation of an antiaromatic intermediate iminium ion 73).\(^{41} \) Under more strongly basic conditions
(e.g., KF/MeOH, K$_2$CO$_3$/MeOH, KOH/MeOH), alcohol 72 was converted back to the starting ester-imide 18b. Upon heating of the alcohol 72 in chlorocarbon solvents its dr changes from 62:1 to 1.2:1. We hypothesized that the observed non-selective formation of trans and cis stereoisomers of 72 was due to intermediate formation of the eight-membered cyclic amide 75a. However, so far we were not able to isolate or trap such an intermediate.

**Scheme I-21.** Formation and Stability of the Alcohol 72

![Scheme I-21](image)

**iii. Silylative Dieckmann-like Cyclization of Esters**

Simple esters are known to be silylated with R$_3$SiOTf in diethyl ether.$^{42}$ As a model I examined the silylation of methyl propionate (59a) under conditions more similar to those used for the cyclization of 18b (Scheme I-22). Namely, in CDCl$_3$ solution I could easily monitor ($^1$H NMR analysis) the extent of conversion to a mixture of SKA 60a and the α-silylated ester 61a, which is more stable than the corresponding SKA 60a due to resonance stabilization of the ester group. Starting with 2 equiv of TMSOTf and TEA, the system equilibrated to a steady state mixture of 59a:60a:61a in a ratio of ~5:trace:1.
Scheme I-22. Silylation of Methyl Propionate (59a)

To probe if \textit{in situ} activation of an ester electrophile might also serve to induce a net, silylative Dieckmann cyclization, Dvornikovs also investigated simple dimethyl \(\alpha,\omega\)-dicarboxylates like 76 and demonstrated this to be an alternative to basic conditions of intramolecular Dieckmann condensation.\(^{13}\) In order to compare the rates of inter- vs. intramolecular Dieckmann condensation, I have studied the rate of cyclization of diester 76 both in the presence of methyl propionate (59a) (Scheme I-23). When a 2:1 mixture of 59a/76 was subjected to TMSOTf/Et\(_3\)N conditions, the only observed products were 77 and 61a. Products of intermolecular addition (\textit{i.e.}, 78, 79a, or 79b) were not observed. We interpret this result to mean that intramolecular addition is faster than the intermolecular reaction, and the initially formed SKAs (\textit{i.e.}, 60a and SKA of 76) have a short life-time (being in equilibrium with the corresponding \(\alpha\)-silylated derivatives and starting esters) and react with the readily available electrophile (intramolecular attack on the ester group in 76 and reaction of 60a with TMSOTf).

Scheme I-23. Inter- vs. Intramolecular Silyl Triflate-Mediated Intramolecular Dieckmann Condensation of Esters

iv. Silylative Dieckmann-like Cyclization of Methyl Maleimidopentanoate (18c)
I have also defined some of the scope of the imide cyclization reaction, particularly with respect to ring size. Methyl maleimidopentanoate (18c) (the one carbon longer homolog of 18b) can be synthesized in two steps from commercially available starting materials. 4-Hydroxybutanoic acid methyl ester (81) was synthesized from δ-valerolactone (80) in MeOH in the presence of H$_2$SO$_4$ in 96% yield. Any attempts to distill alcohol 81 under reduced pressure led to extensive relactonization back to lactone 80. Mitsunobu reaction of 81 with maleimide (82) afforded ester-imide 18c in 50% total yield (the yield of this transformation was diminished by relactonization of 81 to 80 under the reaction conditions). Use of an excess 81 or 82 led to even lower yields (< 30%) of the product 18c.

**Scheme I-24.** Synthesis of Methyl Maleimidopentanoate (18c)

In the presence of R$_3$SiOTf/Et$_3$N 18c smoothly cyclized to the 6/5-bicyclic lactams 83 and 84 with slightly lower levels of dr, compare to 18b (Scheme I-25). The ratio of products was determined by $^1$H NMR spectroscopy, and the relative configurations of 83 and 84 were assigned according to coupling constant analysis and nOe experiments.

**Scheme I-25.** Silylative Dieckmann-like Cyclizations of Methyl Maleimido-pentanoate (18c)
In order to find the thermodynamic ratio of unprotected alcohols 85 and 86, the TMS groups in 83a and 84a were removed, and the resulting mixture of alcohols 85a and 86a was equilibrated (Scheme I-26). Similar to heating of alcohol 72, this equilibration occurs probably via an intermediate amide 75b, since the ratio of the formed alcohols 85a and 86a was only 1.4:1. At this stage I realized that equilibration of the unprotected alcohols was not a viable approach to improve the overall diastereoselectivity of the cyclization.

Scheme I-26. Formation and Equilibration of Alcohols 85a and 86a

\[
\begin{align*}
83a & \quad 84a \\
\text{Conditions} & \quad 85a & 86a \\
5.5 : 1 & \quad 1.4 : 1 \\
\end{align*}
\]

\*a TBAF (1.5 equiv), THF, rt, 17 h, 100% or HF/Py (5 equiv), Py, 4 h, then CDCl\textsubscript{3}, Et\textsubscript{3}N, 70 °C, 24 h, 100%

v. Silylative Dieckmann-like Cyclization of Glutarimide 18d

Starting glutarimide substrate 18d was synthesized analogously to 18b as shown in Scheme I-27. In the presence of R\textsubscript{3}SiOTf/Et\textsubscript{3}N 18d cyclized in high yield, but the stereochemical outcome was quite different. TMSOTf gave rise, predominantly, to the \textit{exo} adduct 90a, suggesting that the saturated (and puckered) glutarimide ring deterred an anti-addition analogous to that indicated in 71-\textit{endo} (the assignment of relative configuration for 89 vs. 90 is based on convincing differences in nOe effects and coupling constant data) (Scheme I-27). On the other hand, the bulkier TIPSOTf reagent gave a nearly 1:1 mixture of adducts 89b and 90b, reflective of a competitive interaction with the silyl moiety in a \textit{synclinal} mode of addition like that in 71-\textit{exo}. The less hindered (and more reactive) TMSOTf also induced competitive elimination of TMS\textsubscript{2}O from 89a and/or 90a under the reaction conditions to give the indolizinone 91. All attempts to remove silyl protecting groups in 89 or 90 led to exclusive formation of the same by-product 91. Fortunately (again), in the UCS1025A-relevant cyclization of 18d
this type of elimination event is thwarted by virtue of destabilization of the carbocationic intermediate 73 (cf. Scheme I-21).

**Scheme I-27.** Synthesis and Silylative Dieckmann-like Cyclizations of Glutarimide 18d

To explore the scope of silylative Dieckmann-like cyclization of enantiopure substrates, we chose to study reactions of tartarimides 96, which I prepared as shown in Scheme I-28. Heating L-tartaric acid (92) in acetyl chloride yielded anhydride 93a, which was opened with amine 65 and closed to imide 94 in 87% yield upon stirring in AcCl. Acetate protecting groups were selectively removed by treating 94 in methanol with AcCl (3.0 equiv), giving bis-alcohol 95 in 80% yield (any attempt to remove acetyl groups under basic conditions resulted in opening of the imide core and formation of the corresponding ester/amide). The secondary hydroxyl groups in 95 were reprotected as silyl ethers giving imides 96a,b. Bis-benzyl protected imide 96c was prepared by a similar sequence of opening of dibenzyl anhydride 93b with amine 64 and subsequent cyclization to imide 96c upon refluxing in AcCl.

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vi. Silylative Dieckmann-like Cyclization of Tartarimides 96
Next, I studied the cyclization of various ether protected tartarimides 96a-c (Scheme I-29). When chiral imide 96a was subjected to TMSOTf/Et$_3$N, lactam 97a was obtained with excellent diastereoselectivity (dr 20:1:0:0). In the endo transition states (99a-$si$ vs. 99a-$re$), approach from the re face of either of the homotopic imide carbonyl groups is disfavored by repulsion between OTMS and the SKA a-H.

Each of the products 97a-d was obtained in good to excellent yield and diastereoselectivity. Each of the minor isomers 98a-c was identified by GC/MS. In addition, 98a was isolated and fully characterized, 98b and 98d were observed by $^1$H NMR analysis of the crude product mixture and had characteristics similar to those of 98a. When tartarimide 96c was subjected to the cyclization conditions, Hünig’s base (DIPEA) was used instead of TEA, since use of the latter resulted in some competitive elimination of the β-OBn group. The stereochemical assignment of the major product 97 was made on the basis of several lines of reasoning. The conversion of 97b into the natural enantiomer of I proved both the relative and absolute configurations of 97b.$^{11}$ In our studies, the $^1$H NMR characteristics of 97a and 98a indicated that each of these diastereomers was an endo adduct (cf. 49c).
Scheme I-29. Silylative Dieckmann-like Cyclization of Tartarimides 96

Further, selective removal\(^{46}\) of the two TMS groups under HF•pyridine conditions (or 0.1 M HCl/AcOH/THF) gave 100 as the major product, although in this case the reaction suffered from substantial elimination of TBSOH and formation of \(\alpha,\beta\)-unsaturated ester in \(\sim20\%\) yield) in 97b gave the crystalline, mono-TBS ether 100, which was subjected to single crystal x-ray structure determination (Figure 5).

Figure 5. Proof of Absolute and Relative Configuration of 97

vii. Silylative Dieckmann-like Cyclization of Methyl Succinimidobutyrate (18e)

Starting parent unsubstituted ester-imide 18e was synthesized from succinic anhydride (101) analogously to 18d (Scheme I-30). Under \(R_3\text{SiOTf/Et}_3\text{N}\) conditions substrate 18e quickly formed the 2,5-bis(trimethylsilyloxy)pyrrole 103 (\textit{in situ} \(^1\text{H}\) NMR analysis),\(^{47}\) which was apparently resistant to cyclization.
Scheme I-30. Synthesis and Reactions with TMSOTf of Succinimide 18e

At low concentrations of 18e (0.1-0.25 M in CDCl3) no further reactions of 103 were observed, and after standard basic work up only starting succinimide 18e was recovered. In the presence of an excess TMSOTf/Et3N and longer reaction times, 103 gave rise to a mixture of bis-C-silylated succinimides 104a, 104b, and mono-silylated succinimide 105 (Scheme I-30).

2. Optimization of the Synthesis of the Triene 45

i. Introduction

Since exploration of the hypothesis on a nonenzymatic IMDA reaction in the biosynthesis of octalinoyl acyltetramic-acid natural products is of interest not only for UCS1025A (1), but also for many other members of the large class of octalinoyl acyltetramic-acid natural products (e.g., Chapters II and III, CJ-16,264 and phomopsichalasin natural products), we wanted a definitive answers to the questions: 1) would the nonenzymatic reaction be fast enough to be the natural event? 2) If so, would the chiral heterocyclic moiety in 45 induce a sufficiently high level of diastereocontrol that none of tetraepi-UCS10125A (56) would have been observed during the isolation of UCS1025A?

Dvornikovs has already answered the first question by demonstrating that in pH 7.4 aqueous buffer triene 45 converts into in its ring-opened form 45c that undergoes the
IMDA reaction of $t_{1/2}=10$ min providing 1c and 56c. However, the second question still remains unanswered, since 1c and 56c are formed in a nearly 1:1 mixture, which is evidence of non-selective diastereocoulalnd induced by the chiral heterocyclic moiety in 45. To answer the second question with certainty, I chose to explore an array of biologically relevant IMDA conditions, therefore I needed an access to sufficient quantities of triene 45. As mentioned earlier, the coupling of 48b with various electrophiles was the most problematic and irreproducible step in our 1st generation total synthesis (cf. Scheme I-16). Hence, the development of a reliable strategy for the synthesis of polyenes like 45 was the next goal of my project.

ii. Scale up of the Iodide 48a

Since Lambert and Danishefsky have demonstrated that TBS-ether-protected iodolactone 10a is stable enough to carry through the synthesis11 and TBS-ether-TIPS-ester is easier to track by $^1$H NMR spectroscopy than the corresponding bis-TIPS compound 48b [in $^1$H NMR (Me$_2$CH)$_3$-Si-O and (Me$_2$CH)$_2$SiOC(O) groups represented by δ 1.01-1.06 (m, 39H)], first I prepared sufficient amounts of alkenyl iodides 48a and 48b using previously described methods. Methyl maleimidobutyrate (18b) was subjected to silylative Dieckmann-like condensation in the presence of TBSOTf (made from TBSCl)$^{48}$ to provide pyrrolizidine 49a in 81% yield, dr 46:1. This reaction could be performed on hundreds of mmol scale, which again demonstrates the versatility of our methodology. Subsequent hydrolysis of the methyl ester 49a and iodolactonization of the resulting acid 13a provided lactone 10a in 95% yield over two steps. Simultaneous opening of the iodolactone 10a and formation of TIPS-ester concluded the synthesis of 48a. Using an analogous sequence I have also synthesized several grams of TIPS-protected iodolactone 10b and bis-TIPS alkenyl iodide 48b.

It is worth noting that alkenyl iodides 48a,b had to be stored in a dry cold place, since over time some decomposition, probably due to hydrolysis of TIPS-ester and/or elimination of TBSOH, was observed. The corresponding alkenyl iodide was purified each time before use by recrystallization from hexanes or purification by MPLC.
**Scheme I-31.** Scale up of Alkenyl Iodides

As shown in Scheme I-32, I have also synthesized other, more stable, alkyl ester analogs 107. Since under strongly acidic conditions compounds 48a,b undergo elimination of TBSOH and/or hydrolysis of TIPS-ester, and, in the presence of RO⁻, 48a,b could undergo ring-opening of pyrrolizidine and/or 1,4-addition, I first tried to effect transesterification of 48a,b under relatively mild conditions (i.e., Otera’s catalyst Bu₈Sn₄H₂O₂Cl₂ and ROH), but this approach proved to be nonproductive. Selective deprotection of the TIPS-ester of 48a,48b under KF/MeOH conditions, followed by treatment with citric acid gave acids 106a,b respectively. When stronger acids (e.g., HCl or TFA) were used for acidification of the initially formed potassium salts of 106, some undesired lactonization and elimination of R₃SiOH were observed. Acid 106b was converted to methyl ester 107a under NaH/MeI conditions. Acids 106a,b could also be cyclized back to the corresponding lactones 10a and 10b respectively, which in turn could be reopened with amine base or K₂CO₃ and esterified with the corresponding R²X to yield benzyl ester 107b or silyl ester 48c in good yield (tBu₂MeSiOTf was made from commercially available tBu₂MeSiH and used in the synthesis of 48c).
Scheme I-32. Synthesis of Various Ester Analogs of 48 and 107

**iii. Anion Formation from Iodides 48 and 107. Deuteration Studies**

Since the major by-product of Dvornikovs’ studies was protonated compound 19b, first I we wanted to learn what was causing its formation. I studied iodine-magnesium exchange in 48a. Direct insertion of Mg⁰ into C-I bond of 48a was not productive. As illustrated in Scheme I-33, addition of i-PrMgCl to solution of iodide 48a in THF at –50 °C induced 108 anion formation, which could be characterized by No-D NMR spectroscopy (δ 6.77 br s, -CH=CMgX). If less than 2.5 equiv of Grignard reagent was used some formation (~30%) of the protonated by-product 19c was observed. Anion 108 could be efficiently quenched with D₂O or AcOD giving deuterated pyrrolizidinone D-19c in high yield with ≥ 90% deuterium content. However, quenching of the anion 108 with TMSCl gave the corresponding product 109 in only 15% yield with substantial formation of 19c. This was the first evidence that 108 is a hindered nucleophile and on a reaction time-scale reacts efficiently only with small electrophiles.
I also studied iodine-magnesium exchange of potassium salt 110 formed by hydrolysis of TIPS-ester in 48a. As illustrated in Scheme I-34, addition of i-PrMgCl to solution of the salt 110 in THF at –50 °C to form anion 111 was not very productive, probably, because of the poor solubility of dianion 111 in THF. The No-D NMR analysis of this solution was not very instructive, and the observed signals were very broad. Quench with D₂O or AcOD of such a solution afforded deuterated product D-13a in less than 5% yield, which was another evidence of unproductive iodine-magnesium exchange in 110. On the other hand, in case of the methyl ester 107a formation of the corresponding anion 112 was quite efficient, especially at temperatures below –10 °C. Anion 112 could be observed by No-D NMR spectroscopy and was quenched with AcOD to give deuterated ester D-49a in 93% yield. If metal-halogen exchange of 107a was performed at higher temperatures (≥ 0 °C), addition of i-PrMgCl to the methyl ester group in 107a with formation of ketone 113 becomes a competitive process. Interestingly, I did not observe any trace of the alcohol formation from second addition of i-PrMgCl to the sterically hindered ketone 113.
iv. **Coupling of Iodides 48 and 107 with Weinreb Amides**

The synthesis of Weinreb amide 47 was worked out by Dr. Dvornikovs, and I reproduced and optimized that approach, as outlined in Scheme I-35. Protection of the alcohol group in 4-chlorobutan-1-ol (114) as its THP-ether gave chloride 115, which was converted to the corresponding Grignard reagent upon heating with Mg\[^{0}\] and catalytic amount of 1,2-dibromoethane. The progress of the reaction was followed by GC/MS. The formed Grignard reagent was coupled with commercially available acetate 116 in the presence of Cu(II) catalyst.\(^{23}\) If performed at elevated temperatures, this coupling could be complicated by substantial formation of the skipped diene 118, a product of S\(_{N} 2'\) substitution, which stays as the corresponding inseparable impurity until the end of the synthesis of 1. For example, addition of 116 to the reaction mixture at ambient temperature gave products 117 and 118 in a 2:1 ratio. Lowering the addition temperature to 0 °C improved the 117:118 ratio to 8:1. Finally, slow addition of 116 at −78 °C resulted in formation of products 117 and 118 in a 19:1 ratio. Deprotection of the acetal
by treatment with TsOH in MeOH and subsequent oxidation under either PCC, Swern, or Parikh-Doering conditions gave aldehyde 21. Although PCC oxidation was technically an easy reaction to perform, it never gave a very high yield of the product 21, presumably due to competitive oxidation of allylic methyl and methylene groups. Horner-Wadsworth-Emmons olefination of aldehyde 21 with phosphonate 119 resulted in formation of Weinreb amide 47 in 85% yield

Scheme I-35. Synthesis of Weinreb Amide 47

To reproduce Dvornikov's results I tried coupling of the alkenyl iodide 48a with the Weinreb amide 47 (Scheme I-36). To my surprise multiple experiments under seemingly the same conditions, indeed, led to very poor and variable yields of the desired triene 50a, significant formation of the protonated by-product 19c, and, in some cases, coproduction of ketone 120. The latter was the product of addition of an excess of i-PrMgCl to Weinreb amide 47. I tried to optimize the reaction yield by varying the number of equivalents of i-PrMgCl used and/or of Weinreb amide 47, by using the reverse order of addition of 48a to a solution of Grignard reagent, by running the reaction on a 1.40 g scale of 48a, by pre-filtering the THF solution of i-PrMgCl through Celite, by screening reaction times, and by using various sources of dry THF. However, none of these attempts led to any improvement in the yield of 50a. In order to identify the source of protons that led to formation of 19c, I did some D₂O-quenching experiments. For instance, when I quenched the reaction with D₂O in 1.5 h after addition of 47, mostly
deuterated by-product D-19c was formed (Scheme I-36). This suggests that anion 108 was still present in the reaction mixture and was too hindered to react with 47 on such a time-scale. However, if the reaction was allowed to proceed for a longer time (~3 h) before being quenched with D₂O, very little deuteration of 19c was observed.

Scheme I-36. Attempts to Reproduce Dvornikovs’ Coupling with Weinreb Amide 47

In attempt to form the corresponding lithium anion from the iodide 48a, substantial decomposition of 48a was observed, presumably due to cleavage of the TIPS-ester and in situ lactonization to 10a. Again the major product of the reaction was 19c. Use of t-BuLi for metal-iodine exchange in 48a led to complete decomposition of the starting materials.

Thinking that lability of the TIPS ester group in 48a could be the source of the problem, I investigated the analogous reaction of alkenyl iodide 107a with Weinreb amide 47 (Scheme I-37). Iodine-magnesium exchange in 107a with an excess i-PrMgCl followed by addition of an excess of Weinreb amide 47 gave only the by-product 49a in 90% yield and ketone 121 in 7% yield. Use of molecular sieves during metal-halogen exchange did not preclude formation of 49a and led to additional formation of the oxidized by-product, the α-ketolactam 122, in 17%. The structure of the latter was confirmed by full spectroscopic analysis, including LCMS, HRMS, ^1H NMR, ^13C NMR, HMQC, HMBC, and IR data. It may arise from the reaction of anion 112 with O₂ present in molecular sieves.
Scheme I-37. Coupling of Iodide 107a with Weinreb amide 47

Use of n-BuLi instead of i-PrMgCl did not lead to any improvement. Purification of reactions with Weinreb amide 47, discussed in Schemes I-36 and I-37, led to recovery of at least 65% of the starting Weinreb amide 47.

It has been shown 55 that with hindered nucleophiles, instead of addition, Weinreb amides could undergo E₂ elimination, generating formaldehyde and the corresponding methyl amide. In my case this could be a possible explanation for the origin of protonation by-products. As shown in Scheme 38, initially formed anion 108 (112) can deprotonate the MeO- group in 47, which leads to formation of 19c (49a), formaldehyde, and magnesium anion of N-methyl amide 123.

Scheme I-38. Possible Explanation for the Origin of Protonated By-Products 19c and 49a

N-tert-Butoxy-N-methylamide has been used 56 instead of N-methoxy-N-methylamide to avoid such a deprotonation side-reaction. Encouraged by this work, I synthesized N-tert-butoxy-N-methylamide of benzoic acid (124) as reported. 56 As illustrated in Scheme
I-39, coupling of 124 with alkenyl iodide 48a was not successful and led to formation of the same by-product 19c and 80% recovery of the amide 124.

**Scheme I-39.** Synthesis of Weinreb Amide 124 and Its Coupling 48a

These collection of observations led me to conclude that the initially formed anion 108 is fairly hindered and finds ways to react with protons from a glassware source, the solvent, or something else faster than it undergoes coupling with Weinreb 47 or its analogs. This observation led me to embark on a search for an alternative electrophile that would react at a faster rate.

**v. Coupling of Iodides 48 and 107 with Acid Chlorides**

Encouraged by Knochel *et al.* reports on reactions of similar magnesium anions with acid chlorides in the presence of 1.0 equiv of CuCN•2LiCl, I decided to study analogous addition of anions 108 (112) to acid chlorides. First, I wanted to check the feasibility of transmetallation of magnesium-anion 108 (112) to the corresponding copper-anion. Generation of anion 108 from iodide 48a in the usual manner, followed by transmetallation to copper with a freshly prepared solution of CuCN•2LiCl and quenching with AcOD, gave the corresponding product of deuteration D-19c in high yield (Scheme I-40). Next, I studied the coupling of iodides 48a/107a with various readily available acid chlorides 125. Usual iodine-magnesium exchange of 48a/107a,
followed by transmetallation to copper, and addition of acid chlorides 125a-e gave products 126a-e in various yields (Scheme I-40).

**Scheme I-40.** Cu-mediated Coupling of Iodides 48a/107a with Acid Chlorides 125

Use of less than 2.0 equiv of i-PrMgCl led to incomplete conversion of 48a/107a into 108 (112) and significant formation of the by-product 19c (49a) (Table 1, entries 1, 5, 6, 10, 11, and 12), which was in agreement with deuteration experiments (cf. Scheme I-33). However, in the presence of an excess of i-PrMgCl/CuCN•2LiCl (2.5 equiv) and 3.0 equiv of acid chloride 125a, the desired compound 126a was the major product of the reaction according to GC/MS data (Table 1, entry 2). Surprisingly, the isolation yield of the product 126a was ≤ 18%. When I attempted the coupling with acid chlorides 125 without addition of a copper reagent, no trace of the formation of the desired products 126 was observed (Table 1, entries 6, 10). I also observed formation of compound 127c, a product of oxidation, and addition to 125c, which could be formed via a reaction of the corresponding copper-anion with molecular oxygen (Table 1, entry 9). In coupling with acid chloride 125e, I observed the formation of the product 126e in only 11% yield (Table 1, entry 12). I was able to isolated small amounts of the coupled 2-chloroketone 126e. Upon attempted Arbuzov reaction of 126e with P(OEt)3/KI to make the corresponding phosphonate, the only isolated products were 19c and its TBSOH-eliminated derivative.
Table 1. Cu-mediated Coupling of Iodides 48a/107a with Acid Chlorides 125

<table>
<thead>
<tr>
<th>#</th>
<th>i-PrMgCl (equiv)</th>
<th>Cu(I) additive (equiv)</th>
<th>R’COCl (equiv)</th>
<th>19c(49a): 126: other products (ratio by GC/MS, yields after MPLC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.1</td>
<td>CuCN•2LiCl (1.2)</td>
<td>125a (1.5)</td>
<td>15% (19c) : 11% (126a) (60% conversion of 48a)</td>
</tr>
<tr>
<td>2</td>
<td>2.4</td>
<td>CuCN•2LiCl (2.5)</td>
<td>125a (3.0)</td>
<td>1 (19c) : 3 (126a)</td>
</tr>
<tr>
<td>3</td>
<td>1.1</td>
<td>CuCN•2LiCl (1.3)</td>
<td>125a (3.0)</td>
<td>1 (19c) : 3.5 (126a) (25% conversion of 48a)</td>
</tr>
<tr>
<td>4</td>
<td>1.6</td>
<td>CuCN•2LiCl (1.6)</td>
<td>125a (1.2)</td>
<td>0% (19c) : 18% (126a)</td>
</tr>
<tr>
<td>5</td>
<td>1.2</td>
<td>CuCN (0.5)</td>
<td>125a (1.3)</td>
<td>4 (19c) : 1 (126a) (50% conversion of 48a)</td>
</tr>
<tr>
<td>6</td>
<td>1.2</td>
<td>-</td>
<td>125a (1.3)</td>
<td>1 (19c) : -</td>
</tr>
<tr>
<td>7</td>
<td>1.2</td>
<td>CuCN•2LiCl (1.5)</td>
<td>125b (1.5)</td>
<td>20% (19c) : 10% (126b) (90% conversion of 48a)</td>
</tr>
<tr>
<td>8</td>
<td>2.5</td>
<td>CuCN•2LiCl (3.0)</td>
<td>125b (4.0)</td>
<td>9 (19c) : 1 (126b)</td>
</tr>
<tr>
<td>9</td>
<td>2.0</td>
<td>CuCN•2LiCl (2.2)</td>
<td>125c (2.4)</td>
<td>33% (49a) : - : 127c 38%</td>
</tr>
<tr>
<td>10</td>
<td>2.2</td>
<td>-</td>
<td>125d (1.3)</td>
<td>1 (19c) : -</td>
</tr>
<tr>
<td>11</td>
<td>1.2</td>
<td>CuCN•2LiCl (1.2)</td>
<td>125e (1.5)</td>
<td>9 (19c) : 1 (126e)</td>
</tr>
<tr>
<td>12</td>
<td>1.0</td>
<td>CuCN•2LiCl (1.3)</td>
<td>125e (1.7)</td>
<td>53% (19c) : 11% (126e)</td>
</tr>
<tr>
<td>13</td>
<td>3.0</td>
<td>CuCN•2LiCl (3.0)</td>
<td>125e (4.2)</td>
<td>~30% (19c) : -</td>
</tr>
</tbody>
</table>

At this stage, considering the need to use an excess of the acid chloride 57, the irreproducibility of this type of coupling, and the low yield of the isolated product 126, I thought that this strategy would not be an optimal approach to synthesis of the desired triene 45. However, I then turned to an encouraging example of a very similar coupling, utilized by Coleman et al. in a total synthesis of lucilactaene 61 (Scheme I-41). In that work researchers performed an analogous iodine-magnesium exchange in pyrrolizidine 128, followed by transmetallation to copper and coupling with acid chloride 129, which resulted in formation of the desired product 130 in 65% yield. Most surprising in this procedure was that after addition of acid chloride 129 the reaction was quenched after only 1 minute.
Scheme I-41. Coleman Cu-mediated Coupling of 128 with Acid Chloride 129

As shown in Scheme I-42, I attempted the coupling of 48a with 125b under Coleman’s conditions, quenched the reaction with D₂O, then immediately adjusted pH to 7.0, at various times, and checked the product ratio by GC/MS. At 2 min the major product of the reaction was 19c (D-19c), which means that reaction was not complete yet; at 12 min the product 126b was formed in ~50% and, additionally, some formation of 127b (with MW(127b)=MW(126b)+16, proposed structure is shown) were observed. However, at 30 min in the amount of 127b increased to ~36%, even though the starting anion was still present, as evidenced by formation of 19c in ~11%. These results were in agreement with my earlier observations that unsatisfactory yields of the coupling with acid chlorides are caused by some sort of product decomposition under the reaction conditions (cf. Table 1).

Scheme I-42. Cu-mediated Coupling of 48a with Acid Chloride 125b

Nevertheless, I wanted to try a coupling of 48a with 3-haloenoyl chlorides like used in Coleman’s work to check if this type of electrophilic acyl halide would be reactive enough to undergo the desired coupling without decomposition of the product.
I made trans-β-iodoacyloyl chloride\textsuperscript{62} (135) and trans-β-bromoacyloyl chloride\textsuperscript{62,63} (137) as illustrated in Scheme I-43. Addition of HI to propiolic acid (132) gave iodo-acid 133,\textsuperscript{62} which was converted to the corresponding acid chloride 134 and isomerized upon heating into the desired trans-acid chloride 135.\textsuperscript{62} The corresponding trans-β-bromoacyloyl chloride (137) was also made from propiolic acid (132) by 1,4-addition\textsuperscript{62,63} of HBr and subsequent conversion of acid 136 into acid chloride 137 by treatment with thionyl chloride.

**Scheme I-43.** Synthesis of Trans-β-Haloacyloyl Chlorides 135 and 137

\[\text{CO}_2\text{H} \xrightarrow{\text{Nal, AcOH, 80 °C, 80%}} \text{Z/E 97:3} \xrightarrow{(\text{COCl})_2; \text{distillation}} \text{Z/E 24:1} \xrightarrow{\Delta, 1h; \text{distillation, 60%}} \text{I} \xrightarrow{\text{COCl}}\]

I found that 48a could be coupled with the acid chloride 135 to give the corresponding diketone 138 in up to 90% yield. The side product 19c was formed in only 0-10% yield! The only limitation of this route was that compound 138 was relatively unstable. Its yield was reduced to 60% after purification by quick chromatography, and it had to be stored in a dark cold place. The yield and purity of 138 greatly depended on the type of work up, e.g., acidic or not-buffered work up caused decomposition of 138, pH 7.0 buffer quenching gave the cleanest product. Use of ether, stabilized with 2% EtOH, for the work up led to isolation of 139a in up to 18% yield, presence of peroxides in the ether caused decomposition of 138. In the presence of trace amounts of water or in non-buffered CDCl\textsubscript{3}, iodide 138 underwent decomposition with formation of by-products with 140-like structure\textsuperscript{i} (such decomposition could be initiated by just one molecule of HI).

\textsuperscript{i} As evidenced by \textsuperscript{1}H NMR of the reaction and its crude after the work up, there are no stereogenic centers in the product of decomposition of iodide 138
Scheme I-44. Cu-mediated Coupling of Alkenyl Iodides 48a/107a with Acid Chlorides 135,137

Nevertheless, compound 138 was relatively stable under aprotic basic conditions (*i.e.*, no trace of decomposition of 138 was observed during its prolonged heating in CDCl₃, buffered with dry solid K₂PO₄). In an attempt to make a more stable alkyl ester analog of 138, I studied an analogous coupling of alkenyl iodide 107a with acid chlorides 135 or 137, I could isolate the corresponding products 141a and 141b in only 11% yield (70% purity, ¹H NMR analysis) (Scheme I-44). Such compounds appeared to be even less stable than the TIPS-ester 138, probably, because the methyl ester in 141 creates a less effective “steric shield” than the TIPS ester in 138.

Since diketone 138 could be synthesized reproducibly in high yield, I revised the retrosynthesis of triene 45 accordingly, utilizing Suzuki-Miyaura reaction of alkenyl iodide 138 with the corresponding alkyl borane 142 (Scheme I-45) to assemble the key-intermediate 50a.
Scheme I-45. Retrosynthesis of Triene 45 Utilizing Suzuki-Miyaura Coupling of Iodide 138 and Borane 142

I chose to use dry K$_3$PO$_4$ as a base and [Pd(dppf)Cl$_2$]•CHCl$_3$ as a catalyst, since the bulky phosphine ligands are known to facilitate reductive elimination in hindered substrates.$^{64}$ To optimize conditions for such Suzuki coupling, I first studied the reaction of β-iodopropenoyl ethyl ester (143) and borane derived from hydroboration of 1-octene (144), as shown in Scheme I-46. When commercial 9-BBN was used for the hydroboration of 1-octene (144), followed by Suzuki coupling with iodide 143, ester 145 was formed in only 10% yield (Scheme I-46, conditions A), and dimer 146 was the major by-product of the reaction. When I switched to a freshly prepared 9-BBN$^{65}$ for hydroboration of 1-octene (144) and THF/DMF as a solvent system for the coupling step, the yield of the formed ester 145 improved to 40% (Scheme I-46, conditions C).

Scheme I-46. Optimization of Suzuki-Miyaura Coupling Conditions

When DMF was used as a major solvent for Suzuki reaction (to increase solubility of K$_3$PO$_4$), the yield of 145 went up to 60%, which is in accordance to literature results for
analogous transformations\textsuperscript{66} (Scheme I-46, conditions D, elevated temperatures were required for such coupling to occur on a reasonable time-scale).

After optimizing the coupling conditions, I turned to synthesis the corresponding triene precursor for the actual borane 142 (cf. Scheme I-45). Initially I attempted to prepare the desired triene 150 in a manner similar to the synthesis of the diene 117 (cf. Scheme I-35), \textit{i.e.,} via Cu-catalyzed reaction of allylmagnesium chloride and acetate 116. Surprisingly, the only products of this reaction were alcohol 147 and 1,5-hexadiene (148). Formation of the latter could be attributed to favorable formation diallylcuprate 149 that could undergo reductive elimination of Cu\textsuperscript{0}. Various loading of Li\textsubscript{2}CuCl\textsubscript{4} or CuCl catalysts, reaction temperatures, or a reverse order of reagent addition did not improve the reaction outcome (Scheme I-47, eq (i)). Palladium-catalyzed coupling of \textit{in situ} generated allylzinc bromide and acetate 116 delivered the triene 150 along with its isomer 151 in a 2:1 ratio as an inseparable mixture (Scheme I-47, eq (ii)). As shown in eq (iii) triene 150 could also be synthesized in a stepwise manner. Palladium-catalyzed alkylation of dimethylmalonate 152 gave products 153 and 154 as a 1:1 mixture. The diene 154 was separated by chromatography and monodecarboxylated to produce ester 155, which was reduced to aldehyde 156. Wittig olefination of 156 gave desired triene 150. Although this approach proved to be viable, we were seeking for a more convergent synthesis of 150. As illustrated in eq (iv), Scheme I-47 I found that diene bromide 157 could be synthesized quite selectively by using NBS/PPh\textsubscript{3} bromination of alcohol 147 (CBr\textsubscript{4}/PPh\textsubscript{3} conditions gave products 157 and 158 in a 4:1 ratio; under MsCl/LiCl/2,6-lutidine chlorination conditions of 147 \textit{S\textsubscript{N}2'} substitution was even more competitive, giving the corresponding chlorides only in a 2:1 ratio).
Scheme I-47. Synthesis of the Triene 150

Regioselective hydroboration\(^{67}\) of 150 with 9-BBN gave the corresponding borane 142, but its subsequent Suzuki-Miyaura coupling with alkenyl iodide 138 under conditions developed in Scheme I-46 resulted only in decomposition of starting material(s). When dioxane was used as a solvent instead, iodide 131 was more stable under the reaction conditions. Hydroboration of 1-octene (144), followed by coupling with alkenyl iodide 138 gave only compound 139b, which could be derived by way of partial TIPS-ester hydrolysis in 138, subsequent addition of TIPSOH to 138, and elimination of I\(^-\) (Scheme I-48).

Since alkenyl iodide 138 was too unstable under Suzuki-Miyaura conditions, I decided to revise the retrosynthesis of triene 45 and to apply 1,4-addition of the corresponding nucleophile 159 [Met = Cu, Zn (Negishi coupling)] to iodide 138 instead (Scheme I-49).

Scheme I-49. Retrosynthesis of Triene 45 Utilizing 1,4-Addition of 159 to 138

To check the viability of such an approach, I first examined copper-mediated 1,4-addition of a readily available BuMgBr in the presence of CuCN•2LiCl. The desired product 161 was formed in only 19% yield, and the major by-product of the reaction was cyanide 160, which could result from addition of CN⁻ to 138 and elimination of I⁻ or from reductive elimination of Cu⁰ from a RCuCN intermediate [Scheme I-50, eq (i)]. Changing the catalyst to CuBr•LiBr led to multiple 1,4-additions of Bu⁻ to both double bonds of 131, which resulted in formation of 162, 163, and some other unidentifiable products [Scheme I-50, eq (ii)]. Use of excess CuBr•LiBr improved the yield of the desired product 161 to 17%. Negishi coupling of the iodide 138 with BuZnCl in the presence of Palladium-catalyst led to formation of the additional by-products 161 and 139c [Scheme
I-50, eq (iii)]. Ni-catalysts are reported\textsuperscript{70} to be efficient in such transformations, but in my case use of Ni(dppf)Cl\textsubscript{2} led again only to formation of the 1,4-addition by-product \textbf{139c} [Scheme I-50, eq (iv)]. When a freshly prepared EtZnI was used, the desired product \textbf{164} was formed in only 3% yield. Additional cleavage of the C7-C(O) bond and formation of \textbf{19c} were significant in this case as well [Scheme I-50, eq (v)].

**Scheme I-50.** Optimization of Conditions for Addition-Elimination in \textbf{138}

I prepared the immediate precursor to the nucleophile \textbf{159} (cf. Scheme I-49), the alkyl bromide \textbf{168}, as illustrated in Scheme I-51. Protection of 3-bromopropan-1-ol (\textbf{165}), followed by Grignard formation with Mg\textsuperscript{0} and Cu-catalyzed coupling with the allyl acetate \textbf{116}, gave diene \textbf{167} in 82% yield. Sequential deprotection of the alcohol and bromide formation under standard conditions gave bromide \textbf{168}. 

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Since iodide 138 proved to be unstable under Suzuki and Negishi reaction conditions, I attempted to improve its reactivity by way of 1,4-addition to the pyrrolizidine double bond (e.g., intramolecular lactonization). However, all attempts to selectively cleave TIPS-ester in 138 were unproductive and led to decomposition of the starting material. This collection of observations led me finally to abandon this approach.

vi. Reformatsky-Type Coupling for the Synthesis of Triene 45

Encouraged by the Lambert and Danishefsky report\textsuperscript{11} on high-yielding Reformatsky-type coupling of iodolactone 10a and aldehyde 11 (cf. Scheme I-3), I decided to investigated the analogous reaction of 10a with α,β-unsaturated aldehydes. As shown in Scheme I-52, Reformatsky-type coupling of 10a with benzaldehyde occurred smoothly with formation of product 169 in 75% yield. However, the yield of product 170 by analogous reaction of 10a with crotonaldehyde was only 45%. In this case, the highest yield was achieved, when 2.0 equiv of aldehyde were employed. Use of a significant excess of crotonaldehyde (e.g., 10.0 equiv) reduced the yield of 170 to 10%. This could be explained by competitive reactions of BEt\textsubscript{3}\textsuperscript{71} with α,β-unsaturated aldehydes. The resulting secondary alcohol 170 could be oxidized to ketone 171 under DMP or TPAP/NMO conditions (Scheme I-52). To my disappointment, the reaction of 10a with aldehyde 23 led only to decomposition of the starting iodolactone and partial decomposition of 23 with no trace of the formation of the desired product.

I also studied generation of silyl or tin-enolate from iodolactone 10a under TiCl\textsubscript{4}, AllTMS\textsuperscript{72} and Bu\textsubscript{2}SnI\textsubscript{2}/MgBr\textsubscript{2}/HMPA conditions\textsuperscript{74} respectively. However, only ring-opening of the intermediate enolate into acid 13a was observed in these cases.
Scheme I-52. Reformatsky-type Coupling of 10a with Aldehydes

Since BE₃-mediated Reformatsky coupling was productive for coupling of 10a with saturated aldehydes, I decided to protect the corresponding double bond of 23 as a sulfide, so that it could be reinstalled later by oxidation to the appropriate sulfoxide and thermal elimination.

As illustrated in Scheme I-53, I made the model aldehyde 171 by 1,4-addition of PhSH to crononaldehyde. However, the protection of the corresponding aldehyde 23 under EtSH/NaH conditions was not very high yielding and gave the desired aldehyde 172 only in 37% yield; one of other isolated by-products was dithiol 173. Since at this stage I was more concerned about feasibility of Reformatsky reaction, I did not optimize the synthesis of 172. When I attempted to couple iodolactone 10a with aldehyde 171, it was surprisingly slow and delivered the desired product 175 in 32-60% yield and oxygenated product 174 (Scheme I-53). In all of the runs most of the leftover starting aldehyde 171 could be recovered. Nevertheless, I showed that secondary alcohol in 175 could be oxidized with DMP to the corresponding enol 176. Next, I studied Reformatsky coupling of iodolactone 10a with the actual aldehyde 172. However, in all my experiments it seemed that, although the initial formation of boron-enolate from 10a
occurred, its addition to aldehyde 172 was too sluggish. Instead, some formation of the oxygenated product 174 and decomposition of the rest of the formed enolate were observed. In all runs 100% of the starting aldehyde 172 was recovered.

**Scheme I-53.** Reformatsky-type Coupling of 10a with Aldehydes

All these experimental results led me to abandon this approach in the end. However, the following observation deserves some attention. The analogous Reformatsky transformation of using the triisopropylsilyl ether analog 10b instead of the TBS-ether substrate 10a, used to generate the products in Schemes I-3 and I-52 (*vide supra*), with benzaldehyde or aldehyde 171 reproducibly led only to formation of equimolar amounts of lactones 20b and 177 (Scheme I-54). Formation of these products was evidence of abstraction of H• from the CH group in TIPS to make a tertiary radical Me2C•, which was more stable than primary radical Et•. Since no addition to aldehyde was observed, we proposed a mechanism that does not go through a boron enolate intermediate (Scheme I-54): formation of the radical 178 by abstraction of l’ in 10b by Et’, which in turn could intramolecularly abstract a methine H• from a i-Pr of its TIPS-group, generating a tertiary radical species like 179. Two molecules of the latter could disproportionate, yielding
equimolar amounts of the reduced lactone 20b and alkene 177. This unusual reaction is strikingly efficient, which we find very interesting, considering that TBS-ether 10a undergoes Reformatsky-aldol reaction cleanly. The only other example of the analogous abstraction of H• from methine of the TIPS-group is reported by Maas, et al.75

Scheme I-54. Reformatsky-type Reaction of TIPS-Iodolactone 10b

vii. Palladium-Catalyzed Couplings for the Synthesis of Triene 45

After unsuccessful studies of nucleophilic addition of various anions derived from iodides 48, 107, and 10 to a range of electrophiles, I decided to try a different approach to the synthesis of polyene 45. Considering numerous developments in palladium-catalyzed transformations alkenyl iodides,76 I decided to explore the scope of transition metal-catalyzed reactions of iodide 48a/107a.

As summarized in Scheme I-55, triene 45 could be synthesized from 50a via straightforward functional group transformations. The latter could be assembled via a Palladium-catalyzed coupling. The two most convergent approaches to assemble a dienone fragment like that in 50a are shown as routes A (Stille coupling77 of 180 with acid chloride 57) and B (carbonylative Stille-coupling78 of iodide 48a with stannane 181
in the presence of CO). Additionally, Dvornikovs previously demonstrated that stannane 181 could be synthesized from aldehyde 21.79

**Scheme I-55.** Retrosynthesis of 45 Employing Palladium-catalyzed Coupling

First, I explored route A (Schemes I-56, I-57). To prepare the stannane 180, I studied generation of an anion of 48a with Na+[naphth], followed by addition of tributyltin chloride.77 However, this resulted only in formation of the protonation by-product 19c (Scheme I-56). Stille-Eaborn 80 coupling proved to be more successful; 180a was generated in 22% yield upon the reaction of 48a with Bu6Sn2 in the presence of Pd(PPh3)2Cl2 as a catalyst.81 The poor yield of 180a could be caused by competitive hydrolysis of the TIPS-ester group in 48a and/or 180a under the reaction conditions. Trimethylstannane 180b was synthesized in 80% yield via a reaction of 48a with Me6Sn2 under more neutral conditions (benzene, Pd(PPh3)4).82 Use of HMPA reduced the yield of 180b to 40%.

To explore the feasibility of route A, I studied reactions of stannane 180 with readily available acid chlorides 125a,b,d. As shown in Scheme I-57, I tried several conditions for Stille-coupling of 180a,b. However, in both cases only decomposition of the starting material 180 was observed. Since lability of the TIPS ester in 180 could be an issue, I examined Stille-coupling of a methyl ester analog of 180, stannane 182 (synthesized from
the iodide 107a) with acid chloride 125c. The ester 49a was the only product of the reaction (Scheme I-57).

**Scheme I-56.** Synthesis of Stannane 180

**Scheme I-57.** Route A: Stille Coupling of Stannanes with Acid Chlorides
Since Stille coupling of the stannane 180 and 182 with various acid chlorides seemed to be ineffective, I decided to explore a carbonylative Stille-coupling approach to the dienone 50a (cf. Route B, Scheme I-55). First, I studied carbonylative Stille-coupling of alkenyl iodides 48a, 106, 107b, and 110 with a commercially available tributylvinyl stannane (183) under a CO atmosphere under conditions that are known to be efficient for analogous transformations (Scheme I-58).76 The results are reported in Table 2.

Scheme I-58. Route B: Carbonylative Stille-Coupling of Iodides 48a, 106, 107b, and 110 with Stannane 183.

The carbonylative Stille-coupling of the iodide 48a with stannane 183 resulted in formation of compound 185 a product of the direct coupling (Table 2, entries 1-4,6). The yield of the carbonylated product 184 was slightly improved, when the reaction was conducted reaction at a higher pressure of CO, but not enough to make this route practical (Table 2, entry 6). Additionally, in some cases the reaction was complicated by competitive hydrolysis of the TIPS-ester in 48a and formation of esters 186 and 187 [these by-products were observed by 1H NMR spectroscopy and GC/MS (Table 2, entries 5,7,8)]. Analogous carbonylative Stille coupling of the benzyl ester 107b resulted only in formation of the direct coupling product 185 (GC/MS) (Table 2, entry 9). Reactions of iodoacid 106, or its potassium or amine salts 110 (formed as shown in Scheme I-32) afforded only protonation by-product 13a (Table 2, entries 10-13).
Table 2. Carbonylative Stille Coupling of Alkenyl Iodides

<table>
<thead>
<tr>
<th>#</th>
<th>R¹</th>
<th>Rxn conditions: catalyst(s), solvent, temp</th>
<th>CO pressure</th>
<th>184 : 185 (GC/MS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TIPS</td>
<td>Pd(OAc)(_2), CuI, PPh(_3), THF, 70 °C, 16 h</td>
<td>15 psi</td>
<td>1 : 17</td>
</tr>
<tr>
<td>2</td>
<td>TIPS</td>
<td>Pd(PPh(_3))(_2)Cl(_2), PPh(_3), i-Pr(_2)NEt, THF, 70 °C, 16 h</td>
<td>15 psi</td>
<td>- : 100</td>
</tr>
<tr>
<td>3</td>
<td>TIPS</td>
<td>Pd(PPh(_3))(_2)Cl(_2), CuI, PPh(_3), THF, 70 °C, 20 h</td>
<td>85 psi</td>
<td>1 : 10</td>
</tr>
<tr>
<td>4</td>
<td>TIPS</td>
<td>Pd(PPh(_3))(_2)Cl(_2), PPh(_3), i-Pr(_2)NEt, THF, 70 °C, 16 h</td>
<td>30 psi</td>
<td>- : 100</td>
</tr>
<tr>
<td>5</td>
<td>TIPS</td>
<td>Pd(dppf)Cl(_2)•CHCl(_3), LiCl, DMF, 60 °C, 16 h</td>
<td>90 psi</td>
<td>- (TIPS ester hydrolysis)</td>
</tr>
<tr>
<td>6</td>
<td>TIPS</td>
<td>Pd(PPh(_3))(_2)Cl(_2), i-Pr(_2)NEt, THF, 60 °C, 16 h</td>
<td>90 psi</td>
<td>1 : 4</td>
</tr>
<tr>
<td>7</td>
<td>TIPS</td>
<td>Pd(PPh(_3))(_2)Cl(_2), LiCl, THF, 60 °C, 20 h</td>
<td>90 psi</td>
<td>only 186</td>
</tr>
<tr>
<td>8</td>
<td>TIPS</td>
<td>Pd(PPh(_3))(_2)Cl(_2), LiCl, i-Pr(_2)NEt,THF, 50 °C, 20 h</td>
<td>90 psi</td>
<td>187 10%, 186</td>
</tr>
<tr>
<td>9</td>
<td>Bn</td>
<td>Pd(PPh(_3))(_2)Cl(_2), LiCl, i-Pr(_2)NEt,THF, 50 °C, 20 h</td>
<td>90 psi</td>
<td>- : 100</td>
</tr>
<tr>
<td>10</td>
<td>K</td>
<td>Pd(PPh(_3))(_2)Cl(_2), LiCl, i-Pr(_2)NEt,THF, 50 °C, 20 h</td>
<td>90 psi</td>
<td>only 10a 9%</td>
</tr>
<tr>
<td>11</td>
<td>K</td>
<td>Pd(PPh(_3))(_2)Cl(_2), LiCl, DMF, 50 °C, 20 h</td>
<td>90 psi</td>
<td>only 13a</td>
</tr>
<tr>
<td>12</td>
<td>H</td>
<td>Pd(PPh(_3))(_2)Cl(_2), LiCl, i-Pr(_2)NEt,THF, 50 °C, 20 h</td>
<td>90 psi</td>
<td>only 13a</td>
</tr>
<tr>
<td>13</td>
<td>Et(_3)N(^+)H(^-)</td>
<td>Pd(PPh(_3))(_2)Cl(_2), LiCl, i-Pr(_2)NEt,THF, 50 °C, 20 h</td>
<td>90 psi</td>
<td>only 13a</td>
</tr>
<tr>
<td>14</td>
<td>DBU(^+)H(^-)</td>
<td>Pd(PPh(_3))(_2)Cl(_2), LiCl, i-Pr(_2)NEt,THF, 50 °C, 20 h</td>
<td>90 psi</td>
<td>only 13a</td>
</tr>
</tbody>
</table>

The carbonylative Stille-coupling of the methyl ester 107a was more successful, since the desired product 184b was isolated in 25% yield. Under carbonylative Stille coupling conditions with AllSnBu\(_3\), iodide 107a remained unreactive, even upon prolonged heating of the reaction mixture.

Scheme I-60. Route B: Carbonylative Stille-Coupling of Alkenyl Iodide 107a

Considering literature reports\(^{83}\) and my observations, I concluded that it is possible to improve the yield of 184a,b (e.g., at higher pressure of CO), but instead I pursued other routes for the synthesis of triene 45.
[2,3]-Rearrangement for the Synthesis of Triene 45. Sonogashira Coupling.

Another approach to triene 45 is summarized in Scheme I-61. It involves introduction of the enone moiety in 50 via [2,3]-sigmatropic rearrangement of alkynyl sulfoxide\(^\text{84}\) 189, which could be derived by chemoselective oxidation of the sulfide 190.\(^\text{85}\) The latter could be synthesized via Sonogashira coupling of alkyne 191 and the corresponding alkenyl iodide 48a/107a. The corresponding alkyne 191 can be made by \(\alpha\)-alkylation of the dianion of sulfide 192 with the appropriate alkyl halide.

**Scheme I-61. Retrosynthesis of 45, Employing [2,3]-Sigmatropic Rearrangement and Sonogashira Coupling**

Considering the difficulties encountered in Stille-coupling of iodides 48a/107a and very few known precedents\(^\text{86}\) of Pd-catalyzed transformations of substrates containing a sulfide functional group, I decided first to explore feasibility of Sonogashira coupling of 48a/107a with the readily available model alkynes 192a,b, which were chosen due to their high molecular weight and low stench properties. Alkynes 192a,b were synthesized in \(~60\%\) yield by alkylation of the corresponding thiols 193a,b with propargyl bromide. The reaction conditions were not optimized, and some formation of air-oxidized disulfides 194a,b and allenes 195a,b was observed as well. Initially, I explored
Sonogashira coupling of alkenyl iodide 48a and alkyne 192a under standard conditions\(^{87}\) (conditions A, Scheme I-62). However, the only isolable product in this case was the diyne 194a, a product of oxidative dimerization of 192a. To reduce competitive oxidative dimerization of the alkyne component, I also explored copper-free conditions\(^{88}\) in this Sonogashira coupling (e.g., Scheme I-62, conditions B-D). However, in all these cases the only detectable product was alkyne-dimer 194a. Trace amounts of the desired enyne 197a were detected only by \(^1\)H NMR analysis of the crude reaction mixture.

**Scheme I-62.** Synthesis of Alkynes 192 and Their Sonogashira Coupling with Iodide 48a

![Scheme I-62](image)

I hypothesized that the reaction was thwarted by inhibition of the palladium (0)-catalyst via a favorable Pd→S complexation. To explore this hypothesis I studied the coupling of alkynes 192a,b with a model substrate, 4-iodoanisole (198) (Scheme I-63, all reactions were conducted with 100% conversion of one of the starting materials). In the Sonogashira reaction of 4-iodoanisole (198) and alkyne 192a the only observed product was the dimer 196a. Use of a BHT as an inhibitor and/or removal of oxygen with freeze-pump-thaw technique did not lead to any improvement. When the sulfide 192b was used as an alkyne component, formation of the desired product was observed. However, the isolated yield of 197b was still poor (e.g., < 20%). Significant amounts of the dimerized by-product 196b were observed as well.
Scheme I-63. Sonogashira Coupling of 4-Iodoanisole (198) with Alkynes 192a,b

Since sulfide-containing alkynes proved to be unsuitable in palladium-catalyzed coupling, I explored reactivity of iodide 48a in a Sonogashira coupling with alkyne 199 derived from TBS protection of the corresponding alcohol (Scheme I-64). By monitoring the progress of the coupling, initially I observed clean formation of the product 201a. However, in two hours even after addition of another portion of Palladium-catalyst and/or alkyne 199 no further formation of 201a was observed. The only other product formed in the course of the coupling was the dimer 200. Use of BHT additive did not improve the reaction outcome.

Scheme I-64. Sonogashira Coupling of Iodide 48a with Alkyne 199
This observation led me to conclude that the poor yield of \(201a\) could be caused by product inhibition of the catalyst, \textit{i.e.}, the initially formed products \(201a\) and/or \(200\) favorably bound to the catalyst, slowing further productive conversion of iodide \(48a\).

\textbf{ix. [2,3]-Rearrangement for the Synthesis of Triene 50. Alkynyl-Stille Coupling.}

Considering the difficulties I encountered during Sonogashira coupling studies (cf. Scheme I-62) and previous work on [2,3]-rearrangement of selenoxides into corresponding \(\alpha,\beta\)-unsaturated ketones,\(^{89}\) I modified the synthesis of triene \(50\), as shown in Scheme I-65.

\textbf{Scheme I-65.} Modified Approach to Synthesis of the Triene \(50\), Employing [2,3]-Rearrangement and Alkynyl-Stille Coupling

I envisioned formation of triene \(50\) by [2,3]-rearrangement of selenoxide \(202\). Selenoxides are known to undergo [2,3]-rearrangement under milder conditions than the corresponding sulfoxides. Compound \(202\) could be formed by selective oxidation of selenide \(203\), which in turn could be accessed via alkynyl-Stille coupling of tributyltinalkyne \(204\) and alkenyl iodides \(48a/107a\). First, I wanted to explore feasibility of the strategy by studying the alkynyl-Stille coupling of iodide \(107a\) with the model stannane \(205\) (Scheme I-66). Deprotonation of alkyne \(199\) with \(n\)-BuLi followed by addition of \(Bu_3SnCl\) gave the desired compound \(205\) in 85\% yield. Alkynyl-Stille coupling of \(205\) with alkenyl iodide \(107a\) under standard unoptimized conditions\(^ {90}\) gave the desired ene-yne \(201b\) in 40\% yield and the by-product \(206\) in 20\% yield.
Scheme I-66. Synthesis of the Stannane 205 and Its Stille Coupling with Iodide 107a

Since most reported [2,3]-sigmatropic rearrangement examples utilize phenyl sulfoxides or phenyl selenoxides as starting materials, I decided to prepare the appropriate alkyne (Scheme I-67). $S_N2$ substitution of propargyl bromide with phenylthiolate afforded only internal alkyne 218. Fortunately, no such complication was observed in the synthesis of the selenoalkyne 210 from diphenyldiselenide (209). However, alkylation of the lithium dianion of alkyne 210 proved to be problematic. It afforded the mixture of products 211, 212, and 213, resulting from monoalkylation, dialkylation, and isomerization of the alkyne to the corresponding allene (Scheme I-67). Although, the desired alkyne 211 could be separated from by-products and converted into stannane 214, its reaction with iodide 48a resulted in formation of the product 215 in only 13% yield (65% conversion of 48a).

Overall, in working with seleno-compounds, I observed that they seemed to have a relatively short shelf-time and undergo spontaneous cleavage of the C-Se bond with formation of Ph$_2$Se$_2$ (209) (it is very non-polar and of a very distinguishable yellow color) in the course of reactions and subsequent purifications. I realized that this would complicate the synthesis of the actual alkyne 202 (cf. Scheme I-65) and all subsequent transformations, since I planned to do [2,3]-rearrangement at the end of the synthesis of the triene 50.
Scheme I-67. Synthesis of Stannane 214 and Its Stille Coupling with Iodide 48a

It is also known\(^9^3\) that the rearrangement of alkynyl selenoxides into enones (cf. 202 into 50) involves an intermediate vinyl selenide like 217, which must be protonated to deliver the enone 50 (Scheme I-68). However, the last protonation step is not necessarily straightforward.\(^9^4\) All these reasons, especially the low yielding formation of the coupled product 215, pointed to inefficiency of this approach and led me to abandon this route as well.

Scheme I-68. Proposed Transformation of Alkyne 202 into Enone 50

x. Negishi Coupling for the Synthesis of Triene 45.

In search for a “magic bullet” solution for the synthesis of trienes 45 and 50, I found reports\(^9^5\) that approach the synthesis of \(\alpha,\beta\)-unsaturated ketones via Negishi coupling of
1-oxy-1,2-dienylzinc halides with alkenyl halides. I revised the retrosynthesis of 50 by planning to make the crucial C-C bond via Negishi coupling of alkenyl iodide 48a/107a with 1-oxy-1,2-dienylzinc chloride 218 (Scheme I-69).

**Scheme I-69.** Revised Retrosynthesis of Triene 50, Employing Negishi Coupling of 1-Oxy-1,2-dienylzinc Chloride 218

I envisioned the synthesis of the intermediate 218 by regioselective metallation of the corresponding oxyallene (R is Me or MOM), formed by a kinetic isomerization of the corresponding alkyne 219. The latter would come from alkylation of alkynes like 220 with previously synthesized alkyl bromide 168 (cf. Scheme I-51).

The synthesis of the propargyl ethers 219a,b is described in Scheme I-70. Protection of propargyl alcohol as a MOM or Me ether followed by alkylation with bromide 168 was uneventful. However, isomerization of the alkynes 220a,b into the allene precursor of 1-oxy-1,2-dienylzinc chloride 218 under various conditions (n-BuLi, TMEDA, then K₂CO₃, MeOH; t-BuOK, THF, Δ) was unproductive. In order to test the feasibility of Negishi coupling I made the simpler analogs 221a,b and the corresponding 1-oxy-1,2-dienylzinc chlorides 222a,b under n-BuLi/ZnCl₂ conditions. It appeared that intermediate 222a was quite unstable under the Negishi reaction conditions; coupling of 222a with 4-iodoanisole (198) or iodides 48a/107a did not give any of the desired products. Zincation of methyl ether 221b into 222b was more productive, since the subsequent coupling of 222b with 4-iodoanisole gave the desired product 223 albeit in a poor yield (~10%). Several other by-products like alkyne 224 could be detected by crude ¹H NMR spectroscopy and GC/MS.
Scheme I-70. Synthesis and Negishi Coupling of 1-Oxy-1,2-dienylzinc Chlorides

After several unsuccessful attempts to optimize this route, I decided to return to the initial iodine-magnesium exchange of 48a/107a and to explore more fully the reactivity of the formed anions with electrophiles, since this approach was the most straightforward and successful in my hands so far.

xi. Addition of Anion of Iodide 48a to Carbonyl Imidazoles.

First, I wanted to investigate carbonyl imidazoles as electrophiles in nucleophilic addition with metallated iodide 48a. Iodine-magnesium exchange of 48a with i-PrMgCl, followed by addition of several imidazolyl electrophiles was unsuccessful in my hands. The only isolable products in this case were 19c and the corresponding isopropyl ester 225 [Scheme I-71, (i)]. To further explore this type of transformation, I studied an analogous nucleophilic addition of anion generated from 4-iodoanisole (198). Although, iodine-magnesium exchange in 198 occurred at a slower rate, the formed anion could be observed by No-D NMR spectroscopy. However, its addition to carbonyl imidazole did not deliver any desired product [Scheme I-71, (ii)].
**Scheme I-71.** Coupling of 48a with Various Carbonyl Imidazole Electrophiles

![Scheme I-71](image)

xii. Addition of Anions of Iodides 48a/107a to Acyl Cyanides

Encouraged by a relevant precedent of addition of magnesium anions to acyl cyanides by Knochel et al.,

we decided to investigate analogous reactions of 48a/107a. The starting acyl cyanides were made by a reaction of the corresponding acyl chlorides with CuCN.

As illustrated in Scheme I-72, eq (i), iodine-magnesium exchange of 48a or 107a followed by Fe(acac)₃-catalyzed coupling with acyl cyanide of crotonic acid was not productive and resulted in formation of the by-product 19c or 49a. Analysis of the reaction mixture of the methyl ester 107a with benzoyl cyanide by AcOD-quench at different reaction times revealed that the initially formed magnesium anion of 107a did not react with acyl cyanides on the time-scale. At longer reaction-times no trace of the desired product was observed, and, instead, the protonation by-product 49a with a smaller deuterium-content along with the benzoyl ester 226 were detected by GC/MS [Scheme I-72, (iii)].

This collection of observations led me to switch to studying the coupling of alkenyl iodides 48a/107a with aldehydes. So far I had been reluctant to do so, since Dvornikovs had shown that although aldehyde 23 could be coupled with alkenyl iodide 48b, the subsequent oxidation of the resulting secondary alcohol 58b into the desired enone 50b was problematic (cf. Scheme I-16).
Scheme I-72. Generation of Anions from Iodides 48a/107a and Their Coupling with Various Acyl Cyanides

![Scheme I-72](image)

xiii. Addition of Anions of Iodides 48a/107a to Aldehydes

To ensure that there was nothing fundamentally wrong with my experimental procedures and that our previous lack of success was due to the unique nature of the anions 108 (112) (cf. Schemes I-33, I-34), I first explored an analogous nucleophilic addition of the anion generated from 4-iodoanisole (198) to anisaldehyde (Scheme I-73).

Scheme I-73. Halogen-Metal Exchange of 198 and Subsequent Nucleophilic Addition to Anisaldehyde

![Scheme I-73](image)

This reaction was straightforward and gave the corresponding secondary alcohol 227 in 95% yield. Encouraged by this result I tried an analogous reaction of alkenyl iodide 48a. Usual generation and subsequent addition of the anion of iodide 48a to various aldehydes gave the desired product 228 in variable yields 0-34% yield. When n-BuLi was used as a metallation reagent, extensive decomposition of 48a and/or 228 occurred
Reduction of the ester with DIBALH gave alcohol conducted at elevated temperatures. IMDA cycloaddition of the ester was observed.

Scheme I-74. Metal-Halogen Exchange of 48a and Subsequent Nucleophilic Addition to Aldehydes

I found that alcohol 228b could be oxidized to the ketone 229 under MnO2 conditions, although the oxidation required sonication and heating and delivered the product 229 in only 20% yield (Scheme I-75).

Scheme I-75. Oxidation of Alcohol 228b

Nevertheless, encouraged by these results I next explored this strategy for the synthesis of the desired polyene 50a. Gram quantities of the required aldehyde 23 were synthesized as outlined in Scheme I-76. Wittig reaction of aldehyde 21 at ambient temperature gave the corresponding α,β-unsaturated ester (when the reaction was conducted at elevated temperatures IMDA cycloaddition of the ester was observed). Reduction of the ester with DIBALH gave alcohol 230, which was oxidized with
DMP$^{103,104}$ or MnO$_2$ to provide the aldehyde 23. Synthesis of the aldehyde 23 via Wittig reaction of aldehyde 21 with an ylide, generated from phosphonium bromide 22$^{21,105}$ was less efficient in my hands. Direct reduction of Weinreb amide 47 with DIBALH gave aldehyde 23 in only 40% isolated yield. Aldehyde 23 was stored in a dark cold place with BHT (1 mol%) and used immediately after its preparation.

**Scheme I-76.** Synthesis of Aldehyde 23

As shown in Scheme I-77, an analogous coupling reaction of iodide 48a with aldehyde 23 resulted in formation of the desired product 58a in only 10% yield. Again, the major by-product of the reaction was 19c.

**Scheme I-77.** Addition of 48a to Aldehyde 23

*Other conditions:
A. i-PrMgCl, 1,10-phenanthroline (5 mol%), MS 4 Å, THF, −78 °C; then solution of activated CeCl$_3$ in THF, −78 °C, 1 h; then 23, −78 °C, 1 h; work up.
B. i-PrMgCl, 1,10-phenanthroline (5 mol%), MS 4 Å, THF, −78 °C; then solution of activated CeCl$_3$ in THF, −78 °C, 1 h; then 23, −78 °C, 3 h; work up.
C. n-BuLi, 1,10-phenanthroline (5 mol%), MS 4 Å, THF, −78 °C; then solution of activated CeCl$_3$ in THF, −78 °C, 1 h; then 23, −78 °C, 1 h, −50 °C 30 min warm up to rt; work up.

Encouraged by the recent precedent$^{106}$ of 1,2-addition of a cerium anion to α,β-unsaturated aldehydes, I studied similar conditions for the coupling. However, all of the attempts A-C resulted only in formation of the by-product 19c and some cleavage of the TIPS-ester in 19c. Use of 1,10-phenanthroline as an indicator to ensure the presence of a
sufficient amount of \( i-\text{PrMgCl} \) or \( n-\text{BuLi} \) in the system did not improve the yield of the product 58a.

In some cases I was also able to detect formation of the reduction products, e.g., alcohol 230 in Scheme I-77 and cyanohydrin 226 in Scheme I-72. I speculated that formation of these compounds as well as of the protonation by-product 19c (49a) could be consequences of our choice of the Grignard reagent, i.e., \( i-\text{PrMgCl} \). Alcohol 230 and cyanohydrin 226 could be formed by transfer of hydride from \( i-\text{PrMgCl} \) to the corresponding aldehyde 23 or benzoyl cyanide [see concerted addition in 231, Scheme I-78, (i)].

**Scheme I-78.** Stability of Anion 108 (112) in the Presence of \( i-\text{PrI} \)

![Scheme I-78](image)

Formation of compound 19c (49a) could be a result of HI elimination from \( i-\text{PrI} \) induced by anion 108 (112) [Scheme I-78, (ii)]. This hypothesis was also confirmed by No-D NMR spectroscopy; I could observe that at the beginning of the experiment anion 108 (112) and \( i-\text{PrI} \) were the major components of the reaction mixture, and as the reaction mixture aged over 2 h, the disappearance of \( \text{Me}_2\text{CHI} \) peak and formation of a characteristic terminal vinyl group in isobutylene and 19c (49a) was observed. Guided by these observations I decided to explore MeMgBr for the iodine-magnesium exchange in alkenyl iodides 48a/107a.

xiv. MeMgBr in Reactions of Iodides 48a/107a
First, I studied the addition of MeMgBr-generated anion of 107a with various electrophiles: benzoyl chloride, benzoyl Weinreb amide,109 and benzaldehyde. All reactions were conducted under the same conditions (Scheme I-79). The reaction progress was followed by GC/MS. When the benzoyl Weinreb amide was used, the coupled product 232a was formed in 35% yield, and the protonation by-product 49a - in 50% yield. In addition, some formation of N-methyl benzamide was observed (cf. Scheme I-38). Coupling with benzoyl chloride was the least productive, leading to predominant formation of 49a and the 4-chlorobutyl ester of benzoic acid, which could be formed by O-acylation of THF with benzoyl chloride followed by opening of the THF ring with Cl-. The reaction with benzaldehyde was the most high-yielding and delivered the corresponding alcohols 232b in 70% yield as a 1:1 mixture of diastereomers. The protonation by-product 49a was isolated in only 23% yield in this case.

Scheme I-79. Addition of Anion of 107a, Generated with MeMgBr, to Electrophiles

Since the reaction of iodide 107a with benzaldehyde was the most productive, I explored MeMgBr-mediated addition of 107a to the actual substrate 23 (Scheme I-80). After optimizing the conditions of coupling, I found that use of 3.0 equiv of MeMgBr and 3.0 equiv of aldehyde 23 was the most efficient and led to consistent formation of the desired product 233 in 72% yield as an inconsequential mixture of diastereomeric alcohols in a 2:1 ratio. Use of 2.0 equiv of MeMgBr led only to partial conversion of 107a, use of 4 equiv of MeMgBr led to substantial addition of MeMgBr to aldehyde 23, and lower yields of the coupled product 233. The diastereomeric alcohols are separable.
by MPLC. I have also demonstrated that each of them could be independently converted into the triene 53a. Interestingly, when i-PrMgCl was employed for the exact same reaction instead of MeMgBr, the yield of the isolated product 233 was less than 5%!

Scheme I-80. MeMgBr-Mediated Addition of 48c to Aldehyde 23

As illustrated in Scheme I-81, the rest of the synthesis of the target triene 45 was quite straightforward. Initially, DMP oxidation of 233 gave the ketone 50c in 80% yield. However, all my subsequent attempts to hydrolyze methyl ester in 50c under various conditions led only to decomposition of the starting material. When I switched the order of the transformations and performed lithium hydroxide hydrolysis of the methyl ester in 233 first, the desired acid 234 was produced in quantitative yield. Oxidation of the alcohol in 234 with DMP followed by spontaneous lactonization was not very clean and gave the product 53a in variable yields (40-60%). One of the other isolated by-products of the reaction was the α-hydroxyketone 235, which presumably was produced by oxidation of the enol in 53a. When MnO₂ was used as an oxidizing reagent, enol 53a was formed cleanly and reproducibly in 90% yield. TBS-ether deprotection with HF•pyridine, buffered with pyridine, led to clean formation of the desired triene 45. When unbuffered HF•pyridine was used, or when deprotection was conducted at high concentration (> 0.05 M in 53a) substantial decomposition and low isolated yields of 45 were observed. Since the final triene 45 was quite prone to spontaneous IMDA cycloaddition (vide infra), the scale up was completed up to the stable enol 53a, and the triene 45 was freshly preformed for each Diels-Alder experiment.
Scheme I-81. Completion of the Synthesis of the Triene 45


i. Introduction

Once we finally had access to sufficient quantities of triene 45 and its precursors, we were able to test more thoroughly our hypothesis on the biosynthesis of UCS1025A (1). As mentioned earlier, in order for UCS1025A to be formed via non-enzymatic intra-molecular Diels-Alder cycloaddition, the transformation must be fast enough to be a natural event, and the chiral heterocyclic moiety in 45 has to induce a sufficiently high level of diastereocontrol that tetraepi-UCS10125A (56) would not have been observed during the isolation of UCS1025A. Dvornikovs demonstrated the first of these requirements by showing that in pH 7.4 aqueous buffer, triene 45 converted into its open-form 45c, and that at least one of the components in this equilibrium mixture underwent IMDA reaction with $t_{1/2}=10$ min providing 1c and 56c. My challenge was to explore whether the chiral heterocyclic moiety in 45 could induce sufficient diastereocontrol to make 1 the predominant product of the cycloaddition by studying an array of biologically relevant IMDA conditions.
ii. Intramolecular Diels-Alder Cycloaddition of Trienes 53a and 235

To explore how much control lactone and TBS-protected alcohol moieties would impose on the diastereoselectivity of cycloaddition, I first studied the IMDA reactivity of the TBS-protected carbinolamide/triene 53a (Scheme I-82). Substrate 53a cyclized only upon prolonged heating, producing the adducts 54a and 55a in a 1.2:1 ratio (determined by $^1$H NMR analysis, and in agreement with Dvornikovs observations for the TIPS-analog 53b). The structures of 54a and 55a were assigned according to their $^1$H NMR data [e.g., H-7a, H-4', and C2'-CH3 chemical shifts of TBS-ether 54a are more upfield than those of 55a. $^1$H NMR data of 54a and 55a was almost identical to the previously reported data of TIPS-ethers 54b and 55b. Dvornikovs had also shown that upon deprotection ethers 54b and 55b could be converted into UCS1025A (1) and tetraepi-UCS1025A (56) respectively (cf. Scheme I-14)\(^{17}\). Triene 53a was not soluble in any aqueous buffers even in the presence of other organic solvents, which thwarted studying its IMDA reactivity under biomimetic conditions.

**Scheme I-82.** Diels-Alder Studies of Trienes 53a and 235

Oxygenated triene 235 was less reactive toward IMDA cycloaddition and required even higher temperatures to undergo cycloaddition on a similar time-scale, giving a
mixture of products 236 and 237 in a 1:4 ratio (their structures were assigned in an analogous way as for compounds 54a and 55a (Scheme I-82)).

iii. Intramolecular Diels-Alder Cycloaddition of Methyl Ester/Triene 50c

To explore how much control the TBS-ether group was imposing on the diastereoselectivity of the cycloaddition, I studied the IMDA reactivity of the triene 50c (Scheme I-83). All of the conditions used are described in Table 3. The ratio of the products 51a to 52a was determined by 1H NMR spectroscopy. Triene 50c underwent IMDA reaction relatively fast under various conditions, which could be attributed to the doubly activated enone moiety in 50c. In DCM or CDCl3 at ambient temperature the triene 50c spontaneously cyclized into 51a and 52a in a 1.2:1 ratio (Table 3, entry 1). Both products were produced via an endo mode of cycloaddition. In solvents like benzene, acetone, or DMSO the rate of cyclization was a bit slower. The level of diastereoselectivity of the IMDA reaction was similar to the selectivity observed in chlorocarbon solvents (Table 3, entries 2-4). Use of a mild Lewis acid like MgBr2 shortened the t1/2 of IMDA reaction of 50c and produced 51a and 52a in a 1:1 ratio (Table 3, entry 5). Use of Evans Cu-box catalyst also increased the rate of cycloaddition, but, surprisingly, it did not appreciably affect the diastereoselectivity of the cyclization (Table 3, entry 6). When TMSOTf was used as a Lewis acid, it led to formation of 51a and 52a in a 1:1 ratio along with significant decomposition of the starting material and/or products, presumably due to TBSOH elimination (Table 3, entry 7). When strong Lewis acids like SnCl4 and Me2AlCl were used, the cycloaddition of 50c occurred almost instantaneously, but the ratio of the formed products was again close to 1:1.

Scheme I-83. Diels-Alder Studies of Triene 50c
Table 3. IMDA Studies of Triene 50c

<table>
<thead>
<tr>
<th>#</th>
<th>Catalyst, solvent</th>
<th>temperature</th>
<th>$t_{1/2}$</th>
<th>dr (51a : 52a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH$_2$Cl$_2$ or CDCl$_3$</td>
<td>rt</td>
<td>24 h</td>
<td>1.2 : 1</td>
</tr>
<tr>
<td>2</td>
<td>Benzene</td>
<td>70 °C</td>
<td>2 h</td>
<td>2 : 1</td>
</tr>
<tr>
<td>3</td>
<td>Acetone</td>
<td>60 °C</td>
<td>4 h</td>
<td>1.5 : 1</td>
</tr>
<tr>
<td>4</td>
<td>DMSO</td>
<td>70 °C</td>
<td>3 h</td>
<td>1 : 1</td>
</tr>
<tr>
<td>5</td>
<td>MgBr$_2$, CH$_2$Cl$_2$</td>
<td>rt</td>
<td>2 h</td>
<td>1 : 1.3</td>
</tr>
<tr>
<td>6</td>
<td>Cu(box)$_{2+}$2SbF$_6^-$, CH$_2$Cl$_2$</td>
<td>rt</td>
<td>~ 2 h</td>
<td>1 : 1</td>
</tr>
<tr>
<td>7</td>
<td>TMSOTf, CH$_2$Cl$_2$</td>
<td>rt</td>
<td>-</td>
<td>1 : 1, decomposition</td>
</tr>
<tr>
<td>8</td>
<td>SnCl$_4$, CH$_2$Cl$_2$</td>
<td>rt</td>
<td>&lt;10 min</td>
<td>1 : 1.3</td>
</tr>
<tr>
<td>9</td>
<td>Me$_2$AlCl, CH$_2$Cl$_2$</td>
<td>–78 °C</td>
<td>-</td>
<td>1 : 1.2</td>
</tr>
</tbody>
</table>

In order to study biomimetic version of IMDA cycloaddition in synthesis of UCS1025A (1) in full detail, I moved on to studying the cycloaddition of the natural triene 45, having the free carbinolamide functionality

iv. Intramolecular Diels-Alder Cycloaddition of Triene 45.

First, I studied the IMDA cycloaddition of triene 45 under “neutral organic” conditions (Scheme I-84, Table 4), since it was the most straightforward way to test reactivity of 45. In CDCl$_3$ triene 45 existed predominantly in its keto-form (ca. 45a : 45b = 11:1) that cyclized into a mixture of 1 and 56 in a 1 : 3.5 ratio (Table 4, entry 2). In more polar organic solvents like DMSO triene 45 existed predominantly in its enol-form 45b, which underwent cycloaddition at a slower rate, but delivered products 1 and 56 in a 1 : 1 ratio (Table 4, entry 3). In acetonitrile triene 45 existed in equilibrium of its keto-45a and enol-45b forms (ca. 1:1). Since keto-form 45a was more reactive toward IMDA cycloaddition, triene 45 eventually siphoned into products 1 and 56 in a 1 : 4 ratio (Table 4, entry 4). When the starting lactone 45a was opened to its carboxylate 45c in the presence of 0.1 M NaHCO$_3$ solution in D$_2$O, only decomposition of the starting materials and no IMDA cycloaddition of 45c were observed (Table 4, entry 5). Attempts to increase the rate of the cycloaddition by addition of various metal salts to the solution of 45c led to conversion of 45c back into the closed forms 45a and 45b. No open-form 45c
was observed, even in the presence of excess of 0.1 M NaHCO₃ solution in D₂O was added (Table 4, entries 6,7). When chlorocarbon solvent and solid metal salts were used as the reaction conditions, the diastereoselectivity of IMDA cycloaddition did not improved, although the reaction rate increased some. I interpreted this result as evidence that under such conditions substrate control was still more significant than catalysis (Table 4, entries 8,9,11,13,14). Use of Evans’ Cu(box)²⁺·2SbF₆ did not affect the ratio of the formed products either (Table 4, entry 12). La(OTf)₃, made from the corresponding oxide and triflic acid, was the only Lewis acid that slightly improved the ratio of 1:56 to 1:1. However, I was not able to improve this ratio further (Table 4, entries 10,15,16). IMDA cycloaddition of the triene 45a in the presence of the catalyst 24a, synthesized as described in Scheme II-11 (vide infra), was also not very selective and led to formation of the tetraepimer 56 as a major product. This observation suggests that the corresponding intermediate iminium ion of the ketone in 45a was not formed under the reaction conditions (Table 4, entry 18).

Scheme I-84. Diels-Alder Studies of Triene 45 under “Neutral Organic” Conditions
Table 4. IMDA Cycloaddition of Triene 45 into UCS1025A (1) and *tetraepi*-UCS1025A (56) under “Neutral Organic” Conditions

<table>
<thead>
<tr>
<th>#</th>
<th>Conditions: catalyst, solvent</th>
<th>Temperature</th>
<th>t_{1/2}^a</th>
<th>Rxn intermediates^b</th>
<th>dr (1:56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Neat</td>
<td>-20 °C</td>
<td></td>
<td></td>
<td>1 : 3</td>
</tr>
<tr>
<td>2</td>
<td>CDCl₃</td>
<td>25 °C</td>
<td>23 h</td>
<td>45a→1a+56a</td>
<td>1 : 3.5</td>
</tr>
<tr>
<td>3</td>
<td>DMSO</td>
<td>70 °C</td>
<td>3 h</td>
<td>45a→45b→1b+56b</td>
<td>1 : 1</td>
</tr>
<tr>
<td>4</td>
<td>CD₃CN</td>
<td>50 °C</td>
<td>2 h</td>
<td>45b→45a→1a+56a</td>
<td>1 : 4.0</td>
</tr>
<tr>
<td>5</td>
<td>CD₃CN, D₂O(v/v 5:1), NaHCO₃ (2.0 equiv)</td>
<td>rt 12 h</td>
<td>45a→45c→ decomposition</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>CD₃CN, D₂O, ZnCl₂ (1.0 equiv), NaHCO₃ (5.0 equiv)</td>
<td>rt 36 h</td>
<td>45b→45a→1a+56a</td>
<td>1.2 : 1</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>CD₃CN, D₂O, MnCl₂ (1.0 equiv), NaHCO₃ (5.0 equiv)</td>
<td>rt 24 h</td>
<td></td>
<td>-</td>
<td>1.2 : 1</td>
</tr>
<tr>
<td>8</td>
<td>CDCl₃, MgCl₂ (2.0 equiv)^c</td>
<td>rt 15 h</td>
<td>45a→1a+56a</td>
<td>1 : 5</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>CDCl₃, ZnCl₂ (2.0 equiv)^c</td>
<td>rt 12 h</td>
<td>45a→1a+56a</td>
<td>1 : 3.7</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>CDCl₃, La(OTf)₃ (2.0 equiv)^c</td>
<td>rt 1 h</td>
<td>45a→1a+56a</td>
<td>1 : 1.2</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>CDCl₃, Yb(OTf)₃ (2.0 equiv)^c</td>
<td>rt &lt;3 h</td>
<td>45a→1a+56a</td>
<td>1 : 6</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Cu(box)²⁺•2SbF₆</td>
<td></td>
<td></td>
<td></td>
<td>1 : 3</td>
</tr>
<tr>
<td>13</td>
<td>SnCl₂ (2.0 equiv)^c, CDCl₃</td>
<td>rt ~20 h</td>
<td>45a→1a+56a</td>
<td>1 : 4.0</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>ZrCl₂ (2.0 equiv)^c, CD₂Cl₂</td>
<td>rt ~20 h</td>
<td>45a→1a+56a</td>
<td>1 : 4.0</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>C₆D₆, La(OTf)₃ (2.0 equiv)^d</td>
<td>rt 1 h</td>
<td>45a→1a+56a</td>
<td>1 : 1.0</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>CD₃CN, La(OTf)₃ (2.0 equiv)^c</td>
<td>rt &lt;1 h</td>
<td>45a→1a+56a</td>
<td>1 : 4.0</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>CD₃CN, ZnCl₂^c</td>
<td>50 °C</td>
<td>2 h</td>
<td>45b→45a→1a+56a</td>
<td>1 : 4.0</td>
</tr>
<tr>
<td>18</td>
<td>MacMillan 24a (20 mol%), CD₃CN (2% D₂O)</td>
<td>rt 72 h</td>
<td>45a→1a+56a</td>
<td>1 : 3.0</td>
<td></td>
</tr>
</tbody>
</table>

^a t_{1/2} is indicated, where it was possible to deduce it.  
^b Rxn intermediates are indicated for reactions, where it was possible to observe them by $^1$H NMR spectroscopy.  
^c Although the indicated number of catalyst equivalents were added, the actual amount of the catalyst in the reaction solution was limited by catalyst solubility and was not determined.

Analysis of the transition states 238a,b, shown in Scheme I-85 (LA= Met⁺ or H⁺), could be used as a possible explanation to the observed level of diastereoselectivity with preferential formation of *tetraepi*-UCS1025A 56. The desired octalin in 1 was produced via the endo-mode $s$-cis-238a or the endo-mode $s$-trans-238a of the IMDA cycloaddition,
which experienced unfavorable steric interactions between lactone moiety and diene. The octalin moiety in 56 was formed via more favorable endo-s-cis-238b or endo-s-trans-238b modes of the IMDA cycloaddition, which in turn experienced less significant unfavorable steric interactions between and hydroxyl and diene moieties.

Scheme I-85. Analysis of the Possible Transition States for the IMDA Cycloaddition of the Triene 45 under “Neutral Organic” Conditions

To answer our question of whether a spontaneous non-enzymatic IMDA event is operative in the biosynthesis of UCS1025A, I next studied the IMDA reactivity of the triene 45 under biomimetic conditions (Scheme I-86, Table 5). Starting triene 45 was not soluble in pure D$_2$O and only slightly soluble in aqueous pH 7.4 buffer. Without addition of an organic co-solvent no conversion of the keto-form 45a into the carboxylate 45c was observed. In order to ensure a sufficient solubility of triene 45 under the reaction conditions I usually used aqueous solvent/acetonitrile as a 5:1 (v/v) mixture. First, I reproduced Dvornikovs’ results by demonstrating that indeed in pH 7.4 phosphate buffer, triene 45 opened into its carboxylate 45c, which underwent IMDA reaction with $t_{1/2}=10$ min, producing 1c and 56c in a 1:1 ratio (Table 5, entry 2). I also studied the IMDA cycloaddition of the triene 45 in various buffers pH 6.0-8.0. The most significant improvement in the diastereomeric ratio of the products I observed was when Tris-buffer
was used; 1:56 were formed in a 1.5:1 ratio (Table 5, entry 3). Use of other buffers led to formation of 1 and 56 in ≤ 1:1 ratio (Table 5, entries 4-7). In attempt to improve the dr of the formed products, addition of various metal salts to pH 7.4 phosphate buffer was explored. However, it led to significant precipitate formation, presumably due to low solubility of the formed metal phosphates. Addition of metal salts to pH 7.4 Tris buffer solution led to relactonization of the initially formed carboxylate 45c into the keto-form 45a, followed by its cyclization into 1a and 56a in dr ≤ 1:1 (Table 5, entries 8-12).

**Scheme I-86.** Diels-Alder Studies of Triene 45 under Biomimetic Conditions
**Table 5.** IMDA Cycloaddition of Triene 45 into UCS1025A (1) and *tetraepi*-UCS1025A (56) under Biomimetic Conditions

<table>
<thead>
<tr>
<th>#</th>
<th>Conditions: catalyst, solvent</th>
<th>Temperature</th>
<th>( t_{1/2} )^a</th>
<th>Rxn intermediates(^b)</th>
<th>dr (1:56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>D(_2)O/CD(_3)CN v/v 5:1</td>
<td>rt</td>
<td>1.5 h</td>
<td>45(\to)45c(\to)1c+56c</td>
<td>1 : 2</td>
</tr>
<tr>
<td>2</td>
<td>pH 7.4 phosphate buffer/CD(_3)CN v/v 5:1</td>
<td>rt</td>
<td>10 min</td>
<td>45(\to)45c(\to)1c+56c</td>
<td>1 : 1</td>
</tr>
<tr>
<td>3</td>
<td>pH 7.4 Tris buffer/CD(_3)CN v/v 5:1</td>
<td>rt</td>
<td>20 min</td>
<td>45(\to)45c(\to)1c+56c</td>
<td>1.5 : 1</td>
</tr>
<tr>
<td>4</td>
<td>pH 7.4 histidine•HCl buffer/CD(_3)CN v/v 5:1</td>
<td>rt</td>
<td>-</td>
<td>45(\to)45c(\to)1c+56c</td>
<td>1 : 1</td>
</tr>
<tr>
<td>5</td>
<td>pH 7.0 Tris buffer/CD(_3)CN v/v 5:1</td>
<td>rt</td>
<td>20 min</td>
<td>45(\to)45c(\to)1c+56c</td>
<td>1 : 1.2</td>
</tr>
<tr>
<td>6</td>
<td>pH 8.4 Tris buffer/CD(_3)CN v/v 5:1</td>
<td>rt</td>
<td>20 min</td>
<td>45(\to)45c(\to)1c+56c</td>
<td>1 : 1</td>
</tr>
<tr>
<td>7</td>
<td>pH 7.4 Tris buffer/CD(_3)CN v/v 5:1,</td>
<td>rt</td>
<td>7 h</td>
<td>45(\to)45c(\to)1c+56c</td>
<td>1 : 1.2</td>
</tr>
<tr>
<td></td>
<td>lysine (2.0 equiv)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>pH 7.4 phosphate buffer/CD(_3)CN v/v 5:1,</td>
<td>rt</td>
<td>-</td>
<td>45(\to)45c(\to)1c+56c</td>
<td>1.2 : 1</td>
</tr>
<tr>
<td></td>
<td>MgBr(_2) (2.0 equiv)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>pH 7.4 Tris buffer/CD(_3)CN v/v 5:1,</td>
<td>rt</td>
<td>10 min</td>
<td>45(\to)1a+56a</td>
<td>0.9 : 1</td>
</tr>
<tr>
<td></td>
<td>MgCl(_2) (2.0 equiv)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>pH 7.4 Tris buffer/CD(_3)CN v/v 5:1,</td>
<td>rt</td>
<td>1.5 h</td>
<td>45(\to)1a+56a</td>
<td>0.9 : 1</td>
</tr>
<tr>
<td></td>
<td>ZnCl(_2) (2.0 equiv)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>pH 7.4 Tris buffer/CD(_3)CN v/v 5:1,</td>
<td>rt</td>
<td>&gt; 3 h</td>
<td>45(\to)1a+56a low conversion</td>
<td>1 : 2.5</td>
</tr>
<tr>
<td></td>
<td>YbCl(_3) (2.0 equiv)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>pH 7.4 Tris buffer/CD(_3)CN v/v 5:1,</td>
<td>rt</td>
<td>&gt; 3 h</td>
<td>45(\to)1a+56a low conversion</td>
<td>1 : 2.5</td>
</tr>
<tr>
<td></td>
<td>La(OTf)(_3) (2.0 equiv)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) \( t_{1/2} \) is indicated, where it was possible to deduce it

\(^b\) Rxn intermediates are indicated for reactions, where it was possible to observe them by \(^1\)H NMR spectroscopy

Lack of diastereoselectivity under biomimetic conditions could be explained by the fact that the *endo*-transition states *s-cis/-s-trans-239a* and *s-cis/-s-trans-239b*, leading to formation of 1 and 56 correspondingly, were now more similar in energy (Scheme I-87). Steric interactions between the diene and the carboxylate moieties in open-forms 239a are less severe than those between the diene and the lactone in 238a (cf. Scheme I-85). On the other hand, solvolysis and protonation of the free hydroxyl group would increase steric interactions between diene and the hydroxyl group moieties in 239b (Scheme I-87, LA = H\(^+\), protonated amine, or Met\(^+\)).
Disappointed by unsuccessful attempts to find biomimetic conditions for the IMDA cycloaddition of 45, we broadened the scope of our studies in search for IMDA conditions that would lead to a diastereoselective formation of UCS1025A. Since triene 45 undergoes an IMDA reaction relatively fast, I reasoned that to alter the diastereoselectivity of the cycloaddition a stronger Lewis acid would be required to intervene with this spontaneous IMDA cyclization process. The results of these studies are summarized in Table 6, Scheme I-88. Use of the most common Diels-Alder catalyst - Me₂AlCl - did not lead to any changes in diastereoselectivity of the formed products (Table 6, entries 1,2). I was happy to see that the use of SnCl₄ or BF₃•OEt₂ at ambient temperature favored the formation of UCS1025A (1). In these cases, IMDA cycloaddition of the triene 45 yielded products 1 and 56 in ~ 2.3:1 ratio. Two equivalents of the Lewis acid were necessary to obtain for the dr. Conducting the experiments at a lower temperature or in solvents other than CHCl₃/DCM, e.g., benzene or 1,2-dichloroethane, led only to reduced drs (Table 6, entries 4-11). I hypothesized that the first equivalent of Lewis acid caps the hydroxyl group, and the second equivalent coordinates to the 1,3-ketolactam moiety to further activate the dienophile for the Diels-
Alder cycloaddition. Scheme I-88 shows the possible transition states for the transformation. As one can see, in transition states *s-cis*-/*s-trans* 240b an unfavorable steric interaction between the diene and –OH group, bound to a Lewis acid, is now present. This makes transition states *s-cis*-/*s-trans* 240b less favorable than *s-cis*-/*s-trans* 240a and leads to preferential formation of UCS1025A (1). Use of other Lewis acids, e.g., TiCl₄, BCl₃, BBr₃, or SbCl₅, led mostly to decomposition of the starting material and/or predominant formation of 56 (Table 6, entries 3, 12-14).

**Scheme I-88.** Diels-Alder Studies of Triene 45 in the Presence of a Strong Lewis Acids
Table 6. IMDA Cycloaddition of Triene 45 into UCS1025A (1) and tetraepi-UCS1025A (56) in the Presence of Strong Lewis Acids

<table>
<thead>
<tr>
<th>#</th>
<th>Conditions: catalyst, solvent</th>
<th>Temperature</th>
<th>( t_{1/2}^a )</th>
<th>Rxn intermediates(^b)</th>
<th>dr (1:56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me(_2)AlCl, CH(_2)Cl(_2)</td>
<td>(-20 \degree C)</td>
<td>-</td>
<td>-</td>
<td>1 : 4.4</td>
</tr>
<tr>
<td>2</td>
<td>Me(_2)AlCl, CH(_2)Cl(_2)</td>
<td>(-20 \degree C)</td>
<td>-</td>
<td>-</td>
<td>1 : 4.0</td>
</tr>
<tr>
<td>3</td>
<td>TiCl(_4) (2.0 equiv), CD(_2)Cl(_2)</td>
<td>(-78 \degree C) to rt</td>
<td>-</td>
<td>-</td>
<td>1 : 1</td>
</tr>
<tr>
<td>4</td>
<td>SnCl(_4) (2.0 equiv), CDCl(_3)</td>
<td>(-50 \degree C) to rt</td>
<td>-</td>
<td>-</td>
<td>2.0 : 1</td>
</tr>
<tr>
<td>5</td>
<td>SnCl(_4) (2.0 equiv), CD(_2)Cl(_2)</td>
<td>rt</td>
<td>-</td>
<td>-</td>
<td>2.13 : 1</td>
</tr>
<tr>
<td>6</td>
<td>SnCl(_4) (0.5 equiv), CD(_2)Cl(_2)</td>
<td>(-94 \degree C) to rt</td>
<td>-</td>
<td>-</td>
<td>1.2 : 1</td>
</tr>
<tr>
<td>7</td>
<td>SnCl(_4) (3.0 equiv), CD(_2)Cl(_2)</td>
<td>(-94 \degree C) to rt</td>
<td>-</td>
<td>-</td>
<td>1 : 1</td>
</tr>
<tr>
<td>8</td>
<td>BF(_3)•OEt(_2) (2.0 equiv), CDCl(_3)</td>
<td>rt</td>
<td>20 min</td>
<td>2.3 : 1</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>BF(_3)•OEt(_2) (2.0 equiv), CD(_2)Cl(_2)</td>
<td>(-78 \degree C) to rt</td>
<td>-</td>
<td>-</td>
<td>1 : 1</td>
</tr>
<tr>
<td>10</td>
<td>BF(_3)•OEt(_2) (2.0 equiv), C(_2)H(_4)Cl(_2)</td>
<td>rt</td>
<td>10 h</td>
<td>extensive decomposition</td>
<td>1 : 2</td>
</tr>
<tr>
<td>11</td>
<td>BF(_3)•OEt(_2) (2.0 equiv), C(_6)D(_6)</td>
<td>rt</td>
<td>15 min</td>
<td>some decomposition</td>
<td>1 : 1</td>
</tr>
<tr>
<td>12</td>
<td>BBr(_3) (2.0 equiv), CDCl(_3)</td>
<td>rt</td>
<td>25 min</td>
<td>extensive decomposition</td>
<td>1 : 2</td>
</tr>
<tr>
<td>13</td>
<td>BCl(_3) (2.0 equiv), CDCl(_3)</td>
<td>rt</td>
<td>10 min</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

\(^a\)\( t_{1/2} \) is indicated, where it was possible to deduce it

\(^b\)Rxn intermediates are indicated for reactions, where it was possible to observe them by \(^1\)H NMR spectroscopy

C. Conclusion

Our unsuccessful attempts to support our hypothesis on spontaneous IMDA cycloaddition in biosynthesis of UCS1025A (1) led us to conclude that this natural product is being synthesized in nature via an alternative pathway. Its biosynthesis could involve the intermediate triene 45, which, while still in the environment of the enzyme that finishes the last step of its synthesis, undergoes spontaneous IMDA cycloaddition. The chiral environment of such an enzyme ensures the formation of UCS1025A (1) as a single diastereomer and the coincidental folding of the substrate in that enzyme active site could lead to enhanced rate of the IMDA cycloaddition, as well. Another alternative
is that the biosynthesis of \( \text{1} \) involves an IMDA intermediate like \( \text{242} \), which still should be fairly reactive towards the cycloaddition. For instance, diketone \( \text{242} \) could be formed in nature via a PKS-mediated intramolecular acylation of the keto-lactam moiety in \( \text{241} \). Once formed diketone \( \text{242} \) could undergo spontaneous IMDA cycloaddition into the octalin \( \text{243} \). The chiral environment of the enzyme that catalyzes the acylation would enable the diastereoselective formation of octalin in \( \text{243} \) (Scheme I-87). The latter could be then finally converted into UCS1025A (\( \text{1} \)) via keto-enol isomerization into \( \text{244} \), protonation to iminium ion \( \text{245} \), hydration to diol \( \text{246} \), dehydration to carbinolamide \( \text{247} \), and lactonization into \( \text{1} \).

**Scheme I-87.** An Alternative Biosynthesis of UCS1025A (1)
Chapter II. Synthetic Efforts Toward CJ-16,264

After exploring various conditions for the IMDA reaction in UCS1025A (1) synthesis, we came to conclusion that our initial hypothesis on the non-enzymatic synthesis of 1 in nature could have been misguided all the way from the outset. To further study the possibility of the spontaneous IMDA cycloaddition in nature and stereo-electronic influence of the pyrrolizidine moiety present in 1, we turned our attention to two natural products, CJ-16,264 (300) and CJ-16,367 (301), (Figure 6) that, as one can easily see, are structurally related to UCS1025A (1).

A. Isolation and Biological Activity of CJ-16,264 and CJ-16,367

In the course of screening for new antibiotics from microbial extracts, new natural products CJ-16,264 (300) and CJ-16,367(301) were isolated from the culture of Agonomycetes class fungus CL39457 in 2001 by Sugie et al. at Pfizer, Japan. Compounds 300 and 301 were the first pyrrolizidinones isolated from fungi.

Figure 6. CJ-16,264 and CJ-16,367 Natural Products

The increasing incidence of infections caused by multi-drug resistant (MDR) bacteria, such as methicillin-resistant strains of Staphylococcus aureus, has been a serious problem in the clinical area. Resistance to antibiotics may emerge within a few years after introduction of an antibiotic as a therapeutic agent. Accordingly, there is a need for new, safe, and effective antibiotics against MDR clinical strains. These novel pyrrolizidinone compounds 300 and 301 show moderate antibacterial activity against Gram-positive MDR bacteria.
CJ-16,264 (300) showed antibacterial activities (MIC = 0.39 ~ 12.5 µg/mL) against Gram-positive MDR strains (*Staphylococcus aureus*, *Staphylococcus haemolyticus*, *Streptococcus agalactiae*, *Streptococcus pyogenes*, *Streptococcus pneumoniae*, and *Eterococcus faecalis*) and some Gram-negative ones (*Moraxella catarrhalis* 87A1055 and *E. coli* 51A1051 *imp* mutant). It also showed weak activity against *Haemophilus influenzae* strains (MIC from 25 ~ 50 µg/mL).

CJ-16,367 (301) showed broad antibacterial activities against Gram-positive strains with MIC = 6.25 - 50 µg/mL (e.g., *Staphylococcus aureus*, *Staphylococcus haemolyticus*, *Streptococcus agalactiae*, *Streptococcus pyogenes*, *Streptococcus pneumoniae*, and *Eterococcus faecalis*), *M. catarrhalis* 87A1055, and *E. coli* 51A1051 *imp*, but the activities were rather weak. The presence of the gamma-lactone seemed to be critical to show stronger antibacterial activities in that 300 was more potent than 301. It is known that dehydropyrrolizine alkaloids converted from pyrrolizidine alkaloids in mammals show acute toxicity, e.g., hepatotoxic, mutagenic, and carcinogenic activities. In fact, compounds 300 and 301 have also showed cytotoxicity against HeLa cells with IC₉₀ values of 8.0 and 6.8 µg/mL, respectively.¹¹²

**B. Our Synthetic Efforts Toward CJ-16,264**

1. Motivation and Hypothesis on Biosynthesis of CJ-16,264 and CJ-16,367

CJ-16,264 (300) and CJ-16,367 (301) attracted our attention by their striking structural resemblance to UCS1025 (1) and UCS1025B (2) natural products. We found CJ-16,264 (300) to be an excellent target to further study our hypothesis on the biosynthetic origin of this class of natural product. It caught our attention that during the isolation studies the amount of natural product 300, isolated from the culture of *Agonomycetes* class fungus CL39457, was ten times higher than that of 301. Considering that the authors used MeOH-0.05% TFA/H₂O as an eluent for HPLC purification of the extract, we could not help but wonder, if CJ-16,367 (301) was an artifact produced by methanolysis during the isolation process. As shown in Scheme II-1, under acidic conditions in the presence of methanol CJ-16,264 (300) could undergo formation of the
iminium ion \textbf{303} (\textbf{300}→\textbf{302}→\textbf{303}), which in turn could be trapped with MeOH yielding an intermediate like \textbf{304}. The latter could undergo intra- or inter-molecular proton transfer followed by lactone-opening to produce CJ-16,367 (\textbf{301}).

\textbf{Scheme II-1.} Possible Origin of CJ-16,367 from CJ-16,264

Taking this into account, we decided to undertake an analogous study of a synthesis of CJ-16,264, the only other octalin tetramic acid, in addition to UC1025A (\textbf{1}), containing the \textbf{Type 1} tricyclic tetramate (cf. Figure 4). In addition to providing fundamental knowledge about these spontaneous and biogenetically relevant [4 + 2] cycloaddition reactions and the role of the heterocyclic pyrrolizidine moiety, this study would also address questions of a structure assignment of CJ-16,264 (\textbf{300}) that are open in our mind. During the isolation the structures and relative configurations of \textbf{300} and \textbf{301} were assigned based on interpretation of their $^1$H 1-D, $^{13}$C 1-D, $^1$H-$^1$H COSY, COLOC INEPT, NOE, and phase sensitive NOESY NMR spectra, and IR and HRFAB-MS data, which we believed could be misinterpreted. No HMQC or x-ray data were reported for either \textbf{300} or \textbf{301}. For example, as assigned, \textbf{300}-I would arise from an \textit{endo}-cycloaddition of the unlikely enone Z-isomer of triene \textbf{306} (or, perhaps, via a stepwise cyclization). We were also surprised to see that C(7a’)/C(7’) stereocenters in the reported structure of CJ-16,264 have a different relative configuration compare to that of UCS1025A (\textbf{1}), considering that
C(7') position is readily enolizable. If, indeed, a spontaneous non-enzymatic IMDA cycloaddition is operative in the biosynthesis of CJ-16,264 the most reasonable biomimetic precursor would be the E-isomer 307, with an opposite configuration of C(6) stereocenter to avoid diaxial interactions. Upon an endo-mode cycloaddition, triene 307 would form 300-II, a 6,8a,7'-tripimer of 300-I (Scheme II-2).

Scheme II-2. Hoye Group’s Hypothesis on Biosynthesis of CJ-16,264

One additional issue that the synthesis of CJ-16,264 (300) addresses is that there is now a pair of stereocontrol elements at work. We thought it would be interesting to see the extent of matching/mismatching imparted by citronellol-derived methyl-bearing center C(6) and Type 1 heterocyclic ‘auxiliary’.

It is also worth noting that to our knowledge there are no other reported efforts toward a synthesis of 300 or 301.

2. Synthetic Efforts Toward CJ-16,264
i. Retrosynthesis of CJ-16,264 (300-II)

Our initial retrosynthetic analysis of CJ-16,264 was based on the proposed structure 300-II and utilized the triene 307, having an E-enone, as a target for IMDA studies (Scheme II-3). Biomimetic endo-selective IMDA cycloaddition of 307 would be used to form the octalin moiety and to install the four final stereocenters in 300-II. The desired triene 307 would be assembled via the previously developed Grignard coupling of alkenyl iodide 107a, synthesized as described in Chapter I, and aldehyde 308.

Scheme II-3. Retrosynthesis of Proposed Structure of CJ-16,264 (300-II)

ii. Synthesis of the Aldehyde 308

The synthesis of the aldehyde 308 was fairly straightforward and completed as described in Schemes II-4, II-5. Commercially available (–)-citronellal (309) ii was converted to the corresponding alkyne 310 according to the Corey-Fuchs protocol.114 Chemoselective ozonolysis of the trisubstituted olefin, carefully monitored by TLC, followed by reductive work-up with NaBH₄, afforded the corresponding alcohol 311a, which was protected as its silyl ether 311b,c. Carboaluminatio-iodination of the terminal alkyne in 311 into 312 was not as straightforward as we initially expected. Under low temperature Wipf conditions,115 the starting alkyne 311 remained unreacted. On the contrary, when 1-undecyne (313) was subjected to the same conditions, the corresponding alkenyl iodide 314 was isolated in 80% yield (Scheme II-4). It is known116 that to undergo initial carboalumination, analogous alkynes with a Me-group in the β-

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ii Acquired from TCI: [α]D²⁵ = -16.6 ° (c = 0.20 g/mL, CHCl₃, ~ 100% ee).
position, had to be heated for 16 h, followed by iodination at lower temperature. These conditions were productive for the synthesis of iodides 312a-c. However, when TBS-ether 311b was heated for longer than 16 h, partial cleavage of TBS-ether was observed, and the alcohol 312a was isolated in addition to 312b. The reduced yield of the corresponding TES-iodide 312c could be explained by the analogous side-reaction.

**Scheme II-4. Synthesis of Iodides 312a-c**

The rest of the synthesis of aldehyde 308 was completed as summarized in Scheme II-5. Since the starting (E)-2-bromo-2-butene (315) was fairly expensive, we decided to prepare it by selective anti-elimination of HBr from a mixture of Z- and E-2-bromo-2-butenes (9:1). No elimination occurred under Et$_3$N/DMSO conditions. On the other hand, t-BuOK/DMSO conditions were not very selective and resulted in elimination of HBr from both isomers of 315. DBU-mediated stereospecific elimination$^{117}$ of HBr in meso-2,3-dibromobutane (317) gave the desired bromooolefin 315 in 95% yield as a single E-isomer ($^1$H NMR analysis). Lithium-bromine exchange followed by addition of trimethyltin chloride yielded stannane$^{118}$ 318 in 81% crude yield. Stille coupling of iodide 312b and stannane 318 under Baldwin conditions$^{119}$ gave the desired diene 319b in 70% yield and protonated by-product 320b in 5% yield, which was only partially separable.
from 319b in my hands; no other by-products were isolated. An analogous coupling of unprotected alcohol 312a with stannane 318 also gave the corresponding diene in 70% yield. Deprotection of the TBS-ether in 319b under standard conditions followed by Parikh-Doering oxidation gave the aldehyde 321 in high yield (PCC or PCC/NaOAc led to decomposition of the product and/or the starting material). Standard Wittig olefination of the aldehyde 321, followed by DIBALH reduction, yielded alcohol 322, which was oxidized to the desired aldehyde 308 in the presence of an excess of manganese dioxide. The relative configuration of the diene unit in 308 was confirmed by NOE signals between H9 and both of H7 and between H10 and C8-Me-group.

### Scheme II-5. Synthesis of Aldehyde 256

iii. IMDA Approach to CJ-16,264 (300)

Following the protocol developed during the 2nd generation synthesis of UCS1025A (1), metal-halogen exchange in (±)-107a followed by addition of chiral aldehyde 308 gave the alcohols 323a,b (along with corresponding 1,7a,1'-tripimers) in a 1:1 ratio in
62% yield (Scheme II-6). Although by $^1$H NMR spectroscopy and TLC each diastereomer 323a and 323b appeared to be a single component each, necessarily, contained the second component 1,7a,1'-triiepi-323a and 1,7a,1'-triiepi-323b respectively, since iodide 107a was used in a racemic form. Hoping that at some later stage it would be possible to separate the *tris*-epimeric component, I separated, isolated, and used alcohols 323a and 323b as a mixture with the corresponding *tris*-epimeric component. Hydrolysis of esters gave the corresponding acids 324a and 324b that again looked as a single component. The same MnO$_2$ oxidation that was utilized in the synthesis of UCS1025A (1) was successfully used to convert both alcohols 324a and 324b into the enol 325, which again appeared to be a single component by TLC and $^1$H NMR spectroscopy. Usual HF•pyridine deprotection of the TBS-ether 325 gave the desired ketone 307 that again looked as a single component by TLC and $^1$H NMR spectroscopy.

**Scheme II-6. Synthesis of the Triene 307**

![Scheme II-6. Synthesis of the Triene 307](image-url)
When I examined the IMDA cycloaddition of the triene 307, I was surprised to learn that it was much less prone to the spontaneous IMDA cycloaddition. Triene 307 did not dissolve in pH 7.4 phosphate buffer/CH$_3$CN 5:1 (v/v) solution. It was soluble in pH 7.4 buffer/CH$_3$CN 1:1 (v/v), but no IMDA cycloaddition occurred under such conditions for 48 h at ambient temperature. In the presence of BF$_3$•OEt$_2$ in DCM the triene 307 underwent extensive decomposition. When the triene 307 was heated in CDCl$_3$ at 65 °C for 7 days, I observed disappearance of the diene moiety (in situ $^1$H NMR analysis). However, most of the resonances associated with enone moiety in 307 remained intact.

While $^1$H NMR analysis showed evidence of some formation of IMDA products 300 [$\delta$ 5.19 (q, 1H, $J$ = 1.7 Hz, H-4') and 5.13 (q, 1H, $J$ = 1.7 Hz, H-4')], HR-MS analysis of the reaction mixture showed evidence of formation of oxygenated, and bis-oxygenated products suggestive of possible autooxidation of the diene moiety (e.g., see structures 326a, b and 327a, b in Scheme II-7). I hypothesized that these by-products came from possible ene-reaction of the diene moiety in 307 with oxygen (Scheme II-7).

**Scheme II-7.** Some Diels-Alder Studies of the Triene 307

However, further analysis of the structures was not successful, since HPLC separation of the mixture was thwarted by keto-enol tautomerism of 300, 326, and 327, the problem
that we encountered earlier during separation of 1 from its tetraepimer 56. Heating of
the triene 307 in CDCl₃ in the presence of solid MgBr₂ or in toluene in a sealed tube
resulted in formation of a similar mixture of inseparable products. The reluctance of the
triene 307 to undergo the IMDA cycloaddition led us to conclude that such spontaneous
cyclization most probably is not operative in the biosynthesis of CJ-16,264, if that
compound has the structure 300-II (cf. Schemes II-2,3).

iv. Revised Retrosynthesis of CJ-16,264

At this stage our main goal turned to proving the correct structure of CJ-16,264 (300-
I vs. 300-II vs. ?). The revised retrosynthesis is described in Scheme II-8. We planned to
synthesized the key-intermediate 328 via the Reformatsky reaction of enantiopure
iodolactone 10a with the corresponding aldehyde 329. The latter could be accessed via
the IMDA cycloaddition of the enal 308 in the presence of a chiral catalyst. We also
considered the possibility of synthesizing various diastereomers of the aldehyde 329 to
prove the structure of CJ-16,264.

Scheme II-8. Revised Retrosynthesis of CJ-16,264 (300-II)

v. Synthesis of the Enantiopure Methyl Ester 49a

In order to do a conclusive assignment the stereochemical features of CJ-16,264, I
needed to prepare the iodolactone 10a in enantiomerically pure form. Following the
Danishefsky approach\textsuperscript{11} to the enantiomerically pure ester \textit{49a}, I initially attempted its synthesis as described in Scheme II-9. The starting bis-TMS ether (\textit{\textminus}-\textit{97b}) was synthesized using previously described methods (see Schemes I-28, I-29). TMS-ether deprotection of (\textit{\textminus}-\textit{97b}) with PPTS/MeOH was not very chemoselective, since substantial formation of the fully deprotected triol (\textit{\textminus}-\textit{331}) was observed in addition to the desired diol (\textit{\textminus}-\textit{100}). Use of HF•pyridine buffered with an excess of pyridine in THF was more productive and yielded diol (\textit{\textminus}-\textit{100}) in 95\% yield. Triflation, followed by elimination, led to formation of the triflate (\textit{\textminus}-\textit{332}) in 70\% yield.

\textbf{Scheme II-9.} Studies Toward the Synthesis of Enantio-Pure Ester \textit{49a}

Following Danishefsky’s protocol of heating the triflate (\textit{\textminus}-\textit{332}) in the presence of Pd(PPh\textsubscript{3})\textsubscript{4} and an excess of tributyltin hydride led to production of the desired ester (\textit{\textminus}-\textit{49a}) in only 20\% isolated yield. The \textalpha{}-ketolactam (\textit{\textminus}-\textit{122}) was a major by-product. Since there were many other tin by-products that were hard to separate from, I decided that this
route was not amenable for a scale-up. Direct stannylation of the triflate (–)-332 was not very productive either. It gave the desired stannane (–)-333 only in 10% yield. Again the α-ketolactam (–)-122 was a major by-product of the reaction. Starting triflate (–)-332 was not very stable and over time underwent elimination with formation of ester 334.

In attempt to synthesize the enantiopure ester 49a, I studied kinetic resolution studies, reported by Christmann and co-workers (Scheme II-10). Resolution of iodoacid (±)-106a with quinine was not very selective and yielded the lactone (–)-10a only in 6% ee. A kinetic resolution of acid (±)-13a in the presence of 0.5 equiv of quinine at room temperature gave the lactone (–)-20a, but with only 49% ee in my hands. Conducting the reaction at a lower temperature increased the ee of the lactone (–)-20a to 57%, although the reaction in my hands was much slower than reported (e.g., 44% conversion of acid (±)-13a required 30 days vs. 7 days in Christmann report18). Trituration of the crude reaction mixture in hot pentane gave (±)-13a as a residual solid and the solution of (+)-13a and (–)-20a. The separation of the mixture of acid (+)-13a and lactone (–)-20a by MPLC led to erosion of ees of the isolated products (ee of the lactone (–)-20a and acid (+)-13a were determined by 1H NMR ratio of C(7)H signals of the quinine salts, formed from the corresponding acids with sub-stochiometric amount of quinine). I attributed this observation to the ease of interconversion between acid 13a and lactone 20a on silica gel, evidence of which could be observed by TLC and/or 1H NMR analysis. Separation of a mixture of lactone (–)-20a and acid (+)-13a by short flash chromatography led to isolation of acid (+)-13a in 95% ee, 12% overall yield, although multiple purifications were required for separation. Acid (+)-13a was converted into iodolactone (+)-10a under standard conditions. The other enantiomer of iodolactone (–)-10a was synthesized from the corresponding acid (–)-13a, which in turn could be accessed via a base-mediated opening of the scalemic lactone (–)-20a (Scheme II-10).
Scheme II-10. Kinetic Resolution of Acids (±)-106a and (±)-13a with Quinine

vi. IMDA Cycloaddition of Aldehyde 308.

To study the IMDA cycloaddition of aldehyde 308, I synthesized MacMillan’s second-generation catalysts 24a,b, as reported in the literature\textsuperscript{15} and shown in Scheme II-11. Esterification of the appropriate enantiomer of phenylalanine (335) followed by formation of the corresponding N-methylamide in the presence of MeNH\textsubscript{2} in H\textsubscript{2}O/MeOH proceeded uneventfully. The subsequent condensation of the N-methylamide with pivaldehyde led to formation of the desired amines 337 and 338. The latter is commonly
used as the corresponding TfOH, TFA, or HClO salt to catalyze various transformations, including an IMDA cycloaddition of enals.\textsuperscript{15}

\textbf{Scheme II-11. Synthesis of the Chiral Catalysts 24a,b}

\[
\begin{align*}
\text{L-Phenylalanine} & \quad 335a \quad \text{(shown)} \\
\text{D-Phenylalanine} & \quad 335b \quad \text{(not shown)}
\end{align*}
\]

The IMDA cycloaddition of the polyenes with 8,10,11-substituted dienes as in aldehyde 308 has not been broadly studied. We found only one other report of the IMDA cycloaddition of achiral 8,10,11-trisubstituted-2,8,10-triene (±)-339 into (±)-340 and (±)-341 under thermal and Lewis acid-catalyzed conditions by Roush \textit{et al} (Scheme II-13).\textsuperscript{120} We were very excited to further explore this type of an IMDA cycloaddition.

\textbf{Scheme II-13. Roush’s IMDA Cycloaddition of 8,10,11-Trisubstituted Triene (±)-339}

We were also aware that such a transformation could be slowed down by the 1,5-H shift of the diene moiety in 308 (Scheme II-14). However, the latter transformation is reversible and results in formation of a substrate 342, which is less prone to undergo an IMDA cycloaddition with formation of the anti-Bredt compound 343. We also plan to study the kinetics of the 1,5-H shift on the substrates like 320 that cannot undergo the IMDA cycloaddition (Scheme II-14).

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Scheme II-14. The 1,5-H-Shift in 1,3,4-Substituted Dienes

When the aldehyde 308 was heated in toluene at 120 °C for 17 days, I observed formation of the two major products in ~ 2:1 ratio. Upon HPLC separation and a detailed analysis of the spectral data of the formed aldehydes (vide infra) these products appeared to be exo-isomer 329b and endo-329a [Scheme II-15, Table 7 (1)]. Some decomposition, analogous to decomposition of the triene moiety in aldehyde 308 was observed as well (cf. Scheme II-7).

Scheme II-15. IMDA Cycloaddition of Aldehyde 308
<table>
<thead>
<tr>
<th>#</th>
<th>Conditions: catalyst, solvent</th>
<th>Temperature</th>
<th>$t_{1/2}$</th>
<th>dr $329a : 329b : 329c : 329d : 329e$; yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Toluene, BHT (~ 2 mol%)</td>
<td>120 °C</td>
<td>7 days</td>
<td>31 : 60 : - : - : 9 (53%)</td>
</tr>
<tr>
<td>2</td>
<td>24a (20 mol%), CD$_3$CN/D$_2$O (98/2)</td>
<td>0 °C</td>
<td>24 h</td>
<td>63 : 37 : - : - : - (15%)</td>
</tr>
<tr>
<td>3</td>
<td>24b (20 mol%), CD$_3$CN/D$_2$O (98/2)</td>
<td>0 °C</td>
<td>24 h</td>
<td>40 : 7 : - : - : 53 (10%)</td>
</tr>
</tbody>
</table>

On the other hand, in the presence of a catalytic amount of S-24a, the IMDA cycloaddition of the aldehyde 308 resulted in formation of aldehydes endo-329a and exo-329b of the reversed 2.2:1 ratio [Scheme II-15, Table 7 (2)]. In the presence of a catalytic amount of the other catalyst R-24b, the IMDA cycloaddition of the aldehyde 256 resulted in formation of three aldehydes in a 40:7:53 ratio [Table 7 (3)]. Upon spectral data analysis we assigned their structures as endo-329a, exo-329b and exo-329e. The later was produced via C1-epimerization of the formed aldehyde exo-329b or E/Z-isomerization of the dienophile moiety in aldehyde 308 or the corresponding iminium ion (vide infra). According to $^1$H NMR data no formation of the other two possible diastereomers endo-329c and exo-329d was observed in either of the IMDA experiments.

I also demonstrated that in the presence of the catalyst S-24a aldehydes 308 and 23 (the latter was used in synthesis of UCS1025A) undergo the IMDA cycloaddition at the same rate. This observation suggested that, in this case, the rate-limiting step of the reaction was the formation of the corresponding iminium intermediates of 308 or 23, which, once formed, quickly undergo the IMDA cyclization into the corresponding products 329a and 329b, or 11. On the other hand, the uncatalyzed IMDA cycloaddition of the aldehyde 23 required only heating at 80 °C for 10 days and resulted in formation of the endo-compound 11 as a major product (Scheme II-16).
Scheme II-16. Comparative Studies of the IMDA Cycloaddition of Aldehyde 23

The selectivity of the IMDA cycloaddition of aldehyde 308, catalyzed by amines 24a,b was first rationalized through a transition states analysis as shown in Schemes II-17, 18. Upon analysis of all possible transition states we considered the following variables: the s-cis/s-trans configuration of the dienophile, equatorial/axial positioning of the C6-Me-group, endo/exo mode of the IMDA cycloaddition, and approach of the diene unit from re or si-face of C2. Iminium ion geometry is known to have the E-configuration. Taking all these facts into consideration we found eight possible transition states A-H. As illustrated in Scheme II-17, when S-24a is used as a catalyst, the most favorable transition states are A-S and B-S, which lead to formation of aldehydes 329a and 329b correspondingly. Transition states C-S, D-S, E-S, and F-S experience additional steric interactions between amine substituents and diene or/dienophile moieties. Transitions states E-S, F-S, G-S, and H-S experience unfavorable 1,7-diaxial interactions between C6-Meax and diene unit.
Scheme II-17. Analysis of All Possible Transition States of the IMDA Cycloaddition of Aldehyde 308 in the Presence of Catalyst S-24a

When R-24a is used as a catalyst, all transition states A-R – H-R experience one or two types of analogous unfavorable interactions. The two minor products under the reaction conditions were aldehydes 274a and 277b, formed presumably through transitions states C-R ad D-R correspondingly (Scheme II-18). The major product under such IMDA conditions was the aldehyde 329c. This product could arise via epimerization of the aldehyde 329b and/or its iminium derivative or, most likely, via the transition state I-R (Scheme II-18). The latter does not experience any unfavorable interactions and could be produced via E/Z-isomerization of the dienophile moiety in D-R. Ironically,
aldehyde 329e has the same relative configuration as the octalin moiety in CJ-16,264 with the structure 300-I from the isolation report (cf. Figure 6).\textsuperscript{112}

**Scheme II-18.** Analysis of Possible Transition States of the IMDA Cycloaddition of Aldehyde 308 in the Presence of Catalyst 24b
Seemingly, 1,7-Me,Me-interactions are the most severe and preclude formation of aldehydes 329c and 329d via transition states E-R(E-S) or G-R(G-S) and F-R(F-S) or H-R(H-S) correspondingly.

Structure assignment of aldehydes 329a,b,e was further confirmed on the basis of thorough analysis of the corresponding $^1$H NMR (coupling constant analysis), $^{13}$C NMR, COSY, HMQC, and HMBC (Tables 8, 9, and 10). The coupling constant analysis was the most informative, and showed that in all three aldehydes 329a,b,e C6-Me is the equatorial position and H-6 – in axial, since H-5ax has two and H-7ax has four large coupling constants (> 12 Hz). Since in all three isolated aldehydes 329a,b,e H-8ax and H-7ax have 3 large coupling constants, it implies that H-8a is the axial position in all three structures. In aldehyde 329a, $J_{1-8a}$ =12.4 Hz and $J_{8ax-8a}$ =12.4 Hz, which puts H-1 and H-8a in trans-diaxial relative position, which leads to the trans-fused octalin system of configuration shown in Figure 7. In the aldehydes 329b $J_{1-8a}$ =1.3 Hz and $J_{8ax-8a}$ =12.4 Hz, which puts H-1 in the equatorial position. In the aldehyde 329e $J_{1-8a}$ = 3.2 Hz and $J_{8ax-8a}$ =12.4 Hz, which again places H-1 in the equatorial position. The final distinction between structures 329b and 329e was based on NOE data, i.e. the NOE signal between Me-C4a and CHO was present in structure 329b, and, on the contrary, the aldehyde 329e showed NOE correlation between H-1 and Me-C4a (Figures 8,9).

**Figure 7.** Structural Assignment of Aldehyde 329a

---

iii $E_{rel}$ is a difference in heat of formations that was calculated using MacroModel conformational search/energy minimization, force field OPLS5

iv Only some of HMBC and NOE signals are shown; correlations that are not shown are also in agreement with the proposed structural assignment
Table 8. $^{13}$C and $^1$H NMR Spectral Data for Aldehyde 329a [C$_6$D$_6$ (CDCl$_3$), 125 and 500 MHz].

<table>
<thead>
<tr>
<th>Atom number</th>
<th>Carbon δ_C</th>
<th>Proton δ_H, mult, J [Hz]</th>
<th>COSY (to proton)</th>
<th>HMBC (from H → C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>51.5</td>
<td>2.39 (2.45) ddd 12.1, 5.9, 4.1</td>
<td>2, 8a, CHO,</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>36.8</td>
<td>2.10 (2.36) dqq 6.8, 6.8, 0.8</td>
<td>1, C2-CH$_3$</td>
<td>C2-CH$_3$, C3, C3-CH$_3$</td>
</tr>
<tr>
<td>3</td>
<td>134.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>135.0</td>
<td>5.07 (5.17) q 1.1</td>
<td></td>
<td>C3-CH$_3$</td>
</tr>
<tr>
<td>4a</td>
<td>36.4</td>
<td></td>
<td></td>
<td>C3, C4a, C5</td>
</tr>
<tr>
<td>5ax</td>
<td>48.6</td>
<td>0.81 (0.91) dd 12.5, 12.5</td>
<td>5eq</td>
<td></td>
</tr>
<tr>
<td>5eq</td>
<td>1.30 (1.45)</td>
<td>ddd 12.8, 3.9, 1.7</td>
<td></td>
<td>5ax</td>
</tr>
<tr>
<td>6</td>
<td>27.8</td>
<td>1.47 (1.65) m</td>
<td></td>
<td>C6-CH$_3$</td>
</tr>
<tr>
<td>7ax</td>
<td>36.2</td>
<td>0.80 (0.98) m</td>
<td></td>
<td>7eq, 8ax</td>
</tr>
<tr>
<td>7eq</td>
<td>1.58 (1.80)</td>
<td>m</td>
<td></td>
<td>7ax</td>
</tr>
<tr>
<td>8ax</td>
<td>24.5</td>
<td>1.06 (1.25) dddd 12.9, 12.9, 12.9, 3.6</td>
<td>7ax, 7eq, 8eq, 8a</td>
<td></td>
</tr>
<tr>
<td>8eq</td>
<td>1.57 (1.58)</td>
<td>m</td>
<td></td>
<td>8ax</td>
</tr>
<tr>
<td>8a</td>
<td>38.6</td>
<td>1.66 (1.81) ddd 12.4, 12.4, 2.8</td>
<td>1, 8ax</td>
<td></td>
</tr>
<tr>
<td>2-Me</td>
<td>15.2</td>
<td>0.89 (1.12) d 7.1</td>
<td>2</td>
<td>C1, C2</td>
</tr>
<tr>
<td>3-Me</td>
<td>21.8</td>
<td>1.47 (1.65) dd 1.5, 0.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4a-Me</td>
<td>20.8</td>
<td>0.74 (0.87) d 0.7</td>
<td></td>
<td>C4a, C5, C8a</td>
</tr>
<tr>
<td>6-Me</td>
<td>23.3</td>
<td>0.79 (0.87) d 6.5</td>
<td>6</td>
<td>C4a, C5, C6</td>
</tr>
<tr>
<td>CHO</td>
<td>205.4</td>
<td>9.59 (9.79) d 4.0</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>
Figure 8. Structural Assignment of Aldehyde 329b

\[ E_{rel} = E^\bullet_E_{329a} \]

\[ 329b \]

\[ \text{exo-1} \]

\[ E_{rel} = +2.92 \text{ kcal/mol} \]

\[ \text{NOE} \]

Table 9. \(^{13}\)C and \(^1\)H NMR Spectral Data for Aldehyde 329b [C\(_6\)D\(_6\) (CDCl\(_3\)), 125 and 500 MHz].

<table>
<thead>
<tr>
<th>Atom number</th>
<th>Carbon (\delta_c)</th>
<th>Proton (\delta_h)</th>
<th>mult</th>
<th>(J) [Hz]</th>
<th>COSY (to proton)</th>
<th>HMBC (from H→ C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>61.1</td>
<td>1.596 (2.01)</td>
<td>dd</td>
<td>1.9, 2.9</td>
<td>1</td>
<td>C2, C8a, CHO</td>
</tr>
<tr>
<td>2</td>
<td>36.8</td>
<td>2.95 (2.82)</td>
<td>qddq</td>
<td>7.3, 2.3, 2.3, 1.2</td>
<td>C2-CH(_3)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>134.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>130.5</td>
<td>4.93 (5.04)</td>
<td>ddq</td>
<td>2.8, 1.4, 1.4</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>4a</td>
<td>29.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5ax</td>
<td>50.1</td>
<td>0.73 (0.92)</td>
<td>dd</td>
<td>12.5, 12.5</td>
<td>5eq</td>
<td></td>
</tr>
<tr>
<td>5eq</td>
<td>1.28 (1.37)</td>
<td>ddd</td>
<td>12.8, 3.4, 2.3</td>
<td>5ax</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>29.5</td>
<td>1.24 (1.35)</td>
<td>m</td>
<td></td>
<td>C6-CH(_3)</td>
<td></td>
</tr>
<tr>
<td>7ax</td>
<td>35.8</td>
<td>0.75 (0.88)</td>
<td>m</td>
<td></td>
<td>7eq</td>
<td></td>
</tr>
<tr>
<td>7eq</td>
<td>1.50 (1.70)</td>
<td>dddddd</td>
<td>12, 3, 3, 3, 3</td>
<td>7ax</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8ax</td>
<td>32.2</td>
<td>1.45 (1.59)</td>
<td>dddd</td>
<td>12.7, 12.7, 12.7, 3.7</td>
<td>8eq, 8a</td>
<td></td>
</tr>
<tr>
<td>8eq</td>
<td>1.15 (1.47)</td>
<td>dddd</td>
<td>12.9, 3.8, 3.8, 3.8</td>
<td>8ax, 8a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8a</td>
<td>41.6</td>
<td>1.65 (2.00)</td>
<td>dddd</td>
<td>12.4, 12.1, 12.1, 3.7</td>
<td>8ax, 8eq</td>
<td></td>
</tr>
<tr>
<td>2-Me</td>
<td>21.7</td>
<td>0.94 (1.13)</td>
<td>d</td>
<td>7.6</td>
<td></td>
<td>C1, C3, C4a</td>
</tr>
<tr>
<td>3-Me</td>
<td>22.4</td>
<td>1.605 (1.72)</td>
<td>dd</td>
<td>1.3, 1.3</td>
<td></td>
<td>C3, C4, C4a</td>
</tr>
<tr>
<td>4a-Me</td>
<td>31.5</td>
<td>0.70 (0.72)</td>
<td>s</td>
<td></td>
<td></td>
<td>C2, C4, C5, C8a</td>
</tr>
<tr>
<td>6-Me</td>
<td>23.0</td>
<td>0.82 (0.85)</td>
<td>d</td>
<td>6.4</td>
<td>6</td>
<td>C5, C6, C7</td>
</tr>
<tr>
<td>CHO</td>
<td>203.4</td>
<td>9.50 (9.75)</td>
<td>s</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^{v}\) \(E_{rel}\) is a difference in heat of formations that was calculated using MacroModel conformational search/energy minimization, force field OPLS5

\(^{vi}\) Only some of HMBC and NOE signals are shown; correlations that are not shown are also in agreement with the proposed structural assignment
Figure 9. Structural Assignment of Aldehyde 329e\textsuperscript{vii,viii}

\[
E_{rel} = E_{329e} - E_{329a}
\]

329e
\[ Z\text{-endo} \]

\[
E_{rel} = +1.27 \text{ kcal/mol}
\]

$vii$ E\textsubscript{rel} is a difference in heat of formations that was calculated using MacroModel conformational search/energy minimization, force field OPLS5

$viii$ Only some of HMBC and NOE signals are shown; correlations that are not shown are also in agreement with the proposed structural assignment

\begin{table}[h]
\centering
\begin{tabular}{lllllll}
\hline
Atom number & Carbon \(\delta_C\) & Proton \(\delta_H\) & Proton mult. & \(J[\text{Hz}]\) & COSY (to proton) & HMBC (from H \(\rightarrow\) C) \\
\hline
1 & 51.3 & 2.62 (2.95) & dd & 7.2, 3.2 & 2, 8a & C2, C2-CH\(_3\), CHO \\
2 & 32.8 & 2.24 (2.61) & br dq & 7.3, 7.3 & 1, C2-CH\(_3\) & C1, C2-CH\(_3\), C3 \\
3 & 135.5 & & & & & \\
4 & 131.7 & 4.94 (5.07) & ddq & 1.6, 1.6, 1.6 & C3-CH\(_3\) & \\
4a & 36.8 & & & & & \\
5ax & 50.5 & 0.82 (0.95) & dd & 13, 12 & 5eq, 6 & \\
5eq & 1.40 (1.54) & ddd & 13.2, 3.1, 2.7 & & 5ax & \\
6 & 30.3 & 1.21 (1.30) & m & & 5ax, C6-CH\(_3\) & \\
7ax & 35.8 & 0.73 (0.82) & dddd & 12.9, 12.9, 12.9, 3.1 & 7eq, 8ax & \\
7eq & 1.49 (1.58) & dddd & 12.6, 3.1, 3.1, 3.1, 3.1 & & 7ax & \\
8ax & 26.8 & 1.28 (1.37) & dddd & 12.9, 12.9, 12.9, 3.4 & 7ax, 8a, 8eq & \\
8eq & 1.65 (1.61) & dddd & 12.9, 3.5, 3.5, 3.5 & & 7ax, 8ax & \\
8a & 40.5 & 1.79 (1.88) & dddd & 12.6, 3.6, 3.4, 1.5 & 1, 8ax, 8eq & \\
2-Me & 16.6 & 1.01 (1.17) & d & 7.5 & 2 & C1, C2, C3 \\
3-Me & 22.1 & 1.57 (1.72) & dd & 1.1, 1.1 & & C2, C3, C4 \\
4a-Me & 31.5 & 0.82 (0.95) & s & & & C4, C5, C8a \\
6-Me & 23.2 & 0.81 (0.83) & d & 6.5 & 6 & C6 \\
CHO & 203.5 & 9.61 (9.90) & s & & & \\
\hline
\end{tabular}
\caption{\(^{13}\)C and \(^1\)H NMR Spectral Data for Aldehyde 329e [C\(_6\)D\(_6\) (CDCl\(_3\)), 125 and 500 MHz].}
\end{table}

To prove the correct structure of CJ-16,264, we next studied Reformatski coupling of iodolactone 10a with aldehydes 329 (Scheme II-19). Since we had an access to the both enantiomers of 10a and three diastereomers of 329, we planned to synthesize all six diastereomeric structures 300 and further study which one of those would correspond to the correct configuration of CJ-16,264.

Scheme II-19. Approach to the Synthesis of CJ-16,264 (300)

The synthesis of structures exo-adducts 328 was achieved as shown in Scheme II-20 via Reformatski coupling of aldehydes 329 with the corresponding iodolactone. Upon DMP oxidation of the secondary alcohol in 328 an evidence for a steady-state concentration of the corresponding ketone 7'-epi-331 was observed throughout the course of the reaction, but after work up and chromatography the resulting products 331 were isolated as a mixture of enol-331 and trans-keto-331 forms. Deprotection of TBS-ether in the presence of HF•pyridine went uneventfully and gave the corresponding product 330. I was able to synthesize all six diastereomers. The comparison of $^1$H and $^{13}$C NMR data of the synthesized compounds 330 and reported CJ-16,264 revealed that the natural product does not possess the configuration of ay of the synthesized 330 (Tables 11, 12).
Scheme II-20. Synthesis and Structure-Proof of CJ-16,264 (300)

(+)-10a
+ \(\text{BET}_3\) at \(-78^\circ\)C
\[329a\] → \[328a\] → 7'-epi-331a enol-331a 3.3 : 1 keto-331a
\[330a\]

(-)-10a
+ \(\text{BET}_3\) at \(-78^\circ\)C
\[329a\] → \[328a'\] → 7'-epi-331a' enol-331a' 7.3 : 1 keto-331a'
\[330a'\]

(+)-10a
+ \(\text{BET}_3\) at \(-78^\circ\)C
\[329b\] → \[328b\] → 7'-epi-331b enol-331b 4.2 : 1 keto-331b
\[330b\]

(-)-10a
+ \(\text{BET}_3\) at \(-78^\circ\)C
\[329b\] → \[328b'\] → 7'-epi-331b' enol-331b' 1.1 : 1 keto-331b'
\[330b'\]

(+)-10a
+ \(\text{BET}_3\) at \(-78^\circ\)C
\[329e\] → \[328c\] → 7'-epi-331c enol-331c 2 : 1 keto-331c
\[330c\]

(-)-10a
+ \(\text{BET}_3\) at \(-78^\circ\)C
\[329e\] → \[328c'\] → 7'-epi-331c' enol-331c' 1 : 4.1 keto-331c'
\[330c'\]
Table 11.1 $^1$H NMR Spectral Data of CJ-16,264 and Its Diastereomers 330 [C$_6$D$_6$, 500 MHz, referenced to benzene peak at 7.20 ppm].

<table>
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<th>330a'</th>
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<tr>
<td>3</td>
<td>5.08 s</td>
<td></td>
<td></td>
</tr>
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<td>4</td>
<td>1.06 m</td>
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</tr>
<tr>
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<td>1.60 m</td>
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<td></td>
</tr>
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<td>1.42 m</td>
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</tr>
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<td>3.56 m</td>
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<tr>
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Table 11.2  $^1$H NMR Spectral Data of CJ-16,264 and Its Diastereomers 330 [C$_6$D$_6$, 500 MHz, referenced to benzene peak at 7.20 ppm].

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</tr>
<tr>
<td>4</td>
<td>5.08 s</td>
<td>5.07 dq 1.6, 1.6</td>
<td>4.99 qd 1.4, 1.2</td>
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</tr>
<tr>
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<td>0.70 dd 12, 12</td>
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<td>1.02 m</td>
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<td>1.40 m</td>
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<td>1.38 ddd 13, 4, 4, 4</td>
</tr>
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<td>1.74 ddd 11.9, 4.2, 1.5, 1.5</td>
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</tr>
<tr>
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<td>4a-Me</td>
<td>0.91 s</td>
<td>0.92 s</td>
<td>0.71 s</td>
</tr>
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<td>0.85 d 6.4</td>
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<td>2.75 d 9</td>
<td>2.69 dd 9.3, 2.1</td>
<td>2.71 dd 9.3, 2.2</td>
</tr>
<tr>
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</tr>
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<td>1.92 ddd 13.7, 9.6, 9.6, 5.7</td>
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<td>2.74 ddd 12.0, 9.8, 5.2</td>
</tr>
<tr>
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<td>4.09 s</td>
<td>4.02 s</td>
<td>4.35 s</td>
</tr>
<tr>
<td>7'a</td>
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<td>4.13 s</td>
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</tr>
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<td>7'b-OH</td>
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<td>5.01 s</td>
<td>4.79 s</td>
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Table 11.3  $^1$H NMR Spectral Data of CJ-16,264 and Its Diastereomers 330 [C$_6$D$_6$, 500 MHz, referenced to benzene peak at 7.20 ppm].

<table>
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<tr>
<th>Atom number</th>
<th>CJ-16,264 $\delta_H$ mult $J$</th>
<th>330c $\delta_H$ mult $J$ Hz</th>
<th>330c' $\delta_H$ mult $J$ Hz</th>
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<td>$\delta_H$</td>
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<td>2.41 dq 7.4, 7.4</td>
</tr>
<tr>
<td>3</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>5.08 s</td>
<td>4.96 q 1.5</td>
<td>5.00 q 1.5</td>
</tr>
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<td>4a</td>
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<td></td>
<td></td>
</tr>
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<td>0.80 dd 13.4, 12.4</td>
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<td>1.40 ddd 13.2, 3.2, 2.6</td>
</tr>
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<td>1.27 m</td>
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</tr>
<tr>
<td>4a-Me</td>
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<td>0.99 s</td>
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</tr>
<tr>
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<tr>
<td>1'</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2'</td>
<td>2.75 d 9</td>
<td>2.67 dd 9.3, 2.1</td>
<td>2.71 dd 9.4, 2.0</td>
</tr>
<tr>
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</tr>
<tr>
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<td>7'b-OH</td>
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Table 12. $^{13}$C NMR Spectral Data of CJ-16,264 and Its Diastereomers 330 [CD$_6$, 125 MHz, referenced to benzene peak at 128.00 ppm]

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However, the striking similarities between CJ-16,264 and 330b NMR data led us to think that CJ-16,264 most likely possesses the octalin configuration of 330b. However, seemingly favorable isomerization of cis-substituted lactone in 7'-epi-331a into trans-keto-331a led us to believe that configuration of the heterocyclic portion of CJ-16,264 was assigned incorrectly. This conclusion was further supported by the absence of any
evidence of cis-330 upon oxidation of alcohol 332 with DMP (1H NMR monitoring, Scheme II-21).

**Scheme II-21.**

![Scheme II-21](image)

**C. Conclusion**

The studies toward proof of the correct structure of CJ-16,264 are currently ongoing in our research group. We hope to finish these experiments in near future and provide further support for our hypothesis about incorrect assignment of CJ-16,264 and its possible biosynthetic origin. We also plan to do additional experiments on synthesis of aldehydes 329a-e and their unambiguous structural assignment. Additionally, the reluctance of the triene 307 to undergo the IMDA cycloaddition led us to conclude that such spontaneous cyclization most probably is not operative in the biosynthesis of CJ-16,264, if that compound has the structure 300-II (cf. Schemes II-2,3, and 7). As in the case of biosynthesis of UCS1025A (1), at this stage we conclude that CJ-16,264 (300) could possibly been synthesized in nature via an alternative pathway (cf. Scheme I-87).
Chapter III. Synthetic Efforts Toward Phomopsichalasin

A. Background

1. Introduction

There are other natural products that could arise in nature via a spontaneous IMDA cycloaddition and contain tetramic acid moiety. Among them are phomopsichalasin\textsuperscript{122} (400), diaporthichalasin\textsuperscript{123} (401), oteromycin\textsuperscript{124} (403), talaroconvolutin A\textsuperscript{125} (403), talaroconvolutin B\textsuperscript{125} (404), and ZG-1494α\textsuperscript{126} (405) (the last two natural products are C5 and/or C26 stereoisomers of one another,\textsuperscript{125} Figure 10).

Figure 10. Phomopsichalasin, Diaporthichalasin, Oteromycin, Talaroconvoltins A,B, and ZG-1494α Natural Products

We were also intrigued by the same question we had been investigating so far: whether or not IMDA cycloaddition(s) step in the biosynthesis of natural products like 400-405 is enzymatically catalyzed? It is also worth noting that, as far as we know, no
synthetic efforts toward natural products 400-405 have been reported in the literature at this point.

2. Isolation of Phomopsichalasin and Diaporthichalasin

Phomopsichalasin (400) and diaporthichalasin (401) are the most complex members of this family of natural products. They possess unprecedented complex and fascinating structure, i.e., they both contain 5 rings and 10 stereocenters. We hypothesize that 400 and 401 could be produced in nature via a pair of spontaneous Diels-Alder cycloadditions from the same polyene precursor 406 (cf. Schemes III-1, III-2, and III-3). Furthermore, we were curious to see, how the single, methyl-bearing stereocenter at C(18) in the precursor 406 would affect the diastereoselectivity of the IMDA cycloadditions. If successful, the increase in structural complexity accompanying these IMDA transformations would be of a nearly unprecedented level.

i. Isolation and Biological Activity of Phomopsichalasin

Phomopsichalasin (400) was isolated by Horn and co-workers and reported in 1995122 from an endophytic Phomopsis sp. fungus fermented on shredded wheat. The authors isolated 5.65 mg of 400 by fermenting a conidial suspension of the Phomopsis isolate on 238 g of Nabisco Original Shredded Wheat. The structure and relative configuration of 400 were assigned according to extensive analysis of NMR (1H NMR, 13C NMR, DEPT, COSY, TOCSY, HMBC, HMQC, and NOESY), HR-MS, and FT-IR spectral data.122 Phomopsichalasin (400) also displayed antibacterial activity in disk diffusion assays against Bacillus subtilis, Salmonella gallinarum, Staphylococcus aureus, and yeast Candida tropicalis.122

ii. Isolation and Biological Activity of Diaporthichalasin

During our work on phomopsichalasin the isolation of the related natural product diaporthichalasin (401) was reported.123 As seen later, this finding did not change the line of our thinking, and it also added some enticement to the project.
Diaporthichalasin (401) was isolated by Pornpakakul and co-workers and reported in 2007 from the filamentous fungus *Diaporthe* sp. Bkk3 (phytogenetic analysis also demonstrated that this species is very close to *Phomopsis* sp., 90% sequence identities of in the DNA ITS region). This fungus was fermented on 20 L of malt extract broth culture medium, containing malt extract, glucose, and bacterial peptone. The most surprising of all was the fact that from 10 g of a crude extract 1.5 g of 401 was isolated. Isolation of such significant amounts of diaporthichalasin allowed the authors to do thorough structural analysis. The structure and relative configuration of 401 were assigned according to extensive analysis of NMR (1H NMR, 13C NMR, COSY, TOCSY, HMBC, HMQC, and NOESY), HR-MS, and x-ray data.

1H NMR data of the natural product 401 is very close to that of 400, although it was taken in a different solvent (cf. Figure 11, Table 13). However, phomopsichalasin and diaporthichalasin showed a different specific optical rotation for 401 [α]D<sup>20</sup> = -135 (c 0.14, MeOH), compared with 400, [α]D<sup>25</sup> = -7.16 (MeOH). Compound 401 also exhibited no antimicrobial activity against *Bacillus subtilis* ATCC 6633, *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853, and *Candida albicans* ATCC 10231 at <125 µg/mL using microtiter plate broth dilution assay like phomopsichalasin (400) did. Diaporthichalasin (401) showed potent inhibition of CYP3A4 enzyme of human liver microsomes with IC<sub>50</sub> value of 0.626 µM.

**B. Our Synthetic Efforts Toward Phomopsichalasin (and Diaporthichalasin)**
1. Our Hypothesis on Biosynthesis of Phomopsichalasin (and Diaporthichalasin)

Initially, when we were considering the structure of 400 that was assigned to phomopsichalasin by Horn et al., we were convinced that its stereochemical assignment as illustrated in Figure 11 was incorrect. Notwithstanding the authors’ statement that “the NOE, identified between H4 and Me27, is the evidence for their cis-relationship”, there is another tell-tale indication that, at the very least, the axial orientation of the C27 methyl group is incorrect. Namely, the high field chemical shifts of protons $H_{ax}17$ ($\delta$ 0.67 ppm) and $H_{ax}19$ ($\delta$ 0.56 ppm) (see Table 13) are not compatible with this structure. In a largely overlooked study by Grant from twenty years ago, which our group frequently relies upon for guidance, the remarkable stereoelectronic impact of an alkyl for proton replacement on a hydrocarbon framework was studied. Most relevant in the case of 400 is the dramatic difference in chemical shifts - greater than 0.5 ppm - induced by an adjacent gauche vs. anti methyl group on a vicinal, axial proton [cf. “Grant numbers” in Figure 11, which reflect the downfield (+) vs. upfield (-) incremental shift relative to parent cyclohexane]. Moreover, if a cycloaddition is involved in the biosynthesis of 400, the transition state geometry for that reaction would necessarily contain a developing syn-pentane interaction between the 1,3-diaxial C26 and C27 methyl groups (vide infra).

Figure 11. Structures of Phomopsichalasin and Diaporthichalasin Natural Products
Table 13. $^1$H and $^{13}$C NMR Data of Phomopsichalasin (400) in CD$_3$OD and Diaporthichalasin (401) in DMSO-$d_6$

<table>
<thead>
<tr>
<th>#</th>
<th>$\delta$$_H$ (mult, $J$, Hz) of 400 (CD$_3$OD)</th>
<th>$\delta$$_H$ (mult, $J$, Hz) of 401 (DMSO-$d_6$)</th>
<th>$\Delta=\delta$$_H$(400) - $\delta$$_H$(401)</th>
<th>$\delta$$_C$ of (400)</th>
<th>$\delta$$_C$ of (401)</th>
<th>$\Delta=\delta$$_C$(400) - $\delta$$_C$(401)</th>
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<tr>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>178.2</td>
<td>174.83</td>
<td>+3.4</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>8.58 (s)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
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<td>-</td>
<td>89.7</td>
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<td>4</td>
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<tr>
<td>5</td>
<td>2.09 (br q, 7.3)</td>
<td>2.03 (m)</td>
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<td>28.82</td>
<td>+1.9</td>
</tr>
<tr>
<td>6</td>
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<td>-</td>
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<td>9</td>
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<td>-</td>
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</tr>
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<td>2.86 (s)</td>
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<td>11</td>
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<td>0.71 (d, 7.2)</td>
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<td>21.0</td>
<td>20.04</td>
<td>+1.0</td>
</tr>
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<td>+0.3</td>
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<td>50.14</td>
<td>+1.9</td>
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<tr>
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<td>-</td>
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<td>128.13</td>
<td>+1.4</td>
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</tr>
<tr>
<td>15</td>
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<td>5.36 (s)</td>
<td>0.00</td>
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<td>137.95</td>
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<td>47.80</td>
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<tr>
<td></td>
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<td>1.41 (br d, 12.8)</td>
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<td>18</td>
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<td>1.54 (m)</td>
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<td>28.4</td>
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<td>+1.7</td>
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<td>0.46 (br q, 12.4)</td>
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<td>36.9</td>
<td>35.37</td>
<td>+1.5</td>
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<td></td>
<td>1.64 obsc</td>
<td>1.62 (br d, 9.2)</td>
<td>+0.02</td>
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<td></td>
<td></td>
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<td>20</td>
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<td>+0.12</td>
<td>24.5</td>
<td>22.99</td>
<td>+1.5</td>
</tr>
<tr>
<td></td>
<td>1.5 obsc</td>
<td>1.37 (m)</td>
<td>+0.13</td>
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<tr>
<td>21</td>
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<td>1.32 (dd, 12.8, 13.2)</td>
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<td>42.2</td>
<td>40.34</td>
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<tr>
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<td>2.03 (dd, 12, 8.4)</td>
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<td>50.8</td>
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<td>+2.0</td>
</tr>
<tr>
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<td>-</td>
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<td>218.95</td>
<td>+2.3</td>
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</tr>
<tr>
<td>24</td>
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<td>1.47 (s)</td>
<td>+0.05</td>
<td>26.3</td>
<td>25.49</td>
<td>+0.8</td>
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<tr>
<td>25</td>
<td>1.88 (br s)</td>
<td>1.82 (s)</td>
<td>+0.06</td>
<td>25.5</td>
<td>24.98</td>
<td>+0.5</td>
</tr>
<tr>
<td>26</td>
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<td>0.74 (s)</td>
<td>+0.06</td>
<td>19.9</td>
<td>19.52</td>
<td>+0.4</td>
</tr>
<tr>
<td>27</td>
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<td>0.75 (d, 7.6)</td>
<td>+0.03</td>
<td>23.1</td>
<td>22.66</td>
<td>+0.4</td>
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<td>1´</td>
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<td>-</td>
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<td>126.69</td>
<td>+2.1</td>
<td></td>
</tr>
<tr>
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<td>7.14 (d, 8.5)</td>
<td>7.09 (d, 8.4)</td>
<td>+0.05</td>
<td>132.8</td>
<td>131.6</td>
<td>+1.2</td>
</tr>
<tr>
<td>3´,5´</td>
<td>6.74 (d, 8.5)</td>
<td>6.67 (d, 8.4)</td>
<td>+0.07</td>
<td>116.1</td>
<td>114.83</td>
<td>+1.3</td>
</tr>
</tbody>
</table>
We were intrigued to see that there were many similarities in the $^1$H NMR data of phomopsichalasin and diaporthichalasin. Recall, that the structure of the latter, namely 401, was secured by single-crystal x-ray analysis. Although, we cannot say with certainty whether the two compounds were the same, since $^1$H NMR data of phomopsichalasin were reported in CD$_3$OD solvent (and it was stated that phomopsichalasin underwent spontaneous dehydration in DMSO-$d_6$), and $^1$H NMR data of 401 were reported in DMSO-$d_6$ (Table 13). Nevertheless, the analogous chemical shifts of 401 for protons H$_{ax}$17 and H$_{ax}$19 were δ 0.58 ppm and 0.56 ppm respectively, which is in accordance to “Grant numbers” effect of 27-Me on H$_{ax}$19 and H$_{ax}$21 chemical shift. These data further support our argument that the spectral of phomopsichalasin is inconsistent with its original assignment (Figure 11).

We hypothesized that phomopsichalasin and diaporthichalasin were produced in nature via a pair of spontaneous IMDA cycloadditions of a single polyene precursor 406, the methyl-bearing stereocenter at C18 of which would induce all nine new stereocenters in phomopsichalasin and diaporthichalasin. If true, this would require that phomopsichalasin and diaporthichalasin (401) be identical. We propose to synthesize the polyene 406 and study its spontaneous IMDA reactivity.

Schemes III-1 and III-2 illustrate transition states and intermediates likely be involved in the biosynthesis of phomopsichalasin and diaporthichalasin to produce structures 400 and 401 respectively. Polyene 406 could undergo two types of IMDA reaction: type A (between enone and diene moieties) and type B (between ene-lactam and diene moieties) (Schemes III-1, 2). An assumption used in this discussion is that all acyclic alkenes have an E-geometry. If phomopsichalasin indeed had structure 400 and spontaneous IMDA cycloadditions were operative in its biosynthesis, then such biosynthesis would involve an intermediate like 407 or 408 (Scheme III-1). The former would be produced via the IMDA B cycloaddition of the polyene 406. To convert into phomopsichalasin of structure 400, the intermediate 407 would have to undergo an IMDA A cycloaddition that
experienced severe 1,7-Me,Me diaxial interactions. The same unfavorable interactions would interfere with the IMDA A of the polyene 406 during formation of the octalin 408 (Scheme III-1). The unlikelyhood of such transformations is further supported by our observations on IMDA cycloadditions of aldehyde 308 in synthesis of the CJ-16,264 (see Chapter II, Schemes 15, 17, and 18).

**Scheme III-1. Analysis of the IMDA Cycloadditions in Biosynthesis of Phomopsichalasin (400)**

On the other hand, the IMDA cycloadditions operative in the biosynthesis leading to diaporthichalasin (401) are more likely. As shown in Scheme III-2, if polyene 406 would first undergo the IMDA A cycloaddition via a transition state with C18-Me in the equatorial position, it would result in formation of the trans-fused octalin 409. Incidentally, such an intermediate would have almost the same structure as another

124
natural product, oteromycin (402) (Scheme III-2). The produced compound 409 could then undergo IMDA B cycloadditions of four types. In two (406-1 and 409-1) with the diene approaches \textit{endo} to the C23 carbonyl moiety, and in the other two (409-2 and not-shown) the diene approaches \textit{endo} to C1-lactam moiety.

\textbf{Scheme III-2.} Analysis of the IMDA Cycloadditions in Biosynthesis of Diaporthichalasin (401)
The first 409-1 would result in formation of diaporthichalasin (401), and the latter in formation of 5,8-diepi-diaporthichalasin (411). Diaporthichalasin (401) could also be formed via an alternative sequence of IMDA cycloadditions, *i.e.* polyene 406 could first undergo the IMDA B cycloaddition to produce lactam 410 that in turn would undergo the IMDA A cycloaddition to produce 401 (Scheme III-2).

At this point, we cannot say with assurance if diaporthichalasin and phomopsichalasin have the same structure. The striking similarities of their $^1$H NMR spectroscopic data, although taken in different deuterated solvents, argue for that, but differences in their optical rotations and bioactivity data argue against. Alternatively, phomopsichalasin could possess one of the structures 401, 410, or 411. The beauty of our proposal is that for our proposed synthesis we do not need to know the correct structure of phomopsichalasin! We were very intrigued to study the Diels-Alder reactivity of the polyene 406, to explore which one of the compounds shown in Schemes III-1,2 would be formed upon double cycloaddition, and to learn more about spontaneous non-enzymatic Diels-Alder in nature. Thus, my next goal was to synthesize the polyene 406.

2. Retrosynthesis of Polyene 406

Since the polyene 406 has a doubly activated double bond that should be “revealed” only at the end of the synthesis, we planned that oxidation of the alcohol and F$^-$-mediated removal of R$^1$-R$^3$ silyl protecting groups in 413 to be the last steps in the preparation of 406 (Scheme III-3). The polyene 412 would be assembled by the previously developed Grignard coupling of alkenyl iodide 413 derived from maleimide and aldehyde 414. The latter could be synthesized by palladium-catalyzed coupling of the previously synthesized alkenyl iodide 312 and triene 415. Triene 415 could be synthesized from the readily available tiglic aldehyde (416) in about 5 steps.
3. Synthesis of Lactam 413

Encouraged by the precedent of Coleman et al., I approached the synthesis of the lactam 413 as shown in Scheme III-4. The route starts from commercially available maleimide (82) (~ 6 S/g), which alternatively could be synthesized in three steps by reaction of maleic anhydride (15) with urea, followed by heating with acetic anhydride, and retro-ene reaction in DMF over 12 h (417). The latter was N-protected with SEMCl (available in one step from trimethylsilylethanol, paraformaldehyde, and HCl(gas)) to give 418, which was iodinated to give the maleimide 419. Unfortunately, nucleophilic addition of Bn\textsubscript{x}InBr\textsubscript{3-x} (pre-made or generated in situ from BnBr and In powder) to 419 did not deliver any desired product 420. Even though Bn\textsubscript{x}InBr\textsubscript{3-x} underwent known addition to the diketone 421 with formation of alcohol 422, it appeared that Bn\textsubscript{x}InBr\textsubscript{3-x} reacts only with reactive electrophiles like 1,2-diketones.
Scheme III-4. The Initial Approach to the Synthesis of Lactam 413

To find an approach to the synthesis of iodide 420, I studied addition of various types of BnMet nucleophiles to maleimide derivatives. As illustrated in Scheme III-5, addition of BnMgCl to 418 resulted in formation of 1,2-addition product 423 in variable yields. The reaction was possibly complicated by 1,4-addition of the nucleophile and/or addition/Br⁻-elimination side-processes. CeCl₃-mediated addition of BnMgCl to N-benzylmaleimide (424) improved the ratio of 1,2- and 1,4-products, 425 and 426 only to 3 : 7. Addition of benzylmagnesium chloride to N-SEM-maleimide 427 gave the desired 1,2-adduct 428 in only 10% yield. This product was quite stable and could be protected as the corresponding TMS-ether 429. Addition of CeCl₃ to the reaction mixture did not improve the yield of alcohol 428.
All these results suggested that, to avoid complication from 1,4-addition of nucleophiles, the maleimide double bond should be protected. Diels-Alder reaction of maleimide (82) with furan was uneventful and at room temperature gave the corresponding product 430 as a 2:1 mixture of endo- and exo-adducts. Upon heating or recrystallization the mixture of such isomers converged into the single exo-product 430. Imide 430 could be protected into 431 under Mitsunobu conditions with 2,4-dimethoxybenzylalcohol (DMBOH) or by alkylation with DMBBr, available in one step from PBr3 and DMBOH. Benzyl magnesium chloride addition to imide 431 occurred uneventfully, producing the tertiary alcohol 432 in 80% yield as a single diastereomer. Upon treating 432 with TMSOTf (in an effort to protect it as the corresponding TMS-ether 433) I observed an unexpected retro-Diels-Alder reaction and concomitant formation of 437a. To the best of our knowledge, this is the first retro-Diels-Alder reaction that occurred at the low temperature and does not require a diene-scavenger or flash vacuum thermolysis at ~ 300 °C. I envision the retro-Diels-Alder process to occur by the mechanism shown in Scheme III-6. O-Silylation of the amide carbonyl group initiates the C-C bond cleavage in 434. Subsequent retro-Michael reaction of 435 produces 436, which is a direct precursor to the product 437a. The progress of the retro-Diels-Alder transformation was followed by 1H NMR spectroscopy, which confirmed formation of furan. However, when I attempted subsequent α-iodination of 437a with
I$_2$/pyridine in various solvents, I did not observe any formation of the desired product 438a, and, instead, TMS-ether deprotection of 437a was observed.

**Scheme III-6.** Silyl Triflate-Mediated Retro-Diels-Alder Transformation for the Synthesis of Lactams 413 (438)

Attempts to do the analogous retro-Diels-Alder transformation of 432 using TBSOTf, to make a more stable TBS-analog of 437a, resulted only in 60% conversion of 432 into 437b. Use of more forcing conditions (heating of the reaction mixture at 40 °C for ~ 5 days in the presence of >7 equiv of TBSOTf) did not improve the reaction outcome. When starting alcohol 432 was used as a mixture of its endo- and exo-isomers, I could observe by $^1$H NMR spectroscopy that the endo-isomer underwent retro-Diels-Alder reaction first, and the exo-isomer isomerized into the endo-isomer first and then underwent the retro-Diels-Alder transformation.

Since installation of the halogen in α-position in 437a was not successful, I next explored an analogous sequence on bromomaleimide 418 (Scheme III-7). The Diels-Alder reaction of the bromomaleimide 418 with furan occurred uneventfully, producing
an exo-adduct 439. However, reaction of BnMgCl with imide 439 resulted in formation of the undesired alcohol 440, a product of addition to a carbonyl group closest to bromide (probably because electronic factors override steric preferences in the Grignard addition).

The analogous trimethylsilyl triflate-mediated protection/retro-Diels-Alder transformation of 440 resulted in formation of a very complex mixture of products that did not converge into a single product even in the presence of an excess of TMSOTf. An attempt to make the N-DMB-analog of 418 resulted in formation of 443 instead. Alkylation of bromomaleimide (417) with DMBBr resulted in decomposition of the starting material.

**Scheme III-7. Silyl Triflate-Mediated Retro-Diels-Alder Transformation for the Synthesis of Lactam 413, Cont’d**

Since the direct modification of maleimide derivatives was not very productive so far, I explored an approach that would introduce the maleimide unsaturation last (Scheme III-8). Addition of benzyl magnesium chloride to N-DMB-succinimide 444,\(^{132}\) available in two steps from succinic anhydride (101), occurred smoothly at room temperature. TBS-protection of the alcohol 445 gave the corresponding TBS-ether 446 in 93% yield. Use of 2 equiv of LiHMDS, followed by sequential addition of PhSeBr and NIS electrophiles, was not very productive, but the installation of PhSeBr, oxidation, and elimination sequence worked well, producing lactam 437b in 80% yield.
I also explored the synthesis of a chiral lactam 438 from L-tartaric acid, as shown in Scheme III-9. Acetyl-protected tartaric anhydride 93a was opened with DMBNH₂, available by LiAlH₄ reduction of the corresponding oxime,¹³³ and reclosed into imide 447 upon treatment with AcCl. Benzyl magnesium chloride addition to 447 resulted only in a deprotection of one acetyl group and formation of alcohol 448, which was further confirmed by formation of the corresponding TBS-ether 449.

Instead, I removed both acetates in 447 and formed the corresponding bis-TMS-ether 450. Successful addition of Grignard reagents to species like 450 is known;¹³⁴ it should be possible to add BnMgCl to initiate the sequence shown, leading to 439b (cf. Scheme II-9). However, I did not pursue this chemistry.

4. Synthetic Efforts Toward Polyene Portion of 406, Aldehyde 414

In addition to synthetic efforts toward the heterocyclic portion, iodide 413 (438), I have also explored synthesis of the corresponding tetraenal 414 (cf. Scheme III-3). Since the synthesis of alkenyl iodide 312 has been developed as illustrated in Scheme II-4, I
focused on the synthesis of the corresponding triene coupling partner 415 (Scheme III-10). We first decided to assemble triene carbon skeleton by aldol reaction of 3-pentanone (451) with tiglic aldehyde (416). Formation of enolate of 451 with LiHMDS followed by addition of 416 gave hydroxyketone 452 as a 1:1 mixture of syn- and anti-diastereomers. Use of TiCl$_4$/i-Pr$_2$NEt conditions was more stereoselective, since it yielded the product 452 as a 10:1 mixture of syn- and anti-isomers.

**Scheme III-10. Approach to Triene 415**

Direct elimination of water from 452 under various conditions (TsOH/solvent, DBU, etc.) was not very productive. Treatment of alcohol 452 with mesyl chloride followed by DBU resulted only in formation of the rearranged product 453 and terminal alkene 454 in 33% and 16% yields. Only when alcohol 452 was converted into the corresponding acetate, the elimination of AcOH with DBU in THF (the elimination was slower in CDCl$_3$) occurred smoothly producing ketone 455 in 83% yield. Unfortunately, all the attempts to make triflate 456 under various conditions resulted only in formation of substantial amounts of by-products like 457 and 458.

Another approach to triene 461 is described in Scheme III-11. Horner-Wadsworth-Emmons homologation of tiglic aldehyde (416), followed by reduction of the formed ester with DIBALH, gave alcohol 459 in 90% yield. Oxidation of alcohol into
aldehyde 460 could be achieved under DMP, Swern, or MnO₂ conditions, the latter conditions were used for preparation of gram-quantities of the aldehyde 460. The Corey-Fuchs homologation/methylation of aldehyde 460 into internal alkyne 461 was not very straightforward, and had to be optimized. For example, at longer reaction times I observed formation of stereoisomers of 461. The alkyne 461 was volatile and could be purified only by quick chromatography in pentane. It had to be stored in a cold dark place and used within 72 h, since over time 461 underwent isomerization and decomposition.

Scheme III-11. Second Generation Approach to Triene 461

Interestingly, I observed that upon homologation of aldehyde 460 with CBr₄/PPh₃ at 0 °C - rt cyclopentenones 462-465 were formed instead of the desired dibromide. A possible mechanism of their formation is described in Scheme III-12. It involves intramolecular attack of the distant olefin on the activated carbonyl group in 466 followed by subsequent isomerization and intra- or inter-molecular hydride shift. Ketones 462, 463, and 464 were isolated upon work-up. However, upon standing and purification 464 isomerizes into the more stable α,β-ketone 465. Alternative mechanisms of 462-465 formation could include HBr catalysis, or formation of a carbene intermediate.
Scheme III-12. Formation of Cyclopentenones 462-465

Nevertheless, I was able to get my hands on sufficient amounts of 461 to explore a hydrostannylation approach to 415. Unfortunately, the formed stannane 415a was very non-polar and hard to separate from other tin by-products. Iodination of 415a resulted in formation of the iodide 470, which could be detected by ^1H NMR spectroscopy of the crude reaction mixture. However, subsequent purification by chromatography in the dark caused its complete decomposition (Scheme III-13).

Scheme III-13. Completion of the Synthesis of the Triene 415

Disappointed by these results, I turned to hydroboration approach to the triene 415. It is known that internal alkynes undergo efficient hydroboration only in the presence of a neat borane, and the presence of solvents like THF interferes with the addition to
alkyne. Hydroboration of 461 with freshly prepared and distilled neat catecholborane 471 was straightforward and gave the desired borane 415b as a single regioisomer, when reaction was performed at rt. Conducting hydroboration at higher temperatures caused substantial formation of 415b isomers, 472 (Scheme III-13).

Suzuki coupling of the borane 415b with the model alkenyl iodide 314 under standard conditions 138 gave the tetraene 473 in 58% yield. Next, I turned to studying the corresponding Suzuki coupling of borane 415b with actual iodides 312a-c (Scheme III-14). Utilizing the same conditions for the reaction of 415b with TBS-ether 312b was most productive and resulted in formation of 474b in 70% yield. The analogous coupling of TES-ether 474c and alcohol 474a was less productive and led to formation of tetraenes 474c and 474a in only 40% and 10% yields, respectively. Compound 474b could be effectively purified by chromatography. However, tetraenes 474c and, especially, 474a decomposed on silica gel and could be only partially purified using Florisil.

**Scheme III-14. Suzuki Coupling Approach for the Synthesis of Tetraenes like 414**

\[
\begin{align*}
\text{314} & \quad + \quad \text{MeMeMeMeC}_9\text{H}_{11}I \quad \rightarrow \quad \text{Pd(PPh}_3)_4, \text{KOH} \\
\text{415b} & \quad \text{THF/H}_2\text{O, 80 °C, 2 h} \quad \rightarrow \quad \text{473}
\end{align*}
\]

In an attempt to further functionalize tetraenes 474a-c, it appeared that tetraene intermediates were quite unstable to various types of chromatographic purifications. For example, as illustrated in Scheme III-15, deprotection of TBS-ether in 474b without purification gave crude alcohol 474a in good yield. The subsequent oxidation of 474a with DMP gave aldehyde 475 (other reagents caused complete starting material and/or product decomposition). Purification of 475 from Dess-Martin by-products was not very efficient, and only milligram quantities of aldehyde 475 could be recovered. Direct Swern
oxidation of TES-analog 474c led to complete decomposition of the tetraene moiety. Iodination of alcohol 474a was low yielding and complicated by substantial isomerization of tetraene.

**Scheme III-15.** Suzuki Coupling Approach to Tetraenes like 414, Cont’d

This collection of observations led us to conclude that the tetraene moiety is quite sensitive to all functional transformations and purifications and has to be installed only at the end of the synthesis.
C. Conclusion

Considering all the difficulties we encountered in synthesis of tetraenes 474-476, we revised the synthesis of polyene 406 as summarized in Scheme III-16. Oxidation of the secondary alcohol and F⁻-mediated deprotection of R¹-R³ silyl protecting groups in 412 would be the last steps of the synthesis. The polyene 412 would be assembled via a palladium-catalyzed coupling of iodide 477 with the diene 478. The substrate 477 could be accessed via a Grignard-mediated coupling of alkenyl iodide 413 with aldehyde 479. The latter could be synthesized from iodide 312 using common functional group transformations. The lactam 314 could be synthesized via a 1,2-addition of BnSiR₃ nucleophiles to a maleimide like 419.

Scheme III-16. Revised Retrosynthesis of the Polyene Precursor 406

Access to polyenes like 406 would allow us to investigate our biosynthetic hypothesis that phomopsichalasin (400) and diaporthichalasin (401) could be produced in nature via
a pair of spontaneous Diels-Alder cycloadditions. Furthermore, we would also be able to study, how the single, methyl-bearing stereocenter at C(18) in the polyene precursor 406 would affect the diastereoselectivity of IMDA cycloadditions (Scheme III-17). If successful, the increase in structural complexity accompanying these IMDA transformations would be of a nearly unprecedented level.

**Scheme III-17.** The IMDA Cycloaddition of the Polyene Precursor 406 in Biosynthesis of Phomopsichalasin (400) and Diaporthichalasin (401)
Summary

Overall in the course of this work, we have developed diastereoselective silylative Dieckmann-like cyclization of ester-imides 18 [Scheme IV-1, (i)], an efficient coupling of vinyl iodides like 107a with various aldehydes [Scheme IV-1, (ii)], and studied the IMDA cycloaddition of trienes 45 and 301 in synthesis of UCS1025A (1) and CJ-16,264 (300) correspondingly [Scheme IV-1, (iii)]. These efforts resulted in the second-generation synthesis of UCS1025A (1).

Scheme IV-1. Summary of the Research Efforts-1

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We have also explored the diastereoselective IMDA cycloaddition of aldehyde 256 into octalins 329a,b,e in the presence of MacMillan’s catalyst 24 [Scheme IV-2, (i)] and Reformatski-coupling in synthesis of various diastereomers of CJ-16,264 300b-f [Scheme IV-2, (ii)]. These studies led us to address some questions on structural assignment of the natural products CJ-16,264 (300) and CJ-16,367 (301). Finally, during our efforts toward total synthesis of phomopsichalasin (400) and diaporthichalasin (401) we explored Suzuki coupling of trieneborate 415b in synthesis of the tetraene moiety of the polyene 406 [Scheme IV-2, (iii)] and the retro-Diels-Alder transformation of malimides like 432 in the synthesis of the lactams like 437 (413) [Scheme IV-2, (iv)].

**Scheme IV-2. Summary of the Research Efforts-2**
Experimental Section

General Methods

Reactions requiring anhydrous conditions were performed under an atmosphere of nitrogen or argon in flame-dried glassware cooled under a stream of nitrogen. Dry 1,2-dichloroethane, diisopropylethylamine, and triethylamine were distilled from CaH$_2$; dried dimethylformamide and dimethylacetamide were distilled from MgSO$_4$ and stored over 3Å MS. Anhydrous THF, diethyl ether, toluene, and methylene chloride were dried by being passed through a column of activated alumina. Pyridine was distilled from KOH prior to use.

$n$BuLi, $^t$PrMgCl, MeMgBr, Me$_3$Al, EtAlCl$_2$, Me$_2$AlCl, DIBALH were titrated with 1,4-cyclooctadiene by No-D NMR spectroscopy.$^{51}$

MPLC refers to medium pressure liquid chromatography (25-60 psi) using hand-packed columns of E. Merck silica gel (18-32 µm, 60 Å), a Waters HPLC pump, and Waters R403 differential refractive index detector.

Analytical TLC was performed using TLC plastic sheets with F$_{254}$ indicator and detection was performed by UV-light or potassium permanganate or cerium ammonium nitrate/ethanol staining.

The $^1$H and $^{13}$C NMR spectra were acquired on a Varian VI-500 (500 MHz $^1$H, 125.7 MHz $^{13}$C), VI-300 (300 MHz $^1$H, 75.4 MHz $^{13}$C), or VXR-300 (300 MHz $^1$H, 75.4 MHz $^{13}$C) spectrometers. $^1$H NMR chemical shifts in CDCl$_3$ are referenced to Me$_4$Si (0.00 ppm), in DMSO to CD$_2$HS(O)CD$_3$ peak (2.50 ppm), in CD$_3$CN to CD$_2$HCN peak (1.94 ppm), D$_2$O to HOD (4.80 ppm), CD$_3$OD to CD$_2$HOD peak (3.31 ppm), C$_6$D$_6$ to C$_6$D$_5$H peak (7.16 ppm). $^{13}$C NMR chemical shifts in CDCl$_3$ are referenced to $^{13}$CDCl$_3$ peak (77.23 ppm). $^{13}$C NMR chemical shifts in C$_6$D$_6$ are referenced to $^{13}$C$_6$D$_6$ peak (128.39 ppm). The following format was used to report $^1$H NMR data: chemical shift in ppm [multiplicity, integral, coupling constant(s) in Hz, assignment]. The following abbreviations are used to describe multiplicities: s (singlet), d (doublet), t (triplet), q (quartet), pent (pentet), m (multiplet), nform (non-first order multiplet), and br (broad).
H NMR assignments are indicated by number (e.g., H-3a), or structural characteristic (e.g., \( \text{CH}_n\text{H}_m \)). The number refers to the corresponding atom belonging to the longest segment of numbered carbons in the CAS name. Complex structures are also numbered in their structures in order to simplify proton assignment numbering and naming.

Infrared (IR) spectra were recorded on a Midac Corporation Prospect 4000 FT-IR spectrometer (only the most intense and/or diagnostic peaks are reported) using a NaCl plate (thin film). Absorptions are reported in cm\(^{-1}\).

High-resolution mass spectra were recorded on a Bruker Biotof II (ESI-TOF) instrument using PEG or PPG as an internal calibrant. Tandem gas chromatography/low resolution mass spectroscopy (GC/MS) using electron impact ionization (EI) was performed at 70 eV on an Agilent Technologies 6890N series gas chromatograph equipped with an Agilent Technologies 5975 inert XL mass selective detector. Tandem liquid chromatography/low resolution mass spectroscopy (LC/MS) using multimode ESI-APCI ionization mode was performed on an Agilent Technologies 1100 series liquid chromatograph equipped with an Agilent Technologies G1956B LC/MSD SL mass selective detector.

Optical rotation data were recorded on a JASCO DIP-370 digital polarimeter using a 100 mm length cell.

Some compounds included in the experimental section are known in the literature.

**Experiments**

\[\text{49c} \quad \text{HF•pyr, pyr, rt, 1 h, 90\% or DBU (0.01 equiv) MeOH, rt, 36 h, 92\%} \]

\[\text{72} \quad \text{TESCI (4 equiv) imid. (5 equiv) DMF, rt, 36 h 86\%} \]

(±)-(1R,7aS)-rel-2,3,5,7a-Tetrahydro-5-oxo-7a-hydroxy-1H-pyrrolizine-1-carboxylic acid methyl ester (72). To HF•pyridine (70% HF, 30% pyridine, 2 drops) in a polyethylene tube MeCN (0.3 mL) and then pyridine (100 µL) were added. To this
mixture TMS-ether 49c (50 mg, 0.186 mmol) in MeCN (0.5 mL) was added. The resulting mixture was stirred for 4 h at room temperature. The reaction partitioned between saturated solution of NaHCO$_3$ (5.0 mL) and DCM (10 mL). The aqueous layer was extracted with DCM (3 x 5.0 mL). The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo. The resulting crude material was purified by filtration through a plug of silica gel (~ 1.0 cm tall) using EtOAc as the eluent, providing alcohol 72 (32 mg, 0.162 mmol, 90%) as a colorless oil.

$^1$H NMR (500 MHz, CDCl$_3$): δ 7.01 (d, 1H, $J = 5.7$ Hz, H-7), 5.98 (d, 1H, $J = 5.7$ Hz, H-7), 3.77 (dt, 1H, $J = 10.9, 8.7$ Hz, H-3), 3.62 (s, 3H, CO$_2$CH$_3$), 3.35 (ddd, 1H, $J = 11.6, 9.0, 3.2$ Hz, H-3), 3.22 (dd, 1H, $J = 7.1, 2.1$ Hz, H-1), 2.80 (br s, 1H, OH), 2.69 (dt, 1H, $J = 13.2, 8.7, 7.3$ Hz, H-2), and 2.52 (ddddd, 1H, $J = 13.6, 8.5, 3.2, 2.2$ Hz, H-2).

TLC: $R_f$ (1:1 hexanes/EtOAc) = 0.15.

(±)-(1R,7aS)-rel-2,3,5,7a-Tetrahydro-5-oxo-7a-[(triethylsilyl)oxy]-1H-pyrroolidine-1-carboxylic acid methyl ester (49d). Alcohol 72 (0.006 g, 0.03 mmol) was dissolved in DMF (1.0 mL), and imidazole (0.020 g, 0.29 mmol) was added followed by TESCl (0.020 mg, 0.13 mmol). The reaction mixture was stirred for ca. 29 h at room temperature and partitioned in DCM/water. The organic layer was separated, and the aqueous layer was extracted back with DCM (3 x 5.0 mL). All organic layers were combined, washed with brine (1 x 10 mL), dried over Na$_2$SO$_4$, and concentrated in vacuo. Chromatography on silica gel (MPLC) using 3:1 hexanes/EtOAc as the eluent yielded 8 mg (86% yield) of TES-ether 49d.

$^1$H NMR (500 MHz, CDCl$_3$): δ 6.96 (d, 1H, $J = 5.8$ Hz, H-7), 5.95 (d, 1H, $J = 5.8$ Hz, H-7), 3.77 (dt, 1H, $J = 10.8, 8.7$ Hz, H-3), 3.57 (s, 3H, CO$_2$CH$_3$), 3.29 (ddd, 1H, $J = 11.2, 9.2, 2.5$ Hz, H-3), 3.16 (dd, 1H, $J = 6.9, 1.3$ Hz, H-1), 2.62 (dt, 1H, $J = 13.2, 9.1, 6.9$ Hz, H-2), 2.48 (ddddd, 1H, $J = 13.0, 8.5, 2.4, 1.4$ Hz, H-2), 0.91 [t, 9H, $J = 7.9$ Hz, -Si(CH$_2$CH$_3$)$_3$], and 0.57 [q, 6H, $J = 8.9$ Hz, -Si(CH$_2$CH$_3$)$_3$].

$^{13}$C NMR (125 MHz, CDCl$_3$): δ 173.7, 171.6, 148.0, 128.0, 100.9, 53.2, 52.2, 42.5, 31.2, 7.0, and 5.7.
IR (thin film) 2956, 2878, 1739, 1721, 1437, 1358, 1321, 1198, 1162, 1092, 1076, 1008, 810, and 744.

HRMS (ESI) Calcd for C_{15}H_{25}NNaO_4Si\(^{+}\) (M•Na\(^{+}\)): 334.1445, found: 334.1449.

TLC: R\(_f\) (3:1 hexanes/EtOAc) = 0.20.

\(\pm\)-(1R,7aS)-rel-2,3,5,7a-Tetrahydro-6-iodo-5-oxo-7a-[(tert-butyldimethylsilyl)oxy]-1H-pyrrolizine-1-carboxylic acid tris(1-methylethyl)silyl ester (48a). Iodolactone 10a (7.493 g, 17.71 mmol) was dissolved in diethyl ether (150 mL), and triethyl amine (2.95 mL, 21.29 mmol) was added followed by TIPSCI (3.86 mL, 18.06 mmol). The reaction mixture was stirred in the dark for 40 h at room temperature and filtered to remove resulting amine salts. The filtrate was collected, concentrated in vacuo, and dried. Recrystallization of the crude from hexanes (50.0 mL) yielded 9.876 (96 % yield) of alkenyl iodide 48a as colorless crystals.

mp = 89-90 °C.

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 7.33 (s, 1H, H-7), 3.78 (dt, 1H, \(J = 10.9, 8.8\) Hz, H-3), 3.35 (ddd, 1H, \(J = 11.3, 8.6, 3.0\) Hz, H-3), 3.15 (dd, 1H, \(J = 6.4, 2.0\) Hz, H-1), 2.57 (ddt, 1H, \(J = 13.2, 8.8, 6.6\) Hz, H-2), 2.48 (dddd, 1H, \(J = 13.3, 8.5, 3.1, 2.1\) Hz, H-2), 1.26 [septet, 3H, \(J = 6.9\) Hz, -OSi(CH(CH\(_3\))\(_2\))], 1.05 [d, 3H, \(J = 7.3\) Hz, -OSi(CH(CH\(_3\))Me\(_3\))], 1.04 [d, 3H, \(J = 7.4\) Hz, -OSi(CH(CH\(_3\)))Me\(_3\)], 0.87 (s, 9H, -SiMe\(_2\)C(CH\(_3\))\(_3\)), 0.06 (s, 3H, -Si(CH\(_3\))\(_2\))\(_{1\text{Bu}}\)), and 0.02 (s, 3H, -Si(CH\(_3\))\(_2\))\(_{1\text{Bu}}\)).

\(^1\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 170.7, 169.3, 153.6, 101.6, 96.6, 54.6, 43.0, 31.3, 25.6, 18.0, 12.1, -3.5, and -3.9.

GC/MS (5029021): \(t_r = 15.82\) min; \(m/z\) 536 (20, M\(^+-\)i-Pr), 522 (100, M\(^+-\)Bu), 404 (30), and 289 (65).
IR (thin film) 2948, 2866, 1730, 1471, 1359, 1330, 1253, 1195, 1091, 1006, 838, and 780.

HRMS (ESI) Calcd for C_{23}H_{43}INO_4Si_2 (M•H^+): 580.1770, found: 580.1730.

TLC: R_f (20:1 hexanes/EtOAc) = 0.30.

(±)-(1R,7aS)-rel-2,3,5,7a-Tetrahydro-6-iodo-5-oxo-7a-[(tert-butyldimethylsilyloxy]-1H-pyrrolizine-1-carboxylic acid methyl ester (107a). Iodolactone 10a (0.120 g, 0.28 mmol) was dissolved in DMF (5.0 mL), and potassium carbonate (0.083 g, 0.60 mmol) was added followed by MeI (0.075 mL, 1.20 mmol). The reaction mixture was stirred for 12 h at room temperature, and partitioned in DCM/water, the organic layer was separated, and the aqueous layer was extracted back with DCM (2 x 10 mL). All organic layers were combined, washed with brine (1 x 10 mL), dried over Na_2SO_4, and concentrated in vacuo. Chromatography on silica gel (MPLC) using 4:1 hexanes/EtOAc as the eluent yielded 120 mg (97% yield) of alkenyl iodide 107a.

^1H NMR (500 MHz, CDCl_3): δ 7.31 (s, 1H, H-7), 3.81 (dt, 1H, J = 11.0, 8.8 Hz, H-3), 3.59 (s, 3H, CO_2CH_3), 3.35 (ddd, 1H, J = 11.3, 9.2, 3.7 Hz, H-3), 3.13 (dd, 1H, J = 6.8, 1.2 Hz, H-1), 2.59 (dtd, 1H, J = 13.2, 9.3, 6.8 Hz, H-2), 2.50 (dddd, 1H, J = 13.2, 8.6, 2.5, 1.3 Hz, H-2), 0.86 (s, 9H, -SiMe_2C(CH_3)_3), 0.06 (s, 3H, -Si(CH_3)_2Bu), and 0.02 (s, 3H, -Si(CH_3)_2Bu).

^13C NMR (125 MHz, CDCl_3): δ 171.1, 169.6, 153.2, 101.6, 95.7, 53.3, 52.4, 43.2, 30.9, 25.6, 18.0, -3.5, and -3.9.

IR (thin film) 2954, 2930, 2857, 1738, 1585, 1472, 1436, 1356, 1327, 1255, 1156, 1135, 1092, 1078, 837, and 780.

HRMS (ESI) Calcd for C_{15}H_{24}INNaO_4Si (M•Na^+): 460.0411, found: 460.0424.

TLC: R_f (4:1 hexanes/EtOAc) = 0.30.
(±)-(1R,7aS)-rel-2,3,5,7a-Tetrahydro-6-deutero-5-oxo-7a-[(tert-butyldimethylsilyl)-oxy]-1H-pyrrolizine-1-carboxylic acid methyl ester (D-49a). The solution of iodide 107a (0.080 g, 0.18 mmol) in THF (2.0 mL) was cooled to –20 °C, and i-PrMgCl (0.28 mL, 2.3 M, 0.64 mmol) was added dropwise. The reaction mixture was stirred for 1 h at –20 °C, warmed up to –10 °C over 20 min, cooled back to –20 °C, quenched with AcOD (1.0 mL), warmed up to room temperature, stirred for additional 15 min, and partitioned in Et2O/HCl aq (0.1 M). The organic layer was separated, and the aqueous layer was extracted back with ether (2x30 mL). All organic layers were combined, washed with a saturated solution of NaHCO3 (1 x 5.0 mL), brine (1 x 10 mL), dried over Na2SO4, and concentrated in vacuo, yielding 57 mg (93 % yield, 80% deuteration) of ester D-49a as a clear oil.

**1H NMR** (500 MHz, CDCl3): δ 6.95 (s, 1H, H-7), 3.79 (dt, 1H, J = 11.1, 8.6 Hz, H-3), 3.58 (s, 3H, CO2CH3), 3.28 (ddd, 1H, J = 11.0, 9.0, 2.4 Hz, H-3), 3.12 (dd, 1H, J = 6.8, 2.0 Hz, H-1), 2.61 (dt, 1H, J = 13.1, 9.1, 6.5 Hz, H-2), 2.50 (dddd, 1H, J = 13.2, 8.5, 2.3, 1.0 Hz, H-2), 0.87 (s, 9H, -SiMe2C(CH3)3), 0.08 (s, 3H, -Si(CH3)2'tBu), and 0.03 (s, 3H, -Si(CH3)2'tBu).

**13C NMR** (125 MHz, CDCl3): δ 173.5, 171.5, 147.9, 128.0, 101.0, 53.0, 52.1, 42.5, 31.2, 28.4, 18.0, -3.3, and -3.9.

**IR** (thin film) 2949, 2928, 2897, 2856, 1733, 1472, 1359, 1250, 1212, 1163, 1089, 838, 777, and 686.

**HRMS** (ESI) Calcd for C15H24DNNaO4Si (M•Na+): 335.1508, found: 335.1484.

**GC/MS** (5029021): tR = 11.05 min; m/z 312 (10, M+H), 297 (10, M+-Me), 255 (100, M+-tBu), 211 (20), 181 (40), and 149 (80).

**TLC**: Rf (3:1 hexanes/EtOAc) = 0.30.
(±)-(1R,7αS)-rel-2,3,5,7α-Tetrahydro-6-deutero-5-oxo-7α-[[(tert-butyldimethylsilyl)-oxy]-1H-pyrrolizine-1-carboxylic acid tris(1-methylethyl)silyl ester (D-19c). The solution of iodide 48a (0.100 g, 0.173 mmol) in THF (1.0 mL) was cooled to −50 °C, and i-PrMgCl (0.37 mL, 1.9 M, 0.69 mmol) was added dropwise. The reaction mixture was stirred for 30 min at −50 °C, quenched with D₂O (1.0 mL), warmed up to room temperature over 2 h, and partitioned in Et₂O/water. The organic layer was separated, and the aqueous layer was extracted back with ether (2 x 10 mL). All organic layers were combined, dried over Na₂SO₄, and concentrated in vacuo, yielding 156 mg (91 % yield, 95% deuteration) of ester D-19c as a colorless oil.

**1H NMR** (500 MHz, CDCl₃): δ 7.00 (s, 1H, H-7), 3.76 (dt, 1H, J = 10.9, 8.5 Hz, H-3), 3.28 (ddd, 1H, J = 11.4, 8.9, 2.8 Hz, H-3), 3.14 (dd, 1H, J = 6.8, 2.0 Hz, H-1), 2.58 (dt, 1H, J = 13.1, 8.9, 6.8 Hz, H-2), 2.47 (dddd, 1H, J = 13.1, 8.3, 2.9, 2.0 Hz, H-2), 1.25 (septet, 3H, J = 7.3 Hz, -CO₂SiCH₂Me), 1.03 (d, 18H, J = 7.4 Hz, -CO₂SiCH(CH₃)₂), 0.87 (s, 9H, -SiMe₂C(CH₃)₃), 0.07 (s, 3H, -Si(CH₃)₂Bu), and 0.02 (s, 3H, -Si(CH₃)₂Bu).

**13C NMR** (125 MHz, CDCl₃): δ 173.4, 171.1, 148.4, 126.5, 93.3, 54.8, 42.1, 31.6, 25.7, 18.9, 18.1, 18.0, 17.9, 12.5, 12.1, -3.3, and -3.8.

**IR** (thin film) 2950, 2930, 2866, 1721, 1463, 1359, 1329, 1281, 1251, 1194, 1161, 1091, 882, 859, 839, 779, and 675.

**HRMS** (ESI) Calcd for C₂₃H₄₂DNNaO₄Si₂⁺ (M+Na⁺): 477.2686, found: 477.2744.

**GC/MS** (5029021): tᵣ = 14.19 min; m/z 454 (10, M⁺), 439 (10, M⁺-Me), 411 (40, M⁺-i-Pr), 397 (100, M⁺-1Bu), and 289 (60).

**TLC:** Rᵣ (20:1 hexanes/EtOAc) = 0.30.
(±)-(1R,7aS)-rel-2,3,5,7a-Tetrahydro-6-iodo-5-oxo-7a-[tris(1-methylethyl)silyl]oxy]-1H-pyrrolizine-1-carboxylic acid benzyl ester (107b). Iodolactone 10b (0.200 g, 0.44 mmol) was dissolved in DMF (1.5 mL), and triethyl amine (0.080 mL, 0.57 mmol) was added followed by BnBr (0.058 mL, 0.48 mmol). The reaction mixture was stirred for 48 h at 40 °C, and partitioned in ether/water, the organic layer was separated, and the aqueous layer was extracted back with ether (2 x 10 mL). All organic layers were combined, washed with brine (1 x 10 mL), dried over Na₂SO₄, and concentrated in vacuo. Chromatography on silica gel (MPLC) using 12:1 hexanes/EtOAc as the eluent yielded 127 mg (52% yield) of alkenyl iodide 107b as a colorless oil.

**1H NMR** (500 MHz, CDCl₃): δ 7.41-7.31 (m, 6H, H-7, H-2', H-3', H-4', H-5', and H-6'), 5.08 (d, 1H, J = 12.0 Hz, H-8), 4.92 (d, 1H, J = 12.0 Hz, H-8), 3.83 (dt, 1H, J = 11.0, 8.6 Hz, H-3), 3.37 (ddd, 1H, J = 11.6, 9.1, 2.9 Hz, H-3), 3.20 (dd, 1H, J = 6.9, 1.6 Hz, H-1), 2.63 (dtd, 1H, J = 13.1, 9.0, 6.9 Hz, H-2), 2.50 (dddd, 1H, J = 13.2, 8.6, 2.9, 1.9 Hz, H-2), and 1.02-1.00 (m, 21H, -OSiC(CH₃)₂).

**13C NMR** (125 MHz, CDCl₃): δ 170.6, 169.3, 152.8, 135.2, 128.9, 128.8, 96.7, 53.7, 43.2, 31.0, 18.1, 18.0, and 12.9.

**IR** (thin film) 2946, 2867, 1738, 1585, 1382, 1347, 1258, 1158, 1094, 1068, 882, 721, and 676.

**HRMS** (ESI) Calcd for C₂₄H₃₄INaO₄Si⁺ (M•Na⁺): 578.1194, found: 578.1218.

**GC/MS** (5029021H): tᵣ = 17.89 min; m/z 512 (40, M⁺-i-Pr), 468 (10), and 91 (100, Bn⁺).

**TLC**: Rᵣ (9:1 hexanes/EtOAc) = 0.30.
(±)-(1R,7aS)-rel-2,3,5,7a-Tetrahydro-6-iodo-5-oxo-7a-[tris(1-methylethyl)silyl]oxy]-1H-pyrrolizine-1-carboxylic acid di(tert-butyl)methylsilyl ester (48c). Iodolactone 10b (0.200 g, 0.44 mmol) was dissolved in ethyl ether (5.0 mL), and triethyl amine (0.070 mL, 0.49 mmol) was added followed by freshly prepared Bu₂MeSiOTf (0.142 g, 0.46 mmol). The reaction mixture was stirred for 4 h at ambient temperature, and partitioned in ether/water, the organic layer was separated, and the aqueous layer was extracted back with ether (2 x 10 mL). All organic layers were combined, washed with brine (1 x 10 mL), dried over Na₂SO₄, and concentrated in vacuo. Chromatography on silica gel (MPLC) using 40:1 hexanes/EtOAc as the eluent yielded 165 mg (60% yield) of alkenyl iodide 48c as white solid.

mp = 93-95 °C

¹H NMR (500 MHz, CDCl₃): δ 7.36 (s, 1H, H-7), 3.82 (dt, 1H, J = 11.0, 8.6 Hz, H-3), 3.38 (ddd, 1H, J = 11.7, 9.1, 2.9 Hz, H-3), 3.18 (dd, 1H, J = 6.9, 1.8 Hz, H-1), 2.62 (ddd, 1H, J = 13.1, 8.9, 6.7 Hz, H-2), 2.50 (dddd, 1H, J = 13.3, 8.6, 2.9, 1.8 Hz, H-2), 1.03-1.01 (m, 21H, -OSiCH(CH₃)₂), 1.02 [s, 9H, -CO₂SiMe³BuC(CH₃)₃], 0.99 [s, 9H, -CO₂SiMe³BuC(CH₃)₃], and 0.24 (s, 3H, -CO₂Si³Bu₂CH₃).

¹³C NMR (125 MHz, CDCl₃): δ 170.4, 169.1, 152.8, 101.5, 97.4, 55.4, 43.0, 31.4, 27.8, 27.7, 20.5, 20.3, 18.1, 18.0, 13.0, and -7.2.

IR (thin film) 2962, 2862, 2864, 1723, 1580, 1470, 1359, 1267, 1214, 1195, 1143, 1011, 999, 880, 825, 720, and 678.

HRMS (ESI) Calcd for C₂₆H₄₈IKNOSi₅⁺ (M•K⁺): 660.1798, found: 660.1879.

GC/MS (5029021): tᵣ = 18.56 min; m/z 534 (10), 404 (100), 331 (50), and 274 (50).

TLC: Rₜ (40:1 hexanes/EtOAc) = 0.30.
(±)-(1R,7aS)-rel-2,3,5,7a-Tetrahydro-6-iodo-5-oxo-7a-[(tert-butylidimethylsilyl)oxy]-1H-pyrrolizine-1-carboxylic acid (106a). TIPS-ester 48a (1.000 g, 1.73 mmol) was dissolved in MeOH (15.0 mL), and potassium fluoride (0.105 g, 1.82 mmol) was added to the solution. The reaction mixture was stirred for 1 h at room temperature, concentrated *in vacuo*, and dried under vacuum, producing the corresponding potassium salt of acid 106a as a white solid. The salt was redissolved in DCM (10.0 mL) and treated with solid citric acid monohydrate (0.763 g, 3.63 mmol). The reaction mixture was stirred for 1 h at room temperature, partitioned between DCM/brine. The organic layer was separated, and the aqueous layer was extracted back with DCM (2 x 5.0 mL). All organic layers were combined, dried over Na$_2$SO$_4$, and concentrated *in vacuo*, yielding iodoacid 106a (0.730 g, 99 % yield) as a white solid.

$\text{mp} = 134-137 ^\circ \text{C}$;

$^1$H NMR (500 MHz, acetone-$d_6$): $\delta$ 7.64 (s, 1H, H-7), 3.69 (dt, 1H, $J = 10.7, 8.7$ Hz, H-3), 3.33 (ddd, 1H, $J = 11.3, 9.1, 3.4$ Hz, H-3), 3.13 (dd, 1H, $J = 6.8, 1.3$ Hz, H-1), 2.61 (dtd, 1H, $J = 13.2, 9.3, 6.8$ Hz, H-2), 2.50 (dddd, 1H, $J = 13.0, 8.4, 2.2, 1.5$ Hz, H-2), 0.90 (s, 9H, -SiMe$_2$C(CH$_3$)$_3$), 0.10 (s, 3H, -Si(CH$_3$)$_2$Bu), and 0.07 (s, 3H, -Si(CH$_3$)$_2$Bu).

$^{13}$C NMR (125 MHz, acetone-$d_6$): $\delta$ 172.3, 170.2, 154.7, 102.5, 96.8, 53.4, 43.8, 31.5, 26.0, 18.5, -3.4, and -3.8.

IR (thin film) 3100, 2955 2930, 2858, 1738, 1583, 1472, 1360, 1332, 1255, 1159, 1138, 1095, 1077, 836, and 780.

HRMS (ESI) Calcd for C$_{14}$H$_{22}$INaO$_4$Si$^+$ (M•Na$^+$): 446.0255, found: 446.0292.

TLC: $R_f$ (1:1 hexanes/EtOAc) = 0.20.
(±)-(1R,7aS)-rel-2,3,5,7a-Tetrahydro-6-trimethylsilyl-5-oxo-7a-[((tert-butyldimethylsilyl)-oxy]-1H-pyrrolizine-1-carboxylic acid tris(1-methylethyl)silyl ester (109) and (±)-(1R,7aS)-rel-2,3,5,7a-Tetrahydro-5-oxo-7a-[((tert-butyldimethylsilyl)-oxy]-1H-pyrrolizine-1-carboxylic acid tris(1-methylethyl)silyl ester (19c). The solution of iodide 48a (0.100 g, 0.173 mmol) in THF (1.0 mL) was cooled to −50 °C, and i-PrMgCl (0.37 mL, 1.9 M, 0.69 mmol) was added dropwise. The reaction mixture was stirred for 30 min at −50 °C, quenched with neat TMSCl (0.222 mL, 1.73 mmol), stirred for additional 1 h at −50 °C, warmed up to room temperature over 2 h, and partitioned in DCM/sat NaHCO3. The organic layer was separated, washed with brine, dried over Na2SO4, and concentrated in vacuo, yielding 14 mg (15% yield) of adduct 109 and 65 mg (83% yield) of ester 19c as colorless oils.

109: 1H NMR (500 MHz, CDCl3): δ 7.02 (s, 1H, H-7), 3.76 (dt, 1H, J = 10.9, 8.6 Hz, H-3), 3.28 (ddd, 1H, J = 11.2, 8.7, 3.0 Hz, H-3), 3.14 (dd, 1H, J = 6.7, 2.1 Hz, H-1), 2.58 (dtd, 1H, J = 13.1, 8.9, 6.7 Hz, H-2), 2.47 (ddd, 1H, J = 13.1, 8.2, 2.9, 1.9 Hz, H-2), 1.24 (septet, 3H, J = 6.8 Hz, -CO2SiCH(Me2)), 1.03 (d, 18H, J = 7.3 Hz, -CO2SiCH(CH3)2), 0.87 (s, 9H, -SiMe2C(CH3)3), 0.07 (s, 3H, -Si(CH3)2Bu), 0.03 (s, 9H, -Si(CH3)3).

GC/MS (5029021): tR = 14.45 min; m/z 525 (10, M+), 510 (20, M+ -Me), 482 (20, M+-i-Pr), 468 (100, M+ -t-Bu), and 350 (60).

TLC: Rf (40:1 hexanes/EtOAc) = 0.33

19c: 1H NMR (500 MHz, CDCl3): δ 7.00 (s, 1H, J = 5.7 Hz, H-7), 5.96 (d, 1H, J = 5.7 Hz, H-6), 3.76 (dt, 1H, J = 10.9, 8.6 Hz, H-3), 3.28 (ddd, 1H, J = 11.2, 8.7, 3.0 Hz, H-3), 3.14 (dd, 1H, J = 6.7, 2.1 Hz, H-1), 2.58 (dtd, 1H, J = 13.1, 8.9, 6.7 Hz, H-2), 2.47 (ddd, 1H, J = 13.1, 8.2, 2.9, 1.9 Hz, H-2), 1.24 (septet, 3H, J = 6.8 Hz, -CO2SiCH(Me2)), 1.03 (d,
18H, J = 7.3 Hz, -CO$_2$SiCH(CH$_3$)$_2$, 0.87 (s, 9H, -SiMe$_2$C(CH$_3$)$_3$), 0.07 (s, 3H, -Si(CH$_3$)$_2$Bu), and 0.03 (s, 3H, -Si(CH$_3$)$_2$Bu).

$^{13}$C NMR (125 MHz, CDCl$_3$): δ 173.5, 171.2, 148.5, 128.3, 100.9, 54.8, 42.1, 31.6, 25.6 18.1, 18.0, 12.1, 11.3, 3.1, and 3.8.

GC/MS (5029021H): $t_r$ = 14.19 min; m/z 453 (10, M$^+$), 438 (10, M$^+$-Me), 410 (40, M$^+$-i-Pr), 396 (100, M$^+$-t-Bu), and 289 (60).

IR (thin film): 2949, 2867, 1725, 1471, 1360, 1251, 1195, 1162, 1091, 1062, 882, 838, and 675.

HRMS (ESI) Calcd for C$_{23}$H$_{43}$NNaO$_4$Si$_2$ (M•Na$^+$): 476.2623, found: 476.2630.

TLC: $R_f$ (40:1 hexanes/EtOAc) = 0.30

(±)-(1R,7aS)-rel-2,3,5,7a-Tetrahydro-1-isobutyryl-5-oxo-7a-[(tert-butyldimethylsilyl)oxy]-1H-pyrrolizine (113). The solution of iodide 107a (0.089 g, 0.204 mmol) in THF (1.0 mL) was cooled to 0 °C, and i-PrMgCl (0.31 mL, 2.3 M, 0.71 mmol) was added dropwise over 10 min. The reaction mixture was stirred for 15 min at 0 °C, quenched with AcOD, warmed up to room temperature over 3 h, and partitioned in Et$_2$O/saturated aqueous solution of NaHCO$_3$. The organic layer was separated, washed with brine, dried over Na$_2$SO$_4$, and concentrated in vacuo. Chromatography on silica gel (MPLC) using 4:1 hexanes/EtOAc as the eluent yielded 20 mg (31% yield) of ketone 113 as a colorless oil and 34 mg (54% yield) of ester D-49a.

Ketone 113:

$^1$H NMR (500 MHz, CDCl$_3$): δ 6.78 (d, 1H, J = 5.7 Hz, H-7), 5.99 (d, 1H, J = 5.7 Hz, H-6), 3.78 (dt, 1H, J = 10.9, 8.2 Hz, H-3), 3.42 (dd, 1H, J = 6.8, 2.6 Hz, H-1), 3.24 (ddd, 1H, J = 10.9, 8.6, 3.5 Hz, H-3), 2.63 (septet, 1H, J = 6.9 Hz, H-2'), 2.48 (ddt, 1H, J =
12.8, 8.4, 6.8 Hz, H-2), 2.26 (dddd, 1H, J = 12.7, 8.3, 3.4, 2.7 Hz, H-2), 1.09 (d, 3H, J = 7.0 Hz, C3'H3-CHMe), 1.02 (d, 3H, J = 6.8 Hz, C3'H3-CHMe), 0.88 (s, 9H, -SiMe2C(CH3)3), 0.08 (s, 3H, -Si(CH3)2tBu), and 0.01 (s, 3H, -Si(CH3)2tBu).

13C NMR (125 MHz, CDCl3): δ 212.6, 173.8, 147.2, 129.0, 100.7, 80.9, 56.9, 42.6, 42.4, 32.1, 25.7, 18.5, 18.0, 17.1, -3.3, and -3.8.

IR (thin film) 2957, 2930, 2857, 1720, 1360, 1331, 1251, 1161, 1115, 1088, and 832.

HRMS (ESI) Calcd for C17H29NNaO3Si+: 346.1809, found: 346.1719.

TLC: RF (4:1 hexanes/EtOAc) = 0.15.

(±)-(1R,7aS)-rel-2,3,5,7a-Tetrahydro-6-\{[(1'E,7'E,9'E)-1',7',9'-dodecatrien]-carbonyl\}-5-oxo-7a-\{(tert-butyldimethylsilyl)oxy\}-1H-pyrrolizine-1-carboxylic acid tris(1-methylethyl)silyl ester (50a) and (4E,10E,12E)-2-Methyl-4,10,12-tetradecatriene-3-one (114). The solution of alkenyl iodide 48a (100 mg, 0.16 mmol) was cooled to –50 °C, and i-PrMgCl (0.16 mL, 2.0 M, 0.32 mmol) was added dropwise over 10 min. The reaction mixture was stirred for 10 min, a solution of Weinreb amide 47 (76 mg, 0.32 mmol) in anhydrous THF (0.3 mL) was added in one portion. The reaction mixture was stirred for 30 min at –50 °C, warmed up to rt, stirred for additional 30 min, and quenched with sat. solution of NaHCO3 (1.0 mL), followed by DCM (20 mL). The layers were separated, and the aqueous layer was extracted with DCM (2 x 10 mL). The combined organic layers were washed with brine, dried over Na2SO4, and evaporated to give a yellow oil. Chromatography on silica gel (MPLC) using 50:1 hexanes/EtOAc as the eluent yielded 2.0 mg (2 %) of ketone 50a and 3.0 mg (5%) of ketone 114.
50a: ¹H NMR (500 MHz, CDCl₃): δ 7.66 (s, 1H, H-7), 7.09 (d, 1H, J = 14.6 Hz, H-3’), 7.07 (dt, 1H, J = 15, 5.6 Hz, H-1’), 6.04-5.95 (m, 2H, H-8’), 5.58 (dq, 1H, J = 13.3, 6.3 Hz, H-10’), 5.52 (dt, 1H, J = 13.5, 6.6 Hz, H-7’), 3.83 (dt, 1H, J = 11.0, 8.5 Hz, H-3), 3.36 (ddd, 1H, J = 11.5, 9.0, 2.7 Hz, H-3), 3.25 (ddd, 1H, J = 6.9, 1.7 Hz, H-1), 2.67 (dd, 1H, J = 12.8, 8.7, 6.8 Hz, H-2), 2.53 (dddd, 1H, J = 13.2, 8.5, 2.8, 1.9 Hz, H-2), 2.27 (dt, 2H, J = 7.4, 6.1 Hz 2H-3’), 2.07 (app q, 2H, J = 7.5 Hz, 2H-6’), 1.73 (d, 3H, J = 6.4 Hz, 2H-11’), 1.50 (m, 2H, 2H-4’), 1.41 (m, 2H, 2H-5’), 1.22 (septet, 3H, J = 7.7 Hz, -Si(CH(CH₃)₂)₃], 1.03-0.99 [m, 27H, -Si(CH(CH₃)₂)₃ and -SiMe₂C(CH₃)₃], 0.08 (s, 3H, -Si(CH₃)Me’Bu), and 0.01 (s, 3H, -Si(CH₃)Me’Bu).

HRMS (ESI) Calcd for C₃₅H₆₉NaO₅Si₂⁺ (M•Na⁺): 652.3824, found: 652.3833.

TLC: Rₚ (50:1 hexanes/EtOAc) = 0.15.

114: ¹H NMR (500 MHz, CDCl₃): δ 6.87 (dt, 1H, J = 15.7, 6.9 Hz, H-5), 6.16 (dt, 1H, J = 15.7, H-4), 6.05-5.97 (m, 2H, H-11,H-12), 5.60 (dt, 1H, J = 14.0, 7.2 Hz, H-10), 5.53 (dq, 1H, J = 13.6, 6.9 Hz, H-13), 2.83 (septet, 1H, J = 6.9, H-2), 2.22 (dt, 2H, J = 7.6, 6.3 Hz 2H-6), 2.07 (app q, 2H, J = 6.8 Hz, 2H-9), 1.74 (d, 3H, J = 6.5 Hz, 2H-14), 1.50 (m, 2H, 2H-7), 1.42 (m, 2H, 2H-8), and 1.11 (d, 6H, J = 6.9 Hz, -CH(CH₃)₂).

GC/MS (5029021): tᵣ = 10.45 min; m/z 220 (10, M⁺), 177 (20, M⁺-i-Pr), and 149 (100, M⁺-i-Pr-C=O).

TLC: Rₚ (50:1 hexanes/EtOAc) = 0.30.

(±)-(1R,7aS)-rel-2,3,5,7a-Tetrahydro-5,6-dioxo-7a-[(tert-butyldimethylsilyl)oxy]-1H-pyrrolizine-1-carboxylic acid methyl ester (122). The solution of alkenyl iodide 107a (100 mg, 0.23 mmol) was cooled to −60 °C, and i-PrMgCl (0.15 mL, 2.3 M, 0.35 mmol) was added dropwise. The reaction mixture was stirred for 20 min at −50 °C, a solution of
Weinreb amide 47 (55 mg, 0.23 mmol) in anhydrous THF (2.0 mL) was added in one portion. The reaction mixture was stirred for 30 min at −50 °C, warmed up to −10 °C over 2 h, and quenched with 0.1 M solution of HCl (1.0 mL), followed by ether (10 mL). The layers were separated, and the aqueous layer was extracted back with ether (3 x 20 mL). All organic layers were combined, washed consequently with water and brine, dried over Na₂SO₄, and evaporated to give yellow oil. Chromatography on silica gel (MPLC), using 5:1 hexanes/EtOAc as the eluent, yielded 13 mg (17% yield) of ketone 122.

**1H NMR** (500 MHz, CDCl₃): δ 3.90 (dt, 1H, J = 12.3, 8.7 Hz, H-3), 3.66 (s, 3H, CO₂C₃H₇), 3.59 (ddd, 1H, J = 12.1, 9.8, 2.1 Hz, H-3), 3.24 (d, 1H, J = 7.5 Hz, H-1), 2.93 (d, 1H, J = 19.8 Hz, H-7), 2.77 (d, 1H, J = 19.8 Hz, H-7), 2.64 (dt, 1H, J = 13.4, 9.4, 7.7 Hz, H-2), 2.32 (ddd, 1H, J = 13.4, 8.5, 2.1 Hz, H-2), 0.87 (s, 9H, -SiMe₂(C(CH₃))₃), 0.10 (s, 3H, -Si(C(CH₃))Me'Bu), and 0.09 (s, 3H, -Si(C(CH₃))Me'Bu).

**13C NMR** (125 MHz, CDCl₃): δ 196.9, 172.1, 160.5, 92.4, 53.0, 52.4, 43.9, 42.3, 28.3, 25.3, 17.7, -3.12, and -3.8.

**LC/MS:** (Method: C₈ column, gradient 50-100%, methanol content, 22 min, MW 200-2000): tᵣ = 8.76 min. (M+NH₄⁺: 345).

**IR** (thin film) 2956, 2930, 2854, 1769, 1725, 1360, 1249, 1170, 1120, 1067, and 836.

**HRMS** (ESI) Calcd for C₁₅H₂₆NO₅Si⁺ (M+H⁺): 328.1575, found: 328.1605.

**TLC:** Rᵣ (4:1 hexanes/EtOAc) = 0.1.


(±)-(1R,7aS)-rel-2,3,5,7a-Tetrahydro-6-[(2'-methyl-1'-propen)carbonyl]-5-oxo-7a-[(tert-butyldimethylsilyl)oxy]-1H-pyrrolizine-1-carboxylic acid tris(1-methylethyl)silyl ester (126a). A solution of i-PrMgCl in Et₂O (2.0 M, 0.19 mL, 0.38 mmol) was added to a solution of vinyl iodide 48a (200 mg, 0.34 mmol) at −30 °C. The reaction mixture was stirred for 30 min and a solution of CuCN•2LiCl in THF (1.0 M, 0.41 mL,
0.42 mmol) was added at –30 °C. The reaction mixture for 30 min, warmed up to –15 °C, and acid chloride 125a (59 µL, 0.52 mmol) was added in one portion. After 2 h the reaction was quenched by the addition of brine and was extracted with Et2O (4 x 10 mL). The combined organic extracts were washed with saturated aqueous NaCl, dried (Na2SO4), and concentrated in vacuo to provide a colorless residue. Chromatography on silica gel (MPLC), using 40:1 hexanes/EtOAc as the eluent, yielded 11 mg (20% yield) of ketone 126a.

1H NMR (500 MHz, CDCl3): \( \delta \) 7.58 (s, 1H, H-1'), 6.98 (sept, 1H, \( J = 1.3 \) Hz, H-1'), 3.80 (dt, 1H, \( J = 11.0, 8.6 \) Hz, H-3), 3.31 (ddd, 1H, \( J = 11.3, 8.9, 2.7 \) Hz, H-3), 3.18 (dd, 1H, \( J = 13.0, 8.3, 6.8 \) Hz, H-2), 2.50 (ddddd, 1H, \( J = 13.0, 8.3, 6.3, 2.7 \) Hz, H-2'), 1.99 (d, 3H, \( J = 1.4 \) Hz, C2'-CH3), 1.23 [sept, 3H, \( J = 7.4 \) Hz, Si((CH)Me2)3], 1.01 [d, 9H, \( J = 7.5 \) Hz, Si((CH)Me(CH)3)3], 0.87 (s, 9H, -SiMe2(C(CH)3)3), 0.07 (s, 3H, -Si(CH3)Me3Bu), and 0.02 (s, 3H, -Si(CH3)Me3Bu).

GC/MS (5029021): \( t_r = 16.57 \) min; \( m/z \) 535 (10, M+), 520 (10, M+ -Me), 492 (90, M+ -i-Pr), and 478 (100, M+ -i-Bu).

TLC: Rf (40:1 hexanes/EtOAc) = 0.17.

(±)-(1R,7aS)-rel-2,3,5,7a-Tetrahydro-6-[2'-methyl-1'-oxo-2'-propen-1'-yl]-5-oxo-7a-[(tert-butyldimethylsilyl)oxy]-1H-pyrrolizine-1-carboxylic acid tris(1-methylethyl)silyl ester (126b) and (±)-(1R,7aS)-rel-2,3,5,7a-Tetrahydro-62'-methyl-1'-oxo-2'-propenoyloxy]-5-oxo-7a-[[(tert-butyldimethylsilyl)oxy]-1H-pyrrolizine-1-carboxylic acid methyl ester (127b). A solution of i-PrMgCl in Et2O (1.87 M, 0.11 mL, 0.21 mmol) was added to a solution of vinyl iodide 48a (100 mg, 0.04 mmol) at –60 °C. The reaction
was allowed to warm to −50 °C and a solution of CuCN•2LiCl in THF (1.0 M, 0.21 mL, 0.21 mmol) was added. The reaction was allowed to warm to −40 °C, and acid chloride 125b (25 µL, 0.36 mmol) was added in one portion. After 1 min, the reaction was quenched by the addition of pH 7.0 buffer at −70 °C and was extracted with Et₂O (4 x 20 mL). The combined organic extracts were washed with saturated aqueous NaCl, dried (Na₂SO₄), and concentrated in vacuo to provide a colorless residue. Chromatography on silica gel (MPLC) using 40:1 hexanes/EtOAc as the eluent yielded 37 mg (20% yield) of ketone 126b and 20 mg (10% yield) of ketone 127b as colorless oils.

126b:

**1H NMR** (500 MHz, CDCl₃): δ 7.12 (s, 1H, H-7), 6.03 (br s, 1H, H-3'), 3.78 (dt, 1H, J = 10.9, 8.8 Hz, H-3), 3.33 (ddd, 1H, J = 11.4, 9.3, 2.4 Hz, H-3), 3.18 (dd, 1H, J = 6.8, 1.3 Hz, H-1), 2.58 (dtt, 1H, J = 13.1, 9.0, 6.8 Hz, H-2), 2.46 (dddd, 1H, J = 13.2, 8.4, 2.2, 1.3 Hz, H-2), 1.99 (t, 3H, J = 1.3 Hz, C3'-CH₃), 1.23 [septet, 3H, J = 7.4 Hz, Si((CH)Me₂)], 1.01 [d, 9H, J = 7.5 Hz, Si((CH)Me(CH₃)]₃), 0.86 (s, 9H, -SiMe₂C(CH₃)₃), 0.07 (s, 3H, -Si(CH₃)Me'Bu), and 0.05 (s, 3H, -Si(CH₃)Me'Bu).

**GC/MS** (5029021): tᵣ = 15.83 min; m/z 521 (10, M⁺), 478 (50, M⁺-i-Pr), 464 (80, M⁺-t-Bu), 346 (40), 290 (20), and 207 (100).

**TLC**: Rₚ (20:1 hexanes/EtOAc) = 0.2.

127b:

**1H NMR** (500 MHz, CDCl₃): δ 6.31 (s, 1H, H-7), 6.00 (br s, 1H, H-3'), 5.99 (br s, 1H, H-3'), 3.76 (dt, 1H, J = 10.9, 8.8 Hz, H-3), 3.31 (ddd, 1H, J = 11.4, 9.3, 2.4 Hz, H-3), 3.16 (dd, 1H, J = 6.8, 1.3 Hz, H-1), 2.56 (dtt, 1H, J = 13.1, 9.0, 6.8 Hz, H-2), 2.45 (dddd, 1H, J = 13.2, 8.4, 2.2, 1.3 Hz, H-2), 1.97 (t, 3H, J = 1.3 Hz, C3'-CH₃), 1.23 [septet, 3H, J = 7.4 Hz, Si((CH)Me₂)], 1.01 [d, 9H, J = 7.5 Hz, Si((CH)Me(CH₃)]₃), 0.85 (s, 9H, -SiMe₂C(CH₃)₃), 0.08 (s, 3H, -Si(CH₃)Me'Bu), and 0.07 (s, 3H, -Si(CH₃)Me'Bu).
GC/MS (5029021): $t_r = 15.68$ min; $m/z$ 522 (10, $M^+\text{-Me}$), 494 (60, $M^+\text{-i-Pr}$), 480 (90, $M^+\text{-i-Bu}$), 436 (60), 194 (80), and 69 (100).

TLC: $R_f$ (20:1 hexanes/EtOAc) = 0.22.

(±)-(1R,7aS)-rel-2,3,5,7a-Tetrahydro-6-[(2'E)-1'-oxo-2'-buten-1'-yl]-5-oxo-7a-[(tert-butyldimethylsilyloxy]-1H-pyrrolizine-1-carboxylic acid methyl ester (126c) and (±)-(1R,7aS)-rel-2,3,5,7a-Tetrahydro-6-[(2'E)-2'-butenoyloxy]-5-oxo-7a-[(tert-butyldimethylsilyloxy]-1H-pyrrolizine-1-carboxylic acid methyl ester (127c).

A solution of $i$-PrMgCl in Et₂O (1.78 M, 0.24 mL, 0.43 mmol) was added to a solution of vinyl iodide 107a (100 mg, 0.22 mmol) at –60 °C. The reaction was allowed to warm to –50 °C and a solution of CuCN•2LiCl in THF (1.0 M, 0.48 mL, 0.48 mmol) was added. The reaction was allowed to warm to –40 °C, and acid chloride 125c (50 µL, 0.52 mmol) was added in one portion. After 1 min, the reaction was quenched by the addition of pH 7.0 buffer, organic layer was separated, and aqueous layer was extracted back with EtOAc (3 x 10 mL). The combined organic extracts were washed with saturated aqueous NaCl, dried (Na₂SO₄), and concentrated in vacuo to provide a colorless residue. Chromatography on silica gel (MPLC) using 4:1 hexanes/EtOAc as the eluent yielded 8 mg (10% yield) of ketone 126c and 31 mg (38% yield) of ester 127c as a colorless oil.

126c: $^1$H NMR (500 MHz, CDCl₃): δ 7.49 (s, 1H, H-7), 7.07 (dq, 1H, $J = 15.5, 6.8$ Hz, H-3'), 6.97 (dq, 1H, $J = 15.5, 1.5$ Hz, H-2'), 3.83 (dt, 1H, $J = 11.3, 9.1$ Hz, H-3), 3.56 (s, 3H, CO₂CH₃), 3.32 (ddd, 1H, $J = 11.0, 9.2, 2.4$ Hz, H-3), 3.17 (dd, 1H, $J = 6.8, 1.3$ Hz, H-1), 2.62 (ddd, 1H, $J = 13.2, 9.2, 6.9$ Hz, H-2), 2.52 (ddddd, 1H, $J = 13.1, 8.5, 2.4, 1.3$ Hz, H-2), 1.96 (dd, 3H, $J = 6.7, 1.4$ Hz, 3H-4'), 0.87 (s, 9H, -SiMe₂C(CH₃)₃), 0.08 (s, 3H, -Si(CH₃)Me'Bu), and 0.01 (s, 3H, -Si(CH₃)Me'Bu).
\(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 185.0, 171.3, 170.0, 151.6, 137.6, 129.3, 98.1, 53.1, 52.3, 42.5, 30.8, 25.6, 18.9, 18.0, -3.1, and -3.8.

IR (thin film): 2929, 2856, 1735, 1718, 1624, 1437, 1359, 1332, 1252, 1157, 1092, 837, and 780.

HRMS (ESI) Calcd for C\(_{19}\)H\(_{29}\)NNaO\(_5\)Si\(^+\) (M•Na\(^+\)): 402.1707, found: 402.1719.

TLC: R\(_f\) (6:1 hexanes/EtOAc) = 0.25.

\(127c\): \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 7.21 (dq, 1H, \(J = 15.6, 6.9\) Hz, H-3\'), 6.74 (s, 1H, H-7), 5.99 (dq, 1H, \(J = 15.6, 1.9\) Hz, H-2\'), 3.80 (dt, 1H, \(J = 10.7, 8.9\) Hz, H-3), 3.58 (s, 3H, CO\(_2\)C\(_6\)H\(_5\)), 3.33 (ddd, 1H, \(J = 11.2, 9.4, 2.3\) Hz, H-3), 3.17 (d, 1H, \(J = 6.6\) Hz, H-1), 2.60 (dtdd, 1H, \(J = 13.2, 9.2, 6.7\) Hz, H-2), 2.48 (dddd, 1H, \(J = 13.0, 8.6, 2.1, 1.3\) Hz, H-2), 1.95 (dd, 3H, \(J = 6.9, 1.6\) Hz, 3H-4\'), 0.86 (s, 9H, \(-\text{SiMe}_2\)C(C\(_6\)H\(_5\))), 0.08 (s, 3H, \(-\text{Si(CH}_3\))Me\(_t\)Bu), and 0.07 (s, 3H, \(-\text{Si(CH}_3\))Me\(_t\)Bu).

\(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 171.6, 167.8, 162.7, 149.3, 142.3, 125.8, 121.1, 97.0, 53.4, 52.2, 42.5, 30.7, 25.7, 18.5, 18.0, -3.2, and -3.9.

IR (thin film): 2954, 2857, 1744, 1731, 1635, 1438, 1363, 1283, 1251, 1156, 1098, 1046, 839, and 781.

HRMS (ESI) Calcd for C\(_{19}\)H\(_{29}\)NNaO\(_6\)Si\(^+\) (M•Na\(^+\)): 418.1656, found: 418.1657.

GC/MS (5029021): \(t_r = 13.08\) min; \(m/z\) 395 (10, M\(^+\)), 338 (30, M\(^+\) - \(t\)-Bu), 270 (30), and 143 (100).

TLC: R\(_f\) (4:1 hexanes/EtOAc) = 0.20.

\((\pm)-(1R,7aS)\)-rel-2,3,5,7a-Tetrahydro-6-(1'-oxo-2'-chloroeth-1'-yl)-5-oxo-7a-[((tert-butylidimethylsilyl)oxy]-1H-pyrrolizine-1-carboxylic acid tris(1-methylethyl)-silyl ester (126e). A solution of \(i\)-PrMgCl in Et\(_2\)O (1.87 M, 0.28 mL, 0.52 mmol) was added to a solution of vinyl iodide 48a (100 mg, 0.17 mmol) at \(-60\) °C. The reaction was
allowed to warm to –40 °C and a solution of CuCN•2LiCl in THF (1.0 M, 0.50 mL, 0.52 mmol) was added. The reaction was allowed to warm to –40 °C, and acid chloride 125e (58 µL, 0.73 mmol) was added in one portion. After 1 min, the reaction was quenched by the addition of pH 7.0 buffer, organic layer was separated, and aqueous layer was extracted back with Et₂O (4 x 10 mL). The combined organic extracts were washed with saturated aqueous NaCl, dried (Na₂SO₄), and concentrated in vacuo to provide a colorless residue. Chromatography on silica gel (MPLC) using 30:1 hexanes/EtOAc as the eluent yielded 9 mg (9% yield) of ketone 126e as a colorless oil and 40 mg (53% yield) of 19c as a colorless oil.

126e: `H NMR (500 MHz, CDCl₃): δ 7.75 (s, 1H, H-7), 4.76 (d, 1H, J = 16.8 Hz, 1H, H-2'), 4.61 (d, 1H, J = 16.8 Hz, 1H, H-2'), 3.78 (dt, 1H, J = 10.9, 8.8 Hz, H-3), 3.33 (dd, 1H, J = 11.2, 8.9, 2.6 Hz, H-3), 3.19 (dd, 1H, J = 6.8, 1.6 Hz, H-1), 2.62 (dtd, 1H, J = 13.3, 9.2, 6.9 Hz, H-2), 2.57 (dddd, 1H, J = 12.9, 8.4, 2.9, 2.1 Hz, H-2), 1.22 [septet, 3H, J = 7.5 Hz, Si((CH)Me₂)₃], 1.01 [d, 9H, J = 7.5 Hz, Si((CH)Me(CH₃))₃], 1.00 [d, 9H, J = 7.5 Hz, Si((CH)Me(CH₃))₃], 0.87 (s, 9H, -SiMe₂C(CH₃)₂), 0.08 (s, 3H, -Si(CH₃)MeBu), and 0.01 (s, 3H, -Si(CH₃)MeBu).

GC/MS (5029021): tᵣ = 15.51 min; m/z 495 (10, M⁺-Cl), 452 (100, M⁺-COCH₂Cl), 331 (30), and 278 (80).

¹TLC: Rₚ (30:1 hexanes/EtOAc) = 0.30.

(±)-(1R,7aS)-rel-2,3,5,7a-Tetrahydro-6-[(2′E)-1′-oxo-3′-iodopropen-1′-yl]-5-oxo-7a-[(tert-butyldimethylsilyl)oxy]-1H-pyrrolizine-1-carboxylic acid tris(1-methylethyl)silyl ester (138). A solution of i-PrMgCl in Et₂O (1.78 M, 0.24 mL, 0.43 mmol) was added to a solution of vinyl iodide 48a (100 mg, 0.17 mmol) at –60 °C. The reaction was
allowed to warm to –50 °C, and a solution of CuCN•2LiCl in THF (1.0 M, 0.52 mL, 0.52 mmol) was added to the reaction mixture. The reaction was allowed to warm to –40 °C, and acid chloride 135 (112 mg, 0.52 mmol) was added in one portion. After 1 min, the reaction was quenched by the addition of pH 7.0 buffer, organic layer was separated, and aqueous layer was extracted back with Et₂O (4 x 20 mL). The combined organic extracts were washed with saturated aqueous NaCl, dried (Na₂SO₄), and concentrated in vacuo to provide a colorless residue. Chromatography on silica gel (MPLC) using 40:1 hexanes/EtOAc as the eluent yielded 63 mg (60% yield) of ketone 138.

**1H NMR** (500 MHz, CDCl₃): δ 7.38 (d, 1H, J = 15.4 Hz, H-2'), 7.31 (d, 1H, J = 14.9 Hz, H-3'), 7.21 (s, 1H, H-7), 3.80 (dt, 1H, J = 11.1, 8.8 Hz, H-3), 3.34 (ddd, 1H, J = 11.2, 8.8, 2.7 Hz, H-3), 3.20 (dd, 1H, J = 6.6, 1.6 Hz-1), 2.62 (dt, 1H, J = 13.3, 9.2, 6.8 Hz, H-2), 2.51 (dddd, 1H, J = 13.0, 8.2, 2.5, 1.7 Hz, H-2), 1.22 [septet, 3H, J = 7.0 Hz, -OSi(CH(CH₃)₂)₃], 1.01 [d, 18H, J = 7.3 Hz, -OSi(CH(CH₃)₂)₃], 0.88 (s, 9H, -SiMe₂C(CH₃)₃), 0.07 (s, 3H, -Si(CH₃)₂'Bu), and 0.01 (s, 3H, -Si(CH₃)₂'Bu).

**13C NMR** (125 MHz, CDCl₃): δ 170.8, 170.1, 166.6, 150.4, 138.1, 132.7, 129.3, 98.4, 54.8, 42.4, 31.3, 25.6, 18.0, 17.9, 12.1, 12.0, -3.1, and -3.8.

**HRMS** (ESI) Calcd for C₂₆H₄₄INaO₅Si₂⁺ (M•Na⁺): 656.1695, found: 656.1694.

**TLC**: Rₚ (20:1 hexanes/EtOAc) = 0.2.

(±)-(1R,7aS)-rel-2,3,5,7a-Tetrahydro-6-[(2′E)-1'-oxo-3'-(ethoxy)propen-1'-yl]-5-oxo-7a-[(tert-butyldimethylsilyl)oxy]-1H-pyrrolizine-1-carboxylic acid tris(1-methyl-ethyl)-silyl ester (139a). When the crude product 138 synthesized as described above was dissolved in ether (2% EtOH) over > 1 h, and the solution was concentrated in vacuo
and purified by chromatography on silica gel (MPLC) using 40:1 hexanes/EtOAc as the eluent, 18 mg (18% yield) of ethoxy-adduct 139a was isolated.

**1H NMR** (500 MHz, CDCl₃): δ 7.25 (d, 1H, J = 16.0 Hz, H-2'), 7.03 (s, 1H, H-7), 7.02 (d, 1H, J = 16.0 Hz, H-3'), 4.25 (q, 2H, J = 7.1 Hz, -OCH₂CH₃), 3.81 (dt, 1H, J = 11.0, 8.8 Hz, H-3), 3.33 (ddd, 1H, J = 11.1, 9.1, 2.7 Hz, H-3), 3.18 (dd, 1H, J = 6.8, 1.6 H-1), 2.61 (dtd, 1H, J = 13.2, 9.1, 6.8 Hz, H-2), 2.50 (dddd, 1H, J = 12.9, 9.0, 3.0, 2.0 Hz, H-2), 1.32 (t, 3H, J = 7.1 Hz, -OCH₂CH₃), 1.23 [septet, 3H, J = 7.5 Hz, -OSi(CH(CH₃)₂)₃], 1.02 [d, 18H, J = 7.5 Hz, -OSi(CH(CH₃)₂)₃], 0.88 (s, 9H, -SiMe₂C(CH₃)₃), 0.07 (s, 3H, -Si(C(CH₃)₂)tBu), and 0.02 (s, 3H, -Si(C(CH₃)₂)tBu).

**13C NMR** (125 MHz, CDCl₃): δ 171.0, 170.9, 166.8, 146.4, 133.9, 132.9, 125.7, 110.3, 98.4, 60.9, 54.9, 42.3, 31.3, 25.7, 18.0, 17.93, 17.91, 14.4, 12.5, 12.1, -3.1, and -3.8.

**IR** (thin film): 2950, 2866, 1718, 1701, 1697, 1465, 1360, 1281, 1177, 1088, 836, and 667.

**HRMS** (ESI) Calcd for C₂₈H₄₉NNaO₆Si₂⁺ (M•Na⁺): 574.2991, found: 574.2973.

**TLC**: Rₐ (40:1 hexanes/EtOAc) = 0.2.

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(5E,7E)-1,5,7-Nonatriene (150) and (5E)-4-Vinyl-1,5-Heptadiene (151). A solution of acetate 116 (1.000 g, 7.14 mmol), allyl bromide (0.62 mL, 7.14 mmol), Pd(acac)₂ (87 mg, 0.29 mmol), Zn dust (1.010 g, 15.54 mmol), and PPh₃ (75 mg, 0.29 mmol) in THF (7.0 mL) was heated at 60 °C for 15 h. The reaction mixture was cooled room temperature, washed with saturated solution of NH₄Cl. The organic layer was separated, and the aqueous layer was extracted back with ether (2 x 40.0 mL). All organic layers were combined, washed with brine, dried over MgSO₄, filtered, and concentrated in vacuo. Chromatography on silica gel using hexanes as the eluent yielded 572 mg (65% yield) of triene 150 and 280 mg (32% yield) of product 151 as colorless oils.
150: $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 6.05-5.99 (m, 2H, H-6, H-7), 5.86-5.78 (m, 1H), 5.62-5.52 (m, 2H), 5.03-5.00 (m, 1H, $J = 17$ Hz, H-1), 4.97-4.95 (m, 1H, $J = 10$ Hz, H-1), 2.16-2.12 (m, 4H, H-3, H-4), and 1.73 (d, 3H, $J = 6.0$ Hz, H-9).

GC/MS (5027016): $t_r = 4.58$ min; $m/z$ 122 (30, M$^+$), 107 (10, M$^+$-Me), and 81 (100).

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 138.4, 131.2, 130.9, 127.3, 114.9, 33.8, 32.2, and 18.2.

IR (thin film): 3077, 2923, 2855, 1641, 1440, 1373, 988, and 911.

TLC: R$_f$ (Hexanes) = 0.55.

(±)-(1R,7aS)-rel-2,3,5,7a-Tetrahydro-6-{(2’E)-1’-oxo-3’-[tris(1-methylethyl)silyl]oxypropen-1’-yl}-5-oxo-7a-[(tert-butyldimethylsilyl)oxy]-1H-pyrrolizine-1-carboxylic acid tris(1-methylethyl)silyl ester (139b). Triene 150 (32 µL, 0.20 mmol) was dissolved in anhydrous THF (0.30 mL), and freshly prepared 9-BBN (27 mg, 0.11 mmol) was added in one portion. The reaction mixture was stirred for 2 h at room temperature. A portion of the solution (150 µL) was added to a solution of iodide 138 (30 mg, 0.05 mmol), grinded K$_3$PO$_4$ (15 mg, 0.08 mmol), and [Pd(dppf)Cl$_2$]•CHCl$_3$ (5 mg, 0.006 mmol) in dioxane (0.20 mL). The reaction mixture was stirred for 72 h at room temperature. The solids were removed by filtration, the filtrated was concentrated in vacuo. Chromatography on silica gel (MPLC) using 20:1 hexanes/EtOAc as the eluent yielded 4 mg (10% yield) of ketone 139b as a colorless oil.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.18 (d, 1H, $J = 15.9$ Hz, H-2’), 7.01 (s, 1H, H-7), 6.99 (d, 1H, $J = 15.9$ Hz, H-3’), 3.80 (dt, 1H, $J = 10.9$, 8.6 Hz, H-3’), 3.32 (ddd, 1H, $J = 11.2$, 8.9, 2.7 Hz, H-3’), 3.17 (dd, 1H, $J = 6.5$, 1.6 H-1’), 2.59 (ddt, 1H, $J = 13.0$, 8.9, 6.8 Hz, H-2’), 2.49 (ddddd, 1H, $J = 13.3$, 8.1, 3.1, 2.2 Hz, H-2’), 1.31 [septet, 3H, $J = 7.5$ Hz, -CHOSi(CH(CH$_3$)$_2$)$_3$], 1.20 [septet, 3H, $J = 7.1$ Hz, -CO$_2$Si(CH(CH$_3$)$_2$)$_3$], 1.10 [d, 18H, $J$
= 7.5 Hz, -OCHSi(CH(CH$_3$)$_2$)$_3$, 1.00 [d, 18H, $J = 7.5$ Hz, -CO$_2$Si(CH(CH$_3$)$_2$)$_3$], 0.87 (s, 9H, -SiMe$_2$C(CH$_3$)$_3$), 0.06 (s, 3H, -Si(CH$_3$)$_2$Bu), and 0.00 (s, 3H, -Si(CH$_3$)$_2$Bu).

TLC: R$_f$ (20:1 hexanes/EtOAc) = 0.30.

(±)-(1R,7aS)-rel-2,3,5,7a-Tetrahydro-6-[(2'E)-1'-oxo-(3'-cyano)propen-1'-yl]-5-oxo-7a-[(tert-butyldimethylsilyl)oxy]-1H-pyrrolizine-1-carboxylic acid tris(1-methylethyl)silyl ester (160) and (±)-(1R,7aS)-rel-2,3,5,7a-Tetrahydro-6-[(2'E)-1'-oxo-hepten-1'-yl]-5-oxo-7a-[(tert-butyldimethylsilyl)oxy]-1H-pyrrolizine-1-carboxylic acid tris(1-methylethyl)silyl ester (161). A solution of BuMgBr in Et$_2$O (0.58 M, 0.35 mL, 0.020 mmol) was added to a solution of iodide 138 (30 mg, 0.047 mmol) and CuCN•2LiCl (0.010 mmol) in ether (0.50 mL) at -50 °C over 10 min. The reaction mixture was stirred at -50 °C for 20 min, quenched by the addition of pH 7.0 buffer (2.0 mL), organic layer was separated, and aqueous layer was extracted back with DCM (3 x 7.0 mL). The combined organic extracts were washed with saturated aqueous NaCl, dried (Na$_2$SO$_4$), and concentrated in vacuo to provide a colorless residue. Chromatography on silica gel (MPLC) using 20:1 hexanes/EtOAc as the eluent yielded 5 mg (19% yield) of the desired product 161.

161: $^1$H NMR (500 MHz, CDCl$_3$): δ 7.28 (d, 1H, $J = 16.5$ Hz, H-2'), 7.08 (d, 1H, $J = 16.0$ Hz, H-3'), 7.06 (s, 1H, H-7), 3.79 (dt, 1H, $J = 11.1$, 8.6 Hz, H-3), 3.31 (ddd, 1H, $J = 11.2$, 9.0, 2.6 Hz, H-3), 3.16 (dd, 1H, $J = 6.7$, 1.4 Hz-1), 2.59 (m, 1H, H-2), 2.59 (t, 2H, $J = 6.9$ Hz, 2H-4'), 2.49 (ddd, 1H, $J = 12.8$, 8.4, 2.6, 1.6 Hz, H-2), 1.61 (pentet, 2H, $J = 7.5$ Hz, 2H-5'), 1.34 (sextet, 2H, $J = 7.4$ Hz, 2H-6'), 1.21 [septet, 3H, $J = 7.4$ Hz, -CO$_2$Si(CH(CH$_3$)$_2$)$_3$], 0.99 [d, 18H, $J = 7.5$ Hz, -CO$_2$Si(CH(CH$_3$)$_2$)$_3$], 0.91 (t, 3H, $J = 7.0$ Hz, 3H-7'), 0.86 (s, 9H, -SiMe$_2$C(CH$_3$)$_3$), 0.05 (s, 3H, -Si(CH$_3$)$_2$Bu), and 0.02 (s, 3H, -Si(CH$_3$)$_2$Bu).
HRMS (ESI) Calcd for C\textsubscript{30}H\textsubscript{53}NNaO\textsubscript{5}Si\textsubscript{2}\textsuperscript{+} (M\textsuperscript{•}Na\textsuperscript{+}): 586.3354, found: 586.3356.

GC/MS (5029021): t\textsubscript{r} = 18.96 min; m/z 5548 (10, M\textsuperscript{+}-Me), 520 (30, M\textsuperscript{+}-i-Pr), 506 (100, M\textsuperscript{+}-i-Bu), and 207 (70).

TLC: R\textsubscript{f} (20:1 hexanes/EtOAc) = 0.35.

(±)-(1R,7aS)-rel-2,3,5,7a-Tetrahydro-6-[(2'-butylhexan)carbonyl]-5-oxo-7a-[(tert-butyldimethylsilyl)oxy]-1H-pyrrolizine-1-carboxylic acid tris(1-methylethyl)silyl ester (162) and (±)-(1R,7aS)-rel-Hexahydro-7-butyl-5-oxo-7a-[(tert-butyldimethylsilyl)oxy]-1H-pyrrolizine-1-carboxylic acid tris(1-methylethyl)-silyl ester (163). A solution of BuMgBr in Et\textsubscript{2}O (0.62 M, 0.15 mL, 0.09 mmol) was added to a solution of iodide 138 (30 mg, 0.047 mmol) and CuBr\textbullet)LiBr (0.005 mmol) in THF (0.20 mL) at –40 °C. The reaction mixture was stirred at –40 °C for 2 min, quenched saturated solution of NH\textsubscript{4}Cl (1.0 mL), organic layer was separated, and aqueous layer was extracted back with ether (3 x 10.0 mL). The combined organic extracts were washed with saturated aqueous NaCl, dried (Na\textsubscript{2}SO\textsubscript{4}), and concentrated \textit{in vacuo} to provide a colorless residue. Chromatography on silica gel (MPLC) using 20:1 hexanes/EtOAc as the eluent yielded 3 mg (9% yield) of 162, 7 mg (10% yield) of product 163, and some other unidentifiable products.

162: \textbf{1H NMR} (500 MHz, CDCl\textsubscript{3}): \textit{δ} 7.56 (s, 1H, H-7), 3.78 (dt, 1H, J = 11.1, 8.6 Hz, H-3), 3.30 (ddd, 1H, J = 11.2, 8.9, 2.6 Hz, H-3), 3.17 (dd, 1H, J = 6.7, 1.5 H-1), 2.95 (dd, 1H, J = 17.1, 6.2 Hz, H-1'), 2.68 (dd, 1H, J = 17.1, 7.0 Hz, H-1'), 2.59 (dd, 1H, J = 13.3, 8.1, 6.8 Hz, H-2), 2.49 (ddt, 1H, J = 12.7, 7.8, 1.9 Hz, H-2), 2.00 (m, 1H, H-2'), 1.37-1.19 [m, 15H, 4H-3', 4H-4', 4H-5',-CO\textsubscript{2}Si(CH(CH\textsubscript{3})\textsubscript{2})\textsubscript{3}], 1.01 [d, 9H, J = 7.5 Hz, -CO\textsubscript{2}Si(CH(CH\textsubscript{3})Me)\textsubscript{3}], 1.00 [d, 9H, J = 7.5 Hz, -CO\textsubscript{2}Si(CH(CH\textsubscript{3})Me)\textsubscript{3}], 0.87 (t, 3H, J =
7.0 Hz, 3H-6'), 0.86 (t, 3H, 7.0 Hz, 3H-6'), 0.86 (s, 9H, -SiMe2C(CH3)3), 0.07 (s, 3H, -Si(CH3)2tBu), and 0.00 (s, 3H, -Si(CH3)2tBu).

**HRMS (ESI)** Calcd for C34H63NNaO5Si2+: 644.4137, found: 644.4168.

**TLC**: Rf (20:1 hexanes/EtOAc) = 0.1

**163** (1.4:1 ratio of diastereomers, data for a major diastereomer is reported):

**1H NMR** (500 MHz, CDCl3): δ 3.71 (dt, 1H, J = 10.9, 9.1 Hz, H-3), 3.24 (ddd, 1H, J = 11.0, 8.2, 2.6 Hz, H-3), 3.11 (td, 1H, J = 6.9, 2.8 Hz, H-1), 2.71 (dd, 1H, J = 17.1, 6.0 Hz, H-6), 2.53 (dtd, 1H, J = 13.0, 10.0, 7.1 Hz, H-2), 2.45 (dd, 1H, J = 17.1, 8.5 Hz, H-6), 2.37 (qd, 1H, J = 6.7, 2.8 Hz, H-7), 2.32 (ddt, 1H, J = 13.4, 7.8, 4.0 Hz, H-2), 1.52 (m, 2H, 2H-1'), 1.32-1.21 [m, 5H, 2H-2', -CO2Si(CH(CH3)2)3], 1.06 (m, 2H, 2H-3'), 1.06 [d, 9H, J = 7.5 Hz, -CO2Si(CH(CH3)Me)3], 1.05 [d, 9H, J = 7.4 Hz, -CO2Si(CH(CH3)Me)3], 0.89 (t, 3H, J = 7.5 Hz, 3H-4'), 0.86 (s, 9H, -SiMe2C(CH3)3), 0.04 (s, 3H, -Si(CH3)2tBu), and 0.01 (s, 3H, -Si(CH3)2tBu).

**TLC**: Rf (20:1 hexanes/EtOAc) = 0.15.

(±)-(1R,7aS)-rel-2,3,5,7a-Tetrahydro-6-{(2'E)-1'-oxo-3'-(butyl)oxy-propen-1'-yl}-5-oxo-7a-{[(tert-butyldimethylsilyl)oxy]-1H-pyrrolizine-1-carboxylic acid tris(1-methylethyl)silyl ester (139c). A solution of BuMgBr in Et2O (0.62 M, 0.15 mL, 0.09 mmol) was added to a solution CuBr•LiBr (0.11 mmol) in THF (0.40 mL) at −50 °C. The reaction mixture was warmed to −40 °C, and the solution of iodide 138 (30 mg, 0.047 mmol) in THF (0.2 mL) was added to it. The reaction mixture was stirred at −40 °C for 2 min, quenched with pH 7.0 buffer (1.0 mL), organic layer was separated, and aqueous layer was extracted back with ether (3 × 10.0 mL). The combined organic extracts were washed with saturated aqueous NaCl, dried (Na2SO4), and concentrated in vacuo to provide a colorless residue. Chromatography on silica gel (MPLC) using 20:1
hexanes/EtOAc as the eluent yielded 3 mg (3% yield) of 162, 8 mg (17% yield) of 161, and 4 mg (12% yield) of 139c.

139c: $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.21 (d, 1H, $J = 16.0$ Hz, H-2'), 7.00 (s, 1H, H-7), 7.00 (d, 1H, $J = 16.0$ Hz, H-3'), 4.17 (non-first order td, 2H, $J = 6.7, 2.0$ Hz, 2H-1''), 3.79 (dt, 1H, $J = 11.0, 8.7$ Hz, H-3), 3.31 (ddd, 1H, $J = 11.2, 9.2, 2.7$ Hz, H-3), 3.16 (dd, 1H, $J = 6.7, 1.4$ Hz, H-1), 2.58 (dtd, 1H, $J = 13.2, 9.1, 6.8$ Hz, H-2), 2.48 (dddd, 1H, $J = 12.9, 8.4, 2.8, 1.7$ Hz, H-2'), 1.65 (pentet, 2H, $J = 6.7$ Hz, 2H-2''), 1.41 (pentet, 2H, $J = 7.3$ Hz, 2H-3'), 1.21 [septet, 3H, $J = 7.5$ Hz, -OSi(CH(CH$_3$)$_2$)$_3$], 0.94 (t, 3H, $J = 7.4$, 3H-4''), 0.86 (s, 9H, -SiMe$_2$C(CH$_3$)$_3$), 0.05 (s, 3H, -Si(CH$_3$)$_2$Bu), and -0.02 (s, 3H, -Si(CH$_3$)$_2$Bu).

TLC: $R_f$ (20:1 hexanes/EtOAc) = 0.30.

(±)-(1R,7aS)-rel-2,3,5,7a-Tetrahydro-6-[1'-oxo-penten-1'-yl]-5-oxo-7a-[(tert-butyl-dimethylsilyl)oxy]-1H-pyrrolizine-1-carboxylic acid tris(1-methylethyl)silyl ester (164). A solution of EtZnI in THF (0.34 M, 0.28 mL, 0.095 mmol) was added to a solution of iodide 138 (40 mg, 0.063 mmol) and Pd(PPh$_3$)$_4$ (3 mg, 0.003 mmol) in THF (0.10 mL) at 0 °C. The reaction mixture was stirred for 30 min, quenched with brine, organic layer was separated, and aqueous layer was extracted back with DCM (3 x 20.0 mL). The combined organic extracts were washed with saturated aqueous NaCl, dried (Na$_2$SO$_4$), and concentrated in vacuo to provide a colorless residue. Chromatography on silica gel (MPLC) using 30:1 hexanes/EtOAc as the eluent yielded 4 mg (12% yield) of by-product 139a and 1 mg (3% yield) of 1,4-adduct 164.

164: $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.29 (d, 1H, $J = 16.0$ Hz, H-2'), 7.09 (d, 1H, $J = 16.0$ Hz, H-3'), 7.04 (s, 1H, H-7), 3.79 (dt, 1H, $J = 11.0, 8.6$ Hz, H-3), 3.31 (ddd, 1H, $J = 11.3, 9.1, 2.6$ Hz, H-3), 3.16 (dd, 1H, $J = 6.7, 1.4$ Hz, H-1), 2.63 (q, 2H, $J = 7.3$ Hz, 2H-4'),
2.58 (m, 1H, H-2), 2.48 (ddt, 1H, J = 13.0, 8.4, 2.3 Hz, H-2), 1.21 [septet, 3H, J = 7.5 Hz, -CO₂Si(CH(CH₃)₂)₃], 1.12 (t, 3H, J = 7.3 Hz, 3H-5'), 0.99 [d, 18H, J = 7.5 Hz, -CO₂Si(CH(CH₃)₂)₃], 0.86 (s, 9H, -SiMe₂C(CH₃)₃), 0.05 (s, 3H, -Si(C(H₃)₂)₂tBu), and -0.02 (s, 3H, -Si(CH₃)₂tBu).

**TLC:** Rₖ (30:1 hexanes/EtOAc) = 0.12.

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**1-Bromo-5,7-nonadiene (166).** Ethylethoxy-ether 165 (0.480 g, 2.26 mmol) was dissolved in MeOH (15.0 mL), and PPTS (0.056 g, 0.22 mmol) was added to the solution. The reaction mixture was stirred for 20 h at room temperature, quenched with solid NaHCO₃, concentrated in vacuo, and partitioned between DCM/brine. The organic layer was separated, and the aqueous layer was extracted back with DCM (3 x 25.0 mL). All organic layers were combined, dried over Na₂SO₄, and concentrated in vacuo. Chromatography on silica gel (MPLC) using 6:1 hexanes/EtOAc as the eluent yielded corresponding alcohol S-1⁴¹ (0.272 g, 86 % yield) as a colorless oil.

Alcohol S-1 (0.270 g, 1.93 mmol) and PPh₃ (0.582 g, 2.20 mmol) were dissolved in DCM (10.0 mL) and cooled to −78 °C, and NBS (0.442 g, 2.51 mmol) was added portionwise to the solution at −78 °C. The reaction mixture was stirred for 30 min at −78 °C, quenched with MeOH (0.5 mL), and partitioned between DCM/water. The organic layer was separated, and the aqueous layer was extracted back with DCM (3 x 15.0 mL). All organic layers were combined, washed with saturated solution of NaHCO₃ (1 x 10 mL), brine (1 x 10 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo. The resulting crude was redissolved in pentane (30 mL) and left in the freezer for 18 h. The formed solids were filtered off, the mother liquor was concentrated in vacuo to give the crude product. Chromatography on silica gel (MPLC) using pentane as the eluent yielded corresponding bromide 168 (0.235 g, 60 % yield) as a colorless oil.
$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 6.04-5.98 (m, 2H, H-7, H-6), 5.59 (dq, 1H, $J = 14.0$, 6.9 Hz, H-8), 5.52 (dt, 1H, $J = 14.4$, 7.1 Hz, H-5), 3.41 (t, 2H, $J = 6.8$ Hz, 2H-1), 2.09 (q, 2H, $J = 7.2$ Hz, 2H-4), 1.86 (2H, $J = 6.9$ Hz, 2H-2), 1.73 (d, 3H, $J = 6.5$ Hz, 3H-9), and 1.53 (2H, $J = 7.3$ Hz, 2H-3).

GC/MS (5029021): $t_r = 7.43$ min; $m/z$ 204 (50, M$^+$), 202 (50, M$^+$), 189 and 187 (10, M$^+$-Me), 123 (20, M$^+$-Br), 95 (50), 81 (100), and 68 (40).

TLC: $R_f$ (Pentane) = 0.25.

(±)-(2aR,7S,7aR,7bR)-(7Z)-Hexahydro-7-[1'-hydroxy-(1'-phenyl)methyl]-7b-[((tert-butylidimethylsilyl)oxy]-furo[2,3,4-gh]pyrrolizine-2,6-dione (169). A mixture of iodolactone 10a (86 mg, 0.203 mmol) and benzaldehyde (52 mg, 0.492 mmol) in toluene (1.8 mL) at –78 °C was treated with Et$_3$B (1M in THF, 0.70 mL, 0.70 mmol). After stirring for 1 h at –78 °C, H$_2$O (2 mL) was added and the cold bath was removed. When the reaction mixture had warmed to room temperature, the layers were separated and the aqueous layer was extracted with Et$_2$O (5 x 10 mL). The combined organic extracts were dried over Na$_2$SO$_4$ and concentrated in vacuo. The crude residue was purified by chromatography on silica gel (MPLC) using 4:1 hexanes/EtOAc as the eluent yielding the alcohol 169 as a white solid as a single diastereomer (60 mg, 75% yield).

mp = 139-142 °C;

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.50 (dd, 2H, $J = 7.2$, 1.5 Hz, H-3', H-7'), 7.39 (dd, 2H, $J = 7.8$, 7.0 Hz, H-4', H-6'), 7.34 (dd, 1H, $J = 7.4$, 7.2 Hz, H-5'), 5.50 (d, 1H, $J = 9.8$ Hz, H-7a), 4.72 (d, 1H, $J = 1.2$ Hz, C1'-OH), 4.28 (d, 1H, $J = 3.8$ Hz, H-1'), 3.85 (dt, 1H, $J = 11.8$, 8.0 Hz, H-4), 3.34 (dddd, 1H, $J = 12.2$, 9.1, 5.4, 0.9 Hz, H-3), 3.24 (dd, 1H, $J = 9.9$, 3.8 Hz, H-7), 3.01 (dd, 1H, $J = 6.9$, 3.7 Hz, H-2a), 2.64-2.59 (m, 2H, H-3), 0.83 (s, 9H, -SiMe$_2$C(CH$_3$)$_3$), 0.11 (s, 3H, -Si(CH$_3$)$_2$Bu), and 0.10 (s, 3H, -Si(CH$_3$)$_2$Bu).
\( ^{13}\text{C NMR} \) (125 MHz, CDCl\(_3\)): \( \delta \) 176.3, 174.8, 140.0, 128.9, 128.6, 126.8, 100.8, 81.9, 71.0, 54.0, 49.3, 42.3, 29.1, 25.5, 17.8, -3.2, and -3.6.

\( \text{IR (thin film)} \) 3462, 2954, 2931, 2858, 1731, 1701, 1379, 1333, 1303, 1253, 1210, 1163, 1143, 1115, 1067, 1014, 897, 839, 780, and 675.

\( \text{HRMS (ESI)} \) Calcd for C\(_{21}\)H\(_{29}\)NNaO\(_5\)Si\(^+\) (M•Na\(^+\)): 426.1707, found: 426.1744.

\( \text{TLC} \): \( R_f \) (4:1 hexanes/EtOAc) = 0.25.

\( \text{mp} = 119-122 \, ^{\circ}\text{C}; \)

\( ^1\text{H NMR} \) (500 MHz, CDCl\(_3\)): \( \delta \) 5.92 (dqd, 1H, \( J = 15.3, 6.5, 0.8 \, \text{Hz, H-3}' \)), 5.49 (ddq, 1H, \( J = 15.3, 7.4, 1.7 \, \text{Hz, H-2}' \)), 4.66 (d, 1H, \( J = 3.9 \, \text{Hz, H-7a} \)), 4.45 (dd, 1H, \( J = 9.7, 7.3, 0.9 \, \text{Hz, H-1}' \)), 3.80 (ddd, 1H, \( J = 12.0, 8.4, 7.5 \, \text{Hz, H-4} \)), 3.32 (dddd, 1H, \( J = 11.9, 8.4, 6.0, 0.9 \, \text{Hz, H-3} \)), 3.06 (dd, 1H, \( J = 7.5, 3.1 \, \text{Hz, H-2a} \)), 3.02 (dd, 1H, \( J = 9.7, 3.9 \, \text{Hz, H-7} \)), 2.66-2.55 (m, 2H, H-3'), 1.75 (dd, 3H, \( J = 6.6, 1.7 \, \text{Hz, H-4}' \)), 0.90 (s, 9H, SiMe\(_2\)C(CH\(_3\))\(_3\)), 0.16 (s, 3H, -Si(CH\(_3\))\(_2\)'Bu), and 0.14 (s, 3H, -Si(CH\(_3\))\(_2\)'Bu).

\( \text{(±)-(2aR,7S,7aR,7bR)-(7Z)-Hexahydro-7-[1'-hydroxy-2'-butenyl]-7b-[\text{tert-butyl-dimethylsilyl}oxy]-furo[2,3,4-gh]pyrrolizine-2,6-dione (170)} \). A mixture of iodolactone 10a (100 mg, 0.24 mmol) and crotonaldehyde (34 mg, 0.48 mmol) in toluene (2.0 mL) at \(-78 \, ^{\circ}\text{C} \) was treated with Et\(_3\)B (1M in THF, 0.65 mL, 0.65 mmol). After stirring for 1 h at \(-78 \, ^{\circ}\text{C} \), H\(_2\)O (2 mL) was added and the cold bath was removed. When the reaction mixture had warmed to room temperature, the layers were separated and the aqueous layer was extracted with Et\(_2\)O (5 x 10 mL). The combined organic extracts were dried over Na\(_2\)SO\(_4\) and concentrated \textit{in vacuo}. The crude residue was purified by chromatography on silica gel (MPLC) using 3:1 hexanes/EtOAc as the eluent yielding the alcohol 170 as a white solid as a single diastereomer (40 mg, 45% yield).

\( \text{mp} = 119-122 \, ^{\circ}\text{C}; \)
**13C NMR** (75 MHz, CDCl₃): δ 176.6, 174.9, 130.6, 128.8, 100.9, 82.1, 69.0, 52.0, 49.3, 42.4, 29.0, 25.5, 18.0, -3.2, and -3.6.

**IR** (thin film) 3483, 2956, 2933, 2901, 2859, 1792, 1707, 1470, 1376, 1333, 1305, 1253, 1211, 1143, 1166, 1089, 1063, 841, and 782.

**HRMS** (ESI) Calcd for C₁₈H₂₉NNaO₅Si⁺ (M•Na⁺): 390.1707, found: 390.1701.

**TLC:** R_f (3:1 hexanes/EtOAc) = 0.32.

\[ \text{DMP, 2,6-lutidine or TPAP, NMO} \]

(±)-(2aR,7R,7aR,7bR)-(7Z)-Hexahydro-7-[1'-hydroxy-2'-buten-1'-ylidene]-7b-[(tert-butyl-dimethylsilyl)oxy]-furo[2,3,4-gh]pyrrolizine-2,6-dione (171). A mixture of alcohol 170 (50 mg, 0.136 mmol) and 2,6-lutidine (16 µL, 0.138 mmol) in DCM (2.0 mL) at 0 °C was treated with DMP (65 mg, 0.130 mmol). After stirring for 1 h at 0 °C and 12 h at room temperature the reaction mixture was quenched with 10% aqueous solution of Na₂S₂O₃ and saturated solution of NaHCO₃, the layers were separated and the aqueous layer was extracted back with DCM (3 x 10 mL). The combined organic extracts were dried over Na₂SO₄ and concentrated in vacuo. The resulting crude was filtered through 3 cm-tall plug of silica gel using DCM (50 mL) as an eluent. The mother liquor was concentrated under reduced pressure, yielding the enol 171 (195 mg, 0.412 mmol, 92% yield, >95% pure by ¹H NMR) as yellow oil.

**¹H NMR** (500 MHz, CDCl₃): δ 11.60 (s, 1H, OH), 6.86 (dq, 1H, J = 15.3, 7.0 Hz, H-3'), 6.06 (dq, 1H, J = 15.3, 1.7 Hz, H-2'), 5.14 (s, 1H, H-7a), 4.03 (ddd, 1H, J = 12.0, 9.0, 6.5 Hz, H-4), 3.45 (dddd, 1H, J = 12.3, 9.2, 6.2 Hz, H-3), 3.22 (d, 1H, J = 8.5 Hz, H-2a), 2.67-2.50 (m, 2H, H-3), 1.95 (dd, 3H, J = 7.0, 1.5 Hz, H-4'), 0.87 (s, 9H, SiMe₂C(CH₃)₃), 0.14 (s, 3H, -Si(CH₃)₂Bu), and 0.10 (s, 3H, -Si(CH₃)₂Bu).

**HRMS** (ESI) Calcd for C₁₉H₂₇NNaO₅Si⁺ (M•Na⁺): 388.1551, found: 388.1539.

**TLC:** R_f (3:1 hexanes/EtOAc) = 0.50.

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172
(8E,10E)-3-(Ethylthio)-8,10-dodecadienal (172) and (2E,8E,10E)-1,1-Bis(ethylthio)-2,8,10-dodecatriene (173). A solution of aldehyde 23 (105 mg, 0.59 mmol) in neat ethylthiol (500 µL) was treated with NaH (2 mg). The reaction mixture was stirred at room temperature for 24 h, diluted with DCM (10.0 mL), filtered, and concentrated in vacuo. The crude residue was purified by chromatography on silica gel (MPLC) using 20:1 hexanes/EtOAc as the eluent yielding the aldehyde 172 (44 mg, 37% yield) and dithiane 173 (15 mg, 10% yield) as colorless oils.

172: \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 9.78 (t, 1H, \(J = 1.9\) Hz, H-1), 6.04-5.97 (m, 2H, H-9, H-10), 5.58 (dq, 1H, \(J = 13.4, 6.6\) Hz, H-11), 5.53 (dt, 1H, \(J = 13.6, 6.7\) Hz, H-8), 3.12 (pentet, 1H, \(J = 6.7\) Hz, H-3), 2.66 (dd, 1H, \(J = 6.2, 1.9\) Hz, H-2), 2.65 (dd, 1H, \(J = 7.3, 2.2\) Hz, H-2), 2.55 (q, 1H, \(J = 7.4\) Hz, SCH\(_2\)Me), 2.06 (q, 2H, \(J = 6.7\) Hz, H-7), 1.73 (d, 3H, \(J = 6.3\) Hz, H-12), 1.60 (m, 2H, 2H-4), 1.48-1.36 (m, 4H, 2H-5, 2H-6), and 1.25 (t, 3H, \(J = 7.4\) Hz, SCH\(_2\)CH\(_3\)).

HRMS (ESI) Calcd for C\(_{14}\)H\(_{24}\)KOS\(^+\) (M•K\(^+\)): 279.1179, found: 279.1163.

GC/MS (5029021): \(t_r = 10.75\) min; \(m/z\) 240 (10, M\(^+\)), 222 (20, M\(^+\)-Et), 211 (30, M\(^+\)-CHO), 193 (40), 161 (40), 119 (70), and 79 (100).

TLC: \(R_f\) (20:1 hexanes/EtOAc) = 0.20.

173: \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 6.04-5.94 (m, 2H, H-9, H-10), 5.62 (dt, 1H, \(J = 14.8, 7.2\) Hz, H-3), 5.58 (dq, 1H, \(J = 13.4, 6.6\) Hz, H-11), 5.54 (dt, 1H, \(J = 13.3, 6.9\) Hz, H-8), 5.42 (dd, 1H, \(J = 15.2, 8.7\) Hz, H-2), 5.42 (dd, 1H, \(J = 15.2, 8.7\) Hz, H-3), 4.32 (d, 1H, \(J = 8.7\) Hz, H-1), 2.71 (q, 4H, \(J = 7.4\) Hz, 2-SCH\(_2\)Me), 2.07-2.03 (m, 4H, 2H-4, 2H-7), 1.73 (d, 3H, \(J = 6.6\) Hz, H-12), 1.41-1.35 (m, 4H, 2H-5, 2H-6), and 1.25 (t, 6H, \(J = 7.5\) Hz, 2-SCH\(_2\)CH\(_3\)).

GC/MS (5029021): \(t_r = 12.13\) min; \(m/z\) 284 (5, M\(^+\)), 255 (30, M\(^+\)-Et), 223 (30, M\(^+\)-SEt), 193 (60), and 161 (100).
TLC: $R_f$ (20:1 hexanes/EtOAc) = 0.40.

(±)-(2aR,7S,7aR,7bR)-(7Z)-Hexahydro-7-hydroxy-7b-[(tert-butyl-dimethylsilyl)oxy]-furo[2,3,4-gh]pyrrolizine-2,6-dione (174) and (±)-(2aR,7S,7aR,7bR)-(7Z)-Hexahydro-7-[1'-hydroxy-3'-pheynlthio)-prop-1'-yl]-7b-[(tert-butyl-dimethylsilyl)oxy]-furo[2,3,4-gh]pyrrolizine-2,6-dione (175). A mixture of iodoactone 10a (70 mg, 0.165 mmol) and aldehyde 171 (52 µL, 0.330 mmol) in toluene (2.0 mL) at –78 °C was treated with Et₃B (1M in THF, 0.5 mL, 0.50 mmol). The reaction mixture was stirred for 2 h at –78 °C and for 48 h at –20 °C, and quenched with pH 7.0 buffer. The layers were separated and the aqueous layer was extracted back with EtOAc (3 x 15 mL). The combined organic extracts were dried over Na₂SO₄ and concentrated in vacuo. The crude residue was purified by chromatography on silica gel (MPLC) using 5:1 hexanes/EtOAc as the eluent yielding oxidized by-product 174 (5 mg, 10% yield) and product 175 (41 mg, 52% yield) as colorless oils.

174: ¹H NMR (500 MHz, CDCl₃): δ 4.63 (s, 1H, H-7a), 4.33 (s, 1H, H-7), 3.88 (ddd, 1H, $J = 12.0, 9.5, 5.3$ Hz, H-4), 3.37 (br s, 1H, OH), 3.34 (ddd, 1H, $J = 12.2, 9.5, 5.7$ Hz, H-4), 3.12 (dd, 1H, $J = 9.4, 2.5$ Hz, H-2a), 2.63 (dtd, 1H, $J = 13.9, 9.5, 5.3$ Hz, H-3), 2.53 (dddd, 1H, $J = 13.8, 9.4, 5.6, 2.5$ Hz, H-3), 1.35 (d, 3H, $J = 6.7$ Hz, H-3'), 0.90 (s, 9H, SiMe₂C(CH₃)₃), 0.21 (s, 3H, -Si(CH₃)₂'Bu), and 0.17 (s, 3H, -Si(CH₃)₂'Bu).

¹³C NMR (75 MHz, CDCl₃): δ 175.0, 173.1, 104.9, 83.2, 50.1, 42.7, 29.9, 25.6, 18.2, -3.3, and -3.5.

IR (thin film): 3503, 2954, 2927, 2854, 1772, 1716, 1377, 1340, 1249, 1145, 1120, 1045, 841, and 781.

HRMS (ESI) Calcd for C₁₄H₂₃NKO₅Si⁺ (M•K⁺): 352.0977, found: 352.0980.
TLC: R_f (3:1 hexanes/EtOAc) = 0.20.

175 (dr 1.9:1 of C1', C3' diastereomers):

major diastereomer: $^1$H NMR (500 MHz, CDCl$_3$): δ 7.47 (d, 2H, $J = 7.6$ Hz, H-2", H-6"), 7.30 (dd, 2H, $J = 7.8$, 7.6 Hz, H-3", H-5"), 7.23 (t, 1H, $J = 7.2$ Hz, H-4"), 4.69 (d, 1H, $J = 4.0$ Hz, H-7a), 4.42 (dddd 1H, $J = 9$, 9, 3, 2 Hz, H-1'), 4.25 (d, 1H, $J = 2$ Hz, O-H), 3.81 (dt, 1H, $J = 12$, 9.3 Hz, H-4), 3.68 (dqd 1H, $J = 10.5$, 6.7, 3.7 Hz, H-3'), 3.31 (m, 1H, H-4), 3.08 (dd, 1H, $J = 8.4$, 2.4 Hz, H-2a), 3.02 (dd, 1H, $J = 9.5$, 4.0 Hz, H-7), 2.64-2.57 (m, 2H, 2H-3), 1.98 (ddd 1H, $J = 13.6$, 9.9, 3.8 Hz, H-2'), 1.72-1.66 (m, 1H, H-2'), 1.34 (d, 3H, $J = 6.7$ Hz, H-4'), 0.87 (s, 9H, SiMe$_2$C(CH$_3$)$_3$), and 0.13 (s, 6H, -Si(CH$_3$)$_2$Bu).

minor diastereomer: $^1$H NMR (500 MHz, CDCl$_3$): δ 7.42 (d, 2H, $J = 7.7$ Hz, H-2", H-6"), 7.31 (dd, 2H, $J = 7.9$, 7.5 Hz, H-3", H-5"), 7.21 (dd, 1H, $J = 7.5$, 7.3 Hz, H-4"), 4.74 (d, 1H, $J = 4.0$ Hz, H-7a), 4.27 (d, 1H, $J = 2$ Hz, O-H), 4.13 (dddd 1H, $J = 9$, 9, 4, 2 Hz, H-1'), 3.82 (dt, 1H, $J = 11$, 9.5 Hz, H-4), 3.53 (dqd 1H, $J = 9.2$, 6.8, 4.5 Hz, H-3'), 3.31 (m, 1H, H-4), 3.08 (dd, 1H, $J = 7.6$, 1.2 Hz, H-2a), 2.96 (dd, 1H, $J = 9.4$, 4.0 Hz, H-7), 2.64-2.57 (m, 2H, 2H-3), 1.77-1.66 (m, 2H, 2H-2'), 1.35 (d, 3H, $J = 6.7$ Hz, H-4'), 0.88 (s, 9H, SiMe$_2$C(CH$_3$)$_3$), 0.15 (s, 3H, -Si(CH$_3$)$_2$Bu), and 0.14 (s, 3H, -Si(CH$_3$)$_2$Bu).

$^{13}$C NMR (75 MHz, CDCl$_3$): δ 176.7, 174.6, 135.3, 133.2, 133.0, 130.1, 129.0, 128.9, 128.7, 127.0, 126.4, 110.0, 109.9, 100.8, 81.7, 66.0, 52.1, 51.7, 49.2, 42.3, 41.2, 41.0, 37.7, 29.0, 25.4, 22.9, 21.9, 19.9, 17.7, -3.3, and -3.7.

IR (thin film): 3500, 2954, 2924, 1797, 1705, 1385, 1339, 1308, 1158, 1116, 841, and 781.

HRMS (ESI) Calcd for C$_{24}$H$_{35}$NNaO$_5$SSi$^+$ (M$\cdot$Na$^+$): 500.1897, found: 500.1921.

TLC: R_f (5:1 hexanes/EtOAc) = 0.15.
(±)-(2aR,7S,7aR,7bR)-(7Z)-Hexahydro-7-[3'-(phenylthio)-propano-1'-yl]-7b-[(tert-butyl-dimethylsilyloxy)-furo[2,3,4-gh]pyrrolizine-2,6-dione (176). A solution of alcohol 175 (10 mg, 0.021 mmol) in CD₂Cl₂ (1.0 mL) at 0 °C was treated with DMP (25 mg, 0.057 mmol). After stirring for 2 h at 0 °C and 24 h at room temperature the reaction mixture was filtered through 1.5 cm-tall plug of silica gel using 3:1 hexanes/EtOAc (50 mL) as an eluent. The crude product was purified by chromatography on silica gel (MPLC) using 2:1 hexanes/EtOAc as the eluent yielding 176 (4 mg, 40% yield) as colorless oil.

176 (dr 1.8:1 of C1', C2' diastereomers):

**major diastereomer:** ¹H NMR (500 MHz, CDCl₃): δ 7.43 (m, 2H, H-2'',H-6''), 7.30 (m, 3H, H-3'',H-5''), 4.94 (s, 1H, H-7a), 3.99 (ddd, 1H, J = 12.2, 9.3, 5.1 Hz, H-4), 3.71 (m 1H, H-3'), 3.32 (ddd, 1H, J = 12.1, 9.8, 5.8 Hz, H-4), 3.18 (m, 2H, H-2a, H-2'), 2.90 (dd, 1H, J = 18.4, 8.5 Hz, H-2'), 2.58 (dtd, 1H, J = 14.6, 9.7, 5.2 Hz, H-3), 2.44 (dtd, 1H, J = 13.9, 9.6, 6.0 Hz, H-3), 1.26 (d, 3H, J = 6.7 Hz, H-4'), 0.91 (s, 9H, SiMe₂C(CH₃)₃), 0.19 (s, 3H, -Si(CH₃)Me'Bu), and 0.16 (s, 3H, -Si(CH₃)Me'Bu).

**TLC:** Rₛ (5:1 hexanes/EtOAc) = 0.45.

**minor diastereomer:** ¹H NMR (500 MHz, CDCl₃): δ 7.42 (m, 2H, H-2'',H-6''), 7.30 (m, 3H, H-3'',H-5''), 5.00 (s, 1H, H-7a), 3.99 (ddd, 1H, J = 12.4, 8.5, 5.4 Hz, H-4), 3.67 (m 1H, H-3'), 3.32 (ddd, 1H, J = 12.1, 9.8, 5.8 Hz, H-4), 3.18 (m, 2H, H-2a, H-2'), 3.02 (dd, 1H, J = 8, 8 Hz, H-2'), 2.58 (dtd, 1H, J = 14.6, 9.7, 5.2 Hz, H-3), 2.45 (dtd, 1H, J = 13.4, 9.4, 5.9 Hz, H-3), 1.30 (d, 3H, J = 6.8 Hz, H-3'), 0.90 (s, 9H, SiMe₂C(CH₃)₃), 0.18 (s, 3H, -Si(CH₃)Me'Bu), and 0.13 (s, 3H, -Si(CH₃)Me'Bu).

**HRMS (ESI)** Calcd for C₂₄H₃₃NNaO₅S:S⁺: [M•Na⁺]: 498.1741, found: 498.1750.

**TLC:** Rₛ (5:1 hexanes/EtOAc) = 0.30.
(2R,7aS,7bR)-7b-{{Tris(1'-methylethyl)silyl]oxy}-hexahydro-furo[2,3,4-gh]-pyrrolizine-2,6-dione (20b) and (2R,7aS,7bR)-7b-{{(1'-Methylethenyl)bis(1''-methylethyl)silyl]oxy}-hexahydro-furo[2,3,4-gh]pyrrolizine-2,6-dione (177).

Experiment was conducted analogous to synthesis of alcohol 169, using iodolactone 10b (72 mg, 0.15 mmol) as a starting material. The crude was purified by chromatography on silica gel (MPLC) using 4:1 hexanes/EtOAc as the eluent yielding lactone 20b\(^{17}\) (23 mg, 45% yield) and lactone 177 (22 mg, 45% yield) as colorless oils.

177: (confirmed by COSY) \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 5.84 (dq, 1H, J = 2.8, 2.0 Hz, H-2'), 5.50 (dq, 1H, J = 2.9, 1.3 Hz, H-2'), 4.84 (d, 1H, J = 4.4 Hz, H-7a), 3.85 (ddd, 1H, J = 11.9, 9.4, 5.9 Hz, H-4), 3.28 (ddddd, 1H, J = 11.9, 9.5, 5.2 Hz, H-3), 3.17 (dd, 1H, J = 9.4, 2.5 Hz, H-2a), 3.10 (dd, 1H, J = 17.8, 4.5 Hz, H-7), 2.62 (d, 1H, J = 17.8 Hz, H-7), 2.62 (dtd, 1H, J = 13.8, 9.3, 5.9 Hz, H-3), 2.54 (ddddd, 1H, J = 14.2, 9.5, 5.3, 2.5 Hz, H-3), 1.88 (dd, 3H, J = 1.6, 1.3 Hz, CH\(_3\)C=CH\(_2\)), 1.16 (septet, 1H, J = 7.6 Hz, CHMe\(_2\)), 1.15 (septet, 1H, J = 7.2 Hz, CHMe\(_2\)), 1.07 (d, 3H, J = 7.7 Hz, CHCH\(_3\)Me), 1.07 (d, 3H, J = 7.4 Hz, CHCH\(_3\)Me), 1.06 (d, 3H, J = 7.2 Hz, CHCH\(_3\)Me), and 1.03 (d, 3H, J = 7.3 Hz, CHCH\(_3\)Me).

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 175.4, 173.9, 142.2, 130.4, 100.8, 82.3, 80.8, 50.0, 43.2, 39.0, 30.4, 23.6, 18.9, 17.9, 17.8, 17.7, 13.0, and 12.9.

IR (thin film): 2945, 2868, 1790, 1725, 1331, 1312, 1160, 1133, 1033, and 882.

HRMS (ESI) Calcd for C\(_{17}\)H\(_{27}\)NNaO\(_4\)S\(^+\) (M•Na\(^+\)): 360.1602, found: 360.1615.

TLC: R\(_f\) (4:1 hexanes/EtOAc) = 0.22.

\((\pm)-(1R,7aS)-rel-2,3,5,7a-Tetrahydro-6-(tributylstannyl)-5-oxo-7a-{[tert-butylidimethyl-silyloxy]-1H-pyrrolizine-1-carboxylic acid tris(1-methylethyl)silyl ester (180a). TIPS-ester 48a (0.200 g, 0.345 mmol) and Pd(PPh\(_3\))\(_2\)Cl\(_2\) (24 mg, 0.034
mmol) were dissolved in DMF (4.0 mL), and hexabutylditin (0.40 mL, 0.794 mmol) was added to the solution. The reaction mixture was stirred for 3 h at 120 °C and for 12 h at room temperature, partitioned between Et₂O/brine. The organic layer was separated, and the aqueous layer was extracted back with ether (3 x 10.0 mL). All organic layers were combined, dried over Na₂SO₄, filtered, and concentrated in vacuo. Chromatography on silica gel (MPLC) using 40:1 hexanes/EtOAc as the eluent yielded 57 mg (22% yield) of product 180a as a colorless oil.

¹H NMR (500 MHz, CDCl₃): δ 7.06 (t, 1H, J_H-Sn = 12.9 Hz, H-7), 3.75 (dt, 1H, J = 10.9, 7.8 Hz, H-3), 3.22 (ddd, 1H, J = 11.4, 9.0, 4.5 Hz, H-3), 3.12 (dd, 1H, J = 7.1, 3.7 Hz, H-1), 2.47 (dq, 1H, J = 12.9, 7.6 Hz, H-2), 2.34 (ddt, 1H, J = 11.9, 8.2, 4.6, 3.8 Hz, H-2), 1.55-1.49 [m, 8H, SnCH₂C(CH₃)₂], 1.39-1.25 [m, 16H, SnC(H₃)₂CH₂C(CH₃)₂Me + 2CHMe₂], 1.06 [d, 9H, J = 7.5 Hz, 3CH-(CH₃)₃], 1.05 [d, 9H, J = 7.5 Hz, 3CH-(CH₃)₃CH₃], 0.90 [t, 9H, J = 7.3 Hz, Sn(CH₂)₃CH₃], 0.87 (s, 9H, -SiMe₂C(CH₃)₃), 0.06 (s, 3H, -Si(CH₃)₂Bu), and 0.01 (s, 3H, -Si(CH₃)₂Bu).

TLC: Rₜ (40:1 hexanes/EtOAc) = 0.17.

(±)-(1R,7aS)-rel-2,3,5,7a-Tetrahydro-6-(trimethylstannyl)-5-oxo-7a-[(tert-butyldimethylsilyloxy]-1H-pyrrolizine-1-carboxylic acid tris(1-methylethyl)-silyl ester (180b). TIPS-ester 48a (100 mg, 0.173 mmol) and Pd(PPh₃)₄ (10 mg, 0.009 mmol) were dissolved in degassed benzene (1.0 mL), and hexamethylditin (72 µL, 0.35 mmol) was added to the solution. The reaction mixture was stirred for 12 h at 80 °C, diluted with EtOAc, and washed with 1M aqueous solution of KF (3 x 5.0 mL) and brine. The organic layer was separated, dried over Na₂SO₄, filtered, and concentrated in vacuo yielding 100 mg (94% yield) of the crude product 180b (>95% by H NMR spectroscopy) as a colorless oil.

¹H NMR (500 MHz, CDCl₃): δ 7.06 (t, 1H, J_H-Sn = 14.7 Hz, H-7), 3.73 (dt, 1H, J = 10.6, 8.2 Hz, H-3), 3.24 (ddd, 1H, J = 10.9, 8.6, 3.4 Hz, H-3), 3.11 (dd, 1H, J = 6.9, 2.7 Hz, H-1), 2.52 (dtd, 1H, J = 13.0, 8.5, 6.9 Hz, H-2), 2.42 (ddt, 1H, J = 13.1, 8.2, 3.2 Hz, H-2), 1.25 [septet, 3H, J = 7.6 Hz, Si(CH(CH₃)₂)₃], 1.04 [d, 9H, J = 7.5 Hz, Si(CH(CH₃)Me)₃], 1.05 [d, 9H, J = 7.5 Hz, Si(CH(CH₃)Me)₃],
1.03 [d, 9H, J = 7.5 Hz, Si(CH(CH₃)Me)₃], 0.87 (s, 9H, -SiMe₂C(CH₃)₃), 0.25 [t, 9H, J₉₋Sn = 29.1 Hz, C7-(SnCH₃)₃], 0.05 (s, 3H, -Si(C(CH₃)₂)₂tBu), and -0.02 (s, 3H, -Si(C(CH₃)₂)₂tBu).

**GC/MS** (5029021H): tᵣ = 14.98 min; m/z 675 (5, M⁺), 602 (60, M⁺-Me), 560 (30, M⁺-tBu), and 289 (100).

**TLC**: Rᵣ (30:1 hexanes/EtOAc) = 0.20.

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(±)-(1R,7aS)-rel-2,3,5,7a-Tetrahydro-6-(trimethylstannyl)-5-oxo-7a-[((tert-butyldimethyl-silyl)oxy]-1H-pyrrolizine-1-carboxylic acid methyl ester (182). The reaction was conducted analogously to synthesis 180b, using ester 107a (100 mg, 0.229 mmol) as a starting material. The crude was purified by chromatography on silica gel (MPLC) using 12:1 hexanes/EtOAc as the eluent producing 76 mg (70% yield) of product 182 as a colorless oil.

**¹H NMR** (500 MHz, CDCl₃): δ 7.00 (t, 1H, J₉₋Sn = 14.9 Hz, H-7), 3.75 (dt, 1H, J = 10.8, 8.7 Hz, H-3), 3.52 (s, 3H, CO₂CH₃), 3.24 (ddd, 1H, J = 11.3, 9.2, 2.5 Hz, H-3), 3.07 (dd, 1H, J = 6.8, 1.2 Hz, H-1), 2.57 (dt, 1H, J = 13.1, 9.1, 6.8 Hz, H-2), 2.48 (dddd, 1H, J = 13.0, 8.4, 2.5, 1.4 Hz, H-2), 0.86 (s, 9H, -SiMe₂C(CH₃)₃), 0.27 [t, 9H, J₉₋Sn = 28.5 Hz, C7-(SnCH₃)₃], 0.05 (s, 3H, -Si(CH₃)₂tBu), and -0.02 (s, 3H, -Si(CH₃)₂tBu).

**¹³C NMR** (125 MHz, CDCl₃): δ 177.6, 171.8, 156.9, 144.2, 102.9, 53.3, 51.9, 42.1, 31.2, 25.7, 18.0, -3.3, -3.9, and -9.6.

**IR** (thin film) 2955, 2930, 2900, 2858, 2941, 1702, 1472, 1436, 1355, 1315, 1252, 1194, 1165, 1135, 1080, 850, 839, and 779.


**GC/MS** (5029021): tᵣ = 12.13 min; m/z 475 (5, M⁺), 460 (80, M⁺-Me), 418 (100, M⁺-tBu), 344 (50), and 312 (70).

**TLC**: Rᵣ (10:1 hexanes/EtOAc) = 0.20.
(±)-(1R,7aS)-rel-2,3,5,7a-Tetrahydro-6-(1'-oxo-2'-propen-1'-yl)-5-oxo-7a-[(tert-butyldimethylsilyl)oxy]-1H-pyrrolizine-1-carboxylic acid tris(1-methylethyl)silyl ester (184a), (±)-(1R,7aS)-rel-2,3,5,7a-Tetrahydro-6-vinyl-5-oxo-7a-[(tert-butyldimethylsilyl)oxy]-1H-pyrrolizine-1-carboxylic acid tris(1-methylethyl)silyl ester (185a), and (±)-(1R,7aS)-rel-2,3,5,7a-Tetrahydro-6-[carbo-[tris(1-methylethyl)silyl]oxy]-5-oxo-7a-[(tert-butyldimethylsilyl)oxy]-1H-pyrrolizine-1-carboxylic acid tris(1-methylethyl)silyl ester (186). A solution of iodide 48a (40 mg, 0.069 mmol), stannane 183 (40 µL, 0.14 mmol), i-Pr₂NEt (30 µL, 0.173 mmol), and Pd(PPh₃)₂Cl₂ (4.8 mg, 0.007 mmol) in THF (2.0 mL) was stirred at 60 °C over CO (90 psi) atmosphere for 18 h. The reaction mixture was filtered through 1.5 cm tall plug of silica gel using DCM as the eluent. The filtrate was concentrated in vacuo and subjected to chromatography on silica gel (MPLC) using 30:1 hexanes/EtOAc as the eluent, which yielded 15 mg (45% yield) of by-product 185a, 5 mg (15% yield) of the product 184a, and 6 mg (15% yield) of by-product 186.

184a: ¹H NMR (500 MHz, CDCl₃): δ 7.65 (s, 1H, H-7), 7.31 (dd, 1H, J = 17.2, 10.5 Hz, H-2'), 6.45 (dd, 1H, J = 17.2, 1.6 Hz, H-3'), 5.85 (dd, 1H, J = 10.5, 1.6 Hz, H-3'), 3.80 (dt, 1H, J = 11.1, 8.6 Hz, H-3), 3.33 (dd, 1H, J = 11.4, 8.9, 2.7 Hz, H-3), 3.20 (dd, 1H, J = 6.8, 2.0 Hz, H-1), 2.62 (ddt, 1H, J = 13.1, 9.0, 6.8 Hz, H-2), 2.49 (dddd, 1H, J = 13.2, 8.2, 2.9, 2.3 Hz, H-2), 1.24 (septet, 3H, J = 7.4 Hz, -OSi(CH(CH₃)₂)₃), 1.102 [d, 9H, J = 7.5 Hz, Si(CH(CH₃)Me)₃], 0.98 [d, 9H, J = 7.5 Hz, Si(CH(CH₃)Me)₃], 0.87 (s, 9H, -SiMe₂C(CH₃)₃), 0.07 (s, 3H, -Si(CH₃)Me'Bu), and 0.01 (s, 3H, -Si(CH₃)Me'Bu).

GC/MS (5029021): tᵣ = 14.95 min; m/z 507 (10, M⁺), 464 (90, M⁺-i-Pr), 450 (100, M⁺-¹Bu), 332 (30), and 304 (60).

TLC: Rᵣ (30:1 hexanes/EtOAc) = 0.15.
**185a:** $^1\text{H NMR (500 MHz, CDCl}_3\): \delta 6.72 (1H, H-7), 6.32 (dd, 1H, J = 17.7, 11.0 Hz, H-1'), 6.21 (dd, 1H, J = 17.7, 1.9 Hz, H-2'), 5.44 (dd, 1H, J = 11.0, 2.0 Hz, H-2'), 3.79 (dt, 1H, J = 10.8, 8.7 Hz, H-3), 3.29 (ddd, 1H, J = 11.2, 9.0, 2.7 Hz, H-3), 3.15 (dd, 1H, J = 6.7, 1.6 Hz, H-1), 2.58 (dt, 1H, J = 13.1, 9.0, 6.9 Hz, H-2), 2.47 (ddt, 1H, J = 13.0, 8.3, 2.3 Hz, H-2), 1.23 [sept, 3H, J = 7.4 Hz, -OSi(CH(CH_3)_2)_3], 1.02 [d, 18H, J = 7.5 Hz, Si(CH(CH_3)_2)_3], 0.87 (s, 9H, -SiMe_2C(CH(CH_3)_3), 0.05 (s, 3H, -Si(CH_3)Me'Bu), and 0.00 (s, 3H, -Si(CH_3)Me'Bu).

**HRMS (ESI) Calcd for C_{25}H_{48}NNaO_4Si_2^+(M•Na^+): 502.2779, found: 502.2819.

**GC/MS (5029021): t_{r} = 14.23 min; m/z 479 (10, M^+), 464 (10, M^+⁻Me), 436 (30, M^+⁻i-Pr), 422 (100, M^+⁻Bu), 304 (50), and 289 (70).

**TLC:** R_{f} (30:1 hexanes/ETOAc) = 0.33.

**186:** $^1\text{H NMR (500 MHz, CDCl}_3\): \delta 7.62 (1H, H-7), 3.79 (dt, 1H, J = 10.9, 8.4 Hz, H-3), 3.31 (ddd, 1H, J = 11.2, 8.6, 3.2 Hz, H-3), 3.20 (dd, 1H, J = 6.6, 2.1 Hz, H-1), 2.58 (ddt, 1H, J = 13.1, 8.9, 6.7 Hz, H-2), 2.48 (ddt, 1H, J = 13.2, 8.2, 2.9 Hz, H-2), 1.36 [septet, 3H, J = 6.6 Hz, -OCO_2Si(CH(CH_3)_3)], 1.26 [septet, 3H, J = 7.0 Hz, -CHCO_2Si(CH(CH_3)_3)], 1.10 [d, 18H, J = 7.3 Hz, Si(CH(CH_3)_3)], 1.02 [d, 18H, J = 7.2 Hz, Si(CH(CH_3)_3)], 0.86 (s, 9H, -SiMe_2C(CH(CH_3)_3), 0.07 (s, 3H, -Si(CH_3)Me'Bu), and 0.01 (s, 3H, -Si(CH_3)Me'Bu).

**GC/MS (5029021H): t_{r} = 20.46 min; m/z 654 (10, M^+), 611 (80, M^+⁻i-Pr), 597 (100, M^+⁻Bu), 396 (30), and 278 (60).

**TLC:** R_{f} (30:1 hexanes/ETOAc) = 0.10.

(±)-(1R,7aS)-rel-2,3,5,7a-Tetrahydro-6-(1'-propenoyl)-5-oxo-7a-[(tert-butyldimethylsilyl)oxy]-1H-pyrrolizine-1-carboxylic acid methyl ester (184b), (±)-(1R,7aS)-rel-2,3,5,7a-Tetrahydro-6-vinyl-5-oxo-7a-[(tert-butyldimethylsilyl)oxy]-1H-
pyrrolizine-1-carboxylic acid methyl ester (185b). A solution of iodide 107a (40 mg, 0.092 mmol), stannane 183 (32 µL, 0.096 mmol), LiCl (12 mg, 0.27 mmol), and Pd(PPh₃)₂Cl₂ (3 mg, 0.004 mmol) in THF (1.0 mL) was stirred at room temperature over CO (90 psi) atmosphere for 18 h. The reaction mixture was filtered through 1.5 cm-tall plug of silica gel using DCM as an eluent. The filtrate was concentrated in vacuo. GC-MS of the crude detected products 184b and 185b in 1:3 ratio. Chromatography on silica gel (MPLC) using 6:1 hexanes/EtOAc as the eluent yielded 18 mg (60% yield) of 184b. The product 185b decomposes during silica gel chromatography.

184b:

**GC/MS (5029021H):** 
- tᵣ = 12.15 min; m/z 365 (10, M⁺), 350 (10, M⁺-Me), 308 (100).
- **TLC:** Rf (6:1 hexanes/EtOAc) = 0.20.

185b: ¹H NMR (500 MHz, CDCl₃): δ 6.67 (s, 1H, H-7), 6.35 (dd, 1H, J = 17.7, 11.0 Hz, H-1'), 6.25 (dd, 1H, J = 17.7, 2.0 Hz, H-2'), 5.45 (dd, 1H, J = 11.0, 2.0 Hz, H-2'), 3.80 (dt, 1H, J = 10.9, 8.7 Hz, H-3), 3.54 (s, 3H, CO₂CH₃), 3.29 (ddd, 1H, J = 11.3, 9.2, 2.4 Hz, H-3), 3.11 (dd, 1H, J = 6.8, 1.1 Hz, H-1), 2.60 (dtd, 1H, J = 13.1, 9.2, 6.9 Hz, H-2), 2.48 (dddd, 1H, J = 12.7, 8.4, 2.4, 1.4 Hz, H-2), 0.87 (s, 9H, -SiMe₂(CH₃)₃), 0.06 (s, 3H, -Si(CH₃)Me₂Bu), and -0.01 (s, 3H, -Si(CH₃)Me₂Bu).

**HRMS (ESI)** Calcd for C₁₇H₂₇NNaO₄Si⁺ (M•Na⁺): 360.1602, found: 360.1635.

**GC/MS (5029021):** 
- tᵣ = 11.23 min; m/z 337 (5, M⁺), 322 (5, M⁺-Me), 280 (100, M⁺-¹Bu), 206 (50), and 174 (90).
- **TLC:** Rf (6:1 hexanes/EtOAc) = 0.25.

1,6-Bis(octadecylthio)-2,4-hexadiyne (196a) and (-)-(1R,7aS)-rel-2,3,5,7a-tetrahydro-6-[3'-(octadecylthio)-1'-propyn-1'-yl]-5-oxo-7a-[t(tert-butyldimethyl-silyl)oxy]-1H-pyrrolizine-1-carboxylic acid tris(1-methylethyl)silyl ester (197a). A solution of
iodide 48a (100 mg, 0.173 mmol), alkyne 192a (84 mg, 0.259 mmol), CuI (2 mg, 0.010 mmol), and Pd(PPh₃)₄ (20 mg, 0.017 mmol) in freshly distilled i-Pr₂NH (1.0 mL) was stirred at room temperature for 18 h. The reaction mixture was filtered through 1.5 cm-tall plug of silica gel using EtOAc as the eluent. The filtrate was concentrated in vacuo and subjected to chromatography on silica gel (MPLC) using 20:1 hexanes/EtOAc as the eluent, which yielded 57 mg (68% yield) of dimer 196a and 6 mg (4% yield) of the product 197a as colorless oils.

**196a**: ¹H NMR (500 MHz, CDCl₃): δ 3.32 (s, 4H, 2H-1, 2H-6), 2.47 (t, 4H, J = 7.4 Hz, H-1'), 1.60 (pentet, 4H, J = 7.6 Hz, H-2'), 1.39 (pentet, 4H, J = 7.8 Hz, H-3'), 1.28-1.26 (m, 56H, H-4' through H-17'), and 0.88 (t, 6H, J = 7.1 Hz, H-18').

HRMS (ESI) Calcd for C₄₂H₇₈NaS₂⁺ (M•Na⁺): 669.5473, found: 669.5491.

TLC: Rₖ (20:1 hexanes/EtOAc) = 0.45.

**197a**: ¹H NMR (500 MHz, CDCl₃): δ 6.96 (s, 1H, H-7), 3.76 (dt, 1H, J = 10.7, 8.6 Hz, H-3), 3.44 (s, 2H, 2H-3'), 3.30 (ddd, 1H, J = 11.2, 8.9, 2.7 Hz, H-3), 3.14 (dd, 1H, J = 13.1, 9.0, 6.8 Hz, H-2), 2.68 (t, 2H, J = 7.4 Hz, H-1''), 2.56 (dtd, 1H, J = 13.1, 9.0, 6.8 Hz, H-2), 2.47 (dddd, 1H, J = 12.9, 8.3, 2.5, 1.6 Hz, H-2), 1.61 (pentet, 2H, J = 7.4 Hz, H-2''), 1.39 (pentet, 2H, J = 7.6 Hz, H-3''), 1.31-1.27 (m, 28H, H-4'' through H-17''), 1.26 [septet, 3H, J = 7.3 Hz, -OSi(CH(CH₃)₂)₃], 1.04 [d, 18H, J = 7.4 Hz, Si(CH(CH₃)₂)₃], 0.87 (s, 3H, -Si(CH₃)Me'Bu), 0.86 (s, 3H, -Si(CH₃)Me'Bu), and 0.04 (s, 3H, -Si(CH₃)Me'Bu).

HRMS (ESI) Calcd for C₄₄H₉₁NNaSSi₂⁺ (M•Na⁺): 798.5317, found: 798.5428.

TLC: Rₖ (20:1 hexanes/EtOAc) = 0.22.
1,6-Bis{(triphenyl)methyl}thio]-2,4-hexadiyne (196a) and 1,1’,1”-{[3-(4-methoxy)-phenyl-2-propyn-1-yl]thio}methylidyne]tris-benzene (197b). A solution of iodoanisol (198) (70 mg, 0.30 mmol), alkyne 192b (103 mg, 0.328 mmol), CuI (8 mg, 0.04 mmol), TEA (0.125 mL, 0.60 mmol), BHT (1 mg), and Pd(PPh₃)₂Cl₂ (21 mg, 0.029 mmol) in toluene (3.0 mL) was stirred at room temperature for 24 h. The reaction mixture was filtered through 1.5 cm-tall plug of silica gel using EtOAc as the eluent. The filtrate was concentrated in vacuo and subjected to chromatography on silica gel (MPLC) using 200:1 hexanes/EtOAc as the eluent, which yielded 60 mg (58% yield) of dimer 196b and 30 mg (18% yield) of the product 197b as colorless oils.

196b: ¹H NMR (500 MHz, CDCl₃): δ 7.39 (d, 12H, J = 7.8 Hz, 6H-3’, 6H-7’), 7.29 (dd, 12H, J = 8.0, 7.4 Hz, 6H-4’, 6H-6’), 7.22 (dd, 6H, J = 7.4, 7.3 Hz, 6H-5’), and 2.87 (s, 4H, 2H-1, 2H-6).


TLC: Rf (200:1 hexanes/EtOAc) = 0.20.

197b: ¹H NMR (500 MHz, CDCl₃): δ 7.45 (d, 6H, J = 7.8 Hz, 3H-3’, 3H-7’), 7.31-7.21 (m, 11H, 3H-4’, 3H-5’, 3H-6’, H-2”, H-6”), 6.80 (d, 2H, J = 8.7, H-3”, H-5”), 3.80 (s, 3H, -OCH₃), and 3.03 (s, 2H, 2H-1).

HRMS (ESI) Calcd for C₂₉H₂₄NaOS⁺ (M•Na⁺): 443.1440, found: 443.1502.

TLC: Rf (200:1 hexanes/EtOAc) = 0.15.

2,7-Di[(tert-butyldimethyl)silyl]-3,5-octadiyne-2,7-diol (200) and (±)-(1R,7aS)-rel-2,3,5,7a-Tetrahydro-6-[3’-(tert-butyldimethylsilyl)oxy-but-1’-ynyl]-5-oxo-7a-[tert-butyldimethyl-silyl]oxy]-1H-pyrrolizine-1-carboxylic acid tris(1-methylethyl)silyl ester (201a). A solution of iodide 48a (100 mg, 0.173 mmol), alkyne 199 (42 µL, 0.21
mmol), CuI (1 mg, 0.005 mmol), BHT (1 mg), Et₃N (120 µL, 0.87 mmol), and Pd(PPh₃)₂Cl₂ (14 mg, 0.034 mmol) in THF (1.0 mL) was stirred at room temperature for 2 h. The reaction mixture was filtered through 1.5 cm-tall plug of silica gel using EtOAc as the eluent. The filtrate was concentrated in vacuo and subjected to chromatography on silica gel (MPLC) using 20:1 hexanes/EtOAc as the eluent, which yielded 13 mg (20% yield) of dimer 200 and 22 mg (20% yield) of the product 201a as colorless oils.

200: ¹H NMR (500 MHz, CDCl₃): δ 4.58 (q, 2H, J = 6.6 Hz, H-2, H-6), 1.44 (d, 6H, J = 6.5 Hz, 3H-1, 3H-7), 0.92 (s, 9H, -SiMe₂C(CH₃)₃), 0.15 (s, 3H, -Si(CH₃)Me'Bu), and 0.14 (s, 3H, -Si(CH₃)Me'Bu).

TLC: Rf (20:1 hexanes/EtOAc) = 0.1.

201a: ¹H NMR (500 MHz, CDCl₃): δ 7.26 (s, 1H, H-7), 4.14 (q, 1H, J = 7.1 Hz, H-3'), 3.80 (dt, 1H, J = 11.1, 8.9 Hz, H-3), 3.37 (dd, 1H, J = 11.4, 8.8, 2.7 Hz, H-3), 3.17 (dd, 1H, J = 6.5, 1.5 Hz, H-1), 2.61-2.54 (m, 1H, H-2), 2.53-2.48 (m, 1H, H-2), 1.44 (d, 3H, J = 6.5 Hz, H-4'), 1.27 [septet, 3H, J = 7.7 Hz, -OSi(CH(CH₃)₂)₃], 1.06 [d, 18H, J = 7.2 Hz, Si(CH(CH₃)₂)₃], 0.93 (s, 9H, -SiMe₂C(CH₃)₃), 0.88 (s, 9H, -SiMe₂C(CH₃)₃), 0.14 (s, 3H, -Si(CH₃)Me'Bu), 0.13 (s, 3H, -Si(CH₃)Me'Bu), 0.08 (s, 3H, -Si(CH₃)Me'Bu), and 0.04 (s, 3H, -Si(CH₃)Me'Bu).

TLC: Rf (20:1 hexanes/EtOAc) = 0.15.

**Tributyl[3-( tert-butyl dimethyl)silyloxy-1-butyn-1-yl]-stannane (205).** A solution of alkyne 199 (100 µL, 0.50 mmol) in THF (1.0 mL) was cooled to −78 °C, and n-BuLi (0.26 mL, 2.05M in hexanes, 0.53 mmol) was added to the reaction mixture at −78 °C. The reaction mixture was stirred for 15 min at −78 °C. Then a solution of the Bu₃SnCl (150 µL, 0.53 mmol) in THF (0.5 mL) was added to the reaction mixture at −78 °C. The resulting solution was stirred at −78 °C for 20 min, then warmed up to −20 °C, stirred for 10 h at such temperature, quenched with water (1.0 mL) at −20 °C, warmed up to room
temperature over 30 min, and diluted with EtOAc. The organic layer was separated, and the aqueous layer was extracted back with EtOAc (3 x 5.0 mL). All organic layers were combined, dried over Na$_2$SO$_4$, and concentrated in vacuo, yielding crude stannane 205 (0.200 g, 85 % yield) as a colorless oil (unstable to silica gel chromatography).

$^1$H NMR (500 MHz, CDCl$_3$): δ 4.52 (q, 1H, $J = 6.5$ Hz, H-3), 1.67-1.61 [m, 6H, SnCH$_2$CH$_2$Et], 1.40 (d, 1H, $J = 6.5$ Hz, 3H-4), 1.36-1.28 [m, 12H, SnCH$_2$CH$_2$CH$_2$Me], 0.90 [t, 9H, $J = 7.3$ Hz, Sn(CH$_2$)$_3$-CH$_3$], 0.90 (s, 9H, -SiMe$_2$C(CH$_3$)$_3$), 0.13 (s, 3H, -Si(CH$_3$)$_2$Bu), and 0.12 (s, 3H, -Si(CH$_3$)$_2$Bu).

(±)-(1R,7aS)-rel-2,3,5,7a-Tetrahydro-6-[3'-((tert-butyldimethylsilyl)oxy-buty-1'-ynyl]-5-oxo-7a-[(tert-butyldimethylsilyl)oxy]-1H-pyrrolizine-1-carboxylic acid methyl ester (201b) and (±)-(1R,7aS)-rel-2,3,5,7a-Tetrahydro-6-buty-5-oxo-7a-[(tert-butyldimethylsilyl)oxy]-1H-pyrrolizine-1-carboxylic acid methyl ester (206). A solution of iodide 107a (200 mg, 0.645 mmol), stannane 205 (0.43 mmol), and Pd(PPh$_3$)$_4$ (38 mg, 0.032 mmol) in benzene (3.0 mL) was stirred at 60 °C for 4 h. The reaction mixture was diluted with EtOAc. The organic layer was separated, washed with 1M aqueous solution of KF (2 x 10 mL) and brine, dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo. Chromatography on silica gel (MPLC) using 8:1 hexanes/EtOAc as the eluent yielded 43 mg (40% yield) of the product 201b and 25 mg (20% yield) of the by-product 206 as colorless oils.

201b: $^1$H NMR (500 MHz, CDCl$_3$): δ 6.91 (s, 1H, H-7), 4.71 (qd, 1H, $J = 6.6, 2.1$ Hz, H-3'), 3.79 (dt, 1H, $J = 11.0, 8.8$ Hz, H-3), 3.60 (s, 3H, CO$_2$CH$_3$), 3.29 (ddd, 1H, $J = 11.1, 9.2, 2.3$ Hz, H-3), 3.11 (d, 1H, $J = 6.6$ Hz, H-1), 2.58 (ddt, 1H, $J = 13.2, 9.2, 6.7$ Hz, H-2), 2.48 (ddt, 1H, $J = 12.6, 8.1, 2.3$ Hz, H-2), 1.73 (d, 3H, $J = 6.2$ Hz, 3H-4'), 0.90 (s, 9H,
-SiMe₂C(CH₃)₃, 0.86 (s, 9H, -SiMe₂C(CH₃)₃), 0.14 (s, 3H, -Si(CH₃)Me'Bu), 0.13 (s, 3H, -Si(CH₃)Me'Bu), 0.06 (s, 3H, -Si(CH₃)Me'Bu), and 0.03 (s, 3H, -Si(CH₃)Me'Bu).

**¹³C NMR (125 MHz, CDCl₃):** δ 171.3, 170.0, 146.9, 121.0, 99.9, 99.0, 81.2, 59.6, 53.3, 53.2, 42.6, 30.8, 25.9, 25.0, 24.9, 21.7, 18.0, -3.3, -3.9, -4.4, and -4.7.

**IR** (thin film) 2954, 2930, 2857, 1738, 1472, 1436, 1360, 1333, 1252, 1159, 1091, 838, and 779.

**HRMS (ESI) Calcd for C₂₅H₄₃NNaO₅Si₂⁺ (M•Na⁺):** 516.2572, found: 516.2584.

**GC/MS (5029021H):** tᵣ = 14.16 min; m/z 493 (5, M⁺), 478 (10, M⁺-Me), 436 (100, M⁺-tBu), and 392 (20).

**TLC:** Rₛ (8:1 hexanes/EtOAc) = 0.25.

**206:¹H NMR (500 MHz, CDCl₃):** δ 6.50 (s, 1H, H-7), 3.75 (dt, 1H, J = 10.7, 8.8 Hz, H-3), 3.54 (s, 3H, CO₂CH₃), 3.27 (dddd, 1H, J = 11.1, 9.2, 2.4 Hz, H-3), 3.08 (d, 1H, J = 6.4 Hz, H-1), 2.58 (ddt, 1H, J = 13.0, 9.2, 6.8 Hz, H-2), 2.46 (dddd, 1H, J = 13.1, 8.1, 2.3, 1.5 Hz, H-2), 2.18 (t, 2H, J = 7.6 Hz, 2H-1'), 1.45 (pentet, 2H, J = 7.6 Hz, 2H-2'), 1.36 (sextet, 2H, J = 7.6 Hz, 2H-3'), 0.91 (t, 3H, J = 7.2 Hz, 3H-4'), 0.86 (s, 9H, -SiMe₂C(CH₃)₃), 0.04 (s, 3H, -Si(CH₃)Me'Bu), and -0.01 (s, 3H, -Si(CH₃)Me'Bu).

**¹³C NMR (125 MHz, CDCl₃):** δ 174.1, 171.8, 141.4, 139.3, 105.0, 53.2, 51.8, 42.1, 31.1, 29.8, 25.6, 22.6, 18.0, 14.0, -3.2, and -3.9.

**IR** (thin film) 2955, 2859, 1719, 1463, 1436, 1360, 1332, 1252, 1196, 1087, 841, and 780.

**HRMS (ESI) Calcd for C₁₉H₃₄NO₅Si⁺ (M•H⁺):** 368.2252, found: 368.2265.

**GC/MS (5029021H):** tᵣ = 12.07 min; m/z 367 (10, M⁺), 352 (10, M⁺-Me), 310 (80, M⁺-tBu), 236 (30), and 204 (100).

**TLC:** Rₛ (8:1 hexanes/EtOAc) = 0.20.
[(1-Ethyl-2-propyn-1-yl)seleno]-benzene (211) and [(1,1-diethyl-2-propyn-1-yl)seleno]-benzene (212). A solution of alkyne 210 (140 mg, 0.718 mmol) in THF (2.0 mL) was cooled to -78 °C, and LDA (1.9 mL, 0.9 M in THF/hexanes, 1.72 mmol) was added to the reaction mixture at -78 °C. The reaction mixture was stirred for 20 min at -78 °C. Then EtI (64 µL, 0.86 mmol) was added to the reaction mixture at -78 °C. The resulting solution was stirred at -78 °C for 30 min, quenched with pH 7.0 buffer (1.0 mL), partitioned between 0.1M HCl/EtOAc. The organic layer was separated, and the aqueous layer was extracted back with EtOAc (2 x 10.0 mL). All organic layers were combined, dried over MgSO₄, and concentrated in vacuo. The resulting crude was filtered through 1.5 cm-tall plug of silica gel using hexanes (70 mL) as the eluent. The filtrate was concentrated in vacuo and subjected to chromatography on silica gel (MPLC) using hexanes as the eluent, which yielded 36 mg (26% yield) of recovered 210, 80 mg (50% yield) of the desired product 211, 38 mg (21% yield) of dialkylated by-product 212, and 6 mg (4% yield) of allene 213.  

211: ¹H NMR (500 MHz, CDCl₃): δ 7.67 (d, 2H, J = 7.1 Hz), 7.38 (t, 1H, J = 7.4 Hz), 7.31 (dd, 2H, J = 7.6, 7.3 Hz, Ph), 2.51 (s, 1H, H-1), 1.70 (nonet, 4H, J = 7.2 Hz, 2-SeC₃H₂Me), and 1.09 (t, 6H, J = 7.4 Hz, 2-SeCH₂C₃H₃).  

HRMS (ESI) Calcd for C₁₁H₁₂KSe⁺ (M•K⁺): 262.9276, found: 262.9733.  

GC/MS (5029021): tᵣ = 8.25 min; m/z 224 (70, M⁺), 209 (50, M⁺-Me), 195 (100, M⁺-Et), 157 (80), 128 (90), and 77 (80).  

TLC: Rf (hexanes) = 0.10.  

212: ¹H NMR (500 MHz, CDCl₃): δ 7.652 (d, 1H, J = 7.6 Hz), 7.648 (d, 1H, J = 7.9 Hz), 7.33-7.28 (m, 3H, Ph), 3.74 (ddd, 1H, J = 8.1, 5.8, 2.5 Hz, H-3), 2.38 (d, 1H, J = 2.5 Hz, H-1), 1.87-1.76 (m, 2H, SeCH₂Me), and 1.09 (t, 3H, J = 7.3 Hz, SeCH₂CH₃).  


GC/MS (5025015): tᵣ = 9.47 min; m/z 253 (50, M⁺), 240 (20, M⁺-Me), 224 (60, M⁺-Et), 157 (70), and 77 (100).  

TLC: Rf (hexanes) = 0.15.
(±)-(1R,7aS)-rel-2,3,5,7a-Tetrahydro-6-[3’-(phenylseleno)-pent-1’y-nyl]-5-oxo-7a-
[(tert-butylidimethyl-silyl)oxy]-1H-pyrrolizine-1-carboxylic acid tris(1-methylethyl)-
silyl ester (215). A solution of iodide 48a (62 mg, 0.107 mmol), stannane 214 (0.128 mmol), and Pd(PPh₃)₄ (6 mg, 0.005 mmol) in benzene (0.8 mL) was stirred at 60 °C for
24 h. The reaction mixture was diluted with Et₂O (10 mL). The organic layer was
separated, washed with 1M aqueous solution of KF (1 x 2 mL), water (1 x 2 mL), and
brine (1 x 2 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo. Chromatography on silica gel (MPLC) using 30:1 hexanes/EtOAc as the eluent yielded 8
mg (13% yield) of the product 215 as a colorless oil and some products of decomposition
of starting iodide 48a.

215: ¹H NMR (500 MHz, CDCl₃): δ 7.69 (d, 2H, J = 7.6 Hz), 7.32-7.27 (m, 3H), 6.88 (s, 1H, H-7), 3.89 (dd, 1H, J = 7.8, 6.0 Hz, H-3’), 3.76 (dt, 1H, J = 10.9, 8.7 Hz, H-4), 3.30 (ddd, 1H, J = 11.1, 8.9, 2.6 Hz, H-4’), 3.13 (dd, 1H, J = 6.7, 1.6 Hz, H-1), 2.57 (dtd, 1H, J = 13.1, 9.0, 6.8 Hz, H-3), 2.47 (dddd, 1H, J = 12.9, 8.2, 2.7, 1.8 Hz, H-3’), 1.84 (m, 2H, CH₂Me), 1.24 [septet, 3H, J = 7.3 Hz, Si(CHMe₂)₃], 1.08 (t, 3H, J = 7.3 Hz, CH₂CH₃), 1.03 [d, 18H, J = 7.4 Hz, Si(CH(CH₃)₂)₃], 0.87 (s, 9H, SiMe₂C(CH₃)₃), 0.16 (s, 3H, -Si(CH₃)Me₂Bu), and 0.03 (s, 3H, -Si(CH₃)Me₂Bu).

HRMS (ESI) Calcd for C₃₄H₅₃NNaO₄SeSi₂⁺ (M•Na⁺): 698.2571, found: 698.2628.

TLC: Rₜ (30:1 hexanes/EtOAc) = 0.10.
1-(Methoxymethoxy)-dodec-8,10-diene-2-yne (219a). A solution of alkyne 220a (82 mg, 0.82 mmol) in THF (0.54 mL) was cooled to –78 °C, and n-BuLi (0.34 mL, 2.05M in hexanes, 0.105 mmol) was added to the reaction mixture at –78 °C. The reaction mixture was warmed up to 10 min at 0 °C and stirred for 15 min. Then a solution of the bromide 168 (110 mg, 0.54 mmol) in DMSO (0.5 mL) was added to the reaction mixture at 0 °C. The resulting solution was warmed up to room temperature, stirred for 5 h, diluted with Et₂O, and quenched with saturated solution of NH₄Cl (5.0 mL). The organic layer was separated, and the aqueous layer was extracted back with Et₂O (2 x 10.0 mL). All organic layers were combined, washed with saturated solution of NaHCO₃ and brine, dried over Na₂SO₄, filtered, and concentrated in vacuo. Chromatography on silica gel (MPLC) using 20:1 hexanes/EtOAc as the eluent yielded 94 mg (80% yield) of the product 219a as a colorless oil.

¹H NMR (500 MHz, CDCl₃): δ 6.05-5.96 (m, 2H, H-9, H-10), 5.58 (dq, 1H, J = 13.9, 6.7 Hz, H-11), 5.53 (dt, 1H, J = 13.3, 6.8 Hz, H-8), 4.71 (s, 2H, O-CH₂-OMe), 4.20 (t, 2H, J = 2.2 Hz, H-1), 3.38 (s, 3H, -OCH₃), 2.22 (tt, 2H, J = 6.9, 2.2 Hz, H-4), 2.06 (q, 2H, J = 6.6 Hz, H-7), 1.73 (d, 3H, J = 6.2 Hz, H-12), and 1.55-1.44 (m, 4H, H-5, H-6).

¹³C NMR (75 MHz, CDCl₃): δ 131.3, 131.1, 130.4, 126.7, 94.3, 86.5, 75.1, 55.3, 54.5, 31.7, 28.3, 27.8, 18.4, and 17.8.

IR (thin film) 3015, 2917, 2852, 1493, 1376, 1152, 1102, 1048, 989, 922, and 674.

GC/MS (5029021): tᵣ = 9.92 min; m/z 221 (5, M⁺-H), 207 (5, M⁺-Me), 192 (10, M⁺-OCH₃), 177 (20), 145 (60), 131 (50), 117 (55), 105 (70), 91 (80), and 79 (100).

TLC: Rₚ (20:1 hexanes/EtOAc) = 0.33.

1-Methoxy-dodec-8,10-diene-2-yne (219b). A solution of alkyne 220b (250 µL, 3.00 mmol) in THF (1.0 mL) was cooled to –78 °C, and n-BuLi (1.48 mL, 2.03M in hexanes,
3.30 mmol) was added to the reaction mixture at −78 °C. The reaction mixture was warmed up to 10 min at 0 °C and stirred for 15 min. Then a solution of the bromide 168 (110 mg, 1.00 mmol) in 3:2 THF/DMSO (1.5 mL) was added to the reaction mixture at 0 °C. The resulting solution was warmed up to room temperature, stirred for 5 h, diluted with Et₂O, and quenched with saturated solution of NH₄Cl (5.0 mL). The organic layer was separated, and the aqueous layer was extracted back with Et₂O (3 x 10.0 mL). All organic layers were combined, washed with saturated solution of NaHCO₃ and brine, dried over MgSO₄, filtered, and concentrated in vacuo. Chromatography on silica gel (MPLC) using 99:1 hexanes/EtOAc as the eluent yielded 133 mg (70% yield) of the product 219b as a colorless oil.

**1H NMR** (500 MHz, CDCl₃): δ 6.05-5.94 (m, 2H, H-9, H-10), 5.55 (dt, 1H, J = 13.4, 6.7 Hz, H-11), 5.54 (dt, 1H, J = 12.6, 6.1 Hz, H-8), 4.06 (t, 2H, J = 2.2 Hz, H-1), 3.35 (s, 3H, -OC₆H₄(Me)), 2.21 (tt, 2H, J = 6.7, 2.2 Hz, H-4), 2.06 (q, 2H, J = 6.8 Hz, H-7), 1.72 (d, 3H, J = 6.1 Hz, H-12), and 1.57-1.41 (m, 4H, H-5, H-6).

**13C NMR** (75 MHz, CDCl₃): δ 131.7, 131.6, 130.8, 127.1, 87.1, 76.0, 60.4, 57.8, 32.2, 28.7, 28.2, 18.8, and 18.2.

**IR** (thin film) 3015, 2988, 2934, 2855, 2820, 1449, 1377, 1357, 1187, 1153, 1130, 1098, 988, and 907.

**GC/MS** (5029021): tᵣ = 8.92 min; m/z 191 (10, M⁺-H), 177 (20, M⁺-Me), 163 (30), 145 (60), 131 (60), 117 (65), 105 (80), 91 (90), and 79 (100).

**TLC**: Rᵥ (99:1 hexanes/EtOAc) = 0.17.

(±)-(1R,7aS)-rel-2,3,5,7a-Tetrahydro-6-[1'-hydroxy-2'-buten-1'-yl]-5-oxo-7a-[(tert-butyldimethylsilyl)oxy]-1H-pyrrolizine-1-carboxylic acid tris(1-methylethyl)-silyl ester (228a), and (±)-(1R,7aS)-rel-2,3,5,7a-Tetrahydro-6-[1'-hydroxy-1'-(4-
methoxyphenyl)meth-1'-yl]-5-oxo-7a-[(tert-butyldimethylsilyl)oxy]-1H-pyrrozline-1-carboxylic acid tris(1-methylethyl)-silyl ester (228b). Alkenyl iodide 48a (100 mg, 0.173 mmol) was dissolved in anhydrous THF (1.5 mL). i-PrMgCl in ether (2.00 M, 0.19 mL, 0.35 mmol) was added at –30 °C. After the reaction mixture was stirred for 1 h at –30 °C, a solution of corresponding aldehyde (0.40 mmol) in anhydrous THF (0.5 mL) was added in one portion. The reaction mixture was stirred for 2 h at –30 °C, warmed up to rt, stirred for 30 min, and quenched by addition of pH 7.0 buffer (2.0 mL), followed by ether (10 mL). The layers were separated, and the aqueous layer was extracted with ether (3 x 10 mL). The combined organic layers dried over Na2SO4 and evaporated to give a yellow oil. Chromatography on silica gel using 20:1 hexanes/EtOAc as the eluent yielded the corresponding alcohol 228 as a colorless oil.

228a (1:1.7 mixture of diastereomers 228a and 231a) 1H NMR (500 MHz, CDCl3): δ 6.67 (d, 1H, J = 1.6 Hz, H7), 6.58 (d, 1H, J = 1.4 Hz, H6), 5.89-5.74 (m, H3+H2, J = 1.6 Hz), 4.88 (d, 1H, J = 7.1 Hz, OHa), 4.81 (d, 1H, J = 7.1 Hz, OHb), 3.80-3.72 (m, H3+Hb-1'), 3.60 (dd, 1H, J = 8, 7 Hz, Ha-1), 3.28 (ddd, Ha-3+ Hb-3, J = 11.4, 9.1, 2.9 Hz), 3.15 (dd, 1H, J = 6.8, 1.7 Hz, Ha-1+ Hb-1), 2.62-2.55 (m, H2-2+ Hb-2), 2.50-2.44 (m, H2-2+ Hb-2), 1.74 (dd, 3Hb-4', J = 6.5, 1.5 Hz), 1.72 (dd, 3Hb-4', J = 6.6, 1.4 Hz), 1.26 [septet, 3Hb, J = 7.5 Hz, Si(CHMe2)], 1.04 [d, 18Hb+18Ha, J = 7.5 Hz, Si(CH(CH3)2)], 0.88 (s, 9Hb, -SiMe2C(CH3)3), 0.87 (s, 9Ha, -SiMe2C(CH3)3), 0.10 (s, 3Hb, -Si(CH3)Me'Bu), 0.09 (s, 3Ha, -Si(CH3)Me'Bu), 0.06 (s, 3Hb, -Si(CH3)Me'Bu), 0.04 (s, 3Hb, -Si(CH3)Me'Bu).

GC/MS (5029021): tR = 16.08 min; m/z 523 (10, M+), 480 (80, M+ -i-Pr), 466 (100, M+ -1Bu), and 448 (40).

TLC: Rf (6:1 hexanes/EtOAc) = 0.3.

228b (1.2 :1 mixture of diastereomers 228b-1 and 228b-2):

228b-1 (less polar diastereomer): 1H NMR (500 MHz, CDCl3): δ 7.36 (d, 2H, J = 8.9 Hz, H3', H7'), 6.88 (d, 2H, J = 8.8 Hz, H4', H6'), 6.53 (d, 1H, J = 1.6 Hz, H7), 5.49 (br s, 1H, H1'), 3.81 (s, 3H, OCH3), 3.76 (dt, 1H, J = 11.0, 8.5 Hz, H3), 3.25 (ddd, 1H, J = 11.2, 8.6, 3.0 Hz, H3), 3.13 (br s, 1H, OHa), 3.11 (dd, 1H, J = 6.8, 2.3 Hz, H-1), 2.64-
2.52 (m, 1H, H-2), 2.46 (ddt, 1H, J = 13.5, 8.3, 2.2 Hz, H-2), 1.26 [septet, 3H, J = 7.0 Hz, Si(CHMe₂)₃], 1.05 [d, 18H, J = 7.2 Hz, Si(CH(CH₃)₂)₃], 0.84 (s, 9H, -SiMe₂(CH₃)₃), 0.05 (s, 3H, -Si(CH₃)Me'Bu), and 0.01 (s, 3H, -Si(CH₃)Me'Bu).

**GC/MS (5029021):** tᵣ = 15.03 min; m/z 546 (40, M⁺-i-Pr), 532 (100, M⁺-¹Bu), and 514 (30).

**TLC:** Rᵣ (8:1 hexanes/EtOAc) = 0.15.

228b-2 (polar diastereomer): ¹H NMR (500 MHz, CDCl₃): δ 7.31 (d, 2H, J = 8.8 Hz, H-3', H-7'), 6.90 (d, 2H, J = 8.7 Hz, H-4', H-6'), 6.27 (d, 1H, J = 1.5 Hz, H-7), 5.41 (dd, 1H, J = 3.8, 1.6 Hz, H-1'), 4.05 (d, 1H, J = 3.8 Hz, OH), 3.82 (s, 3H, OCH₃), 3.78 (dt, 1H, J = 10.9, 8.5 Hz, H-3), 3.30 (dd, 1H, J = 11.1, 8.7, 3.0 Hz, H-3), 3.09 (dd, 1H, J = 6.8, 2.1 Hz, H-1), 2.60 (dt, 1H, J = 13.1, 8.7, 6.7 Hz, H-2), 2.45 (ddt, 1H, J = 13.3, 8.3, 2.8 Hz, H-2), 1.25 [septet, 3H, J = 6.9 Hz, Si(CHMe₂)₃], 1.05 [d, 18H, J = 7.2 Hz, Si(CH(CH₃)₂)₃], 0.84 (s, 9H, -SiMe₂(CH₃)₃), 0.03 (s, 3H, -Si(CH₃)Me'Bu), and 0.01 (s, 3H, -Si(CH₃)Me'Bu).

**GC/MS (5029021):** tᵣ = 15.26 min; m/z 546 (40, M⁺-i-Pr), 532 (100, M⁺-¹Bu), and 514 (30).

**TLC:** Rᵣ (8:1 hexanes/EtOAc) = 0.10.

(±)-(1R,7aS)-rel-2,3,5,7a-Tetrahydro-6-[(4'-methoxy)benzoyl]-5-oxo-7a-[(tert-butyl-dimethylsilyl)oxy]-1H-pyrrolizine-1-carboxylic acid tris(1-methylethyl)silyl ester (229). Alcohol 228b (30 mg, 0.05 mmol) was dissolved in DCM (3.0 mL). Solid MnO₂ (88 mg, 1.00 mmol) was added in one portion at room temperature. The reaction mixture was sonicated for 6 h and stirred at room temperature for additional 72 h. Upon complete conversion of 228b the reaction mixture was filtered through 2 cm-tall plug of silica gel using 2:1 hexanes/EtOAc (100 mL) as an eluent. The mother liquor was concentrated...
under reduced pressure, and subjected to chromatography on silica gel using 30:1 hexanes/EtOAc as the eluent yielded 7 mg (20% yield) of ketone 229 as a colorless oil.

229: \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 7.25 (d, 2H, \(J = 8.3\) Hz, H-3', H-7'), 7.25 (s, 1H, H-7), 6.89 (d, 2H, \(J = 8.7\) Hz, H-4', H-6'), 3.89 (s, 3H, O-CH\(_3\)), 3.81 (dt, 1H, \(J = 11.1, 8.5\) Hz, H-3), 3.37 (ddd, 1H, \(J = 11.4, 8.7, 3.0\) Hz, H-3), 3.25 (dd, 1H, \(J = 7.0, 2.4\) H-1), 2.71 (ddt, 1H, \(J = 13.4, 8.8, 7.0\) Hz, H-2), 2.51 (ddt, 1H, \(J = 13.4, 8.0, 3.0\) Hz, H-2), 1.02 [m, 27H, Si(CH(CH\(_3\))\(_2\))\(_2\)], 0.89 (s, 9H, -SiMe\(_2\)C(CH\(_3\))\(_3\)), 0.14 (s, 3H, -Si(CH\(_3\))\(_2\)tBu), and 0.11 (s, 3H, -Si(CH\(_3\))\(_2\)tBu).

TLC: \(R_f\) (20:1 hexanes/EtOAc) = 0.12.

(±)-(1R,7aS)-rel-2,3,5,7a-Tetrahydro-6-\([(2'E,8'E,10'E)-1'-hydroxy-2',8',10'-dodeca- trienyl]-5-oxo-7a-[((tert-butyldimethylsilyl)oxy]-1H-pyrrolizine-1-carboxylic acid tris(1-methylethyl)silyl ester (58a). Alkenyl iodide 48a (169 mg, 0.292 mmol) was dissolved in anhydrous THF (1.5 mL). i-PrMgCl in ether (1.87 M, 0.312 mL, 0.584 mmol) was added at –50 °C. After the reaction mixture was stirred for 1 h at –50 °C, a solution of aldehyde 23 (104 mg, 0.584 mmol) in anhydrous THF (0.5 mL) was added in one portion. The reaction mixture was stirred for 1 hour at –50 °C, warmed up to rt, stirred for 1 h, and quenched by addition of pH 7.0 buffer (2.0 mL), followed by ether (10 mL). The layers were separated, and the aqueous layer was extracted with ether (3x10 mL). The combined organic layers dried over Na\(_2\)SO\(_4\) and evaporated to give a yellow oil. Chromatography on silica gel using 20:1 hexanes/EtOAc as the eluent helped to yield the corresponding alcohol 58a as a colorless oil.

58a (1:1 mixture of two diastereomers) \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 6.67 (d, 1H, \(J = 1.7\) Hz, H-7), 6.56 (d, 1H, \(J = 1.5\) Hz, H-7), 6.03-5.98 (m, 2H, H-10'+H-10', H-9'+H-9'), 5.62-5.50 (m, 2H, H-2'+H-2', H-3'+H-3'), 4.89 (d, 1H, \(J = 7.6\) Hz, H-1'), 4.81 (d, 1H, \(J = \))
7.3 Hz, H-1'), 4.51 (d, 1H, J = 7.3 Hz, OH), 4.09 (d, 1H, J = 6.0 Hz, OH), 3.77 (dt, 1H, J = 10.7, 8.5 Hz, H-3+H-3), 3.28 (ddd, 1H, J = 11.0, 8.9, 2.8 Hz, H-3+H-3), 3.15 (dd, 1H, J = 6.8, 1.7 Hz, H-1+H-1), 2.56 (dt, 1H, J = 13.2, 8.9, 6.9 Hz, H-2+H-2), 2.48 (ddt, 1H, J = 13.2, 8.3, 2.6 Hz, H-2+H-2), 2.12-2.05 (m, 2H-7'+2H-7', 2H-4'+2H-4'), 1.74 (d, 3H, J = 6.5 Hz, H-3H-12'), 1.73 (d, 3H, J = 7.3 Hz, H-3H-12'), 1.42-1.38 (m, 2H-6'+2H-6', 2H-5'+2H-5'), 1.24 [sept, 3H+3H, J = 7.0 Hz, Si(CH(C5')3)], 1.05 [d, 18H+18H, J = 7.2 Hz, Si(CH(CH3)2)3], 0.88 (s, 9H, -SiMe2C(CH3)3), 0.08 (s, 3H+3H, -Si(CH3)MeBu), 0.07 (s, 3H+3H, -Si(CH3)MeBu), and 0.05 (s, 3H, -Si(CH3)MeBu).

**TLC:** Rf (8:1 hexanes/EtOAc) = 0.20.

(±)-(1R,7aS)-rel-2,3,5,7a-Tetrahydro-6-benzoyl-5-oxo-7a-[(tert-butyl dimethylsilyl)oxy]-1H-pyrrolizine-1-carboxylic acid methyl ester (232a). Alkenyl iodide 107a (100 mg, 0.229 mmol) was dissolved in anhydrous THF (2.0 mL). MeMgBr in ether (2.82 M, 0.20 mL, 0.573 mmol) was added at −78 °C. After the reaction mixture was stirred for 10 min at −78 °C, then corresponding neat Weinreb amide (113 mg, 0.685 mmol) was added in one portion. The reaction mixture was stirred for 10 min at −70 °C, warmed up to rt, stirred for 5 min, and quenched by addition of AcOD (1.0 mL), followed by ether (10 mL). The layers were separated, and the aqueous layer was extracted with ether (3 x 10 mL). The combined organic layers were washed with water and brine, dried over Na2SO4, and evaporated to give yellow oil. Chromatography on silica gel using 4:1 hexanes/EtOAc as the eluent yielded 31 mg (35 %) of the product 232a as a colorless oil.

**1H NMR** (500 MHz, CDCl3): δ 7.88 (d, 2H, J = 7.2 Hz, H-3', H-7'), 7.61 (dd, 1H, J = 7.5, 7.3 Hz, H-5'), 7.49 (dd, 2H, J = 7.9, 7.6 Hz, H-4', H-6'), 7.23 (s, 1H, H-7), 3.88 (dt, 1H, J = 10.8, 8.9 Hz, H-3), 3.66 (s, 3H, CO2CH3), 3.37 (ddd, 1H, J = 11.3, 9.1, 2.2 Hz, H-3), 3.23 (d, 1H, J = 6.8, H-1), 2.68 (ddt, 1H, J = 12.9, 9.1, 6.6 Hz, H-2), 2.57 (dddd,
$^1$H, J = 13.2, 8.7, 2.2, 1.5 Hz, H-2), 0.89 (s, 9H, -SiMe$_2$C(CH$_3$)$_3$), 0.14 (s, 3H, -Si(CH$_3$)$_2$Bu), and 0.10 (s, 3H, -Si(CH$_3$)$_2$Bu).

$^{13}$C NMR (125 MHz, CDCl$_3$): δ 196.5, 169.2, 168.9, 149.0, 138.5, 136.1, 134.2, 129.9, 128.8, 99.1, 53.2, 52.4, 42.6, 31.1, 25.6, 18.0, -3.0, and -3.8.

IR (thin film) 3551, 2964, 2926, 2858, 1736, 1720, 1660, 1440, 1360, 1325, 1261, 1158, 1112, and 674.

HRMS (ESI) Calcd for C$_{22}$H$_{29}$NNaO$_5$Si$^+$ (M$^+$Na$^+$): 438.1707, found: 438.1658.

GC/MS (5029021H): t$_r$ = 14.65 min; m/z 415 (10, M$^+$), 400 (10, M$^+$-Me), 358 (100, M$^+$-tBu), 330 (20), 282 (30), and 105 (70).

TLC: R$_f$(4:1 hexanes/EtOAc) = 0.20.

(±)-(1R,7aS)-rel-2,3,5,7a-Tetrahydro-6-[1'-hydroxy-(1'-phenyl)methyl]-5-oxo-7a-[(tert-butyldimethylsilyl)oxy]-1H-pyrrolizine-1-carboxylic acid methyl ester (232b).

Alkenyl iodide 107a (100 mg, 0.229 mmol) was dissolved in anhydrous THF (2.0 mL). MeMgBr in ether (2.82 M, 0.20 mL, 0.573 mmol) was added at –78 °C. After the reaction mixture was stirred for 10 min at –78 °C, then neat benzaldehyde (70 µL, 0.703 mmol) was added in one portion. The reaction mixture was stirred for 10 min at –70 °C, warmed up to rt, stirred for 5 min, and quenched by addition of AcOD (1.0 mL), followed by ether (10 mL). The layers were separated, and the aqueous layer was extracted with ether (3 x 10 mL). The combined organic layers were washed with water and brine, dried over Na$_2$SO$_4$, and evaporated to give yellow oil. Chromatography on silica gel using 4:1 hexanes/EtOAc as the eluent yielded 30 mg (35%) of each alcohol diastereomer 232b-1 and 232b-2 as colorless oils.

232b-1 (less polar diastereomer):
$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.38-7.27 (m, 5H, H-3', H-4', H-5', H-6', and H-7'), 6.37 (d, 1H, $J = 1.5$ Hz, H-7), 5.47 (d, 1H, $J = 1.4$ Hz, H-1'), 3.76 (dt, 1H, $J = 11.0$, 8.9 Hz, H-3), 3.451 (s, 3H, CO$_2$CH$_3$), 3.449 (br d, 1H, $J = 2.6$ Hz, Cl'-OH), 3.27 (ddd, 1H, $J = 11.3$, 9.3, 2.3 Hz, H-3), 3.04 (d, 1H, $J = 6.5$, H-1), 2.58 (ddt, 1H, $J = 13.7$, 9.2, 6.8 Hz, H-2), 2.48 (ddt, 1H, $J = 13.4$, 10.8, 2.3, 2.6 Hz, H-2), 0.81 (s, 3H, -SiMe$_2$C(CH$_3$)$_3$), -0.01 (s, 3H, -Si(C$_x$H$_y$)$_3$)$_2$tBu), and -0.09 (s, 3H, -Si(CH$_3$)$_2$Bu).

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 173.0, 171.4, 142.0, 140.8, 140.3, 128.7, 128.2, 126.4, 99.1, 69.7, 53.1, 52.1, 42.1, 31.2, 25.6, 18.0, -3.2, and -3.9.

IR (thin film) 3551, 3409, 2955, 2929, 2858, 1735, 1701, 1361, 1252, 1157, 1091, 837, and 675.

HRMS (ESI) Calcd for C$_{22}$H$_{31}$NNaOSi$^+$ (M•Na$^+$): 440.1864, found: 440.1874.

GC/MS (5029021H): $t_r = 14.30$ min; $m/z$ 417 (10, M$^+$), 402 (5, M$^+$-Me), 360 (100, M$^+$-tBu), 342 (40), and 105 (50).

TLC: $R_f$ (4:1 hexanes/EtOAc) = 0.17.

232b-2 (polar diastereomer):

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.37-7.27 (m, 5H, H-3', H-4', H-5', H-6', and H-7'), 6.29 (d, 1H, $J = 1.7$ Hz, H-7), 5.54 (s, 1H, H-1'), 3.81 (br d, 1H, $J = 2.6$ Hz, Cl'-OH), 3.78 (dt, 1H, $J = 10.9$, 8.8 Hz, H-3), 3.47 (s, 3H, CO$_2$CH$_3$), 3.26 (ddd, 1H, $J = 11.3$, 9.3, 2.3 Hz, H-3), 3.03 (d, 1H, $J = 6.6$, H-1), 2.59 (ddt, 1H, $J = 13.2$, 9.3, 6.8 Hz, H-2), 2.49 (dddd, 1H, $J = 13.2$, 8.3, 2.3, 1.0 Hz, H-2), 0.82 (s, 3H, -SiMe$_2$C(CH$_3$)$_3$), 0.00 (s, 3H, -Si(CH$_3$)$_2$Bu), and -0.09 (s, 3H, -Si(CH$_3$)$_2$Bu).

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 173.3, 171.4, 141.9, 140.4, 140.3, 128.7, 128.3, 126.4, 99.1, 69.7, 52.8, 52.0, 41.9, 31.1, 25.6, 18.0, -3.2, and -3.9.

IR (thin film) 3443, 2954, 2929, 2857, 1739, 1701, 1361, 1252, 1154, 1089, 838, and 780.

HRMS (ESI) Calcd for C$_{22}$H$_{31}$NNaOSi$^+$ (M•Na$^+$): 440.1864, found: 440.1908.

GC/MS (5029021H): $t_r = 14.29$ min; $m/z$ 417 (10, M$^+$), 360 (100, M$^+$-tBu), 342 (40), and 105 (50).

TLC: $R_f$ (4:1 hexanes/EtOAc) = 0.17.
(±)-(1R,7aS)-rel-2,3,5,7a-Tetrahydro-6-[(2′E,8′E,10′E)-1′-hydroxy-2′,8′,10′-dodecatrien-1′-yl]-5-oxo-7a-[(tert-butyldimethylsilyl)oxy]-1H-pyrrolizine-1-carboxylic acid methyl ester (233a and 233b). Alkenyl iodide 107a (200 mg, 0.45 mmol) was dissolved in anhydrous THF (2.0 mL). MeMgBr in ether (2.82 M, 0.49 mL, 1.37 mmol) was added at −78 °C. After the reaction mixture was stirred for 30 min at −78 °C, a solution of aldehyde 23 (245 mg, 1.37 mmol) in anhydrous THF (1.0 mL) was added in one portion. The reaction mixture was stirred for 1 hour at −78 °C, warmed up to rt, stirred for 30 min, and quenched by addition of pH 7.0 buffer (2.0 mL), followed by ether (10 mL). The layers were separated, and the aqueous layer was extracted with ether (3 x 10 mL). The combined organic layers dried over Na$_2$SO$_4$ and evaporated to give a yellow oil. Chromatography on silica gel (MPLC) using 4.5:1 hexanes/EtOAc as the eluent yielded 110 mg (50 %) of alcohol 233a and 48 mg (22%) of alcohol 233b as colorless oils.

The compound 233a:

$^1$H NMR (500 MHz, CDCl$_3$): δ 6.57 (d, 1H, J = 1.0 Hz, H-7), 6.01 (ddq, 1H, J = 15.0, 10.3, 1.6 Hz, H-10'), 6.00 (ddt, 1H, J = 14.0, 10.3, 1.6 Hz, H-9'), 5.76 (dt, 1H, J = 15.4, 6.8 Hz, H-3'), 5.58 (ddt, 1H, J = 15.6, 6.9, 1.5 Hz, H-8'), 5.57 (dd, 1H, J = 14.8, 6.7 Hz, H-2'), 5.52 (dq, 1H, J = 14.2, 6.75 Hz, H-11'), 4.79 (dd, 1H, J = 6.7, 6.1 Hz, H-1'), 3.77 (dt, 1H, J = 10.9, 8.8 Hz, H-3), 3.56 (s, 3H, CO$_2$CH$_3$), 3.27 (ddd, 1H, J = 10.9, 9.3, 2.3 Hz, H-3), 3.23 (d, 1H, J = 5.9 Hz, C(1')OH), 3.09 (dd, 1H, J = 6.7, 1.0 Hz, H-1), 2.61 (ddtd, 1H, J = 13.0, 9.3, 6.7 Hz, H-2), 2.46 (ddddd, 1H, J = 13.2, 8.3, 2.0, 1.0 Hz, H-2), 2.05 (app pent, 2H, J = 6.4 Hz, 4H, 2H-7' and 2H-4'), 1.72 (d, 3H, J = 6.3 Hz, 3H-12'), 1.39 (m, 4H, J = 7.2 Hz, 2H-6' and 2H-5'), 0.86 (s, 9H, -SiMe$_2$C(CH$_3$)$_3$), 0.05 (s, 3H, -Si(CH$_3$)$_2$Bu), and 0.01 (s, 3H, -Si(CH$_3$)$_2$Bu).
\textbf{13C NMR (125 MHz, CDCl\textsubscript{3})}: \delta 173.2, 171.5, 140.9, 139.4, 134.2, 131.9, 131.8, 130.7, 128.8, 127.1, 99.3, 68.8, 52.9, 52.1, 41.9, 32.5, 32.2, 31.2, 29.1, 28.7, 25.7, 18.2, 18.0, 0.2, -3.0, and -3.8.

\textbf{IR (thin film)} 3818, 2952, 2930, 2853, 1738, 1703, 1360, 1332, 1155, 1090, 986, 838, 780, and 674.

\textbf{HRMS (ESI)} Calcd for C\textsubscript{27}H\textsubscript{43}NNaO\textsubscript{5}Si\textsuperscript{+} (M•Na\textsuperscript{+}): 512.2803, found: 512.2826.

\textbf{GC/MS (5029021H)}: \textit{t}\textsubscript{r} = 17.33 min; m/z 489 (10, M\textsuperscript{+}), 471 (20, M\textsuperscript{+}-H\textsubscript{2}O), 432 (80, M\textsuperscript{+}-t\textsubscript{Bu}), 207 (100), and 75 (100).

\textbf{TLC}: \textit{R}\textsubscript{f} (4.5:1 hexanes/EtOAc) = 0.25.

The compound 233b:

\textbf{1H NMR (500 MHz, CDCl\textsubscript{3})}: \delta 6.50 (d, 1H, \textit{J} = 1.5 Hz, H-7), 6.01 (ddq, 1H, \textit{J} = 15.2, 11.3, 1.6 Hz, H-10'), 5.99 (ddt, 1H, \textit{J} = 15.0, 10.2, 1.2 Hz, H-9'), 5.80 (dtd, 1H, \textit{J} = 15.4, 6.2, 0.8 Hz, H-3'), 5.58 (dt, 1H, \textit{J} = 13.8, 6.7 Hz, H-2'), 5.52 (dd, 1H, \textit{J} = 15.2, 7.0 Hz, H-11'), 5.52 (ddt, 1H, \textit{J} = 15.2, 7.0, 1.5 Hz, H-8'), 4.89 (d, 1H, \textit{J} = 6.7 Hz, H-1'), 3.78 (dt, 1H, \textit{J} = 10.9, 8.8 Hz, H-3), 3.57 (s, 3H, CO\textsubscript{2}C\textsubscript{6}H\textsubscript{5}), 3.28 (ddd, 1H, \textit{J} = 11.2, 9.3, 2.3 Hz, H-3), 3.12 (br s, 1H, C(1')O\textsubscript{H}), 3.10 (dd, 1H, \textit{J} = 6.7, 0.8 Hz, H-1), 2.61 (dtd, 1H, \textit{J} = 13.2, 9.2, 6.7 Hz, H-2), 2.50 (dddd, 1H, \textit{J} = 13.2, 8.6, 2.3, 1.2 Hz, H-2), 2.06 (app pent, 2H, \textit{J} = 6.6 Hz, 4H, 2H-7' and 2H-4'), 1.73 (d, 3H, \textit{J} = 6.4 Hz, 3H-12'), 1.38 (m, 4H, \textit{J} = 7.3 Hz, 2H-6' and 2H-5'), 0.86 (s, 9H, -SiMe\textsubscript{2}C(C\textsubscript{6}H\textsubscript{5})\textsubscript{3}), 0.05 (s, 3H, -Si(CH\textsubscript{3})\textsubscript{2}t\textsubscript{Bu}), and 0.01 (s, 3H, -Si(CH\textsubscript{3})\textsubscript{2}t\textsubscript{Bu}).

\textbf{13C NMR (125 MHz, CDCl\textsubscript{3})}: \delta 173.2, 171.5, 141.3, 139.4, 134.5, 131.9, 131.8, 130.7, 128.4, 127.1, 99.2, 68.8, 52.9, 52.1, 41.9, 32.5, 32.2, 31.1, 29.1, 28.7, 25.6, 18.2, 18.0, 0.2, -3.0, and -3.8.

\textbf{IR (thin film)} 3447, 2953, 2928, 2856, 1738, 1717, 1436, 1360, 1332, 1251, 1208, 1154, 1088, 987, 837, 780, and 675.

\textbf{HRMS (ESI)} Calcd for C\textsubscript{27}H\textsubscript{43}NNaO\textsubscript{5}Si\textsuperscript{+} (M•Na\textsuperscript{+}): 512.2803, found: 512.2806.

\textbf{GC/MS (5029021H)}: \textit{t}\textsubscript{r} = 17.33 min; m/z 489 (10, M\textsuperscript{+}), 471 (20, M\textsuperscript{+}-H\textsubscript{2}O), 432 (80, M\textsuperscript{+}-t\textsubscript{Bu}), 207 (100), and 75 (100).

\textbf{TLC}: \textit{R}\textsubscript{f} (4.5:1 hexanes/EtOAc) = 0.15.

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(±)-(1R,7aS)-rel-2,3,5,7a-Tetrahydro-6-[(1’E,7’E,9’E)-1’,7’,9’-undecatrien]-carbonyl]-5-oxo-7a-[(tert-butyldimethylsilyl)oxy]-1H-pyrrolizine-1-carboxylic acid methyl ester (50c). A solution of alcohol 233a (or 233b) (13 mg, 0.027 mmol) in DCM (3.0 mL) at 0 °C was treated with DMP (15 mg, 0.035 mmol). After stirring for 1 h at 0 °C and 1 h at room temperature the reaction mixture filtered through 3 cm-tall plug of alumol gel (Al₂O₃) using DCM (30 mL) as an eluent. The mother liquor was concentrated under reduced pressure, yielding the ketone 50c (10 mg, 80% yield, >95% pure by ¹H NMR) as a colorless oil.

¹H NMR (500 MHz, CDCl₃): δ 7.49 (s, 1H, H-7), 7.04 (dt, 1H, J = 15.8, 6.8 Hz, H-2'), 6.93 (dt, 1H, J = 15.6, 1.3 Hz, H-1'), 6.01 (ddq, 1H, J = 15.1, 10.2, 1.2 Hz, H-9'), 5.98 (ddt, 1H, J = 14.0, 10.1, 1.6 Hz, H-8'), 5.58 (dq, 1H, J = 13.3, 6.8 Hz, H-10'), 5.52 (dt, 1H, J = 12.6, 6.5 Hz, H-11'), 3.82 (dt, 1H, J = 11.0, 8.8 Hz, H-3), 3.56 (s, 3H, CO₂CH₃), 3.32 (ddd, 1H, J = 11.2, 9.2, 2.4 Hz, H-3), 3.17 (dd, 1H, J = 6.7, 1.3 Hz, H-1), 2.62 (dd, 1H, J = 13.1, 9.2, 6.8 Hz, H-2), 2.51 (dddd, 1H, J = 13.2, 8.5, 2.6, 1.4 Hz, H-2), 2.28 (app q, 2H, J = 8.0 Hz, 2H-3'), 2.06 (app q, 2H, J = 8.0 Hz, 2H-3'), 1.72 (d, 3H, J = 6.1 Hz, 3H-11'), 1.53-1.47 (m, 2H, 2H-4'), 1.45-1.39 (m, 2H, 2H-5'), 0.87 (s, 9H, -SiMe₂C(CH₃)₃), 0.07 (s, 3H, -Si(CH₃)₂tBu), and 0.01 (s, 3H, -Si(CH₃)₂tBu).

HRMS (ESI) Calcd for C₂₇H₄₁NNaO₅Si:\(\text{Na}^+\): 510.2646, found: 510.2691.

GC/MS (5029021H): tᵣ = 16.78 min; m/z 487 (20, M⁺), 450 (80, M⁺ - tBu), 282 (50), and 207 (100).

TLC: Rᵣ (3:1 hexanes/EtOAc) = 0.60.
(±)-(1R,7aS)-rel-2,3,5,7a-Tetrahydro-6-[(2′E,8′E,10′E)-1'-hydroxy-2',8',10'-dodecatrien-1'-yl]-5-oxo-7a-[(tert-butyldimethylsilyl)oxy]-1H-pyrrolizine-1-carboxylic acid (234a,b). A mixture of alcohols 233a and 233b (241 mg, 0.49 mmol) was dissolved in THF (3.0 mL). Solid LiOH•H2O (103 mg, 2.47 mmol) was added to the reaction mixture at rt, following by addition of water (1.5 mL). The reaction mixture was stirred at rt for 3 hours, quenched by addition of solid citric acid (630 mg, 3.0 mmol), followed by ether (20 mL) and brine (5.0 mL). The layers were separated, and the aqueous layer was extracted with ether (4 x 10 mL). The combined organic layers were dried over Na2SO4 and evaporated to give the acids 234a,b (213 mg, 0.448 mmol, 91% yield, >95% pure by 1H NMR) as a mixture of the corresponding diastereomers, yellow oil, which was used without any further purification in the next step.

234a: 1H NMR (500 MHz, CDCl3): δ 6.63 (d, 1H, J = 1.0 Hz, H-7), 6.03-5.95 (m, 2H, H-9' and H-10'), 5.77 (dt, 1H, J = 15.4, 6.7, H-3'), 5.61 (dd, 1H, J = 15.4, 7.0 Hz, H-2'), 5.56 (dd, 1H, J = 13.9, 6.7 Hz, H-8'), 5.52 (dd, 1H, J = 14.2, 6.8 Hz, H-11'), 4.82 (d, 1H, J = 7.2 Hz, H-1'), 3.76 (dt, 1H, J = 10.7, 8.8 Hz, H-3), 3.27 (dd, 1H, J = 11.0, 9.0, 2.3 Hz, H-3), 3.11 (dd, 1H, J = 7.0, 0.8 Hz, H-1), 2.62 (ddt, 1H, J = 12.9, 9.2, 6.6 Hz, H-2), 2.52 (dddd, 1H, J = 12.3, 8.5, 2.2, 1.2 Hz, H-2), 2.05 (app pent, 2H, J = 7.1 Hz, 4H, 2H-7' and 2H-4'), 1.72 (d, 3H, J = 6.5 Hz, 3H-12'), 1.37 (m, 4H, J = 7.1 Hz, 2H-6' and 2H-5'), 0.86 (s, 9H, -SiMe2C(CH3)3), 0.05 (s, 3H, -Si(CH3)2'Bu), and 0.01 (s, 3H, -Si(CH3)2'Bu).
234b: $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 6.72 (d, 1H, $J = 1.6$ Hz, H-7), 6.03-5.95 (m, 2H, H-9' and H-10'), 5.82 (dt, 1H, $J = 15.6$, 6.2, H-3'), 5.60 -5.45 (m, 3H, H-2', H-11', H-8'), 4.89 (d, 1H, $J = 7.3$ Hz, H-1'), 3.76 (dt, 1H, $J = 15.6$, 6.2 Hz, H-3'), 3.61 (dd, 1H, $J = 15.6$, 6.2 Hz, H-1'), 2.64 (dtd, 1H, $J = 13.3$, 9.0, 6.1 Hz, H-2), 2.50 (dddd, 1H, $J = 13.3$, 9.0, 6.1 Hz, H-2), 2.06 (app pent, 2H, $J = 6.6$ Hz, 4H, 2H-7' and 2H-4'), 1.73 (d, 3H, $J = 7.3$ Hz, 3H-12'), 1.37 (m, 4H, $J = 7.1$ Hz, 2H-6' and 2H-5'), 0.86 (s, 9H, -SiMe$_2$(CH$_3$)$_3$), 0.04 (s, 3H, -Si(C$_2$H$_3$)$_2$tBu), and 0.00 (s, 3H, -Si(C$_2$H$_3$)$_2$tBu).

(±)-(2aR,7aS,7bS)-(7Z)-Hexahydro-7-[(2'E,8'E,10'E)-1'-hydroxy-2',8',10'-dodecatrien-1'-ylidene]-7b-[((tert-butyldimethylsilyl)oxy]-furo[2,3,4-gh]pyrrolo[2,6-d]dione (53a). A mixture of acids 234a and 234b (213 mg, 0.448 mmol) was dissolved in DCM (5.0 mL). Solid MnO$_2$ (Acros, 221 mg, 2.24 mmol) was added in three portions of 5.0 equiv every 2 hours at rt. The progress of the reaction was closely followed by LC-MS [C$_8$, 2.1x150 mm, 5µm, 0.5 mL/min, water/MeOH 50-100%, methanol content, the best ionization was in ESI-Neg, (M-H)$^-$ ion, ret time = 12.6 min], the completion of the reaction was judged by disappearance of the starting material. Upon complete conversion of the 234a,b, the reaction mixture was filtered through 3 cm-tall plug of silica gel using DCM (100 mL) as an eluent (!!! purification of the crude reaction mixture by MPLC 6:1 hexanes : EtOAc resulted in a low yield of the 53a, because 53a converts into a more polar acid S-2 on a silica gel column, which is difficult to trace from a column. This implies that any other protocol of 234a,b oxidation that requires a more thorough chromatographic purification than a quick flash through a silica plug, needs to be run with keeping this potential subsequent purification problem in mind). The mother liquor was concentrated under reduced pressure, yielding the enol 53a (195 mg, 0.412 mmol, 92% yield, >95% pure by $^1$H NMR) as yellow oil.

The compound 53a:

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 11.59 (s, 1H, C1'-OH), 6.84 (dt, 1H, $J = 15.4$, 6.9 Hz, H-3'), 6.05-5.97 (m, 3H, H-2', H-9', H-10'), 5.59 (dq, 1H, $J = 13.6$, 6.4 Hz, H-11'), 5.53 (dt, 1H, $J = 13.6$, 6.9 Hz, H-8'), 5.20 (s, 1H, H-7), 3.93 (ddd, 1H, $J = 12.5$, 9.1, 3.9 Hz, H-3),
3.35 (dt, 1H, J = 12.0, 8.11 Hz, H-3), 3.23 (dd, 1H, J = 10.0, 4.4 Hz, H-1), 2.64 (dtd, 1H, J = 13.7, 9.0, 3.9 Hz, H-2), 2.41 (dddd, 1H, J = 13.5, 8.9, 8.9, 4.4 Hz, H-2), 2.26 (q, 2H, J = 6.9 Hz, 2H-4'), 2.08 (q, 2H, J = 7.2 Hz, 2H-7'), 1.73 (d, 3H, J = 6.5 Hz, 3H-12'), 1.52-1.40 (m, 4H, 2H-5' and 2H-6'), 0.88 (s, 9H, -SiMe₂C(CH₃)₃), 0.10 (s, 3H, -Si(CH₃)₂tBu), and 0.06 (s, 3H, -Si(CH₃)₂tBu).

13C NMR (125 MHz, CDCl₃): δ 175.9, 166.4, 145.4, 131.7, 131.6, 130.9, 127.3, 120.6, 102.5, 100.6, 81.6, 50.9, 45.0, 33.1, 32.5, 31.4, 29.2, 28.0, 25.7, 25.6, 18.9, 18.2, 17.8, 0.2, and -3.4.

IR (thin film) 3015, 2954, 2930, 2857, 1783, 1673, 1651, 1611, 1390, 1331, 1320, 1252, 1132, 977, 840, 781, and 675.

HRMS (ESI) Calcd for C₂₆H₃₉NNaO₅Si+ (M•Na+): 496.2490, found: 496.2491.

LC/MS: (Method: C₈ column, gradient 50-100%, methanol content, 22 min, MW 200-2000, negative ES, ES+APCI, APCI): tᵣ = 10.1 min. (M-H: 472).

TLC: Rᵢ (6:1 hexanes/EtOAc) = 0.5.

(±)-(2aR,7aS,7bS)-7-Hydroxyhexahydro-7-[(1'E,7'E,9'E)-1',7',9'-undecatrienyl][carbonyl]-7b-[[(tert-butyldimethylsilyl)oxy]-furo[2,3,4-gh]-pyrrolizine-2,6-dione (235). A solution of alcohol 234a (and/or 234b) (30 mg, 0.063 mmol) in DCM (1.0 mL) at 0 °C was treated with DMP (30 mg, 0.070 mmol). After stirring for 30 min at 0 °C and 30 min at room temperature the reaction mixture was diluted with hexanes and filtered through 3 cm-tall plug of Celite® using 3:1 hexanes/EtOAc (30 mL) as an eluent. The filtrate was concentrated under reduced pressure. Chromatography on silica gel (MPLC) using 5:1 hexanes/EtOAc as the eluent yielded 12 mg (40% yield) of the product 53a and 3 mg (10% yield) of oxidized product 235 of as a colorless oil.

235:

¹H NMR (500 MHz, CDCl₃): δ 7.16 (dt, 1H, J = 15.5, 7.1 Hz, H-3'), 6.67 (dt, 1H, J = 15.5, 1.6 Hz, H-2'), 6.04-5.96 (m, 2H, H-9', H-10'), 5.58 (dq, 1H, J = 13.5, 6.7 Hz, H-11'), 5.51 (dt, 1H, J = 13.3, 6.8 Hz, H-8'), 5.04 (s, 1H, H-7), 3.99 (ddd, 1H, J = 12.4, 9.8, 5.7 Hz, H-3), 3.42 (s, 1H, C7-OH), 3.34 (ddd, 1H, J = 12.2, 9.7, 5.5 Hz, H-3), 3.19 (dd, 1H, J = 9.4, 2.4 Hz, H-1), 2.58 (ddd, 1H, J = 13.9, 9.6, 5.7 Hz, H-2), 2.74 (dddd, 1H, J =
13.8, 9.6, 5.6, 2.4 Hz, H-2), 2.26 (qd, 2H, J = 7.3, 1.6 Hz, 2H-4'), 2.06 (q, 2H, J = 7.1 Hz, 2H-7'), 1.73 (d, 3H, J = 6.2 Hz, 3H-12'), 1.51-1.45 (m, 2H, 2H-5'), 0.89 (s, 9H, -SiMe2C(CH3)3), 0.17 (s, 3H, -Si(C2H5)2tBu), and 0.14 (s, 3H, -Si(CH3)2'tBu).

HRMS (ESI) Calcd for C26H39NNaO6Si+ (M•Na+): 512.2439, found: 512.2436.

LC/MS: (Method: C8 column, gradient 50-100%, methanol content, 22 min, MW 200-2000, ES+APCI): tR = 10.8 min. (M-H+: 488).

TLC: Rf (4:1 hexanes/EtOAc) = 0.10.

(±)-(2aR,7aS,7bS)-rel-(7Z)-Hexahydro-7-{hydroxy[(1'S,2'S,4'aR,8'aS)-1',2',4'a,5',6',7',8',8'a-octahydro-2'-methyl-1'-naphthalenyl]methylene}-7b-[(tert-butyldimethylsilyl)oxy]-furo[2,3,4-gh]-pyrrolizine-2,6-dione (54a) and (±)-(2aR,7aS,7bS)-rel-(7Z)-Hexahydro-7-{hydroxy[(1'R,2'R,4'aS,8'aR)-1',2',4'a,5',6',7',8',8'a-octahydro-2'-methyl-1'-naphthalenyl]methylene}-7b-[(tert-butyldimethylsilyl)oxy]-furo[2,3,4-gh]-pyrrolizine-2,6-dione (55a). A solution of triene 53a (7 mg, 0.015 mmol) was dissolved in anhydrous DMSO-d6 (0.7 mL), and the resulting mixture was heated at 55 °C over 7 days. The progress of the reaction and the ratio of the formed products were closely followed by 1H NMR spectroscopy. Upon complete conversion of 53a, compounds 54a and 55a were formed in 1.2:1 ratio.

54a and 55a (both isomers):

1H NMR (500 MHz, CDCl3): δ 11.90 (br s, 1H), 11.61 (br s, 1H), 5.55 (ddd, 1H, J = 10.0, 4.4, 2.9 Hz, H-3' of 54a and H-3' of 55a), 5.43 (d, 1H, J = 10.0 Hz, H-4'), 5.39 (d, 1H, J = 9.8 Hz, H-4'), 5.17 (s, 1H, H-7a), 5.15 (s, 1H, H-7a), 3.91 (ddd, 2H, J = 12.6, 9.2, 4.2 Hz, H-4+H-4), 3.36 (ddd, 2H, J = 11.9, 8.2, 7.7 Hz, H-4+H-4), 3.24-3.22 (m,
2H, H-1'±H-1'), 2.66-2.60 (m), 2.48-2.39 (m), 2.37-2.23 (m), 1.78-1.52 (m), 1.48-1.28 (m), 1.11 (s, 18H, 2-SiMe₂C(CH₃)₃), 1.05 (d, 3H, J = 7.1 Hz, CH₃), 1.00 (d, 3H, J = 7.0 Hz, CH₃), 0.10 (s, 3H, -Si(CH₃)₂Bu), 0.09 (s, 3H, -Si(CH₃)₂Bu), 0.06 (s, 3H, -Si(CH₃)₂Bu), and 0.05 (s, 3H, -Si(CH₃)₂Bu).

**HRMS (ESI)** Calcd for C₆₂H₃₉NNaO₅Si+ (M•Na+): 496.2490, found: 496.2523.

**TLC:** Rₜ (6:1 hexanes/EtOAc) = 0.35.

(±)-(2aR,7aS,7bS)-rel-7-Hydroxyhexahydro-7-\{-[(1'S,2'S,4'aR,8'aS)-1',2',4'a,5',6',7',8',8'a-octahydro-2'-methyl-1'-naphthalenyl]carbonyl\}-7b-[(tert-butyldimethylsilyl)oxy]-furo[2,3,4-gh]-pyrrolizine-2,6-dione (236) and (±)-(2aR,7aS,7bS)-rel-7-Hydroxyhexahydro-7-\{-[(1'R,2'R,4'aS,8'aR)-1',2',4'a,5',6',7',8',8'a-octahydro-2'-methyl-1'-naphthalenyl]carbonyl\}-7b-[(tert-butyldimethylsilyl)oxy]-furo[2,3,4-gh]-pyrrolizine-2,6-dione (237). A solution of triene 235 (3 mg, 0.006 mmol) was dissolved in anhydrous DMSO-d₆ (0.7 mL), and the resulting mixture was heated at 90 °C over 4 days. The progress of the reaction and the ratio of the formed products were closely followed by ¹H NMR spectroscopy. Upon complete conversion of 235, compounds 236 and 237 were formed in 1:4 ratio. Chromatography on silica gel (HPLC, normal phase) using 3:1 hexanes/EtOAc as the eluent yielded 0.5 mg of the product 236 and 1 mg of 237.

**236 (minor isomer):**

**¹H NMR** (500 MHz, CDCl₃): δ 5.60 (ddd, 1H, J = 9.9, 4.6, 2.6 Hz, H-3'), 5.36 (dt, 1H, J = 10.3, 2.2 Hz, H-4'), 4.99 (s, 1H, H-7a), 3.99 (ddd, 1H, J = 12.4, 9.4, 5.2 Hz, H-4), 3.36-3.29 (m, 2H, H-1' and H-4), 3.29 (s, 1H, OH), 3.21 (dd, 1H, J = 9.4, 2.3 Hz, H-1), 2.80 (br q, 1H, J = 5.0 Hz, H-2'), 2.58 (ddt, 1H, J = 13.5, 9.6, 4.8 Hz, H-3), 2.42-1.09 (m,
10H), 0.91 (s, 9H, -SiMe2C(CH3)3), 0.89 (nfom, 1H), 0.87 (d, 3H, J = 7.0 Hz, CH3). 0.23 (s, 3H, -Si(CH3)2Bu), and 0.20 (s, 3H, -Si(CH3)2Bu).

**HRMS (ESI)** Calcd for C26H39NNaO6Si+ (M•Na+): 512.2439, found: 512.2427.

**TLC:** Rf (3:1 hexanes/EtOAc) = 0.31.

**237** (major diastereomer):

**1H NMR** (500 MHz, CDCl3): δ 5.54 (ddd, 1H, J = 9.8, 1.7 Hz, H-4'), 5.09 (s, 1H, H-7a), 4.03 (ddd, 1H, J = 12.1, 6.7 Hz, H-4), 3.41 (dd, 1H, J = 11.4, 0.8 Hz, H-1'), 3.32 (s, 1H, OH), 3.31 (ddd, 1H, J = 12.6, 9.2, 6.2 Hz, H-4), 3.23 (dd, 1H, J = 9.7, 2.7 Hz, H-1), 2.80 (br q, 1H, J = 5.0 Hz, H-2'), 2.58 (ddt, 1H, J = 13.5, 9.6, 4.8 Hz, H-3), 2.42 (ddd, 1H, J = 14.1, 9.3, 6.3, 2.8 Hz, H-3), 1.72 (m, 3H), 1.65 (m, 1H), 1.55 (m, 1H), 1.53 (ddd, 1H, J = 11, 11, 11, 2.9 Hz, H-8'a), 1.27 (m, 2H), 1.09 (br ddd, 1H, J = 12, 12, Hz, H-5'a), 0.94 (s, 9H, -SiMe2C(CH3)3), 0.89 (nfom, 1H), 0.86 (d, 3H, J = 7.0 Hz, CH3). 0.26 (s, 3H, -Si(CH3)2Bu), and 0.18 (s, 3H, -Si(CH3)2Bu).

**HRMS (ESI)** Calcd for C26H39NNaO6Si+ (M•Na+): 512.2439, found: 512.2424.

**TLC:** Rf (3:1 hexanes/EtOAc) = 0.32.

(±)-(1R,6R,7S,7aR)-(7Z)-Hexahydro-7-[(1'E,7'E,9'E)-1',7',9'-undecatrienyl]-7b-hydroxy-furo[2,3,4-gh]pyrrolizine-2,6-dione (45). To HF•pyridine (70% HF, 30% pyridine, 4 drops) in a polyethylene tube MeCN (0.5 mL) and then pyridine (200 µL) were added. To this mixture tetraene 53a (40 mg, 0.085 mmol) in MeCN (1.0
mL) was added. The resulting mixture was stirred for ca. 48 h at room temperature. The progress of the reaction was closely followed by LC-MS [C₈, 2.1x150 mm, 5 µm, 0.5 mL/min, water/MeOH 50-100%, methanol content, the best ionization was in ESI-Neg, (M-H)⁻ ion, ret.time=7.4 min], the completion of the reaction was judged by disappearance of the starting material. The reaction partitioned between water (5.0 mL) and DCM (10 mL). The aqueous layer was extracted with DCM (3 x 5.0 mL). The combined organic layers were dried over Na₂SO₄, evaporated, and filtered through a plug of silica gel (~1.5 cm tall) using EtOAc as the eluent. Evaporation provided tetraene 45 (27 mg, 0.076 mmol, 90%) as a pale yellow oil. Since the triene 45 is relatively unstable, i.e., it undergoes the IMDA cyclization at rt, it was used in IMDA experiments right away or over the next 2-3 days, during which 45 was stored in a freezer at -20 °C.

The compound 45:

H NMR (500 MHz, CDCl₃): δ. δ 7.27 (dt, 1H, J = 15.9, 6.9 Hz, H-2'), 6.29 (d, 1H, J = 15.9 Hz, H-1'), 6.01 (m, 2H, H-8', H-9'), 5.59 (dt, 1H, J = 13.6, 6.7 Hz, H-7'), 5.52 (dq, 1H, J = 14.1, 6.9 Hz, H-10'), 4.89 (s, 1H, H-7), 4.68 (br s, 1H, C7a-OH), 4.34 (s, 1H, H-6), 3.83 (ddd, 1H, J = 12.0, 9.4, 5.6 Hz, H-4), 3.33 (ddd, 1H, J = 12.0, 9.8, 5.2 Hz, H-4), 3.28 (dd, 1H, J = 9.4, 1.7 Hz, H-2a), 2.75 (dddd, 1H, J = 14, 9.7, 9.7, 5.6 Hz, H-3), 2.58 (dddd, 1H, J = 14, 9.3, 5.2, 1.9 Hz, H-2), 2.36 (dt, 2H, J = 7, 7 Hz, 2H-3'), 2.08 (dt, 2H, J = 7, 7 Hz, 2H-6'), 1.73 (d, 3H, J = 6.4 Hz, 3H-11'), 1.54 (m, 2H, 2H-4'), and 1.44 (m, 2H, 2H-5').

LC/MS: (Method: C₈ column, gradient 50-100%, methanol content, 22 min, MW 200-2000, negative ES): tᵣ = 3.96 min. (M-H⁻: 358).

TLC: Rf (1:1 hexanes/EtOAc) = 0.22.

(±)-UCS1025A (1) and (±)-9,10,15,18-tetraepi-UCS1025A (56)

Examples of IMDA conditions:

A. pH 7.4 phosphate buffer:

To a solution of 45 (10 mg, 0.028 mmol) in CD₃CN (0.1 mL) pH 7.4 phosphate buffer
(0.1 mM in D₂O, 0.5 mL) was added. Progress of the reaction was monitored by ¹H NMR spectroscopy. In 10 min all of the lactone 45 was transformed into 45c (an open-form, carboxylate), which underwent the IMDA reaction with $t_{1/2} \sim 10$ min to produce 1 and 56 in a 1:1 ratio. The reaction was kept at rt for 2 h, the complete disappearance of the starting material was observed (at reaction times of $>3$ h the side-reaction, the formation of a hydration products, was observed at the expense of both 1 and 56). Then the reaction was partitioned between brine (1.0 mL) and DCM (5 mL). The aqueous layer was extracted with DCM (3 x 5.0 mL). The combined organic layers were dried over Na₂SO₄ and evaporated, providing a mixture of 1 and 56 (9 mg, 0.025 mmol, 90%), which could be separated by normal-phase HPLC, using 2:1 hexanes/EtOAc as the eluent.

B. pH 7.4 Tris buffer:

To a solution of 45 (10 mg, 0.028 mmol) in CD₃CN (0.1 mL) pH 7.4 Tris buffer (0.1 mM in D₂O, 0.5 mL) was added. Progress of the reaction was monitored by ¹H NMR spectroscopy. In 10 min all of the lactone 45 was transformed into 45c (an open-form, carboxylate), which underwent the IMDA cycloaddition with $t_{1/2} \sim 20$ min to produce 1 and 56 in a 1.5:1 ratio. The reaction was kept at rt for 2 h, the complete disappearance of the starting material was observed (at reaction times of $>3$ h the side-reaction, the formation of a hydration products, was observed at the expense of both 1 and 56). Then the reaction was partitioned between brine (1.0 mL) and DCM (5 mL). The aqueous layer was extracted with DCM (3 x 5.0 mL). The combined organic layers were dried over Na₂SO₄ and evaporated, providing a mixture of 1 and 56 (9 mg, 0.025 mmol, 90%).

C. BF₃•OEt₂:

To a solution of 45 (10 mg, 0.028 mmol) in CD₂Cl₂ (0.6 mL) neat BF₃•OEt₂ (10 µL, 0.08 mmol) was added. Progress of the reaction was monitored by ¹H NMR spectroscopy. In 2 h all of the lactone 45 underwent the IMDA reaction to produce 1 and 56 in a 2.3:1 ratio with $t_{1/2} \sim 20$ min. Then the reaction was partitioned between pH 7.0 buffer (1.0 mL)
and DCM (5 mL). The aqueous layer was extracted with DCM (3 x 5.0 mL). The combined organic layers were dried over Na$_2$SO$_4$ and evaporated, providing a mixture of 1 and 56 (9 mg, 0.025 mmol, 90%). Sometimes upon work up some of 1 and 56 enol-forms formed, for the correct estimation of the reaction diastereoselectivity the mixture of 1a, 1b, 56a, and 56b is equilibrated into 1a and 56a by heating in CDCl$_3$ at 40 °C for 24 h.

D. MgCl$_2$:

To a solution of 45 (10 mg, 0.028 mmol) in CDCl$_3$ (0.6 mL) solid MgCl$_2$ (6 mg, 0.06 mmol) was added. Progress of the reaction was monitored by $^1$H NMR spectroscopy. In 72 h all of the lactone 45 underwent the IMDA cycloaddition to produce 1 and 56 in a 1:5 ratio with $t_{1/2}$ ~15 h. Then the reaction was partitioned between pH 7.0 buffer (1.0 mL) and DCM (5 mL). The aqueous layer was extracted with DCM (3 x 5.0 mL). The combined organic layers were dried over Na$_2$SO$_4$ and evaporated, providing a mixture of 1 and 55 (9 mg, 0.025 mmol, 90%).

UCS1025A (1) (keto-form):

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 5.59 (ddd, 1H, $J$ = 9.6, 4.5, 2.4 Hz, H-17), 5.41 (br d, 1H, $J$ = 9.7 Hz, H-16), 4.74 (s, 1H, H-7a), 4.73 (s, 1H, OH), 4.07 (s, 1H, H-7), 3.84 (ddd, $J$ = 12.1, 9.6, 5.7 Hz, Ha4), 3.37 (ddd, 1H, $J$ = 12.0, 10.0, 5.2 Hz, Hb4), 3.26 (dd, 1H, $J$ = 9.3, 1.6 Hz, H-2a), 3.18 (dd, 1H, $J$ = 11.2, 5.4 Hz, H-9), 2.92 (br q, $J$ = 6 Hz, H-18), 2.74 (ddddd, $J$ = 14.8, 9.8, 9.8, 5.7 Hz, Ha3), 2.57 (ddddd, $J$ = 14.2, 9.3, 5.1, 2.1 Hz, Hb3), 1.77 (m, 5H), 1.53 (ddddd, $J$ = 11, 11, 11, 2.5 Hz, H-10), 1.34 (m, 2H), 1.09 (br ddd, 1H, $J$ = 12, 12, 12 Hz, H-14), 0.89 (nfo, 1H), and 0.79 (d, 3H, $J$ = 7.0 Hz, CH$_3$).

$^1$H NMR (500 MHz, C$_6$D$_6$): $\delta$ 5.41 (ddd, 1H, $J$ = 9.9, 4.8, 2.3 Hz, H-17), 5.27 (br d, 1H, $J$ = 9.8 Hz, H-16), 4.71 (s, 1H, H-7a), 4.11 (s, 1H, H-7), 3.70 (s, 1H, OH), 3.44 (ddd, $J$ = 11.9, 9.2, 6.0 Hz, Ha4), 2.93 (br q, $J$ = 6 Hz, H-18), 2.70 (ddd, 1H, $J$ = 12.0, 9.8, 4.9 Hz, Hb4), 2.62 (dd, 1H, $J$ = 9.3, 2.2 Hz, H-2a), 2.57 (dd, 1H, $J$ = 10.8, 5.5 Hz, H-9), 2.02 (ddddd, $J$ = 14.0, 9.3, 4.9, 2.0 Hz, Hb3), 1.87 (dtd, $J$ = 13.7, 9.6, 6.0 Hz, Ha3), 1.69-1.54
(m, 4H), 1.45 (dt, 1H, J = 8.8, 2.5 Hz), 1.43 (m, 1H), 1.23-1.09 (m, 2H), 1.18 (br ddd, 1H, J = 12, 12, 12 Hz, H-14), 0.88 (nfom, 1H), and 0.83 (d, 3H, J = 7.0 Hz, CH-CH3).

\(^{13}\)C-NMR (125 MHz, CDCl3): δ 209.1 (C8), 174.8 (C2), 167.1 (C6), 130.8 (C16), 130.6 (C17), 101.2 (C7b), 80.4 (C7a), 66.7, 59.0, 47.9, 42.4, 42.0, 36.9, 33.0, 30.3, 30.2, 30.1, 26.73, 26.66, and 17.8.

IR (thin film) 3197 (br), 3026, 3013, 2975, 2952, 2919, 2881, 2852, 2830, 1787, 1711, 1665, 1450, 1379, 1337, 1280, 1253, 1172, 1160, 1138, 1113, and 1020.

HRMS (ESI) Calcd for C\(_{26}\)H\(_{39}\)NNaO\(_5\)Si\(^+\) (M•Na\(^+\)): 382.1630, found: 382.1640.

TLC: R\(_f\) (1:1 hexanes/EtOAc) = 0.30.

\((\pm)-9,10,15,18\)-tetraepi-UCS1025A (56) (keto-form):

\(^1\)H NMR (500 MHz, CDCl3): δ 5.58 (ddd, 1H, J = 9.8, 4.5, 2.6 Hz, H-17), 5.45 (br d, 1H, J = 9.9 Hz, H-16), 4.81 (s, 1H, H-7a), 4.72 (br s, 1H, O\(_H\)), 4.10 (s, 1H, H-7), 3.84 (ddd, J = 1H, J = 11.9, 9.8, 5.4 Hz, H\(_a\)4), 3.36 (ddd, 1H, J = 11.9, 9.8, 5.4 Hz, H\(_b\)4), 3.29 (dd, 1H, J = 11.0, 5.8 Hz, H-9), 3.28 (dd, 1H, J = 9.2, 2.1 Hz, H-2a), 2.75 (dddd, 1H, J = 15.0, 9.7, 9.7, 5.5 Hz, H\(_a\)3), 2.73 (m, 1H, H-18), 2.56 (dddd, 1H, J = 14.0, 9.2, 5.0, 2.0 Hz, H\(_b\)3), 1.73 (m, 5H), 1.46 (dddd, 1H, J = 11, 11, 11, 2.4 Hz, H-10), 1.30 (m, 2H, H\(_{ax}\)12 and H\(_{ax}\)13), 1.08 (m, 1H, H\(_{ax}\)14), and 0.84 (d, 3H, J = 7.0 Hz, CH\(_3\)).

\(^{13}\)C-NMR (125 MHz, CDCl3): δ 208.4 (C8), 174.9 (C2), 166.9 (C6), 132.0 (C16), 129.8 (C17), 101.1 (C7b), 80.3 (C7a), 65.4 (C7), 56.3 (C9), 48.5 (C2a), 42.1 (C4), 41.7 (C15), 35.8 (C10), 33.1 (C14), 31.2 (C18), 30.2 (C3), 29.1 (C11), 26.6 (C13), 26.5 (C12), and 18.8 (C19).

IR (thin film) 3450 (br), 3007, 2966, 2929, 2854, 1792, 1720, 1699, 1425, 1342, 1287, 1252, 1167, 1120, 1096, and 1020.

HRMS (ESI) Calcd for C\(_{26}\)H\(_{39}\)NNaO\(_5\)Si\(^+\) (M•Na\(^+\)): 382.1630, found: 382.1624.

TLC: R\(_f\) (1:1 hexanes/EtOAc) = 0.35.
Table 14. $^1$H NMR Spectral Data of UCS1025A and tetraepi-UCS1025A [C$_6$D$_6$, 500 MHz, referenced to benzene peak at 7.16 ppm].

| Atom number | UCS1025A (I) | | | 9,10,15,18-tetraepi-UCS1025A (56) | | |
|-------------|---------------|---------------|---------------|---------------|---------------|
|             | $\delta$H  | mult | $J$ Hz | $\delta$H  | mult | $J$ Hz |
| 2a          | 2.62         | dd   | 9.2, 2.0 | 2.66         | dd   | 9.3, 2.2 |
| 3           | 2.02         | dddd | 14.1, 9.5, 5.1, 2.1 | 2.02 | dddd | 14.1, 9.3, 5.1, 2.1 |
|             | 1.86         | dddd | 13.9, 9.7, 9.7, 6.1 | 1.87 | dddd | 13.6, 9.6, 9.6, 5.8 |
| 4           | 3.44         | ddd  | 12.0, 9.3, 6.1 | 3.44 | ddd  | 12.0, 9.4, 5.9 |
|             | 2.71         | ddd  | 11.9, 9.8, 4.8 | 2.71 | ddd  | 12.0, 9.8, 5.9 |
| 7           | 3.70         | s    |         | 3.87         | s    |         |
| 7a          | 4.12         | s    |         | 4.23         | s    |         |
| 9           | 2.57         | ddd  | 10.9, 5.5 | 3.16 | dd   | 10.8, 5.9 |
| 10          | 1.44         | m    |         | 1.44         | ddd  | 11, 11, 2.6 |
| 11ax        | 0.44         | m    |         | 0.77         | dddd | 12.8, 12.8, 12.8, 3.6 |
| 11eq        | 1.67         | m    |         | 1.84         | m    |         |
| 12ax        | 1.17         | m    |         | 1.15         | ddddd | 13.3, 13.3, 13.3, 3.6, 3.6 |
| 12eq        | 1.61         | m    |         | 1.52         | m    |         |
| 13ax        | 1.17         | m    |         | 1.05         | dddddd | 12.9, 12.9, 12.9, 3.9, 3.9 |
| 13eq        | 1.61         | m    |         | 1.49         | m    |         |
| 14ax        | 0.95         | m    |         | 0.91         | dddd | 13, 13, 13, 3 |
| 14eq        | 1.55         | m    |         | 1.52         | m    |         |
| 15          | 1.44         | m    |         | 1.43         | m    |         |
| 16          | 5.27         | brd  | 9.5     | 5.29         | brd  | 10.2    |
| 17          | 5.41         | ddd  | 10.0, 4.6, 2.0 | 5.32 | ddd  | 9.8, 3.9, 1.9 |
| 18          | 2.93         | brq  | 6.7     | 1.99         | brq  | 7       |
| 18-Me       | 0.83         | d    | 7.0     | 0.57         | d    | 7.1     |
| 7b-OH       | 4.71         | s    |         | 4.72         | s    |         |
(−)-(4S)-4-Methyl-6-heptyn-1-ol (311a). Alkene 310 (3.900 g, 0.026 mol) was dissolved in DCM (70.0 mL), and pyridine (3.13 mL, 0.039 mol) was added to the solution. The reaction mixture was cooled to −78 °C, and ozone was sparged through the solution using a pipette tip. The reaction was closely monitored by TLC for complete consumption of the starting material 310 (ca. 40 min). Oxygen was sparged through the solution for 5 min to remove any residual ozone in the reaction mixture. Solid NaBH₄ (3.952 g, 0.104 mol) was added portionwise to the reaction mixture at −78 °C. The reaction mixture was diluted with MeOH (70 mL), warmed to room temperature over 2 h, stirred for 12 h, concentrated in vacuo, and partitioned between Et₂O/water. The organic layer was separated, and the aqueous layer was extracted with ether (3 x 40 mL). All organic layers were combined, washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo. Flash chromatography (3:1 hexanes/EtOAc) afforded alcohol 311a (2.687 g, 82%) as a colorless oil.

[α]D²⁵ −1.8° (c = 0.82 g/100 mL, CHCl₃)

1H NMR (500 MHz, CDCl₃): δ 3.65 (t, 2H, J = 6.6 Hz, 2H-1), 2.19 (ddd, 1H, J = 16.7, 5.9, 2.7 Hz, H-5), 2.11 (ddd, 1H, J = 16.7, 6.7, 2.7 Hz, H-5), 1.97 (t, 1H, J = 2.7 Hz, H-7), 1.68 (app octet, 1H, J = 6.5 Hz, H-4), 1.63-1.50 (m, 2H, 2H-2), 1.50 (m, 1H, H-3), 1.29 (dddd, 1H, J = 13.0, 10.0, 7.7, 5.3 Hz, H-3), 1.26 (br s, 1H, OH), and 1.01 (d, 3H, J = 6.7 Hz, C4-C₃H₃).

13C NMR (75 MHz, CDCl₃): δ 83.3, 69.4, 63.1, 32.3, 32.0, 30.4, 25.8, and 19.5.

IR (thin film) 3307, 2957, 2937, 2874, 21051459, 1429, 1380, 1256, 1058, and 630.

GC/MS (5029021): tᵣ = 5.50 min; m/z 126 (5, M⁺), 111 (10, M⁺-Me), 93 (30), and 69 (100).

TLC: Rf (6:1 hexanes/EtOAc) = 0.15.
(+)-(4S)-(tert-Butyldimethyl)silyl-4-methyl-6-heptyl-1-ol (311b) and (−)-(4S)-(Triethyl)silyl-4-methyl-6-heptyl-1-ol (311c). Alcohol 311a (143 mg, 1.135 mmol) was dissolved in DCM (4.0 mL), and imidazole (154 mg, 2.27 mmol) followed by corresponding silyl chloride (1.703 mmol) were added to the solution at 0 °C. The reaction mixture was warmed up to room temperature over 1 h, stirred for 16 h at ambient temperature, diluted with ether, washed with water. The organic layer was separated, and the aqueous layer was extracted back with ether (3 x 10.0 mL). All organic layers were combined, washed with brine (1 x 5.0 mL), dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo. Chromatography on silica gel (MPLC) using 99:1 hexanes/EtOAc as the eluent yielded the corresponding silyl ether as a colorless oil.

311b (272 mg, 99% yield):

$[\alpha]_{25}^D$ +0.82° (c = 0.092 g/mL, CHCl$_3$)

$^1$H NMR (500 MHz, CDCl$_3$): δ 3.60 (t, 2H, $J = 6.5$ Hz, 2H-1), 2.18 (ddd, 1H, $J = 16.7$, 5.7, 2.7 Hz, H-5), 2.09 (ddd, 1H, $J = 16.7$, 6.9, 2.7 Hz, H-5), 1.95 (dd, 1H, $J = 2.7$, 2.6 Hz, H-7), 1.68 (app octet, 1H, $J = 6.9$ Hz, H-4), 1.60-1.42 (m, 3H, 2H-2, H-3), 1.24 (ddddd, 1H, $J = 13.0$, 10.4, 7.8, 5.4 Hz, H-3), 1.00 (d, 3H, $J = 6.7$ Hz, C4-CH$_3$), 1.37 (s, 9H, -OSiMe$_2$C(CH$_3$)$_3$), and 0.05 (s, 6H, -OSi(CH$_3$)$_2$-tBu).

$^{13}$C NMR (75 MHz, CDCl$_3$): δ 83.5, 69.3, 63.6, 32.4, 32.2, 30.6, 26.2, 26.0, 19.6, 18.6, and -5.1.

IR (thin film) 3314, 2956, 2930, 2858, 1472, 1463, 1388, 1256, 1103, 836, 775, and 628.

HRMS (ESI) Calcd for C$_{14}$H$_{28}$NaOSi$^+$ (M•Na$^+$): 263.1802, found: 263.1756

GC/MS (5029021): $t_r$ = 7.88 min; $m/z$ 225 (5, M$^+$-Me), 183 (40, M$^+$-tBu), and 75 (100).

TLC: R$_f$ (20:1 hexanes/EtOAc) = 0.40.

311c (270 mg, 98% yield):
\( ^1H \) NMR (500 MHz, CDCl\(_3\)): \( \delta \) 3.60 (t, 2H, \( J = 6.8 \) Hz, 2H-1), 2.18 (ddd, 1H, \( J = 16.6, 5.7, 2.7 \) Hz, H-5), 2.09 (ddd, 1H, \( J = 16.7, 7.0, 2.7 \) Hz, H-5), 1.95 (dd, 1H, \( J = 2.7, 2.6 \) Hz, H-7), 1.68 (app oct, 1H, \( J = 6.6 \) Hz, H-4), 1.60-1.45 (m, 2H, 2H-2), 1.45 (dddd, 1H, \( J = 11.0, 9.0, 5.6, 5.6 \) Hz, H-3), 1.24 (dddd, 1H, \( J = 13.0, 10.0, 7.5, 5.4 \) Hz, H-3), 1.00 (d, 3H, \( J = 6.7 \) Hz, C4-CH\(_3\)), 1.96 (t, 9H, \( J = 8.0 \) Hz, -OSi(CH\(_2\)CH\(_3\))\(_3\)), and 0.60 (t, 6H, \( J = 8.0 \) Hz, -OSi(CH\(_2\)CH\(_3\))\(_3\)).

HRMS (ESI) Calcd for C\(_{14}H_{28}\)NaOSi\(^+\) (M\(^+\)Na\(^+\)): 263.1802, found: 263.1767.

TLC: \( R_f \) (99:1 hexanes/EtOAc) = 0.35.

\[ \text{311a-c} \]
\[ \text{312a-c} \]

\(+\)-(4S)-(6E)-7-Iodo-4,6-dimethyl-6-hepten-1-ol \( (312a) \), \(+\)-(4S)-(6E)-(tert-Butyldimethyl)silyl-7-iodo-4,6-dimethyl-6-hepten-1-ol \( (312b) \), and \(+\)-(4S)-(6E)-(Triethyl)silyl-7-iodo-4,6-dimethyl-6-hepten-1-ol \( (312c) \). To a solution of Cp\(_2\)ZrCl\(_2\) (262 mg, 0.897 mmol) in Cl(CH\(_2\))\(_2\)Cl (5.0 mL) was added AlMe\(_3\) (1.61 mL, 2.90 mmol, 1.8 M in toluene). This mixture was stirred for 40 min at room temperature, then corresponding alkyne \( 311a-c \) (0.69 mmol) in Cl(CH\(_2\))\(_2\)Cl (1.5 mL) was added to the reaction mixture. The resulting solution was heated at 60 °C for 14 h, then cooled to -50 °C. A solution of iodine (561 mg, 2.210 mmol) in THF (2.0 mL) was added, and the resulting dark solution was stirred for 1 h at -50 °C, warmed up to 0 °C, and stirred for 1 h. The reaction mixture was quenched with saturated solution of K\(_2\)CO\(_3\), the formed solids were filtered off and thoroughly washed with ether. The resulting ether filtrate was washed with aqueous saturated solution of Na\(_2\)S\(_2\)O\(_3\) (1 x 10 mL), aqueous saturated solution of NaHCO\(_3\) (1 x 10 mL), and brine, dried over Na\(_2\)SO\(_4\), filtered, and concentrated in vacuo.

\( 312a \): The crude product was purified by chromatography (MPLC) using 4:1 hexanes/EtOAc as the eluent to afford iodide \( 312a \) (75% yield) as a light yellow oil.
[α]$_D^{25}$ +3.2° (c = 0.092 g/mL, CHCl$_3$)

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.54 (q, 1H, $J = 1.2$ Hz, H-7), 5.64 (td, 2H, $J = 6.6$, 3.2 Hz, 2H-1), 2.15 (dd, 1H, $J = 13.6$, 6.3 Hz, H-5), 2.02 (dd, 1H, $J = 13.5$, 8.3 Hz, H-5), 1.80 (d, 3H, $J = 0.9$ Hz, 3H-6), 1.65 (pentetdd, 1H, $J = 6.0$, 3.3, 2.9 Hz, H-2), 1.60 (dd, 1H, $J = 13.6$, 6.0 Hz, H-4), 1.52 (qd, 1H, $J = 6.6$, 5.2 Hz, H-2), 1.35 (ddt, 1H, $J = 13.4$, 10.7, 5.3 Hz, H-3), 1.23 (br t, 1H, $J = 4.0$ Hz, OH), 1.14 (dddd, 1H, $J = 13.3$, 10.9, 8.1, 5.2 Hz, H-3), and 0.84 (d, 3H, $J = 6.6$ Hz, C4-C$_3$).

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 151.8, 75.5, 63.2, 47.6, 32.8, 30.9, 30.3, 23.9, and 19.5.

IR (thin film) 3324, 2952, 2931, 2871, 1457, 1377, 1272, 1143, 1058, 762, and 668.

GC/MS (5027016): $t_r = 8.88$ min; $m/z$ 268 (5, M$^+$), 253 (5, M$^+$-Me), 208 (15), 182 (40), 85 (100), and 69 (90).

TLC: $R_f$ (4:1 hexanes/EtOAc) = 0.20.

312b: The crude product was purified by chromatography (MPLC) using 90:1 hexanes/EtOAc as the eluent to afford iodide 312b (88% yield) as a light yellow oil.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 5.83 (s, 1H, H-7), 3.58 (t, 2H, $J = 6.6$ Hz, 2H-1), 2.00 (dd, 1H, $J = 13.4$, 8.3 Hz, H-5), 1.80 (d, 3H, $J = 1.2$ Hz, 3H-6), 1.63 (tdd, 1H, $J = 10.6$, 6.5, 2.3, 2.3 Hz, H-2), 1.55 (qpent, 1H, $J = 6.5$, 6.2 Hz, H-4), 1.48 (dddd, 1H, $J = 10.6$, 6.7, 5.2, 2.6, 1.3 Hz, H-2), 1.32 (ddt, 1H, $J = 13.3$, 10.7, 5.2 Hz, H-3), 1.08 (dddd, 1H, $J = 13.3$, 10.7, 8.0, 5.2 Hz, H-3), 0.90 (s, 9H, -OSiMe$_2$C(CH$_3$)$_3$), 0.82 (d, 3H, $J = 6.6$ Hz, C4-C$_3$), and 0.05 (s, 6H, -OSi(CH$_3$)$_2$Bu).

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 147.8, 75.4, 63.6, 47.8, 32.9, 31.0, 30.5, 26.2, 19.5, 18.6, and -5.0.

IR (thin film) 2953, 2927, 2855, 1471, 1462, 1377, 1255, 1101, 835, 774, and 667.

GC/MS (5029021H): $t_r = 10.56$ min; $m/z$ 367 (5, M$^+$-Me), 325 (100, M$^+$-t-Bu), and 185 (50).

TLC: $R_f$ (90:1 hexanes/EtOAc) = 0.40.

312c: The crude product was purified by chromatography (MPLC) using 90:1 hexanes/EtOAc as the eluent to afford iodide 312c (143 mg, 53% yield) as a light yellow oil.

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$[\alpha]^2_D + 2.5^\circ$ (c = 0.362 g/100 mL, CHCl$_3$).

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 5.83 (s, 1H, H-7), 3.58 (t, 2H, $J = 6.7$ Hz, 2H-1), 2.20 (dd, 1H, $J = 13.5$, 6.2 Hz, H-5), 2.00 (dd, 1H, $J = 13.5$, 9.0 Hz, H-5), 1.80 (d, 3H, $J = 1.0$ Hz, 3H-6), 1.63 (tt, 1H, $J = 6.5$, 6.4, 1.5 Hz, H-2), 1.54 (qpent, 1H, $J = 6.5$, 6.0 Hz, H-4), 1.48 (qd, 1H, $J = 6.7$, 5.1 Hz, H-2), 1.32 (ddt, 1H, $J = 13.3$, 10.9, 5.2 Hz, H-3), 0.96 (t, 9H, $J = 7.9$ Hz, -OSi(CH$_2$CH$_3$)$_3$), 0.82 (d, 3H, $J = 6.6$ Hz, C$_4$-C$_3$H$_3$), and 0.60 (q, 6H, $J = 8.0$ Hz, -OSi(CH$_2$CH$_3$)$_3$).

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 147.4, 75.5, 63.3, 47.7, 32.9, 31.1, 30.5, 23.9, 19.5, 7.0, and 4.6.

IR (thin film) 2953, 2914, 2875, 1457, 1377, 1272, 1239, 1143, 1049, 1016, 797, 742, and 668.

GC/MS (5029021): $t_r = 11.25$ min; $m/z$ 382 (5, M$^+$), 353 (100, M$^+$-Et), 213 (80), and 123 (100).

TLC: $R_f$ (90:1 hexanes/EtOAc) = 0.40.

(+)-(4S)-(6E,8E)-4,6,8-trimethyl-8,6-decadien-1-ol (319a), (+)-(4S)-(6E,8E)-(tert-Butyldimethyl)silyl-4,6,8-trimethyl-6,8-decadien-1-ol (319b), and (−)-(4S)-4,6-dimethyl-6-hepten-1-ol (320a). A solution of iodide 312 (0.182 mmol), stannane 318 (45 mg, 0.258 mmol), Cul (6 mg, 0.029 mmol), BHT (1 mg), CsF (70 mg, 0.458 mmol), and Pd(PPh$_3$)$_4$ (21 mg, 0.018 mmol) in DMF (1.5 mL) was stirred at 45 °C for 1.5 h. The reaction mixture was taken up in water (10 mL) and Et$_2$O (2 x 10 mL). The two layers were separated, the aqueous layer was extracted back with ether (3 x 5 mL). All organic layers were combined, washed with water and brine, dried over MgSO$_4$, filtered, and concentrated in vacuo.
**319a and 320a:** The crude was subjected to chromatography on silica gel (MPLC) using 3:1 hexanes/EtOAc as the eluent, which yielded 25 mg (70% yield) of product 319a and 3 mg (10% yield) of the by-product 320a as colorless oils.

**319a:**
\[ [\alpha]_{D}^{25} +7.1^\circ \ (c = 0.421 \text{ g/100 mL, CHCl}_3) \]

**\( ^1\text{H NMR} \) (500 MHz, CDCl\(_3\)):** δ 5.60 (s, 1H, H-7), 5.32 (br q, 1H, J = 6.9 Hz, H-9), 3.63 (q, 2H, J = 6.3 Hz, 2H-1), 2.04 (dd, 1H, J = 12.9, 6.0 Hz, H-5), 1.80 (dd, 1H, J = 13.1, 8.3 Hz, H-5), 1.71 (s, 6H, C6-C\(_3\)H\(_3\), C8-C\(_3\)H\(_3\)), 1.67 (d, 3H, J = 7.1 Hz, 3H-10), 1.63 (sextetd, 1H, J = 6.6, 2.5, 1.5 Hz, H-2), 1.59-1.50 (m, 2H, H-4, H-2), 1.36 (ddt, 1H, J = 13.3, 10.9, 5.8 Hz, H-3), 1.20 (t, 1H, J = 5.6 Hz, O\( \text{H} \)), 1.14 (ddddd, 1H, J = 13.4, 10.8, 8.2, 5.2 Hz, H-3), and 0.85 (d, 3H, J = 6.5 Hz, C4-C\(_3\)H\(_3\)).

**\( ^{13}\text{C NMR} \) (125 MHz, CDCl\(_3\)):** δ 134.2, 133.9, 130.6, 123.3, 63.6, 48.9, 32.9, 31.0, 30.5, 19.6, 17.9, 17.0, and 13.8.

**IR** (thin film) 3339, 2961, 2872, 1456, 1377, 1058, 1035, and 888.

**GC/MS** (5029021H): t\(_r\) = 8.58 min; m/z 196 (35, M\(^+\)), 137 (60), 109 (90), 95 (100), and 67 (100).

**TLC:** R\(_f\) (3:1 hexanes/EtOAc) = 0.30.

**320a:**
\[ [\alpha]_{D}^{25} -0.7^\circ \ (c = 0.271 \text{ g/100 mL, CHCl}_3) \]

**\( ^1\text{H NMR} \) (500 MHz, CDCl\(_3\)):** δ 4.74 (s, 1H, H-7), 4.66 (s, 1H, H-7), 3.64 (t, 2H, J = 6.7 Hz, 2H-1), 2.03 (dd, 1H, J = 13.4, 6.0 Hz, H-5), 1.83 (dd, 1H, J = 13.5, 8.1 Hz, H-5), 1.69 (s, 3H, 3H-6), 1.62 (m, 1H, H-2), 1.54 (dquintet, 1H, J = 10.6, 6.7 Hz, H-2), 1.42-1.34 (m, 2H, H-4, H-3), 1.20 (s, 1H, O\( \text{H} \)), 1.13 (ddddd, 1H, J = 13.2, 10.8, 8.0, 5.1 Hz, H-3), and 0.87 (d, 3H, J = 6.7 Hz, C4-C\(_3\)H\(_3\)).

**\( ^{13}\text{C NMR} \) (125 MHz, CDCl\(_3\)):** δ 144.7, 111.5, 63.3, 46.0, 32.7, 30.5, 30.3, 21.4, and 19.4.

**IR** (thin film) 3339, 2961, 2872, 1456, 1377, 1058, 9667, and 888.

**GC/MS** (5027016): t\(_r\) = 5.77 min; m/z 142 (10, M\(^+\)), 127 (15, M\(^+\)-Me), 190 (30), 83 (70), 69 (100), and 56 (50).

**TLC:** R\(_f\) (3:1 hexanes/EtOAc) = 0.30.
319b and 320b: The crude was subjected to chromatography on silica gel (MPLC) using 50:1 hexanes/EtOAc as the eluent, which yielded 40 mg (70% yield) of product 319b and 5 mg (10% yield) of the by-product 320b as colorless oils.

319b:

$\left[\alpha\right]_{D}^{25} +9.0^\circ$ (c = 0.304 g/100 mL, CHCl$_3$).

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 5.60 (s, 1H, H-7), 5.31 (br q, 1H, J = 7.0 Hz, H-9), 3.59 (t, 2H, J = 6.7 Hz, 2H-1), 2.02 (dd, 1H, J = 13.3, 6.2 Hz, H-5), 1.83 (br s, 3H, C8-CH$_3$), 1.78 (dd, 1H, J = 12.9, 8.5 Hz, H-5), 1.71 (s, 3H, C6-CH$_3$), 1.67 (d, 3H, J = 7.1 Hz, 3H-10), 1.63-1.56 (m, 2H), 1.51-1.44 (m, 2H), 1.33 (ddt, 1H, J = 13.3, 10.5, 5.1 Hz, H-3), 1.08 (dddd, 1H, J = 13.1, 11.0, 7.9, 5.1 Hz, H-3), 0.89 [s, 9H, Si(Me$_2$C(CH$_3$)$_2$)], 0.83 (d, 3H, J = 7.0 Hz, C4-CH$_3$), and 0.08 [s, 6H, Si((CH$_3$)$_2$)Bu]]

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 134.1, 133.7, 130.3, 122.9, 63.6, 48.8, 32.9, 30.8, 30.5, 26.0, 19.5, 18.4, 17.7, 16.8, -2.9, and -5.2.

IR (thin film) 2953, 2930, 2858, 1462, 1377, 1254, 1098, 1005, 938, 837, 775, and 667.

GC/MS (5027016): $t_r = 10.35$ min; m/z 310 (20, M$^+$), 295 (5, M$^+$-Me), 253 (70, M$^+$-Bu), 211 (40), 197 (50), 121 (40), and 75 (100).

TLC: R$_f$ (90:1 hexanes/EtOAc) = 0.40.

TBS-ether 319b can also be converted into alcohol 319a by using the following procedure: Ether 319b (40 mg, 0.129 mmol) was dissolved in THF (2.0 mL), and TBAF (0.5 mL, 1M solution in THF) was added to the solution at room temperature. The reaction mixture was stirred for 10 h at ambient temperature, diluted with ether, washed with washed with saturated solution of NH$_4$Cl, saturated solution of NaHCO$_3$, and brine, dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo. Chromatography on silica gel (MPLC) using 3:1 hexanes/EtOAc as the eluent yielded alcohol 319a (25 mg, 100% yield).
(4S)-(6E,8E)-4,6,8-Trimethyl-6,8-decadienal (321). Alcohol 319a (0.424 g, 2.16 mmol) was dissolved in DCM (80 mL), i-Pr2NEt (6.8 mL, 38.88 mmol) was added to the solution, and the mixture was cooled to 0 °C. In a separate flask, SO3•pyridine complex (2.936 g, 18.47 mmol) was dissolved in DMSO (13 mL). The SO3•pyridine/DMSO solution was added to the reaction mixture dropwise and the cooling bath was removed. The mixture was maintained at ambient temperature for 2 h, and then the reaction was quenched with saturated aqueous solution of NH4Cl. The layers were separated. The aqueous layer was extracted back with DCM (2 x 50.0 mL). All organic layers were combined, washed with water and brine, dried over Na2SO4, filtered, and concentrated in vacuo. Flash chromatography on silica gel using 6:1 hexanes/EtOAc as the eluent yielded 356 mg (85% yield) of aldehyde 321 as a colorless oil.

1H NMR (500 MHz, CDCl3): δ 9.77 (t, 1H, J = 1.8 Hz, H-1), 5.62 (s, 1H, H-7), 5.32 (br q, 1H, J = 6.8 Hz, H-9), 2.45 (qd, 2H, J = 6.2, 2.1 Hz, 2H-1), 2.02 (dd, 1H, J = 12.9, 6.4 Hz, H-5), 1.84 (dd, 1H, J = 13.1, 7.9 Hz, H-5), 1.71 (s, 6H, C6-C6H3, C8-C8H3), 1.67 (d, 3H, J = 7.0 Hz, 3H-10), 1.63-1.46 (m), 1.44-1.37 (m), and 0.85 (d, 3H, J = 6.5 Hz, C4-C4H3).

GC/MS (5029021H): tr = 8.18 min; m/z 194 (30, M+), 165 (45, M+ CHO), 137 (30), 121 (60), 109 (80), and 67 (100).

TLC: Rf (6:1 hexanes/EtOAc) = 0.55.

(+)-(6S)-(2E,8E,10E)-6,8,10-Trimethyl-2,8,10-dodecatrienoic acid ethyl ester (S-3). Aldehyde 321 (1.290 g, 6.65 mmol) was dissolved in toluene (50.0 mL), and Wittig ylide (3.471 g, 9.98 mmol) was added to the solution at 0 °C. The reaction mixture was gradually warmed up to room temperature over 2 h, stirred for 12 h at ambient temperature, concentrated in vacuo, and diluted with 1:3 ether/hexanes. The formed solids were filtered off and thoroughly washed with hexanes, the mother liquor was
concentrated in vacuo producing the crude product. Chromatography on silica gel (MPLC) using 40:1 hexanes/EtOAc as the eluent yielded (1.668 g, 95% yield) of ester S-3 as a colorless oil.

$[\alpha]^{25}_D +11.3^\circ$ (c = 0.310 g/100 mL, CHCl$_3$).

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 6.96 (dt, 1H, $J = 15.6, 7.0$ Hz, H-3), 5.81 (dt, 1H, $J = 15.6, 1.6$ Hz, H-2), 5.60 (br s, 1H, H-9), 5.32 (br q, 1H, $J = 6.9$ Hz, H-11), 4.18 (q, 2H, $J = 7.1$ Hz, CO$_2$CH$_2$Me), 2.26 (qd, 1H, $J = 15.6, 1.6$ Hz, H-7), 1.81 (dd, 1H, $J = 12.5, 8.1$ Hz, H-7), 1.71 (s, 3H, C10-CH$_3$), 1.70 (s, 3H, C8-CH$_3$), 1.68 (d, 3H, $J = 7.8$ Hz, H-12), 1.58 (m), 1.47 (m), 1.36 (dtd, 1H, $J = 13.3, 7.9, 5.5$ Hz, H-5), 1.29 (t, 3H, $J = 7.1$ Hz, CO$_2$CH$_2$CH$_3$), 1.23 (m), 1.14 (m), and 0.85 (d, 3H, $J = 6.6$ Hz, C6-CH$_3$).

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 166.8, 149.6, 133.6, 133.5, 130.6, 123.1, 121.1, 60.1, 48.6, 35.0, 30.5, 29.8, 21.4, 19.3, 17.7, 16.8, 14.3, and 13.6.

IR (thin film) 2955, 2917, 2871, 1722, 1653, 1456, 1368, 1266, 1183, 1166, 1048, 944, and 852.

HRMS (ESI) Calcd for C$_{17}$H$_{28}$NaO$_2$$^+$(M•Na$^+$): 287.1982, found: 287.1945.

GC/MS (5022014): $t_r = 10.66$ min; $m/z$ 264 (15, M$^+$), 249 (5, M$^+$-Me), 235 (15, M$^+$-Et), 207 (25), 191 (40), and 109 (100).

TLC: $R_f$ (20:1 hexanes/EtOAc) = 0.40.

(+)-(6S)-(2E,8E,10E)-6,8,10-Trimethyl-2,8,10-dodecatrien-1-ol (322). Ester S-3 (1.668 g, 6.31 mmol) was dissolved in toluene (23.0 mL). DIBALH (13.3 mL, 1.3 M solution in toluene, 17.29 mmol) was added dropwise to the reaction mixture at 0 °C. The reaction mixture was stirred for 3 h at 0 °C, quenched with 0.2 M aqueous solution of Rochelle salt. The layers were separated. The aqueous layer was extracted back with Et$_2$O (3 x 50.0 mL). All organic layers were combined, washed with saturated solution of NaHCO$_3$ and brine, dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo. Chromatography on silica gel (MPLC) using 5:1 hexanes/EtOAc as the eluent yielded (1.346 g, 96% yield) of alcohol 322 as a colorless oil.

$[\alpha]^{25}_D +11.1^\circ$ (c = 0.396 g/100 mL, CHCl$_3$).
$^1$H NMR (500 MHz, CDCl$_3$): δ 5.72-5.62 (m, 2H, H-2, H-3), 5.60 (br s, 1H, H-9), 5.32 (br q, 1H, $J = 6.8$ Hz, H-11), 4.09 (t, 2H, $J = 5.6$ Hz, 2H-1), 2.12 (qt, 1H, $J = 9.9$, 5.9 Hz, H-4), 2.06-1.99 (m, H-4, H-7), 1.79 (dd, 1H, $J = 13.2$, 8.3 Hz, H-4), 1.72 (s, 6H, C10-CH$_3$), 1.71 (s, 3H, C8-CH$_3$), 1.67 (d, 3H, $J = 7.5$ Hz, 3H-12), 1.66-1.54 (m), 1.40 (ddt, 1H, $J = 13.5$, 9.9, 5.6 Hz, H-5), 1.20 (m), 1.16 (ddt, 1H, $J = 13.3$, 9.9, 7.9, 5.5 Hz, H-5), and 0.83 (d, 3H, $J = 6.6$ Hz, C6-CH$_3$).

$^{13}$C NMR (125 MHz, CDCl$_3$): δ 134.0, 133.7, 133.6, 130.4, 128.8, 123.0, 112, 63.9, 48.7, 36.2, 30.5, 29.8, 19.3, 17.7, 16.8, and 13.6.

IR (thin film) 3325, 2954, 2929, 2869, 1456, 1376, 1088, 1003, 971, and 888.

GC/MS (5027016): t$_r$ = 9.79 min; m/z 222 (20, M$^+$), 207 (20, M$^+$-Me), 191 (40), 137 (45), 121 (430), 109 (100), 95 (70), 81 (60), and 67 (70).

TLC: R$_f$ (5:1 hexanes/EtOAc) = 0.20.

(+)-(6S)-(2E,8E,10E)-6,8,10-Trimethyl-2,8,10-dodecatrienal (308). Alcohol 322 (380 mg, 1.716 mmol) was dissolved in DCM (6.0 mL). Solid MnO$_2$ (3.384 g, 34.32 mmol) was added in four portions at room temperature over 6 h. The reaction mixture was stirred for additional 6 h at room temperature. Upon complete conversion of 322 the reaction mixture was filtered through 3 cm-tall plug of silica gel using DCM (100 mL) as an eluent. The mother liquor was concentrated under reduced pressure, and subjected to chromatography on silica gel using 20:1 hexanes/EtOAc as the eluent yielded 295 mg (78% yield) of aldehyde 308.

[α]$^D$ +11.0° (c = 0.32 g/100 mL, CHCl$_3$).

$^1$H NMR (500 MHz, CDCl$_3$): δ 9.51 (d, 1H, $J = 7.9$ Hz, H-1), 6.85 (dt, 1H, $J = 15.6$, 6.8 Hz, H-3), 6.12 (ddt, 1H, $J = 15.6$, 7.9, 1.4 Hz, H-2), 5.61 (br s, 1H, H-9), 5.32 (br q, 1H, $J = 6.8$ Hz, H-11), 2.41 (m, 1H, H-4), 2.32 (ddt, 1H, $J = 15.5$, 9.6, 6.0 Hz, H-4), 2.03 (dd, 1H, $J = 13.2$, 6.6 Hz, H-7), 1.84 (dd, 1H, $J = 13.2$, 8.0 Hz, H-7), 1.71 (s, 6H, C8-CH$_3$, C10-CH$_3$), 1.67 (d, 3H, $J = 6.8$ Hz, 3H-12), 1.66-1.49 (m), 1.32-1.24 (m), 0.98 (m), and 0.87 (d, 3H, $J = 6.8$ Hz, C6-CH$_3$).

$^{13}$C NMR (125 MHz, CDCl$_3$): δ 194.4, 159.4, 133.5, 133.1, 130.9, 123.5, 112, 48.7, 34.9, 30.8, 30.6, 19.5, 17.9, 17.0, and 13.8.
IR (thin film) 2955, 2925, 2872, 1693, 1377, 1147, 1098, and 978.

GC/MS (5027016): 13.71 (br s, 6H, C8'), 7.4, 5.3 Hz, H1H, 3.10 (d, 1H, J = 6.6 Hz, C(1')OH), 2.61 (dt, 1H, J = 13.1, 9.2, 6.7 Hz, H-2), 2.49 (dddd, 1H, J = 13.7, 8.6, 1.9, 0.8 Hz, H-2'), 2.06 (pentet, 1H, J = 7 Hz, H-4'), 2.01 (tt, 1H, J = 7.4, 5.3 Hz, H-4'), 1.81 (dd, 1H, J = 14, 8 Hz, H-7'), 1.78 (dd, 1H, J = 13.7, 8.2 Hz, H-7'), 1.71 (br s, 6H, C8'-CH3, C10'-CH3), 1.67 (d, 3H, J = 7.8 Hz, H-12'), 1.50-1.43 (m), 1.37-1.36 (m), 1.20-1.14 (m), 0.86 (s, 9H, -SiMe2C(CH3)3), 0.82 (d, 3H, J = 6.6 Hz, C4'-CH3), 0.06 (s, 3H, -Si(CH3)2Bu), and 0.01 (s, 3H, -Si(CH3)2Bu).

HRMS (ESI) Calcd for C30H49NNaO5Si+ (M+Na+): 554.3272, found: 554.3294.

TLC: Rf (4:1 hexanes/EtOAc) = 0.30.
The compound 323b:

$^1$H NMR (500 MHz, CDCl$_3$): δ 6.60 (s, 1H, H-7), 5.80 (dt, 1H, $J = 15.1, 6.5$ Hz, H-3'), 5.60 (br s, 1H, H-9'), 5.53 (dd, 1H, $J = 15.4, 7.4, 1.8$ Hz, H-2'), 5.32 (br q, 1H, $J = 6.5$ Hz, H-11'), 4.89 (dd, 1H, $J = 7.0, 3.9$ Hz, H-1'), 3.78 (dt, 1H, $J = 10.6, 8.9$ Hz, H-3), 3.57 (s, 3H, CO$_2$CH$_3$), 3.28 (ddd, 1H, $J = 11.2, 9.6, 2.3$ Hz, H-3), 3.10 (d, 1H, $J = 7.3$ Hz, C(1')OH), 3.09 (dd, 1H, $J = 8.2, 1.6$ Hz, H-1), 2.61 (ddt, 1H, $J = 13.3, 9.4, 6.8$ Hz, H-2), 2.50 (ddd, 1H, $J = 13.2, 8.3, 2.2, 1.0$ Hz, H-2), 2.12 (m, 1H, H-4'), 2.02 (dq, 1H, $J = 13.2, 6.3$ Hz, H-4'), 1.82 (dd, 1H, $J = 15.2, 8.3$ Hz, H-7'), 1.79 (dd, 1H, $J = 15.0, 8.3$ Hz, H-7'), 1.71 (br s, 6H, C8'-CH$_3$, C10'-CH$_3$), 1.67 (d, 3H, $J = 8.8$ Hz, 3H-12'), 1.65-1.57 (m), 1.44-1.37 (m), 1.17(dtt, 1H, $J = 13.2, 9.2, 4.6$ Hz), 0.86 (s, 9H, -SiMe$_2$C(CH$_3$)$_3$), 0.83 (d, 3H, $J = 6.5$ Hz, C4'-CH$_3$), 0.06 (s, 3H, -Si(CH$_3$)$_2$Bu), and 0.00 (s, 3H, -Si(CH$_3$)$_2$Bu).

HRMS (ESI) Calcd for C$_{32}$H$_{49}$NNaO$_5$Si (M•Na$^+$): 554.3272, found: 554.3287.

TLC: R$_f$ (4:1 hexanes/EtOAc) = 0.20.

(6'S)-(±)-(1R,7aS)-rel-2,3,5,7a-Tetrahydro-6-[(2'F,8'E,10'E)-1'-hydroxy-6',8',10'-trimethyl-2',8',10'-dodecatrien-1'-yl]-5-oxo-7a-[(tert-butylidimethylsilyl)oxy]-1H-pyrrolizine-1-carboxylic acids (324a,b). Acids 324a,b were synthesized analogously to synthesis of acids 234a,b from esters 323a (and/or 323b) (67 mg, 0.125 mmol) as starting materials in 95% yield (>95%) pure by $^1$H NMR as a mixture of the corresponding diastereomers, yellow oil, which was used without any further purification in the next step.

324a: $^1$H NMR (500 MHz, CDCl$_3$): δ 6.63 (s, 1H, H-7), 5.78 (dt, 1H, $J = 14.8, 7.6$ Hz, H-3'), 5.61 (dd, 1H, $J = 14, 7.2$ Hz, H-2'), 5.59 (br s, 1H, H-9'), 5.31 (br q, 1H, $J = 7.3$ Hz, H-11'), 4.83 (d, 1H, $J = 7.1$ Hz, H-1'), 3.77 (dt, 1H, $J = 10, 8.6$ Hz, H-3), 3.28 (ddd,
1H, J = 11.1, 9.6, 2.1 Hz, H-3), 3.11 (dd, 1H, J = 6.0 Hz, H-1), 3.10 (s, 1H, C(1')OH), 2.63 (ddt, 1H, J = 12.9, 8.8, 6.3 Hz, H-2), 2.52 (dddd, 1H, J = 13.6, 8.5, 3.0, 1.2 Hz, H-2), 2.16–2.00 (m, 2H, H-4'), 1.84–1.76 (m, 2H, H-7'), 1.71 (br s, 6H, C8'-CH3, C10'-CH3), 1.67 (d, 3H, J = 7.9 Hz, 3H-12'), 1.60 (m), 1.41-1.38 (m), 0.86 (s, 9H, -SiMe2C(CH3)3), 0.82 (d, 3H, J = 6.5 Hz, C4'-CH3), 0.07 (s, 3H, -Si(CH3)2'Bu), and 0.06 (s, 3H, -Si(CH3)2'Bu).

**LC/MS:** (Method: C8 column, gradient 50-100%, methanol content, 22 min, MW 200-2000, negative ES): tR = 9.86 min. (M-H+: 516).

**324b:** 1H NMR (500 MHz, CDCl3): δ 6.65 (s, 1H, H-7), 5.79 (dt, 1H, J = 15.5, 6.1 Hz, H-3'), 5.63 (dd, 1H, J = 15.2, 6.5 Hz, H-2'), 5.61 (br s, 1H, H-9'), 5.33 (br q, 1H, J = 6.5 Hz, H-11'), 4.85 (d, 1H, J = 7.1 Hz, H-1'), 3.78 (dt, 1H, J = 10.8, 8.9 Hz, H-3), 3.77 (s, 1H, C(1')OH), 3.28 (ddd, 1H, J = 11.5, 9.5, 2.3 Hz, H-3), 3.11 (dd, 1H, J = 6.6 Hz, H-1), 2.64 (ddt, 1H, J = 13.4, 9.3, 6.9 Hz, H-2), 2.53 (dddd, 1H, J = 14, 8.6, 2.3, 1.3 Hz, H-2), 2.17-1.99 (m, 2H, H-4'), 1.80 (dd, 1H, J = 13.3, 8.3 Hz, H-7'), 1.79 (dd, 1H, J = 13, 8 Hz, H-7'), 1.72 (br s, 6H, C8'-CH3, C10'-CH3), 1.68 (d, 3H, J = 7.5 Hz, 3H-12'), 1.66-1.56 (m), 1.44-1.37 (m), 1.21-1.14 (m), 0.87 (s, 9H, -SiMe2C(CH3)3), 0.83 (d, 3H, J = 6 Hz, C4'-CH3), 0.06 (s, 3H, -Si(CH3)2'Bu), and -0.01 (s, 3H, -Si(CH3)2'Bu).

**LC/MS:** (Method: C8 column, gradient 50-100%, methanol content, 22 min, MW 200-2000, negative ES, ES+APCI, APCI): tR = 10.08 min. (M-H+: 514).

(6'S)-(±)-(2aR,7aS,7bS)-(7Z)-Hexahydro-7-[(2'E,8'E,10'E)-1'-hydroxy-6',8',10'-trimethyl-2',8',10'-dodecatrien-1'-ylidene]-7b-[tert-butyldimethylsilyloxy]-furo[2,3,4-gh]pyrrolizine-2,6-dione (325). Enol 325 was synthesized analogously to synthesis of enol 53a from acids 324a (and/or 324b) (50 mg, 0.100 mmol) as starting material in 90% yield (>95% pure by 1H NMR) as a mixture of the corresponding...
diastereomers, yellow oil, which was used without any further purification in the next step.

The compound 325:

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 11.60 (s, 1H, C'1-OH), 6.85 (dt, 1H, $J = 15.4$, 7.2 Hz, H-3'), 6.02 (d, 1H, $J = 15.4$ Hz, H-2'), 5.61 (br s, 1H, H-9'), 5.33 (br q, 1H, $J = 6.8$ Hz, H-9'), 5.21 (s, 1H, H-7), 3.93 (ddd, 1H, $J = 12.7$, 9.0, 4.0 Hz, H-3), 3.35 (dt, 1H, $J = 11.7$, 8.2 Hz, H-3), 3.23 (dd, 1H, $J = 10.0$, 4.4 Hz, H-1), 2.64 (dddd, 1H, $J = 13.8$, 9.9, 8.6, 4.0 Hz, H-2), 2.41 (dddd, 1H, $J = 13.6$, 9.2, 7.4, 4.4 Hz, H-2), 2.33 (dt, 1H, $J = 9.4$, 6.8 Hz, H-4'), 2.33 (dq, 1H, $J = 15$, 6.8 Hz, H-4'), 2.24 (dq, 1H, $J = 15$, 8.1 Hz, H-4'), 2.04 (dd, 1H, $J = 13.4$, 6.3 Hz, H-7'), 1.82 (dd, 1H, $J = 13.0$, 8.1 Hz, H-7'), 1.72 (br s, 6H, C8'-CH$_3$, C10'-CH$_3$), 1.67 (d, 3H, $J = 6.9$ Hz, 3H-12'), 1.62-1.46 (m), 1.31-1.23 (m), 0.88 (s, 9H, -SiMe$_2$C(CH$_3$)$_3$), 0.86 (s, 3H, C6'-CH$_3$), 0.10 (s, 3H, -Si(CH$_3$)Me$^t$Bu), and 0.07 (s, 3H, -Si(CH$_3$)Me$^t$Bu).

LC/MS: (Method: C$_8$ column, gradient 50-100%, methanol content, 22 min, MW 200-2000, negative ES, ES+APCI, APCI): $t_R = 12.17$ min. (M-H$^-$: 514).

HRMS (ESI) Calcd for C$_{29}$H$_{45}$NNaO$_5$Si+: (M•Na$^+$): 538.2959, found: 554.2881.

TLC: $R_f$ (6:1 hexanes/EtOAc) = 0.55.

(5'S)-(±)-(1R,6R,7S,7aR)-(7Z)-Hexahydro-7-{[(1'E,7'E,9'E)-5',7',9'-trimethyl-1',7',9'-undecatrien]carbonyl}-7b-hydroxy-furo[2,3,4-gh]pyrrolizine-2,6-dione (307). Ketone 307 was synthesized analogously to synthesis of ketone 45 from enol 325 (14 mg, 0.037 mmol) as starting material in 95% yield (>95% pure by $^1$H NMR) as a mixture of the corresponding diastereomers, yellow oil, which was used without any further purification in the next step.
\textbf{1H NMR} (500 MHz, CDCl$_3$): $\delta$ 7.22 (dt, 1H, $J = 15.6, 6.9$ Hz, H-3'), 6.23 (d, 1H, $J = 15.6$ Hz, H-2'), 5.54 (br s, 1H, H-9'), 5.26 (br q, 1H, $J = 7.0$ Hz, H-9'), 4.82 (s, 1H, H-7), 4.27 (s, 1H, H-7a), 3.76 (ddd, 1H, $J = 12.0, 9.4, 5.6$ Hz, H-3), 3.26 (ddd, 1H, $J = 12.0, 9.9, 5.3$ Hz, H-3), 3.21 (dd, 1H, $J = 9.3, 2.1$ Hz, H-2'), 2.68 (dd, 1H, $J = 14.0, 9.6, 5.6$ Hz, H-2), 2.51 (dd, 1H, $J = 14.1, 9.4, 5.3$ Hz, H-2), 2.39-2.2 (m, 1H, H-4'), 2.31-2.22 (m, 1H, H-4'), 1.96 (dd, 1H, $J = 12.9, 6.5$ Hz, H-7'), 1.77 (dd, 1H, $J = 13.0, 8.0$ Hz, H-7'), 1.65 (d, 3H, $J = 1.4$ Hz, C8'-CH$_3$), 1.64 (br s, 3H, C10'-CH$_3$), 1.60 (d, 3H, $J = 6.8$ Hz, 3H-12'), 1.52-1.42 (m), 1.28-1.15 (m), and 0.80 (d, 3H, $J = 6.6$ Hz, C6'-CH$_3$).

\textbf{HRMS (ESI)} Calcd for C$_{23}$H$_{31}$NNaO$_5$ (M$\cdot$Na$^+$): 424.2094, found: 424.2115.

\textbf{LC/MS:} (Method: C$_8$ column, gradient 50-100%, methanol content, 22 min, MW 200-2000, negative ES, ES+APCI, APCI): $t_R = 6.62$ min. (M-H: 400).

\textbf{TLC:} $R_f$ (1:1 hexanes/EtOAc) = 0.40.

(1S,2S,4aS,6S,8aR)-, (1S,2R,4aR,6S,8aR)-, and (1R,2R,4aR,6S,8aR)-1,2,4a,5,6,7,8,8a-Octahydro-2,3,4a,6-tetramethyl-1-naphthalenecarboxaldehydes (329a, 329b, and 329e, respectively).

Solid catalyst 24a (14 mg, 0.035 mmol) was added to a solution of aldehyde 308 (32 mg, 0.145 mmol) in CD$_3$CN/D$_2$O (v/v 98:2) in an NMR tube at 0 °C. The progress of the reaction was observed by $^1$H NMR spectroscopy. Upon complete conversion of aldehyde 255, the reaction mixture was concentrated, diluted with EtOAc, filtered through a SiO$_2$ in a Pasteur pipette using EtOAc as an eluent. The resulting mother liquor was concentrated, purified by chromatography on silica gel (MPLC) using 99:1 hexanes/EtOAc as the eluent yielded a mixture of aldehydes 329a and 329b, which was further purified by HPLC using 99:1 hexanes/EtOAc as the eluent, producing aldehyde 329a (5 mg, 16% yield) and 329b (11 mg, 34% yield).
329a: $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 9.79 (d, 1H, $J = 4.5$ Hz, CHO), 5.17 (q, 1H, $J = 1.1$ Hz, 1H, H-4), 2.45 (ddd, 1H, $J = 12.1, 6.0, 4.5$ Hz, H-1), 2.36 (dq, 1H, $J = 6.5, 6.5, 0.7$ Hz, H-2), 1.81 (ddd, 1H, $J = 12.2, 12.2, 2.9$ Hz, H-8a), 1.80 (dddd, 1H, $J = 12.9, 4.3, 4.3, 2.6, 1.8$ Hz, H-8eq), 1.70 (ddqdd, 1H, $J = 12, 12, 7, 4, 4$ Hz, H-6ax), 1.65 (dd, 3H, $J = 1.5, 0.5$ Hz, C3-CH$_3$), 1.58 (dddd, 1H, $J = 13.4, 4.7, 2.6, 2.6$ Hz, H-8eq), 1.45 (ddd, 1H, $J = 12.8, 4.0, 1.9$ Hz, H-5eq), 1.25 (dddd, 1H, $J = 13.0, 13.0, 13.0, 3.8$ Hz, H-8ax), 1.12 (d, 3H, $J = 7.1$ Hz, C2-CH$_3$), 0.98 (dd, 1H, $J = 13.0, 13.0, 13.0, 4.4$ Hz, H-7ax), 0.91 (ddq, 1H, $J = 12.6, 12.6, 0.7$ Hz, H-5ax), 0.864 (d, 3H, $J = 0.6$ Hz, C4a-CH$_3$), and 0.863 (d, 3H, $J = 6.5$ Hz, C6-CH$_3$).

329a: $^1$H NMR (500 MHz, C$_6$D$_6$): $\delta$ 9.59 (d, 1H, $J = 4.0$ Hz, CHO), 5.07 (q, 1H, $J = 1.1$ Hz, 1H, H-4), 2.39 (ddd, 1H, $J = 12.1, 5.9, 4.1$ Hz, H-1), 2.10 (dq, 1H, $J = 6.8, 6.8, 0.8$ Hz, H-2), 1.66 (ddd, 1H, $J = 12.5, 12.5, 2.8$ Hz, H-8a), 1.58 (m, 1H, H-7eq), 1.57 (m, 1H, H-8eq), 1.47 (dd, 3H, $J = 1.5, 0.6$ Hz, C3-CH$_3$), 1.47 (m, 1H, H-6ax), 1.30 (ddd, 1H, $J = 12.8, 3.9, 1.8$ Hz, H-5eq), 1.06 (dddd, 1H, $J = 12.9, 12.9, 12.9, 3.6$ Hz, H-8ax), 0.89 (d, 3H, $J = 7.1$ Hz, C2-CH$_3$), 0.81 (brdd, 1H, $J = 12.5, 12.5$ Hz, H-5ax), 0.80 (m, 1H, H-7ax), 0.79 (d, 3H, $J = 6.5$ Hz, C6-CH$_3$), and 0.74 (d 3H, $J = 0.7$ Hz, C4a-CH$_3$).

329a: $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 208.0, 134.7, 51.3, 48.1, 38.2, 36.8, 35.8, 27.5, 24.4, 23.0, 21.6, 20.7, and 15.0.

329a: $^{13}$C NMR (125 MHz, C$_6$D$_6$): $\delta$ 205.4 (CHO), 135.0 (C-4), 134.0, (C-3) 51.5 (C-1), 48.6 (C-5), 38.6 (C-8a), 36.8 (C-2), 36.4 (C-4a), 36.2 (C-7), 27.8 (C-6), 24.5 (C-8), 23.3 (C6-CH$_3$), 21.8 (C3-CH$_3$), 20.9 (C4a-CH$_3$), and 15.2 (C2-CH$_3$).

GC/MS (5027016): $t_r$ = 9.31 min; $m/z$ 220 (20, M$^+$), 205 (20, M$^+$-Me), 191 (50, M$^+$-CHO), 175 (40), 164 (100), 133 (40), and 119 (90).

TLC: R$_f$ (99:1 hexanes/EtOAc) = 0.33.

329b: $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 9.75 (s, 1H, CHO), 5.04 (dq, 1H, $J = 2.8, 1.4, 1.4$ Hz, 1H, H-4), 2.82 (qddq, 1H, $J = 7.3, 2.2, 2.2, 1.1$ Hz, H-1), 2.01 (ddd, 1H, $J = 2, 2$ Hz, H-2), 1.99 (dddd, 1H, $J = 11.9, 4.0, 1.6, 1.6$ Hz, H-8a), 1.71 (dd, 3H, $J = 1.3, 1.3$ Hz, C3-CH$_3$), 1.63 (m, 1H, H-7eq), 1.61 (dddd, 1H, $J = 12.9, 12.9, 12.9, 3.8$ Hz, H-8ax), 1.48 (nfom, 1H, H-8eq), 1.45 (ddd, 1H, $J = 13.2, 3.5, 2.2$ Hz, H-5eq), 1.35 (m, 1H, H-6), 1.13 (d, 3H, $J = 7.6$ Hz, C2-CH$_3$), 0.92 (dd, 1H, $J = 13.2, 11.9$ Hz, H-5ax), 0.90 (nfom, 1H, H-7ax), 0.85 (d, 3H, $J = 6.6$ Hz, C6-CH$_3$), and 0.72 (s, 3H, C4a-CH$_3$).
329b: \( ^1H\) NMR (500 MHz, \( C_6D_6 \)): \( \delta \) 9.50 (s, 1H, CHO), 4.93 (ddq, 1H, \( J = 2.8, 1.4, 1.4 \) Hz, 1H, H-4), 2.95 (qddq, 1H, \( J = 7.6, 2.3, 2.3, 1.2 \) Hz, H-2), 1.65 (dddd, 1H, \( J = 12.4, 4.1, 1.6, 1.6 \) Hz, H-8a), 1.604 (dd, 3H, \( J = 1.3, 1.3 \) Hz, C3-\( CH_3 \)), 1.596 (dd, 1H, \( J = 1.9, 1.9 \) Hz, H-1), 1.50 (ddddd, 1H, \( J = 12, 3, 3, 3, 3 \) Hz, H-7eq), 1.45 (ddddd, 1H, \( J = 12.7, 12.7, 12.7, 3.7 \) Hz, H-8ax), ca. 1.23 (m, 1H, H-6), 1.28 (dd, 1H, \( J = 12.8, 3.4, 2.3 \) Hz, H-5eq), 1.15 (ddddd, 1H, \( J = 12.9, 3.8, 3.8, 3.8 \) Hz, H-8eq), 0.94 (d, 3H, \( J = 7.6 \) Hz, C2-\( CH_3 \)), 0.82 (d, 3H, \( J = 6.4 \) Hz, C6-\( CH_3 \)), 0.75 (m, 1H, H-7ax), 0.73 (dd, 1H, \( J = 12.5, 12.5 \) Hz, H-5ax), and 0.70 (s, 3H, C4a-\( CH_3 \)).

329b: \( ^13C\) NMR (125 MHz, \( C_6D_6 \)): \( \delta \) 203.3 (CHO), 134.4 (C-3), 130.5 (C-4), 61.1 (C-1), 50.1 (C-5), 41.6 (C-8a), 36.8 (C-4a), 35.7 (C-7), 32.2 (C-8), 31.5 (C4a-\( CH_3 \)), 29.6 (C-6), 29.0 (C-2), 23.6 (C6-\( CH_3 \)), 22.3 (C3-\( CH_3 \)), and 21.7 (C2-\( CH_3 \)).

GC/MS (5027016): \( t_r = 9.04 \) min; \( m/z \) 220 (20, M+), 205 (10, M+ -Me), 191 (100, M+ -CHO), 175 (60), 133 (30), and 119 (60).

TLC: \( R_f \) (99:1 hexanes/EtOAc) = 0.34.

Use of enantiomeric catalyst 24b in cyclization of aldehyde 308 yielded aldehydes 329a, 329b, and 329e in 40%, 7%, and 53% yields correspondingly.

329e: \( ^1H\) NMR (500 MHz, CDCl3): \( \delta \) 9.90 (s, 1H, CHO), 5.07 (ddq, 1H, \( J = 1.5, 1.5, 1.5 \) Hz, 1H, H-4), 2.95 (dd, 1H, \( J = 7.2, 3.2 \) Hz, H-1), 2.61 (ddqd, 1H, \( J = 7.4, 7.4, 1.7, 0.8 \) Hz, H-2), 1.88 (ddddd, 1H, \( J = 12.4, 3.4, 3.4, 1.4 \) Hz, H-8a), 1.72 (dd, 3H, \( J = 1.3, 1.0 \) Hz, C3-\( CH_3 \)), 1.61 (ddddd, 1H, \( J = 12.8, 3.3, 3.3, 3.3 \) Hz, H-8eq), 1.58 (ddddd, 1H, \( J = 12, 3, 3, 3, 3 \) Hz, H-7eq), 1.54 (dd, 1H, \( J = 13.3, 3.3, 2.4 \) Hz, H-5eq), 1.37 (ddddd, 1H, \( J = 12.7, 12.7, 12.7, 3.3 \) Hz, H-8ax), 1.30 (m, 1H, H-6ax), 1.17 (d, 3H, \( J = 7.5 \) Hz, C2-\( CH_3 \)), 0.96 (dd, 1H, \( J = 13.5, 12.0 \) Hz, H-5ax), 0.95 (s, 3H, C4a-\( CH_3 \)), 0.83 (d, 3H, \( J = 6.5 \) Hz, C6-\( CH_3 \)), and 0.82 (ddddd, 1H, \( J = 12.4, 12.4, 3.1 \) Hz, H-7ax).

329e: \( ^1H\) NMR (500 MHz, \( C_6D_6 \)): \( \delta \) 9.61 (s, 1H, CHO), 4.94 (ddq, 1H, \( J = 1.6, 1.6, 1.6 \) Hz, 1H, H-4), 2.62 (dd, 1H, \( J = 7.2, 3.2 \) Hz, H-1), 2.24 (br dq, 1H, \( J = 7.3, 7.3 \) Hz, H-2), 1.79 (ddddd, 1H, \( J = 12.6, 3.6, 3.4, 1.5 \) Hz, H-8a), 1.65 (ddddd, 1H, \( J = 12.9, 3.5, 3.5, 3.5 \) Hz, H-8eq), 1.57 (dd, 3H, \( J = 1.1, 1.1 \) Hz, C3-\( CH_3 \)), 1.49 (ddddd, 1H, \( J = 12.6, 3.1, 3.1, 3.1 \) Hz, H-7eq), 1.40 (dd, 1H, \( J = 13.3, 3.5, 2.4 \) Hz, H-5eq), 1.28 (ddddd, 1H, \( J = 12.9, 12.9, 12.9, 3.4 \) Hz, H-8ax), 1.21 (m, 1H, H-6ax), 1.01 (d, 3H, \( J = 7.5 \) Hz, C2-\( CH_3 \)), 0.82 (s, 3H, C4a-\( CH_3 \)), 0.82 (dd, 1H, \( W_{tot} = 25.5 \) Hz, H-5ax), 0.81 (d, 3H, \( J = 6.5 \) Hz, C6-\( CH_3 \)), and
0.73 (ddddd, 1H, J = 12.9, 12.9, 12.9, 3.1 Hz, H-7ax).

329e: $^{13}$C NMR (125 MHz, C$_6$D$_6$): δ 203.8 (CHO), 135 (C-3), 131.7 (C-4), 51.3 (C-1), 50.5 (C-5), 40.5 (C-8a), 36.8 (C-4a), 35.8 (C-7), 32.8 (C-2), 31.5 (C4a-CH$_3$), 30.3 (C-6), 26.8 (C-8), 23.2 (C6-CH$_3$), 22.1 (C3-CH$_3$), and 16.6 (C2-CH$_3$).

GC/MS (5027016): $t_r$ = 9.21 min; m/z 220 (30, M$^+$), 205 (40, M$^+$-Me), 177 (100), 137 (70), 121 (80), and 95 (70).

TLC: R$_f$ (99:1 hexanes/EtOAc) = 0.32.

(2aS,7S,7aR,7bS)-7b-[[1,1-Dimethylethyl]dimethylsilyloxy]hexahydro-7-[hydroxy-[(1'S,2'R,4'aS,6'S,8'aR)-1',2',4'a,5',6',7',8'a-octahydro-2',3',4'a,6'-tetramethyl-1'-naphthalenyl]methyl]furo[2,3,4-gh]pyrrolizine-2,6-dione (328a)

(2aS,7R,7aR,7bS)-7b-[[1,1-Dimethylethyl]dimethylsilyloxy]hexahydro-7-[hydroxy-[(1'S,2'S,4'aR,6'S,8'aR)-1',2',4'a,5',6',7',8'a-octahydro-2',3',4'a,6'-tetramethyl-1'-naphthalenyl]methyl]furo[2,3,4-gh]pyrrolizine-2,6-dione (328b)

(2aS,7R,7aR,7bS)-7b-[[1,1-Dimethylethyl]dimethylsilyloxy]hexahydro-7-[hydroxy-[(1'R,2'S,4'aR,6'S,8'aR)-1',2',4'a,5',6',7',8'a-octahydro-2',3',4'a,6'-tetramethyl-1'-naphthalenyl]methyl]furo[2,3,4-gh]pyrrolizine-2,6-dione (328c)

(2aR,7S,7aS,7bR)-7b-[[1,1-Dimethylethyl]dimethylsilyloxy]hexahydro-7-[hydroxy-[(1'S,2'R,4'aS,6'S,8'aR)-1',2',4'a,5',6',7',8'a-octahydro-2',3',4'a,6'-tetramethyl-1'-naphthalenyl]methyl]furo[2,3,4-gh]pyrrolizine-2,6-dione (328a')
(2\(a\)\(R\),7\(S\),7\(a\)\(S\),7\(b\)\(R\))-7b-\(((1,1\text{-Dimethylethyl})\text{dimethylsilyl})\text{oxy}])\text{hexahydro-7-[hydroxy-}[1'\(S\),2'\(S\),4'a\(R\),6'S,8'a\(R\)]-1',2',4'a,5',6',7',8',8'a-octahydro-2',3',4'a,6'-tetramethyl-1'\text{-naphthalenyl}]methyl]furo[2,3,4-\(gh\])pyrrolizine-2,6-dione (328b')

(2\(a\)\(R\),7\(S\),7\(a\)\(S\),7\(b\)\(R\))-7b-\(((1,1\text{-Dimethylethyl})\text{dimethylsilyl})\text{oxy}])\text{hexahydro-7-[hydroxy-}[1'\(R\),2'\(S\),4'a\(R\),6'S,8'a\(R\)]-1',2',4'a,5',6',7',8',8'a-octahydro-2',3',4'a,6'-tetramethyl-1'\text{-naphthalenyl}]methyl]furo[2,3,4-\(gh\])pyrrolizine-2,6-dione (328c').

Typical/general procedure for boron-Reformatsky addition reactions: A mixture of iodolactone (+)-10a or (–)-10a (10 mg, 0.02 mmol) and aldehyde 329a, 329b, or 329e (10 mg, 0.04 mmol) in toluene (0.5 mL) at –78 °C was treated with Et\(_3\)B (1M in hexanes, 0.20 mL, 0.20 mmol). After stirring for 2 h at –78 °C, H\(_2\)O (1 mL) was added and the cold bath was removed. When the reaction mixture had warmed to room temperature, the layers were separated and the aqueous layer was extracted with Et\(_2\)O (5 x 5 mL). The combined organic extracts were dried over Na\(_2\)SO\(_4\), and concentrated. The crude residue was purified by flash chromatography on silica gel chromatography (6:1 hexanes/EtOAc) to provide ~8 mg (78%) of the corresponding alcohol 328.

328a: \(^1\text{H NMR}\) (500 MHz, CDCl\(_3\)): \(\delta\) 5.08 (br s, 1H, H-4'), 4.81 (d, 1H, \(J = 3.8\) Hz, H-7a), 4.23 (ddd, 1H, \(J = 10.1, 3.2, 0.7\) Hz, H-8), 3.93 (br s, 1H, OH), 3.80 (ddd, 1H, \(J = 11.8, 8.3, 8.3\) Hz, H-4m), 3.33 (dd, 1H, \(J = 10.3, 3.9\) Hz, H-7), 3.30 (ddd, 1H, \(J = 12.4, 8.4, 5.6\) Hz, H-4n), 3.06 (dd, 1H, \(J = 7.2, 3.6\) Hz, H-2a), 2.65-2.55 (m, 2H, H-3m and H-3n), 2.04 (br qd, 1H, \(J = 7, 5\) Hz, H-2'), 1.90 [m, 1H, with one large (13 Hz) \(J\) value], 1.79 (ddddd, 1H, \(J = 12.8, 3, 3, 2\) Hz, H-7'eq), 1.74 (ddd, 1H, \(J = 11.3, 4.7, 3.5\) Hz), 1.7 (m, 1H), 1.65 (d, 3H, \(J = 1.4\) Hz, C3'-CH\(_3\)), 1.40 (ddd, 1H, \(J = 12.7, 3.8, 2.0\) Hz, H-5'eq), 1.25 (d, 3H, \(J = 7\) Hz, 3H, C2'-CH\(_3\)), 1.30-1.20 (m, 2H), 0.91 [s, 9H, SiMe\(_2\)C(CH\(_3\))\(_3\)], 0.90-0.86 (m, 2H), 0.85 (s, 3H, C4'a-CH\(_3\)), 0.84 (d, 3H, \(J = 6.5\) Hz, C6'-CH\(_3\)), 0.20 [s, 3H, Si(CH\(_3\))MeCMe\(_3\)], and 0.16 [s, 3H, Si(CH\(_3\))MeCMe\(_3\)].

HRMS (ESI) Calcd for C\(_{29}\)H\(_{47}\)NNaO\(_5\)Si\(_5\)\(^+\) (M•Na\(^+\)): 540.3116, found: 540.3123.

TLC: \(R_f\) (6:1 hexanes/EtOAc) = 0.30.

328a': \(^1\text{H NMR}\) (500 MHz, CDCl\(_3\)): \(\delta\) 5.02 (br s, 1H, H-4'), 4.75 (d, 1H, \(J = 4.0\) Hz, H-
7a), 4.16 (dd, 1H, J = 10.2, 1.9 Hz, H-8), 3.96 (dd, 1H, J = 1.6, 1.6 Hz, OH), 3.80 (ddd, 1H, J = 12.0, 9.1, 7.2 Hz, H-4m), 3.42 (dd, 1H, J = 10.2, 4.0 Hz, H-7), 3.30 (ddd, 1H, J = 11.7, 8.7, 4.6 Hz, H-4b), 3.08 (dd, 1H, J = 7.6, 2.9 Hz, H-2a), 2.54-2.65 (m, 2H, H-3m and H-3n), 2.30 (dddd, 1H, J = 11.7, 3.3, 3.3, 3.3 Hz, H-8'eq), 2.03 (qd, 1H, J = 7.0, 4.8 Hz, H-2'), 1.7 (m, 1H, H-7'eq), 1.78 (br ddd, 1H, J = 11.5, 5.3, 1.7 Hz, H-1'), 1.68 (dd, 1H, J = 11.8, 11.8, 2.9 Hz, H-8'a), 1.62 (d, 3H, J = 1.4 Hz, C3'-CH3), 1.41 (br d, 1H, with one large (12.1 Hz) J value, H-5'eq), 1.25 (m, 1H, H-6'ax), 1.22 (dddd, 1H, J = 12.2, 12.2, 12.2, 3.5 Hz, H-8'ax), 1.14 (d, 3H, J = 7.1 Hz, C2'-CH3), 0.91 [s, 9H, SiMe2C(CH3)3], 0.9 (s, 3H, C4'a-CH3), 1.1-0.85 (m, H-5'ax, H-7'ax), 0.85 (d, 3H, J = 6.4 Hz, C6'-CH3), 0.18 [s, 3H, Si(CH3)MeCMe3], and 0.15 [s, 3H, Si(CH3)MeCMe3].

HRMS (ESI) Calcd for C29H47NNaO5Si+ (M•Na+) : 540.3116, found: 540.3140.

TLC: R_f (6:1 hexanes/EtOAc) = 0.30.

328b: 1H NMR (500 MHz, CDCl3): δ 5.09 (ddq, 1H, J = 2.5, 1.3, 1.3, Hz, H-4'), 4.82 (d, 1H, J = 4.0 Hz, H-7a), 4.13 (ddd, 1H, J = 7.4, 4.5, 2.8 Hz, H-8), 4.06 (br d, 1H, J = 2.7 Hz, OH), 3.83 (ddd, 1H, J = 12.0, 9.1, 7.1 Hz, H-4m), 3.31 (ddddd, 1H, J = 11.9, 9.1, 5.0, 1.0 Hz, H-4n), 3.23 (dd, 1H, J = 7.6, 4.0 Hz, H-7), 3.10 (dd, 1H, J = 8.0, 2.9 Hz, H-2a), 2.54-2.65 (m, 2H, H-3m and H-3n), 2.48 (qddd, 1H, J = 7.3, 2.5, 2.5, 1 Hz, H-2'), 1.73 (dd, 3H, J = 1.2, 1.2 Hz, C3'-CH3), 1.6-1.4 (m, ~ 5H), 1.35 (m, 1H, H-6'ax), 1.18 (d, 3H, J = 7.5 Hz, C2'-CH3), 1.06 (s, 3H, C4'a-CH3), 0.91 [s, 9H, SiMe2C(CH3)3], 0.93-0.85 (m, 2H, H-5'ax, H-7'ax), 0.83 (d, 3H, J = 6.6 Hz, C6'-CH3), 0.18 [s, 3H, Si(CH3)MeCMe3], and 0.16 [s, 3H, Si(CH3)MeCMe3].

HRMS (ESI) Calcd for C29H47NNaO5Si+ (M•Na+) : 540.3116, found: 540.3127.

TLC: R_f (6:1 hexanes/EtOAc) = 0.30.

328b': 1H NMR (500 MHz, CDCl3): δ 5.28 (ddq, 1H, J = 2.8, 1.4, 1.4 Hz, H-4'), 4.78 (d, 1H, J = 3.8 Hz, H-7a), 4.33 (br s, 1H, OH), 4.18 (dd, 1H, J = 9.5, 3.0 Hz, H-8), 3.82 (ddd, 1H, J = 11.9, 8.0, 8.0 Hz, H-4m), 3.30 (ddd, 1H, J = 12.0, 8.4, 5.6 Hz, H-4n), 3.23 (dd, 1H, J = 9.4, 3.8 Hz, H-7), 3.07 (dd, 1H, J = 7.4, 3.3 Hz, H-2a), 2.64-2.56 (m, 2H, H-3m and H-3n), 2.31 (qd, 1H, J = 7, 7 Hz, H-2'), 1.73 (dd, 3H, J = 1.5, 1.5 Hz, C3'-CH3), 1.70-1.28 (m,
5H, H-1', H-8'a, H-8'eq, H-7'eq, H-6'ax, H-5'eq), 1.37 (dddd, 1H, J = 13.1, 13.1, 13.1, 3.2 Hz, H-8'ax), 1.09 (d, 3H, J = 7.0 Hz, C2'-CH3), 1.00 (s, 3H, C4'a-CH3), 0.90 [s, 9H, SiMe2C(CH3)3], 0.90 (m, 1H, H-5'ax), 0.84 (d, 3H, J = 6.5 Hz, C6'CH3), 0.79 (dddd, 1H, J = 12, 12, 12, 4 Hz, H-7'ax), 0.18 [s, 3H, Si(CH3)MeCMe3], and 0.15 [s, 3H, Si(CH3)MeCMe3].

HRMS (ESI) Calcd for C29H47NNaO5Si (M•Na+): 540.3116, found: 540.3135.

TLC: Rf (6:1 hexanes/EtOAc) = 0.30.

328c: 1H NMR (500 MHz, CDCl3): δ 5.04 (ddq, 1H, J = 1.5, 1.5, 1.5 Hz, H-4'), 4.77 (d, 1H, J = 4.1 Hz, H-7a), 4.31 (ddd, 1H, J = 6.8, 5.2, 3.9 Hz, H-8), 3.85 (ddd, 1H, J = 11.9, 9.1, 6.7 Hz, H-4m), 3.61 (dd, 1H, J = 3.9, 0.8 Hz, OH), 3.34 (dd, 1H, J = 6.9, 4.2 Hz, H-7), 3.30 (ddd, 1H, J = 11.6, 9.3, 4.7, 0.8 Hz, H-4n), 3.11 (dd, 1H, J = 8.5, 2.5 Hz, H-2a), 2.62 (dddd, 1H, J = 14.1, 11.8, 10.0, 5.4 Hz, H-3m), 2.56 (dddd, 1H, J = 13.9, 9.1, 5.0, 2.5 Hz, H-3n), 2.46 (ddd, 1H, J = 7.3, 5.2, 2.5 Hz, H-1'), 2.14 (br qd, 1H, J = 7.4, 7.4, 1 Hz, H-2'), 2.00 (dddd, 1H, J = 13.3, 3.4, 3.4, 3.4 Hz, H-8'eq), 1.70 (dd, 3H, J = 1.3, 0.7 Hz, C3'-CH3), 1.63 (ddd, 1H, J = 12.5, 3.7, 2.5, 1.5 Hz, H-8'a), 1.59 (dddd, 1H, J = 12.4, 3, 3, 3, 3 Hz, H-7'eq), 1.52 (ddd, 1H, J = 13.0, 2.8, 2.1 Hz, H-5'eq), 1.41 (dddd, 1H, J = 13.0, 13.0, 13.0, 3.3 Hz, H-8'ax), 1.30 (m, 1H, H-6'ax), 1.20 (d, 3H, J = 7.5 Hz, C2'-CH3), 0.99 (s, 3H, C4'a-CH3), 0.91 [s, 9H, SiMe2C(CH3)3], 0.91 (dd, 1H, J = 12.3, 12.3 Hz, H-5'ax), 0.82 (d, 3H, J = 6.5 Hz, C6'-CH3), 0.74 (dddd, 1H, J = 12.8, 12.8, 12.8, 3.1 Hz, H-7'ax), 0.18 [s, 3H, Si(CH3)MeCMe3], and 0.16 [s, 3H, Si(CH3)MeCMe3].

HRMS (ESI) Calcd for C29H47NNaO5Si (M•Na+): 540.3116, found: 540.3117.

TLC: Rf (6:1 hexanes/EtOAc) = 0.30.

328c': 1H NMR (500 MHz, CDCl3): δ 5.02 (br q, 1H, J = 1.3 Hz, H-4'), 4.87 (d, 1H, J = 3.8 Hz, H-7a), 4.36-4.32 (m, 2H, H-8, OH), 3.81 (ddd, 1H, J = 11.8, 8.4, 8.4 Hz, H-4), 3.32 (ddd, 1H, J = 12.0, 8.2, 5.5 Hz, H-4m), 3.22 (dd, 1H, J = 6.4, 3.8 Hz, H-2a), 3.11 (dd, 1H, J = 7.0, 3.5 Hz, H-7), 2.62-2.54 (m, 2H, H-3m and H-3n), 2.38 (qd, 1H, J = 7.8, 6.7 Hz, H-2'), 1.71 (ddd, 3H, J = 1.0, 1.0, 1.0 Hz, C3'-CH3), 1.62 (dddd, 1H, J = 12.7, 3, 3, 3 Hz, H-7'eq), 1.57-1.51 (m, 3H, H-1', H-8'a, H-8'eq), 1.46 (dddd, 1H, J = 12.8, 12.8, 12.8, 3.3
Hz, H-8'ax), 1.35-1.25 (m, 2H, H-5'eq, H-6'), 1.18 (d, 3H, J = 7.4 Hz, C2'-CH3), 0.99 (s, 3H, C4'a-CH3), 0.91 [s, 9H, SiMe2C(CH3)3], 0.88 (m, 1H, H-5'ax), 0.82 (d, 3H, J = 6.5 Hz, C6'-CH3), 0.65 (ddddd, 1H, J = 12.5, 12.5, 12.5, 3.5 Hz, H-7'ax), 0.18 [s, 3H, Si(CH3)MeCMe3], and 0.16 [s, 3H, Si(C2H5)MeCMe3].


TLC: Rf (6:1 hexanes/EtOAc) = 0.30

Note: For consistency with the numbering used in the report describing CJ-16,264, the primed and unprimed atom numbers have been switched in structures 331 and 330 from what they are in 328.

(2'aS,7'S,7'aR,7'bS)-7b-[(1,1-Dimethylethyl)dimethylsilyl]oxy]hexahydro-7-[[1S,2R,4aS,6S,8aR]-1,2,4a,5,6,7,8,8a-octahydro-2,3,4a,6-tetramethyl-1-naphthalenyl]carbonyl)furo[2,3,4-gh]pyrrolizine-2',6'-dione (331a).

Dess-Martin periodinane (8 mg, 0.019 mmol) was added to the alcohol 328a (6.0 mg, 0.012 mmol) in CDCl3 (0.6 mL) at 0 °C. The reaction mixture was warmed to room temperature over 20 min and monitored by 1H NMR spectroscopy. When conversion was complete (~ 40 min), the reaction mixture was diluted with Et2O, filtered through Celite, and concentrated. The crude residue was purified by short silica gel chromatography (8:1 hexanes/EtOAc) to provide ~ 5 mg (80%) of 331a as a 2:1 mixture of its enol- and keto-tautomers (enol-331a and keto-331a) in CDCl3 solution. Evidence
for a small steady-state concentration of ketone 7′-epi-331a was observed throughout the course of the reaction, but it was not seen following work up and chromatography.

### 331a: 1H NMR (500 MHz, CDCl3): δ 11.95 (br s, 1H, enol-OH), 5.18-5.13 (overlapping m’s, enol-H-4, enol-H-7’a, keto-H-4), 4.98 (s, 1H, keto-H-7’a), 4.44 (s, 1H, keto-H-7’), 3.95 (n/fom, 1H, keto-H-4’m), 3.90 (ddd, 1H, J = 11.8, 8.9, 4.5 Hz, enol-H-4’m), 3.61 (dd, 1H, J = 11.6, 5.7 Hz, keto-H-1), 3.34 (ddd, 1H, J = 11.8, 8.8, 6.9 Hz, enol-H-4’n), 3.30 (ddd, 1H, J = 12.0, 9.4, 7.1 Hz, keto-H-4’n), 3.20 (dd, 1H, J = 10.0, 4.0 Hz, enol-H-2’a), 3.12 (dd, 1H, J = 9.4, 2.7 Hz, keto-H-2’a), 2.75 (dd, 1H, J = 11.9, 6.0 Hz, enol-H-1), 2.63 (dddd, 1H, J = 13.6, 9.9, 8.7, 4.3 Hz, enol-H-3’m), 2.60-2.45 (m, 2H, keto-H-3’m and keto-H-3’n), 2.44 (dddd, 1H, J = 13.4, 9.1, 7.0, 4.0 Hz, enol-H-3’), 2.40 (m, 1H, keto-H-2), 2.14 (qd, 1H, J = 7, 7 Hz, enol-H-2), 1.75-1.20 (overlapping m’s), 1.68 (d 3H, J = 1.4 Hz, keto-C3-CH3), 1.67 (d, 3H, J = 1.4, enol-C3-CH3), 1.10 (d, 3H, J = 7.1 Hz, enol-C2-CH3), 1.04 (d, 3H, J = 7.4 Hz, keto-C2’-CH3), 0.90 (s, 3H, enol-C4a-CH3), 0.92 [s, 9H, keto-SiMe2C(CH3)3], 0.89 [s, 9H, enol-SiMe2C(CH3)3], 0.87 (d, 3H, J = 6.8 Hz, enol-C6-CH3), 0.84 (d, 3H, J = 6.4 Hz, keto-C6-CH3), 0.90-0.86 (overlapping m’s), 0.19 [s, 3H, keto-Si(CH3)MeCMe3], 0.14 [s, 3H, keto-Si(CH3)MeCMe3], 0.11 [s, 3H, enol-Si(CH3)MeCMe3], and 0.08 [s, 3H, enol-Si(CH3)MeCMe3].

**HRMS (ESI) Calcd for C29H45NNaO5Si+ (M•Na+): 538.2959, found: 538.2935.**

**LC/MS: (Method: C8 column, gradient 50-100% methanol content, 22 min, MW 200-2000, negative ES, ES+APCI, APCI): tR = 14.8 min. (M-H+: 514).**

**TLC: Rf (8:1 hexanes/ EtOAc) = 0.35.**

\[(2′aR,7′R,7′aS,7′bR)-7b-||[(1,1-Dimethyllethyl)dimethylsilyloxy]hexahydro-7-||[(1S,2R,4aS,6S,8aR)-1,2,4a,5,6,7,8,8a-octahydro-2,3,4a,6-tetramethyl-1-naphthalenyl]carbonylfuro[2,3,4-gh]pyrrolizine-2′,6′-dione (331a′).\]

The reaction was conducted analogously to that used to prepare 331a, using ester 328a′ (6 mg, 0.012 mmol) as a starting material. The crude residue was purified by short silica gel chromatography (8:1 hexanes/ EtOAc) to provide ~ 5 mg (80%) of 331a′ as a 7.3:1 mixture of its enol- and keto-tautomers (enol-331a′ and keto-331a′) in CDCl3 solution. Evidence for a small steady-state concentration of ketone 7′-epi-331a′ was observed throughout the course of the reaction, but it was not seen following work up and
chromatography.

enol-331a: $^1$H NMR (500 MHz, CDCl$_3$): δ 11.95 (br s, 1H, OH), 5.15 (s, 1H, H-7’a), 5.13 (br s, 1H, H-4), 3.90 (ddd, 1H, J = 11.9, 9.0, 4.0 Hz, H-4’m), 3.34 (ddd, 1H, J = 11.9, 8.8, 7.2 Hz, H-4’n), 3.20 (dd, 1H, J = 10.0, 4.1 Hz, H-2’a), 2.68 (dd, 1H, J = 11.8, 5.9 Hz, H-1), 2.64 (m, 1H, H-3’m), 2.46 (dddd, 1H, J = 13.5, 9.2, 7.2, 4.1 Hz, H-3’n), 2.28 (br qd, 1H, J = 6.6, 6.6 Hz, H-2), 1.75 (br d, 1H, J = 13 Hz, H-8eq), 1.7 (m, H-7eq), 1.71 (ddd, 1H, J = 11.9, 11.9, 2.6 Hz, H-8a), 1.65 (d, 3H, J = 1.2 Hz, C3-CH$_3$), 1.44 (ddd, 1H, J = 13.2, 4.2, 1.8 Hz, H-5eq), 1.26 (m, 1H, H-6), 1.12 (m, 1H, H-8ax), 1.06 (d, 3H, J = 7.1 Hz, C2-CH$_3$), 1.00-0.86 (m, H-5ax, H-7ax), 0.89 (s, 3H, C4a-CH$_3$), 0.88 [s, 9H, SiMe$_2$C(CH$_3$)$_3$], 0.86 (d, 3H, J = 6.4 Hz, C6-CH$_2$), 0.10 [s, 3H, Si(CH$_3$)MeCMe$_2$], and 0.07 [s, 3H, Si(CH$_3$)MeCMe$_3$].

HRMS (ESI) Calcd for C$_{29}$H$_{38}$NNaO$_5$Si$^+$ (M•Na$^+$): 538.2959, found: 538.2940.

LC/MS: (Method: C$_8$ column, gradient 50-100% methanol content, 22 min, MW 200-2000, negative ES, ES+APCI, APCI): t$_R$ = 14.8 min. (M-H$^-$: 514).

TLC: R$_f$ (8:1 hexanes/EtOAc) = 0.35.

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(2’aS,7’S,7’aR,7’bS)-7b-[(1,1-Dimethylethyl)dimethylsilyl]oxy]hexahydro-7-
[(1S,2’S,4aR,6’S,8aR)-1,2,4a,5,6,7,8,8a-octahydro-2,3,4a,6-tetramethyl-1-
naphthalenyl]carbonyl]furo[2,3,4-h]pyrrolizine-2’,6’-dione (331b)
The reaction was conducted analogously to that used to prepare 331a, using ester 328b (6
mg, 0.012 mmol) as the starting material. When conversion was complete (~ 40 min), the crude residue was purified by short silica gel chromatography (8:1 hexanes/EtOAc) to provide ~ 5 mg (80%) of 331b as a 4.2:1 mixture of its enol- and keto-forms in CDCl₃ solution. Evidence for a steady-state concentration of ketone 7'-epi-331b was observed throughout the course of the reaction. The concentration was sufficient to assign the ¹H NMR spectrum from the reaction solution in CDCl₃. This epimer was no longer observed following work up and chromatography.

7-epi-331b: ¹H NMR (500 MHz, CDCl₃): δ 5.11 (d, 1H, J = 3.3 Hz, H-7a), 5.00 (ddq, 1H, J = 2.2, 1.1, 1.1 Hz, H-4), 4.37 (d, 1H, J = 3.4 Hz, H-7), 3.72 (ddd, 1H, J = 11.9, 8.2, 8.2 Hz, H-4'), 3.35 (ddd, 1H, J = 12.1, 9.4, 4.3 Hz, H-4'n), 3.09 (dd, 1H, J = 7.8, 2.2 Hz, H-2a), 3.03 (dd, 1H, J = 2.3, 2.0 Hz, H-1), 3.02 (qddq, 1H, J = 7, 2.2, 1.1, 1.1 Hz, H-2), 2.64-2.55 (m, 2H, H-3'm and H-3'n), 1.89 (dddd, 1H, J = 12, 3.5, 2.4, 1.1 Hz, H-8a), 1.78 (dddd, 1H, J = 12.7, 4, 4 Hz, H-8eq), 1.73 (dd, 3H, J = 1.1, 1.1 Hz, C3-CH₃), 1.65 (m, 1H, H-7eq), 1.61 (dddd, 1H, J = 12.7, 12.7, 12.7, 3.8 Hz, H-8ax), 1.45 (ddd, 1H, J = 13.2, 3.5, 2.4 Hz, H-5eq), 1.38 (m, 1H, H-6), 1.09 (d, 3H, J = 7.5 Hz, C2-CH₃), 0.91 [s, 9H, SiMe₂C(CH₃)₃], 0.95 -0.85 (m, H-5ax, H-7ax), 0.84 (d, 3H, J = 6.5 Hz, C6-CH₃), 0.77 (s, 3H, C4a-CH₃), 0.19 [s, 3H, Si(CH₃)MeCMe₃], and 0.17 [s, 3H, Si(CH₃)MeCMe₃].

331b: ¹H NMR (500 MHz, CDCl₃): δ 12.08 (br s, 1H, enol-OH), 5.22 (q, 1H, J = 1.5 Hz, enol-H-4), 5.18 (s, 1H, enol-H-7a), 5.13 (q, 1H, J = 1.5 Hz, keto-H-4), 4.91 (s, 1H, keto-H-7'), 4.00 (s, 1H, keto-H-7), 3.98 (ddd, 1H, J = 11.7, 9.4, 5.0 Hz, keto-H-4'), 3.85 (ddd, 1H, J = 11.8, 9.2, 5.2 Hz, enol-H-4'), 3.41 (ddd, 1H, J = 11.8, 9.0, 6.2 Hz, enol-H-4'), 3.33 (ddd, 1H, J = 12.1, 9.5, 6.2 Hz, keto-H-4'), 3.18 (dd, 1H, J = 9.7, 3.5 Hz, enol-H-2a), 3.13 (dd, 1H, J = 9.7, 2.9 Hz, keto-H-2a), 2.64 (dddd, 1H, J = 14.2, 9.2, 9.2, 5.2 Hz, enol+keto-H-3'), 2.53 (dddd, 1H, J = 13.0, 9.5, 6.3, 3.6 Hz, enol+keto-H-3'), 2.36 (dd, 1H, J = 7.6, 7.6 Hz, keto-H-1), 2.27 (dd, 1H, J = 9, 9 Hz, enol-H-1), 1.79-1.67 (m, 4H, H-8eq, H-7eq, H-8a, H-2), 1.69 (br s, 3H, keto+enol-C3-CH₃), 1.44 (m, 1H, H-5eq), 1.28 (m, 1H, H-6), 1.09 (s, 3H, C4a-CH₃), 1.05 (d, 3H, J = 7.1 Hz, keto-C2-CH₃), 0.97 (d, 3H, J = 6.5 Hz, keto-C6-CH₃), 0.87 [s, 9H, enol-SiMe₂C(CH₃)₃], 0.90-0.76 (m, 2H, keto+enol-H-5ax, H-7ax), 0.19 [s, 3H, keto-Si(CH₃)MeCMe₃], 0.18 [s, 3H, keto-Si(CH₃)MeCMe₃], 0.13 [s, 3H, enol-Si(CH₃)MeCMe₃], and 0.10 [s, 3H, enol-Si(CH₃)MeCMe₃].

HRMS (ESI) Calcd for C₂₉H₄₅NNaO₅Si⁺ (M•Na⁺): 538.2959, found: 538.2935.
LC/MS: (Method: C$_8$ column, gradient 50-100% methanol content, 22 min, MW 200-2000, negative ES, ES+APCI, APCI): t$_R$ = 14.8 min. (M-H$^-$: 514).

TLC: R$_f$ (8:1 hexanes/EtOAc) = 0.35.

(2'aR,7'R,7'aS,7'bR)-7b-[[1-(1,1-Dimethylethyl)dimethylsilyl]oxy]hexahydro-7-
[[1S,2S,4aR,6S,8aR]-1,2,4a,5,6,7,8,8a-octahydro-2,3,4a,6-tetramethyl-1-
naphthalenyl]carbonyl][furo[2,3-gh]pyrrolizine-2',6'-dione (331b')

The reaction was conducted analogously to synthesis 331a, using ester 328b (6 mg, 0.012 mmol) as a starting material. When conversion was complete (~ 40 min), clean formation of 7-epi-331b' was observed, than the reaction mixture was diluted with Et$_2$O, filtered through Celite and concentrated. The crude residue was purified by short silica gel chromatography (8:1 hexanes/EtOAc) to provide ~ 5 mg (80%) of 331b' as a 1.1:1 mixture of its enol- and keto-forms in CDCl$_3$ solution. The crude was purified by chromatography on silica gel using 8:1 hexanes/EtOAc as the eluent producing 5 mg (80% yield) of product 331b' as a colorless oil.

7-epi-331b': $^1$H NMR (500 MHz, CDCl$_3$): δ 5.11 (br s, 1H, H-4), 5.00 (d, 1H, J = 4.5 Hz, H-7'a), 4.30 (d, 1H, J = 4.6 Hz, H-7'), 3.91 (ddd, 1H, J = 12.1, 9.1, 6.5 Hz, H-4'), 3.34 (ddd, 1H, J = 12.0, 8.9, 5.9 Hz, H-4'), 3.18 (dd, 1H, J = 8.3, 3.4 Hz, H-2'a), 2.93 (m, 1H, H-2), 2.66-2.48 (m, 2H, 2H-3'), 2.42 (dd, 1H, J = 4.6, 2.3 Hz, H-1), 1.72 (br s, 3H, C3-CH$_3$), 1.70-1.40 (m, 5H, H-8a, H-8eq, H-8ax, H-6, H-5eq), 1.06 (d, 3H, J = 7.4 Hz, C2-CH$_3$), 0.92 [s, 9H, SiMe$_2$C(CH$_3$)$_3$], 0.90 (d, 3H, J = 6.5 Hz, C6-CH$_3$), 0.84 (s, 3H, C4a-CH$_3$), 0.95 - 0.86 (m, 2H, H-5ax, H-7ax), 0.19 [s, 3H, Si(CH$_3$)MeCMe$_3$], and 0.16 [s, 3H, Si(CH$_3$)MeCMe$_3$]

331b': $^1$H NMR (500 MHz, CDCl$_3$): δ 12.19 (br s, 1H, enol-OH), 5.30 (s, 1H, keto-H-7'a), 5.25 (s, 1H, enol-H-7'a), 5.15 (br s, 1H, enol-H-4), 5.06 (br s, 1H, keto-H-4), 4.21 (s, 1H, keto-H-7'), 3.92 (ddd, 1H, J = 12.2, 9.3, 5.6 Hz, keto-H-4'), 3.87 (ddd, 1H, J = 11.9, 9.2, 5.0 Hz, enol-H-4'), 3.41 (ddd, 1H, J = 11.9, 8.9, 6.5 Hz, enol-H-4'), 3.33 (ddd, 1H, J = 12.2, 9.4, 5.8 Hz, keto-H-4'), 3.19 (dd, 1H, J = 9.9, 3.7 Hz, enol-H-2'a), 3.15 (dd, 1H, J = 9.3, 2.9 Hz, keto-H-2'a), 2.92 (m, 1H, J = 7.8 Hz, enol-H-2), 2.74 (m, 1H, keto-H-2), 2.68-2.45 (m, 2H, enol+keto-2H-3'), 2.32 (m, 1H, enol+keto-H-1), 2.09 (m, 1H, enol-H-8a), 2.02 (m, 1H, enol-H-8a)
keto-H-8a), 1.72 (br s, 3H, enol-C3-CH3), 1.67 (br s, 3H, keto-C3-CH3), 1.83-1.26 (m, 5H, H-8eq, H-7eq, H-8ax, H-5eq, H-6), 1.11 (s, 3H, C4a-CH3), 1.01 (d, 3H, J = 7.1 Hz, keto-C2'-CH3), 1.00 (d, 3H, J = 7.1 Hz, keto-C2'-CH3), 0.90 [s, 9H, enol-SiMe2C(CH3)3], 0.88 [s, 9H, keto-SiMe2C(CH3)3], 0.90-0.76 (m, 5H, keto+enol-5ax, H-7ax, C6-CH3), 0.15 [s, 3H, keto-Si(CH3)MeCMe3], 0.12 [s, 3H, keto-Si(CH3)MeCMe3], 0.11 [s, 3H, enol-Si(CH3)MeCMe3], and 0.08 [s, 3H, enol-Si(CH3)MeCMe3].

**HRMS** (ESI) Calcd for C29H48NNaO5Si+ (M•Na+): 538.2959, found: 538.2967.

**LC/MS:** (Method: C8 column, gradient 50-100% methanol content, 22 min, MW 200-2000, negative ES, ES+APCI, APCI): tR = 14.8 min. (M-H+: 514).

**TLC:** Rf (8:1 hexanes/EtOAc) = 0.35.

(2'aS,7'S,7'aR,7'bS)-7b-[[1,1-Dimethylethyl]dimethylsilyl]oxy]hexahydro-7-(((1R,2S,4aR,6S,8aR)-1,2,4a,5,6,7,8,8a-octahydro-2,3,4a,6-tetramethyl-1-naphthalenyl]carbonyl]furo[2,3,4-gh]pyrrolizine-2',6'-dione (331c).

The reaction was conducted analogously to synthesis 331a, using ester 328c (6 mg, 0.012 mmol) as a starting material. When conversion was complete (~ 40 min), clean formation of 7-epi-331c was observed, than the reaction mixture was diluted with Et2O, filtered through Celite and concentrated. The crude residue was purified by short silica gel chromatography (8:1 hexanes/EtOAc) to provide ~ 5 mg (80%) of 331c as a 2:1 mixture of its enol- and keto-forms in CDCl3 solution. The crude was purified by chromatography on silica gel using 8:1 hexanes/EtOAc as the eluent producing 5 mg (80% yield) of
product 331c as a colorless oil.

7-epi-331c: ^1^H NMR (500 MHz, CDCl₃): δ 5.07 (d, 1H, J = 3.5 Hz, H-7'a), 5.06 (br s, 1H, H-4), 4.10 (d, 1H, J = 3.5 Hz, H-7'), 3.94 (dd, 1H, J = 6.7, 2.5 Hz, H-1), 3.74 (ddd, 1H, J = 11.9, 8.2, 8.2 Hz, H-4'), 3.32 (ddd, 1H, J = 12.0, 8.9, 4.5 Hz, H-4'), 3.09 (dd, 1H, J = 7.3, 2.9 Hz, H-2'a), 2.64 (qd, 1H, J = 7, 7 Hz, H-2), 2.62-2.54 (m, 2H, 2H-3'), 1.74 (ddd, 1H, J = 12.9, 3.2, 2 Hz, H-8a), 1.72 (br s, 3H, C3-CH₃), 1.70-1.55 (m, 2H, H-8eq, H-7eq), 1.50 (ddd, 1H, J = 13.4, 2.8, 2.8 Hz, H-5eq), 1.32 (dddd, 1H, J = 12.5, 12.5, 12.5, 3.5 Hz, H-8ax), 1.28 (m, 1H, H-6), 1.09 (d, 3H, J = 7.5 Hz, C2-CH₃), 0.90 [s, 3H, C4a-CH₃], 0.94 (dd, 1H, J = 12.5, 12.5 Hz, H-5ax), 0.90 [s, 9H, SiMe₂C(CH₃)₃], 0.81 (d, 3H, J = 6.5 Hz, C6-CH₃), 0.76 (dddd, 1H, J = 13.0, 13.0, 13.0, 3.0 Hz, H-7ax), 0.17 [s, 3H, Si(CH₃)MeCMe₃], and 0.16 [s, 3H, Si(CH₃)MeCMe₃].

331c: ^1^H NMR (500 MHz, CDCl₃): δ 12.23 (br s, 1H, enol-OH), 5.14 (s, 1H, enol-H-7'a), 5.12 (s, 1H, keto-H-7'a), 5.07 (br s, 1H, enol-H-4), 5.04 (br s, 1H, keto-H-4), 4.01 (s, 1H, keto-H-7'a), 3.94 (ddd, 1H, J = 12.3, 9.3, 5.5 Hz, keto-H-4'), 3.91 (ddd, 1H, J = 12.0, 9.2, 4.1 Hz, enol-H-4'), 3.56 (dd, 1H, J = 6.6, 2.8 Hz, keto-H-1), 3.34 (ddd, 1H, J = 11.9, 8.9, 7.1 Hz, enol-H-4'), 3.32 (ddd, 1H, J = 12.1, 9.2, 6.0 Hz, keto-H-4'), 3.28 (dd, 1H, J = 7.2, 1.7 Hz, enol-H-1), 3.20 (dd, 1H, J = 10.0, 4.1 Hz, enol-H-2'a), 3.14 (dd, 1H, J = 9.4, 2.6 Hz, keto-H-2'a), 2.65 (dddd, 1H, J = 13.9, 8.1, 8.1, 4.4 Hz, enol+keto-H-3'), 2.46 (dddd, 1H, J = 13.5, 9.3, 7.1, 4.2 Hz, enol+keto-H-3'), 2.36 (qd, 1H, J = 7.5, 7.5 Hz, enol-H-2), 2.16 (m, 1H, keto-H-2), 1.71 (br s, 3H, enol-C3-CH₃), 1.70 (br s, 3H, keto-C3-CH₃), 1.70-1.20 (m, 4H, H-8eq, H-7eq, H-8ax, H-5eq, H-6), 1.42 (d, 3H, J = 7.5 Hz, keto-C2'-CH₃), 1.17 (d, 3H, J = 7.5 Hz, enol-C2'-CH₃), 1.05 (s, 3H, keto-C4a-CH₃), 1.01 (s, 3H, enol-C4a-CH₃), 0.90 [s, 9H, keto-SiMe₂C(CH₃)₃], 0.88 [s, 9H, enol-SiMe₂C(CH₃)₃], 0.00-0.76 (m, 2H, keto+enol-H-5ax, H-7ax), 0.82 (d, 3H, J = 6.5 Hz, keto-C6-CH₃), 0.17 [s, 3H, keto-Si(CH₃)MeCMe₃], 0.16 [s, 3H, keto-Si(CH₃)MeCMe₃], 0.10 [s, 3H, enol-Si(CH₃)MeCMe₃], and 0.08 [s, 3H, enol-Si(CH₃)MeCMe₃].

HRMS (ESI) Calcd for C₂₉H₄₅NNaO₅Si⁺ (M•Na⁺): 538.2959, found: 538.3001.

LC/MS: (Method: C₈ column, gradient 50-100%, methanol content, 22 min, MW 200-2000, negative ES, ES+APCI, APCI): tᵣ = 14.8 min. (M-H⁺: 514).

TLC: Rₜ (8:1 hexanes/EtOAc) = 0.35.
The reaction was conducted analogously to synthesis 331a, using ester 328c (6 mg, 0.012 mmol) as a starting material. When conversion was complete (~ 40 min), clean formation of 7-epi-331c' was observed, and the reaction mixture was diluted with Et₂O, filtered through Celite and concentrated. The crude residue was purified by short silica gel chromatography (8:1 hexanes/EtOAc) to provide ~ 5 mg (80%) of 331c' as a 1:4.1 mixture of its enol- and keto-forms in CDCl₃ solution. The crude was purified by chromatography on silica gel using 8:1 hexanes/EtOAc as the eluent producing 5 mg (80% yield) of product 331c' as a colorless oil.

7-epi-331c': ¹H NMR (500 MHz, CDCl₃): δ 5.08 (br s, 1H, H-4), 4.98 (d, 1H, J = 4.5 Hz, H-7'a), 4.27 (d, 1H, J = 4.5 Hz, H-7'), 3.90 (ddd, 1H, J = 12.0, 9.0, 5.0 Hz, H-4'), 3.39 (dd, 1H, J = 7.0, 2.7 Hz, H-1), 3.34 (ddd, 1H, J = 12.0, 9.0, 5.0 Hz, H-4'), 3.12 (dd, 1H, J = 8.8, 2.9 Hz, H-2'a), 2.65-2.50 (m, 2H, H-3'), 1.93 (dd, 1H, J = 13.1, 3.4, 3.4, 3.4 Hz, H-8eq), 1.80 (ddd, 1H, J = 12.6, 3.6, 3.6 Hz, H-8a), 1.73 (br s, 3H, C3-C₃H₃), 1.59 (dd, 1H, J = 12.8, 3, 3, 3 Hz, H-7eq), 1.52 (ddd, 1H, J = 13.5, 3, 3 Hz, H-5eq), 1.36 (dd, 1H, J = 13.1, 13.1, 3.5 Hz, H-8ax), 1.28 (m, 1H, H-6), 1.18 (d, 3H, J = 7.5 Hz, C2-C₃H₃), 0.91 [s, 9H, SiMe₂C(CH₃)₃], 0.87 (s, 3H, C4a-C₃H₃), 0.81 (d, 3H, J = 6.5 Hz, C6-C₃H₃), 0.95 (m, 1H, H-5ax), 0.77 (dd, 1H, J = 13, 13, 13, 3 Hz, H-7ax), 0.18 [s, 3H, Si(CH₃)₂MeCMe₃], and 0.16 [s, 3H, Si(CH₃)₂MeCMe₃].

331c': ¹H NMR (500 MHz, CDCl₃): δ 12.42 (br s, 1H, enol-OH), 5.27 (s, 1H, keto-H-7'a), 5.20 (s, 1H, enol-H-7'a), 5.11 (br s, 1H, enol-H-4), 5.07 (br s, 1H, keto-H-4), 3.94 (s, 1H, keto-H-7'), 3.90 (ddd, 1H, J = 12.2, 9.3, 5.4 Hz, keto-H-4'), 3.81 (ddd, 1H, J = 12.0, 9.3, 7.1 Hz, enol-H-4'), 3.66 (dd, 1H, J = 7.0, 2.6 Hz, keto-H-1), 3.37 (dd, 1H, J = 7.0, 2.9 Hz, enol-H-1), 3.33 (ddd, 1H, J = 12.2, 9.4, 5.9 Hz, keto+enol-H-4'), 3.20 (dd, 1H, J = 9.1, 4.1 Hz, enol-H-2'a), 3.15 (dd, 1H, J = 9.4, 2.8 Hz, keto-H-2'a), 2.84 (qd, 1H, J = 7.6, 7.6 Hz, keto-H-2), 2.63 (dd, 1H, J = 14.6, 9.4, 9.4, 5.5 Hz, enol+keto-H-3'), 2.55 (dd, 1H, J = 14.2, 9.0, 5.6, 2.8 Hz, enol+keto-H-3'), 2.25 (qd, 1H, J = 7.4, 7.4 Hz, enol-H-2), 2.19 (dd, 1H, J = 13.2, 3.4, 3.4, 3.4 Hz, enol-H-8eq), 2.01 (dd, 1H, J = 2.9, 3.4, 3.4, 3.4 Hz, keto-H-
(2'aS,7'S,7'aR,7'bS)-7b-[(hydroxy)hexahydro-7-[(1S,2R,4aS,6S,8aR)-
1,2,4a,5,6,7,8,8a-octahydro-2,3,4a,6-tetramethyl-1-naphthalenyl]carbonyl]-
furo[2,3,4-gh]pyrrolizine-2',6'-dione (330a).

(2'aR,7'R,7'aS,7'bR)-7b-[(hydroxy)hexahydro-7-[(1S,2R,4aS,6S,8aR)-
1,2,4a,5,6,7,8,8a-octahydro-2,3,4a,6-tetramethyl-1-naphthalenyl]carbonyl]-
furo[2,3,4-gh]pyrrolizine-2',6'-dione (330a').

(2'aS,7'S,7'aR,7'bS)-7b-[(hydroxy)hexahydro-7-[(1S,2S,4aR,6S,8aR)-
1,2,4a,5,6,7,8,8a-octahydro-2,3,4a,6-tetramethyl-1-naphthalenyl]carbonyl]-
furo[2,3,4-gh]pyrrolizine-2',6'-dione (330b).

(2'aR,7'R,7'aS,7'bR)-7b-[(hydroxy)hexahydro-7-[(1S,2S,4aR,6S,8aR)-1,2,4a,5,6,7,8,8a-octahydro-2,3,4a,6-tetramethyl-1-naphthalenyl|carbonyl]-furo[2,3,4-gh]pyrrolizine-2',6'-dione (330b').

(2'aS,7'S,7'aR,7'bS)-7b-[(hydroxy)hexahydro-7-[(1R,2S,4aR,6S,8aR)-1,2,4a,5,6,7,8,8a-octahydro-2,3,4a,6-tetramethyl-1-naphthalenyl|carbonyl]-furo[2,3,4-gh]pyrrolizine-2',6'-dione (330c).

(2'aR,7'R,7'aS,7'bR)-7b-[(hydroxy)hexahydro-7-[(1R,2S,4aR,6S,8aR)-1,2,4a,5,6,7,8,8a-octahydro-2,3,4a,6-tetramethyl-1-naphthalenyl|carbonyl]-furo[2,3,4-gh]pyrrolizine-2',6'-dione (330c').

To HF•pyridine (70% HF, 30% pyridine, 3 drops) in a polyethylene tube MeCN (0.4 mL) and then pyridine (200 µL) were added. To this mixture TBS-ether 331 (4 mg, 0.008 mmol) in MeCN (0.5 mL) was added. The resulting mixture was stirred for ca. 72 h at room temperature. The progress of the reaction was closely followed by LC-MS, the completion of the reaction was judged by disappearance of the starting material. The reaction partitioned between water (5.0 mL) and DCM (10 mL). The aqueous layer was extracted with DCM (3 x 5.0 mL). The combined organic layers were dried over Na₂SO₄, evaporated, and filtered through a plug of silica gel (~ 1.5 cm tall) using EtOAc as the eluent. The resulting crude was purified by HPLC using 2:1 hexanes/EtOAc as an eluent. Evaporation provided the corresponding product 330 (2 mg, ~ 80%) as a colorless oil.

330a: ¹H NMR (500 MHz, C₆D₆): reported in Table 11.1
HRMS (ESI) Calcd for C₂₃H₃₁NNaO₅⁺ (M•Na⁺): 424.2094, found: 424.2096.
LC/MS: (Method: C₈ column, gradient 50-100%, methanol content, 22 min, MW 200-2000, negative ES, ES+APCI, APCI): tᵣ = 10.8 min. (M-H⁻: 400).
TLC: R₉ (1:1 hexanes/EtOAc) = 0.45.
330a': $^1$H NMR (500 MHz, $C_6D_6$): reported in Table 11.1

HRMS (ESI) Calcd for $C_{23}H_{31}N\text{NaO}_5^+$ (M•Na$^+$): 424.2094, found: 424.2090.

LC/MS: (Method: $C_8$ column, gradient 50-100%, methanol content, 22 min, MW 200-2000, negative ES, ES+APCI, APCI): $t_R = 10.8$ min. (M-H$^-$: 400).

TLC: $R_f$ (1:1 hexanes/EtOAc) = 0.45.

330b: $^1$H NMR (500 MHz, $C_6D_6$): reported in Table 11.2.

$^{13}$C-NMR (125 MHz, $C_6D_6Cl_3$): δ 209.8, 173.9, 165.2, 133.10, 131.4, 100.8, 81.1, 63.7, 63.6, 48.8, 47.5, 41.8, 38.9, 37.0, 34.2, 31.9, 29.7, 29.7, 29.1, 28.8, 22.3, 21.6, and 21.0.

HRMS (ESI) Calcd for $C_{23}H_{31}N\text{NaO}_5^+$ (M•Na$^+$): 424.2094, found: 424.2087.

LC/MS: (Method: $C_8$ column, gradient 50-100%, methanol content, 22 min, MW 200-2000, negative ES, ES+APCI, APCI): $t_R = 10.8$ min. (M-H$^-$: 400).

TLC: $R_f$ (1:1 hexanes/EtOAc) = 0.45.

330b': $^1$H NMR (500 MHz, $C_6D_6$): reported in Table 11.2.

HRMS (ESI) Calcd for $C_{23}H_{31}N\text{NaO}_5^+$ (M•Na$^+$): 424.2094, found: 424.2099.

LC/MS: (Method: $C_8$ column, gradient 50-100%, methanol content, 22 min, MW 200-2000, negative ES, ES+APCI, APCI): $t_R = 10.8$ min. (M-H$^-$: 400).

TLC: $R_f$ (1:1 hexanes/EtOAc) = 0.45.

330c: $^1$H NMR (500 MHz, $C_6D_6$): reported in Table 11.3.

HRMS (ESI) Calcd for $C_{23}H_{31}N\text{NaO}_5^+$ (M•Na$^+$): 424.2094, found: 424.2075.

LC/MS: (Method: $C_8$ column, gradient 50-100%, methanol content, 22 min, MW 200-2000, negative ES, ES+APCI, APCI): $t_R = 10.8$ min. (M-H$^-$: 400).

TLC: $R_f$ (1:1 hexanes/EtOAc) = 0.45.

330c': $^1$H NMR (500 MHz, $C_6D_6$): reported in Table 11.1

HRMS (ESI) Calcd for $C_{23}H_{31}N\text{NaO}_5^+$ (M•Na$^+$): 424.2094, found: 424.2076.
**LC/MS:** (Method: C₈ column, gradient 50-100%, methanol content, 22 min, MW 200-2000, negative ES, ES+APCI, APCI): tᵣ = 10.8 min. (M-H⁻: 400).

**TLC:** Rᵣ (1:1 hexanes/EtOAc) = 0.45.

1,5-Dihydro-5-hydroxy-5-benzyl-3-bromo-1-[[2-(trimethylsilyl)ethoxy)methyl]-2H-pyrrol-2-one (423). Bromomaleimide 418 (0.100 g, 0.325 mmol) was dissolved in 3:2 DCM/diethyl ether (1.0 mL), and benzyl magnesium chloride (0.25 mL, 1.33 M in ether) was added to the solution at −78 °C under inert atmosphere. The reaction mixture was stirred for 1 h at −78 °C, then it was warmed up to room temperature, stirred for 2 h at room temperature, and quenched with pH 7.0 buffer (1.0 mL), and organic layer was separated. The aqueous layer was extracted back with Et₂O (3 x 20 mL). All organic layers were combined, washed with brine (1 x 10.0 mL), and dried over Na₂SO₄. Chromatography on silica gel (MPLC) using 4:1 hexanes/EtOAc as the eluent yielded 38 mg (29% yield) of alcohol 423 (as a 3:1 mixture of two regioisomers).

423 (major component, the desired regioisomer, shown):

**¹H NMR** (500 MHz, CDCl₃): δ 7.34-7.28 (m, 3H, H-3'',H-4'',H-5''), 7.23 (d, 2H, J = 8.0 Hz, H-2'',H-6''), 6.99 (s, 1H, H-4), 5.06 (d, 1H, J = 11.0 Hz, H-6), 4.95 (d, 1H, J = 11.1 Hz, H-6), 3.67-3.59 (non-first order m, 2H, 2H-1''), 3.48 (d, 1H, J = 14.0 Hz, H-7), 2.98 (d, 1H, J = 14.0 Hz, H-7), 2.73 (s, 1H, -OH), 1.00-0.88 (non-first order m, 2H, 2H-2''), and 0.02 (s, 9H, -Si(CH₃)₃).

**¹³C NMR** (125 MHz, CDCl₃): δ 165.1, 146.6, 134.7, 130.5, 128.7, 120.3, 116.9, 93.3, 69.3, 66.9, 43.9, 18.4, and -1.2.

**IR** (thin film) 3405, 2953, 2925, 1706, 1701, 1607, 1361, 1079, 860, 836, 701, and 668.

**HRMS** (ESI) Calcd for C₁₇H₂₄BrNNaO₃Si⁺ (M•Na⁺): 420.0601, found: 420.0614.
LR-MS (ESI) Calcd for C\textsubscript{26}H\textsubscript{38}NO\textsubscript{4}Si\textsuperscript{+} (M•Na\textsuperscript{+}): 420.06 and 422.05, found: 420.11 and 422.09.

LC/MS: (Method: C\textsubscript{8} column, gradient 50-100%, methanol content, 22 min, MW 200-2000, negative ES, ES+APCI, APCI): t\textsubscript{R} = 9.6 min. (M-H\textsuperscript{-}: 398 and 396).

TLC: R\textsubscript{f} (4:1 hexanes/EtOAc) = 0.20.

\[\text{[2-\{(Trimethylsilyl)ethoxy\}methyl]-maleimide (427)}\]. A solution of maleimide (82) (0.414 g, 3.00 mmol) in DMF (50 mL) at \(-40^\circ\text{C}\) was treated with \(i\)-Pr\textsubscript{2}NEt (0.84 mL, 4.80 mmol) and SEMCl (0.80 mL, 4.50 mmol) dropwise. The reaction mixture was stirred for 2 h at \(-40^\circ\text{C}\), and was allowed to warm to 25 °C. The reaction was quenched by the addition of saturated aqueous NH\textsubscript{4}Cl, concentrated to 10 mL. The mixture was diluted with deionized water and was extracted with Et\textsubscript{2}O (5 x 10 mL). The combined organic extracts were washed with saturated aqueous NaCl (10 mL), dried Na\textsubscript{2}SO\textsubscript{4}, and concentrated \textit{in vacuo}. Chromatography on silica gel (MPLC) using 3:1 hexanes/EtOAc as the eluent yielded 477 mg (70% yield) of 427.

\(^1\text{H} \text{NMR} \) (500 MHz, CDCl\textsubscript{3}): \(\delta\) 6.78 (s, 2H, -CH=CH-) , 4.95 (s, 2H, NCH\textsubscript{2}O), 3.58 (dd, 2H, \(J = 8.0\), 8.5 Hz, OCH\textsubscript{2} ), 0.93 (dd, 2H, \(J = 8.5\), 8.5 Hz, CH\textsubscript{2}TMS), and 0.00 (s, 9H, Si(CH\textsubscript{3})\textsubscript{3}).

GC/MS (5029021): \(t_r = 8.49\) min; \(m/z\) 212 (5, M\textsuperscript{+}-Me), 184 (40), and 154 (100, M\textsuperscript{+}-TMS).

TLC: R\textsubscript{f} (3:1 hexanes/EtOAc) = 0.30.

\textbf{1,5-Dihydro-5-hydroxy-5-benzyl-1-\{[2-(trimethylsilyl)ethoxy]methyl\}-2\textsubscript{H}-pyrrol-2-one (428)}. Maleimide 428 (0.050 g, 0.220 mmol) was dissolved in THF (0.7 mL), and benzyl magnesium chloride (0.17 mL, 1.33 M in ether) was added to the solution at \(-78^\circ\text{C}\) under inert atmosphere. The reaction mixture was stirred for 1 h at \(-78^\circ\text{C}\), then it was
warmed up to room temperature, stirred for 1 h at room temperature, and quenched with pH 7.0 buffer (1.0 mL), and organic layer was separated. The aqueous layer was extracted back with Et$_2$O (3 x 20 mL). All organic layers were combined, washed with brine (1 x 10.0 mL), and dried over Na$_2$SO$_4$. Chromatography on silica gel (MPLC) using 3:1 hexanes/EtOAc as the eluent yielded 4 mg (6% yield) of alcohol 428.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.31-7.27 (m, 3H, H-3",H-4",H-5"), 7.22 (d, 2H, $J = 8.0$ Hz, H-2",H-6"), 6.80 (d, 1H, $J = 6.0$ Hz, H-4), 6.04 (d, 1H, $J = 6.0$ Hz, H-3), 5.03 (d, 1H, $J = 11.0$ Hz, H-6), 4.91 (d, 1H, $J = 11.1$ Hz, H-6), 3.62 (dd, 2H, $J = 8.5$, 8.0 Hz, 2H-1'), 3.45 (d, 1H, $J = 14.0$ Hz, H-7), 3.00 (d, 1H, $J = 14.0$ Hz, H-7), 2.75 (s, 1H, -OH), 1.01-0.88 (non-first order m, 2H, 2H-2'), and 0.02 (s, 9H, -Si(CH$_3$)$_3$).

HRMS (ESI) Calcd for C$_{17}$H$_{25}$NNaO$_3$Si$^+$ (M$^+$Na$^+$): 342.1496, found: 342.1518.

GC/MS (5029021): $t_r = 12.61$ min; $m/z$ 304 (10, M$^+$-Me), 276 (100), and 246 (100, M$^+$-TMS).

TLC: $R_f$ (3:1 hexanes/EtOAc) = 0.10.

1,5-Dihydro-5-(trimethylsilyloxy)-5-benzyl-1-{[2-(trimethylsilyl)ethoxy]methyl}-2H-pyrrol-2-one (429). Alcohol 428 (4 mg, 0.013 mmol) was dissolved in DCM (0.4 mL), and 2,6-dimethylpyridine (5 µL, 0.039 mmol), followed by TMSOTf (6 µL, 0.030 mmol) were added to the solution at ambient temperature. The reacion mixture was stirred for additional 10 h, quenched with NaHCO$_3$ solution (0.2 mL), and extracted with DCM (3 x 1.0 mL). The combined organic layers were washed with brine (1 x 2.0 mL), dried over Na$_2$SO$_4$, and evaporated to give a yellow oil. Chromatography on silica gel (MPLC) using 4:1 hexanes/EtOAc as the eluent, yielded 6 mg (90% yield) of TMS-ether 429.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.30-7.23 (m, 5H, H-2",H-3",H-4",H-5",H-6"), 6.78 (d, 1H, $J = 6.0$ Hz, H-4), 6.09 (d, 1H, $J = 6.0$ Hz, H-3), 5.01 (d, 1H, $J = 11.0$ Hz, H-6), 4.76 (d, 1H, $J = 11.1$ Hz, H-6), 3.67 (ddd, 1H, $J = 10.9$, 9.7, 5.8 Hz, H-1'), 3.59 (ddd, 1H, $J = 10.9$, 9.7, 5.9 Hz, H-1'), 3.52 (d, 1H, $J = 13.5$ Hz, H-7), 2.78 (d, 1H, $J = 13.5$ Hz, H-7), 1.01 (ddd, 1H, $J = 13.8$, 11.0, 5.8 Hz, H-2'), 0.92 (ddd, 1H, $J = 13.8$, 10.9, 5.8 Hz, H-2'), 0.02 [s, 9H, -CH$_2$Si(CH$_3$)$_3$], and -0.07 [s, 9H, -OSi(CH$_3$)$_3$].
\(^{13}\text{C NMR}\) (125 MHz, CDCl\(_3\)): \(\delta\) 170.0, 148.2, 133.7, 130.8, 128.2, 126.3, 96.4, 68.6, 66.2, 46.9, 22.2, 1.4, 0.2, and -1.2.

IR (thin film) 2955, 2922, 2851, 1717, 1368, 1252, 1159, 1119, 1075, and 841.

HRMS (ESI) Calcd for C\(_{20}\)H\(_{33}\)NNaO\(_3\)Si\(_2\) \(\text{([M•Na\(^+\])}}\): 414.1891, found: 414.1897.

TLC: \(R_f\) (8:1 hexanes/EtOAc) = 0.50.

(3\(\alpha\),4\(\beta\),7\(\beta\),7\(\alpha\))−3a,4,7,7a−Tetrahydro−2−[(2′,4′−dimethoxy)phenyl−methyl]−4,7−epoxy−1\(H\)−isoindole−1,3(2\(H\))−dione (431). A solution of imide 430 (0.289 g, 1.75 mmol) in DMF (15 mL) at was treated with K\(_2\)CO\(_3\) (1.208 g, 8.75 mmol) and DMBBr (580 mg, 2.50 mmol) portionwise at room temperature. The reaction mixture was stirred for 2 h at 50 °C. The reaction was quenched with deionized water, and the organics were extracted back with EtOAc (5 x 30 mL). The combined organic extracts were washed with saturated aqueous NaCl (10 mL), dried over MgSO\(_4\), and concentrated in vacuo. Chromatography on silica gel (MPLC) using 1:1 hexanes/EtOAc as the eluent yielded 386 mg (70% yield) of 431.

431 (exo−isomer) \(^1\text{H NMR}\) (500 MHz, CDCl\(_3\)): \(\delta\) 6.88 (dt, 1H, \(J = 8.2, 1.7\) Hz, H−5′), 6.86 (d, 1H, \(J = 1.9\) Hz, H−3′), 6.77 (d, 1H, \(J = 8.1\) Hz, H−6′), 6.13 (s, 2H, H−5, H−6), 5.29 (d, 1H, \(J = 3.8\) Hz, H−4, H−7), 4.04 (s, 2H, H−8), 3.864 (s, 3H, -OCH\(_3\)), 3.860 (s, 3H, -OCH\(_3\)), and 3.50 (dt, 1H, \(J = 3.5, 1.6\) Hz, H−3a, H−7a).

TLC: \(R_f\) (3:1 hexanes/EtOAc) = 0.30.

(3\(\beta\),3\(\alpha\),4\(\beta\),7\(\beta\),7\(\alpha\))−2,3,3a,4,7,7a−Hexahydro−3−benzyl−3−hydroxy−2−[(2′,4′−dimethoxy)phenylmethyl]−4,7−epoxy−1\(H\)−isoindole−1−one (432). Imide 431 (0.349 g, 1.107 mmol) was dissolved in THF (10 mL), and benzyl magnesium chloride (1.2 mL, 1.33 M in ether) was added to the solution at 0 °C under inert atmosphere. The reaction
mixture was warmed up to room temperature, stirred for 4 h at room temperature, quenched with saturated aqueous NH₄Cl solution (2.0 mL), and extracted with EtOAc+1% Et₃N (2 x 20.0 mL). All organic layers were combined, washed with brine (1 x 15.0 mL), and dried over anhydrous K₂CO₃. Chromatography on silica gel (MPLC) using 2:1 DCM/EtOAc as the eluent yielded 240 mg (54% yield) of alcohol 432.

**¹H NMR** (500 MHz, CDCl₃): δ 7.28 (m, 2H, J = 8.3 Hz, H-3", H-5"), 7.20 (dd, 1H, J = 8.0, 7.0 Hz, H-4"), 7.14 (dd, 2H, J = 6.8 Hz, H-2", H-6"), 6.92 (d, 1H, J = 1.6 Hz, H-3'), 6.88 (dd, 1H, J = 8.1, 1.7 Hz, H-5'), 6.79 (d, 1H, J = 8.2 Hz, H-6'), 6.33 (dd, 1H, J = 5.8, 1.7 Hz, H-6), 6.21 (dd, 1H, J = 5.8, 1.8 Hz, H-5), 5.08 (d, 1H, J = 5.7 Hz, H-7), 4.88 (d, 1H, J = 5.4 Hz, H-4), 4.74 (d, 1H, J = 14.8 Hz, H-8), 3.88 (s, 3H, -OCH₃), 3.87 (s, 3H, -OCH₃), 3.74 (d, 1H, J = 13.7 Hz, H-9), 3.03 (dd, 1H, J = 8.7, 5.9 Hz, H-7a), 3.20 (d, 1H, J = 13.5 Hz, H-7), 2.72 (dd, 1H, J = 8.8, 5.6 Hz, H-3a), and 2.93 (s, 1H, -OH).

**¹³C NMR** (125 MHz, CDCl₃) (for mixture of adducts to **endo-** and **exo-431**): δ 172.2, 149.3, 149.1, 148.7, 135.5, 135.2, 134.5, 130.8, 130.6, 130.4, 139.0, 128.6, 127.7, 127.3, 121.0, 120.0, 112.9, 111.3, 111.0, 91.2, 90.3, 80.9, 80.4, 78.9, 56.1, 49.5, 49.3, 46.5, 46.3, 45.3, 45.1, and 42.1.

**IR** (thin film) 3552, 3340, 3005, 2933, 2836, 1654, 1516, 1456, 1260, 1159, 1140, 1122, 1027, 912, and 840.

**HRMS (ESI)** Calcd for C₂₄H₂₅NNaO₅⁺ (M•Na⁺): 430.1625, found: 430.1628.

**TLC**: Rf (2:1 DCM/EtOAc) = 0.15.

(3β,3αγ,4β,7β,7αa)-2,3,3a,4,7,7a-Hexahydro-3-benzyl-3-(trimethylsilyloxy)-2-[(2',4'-dimethoxy)phenylmethyl]-4,7-epoxy-1H-isoinole-1-one (433). Alcohol 432
(37 mg, 0.091 mmol) was dissolved in DCM (0.5 mL), and 2,6-lutidine (42 µL, 0.364 mmol) followed by TMSOTf (50 µL, 0.270 mmol) were added to the solution at ambient temperature. When the reaction mixture was quenched after 10 min with saturated solution of NaHCO₃, diluted with DCM. The organic layer was separated, and the aqueous layer was extracted back with ether (3 x 3.0 mL). All organic layers were combined, washed with brine (1 x 1.0 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo providing crude ether 433 (45 mg, 100% yield) as a colorless oil.

**1H NMR** (500 MHz, CDCl₃): δ 7.29-7.20 (m, 3H, H-3", H-4", H-5"'), 7.07 (d, 1H, J = 7.8 Hz, H-2"), 6.96 (d, 2H, J = 7.4 Hz, H-6"), 6.92 (dd, 1H, J = 2.0 Hz, H-3'), 6.88 (dd, 1H, J = 8.1, 2.0 Hz, H-5'), 6.79 (d, 1H, J = 8.1 Hz, H-6'), 6.33 (dd, 1H, J = 5.8, 1.8 Hz, H-4), 6.21 (dd, 1H, J = 5.8, 1.7 Hz, H-5), 5.09 (d, 1H, J = 5.8 Hz, H-3), 4.88 (d, 1H, J = 5.1 Hz, H-6), 4.74 (d, 1H, J = 14.9 Hz, H-7), 4.07 (d, 1H, J = 15.0 Hz, H-6), 3.88 (s, 3H, -OCH₃), 3.14 (d, 1H, J = 13.5 Hz, H-8), 3.04 (dd, 1H, J = 8.8, 5.0 Hz, H-3a), 2.71 (dd, 1H, J = 8.8, 5.6 Hz, H-3a), 3.03 (d, 1H, J = 13.5 Hz, H-8), and 0.00 [s, 9H, -OSi(CH₃)₃].

**TLC**: R_f (3:1 hexanes/EtOAc) = 0.70.

When the reaction mixture was quenched after 2 h with saturated solution of NaHCO₃ and worked up as described above in synthesis of 433. Chromatography on silica gel (MPLC) using 3:1 hexanes/EtOAc as the eluent yielded the corresponding silyl ether 437a (34 mg, 91% yield) as a colorless oil.

**1H NMR** (500 MHz, CDCl₃): δ 7.24-7.21 (m, 3H, H-3", H-4", H-5"), 7.07 (d, 1H, J = 7.8 Hz, H-2"), 7.06 (d, 1H, J = 7.4 Hz, H-6"), 6.96 (dd, 1H, J = 8.1, 2.0 Hz, H-3'), 6.94 (d, 1H, J = 2.0 Hz, H-3'), 6.79 (d, 1H, J = 8.2 Hz, H-6'), 6.72 (d, 1H, J = 6.0 Hz, H-4), 6.15 (d, 1H, J = 6.0 Hz, H-3), 4.75 (d, 1H, J = 15.0 Hz, H-6), 4.35 (d, 1H, J = 15.0 Hz, H-6), 3.88 (s, 3H, -OCH₃), 3.86 (s, 3H, -OCH₃), 3.15 (d, 1H, J = 13.5 Hz, H-7), 2.49 (d, 1H, J = 13.5 Hz, H-7), and -0.10 [s, 9H, -OSi(CH₃)₃].

**13C NMR** (125 MHz, CDCl₃): δ 170.2, 160.1, 158.2, 148.4, 134.2, 130.6, 128.2, 121.0, 113.9, 111.0, 105.0, 101.2, 96.8, 55.0, 54.5, 41.2, 26.8, and -2.1.

**IR** (thin film) 2963, 2928, 1735, 1466, 1370, 1238, 1159, 1114, and 1056.
HRMS (ESI) Calcd for C_{23}H_{29}NNaO_4Si^+ (M•Na^+): 434.1758, found: 434.1761.

GC/MS (5029021H): t_r = 14.91 min; m/z 411 (15, M^+), 320 (35, M^+-Bn), 246 (20), and 151 (100, DMB^+).

TLC: R_f (3:1 hexanes/EtOAc) = 0.30.

(3α,4β,7β,7αα)-3a,4,7,7α-Tetrahydro-3a-bromo-2-[[2'-[(trimethylsilyl)ethoxy]methyl]-4,7-epoxy-1H-isoindole-1,3(2H)-dione (439). Furan (0.30 mL) was added to a solution of maleimide 418 (100 mg, 0.568 mmol) in Et_2O (2.8 mL). The reaction mixture was stirred for 72 h at 65 °C. The reaction was concentrated in vacuo. Chromatography on silica gel (MPLC) using 6:1 hexanes/EtOAc as the eluent yielded 104 mg (75% yield) of 439.

\[
\begin{align*}
\text{1H NMR} & (500 MHz, CDCl}_3): \delta 6.69 (d, 1H, H-5), 6.68 (s, 1H, H-6), 5.31 (dd, 1H, J = 1.1 Hz, H-4), 5.30 (dd, 1H, J = 1.2 Hz, H-7), 4.98 (s, 1H, H-8), 4.97 (s, 1H, H-8), 3.59 (dd, 2H, J = 8.7, 7.8 Hz, H-1'), 2.90 (s, 1H, H-7a), 0.94 (dd, 2H, J = 8.3, 7.2 Hz, H-2'), and 0.01 (s, 9H, Si(CH_3)_3). \\
\text{13C NMR} & (125 MHz, CDCl}_3): \delta 173.4, 173.2, 136.8, 136.7, 83.5, 83.2, 68.4, 67.6, 56.1, 56.0, 17.9, and -1.3.
\end{align*}
\]

IR (thin film) 2953, 2919, 2898, 2254, 1789, 1719, 1446, 1412, 1343, 1246, 1177, 1096, 1023, 908, 869, 839, and 742.

HRMS (ESI) Calcd for C_{14}H_{28}BrNNaO_4Si^+ (M•Na^+): 396.0237, found: 396.0284.

TLC: R_f (6:1 hexanes/EtOAc) = 0.16.

(3β,3αα,4β,7β,7αα)-2,3,3a,4,7,7α-Hexahydro-3-benzyl-3a-bromo-3-hydroxy-2-[[2'-[(trimethylsilyl)ethoxy]methyl]-4,7-epoxy-1H-isoindole-1-one (440). Imide 439 (0.050 g, 0.168 mmol) was dissolved in Et_2O (1.0 mL), and benzyl magnesium chloride (0.6 mL,
1.33 M in ether) was added to the solution at 0 °C under inert atmosphere. The reaction mixture was warmed up to room temperature, stirred for 2 h at room temperature, quenched with saturated aqueous NH₄Cl solution (1.0 mL), and extracted with EtOAc+1% Et₃N (2 x 10.0 mL). All organic layers were combined, washed with brine (1 x 15.0 mL), and dried over anhydrous K₂CO₃. Chromatography on silica gel (MPLC) using 4:1 hexanes/EtOAc as the eluent yielded 30 mg (53% yield) of alcohol 440.

^1H NMR (500 MHz, CDCl₃): δ 7.32-7.25 (m, 5H, H-2"-H-6"), 6.57 (dd, 1H, J = 5.6, 1.6 Hz, H-6), 6.43 (dd, 1H, J = 5.8, 1.9 Hz, H-5), 5.11 (s, 1H, J = 1.1 Hz, H-7), 5.107 (s, 1H, H-4), 5.03 (d, 1H, J = 10.9 Hz, H-8), 4.84 (d, 1H, J = 10.9 Hz, H-8), 3.66 (t, 2H, J = 8.1 Hz, H-1'), 3.37 (d, 1H, J = 14.0 Hz, H-9), 3.24 (s, 1H, OMe), 3.05 (d, 1H, J = 14.0 Hz, H-9), 2.50 (s, 1H, H-7a), 0.95 (dd, 2H, J = 8.5, 8.2 Hz, H-2'), and 0.01 (s, 9H, Si(CH₃)₃).

TLC: Rᵥ (4:1 hexanes/EtOAc) = 0.20.

1-[(2',4'-Dimethoxy)phenylmethyl]-5-hydroxy-5-(phenylmethyl)-2-pyrrolidinone (445). Succinimide 444 (0.100 g, 0.40 mmol) was dissolved in diethyl ether (4.0 mL), and benzyl magnesium chloride (0.45 mL, 1.8 M) was added to the solution at ambient temperature under inert atmosphere. The reaction mixture was stirred for 5 h at room temperature, quenched with saturated aqueous NH₄Cl solution (1.0 mL), and extracted with EtOAc+1% Et₃N (2 x 5.0 mL). All organic layers were combined, washed with brine (1 x 5.0 mL), and dried over anhydrous K₂CO₃. Evaporation of the solvents under reduced pressure afforded crude hemiaminal 445 (0.130 g, 0.38 mmol, >95% pure by ^1H NMR spectroscopy) in 95% yield.

^1H NMR (500 MHz, CDCl₃): δ 7.45 (t, 2H, J = 8.3 Hz, H-3",H-5"), 7.30-7.27 (m, 3H, H-2",H-4",H-6"), 7.19 (dd, 1H, J = 8.5, 1.4 Hz, H-6'), 6.51 (dd, 1H, J = 8.3, 2.3 Hz, H-5'),
6.48 (d, 1H, J = 2.6 Hz, H-3'), 4.67 (d, 1H, J = 15.1 Hz, H-6), 4.45 (d, 1H, J = 15.1 Hz, H-6), 3.92 (s, 3H, -OCH3), 3.80 (s, 3H, -OCH3), 3.41 (s, 1H, -OH), 3.13 (d, 1H, J = 13.7 Hz, H-7), 3.02 (d, 1H, J = 13.7 Hz, H-7), 2.33 (ddd, 1H, J = 14.0, 7.7, 4.6 Hz, H-3), 2.21 (ddd, 1H, J = 14.0, 8.3, 4.5 Hz, H-3), 1.86 (ddd, 1H, J = 9.4, 6.0, 6.0 Hz, H-4), and 1.78 (ddd, 1H, J = 9.5, 6.7, 6.7 Hz, H-4).

TLC: Rf (1:3 hexanes/EtOAc) = 0.15.

1-[(2',4'-Dimethoxyphen)-1'-ylmethyl]-5-[(tert-butyldimethylsilyl)oxy]-5-benzyl-2-pyrrolidinone (446). Crude hemiaminal 445 (0.130 g, 0.38 mmol) was dissolved in DCM (1.4 mL), and 2,6-dimethylpyridine (0.19 mL, 1.5 mmol), followed by TBSOTf (0.28 mL, 1.14 mmol) were added to the solution at 0 °C, under inert atmosphere. The reaction mixture was gradually warmed to ambient temperature over 2 h, stirred for additional 14 h, quenched with NaHCO3 solution (2.0 mL), and extracted with DCM (3 x 5.0 mL). The combined organic layers were washed with brine (1 x 2.0 mL), dried over Na2SO4, and evaporated to give a yellow oil. Chromatography on silica gel (MPLC) using 2:1 hexanes/EtOAc as the eluent, yielded 160 mg (93 %) of TBS-ether 446 as a colorless solid.

mp = 89-93 °C;

1H NMR (500 MHz, CDCl3): δ 7.27-7.19 (m, 5H, H-2", H-3",H-4",H-5",H-6"), 7.09 (dd, 1H, J = 7.8, 1.9 Hz, H-6'), 6.45 (dd, 1H, J = 8.4, 2.5 Hz, H-5'), 6.42 (d, 1H, J = 2.5 Hz, H-3'), 4.61 (d, 1H, J = 15.7 Hz, H-6), 4.53 (d, 1H, J = 15.7 Hz, H-6), 3.84 (s, 3H, -OCH3), 3.77 (s, 3H, -OCH3), 2.96 (d, 1H, J = 13.4 Hz, H-7), 2.77 (d, 1H, J = 13.4 Hz, H-7), 2.35-2.28 (m, 2H, 2H-3), 1.94-1.84 (m, 2H, 2H-4), 0.84 (s, 9H, -OSiMe2C(CH3)3), 0.11 (s, 3H, -OSi(CH3)2'Bu), and 0.01 (s, 3H, -OSi(CH3)2'Bu).

13C NMR (125 MHz, CDCl3): δ 174.6, 160.0, 157.5, 135.9, 130.6, 130.0, 128.2, 126.9, 119.3, 104.5, 98.3, 94.3, 55.5, 55.4, 47.1, 36.3, 32.6, 29.8, 25.8, 18.3, -2.8, and -2.9.

IR (thin film) 2954, 2933, 2856, 1698, 1615, 1590, 1508, 1463, 1456, 1402, 1290, 1261, 1208, 1187, 1157, 1124, 1087, 1065, 1034, 1003, 836, 776, and 702.

HRMS (ESI) Calcd for C26H38NO4Si+: 456.2565, found: 456.2617.

TLC: Rf (2:1 hexanes/EtOAc) = 0.20.
(3R,4S)-3,4-Bis-(Hydroxy)-1-[(3',5'-dimethoxyphenyl)methyl]-2,5-pyrrolidinedione (S-4). Acetyl chloride (0.67 mL) was added to a solution of diacetate 447 (1.380 g, 3.15 mmol) in MeOH (40 mL) at 0 °C. After 13 h the reaction mixture was concentrated in vacuo yielding the crude product S-4 (1.050 g, 100% yield) as a colorless oil.

\[^1\text{H NMR}\ (500 \text{ MHz, CDCl}_3): \delta 7.18 (d, 1H, J = 8.0 \text{ Hz, H-7}', 6.43 (dd, 1H, J = 8.5, 2.2 Hz, H-6'), 6.42 (s, 1H, H-4'), 4.72 (d, 1H, J = 14.7 \text{ Hz, H-1}', 4.58 (d, 1H, J = 14.7 \text{ Hz, H-1'}), 4.56 (s, 2H, H-3, H-4), 3.88 (s, 2H, -OH), 3.794 (s, 3H, -OC\text{H}_3), and 3.790 (s, 3H, -OC\text{H}_3).\]

**TLC:** \(R_f\) (1:1 hexanes/EtOAc) = 0.10.

(3R,4S)-3,4-Bis-(Trimethylsilyloxy)-1-[(3',5'-dimethoxyphenyl)methyl]-2,5-pyrrolidinedione (450). Alcohol S-4 (1.050 g, 3.74 mmol) was dissolved in DCM (15.0 mL), and pyridine (0.904 mL, 11.22 mmol) followed by TMSCl (1.18 mL,) were added to the solution at 0 °C. The reaction mixture was warmed up to room temperature over 1 h, stirred for 16 h at ambient temperature, diluted with ether, washed with water. The organic layer was separated, and the aqueous layer was extracted back with ether (3 x 50.0 mL). All organic layers were combined, washed with brine (1 x 25.0 mL), dried over \(\text{Na}_2\text{SO}_4\), filtered, and concentrated in vacuo. Chromatography on silica gel (MPLC) using 5:1 hexanes/EtOAc as the eluent yielded the corresponding silyl ether 450 (1.272 g, 80% yield) as a colorless oil.

\[^1\text{H NMR}\ (500 \text{ MHz, CDCl}_3): \delta 7.14 (d, 1H, J = 8.0 \text{ Hz, H-7}), 6.41 (dd, 1H, J = 7.5, 2.5 Hz, H-6'), 6.40 (d, 1H, J = 2.5 \text{ Hz, H-4'}), 4.72 (d, 1H, J = 14.5 \text{ Hz, H-1'}), 4.51 (d, 1H, J = 14.5 \text{ Hz, H-1'}), 4.42 (s, 2H, H-3, H-4), 3.779 (s, 3H, -OCH_3), 3.777 (s, 3H, -OCH_3), and 0.23 (s, 18H, -OSi(CH_3)_3).\]

\[^{13}\text{C NMR}\ (75 \text{ MHz, CDCl}_3): \delta 160.8, 158.4, 130.8, 115.8, 104.2, 98.7, 76.7, 55.6, 37.7, and 0.3.\]
IR (thin film) 2958, 1726, 1616, 1590, 1510, 1464, 1439, 1377, 1334, 1254, 1210, 1159, 1137, 1073, 1037, 916, 850, and 758.

GC/MS (5029021H): tR = 13.04 min; m/z 425 (50, M+), and 151 (100, DMB+).

HRMS (ESI) Calcd for C19H31NNaO6Si+ (M•Na+): 448.1582, found: 448.1615.

TLC: Rf (5:1 hexanes/EtOAc) = 0.30.

(5E)-7-Chloro-4,6-dimethyl-5-octen-3-one (453) and 4,6-Dimethyl-5,7-octadien-3-one (454). Hydroxyketone 452 (0.060 g, 0.35 mmol) was dissolved in DCM (2.0 mL), and TEA (97 µL, 0.70 mmol) was added followed by MsCl (27 µL, 0.35 mmol) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C, treated with DBU (100 µL, 0.70 mmol), warmed up to room temperature, stirred for additional 2 h, quenched with water, and diluted with ether. The organic layer was separated, and the aqueous layer was extracted back with ether (3 x 15.0 mL). All organic layers were combined, washed with brine (1 x 5.0 mL), dried over Na2SO4, filtered, and concentrated in vacuo. Chromatography on silica gel (MPLC) using 40:1 hexanes/EtOAc as the eluent yielded 22 mg (33% yield) of ketone 453 (as a 2:1 mixture of syn and anti diastereomers) and 9 mg (16% yield) of ketone 454 as colorless oils.

453 (data reported for a major isomer):

1H NMR (500 MHz, CDCl3): δ 5.42 (dq, 1H, J = 9.7, 1.5 Hz, H-5), 4.57 (q, 1H, J = 7.0 Hz, H-7), 3.39 (dq, 1H, J = 9.7, 6.8 Hz, H-4), 2.49 (dq, 1H, J = 17.9, 7.3 Hz, H-2), 2.42 (dq, 1H, J = 17.9, 7.3 Hz, H-2), 1.81 (d, 3H, J = 1.5 Hz, C6-CH3), 1.60 (d, 3H, J = 6.8 Hz, 3H-8), 1.13 (d, 3H, J = 6.8 Hz, C4-CH3), and 1.03 (t, 3H, J = 7.3 Hz, 3H-1).

TLC: Rf (40:1 hexanes/EtOAc) = 0.30.

454 (data reported for a major isomer):

1H NMR (500 MHz, CDCl3): δ 6.36 (dd, 1H, J = 17.4, 10.7 Hz, H-7), 5.37 (br d, 1H, J = 9.7 Hz, H-5), 5.18 (d, 1H, J = 17.4 Hz, H-8), 5.03 (d, 1H, J = 10.7 Hz, H-8), 3.52 (dq,
1H, J = 9.7, 6.9 Hz, H-4), 2.50 (dq, 1H, J = 17.9, 7.3 Hz, H-2), 2.41 (dq, 1H, J = 17.9, 7.3 Hz, H-2), 1.83 (d, 3H, J = 1.4 Hz, C6-CH3), 1.17 (d, 3H, J = 6.8 Hz, C4-CH3), and 1.02 (t, 3H, J = 7.3 Hz, 3H-1).

**GC/MS (5029021):** t_r = 6.16 min; m/z 152 (30, M+), 95 (100), 67 (50), and 57 (70).

**TLC:** R_f (40:1 hexanes/EtOAc) = 0.25.

(±)-(4R,5R,6E)-rel-5-Acetyloxy-4,6-dimethyl-6-octen-3-one (S-5). Hydroxyketone 452 (0.050 g, 0.30 mmol) was dissolved in THF (1.0 mL), and pyridine (0.050 mL, 0.60 mmol) was added followed by acetic anhydride (0.056 mL, 0.60 mmol). The reaction mixture was stirred for 14 h at ambient temperature, diluted with ether, washed with water. The organic layer was separated, and the aqueous layer was extracted back with ether (3 x 5.0 mL). All organic layers were combined, washed with brine (1 x 5.0 mL), dried over Na2SO4, filtered, and concentrated in vacuo. Chromatography on silica gel (MPLC) using 12:1 hexanes/EtOAc as the eluent yielded 63 mg (99% yield) of ketone S-5 as a colorless oil.

**1H NMR** (500 MHz, CDCl3): δ 5.49 (qpent, 1H, J = 6.8, 1.3 Hz, H-7), 5.38 (d, 1H, J = 7.7 Hz, H-5), 2.92 (pent, 1H, J = 7.0 Hz, H-4), 2.44 (q, 2H, J = 7.2 Hz, H-2), 2.06 (s, 3H, -OC(O)CH3), 1.61 (q, 3H, J = 1.3 Hz, C6-CH3), 1.58 (d, 3H, J = 6.8, 1.3 Hz, 3H-8), 1.08 (d, 3H, J = 6.9 Hz, C4-CH3), and 1.01 (t, 3H, J = 7.3 Hz, 3H-1).

**TLC:** R_f (6:1 hexanes/EtOAc) = 0.60.

(4E,6E)-4,6-Dimethyl-4,6-octadiene-3-one (455). Acetylketone S-5 (0.062 g, 0.30 mmol) was dissolved in THF (1.0 mL), and DBU (0.200 mL, 1.30 mmol) was added to the solution. The reaction mixture was stirred for 48 h at ambient temperature, diluted with ether, washed with water. The organic layer was separated, and the aqueous layer was extracted back with ether (3 x 5.0 mL). All organic layers were combined, washed with brine (1 x 5.0 mL), dried over Na2SO4, filtered, and concentrated in vacuo.
Chromatography on silica gel (MPLC) using 40:1 hexanes/EtOAc as the eluent yielded 38 mg (83% yield) of ketone 455 as a colorless oil.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 6.97 (s, 1H, H-5), 5.75 (qpent, 1H, $J = 7.0, 1.3$ Hz, H-7), 2.71 (q, 2H, $J = 7.3$ Hz, H-2), 2.08 (d, 3H, $J = 1.5$ Hz, C4-C$_3$H$_7$), 1.87 (pent, 3H, $J = 1.3$ Hz, C6-C$_3$H$_7$), 1.77 (d, 3H, $J = 7.0$ Hz, 3H-8), and 1.11 (t, 3H, $J = 7.3$ Hz, 3H-1).

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 203.7, 143.1, 134.1, 133.6, 131.4, 30.8, 16.4, 14.3, 13.3, and 9.2.

IR (thin film) 2978, 2937, 1667, 1623, 1379, 1213, and 1043.

HRMS (ESI) Calcd for C$_{10}$H$_{16}$NaO$_2$ (M•Na$^+$): 175.1093, found: 175.1120.

GC/MS (5029021): $t_r = 6.96$ min; $m/z$ 152 (10, M$^+$), 137 (100, M$^+$-Me), 95 (40), and 67 (30).

TLC: R$_f$ (40:1 hexanes/EtOAc) = 0.30.

Butyl (2E,4E)-1-ethylidene-2,4-hexadienyl ether (457). A solution of ketone 455 (100 mg, 0.660 mmol) in THF (2.0 mL) was cooled to −78 °C, and a solution of freshly prepared LDA (2.00 mmol) was added to the reaction mixture at −78 °C. The reaction mixture was stirred for 2 h at −78 °C. Then a solution of Tf$_2$NPh (471 mg, 1.32 mmol) in THF (2.0 mL) was added to the reaction mixture at −78 °C. The resulting solution was stirred at 0 °C for 15 h, quenched with saturated solution of NaHCO$_3$ (1.0 mL). The organic layer was separated, and the aqueous layer was extracted back with Et$_2$O (2 x 10.0 mL). All organic layers were combined, dried over Na$_2$SO$_4$, and concentrated in vacuo. Chromatography on silica gel (MPLC) using 99:1 hexanes/EtOAc as the eluent yielded 40 mg (30% yield) of 457.

457 (1-E)/(1-Z)~ 6:1, data reported for the major isomer:
**1H NMR** (500 MHz, CDCl$_3$): δ 6.21 (br s, 1H, H-5), 5.41 (qpent, 1H, $J = 6.9$, 1.5 Hz, H-7), 5.12 (q, 1H, $J = 7.0$ Hz, H-2), 3.60 (t, 2H, $J = 6.6$ Hz, 2H-1'), 1.84 (d, 3H, $J = 1.4$ Hz, CH$_3$-C4), 1.76 (t, 3H, $J = 1.4$ Hz, CH$_3$-C6), 1.71 (d, 3H, $J = 6.9$ Hz, 3H-8), 1.70 (d, 3H, $J = 6.9$ Hz, 3H-1), 1.67 (pent, 2H, $J = 6.6$ Hz, 2H-2'), 1.48 (pent, 2H, $J = 7.4$ Hz, 2H-3'), and 0.95 (t, 3H, $J = 7.4$ Hz, 3H-4').

**13C NMR** (125 MHz, CDCl$_3$): δ 157.5, 133.8, 129.8, 128.7, 125.1, 113.1, 109.1, 67.8, 30.5, 19.6, 17.1, 15.1, 14.2, 14.0, and 11.4.

**IR** (thin film) 2959, 2930, 2856, 1448, 1378, 1300, 1244, 1076, and 796.

**HRMS** (ESI) Calcd for C$_{14}$H$_{24}$NaO$^+$ (M•Na$^+$): 231.1719, found: 231.1706.

**GC/MS** (5029021): $t_r = 8.29$ min; $m/z$ 208 (20, M$^+$), 193 (10, M$^+$-Me), 152 (30, M$^+$-Bu), and 137 (100).

**TLC**: $R_f$ (40:1 hexanes/EtOAc) = 0.72.

**3Z,SE)-4,6-Dimethyl-3,5,7-octatrien-3-yl ester of 1,1,1-trifluoromethanesulfonic acid** (458). A solution of ketone 455 (50 mg, 0.330 mmol) in 4:1 THF/HMPA (1.25 mL) was cooled to 0 °C, and a solution of LHMDS (0.4 mL, 1M in THF, 0.40 mmol) was added to the reaction mixture at 0 °C. Then a solution of Tf$_2$NPh (141 mg, 0.40 mmol) in THF (1.0 mL) was added to the reaction mixture at 0 °C. The resulting solution was stirred at 0 °C for 1 h and for 8 h at room temperature, quenched with saturated solution of NH$_4$Cl (1.0 mL). The organic layer was separated, and the aqueous layer was extracted back with Et$_2$O (2 x 10.0 mL). All organic layers were combined, washed with saturated solution of NaHCO$_3$ and brine, dried over Na$_2$SO$_4$, and concentrated in vacuo. Chromatography on silica gel (MPLC) using 99:1 hexanes/EtOAc as the eluent yielded 12 mg (13% yield) of 458.

**1H NMR** (500 MHz, CDCl$_3$): δ 6.41 (dd, 1H, $J = 17.7$, 11.0 Hz, H-7), 5.85 (br s, 1H, H-5), 5.28 (d, 1H, $J = 17.1$ Hz, H-8), 5.11 (d, 1H, $J = 11.1$ Hz, H-8), 2.31 (q, 2H, $J = 7.4$ Hz, 2H-2), 1.92 (s, 6H, C4-CH$_3$ and C6-CH$_3$), 1.17 (d, 3H, $J = 6.8$ Hz, C4-CH$_3$), and 1.26 (t, 3H, $J = 7.3$ Hz, 3H-1).

**TLC**: $R_f$ (99:1 hexanes/EtOAc) = 0.50.
(3E,5E)-1,1-Dibromo-3,5-dimethyl-1,3,5-heptatriene (S-6). To a solution of PPh3 (4.755 g, 18.15 mmol) in DCM (20 mL) at 0 °C was added CBr₄ (3.14 g, 9.43 mmol) in small portions over 30 min. The mixture was stirred for 30 min, and then a solution of aldehyde 460₁³⁵ (0.450 g, 4.032 mmol) in DCM (7.0 mL) was added. After stirring for 1 h at 0 °C, the reaction mixture was poured into ether (200 mL), and the solids were removed by filtration. The filtrate was washed with saturated aqueous solution of NaHCO₃ (1 x 50 mL), water (1 x 50 mL), and brine (1 x 50 mL). The organic solution was dried (Na₂SO₄), filtered, and evaporated in vacuo. Chromatography on silica gel (MPLC) using hexanes as the eluent yielded 959 mg (85% yield) of dibromide S-6 as a yellow oil.

¹H NMR (500 MHz, CDCl₃): δ 6.97 (s, 1H, H-2), 6.03 (s, 1H, H-4), 5.52 (q, 1H, J = 6.8 Hz, H-6), 2.02 (s, 3H, C₃-C₃H₃), 1.77 (s, 3H, C₅-C₅H₃), and 1.70 (d, 3H, J = 6.5 Hz, 3H-8).

GC/MS (5029021): tᵣ = 8.54 min; m/z 282, 280, and 278 (10, M⁺), 267, 265, and 263 (15, M⁺-Me), 201 and 119 (20, M⁺-Br), 120 (100), and 105 (80).

TLC: Rf (hexanes) = 0.35.

(4E,6E)-4,6-Dimethyl-4,6-octadien-2-yne (461). A solution of dibromide S-6 (744 mg, 2.657 mmol) in THF (8.0 mL) was cooled to −78 °C, and n-BuLi (2.9 mL, 2.0 M in hexanes, 5.845 mmol) was added to the reaction mixture at −78 °C. The reaction mixture was stirred for 30 min at −78 °C. Then neat MeI (0.827 mL, 13.29 mmol) was added to the reaction mixture at −78 °C. The resulting solution was stirred at −78 °C for 30 min and for 1 h at room temperature, quenched with saturated solution of NH₄Cl (10.0 mL). The organic layer was separated, and the aqueous layer was extracted back with pentane (2 x 40.0 mL). All organic layers were combined, washed with saturated solution of NaHCO₃ and brine, dried over Na₂SO₄, and concentrated at 40 °C (12 mmHg).
Chromatography on silica gel (MPLC) using pentane as the eluent yielded 136 mg (40% yield) of alkyne 461.

**1H NMR** (500 MHz, CDCl₃): δ 6.17 (s, 1H, H-5), 5.44 (q, 1H, J = 6.9 Hz, H-7), 1.95 (s, 3H, CH₃), 1.92 (s, 3H, CH₃), 1.75 (s, 3H, CH₃), and 1.69 (d, 3H, J = 7.1 Hz, CH₃).

**GC/MS** (5029021): tᵣ = 6.11 min; m/z 134 (30, M⁺), 119 (100, M⁺-Me), and 91 (50).

**TLC**: Rₓ (pentane) = 0.35.

(±)-(4S,5S)-*rel*-2,4,5-Trimethyl-2-penten-1-one (462), (±)-(4S,5R)-*rel*-2,4,5-Trimethyl-2-penten-1-one (463), 2,3,5-Trimethyl-3-penten-1-one (464). Solid PPh₃ (1.602 g, 7.26 mmol) was added over 30 min in small portions to a solution of aldehyde 460 (0.450 g, 4.032 mmol) and CBr₄ (2.407 g, 7.26 mmol) in DCM (15.0 mL) at 0 °C. After stirring for 10 min at 0 °C, the reaction mixture was poured into pentane (200 mL), and the solids were removed by filtration. Chromatography on silica gel (MPLC) using 20:1 hexanes/EtOAc as the eluent yielded 10 mg (4% yield) of ketone 462, 10 mg (4% yield) of ketone 463, and 70 mg (30% yield) of ketone 464 as colorless oils.

462:

**1H NMR** (500 MHz, CDCl₃): δ 7.20 (dq, 1H, J = 2.6, 1.3 Hz H-3), 2.95 (pentpent, 1H, J = 7.0, 2.5 Hz, H-4), 2.48 (pentet, 1H, J = 7.5 Hz, H-5), 1.76 (d, 3H, J = 1.5 Hz, C2-CH₃), 1.08 (d, 3H, J = 7.6 Hz, C4-CH₃), and 1.03 (d, 3H, J = 7.4 Hz, C5-CH₃).

**GC/MS** (5029021): tᵣ = 4.76 min; m/z 124 (50, M⁺), 109 (100, M⁺-Me), 96 (40), and 81 (100).

**TLC**: Rₓ (20:1 hexanes/EtOAc) = 0.40.

463: **1H NMR** (500 MHz, CDCl₃): δ 7.11 (dq, 1H, J = 2.5, 1.5 Hz H-3), 2.39 (qsextet, 1H, J = 7.0, 2.5 Hz, H-4), 1.88 (qd, 1H, J = 7.5, 2.5 Hz, H-5), 1.61 (d, 3H, J = 1.5 Hz, C2-CH₃), 1.18 (d, 3H, J = 7.3 Hz, C4-CH₃), and 1.17 (d, 3H, J = 7.4 Hz, C5-CH₃).
GC/MS (5029021): \( t_r = 5.22 \) min; \( m/z \) 124 (60, \( M^+ \)), 109 (100, \( M^+\text{-Me} \)), 96 (40), and 81 (100).

TLC: \( R_f \) (20:1 hexanes/EtOAc) = 0.45.

464 (observed as a mixture of the syn and anti isomers, major and minor = 1.7:1):

\[ \text{**1H NMR** (500 MHz, CDCl}_3\text{):} \delta 5.65 \text{ (sextet, 1H, } J = 1.8 \text{ Hz, H-4_maj,)} \]
\[ 5.63 \text{ (sextet, 1H, } J = 1.8 \text{ Hz, H-4_min,)} \]
\[ 2.93 \text{ (qq, 1H, } J = 7.5, 2.5 \text{ Hz, H-2_min,)} \]
\[ 2.88 \text{ (qq, 1H, } J = 7.6, 2.5 \text{ Hz, H-2_maj,)} \]
\[ 2.73 \text{ (qsextet, 1H, } J = 7.5, 2.5 \text{ Hz, H-5_min,)} \]
\[ 2.71 \text{ (qdq, 1H, } J = 7.5, 2.0, 1.0 \text{ Hz, H-5_maj,)} \]
\[ 1.79 \text{ (m, 3H+3H, C3_maj-C3_maj-C3_min,)} \]
\[ 1.15 \text{ (d, 3H, } J = 7.7 \text{ Hz, C5-C5_min,)} \]
\[ 1.13 \text{ (d, 3H, } J = 7.7 \text{ Hz, C5-C5_maj,)} \]
\[ 1.12 \text{ (d, 3H, } J = 7.4 \text{ Hz, C2-C2_maj,)} \]
\[ 1.11 \text{ (d, 3H, } J = 7.4 \text{ Hz, C2-C2_min,)} \]

GC/MS (5029021): \( t_r = 5.59 \) min; \( m/z \) 124 (80, \( M^+ \)), 109 (100, \( M^+\text{-Me} \)), 96 (30), and 81 (70).

TLC: \( R_f \) (20:1 hexanes/EtOAc) = 0.35.

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**Tributyl[(1E,3E,5E)-1,3,5-trimethyl-1,3,5-heptatrien-1-yl]stannane (415a)** (The reaction and purifications were performed in the dark). A solution of CuCN (46 mg, 0.512 mmol) in THF (2.0 mL) was cooled to –50 °C, and \( n\text{-BuLi} \) (0.55 mL, 2.0 M in hexanes, 1.10 mmol) was added to the reaction mixture at –50 °C. The reaction mixture was stirred for 15 min at –50 °C. Then neat Bu\(_3\)SnH (0.280 mL, 1.03 mmol) was added to the reaction mixture at –50 °C. The resulting solution was stirred at –50 °C for 30 min, then a solution of alkyne 461 (49 \( \mu \)L, 0.366 mmol) in THF (1.0 mL) was added to the reaction mixture at –50 °C. The resulting solution was stirred at –50 °C for 3 h, quenched with MeOH (2.2 mL), and stirred at 0 °C for 10 h. The reaction was partitioned between saturated aqueous solution of NH\(_4\)Cl/pentane (10.0 mL). The organic layer was separated, and the aqueous layer was extracted back with pentane (3 x 10.0 mL). All organic layers were combined, washed with saturated solution of NaHCO\(_3\) and brine, dried over
Na₂SO₄, and concentrated in vacuo, yielding crude stannane 415a as a mixture with other tin by-products, which was unstable to chromatographic purification, even when hexanes (+3% Et₃N) was used as an eluent.

**¹H NMR** (500 MHz, CDCl₃): δ 5.60 (br s, 1H, H-4), 5.74 (br s, 1H, H-2), 5.43 (q, 1H, J = 7.5 Hz, H-6), 2.04 (d, 3H, J = 2.0 Hz, C5-CH₃), 1.90 (br s, 3H, C3-CH₃), 1.77 (br s, 3H, C1-CH₃), 1.70 (d, 3H, J = 7.3 Hz, 3H-7), 1.50-1.43 (m, 6H, SnCH₂-C₄H₃-Et), 1.30 (m, 6H, J = 7.3 Hz, Sn(CH₂)₂-C₄H₃), 0.88 (tt, 6H, J=3 Hz, J=8.0 Hz, Sn-C₂H₄-Pr), and 0.88 (t, 9H, J = 7.3 Hz, 3-CH₂-CH₃).

**GC/MS** (5027016): tᵣ = 11.69 min; m/z 426 (10, M⁺), 369 (100, M⁺-Bu), 313 (60, M⁺-Bu, butene), 255 (60), 177 (30), and 199 (30).

**TLC**: Rᶠ (pentane) = 0.80.

(2E,4E,6E)-2-Iodo-4,6-dimethyl-2,4,6-octatriene (470) (The reaction and purifications were performed in the dark). A solution of unpurified stannane 415a (~3.1 g, ca. 20% pure by ¹H NMR spectroscopy, ~2.2 mmol) in ether (25 mL) was cooled to 0 °C, and a solution of I₂ (3.7 g, 14.6 mmol) was added to the reaction mixture at 0°C. The reaction mixture was stirred for 1 h at 0 °C, quenched with saturated solution of NaHCO₃. The organic layer was separated, washed with brine, dried over Na₂SO₄, and concentrated in vacuo, yielding crude iodide 470 (300 mg, ~40% pure by ¹H NMR spectroscopy), which was unstable to chromatographic purification on silica gel.

**¹H NMR** (500 MHz, CDCl₃): δ 6.67 (br s, 1H, H-3), 5.74 (br s, 1H, H-5), 5.45 (q, 1H, J = 7.8 Hz, H-7), 2.58 (d, 3H, J = 1.6 Hz, C4-CH₃), 1.86 (br s, 3H, C6-CH₃), 1.75 (br s, 3H, 3H-1), and 1.69 (d, 3H, J = 6.8 Hz, 3H-8).

**GC/MS** (5027016): tᵣ = 8.18 min; m/z 262 (20, M⁺), 135 (100, M⁺-I), 119 (50), 105 (60), and 91 (40).

**TLC**: Rᶠ (pentane) = 0.80.
2-[[1Z,3E,5E]-1,3,6-Trimethyl-1,3,5-Heptatrien-1-yl]-1,3,2-benzodioxaborole (415b). (The reaction and purifications were performed in the dark). Freshly prepared neat catecholborane (357) (40 µl, 0.373 mmol) was added to neat freshly prepared alkyne 461 (50 mg, 0.373 mmol). The reaction mixture was stirred at rt for 20 h, yielding borane 415b in 100% yield (>95% by 1H NMR spectroscopy).

1H NMR (500 MHz, CDCl3): δ 6.89-6.86 (m, 2H, 2CAr-H), 6.84-6.81 (m, 2H, 2CAr-H), 6.09 (br s, 1H, H-4), 5.54 (q, 1H, J = 7.4 Hz, H-6), 5.02 (s, 1H, H-2), 2.13 (d, 3H, J = 1.5 Hz, CH3), 2.06 (s, 3H, CH3), 1.81 (s, 3H, CH3), and 1.74 (d, 3H, J = 7.1 Hz, 3H-7).

GC/MS (5029021): tᵣ = 8.97 min; m/z 208 (10), 182 (30), 123 (30), 85 (100), and 69 (90).

(2E,4E,6E,8E)-3,5,7,9-Tetramethyl-6,8,9,12-octadecatetraene (473). (The reaction and purifications were performed in the dark). A solution of iodide 314 (106 mg, 0.32 mmol), and Pd(PPh3)4 (17 mg, 0.014 mmol) in THF (1.0 mL) was stirred in the dark under Ar for 10 min, then neat borane 415b (0.373 mmol) was added to the reaction mixture, and it was stirred for additional 5 min. Solution of KOH (0.66 mL, 1M in water, 0.66 mmol) was added, and the resulting solution was heated at 80 °C for 2 h. The reaction mixture was cooled to room temperature, poured into ether. The organic layer was separated, and aqueous layer was extracted back with Et2O (2 x 20 mL). All organic layers were combined, washed with brine, dried over Na2SO4, filtered, and concentrated in vacuo. Chromatography on silica gel (MPLC) using hexanes as the eluent yielded 46 mg (58% yield) of product 473 as a colorless oil.

1H NMR (500 MHz, CDCl3): δ 5.78 (br s, 1H, H-4), 5.76 (br s, 1H, H-6), 5.68 (br s, 1H, H-8), 5.44 (q, 1H, J = 7.3 Hz, H-2), 2.04-1.98 (m, 2H, J = 6.9 Hz, 2H-10), 1.91 (d, 3H, J = 1.3 Hz, CH3), 1.90 (d, 3H, J = 1.5 Hz, CH3), 1.79 (d, 3H, J = 1.4 Hz, CH3), 1.71 (d, 3H, J = 7.3 Hz, CH3), 1.45-1.39 (m, 2H, 2H-11), 1.30-1.24 (m, 12H, H-12,13,14,15,16,17), and 0.88 (t, 3H, J = 7.0 Hz, 3H-18).
**GC/MS** (5029021): $t_r = 11.54$ min; $m/z$ 302 (60, $M^+$), 287 (50, $M^+$-Me), 175 (70), and 133 (100).

**TLC**: $R_f$ (hexanes) = 0.70.

(4$S$)-(6$E$,8$E$,10$E$,12$E$)-4,6,8,10,12-Pentamethyl-6,8,9,12-tetradecatetraen-1-ol (474a), (4$S$)-(6$E$,8$E$,10$E$,12$E$)-(tert-Butyldimethyl)silyl-4,6,8,10,12-pentamethyl-6,8,9,12-tetradecatetraen-1-ol (474b), and (4$S$)-(6$E$,8$E$,10$E$,12$E$)-(tert-Triethyl)-silyl-4,6,8,10,12-pentamethyl-6,8,9,12-tetradecatetraen-1-ol (474c). (The reactions and purifications were performed in the dark). The reactions were conducted analogously to synthesis 473, using the corresponding iodide 312.

**474a**: The crude was subjected to a quick pipette column on Florisil support using 3:1 hexanes/EtOAc as the eluent, which yielded 10 mg (10% yield) of product 474a as a colorless oil.

$^1$H NMR (500 MHz, CDCl$_3$): δ 5.79 (br s, 1H, H-9), 5.77 (br s, 1H, H-11), 5.67 (br s, 1H, H-7), 5.44 (q, 1H, $J = 6.8$ Hz, H-13), 3.64 (t, 2H, $J = 6.7$ Hz, 2H-1), 2.07 (dd, 1H, $J = 12.9$, 6.1 Hz, H-5), 1.92 (br s, 3H, CH$_3$), 1.91 (br s, 3H, CH$_3$), 1.77 (s, 3H, CH$_3$), 1.71 (d, 3H, $J = 8.3$ Hz, CH$_3$), 1.92 (dd, 1H, $J = 13.4$, 8.3 Hz, H-5), 1.80 (d, 1H, $J = 1.2$ Hz, 3H-6), 1.94-1.50 (m), 1.38 (m, 1H, $J = 10.6$, 6.5, 5.2 Hz), 1.30-1.24 (m), 1.14 (m, 1H, $J = 10$, 7, 5 Hz, H-2), 0.97 (d, 3H, $J = 6.6$ Hz, C4-CH$_3$), and 0.90-0.84 (m).

**GC/MS** (5029021): $t_r = 11.22$ min; $m/z$ 276 (50, $M^+$), 261 (30, $M^+$-Me), 175 (50), and 133 (100).

**TLC**: $R_f$ (3:1 hexanes/EtOAc) = 0.60.

**474b**: The crude was subjected to chromatography on silica gel (MPLC) using 200:1 hexanes/EtOAc as the eluent, which yielded 68 mg (70% yield) of product 474b as a colorless oil.
\(^1\text{H NMR}\) (500 MHz, CDCl\(_3\)): \(\delta\ 5.83\) (br s, 1H, H-9), 5.78 (br s, 1H, H-11), 5.66 (br s, 1H, H-7), 5.43 (q, 1H, \(J = 8.3\) Hz, H-13), 3.59 (t, 2H, \(J = 6.7\) Hz, 2H-1), 2.19 (dd, 1H, \(J = 13.3, 6.3\) Hz, H-5), 2.05 (dd, 1H, \(J = 13.3, 6.3\) Hz, H-5), 1.93 (br s, 3H, CH\(_3\)), 1.90 (br s, 3H, CH\(_3\)), 1.79 (s, 3H, CH\(_3\)), 1.76 (s, 3H, CH\(_3\)), 1.71 (d, 1H, \(J = 8.3\) Hz, 3H-13), 1.94-1.54 (m), 1.38 (m, 1H, \(J = 6\) Hz), 1.38-1.27 (m), 1.08 (m, 1H, \(J = 10, 7, 5\) Hz, H-2), 0.89 [s, 9H, -OSiMe\(_2\)C(CH\(_3\))\(_3\)], 0.84 (d, 3H, \(J = 6.5\) Hz, C4-C(CH\(_3\))\(_3\)), and 0.15 (s, 6H, -OSi(C(CH\(_3\)))\(_2\)tBu).

\(\text{GC/MS}\) (5029021): \(t_r = 11.54\) min; \(m/z\) 390 (20, M\(^+\)), 375 (10, M\(^+\)-Me), 213 (100), and 120 (80).

\(\text{TLC}\): \(R_f\) (200:1 hexanes/EtOAc) = 0.30.

\(474c\): The crude was subjected to chromatography on silica gel (MPLC) using 200:1 hexanes/EtOAc as the eluent, which yielded 38 mg (40% yield) of product \(474c\) as a colorless oil.

\(^1\text{H NMR}\) (500 MHz, CDCl\(_3\)): \(\delta\ 5.78\) (br s, 1H, H-9), 5.74 (br s, 1H, H-11), 5.66 (br s, 1H, H-7), 5.44 (q, 1H, \(J = 7.0\) Hz, H-13), 3.58 (t, 2H, \(J = 6.7\) Hz, 2H-1), 2.05 (dd, 1H, \(J = 13.3, 6.6\) Hz, H-5), 2.00 (dd, 1H, \(J = 13.5, 8.0\) Hz, H-5), 1.91 (br s, 3H, CH\(_3\)), 1.90 (br s, 3H, CH\(_3\)), 1.79 (s, 3H, CH\(_3\)), 1.76 (s, 3H, CH\(_3\)), 1.71 (d, 1H, \(J = 6.9\) Hz, 3H-13), 1.94-1.54 (m), 1.38-1.27 (m), 1.08 (m, 1H, H-2), 0.96 [t, 9H, \(J = 7.9\) Hz, -OSi(CH\(_2\)CH\(_3\))\(_3\)], and 0.57 (q, 6H, \(J = 8.0\) Hz, -OSi(CH\(_2\)CH\(_3\))\(_3\)).

\(\text{GC/MS}\) (5029021): \(t_r = 12.74\) min; \(m/z\) 390 (20, M\(^+\)), 375 (10, M\(^+\)-Me), 241 (60), and 120 (100).

\(\text{TLC}\): \(R_f\) (200:1 hexanes/EtOAc) = 0.30.

\((4S)-(6E,8E,10E,12E)-4,6,8,10,12\text{-Pentamethyl-6,8,9,12-tetradecatetraenal} \ (475)\). (The reaction and purifications were performed in the dark). A solution of alcohol \(474a\) (13 mg, 0.046 mmol) in CDCl\(_3\) (1.0 mL) at 0 °C was treated with DMP (23 mg, 0.054
mmol). After stirring for 48 h at 0 °C the reaction mixture was filtered through 1.5 cm-tall plug of Florisil using DCM (10 mL) as an eluent, which gave the crude 475 (~70% pure by $^1$H NMR spectroscopy) as a colorless oil.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 9.77 (d, 1H, $J = 1.7$ Hz, H-1), 5.88 (br s, 1H, H-11), 5.84 (br s, 1H, H-7), 5.77 (br s, 1H, H-7), 5.44 (q, 1H, $J = 7.9$ Hz, H-13), 2.22-2.18 (m, 1H, H-5), 2.04 (br s, 3H, CH$_3$), 1.81 (br s, 3H, CH$_3$), 1.80 (s, 3H, CH$_3$), 1.71 (d, 3H, $J = 8.3$ Hz, CH$_3$), 2.04-1.40 (m), 1.30-1.20 (m), 0.97 (d, 3H, $J = 6.5$ Hz, C4-CH$_3$), and 0.90-0.80 (m).

GC/MS (5029021): $t_r = 10.91$ min; $m/z$ 274 (60, M$^+$), 259 (20, M$^+$-Me), 175 (60), and 133 (100).

TLC: $R_f$ (6:1 hexanes/EtOAc) = 0.50.

(45)-(6E,8E,10E,12E)-1-Iodo-4,6,8,10,12-pentamethyl-6,8,9,12-tetradecatetraene (476). (The reaction and purifications were performed in the dark). A solution of I$_2$ (11 mg, 0.044 mmol) in Et$_2$O (0.2 mL) was added to a solution of alcohol 475a (7 mg, 0.025 mmol), imidazole (7 mg, 0.094 mmol), and PPh$_3$ (12 mg, 0.046 mmol) in 2:1 Et$_2$O/benzene (0.6 mL) at 0 °C. The reaction mixture was for 12 h at room temperature, partitioned between 10% aqueous solution of Na$_2$S$_2$O$_3$/DCM. The organic layer was separated, the aqueous layer was extracted back with DCM (3 x 3.0 mL). All organic layers were combined, washed with brine (1 x 2.0 mL), dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo. Chromatography on silica gel (HPLC, normal phase), using hexanes as the eluent, yielded partially purified product 476 (<1 mg, ~50% pure by $^1$H NMR spectroscopy).

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 5.92 (br s, 1H, H-9), 5.82 (br s, 1H, H-11), 5.78 (br s, 1H, H-7), 5.36 (q, 1H, $J = 7.5$ Hz, H-13), 3.17 (t, 2H, $J = 6.7$ Hz, 2H-1), 2.06-1.99 (m,
2H), 1.93 (br s, 3H, \(CH_3\)), 1.91 (br s, 3H, \(CH_3\)), 1.87 (s, 3H, \(CH_3\)), 1.84-1.66 (m), 1.45-1.39 (m, 2H), 1.22-1.14 (m, 2H), and 0.86 (d, 3H, \(J = 6.6 \text{ Hz, } C4-CH_3\)).

**GC/MS (5029021):** \(t_r = 11.84 \text{ min; } m/z \ 386 \ (10, M^+)\), 371 (5, \(M^+\)-Me), 120 (100), and 105 (40).

**TLC:** \(R_f\) (hexanes) = 0.50.
Bibliography

14. Although in the paper the authors reported an optional synthesis of an enantiopure 10 starting from a tartaric acid derivative, in email communication with S. J. Danishefsky and personal communication with T. H. Lambert they implied that for the actual completion of a total synthesis of UCS1025A they used 10, prepared from a racemic starting material and separated by HPLC on a chiral support.


49. Otera’s catalyst was freshly prepared before use from Bu₂SnO and Bu₂SnCl₂ according to: Otera, J.; Dahon, N.; Nozaki, H. J. Org. Chem. 1991, 56, 5307-5311.


79. Unpublished results. From personal communication with Dr. Dvornikovs
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