Utility of the Catalytic, Asymmetric Acyl Halide-Aldehyde Cyclocondensation Reaction in Natural Product Synthesis

by

Andrew S. Wasmuth

B.Sc., University of Rochester, 2001

Submitted to the Graduate Faculty of

the Department of Chemistry in partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

University of Pittsburgh

2006

UNIVERSITY OF PITTSBURGH

ARTS AND SCIENCES

This dissertation was presented

by

Andrew S. Wasmuth

It was defended on

September 6, 2006

and approved by

Scott G. Nelson, Ph.D., Associate Professor

Craig S. Wilcox, Ph.D., Professor

Peter Wipf, Ph.D., University Professor

Billy Day, Ph.D., Associate Professor

Dissertation Advisor: Scott G. Nelson, Ph.D., Associate Professor

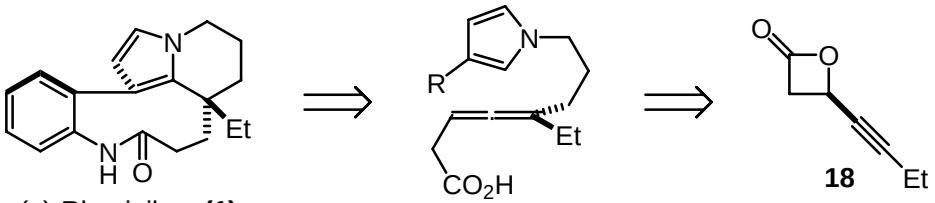
Utility of the Catalytic, Asymmetric Acyl Halide-Aldehyde Cyclocondensation Reaction in Natural Product Synthesis

Andrew S. Wasmuth, Ph. D.

University of Pittsburgh, 2006

Abstract

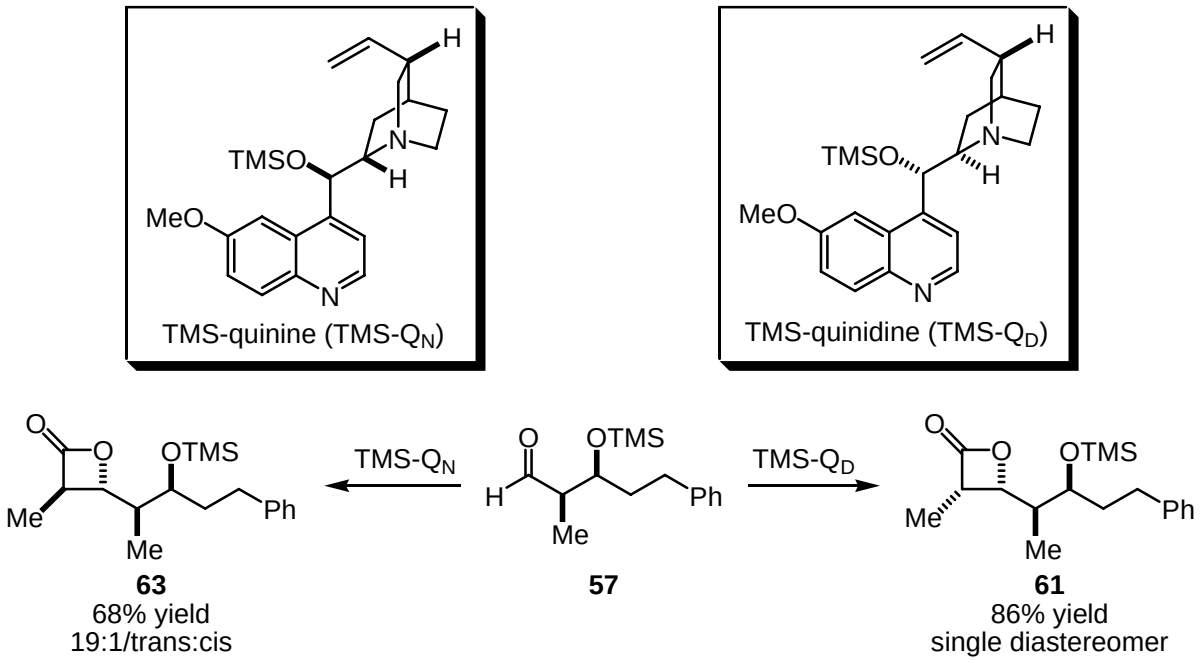
The ability of the catalytic, asymmetric acyl halide-aldehyde cyclocondensation (AAC) reaction to produce stereoenriched β-lactone products has found extensive utility in natural product synthesis. The asymmetric Al(III)-catalyzed AAC-S_N2' ring opening sequence was exploited in synthetic efforts towards the enantioselective total synthesis of the aspidospermane alkaloid (–)-rhazinilam **(1)**. The synthetic sequence features an enantioselective cyclization of a tethered pyrrole moiety onto an optically-active allene to set the quaternary carbon stereocenter while concomitantly forming rhazinilam's tetrahydroindolizine core. In addition, attempts at forming the requisite biaryl bond *via* a Pd-catalyzed cross-coupling reaction are also discussed.



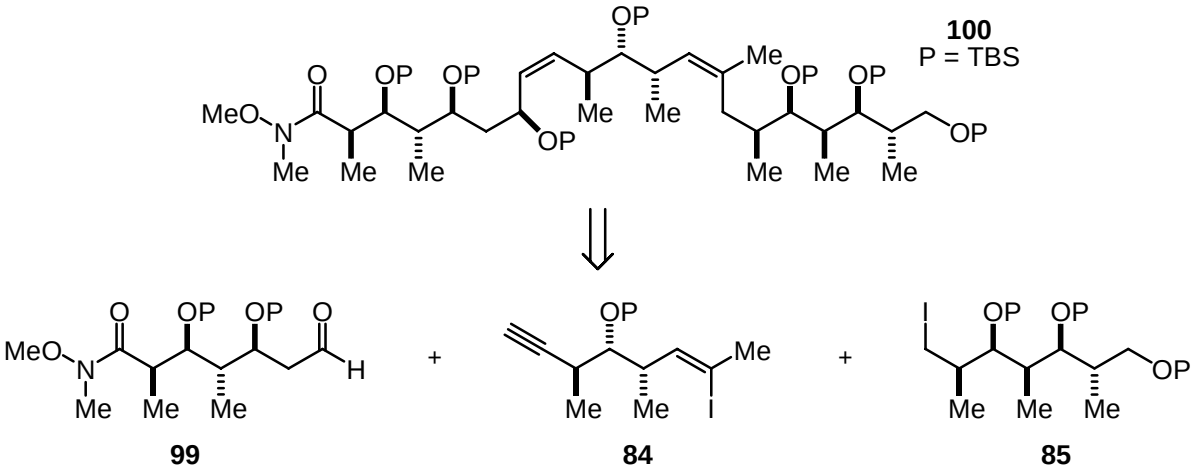
(–)-Rhazinilam **(1)**

Recently, it was found that the *Cinchona* alkaloids quinine and quinidine can catalyze the AAC reaction to produce disubstituted β-lactones in high yield and in essentially enantiomerically and diastereomerically pure form. Reaction conditions were developed which allowed for the

effective formation of masked polypropionate units by employing the C*inchona* alkaloid-catalyzed AAC reaction. Based on the pseudoenantiomer of the C*inchona* alkaloid used, different stereoarrays of polypropionate units are obtained. A variety of optically active aldehydes are viable in this transformation as reaction conditions can be optimized for a specific substrate. A matched/mismatched phenomenon was observed where the matched case produced the desired polypropionate unit in good yield and high diastereoselectivity and the mismatched case afforded an unexpected β-lactone product in diminished yield and diastereoselectivity.



(+)-Discodermolide **(81)** is a marine, microtubule-stabilizing polyketide that can only be isolated in scarce amounts from nature. Due to our inability to harvest it in supple amounts, the total synthesis of (+)-discodermolide has been the focus of many research groups. Application of the cinchona alkaloid-catalyzed AAC reaction towards the catalytic, asymmetric total synthesis of an analogue of (+)-discodermolide **(100)** is discussed.



100
P = TBS

99 **84** **85**

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF SCHEMES

PREFACE

Table of Abbreviations

AAC	Acyl halide-aldehyde cyclocondensation
BINOL	1,1′-Bi-2-naphthol
Bn	Benzyl
BnOH	Benzyl alcohol
Boc	*tert*-Butoxycarbonyl
$(Boc)_2O$	*tert*-Butoxycarbonyl anhydride
$(BzO)_2$	Benzoyl peroxide
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DMP	Dess-Martin periodinane; 1,1,1-Tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one
DMS	Dimethyl sulfide
DMSO	Dimethyl sulfoxide
dppf	1,1'-Bis(diphenylphosphino)ferrocene
d.r.	Diastereomeric ratio
ee	Enantiomeric excess
EtOAc	Ethyl acetate
HOAc	Acetic acid
LA	Lewis acid
LAH	Lithium aluminum hydride
LDA	Lithium diisopropylamide
MOM	Methoxymethyl
MsOH	Methanesulfonic acid

NaHMDS	Sodium bis(trimethylsilyl)amide
NBS	*N*-Bromosuccinimide
NMO	*N*-Methylmorpholine *N*-oxide
$Pd(OAc)_2$	Palladium(II) acetate
PMB	*p*-Methoxybenzyl
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
TBSOTf	*tert*-Butyldimethylsilyl trifluoromethanesulfonate
TEA	Triethylamine
TESCl	Triethylsilyl chloride
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
Tf_2O	Trifluoromethanesulfonic anhydride
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TIPSOTf	Triisopropylsilyl trifluoromethanesulfonate
TLC	Thin-layer chromatography
TMEDA	*N*,*N*,*N*′,*N*′-Tetramethylethylenediamine
TMS	Trimethylsilyl
$TMSCHN_2$	(Trimethylsilyl)diazomethane
TMSCl	Chlorotrimethylsilane
TMS-Q_D	Trimethylsilylquinidine
TMS-Q_N	Trimethylsilylquinine
TPAP	Tetrapropylammonium perruthenate
Ts	Tosyl

Acknowledgements

First, I would like to thank those members of my chemical family who have helped me with my professional accomplishments. I would like to especially thank Professors Scott G. Nelson and Robert K. Boeckman, Jr. for their constant support and advice throughout my academic career and aid during my development as a scientist. Additionally, I am very grateful they possessed the courage to give a young, scrappy, wannabe chemist from Brooklyn a chance to get his hands dirty on such challenging and interesting projects. I would like to thank Professors Craig S. Wilcox, Peter Wipf, Billy W. Day and Paul Floreancig for their guidance during my time at the University of Pittsburgh.

I would like to thank Andrew Kassick, Apsara Gopalarathnam, Benjamin Stevens, Xiaoqiang Shen and Cheng Zhu as well as the past and present members of the Nelson research group for their friendship, advice and support during my graduate school career. Additionally, I would like to thank all my great friends in the chemistry department who were kind enough to put up with me during my time here. There are way too many of them to list here but those poor souls know who they are. Of course, special thanks to the main office gals (especially my chemistry mom Fran Nagy) for being so friendly and feeding a poor and hungry graduate student with your delicious food.

As for my non-chemical family (who I think about often), I would like to thank my mom, dad, and sister for their overwhelming love and compassion during my entire life. Never once have I ever doubted your love and support for me and all that I do. Your cheers are always the loudest, your words always the kindest, and for that I love you eternally. I would like to thank my extended family and family friends whose faces I may not see that often, but whose support

is constantly heard. I would like to thank Ethan Kross, Kevin and Kay Ohannessian, June Hou and the rest of my friends for their companionship during my existence. I truly cherish all of you and all the time we spend together. You have always ensured that I fight the good fight and have always had my back no matter how daunting the opposition.

Five long, hard years of graduate school, four challenging years of research, three very stimulating projects, two published papers and one Ph.D.. Not bad for a kid from Brooklyn…

"Life is for those who are willing to take on the weight of the universe in order to take one more step over its horizon."

1.0 EFFORTS TOWARDS THE TOTAL SYNTHESIS OF (-)-RHAZINILAM

1.1 ISOLATION AND BIOACTIVITY

(−)-Rhazinilam **(1)** is a naturally occurring antimitotic agent isolated from the plants *Melodinus australis* (1965)[1], *Rhazya stricta* (1970)[2] and most recently *Kopsia singapurensis* (1987)[3] (Figure 1). Single crystal X-ray diffraction studies (1972) unambiguously elucidated the tetracyclic skeleton of rhazinilam, which is a relative of the *Aspidosperma* class of alkaloids.[4] Rhazinilam was found to possess a 5,6,7,8-tetrahydroindolizine subunit, a phenyl-pyrrole biaryl bond with a dihedral angle of 95° and a nine-membered lactam. It is believed that rhazinilam is an artifact of the isolation process, potentially arising from oxidation of (+)-1,2-dehydroaspidospermidine **(2)**.[5,6] Strong evidence for this comes from the observation that precursor **2**, upon prolonged exposure to air does, in fact, form rhazinilam.[7]

---

[1] Banerji, A.; Majumder, P. L.; Chatterjee, A. G. *Phytochemistry* **1970**, *9*, 1491-1493.
[2] Linde, H. H. A. *Helv. Chim. Acta.* **1965**, *48*, 1822-1842.
[3] Thoison, O.; Guénard, D.; Sévenet, T.; Kan-Fan, C.; Quirion, J.-C.; Husson, H.-P.; Deverre, J.-R.; Chan, K. C.; Potier, P. *C. R. Acad. Sci. Paris II* **1987**, *304*, 157-160.
[4] Abraham, D. J.; Rosenstein, R. D. *Tetrahedron Lett.* **1972**, *13*, 909-912.
[5] De Silva, K. T.; Ratcliffe, A. H.; Smith, G. F.; Smith, G. N. *Tetrahedron Lett.* **1972**, *13*, 913-916.
[6] Lévy, J.; Soufyane, M.; Mirand, C.; de Maindreville, M. D.; Royer, D. *Tetrahedron: Asymm.* **1997**, *8*, 4127-4133.
[7] Goh, S. H.; Ali, A. R. M.; Wong, W. H. *Tetrahedron* **1989**, *45*, 7899-7920.

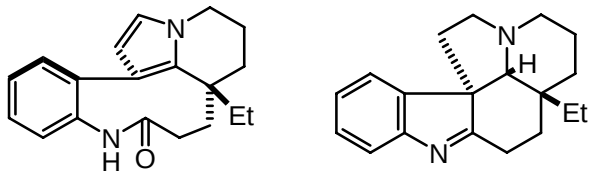


Figure 1: (-)-Rhazinilam (1) and (+)-1,2-dehydroaspidospermidine (2)

Rhazinilam has attracted attention as a potential cancer chemotherapeutic agent due to its ability to disrupt mitosis. Biological studies have shown that rhazinilam mimics the effects of both vinblastine and Taxol™ on microtubule dynamics.[8] *In vitro*, rhazinilam expresses the vinblastine-type effect of inducing non-reversible assembly of tubulin into spiral polymer and the Taxol™-type effect of inhibiting cold-induced disassembly of microtubules. In addition, rhazinilam possesses the ability to induce the formation of asters in mitotic cells and microtubule bundles in interphase cells. Rhazinilam displays cytotoxic activity against the KB cell line, as well as inhibition of microtubule disassembly in low micromolar concentrations (IC_{50} = 2 μM and IC_{50} = 3 μM, respectively).[9]

Due to its interesting pharmacological profile, structurally less complex congeners of rhazinilam have been synthesized and subjected to structure-activity relationship studies in order to determine the relevant biologically active areas.[9,10a-e] The studies suggest that the presence of the phenyl-pyrrole subunit and the lactam functionality are imperative for antitubulin activity. In

---

[8] (a) David, B.; Sévenet, T.; Morgat, M.; Guénard, D.; Moisand, A.; Tollon, Y.; Thoison, O.; Wright, M. *Cell Motil. Cytoskeleton* **1994**, *28*, 317-326. (b) Banwell, M.; Edwards, A.; Smith, J.; Hamel, E.; Verdier-Pinard, P. *J. Chem. Soc., Perkin Trans. 1*, **2000**, 1497-1499.

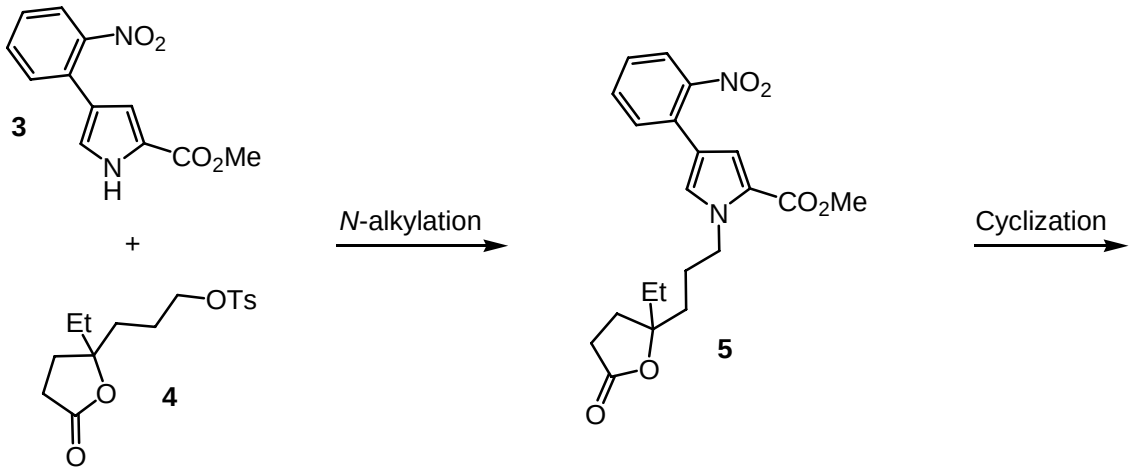
[9] Dupont, C.; Guénard, D.; Tchertanov, L.; Thoret, S.; Guéritte, F. *Biorg. Med. Chem.* **1999**, *7*, 2961-2969.

[10] (a) David, B.; Sévenet, T.; Thoison, O.; Awang, K.; Païs, M.; Wright, M.; Guénard, D. *Biorg. Med. Chem. Lett.* **1997**, *7*, 2155-2158. (b) Pascal, C.; Dubois, J.; Guénard, D.; Tchertanov, L.; Thoret, S.; Guéritte, F. *Tetrahedron* **1998**, *54*, 14737-14756. (c) Dupont, C.; Guénard, D.; Thal, C.; Thoret, S.; Guéritte, F. *Tetrahedron Lett.* **2000**, *41*, 5853-5856. (d) Alazard, J.-P.; Millet-Paillusson, C.; Boyé, O.; Guénard, D.; Chiaroni, A.; Riche, C.; Thal, C. *Biorg. Med. Chem. Lett.* **1991**, *1*, 725-728. (e) Pascal, C.; Dubois, J.; Guénard, D.; Guéritte, F. *J. Org. Chem.* **1998**, *63*, 6414-6420.

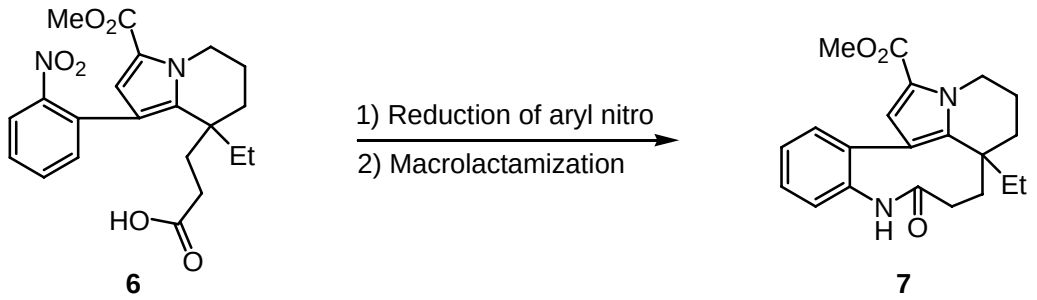
addition, studies point to restricted rotation around the biaryl bond and/or the ethyl group as having a pivotal role in bioactivity as well. Overall, none of the synthetic analogues performed as well as (–)-rhazinilam **(1)**.

1.2 PAST SYNTHESES

To date, four racemic syntheses and one asymmetric synthesis of rhazinilam have been reported. The first of these was a racemic synthesis by Smith in 1973 (Figure 2).[11] The key transformation in Smith's synthesis involved formation of the tetrahydroindolizine skeleton, which commenced with *N*-alkylation of pyrrole **3** with tosylate **4** to yield pyrrole **5**. Treatment of pyrrole **5** with $AlCl_3$ facilitated an intramolecular cyclization of the heterocycle onto the γ-lactone to afford tetrahydroindolizine **6**. Subsequent formation of tetracycle **7** was achieved by reduction of the aryl nitro group followed by macrolactamization.



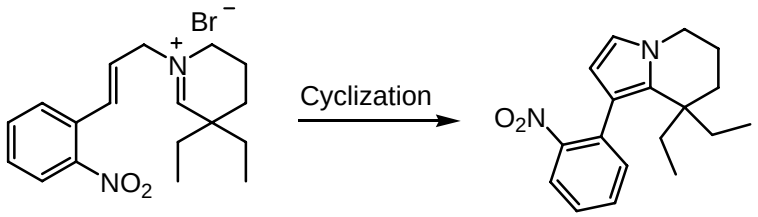
[11] Ratcliffe, A. H.; Smith, G. F.; Smith, G. N. *Tetrahedron Lett.* **1973**, *14*, 5179-5184.



6 **7**

Figure 2: Key steps in Smith's synthesis of rhazinilam

It was not until almost 30 years after Smith's total synthesis of rhazinilam when Sames reported a second racemic synthesis.[12] The key steps involved formation of tetrahydroindolizine **9** *via* Grigg cyclization of prepared iminium salt **8** and utilization of a stoichiometric amount of platinum complex to dehydrogenate one of the *gem*-diethyl groups on tricycle **10**, *via* C-H activation, to afford alkene **11** (Figure 3). This methodology was later employed again by Sames in the only asymmetric synthesis of rhazinilam to date.[13] With the aid of a chiral auxiliary, the platinum complex was able to selectively distinguish between the two *gem*-diethyl groups to set the proper ethyl-bearing stereocenter needed for the asymmetric synthesis of (–)-rhazinilam. While highly innovative, the stereodefining transformation not only was plagued with an inverse relationship between the diastereoselectivity and isolated yield obtained, but also required the use of a stoichiometric amount of the platinum complex.



8 **9**

[12] Johnson, J. A.; Sames, D. *J. Am. Chem. Soc.* **2000**, *122*, 6321-6322.
[13] Johnson, J. A.; Li, N.; Sames, D. *J. Am. Chem. Soc.* **2002**, *124*, 6900-6903.

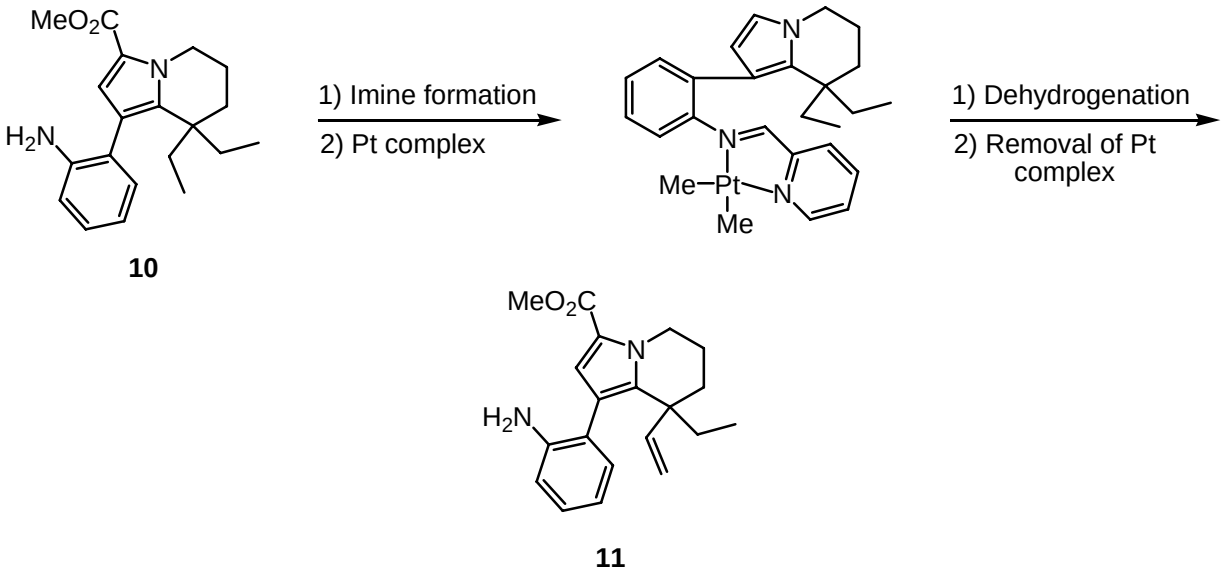
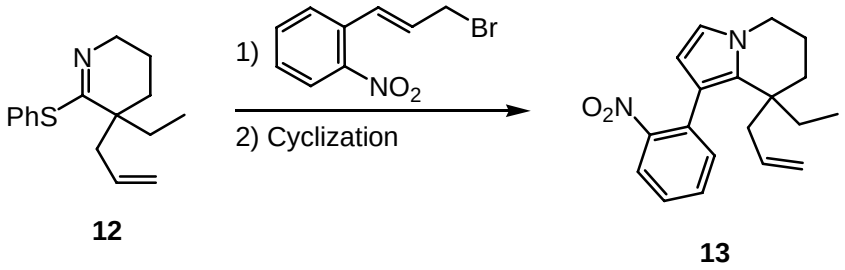


Figure 3: Key steps in Sames' syntheses of rhazinilam

In the time between the racemic and asymmetric syntheses reported by Sames, Magnus completed a total synthesis of racemic rhazinilam which yielded the natural product in nine steps in 8% overall yield (Figure 4).[14] In a similar fashion to Sames' sequence, the key transformation was formation of tetrahydroindolizine **13** *via* alkylation then Grigg cyclization of thiophenyl imine **12**. The natural product was completed by first reducing the aryl nitro group present in carboxylic acid **14** followed by macrolactamization.



[14] Magnus, P.; Rainey, T. *Tetrahedron* **2001**, *57*, 8647-8651.

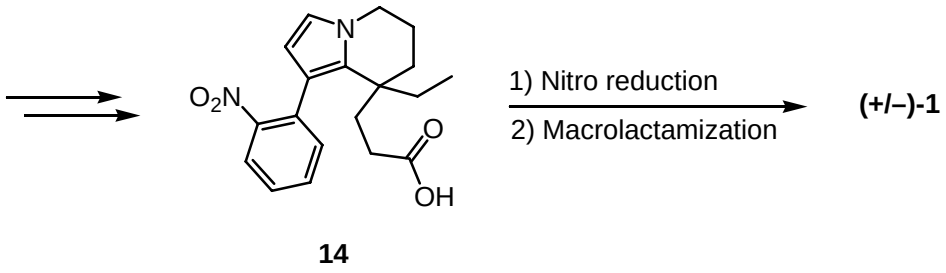


Figure 4: Key steps in Magnus' synthesis of rhazinilam

In 2005, after the Nelson group's initial attempt at an asymmetric total synthesis of (–)-rhazinilam, a concise racemic synthesis of rhazinilam was published by Trauner and coworkers.[15] The key transformation in Trauner's synthesis forms the nine-membered lactam **15** *via* an intramolecular Pd(0)-catalyzed cross-coupling reaction using an unfunctionalized pyrrole as a coupling partner (Figure 5). This transformation unquestionably demonstrates the electron-rich nature and nucleophilicity of the pyrrole moiety existent in the tetrahydroindolizine core.

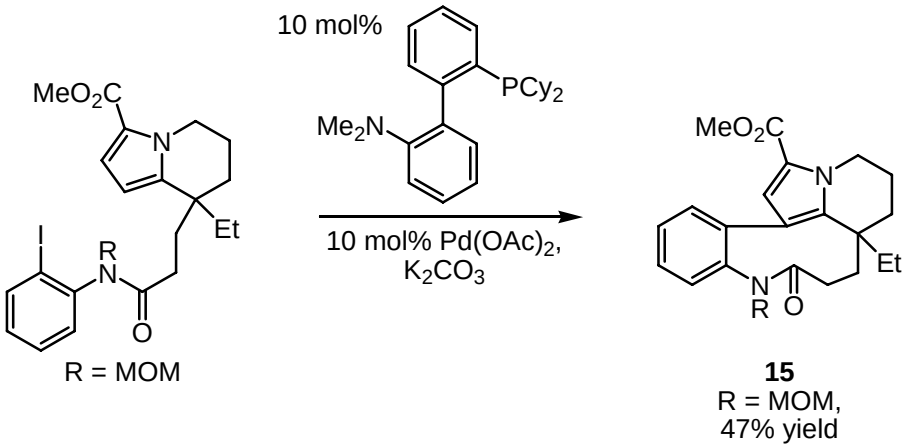
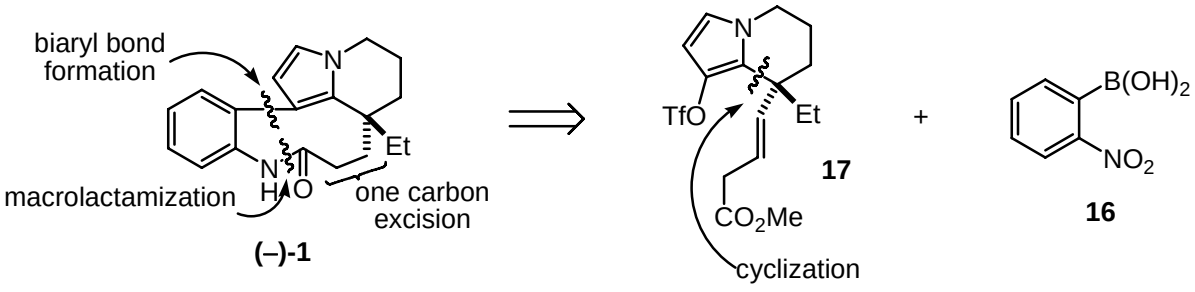


Figure 5: Key step in Trauner's synthesis of rhazinilam

[15] Bowie, A. L.; Hughes, C. C.; Trauner, D. *Org. Lett.* **2005**, *7(23)*, 5207-5209.

1.3 RETROSYNTHETIC ANALYSIS AND AAC TECHNOLOGY

The key step in our synthetic approach to an enantioselective synthesis of (–)-rhazinilam is based upon concomitant formation of the quaternary carbon stereocenter and tetrahydroindolizine core *via* cyclization of a pyrrole moiety onto an optically active allene. The strategy envisioned entails formation of the stereogenic center and tetrahydroindolizine core first with latter installation of the biaryl bond and lactam (Figure 6). The retrosynthetic analysis of the natural product opens the nine-membered lactam by cleaving across two bonds to yield two separate fragments. The first disconnection comes from cleavage of the amide bond, which can be made by an intramolecular macrolactamization reaction. The second disconnection occurs across the biaryl bond, which can be derived from a Suzuki-type cross-coupling between boronic acid **16** and triflate **17**. The tetrahydroindolizine intermediate **17** will come from a Lewis acid-catalyzed cyclization of the pyrrole moiety onto an optically-active allene. Utilizing both the catalytic asymmetric acyl halide-aldehyde cyclocondensation (AAC) reaction and the S_N2' ring opening developed in the Nelson group, the chiral allenic precursor can be made from nucleophilic attack of a pyrrole-containing organocuprate onto propargylic β-lactone **18**.



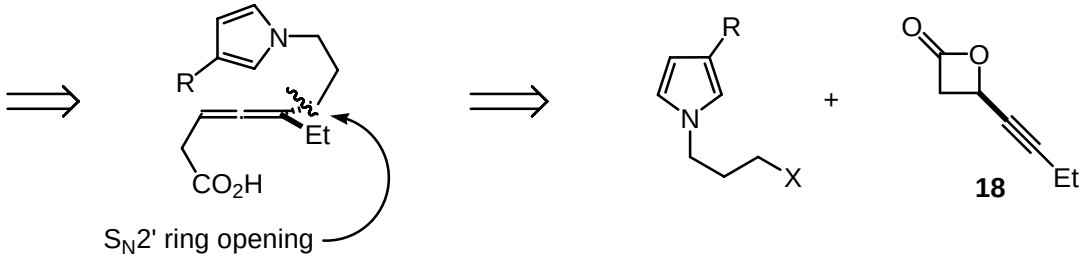
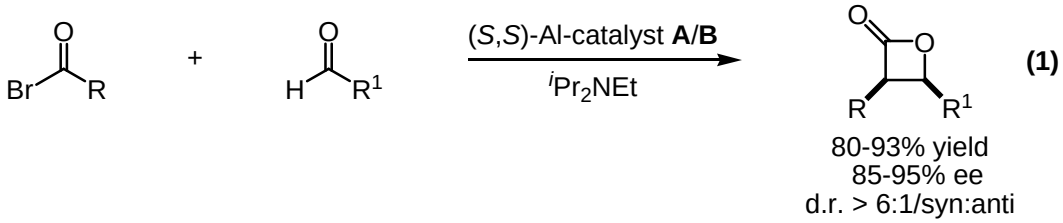
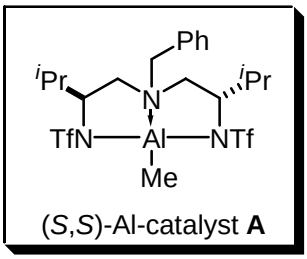


Figure 6: The Nelson Group's retrosynthetic analysis of (-)-rhazinilam

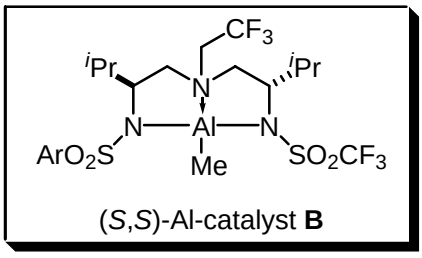
In 1999, the original asymmetric aluminum(III)-catalyzed AAC reaction was developed by the Nelson group as an alternative method for the production of aldol adducts (Eq. 1).[16a-c] In this transformation, ketene is generated *in situ* by reaction of an acyl bromide with Hünig's base. Then, under catalysis of the symmetric Al(III) triamine catalyst **A**, the generated ketene undergoes a [2+2] cycloaddition with an aldehyde to yield enantiomerically enriched β-lactones. In 2004 a second evolution of the catalyst was developed, the unsymmetric Al(III) triamine **B**, which allows for the incorporation of substituted ketenes in the [2+2] cycloaddition reaction. Some attractive attributes of these AAC reactions are the ability to employ a wide variety of aldehydes in this transformation and the fact that the Al(III)-catalyzed AAC reaction can be scaled up without any deleterious effects.



[16] (a) Nelson, S. G.; Peelen, T. J.; Wan, Z. *J. Am. Chem. Soc.* **1999**, *121*, 9742-9743. (b) Nelson S. G.; Kim, B.-K.; Peelen, T. J. *J. Am. Chem. Soc.* **2000**, *122*, 9318-9319. (c) Nelson S. G.; Zhu, C.; Shen, X. *J. Am. Chem. Soc.* **2004**, *126*, 14-15. (d) Nelson, S. G.; Cheung, W. S.; Kassick, A. J.; Hilfiker, M. A. *J. Am. Chem. Soc.* **2002**, *124*, 13654-13655.

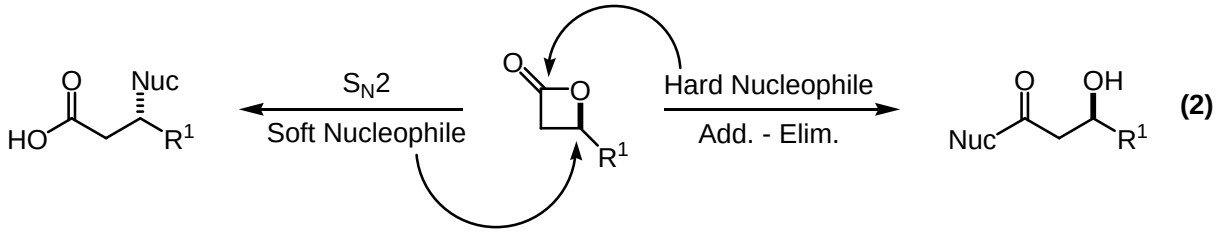


(*S*,*S*)-Al-catalyst **A**



(*S*,*S*)-Al-catalyst **B**

The unique electrophilicity possessed by these enantiomerically enriched β-lactones allows for reactivity diversification based on the type of nucleophile employed (Eq. 2). Hard nucleophiles add directly to the lactone carbonyl, furnishing addition-elimination products while soft nucleophiles attack in a S_N2 fashion, yielding β-substituted carboxylic acids. These different optically active ring-opened products are suited for further facile structural manipulation in many different directions. For this reason, β-lactones are useful intermediates and building blocks in organic synthesis.[16d]



(2)

In addition to the normal modes of reactivity expressed by optically active β-lactones, propargylic β-lactones are also subject to S_N2' ring opening by organocuprate reagents. The products from these reactions are axially chiral allenes, which are useful intermediates in organic synthesis (Figure 7). By employing this AAC-S_N2' ring opening sequence, a concise asymmetric

total synthesis of the naturally occurring antibiotic (–)-malyngolide **(19)** was achieved.[17] It was believed that (–)-rhazinilam could also be synthesized utilizing the AAC-S_N2' ring opening sequence, where the chirality of the molecule is set during subsequent cyclization upon the optically active β-allenic acid.

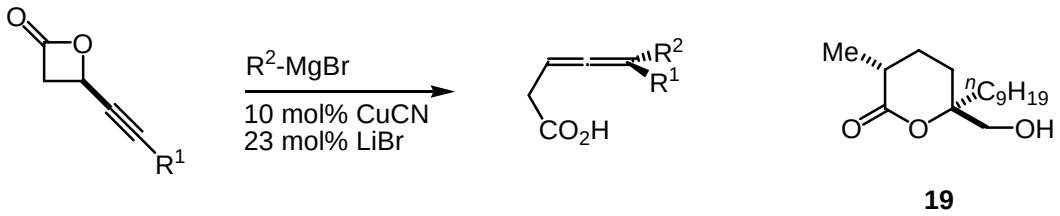


Figure 7: The AAC-S_N2' ring opening sequence and (-)-malyngolide (19)

1.4 RESULTS AND DISCUSSION

1.4.1 Background

In order to proceed with the synthesis of (–)-rhazinilam **(1)** as envisioned, the first major synthetic target would be an appropriate Grignard precursor to open the ring of the enantioenriched β-lactone **18**. First, the synthon had to be a pyrrole substituted at nitrogen with a 3-halo propyl chain. This would allow for the formation of the tetrahydroindolizine skeleton upon intramolecular cyclization of the pyrrole moiety onto the tethered allene (Figure 8). Secondly, the pyrrole would have to be functionalized in the 3-position so to allow for future installation of the biaryl bond via a Pd^0-catalyzed cross-coupling reaction. Lastly, it was imperative that the functionality at the 3-position of the pyrrole be compatible with the ensuing

[17] Wan, Z.; Nelson, S. G. *J. Am. Chem. Soc.* **2000**, *122*, 10470-10471.

Lewis-acid catalyzed cyclization. Possibilities of poisoning the Lewis acid catalyst, as well as deactivation of the pyrrole moiety either electronically or sterically, were issues to be addressed.

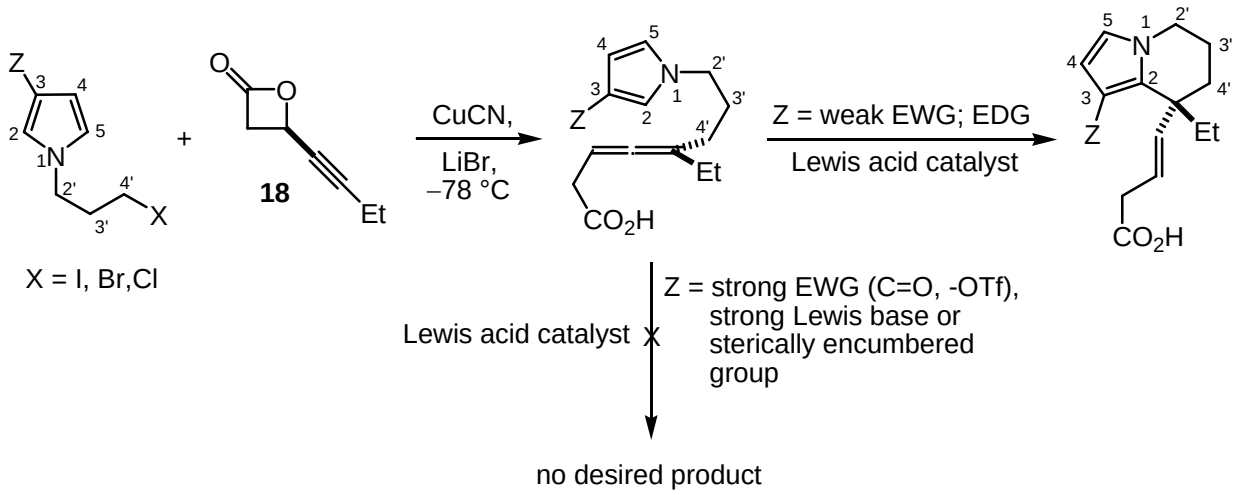


Figure 8: Restrictions for Grignard precursor

Based on these considerations, it was decided that a pyrrole with either an alkyl or silyl ether substituent at the 3-position would be a good candidate for the Grignard precursor (Figure 9). In addition to being amenable to subsequent elaboration into a viable Pd^0 cross-coupling partner (triflate) for the biaryl bond formation, it was speculated that having a 3-alkoxy substituted pyrrole would also aid the desired regioselectivity in the ensuing cyclization. Though they are inductively electron-withdrawing groups (EWG), alkyl ethers are resonance electron donating groups (EDG). As a result of this resonance donation, the C-2 carbon of the pyrrole moiety will be more electron rich, and hence favored to cyclize rather than the less activated C-5 position.

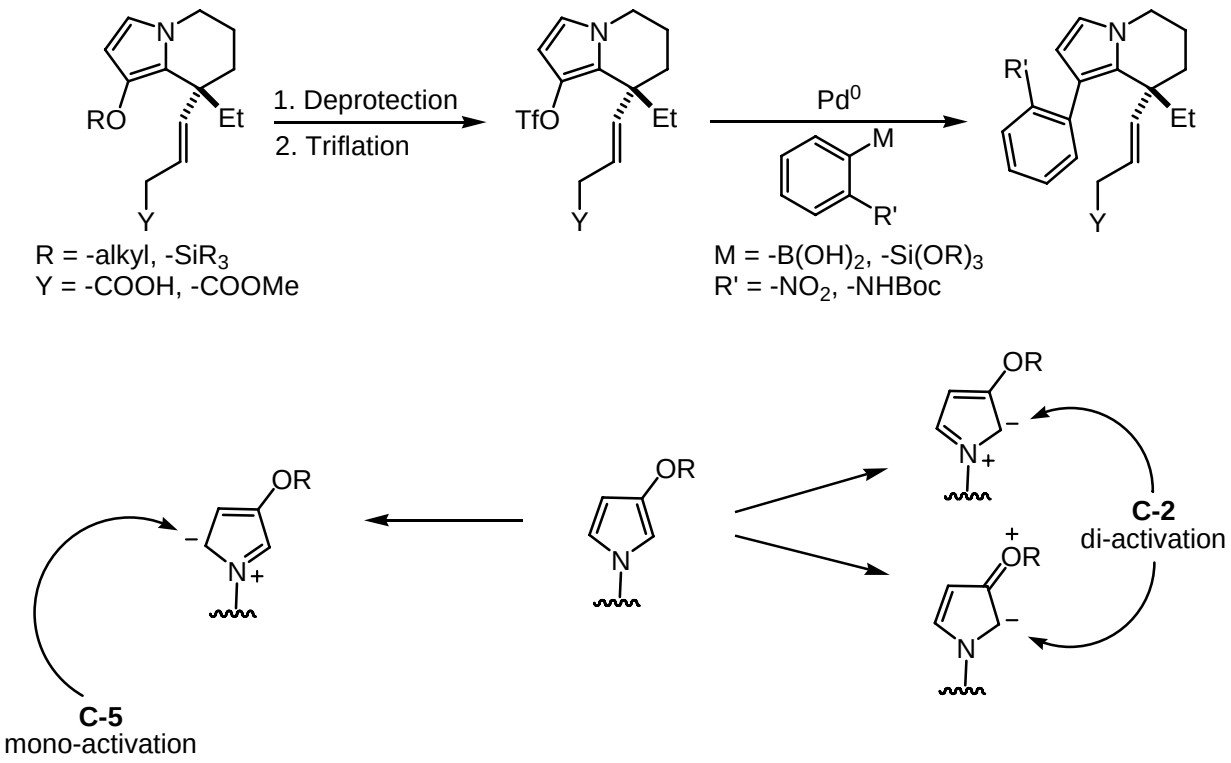


Figure 9: 3-Alkoxy/silyloxy substituted pyrroles as Grignard precursors

1.4.2 Synthesis of 1-silyloxy-5,6,7,8-tetrahydroindolizine 28

The initial approach to (−)-rhazinilam was made using 3-silyloxy pyrrole **20** as the requisite precursor for eventual formation of the tetrahydroindolizine skeleton (Figure 10). Retrosynthetically, pyrrole **20** could be derived from 3-hydroxy-2-carboxylate pyrrole **21** via a deprotection/protection process. Utilizing extensive research done by Wasserman and coworkers, pyrrole **21** could be derived from vicinal tricarbonyl species **22**.[18] Trione **22** can be synthesized from the commercially available phosphorous ylide **23**.

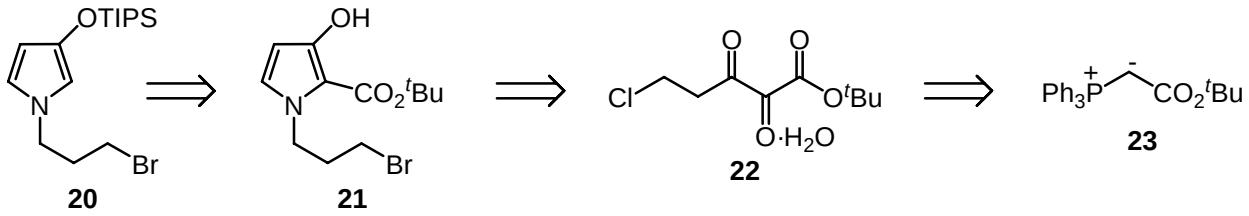
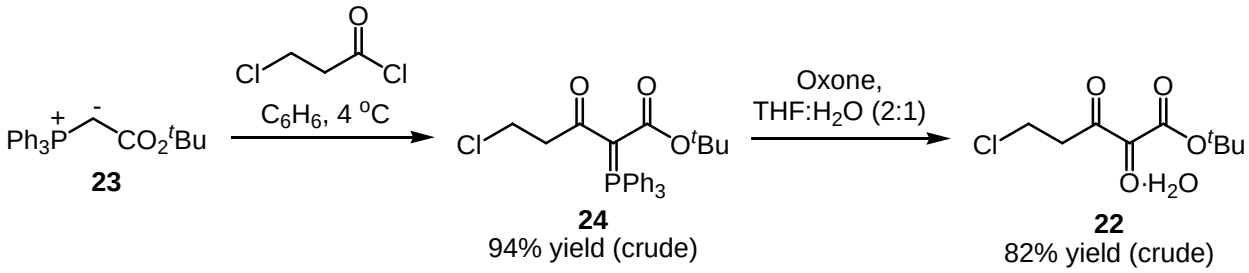


Figure 10: Synthetic analysis of 3-silyloxy pyrrole 20

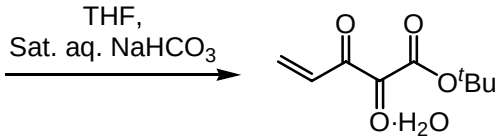
Starting from phosphorus ylide **23**, addition of a solution of 3-chloropropionyl chloride in benzene produced the addition-elimination adduct **24** in 94% yield (crude) (Scheme 1).[19] Oxidative cleavage of phosphoranylidine **24** was achieved by stirring with Oxone™,[18i] affording chloro-tricarbonyl **22** in 82% yield (crude).[18d] Reaction of primary chloride **22** with saturated aqueous $NaHCO_3$ afforded a 98% yield (crude) of the elimination product, ene-trione **25**.

Scheme 1



[18] (a) Wasserman, H. H.; Han, W. T. *Tetrahedron Lett.* **1984**, *25*, 3743-3746. (b) Wasserman, H. H.; Cook, J. D.; Fukuyama, J. M.; Rotello, V. M. *Tetrahedron Lett.* **1989**, *30*, 1721-1724. (c) Wasserman, H.H.; Lombardo, L. J. *Tetrahedron Lett.* **1989**, *30*, 1725-1728. (d) Wasserman, H. H.; Fukuyama, J.; Murugesan, N.; van Duzer, J.; Lombardo, L.; Rotello, V.; McCarthy, K. *J. Am. Chem. Soc.* **1989**, *111*, 371-372. (e) Wasserman, H. H.; Rotello, V. M. *J. Org. Chem.* **1989**, *54*, 2785-2786. (f) Wasserman, H. H.; Cook, J. D.; Vu, C. B. *Tetrahedron Lett.* **1990**, *31*, 4945-4948. (g) Wasserman, H. H.; Kuo, G.-H. *Tetrahedron* **1992**, *48*, 7071-7082. (h) Wasserman, H. H.; Vu, C. B.; Cook, J. D. *Tetrahedron* **1992**, *48*, 2101-2112. (i) Wasserman, H. H.; Ennis, D. S.; Blum, C. A.; Rotello, V. M. *Tetrahedron Lett.* **1992**, *33*, 6003-6006. (j) Wasserman, H. H.; Blum, C. A. *Tetrahedron Lett.* **1994**, *35*, 9787-9790. (k) Wasserman, H. H.; Baldino, C. M.; Coats, S. J. *J. Org. Chem.* **1995**, *60*, 8231-8235.

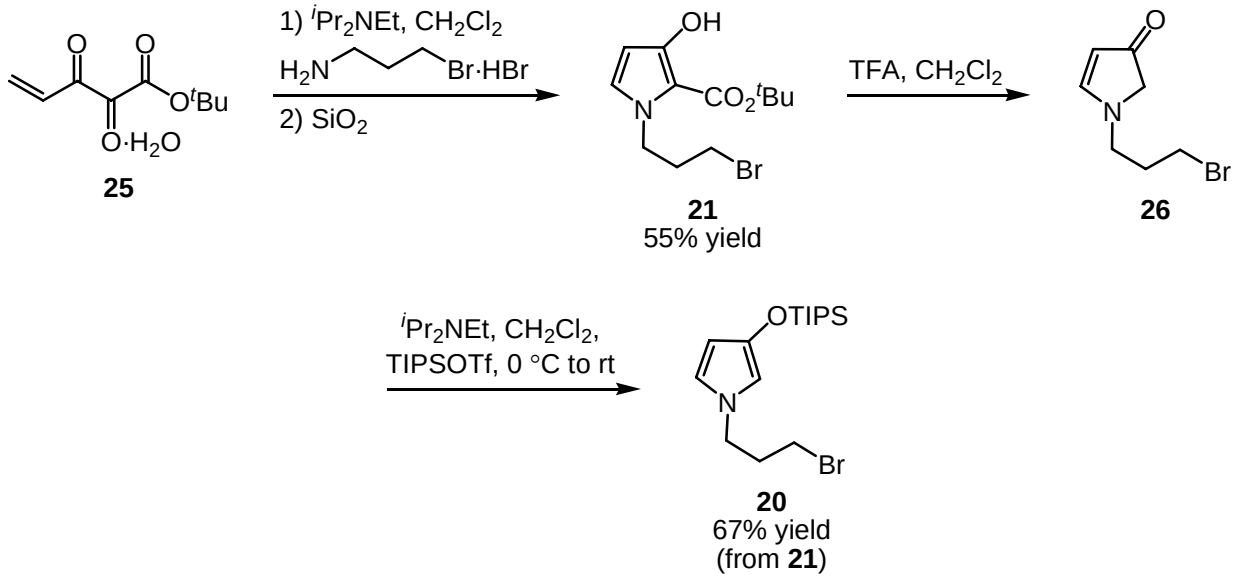
[19] This ylide is commercially available but can also be made easily on large scale (25g-30g, 97% yield); Cooke, Jr., M. P.; Burman, D. L. *J. Org. Chem.* **1982**, *47*, 4955-4963.



25
98% yield (crude)

Due to a unique reactivity pattern, vicinal tricarbonyls are synthetic platforms for the production of a variety of heterocycles.[18b,f-h,j] Reacting the very electrophilic tricarbonyl **25** with 3-bromopropylamine in the presence of $^{i}Pr_2NEt$, followed by silica gel-induced dehydration and aromatization gave 3-hydroxy-2-carboxylate pyrrole **21** in 55% yield (Scheme 2).[18b] Treatment of pyrrole **21** with trifluoroacetic acid (TFA) initiated a tandem ^{t}butyl-ester deprotection/decarboxylation sequence, producing the very light- and air-sensitive pyrrolone **26**.[20] Immediate silylation of the pyrrolone with TIPSOTf provided 3-silyloxy pyrrole **20** in 67% yield over the two steps.

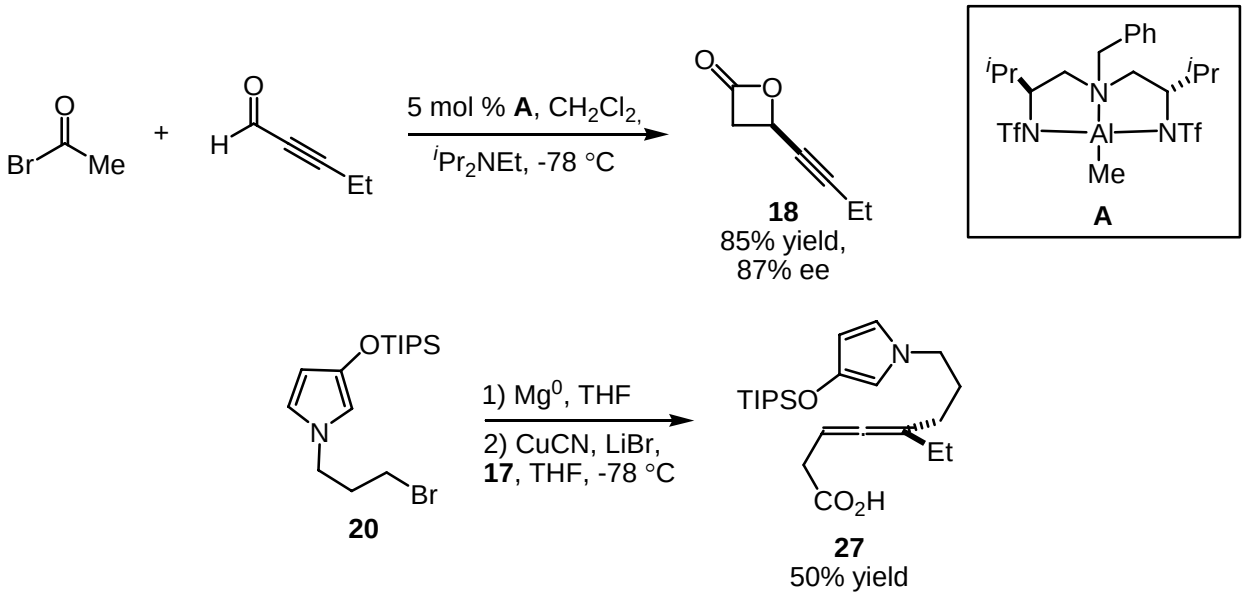
Scheme 2



[20] ^{1}H NMR data for crude pyrrolone **26** can be found in the experimental section.

Preparation of β-lactone **18**,[21] required for coupling with the Grignard reagent derived from 3-silyloxy pyrrole **20**, was undertaken using the AAC methodology developed in the Nelson group.[16] Reacting acetyl bromide and pent-2-ynal in the presence of a catalytic amount of (*S,S*)-aluminum triamine catalyst **A** produced β-lactone **18** in 85% yield and 87% ee (Scheme 3). The Grignard reagent from pyrrole **20**, needed to open β-lactone **18**, was formed by adding a solution of bromide **20** in THF to Mg^0 activated by 1,2-dibromoethane. Slow addition of the generated Grignard reagent to a solution of CuCN, LiBr and β-lactone **18** in THF at −78 °C provided the desired S_N2' adduct, β-allenic acid **27**, in 50% yield.[17] Unfortunately, despite multiple attempts, the yield of this transformation could not be improved.[22]

Scheme 3



[21] Wan, *Z. Ph. D. Thesis, University of Pittsburgh* **2001**, 121.

[22] The Grignard reagent produced for bromide **20** seemed to be short-lived. Even immediate use of the prepared Grignard reagent after all starting bromide was consumed (as monitored by TLC) gave only 50% of allenic acid **27**. Considerable amounts of protonated Grignard reagent, as well as some Wurtz-coupled product, were always observed.

Despite the low yield, this sequence provided the compound required to test the intramolecular cyclization of the pyrrole moiety onto the optically active allene. Subjecting allene **27** to a substoichiometric amount of $Cl_2Pd(MeCN)_2$ (20 mol%) afforded the desired cyclized product, tetrahydroindolizine **28**, in 50% yield (Figure 11).[23] Equally important, almost complete transfer of chirality from the enantioenriched β-lactone to the bicycle was observed. Stereoselectivity for this transformation arises from facial selectivity of the ensuing cyclization due to complexation of the Pd^{2+} metal center to the carboxylate *and* proximal olefin. This coordination directs the pyrrole to approach from the β-face (as drawn in Figure 11) in order to satisfy the stereoelectronic requirement of antiperiplanar addition to the activated alkene.

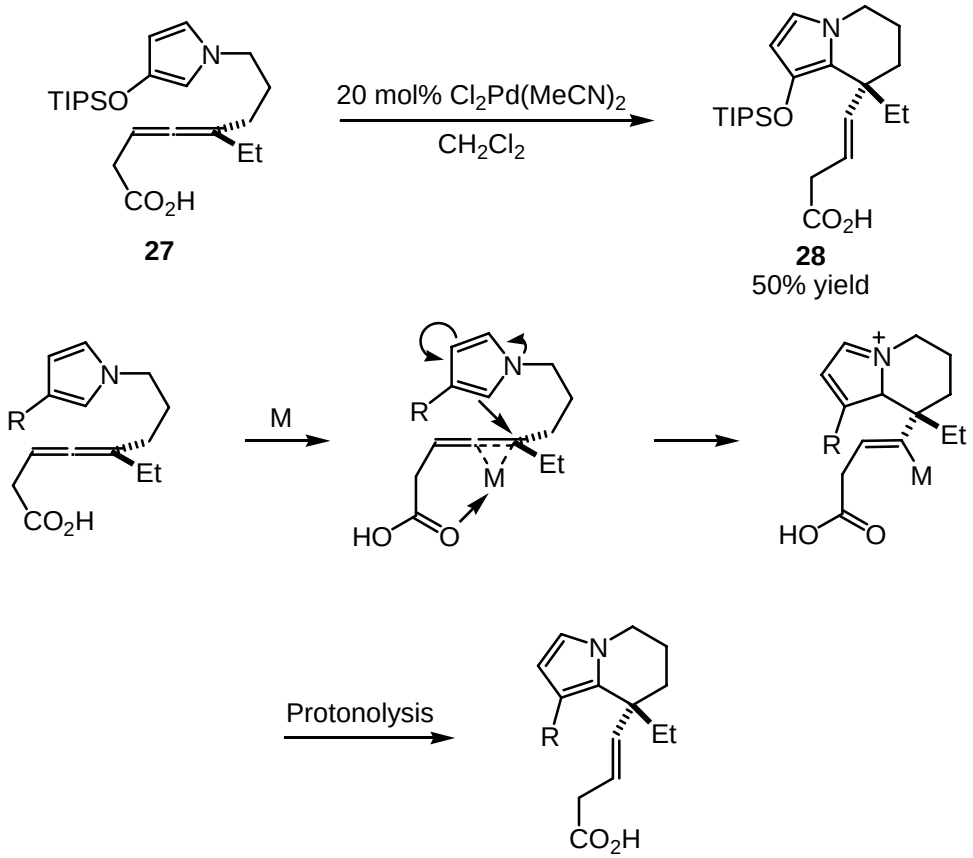


Figure 11: Proposed mechanism for Pd(II)-catalyzed cyclization (M = Pd)

[23] Zipp, G. G. *Unpublished results*.

As anticipated, 3-silyloxy pyrrole **20** could be elaborated to the tetrahydroindolizine fragment of the (–)-rhazinilam skeleton, even allowing further elaboration to a triflate cross-coupling partner, albeit in low yield.[23] However, in the latter half of the sequence, the compounds became increasingly more unstable. In each reaction, as well as in storage, decomposition occurred which attenuated yields. For this reason a more optimal route was sought.

1.4.3 Synthesis of 1-benzyloxy-5,6,7,8-tetrahydroindolizine 35

After failure of converting silyloxy tetrahydroindolizine **28** to an acceptable amount of the desired triflate precursor needed for the studies of using a Pd^0-catalyzed cross-coupling reaction to form the biaryl bond, different protecting groups for the requisite hydroxy group were considered. The main concerns for proper choice of a protecting group were not only that the integrity of the protecting group be uncompromised during the Grignard reagent formation, but that it also be labile enough to be removed easily after formation of the tetrahydroindolizine core. After deliberation, it was felt that a pyrrole with a benzyloxy group in the 3-position would be a suitable candidate.

To pursue this strategy, 3-benzyloxy pyrrole **29** became the new synthetic target. Pyrrole **29** is derived from ethoxy pyrrolone **30** by transetherification followed by hydride reduction (Figure 12). Ethoxy pyrrolone **30** could be synthesized from commercially available ethyl acetoacetate in three steps. Reacting ethyl acetoacetate with triethyl orthoformate in the presence of a catalytic amount of H_2SO_4 provided ester **31** in 86% yield.[24] Allylic bromination of ester **31** with NBS provided a 90% yield of bromide **32**[24b] which, upon subjection to a mixture of 3-

[24] (a) Smissman, E. E; Voldeng, A. N. *J. Org. Chem.* **1964**, *29*, 3161-3165. (b) Kochhar, K. S.; Pinnick, H. W. *J. Org. Chem.* **1984**, *49*, 3222-3224.

chloropropylamine hydrochloride and 1.0 M aqueous NaOH in CH_2Cl_2, afforded ethoxy pyrrolone **30** in 62% yield.[25]

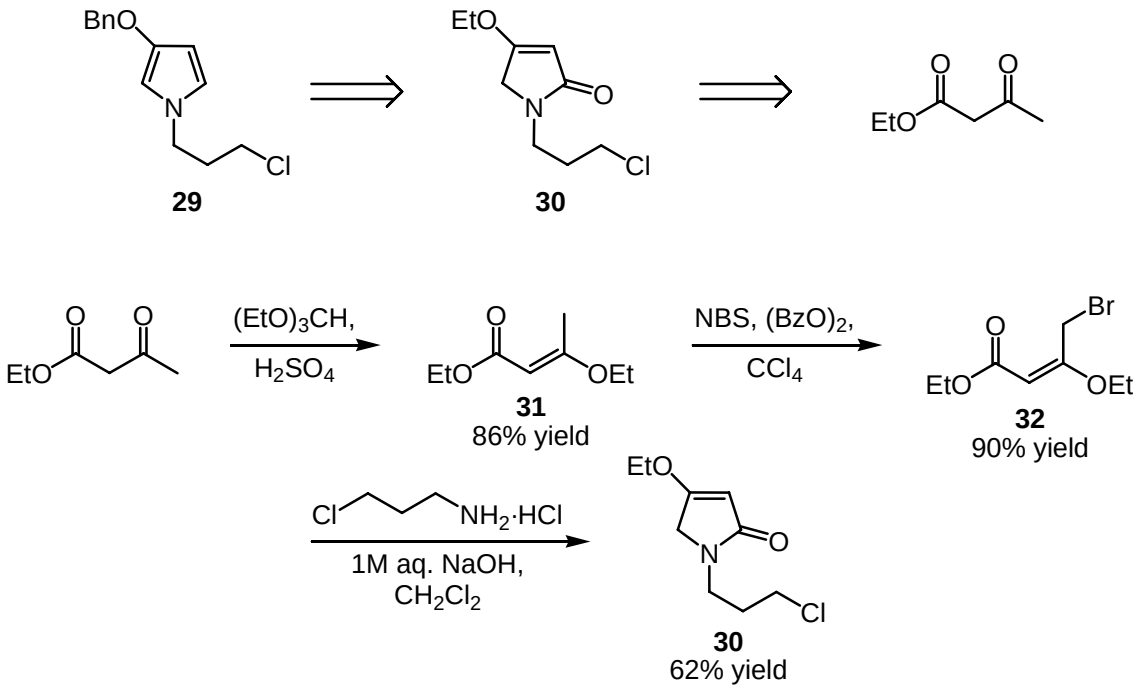


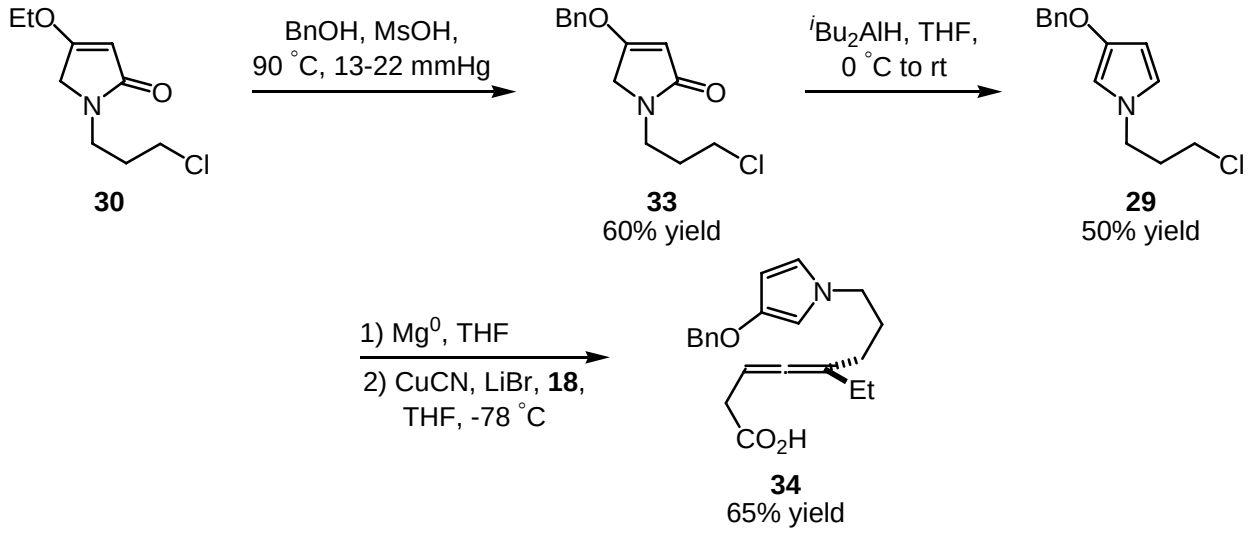
Figure 12: Synthetic analysis of pyrrole 29 and synthesis of pyrrolone 30

In order to obtain the benzyloxy analogue of optically active allene **27**, 3-benzyloxy pyrrole **29** had to be synthesized. Transetherification of ethoxy pyrrolone **30** with benzyl alcohol proceeded under acid catalysis at 90 °C and reduced pressure (13-22 mmHg) to yield 3-benzyloxy pyrrolone **33** in 60% yield (Scheme 4).[26] Reduction of **33** with excess $^{i}Bu_2AlH$ afforded a 50% yield of 3-benzyloxy pyrrole **29**.[24b] Optically active β-allenic acid **34** was synthesized in 65%

[25] Kochhar, K. S.; Carson, H. J.; Clouser, K. A.; Elling, J. W.; Gramens, L. A.; Parry, J. L.; Sherman, H. L.; Braat, K.; Pinnick, H. W. *Tetrahedron Lett.* **1984**, *25*, 1871-1874.
[26] Laffan, D. D. P.; Bänziger, M.; Duc, L.; Evans, A.; McGarrity, J. F.; Meul, T. *Helv. Chem. Acta* **1992**, *75*, 892-900.

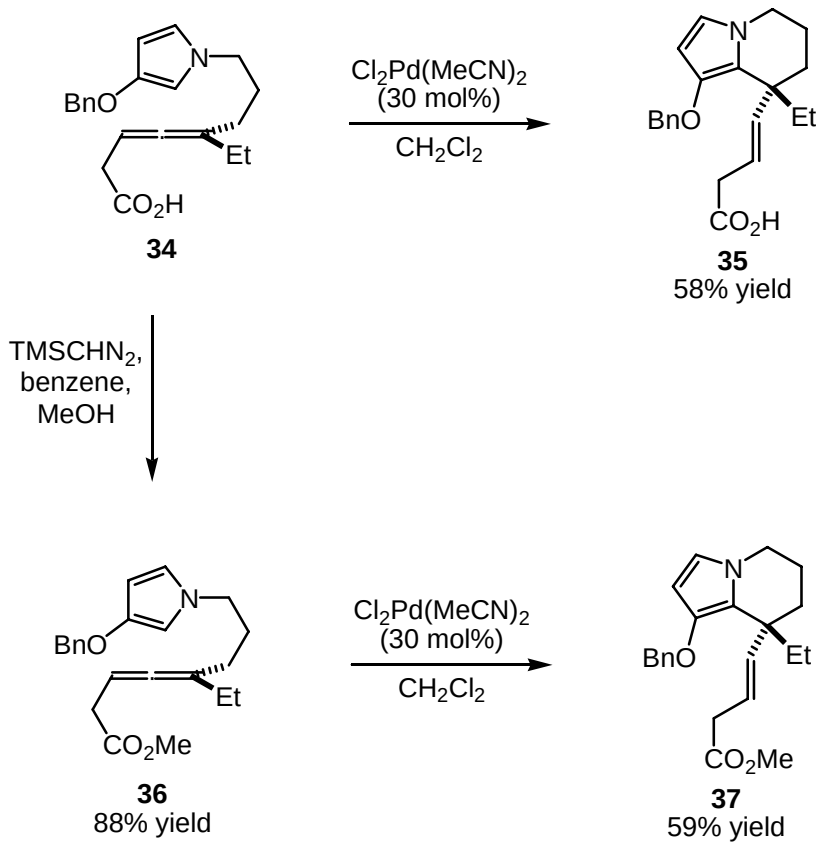
yield by adding the pre-formed Grignard reagent of chloride **29** to a –78 °C solution of β-lactone **18**, CuCN and LiBr in THF.

Scheme 4



With the synthesis of the benzyloxy allenic acid **34** now completed, the next goal was to cyclize the pyrrole and form the tetrahydroindolizine core. Subjecting optically active allene **34** to a substoichiometric amount of $Cl_2Pd(MeCN)_2$ in CH_2Cl_2 provided the desired 1-benzyloxy-tetrahydroindolizine **35** in 58% yield and 72% ee (Scheme 5). However unlike the silyloxy derivative, 30 mol% of the $Cl_2Pd(MeCN)_2$ was needed for complete consumption of the starting material. The necessity of the higher catalyst loading may be due to a few reasons. First, the benzyloxy substituent is more inductively electron-withdrawing than the silyloxy group, which would decrease the electron density in the pyrrole ring. This would render the pyrrole less nucleophilic, thus deactivating the heterocycle towards cyclization. Second, a benzyloxy group is a more efficient coordinating group than a silyloxy group and therefore the benzyl ether may be unproductively sequestering some of the Pd catalyst needed for activation of the allene.

Scheme 5



An attempt to improve the yield of the cyclized product was made by esterifying acid **34** with $TMSCHN_2$ to produce methyl ester allene **36** in 88% yield. By transforming the acid functionality into an ester, the stability of the starting allene as well as isolation of the desired bicyclic product would both be aided.[27] Disappointingly, methyl ester allene **36** performed no better in the cyclization than allenic acid **34**, yielding 59% of the methyl ester tetrahydroindolizine **37** in 72% ee.

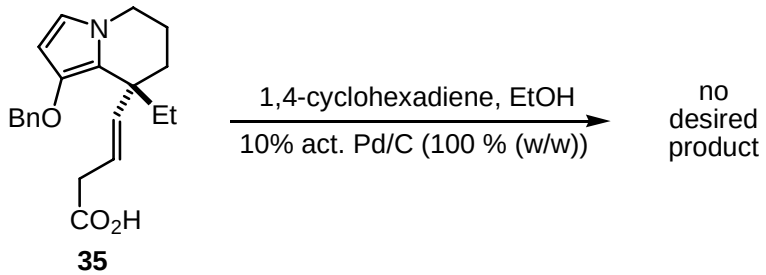
[27] Based on observations made from storage, the methyl ester allene seemed to have a slower rate of decomposition than the corresponding β-allenic acid.

1.4.4 Formation of triflate precursor 45

With the benzyloxy bicycle now formed, efforts were focused on transforming the tetrahydroindolizine core into a viable cross-coupling partner. In order to form the biaryl bond present in the skeleton of (–)-rhazinilam, the benzyl ether on the tetrahydroindolizine core needed to be deprotected and a triflate group installed. Removal of the benzyl group was initially undertaken using transfer hydrogenation conditions. Due to the slower rates associated with transfer hydrogenation compared to the use of hydrogen gas, we felt we would be able to monitor the reaction by TLC and quench the reaction mixture after the more active benzyl group was removed, but before the pendant *neo*-pentyl double bond was reduced.

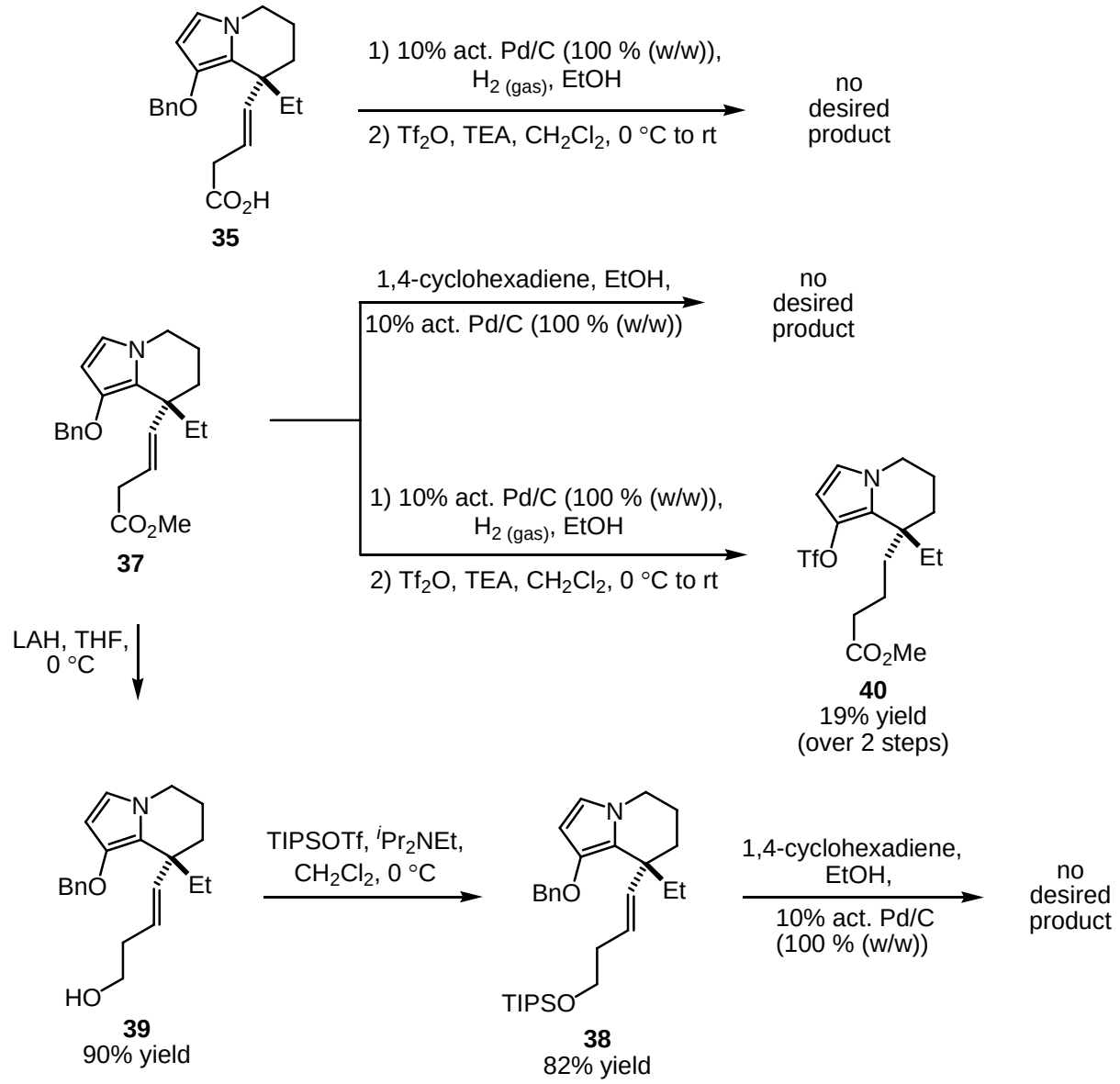
The initial conditions attempted for this transformation consisted of 1,4-cyclohexadiene as the source of molecular hydrogen and 10% activated Pd/C (100% (w/w)) in EtOH (Scheme 6).[28] Tetrahydroindolizines **35**, **37** and **38** (obtained by reducing **37** with LAH (90% yield) followed by silylation of **39** with TIPSOTf (82% yield)) were subjected to these conditions. Unfortunately, none of the transfer hydrogenation experiments produced any desired product. While in all cases the starting material was consumed, the crude ^{1}H NMR spectra from the reactions did not show definitive peaks that would correlate to the expected pyrrolone products.

Scheme 6



35

[28] Felix, A. M.; Heimer, E. P.; Lambros, T. J.; Tzougraki, C.; Meienhofer, J. *J. Org Chem* **1978**, *43*, 4194-4196.

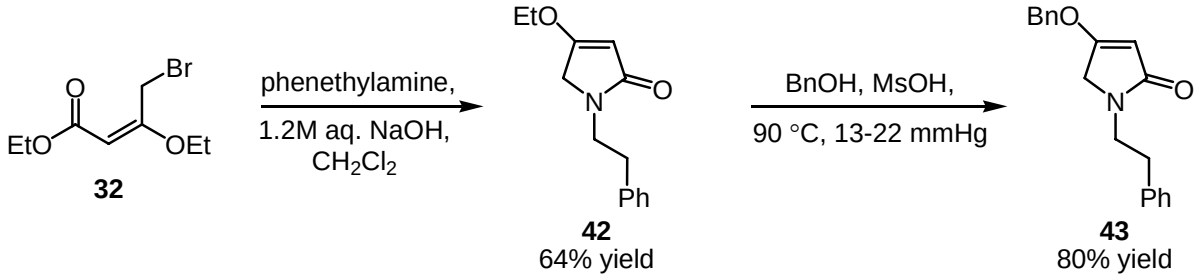


A second attempt at the deprotection of the benzyl ether on the tetrahydroindolizine core was made, this time subjecting both **35** and **37** to hydrogen gas with 10% activated Pd/C (100% w/w) in EtOH. Similar to the transfer hydrogenation experiments, **35** and **37** were consumed completely, though again producing crude ^{1}H NMR spectra that were indistinctive. However, subjecting the crude products from the deprotection reactions to triflic anhydride in the presence

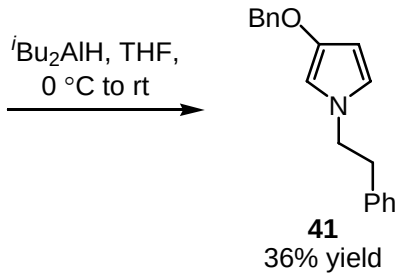
of triethylamine actually yielded 19% of triflate tetrahydroindolizine **40** (from **37**).[29] An interesting observation from this result is that the *neo*-pentyl double bond, thought to be less activated towards reduction in these conditions due to sterics, was reduced in the same amount of time it took for the aryl benzyl group to be removed.

In order to maintain the integrity of the pendant olefin and to optimize the deprotection, alternative conditions were sought to debenzylate the pyrrole. Experiments were conducted using model 3-benzyloxy pyrrole **41**, which was synthesized in a similar manner as 3-benzyloxy pyrrole **29**. Reacting phenethylamine with allylic bromide **32** afforded the ethoxy pyrrolone **42** in 64% yield (Scheme 7). Transetherifying **42** with benzyl alcohol produced an 80% yield of benzyl ether **43** which was subsequently reduced with $^{i}Bu_2AlH$ to yield 36% of model benzyloxy pyrrole **41**. The studies conducted on model pyrrole **41** included an investigation of the acceleration effect of acetic acid as a media for transfer hydrogenation, as well as some Brønsted acid and Brønsted acid-Lewis base conditions to remove a benzyl group (Table 1).[30]

Scheme 7

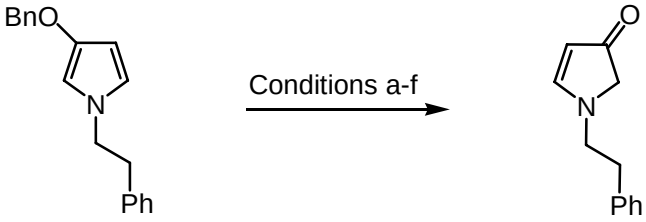


[29] Characterized by ^{1}H NMR, LRMS and HRMS data.
[30] (a) Kalinin, A. V.; Reed, M. A.; Norman, B. H.; Snieckus, V. *J. Org. Chem.* **2003**, *68*, 5992-5999. (b) Kiso, Y.; Ukawa, K.; Nakamura, S.; Ito, K.; Akita, T. *Chem. Pharm. Bull.* **1980**, *28*, 673-676. (c) Matteson, D. S.; Man, H.-W.; Ho, O. C. *J. Am. Chem. Soc.* **1996**, *118*, 4560-4566. (d) Node, M.; Kodama, S.; Hamashima, Y.; Baba, T.; Hamamichi, N.; Nishide, K. *Angew. Chem. Int. Ed.* **2001**, *40*, 3060-3062.



41
36% yield

Table 1: Deprotection of model 3-benzyloxy pyrrole 41



41

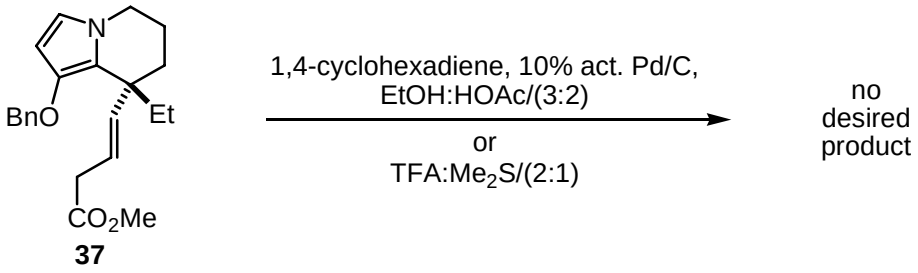
entry	Conditions[a]	Time	Results[b]
a	1,4-cyclohexadiene, 10% act. Pd/C, EtOH:HOAc/(3:2)[c]	10 hours	>95% conv. (78%)[d]
b	1,4-cyclohexadiene, 10% act. Pd/C, HOAc[c]	8 hours	>95% conv. (61%)[d]
c	MsOH in $CHCl_3$	5.5 hours	~50% conv.
d	MsOH in Me_2S	20 hours	~67% conv.
e	TFA	16 hours	no conv.[e]
f	TFA:Me_2S/(2:1)	20 hours	~95% conv.

[a] Trials a, b, d and f were run using 0.070 g (0.253 mmol) of **41**. Trials c and e were run using 0.050 g (0.180 mmol) of **41**. Reactions were run at 0.10M in the respective solvents. [b] Based on crude ^{1}H NMR. In all cases, the ^{1}H NMRs showed a mix of desired product and starting material. [c] Used 100% (w/w) of 10% activated Pd/C. [d] Crude yields. [e] Based on TLC, no crude ^{1}H NMR taken.

As was expected, the use of HOAc as the solvent increased the rate at which the transfer hydrogenation occurred, albeit at a lower isolated yield. In addition, the Brønsted acid-Lewis base condition of TFA:Me_2S, which should have no affect on the pendant *neo*-pentyl olefin,

yielded a promising result. Unfortunately, when these conditions were employed for the removal of the benzyl ether on tetrahydroindolizine **37**, no desired product was obtained (Scheme 8). It was hypothesized that deprotection of the benzyl ether was being inductively stymied by the electron-rich nature of the pyrrole moiety. Installation of an electron withdrawing group, in this case a carbomethoxy group, onto the pyrrole should rectify this problem. An electron-withdrawing group would decrease the electron density within the pyrrole moiety thereby inductively labilizing the benzyl ether.

Scheme 8

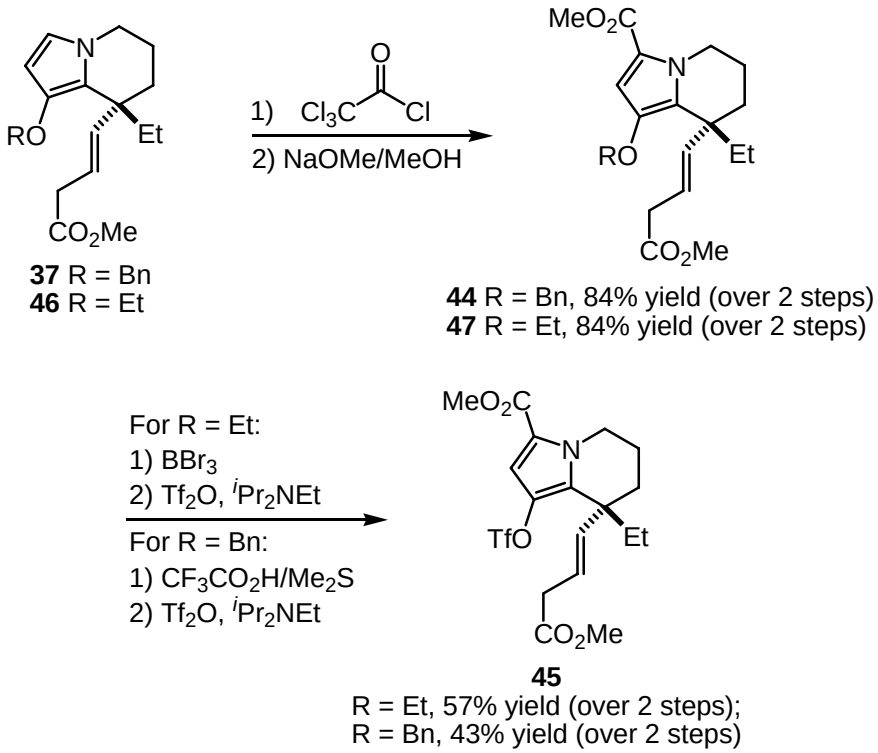


The carbomethoxy group was easily installed onto the heterocyclic core in two steps. Acylation of tetrahydroindolizine **37** with trichloroacetyl chloride followed by methanolysis with freshly prepared sodium methoxide produced benzyl ether **44** in 84% overall yield (Scheme 9). As hypothesized, the carbomethoxy group did facilitate the deprotection of the hydroxy group. Subjection of benzyl ether **44** to TFA:Me_2S/(2:1) successfully cleaved the benzyl group.[31] The intermediate pyrrolone was too unstable to purify so the crude residue was treated directly with Tf_2O and Hünig's base to yield 43% of the desired cross-coupling partner, triflate **45**. Installation of the carbomethoxy group proved even more efficacious as incorporation of the

[31] Verified by crude ^{1}H NMR analysis

electron-withdrawing substituent onto tetrahydroindolizine **46,**[32] to form ethyl ether **47**, enabled removal of the ethyl substituent from the pyrrolo-ether by using BBr_3. Subsequent treatment of the crude pyrrolone with Tf_2O and Hünig's base produced triflate **45** in 57% yield.[31] With the desired triflate at hand, it was time to attempt formation of the biaryl bond.

Scheme 9



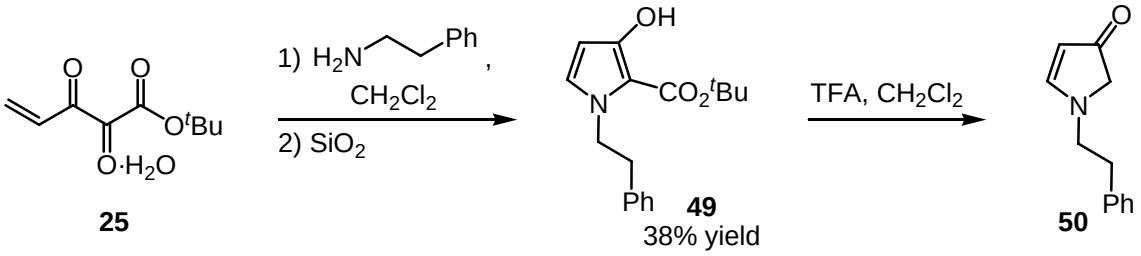
[32] Received from G. Greg Zipp

1.4.5 Attempts at forming the biaryl bond

1.4.5.1 Exploring siloxanes as cross-coupling partners

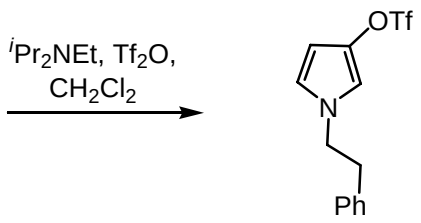
Due to the existence of a variety of literature procedures to form biaryl bonds *via* Pd^0-mediated cross-coupling reactions, formation of the requisite bond between pyrrole triflate **45** and an aniline derivative was studied on multiple fronts at once. Turning to coupling chemistry developed by Hiyama and DeShong, siloxanes were explored as potential cross coupling partners.[33] Model triflate **48** was synthesized in a similar fashion as 3-siloxy pyrrole **20** (Scheme 10). Starting with ene-trinone **25**, addition of phenethylamine followed by stirring with silica gel provided 3-hydroxy-2-carboxylate pyrrole **49** in 38% yield. Treatment of **49** with TFA induced a tandem ^{t}butyl-ester deprotection/decarboxylation sequence to afford the very light and air sensitive pyrrolone **50** that underwent immediate triflation with Tf_2O to yield model triflate **48** in 70% overall yield from **49**.[34]

Scheme 10



[33] (a) Hatanaka, Y.; Hiyama, T. *Synlett* **1991**, 845-853. (b) Mowery, M. E.; DeShong, P. *J. Org. Chem.* **1999**, *64*, 3266-3270. (c) Mowery, M. E.; DeShong, P. *Org. Lett.* **1999**, *1*, 2137-2140. (d) DeShong, P.; Handy, C. J.; Mowery, M. E. *Pure Appl. Chem.* **2000**, *72*, 1655-1658. (e) Manoso, A. S.; DeShong, P. *J. Org. Chem.* **2001**, *66*, 7449-7455. (f) Denmark, S. E.; Sweis, R. F. *Acc. Chem. Res.* **2002**, *35*, 835-846.

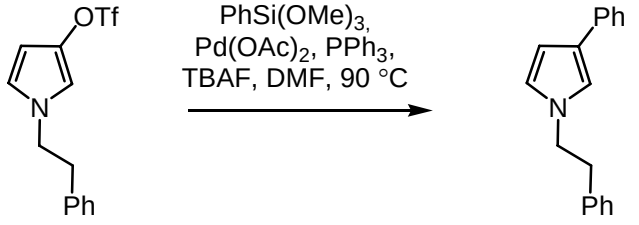
[34] ^{1}H NMR data for crude pyrrolone **50** can be found in the experimental section.



48
70% yield

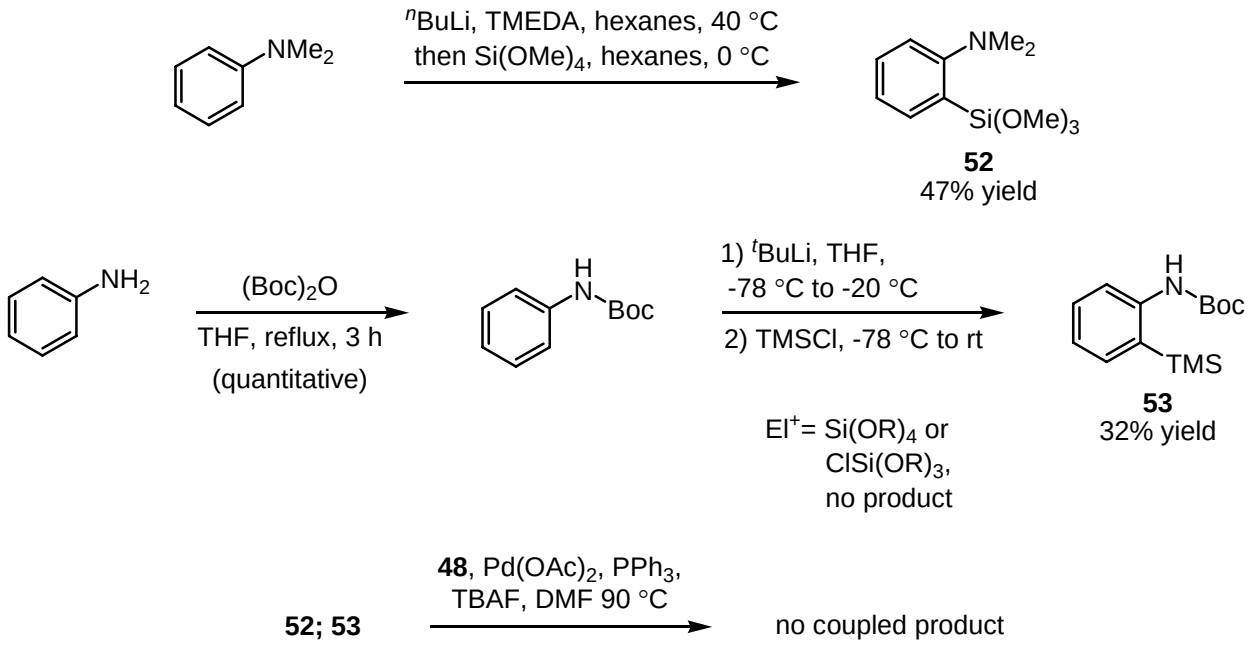
In order to gauge the reactivity of pyrrole triflates in these siloxane cross-coupling reactions, a coupling reaction between model triflate **48** and commercially available phenyltrimethoxysilane was conducted. Subjection of the model triflate to conditions developed by DeShong produced biaryl **51** in 17% yield (Scheme 11).[33c] Though the yield of the coupled product was poor, it demonstrated that the pyrrole triflates possessed some potential coupling ability with siloxanes. Consequently, syntheses of different phenylsiloxane cross-coupling partners that contained a nitrogen functionality in the 2-position was attempted. Disappointingly, only two *ortho*-silyl compounds, *N*,*N*-dimethyl aniline siloxane **52** (47% yield) and *N*-Boc aniline trimethylsilane **53** (32% yield), could be synthesized.[35] However, subjecting both **52** and **53** to the same conditions that afforded biaryl **51** failed to yield any coupled product.

Scheme 11



48 **51**
17% yield

[35] (a) Tacke, R.; Wiesenberger, F.; Lopez-Mras, A.; Sperlich, J.; Mattern, G. *Z. Naturforsch* **1992**, *47b*, 1370-1376. (b) The *N*-Boc aniline starting material used in the production of **53** is commercially available.



Due to the inability to synthesize the desired siloxane cross-coupling partners, as well as the failure to couple the available aniline-derived coupling precursors to model triflate **48**, no further studies in the area of using siloxanes as potential cross-coupling partners were conducted.

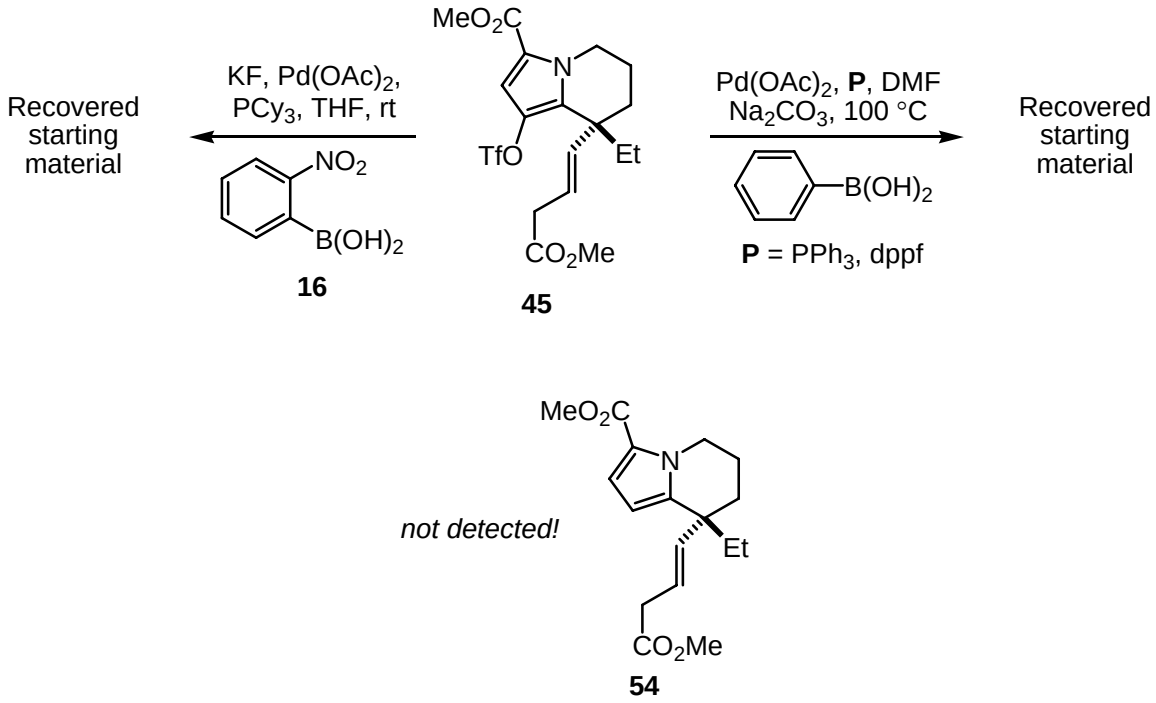
1.4.5.2 Attempts at using a Suzuki cross-coupling reaction

At the same time at which siloxanes were being tested as potential cross-coupling partners, the use of boronic acids as viable cross-coupling partners showed some promise in model studies.[23] However, attempts to utilize aryl boronic acids with triflate **45** in a Suzuki cross-coupling reaction to form the requisite biaryl bond proved fruitless.[36] Efforts to couple triflate **45** with commercially available *o*-nitro phenyl boronic acid **(16)** and phenyl boronic acid did not produce

[36] A combination of trials were run by Zuosheng Liu, G. Greg Zipp and the author of this document. The trials depicted in Scheme 12 were run by the author of this document.

any desired biaryl product (Scheme 12). Surprisingly, unreacted starting material was fully recovered as reduction product **54** was not detected.

Scheme 12



It is speculated that the failure of the Suzuki cross-coupling reactions to produce any desired product and any reduced starting material may be caused by two reasons. First, despite the inductive electron-withdrawing nature of the carbomethoxy group the pyrrole-triflate bond may still not be labile enough for the Pd^0 to insert into. Second, the very sterically cumbersome quaternary carbon stereocenter which is in close proximity to the pyrrole-triflate bond may be sterically blocking the Pd^0 from getting close enough to the desired bond.

Due to the failure to form the biaryl bond *via* cross-coupling reaction using a pyrrole triflate, in addition to the moderate yields obtained during key reactions in the synthetic

sequence, synthetic efforts towards the total synthesis of (–)-rhazinilam were temporarily ceased in order to revise the synthetic sequence.

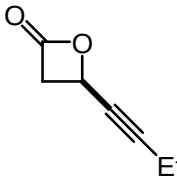
1.5 EXPERIMENTAL

General Information: ^{1}H NMR spectra were recorded on Bruker DPX 301 and DPX 302 (300 MHz) spectrometers. Chemical shifts are reported in ppm from tetramethylsilane with either the solvent resonance as the internal standard ($CHCl_3$: δ 7.27 ppm) or tetramethylsilane as an external standard (TMS: δ 0.00 ppm). Data is reported as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet app = apparent, br = broad, m = multiplet), coupling constants (Hz), integration. ^{13}C NMR spectra were recorded on Bruker DPX 301 and DPX 302 spectrometers (75 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with either the solvent resonance as the internal standard ($CDCl_3$: δ 77.0 ppm; C_6D_6: δ 128 ppm) or tetramethylsilane as an external standard (TMS: δ 0.00 ppm). Optical rotations were measured on a Perkin-Elmer 241 digital polarimeter with a sodium lamp at ambient temperature and are reported as follows: $[\alpha]_D$ (*c* g/100 mL) with units of degree•g•cm^{-3}. Infrared spectra were recorded on a Nicolet Avatar 360 FT-IR spectrometer. Mass spectra were obtained on a VG-7070 or Fisons Autospec high resolution magnetic sector mass spectrometer.

Analytical thin layer chromatography (TLC) was performed on EM Reagent 0.25 mm silica gel 60-F plates. Flash chromatography was performed as previously described on EM

silica gel 60 (230-240 mesh).[37] Analytical gas liquid chromatography (GLC) was performed on a Varian 3900 gas chromatograph with a flame ionization detector and split mode capillary injection system using a VarianCP Wax 52CB column (30 m x 0.25 mm). Hydrogen was used as the carrier gas at the indicated pressures. Analytical high performance liquid chromatography (HPLC) was performed on a Hewlett Packard 1100 liquid chromatograph equipped with a variable wavelength UV detector (deuterium lamp, 190-600 nm), using a Daicel Chiralcel™ OD-H column (250 x 4.6 mm) (Daicel Inc.). HPLC grade isopropanol and hexanes were used as the eluting solvents. Melting points were taken using a Mel-Temp apparatus and are uncorrected.

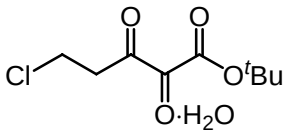
Unless otherwise stated, all experiments were carried out under a nitrogen atmosphere in oven or flame-dried glassware using standard inert atmosphere techniques for introducing reagents and solvents. Anhydrous solvents were obtained by passage through successive alumina- and Q5 reactant-packed columns on a solvent purification system. All water used in reactions and in aqueous solutions was deionized. Acetyl bromide and Tf_2O were distilled from P_2O_5. Phenethylamine, TMEDA, *N*,*N*-dimethylaniline, TMSCl and $^{i}Pr_2NEt$ were distilled from CaH_2. TIPSOTf and 3-chloropropionyl chloride were distilled prior to use. All other reagents were used as purchased. The yields reported are unoptimized.



(*R*)-4-(But-1-ynyl)oxetan-2-one (18): To a solution of (S,S)-ligand **A** (0.461g, 0.853 mmol) in CH_2Cl_2 (4.5 mL) at ambient temperature was added $AlMe_3$ (0.470 mL, 0.938 mmol, 2.0 M in hexanes) in a slow, dropwise manner. Gas evolution was observed almost immediately upon addition. The clear solution was stirred for 4 hours at ambient temperature, after which the reaction mixture was diluted with CH_2Cl_2 (35 mL)

[37] Still, W.C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2925.

and subsequently cooled to −78 °C. To the solution was added $^{i}Pr_2NEt$ (5.00 mL, 29.0 mmol) followed by slow, dropwise addition of acetyl bromide (2.40 mL, 32.4 mmol). The reaction mixture was stirred for 15 minutes at −78 °C. Subsequently, neat aldehyde (1.40 g, 17.1 mmol) was added in a dropwise fashion. The resulting solution was stirred at −78 °C until complete consumption of the starting material, as monitored by TLC. The reaction mixture was poured into cold ether (150 mL) and filtered through a plug of silica, eluting with more cold ether. Concentrated the ethereal filtrate *in vacuo* and purified the crude oil via bulb-to-bulb distillation (pot temperature 40 ^{o}C @ 0.1 mb). In some cases, additional purification was performed using silica gel chromatography (10:1/pentanes:ether) to yield the title compound as a pale yellow oil (1.80 g, 85%): ^{1}H NMR (300MHz, $CDCl_3$) δ 5.03 (ddt, *J* = 6.3, 4.4, 1.9 Hz, 1H), 3.75 (dd, *J* = 16, 6.2 Hz, 1H), 3.48 (dd, *J* = 16, 4.5 Hz, 1H), 2.28 (qd, *J* = 7.5, 1.9 Hz, 2H), 1.17 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2, 92.8, 74.5, 59.1, 46.2, 13.3, 12.5. Separation of the enantiomers by chiral HPLC [Daicel Chiracel™ OD-H column, flow rate 0.950 mL/min., 15% ^{i}PrOH, 85% hexane, T_r: 8.25 min (*S*), 10.1 min (*R*)] provided the enantiomeric excess to be 87%.[38]

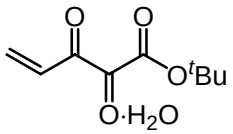


5-Chloro-2,3-dioxopentanoic acid *tert*-butyl ester (22): To a solution of ylide **23** (2.58 g, 6.85 mmol) in benzene (17.6 mL) at ~4 °C was added a solution of 3-chloropropionyl chloride (0.327 mL, 3.43 mmol) in benzene (1.7 mL) in a slow, dropwise fashion. Upon complete addition of the acyl chloride, the reaction mixture was warmed to ambient temperature and stirred for 30 minutes. The reaction mixture

[38] The β-lactone was opened via addition-elimination to the lactone carbonyl by benzylamine. The enantiomeric excess of the resulting amide was measured.

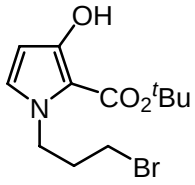
was then diluted with cold ether (25 mL) and stirred vigorously for an additional 5 minutes. Filtered off the precipitate *via* vacuum filtration and washed the solid with cold ether (2 x 100 mL). The filtrate was then concentrated *in vacuo* to yield dione ylide **24** as a yellow-white solid (1.44 g, 94%) that was used without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74-7.43 (m, 15H), 3.83 (t, *J* = 6.8 Hz, 2H), 3.38 (t, *J* = 6.8 Hz, 2H), 1.06 (s, 9H); EI-MS *m/z* 466 (M^+), 431, 374, 347, 277, 201; HRMS calcd for $C_{27}H_{28}ClO_3P$: 466.1465; found 466.1473.

To a mixture of the dione ylide **24** in THF (34 mL) and water (17 mL) was added oxone® (3.19 g, 5.19 mmol). Stirred the resulting biphasic mixture vigorously for 4 hours, after which the reaction mixture was diluted with water (30 mL). Separated the layers and extracted the aqueous layer with EtOAc (3 x 40 mL). The combined organic extracts were washed with brine (1x), dried over Na_2SO_4, filtered and concentrated *in vacuo* to yield a yellow oil. The yellow oil was dissolved in 1:1/hexanes:ethyl acetate (10 mL) and stirred at ambient temperature for 1 hour. The resulting white precipitate was removed via quick filtration over a plug of silica that was washed with 1:1/hexanes:ethyl acetate (2-3 column volumes). Concentrated the filtrate *in vacuo* to yield the title compound as a 'wet' solid (0.603 g, 82%) that was used without any further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.88 (s, 2H), 3.81 (t, *J* = 6.3 Hz, 2H), 3.07 (t, *J* = 6.3 Hz, 2H), 1.52 (s, 9H).

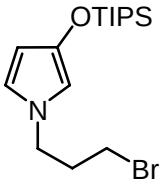


2,3-Dioxopent-4-enoic acid *tert*-butyl ester (25): To a solution of trione **22** (0.603 g, 2.53 mmol) in THF (16 mL) was added saturated aqueous $NaHCO_3$ (12 mL). The biphasic mixture was stirred vigorously for 4 hours, after which the reaction mixture was diluted with water (15 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 25 mL). The combined organic extracts were then washed with brine

(1 x 15 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to yield the title compound as a yellow solid (0.500 g, 98%) that was used without further purification: m.p. 59-62 ^oC; IR (thin film) 3382, 2984, 2930, 1746, 1712, 1612, 1106, 1058 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.58 (d, J = 7.7 Hz, 1H), 6.57 (d, J = 3.8 Hz, 1H), 6.02 (dd, J = 7.7, 4.2 Hz, 1H), 5.00 (s, 2H), 1.48 (s, 9H).



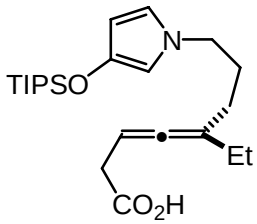
1-(3-Bromopropyl)-3-hydroxy-1*H*-pyrrole-2-carboxylic acid *tert*-butyl ester (21): To a mixture of ene-trinone **25** (5.33 g, 26.4 mmol) and 3-bromopropylamine hydrobromide (5.77 g, 26.4 mmol) in CH_2Cl_2 (470 mL) at ambient temperature was slowly added $^iPr_2NEt$ (4.60 mL, 26.4 mmol). The dark yellow solution became homogenous and was stirred for an additional 30 minutes at ambient temperature. Silica gel (118 g) was then added and the resulting mixture was allowed to stir vigorously overnight. The silica gel was filtered off and washed with a copious amount of CH_2Cl_2. The filtrate was concentrated *in vacuo* and purified by silica gel chromatography (50:1/hexanes:ethyl acetate) to yield the title compound as a yellow oil (8.07 g, 55%): IR (thin film) 2973, 1642, 1555, 1393, 1367, 1107 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.44 (br s, 1H), 6.61 (d, J = 2.7 Hz, 1H), 5.67 (d, J = 2.8 Hz, 1H), 4.17 (t, J = 6.1 Hz, 2H), 3.22 (t, J = 6.2 Hz, 2H), 2.18 (app p, J = 6.1 Hz, 2H), 1.57 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.6, 156.2, 127.7, 106.2, 96.2, 82.0, 47.8, 34.2, 30.4, 28.7; EI-MS *m/z* 303 (M^+), 247, 229, 123; HRMS calcd for $C_{12}H_{18}BrNO_3$: 303.0470, found 303.0471.



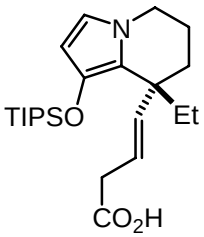
1-(3-Bromopropyl)-3-triisopropylsilanyloxy-1*H*-pyrrole (20): To a solution of 3-hydroxy-2-carboxylate pyrrole **21** (1.10 g, 3.60 mmol) in CH_2Cl_2 (80 mL) was added trifluoroacetic acid (11 mL). Stirred the solution vigorously for 6 hours at ambient temperature, after which the reaction mixture was cooled to 0 °C and quenched with saturated aqueous $NaHCO_3$. Diluted the reaction mixture with CH_2Cl_2, separated the layers and washed the organic layer with saturated aqueous $NaHCO_3$ (1x). The aqueous layer was extracted with CH_2Cl_2 (1x) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo* to yield 1,2-dihydro-pyrrolone **26** as an oil that was used without further purification: Crude ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, J = 3.0 Hz, 1H), 5.15 (d, J = 3.2 Hz, 1H), 3.71 (s, 2H), 3.57 (t, J = 6.5 Hz, 2H), 3.42 (t, J = 6.0 Hz, 2H), 2.14 (app p, J = 6.3 Hz, 2H).

The crude 1,2-dihydropyrrolone **26** was dissolved in CH_2Cl_2 (80 mL) and the solution cooled to 0 °C. To the reaction mixture was added ^{i}Pr$_2$NEt (20 mL), followed by slow, dropwise addition of TIPSOTf (1.17 mL, 4.34 mmol). The resulting solution was stirred at 0 °C for 20 minutes and then allowed to warm to ambient temperature overnight. Subsequently, the reaction mixture was cooled to 0 °C and quenched with water and then diluted with ether. The layers were separated and organic layer washed with saturated aqueous NH_4Cl. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford a crude oil that was purified by silica gel chromatography (50:1/hexanes:ethyl acetate) to yield the title compound as an orange oil (0.860 g, 67% overall yield from **21**): IR (thin film) 2943, 2866, 1556, 1346, 1006, 676 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.35 (app t, J = 2.7 Hz, 1H), 6.22 (app t, J = 2.0 Hz, 1H), 5.74 (dd, J = 2.8, 1.9 Hz, 1H), 3.91 (t, J = 6.2 Hz, 2H), 3.26 (t, J = 6.2 Hz, 2H), 2.17 (app p, J = 6.2 Hz, 2H), 1.20 (m, 3H), 1.09 (d, J = 6.3 Hz, 18 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.8,

117.9, 107.3, 101.3, 47.4, 34.1, 30.3, 17.9, 12.4; EI-MS *m/z* 359 (M^+), 316, 280, 252, 208, 180, 152; HRMS calcd for $C_{16}H_{30}BrNOSi$: 359.1280, found 359.1286.

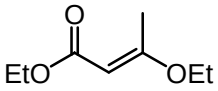


5-Ethyl-8-(3-triisopropylsilanyloxypyrrol-1-yl)octa-3,4-dienoic acid (27): To a mixture of Mg^0 (0.107 g, 4.40 mmol) in THF (5.5 mL) was added dibromoethane (14 μL). After gas evolution occurred, to the activated Mg^0 was added a solution of bromide **20** (0.792 g, 2.20 mmol) in THF (5.5 mL) over 10 mins. The mixture was stirred until all the starting material was consumed, as monitored by TLC. The prepared Grignard reagent was then added to a flask containing a −78 °C solution of β-lactone **18** (0.273 g, 2.20 mmol), CuCN (0.020 g, 0.220 mmol) and LiBr (0.044 g, 0.510 mmol) in THF (24 mL). Stirred the reaction mixture for 1 hour, after which the reaction was quenched with saturated aqueous NH_4Cl. The reaction mixture was allowed to warm to ambient temperature, after which the layers were separated and the aqueous layer extracted with ether (3 x 100mL). The combined organic extracts were then washed with saturated aqueous NH_4Cl (5 X 50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purified the resultant oil by silica gel chromatography (6:1/hexanes:ethyl acetate) to yield the title compound as a yellow-orange oil (0.425 g, 50%): *Unable to characterize due to product instability.*

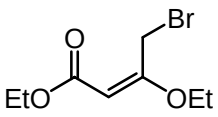


(*E*)-4-((*R*)-1-(Triisopropylsilyloxy)-8-ethyl-5,6,7,8-tetrahydroindolizin-8-yl)but-3-enoic acid (28): To a solution of allenic acid **27** (0.177 g, 0.440 mmol) in CH_2Cl_2 (8.1 mL) was added $Cl_2Pd(MeCN)_2$ (0.023 g, 8.73 x 10^{-5} mol). The resulting solution was stirred vigorously at ambient temperature for 8 hours. The

reaction mixture was diluted with 1:1/hexanes:ethyl acetate (12 mL) then quickly filtered over a plug of silica gel that was washed exhaustively with 1:1/hexanes:ethyl acetate. Concentrated the filtrate *in vacuo* and purified the oil by silica gel chromatography (4:1/hexanes:ethyl acetate) to yield the title compound as an oil (0.090 g, 50%): *Unable to characterize due to product instability.*

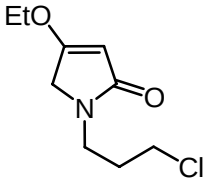


3-Ethoxy-but-2-enoic acid ethyl ester (31): A solution of ethyl acetoacetate (25.5 mL, 200 mmol) and triethyl orthoformate (33.3 mL, 200 mmol) was treated with concentrated H_2SO_4 (6 drops from a pipet) and the resulting dark solution stirred at ambient temperature for 12 hours. The reaction mixture was then treated with quinoline (10 drops from a pipet) and via fractional vacuum distillation (50 °C, 0.075 mb) the title compound collected as a clear oil (27.2g, 86%) that was used without further purification: IR (thin film) 2982, 1712, 1624, 1275, 1143, 1054 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.00 (s, 1H), 4.06 (q, *J* = 7.1 Hz, 2H), 3.80 (q, *J* = 7.0 Hz, 2H). 2.24 (s, 3H), 1.30 (t, *J* = 7.0 Hz, 3H), 1.21 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 167.5, 90.8, 63.9, 59.1, 18.9, 14.6, 14.4; EI-MS *m/z* 158 (M^+), 143, 129, 113, 85; HRMS calcd for $C_8H_{14}O_3$: 158.0943, found 158.0935.

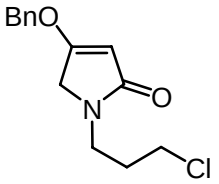


4-Bromo-3-ethoxybut-2-enoic acid ethyl ester (32): To a mixture of ester **31** (64.60 g, 0.410 mol), *N*-bromosuccinimde (76.20 g, 0.430 mol) and CCl_4 (408 mL) was added benzoyl peroxide (1.02 g). The resulting mixture was heated to reflux for 3 hours, after which the solids were filtered off and the filtrate dried over $MgSO_4$. Filtered off the solids, concentrated the filtrate *in vacuo* and collected the title compound, via vacuum distillation (77 °C, 0.21 mb), as a yellow-tinged oil (87.4 g, 90%) that was used without further purification:

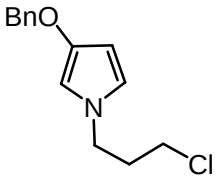
IR (thin film) 2982, 1708, 1624, 1154, 1128; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.10 (s, 1H), 4.52 (s, 2H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.90 (q, *J* = 7.0 Hz, 2H), 1.37 (t, *J* = 7.0 Hz, 3H), 1.27 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 166.3, 93.4, 64.6, 59.8, 26.0, 14.4, 14.0; EI-MS *m/z* 236 (M^+), 208, 190, 162, 84; HRMS calcd for $C_8H_{13}BrO_3$: 236.0048, found 236.0045.



1-(3-Chloropropyl)-4-ethoxy-1,5-dihydropyrrol-2-one (30): To a solution of NaOH (3.42 g, 85.5 mmol) in water (35 mL) at ambient temperature was added 3-chloropropylamine hydrochloride (11.1 g, 85.5 mmol). Once the solution was homogenous, CH_2Cl_2 (60 mL) was added followed by dropwise addition of allyl bromide **32** (4.05 g, 17.1 mmol) in CH_2Cl_2 (10 mL). The biphasic mixture was stirred vigorously overnight, after which the layers were separated and the aqueous extracted with ether (3x). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The resulting oil was allowed to sit at ambient temperature overnight and upon completion of cyclization, as monitored by TLC, purified by silica gel chromatography (1:1/hexanes:ethyl acetate) to yield the title compound as an orange-red solid (4.29 g, 62%): IR (thin film) 2924, 1675, 1619, 1219 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.01 (s, 1H), 4.00 (q, *J* = 7.1 Hz, 2H), 3.89 (s, 2H), 3.56 (t, *J* = 6.6 Hz, 2H), 3.52 (t, *J* = 6.8 Hz, 2H), 2.04 (app p, *J* = 6.6 Hz, 2H), 1.39 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 172.1, 94.4, 66.9, 51.2, 42.2, 39.2, 31.5, 14.0; EI-MS *m/z* 203 (M^+), 168, 154, 140, 111; HRMS calcd for $C_9H_{14}ClNO_2$: 203.0713, found 203.0713.

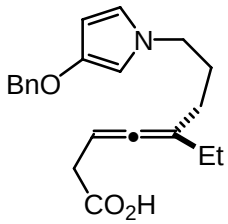


4-Benzyloxy-1-(3-chloropropyl)-1,5-dihydropyrrol-2-one (33): To a solution of 1,5-dihydropyrrolone **30** (0.584 g, 2.87 mmol) in benzyl alcohol (1.80 mL, 17.2 mmol) was added methanesulfonic acid (20.0 μL, 0.320 mmol). The solution was stirred vigorously for 3 hours at 90 °C under reduced pressure (~12 mmHg). Diluted the reaction mixture with 1:1/hexanes:ethyl acetate (20 mL) and purified by silica gel chromatography (1:1/hexanes:ethyl acetate) to yield the title compound as a solid (0.454 g, 60%): m.p. 62-64^{o}C; IR (thin film) 2924, 2866, 1676, 1623, 1450, 1340, 1220, 970 cm $^{-1}$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.29 (m, 5H), 5.12 (s, 1H), 4.94 (s, 2H), 3.91 (s, 2H), 3.54 (t, *J* = 6.5 Hz, 2H), 3.50 (t, *J* = 6.9 Hz, 2H), 2.02 (app p, *J* = 6.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 171.8, 134.7, 128.8, 128.0, 95.6, 73.1, 51.3, 42.2, 39.3, 31.6; EI-MS *m/z* 265 (M^+), 230, 202, 91; HRMS calcd for $C_{14}H_{16}ClNO_2$: 265.0870, found 265.0875.



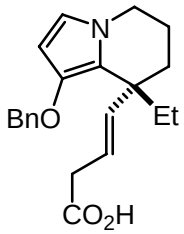
3-Benzyloxy-1-(3-chloropropyl)-1*H*-pyrrole (29): To a solution of benzyloxy-1,5-dihydropyrrolone **33** (1.04 g, 5.10 mmol) in THF (90 mL) at 0 °C was added $^{i}Bu_2AlH$ (25.5 ml, 25.5 mmol, 1 M in hexanes) over 5 minutes. The yellow-tinged solution was stirred vigorously for 18 hours at ambient temperature before the solution was poured into cold, aqueous 1M NaOH (250 mL). The layers were separated and the aqueous layer extracted with ether (3 x 200 mL). The combined organic extracts were dried over $MgSO_4$ and the mixture stirred vigorously for 1 hour. Filtered the resulting mixture over a plug of celite, concentrated the filtrate *in vacuo* and purified the resulting oil by silica gel chromatography (50:1/hexanes:ethyl acetate) to yield the title compound as a light orange-brown oil (0.475 g, 50%): IR (thin film) 2931, 2868, 1717, 1557, 1499, 1330, 1025 cm $^{-1}$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.28 (m, 5H), 6.42 (app t, *J* = 2.7

Hz, 1H), 6.25 (app t, *J* = 2.2 Hz, 1H), 5.86 (dd, *J* = 2.9, 1.9 Hz, 1H), 4.89 (s, 2H), 3.94 (t, *J* = 6.4 Hz, 2H), 3.42 (t, *J* = 6.0 Hz, 2H), 2.11 (app p, *J* = 6.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.9, 137.7, 128.4, 127.8, 127.6, 118.8, 103.7, 97.8, 72.8, 46.5, 41.6, 33.9; EI-MS *m/z* 249 (M^+), 186, 158, 91; HRMS calcd for $C_{14}H_{16}ClNO$: 249.0920, found 249.0918.

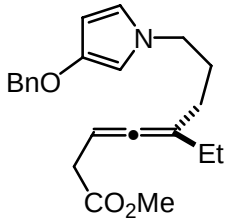


8-(3-Benzyloxypyrrol-1-yl)-5-ethylocta-3,4-dienoic acid (34): To a mixture of flame-dried Mg^0 (0.456 g, 18.8 mmol) in THF (3.4 mL) was added dibromoethane (0.162 mL, 1.88 mmol). While the Mg^0 was being activated, a solution of chloride **29** (0.938 g, 3.76 mmol) in THF (8.2 mL) was slowly added to the reaction flask and the resulting mixture was allowed to stir at 30 °C overnight. The prepared Grignard reagent was then slowly added to a solution of LiBr (0.075 g, 0.864 mmol), CuCN (0.034g, 0.376 mmol) and β-lactone **18** (0.396 g, 3.19 mmol) in THF (26 mL) at −78 °C. The reaction mixture was stirred for 1 hour at −78 °C, and then quenched with saturated aqueous NH_4Cl. The resulting mixture was warmed to ambient temperature, after which the layers were separated and the aqueous layer extracted with ether (3x). The combined organic extracts were washed with saturated aqueous NH_4Cl (4x), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purified by silica gel chromatography (6:1/hexanes:ethyl acetate) to yield the title compound as an orange oil (0.680, 65%): $[\alpha]_D$ = + 4.0 (*c* 1.3, $CHCl_3$); IR (thin film) 3088 (br), 2960, 2929, 1705, 1552, 1335 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.25 (m, 5H), 6.38 (app t, *J* = 2.7 Hz, 1H), 6.24 (app t, *J* = 2.3 Hz, 1H), 5.84 (dd, *J* = 2.8, 2.0 Hz, 1H), 5.29 (m, 1H), 4.88 (s, 2H), 3.74 (t, *J* = 6.6 Hz, 2H), 3.03 (d, *J* = 7.2 Hz, 2H), 1.96-1.78 (m, 6H), 0.97 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.7, 177.9, 147.5, 137.8, 128.3, 127.6, 118.4, 107.0, 103.5,

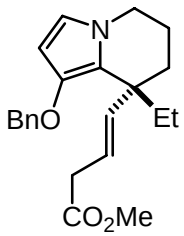
97.1, 85.9, 72.6, 49.3, 35.2, 29.0, 25.7, 12.1; EI-MS *m/z* 339 (M^+), 310, 280, 248, 202, 188; HRMS calcd for $C_{21}H_{25}NO_3$: 339.1834, found 339.1827.



(*E*)-4-((*R*)-1-(Benzyloxy)-8-ethyl-5,6,7,8-tetrahydroindolizin-8-yl)but-3-enoic acid (35): To a solution of allenic acid **34** (0.086 g, 0.250 mmol) in CH_2Cl_2 (2.5 mL) was added $Cl_2Pd(MeCN)_2$ (0.020 g, 76.2 μmol). The resulting solution was vigorously stirred for 6 hours at ambient temperature. Diluted the reaction mixture with 1:1/hexanes:ethyl acetate (2.5 mL) then quickly filtered the mixture over a plug of silica gel that was washed exhaustively with EtOAc. The filtrate was concentrated *in vacuo* and purified by silica gel chromatography (4:1/hexanes:ethyl acetate) to yield the title compound as a deep red oil (0.050 g, 58%): $[\alpha]_D$ = +12.6 (*c* 1.6, $CHCl_3$); IR (thin film) 3023 (br), 2931, 2868, 1702, 1562, 1451, 1339 cm $^{-1}$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.27 (m, 5H), 6.32 (d, *J* = 3.0 Hz, 1H), 5.90 (d, *J* = 3.0 Hz, 1H), 5.73 (d, *J* = 15.5 Hz, 1H), 5.26 (dt, *J* = 15.4, 7.0 Hz, 1H), 4.94 (s, 2H), 3.87 (ddd, *J* = 11.4, 5.0, 3.9 Hz, 1H), 3.74 (td, *J* = 10.5, 4.4 Hz, 1H), 3.06 (dd, *J* = 7.1, 1.3 Hz, 2H), 2.09-1.72 (m, 6H), 0.82 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.1, 142.4, 141.1, 138.6, 128.2, 127.3, 127.2, 118.7, 117.0, 115.1, 96.5, 72.9, 46.0, 41.9, 37.7, 31.2, 30.4, 20.3, 8.5; EI-MS *m/z* 339 (M^+), 310, 248, 204, 148; HRMS calcd for $C_{21}H_{25}NO_3$: 339.1834, found 339.1833. Separation of the enantiomers by chiral HPLC [Daicel Chiracel™ OD-H column, flow rate 1.00 mL/min., 10% ^{i}PrOH, 90% hexane, T_r: 16.88 min (*R*), 19.30 min (*S*)] provided the enantiomeric excess to be 72%.

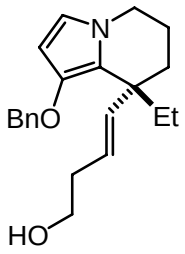


8-(3-Benzyloxypyrrol-1-yl)-5-ethylocta-3,4-dienoic acid methyl ester (36): To a solution of allenic acid **34** (0.597 g, 1.76 mmol) in benzene (12.6 mL) and MeOH (3.40 mL) at ambient temperature was added $TMSCHN_2$ (1.50 mL, 3.00 mmol, 2.0 M in hexanes) in a dropwise fashion. The resulting mixture was stirred for 30 minutes, after which the mixture was concentrated *in vacuo* and purified by silica gel chromatography (15:1/hexanes:ethyl acetate) to yield the title compound as a orange oil (0.545 g, 88%): $[\alpha]_D$ = +8.1 (*c* 1.3, $CHCl_3$); IR (thin film) 2962, 2931, 1738, 1558, 1505, 1454, 1435, 1333, 1163 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45-7.28 (m, 5H), 6.41 (app t, *J* = 2.6 Hz, 1H), 6.27 (app t, *J* = 2.4 Hz, 1H), 5.86 (dd, *J* = 2.8, 1.9 Hz, 1H), 5.32 (m, 1H), 4.90 (s, 2H), 3.78 (t, *J* = 6.7 Hz, 2H), 3.69 (s, 3H), 3.02 (d, *J* = 7.1 Hz, 2H), 1.98-1.80 (m, 6H), 0.99 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.8, 172.2, 147.7, 138.0, 128.4, 127.7, 127.6, 118.5, 106.9, 103.8, 97.2, 86.4, 72.8, 51.7, 49.5, 35.3, 29.1, 25.8, 12.2; EI-MS *m/z* 353 (M^+), 322, 294, 263, 230, 202, 188; HRMS calcd for $C_{22}H_{27}NO_3$: 353.1991, found 353.2003



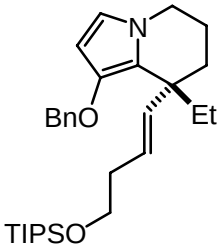
(*E*)-Methyl-4-((*R*)-1-(benzyloxy)-8-ethyl-5,6,7,8-tetrahydroindolizin-8-yl)but-3-enoate (37): To a solution of allenic methyl ester **36** (0.408 g, 1.16 mmol) in CH_2Cl_2 (11.5 mL) was added $Cl_2Pd(MeCN)_2$ (0.089 g, 0.350 mmol). The resulting solution was stirred vigorously at ambient temperature for 6 hours. The reaction mixture was diluted with 1:1/hexanes:ethyl acetate (12 mL) then quickly filtered over a plug of silica gel that was washed exhaustively with EtOAc. Concentrated the filtrate *in vacuo* and purified the oil by silica gel chromatography (12:1/hexanes:ethyl acetate) to yield the title compound as an orange oil (0.240 g, 59%): $[\alpha]_D$ = +15.4 (*c* 1.9, $CHCl_3$); IR (thin film) 2948, 2874, 1738, 1563, 1453, 1435, 1342, 1205, 1158 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41-7.25

(m, 5H), 6.30 (d, J = 2.5 Hz, 1H), 5.89 (d, J = 2.1 Hz, 1H), 5.69 (dt, J = 15.5, 1.2 Hz, 1H), 5.26 (dt, J = 15.5, 7.0 Hz, 1H), 4.93 (s, 2H), 3.86 (ddd, J = 11.5, 4.8, 3.8 Hz, 1H), 3.73 (td, J = 11.6, 4.4 Hz, 1H), 3.59 (s, 3H), 3.01 (dd, J = 7.0, 1.2 Hz, 2H), 2.11-1.71 (m, 6H), 0.82 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 142.5, 140.6, 138.8, 128.2, 127.3, 127.2, 119.4, 117.1, 115.1, 96.6, 72.9, 51.5, 46.0, 41.9, 37.8, 31.3, 30.5, 20.4, 8.6; EI-MS *m/z* 353 (M^+), 324, 294, 262, 234; HRMS calcd for $C_{22}H_{27}NO_3$: 353.1991, found 353.1974. Separation of the enantiomers by chiral HPLC [Daicel Chiracel™ OD-H column, flow rate 1.00 mL/min., 5% ^{i}PrOH, 95% hexane, T_r: 6.29 min (*R*), 8.18 min (*S*)] provided the enantiomeric excess to be 72%.

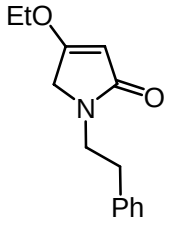


(*E*)-4-((*R*)-1-(Benzyloxy)-8-ethyl-5,6,7,8-tetrahydroindolizin-8-yl)but-3-en-1-ol (39): To a solution of methyl ester **37** (0.047 g, 0.133 mmol) in THF (1.7 mL) cooled to 0 °C was added LAH (0.027 g, 0.710 mmol). The reaction mixture was stirred for 30 minutes at 0 °C before being diluted with ether (2.0 mL) then quenched by sequentially adding H_2O (40 μL), 5.0 N aqueous NaOH (40 μL) and H_2O (110 μL). The resulting mixture was dried over $MgSO_4$, filtered over celite and concentrated *in vacuo* to afford a crude oil that was purified by silica gel chromatography (9:1/hexanes:ethyl acetate) to yield the title compound as a clear oil (0.039 g, 90%): $[\alpha]_D$ = +9.7 (*c* 1.0, $CHCl_3$); IR (thin film) 3394 (br), 2933, 2873, 1562, 1453, 1376, 1341, 1205, 1055 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.23 (m, 5H), 6.30 (d, J = 3.0 Hz, 1H), 5.88 (d, J = 3.0 Hz, 1H), 5.63 (d, J = 15.4 Hz, 1H), 5.08 (dt, J = 15.4, 7.1 Hz, 1H), 4.93 (s, 2H), 3.85 (dt, J = 11.7, 4.0 Hz, 1H), 3.73 (td, J = 11.7, 4.6 Hz, 1H), 3.50 (t, J = 6.1 Hz, 2H), 2.22 (app q, J = 6.1 Hz, 2H), 2.10-1.98 (m, 2H), 1.90-1.65 (m, 4H), 0.82 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.3, 140.2, 138.5, 128.3,

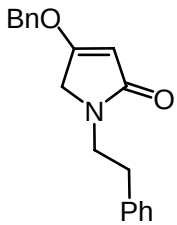
127.5, 127.3, 123.6, 117.4, 115.0, 96.4, 72.9, 61.7, 46.1, 41.8, 35.9, 31.4, 31.0, 29.7, 20.4, 8.7; EI-MS *m/z* 325 (M^+), 296, 234, 160; HRMS calcd for $C_{21}H_{27}NO_2$: 325.2042, found 325.2044.



(*R*)-1-(Benzyloxy)-8-((*E*)-4-triisopropylsilanyloxybut-1-enyl)-8-ethyl-5,6,7,8-tetrahydroindolizine (38): To a solution of homoallylic alcohol **39** (0.230 g, 0.707 mmol) in CH_2Cl_2 (6.8 mL) cooled to 0 °C was slowly added $^iPr_2NEt$ (0.160 mL, 0.919 mmol) followed by TIPSOTf (0.230 mL, 0.848 mmol). The resulting solution was stirred for 30 minutes, after which the reaction mixture was quenched with saturated aqueous NH_4Cl. The mixture was partitioned with ether and the organic layer washed with saturated aqueous NH_4Cl (1x). Subsequently, the aqueous layer was extracted with ether (1x) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purified by silica gel chromatography (50:1/hexanes:ethyl acetate) to yield the title compound as a clear, colorless oil (0.279g, 82%): $[\alpha]_D$ = +14.2 (*c* 2.1, $CHCl_3$); IR (thin film) 2941, 2864, 1564, 1461, 1341, 1097, 1071 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$) δ 7.41-7.21 (m, 5H), 6.28 (d, *J* = 3.0 Hz, 1H), 5.88 (d, *J* = 3.0 Hz, 1H), 5.60 (br d, *J* = 15 Hz, 1H), 5.15 (dt, *J* = 15, 6.9 Hz, 1H), 3.83 (ddd, *J* = 11.0, 4.8, 3.6 Hz, 1H), 3.71 (td, *J* = 11.0, 4.3 Hz, 1H), 3.62 (t, *J* = 7.0 Hz, 2H), 2.24 (app q, *J* = 6.9 Hz, 2H), 2.04 (dq, *J* = 11.0 Hz, 7.4 Hz, 1H), 1.95-1.85 (m, 1H), 1.81-1.67 (m, 4H), 1.02 (br d, *J* = 2.5 Hz, 21H), 0.81 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.3, 138.8, 138.3, 128.2, 127.2, 127.1, 124.1, 117.8, 114.8, 96.5, 72.9, 63.6, 46.1, 41.9, 36.5, 31.5, 30.7, 20.4, 18.0, 12.0, 8.7; EI-MS *m/z* 481 (M^+), 452, 438, 390, 362, 360, 318, 254, 188; HRMS calcd for $C_{30}H_{47}NO_2Si$: 481.3376, found 481.3376.

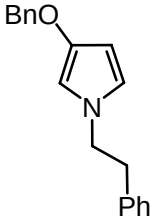


4-Ethoxy-1-phenethyl-1,5-dihydropyrrol-2-one (42): To a solution of NaOH (1.05 g, 26.2 mmol) in water (21 mL) at ambient temperature was added CH_2Cl_2 (63 mL) followed by phenethylamine (13.3 mL, 106 mmol). To the resulting mixture was added a solution of allyl bromide **32** (5.00 g, 21.1 mmol) in CH_2Cl_2 (16 mL) in a dropwise manner. The reaction mixture was stirred vigorously at ambient temperature overnight. Subsequently, the layers of the mixture were separated and the aqueous layer extracted with ether (2 x 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* and the resulting oil was allowed to stand at ambient temperature 8-10 hours. Upon completion of cyclization, as monitored by TLC, the volatiles were removed *in vacuo* and the oil purified by silica gel chromatography (3:1/ethyl acetate:hexanes) to yield the title compound as an off-white solid (3.12 g, 64%): m.p. 56-58 °C; IR (KBr plate) 3106, 2938, 1665, 1620, 1378, 1226, 1031 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29-7.16 (m, 5H), 4.97 (s, 1H), 3.91 (q, *J* = 7.1 Hz, 2H), 3.62 (s, 2H), 3.61 (t, *J* = 7.5 Hz, 2H), 2.84 (t, *J* = 7.4 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.34, 172.30, 139.1, 128.9, 128.8, 126.4, 94.5, 66.8, 51.2, 43.0, 35.1, 14.1; EI-MS *m/z* 231 (M^+), 140, 112; HRMS calcd for $C_{14}H_{17}NO_2$: 231.1259, found 231.1268.



4-Benzyloxy-1-phenethyl-1,5-dihydropyrrol-2-one (43): To a solution of *N*-phenethyl-1,5-dihydropyrrolone **42** (6.24 g, 27.0 mmol) in benzyl alcohol (20.0 mL, 192 mmol) was added methanesulfonic acid (0.230 mL, 3.56 mmol). The resulting mixture was heated to 90 °C and stirred vigorously for 3 hours, under reduced pressure (13-22 mmHg). Diluted the reaction mixture with 1:1/hexanes:ethyl acetate

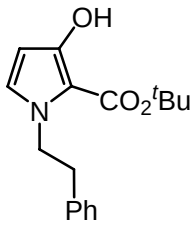
(20 mL) and purified by silica gel chromatography (1:1/hexanes:ethyl acetate) to yield the title compound as an off-white solid (6.37 g, 80%): m.p. 88-89 °C IR (thin film) 2931, 2869, 1671, 1623, 1454, 1348, 1219 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37-7.14 (m, 10H), 5.08 (s, 1H), 4.85 (s, 2H), 3.62 (s, 2H), 3.59 (t, *J* = 7.2 Hz, 2H), 2.82 (t, *J* = 7.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 171.6, 138.9, 134.7, 128.6, 128.5, 127.8, 126.3, 95.4, 72.8, 51.1, 42.9, 35.0; EI-MS *m/z* 293 (M^+), 202, 91; HRMS calcd for $C_{19}H_{19}NO_2$: 293.1416, found 293.1406.



3-Benzyloxy-1-phenethyl-1*H*-pyrrole (41): To a solution of 1,5-dihydropyrrolone **43** (3.19 g, 12.4 mmol) in THF (248 mL) at 0 °C was added $^iBu_2AlH$ (49.6 ml, 49.6 mmol, 1 M in hexanes) over 5 minutes. The yellow solution was stirred vigorously at ambient temperature for 18 hours. Subsequently, the solution was poured into cold, aqueous 1M NaOH (478 mL) and extracted with ether (3 x 225 mL). The combined organic extracts were dried over $MgSO_4$ and the resulting mixture stirred vigorously for 1 hour. The mixture was filtered over a plug of celite and the filtrate concentrated *in vacuo*. Purified the residual oil by silica gel chromatography (50:1/hexanes:ethyl acetate) to yield the title compound as an off-white solid (1.24g, 36%): m.p. 64-66 °C; IR (thin film) 2928, 1548, 1508, 1451, 1019 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$) δ 7.36-7.33 (m, 2H), 7.29-7.10 (m, 6H), 6.96-6.94 (m, 2H), 6.20 (app t, *J* = 2.5 Hz, 1H), 6.13 (app t, *J* = 2.0 Hz, 1H), 5.80 (dd, *J* = 2.3, 2.1 Hz, 1H), 4.80 (s, 2H), 3.78 (t, *J* = 7.3 Hz, 2H), 2.84 (t, *J* = 7.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.4, 138.3, 137.6, 128.4, 128.2, 128.1, 127.3, 127.2, 126.2, 118.1, 103.3, 97.1, 72.4, 51.2, 37.7; EI-MS *m/z* 277 (M^+), 186; HRMS calcd for $C_{19}H_{19}NO$: 277.1467, found 277.1464.

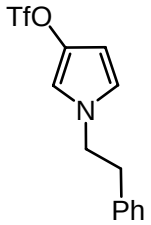
General procedure for removal of the benzyl group on 41 via transfer hydrogenation: To a solution of model benzyloxy pyrrole **41** (0.070 g, 0.253 mmol) in HOAc (2.5 mL) was added Pd/C (0.070 g, 10% act. on carbon) followed by 1,4-cyclohexadiene (0.240 mL, 2.53 mmol). The reaction mixture was stirred vigorously at ambient temperature until complete, as monitored by TLC. The mixture was then diluted with CH_2Cl_2 and filtered over a plug of celite, washing with more CH_2Cl_2. Cooled the collected organic layer to 0 °C and slowly quenched with saturated aqueous $NaHCO_3$. The layers were separated and the organic layer washed once more with saturated aqueous $NaHCO_3$. The organic layer was then dried over Na_2SO_4, filtered, and concentrated *in vacuo*.

General procedure for removal of the benzyl group on 41 via Brønsted acid and Brønsted acid-Lewis base conditions: To a solution of model benzyloxy pyrrole **41** (0.070 g, 0.253 mmol) in DMS (0.77 mL) at ambient temperature was added TFA (1.53 mL). The reaction mixture was stirred vigorously at ambient temperature until complete, as monitored by TLC. The resulting solution was diluted with CH_2Cl_2 and cooled to 0 °C before it was slowly quenched with saturated aqueous $NaHCO_3$. The layers were separated and the organic layer washed once more with saturated aqueous $NaHCO_3$. The organic layer was then dried over Na_2SO_4, filtered and concentrated *in vacuo*.



3-Hydroxy-1-phenethyl-1*H*-pyrrole-2-carboxylic acid *tert*-butyl ester (49): To a solution of ene-trinone **25** (4.97 g, 24.6 mmol) in CH_2Cl_2 (391 mL) at ambient temperature was slowly added phenethylamine (3.08 mL, 24.6 mmol).

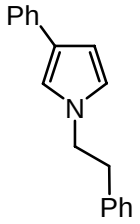
The dark yellow solution was stirred for 30 minutes, after which silica gel (111 g) was added and the resulting mixture stirred vigorously overnight. The silica gel was filtered off and washed with a copious amount of CH_2Cl_2. The filtrate was concentrated *in vacuo* and the resulting oil purified by silica gel chromatography (50:1/hexanes:ethyl acetate) to yield the title compound as a yellow oil (2.7 g, 38%): IR (thin film) 2975, 1639, 1553, 1393, 1154, 1108 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.53 (br s, 1H), 7.21-7.10 (m, 3H), 6.98-6.95 (m, 2H), 6.18 (d, J = 2.8 Hz, 1H), 5.57 (d, J = 2.9 Hz, 1H), 4.18 (t, J = 6.9 Hz, 2H), 2.89 (t, J = 6.9 Hz, 2H), 1.55 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.5, 156.0, 138.3, 128.7, 128.4, 127.2, 126.5, 105.9, 95.7, 81.6, 51.1, 38.2, 28.6; EI-MS *m/z* 287 (M^+), 231, 213, 186, 122, 109; HRMS calcd for $C_{17}H_{21}NO_3$: 287.1521, found 287.1511.



Trifluoromethanesulfonic acid 1-phenethyl-1*H*-pyrrol-3-yl ester (48): To a solution of *N*-phenethyl-3-hydroxy-2-carboxylate pyrrole **49** (1.10 g, 3.83 mmol) in CH_2Cl_2 (80 mL) at ambient temperature was added trifluoroacetic acid (10 mL). The reaction mixture was stirred vigorously for 6 hours, after which it was cooled to 0 °C and quenched with saturated aqueous $NaHCO_3$. The resulting mixture was diluted with CH_2Cl_2, the layers separated and the organic layer washed with saturated aqueous $NaHCO_3$ (1x). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield 1,2-dihydropyrrolone **50** as an oil that was used without further purification: Crude ^1H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, J = 2.9 Hz, 1H), 7.35-7.25 (m, 3H), 7.15- 7.13 (m, 2H), 5.04 (d, J = 3.2 Hz, 1H), 3.69 (s, 2H), 3.61 (t, J = 6.9 Hz, 2H), 2.9 (t, J = 6.9 Hz, 2H).

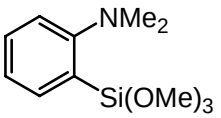
The crude 1,2-dihydropyrrolone **50** was dissolved in CH_2Cl_2 (80 mL) and the solution cooled to 0 °C. To the reaction mixture was slowly added $^iPr_2NEt$ (12 mL), followed by slow

addition of Tf_2O (0.770 mL, 4.60 mmol). The reaction mixture was stirred at 0 °C for 20 minutes then allowed to warm to ambient temperature overnight. The resulting brown solution was then cooled to 0 °C and quenched with water. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2x). The combined organic extracts were then washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to produce an oil that was purified by silica gel chromatography (50:1/hexanes:ethyl acetate) to yield the title compound as an orange-red oil (1.70 g, 70% overall yield from **49**): IR (thin film) 3141, 3030, 2938, 1420, 1332, 1242, 1210, 1138, 979 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27-7.16 (m, 3H), 7.00-6.97 (m, 2H), 6.50 (app t, J = 2.2 Hz, 1H), 6.31 (app t, J = 2.7 Hz, 1H), 5.98 (dd, J = 2.9, 1.8 Hz, 1H), 3.96 (t, J = 7.0 Hz, 2H), 2.94 (t, J = 7.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.0, 135.2, 129.0, 128.9, 127.2, 119.4, 119.2 (q, J = 319 Hz, -CF_3), 111.5, 101.4, 52.5, 38.1; EI-MS *m/z* 319 (M^+), 186, 158, 115, 130, 105; HRMS calcd for $C_{13}H_{12}F_3NO_3S$: 319.0490, found 319.0475.

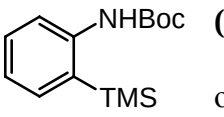


1-Phenethyl-3-phenyl-1*H*-pyrrole (51): To a solution of triflate **48** (0.230 g, 0.720 mmol), $Pd(OAc)_2$ (0.016 g, 0.070 mmol) and triphenylphosphine (0.038 g, 0.144 mmol) in DMF (7.2 mL) was added phenyltrimethoxysilane (0.269 mL, 1.44 mmol) followed by TBAF (1.45 mL, 1.44 mmol, 1.0 M in THF). The mixture was stirred at ambient temperature for 5 minutes, then degassed via one freeze-pump-thaw cycle. The reaction was then heated to 90 °C and stirred vigorously for 24 hours. The resulting black mixture was allowed to cool to ambient temperature before being quenched with water (7.2 mL) and diluted with ether (10 mL). The layers were separated and the ethereal layer was washed with water (7 x 15 mL). The aqueous layer was then extracted with ether (1 x 20 mL) and the combined organic extracts dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purified by

silica gel chromatography (40:1/hexanes:ethyl acetate) to yield the title compound as a off-white solid (0.030 g, 17%): m.p. 67-70 °C; IR (thin film) 3027, 2927, 1554, 1497, 1453; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48-7.45 (m, 2H), 7.32-7.20 (m, 5H), 7.15-7.08 (m, 3H), 6.87 (app t, *J* = 2.0 Hz, 1H), 6.57 (app t, *J* = 2.5 Hz, 1H), 6.41 (dd, *J* = 2.7, 1.9 Hz, 1H), 4.08 (t, *J* = 7.2 Hz, 2H), 3.05 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.3, 136.0, 128.7, 128.6, 128.5, 126.7, 125.2, 125.0, 124.8, 121.5, 117.3, 106.2, 51.4, 38.3; EI-MS *m/z* 247 (M^+), 156, 143; HRMS calcd for $C_{18}H_{17}N$: 247.1361, found 247.1361.



[(2-Dimethylamino)phenyl]trimethoxysilane (52): To a solution of *N*,*N*-dimethylaniline (5.23 mL, 41.3 mmol), and TMEDA (6.22 mL, 41.3 mmol) in hexanes (26 mL) at 40 °C was added ^{n}BuLi (26.0 mL, 41.3 mmol, 1.6 M in hexanes). Stirred the reaction mixture for 6 hours, after which the yellow heterogeneous mixture was added to a solution of tetramethyl orthosilicate (5.33 mL, 36.1 mmol) in hexanes (26 mL) at 0 °C. The resulting mixture was stirred at ambient temperature for 14 hours and subsequently filtered, washing the removed solids with pentanes. The filtrate was concentrated *in vacuo* to yield a crude yellow oil that was purified via bulb-to-bulb distillation (pot temp. 40^{o}C @ 0.075 mb first to remove left over tetramethyl orthosilicate, then 60^{o}C @ 0.075 mb to collect desire product) to yield the title compound as a pale yellow oil (4.70 g, 47%): ^{13}C NMR (75 MHz, C_6D_6) δ 161.6, 138.0, 132.0, 128.8, 124.3, 120.4, 50.6, 46.4; EI-MS *m/z* 241 (M^+), 226, 210, 195, 120; HRMS calcd for $C_{11}H_{19}NO_3Si$: 241.1134, found 241.1136.



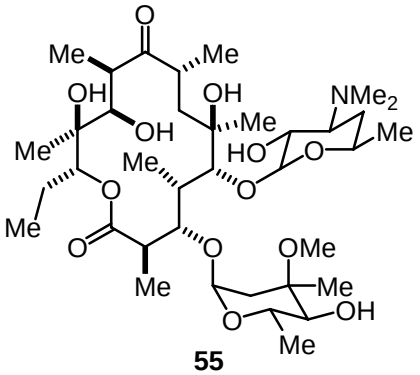
(2-Trimethylsilanylphenyl)carbamic acid *tert*-butyl ester (53): To a solution of *N*-Boc aniline (1.00 g, 5.17 mmol) in THF (21 mL) at −78 °C was slowly

added ^{t}BuLi (7.50 mL, 12.5 mmol, 1.7 M in pentanes). The solution was stirred at −78 °C for 15 minutes and then warmed to −20 ^{o}C for 2 hours. To the reaction mixture was added TMSCl (1.64 mL, 12.9 mmol) in a slow, dropwise manner and then warmed the reaction mixture to ambient temperature. Stirred the mixture at ambient temperature for 24 hours, after which diluted the reaction with water, separated the layers and extracted the aqueous layer with EtOAc (3x). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purified the resulting oil by silica gel chromatography (30:1/hexanes:ethyl acetate) to yield the title compound as a off-white solid (0.444 g, 32%): m.p. 58-59 °C; IR (thin film) 3252, 2976, 1695, 1513, 1365, 1248, 1175 cm $^{-1}$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (br d, J = 7.8 Hz, 1H), 7.42-7.32 (m, 2H), 7.11 (app t, J = 7.3 Hz, 1H), 6.39 (br s, 1H), 1.51 (s, 9H), 0.35 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.5, 142.5, 134.5, 131.0, 130.2, 124.1, 123.0, 80.2, 28.4, -0.47; EI-MS *m/z* 265 (M^+), 209, 194, 149, 134, 119; HRMS calcd for $C_{14}H_{23}NO_2Si$: 265.1498, found 265.1490.

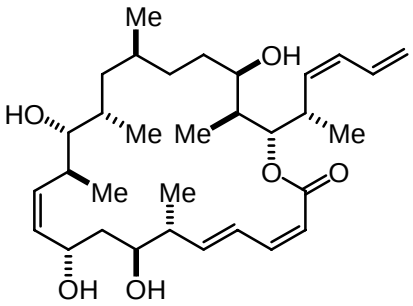
2.0 EFFICIENT FORMATION OF POLYPROPIONATE UNITS VIA THE CINCHONA ALKALOID-CATALYZED AAC REACTION

2.1 BACKGROUND

Propionate and polypropionate subunits are common structural motifs found in many biologically active natural products such as antibiotics and antitumor agents (Figure 13).[39] While the synthesis of polypropionate units has drawn much research interest, the formation of different arrays of these subunits still poses a significant challenge for the synthetic chemist. Biochemically, the production of polypropionate units is accomplished under the influence of two types of enzymatic catalysts, aldolases and antibodies (Figure 14).[40]



55



56

Figure 13: Erythromycin (55) and (–)-dictyostatin (56)

[39] (a) Defosseux, M.; Blanchard, N.; Meyer, C.; Cossy, J. *Tetrahedron* **2005**, *61*, 7632-7653. (b) Mochirian, P.; Cardinal-David, B.; Guérin, B.; Prévost, M.; Guidon, Y. *Tetrahedron Lett.* **2002**, *43*, 7067-7071.
[40] (a) Gijsen, H. J. M.; Wong, C.-H. *J. Am. Chem. Soc.* **1995**, *117*, 7585-7591. (b) Machajewski, T. D.; Wong, C.-H. *Angew. Chem. Int. Ed.* **2000**, *39*, 1352-1375.

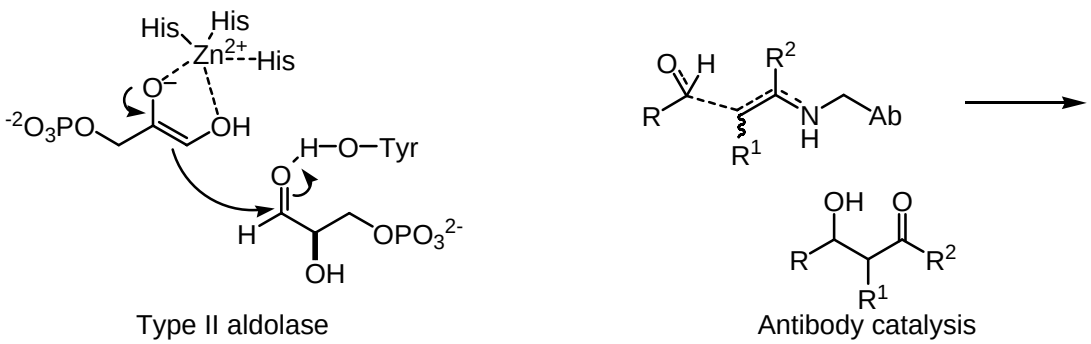


Figure 14: Formation of propionate units via enzymatic catalysis

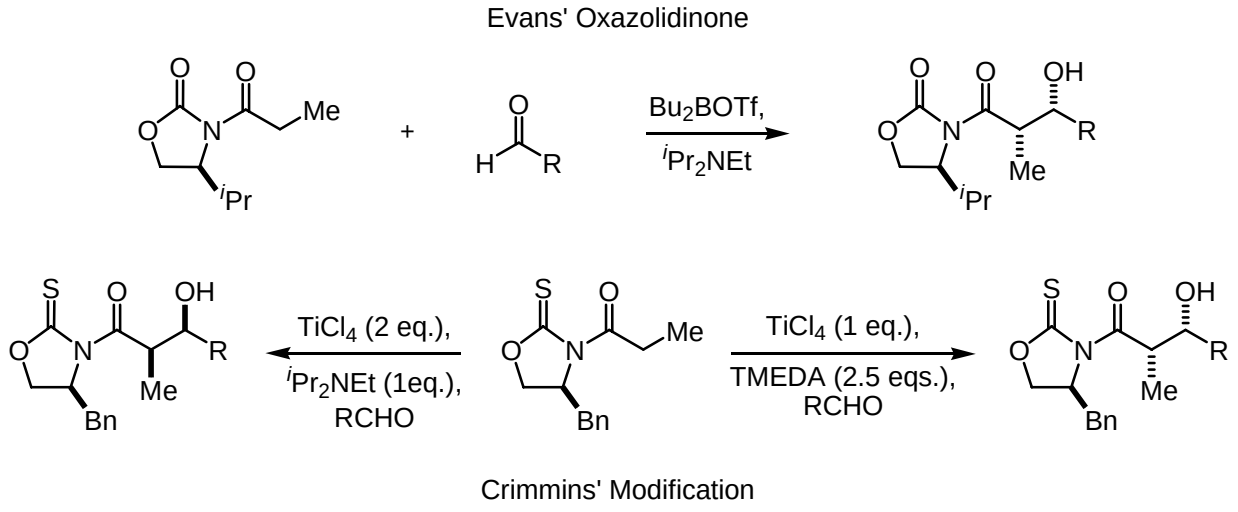
The most heavily studied and classical synthetic method for the formation of these subunits is undoubtedly the aldol reaction.[41] The aldol addition reaction is recognized as a fundamental tool for the formation of C-C bonds in synthetic organic chemistry. Due to the widespread use of this transformation in organic synthesis, there has been extensive exploration into performing it asymmetrically. These asymmetric variants can be categorized into two major subclasses: those that use a stoichiometric amount of chiral modifier and those that are catalytic.

Stoichiometric variants of the asymmetric aldol reaction consist of examples where asymmetric induction occurs *via* a chiral auxiliary that is incorporated onto an achiral substrate donor (Scheme 13). While additional steps in a synthetic sequence are needed for the installation and removal of the chiral auxiliary, this drawback is outweighed by the benefits gained from their use. First, the chiral auxiliaries utilized in the aldol addition reaction are normally prepared in a straightforward fashion from commercially available material. Second, these moieties often facilitate the isolation-separation-purification processes of the incipient aldol adducts. Lastly, the high diastereoselective reliability of these auxiliary-based aldol reactions makes this transformation very practical for both academic and industrial laboratories.

---

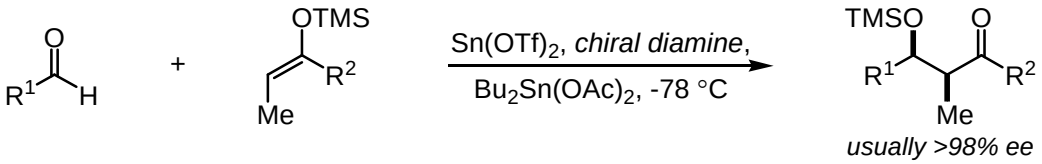
[41] (a) Palomo, C.; Oiarbide, M.; García, J. M. *Chem. Eur. J.* **2002**, *8*, 36-44. (b) Palomo, C.; Oiarbide, M.; García, J. M. *Chem. Soc. Rev.* **2004**, *33*, 65-75.

Scheme 13

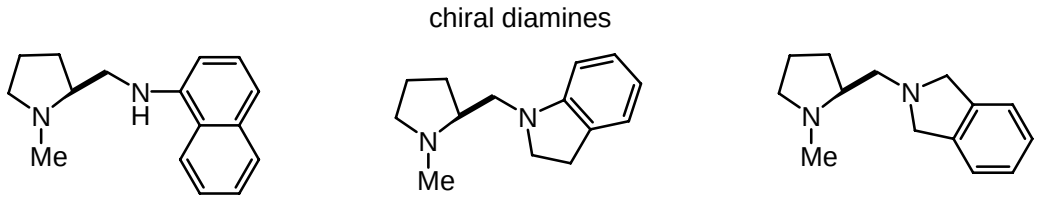


Despite the benefits gained by using chiral auxiliaries, they ultimately suffer from the fact that they are used in a stoichiometric amount. A more economical and elegant way to carry out these transformations is to introduce diastereoselectivity by employing a catalytic amount of chiral inductor.[40b,42] This goal has been achieved by introducing asymmetric induction using a few different approaches. In 1996, Mukaiyama and coworkers succeeded in performing the first catalytic, asymmetric aldol reaction by utilizing substoichiometric amounts of a chiral tin(II) complex as a Lewis acid to activate the aldehyde acceptor (Scheme 14). Since this pioneering discovery, a steady improvement of chiral Lewis acids to perform this asymmetric transformation has been observed.

Scheme 14

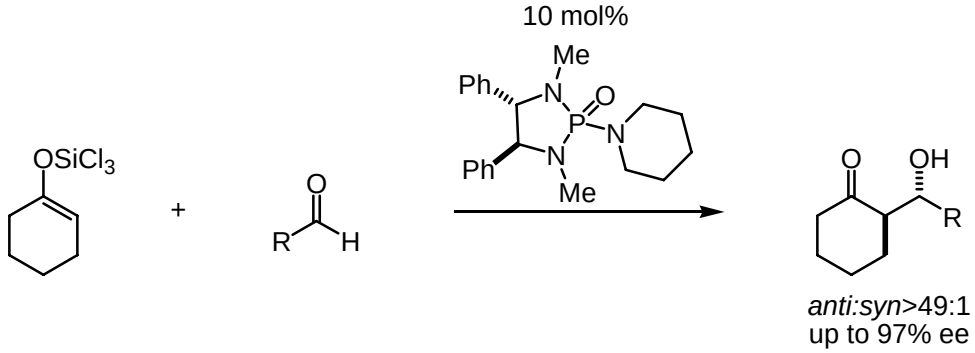


[42] Alcaide, B.; Almendros, P. *Eur. J. Org. Chem.* **2002**, 1595-1601.



Another successful attempt at performing a catalytic, asymmetric aldol addition reaction occurred by mediation with a chiral Lewis base where the aldol donor is activated. This conceptually different approach was accomplished in 2000 by Denmark and coworkers (Scheme 15). In this reaction, trichlorosilyl enolates are used as the aldol donors and are activated by a catalytic amount of chiral phosphoramide Lewis base promoter. The afforded aldol adducts were obtained in good yield with a high degree of enantioselectivity (up to 97% ee).

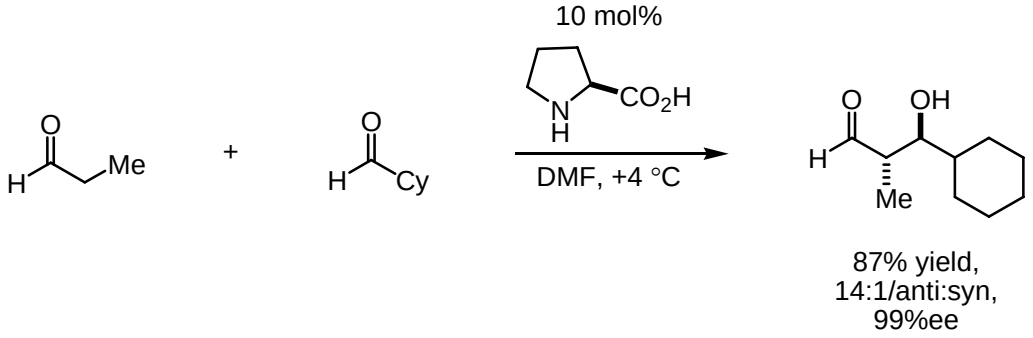
Scheme 15



An innovative variant to the "standard" aldol methodologies which has gained an increasing amount of attention in recent years is the use of organocatalysts to perform asymmetric aldol reactions. An enticing attribute of these organocatalytic reactions is the alleviation of having to pregenerate enolates or enolate equivalents. Seminal research in this area, performed by List, Barbas III and coworkers, has shown that the simple amino acid L-proline promotes a

diastereoselective aldol addition reaction between hydroxyacetone and an aldehyde.[43] Subsequent studies conducted by Macmillan and coworkers further demonstrated the utility of L-proline by successfully cross-coupling two different aldehydes with one another in an enantio- and diastereoselective fashion (Scheme 16).[44] To date, a large variety of proline variants have been synthesized and screened for catalytic activity.

Scheme 16

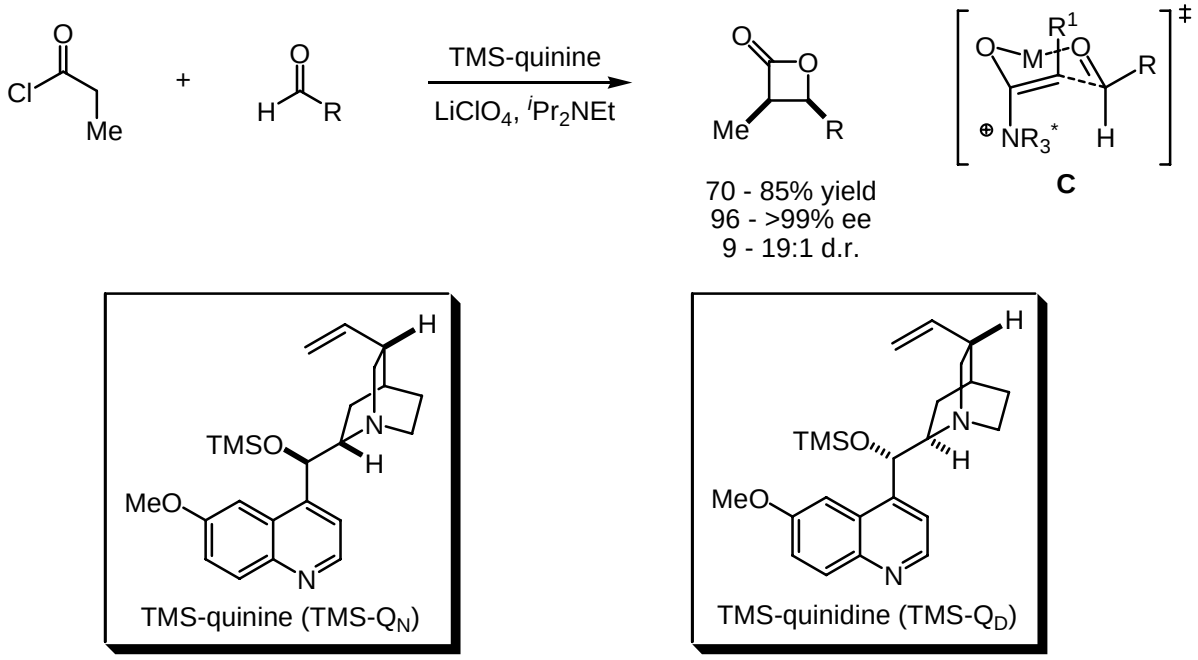


In 2004, the Nelson group developed an alternative method for the production of propionate units by employing a substoichiometric amount of chiral cinchona alkaloid in the AAC reaction (Scheme 17).[45] In this 2nd generation AAC reaction, propionyl chloride undergoes a dehydrohalogenation reaction in the presence of Hünig's base to generate methyl ketene *in situ*. Methyl ketene is then intercepted by a catalytic amount of either TMS-quinine or the pseudoenantiomeric TMS-quinidine to produce exclusively a chiral (*Z*)-enolate. Subsequently, this chiral nucleophile reacts with an aldehyde *via* Zimmerman-Traxler chair transition state **C** to yield a *syn*-disubstituted β-lactone product in good yield and in essentially enantio- and diastereomerically pure form.

---

[43] Notz, W.; Tanaka, F.; Barbas III, C. F. *Acc. Chem. Res.* **2004**, *37*, 580-591.
[44] Northrup, A. B.; Macmillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798-6799.
[45] Zhu, C.; Shen, X.; Nelson, S. G. *J. Am. Chem. Soc.* **2004**, *126*, 5352-5353.

Scheme 17



Due to the highly efficient nature of this transformation, the Nelson group became intrigued by the further potential that this *Cinchona* alkaloid-catalyzed AAC possessed. More specifically, interest in the effect double diastereoselection would have on the AAC reaction of chirally-substituted aldehydes was piqued (Figure 15). If the cinchona alkaloid-catalyzed AAC reaction is amenable to these more elaborate aldehydes, it would afford a new and efficient method for the formation of polypropionate units in an iterative fashion.

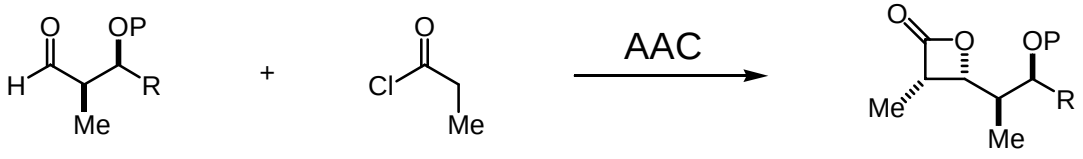


Figure 15: Formation of polypropionate units via the alkaloid-catalyzed AAC

2.2 RESULTS AND DISCUSSION

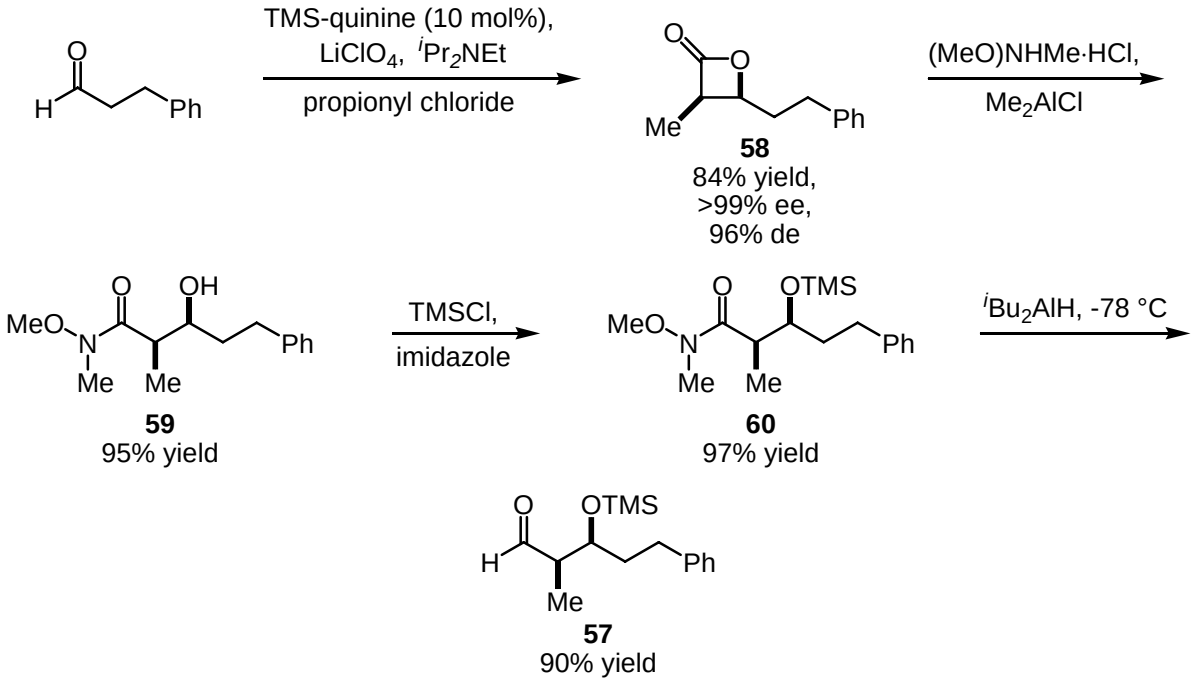
In order to determine the potential of the C*inchona* alkaloid-catalyzed AAC reaction to form polypropionate units, a variety of model aldehydes were synthesized and tested. These aldehydes varied in stereo- and regiochemical content to observe not only the reactivity of these aldehydes in the AAC reaction but also the effect different substitution patterns would have on the diastereoselectivity of the ensuing cyclocondensation. All the model aldehydes were synthesized using similar, straightforward reaction sequences which could be scaled up with no diminishing effects.

2.2.1 Synthesis and reactivity of model aldehyde 57

The initial studies to determine the potential of the cinchona alkaloid-catalyzed AAC reaction to form polypropionate subunits were made using model α,β-disubstituted *syn*-aldehyde **57** (Scheme 18).[46] The synthesis of aldehyde **57** began with commercially available hydrocinnamaldehyde which was subjected to the original C*inchona* alkaloid-catalyzed AAC reaction to produce disubstituted β-lactone **58** in 84% yield and in essentially enantio- and diastereomerically pure form. Opening of β-lactone **58** with (MeO)NHMe·HCl in the presence of Me_2AlCl afforded a 95% yield of β-hydroxy amide **59**. Protection of the now unmasked hydroxy group on amide **59** with TMSCl produced silyl ether **60** in 97% yield. Subsequent reduction of the Weinreb amide moiety on silyl ether **60** with $^{i}Bu_2AlH$ afforded a 90% yield of the desired model aldehyde **57**.

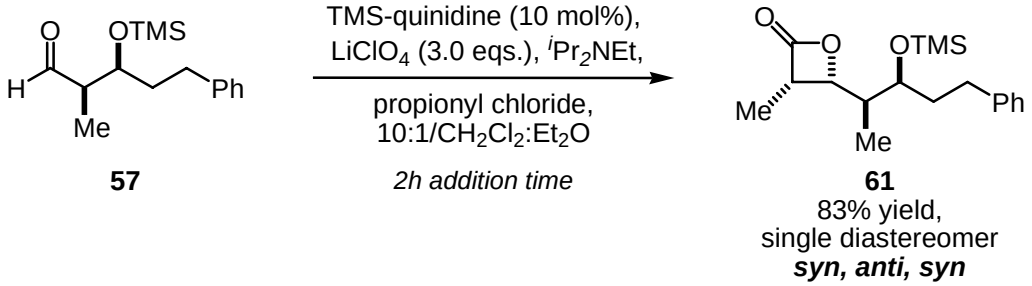
[46] The studies concerning model *syn*-aldehyde **57** were performed by Dr. Jeff Wallace and Dr. Cheng Zhu. The matched AAC reaction with aldehyde **57** where DMF was used as the cosolvent was performed by the author of this document (see Experimental).

Scheme 18



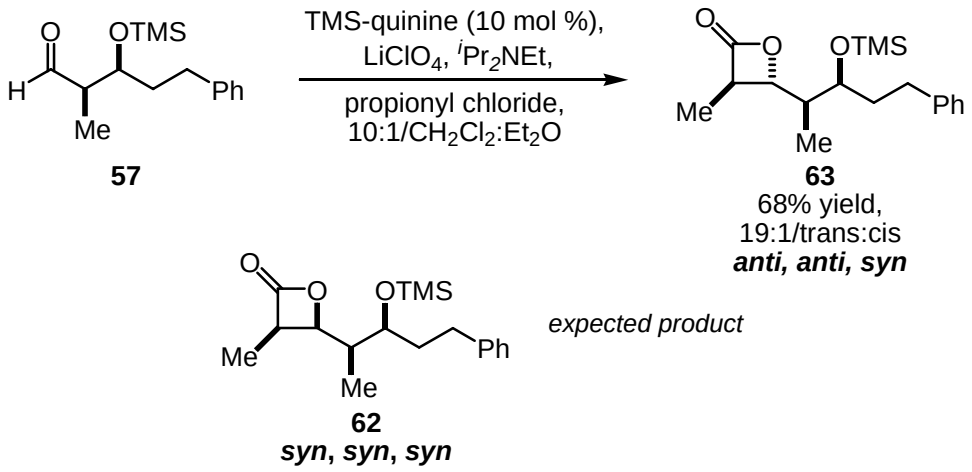
With the desired model substrate at hand, *syn*-aldehyde **57** was subjected to the original C*inchona* alkaloid-catalyzed AAC reaction conditions previously reported by the Nelson group.[45] As expected, the added steric components on model aldehyde **57** greatly attenuated the reactivity of the aldehyde in the AAC reaction, with β-lactone **61** being produced in low yield.[46] However while the yield of β-lactone **61** was low, the reaction did prove that the alkaloid-catalyzed AAC reaction had potential to produce iterative polypropionate units. After optimization of the original AAC reaction conditions, which included changing the solvent ratio (10:1), using an excess of Lewis acid (3.0 equivs.) and elongating the addition time of the solution of PrCl in CH_2Cl_2, reaction conditions were found that produced the desired *syn*, *anti*, *syn* masked polypropionate unit **61** in 83% yield and as a single diastereomer (Scheme 19).

Scheme 19



After successfully synthesizing the desired *syn*, *anti*, *syn* masked polypropionate **61,** model *syn*-aldehyde **57** was then subjected to a catalytic amount of the pseudoenantiomeric TMS-Q_N using the same optimized reaction conditions (Scheme 20). The expected product from this reaction was β-lactone **62** which possesses an all *syn* stereoarray. Surprisingly, only a very small amount of desired β-lactone **62** was obtained. Instead, the major product obtained was the unexpected *anti*, *anti*, *syn* masked polypropionate unit **63**, produced in 68% yield with a d.r. = 19:1/*trans*:*cis*.[47] Despite many efforts, the *syn*, *syn*, *syn* masked polypropionate unit **62** has yet to be synthesized using the C*inchona* alkaloid-catalyzed AAC reaction.

Scheme 20



[47] The absolute stereochemistry of masked polypropionate unit **63** was unambiguously proven *via* x-ray crystallography following derivatization.

In order to explain the production of both the expected and unexpected β-lactone products, the transition states which they come from need to be examined. As before with the original cinchona alkaloid-catalyzed AAC reaction, it is felt that this cyclocondensation occurs *via* a closed Zimmerman-Traxler transition state (Figure 16). However, while invoking this closed transition state two important requirements must be accounted for. First, since an α-chiral aldehyde is being used, the chiral (*Z*)-enolates that are generated *in situ* will prefer to approach the recipient aldehydes from an *anti*-Felkin trajectory to avoid a highly unfavored *syn*-pentane interaction from occurring. Second, the preferred reactive enantioface of the chiral enolate is going to be solely dependent on the C*inchona* alkaloid that is being employed.

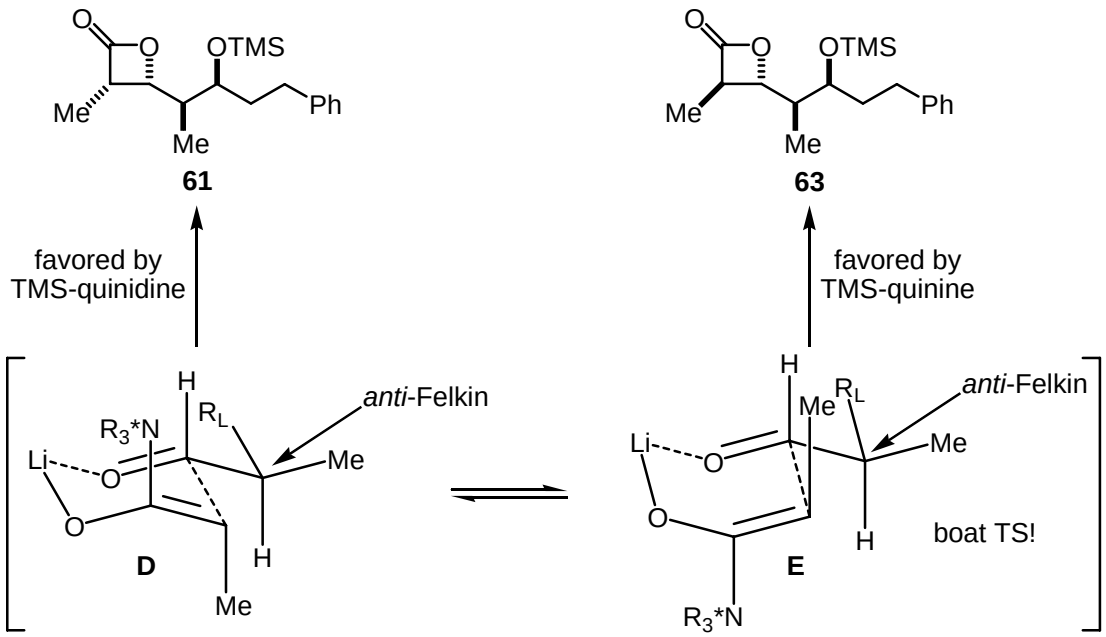


Figure 16: Explanation of beta-lactone products from aldehyde 57

As depicted in transition state **D** in Figure 16, the expected *syn*, *anti*, *syn* masked polypropionate unit **61** is prepared from reaction of the chiral (*Z*)-enolate derived from TMS-quinidine with aldehyde **57** *via* a closed Zimmerman-Traxler chair transition state. However, for the case of

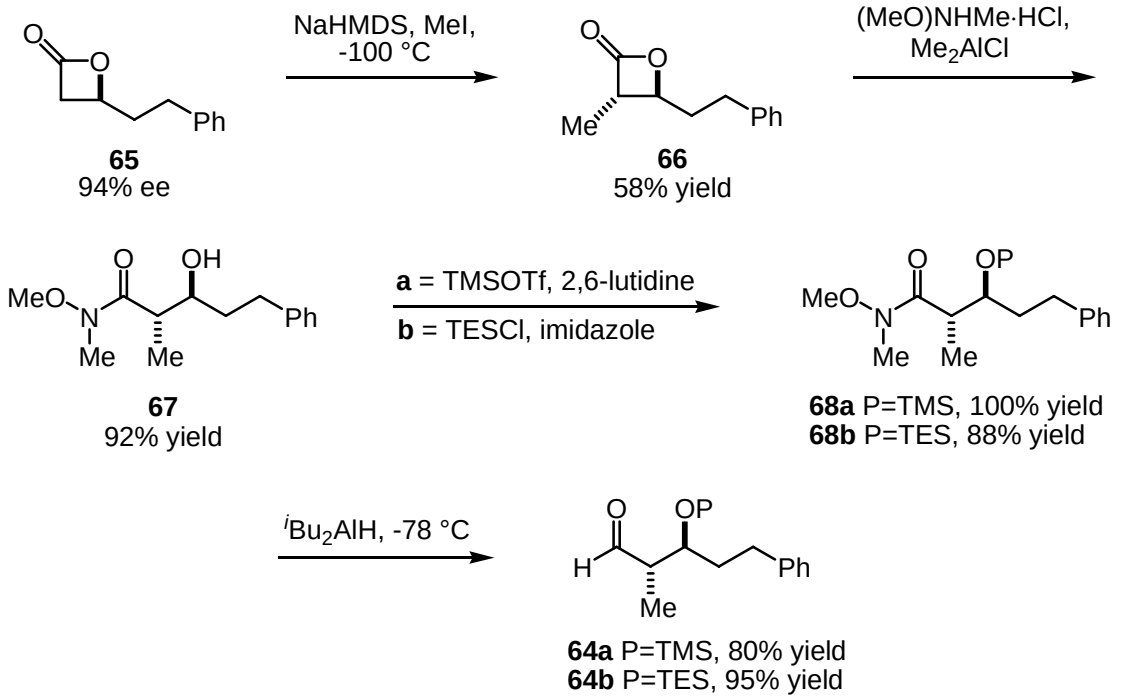
unexpected *anti*, *anti*, *syn* β-lactone product **63**, this transition state is not operative. Due to the fact that quinine and quinidine are pseudoenantiomers, their respective chiral enolates will prefer opposite enantiofaces when reacting with aldehyde **57**. In light of this, the (*Z*)-enolate derived from TMS-quinine reacts with *syn*-aldehyde **57** *via* boat transition state **E** to expose the oppose enantioface of the enolate to the aldehyde while maintaining an *anti*-Felkin approach. Reaction through this transition state leads to production of the unexpected *anti*, *anti*, *syn* masked polypropionate unit **63**.

2.2.2 Synthesis and reactivity of model aldehyde 64

At the same time at which model *syn*-aldehyde **57** was being tested in the cinchona alkaloid-catalyzed AAC reaction, model *anti*-aldehydes were also being tested. The synthesis of model aldehydes **64a,b** began with monosubstituted β-lactone **65**, which was produced in 94% ee from the Al(III)-catalyzed AAC (Scheme 21). Using chemistry developed in the Nelson group, β-lactone **65** was α-methylated with MeI and NaHMDS to produce disubstituted *trans*-β-lactone **66** in 58% yield.[48] Subsequent opening of β-lactone **66** proceeded in 92% yield to afford β-hydroxy Weinreb amide **67**. At this point two different silyl ether derivatives, trimethylsilyloxy and triethylsilyloxy amides **68a** and **68b**, respectively, were made in order to test the effect the protecting group would have on the AAC reaction. Silylation of the β-hydroxy group on amide **67** using standard silylation conditions followed by $^{i}Bu_2AlH$ reduction of the Weinreb amide moiety afforded model aldehydes **64a,b** in good overall yield.

[48] Kassick, A. J. *unpublished results.*

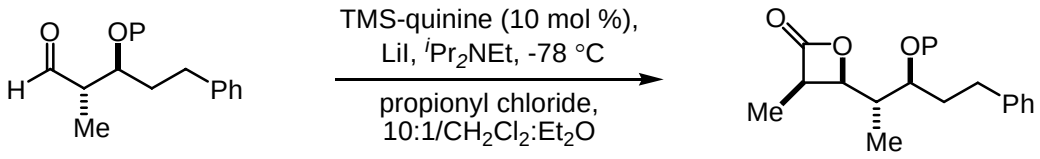
Scheme 21



For the initial studies to determine the viability of aldehydes **64a,b** in the AAC reaction, conditions using a catalytic amount of TMS-quinine were selected (Table 2). The major product obtained for all the aldehydes tested was the expected *syn*, *anti*, *anti* polypropionate unit **69**. More interesting though was the inverse trend between yield and d.r. observed when taking into account the nature of the β-hydroxy protecting group. For protecting groups that allowed the β-hydroxy group to participate in chelation (TMS, PMB)[49] the reactivity of the aldehyde in the AAC was high (~90% conversion) with the β-lactone product being produced with good diastereoselectivity (7-9:1/*cis*:*trans*). However in the case where a bulkier silyl group was employed (TES), though the reactivity of the aldehyde was decreased (75% conversion) the β-lactone product was produced in high diastereoselectivity (15:1/*cis*:*trans*).

[49] The *anti*-aldehyde possessing a β-PMB ether was only synthesized for testing the protecting group effect and was not characterized.

Table 2: Protecting group effect on aldehyde 64 in the AAC



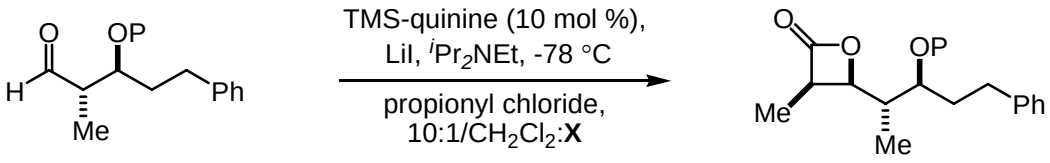
69
syn*, *anti*, *anti

entry	-OP	Conversion	d.r.
a	-OPMB[a]	~92%	~7.5:1
b	-OTMS[b]	90%	9:1
c	-OTES[b]	75%	15:1

[a] Based on crude ^{1}H NMR. [b] Conversions and d.r. measured using HPLC analysis (see Experimental for condition details). Major diastereomer is the depicted *cis* β-lactone product

Further optimization of the C*inchona* alkaloid-catalyzed AAC reaction for *anti*-aldehydes **64a,b** continued by testing the effect the co-solvent had on the outcome of the reaction (Table 3). For both substrates tested, all the co-solvents employed had a minor effect on the conversion of the starting aldehydes to the β-lactone products, with DMF slightly hindering the reaction. The most drastic effect though was observed in the diastereoselectivity of the β-lactone products obtained. Based on the diastereoselectivities, the use of DMF as a co-solvent was far superior to both THF and Et_2O for aldehydes **64a,b**. When DMF was used, the desired *syn*, *anti*, *anti* polypropionate units **69a,b** were both produced exclusively as a single diastereomer.

Table 3: Co-solvent effect on the AAC reaction of aldehydes 64a,b



64a,b **69a,b**
syn*, *anti*, *anti

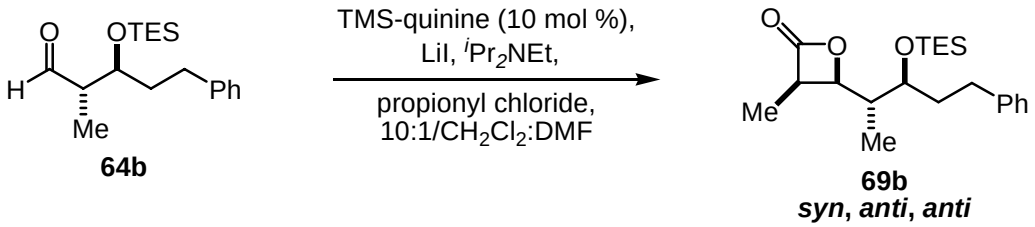
entry	Aldehyde	X	Conversion	d.r.
a	64a[a]	THF	~86%	5:1
b	64a[b]	Et_2O	90%	9:1
c	64a[b]	DMF	83%	>50:1
d	64b[b]	Et_2O	75%	15:1
e	64b[b]	DMF	76%	>50:1

[a] Based on crude ^{1}H NMR. [b] Conversions and d.r. measured using HPLC analysis (see Experimental for condition details). Major diastereomer is the depicted *cis* β-lactone product

Since the diastereoselectivities achieved by model aldehydes **64a,b** in the AAC reaction were equivalent up to this point, it was decided to use only one of the substrates for further studies. Due to the extra stability possessed by a TES protecting group compared to a TMS protecting group, as well as to demonstrate that aldehydes with bulkier silyl groups in the β-position can be used in the AAC reaction, *anti*-aldehyde **64b** was chosen for further studies. Since β-lactone **69b** was already being produced as a single diastereomer, the only aspect of the reaction left to optimize was to increase the conversion of aldehyde **64b** into the β-lactone product. It was felt that the best way to accomplish this would be to increase the temperature at which the reaction was run. With that in mind, a temperature study for the AAC reaction of aldehyde **64b** was conducted (Table 4). Gratifyingly, it was found that by performing the reaction at –50 ºC

provided almost complete consumption of aldehyde **64b** while still upholding the production of β-lactone **69b** as a single diastereomer.

Table 4: Temperature effect on the AAC reaction of aldehyde 64b



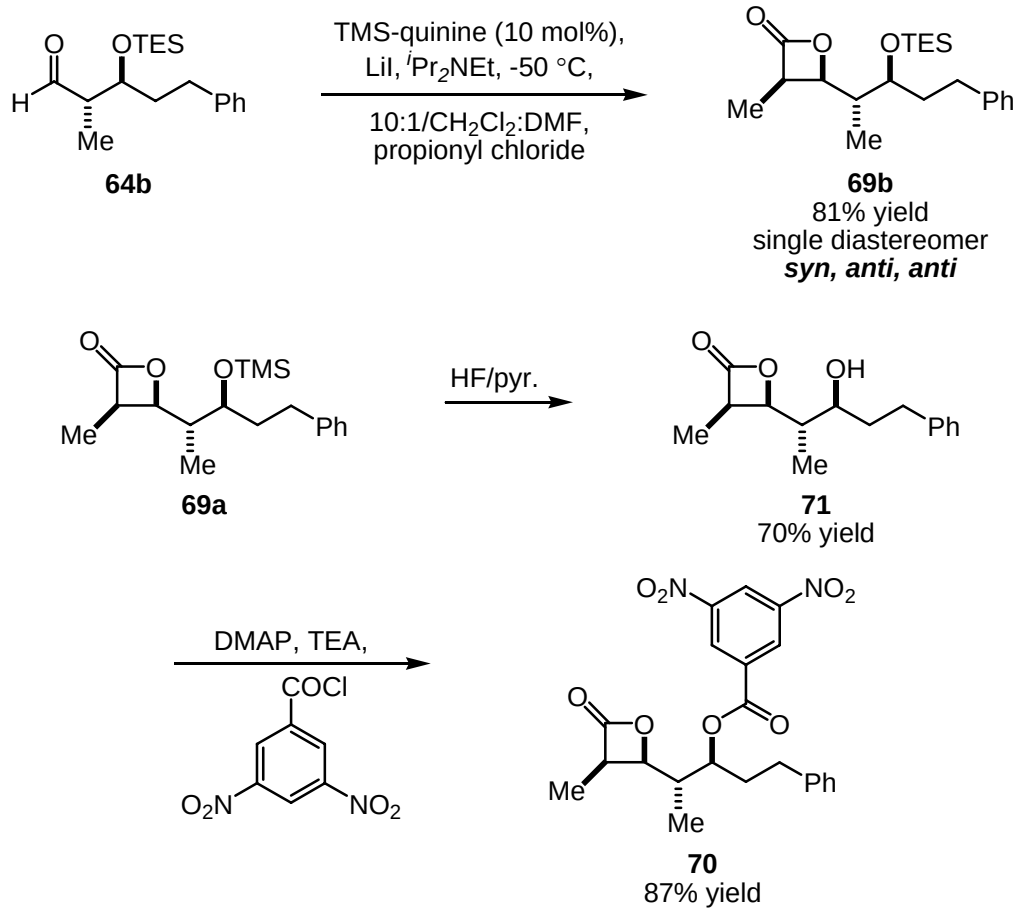
entry	Temperature	Conversion	d.r.
a	–78 °C	76%	single diastereomer
b	–60 °C	92%	single diastereomer
c	–50 °C	97%	single diastereomer
d	–25 °C	86%	single diastereomer

Conversions and diastereomeric ratios measured by HPLC analysis (see Experimental for condition details).

The overall optimized reaction for aldehyde **64b** in the presence of a catalytic amount of TMS-Q_N produced the desired β-lactone **69b** in 81% yield as a single diastereomer (Scheme 22). In order to unambiguously prove the stereochemistry of the β-lactone product, highly crystalline β-lactone **70** was synthesized. Starting with β-lactone **69a**, removal of the silyl protecting group with HF/pyridine provided alcohol **71** in 70% yield. Subsequent formation of the ester with 3,5-dinitrobenzoyl chloride in the presence of DMAP yielded β-lactone **70** in 87% yield. After recrystallization *via* slow vapor diffusion, the X-ray data obtained unambiguously proved that

the matched AAC reaction for aldehydes **64a,b** yielded β-lactone products that possessed the expected *syn*, *anti*, *anti* stereoarray (Appendix A).

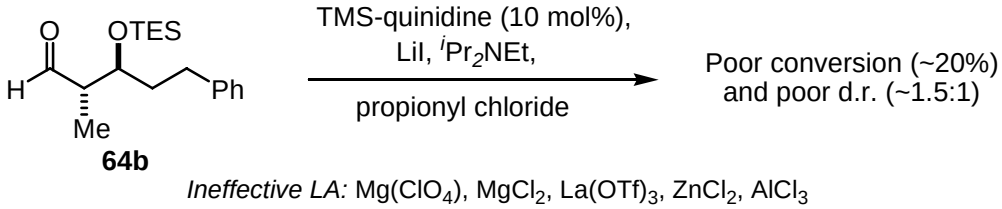
Scheme 22



As with the model *syn*-aldehyde, when the *anti*-aldehyde was subjected to the AAC reaction in the presence of the pseudoenantiomeric TMS-Q_D a similar type of matched /mismatched phenomenon was observed, however to a more severe extent. While subjection of aldehyde **64b** to the AAC reaction with TMS-Q_N yielded expected β-lactone product **69b**, subjection of the aldehyde to the AAC reaction with TMS-Q_D yielded only a minor amount (~20% conversion) of β-lactone product (Scheme 23). Efforts to improve this transformation, which included

screening various Lewis acids, proved fruitless as the reactivity of aldehyde **64b** in the TMS-Q_D-catalyzed AAC reaction remained poor.

Scheme 23



In general, the reactivity of *syn*-aldehyde **57** seems to be greater than that of *anti*-aldehyde **64b** in the AAC reaction. To explain this, as well as speculate on the greater disparity observed in the matched/mismatched phenomenon with the *anti*-aldehyde versus the *syn*-aldehyde, the reactive conformers of the aldehydes needed to be determined. In order to do so, the Reetz-Evans model for the preferred reactive conformers of substituted aldehydes will be invoked.[50] It is crucial though to keep in mind that since (*Z*)-enolates are exclusively being formed that an *anti*-Felkin trajectory of the enolate to the aldehyde is preferred. Therefore, in the case of *syn*-aldehyde **57** it can be seen that in both transition states **F** and **G** the *syn*-aldehyde is able to attain a reactive conformer where both the α- and β-stereocenters are in a desired arrangement (Figure 17). This conformer should be the lowest energy conformer that the aldehyde can attain, thereby facilitating the reaction.

[50] (a) Reetz, M. T.; Kesseler, K. Jung, A. *Tetrahedron* **1984**, *40*, 4327-4336. (b) Reetz, M. T.; Kesseler, K. *J. Chem. Soc., Chem. Commun.* **1984**, 1079-1080. (c) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322-4343.

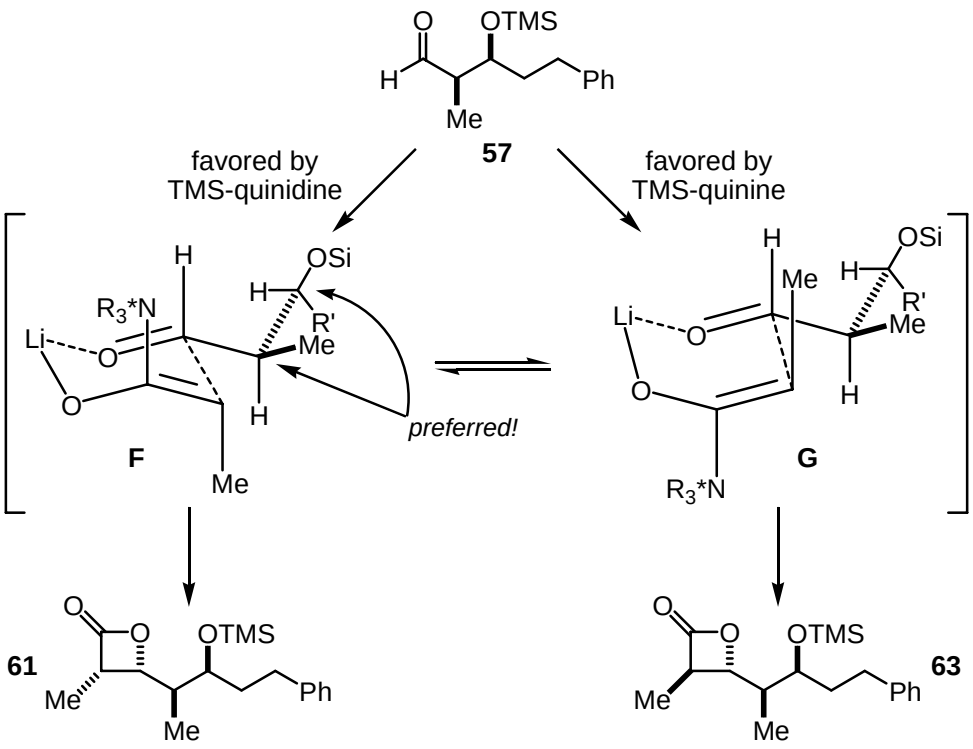


Figure 17: Reetz-Evans model of aldehyde 57

Applying the Reetz-Evans model to *anti*-aldehyde **64b** shows that unlike *syn*-aldehyde **57**, in transition states **H** and **I** the reactive conformer of the *anti*-aldehyde can only have the α-stereocenter in a preferred arrangement (Figure 18). Due to the relative stereochemistry in the starting aldehyde, as well as the strong preference for an *anti*-Felkin approach, the β-stereocenter on the aldehyde is unable to attain the lowest energy conformation. It is speculated that the higher reactivity of the *syn*-aldehyde in the AAC reaction is due to the difference in energies between the possible reactive conformers of the *syn*- and *anti*-aldehydes. Additionally, it is speculated that in the mismatched AAC reaction with *anti*-aldehyde **64b** (transition state **I**) the reaction is more disfavored and sluggish due to the higher energy of the operative transition state of this cyclocondensation (reactive conformer's energy plus the boat transition state).

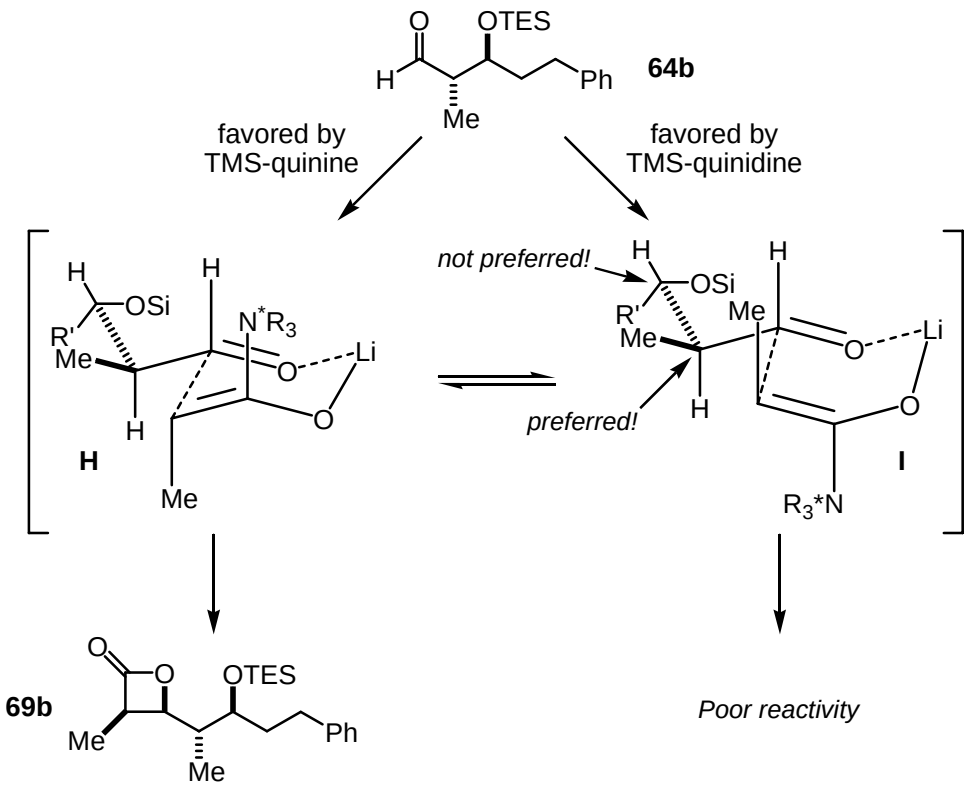


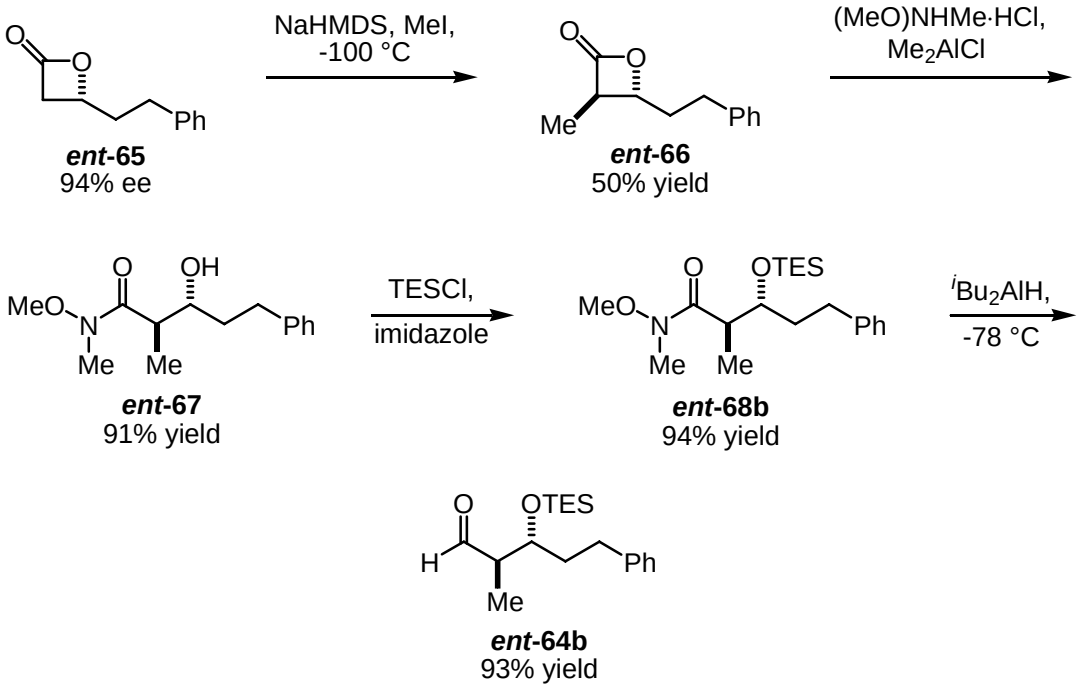
Figure 18: Reetz-Evans model of aldehyde 64b

2.2.3 Synthesis and reactivity of aldehyde ent-64b

To determine the relationship between the enantiomer of the starting aldehyde and the C*inchona* alkaloid employed, the enantiomer of model *anti*-aldehyde **64b** was synthesized and tested in the AAC reaction. The synthetic sequence commenced by α-methylating known β-lactone ***ent*-65** (94% ee) with NaHMDS and MeI to produce *trans*-β-lactone ***ent*-66** in 50% yield (Scheme 24).[48] Subsequent ring-opening of β-lactone ***ent*-66** to β-hydroxy Weinreb amide ***ent*-67** with (MeO)NHMe·HCl and Me_2AlCl proceeded in 91% yield. Silylation of the β-hydroxy group of amide ***ent*-67** using TESCl in the presence of imidazole afforded a 94% yield of silyl ether ***ent*-**

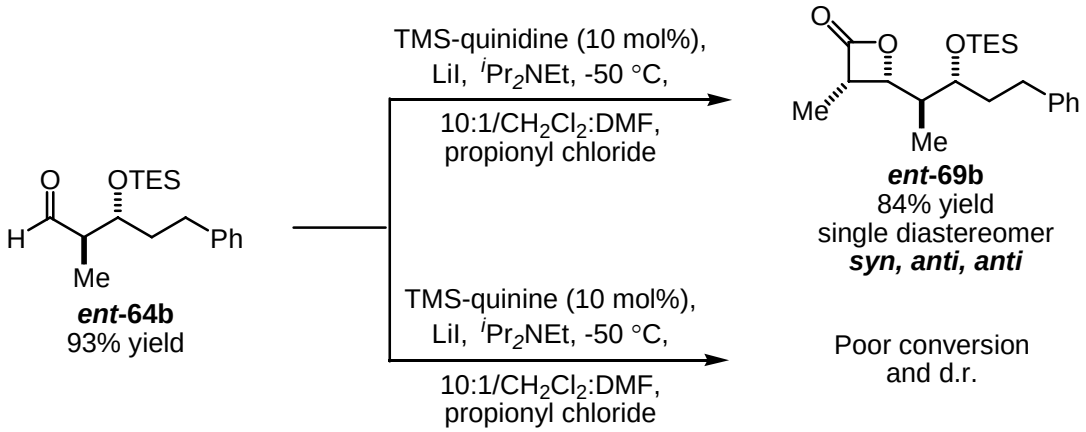
68b. Reduction of the Weinreb amide moiety on silyl ether ***ent*-68b** with $^{i}Bu_2AlH$ afforded the desired model aldehyde, ***ent*-64b,** in 93% yield.

Scheme 24



As presumed, when aldehyde ***ent*-64b** was subjected to the AAC reaction conditions optimized for aldehyde **64b** the matched reaction was now with the pseudoenantiomeric TMS-Q_D (Scheme 25). The β-lactone product from that reaction was the expected *syn*, *anti*, *anti* masked polypropionate unit ***ent*-69b** which was synthesized in 84% yield and as a single diastereomer. Similar to aldehyde **64b**, when aldehyde ***ent*-64b** was subjected to the AAC reaction under the catalytic influence of the other cinchona alkaloid, TMS-Q_N, poor conversion to the β-lactone product was observed.

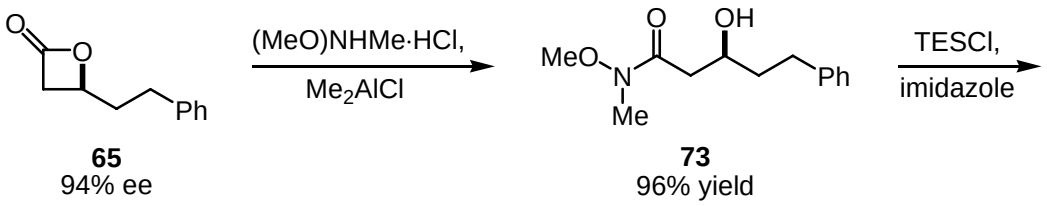
Scheme 25

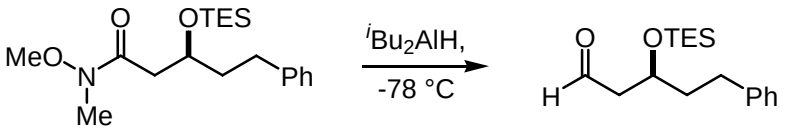


2.2.4 Synthesis and reactivity of aldehyde 72

Another type of aldehyde that was synthesized and tested in the C*inchona* alkaloid-catalyzed AAC reaction was a monosubstituted substrate that possessed a β-silyloxy group and no α-substituent. The product from this AAC reaction would be a "skipped" polypropionate unit. Aldehyde **72** was chosen as the model substrate and the synthesis of **72** began by opening known β-lactone **65** (94% ee) to β-hydroxy Weinreb amide **73** with (MeO)NHMe·HCl and Me_2AlCl in 96% yield (Scheme 26). Silylation of the β-hydroxy group of amide **73** using TESCl and imidazole afforded a 99% yield of silyl ether **74**. Reduction of the Weinreb amide moiety on silyl ether **74** with $^{i}Bu_2AlH$ afforded the desired model aldehyde **72** in 81% yield.

Scheme 26



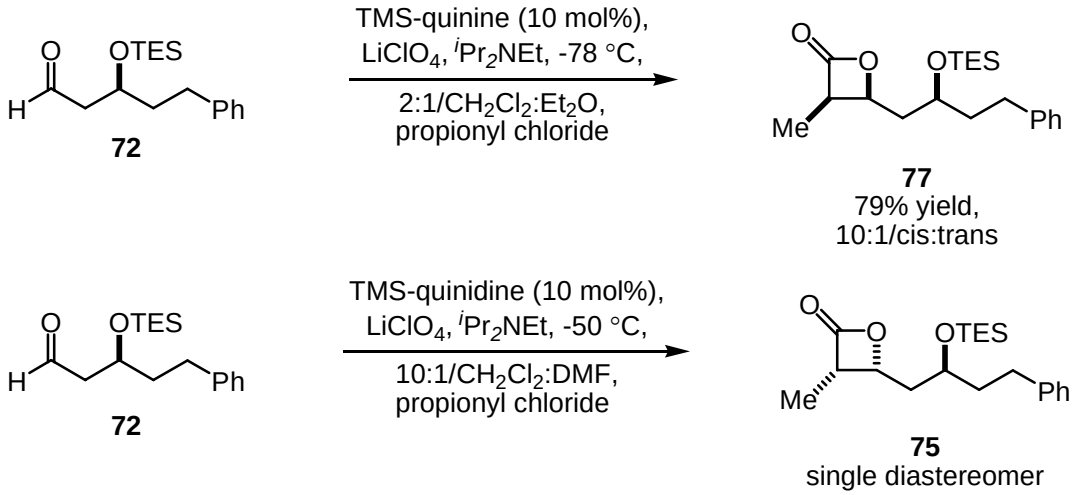


74
99% yield

72
81% yield

Since aldehyde **72** possessed no α-substituent, the observed reactivity was greater than other aldehydes previously tested in the AAC reaction. Therefore, some minor optimization of reaction conditions needed to be carried out. It was found that when β-triethylsilyloxy aldehyde **72** was subjected to the AAC reaction in the presence of a catalytic amount of TMS-Q_D, expected β-lactone product **75** was formed as a single diastereomer (Scheme 27). Due to an inability to isolate the desired product in pure form, crude β-lactone **75** was opened to the corresponding bis-hydroxy Weinreb amide using (MeO)NHMe·HCl and Me_2AlCl to produce amide **76** in 71% yield over the two steps. Alternatively, it was found that the optimal conditions for the AAC reaction of aldehyde **72** catalyzed by TMS-Q_N was in a 2:1/CH_2Cl_2:Et_2O solvent system where β-lactone **77** was formed in 79% yield as a 10:1 inseparable mixture of diastereomers, with the *cis*-diastereomer predominating.

Scheme 27

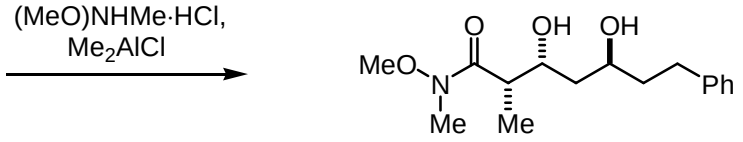


72

77
79% yield,
10:1/cis:trans

72

75
single diastereomer

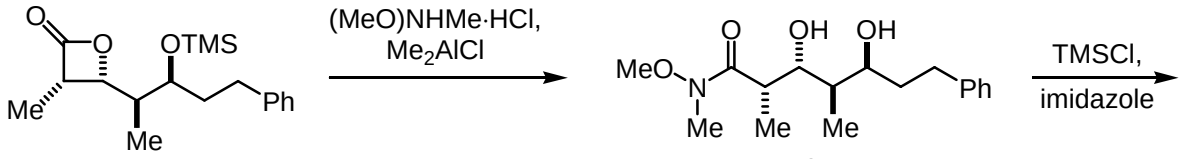


76
71% yield
(over 2 steps)

2.2.5 Iterative polypropionate unit formation

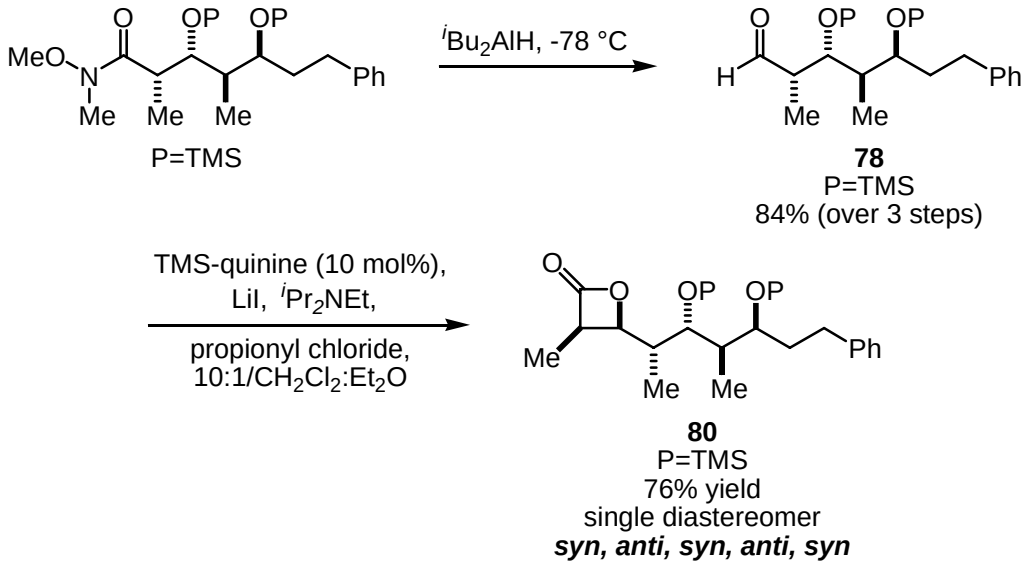
To test the further potential of this transformation, tetrasubstituted aldehyde **78** was synthesized to demonstrate the capability of the C*inchona* alkaloid-catalyzed AAC reaction to form iterative polypropionate units. If successful, the β-lactone product from the AAC reaction would be a masked polypropionate unit with six contiguous stereocenters. The synthesis of tetrasubstituted aldehyde **78** commenced with opening of β-lactone **61** using (MeO)NHMe·HCl and Me_2AlCl, with concomitant cleavage of the TMS ether, to produce bis-hydroxy amide **79** (Scheme 28). Protection of both hydroxy groups with TMSCl, followed by treatment of the crude residue with $^{i}Bu_2AlH$ afforded tetrasubstituted aldehyde **78** in 84% overall yield. Gratifyingly, aldehyde **78** was a competent substrate in the AAC reaction, producing the desired *syn*, *anti*, *syn*, *anti*, *syn* masked polypropionate unit **80** as a single diastereomer in 76% yield.

Scheme 28



61
syn, anti, syn

79



The Nelson group was successful in developing an efficient alternative method for the production of polypropionate units utilizing a modified version of the asymmetric C*inchona* alkaloid-catalyzed AAC reaction. A variety of aldehydes proved amenable to this transformation as flexibility in reaction conditions allowed for optimization of the AAC reaction for a specific aldehyde.[51] In most cases, the transformation was clean and the β-lactone products were easily isolated or could be used crude in subsequent elaborations. The potential of this cyclocondensation for the synthesis of iterative polypropionate units was further demonstrated by synthesizing a masked polypropionate unit possessing six contiguous stereocenters in diastereomerically pure form.

[51] Additional aldehydes not presented here were synthesized and tested by Ms. Junping Zhao.

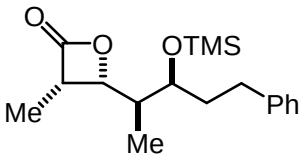
2.3 EXPERIMENTAL

General Information: ^{1}H NMR spectra were recorded on Bruker DPX 301 and DPX 302 (300 MHz) spectrometers. The chemical shifts are reported in ppm from tetramethylsilane with either the solvent resonance as the internal standard ($CHCl_3$: δ 7.27 ppm) or tetramethylsilane as an external standard (TMS: δ ppm). Data is reported as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, app = apparent, br = broad, m = multiplet), coupling constants (Hz), integration. ^{13}C NMR spectra were recorded on Bruker DPX 301 and DPX 302 spectrometers (75 MHz) with complete proton decoupling. The chemical shifts are reported in ppm from tetramethylsilane with either the solvent resonance as the internal standard ($CDCl_3$: δ 77.0 ppm) or tetramethylsilane as an external standard (TMS: δ ppm). Optical rotations were measured on a Perkin-Elmer 241 digital polarimeter with a sodium lamp at ambient temperature and are reported as follows: $[\alpha]_D$ (*c* g/100 mL) with units of degree•g•cm^{-3}. Infrared spectra were taken on a Nicolet Avatar 360 FT-IR spectrometer. Mass spectra were obtained on a VG-7070 or Fisons Autospec high resolution magnetic sector mass spectrometer.

Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60-F plates. Flash chromatography was performed as previously described on EM silica gel 60 (230-240 mesh).[37] Automated flash chromatography was performed using an ISCO CombiFlash® Companion™ using disposable RediSep™ columns. Analytical gas liquid chromatography (GLC) was performed on a Varian 3900 gas chromatograph with a flame ionization detector and split mode capillary injection system using a VarianCP Wax 52CB column (30 m x 0.25 mm). Hydrogen was used as the carrier gas at the indicated pressures. Analytical high performance liquid chromatography (HPLC) was performed on a Hewlett Packard 1100 liquid chromatograph equipped with a variable wavelength UV detector (deuterium lamp, 190-600 nm), using a Daicel

Chiralcel™ OD-H column (250 x 4.6 mm) (Daicel Inc.). HPLC grade isopropanol and hexanes were used as the eluting solvents. Melting points were measured using a Mel-Temp apparatus and are uncorrected.

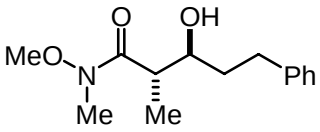
Unless otherwise stated, all experiments were carried out under a nitrogen atmosphere in oven or flame-dried glassware using standard inert atmosphere techniques for introducing reagents and solvents. Anhydrous solvents were obtained by passage through successive alumina- and Q5 reactant-packed columns on a solvent purification system. Amines were purified *via* distillation from CaH_2. Propionyl chloride was purified by distillation prior to use. Unless otherwise stated, commercially available reagents were used as received without any further purification. All water used in reactions and in aqueous solutions was deionized.



(3*S*,4*R*)-4-((2*R*,3*S*)-3-Trimethylsilyloxy-5-phenylpentan-2-yl)-3-methyloxetan-2-one (61):[52] A flame-dried 25 mL round bottom flask was charged with TMS-quinidine (45 mg, 1.14 x 10^{-4} mol) and LiI (0.456 g, 3.41 mmol). To the mixture was added sequentially CH_2Cl_2 (3.3 mL), DMF (0.3 mL) and $^{i}Pr_2NEt$ (0.50 mL, 2.84 mmol). The resulting mixture was stirred at ambient temperature for 5 min then cooled to −50 °C. To the reaction mixture was added aldehyde **57** (0.300 g, 1.14 mmol) followed by dropwise addition of a solution of propionyl chloride (0.20 mL, 2.27 mmol) in CH_2Cl_2 (0.76 mL) over 2 h. The resulting heterogeneous reaction mixture was stirred vigorously overnight at −50 °C, after which the reaction mixture was partitioned between ether (15 mL) and H_2O (15 mL). The layers were separated and the aqueous layer extracted with ether (2x). The combined organic extracts were then washed with water (2x) and then brine (1x). The

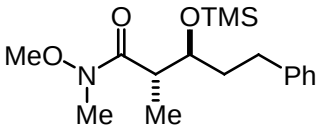
[52] Reaction with DMF that the author of this document performed.

combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified *via* column chromatography (24:1/hexanes:ethyl acetate) to yield 0.300 g (83%) of β-lactone **61**: Diastereomeric ratio determined by crude ^{1}H NMR (300 MHz; δ 4.40 ppm) showed the title compound was produced as a single diastereomer; $[\alpha]_D$ = +23.4 (*c* 2.2, $CHCl_3$); IR (thin film) 2952, 1827, 1250, 1148, 1118, 1044, 1001 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33-7.18 (m, 5H), 4.40 (dd, *J* = 11.0, 6.3 Hz, 1H), 4.01 (td, *J* = 6.6, 0.9 Hz, 1H), 3.77 (app p, *J* = 7.6 Hz, 1H), 2.67 (ddd, *J* = 13.5, 10.8, 6.0 Hz, 1H), 2.54 (ddd, *J* = 13.5, 10.7, 6.0 Hz, 1H), 1.91-1.70 (m, 3H), 1.33 (d, *J* = 7.7 Hz, 3H), 0.85 (d, *J* = 6.6 Hz, 3H), 0.14 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.4, 141.7, 128.3 (2C), 128.1 (2C), 125.7, 75.9, 70.1, 46.3, 37.2, 37.0, 32.5, 8.3, 7.4, 0.3 (3C); EI-MS *m/z* 320 $(M)^+$, 305, 249, 230, 207; HRMS calcd for $C_{18}H_{28}O_3Si$: 320.1808, found 320.1804.



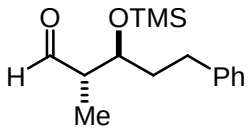
(2*S*,3*S*)-3-Hydroxy-*N*-methoxy-*N*,2-dimethyl-5-phenylpentanamide (67): To a 0 °C mixture of *N*,*O*-dimethylhydroxylamine hydrochloride (6.44 g, 66.0 mmol) in CH_2Cl_2 (122 mL) was added dimethylaluminum chloride (66.0 mL, 66.0 mmol, 1.0 M in hexanes) in a slow, dropwise fashion. The resulting solution was allowed to warm to ambient temperature and stirred for 2 h. Subsequently, the homogenous solution was cooled to 0 °C and diluted with CH_2Cl_2 (72 ml). To the resulting solution was added a solution of β-lactone **66** (6.26 g, 33.0 mmol) in CH_2Cl_2 (50 mL). The reaction mixture was then warmed to ambient temperature and allowed to stir for 3 h. Cooled the reaction mixture to 0 °C and quenched slowly with aqueous phosphate buffer (100 mL, pH = 7). The resulting biphasic mixture was warmed to ambient temperature and stirred vigorously for 1h. The layers of the mixture were then separated and the aqueous extracted with CH_2Cl_2 (3x). The

combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude oil was purified by silica gel chromatography (3:1/hexanes:ethyl acetate) to provide 7.59 g (92%) of amide **67**: $[\alpha]_D$ = +13.4 (*c* 2.5, $CHCl_3$); IR (thin film) 3434, 2937, 1636, 1495, 1454, 1388 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.31-7.16 (m, 5H), 3.71 (s, 3H), 3.71-3.61 (m, 1H), 3.51 (d, *J* = 8.0 Hz, 1H), 3.20 (s, 3H), 2.97-2.87 (m, 2H), 2.70 (dt, *J* = 13.8, 8.3 Hz, 1H), 1.81-1.74 (m, 2H), 1.25 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.7, 141.8, 128.0 (2C), 127.8 (2C), 125.2, 72.5, 61.0, 39.8, 36.7, 31.7, 31.3, 14.4; EI-MS *m/z* 251 (M^+) 191, 173, 145; HRMS calcd for $C_{14}H_{21}NO_3$: 251.1521, found 251.1519.

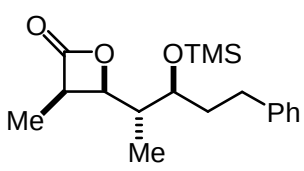


(2*S*,3*S*)-3-Trimethylsilyloxy-*N*-methoxy-*N*,2-dimethyl-5-phenylpentanamide (68a): To a solution of β-hydroxyl amide **67** (2.60 g, 10.4 mmol) in CH_2Cl_2 (116 mL) at ambient temperature was added 2,6-lutidine (1.81 mL, 15.5 mmol). The resulting solution was cooled to −78 °C and TMSOTf (2.25 mL, 12.4 mmol) was added, after which the reaction mixture was stirred at −78 °C for 0.5 h and then warmed to ambient temperature and stirred for an additional 2 h. The reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$ (40 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2x). The combined organic extracts were washed with 1.0 M $NaHSO_4$ (1x) and brine (1x), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude oil was purified by silica gel chromatography (9:1/hexanes:ethyl acetate) to provide 3.4 g (100%) of amide **68a**: $[\alpha]_D$ = +33.0 (*c* 1.0, $CHCl_3$); IR (thin film) 2954, 1660, 1454, 1249, 1097, 1071, 1053 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$): δ 7.32-7.17 (m, 5H), 4.03 (ddd, *J* = 9.7, 8.2, 3.0 Hz, 1H), 3.72 (s, 3H), 3.20 (s, 3H), 3.20-3.13 (m, 1H), 2.76 (td, *J* = 13.3, 5.4 Hz, 1H), 2.62 (td, *J* = 13.4, 5.3 Hz, 1H), 1.91-1.69 (m, 2H), 1.06 (d, *J* = 6.9 Hz, 3H), 0.12 (s, 9H); ^{13}C NMR (75MHz,

$CDCl_3$): δ 176.0, 142.3, 128.2 (4C), 125.6, 73.7, 61.2, 41.2, 35.8, 31.7, 31.1, 13.4, 0.3 (3C); ESI-MS *m/z* 346.3 $(M + Na)^+$, 234.2; HRMS calcd for $C_{17}H_{29}NNaO_3Si$ $(M + Na)^+$: 346.1814 , found 346.1803.

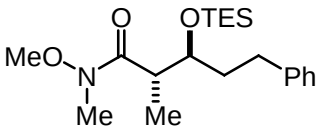


(2*S*,3*S*)-3-Trimethylsilyloxy-2-methyl-5-phenylpentanal (64a): To a –78 °C solution of amide **68a** (1.59 g, 4.90 mmol) in THF (46 mL) was added $^{i}Bu_2AlH$ (6.90 mL, 6.90 mmol, 1.0 M in hexanes) in a slow, dropwise fashion. The resulting solution was maintained at –78 °C for 3 h after which saturated aqueous Rochelle's salts was added (25 mL). The biphasic mixture was allowed to warm to ambient temperature and was stirred vigorously for 1 h. The layers were separated and the aqueous layer was extracted with ether (3x). The combined organic extracts were washed with brine (1x), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude oil was purified by silica gel chromatography (30:1/hexanes:ethyl acetate) to provide 1.00 g (80%) of aldehyde **64a**: $[\alpha]_D$ = +26.6 (*c* 2.7, $CHCl_3$); IR (thin film) 2954, 1726, 1454, 1251, 1069 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.76 (d, *J* = 2.3 Hz, 1H), 7.33-7.18 (m, 5H), 4.00 (dt, *J* = 6.4, 5.2 Hz, 1 H), 2.78-2.63 (m, 2H), 2.56 (qdd, *J* = 7.1, 5.7, 2.4 Hz, 1H), 1.94-1.75 (m, 2H), 1.11 (d, *J* = 7.0 Hz, 3H), 0.16 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.9, 141.5, 128.1 (2C), 128.0 (2C), 125.6, 72.7, 51.1, 36.4, 31.2, 10.0, 0.1 (3C); EI-MS *m/z* 265 $(M)^+$, 249, 207, 190, 174; HRMS calcd for $C_{15}H_{24}O_2Si$: 264.1546, found 264.1554.



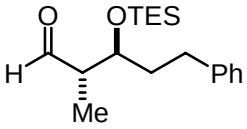
(3*R*,4*S*)-4-((2*S*,3*S*)-3-Trimethylsilyloxy-5-phenylpentan-2-yl)-3-methyloxetan-2-one (69a): A flame-dried 25 mL round bottom flask was charged with TMS-quinine (30 mg, 7.56 x 10^{-5} mol) and LiI (0.304 g,

2.27 mmol). To the mixture of solids was added CH_2Cl_2 (2.1 mL), THF (0.20 mL) and $^iPr_2NEt$ (0.330 mL, 1.90 mmol). The resulting mixture was stirred at ambient temperature for 5 minutes then cooled to −78 °C. To the reaction mixture was added aldehyde **64a** (0.200 g, 0.760 mmol) followed by dropwise addition of a solution of propionyl chloride (0.130 mL, 1.51 mmol) in CH_2Cl_2 (0.5 mL) over 4 h. The heterogeneous reaction mixture was stirred vigorously overnight at −78 °C. The reaction mixture was quenched with ether (4 mL) and the white precipitate was filtered off over a plug of silica which was eluted with ether (80 mL). The filtrate was then concentrated *in vacuo* and the resulting residue purified *via* column chromatography (24:1/hexanes:ethyl acetate) to yield 0.190 g (78%) of β-lactone **69a**: Diastereomeric ratio determined by crude ^{1}H NMR (300 MHz): 82% (δ 4.36 ppm) : 18 % (δ 4.19 ppm) / cis β-lactone **69a** (title compound) : trans β-lactone (not isolated); m.p. = 76-77 °C; $[\alpha]_D$ = –49.1 (*c* 1.3, $CHCl_3$); IR (CH_2Cl_2) 2954, 1826, 1250, 1118, 1087, 1066 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32-7.17 (m, 5H), 4.36 (dd, *J* = 11.3, 6.3 Hz, 1H), 3.97-3.92 (m, 1H), 3.78 (app p, *J* = 7.7 Hz, 1H), 2.80 (ddd, *J* = 13.6, 10.0, 6.6 Hz, 1H), 2.52 (ddd, *J* = 13.5, 9.6, 7.0 Hz, 1H), 2.10 (dqd, *J* = 10.3, 6.8, 3.3 Hz, 1H), 1.80-1.70 (m, 2H), 1.35 (d, *J* = 7.7 Hz, 3H), 0.89 (d, *J* = 6.8 Hz, 3H), 0.16 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.7, 141.9, 128.0 (4C), 125.4, 75.8, 72.0, 47.1, 38.5, 33.5, 32.6, 9.5, 8.2, 0.1 (3C) ; EI-MS *m/z* 320 $(M)^+$, 261, 249, 230, 207, 174; HRMS calcd for $C_{18}H_{28}O_3Si$: 320.1808, found 320.1825.



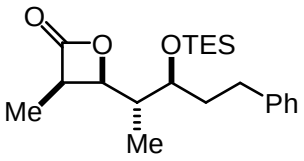
(2*S*,3*S*)-3-Triethylsilyloxy-*N*-methoxy-*N*,2-dimethyl-5-phenylpentanamide (68b): To a solution of β-hydroxyl amide **67** (1.00 g, 4.00 mmol) in CH_2Cl_2 (44 mL) was added imidazole (0.463 g, 6.80 mmol). The homogenous solution was cooled to 0 °C and TESCl (1.00 mL, 6.00 mmol) was added in a dropwise fashion.

After complete addition, the resulting heterogeneous mixture was warmed to ambient temperature and stirred overnight. The reaction mixture was then quenched by addition of saturated aqueous $NaHCO_3$ (20 mL), the layers separated and the organic layer washed with 1.0 M aqueous $NaHSO_4$ (1x). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude oil was purified by silica gel chromatography (9:1/hexanes:ethyl acetate) to provide 1.29 g (88%) of amide **68b**: $[\alpha]_D$ = +32.6 (*c* 2.3, $CHCl_3$); IR (thin film) 2953, 2911, 2876, 1663, 1456, 1416, 1093, 1002 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.32-7.16 (m, 5H), 4.09 (dt, *J* = 8.6, 4.5 Hz, 1H), 3.73 (s, 3H), 3.20 (s, 3H), 3.20-3.15 (m, 1H), 2.71 (dd, *J* = 10.0, 6.7 Hz, 2H), 1.87-1.80 (m, 2H), 1.07 (d, *J* = 7.0 Hz, 3H), 0.98 (t, *J* = 7.9 Hz, 9H), 0.63 (q, *J* = 7.8 Hz, 6H) ; ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.5, 142.1, 127.9 (4C), 125.3, 72.6, 60.8, 40.1, 35.3, 31.4, 29.8, 12.8, 6.5, 4.6; EI-MS *m/z* 365 $(M)^+$, 336, 305, 249, 145; HRMS calcd for $C_{20}H_{35}NO_3Si$: 365.2386, found 365.2394.



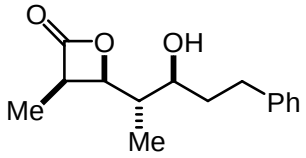
(2*S*,3*S*)-3-Triethylsilyloxy-2-methyl-5-phenylpentanal (64b): To a –78 °C solution of amide **68b** (2.91 g, 8.00 mmol) in THF (75 mL) was added $^iBu_2AlH$ (11.2 mL, 11.2 mmol, 1.0 M in hexanes) in a slow, dropwise fashion. The resulting solution was maintained at –78 °C for 3 h after which saturated aqueous Rochelle's salts was added (50 mL). The biphasic mixture was allowed to warm to ambient temperature and was stirred vigorously for 1 h. The layers were separated and the aqueous layer was extracted with ether (3x). The combined organics were washed with brine (1x), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude oil was purified by silica gel chromatography (30:1/hexanes:ethyl acetate) to provide 2.31 g (95%) of aldehyde **64a**: $[\alpha]_D$ = +29.6 (*c* 2.8, $CHCl_3$); IR (thin film) 2954, 2876, 1725, 1455, 1093, 1007 cm^{-1}; ^1H NMR (300

MHz, $CDCl_3$): δ 9.77 (d, *J* = 2.2 Hz, 1H), 7.32-7.17 (m, 5H), 4.04 (app q, *J* = 5.3 Hz, 1H), 2.69 (app t, *J* = 8.4 Hz, 2H), 2.59 (qdd, *J* = 7.2, 5.3, 2.2 Hz, 1H), 1.95-1.74 (m, 2H), 1.12 (d, *J* = 7.0 Hz, 3H), 0.98 (t, *J* = 7.9 Hz, 9H), 0.63 (q, *J* = 7.7 Hz, 6H) ; ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.2, 141.7, 128.3 (2C), 128.1 (2C), 125.7, 72.8, 51.2, 36.6, 31.1, 10.0, 6.7 (3C), 5.0 (3C) ; EI-MS *m/z* 277 $(M–Et)^+$, 249, 173, 143; HRMS calcd for $C_{16}H_{25}O_2Si$ $(M–Et)^+$: 277.1624, found 277.1632.



(3*R*,4*S*)-4-((2*S*,3*S*)-3-Triethylsilyloxy-5-phenylpentan-2-yl)-3-methyloxetan-2-one (69b): A flame-dried 25 mL round bottom flask was charged with TMS-quinine (52 mg, 0.13 mmol) and LiI (0.522 g, 3.90 mmol). To the mixture of solids was sequentially added CH_2Cl_2 (3.6 mL), DMF (0.35 mL) and $^{i}Pr_2NEt$ (0.570 mL, 3.25 mmol). The resulting mixture was stirred at ambient temperature for 5 minutes then cooled to −50 °C. To the reaction mixture was added aldehyde **64b** (0.400 g, 1.30 mmol) followed by dropwise addition of a solution of propionyl chloride (0.230 mL, 2.60 mmol) in CH_2Cl_2 (0.86 mL) over 4 h. The heterogeneous reaction mixture was stirred vigorously overnight at −50 °C. The resulting mixture was partitioned between ether (15 mL) and H_2O (15 mL). The layers were separated and the aqueous layer extracted with ether (2x). The combined organic extracts were then washed with water (2x) followed by brine (1x). The combined organic extracts were then dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified *via* column chromatography (24:1/hexanes:ethyl acetate) to yield 0.381 g (81%) of β-lactone **69b**: Diastereomeric ratio determined by crude ^1H NMR (300 MHz; δ 4.35 ppm) and HPLC analysis (column OD-H, eluent 1.5:98.5/^{i}PrOH:hexanes, flow rate 1mL/min; T_r

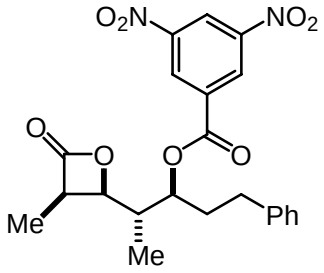
7.014 min) showed that the title compound was produced as a single diastereomer;[53] $[\alpha]_D$ = –44.1 (*c* 1.6, $CHCl_3$); IR (thin film) 3435, 2953, 2876, 1826, 1455, 1117, 1087 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.35-7.17 (m, 5H), 4.35 (dd, *J* = 11.3, 6.3 Hz, 1H), 3.98 (dt, *J* = 8.3, 3.6 Hz, 1H), 3.78 (qd, *J* = 7.7, 6.4 Hz, 1H), 2.83 (ddd, *J* = 13.4, 10.4, 6.3 Hz 1H), 2.54 (ddd, *J* = 13.3, 10.5, 6.2 Hz, 1H), 2.13 (dqd, *J* = 10.2, 6.8, 3.3 Hz, 1H), 1.78-1.68 (m, 2H), 1.35 (d, *J* = 7.7 Hz, 3H), 1.0 (t, *J* = 7.7 Hz, 9H), 0.90 (d, *J* = 6.9 Hz, 3H), 0.65 (q, *J* = 7.5 Hz, 6H); ^{13}C NMR (75MHz, $CDCl_3$): δ 172.1, 142.3, 128.2 (4C), 125.7, 76.1, 71.9, 47.4, 38.9, 33.8, 32.9, 9.5, 8.4, 6.8 (3C), 5.0 (3C); EI-MS *m/z* 363 $(M)^+$, 333, 289, 277, 249, 173; HRMS calcd for $C_{21}H_{34}NaO_3Si$ $(M+Na)^+$: 385.2175, found ESI-MS 385.2194.



(3*R*,4*S*)-4-((2*S*,3*S*)-3-Hydroxy-5-phenylpentan-2-yl)-3-methyloxeta-n-2-one (71): To a 0 °C solution of silyl ether **69a** (0.340 g, 1.06 mmol) in THF (4.6 mL) was added HF/pyridine (0.23 mL). The resulting solution was maintained at 0 °C for 5 min then warmed to ambient temperature and allowed to stir for 2 h. The reaction mixture was cooled to 0 °C and quenched by slow addition of saturated aqueous $NaHCO_3$ (5 mL). The layers were partitioned with CH_2Cl_2 (5 mL), separated and the aqueous layer extracted with CH_2Cl_2 (3x). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude oil was purified by silica gel chromatography (9:1/hexanes:ethyl acetate → 2:1/hexanes:ethyl acetate) to provide 0.236 g (70%) of β-lactone **71**: m.p. = 62-63 °C; $[\alpha]_D$ = –31.1 (*c* 1.7, $CHCl_3$); IR (CH_2Cl_2) 3448 (br), 2973, 2942, 1813, 1454, 1152 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.33-7.18 (m, 5H), 4.42 (dd, *J* = 11.1, 6.4 Hz, 1H), 3.89-3.77 (m, 2H), 2.88 (ddd, *J* = 14.1, 9.4, 5.9 Hz, 1H), 2.70 (ddd, *J* =

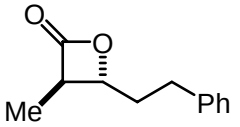
[53] In trials where one of the trans β-lactone diastereomers could be seen, the distinctive ^1H NMR shift and HPLC retention time of that trans-diastereomer is δ 4.22 ppm and T_r = 8.955 min, respectively.

13.7, 9.1, 7.0 Hz, 1H), 2.09 (dqd, *J* = 12.1, 6.8, 5.2 Hz, 1H), 1.91-1.73 (m, 3H), 1.37 (d, *J* = 7.8 Hz, 3H), 0.88 (d, *J* = 6.8 Hz, 3H) ; ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.1, 141.7, 128.0 (2C), 127.9 (2C), 125.4, 76.7, 72.0, 47.4, 38.3, 34.2, 32.0, 10.6, 8.0 ; EI-MS *m/z* 248 $(M)^+$, 230, 157, 134, 117 ; HRMS calcd for $C_{15}H_{18}O_2$ $(M–H_2O)^+$: 230.1307, found 230.1309.

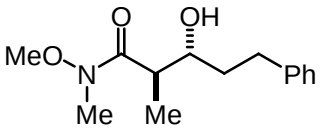


(3*S*,4*S*)-4-((2*S*,3*R*)-3-Methyl-4-oxooxetan-2-yl)-1-phenylpentan-3-yl 3,5-dinitrobenzoate (70): To a solution of alcohol **71** (41 mg, 0.17 mmol) in CH_2Cl_2 (1.0 mL) was added 3,5-dinitrobenzoyl chloride (50 mg, 0.22 mmol). To the reaction mixture was then added DMAP (1.0 mg, 8.3 x 10^{-6} mol) followed by triethylamine (35 μL, 0.25 mmol). The resulting solution was stirred at ambient temperature for 8 h, after which the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (3 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic extracts were washed with brine (1x), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude oil was purified by silica gel chromatography (2:1/hexanes:ethyl acetate) to provide 64 mg (87%) of β-lactone **70**. The afforded solid was recrystallized *via* vapor diffusion recrystallization (CH_2Cl_2/hexanes): m.p. = 167-168 °C; $[\alpha]_D$ = –35.6 (*c* 1.0, $CHCl_3$); IR (CH_2Cl_2) 3054, 2986, 1827, 1731, 1548, 1345, 1265 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.21 (app t, *J* = 1.9 Hz, 1H); 9.00 (d, *J* = 1.9 Hz, 2H), 7.22-7.02 (m, 5H), 5.47 (ddd, *J* = 8.9, 5.2, 3.0 Hz, 1H), 4.45 (dd, *J* = 11.0, 6.2 Hz, 1H), 3.84 (qd, *J* = 7.4, 6.7 Hz, 1H), 2.74 (m, 2H), 2.49-2.37 (m, 1H), 2.30-2.06 (m, 2H), 1.37 (d, *J* = 7.8 Hz, 3H), 1.00 (d, *J* = 6.8 Hz, 3H) ; ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.2, 162.1, 148.5 (2C), 140.7, 133.8, 129.3 (2C), 128.5 (2C), 128.2 (2C), 126.0, 122.3, 78.0, 75.9, 48.2, 36.8, 32.3, 31.7, 11.4,

8.5 ; ESI-MS *m/z* 465.22 $(M + Na)^+$, 357, 229; HRMS calcd for $C_{22}H_{22}N_2NaO_8$ $(M + Na)^+$: 465.1274, found 465.1274.

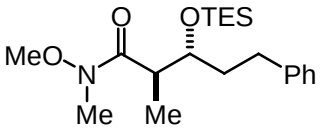


(3*R*,4*R*)-3-methyl-4-phenethyloxetan-2-one (*ent*-66): To a −100 °C solution of β-lactone ***ent*-65** (2.50 g, 14.2 mmol) in THF (710 mL) was added MeI (4.42 mL, 71.0 mmol). Subsequently, NaHMDS (14.2 mL, 14.2 mmol, 1.0 M in THF) was added to the reaction mixture in a dropwise fashion over 2 h. After complete addition, the resulting solution was maintained for an additional hour at −100 °C. The reaction mixture was quenched by addition of saturated aqueous NH_4Cl (50 mL) and allowed to warm to ambient temperature. The layers were separated and the aqueous layer extracted with ethyl acetate (2x). The combined organic extracts were washed with brine (1x), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude oil was purified using an ISCO CombiFlash® Companion™ (hexanes→ 5% ethyl acetate, 330 g column) to yield 1.35 g (50%) of disubstituted β-lactone ***ent*-66**: $[\alpha]_D$ = +72.7 (*c* 1.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34-7.18 (m, 5H), 4.17 (ddd, *J* = 7.4, 5.9, 4.0 Hz, 1H), 3.20 (qd, *J* = 7.5, 3.9 Hz, 1H), 2.83 (ddd, *J* = 14.0, 8.7, 5.8 Hz, 1H), 2.76-2.66 (m, 1H), 2.26-2.02 (m, 2H), 1.32 (d, *J* = 7.5 Hz, 3H).



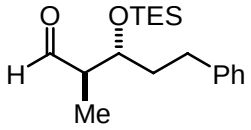
(2*R*,3*R*)-3-Hydroxy-*N*-methoxy-*N*,2-dimethyl-5-phenylpentanamide (*ent*-67): To a 0 °C mixture of *N*,*O*-dimethylhydroxylamine hydrochloride (1.38 g, 14.2 mmol) in CH_2Cl_2 (25 mL) was added dimethylaluminum chloride (14.2 mL, 14.2 mmol, 1.0 M in hexanes) in a slow, dropwise fashion. The resulting solution was allowed to warm to ambient temperature and stirred for 2 h. Subsequently, cooled the homogenous solution to 0 °C and added a solution of β-lactone ***ent*-66** (1.35 g, 7.08 mmol) in

CH_2Cl_2 (25 mL) *via* syringe. The reaction mixture was then warmed to ambient temperature and allowed to stir for 3 h. Cooled the reaction mixture to 0 °C and quenched slowly with aqueous phosphate buffer (25 mL, pH = 7). The resulting biphasic mixture was warmed to ambient temperature and stirred vigorously for 1 h. The layers of the mixture were separated and the aqueous extracted with CH_2Cl_2 (3x). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude oil was purified by silica gel chromatography (3:1/hexanes:ethyl acetate) to provide 1.62 g (91%) of amide ***ent*-67**: $[\alpha]_D$ = –14.2 (*c* 1.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32-7.17 (m, 5H), 3.71 (s, 3H), 3.71-3.61 (m, 1H), 3.21 (s, 3H), 2.97-2.87 (m, 2H), 2.71 (dt, *J* = 13.8, 8.3 Hz, 1H), 1.82-1.75 (m, 2H), 1.25 (d, *J* = 7.1 Hz, 3H).

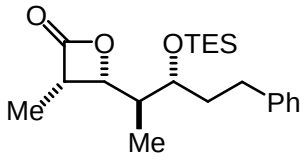


(2*R*,3*R*)-3-Triethylsilyloxy-*N*-methoxy-*N*,2-dimethyl-5-phenylpentanamide (*ent*-68b): To a solution of β-hydroxyl amide ***ent*-67** (1.78 g, 7.08 mmol) in CH_2Cl_2 (78 mL) was added imidazole (0.819 g, 12.0 mmol). The homogenous solution was cooled to 0 °C and TESCl (1.78 mL, 10.6 mmol) was added in a dropwise fashion. After complete addition, the resulting heterogeneous mixture was warmed to ambient temperature and stirred overnight. The reaction mixture was then quenched by addition of saturated aqueous $NaHCO_3$ (35 mL), the layers separated and the organics washed with 1.0 M aqueous $NaHSO_4$ (1x). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude oil was purified by silica gel chromatography (9:1/hexanes:ethyl acetate) to provide 2.44 g (94%) of amide ***ent*-68b**: $[\alpha]_D$ = –32.5 (*c* 2.0, $CHCl_3$); ^{1}H NMR (300MHz, $CDCl_3$): δ 7.31-7.16 (m, 5H), 4.08 (dt, *J* = 8.6, 4.5 Hz, 1H), 3.72 (s,

3H), 3.19 (s, 3H), 3.19-3.15 (m, 1H), 2.71 (dd, *J* = 9.9, 6.8 Hz, 2H), 1.87-1.79 (m, 2H), 1.06 (d, *J* = 7.0 Hz, 3H), 0.97 (t, *J* = 8.0 Hz, 9H), 0.62 (q, *J* = 7.9 Hz, 6H).

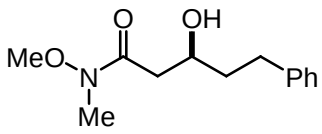


(2*R*,3*R*)-3-Triethylsilyloxy-2-methyl-5-phenylpentanal (*ent*-64b): To a –78 °C solution of amide ***ent*-68b** (2.44 g, 6.68 mmol) in THF (63 mL) was added $^{i}Bu_2AlH$ (9.40 mL, 9.35 mmol, 1.0 M in hexanes) in a slow, dropwise fashion. The resulting solution was maintained at –78 °C for 3 h after which saturated aqueous Rochelle's salts was added (30 mL). The biphasic mixture was allowed to warm to ambient temperature and was stirred vigorously for 1 h. The layers were separated and the aqueous layer extracted with ether (3x). The combined organic extracts were washed with brine (1x), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude oil was purified by silica gel chromatography (30:1/hexanes:ethyl acetate) to provide 1.90 g (93%) of aldehyde ***ent*-64b**: $[\alpha]_D$ = –32.1 (*c* 2.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): 9.76 (d, *J* = 2.2 Hz, 1H), 7.32-7.16 (m, 5H), 4.04 (app q, *J* = 5.4 Hz, 1H), 2.68 (app t, *J* = 8.4 Hz, 2H), 2.58 (qdd, *J* = 7.1, 5.3, 2.2 Hz, 1H), 1.93-1.73 (m, 2H), 1.11 (d, *J* = 7.0 Hz, 3H), 0.97 (t, *J* = 8.0 Hz, 9H), 0.63 (q, *J* = 7.7 Hz, 6H).



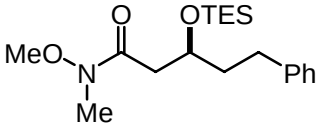
(3*S*,4*R*)-4-((2*R*,3*R*)-3-Triethylsilyloxy-5-phenylpentan-2-yl)-3-methyloxetan-2-one (*ent*-69b): A flame-dried 25 mL round bottom flask was charged with TMS-quinidine (30 mg, 7.56 x 10^{-5} mol) and LiI (0.303 g, 2.27 mmol). To the mixture was sequentially added CH_2Cl_2 (2.1 mL), DMF (0.20 mL) and $^{i}Pr_2NEt$ (0.330 mL, 1.89 mmol). The resulting mixture was stirred at ambient temperature for 5 min then cooled to –50 °C. To the reaction mixture was added aldehyde ***ent*-64b** (0.232 g, 0.760 mmol) followed by dropwise addition of a solution of propionyl chloride (0.131 mL, 1.51

mmol) in CH_2Cl_2 (0.50 mL) over 4 h after which the heterogeneous reaction mixture was stirred vigorously overnight at −50 °C. The reaction mixture was partitioned between ether (15 mL) and H_2O (15 mL), the layers separated and the aqueous layer extracted with ether (2x). The combined organic extracts were washed with water (2x) followed by brine (1x) and then were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified *via* column chromatography (24:1/hexanes:ethyl acetate) to yield 0.234 g (84%) of β-lactone ***ent*-69b**: Diastereomeric ratio determined by crude ^{1}H NMR (300 MHz; δ 4.35 ppm) showed the title compound was produced as a single diastereomer; $[\alpha]_D$ = +40.0 (*c* 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32-7.16 (m, 5H), 4.35 (dd, *J* = 11.3, 6.3 Hz, 1H), 3.98 (dt, *J* = 8.3, 3.5 Hz, 1H), 3.78 (qd, *J* = 7.7, 6.2, 1H), 2.83 (ddd, *J* = 13.4, 10.5, 6.2 Hz, 1H), 2.54 (ddd, *J* = 13.5, 10.6, 6.2 Hz, 1H), 2.14 (dqd, *J* = 10.2, 6.8, 3.4 Hz, 1H), 1.80-1.68 (m, 2H), 1.35 (d, *J* = 7.7 Hz, 3H), 1.0 (t, *J* = 7.7 Hz, 9H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.65 (q, *J* = 7.5 Hz, 6H).



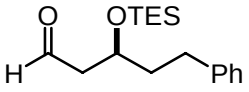
(*S*)-3-Hydroxy-*N*-methoxy-*N*-methyl-5-phenylpentanamide (73): To a 0 °C mixture of *N*,*O*-dimethylhydroxylamine hydrochloride (1.66 g, 17.0 mmol) in CH_2Cl_2 (30 mL) was added dimethylaluminum chloride (17.0 mL, 17.0 mmol, 1.0 M in hexanes) in a slow, dropwise fashion. The resulting solution was allowed to warm to ambient temperature and stirred for 2 h. Subsequently, cooled the homogenous solution to 0 °C and added a solution of β-lactone **65** (1.50 g, 8.51 mmol) in CH_2Cl_2 (30 mL) *via* syringe. The reaction mixture was then warmed to ambient temperature and allowed to stir for 3 h. Cooled the reaction mixture once again to 0 °C and quenched slowly with aqueous phosphate buffer (50 mL, pH = 7). The resulting biphasic mixture was warmed to ambient temperature and stirred vigorously for 1 h. The layers of the mixture were separated and the aqueous layer

extracted with CH_2Cl_2 (3x). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude oil was purified by silica gel chromatography (3:1/hexanes:ethyl acetate) to provide 1.93 g (96%) of amide **73**: $[\alpha]_D$ = +29.0 (*c* 1.8, $CHCl_3$); IR (thin film) 3435, 2937, 1639, 1454, 1389 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.31-7.16 (m, 5H), 4.09-4.00 (m, 1H), 3.89 (d, *J* = 2.8 Hz, 1H), 3.67 (s, 3H), 3.19 (s, 3H), 2.86 (ddd, *J* = 14.0, 9.7, 5.5 Hz, 1H), 2.77-2.64 (m, 2H), 2.48 (dd, *J* = 16.8, 9.4 Hz, 1H), 1.89 (dtd, *J* = 13.9, 9.0, 5.5 Hz, 1H), 1.74 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.4, 141.3, 127.6 (2C), 127.4 (2C), 124.8, 66.2, 60.2, 37.8, 37.7, 31.0, 30.8; EI-MS *m/z* 237 $(M)^+$, 159, 135, 117; HRMS calcd for $C_{13}H_{19}NO_3$: 237.1365, found 237.1361.

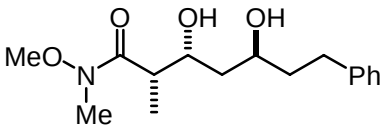


(*S*)-3-Triethylsilyloxy-*N*-methoxy-*N*-methyl-5-phenylpentanamide (74): To a solution of β-hydroxyl amide **73** (1.93 g, 8.13 mmol) in CH_2Cl_2 (90 mL) was added imidazole (0.941 g, 13.8 mmol). The homogenous solution was cooled to 0 °C and TESCl (2.05 mL, 12.2 mmol) added in a dropwise fashion. After complete addition, the resulting heterogeneous mixture was warmed to ambient temperature and stirred overnight. The reaction mixture was then quenched by addition of saturated aqueous $NaHCO_3$ (40 mL), the layers separated and the organics washed with 1.0 M aqueous $NaHSO_4$ (1x). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purified the crude oil by silica gel chromatography (9:1/hexanes:ethyl acetate) to provide 2.83 g (99%) of amide **74**: $[\alpha]_D$ = +17.9 (*c* 1.4, $CHCl_3$); IR (thin film) 2953, 2912, 2875, 1663, 1455, 1415, 1385, 1091 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.31-7.16 (m, 5H), 4.34 (app p, *J* = 6.1 Hz, 1H), 3.69 (s, 3H), 3.19 (s, 3H), 2.81-2.60 (m, 3H), 2.52 (dd, *J* = 15.0, 5.8 Hz, 1H), 1.94-1.74 (m, 2H), 0.97 (t, *J* = 7.7 Hz, 9H), 0.63 (q, *J* = 8.0 Hz, 6H); ^{13}C NMR (75MHz, $CDCl_3$): δ 171.8, 141.9, 127.9

(4C), 125.3, 68.6, 60.8, 39.4, 31.5, 31.2, 6.5 (3C), 4.7 (3C); EI-MS *m/z* 351 $(M)^+$, 321, 291, 248, 218; HRMS calcd for $C_{19}H_{33}NO_3Si$: 351.2230, found 351.2219.



(*S*)-3-Triethylsilyloxy-5-phenylpentanal (72): To a −78 °C solution of amide **74** (2.53 g, 7.19 mmol) in THF (67 mL) was added $^{i}Bu_2AlH$ (10.1 mL, 10.1 mmol, 1.0 M in hexanes) in a slow, dropwise fashion. The resulting solution was maintained at −78 °C for 3 h after which saturated aqueous Rochelle's salts was added (40 mL). The biphasic mixture was allowed to warm to ambient temperature and stirred vigorously for 1 h. The layers were separated and the aqueous layer extracted with ether (3x). The combined organic extracts were washed with brine (1x), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude oil was purified by silica gel chromatography (30:1/hexanes:ethyl acetate) to provide 1.71 g (81%) of aldehyde **72**: $[\alpha]_D$ = +9.1 (*c* 1.5, $CHCl_3$) ; IR (thin film) 2954, 2912, 2876, 1726, 1455, 1239, 1110 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.83 (app t, *J* = 2.2 Hz, 1H), 7.32-7.15 (m, 5H), 4.28 (app p, *J* = 5.8 Hz, 1H); 2.68 (td, *J* = 7.6, 3.5 Hz, 2H); 2.60 (dt, *J* = 5.9, 2.7 Hz, 2H), 1.91-1.84 (m, 2H), 0.97 (t, *J* = 7.9 Hz, 9H), 0.63 (q, *J* = 7.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.6, 141.3, 128.0 (2C), 127.9 (2C), 125.5, 67.2, 50.4, 39.3, 31.1, 6.5 (3C), 4.6 (3C); EI-MS *m/z* 263 $(M–Et)^+$, 159, 143, 129; HRMS calcd for $C_{15}H_{23}O_2Si$ $(M–Et)^+$: 263.1467, found 263.1470.

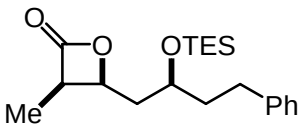


(2*S*,3*R*,5*S*)-3,5-Dihydroxy-*N*-methoxy-*N*,2-dimethyl-7-phenylheptanamide (76): A flame-dried 25 mL round bottom flask was charged with TMS-quinidine (15 mg, 3.75 x 10^{-5} mol) and $LiClO_4$ (0.120 g, 1.13 mmol). To the mixture of solids was sequentially added CH_2Cl_2 (1.1 mL), DMF (0.1 mL) and $^{i}Pr_2NEt$ (0.16

mL, 0.94 mmol). The resulting mixture was stirred at ambient temperature for 5 min then cooled to −50 °C. To the reaction mixture was added aldehyde **72** (0.110 g, 0.380 mmol) followed by dropwise addition of a solution of propionyl chloride (65 μL, 0.75 mmol) in CH_2Cl_2 (0.25 mL) over 2 h. The heterogeneous reaction mixture was stirred vigorously overnight at −50 °C. The resulting mixture was partitioned between ether (10 mL) and H_2O (10 mL), the layers separated and the aqueous layer extracted with ether (2x). The combined organic extracts were then washed with water (2x) followed by brine (1x). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified *via* column chromatography (24:1/hexanes:ethyl acetate) to yield 0.118 g (90%) of β-lactone **75** which contained a slight amount of an inseparable silyl impurity: Diastereomeric ratio determined by crude ^{1}H NMR (300 MHz; δ 4.79 ppm) showed that β-lactone **75** was produced as a single diastereomer.

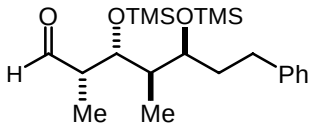
To a 0 °C mixture of *N*,*O*-dimethylhydroxylamine hydrochloride (66 mg, 0.68 mmol) in CH_2Cl_2 (1.3 mL) was added dimethylaluminum chloride (0.68 mL, 0.68 mmol, 1.0 M in hexanes) in a slow, dropwise fashion. The resulting solution was allowed to warm to ambient temperature and stirred for 2 h. Subsequently, cooled the homogenous solution to 0 °C and added a solution of impure β-lactone **75** (0.118 g, 0.340 mmol) in CH_2Cl_2 (3 mL) *via* syringe. The reaction mixture was then warmed to ambient temperature and allowed to stir for 18 h. Cooled the reaction mixture once again to 0 °C and quenched slowly with aqueous phosphate buffer (25 mL, pH = 7). The resulting biphasic mixture was filtered over a plug of celite which was washed with CH_2Cl_2 (35 mL). The layers of the filtrate were then separated and the aqueous layer extracted with CH_2Cl_2 (3x). The combined organic extracts were washed with brine (1x), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude oil was purified by silica gel chromatography (1:1/hexanes:ethyl acetate) to provide 79 mg (79%) of amide **76** (71 % yield

over 2 steps): $[\alpha]_D$ = +2.3 (*c* 1.0, $CHCl_3$); IR (thin film) 3415 (br), 2937, 1635, 1455, 1388 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.32-7.16 (m, 5H), 4.24 (dt, *J* = 10.2, 2.7 Hz, 1H), 4.00-3.93 (m, 2H), 3.69 (s, 3H), 3.20 (s, 3H), 2.89-2.80 (m, 2H), 2.69 (ddd, *J* = 13.7, 9.6, 6.7 Hz, 1H), 2.45 (br s, 1H), 1.95-1.74 (m, 3H), 1.42 (ddd, *J* = 14.1, 7.9, 2.7 Hz, 1H), 1.21 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.8, 142.1, 128.3 (2C), 128.2 (2C), 125.6, 68.7, 68.5, 61.4, 40.3, 39.5, 39.1, 32.2, 31.9, 10.9; ESI-MS *m/z* 318 $(M+Na)^+$; HRMS calcd for $C_{16}H_{25}NNaO_4$ $(M+Na)^+$: 318.1681, found 318.1679.



(3*R*,4*S*)-4-((*S*)-2-Triethylsilyloxy-4-phenylbutyl)-3-methyloxetan-2-one (77): A flame-dried 25 mL round bottom flask was charged with TMS-quinine (14 mg, 3.42 x 10^{-5} mol) and $LiClO_4$ (0.109 g, 1.03 mmol). To the mixture of solids was sequentially added CH_2Cl_2 (0.68 mL), Et_2O (0.34 mL) and $^iPr_2NEt$ (0.15 mL, 0.86 mmol). The resulting mixture was stirred at ambient temperature for 5 min then cooled to −78 °C. To the reaction mixture was added aldehyde **72** (0.100 g, 0.34 mmol) followed by dropwise addition of a solution of propionyl chloride (60 μL, 0.68 mmol) in CH_2Cl_2 (0.24 mL) over 2 h. The heterogeneous reaction mixture was stirred vigorously overnight at −78 °C. The resulting mixture was partitioned between ether (10 mL) and H_2O (10 mL). The layers were separated and the aqueous layer extracted with ether (2x). The combined organic extracts were then washed with water (1x) followed by brine (1x). Dried the organic layer over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified *via* column chromatography (24:1/hexanes:ethyl acetate) to yield 0.094 g (79%) of an inseparable mixture of β-lactone diastereomers. Diastereomeric ratio determined by crude ^1H NMR (300 MHz): 91.5% (δ 4.82 ppm) : 8.5 % (δ 4.41 ppm) / cis β-lactone **77** (title compound) : trans β-lactone. Characterization

data for cis β-lactone **77** (title compound): IR (thin film) 2954, 2912, 2876, 1826, 1111, 1068 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.32-7.18 (m, 5H), 4.82 (ddd, *J* = 10.3, 6.5, 4.1 Hz, 1H), 3.94 (app p, *J* = 5.9 Hz, 1H), 3.79 (qd, *J* = 7.7, 14.4 Hz, 1H), 2.76-2.60 (m, 2H), 2.01 (ddd, *J* = 14.4, 9.0, 4.8 Hz, 1H), 1.93-1.77 (m, 3H), 1.28 (d, *J* = 7.7 Hz, 3H), 0.98 (t, *J* = 8.0 Hz, 9H), 0.62 (q, *J* = 8.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.4, 141.8, 128.3 (2C), 128.2 (2C), 125.8, 72.1, 68.6, 47.5, 38.4, 36.9, 31.6, 8.4, 6.8 (3C), 4.9 (3C); EI-MS *m/z* 319 $(M–Et)^+$, 275, 263, 249, 185, 159; HRMS calcd for $C_{18}H_{27}O_3Si$ $(M–Et)^+$: 319.1729, found 319.1734.

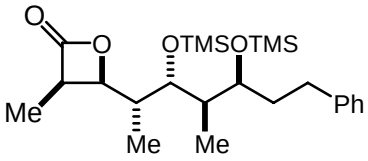


(2*S*, 3*R*, 4*R*, 5*S*)-3,5-Bistrimethylsilyloxy-2,4-dimethyl-7-phenylheptanal (78): To a 0 °C mixture of *N*,*O*-dimethylhydroxylamine hydrochloride (0.770 g, 7.90 mmol) in CH_2Cl_2 (9.7 mL) was added dimethylaluminum chloride (7.90 mL, 7.90 mmol, 1.0 M in hexanes) in a slow, dropwise fashion. The resulting solution was allowed to warm to ambient temperature and stirred for 2 h. Subsequently, cooled the homogenous solution to 0 °C and added a solution of β-lactone **61** (0.842 g, 2.63 mmol) in CH_2Cl_2 (9.7 mL) *via* syringe. The reaction mixture was then warmed to ambient temperature and allowed to stir overnight. Cooled the reaction mixture once again to 0 °C and quenched slowly with aqueous phosphate buffer (25 mL, pH = 7). The layers of the biphasic mixture were separated and the aqueous layer extracted with CH_2Cl_2 (3x). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*.

To a solution of the crude residue in CH_2Cl_2 (26 mL) at ambient temperature was added imidazole (0.590 g, 8.68 mmol). The resulting solution was cooled to −78 °C and TMSCl (1.00 mL, 7.90 mmol) was added. Subsequently warmed the reaction mixture to ambient temperature and stirred overnight. Quenched the reaction mixture by addition of saturated aqueous $NaHCO_3$

(20 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*.

To a −78 °C solution of the crude residue in THF (26 mL) was added $^{i}Bu_2AlH$ (3.70 mL, 3.70 mmol, 1.0 M in hexanes) in a slow, dropwise fashion. The resulting solution was maintained at −78 °C for 3 h after which saturated aqueous Rochelle's salts was added (30 mL). The biphasic mixture was allowed to warm to ambient temperature and was stirred vigorously for 1 h. The layers were separated and the aqueous layer extracted with ether (3x). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude oil was purified by silica gel chromatography (24:1/hexanes:ethyl acetate) to provide 0.870 g (84% over 3 steps) of aldehyde **78**: $[\alpha]_D$ = +43.2 (*c* 1.06, $CHCl_3$) ; IR (thin film) 2954, 1728, 1251, 1108, 1080, 1032 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.72 (s, 1H), 7.32-7.18 (m, 5H), 4.26 (dd, *J* = 8.0, 2.4 Hz, 1H), 3.96 (td, *J* = 6.8, 2.6 Hz, 1H), 2.61-2.47 (m, 3H), 1.91-1.82 (m, 2H), 1.75-1.69 (m, 1H), 1.11 (d, *J* = 7.0 Hz, 3H), 0.85 (d, *J* = 7.0 Hz, 3H), 0.14 (s, 9H), 0.08 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.3, 141.6, 128.2 (2C), 128.0 (2C), 125.6, 72.2, 71.9, 49.7, 41.0, 37.2, 32.1, 9.75, 6.69, 1.07 (3C), 0.55 (3C); ESI-MS *m/z* 417 $(M+Na)^+$; HRMS calcd for $C_{21}H_{38}NaO_3Si_2$ $(M+Na)^+$: 417.2257, found 417.2273.



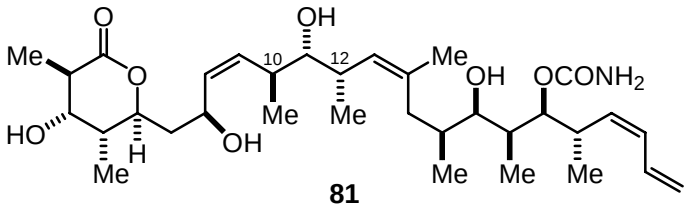
(3*R*, 4*S*)-4-((2*S*, 3*R*, 4*R*, 5*S*)-3,5-Bistrimethylsilyloxy-4-methyl-7-phenylheptan-2-yl)-3-methyloxetan-2-one (80): A flame-dried 25 mL round bottom flask was charged with TMS-quinine (29 mg, 72.0 μmol) and LiI (0.289 g, 2.16 mmol). To the mixture of solids was sequentially added CH_2Cl_2 (2.1 mL), Et_2O (0.20 mL) and $^{i}Pr_2NEt$ (0.310 mL, 1.80 mmol). The resulting mixture was stirred at ambient temperature for 5 min then cooled to −50 °C. To the reaction

mixture was added aldehyde **78** (0.284 g, 0.720 mmol) followed by dropwise addition of a solution of propionyl chloride (0.130 mL, 1.44 mmol) in CH_2Cl_2 (0.48 mL) over 2h. The heterogeneous reaction mixture was stirred vigorously overnight at –50 °C. The resulting mixture was diluted with ether and filtered over a plug of silica gel, eluting with ether. The filtrate was concentrated *in vacuo* and the crude residue purified *via* column chromatography (24:1/hexanes:ethyl acetate) to yield 0.248 g (76%) of β-lactone **80**: Diastereomeric ratio determined by crude ^{1}H NMR (300 MHz; δ 4.37 ppm) showed the title compound was produced as a single diastereomer; $[\alpha]_D$ = –4.0 (*c* 1.0, $CHCl_3$) ; IR (thin film) 2954, 1828, 1250, 1148, 1117, 1080, 1050, 1002 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32-7.18 (m, 5H), 4.37 (dd, *J* = 11.1, 6.3 Hz, 1H), 3.95-3.91 (m, 2H), 3.77 (dq, *J* = 14.1, 7.7 Hz, 1H), 2.59 (dd, *J* = 10.1, 6.4 Hz, 2H), 2.00-1.82 (m, 3H), 1.74-1.65 (m, 1H), 1.34 (d, *J* = 7.8 Hz, 3H), 0.83 (d, *J* = 7.0 Hz, 3H), 0.82 (d, *J* = 6.6 Hz, 3H), 0.14 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.1, 141.8, 128.2 (2C), 128.0 (2C), 125.6, 75.9, 72.3, 71.7, 46.3, 41.2, 37.3, 35.2, 32.0, 9.6, 8.2, 7.9, 1.2 (3C), 0.6 (3C); ESI-MS *m/z* 473 $(M+Na)^+$; HRMS calcd for $C_{24}H_{42}NaO_4Si_2$ $(M+Na)^+$: 473.2519, found 473.2532.

3.0 EFFORTS TOWARDS A CATALYTIC, ASYMMETRIC SYNTHESIS OF AN ANALOGUE OF (+)-DISCODERMOLIDE

3.1 ISOLATION AND BIOACTIVITY

(+)-Discodermolide **(81)** is a naturally occurring marine polyketide metabolite that was isolated from the rare deep sea sponge *Discodermia dissoluta* by Gunasekara and coworkers in 1990 at the Harbor Branch Oceanographic Institution (Figure 19).[54] (+)-Discodermolide's structure, as determined by spectroscopic studies and single crystal X-ray crystallography, contains 13 stereocenters (six of which are hydroxyl-bearing), a tetrasubstituted δ-lactone, one disubstituted and one trisubstituted (*Z*)-olefin, a carbamate moiety and a terminal (*Z*)-diene.[55] In order to minimize 1,3-allylic strain and the *syn*-pentane interactions along the skeleton, discodermolide adopts a U-shaped conformation with the bend occurring at the central stereotriad (C_{10}-C_{12}).



81

Figure 19: (+)-Discodermolide (81)

[54] Paterson, I.; Florence, G. J. *Eur. J. Org. Chem.* **2003**, 2193-2208.
[55] Arefolov, A.; Panek, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 5596-5603.

Discodermolide possesses a very impressive pharmacological profile as an immunosuppressive agent with some additional anti-fungal properties. Recent studies have revealed that discodermolide is a potent antimitotic agent and is recognized as a member of a specialized group of natural products, which includes cytotoxins such as Taxol® and laulimalide, that act as microtubule-stabilizing agents and mitotic spindle poisons. Biological testing has unveiled that discodermolide possesses impressive cytotoxicity in a variety of human cell lines (IC_{50} 3-80 nM) causing cell death by apoptosis.[56] Comparative studies have shown that discodermolide was 1000-fold more active than Taxol® in promoting the same microtubule polymerization and bundling.[57] In addition to discodermolide's inherent cytotoxic capabilities, it has also shown amplified synergistic cytotoxicity when combined with other antimitotic agents.[58]

3.2 PAST SYNTHESES AND RETROSYNTHETIC ANALYSIS

Due to the strong cytotoxic profile possessed by discodermolide, as well as our ability to harvest it from nature in only scarce amounts (isolation yield is 0.002% w/w from frozen sponge; 7 mg of natural product from 434 g of sponge), discodermolide has drawn the attention of many research groups.[59] The problem of limited supply can only be solved by total synthesis of the natural product as no semi-synthetic pathways or fermentation processes currently exist for its production. Consequently, there exists several total syntheses and numerous partial syntheses of

---

[56] (a) ter Haar, E.; Kowalski, R. J.; Hamel, E.; Lin, C. M.; Longley, R. E.; Gunasekera, S. P.; Rosenkranz, H. S.; Day, B. W. *Biochemistry* **1996**, *35*, 243-250. (b) Kowalski, R. J.; Giannakakou, P.; Gunasekera, S. P.; Longley, R. E.; Day, B. W.; Hamel, E. *Mol. Parmacol*. **1997**, *52*, 613-622. (c) Balachandran, R.; ter Haar, E.; Welsh, M. J.; Grant, S. C.; Day, B. W. *Anti-Cancr Drugs* **1998**, 9, 67-76.
[57] Paterson, I.; Lyothier, I. *J. Org. Chem*. **2005**, *70*, 5494-5507.
[58] Harried, S. S.; Lee, C. P; Yang, G.; Lee, T. I. H.; Myles, D. C. *J. Org. Chem.* **2003**, *68*, 6646-6660.
[59] Smith III, A. B.; Kaufman, M. D.; Beauchamp, T. J.; LaMarche, M. J.; Arimoto, H. *Org. Lett.* **1999**, *1*, 1823-1826.

discodermolide. Included within the total syntheses to date is an industrial synthesis completed by Novartis Pharmaceutical Corporation who brought discodermolide into clinical trials.[57]

It is not surprising that all the total syntheses of discodermolide disconnect the polypropionate backbone into three fragments of similar size and stereochemical complexity (Figure 20). Most of the syntheses disassembly the skeleton at or in close proximity of the two (*Z*)-alkenes, highlighting the larger number of present methodologies to form these types of bonds. The polypropionate backbone of discodermolide has been made utilizing an assortment of asymmetric technologies including auxiliary/non-auxiliary controlled aldol reactions and crotylsilane and allenylstannane additions to aldehydes.

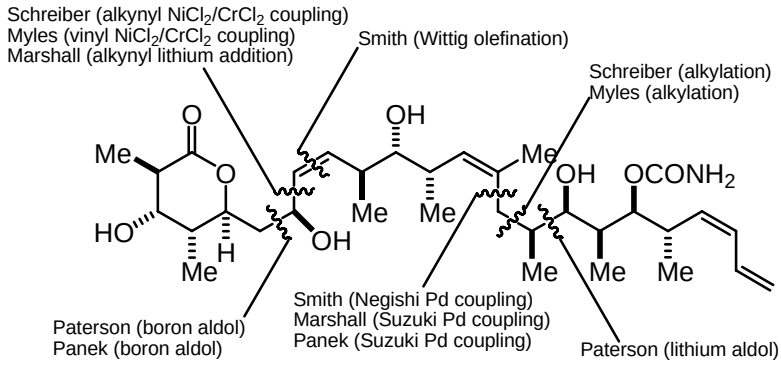


Figure 20: Retrosyntheses of (+)-discodermolide

Interest in discodermolide as a synthetic target was piqued because of the heavily polypropionate-containing skeleton that it possesses. It was felt that discodermolide would provide an ideal platform to demonstrate the utility of the recently developed C*inchona* alkaloid-catalyzed AAC reaction for polypropionate unit formation in complex natural product synthesis. With that goal in mind, and taking into consideration the existence of numerous completed total syntheses of discodermolide, a derivative of the natural product, polysilylated analogue **82**, became the main synthetic target (Figure 21).

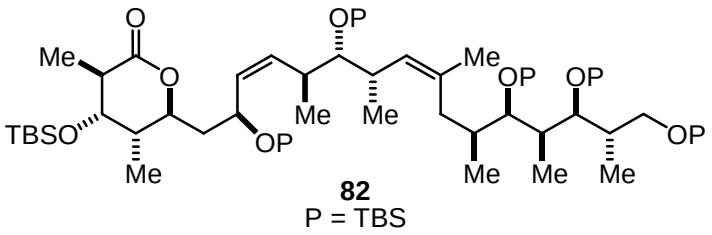


Figure 21: Polysilylated analogue 82

Since the main concern was formation of the polypropionate unit skeleton using AAC technology, the proposed retrosynthetic strategy for analogue **82** is similar to those already proposed for discodermolide. It was decided to disassemble the molecule into three fragments, all of somewhat equal size and complexity, near the two (*Z*)-alkenes (Figure 22). The initial disconnection is the same used by Marshall and coworkers in their synthesis of discodermolide where the C_7-C_8 bond is cleaved. It is felt that this bond can be made, with concomitant setting of the C_7-stereocenter, by addition of an alkyne into aldehyde **83**, the left fragment. The second disconnection is at the trisubstituted olefin and is similar to the Novartis synthesis of discodermolide where the C_{14}-C_{15} bond is made *via* a Suzuki cross-coupling reaction. This disconnection generates the other two fragments, center fragment **84** and right fragment **85**.

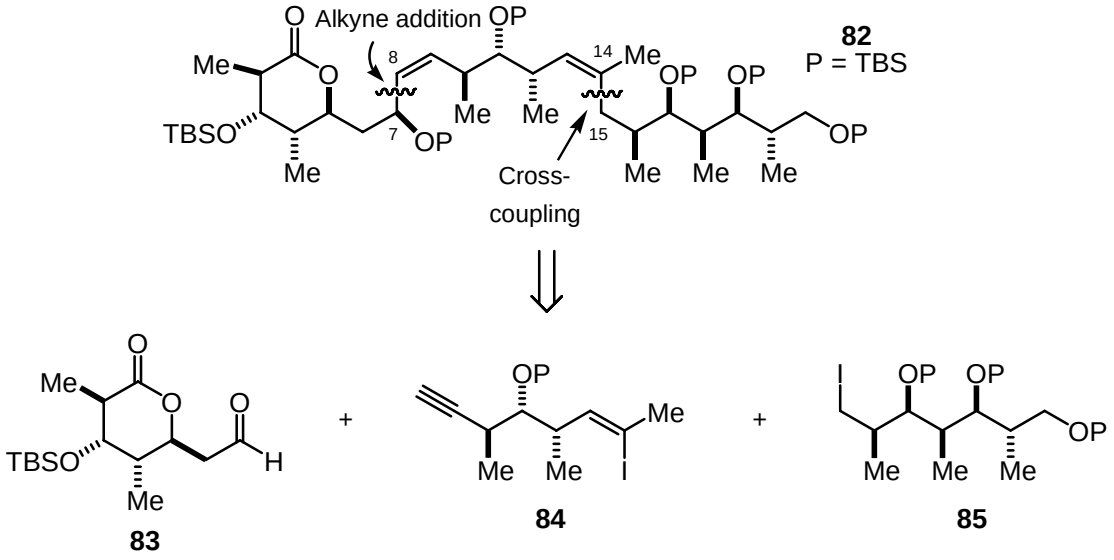


Figure 22: Retrosynthetic analysis of analogue 82

Further disassembly of aldehyde **83** shows that the δ-lactone can be synthesized from masked polypropionate unit **86**, which is a product from the C*inchona* alkaloid-catalyzed AAC reaction (Figure 23). Polypropionate unit **86** is derived from disubstituted *trans*-β-lactone **87** which, using chemistry developed in the Nelson group, can be made from commercially available 3-benzyloxy-1-propanol.

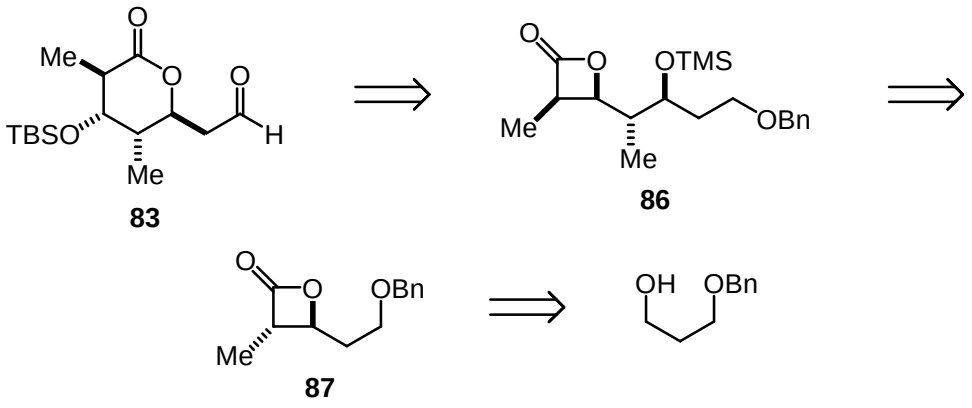


Figure 23: Retrosynthetic analysis of left fragment 83

As other research groups have also realized, the center and right fragments possess the same stereotriad and therefore can be derived from the same common intermediate. Alkyne **84** and iodide **85** can both be formed from a common intermediate, elaborate Weinreb amide **88** (Figure 24). Amide **88** can be made from β-lactone **89**, which is a product derived using AAC technology. Masked polypropionate unit **89** can be synthesized from the commercially available (*S*)-Roche ester in four steps.

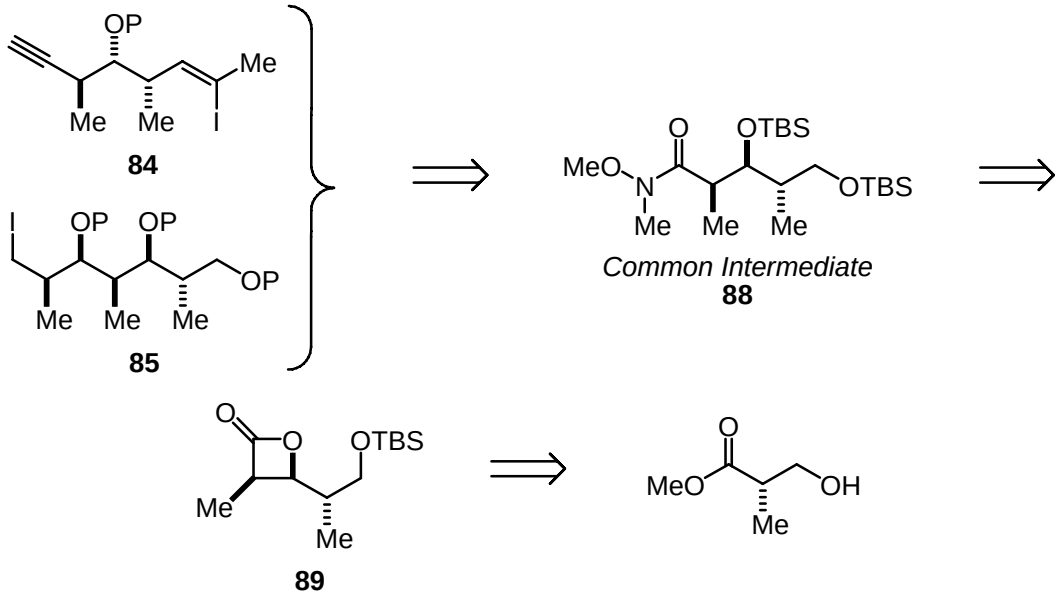


Figure 24: Retrosynthetic analysis of fragments 84 and 85

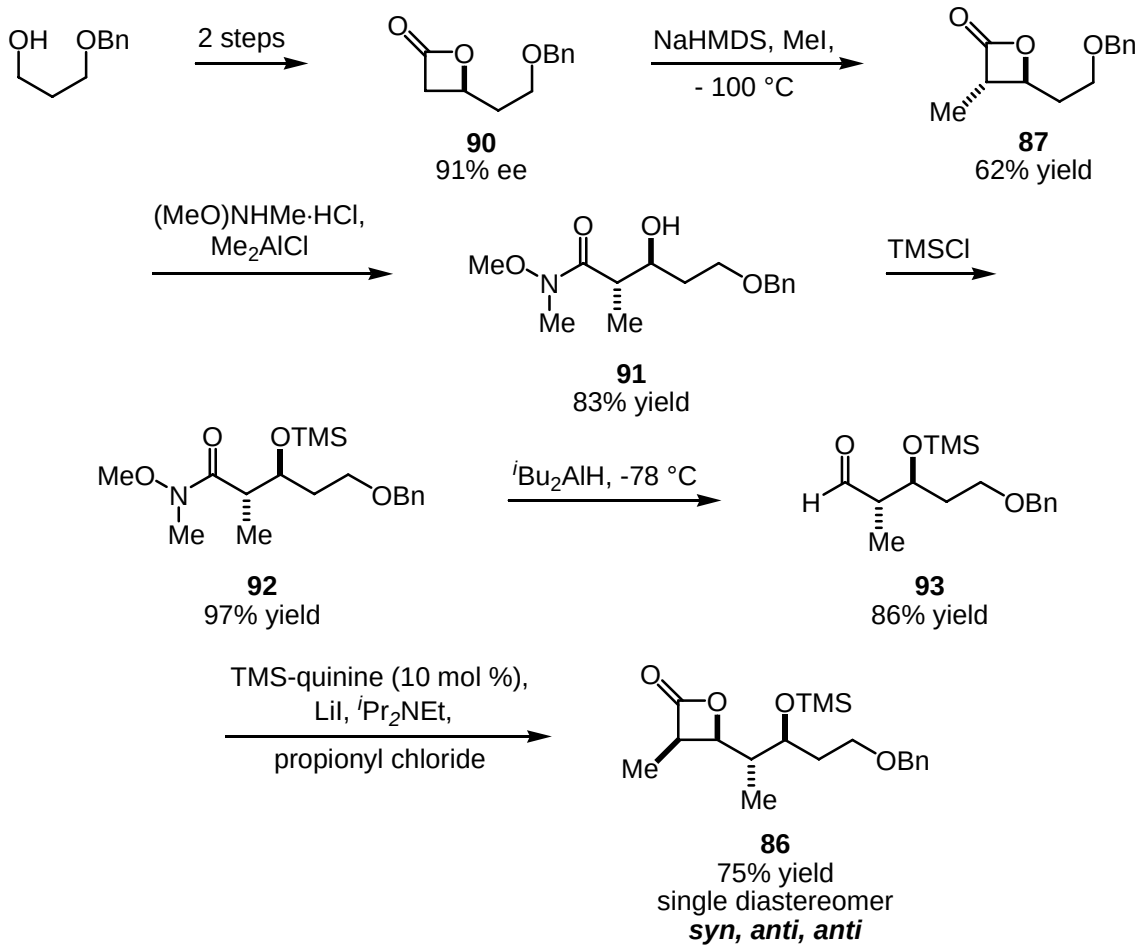
3.3 RESULTS AND DISCUSSION

3.3.1 Synthesis of aldehyde 83

Synthetic efforts towards the catalytic, asymmetric synthesis of analogue **82** began with formation of the initial desired left fragment, aldehyde **83**. The sequence began with known β-

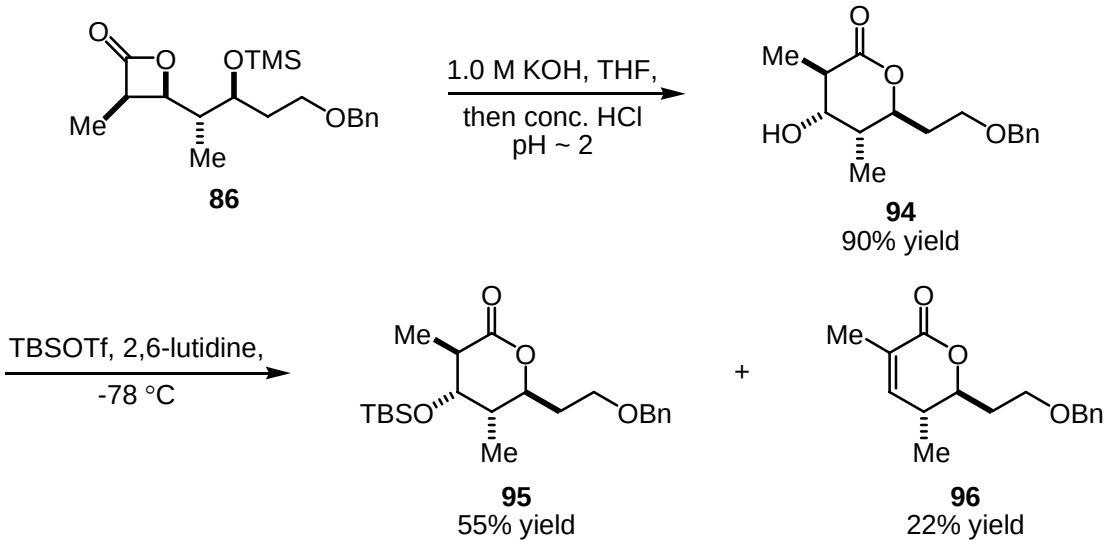
lactone **90** (91% ee) which is made from commercially available 3-benzyloxy-1-propanol in two steps (Scheme 29). Alkylation of β-lactone **90** with NaHMDS and MeI at −100 ºC afforded α-methylated β-lactone **87** in 62% yield. Opening of β-lactone **87** with (MeO)NHMe·HCl and Me_2AlCl produced β-hydroxy Weinreb amide **91** in 83% yield. Silylation of amide **91** with TMSCl afforded a 97% yield of silyl ether **92**, which was subsequently treated with $^{i}Bu_2AlH$ to produce aldehyde **93** in 86% yield. Subjection of aldehyde **93** to the AAC reaction catalyzed by TMS-Q_N yielded masked polypropionate **86** in 75% yield as a single diastereomer. It is worth noting that for this AAC reaction a 6 hour addition time for the solution of propionyl chloride in CH_2Cl_2 was found to be optimal.

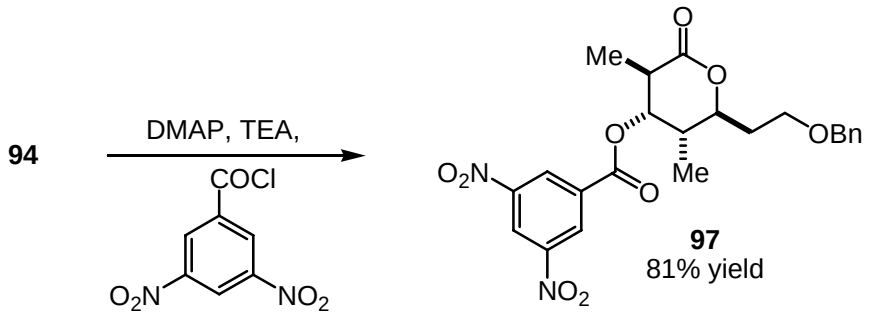
Scheme 29



Hydrolysis of β-lactone **86** with a biphasic mixture of aqueous KOH and THF, followed by acidification of the reaction mixture to a pH ~ 2 with concentrated HCl, afforded δ-lactone **94** in 90% yield (Scheme 30). Protection of the β-hydroxy group on δ-lactone **94** as a TBS-ether proved difficult, as a mixture of desired silyl ether **95** (55% yield) and undesired enoate **96** (22% yield) was obtained. It is speculated that this undesired elimination reaction was the effect of the very Lewis acidic TBSOTf in the presence of base, as well as trans-annular strain caused by the bulky β-silyloxy group in the δ-lactone. The latter hypothesis was validated by acylating the β-hydroxy group in δ-lactone **94** as a 3,5-dinitrobenzoyl group (81% yield) and obtaining a X-ray crystal structure of tetrasubstituted δ-lactone **97** (Appendix A). From the crystal structure it can be seen that the protected β-hydroxy group on the lactone is in the axial position, thereby facilitating the undesired elimination reaction.

Scheme 30

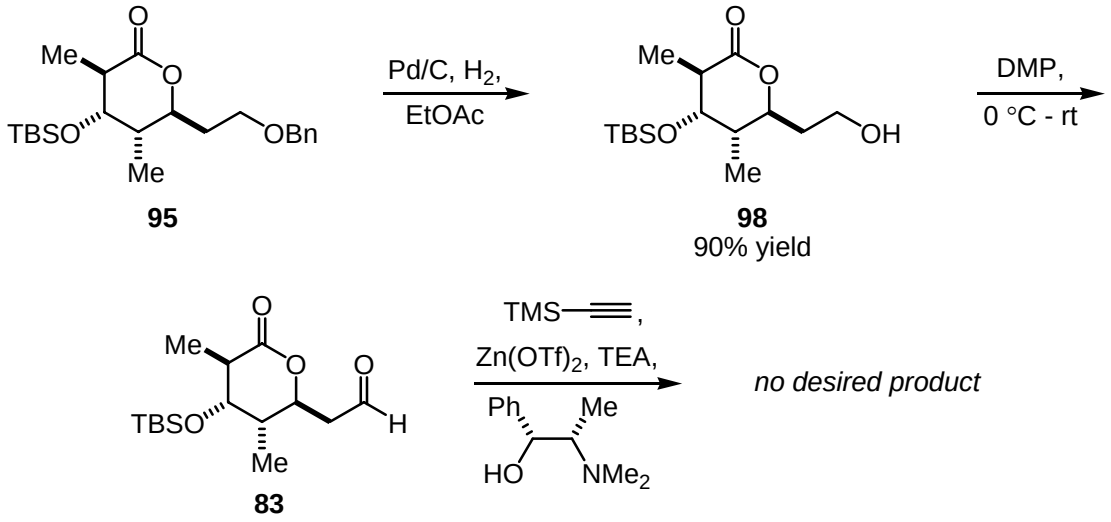




Even though silylation of the hydroxy group was problematic, the synthesis of aldehyde **83** was continued in order to test the aldehyde-alkyne coupling. Removal of the benzyl ether on **95** *via* hydrogenolysis yielded primary alcohol **98** in 90% yield (Scheme 31). The left fragment was completed by oxidation of primary alcohol **98** to aldehyde **83** using DMP. The aldehyde proved to be somewhat unstable and could not be purified, so the crude product was used in the attempted coupling reaction. The initial hope was to perform an asymmetric addition of the center fragment into the left fragment, therefore a very simplistic test reaction using Carreira's *N*-methylephedrine modified zinc-acetylide addition reaction was performed.[60] However, immediately upon subjection of aldehyde **83** to the reaction conditions, the starting material decomposed to yield a mixture of different α, β-unsaturated carbonyl products. As previously hypothesized, it was felt that the trans-annular strain across the δ-lactone was the cause of the problem. At this point it was realized that aldehyde **83** would not be a viable fragment and decided to revise our target substrate.

[60] Boyall, D.; Frantz, D. E.; Carreira, E. M. *Org. Lett.* **2002**, *4*, 2605-2606.

Scheme 31



3.3.2 Synthesis of aldehyde 99

The initial failure at forming the C_7-C_8 bond was felt to be a direct cause of the instability of the target fragment chosen rather than the method of formation of the bond, so the target was revised to a more stable and easily handled alternative. Since inherent strain in the δ-lactone was believed to be the source of the problem, a logical choice for an alternative fragment would be an acyclic variant that could be transformed into the δ-lactone if desired. Additionally, the new target had to be a potentially viable substrate for the aldehyde-alkyne coupling reaction and not introduce any chemoselectivity issues. With this in mind, it was felt that aldehyde **99** was a suitable choice for the revised left fragment (Figure 25).

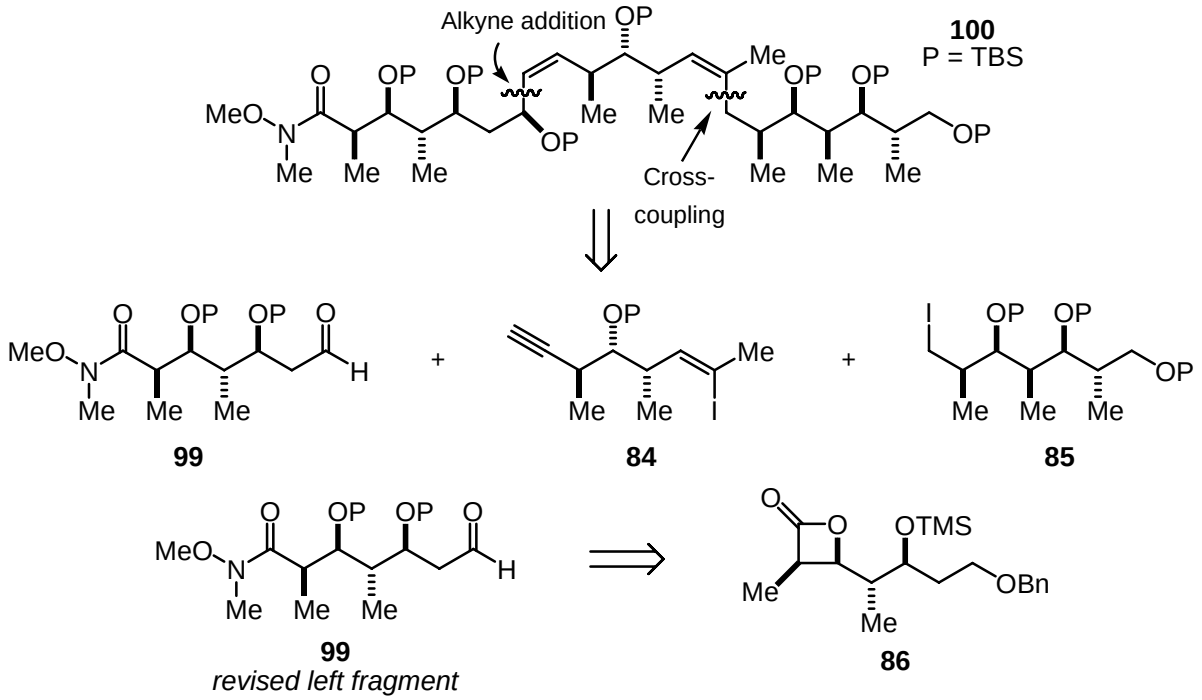
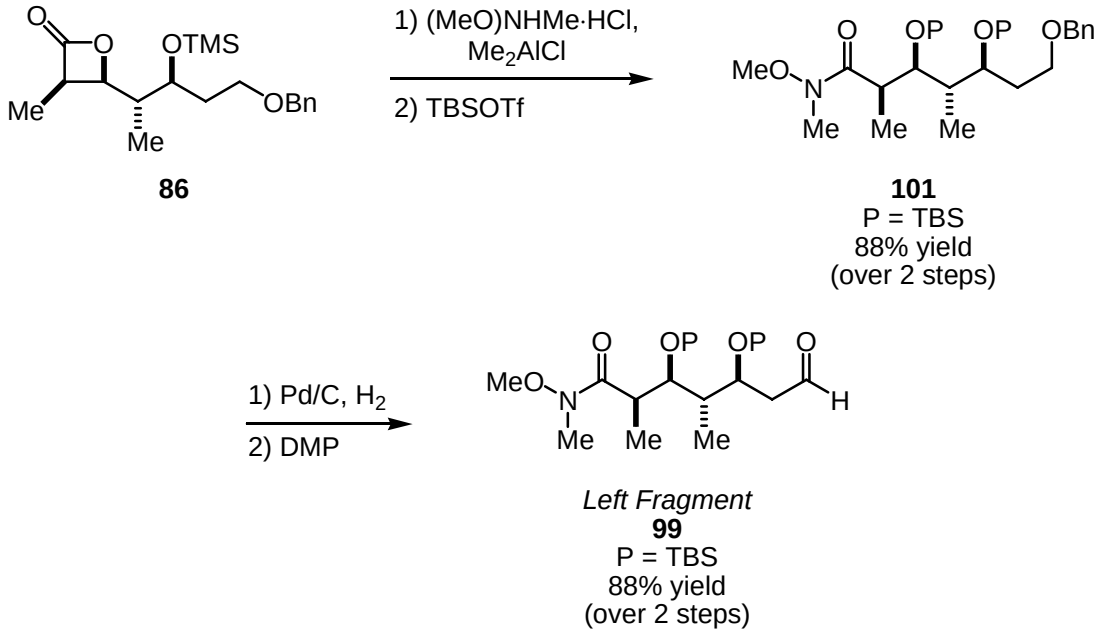


Figure 25: Revised retrosynthetic analysis

As depicted in Figure 25, the revised left fragment **99** can be derived from known β-lactone **86** and therefore the already developed forward sequence. Opening of β-lactone **86** with (MeO)NHMe·HCl in the presence of Me_2AlCl, with concomitant cleavage of the silyl ether, produced an intermediate bis-hydroxy Weinreb amide that was treated with TBSOTf to afford elaborate Weinreb amide **101** in 88% yield over two steps (Scheme 32). Deprotection of the benzyl ether *via* hydrogenolysis, followed by oxidation of the crude primary alcohol with DMP completed the revised left fragment, aldehyde **99**, in 88% yield over two steps.

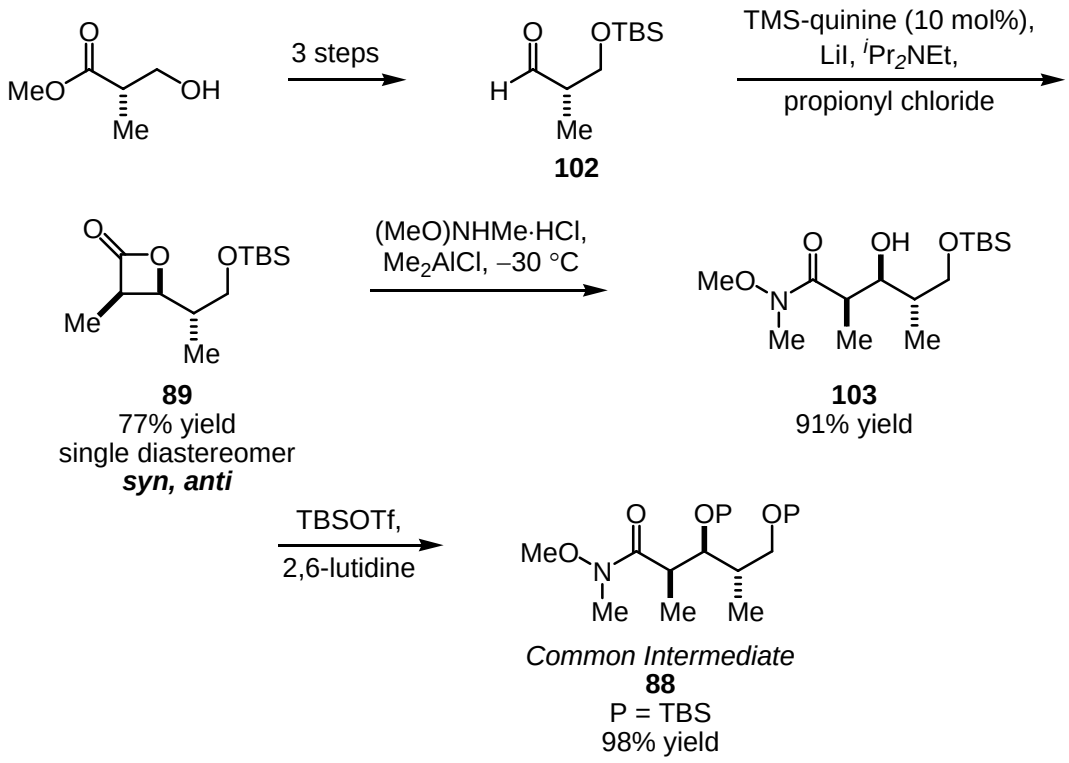
Scheme 32



3.3.3 Synthesis of iodide 85

With the synthesis of the left fragment completed, the synthesis of the right fragment, iodide **85**, commenced. The synthesis of iodide **85** began with aldehyde **102** which can be made from the commercially available (*S*)-Roche ester in 3 steps (Scheme 33). Subjection of aldehyde **102** to the C*inchona* alkaloid-catalyzed AAC reaction in the presence of a catalytic amount of TMS-Q_N produced β-lactone **89** in 77% yield as a single diastereomer. Treatment of β-lactone **89** with (MeO)NHMe·HCl and Me_2AlCl at −30 ºC afforded a 91% yield of β-hydroxy Weinreb amide **103**. Silylation of amide **103** with TBSOTf produced the common synthetic intermediate for the center and right fragment, amide **88**, in 98% yield.

Scheme 33

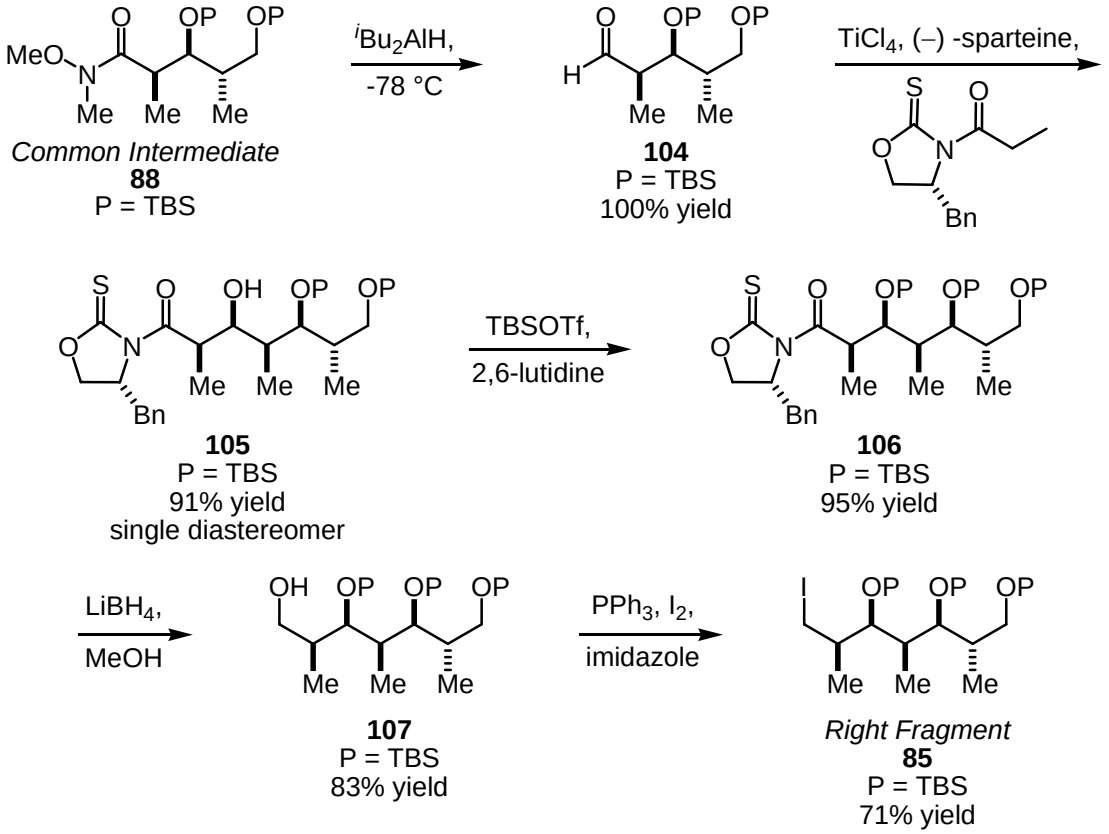


The synthesis of the completed right fragment was accomplished in 5 steps from common intermediate **88** (Scheme 34). Reduction of the Weinreb amide moiety in common intermediate **88** with $^{i}Bu_2AlH$ afforded a quantitative yield of aldehyde **104**. As mention previously, the desired *syn*, *syn*, *syn* polypropionate unit is unable to be produced using the AAC technology. Since a more elaborate variant of this subunit is needed for the right fragment of discodermolide, alternative methods were employed to obtain the desired stereoarray. Utilizing auxiliary-controlled aldol chemistry developed by Crimmins and coworkers, the desired *syn*, *syn*, *syn*, *anti* polypropionate unit **105** was synthesized from aldehyde **104** in 91% yield as a single diastereomer.[61] Protection of the hydroxy group in **105** with TBSOTf yielded oxazolidithione **106** in 95% yield. Subsequent removal of the chiral oxazolidithione auxiliary on **106** with $LiBH_4$

[61] Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem.* **2001**, *66*, 894-902.

in MeOH afforded primary alcohol **107** in 83% yield. The synthesis of the right fragment was completed by subjecting alcohol **107** to PPh_3, iodine and imidazole to produce primary iodide **85** in 71% yield.

Scheme 34

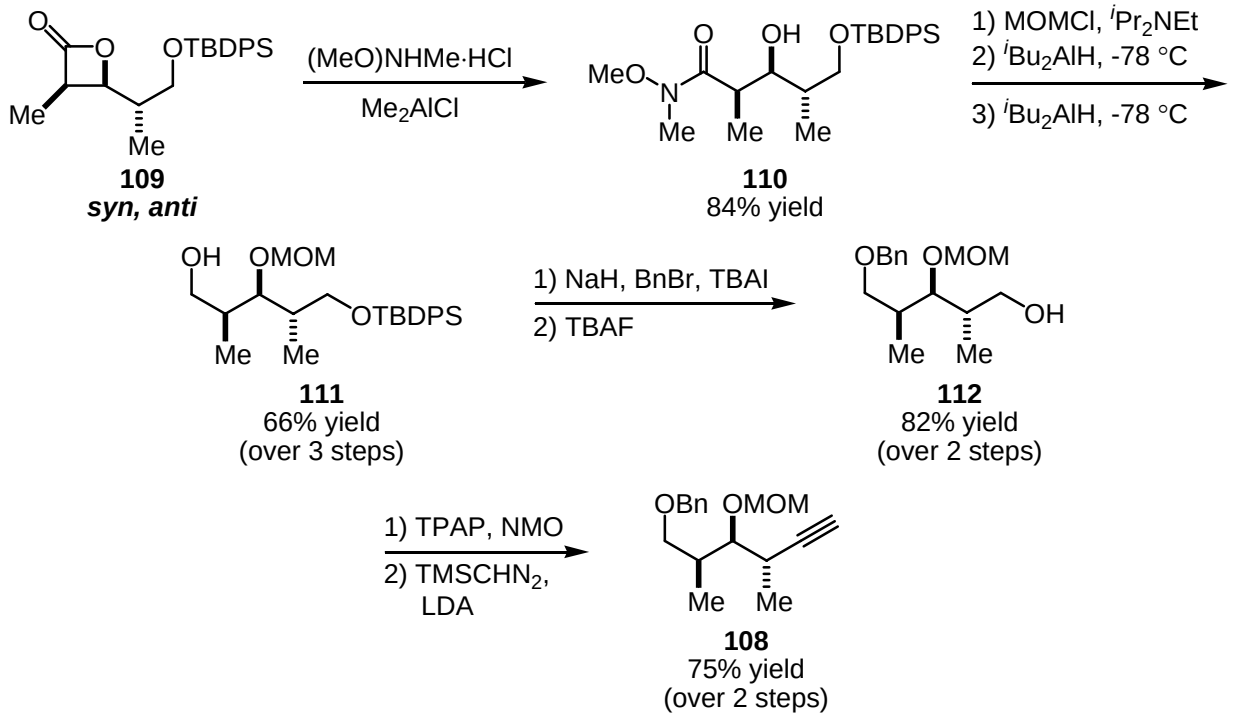


3.3.4 Synthesis of the model alkyne 108

Before efforts towards the synthesis of the actual center fragment commenced, model center fragment **108** was synthesized in order to test the coupling of the center and left fragments. The synthesis of the model alkyne began by treating known β-lactone **109** with (MeO)NHMe·HCl and Me_2AlCl to produce an 84% yield of β-hydroxy amide **110** (Scheme 35). Protection of the

free alcohol on amide **110** as a MOM ether, followed by twofold reduction of the amide moiety with $^{i}Bu_2AlH$ afforded primary alcohol **111** in 66% overall yield. Formation of a benzyl ether using BnBr and NaH in the presence of TBAI, followed by subsequent deprotection of the TBDPS ether with TBAF produced an 82% yield of benzyl ether **112** over the two steps. Oxidation of the primary alcohol on **112** with DMP, followed by subjection of the intermediate aldehyde to $TMSCHN_2$ and freshly generated LDA completed the synthesis of the model center fragment, alkyne **108**, in 75% yield over the final two steps.

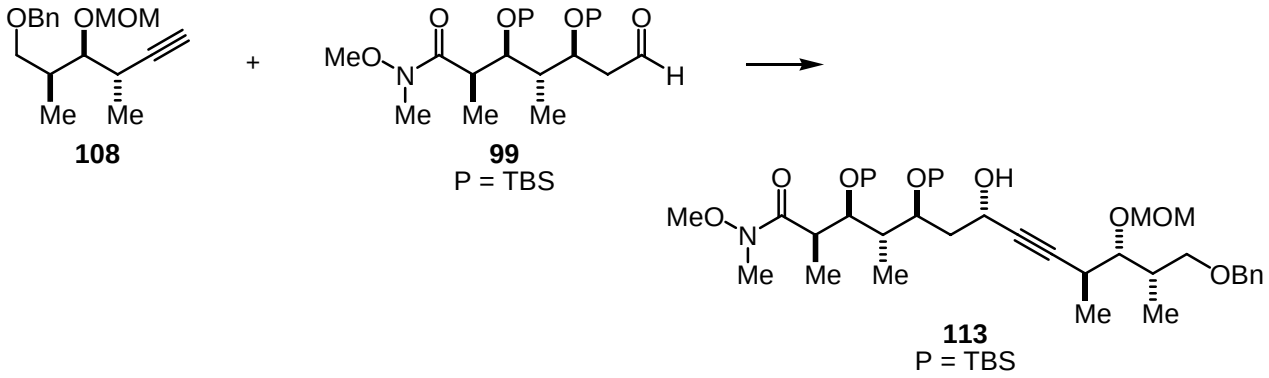
Scheme 35



With the synthesis of the model alkyne completed, it was time to test the aldehyde-alkyne coupling. As discussed before, the initial hope was to perform an asymmetric addition of the center fragment into the left fragment in order to reinforce setting the C_7-stereocenter with the proper stereochemistry. To do so, two of the more common asymmetric addition reactions,

conditions developed by Pu and coworkers [Ti(O^iPr)$_4$-$ZnEt_2$-BINOL] and conditions developed by Chan and coworkers [Ti(O^iPr)$_4$-$ZnMe_2$-BINOL], were attempted (Table 5).[62] Additionally, the more recent $InBr_3$-BINOL reaction conditions developed by Shibasaki and coworkers were attempted.[63] Disappointingly, while these reaction conditions work well for simple aldehydes and alkynes, they failed to produce any desired product when the complex aldehyde and alkyne fragments were used.

Table 5: Addition of model alkyne 108 into aldehyde 99



entry	Conditions	Results[a]
a	$ZnMe_2$, Ti(O^iPr)$_4$, (*R*)–BINOL	no desired product
b	$ZnEt_2$, Ti(O^iPr)$_4$, (*R*)–BINOL	no desired product
c	$InBr_3$, (*S*)–BINOL, Cy_2NMe	no desired product
d	^{n}BuLi, LiBr, toluene, –78 °C	2.5:1/desired:undesired (~8% enal)
e	^{n}BuLi, LiBr, THF, –78 °C	4.4:1/desired:undesired (~8% enal)
f	^{n}BuLi, $MgBr_2 \cdot OEt_2$, THF, –78 °C	6.0:1/desired:undesired (~8% enal)

[a] Determined using crude ^{1}H NMR and HPLC analysis. The desired diastereomer is amide **113** which is depicted. Isolated yields not obtained

[62] (a) Gao, G.; Moore, D.; Xie, R.-G.; Pu, L. *Org. Lett.* **2002**, 4143-4146. (b) Pu, L. *Tetrahedron* **2003**, *59*, 9873-9886. (c) Li, X.-S.; Lu, G.; Kwok, W. H.; Chan, A. S. C. *J. Am. Chem. Soc.* **2002**, *124*, 12636-12637.
[63] Takita, R.; Yakura, K.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 13760-13761.

After the failure of the asymmetric alkyne addition reactions to produce any desired product, unmodified anionic acetylide addition reactions into aldehyde **99** were attempted. Based on the electrostatic minimization model proposed by Reetz and Evans, aldehyde **99** should adopt a reactive conformer that inherently favors production of the desired 1,3-*anti* diastereomer, alcohol **113**, as the major product.[50] Preliminary studies with this type of addition were performed using the lithium acetylide of alkyne **108** generated from deprotonation with ^{n}BuLi. Addition of the lithium acetylide into aldehyde **99** in toluene at −78 ºC did yield the aldehyde addition products and a minor amount of enal (~8% yield).[64] As hypothesized, the desired alcohol **113** was the major product, being produced in a diastereomeric ratio of 2.5:1 with the undesired diastereomer. A quick survey of conditions showed that changing the solvent to THF had a beneficial effect as the diastereomeric ratio increased to 4.4:1/desired:undesired. The best diastereomeric ratio (6.0:1/desired:undesired) was obtained in THF when the lithium acetylide was transmetallated into a magnesium bromide acetylide prior to addition to the aldehyde.

3.3.5 First attempt at the synthesis of alkyne 84

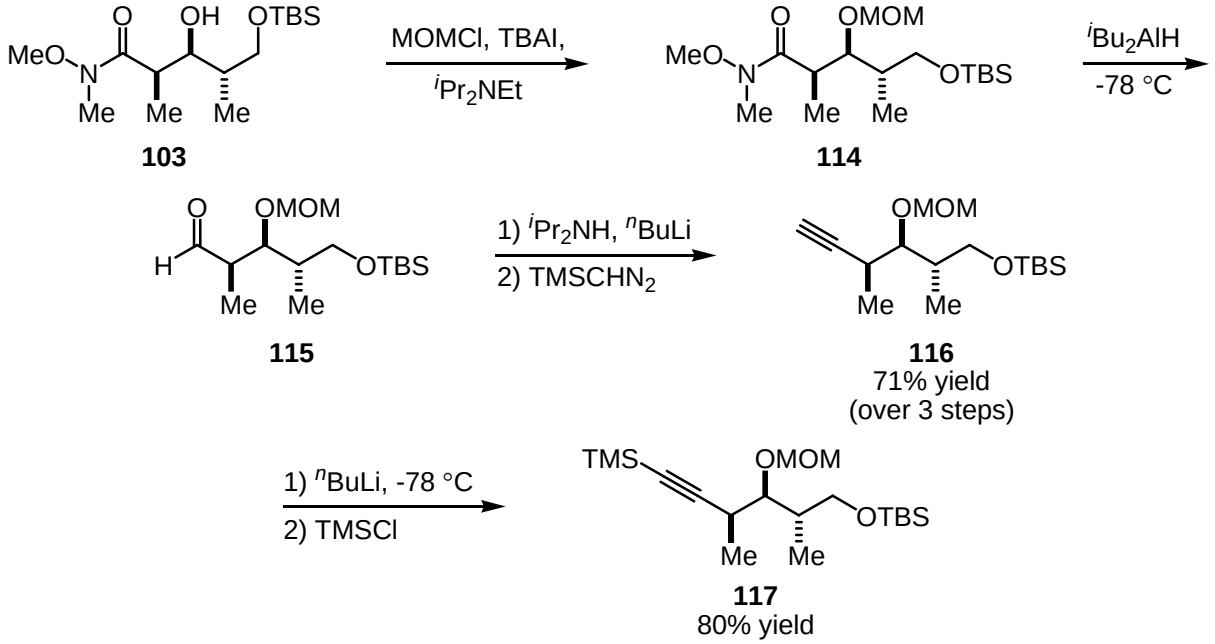
With the testing of the aldehyde-alkyne coupling reaction complete, the synthesis of the actual center fragment was undertaken.[65] Besides formation of the polypropionate unit backbone, the center fragment also possessed the challenge of making a trisubstituted (*Z*)-olefin with one of the substituents being an iodide. In the preliminary studies for the synthesis of alkyne **84**, Panek's method of using hydrozirconation to form the trisubstituted olefin was employed.[55] In this sequence, a vinyl TMS group acts as a masked vinyl iodide.

---

[64] Alcohol **113** was not purified or fully characterized, only crude ^{1}H NMR was used.
[65] When this route was attempted, amide **103** was the common intermediate. Upon failure of this route, the common intermediate became amide **88**.

The synthetic sequence begins with protection of the β-hydroxy group on Weinreb amide **103** as a MOM-ether using MOMCl and TBAI to produce amide **114** (Scheme 36). Reduction of the Weinreb amide moiety on amide **114** with $^{i}Bu_2AlH$, followed by transformation of aldehyde **115** into an alkyne with $TMSCHN_2$ and freshly prepared LDA afforded alkyne **116** in 71% overall yield. Deprotonation of the terminal alkyne **116** using $^{n}BuLi$ with subsequent reaction of the generated lithium acetylide with TMSCl produced an 80% yield of silyl ether **117**.

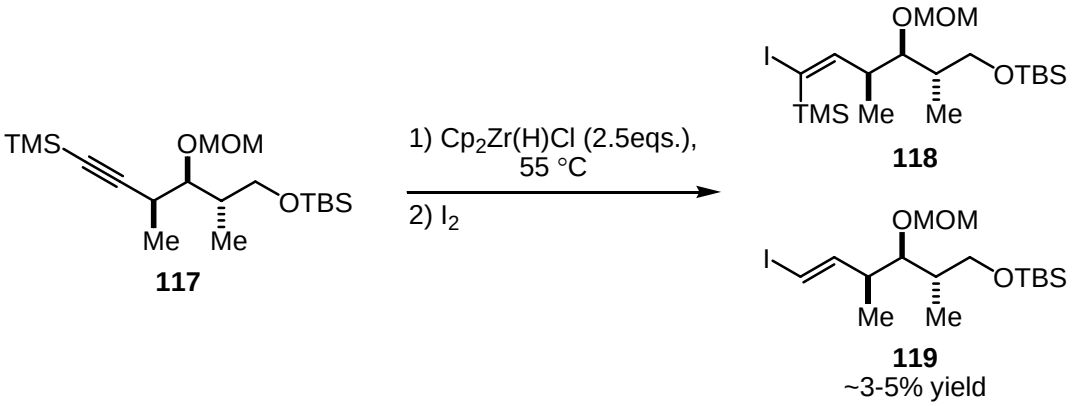
Scheme 36



With alkyne **117** synthesized, attempts at forming the requisite trisubstituted olefin utilizing Panek's methodology were made. Unfortunately, despite multiple attempts the desired olefin was unable to be obtained (Scheme 37). The hydrozirconation/iodination reaction proved to be irreproducible as the amount of starting material that was converted to desired product **118** varied greatly. Additionally, desired iodide **118** was contaminated with a minor amount of an

undesired alkene byproduct (~3-5% yield) that was unable to be removed. Based on crude ^{1}H NMR data, this undesired olefin byproduct is speculated to be alkene **119**.

Scheme 37



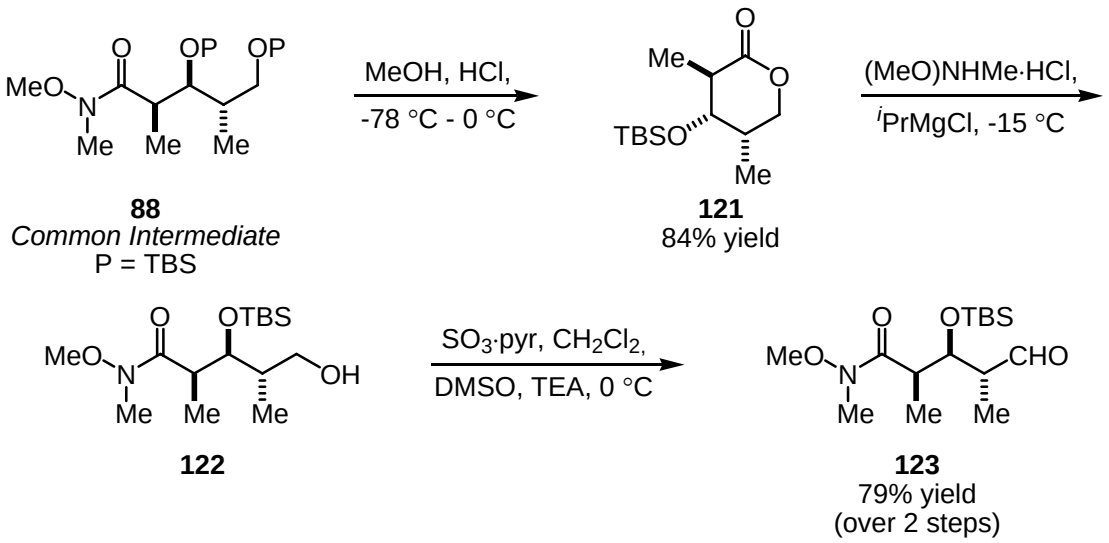
To complicate the reaction sequence further, the subsequent Negishi cross-coupling reaction to install the methyl group was very problematic as well. While the desired trisubstituted (*Z*)-olefin **120** was obtained from the cross-coupling reaction, there was a persistent failure to achieve full consumption of the starting material despite the use of an excess amount of MeZnCl (Scheme 38). Also, as with the hydrozirconation/iodination reaction, this reaction formed an undesired olefin containing byproduct (~3-10%) that was inseparable from the desired product. Due to the problems associated with these two synthetic steps, this route to alkyne **84** was abandoned.

Scheme 38

3.3.6 Revised synthesis of alkyne 84

After the failure of Panek's methodology to form the requisite trisubstituted olefin from alkyne **117**, an alternative sequence to the olefin using the Zhao-Wittig olefination was attempted.[66] The synthetic sequence to the precursor for the Zhao-Wittig olefination can be made from common intermediate **88** in 6 steps. Treatment of amide **88** with HCl and MeOH cleaved the primary silyl ether and catalyzed lactonization to produce an 84% yield of δ-lactone **121** (Scheme 39). Opening of δ-lactone **121** to a Weinreb amide with ensuing Parikh-Doering oxidation of primary alcohol **122** afforded a 79% yield of aldehyde **123** over the two steps.

Scheme 39

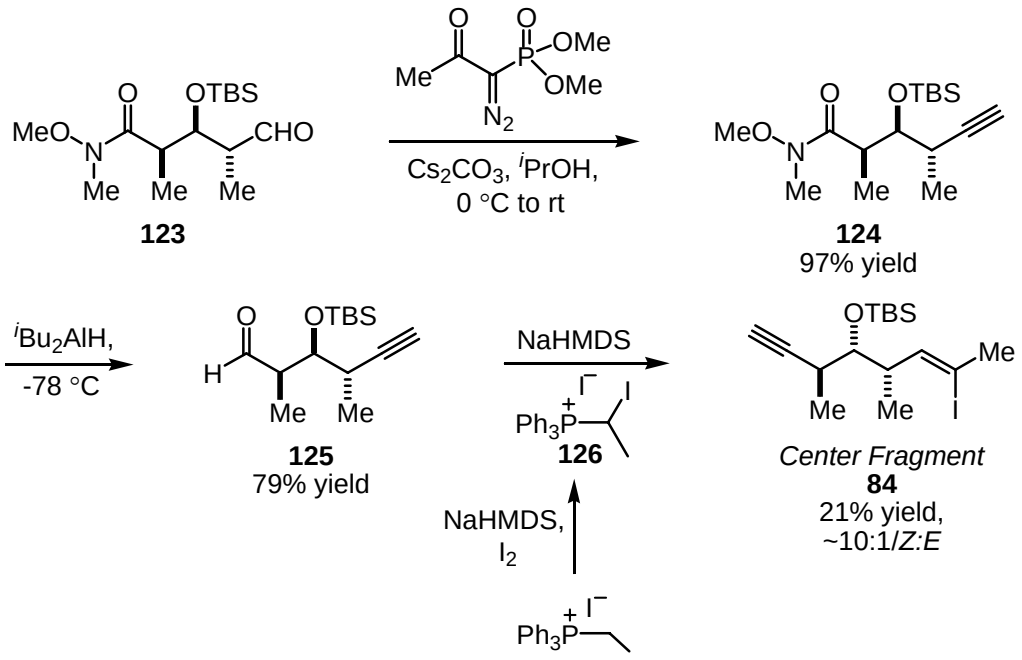


Transformation of the aldehyde functionality in **123** to a terminal alkyne required the use of mild reaction conditions as the aldehyde proved to be somewhat sensitive. Employing Ohira's reagent

[66] Chen, J.; Zhao, K. *Tetrahedron Lett.* **1994**, *35*, 2827-2828.

with Cs_2CO_3 in ^{i}PrOH, alkyne **124** was produced in 97% yield from aldehyde **123**.[67] Reduction of amide **124** with $^{i}Bu_2AlH$ yielded the precursor for the Zhao-Wittig olefination, aldehyde **125**, in 79% yield. While the Zhao-Wittig olefination is not an extremely efficient reaction (normally 20-40% yield, 6-19:1/*Z*:*E*), this transformation installs the necessary functionalities to complete the target center fragment in one step. Subjection of aldehyde **125** to a solution of freshly prepared phosphonium salt **126** in the presence of NaHMDS afforded the completed center fragment **84** in 21% yield as a 10:1/*Z*:*E* inseparable mixture of olefin isomers.

Scheme 40



Currently, the Nelson group possesses a working synthetic sequence to all the target fragments of analogue **100**. Most of the polypropionate units along the backbone of analogue **100** were successfully set using AAC chemistry, with the center and right fragments both being formed from an elaborate common intermediate. Subsequent studies on the coupling of these three

[67] Ghosh, A.; Bischoff, A.; Cappiello, J. *Eur. J. Org. Chem.* **2003**, 821-832.

fragments into analogue **100**, as well as derivatization of the analogue into other congeners of (+)-discodermolide, will be conducted in the future.

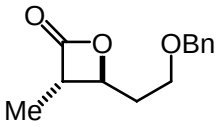
3.4 EXPERIMENTAL

General Information: ^{1}H NMR spectra were recorded on Bruker DPX 301 and DPX 302 (300 MHz) spectrometers. Chemical shifts are reported in ppm from tetramethylsilane with either the solvent resonance as the internal standard ($CHCl_3$: δ 7.27 ppm) or tetramethylsilane as an external standard (TMS: δ ppm). Data is reported as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septet, app = apparent, br = broad, m = multiplet), coupling constants (Hz), integration. ^{13}C NMR spectra were recorded on Bruker DPX 301 and DPX 302 spectrometers (75 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with either the solvent resonance as the internal standard ($CDCl_3$: δ 77.0 ppm) or tetramethylsilane as an external standard (TMS: δ ppm). Optical rotations were measured on a Perkin-Elmer 241 digital polarimeter with a sodium lamp at ambient temperature and are reported as follows: $[\alpha]_D$ (*c* g/100 mL) with units of degree•g•cm^{-3}. Infrared spectra were recorded on a Nicolet Avatar 360 FT-IR spectrometer. Mass spectra were obtained on a VG-7070 or Fisons Autospec high resolution magnetic sector mass spectrometer.

Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60-F plates. Flash chromatography was performed as previously described on EM silica gel 60 (230-240 mesh).[37] Automated flash chromatography was performed using an ISCO CombiFlash® Companion™ using disposable RediSep™ columns. Analytical gas liquid chromatography (GLC)

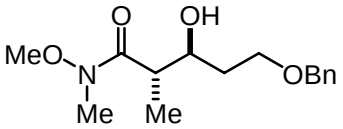
was performed on a Varian 3900 gas chromatograph with a flame ionization detector and split mode capillary injection system using a VarianCP Wax 52CB column (30 m x 0.25 mm). Hydrogen was used as the carrier gas at the indicated pressures. Analytical high performance liquid chromatography (HPLC) was performed on a Hewlett Packard 1100 liquid chromatograph equipped with a variable wavelength UV detector (deuterium lamp, 190-600 nm), using a Daicel Chiralcel™ OD-H column (250 x 4.6 mm) (Daicel Inc.). HPLC grade isopropanol and hexanes were used as the eluting solvents. Melting points were measured using a Mel-Temp apparatus and are uncorrected.

Unless otherwise stated, all experiments were carried out under a nitrogen atmosphere in oven or flame-dried glassware using standard inert atmosphere techniques for introducing reagents and solvents. Anhydrous solvents were obtained by passage through successive alumina- and Q5 reactant-packed columns on a solvent purification system. Amines were purified *via* distillation from CaH_2. Propionyl chloride, TBSOTf and MOMCl were purified by distillation prior to use. Unless otherwise stated, commercially available reagents were used as received without any further purification. All water used in reactions and in aqueous solutions was deionized.



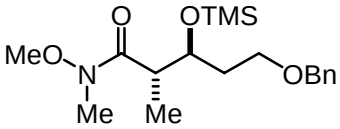
(3*S*,4*S*)-4-(2-(Benzyloxy)ethyl)-3-methyloxetan-2-one (87): To a solution of β-lactone **90** (2.88 g, 14.0 mmol) in THF (700 mL) at ambient temperature was added MeI (4.35 mL, 69.9 mmol). The reaction mixture was then cooled to −100 °C and NaHMDS (14.0 mL, 14.0 mmol, 1.0 M in THF) was added in a dropwise fashion over 2 h. After complete addition the resulting solution was maintain for an additional hour at −100 °C. The reaction mixture was quenched by addition of saturated aqueous NH_4Cl (50 mL) and allowed to

warm to ambient temperature. The layers were separated and the aqueous layer extracted with ethyl acetate (3x). The combined organic extracts were washed with brine (1x), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (19:1/hexanes:ethyl acetate) to provide 1.91 g (62%) of disubstituted β-lactone **87**: $[\alpha]_D = -39.6$ (*c* 1.4, $CHCl_3$); IR (thin film) 2935, 2872, 1824, 1454, 1385, 1363, 1124 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.40-7.31 (m, 5H), 4.52 (br s, 2H), 4.38 (td, *J* = 6.6, 4.0 Hz, 1H), 3.67-3.56 (m, 2H), 3.36 (qd, *J* = 7.6, 4.0 Hz, 1H), 2.16-2.08 (m, 2H), 1.37 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.4, 137.6, 127.8 (2C), 127.1, 127.0 (2C), 76.7, 72.4, 65.3, 50.4, 33.5, 11.6; EI-MS *m/z* 205 $(M-Me)^+$ 192, 174, 146; HRMS calcd for $C_{12}H_{16}O_2$ $(M-CO)^+$: 192.1150, found 192.1148.



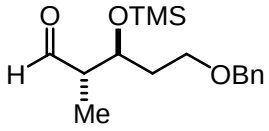
(2*S*,3*S*)-5-(Benzyloxy)-3-hydroxy-*N*-methoxy-*N*,2-dimethylpentanamide (91): To a 0 °C mixture of *N*,*O*-dimethylhydroxylamine hydrochloride (6.77 g, 69.4 mmol) in CH_2Cl_2 (125 mL) was added dimethylaluminum chloride (69.0 mL, 69.4 mmol, 1.0 M in hexanes) in a slow, dropwise fashion. The resulting solution was allowed to warm to ambient temperature and stirred for 2 h. Subsequently, the homogenous solution was cooled to 0 °C and diluted with CH_2Cl_2 (75 ml). To the resulting solution was added a solution of β-lactone **87** (7.64 g, 34.7 mmol) in CH_2Cl_2 (50 mL) *via* syringe. The reaction mixture was then warmed to ambient temperature and allowed to stir for 2 h. Cooled the reaction mixture once again to 0 °C and quenched slowly with aqueous phosphate buffer (100 mL, pH = 7). The resulting biphasic mixture was warmed to ambient temperature and stirred vigorously for 1 h. The layers of the mixture were then separated and the aqueous layer extracted with CH_2Cl_2 (3x). The combined organic extracts were dried over Na_2SO_4, filtered and

concentrated *in vacuo*. The crude oil was purified by silica gel chromatography (2:1/hexanes:ethyl acetate) to provide 8.10 g (83%) of amide **91**: $[\alpha]_D$ = +13.6 (*c* 1.0, $CHCl_3$); IR (thin film) 3443 (br), 2938, 2866, 1636, 1454, 1420, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.35-7.27 (m, 5H), 4.53 (br s, 2H), 3.89 (dtd, *J* = 9.4, 6.2, 3.1 Hz, 1H), 3.77-3.62 (m, 3H), 3.69 (s, 3H), 3.20 (s, 3H), 2.99-2.96 (m, 1H), 1.91-1.70 (m, 2H), 1.22 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.6, 138.0, 128.0 (2C), 127.3 (2C), 127.2, 72.8, 71.7, 67.8, 61.1, 40.0, 34.6, 31.4, 14.3; EI-MS *m/z* 221 $(M–(MeO)NMe)^+$ 221, 157, 151, 146; HRMS calcd for $C_{13}H_{17}O_3$ $(M–(MeO)NMe)^+$: 221.1178, found 221.1177.

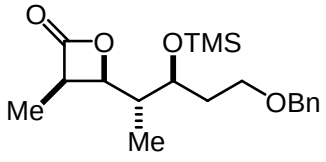


(2*S*,3*S*)-5-(Benzyloxy)-3-trimethylsilyloxy-*N*-methoxy-*N*,2-dimethylpentanamide (92): To a solution of β-hydroxyl amide **91** (2.24 g, 7.97 mmol) in CH_2Cl_2 (100 mL) at 0 °C was added 2,6-lutidine (2.32 mL, 19.9 mmol). Subsequently, freshly distilled TMSCl (2.22 mL, 17.5 mmol) was added to the reaction mixture. The resulting solution was warmed to ambient temperature and stirred 1 h, after which the reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$ (40 mL). The layers were separated and the organic layer washed with 1.0 M aqueous $NaHSO_4$ (1x). The combined aqueous layers were then extracted with CH_2Cl_2 (3x) and the combined organic extracts dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude oil was purified by silica gel chromatography (6:1/hexanes:ethyl acetate) to provide 2.74 g (97%) of silyl ether **92**: $[\alpha]_D$ = +18.1 (*c* 1.2, $CHCl_3$); IR (thin film) 2957, 2898, 1660, 1454, 1248, 1112 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.36-7.28 (m, 5H), 4.51 (d, *J* = 3.7 Hz, 2H), 4.11 (td, *J* = 8.4, 2.9 Hz, 1H), 3.69 (s, 3H), 3.63-3.57 (m, 2H), 3.19 (s, 3H), 3.15-3.02 (m, 1H), 1.93 (dtd, *J* = 14.1, 7.4, 3.0 Hz, 1H), 1.69 (ddt, *J* = 14.2, 8.2, 6.1 Hz, 1H), 1.06 (d, *J* = 6.9 Hz, 3H), 0.08 (s, 9H); ^{13}C NMR (75 MHz,

$CDCl_3$): δ 175.2, 138.0, 127.6 (2C), 126.9 (2C), 126.8, 72.2, 70.7, 65.9, 60.5, 41.3, 33.2, 31.1, 12.7, –0.3 (3C); EI-MS *m/z* 338 $(M–Me)^+$ 293, 157; HRMS calcd for $C_{18}H_{31}NO_4Si$: 353.2022, found 353.2023.

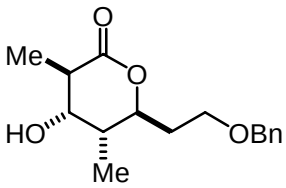


(2*S*,3*S*)-5-(Benzyloxy)-3-trimethylsilyloxy-2-methylpentanal (93): To a –78 °C solution of amide **92** (2.74 g, 7.75 mmol) in THF (75 mL) was added $^{i}Bu_2AlH$ (11.0 mL, 10.9 mmol, 1.0 M in hexanes) in a slow, dropwise fashion. The resulting solution was maintained at –78 °C for 2 h after which saturated aqueous Rochelle's salts (30 mL) was added. The biphasic mixture was allowed to warm to ambient temperature and stirred vigorously for 1 h. The layers were separated and the aqueous layer extracted with ether (3x). The combined organic extracts were washed with brine (1x), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude oil was purified by silica gel chromatography (30:1/hexanes:ethyl acetate) to provide 1.97 g (86%) of aldehyde **93**: $[\alpha]_D$ = +12.9 (*c* 1.2, $CHCl_3$); IR (thin film) 2956, 2860, 1725, 1251, 1110 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.73 (d, *J* = 2.3 Hz, 1H), 7.36-7.30 (m, 5H), 4.50 (d, *J* = 3.5 Hz, 2H), 4.15 (dt, *J* = 6.6, 5.3 Hz, 1H), 3.60-3.54 (m, 2H), 2.50 (qdd, *J* = 7.1, 5.1, 2.3 Hz, 1H), 1.86-1.79 (m, 2H), 1.11 (d, *J* = 7.0 Hz, 3H), 0.12 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.3, 138.0, 127.9 (2C), 127.0 (2C), 126.9, 72.3, 70.1, 66.0, 51.3, 34.4, 9.8, –0.2 (3C); EI-MS *m/z* 237 $(M–C_3H_5O)^+$ 187, 176, 159; HRMS calcd for $C_{16}H_{26}O_3Si$: 294.1651, found 294.1641.



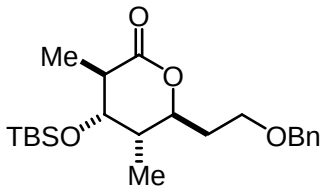
(3*R*,4*S*)-4-((2*S*,3*S*)-5-(Benzyloxy)-3-trimethylsilyloxypentan-2-yl)-3-methyloxetan-2-one (86): A flame-dried round bottom flask was charged with TMS-quinine (0.350 g, 0.883 mmol) and LiI (3.55 g,

26.5 mmol). To the mixture of solids was sequentially added CH_2Cl_2 (26 mL), DMF (2.6 mL) and $^{i}Pr_2NEt$ (3.85 mL, 22.1 mmol). The resulting mixture was stirred at ambient temperature for 5 min then cooled to –40 °C. To the reaction mixture was added aldehyde **93** (2.60 g, 8.83 mmol) followed by dropwise addition of a solution of propionyl chloride (1.54 ml, 17.7 mmol) in CH_2Cl_2 (7.3 mL) over 6 h. The heterogeneous reaction mixture was stirred vigorously overnight at –40 °C. The reaction mixture was quenched with ether and the white precipitate filtered off over a plug of silica which was eluted with ether. The filtrate was then concentrated *in vacuo* and the resulting residue purified *via* silica gel chromatography (9:1/hexanes:ethyl acetate) to yield 2.32 g (75%) of β-lactone **86**: Diastereomeric ratio determined by crude ^{1}H NMR (300 MHz, δ 4.34 ppm) determined the title compound was produced as a single diastereomer; $[\alpha]_D$ = –23.3 (*c* 1.0, $CHCl_3$); IR (thin film) 2956, 1826, 1454, 1251, 1153, 1099 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33-7.24 (m, 5H), 4.47 (d, *J* = 4.2 Hz, 2H), 4.34 (dd, *J* = 11.2, 6.3 Hz, 1H), 4.04 (dt, *J* = 7.4, 3.3 Hz, 1H), 3.74 (app p, *J* = 7.7 Hz, 1H), 3.57-3.46 (m, 2H), 2.02 (app pd, *J* = 6.9, 3.1 Hz, 1H), 1.82-1.65 (m, 2H), 1.30 (d, *J* = 7.7 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H), 0.09 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.9, 138.2, 128.1 (2C), 127.4 (2C), 127.2, 75.8, 72.6, 69.4, 67.1, 47.2, 38.5, 32.0, 10.0, 8.3, 0.1 (3C) ; EI-MS *m/z* 350 $(M)^+$, 305, 277, 237, 179; HRMS calcd for $C_{13}H_{21}O_2Si$ $(M–C_6H_9O_2)^+$: 237.1311, found 237.1320.



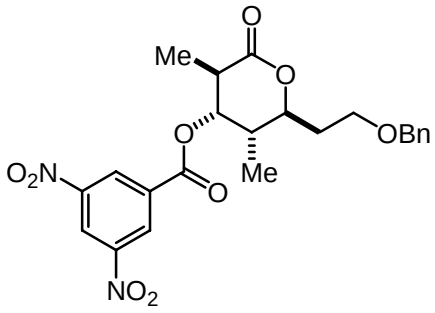
(3*R*,4*S*,5*R*,6*S*)-6-(2-(Benzyloxy)ethyl)-tetrahydro-4-hydroxy-3,5-dimethylpyran-2-one (94): To a solution of β-lactone **86** (0.348 g, 1.00 mmol) in THF (2 mL) at ambient temperature was added KOH (2.0 mL, 1.0 M in H_2O). The biphasic reaction mixture was stirred vigorously at ambient temperature for 8 hours. Subsequently, the reaction mixture was cooled to 0 °C and acidified to

a pH = 2 by slow addition of conc. HCl. The resulting reaction mixture was then warmed to ambient temperature and stirred vigorously for 1 hour. The reaction mixture was diluted with EtOAc (5 mL) and the layers separated. The organic layer was washed with sat. aq. $NaHCO_3$ (1x) followed by H_2O (1x). Subsequently, the combined aqueous layers were extracted with EtOAc (3x). The combined organic extracts were then dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude oil was purified by silica gel chromatography (2:1/hexanes:ethyl acetate) to provide 0.248 g (90%) of alcohol **94**: $[\alpha]_D = -50.7$ (*c* 1.1, $CHCl_3$); IR (thin film) 3434 (br), 2972, 2936, 2881, 1727, 1455, 1236, 1096 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.36-7.26 (m, 5H), 4.57-4.47 (m, 3H), 3.75-3.68 (m, 3H), 2.67 (qd, *J* = 7.4, 4.3 Hz, 1H), 2.11-1.92 (m, 3H), 1.82 (ddt, *J* = 14.5, 10.2, 5.3 Hz, 1H), 1.31 (d, *J* = 7.3 Hz, 3H), 1.07 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.7, 137.9, 128.1 (2C), 127.4 (2C), 127.3, 77.7, 72.9, 72.3, 65.8, 43.0, 34.8, 33.1, 15.4, 12.4; EI-MS *m/z* 278 $(M)^+$ 173, 164, 146; HRMS calcd for $C_{16}H_{22}O_4$: 278.1518, found 278.1510.



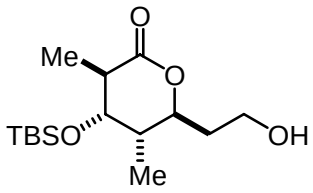
(3*R*,4*S*,5*R*,6*S*)-6-(2-(Benzyloxy)ethyl)-tetrahydro-4-*tert*-butyldimethylsilyloxy-3,5-dimethylpyran-2-one (95): To a solution of alcohol **94** (1.20 g, 4.33 mmol) in CH_2Cl_2 (7.3 mL) at ambient temperature was added 2,6-lutidine (0.76 mL, 6.50 mmol). The resulting reaction mixture was cooled to −78 °C and then TBSOTf (1.30 mL, 5.63 mmol) was added in a slow, dropwise fashion. The reaction mixture was stirred at −78 °C for 2 hours. Subsequently, the reaction mixture was quenched by addition of H_2O (5 mL) and warmed to ambient temperature. The layers were separated and the aqueous layer was extracted with ether (3x). The combined organic extracts were then dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude oil

was purified by silica gel chromatography (5:1/hexanes:ethyl acetate) to provide 1.38 g (55%) of silyl ether **95** and 0.248 g (22%) of enoate **96**. Characterization data for silyl ether **95**: $[\alpha]_D$ = –23.8 (*c* 1.3, $CHCl_3$); IR (thin film) 2955, 2930, 2883, 2857, 1735, 1462, 1253, 1095, 1067 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.34-7.28 (m, 5H), 4.55-4.48 (m, 3H), 3.73-3.65 (m, 3H), 2.64 (qd, *J* = 7.6, 3.1 Hz, 1H), 2.10-1.75 (m, 3H), 1.25 (d, *J* = 7.6 Hz, 3H), 1.01 (d, *J* = 6.7 Hz, 3H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.3, 137.9, 127.8 (2C), 127.0 (3C), 77.8, 73.8, 72.6, 65.6, 43.4, 33.4, 33.1, 25.3 (3C), 17.5, 15.7, 13.4, –5.03, –5.26; EI-MS *m/z* 335 $(M-{}^tBu)^+$ 305, 279, 173; HRMS calcd for $C_{22}H_{36}O_4Si$: 392.2383, found 392.2379. Characterization data for enoate **96**: $[\alpha]_D$ = –35.4 (*c* 1.0, $CHCl_3$); IR (thin film) 2926, 1717, 1453, 1363, 1217, 1101 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.35-7.30 (m, 5H), 6.35 (dd, *J* = 2.3, 1.4 Hz, 1H), 4.52 (d, *J* = 2.7 Hz, 2H), 4.22 (td, *J* = 9.6, 2.9 Hz, 1H), 3.76-3.65 (m, 2H), 2.50 (qdd, *J* = 7.1, 4.7, 2.3 Hz, 1H), 2.12-2.00 (m, 2H), 1.98-1.85 (m, 3H), 1.11 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.4, 145.6, 138.0, 128.1 (2C), 127.4 (3C), 126.7, 80.4, 72.8, 65.5, 33.4, 32.8, 16.6, 16.3; EI-MS *m/z* 260 $(M)^+$ 173, 154, 147, 125; HRMS calcd for $C_{16}H_{20}O_3$: 260.1412, found 260.1402.



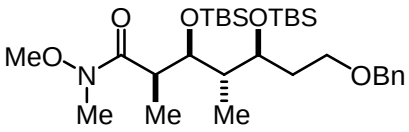
(2*S*,3*S*,4*S*,5*R*)-2-(2-(Benzyloxy)ethyl)-tetrahydro-3,5-dimethyl-6-oxo-2H-pyran-4-yl 3,5-dinitrobenzoate (97): To a solution of alcohol **94** (0.109 g, 0.390 mmol) in CH_2Cl_2 (2.5 mL) at ambient temperature was added DMAP (3.0 mg) followed by 3,5-dinitrobenzoyl chloride (0.117 g, 0.510 mmol). The reaction mixture was then treated with triethylamine (82 μL, 0.590 mmol) and was subsequently stirred at ambient temperature overnight. Quenched the reaction by addition of sat.

aq. $NaHCO_3$, separated the layers and washed the organic layer with 1.0 M aqueous $NaHSO_4$ (1x). The aqueous layer was extracted with CH_2Cl_2 (3x) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (4:1/hexanes:ethyl acetate) to provide 0.150 g (81%) of δ-lactone **97**: $[\alpha]_D$ = –26.1 (*c* 0.9, $CHCl_3$); IR (thin film) 3100, 2936, 1735, 1628, 1545, 1459, 1345, 1275 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.28-9.27 (m, 1H), 9.12-9.11 (m, 2H), 7.37-7.20 (m, 5H), 5.29 (app t, *J* = 4.3 Hz, 1H), 4.65 (td, *J* = 9.3, 2.9 Hz, 1H), 4.60 (d, *J* = 11.9 Hz, 1H), 4.52 (d, *J* = 11.8 Hz, 1H), 3.81-3.71 (m, 2H), 2.97 (qd, *J* = 7.2, 4.6 Hz, 1H), 2.37 (dqd, *J* = 10.4, 6.9, 4.5 Hz, 1H), 2.21-2.10 (m, 1H), 1.92 (ddt, *J* = 13.9, 9.3, 4.9 Hz, 1H), 1.42 (d, *J* = 7.4 Hz, 3H), 1.10 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.7, 161.9, 148.6 (2C), 138.0, 132.9, 129.2 (2C), 128.3 (2C), 127.5 (3C), 122.7, 77.9, 77.7, 73.2, 65.3, 39.9, 33.7, 33.4, 15.6, 12.6; EI-MS *m/z* 472 $(M)^+$ 455, 422, 293, 260, 212; HRMS calcd for $C_{23}H_{24}N_2O_9$: 472.1482, found 472.1469. An x-ray crystal structure of the title compound was obtained from crystals grown *via* slow vapor diffusion using hexanes and ethyl acetate as the recrystallization solvents.



(3*R*,4*S*,5*R*,6*S*)-6-(2-(Hydroxy)ethyl)-tetrahydro-4-*tert*-butyldimethylsilyloxy-3,5-dimethylpyran-2-one (98): To a solution of benzyl ether **95** (1.35 g, 3.44 mmol) in ethyl acetate (7.4 mL) at ambient temperature was added Pd/C (10% activated, 0.370 g). The atmosphere was evacuated and refilled with $H_{2(g)}$ (3x) and then vigorously stirred at ambient temperature overnight. The heterogeneous reaction mixture was filtered over a plug of celite and the filtrate concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (2:1/hexanes:ethyl acetate) to provide 0.936 g (90%) of alcohol **98**: $[\alpha]_D$ = –18.6 (*c* 1.0, $CHCl_3$); IR (thin film) 3442 (br),

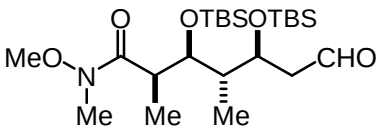
2955, 2884, 2857, 1731, 1462, 1252, 1098, 1055 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.52 (td, *J* = 9.8, 2.6 Hz, 1H), 3.90-3.87 (m, 2H), 3.68 (app t, *J* = 2.6 Hz, 1H), 2.67 (qd, *J* = 7.6, 3.0 Hz, 1H), 2.06-1.92 (m, 3H), 1.86-1.73 (m, 1H), 1.28 (d, *J* = 7.6 Hz, 3H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.90 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.0, 79.0, 74.1, 58.7, 43.7, 35.9, 34.0, 25.6 (3C), 17.8, 16.1, 13.8, –4.7, –4.9; EI-MS *m/z* 303 $(M)^+$ 287, 257, 245, 215, 189; HRMS calcd for $C_{11}H_{21}O_4Si$ $(M-{}^tBu)^+$: 245.1209, found 245.1202.



(2*R*,3*S*,4*S*,5*S*)-7-(Benzyloxy)-3,5-bis-(*tert*-butyldimethylsilyloxy)-*N*-methoxy-*N*,2,4-trimethylheptanamide (101): To a 0 °C mixture of *N*,*O*-dimethylhydroxylamine hydrochloride (0.254 g, 2.60 mmol) in CH_2Cl_2 (3.3 mL) was added dimethylaluminum chloride (2.60 mL, 2.60 mmol, 1.0 M in hexanes) in a slow, dropwise fashion. The resulting solution was allowed to warm to ambient temperature and was stirred for 2 h. Subsequently, the homogenous solution was cooled to 0 °C and diluted with CH_2Cl_2 (1.0 ml). To the resulting solution was added a solution of β-lactone **86** (0.304 g, 0.870 mmol) in CH_2Cl_2 (2.3 mL) *via* syringe. The reaction mixture was then warmed to ambient temperature and allowed to stir for 2 h. Cooled the reaction mixture once again to 0 °C and quenched slowly with aqueous phosphate buffer (pH = 7). The resulting biphasic mixture was warmed to ambient temperature and stirred vigorously for 1 h. The layers of the mixture were then separated and the aqueous extracted with EtOAc (3x). The combined organic extracts were washed with brine (1x), dried over Na_2SO_4, filtered and concentrated *in vacuo*.

To a solution of the crude residue in CH_2Cl_2 (2.0 mL) at ambient temperature was added 2,6-lutidine (0.30 mL, 2.60 mmol). Subsequently, the reaction mixture was cooled to –78 °C

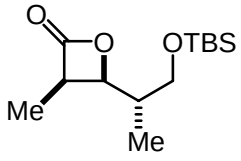
and TBSOTf (0.50 mL, 2.17 mmol) was added in a dropwise fashion. The resulting solution was warmed to 0 °C and stirred for 2 h. The reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$, the layers separated and the organic layer washed with 1.0 M aqueous $NaHSO_4$ (1x). The combined aqueous layers were then extracted with EtOAc (3x) and the combined organic extracts dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude oil was purified by silica gel chromatography (6:1/hexanes:ethyl acetate) to provide 0.431 g (88% over 2 steps) of silyl ether **101**: $[\alpha]_D$ = –22.8 (*c* 1.0, $CHCl_3$); IR (thin film) 2955, 2929, 2885, 2856, 1667, 1471, 1254, 1092 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.34-7.28 (m, 5H), 4.48 (s, 2 H), 4.03 (ddd, *J* = 10.0, 4.0, 2.4 Hz, 1H), 3.98 (dd, *J* = 6.9, 4.5 Hz, 1H), 3.59 (s, 3H), 3.61-3.49 (m, 2H), 3.15 (s, 3H), 2.98-2.91 (m, 1H), 1.92-1.80 (m, 2H), 1.74-1.62 (m, 1H), 1.11 (d, *J* = 6.9 Hz, 3H), 0.93-0.89 (m, 12H), 0.87 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H), 0.01 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.8, 138.4, 128.1 (2C), 127.6 (2C), 127.3, 74.3, 72.9, 68.7, 67.8, 60.5, 43.4, 39.2, 32.0, 31.6, 26.1 (3C), 25.8 (3C), 18.2, 17.9, 11.6, 10.4, –3.6, –4.1, –4.5, –5.0; ESI-MS HRMS calcd for $C_{30}H_{57}NNaO_5Si_2$ $(M+Na)^+$: 590.3673, found 590.3616.



(2*R*,3*S*,4*S*,5*S*)-6-Formyl-3,5-bis-(*tert*-butyldimethylsilyloxy)-*N*-methoxy-*N*,2,4-trimethylhexanamide (99): To a solution of benzyl ether **101** (0.353 g, 0.620 mmol) in ethyl acetate (2.2 mL) at ambient temperature was added Pd/C (10 % activated, 0.084 g). The atmosphere was evacuated and refilled with $H_{2(g)}$ (3x) and then vigorously stirred at ambient temperature for 2h. The heterogeneous reaction mixture was filtered over a plug of celite and the filtrate concentrated *in vacuo*.

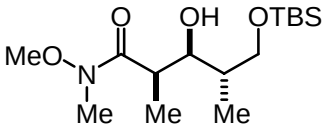
To a solution of the crude residue in CH_2Cl_2 (6.2 mL) was added $NaHCO_3$ (0.157 g, 1.87 mmol). Subsequently, cooled the reaction mixture to 0 °C and added DMP (0.304 g, 0.716

mmol). The resulting mixture was warmed to ambient temperature and stirred for 2h. The reaction was quenched by addition of hexanes (6 mL) and filtered over a plug of florisil which was washed with a solution of 4:1/hexanes:EtOAc. Concentrated the filtrate *in vacuo* and purified the crude residue by silica gel chromatography (4:1/hexanes:ethyl acetate) to provide 0.260 g (88% over 2 steps) of aldehyde **99**: $[\alpha]_D$ = –22.3 (*c* 1.1, $CHCl_3$); IR (thin film) 2955, 2930, 2886, 2857, 1728, 1667, 1471, 1463, 1254, 1087, 1055, 1022, 1004 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.80 (app t, *J* = 2.3 Hz, 1H), 4.54 (dt, *J* = 8.1, 3.8 Hz, 1 H), 3.93 (app t, *J* = 5.8 Hz, 1H), 3.72 (s, 3H), 3.18 (s, 3H), 3.00 (app p, *J* = 6.7 Hz, 1H), 2.61-2.46 (m, 2H), 1.95 (dp, *J* = 11.4, 6.9 Hz, 1H), 1.14 (d, *J* = 7.0 Hz, 3H), 0.94-0.92 (m, 12H), 0.85 (s, 9H), 0.06 (s, 6H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.4, 175.6, 74.8, 67.3, 60.8, 46.5, 43.2, 39.3, 31.9, 26.1 (3C), 25.5 (3C), 18.2, 17.7, 12.9, 10.6, –3.4, –4.1, –4.5, –5.1; EI-MS *m/z* 460 $(M–Me)^+$, 418, 300, 286, 260, 197; HRMS calcd for $C_{23}H_{49}NO_5Si_2$ $(M–Me)^+$: 460.2915, found 460.2906.



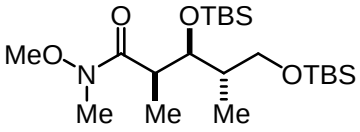
(3*R*,4*S*)-4-((*S*)-1-(*tert*-Butyldimethylsilyloxy)propan-2-yl)-3-methyloxetan-2-one (89): A flame-dried round bottom flask was charged with TMS-quinine (63 mg, 0.160 mmol) and LiI (0.428 g, 3.20 mmol). To the mixture of solids was sequentially added CH_2Cl_2 (4.0 mL), Et_2O (0.4 mL) and $^iPr_2NEt$ (0.70 mL, 4.00 mmol). The resulting mixture was stirred at ambient temperature for 5 min then cooled to −78 °C. To the reaction mixture was added aldehyde **102** (0.323 g, 1.60 mmol) followed by dropwise addition of a solution of propionyl chloride (0.28 mL, 3.20 mmol) in CH_2Cl_2 (0.8 mL) over 1.5 h. The heterogeneous reaction mixture was stirred vigorously overnight at –78 °C. The reaction mixture was quenched with ether and the white precipitate was filtered off over a plug

of silica which was eluted with ether. The filtrate was then concentrated *in vacuo* and the resulting residue purified *via* silica gel chromatography (19:1/hexanes:ethyl acetate) to yield 0.318 g (77%) of β-lactone **89**: Diastereomeric ratio determined by crude ^{1}H NMR (300 MHz, δ 4.42 ppm) determined the title compound was produced as a single diastereomer; $[\alpha]_D = -25.1$ (*c* 1.0, $CHCl_3$); IR (thin film) 2955, 2930, 2889, 2857, 1828, 1471, 1255, 1117 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.42 (dd, *J* = 11.0, 6.3 Hz, 1H), 3.77 (qd, *J* = 7.7, 6.6 Hz, 1H), 3.73-3.65 (m, 2H), 1.97 (qdd, *J* = 6.7, 4.4, 3.4 Hz, 1H), 1.35 (d, *J* = 7.7 Hz, 3H), 0.97 (d, *J* = 6.7 Hz, 3H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.4, 75.8, 63.5, 46.6, 35.7, 25.7(3C), 18.1, 12.2, 8.4, –5.6, –5.7; EI-MS *e/v* 243 $(M-Me)^+$, 201, 187, 171, 157, 145; HRMS calcd for $C_{12}H_{23}O_3Si$ $(M-Me)^+$: 243.1416, found 243.1433.



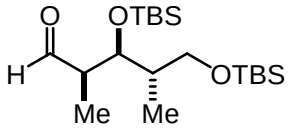
(2*R*,3*S*,4*S*)-5-(*tert*-Butyldimethylsilyloxy)-3-hydroxy-*N*-methoxy-*N*,2,4-trimethylpentanamide (103): To a 0 °C mixture of *N*,*O*-dimethylhydroxylamine hydrochloride (2.76 g, 28.3 mmol) in CH_2Cl_2 (50 mL) was added dimethylaluminum chloride (28.2 mL, 28.2 mmol, 1.0 M in hexanes) in a slow, dropwise fashion. The resulting solution was allowed to warm to ambient temperature and stirred for 2 h. Subsequently, the homogenous solution was cooled to –30 °C and diluted with CH_2Cl_2 (30 ml). To the resulting solution was added a solution of β-lactone **89** (3.65 g, 14.1 mmol) in CH_2Cl_2 (20 mL) *via* syringe. The reaction mixture was then allowed to stir at –30 °C until complete consumption of the starting material (monitored by TLC). Cooled the reaction mixture once again to 0 °C and quenched slowly with aqueous phosphate buffer (pH = 7). The resulting biphasic mixture was warmed to ambient temperature and stirred vigorously for 1 h. The layers of the mixture were then separated and the aqueous extracted with EtOAc (3x). The combined

organic extracts were washed with brine (1x), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude oil was purified by silica gel chromatography (3:1/hexanes:ethyl acetate) to provide 4.09 g (91%) of amide **103**: $[\alpha]_D = -8.1$ (*c* 1.1, $CHCl_3$); IR (thin film) 3468, 2957, 2857, 1639, 1462, 1254, 1089 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.00 (d, *J* = 3.1 Hz, 1H), 3.80-3.67 (m, 3H), 3.72 (s, 3H), 3.20 (s, 3H), 3.08-3.04 (m, 1H), 1.78-1.67 (m, 1H), 1.20 (d, *J* = 7.0 Hz, 3H), 0.96 (d, *J* = 6.9 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.3, 73.2, 64.9, 60.8, 37.0, 36.2, 31.4, 25.4 (3C), 17.6, 13.3, 10.2, –6.0 (2C); EI-MS *m/z* 304 $(M-Me)^+$, 285, 262, 232, 201, 145; HRMS calcd for $C_{14}H_{30}NO_4Si$ $(M-Me)^+$: 304.1944, found 304.1946.

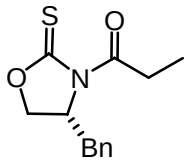


(2*R*,3*S*,4*S*)-3,5-Bis(*tert*-butyldimethylsilyloxy)-*N*-methoxy-*N*,2,4-trimethylpentanamide (88): To a solution of alcohol **103** (1.60 g, 5.01 mmol) in CH_2Cl_2 (11.6 mL) at ambient temperature was added 2,6-lutidine (0.94 mL, 8.01 mmol). Subsequently, the reaction mixture was cooled to –78 °C and TBSOTf (1.50 mL, 6.51 mmol) was added in a dropwise fashion. The resulting solution was warmed to 0 °C and stirred for 2 h. The reaction mixture was then quenched by addition of saturated aqueous $NaHCO_3$. The layers were separated and the organic layer washed with 1.0 M aqueous $NaHSO_4$ (1x). The combined aqueous layers were then extracted with CH_2Cl_2 (3x) and the combined organic extracts dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude oil was purified by silica gel chromatography (7:1/hexanes:ethyl acetate) to provide 2.12 g (98%) of silyl ether **88**: $[\alpha]_D = -11.0$ (*c* 1.5, $CHCl_3$); IR (thin film) 2956, 2929, 2885, 2857, 1668, 1471, 1255, 1086 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.95 (dd, *J* = 7.0, 4.0 Hz, 1H), 3.72 (dd, *J* = 9.9, 4.5 Hz, 1H), 3.70 (s, 3H), 3.32 (dd, *J* = 9.8, 8.5 Hz, 1H), 3.17 (s, 3H), 3.17-3.07 (m, 1H), 1.76 (tqd, *J*

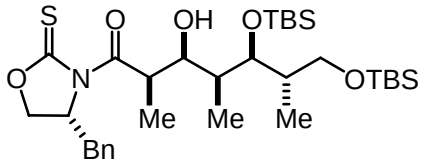
= 8.3, 6.9, 4.3 Hz, 1H), 1.12 (d, *J* = 6.9 Hz, 3H), 0.98 (d, *J* = 6.9 Hz, 3H), 0.91 (s, 9H), 0.89 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.0, 74.3, 64.4, 60.5, 41.3, 38.3, 31.7, 25.7 (3C), 25.5 (3C), 17.8, 17.7, 13.8, 13.2, –4.4, –4.6, –5.8 (2C); EI-MS *m/z* 418 $(M–Me)^+$, 376, 260, 204, 185; HRMS calcd for $C_{20}H_{44}NO_4Si_2$ $(M–Me)^+$: 418.2809, found 418.2801.



(2*R*,3*S*,4*S*)-3,5-Bis(*tert*-butyldimethylsilyloxy)-2,4-dimethylpentanal (104): To a –78 °C solution of amide **88** (2.12 g, 4.89 mmol) in THF (47 mL) was added $^{i}Bu_2AlH$ (9.80 mL, 9.78 mmol, 1.0 M in hexanes) in a slow, dropwise fashion. The resulting solution was maintained at –78 °C for 2 h after which saturated aqueous Rochelle's salts (30 mL) was added. The biphasic mixture was allowed to warm to ambient temperature and stirred vigorously for 1 h. The layers were separated and the aqueous layer extracted with ether (3x). The combined organic extracts were washed with brine (1x), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude oil was purified by silica gel chromatography (24:1/hexanes:ethyl acetate) to provide 1.83 g (quantitative) of aldehyde **104**: $[\alpha]_D$ = –36.5 (*c* 1.26, $CHCl_3$); IR (thin film) 2956, 2929, 2884, 2857, 1729, 1472, 1254, 1091 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.72 (s, 1H), 4.24 (dd, *J* = 6.6, 3.1 Hz, 1H), 3.61 (dd, *J* = 10.0, 5.6 Hz, 1H), 3.52 (dd, *J* = 10.0, 5.9 Hz, 1H), 2.50 (qd, *J* = 6.9, 3.1 Hz, 1H), 1.87 (app. sept., *J* = 6.7 Hz, 1H), 1.11 (d, *J* = 6.9 Hz, 3H), 0.93-0.91 (m, 12H), 0.87 (s, 9H), 0.08 (s, 3H), 0.05 (s, 6H), 0.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.9, 71.4, 64.4, 49.5, 40.3, 25.7 (3C), 25.6 (3C), 18.0 (2C), 13.4, 7.6, –4.4, –4.5, –5.5, –5.7; EI-MS *m/z* 317 $(M–^{t}Bu)^+$, 259, 201, 185; HRMS calcd for $C_{15}H_{33}O_3Si_2$ $(M–^{t}Bu)^+$:317.1968, found 317.1981.

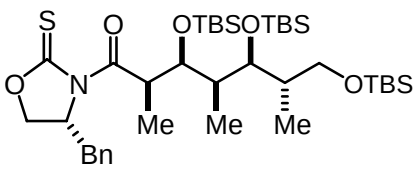


1-((*R*)-4-Benzyl-2-thioxooxazolidin-3-yl)propan-1-one: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37-7.20 (m, 5H), 4.95 (ddt, *J* = 10.2, 6.7, 3.2 Hz, 1H), 4.40-4.26 (m, 2H), 3.43 (dq, *J* = 18.0, 7.3 Hz, 1H), 3.35-3.20 (m, 2H), 2.78 (dd, *J* = 13.2, 10.1 Hz, 1H), 1.24 (app t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 184.9, 174.2, 134.9, 129.0 (2C), 128.5 (2C), 126.9, 70.0, 59.4, 37.1, 31.0, 8.1.



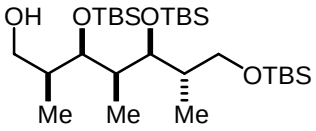
(2*R*,3*S*,4*S*,5*S*,6*S*)-1-((*R*)-4-Benzyl-2-thioxooxazolidin-3-yl)-5,7-bis(*tert*-butyldimethylsilyloxy)-3-hydroxy-2,4,6-trimethylheptan-1-one (105): To a solution of oxazolidinethione (0.082 g, 0.330 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C was added $TiCl_4$ (0.330 mL, 0.330 mmol, 1.0 M in CH_2Cl_2) and the resulting yellow, homogenous solution was allowed to stir at 0 °C for 5 minutes. Subsequently, to the reaction mixture was added (–)-sparteine (0.190 mL, 0.825 mmol) in a dropwise fashion and the resulting mixture was stirred at 0 °C for an additional 20 minutes. To the deep-red reaction mixture was added a solution of aldehyde **104** (0.110 g, 0.300 mmol) in CH_2Cl_2 (1.0 mL) and the resulting reaction mixture allowed to stir at 0 °C for 1h. The reaction was quenched by addition of half-saturated aqueous NH_4Cl, the layers separated and the aqueous layer extracted with CH_2Cl_2 (3x). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude oil was purified by silica gel chromatography (10:1/hexanes:ethyl acetate) to provide 0.171 g (91%) of alcohol **105**: Diastereomeric ratio determined by crude ^{1}H NMR (300 MHz) determined the title compound was produced as a single diastereomer; $[\alpha]_D$ = –39.2 (*c* 1.1, $CHCl_3$); IR (thin film) 3534, 2955, 2929, 2884, 2856, 1678, 1497, 1368, 1318, 1087 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38-7.21 (m, 5H), 4.96 (ddt, *J* = 10.2, 6.0, 3.2 Hz, 1H), 4.79 (qd, *J* = 6.9, 4.9 Hz, 1H), 4.36-4.23 (m, 2H), 3.98 (ddd, *J* = 6.2,

4.8, 2.7 Hz, 1H), 3.76 (dd, *J* = 6.2, 2.8 Hz, 1H), 3.66 (dd, *J* = 9.9, 5.8 Hz, 1H), 3.49 (dd, *J* = 10.0, 6.3 Hz, 1H), 3.24 (dd, *J* = 13.2, 3.5 Hz, 1H), 3.24 (d, *J* = 2.7 Hz, 1H), 2.76 (dd, *J* = 13.3, 10.1 Hz, 1H), 1.91 (app sept., *J* = 6.5 Hz, 1H), 1.77 (pd, *J* = 6.7, 3.0 Hz, 1H), 1.35 (d, *J* = 6.9 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.93-0.90 (m, 21H), 0.08 (s, 3H), 0.07 (s, 6H), 0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 184.1, 178.0, 135.0, 129.0 (2C), 128.6 (2C), 127.0, 73.9, 73.0, 69.8, 64.8, 59.4, 40.1, 39.8, 37.7, 37.1, 25.7 (3C), 25.6 (3C), 18.0, 17.9, 13.7, 11.9, 9.1, –4.2, –4.3, –5.6, –5.7; ESI-MS HRMS calcd for $C_{32}H_{57}NNaO_5SSi_2$ $(M+Na)^+$: 646.3394, found 646.3387.

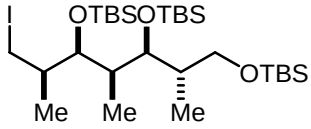


(2*R*,3*S*,4*R*,5*S*,6*S*)-1-((*R*)-4-Benzyl-2-thioxooxazolidin-3-yl)-3,5,7-tris(*tert*-butyldimethylsilyloxy)-2,4,6-trimethylheptan-1-one (106): To a solution of alcohol **105** (2.05 g, 3.29 mmol) in CH_2Cl_2 (12.2 mL) at ambient temperature was added 2,6-lutidine (0.61 mL, 5.26 mmol). Subsequently, the reaction mixture was cooled to −78 °C and TBSOTf (1.00 mL, 4.28 mmol) was added in a dropwise fashion. The resulting solution was warmed to 0 °C and stirred for 2 h. The reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$, the layers separated and the organic layer washed with 1.0 M aqueous $NaHSO_4$ (1x). The combined aqueous layers were then extracted with CH_2Cl_2 (3x) and the combined organic extracts dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude oil was purified by silica gel chromatography (15:1/hexanes:ethyl acetate) to provide 2.30 g (95%) of silyl ether **106**: $[\alpha]_D$ = –58.3 (*c* 0.5, $CHCl_3$); IR (thin film) 2927, 2856, 1693, 1471, 1361, 1252, 1186, 1027 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34-7.23 (m, 5H), 4.95-4.85 (m, 2H), 4.34-4.24 (m, 2H), 4.14 (dd, *J* = 6.9, 3.0 Hz, 1H), 3.74 (dd, *J* = 9.7, 4.0 Hz, 1H), 3.57 (dd, *J* = 7.9, 2.4 Hz, 1H), 3.40 (app t, *J* = 9.5 Hz, 1H), 3.23 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.73 (dd, *J* = 13.1, 10.3 Hz, 1H), 2.06-1.93 (m, 1H),

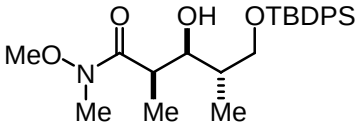
1.70-1.60 (m, 1H), 1.30 (d, J = 6.9 Hz, 3H), 1.03 (d, J = 6.9 Hz, 3H), 0.95 (s, 9H), 0.92-0.90 (m, 21H), 0.13 (s, 6H), 0.07 (s, 9H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 184.4, 176.6, 135.0, 129.2 (2C), 128.8 (2C), 127.2, 75.9, 73.6, 69.7, 63.8, 59.9, 42.3, 41.6, 38.8, 37.4, 26.2 (6C), 25.9 (3C), 18.5, 18.4, 18.2, 15.9, 14.7, 11.5, –3.2, –3.3, –3.5, –3.6, –5.3 (2C); ESI-MS HRMS calcd for $C_{38}H_{71}NNaO_5SSi_3$ $(M+Na)^+$: 760.4258, found 760.4280.



(2*S*,3*R*,4*S*,5*S*,6*S*)-3,5,7-Tris(*tert*-butyldimethylsilyloxy)-2,4,6-trimethylheptan-1-ol (107): To a solution of oxazolidinethione **106** (0.190 g, 0.260 mmol) in THF (1.4 mL) at 0 °C was added MeOH (21 μL, 0.52 mmol). Subsequently, $LiBH_4$ (0.26 mL, 0.52 mmol, 2.0 M in THF) was added to the reaction mixture in a dropwise fashion. The resulting solution was stirred at 0 °C for 0.5 h, after which it was warmed to ambient temperature and stirred an additional 2h. The reaction was quenched by the addition of saturated aqueous Rochelle's salts and stirred vigorously at ambient temperature for 1h. The layers were then separated and the aqueous layer extracted with ether (3x). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude oil was purified by silica gel chromatography (20:1/hexanes:ethyl acetate) to provide 0.119 g (83%) of alcohol **107**: $[\alpha]_D$ = –2.0 (*c* 0.5, $CHCl_3$); IR (thin film) 3456 (br s), 2956, 2885, 2857, 1472, 1463, 1255, 1092, 1028 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.73-3.57 (m, 4H), 3.49 (dt, J = 10.8, 5.4 Hz, 1H), 3.40 (dd, J = 9.7, 6.8 Hz, 1H), 2.00-1.78 (m, 3H), 1.65 (app t, J = 4.2 Hz, 1H), 0.97 (d, J = 5.9 Hz, 3H), 0.92 (s, 18H), 0.90 (s, 9H), 0.08-0.04 (m, 18H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 74.1, 73.7, 66.0, 65.1, 41.0, 39.5, 38.3, 26.2 (3C), 26.1 (3C), 25.9 (3C), 18.4 (2C), 18.2, 14.7, 12.1, 10.7, –3.3, –3.5, –3.8, –3.9, –5.3, –5.4; EI-MS *m/z* 491 $(M-{}^t\!Bu)^+$, 401, 359, 317, 243; HRMS calcd for $C_{24}H_{55}O_4Si_3$ $(M-{}^t\!Bu)^+$: 491.3408, found 491.3416.

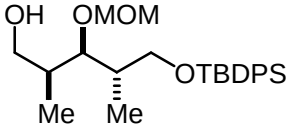


1-(((2*S*,3*S*,4*R*,5*S*,6*R*)-3,5-Bis(*tert*-butyldimethylsilyloxy)-7-iodo-2,4,6-trimethylheptyloxy)methyl)benzene (85): To a solution of PPh_3 (0.054g, 0.206 mmol) in CH_2Cl_2 (0.7 mL) at 0 °C was added I_2 (0.052 g, 0.206 mmol). The heterogeneous solution was allowed to stir at 0 °C for 10 minutes. Subsequently, a solution of alcohol **107** (0.075g, 0.137 mmol) and imidazole (0.027 g, 0.400 mmol) in CH_2Cl_2 (1.0 mL) was cannulated into the reaction mixture and the resulting mixture was warmed to ambient temperature and stirred for 6 hours. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$, the layers separated and the aqueous extracted with CH_2Cl_2 (3x). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude oil was purified by silica gel chromatography (50:1/hexanes:ethyl acetate) to provide 0.064 g (71%) of iodide **85**: $[\alpha]_D$ = +4.3 (*c* 1.6, $CHCl_3$); IR (thin film) 2956, 2929, 2885, 2857, 1471, 1256, 1089, 1028 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.65-3.62 (m, 2H), 3.59 (dd, *J* = 10.0, 6.3, Hz 1H), 3.41 (dd, *J* = 10.0, 6.5 Hz, 1H), 3.23 (dd, *J* = 9.5, 6.3 Hz, 1H), 3.10 (dd, *J* = 9.4, 7.8 Hz, 1H), 2.15-2.00 (m, 1H), 1.87-1.76 (m, 2H), 0.98 (d, *J* = 6.7 Hz, 3H), 0.95-0.88 (m, 33H), 0.11 (s, 3H), 0.09 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 76.0, 73.6, 65.1, 41.6, 40.8, 39.0, 26.3 (3C), 26.2 (3C), 26.0 (3C), 18.6, 18.5, 18.3, 14.2, 14.1, 14.0, 12.4, –3.2, –3.3, –3.4, –3.8, –5.2, –5.3; EI-MS *m/z* 643 $(M–Me)^+$, 601, 511, 469, 429, 395, 358, 341; HRMS calcd for $C_{24}H_{54}IO_3Si_3$ $(M–^tBu)^+$: 601.2425, found 601.2443.



(2*R*,3*S*,4*S*)-5-(*tert*-Butyldiphenylsilyloxy)-3-hydroxy-*N*-methoxy-*N*,2,4-trimethylpentanamide (110): To a 0 °C mixture of *N*,*O*-dimethylhydroxylamine hydrochloride (3.74 g, 38.4 mmol) in CH_2Cl_2 (68 mL) was added

dimethylaluminum chloride (38.4 mL, 38.4 mmol, 1.0 M in hexanes) in a slow, dropwise fashion. The resulting solution was allowed to warm to ambient temperature and stirred for 1.5 h. Subsequently, the homogenous solution was cooled to 0 °C and diluted with CH_2Cl_2 (38 ml). To the resulting solution was added a solution of β-lactone **109** (7.34 g, 19.2 mmol) in CH_2Cl_2 (30 mL) *via* syringe. The reaction mixture was then allowed to warm to ambient temperature and was stirred for 2 hours. Cooled the reaction mixture once again to 0 °C and quenched slowly with aqueous phosphate buffer (pH = 7). The resulting biphasic mixture was warmed to ambient temperature, the layers separated and the aqueous extracted with CH_2Cl_2 (3x). The combined organic extracts were washed with brine (1x), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude oil was purified by silica gel chromatography (3:1/hexanes:ethyl acetate) to provide 7.16 g (84%) of amide **110**: $[\alpha]_D$ = +2.3 (*c* 0.6, $CHCl_3$); IR (thin film) 3462, 2961, 2932, 1637, 1472, 1112, 1068 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.71-7.67 (m, 4H), 7.46-7.35 (m, 6H), 4.01 (d, *J* = 2.8 Hz, 1H), 3.89 (dd, *J* = 9.8, 4.8 Hz, 1H), 3.83-3.80 (m, 1H), 3.77 (dd, *J* = 9.8, 3.7 Hz, 1H), 3.67 (s, 3H), 3.19 (s, 3H), 3.12- 3.01 (m, 1H), 1.84-1.72 (m, 1H), 1.19 (d, *J* = 7.0 Hz, 3H), 1.07 (s, 9H), 1.02 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.8, 135.4 (4C), 133.3 (2C), 129.4 (2C), 127.4 (4C), 73.3, 65.9, 61.1, 37.4, 36.3, 31.8, 26.7 (3C), 19.1, 13.8, 10.2; EI-MS *m/z* 444 $(M)^+$, 386, 356, 308, 269, 239.



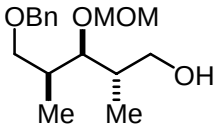
(2*S*,3*R*,4*S*)-5-(*tert*-Butyldiphenylsilyloxy)-3-(methoxymethoxy)-2,4-dimethylpentan-1-ol (111): To a solution alcohol **110** (2.43 g, 5.49 mmol) in $^iPr_2NEt$ (22 mL) at ambient temperature was added TBAI (0.202 g, 0.549 mmol). Subsequently, added freshly distilled MOMCl (2.00 mL, 27.5 mmol) and allowed the reaction mixture to stir at ambient temperature for 3 hours. After this time, another portion of MOMCl

(2.00 mL, 27.5 mmol) was added and the resulting reaction mixture allowed to stir for an additional 4 hours. Cooled the reaction mixture to 0 °C and quenched by slow addition of 1.0 M aqueous HCl. Separated the layers and extracted the aqueous with CH_2Cl_2 (3x). Washed the combined organic extracts with brine (1x), dried over Na_2SO_4, filtered and concentrated *in vacuo*.

To a −78 °C solution of the crude oil in THF (72 mL) was added $^{i}Bu_2AlH$ (7.70 mL, 7.66 mmol, 1.0 M in hexanes) in a slow, dropwise fashion. The resulting solution was maintained at −78 °C for 2 h after which saturated aqueous Rochelle's salts (30 mL) was added. The biphasic mixture was allowed to warm to ambient temperature and was stirred vigorously for 1 h. The layers were separated and the aqueous layer extracted with ether (3x). The combined organic extracts were washed with brine (1x), dried over Na_2SO_4, filtered and concentrated *in vacuo*.

To a −78 °C solution of the crude oil in THF (72 mL) was added $^{i}Bu_2AlH$ (7.70 mL, 7.66 mmol, 1.0 M in hexanes) in a slow, dropwise fashion. The resulting solution was maintained at −78 °C for 2 h after which saturated aqueous Rochelle's salts (30 mL) was added. The biphasic mixture was allowed to warm to ambient temperature and was stirred vigorously for 1 h. The layers were separated and the aqueous layer extracted with EtOAc (3x). The combined organic extracts were washed with brine (1x), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude oil was purified by silica gel chromatography (5:1/hexanes:ethyl acetate) to provide 1.55 g (66% over 3 steps) of alcohol **111**: $[\alpha]_D$ = +53.4 (*c* 1.1, $CHCl_3$); IR (thin film) 3440, 3070, 2961, 2931, 2882, 2857, 1471, 1144, 1112, 1032 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.69-7.62 (m, 4H), 7.47- 7.35 (m, 6H), 4.69 (d, *J* = 6.5 Hz, 1 H), 4.44 (d, *J* = 6.5 Hz, 1H), 3.77-3.63 (m, 3H), 3.50 (dd, *J* = 8.7, 6.9 Hz, 2H), 3.35 (s, 3H), 3.19 (dd, *J* = 7.6, 6.5 Hz, 1H), 1.99-1.86 (m, 1H), 1.86-1.75 (m, 1H), 1.10 (s, 9H), 0.95 (d, *J* = 6.9 Hz, 3H), 0.75 (d, *J* = 6.9Hz, 3H);

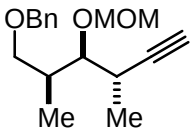
^{13}C NMR (75 MHz, $CDCl_3$): δ 135.4 (2C), 135.3 (2C), 133.3, 133.2, 129.3 (2C), 127.3 (2C), 127.2 (2C), 98.2, 79.7, 65.3, 64.4, 55.4, 38.1, 36.4, 26.7 (3C), 18.9, 14.0, 9.3; ESI-MS HRMS calcd for $C_{25}H_{38}NaO_4Si$ $(M+Na)^+$: 453.2437, found 453.2395.



(2*S*,3*S*,4*S*)-5-(Benzyloxy)-3-(methoxymethoxy)-2,4-dimethylpentan-1-ol (112): To a suspension of NaH (0.170 g, 7.10 mmol, 60% dispersion) in THF (12 mL) was added TBAI (0.175 g, 0.473 mmol) followed by a solution of alcohol **111** (2.04 g, 4.73 mmol) in THF (12 mL). After stirring at ambient temperature for 0.5 h, BnBr (0.730 mL, 6.15 mmol) was then added and the reaction mixture was allowed to stir at ambient temperature overnight. The reaction was quenched by the addition of water, the layers were separated and the aqueous layer extracted with EtOAc (3x). The combined organic extracts were washed with brine (1x), dried over Na_2SO_4, filtered and concentrated *in vacuo*.

To a solution of the crude residue in THF (25 mL) at 0 °C was added TBAF (14 mL, 14.2 mmol, 1.0 M in THF). The reaction mixture was warmed to ambient temperature and stirred for 3 hours. Subsequently, the reaction was quenched with saturated aqueous $NaHCO_3$, the layers separated and the aqueous extracted with EtOAc (3x). The combined organic extracts were washed with brine (1x), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude oil was purified by silica gel chromatography (3:1/hexanes:ethyl acetate→1:1/hexanes:ethyl acetate) to provide 1.01 g (82% over two steps) of alcohol **112**: $[\alpha]_D = -33.5$ (*c* 1.06, $CHCl_3$); IR (thin film) 3456, 2965, 2933, 1454, 1209, 1140, 1093 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62-7.28 (m, 5H), 4.68 (d, *J* = 6.3 Hz, 1 H), 4.60 (d, *J* = 6.3 Hz, 1H), 4.50 (s, 2H), 3.84 (ddd, *J* = 11.4, 6.5, 3.5 Hz, 1H), 3.69 (dd, *J* = 9.3, 2.3 Hz, 1H), 3.52 (ddd, *J* = 11.3, 7.2, 4.1 Hz, 1H), 3.41 (s, 3H), 3.41-3.34 (m, 2H), 2.97 (app t, *J* = 6.6, 6.6 Hz, 1H), 2.06 (m, 1H), 1.85 (m, 1H), 0.95 (d, *J* = 7.0

Hz, 3H), 0.86 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.8, 127.8 (2C), 127.1 (2C), 127.0, 98.0, 80.6, 72.3 (2C), 64.2, 55.3, 37.2, 34.5, 13.8, 9.7; ESI-MS HRMS calcd for $C_{16}H_{26}NaO_4$ $(M+Na)^+$: 305.1729, found 305.1701.

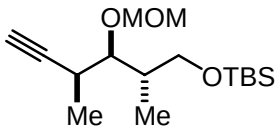


1-(((2*S*,3*S*,4*S*)-3-(Methoxymethoxy)-2,4-dimethylhex-5-ynyloxy)methyl)-benzene (108): To a solution of alcohol **112** (0.167 g, 0.600 mmol) in CH_2Cl_2 (4.0 mL) was added NMO (0.112 g, 0.950 mmol) followed by powdered 4 Å molecular sieves (0.297 g). The mixture was allowed to stir at ambient temperature for 15 minutes, after which TPAP (0.011 g, 3.0 x 10^{-5} mol) was added in one portion. The resulting reaction mixture was stirred for 2 h at ambient temperature and subsequently filtered through a plug of florisil which was washed with a solution of 4:1/hexanes:ethyl acetate. The filtrate was concentrated *in vacuo*.

To a solution of diisopropylamine (0.110 mL, 0.780 mmol) in THF (2.0 mL) at 0 °C was added ^{n}BuLi (0.450 mL, 0.715 mmol, 1.6 M in hexanes) in a dropwise fashion. The homogenous solution was allowed to stir at 0 °C for 10 minutes before it was cooled down to −78 °C. To the reaction mixture was added $TMSCHN_2$ (0.360 mL, 0.715 mmol, 2.0 M in Et_2O) and the resulting solution was stirred at −78 °C for 0.5 h. Subsequently, a solution of the crude residue in THF (3.2 mL) was then added and the resulting reaction mixture was allowed to warm to ambient temperature overnight. The reaction was quenched with water, the layers separated and the aqueous extracted with Et_2O (3x). The combined organic extracts were washed with water (1x) and brine (1x), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude oil was purified by silica gel chromatography (24:1/hexanes:ethyl acetate) to provide 0.124 g (75% over two steps) of alkyne **108**: $[\alpha]_D$ = +26.6 (*c* 1.1, $CHCl_3$); IR (thin film) 3290, 2935, 1454, 1364, 1150, 1091, 1034 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36-7.27 (m, 5H), 4.88 (d, J = 6.8

Hz, 1 H), 4.81 (d, *J* = 6.8 Hz, 1H), 4.59 (d, *J* = 3.3 Hz, 2H), 3.66 (dd, *J* = 5.9, 4.3 Hz, 1H), 3.58 (dd, *J* = 9.2, 6.7 Hz, 1H), 3.49 (dd, *J* = 9.1, 5.9 Hz, 1H), 3.48 (s, 3H), 2.83 (dqd, *J* = 9.5, 7.0, 2.5 Hz, 1H), 2.18-2.08 (m, 2H), 1.23 (d, *J* = 7.1 Hz, 3H), 0.99 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.3, 128.1 (2C), 127.4 (2C), 127.3, 98.0, 86.4, 81.8, 72.8, 72.7, 69.6, 55.8, 35.9, 29.5, 17.7, 11.7; EI-MS *m/z* 231 $(M–CH_2OMe)^+$, 223, 193, 173, 161; HRMS calcd for $C_{15}H_{19}O_2$ $(M–CH_2OMe)^+$: 231.1385, found 231.1390.

General procedure for addition of alkyne 108 into aldehyde 99: To a solution of alkyne **108** (3.2 equivs.) in the designated solvent at −78 °C was added ^{n}BuLi (3.0 equivs.) and the resulting reaction mixture allowed to stir at −78 °C for 30 minutes. The lithium alkynylide solution was then transferred *via* cannula into a −78 °C solution of either LiBr or $MgBr_2{\cdot}OEt_2$ (3.2 equivs.) in the designated solvent and the resulting reaction mixture stirred at −78 °C for 1 hour. Subsequently, a precooled (−78 °C) solution of aldehyde **99** (1 equiv.) in the designated solvent was cannulated into the reaction mixture and the resulting reaction mixture allowed to stir an additional 0.5 h at −78 °C. Quenched the reaction by addition of saturated aqueous NH_4Cl and separated the layers. Extracted the aqueous with EtOAc (3x) then dried the combined organic extracts over Na_2SO_4, filtered and concentrated *in vacuo*. Excess alkyne **108** was recovered by silica gel chromatography (4:1/hexanes:ethyl acetate) and the two diastereomeric alkyne addition products were collected and combined. The diastereomeric ratio was determined by HPLC analysis (column Zorbax, eluent 5.0:95.0/^{i}PrOH:hexanes, flow rate 1mL/min; T_r: 7.010 min (**113**, desired), 11.622 min (undesired)).

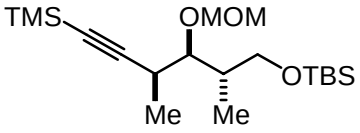


((2*S*,3*R*,4*S*)-3-(Methoxymethoxy)-2,4-dimethylhex-5-ynyloxy)*tert*-butyldimethylsilane (116): To a 0 °C solution of alcohol **103** (3.78 g, 11.8 mmol) in CH_2Cl_2 (95 mL) was added sequentially $^{i}Pr_2NEt$ (41.3 mL, 0.237 mol), TBAI (0.437 g, 1.18 mmol) and MOMCl (9.00 mL, 0.118 mol). The reaction mixture was covered from light and stirred for 18 hours at ambient temperature. Quenched the reaction mixture by addition of saturated aqueous $NaHCO_3$, separated the layers and washed the organic layer with 1.0 M aqueous $NaHSO_4$. The combined aqueous layers were extracted with ether (3x) and the combined organic extracts were washed with brine (1x), dried over Na_2SO_4, filtered and concentrated *in vacuo*.

To a −78 °C solution of the crude oil in THF (116 mL) was added $^{i}Bu_2AlH$ (17.8 mL, 17.8 mmol, 1.0 M in hexanes) in a slow, dropwise fashion. The resulting solution was maintained at −78 °C for 2 h after which saturated aqueous Rochelle's salts (60 mL) was added. The biphasic mixture was allowed to warm to ambient temperature and stirred vigorously for 1 h. The layers were separated and the aqueous layer extracted with ether (3x). The combined organic extracts were washed with brine (1x), dried over Na_2SO_4, filtered and concentrated *in vacuo*.

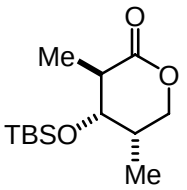
To a solution of diisopropylamine (2.20 mL, 15.4 mmol) in THF (39 mL) at 0 °C was added $^{n}BuLi$ (8.90 mL, 14.2 mmol, 1.6 M in hexanes) in a dropwise fashion. The homogenous solution was allowed to stir at 0 °C for 10 mins. before it was cooled down to −78 °C. To the reaction mixture was then added $TMSCHN_2$ (7.10 mL, 14.2 mmol, 2.0 M in Et_2O) and the resulting solution was stirred at −78 °C for 0.5h. Subsequently, a solution of the crude residue in THF (64 mL) was then added and the resulting reaction mixture was allowed to warm to ambient temperature overnight. The reaction was quenched with water, the layers were separated and the aqueous extracted with Et_2O (3x). The combined organic extracts were washed with water (1x)

and brine (1x), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude oil was purified by silica gel chromatography (30:1/hexanes:ethyl acetate) to provide 2.53 g (71% over 3 steps) of alkyne **116**: $[\alpha]_D = -32.0$ (*c* 0.8, $CHCl_3$); IR (thin film) 3312, 2955, 2929, 2884, 2857, 1471, 1090, 1034 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.79 (d, *J* = 6.5 Hz, 1 H), 4.73 (d, *J* = 6.5 Hz, 1H), 3.79 (dd, *J* = 9.8, 4.5 Hz, 1H), 3.57 (dd, *J* = 9.8, 6.7 Hz, 1H), 3.48 (app t, *J* = 5.6 Hz, 1H), 3.43 (s, 3H), 2.82-2.74 (m, 1H), 2.09 (d, *J* = 2.5 Hz, 1H), 2.01 (dp, *J* = 13.5, 6.8 Hz, 1H), 1.22 (d, *J* = 7.0 Hz, 3H), 0.98 (d, *J* = 6.9 Hz, 3H), 0.91 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 98.2, 87.4, 83.1, 70.0, 64.9, 56.3, 38.8, 29.0, 26.2 (3C), 18.5, 16.5, 14.7, 5.2 (2C); EI-MS *m/z* 269 $(M-OMe)^+$, 255, 247, 213, 201, 145; HRMS calcd for $C_{15}H_{29}O_2Si$ $(M-OMe)^+$: 269.1937, found 269.1954.

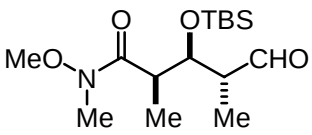


((3*S*,4*R*,5*S*)-5-((*tert*-Butyldimethylsilyloxy)methyl)-4-(methoxymethoxy)-3-methylhex-1-ynyl)trimethylsilane (117): To a solution of alkyne **116** (1.02 g, 3.39 mmol) in THF (5.1 mL) at –78 °C was added ^{n}BuLi (2.40 mL, 3.73 mmol, 1.6 M in hexanes) in a dropwise fashion. The reaction mixture was stirred at –78 °C for 1 h. Freshly distilled TMSCl (0.52 mL, 4.07 mmol) was then added and the reaction mixture was warmed to ambient temperature and stirred for 2 hours. The reaction was quenched by the addition of water, the layers were separated and the aqueous extracted with ether (3x). The combined organic extracts were washed with brine (1x), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude oil was purified by silica gel chromatography (30:1/hexanes:ethyl acetate) to provide 1.00 g (80%) of alkyne **117**: $[\alpha]_D = -33.8$ (*c* 0.7, $CHCl_3$); IR (thin film) 2957, 2929, 2885, 2857, 2167, 1471, 1250, 1090, 1034 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.80 (d, *J* = 6.5 Hz, 1 H), 4.71 (d, *J* = 6.5 Hz, 1H), 3.81 (dd, *J* = 9.8, 4.6 Hz, 1H), 3.54

(dd, J = 9.7, 7.0 Hz, 1H), 3.49-3.42 (m, 4H), 2.76 (dq, J = 13.7, 6.9 Hz, 1H), 2.05-1.92 (m, 1H), 1.20 (d, J = 6.9 Hz, 3H), 0.96 (d, J = 6.9 Hz, 3H), 0.91 (s, 9H), 0.15 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 110.1, 98.1, 85.6, 82.9, 64.8, 56.2, 38.7, 29.7, 25.9 (3C), 18.3, 16.2, 14.3, 0.06 (3C), −5.4 (2C); EI-MS *m/z* 341 $(M–OMe)^+$, 315, 295, 283, 247, 201; HRMS calcd for $C_{15}H_{31}O_3Si_2$ $(M–^tBu)^+$: 315.1812, found 315.1814.



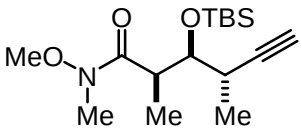
(3*R*,4*S*,5*S*)-Tetrahydro-4-*tert*-butyldimethylsilyloxy-3,5-dimethylpyran-2-one (121): To a −78 ºC solution of amide **88** (1.06 g, 2.44 mmol) in MeOH (25 mL) was added conc. HCl (3.0 mL) in a dropwise fashion. The reaction mixture was warmed to 0 ºC and stirred for 2 hours. After that time, the reaction mixture was slowly quenched with saturated aqueous $NaHCO_3$. The layers were separated and the aqueous extracted with CH_2Cl_2 (3x). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude oil was purified by silica gel chromatography (9:1/hexanes:ethyl acetate) to provide 0.530 g (84%) of δ-lactone **121**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.26 (app t, J = 10.8 Hz, 1H), 4.13 (dd, J = 10.9, 4.9 Hz, 1H), 3.70 (app t, J = 3.0 Hz, 1H), 2.63 (qd, J = 7.6, 3.8 Hz, 1H), 2.20 (dqdd, J = 9.4, 6.8, 4.8, 2.5 Hz, 1H), 1.31 (d, J = 7.6 Hz, 3H), 0.98 (d, J = 6.8 Hz, 3H), 0.91 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.4, 72.6, 69.2, 42.8, 29.5, 24.9 (3C), 17.1, 15.2, 11.1, −5.5, −5.6.



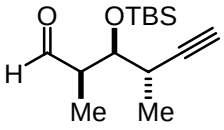
(2*R*,3*S*,4*R*)-4-Formyl-3-*tert*-butyldimethylsilyloxy-*N*-methoxy-*N*,2-dimethylpentanamide (123): To a solution of lactone **121** (0.100 g, 0.390 mmol) in THF (1.3 mL) at ambient temperature was added (MeO)NHMe·HCl (0.059 g, 0.600 mmol) in one portion. Cooled the resulting heterogeneous mixture to −15 ºC and added a

solution of ^{i}PrMgCl (0.580 mL, 1.16 mmol, 2.0 M in THF) in a slow, dropwise fashion. After complete addition, the reaction mixture was stirred an additional 1.5 h at −15 ºC before being diluted with ether and quenched with a solution of H_2O (1 mL) and saturated aqueous NH_4Cl (1 mL). Warmed the biphasic mixture to ambient temperature and stirred until all the salts dissolved. The layers were then separated and the aqueous extracted with Et_2O (3x). The combined organic extracts were washed with brine (1x), dried over Na_2SO_4, filtered and concentrated *in vacuo*.

To a solution of crude residue in CH_2Cl_2 (0.4 mL) at 0 ºC was added TEA (0.22 mL) followed by DMSO (0.8 mL). Subsequently added SO_3·pyr (0.185 g, 1.16 mmol) in one portion and stirred at 0 ºC for 1.5 h. Diluted the reaction mixture with ether and then quenched by dropwise addition of 1.0 M aqueous $NaHSO_4$ (1.4 mL) and H_2O (0.4 mL) afterwards stirring the resulting biphasic mixture at 0 ºC for 15 minutes. The layers were separated and the aqueous layer extracted with ether (3x). The combined organic extracts were washed with a solution of saturated aqueous $NaHCO_3$ (2 mL) and H_2O (2 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude oil was purified by silica gel chromatography (6:1/hexanes:ethyl acetate) to provide 0.097 g (79% over 2 steps) of aldehyde **123**: m.p. 41-43 ºC; $[\alpha]_D$ = −64.2 (*c* 0.7, $CHCl_3$); IR (thin film) 2936, 2885, 2857, 1723, 1655, 1462, 1256, 1101, 1077, 1044 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.72 (d, *J* = 1.6 Hz, 1H), 4.26 (dd, *J* = 9.0, 2.6 Hz, 1H), 3.72 (s, 3H), 3.20-3.14 (m, 1H), 3.14 (s, 3H), 2.53-2.45 (m, 1H), 1.20 (d, *J* = 6.9 Hz, 3H), 1.14 (d, *J* = 7.0 Hz, 3H), 0.91 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.4, 174.6, 74.2, 60.7, 51.3, 38.6, 31.2, 25.2 (3C), 17.4, 14.4, 9.2, –4.9, –5.0; ESI-MS HRMS calcd for $C_{15}H_{31}NNaO_4Si$ $(M+Na)^{+}$: 340.1920, found 340.1933.

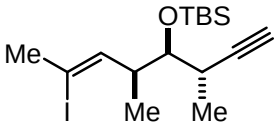


(2*R*,3*S*,4*S*)-3-*tert*-Butyldimethylsilyloxy-*N*-methoxy-*N*,2,4-trimethylhex-5-ynamide (124): To a solution of aldehyde **123** (1.50 g, 4.74 mmol) and Ohira's reagent (2.00 g, 10.4 mmol) in ^{i}PrOH (66 mL) at 0 ºC was added Cs_2CO_3 (4.63 g, 14.2 mmol) in one portion. The resulting mixture was stirred at 0 ºC for 1 hour then warmed to ambient temperature and stirred an additional 11 hours. Subsequently cooled the reaction mixture to 0 ºC and quenched by addition of H_2O. The layers were separated and the aqueous layer extracted with EtOAc (3x). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude oil was purified by silica gel chromatography (8:1/hexanes:ethyl acetate) to provide 1.46 g (97%) of alkyne **124**: $[\alpha]_D = -29.7$ (*c* 1.0, $CHCl_3$); IR (thin film) 3310, 3250, 2936, 2894, 2856, 1655, 1461, 1254, 1074 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.93 (dd, *J* = 8.8, 2.4 Hz, 1H), 3.77 (s, 3H), 3.30-3.20 (m, 1H), 3.18 (s, 3H), 2.62 (qdd, *J* = 7.1, 6.5, 2.6 Hz, 1H), 2.04 (d, *J* = 2.5 Hz, 1H), 1.24 (d, *J* = 7.1 Hz, 3H), 1.17 (d, *J* = 7.0 Hz, 3H), 0.95 (s, 9H), 0.11 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.1, 85.3, 74.9, 70.0, 61.0, 39.5, 31.7, 31.3, 25.6 (3C), 17.9, 17.4, 14.8, –3.9, –4.4; *mass spectroscopy data pending.*



(2*R*,3*S*,4*S*)-3-*tert*-Butyldimethylsilyloxy-2,4-dimethylhex-5-ynal (125): To a −78 °C solution of amide **124** (0.314 g, 1.00 mmol) in THF (7.4 mL) was added $^{i}Bu_2AlH$ (1.40 mL, 1.40 mmol, 1.0 M in hexanes) in a slow, dropwise fashion. The resulting solution was maintained at −78 °C for 2 h after which saturated aqueous Rochelle's salts was added. The biphasic mixture was allowed to warm to ambient temperature and stirred vigorously for 1 h. The layers were separated and the aqueous layer extracted with ether (3x). The combined organics were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude

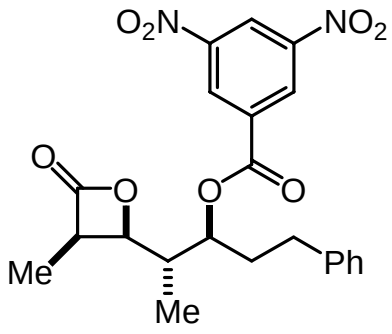
oil was purified by silica gel chromatography (50:1/hexanes:ethyl acetate) to provide 0.201 g (79%) of aldehyde **125**: $[\alpha]_D$ = –48.8 (*c* 0.7, $CHCl_3$); IR (thin film) 3311, 2955, 2931, 1724, 1472, 1254, 1089, 1045 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.90 (d, *J* = 1.0 Hz, 1H), 4.10 (app t, *J* = 4.6 Hz, 1H), 2.75-2.60 (m, 2H), 2.11 (d, *J* = 2.5 Hz, 1H), 1.23 (d, *J* = 7.1 Hz, 3H), 1.14 (d, *J* = 7.1 Hz, 3H), 0.91 (s, 9H), 0.12 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.7, 85.4, 73.6, 71.7, 50.4, 31.0, 25.7 (3C), 18.1, 16.9, 9.4, –4.4, –4.5; *mass spectroscopy data pending*.



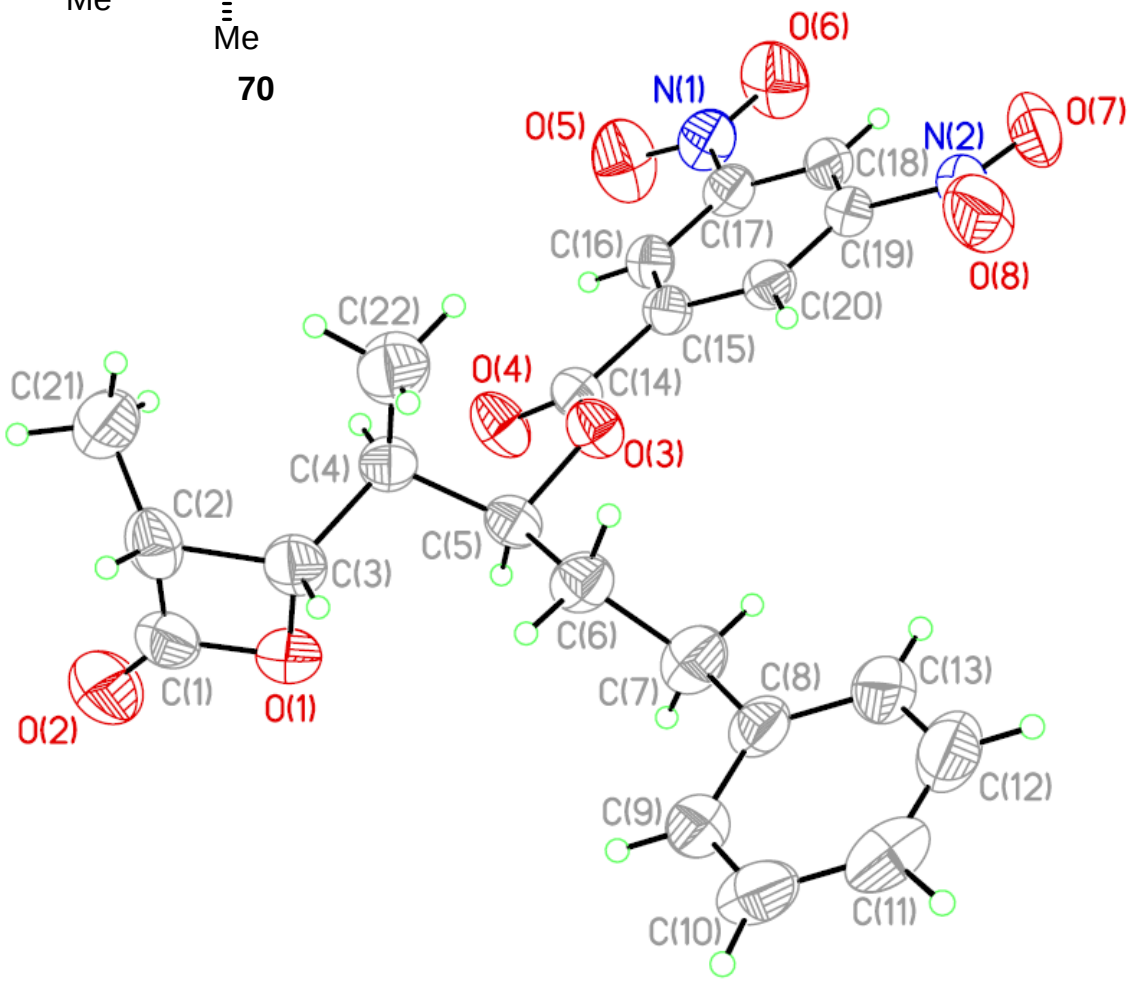
((*Z*,3*S*,4*R*,5*S*)-7-iodo-3,5-dimethyloct-6-en-1-yn-4-yloxy)*tert*-butyldimethylsilane (84): A suspension of ethyltriphenylphosphonium iodide (0.594 g, 1.42 mmol) in THF (6.0 mL) at ambient temperature was treated dropwise with NaHMDS (1.50 mL, 1.50 mmol, 1.0 M in THF). The reaction mixture immediately turned orange. The resulting mixture was stirred at ambient temperature for 0.5 h before being added over a 1 h time period to a solution of iodine (0.360 g, 1.42 mmol) in THF (12 mL) at –78 °C. The resulting phosphonium salt **126** precipitated as a brown solid. After stirring the suspension at –78 °C for 15 minutes, NaHMDS (1.40 mL, 1.42 mmol, 1.0 M in THF) was added in a dropwise fashion and the reaction mixture gradually cleared and became red. The homogenous solution was stirred at –78 °C for 0.5 h after which a precooled (–78 °C) solution of aldehyde **125** (0.201 g, 0.790 mmol) in THF (2.0 mL) was added. The resulting reaction mixture was stirred at –78 °C for 1.5 h before it was warmed to –20 °C and quenched with saturated aqueous NH_4Cl (65 μL). The beige suspension was partially concentrated to 18 mL of distillate then diluted with pentane (6 mL). The mixture was partially concentrated again to 6 mL, then filtered and the filtercake washed with pentanes. Concentrated the filtrate *in vacuo* and purified the residue *via*

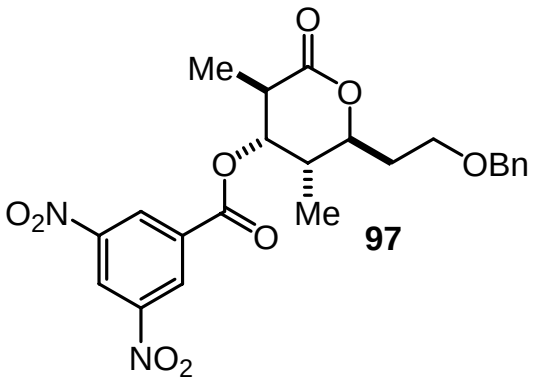
column chromatography (100:1/hexanes:ethyl acetate) to yield 65 mg (21%) of iodide **84** as an inseparable mixture of olefin isomers. Diastereomeric ratio determined by crude ^{1}H NMR (300 MHz): 90.9% (δ 3.62 ppm) : 9.1 % (δ 3.41 ppm) / (*Z*)-vinyl iodide **84** (title compound) : (*E*)-vinyl iodide. Characterization data for (*Z*)-vinyl iodide **84** (title compound): $[\alpha]_D$ = +39.1 (*c* 1.0, $CHCl_3$); IR (thin film) 3310, 2956, 2929, 2856, 1471, 1252, 1025 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.42 (dd, *J* = 8.8, 1.4 Hz, 1H), 3.62 (app t, *J* = 5.6 Hz, 1H), 2.67-2.56 (m, 2H), 2.48 (d, *J* = 1.3 Hz, 3H), 2.08 (d, *J* = 2.6 Hz, 1H), 1.22 (d, *J* = 7.1 Hz, 3H), 0.99 (d, *J* = 6.7 Hz, 3H), 0.93 (s, 9H), 0.10 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.9, 99.4, 87.0, 70.3, 45.1, 33.6, 31.7, 30.3, 26.0 (3C), 18.3, 17.0, 14.9, –3.9, –4.0; *mass spectroscopy data pending*.

APPENDIX A

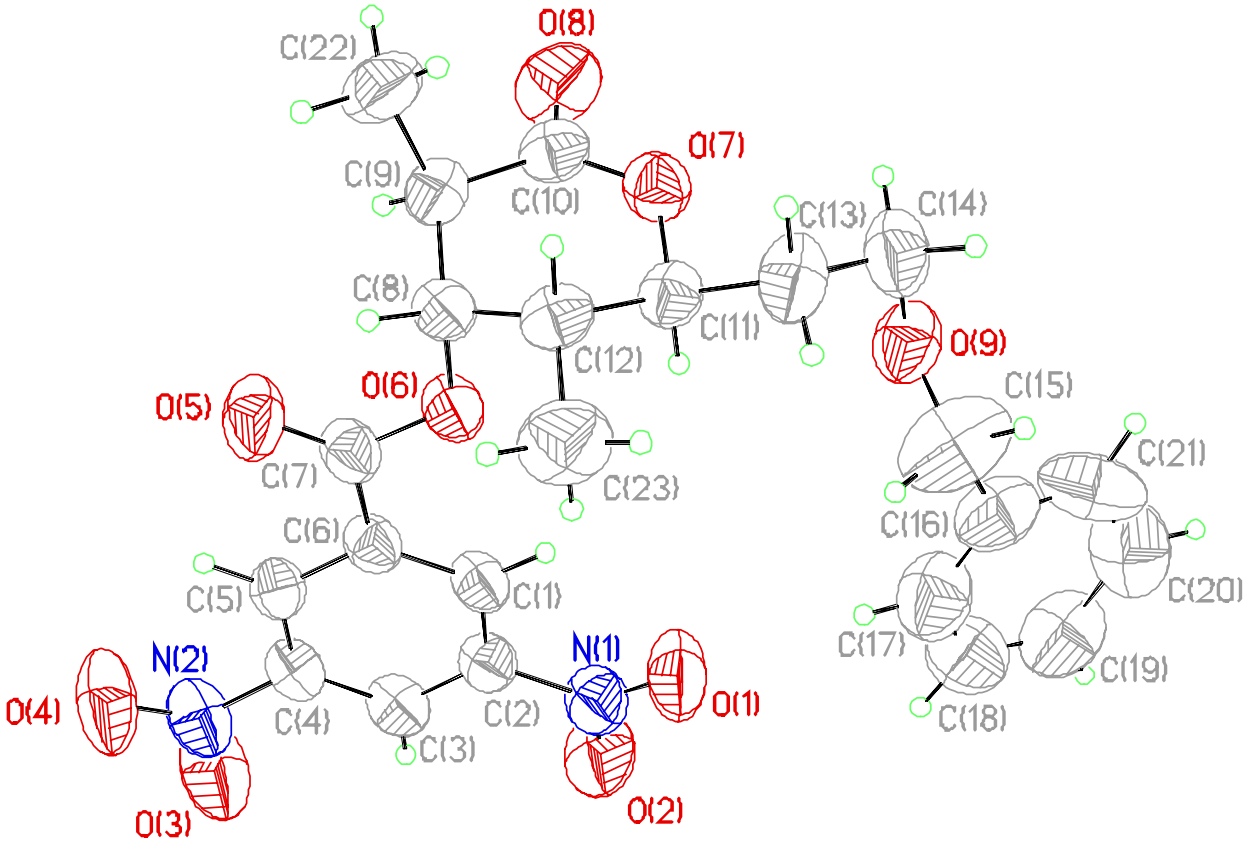


70




O
Me
O
O
OBn
O2N
Me
O
NO2

97


O(8)
C(22)
O(7)
C(9)
C(10)
C(13)
C(14)
C(8)
C(11)
C(12)
O(9)
O(6)
C(15)
O(5)
C(21)
C(7)
C(23)
C(16)
C(6)
C(20)
C(5)
C(1)
C(17)
N(2)
N(1)
C(19)
O(4)
C(4)
C(2)
O(1)
C(18)
C(3)
O(2)
O(3)

BIBLIOGRAPHY

[1] Banerji, A.; Majumder, P. L.; Chatterjee, A. G. *Phytochemistry* **1970**, *9*, 1491-1493.

[2] Linde, H. H. A. *Helv. Chim. Acta.* **1965**, *48*, 1822-1842.

[3] Thoison, O.; Guénard, D.; Sévenet, T.; Kan-Fan, C.; Quirion, J.-C.; Husson, H.-P.; Deverre, J.-R.; Chan, K. C.; Potier, P. *C. R. Acad. Sci. Paris II* **1987**, *304*, 157-160.

[4] Abraham, D. J.; Rosenstein, R. D. *Tetrahedron Lett.* **1972**, *13*, 909-912.

[5] De Silva, K. T.; Ratcliffe, A. H.; Smith, G. F.; Smith, G. N. *Tetrahedron Lett.* **1972**, *13*, 913-916.

[6] Lévy, J.; Soufyane, M.; Mirand, C.; de Maindreville, M. D.; Royer, D. *Tetrahedron: Asymm.* **1997**, *8*, 4127-4133.

[7] Goh, S. H.; Ali, A. R. M.; Wong, W. H. *Tetrahedron* **1989**, *45*, 7899-7920.

[8] (a) David, B.; Sévenet, T.; Morgat, M.; Guénard, D.; Moisand, A.; Tollon, Y.; Thoison, O.; Wright, M. *Cell Motil. Cytoskeleton* **1994**, *28*, 317-326. (b) Banwell, M.; Edwards, A.; Smith, J.; Hamel, E.; Verdier-Pinard, P. *J. Chem. Soc., Perkin Trans. 1*, **2000**, 1497-1499.

[9] Dupont, C.; Guénard, D.; Tchertanov, L.; Thoret, S.; Guéritte, F. *Biorg. Med. Chem.* **1999**, *7*, 2961-2969.

[10] (a) David, B.; Sévenet, T.; Thoison, O.; Awang, K.; Païs, M.; Wright, M.; Guénard, D. *Biorg. Med. Chem. Lett.* **1997**, *7*, 2155-2158. (b) Pascal, C.; Dubois, J.; Guénard, D.; Tchertanov, L.; Thoret, S.; Guéritte, F. *Tetrahedron* **1998**, *54*, 14737-14756. (c) Dupont, C.; Guénard, D.; Thal, C.; Thoret, S.; Guéritte, F. *Tetrahedron Lett.* **2000**, *41*, 5853-5856. (d) Alazard, J.-P.; Millet-Paillusson, C.; Boyé, O.; Guénard, D.; Chiaroni, A.; Riche, C.; Thal, C. *Biorg. Med. Chem. Lett.* **1991**, *1*, 725-728. (e) Pascal, C.; Dubois, J.; Guénard, D.; Guéritte, F. *J. Org. Chem.* **1998**, *63*, 6414-6420.

[11] Ratcliffe, A. H.; Smith, G. F.; Smith, G. N. *Tetrahedron Lett.* **1973**, *14*, 5179-5184.

[12] Johnson, J. A.; Sames, D. *J. Am. Chem. Soc.* **2000**, *122*, 6321-6322.

[13] Johnson, J. A.; Li, N.; Sames, D. *J. Am. Chem. Soc.* **2002**, *124*, 6900-6903.

[14] Magnus, P.; Rainey, T. *Tetrahedron* **2001**, *57*, 8647-8651.

[15] Bowie, A. L.; Hughes, C. C.; Trauner, D. *Org. Lett.* **2005**, *7(23)*, 5207-5209.

[16] (a) Nelson, S. G.; Peelen, T. J.; Wan, Z. *J. Am. Chem. Soc*. **1999**, *121*, 9742-9743. (b) Nelson S. G.; Kim, B.-K.; Peelen, T. J. *J. Am. Chem. Soc.* **2000**, *122*, 9318-9319. (c) Nelson S. G.; Zhu, C.; Shen, X. *J. Am. Chem. Soc.* **2004**, *126*, 14-15. (d) Nelson, S. G.; Cheung, W. S.; Kassick, A. J.; Hilfiker, M. A. *J. Am. Chem. Soc.* **2002**, *124*, 13654-13655.

[17] Wan, Z.; Nelson, S. G. *J. Am. Chem. Soc.* **2000**, *122*, 10470-10471.

[18] (a) Wasserman, H. H.; Han, W. T. *Tetrahedron Lett.* **1984**, *25*, 3743-3746. (b) Wasserman, H. H.; Cook, J. D.; Fukuyama, J. M.; Rotello, V. M. *Tetrahedron Lett.* **1989**, *30*, 1721-1724. (c) Wasserman, H.H.; Lombardo, L. J. *Tetrahedron Lett.* **1989**, *30*, 1725-1728. (d) Wasserman, H. H.; Fukuyama, J.; Murugesan, N.; van Duzer, J.; Lombardo, L.; Rotello, V.; McCarthy, K. *J. Am. Chem. Soc.* **1989**, *111*, 371-372. (e) Wasserman, H. H.; Rotello, V. M. *J. Org. Chem.* **1989**, *54*, 2785-2786. (f) Wasserman, H. H.; Cook, J. D.; Vu, C. B. *Tetrahedron Lett.* **1990**, *31*, 4945-4948. (g) Wasserman, H. H.; Kuo, G.-H. *Tetrahedron* **1992**, *48*, 7071-7082. (h) Wasserman, H. H.; Vu, C. B.; Cook, J. D. *Tetrahedron* **1992**, *48*, 2101-2112. (i) Wasserman, H. H.; Ennis, D. S.; Blum, C. A.; Rotello, V. M. *Tetrahedron Lett.* **1992**, *33*, 6003-6006. (j) Wasserman, H. H.; Blum, C. A. *Tetrahedron Lett.* **1994**, *35*, 9787-9790. (k) Wasserman, H. H.; Baldino, C. M.; Coats, S. J. *J. Org. Chem.* **1995**, *60*, 8231-8235.

[19] This ylide is commercially available but can also be made easily on large scale (25g-30g, 97% yield); Cooke, Jr., M. P.; Burman, D. L. *J. Org. Chem.* **1982**, *47*, 4955-4963.

[20] ^{1}H NMR data for crude pyrrolone **26** can be found in the experimental section.

[21] Wan, Z. *Ph. D. Thesis, University of Pittsburgh* **2001**, 121.

[22] The Grignard reagent produced for bromide **20** seemed to be short-lived. Even immediate use of the prepared Grignard reagent after all starting bromide was consumed (as monitored by TLC) gave only 50% of allenic acid **27**. Considerable amounts of protonated Grignard reagent, as well as some Wurtz-coupled product, were always observed.

[23] Zipp, G. G. Unpublished results.

[24] (a) Smissman, E. E; Voldeng, A. N. J. Org. Chem. **1964**, 29, 3161-3165. (b) Kochhar, K. S.; Pinnick, H. W. J. Org. Chem. **1984**, 49, 3222-3224.

[25] Kochhar, K. S.; Carson, H. J.; Clouser, K. A.; Elling, J. W.; Gramens, L. A.; Parry, J. L.; Sherman, H. L.; Braat, K.; Pinnick, H. W. Tetrahedron Lett. **1984**, 25, 1871-1874.

[26] Laffan, D. D. P.; Bänziger, M.; Duc, L.; Evans, A.; McGarrity, J. F.; Meul, T. Helv. Chem. Acta **1992**, 75, 892-900.

[27] Based on observations made from storage, the methyl ester allene seemed to have a slower rate of decomposition than the corresponding β-allenic acid.

[28] Felix, A. M.; Heimer, E. P.; Lambros, T. J.; Tzougraki, C.; Meienhofer, J. *J. Org Chem* **1978**, *43*, 4194-4196.

[29] Characterized by ^{1}H NMR, LRMS and HRMS data.

[30] (a) Kalinin, A. V.; Reed, M. A.; Norman, B. H.; Snieckus, V. *J. Org. Chem.* **2003**, *68*, 5992-5999. (b) Kiso, Y.; Ukawa, K.; Nakamura, S.; Ito, K.; Akita, T. *Chem. Pharm. Bull.* **1980**, *28*, 673-676. (c) Matteson, D. S.; Man, H.-W.; Ho, O. C. *J. Am. Chem. Soc.* **1996**, *118*, 4560-4566. (d) Node, M.; Kodama, S.; Hamashima, Y.; Baba, T.; Hamamichi, N.; Nishide, K. *Angew. Chem. Int. Ed.* **2001**, *40*, 3060-3062.

[31] Verified by crude ^{1}H NMR analysis.

[32] Received from G. Greg Zipp.

[33] (a) Hatanaka, Y.; Hiyama, T. *Synlett* **1991**, 845-853. (b) Mowery, M. E.; DeShong, P. *J. Org. Chem.* **1999**, *64*, 3266-3270. (c) Mowery, M. E.; DeShong, P. *Org. Lett.* **1999**, *1*, 2137-2140. (d) DeShong, P.; Handy, C. J.; Mowery, M. E. *Pure Appl. Chem.* **2000**, *72*, 1655-1658. (e) Manoso, A. S.; DeShong, P. *J. Org. Chem.* **2001**, *66*, 7449-7455. (f) Denmark, S. E.; Sweis, R. F. *Acc. Chem. Res.* **2002**, *35*, 835-846.

[34] ^{1}H NMR data for crude pyrrolone **50** can be found in the experimental section.

[35] (a) Tacke, R.; Wiesenberger, F.; Lopez-Mras, A.; Sperlich, J.; Mattern, G. *Z. Naturforsch* **1992**, *47b*, 1370-1376. (b) The *N*-Boc aniline starting material used in the production of **53** is commercially available.

[36] A combination of trials were run by Zuosheng Liu, G. Greg Zipp and the author of this document. The trials depicted in Scheme 12 were run by the author of this document.

[37] Still, W.C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2925.

[38] The β-lactone was opened via addition-elimination to the lactone carbonyl by benzylamine. The enantiomeric excess of the resulting amide was measured.

[39] (a) Defosseux, M.; Blanchard, N.; Meyer, C.; Cossy, J. *Tetrahedron* **2005**, *61*, 7632-7653. (b) Mochirian, P.; Cardinal-David, B.; Guérin, B.; Prévost, M.; Guidon, Y. *Tetrahedron Lett.* **2002**, *43*, 7067-7071.

[40] (a) Gijsen, H. J. M.; Wong, C.-H. *J. Am. Chem. Soc.* **1995**, *117*, 7585-7591. (b) Machajewski, T. D.; Wong, C.-H. *Angew. Chem. Int. Ed.* **2000**, *39*, 1352-1375.

[41] (a) Palomo, C.; Oiarbide, M.; García, J. M. *Chem. Eur. J.* **2002**, *8*, 36-44. (b) Palomo, C.; Oiarbide, M.; García, J. M. *Chem. Soc. Rev.* **2004**, *33*, 65-75.

[42] Alcaide, B.; Almendros, P. *Eur. J. Org. Chem.* **2002**, 1595-1601.

[43] Notz, W.; Tanaka, F.; Barbas III, C. F. *Acc. Chem. Res.* **2004**, *37*, 580-591.

[44] Northrup, A. B.; Macmillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798-6799.

[45] Zhu, C.; Shen, X.; Nelson, S. G. *J. Am. Chem. Soc.* **2004**, *126*, 5352-5353.

[46] The studies concerning model *syn*-aldehyde **57** were performed by Dr. Jeff Wallace and Dr. Cheng Zhu. The matched AAC reaction with aldehyde **57** where DMF was used as the cosolvent was performed by the author of this document (see Experimental).

[47] The absolute stereochemistry of masked polypropionate unit **63** was unambiguously proven *via* x-ray crystallography following derivatization.

[48] Kassick, A. J. *unpublished results.*

[49] The *anti*-aldehyde possessing a β-PMB ether was only synthesized for testing the protecting group effect and was not characterized.

[50] (a) Reetz, M. T.; Kesseler, K. Jung, A. *Tetrahedron* **1984**, *40*, 4327-4336. (b) Reetz, M. T.; Kesseler, K. *J. Chem. Soc., Chem. Commun.* **1984**, 1079-1080. (c) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322-4343.

[51] Additional aldehydes not presented here were synthesized and tested by Ms. Junping Zhao.

[52] Reaction with DMF that the author of this document performed.

[53] In trials where one of the trans β-lactone diastereomers could be seen, the distinctive ^{1}H NMR shift and HPLC retention time of that trans-diastereomer is δ 4.22 ppm and T_r = 8.955 min, respectively.

[54] Paterson, I.; Florence, G. J. *Eur. J. Org. Chem.* **2003**, 2193-2208.

[55] Arefolov, A.; Panek, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 5596-5603.

[56] (a) ter Haar, E.; Kowalski, R. J.; Hamel, E.; Lin, C. M.; Longley, R. E.; Gunasekera, S. P.; Rosenkranz, H. S.; Day, B. W. *Biochemistry* **1996**, *35*, 243-250. (b) Kowalski, R. J.; Giannakakou, P.; Gunasekera, S. P.; Longley, R. E.; Day, B. W.; Hamel, E. *Mol. Parmacol*. **1997**, *52*, 613-622. (c) Balachandran, R.; ter Haar, E.; Welsh, M. J.; Grant, S. C.; Day, B. W. *Anti-Cancr Drugs* **1998**, 9, 67-76.

[57] Paterson, I.; Lyothier, I. *J. Org. Chem*. **2005**, *70*, 5494-5507.

[58] Harried, S. S.; Lee, C. P; Yang, G.; Lee, T. I. H.; Myles, D. C. *J. Org. Chem.* **2003**, *68*, 6646-6660.

[59] Smith III, A. B.; Kaufman, M. D.; Beauchamp, T. J.; LaMarche, M. J.; Arimoto, H. *Org. Lett.* **1999**, *1*, 1823-1826.

[60] Boyall, D.; Frantz, D. E.; Carreira, E. M. *Org. Lett.* **2002**, *4*, 2605-2606.

[61] Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem.* **2001**, *66*, 894-902.

[62] (a) Gao, G.; Moore, D.; Xie, R.-G.; Pu, L. *Org. Lett.* **2002**, 4143-4146. (b) Pu, L. *Tetrahedron* **2003**, *59*, 9873-9886. (c) Li, X.-S.; Lu, G.; Kwok, W. H.; Chan, A. S. C. *J. Am. Chem. Soc.* **2002**, *124*, 12636-12637.

[63] Takita, R.; Yakura, K.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 13760-13761.

[64] Alcohol **113** was not purified or fully characterized, only crude ^{1}H NMR was used.

[65] When this route was attempted, amide **103** was the common intermediate. Upon failure of this route, the common intermediate became amide **88**.

[66] Chen, J.; Zhao, K. *Tetrahedron Lett.* **1994**, *35*, 2827-2828.

[67] Ghosh, A.; Bischoff, A.; Cappiello, J. *Eur. J. Org. Chem.* **2003**, 821-832.