Extension of ketene-mediated asymmetric methodology

Part 1: Expansion of the acyl halide-aldehyde cyclocondensation reaction (AAC) and its application in the approach to motuporin

Part 2: Development of a ketene-Claisen rearrangement

by

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Extension of ketene-mediated asymmetric methodology

Part 1: Expansion of the acyl halide-aldehyde cyclocondensation reaction (AAC) and its application to the total synthesis of motuporin

Part 2: Development of a ketene-Claisen rearrangement

Jeremy M. Raelin, M.S.

University of Pittsburgh, 2005

Ketenes are molecules containing a carbonyl group connected to an alkylidene group by way of a double bond (a π-bond). The electrophilic nature of ketenes at their center, sp-hybridized carbon atom is the origin of many of the chemical transformations available to these molecules. Previously in the Nelson laboratory, ketenes had been successfully employed in the acyl halide-aldehyde cyclocondensation (AAC) reaction. Both Lewis acid- and Lewis base-catalyzed AAC processes provide access to optically active 3,4-disubstituted-*syn*-2-oxetanones. The work described herein employs ketene in the Lewis base-catalyzed AAC reaction in an attempt to improve and expand the general utility of this reaction technology. This improved AAC methodology was then applied in the total synthesis of the natural product motuporin. Ketene was subsequently employed in the development of a novel ketene-Claisen rearrangement.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF EQUATIONS

LIST OF SCHEMES

PREFACE

Special thanks must be given to Dr. Scott G. Nelson for providing the opportunity to undertake these research projects. The members of the Nelson group, both past and present, are also thanked for innumerable discussions and advice. Finally, my committee members, Drs. Wipf and Wilcox, are thanked for advice and added input.

1.0 THE ACYL HALIDE-ALDEHYDE CYCLOCONDENSATION (AAC)

1.1 MOTUPORIN: AN INTRODUCTION

Motuporin (**1**) is a cyclic pentapeptide that was isolated from the marine sponge *Theonella swinhoei* Gray found in Papua New Guinea. The natural product is a protein phosphatase-1 (PP-1) inhibitor and cytotoxin. Through spectroscopic analysis and discretionary chemical degradation, the structure of motuporin was elucidated as shown in Figure 1.[1]

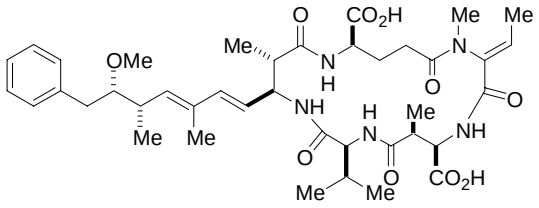

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Figure 1: The structure of motuporin (1).

Motuporin consists of two natural and three unnatural amino acids (Figure 2). The two common amino acids are D-glutamic acid (**2**) and L-valine (**3**). The three atypical amino acids are dehydrated threonine (**4**), β-methyl-D-aspartate (**5**), and (2*S*,3*3*,8*S*,9*S*,4*E*,6*E*)-3-amino-9-methoxy-2,6-8-trimethyl-10-phenyldeca-4,6-dienoic acid (Adda, **6**).[1] The latter, Adda (**6**), is also a building block in the structurally analogous nodularin and the microcystins.[2]

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[1] Dilip de Silva, E.; Williams, D. E.; Andersen, R. J.; Klix, H.; Holmes, F. B.; Allen, T. M. *Tetrahedron* **1992**, *33*, 1561-1564.

[2] (a) Sin, N.; Kallmerten, J. *Tetrahedron Lett.* **1996**, *37*, 5645-5648. (b) Gulledge, B. M.; Aggen, J. B.; Huang, H.-B.; Nairn, A. C.; Chamberlin, A. R. *Cur. Med. Chem.* **2002**, *9*, 1991-2003.

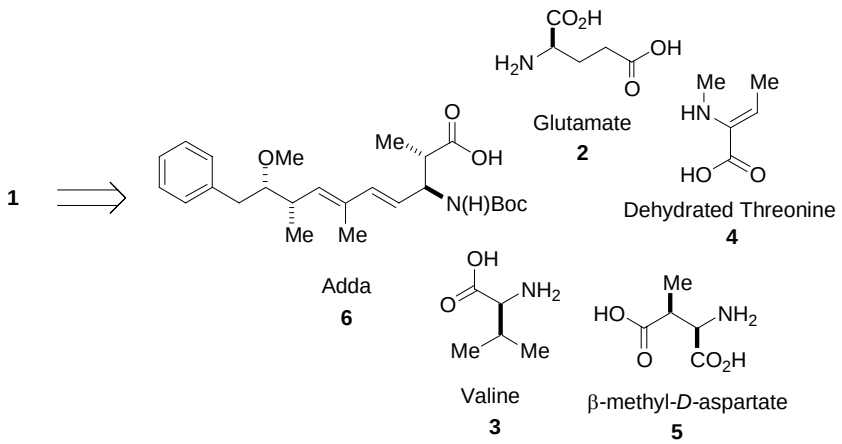


Figure 2: The five constituent amino acids of motuporin (1).

1.2 RETROSYNTHESIS

To date, there are four previously reported total syntheses of motuporin.[3] Although aspects of these syntheses are noteworthy, we sought to construct **1** in an expedient manner utilizing reaction technology previously developed in the Nelson laboratory. Cyclic pentapeptide **1** was dissected into three strategic optically active *syn*-3,4-disubstituted-(β)-lactones. These lactones (**8**, **13**, and **16**) serve as essential precursors to the two unnatural amino acids of motuporin (Figure 3).

[3] (a) Valentekovich, R. J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1995**, *117*, 9069-9070. (b) Hu, T.; Panek, J. S. *J. Org. Chem.* **1999**, *64*, 3000-3001. (c) Bauer, S. M.; Armstrong, R. W. *J. Am. Chem. Soc.* **1999**, *121*, 6355-6366. (d) Samy, R.; Kim, H. Y.; Bradu, M.; Toogood, P. L. *J. Org. Chem.* **1999**, *64*, 2711-2728.

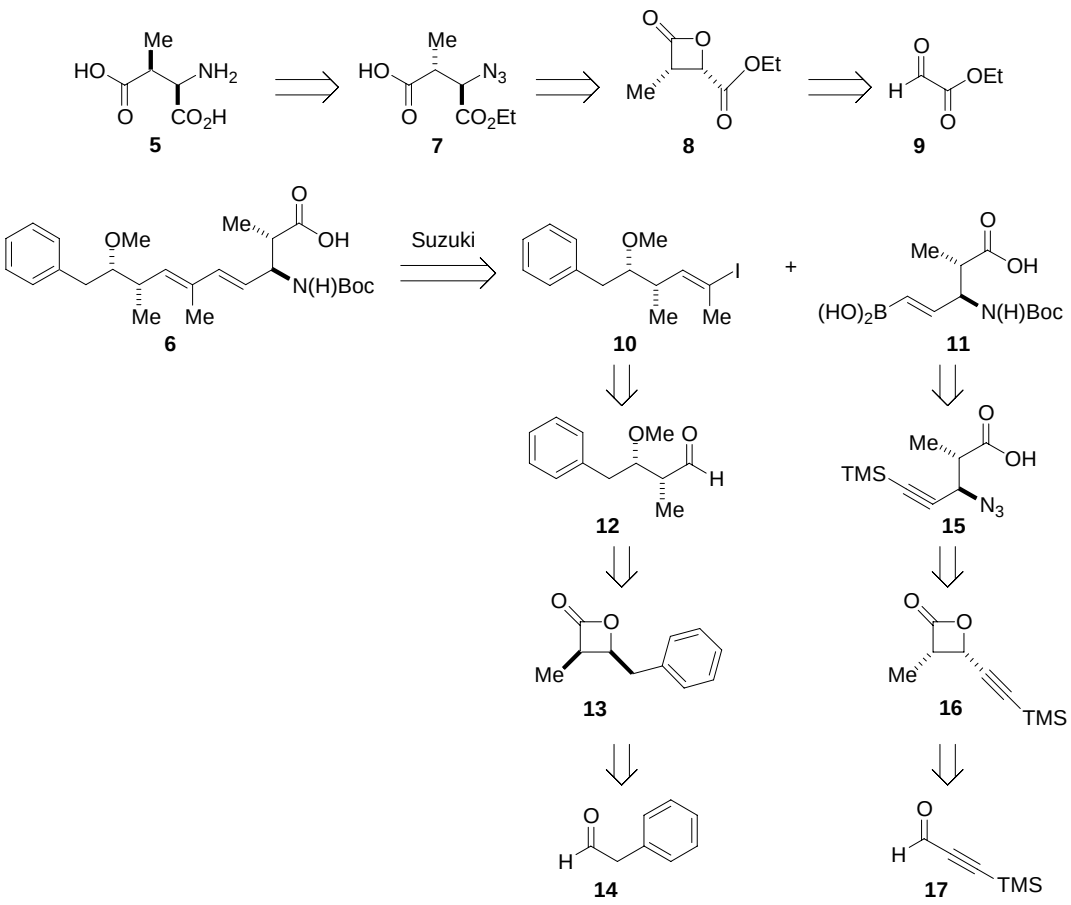


Figure 3: Retrosynthetic analysis of uncommon amino acids 5 and 6.

The unnatural β-methyl-D-aspartate (**5**) was envisaged as resulting from a three-step sequence. β-Amino acid **5** would be obtained from reduction of the azide moiety of β-azido acid **7**. Acid **7** would derive from S_N2 ring-opening of β-lactone **8** with sodium azide. Finally, lactone **8** was envisioned from a trimethylsilylquinidine (TMSQD)-catalyzed AAC reaction between ethyl glyoxylate (**9**) and propionyl chloride.

In spite of the innumerable syntheses of Adda, we envisioned an expedient and diversity-oriented synthesis of **6** utilizing AAC chemistry.[4] Adda would be obtained from Suzuki

[4] For example, refer to: (a) Pearson, C.; Rinehart, K. L.; Sugano, M.; Costerison, J. R. *Org. Lett.* **2000**, *2*, 2901-2903. (b) Beatty, M. F.; Jennings-White, C.; Avery, M. A. *J. Chem. Soc. Perkin Trans. 1* **1992**, 1637-1641. (c) Chakraborty, T. K.; Joshi, S. P. *Tetrahedron Lett.* **1990**, *31*, 2043-2046. (d) Cundy, D. J.; Donohue, A. C.;

precursors **10** and **11**. Vinyl iodide **10** was thought to be available from aldehyde **12** by way of a Corey-Fuchs reaction with ensuing reduction to the vinyl iodide promoted by Schwartz's reagent in the presence of iodine. Aldehyde **12** would be fabricated from Weinreb amine opening and ensuing DIBAL-H reduction of β-lactone **13**. This lactone could further be dissected to a trimethylsilylquinine (TMSQN)-catalyzed AAC reaction between phenylacetaldehyde (**14**) and propionyl chloride.

The complementary Suzuki fragment (**12**) was seen as the result of the reduction of β-azido acid **15** followed by silyl deprotection and subsequent hydroboration. Acid **15** would be produced from S_N2-ring opening of β-lactone **16**. Lactone **16** was to be fashioned from a TMSQD-catalyzed AAC reaction between 3-trimethylsilyl-2-propynal (**17**) and propionyl chloride.

Once both **5** and **6** were in hand, the synthesis of motuporin becomes straightforward. Carpino's activated conditions for peptide coupling could be employed to join all common and uncommon amino acids together.[5] In the end, a unique synthesis of **1** would be achieved utilizing the AAC reaction as the principle vehicle for asymmetric construction.

With retrosynthetic analysis of motuporin complete, the goal became the realization of the total synthesis. The immediate objective concentrated on the production of β-lactones **8**, **13**, and **16** by way of the alkaloid-catalyzed AAC reaction. It was theorized that, once fabrication of these optically active 2-oxetanones was achieved, motuporin could be synthesized in a relatively expedient manner.

McCarthy, T. D. *J. Chem Soc. Perkin Trans. 1* **1999**, 559-567. (e) D'Aniello, F.; Mann, A.; Schoenfelder, A.; Taddei, M. *Tetrahedron* **1997**, *53*, 1447-1456.

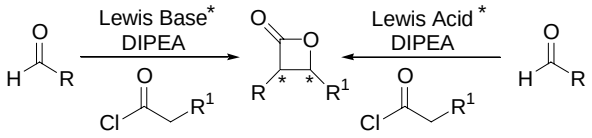
[5] Carpino, L. A. *J. Am. Chem. Soc.* **1991**, *115*, 4397-4398.

1.3 THE ACYL HALIDE-ALDEHYDE CYCLOCONDENSATION (AAC) REACTION

1.3.1 Introduction

The acyl halide-aldehyde cyclocondensation (AAC) is a transformation that combines a diverse array of substituted aldehydes and ketenes *via* a [2+2]-cycloaddition (or formal [2+2]-cycloaddition) to yield enantioenriched *syn*-3,4-substituted-(β)-lactones (Equation 1).[6] Although both yields and enantioselectivities range from good to excellent, the AAC has been an under utilized reaction technology in target-oriented synthesis.[7]

Equation 1



The AAC is a distinctive reaction because it can be catalyzed by either Lewis acids (LA) or Lewis bases (LB). Although initial inspection would presume that the aldehyde and the *in situ* generated ketene would combine *via* a simple [2+2]-cycloaddition, studies have implied that the reaction is more complex.[8] Both Lewis acid-catalyzed and Lewis base-catalyzed processes are multifaceted.

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[6] (a) Nelson, S. G.; Peelen, T. J.; Wan, Z. *J. Am. Chem. Soc.* **1999**, *121*, 9742-9743. (b) Nelson, S. G.; Zhu, C.; Shen, X. *J. Am. Chem. Soc.* **2004**, *126*, 14-15. (c) Zhu, C.; Shen, X.; Nelson, S. G. *J. Am. Chem. Soc.* **2004**, *126*, 5352-5353.
[7] Nelson, S. G.; Cheung, W. S.; Kassick, A. J.; Hilfiker, M. A. *J. Am. Chem. Soc.* **2002**, *124*, 13654-13655.
[8] (a) Nelson, S. G.; Wan, Z. *Org. Lett.* **2000**, *2*, 1883-1886. (b) Wynberg, H.; Staring, E. G. J. *J. Am. Chem. Soc.* **1982**, *104*, 166-168.

1.3.2 The aluminum-triamine catalyst system

The Lewis acid-catalyzed AAC reaction presumably transpires through a direct [2+2]-cycloaddition. Ketene formation from the acid bromide in the presence of a trialkylamine occurs rapidly. The electrophilic ketene then combines with an aldehyde, activated by pre-coordination of a Lewis acid, in a [2+2]-cycloaddition to yield a β-lactone. After the [2+2], the Lewis acid is reintroduced into the catalytic cycle. If the Lewis acid is optically active, the transient Lewis acid-aldehyde complex becomes optically active. Therefore, chirality transfer occurs to provide a quick route from aldehydes to optically active β-lactones.[8a]

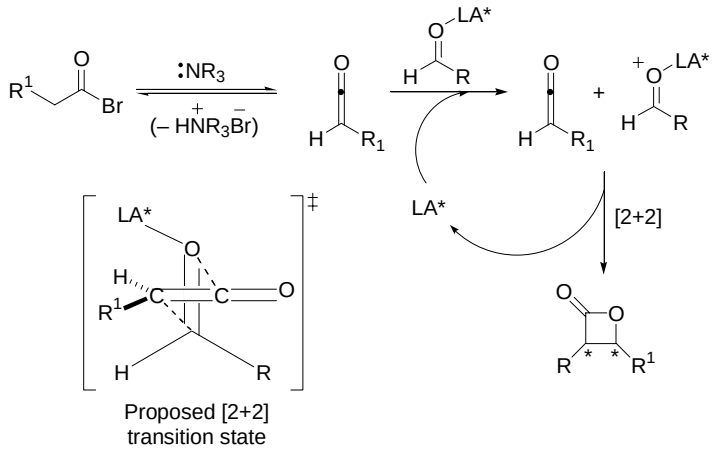


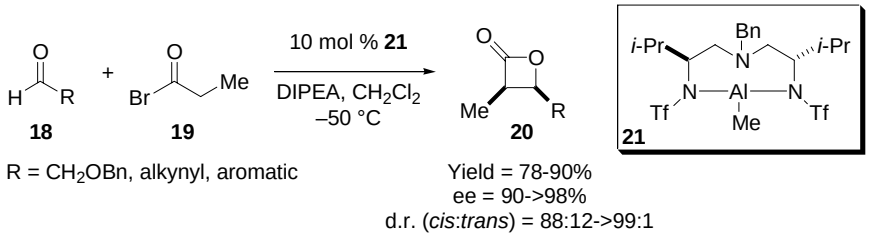
Figure 4: The Lewis acid (LA)-catalyzed AAC reaction.

A novel Lewis acid-catalyzed AAC reaction developed by Nelson and coworkers involves strain-release Lewis acidity. Despite initial methods employing the use of catalytic $AlCl_3$ with $AgSbF_6$,[9] a strain-release technology utilizing an aluminum-triamine complex was quickly adopted. This aluminum-triamine complex (**21**) acts as a Lewis acid catalyst to combine various alkyl, alkynyl, and aromatic aldehydes (**18**) with propionyl bromide (**19**) to yield *syn*-3,4-

[9] Nelson, S. G.; Peelen, T. J.; Wan, Z. *Tetrahedron Lett.* **1999**, *40*, 6541-6543.

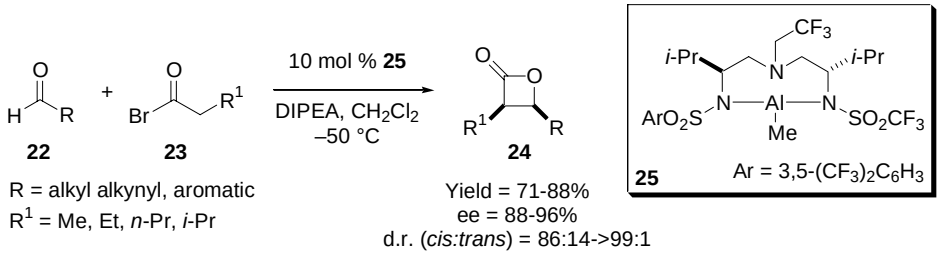
disubstituted-(β)-lactones (**20**) in high yields, diastereoselectivities, and enantioselectivities (Equation 2).[8a]

Equation 2



Nelson and coworkers followed up this initial report of a strain-release Lewis acid-catalyzed AAC reaction with an improved process. The second generation aluminum triamine complex (**25**) promoted the formation of *syn*-(β)-lactones in an enantioselective and diastereoselective manner with an increased substrate scope, in terms of both aldehydes (**22**) and ketenes (**23**) (Equation 3).[6b]

Equation 3



Despite the utility of aluminum-triamine system in the AAC reaction, this Lewis acid-catalyzed process contains some considerable limitations. For one, the complex triamine ligand (especially the second generation ligand) is nontrivial to synthesize. Secondly, the triamine ligands often coelute with the lactone products, complicating isolation. Finally, although the aluminum-triamine complexes can provide *syn*-(β)-lactones in high yields, diastereoselectivities, and enantioselectivities, the substrate scope contains many limitations.

1.3.3 The cinchona alkaloid catalyst system

The contrasting AAC reaction, the Lewis base-catalyzed process, is theorized to react through a six-membered chair-like transition state. Initially, an acid chloride is transformed into ketene *via* trialkylamine deprotonation with concomitant elimination of chloride ion. Ketene is poised for interception by the nucleophilic Lewis base to provide an enolate (i.e., an ammonium enolate if a tertiary amine is the Lewis base). This enolate partakes in an aldol reaction with an activated aldehyde (activated either by inherent electrophilicity or by a Lewis acid) to provide a β-alkoxy carbonyl compound. The ensuing alkoxide then collapses onto the carbonyl to provide the β-lactone, reintroducing the Lewis base to the catalytic cycle. The combination of a Lewis acid and a Lewis base allows for a unique dual-activation mechanism that allows the system to be favored by both enthalpic and entropic activation of the ensuing enolate-aldehyde addition.[6c] If the Lewis base is optically active, chirality transfers to produce optically active 2-oxetanones.

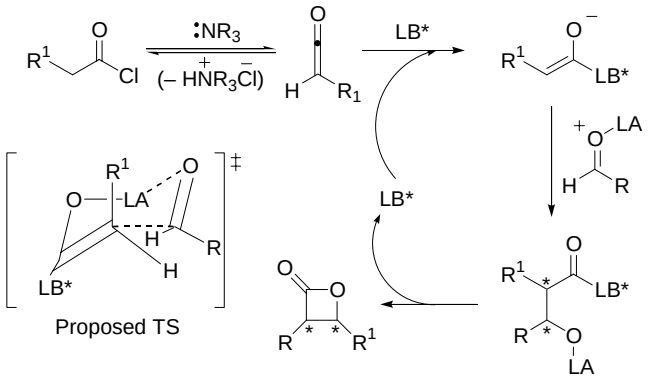
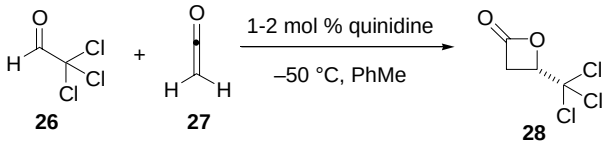


Figure 5: The Lewis base (LB)-catalyzed AAC process.

In 1982, Wynberg and Staring first noted that a catalytic quantity of quinidine (1-2 mol %) catalyzes the formal [2+2]-cycloaddition between chloral (**26**) and ketene (**27**) at –50 °C in toluene to yield β-(trichloromethyl)-β-propiolactone (**28**) in 89% yield and 98% ee (Equation 4).[8b] Unfortunately, this variation of the seminal reaction first reported by Borrmann and Wegler

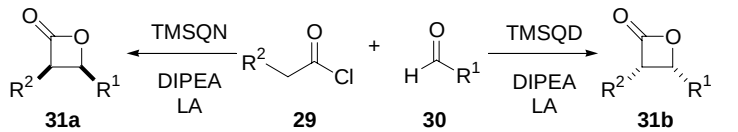
is limited to highly electrophilic aldehydes.[10] Although this constraint is considerable, one significant advantage of the Wynberg system is that judicious choice of the cinchona alkaloid (either quinidine or quinine) will lead to a desired enantiomer of β-lactone **28**.

Equation 4



Although there have been some modest modifications to the original Wynberg system, each of these systems contains significant limitations. Reaction success depends on the use of highly electrophilic aldehydes.[11] In order to overcome this electrophilic aldehyde requirement, Nelson and coworkers incorporated both a Lewis acid and a Lewis base within the reaction manifold, providing a dually activated system. While Lewis acid activation of the aldehydes allows for a significant increase in substrate scope over the Wynberg scheme, Lewis base catalysis (as with the Wynberg system) allows for formation of a specific enantiomer of the optically active 2-oxetanone (Equation 5).[6c]

Equation 5



As with the previously reported aluminum-triamine system, *syn*-3,4-disubstituted oxetan-2-ones are produced in high yields, diastereoselectivities, and enantioselectivities. Although this

[10] Borrmann, D.; Wegler, R. *Chem. Ber.* **1966**, *99*, 1245-1251.
[11] For instance, refer to: (a) Tennyson, R.; Romo, D. *J. Org. Chem.* **2000**, *65*, 7248-7252. (b) Calter, M. A.; Tretyak, O. A.; Flaschenriem, C. *Org. Lett.* **2005**, *7*, 1809-1812.

transformation is synthetically useful, the process does contain some significant substrate limitations. For one, the reaction is limited to either ketene or methyl ketene. Secondly, aldehyde variation is constrained to either alkyl or aromatic aldehydes. Expansion of the substrate scope of this cinchona alkaloid-catalyzed AAC system is essential in regards to the total synthesis of motuporin.

1.4 USEFUL TRANSFORMATIONS OF ENANTIOENRICHED β-LACTONES

The versatility of the β-lactones derived from the AAC reaction is considerable. These enantioenriched 2-oxetanones serve as templates for a diverse array of structures. Although specific transformations relating to the motuporin synthesis will be discussed in ensuing sections, it is worth noting that in one synthetic operation, optically active 2-oxetanones have provided such important structures as β-hydroxy esters, β-hydroxy amides, β-hydroxy thioesters, β-amino acids, β-alkoxy acids, β-allenyl acids, and 1,3-diols.[12]

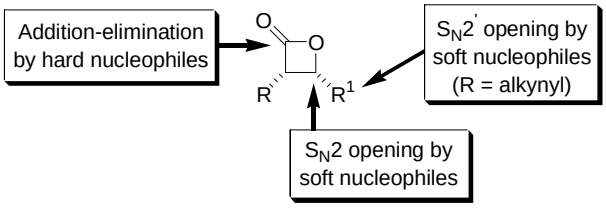


Figure 6: The β-lactone template has the ability to provide a diverse array of structures.

[12] (a) Nelson, S. G.; Spencer, K. L. *Angew. Chem. Int. Ed.* **2000**, *39*, 1323-1325. (b) Nelson, S. G.; Wan, Z.; Stan, M. A. *J. Org. Chem.* **2002**, *67*, 4680-4683. (c) Nelson, S. G.; Spencer, K. L.; Cheung, W. S.; Mami, S. J. *Tetrahedron* **2002**, *58*, 7081-7091. (d) Zipp, G. G.; Hilfiker, M. A.; Nelson, S. G. *Org. Lett.* **2002**, *4*, 1823-1826. (e) Wan, Z.; Nelson, S. G. *J. Am. Chem. Soc.* **2000**, *122*, 10470-10471.

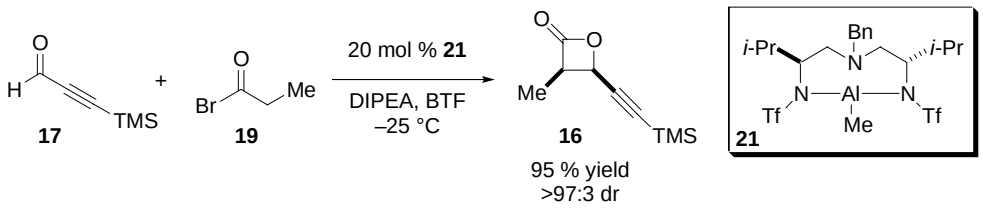
1.5 RESULTS AND DISCUSSION

The enantioselective total synthesis of motuporin necessitates the formation of three essential β-lactones (**8**, **13**, and **16**). Production of these three lactones was previously unattainable *via* the alkaloid-catalyzed AAC reaction. Consequently, the objective described herein materialized as the expansion of alkaloid-catalyzed AAC methodology to include a wider substrate scope, specifically providing β-lactones **8**, **13**, and **16**.

1.5.1 Synthesis of β-lactone 16

Due to precedent, β-lactone **16** was the initial target. Studies commenced with the AAC reaction between 3-trimethylsilyl-2-propynal (**17**) and propionyl chloride. Repeating experiments utilizing the aluminum-triamine system proved promising. Exploiting the first-generation aluminum triamine catalyst (**21**), Wan and Nelson were able to produce lactone **16** in 90% yield, in a *syn*:*anti* ratio of >99:1 and in 90% ee.[8a] To verify this result, we employed first generation catalyst **21** under the improved second generation conditions.[6b] This unique combination yielded lactone **16** as a single diastereomer (as assessed by ^{1}H-NMR) in 95% yield (Equation 6).

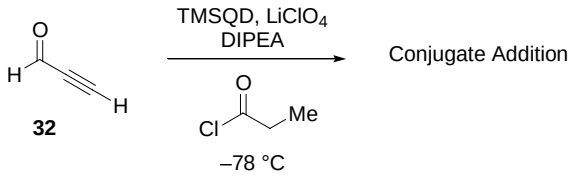
Equation 6



Since the aluminum-triamine system provided **16** in high yields and diastereoselectivities, the Lewis acid-catalyzed AAC was adopted as the contingency plan for motuporin. Production of lactone **16** through a Lewis base-catalyzed process was still the primary objective. Initial

investigation of the alkaloid-catalyzed system initiated with propynal (**32**) under a TMSQD-catalyzed AAC process. The result of this experiment was polymerization. Presumably, the alkaloid participated in conjugate addition with the aldehyde, leading to Baylis-Hillman polymerization.[13] This result indicated the necessity of the terminal trimethylsilyl group of **17** in the alkaloid-catalyzed AAC to prevent conjugate addition (Equation 7).

Equation 7



Subsequent experimentation subjected aldehyde **17** to the alkaloid-catalyzed AAC reaction (Table 1). Although initial results with TMSQD and lithium perchlorate produced lactone **16**, diastereoselectivity was far from synthetically useful (entry 1, 45.4:54.6 *syn*:*anti* lactone). It was hypothesized that the more reactive methylquinidine (MeQD) would provide an expedient reaction, favoring the kinetic *syn*-lactone. Initial tests with MeQD employed an 8:1 CH_2Cl_2:DMF solvent ratio due to uncertainty regarding the solubility of MeQD. Reactions with two Lewis acids, $LiClO_4$ and the more soluble LiI, both failed to produce **16** in high diastereoselectivities (entries 2 and 3, respectively). In these two reactions, it was theorized that the DMF may have swamped the intermediary ammonium enolate. The effect of this coordination would force the aldol reaction through an open transition state (in competition with a closed transition state), resulting in poorer diastereoselectivity (Figure 7). Therefore, the DMF was removed from the MeQD-catalyzed reaction (entry 4). Utilizing a 2:1 CH_2Cl_2:Et_2O solvent

[13] Dr. Cheng Zhu, unpublished results.

ratio with $LiClO_4$ provided *syn*-lactone **16** in 89% yield as one visible diastereomer and in >98% ee (as assessed by GC).

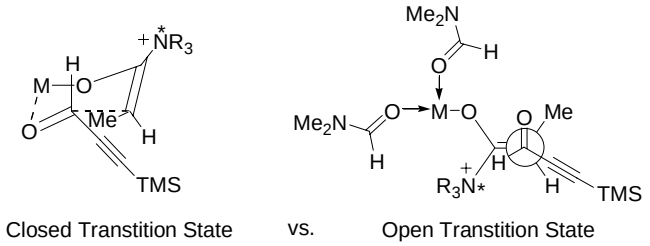
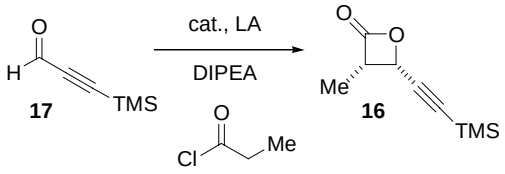


Figure 7: Closed versus open transition states in the AAC of aldehyde 17.

The MeQD conditions produced lactone **16** in high yield, diastereoselectivity, and enantioselectivity; however, the result proved to be far from general (entry 4). Although the MeQD system was successful in the AAC reaction between **17** and methyl ketene, the system provided conversion problems when employing other monoalkyl ketenes. Therefore, our focus shifted to the milder TMSQD because we believed it to have the greatest potential for inclusion of a broader range of substituted ketenes. Unfortunately, under the previously successful MeQD conditions (entry 4), the reaction with TMSQD continued to present problems with diastereoselectivity (entry 5).

Table 1: The alkaloid-catalyzed AAC reaction of aldehyde 17



Entry	cat.	Lewis Acid (LA)	Solvent Ratio (CH_2Cl_2:X)	Result[a]
1	TMSQD	$LiClO_4$ (2.0 eq)	2:1 Et_2O	45:55 *syn:anti*
2	MeQD	$LiClO_4$ (2.0 eq)	8:1 DMF	42:58 *syn:anti*
3	MeQD	LiI (2.0 eq)	8:1 DMF	50:50 *anti*:elim.[b]
4	MeQD	$LiClO_4$ (2.0 eq)	2:1 Et_2O	*syn* (89% yield, >98% ee)
5[c]	TMSQD	$LiClO_4$ (2.0 eq)	2:1 Et_2O	67:33 *syn:anti*

Unless otherwise noted, all reactions employed 10 mol % cat., 2.5 equiv. of DIPEA, and 2.0 equiv. of propionyl chloride at –78 °C. [a]All ratios obtained by ^{1}H-NMR. [b]The eliminated product trimethyl-pent-3-en-1-ynyl-silane was observed. [c]A 2 h addition of the acid chloride was utilized.

In order to overcome this predicament, subsequent investigation focused on ascertaining the origin of the diastereoselectivity quandary. As previously mentioned, the alkaloid-catalyzed AAC reaction is thought to proceed *via* a chair-like transition state for the initial aldol reaction. Assessment of the possible transition states leading to both *syn*- and *anti*-lactones provided a potential explanation. In the transition state, the developing 1,3-diaxial interaction between the metal ligand(s) and either the acyl hydrogen or R appendage of the aldehyde may promote diastereodifferentiation. In most AAC reactions, R and H are sterically dissimilar, favoring a *pseudo*-equatorial R-group to minimize steric interactions. The result of this orientation is the observed *syn*-(β)-lactone. In the transition state of the AAC reaction with aldehyde **17**, the alkynyltrimethylsilyl group and the acyl hydrogen appear to be sterically similar. Therefore, both equatorial and axial orientations for the alkynyltrimethylsilyl appendage will have similar energy. This consequence may explain the lack of diastereoselectivity observed in the reaction.

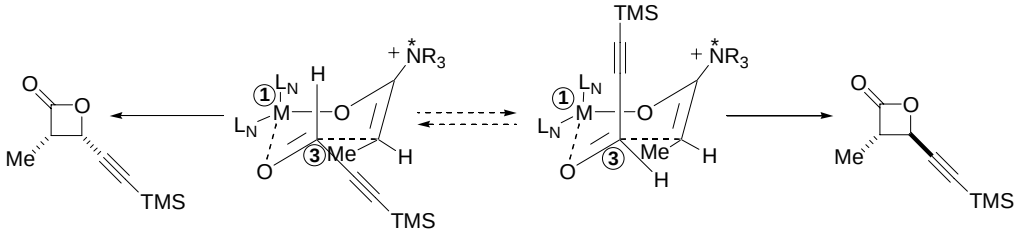
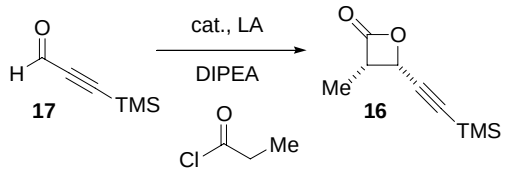


Figure 8: The 1,3-diaxial interaction in the transition state.

Based on this analysis, some potential solutions were promptly assessed in attempt to drive diastereoselectivity towards the *syn*-diastereomer (Table 2). Again, TMSQD failed to provide adequate selectivity under conditions that were successful for the MeQD-catalyzed reaction (entry 1). The first proposed solution was to augment the size of the alkaloid, thereby increasing steric interactions in the transition state to prevent any possible contacts between the alkaloid and the Lewis acid. The sterically encumbered alkaloid dimer $(DHQD)_2PHAL$ was exploited with little to no effect on diastereoselectivity (entry 2). The implication of this result

was twofold. First, the increased sterics of $(DHQD)_2PHAL$ failed to improve diastereoselectivity, indicating that alkaloid sterics has minimal role in influencing diastereoselectivity in the transition state. Second, this result negated the idea that, in the transition state, the alkaloid was somehow interacting with the Lewis acid in such a way as to affect diastereoselectivity.

Table 2: Assessing the diastereoselectivity of the AAC reaction of 17



Entry	cat.	Lewis Acid (LA)	Solvent Ratio (CH_2Cl_2:X)	Result[a]
1[b]	TMSQD	$LiClO_4$ (2.0 eq)	2:1 Et_2O	67:33 *syn:anti*
2	$(DHQD)_2PHAL$	$LiClO_4$ (0.5 eq)	2:1 Et_2O	46:55 *syn:anti*
3	TMSQD	$LiClO_4$ (1.0 eq)	2:1 Dioxane	71:29 *syn:anti*
4	TMSQD	$MgCl_2$ (1.0 eq)	2:1 Dioxane	>99:1 *syn*:*anti*
5	TMSQD	$MgCl_2$ (1.0 eq)	2:1 Et_2O	*syn* (96% yield, >99% ee)

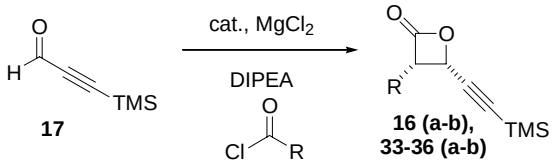
Unless otherwise noted, all reactions were employed with 10 mol % cat., 2.5 equiv. of DIPEA, and 2.0 equiv. of propionyl chloride at –78 °C. [a]All ratios obtained as by ^{1}H-NMR. [b]A 2 h addition of the acid chloride was utilized.

Since increasing alkaloid sterics failed to improve diastereoselectivity, inspection shifted to the solvent variable. It was thought that increasing solvent coordination could increase relative sterics around the metal, thereby increasing the aforementioned 1,3-diaxial interaction. Replacing diethyl ether with the more coordinative and sterically demanding dioxane improved the *syn*:*anti* ratio to 71.4:28.6 (entry 3). Subsequently, a stronger (and more coordinative) Lewis acid was introduced to shorten the bonds in the transition state, increasing all steric interactions. Utilization of $MgCl_2$ under the dioxane conditions provided diastereomerically pure *syn*-lactone **16** (entry 4). The final experiment investigated the necessity of dioxane, since the latter is known to be entrained with a considerable quantity of water. Entry 5 displays the optimized

conditions, employing 100 mol % $MgCl_2$ with 10 mol % TMSQD in a 2:1 CH_2Cl_2:Et_2O solvent ratio to provide lactone **16** in 96% yield as one visible diastereomer in >99% ee (as assessed by GC).

Successful production of lactone **16** is essential for the total synthesis of motuporin. Since this aim had been realized, the generality of the TMSQD-$MgCl_2$ system was examined. The alkaloid-catalyzed AAC reaction for aldehyde **17** was found to be effective for a variety of alkyl ketenes (Table 3). Both enatio- and diastereoselectivities are excellent with one exception; the reaction fails to provide acceptable selectivities with *iso*-propyl ketene. An important note is that, of all the [2+2]-adducts, the 3-*iso*-propyl oxetan-2-ones were the most volatile (explaining the lower yields). Enantioselectivity may have been diminished due to the steric bulk of the *iso*-propyl substituent in the transition state or from product instability. One final result not indicated in Table 3 is that the reaction fails for benzyloxy ketene, phenyl ketene, and bromo ketene. These results are not surprising, though, since these three ketenes have continued to fail in every respect in our alkaloid-catalyzed AAC reaction.

Table 3: The substrate scope of the alkaloid-catalyzed AAC reaction of 17



Entry	cat.	Lactone	R	Yield (%)	dr (*syn*:*anti*)[a]	ee (%)[a]
1	TMSQD	**33a**	H	86	--	>99
2	TMSQN	**33b**	H	89	--	>99
3	TMSQD	**16a**	Me	91	>97:3	>99
4	TMSQN	**16b**	Me	87	>98:2	>99
5	TMSQD	**34a**	Et	88	>92:8	>99
6	TMSQN	**34b**	Et	85	>90:10	>99
7	TMSQD	**35a**	*n*-Pr	84	>99:1	>99
8	TMSQN	**35b**	*n*-Pr	85	>99:1	>99
9	TMSQD	**36a**	*i*-Pr	80	>99:1	>70
10	TMSQN	**36b**	*i*-Pr	78	>99:1	0

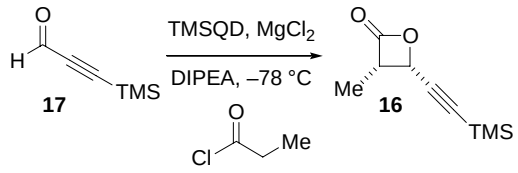
All reactions employed 2.00 mmol of aldehyde with 10 mol % cat., 2.5 equiv. of DIPEA, and 2.0 equiv. of propionyl chloride added over 1 h to a 2:1 solvent mixture of CH_2Cl_2:Et_2O at –78 °C. [a]Determined by GC.

The results indicated in Table 3 are of interest because the alkaloid-catalyzed AAC reaction had previously proved to be ineffective with substituted ketenes other than methyl ketene.[14] The generality of aldehyde **17** suggests that a wider array of substituted ketenes may be incorporated into the general alkaloid-catalyzed AAC reaction manifold. In addition, the stoichiometric $MgCl_2$ is a novel observation. Previously, lithium perchlorate and lithium iodide were the two Lewis acids of choice in the cinchona alkaloid-catalyzed AAC. The exploitation of magnesium chloride indicates that previously unsuccessful reactions under the first-generation alkaloid-catalyzed system may become productive processes with judicious choice of Lewis acid.[6c]

[14] The exception to this is the successful utilization of ethyl ketene with a handful of aromatic aldehydes catalyzed by MeQN, unpublished results obtained by Mr. Xiaoqiang Shen, University of Pittsburgh.

Due to the success of $MgCl_2$ in the alkaloid-catalyzed AAC reaction of **17**, the generality of magnesium was examined. Attempts were made to ascertain the effect of varying magnesium chloride stoichiometry in the AAC reaction between benzaldehyde and methyl ketene. Surprisingly, no reaction occurred. Therefore, to obtain the desired data, varying amounts of $MgCl_2$ were tested in the reaction of methyl ketene and **17** (Table 4). The experiments demonstrate that 10 mol % $MgCl_2$ (entry 1) is equally as effective as 200 mol % (entry 5) in the AAC reaction of **17**. The five differing quantities of magnesium chloride were, within experimental error, identical. Each quantity provided lactone **16** as one diastereomer in similar yields. This result indicates that substoichiometric quantities of magnesium are active enough with TMSQD and aldehyde **17** to provide near quantitative conversion to **16** as one diastereomer. Thus, in terms of the synthesis of motuporin (**1**), lactone **16** can now efficiently be produced in near-enantiopure form utilizing 10 mol % of $MgCl_2$.

Table 4: Investigating the stoichiometry of $MgCl_2$

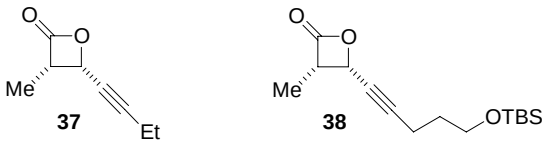


Entry	$MgCl_2$ (equiv.)	Yield (%)
1	0.10	91
2	0.20	90
3	0.50	86
4	1.00	90
5	2.00	89

All reactions employed 2.00 mmol of the aldehyde with 10 mol % cat., 2.5 equiv. of DIPEA, and 2.0 equiv. of propionyl chloride added over 1 h to a 2:1 solvent mixture of CH_2Cl_2:Et_2O at –78 °C.

In order to assess the generality of magnesium chloride in the alkaloid-catalyzed AAC reaction, two additional alkynyl aldehydes were studied under the 100 mol % magnesium

chloride conditions. The TMSQD-catalyzed AAC reactions of both pent-2-ynal and 6-(*t*-butyldimethylsiloxy)hex-2-ynal provided the desired 2-oxetanones **37** (an essential intermediate in the total synthesis of rhazanilam) and **38**, respectively. The reason for the lower yield of lactone **37** is volatility, as crude ^{1}H-NMR indicated complete conversion. 2-Oxetanone **38** provided a lower yield most likely due to decreased reactivity. Although these studies were by no means exhaustive, they do indicate that the magnesium chloride system may succeed for a variety of terminally substituted alkynyl aldehydes.



37

Yield = 66%
d.r. = >99:1
ee = >99%

38

Yield = 58%
d.r. = 83:7
ee = 97%

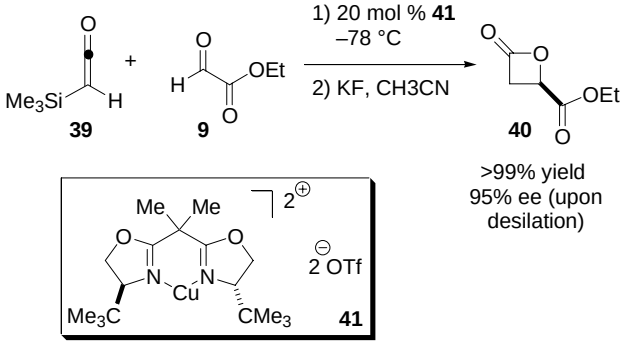
Figure 9: Added substrates for the AAC under the substoichiometric $MgCl_2$ conditions.

In summation, the magnesium-alkaloid system is able to provide access to a wide array of structurally diverse optically active *syn*-3-alkynyl-2-oxetanones. In terms of motuporin, lactone **16** can be prepared in 96% yield as one visible diastereomer and in >99% ee. Comparing this result to those obtained utilizing the aluminum-triamine system (namely, production of **16** in 90% yield in a *syn*:*anti* ratio of >99:1 in 90% ee) indicates the alkaloid-catalyzed system to be superior.[8a] An added advantage of the Lewis base-catalyzed system is the ease of separation of the catalyst from **16** (something of difficulty with the Lewis acid-catalyzed system). A final advantage of this system is the increased reaction scale (successful reactions have been employed utilizing up to 20 mmol of **17**).

1.5.2 Synthesis of β-lactone 8

Another indispensable β-lactone in the total synthesis of **1** is lactone **8**, derived from the AAC reaction between a protected glyoxylate and methyl ketene. Precedent for such a transformation derives from the Evans group. In 2001, Evans and Janey reported that trimethylsilylketene (**39**) reacted with freshly distilled ethyl glyoxylate (**9**) *via* a copper(II)-catalyzed [2+2] reaction. The resulting 4-oxo-oxetane-2-(*R*)-carboxylic acid ethyl ester (**40**) was, upon desilation, produced in >99% yield with 95% ee (Equation 8).[15]

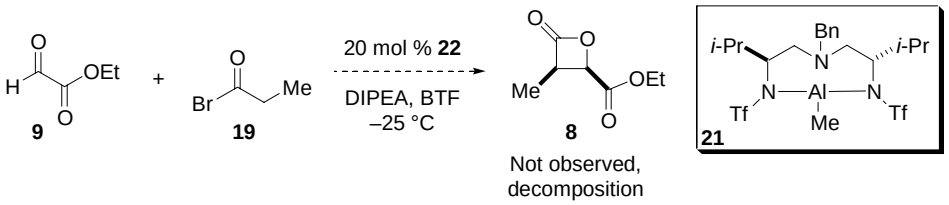
Equation 8



Even though Evans' precedent is noteworthy, the reaction seemingly fails for all other ketenes. As a result of this shortcoming, the goal to produce a variety of glyoxylate-derived (β)-lactones was formulated. As before, the first generation aluminum-triamine ligand (**21**) was employed in the AAC reaction with **9** under second generation conditions (Equation 9). Unfortunately, the results were inconclusive as polymerization and decomposition were observed.

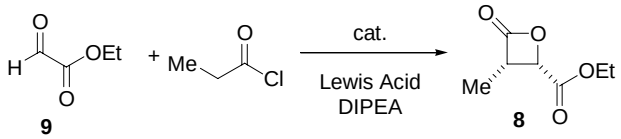
[15] Evans, D. A.; Janey, J. M. *Org. Lett.* **2001**, *3*, 2125-2128.

Equation 9



With the failure of the Lewis acid-catalyzed system to produce **8**, efforts were focused on the alkaloid-catalyzed reaction manifold (Table 5). Initial experiments employed the highly active MeQD and the more soluble lithium iodide (entry 1). Using 10 mol % of MeQD with lithium iodide in the AAC reaction between methyl ketene and **9** produced lactone **8** in 91% yield and in 95% ee after a quick purification. In order to assess reliability, the same reaction was repeated; however, decomposition occurred with no discernible lactone remaining after purification. To verify if this decomposition was MeQD-dependent, TMSQD was employed; however, decomposition resulted yet again (entry 3).

Table 5: Initial results of the AAC reaction of 9



Entry	cat.	Lewis Acid	Solvent Ratio (CH_2Cl_2:X)	Result[a]
1	MeQD	LiI (2.0 equiv.)	2:1 Et_2O	91% (>95% ee)[c]
2[b]	MeQN	LiI (2.0 equiv.)	2:1 Et_2O	Decomposition
3	TMSQD	LiI (2.0 equiv.)	2:1 Et_2O	Decomposition
4	MeQD	LiI (2.0 equiv.)	8:1 DMF	95%
5	MeQD	LiI (2.0 equiv.)	8:1 DMF	Decomposition
6	TMSQD	$MgCl_2$ (2.0 equiv.)	8:1 DMF	Decomposition
7	TMSQD	$MgCl_2$ (1.0 equiv.)	8:1 DMF	90%
8	TMSQD	LiI (2.0 equiv.)	2:1 Et_2O	34%

All reactions employ 10 mol % cat., 2.5 equiv. of DIPEA, and 2.0 equiv. of propionyl chloride at –78 °C. [a]All yields obtained for product purified on silica gel. [b]Attempted purification on neutral Iatrobeads. [c]Enantiomeric excess (ee) ascertained by GC.

Since variation of the alkaloid proved unsuccessful in preventing decomposition of **8**, solvent ratio was the next variable inspected. It was hoped that altering the reaction medium from 2:1 CH_2Cl_2:Et_2O to the more solublizing 8:1 CH_2Cl_2:DMF would help dissolve both the Lewis acid and alkaloid, providing for a more efficient reaction and an improved work-up (entries 4-7). The outcome of these studies was still unreliable decomposition. The final modification to the system was variation of the Lewis acid. Attempts with the stronger $MgCl_2$ failed to solve the reproducibility errors (entries 6-7).

These problems regarding reproducible production of **8** were disconcerting. Although the purity of **9** was always variable (the commercially available glyoxylate trimer had to be "cracked" and distilled), it was assumed that β-lactone **8** was formed in the reaction. Indeed, crude ^{1}H-NMR spectra continued to indicate that β-lactone **8** was present in the crude reaction mixture. The difficulty in reproducibility seems to be isolation of, not production of, the resultant lactone.

This hypothesis regarding decomposition of **8** instigated studies regarding product isolation. Attempted purification of crude **8** on normal silica, Et_3N-washed silica, Iatrobeads (neutral silica), the MPLC, and neutral and basic alumina (both activated and deactivated) all failed to prevent decomposition. Therefore, distillation was investigated, both bulb-to-bulb (*via* a Kugelroar) and standard short path distillation. These methods, much like the results obtained from chromatography, afforded decomposition.

Although the potential methods for decomposition of β-lactone **8** are numerous, two major pathways were viewed as the most probable. Either during the reaction or during purification, the nucleophilic alkaloid could add into the ethyl ester. The resultant ethoxide species could participate in a variety of addition/elimination or deprotonation pathways that

would lead to a variety of decomposition products. Secondly, the ethyl ester moiety could also assist in another decomposition route, attenuating the acidity of the α-proton (in relation to the ester). Deprotonation at this position renders an enolate that is poised to either decompose or polymerize. One final drawback of **8** is its excessive volatility, attenuating difficulties in product isolation.

Although β-lactone **8** was produced, reproducibility continued to be evasive. In terms of the total synthesis of **1**, a more reliable method to produce **8** was required. To realize this aim, alternative glyoxylates were tested in the alkaloid-catalyzed AAC reaction. It was hoped that differing ester functionalities would allow for a more stable β-lactone, facilitating reproducibility.

Investigation began with the more robust benzyl glyoxylate (**43**). Glyoxylate **43** was chosen due to its increased molecular weight and the added advantage of a chromophore. Initial attempts employing periodic acid to cleave 2,3-dihydroxy-succinic acid dibenzyl ester to **43** failed to supply the glyoxylate in sufficient purity for successful application in the alkaloid-catalyzed AAC.[16] Since this simpler method was unsuccessful, Jung's ozonolysis protocol was adopted.[17]

Ozonolysis of either dibenzyl fumarate (**42**) provided the desired ozonide in near quantitative yield. Through introduction of DMS, the ozonide was broken down to desired **43** which, after distillation, could be obtained in high purity. Although distillation was successful in furnishing **43**, over time, polymerization and subsequent decomposition proved this method to be less reliable than was desired.

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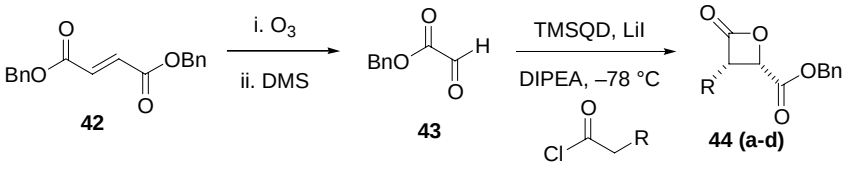
[16] Trova, M. P.; Gauuan, P. J. F.; Pechulis, A. D.; Bubb, S. M.; Bocckino, S. B.; Crap, J. D.; Day, B. J. *Bioorg. Med. Chem.* **2003**, *11*, 2695-2707.
[17] Jung, M. E.; Shishido, K.; Davis, L. H. *J. Org. Chem.* **1982**, *47*, 891-892.

Table 6: Attempts at the AAC with benzyl glyoxylate



Entry	R	Temp. (°C)	Lactone	Result
1	Me	–78	**44a**	Decomposition
2	Me	–50	**44a**	Decomposition
3	H	–78	**44b**	Decomposition
4	H	–60	**44b**	Decomposition
5	Et	–78	**44c**	Decomposition
6	*n*-Pr	–78	**44d**	Decomposition

Dibenzyl fumarate was ozonized and quenched with 1.11 equiv. DMS.[17] All reactions employed 10 mol % cat., 2.5 equiv. of DIPEA, and 2.0 equiv. of propionyl chloride.

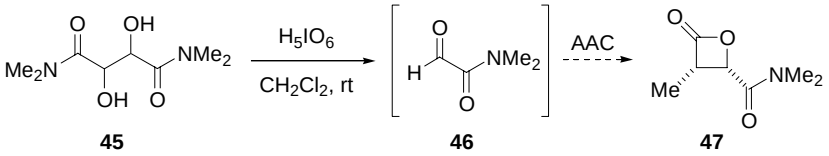
With pure **43** available, the glyoxylate was introduced into the alkaloid-catalyzed AAC reaction in an attempt to synthesize β-lactone **44a** (Table 6). Unfortunately, standard AAC reaction conditions with methyl ketene and TMSQD failed to provide any discernable lactone after purification (entry 1). Increasing the temperature to –50 °C in an attempt to push the reaction towards **44a** also proved unsuccessful (entry 2). Finally, varying ketene substitution also failed to produce the desired β-lactone (entries 3-6).

With the failure to produce β-lactone **44**, the reaction was analyzed to discover the basis for this decomposition. As previously observed, it seems that the β-lactone was formed during the reaction; however, decomposition was again transpiring either during the reaction or during purification. ^{1}HNMR studies indicated that the favored methods of decomposition were through carbon dioxide elimination and through de-esterification. A handful of attempts employing *t*-butyl glyoxylate (derived from ozonolysis of di-*t*-butyl maleate) provided similar results.

The ester substituents of lactones **8** and **44** seemed to facilitate decomposition, so a more stable carbonyl-containing substituent was sought to increase lactone stability. In this regard, the

more stable *N*,*N*-dimethyl glyoxamide (**46**) was evaluated in the alkaloid-catalyzed AAC. Unfortunately, the reaction resulted in decomposition. As previously observed, the failure of this reaction is thought to result from the lack of purity of the resultant **46** ensuing from periodic acid cleavage (Equation 10).[16]

Equation 10



45 **46** **47**

Lactone **8** or a variant thereof is critical for the total synthesis of motuporin. Although reliable production of **8** was unattainable, at the very least, it was produced. Therefore, **8** was synthesized in as pure a form as possible (disregarding lower yields) and was carried on in the total synthesis of **1**. It was hoped that future examination would eventually solve the difficulties in reproducibility in the synthesis of **8**.

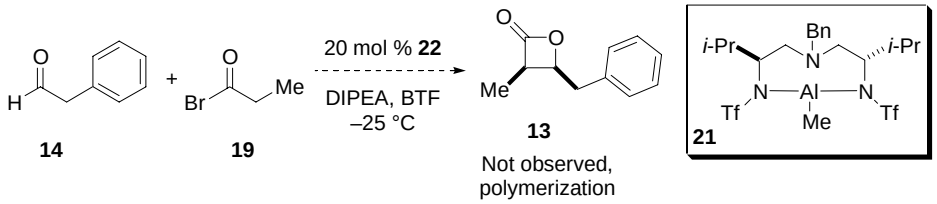
1.5.3 Synthesis of β-lactone 13

The designed total synthesis of motuporin (**1**) requires three key β-lactones for its success. Successful production of lactone **16** had been achieved along with unreliable production of **8**. With these two β-lactones in hand, production of the final critical lactone, 4-benzyl-3-methyl-oxetan-2-one (**13**), was undertaken.

As with the initial investigations of aldehydes **9** and **17**, aldehyde **14** was first utilized in the Lewis acid-catalyzed AAC reaction. Aldehyde **14** was subjected to catalyst **21** under the second-generation AAC conditions. Under these conditions, it appeared that **14** enolized and

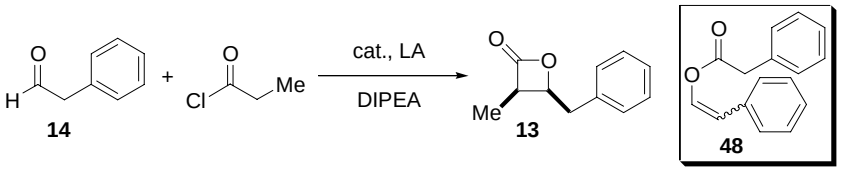
then polymerized (Equation 11). With this failure, the Lewis base-catalyzed AAC was investigated.

Equation 11



Phenylacetaldehyde (**14**) was exploited in the alkaloid-catalyzed AAC reaction utilizing a solvent ratio of 2:1 CH_2Cl_2:Et_2O (Table 7). Initial experimentation employed either TMSQN or MeQN with the soluble LiI in an attempt to produce **13** (entries 1 and 2, respectively). As noted before with the aluminum-triamine system, enolization and subsequent polymerization was the result. Variations involving replacement of LiI with the less soluble $LiClO_4$ utilizing both MeQN and TMSQN failed to produce **13** (entries 3 and 4, respectively). It was hoped that these milder conditions would favor β-lactone formation over polymerization; however, this proved to be erroneous. Final attempts were made to increase Lewis acidity in order to favor a quicker AAC reaction, but again, these attempts proved futile (entries 6 and 7, respectively).

Table 7: Attempted alkaloid-catalyzed AAC of phenylacetaldehyde (14)



Entry	cat.	LA	Result
1	TMSQN	LiI (2.0 equiv.)	Polymerization
2	MeQN	LiI (0.5 equiv.)	Polymerization
3	MeQN	$LiClO_4$ (0.5 equiv.)	Polymerization
4	TMSQN	$LiClO_4$ (0.5 equiv.)	Polymerization
5[a]	TMSQN	$LiClO_4$ (0.5 equiv.)	Polymerization
6	TMSQN	$MgCl_2$ (1.0 equiv.)	Polymerization + **48**
7	TMSQN	$LiClO_4$ (1.5 equiv.)	Polymerization

All reactions employed 10 mol % cat., 2.5 equiv. of DIPEA, and 2.0 equiv. of propionyl chloride. [a]Added 1.0 mL of EtOAc to further dissolve all $LiClO_4$.

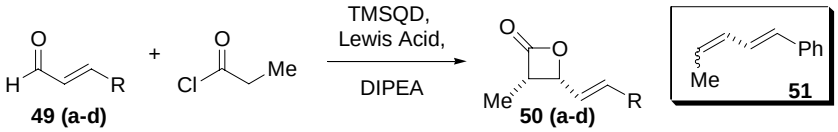
It seems that the phenyl group of **14** lowers the pK_a of the α-protons to such an extent that exposure to DIPEA causes immediate enolization and ensuing self-condensation. This polymerization, although enhanced under the Lewis basic AAC reaction, occurs under the Lewis acidic aluminum-triamine conditions. All investigated iterations, both Lewis acid-catalyzed and Lewis base-catalyzed, failed to prevent this enolization-polymerization pathway. Due to this predicament, direct production of β-lactone **13** was abandoned. Instead, alternative methods to arrive at aldehyde **12** were investigated; however, these will be discussed later in their context to the total synthesis of motuporin.

1.5.4 Synthesis of 4-substituted α,β-unsaturated β-lactones

With investigations underway to produce the three essential β-lactones vital for the total synthesis of motuporin (**1**), attention shifted to expansion of the substrate scope of the alkaloid-catalyzed AAC reaction. Productive synthesis of β-lactone **16** *via* the alkaloid-catalyzed AAC

was the first example of the inclusion of an α,β-unsaturated aldehyde in the alkaloid-catalyzed AAC. Fueled by this success, the viability of other α,β-unsaturated aldehydes proceeded to the forefront. Excluding alkynes, α,β-unsaturated aldehydes remained ineffective in the AAC (both Lewis acid-catalyzed and Lewis base-catalyzed). Therefore, various α,β-unsaturated aldehydes were subjected to the alkaloid-catalyzed AAC reaction (Table 8).

Table 8: α,β-Unsaturated aldehydes in the AAC reaction



49 (a-d) **50 (a-d)**

Entry	R	Lewis Acid	Temp. (°C)	Lactone	Result
1	Ph (**49a**)	$LiClO_4$ (2.0 equiv.)	–25	**50a**	**49a**, Polymer
2	Ph (**49a**)	$AlCl_3$ (2.0 equiv.)	–40	**50a**	Polymer
3	Ph (**49a**)	$MgBr_2$ (1.0 equiv.)	–36	**50a**	Decomp
4	Ph (**49a**)	$MgCl_2$ (1.0 equiv.)	–36	**50a**	**49a**
5	Ph (**49a**)	$MgCl_2$ (1.0 equiv.)	0	**50a**	**51**
6	*i*-Pr (**49b**)	$TiCl_2{\cdot}(THF)_2$ (1.0 equiv.)	–78	**50b**	**49b**, decomp
7	*i*-Pr (**49b**)	$InCl_3$ (1.0 equiv.)	–78	**50b**	**49b**
8	*i*-Pr (**49b**)	$BF_3{\cdot}OEt_2$ (0.10 equiv.)	–78	**50b**	**49b**
9	*i*-Pr (**49b**)	$MgCl_2$ (1.0 equiv.)	0	**50b**	**49b**
10	*n*-Pn (**49c**)	$MgCl_2$ (2.0 equiv.)	–30	**50c**	**49c**

All reactions employed 10 mol % TMSQD, 2.5 equiv. of DIPEA, and 2.0 equiv. of propionyl chloride in a 2:1 solvent mixture of CH_2Cl_2:Et_2O. [a] *n*-Pn = *n*-pentyl.

To address this quandary, *trans*-cinnamaldehyde (**49a**) was chosen as the preliminary test substrate (entries 1-5). Since initial attempts with a variety of Lewis acids at –78 °C failed to provide any discernible reaction, temperatures were increased. When the milder lithium perchlorate (entry 1) failed to provide **50a**, the more active $AlCl_3$ and $MgBr_2$ were employed to push the reaction forward (entries 2 and 3, respectively). Unfortunately, these stronger Lewis acids lead to decomposition.

Due to its previous success with the alkynyl substrates, $MgCl_2$ was endeavored in these reactions. Although no discernible reaction occurred at –36 °C (entry 4), when the temperature was increased to 0 °C, diene **51** was produced. This diene is clearly a product of a successful AAC reaction to **50a** followed by elimination of CO_2. It was thought that the conjugating 3-phenyl group of **49a** could favor elimination. Consequently, aldehyde **49b** was adopted as the next test substrate.

Again, a variety of Lewis acids, ranging from $MgCl_2$ to the stronger $BF_3{\cdot}OEt_2$, all failed to provide any desirable β-lactone (entries 6-9). Attempts with the less sterically encumbered *normal*-pentyl unsaturated aldehyde (**49c**) also failed to provide any desirable reaction (entry 10). These results implied that, under the Lewis base-catalyzed AAC conditions, α,β-unsaturated aldehydes were not active enough to react at lower temperatures; however, reactions at elevated temperatures were followed by decomposition (i.e. the β-lactones were unstable under the reaction conditions at elevated temperatures).

With the possibility for a successful AAC reaction of α,β-unsaturated aldehydes dwindling, precedent was found in the literature. Hagemeyer and Kung independently observed that, in specific cases, $AlCl_3$, $ZnCl_2$, and $BF_3{\cdot}OEt_2$ could catalyze the thermal [2+2]-cycloaddition between ketene (and methyl ketene) and α,β-unsaturated aldehydes.[18] The resulting racemic 4-substituted α,β-unsaturated-(β)-lactones were isolated and characterized.

This precedent encouraged an additional trial with *trans*-cinnamaldehyde (**49a**). The TMSQD-catalyzed AAC reaction of **49a** with 1.0 equiv. of $ZnCl_2$ at 0 °C produced, along with diene **51**, a trace quantity of the desired **50a** (Equation 12).

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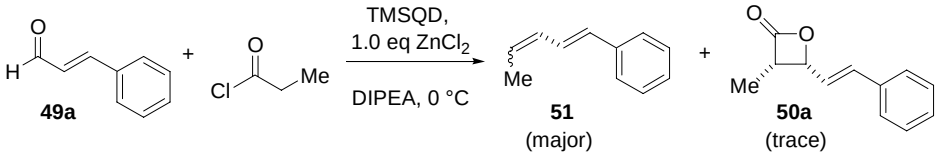
[18] (a) Hagemeyer, Jr., H. J. **1949**. *US Patent* 2,478,388. (b) Kung, F. E. **1944**. *US Patent* 2,356,459.

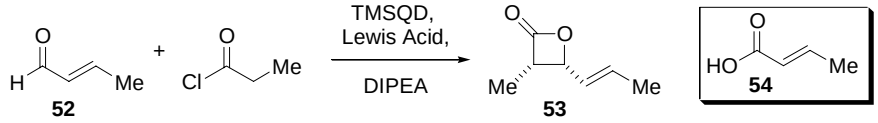
Equation 12



In order to better assess the reaction, crotonaldehyde (**52**) was utilized (Table 9). Initial attempts were again endeavored with $LiClO_4$ and $MgCl_2$ under milder conditions to ascertain if the reaction could proceed under a gentler reaction environment (entries 1-3). Due to precedent, subsequent tests employed the stronger $BF_3{\cdot}OEt_2$ and $AlCl_3$ (entries 4 and 5, respectively).[18] All of these trials failed to provide any desirable reaction.

Finally, encouraged by the previous result of $ZnCl_2$ with aldehyde **49a**, zinc chloride was dispensed in the TMSQD-catalyzed AAC reaction of **52** (Table 9, entries 6-7). At 0 °C, 2.0 equiv. of $ZnCl_2$ provided desired (β)-lactone **53** as one visible diastereomer in a 63.0:37.0 ratio of product to starting material (as assessed by ^{1}H-NMR). Unfortunately, this β-lactone was unstable to column chromatography. Therefore, although this unoptimized result shows promise, further investigation is required to improve conversion and isolate the desired β-lactone to provide solid proof of its existence.

Table 9: Crotonaldehyde (52) in the AAC reaction



Entry	cat.	Lewis Acid	Temp. (°C)	Result
1	TMSQD	$LiClO_4$ (2.0 equiv.)	–78	**52**
2	TMSQD	$MgCl_2$ (1.0 equiv.)	–25	**52**
3	TMSQD	$MgCl_2$ (2.0 equiv.)	–25	**52** and **54**
4	TMSQN	$BF_3{\cdot}OEt_2$ (0.05 equiv.)	–40	**52**
5	TMSQD	$AlCl_3$ (1.0 equiv.)	0	Polymerized
6	TMSQD	$ZnCl_2$ (1.0 equiv.)	0	**52**
7	TMSQD	$ZnCl_2$ (2.0 equiv.)	0	63.0:37.0 **53**:**52**

All reactions employed 10 mol % cat., 2.5 equiv. of DIPEA, and 2.0 equiv. of propionyl chloride in a 2:1 solvent mixture of CH_2Cl_2:Et_2O.

One final substrate that was previously unavailable from either the aluminum triamine-catalyzed or the alkaloid-catalyzed AAC reactions is that of (β)-lactone **55** (which matches onto the natural product erythronolide B). Preliminary results indicated that methacrolein may be a viable aldehyde in the AAC reaction.[19] After optimization, the TMSQD-catalyzed AAC reaction between methacrolein and methyl ketene produced the highly volatile 4-isopropenyl-3-methyl-oxetan-2-one (**55**) in high yield, diastereoselectivity, and enantioselectivity. This result provides another aldehyde template to explore in the alkaloid-catalyzed AAC reaction.

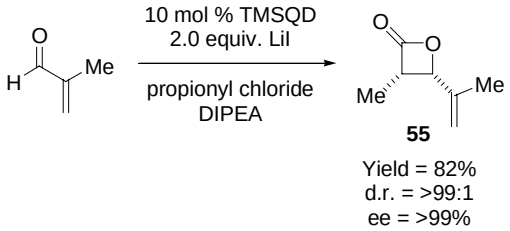


Figure 10: Methacrolein successfully employed in the alkaloid-catalyzed AAC.

[19] Preliminary results obtained by Xiao Wang in Dr. Curran's group indicated successful production of **55** (by ^{1}H-NMR); however, the lactone was not isolated.

1.6 CONCLUSION

Experimentation was performed to achieve the three critical β-lactones (**8**, **13**, and **16**) for the planned total synthesis of motuporin. β-Lactone **16** was the only lactone of the three to be successfully realized. Although β-lactone **8** can now be produced, reliability is still a significant drawback. Finally, β-lactone **13** is unobtainable by both Lewis acid-catalyzed and Lewis base-catalyzed iterations of the AAC.

Although production of lactone **8** is still unreliable, alternative Lewis base-catalyzed AAC reactions still possess potential for realization. Evans' precedent for the solid, stable *N*-phenyl glyoxamide as well as the stable "Weinreb glyoxamide" are still untested possibilities.[20,21] Alternatively, there still remain a plethora of available glyoxylates that are untested.[16] Careful investigation of these species may provide a stable lactone product under the alkaloid-catalyzed AAC conditions.

The substrate scope of the Lewis base-catalyzed AAC has been greatly expanded in terms of both aldehydes and ketenes. For one, monoalkylated ketenes have been successfully employed for the first time with nonaromatic aldehydes in the Lewis base-catalyzed AAC process. Although branching in ketene substitution still causes problems, future studies may overcome this barrier. Finally, heteroatom-substituted ketenes are still ineffective in the AAC reaction; however, future work should solve this problem.

In terms of aldehyde diversity, various terminally substituted 2-alkynyl aldehydes are now incorporated within the Lewis base-catalyzed AAC reaction manifold. Previously, a limited number of these substrates were included only in the aluminum-triamine system. The terminal

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[20] Evans, D. A.; Wu, J. *J. Am. Chem. Soc.* **2005**, *127*, 8006-8007.
[21] Parhi, A. K.; Franck, R. W. *Org. Lett.* **2004**, *6*, 3063-3065.

alkynyl substituent was proven to be necessary in the alkaloid-catalyzed system to prevent conjugate addition, followed by Baylis-Hillman-type polymerization. The inclusion of these substrates also documented the unique action of magnesium chloride in the Lewis base-catalyzed system. Additional studies are still required to further expand this class of aldehydes.

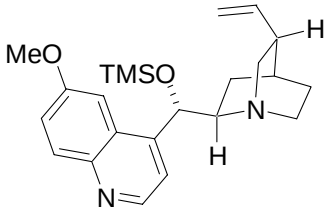
Finally, recent advances have indicated a possibility for the incorporation of α,β-unsaturated aldehydes into the alkaloid-catalyzed AAC reaction manifold. Additional experimentation with crotonaldehyde (**52**) must commence in order to optimize the system to provide purified **53**. Once this is completed, subsequent studies must be endeavored to examine how pervasive the alkaloid-catalyzed AAC system will be in the integration of a variety of α,β-unsaturated aldehydes.

1.7 EXPERIMENTALS

General Notes: Unless otherwise noted, all reactions were performed under anhydrous conditions (dry glassware was utilized under an atmosphere of nitrogen). All crude organic products were dried over magnesium sulfate and were concentrated under reduced pressure by rotary evaporation.

General procedure for the aluminum-triamine catalyzed AAC: To a round bottom flask was added 0.117 g (0.20 mmol) of triamine ligand **21** and 2.00 mL of anhydrous BTF. At room temperature, 0.10 mL (0.20 mmol) of a 2.0 M solution of $AlMe_3$ in hexanes was added and the reaction was allowed to stir for 2 h. The reaction was cooled to –25 °C and 0.35 mL (2.00 mmol) of DIPEA was then added and the solution was stirred at –25 °C for 15 min. Propionyl

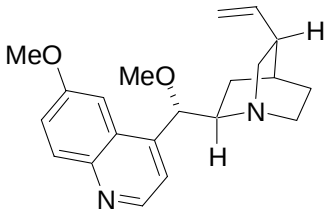
bromide, 0.36 mL (4.00 mmol), was added and 1.00 mmol of the desired aldehyde was added dropwise. The reaction was stirred overnight at –25 °C, 10 mL of a 3% solution of NEt_3 in diethyl ether (v:v) was added and the reaction was stirred up to ambient temperature over the course of 1 h. Following an extraction with 20 mL of a saturated solution of $NaHCO_3$, the organic layer was separated. The aqueous layer was washed with diethyl ether (3 X 15 mL) and all organics were combined and dried. The crude reaction mixture was purified on silica gel.



Synthesis of trimethylsilylquinidine (or trimethylsilylquinine):[22] To a round-bottom flask was added either 10.36 g (31.92 mmol) of quinidine or quinine and 50 mL of anhydrous CH_2Cl_2. The flask was stirred at ambient temperature to dissolve all of the alkaloid and was cooled to 0 °C. Trimethylsilylchloride (4.86 mL, 38.31 mmol) was added neat *via* syringe and the reaction was stirred at 0 °C for 30 minutes. The reaction was allowed to warm up to ambient temperature and was allowed to stir for 24 h. The reaction was quenched with 75 mL of a saturated solution of $NaHCO_3$ and the organic layer was separated. The aqueous layer was washed with CH_2Cl_2 (2 X 25mL) and all organic layers were combined and dried. After purification on silica gel utilizing a gradient of 1% MeOH in CH_2Cl_2 up to 5% MeOH in CH_2Cl_2 (about 200 mL of each percentage), pure trimethylsilylquinidine (or trimethylsilylquinine) was concentrated under reduced pressure and was dried under high vacuum for 48 h to yield 12.9 g of TMSQD (85% yield) as a light yellow sticky oil or TMSQN in 4.85 g (77% yield, starting from 5.191 g, 19 mmol, of quinine) as a white solid. ^{1}H-NMR ($CDCl_3$): δ 8.64 (br s, 1 H), 7.95 (d, J = 9.2 Hz, 1

[22] Calter, M. A. *J. Org. Chem.* **1996**, *61*, 8006-8007.

H), 7.42-7.22 (m, 5 H), 5.62 (br s, 2 H), 4.87-4.77 (m, 3 H), 3.87 (s, 4 H), 3.37 (s, 2 H), 3.03 (m, 3 H), 2.59 (br s, 3 H), 2.18 (br s, 1 H), 1.72-1.64 (m, 7 H), 1.43 (m, 2 H), 0.03 (s, 9 H).



Synthesis of methylquinidine:[23] To a round-bottom flask was added 390 mg (16.3 mmol) of NaH as a 60% dispersion in mineral oil. Anhydrous pentane (10 mL) was added and the solution was stirred vigorously for 10 min. Once the solution settled, the pentane was removed *via* cannula and the process was repeated two more times to fully activate the sodium hydride. The activated NaH was cooled to 0 °C, 10 mL of dry THF was added, and 2.00 g (6.17 mmol) of quinidine was slowly added as a solution, pre-dissolved in 18 mL of dry THF. The reaction was stirred at 0 °C for 1 h and was then warmed to ambient temperature and was allowed to stir for 6 h. After re-cooling to 0 °C, 0.400 mL (6.47 mmol) of MeI was added dropwise and the reaction was allowed to stir at 0 °C for 1 h. After warming to ambient temperature, the reaction was stirred for 96 h. Water (20 mL) was added to quench the reaction and the organic layer was immediately separated. The aqueous layer was washed with diethyl ether (3 X 15 mL) and all organics were combined and dried. After concentration under reduced pressure, the crude reaction mixture was passed through a plug of silica utilizing 2% MeOH in EtOAc as elutent to yield 1.07 g (94%) of pure methyl quinidine as a light yellow solid. ^{1}H-NMR ($CDCl_3$): δ 8.85 (d, J = 4.3 Hz, 1 H), 8.04 (d, J = 9.2 Hz, 1 H), 7.62-7.34 (m, 5 H), 6.58 (br s, 1 H), 6.01 (ddd, J = 13.9, 7.2, 3.2 Hz, 1 H), 5.37-5.19 (m, 3 H), 4.14 (s, 4 H), 3.52 (s, 3 H), 3.52-3.37 (m, 3 H), 2.70 (br q, J = 8.0 Hz, 1 H), 2.58 (br s, 1 H), 2.47 (br t, J = 11.8 Hz, 1 H), 2.07-1.95 (m, 2 H), 1.81-1.63 (m, 1 H), 1.25-1.15 (m, 1 H).

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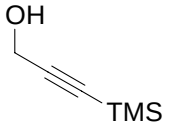
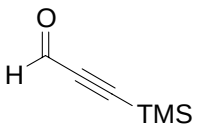
[23] Papageourgiou, C. D.; Cubillo de Dios, M. A.; Ley, S. V.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2004**, *43*, 4641-4644.



Synthesis of 3-trimethylsilanyl-prop-2-yn-1-ol:[24] To a round bottom flask was added 5.27 mL (89.2 mmol) of propargyl alcohol and 50 mL of anhydrous THF. After cooling to 0 °C, 117 mL (188 mmol) of a 1.6 M solution of *n*-BuLi in hexanes was added dropwise. The reaction was stirred for 1 h, then 23.80 mL (188 mmol) of TMSCl was added dropwise and the solution was stirred at 0 °C for 10 min. The solution was warmed to ambient temperature and was allowed to stir for 30 min. A 5% solution of citric acid in methanol was added to the solution until it was acidified (~200 mL). The solution was stirred at ambient temperature for 20 min. and was washed with 150 mL of water. The organic layer was separated and the aqueous layer was washed with diethyl ether (3 X 50 mL). All organics were combined and washed with water (3 X 100 mL) and were dried. Purification on silica gel utilizing 20% EtOAc in hexanes afforded pure 3-trimethylsilanyl-prop-2-yn-1-ol, 7.85 g (70%). ^{1}H-NMR ($CDCl_3$): δ 4.25 (s, 2 H), 0.20 (s, 9 H); ^{13}C-NMR ($CDCl_3$): δ 103.7, 90.7, 51.6, 0.20.

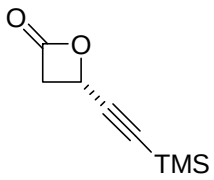


Synthesis of 3-trimethylsilylpropynal (17):[24] To an Erlenmeyer flask was added 5.07 g (23.6 mmol) of PCC and 24 mL of anhydrous methylene chloride. At ambient temperature, 1.50 g (11.8 mmol) of purified 3-trimethylsilanyl-prop-2-yn-1-ol was added dropwise over 5 min. The reaction was allowed to stir at ambient temperature overnight. The PCC was removed by filtration over a plug of fluorosil and the solid was washed multiple times with methylene chloride. The crude aldehyde was filtered over a plug of silica using methylene chloride as elutent and the resulting pure aldehyde (**17**) was concentrated under

[24] Harris, N. J.; Gajewksi, J. J. *J. Am. Chem. Soc.* **1994**, *116*, 6121-6129.

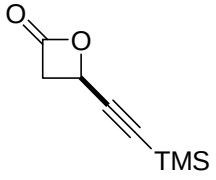
reduced pressure, yielding 0.83 g (57%) of 3-trimethylsilanyl-propynal (**17**). ^{1}H-NMR ($CDCl_3$): δ 9.17 (s, 1 H), 0.26 (s, 9 H); ^{13}C-NMR ($CDCl_3$): δ 176.70, 103.01, 102.15, -0.97.

General procedure for the AAC reaction of 3-alkynyl aldehydes: To a round-bottom flask was added 80 mg (0.20 mmol) of either TMSQD or TMSQN and the flask was transferred to the glove box. Anhydrous $MgCl_2$, 190 mg (2.00 mmol), was added and the flask was removed from the glove box. Under an atmosphere of nitrogen, diethyl ether (2.00 mL) was added and the solution was stirred at ambient temperature for 5 min. Methylene chloride (4.00 mL) was added and the reaction mixture was cooled to –78 °C. To the reaction mixture was added 0.88 mL (5.0 mmol) of *N*, *N*-diisopropylethylamine and the reaction was allowed to stir for 15 min. The desired 3-alkynyl aldehyde (2.00 mmol) was added and a solution of 4.00 mmol of the desired acid chloride in 1.00 mL of CH_2Cl_2 was added over 1 h *via* syringe pump. The reaction mixture was stirred for 7-16 h and was quenched at the reaction temperature with 10 mL of a saturated solution of NH_4Cl. Additional NH_4Cl (25 mL) was added whereupon the organic layer was separated. The organic mixture was extracted with CH_2Cl_2 (3 X 15 mL) and the organic layers were dried. The crude product mixture was purified by flash chromatography.

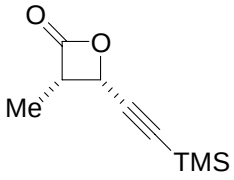


(*S*)-4-(2-(Trimethylsilyl)ethynyl)oxetan-2-one (33a). The general procedure for the AAC reaction of 3-alkynyl aldehydes was followed employing 40 mg of TMSQD (0.10 mmol, 10 mol %), 95 mg of $MgCl_2$ (1.00 mmol, 100 mol %), 126 mg of 3-(trimethylsilyl)prop-2-ynaldehyde (1.00 mmol), 0.437 mL (2.50 mmol) of DIPEA, and 0.141 mL of acetyl chloride (2.00 mmol) at a reaction temperature of –78 °C. Purification by flash chromatography (5% ethyl acetate in hexanes) gave 146 mg (87%) of the

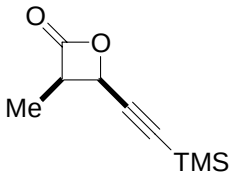
title compound as a colorless oil. Separation of the enantiomers by chiral GLC [Chiraldex™ G-TA column 20 m x 0.25 mm, flow rate 0.5 mL/min, method: 80 °C for 5.0 min, ramp @ 1.0 °C/min to 90 °C for 10.0 min, ramp @ 1.0 °C/min to 100 °C for 5.0 min, ramp @ 5.0 °C/min to 130 °C for 20.0 min, T_r: 29.4 min (4*R*), T_r: 29.6 min (4*S*)] provided the enantiomer ratio: (*S*):(*R*) = >99:1 (>99% ee). $[\alpha]_D$ −5.8 (*c* 1.21, $CHCl_3$). IR (thin film): 2963, 2359, 2342, 1838, 1251, 1131, 1008, 946, 847, 642 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 5.02 (dd, J = 6.2, 4.6 Hz, 1 H), 3.78 (dd, J = 16.3, 6.3 Hz, 1 H), 3.55 Hz (dd, J = 16.3, 4.6 Hz, 1 H), 0.23 Hz (9 H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 166.7, 99.2, 96.0, 58.5, 46.1, -0.6. MS (EI, 70eV): *m/z* 153 (M^+–CH_3), 124 (M^+–CO_2), 109 (M^+–CH_3, CO_2). HRMS *m/z* calcd for $C_8H_{12}O_2Si$: 168.0607; found 168.0569.



(*R*)-4-(2-(Trimethylsilyl)ethynyl)oxetan-2-one (33b). The general procedure for the AAC reaction of 3-alkynyl aldehydes was followed employing 80 mg of TMSQN (0.20 mmol, 10 mol %), 190 mg of $MgCl_2$ (2.00 mmol, 100 mol %), 252 mg of 3-(trimethylsilyl)prop-2-ynaldehyde (2.00 mmol), 0.837 mL (5.00 mmol) of DIPEA, and 0.282 mL of acetyl chloride (4.00 mmol) at a reaction temperature of –78 °C. Purification by flash chromatography (5% ethyl acetate in hexanes) gave 300 mg (89%) of the title compound as a colorless oil. Separation of the enantiomers by chiral GLC [Chiraldex™ G-TA column 20 m x 0.25 mm, flow rate 0.5 mL/min, method: 80 °C for 5.0 min, ramp @ 1.0 °C/min to 90 °C for 10.0 min, ramp @ 1.0 °C/min to 100 °C for 5.0 min, ramp @ 5.0 °C/min to 130 °C for 20.0 min, T_r: 29.4 min (4*R*), T_r: 29.6 min (4*S*)] provided the enantiomer ratio: (*R*):(*S*) = >99:1 (>99% ee). $[\alpha]_D$ +6.2 (*c* 1.26, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 5.02 (dd, J = 6.2, 4.6 Hz, 1 H), 3.78 (dd, J = 16.3, 6.3 Hz, 1 H), 3.55 Hz (dd, J = 16.3, 4.6 Hz, 1 H), 0.22 Hz (9 H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 166.7, 99.2, 96.2, 58.6, 46.3, -0.5.

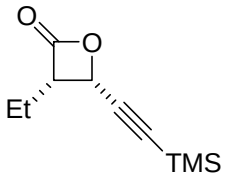


(3*S*,4*S*)-3-Methyl-4-(2-(trimethylsilyl)ethynyl)oxetan-2-one (16a). The general procedure for the AAC reaction of 3-alkynyl aldehydes was followed employing 400 mg of TMSQD (1.00 mmol, 10 mol %), 950 mg of $MgCl_2$ (10.00 mmol, 100 mol %), 1.26 g of 3-(trimethylsilyl)prop-2-ynaldehyde (10.00 mmol), 4.48 mL (25.00 mmol), and 1.72 mL (20.00) of propionyl chloride (4.00 mmol) at a reaction temperature of –78 °C. Purification by flash chromatography (5% ethyl acetate in hexanes) gave 1.76 g (96%) of the title compound as a colorless oil. Separation of the enantiomers by chiral GLC [Chiraldex™ G-TA column 20 m x 0.25 mm, flow rate 0.5 mL/min, method: 100 °C for 10.0 min, ramp @ 5.0 °C/min to 130 °C for 12.0 min, ramp @ 10.0 °C/min to 160 °C for 15.0 min, T_r: 13.7 min (3*S*,4*R*), T_r: 15.2 min (3*R*,4*R*), T_r: 16.3 min (3*S*,4*S*)] provided the enantiomer and diastereomer ratios: (*S,S*):(*R,R*) = >99:1 (>99% ee), *cis:trans* = >32:1 (>93% de). $[\alpha]_D$ +8.7 (*c* 1.11, $CHCl_3$). IR (thin film): 2962, 2180, 1839, 1252, 1139, 1018, 844, 648 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 5.13 (d, J = 6.4 Hz, 1 H), 3.86 (dq, J = 7.6 Hz, 1 H), 1.44 (d, J = 7.7 Hz, 3 H), 0.22 (s, 9 H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 171.1, 98.5, 96.8, 64.6, 50.0, 10.3, -0.5. MS (EI, 70eV): *m/z* 167 (M^+–CH_3), 138 (M^+–CO_2), 123 (M^+–CH_3, CO_2). HRMS *m/z* calcd for $C_9H_{14}O_2Si$: 182.0763; found 182.0720.



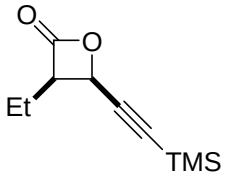
(3*R*,4*R*)-3-Methyl-4-(2-(trimethylsilyl)ethynyl)oxetan-2-one (16b). The general procedure for the AAC reaction of 3-alkynyl aldehydes was followed employing 80 mg of TMSQN (0.20 mmol, 10 mol %), 190 mg of $MgCl_2$ (2.00 mmol, 100 mol %), 252 mg of 3-(trimethylsilyl)prop-2-ynaldehyde (2.00 mmol), 0.837 mL (5.00 mmol) of DIPEA, and 0.348 mL of propionyl chloride (4.00 mmol) at a reaction

temperature of –78 °C. Purification by flash chromatography (5% ethyl acetate in hexanes) gave 317 mg (87%) of the title compound as a colorless oil. Separation of the enantiomers by chiral GLC [Chiraldex™ G-TA column 20 m x 0.25 mm, flow rate 0.5 mL/min, method: 100 °C for 10.0 min, ramp @ 5.0 °C/min to 130 °C for 12.0 min, ramp @ 10.0 °C/min to 160 °C for 15.0 min, T_r: 13.7 min (3*R*,4*S*), T_r: 10.3 min (3*R*,4*R*), T_r: 16.3 min (3*S*,4*S*)] provided the enantiomer and diastereomer ratios: (*R,R*):(*S,S*) = >99:1 (>99% ee), *cis:trans* = >82:1 (>93% de). $[\alpha]_D$ –8.4 (*c* 0.92, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 5.13 (d, J = 6.4 Hz, 1 H), 3.87 (dq, J = 7.3 Hz, 1 H), 1.43 (d, J = 7.7 Hz, 3 H), 0.22 (s, 9 H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 171.1, 98.6, 96.8, 64.6, 49.7, 10.3, -0.5.

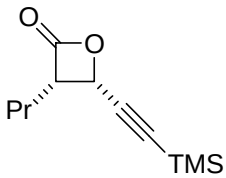


(3*S*,4*S*)-3-Ethyl-4-(2-(trimethylsilyl)ethynyl)oxetan-2-one (34a). The general procedure for the AAC reaction of 3-alkynyl aldehydes was followed employing 80 mg of TMSQD (0.20 mmol, 10 mol %), 190 mg of $MgCl_2$ (2.00 mmol, 100 mol %), 252 mg of 3-(trimethylsilyl)prop-2-ynaldehyde (2.00 mmol), 0.837 mL (5.00 mmol) of DIPEA, and 0.419 mL of butyryl chloride (4.00 mmol) at a reaction temperature of –78 °C. Purification by flash chromatography (5% ethyl acetate in hexanes) gave 382 mg (97%) of the title compound as a colorless oil. Separation of the enantiomers by chiral GLC [Chiraldex™ G-TA column 20 m x 0.25 mm, flow rate 0.5 mL/min, method: 80 °C for 5.0 min, ramp @ 1.0 °C/min to 100 °C for 10.0 min, ramp @ 1.0 °C/min to 130 °C for 5.0 min, T_r: 12.6 min (3*S*,4*R*), T_r: 42.5 min (3*S*,4*S*), T_r: 43.1 min (3*R*,4*R*)] provided the enantiomer and diastereomer ratios: (*S,S*):(*R,R*) = >99:1 (>99% ee), *cis:trans* = 12:1 (84% de). $[\alpha]_D$ +18.1 (*c* 1.22, $CHCl_3$). IR (thin film): 2968, 2359, 1837, 1252, 1128, 1089, 847, 649 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 5.10 (d, J = 6.4 Hz, 1 H), 3.67 (ddd, J = 8.2, 7.6, 1.1 Hz, 1 H), 1.93 (m, 2 H),

1.10 (t, J = 7.5 Hz, 3 H), 0.22 (s, 9 H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 170.3, 98.2, 97.0, 63.9, 56.4, 19.5, 11.2, -0.6. MS (EI, 70eV): *m/z* 152 (M^+–CO_2), 137 (M^+–CH_3, CO_2). HRMS *m/z* calcd for $C_{10}H_{16}O_2Si$: 196.0920; found 196.0917.

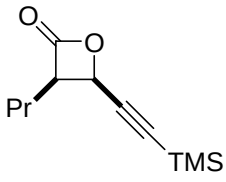


(3*R*,4*R*)-3-Ethyl-4-(2-(trimethylsilyl)ethynyl)oxetan-2-one (34b). The general procedure for the AAC reaction of 3-alkynyl aldehydes was followed employing 80 mg of TMSQN (0.20 mmol, 10 mol %), 190 mg of $MgCl_2$ (2.00 mmol, 100 mol %), 252 mg of 3-(trimethylsilyl)prop-2-ynaldehyde (2.00 mmol), 0.837 mL (5.00 mmol) of DIPEA, and 0.419 mL of butyryl chloride (4.00 mmol) at a reaction temperature of –78 °C. Purification by flash chromatography (5% ethyl acetate in hexanes) gave 335 mg (85%) of the title compound as a colorless oil. Separation of the enantiomers by chiral GLC [Chiraldex™ G-TA column 20 m x 0.25 mm, flow rate 0.5 mL/min, method: 80 °C for 5.0 min, ramp @ 1.0 °C/min to 100 °C for 10.0 min, ramp @ 1.0 °C/min to 130 °C for 5.0 min, T_r: 12.5 min (3*R*,4*S*), T_r: 42.5 min (3*S*,4*S*), T_r: 43.1 min (3*R*,4*R*)] provided the enantiomer and diastereomer ratios: (*R,R*):(*S,S*) = >99:1 (>99% ee), *cis:trans* = 10:1 (81% de). $[\alpha]_D$ –18.5 (*c* 1.05, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 5.10 (d, J = 6.4 Hz, 1 H), 3.68 (ddd, J = 8.2, 7.5, 1.2 Hz, 1 H), 1.93 (m, 2 H), 1.10 (t, J = 7.5 Hz, 3 H), 0.23 (s, 9 H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 170.4, 98.3, 97.0, 64.0, 56.4, 19.5, 11.3, -0.5.



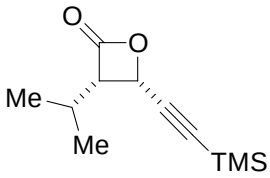
(3*S*,4*S*)-4-(2-(Trimethylsilyl)ethynyl)-3-propyloxetan-2-one (35a). The general procedure for the AAC reaction of 3-alkynyl aldehydes was followed employing 80 mg of TMSQD (0.20 mmol, 10 mol %), 190 mg of $MgCl_2$ (2.00 mmol, 100 mol %), 252 mg of 3-(trimethylsilyl)prop-2-ynaldehyde (2.00 mmol), 0.837 mL

(5.00 mmol) of DIPEA, and 0.485 mL of valeryl chloride (4.00 mmol) at a reaction temperature of –78 °C. Purification by flash chromatography (5% ethyl acetate in hexanes) gave 352 mg (84%) of the title compound as a colorless oil. Separation of the enantiomers by chiral GLC [Chiraldex™ G-TA column 20 m x 0.25 mm, flow rate 0.5 mL/min, method: 80 °C for 5.0 min, ramp @ 1.0 °C/min to 100 °C for 10.0 min, ramp @ 1.0 °C/min to 130 °C for 5.0 min, T_r: 53.8 min (3*S*,4*S*), T_r: 54.0 min (3*R*,4*R*)] provided the enantiomer and diastereomer ratios: (*S,S*):(*R,R*) = >99:1 (>99% ee), *cis:trans* = >99:1 (>99% de). $[\alpha]_D$ +32.0 (*c* 1.25, $CHCl_3$). IR (thin film): 2360, 2341, 2184, 1838, 1252, 1127, 940, 844, 649 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 5.09 (d, J = 6.4 Hz, 1 H), 3.75 (dd, J = 7.9, 6.4 Hz, 1 H), 1.87 (aq, J = 7.9, 7.5 Hz, 2 H), 1.49 (tq, J = 7.5, 2.7 Hz, 2 H), 0.96 (t, J = 7.3 Hz, 3 H), 0.21 (s, 9 H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 170.5, 98.2, 97.1, 64.1, 54.7, 27.9, 20.0, 13.7, -0.6. MS (EI, 70eV): *m/z* 166 (M^+–CO_2), 151 (M^+–CH_3, CO_2). HRMS *m/z* calcd for $C_{10}H_{18}Si$: 166.1178; found 166.1170.

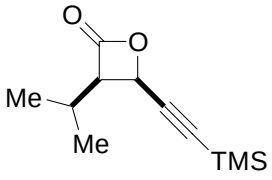


(3*R*,4*R*)-4-(2-(Trimethylsilyl)ethynyl)-3-propyloxetan-2-one (35b). The general procedure for the AAC reaction of 3-alkynyl aldehydes was followed employing 80 mg of TMSQN (0.20 mmol, 10 mol %), 190 mg of $MgCl_2$ (2.00 mmol, 100 mol %), 252 mg of 3-(trimethylsilyl)prop-2-ynaldehyde (2.00 mmol), 0.837 mL (5.00 mmol) of DIPEA, and 0.485 mL of valeryl chloride (4.00 mmol) at a reaction temperature of –78 °C. Purification by flash chromatography (5% ethyl acetate in hexanes) gave 347 mg (83%) of the title compound as a colorless oil. Separation of the enantiomers by chiral GLC [Chiraldex™ G-TA column 20 m x 0.25 mm, flow rate 0.5 mL/min, method: 80 °C for 5.0 min, ramp @ 1.0 °C/min to 100 °C for 10.0 min, ramp @ 1.0 °C/min to 130 °C for 5.0 min, T_r: 53.8 min (3*S*,4*S*), T_r: 54.0 min (3*R*,4*R*)] provided the enantiomer and diastereomer ratios: (*R,R*):(*S,S*)

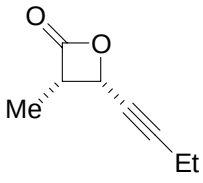
= >99:1 (>99% ee), *cis:trans* = >99:1 (>99% de). $[\alpha]_D$ –31.6 (*c* 1.12, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 5.10 (d, J = 6.4 Hz, 1 H), 3.75 (dd, J = 7.3, 6.4 Hz, 1 H), 1.87 (aq, J = 7.9, 7.5 Hz, 2 H), 1.49 (tq, J = 7.5, 2.7 Hz, 2 H), 0.96 (t, J = 7.3 Hz, 3 H), 0.21 (s, 9 H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 170.5, 98.3, 97.1, 64.1, 54.8, 27.9, 20.1, 13.7, -0.5.



(3*S*,4*S*)-3-Isopropyl-4-(2-(trimethylsilyl)ethynyl)oxetan-2-one (36a). The general procedure for the AAC reaction of 3-alkynyl aldehydes was followed employing 80 mg of TMSQD (0.20 mmol, 10 mol %), 190 mg of $MgCl_2$ (2.00 mmol, 100 mol %), 252 mg of 3-(trimethylsilyl)prop-2-ynaldehyde (2.00 mmol), 0.837 mL (5.00 mmol) of DIPEA, and 0.485 mL of isovaleryl chloride (4.00 mmol) at a reaction temperature of –78 °C. Purification by flash chromatography (5% ethyl acetate in hexanes) gave 334 mg (80%) of the title compound as a colorless oil. Separation of the enantiomers by chiral GLC [Chiraldex™ G-TA column 20 m x 0.25 mm, flow rate 0.5 mL/min, method: 80 °C for 5.0 min, ramp @ 1.0 °C/min to 100 °C for 10.0 min, ramp @ 1.0 °C/min to 130 °C for 5.0 min, T_r: 49.1 min (3*S*,4*S*), T_r: 50.5 min (3*R*,4*R*)] provided the enantiomer and diastereomer ratios: (*S,S*):(*R,R*) = 5:1 (70% ee), *cis:trans* = >99:1 (>99% de). $[\alpha]_D$ +40.4 (*c* 0.99, $CHCl_3$). IR (thin film): 2962, 2876, 1841, 1252, 1123, 1016, 848, 647 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 5.07 (d, J = 6.4 Hz, 1 H), 3.43 (dd, J = 17.2, 6.4 Hz, 1 H), 2.34 (m, 1 H), 1.18 (d, J = 6.7 Hz, 3 H), 1.03 (d, J = 6.5 Hz, 3 H), 0.20 (s, 9 H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 169.7, 98.1, 97.4, 63.7, 61.9, 26.7, 20.7, 19.5, -0.6. MS (EI, 70eV): *m/z* 166 (M^+–CO_2), 151 (M^+–CH_3, CO_2). HRMS *m/z* calcd for $C_{11}H_{18}O_2Si$: 210.1076; found 210.1154.

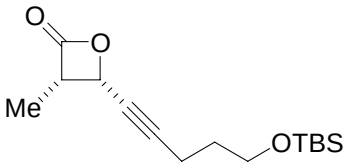


(3*R*,4*R*)-3-Isopropyl-4-(2-(trimethylsilyl)ethynyl)oxetan-2-one (36b). The general procedure for the AAC reaction of 3-alkynyl aldehydes was followed employing 80 mg of TMSQN (0.20 mmol, 10 mol %), 190 mg of $MgCl_2$ (2.00 mmol, 100 mol %), 252 mg of 3-(trimethylsilyl)prop-2-ynaldehyde (2.00 mmol), 0.837 mL (5.00 mmol) of DIPEA, and 0.485 mL of isovaleryl chloride (4.00 mmol) at a reaction temperature of –78 °C. Purification by flash chromatography (5% ethyl acetate in hexanes) gave 326 mg (78%) of the title compound as a colorless oil. Separation of the enantiomers by chiral GLC [Chiraldex™ G-TA column 20 m x 0.25 mm, flow rate 0.5 mL/min, method: 80 °C for 5.0 min, ramp @ 1.0 °C/min to 100 °C for 10.0 min, ramp @ 1.0 °C/min to 130 °C for 5.0 min, T_r: 35.7 min (3*S*,4*R*), T_r: 36.1 min (3*R*,4*S*), T_r: 49.1 min (3*S*,4*S*), T_r: 50.5 min (3*R*,4*R*)] provided the enantiomer and diastereomer ratios: (*R,R*):(*S,S*) = >1.1:1 (>0.4% ee), *cis:trans* = 95:1 (94% de). $[\alpha]_D$ –1.2 (*c* 0.78, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 5.08 (d, J = 6.0 Hz, 1 H), 3.44 (dd, J = 17.3, 6.3 Hz, 1 H), 2.35 (m, 1 H), 1.19 (d, J = 6.7 Hz, 3 H), 1.04 (d, J = 6.5 Hz, 3 H), 0.21 (s, 9 H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 169.7, 98.1, 97.4, 63.7, 62.0, 26.7, 20.8, 19.6, -0.6.



(3*S*,4*S*)-4-(But-1-ynyl)-3-methyloxetan-2-one (37). The general procedure for the AAC reaction of 3-alkynyl aldehydes was followed employing 67 mg of TMSQD (0.17 mmol, 10 mol %), 16 mg of $MgCl_2$ (0.17 mmol, 10 mol %), 140 mg of pent-2-ynal (1.71 mmol), 0.749 mL (4.28 mmol) of DIPEA, and 0.297 mL (3.42 mmol) of propionyl chloride at a reaction temperature of –78 °C. Purification by flash chromatography (5% ethyl acetate in hexanes) gave 155 mg (66%) of the title compound as a colorless oil. Separation of the enantiomers by chiral GLC [Chiraldex™ G-TA column 20 m x 0.25 mm, flow rate 0.5 mL/min, method: 80 °C for 5.0 min, ramp @ 5.0 °C/min to 100 °C for

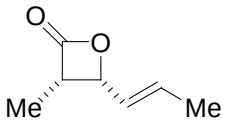
10.0 min, ramp @ 5.0 °C/min to 130 °C for 5.0 min, Tr: 21.3 min (3S,4S), Tr: 21.8 min (3R,4R)] provided the enantiomer and diastereomer ratios: (S,S):(R,R) = >99:1 (>99% ee), cis:trans = >99:1 (>99% de). [α]D +18.6 (c 0.63, CHCl3). IR (thin film): 2981, 2940, 2359, 2246, 1829, 1141, 1103, 972, 879 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 5.15 (dt, J = 6.4, 2.0 Hz, 1 H), 3.83 (dq, J = 6.4, 1.3 Hz, 1 H), 2.33 (dq, J = 7.5, 2.0 Hz, 2 H), 1.42 (d, J = 7.7 Hz, 3 H), 1.19 (t, J = 7.5 Hz, 3 H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 171.5, 95.1, 71.9, 65.1, 49.5, 13.4, 12.5, 10.3. MS (EI, 70eV): *m/z* 94 (M^+–CO_2), 79 (M^+–CH_3, CO_2). HRMS *m/z* calcd for C_7H_{10}: 94.0783; found 94.0776.



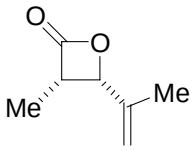
(3*S*,4*S*)-4-[(5-*t*-Butyldimethylsilyloxy)pent-1-ynyl]-3-methyloxetan-2-one (38). The general procedure for the AAC reaction of 3-alkynyl aldehydes followed employing 80 mg of TMSQD (0.20 mmol, 10 mol %), 522 mg of LiI (4.00 mmol, 200 mol %), 452 mg of 6-(t-butyldimethylsilyloxy)hex-2-ynal (2.00 mmol), 0.837 mL (5.00 mmol) of DIPEA, and 0.348 mL of propionyl chloride (4.00 mmol) at a reaction temperature of –78 °C. Purification by flash chromatography (5% ethyl acetate in hexanes) gave 324 mg (58%) of the title compound as a colorless oil. Separation of the enantiomers by chiral GLC [Chirasil-dex CD DF=0.25 column 25 m x 0.25 mm, T_{Max} = 225 °C, flow rate 0.5 mL/min, method: 80 °C for 5.0 min, ramp @ 5.0 °C/min to 100 °C for 10.0 min, ramp @ 5.0 °C/min to 130°C for 10.0 min, T_r: 24.4 min (3*S*,4*S*), T_r: 25.3 min (3*R*,4*R*), T_r: 16.1 min (3*S*,4*R*)] provided the enantiomer and diastereomer ratios: (*S,S*):(*R,R*) = 98:2 (97% ee), *cis:trans* = 83:7 (63% de).[25] $[\alpha]_D$ +10.5 (*c* 0.98, $CHCl_3$). IR (thin film): 3054, 2987, 2957, 2858, 2306, 1830, 1265, 896, 837, 742, 706 cm^{-1}; ^{1}H-NMR (300 MHz,

[25] Enantiomeric excess and diastereomeric excess both assessed by GC on the desilated β-lactone (fabricated by introduction of the β-lactone to TBAF).

$CDCl_3$): δ 5.15 (dt, J = 6.4, 2.0 Hz, 1 H), 3.84 (dq, J = 6.5, 1.3 Hz, 1 H), 3.69 (t, J = 2.4 Hz, 2 H), 2.41 (dt, J = 7.1, 2.0 Hz, 2 H), 1.75 (dq, J = 6.0, 1.0 Hz, 2 H), 1.42 (d, J = 7.7 Hz, 3 H), 0.90 (s, 9 H), 0.06 (s, 6H); ^{13}C-NMR (75 MHz, CDCl3): δ 171.5, 93.5, 72.6, 65.0, 61.3, 49.5, 31.3, 25.9, 18.3, 15.2, 10.4, -5.4. MS (EI, 70eV): *m/z* 282 (M^+), 281 (M^+–H), 225 (M^+–CH_3, CO_2), 225 (M^+–$C(CH_3)_3$), 181 (M^+–$C(CH_3)_3$, $TBSO^+$), 131 ($TBSO^+$). HRMS *m/z* calcd for $C_{11}H_{17}O_3Si$: 225.0947, for $C_{15}H_{13}O_2$ 225.0916, for $C_7H_{21}O_4Si_2$ 225.0978; found 225.0943.



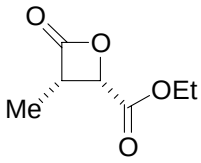
3-(*S*)-Methyl-4-(*R*)-propenyl-oxetan-2-one (53):[18,26] The general procedure for the AAC reaction of 3-alkynyl aldehydes was followed employing 80 mg of TMSQD (0.20 mmol, 10 mol %), 272 mg of $ZnCl_2$ (2.00 mmol, 100 mol %), 0.166 mL of crotonaldehyde (2.00 mmol), 0.837 mL (5.00 mmol) of DIPEA, and 0.348 mL of propionyl chloride (4.00 mmol) at a reaction temperature of 0 °C. ^{1}H-NMR ($CDCl_3$): δ 6.98-6.82 (m, 1 H), 6.18 (dq, J = 4.4, 1.6 Hz, 1 H), 4.74 (dq, J = 5.6, 1.4 Hz, 1 H), 3.95 (tq, J = 7.6, 1.3 Hz, 1 H), 1.69 (dd, J = 5.6, 1.4 Hz, 3 H), 1.42 (d, J = 7.6 Hz, 3 H).



(3*S*,4*S*)-3-Methyl-4-(prop-1-en-2-yl)oxetan-2-one (55). The general procedure for the AAC reaction of 3-alkynyl aldehydes was followed employing 80 mg of TMSQD (0.20 mmol, 10 mol %), 522 mg of LiI (4.00 mmol, 200 mol %), 0.166 mL of methacrolein (2.00 mmol), 0.837 mL (5.00 mmol) of DIPEA, and 0.348 mL of propionyl chloride (4.00 mmol) at a reaction temperature of –78 °C. Purification by flash chromatography (5% ethyl acetate in hexanes) gave 103 mg (82%) of the title compound as a colorless oil. Separation of the enantiomers by chiral GLC [Chirasil-dex CD

[26] Data obtained from crude ^{1}H-NMR.

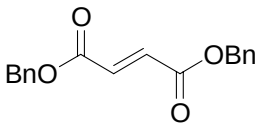
DF=0.25 column 25 m x 0.25 mm, T_{Max} = 225 °C, flow rate 0.5 mL/min, method: 80 °C for 5.0 min, ramp @ 5.0 °C/min to 100 °C for 10.0 min, ramp @ 5.0 °C/min to 130 °C for 5.0 min, T_r: 26.0 min (3*S*,4*S*), T_r: 26.9 min (3*R*,4*R*)] provided the enantiomer and diastereomer ratios: (*S,S*):(*R,R*) = >99:1 (>99% ee), *cis:trans* = >99:1 (>99% de). $[\alpha]_D$ –10.4 (*c* 0.92, $CHCl_3$). IR (thin film): 2981, 2947, 1829, 1455, 1378, 1262, 1008, 993, 922, 730 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 5.18 (dd, J = 5.4, 1.3 Hz, 2 H), 4.93 (d, J = 6.5 Hz, 1 H), 3.86 (dd, J = 7.7, 1.1 Hz, 1H), 1.74 (dd, J = 0.8, 0.7 Hz, 3 H), 1,19 (d, J = 6.4 Hz, 3 H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 171.8, 138.2, 113.3, 75.9, 48.7, 19.0, 8.5. MS (EI, 70eV): *m/z* 126 (M^+), 111 (M^+–CH_3), 82 (M^+–CO_2), 67 (M^+–CH_3, CO_2). HRMS *m/z* calcd for $C_7H_{10}O_2$: 126.0681; found 126.0664.



Synthesis of 3-(*S*)-methyl-4-(*R*)-oxo-oxetane-2-carboxylic acid ethyl ester (8): Ethyl glyoxylate (**9**), purchased as a trimeric solution in toluene, was added to a flask with distillation head and receiving flask (all under an atmosphere of nitrogen). This solution was heated to 110 °C and all toluene was distilled off. The neat solution of ethyl glyoxylate trimer was heated to 175 °C for 4 h. The solution was then heated up to 180 °C wherein the "cracked" trimer was distilled over into a round bottom flask at a temperature of –78 °C. The pure ethyl glyoxylate (**9**), a lightly colored yellow, clear viscous oil was weighed out and used immediately in the subsequent reaction.

To a round bottom flask was added the indicated Lewis acid and 1.0 mL of dry Et_2O. The mixture was stirred at ambient temperature to fully dissolve the Lewis acid. Once completed, 2.0 mL of anhydrous CH_2Cl_2 and either 39 mg of TMSQD (0.10 mmol) or 34 mg of MeQD (0.10 mmol) was added. The solution was cooled to –78 °C, 0.448 mL (2.50 mmol) of DIPEA was added and the reaction was allowed to stir for 15 min. Freshly cracked ethyl

glyoxylate (**9**), 102 mg (1.00 mmol), was added. Propionyl chloride, 0.174 mL (2.00 mmol), was added as a solution in 0.5 mL of dry CH_2Cl_2 over 1 h *via* a syringe pump. The solution was stirred at the indicated temperature over night. The reaction was quenched with 10 mL of a saturated solution of NH_4Cl and the organic layer was separated. The aqueous layer was washed with CH_2Cl_2 (3 X 15 mL) and all organics were combined and dried. Purification on silica gel employing 2% MeOH in CH_2Cl_2 provided 0.144 g (91%) of the title compound (non-reproducible). Separation of the enantiomers by chiral GLC [Chirasil-dex CD DF=0.25 column 25 m x 0.25 mm, T_{Max} = 225 °C, flow rate 0.5 mL/min, method: 100 °C for 10.0 min, ramp @ 5.0 °C/min to 130 °C for 12.0 min, ramp @ 10.0 °C/min to 160 °C for 15.0 min, T_r: 19.3 min (3*R*,4*S*), T_r: 33.8 min (3*R*,4*R*), T_r: 29.6 min (3*S*,4*S*)] provided the enantiomer ratio and diastereomer ratios: (*S*,*S*):(*R*,*R*) = >41:1 (>95% ee), *cis:trans* = >54:1 (>96% de). $[\alpha]_D$ –16.0 (*c* 1.50, $CHCl_3$). IR (thin film): 2985, 2943, 2361, 2342, 1843, 1755, 1462, 1377, 12101138, 1115, 1026, 691 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 4.95 (d, J = 6.9 Hz, 1 H), 4.33 (q, J = 7.1 Hz, 2 H), 4.07 (quintet, J = 7.2 Hz, 1 H), 1.35 (t, J = 7.1 Hz, 3 H), 1.32 (d, J = 7.7 Hz, 3 H); ^{13}C-NMR ($CDCl_3$): δ 169.78, 167.00, 70.13, 61.64, 49.79, 13.85, 9.03. MS (EI, 70eV): *m/z* 114 (M^+–CO_2), 86 (M^+–CO_2, CH_3, CH), 85 (M^+–$CO_2CH_2CH_3$), 69 (M^+–CO_2, OCH_2CH_3). HRMS *m/z* calcd for $C_6H_{10}O_2$: 114.0681; found 114.0676.



Synthesis of dibenzyl fumarate (42):[27] To a round bottom flask equipped with Dean-Stark apparatus and condenser was added 15.05 g (129.66 mmol) of fumaric acid, 0.308 g (1.62 mmol) of *p*-TsOH, and 150 mL of dry toluene. Next, 40.45 mL (388.99 mmol) of BnOH was added and the mixture was heated to 130 °C over night

[27] Furuta, K.; Gao, Q.-Z.; Yamamoto, H. *Org. Synth.* **1995**, *72*, 86-94.

to remove all water. The reaction was cooled to ambient temperature and the reaction mixture was diluted with 100 mL of diethyl ether. The solution was washed with 150 mL of a saturated solution of $NaHCO_3$ and the organics were separated. The aqueous layer was washed with diethyl ether (3 X 25 mL) and all organics were dried. The crude mixture was recrystallized from ethyl acetate and hexanes to yield pure **42**, 32.71 g (85.1 %). ^{1}H-NMR ($CDCl_3$): δ 7.38 (s, 5 H), 6.8 (s, 1 H), 5.38 (s, 2 H); ^{13}C-NMR ($CDCl_3$): δ 164.66, 133.72, 128.64, 128.53, 128.34, 67.11.

Ozonolysis of dibenzyl fumarate (42) and subsequent AAC reaction: In a round bottom flask was added 6.09 g (20.95 mmol) of dibenzyl fumarate (**42**) and 50 mL of dry CH_2Cl_2. The mixture was cooled to –78 °C and the solution was then ozonized with O_3 until a dark blue color persisted (indicating that the solution was saturated with ozone). Once this blue persisted, the solution was warmed to ambient temperature and 1.71 mL (23.25 mmol) of DMS was added. The reaction was stirred under nitrogen at ambient temperature over night. The volatiles were removed under reduced pressure and then, *via* bulb-to-bulb distillation, DMSO was removed. Next, within a temperature range of 60-70 °C and at a pressure of 15 mbar, pure benzyl glyoxylate (**43**) was distilled. The clear, somewhat viscous, clear, colorless solution was used immediately in the AAC reaction.

To a round bottom flask was added the indicated Lewis acid and 1.0 mL of dry Et_2O. The mixture was stirred at ambient temperature to fully dissolve the Lewis acid. Anhydrous CH_2Cl_2 (2.0 mL) and either 39 mg of TMSQD (0.10 mmol) or 34 mg of MeQD (0.10 mmol) was added. The reaction was cooled to –78 °C, 0.448 mL (2.50 mmol) of DIPEA was added and the reaction was allowed to stir for 15 min. Freshly distilled **43**, 0.102 g (1.00 mmol), was then

added and propionyl chloride, 0.174 mL (2.00 mmol), was added as a solution in 0.5 mL of dry CH_2Cl_2 over 1 h *via* a syringe pump. The solution was stirred at the indicated temperature over night. The reaction was quenched with 10 mL of a saturated solution of NH_4Cl and the organic layer was separated. The aqueous layer was washed with CH_2Cl_2 (3 X 15 mL) and all organics were combined and dried.

2.0 EFFORTS TOWARD THE TOTAL SYNTHESIS OF MOTUPORIN

2.1 MOTUPORIN: BIOACTIVITY

Marine sponges belonging to the genus *Theonella* have recently proven to be a rich source of biologically active cyclic peptides, each containing at least one previously unknown amino acid. Examples of such *Theonella* peptides are orbiculamide A, keramamides B-D, cyclothoenamides A and B, and theonellamides B and F. Upon its isolation in 1992, motuporin (**1**) readily assimilated into this category.[1]

Motuporin has proven to be a viable synthetic target not only because of its alluring structure. Synthetic ambition has been further enhanced due to its elevated bioactivity. The cyclic pentapeptide inhibits protein phosphatase-1 (PP-1) in a standard phosphorylase assay at subnanomolar concentrations (K_d<1nM), making it one of the most potent PP-1 inhibitors known. It also displays considerable *in vitro* cytotoxicity against murine leukemia (P388: IC_{50} 6μg/mL), human lung (A549: IC_{50} 2.4μg/mL), ovarian (HEY: IC_{50} 2.8μg/mL), colon (LoVo: IC_{50} 2.3μg/mL), breast (MCF7: IC_{50} 12.4μg/mL), and brain (U373MG: IC_{50} 2.4μg/mL) cancer cell lines. Curiously, **1** expresses antineoplastic activity, while the structurally analogous nodularin (**56**) and microcystin LR (**57b**) are both tumor promoting substances (Figure 11).[1]

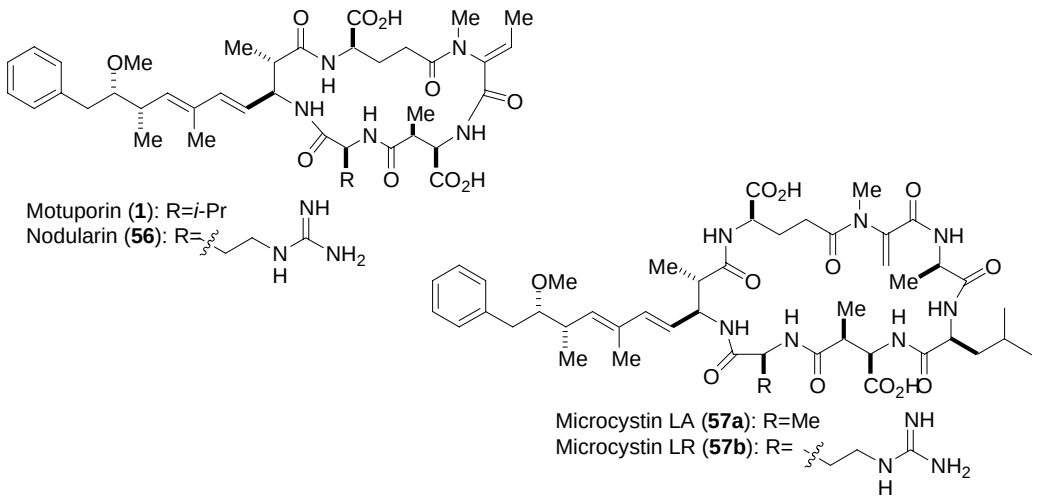
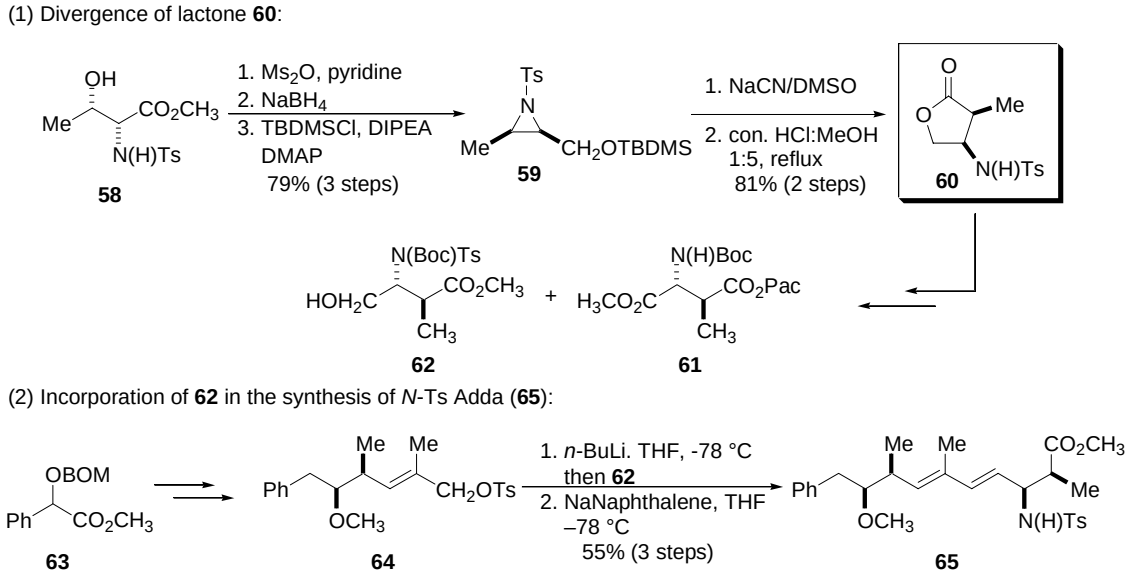


Figure 11: The structurally analogous motuporin (1), nodularin (56), and the microcystins (57 a-b).

2.2 PREVIOUS SYNTHESES OF MOTUPORIN

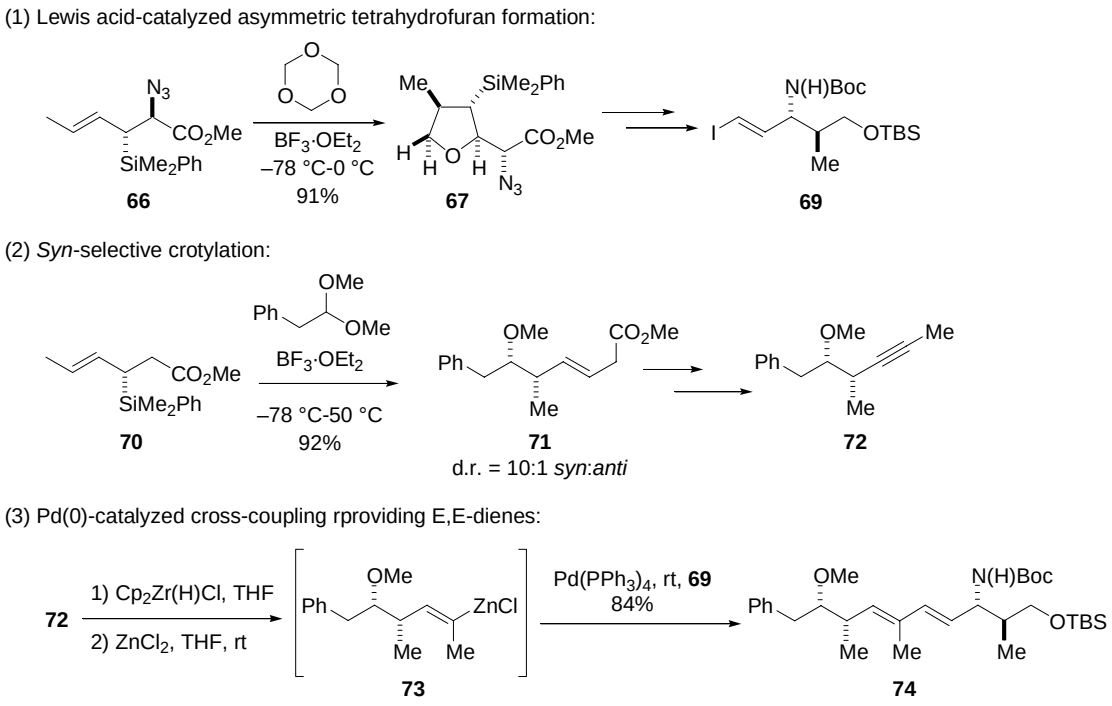
The first total synthesis of motuporin (**1**) was achieved in an enantioselective manner by Schreiber and Valentekovich in 1995. One of the main advantages of Schreiber's synthesis is its convergence. In the synthetic scheme, γ-lactone **60** was viewed as a critical intermediate in the production of both α-amino methyl ester **61** and β-amino acid **62**. The latter was then incorporated into the synthesis of *N*-Ts Adda (**65**). Subsequently, ester **61** was introduced alongside the common amino acids of motuporin in order to complete the synthesis.[3a]



Scheme 1: Synthesis of intermediate γ-lactone 63.

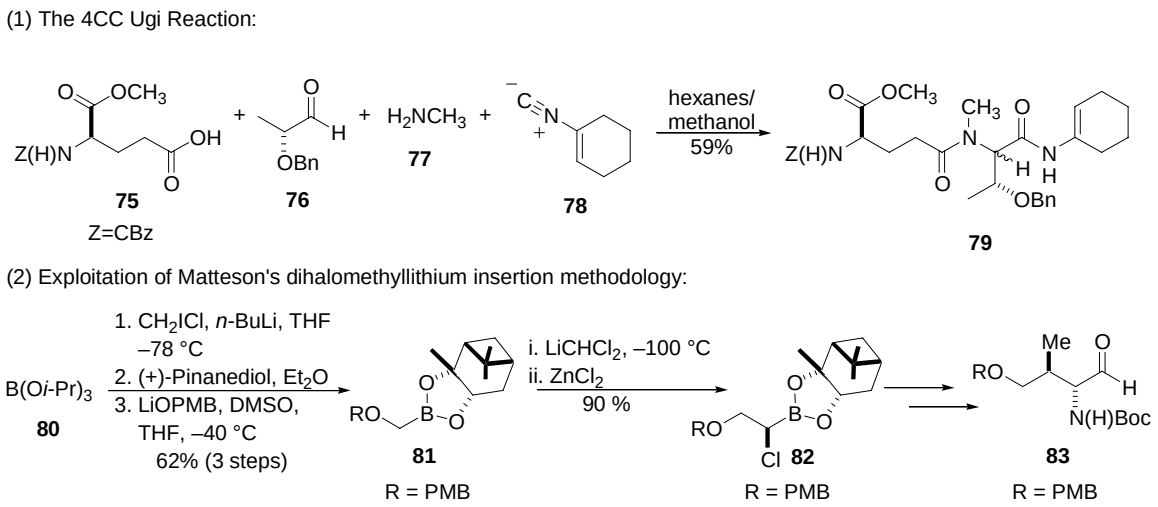
In 1999, Panek and Hu reported their total synthesis of (–)-motuporin. The impetus for this synthesis was the exploitation of three unique methodologies: (1) a protocol for Lewis acid-catalyzed asymmetric tetrahydrofuran formation, (2) a *syn*-selective crotylation *via* an intermediary oxocarbenium species, and (3) a novel Pd(0)-catalyzed cross-coupling reaction between vinyl metals and vinyl halides (providing *E*,*E*-dienes from the corresponding *Z*-vinyl iodides). When combined, these three methodologies provided a novel, selective total synthesis of **1**.[3b,28]

[28] (a) Hu, T.; Panek, J. S. *J. Am. Chem. Soc.* **2002**, *124*, 11368-11378. (b) Panek, J. S.; Hu, T. *J. Org. Chem.* **1997**, *62*, 4912-4913. (c) Panek, J. S.; Hu, T. *J. Org. Chem.* **1997**, *62*, 4914-4915.



Scheme 2: The three key methodologies exploited in Panek's synthesis of motuporin.

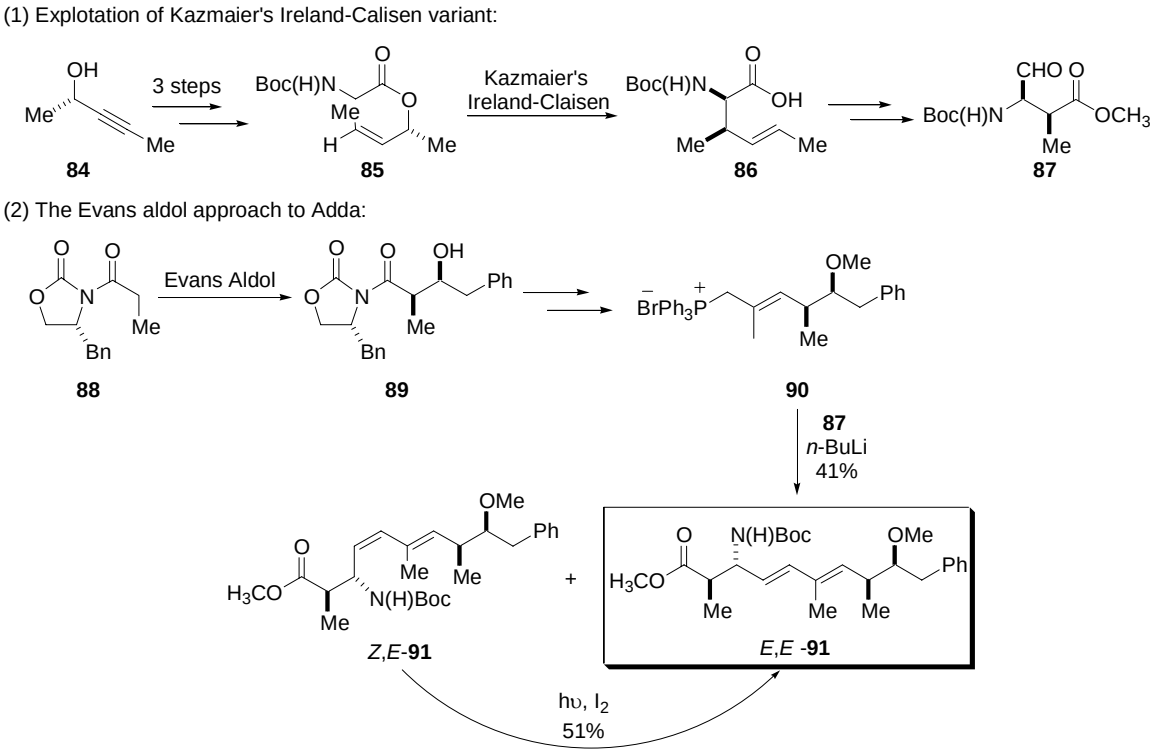
In 1999, Armstrong and Bauer also published their synthetic efforts toward motuporin.[3c] The two chief methodologies exploited were a four-component Ugi condensation (4CC) reaction to synthesize residue **79** and Matteson's dihalomethyllithium insertion methodology for the construction of key fragment **83**. With success in the production of both **79** and **83**, the total synthesis of motuporin was completed utilizing common peptide coupling strategies.



Scheme 3: The key methodologies exploited by Armstrong and coworkers.

The final total synthesis to be surmised was reported by Toogood and coworkers, again in 1999.[3d,29] Arguably the most attractive method employed in this synthesis was the unique synthesis of *N*-Boc Adda (*E*,*E*-**91**). To begin, alkynyl alcohol **84** was transformed into glycine ester **85** exploiting methods developed by Kazmaier.[30] Utilization of Kazmaier's chelated Ireland-Claisen variant allowed for the formation of carboxylic acid **86**. Following standard transformations, ester **87** was fabricated. Subsequently, an Evans aldol was utilized to produce optically active amide **89**. This amide was transformed into bromide salt **90** and was then combined with ester **87** utilizing a Wittig reaction to produce a mixture of *E*,*E*-**91** and *Z*,*E*-**91**. Isomerization of the undesired *Z*,*E*-**91** with light and iodine proceeded to the desired *E*,*E*-**91** in 51% yield. With this variant of Adda in hand, the synthesis of motuporin became relatively straightforward.

[29] Kim, H. Y.; Toogood, P. L. *Tetrahedron Lett.* **1996**, *37*, 2349-2352.
[30] Kazmaier, U. *Angew. Chem. Int. Ed.* **1994**, *33*, 998-999.



Scheme 4: Toogood's utilization of Kazmaier's Ireland-Claisen Rearrangement.

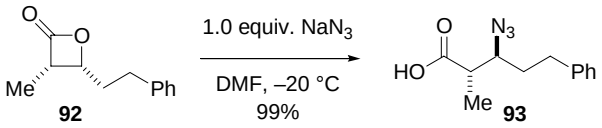
2.3 RESULTS AND DISCUSSION

2.3.1 Synthesis of β-amino acid 6

The key methodologies exploited in our outlined total synthesis of motuporin (**1**) are the utilization of the alkaloid-catalyzed AAC reaction to provide critical β-lactones **8**, **13**, and **16** along with sodium azide-mediated lactone ring-opening (β-lactones **8** and **16**, specifically) to produce β-azido acids. As indicated in the previous chapter, lactones **8** and **16** had been synthesized, although the former still contained problems with isolation. With both **8** and **16** in hand, the viability of the azide-mediated S_N2 ring-opening was investigated.

Sodium azide had been previously exploited in the S_N2 ring-opening of mono-substituted optically active β-lactones to provide β-azido acids.[12a,c] In order to assess the feasibility of S_N2 ring-opening of disubstituted lactones, β-lactone **92** was subjected to sodium azide.[31] Employing 1.0 equiv. of sodium azide with purified **92**, resulting β-azido acid **93** was prepared in 99% yield after purification (Equation 13).

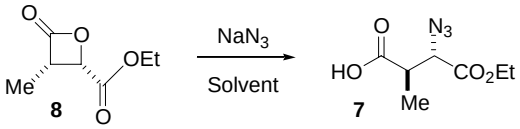
Equation 13



Due to the promising result of S_N2 ring-opening of **92**, lactone **8** was subjected to azide-mediated ring-opening. Although difficulties in reproducible production and purification of **8** still remained, enough crude **8** was produced to assess the viability of the azide opening (Table 10). Initial results employing 2.0 equiv. of sodium azide at 50 °C overnight provided a 47.4:52.6 ratio of desired *anti*-β-azido acid to epimerized *syn*-β-azido acid (entry 1). Unfortunately, attempts to purify acid **7** by column chromatography were unproductive, resulting in elimination of the azide down to the conjugated olefin. Therefore, it was decided that the diastereoselectivity quandary should be resolved before an effective method of purification was assessed.

[31] Lactone **92** was prepared from the AAC reaction between methyl ketene and hydrocinnamaldehyde.

Table 10: Sodium azide opening of lactone 8



Entry	NaN_3 (equiv.)	Solvent	Temp. (°C), Time	Result (*anti*:*syn*)[a]
1	2.0	DMSO	50, ON	47.4:52.6
2	2.0	DMSO	50, 3 h	66.7:33.3
3	2.0	DMSO[b]	50, 4 h	91.5:8.5
4	1.0	DMSO[b]	rt, 2 h	20% *anti*
5	1.0	DMSO[b]	rt, ON	32% *anti*
6	1.0	DMF[b]	rt, 30 min.	80.8:19.2
7[c]	2.0	CH_2Cl_2	0, 90 min.	Decomposition

[a]Results listed as ratio of desired (*anti*) to epimerized (*syn*) product. All ratios resolved from ^{1}H-NMR. [b]4Å mol. sieves used 1:1 by wt. with lactone where noted. [c]TMGA was employed instead of NaN_3.

In order to ascertain if epimerization was a result of reaction time, lactone **8** was again subjected to 2.0 equiv. of sodium azide at 50 °C; however, the reaction was stopped after 3 h. Under this abbreviated reaction time, the quantity of epimerized product decreased, providing a 66.7:33.3 *anti*:*syn* ratio (entry 2). Although this improvement was notable, diastereoselectivity was still less than desirable.

To further improve selectivity, the origin of the inadequate diastereoselectivity was questioned. Epimerization of **7** was thought to transpire through three possible mechanisms: (1) a reversible enolization, (2) a reversible α-deprotonation/β-elimination, and/or (3) a reversible allylic azide rearrangement.[3b,32] Since DMSO is commonly entrained with water, molecular sieves were introduced to help alleviate deprotonation by water (or hydroxide) (entries 3-6). This alteration immediately improved the epimerization quandary, increasing the product ratio to 91.5:8.5 *anti*:*syn* (entry 3). Since epimerization still occurred, two simultaneous modifications

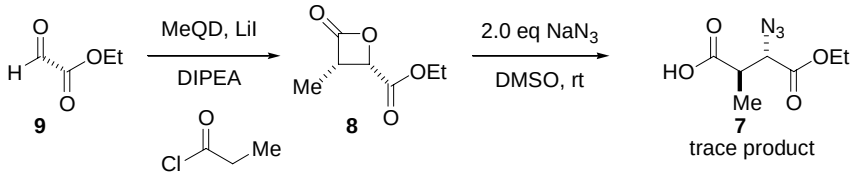
[32] Feldman, A. K.; Colasson, B.; Sharpless, K. B.; Fokin, V. V. *J. Am. Chem. Soc.* **2005**, *127*, 13444-13445.

were employed. The temperature was lowered from 50 °C to ambient temperature and the quantity of sodium azide was decreased to 1.0 equiv. (entry 4). Subjecting **8** to these conditions for 2 h resulted in *anti*-**7** devoid of the epimerized product. In order to obtain purified product, *anti*-**7** was subjected to chromatography, providing isolated **7** in a 20% yield (due to elimination). To further increase conversion, the room temperature reaction was allowed to proceed overnight (entry 5). This increased both conversion and yield (from 20% up to 32% after column chromatography) without producing any undesired epimerized product. Therefore, the adopted reaction protocol employed 1.0 equiv. of sodium azide with molecular sieves in DMSO stirred overnight at ambient temperature.

Ensuing studies were undertaken to ascertain an effective method of purification. Owing to the observed elimination on silica gel, distillation was considered as a possible solution; however, β-azido acid **7** also eliminated upon distillation. Therefore, column chromatography was again adopted. In an attempt to reduce contact time with silica gel, acid **7** was protected as the methyl ester (utilizing either DCC/DMAP/MeOH or trimethylsilyldiazomethane); however, a significant amount of elimination still persisted following purification.

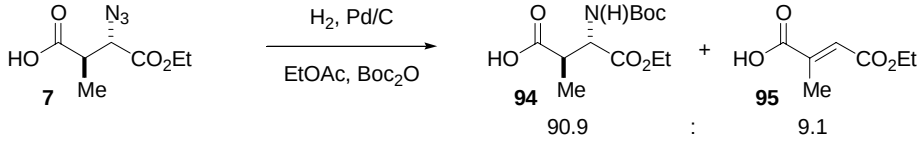
With setbacks impeding progress in terms of β-lactone and β-azido acid purification, attempts were made to carry crude **8** through the sequence. Unfortunately, although lactone formation occurred in high conversion (as judged by ^{1}H-NMR), the sodium azide-mediated ring opening failed when applied to crude lactone (Equation 14).

Equation 14



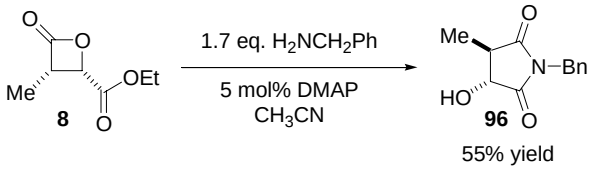
Since purification of both **7** and **8** was impractical under the investigated methods, it was decided to push crude β-azido acid through to the β-amino acid. A ^{1}H-NMR study was executed to assess the viability for an *in situ* reduction/*N*-Boc protection of azide **7**. The experiment resulted in a product ratio of 90.9:9.1 desired *N*-Boc amino acid **94** to eliminated acid **95** (Equation 15). Serious studies will soon be undertaken to assess yields and the overall efficiency of this route.

Equation 15



With preliminary studies underway to test the viability of azide reduction, one alternate route was investigated. The addition/elimination protocol for ring-opening of **8** was evaluated in an attempt to unveil a β-hydroxy amide. This method was examined because the ostensibly more robust β-hydroxy amide should provide an *anti*-β-amino amide following inversion to the desired amine *via* a Mitsunobu reaction. Purified **8** was introduced to benzyl alcohol in the presence of catalytic DMAP; however, the β-hydroxy amide was not observed. Instead, *N*-benzyl-3-(*R*)-hydroxy-4-(*S*)-methyl-pyrrolidine-2,5-dione (**96**) was the sole product, isolated in an unoptimized yield of 55% (Equation 16). Although this result is noteworthy, the route was abandoned in its relation to motuporin.

Equation 16

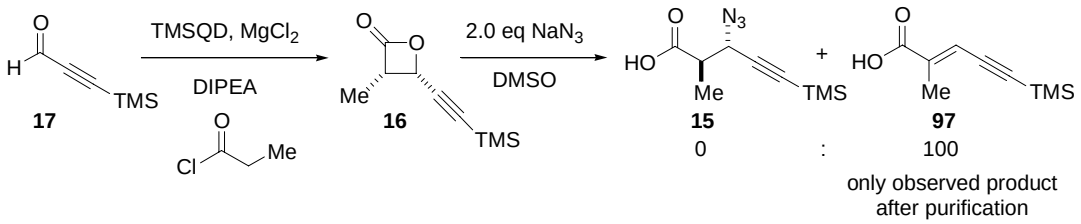


2.3.2 Synthesis of β-amino acid 11

Since reliable production of crude β-azido acid **7** had been accomplished along with progress towards production of *N*-Boc protected β-amino acid **94**, further studies with lactone **8** were placed on hold. It was decided that ensuing optimization of this route should be delayed until a reliable method of lactone production could be realized. Therefore, efforts regarding azido lactone opening were shifted to β-lactone **16**.

Initial experimentation focused on an *in situ* azide opening of crude **16**, but the only observed product after purification was conjugated **97** (Equation 17). Although this indicated that S_N2 azide-mediated ring-opening may have occurred, the resulting azide moiety presumably eliminated on silica gel.

Equation 17

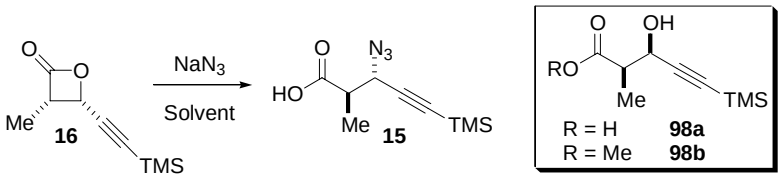


Since this *in situ* method failed, the azide-mediated ring-opening of **16** was investigated in a more meticulous manner (Table 11). As previously observed with lactone **8**, diastereoselection was an immediate problem (entry 1). When **16** was subjected to 2.0 equiv. of sodium azide at 50 °C for 1.5 h, the result was a 76.2:23.8 ratio of desired *anti*-**15**:epimerized

syn-**15**. Subsequent purification of **15** resulted in complete elimination to **97**. Therefore, the epimerization quandary was again assessed before purification.

To verify the effect of reaction time on this epimerization, the reaction was allowed to proceed in the presence of molecular sieves for 3.5 h (entry 2). The result of this experiment was not the expected increase in epimerization, but rather, complete elimination of the azide functionality. This result suggested that the azide moiety in **15** was far more labile than that of β-azido acid **7**.

Table 11: Azide opening of lactone 16



Entry	NaN_3 (equiv.)	Solvent	Temp. (°C), Time	Result[a]
1	2.0	DMSO	50, 1.5 h	**15** (76.2:23.8 *anti*:*syn*)
2	2.0	DMSO[b]	50, 3.5 h	**97**
3	1.0	2:1 CH_2Cl_2:MeOH[b]	rt, ON	**15** (78.7:21.3 *anti*:*syn*) and **98b**
4	1.0	10:1 CH_2Cl_2:DMSO[b]	rt, ON	**15** (75.0:25.0 *anti*:*syn*) and **98a**
5[c]	1.0	DMSO[b]	rt, 30 min.	*anti*-**15** and **97**
6	1.0	DMF[b]	rt, ON	**15** (>99:1 *anti*:*syn*)
7[d]	1.0	CH_2Cl_2	0-rt, ON	**15** (71.4:28.6 *anti*:*syn*)

[a]Ratios listed as desired to epimerized product. All ratios taken from ^{1}H-NMR. [b]4Å mol. sieves used 1:1 by wt. with lactone where noted. [c]Purification was attempted employing the methyl ester instead of the acid. [d]TMGA used instead of NaN_3.

Production of **97** (entries 2 and 5) raised questions regarding the origins of elimination. For one, the alkyne and carboxylic acid moieties of **15** clearly increase the acidity of the proton α to the ester. This increased acidity, when coupled to the thermodynamic stability of the conjugated system resulting from elimination (**97**), led us to believe that any latent base in the reaction medium would cause immediate elimination. To slow elimination, three alterations were simultaneously employed: (1) the equivalents of the basic sodium azide were decreased, (2)

molecular sieves were introduced to remove any traces of water, and (3) the reaction was cooled to ambient temperature.

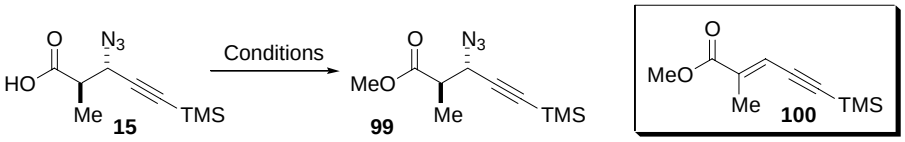
With these aforementioned changes, DMSO was utilized to dissolve the azide, favoring a quicker reaction (entry 5). Although this protocol removed the epimerization problem, elimination still transpired. Attempts with the organosoluble TMGA removed the presence of **97**, but reintroduced epimerization (entry 7). Final attempts were employed with anhydrous DMF in the presence of molecular sieves along with 1.0 equiv. of sodium azide at ambient temperature (entry 6). This modification in solvent solved both the epimerization and elimination problems, resulting in the desired *anti*-**15**.

Since the difficulties with production of **15** were solved, purification was addressed. Unfortunately, elimination occurred under both chromatography and distillation. This elimination to **97** occurred even when acid **15** was stirred at ambient temperature in MeOH. Luckily, when exceedingly pure lactone **16** was utilized in the sodium azide reaction, **15** resulted in a relatively pure state (as assessed by ^{1}H-NMR). Therefore, it was decided to reduce the azide moiety of crude **15** with hopes to purify the resulting β-amino acid.

Before this ambition was realized, the immediate task focused on the esterification of **19** to the corresponding methyl ester (Table 12). Methyl ester **99** was desired so that a comprehensive study of azide reduction methods could be explored. Unfortunately, the most straightforward method utilizing trimethylsilyldiazomethane caused epimerization (entry 1). Presumably, along with unknown impurities associated with the reagent, the trimethylsilyl cation byproduct could have aided in epimerization. Therefore, a more dependable method of esterification was required. The mild EDCI was selected as the esterification agent of choice (entry 5). Employing EDCI/DMAP/MeOH at –78 °C provided methyl ester **99** in the same

purity as the starting β-azido acid (excess EDCI and ensuing byproducts were removed *via* a simple acidic work up).[33]

Table 12: Conversion of β-azido acid 15 to β-azido methyl ester 99



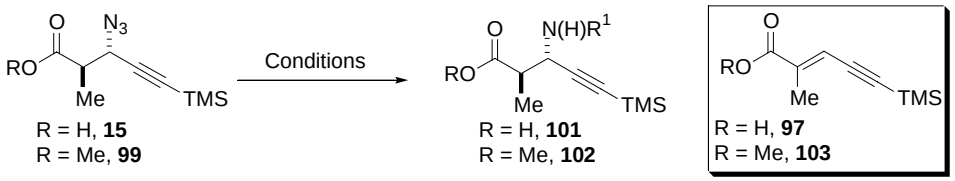
Entry	Conditions	Temp. (°C)	Result[a]
1	1.00 eq $TMSCHN_2$, Et_2O	0	69.7:30.3 **99**:epimer
2	1.2 equiv. DCC, 0.10 equiv. DMAP, 5 equiv. MeOH	rt	27.8:72.2 **99**:**100**
3	1.2 equiv. DCC, 0.10 equiv. DMAP, 2 equiv. MeOH	0	71.4:28.6 **99**:**100**
4	1.2 equiv. DCC, 0.10 equiv. DMAP, 5 equiv. MeOH	–78	58.8:41.2 **99**:**100**
5	1.1 equiv. EDC, 0.10 equiv. DMAP, 1.14 equiv. MeOH	–78	~71% **99**[b]

[a]All ratios obtained from ^{1}H-NMR. [b]Weight of unpurified product (trace impurities)

With convenient methods set in place to arrive at relatively pure acid **15** and ester **99**, the ensuing reduction of the azide functionality was investigated. Primary trials employed the Staudinger reaction and Evans' Sn(II) methodology (Table 13).[34]

[33] (a) Dhaon, M. K.; Olsen, R. K.; Ramasamy, K. *J. Org. Chem.* **1982**, *47*, 1962-1965. (b) Jiang, W.; Wanner, J.; Lee, R. J.; Bounaud, P.-Y.; Boger, D. L. *J. Am. Chem. Soc.* **2003**, *125*, 1877-1887.
[34] (a) For the Staudinger reaction, refer to: Vaultier, M.; Knouzi, N.; Carrie, R. *Tetrahedron Lett.* **1983**, *24*, 763-764. (b) For the Sn(II)-mediated reduction, refer to: Evans, D. A.; Evrard, D. A.; Rychnovsky, S. D.; Früh, T.; Whittingham, W. G.; DeVries, K. M. *Tetrahedron Lett.* **1992**, *33*, 1189-1192.

Table 13: PPh_3 and Sn(II)-mediated reduction of azides 15 and 99



Entry	R	R^1	Conditions	Result
1	Me	Boc	1. PPh_3, THF, H_2O, 60 °C 2. 1 M NaOH, Boc_2O, 0 °C	**103**
2	Me	H	i. PPh_3, THF, 60 °C, ii. H_2O	**103**
3	H	H	i. PPh_3, THF, reflux, ii. H_2O, –78 °C	**97**
4	Me	Boc	i. $SnCl_2$, 2:1 dioxane:H_2O, 0 °C-rt ii. Boc_2O, $NaHCO_3$	**103**, decomposition
5	H	Boc	i. $SnCl_2$, 2:1 dioxane:H_2O, 0 °C-rt ii. Boc_2O, $NaHCO_3$	**97**, decomposition
6	Me	H	$SnCl_2$, 3:1 dioxane:H_2O, rt	decomposition
7	H	H	$SnCl_2$, 3:1 dioxane:H_2O, rt	**15**, decomposition

Initial attempts to reduce the azide moiety of ester **99** employing Staudinger conditions with *in situ N*-Boc amine protection provided complete elimination of the azide (entry 1). Attempts were made to reduce the azide without subsequent protection, but this experiment also resulted in complete elimination to **103** (entry 2). Acid **15** provided similar results under the Staudinger conditions (entry 3). Elimination was thought to result from triphenylphosphine merely acting as a base. This β-elimination could occur almost immediately, especially in the presence of water.

Since the Staudinger reaction failed to provide any discernible azide reduction, Evans' methodology was exploited.[34b] Again, **15** and **99** were both subjected to attempts for an *in situ N*-Boc protection of the amine; however, elimination and decomposition were the results (entries 4 and 5, respectively). Next, attempts for direct reduction to the amine with Sn(II) were endeavored; however, both **15** and **99** failed to provide any progress in this regard (entries 6 and 7, respectively). It appears that the water required for this reaction may be its very downfall. As

previously observed, **15** and **99** are extremely water-sensitive, favoring decomposition in preference to reduction.

Given the failures of the more traditional methods to reduce the azide moiety, more uncommon reduction schemes were employed (Table 14). Initially, both **15** and **99** were subjected to the mild reducing agent iodotrimethylsilane, generated *in situ* from TMSCl and NaI (entries 1 and 2, respectively). As previously observed, elimination was the only observed reaction.[35] Next, mild conditions employing triethylsilane were attempted with an *in situ N*-Boc protection; however, no discernible reaction occurred (entry 3).[36] Both zinc(0) and zirconium(IV) were evaluated in an attempt to generate *in situ* the corresponding metal hydride species, but untouched starting material prevailed (entries 4 and 5, respectively).[37] It is noteworthy to recognize that the zirconium(IV) system provided resonances in the ^{1}H-NMR that corresponded with what would be expected for **101**; however, this trace quantity could not be isolated. Both Co(II) and Cu(II) were utilized, again in an attempt to form the corresponding metal hydride *in situ*; however, elimination predominated (entries 6 and 7, respectively).[38] In a final attempt to produce **101**, hydrogenation was appraised (entries 8 and 9).[39] Unfortunately, alkyne reduction transpired more expediently than azide reduction.

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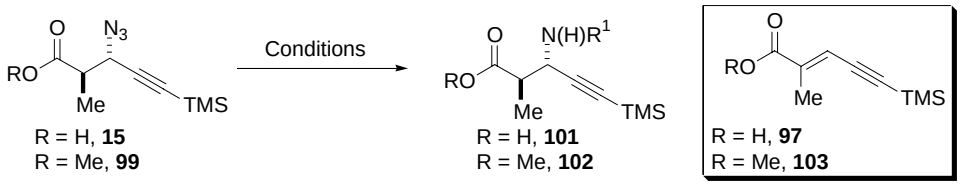
[35] Kamal, A.; Rao, N. V.; Laxman, E. *Tetrahedron Lett.* **1997**, *38*, 6945-6948.
[36] Kotsuki, H.; Ohishi, T.; Araki, T. *Tetrahedron Lett.* **1997**, *38*, 2129-2132.
[37] For zinc(0), refer to: Pathak, D.; Laskar, D. D.; Prajapati, D.; Sandhu, J. S. *Chem. Lett.* **2000**, *7*, 816-817. For Zr(IV), refer to: Chary, K. P.; Raja Ram, S.; Salahuddin, S.; Iyengar, D. S. *Synth. Commun.* **2000**, *30*, 3559-3563.
[38] For Co(II), refer to: Fringuelli, F.; Pizzo, F.; Vaccaro, L. *Synthesis* **2000**, *5*, 646-650. For Cu(II), refer to: Rao, H. S. P.; Siva, P. *Synth. Commun.* **1994**, *24*, 548-555.
[39] Venkatesan, H.; Davis, M. C.; Altas, Y.; Snyder, J. P.; Liotta, D. C. *J. Org. Chem.* **2001**, *66*, 3653-3661.

Table 14: Nontraditional azide reduction schemes



Entry	R	R^1	Conditions	Result[a]
1	H	H	NaI, TMSCl, CH_3CN	41.7:58.3 **15**:**97**
2	Me	H	NaI, TMSCl, CH_3CN	50.0:50.0 **99**:**103**
3	Me	Boc	Et_3SiH, Boc_2O, 20% Degussa Pd/C	**103**, decomposition
4	H	H	Zn(0), $FeCl_3$, EtOH	**97**
5	H	H	$ZrCl_4$, $NaBH_4$, THF	**15**, trace **101**
6	H	H	$CoCl_2 \cdot H_2O$,$NaBH_4$, H_2O, rt	**97**, decomposition
7	H	H	$CuSO_4 \cdot 5\ H_2O$, $NaBH_4$, MeOH, 0 °C	**97**
8	H	H	H_2, Lindlar's cat. (4% by wt.), DMF, rt, 10min	90.1:9.9 **15**:**97**
9	H	H	H_2, Pd/C(10% by wt), EtOAc, rt, 7h	**97**, decomposition

[a]All ratios obtained from ^{1}H-NMR.

The above failures proved that, for **15** and **99**, the dichotomy between reactivity and hyper-reactivity is minuscule. When conditions are too mild, no discernible reduction occurs. On the other hand, when reactivity is attenuated, elimination predominates. The amplified acidity of the α-proton in this system seems to be the downfall; elimination was even observed during hydrogenation.

Since no discernible reduction occurred, one final reduction method was employed. H. C. Brown had previously reported that the dichloroborane-dimethyl sulfide complex has the ability to reduce azides.[40] Based upon this principle, a one-pot procedure utilizing boranes to both reduce the azide and hydroborate the alkyne was explored. Due to Knochel's precedent

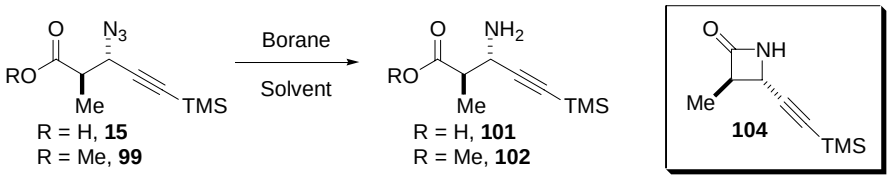
[40] Salunkhe, A. M.; Ramachandran, P. V.; Brown, H. C. *Tetrahedron* **2002**, *58*, 10059-10064.

concerning the hydroboration of functionalized alkynes, pinacolborane was utilized in the first trial.[41] Unfortunately, this provided no reaction. It is assumed that this alkyne is too sterically encumbered to undergo hydroboration with the bulky pinacolborane.

With the failure of pinacolborane, a relative to Brown's system was implemented (Table 15). The first attempt employing dicyclohexylborane-dimethyl sulfide complex provided an exciting result (entry 1). When **15** was subjected to 2.0 equiv. of dicyclohexylborane-dimethyl sulfide complex in dry THF at 0 °C, β-lactam **104** was produced in a 46% yield. This lactam clearly resulted from boron activation of the acid, followed by ring-closure (either from azide reduction and subsequent amino ring closure or from azido ring closure followed by azide reduction). With this result in hand, identical conditions were applied to methyl ester **99** to obtain pure β-amino ester **102**; however, no reaction occurred (entry 2). Curiously, repetitive trials to provide **104** failed in every respect. When borane itself was utilized (from a neat solution in Me_2S, a 2.0 M solution in THF, or a 1.0 M solution in CH_2Cl_2) in the reduction of **15**, starting material remained untouched (entries 4-6).

[41] Tucker, C. E.; Davidson, J.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 3482-3485.

Table 15: Borane reduction of azides 15 and 99



R = H, **15**
R = Me, **99**

R = H, **101**
R = Me, **102**

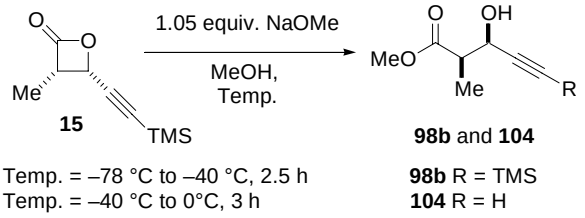
Entry	R	Borane	Solvent	Temp. (°C)	Result
1	H	2.0 equiv. $HBCy_2{\cdot}SMe_2$ (neat in SMe_2)	THF	0	46% **104**
2	Me	1.5 equiv. $HBCy_2{\cdot}SMe_2$ (neat in SMe_2)	THF	0-rt	**99**, decomposition
3	H	2.0 equiv. $HBCy_2{\cdot}SMe_2$ (neat in SMe_2)	THF	0-rt	**15**, decomposition
4	H	2.0 equiv. $BH_3{\cdot}SMe_2$ (neat in SMe_2)	THF	0-rt	**15**, decomposition
5	H	2.0 equiv. $BH_3{\cdot}SMe_2$ (2.0 M in THF)	THF	0-rt	**15**, decomposition
6	Me	1.5 equiv. $BH_3{\cdot}SMe_2$ (1.0 M in CH_2Cl_2)	CH_2Cl_2	0-rt	decomposition

The failure to reduce the azide moiety of **15** and **99** is not necessarily surprising, especially when coupled with the observed decomposition. Presumably, borane could hydroborate the alkyne, facilitating elimination and other methods of decomposition. With this being said, the result displayed in entry 1 of Table 15 is still a perplexity. Although the mechanism to arrive at lactam **104** is seemingly straightforward, reasons why the result was unrepeatable, even when utilizing identical conditions with the same source of reagents, are still a mystery.

The final route examined to arrive at reduced amine **101** involved an addition/elimination protocol mediated by sodium methoxide. It was thought that methoxide opening of **16** would provide the β-hydroxy substituent in the undesired *syn*-configuration. This stereocenter could theoretically be inverted to the amine by way of a Mitsunobu reaction. When NaOMe was exploited in lactone ring-opening, it was immediately observed that the process is temperature dependent. When carried out within the range of –78 °C to –40 °C, the resulting product mostly

maintains its terminal trimethylsilyl group (**98b**). On the other hand, when the reaction is warmed within the range of –40 °C to 0 °C, opening occurs with concomitant removal of the trimethylsilyl group (**105**) (Equation 18). Studies are currently underway to optimize this process.

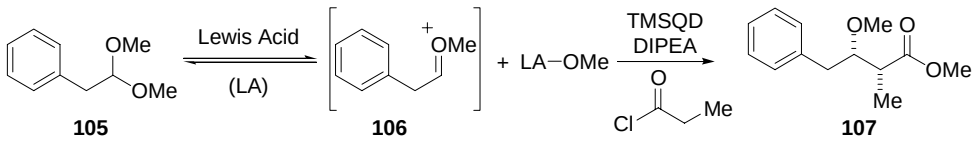
Equation 18



2.3.3 Synthesis of aldehyde 12

While on-going investigations were being explored to arrive at β-azido acids **7** and **15** and/or the corresponding β-amino acids, it was necessary to revisit lactone **13**. Since both the aluminum-triamine-catalyzed and alkaloid-catalyzed AAC reaction manifolds had failed to produce **13**, alternative routes were investigated. The first scheme utilized familiar reaction technology. Applying the alkaloid-catalyzed AAC reaction manifold to acetals (or, more accurately, to oxocarbenium ions) was theorized to bestow an asymmetric aldol reaction resulting in 2,3-*syn*-disubstituted esters (Equation 19).[28c,42]

Equation 19

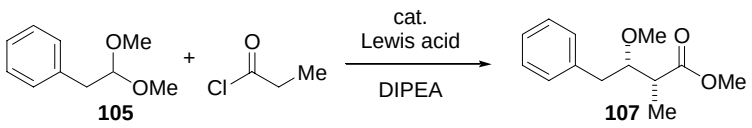


[42] Murata, S.; Suzuki, M.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 3248-3249.

Exploiting alkaloid-catalyzed AAC conditions with acetal **105** should result in *syn*-ester **107**. Simple DIBAL-H reduction of **107** could then provide aldehyde **12**, rejoining the previously fabricated synthetic scheme for motuporin. In order to assess the legitimacy of oxocarbenium ion **106**, 0.90 equiv. of $BF_3{\cdot}OEt_2$ was introduced to phenylacetaldehyde dimethyl acetal (**105**). Attempts to trap the presumed intermediary **106** with an array of mild nucleophiles (such as allyltrimethylsilane) failed to provide any conclusive results. Alternative reagents were examined in an attempt to produce **107** under milder conditions; however, LiI, $LiClO_4$, and $ZnCl_2$ all proved incapable of providing solid evidence that the oxocarbenium ion had indeed been realized.

The validity of full realization of intermediate **106** was soon dismissed because, under the designed reaction manifold, actual achievement of an isolated intermediary oxocarbenium ion was unnecessary. During the proposed reaction, Lewis acid coordination should be sufficient enough to pull on a methoxy substituent to allow the aldol reaction to occur.

Table 16: Attempts at the acyl halide-acetal condensation

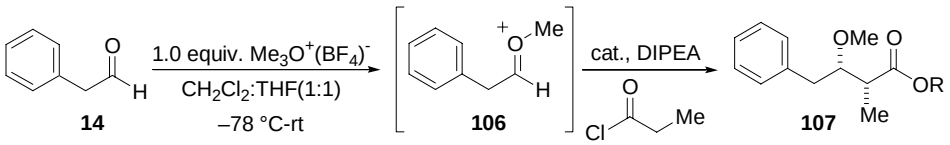


Entry	cat.	Lewis Acid	Temp (°C)	Result
1	MeQD	LiI (3.0 equiv.)	–78	**105**
2	MeQD	$MgCl_2$ (2.0 equiv.)	–78	**105**
3	MeQD	$BF_3{\cdot}OEt_2$ (0.9 equiv.)	–78	**105**, decomposition
4	MeQD	LiI (2.0 equiv.)	–40 to rt	**105**
6	MeQD	$ZnCl_2$ (1.0 equiv.)	–25	**105**
7	TMSQD	Me_2AlCl (1.0 equiv.)	–78	**105**
8	TMSQD	TMSOTf (1.0 equiv.)	–78	Trace **105**, polymerization
9	DMAP	$MgCl_2$ (1.2 equiv.)	–78	**105**

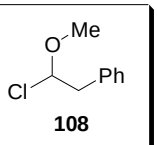
All reactions performed with 10 mol % catalyst, 2.50 equiv. DIPEA, and 2.0 equiv. propionyl chloride with a solvent ratio of 2:1 CH_2Cl_2:Et_2O at the indicated temperature.

A variety of Lewis acids were employed in the attempted acyl halide-acetal condensation; however, a successful transformation continued to elude (Table 16). Varying Lewis acids in terms of both strength and quantity failed to promote any discernible progress besides decomposition and polymerization. Increasing reaction temperature also failed to improve conversion to **107**. Due to this documented failure of the reaction, the question of the oxocarbenium resurfaced. It was surmised that the evaluated conditions were either too mild to allow the reaction to occur or were too strong, causing decomposition (entries 3 and 8).

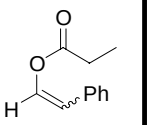
Table 17: The use of Meerwein salt in the acyl halide-acetal condensation



Entry	Time[a]	cat.	Temp. (°C)[b]	Result
1	1 h	DMAP (2.0 equiv.)	–78	**14** (R = H)
2	3 h	DMAP (1.0 equiv.)	–78	**14** (R = H)
3	3 h	TMSQD (10 mol %)	–78	**14** (R = H)
4[c]	3 h	TMSQD (10 mol %)	–78	**14** (R = *i*-Pr)
5[c]	1 h	TMSQD (1.0 equiv.)	–78	28.6: 71.4 **108**:**109** (R = *i*-Pr)



108



109

All reactions performed with 10 mol % catalyst, 2.50 equiv. DIPEA, and 2.0 equiv. propionyl chloride with a solvent ratio of 2:1 CH_2Cl_2:Et_2O at the indicated temperature. [a]Time for oxocarbenium ion formation. [b]Temperature of the ensuing AAC-like reaction. [c]*i*-PrOH was added, R = *i*-Pr.

In order to avoid all suspicion, trimethyloxonium tetrafluoroborate (Meerwein's salt) was exploited to assure oxocarbenium ion formation (Table 17). Stoichiometric quantities of DMAP were first employed to test the viability of the reaction (entries 1 and 2). Unfortunately, no discernible reaction transpired. Subsequently, both catalytic and stoichiometric quantities of TMSQD were assessed in the reaction; however, no noticeable conversion occurred (entries 3 and 4). Allowing extra time for the oxocarbenium ion to form also failed to promote formation of **107** (entries 2-4). Finally, *iso*-propanol was added to promote turnover (entries 4 and 5). The

addition of *iso*-propanol alongside stoichiometric TMSQD failed to provide **131**; however, both chlorohydrin **108** and ester **109** were observed (entry 5). Although the presence of **108** indicated that **106** may have formed, the presence of **109** also suggested that enolization of **14** was a significant side reaction.

The reason for the failure of this iteration of the acyl halide-acetal condensation was thought to be reversibility of oxocarbenium ion formation. Although both oxocarbenium ion formation and the subsequent aldol may have occurred, these steps are reversible. Seemingly, the oxocarbenium ion may have been reversibly intercepted by the alkaloid (or DMAP) in preference to partaking in the aldol. This is hypothesized since, under the reaction conditions, no aldol product was ever observed. In order for the acyl halide-acetal condensation to be successful, the optically active ammonium enolate must be stimulated to undergo the aldol with **106** in preference to reversible alkaloid attack.

Since a reliable method to achieve aldehyde **12** is a necessity for the outlined synthesis of motuporin, an alternative strategy was adopted (Figure 32). The precedented Evans aldol approach was employed (Scheme 5).[4a,43] Acylation of oxazolidinone **110** with propionyl chloride proceeded in near quantitative yield (99%). The Evans aldol, performed with dibutylborontriflate and phenylacetaldehyde (**14**), provided chiral amide **89** in a 97% yield as one visible diastereomer by ^{1}H-NMR. Following transamidation to Weinreb amide **111**, which proceeded in 89% yield, methylation of the β-hydroxy of **111** produced **112** in 75% yield. Finally, DIBAL-H reduction to aldehyde **12** proceeded in 86% yield.

Successful formation of **12** allows for the outlined synthesis of **1** to be feasible. As designed, a Corey-Fuchs reaction of **12**, followed by subsequent methylation of the terminal

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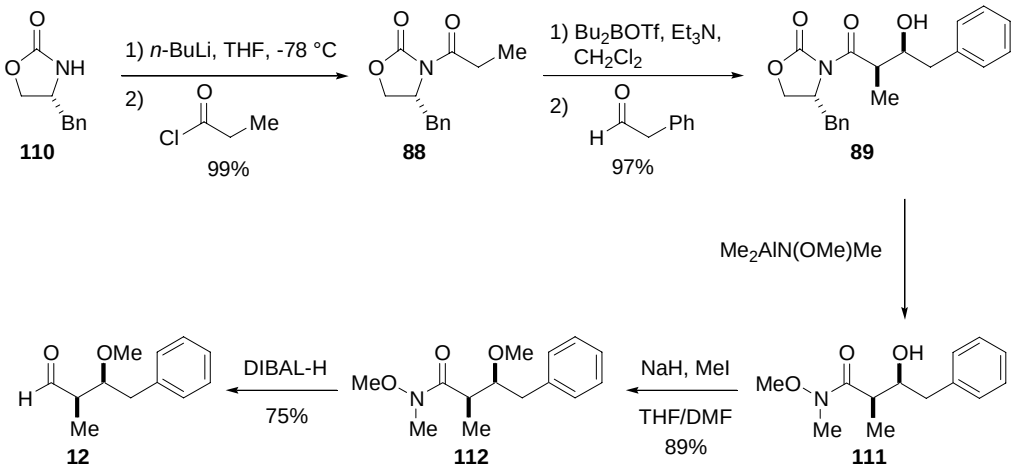
[43] Humphrey, J. M.; Aggen, J. B.; Chamberlin, A. R. *J. Am. Chem. Soc.* **1996**, *118*, 11759-11770.

alkynyl position will lead to the direct precursor of vinyl iodide **10**. Following reduction with Schwartz's reagent and ensuing iodination, vinyl iodide **10** should be ready for coupling with vinyl borane **11**.



Scheme 5: The Evans aldol approach to aldehyde 12.

2.4 CONCLUSION

In summary, there is still considerable work remaining in the enantioselective total synthesis of motuporin (**1**). For one, reproducible production of purified lactone **8** is still problematic. The azide-mediated S_N2 ring-openings of both **8** and **16** also need further optimization. Since it appears that purification of β-azido acids **7** and **15** may be impractical, reliable means of azide reduction need to be discovered. Otherwise, optimization of the methoxide ring-opening with ensuing Mitsunobu reaction should be researched.

One possible solution to the β-amino acid quandary that was not discussed is that of S_N2 ring-opening with sodium nosylate to directly provide the *N*-nosyl protected β-amino acids. It is surmised that once the β-amino acids are achieved, the majority of the purification problems

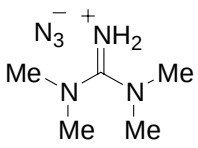
should dissipate. These β-amino acids should be resistant to elimination and should epimerize less readily than their β-azido acid counterparts.

Finally, although the Evans aldol pathway to aldehyde **12** shows promise, we would like to employ innovative methodology towards its production. Additional experimentation needs to be applied to the acyl-halide acetal condensation (varying temperature, Lewis acid, and reaction time) in order to provide for a successful transformation. Otherwise, alternate strategies employing an α-halo aldehyde in the AAC should provide a β-lactone that is poised for incorporation into the outlined synthetic scheme for motuporin.

2.5 EXPERIMENTALS

General Notes: Unless otherwise noted, all reactions were performed under anhydrous conditions (dry glassware was utilized under an atmosphere of nitrogen). All crude organic products were dried over magnesium sulfate and were concentrated under reduced pressure by rotary evaporation.

General procedure for the sodium azide-mediated opening of β-lactones: To a solution of 1.00 mmol of lactone in 2.0 mL of anhydrous DMSO was added 130 mg (2.00 mmol) of sodium azide and the reaction was stirred until completion (as monitored by TLC where applicable, approximate time 4-8 h). Saturated aqueous NH_4Cl (10 mL) was added and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 X 15 mL) and all organics were combined and washed with water (5 X 20 mL). The combined organics were dried over $MgSO_4$, filtered, and the crude reaction mixture was concentrated.

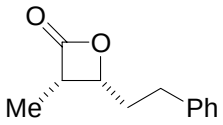


Synthesis of tetramethylguanidinium azide (TMGA):[44] In a round bottom flask, hydrazoic acid was prepared as follows: at 0 °C, sodium azide, 13.0 g (200 mmol), was added to 50 mL of water and the mixture was carefully monitored. Concentrated HCl (16.0 mL) was added over 30 min. and the solution was extracted three successive times with diethyl ether (140 mL) to remove all hydrazoic acid. This acid was added to another Erlenmeyer flask containing 25.10 mL (200 mmol) tetramethylguanidine in 50 mL of diethyl ether at 0 °C over a period of 3 h with care taken to make sure the reaction temperature did not rise above 0 °C. The reaction was allowed to stand at ambient temperature for 12 h. The ether was decanted off and the solid was collected. A slurry was created with two 100 mL portions of diethyl ether. After concentration under reduced pressure, the product was recrystallized from diethyl ether and hexanes to produce 29.50 g (93%) of pure TMGA was formed. ^{1}H-NMR ($CDCl_3$): δ 8.76 (br s, 2 H), 2.91 (s, 12 H); ^{13}C-NMR ($CDCl_3$): δ 161.63, 40.06.

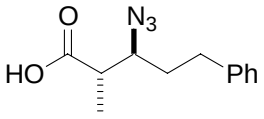
General procedure for the TMGA-mediated opening of β-lactones: To a round bottom flask was added 1.00 mmol of lactone and 3.0 mL of dry CH_2Cl_2. The solution was cooled to 0 °C and 316 mg (2.00 mmol) of TMGA was carefully added as a solution predissolved in 1.0 mL of dry CH_2Cl_2. The reaction was stirred at 0 °C for 1.5 h and was then quenched with 20 mL of a saturated solution of $NaHCO_3$. The organic layer was washed with a saturated solution of $NaHCO_3$ (2 X 20 mL) and with a saturated solution of Na_2CO_3 (2 X 20 mL). The aqueous layers were all combined and were carefully acidified with 1 M HCl to pH 2. Following three extractions of the acidified aqueous layer with CH_2Cl_2 (20 mL), the organic layers were

[44] Papa, A. J. *J. Org. Chem.* **1966**, *31*, 1426-1430.

combined and were dried over $MgSO_4$ and the crude reaction mixture was concentrated under reduced pressure.

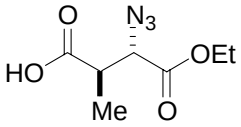


3-(*S*)-methyl-4-(*R*)-2-phenylethyl-oxetan-2-one (92):[6c] Prepared under standard TMSQD-catalyzed AAC reaction conditions with 1.32 mL (10.00 mmol) of hydrocinnamaldehyde, 0.532 g (5.00 mmol) of $LiClO_4$, 0.400 g (1.00 mmol) of TMSQD, 4.37 mL (25.00 mmol) of DIPEA, and 1.67 mL (20.00 mmol) of propionyl chloride. The crude product was purified on silica gel using 10% ethyl acetate and hexanes as elutent to provide 1.77g (93%) of the purified title compound. ^{1}H-NMR ($CDCl_3$): δ 7.37-7.22 (m, 5 H), 4.57 (ddd, J = 4.2, 2.3, 0.5 Hz, 1 H), 3.75 (dt, J = 7.7, 1.2 Hz, 1 H), 2.89 (dq, J = 4.9 Hz Hz, 1 H), 2.72 (br ddd, J = 7.6, 2.4, 0.9 Hz, 1 H), 2.11 (dq, J = 5.2, 3.9 Hz, 1 H), 2.04-1.92 (m, 1 H), 1.28 (d, J = 7.8 Hz, 3 H); ^{13}C-NMR ($CDCl_3$): δ 172.44, 140.32, 128.54, 128.38, 126.27, 74.56, 47.11, 31.86, 31.44, 8.03.

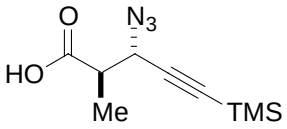


3-(*S*)-Azido-2-(*S*)-methyl-5-phenyl-pentanoic acid (93): Prepared following the general procedure for sodium azide-mediated opening of β-lactones. The crude product was purified on silica gel utilizing 10% ethyl acetate in hexanes as elutent to provide 0.459 g (98%) of the purified title compound. $[\alpha]_D$ −1.1 (*c* 1.35, $CHCl_3$). IR (thin film): 3063, 3027, 2983, 2956, 2642, 2100, 1710, 1496, 1454, 1419, 1252, 913, 747, 700 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 7.35-7.20 (m, 5 H), 3.59 (dq, J = 3.8 2.5 Hz, 1 H), 2.93-2.84 (m, 1 H), 2.76-2.63 (m, 2 H), 2.02-1.77 (m, 2 H), 1.24 (d, J = 7.1 Hz, 3 H); ^{13}C-NMR ($CDCl_3$): δ 179.50, 149.68, 128.60, 128.40, 126.25, 63.60, 43.96, 33.10, 32.24, 13.52. MS (EI, 70eV): *m/z* 205

(M^+–N_2), 190 (M^+–HN_3), 132 (M^+–N_3, CH_3, CO_2). HRMS *m/z* calcd for $C_{12}H_{15}NO_2$: 205.1103, for $C_{10}H_{13}N_4O$: 205.1089; found 205.1098.

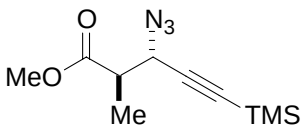


2-Azido-3-methyl-succinic acid 1-ethyl ester (7):[45] Prepared following the general procedure for sodium azide-mediated opening of β-lactones. The crude product could not be purified. $[\alpha]_D$ +18.4 (*c* 1.59, $CHCl_3$). IR (thin film): 3352, 2986, 2115, 1742, 1713, 1466, 1372, 1267, 1205, 1092, 1023 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 4.45 (d, J = 5.7 Hz, 1 H), 4.29 (q, J = 7.1 Hz, 3 H), 4.17 (d, J = 6.2 Hz, 1 H), 3.06 (quintet, J = 6.4 Hz, 2 H), 1.30 (dt, J = 7.3 Hz, 3 H); ^{13}C-NMR ($CDCl_3$): δ 178.57, 177.91, 168.84, 168.51, 40.97, 14.09, 12.00. MS (EI, 70eV): *m/z* 186 (M^+–CH_3), 159 (M^+–N_3), 141 (M^+–HCO_2, CH_3), 113 (M^+–$CO_2CH_2CH_3$, CH_3).

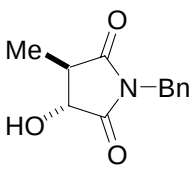


3-(*R*)-Azido-2-(*R*)-methyl-5-trimethylsilanyl-pent-4-ynoic acid (25): Prepared following the general procedure for sodium azide-mediated opening of β-lactones. The crude product could not be purified. IR (thin film): 2961, 2901, 2652, 2105, 1705, 1421, 1251, 1086, 845, 761 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 4.42 (d, J = 8.5 Hz, 1 H), 2.71 (dt, J = 7.1, 0.7 Hz, 1 H), 1.34 (d, J = 7.1 Hz, 3 H), 0.21 (s, 9 H); ^{13}C-NMR ($CDCl_3$): δ 171.94, 139.29, 121.49, 100.92, 94.74, 15.07, -0.29. MS (EI, 70eV): *m/z* 182 (M^+–HN_3), 181 (M^+–CO_2), 167 (M^+–CH_3, HN_3), 152 (M^+–$Si(CH_3)_3$), 123 (M^+–CH_3, HN_3, CO_2). HRMS *m/z* calcd for $C_9H_{14}O_2Si$: 182.076308, for $C_7H_{12}N_3OSi$: 182.074966, for $C_3H_{16}N_3O_2Si_2$: 182.078109, for $C_{13}H_{10}O_2$: 182.0732; found 182.0763.

[45] Data for HRMS in submission.

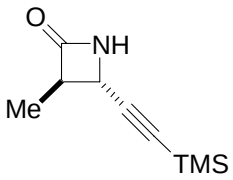


Synthesis of 3-(*R*)-Azido-2-(*R*)-methyl-5-trimethylsilanyl-pent-4-ynoic acid methyl ester (99): To a round bottom flask was added 1.28 g (5.67 mmol) of 3-(*R*)-Azido-2-(*R*)-methyl-5-trimethylsilanyl-pent-4-ynoic acid (**25**) as a solution in 20 mL of anhydrous methylene chloride. To this solution was added 69 mg (0.567 mmol) of DMAP and 1.20 g (6.24 mmol) of EDC. The solution was stirred to dissolve all solids and was then cooled to –78 °C. Methanol, 2.62 mL (6.46 mmol), was added and the reaction was stirred overnight at –78 °C. The reaction was diluted with 50 mL of ethyl acetate and was washed with a saturated solution of $NaHCO_3$ (50 mL), an aqueous solution of 1 M HCl (2 X 50 mL), and a saturated solution of NaCl (50 mL). The crude reaction mixture was dried with $MgSO_4$ and was then concentrated under reduced pressure to provide mostly pure 3-(*R*)-Azido-2-(*R*)-methyl-5-trimethylsilanyl-pent-4-ynoic acid methyl ester (**99**). The product could not be purified. IR (thin film): 2960, 2358, 2103, 1745, 1454, 1251, 1037, 845, 761, 637 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 4.41 (d, J = 8.7 Hz, 1 H), 3.73 (s, 3 H), 2.67 (dt, J = 7.1, 1.4 Hz, 1 H), 1.31 (d, J = 6.5 Hz, 3 H), 0.21 (s, 9 H); ^{13}C-NMR ($CDCl_3$): δ 173.25, 97.58, 94.40, 55.55, 52.06, 44.74, 13.95, -0.28. MS (EI, 70eV): *m/z* 239 (M^+), 197 (M^+–N_3), 167 (M^+–$Si(CH_3)_3$), 167 (M^+–N_3, OCH_3), 165 (M^+–CH_3, CO_2), 97 (M^+–$Si(CH_3)_3$, CO_2, HN_3). HRMS *m/z* calcd for $C_{10}H_{17}N_3O_2Si$: 239.1090, for $C_{12}H_{19}O_3Si$: 239.1104, for $C_{16}H_{15}O_2$: 239.1072, for $C_6H_{21}N_3O_3Si_2$: 239.1122, for $C_{14}H_{13}N_3O$: 239.1057, for $C_{15}H_{17}NSi$: 239.1130, for $C_5H_{17}N_5O_4Si$: 239.1050, for $C_8H_{23}O_4Si_2$: 239.1135; found 239.1091.



Synthesis of 1-Benzyl-3-hydroxy-4-methyl-pyrrolidine-2,5-dione (96): To a round bottom flask was added 418 mg (2.66 mmol) of 3-(*S*)-methyl-4-(*R*)-oxo-oxetane-2-carboxylic acid ethyl ester (**8**) and 1.0 mL of anhydrous acetonitrile.

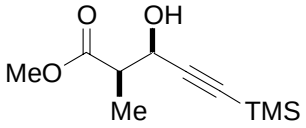
Benzylamine, 0.49 mL (4.44 mmol), was added alongside 32.50 mg (0.27 mmol) of DMAP at ambient temperature and the reaction was stirred overnight. The crude reaction mixture was concentrated under reduced pressure and was purified on silica gel using 10% EtOAc in hexanes to yield 1-benzyl-3-(*S*)-hydroxy-4-(*R*)-methyl-pyrrolidine-2,5-dione (**96**). The product was recrystallized from methylene chloride and hexanes to yield 319 mg (55%) of pure 1-benzyl-3-hydroxy-4-methyl-pyrrolidine-2,5-dione (**96**). $[\alpha]_D$ −54.2 (*c* 0.38, $CHCl_3$). IR (thin film): 3375, 3064, 3032, 2979, 2937, 1783, 1709, 1345, 1169, 1112, 978, 750, 700 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 7.37-7.20 (m, 5 H), 4.63 (d, J = 1.3 Hz, 1 H), 4.20 (d, J = 6.9 Hz, 1 H), 2.77 (dq, J = 7.3, 1.3 Hz, 1 H), 1.39 (d, J = 7.3 Hz, 3 H); ^{13}C-NMR ($CDCl_3$): δ 177.24, 176.50, 135.28, 128.65, 128.00, 74.25, 43.77, 42.37, 13.05. MS (EI, 70eV): *m/z* 219 (M^+), 191 (M^+–CH_2CH_3), 163 (M^+–CH_3CH_2C=O), 162 (M^+–$HOCH_2C$=O), 106 (M^+–O=CCH(CH_3)CH(OH)C=O), 91 (M^+–O=CCH(CH_3)CH(OH)C(O)N). HRMS *m/z* calcd for $C_{12}H_{13}NO_3$: 219.0895; found 219.0906.



Synthesis of 3-Methyl-4-trimethylsilanylethynyl-azetidin-2-one (104): To a round bottom flask was added 0.20 mL (2.00 mmol) of $BH_s{\cdot}SMe_2$ neat in dimethyl sulfide in 5.0 mL of dry THF. The solution was cooled to 0 °C and 0.41 mL (4.00 mmol) of cyclohexene was added dropwise. The reaction was stirred for 3 h at 0 °C and then, 0.23 g (1.00 mmol) of β-azido acid **15** was added dropwise and the reaction was stirred at 0 °C for 1 h. The reaction was warmed to ambient temperature and was stirred for an additional 3 h. All volatiles were removed under reduced pressure and the crude reaction mixture was then purified on silica gel using 5% MeOH in CH_2Cl_2 as elutent to provide 0.083 g (45.9%) of pure 3-methyl-4-trimethylsilanylethynyl-azetidin-2-one (**104**). Separation of the

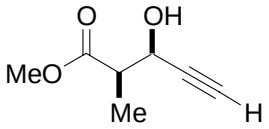
enantiomers by chiral GLC [Chirasil-dex CD DF=0.25 column 25 m x 0.25 mm, T_{Max} = 225°C, flow rate 0.5 mL/min, method: 80 °C for 5 min, ramp @ 5.0 °C/min to 100 °C for 10.0 min, ramp @ 5.0 °C/min to 130 °C for 5.0 min, T_r: 17.9 min (3*R*,4*S*), T_r: 24.4 min (3*S*,4*S*)] provided the diastereomer ratio: (3*R*,4*S*):(3*S*,4*R*) = 1.75:100 (27.25% de). $[\alpha]_D$ +51.1 (*c* 0.39, $CHCl_3$). IR (thin film): 2962, 2938, 1838, 1252, 1018, 844, 532 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 5.13 (d, J = 6.4 Hz, 1 H), 3.84 (dq, J = 7.7, 1.2 Hz, 1 H), 1.43 (d, J = 7.7 Hz, 3 H), 0.22 (s, 9 H); ^{13}C-NMR ($CDCl_3$): δ 171.09, 98.43, 96.82, 64.54, 49.6, 10.2, -0.64. MS (EI, 70eV): *m/z* 167 (M^+–CH_3), 138 (M^+–HN=C=O), 123 (M^+–CH_3, HN=C=O). HRMS *m/z* calcd for $C_8H_{14}Si$: 138.0865; found 138.0869.

General procedure for the sodium methoxide opening of lactone 16: To a round bottom flask was added 0.113 g (2.10 mmol) of NaOMe and 4 mL of MeOH. The reaction was cooled to –40 °C and a solution of 0.367 g (2.00 mmol) of lactone **16** was added dropwise in 6.0 mL of MeOH. The reaction was stirred for 2.5 h at –40 °C (or 0 °C for production of **104**). The reaction was quenched with 20 mL of water and the organic layer was separated. The aqueous layer was washed with diethyl ether (3 X 15 mL) and was acidified with 1 M HCl. The combined organic layers were extracted with diethyl ether (3 X 20 mL) and all organics were combined and dried. The crude reaction mixture was concentrated under reduced pressure and was purified on silica gel to produce either purified **98b** or **104**.

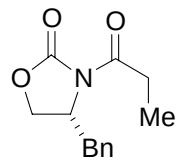


3-(*R*)-hydroxy-2-(*R*)-methyl-5-trimethylsilanyl-pent-4-ynoic acid methyl ester (98b):[45] The general procedure for the sodium methoxide opening of lactone **16** was followed at –40 °C to yield 0.22 g (78%) of 3-(*R*)-hydroxy-2-(*R*)-

methyl-5-trimethylsilanyl-pent-4-ynoic acid methyl ester (**98b**). $[\alpha]_D$ –9.1 (*c* 1.43, $CHCl_3$). IR (thin film): 29.58, 2900, 2175, 1740, 1459, 1437, 1348, 1251, 1203, 1031, 992, 845 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 4.62 (d, J = 4.0 Hz, 1 H), 3.74 (s, 3 H), 2.75 (dq, J = 4.1 Hz, 1 H), 1.30 (d, J = 7.2 Hz, 3 H), 0.17 (s, 9 H); ^{13}C-NMR ($CDCl_3$): δ 187.41, 103.67, 77.19, 64.06, 51.95, 45.33, 11.66, -0.26. MS (EI, 70eV): *m/z* 127 (M^+–$Si(CH_3)_3$, CH_3), 111 (M^+–$Si(CH_3)_3$, OCH_3), 88 (M^+–$Si(CH_3)_3$, HC≡CCHOH).

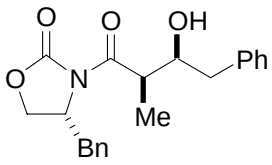


3-(*R*)-hydroxy-2-(*R*)-methyl-pent-4-ynoic acid methyl ester (104): The general procedure for the sodium methoxide opening of lactone **16** was followed at 0 °C to yield 827 mg (29%) of pure 3-(*R*)-hydroxy-2-(*R*)-methyl-pent-4-ynoic acid methyl ester (**104**), the low yield being a result of the extreme volatility of **104**. $[\alpha]_D$ –9.8 (*c* 0.90, $CHCl_3$). IR (thin film): 3445, 3290, 2988, 2955, 2885, 2358, 2337, 1732, 1459, 1438, 1206, 1094, 1064, 1037, 991, 681 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 4.62 (br s, 1 H), 3.75 (s, 3 H), 3.15 (br d, J = 6.1 Hz, 1 H), 2.79 (dq, J = 4.2, 3.1 Hz, 1 H), 2.47 (d, J = 2.2 Hz, 1 H), 1.71 (br s, 1 H), 1.32 (d, J = 7.3 Hz, 3 H); ^{13}C-NMR ($CDCl_3$): δ 174.43, 82.03, 73.88, 63.50, 52.08, 45.02, 11.78. MS (EI, 70eV): *m/z* 127 (M^+–CH_3), 111 (M^+–OCH_3), 88 (M^+–HC≡CCHOH), 83 (M^+–CO_2CH_3). HRMS *m/z* calcd for $C_6H_7O_3$: 127.0395; found 127.0394.



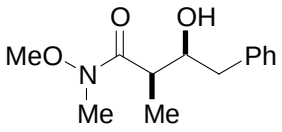
Synthesis of 4-(*R*)-Benzyl-3-propionyl-oxazolidin-2-one (88):[4a] To a round bottom flask was added 2.66 g (15 mmol) of (*R*)-(+)-4-benzyl-2-oxazolidinone (**110**). Anhydrous THF (5.0 mL) was added and the solution was cooled to –78 °C. A 1.6 M solution of *n*-BuLi in hexanes, 9.45 mL (15.15 mmol), was added dropwise and the

solution was stirred for 1 h. Freshly distilled propionyl chloride, 1.43 mL (16.5 mmol), was added, all in one portion. The solution was stirred for 30 min. at –78 °C and the reaction was warmed to ambient temperature. The reaction was stirred to completion (as assessed by TLC) and excess propionyl chloride was quenched with 30 mL of a saturated solution of NH_4Cl. The organic layer was separated and the aqueous layer was washed with diethyl ether (3 X 15 mL). All organics were combined and were washed with 30 mL of 1 M NaOH and then with 30 mL of brine. The organics were once again combined and were dried over magnesium sulfate. The crude reaction mixture was concentrated under reduced pressure and was then placed in a –25 °C refrigerator over night to crystallize. The pure crystals of 4-(*R*)-benzyl-3-propionyl-oxazolidin-2-one (**88**) were taken the next day and were triturated with a minimum amount of hexanes and were filtered and dried. They were used ahead in the next reaction without further purification.



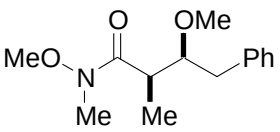
Synthesis of (2'*R*,3'*S*,4'*R*)-4-Benzyl-3-[3'-hydroxy-2'-methyl-4'-phenylbutanoyl]-oxazolidin-2-one (89):[4a] In a round bottom flask was added 3.29 g (14.10 mmol) of the crystallized acylated oxazolidinone (**88**) and 50.0 mL of dry CH_2Cl_2. A thermometer was inserted through the septum and the reaction was cooled to 0 °C (monitored by the internal temperature). Freshly distilled Bu_2BOTf, 4.45 g (16.22 mmol), was carefully added and then, 2.46 mL (17.64 mmol) of triethylamine was added. Both were added slowly enough so that the internal reaction temperature did not rise above 3 °C. The reaction was cooled to –78 °C and 1.98 mL (16.93 mmol) of phenylacetaldehyde (**14**) was added slowly enough so that the internal temperature did not rise above –65 °C. The reaction was stirred at –78 °C for 20 min and was warmed to 0 °C and was stirred for an additional hour. The reaction was quenched with 15 mL of pH 7 aqueous phosphate buffer and 15 mL of MeOH.

To this 0 °C solution was slowly added 25 mL of 2:1 MeOH:30% H_2O_2 *via* syringe in such a way that the internal temperature did not rise above 10 °C. The reaction was stirred at 0 °C for an additional hour and the volatiles were removed under reduced pressure. The organic layer was separated and the aqueous layer was washed with diethyl ether (3 X 15 mL). The organics were combined were washed once with 30 mL of a saturated solution of $NaHCO_3$ and once with 30 mL of brine. The organics were dried and the crude organic mixture was concentrated under reduced pressure. This crude reaction mixture was purified on silica gel using 10% EtOAc in hexanes. Recrystallization of the white powdery solid with EtOAc and hexanes yielded 4.83 g (97.18%) of 2'*R*,3'*S*,4'*R*)-4-benzyl-3-[3'-hydroxy-2'-methyl-4'-phenylbutanoyl]-oxazolidin-2-one (**89**). ^{1}H-NMR ($CDCl_3$): δ 7.28 (m, 10 H), 4.66 (ddt, J = 14.2, 6.6, 3.3 Hz, 1 H), 4.19 (ovrlp, 9 lines, 3 H), 3.82 (qd, J = 7.0, 3.4 Hz, 1 H), 3.24 (dd, J = 13.5, 3.3 Hz, 1 H), 2.81 (ovrlp, 11 lines, 4 H), 1.37 (d, J = 6.8 Hz, 3 H); ^{13}C-NMR ($CDCl_3$): δ 177.24, 153.10, 138.49, 135.21, 129.64, 129.51, 129.19, 128.74, 127.65, 126.76, 72.93, 66.34, 55.28, 42.00, 40.70, 37.97, 11.15.



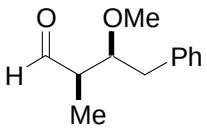
Synthesis of (2*R*,3*S*)-*N*-methyl-*N*-methoxy-2-methyl-3-hydroxy-4-phenylbutanamide (111):[42] To a round bottom flask was added 1.74 g (17.84 mmol) of HN(OMe)Me and 20 mL of dry THF. At 0 °C, 8.92 mL (17.84mmol) of 2.0 M solution of $AlMe_3$ in hexanes was added over 20 min. and the reaction was stirred for 30 min. at 0 °C. Amide **89**, 32.27 g, (6.44 mmol), was added in 7 mL of dry THF over a 15 min. period and the solution was then stirred for 1 h at 0 °C. Ice-cold 1 M HCl (20 mL) was slowly added into the reaction and the solution was allowed to warm to ambient temperature. The organic layer was separated and the aqueous layer was washed with EtOAc (2 X 15 mL). All organics were combined and were dried. The crude reaction was flashed on silica gel using 40% EtOAc in

hexanes. This yielded 1.36 g (89.3%) of purified (2*R*,3*S*)-*N*-methyl-*N*-methoxy-2-methyl-3-hydroxy-4-phenylbutanamide (**111**). ^{1}H-NMR ($CDCl_3$): δ 7.30-7.21 (m, 5 H), 4.11 (dt, J = 7.0, 3.0 Hz, 1 H), 3.65 (br s, 3 H), 3.46 (br s, 3 H), 2.89 (dd, J = 13.5, 7.5 Hz, 1 H), 2.85 (par obsc, 1 H), 2.71 (dd, J = 13.5, 7.0 Hz, 1 H), 1.23 (d, J = 7.0 Hz, 3 H); ^{13}C-NMR ($CDCl_3$): δ 177.90, 138.30, 129.10, 128.40, 126.3, 72.86, 61.20, 40.01, 37.21, 31.75, 10.03.



Synthesis of (2*R*,3*S*)-*N*-methyl-*N*-methoxy-2-methyl-3-methoxy-4-phenylbutanamide (112):[42] To a round bottom flask was added 0.702 g (29.34 mmol) of NaH as a 60% dispersion in mineral oil. Anhydrous pentane (10 mL) was added and the solution was stirred vigorously for 10 min. and was then allowed to settle. The pentane was removed *via* cannula and the process was repeated two more times to fully activate the sodium hydride. The reaction flask was cooled to 0 °C and 40 mL of anhydrous THF and 20 mL of anhydrous DMF (2:1 THF:DMF by volume) were added. Amide **111**, 2.319 g (9.78 mmol), was added and then, 6.05 mL (9.94 mmol) of MeI was added. The solution was stirred at 0 °C for 2 h. While still at 0 °C, the solution was poured into 200 mL of ice-cold pH 7 phosphate buffer. The organic layer was separated and the aqueous layer was washed with EtOAc (2 X 150 mL). The organic layers were combined and washed sequentially with water (1 X 100 mL) and brine (1 X 100 mL). The crude reaction mixture was dried and concentrated under reduced pressure. Purification was carried out on silica gel using 25% EtOAc in hexanes to yield 1.84 g (75.1 %) of pure (2*R*,3*S*)-*N*-methyl-*N*-methoxy-2-methyl-3-methoxy-4-phenylbutanamide (**112**). ^{1}H-NMR ($CDCl_3$): δ 7.23-7.17 (m, 5 H), 3.61 (app t, J = 7, 4 Hz, 1 H), 3.44 (br s, 3 H), 3.24 (s, 3 H), 3.15 (s, 3 H), 2.90 (obsc dq, 1 H), 2.86 (dd, J = 14, 3.5 Hz, 1 H),

2.74 (dd, J = 14, 7.0 Hz, 1 H), 1.21 (d, J = 7.0 Hz, 3 H); ^{13}C-NMR ($CDCl_3$): δ 175.95, 138.77, 129.51, 128.04, 125.97, 83.75, 60.95, 58.84, 39.62, 38.48, 32.01, 13.43.



Synthesis of (2*E*,4*S*,5*S*)-5-methoxy-2,4-dimethyl-6-phenyl-2-hexanal (12):[4a] To a round bottom flask was added 1.842 g (7.33 mmol) of Weinreb amide **112** and 60 mL of anhydrous diethyl ether. The solution was cooled to –78 °C and 8.80 mL (8.80 mmol) of a 1.0 M solution of DIBAL-H in hexanes was added dropwise. The solution was stirred at –78 °C for 1 h. The excess DIBAL-H was carefully quenched at –78 °C with 5 mL of EtOAc and the solution was stirred at that temperature for an addition 15 min. The reaction mixture was poured into 120 mL of a 0.5 M solution of tartaric acid in water and diethyl ether (2.5:1 water:diethyl ether) and the solution was stirred at room temperature for 1 h. The organics were separated and the aqueous layer was washed with diethyl ether (3 X 20 mL). The organics were combines and dried and concentrated under reduced pressure to produce 1.212 g, (86.0%) of pure (2*E*,4*S*,5*S*)-5-methoxy-2,4-dimethyl-6-phenyl-2-hexanal (**12**). ^{1}H-NMR ($CDCl_3$): δ 7.27 (m, 2 H), 7.19 (m, 3 H), 5.32 (dq, J =9.8, 1.3 Hz, 1 H), 3.99 (d, J = 4.8 Hz, 2 H), 3.24 (s, 3 H), 3.20 (ddd, J = 7.6, 6.3, 4.8 Hz, 1 H), 2.80 (dd, J = 13.8, 4.8 Hz, 1 H), 2.71 (dd, J = 13.9, 7.5 Hz, 1 H), 2.55 (dqu, J = 9.8, 6.6 Hz, 1 H), 1.57 (d, J = 1.3 Hz, 3 H), 1.29 (br t, J = 5.8 Hz, 1 H), 1.02 (d, J = 6.7 Hz, 3 H); ^{13}C-NMR ($CDCl_3$): δ 139.77, 134.99, 129.58, 128.69, 128.37, 126.14, 87.21, 68.92, 58.67, 38.24, 36.18, 18.58, 14.01.

3.0 THE KETENE-CLAISEN REARRANGEMENT

3.1 THE CLAISEN REARRANGEMENT

The Claisen rearrangement, arguably the most prevalent of the [3,3]-sigmatropic processes, was discovered in 1912 by its namesake.[46] This process is essentially an oxygenated analogue of the Cope rearrangement leading from vinyl ethers to γ,δ-enones. The process is stereospecific with respect to the olefin in the starting allylic alcohol.[47]

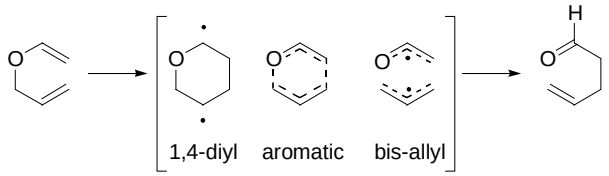


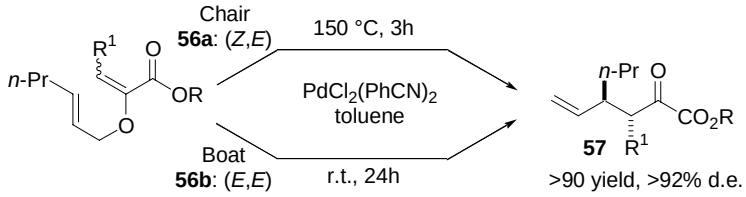
Figure 12: The generic Claisen rearrangement with three possible intermediates.

Although, in general, Claisen rearrangements prefer to react through chair-like transition states, boat-like transition states are feasible. In the early- to mid-1960s, Doering and Gilman both noted this detail in the related Cope rearrangement, although they were not the first to make this observation.[48] One recent illustration of the feasibility of both chair-like and boat-like transition states comes from Hiersemann. In 1999, he showed that (*Z*,*E*)-**56a** undergoes a

[46] (a) Claisen, L. *Ber. Dtsch. Chem. Ges.* **1912**, *45*, 3157-3166. (b) Li, J. J. *Name Reactions*. Ann Arbor, MI: Springer, 2003, pp. 74-75.
[47] (a) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*. New York, NY: HarperCollin*gPublishers*, 1987, pp. 968-969. (b) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry. Part B: Reactions and Synthesis*. New York: Kluwer Academic/Plenum Publishers, 1971, p. 388.
[48] (a) Doering, W. v. E.; Roth, W. R. *Tetrahedron* **1962**, *18*, 67-74. (b) Hill, R. K.; Gilman, N. W. *Chem. Commun.* **1967**, 619-620.

thermal Claisen *via* a chair-like transition state to produce *anti*-γ,δ-unsaturated ester **57**. On the other hand, the isomer (*E*,*E*)-**56b**, in the presence of Pd(II), rearranges *via* a boat-like transition state to produce *anti*-γ,δ-unsaturated ester **57** (Equation 20).[49]

Equation 20



3.2 THE IRELAND-CLAISEN REARRANGEMENT

Although the traditional Claisen rearrangement has been used extensively within the scientific community, the innumerable variations of the seminal reaction have, in their own right, become more pervasive in literature. A short list of these related processes include the Marbet-Saucy reaction, the Carrol reaction (a.k.a. the Kimel-Cope rearrangement), the Johnson Orthoester rearrangement, the Eschenmoser-Claisen rearrangement, and the Ireland-Claisen rearrangement.[50] The latter, which facilitates the rearrangement of the esters of allylic alcohols into γ,δ-unsaturated carboxylic esters (most often through an intermediary *O*-trimethylsilyl ether of the ester enolate), will be discussed in the ensuing sections.

A significant advantage of the Ireland-Claisen is the mild conditions required (Equation 21). In general, these ester enolate rearrangements occur at slightly elevated temperatures, which is seldom the case for traditional Claisens.[46a]

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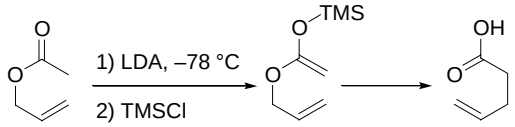
[49] Hiersemann, M. *Synlett* **1999**, 1823-1825.
[50] Smith, M. B. *Organic Synthesis*. Boston: McGraw-Hill, 2002, pp. 1021-1026.

Equation 21



As with all Claisen variants, the stereochemical distribution of products is controlled by the geometry of the olefin of the starting allylic alcohol; however, the Ireland variant is unique because stereochemistry is also controlled by the geometry of the starting silyl enol ether. For a simplified chair-like transition state, the configuration at the newly formed C-C bond can be determined from the *E*- or *Z*-configuration of the silyl enol ether.[51]

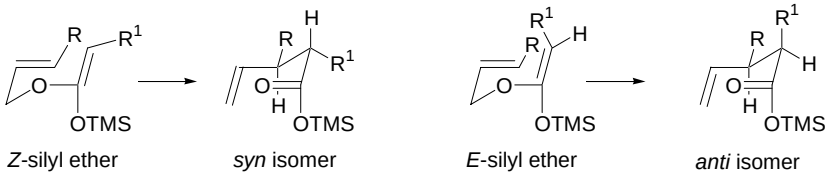


Figure 13: The geometry of the starting olefin produces products stereospecifically.

Ireland and coworkers have observed that *trans*-olefins in the starting ester result in the corresponding geometrical outcome when coupled to enolate (or latent enolate equivalent) geometry: *cis*-enolates generate *anti* products, whereas *trans*-enolates yield *syn* products. This result can be extrapolated for *cis*-olefins as well; *cis*-enolates predominate in *syn* products, while *trans*-enolates favor *anti* products.[52]

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[51] Carey, R. A.; Sundberg, R. J. *Advanced Organic Chemistry. Part B: Reactions and Synthesis*. New York: Kluwer Academic/Plenum Publishers, 1971, pp. 389.
[52] Ireland, R. E.; Wipf, P.; Armstrong III, J. D. *J. Org. Chem.* **1991**, *56*, 650-657.

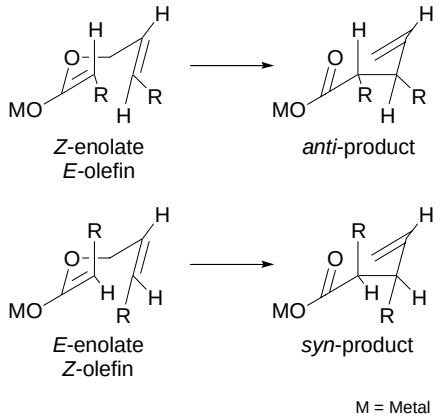


Figure 14: In the Ireland Claisen, both olefin and enolate geometry control product distribution.

Since the *E*/*Z* ratio of the starting ester can be controlled with explicit choice of substrate, the question of silyl enol ether geometry arises. As with typical enolate formation, the stereochemistry of the silyl enol ether can be controlled with judicious selection of conditions. Lithium diisopropylamine (LDA) is often utilized for such an enterprise. If the intermediary enolate is prepared with LDA in dry THF, the *E*-enolate predominates. This *E* stereochemistry is maintained upon silylation to yield the corresponding *E*-silyl ketene acetal. *E*-enolate predominance under these conditions originates from a cyclic transition state wherein a proton is abstracted from the stereoelectronically preferred orientation.

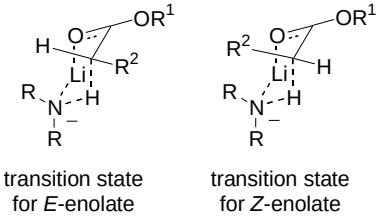


Figure 15: *E*- versus *Z*-enolate formation.

In order to attain *Z*-enolate predominance, solvating reagents are often employed. The most common of these are hexamethylphosphoramide (HMPA) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone (DMPU). A simplified rationalization for this switch in enolate

geometry is that solvation of the lithium ion results in a loose, acyclic transition state.[53] Ireland and coworkers have further extrapolated that, when enolization occurs in the less coordinating THF (as compared to HMPA), the interactions between the carbonyl oxygen with the lithium cation (during enolization) appear to be relatively significant. This nonbonding interaction causes the carbonyl group to be effectively bulkier than OR, forcing the molecule to adopt a lower energy conformation in the transition state, leading to *Z*-enolate predominance. On the other hand, with HMPA present, a far greater solvation of the lithium cation persists along with an enhanced reactivity of the amide base. Taken together, these factors weaken the nonbonding interaction between the lithium cation and the carbonyl oxygen causing a lower energy transition state conformation with the carbonyl as the smaller group and OR as the larger.[52] These factors help populate the *E*-enolate in preference to the *Z*-enolate.[54]

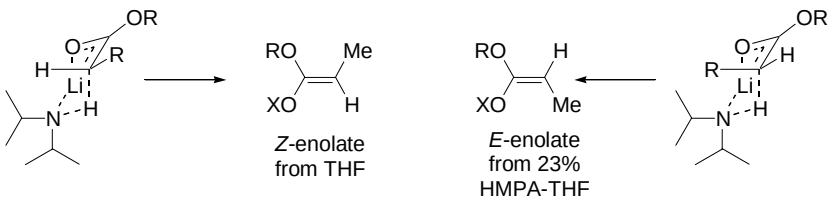


Figure 16: Transition states leading to both the *Z*- and *E*-enolates.

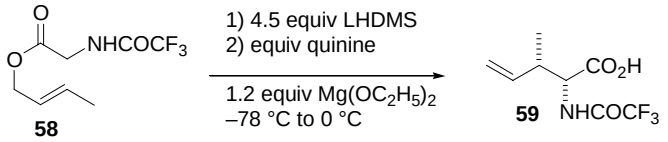
As with the traditional Claisen, catalytic amounts of Lewis acid can promote the ester enolate rearrangement. Romero-Giron and coworkers have identified that, in the presence of a catalytic amount of $TiCl_4$, silyl ketene acetals of *trans* allylic esters undergo a highly diastereoselective Ireland-Claisen to the corresponding carboxylic acids. Diastereoselectivities

[53] (a) Ireland, R. E.; Willard, A. K. *Tetrahedron Lett.* **1975**, *16*, 3975-3978. (b) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868-2877.
[54] Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E. *J. Org. Chem.* **1980**, *45*, 1066-1081.

of up to 15:1 were observed, whereas the uncatalyzed process proceeds much more slowly and with worse selectivity.[55]

Enantioselective variations for the ester enolate Claisen rearrangement have also been developed. Kazmaier and Krebs demonstrated that cinchona alkaloids can be utilized, along with a chelating metal, to achieve respectable enantioselectivities. Ester **58** was transformed into α-amino acid **59** with an enantiomeric excess of up to 88% (Equation 22).[56]

Equation 22



97% yield, 88% e.e.

Kazmaier has also employed an ester-enolate rearrangement of chelated *N*-protected cycloalkenyl glycinates to γ,δ-unsaturated amino acids in good yields and high diastereoselectivities. After *N*-protected glycine allylesters (**59**) were enolized with LDA at –78 °C, transmetallation occurred with $ZnCl_2$ (Equation 23). The ensuing rearrangement proceeds with a high degree of diastereoselectivity due to the fixed enolate geometry formed as a result of chelation. Product stereoselectivity is independent of both substitution pattern and protecting groups used. In contrast to the corresponding lithium enolates, these chelated zinc enolates are robust enough to survive at ambient temperatures. In general, the rearrangement proceeds at –20 °C.[57]

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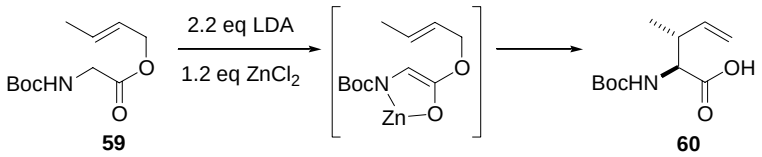
[55] Koch, G.; Janser, P.; Kottirsh, G.; Romero-Giron, E. *Tetrahedron Lett.* **2002**, *43*, 4837-4840.
[56] Kazmaier, U.; Krebs, A. *Tetrahedron Lett.* **1999**, *40*, 479-482.
[57] Kazmaier, U. *Tetrahedron* **1994**, *50*, 12895-12902.

Equation 23

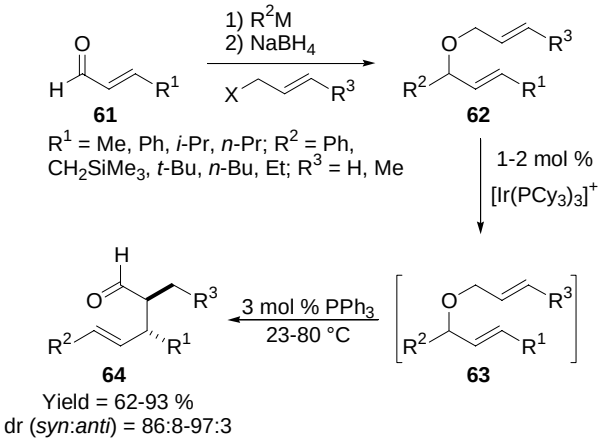


3.3 THE ZINC-PROMOTED ESTER ENOLATE CLAISEN

3.3.1 Proposal of a novel ketene-Claisen rearrangement

In 2003, Nelson and coworkers reported a unique isomerization-Claisen rearrangement (ICR) (Scheme 6). Metallated reagents were employed in 1,2-additions of alkyl and aromatic moieties into α,β-unsaturated aldehydes (**61**). The resulting alkoxide species could, in the presence of base, be trapped with allylic halides to afford bis(allyl) ethers (**61**). When these bis(allyl) ethers were subjected to cationic iridium(I), the less substituted olefin isomerized to provide the intermediary Claisen precursors (**63**). At slightly elevated temperatures, these precursors (**63**) underwent a highly diastereoselective Claisen rearrangement to yield a diverse array of γ,δ-unsaturated aldehydes in good yields and diastereoselectivities.[58]

[58] Nelson, S. G.; Bungard, C. J.; Wang, K. *J. Am. Chem. Soc.* **2003**, *125*, 13000-13001.



Scheme 6: The olefin isomerization-Claisen rearrangement (ICR).

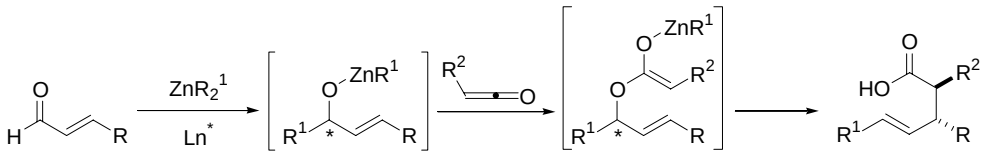
Although this in-house chemistry provided an efficient route to γ,δ-unsaturated aldehydes, it was thought that the methodology could be expanded. The alkoxide resulting from 1,2-alkyl addition into α,β-unsaturated aldehydes provided an opportunity to explore molecular diversity. Trapping this species with a diverse collection of electrophiles should provide access to precursors of the Ireland-Claisen and Johnson-Claisen rearrangements, among others. Successful achievement of these transformations would produce an important assortment of γ,δ-unsaturated acids and esters that could be further manipulated to provide important biologically active compounds.

The previous success of the ICR chemistry, as well as the success of ester enolate Claisen rearrangements in general, was the impetus for the formulation of a novel Claisen rearrangement. Precedent for asymmetric 1,2-diethyl zinc addition to α,β-unsaturated aldehydes was combined with Tidwell's observation that alkoxides acylate at the internal carbon of substituted ketenes.[59,60] Consequently, a ketene-Claisen rearrangement was postulated to arise from an

[59] (a) Sola, L.; Reddy, K. S.; Vidal-Ferran, A.; Moyano, A.; Perciàs, M. A.; Riera, A.; Alvarez-Larena, A.; Piniella, J.-F. *J. Org. Chem.* **1998**, *63*, 7978-7082. (b) Mori, M.; Nakai, T. *Tetrahedron Lett.* **1997**, *38*, 6233-6236. (c) Zhang, F.-Y.; Chan, A. S. C. *Tetrahedron: Asymmetry* **1997**, *8*, 3651-3655. (e) Wu, K.-H.; Gau, H.-M. *Organometallics* **2004**, *23*, 580-588. (f) Kang, S-W.; Ko, D-H.; Kim, K. H.; Ha, D-C. *Org. Lett.* **2003**, *5*, 4517-4519.

asymmetric diethyl zinc addition to an α,β-unsaturated aldehyde with concomitant acylation of the *in situ* generated zinc alkoxide by a substituted ketene. The resulting zinc ester enolate should then proceed through an Ireland-like ester enolate Claisen to yield a γ,δ-unsaturated acid (equation 24).

Equation 24



This proposed ketene-Claisen rearrangement is potentially a synthetically useful process. In one synthetic operation, simple, readily available α,β-unsaturated aldehydes could be transformed into complex, enantio- and diastereoenriched γ,δ-unsaturated carboxylic acids. This process has a few advantages over existing methods to obtain γ,δ-unsaturated carboxylic acids. For the prototypical ester enolate rearrangement, the desired α,β-unsaturated ester needs to be prefabricated. Second, enolization provides problems in regards to the stability of the resulting ester enolate (these tend to be unstable, generally necessitating the formation of intermediary silyl enol ethers). Finally, enolate selectivity is yet another variable that necessitates judicious choice of reaction conditions to obtain acceptable levels of selectivity.

The proposed ketene-Claisen rearrangement should bypass most of these problems. For one, the process is expedient, providing a one-pot procedure to obtain the desired Ireland-Claisen adducts. Secondly, zinc ester enolates are thought to be more robust than their lithium counterpart, providing a more stable intermediary reactive intermediate. Finally, enolate selectivity should be governed by Tidwell's precedent that addition into substituted ketenes

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[60] Tidwell, T. *Acc. Chem. Res.* **1990**, *23*, 273-279.

occurs from the less sterically encumbered face (providing *E*-ester enolates in this case).[61] All in all, the proposed Claisen rearrangement should provide a complimentary process to the ICR reaction technology, yielding the corresponding γ,δ-unsaturated acids.[57]

In order to ensure the success of the proposed rearrangement, a few key tenets must be assessed. First, although precedent exists for the asymmetric 1,2-diethyl zinc addition into α,β-unsaturated aldehydes, subsequent trapping of the resulting zinc alkoxide with ketene needs to be verified.[58] Secondly, the stability of the ensuing zinc ester enolates needs to be assessed in terms of lifetime and durability. Finally, the propensity of these zinc ester enolates to react must be evaluated, especially in terms of the Claisen rearrangement.

3.3.2 Precedent for the zinc-promoted ester enolate Claisen

One of the key tenets of the proposed ketene-Claisen reaction is the acylation of ketenes by a zinc alkoxide. Ketenes, defined as "compounds in which a carbonyl group is connected by a double bond to an alkylidene group," tend to be electrophilic in their center, sp-hybridized carbon.[62] Melman and coworkers have demonstrated this concept with their acylation work of monosubstituted ketenes **66** with various alcohols (Equation 25).[63]

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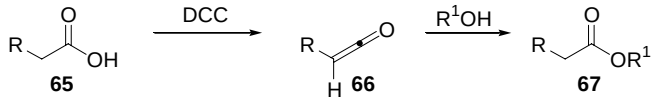
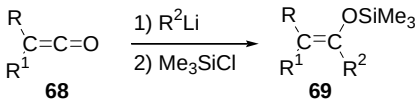
[61] Baigrie, L. M.; Seiklay, H. R.; Tidwell, T. T. *J. Am. Chem. Soc.* **1985**, *107*, 5391-5396.
[62] IUPAC. *IUPAC Compendium of Chemical Terminology*. IUPAC. 2003. http://www.iupac.org/publications/compendium/index.html (7 June 2004).
[63] Nahmany, M.; Melman, A. *Org. Lett.* **2001**, *3*, 3733-3735.

Equation 25



Tidwell has devoted extensive efforts to the investigation of the electrophilicity of ketenes. When Tidwell and coworkers subjected unsymmetrical ketenes to organolithium reagents coupled with an *in situ* silylation protocol with TMSCl, they observed stereospecific formation of a single silyl enol ether (**69**). This synthetic route provides a stereospecific method to reach silylated enolate-equivalents generally not accessible in high selectivities.

Table 18: Tidwell's silyl enol ether formation from substituted ketenes



R	R^1	R^2	Yield (%)
Ph	Me	*n*-Bu	50
Ph	Et	*n*-Bu	76
$SiMe_3$	Et	*n*-Bu	77
t-Bu	H	*t*-Bu	62

The rationale for this result is that the nucleophilic organolithium reagents preferentially attack in the plane of the ketene, specifically from the side opposite the more sterically demanding group. Therefore, the steric interactions between the approaching organolithium and the substituents on ketene will determine the preferential direction of attack. This observation is as expected since the nucleophilic attack of an organolithium reagent on ketene should occur on the C=O π-bond in the plane of the substituted ketene leading directly to the product enolate. Bond formation occurs between the HOMO of the organolithium and the LUMO of the ketene.[60]

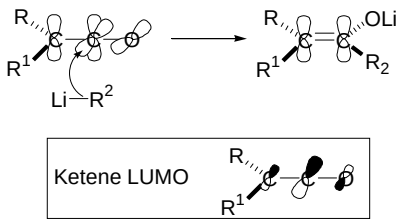


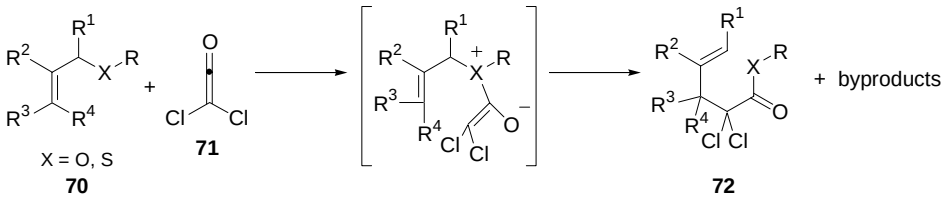
Figure 17: An orbital diagram of organolithium attack on substituted ketenes.

Tidwell's precedent illustrates that lithium alkoxides can be acylated by ketene at the internal carbon. Although these studies were not extrapolated to zinc alkoxides, the documented success of selective *E*-silyl enol ether formation (Table 18) provides optimism regarding the analogous reaction to form a zinc ester enolate. Therefore, precedent for the first key tenet of the proposed ketene-Claisen reaction has been established.

Although precedent exists for metal alkoxide acylation by ketene, the reactivity of the intermediary metalloester enolate remains a question. The Belluš reaction (or Belluš-Claisen rearrangement) provides evidence that the ester enolate of the proposed ketene-Claisen reaction may be able to undergo the desired rearrangement. In 1983, when studying reactions of haloketenes with ethers and thioethers, Belluš, Malherbe, and Rist detected a novel ketene-Claisen rearrangement. When both α,β-unsaturated ethers and thioethers were acylated with substituted haloketenes, the intermediary "onium" species rearranged to the corresponding Claisen adduct (Equation 26).[64] Although the utility of the Belluš-Claisen is seemingly endless, initial studies proved the reaction to be limited to highly electrophilic ketenes, such as dichloroketene, dibromoketene, and difluoroketene.

[64] (a) Malherbe, R.; Rist, G.; Belluš, D. *J. Org. Chem.* **1983**, *48*, 860-869. (b) Gonda, J. *Angew. Chem. Int. Ed.* **2004**, *43*, 3516-3524.

Equation 26



The importance of the Belluš-Claisen cannot be overlooked. Although the reaction does contain considerable limitations, the successful transformation provides insight into our proposed ketene-Claisen rearrangement. First and foremost, although the Belluš system is altered from the proposed reaction manifold, it does indicate that ketene acylation of an α,β-unsaturated alcohol is possible. Secondly, the Belluš-Claisen proves that intermediary α,β-unsaturated ester enolates can undergo [3,3]-sigmatropic rearrangements.

The next critical principle of the proposed ketene-Claisen rearrangement is the successful attainment of the transient zinc ester enolate prior. In order to assess the viability of this protocol, the properties of zinc enolates must first be evaluated. Zinc enolates generally possess a greater stability over their lithium counterparts.[65] Although zinc enolates appear to be more robust, Heathcock's observation that they have ^{13}C-NMR spectra similar to alkali metal enolates implies that they may react in a similar manner.[66] Perhaps the most common method of zinc enolate assemblage is through House's method, reacting lithium enolates with either zinc chloride or zinc bromide.[67]

Since Heathcock and House have assessed the durability and general reactivity of zinc enolates, the formation of a zinc ester enolate *via* the acylation of an alkoxide can be inferred. Therefore, the final tenet to be addressed regarding the proposed ketene-Claisen rearrangement is

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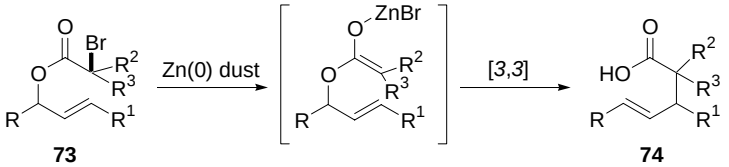
[65] Trost, B. M. (Ed.-in-Chief). *Comprehensive Organic Synthesis: Selectivity, Strategy, and Efficiency in Modern Organic Synthesis*. *Volume 2: Additions to C-X π-Bonds, Part 2*. Oxford: Pergamon Press, 1992, pp. 123.
[66] Hansen, M. M.; Bartlett, P. A.; Heathcock, C. H. *Organometallics* **1987**, *6*, 2069-2074.
[67] House, H. O.; Crumrine, D. S.; Teranishi, A. Y.; Olmstead, H. D. *J. Am. Chem. Soc.* **1973**, *95*, 3310-3324.

that of the Claisen itself. The question remains as to whether or not zinc ester enolates can rearrange to γ,δ-unsaturated acids.

In 1973, Baldwin and Walker discovered a new category of [3,3]-sigmatropic rearrangements, the Reformatsky-Claisen reaction.[68] Initial formation of an α-bromo unsaturated ester (formed *via* the acylation of α,β-unsaturated alcohols with α-bromo acid bromides) proceeds with yields greater than 90%. Upon treatment with zinc(0), the Reformatsky reaction transpires with zinc insertion into the C-Br bond which, along with concurrent elimination, forms the bromozinc enolate. When the stable enolate is subjected to high temperatures, an ester enolate Claisen reaction occurs, transforming the α-halo ester (**73**) into the zinc carboxylate of a γ,δ-unsaturated carboxylic acid (**74**). Although the Reformatsky-Claisen rearrangement occurs with varying yields, olefin selectivity of the resulting Claisen adduct remains relatively high throughout. The *E*/*Z* ratio for the rearrangement of α-bromopropionate to 2-methylhex-4-enoic acid was 93:7.

Table 19: Baldwin's Reformatsky-Claisen Reaction



73 **74**

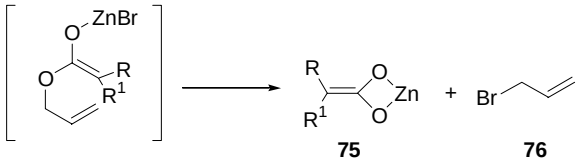
Entry	R	R^1	R^2	R^3	Solvent	Temp (°C)	Yield (%)
1	H	H	Me	Me	Benzene	80	100
2	Me	H	Me	H	Toluene	110	96
3	H	H	H	H	Xylene	140	<15
4	H	Ph	Me	H	Toluene	110	16

Despite precedent for the Reformatsky reaction proceeding through a zinc enolate, there are still alternative mechanisms possible for the Claisen-type rearrangement observed by

[68] Baldwin, J. E.; Walker, J. A. *J. Chem. Soc., Chem. Commun.* **1973**, 117-118.

Baldwin and coworkers. Proof of a zinc ester enolate was found when the zinc enolates derived from acetic esters yielded 1,3-dicarbonyl compounds **75** and **76**, the representative byproducts of the classical Reformatsky reaction (Equation 27).[67]

Equation 27



75 **76**

This initial observation by Baldwin and Walker is critical to the proposed ketene-Claisen rearrangement. The production of Reformatsky byproducts **75** and **76** infers that the [3,3]-sigmatropic rearrangement occurs through an intermediary bromozinc ester enolate. This is significant because it supposes that intermediary α,β-unsaturated zinc ester enolates can indeed rearrange to γ,δ-unsaturated carboxylic acids. Another consequence of Baldwin's work is that the bromozinc enolates are able to survive under extreme conditions (namely 80-140 °C). This signifies that the bromozinc ester enolates are considerably more robust than their lithium counterparts.

Although Baldwin and Walker's result is of the utmost importance in regards to the proposed ketene-Claisen rearrangement, additional precedent was sought to verify the viability of [3,3]-sigmatropic rearrangements of zinc ester enolates. Further encouragement was derived from the Reformatsky-Claisen rearrangement utilized by Grueter and coworkers. This zinc-promoted process involves the rearrangement of allyl chlorodifluoroacetate (**77**) in the presence of TMSCl to afford 2,2-difluoro-4-pentenoic acid (**78**) in 78% yield (Equation 28).[69]

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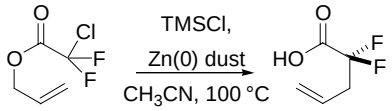
[69] Grueter, H.; Land, R. W.; Romann, A. J. *Tetrahedron Lett.* **1988**, *29*, 3291-3299.

Equation 28



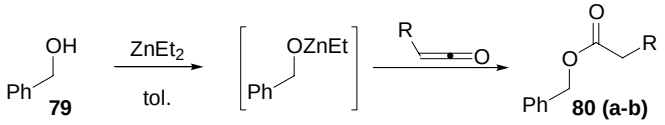
77 **78**
78% Yield

In summations precedent for the proposed ketene-Claisen rearrangement has been established. First, the viability of ketene acylation by a zinc alkoxide has been inferred by the work of Tidwell. In general, it is presumed that our zinc alkoxide will attack from the least sterically encumbered face of a substituted ketene to selectively form an *E*-zinc ester enolate. Next, the Belluš-Claisen has indicated that the resulting α,β-unsaturated zinc ester enolate may rearrange through a [3,3] process. More importantly, the work of Baldwin and Grueter have shown that α,β-unsaturated halozinc ester enolates can indeed rearrange to γ,δ-unsaturated carboxylic acids. With precedent set for each key tenet of the proposed transformation, experimentation was commenced.

3.4 RESULTS AND DISCUSSION

With precedent set for the zinc-promoted ketene-Claisen rearrangement, efforts were made to realize the proposal. Since the asymmetric diethyl zinc addition to α,β-unsaturated aldehydes is well established, exploration began with assessment of the feasibility of ketene acylation of a zinc alkoxide.[58] Preliminary studies were performed with benzyl alcohol (**79**) and the commercially available trimethylsilylketene (Table 20).

Table 20: The viability of zinc-promoted ketene acylation of alcohols



Entry	ROH	$ZnEt_2$	R	Ketene	Temp. (°C)	Product (conversion %)[a]
1[b]	1.0 mmol	0.5 mmol	TMS	1.5 mmol	rt	36 **80a**
2	1.0 mmol	0.5 mmol	TMS	1.5 mmol	0	44 **80a**
3	1.0 mmol	1.0 mmol	TMS	1.5 mmol	0	63 **80a**
4	1.0 mmol	0.5 mmol	Me	1.5 mmol	-78	22 **80b**

[a]Conversion of **79** to **80 (a-b)** was assessed by ^{1}H-NMR. [b]1.0 mL of anhydrous THF was added to the reaction.

Initial formation of the zinc alkoxide was achieved by introduction of diethyl zinc to **79**. Next, commercially available trimethylsilylketene was injected into the reaction medium. The first trial employed 0.50 mmol of diethyl zinc in the presence of 1.0 mL of anhydrous THF at ambient temperature (entry 1). The presence of THF was thought to be necessary to break up the tetrameric aggregation of the ethyl zinc alkoxide in solution; however, ensuing studies proved this addition to be unnecessary.[70] Regardless, this experimentation produced **80a** in 36% conversion. The significance of this result must be noted. Since the acylating agent was a substituted ketene, the transient zinc ester enolate must have been achieved. After formation, the ester enolate was quenched to provide **80a**. Limited attempts were made to isolate **80a**; however, the product was always entrained with its desilated partner. Therefore, conversion of starting material to product was thought to be a more accurate measure to assess reaction success.

In order to increase conversion, reaction temperature was first lowered to 0 °C (entry 2). Although this did improve conversion, additional modifications were employed to further

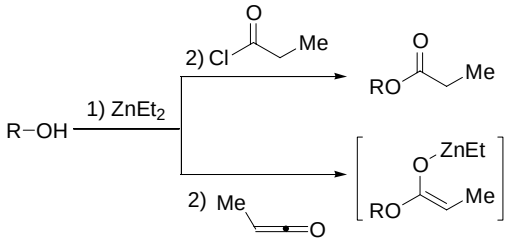
[70] Boersma, J.; Noltes, J. G. *Tetrahedron Lett.* **1966**, *14*, 1521-1525.

increase reaction efficiency. Raising the amount of diethyl zinc to a stoichiometric quantity further enhanced conversion to 63% (entry 3). The reason for the lack of full conversion was thought to derive from the impurities associated with the commercially available trimethylsilylketene (i.e., the corresponding carboxylic acid).

All in all, the results of the alkoxide acylation with trimethylsilylketene are of utmost importance. First, they prove that ketenes can acylate zinc alkoxides. Second, and most importantly, production of **80a** indicates that the zinc ester enolate was achieved. Since the reaction proved successful with commercially available trimethylsilylketene, synthetic ketenes were the next challenge to be evaluated.

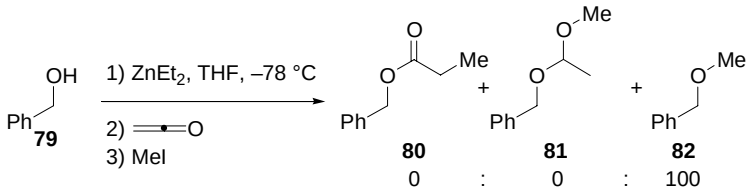
Methyl ketene was formed from the reaction of propionyl chloride and DIPEA at –78 °C.[6b,c] This synthetic methyl ketene was introduced to the zinc alkoxide of **79** at 0 °C to produce **80b** in a 22% unoptimized conversion (entry 4). Despite the presence of **80b**, care was taken to avoid drawing inaccurate conclusions from this result. Although methyl ketene was prefabricated, there exists the possibility that ketene was not the acylating agent. In general, for reactions with synthetic ketene, there are two possible routes to acylation (Equation 29). The first is a direct acylation with unreacted acid chloride to yield the allyl ester. The second, and desired, route is acylation of the zinc alkoxide with ketene, resulting in an intermediary zinc ester enolate.

Equation 29



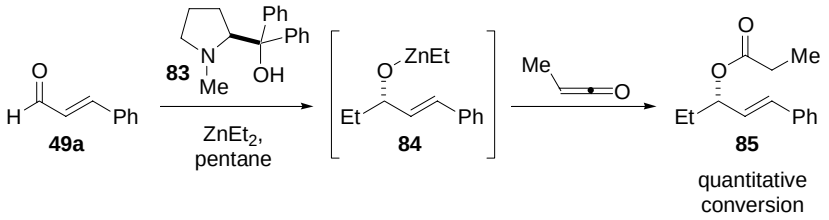
In order to assess whether or not the acylation mode observed in the previous experiment was occurring through ketene, some attempts were made to trap the elusive zinc enolate. Efforts were employed with methyl iodide and ketene in the hopes that the zinc ester enolate would react to either produce *C*-alkylation **80**, *O*-alkylation **81**, or a mixture of the two (Equation 30). Unfortunately, studies indicated the preferential product to be exclusive *O*-methylation of the starting benzyl alcohol to produce **82**.

Equation 30



Since methyl ketene had proven to be a viable acylating agent, studies were focused on the actual Claisen rearrangement. The presence of the intermediary zinc ester enolate was presumed, suggesting that rearrangement should be a distinct possibility. Due to precedent from the ICR chemistry, *trans*-cinnamaldehyde (**49a**) was subjected to asymmetric diethyl zinc addition with prolinol **83**.[54] The resultant zinc alkoxide (**84**) was then acylated with preformed methyl ketene. Although quantitative acylation was observed in the form of α,β-unsaturated ester (**85**), no Claisen rearrangement was observed (Equation 31).

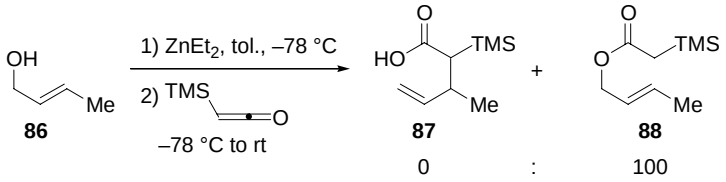
Equation 31



Unfortunately, the zinc-promoted process from α,β-unsaturated aldehyde to γ,δ-unsaturated acid was unsuccessful. Production of **85** indicated that both diethyl zinc addition and ketene acylation were successful, but the Claisen rearrangement did not occur. It was unclear if the zinc ester enolate had been quenched by the extraneous proton from the ligand or through another source. Therefore, ensuing studies were simplified to exclusively assess the propensity of α,β-unsaturated zinc ester enolates to rearrange.

Initial tests were performed with 1.00 mmol of crotyl alcohol (**86**), 0.50 mmol of diethyl zinc, and 2.0 mL of dry toluene at –78 °C. After 30 min., 1.0 mmol of anhydrous THF was incorporated to break up potential zinc alkoxide aggregation. Following this addition, trimethylsilylketene was added dropwise. Upon warming to ambient temperature, the reaction was stirred for three hours and was then quenched with saturated ammonium chloride. The resulting product ratio, as assessed by ^{1}H-NMR, was 100:0 of acylated product **88** to Claisen adduct **87** (Equation 32). This outcome provided insight into the potential proceedings of the reaction. Again, the use of trimethylsilylketene ensured that the zinc ester enolate was attained. Since full conversion to **88** was observed, it can be concluded that the zinc ester enolate was stable to the reaction conditions (i.e., it did not decompose back to allylic alcohol **86**). This is noteworthy because, at room temperature, the corresponding lithium enolates decompose.[66] This result supports Baldwin's observation that zinc ester enolates can survive at elevated temperatures.[68]

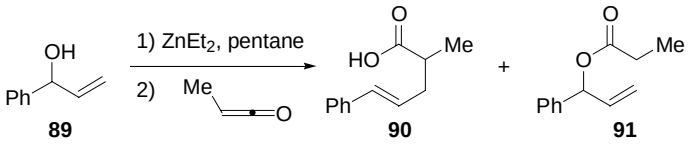
Equation 32



Unfortunately, the zinc ester enolate for the aforementioned reaction did not rearrange to Claisen adduct **87**. This caused the stability of the zinc ester enolate to come into question. Either the enolate was highly stable, providing a covalent zinc-oxygen (or zinc carbon) linkage that failed to undergo the rearrangement or it was sufficiently short lived, quenching to provide ester **88** (in preference to decomposition back to starting material). The commercially available trimethylsilylketene contained one additional variable that could have prevented the rearrangement. Although the commercially available reagent is relatively pure, it does contain some impurities that could have protonated the enolate. To remove this uncertainty, the potential ketene-Claisen rearrangement was tested with synthetic ketenes.

To begin, allylic alcohol **89** was chosen as the test substrate (Table 21). This choice was made because of the previous failure of the rearrangement to occur. The phenyl group of **89** should promote rearrangement to provide the substituted, conjugated olefin in the γ,δ-unsaturated acid product (**90**). This added thermodynamic stability of the product was thought to, at the very least, increase the chances of observing the rearrangement.

Table 21: The attempted ketene-Claisen rearrangement of 89



89 **90** **91**

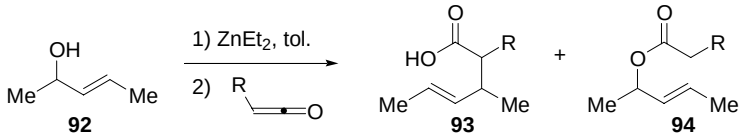
Entry	ROH	$ZnEt_2$	ketene	Temp. (°C)	Product Ratio (**90**:**91**)
1[a]	1.0 mmol	0.5 mmol	1.5 mmol	–78	0:100
2	1.0 mmol	0.5 mmol	1.5 mmol	–78	0:100
3[b]	1.0 mmol	0.5 mmol	1.5 mmol	0	0:100
4	1.0 mmol	0.5 mmol	1.5 mmol	rt	0:100
5[c]	1.0 mmol	0.5 mmol	1.5 mmol	–78	Decomposed

Unless otherwise noted, ketene was fabricated from 1.5 equiv. or propionyl chlordie and 1.5 equiv. of DIPEA at –78 °C. [a]The reaction was performed in toluene instead of pentane. [b]1.0 mL of anhydrous THF was added at –78 °C and 3.0 equiv. of DIPEA was used to make ketene. [c]Anhydrous CH_2Cl_2 (5.0 mL) and THF (1.0 mL) were employed and 2.32 equiv. of K_2CO_3 was to make ketene used instead of DIPEA.

Initial attempts employing 0.50 mmol of diethyl zinc with 1.5 mmol of methyl ketene in toluene at –78 °C provided full conversion to acylated **91**. In order to favor the rearrangement, reaction temperature was first increased to 0 °C and then up to ambient temperature; however, **91** was the only observed product (entries 3 and 4, respectively). As before, it was presumed that the zinc ester enolate was achieved upon acylation by ketene. The failure to observe any Claisen process was thought to be a result of one of two factors; either the zinc ester enolate was too covalent to react under mild conditions and proceeded to remain until quenched during work-up or the enolate was quenched immediately by the presence of *i*-$Pr_2NEt{\cdot}HCl$ salt (a byproduct of ketene formation). In an attempt to prohibit the latter from impeding the rearrangement, the above reactions were performed in the nonpolar toluene or pentane in the hopes of precipitating out the amine salt. Unfortunately, the salt was so fine that precipitation and removal was less than straightforward. Therefore, the insoluble base, potassium carbonate, was utilized in the reaction of **89** in the hopes of removing extraneous protons, but decomposition resulted (entry 5).

Since no Claisen adduct had formed from **89**, another substrate was sought to verify if the reaction would work for a different substrate (Table 22). Pent-3-en-2-ol (**92**) was first tested with a prefabricated solution of ketene, synthesized from acetyl bromide; however the excessive bromide salts present caused decomposition (entry 1). As expected, when the reaction was carried out with methyl ketene (synthesized from propionyl chloride) at –78 °C, the reaction proceeded to acylated **94** in full conversion (entry 2). Curiously, when this methyl ketene reaction was warmed to ambient temperature, the reaction failed to proceed to **94** in full conversion (entry 3).

Table 22: The attempted ketene-Claisen rearrangement of pent-3-en-2-ol (92)



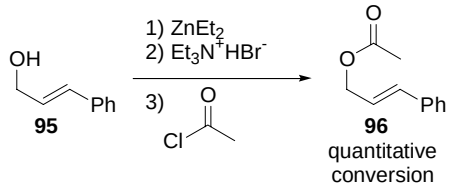
92 **93** **94**

Entry	ROH	$ZnEt_2$	Ketene	Temp. (°C)	Product Ratio (**92:93:94**)
1	1.0 mmol	0.5 mmol	R=H, 1.5 mmol	rt	Decomposition
2	1.0 mmol	0.5 mmol	R=Me,1.5 mmol	–78	0:0:100
3	1.0 mmol	0.5 mmol	R=Me,1.5 mmol	–78-rt	76.2:0:23.8

The failure of allylic alcohol **92** to provide full conversion to **94** under the conditions displayed in entry 3 of Table 22 was troublesome. It was postulated that the *i*-Pr_2NEt·HCl salt, present as a byproduct of ketene formation, may be the problem. As previously inferred, although the salt should precipitate in nonpolar solvents, it is such a fine precipitate that it is hard to remove from the reaction (possible redissolving during the reaction). Therefore, the effect of an amine·HCl salt on a zinc alkoxide was tested (Equation 33). Allylic alcohol **95** was subjected to 1.0 equiv. of diethyl zinc to form the resulting zinc alkoxide at ambient temperature. After 30 min., previously manufactured Et_3N·HCl salt (1.5 equiv.) was added and the reaction was stirred for two hours. Acetyl chloride was then added in an attempt to acylate the zinc alkoxide. The

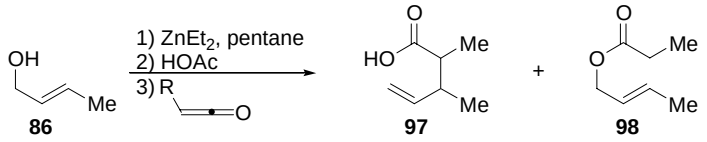
experiment resulted in quantitative conversion to **96**. This outcome unequivocally proved that the *i*-Pr_2NEt·HCl (or Et_3N·HCl) was not hindering zinc alkoxide acylation.

Equation 33



Since traditional methods failed to yield any Claisen adducts, the activity of the zinc ester enolate was questioned. Baldwin's Reformatsky-Claisen utilized a bromozinc ester enolate, a species known to be more reactive than an ethylzinc ester enolate.[68] Since Baldwin's Claisen rearrangement necessitated extreme reaction temperatures, forming a more reactive zinc species became a requisite. In-house results from the Nelson group indicated that addition of acetic acid to an ethylzinc alkoxide forms an activated acetylzinc alkoxide.[71] Therefore, allylic alcohol **86** was subjected to these activated acetic acid conditions (Table 23). Following formation of the ethylzinc alkoxide, acetic acid was introduced to the reaction medium in order to form an acetylzinc alkoxide. A variety of reaction temperatures and equivalents of acetic acid were employed in the reaction; however, the acylated **98** was the only observed product.

Table 23: The effect of acetic acid in the ketene-Claisen rearrangement of 86

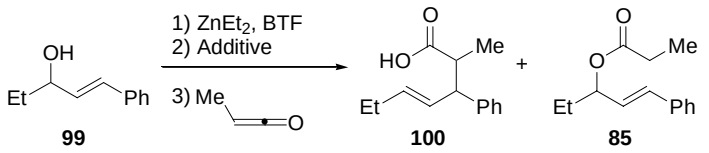


Entry	ROH	$ZnEt_2$	HOAc	Ketene	Temp. (°C)	Product Ratio (**97**:**98**)
1[a]	1.0 mmol	1.0 mmol	1.0 mmol	1.5 mmol	rt	0:100
2[b]	1.0 mmol	3.0 mmol	3.0 mmol	1.5 mmol	–78	0:100
3[a]	1.0 mmol	1.0 mmol	1.0 mmol	1.5 mmol	35-6	0:100

[71] Unpublished results, Mr. Kan Wang, University of Pittsburgh.

The results of the acetic acid experiments indicated that the zinc ester enolates (both ethylzinc and acetylzinc) were not active enough to undergo the Claisen rearrangement. Therefore, alcohol **99** was subjected to elevated temperatures, reminiscent of Baldwin's Reformatsky-Claisen rearrangement (Table 24).[68]

Table 24: The ketene-Claisen reaction of 99



99 **100** **85**

Entry	ROH	$ZnEt_2$	Additive	ketene	Temp. (°C)	Product Ratio (**99**:**100**:**85**)
1	1.0 mmol	0.8 mmol	--	2.42 mmol	–25 to 100	0:4.7:95.3
2[a,b]	1.0 mmol	0.5 mmol	LDA (4.0 equiv.)	1.50 mmol	–25-rt	100:0:0
3[c,d]	1.0 mmol	1.00 mmol	HBr (1.5 equiv.)	1.21 mmol	rt-110	20.4:0:79.6
4[e]	1.0 mmol	1.00 mmol	DMPU	1.50 mmol	–78 to 110	0:100
5[d,e]	1.0 mmol	1.00 mmol	DMPU	1.50 mmol	–78 to 110	0:100
6	1.0 mmol	1.00 mmol	ethylene glycol (1.0 equiv.)	1.50 mmol	–78 to 100	77.8:22.2 **85**:diacylated

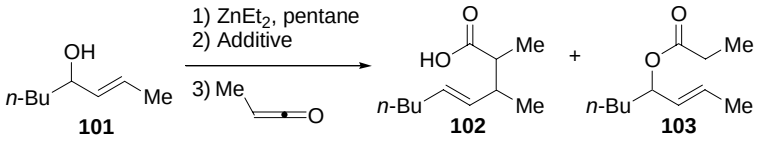
Unless otherwsie noted, all reactions were performed with 2.42 mmol of DIPEA the indicated amount of propionyl chloride (i.e., the amount of ketene). [a]1.50 mmol of acetyl chloride was used. [b]LDA added at –25 °C, 4 h after methyl ketene addition. [c]HBr made *in situ* from AcBr and MeOH. [d]Reaction performed in toluene. [e]DMPU used in a ratio of 10:8 solvent:DMPU.

Allylic alcohol **99** was subjected to diethyl zinc at –25 °C and was then acylated with methyl ketene. Once the acylation was complete (as assessed by TLC), the reaction was heated to 100 °C (entry 1). Unfortunately, acylated **85** was the only result. When attempts were made to re-enolize **85** with LDA, the reaction decomposed back to starting alcohol **99** (entry 2). In order to convene with Balwdin's precedent, *in situ* generated HBr was added to the ethylzinc alkoxide in order to produce a bromozinc alkoxide (entry 3). Unfortunately, at 110 °C, the reaction failed to undergo the Claisen rearrangement. In an attempt to ionize the zinc ester enolate, DMPU was added to the reaction, but acylated **85** resulted (entries 4 and 5).[52] In the

same vein, ethylene glycol was added to the zinc alkoxide in an attempt to chelate the zinc species; however, this resulted in a mixture of **85** and the diacylated species.

With the failure of elevated temperatures to promote a successful Claisen rearrangement, two additional additives were utilized in an attempt to promote the Claisen rearrangement (Table 25). First, *trans*-oct-2-en-4-ol (**101**) was subjected to standard conditions to produce acylated **103** (entry 1). DMPI was chosen as a possible additive because it should favor an instantaneous [3,3]-sigmatropic rearrangement (since it would activate the ketene).[72] When it was added to the reaction mixture prior to ketene addition, decomposition back to **103** resulted (entry 2). An initial attempt was made to shift the ketene-Claisen reaction over to the Ireland-Claisen manifold; however, addition of TMSCl caused complete decomposition (entry 3).

Table 25: Study of additives in the ketene-Claisen reaction



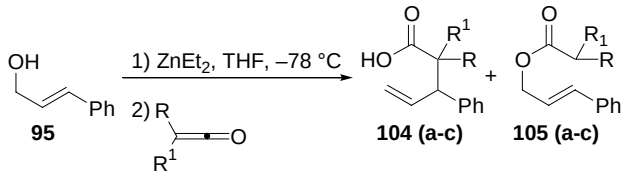
Entry	ROH	$ZnEt_2$	Ketene	Additive	Temp. (°C)	Product Ratio (**101**:**102**:**103**)
1	1.0 mmol	0.5 mmol	1.5 mmol	--	–78	0:0:100
2	1.0 mmol	0.5 mmol	1.5 mmol	3.0 mmol DMPU	–78	100:0:0
3	1.0 mmol	0.5 mmol	1.5 mmol	1.5 mmol TMSCl	–78-rt	Decomposition

No discernible Claisen adduct had yet been produced under all of the previously reported reaction conditions. The one constant with all of the trials concerning synthetic ketene was the presence of the amine·HCl. Although it was previously ascertained that this salt had no ill effects regarding alkoxide acylation, the effect of the salt on enolate lifetime was still unknown.

[72] Nicholson, D. A.; Vaughn, H. *J. Org. Chem.* **1971**, *36*, 3843-3845.

Therefore, synthetic, salt-free ketenes were introduced to the ketene-Claisen rearrangement (Table 26).

Table 26: The study of ketenes in the [3,3]-sigmatropic rearrangement



Entry	ROH	R	R^1	Temp (°C)	Products	Product Ratio (**104**:**105**)
1[a]	1.0 mmol	Cl	Cl	–78 to 110	**104a**, **105a**	0:100
2[a,b]	1.0 mmol	Cl	Cl	–78 to 110	**104a**, **105a**	0:100
3[b]	1.0 mmol	H	H	75	**104b**, **105b**	0:100
4[b,c]	1.0 mmol	H	H	75	**104b**, **105b**	0:100
5[d]	1.0 mmol	Me	H	–78	**104c**, **105c**	0:100
6[d]	1.0 mmol	Me	H	–78 to 110	**104c**, **105c**	0:100

All reactions refluxed overnight (except reaction 5) with 2.0 equiv. of ketene. [a]Reaction performed in toluene. [b]Salt-free ketene was used. [c]1.0 equiv. of acetic acid added. [d]Methyl ketene formed from reaction of 2.0 equiv. α-bromopropionyl bromide with 2.0 equiv. of activated Zn(0) in 2.0 mL of dry THF.

Initial studies with allylic alcohol **95** employed dichloroketene (due to precedent concerning the Belluš-Claisen).[64,73] For comparison, synthetic dichloroketene and salt-free dichloroketene (fabricated in the same manner, but distilled off from the amine salt) were assessed (entries 1 and 2, respectively). Unfortunately, even at 110 °C, both experiments provided complete conversion to **105a** as the only result. Subsequently, salt-free ketene was employed in the reaction. This salt-free ketene was prepared by pyrolysis of acetone in a ketene generator.[74] At 75 °C, salt free ketene with and without the addition of acetic acid (to activate the zinc ester enolate) failed to promote the Claisen rearrangement (entries 3 and 4, respectively). Finally, a variant of Baldwin's Reformatsky reaction was endeavored. Methyl ketene was

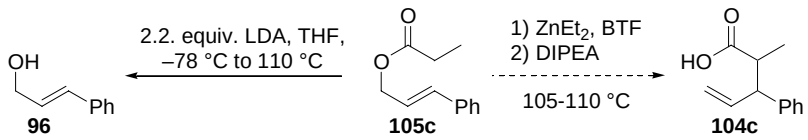
[73] Nubbemeyer, U.; Öhrlein, J.; Gonda, J.; Ernst, B., Belluš, D. *Angew. Chem. Int. Ed.* **1991**, *30*, 1465-1467.
[74] Wynberg, H.; Staring, E. G. *J. Org. Chem.* **1985**, *50*, 1977-1979.

formed from the Reformatsky reaction of α-bromopropionyl bromide with activated Zn(0).[68] It was hoped that the extraneous zinc bromide resulting from the Reformatsky reaction would help promote the Claisen rearrangement; however, this proved to be incorrect, even at 110 °C (entry 6). Taken together, these trials indicated that it was not the amine salt that was hindering the [3,3]-sigmatropic rearrangement, but rather the reactivity of the zinc ester enolates.

To summarize all the previous experiments, although successful proof of zinc alkoxide addition into ketene had established, the ensuing zinc ester enolates had failed to rearrange under various reaction conditions. Although it was initially assumed that the amine salt was impeding rearrangement, this was found to be less of a factor than zinc ester enolate activity. Therefore, the reaction was simplified even further to merely assess the propensity for zinc ester enolates to undergo a [3,3]-rearrangement.

Initial attempts with propionic acid 3-phenyl-allyl ester (**105c**) under soft enolization methods with diethylzinc failed to provide any reaction. Increasing reaction temperature to 105-110 °C continued to result in seemingly untouched starting material (**105c**). As anticipated, when the corresponding lithium enolate was tested under these conditions, formed from enolization of **105c** in THF with 2.2 equiv. of LDA at –78 °C and then warmed to 110 °C, decomposition down allylic alcohol **95** proceeded in preference to the rearrangement (Equation 34).

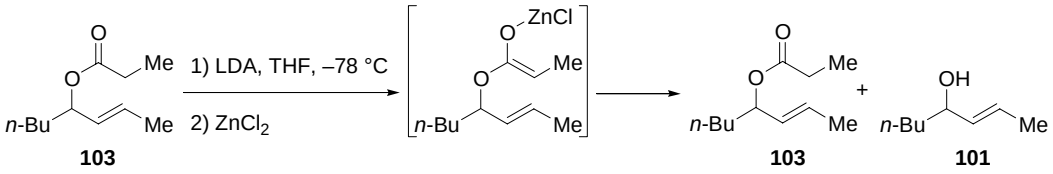
Equation 34



Although the above transformation provided expected results concerning the experiment with LDA, the zinc ester enolate may not have been achieved. Therefore, it was necessary to

arrive at a zinc ester enolate in a reliable, precedented method in order to assess the true reactivity of the zinc enolates. To this end, House's protocol for the transmetallation of lithium enolates with zinc chloride was employed (Table 27).[67] The control experiment, enolizing ester **103** followed by warming to ambient temperature produced **101** (entry 1). When a similar protocol was carried out with transmetallation with zinc chloride, the result was still acylated **101** (entry 2). This result proves not only that the zinc ester enolate was achieved (because decomposition down to **101** did not occur), but also that the zinc ester enolate is indeed more robust than its lithium counterpart. Although the Claisen rearrangement did not occur under this reaction protocol, it does indicate that the previous ketene-acylation studies had achieved a zinc ester enolate.

Table 27: Zinc enolate durability



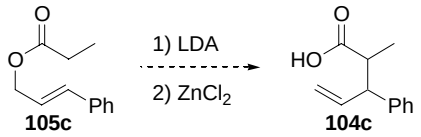
103 **103** **101**

Entry	LDA	$ZnCl_2$	Product Ratio (**103**:**101**)
1	1.2 mmol	--	0:100
2	1.2 mmol	1.6 mmol	100:0

Since proof of the zinc ester enolate had been discovered *via* House's transmetallation route, this method was utilized in an attempt to promote the ester enolate Claisen rearrangement (Table 28). Ester **105c** was enolized with LDA and was then transmetallated with zinc chloride. Unfortunately, when the ensuing zinc ester enolate was heated to 110 °C, the Claisen rearrangement failed to proceed (entries 1 and 2). Addition of DMPU, reminiscent of the Ireland protocol, also failed to attenuate the reactivity of the chlorozinc ester enolate (entry 3).[52] In a final attempt to connect with Baldwin's Reformatsky-Claisen, ammonium bromide was added.[68]

Although the ensuing bromozinc ester enolate may have been achieved, the reaction still failed to progress to the desired γ,δ-unsaturated acid **104c**.

Table 28: Potential Claisen from a zinc ester enolate



105c **104c**

Entry	Ester	Additive	Temp (°C)	Result
1	1.0 mmol	--	–78 to 110	**105c**
2[a]	1.0 mmol	--	–78 to 110	**105c**
3	1.0 mmol	8 mL DMPU	–78 to 110	**105c**
4	1.0 mmol	8 mL DMPU, 2.63 eq NH_4Br	–78 to 110	**105c**

Unless otherwise noted, all reactions were performed with 1.5 equiv. LDA in 10 mL toluene with 2.0 equiv. of $ZnCl_2$. [a]1.0 equiv. of $ZnCl_2$ was utilized.

Since no Claisen rearrangement had yet been observed, studies regarding the zinc-promoted ketene Claisen were placed on hold. The final results shown in Table 28 are of consequence, however, because they indicate that α,β-unsaturated zinc ester enolates may not be active enough under the explored reaction conditions to undergo a general Claisen rearrangement.

3.5 CONCLUSION

A ketene-Claisen reaction promoted by zinc(II) was investigated with unsuccessful promotion of the actual Claisen rearrangement. Although numerous variables were tested, including solvent, temperature, ketene source, and source of zinc, no isolable γ,δ-unsaturated acid was ever observed. It was shown, however, that α,β-unsaturated aldehydes can be carried through to allyl

esters following asymmetric 1,2-ethyl addition with *in situ* trapping of the zinc alkoxide by ketene. Proof of enolate formation from ketene acylation has been inferred along with proof that the amine salt resulting from ketene formation is not the critical problem impeding rearrangement.

Under the various reaction conditions exploited, the intermediary zinc ester enolates did not rearrange to the desired Claisen adducts. Regardless, there is still hope that the rearrangement could occur. Additional efforts must be focused to either isolate or trap the zinc ester enolate species to unequivocally prove that it is being formed from synthetic ketene acylation. After this proof is obtained, more elevated temperature studies should be conducted to observe when the Claisen actual occurs. If a more mild reaction is required, chelating groups can be employed. Both Kazmaier and Aggarwal have utilized α-amino or α-oxygen-containing esters.[56,75] These zinc-promoted chelated Claisens tend to rearrange under milder conditions. Otherwise, a variant of MacMillan's titanium-promoted ammonium enolate ketene-Claisen can be investigated.[76] The ensuing titanium(IV) ester enolates may have a higher propensity to rearrange than their zinc counterparts. Finally, Heathcock has proven that ethylzinc enolates can be transmetallated with TMSCl to provide silyl enol ethers.[62] If desired, addition of TMSCl to the zinc ester enolates should provide a road to connect with the precedented Ireland-Claisen protocol.

Despite the failures to observe a successful Claisen reaction, I still maintain that this reaction, whether by means of titanium or by zinc, has a high degree of probability for success.

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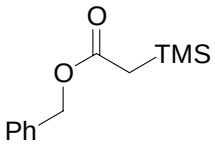
[75] Aggarwal, V. K.; Lattanzi, A.; Fuentes, D. *Chem. Comm.* **2002**, 2534-2535.
[76] (a) Yoon, T. P.; Deng, V. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **1999**, *121*, 9726-9727. (b) Yoon, T. P.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 2911-2912.

If careful investigation is undertaken, a successful transformation should be achieved in the near future.

3.6 EXPERIMENTALS

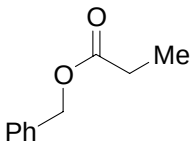
General Notes: Unless otherwise noted, all reactions were performed under anhydrous conditions (dry glassware was utilized under an atmosphere of nitrogen). All crude organic products were dried over magnesium sulfate and were concentrated under reduced pressure by rotary evaporation.



Synthesis of trimethylsilyl-acetic acid benzyl ester (80a):[77] A round bottom flask was charged with 0.104 mL (1.00 mmol) of the benzyl alcohol and 2.0 mL of dry toluene. At 0 °C, 0.5 mL (0.50 mmol) of a 1 M solution of diethyl zinc in hexanes was added dropwise to the reaction. The solution was stirred for 30 min. at 0 °C and 0.211 mL (1.5 mmol) of trimethylsilylketene was added to the solution. The reaction was allowed to warm to ambient temperature and was stirred for two hours. The reaction was quenched with 25 mL of 1M HCl. The organic layer was separated and the aqueous layer was washed with diethyl ether (3 X 20 mL). The organics were combined and were washed with 25 mL of a saturated solution of NaCl. The combined organic layers were dried over magnesium sulfate the crude reaction mixture was then concentrated under reduced pressure. The crude product was purified on silica gel using 5% EtOAc in hexanes to provide 0.115g (51.8%) of

[77] Data obtained from crude spectrum. Emde, H.; Simchen, G. *Synthesis* **1977**, 867-869.

trimethylsilyl-acetic acid benzyl ester (**80a**). ^{1}H-NMR ($CDCl_3$): δ 7.40 (s, 5 H), 5.10 (s, 2 H), 1.95 (s, 2 H), 0.10 (s, 9 H).

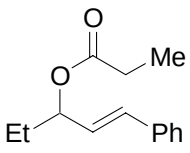


Synthesis of propionic acid benzyl ester (80b):[78] A round bottom flask was charged with 0.104 mL (1.00 mmol) of benzyl alcohol and 2.0 mL of dry toluene. At ambient temperature, 0.5 mL (0.50 mmol) of a 1 M solution of diethyl zinc in hexanes was added dropwise to the reaction. After 30 minutes of stirring the reaction was cooled to –78 °C and 1.5 mmol of methyl ketene was added dropwise. [Note: Methyl ketene was formed in a separate round bottom flask over 30 min. from 0.26 mL (1.5 mmol) of DIPEA and 0.13 mL (1.5 mmol) of propionyl chloride in 2.0 mL of dry toluene at –78 °C]. The reaction was stirred at –78 °C for three hours and was then quenched with 25 mL of saturated NH_4Cl. The organic layer was separated and the aqueous layer was extracted with diethyl ether (3 X 20 mL). All organic layers were combined, dried, and concentrated under reduced pressure. The crude product was purified on silica gel using 5% EtOAc in hexanes to provide 29 mg (18%) of propionic acid benzyl ester (**80b**). ^{1}H-NMR ($CDCl_3$): δ 7.37 (s, 5 H), 5.15 (s, 2 H), 2.40 (t, J = 7.9 Hz, 3 H), 1.19 (q, J = 7.4 Hz, 2 H); ^{13}C-NMR ($CDCl_3$): δ 174.18, 136.05, 128.45, 128.07, 66.02, 27.50, 9.01.

Procedure for alkyl-iodide trapping of the zinc ester enolate: To a round bottom flask was added 0.10 mL (1.00 mmol) of BnOH and 5.0 mL of dry THF. At –78 °C, 1.4 mL (1.4 mmol) of a 1 M solution of $ZnEt_2$ in hexanes was added dropwise. At –78 °C, the solution was stirred 30 min.. Freshly prepared ketene (0.80 mmol) was then added dropwise *via* a cannula. [Note:

[78] Westwell, A. D.; Williams, J. M. J. *Tetrahedron* **1997**, *53*, 13063-13078.

Ketene was formed in a separate round bottom flask over 30 min. from 0.06 mL (0.80 mmol) of AcBr and 0.11 mL (0.80 mmol) of DIPEA in 1.0 mL of dry THF at –78 °C]. The reaction was stirred for 1 h at –78 °C. Methyl iodide, 0.78 mL (1.20 mmol), was added dropwise the reaction was stirred for 1 h at –78 °C. The reaction was warmed to ambient temperature and was stirred for an additional hour. The reaction was quenched with 20 mL of a saturated solution of ammonium chloride and the organic layer was separated. The aqueous layer was washed with diethyl ether (3 X 15 mL) and all organics were combines and dried over magnesium sulfate. The crude reaction mixture was concentrated under reduced pressure to produce crude methyl benzyl ether (**82**).

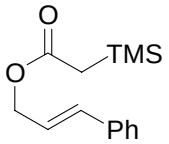


Synthesis of propionic acid 1-ethyl-3-phenyl-allyl ester (85) *via* asymmetric diethylzinc addition to and subsequent acylation of *trans*-cinnamaldehyde (49a): A round-bottom flask was charged with 0.126 mL (1.00 mmol) of *trans*-cinnamaldehyde (**49a**), 5.4 mg (0.02 mmol) of 2-[(*S*)-1,1-diphenyl-1-hydroxymethyl)-N-methylpyrrolidine (**83**), and 5.0 mL anhydrous pentane. The heterogeneous mixture was refluxed for 20 minutes and was then cooled to 0 °C. A 1M solution of diethyl zinc in hexanes, 1.0 mL (1.00 mmol), was added dropwise and the reaction was stirred 0 °C for 3 h. In a separate round-bottom flask, 0.26 mL (1.50 mmol) of DIPEA in 2.0 mL of anhydrous pentane was added and cooled to –78 °C. To this flask was added 0.13 mL (1.5 mmol) of propionyl chloride dropwise and the reaction was stirred for 1 h at –78 °C. The zinc alkoxide was cooled to –78 °C and the solution of methyl ketene in pentane was transferred to the zinc alkoxide *via* cannula. The reaction was stirred at –78 °C for 3 h and was then warmed to ambient temperature. The reaction mixture was quenched with 20 mL of a saturated solution of NH_4Cl. The organic layer

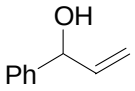
was separated and solution was extracted with diethyl ether (3 X 15 mL). All organic layers were combined and dried. The crude solution was concentrated under reduced pressure to yield crude propionic acid 1-ethyl-3-phenyl-allyl ester (**85**). IR (thin film): 2969, 2939, 2878, 1735, 1462, 1380, 1272, 1186, 1080, 748, 693 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 7.49-7.20 (m, 5 H), 6.63 (d, J = 16.0 Hz, 1 H), 6.16 (dd, J = 8.7, 7.2 Hz, 1 H), 5.39 (q, 6.9 Hz, 1 H), 2.39 (q, J = 7.5, 2 H), 1.78 (dq, J = 6.9, 6.5 Hz, 2 H), 1.19 (t, J = 7.5 Hz, 3 H), 0.97 (t, J = 7.4 Hz, 3 H); ^{13}C-NMR ($CDCl_3$): δ 173.77, 136.36, 132.40, 128.48, 127.78, 127.59, 126.49, 75.69, 31.54, 27.83, 27.59, 22.61, 14.07, 9.52, 9.13. MS (EI, 70eV): *m/z* 218 (M^+), 202 (M^+–O), 189 (M^+–CH_2CH_3), 161 (M^+–$C(O)CH_2CH_3$), 145 (M^+–$CO_2CH_2CH_3$), 129 (M^+–$HCO_2CH_2CH_3$, CH_3), 57 (M^+–$CH_3CH_2CHCH{=}CHC_6H_5$). HRMS *m/z* calcd for $C_{14}H_{18}O_2$: 218.1307; found 218.1304.

General procedure for methyl ketene acylation of a zinc alkoxide followed by attempted Claisen rearrangement: To a round bottom flask was added 1.00 mmol of the desired allylic alcohol and 2.0 mL of anhydrous pentane. At room temperature, 0.5 mL (0.50 mmol) of a 1 M solution of diethyl zinc in hexanes was added dropwise. The reaction was stirred for 30 min. at ambient temperature and the reaction was cooled to –78 °C. A preformed solution of methyl ketene (1.5 mol in 2.0 mL of toluene) was added *via* cannula to the reaction mixture at –78 °C. [Note: Methyl ketene was formed in a separate round bottom flask over 30 min. from 0.26 mL (1.5 mmol) of DIPEA and 0.13 mL (1.5 mmol) of propionyl chloride in 2.0 mL of dry toluene at –78 °C]. The reaction was stirred for the indicated time at –78 °C. The reaction was warmed to ambient temperature and was quenched with 20 mL of a saturated solution of NH_4Cl. The organic layer was separated and the aqueous layer was extracted with diethyl ether (3 X 15 mL).

The organic layers were combined and dried with magnesium sulfate. The magnesium salt was removed and the crude reaction was concentrated under reduced pressure.



Trimethylsilanyl-acetic acid 3-phenyl-allyl ester (88): The general procedure for methyl ketene acylation of a zinc alkoxide was followed. ^{1}H-NMR ($CDCl_3$): δ 7.64-7.35 (m, 5 H), 6.71 (d, J = 15.9 Hz, 1 H), 6.46 (dt, J = 15.9, 5.7 Hz, 1 H), 4.42 (d, J = 5.6 Hz, 2 H), 2.20 (s,2 H), 0.16 (s, 9 H).



Synthesis of 1-phenyl-prop-2-en-1-ol (89):[79] To a round bottom flask was added 1.92 mL (18.82 mmol) of benzaldehyde (passed through a plug of alumina to remove benzoic acid) and 50 mL of anhydrous Et_2O. The solution was cooled to –78 °C and 22.6 mL (22.30 mmol) of vinyl magnesium bromide was added dropwise as a 1 M solution in THF. The reaction was stirred for 30 min. at –78 °C and was then warmed to ambient temperature. The reaction was quenched with 50 mL of saturated NH_4Cl and was extracted with diethyl ether (3 X 25 mL). The crude reaction mixture was dried and concentrated under reduced pressure. The crude product was purified on silica gel using 10% EtOAc in hexanes to provide pure 2.28 g (90%) of 1-phenyl-prop-2-en-1-ol (**89**). ^{1}H-NMR ($CDCl_3$): δ 7.41-7.28 (m, 5 H), 6.07 (ddd, J = 6.1, 4.0, 0.8 Hz, 1 H), 5.40 (t, J = 1.8 Hz, 1 H), 5.34 (t, J = 1.3 Hz, 1 H), 5.23 (dd, J = 1.3, 0.4 Hz, 1 H), 1.91 (br s, 1 H); ^{13}C-NMR ($CDCl_3$): δ 142.56, 140.20, 128.53, 127.73, 126.28, 115.09, 75.33.

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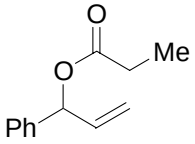
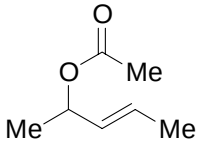
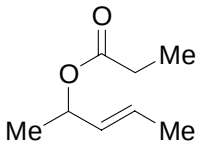
[79] Pak, C. S.; Lee, E.; Lee, G. H. *J. Org. Chem.* **1993**, *58*, 1523-1530.



Propionic acid 1-phenyl-allyl ester (91): The general procedure for methyl ketene acylation of a zinc alkoxide was followed. IR (thin film): 2959, 2353, 1740, 1275, 1187, 1082, 749, 700 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 7.39-7.31 (m, 5 H), 6.29 (dt, J = 7.2, 1.3 Hz, 1 H), 6.02 (ddd, J = 5.9, 4.9, 0.8 Hz, 1 H), 5.33 (*Z*, t, J = 1.4 Hz, 1 H), 5.23 (*E*, t, J = 1.3 Hz, 1 H), 2.41 (dq, J = 6.1, 1.3 Hz, 2 H), 1.17 (t, J = 7.6 Hz, 3 H); ^{13}C-NMR ($CDCl_3$): δ 173.40, 138.99, 136.36, 128.52, 128.09, 127.06, 116.80, 75.95, 27.80, 9.05. MS (EI, 70eV): *m/z* 190 (M^+), 163 (M^+–CH=CH_2), 134 (M^+– CH=CH_2, CH_2CH_3), 117 (M^+–$CO_2CH_2CH_3$). HRMS *m/z* calcd for $C_{12}H_{14}O_2$: 190.0994; found 190.0992.



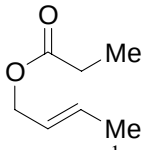
Acetic acid 1-methyl-but-2-enyl ester (94a):[80] The general procedure for methyl ketene acylation of a zinc alkoxide was followed employing ketene instead of methyl ketene. ^{1}H-NMR ($CDCl_3$): δ 5.71 (dq, J = 15.2, 6.5 Hz, 1 H), 5.46 (ddq, J = 9.8, 6.8, 1.5 Hz, 1 H), 5.29 (quintet, J = 6.5 Hz, 1 H), 2.02 (s, 3 H), 1.68 (dd, J = 5.8, 0.6 Hz, 3 H), 0.88 (t, J = 6.9 Hz, 3 H); ^{13}C-NMR ($CDCl_3$): δ 170.34, 130.71, 128.12, 71.12, 31.56, 22.62, 21.37, 20.24, 17.62, 14.07.



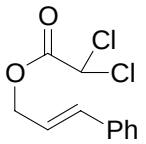
Propionic acid 1-methyl-but-2-enyl ester (94b):[45] The general procedure for methyl ketene acylation of a zinc alkoxide was followed employing ketene instead of methyl ketene. IR (thin film): 2975, 2932, 1874, 1762, 1736, 1673, 1449, 1371, 1241, 1221, 1074, 1041, 967, 940, 892 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 5.70 (ddq, J = 15.3, 6.5, 0.8 Hz, 1 H), 5.46 (ddq, J = 8.5, 6.8, 1.6 Hz, 1 H), 5.30 (quintet, J = 6.6 Hz, 1 H), 2.29 (q, J = 7.6 Hz, 2 H), 1.67 (dt, J = 7.2, 0.7 Hz, 3 H), 1.26 (d, J = 6.4 Hz, 3 H), 1.11 (t, J = 7.5 Hz, 3 H); ^{13}C-NMR

[80] von Matt, P.; Loiseleur, O.; Koch, G.; Pfaltz, A. *Tetrahedron: Asymmetry* **1994**, *5*, 573-584.

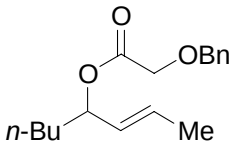
($CDCl_3$): δ 173.72, 130.80, 127.93, 70.84, 27.84, 20.25, 17.61, 9.03. MS (EI, 70eV): *m/z* 127 (M^+–CH_3), 113 (M^+–CH_2CH_3), 85 (M^+–$CO_2CH_2CH_3$) 69 (M^+–$HCO_2CH_2CH_3$, CH_3).



Propionic acid but-2-enyl ester (98):[53b] The general procedure for methyl ketene acylation of a zinc alkoxide was followed employing ketene instead of methyl ketene. ^{1}H-NMR ($CDCl_3$): δ 5.79-5.70 (m, 1 H), 5.60-5.51 (m, 1 H), 4.47 (d, J = 5.6, 0.8 Hz, 2 H), 2.30 (q, J = 7.6 Hz, 2 H); 1.69 (d, J = 6.4 Hz, 3 H), 1.10 (t, J = 7.6 Hz, 3 H); ^{13}C-NMR ($CDCl_3$): δ 174.11, 131.06, 125.15, 64.93, 31.48, 27.45, 22.54, 17.62, 13.96, 8.96.



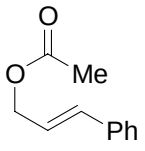
Dichloro-acetic acid 3-phenyl-allyl ester (104a): The general procedure for methyl ketene acylation of a zinc alkoxide was followed employing ketene instead of methyl ketene. IR (thin film): 3027, 2959, 2873, 1761, 1495, 1449, 1380, 1302, 1274, 1164, 964, 815, 746, 692 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 7.44-7.27 (m, 5 H), 6.76 (d, J = 15.8 Hz, 1 H), 6.31 (dt, 15.8, 6.6 Hz, 1 H), 5.99 (d, J = 0.4 Hz, 1 H), 4.93 (dd, J = 6.6, 1.2 Hz, 2 H); ^{13}C-NMR ($CDCl_3$): δ 164.32, 136.03, 135.67, 128.65, 128.47, 126.75, 121.03, 67.96, 64.23. MS (EI, 70eV): *m/z* 244 (M^+), 133 (M^+–$C(O)CHCl_2$), 117 (M^+–CO_2CHCl_2). HRMS *m/z* calcd for $C_{11}H_{10}O_2Cl_2$: 244.0058; found 244.0052.



Benzyloxy-acetic acid 1-butyl-but-2-enyl ester:[81] The general procedure for methyl ketene acylation of a zinc alkoxide was followed employing ketene instead of methyl ketene. ^{1}H-NMR ($CDCl_3$): δ 7.40-7.31 (m, 5 H), 5.76 (dt, J = 8.1, 0.4 Hz, 1 H), 5.45 (dq, J = 7.7, 1.6 Hz, 1 H), 5.30 (q, J = 7.1 Hz, 1 H), 4.64 (s, 2 H), 4.08 (s, 1 H),

[81] Uchiyama, H.; Kawano, M.; Katsuki, T.; Yamaguchi, M. *Chem. Lett.* **1987**, *2*, 351-354.

1.70 (dd, J = 5.0, 1.5 Hz, 3 H), 1.65-1.51 (m, 2 H), 1.36-1.23 (m, 4 H), 0.90 (t, J = 7.0 Hz, 3 H); ^{13}C-NMR ($CDCl_3$): δ 169.76, 137.17, 129.85, 129.24, 128.44, 128.06, 127.94, 75.79, 73.25, 67.33, 34.12, 27.30, 22.40, 17.73, 13.95.



Synthesis of acetic acid 3-phenyl-allyl ester (96) to assess the durability of the zinc alkoxide with triethylamine hydrobromide:[82] To a round-bottom flask was added 0.134 g (1.00 mmol) of *trans*-cinnamyl alcohol (**95**) and 10 mL of anhydrous pentane. At room temperature, 1.0 mL (1.00 mmol) of a 1 M solution of diethylzinc in hexanes was added dropwise. The reaction was stirred for 2 h. at ambient temperature, a solution of prefabricated triethylamine hydrobromide, 0.548 g (4.00 mmol), in 1.0 mL anhydrous methylene chloride was added to the reaction mixture. The solution was stirred for 1 h, 0.07 mL (1.00 mmol) of acetyl chloride was added to the reaction mixture and the reaction was stirred over night at ambient temperature. The reaction was quenched with 25 mL of a saturated solution of ammonium chloride, the organic layer was separated. Three extractions with diethyl ether (20 mL) were performed on the aqueous layer and all organics were combined and dried with magnesium sulfate. The crude reaction mixture was concentrated under reduced pressure to yield quantitative conversion of the crude acetic acid 3-phenyl-allyl ester (**96**). ^{1}H-NMR ($CDCl_3$): δ 7.42-7.25 (m, 5 H), 6.67 (d, J = 15.8 Hz, 1 H), 6.28 (dd, J = 6.5, 2.3 Hz, 1 H), 4.74 (dd, J = 6.4, 1.3 Hz, 2 H), 2.09 (s, 3 H); ^{13}C-NMR ($CDCl_3$): δ 170.72, 136.09, 134.09, 128.50, 127.97, 126.51, 123.06, 64.97, 20.88.

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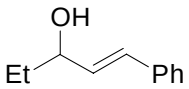
[82] Chen, C.-T.; Kuo, J.-H.; Pawar, V. D.; Munot, Y. S.; Weng, S.-S.; Ku, C.-H.; Liu, C.-Y. *J. Org. Chem.* **2005**, *70*, 1188-1197.

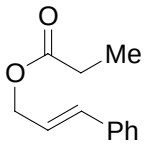
General procedure for ketene-Claisen reactions performed in BTF: To a round-bottom flask was added 1.00 mmol 1-phenyl-pent-1-en-3-ol (**99**) and 3.0 mL of anhydrous BTF. At room temperature, 1.0 mL (1.0 mmol) of a 1 M solution of diethyl zinc in hexanes was added dropwise. The reaction was stirred at ambient temperature for 30 min. and the reaction was cooled to –25 °C (using a Cryocool). A preformed solution of methyl ketene (1.5 mol in 2.0 mL of BTF) was added *via* cannula to the reaction mixture at –25 °C. Additives such as tetrahydrofuran or acetic acid were then added as indicated. The reaction was stirred for 1.5 h and the reaction was allowed to warm to ambient temperature. The reaction was then heated to the indicated temperature and was stirred at that temperature overnight. The reaction mixture was quenched with 20 mL of a saturated solution of NH_4Cl. The organic layer was separated and three subsequent extractions of the aqueous layer were performed with diethyl ether (15 mL). The organic layers were combined, dried with magnesium sulfate, and the crude solution was concentrated under reduced pressure to provide crude propionic acid 1-ethyl-3-phenyl-allyl ester (**85**).



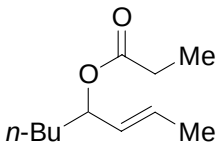
Synthesis of 1-phenyl-pent-1-en-3-ol (68):[83] To a round bottom flask was added 10 mL of anhydrous THF and 0.132 g (1.00 mmol) of *trans*-cinnamaldehyde (**49a**). The solution was cooled to –78 °C and 0.377 mL (1.20 mmol) of ethyl magnesium bromide was added dropwise as a 3.18 M solution in diethyl ether. The reaction was stirred for 1 h at –78 °C and was warmed to ambient temperature and was stirred overnight. The reaction was quenched with 25 mL of a saturated solution of NH_4Cl and was extracted with diethyl ether (3 X 15 mL). The organic layers were combined, dried, and concentrated under

[83] Lutz, C.; Knochel, P. *J. Org. Chem.* **1997**, *62*, 7895-7898.

reduced pressure. Purification on silica gel using 10% EtOAc in hexanes afforded 0.145 g (90%) of 1-phenyl-pent-1-en-3-ol (**68**). ^{1}H-NMR ($CDCl_3$): δ 7.41-7.21 (m, 5 H), 6.58 (d, J = 16.0 Hz, 1 H), 6.22 (dd, J = 9.2, 6.7 Hz, 1 H), 4.23 (dq, J = 6.5, 0.93 Hz, 2 H), 1.72-1.59 (m, 1 H), 0.98 (t, J = 7.5 Hz, 3 H); ^{13}C-NMR ($CDCl_3$): δ 136.70, 132.26, 130.24, 128.47, 127.49, 126.35, 74.25, 30.13, 9.68.



Propionic acid 3-phenyl-allyl ester (72):[84] The general procedure for methyl ketene acylation of a zinc alkoxide was followed employing ketene instead of methyl ketene. ^{1}H-NMR ($CDCl_3$): δ 7.35-7.18 (m, 5 H), 6.60 (d, J = 15.9 Hz, 1 H), 6.25 (dt, J = 15.9, 6.4 Hz, 1 H), 4.69 (dd, J = 6.4, 1.3 Hz, 2 H), 2.33 (q, J = 7.6 Hz, 2 H), 1.12 (t, J = 7.6 Hz, t); ^{13}C-NMR ($CDCl_3$): δ 174.25, 136.21, 134.05, 128.56, 128.01, 126.57, 123.30, 64.91, 27.57, 9.09.

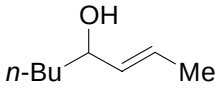


Propionic acid 1-butyl-but-2-enyl ester (103): The general procedure for methyl ketene acylation of a zinc alkoxide was followed employing ketene instead of methyl ketene. IR (thin film): 2959, 2938, 2874, 2862, 1737, 1463, 1363, 1274, 1187, 1081, 965 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 5.71 (td, J = 7.9, 0.8 Hz, 1 H), 5.42 (dq, J = 7.4, 1.6 Hz, 1 H), 5.19 (q, J = 6.8 Hz, 1 H), 2.31 (q, J = 7.6 Hz, 2 H), 1.69 (ddd, J = 4.3, 1.0, 0.6 Hz, 3 H), 1.62-1.53 (m, 2 H), 1.35-1.22 (m, 4 H), 1.13 (t, J = 7.6 Hz, 3 H), 0.88 (t, J = 5.3 Hz, 3 H); ^{13}C-NMR ($CDCl_3$): δ 183.83, 129.85, 128.81, 74.73, 34.22, 27.91, 27.33, 22.43, 17.69, 13.93, 9.13. MS (EI, 70eV): *m/z* 184 (M^+), 155 (M^+–CH_2CH_3), 127 (M^+–$C(O)CH_2CH_2$), 127

[84] Daub, G. W.; McCoy, M. A.; Sanchez, M. G.; Carter, J. S. *J. Org. Chem.* **1983**, *48*, 3876-3883.

(M^+–$CH_2CH_2CH_2CH_3$), 110 (M^+–$CO_2CH_2CH_2$), 71 (M^+–$HCO_2CH_2CH_2$, $CH_2CH_2CH_2CH_3$). HRMS *m/z* calcd for $C_{11}H_{20}O_2$: 184.1463; found 184.1463.

Proposed decomposition of propionic acid 1-butyl-but-2-enyl ester (103): A round bottom flask was charged with 1.00 mmol of propionic acid 1-butyl-but-2-enyl ester (**103**) and 10 mL of anhydrous THF. At –78 °C, 1.2 mmol of a freshly prepared solution of LDA in 2.0 mL of THF was added dropwise. The solution was stirred for 30 min. and 1.6 mL (1.6 mmol) of zinc chloride was added dropwise as a 1.0 M in solution dichloromethane. The solution was stirred at –78 °C for 2 h and was then warmed to ambient temperature. The reaction was quenched with 20 mL of a saturated solution of ammonium chloride. The organic layer was separated and was extracted with diethyl ether (3 X 15 mL). The organic layers were combined, dried with magnesium sulfate, and the crude product mixture was concentrated under reduced pressure to produce either propionic acid 1-butyl-but-2-enyl ester (**103**).



Synthesis of Oct-2-en-4-ol (101): A round bottom flask was charged with 5.00 mL (60 mmol) of crotonaldehyde and 20 mL of anhydrous THF. The reaction was cooled to –50 °C and 45.0 mL (72.00 mmol) of *n*-butyl lithium was added dropwise as a 1.6 M solution in hexanes. The reaction was stirred at –50 °C for 2 h and was then warmed up to ambient temperature and was stirred overnight. The reaction was quenched with 25 mL of a saturated solution of NH_4Cl and was extracted with diethyl ether (3 X 15 mL). The organic layers were combined, dried, and concentrated. The crude product was purified on silica gel utilizing 10% EtOAc in hexanes to give 6.07 g (79%) of oct-2-en-4-ol (**101**). IR (thin film): 3356, 2958, 2931, 2859, 2359, 2340, 1455, 1378, 964 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 5.89 (*E*, dq, J =

6.4, 0.8 Hz, 1 H), 5.64 (*Z*, dq, J = 6.4, 0.7), 5.50 (*Z*, ddd, J = 5.6, 1.4, 1.3 Hz, 1 H), 5.46 (*E*, ddd, J = 7.1, 1.5, 1.3 Hz, 1 H), 4.03 (q, J = 6.6 Hz, 1 H), 1.70 (dt, 7.0, 0.9 Hz, 3 H), 1.62-1.46 (m, 2 H), 1.37-1.24 (m, 4 H), 0.91 (t, J = 9.6 Hz, 3 H); ^{13}C-NMR ($CDCl_3$): δ 134.38, 126.72, 73.18, 36.99, 27.65, 22.63, 17.66, 14.04. MS (EI, 70eV): *m/z* 127 (M^+–H), 110 (M^+–OH), 71 (M^+–$CH_2CH_2CH_2CH_3$). HRMS *m/z* calcd for $C_8H_{15}O$: 127.1123; found 127.1127.

General procedure to generate a zinc enolate directly from the allyl ester: To a round bottom flask was added 0.189 g (1.00 mmol) of propionic acid 3-phenyl-allyl ester (**105c**) in 10 mL of anhydrous toluene. The reaction was cooled to –78 °C and 1.5 mmol of freshly prepared LDA was added dropwise (if required, DMPU was added after stirring the lithium enolate for 1 h at –78 °C).[85] The reaction was stirred for 1 h at –78 °C and 2.0 mL (2.00 mmol) of a 1 M solution of zinc chloride in methylene chloride was added dropwise. The reaction was stirred for 1 h at –78 °C and the system was warmed to ambient temperature and the indicated additives was introduced. The reaction was refluxed overnight at 100 °C. The reaction was diluted with 20 mL of diethyl ether and the organic layers were separated and washed with 3 X 10 mL of 2 M NaOH. The basic aqueous layers were combined, cooled to 0 °C, and acidified with 6 M HCl to a pH 2. The combined organic layers were extracted with diethyl ether (4 X 15 mL) and the were dried with magnesium sulfate. The crude reaction mixture was concentrated under reduced pressure to provide the starting propionic acid 3-phenyl-allyl ester (**105c**).

[85] LDA was prepared from 0.94 mL (1.5 mmol) of a 1.6 M solution of *n*-BuLi in hexanes and 0.20 mL (1.5 mmol) of diisopropylamine in 1.0 mL of anhydrous THF.

APPENDIX

ABBREVIATIONS

Full terminology	Abbreviation
acyl halide-aldehyde cyclocondensation	AAC
(2*S*,3*3*,8*S*,9*S*,4*E*,6*E*)-3-amino-9-methoxy-2,6-8-trimethyl-10-phenyldeca-4,6-dienoic acid	Adda
benzotrifluoride	BTF
carbon-13 nuclear magnetic resonance	^{13}C-NMR
catalyst	cat.
chirality	*
diastereomeric excess	de
diastereomeric ratio	dr
diisopropylethylamine (Hunig's Base)	DIPEA
enantiomeric excess	ee
equivalent	equiv.
gas chromatography	GC
heat	Δ
high-pressure liquid chromatography	HPLC
high-resolution mass spectrum	HRMS
hour(s)	h
hydroquinidine 1,4-phthalazinediyl diether	$(DHQD)_2PHAL$
isomerization-Claisen rearrangement	ICR

Lewis acid	LA
Lewis base	LB
ligand	L_N
medium-pressure liquid chromatography	MPLC
methylquinidine	MeQD
methylquinine	MeQN
minute(s)	min.
mass spectrum	MS
molarity	M
overnight	ON
normal-pentyl	*n*-Pn
proton nuclear magnetic resonance	^{1}H-NMR
quinidine	QD
quinine	QN
room temperature	rt
tetrabutylammonium fluoride	TBAF
N,*N*,*N*'*N*'-tetramethylguanidinium azide	TMGA
thin-layer chromatography	TLC
transition state	TS
trialkylamine	NR_3
trimethylsilylquinidine	TMSQD
trimethylsilylquinine	TMSQN

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