Rearrangement and Cascade Reactions: New Synthetic Methods and the Total Synthesis of Diazonamide A

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Rearrangement and Cascade Reactions: New Synthetic Methods and the Total Synthesis of Diazonamide A

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This dissertation describes the development of several cascade reactions and their application to the synthesis of structurally and/or biologically relevant molecules. We successfully developed a three-step, one-pot carboalumination-Claisen rearrangement-addition reaction, which provides complex allylic alcohols from simple starting materials. While attempting to extend this methodology to nitrogen-containing substrates, a tandem hydrozirconation-iminium ion addition reaction was developed that allows simple access to functionalized isoindolinones. An oxidative rearrangement of enol ethers to spiroketals was developed, contributing an unusual approach to these highly sought after functionalities. Finally, an approach to the complex natural product diazonamide A was investigated with the intention of applying the Chan rearrangement. Eventually, the complexities of total synthesis forbid the use of the Chan rearrangement, and an alternative pathway was developed that led to the application of a cascade acyl chloride-oxazoline ring scission to install critical components of diazonamide.

Acknowledgments

A Ph.D. is greater than the sum of its parts, and certainly greater than what appears within this document. It is an experience, and comprises the fullest meaning of "the journey is its own reward". I gratefully acknowledge Professor George Majetich of the University of Georgia for starting me down this road and introducing me to the beautiful world of molecules.

Graduate school has been an outstanding experience, and I thank Prof. Peter Wipf for continually raising the bar, providing endless knowledge and for allowing me to be a part of the diazonamide story. I also would like to thank Professors Nelson, Floreancig, Lazo, Brummond and Wilcox for serving on committees at various points. I would like to thank the numerous co-workers with whom I have interacted with in fruitful ways over the years. We have learned much about life and science, and I hope that you learned something from me. Additionally, I would like to thank Bayer, Roche, Merck, NIH and NSF (and hence the U. S. taxpayer) for funding over the years.

Finally, I would like to express my love and admiration for my parents, two amazing people who let me become whatever I wanted to be, and supported me every step of the way. My brother and grandmothers have also been unbelievably supportive over the years, and kept me close to home despite the distance. As I head to Harvard with my beloved siamese cat Bailey, I look forward to more wonderful experiences and people like those here in Pittsburgh.

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ABBREVIATIONS

Ac	acetyl
AlR_3	trialkylaluminum
Boc	*tert*-butyloxycarbonyl
Bn	benzyl
Cbz	benzyloxycarbonyl
dba	dibenzylidineacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
d,*l*-CSA	*d*,*l*-camphorsulfonic acid
DIAD	diisopropylazodicarboxylate
DIPEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
dppb	diphenylphosphinobutane
dr	diastereomeric ratio
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
ee	enantiomeric excess
IBCF	isobutyl chloroformate
KHMDS	potassium hexamethyldisilazide

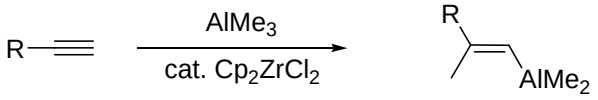
LHMDS	lithium hexamethyldisilazide
m-CPBA	*meta*-chloroperoxybenzoic acid
Mes	mesityl
Ms	methanesulfonyl
NMM	*N*-methyl morpholine
Tf	trifluoromethanesulfonyl
Piv	pivaloyl
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TIPS	triisopropylsilyl
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl

1. WATER ACCELERATED CASCADE REACTIONS

1.1 INTRODUCTION

1.1.1 Carboalumination of Alkynes

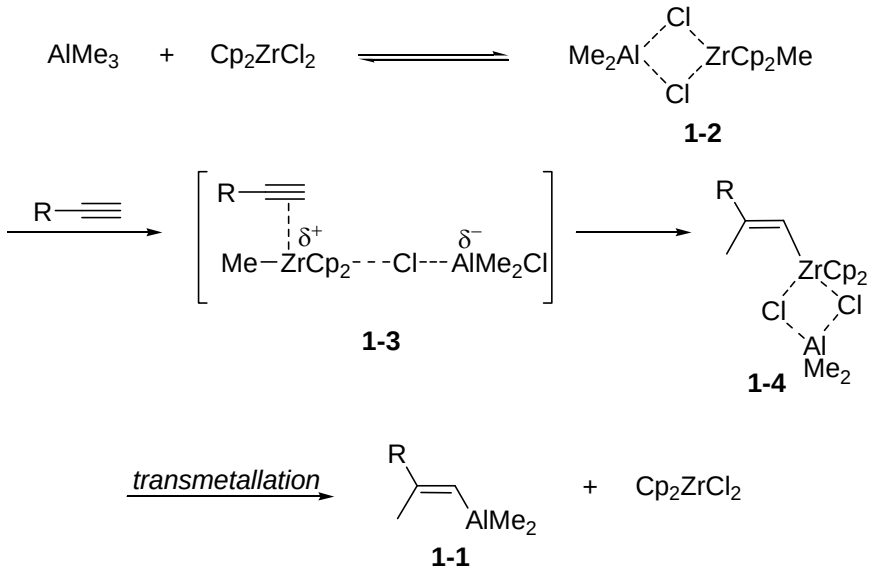
Some of the earliest accounts of the carbometallation of alkynes appeared around 1970 and included metals such as Mg,[1] Rh,[2] and Cu.[3] An preliminary report detailing carboalumination appeared in 1960,[4] demonstrating the reaction of acetylene with triethylaluminum at 60 °C. Of all of these carbometallations, the method which proved most general was carbocupration,[5] until the catalytic carboalumination was published. The zirconium-catalyzed carboalumination of alkynes (Scheme 1-1) was discovered by Negishi and co-workers in 1978.[6]



1-1

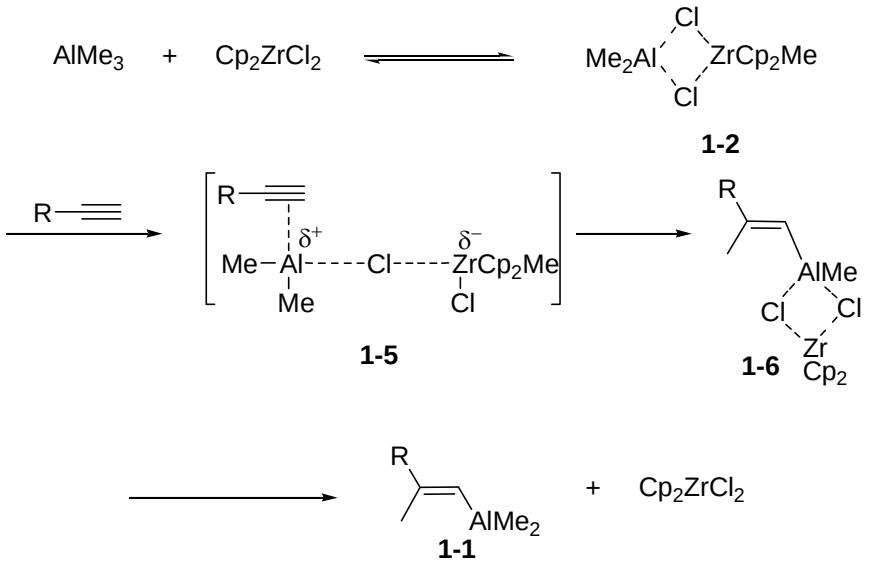
Scheme 1-1. Zirconium-catalyzed carboalumination.

The carboalumination of alkynes is one of the most versatile methods for the preparation of olefins with defined geometry. Terminal alkynes give excellent regioselectivity, often greater than 95:5 in favor of terminal metallation. Internal symmetrical alkynes also give excellent stereoselectivity.[7] The mechanism of carbometallation was initially thought to involve carbozirconation by $MeZrCp_2Cl$, followed by transmetallation to Al (Scheme 1-2).[8]



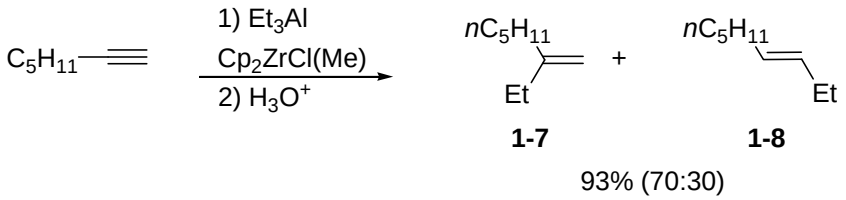
Scheme 1-2. Initially proposed mechanism of zirconium-catalyzed carboalumination.

Subsequent mechanistic investigations weakened support for the carbozirconation/transmetallation mechanism. A mixture of Me_2AlCl-Cp_2ZrCl_2 was also found to be a good methylating agent, although no Cl-Me exchange could be observed by NMR. The formation of $MeCp_2ZrCl$ would be necessary for the mechanism in Scheme 1-2 to be valid. NMR data clearly indicated the reversible Cl-Me exchange between Zr and Al in mixtures of $AlMe_3$-Cp_2ZrCl_2. These data led to a revision of the proposed mechanism of carboalumination to a Zr-assisted direct Al-C bond addition to the alkyne (Scheme 1-3).



Scheme 1-3. Revised and generally accepted mechanism of carboalumination.

Furthermore, when a 1:1 mixture of $AlEt_3$ and $Cl(Me)ZrCp_2$ was treated with 1-heptyne, only **1-7** and **1-8** were isolated in a combined 93% yield, with only trace amounts of the product derived from methylalumination formed (Scheme 1-4).

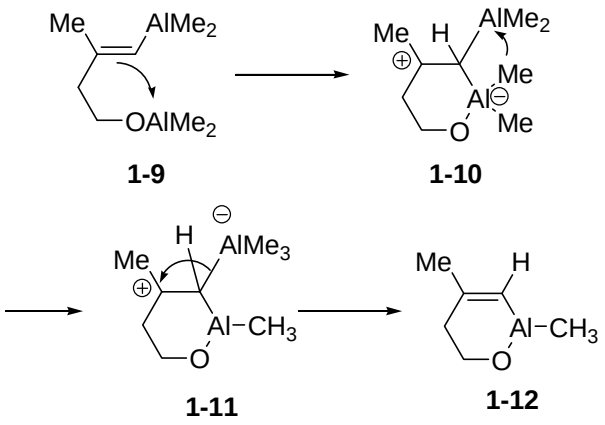


Scheme 1-4. Attempted crossover experiment demonstrating that $Cp_2ZrCl(Me)$ is not the active methylating agent in zirconium-catalyzed carboalumination.

A solvent effect is also observed in the zirconium-catalyzed carboalumination of alkynes. The relative rate of the reaction decreases on going from 1,2-dichloroethane to chlorobenzene to benzene, following the general trend of the dielectric constants of the solvents ($\varepsilon = 10.4$, 5.6, and 2.3,

respectively). This observation is in agreement with the existence of the highly polarized intermediate **1-5**.

A complementary method that furnishes the products of a net *anti*-carbometallation has been reported recently.[9] Homopropargyl alcohols as well as their one carbon homologues undergo standard zirconium-catalyzed carboalumination, but when heated, the products of an *anti*-carbometallation were isolated. Negishi has proposed a thermal isomerization through bis-alane intermediate **1-10**. Methyl transfer to aluminum and reformation of the olefin generates metallacycle **1-12**, the masked product of *anti*-carboalumination of the alkyne (Scheme 1-5). Good yields and excellent *anti/syn* selectivities are observed (>98:2). It is interesting that this isomerization is thermally induced. Without heating, only *syn*-carbometallation products are isolated.

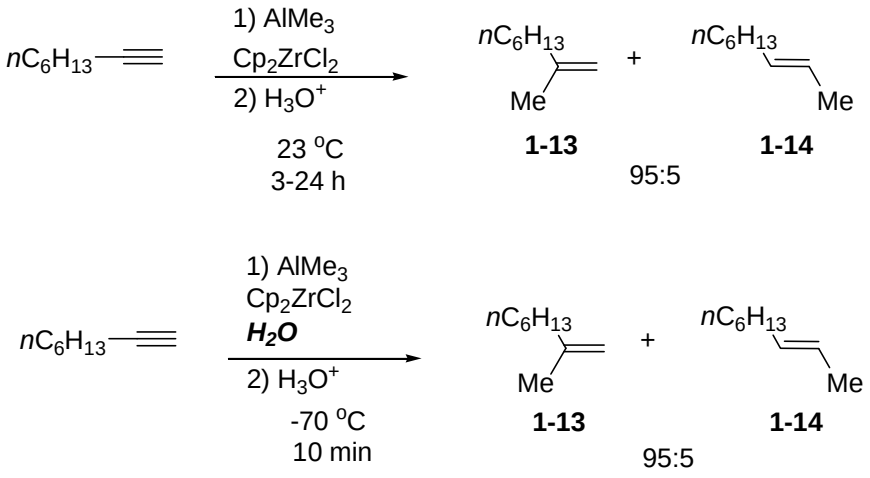


Scheme 1-5. Mechanism of thermal isomerization resulting in *anti*-carboalumination.

Vinyl alanes resulting from carboaluminations of alkynes can be transformed in a variety of ways, making them versatile intermediates. The Al of the resulting vinyl alane can be readily exchanged with H(D),[6] I,[10] Hg,[11] B,[12] Zr,[12] trapped with epoxides,[13] chloroformates,[13] and imines[14]

or coupled to vinyl[15] or aryl halides.[16] Carboalumination has found recent utility in the synthesis of the carotenoids[17] and the insect juvenile hormones I and II.[18]

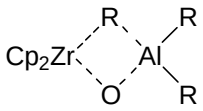
In 1993, Wipf and Lim reported dramatic rate enhancing effects of water on carboaluminations.[13] Standard Negishi carboalumination of 1-octyne proceeds in 3 hours at room temperature to yield a 95:5 mixture of regioisomers following aqueous acidic workup (Scheme 1-6). Addition of stoichiometric amounts of water allows for the same carboalumination to proceed at -70 °C within minutes. Yields and selectivities are identical to those reported by Negishi.[3]



Scheme 1-6. The Negishi carboalumination and the water-accelerated carboalumination discovered by Wipf and Lim.

The vinyl alane intermediates obtained from the water-accelerated carboalumination can be manipulated in the same fashion as standard carbometallation intermediates. The structure of the active carboaluminating reagent, however, remains elusive. The origin of the rapid rate acceleration also remains in doubt. Wipf proposed the oxo-bridged dimer **1-15** (Scheme 1-7) as the catalytically active species, although its existence at temperatures above 0 °C was questionable at the time of

publication. More recent results from the Wipf group[19,20] indicate that temperature is not a factor in the rate enhancement.



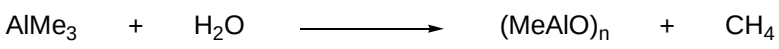
1-15

Scheme 1-7. Proposed oxo-bridged intermediate responsible for water related rate enhancement of carboalumination.

1.1.2 The Nature of Water/Alane Mixtures

The composition of mixtures of alkylalalanes and water is the subject of considerable research.[21] This effort is largely funded by the polymer industry because these mixtures are known to efficiently co-promote olefin polymerization in the presence of group 4 metallocenes.[22] Methylaluminoxane (MAO) is, by far, the most popular and effective polymerization co-catalyst. MAO has been known to promote the polymerization of monomers since the early 1960s.[23] MAO is generated by the controlled hydrolysis of $AlMe_3$, forming the Al-O-Al linkage with the extrusion of CH_4 gas. This relates it to the accelerated carboalumination conditions developed by Wipf and Lim. Although the structure and reactivity of MAO is highly dependent on the method of preparation,[24] MAO most likely approximates the nature of the mixtures formed when water-accelerated carboalumination conditions are generated in the laboratory. Despite its widespread use, little is known about its structure or physical properties. MAO is, however, known to be an equilibrating mixture of oligomers with an average molecular weight of 1100.[25] Substantial efforts have been made to acquire information about the structure of MAO and related systems with ^{27}Al NMR, mass

spectrometry, and computational methods.[26,27] These efforts have generated some concrete findings, but are plagued by inconsistencies associated with the handling of MAO. The reaction of water and alkyl alanes (Scheme 1-8) has been followed by NMR and reported to be dependant on temperature, with full consumption of the water protons occurring around 0 °C.[28]

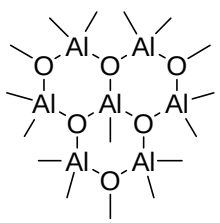


Scheme 1-8. The reaction of $AlMe_3$ with water.

It should be noted that these NMR experiments were performed in diethyl ether, and the reaction was followed by observing the proton resonances of the alkyl groups on aluminum. It is generally accepted that MAO is *always* contaminated with free $AlMe_3$ (if it is removed, the MAO oligomer will release more $AlMe_3$) and contains a constant Me/Al ratio of 1.5[29]. Multinuclear NMR investigations have shown that four-coordinate aluminum centers predominate in MAO, although some three-coordinate centers do exist.[30] All of the oxygen atoms in MAO are believed to be three-coordinate.[24] About 15-20% of the methyl groups of MAO are believed to be bridging between Al atoms in a rapidly exchanging fashion[31] and these methyl groups participate in reactions which activate metallocenes for catalytic olefin polymerization.

The Lewis acidity of the reagent has been proposed to be very similar to that of $AlMe_3$.[24,32] This acidity has been attributed to either free $AlMe_3$ or open sites on oligomeric aluminoxanes. The actual structures which most commonly are postulated for MAO are shown in Scheme 1-9. Cyclic 6-membered fused rings (**1-16**) of varying length and 4-membered rings[33] (**1-17**) were observed by X-ray diffraction. More recently, Sinn and co-workers[34] have proposed structures representing the *tetramer* of **1-18**, which is based on the *tert*-butyl monomer **1-19** which has been observed by X-ray

diffraction. Thus, the structure of MAO can be drawn as a collection of rapidly equilibrating oligomers which contain acidic sites that participate in chemical reactions.



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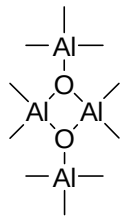

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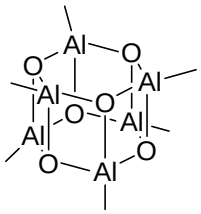

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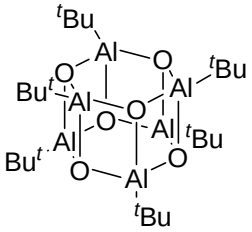
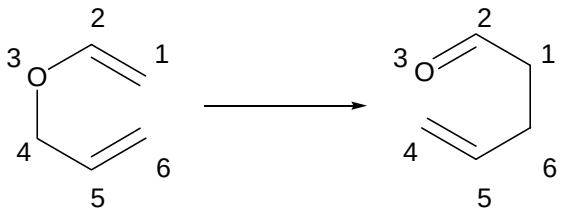


1-19

Scheme 1-9. Proposed structures of aluminoxanes.

1.1.3 The Claisen Rearrangement

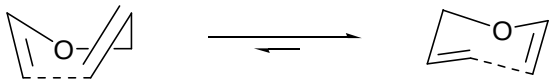
The Claisen rearrangement of allyl vinyl ethers (**1-20→1-21,** Scheme 1-10) was discovered in 1912.[35] Since this initial report, it has become one of the most utilized methods for introducing molecular complexity.[36]



1-20 **1-21**

Scheme 1-10. The Claisen rearrangement and the numbering of the allylic vinyl ether system.

The Claisen rearrangement is a concerted, non-synchronous[37] pericyclic reaction that shows a strong preference for a chair-like transition state. Calculations have estimated the stability of the chair transition state (**1-23**) over the boat transition state (**1-22**) of allyl vinyl ether to be 6.6 Kcal/mol (Scheme 1-11).[38] The preference for the chair-like transition state can, however, be overridden by conformational constraints.



1-22 **1-23**

Scheme 1-11. The possible boat (**1-22**) and chair (**1-23**) conformations of the Claisen rearrangement.

In most cases, the electronic structure of the transition state is thought to range from a number of limiting electronic distributions (**1-25**, **1-26**) which can be derived from the traditional aromatic transition state (**1-24**)(Scheme 1-12). However, the electronic structure of the transition state continues to be debated since it is highly dependant on substitution.[39]

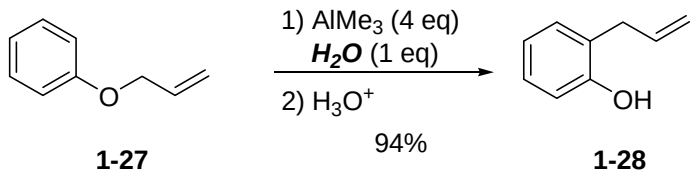
1-24 **1-25** **1-26**

Scheme 1-12. Proposed transition states of the Claisen rearrangement.

The Claisen rearrangement benefits thermodynamically from the scission of a C-O σ-bond and two C-C π-bonds and the formation of a new C-O π-bond, a new C-C σ-bond and a new C-C π-

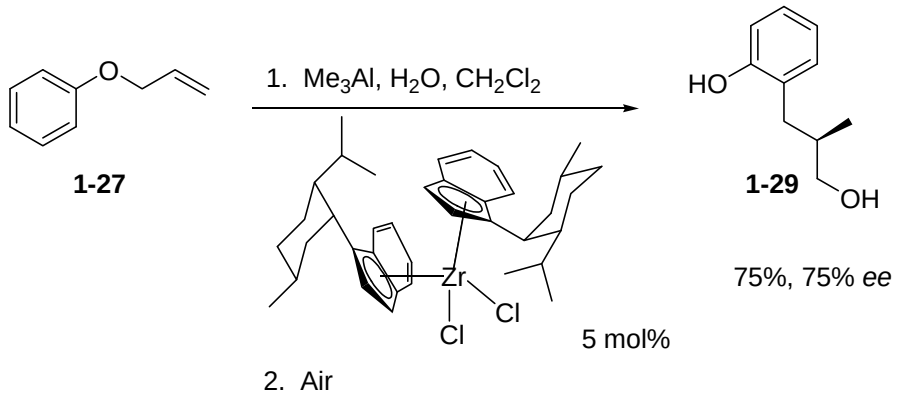
bond. This benefit of roughly 20 kcal/mol is derived mainly from the conversion of the C-C π-bond into a C-O π-bond.

The synthetic utility of the Claisen rearrangement has been well documented over the 105 years since its discovery. Advances have been made steadily over the years, including the study of the metal-promoted rearrangement. Protic as well as Lewis acids were found to effectively promote the Claisen rearrangement and other closely related [3,3] sigmatropic rearrangements. Aluminum has proven to be a most effective and widely used metal for the promotion of the Claisen rearrangement.[40] In a recent example, Wipf and co-workers reported an accelerated aromatic Claisen rearrangement using water-activated alanes (Scheme 1-13).[40(b)]



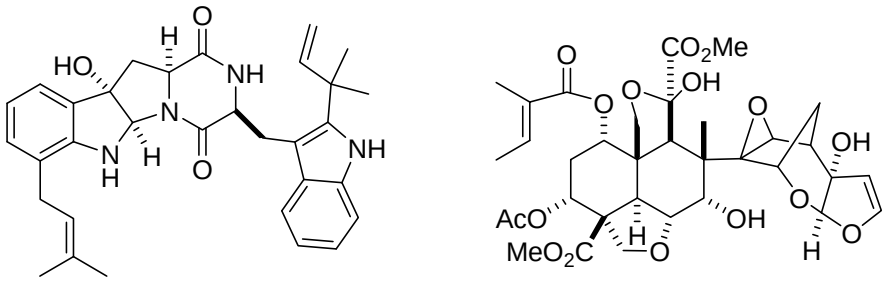
Scheme 1-13. The aromatic Claisen rearrangement promoted by water-activated alane.

Recently, transition metals have found increased use for the catalysis of the Claisen rearrangement, including highly diastereoselective and enantioselective variants.[41] A testament to the utility of the Claisen rearrangement and its variants is its continued use in tandem methodology and in the synthesis of complex natural products. For example, Wipf and co-workers reported a tandem aromatic Claisen rearrangement/catalytic asymmetric carboalumination (Scheme 1-14) utilizing water-activated alane and Erker's catalyst.[42]



Scheme 1-14. Tandem Claisen rearrangement/carboalumination in the presence of Erker's catalyst.

Ganesan and co-workers recently completed the total synthesis of okaramine J using an aza-Claisen rearrangement (Scheme 1-15).[43] An advanced intermediate in a total synthesis of the complex natural product azadirachtin was accessed using a microwave-assisted Claisen rearrangement.[44]

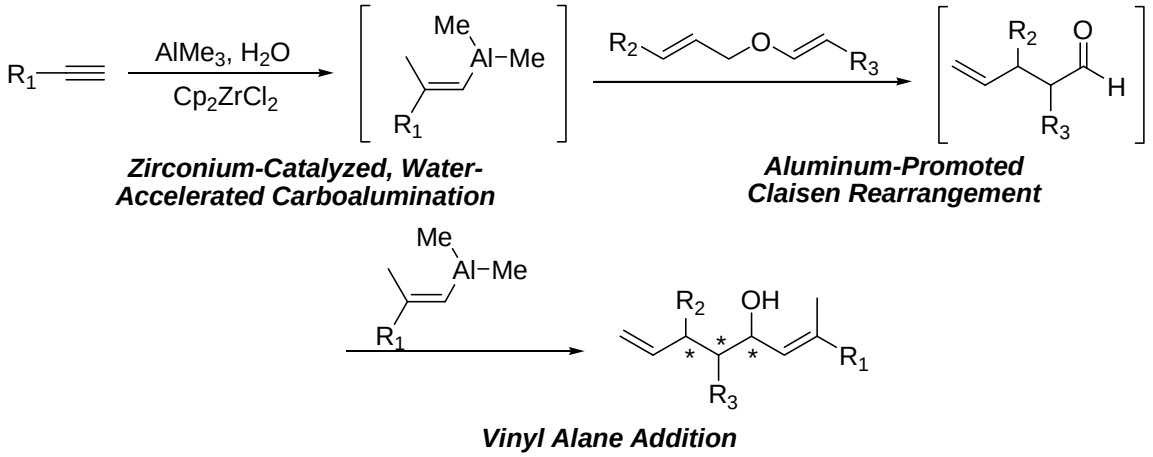


Scheme 1-15. Structures of okaramine J and azadirachtin.

1.2 RESULTS AND DISCUSSION

1.2.1 Proof-of-Concept Studies

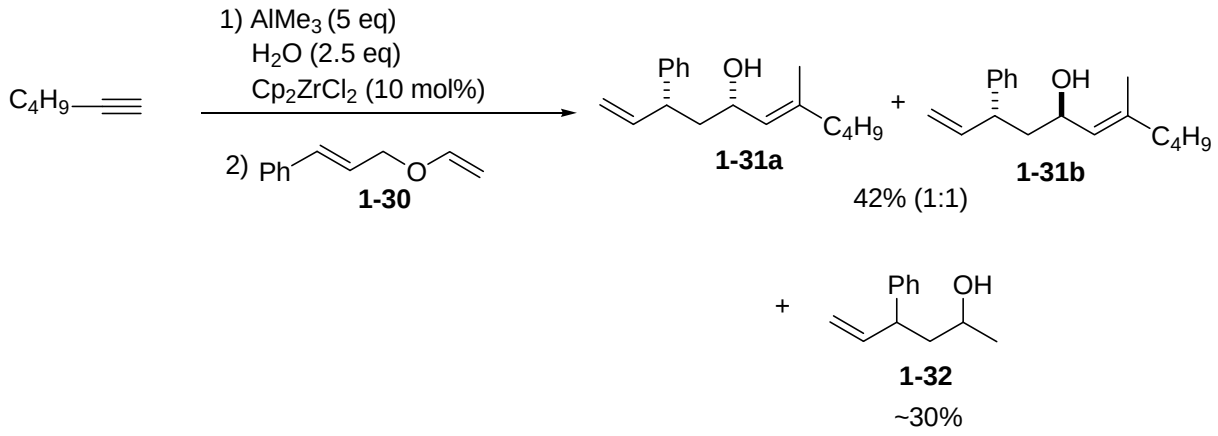
Based on results of the Wipf group on water-accelerated processes, a cascade involving a water-accelerated carboalumination and an *aliphatic* Claisen rearrangement was envisioned. Since the aliphatic Claisen rearrangement gives rise to an aldehyde, vinyl addition should follow rearrangement, thereby comprising a cascade reaction (Scheme 1-16). This proposed sequence will form three new C-C bonds by converting an achiral allyl vinyl ether into an allylic alcohol containing three contiguous stereocenters.



Scheme 1-16. Proposed three-step cascade reaction to form allylic alcohols.

The initial proof-of-concept reaction was performed with cinnamyl vinyl ether (**1-30**). Treatment of the carboalumination product of 1-hexyne with **1-30** in CH_2Cl_2 at -78 °C gave a 42% yield of **1-31a** and **1-31b** as a 1:1 mixture of diastereomers (Scheme 1-17). The desired product was

accompanied by substantial amounts of **1-32**, which was characterized by ^{1}H NMR and mass spectroscopy.

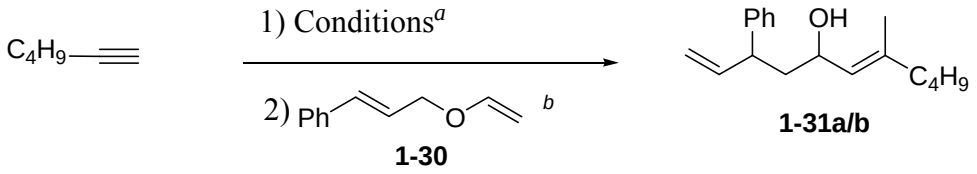


Scheme 1-17. Proof-of-concept experiment.

1.2.2 Optimization Studies

Optimization of the cascade reaction was performed with cinnamyl vinyl ether **(1-30**) and 1-hexyne. The initial goal was to increase the yield of **1-31** by suppressing the formation of **1-32**, derived from methyl addition to the aldehyde (Table 1-1). It was postulated that the large excess of $AlMe_3$ (5 eq) present in the reaction mixture was responsible for the methyl addition to the aldehyde. Reduction of the equivalents of both $AlMe_3$ and H_2O to 2.2 and 1.1, respectively (Entry 1), suppressed the undesired methyl addition to nearly undetectable levels. Further reduction to 2 equivalents of $AlMe_3$ and 1 equivalents H_2O (Entry 2) furnished the desired product in 60% yield with no evidence of the methyl transfer by-product; however some hydrolysis of the starting vinyl ether was indicated by TLC analysis.

Table 1-1. Cascade carboalumination/Claisen rearrangement optimization.



1-30 **1-31a/b**

Entry	$AlMe_3$ (eq)	H_2O (eq)	Solvent	Yield[c]
1	2.2	1.1	CH_2Cl_2	56
2	2.05	1.0	CH_2Cl_2	60
3	1.5	0.75	CH_2Cl_2	0
4	1.0	0.5	CH_2Cl_2	0
5	2.5	1.25	CH_2Cl_2	60
6	2.2	2.25	CH_2Cl_2	25
7	2.25	0.56	CH_2Cl_2	61
8	2	1	$ClCH_2CH_2Cl$	60
9	2.25	1.2	Toluene	48

[a] Carboalumination performed at 0 °C in the presence of 10 mol % Cp_2ZrCl_2. [b] **1-30** added at -78 °C and allowed to warm to ambient temperature. [c] dr = 1:1.

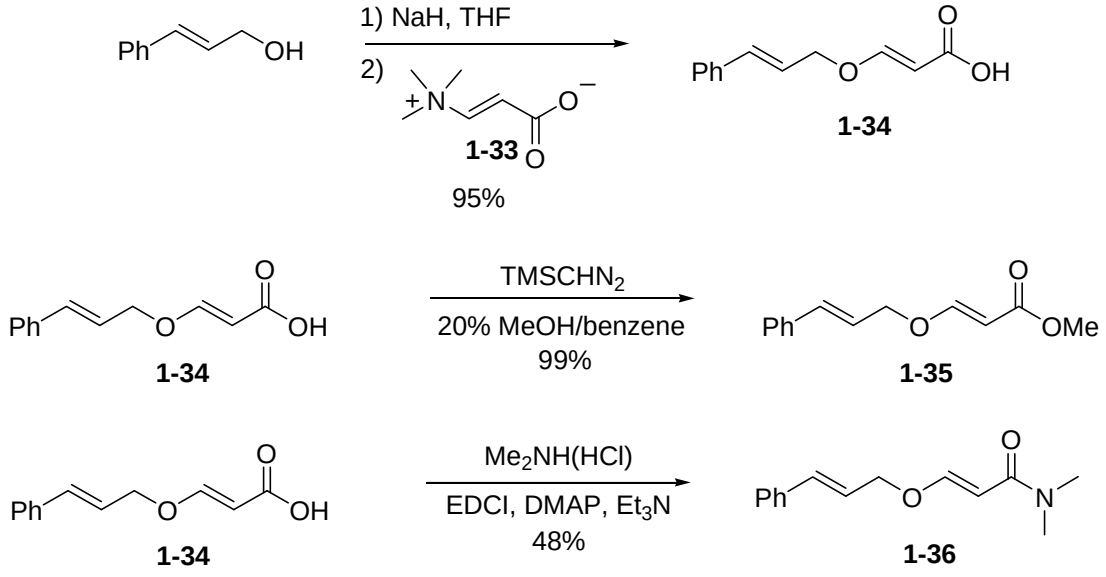
Reduction of the amount of $AlMe_3$ to levels below 2 equivalents resulted in no reaction or only a trace of conversion (Entries 3 and 4). Raising the amount of $AlMe_3$ to 2.5 equivalents and H_2O to 1.25 equivalents had little effect on the yield (Entry 5).

With the conditions optimized for vinyl ether **1-30**, the amount of water added to the reaction was further investigated. Equimolar amounts of $AlMe_3$ and H_2O gave a very slow reaction and lowered the yield substantially (Entry 6). Interestingly, good yields were obtained with substoichiometric amounts of H_2O (Entry 7); however, this was unique to simple unfunctionalized allyl vinyl ethers. The optimum stoichiometry was 2 equivalents of $AlMe_3$ and 1 equivalent of H_2O, with a yield of approximately 60%. No change in the rate of the reaction in CH_2Cl_2 was observed

with the exception of a large amount of water, which slowed the reaction. The reaction proved to be somewhat sensitive to solvent. Conducting the entire reaction in dichloroethane showed no benefit over dichloromethane (Entry 8). When toluene was used as a solvent, the rearrangement/addition step was very slow and gave a yield of only 50% (Entry 9). Therefore, dichloromethane was chosen as the solvent of choice for this transformation. To extend the method to a synthetically useful state, the scope of the cascade was examined and the results are discussed below.

1.2.3 Synthesis and Cascade Reaction of Carboxyl-Substituted Vinyl Ethers

The first group of substrates tested with the optimized conditions contained a carboxyl group. Acid **1-34** was prepared in 95% yield by treating the sodium salt of cinnamyl alcohol with betaine **1-33**, according to the method of Büchi (Scheme 1-18).[45]

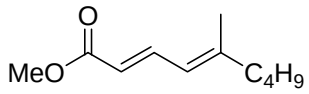
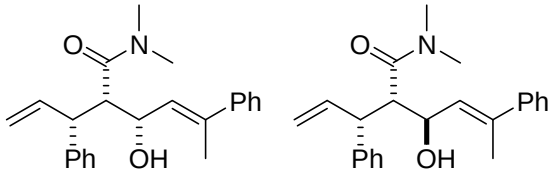


Scheme 1-18. Preparation of carboxyl group containing substrates.

Treatment of **1-34** with $TMSCHN_2$ in methanolic benzene[46] furnished methyl ester **1-35** in quantitative yield. Acid **1-34** was also coupled with dimethyl amine using standard coupling methods to give the corresponding dimethyl amide **1-36** in a modest 48% yield (Scheme 1-18).

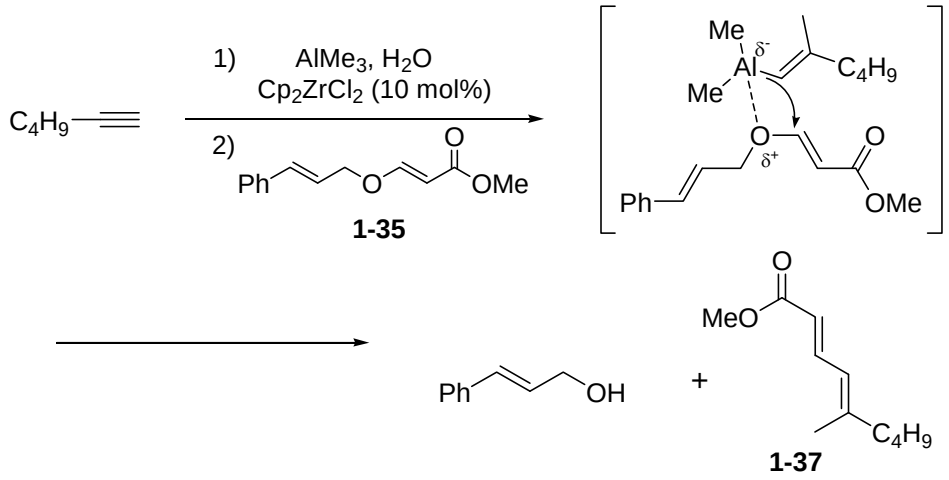
These substrates were submitted to the cascade reaction, with the results summarized in Table 1-2. Acid **1-34** was incompatible with the reaction conditions, resulting in immediate decomposition with no recovery of any starting material (Table 1-2, Entry 1).

Table 1-2. Summary of results of the cascade reaction with carboxyl group-containing substrates.

Entry	Substrate	Conditions	Products (major:minor)[a]	Yield (%) (dr)[b]
1	**1-34**	i	Decomposition	0
2	**1-35**	ii	 **1-37**	37
3	**1-36**	iii	 **1-38** **1-39**	10 (5:1)

Reaction Conditions: (i) 5 eq $AlMe_3$, 2.5 eq H_2O, 10 mol % Cp_2ZrCl_2, 2 eq hexyne (ii) 2.5 eq $AlMe_3$, 1.25 eq H_2O, 10 mol % Cp_2ZrCl_2, 2 eq hexyne (iii) 10 eq $AlMe_3$, 4 eq H_2O, 10 mol % Cp_2ZrCl_2, 2 eq hexyne. [a] Shown as major (left):minor (right). [b] Determined by integration of the ^1H NMR spectrum of the product mixture.

When ester **1-35** was submitted to the reaction, only dienoate **1-37** (37%) and cinnamyl alcohol (47%) were isolated (Table 1-2, Entry 2). Dienoate **1-37** is the result of vinyl alane addition into the α,β-unsaturated ester with subsequent elimination of cinnamyl alkoxide (Scheme 1-19). This result demonstrated the incompatibility of good Michael acceptors with the water-activated vinyl alanes.

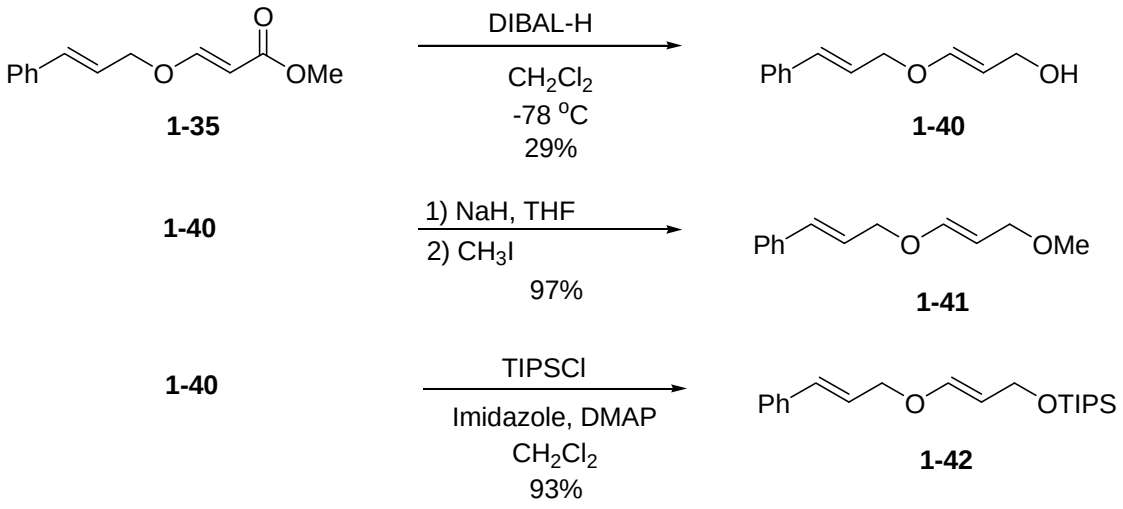


Scheme 1-19. Proposed fragmentation mechanism of ester **1-35** during the cascade reaction.

Amide **1-36** was submitted to the cascade reaction and required 10 and 4 equivalents of $AlMe_3$ and H_2O, respectively, for any reaction to occur. The reaction proceeded in very low yield (10%) but with a diastereoselectivity of 5:1 (Table 1-2, Entry 3). This lack of reactivity could be due to the highly aggregated $AlMe_3/H_2O$ mixtures that coordinate to the amide oxygen and thus block the reactive Lewis acidic sites of aluminum.

1.2.4 Synthesis and Cascade Reactions of Alkoxy Propenols

The next class of substrates tested were derived from allylic alcohols. Ester **1-35** was reduced with DIBAL-H to give a low yield of the desired allyl alcohol **1-40** (31%) and cinnamyl alcohol, resulting from 1,4-reduction and subsequent expulsion of alkoxide ion. A wide variety of reducing agents were screened but DIBAL-H proved to be the most effective (Scheme 1-20).

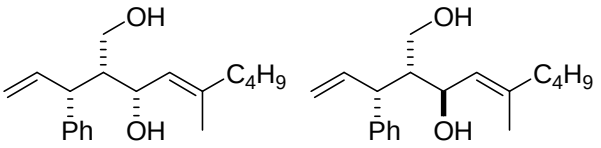
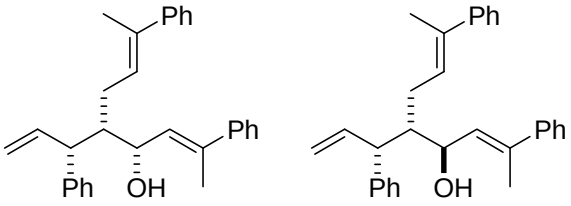
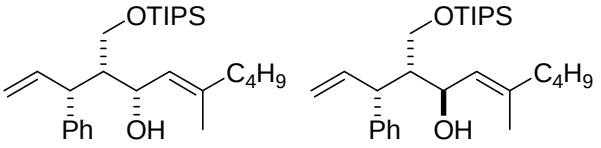


Scheme 1-20. Preparation of alkoxy propenol derivatives.

The allylic alcohol **1-40** was treated with NaH followed by CH_3I to provide methyl ether **1-41** in 97% yield. **1-40** was also silylated with TIPSCl in the presence of imidazole and DMAP to furnish silyl alcohol **1-42** in 93% yield (Scheme 1-20).

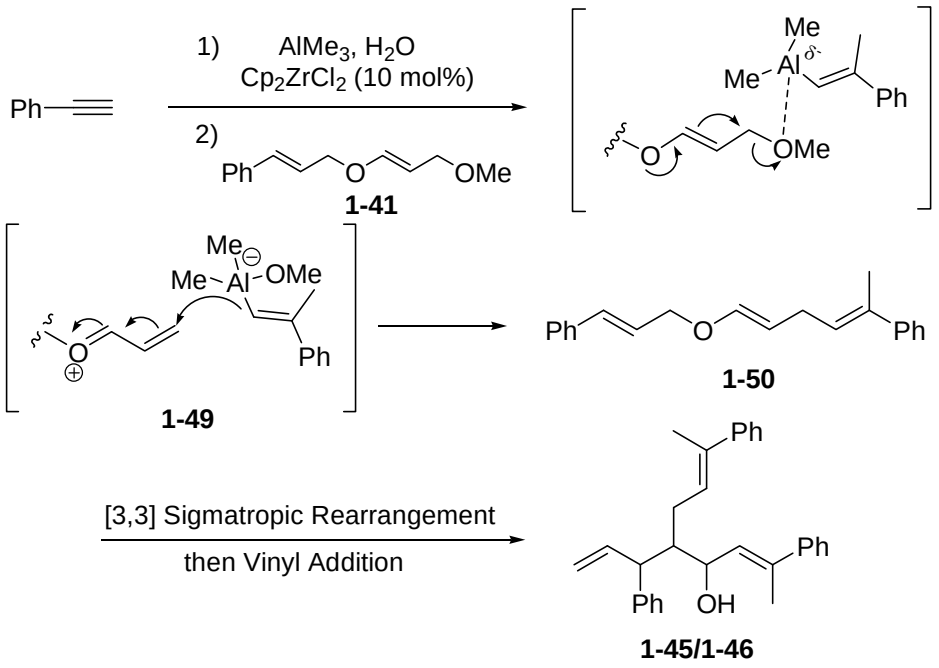
Allylic alcohol **1-40** was submitted to the standard cascade reaction conditions, i.e. 4 equivalents of $AlMe_3$ and 2 equivalents of H_2O. The reaction proceeded to completion within 10 min and led to rearrangement products **1-43** and **1-44** in 30% yield and 10:1 diastereoselectivity (Table 1-3, Entry 1). The configuration of the major diastereomer (**1-43**) was determined to be all *syn* by x-ray analysis of a derivative (*vide infra*). The low yield can be attributed to multiple background reactions taking place, as indicated by TLC and GC analysis. Two identifiable side-reactions were the hydrolysis of the starting vinyl ether and methyl addition to the intermediate aldehyde.

Table 1-3. Summary of results of cascade reactions of alkoxy propenol derivatives.

Entry	Substrate	Conditions	Products (major:minor)[a]	Yield (%) (dr)[b]
1	**1-40**	i	 **1-43** **1-44**	30 (10:1)
2	**1-41**	ii	 **1-45** **1-46**	12 (8:1)
3	**1-42**	iii	 **1-47** **1-48**	60 (10:1)

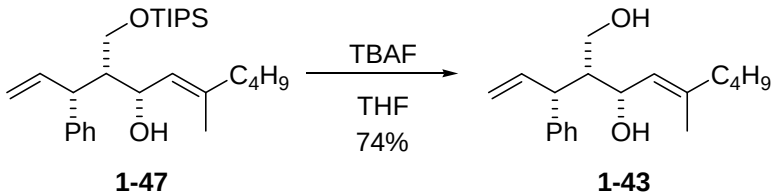
Reaction Conditions: (i) 4 eq $AlMe_3$, 2 eq H_2O, 10 mol % Cp_2ZrCl_2, 2 eq hexyne (ii) 2.1 eq $AlMe_3$, 1 eq H_2O, 10 mol % Cp_2ZrCl_2, 2 eq phenylacetylene (iii) 2.1 eq $AlMe_3$, 1 eq H_2O, 10 mol % Cp_2ZrCl_2, 2 eq hexyne. [a] Shown as major (left):minor (right). [b] Determined by integration of the ^1H NMR spectrum of the product mixture.

Methyl ether **1-41** failed to undergo the desired process, instead giving only decomposition products, and **1-45** and **1-46** were isolated in 12% combined yield (Table 1-3, Entry 2). These compounds are derived from the process shown in Scheme 1-21. Coordination and elimination of the methoxy group generated the oxocarbenium ion **1-49**. Readdition of the vinyl alane in a conjugate fashion into **1-49** generated intermediate **1-50** which underwent the cascade Claisen rearrangement-vinyl alane addition.



Scheme 1-21. Fragmentation pathway leading to **1-45/1-46.**

Although an interesting process, cleavage of this type renders ether moieties with sterically accessible oxygen atoms incompatible with the Lewis acidic water-activated alane. The bulky TIPS ether **1-42** did not suffer from this problem. Allyl vinyl ether **1-42** underwent the cascade reaction in good yield (60%) and in high diastereoselectivity (10:1) to provide the monoprotected alcohols **1-47** and **1-48** (Table 1-3, Entry 3). To assign the stereochemistry of **1-47**, it was desilylated with TBAF to furnish the corresponding diol which had spectral data identical to **1-43**, confirming its stereochemistry as all *syn* (Scheme 1-22).

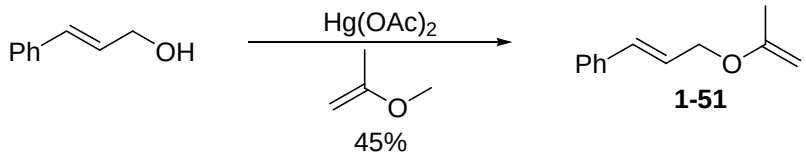


1-47 **1-43**

Scheme 1-22. Deprotection of **1-47**.

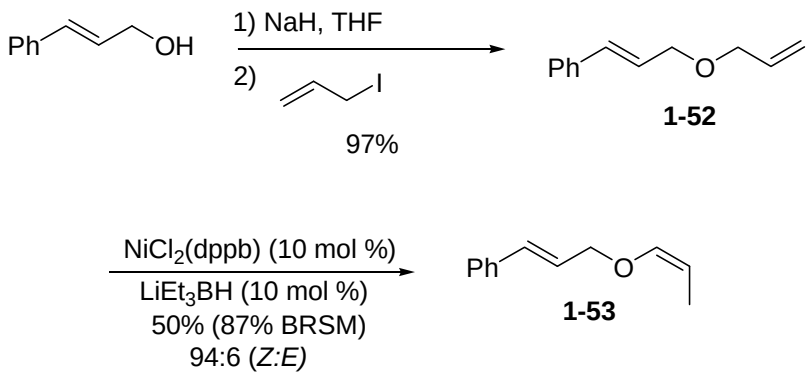
1.2.5 Synthesis and Cascade Reactions of Alkylated Vinyl Ethers

Allylic vinyl ethers which bear alkyl substitution at the 1 and/or 2 position are difficult to prepare. However, isopropenyl ether **1-51** was prepared via Hg(II)-catalyzed alcohol exchange with 2-methoxypropene,[47] in 45% yield (Scheme 1-23).



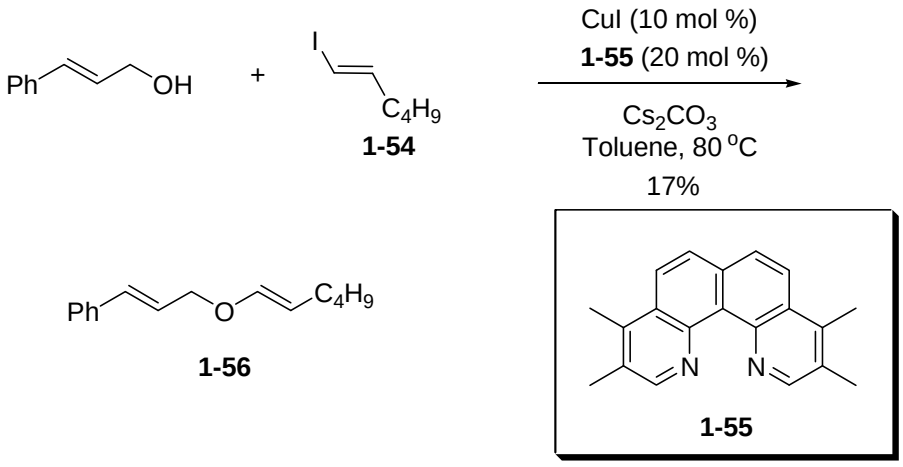
Scheme 1-23. Preparation of **1-51.**

One of the most mild and selective methods for the formation of allylic vinyl ethers is the alkene isomerization method of Frauenrath.[48] This method uses Ni-centered catalysts, usually $NiCl_2$(dppb), which must be activated with $Li(Et)_3BH$. Generally, stereoselectivities are 95:5 or greater and there is a good regioselectivity for terminal olefins. Bis-allyl ether **1-52** was constructed by alkylation of the sodium salt of cinnamyl alcohol in 97% yield (Scheme 1-24). Treatment of bis-allyl ether **1-52** and catalytic $NiCl_2$(dppb) in THF with catalytic $Li(Et)_3BH$ generated the Ni-H containing catalyst necessary to effect terminal olefin isomerization. Vinyl ether **1-53** was isolated in 50% yield in a 94:6 ratio in favor of the (*Z*)-isomer.



Scheme 1-24. Preparation of **1-53** via alkene isomerization.

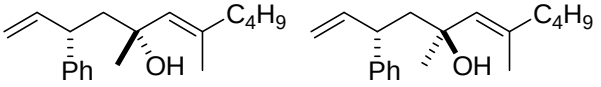
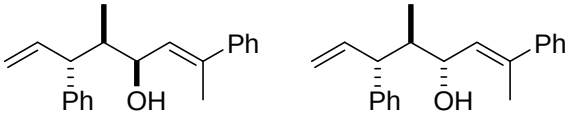
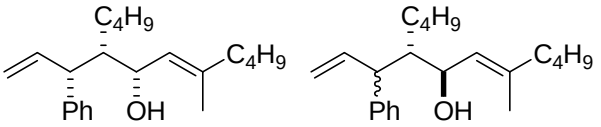
A recent addition to the literature on the preparation of allylic vinyl ethers by Buchwald and co-workers demonstrated the copper-mediated coupling of vinyl iodides and bromides with alcohols.[49] The process is catalytic and the olefin geometry is retained throughout the process. The conversion does require the presence of commercially available phenanthroline **1-55**. Yields are variable, but the reaction scales very well. This chemistry was used for the synthesis of butyl-substituted vinyl ether **1-56**. Vinyl iodide **1-54**[50] was coupled to cinnamyl alcohol in the presence of CuI, $CsCO_3$, and **1-55**. After heating the mixture for 24 hours, a low 17% yield of vinyl ether **1-56** was obtained as a pure geometric (*E*,*E*)-isomer (Scheme 1-25).



Scheme 1-25. Preparation of **1-56** via Cu-catalyzed coupling.

With the alkyl substituted vinyl ethers in hand, **1-51** was submitted to the standard conditions, affording tertiary alcohols **1-57** and **1-58** in 75% yield but in poor diastereoselectivity of 3:2 (Table 1-4, Entry 1). Vinyl ether **1-53** underwent the cascade rearrangement/addition in 65% yield and with a 10:1 diastereoselectivity, partially derived from the mixture of olefins that went into the reaction, therefore this is indicative of a highly diastereoselective process (Table 1-4, Entry 2). Butyl-substituted vinyl ether **1-56** also underwent the cascade rearrangement/addition in 90% yield and good diastereoselectivity, although a third diastereomer was present according to ^{1}H NMR analysis. (Table 1-4, Entry 3).

Table 1-4. Summary of results of the cascade reaction of alkylated allyl vinyl ethers.

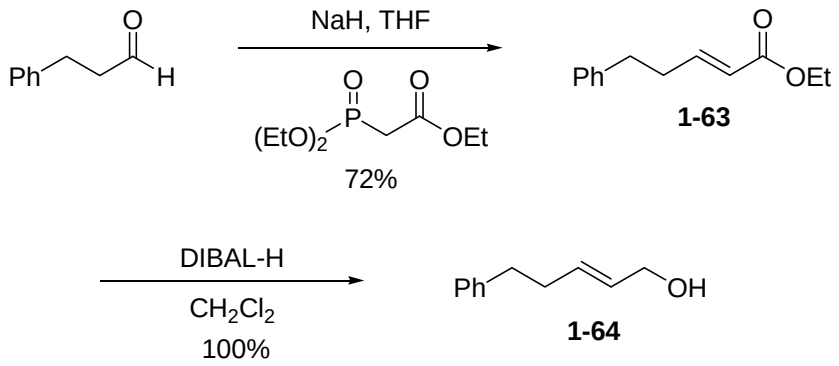
Entry	Substrate	Conditions	Products (major:minor)[a]	Yield (%) (dr)[b]
1[c]	**1-51**	i	 **1-57** **1-58**	75 (3:2)
2	**1-53**	ii	 **1-59** **1-60**	65 (10:1)
3[d]	**1-56**	iii	 **1-61** **1-62**	90 (10:1:0.8)

Reaction Conditions: (i) 2.1 eq $AlMe_3$, 1 eq H_2O, 10 mol % Cp_2ZrCl_2, 2 eq hexyne (ii) 2.1 eq $AlMe_3$, 1 eq H_2O, 10 mol % Cp_2ZrCl_2, 2 eq phenylacetylene (iii) 2.1 eq $AlMe_3$, 1 eq H_2O, 10 mol % Cp_2ZrCl_2, 2 eq hexyne. [a] Shown as major (left):minor (right). [b] Determined by integration of the ^1H NMR spectrum of the product mixture. [c] Major and minor diastereomers are unassigned. [d] Minor diastereomers are unassigned as indicated.

1.2.6 Synthesis and Cascade Reactions of Phenethyl-Substituted Vinyl Ethers

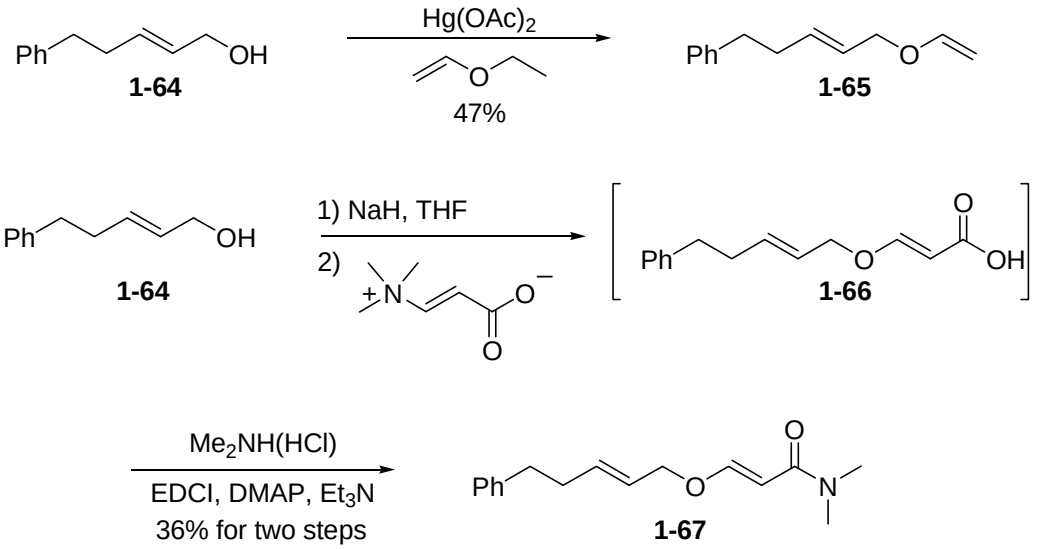
All of the examples presented thus far demonstrate the cascade reaction on substrates based on the cinnamyl alcohol moiety. A series of substrates based on allylic alcohol **1-64** was synthesized to demonstrate the chemistry with alkyl substitution at the 6-position of the allylic vinyl ether system. Allylic alcohol **1-64** was synthesized according to a literature protocol (Scheme 1-26).[51] Horner-Wadsworth-Emmons olefination of hydrocinnamaldehyde furnished enoate **1-63** in 72%

yield as a single geometric isomer (*E*). Reduction of **1-63** with DIBAL proceeded in quantitative yield to give the desired (*E,E*)-allylic alcohol **1-64**.



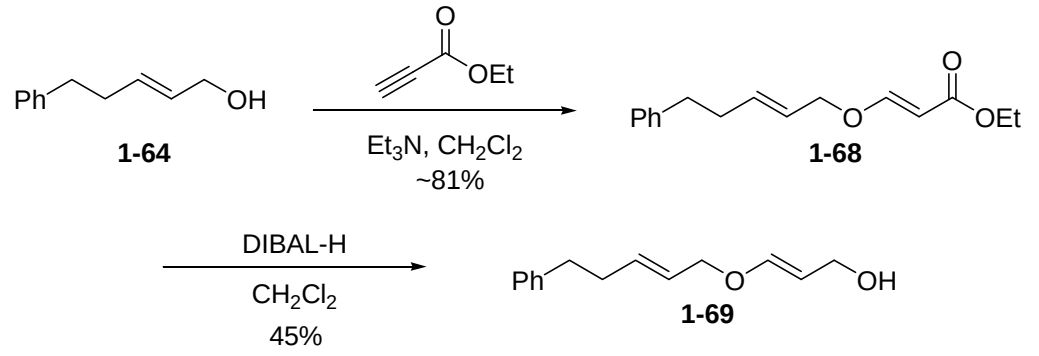
Scheme 1-26. Preparation of allylic alcohol **1-64.**

Using previous methods, a series of analogous substrates were synthesized. Alcohol **1-64** underwent Hg(II)-catalyzed alcohol exchange with ethyl vinyl ether in a moderate 47% yield to give vinyl ether **1-65** (Scheme 1-27). Allylic alcohol **1-64** was coupled to betaine to furnish the unstable acid **1-66**. This acid was immediately coupled with dimethyl amine (EDCI, DMAP) to yield the dimethyl amide **1-67** in 36% overall yield.



Scheme 1-27. Preparation of hydrocinnamate derivatives **1-65** and **1-67.**

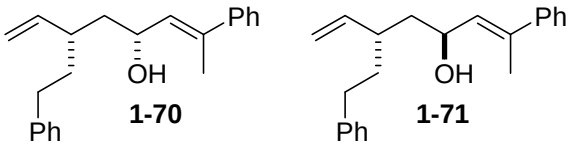
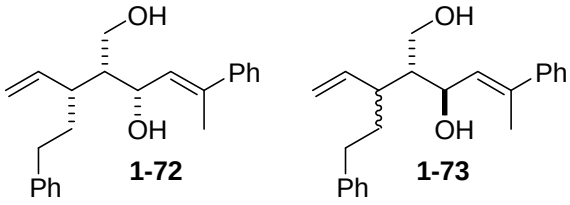
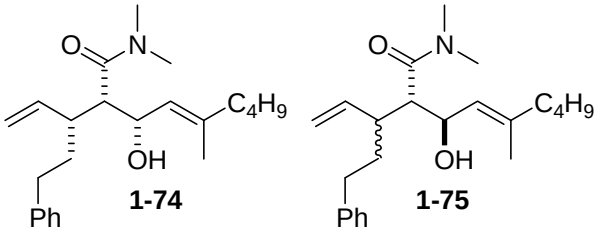
To access allylic alcohol **1-69**, **1-64** was condensed with ethyl propiolate in the presence of Et_3N to give an 81% yield of the (*E,E*)-ester **1-68** (Scheme 1-28, geometry assigned based on J = 12.5 Hz for α-hydrogen). Ester **1-68** was directly subjected to DIBAL reduction, from which only the (*E*)-allylic alcohol **1-69** was isolated in 45% yield, along with alcohol **1-64,** derived from 1,4-reduction and elimination of alkoxide.



Scheme 1-28. Preparation of allylic alcohol **1-69.**

Vinyl ether **1-65** underwent the cascade reaction in 78% yield to furnish a 3:2 mixture of separable diastereomers, **1-70** and **1-71** (Table 1-5, Entry 1). Allylic alcohol **1-69** provided diols **1-72** and **1-73** in 17% yield as a 10:0.8:0.5 mixture of diastereomers (Table 1-5, Entry 2). The lower yield can be attributed to the significant number of side-products formed in this reaction. Once again, amide **67** failed to undergo the desired reaction until the equivalents of $AlMe_3$ and H_2O were raised to 10 and 4, respectively, furnishing amide alcohols **1-74** and **1-75** in 34% yield as a 10:4:1 mixture of diastereomers (Table 1-5, Entry 3). These examples demonstrate that alkyl-substituted allyl vinyl ethers undergo the cascade reaction as effectively as the aryl-substituted derivatives.

Table 1-5. Summary of results of the cascade reaction of phenethyl-substituted vinyl ethers.

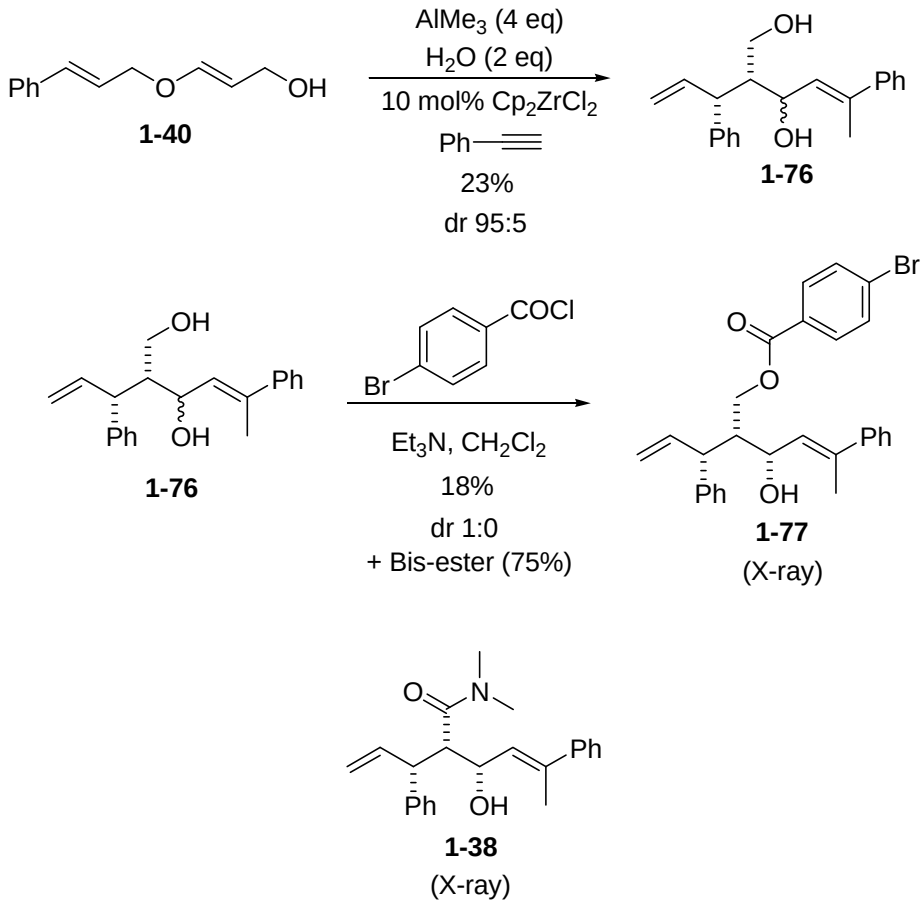
Entry	Substrate	Conditions	Products (major:minor)[a]	Yield (%) (dr)[b]
1[c]	**1-65**	i	 **1-70** **1-71**	78 (5:3)
2[d]	**1-69**	ii	 **1-72** **1-73**	17 (10:0.8:0.5)
3[d]	**1-67**	iii	 **1-74** **1-75**	34 (10:4:1)

Reaction Conditions: (i) 2.1 eq $AlMe_3$, 1 eq H_2O, 10 mol% Cp_2ZrCl_2, 2 eq phenylacetylene (ii) 4 eq $AlMe_3$, 2 eq H_2O, 10 mol% Cp_2ZrCl_2, 2 eq phenylacetylene (iii) 10 eq $AlMe_3$, 4 eq H_2O, 10 mol% Cp_2ZrCl_2, 2 eq hexyne. [a] Shown as major (left):minor (right). [b] Determined by integration of the ^1H NMR spectrum of the product mixture. [c] Major and minor diastereomers are unassigned. [d] Minor diastereomers are unassigned as indicated.

1.2.7 Stereochemistry of the Cascade Process

In order to assign the relative configuration of the major diastereomers, diol **1-76**, the product of the cascade reaction of **1-40** with phenylacetylene, was derivatized to its mono-*p*-bromobenzoyl ester **1-77**, and shown by x-ray diffraction to be all *syn* (Scheme 1-29). In addition to mono-benzoate **1-77**, a 75% yield of the bis-benzoate was also obtained, but the latter was not

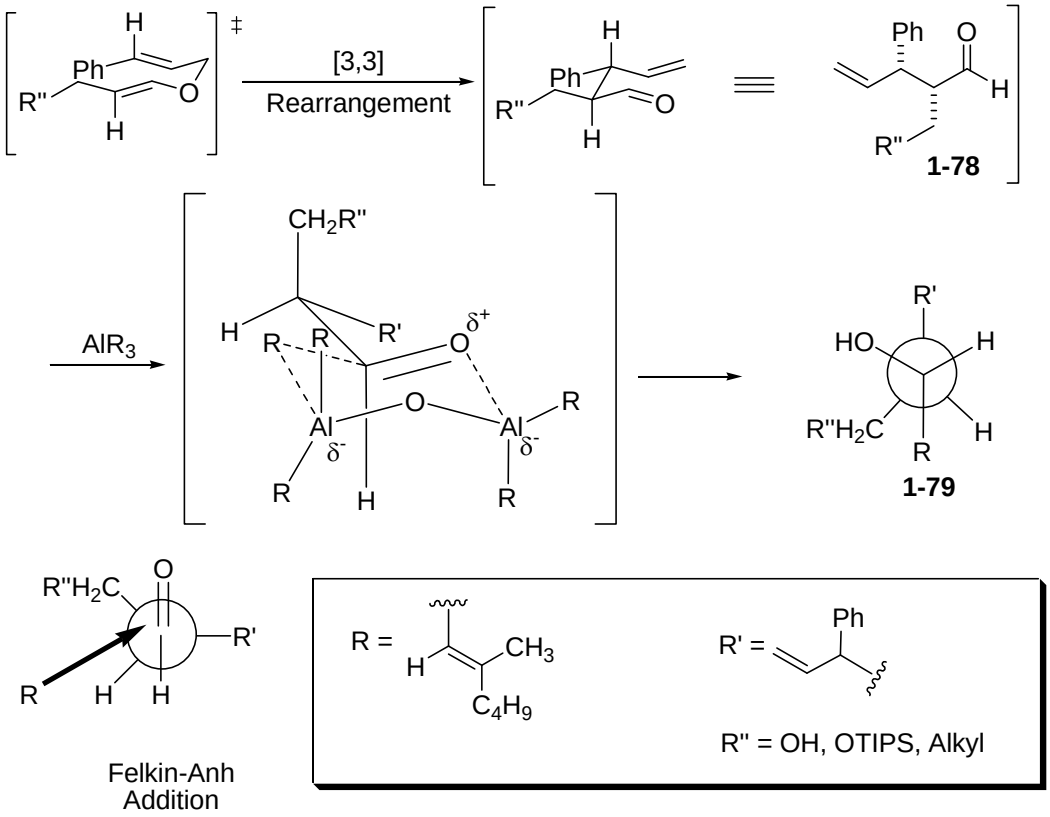
diastereomerically pure and therefore unsuitable for analysis. Additionally, amide **1-38** (see Table 1-2) was assigned as the all *syn* diastereomer by X-ray diffraction.



Scheme 1-29. X-ray analysis of ester **1-77** and **1-38** confirm the *syn*,*syn*-configuration for the major diastereomers.

The all *syn* configuration of the major diastereomer formed in the cascade process can be explained by a chair-like transition state for the accelerated Claisen rearrangement (Scheme 1-30).[36a,52,53] The resulting aldehyde (or ketone) is then subjected to a highly selective Felkin-Anh addition[54] of the vinyl alane, directed by the α-stereocenter. After aldehyde **1-78** is formed, addition takes place with the most bulky substituent orthogonal to the carbonyl π-bond. This conformation

follows the Felkin-Anh model and allows the nucleophile to assume a Bürgi-Dunitz trajectory for attack onto the carbonyl group,[55] resulting in the observed *syn* stereochemistry (**1-79**).

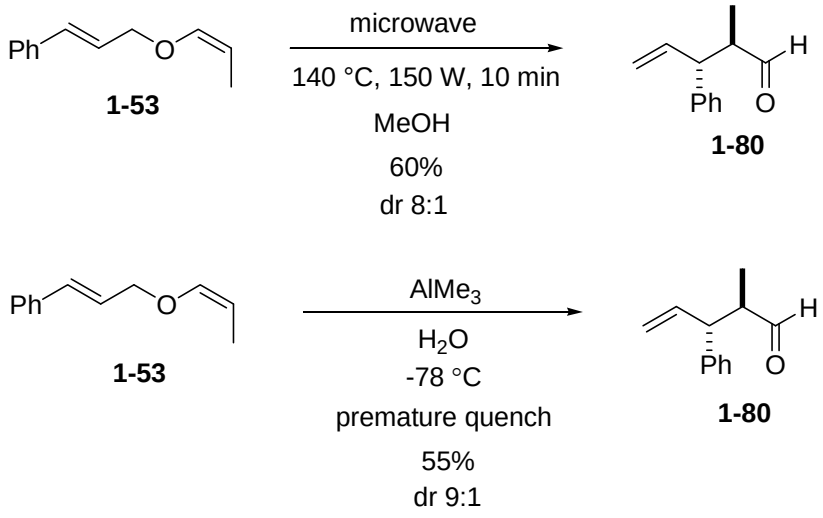


Scheme 1-30. Proposed mechanism for cascade reaction.

In the addition of alkylaluminum reagents to aldehydes, a 6-membered transition state is generally preferred over a 4-membered transition state when more than one equivalent of AlR_3 is employed.[56] In the present case, chelation control in the addition can be ruled out since substrates **1-40** and **1-42** gave identical diastereomers (*vide supra*). The stereodirecting effect of the newly formed aldehyde α-stereocenter, in combination with the steric demand of the oligomeric alane nucleophile,[57] leads to a high overall induction in the carbonyl addition step. Further support for the significance of steric effects is provided by the poor diastereoselectivity of substrates that lack an α-

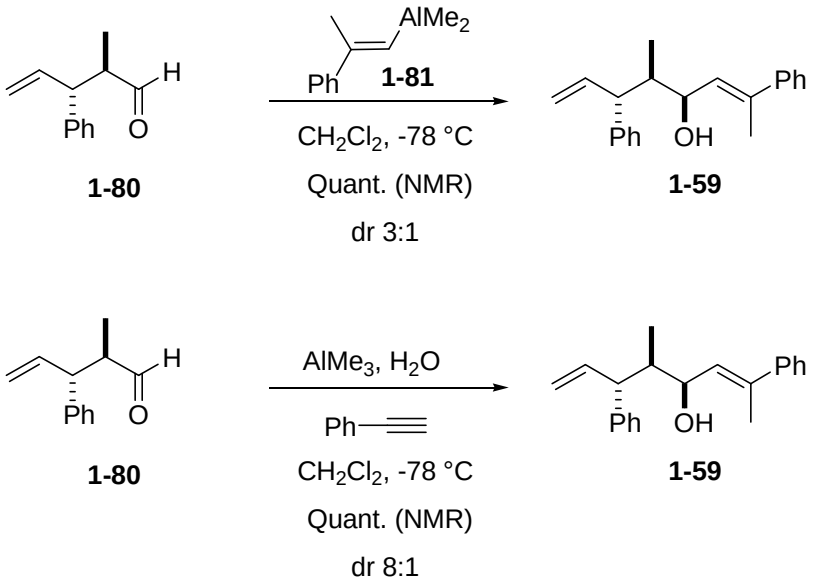
stereocenter. Poor diastereoselectivity is also observed if the intermediate is a ketone, such as **1-51**, which is known to exhibit diminished, substituent dependent complexation to aluminum Lewis acids compared to aldehydes.[58]

It is possible that the intermediate aldehyde **1-78** might epimerize under the reaction conditions, leading to decreased product diastereomeric ratio; therefore, it was attempted to isolate this intermediate and compare it to the product of a thermal Claisen rearrangement with a substrate of known configuration. Allyl vinyl ether **1-53**, when subjected to microwave heating,[59] underwent a [3,3] sigmatropic rearrangement in 10 min to yield aldehyde **1-80** in 60% yield as a 10:1 mixture of diastereomers (Scheme 1-31).[60] Conversely, attempts to quench a cascade carboalumination-Claisen rearrangement-vinyl alane addition reaction before the allyl vinyl ether was consumed resulted only in recovered starting material and final cascade reaction products. Presumably, nucleophilic addition to the intermediate aldehyde was too rapid for preparative isolation. However, the addition of alkyl alanes to carbonyl groups is slower than vinyl transfer, and when the reaction with an *alkyl* aluminoxane was quenched prematurely, aldehyde **1-80** was isolated in 55% yield. A 9:1 diastereoselectivity was observed in this reaction, and the configuration of **1-80** was identical to the aldehyde obtained by thermal rearrangement, thus indicating that α-epimerization during the cascade reaction was unlikely.



Scheme 1-31. Control reactions for test of stereochemical integrity of the aldehyde intermediate.

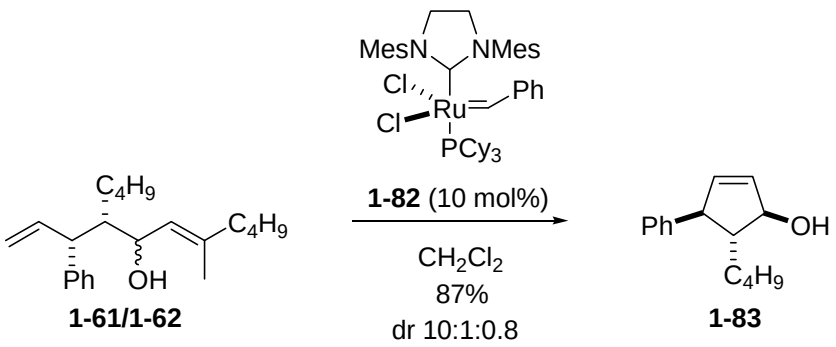
Since the addition of water to mixtures of alane and zirconocene leads to a significant rate increase in the alkyne carboalumination,[13] the potential accelerating effect of water in the aldehyde addition was probed. Treatment of aldehyde **1-80** at -78 °C with vinyl alane **1-81**, prepared via Negishi carboalumination[61] in the absence of water, led in less than 1 min to addition product **1-59** as a modest 3:1 mixture of diastereomers (Scheme 1-32). In the presence of stoichiometric quantities of water, the vinyl alane also rapidly added to this aldehyde, but in 8:1 diastereocontrol. These results indicate that, while no measurable rate enhancement in the already fast 1,2-addition is gained at -78 °C from the addition of water, the larger aluminoxane cluster acting as a bulky nucleophile in the 1,2-addition or a tighter transition state leads indeed to improved facial selectivity in the carbonyl addition step.



Scheme 1-32. Control experiments establish the beneficial effect of water on the diastereoselectivity of the addition process.

1.2.8 Conversion of 1,6-Diene to Cyclopentene

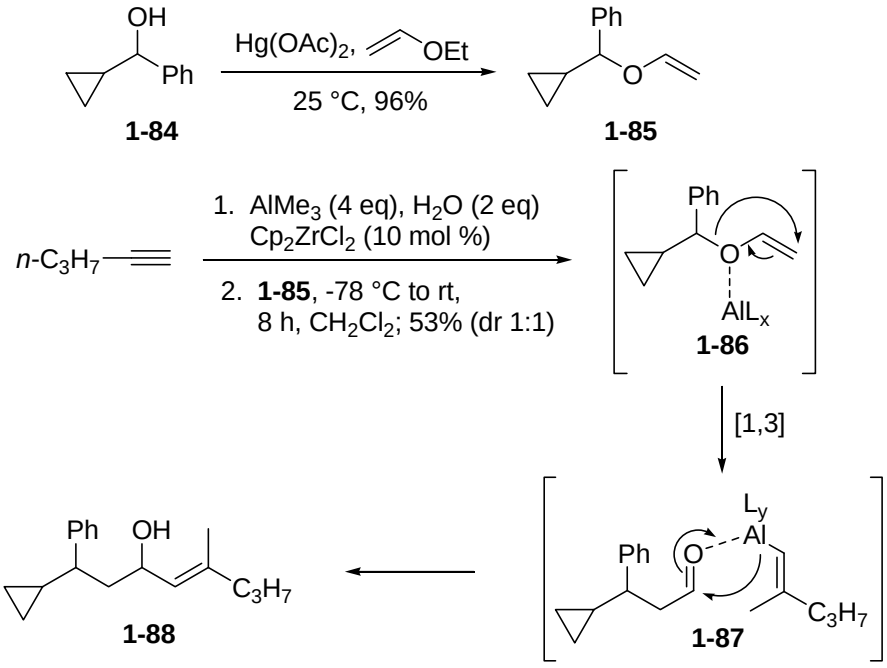
As a practical demonstration of the synthetic potential of this new cascade reaction, a 10:1:0.8 mixture of the 1,6-dienes **1-61** and **1-62** was converted to cyclopentenol **1-83** in the presence of ruthenium catalyst **1-82**[62] (Scheme 1-33). These substituted cyclopentenes have found use in the preparation of carbocyclic nucleosides, some of which are potent antiviral agents lacking the labile anomeric linkage that increases susceptibility to degradative enzymes such as phosphorylases.[63,64]



Scheme 1-33. Preparation of cyclopentenes by ring closing metathesis.

1.2.9 [1,3] vs [3,3] Rearrangement.

The [1,3] sigmatropic rearrangement of allyl vinyl ethers can compete with the [3,3] sigmatropic shift[36a] especially in the presence of strong Lewis acids and with substrates that favor allyl cation intermediates.[65] While reaction products in the cascade process derived from [1,3] rearrangement have not been observed, this process is feasible under the typical reaction conditions. To attempt to observe the [1,3] rearrangement, cyclopropylmethyl vinyl ether **1-85** was prepared in high yield from alcohol **1-84** by a Hg(II)-mediated vinyl ether exchange. Indeed, **1-85** was smoothly converted into allylic alcohol **1-88** under the cascade conditions(Scheme 1-34). The conversion of **1-85** to **1-88** appears to be the first case of a [1,3] sigmatropic rearrangement of a cyclopropane analog of an allyl vinyl ether.[66]



Scheme 1-34. [1,3] Rearrangement of cyclopropylmethyl vinyl ether **1-85**.

1.2.10 Conclusions

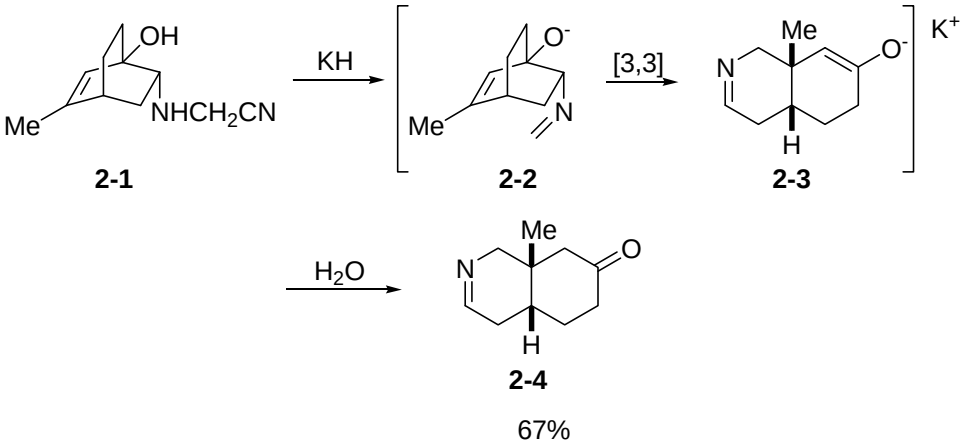
A rapid diastereoselective three-step cascade carboalumination-Claisen rearrangement-carbonyl addition process leading to 1-6-diene functionalities containing allylic alcohols with up to three contiguous stereocenters has been developed. The stoichiometric quantities of water that are used as an additive increase the rate of the [3,3] sigmatropic rearrangement as well as the diastereoselectivity of the carbonyl addition. The resulting products are readily converted to substituted cyclopentenes. The cascade strategy has also be extended to a sequence involving a [1,3] sigmatropic shift.

2. AZA-COPE REARRANGEMENTS AND *N*-ACYL IMINIUM ION CHEMISTRY

2.1 INTRODUCTION

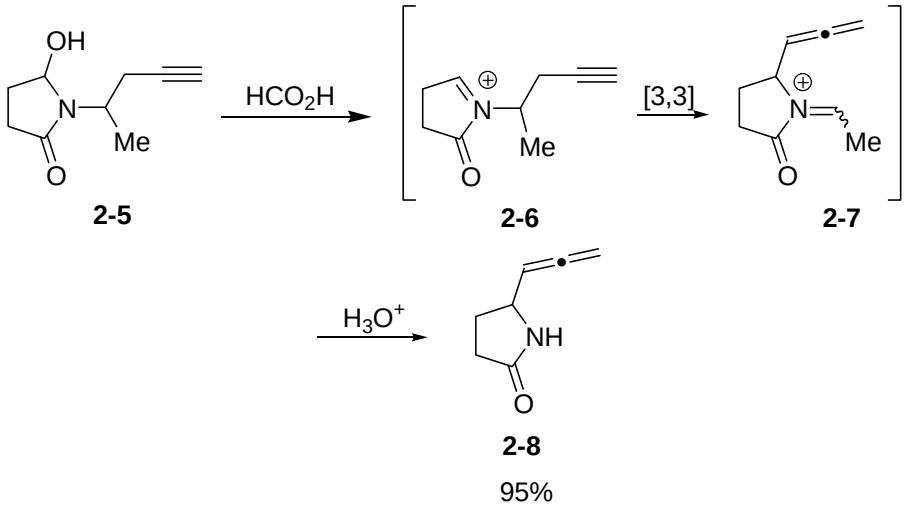
2.1.1 Aza-Cope Rearrangements

The studies on Claisen rearrangements promoted by water-activated alanes described in the previous chapter prompted an investigation into whether the same strategy could be used to promote other sigmatropic rearrangements. The aza-Cope rearrangement is a closely related sigmatropic process which has been extensively utilized in synthesis. For example, Overman and co-workers have used the aza-Cope rearrangement to form intermediate ketone **2-4** during their synthesis of gelsemine (Scheme 2-1).[67]



Scheme 2-1. Aza-Cope rearrangement to access **2-4** in Overman's synthesis of gelsemine.

The aza-Cope rearrangement is known to be catalyzed by acids and bases. Krantz and co-workers have used protic acids as promoters of sigmatropic processes which form allenes.[68] As shown in Scheme 2-2, when aminal **2-5** was treated with formic acid, iminium ion formation followed by sigmatropic rearrangement furnished the allenyl lactam **2-8** after workup.



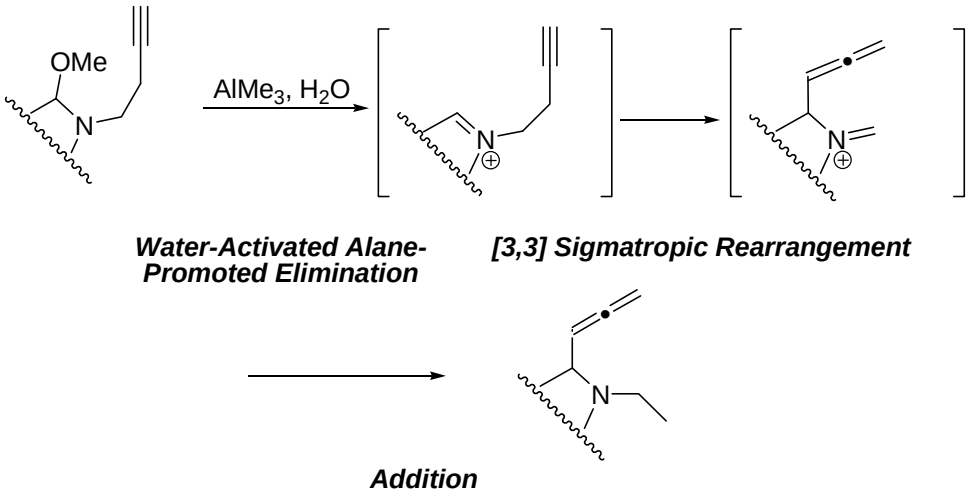
Scheme 2-2. Aza-Cope rearrangement to furnish allene **2-8.**

2.2 RESULTS AND DISCUSSION

2.2.1 Preliminary Investigations

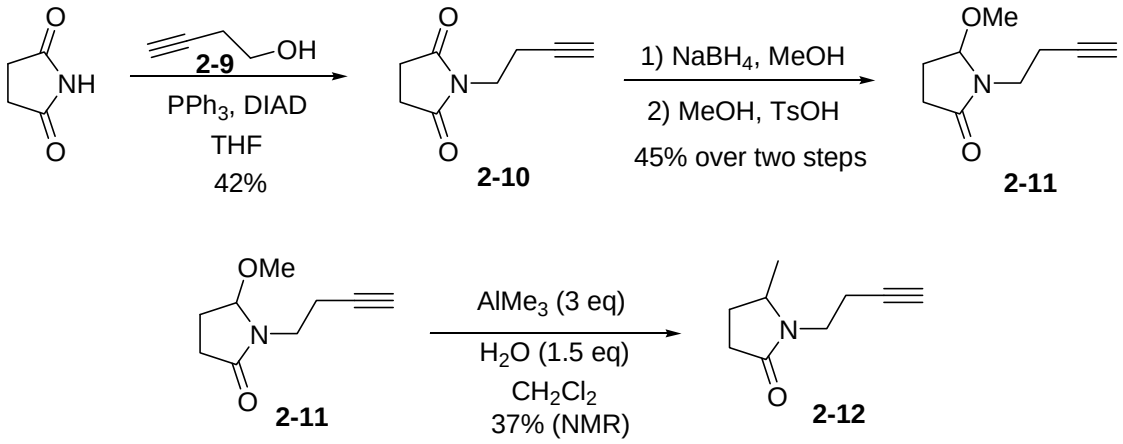
Although there are examples to the contrary, a common problem with the aza-Cope rearrangement is prolonged reaction times. It was anticipated that water-activated alane could dramatically increase the rates of these reactions. Extending on some models by Krantz,[69] an acidic cascade would generate an iminium ion from an aminal using water-activated alane (Scheme 2-3).

The iminium ion would then undergo an aza-Cope rearrangement and be trapped by addition of a methyl group from the alane, generating an allene.



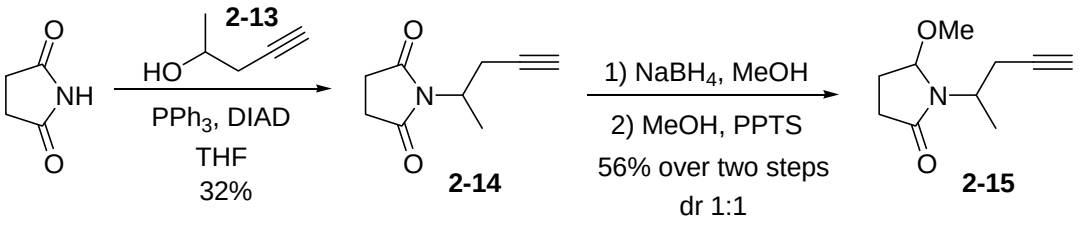
Scheme 2-3. Proposed aza-Cope rearrangement promoted by water-activated alane.

Initial exploration of the water-activated, alane-promoted aza-Cope rearrangement reaction began with preparation of methoxylactam **2-11**, accessible in three steps from succinimide. Mitsunobu alkylation with alcohol **2-9** proceeded in 42% yield to furnish imide **2-10** which was readily reduced with $NaBH_4$ (Scheme 2-4). The crude corresponding hydroxy lactam was subjected to acid-catalyzed methanol exchange to provide the model lactam **2-11** in 45% yield. Lactam **2-11** was added to a -78 °C solution of $AlMe_3$ (3 eq.) and H_2O (1.5 eq.). After 24 h at room temperature, only lactam **2-12** and starting material could be observed by ^1H NMR (Scheme 2-4). All of the exploratory reactions towards the aza-Cope rearrangement were studied by ^1H NMR analysis of the crude reaction mixtures.[70]



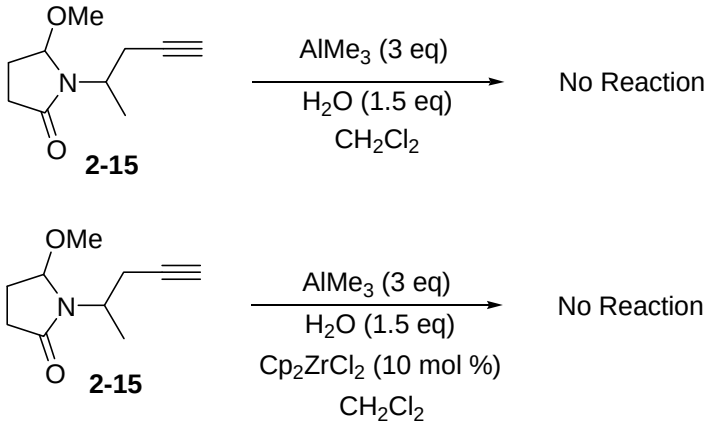
Scheme 2-4. Preparation and reactions of model substrate **2-11**.

The formation of **2-12** indicated that the desired ionization was occurring, however addition of a methyl group from $AlMe_3$ was quenching the iminium ion needed for sigmatropic rearrangement. The elimination of the methoxy group was extremely slow at room temperature, contrary to the reactivity observed with water-activated alane in other reaction manifolds. The studies of Hart and co-workers on iminium ion sigmatropic rearrangements suggested that substitution at the nitrogen bearing *exo*-carbon in pyrrolidones can promote the aza-Cope rearrangement.[71] Thus, branched methoxy lactam **2-15** was explored. This compound was prepared in an analogous fashion to methoxylactam **2-11**. Mitsunobu alkylation of succinimide with secondary alcohol **2-13** proceeded sluggishly to provide imide **2-14** in a 32% yield (Scheme 2-5). The imide was reduced with sodium borohydride and converted to its corresponding methoxy lactam **2-15** in 56% yield over two steps as a 1:1 mixture of diastereomers.



Scheme 2-5. Preparation of alkyl-branched substrate **2-15**.

Addition of **2-15** to a mixture of $AlMe_3$ (3 eq.) and H_2O (1.5 eq.) provided, after 24 h at room temperature, only recovered starting material (Scheme 2-6). A water-accelerated zirconium-catalyzed carboalumination was attempted on methoxy lactam **2-15**, however after 24 h at room temperature, only starting material was recovered. The lack of reactivity indicated that the succinimide scaffold was unsuitable for this chemistry.

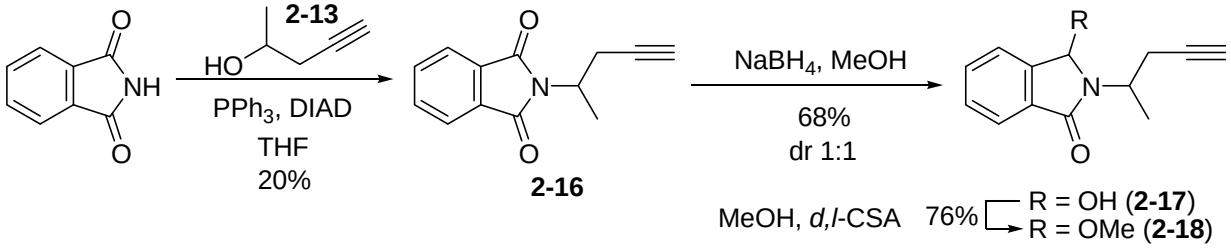


Scheme 2-6. Attempted reactions of alkyl branched substrate **2-15**.

Before the rate of the sigmatropic rearrangement vs. methyl addition could be addressed, iminium ion formation had to occur. Therefore, a more ideal substrate would include a more

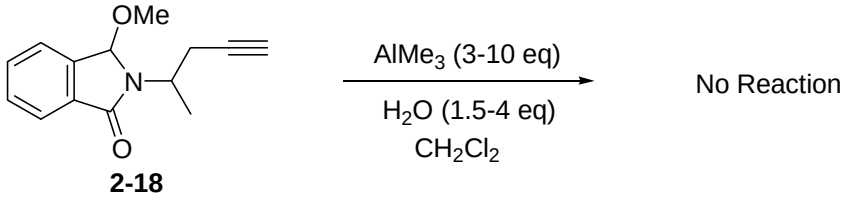
activated leaving group. An analogous phthalimide derivative seemed promising since the site of elimination would now be activated by both the amide nitrogen and the aromatic ring.

The alkyl branched methoxy lactam **2-18** was selected as the next target substrate. Mitsunobu alkylation of phthalimide with secondary alcohol **2-13** provided the alkylated imide **2-16** in a low 20% yield (Scheme 2-7). Sodium borohydride reduction of imide **2-16** proceeded in moderate yield to provide hydroxy lactam **2-17** as a 1:1 mixture of diastereomers. Acid mediated methanol exchange with hydroxy lactam **2-17** furnished methoxylactam **2-18** in 76% yield.



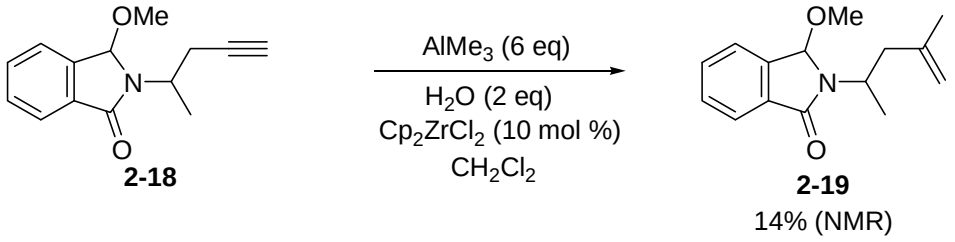
Scheme 2-7. Preparation of phthalimide substrate **2-18**.

Treatment of methoxy lactam **2-18** with $AlMe_3$ (3 eq.) and H_2O (1.5 eq.) in CH_2Cl_2 returned only starting material. Increasing both the stoichiometry between $AlMe_3$ and H_2O and the overall equivalents did not impart any detectable conversion (Scheme 2-8).



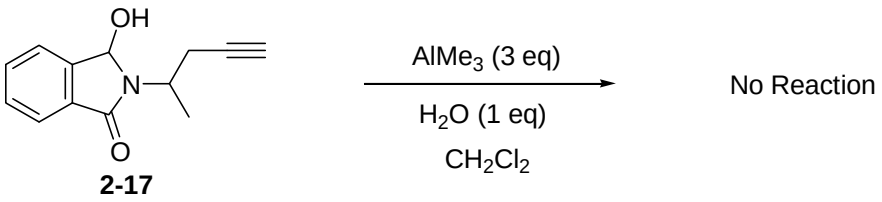
Scheme 2-8. Attempted reactions of phthalimide substrate **2-18**.

Again, a water-accelerated zirconium-catalyzed carboalumination was attempted on methoxylactam **2-18**. Conditions which employed $AlMe_3$ (3 eq.), H_2O (1.5 eq.), and catalytic zirconocene dichloride led only to starting material (Scheme 2-9). This time, an increase in $AlMe_3$ and H_2O (6 and 2 eq., respectively) furnished a low conversion to olefin **2-19**.



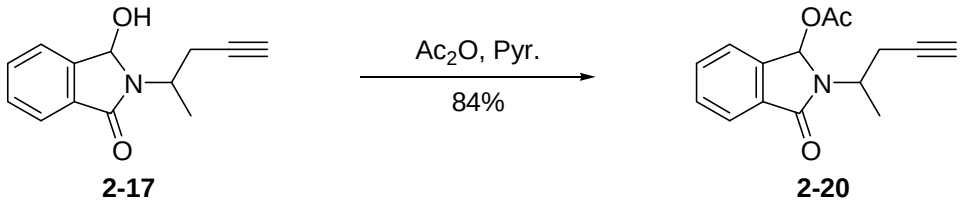
Scheme 2-9. Attempted carboalumination of **2-18**.

In the absence of any evidence of iminium ion formation, a change in the leaving group was investigated. Hydroxy lactam **2-17**, an intermediate in the preparation of methoxy lactam **2-18**, was tested under the standard conditions (3 eq. $AlMe_3$ and 1 eq. H_2O). Unfortunately, only starting material was observed by NMR (Scheme 2-10).



Scheme 2-10. Attempted aza-Cope rearrangement of hydroxy lactam **2-17**.

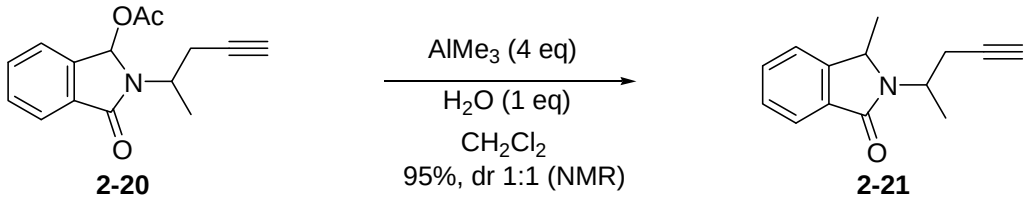
The acylation of hydroxy lactam **2-17** was completed to provide a substrate more prone to undergo elimination (Scheme 2-11).[72]



2-17 **2-20**

Scheme 2-11. Preparation of **2-20**.

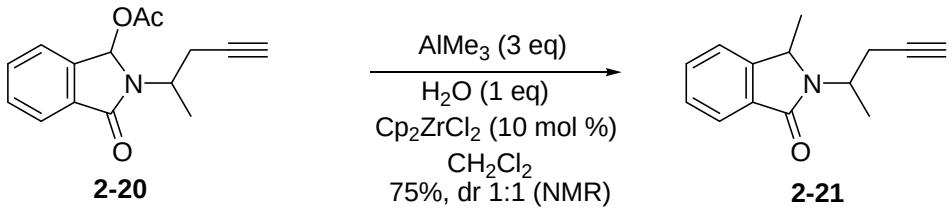
Acetoxy lactam **2-20** was added to a solution of $AlMe_3$ (4 eq.) and H_2O (1 eq.) (Scheme 2-12). After 5 min at room temperature, NMR analysis indicated only alkylated lactam **2-21**, derived from elimination and addition of a methyl group onto the iminium ion.



2-20 **2-21**

Scheme 2-12. Attempted aza-Cope rearrangement of acetoxy lactam **2-20.**

The rapid formation of **2-21** in high yield indicated that the desired type of reactivity was demonstrated by the substrate. Unfortunately, no sigmatropic rearrangement had occurred. The same reaction was then studied in the presence of zirconocene dichloride. Acetoxy lactam **2-20** was added to a solution of $AlMe_3$ (3 eq.), H_2O (1 eq.), and catalytic zirconocene dichloride (Scheme 2-13). Again, after 5 min at room temperature, only lactam **2-21** was formed.



Scheme 2-13. Attempted carboalumination of **2-20**.

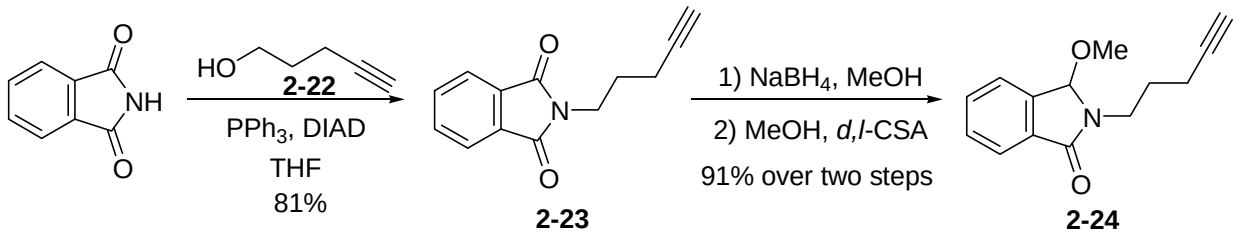
These results indicated that an elimination process, followed by a sigmatropic rearrangement seemed unlikely to occur given the high nucleophilicity of the water-activated alane. The lifetime of the iminium ion would have to be sufficiently long to allow for the sigmatropic rearrangement to occur. Given the rapid addition to the iminium ion at low temperatures, this tandem reaction manifold was abandoned.

2.2.2 Carboalumination Studies on Lactam-based Substrates and Medium Ring Formation

The investigations of the water-activated alane-promoted aza-Cope rearrangement raised some intriguing questions about the reactivity of water-activated alane and the scope of water-accelerated carboalumination. Previous work has clearly demonstrated that these reagents were highly Lewis acidic, yet no elimination/iminium ion formation was observed with substrates known to undergo acid-mediated elimination. Further, the resistance to carboalumination that the lactam-based substrates demonstrated was quite unusual. This prompted an investigation into whether proximity to Lewis basic functionality affects carboalumination.

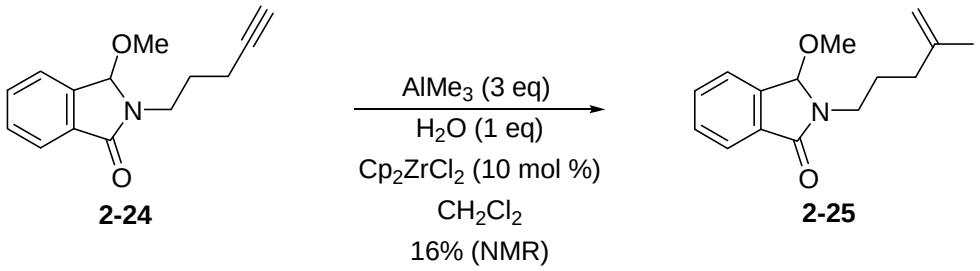
Towards this end, methoxy lactam **2-24**, which contained a three-carbon spacer between the alkyne and amide functionality, was synthesized (Scheme 2-14). Mitsunobu alkylation of

phthalimide with alkynol **2-22** gave the alkylated imide **2-23** in 81% yield. Sodium borohydride reduction followed by acid-mediated methanol exchange furnished the methoxylactam **2-24** in 91% over two steps.



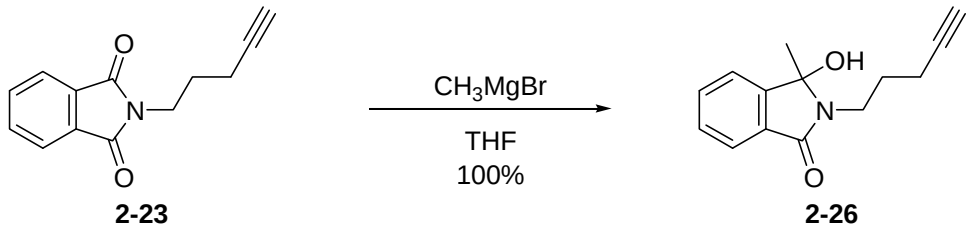
Scheme 2-14. Preparation of **2-24**, containing a three carbon spacer between amide and alkyne.

The addition of **2-24** to a solution of $AlMe_3$ (3 eq.) and H_2O (1 eq.) returned only starting material after 24 h at room temperature. The addition of **2-24** to a solution of $AlMe_3$ (3 eq.) and H_2O (1 eq.) and catalytic zirconocene dichloride furnished a mixture of starting material (84%) and carboalumination product **2-25** (16%) by NMR analysis (Scheme 2-15).



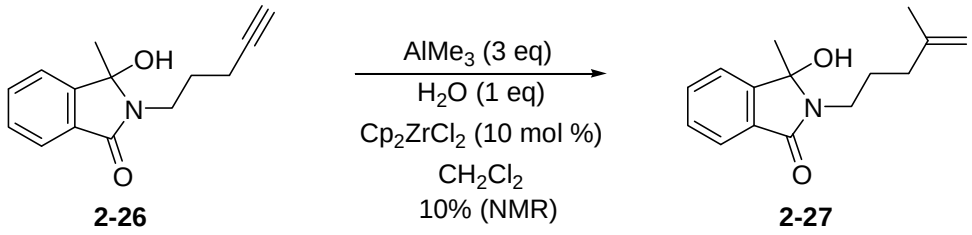
Scheme 2-15. Reaction of **2-24** under carboalumination conditions.

Since carboalumination was observed at a slow rate, and no elimination occurred, the next step was the synthesis of tertiary alcohol **2-26** to investigate its effect on elimination Thus, addition of MeMgBr to imide **2-23** proceeded smoothly to furnish **2-26** (Scheme 2-16).



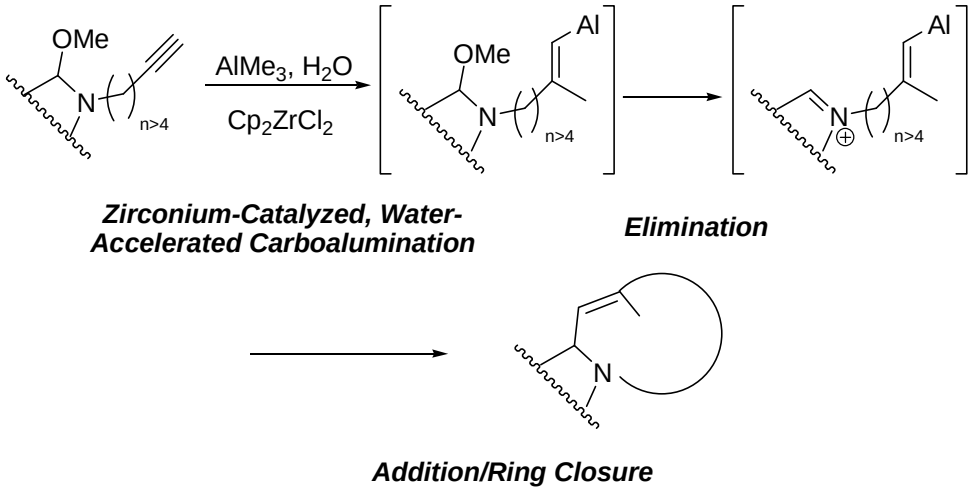
Scheme 2-16. Preparation of **2-26.**

When hydroxy lactam **2-26** was added to a solution of $AlMe_3$ (3 eq.), H_2O (1 eq.) and catalytic zirconocene dichloride, NMR analysis of the reaction mixture after 24 h indicated approximately 10% carboalumination (**2-27**) with only starting material remaining (Scheme 2-17). Thus, the tertiary hydroxy group was not any more reactive towards elimination than the secondary hydroxyl group.



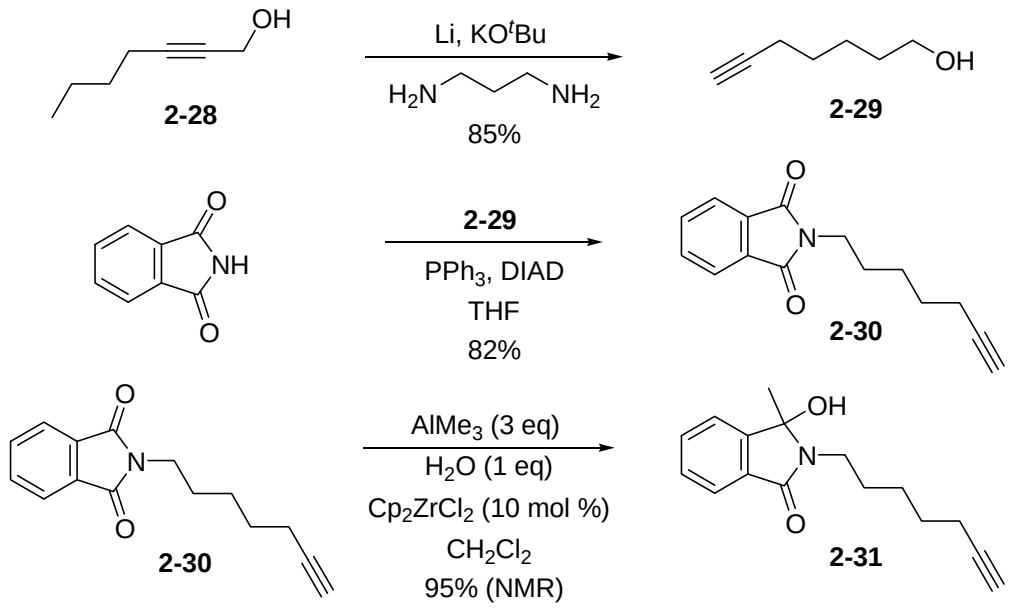
Scheme 2-17. Attempted carboalumination of tertiary alcohol **2-27**.

Subsequently, the alkyne was tethered further away from the central region of the substrate. A longer tether might also provide a novel method to form medium or large rings which contain olefins of defined geometry by a three step, one pot operation: carboalumination, elimination and vinyl alane addition (Scheme 2-18). Preliminary investigations into this method began by constructing a precursor which would be cyclized to form a 9-membered ring.



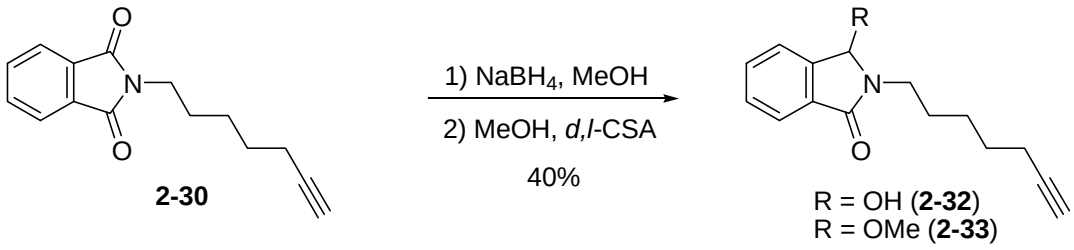
Scheme 2-18. Proposed cascade cyclization sequence.

Alcohol **2-29** was synthesized by the isomerization of the commercially available hept-3-yne-1-ol with the KAPA reagent[73] in 85% yield (Scheme 2-19). Imide **2-30** was then constructed by Mitsunobu alkylation of phthalimide with alkynol **2-29**, which proceeded in 82% yield. This material was submitted to standard carboalumination conditions, $AlMe_3$ (3 eq.), H_2O (1 eq.) and zirconocene dichloride (10 mol%); however, only methyl addition to the imide was observed.



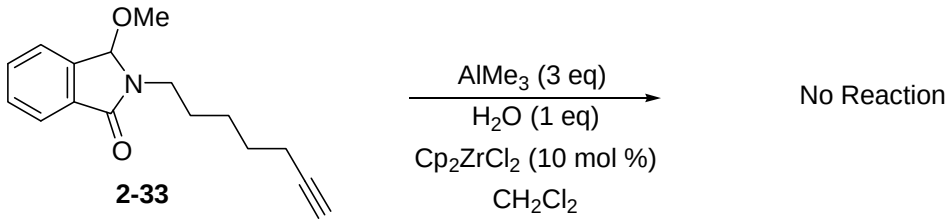
Scheme 2-19. Preparation and model reaction of **2-31**.

Imide **2-30** was reduced with sodium borohydride, followed by methanol exchange to give methoxylactam **2-33** in 40% overall yield (Scheme 2-20).



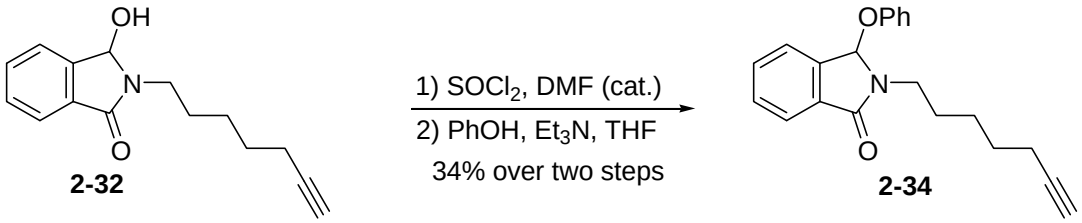
Scheme 2-20. Preparation of lactam **2-33**.

Treatment of a solution of $AlMe_3$ (3 eq.), H_2O (1 eq.) and zirconocene dichloride (10 mol%) with methoxylactam **2-33** returned only starting material with no evidence for elimination or carboalumination (Scheme 2-21).



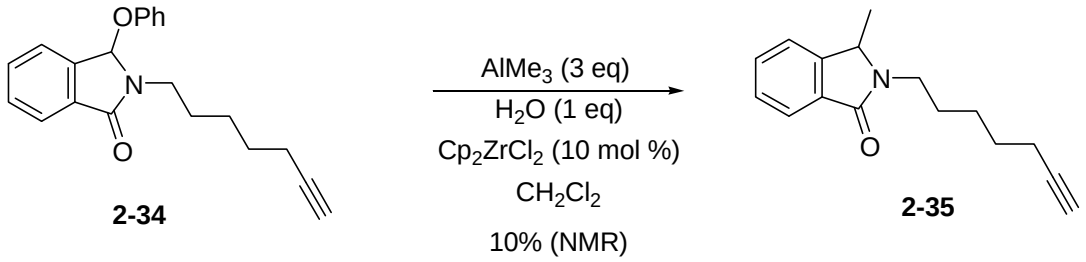
Scheme 2-21. Attempted cascade cyclization of **2-33**.

It was anticipated that a phenoxy group would be a better leaving group. This lead to the synthesis of lactam **2-34**. Treatment of **2-32** with $SOCl_2$ and catalytic DMF furnished the corresponding unstable chloride, which was immediately treated with phenol in the presence of triethylamine to yield phenoxy lactam **2-34** in 34% yield (Scheme 2-22).[74]



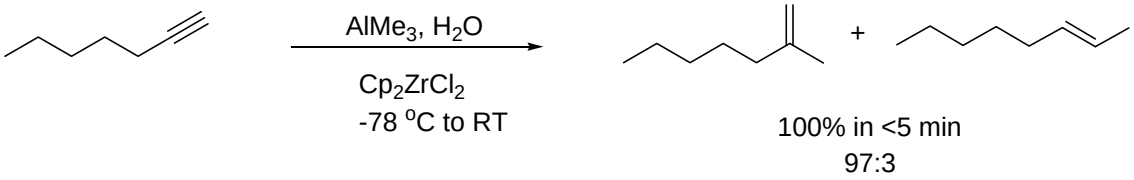
Scheme 2-22. Preparation of phenoxy lactam **2-34**.

Addition of **2-34** to a solution of $AlMe_3$ (3 eq.), H_2O (1 eq.) and zirconocene dichloride (10 mol%) furnished alkylated lactam **2-35** (10%), starting material (52%), and decomposition products (Scheme 2-23).



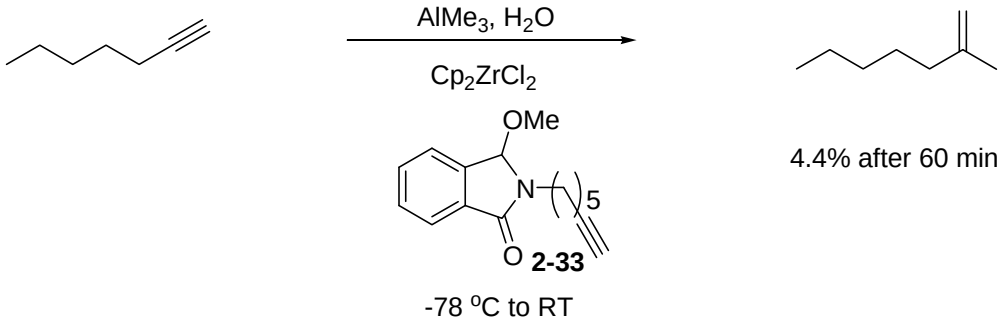
Scheme 2-23. Attempted cascade cyclization of **2-34**.

These experiments demonstrated that the functionality present in these substrates was inhibiting the usually fast carboalumination. It was postulated that the amide group was inhibiting carbometallation, and a series of GC experiments were performed to test this hypothesis. An alkyne, which was known to undergo rapid water-accelerated carboaluminations, was submitted to the standard water-accelerated carboalumination conditions in the presence of lactam **2-33**. A control experiment demonstrated that the carboalumination of heptyne with $AlMe_3$ (3 eq.), H_2O (1 eq.), and Cp_2ZrCl_2 (10 mol %) proceeded to completion in under 5 min at low temperatures (-78 °C to -25 °C) to furnish a 97:3 mixture of regioisomers by GC (Scheme 2-24).



Scheme 2-24. GC control experiment of the water-accelerated carboalumination of heptyne.

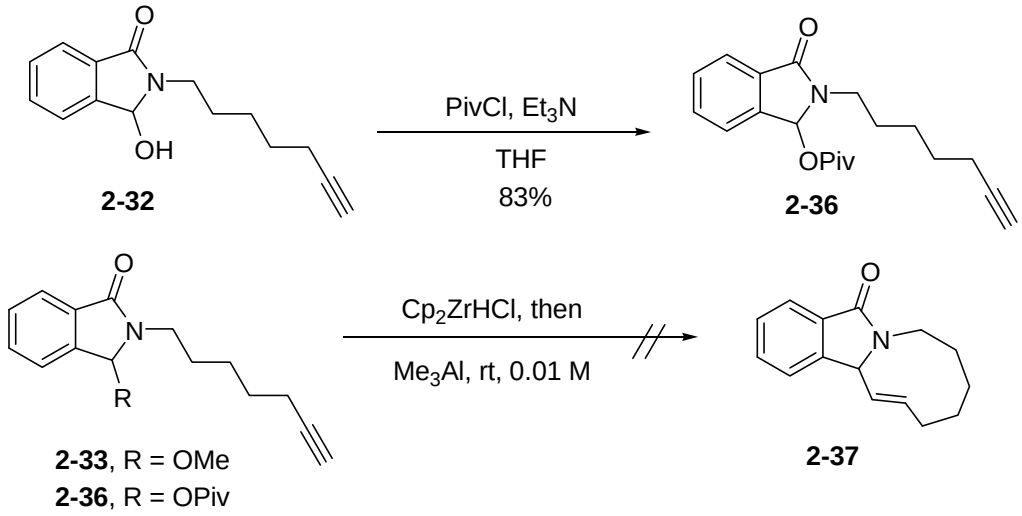
Conducting the identical experiment in the presence of 1 eq. of methoxylactam **2-33** dramatically inhibited carboalumination, with only 4.4% of heptyne undergoing conversion after 1 h (Scheme 2-25).



Scheme 2-25. GC analysis of the water-accelerated carboalumination of heptyne in the presence of **2-33**.

One possibility for this inhibition is that highly Lewis basic functionality coordinates to $AlMe_3$ oligomers, thus inhibiting alkyne carboalumination. This could explain why one equivalent of lactam can inhibit 3 equivalents of $AlMe_3$.

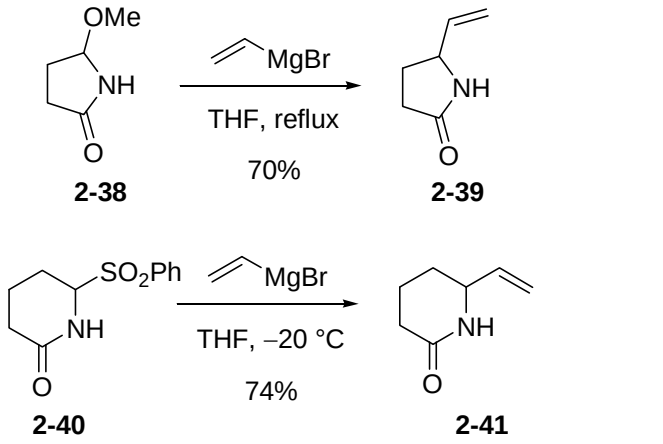
Due to the lack of reactivity in the carboalumination approach, hydrozirconation was chosen as an alternative, known to be quite tolerant of diverse functionality.[75] Pivaloate lactam **2-36** was synthesized in an attempt to increase the rate of elimination. Unfortunately, when lactam **2-33** or **2-36** was treated with Cp_2ZrHCl, only the corresponding alkene was recovered (Scheme 2-26). Treatment of the intermediate alkenylzirconocene with $AgClO_4$ or trimethylaluminum also provided no desired cyclization products. Highly concentrated reaction mixtures or prolonged heating resulted only in slow methyl group addition. Possibly, the ring strain present in the desired products is too high to allow the reaction to proceed under these conditions.



Scheme 2-26. Attempted hydrozirconation and medium ring formation.

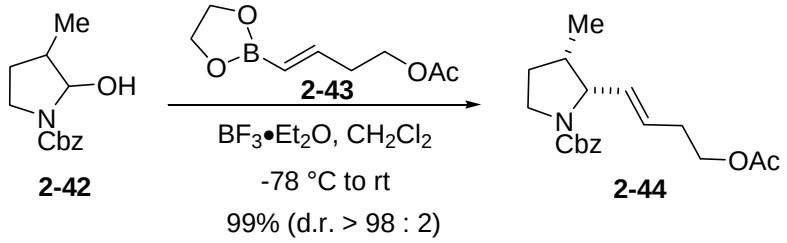
2.2.3 Intermolecular Alkenylation of *N*-Acyl Iminium Ions

Since the intramolecular cyclizations proved elusive, we turned our attention toward an alternative construction of these systems starting with an intermolecular addition process. Intermolecular alkenylation of *N*-acyliminium ions can often require harsh reaction conditions such as extended periods of heating,[76] or unusual anomeric leaving groups (Scheme 2-27).[77]



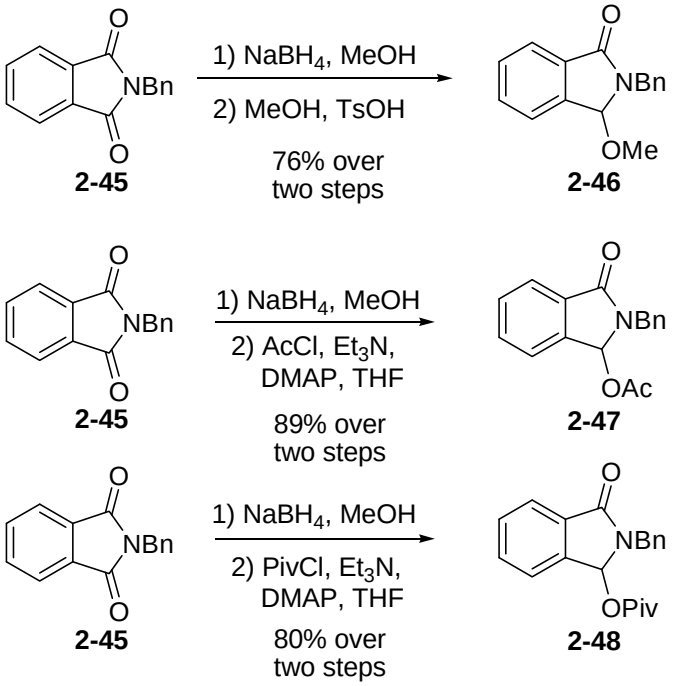
Scheme 2-27. Selected literature examples of intermolecular alkenylation.

An exception to this trend is the mild intermolecular addition of alkenyl boronates reported by Batey.[78] For example, when aminal **2-42** was treated with alkenyl boronate **2-43** and $BF_3 \bullet Et_2O$, addition product **2-44** was isolated in 99% yield as a > 98:2 ratio of diastereomers (Scheme 2-28).



Scheme 2-28. Alkenylation with alkenyl boronates.

For model purposes, lactams **2-46** to **2-48** were chosen, bearing methoxy, acetoxy and pivaloyl leaving groups, respectively. Each of these substrates was made using standard procedures (Scheme 2-29).

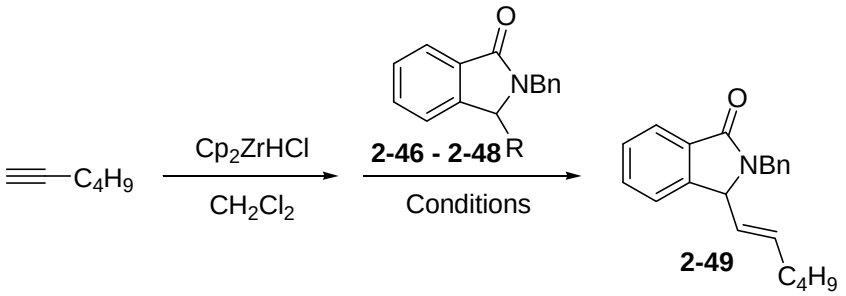


Scheme 2-29. Preparation of model lactams.

The hydrozirconation of terminal alkynes was first explored as a method to generate alkenyl nucleophiles (Table 2-1). Hydrozirconation of 1-hexyne, followed by treatment with silver perchlorate[79] and lactam **2-46** yielded only a trace of addition product after 24 h at rt (entry 1, Table 2-1). Transmetallation to dimethylzinc also proved unsuccessful (entry 2, Table 2-1). Gratifyingly, hydrozirconation-transmetallation to trimethylaluminum[80] generated an alkenylalane that reacted with lactam **2-46** in a moderate 43% yield (entry 3, Table 2-1). The leaving group ability was further increased by using acetate **2-47**; however, product **2-49** was only formed in 30% yield while the remaining starting material was consumed (entry 4, Table 2-1). Attempts to perform this reaction in THF or toluene led to recovered starting material. Pivaloate **2-48**, when treated with the *in situ* generated alane, provided hexenyl isoindolinone **2-49** in 81% yield without any observed isomerization of the alkene moiety (entry 5, Table 2-1). Attempts to achieve this transformation under cationic conditions with silver perchlorate led to complex mixtures, seemingly arising from

alkene isomerization (entry 6, Table 2-1). The mild conditions under which the addition proceeds and the ability to utilize readily available alkynes and pivaloate iminium ion precursors encouraged further exploration.

Table 2-1. Optimization of the intermolecular alkenylation of acyl-iminium ions to generate isoindolinones.



Entry	Substrate	Conditions	Yield (**2-49**, %)
1	**2-46**	i	trace[a]
2	**2-46**	ii	-
3	**2-46**	iii	43[b]
4	**2-47**	iii	30
5	**2-48**	iii	81
6	**2-48**	i	ND[a]

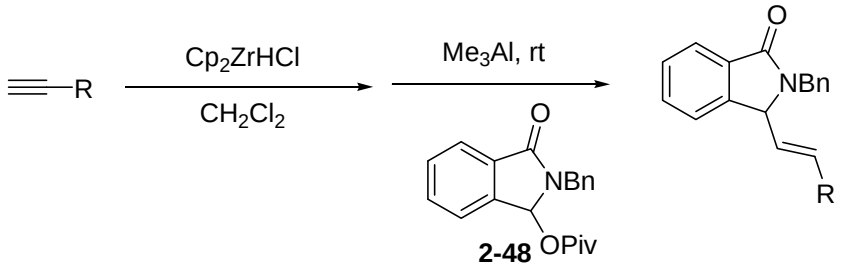
Reaction Conditions: (i) $AgClO_4$ (ii)Me_2Zn (iii) Me_3Al. [a] Product was formed as a mixture of alkene isomers. [b] Starting material observed after 12 h. ND = not determined.

Among the numerous methods known for the synthesis of substituted isoindolinones,[81] only a few examples of Heck-type coupling install an alkenyl moiety at the 3-position.[82] The synthesis of

isoindolinones presents significant opportunities for preparing biologically active molecules as well. Isoindolinones demonstrate a remarkably wide array of biological activities, including anti-inflammatory,[83] antihypertensive,[84] antipsychotic,[85] vasodilatory,[86] and antileukemic[87] effects.

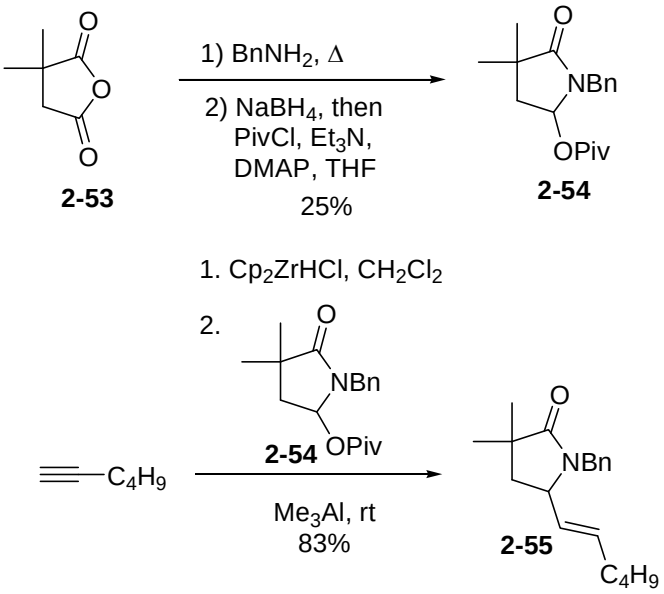
The modularity of the current approach warranted further investigation into the substrate scope of this process. As shown in Table 2-2, silyl ether, carbamate, and sulfonamide functionalities are well tolerated, generating functionalized isoindolinones in a high yielding, one-pot procedure.

Table 2-2. Addition of various alkenyl nucleophiles to generate isoindolinones.



Entry	**R** (alkyne)	**Product** [%]
1	C_4H_9	**2-49** [81]
2	*c*-C_6H_{11}	**2-50** [79]
3	$CH_2CH_2OTBDPS$	**2-51** [71]
4	$CH_2CH_2N(CO_2Me)Ts$	**2-52** [62]

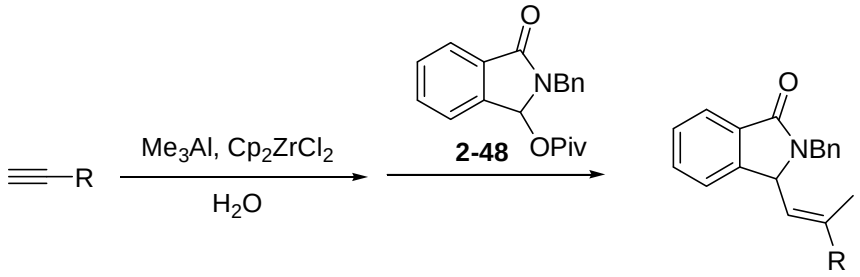
To further probe the scope of this reaction, succinimide-derived pivaloate **2-54** was synthesized from dimethyl succinic anhydride (**2-53**) and subjected it to the optimized conditions (Scheme 2-30). Addition product **2-55** was isolated in 83% yield which bodes well for the extension of the cyclic iminium ion alkenylation methodology toward a broad class of heterocyclic electrophiles.



Scheme 2-30. Preparation of **2-55**.

The use of trisubstituted alkenes was also investigated in this transformation. Although the lactam functionality had prevented an intramolecular addition, pre-forming the alkenylalane under water-accelerated conditions, followed by addition of **2-48**, provided isoindolinones **2-56** and **2-57** in 77% yield after only 15 minutes (Table 2-3).

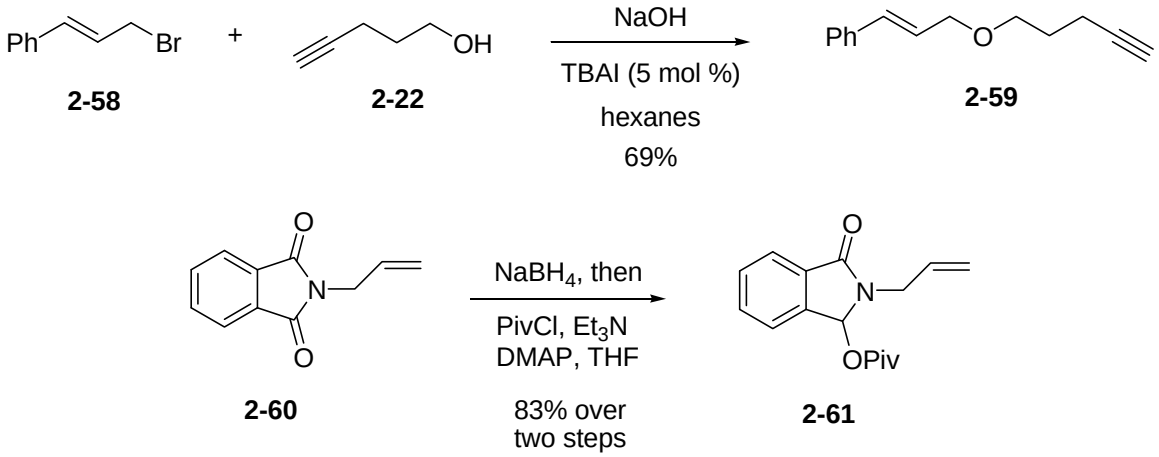
Table 2-3. Addition of trisubstituted alkenyl alanes to provide isoindolinones **2-56** and **2-57**.



Entry	R	Product [%]
1	C_4H_9	**2-56** [77]
2	Ph	**2-57** [77][a]

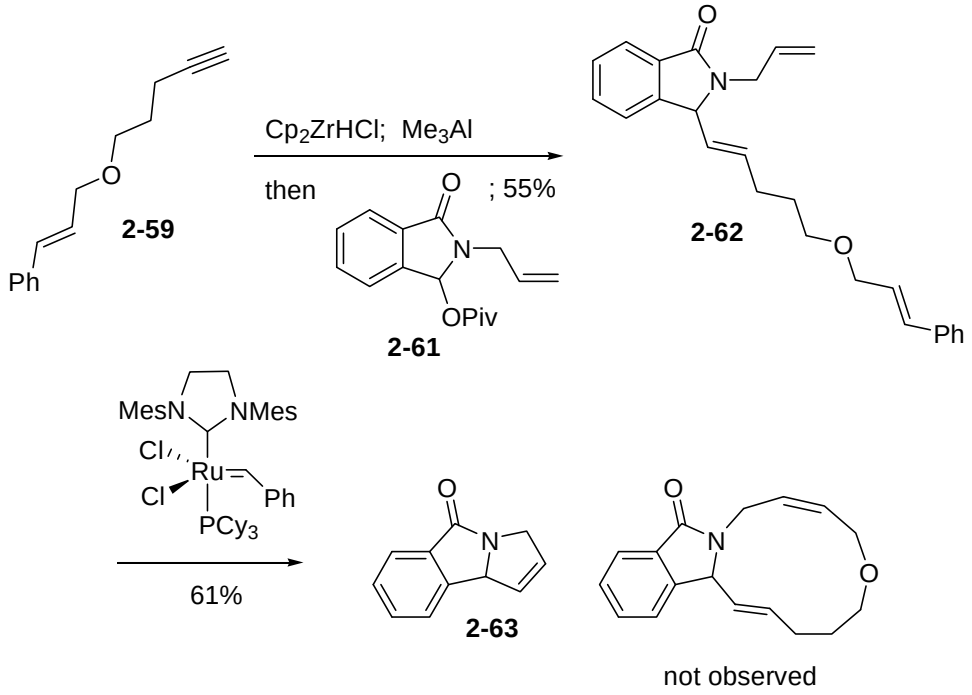
[a] Product contains ~5% of a carbometallation regioisomer.

Since this strategy provided a rapid access toward alkenyl-functionalized phthalimides, the initial goal of generating medium rings was revisited. As a model system, alkyne **2-59** was prepared by alkylation of alkynol **2-22**, and allyl-pivaloate **2-61** was synthesized using the standard method (Scheme 2-31).



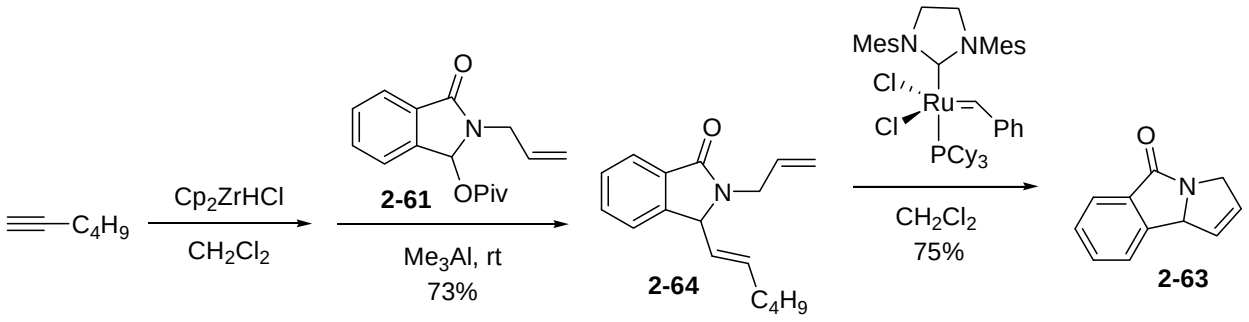
Scheme 2-31. Preparation of alkyne **2-59** and pivaloate **2-61.**

Subsequently, **2-60** and **2-61** were subjected to the hydrozirconation-transmetallation conditions to generate **2-62** in 55% yield accompanied by considerable amounts of methyl addition side product (Scheme 2-32). It should be noted that carboalumination of **2-59** failed and the rate of addition for the alkenylalane generated via the transmetallation reaction was retarded due to the presence of the ether functionality. With **2-62** in hand, conditions were screened to form the desired 12-membered macrocycle. Although ring closing metathesis methodology has been found to perform well for the synthesis of a variety of macrocycles,[88] a rapid formation of the undesired 5-membered ring **2-63** was observed.[89] Increasing dilution, change of metathesis catalyst, addition of $Ti(O^iPr)_4$,[90] or varying solvents did not influence the reaction pathway.



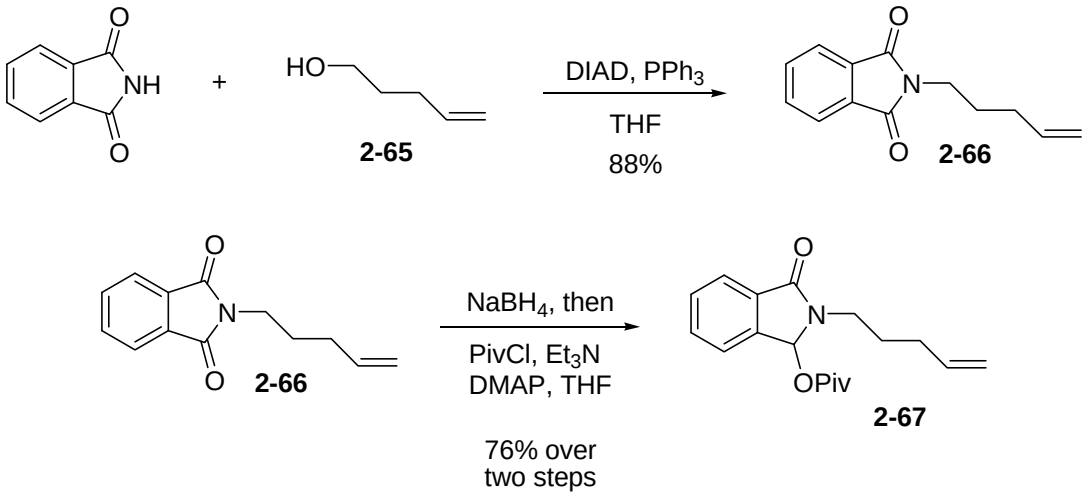
Scheme 2-32. Preparation of **2-62** and attempted macrocyclization via alkene metathesis.

Due to the ease of formation of pyrrolizidine **2-63**, a more generalized synthesis of this compound was explored. Addition of hexenylalane to **2-61** furnished diene **2-64**, which smoothly underwent the metathesis in 75% yield to furnish pyrrolizidine **2-63** (Scheme 2-33).



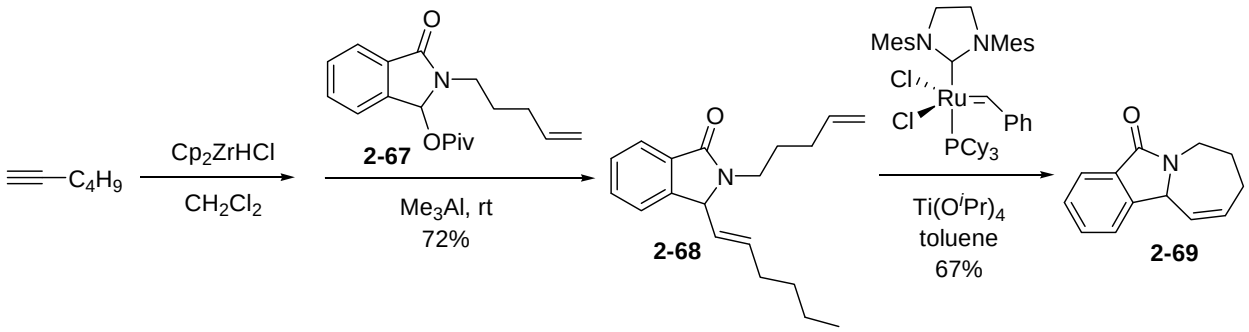
Scheme 2-33. Preparation of **2-63.**

To access the desired medium ring systems through this approach, imide **2-66** was prepared via Mitsunobu alkylation (Scheme 2-34). Reduction of **2-66** and acylation proceeded in 76% over the two steps to provide **2-67**.



Scheme 2-34. Preparation of pivaloate **2-67.**

The synthesis of fused azepines was achieved from indolinone **2-68**, prepared from **2-67** and 1-hexyne in 72% yield (Scheme 2-35). Ring closing metathesis of **2-68** proved to be problematic in CH_2Cl_2 with several ruthenium catalysts, yielding only starting material or decomposition products. Addition of $Ti(O^iPr)_4$ in toluene at room temperature resolved these issues and yielded 67% of **2-69**. Possible deactivation of the metathesis intermediate by the neighboring amide carbonyl could explain the difficulty in this transformation.[91] While not fully optimized, these reactions provide proof of concept for the conversion of our phthalimide substrates to structurally diverse tricyclic products.



Scheme 2-35. Synthesis of azepine **2-69** via ring-closing metathesis**.**

2.2.4 Conclusions

In situ generated alkenylalanes constitute versatile nucleophiles for additions to *N*-acyliminium ions. While direct intramolecular cyclization strategies suffer from inhibition of the carboalumination reaction by Lewis basic functional groups, preforming alkenylalanes via hydrozirconation-transmetallation or carboalumination and subsequent addition to the lactam acetal substrates yields functionalized isoindolinones. This method applies easily prepared or

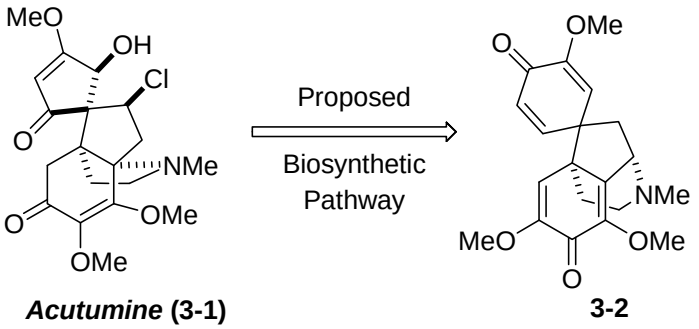
commercially available starting materials that provide opportunities for diversification at numerous points and yields synthetically useful heterocyclic products in a one-pot transformation. Further elaboration of the alkenyl heterocycles through the use of ring closing metathesis leads to tricyclic products that are common motifs in natural products and drug-like molecules.

3. SPRIOKETALS VIA OXIDATIVE REARRANGEMENT OF ENOL ETHERS

3.1 INTRODUCTION

3.1.1 Barton's Proposal for the Biosynthesis of Acutumine

Acutumine (**3-1**, Scheme 3-1) is a chlorinated tetracyclic alkaloid whose isolation was first reported in 1929.[92] Although the structure was initially misassigned, a series of chemical and X-ray structures established the correct structure of acutumine in 1967.[93]

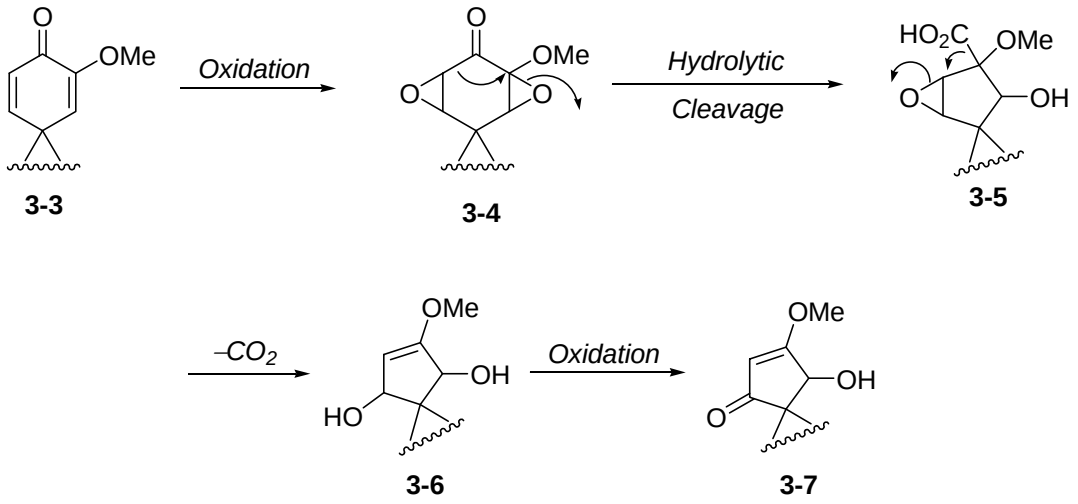


***Acutumine* (3-1)** **3-2**

Scheme 3-1. Barton's proposed biosynthetic precursor of acutumine **(3-1).**

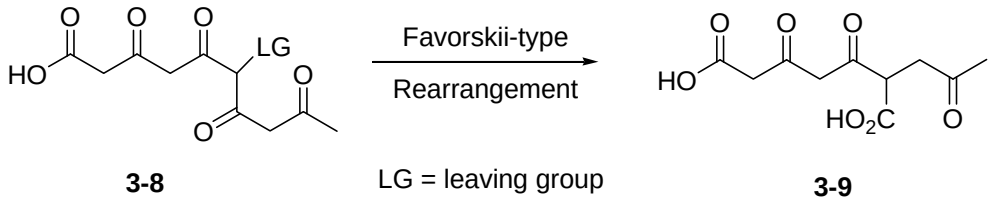
Shortly thereafter, Sir Derek Barton proposed a biosynthesis for the spiro-fused vinylogous ester moiety of acutumine.[94] In this proposal, Barton suggested spirodienone **3-2** as a possible biosynthetic branching point (Scheme 3-1). As shown in Scheme 3-2, Barton proposed that double epoxidation of **3-3** followed by a hydrolytic Favorskii-type rearrangement would give acid **3-5**.

Decarboxylation and epoxide opening affords allylic diol **3-6**, which is only a single oxidation level below vinylogous ester **3-7**.



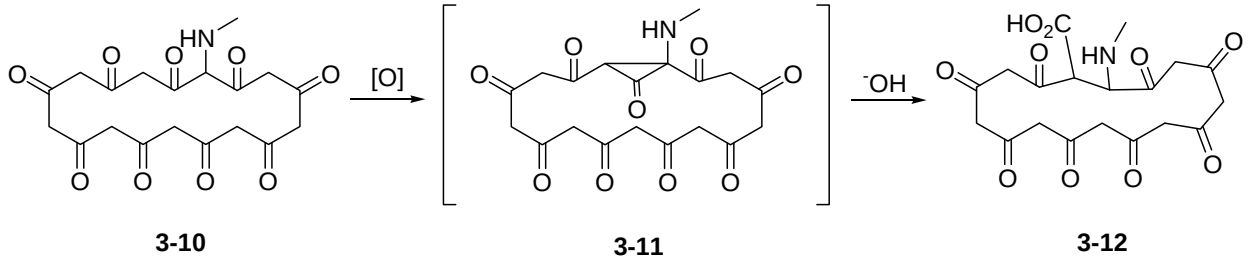
Scheme 3-2. Proposed mechanistic conversion of **3-3** to **3-7**.

Barton's proposal contained several interesting components, including the Favorskii-type ring contraction. At the time of publication, it was the first proposed Favorskii rearrangement in a biosynthesis. Since Barton's proposal, the Favorskii rearrangement has rarely been proposed in biosynthetic sequences, and has therefore been controversial. In 1975, the Favorskii rearrangement was proposed by Simpson during the biosynthesis of pyrone containing polyketides. For example, a polyketide such as **3-8** with a non-specified leaving group (LG) was proposed to undergo a hydrolytic Favorskii-type rearrangement to furnish the branched polyketide **3-9** (Scheme 3-3).[95]



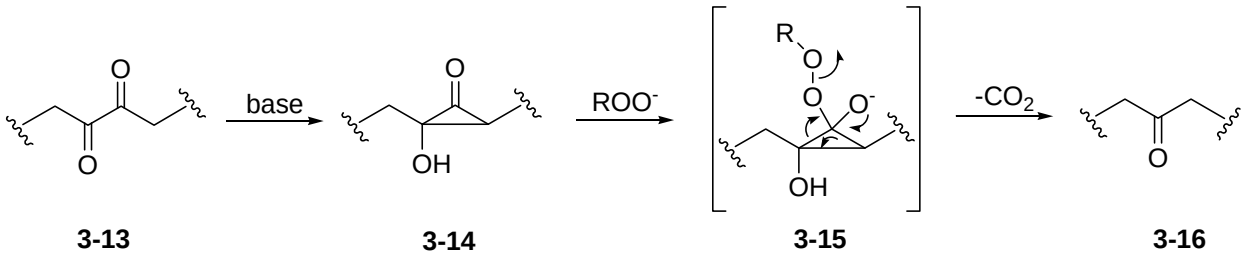
Scheme 3-3. Proposed Favorskii-type rearrangement to generate branched polyketides.

A similar rearrangement was postulated by Kakinuma to account for the unusual 17-membered carbocyclic ring system in the lankacidin anitibiotics. Macrocycle **3-10** was proposed to undergo a non-specific oxidation to the cyclopropanone intermediate **3-11**, which would be opened with hydroxide to effect a one-carbon ring contraction and furnish acid **3-12** (Scheme 3-4).[96]



Scheme 3-4. Proposed Favorskii-type rearrangement to effect ring contraction in a polyketide.

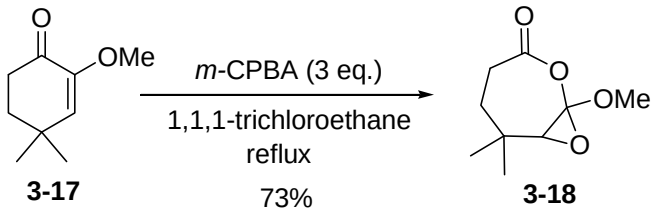
The Favorskii-type rearrangement has recently been proposed by Wright to account for carbon deletions in the biosynthesis of the polyketide shellfish toxins DTX-1 and DTX-2. Wright proposed that an α-diketone, such as **3-13**, would undergo intramolecular closure to furnish cyclopropanone **3-14** (Scheme 3-5).[97] Attack by a peroxide and collapse of the peroxy-ketal **3-15** generates ketone **3-16** after the extrusion of CO_2.



3-13 **3-14** **3-15** **3-16**

Scheme 3-5. Wright's proposed Favorskii-type rearrangement to effect carbon deletion in polyketide natural prouducts.

Barton's proposal represented a key unsolved problem (or unconfirmed proposal) in natural product chemistry. Combined with our interest in densely oxygenated natural products, we began investigations into this hypothesis. An examination of the literature reveals a previous attempt to model the Barton proposal in 1984. The Matoba group treated enone **3-17** with *m*-CPBA in refluxing trichloroethane and assigned the product as **3-18** (Scheme 3-6).[98] Based on the results presented herein, it appears that compound **3-18** was incorrectly assigned.

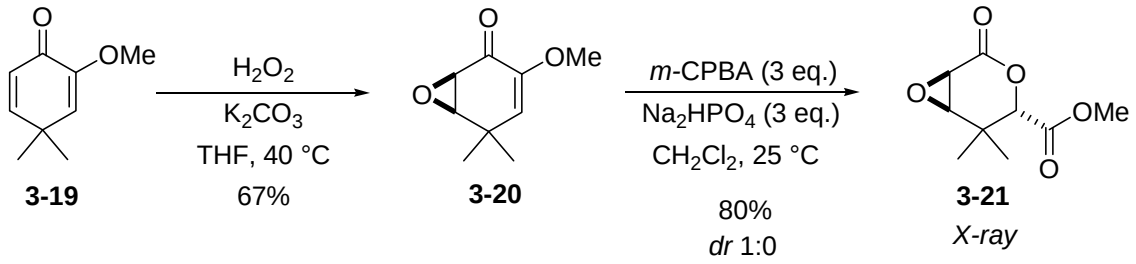


3-17 **3-18**

Scheme 3-6. Attempted modeling of Barton's proposal by Matoba.

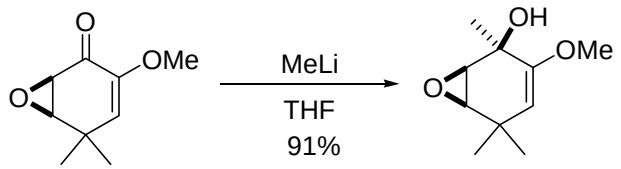
3.2 RESULTS AND DISCUSSION

Due to the ready access to dienones of type **3-3** in Barton's proposed biosynthesis,[99] this hypothetical ring contraction provides an attractive entry to the acutumine skeleton. Our first approach to model this proposal began with dienone **3-19** (Scheme 3-7). Epoxidation of **3-19** provided epoxyketone **3-20**, a theoretical intermediate in Barton's proposed biosynthesis. When **3-20** was treated with 3 equivalents of *m*-CPBA buffered by Na_2HPO_4, we expected that the intermediate bis-epoxide would undergo Barton's proposed cascade, however we isolated only epoxy lactone **3-21** in 80% yield as a single diastereomer, which was characterized by X-ray crystallography. It was determined that the crude diastereoselectivity of the reaction in the absence of a basic workup was only 2:1, although this mixture equilibrated to a single diastereomer after washing with aqueous $NaHCO_3$.



Scheme 3-7. Preparation of model epoxy ketone **3-20** and attempted rearrangement.

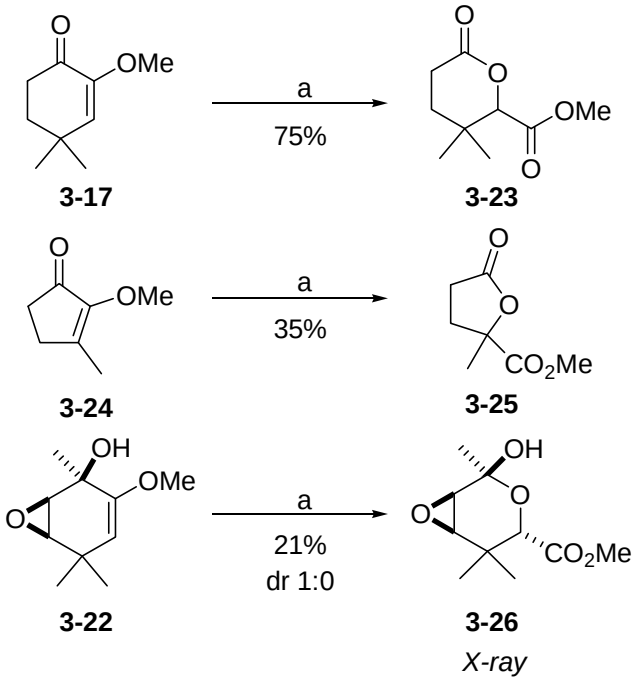
In order to prepare another substrate for experimentation, epoxy alcohol **3-22** was prepared from intermediate **3-20** by the addition of MeLi, which proceeded in 91% yield (Scheme 3-8). With a small collection of substrates in hand, the scope of the oxidative rearrangement was probed.



3-20 **3-22**

Scheme 3-8. Preparation of ketone **3-22.**

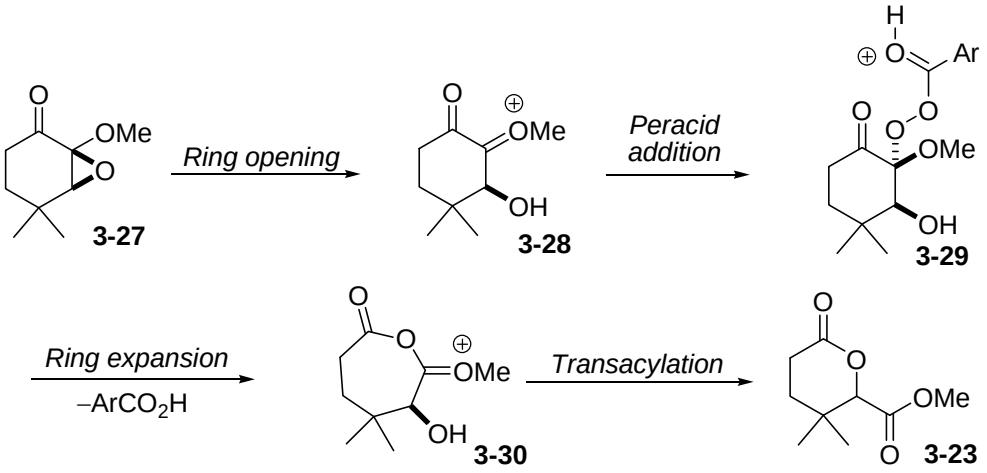
Enone **3-17** lacking the epoxide underwent rearrangement to lactone **3-23** in 75% yield, while five-membered enone **3-24** was converted to lactone **3-25** in only 35% yield, although the reaction does generate a tetrasubstituted carbon (Scheme 3-9).[100] To ascertain whether the carbonyl functionality was needed to facilitate rearrangement, **3-22** was submitted to the oxidative rearrangement and was converted to hemiacetal **3-26** in only 21% yield as a single diastereomer, which was characterized by X-ray crystallography. The above preliminary results were obtained by Corey R. J. Stephenson while working as a graduate student in the Wipf group.



Conditions: (a) *m*-CPBA (3 eq.), Na_2HPO_4 (3 eq.), CH_2Cl_2, 18h.

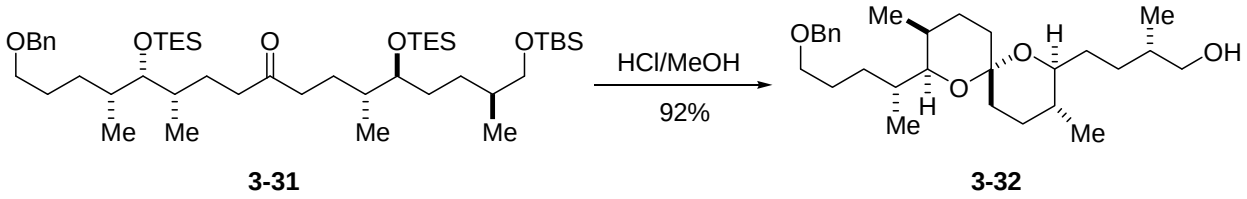
Scheme 3-9. Examples of oxidative rearrangement of enol ethers.

A proposal for the oxidative rearrangement of **3-17** is outlined in Scheme 3-10. The epoxy ether intermediate **3-27** opens to the alkoxycarbenium ion **3-28** in the presence of a proton donor. This species is then intercepted by another equivalent of peracid to give peroxy ketal **3-29**. A methyl ether assisted acyl shift generates the seven-membered lactone **3-30** which can undergo a ring contraction to generate the product lactone ester **3-23**, which is epimerizable at the α-position to the ester moiety, resulting in the thermodynamically more stable equatorial ester after basic workup and isolation. This sequence constitutes a net addition of two oxygen atoms concomitant with a skeletal rearrangement.[101]



Scheme 3-10. Proposed mechanism for oxidative rearrangement of enol ethers.

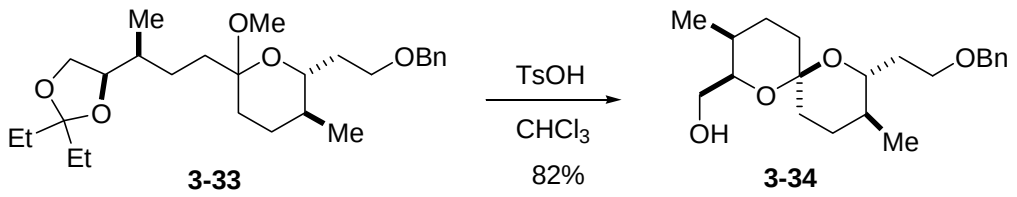
Due to their occurrence in many biologically active molecules,[102] the potential formation of acetals and ketals such as **3-18** appeared to offer convenient access to these motifs. There are several known methods for the formation of spiroketals,[103] many based on the cyclization of hydroxy ketones. For example, in Marshall's synthesis of a fragment of tautomycin, ketone **3-31** was converted through in-situ deprotection of the silyl ethers and subsequent intramolecular ketalization to **3-32** in 92% yield (Scheme 3-11).[104]



Scheme 3-11. Acid-promoted tandem deprotection-ketalization by Marshall.

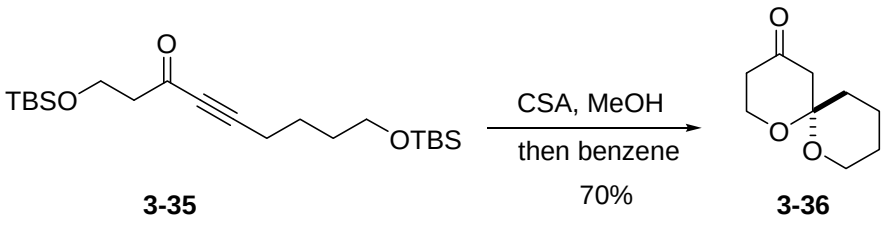
A similar method was used by Kiyota's group during their approach to spirofungins A and B.[105] When bisketal **3-33** was subjected to acidic conditions, the deprotected secondary hydroxy

group underwent transketalization in 82% overall yield to furnish the spiroketal **3-34** as the major product (Scheme 3-12).



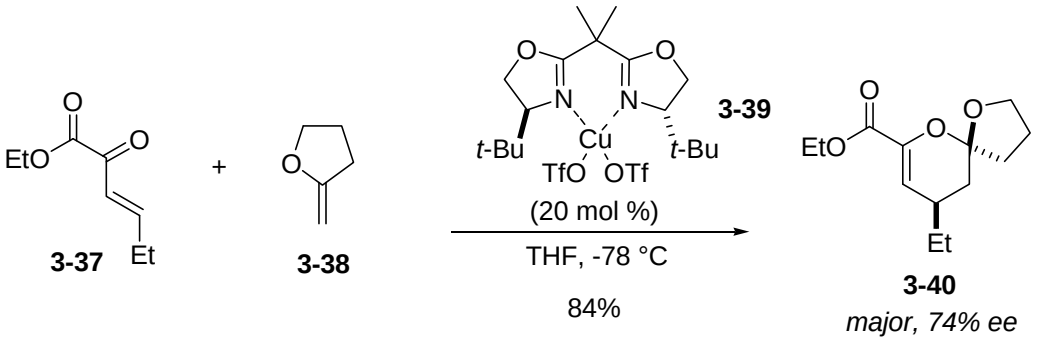
Scheme 3-12. Acid-promoted transketalization to form **3-34** by Kiyota**.**

Forsyth and co-workers took a different approach during their approach to a family of fly phermones.[106] For example, ketone **3-35** was treated with CSA in methanol to induce deprotection of the silyl ethers (Scheme 3-13). A solvent switch to benzene facilitated double Michael addition of the hydroxy groups to provide the spiroketal **3-36** in 70% yield.



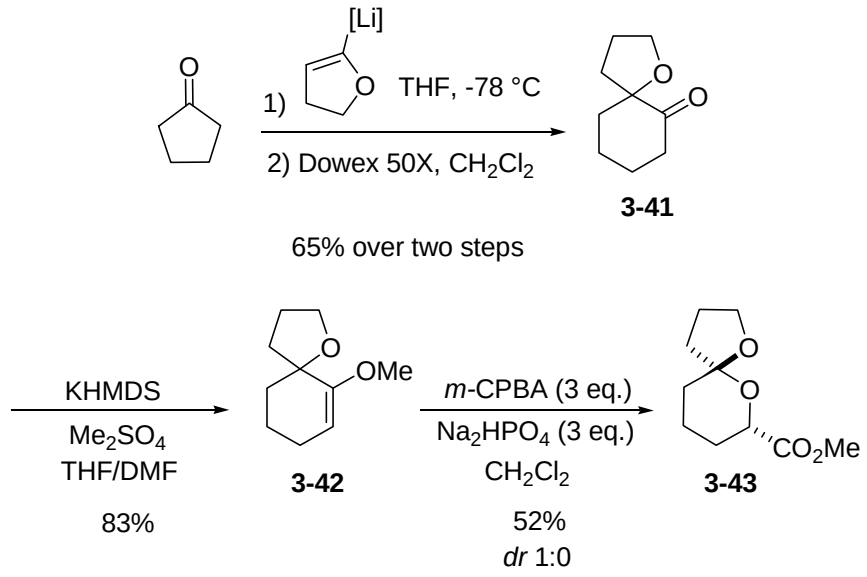
Scheme 3-13. Tandem Michael addition to form ketal **3-36** by Forsyth**.**

Although many ketalization methods proceed under dehydrating or oxidative conditions, Jorgenson and co-workers have reported a hetero Diels-Alder pathway mediated by copper catalysis.[107] Upon treatment with chiral copper catalyst **3-39**, ketoester **3-37** and vinyl ether **3-38** underwent cycloaddition in 84% yield to provide ester **3-40** as the major product in 74% ee (Scheme 3-14). The epimer at the ketal center constituted the remaining material.



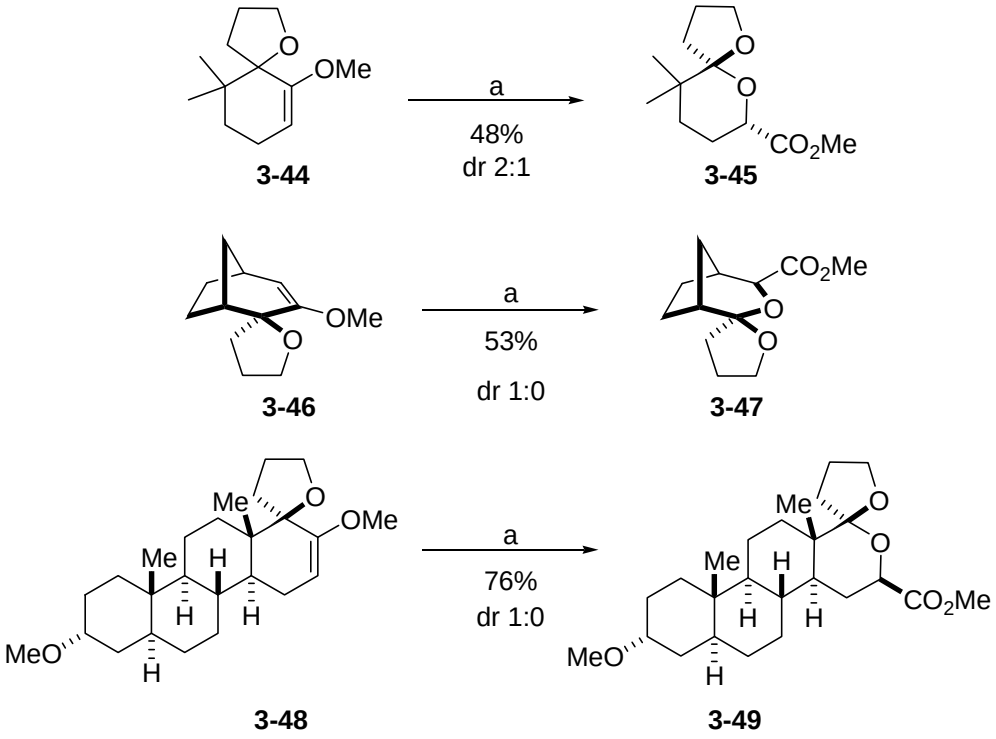
Scheme 3-14. Copper-catalyzed enantioselective cycloaddition to form ketal **3-40** by Jorgenson**.**

Although the oxidative rearrangement of **3-22** proceeded in low yield (as shown in Scheme 3-9), it was hypothesized that masking the free alcohol as a cyclic ether would improve the efficiency of the reaction by avoiding the formation of sensitive hemiacetals. Toward this end, cyclopentanone was treated with 5-lithio-2,3-dihydrofuran according to a protocol by Paquette,[108] which furnished an intermediate tertiary allylic alcohol which could be rearranged under acidic catalysis to the spirocyclic ketone **3-41** in 65% yield overall (Scheme 3-15). At this stage, all that was required to set up the oxidative rearrangement was O-alkylation of the corresponding enolate of **3-41**. Following treatment with KHMDS, addition of DMF and dimethylsulfate furnished the methyl enol ether **3-42** in 83% yield. When **3-42** was submitted to the oxidative rearrangement, the volatile spiroketal **3-43** was obtained as the sole product in 52% yield.



Scheme 3-15. Preparation of spiroether **3-42** and rearrangement to spiroketal **3-43.**

Seeking to expand this spiroketal methodology, methyl enol ethers **3-44**, **3-46** and androsterone-based **3-48** were prepared in an identical fashion to **3-42**.[109] When **3-44** was submitted to the rearrangement, volatile spiroketal **3-45** was isolated in 48% yield as a modest 2:1 mixture of diastereomers (Scheme 3-16). Methyl enol ether **3-46** smoothly underwent rearrangement in 53% yield, and **3-47** was isolated as a single diastereomer. Additionally, **3-48** was converted to pentacyclic spiroketal **3-49** in 76% yield as a single diastereomer. The configurations of **3-45**, **3-47**, and **3-49** were assigned in analogy to **3-21** and **3-26**, which were characterized by X-ray analysis.

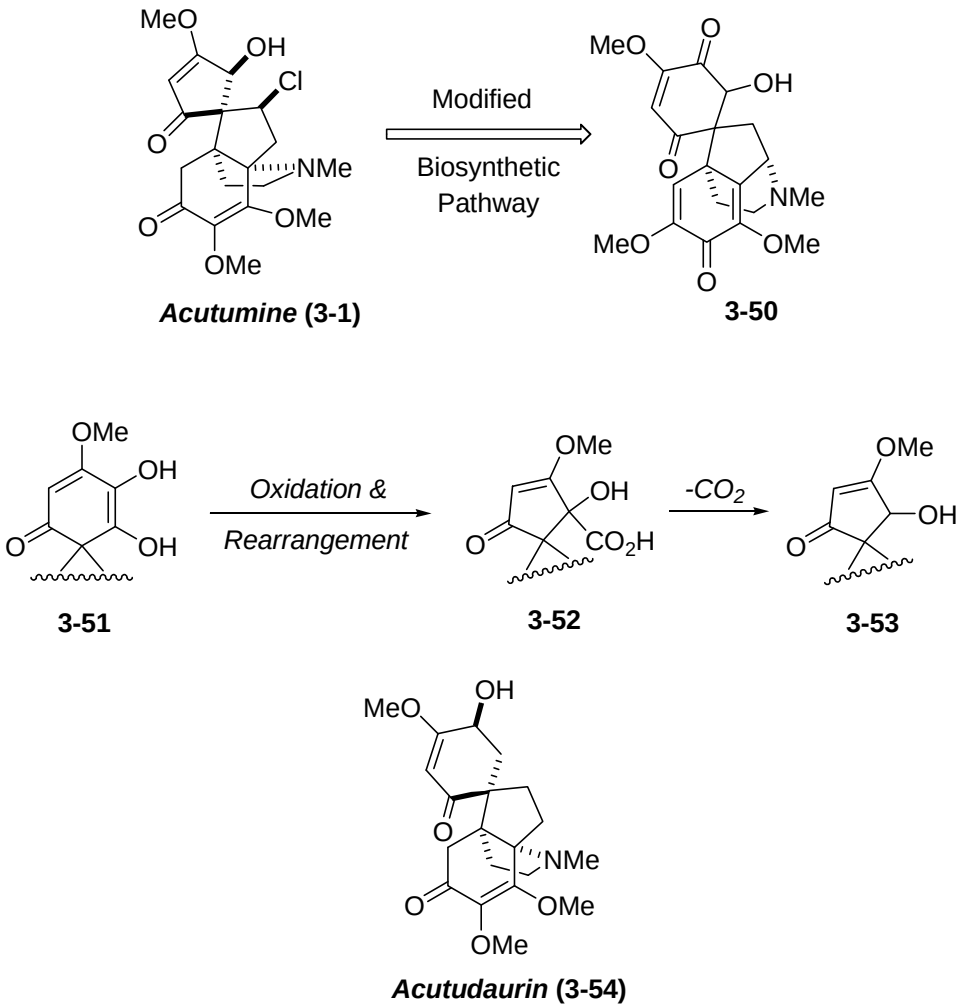


Conditions: (a) *m*-CPBA (3 eq.), Na_2HPO_4 (3 eq.), CH_2Cl_2, 18h.

Scheme 3-16. Oxidative rearrangement of various enol ethers to spiroketals.

In conclusion, an efficient oxidative rearrangement of alkyl enol ethers to lactone and spiroketal esters has been demonstrated. This method allows rapid access to these common structural subunits under relatively mild conditions. Although this investigation was inspired by Barton's proposal for the biosynthesis of acutumine, no experimental support for the dienone diepoxide rearrangement was achieved. It appears that α-epoxy ethers of type **3-27** prefer alternative rearrangements to a migratory ring contraction. The recent isolation of acutudaurin (**3-54**, Scheme 3-17),[110] a possible precursor of acutumine-type natural products, lends support to a modified biosynthetic pathway. As shown in scheme 3-17, the tricarbonyl tyrosine dimer **3-50** can be envisioned as a direct precursor of acutumine (**3-1)** after oxidation and benzilic acid rearrangement (**3-51** to **3-52**), followed by decarboxylation to generate the cyclopentanone subunit

3-53. This pathway is supported by experimental observations in the literature,[111] and the oxygenation pattern on spirocycle **3-54** is in good agreement with the structure of acutudaurin.



***Acutumine* (3-1)** **3-50**

3-51 **3-52** **3-53**

***Acutudaurin* (3-54)**

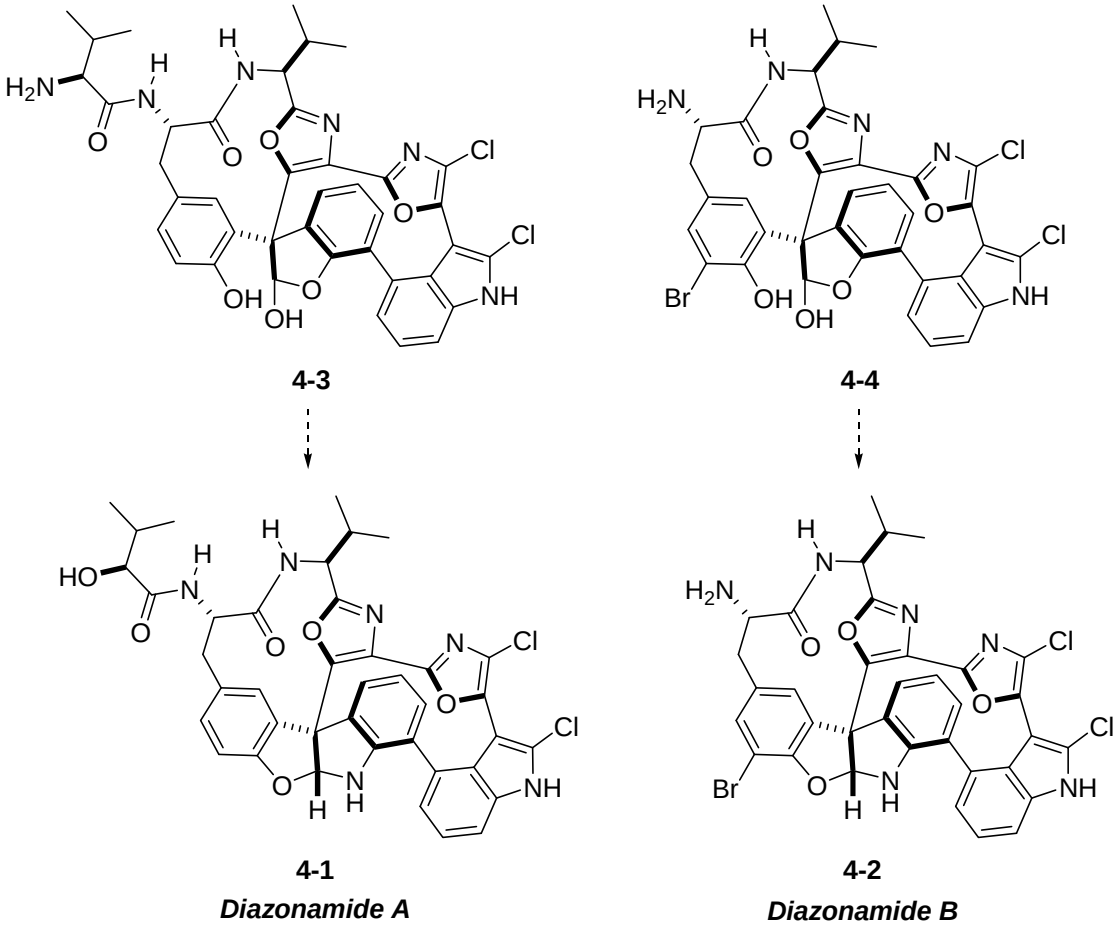
Scheme 3-17. Revised biosynthetic proposal for acutumine (**3-1**)**.**

4. TOTAL SYNTHESIS OF DIAZONAMIDE A

4.1 INTRODUCTION

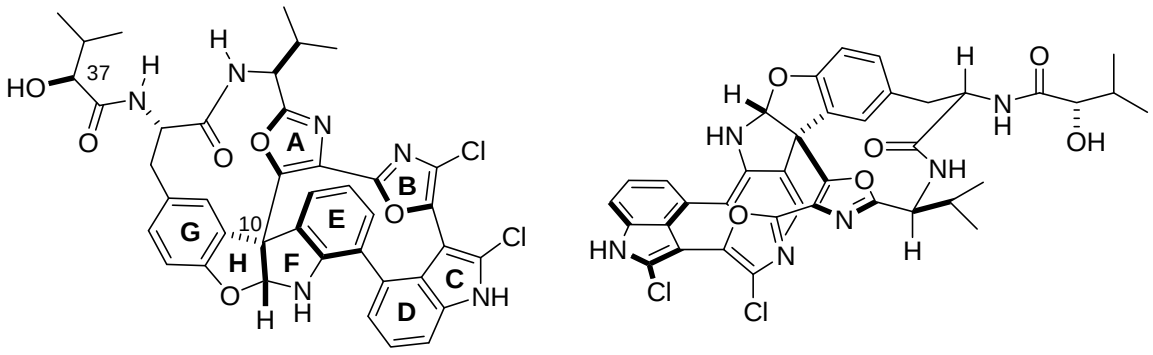
4.1.1 Isolation and Structure

The diazonamides (**4-1** and **4-2**, Scheme 4-1) were isolated in 1991 from *Diazona angulata*, a rare marine ascidian found in the coastal caves of Siquijor island, Philippines.[112] The structure of diazonamide A was assigned as **4-3** by ^{1}H NMR analysis and spectral similarity to diazonamide B (**4-2**). The first and only synthesis of **4-3** was reported 10 years later by Harran and revealed a structural misassignment.[113] Harran then proposed **4-1** as the correct structure of diazonamide A based on the reported X-ray data and ^{1}H NMR studies of related compounds.[114] Nearly two years later, Nicolaou reported the first total synthesis of diazonamide A, and confirmed **4-1** as the correct structure.[115]



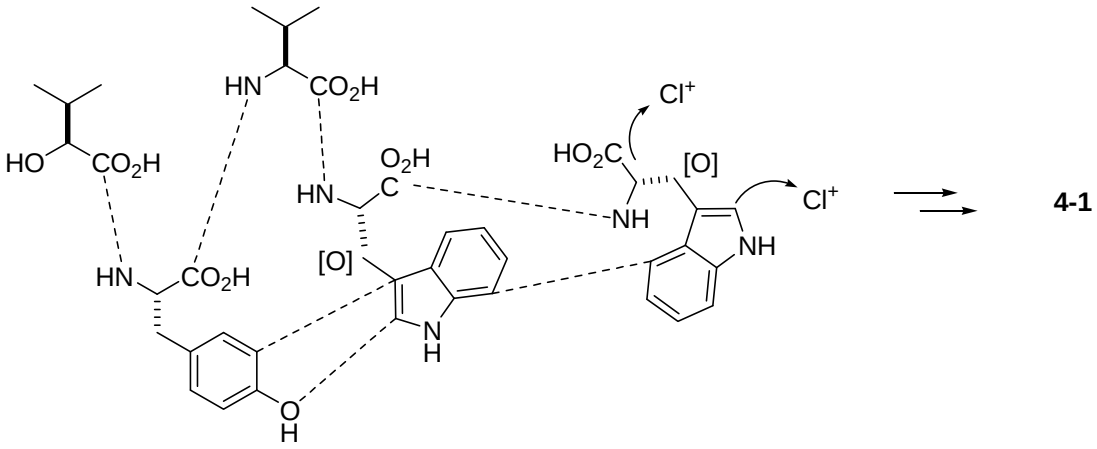
Scheme 4-1. Originally proposed and revised structures of diazonamide A and B.

The diazonamides possess unique structures which include ten rings spanning two macrocyclic domains (Scheme 4-2). These domains are anchored by the C10 quaternary center, which lies deep within the core of the molecule. Three biaryl bonds link together the lower polyaromatic domain that exists as a single atropisomer. Additionally, the diazonamides were the first natural products isolated to contain the bis-indole, bis-oxazole motif.



Scheme 4-2. Ring lettering and perspective view of diazonamide A.

As part of his structural reassignment, Harran suggested a biosynthetic pathway for **4-1**.[115] The complex structure of diazonamide A was proposed to be derived from five simple components, along with multiple oxidation state changes (Scheme 4-3).

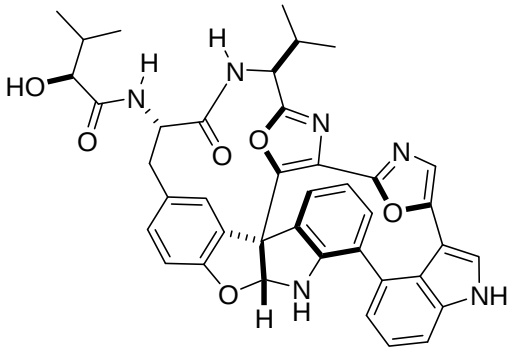


Scheme 4-3. Biosynthetic origin of diazonamide A as proposed by Harran.

4.1.2 Biological Activity

Diazonamide A possesses not only a tremendously complex structure, but is also significantly cytotoxic. Initial assays revealed IC_{50} values against HCT-116 human colon carcinoma and B-16 murine melanoma cell lines of less than 15 ng/mL, with diazonamide B less potent.[113] Assays at the National Cancer Institute indicated that diazonamide A had a mean GI_{50} of 4.9 nM against a standardized panel of human cancer cell lines.[114] Cruz-Montseratte reported detailed studies which indicated that **4-1** arrests cells at the G2/M phase of the cell cycle through inhibition of tubulin assembly.[116] The Nicolaou group also tested diazonamide A (and its C37 epimer) against six human cancer cell lines, four of which were standard: 1A9 human ovarian carcinoma, PC-3 human prostate carcinoma, MCF-7 human breast carcinoma, and A549 human lung carcinoma.[117] Two were drug-resistant cell lines from 1A9 parental cells, one with a multidrug resistant phenotype due to high expression of the drug-efflux pump P-glycoprotein (PGP) and the other Taxol-resistant because of an acquired β-tublin mutation. Diazonamide A demonstrated IC_{50} values of 2-5 nM against every cell line except the multidrug resistant cell line, suggesting that diazonamide is a substrate for PGP. The C37 epimer of diazonamide was 3- to 5-times less potent. Interestingly, diazonamide A and its C37 epimer were active against the taxol-resistant cell line, suggesting that diazonamide had a binding site on tublin distinct from taxol. Recently, Harran reported that diazonamide A blocks mitotic spindle assembly through binding to ornithine δ-amino transferase (OAT).[118] To confirm the mechanism, it was demonstrated using RNAi that OAT knockdown "blocks cell division and causes cell death, the effects largely phenocopying diazonamide A treatment". This study revealed a new role for OAT in mitosis and makes it a target for drug development.

Harran has also reported that diazonamide analog **4-7**, which lacks chlorination, is as potent as diazonamide A against multiple cancer types, yet displays no toxicity (Scheme 4-4).[119] Analog **4-7** demonstrated anti-cancer activity in animals with xenografted tumors that was comparable to taxanes or vinca alkaloids. Mice treated with **4-7** demonstrated no weight loss, no change in appearance, and no evidence of white-blood cell loss. This exciting result suggests that **4-7** could have potential in a clinical setting.



4-7

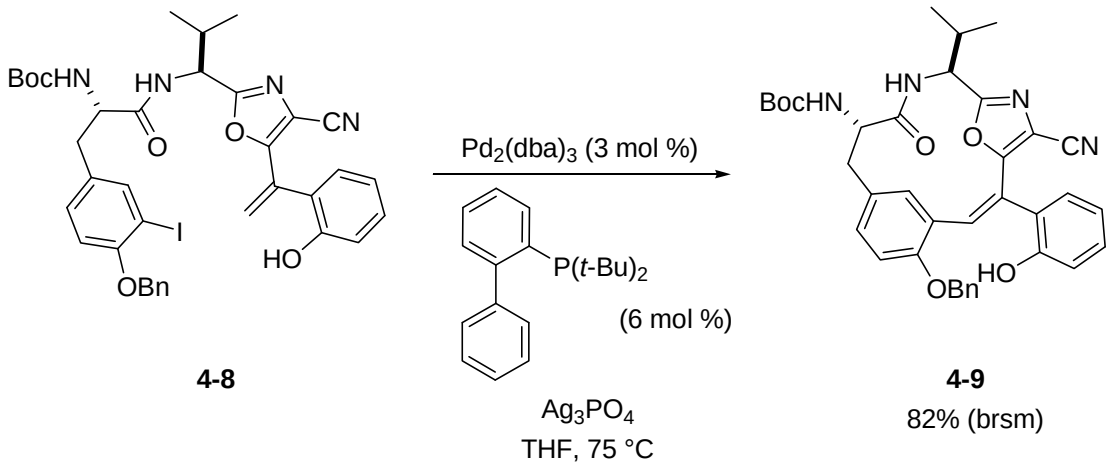
Scheme 4-4. Diazonamide analog developed by Harran.

4.1.3 Previous Total Syntheses

Diazonamide attracted the attention of the synthesis community immediately, and several groups have reported progress toward its total synthesis.[120] Despite this intense effort, only two groups have reported successful total syntheses, and one has reported a formal synthesis. Only the work resulting in total (or formal) syntheses will be addressed here.

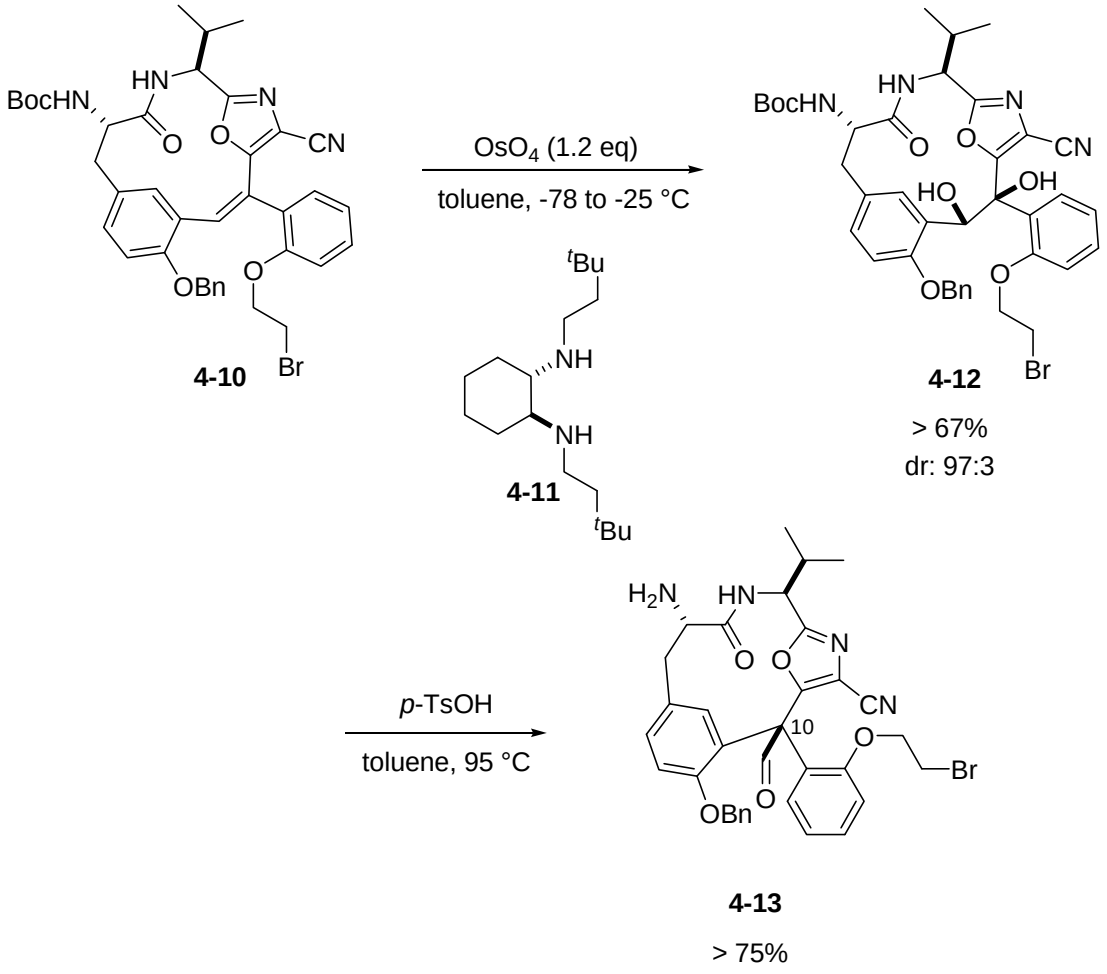
The Harran group approached the originally proposed structure of diazonamide by utilizing a Heck macrocyclization to construct triarylalkene **4-9** from **4-8** (Scheme 4-5). This brought together

the components of diazonamide's macrolactam ring, but still required some skeletal rearrangement to install the C10 quaternary center.



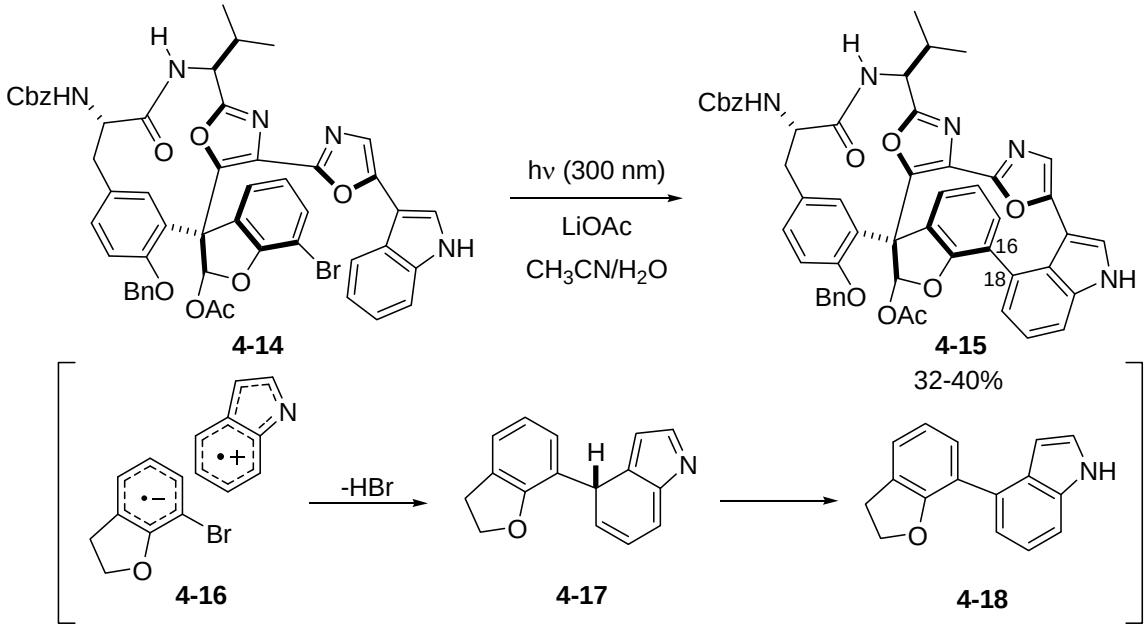
Scheme 4-5. Macrocyclic Heck cyclization utilized during Harran's synthesis of the originally proposed structure of diazonamide A.

Following protection of the free phenol, Harran dihydroxylated alkene **4-10** to provide diol **4-12** in excellent yield and diastereoselectivity (Scheme 4-6).[114] Treatment of diol **4-12** with *p*-TsOH in toluene initiated a ring-contracting pinacol rearrangement to furnish aldehyde **4-13**, containing the proper architecture required for the macrolactam region of diazonamide.



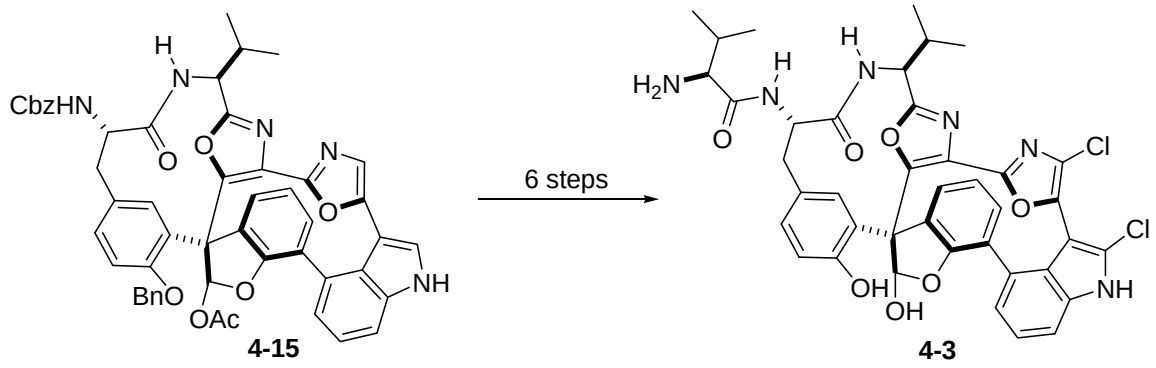
Scheme 4-6. Key dihydroxylation and pinacol rearrangement in Harran's total synthesis of the originally proposed structure of diazonamide A.

After converting aldehyde **4-13** to indole-containing **4-14**, Harran utilized a photochemical Witkop-type cyclization to forge the C16-C18 bond in ~ 35% yield (Scheme 4-7). This transformation is proposed to proceed through intermediates **4-16** and **4-17**, with a final aromatization to furnish the product. This operation completed the polyaromatic lower domain of diazonamide and provided a unique approach to the biaryl linkage between the D and E rings of diazonamide.



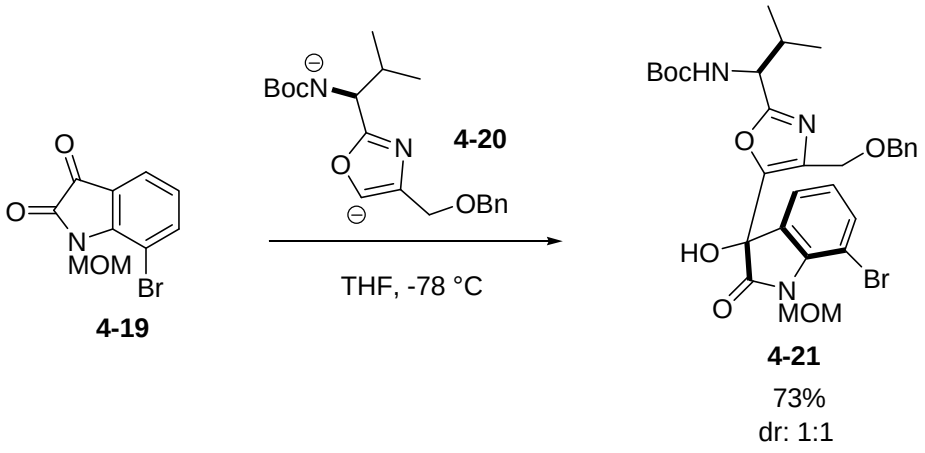
Scheme 4-7. Witkop-type cyclization developed by Harran to form C16-C18 bond.

Harran converted **4-15** to the proposed structure for diazonamide A through 6 steps (Scheme 4-8). Upon completion, **4-3** neither matched the reported data for diazonamide nor was stable for significant periods of time. Upon comparison of the reported spectral data for diazonamide as well as the X-ray data, Harran proposed **4-1** (See Scheme 4-1) as the correct structure of diazonamide A.[115] Once again, a total synthesis of **4-1** would be required to confirm this assignment.



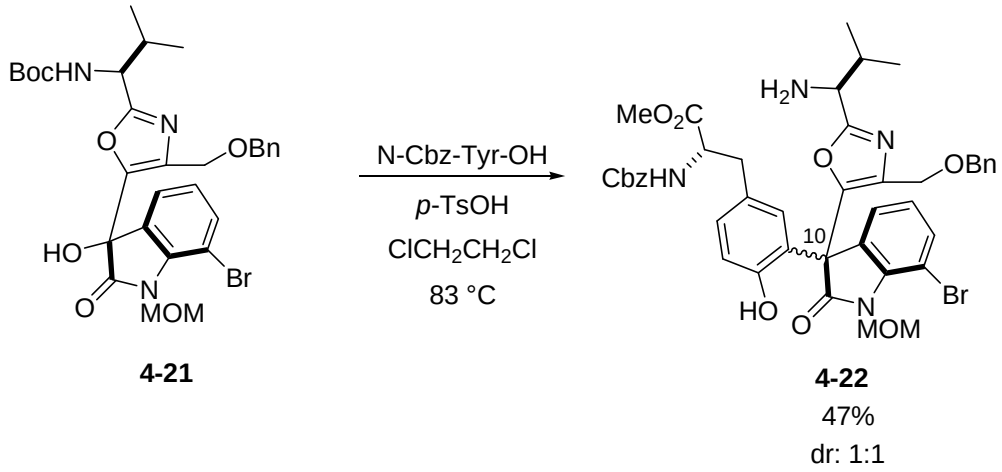
Scheme 4-8. Final conversion of Witkop product **4-15** to the originally proposed structure of diazonamide A.

The Nicolaou group had been working towards diazonamide when the structure revision was published by Harran. A revised strategy toward the complex elements of the diazonamide skeleton began by adding oxazole dianion **4-20** to isatin **4-19**, which proceeded in 73% yield and provided a 1:1 mixture of diastereomers (Scheme 4-9).[116]



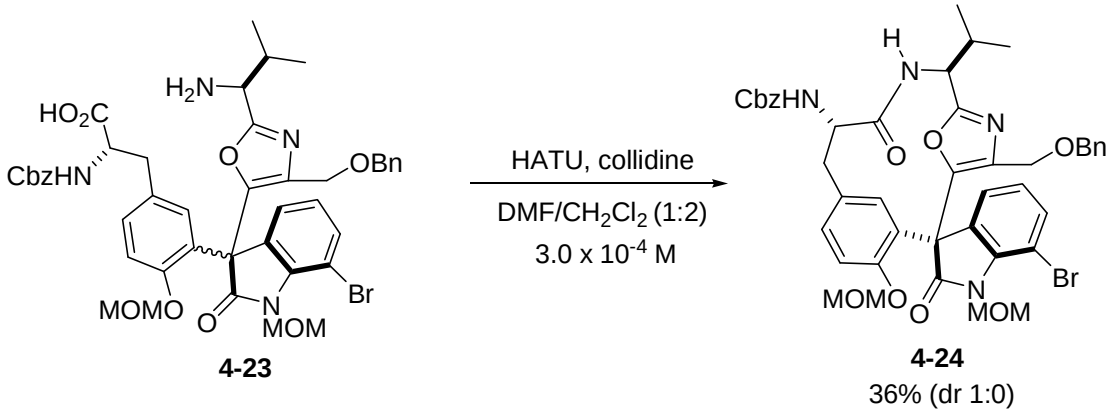
Scheme 4-9. Formation of key tertiary alcohol **4-21** in Nicolaou's first total synthesis of diazonamide A.

Upon treatment with p-TsOH, a mixture of tertiary alcohol **4-21** and *N*-Cbz-Tyr-OMe furnished triaryl lactam **4-22** in 47% yield and as a 1:1 mixture of diastereomers (Scheme 4-10). This transformation installed the critical C10 quaternary center, although only half of the material had the configuration required for the natural product.



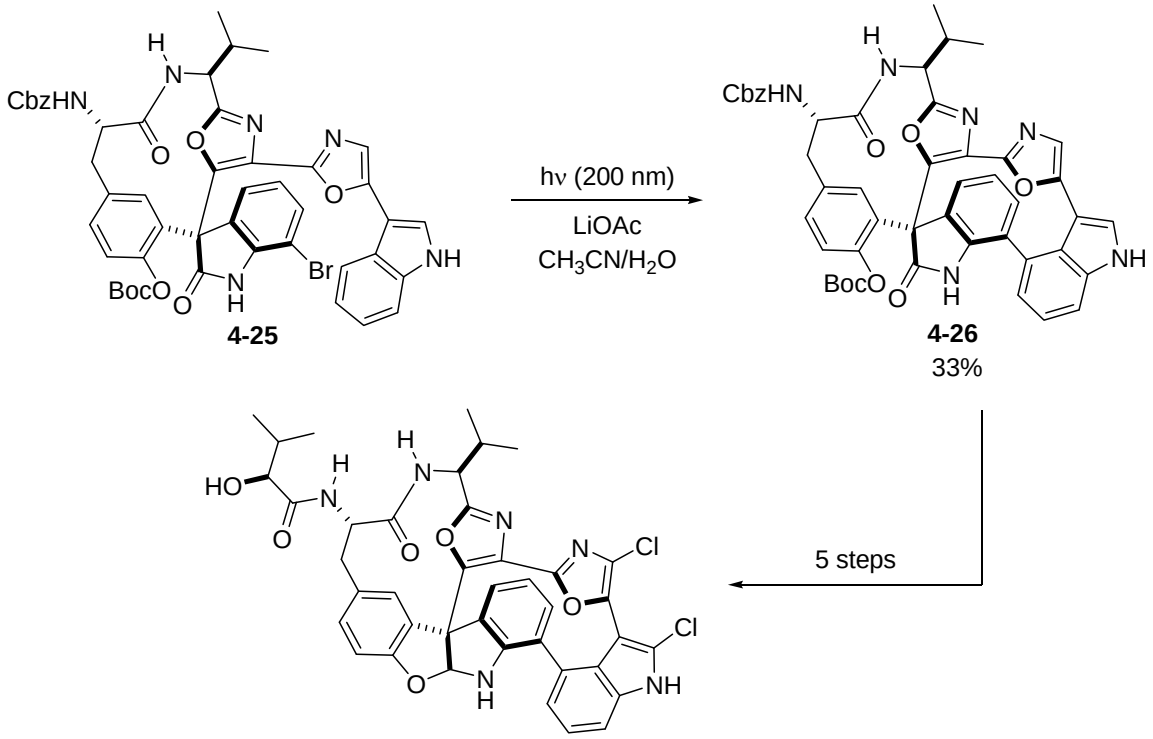
Scheme 4-10. Formation of C10 center during Nicolaou's first total synthesis of diazonamide A.

Having installed diazonamide's C10 center, Nicolaou then turned to closing the macrolactam region of the molecule. With amino acid **4-23** in hand, macrocyclization proceeded in 36% yield, since only the correct diastereomer required for diazonamide cyclized (Scheme 4-11). Material containing the incorrect configuration was reported to dimerize or oligomerize.



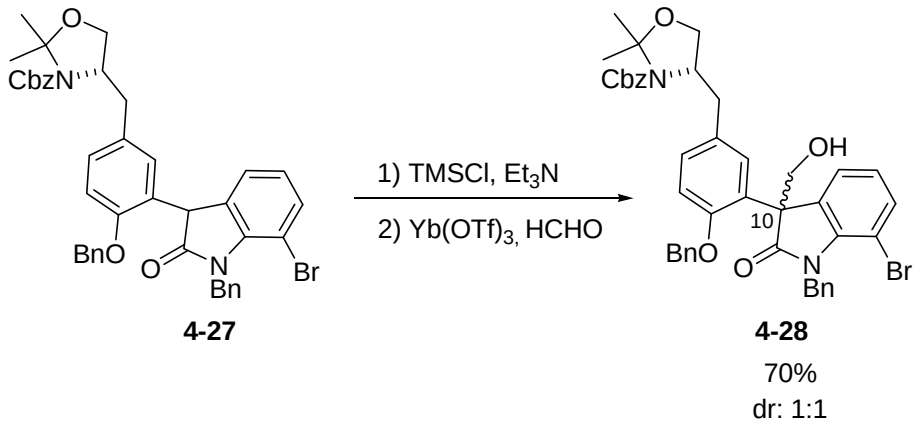
Scheme 4-11. Macrolactamization in Nicolaou's first total synthesis of diazonamide A.

With one of the major domains in place, Nicolaou turned to Harran's method to form the lower, polyaromatic domain. Compound **4-25**, when irradiated at 200 nm, underwent the Witkop-type cyclization to furnish **4-26** in 33% yield (Scheme 4-12). The low yield reflects the highly strained nature of the large rings being formed. After 5 more straightforward steps, the Nicolaou group completed the first total synthesis of diazonamide A, confirming Harran's revised structure (**4-1**).



Scheme 4-12. Nicolaou's use of Witkop-type cyclization to form lower macrocycle and completion of diazonamide A.

Shortly after the Nicolaou group confirmed the assignment of diazonamide A, they reported another approach which also resulted in a successful total synthesis.[121] The key C10 quaternary center was formed through a two-step hydroxymethylation of oxindole **4-27** (Scheme 4-13). As in their first synthesis, the Nicolaou group chose to form the C10 center in a non-selective fashion.



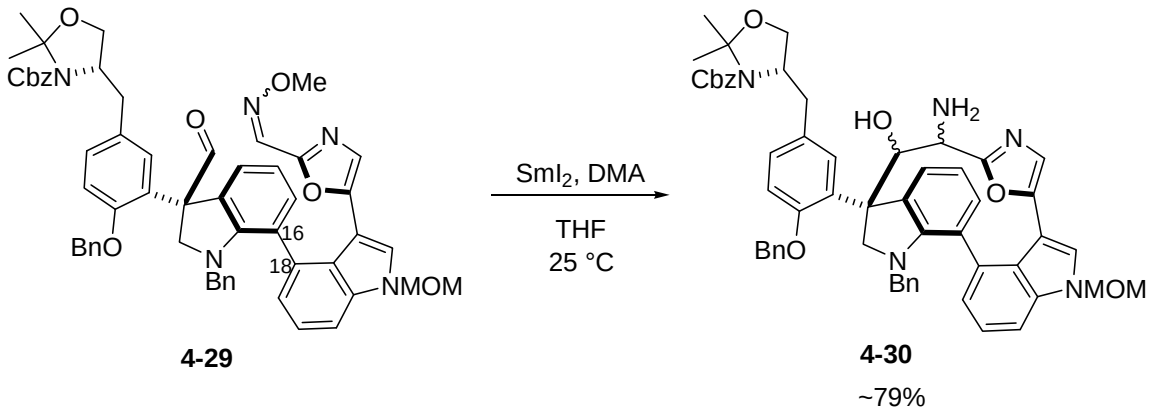
4-27 **4-28**

70%

dr: 1:1

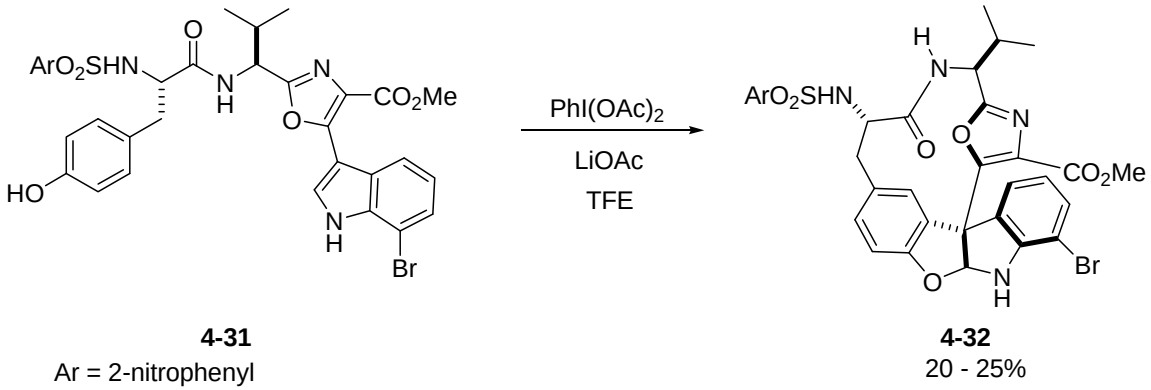
Scheme 4-13. Formation of the C10 quaternary center in Nicolaou's second total synthesis of diazonamide A.

Oxindole **4-28** was readily converted to the oxime **4-29** through a biaryl coupling at the C16-C18 bond, which set the stage for a hetero-pinacol macrocyclization. Following treatment with SmI_2, the macrocyclization proceeds smoothly to yield amino alcohol **4-30** in excellent yield (Scheme 4-14). This approach allows for a convergent approach to the polyaromatic core of diazonamide A. The Nicolaou group carried out the remaining macrolactamazation and structural elaboration to complete a second total synthesis of diazonamide A.



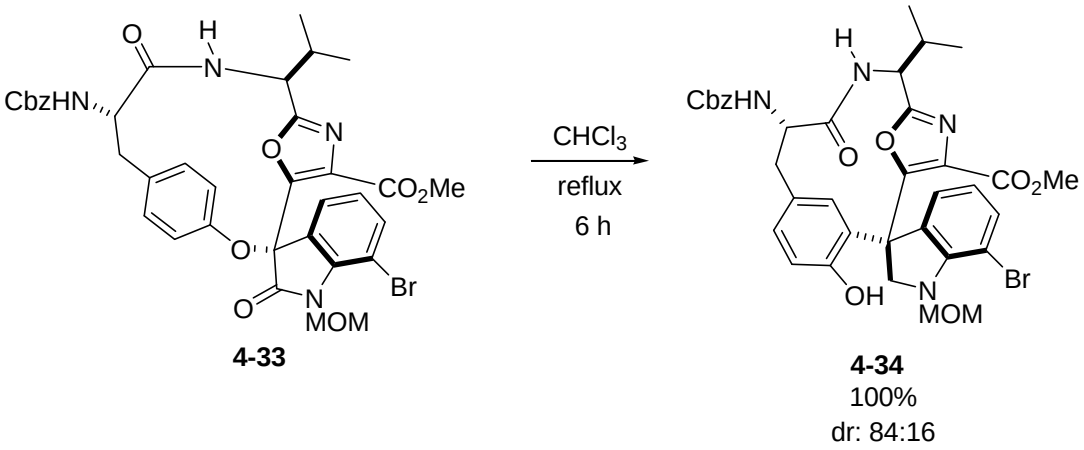
Scheme 4-14. SmI_2-mediated heteropinacol macrocyclization in Nicolaou's second total synthesis of diazonamide A.

The Harran group continued their investigations into the revised structure of diazonamide and published an extremely efficient approach in 2003.[122] Readily prepared **4-31**, when treated with $PhI(OAc)_2$, underwent oxidative cyclization to form **4-32** in 20-25% yield as a single diastereomer (Scheme 4-15). Despite the low yield, this represents the most effective approach to diazonamide reported to date. Harran carried **4-32** on to complete his total synthesis of diazonamide A, utilizing the Witkop-type macrocyclization to append the remainder of the molecule.



Scheme 4-15. Harran's key oxidative cyclization in his total synthesis of diazonamide A.

In 2007, Magnus reported a formal synthesis of diazonamide A, intercepting an intermediate in Nicolaou's first synthesis.[123] Magnus' approach relied on a thermal *O*- to *C*-aryl migration. Specifically, when **4-33** was refluxed in $CHCl_3$, migration of the aryl ring to form **4-34** in quantitative yield as an 84:16 ratio of diastereomers (only major is drawn, Scheme 4-16). A formal synthesis required 3 synthetic operations to reach macrolactam **4-24** (see Scheme 4-11).



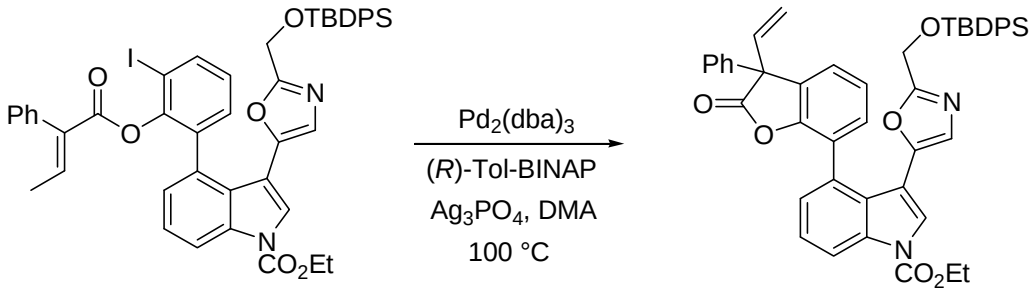
Scheme 4-16. Magnus' *O*- to *C*-aryl migration to form the C10 quaternary center in his formal synthesis of diazonamide A.

4.2 RESULTS AND DISCUSSION

4.2.1 Previous Work Towards Diazonamide A in the Wipf group

Diazonamide presented a difficult problem, and therefore an exciting opportunity to construct a complex array of heterocycles within a dense, rigid framework. Additionally, its potent biological activity encouraged work in the Wipf group directed at the originally proposed (incorrect) structure.

An approach based upon an enantioselective Heck cyclization was reported in 1998 and is shown in Scheme 4-17.[124] Ester **4-35** underwent Heck cyclization to furnish model lactone **4-36** in 47% yield, but only 19% *ee*. This transformation established a model for generating the C10 quaternary center, although the structure revision would render this approach unusable.

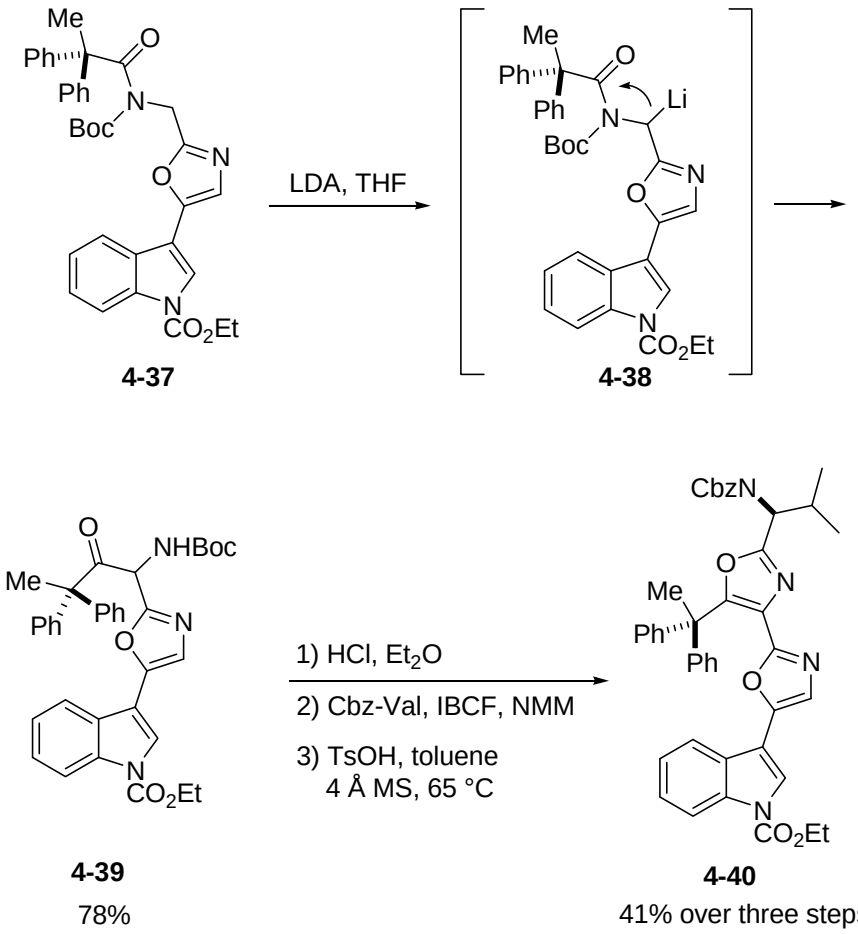


4-35 **4-36**

47%, 19% *ee*

Scheme 4-17. Enantioselective Heck cyclization reported by Wipf as an approach to the originally proposed structure of diazonamide A.

Additional work in the Wipf group developed a method for installing the central oxazole of the diazonamide skeleton utilizing a Chan-type rearrangement.[125] The key to this approach was the rapid preparation of the α-amino ketone motif required for the central oxazole. Towards this end, Boc-imide **4-37** was treated with LDA to furnish the intermediate anion **4-38** (Scheme 4-18). Immediate acyl migration resulted in aminoketone **4-39** in 78% yield. Subsequent deprotection, coupling to Cbz-protected valine and cyclodehydration provided the bis-oxazole **4-40** in 41% over the three steps, and provided a model for constructing this region of the molecule once the C10 quaternary center had been formed.

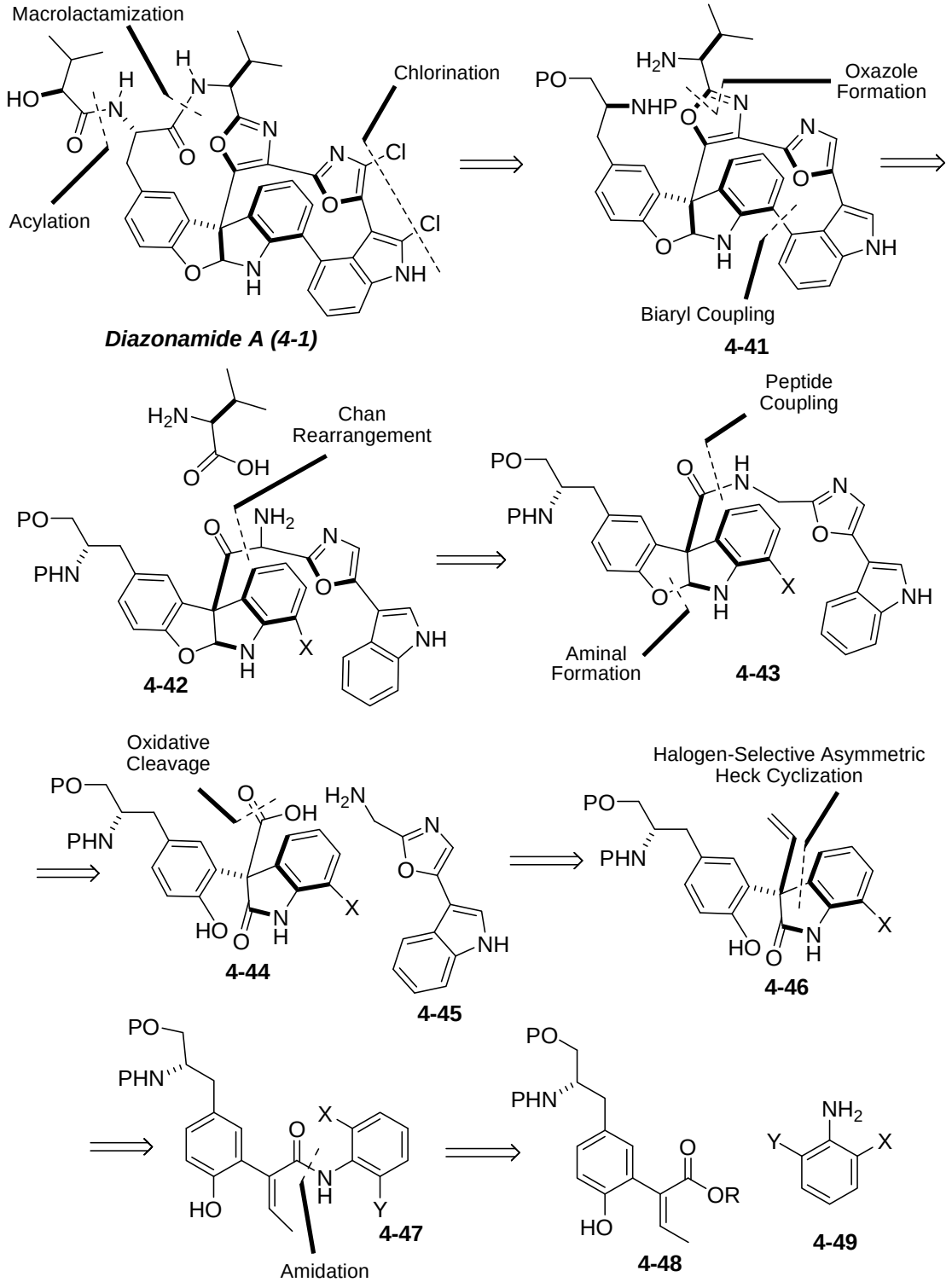


Scheme 4-18. Wipf's Chan rearrangement approach to the indole bis-oxazole motif in diazonamide A.

4.2.2 Retrosynthetic Analysis

The planned approach to diazonamide A centered on forming the C10 center using an enantioselective Heck cyclization. In the retrosynthetic sense, diazonamide can be stripped of its adorning acyl- and chlorine substituents, and opened at the peptide bond to furnish **4-41** (Scheme 4-19). Cleavage through the indole-indole biaryl axis and central oxazole excises valine and reveals Chan-rearrangement product **4-42**. Rupture of the aminal linkage and hydrolytic cleavage of the

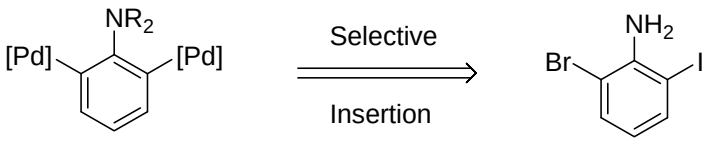
peptide bond reveals the key C10 anchored acid **4-44** and known indole-oxazole fragment **4-45**. Acid **4-44** is accessible from Heck cyclization product **4-46** through oxidative cleavage of an alkene. The required Heck precursor **4-47** is easily deconstructed as the condensation product of an ester (**4-48**) and a functionalized aniline **4-49**.



Scheme 4-19. Retrosynthetic analysis for diazonamide A.

4.2.3 Preparation of Aniline 4-51

An ideal aniline fragment would allow for selective insertion of palladium during the Heck cyclization, and allow a handle for the palladium-mediated formation of the indole-indole biaryl linkage later in the synthesis (Scheme 4-20). Aniline **4-51** was chosen as a suitable target since the halogen substituents would be relatively stable during synthetic operations (as opposed to a triflate), yet provide sufficient reactivity in a complex system.

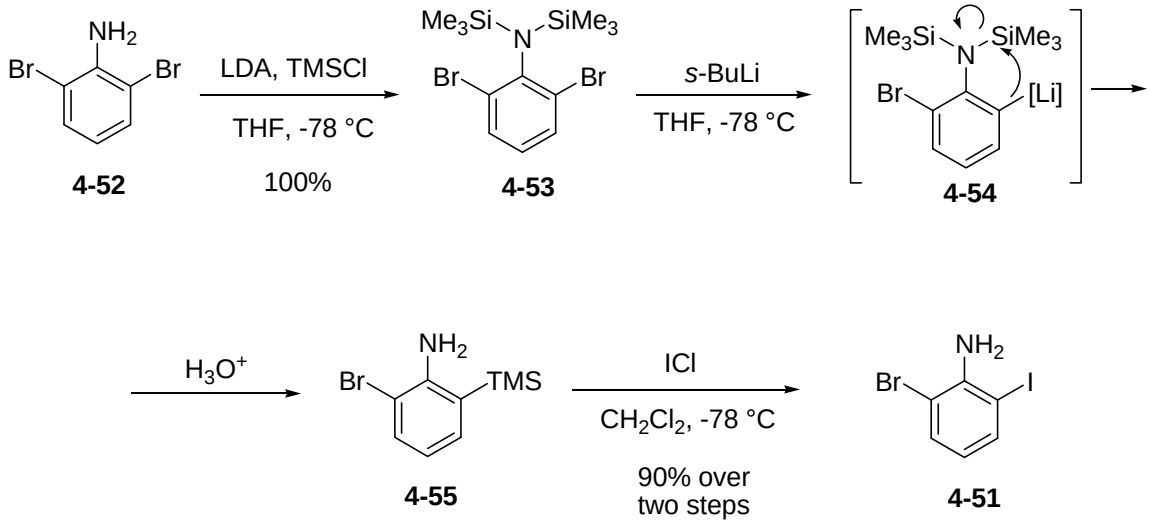


4-50 **4-51**

Scheme 4-20. Requirement for aniline fragment to be selectively activated by Pd(0).

Perusal of the literature revealed a single method for constructing mixed 2,6-dihaloanilines, consisting of 5 to 7 steps and requiring tedious separation throughout the sequence.[126] Furthermore, compound **4-51** itself had never been reported, indicating potential difficulty in its preparation. Therefore, a new preparation was developed utilizing an *N*- to *C*-silyl transfer reaction.[127] Commercially available 2,6-dibromoaniline (**4-52**) was doubly silylated to provided **4-53** in 99% yield (Scheme 4-21). Treatment with 2 eq of *s*-BuLi generated intermediate lithiate **4-54** which induced migration of one silyl group from nitrogen, which furnished the key differentially substituted aniline **4-55** upon acidic workup. This crude material rapidly underwent iododesilylation with ICl to provide the desired aniline **4-51** in 90% yield over the two steps. This approach has

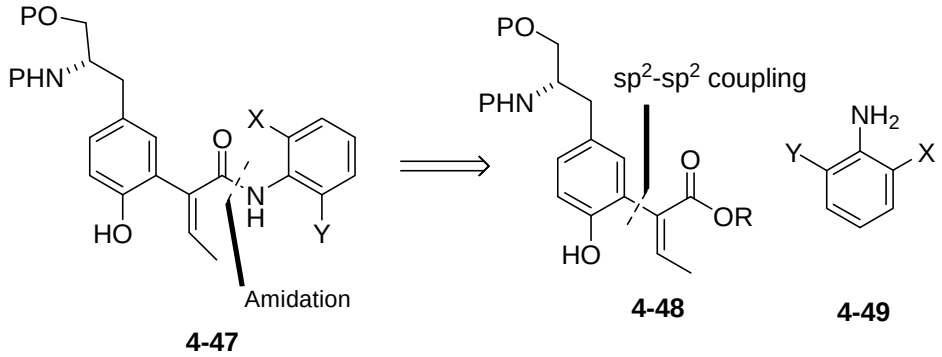
proven to be very scalable, and a simple recrystallization of **4-51** makes the final purification simple and effective.



Scheme 4-21. Preparation of aniline **4-51** utilizing an *N*- to *C*-silane transfer.

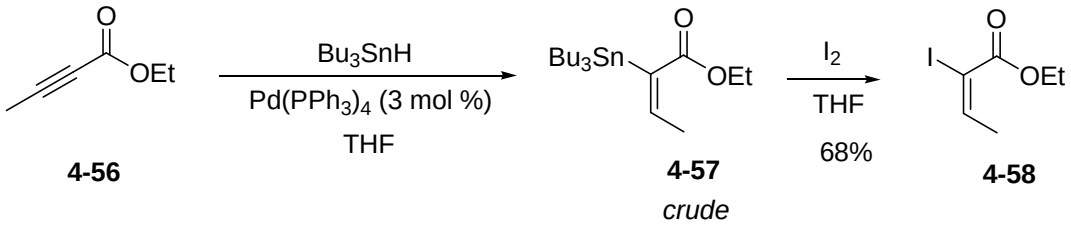
4.2.4 Incorporation of Tyrosine Backbone and Installation of C10 Quaternary Center

As shown in Scheme 4-22, ester **4-48** was required to complete the synthesis of the key Heck cyclization precursor. An sp^2-sp^2 coupling was initially employed to access to this fragment.



Scheme 4-22. Retrosynthetic analysis for key intermediate **4-47.**

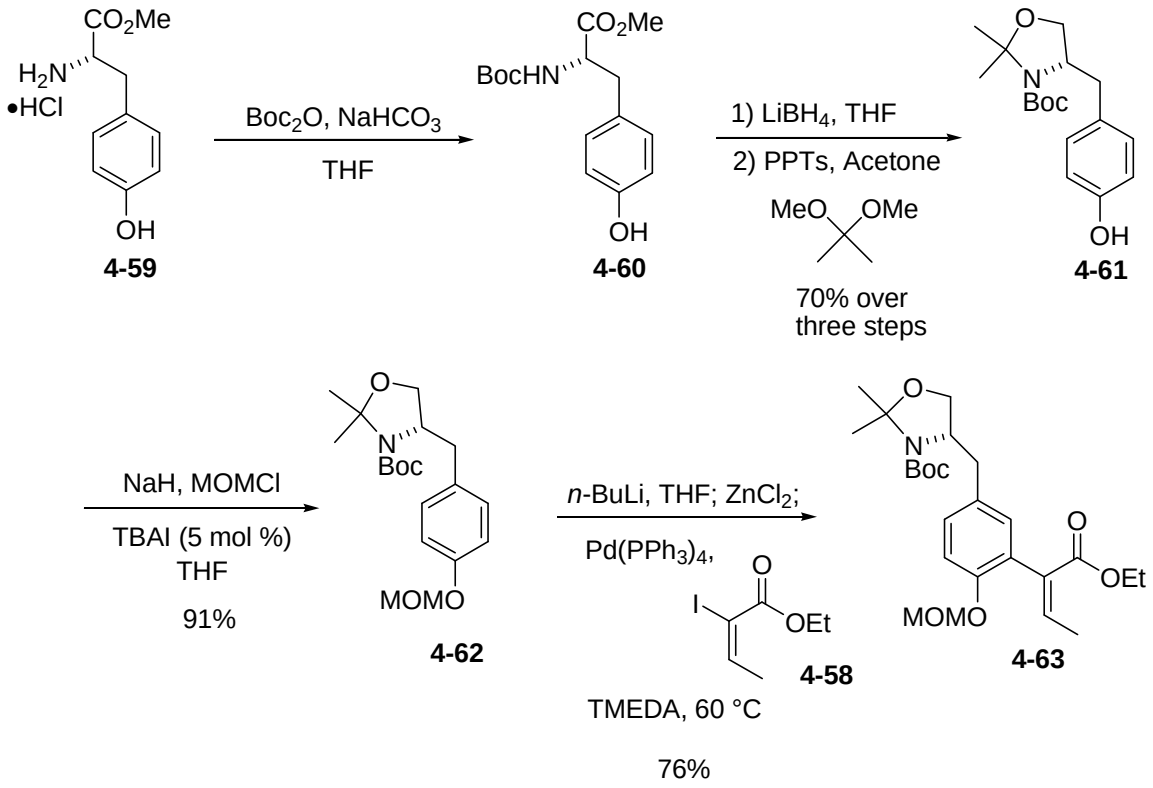
Toward this end, iodoenoate **4-58** was prepared from ethyl ester **4-56** beginning with a palladium-catalyzed hydrostannylation to furnish crude stannane **4-57** followed by iododestannylation in 68% yield (Scheme 4-23).[128]



4-56 **4-57** *crude* **4-58**

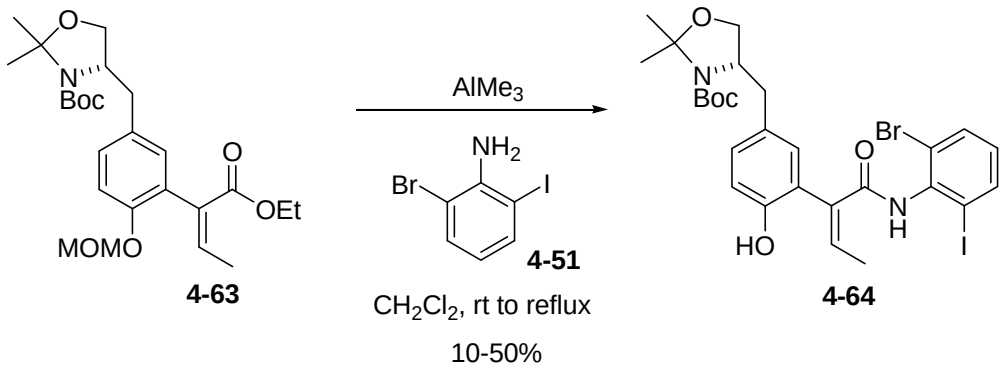
Scheme 4-23. Hydrostannylation of **4-56** and iodination of stannane **4-57.**

Preparation of the coupling partner for **4-58** began with Boc protection of *L*-Tyr-OMe-HCl to furnish **4-60** (Scheme 4-24). Reduction of crude **4-60** with $LiBH_4$ followed by protection of the amino alcohol as the isopropylidene aminal generated **4-61** in 70% over the three steps. Subsequent protection of the crude phenol as the MOM-ether furnished the desired coupling partner **4-62** in 91% yield. A Negishi coupling was employed to couple **4-62** and **4-58**.[129] Thus, directed *ortho*-lithiation with *n*-BuLi followed by transmetallation to zinc generated an arylzinc reagent that smoothly underwent cross-coupling with vinyl iodide **4-58** in the presence of $Pd(PPh_3)_4$ to furnish enoate **4-63** in 76% yield.[130]



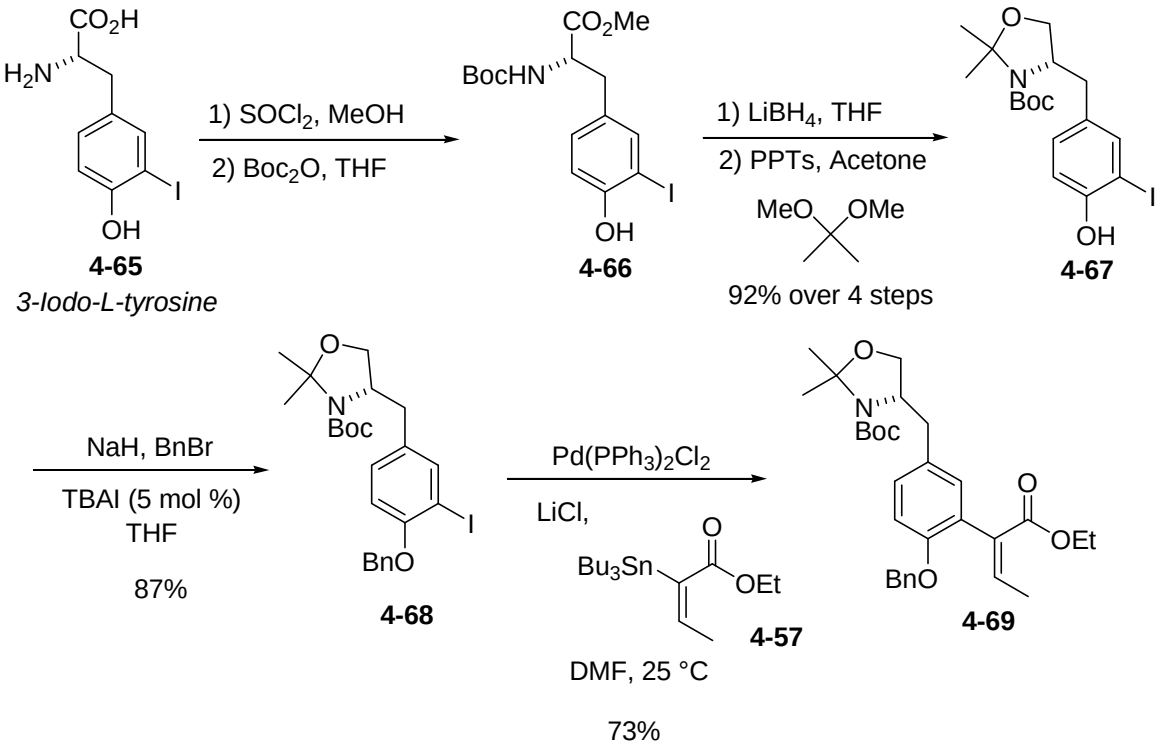
Scheme 4-24. Preparation of ester **4-63.**

With ester **4-63** in hand, condensation of aniline **4-51** in the presence of $AlMe_3$ proceeded unreliably in 10-50% yield, and furnished only material lacking the MOM ether (Scheme 4-25). Unfortunately, any attempt to couple aniline **4-51** to any derivative of ester **4-63** was unsuccessful, including the acid, mixed anhydride, acyl fluoride and chloride.



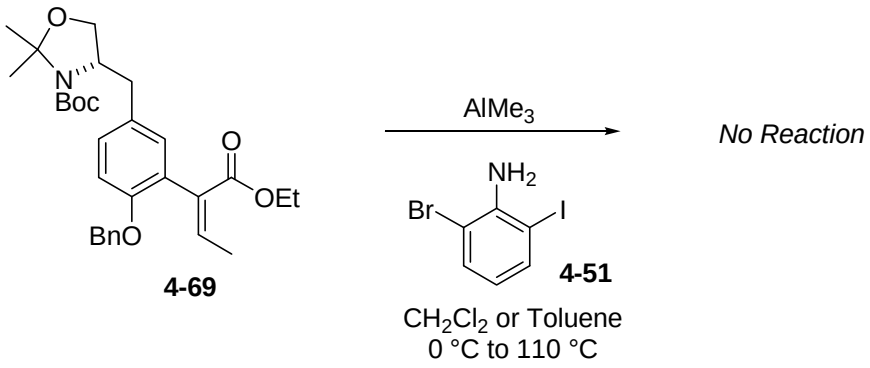
Scheme 4-25. Condensation of aniline **4-51** with ester **4-63**.

Given the clear lability of the MOM ether during the aluminum mediated condensation, the corresponding benzyl ether was prepared as shown in Scheme 4-26. Beginning with commercial 3-iodo-*L*-tyrosine (**4-65**), the free acid was converted to the methyl ester with $SOCl_2$ in methanol. Subsequent Boc-protection of the nitrogen furnished **4-66**. Crude ester **4-66** was reduced with $LiBH_4$ and the resulting amino alcohol protected as the isopropylidene ketal to generate the phenol **4-67** in 92% yield over four steps. This crude phenol was then benzylated to provide **4-68** in 87% yield. Subsequent Stille coupling to stannane **4-57** proceeded in 73% yield to furnish the desired benzyl protected enoate **4-69**.[131]



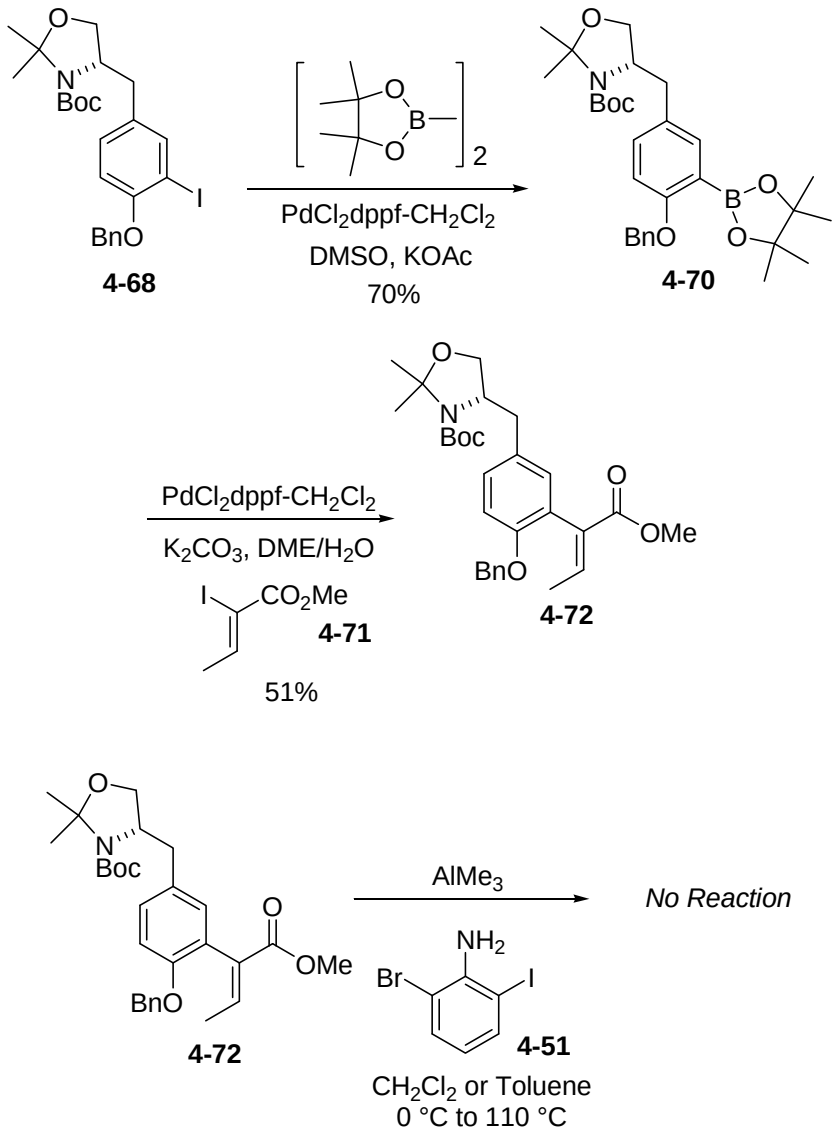
Scheme 4-26. Preparation of the *O*-benzyl protected ester **4-69**.

Ester **4-69** resisted aluminum-mediated condensation with aniline **4-51** under any set of stoichiometry, solvent or temperature conditions applied (Scheme 4-27). Given the necessity of this transformation, further optimization of the ester substrate was attempted. This time, the alkene geometry would be reversed to *trans*, moving the methyl group away from the sterically encumbering *cis* orientation.



Scheme 4-27. Attempted condensation of aniline **4-51** with ester **4-69.**

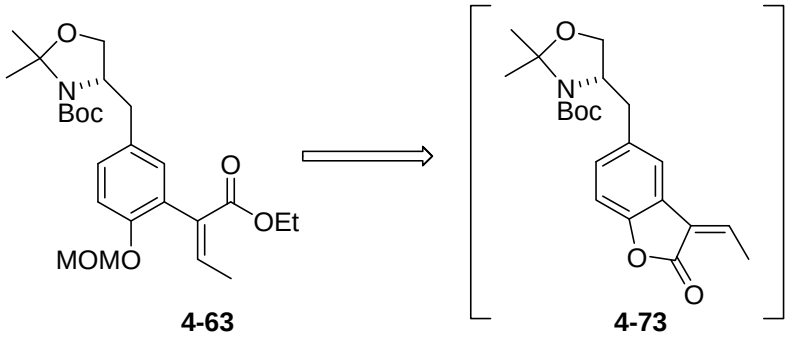
Benzylated phenol **4-68** provided an ideal starting point for the preparation of the desired ester. Conversion of the iodide to the corresponding pinacol boronate ester **4-70** proceeded in 70% yield (Scheme 4-28). Subsequent Suzuki coupling with iodide **4-71** generated the desired *trans* ester **4-72** in 51% yield.[132] Surprisingly, ester **4-72** also proved to be unreactive under any set of amidation conditions applied.



Scheme 4-28. Preparation of ester **4-72** containing the (*E*) alkene geometry and attempted condensation with aniline **4-51.**

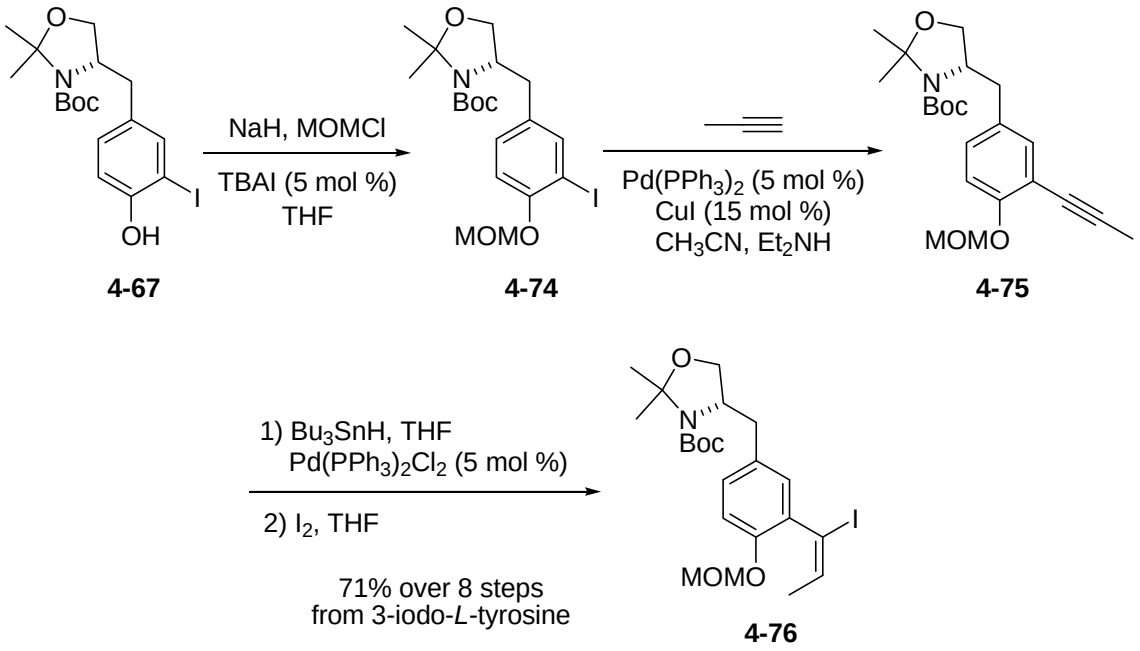
This result suggests that the MOM ether may be necessary for condensation to occur. It is conceivable that an *in situ* lactonization is required and that the lactone intermediate is the actual substrate undergoing amidation (Scheme 4-29). Additional concerns about material throughput

prompted a revised approach to this critical fragment that would include the MOM functionality, avoid tedious separations, and provide substantial amounts of material.



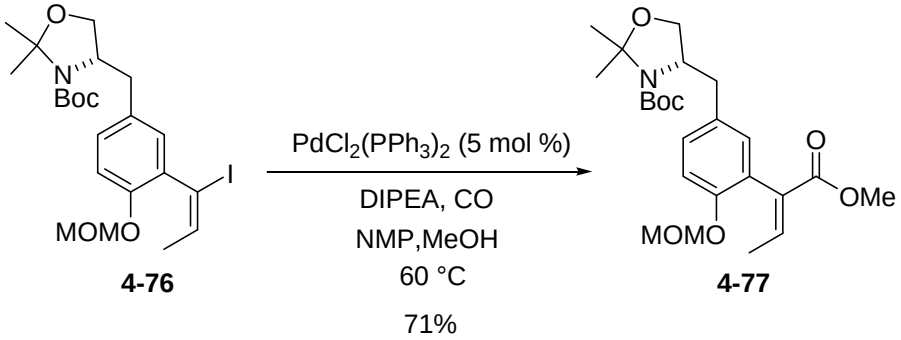
Scheme 4-29. Possible intermediate required for successful amidation of esters of type **4-63.**

As before, carrying commercial 3-iodo-*L*-tyrosine (**4-65**) through to intermediate **4-67** and subsequent protection as the MOM ether generated **4-74**. Crude MOM ether **4-74** underwent a Sonagashira coupling with propyne to furnish **4-75** which was pure enough to carry on crude (Scheme 4-30). This alkyne was hydrostannylated under palladium catalysis and the resulting alkenylstanne was iodinated to furnish alkenyiodide **4-76** in 71% yield over the 8 steps from 3-iodo-*L*-tyrosine. This approach allowed the installation of the desired alkenyl moiety in a very high-yielding sequence, although it was slightly longer than the previous approach. On large scale, the chemistry could be performed reliably with only a single purification of the alkenyliodide on SiO_2, and proceeded in 70-80% over 8 steps, or about 97% per synthetic step. The operational benefits of this approach far outweighed the additional steps.



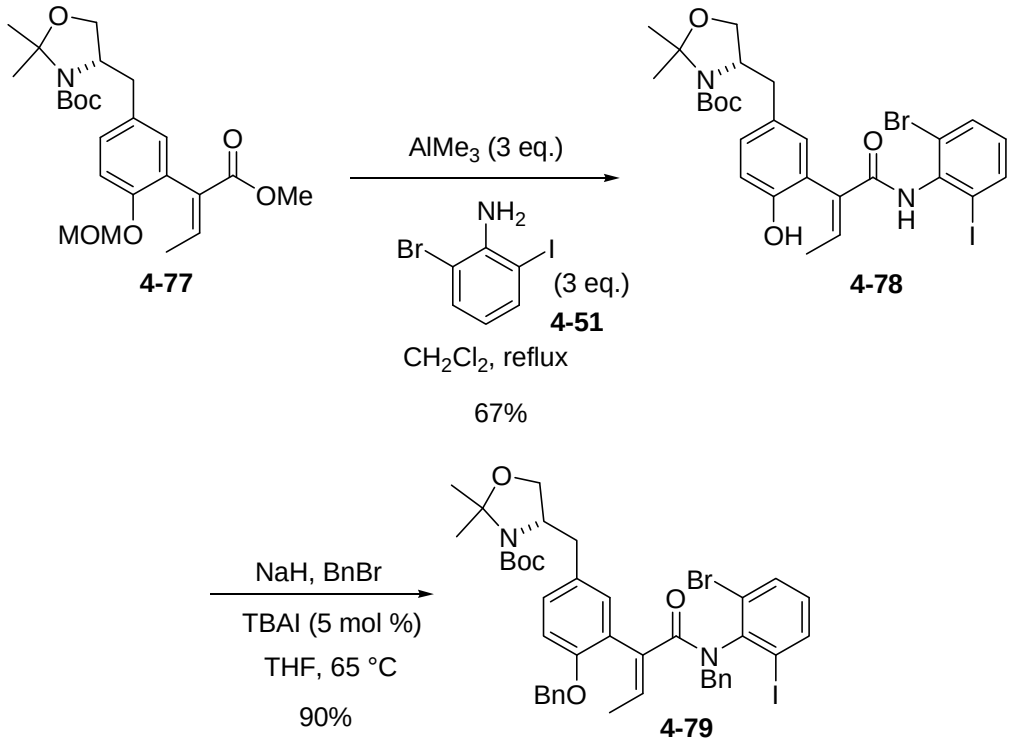
Scheme 4-30. Preparation of vinyl iodide **4-76.**

With alkenyliodide **4-76** in hand, continued elaboration to the desired Heck cyclization precursor was required. Any attempt to perform lithium-halogen exchange on iodide **4-76** was met with failure. Therefore, a palladium-catalyzed carbonylation was performed in methanol, which gave rise to methyl ester **4-77** in 71% yield (Scheme 4-31).[133,134]



Scheme 4-31. Carbonylation of vinyl iodide **4-76** to prepare key ester **4-77**.

Ester **4-77** now contained all of the attributes that were presumed to aid the aluminum-mediated amidation: MOM-protection on the phenol, *trans* alkene geometry and the methyl (as opposed to ethyl) ester. Optimization of the amidation with ester **4-77** gave rise to anilide **4-78** in 67% yield, which varied only slightly on differing scales (Scheme 4-32). Double benzylation of anilide **4-78** furnished the desired Heck cyclization precursor **4-79** in 90% yield.

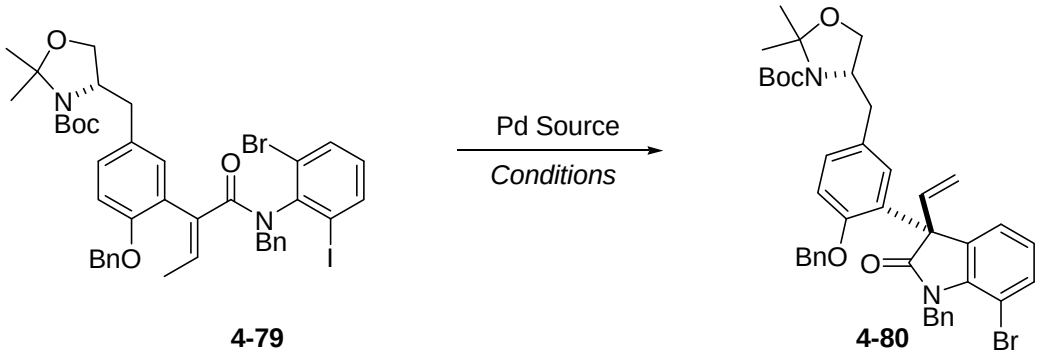


Scheme 4-32. Condensation of aniline **4-51** with ester **4-77** and subsequent elaboration to key Heck cyclization precursor **4-79**.

The critical enantioselective Heck cyclization was investigated next.[135] Initially employing Overman's Ag-promoted conditions with *rac*-BINAP as the ligand and DMA as solvent provided the desired cyclization product **4-80** in 53% yield, with some evidence of decomposition, most likely from the prolonged heating (Entry 1, Table 4-1). Performing the reaction with (*S*)-BINAP and

reducing the reaction time provided an improved yield (63%) but the enantioselectivity (*ee*) was poor and some starting material remained (Entry 2).[136] A switch to "base-promoted" conditions dramatically increased the yield to 97%, yet the *ee* remained at 30% (Entry 3). A switch to NMP as solvent dramatically increased the *ee* (60%) reduced the reaction time to ~3.5 h and provided an excellent yield (Entry 4). A decrease in *ee* from 60 to 50% was observed when (*S*)-Tol-BINAP was employed as the ligand (Entry 5). The temperature dependence of the cyclization was investigated next. Conducting the reaction at 95 °C required 6 h, and the *ee* dropped to 41% (Entry 6); however, at 135 °C the reaction proceeded in only 1h, and the *ee* was 55% (Entry 7). Thus, the optimal conditions chosen were (*S*)-BINAP as the ligand, PMP as the additive, NMP as solvent and a reaction temperature of ~110 °C. These conditions proved to be amenable to scale-up as demonstrated in entries 8-11, where increasingly larger scale reactions provided consistent yields and enantioselectivities. The optimized Heck cyclization did not perform at extreme levels of efficiency in terms of enantioselectivity, but effectively provided an average of 68% of the desired stereoisomer required for diazonamide A (based on the average yield and *ee* in Entries 8-11). Given the substantial challenges that were ahead in the synthesis, the optimized conditions would provide sufficient material throughput. Although attempts to confirm the relative stereochemistry of **4-80** by X-ray crystallography failed, the stereochemistry was assigned based on analogy to several similar substrates reported by Overman.[136]

Table 4-1. Enantioselective Heck cyclization to set the C10 quaternary center of diazonamide A.



4-79 **4-80**

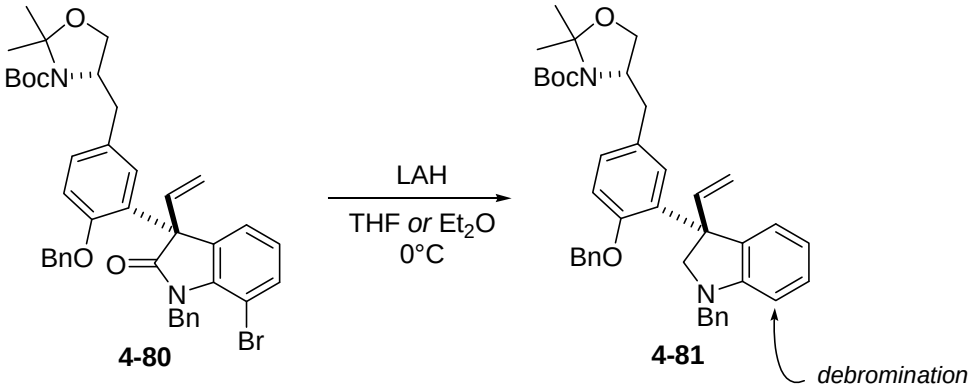
Entry	Pd Source	Ligand	Additive	Solvent	Temp (°C)	time (h)	yield (%)[a]	ee (%)[f]
1	a	*rac*-BINAP	Ag_3PO_4	DMA	100	20	53%	0
2	b	(*S*)-BINAP	Ag_3PO_4	DMA	95	12	68 + SM	30
3	b	(*S*)-BINAP	PMP	DMA	110	6	97	30
4	b	(*S*)-BINAP	PMP	NMP	110	3.5	99	60
5	b	(*S*)-Tol-BINAP	PMP	NMP	110	3.5	86	50
6	b	(*S*)-BINAP	PMP	NMP	95	6	90	41
7	b	(*S*)-BINAP	PMP	NMP	135	1	78	55
8[b]	b	(*S*)-BINAP	PMP	NMP	110	2.5	88	53
9[c]	b	(*S*)-BINAP	PMP	NMP	110	3.5	84	54
10[d]	b	(*S*)-BINAP	PMP	NMP	110	3.5	87	54
11[e]	b	(*S*)-BINAP	PMP	NMP	110	3.5	94	54

Reaction conditions: Pd source (10 mol %) (a = Pd_2dba_3 or b = Pd_2dba_3•$CHCl_3$), ligand (22 mol %), additive Ag_3PO_4 (2 eq.) or PMP (4 eq.), ~0.1 M in degassed solvent. [a]Stereochemistry assigned by analogy to similar substrates reported for this transformation by Overman.[136] [b]Reaction performed on 0.6 mmol scale. [c]Reaction performed on 3.52 mmol. [d]Reacion performed on 4.76 mmol scale. [e]Reaction performed on 5.03 mmol scale. [f]Enantioselectivity determined by HPLC on a Chiracel OD column, 10% *i*-PrOH/hexanes, flow rate 1 mL/min.

4.2.5 Installation of Diazonamide's Central Oxazole

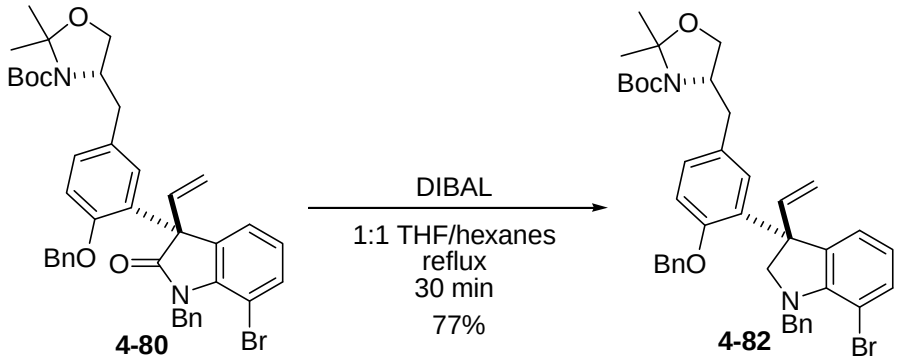
With a reliable route to significant quantities of oxindole **4-80**, the oxidative cleavage of its alkene was investigated, as this was our key fragment (see retrosynthetic analysis, Scheme 4-19). Not surprisingly, any attempted cleavage of the alkene in the presence of the lactam carbonyl resulted in decomposed material, presumably through decarboxylation. Therefore, the lactam would

be reduced to eliminate this undesired β-keto acid-type arrangement. Treatment of oxindole **4-80** with LAH in Et_2O or THF resulted in the desired reduction, along with unexpected debromination as indicated by ^1H NMR and MS analysis (Scheme 4-33, δ 6.46 (d, 1 H, J = 7.8 Hz, m/z = 631.5 ($[M+H]^+$ for **4-81**).



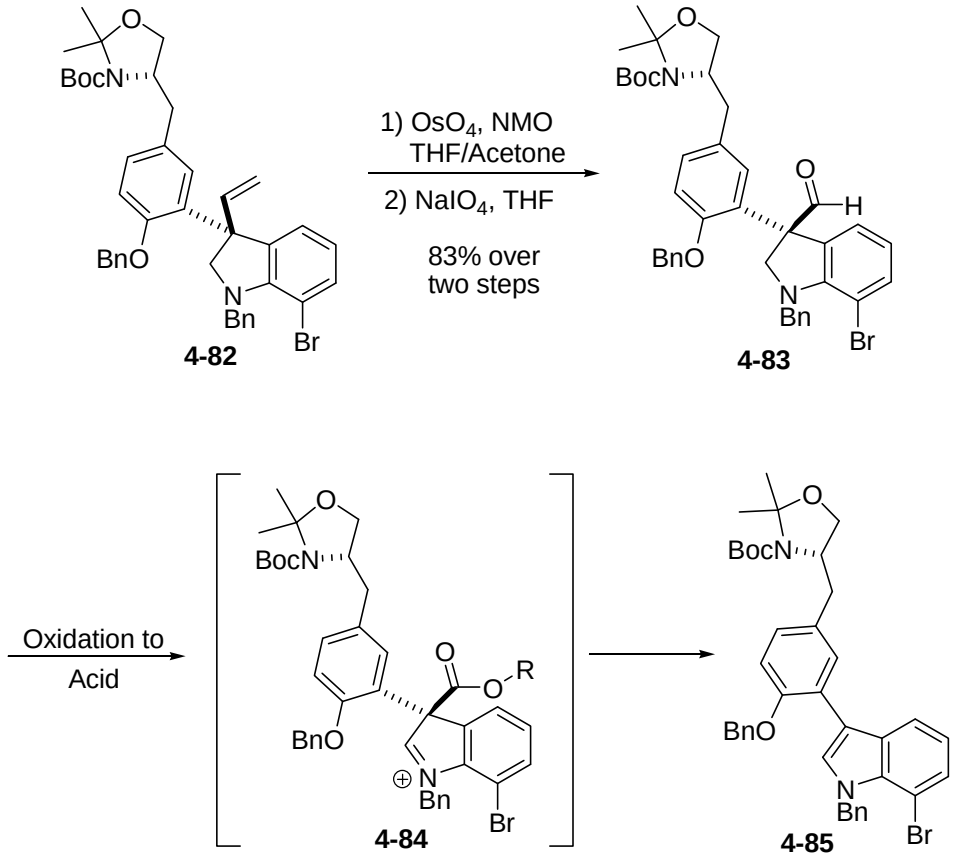
Scheme 4-33. Debromination observed during attempted reduction of oxindole **4-80.**

To circumvent the debromination issue, DIBAL was employed and delivered the desired hydroindole **4-82** in 77% yield (Scheme 4-34). Although this reaction was plagued by decomposition issues at room temperature, immediately heating the reaction mixture at reflux under concentrated conditions (~0.5 M) resulted in shorter reaction times and improved the recovery of the product.



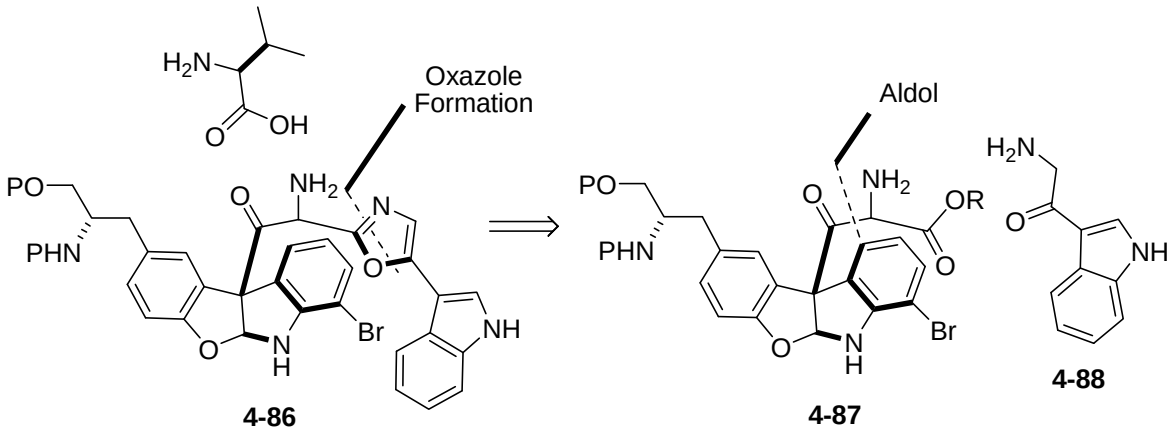
Scheme 4-34. Reduction of oxindole **4-80** with DIBAL.

Hydroindole **4-82** was now ready to be converted to the corresponding acid through oxidative cleavage of the alkene. A two-step dihydroxylation-oxidative cleavage furnished the desired aldehyde **4-83** in 83% yield over the two steps (Scheme 4-35). Surprisingly, aldehyde **4-83** could not be converted to the corresponding acid under any conditions that were attempted, including: Cr- and Ru- based oxidants, O_3, Oxone®, $NaClO_2$, NaClO, and Br_2. The product of nearly all of these attempts was indole **4-85**. Strictly controlling stoichiometry did not alter the reaction outcome to any detectable extent. The intermediacy of **4-84** is presumed to be the culprit in this decarboxylation. This result effectively terminated our Chan rearrangement approach to the central oxazole of diazonamide A, making aldehyde **4-83** a critical intermediate from which to proceed.



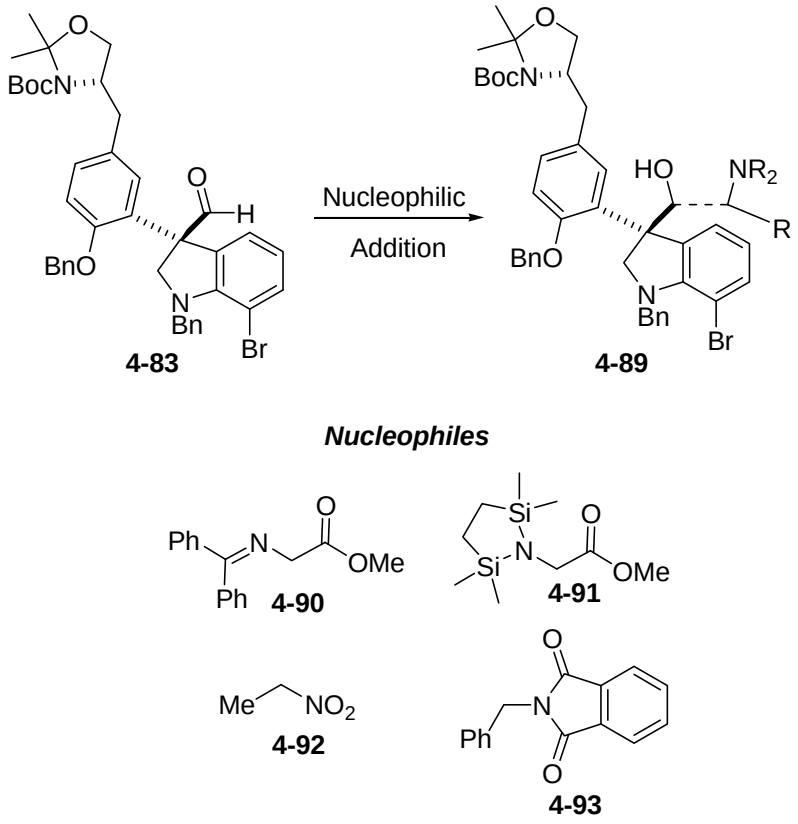
Scheme 4-35. Oxidative cleavage of alkene **4-82** and unexpected decarboxylation during attempted oxidation of aldehyde **4-83**.

A revised approach to the α-amino ketone motif required for the central oxazole of diazonamide centered on an aldol-type addition of a glycine equivalent to aldehyde **4-83** (Scheme 4-36). This would allow for construction of the lower indole-containing subunit by appending **4-88** to the substrate.



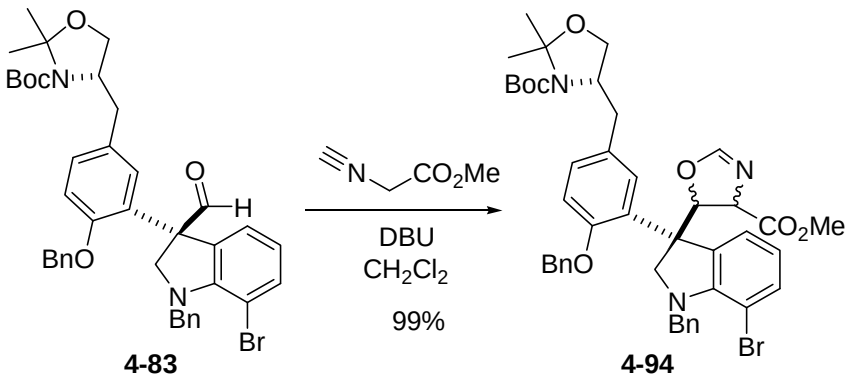
Scheme 4-36. Revised retrosynthetic analysis for diazonamide A.

The literature revealed several suitable glycine equivalents, such as **4-90** and **4-91**,[137] which could serve as nucleophiles (Scheme 4-37). Any attempted addition of their corresponding enolates consistently returned only starting materials. Henry-type additions of nitroethane (**4-92**) or N-benzylphthalimide (**4-93**) also returned only starting materials. These results were somewhat surprising, but appear to be due to the sterically hindered nature of the aldehyde increasing the potential for retro-aldol fragmentation.



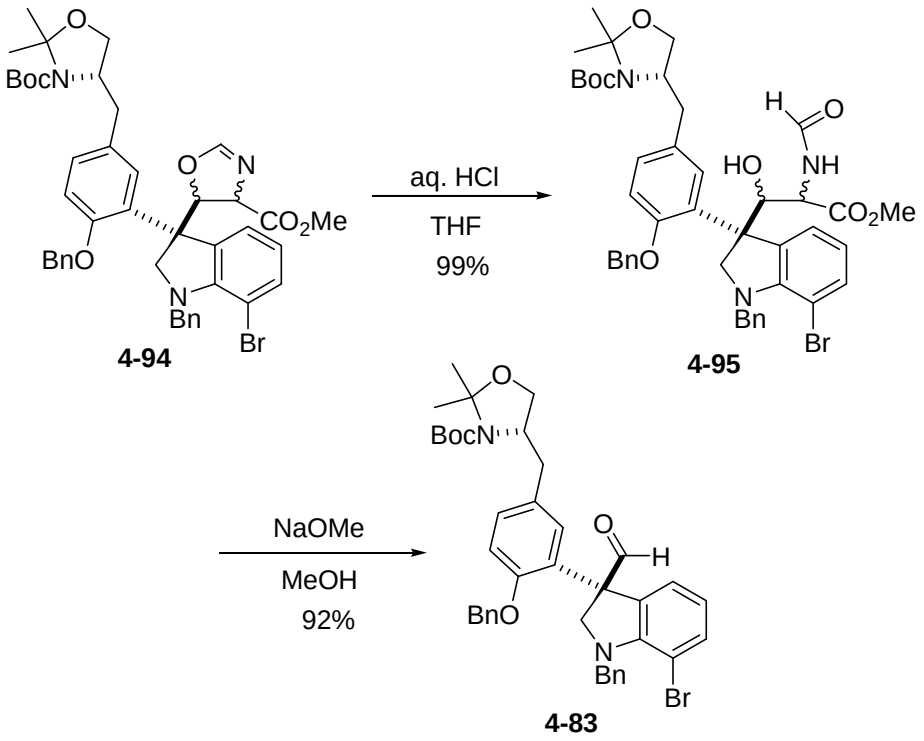
Scheme 4-37. Attempted addition to aldehyde **4-83**.

If retro-aldol fragmentation was indeed the obstacle to enolate addition, then *in situ* trapping of the alkoxide intermediate would disable this pathway. Methyl isocyanoacetate was chosen since it contained a trapping function along with the desired α-amino substitution. Indeed, upon treatment with DBU, a mixture of aldehyde **4-83** and methyl isocyanoacetate rapidly condensed to furnish oxazoline **4-94** in 99% yield as a mixture of several diastereomers (Scheme 4-38).



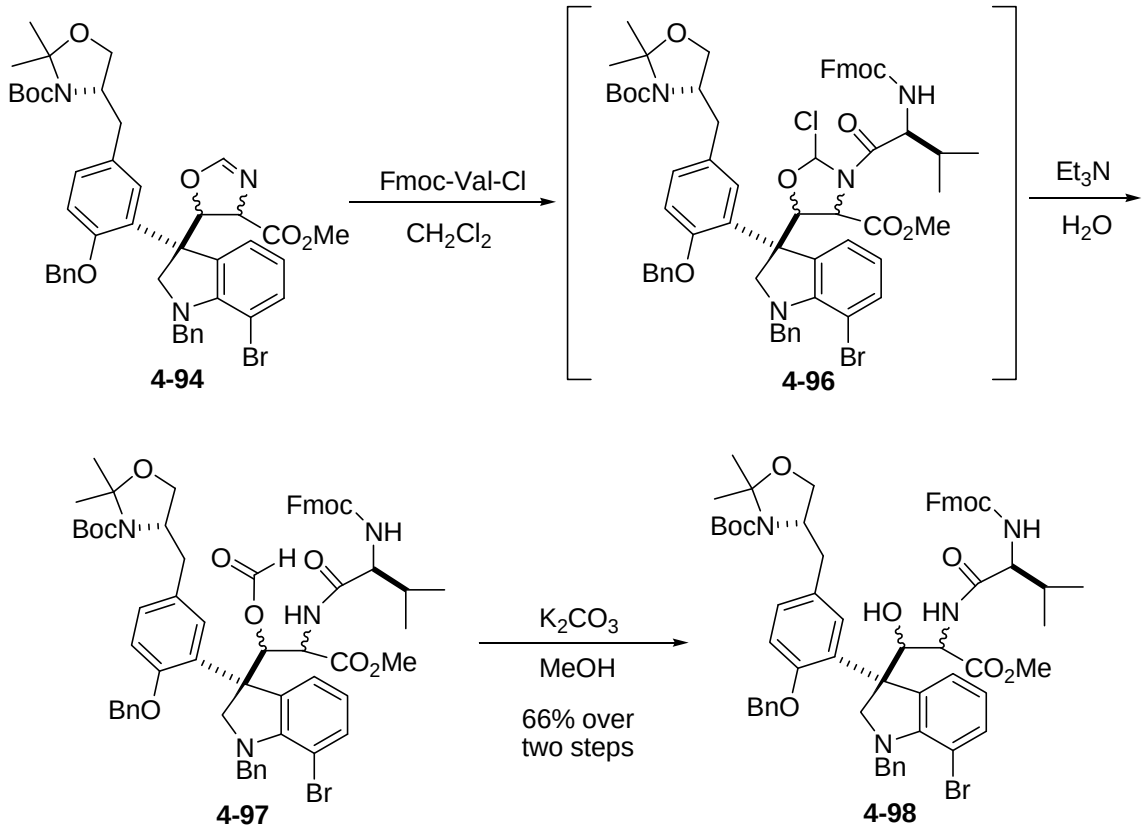
Scheme 4-38. Preparation of oxazoline **4-94**.

In an effort to access the corresponding free amino alcohol, oxazoline **4-94** was hydrolyzed with dilute aqueous HCl to furnish formamide **4-95** in 99% yield (Scheme 4-39). Attempted deformylation of this substrate proved difficult, as the strongly acidic conditions typically applied rapidly decomposed the molecule. However, immediate deformylation with NaOMe furnished only the retro-aldol product **4-83** in 92% yield, which provided some indirect evidence that fragmentation of this delicate intermediate was indeed a favored pathway.



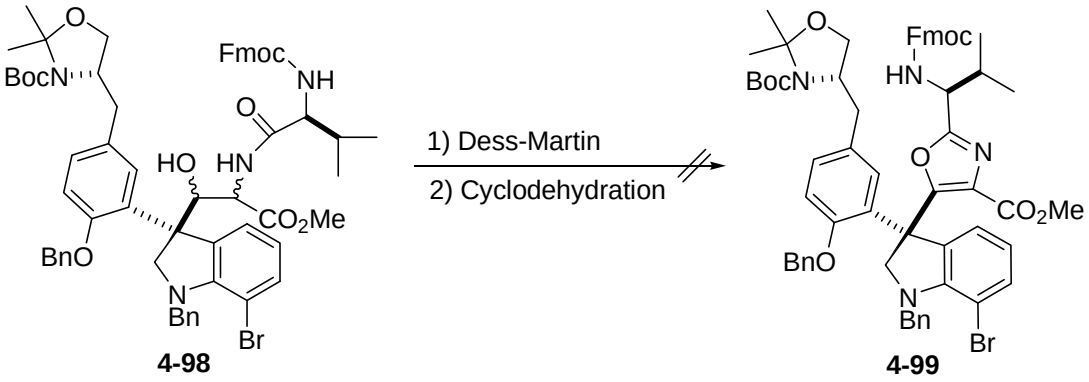
Scheme 4-39. Hydrolysis of oxazoline **4-94** and attempted deformylation of **4-95**.

An alternative use of oxazoline **4-94** was required that would circumvent the formation of sensitive intermediates. Inspiration from *N*-acyl pyridine chemistry led to the attempted direct acylation of the oxazoline nitrogen with the acyl chloride derived from Fmoc-protected valine.[138] When treated with Fmoc-Val-Cl, oxazoline **4-94** was rapidly consumed according to TLC analysis, presumably converted to chloroaminal **4-96** (Scheme 4-40). Hydrolytic workup of the reaction mixture revealed formate **4-97**, which was immediately deformylated in basic methanol to provide alcohol **4-98** in 66% yield over the two steps as a mixture of several diastereomers. This method provided a rapid method to incorporate the valine residue required for diazonamide A. Unfortunately, the analytical data for **4-94** and subsequent intermediates is poorly resolved due to the mixtures of diastereomers present (melting ranges are also very large), although the ^{1}H and ^{13}C spectra are consistent with the assigned structures.



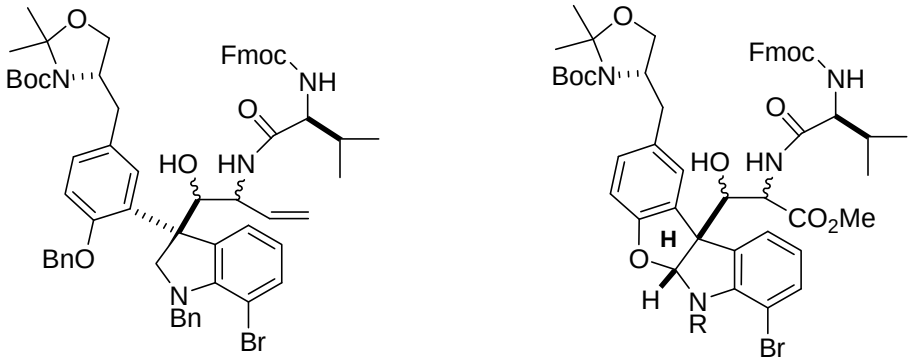
Scheme 4-40. Installation of valine residue through acylation of oxazoline **4-94**.

With alcohol **4-98** in hand, cyclization of diazonamide's central oxazole seemed within reach. Oxidation of the secondary alcohol with Dess-Martin periodinane furnished the corresponding crude ketone (structure tentatively assigned based on MS analysis) which was poised for cyclodehydration to **4-99**, a substrate containing the fully functionalized quaternary center required for diazonamide A (Scheme 4-41). Unfortunately, under any of the cyclodehydration conditions applied including $POCl_3$, PPh_3/Cl_3CCCl_3, $PPh_3/BrCl_2CCCl_2Br$, Burgess reagent, and TsOH/toluene only decomposed or starting material was recovered. Mass analysis of the crude reaction mixtures indicates some partial loss of H_2O when $POCl_3$ in pyridine conditions are applied, but none of the desired oxazole has been recovered. This lack of reactivity has been observed by the Nicolaou and MacMillan groups in similar systems.[139]



Scheme 4-41. Oxidation of alcohol **4-98** and cyclodehydration to key oxazole **4-99**.

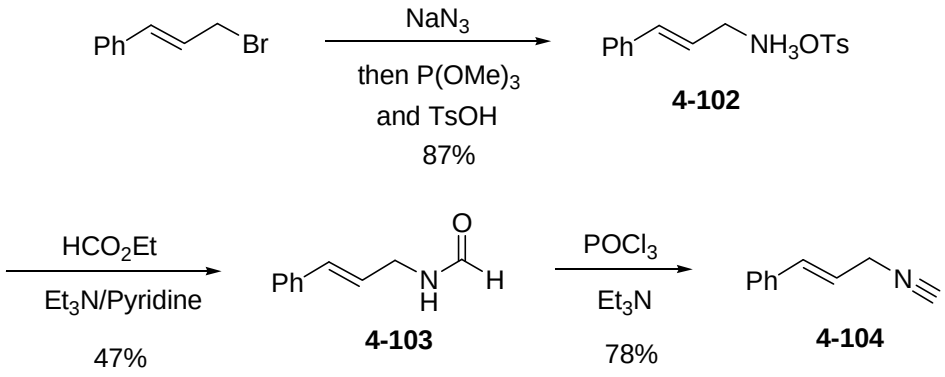
Several potential solutions to the oxazole cyclization problem remain to be explored. Although the issues preventing cyclodehydration in Scheme 4-41 are currently unknown, substrate **4-100** lacking ester substitution could be accessed by addition of allyl isocyanide to aldehyde **4-83**. Conversely, polycycle **4-101** containing a fused H-ring may reduce the steric bulk around the C10 center and aid in cyclodehydration.



Scheme 4-42. Alternative substrates to proceed to the late stages of the synthesis.

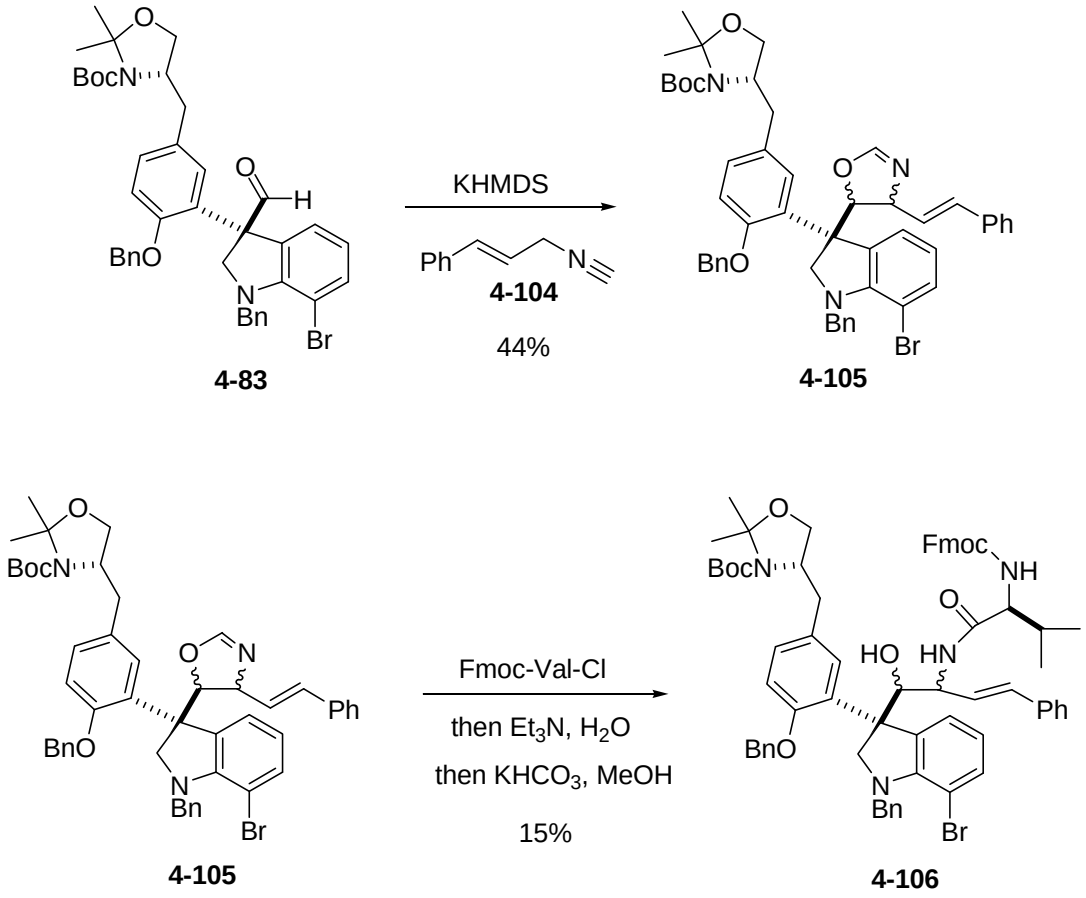
Preliminary results toward an alternative cyclodehydration substrate have been achieved (although the structures are tentative until full characterization can be performed). Beginning with

cinnamyl bromide, displacement with NaN_3 yielded cinnamyl azide which was reduced with $P(OMe)_3$ and the resulting amine isolated as tosylate salt **4-102** in 87% overall (Scheme 4-43). Subsequent condensation with ethyl formate furnished formamide **4-103**, which was dehydrated to the corresponding isocyanide **4-104** in 78% yield.



Scheme 4-43. Preparation of isocyanide **4-104.**

The potassium anion of isocyanide **4-104** condensed with aldehyde **4-83** in 44% yield to furnish oxazoline **4-105** (Scheme 4-44). Acylation of the oxazoline with Fmoc-Val-Cl and subsequent hydrolysis provided alcohol **4-106** in only 15% yield (unoptimized). Alcohol 4-106 could be potentially be cyclized directly to the corresponding oxazoline and then oxidized to the desired oxazole. Conversely, it could be oxidized to the ketone and cyclodehydrated to the corresponding oxazole.



Scheme 4-44. Preparation of oxazoline **4-105** and subsequent acylation.

4.2.6 Conclusions

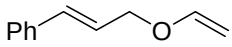
An approach to advanced intermediates for the synthesis of diazonamide has been developed that allows for the convenient preparation of multigram quantities of late stage material. Several key elements have been introduced, including the C10 quaternary center which was installed using an enantioselective Heck cyclization. Additionally, the valine residue has been efficiently introduced utilizing an *N*-acyl iminium ion cascade. The remainder of the molecule is fully functionalized in terms of appending the remainder of the diazonamide skeleton, and work continues toward this goal.

5. EXPERIMENTAL SECTION

All moisture sensitive reactions were performed under an N_2 atmosphere and all glassware was flame dried under vacuum prior to use. THF and Et_2O were dried by distillation over Na/benzophenone under a nitrogen atmosphere. Dry CH_2Cl_2 and Et_3N were obtained by distillation from CaH_2. All reactions were monitored by TLC analysis until the starting material had been consumed. Unless otherwise stated, solvents or reagents were used as received without further purification. Analytical thin layer chromatography (TLC) was performed on pre-coated silica gel 60 F-254 plates (particle size 0.040-0.055 mm, 230-400 mesh) and visualization was accomplished using UV light or by staining with basic $KMnO_4$ or anisaldehyde dye. NMR spectra were recorded at 300 MHz/75 MHz ($^1H/^{13}C$ NMR) in $CDCl_3$ unless otherwise stated on either a Bruker AVANCE 300 MHz or a Bruker QM-300 MHz spectrometer at 23 °C. Chemical shifts (δ) are reported in parts per million and the residual solvent peak was used as an internal standard (δ 7.261/77.0, $^1H/^{13}C$ NMR). Data are reported as follows: Chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, s = sextet, m = multiplet, b = broad, app = apparent), integration, and coupling constant(s) (Hz). IR spectra were obtained on a Nicolet AVATAR 360 FT-IR E.S.P spectrometer. Mass spectra were obtained on a Micromass Autospec double focusing instrument. Melting points were determined using a Laboratory Devices Mel-Temp II and are uncorrected.

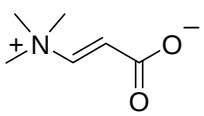
Authors note: Compounds **2-36**, **2-48**, **2-49**, **2-50**, **2-51**, **2-52**, **2-59**, **2-61**, **2-63**, **2-69** and relevant precursors thereof were prepared by Joshua G. Pierce, University of Pittsburgh. Compounds **3-21**, **3-23**, **3-25**, **3-26** and relevant precursors thereof were prepared by Corey R. J. Stephenson, University of Pittsburgh.

5.1 WATER ACCELERATED CASCADE REACTIONS



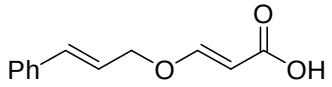
1-((*E*)-3-(Vinyloxy)prop-1-enyl)benzene (1-30).[140] To a solution of cinnamyl alcohol (5.80 g, 43.3 mmol) in ethyl vinyl ether (90 mL) at ambient temperature was added $Hg(OAc)_2$ (5.11g, 16.0 mmol). The reaction mixture was heated at reflux for 4 h, cooled, treated with K_2CO_3 (2 g) and filtered through a pad of Al_2O_3. The filtrate was concentrated, dissolved in hexanes (10 mL) and filtered through a 1.5 inch pad of SiO_2. The filtrate was concentrated to provide allylic vinyl ether **1-30** (4.02 g, 25.1 mmol, 58%) as a colorless oil: ^{1}H NMR δ 7.51-7.33 (m, 5 H), 6.75 (d, 1 H, *J* = 16.0 Hz), 6.64 (dd, 1 H, *J* = 14.3, 6.8 Hz), 6.41 (dt, 1 H, *J* = 16.0, 5.8 Hz), 4.47 (dd, 2 H, *J* = 5.9, 1.4 Hz), 4.41 (dd, 1 H, *J* = 14.3, 2.1 Hz), 4.20 (dd, 1 H, *J* = 6.8, 2.1 Hz); ^{13}C NMR δ 151.3, 136.3, 132.6, 128.4 (2 C), 127.7, 126.4 (2 C), 124.2, 87.1, 68.6.

(*E*,3*S,5*R**)-7-Methyl-3-phenylundeca-1,6-dien-5-ol (1-31a)** and **(*E*,3*S**,5*S**)-7-methyl-3-phenylundeca-1,6-dien-5-ol (1-31b)**. **General Protocol A**. To a -30 °C solution of $AlMe_3$ (540 mg, 7.35 mmol) and Cp_2ZrCl_2 (85.8 mg, 0.294 mmol) in CH_2Cl_2 (6 mL) was added H_2O (66.1 μL, 3.67 mmol) dropwise. The reaction mixture was warmed to ambient temperature and then cooled to 0 °C and treated with 1-hexyne (676 μL, 5.88 mmol). The mixture was stirred for 30 min, cooled to -78 °C, and treated with vinyl ether **1-30** (470 mg, 2.94 mmol) in CH_2Cl_2 (1.5 mL). The mixture was warmed to ambient temperature over 10 min and quenched with 1 M Rochelle's salt (3 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on SiO_2 (hexanes/EtOAc, 5:1) to furnish alcohols **1-31a** and **1-31b** as a colorless oil which was a 1:1 mixture of inseparable diastereomers as indicated by ^{1}H NMR analysis: (1:1 mixture of diastereomers) IR (neat) 3334, 2956, 2929, 1452, 996, 913, 700 cm^{-1}; ^{1}H NMR δ 7.34-7.18 (m, 5 H), 6.03-5.92 (m, 1 H), 5.22-5.17 (m, 1 H), 5.11-5.02 (m, 2 H), 4.31-4.26 (m, 1 H), 3.49-3.39 (m, 1 H), 2.09-1.96 (m, 3 H), 1.88-1.74 (m, 1 H), 1.54 (2 br s, 3 H), 1.42-1.20 (m, 4 H), 0.94 (t, 1.5 H, J = 4.7 Hz), 0.91 (t, 1.5 H, J = 4.5 Hz); ^{13}C NMR δ 143.8 (2 C), 142.3, 141.9, 139.5, 139.0, 128.4 (4 C), 127.6 (5 C), 127.2, 126.2 (2 C), 114.2, 114.0, 66.6, 66.4, 46.2, 46.1, 43.0, 42.9, 39.2 (2 C), 29.9 (2 C), 22.3 (2 C), 16.5 (2 C), 13.9 (2 C); MS (EI) *m/z* (rel intensity) 240 ([M-H_2O]$^+$, 34), 201 (30), 183 (62), 155 (16), 117 (100); HRMS (EI) *m/z* calcd for $C_{18}H_{26}O$ 258.1984, found 258.1982.

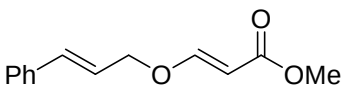


(*E*)-(Carboxyvinyl)trimethylammonium betaine (1-33).[141] To a mixture of ethyl propiolate (5.32 g, 54.0 mmol) in CH_2Cl_2 (3 mL) and H_2O (90 mL) at 5 °C was added Me_3N (25%

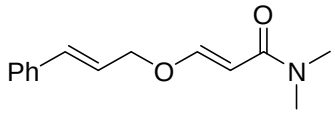
solution in water, 18.0 mL, 75.6 mmol) dropwise over 30 min. The temperature was kept under 30 °C during the addition. The mixture was warmed to ambient temperature and stirred for 3 h. The organic layer was separated and the aqueous layer was washed with CH_2Cl_2 (2 x 15 mL). The aqueous layer was azeotroped to dryness with 1,4-dioxane and the resulting solid washed with CH_3CN (10 mL). The solid cake was dried *in vacuo* for 24 h to provide betaine **1-33** (5.25 g, 40.4 mmol, 76%) as a beige powder: Mp 174.1-176.0 °C (dec., 1,4-dioxane); (lit. 176-177 °C (dec.)); ^{1}H NMR δ 7.07 (d, 1 H, J = 13.8 Hz), 6.57 (d, 1 H, J = 14.0 Hz), 3.49 (s, 9 H).



(2*E*)-3-(Cinnamyloxy)acrylic acid (1-34).[111] Hexane-washed NaH (830 mg, 34.6 mmol) was suspended in THF (40 mL) and cooled to 0 °C. A solution of cinnamyl alcohol (3.86 g, 28.8 mmol) in THF (40 mL) was added dropwise over 30 min and the reaction mixture was warmed to ambient temperature and stirred for 30 min. To this pink solution was added betaine **1-33** (4.70 g, 36.2 mmol) in one portion. The mixture was heated at reflux for 4 h, cooled to ambient temperature and treated with water (10 mL). The aqueous layer was washed with Et_2O (2 x 100 mL), acidified to pH 1 with 10.0 M hydrochloric acid, extracted with Et_2O (3 x 100 mL), dried ($MgSO_4$), and concentrated. The resulting white powder was dried at 0.1 mmHg for 24 h to furnish **1-34** (5.23 g, 25.6 mmol, 95%) as a white powder: Mp 139.0-141.9 °C (Et_2O); (lit. 140-141.5 °C); ^{1}H NMR δ 12.00 (br s, 1 H), 7.73 (d, 1 H, J = 12.5 Hz), 7.43-7.27 (m, 5 H), 6.69 (d, 1 H, J = 16.0 Hz), 6.30 (dt, 1 H, J = 15.9, 6.2 Hz), 5.29 (d, 1 H, 12.5 Hz), 4.58 (dd, 2 H, J = 6.0, 0.7 Hz).

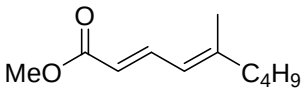


(2*E*)-Methyl 3-(cinnamyloxy)acrylate (1-35). A solution of acid **1-34** (500 mg, 2.45 mmol) in MeOH (5 mL) and benzene (19 mL) was treated at ambient temperature with $TMSCHN_2$ (2.0 M solution in hexanes, 1.72 mL, 3.43 mmol) and stirred for 90 min. The reaction mixture was concentrated and chromatographed on SiO_2 (hexanes/EtOAc, 3:1) to yield **1-35** (530 mg, 2.45 mmol, 99%) as a colorless oil: IR (neat) 1710, 1643, 1624, 1190, 1137, 967, 745 cm^{-1}; ^1H NMR δ 7.62 (d, 1 H, *J* = 12.6 Hz), 7.42-7.19 (m, 5 H), 6.68 (d, 1 H, *J* = 15.9 Hz), 6.29 (dt, 1 H, *J* = 15.9, 6.0 Hz), 5.30 (d, 1 H, *J* = 12.4 Hz), 4.55 (dd, 2 H, *J* = 6.1, 1.2 Hz), 3.71 (s, 3 H); ^{13}C NMR δ 168.1, 162.0, 135.8, 134.4, 128.6 (2 C), 128.3, 126.6 (2 C), 122.5, 96.9, 71.6, 51.1; MS (EI) *m/z* (rel intensity) 218 ($[M]^+$, 41), 200 (14), 158 (8), 129 (12), 117 (100), 91 (49); HRMS (EI) *m/z* calcd for $C_{13}H_{14}O_3$ 218.0942, found 218.0932.

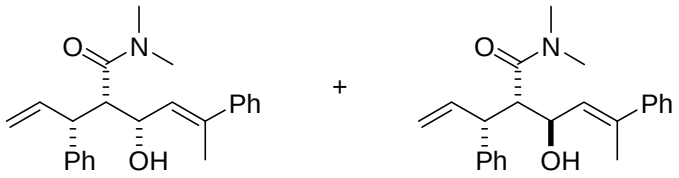


(2*E*)-3-(Cinnamyloxy)-*N,N*-dimethylacrylamide (1-36). Acid **1-34** (1.08 g, 5.27 mmol), EDCI (1.31 g, 6.85 mmol), DMAP (64.3 mg, 0.53 mmol), and dimethylamine hydrochloride (1.07 g, 13.2 mmol) were combined in CH_2Cl_2 (10 mL) at ambient temperature and DIPEA (3.4 mL, 18.4 mmol) was added dropwise over 5 min. The reaction mixture was stirred for 30 h and quenched with H_2O (5 mL). The aqueous layer was extracted with CH_2Cl_2 (4 x 10 mL) and the combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated. The resulting residue was chromatographed on SiO_2 (EtOAc) to give amide **1-36** (624 mg, 2.70 mmol, 48%) as a white solid: mp 58.4-59.6 °C (EtOAc); IR (KBr) 2931, 1651, 1591, 1495, 1449, 1254, 1119, 967, 746 cm^{-1}; ^1H NMR δ 7.53 (d, 1 H, *J* = 11.8 Hz), 7.34-7.22 (m, 5 H), 6.60 (d, 1 H, *J* = 15.9 Hz), 6.22 (dt, 1 H, *J* = 15.9, 6.1 Hz), 5.67 (d, 1 H, *J* = 11.8 Hz), 4.48 (dd, 2 H, *J* = 6.1, 1.2 Hz), 2.93 (s, 6 H);

^{13}C NMR δ 166.9, 160.4, 135.7, 133.8, 128.4 (2 C), 127.9, 126.4 (2 C), 122.9, 96.4, 71.9, 36.9, 35.1; MS (EI) *m/z* (rel intensity) 231 ([M]$^+$, 12), 203 (21), 117 (100), 91 (36), 72 (15); HRMS (EI) *m/z* calcd for $C_{14}H_{17}NO_2$ 231.1260, found 231.1250.

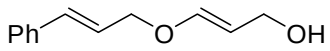


(2*E*,4*E*)-Methyl 5-methylnona-2,4-dienoate (1-37). According to the general protocol A, $AlMe_3$ (206 mg, 2.88 mmol), Cp_2ZrCl_2 (33.6 mg, 0.115 mmol), H_2O (25.9 μL, 1.44 mmol), 1-hexyne (264 μL, 2.30 mmol) and ester **1-35** (250 mg, 1.15 mmol) afforded dienoate **37** (79 mg, 0.193 mmol, 37%) as a colorless oil: ^{1}H NMR δ 7.58 (dd, 1 H, *J* = 15.1, 11.6 Hz), 5.98 (d, 1 H, *J* = 11.3 Hz), 5.77 (d, 1 H, *J* = 15.1 Hz), 3.73 (s, 3 H), 2.13 (t, 2 H, *J* = 7.2 Hz), 1.88 (br s, 3 H), 1.49-1.39 (m, 2 H), 1.36-1.24 (m, 2 H), 0.90 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR δ 168.0, 150.4, 141.2, 122.9, 118.1, 51.2, 39.8, 29.7, 22.3, 17.2, 13.8; MS (EI) 182 ([M]$^+$, 23), 167 (15), 151 (23), 125 (85), 111 (39).



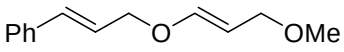
(*E*,2*S,3*S**)-3-Hydroxy-*N*,*N*-dimethyl-5-phenyl-2-((*R**)-1-phenylallyl)hex-4-enamide (1-38)** and **(*E*,2*S**,3*R**)-3-hydroxy-*N*,*N*-dimethyl-5-phenyl-2-((*R**)-1-phenylallyl)hex-4-enamide (1-39)**. According to the general protocol A, $AlMe_3$ (645 mg, 8.96 mmol), Cp_2ZrCl_2 (26.2 mg, 0.0896 mmol), H_2O (64.5 μL, 0.0896 mmol), phenylacetylene (197 μL, 1.79 mmol) and amide **1-36** (207 mg, 0.896 mmol) afforded, after chromatography on SiO_2 (hexanes/EtOAc, 3:1), hydroxy amides **1-**

38 and **1-39** (31.9 mg, 0.0914 mmol, 10%) as a white solid which was a 5:1 mixture (**1-38**:**1-39**) of partially separable diastereomers by ^{1}H NMR analysis of the crude reaction mixture. **1-38**: Mp 142.8-145.9 °C (hexanes/EtOAc); IR (KBr) 3388, 3059, 3028, 2930, 1614, 1494, 1445, 1147, 1051, 760, 702 cm^{-1}; ^{1}H NMR δ 7.33-7.22 (m, 10 H), 6.21 (ddd, 1 H, *J* = 17.0, 10.0, 9.4 Hz), 5.72 (dd, 1 H, *J* = 8.4, 1.3 Hz), 5.43 (d, 1 H, *J* = 17.0 Hz), 5.33 (dd, 1 H, *J* = 10.2, 1.5 Hz), 5.20 (d, 1 H, *J* = 9.9 Hz, exchanges with D_2O), 4.87-4.80 (m, 1 H), 4.06 (dd, 1 H, *J* = 9.5, 9.5 Hz), 3.05 (dd, 1 H, *J* = 11.1, 2.7 Hz), 2.63 (s, 3 H), 2.48 (s, 3 H), 2.11 (d, 3 H, *J* = 1.3 Hz); ^{13}C NMR δ 174.3. 142.9, 141.6, 137.3, 135.6, 130.3, 128.3 (2 C), 128.2 (2 C), 127.9 (2 C), 127.2, 126.8, 125.7 (2 C), 118.2, 67.9, 49.9, 49.6, 37.4, 35.1, 16.2; MS (EI) *m/z* (rel intensity) 259 ([M-$C_3H_8O_2N$]$^+$, 34), 240 (21), 232 (32), 176 (12), 131 (15), 117 (63), 72 (100); HRMS (EI) *m/z* calcd for $C_{20}H_{19}$ [M-$C_3H_8O_2N$] 259.1487, found 259.1475. Characteristic data for **1-39**: ^{1}H NMR δ 7.50 (d, 2 H, *J* = 7.0 Hz), 6.51 (dt, 1 H, *J* = 17.0, 10.1 Hz), 3.90 (app t, 1 H, *J* = 10.1 Hz), 3.25 (dd, 1 H, *J* = 10.0, 8.5 Hz), 2.37 (s, 3 H), 1.90 (d, 3 H), 1.51 (s, 3 H).

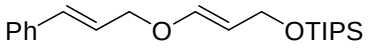


(2*E*)-3-(Cinnamyloxy)prop-2-en-1-ol (1-40). A solution of ester **1-35** (10.2 g, 47.3 mmol) in CH_2Cl_2 (50 mL) was treated at -78 °C with DIBAL-H (1.0 M solution in hexanes**,** 99.2 mL, 99.2 mmol). The reaction mixture was allowed to warm to ambient temperature over 25 min and quenched with 1 M NaOH (10 mL). The aqueous layer was extracted with CH_2Cl_2 (5 x 35 mL). The combined organic layers were washed with water and brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on SiO_2 (Et_2O/hexanes, 3:1) to yield **1-40** (2.61 g, 13.7 mmol, 29%) as a white solid: Mp 49.5-51.4 °C (Et_2O/hexanes); IR (KBr) 3325, 2909, 2863, 1652, 1449, 1181, 971, 744 cm^{-1}; ^{1}H NMR δ 7.41-7.25 (m, 5 H), 6.66 (d, 1 H, *J* = 15.9 Hz), 6.57 (d, 1 H, *J* = 12.6

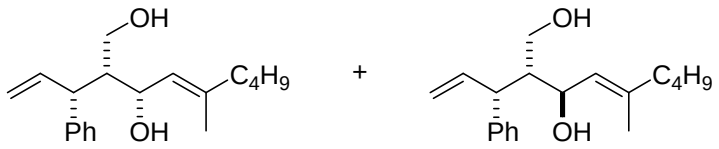
Hz), 6.30 (dt, 1 H, J = 15.9, 5.9 Hz), 5.13 (dt, 1 H, J = 12.5, 7.5 Hz) 4.42 (d, 2 H, J = 6.0 Hz), 4.07 (app t, 2 H, J = 5.7 Hz) 1.14 (t, 1 H, J = 5.6 Hz); ^{13}C NMR δ 149.3, 136.1, 133.0. 128.4 (2 C), 127.8, 126.4 (2 C), 124.0, 103.4, 69.7, 60.2; MS (EI) *m/z* (rel intensity) 190 ([M]$^+$, 15), 172 (47), 159 (88), 117 (100), 91 (34); HRMS (EI) *m/z* calcd for $C_{12}H_{14}O_2$ 190.0993, found 190.0984.



1-((1*E*)-3-((*E*)-3-Methoxyprop-1-enyloxy)prop-1-enyl)benzene (1-41). To a suspension of NaH (30.3 mg, 1.26 mmol) in THF (3 mL) at ambient temperature was added a solution of alcohol **1-40** (200 mg, 1.05 mmol) in THF (2 mL). The reaction mixture was stirred at ambient temperature for 45 min and treated with CH_3I (164 μL, 2.63 mmol) over 3 min. The mixture was stirred at ambient temperature for 12 h and quenched with H_2O (1 mL). The aqueous layer was extracted with Et_2O (3 x 2 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated. The residue was chromatographed on SiO_2 (hexanes/EtOAc, 3:1) to yield methyl ether **1-41** (207 mg, 1.02 mmol, 97%) as a colorless oil: IR (neat) 3060, 2924, 2855, 2821, 1652, 1496, 1383, 1174, 1086, 967, 745 cm^{-1}; ^{1}H NMR δ 7.42-7.28 (m, 5 H), 6.65 (d, 1 H, J = 16.0 Hz), 6.57 (d, 1 H, J = 12.6 Hz), 6.31 (dt, 1 H, J = 15.9, 5.9 Hz), 5.04 (dt, 1 H, J = 12.6, 7.4 Hz), 4.41 (dd, 2 H, J = 5.9, 1.3 Hz), 3.86 (dd, 2 H, J = 7.4, 0.8 Hz), 3.31 (s, 3 H); ^{13}C NMR δ 149.9, 136.1, 132.8, 128.3 (2 C), 127.7, 126.3 (2 C), 123.9, 100.2, 69.7, 69.5, 56.8; MS (EI) *m/z* (rel intensity) 204 ([M]$^+$, 16), 186 (16), 172 (31), 159 (72), 148 (70), 131 (42), 117 (100), 91 (15); HRMS (EI) *m/z* calcd for $C_{11}H_{11}O$ [M-C_2H_5O] 159.0809, found 159.0797.

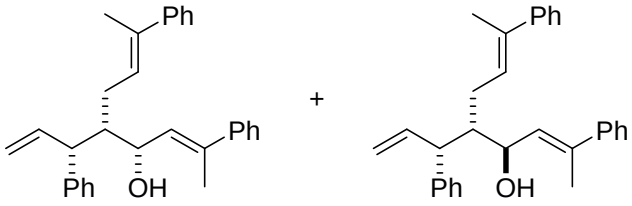


((2*E*)-3-(Cinnamyloxy)allyloxy)triisopropylsilane (1-42). A solution of imidazole (101 mg, 1.47 mmol), TIPSCl (235 μL, 1.10 mmol), and DMAP (13.4 mg, 0.112 mmol) in CH_2Cl_2 (3 mL) was cooled to 0 °C and treated with a solution of alcohol **1-40** (200 mg, 1.05 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was warmed to ambient temperature, stirred for 4 h, and quenched with H_2O (1 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 2 mL) and the combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated. The residue was chromatographed on SiO_2 (hexanes/EtOAc, 9:1) to yield silyl ether **1-42** (338 mg, 0.974 mmol, 93%) as a colorless oil: IR (neat) 2942, 2891, 2865, 1672, 1652, 1463, 1283, 1181, 1054, 965, 690 cm^{-1}; ^1H NMR δ 7.40-7.24 (m, 5 H), 6.64 (d, 1 H, *J* = 16.0 Hz), 6.53 (d, 1 H, *J* = 12.6 Hz), 6.30 (dt, 1 H, *J* = 15.9, 5.9 Hz), 5.06 (dt, 1 H, *J* = 12.5, 6.6 Hz), 4.39 (dd, 2 H, *J* = 5.9, 1.3 Hz), 4.20 (dd, 2 H, *J* = 6.5, 1.2 Hz), 1.18-1.03 (m, 21 H); ^{13}C NMR δ 147.8, 136.4, 132.9, 128.5 (2 C), 127.8, 126.5 (2 C), 124.4, 104.2, 69.7, 61.1, 18.0, 12.0; MS (EI) *m/z* (rel intensity) 347 ($[M]^+$, 9), 303 (27), 247 (24), 145 (6), 117 (100), 84 (25); HRMS (EI) *m/z* calcd for $C_{21}H_{34}O_2Si$ 347. 2406, found 347.2396.



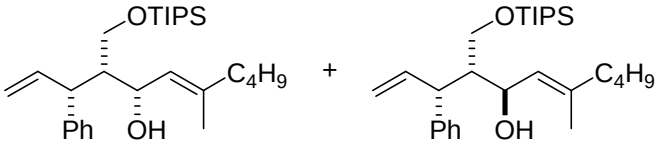
(*E*,2*R,3*S**)-5-Methyl-2-((*R**)-1-phenylallyl)non-4-ene-1,3-diol (1-43)** and **(*E*,2*R**,3*R**)-5-methyl-2-((*R**)-1-phenylallyl)non-4-ene-1,3-diol (1-44)**. According to general protocol A, $AlMe_3$ (2.12 g, 29.5 mmol), Cp_2ZrCl_2 (215 mg, 0.737 mmol), H_2O (265 μL, 14.7 mmol), 1-hexyne (1.69 mL, 14.7 mmol) and alcohol **1-40** (1.40 g, 7.37 mmol) afforded, after chromatography on SiO_2 (hexanes/EtOAc, 3:1), diols **1-43** and **1-44** (636 mg, 2.21 mmol, 30%) as a colorless oil which was a 10:1 mixture (**1-43**:**1-44**) of inseparable diastereomers as indicated by ^1H NMR analysis. **1-43**: IR (neat) 3342, 2956, 2929, 1453, 1034, 915, 759, 700 cm^{-1}; ^1H NMR δ 7.33-7.18 (m, 5 H), 6.09 (dt, 1

H, J = 16.9, 9.8 Hz), 5.48 (d, 1 H, J = 8.5 Hz), 5.21 (d, 1 H, J = 17.1 Hz), 5.13 (dd, 1 H, J = 10.1, 1.2 Hz), 4.80-4.77 (m, 1 H), 3.93 (br d, 1 H, J = 11.1 Hz), 3.79 (t, 1 H, J = 9.6 Hz), 3.38-3.31 (m, 1 H), 2.92-2.90 (m, 1 H, exchanges with D_2O), 2.56 (br d, 1 H, J = 4.1 Hz, exchanges with D_2O), 2.02 (t, 2 H, J = 7.0 Hz), 1.81-1.71 (m, 1 H), 1.64 (s, 3 H), 1.46-1.36 (m, 2 H), 1.34-1.24 (m, 2 H), 0.91 (t, 3 H, J = 7.1 Hz); ^{13}C NMR δ 142.6, 140.5, 138.6, 128.6 (2 C), 128.0 (2 C), 126.7, 126.4, 115.9, 70.3, 61.3, 49.3, 48.8, 39.3, 29.9, 22.3, 16.5, 13.9; MS (EI) *m/z* (rel intensity) 270 ([M-H_2O]$^+$, 18), 252 (52), 240 (52), 209 (36), 195 (61), 155 (56), 117 (100); HRMS (EI) *m/z* calcd for $C_{19}H_{26}O$ [M-H_2O] 270.1984, found 270.1982. Characteristic data for **1-44**: ^{1}H NMR δ 5.39 (d, 1 H, J = 7.4 Hz), 2.41 (br d, 1 H, J = 3.4 Hz, exchanges with D_2O); 13C NMR δ 143.1, 139.3, 138.4, 127.8, 70.5, 61.4, 49.6, 16.2.

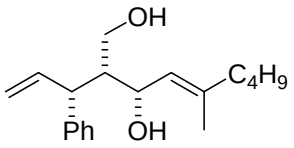


(2*E*,4*R,5*S**,7*E*)-2,8-Diphenyl-5-((*R**)-1-phenylallyl)nona-2,7-dien-4-ol (1-45)** and **(2*E*,4*S**,5*S**,7*E*)-2,8-diphenyl-5-((*R**)-1-phenylallyl)nona-2,7-dien-4-ol (1-46)**. According to general protocol A, $AlMe_3$ (58.3 mg, 0.810 mmol), Cp_2ZrCl_2 (10.7 mg, 0.0368 mmol), H_2O (7.29 μL, 0.405 mmol), phenylacetylene (101 μL, 0.920 mmol) and methyl ether **1-41** (75.0 mg, 0.368 mmol) afforded, after chromatography on SiO_2 (hexanes/EtOAc, 5:1), alcohols **1-45** and **1-46** (18.0 mg, 0.044 mmol, 12%) as a colorless oil which was an 8:1 mixture (**1-45**:**1-46**) of inseparable diastereomers as indicated by ^{1}H NMR analysis: **1-45**: ^{1}H NMR δ 7.50-7.29 (m, 15 H), 6.38 (dt, 1 H, J = 15.6, 9.8 Hz), 6.14 (dd, 1 H, J = 8.4, 1.3 Hz), 5.93-5.88 (m, 1 H), 5.37 (dd, 1 H, J = 16.8, 1.1 Hz), 5.30 (dd, 1 H, J = 10.0, 1.7 Hz), 5.08-5.05 (m, 1 H), 3.73 (t, 1 H, J = 4.9 Hz), 2.59-2.49 (m, 1

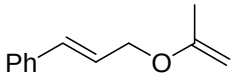
H), 2.41-2.28 (m, 2 H), 2.18 (d, 3 H, J = 1.2 Hz), 2.01 (s, 3 H), 1.82 (d, 1 H, J = 4.8 Hz, exchanges with D_2O); MS (EI) *m/z* (rel intensity) 390 ($[M-H_2O]^+$, 43), 285 (41), 155 (79), 131 (89), 105 (96), 91 (100). Characteristic data for **1-46**: ^{1}H NMR δ 6.06 (dd, 1 H, J = 8.2, 1.3 Hz), 1.97 (d, 3 H, J = 1.2 Hz).



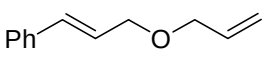
(*E*,2*R,3*S**)-5-Methyl-2-((*R**)-1-phenylallyl)non-4-ene-1-triisopropylsilyloxy-3-ol (1-47)** and **(*E*,2*R**,3*R**)-5-methyl-2-((*R**)-1-phenylallyl)non-4-ene-1-triisopropylsilyloxy-3-ol (1-48)**. According to general protocol A, $AlMe_3$ (39.1 mg, 0.258 mmol), Cp_2ZrCl_2 (7.53 mg, 0.0258 mmol), H_2O (4.64 μL, 0.258 mmol), 1-hexyne (59.4 μL, 0.517 mmol) and silyl ether **1-42** (89.4 mg, 0.258 mmol) afforded, after chromatography on SiO2 (hexanes/EtOAc, 9:1), alcohols **1-47** and **1-48** (68.1 mg, 0.153 mmol, 60%) as a colorless oil which was a 10:1 mixture (**1-47**:**1-48**) of inseparable diastereomers as indicated by ^{1}H NMR analysis. **1-47**: IR (neat) 3508, 2929, 2866, 1464, 1071, 882, 700 cm^{-1}; ^{1}H NMR δ 7.38-7.33 (m, 3 H), 7.28-7.24 (m, 2 H), 6.17 (dt, 1 H, J = 16.9, 9.8 Hz), 5.57 (d, 1 H, J = 8.2 Hz), 5.28 (d, 1 H, J = 17.0 Hz), 5.18 (dd, 1 H, J = 10.1, 1.2 Hz), 4.79 (td, 1 H, J = 8.1, 3.5 Hz), 4.10 (dd, 1 H, J = 10.2, 2.9 Hz), 3.92 (t, 1 H, J = 9.5 Hz), 3.84 (d, 1 H, J = 8.1 Hz, exchanges with D_2O), 3.65 (dd, 1 H, J = 10.1, 3.7 Hz), 2.09 (t, 2 H, J = 7.8 Hz), 1.93-1.86 (m, 1 H), 1.80 (s, 3 H), 1.54-1.44 (m, 2 H), 1.41-1.34 (m, 2 H), 1.06-1.04 (m, 21 H), 0.98 (t, 3 H, J = 7.2 Hz); ^{13}C NMR δ 142.6, 140.7, 136.9, 128.5 (2 C), 128.2 (2 C), 127.6, 126.3, 115.9, 69.7, 62.9, 48.7, 48.6, 39.3, 29.8, 22.4, 17.9 (6 C), 16.4, 14.0, 11.7 (3 C); MS (EI) *m/z* (rel intensity) 444 ($[M]^+$, 5), 401 (42), 383 (8), 309 (21), 253 (13), 117 (100); HRMS (EI) *m/z* calcd for $C_{28}H_{48}O_2Si$ 444.3424, found 444.3408. Characteristic data for **1-48**: ^{1}H NMR δ 5.47 (d, 1 H, J = 7.6 Hz).



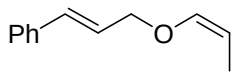
(*E*,2*R,3*S**)-5-Methyl-2-((*R**)-1-phenylallyl)non-4-ene-1,3-diol (1-43).** To a solution of **1-47** and **1-48** (48.0 mg, 0.108 mmol) in THF (1.1 mL) at ambient temperature was added TBAF (1.0 M solution in THF, 216 μL, 0.216 mmol). The reaction mixture was stirred for 1 h and quenched with H_2O (1 mL). The mixture was extracted with Et_2O (3 x 3 mL) and the combined organic layers were washed with H_2O, brine, dried (Na_2SO_4) and concentrated. The residue was chromatographed on SiO_2 (hexanes/EtOAc, 5:1) to yield diol **1-43** (22.9 mg, 0.0795 mmol, 74%) as a colorless oil.



1-((*E*)-3-(Prop-1-en-2-yloxy)prop-1-enyl)benzene (1-51).[110] To a solution of cinnamyl alcohol (1.00 g, 7.46 mmol) in isopropenyl methyl ether (3 mL) was added $Hg(OAc)_2$ (1.19 g, 3.73 mmol) at ambient temperature. The mixture was allowed to stir for 30 h treated with solid K_2CO_3 (1 g) and filtered. The filtrate was evaporated and the residue chromatographed on SiO_2 (hexanes/EtOAc, 9:1) to yield vinyl ether **1-51** (483 mg, 2.78 mmol, 45%) as a colorless oil: ^{1}H NMR δ 7.45-7.28 (m, 5 H), 6.69 (d, 1 H, J = 15.9 Hz), 6.44-6.34 (m, 1 H), 4.41 (dd, 2 H, J = 6.0, 1.2 Hz), 3.96 (d, 2 H, J = 4.2 Hz), 1.92 (s, 3 H); ^{13}C NMR δ 159.5, 136.6, 132.6, 128.5 (2 C), 127.7, 126.5 (2 C), 124.7, 81.8, 67.9, 21.0.

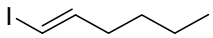


1-((*E*)-3-(Allyloxy)prop-1-enyl)benzene (1-52).[142] To suspension of NaH (752 mg, 31.1 mmol) in THF (5 mL) at ambient temperature was added a solution of cinnamyl alcohol (3.00 g, 22.4 mmol) in THF (10 mL) dropwise over 10 min. The reaction mixture was stirred for 40 min, cooled to 0 °C, treated with allyl iodide (2.47 mL, 26.9 mmol) and warmed to ambient temperature and stirred overnight. The reaction mixture was quenched with H_2O (5 mL) and the aqueous layer extracted with hexanes/EtOAc (1:1, 3 x 25 mL)**.** The combined organic layers were washed with H_2O, brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed on SiO_2 (hexanes/EtOAC, 9:1) followed by Kugelrohr distillation to yield allyl ether **1-52** (3.90 g, 22.4 mmol, 97%) as a colorless oil: bp 82 °C (0.1 mmHg); ^{1}H NMR δ 7.44-7.24 (m, 5 H), 6.65 (d, 1 H, *J* = 15.9 Hz), 6.33 (dt, 1 H, *J* = 15.9, 5.9 Hz), 6.06-5.94 (m, 1 H), 5.36 (dd, 1 H, *J* = 17.1, 1.5 Hz), 5.25 (dd, 1 H, *J* = 10.4, 0.7 Hz), 4.17 (dd, 2 H, *J* = 5.8, 1.0 Hz), 4.06 (d, 2 H, *J* = 5.5 Hz); ^{13}C NMR δ 136.5, 134.5, 132.0, 128.3 (2 C), 127.4, 126.2 (2 C), 125.8, 116.8, 70.8, 70.4.

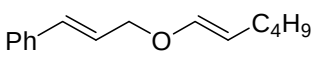


1-((1*E*)-3-(Prop-1-enyloxy)prop-1-enyl)benzene (1-53). To a solution of **1-52** (241 mg, 1.39 mmol) and $NiCl_2$(dppb)[42] (77.3 mg, 0.139 mmol) in THF (700 μL) at -5 °C was added $Li(Et)_3BH$ (1.0 M solution in THF, 139 μL, 0.139 mmol) dropwise. The reaction mixture was stirred for 25 min and filtered through basic Al_2O_3 (hexanes) and celite (hexanes). The filtrate was concentrated and the residue chromatographed on SiO_2 (hexanes/EtOAc, 20:1) to furnish vinyl ether **1-53** (120 mg, 0.690 mmol, 50%) as a 94:6 mixture of (*Z*:*E*) isomers (as indicated by ^{1}H NMR analysis) and starting material (103 mg, 0.592 mmol, 43%): (*E,Z*)-**1-53**: IR (neat) 3028, 2918, 2863, 1668, 1356, 1131, 1077, 966, 692 cm^{-1}; ^{1}H NMR δ 7.44-7.24 (m, 5 H), 6.65 (d, 1 H, *J* = 15.9 Hz), 6.32 (dt, 1 H, *J* = 15.9, 5.9 Hz), 6.06 (dq, 1 H, *J* = 6.2, 1.7 Hz), 4.48 (qd, 1 H, *J* = 6.8, 0.6 Hz), 4.44

(dd, 2 H, J = 5.8, 1.4 Hz), 1.66 (dd, 3 H, J = 6.8, 1.7 Hz); ^{13}C NMR δ 145.0, 136.4, 132.6, 128.5 (2 C), 127.8, 126.5 (2 C), 125.3, 101.4, 72.2, 9.3; MS (EI) *m/z* (rel intensity) 174 ([M]$^+$, 17), 131 (11), 117 (100), 104 (12); HRMS (EI) *m/z* calcd for $C_{12}H_{14}O$ 174.1045, 174.1050. Characteristic ^{1}H NMR data for (*E,E*)-**1-53**: ^{1}H NMR δ 1.60 (dd, 3 H, J = 6.7, 1.6 Hz).



(*E*)-1-Iodohex-1-ene (1-54).[143] To a solution of 1-hexyne (4.10 g, 49.9 mmol) in *n*-heptane (10 mL) at ambient temperature was added DIBAL-H (1.0 M solution in hexanes, 50.0 mL, 50.0 mmol) dropwise with the temperature not rising above 40 °C. The reaction mixture was heated at 50 °C for 2 h. The *n*-heptane and hexane were distilled off and the residue was dissolved in THF (20 mL) and cooled to -78 °C. A solution of I_2 (14.1 g, 54.9 mmol) in THF (25 mL) was added dropwise. The reaction mixture was warmed to ambient temperature after the addition, quenched with 10% HCl until gas evolution ceased, poured into a slurry of 10% HCl and ice and extracted with pentane (3 x 20 mL). The combined organic layers were washed with sat. $Na_2S_2O_3$, sat. $NaHCO_3$, dried ($MgSO_4$), filtered and concentrated. The residue was distilled to furnish vinyl iodide **1-54** (6.92 g, 33.0 mmol, 66%) as a light yellow oil: bp 56-58 °C (2 mmHg), (lit.[59] 50-52 °C, 3 mmHg); ^{1}H NMR δ 6.50 (dt, 1 H, J = 14.1, 7.2 Hz), 5.97 (dt, 1 H, J = 14.3, 1.3 Hz), 2.06-2.01 (m, 2 H), 1.42-1.27 (m, 4 H), 0.89 (t, 3 H, J = 4.9 Hz).

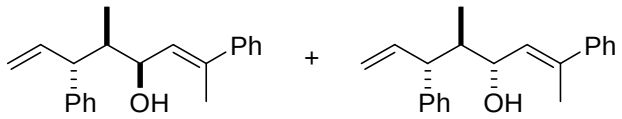


1-((1*E*)-3-((*E*)-Hex-1-enyloxy)prop-1-enyl)benzene (1-56). A suspension of cinnamyl alcohol (2.00 g, 14.9 mmol), vinyl iodide **1-54** (1.57 g, 7.46 mmol), Cs_2CO_3 (3.64 g, 11.2 mmol), CuI (142 mg, 0.750 mmol) and 3,4,7,8-tetramethyl-1,10-phenanthroline (353 mg, 1.49 mmol) in

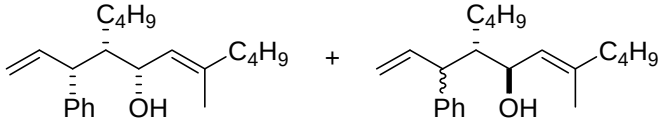
toluene (5 mL) was heated, open to air, at 80 °C for 24 h. The mixture was cooled and filtered through a pad of SiO_2, eluting with Et_2O (15 mL). The filtrate was concentrated and chromatographed on SiO_2 (hexanes/EtOAc, 9:1) to give allylic vinyl ether **1-56** (270 mg, 1.25 mmol, 17%) as a light yellow oil which was a single geometric isomer (*E,E*): IR (neat) 3057, 3027, 2956, 2925, 2854, 1671, 1651, 1449, 1166, 965, 735 cm^{-1}; ^1H NMR δ 7.53-7.36 (m, 5 H), 6.76 (d, 1 H, *J* = 16.0 Hz), 6.46-6.38 (m, 2 H), 5.00 (dt, 1 H, *J* = 12.5, 7.4 Hz), 4.46 (dd, 2 H, *J* = 5.8, 1.0 Hz), 2.07-2.03 (m, 2 H), 1.49-1.44 (m, 4 H), 1.03 (t, 3 H, *J* = 5.3 Hz); ^{13}C NMR δ 145.5, 136.5, 132.6, 128.4 (2 C), 127.7, 126.4 (2 C), 124.9, 105.1, 69.7, 32.8, 27.3, 22.0, 13.9; MS (EI) *m/z* (rel intensity) 216 ($[M]^+$, 11), 160 (45), 131 (14), 117 (100), 91 (24), 65 (5); HRMS (EI) *m/z* calcd for $C_{15}H_{20}O$ 216.1514, found 216.1515.

(*E*,4*R,6*S**)-4-Methyl-2,6-diphenylocta-2,7-dien-4-ol (1-57)** and **(*E*,4*S**,6*S**)-4-methyl-2,6-diphenylocta-2,7-dien-4-ol (1-58)**. According to the general protocol A, $AlMe_3$ (131 mg, 1.82 mmol), Cp_2ZrCl_2 (25.3 mg, 0.0868 mmol), H_2O (15.6 μL, 0.868 mmol), phenylacetylene (190 μL, 1.74 mmol) and vinyl ether **1-51** (151 mg, 0.868 mmol) afforded, after chromatography on SiO_2 (hexanes/EtOAc, 5:1), alcohols **1-57** and **1-58** (189 mg, 0.647 mmol, 75%) as a colorless oil which was an 3:2 mixture (diastereomers unassigned) of inseparable diastereomers as indicated by ^{13}C NMR analysis. Mixture of diastereomers: IR (neat) 3565, 3446, 2927, 1599, 1493, 1377, 914, 755, 699 cm^{-1}; ^1H NMR δ 7.36-7.19 (m, 10 H), 6.21-6.02 (m, 1 H), 5.78 (dd, 1 H, *J* = 10.3, 1.1 Hz), 5.17-5.03 (m, 2 H), 3.72-3.62 (m, 1 H), 2.30-2.19 (m, 5 H), 1.43 (2 s, 3 H); ^{13}C NMR δ 144.9 (2 C), 144.7, 143.8, 143.2, 136.9, 136.7, 134.7, 134.5, 128.8 (2 C), 128.7 (2 C), 128.1 (4 C), 127.8 (2 C),

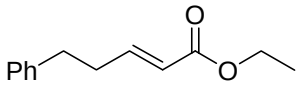
127.4 (2 C), 126.8 (2 C), 126.6 (2 C), 126.4, 125.9 (4 C), 114.8, 113.9, 74.5, 74.3, 49.5, 48.9, 47.0, 46.4, 27.8, 29.6, 16.8 (2 C); MS (EI) *m/z* (rel intensity) 292 ([M]$^+$, 13), 274 (18), 161 (62), 117 (100); HRMS (EI) *m/z* calcd for $C_{21}H_{24}O$ 292.1827, found 292.1833.



(*E*,4*S,5*R**,6*R**)-5-Methyl-2,6-diphenylocta-2,7-dien-4-ol (1-59) and (*E*,4*R**,5*R**,6*R**)-5-methyl-2,6-diphenylocta-2,7-dien-4-ol (1-60)**. According to the general protocol A, $AlMe_3$ (31.3 mg, 0.434 mmol), Cp_2ZrCl_2 (6.04 mg, 0.0207 mmol), H_2O (3.91 μL, 0.217 mmol), phenylacetylene (45.4 μL, 0.414 mmol) and vinyl ether **1-53** (36.0 mg, 0.207 mmol) afforded, after chromatography on SiO_2 (hexanes/EtOAc, 5:1), alcohols **1-59** and **1-60** (39.3 mg, 0.135 mmol, 65%) as a colorless oil which was a 10:1 mixture (**1-59**:**1-60**) of inseparable diastereomers as indicated by ^{1}H NMR analysis. **1-59**: IR (neat) 3393, 2974, 1637, 1493, 1451, 977, 757, 700 cm^{-1}; ^{1}H NMR δ 7.44-7.22 (m, 10 H), 6.04 (dt, 1 H, *J* = 17.5, 9.5 Hz), 5.89 (dd, 1 H, *J* = 8.2, 1.1 Hz), 5.13 (dd, 1 H, *J* = 7.4, 1.7 Hz), 5.08 (s, 1 H), 4.31-4.28 (m, 1 H), 3.42 (app t, 1 H, *J* = 9.3 Hz), 2.03-1.95 (m, 1 H), 1.85 (d, 3 H, *J* = 1.1 Hz), 1.39 (br s, 1 H, exchanges with D_2O), 1.10 (d, 3 H, *J* = 6.8 Hz); ^{13}C NMR δ 143.9, 143.1, 140.2, 136.3, 130.3, 128.6 (2 C), 128.2 (2 C), 127.8 (2 C), 127.1, 126.3, 125.8 (2 C), 115.8, 69.6, 53.5, 43.8, 16.2, 11.1; MS (EI) *m/z* (rel intensity) 292 ([M]$^+$, 13), 274 (9), 147 (100), 117 (39); HRMS (EI) *m/z* calcd for $C_{21}H_{24}O_2$ 292.1827, found 292.1825. Characteristic data for **1-60**: 0.84 (d, 3 H, *J* = 6.9 Hz).

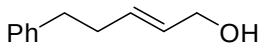


(*E*,5*S,6*R**)-8-Methyl-5-((*R**)-1-phenylallyl)dodec-7-en-6-ol (1-61)** and **(*E*,5*S**,6*S**)-8-methyl-5-((*R***S**)-1-phenylallyl)dodec-7-en-6-ol (1-62a/b)**. According to general protocol A, $AlMe_3$ (79.1 mg, 1.10 mmol), Cp_2ZrCl_2 (15.3mg, 0.0523 mmol), H_2O (9.42 μL, 0.523 mmol), 1-hexyne (120 μL, 1.05 mmol) and vinyl ether **1-56** (113 mg, 0.523 mmol) afforded alcohols **1-61** and **1-62** (147 mg, 0.468 mmol, 90%,) as a colorless oil which was a 10:1:0.8 mixture (**1-61**:**1-62a/b**) of inseparable diastereomers as indicated by ^{1}H NMR analysis of derivative **1-78**. **1-61**: IR (neat) 3444, 3062, 3027, 2928, 2858, 1635, 1600, 1454, 994, 701 cm^{-1}; ^{1}H NMR δ 7.34-7.20 (m, 5 H), 6.21 (dt, 1 H, *J* = 17.0, 9.9 Hz), 5.39 (dd, 1 H, *J* = 8.6 1.2 Hz), 5.19-5.00 (m, 2 H), 4.65-4.61 (m, 1 H), 3.45 (t, 1 H, *J* = 4.2 Hz), 2.02 (m, 2 H), 1.90-1.83 (m, 1 H), 1.59 (d, 3 H, *J* = 1.2 Hz), 1.46-1.14 (m, 8 H), 0.94 (t, 3 H, *J* = 7.1 Hz), 0.78 (t, 3 H, *J* = 6.1 Hz); ^{13}C NMR δ 143.8, 141.5, 138.0, 128.4 (2 C), 128.0 (2 C), 126.3, 126.1, 115.2, 69.4, 52.9, 48.9, 39.3, 30.9, 29.8, 27.0, 22.9, 22.3, 16.4, 13.9, 13.8; MS (EI) *m/z* (rel intensity) 296 ([M-H_2O]$^+$, 14), 239 (9), 197 (21), 179 (100), 155 (17), 127 (88); HRMS (EI) *m/z* calcd for $C_{22}H_{32}$ [M-H_2O] 296.2504, found 296.2502. Characteristic data for **1-62a**: ^{1}H NMR δ 6.06-5.91 (m, 1 H), 4.21-4.17 (m, 1 H), 1.63 (d, 3 H, *J* = 1.2 Hz). Characteristic data for **1-62b**: ^{1}H NMR δ 4.44-4.39 (m, 1 H). Characteristic data for **1-62a/b**: ^{13}C NMR δ 141.2, 125.4, 52.1, 31.9, 27.8.

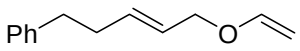


(*E*)-Ethyl 5-phenylpent-2-enoate (1-63).[144] To a suspension of NaH (1.95 g, 81.3 mmol) in THF (200 mL) at 0 °C was added triethylphosphonoacetate (16.0 mL, 80.8 mmol) over 10 min and the mixture was warmed to ambient temperature. After 15 min, the solution was cooled to 0 °C, hydrocinnamaldehyde (10.32 g, 77.0 mmol) was added dropwise over 10 min, and the mixture was

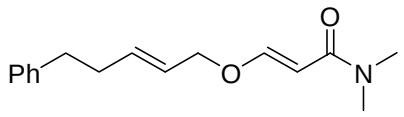
warmed to ambient temperature. After 14 h, the solution was poured into H_2O (100 mL) and extracted with EtOAc (4 x 20 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, concentrated and the residue was chromatographed on SiO_2 (hexanes/EtOAc, 17:3) to yield (*E*)-**1-63** (10.5 g, 51.5 mmol, 72%) as a colorless oil: ^{1}H NMR δ 7.34-7.18 (m, 5 H), 7.04 (dt, 1 H, *J* = 15.6, 6.8 Hz), 5.88 (dt, 1 H, *J* = 15.7, 1.4 Hz), 4.20 (q, 2 H, *J* = 7.1 Hz), 2.78 (t, 2 H, *J* = 7.3 Hz), 2.56-2.49 (m, 2 H), 1.30 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR δ 166.2, 147.7, 140.5, 128.2 (2 C), 128.1 (2 C), 125.9, 121.7, 59.8, 34.1, 33.6, 14.0.



(*E*)-5-Phenylpent-2-en-1-ol (1-64).[114] To a flask containing DIBAL-H (1.0 M solution in hexanes, 54.0 mL, 53.9 mmol) at -78 °C was added a solution of ester **1-63** (5.00 g, 24.5 mmol) in CH_2Cl_2 (30 mL) over 30 min. The reaction mixture was stirred at -78 °C for 30 min, treated with 1 M HCl (10 mL), and warmed to ambient temperature, and the solid salts were filtered off. The filtrate was extracted with CH_2Cl_2 (2 x 25 mL) and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed on SiO_2 (hexanes/EtOAc, 5:1) to yield allylic alcohol **1-64** (3.97 g, 24.5 mmol, 100%) as a colorless oil: ^{1}H NMR δ 7.34-7.20 (m, 5 H), 5.79-5.65 (m, 2 H), 4.08 (d, 2 H, *J* = 5.0 Hz), 2.74 (t, 2 H, *J* = 15.6 Hz), 2.45-2.37 (m, 2 H), 2.07-2.00 (m, 1 H, exchanges with D_2O); ^{13}C NMR δ 141.6, 131.9, 129.5, 128.3 (2 C), 128.2 (2 C), 125.8, 63.4, 35.4, 33.9.

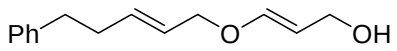


1-((*E*)-5-(Vinyloxy)pent-3-enyl)benzene (1-65). A solution of allylic alcohol **1-64** (158 mg, 0.975 mmol) in ethyl vinyl ether (4 mL) at ambient temperature was treated with $Hg(OAc)_2$ (208 mg, 0.653 mmol) and stirred for 24 h. K_2CO_3 (500 mg) was added and the mixture was filtered through Al_2O_3, eluting with hexanes (5 mL). The filtrate was concentrated and the residue was chromatographed on SiO_2 (hexanes/EtOAc, 9:1) to yield allylic vinyl ether **1-65** (86.0 mg, 0.457 mmol, 47%) as a colorless oil: IR (neat) 3027, 2926, 2857, 1635, 1613, 1496, 1454, 1320, 1196, 1049, 970, 699 cm^{-1}; ^1H NMR δ 7.37-7.24 (m, 5 H), 6.52 (dd, 1 H, *J* = 14.3, 6.8 Hz), 5.90-5.83 (m, 1 H), 5.76-5.69 (m, 1 H), 4.28 (dd, 1 H, *J* = 14.3, 2.0 Hz), 4.23 (d, 2 H, *J* = 5.8 Hz), 4.09 (dd, 1 H, *J* = 6.8, 2.0 Hz), 2.79 (t, 2 H, *J* = 7.3 Hz), 2.50-2.43 (m, 2 H); ^{13}C NMR δ 151.4, 141.5, 134.3, 128.3 (2 C), 128.2 (2 C), 125.8, 125.3, 86.9, 68.7, 35.3, 34.0; MS (EI) *m/z* (rel intensity) 144 ($[M-C_2H_4O]^+$, 14), 129 (7), 91 (100); HRMS (EI) *m/z* calcd for $C_{11}H_{12}$ [M- C_2H_4O] 144.0939, found 144.0932.



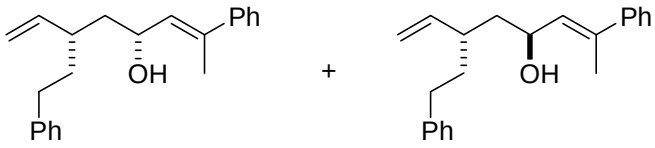
(2*E*)-3-((*E*)-5-Phenylpent-2-enyloxy)-N,N-dimethylacrylamide (1-67). To a suspension of NaH (42.4 mg, 1.77 mmol) in THF (1.5 mL) at ambient temperature was added alcohol **1-64** (220 mg, 1.36 mmol) as a solution in THF (2.5 mL). The reaction mixture was stirred for 45 min, treated with betaine **1-33** (247 mg, 1.90 mmol) in one portion and heated at reflux for 14 h. The cooled mixture was poured into H_2O (20 mL) and the aqueous layer was washed with Et_2O (2 x 5 mL) and then acidified to pH = 4 with 10% HCl (~15 drops). The mixture was extracted with Et_2O (3 x 5 mL) and the combined organic layers were washed with H_2O, brine, dried (Na_2SO_4) and concentrated. The unstable crude acid **1-66** was added to a solution of EDCI (202 mg, 1.05 mmol), DMAP (9.98 mg, 0.0810 mmol), and dimethylamine hydrochloride (165 mg, 2.03 mmol) in CH_2Cl_2

(8 mL) at ambient temperature. DIPEA (564 μL, 3.24 mmol) was added dropwise over 5 min and the reaction mixture was stirred for 24 h and quenched with H_2O (2 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic layers were washed with brine, dried (Na_2SO_4), concentrated and chromatographed on SiO_2 (hexanes/EtOAc, 1:4) to yield amide **1-67** (126 mg, 0.485 mmol, 36% over two steps) as a yellow oil: IR (neat) 3026, 2926, 1652, 1594, 1496, 1454, 1396, 1115, 968, 700 cm^{-1}; ^1H NMR δ 7.51 (d, 1 H, J = 11.8 Hz), 7.29-7.14 (m, 5 H), 5.82 (dt, 1 H, J = 15.4, 6.6 Hz), 5.67-5.58 (m, 2 H), 4.31 (d, 2 H, J = 6.1 Hz), 2.97 (br s, 6 H), 2.69 (t, 2 H, J = 7.3 Hz), 2.39-2.34 (m, 2 H); ^{13}C NMR δ 167.1, 160.5, 141.2, 135.4, 128.2 (4 C), 125.7, 124.4, 96.2, 72.0, 37.0, 35.2, 35.0, 33.8; MS (EI) *m/z* (rel intensity) 259 ($[M]^+$, 48), 231 (80), 216 (50), 188 (9), 115 (12), 91 (100); HRMS (EI) *m/z* calcd for $C_{16}H_{21}NO_2$ 259.1572, found 259.1557.



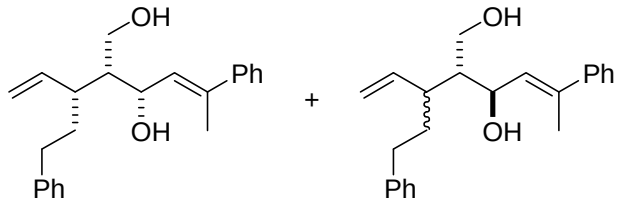
(2*E*)-3-((*E*)-5-Phenylpent-2-enyloxy)prop-2-en-1-ol (1-69). To a solution of ethyl propiolate (2.51 g, 25.6 mmol) and allylic alcohol **1-64** (4.36 g, 26.9 mmol) in CH_2Cl_2 (250 mL) at 0 °C was added Et_3N (4.28 mL, 30.7 mmol) dropwise over 15 min. The reaction mixture was stirred at ambient temperature for 14 h and quenched with 10% HCl (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL) and the combined organic layers were washed with 10% HCl, brine and dried ($MgSO_4$). The solution was filtered, concentrated and the residue was chromatographed on SiO_2 (hexanes/EtOAc, 5:1) to furnish ester **1-68** (5.67 g, 21.8 mmol, 81%) as a colorless oil which contained ~15% of an unknown impurity. This mixture was carried directly into the next step without further purification. A solution of ester **1-68** (1.51 g, 5.81 mmol) in toluene (12 mL) was cooled to -78 °C and treated dropwise over 5 min with a solution of DIBAL-H (1.0 M solution in hexanes, 12.8 mL, 12.8 mmol). The reaction mixture was stirred for 2 h at -78 °C,

warmed to ambient temperature, and quenched with 1 M Rochelle's Salt (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic layers were washed with brine, dried ($MgSO_4$), concentrated, filtered and chromatographed on SiO_2 (Et_2O/hexanes, 3:1) to yield alcohol **1-69** (573 mg, 2.63 mmol, 45%) as a colorless oil: IR (neat) 3361, 3061, 2924, 2859, 1652, 1496, 1175, 997, 747 cm^{-1}; ^1H NMR δ 7.35-7.20 (m, 5 H), 6.50 (d, 1 H, *J* = 12.6 Hz), 5.83 (dt, 1 H, *J* = 15.4, 6.5 Hz), 5.65 (dt, 1 H, *J* = 15.4, 6.0 Hz), 5.07 (dt, 1 H, *J* = 12.6, 7.4 Hz), 4.20 (dd, 2 H, *J* = 5.9, 0.7 Hz), 4.04 (d, 2 H, *J* = 7.3 Hz), 2.75 (t, 2 H, *J* = 7.3 Hz), 2.46-2.38 (m, 2 H), 2.30 (br s, 1 H, exchanges with D_2O); ^{13}C NMR δ 149.2, 141.3, 134.4, 128.2 (2 C), 128.1 (2 C), 125.7, 125.1, 103.1, 69.7, 60.1, 35.1, 33.8; MS (EI) *m/z* (rel intensity) 218 ($[M]^+$, 1), 169 (8), 145 (69), 144 (100), 129 (49); HRMS (EI) *m/z* calcd for $C_{11}H_{12}$ [M-$C_3H_6O_2$] 144.0939, found 144.0934.



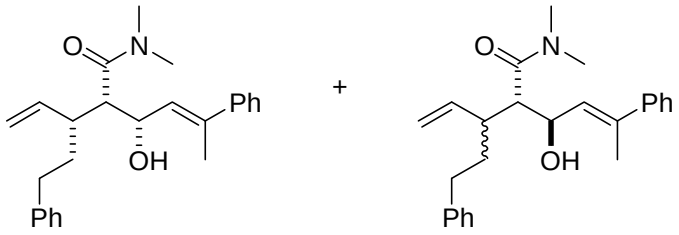
(*E*,4*R,6*S**)-6-Phenethyl-2-phenylocta-2,7-dien-4-ol (1-70) and (*E*,4*S**,6*S**)-6-phenethyl-2-phenylocta-2,7-dien-4-ol (1-71)**. According to the general protocol A, $AlMe_3$ (169 mg, 2.34 mmol), Cp_2ZrCl_2 (31.0 mg, 0.106 mmol), H_2O (21.0 μL, 1.17 mmol), phenylacetylene (257 μL, 2.34 mmol) and vinyl ether **1-65** (200 mg, 1.06 mmol) afforded, after chromatography on SiO_2 (hexanes/EtOAc, 5:1), alcohols **1-70** and **1-71** (major: 153 mg, 0.500 mmol, 47%, R_f = 0.31, minor: 102 mg, 0.333 mmol, 31%, R_f = 0.21) as colorless oils (diastereomers unassigned): Major diastereomer: IR (neat) 3376, 2924, 1495, 1453, 1029, 998, 913, 757, 697 cm^{-1}; ^1H NMR δ 7.42-7.15 (m, 10 H), 5.80 (dd, 1 H, *J* = 8.5, 1.3 Hz), 5.68 (dt, 1 H, *J* = 15.9, 9.0 Hz), 5.19 (s, 1 H), 5.14 (dd, 1 H, *J* = 7.2, 2.0 Hz), 4.66-4.57 (m, 1 H), 2.7 (ddd, 1 H, *J* = 13.7, 10.4, 5.4 Hz), 2.57 (ddd, 1 H, *J* = 13.7, 10.2, 6.5 Hz), 2.43-2.33 (m, 1 H), 2.07 (d, 3 H, *J* = 1.3 Hz), 1.81-1.45 (m, 4 H); ^{13}C NMR δ

142.9, 142.6, 142.2, 136.3, 131.0, 128.4 (2 C), 128.3 (2 C), 128.2 (2 C), 127.2, 125.8 (2 C), 125.6, 115.8, 66.9, 42.7, 40.3, 37.3, 33.5, 16.2; MS (EI) *m/z* (rel intensity) 306 ($[M]^+$, 15), 288 (37), 201 (33), 183 (23), 147 (77), 129 (63), 105 (89), 91 (100); HRMS (EI) *m/z* calcd for $C_{22}H_{26}O$ 306.1984, found 106.1976. Minor diastereomer: IR (neat) 3346, 3061, 2922, 1495, 1453, 1029, 997, 913, 758 cm^{-1}; ^1H NMR δ 7.40-7.16 (m, 10 H), 5.77-5.65 (m, 2 H), 5.11 (dd, 1 H, *J* = 10.2, 1.9 Hz), 5.04 (dd, 1 H, *J* = 17.3, 1.9 Hz), 4.64-4.56 (m, 1 H), 2.67 (ddd, 1 H, *J* = 13.8, 10.3, 5.5 Hz), 2.54 (ddd, 1 H, *J* = 14.0, 10.1, 6.4 Hz), 2.18-2.06 (m, 1 H), 2.08 (d, 3 H, *J* = 1.3 Hz), 1.84-1.50 (m, 4 H); ^{13}C NMR δ 143.0, 142.8, 142.5, 130.5, 128.4 (2 C), 128.3 (3 C), 128.2 (2 C), 127.3, 125.9 (2 C), 125.7, 115.4, 67.5, 43.1, 40.9, 37.1, 33.3, 16.5; MS (EI) *m/z* (rel intensity) 306 ($[M]^+$, 18), 288 (14), 201 (23), 147 (100), 129 (63), 105 (96), 91 (100); HRMS (EI) *m/z* calcd for $C_{22}H_{26}O$ 306.1984, found 306.1979.



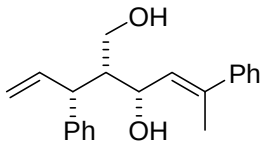
(*E*,2*R,3*S**)-5-Phenyl-2-((*R**)-5-phenylpent-1-en-3-yl)hex-4-ene-1,3-diol (1-72)** and **(*E*,2*R**,3*S**)-5-Phenyl-2-((*R***S**)-5-phenylpent-1-en-3-yl)hex-4-ene-1,3-diol (1-73a/b)**. According to general protocol A, $AlMe_3$ (373 mg, 5.17 mmol), Cp_2ZrCl_2 (37.7 mg, 0.129 mmol), H_2O (46.6 μL, 2.59 mmol), phenylacetylene (284 μL, 2.59 mmol) and alcohol **1-69** (282 mg, 1.29 mmol) afforded, after chromatography on SiO2 (hexanes/EtOAc, 2:1), diols **1-72** and **1-73** (72.0 mg, 0.214 mmol, 17%) as a colorless oil which was a 10:0.8:0.5 mixture of inseparable diastereomers as indicated by ^1H NMR analysis. **1-72**: IR (neat) 3334, 2922, 1495, 1445, 1030, 999, 758, 697 cm^{-1}; ^1H NMR δ 7.40-7.15 (m, 10 H), 5.95 (dd, 1 H, *J* = 9.8, 1.2 Hz), 5.80 (dt, 1 H, *J* = 17.0, 9.2 Hz),

5.25-5.14 (m, 2 H), 4.89-4.83 (m, 1 H), 4.06-3.99 (m, 1 H), 3.91-3.83 (m, 1 H), 2.89 (t, 1 H, J = 5.6 Hz, exchanges with D_2O), 2.76-2.67 (m, 1 H), 2.52-2.38 (m, 3 H, one hydrogen exchanges with D_2O), 2.03 (d, 3 H, J = 1.3 Hz), 1.98-1.87 (m, 1 H), 1.63-1.49 (m, 2 H); ^{13}C NMR δ 142.7, 142.3, 140.8, 136.8, 129.9, 128.3 (4 C), 128.2, 127.3, 125.8, 125.7, 116.7, 62.0, 49.3, 42.4, 33.9, 32.5, 16.2; MS (EI) *m/z* (rel intensity) 336 ([M]$^+$, 54), 318 (83), 300 (61), 183 (15), 147 (54), 105 (62), 91 (100); HRMS (EI) *m/z* calcd for $C_{23}H_{28}O_2$ 336.2089, found 336.2085. Characteristic data for **1-73a**: ^{1}H NMR δ 2.11 (d, 3 H, J = 1.1 Hz). Characteristic data for **1-73b**: ^{1}H NMR δ 2.09 (d, 3 H, J = 1.3 Hz).

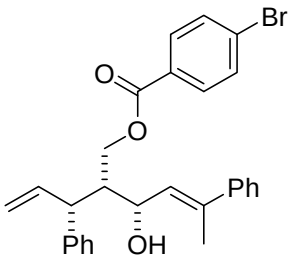


(*E*,2*S,3*S**)-3-Hydroxy-*N*,*N*-dimethyl-5-phenyl-2-((*R**)-5-phenylpent-1-en-3-yl)hex-4-enamide (1-74)** and **(*E*,2*S**,3*R**)-3-hydroxy-*N*,*N*-dimethyl-5-phenyl-2-((*R***S**)-5-phenylpent-1-en-3-yl)hex-4-enamide (1-75a/b)**. According to the general protocol A, $AlMe_3$ (27.7 mg, 0.385 mmol), Cp_2ZrCl_2 (1.12 mg, 0.00385 mmol), H_2O (2.77 μL, 0.154 mmol), phenylacetylene (8.53 μL, 0.0769 mmol) and amide **1-67** (10.0 mg, 0.0385 mmol) furnished, after chromatography on SiO_2 (hexanes/EtOAc 1:2), amide alcohols **1-74** and **1-75a/b** (5.0 mg, 0.0133 mmol, 34%) as a light yellow oil which was a 100:43:13 mixture of inseparable diastereomers as indicated by ^{1}H NMR analysis. **1-74**: IR (neat) 3395, 2926, 1620, 1495, 1399, 1143, 917, 760, 699 cm^{-1}; ^{1}H NMR δ 7.42 (m, 10 H), 6.10 (d, 1 H, J = 8.8 Hz), 5.78-5.63 (m, 1 H), 5.23-5.14 (m, 2 H), 4.82 (br t, 1 H, J = 7.0 Hz), 4.75 (d, 1 H, J = 2.8 Hz, exchanges with D_2O), 3.09 (s, 3 H), 2.96 (s, 3 H), 2.78-2.59 (m, 2 H), 2.54-2.39 (m, 1 H), 2.07 (s, 3 H), 1.89-1.79 (m, 1 H), 1.70-1.64 (m, 1 H), 1.56-1.41 (m, 1 H); ^{13}C NMR δ 173.2, 143.1, 142.4, 140.7, 137.8, 128.4 (2 C), 128.3 (2 C), 127.2, 125.8, 125.7, 117.4, 70.0,

50.8, 44.5, 38.2, 35.7, 34.0, 33.6, 16.4; MS (EI) *m/z* (rel intensity) 377 ([M]$^+$, 52), 286 (36), 232 (77), 126 (99), 91 (77); HRMS (EI) *m/z* calcd for $C_{24}H_{31}NO_2$ 377.2355, found 377.2372. Characteristic data for **1-75a**: ^{1}H NMR δ 5.92 (d, 1 H, *J* = 8.7 Hz), 5.38 (m, 2 H), 2.99 (s, 3 H), 2.94 (s, 3 H). Characteristic data for **1-75b**: 1H NMR δ 3.04 (s, 3 H), 2.90 (s, 3 H). Characteristic data for **1-75a/b**: ^{13}C NMR δ 175.0, 142.8, 142.2, 138.8, 135.4, 130.3, 127.5, 48.9, 16.1.

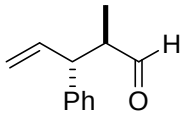


(*E*,2*R,3*S**)-5-Phenyl-2-((*R**)-1-phenylallyl)hex-4-ene-1,3-diol (1-76)**. According to the general protocol A, $AlMe_3$ (790 mg, 11.0 mmol), Cp_2ZrCl_2 (91.4 mg, 0.313 mmol), H_2O (84.6 μL, 4.70 mmol), phenylacetylene (687 μL, 6.26 mmol) and alcohol **1-40** (595 mg, 3.13 mmol) afforded, after chromatography on SiO_2 (hexanes/EtOAc, 4:1), diol **1-76** (222 mg, 0.721 mmol, 23%) as a colorless oil which was a 95:5 mixture of inseparable diastereomers as indicated by ^{1}H NMR analysis. **1-76**: IR (neat) 3342, 3028, 1493, 1032, 758, 700 cm^{-1}; ^{1}H NMR δ 7.43-7.19 (m, 10 H), 6.14 (ddd, 1 H, *J* = 17.0, 10.0, 9.2 Hz), 6.10-6.06 (m, 1 H), 5.27 (ddd, 1 H, *J* = 17.0, 1.6, 0.9 Hz), 5.18 (dd, 1 H, *J* = 10.1, 1.2 Hz), 5.02-4.96 (m, 1 H), 4.00 (ddd, 1 H, *J* = 11.3, 3.8, 2.4 Hz), 3.87 (app t, 1 H, *J* = 9.7 Hz), 3.46-3.38 (m, 1 H), 2.54 (d, 1 H, *J* = 5.2 Hz, exchanges with D_2O), 2.46 (dd, 1 H, *J* = 6.8, 3.9 Hz, exchanges with D_2O), 2.07 (d, 3 H, *J* = 1.3 Hz), 1.94-1.86 (m, 1 H); ^{13}C NMR δ 142.7, 142.3, 140.3, 136.2, 130.2, 128.6 (2 C) 128.2 (2 C), 128.0 (2 C), 127.2, 126.4, 125.7 (2 C), 116.2, 70.6, 61.3, 48.9, 48.7, 16.2 ; MS (EI) *m/z* (rel intensity) 308 ([M]$^+$, 6), 290 (17), 260 (49), 215 (70), 117 (100); HRMS (EI) *m/z* calcd for $C_{21}H_{24}O_2$ 308.1776, found 308.1788.

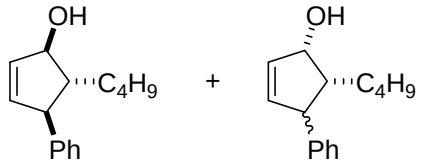


(*E*,2*R,3*S**)-5-Phenyl-2-((*R**)-1-phenylallyl)hex-4-ene-3-*p*-bromobenzoyloxy-1-ol (1-77)**.

To a solution of diol **1-76** (67.0 mg, 0.217 mmol) and Et_3N (70.7 μL, 0.500 mmol) in CH_2Cl_2 (2.2 mL) at ambient temperature was added *p*-bromobenzoyl chloride (143 mg, 0.652 mmol). The reaction mixture was stirred for 12 h and quenched with H_2O (1 mL). The aqueous layer was extracted with CH_2Cl_2 (4 x 3 mL) and the combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated. The residue was chromatographed on SiO_2 (hexanes/EtOAc, 3:1) to furnish the corresponding bis-ester (110 mg, 0.163 mmol, 75%) and the mono-acylated alcohol **77** (20.0 mg, 0.0407 mmol, 18%) as colorless solids of which only the mono-acylated product was characterized as a single diastereomer. Mp 114.0-116.0 °C ($CDCl_3$/MeOH); IR (neat) 3502, 2920, 2851, 1718, 1590, 1271, 1012, 757 cm^{-1}; ^1H NMR δ 7.67 (d, 2 H, *J* = 8.6 Hz), 7.39 (d, 2 H, *J* = 7.4 Hz), 7.31-7.25 (m, 10 H), 6.19 (dt, 1 H, *J* = 16.8, 9.9 Hz), 6.01 (dd, 1 H, *J* = 8.3, 1.3 Hz), 5.26 (d, 1 H, *J* = 16.9 Hz), 5.18 (dd, 1 H, *J* = 10.0, 1.5 Hz), 4.99-4.96 (m, 1 H), 4.38 (d of AB, 1 H, *J* = 11.6, 6.9 Hz), 4.30 (d of AB, 1 H, *J* = 11.6, 4.3 Hz), 3.66 (t, 1 H, *J* = 9.6 Hz), 2.50-2.42 (m, 1 H), 2.04 (d, 3 H, *J* = 1.2 Hz), 1.83 (br s, 1 H, exchanges with D_2O); ^{13}C NMR δ 165.7, 142.6, 142.2, 140.2, 136.4, 131.6 (2 C), 131.0 (2 C), 129.8, 128.7 (2 C), 128.3 (2 C), 127.9 (2 C), 127.7, 127.3, 126.8, 125.7 (2 C), 116.4, 68.4, 63.5, 50.5, 47.9, 16.2; MS (EI) *m/z* (rel intensity) 490 ($[M-H]^+$, 15), 386 (51), 272 (26), 183 (67), 117 (100); HRMS (EI) *m/z* calcd for $C_{28}H_{26}BrO_3$ [M-H] 490.1144, found 490.1166.

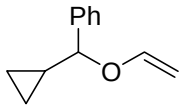


(2*R,3*R**)-2-Methyl-3-phenylpent-4-enal (1-80).** A solution of vinyl ether **1-53** (5.0 mg, 0.0287 mmol) in MeOH-d_4 (1 mL) was heated at 140 °C in a microwave (150 W) for 10 min. The solvent was evaporated and the residue was chromatographed on SiO_2 (hexanes/EtOAc, 15:1) to furnish aldehyde **1-80** (3.0 mg, 0.0172 mmol, 60%) as a colorless oil which was an inseparable 10:1 mixture of diastereomers as indicated by ^{1}H NMR analysis. **1-80**: IR (neat) 3082, 3028, 2977, 2875, 1724, 1493, 1453, 994, 919, 702 cm$^{-1;}$ ^{1}H NMR δ 9.55 (d, 1 H, *J* = 2.4 Hz), 7.35-7.29 (m, 2 H), 7.25-7.17 (m, 3 H), 6.03-5.91 (m, 1 H), 5.16 (d, 1 H, *J* = 0.7 Hz), 5.11-5.07 (m, 1 H), 3.59 (app t, 1 H, *J* = 8.7 Hz), 2.87-2.72 (m, 1 H), 1.13 (d, 3 H, *J* = 7.0 Hz); ^{13}C NMR δ 204.2, 141.3, 138.0, 128.7 (2 C), 126.8 (2 C), 116.9, 51.4, 50.4, 11.9; MS (EI) *m/z* (rel intensity) 174 ([M]$^+$, 7), 159 (7), 131 (7), 117 (100). Characteristic data for minor diastereomer: ^{1}H NMR δ 9.70 (d, 1 H, *J* = 2.9 Hz); ^{13}C NMR δ 204.6, 140.7, 139.0, 128.0, 116.3, 12.5.



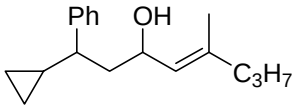
(1*R,4*S**,5*R**)-5-Butyl-4-phenylcyclopent-2-enol (1-83a)** and **(1*S**,4*R***S**,5*R**)-5-butyl-4-phenylcyclopent-2-enol (1-83b/c)**. To a solution of allylic alcohol **1-61/1-62** (41.0 mg, 0.130 mmol in CH_2Cl_2 (2 mL) at room temperature was added Grubbs' second generation catalyst ((1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)-dichloro-(phenylmethylene)-(tricyclohexylphosphine) ruthenium) (11.1 mg, 0.0130 mmol). The reaction mixture was stirred for 4 h, the volatiles were evaporated, then CH_2Cl_2 (2 mL) and activated charcoal (100 mg) were added. The suspension was stirred for 12 h and filtered through SiO_2 (eluting with hexanes/EtOAc, 1:1, 5 mL). The filtrate was

evaporated and chromatographed on SiO_2 (hexanes/EtOAc, 9:1) to yield cyclopentene **1-83** (26.0 mg, 0.110 mmol, 87%) as a colorless oil which was a 10:1:0.8 mixture of inseparable diastereomers as indicated by ^{1}H NMR analysis. **1-83a**: IR (neat) 3331, 3058, 2956, 2925, 2856, 1601, 1492, 1454, 1075, 700 cm^{-1}; ^{1}H NMR δ 7.42-7.24 (m, 5 H), 5.94 (dt, 1 H, *J* = 5.6, 2.0 Hz), 5.87 (dt, 1 H, *J* = 5.6, 1.5 Hz), 4.61 (dd, 1 H, *J* = 5.2, 1.5 Hz), 3.41 (dd, 1 H, *J* = 6.3, 1.8 Hz), 1.94-1.86 (m, 1 H), 1.71-1.60 (m, 2 H), 1.49-1.19 (m, 4 H), 0.90 (t, 3 H, *J* = 7.0 Hz); ^{13}C NMR δ 144.7, 136.6, 133.8, 128.4 (2 C), 127.6 (2 C), 126.4, 83.2, 59.0, 56.7, 32.9, 29.9, 23.0, 14.0; MS (EI) *m/z* (rel intensity) 216 ([M-H_2O]$^+$, 24), 198 (25), 173 (40), 159 (90), 155 (78), 115 (48), 91 (100); HRMS (EI) *m/z* calcd for $C_{15}H_{18}$ [M-H_2O] 216.1514, found 216.1513. Characteristic data for **1-83b**: ^{1}H NMR δ 4.82 (d, 1 H, *J* = 5.8 Hz), 3.58 (d, 1 H, *J* = 7.0 Hz). Characteristic data for **1-83c**: ^{1}H NMR δ 4.72 (dd, 1 H, *J* = 5.0, 2.0 Hz).



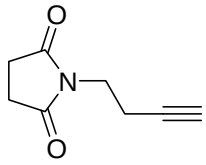
1-(Cyclopropyl(vinyloxy)methyl)benzene (1-85). A solution of cyclopropyl alcohol **1-84** (1.00 g, 6.75 mmol) in ethyl vinyl ether (14 mL) at ambient temperature was treated with $Hg(OAc)_2$ (1.44 g, 4.52 mmol) and heated at reflux for 4 h. K_2CO_3 (1 g) was added and the mixture was filtered through Al_2O_3, eluting with hexanes (20 mL). The filtrate was concentrated and the residue was purified by chromatography on SiO_2 (hexanes/EtOAc/Et_3N, 95:4:1) to yield cyclopropyl vinyl ether **1-85** (1.11 g, 6.45 mmol, 96%) as a colorless oil: IR (neat) 3083, 3008, 1636, 1615, 1492, 1453, 1186, 1023, 865, 700 cm^{-1}; ^{1}H NMR δ 7.43-7.32 (m, 5 H), 6.39 (dd, 1 H, *J* = 14.1, 6.6 Hz), 4.31 (dd, 1 H, *J* =14.1, 1.8 Hz), 4.25 (d, 1 H, *J* = 7.7 Hz), 4.02 (dd, 1 H, *J* = 6.6, 1.6 Hz), 1.37-1.26 (m, 1 H), 0.76-0.67 (m, 1 H), 0.60-0.53 (m, 2 H), 0.47-0.39 (m, 1 H); ^{13}C NMR δ 150.7, 141.0,

128.3 (2 C), 127.6, 126.3 (2 C), 89.3, 85.1, 17.5, 3.8, 2.3; MS (EI) *m/z* (rel intensity) 174 ($[M]^+$, 21), 156 (26), 131 (100), 115 (32); HRMS (EI) *m/z* calcd for $C_{12}H_{14}O$ 174.1045, found 174.1038.

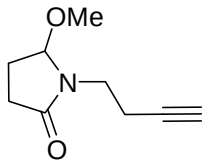


(*E*)-1-Cyclopropyl-5-methyl-1-phenyloct-4-en-3-ol (1-88). According to the general protocol A, $AlMe_3$ (288 mg, 4.00 mmol), Cp_2ZrCl_2 (29.2 mg, 0.100 mmol), H_2O (36.0 μL, 2.00 mmol), 1-pentyne (197 μL, 2.00 mmol) and cyclopropyl vinyl ether **1-85** (174 mg, 1.00 mmol) afforded, after chromatography on SiO_2 (hexanes/EtOAc, 5:1), alcohol **1-88** (136 mg, 0.527 mmol, 53%) as a colorless oily a 1:1 mixture of inseparable diastereomers as indicated by ^{1}H NMR analysis: (1:1 mixture of diastereomers) IR (neat) 3363, 3076, 2958, 2930, 2871, 1494, 1453, 1380, 1017, 742, 700 cm^{-1}; ^{1}H NMR δ 7.34-7.16 (m, 5 H), 5.18 (dd, 0.5 H, *J* = 8.5, 1.2 Hz), 5.13 (dd, 0.5 H, *J* = 9.0, 1.1 Hz), 4.31 (ddd, 0.5 H, *J* = 7.8, 6.5, 6.5 Hz), 4.25-4.16 (m, 0.5 H), 2.21-1.79 (m, 5 H), 1.48 (d, 1.5 H, *J* = 1.2 Hz), 1.47 (d, 1.5 H, *J* = 1.2 Hz), 1.45-1.33 (m, 2 H), 1.05-0.95 (m, 2 H), 0.89 (t, 1.5 H, *J* = 7.3 Hz), 0.86 (t, 1.5 H, *J* = 7.2 Hz), 0.65-0.54 (m, 1 H), 0.41-0.30 (m, 1 H), 0.29-0.19 (m, 1 H), 0.14-0.05 (m, 1 H); ^{13}C NMR δ 145.5, 145.4, 139.3, 138.1, 128.3 (2 C), 127.6 (4 C), 126.1 (2 C), 66.7, 66.5, 47.4, 47.3, 44.6, 44.4, 41.7, 41.5, 20.8, 20.7, 17.9 (2 C), 16.4, 16.3, 13.7 (2 C), 5.5, 5.4, 4.0, 3.6; MS (EI) *m/z* (rel intensity) 258 ($[M]^+$, 8), 240 (28), 215 (97), 131 (100), 113 (18); HRMS (EI) *m/z* calcd for $C_{18}H_{26}O$ 258.1984, found 258.1971.

5.2 AZA-COPE REARRANGEMENTS AND *N*-ACYL IMINIUM ION CHEMISTRY

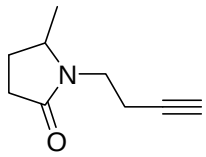


1-(But-3-ynyl)pyrrolidine-2,5-dione (2-10).[145] To a solution of succinimide (2.17 g, 31.0 mmol), DEAD (3.47 mL, 31.0 mmol) and PPh_3 (5.76 g, 31.0 mmol) in THF (31 mL) was added 3-butyn-1-ol (1.65 mL, 32.6 mmol) at 0 °C. The reaction mixture was warmed to ambient temperature and stirred for 36 h. The solvent was evaporated *in vacuo*, the residue was suspended in hexanes/EtOAc (1:1, 10 mL) and the mixture was filtered. The filtrate was allowed to stand for 12 h, filtered, dried ($MgSO_4$), and concentrated. The residue was chromatographed on SiO_2 (hexanes/EtOAc, 1:5) to furnish imide **2-10** (1.37 g, 9.07 mmol, 42%) as a colorless oil: IR (neat) 3273, 2948, 1775, 1699, 1435, 1404, 1166, 1077, 821 cm^{-1}; ^1H NMR δ 3.53 (t, 2 H, J = 7.1 Hz), 2.60 (s, 4 H), 2.36 (td, 2 H, J = 7.1, 2.7 Hz), 1.88 (t, 1 H, J = 2.5 Hz).

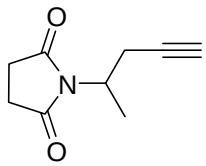


1-(But-3-ynyl)-5-methoxypyrrolidin-2-one (2-11). To a 0 °C solution of imide **90** (1.49 g, 9.87 mmol) in MeOH (20 mL) was added $NaBH_4$ (375 mg, 9.87 mmol) in one portion. The reaction mixture was stirred for 1 h, the solvent was evaporated and the residue was partitioned between H_2O (10 mL) and CH_2Cl_2 (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL), and the combined organic layers were washed with H_2O, brine, dried (Na_2SO_4), filtered and evaporated. The

residue was chromatographed on SiO_2 (EtOAc containing 1% Et_3N) to furnish the corresponding hydroxy lactam (920 mg, 6.01 mmol, 61%) as a colorless oil which was used directly in the next step. The reaction was repeated to generate material with identical results. A solution of the hydroxylactam (1.50 g, 9.87 mmol) in MeOH (90 mL) at ambient temperature was treated with TsOH (187 mg, 0.987 mmol) in one portion. The reaction mixture was stirred for 8 h and the MeOH was evaporated *in vacuo*. The residue was chromatographed on SiO_2 (EtOAc containing 1% Et_3N) to furnish methoxy lactam **2-11** (1.19 g, 7.13 mmol, 45% over two steps) as a colorless oil: IR (neat) 3249, 2118, 1697, 1420, 1171, 1076, 884 cm^{-1}; ^1H NMR δ 5.08 (dd, 1 H, J = 6.2, 1.4 Hz), 3.64 (ddd, 1 H, J = 13.4, 7.4, 5.7 Hz), 3.37-3.28 (m, 1 H),3.28 (s, 3 H), 2.57-2.28 (m, 5 H), 2.23-2.10 (m, 1 H), 1.98 (t, 1 H, J = 2.4 Hz); ^{13}C NMR δ 175.1, 90.6, 81.6, 69.7, 53.0, 39.4, 28.8, 23.9, 18.0; MS (EI) *m/z* (rel intensity) 167 ($[M]^+$, 11), 151 (19), 135 (29), 96 (100); HRMS (EI) *m/z* calcd for $C_9H_{13}NO_2$ 167.0946, found 167.0946.

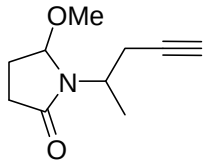


1-(But-3-ynyl)-5-methylpyrrolidin-2-one (2-12). Characteristic data: ^1H NMR δ 1.26 (d, 3 H, J = 7.4 Hz).



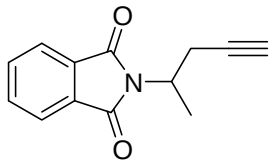
1-(Pent-4-yn-2-yl)pyrrolidine-2,5-dione (2-14). To a solution of succinimide (2.20 g, 22.2 mmol), **2-13** (2.20 mL, 22.2 mmol), and PPh_3 (5.83 g, 22.2 mmol) in THF (200 mL) at 0 °C was

added DEAD (3.52 mL, 22.2 mmol) dropwise over 10 min. The reaction mixture was stirred for 36 h, the solvent was removed *in vacuo* and the residue was dissolved in hexanes/EtOAc 1:1, 20 mL). The solids were filtered off the filtrate was evaporated. The residue was chromatographed on SiO_2 (hexanes/EtOAc, 1:3) to furnish imide **2-14** (1.19 g, 7.21 mmol, 32%) as a colorless oil: IR (neat) 3276, 2984, 2942, 1773, 1693, 1371, 1183 cm^{-1}; ^1H NMR δ 4.34-4.22 (m, 1 H), 2.74 (ddd, 1 H, J = 16.7, 9.2, 2.5 Hz), 2.57 (s, 3 H), 2.46 (ddd, 1 H, J = 16.8, 6.6, 2.6 Hz), 1.86 (t, 1 H, J = 2.6 Hz), 1.29 (d, 3 H, J = 7.0 Hz); ^{13}C NMR δ 176.9 (2 C), 80.3, 69.8, 46.5, 27.7 (2 C), 22.3, 16.8; MS (EI) *m/z* 165 ($[M]^+$, 15), 150 (14), 126 (100), 100 (48); HRMS (EI) *m/z* calcd for $C_9H_{11}NO_2$ 165.0790, found 165.0788.



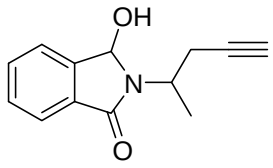
5-Methoxy-1-(pent-4-yn-2-yl)pyrrolidin-2-one (2-15). To a 0 °C solution of imide **2-14** (759 mg, 4.60 mmol) in MeOH (10 mL) was added $NaBH_4$ (511 mg, 13.8 mmol) in one portion. The reaction mixture was stirred for 3 h and the solvent was removed *in vacuo*. The residue was partitioned between CH_2Cl_2 (5 mL) and H_2O (5 mL) and the aqueous layer was extracted with CH_2Cl_2 (5 x 5 mL). The combined organic layers were washed with brine, dried (MgSO4) filtered and concentrated. The resulting crude hydroxylactam was immediately dissolved in MeOH (2 mL) and PPTS (49.3 mg, 0.196 mmol) was added. The mixture was stirred for 24 h at ambient temperature and the MeOH was removed *in vacuo*. The residue was partitioned between CH_2Cl_2 (5 mL) and H_2O (5 mL) and the aqueous layer was extracted with CH_2Cl_2 (4 x 5 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), evaporated and the residue was chromatographed on SiO_2 (hexanes/EtOAc, 1:1) to yield methoxylactam **2-15** (200 mg, 1.10 mmol,

56%) as a colorless oil which was a 1:1 mixture of inseparable diastereomers as indicated by ^{1}H NMR: IR (neat) 3251, 2980, 2938, 2829, 2118, 1697, 1418, 1376, 1075 cm^{-1}; ^{1}H NMR δ 5.10 (dd, 0.5 H, *J* = 5.7, 1.2 Hz), 4.97 (dd, 0.5 H, *J* = 5.9, 1.4 Hz), 4.27-4.03 (m, 1 H), 3.27 (s, 1.5 H), 3.26 (s, 1.5 H), 2.71 (ddd, 0.5 H, *J* = 16.6, 6.5, 2.7 Hz), 2.62-2.25 (m, 4 H), 2.10-1.94 (m, 3.5 H), 1.37 (d, 1.5 H, *J* = 6.9 Hz), 1.33 (d, 1.5 H, *J* = 6.9 Hz); ^{13}C NMR δ 175.0, 174.7, 89.7, 88.9, 81.6, 80.6, 70.1, 69.5, 52.3, 47.5, 46.7, 29.1, 28.9, 24.6, 23.9, 23.8, 23.6, 18.3, 16.6; MS (EI) *m/z* (rel intensity) 181 ([M]$^+$, 15), 166 (10), 149 (32), 110 (100); HRMS (EI) *m/z* calcd for $C_{10}H_{15}NO_2$ 181.1103, found 181.1108.

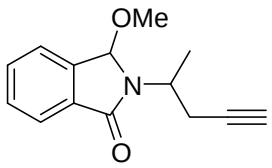


2-(Pent-4-yn-2-yl)isoindoline-1,3-dione (2-16). To a solution of phthalimide (3.24 g, 22.0 mmol), **2-13** (2.17 mL, 22.0 mmol), and PPh_3 (5.77 g, 22.0 mmol) in THF (50 mL) was added DIAD (4.33 mL, 22.0 mmol) at 0 °C. The reaction mixture was warmed to ambient temperature and stirred for 48 h. The solvent was removed *in vacuo* and the residue was dissolved in hexanes/EtOAc (1:1, 40 mL). The solids were filtered off and the filtrate was concentrated and chromatographed on SiO_2 (hexanes/EtOAc, 3:1) to yield imide **2-16** (939 mg, 4.41 mmol, 20%) as a white solid: Mp 97.3-99.9 °C (hexanes/EtOAc); IR (neat) 3281, 2923, 2120, 1773, 1706, 1467, 1360, 1025, 794, 719 cm^{-1}; ^{1}H NMR δ 7.85-7.81 (m, 2 H), 7.75-7.70 (m, 2 H), 4.62-4.55 (m, 1 H), 2.95 (dd, 1 H, *J* = 16.6, 2.4 Hz), 2.70 (dd, 1 H, *J* = 16.9, 2.5 Hz), 1.91 (t, 1 H, *J* = 2.3 Hz), 1.54 (d, 3 H, *J* = 7.2 Hz); ^{13}C NMR δ 168.2 (2 C), 133.9 (2 C), 131.8 (2 C), 123.2 (2 C), 80.7, 70.1, 46.4, 23.7, 18.0; MS (EI) *m/z* (rel

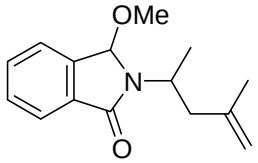
intensity) 213 ([M]$^+$, 12), 198 (40), 174 (100), 147 (21), 130 (30), 102 (14); HRMS (EI) *m/z* calcd for $C_{13}H_{11}NO_2$ 213.0790, found 213.0783.



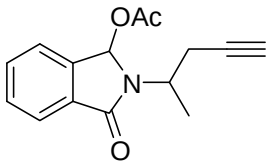
3-Hydroxy-2-(pent-4-yn-2-yl)isoindolin-1-one (2-17). To a solution of imide **2-16** (245 mg, 1.15 mmol) in MeOH (4 mL) at ambient temperature was added $NaBH_4$ (46.0 mg, 1.15 mmol) portionwise. The reaction mixture was stirred for 3 h, treated with H_2O (1 mL) and extracted with CH_2Cl_2 (5 x 5 mL). The organic layers were washed with brine, dried ($MgSO_4$), concentrated and the residue was chromatographed on SiO_2 (hexanes/EtOAc, 1:1) to yield hydroxylactam **2-17** (167 mg, 0.777 mmol, 68%) as a white solid which was a 1:1 inseparable mixture of diastereomers as indicated by ^{1}H NMR: Mp 95.0-95.5 °C (hexanes/EtOAc); IR (KBr) 3297, 1674, 1415, 1362, 1053, 747, 697 cm^{-1}; ^{1}H NMR δ 7.67-7.63 (m, 1 H), 7.55-7.43 (m, 3 H), 5.97 (d, 0.5 H, *J* = 9.3 Hz), 5.93 (d, 0.5 H, *J* = 9.0), 4.44-4.23 (m, 1 H), 3.54 (d, 0.5 H, *J* = 10.9 Hz), 3.40 (d, 0.5 H, *J* = 11.3 Hz), 2.86-2.75 (m, 1 H), 2.67-2.57 (m, 1 H), 1.99 (t, 0.5 H, *J* = 2.7 Hz), 1.96 (t, 0.5 H, *J* = 2.7 Hz), 1.49 (d, 1.5 H, *J* = 3.5 Hz), 1.47 (d, 1.5 H, *J* = 3.5 Hz); ^{13}C NMR δ 167.3, 167.2, 143.9, 143.8, 132.2 (2 C), 131.7, 131.6, 129.8 (2 C), 123.3, 123.2, 81.9, 81.7 (2 C), 81.6, 70.5, 70.3, 47.6, 47.2, 25.2, 24.0, 19.1, 17.8; MS (rel intensity) (EI) *m/z* 176 ([M-C_3H_3]$^+$, 92), 133 (100), 105 (18); HRMS (EI) *m/z* calcd for $C_{10}H_{10}NO_2$ [M-C_3H_3] 176.0712, found 176.0711.



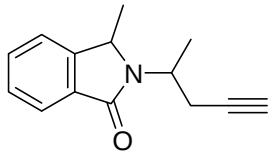
3-Methoxy-2-(pent-4-yn-2-yl)isoindolin-1-one (2-18). To a solution of hydroxylactam **2-17** (620 mg, 2.88 mmol) in MeOH (5 mL) was added *d,l*-camphorsulfonic acid (116 mg, 0.288 mmol) in one portion. The reaction mixture was stirred at ambient temperature for 30 h and concentrated. The residue was dissolved in CH_2Cl_2 (10 mL) and washed with H_2O (5 mL). The aqueous layer was extracted with CH_2Cl_2 (4 x 15 mL) and the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on SiO_2 (hexanes/EtOAc, 5:1) to yield methoxy lactam **2-18** (502 mg, 2.19 mmol, 76%) as a white solid which was a 1:1 mixture of inseparable diastereomers as indicated by ^{1}H NMR: Mp 85.4-88.8 °C; IR (KBr) 3295, 2978, 2937, 2118, 1701, 1615, 1401, 1210, 1068, 748 cm^{-1}; ^{1}H NMR δ 7.82-7.79 (m, 1 H), 7.60-7.47 (m, 3 H), 6.13 (s, 0.5 H), 6.02 (s, 0.5 H), 4.48-4.41 (app s, 0.5 H, *J* = 7.2 Hz), 4.35-4.24 (app s, 0.5 H, *J* = 7.2 Hz), 2.94 (s, 1.5 H), 2.90 (s, 1.5 H), 2.85 (ddd, 0.5 H, *J* = 16.5, 7.7, 2.7 Hz), 2.71 (d, 0.5 H, *J* = 2.6 Hz), 2.69 (d, 0.5 H, *J* = 2.6 Hz), 2.53 (ddd, 0.5 H, *J* = 16.6, 7.3, 2.7 Hz), 1.96 (t, 0.5 H, *J* = 2.7 Hz), 1.94 (t, 0.5 H, *J* = 2.7 Hz), 1.52 (d, 1.5 H, *J* = 6.9 Hz), 1.45 (d, 1.5 H, *J* = 6.9 Hz); ^{13}C NMR δ 167.9, 167.7, 140.5, 140.2, 133.1, 132.8, 132.0 (2 C), 129.8 (2 C), 123.5, 123.2, 86.8, 86.0, 81.7, 81.0, 70.5, 69.9, 49.5, 49.0, 47.9, 47.2, 24.4, 24.0, 18.3, 17.7; MS (EI) *m/z* (rel intensity) 190 ([M-C_2H_3]$^+$, 11), 183 (17), 147 (45), 105 (64), 91 (100); HRMS (EI) *m/z* calcd for $C_{12}H_{12}NO_2$ [M-C_2H_3] 190.0868, found 190.0866.



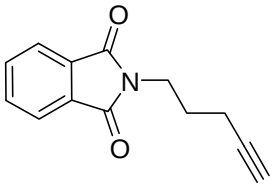
3-Methoxy-2-(4-methylpent-4-en-2-yl)isoindolin-1-one (2-19). Characteristic data for 1:1 mixture of diastereomers: ^{1}H NMR δ 4.78 (br s, 2 H), 4.71 (br s, 2 H), 1.81 (s, 3 H), 1.75 (s, 3 H).



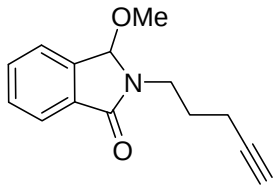
1-Oxo-2-(pent-4-yn-2-yl)isoindolin-3-yl acetate (2-20). To a solution of hydroxylactam **2-17** (75.0 mg, 0.349 mmol) in pyridine (2 mL) at ambient temperature was added acetic anyhydride (164 μL, 1.74 mmol) dropwise. The reaction mixture was stirred for 18 h, concentrated *in vacuo*, and the residue was dissolved in CH_2Cl_2 (10 mL) and washed with 10% HCl, brine and dried ($MgSO_4$). The solution was filtered, concentrated and the residue was chromatographed on SiO_2 (hexanes/EtOAc, 3:1) to furnish acetoxy lactam **2-20** (75.0 mg, 0.292 mmol, 84%) as a colorless oil which was a 1.5:1 mixture of inseparable diastereomers as indicated by ^{1}H NMR analysis: IR (neat) 3294, 2926, 2119, 1740, 1712, 1402, 1229, 1013, 756 cm^{-1}; ^{1}H NMR δ 7.82-7.76 (m, 1 H), 7.56-7.51 (m, 3 H), 7.24 (s, 0.5 H), 7.12 (s, 0.5 H), 4.48-4.39 (m, 0.5 H), 4.37-4.27 (m, 0.5 H), 2.81 (ddd, 0.5 H, *J* = 16.7, 7.0, 2.7 Hz), 2.66 (dd, 1 H, *J* = 6.9, 2.6 Hz), 2.51 (ddd, 0.5 H, *J* = 16.7, 7.4, 2.6 Hz), 2.16 (s, 1.5 H), 2.14 (s, 1.5 H), 2.00 (t, 0.5 H, *J* = 2.6 Hz), 1.97 (t, 0.5 H, *J* = 2.6 Hz), 1.48 (d, 1.5 H, *J* = 7.0 Hz), 1.43 (d, 1.5 H, *J* = 7.0 Hz); ^{13}C NMR δ 170.2 (2 C), 168.0, 167.8, 141.4, 141.3, 132.5 (2 C), 132.0, 131.8, 130.2 (2 C), 123.9, 123.7, 123.5 (2 C), 81.6, 81.1, 81.0, 80.5, 70.8, 70.3, 47.9, 47.3, 24.9, 24.2, 21.3 (2 C), 18.4, 17.6; MS (EI) *m/z* (rel intensity) 257 ([M]$^+$, 12), 218 (62), 198 (20), 132 (100), 105 (19); HRMS (EI) *m/z* calcd for $C_{15}H_{15}NO_3$ 257.1052, found 257.1050.



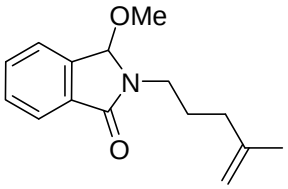
3-Methyl-2-(pent-4-yn-2-yl)isoindolin-1-one (2-21). Characteristic data for 1:1 mixture of diastereomers: ^{1}H NMR δ 4.67 (q, 1 H, *J* = 6.6 Hz), 4.66 (q, 1 H, *J* = 6.7 Hz), 1.54 (d, 3 H, *J* = 6.7 Hz), 1.48 (d, 3 H, *J* = 6.9 Hz).



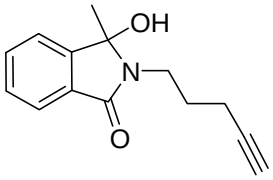
2-(Pent-4-ynyl)isoindoline-1,3-dione (2-23). To a solution of phthalimide (2.00 g, 13.6 mmol), **2-22** (1.27 mL, 13.6 mmol), and PPh_3 (3.57 g, 13.6 mmol) in THF (30 mL) was added DIAD (2.68 mL, 13.6 mmol) at 0 °C. The reaction mixture was warmed to ambient temperature and stirred for 36 h and the solvent was removed *in vacuo*. The residue was dissolved in hexanes/EtOAc (1:1, 20 mL) and the solids were filtered off. The filtrate was concentrated and chromatographed on SiO_2 (hexanes/EtOAc, 4:1) to yield imide **2-23** (2.35 g, 11.0 mmol, 81%) as a white powder: Mp 89.9-91.7 °C (hexanes/EtOAc); IR 3268, 2942, 2115, 1772, 1708, 1399, 1122, 1018, 885, 722 cm^{-1}; ^{1}H NMR δ 7.74-7.70 (m, 2 H), 7.65-7.60 (m, 2 H), 3.69 (t, 2 H, *J* = 2.0 Hz), 2.17 (td, 2 H, *J* = 7.1, 2.6 Hz), 1.88-1.78 (m, 3 H); ^{13}C NMR δ 168.0 (2 C), 133.6 (2 C), 131.8 (2 C), 122.9 (2 C), 82.8, 68.9, 36.9, 27.0, 16.0; MS (EI) m/z (rel intensity) 213 ([M]$^{+}$, 18), 212 (23), 185 (25), 160 (100), 148 (28), 130 (28); HRMS (EI) m/z calcd for $C_{13}H_{11}NO_2$ 212.0712, found 212.0708.



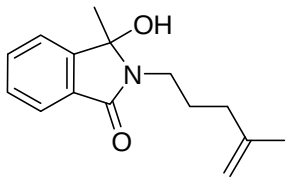
3-Methoxy-2-(pent-4-ynyl)isoindolin-1-one (2-24). To a solution of imide **2-23** (323 mg, 1.52 mmol) in MeOH (4 mL) at 0 °C was added $NaBH_4$ (45.5 mg, 1.14 mmol) in one portion. The reaction mixture was stirred for 30 min at 0 °C and at ambient temperature for 3 h, and quenched with H_2O (1 mL). The aqueous layer was extracted with CH_2Cl_2 (5 x 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated to furnish the crude hydroxylactam (323 mg, 1.50 mmol, 99%) which was used in the next step without further purification. To a solution of the crude hydroxylactam (323 mg, 1.50 mmol) in MeOH (5 mL) at ambient temperature was added *d,l*-camphorsulfonic acid (35.0 mg, 0.150 mmol). The reaction mixture was stirred for 48 h. The solvent was removed *in vacuo* and the residue was partitioned between CH_2Cl_2 (10 mL) and H_2O (10 mL). The aqueous layer was extracted with CH_2Cl_2 (5 x 10 mL) and the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated to furnish methoxy lactam **2-24** (315 mg, 1.38 mmol, 91% over two steps) as a colorless oil: IR (neat) 3294, 2935, 2116, 1705, 1413, 1073, 747, 696 cm^{-1}; ^1H NMR δ 7.77 (dd, 1 H, J = 6.9, 0.8 Hz), 7.57-7.44 (m, 3 H), 5.85 (s, 1 H), 3.79 (ddd, 1 H, J = 14.5, 7.5, 7.5 Hz), 3.34 (ddd, 1 H, J = 14.1, 7.3, 7.3 Hz), 2.84 (s, 3 H), 2.23 (br t, 2 H, J = 7.1 Hz), 1.93-1.82 (m, 3 H); ^{13}C NMR δ 167.6, 140.2, 132.9, 131.9, 129.8, 123.3 (2 C), 86.3, 83.0, 68.9, 49.1, 38.6, 26.7, 16.1; MS (EI) *m/z* (rel intensity) 228 ($[M]^+$, 28), 214 (70), 198 (70), 170 (91), 146 (100), 132 (47); HRMS (EI) *m/z* calcd for $C_{14}H_{15}NO_2$ 228.1025, found 228.1025.



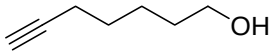
3-Methoxy-2-(4-methylpent-4-enyl)isoindolin-1-one (2-25). Characteristic data: ^{1}H NMR δ 4.72 (br d, 2 H, *J* = 8.0 Hz), 1.72 (s, 3 H).



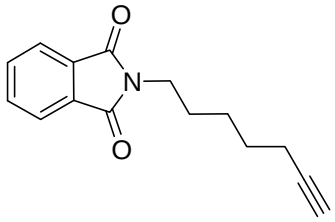
3-Hydroxy-3-methyl-2-(pent-4-ynyl)isoindolin-1-one (2-26). To a solution of imide **2-23** (100 mg, 0.469 mmol) in THF (5 mL) at -78 °C was added MeMgBr (3.0 M solution in ether, 187 μL, 0.563 mmol) dropwise over 3 min. The red reaction mixture was stirred at -78 °C for 1 h and was quenched with sat. NH_4Cl (2 mL). The THF was removed *in vacuo* and the residue was extracted with CH_2Cl_2 (4 x 5 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to provide hydroxylactam **2-26** (108 mg, 0.469 mmol, 100%) as a light yellow oil which was used without further purification: IR (neat) 3296, 2982, 2936, 2116, 1681, 1409, 1141, 1080, 698 cm^{-1}; ^{1}H NMR δ 7.52-7.50 (m, 2 H), 7.48-7.46 (m, 1 H), 7.41-7.33 (m, 1 H), 4.10 (s, 1 H, exchanges with D_2O), 3.46 (ddd, 1 H, *J* = 14.9, 9.4, 5.8 Hz), 3.12 (ddd, 1 H, *J* = 15.2, 9.3, 6.0 Hz), 2.22-2.16 (m, 2 H), 1.94 (t, 1 H, *J* = 2.6 Hz), 1.91-1.82 (m, 1 H), 1.80-1.70 (m, 1 H), 1.66 (s, 3 H); ^{13}C NMR δ 167.2, 148.2, 132.2, 130.2, 129.3, 123.1, 121.5, 88.7, 83.7, 68.9, 37.7, 27.7, 24.3, 16.4; MS (EI) *m/z* (rel intensity) 228 ([M-H]$^+$, 7), 214 (15), 186 (75), 160 (35), 147 (100), 130 (18); HRMS (EI) *m/z* calcd for $C_{14}H_{15}NO_2$ 229.1103, found 229.1106.



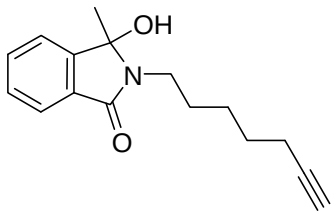
3-Hydroxy-3-methyl-2-(4-methylpent-4-enyl)isoindolin-1-one (2-27). Characteristic data: ^{1}H NMR δ 4.70 (br d, 2 H, *J* = 8.2 Hz), 1.83 (s, 3 H).



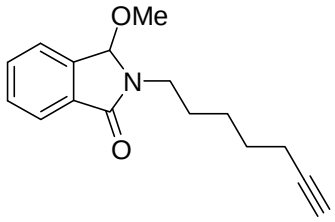
Hept-6-yn-1-ol (2-29).[146] Li wire (483 mg, 69.6 mmol) was degreased with hexanes and pumped to dryness under vacuum. Diaminopropane (34.8 mL, 41.7 mmol) was added and the reaction mixture was stirred at 70 °C for 2 h, cooled to room temperature and treated with solid KO^{t}Bu (4.33 g, 42.9 mmol). The yellow solution was stirred for 20 min, treated with hept-3-yn-1-ol (1.36 mL, 10.7 mmol) and stirred for 2 h before being poured into H_2O (150 mL). After addition of CH_2Cl_2 (20 mL), the aqueous layer was extracted with CH_2Cl_2 (5 x 10 mL) and the combined organic extracts were washed with brine and dried ($MgSO_4$). After filtration and evaporation, the residue was distilled to furnish alcohol **2-29** (1.02 g, 9.12 mmol, 85%) as a colorless oil: Bp 96 °C (0.1 mmHg); ^{1}H NMR δ 3.65 (t, 2 H, *J* = 5.6 Hz), 2.23-2.18 (m, 2 H), 1.94 (t, 1 H, *J* = 2.6 Hz), 1.63-1.54 (m, 6 H), 1.33 (br s, 1 H).



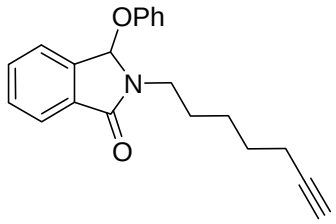
2-(Hept-6-ynyl)isoindoline-1,3-dione (2-30). A solution of alcohol **2-29** (228 mg, 2.04 mmol), phthalimide (302 mg, 2.04 mmol), and PPh_3 (540 mg, 2.04 mg) in THF (20 mL) was cooled to 0 °C and treated with DIAD (403 μL, 2.04 mmol) over 5 min. The reaction mixture was warmed to ambient temperature and stirred for 56 h. The solvent was evaporated, the residue was dissolved in hexanes/EtOAc (1:1, 10 mL) and the solids were filtered off. The filtrate was concentrated and chromatographed on SiO_2 (hexanes/EtOAc, 5:1) to yield imide **2-30** (407 mg, 1.69 mmol, 82%) as a colorless oil: IR (neat) 3466, 3283, 2941, 2862, 2115, 1772, 1709, 1615, 1397, 1046, 720 cm^{-1}; ^1H NMR δ 7.84-7.79 (m, 2 H), 7.72-7.67 (m, 2 H), 3.67 (t, 2 H, *J* = 7.1 Hz), 2.17 (td, 2 H, *J* = 6.8, 2.6 Hz), 1.91 (t, 1 H, *J* = 2.6 Hz), 1.75-1.61 (m, 2 H), 1.58-1.51 (m, 2 H), 1.49-1.38 (m, 2 H); ^{13}C NMR δ 168.3 (2 C), 133.8 (2 C), 132.1 (2 C), 123.1 (2 C), 84.2, 68.4, 37.7, 28.0, 27.9, 25.8, 18.2; MS (EI) *m/z* (rel intensity) 241 ($[M]^+$, 11), 186 (6), 173 (10), 160 (100), 148 (31), 130 (29), 104 (27); HRMS (EI) *m/z* calcd for $C_{15}H_{15}NO_2$ 241.1103, found 241.1107.



2-(Hept-6-ynyl)-3-hydroxy-3-methylisoindolin-1-one (2-31). Characteristic data: ^1H NMR δ 1.64 (s, 3 H).

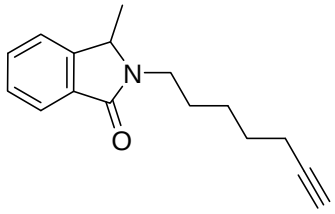


2-(Hept-6-ynyl)-3-methoxyisoindolin-1-one (2-33). To a 0 °C solution of imide **2-30** (40.0 mg, 0.166 mmol) in MeOH (4 mL) was added $NaBH_4$ (4.98 mg, 0.125 mmol). The reaction mixture was stirred at ambient temperature for 2.5 h, quenched with H_2O (1 mL) and the MeOH was removed *in vacuo*. The residue was extracted with CH_2Cl_2 (5 x 3 mL) and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to provide crude the hydroxylactam **2-32** which was immediately dissolved in MeOH (4 mL), treated with *d,l*-camphorsulfonic acid (3.85 mg, 0.0166 mmol) and stirred for 16 h. The solvent was removed *in vacuo* and the residue was partitioned between H_2O (5 mL) and CH_2Cl_2 (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), concentrated and chromatographed on SiO_2 (hexanes/EtOAc, 4:1) to yield methoxy lactam **2-33** (17.0 mg, 0.0661 mmol, 40% over two steps) as a colorless oil: IR (neat) 3298, 2925, 2854, 2115, 1702, 1466, 1412, 1059, 746 cm^{-1}; ^1H NMR δ 7.84-7.80 (m, 1 H), 7.61-7.49 (m, 3 H), 5.88 (s, 1 H), 3.79 (ddd, 1 H, *J* = 15.6, 8.1, 7.3 Hz), 3.24 (ddd, 1 H, *J* = 14.0, 8.0, 6.3 Hz), 2.87 (s, 3 H), 2.19 (td, 2 H, *J* = 6.7, 2.6 Hz), 1.92 (t, 1 H, *J* = 2.6 Hz), 1.75-1.63 (m, 2 H), 1.62-1.43 (m, 4 H); ^{13}C NMR δ 167.6, 140.3, 133.2, 131.9, 129.9, 123.4 (2 C), 86.2, 84.3, 68.4, 49.1, 39.3, 28.0, 27.6, 26.0, 18.3; MS (EI) *m/z* (rel intensity) 257 ($[M]^+$,18), 242 (17), 226 (20), 176 (66), 146 (100), 132 (39), 117 (21); HRMS (EI) *m/z* calcd for $C_{16}H_{19}NO_2$ 257.1416, found 257.1419.

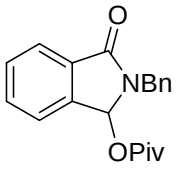


2-(Hept-6-ynyl)-3-phenoxyisoindolin-1-one (2-24). A 0 °C solution of imide **2-30** (307 mg, 1.27 mmol) in MeOH (20 mL) was treated with $NaBH_4$ (36.3 mg, 0.953 mmol), warmed to

ambient temperature and stirred for 1 h. The reaction mixture was quenched with H_2O (10 mL) and the MeOH was removed *in vacuo*. The residue was extracted with CH_2Cl_2 (6 x 10 mL) and the combined organic layers washed with brine, dried (Na_2SO_4) and concentrated to yield crude hydroxylactam **2-32** as a colorless oil. A portion of the crude hydroxylactam (101 mg, 0.416 mmol) was immediately dissolved in THF (5 mL) at ambient temperature and treated with $SOCl_2$ (30.3 μL, 0.416 mmol) and DMF (1 drop) and stirred for 14 h. The volatiles were removed under reduced pressure and the residue was dried *in vacuo* for 12 h. The unstable crude chloride was obtained as a colorless oil and immediately dissolved in THF (4.1 mL) at ambient temperature. This solution was treated with phenol (58.0 mg, 0.620 mmol) and Et_3N (288 μL, 2.07 mmol) and stirred for 2 h. The reaction mixture was quenched with H_2O (1 mL) and the THF was removed *in vacuo*. The residue was extracted with CH_2Cl_2 (4 x 5 mL) and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was chromatographed on SiO_2 (hexanes/EtOAc, 3:1) to yield phenoxylactam **2-34** (45.0 mg, 1.41 mmol, 34% over two steps) as a colorless oil: IR (neat) 3296, 2936, 2115, 1707, 1588, 1491, 1415, 1222, 992, 780 cm^{-1}; ^1H NMR δ 7.85-7.79 (m, 1 H), 7.53-7.46 (m, 3 H), 7.33-7.27 (m, 2 H), 7.08-6.98 (m, 3 H), 6.42 (s, 1 H), 3.80 (dt, 1 H, *J* = 14.2, 7.4 Hz), 3.44 (ddd, 1 H, *J* = 14.0, 7.8, 6.4 Hz), 2.16 (td, 2 H, *J* = 6.7, 2.6 Hz), 1.91 (t, 1 H, *J* = 2.6 Hz), 1.78-1.61 (m, 2 H), 1.57-1.39 (m, 4 H); ^{13}C NMR δ 167.4, 156.3, 141.3, 132.3, 132.0, 130.0, 129.7 (2 C), 123.5, 123.3, 123.1, 118.1 (2 C), 86.8, 84.2, 68.4, 40.0, 27.9, 27.6, 25.9, 18.2; MS (EI) *m/z* (rel intensity) 319 ($[M]^+$, 70), 265 (28), 226 (100), 198 (8), 146 (52), 132 (65); HRMS (EI) *m/z* calcd for $C_{21}H_{21}NO_2$ 319.1572, found 319.1573.

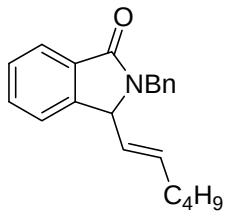


2-(Hept-6-ynyl)-3-methylisoindolin-1-one (2-35). Characteristic data: ^{1}H NMR δ 4.55 (q, 1 H, *J* = 6.7 Hz), 1.48 (d, 3 H, *J* = 6.7 Hz).

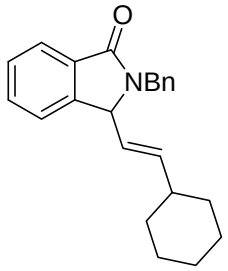


2-Benzyl-3-oxoisoindolin-1-yl pivaloate (2-48). To a solution of benzyl phthalimide (8.89 g, 37.5 mmol) in MeOH (130 mL) was added sodium borohydride (1.42 g, 37.5 mmol) at 0 °C. The resulting reaction mixture was stirred at 0 °C for 2 h and carefully quenched with H_2O. The aqueous layer was extracted with EtOAc (2x) and the organic layer was separated, dried ($MgSO_4$) and concentrated. The residue was dried to yield a white solid which was carried on to the next step without further purification. To a solution of the crude reduced phthalamide (1.00 g, 4.20 mmol) in THF (30 mL) was added Et_3N (1.17 mL, 8.40 mmol) and pivaloyl chloride (621 μL, 5.04 mmol) at 0 °C and the reaction mixture was allowed to warm to rt and stirred at this temperature for 4 h. The mixture was quenched with sat. aq. $NaHCO_3$, extracted with EtOAc (2x), dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (EtOAc:Hex, 3:7) to yield 1.09 g (80% over 2 steps) of **2-48** as a colorless solid: mp 88.1 - 89.0 °C (CH_2Cl_2); IR (neat) 3419, 3062, 3031, 2973, 2934, 2872, 1717, 1408, 1276, 1122, 959, 751 cm^{-1}; ^{1}H NMR δ 7.92-7.84 (m, 1 H), 7.61-7.53 (m, 2 H), 7.50-7.43 (m, 1 H), 7.38-7.22 (m, 5 H), 6.89 (s, 1 H), 5.01 (d, 1 H, *J* = 15 Hz), 4.44 (d, 1 H, *J* = 15 Hz), 1.13 (s, 9 H); ^{13}C NMR δ 178.4, 167.9, 141.3, 136.8, 132.5, 131.9, 130.2,

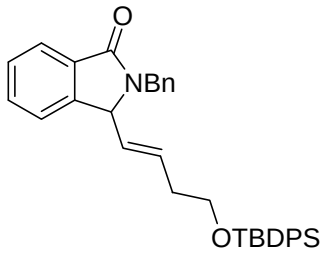
128.7, 128.1, 127.7, 123.7, 123.7, 81.0, 44.2, 39.0, 26.8; MS (EI) *m/z* (rel intensity) 323 ($[M]^+$, 35), 221 (100), 133 (65), 91 (100); HRMS (EI) *m/z* calcd for $C_{21}H_{23}NO$ 323.1521, found 323.1515.



(*E*)-2-Benzyl-3-(hex-1-enyl)isoindolin-1-one (2-49). General Protocol A. To a solution of 1-hexyne (60.5 μL, 0.526 mmol) in CH_2Cl_2 (1.5 mL) was added zirconocene hydrochloride (156 mg, 0.605 mmol) and the resulting suspension was stirred at rt for 10 min. The resulting yellow solution was cooled to 0 °C and Me_3Al (1.0 M in CH_2Cl_2, 0.605 mL, 0.605 mmol) and **2-48** (85.0 mg, 0.263 mmol) were added. The mixture was warmed to rt and stirred at this temperature for 1 h, quenched with sat. aq. NH_4Cl, and extracted with CH_2Cl_2. The organic layers were separated, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (EtOAc:Hex, 3:7) to yield 65.1 mg (81%) of **2-49** as a colorless oil: IR (neat) 3479, 3031, 2927, 2857, 1694, 1615, 1400, 972 cm^{-1}; ^1H NMR δ 7.91-7.86 (m, 1 H), 7.56-7.42 (m, 2 H), 7.36-7.21 (m, 6 H), 5.90 (dt, 1 H, *J* = 15.0, 6.8 Hz), 5.30 (d, 1 H, *J* = 14.8 Hz), 5.09 (dd, 1 H, *J* = 15.2, 9.2 Hz), 4.70 (d, 1 H, *J* = 9.2 Hz), 4.17 (d, 1 H, *J* = 14.9 Hz), 2.13 (app q, 2 H, *J* = 6.7 Hz), 1.50-1.30 (m, 4 H), 0.94 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR δ 167.9, 145.1, 138.3, 137.5, 131.8, 131.5, 128.6, 128.3, 127.3, 126.1, 123.6, 123.0, 62.7, 43.8, 31.8, 31.1, 22.1, 13.8; MS (EI) *m/z* (rel intensity) 305 ($[M]^+$, 100), 248 (40), 237 (70), 214 (40); HRMS (EI) *m/z* calcd for $C_{21}H_{23}NO$ 305.1780, found 305.1785.

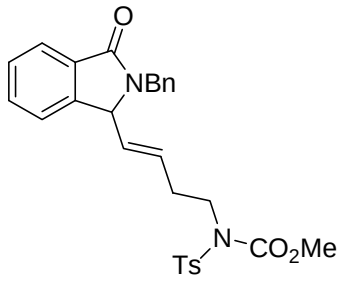


(*E*)-2-Benzyl-3-(2-cyclohexylvinyl)isoindolin-1-one (2-50). According to general protocol A, cyclohexylacetylene (66.9 mg, 0.618 mmol), CH_2Cl_2 (1.5 mL), zirconocene hydrochloride (183 mg, 0.711 mmol), Me_3Al (1.0 M in CH_2Cl_2, 0.711 mL, 0.711 mmol) and **2-48** (100 mg, 0.309 mmol) afforded 80.8 mg (79%) of **2-50** as a colorless oil after purification on SiO_2 (EtOAc:Hex, 3:7): IR (neat) 3375, 3030, 2921, 2851, 2243, 1220, 1200, 1097, 844 cm^{-1}; ^1H NMR δ 7.92-7.86 (m, 1 H), 7.54-7.41 (m, 2 H), 7.35-7.20 (m, 6 H), 5.85 (dd, 1 H, *J* = 15.3, 6.6 Hz), 5.28 (d, 1 H, *J* = 14.8 Hz), 5.02 (ddd, 1 H, *J* = 15.3, 9.2, 1.2 Hz), 4.67 (d, 1 H, *J* = 9.2 Hz), 4.18 (d, 1H, *J* = 14.8 Hz), 2.14-1.96 (m, 1 H), 1.85-1.60 (m, 4 H), 1.42-1.00 (m, 6 H); ^{13}C NMR δ 167.9, 145.1, 144.1, 137.4, 131.8, 131.4, 128.5, 128.3, 128.2, 127.3, 123.6, 122.9, 62.8, 43.8, 40.3, 32.6, 26.0, 25.8; MS (EI) *m/z* (rel intensity) 331 ($[M]^+$, 86), 248 (40), 237 (100); HRMS (EI) *m/z* calcd for $C_{23}H_{25}NO$ 331.1936, found 331.1951.



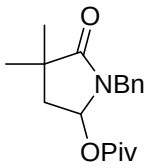
(*E*)-2-Benzyl-3-(4-(*tert*-butyldiphenylsilyloxy)but-1-enyl)isoindolin-1-one (2-51). According to general protocol A, *O*-TBDPS-3-butynol (94.4 mg, 0.306 mmol), CH_2Cl_2 (1 mL), zirconocene hydrochloride (78.9 mg, 0.306 mmol), Me_3Al (1.0 M in CH_2Cl_2, 0.306 mL, 0.306

mmol) and **2-48** (50.0 mg, 0.153) afforded 57.6 mg (71%) of **2-51** as a colorless oil after purification on SiO_2 (EtOAc:Hex, 2:8): IR (neat) 3450, 2930, 2857, 1692, 1428, 1111, 735, 701 cm^{-1}; ^1H NMR δ 7.92-7.86 (m, 1 H), 7.72-7.65 (m, 4 H), 7.53-7.35 (m, 9 H), 7.32-7.21 (m, 5 H), 5.96 (dt, 1 H, *J* = 15.3, 6.8 Hz), 5.27 (d, 1 H, *J* = 14.9 Hz), 5.16 (dddd, 1 H, *J* = 15.3, 9.1, 1.2, 1.2 Hz), 4.71 (d, 1 H, *J* = 9.1 Hz), 4.16 (d, 1 H, *J* = 14.9 Hz), 3.77 (dt, 2 H, *J* = 6.3, 1.2 Hz), 2.37 (app q, 2 H, *J* = 6.6 Hz), 1.08 (s, 9 H); ^{13}C NMR δ 168.0, 144.9, 137.5, 135.6, 134.8, 133.8, 131.9, 131.5, 129.7, 128.6, 128.4, 128.2, 127.7, 127.4, 123.6, 123.1, 63.2, 62.6, 43.9, 35.6, 26.9, 19.2; MS (EI) *m/z* (rel intensity) 532 ($[M]^+$, 35), 488 (100), 474 (45), 306 (65), 252 (75); HRMS (EI) *m/z* calcd for $C_{35}H_{37}NO_2Si$ 532.2664, found 532.2664.



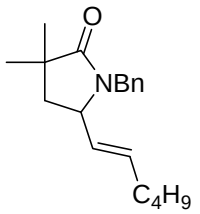
(*E*)-Methyl 4-(2-benzyl-3-oxoisoindolin-1-yl)-but-3-enyl-(tosyl)-carbamate (2-52). According to general protocol A, methyl but-3-ynyl(tosyl)carbamate (174 mg, 0.618 mmol), CH_2Cl_2 (1.5 mL), zirconocene hydrochloride (183 mg, 0.711 mmol), Me_3Al (1.0 M in CH_2Cl_2, 0.711 mL, 0.711 mmol) and **2-48** (100 mg, 0.309) afforded 95.1 mg (62%) of **2-52** as a colorless oil after purification on SiO_2 (acetone:CH_2Cl_2, 0.3:9.7): IR (neat) 3467, 3032, 2957, 2245, 1735, 1686, 1359, 1168, 733 cm^{-1}; ^1H NMR δ 7.92-7.78 (m, 3 H), 7.56-7.41 (m, 2 H), 7.39-7.18 (m, 9 H), 5.93 (dt, 1 H, *J* = 15.2, 7.0 Hz), 5.26 (d, 1 H, *J* = 14.9 Hz), 5.21 (dd, 1 H, *J* = 15.1, 9.1 Hz), 4.73 (d, 1 H, *J* = 9.0), 4.18 (d, 1 H, *J* = 14.9 Hz), 3.95 (t, 2 H, *J* = 7.0 Hz), 3.69 (s, 3 H), 2.58 (app q, 2 H, *J* = 7.0 Hz), 2.43 (s, 3 H); ^{13}C NMR δ 168.0, 152.8, 144.8, 144.6, 137.4, 136.5, 133.0, 131.7, 131.6, 129.7, 129.4,

128.6, 128.3, 128.3, 127.4, 123.6, 123.2, 62.3, 53.8, 46.5, 43.8, 32.9, 21.6; MS (EI) *m/z* (rel intensity) 504 ($[M]^+$, 50), 262 (40), 155 (100); HRMS (EI) *m/z* calcd for $C_{28}H_{28}N_2O_5S$ 504.1719, found 504.1724.

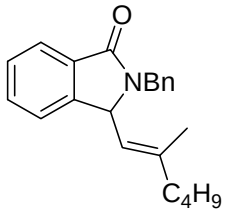


1-benzyl-4,4-dimethyl-5-oxopyrrolidin-2-yl pivalate (2-54). A mixture of 2,2-dimethylsuccinic anhydride (710 mg, 5.55 mmol) and benzyl amine (712 mg, 6.66 mmol, 1.2 eq) was heated over a bunsen burner for ~ 1 min. The cooled mixture was purified by chromatography on SiO_2 (1:1 Hex/EtOAc) to furnish the corresponding imide (1.14 g, 95%) as a colorless oil: IR (neat) 2969, 2933, 1777, 1702, 1344, 1142, 709 cm^{-1}; ^1H NMR δ 7.29-7.21 (m, 5 H), 4.57 (s, 2 H), 2.47 (s, 2 H), 1.22 (s, 6 H); ^{13}C NMR δ 182.5, 175.1, 135.8, 128.3 (2 C), 128.1 (2 C), 127.5, 43.2, 42.0, 39.7, 25.1 (2 C); MS (EI) *m/z* (rel intensity) 217 ($[M]^+$, 100), 174 (33), 133 (22); HRMS (EI) *m/z* calcd for $C_{13}H_{15}NO_2$, found. A solution of this imide (1.14 g, 5.25 mmol) in MeOH (53 mL) was treated with $NaBH_4$ (200 mg, 2.62 mmol, 1 eq) at ambient temperature. After 6 h, the reaction mixture was concentrated, the residue dissolved in CH_2Cl_2 (50 mL) and treated with aq. NH_4Cl (aq.). The aqueous layer was separated and washed with CH_2Cl_2 (2 x 25 mL) and the combined organic layers were dried ($MgSO_4$), filtered, concentrated and the resulting oil used without further purification. The crude oil was dissolved in CH_2Cl_2 (50 mL) and treated sequentially with Et_3N (2.19 mL, 15.7 mmol, 3 eq), DMAP (128 mg, 1.05 mmol, 20 mol %) and pivaloyl chloride (1.29 mL, 10.5 mmol, 2 eq) at ambient temperature. After 6 h, the reaction mixture was quenched with 3 M HCl (aq., 10 mL) and the aqueous layer washed with CH_2Cl_2 (3 x 15 mL). The combined organic layers were washed with H_2O, dried ($MgSO_4$), filtered, concentrated and the residue purified by

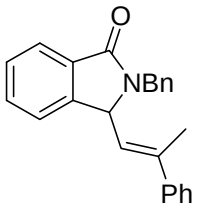
chromatography on SiO_2 (2:1 Hex/EtOAc) to yield **2-54** (398 mg, 25%) as a colorless oil: IR (neat) 2971, 1710, 1419, 1125, 707 cm^{-1}; ^1H NMR δ 7.33-7.21(m, 5 H), 5.99 (d, 1 H, *J* = 6.3 Hz), 4.74 (d, 1 H, *J* = 14.7 Hz), 4.15 (d, 1 H, *J* = 14.7 Hz), 2.14 (dd, 1 H, *J* = 14.1, 6.3 Hz), 1.87 (d, 1 H, *J* = 14.4 Hz), 1.32 (s, 3 H), 1.22 (s, 3 H), 1.10 (s, 9 H); ^{13}C NMR δ 180.6, 177.9, 136.6, 128.7 (2 H), 128.2 (2 H), 127.6, 82.1, 44.8, 41.5, 39.3, 38.7, 26.8 (3 C), 26.5, 25.6; MS (EI) *m/z* (rel intensity) 303 ($[M]^+$, 36), 275 (15), 202 (85), 158 (46); HRMS (EI) *m/z* calcd for $C_{18}H_{25}NO_3$, found.



(*E*)-1-Benzyl-5-(hex-1-enyl)-3,3-dimethylpyrrolidin-2-one (2-55). According to general protocol A, hexyne (9.77 mg, 0.119 mmol), CH_2Cl_2 (1 mL), zirconocene hydrochloride (30.7 mg, 0.119 mmol), Me_3Al (1.0 M in CH_2Cl_2, 0.119 mL, 0.119 mmol) and **2-54** (18.0 mg, 0.0593 mmol) afforded 14.0 mg (83%) of **2-55** as a colorless oil after purification on SiO_2 (EtOAc:hex, 2.5:7.5): IR (neat) 2958, 2928, 2868, 1692, 1411, 1262, 972, 752 cm^{-1}; ^1H NMR δ 7.35-7.23 (m, 3 H), 7.21-7.13 (m, 2 H), 5.53 (dt, 1 H, *J* = 15.0, 6.6 Hz), 5.16 (dd, 1 H, *J* = 15.3, 9.0 Hz), 4.94 (d, 1 H, *J* = 14.4 Hz), 3.88 (d, 1 H, *J* = 14.4 Hz), 3.73 (app q, 1 H, *J* = 7.8 Hz), 2.10-1.98 (m, 2 H), 1.99 (dd, 1 H, *J* = 12.9, 7.2 Hz), 1.58 (dd, 1 H, *J* = 12.9, 8.1 Hz), 1.42-1.28 (m, 4 H), 1.24 (s, 3 H), 1.11 (s, 3 H), 0.92 (t, 3 H, *J* = 6.9 Hz); ^{13}C NMR δ 179.6, 137.2, 135.8, 129.8, 128.4, 128.3, 127.2, 56.9, 44.2, 42.0, 40.3, 31.8, 31.2, 25.5, 24.7, 22.2, 13.9; MS (EI) *m/z* (rel intensity) 285 ($[M]^+$, 20), 228 (20), 175 (30), 91 (100); HRMS (EI) *m/z* calcd for $C_{19}H_{27}NO$ 285.2093, found 285.2090.

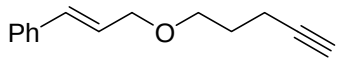


(*E*)-2-Benzyl-3-(2-methylhex-1-enyl)isoindolin-1-one (2-56). General Protocol B. To a -30 °C solution of $AlMe_3$ (89.0 mg, 1.24 mmol) and Cp_2ZrCl_2 (9.00 mg, 0.0309 mmol) in CH_2Cl_2 (1.5 mL) was added H_2O (11.1 mg, 0.619 mmol) dropwise. The reaction mixture was warmed to ambient temperature, cooled to 0 °C, treated with 1-hexyne (71.0 μL, 0.619 mmol), stirred for 30 min and treated with **2-48** (100 mg, 0.309 mmol). The reaction mixture was warmed to rt and stirred at this temperature for 1 h, quenched with sat. aq. NH_4Cl, and extracted with CH_2Cl_2. The organic layers were separated, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (EtOAc:Hex, 3:7) to yield 76.0 mg (77%) of **2-56** as a colorless oil: IR (neat) 2956, 2929, 2858, 1694, 1468, 1401, 749, 703 cm^{-1}; ^1H NMR δ 7.89-7.50 (m, 1 H), 7.53-7.40 (m, 2 H), 7.35-7.20 (m, 6 H), 5.31 (d, 1 H, *J* = 14.9 Hz), 5.06 (d, 1 H, *J* = 9.8), 4.81 (dq, 1 H, *J* = 9.8, 1.2 Hz), 4.09 (d, 1 H, *J* = 14.9 Hz), 2.07 (t, 2 H, *J* = 7.1 Hz), 1.67 (d, 3 H, *J* = 1.3 Hz), 1.50-1.22 (m, 4 H), 0.91 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR δ 168.1, 145.7, 143.4, 137.5, 132.0, 131.4, 128.5, 128.2, 128.0, 127.3, 123.6, 122.8, 120.6, 57.9, 43.9, 39.3, 29.8, 22.2, 16.5, 13.8; MS (EI) *m/z* (rel intensity) 319 ($[M]^+$, 100), 221 (40); HRMS (EI) *m/z* calcd for $C_{22}H_{25}NO$ 319.1936, found 319.1921.

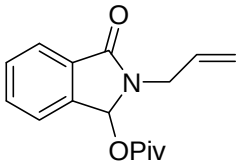


(*E*)-2-Benzyl-3-(2-phenylprop-1-enyl)isoindolin-1-one (2-57). According to general protocol B, phenylacetylene (68.0 μL, 0.619 mmol), $AlMe_3$ (89.0 mg, 1.24 mmol), Cp_2ZrCl_2 (9.00

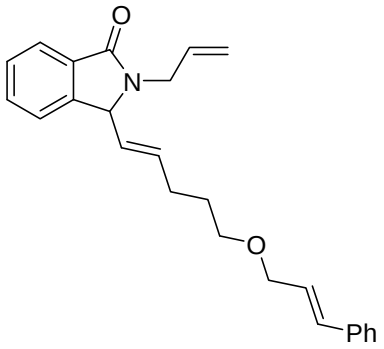
mg, 0.0309 mmol), CH_2Cl_2 (1.5 mL), H_2O (11.1 mg, 0.619 mmol) and **2-48** (100 mg, 0.309 mmol) afforded 81.0 mg (77%) of **2-57** as a colorless oil and a 95:5 mixture of regioisomers after purification on SiO_2 (EtOAc:Hex, 1:3): Major isomer: IR (neat) 3030, 2918, 1693, 1602, 1432, 1400, 1250, 749 cm^{-1}; ^1H NMR δ 7.93 (dd, 1 H, *J* = 6.3, 2.1 Hz), 7.54-7.46 (m, 2 H), 7.35-7.26 (m, 11 H), 5.41 (dd, 1 H, *J* = 9.6, 0.9 Hz), 5.35 (d, 1 H, *J* = 15.0 Hz), 5.27 (d, 1 H, *J* = 9.9 Hz), 4.21 (d, 1 H, *J* = 15.0 Hz), 2.12 (d, 3 H, *J* = 0.9 Hz); ^{13}C NMR δ 168.1, 145.0, 142.0, 141.3, 137.4, 132.0, 131.6, 128.6, 128.3, 127.8, 127.5, 125.8, 123.8, 123.7, 122.9, 58.2, 44.3, 16.3; MS (EI) *m/z* (rel intensity) 339 ($[M]^+$, 41), 248 (47), 234 (77), 91 (100); HRMS (EI) *m/z* calcd for $C_{24}H_{21}NO$ 339.1623, found 339.1631. Minor isomer (characteristic peaks): ^1H NMR δ 1.44 (d, 3 H, *J* = 6.9 Hz); ^{13}C NMR δ 128.0, 121.9, 18.0.



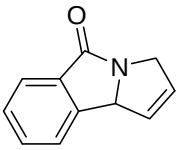
(*E*)-(3-(Pent-4-ynyloxy)prop-1-enyl)benzene (2-59). To a solution of 4-pentyn-1-ol (4.03 mL, 43.3 mmol) in hexanes (75 mL) was added 50% NaOH (75 mL), TBAI (801 mg, 2.17 mmol) and cinnamyl bromide (8.97 g, 45.5 mmol). The reaction mixture was rapidly stirred for 10 h, the organic layer was separated, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (EtOAc:Hex, 1:9) to yield 9.00 g (69%) of **2-59** as a colorless oil: IR (neat) 3298, 3027, 2951, 2854, 2117, 1478, 1365, 1111, 967 cm^{-1}; ^1H NMR δ 7.44-7.37 (m, 2 H), 7.37-7.27 (m, 2 H), 7.27-7.21 (m, 1 H), 6.62 (d, 1 H, *J* = 15.9 Hz), 6.30 (dt, 1 H, *J* = 15.9, 6.0), 4.15 (dd, 2 H, *J* = 6.0, 0.9 Hz), 3.60 (t, 2 H, *J* = 6.3 Hz), 2.34 (dt, 2 H, *J* = 7.2, 2.7 Hz), 1.96 (t, 1 H, *J* = 2.7 Hz), 1.85 (app p, 2 H, *J* = 6.6 Hz); ^{13}C NMR δ 136.5, 131.8, 128.3, 127.4, 126.2, 126.0, 83.7, 71.2, 68.5, 68.3, 28.5, 15.1; MS (EI) *m/z* (rel intensity) 199 ($[M]^+$, 100), 186 (35), 173 (35), 131 (100); HRMS (EI) *m/z* calcd for $C_{14}H_{16}O$ 199.1123, found 199.1126.



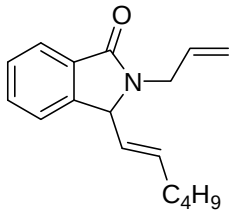
2-Allyl-3-oxoisoindolin-1-yl pivalate (2-61). To a solution of 2-allylisoindoline-1,3-dione (3.64 g, 19.4 mmol) in MeOH (100 mL) was added sodium borohydride (734 mg, 19.4 mmol) at 0 °C. The resulting reaction mixture was stirred at 0 °C for 2 h and carefully quenched with H_2O. The aqueous layer was extracted with EtOAc (2x) and the organic layer was separated, dried ($MgSO_4$) and concentrated. The residue was dried to yield a white solid which was carried on to the next step without further purification. To a solution of the crude reduced phthalamide (3.60 g, 19.0 mmol) in THF (100 mL) was added Et_3N (7.90 mL, 57.0 mmol) and pivaloyl chloride (2.81 mL, 22.8 mmol) at 0 °C and the reaction mixture was allowed to warm to rt and stirred at this temperature for 4 h. The mixture was quenched with sat. aq. $NaHCO_3$, extracted with EtOAc (2x), dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (EtOAc:Hex, 2.5:7.5) to yield 4.40 g (83% over 2 steps) of **2-61** as a colorless oil: IR (neat) 2976, 1716, 1405, 1135, 753; ^{1}H NMR δ 7.88-7.80 (m, 1 H), 7.62-7.46 (m, 3 H), 6.99 (s, 1 H), 5.94-5.77 (m, 1 H), 5.29-5.15 (m, 2 H), 4.44 (dd, 1 H, *J* = 15.9, 5.1 Hz), 3.88 (dd, 1 H, *J* = 15.3, 6.6 Hz), 1.23 (s, 9 H) cm^{-1}; ^{13}C NMR δ 178.3, 167.5, 141.2, 132.4, 132.4, 131.8, 130.0, 123.6, 123.5, 118.0, 80.9, 42.8, 39.0, 26.9; MS (EI) *m/z* (rel intensity) 273 ([M]$^+$, 60), 172 (100; HRMS (EI) *m/z* calcd for $C_{16}H_{19}NO_3$ 273.1365, found 273.1358.



2-Allyl-3-((*E*)-5-(cinnamyloxy)pent-1-enyl)isoindolin-1-one (2-62). According to general protocol A, alkyne **2-59** (733 mg, 3.66 mmol), CH_2Cl_2 (10 mL), zirconocene hydrochloride (944 mg, 3.66 mmol), Me_3Al (1.0 M in CH_2Cl_2, 3.66 mL, 3.66 mmol) and **2-61** (500 mg, 1.83 mmol) (reaction time increased to 12 h) afforded 376 mg (55%) of **2-62** as a colorless oil after purification on SiO_2 (Acetone:CH_2Cl_2, 0.7:9.3): IR (neat) 2924, 2853, 1694, 1468, 1289, 1098, 968, 746 cm^{-1}; ^1H NMR δ 7.85 (d, 1 H, *J* = 6.6 Hz), 7.57-7.20 (m, 8 H), 6.61 (d, 1 H, *J* = 15.9 Hz), 6.29 (dt, 1 H, *J* = 15.9, 6.0 Hz), 6.02 (dt, 1 H, *J* = 13.8, 6.9 Hz), 5.90-5.73 (m, 1 H), 5.25-5.07 (m, 3 H), 4.87 (d, 1 H, *J* = 9.0 Hz), 4.60 (ddd, 1 H, *J* = 15.6, 4.5, 2.7 Hz), 4.15 (dd, 2 H, *J* = 6.0, 1.2 Hz), 3.70 (dd, 1 H, *J* = 15.3, 7.2 Hz), 3.53 (t, 2 H, *J* = 6.3 Hz), 2.25 (app q, 2 H, *J* = 6.9 Hz), 1.77 (app p, 2 H, *J* = 7.8 Hz); ^{13}C NMR δ 167.7, 144.9, 137.2, 136.6, 133.2, 132.3, 131.8, 131.4, 128.5, 128.3, 127.6, 126.7, 126.4, 126.1, 123.5, 122.9, 117.5, 71.5, 69.4, 62.9, 42.5, 29.2, 28.9; MS (ESI) *m/z* (rel intensity) 396 ($[M+Na]^+$, 100), 307 (20), 297 (20); HRMS (ESI) *m/z* calcd for $C_{25}H_{27}NO_2Na$ 396.1939, found 396.1928

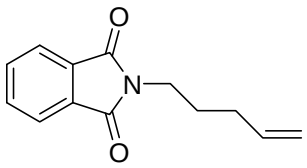


3*H*-Pyrrolo[2,1-*a*]isoindol-5(9b*H*)-one (2-63). To a solution of **2-62** (41.7 mg, 0.112 mmol) in CH_2Cl_2 (6 mL) was added Grubbs 2nd generation catalyst (4.75 mg, 5.60 mmol) and the red solution was heated at 50 °C for 1 h, cooled to rt and concentrated. The residue was purified by chromatography on SiO_2 (Acetone:CH_2Cl_2, 0.4:9.6) to yield 11.7 mg (61%) of **2-63** as a colorless oil: IR (neat) 2872, 1614, 1468, 1395, 1366, 1080, 746 cm^{-1}; ^1H NMR δ 7.74-7.66 (m, 2 H), 7.66-7.58 (m, 1 H), 7.54-7.45 (m, 1 H), 6.28-6.20 (m, 1 H), 6.08-5.99 (m, 1 H), 5.53 (app d, 1 H, *J* = 1.8 Hz), 4.57-4.43 (m, 1 H), 3.98-3.83 (m, 1 H); ^{13}C NMR δ 175.4, 148.4, 133.6, 133.1, 131.9, 129.4, 129.2, 124.6, 124.0, 71.1, 52.0; MS (EI) *m/z* (rel intensity) 171 ($[M]^+$, 60), 160 (70), 130 (55), 105 (60), 83 (100); HRMS (EI) *m/z* calcd for C11H9NO 171.0684, found 171.0676.

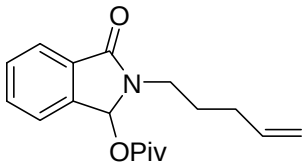


(*E*)-2-Allyl-3-(hex-1-enyl)isoindolin-1-one (2-64). According to general protocol A, hexyne (420 μL, 3.66 mmol), CH_2Cl_2 (10 mL), zirconocene hydrochloride (944 mg, 3.66 mmol), Me_3Al (1.0 M in CH_2Cl_2, 3.66 mL, 3.66 mmol) and **2-61** (500 mg, 1.83 mmol) afforded 341 mg (73%) of **2-64** as a colorless oil after purification on SiO_2 (EtOAc:Hex, 3:7): IR (neat) 2957, 2926, 1697, 1468, 1396, 971, 748 cm^{-1}; ^1H NMR δ 7.83 (d, 1 H, *J* = 7.2 Hz), 7.57-7.38 (m, 2 H), 7.33 (d, 1 H, *J* = 7.5 Hz), 5.97 (dt, 1 H, *J* = 15.0, 6.9 Hz), 5.88-5.71 (m, 1 H), 5.22-4.97 (m, 3 H), 4.85 (d, 1 H, *J* = 9.3 Hz), 4.59 (dd, 1 H, *J* = 15.6, 4.5 Hz), 3.69 (dd, 1 H, *J* = 15.3, 7.2 Hz), 2.12 (app q, 2 H, *J* = 6.6 Hz), 1.48-1.28 (m, 4 H), 0.91 (t, 3 H, *J* = 6.9 Hz); ^{13}C NMR δ 167.7, 145.0, 138.2, 133.1, 131.7, 131.4, 128.2, 126.0, 123.4, 122.9, 117.4, 62.9, 42.5, 31.8, 31.1, 27.0, 22.0, 13.8; MS (EI) *m/z* (rel

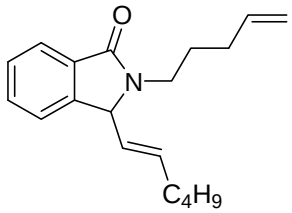
intensity) 255 ([M]$^+$, 30), 198 (100), 172 (55); HRMS (EI) *m/z* calcd for $C_{17}H_{21}NO$ 255.1623, found 255.1627.



2-(Pent-4-enyl)isoindoline-1,3-dione (2-66). A solution of 4-penten-1-ol (**2-65**, 3.51 mL, 34.0 mmol), phthalimide (5.00 mg, 34.0 mmol), and PPh_3 (8.92 g, 34.0 mmol) in THF (220 mL) was cooled to 0 °C and treated with DIAD (6.69 mL, 34.0 mmol) over 5 min. The reaction mixture was warmed to rt and stirred for 6 h. The solvent was evaporated, the residue was dissolved in EtOAc/hex (1:1, 100 mL) and the solids were filtered off. The filtrate was concentrated and chromatographed on SiO_2 (EtOAc:hex, 1:5) to yield 6.44 g (88%) of imide **2-66** as a colorless oil: IR (neat) 3466, 3077, 2939, 1773, 1641, 1397, 995, 720 cm^{-1}; ^{1}H NMR δ 7.88-7.81 (m, 2 H), 7.76-7.67 (m, 2 H), 5.90-5.73 (m, 1 H), 5.12-4.94 (m, 2 H), 3.70 (dt, 2 H, J = 7.5, 4.5 Hz), 2.20-2.07 (m, 2 H), 1.87-1.73 (m, 2 H); ^{13}C NMR δ 168.1, 137.1, 133.7, 131.9, 122.9, 115.1, 37.3, 30.8, 27.4; MS (EI) *m/z* (rel intensity) 215 ([M]$^+$, 45), 173 (70), 160 (100), 148 (80), 130 (80), 104 (90); HRMS (EI) *m/z* calcd for $C_{13}H_{13}NO_2$ 215.0946, found 215.0946.

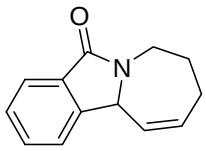


3-Oxo-2-(pent-4-enyl)isoindolin-1-yl pivalate (2-67). To a solution of imide **2-66** (4.42 g, 20.5 mmol) in MeOH (100 mL) was added sodium borohydride (776 mg, 20.5 mmol) at 0 °C. The resulting reaction mixture was stirred at 0 °C for 2 h and carefully quenched with H_2O. The aqueous layer was extracted with EtOAc (2x) and the organic layer was separated, dried ($MgSO_4$) and concentrated. The residue was dried to yield a white solid which was carried on to the next step without further purification. To a solution of the crude reduced phthalamide (4.23 g, 19.5 mmol) in THF (100 mL) was added Et_3N (8.15 mL, 58.5 mmol), pivaloyl chloride (3.61 mL, 29.3 mmol) and DMAP (119 mg, 0.975 mmol) at 0 °C and the reaction mixture was allowed to warm to rt and stirred at this temperature for 8 h. The mixture was quenched with sat. aq. $NaHCO_3$, extracted with EtOAc (2x), dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (EtOAc:Hex, 1:5) to yield 4.70 g (76% over 2 steps) of **2-67** as a colorless oil: IR (neat) 3077, 2974, 2873, 1739, 1641, 1618, 1369, 1208, 1141, 959, 751 cm^{-1}; ^1H NMR δ 7.67 (d, 1 H, J = 6.0 Hz), 7.49-7.32 (m, 3 H), 6.89 (s, 1 H), 5.79-5.58 (m, 1 H), 4.91 (d, 1 H, J = 17.1 Hz), 4.84 (d, 1 H, J = 10.5 Hz), 3.73-3.55 (m, 1 H), 3.27-3.09 (m, 1 H), 2.07-1.93 (m, 2 H), 1.77-1.50 (m, 2 H), 1.11 (s, 9 H); ^{13}C NMR δ 178.2, 167.4, 140.9, 137.1, 132.0, 131.8, 129.8, 123.2, 123.1, 114.9, 80.8, 39.5, 38.7, 30.7, 27.1, 26.6; MS (EI) *m/z* (rel intensity) 301 ($[M]^+$, 15), 246 (45), 216 (65), 200 (85), 146 (85), 133 (65); HRMS (EI) *m/z* calcd for $C_{18}H_{23}NO_3$ 301.1678, found 301.1681.



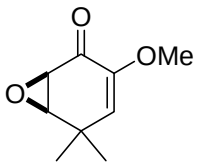
(*E*)-3-(Hex-1-enyl)-2-(pent-4-enyl)isoindolin-1-one (2-68). According to general protocol A, hexyne (420 μL, 3.66 mmol), CH_2Cl_2 (10 mL), zirconocene hydrochloride (944 mg, 3.66 mmol),

Me_3Al (1.0 M in CH_2Cl_2, 3.66 mL, 3.66 mmol) and **2-67** (552 mg, 1.83 mmol) afforded 368 mg (72%) of **2-68** as a colorless oil after purification on SiO_2 (EtOAc:Hex, 3:7): IR (neat) 3076, 2967, 2928, 2860, 1693, 1468, 1404, 972, 749 cm^{-1}; ^1H NMR δ 7.72 (d, 1 H, *J* = 7.5 Hz), 7.44-7.28 (m, 2 H), 7.23 (d, 1 H, *J* = 7.2 Hz), 5.94 (dt, 1 H, *J* = 14.4, 6.6 Hz), 5.80-5.63 (m, 1 H), 5.03-4.82 (m, 3 H), 4.75 (d, 1 H, *J* = 9.0 Hz), 3.83-3.65 (m, 1 H), 3.23-3.07 (m, 1 H), 2.13-1.93 (m, 4 H), 1.75-1.51 (m, 2 H), 1.42-1.19 (m, 4 H), 0.83 (t, 3 H, *J* = 6.9 Hz); ^{13}C NMR δ 167.6, 144.6, 137.5, 137.3, 131.7, 131.0, 127.9, 126.2, 122.9, 122.6, 114.7, 39.4, 31.5, 30.8, 30.7, 27.3, 26.9, 21.8, 13.5; MS (EI) *m/z* (rel intensity) 283 ($[M]^+$, 20), 228 (70), 160 (100), 146 (50), 76 (50); HRMS (EI) *m/z* calcd for $C_{19}H_{25}NO$ 283.1936, found 283.1934.

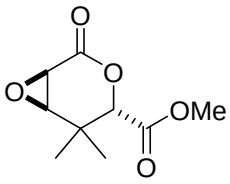


(*Z*)-7,8,9,11a-Tetrahydro-5*H*-azepino[2,1-*a*]isoindol-5-one (2-69). To a solution of **37** (150 mg, 0.529 mmol) in toluene (100 mL) was added $Ti(O^iPr)_4$ (157 μL, 0.529 mmol) and Grubbs 2nd generation catalyst (22.5 mg, 0.0265 mmol) and the red solution was stirred at rt for 12 h and concentrated. The residue was purified by chromatography on SiO_2 (Acetone:CH_2Cl_2, 0.4:9.6) to yield 70.7 mg (67%) of **2-69** as a colorless oil: IR (neat) 3024, 2926, 1680, 1469, 1419, 1298, 938, 709 cm^{-1}; ^1H NMR δ 7.76 (dd, 1 H, *J* = 6.9, 1.2 Hz), 7.58-7.51 (m, 1 H), 7.46 (app t, 2 H, 7.2 Hz), 6.13-6.02 (m, 1 H), 6.02-5.91 (m, 1 H), 4.49 (dd, 1 H, *J* = 11.4, 2.1 Hz), 4.26 (ddd, 1 H, *J* = 13.5, 6.6, 3.0 Hz), 3.22 (ddd, 1 H, *J* = 12.6, 9.6, 2.7 Hz), 2.81 (app ddd, 1 H, *J* = 15.9, 7.8, 2.4 Hz), 2.53-2.26 (m, 2 H), 2.25-2.09 (m, 1 H); ^{13}C NMR δ 167.5, 145.9, 133.0, 132.7, 131.6, 128.8, 128.5, 123.5, 122.4, 60.6, 41.6, 35.2, 28.2; MS (EI) *m/z* (rel intensity) 199 ($[M]^+$, 45), 145 (100), 117 (40), 90 (35); HRMS (EI) *m/z* calcd for $C_{13}H_{13}NO$ 199.0997, found 199.0991.

5.3 SPIROKETALS VIA OXIDATIVE REARRANGEMENT OF ENOL ETHERS

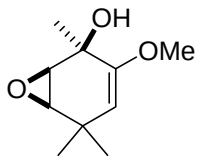


(1*R,6*R**)-3-Methoxy-5,5-dimethyl-7-oxabicyclo[4.1.0]hept-3-en-2-one** (**3-20**). To a 40 °C solution of **3-19** (0.20 g, 1.3 mmol) in THF (30 mL) was added H_2O_2 (10 mL, 30% v/v in H_2O) and K_2CO_3 (5 mL, 0.4 M in H_2O). The reaction mixture was stirred for 6 h, diluted with EtOAc, washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by chromatography on SiO_2 (4:1 hexanes/EtOAc) to afford **3-20** (0.11 g, 67%) as a colorless oil: IR (neat) 2965, 1694, 1627, 1205, 1158, cm^{-1}; ^1H NMR δ 5.23 (d, *J* = 2.5 Hz, 1 H), 3.54 (s, 3 H), 3.50 (d, *J* = 3.8 Hz, 1 H), 3.35 (dd, *J* = 3.8, 2.5 Hz, 1 H), 1.33 (s, 3 H), 1.20 (s, 3 H); ^{13}C NMR δ 189.4, 146.8, 120.8, 61.2, 55.0, 54.8, 34.6, 28.3, 25.9; MS (EI) *m/z* (intensity) 168 ($[M-H_2O]^+$, 57), 153 (55), 125 (100); HRMS (EI) *m/z* calculated for $C_9H_{12}O_3$ [M-H_2O] 168.0786, found 168.0784.

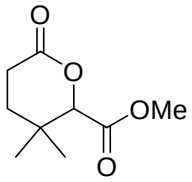


(1*R,3*S**,6*R**)-Methyl-2,2-dimethyl-5-oxo-4,7-dioxabicyclo[4.1.0]heptane-3-carboxylate** (**3-21**). **General Protocol A**. To a solution of **3-20** (35 mg, 0.21 mmol) in dry CH_2Cl_2 (2.0 mL) was added *m*-CPBA (0.15 g, 0.62 mmol, ~70 wt % *m*-CPBA) and Na_2HPO_4 (89 mg, 0.62 mmol) and the reaction mixture was stirred for 12 h, treated with 2-methyl-2-butene (0.10 mL of a 2 M solution in THF), stirred for 2 h, diluted with CH_2Cl_2 and washed with sat. $NaHCO_3$ (5x). The organic layer

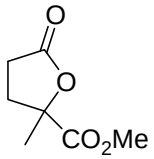
was dried (Na_2SO_4) and concentrated to afford **3-21** a colorless solid (42 mg, 80%, contaminated with 10% 3-chlorobenzoic acid). The material was purified by chromatography on SiO_2 (4:1 hexanes/EtOAc) for analysis: IR (neat) 2966, 1752, 1465, 1250, 1209, 907 cm^{-1}; NMR δ 4.81 (s, 1 H), 3.82 (s, 3 H), 3.64 (d, *J* = 4.0 Hz, 1 H), 3.32 (d, *J* = 3.9 Hz, 1 H), 1.37 (s, 3 H), 1.07 (s, 3 H); ^{13}C NMR δ 167.5, 165.5, 78.6, 61.1, 52.7, 49.8, 34.9, 22.7, 17.8; MS (EI) *m/z* (intensity) 141 ([M-$CO_2Me]^+$, 7), 84 (16); HRMS (EI) *m/z* calculated for $C_7H_9O_3$ [M-CO_2Me] 141.0552, found 141.0550.



(1*R,2*R**,6*R**)-3-Methoxy-2,5,5-trimethyl-7-oxabicyclo[4.1.0]hept-3-en-2-ol** (**3-22**). To a cooled (-78 °C) solution of **3-20** (28 mg, 0.17 mmol) in dry THF (4.0 mL) was added MeLi (0.19 mL, 0.30 mmol, 1.6 M in Et_2O). After 30 min, the reaction mixture was quenched with H_2O (1 mL) and extracted with Et_2O (3 x 5 mL). The combined organic layers were washed with H_2O, brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by chromatography on SiO_2 (3:1 hexanes/EtOAc) to afford **3-22** (28 mg, 91%) as a colorless oil: IR (neat) 3479, 2962, 1667, 1469, 1212, 1162, 1059 cm^{-1}; ^1H NMR δ 4.15 (d, *J* = 2.3 Hz, 1 H), 3.51 (s, 3 H), 3.32 (d, *J* = 4.1 Hz, 1 H), 3.06 (dd, *J* = 4.3, 2.1 Hz, 1 H), 1.42 (s, 3 H), 1.20 (s, 3 H), 1.09 (s, 3 H); ^{13}C NMR δ 152.4, 100.4, 69.2, 61.1, 60.2, 54.5, 33.5, 27.7, 27.1, 25.2; MS (EI) *m/z* (intensity) 184 ($[M]^+$, 17), 169 (44), 137 (13); HRMS (EI) *m/z* calculated for $C_{10}H_{16}O_3$ 184.1099, found 184.1103.

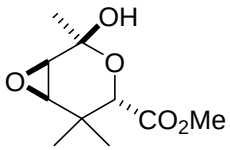


Methyl tetrahydro-3,3-dimethyl-6-oxo-2*H*-pyran-2-carboxylate (**3-23**). According to General Protocol A, a solution of **3-17** (0.14 g, 0.97 mmol), *m*-CPBA (0.67 g, 2.7 mmol, ~70 wt % *m*-CPBA) and Na_2HPO_4 (0.39 g, 2.7 mmol) in CH_2Cl_2 (10 mL) afforded, after 12 h, **3-23** as a light yellow solid (0.13 g, 75%, contaminated with 15% 3-chlorobenzoic acid): IR (neat) 2965, 1751, 1469, 1204, 1159, 1080 cm^{-1}; ^1H NMR δ 4.53 (d, J = 1.4 Hz, 1 H), 3.79 (s, 3 H), 2.67, 2.60 (AB of ABMX, J_{AB} = 18.8, J_{AM} = 7.8 Hz, J_{AX} = 4.3 Hz, 2 H), 1.89-1.79 (m, 1 H), 1.60 (dddd, J = 13.6, 5.7, 4.3, 1.4 Hz, 1 H), 1.20 (s, 3 H), 1.03 (s, 3 H); ^{13}C NMR δ 169.5 (2C), 85.1, 52.3, 31.4, 31.0, 26.8, 25.3, 24.2; MS (EI) *m/z* (intensity) 171 ($[M-CH_3]^+$, 3), 156 (70), 139 (88), 127(100); HRMS (EI) *m/z* calculated for $C_9H_{14}O_4$ 186.0892, found 186.0895.

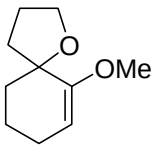


Methyl tetrahydro-2-methyl-5-oxofuran-2-carboxylate (**3-25**). According to General Protocol A, a solution of **3-24** (0.11 g, 0.87 mmol) in CH_2Cl_2 (5.0 mL), *m*-CPBA (0.64 g, 2.6 mmol, ~70 wt % *m*-CPBA) and Na_2HPO_4 (0.37 g, 2.6 mmol) afforded, after 12 h, **3-25** (48 mg, 35%, corrected for 3-chlorobenzoic acid~10%) as a colorless solid: IR (neat) 2992, 2957, 1788, 1743, 1457, 1201, 1140 cm^{-1}; ^1H NMR δ 3.78 (s, 3 H), 2.73-2.48 (m, 3 H), 2.19-2.08 (m, 1 H), 1.65 (s, 3

H); ^{13}C NMR δ 175.8, 172.1, 83.7, 52.9, 32.9, 28.3, 23.7; MS (EI) *m/z* (intensity) 99 ([M-CO_2Me]$^+$,48), 73 (100); HRMS (EI) *m/z* calculated for $C_5H_7O_2$ [M-CO_2Me] 99.0446, found 99.0447.

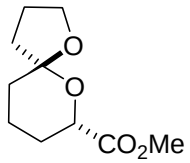


(1*R,3*S**,5*S**,6*R**)-Methyl-5-hydroxy-2,2,5-trimethyl-4,7-dioxabicyclo[4.1.0]heptane-3-car-boxylate** (**3-26**). According to General Protocol A, enol ether **3-22** (24 mg, 0.13 mmol) in CH_2Cl_2 (1.3 mL), Na_2HPO_4 (55 mg, 0.39 mmol) and *m*-CPBA (96 mg of ~70% *m*-CPBA) furnished, after 18 h and purification on SiO_2 (1:1 hexanes/EtOAc), ester **3-26** (5.6 mg, 20%) as a white solid which was a single diastereomer as indicated by ^{1}H NMR : Mp 114.5-116.3 °C (hexanes/EtOAc); IR (KBr) 3466, 2973, 1737, 1214, 1086, 920 cm^{-1}; ^{1}H NMR δ 4.10 (s, 1 H), 3.75 (s, 3 H), 3.52 (s, 1 H), 3.33 (d, 1 H, *J* = 3.8 Hz), 3.10 (d, 1 H, *J* = 4.0 Hz), 1.64 (s, 3 H), 1.22 (s, 3 H), 1.00 (s, 3 H); ^{13}C NMR δ 170.0, 92.4, 71.7, 63.4, 57.7, 51.8, 33.7, 26.5, 22.3, 18.5; MS (EI) *m/z* (intensity) 198 ([M-H_2O]$^+$, 49), 156 (32), 139 (76), 114 (77); HRMS (EI) *m/z* calculated for $C_{10}H_{14}O_4$ [M-H_2O] 198.0892, found 198.0891.

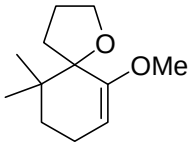


6-Methoxy-1-oxaspiro[4.5]dec-6-ene (3-42). General Protocol B. A solution of ketone **3-41** (155 mg, 1.01 mmol) in THF (3 mL) was added dropwise to a solution of KHMDS (241 mg, 1.21 mmol) in THF (7 mL) at -78 °C. After 10 min, DMF (2.5 mL) was added. After 10 min, dimethylsulfate (254 mg, 2.01 mmol) was added and the reaction mixture was warmed to ambient

temperature over 4 h. Subsequently, sat. aq. $NaHCO_3$ (5 mL) was added and the aqueous layer was extracted with Et_2O (4 x 10 mL). The combined organic layers were washed with H_2O, brine, dried (Na_2SO_4), filtered, concentrated and purified on SiO_2 (85:15 pentane/Et_2O) to furnish enol ether **3-42** (155 mg, 0.923 mmol, 89%) as a volatile, colorless oil: IR (neat) 2948, 2875, 1717, 1601, 1441, 1367, 1224, 1060, 926 cm^{-1}; ^1H NMR δ 4.72 (dd, 1 H, J = 3.9, 3.9 Hz), 3.97-3.80 (m, 2 H), 3.51 (s, 3 H), 2.24-1.51 (m, 10 H); ^{13}C NMR δ 156.9, 96.4, 81.2, 68.6, 54.2, 37.2, 35.1, 26.9, 23.9, 20.5; MS (EI) *m/z* (intensity) 168 ($[M]^+$, 43), 140 (40), 137 (37), 123 (52); HRMS (EI) *m/z* calculated for $C_{10}H_{16}O_2$ 168.1150, found 168.1151.



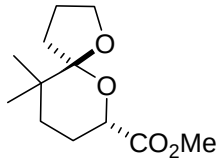
Methyl 1,6-dioxaspiro[4.5]decane-7-carboxylate (3-43). According to General Protocol A, enol ether **3-42** (100 mg, 0.595 mmol), Na_2HPO_4 (1.79 mmol, 246 mg) and *m*-CPBA (1.79 mmol, 411 mg of ~70% *m*-CPBA) in CH_2Cl_2 (6 mL) furnished, after 18 h and purification on SiO_2 (4:1 pentane/Et_2O), spiroketal ester **3-43** (62 mg, 0.31 mmol, 52%) as a colorless oil and a single diastereomer as indicated by ^1H NMR: IR (neat) 2951, 2882, 1760, 1738, 1456, 1439, 1201, 1011, 857 cm^{-1}; ^1H NMR (CD_2Cl_2) δ 4.38 (dd, 1 H, J = 12.1, 2.4 Hz), 3.89-3.83 (m, 2 H), 3.68 (s, 3 H), 2.08-1.96 (m, 2 H), 1.92-1.60 (m, 8 H); ^{13}C NMR (CD_2Cl_2) δ 172.8, 106.9, 70.6, 67.7, 52.0, 38.1, 33.0, 28.5, 24.1, 20.5; MS (EI) *m/z* (rel intensity) 200 ($[M]^+$, 53), 184 (6), 172 (10), 141 (100), 114 (14); HRMS (EI) *m/z* calculated for $C_{10}H_{16}O_4$ 200.1049, found 200.1053.



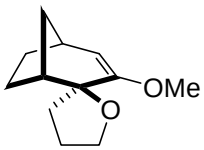
6-Methoxy-10,10-dimethyl-1-oxaspiro[4.5]dec-6-ene (3-36). **General Protocol C.** A solution of 2,3-dihydrofuran in THF (90 mL) was treated with *t*-BuLi (10.7 mmol, 6.3 mL of a 1.7 M solution in pentane) at -78 °C. After 30 min, the reaction mixture was warmed to 0 °C for 30 min, recooled to -78 °C and treated with 2,2-dimethyl cyclopentanone. The reaction mixture was warmed to ambient temperature and quenched after 6 h with aq. $NaHCO_3$. The aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined organic layers washed with H_2O, brine, dried (Na_2SO_4), filtered, concentrated and the crude tertiary alcohol was used directly in the next step. A solution of the crude tertiary alcohol in CH_2Cl_2 (100 mL) was treated with Dowex-50X resin (4.71 g, 0.528 g/mmol) and stirred at ambient temperature for 24 h. The mixture was filtered, concentrated and the residue purified by chromatography on SiO_2 (4:1 hexanes/EtOAc) to furnish the α-spiroether ketone (1.32 g, 81% over two steps) as a colorless oil: IR (neat) 2965, 2872, 1717, 1462, 1056 cm^{-1}; ^1H NMR δ 3.88-3.79 (m, 1 H), 3.73-3.66 (m, 1 H), 2.82-2.72 (m, 1 H), 2.29-2.19 (m, 2 H), 1.93-1.66 (m, 6 H), 1.43-1.35 (m, 1 H), 0.96 (s, 3 H), 0.83 (s, 3 H); ^{13}C NMR δ 212.1, 92.8, 68.7, 40.8, 37.3, 36.0, 26.3, 25.9, 23.1, 22.3, 21.9; MS (EI) *m/z* (intensity) 182 ($[M]^+$,30), 154 (8), 111 (63); HRMS (EI) *m/z* calculated for $C_{11}H_{18}O_2$ 182.1307, found 182.1299.

According to General Protocol B, the α-spiroether ketone (180 mg, 0.988 mmol), KHMDS (236 mg, 1.19 mmol), and Me_2SO_4 (249 mg, 1.98 mmol) furnished **3-44** (163 mg , 84%) as a colorless oil: IR (neat) 2926, 1662, 1464, 1215, 1122, 1054 cm^{-1}; ^1H NMR δ 4.56 (dd, 1 H, J = 3.8 Hz), 3.99-3.92 (m, 1 H), 3.78-3.71 (m, 1 H), 3.47 (s, 3 H), 2.08-1.63 (m, 10 H), 1.29 (ddd, 1 H, J = 12.9, 5.4, 5.4 Hz), 0.94 (s, 3 H), 0.86 (s, 3 H); ^{13}C NMR δ 157.6, 93.6, 86.5, 69.8, 54.3, 37.6, 33.6,

30.0, 28.1, 23.1, 22.6, 20.6; MS (EI) *m/z* (intensity) 196 ([M]$^+$, 14), 182 (7), 164 (27), 149 (43), 140 (100); HRMS *m/z* calculated for $C_{12}H_{20}O_2$ 196.1463, found 196.1458.

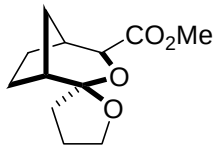


(5*S,7*S**)-Methyl 10,10-dimethyl-1,6-dioxaspiro[4.5]decane-7-carboxylate (3-45)**. According to General Protocol A, enol ether **3-44** (57 mg, 0.29 mmol), *m*-CPBA (200 mg of ~70% *m*-CPBA, 0.871 mmol) and Na_2HPO_4 (123 mg, 0.871 mmol) furnished, after 18 h and purification by chromatography on SiO_2 (6:1 pentanes/Et_2O), spiroketal **3-45** (32 mg, 48%) as a 2:1 mixture of diastereomers as indicated by NMR analysis: Major diastereomer: IR (neat) 2954, 2879, 1760, 1740, 1439, 1205, 1064 cm^{-1}; ^{1}H NMR δ 4.40 (dd, 1 H, *J* = 11.1, 3.6 Hz), 3.94-3.86 (m, 2 H), 3.73 (s, 3 H), 2.08-2.00 (m, 1 H), 1.96-1.62 (m, 6 H), 1.38-1.33 (m, 1 H), 1.07 (s, 3 H), 0.90 (s, 3 H); ^{13}C NMR δ 172.9, 111.6, 69.3, 67.9, 51.9, 34.7, 34.1, 32.1, 25.4, 25.1, 23.9, 23.3; MS (EI) *m/z* (intensity) 228 ([M]$^+$, 10), 213 (8), 198 (11), 169 (57), 142 (57); HRMS (EI) *m/z* calculated for $C_{10}H_{17}O_2$ [M-CO_2Me] 169.1229, found 169.1229. Characteristic data for minor diastereomer: ^{1}H NMR δ 4.17 (dd, 1 H, *J* = 5.1, 2.1 Hz), 3.74 (s, 3 H); ^{13}C NMR δ 173.4, 112.1, 70.0, 68.7, 51.7, 35.1, 32.2, 31.0, 25.0, 24.8, 23.4, 21.4.

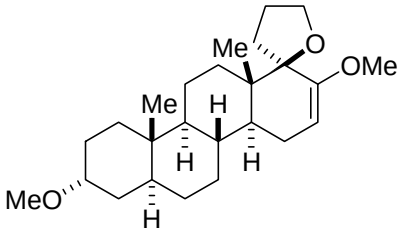


(1*S)-3-Methoxy-4',5'-dihydro-3'H-spiro[bicyclo[3.2.1]oct[3]ene-2,2'-furan] (3-46).** According to General Protocol B, bicyclic α-spiroether ketone (430 mg, 2.39 mmol),[147] KHMDS

(571 mg, 2.86 mmol) and Me_2SO_4 (451 mg, 3.58 mmol) furnished, after chromatography on SiO_2 (3:1 hexanes/EtOAc), enol ether **3-46** (308 mg, 67%) as a colorless oil: IR (neat) 2941, 2864, 1647, 1370, 1214, 1053 cm^{-1}; ^1H NMR δ 4.80 (d, 1 H, *J* = 7.1 Hz), 3.92 (ddd, 1 H, *J* = 7.8, 7.8, 4.8 Hz), 3.72 (ddd, 1 H, *J* = 7.8, 7.8, 6.6 Hz), 3.41 (s, 3 H), 2.52-2.41 (m, 1 H), 2.22-1.34 (m, 10 H), 1.26-1.19 (m, 1 H); ^{13}C NMR δ 155.8, 101.9, 86.7, 68.3, 54.1, 44.9, 34.5, 34.0, 32.1, 31.8, 27.4, 23.7; MS (EI) *m/z* (intensity) 194 ($[M]^+$, 24), 162 (56), 153 (36), 135 (17); HRMS (EI) *m/z* calculated for $C_{12}H_{18}O_2$ 194.1307, found 194.1311.



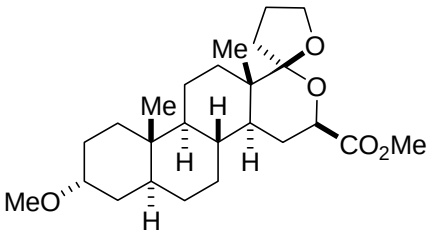
(1S*,4S*)-Methyldihydro-3'H-3-oxaspiro[bicyclo[3.2.1]octane-2,2'-furan]-4-carboxylate (3-47). According to General Protocol A, **3-46** (303 mg, 1.56 mmol), *m*-CPBA (1.08 g of ~70% *m*-CPBA, 4.68 mmol), and Na_2HPO_4 (664 mg, 4.68 mmol) furnished, after 18 h and purification by chromatography on SiO_2 (3:1 hexanes/EtOAc), spiroketal **3-47** (187 mg, 53%) as a single diastereomer as indicated by NMR analysis: IR (neat) 2950, 2872, 1759, 1733, 1201, 1043 cm^{-1}; ^1H NMR δ 4.37 (s, 1 H), 3.93-3.85 (m, 2 H), 3.72 (s, 3 H), 2.41 (app t, 1 H, *J* = 5.1 Hz), 2.27 (app d, 1 H, *J* = 11.1 Hz), 2.16-1.99 (m, 3 H), 1.88-1.77 (m, 1 H), 1.73-1.62 (m, 3 H), 1.59-1.42 (m, 3 H); ^{13}C NMR δ 171.9, 110.1, 75.6, 67.5, 51.8, 42.8, 37.8, 36.3, 33.1, 26.3, 24.1, 23.4; MS (EI) *m/z* (intensity) 226 ($[M]^+$, 28), 138 (21), 108 (37); HRMS (EI) *m/z* calculated for $C_{12}H_{18}O_4$ 226.1205, found 226.1203.



(1*S*,4a*S*,4b*R*,6a*S*,8*R*,10a*S*,10b*S*,12a*S*)-2,8-Dimethoxy-10a,12a-dimethyl-4a,4b,4',5,5'-6,6a,7,8,9,10,10a,10b,11,12,12a-hexa-decahydro-3'*H*,4*H*-spiro-[chrysene-1,2'-furan] (3-48). According to General Protocol C, androsterone (1.0 g, 3.44 mmol), 2,3-dihydrofuran (507 mg, 7.23 mmol), *t*-BuLi (4.5 mL of a 1.7 M solution in pentanes, 7.57 mmol), and Dowex 50X (1.82 g, 0.528 g/mmol) furnished, after chromatography on SiO_2 (6:1 hexanes/EtOAc), the α-spiroether ketone (754 mg, 61%) as a white solid and as a single diastereomer as determined by NMR analysis: Mp 196.8-198.5 °C (hexanes/EtOAc); IR (KBr) 3399, 2930, 2865, 1716, 1452, 1052, 732 cm^{-1}; ^1H NMR δ 3.99 (br s, 1 H), 3.72 (ddd, 1 H, *J* = 7.7, 7.0, 7.0 Hz), 3.57 (ddd, 1 H, *J* = 7.9, 6.8, 6.8 Hz), 2.86 (ddd, 1 H, *J* = 13.5, 13.5, 7.2 Hz), 2.38 (ddd, 1 H, *J* = 6.5, 6.1, 6.1 Hz), 2.17 (dd, 1 H, *J* = 5.6, 2.8 Hz), 2.04-1.99 (m, 1 H), 1.83-1.69 (m, 5 H), 1.63-1.08 (m, 15 H), 0.94-0.83 (m, 2 H), 0.69 (s, 3 H), 0.61 (s, 3 H); ^{13}C NMR δ 211.3, 92.7, 68.5, 66.3, 53.3, 44.2, 43.3, 38.6, 37.0, 36.2, 36.0, 32.0, 31.3, 31.2 (2 C), 29.1, 28.7, 26.3, 25.7, 23.1, 20.1, 14.7, 11.0; MS (ESI) *m/z* (intensity) 383 ($[M+Na]^+$, 38), 361 (86), 272 (15); HRMS (ESI) *m/z* calculated for $C_{23}H_{36}O_3Na$ [M+Na] 383.2562, found 383.2545.

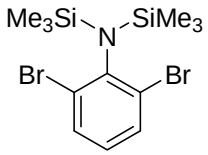
According to General Protocol B, the α-spiroether ketone (754 mg, 2.09 mmol), KHMDS (918 mg, 4.60 mmol) and Me_2SO_4 (1.05 g, 8.37 mmol) furnished, after chromatography on SiO_2 (6:1 hexanes/EtOAc), enol ether **3-48** (443 mg, 59%) as a white solid: Mp 157.1-158.5 °C (hexanes/EtOAc); IR (KBr) 2934, 1671, 1447, 1362, 1212, 1092 cm^{-1}; ^1H NMR δ 4.60 (dd, 1 H, *J* = 5.0, 1.0 Hz), 3.96 (ddd, 1 H, *J* = 7.7, 7.7, 2.6 Hz), 3.64-3.57 (m, 1 H), 3.46 (s, 3 H), 3.41 (br s, 1 H),

3.27 (s, 3 H), 2.31-2.18 (m, 1 H), 2.13-1.93 (m, 2 H), 1.93-1.70 (m, 4 H), 1.66-1.32 (m, 10 H), 1.26-1.03 (m, 5 H), 0.97-0.81 (m, 2 H), 0.77 (s, 3 H), 0.74 (s, 3 H); ^{13}C NMR δ 156.4, 94.1, 87.5, 75.4, 69.5, 55.5, 54.1, 52.6, 41.3, 40.8, 38.7, 36.8, 35.8, 32.6, 32.2, 30.7, 30.6, 28.6, 28.3, 27.2, 25.5, 25.0, 20.0, 15.1, 11.2; MS (EI) *m/z* (intensity) 389 ([M+H]$^+$, 12), 388 (50), 374 (11), 357 (10), 154 (66), 141 (100); HRMS (EI) *m/z* calculated for $C_{24}H_{37}O_2$ [M-OCH_3] 357.2794, found 357.2797.

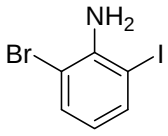


(1'*R*,3'*S*,4a'*S*,4b'*R*,6a'*S*,8'*R*,10a'*S*,10b'*S*,12a'*S*)-Methyl 8'-methoxy-10a',12a'-dimethyl octa-deca-hydro-3*H*-spiro-[furan-2,1'-naphtho-[2,1-*f*]-isochromene]-3'-carboxylate (3-49). According to General Protocol A, enol ether **3-48** (443 mg, 1.24 mmol), *m*-CPBA (855 mg of ~70% *m*-CPBA, 3.72 mmol), Na_2HPO_4 (528 mg, 3.72 mmol) furnished, after 18 h and chromatography on SiO_2 (3:1 hexanes/EtOAc), spiroketal **3-49** (396 mg, 76%) as a colorless oil and as a single diastereomer by NMR: IR (neat) 2929, 1755, 1446, 1090, 732 cm^{-1}; ^{1}H NMR δ 4.38 (dd, 1 H, *J* = 12.4, 3.2 Hz), 3.92-3.75 (m, 2 H), 3.70 (s, 3 H), 3.41-3.40 (m, 1 H), 3.27 (s, 3 H), 2.04-1.98 (m, 1 H), 1.88-1.74 (m, 7 H), 1.68-1.09 (m, 14 H), 0.98 (s, 3 H), 0.91-0.81 (m, 2 H), 0.74 (s, 3 H); ^{13}C NMR δ 172.9, 111.7, 75.4, 70.0, 67.7, 55.6, 53.1, 51.8, 42.9, 38.9, 38.8, 35.9, 35.0, 32.6, 32.4, 32.2, 31.5, 30.5, 28.5, 27.4, 25.1, 23.8, 19.7, 15.8, 11.3; MS (EI) *m/z* (intensity) 421 ([M+H]$^+$, 27), 361 (51), 334 (80), 248 (100), 216 (95), 190 (87); HRMS (EI) *m/z* calculated for $C_{25}H_{41}O_5$ [M+H] 421.2954, found 421.2962.

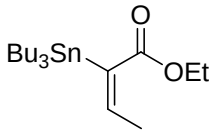
5.4 ENANTIOSELECTIVE TOTAL SYNTHESIS OF DIAZONAMIDE A



2,6-Dibromo-*N*,*N*-bis(trimethylsilyl)benzenamine (4-53). A solution of 2,6-dibromoaniline **4-52** (15.7 g, 62.6 mmol) in THF (400 mL) was treated with LDA (34.4 mL of a 2M solution, 68.8 mmol) at -78 °C. After 5 min, TMSCl (9.53 mL, 75.1 mmol) was added. After 15 min, LDA (34.4 mL of a 2M solution, 68.8 mmol) was added and the reaction mixture was held at -78 °C for 20 min. TMSCl (9.53 mL, 75.1 mmol) was added and the reaction mixture was warmed to room temperature and quenched with aq. $NaHCO_3$ (~100 mL). The aqueous layer was washed with Et_2O (3 x 100 mL) and the combined organic layers were washed with H_2O, brine, dried ($MgSO_4$), filtered, concentrated and purified by chromatography on SiO_2 (hexanes) to furnish aniline **4-53** (24.6 g, 100%) as a colorless oil: IR (neat) 2953, 2898, 1422, 1251, 911 cm^{-1}; ^1H NMR δ 7.52 (d, 2 H, J = 8.0 Hz), 6.75 (t, 1 H, J = 8.0 Hz), 0.18 (s, 18 H); ^{13}C NMR δ 132.2 (2C), 127.8, 125.6, 2.6 (6C); MS (EI) *m/z* (rel intensity) 380 ($[M-CH_3]^+$, 100, 301 (15); HRMS (EI) *m/z* calcd for $C_{11}H_{18}BrNSi_2$ [M-CH_3] 377.9345, found 377.9334.

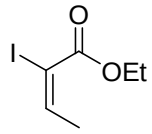


2-Bromo-6-iodobenzenamine (4-51). A solution of aniline **4-53** (24.6 g, 62.6 mmol) in THF (400 mL) was treated with s-BuLi (93.9 mL of a 1.4 M solution, 131.4 mmol) at -78 °C. After 15 min, the reaction mixture was warmed to 0 °C, treated with 3M HCl (aq, ~200 mL) and vigorously stirred for 1 h. The aqueous layer was extracted with Et_2O (3 x 100 mL) and the combined organic layers were washed with H_2O, brine, dried (Na_2SO_4), filtered and concentrated to yield crude aniline **4-55** which was immediately carried on to the next step. A solution of **4-55** (15.3 g, 62.6 mmol, based on 100% in previous reaction) in CH_2Cl_2 (340 mL) was cooled to -78 °C and treated with ICl (68.9 mL of a 1M solution, 68.9 mmol) over 30 minutes. The reaction mixture was warmed to 0 °C and quenched with $Na_2S_2O_3$ (aq, ~150 mL). The organic layer was washed with H_2O, brine, dried (Na_2SO_3), filtered, concentrated, and recrystallized from hexanes (3x) to furnish aniline **4-51** (16.8 g, 90% over two steps) as light brown needles: IR (neat) 3416, 3317, 1607, 1448, 1293, 1037, 754 cm^{-1}; ^{1} H NMR δ 7.59 (dd, 1 H, *J* = 8.1, 1.5 Hz), 7.40 (dd, 1 H, *J* = 7.8, 1.2 Hz), 6.33 (t, 1 H, *J* = 7.8 Hz), 4.59 (br s, 1 H); ^{13}C NMR δ 144.1, 138.2, 132.8, 120.4, 107.3, 83.0; MS (ESI) *m/z* (rel intensity) 299 ($[M+H]^+$, 15), 279 (31); HRMS (ESI) *m/z* calcd for C_6H_6BrIN [M+H] 297.8728, found 297.8715.



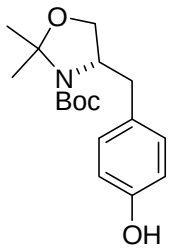
(*E*)-Ethyl 2-(tributylstannyl)but-2-enoate (4-57). A solution of ethyl propiolate **4-56** (4.44g, 39.6 mmol) in THF (200 mL, degassed) and $Pd(PPh_3)_4$ (915 mg, 0.792 mmol) at room temperature was treated with a solution of Bu_3SnH (11.7 mL, 43.55 mmol) in THF (40 mL, degassed) over 1 h. After 1.5 h, TLC analysis indicated consumption of the starting material, and the

solvent was evaporated and the residue dissolved in hexanes (~200 mL). After 1 h, the precipitates were filtered off and the filtrate concentrated. A small portion of this material could be purified by chromatography on SiO_2 (hexanes→9:1 hexanes/EtOAc) to provide stannane **4-57** (5:1 ratio of α:β regioisomers by ^{1}H NMR) as a colorless oil, which was carried on to the next step without further purification: IR 2957, 2926, 1708, 1461, 1180, 1036 cm^{-1}; ^{1}H NMR δ 6.16 (q, 1 H, *J* = 6.6 Hz), 4.14 (q, 2 H, *J* = 7.2 Hz), 2.00 (d, 3 H, *J* = 6.6 Hz), 1.53-1.42 (m, 6 H), 1.35-1.21 (m, 12 H), 0.98-0.82 (m, 12 H); ^{13}C NMR δ 171.1, 147.9, 128.1, 59.9, 28.9, 27.2, 18.1, 14.3, 13.6, 10.2; HRMS (ESI) *m/z* calcd for $C_{18}H_{36}O_2SnNa$ [M+Na] 427.1635, found 427.1637. Characteristic data for β isomer: ^{1}H NMR δ 5.95 (q, 1 H, *J* = 1.8 Hz), 2.38 (d, 1 H, *J* = 1.8 Hz); ^{13}C NMR δ 136.9, 59.4, 9.4.



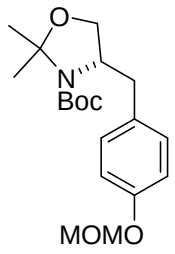
(***E*)-Ethyl 2-iodobut-2-enoate (4-58)**. The crude stannane residue was dissolved in THF (~250 mL) and treated with a solution of I_2 (13.7 g, 51.5 mmol) in THF (250 mL). After 30 min, TLC analysis indicated consumption of the stannane and the solvent was removed. The residue was dissolved in Et_2O (200 mL) and stirred with semisaturated KF for 1 h. Following, the solids were filtered off, and the aqueous layer extracted with Et_2O (3 x 100 mL). The combined organic layers were washed with H_2O, brine, dried ($MgSO_4$), filtered, concentrated, and the residue purified by chromatography on SiO_2 (95:5 hexanes/Et_2O) to provide iodide **4-58** (6.46 g, 68%) as a light yellow oil: IR 2981, 1713, 1368, 1220, 1027 cm^{-1}; ^{1}H NMR δ 6.98 (q, 1 H, *J* = 9.0 Hz), 4.25 (q, 2 H, *J* = 9.0 Hz), 1.99 (d, 3 H, *J* = 8.1 Hz), 1.32 (t, 3 H, *J* = 6.6 Hz); ^{13}C NMR δ 163.8, 150.8, 85.5, 62.1,

19.3, 14.1; MS (EI) *m/z* (rel intensity) 240 ($[M+H]^+$, 100), 212 (82), 195 (42); HRMS (EI) *m/z* calcd for $C_6H_9O_2I$ 239.9647, found 239.9638.



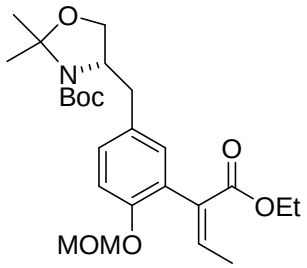
(*S*)-*tert*-Butyl 4-(4-hydroxybenzyl)-2,2-dimethyloxazolidine-3-carboxylate (4-61).[148] A suspension of salt **4-59** (10.0 g, 43.2 mmol) and $NaHCO_3$ (7.25 g, 86.0 mmol) in THF/MeOH (200 mL/60 mL) was treated with Boc_2O (9.40 g, 43.2 mmol) at room temperature. After 24 h, the reaction mixture was concentrated and the residue dissolved in CH_2Cl_2 (~150 mL) and washed with H_2O, dried ($MgSO_4$), filtered, and concentrated to give crude **4-60** which was used without further purification. This crude material was dissolved in THF (200 mL) and treated with $LiBH_4$ (86.5 mL of a 2 M solution, 173 mmol) at 0 °C while vigorously stirring. After 6 h, 3M HCl was added dropwise and the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with H_2O, brine, dried ($MgSO_4$), filtered and concentrated to furnish the crude alcohol which was used without further purification. The crude alcohol was dissolved in dimethoxypropane/acetone (1:1, 160 mL) and treated with *p*-TsOH (821 mg, 4.32 mmol) at room temperature. After 4 h, the reaction mixture was poured into H_2O, and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, concentrated and the solid recrystallized from hexanes (2x) to furnish phenol **4-61** (9.37 g, 70% over three steps) as a white powder: mp 104-106 °C (hexanes), lit. 107 °C; ^{1}H NMR

(CD_3CN, 333 K) δ 7.05 (d, 2 H, *J* = 8.4 Hz), 6.74 (d, 2 H, *J* = 8.4 Hz), 6.51 (s, 1 H), 4.02-3.92 (m, 1 H), 3.81 (dd, 1 H, *J* = 9.0, 6.0 Hz), 3.71 (dd, 1 H, *J* = 8.7, 1.5 Hz), 2.99 (dd, 1 H, *J* = 13.2, 3.6 Hz), 2.62 (dd, 1 H, *J* = 13.2, 9.6 Hz), 1.49 (s, 12 H), 1.44 (s, 3 H); $[\alpha]_D^{23}$: -30.1 (*c* 1.0, EtOH), lit. -32.6 (*c* 0.98, EtOH).



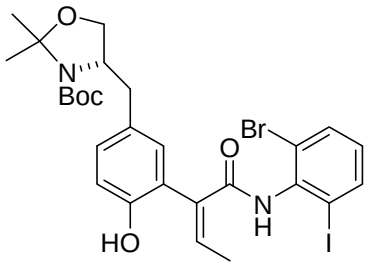
(*S*)-*tert*-Butyl 4-(4-(methoxymethoxy)benzyl)-2,2-dimethyloxazolidine-3-carboxylate (**4-62**). A suspension of NaH (568 mg of 60% NaH, 14.2 mmol) was degreased with hexanes and suspended in THF (~30 mL). A solution of phenol **4-61** (3.96 g, 12.9 mmol) in THF (~30 mL + 10 mL rinse) was added via cannula to the NaH at room temperature. After 30 min, the white solution was treated with TBAI (476 mg, 1.29 mmol) and MOMCl (2.55 mL, 33.5 mmol) was then added dropwise at 0 °C. After 12 h, H_2O was added to the reaction mixture and the aqueous layer was extracted with Et_2O (3 x 25 mL). The combined organic layers were washed with H_2O, brine, dried (Na_2SO_4), filtered, concentrated and purified by chromatography on SiO_2 (5:1 hexanes/EtOAc) to furnish MOM-ether **4-62** (4.12 g, 91%) as a colorless oil: IR 2978, 2934, 1698, 1388, 1078, 857 cm^{-1}; ^1H NMR (CD_3CN, 353 K) δ 7.15 (d, 2 H, *J* = 8.7 Hz), 6.97 (d, 2 H, *J* = 8.4 Hz), 5.14 (s, 2 H), 4.06-3.98 (m, 1 H), 3.83 (dd, 1 H, J = 9.0, 5.7 Hz), 3.73 (dd, 1 H, *J* = 9.0, 1.8 Hz), 3.43 (s, 3 H), 3.03 (dd, 1 H, *J* = 13.2, 3.6 Hz), 2.68 (dd, 1 H, J = 13.2, 9.6 Hz), 1.50 (s, 12 H), 1.45 (s, 3 H); ^{13}C NMR (CD_3CN, 353 K) δ 157.4, 153.2, 133.6, 131.7 (2 C), 117.9 (2 C), 96.0, 94.9, 80.7, 67.4, 60.3, 56.5,

39.7, 29.1 (3 C), 27.7, 24.6; MS (ESI) *m/z* (rel intensity) 375 ([M+Na]$^+$, 6), 322 (47), 224 (42); HRMS (ESI) *m/z* calcd for $C_{19}H_{29}NO_5Na$ [M+Na] 374.1943, found 374.1956; $[\alpha]_D^{23}$ -19.2 (*c* 1.0, CH_2Cl_2).



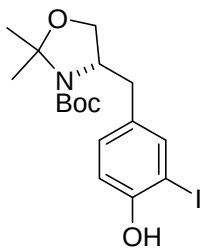
(*S*)-*tert*-Butyl 4-(3-((Z)-1-(ethoxycarbonyl)prop-1-enyl)-4-(methoxymethoxy)benzyl)-2,2-dimethyloxazolidine-3-carboxylate (4-63). A solution of MOM-ether **4-62** (1.30 g, 3.71 mmol) and distilled TMEDA (600 μL, 3.98 mmol) in THF (12 mL) were treated with *n*-BuLi (3.06 mL of a 1.3 M solution, 3.98 mmol) at -78 °C. The yellow reaction mixture was warmed to room temperature for 45 min and recooled to 0 °C, and a solution of freshly fused $ZnCl_2$ (560 mg, 4.11 mmol) in THF (~3 mL) was added via cannula. After 15 min at 0 °C, a solution of vinyl iodide **4-58** (636 mg, 2.65 mmol) and $Pd(PPh_3)_4$ (153 mg, 0.132 mmol) in THF (9 mL) was added via cannula and the reaction mixture was heated at 60 °C for 14 h. The cooled reaction mixture was treated with aq. $NaHCO_3$ and the aqueous layer extracted with Et_2O (4 x 5 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, concentrated and the residue purified by chromatography on SiO_2 (3:1 hexanes/EtOAc) to furnish ester **4-63** (836 mg, 76% as a yellow oil: IR 2979, 2936, 1720, 1698, 1389, 1210, 1055 cm^{-1}; ^{1}H NMR (CD_3CN, 333 K) δ 7.12 (dd, 1 H, *J* = 9.0, 2.1 Hz), 7.07 (d, 1 H, *J* = 2.1 Hz), 7.00 (d, 1 H, *J* = 8.3 Hz), 6.24 (q, 1 H, *J* = 7.2 Hz), 5.07 (s, 2 H), 4.20 (q, 2 H, *J* = 6.9 Hz), 4.07-3.98 (m, 1 H), 3.87 (dd, 1 H, *J* = 9.0, 6.0 Hz), 3.76 (dd, 1 H, *J* =

9.0, 1.8 Hz), 3.40 (s, 3 H), 3.01 (dd, 1 H, *J* = 13.2, 3.3 Hz), 2.73 (dd, 1 H, *J* = 13.2, 9.3 Hz), 2.05 (d, 3 H, *J* = 7.2 Hz), 1.50 (s, 9 H), 1.45 (s, 6 H), 1.23 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR (CD_3CN, 333 K) δ 169.1, 155.0, 153.7, 138.6, 134.9, 134.0, 133.0, 131.8, 131.6, 116.5, 96.9, 95.4, 81.2, 67.9, 61.8, 60.6, 57.3, 29.6, 28.1 (3 C), 16.6, 15.4; MS (EI) *m/z* (rel intensity) 463 ($[M]^+$, 8), 265 (13), 200 (46); HRMS (ESI) *m/z* calcd for $C_{25}H_{37}NO_7Na$ [M + Na] 486.2468, found 486.2454; $[\alpha]_D^{23}$ -19.2 (*c* 1.0, CH_2Cl_2).



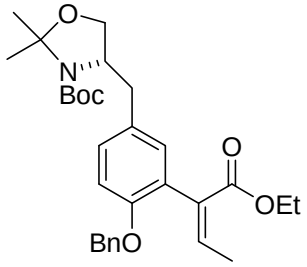
(*S,Z*)-*tert*-Butyl-4-(3-(1-(2-bromo-6-iodophenylamino)-1-oxobut-2-en-2-yl)-4-hydroxy benzyl)-2,2-dimethyloxazolidine-3-carboxylate (4-64). A solution of $AlMe_3$ (297mg, 0.998 mmol) in CH_2Cl_2 (1 mL) was treated with a solution of aniline **4-51** (297 mg, 0.998 mmol) in CH_2Cl_2 (1 mL) at 0° C. After 15 min, a white precipitate had formed. The reaction mixture was treated with a solution of ester **4-63** (154 mg, 0.333 mmol) in CH_2Cl_2 (2 mL) and warmed to ambient temperature. After 2 h, aq. Rochelle's salt was added and the aqueous layer extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, concentrated and the residue purified by chromatography on SiO_2 (5:1 hex/EtOAc→3:1 hex/EtOAc) to provide anilide **4-64** (83 mg, 35%) as a colorless film which demonstrated hindered rotation by ^{1}H NMR, even at elevated temperatures: IR 3289, 2977, 1687, 1483, 1390, 1255 cm^{-1}; ^{1}H NMR (CD_3CN, 353 K, reported as seen) δ 7.88 (dd, 1 H, *J* = 8.7, 1.8 Hz), 7.66 (dd, 1 H, *J* = 8.4, 1.5 Hz),

7.60-7.30 (br s, 1 H), 7.17-7.04 (m, 3 H), 6.94-6.86 (m, 2 H), 4.19-4.04 (br s, 1 H), 3.91-3.75 (m, 2 H), 3.01 (dd, 1 H, J = 12.6, 4.8 Hz), 2.77 (dd, 1 H, J = 15.0, 10.2 Hz), 1.72 (d, 3 H, J = 6.6 Hz), 1.50-1.38 (m, 15 H); ^{13}C NMR (CD_3CN, 353 K, reported as seen) δ 167.5, 154.7, 153.2, 140.3, 139.9, 134.4, 133.6, 132.2, 131.7, 131.6, 124.5, 123.0, 117.7, 102.0, 94.9, 80.7, 67.8, 60.2, 39.7, 29.1 (3 C), 28.0, 24.8, 15.7; MS (ESI) *m/z* (rel intensity) 693 ([M+Na]$^+$, 100), 592 (44); HRMS (ESI) *m/z* calcd for $C_{27}H_{32}BrIN_2O_5Na$ [M+Na] 693.0437, found 693.0423; $[\alpha]_D^{23}$ -8.7 (*c* 1.0, CH_2Cl_2).



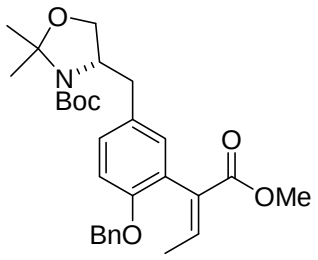
(*S*)-*tert*-Butyl 4-(4-hydroxy-3-iodobenzyl)-2,2-dimethyloxazolidine-3-carboxylate (4-67). A solution of iodotyrosine (**4-65**, 49.2 mmol) in MeOH (350 mL) was treated with $SOCl_2$ (35.9 mL, 492 mmol) over 30 min at 0 °C and then heated at 70 °C for 2 h. The volume of the reaction was reduced to about one-third in vacuo and the remaining solution poured into anhydrous Et_2O (500 mL). The resulting white precipitate was filtered off, dried in vacuo, and used directly in the next step. A suspension of this white precipitate in THF/MeOH (300/120 mL) was treated with $NaHCO_3$ (8.26 g, 98.3 mmol) and Boc_2O (10.7 g, 49.2 mmol) at ambient temperature. After 24 h, the reaction mixture was concentrated to about one-third of its volume and partitioned between CH_2Cl_2 and H_2O (200 mL/200 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL) and the combined organic layers washed with brine, dried (Na_2SO_4), filtered, and concentrated to provide ester **4-66** as a colorless oil that was used directly in the next step. A solution of **4-66** in THF (550 mL) was

treated dropwise with $LiBH_4$ (96.5 mL of a 2 M solution, 193 mmol) at 0 °C. The mixture was vigorously stirred and warmed to ambient temperature. After 4 h, aq. HCl was added until all additional $LiBH_4$ had been quenched. The aqueous layer was extracted with EtOAc (3 x 100 mL) and the combined organic layers washed with brine, dried (Na_2SO_4), filtered, and concentrated to provide the intermediate reduced ester as a colorless oil which was used directly without further purification. A solution of alcohol in acetone/2,2-dimethoxypropane (100 mL/100 mL) was treated with TsOH (918 mg, 4.82 mmol) at ambient temperature. After 1 h, aq. $NaHCO_3$ was added and the aqueous layer was extracted with EtOAc (4 x 100 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, concentrated, and the residue purified by chromatography on SiO_2 (3:1 hexanes/EtOAc) to provide phenol **4-67** (19.6 g, 93% over four steps) as a colorless oil: IR 3307, 2979, 2935, 1663, 1409, 1253, 1097 cm^{-1}; ^1H NMR (CD_3CN, 353 K) δ 7.57 (d, 1 H, *J* = 2.1 Hz), 7.08 (dd, 1 H, *J* = 8.1, 2.1 Hz), 7.03 (br s, 1 H), 6.84 (d, 1 H, *J* = 8.1 Hz), 4.03-3.94 (m, 1 H), 3.85 (dd, 1 H, *J* = 8.4, 6.0 Hz), 3.72 (dd, 1 H, *J* = 9.0, 1.5 Hz), 2.92 (dd, 1 H, *J* = 13.5, 3.6 Hz), 2.67 (dd, 1 H, *J* = 13.2, 9.0 Hz), 1.49 (s, 9 H), 1.47 (s, 3 H), 1.44 (s, 3 H); ^{13}C NMR (CD_3CN, 353 K) δ 155.9, 153.2, 141.1, 133.9, 132.1, 116.3, 94.9, 84.8, 80.7, 67.4, 60.0, 38.8, 29.0 (3 C), 27.6, 24.4; MS (EI) *m/z* (rel intensity) 433 ($[M]^+$, 19), 360 (17), 233 (53); HRMS (EI) *m/z* calcd for $C_{17}H_{24}INO_4$ 433.0750, found 433.0746; $[\alpha]_D^{23}$ -21.4 (*c* 1.0, CH_2Cl_2).



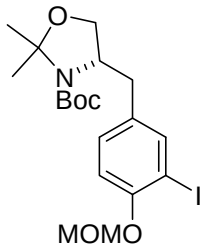
(*S*)-*tert*-Butyl-(3-((*Z*)-1-(ethoxycarbonyl)prop-1-enyl)-4-(benzyloxy)benzyl)-2,2-dimethyl oxazolidine-3-carboxylate (4-69). A solution of phenol **4-67** (7.69 g, 17.7 mmol) in THF (200 mL) was treated with NaH (1.06 g of 60% NaH in oil, 26.6 mmol) at 0 °C and the resulting slurry stirred for 30 min. TBAI (655 mg, 1.77 mmol) and BnBr (5.28 mL, 44.4 mmol) were added and the reaction mixture was warmed to ambient temperature. After 14 h, aq. NH_4Cl was added and the aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with H_2O, brine, dried (Na_2SO_4), filtered, concentrated and purified by chromatography on SiO_2 (6:1 hexanes/EtOAc) to proved benzyl ether **4-68** (8.04 g, 87%) as a yellow oil that was used directly in the next step. A solution of benzyl ether **4-68** (624 mg, 1.19 mmol), stannane **4-57** (438 mg, 1.08 mmol) and LiCl (138 mg, 3.24 mmol) were dissolved/suspended in DMF (3 mL). $Pd(PPh_3)_4$ (37.9 mg, 0.054 mmol) was added and the mixture was degassed by F-P-T (3 x). The reaction mixture was heated to 85 °C for 18 h. Following, the cooled reaction mixture was partitioned between H_2O and Et_2O (10 mL/10 mL). The aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined organic layers were washed with H_2O, brine, dried (Na_2SO_4), filtered, concentrated and the residue purified by chromatography on SiO_2 (5:1 hexanes/EtOAc) to provide ester **4-69** as a colorless oil and approximately 2:1 mixture of regioisomers (α:β) by ^{1}H NMR: IR 2979, 2395, 1697, 1389, 1259, 1095, 1026 cm^{-1}; ^{1}H NMR (CD_3CN, 353 K, reported as seen) δ 7.56-7.30 (m, 4 H), 7.22-6.97 (m, 3 H), 6.96 (m, 1 H), 6.27 (q, 1 H, *J* = 7.2 Hz), 5.13-5.08 (m, 0.5 H), 5.07-5.03 (m, 1.5 H), 4.10 (q, 2 H, *J* = 7.2 Hz), 4.11-4.03 (m, 1 H), 3.93-3.84 (m, 1 H), 3.83-3.75 (m, 1 H), 3.12-2.98 (m, 1 H), 2.84-2.69 (m, 1 H), 2.48 (d, 1 H, *J* = 1.2 Hz), 2.08 (d, 2 H, *J* = 7.2 Hz), 1.58-1.48 (m, 15 H), 1.31 (t, 1 H, *J* = 7.2 Hz), 1.18 (t, 2 H, *J* = 7.2 Hz); ^{13}C NMR (CD_3CN, 353 K) δ 168.6, 156.3, 153.4, 138.9, 138.2, 134.7, 132.8, 131.2, 129.9, 129.7 (2 C), 129.1, 128.9, 128.8 (2 C), 114.2, 95.1, 80.8, 72.0, 67.7, 61.3, 60.3, 39.6, 29.3 (3 C), 27.8, 25.0, 16.2, 14.9 ; MS (ESI) *m/z* (rel intensity) 532

([M+Na]$^+$, 4), 432 (100), 365 (14); HRMS (ESI) *m/z* calcd for $C_{30}H_{39}NO_6Na$ [M+Na] 532.2675, found 532.2674; $[\alpha]_D^{23}$ -14.7 (*c* 1.0, CH_2Cl_2).



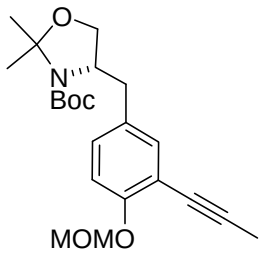
(*S*)-*tert*-Butyl-4-(3-((*E*)-1-(methoxycarbonyl)prop-1-enyl)-4-(benzyloxy)benzyl)-2,2-dimethyloxazolidine-3-carboxylate (4-72). A solution of benzyl ether **4-68** (539 mg, 1.03 mmol), pinacolato diboron (288 mg, 1.13 mmol), $PdCl_2$dppf-CH_2Cl_2 (168 mg, 0.206 mmol), and KOAc (303 mg, 3.09 mmol) in DMSO (5 mL) was stirred for 12 h. Following, H_2O was added and the solution was extracted with EtOAc (3 x 10 mL) and the combined organic layers were washed with brine, dried (Na_2SO_4), filtered, concentrated and the residue purified by chromatography in SiO_2 (1:1 hexanes/EtOAc) to proved boronate ester **4-70** (378 mg, 70%) as a colorless oil which was used directly in the next step. A solution of vinyl iodide **4-71**[149] (147 mg, 0.65 mmol), boronate 4-70 (374 mg, 0.715 mmol), K_2CO_3 (155 mg, 1.12 mmol), and $PdCl_2$dppf-CH_2Cl_2 (45.9 mg, 0.056 mmol) in DME (6 mL) was heated at 50 °C for 8 h. The cooled reaction mixture was diluted with H_2O and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with H_2O, brine, dried (Na_2SO_4), filtered, concentrated and the residue purified by chromatography on SiO_2 (3:1 hexanes/EtOAc) to provide ester **4-72** (165 mg, 51%) as a colorless oil which demonstrated evidence of hindered rotation by ^{1}H NMR, even at elevated temperatures: IR 2978, 2873, 1699, 1389, 1259, 736 cm^{-1}; ^{1}H NMR (CD_3CN, 353 K) δ 7.40-7.33 (m, 3 H), 7.27-7.24 (m, 1 H), 7.19-7.13 (m, 2 H),

7.10-6.99 (m, 2 H), 6.98-6.94 (m, 1 H), 5.05-5.01 (m, 2 H), 4.08-3.92 (m, 1 H), 3.89-3.81 (m, 1 H), 3.79-3.71 (m, 1 H), 3.68 (s, 0.5 H), 3.63 (s, 2.5 H), 3.03 (dd, 1 H, *J* = 13.2, 3.0 Hz), 2.73 (dd, 1 H, *J* = 13.2, 9.6 Hz), 1.69 (d, 3 H, *J* = 6.9 Hz), 1.52-1.48 (m, 8 H), 1.48-1.43 (m, 7 H); ^{13}C NMR (CD_3CN, 353 K) δ 168.6, 156.6, 153.2, 140.7, 138.9, 133.7, 132.2, 131.3, 129.7 (2 C), 129.6, 129.1, 128.7 (2 C), 126.4, 114.2, 94.9, 80.7, 71.6, 67.3, 60.2, 52.4, 39.5, 29.1 (3 C), 27.7, 24.7, 15.9; MS (ESI) *m/z* (rel intensity) 518 ([M+Na]$^+$, 100), 418 (100); HRMS (ESI) *m/z* calcd for$C_{29}H_{37}NO_6Na$ [M+Na] 518.2519, found 518.2534; $[\alpha]_D^{23}$ -16.3 (*c* 1.0, CH_2Cl_2).



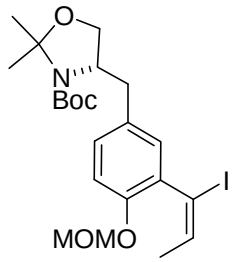
(*S*)-*tert*-Butyl-4-(3-iodo-4-(methoxymethoxy)benzyl)-2,2-dimethyloxazolidine-3-carboxyl ate (4-74). A solution of phenol **4-67** (24.3 g, 56.1 mmol) in THF (500 mL) was treated with NaH (3.36 g of 60% NaH in grease, 84.0 mmol) portionwise at 0 °C. After 45 min, solid TBAI (2.07 g, 5.61 mmol) was added, followed by MOMCl (12.8 mL, 169 mmol) dropwise. After 6 h at room temperature, the reaction was quenched by the addition of H_2O and the aqueous layer was extracted with Et_2O (3 x 100 mL). The combined organic layers were washed with H_2O, brine, dried ($MgSO_4$), filtered, and concentrated. The bulk of the crude MOM ether was carried on crude, but an analytical sample was purified by chromatography on SiO_2 (6:1 hexanes/EtOAc) to provide **4-74** as a colorless oil: IR (neat) 2976, 2930, 1697, 1388, 1241, 1085, 992 cm^{-1}; ^{1}H NMR (DMSO-d_6, 353 K) δ 7.60 (d, 1 H, *J* = 2.1 Hz), 7.15 (dd, 1 H, *J* = 8.4, 2.1 Hz), 7.02 (d, 1 H, *J* = 8.1 Hz), 5.19 (s, 2 H), 4.02-3.93 (m, 1 H), 3.84 (dd, 1 H, *J* = 9.0, 6.0 Hz), 3.69 (dd, 1 H, *J* = 9.0, 1.8 Hz), 3.43 (s, 3 H), 2.88

(dd, 1 H, J = 13.2, 3.6 Hz), 2.67 (dd, 1 H, J = 13.2, 8.7 Hz), 1.44 (s, 9 H), 1.42 (s, 3 H), 1.41 (s, 3 H); ^{13}C NMR (DMSO-d_6, 353 K) δ 154.0, 150.8, 139.2, 133.5, 129.9, 114.9, 94.7, 92.8, 86.9, 78.7, 65.6, 57.7, 55.5, 37.0, 27.7 (3 C), 26.2, 23.4; MS (EI) *m/z* (rel intensity); HRMS (EI) *m/z* calcd for $C_{19}H_{28}NO_5Na$ [M+ Na] 500.0910, found 500.0886; $[\alpha]_D^{23}$: -24.1 (c = 1.0, CH_2Cl_2).



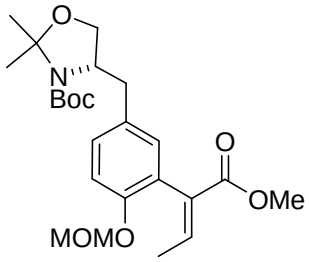
(*S*)-*tert*-Butyl 4-(4-(methoxymethoxy)-3-(prop-1-ynyl)benzyl)-2,2-dimethyloxazolidine-3-carboxylate (4-75). A solution of MOM-ether **4-74** (26.8 g, 56.1 mmol based on 100% from previous reaction), $PdCl_2(PPh_3)_2$ (787 mg, 1.12 mmol), and CuI (1.60 g, 8.4 mmol) was dissolved in CH_3CN/Et_2NH (400 mL/100 mL) and cooled to -20 °C. A cold-finger containing dry ice/acetone was attached to the flask and a 25 g (625 mmol) container of propyne was condensed into the reaction mixture. Following, the reaction mixture was warmed to room temperature, stirred for 12 h, and the volatile components evaporated. The residue was dissolved in boiling hexanes and then cooled to room temperature. The precipitates were filtered off (celite) and the orange filtrate was concentrated and carried to the next step without further purification. An analytical sample was purified by chromatography on SiO_2 (6:1 hexanes/EtOAc) to provide 4-75 as a colorless oil: IR (neat) 2978, 2234, 1740, 1701, 1078, 998 cm^{-1}; ^{1}H NMR (DMSO-d_6, 353 K) δ 7.15 (d, 1 H, J = 2.1 Hz), 7.08 (dd, 1 H, J = 8.7, 2.1 Hz), 7.02 (d, 1 H, J = 8.4 Hz), 5.17 (s, 2 H), 4.10-3.93 (m, 1 H), 3.83 (dd, 1 H, J = 9.0, 6.0 Hz), 3.68 (dd, 1 H, J = 9.0, 1.8 Hz), 3.42 (s, 3 H), 2.90 (dd, 1 H, J = 13.2, 3.6

Hz), 2.64 (dd, 1 H, J = 13.2, 9 Hz), 2.04 (s, 3 H), 1.45 (s, 9 H), 1.43 (s, 3 H), 1.41 (s, 3 H); ^{13}C NMR (DMSO-d_6, 353 K) δ 155.6, 150.8, 133.3, 131.4, 129.3, 115.6, 114.0, 94.7, 92.7, 89.3, 78.7, 75.6, 65.6, 57.7, 55.2, 37.3, 27.7 (3 C), 26.3, 23.4, 3.5; MS (EI) *m/z* (rel intensity) 390 ($[M+H]^+$, 8), 389 ($[M]^+$, 30), 200 (68); HRMS (EI) *m/z* calcd for $C_{22}H_{31}NO_5$ 389.2202, found 389.2196; $[\alpha]_D^{23}$ -44.4 (*c* 1.0, CH_2Cl_2).



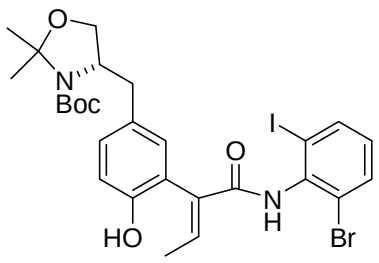
(*S*)-*tert*-Butyl 4-(3-((*E*)-1-iodoprop-1-enyl)-4-(methoxymethoxy)benzyl)-2,2-dimethyl oxazolidine-3-carboxylate (4-76). A solution of alkyne **4-75** (21.9 g, 56.1 mmol based on 100% from previous reaction) and $PdCl_2(PPh_3)_2$ (1.18 g, 1.68 mmol) in THF (220 mL, degassed) at room temperature was treated with a solution of Bu_3SnH (18.1 mL, 67.4 mmol) in THF (40 mL, degassed) dropwise. Once the addition was finished, the reaction mixture was evaporated and the residue dissolved in hexanes (~400 mL), filtered through celite, and the filtrate evaporated. The residue was dissolved in THF (300 mL) and treated with a solution of I_2 (18.5 g, 72.9 mmol) in THF (100 mmL) over 30 min. Following, the reaction mixture was treated with aq. $Na_2S_2O_3$ and the aqueous layer was extracted with Et_2O (3 x 100 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, concentrated and purified by chromatography on SiO_2 (6:1→3:1 hexanes/EtOAc, 3x) to provide vinyl iodide **4-76** (20.6 g, 71% over 8 steps) as a yellow oil: IR (neat) 2976, 1696, 1390, 1309, 1168, 1000, 923 cm^{-1}; ^{1}H NMR (DMSO-d_6, 353 K) δ 7.10 (dd, 1 H, J = 8.4, 2.1 Hz),

7.02 (d, 1 H, J = 8.4 Hz), 6.95 (d, 1 H, J = 2.1 Hz) 6.51 (q, 1 H, J = 6.9 Hz), 5.18 (s, 2 H), 4.01-3.93 (m, 1 H), 3.85 (dd, 1 H, J = 8.7, 6.0 Hz), 3.70 (dd, 1 H, J = 9.0, 1.8 Hz), 3.43 (s, 3 H), 2.91 (dd, 1 H, J = 13.2, 3.3 Hz), 2.70 (dd, 1 H, J = 13.5, 9.0 Hz), 1.47 (s, 9 H), 1.45 (d, 3 H, J = 6.6 Hz), 1.41 (s, 3 H), 1.39 (s, 3 H); ^{13}C NMR (DMSO-d_6, 353 K) δ 151.3, 150.8, 138.1, 130.9, 130.3, 130.2, 129.9, 114.9, 94.0, 92.8, 89.7, 78.7, 65.4, 57.7, 55.4, 37.2, 27.7 (3 C), 26.2, 23.4, 16.9; MS (ESI) *m/z* (rel intensity) 540 ([M+Na]$^+$, 13), 500 (100), 430 (53); HRMS (ESI) *m/z* calcd for $C_{22}H_{32}INO_5Na$ 540.1223 [M+Na], found 540.1224; $[\alpha]_D^{23}$ -43.9 (*c* 1.0, CH_2Cl_2).



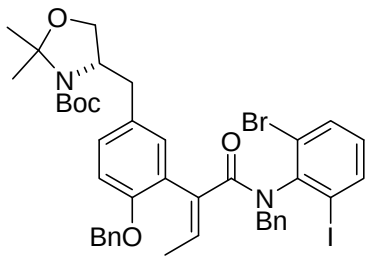
(*S*)-*tert*-Butyl 4-(3-((*E*)-1-(methoxycarbonyl)prop-1-enyl)-4-(methoxymethoxy)benzyl)-2,2-dimethyloxazolidine-3-carboxylate (4-77). A solution of alkenyl iodide **4-76** (10.2 g, 19.7 mmol), DIPEA (13.7 mL, 78.9 mmol), $PdCl_2(PPh_3)_2$ (692 mg, 0.986 mmol), and MeOH (23.9 mL, 591 mmol) was purged with CO for 30 min and then heated at 60 °C under a balloon of CO for 8 h. The cooled reaction mixture was poured into brine (500 mL) and the mixture extracted with Et_2O (5 x 150 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, concentrated, and the residue purified by chromatography on SiO_2 (5:1→3:1 hexanes/EtOAc) to furnish ester **4-77** (4.87 g, 55%) as a yellow oil: IR (neat) 2978, 1718, 1697, 1389, 1258, 1077 cm^{-1}; ^{1}H NMR (DMSO-d_6, 353 K) δ 7.12 (dd, 1 H, J = 8.4, 2.1 Hz), 7.05 (d, 1 H, J = 8.4 Hz), 7.01 (q, 1 H, J = 6.9 Hz), 6.88 (d, 1 H, J = 2.1 Hz), 5.05 (s, 2 H), 4.02-3.93 (m, 1 H), 3.85 (dd, 1 H, J = 9.0, 6.0

Hz), 3.72 (dd, 1 H, J = 9.0, 1.8 Hz), 3.62 (s, 3 H), 3.32 (s, 3 H), 2.95 (dd, 1 H, J = 13.2, 3.3 Hz), 2.69 (dd, 1 H, J = 13.2, 9.3 Hz), 1.65 (d, 3 H, J = 7.2 Hz), 1.46 (s, 9 H), 1.41 (s, 6 H); ^{13}C NMR (DMSO-d_6, 353 K) δ 166.2, 152.8, 150.8, 138.8, 131.4, 131.1, 130.7, 129.2, 124.7, 114.6, 94.2, 92.8, 78.7, 65.4, 57.9, 55.0, 50.9, 37.3, 27.7 (3 C), 26.2, 23.4, 14.5; MS (ESI) *m/z* (rel intensity) 472 ([M+Na]$^+$, 100), 416 (46); HRMS (ESI) *m/z* calcd for $C_{24}H_{35}NO_7Na$ 472.2311 [M+Na], found 472.2291; $[\alpha]_D^{23}$ -23.6 (*c* 1.0, CH_2Cl_2).



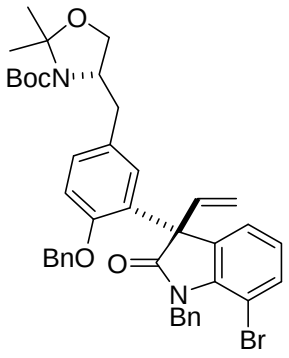
(*S*,*E*)-*tert*-Butyl-4-(3-(1-(2-bromo-6-iodophenylamino)-1-oxobut-2-en-2-yl)-4-hydroxy benzyl)-2,2-dimethyloxazolidine-3-carboxylate (4-78). A solution of aniline **4-51** (9.55 g, 32.1 mmol) in CH_2Cl_2 (60 mL) was added to a solution $AlMe_3$ (2.31 g, 32.1 mmol, neat) in CH_2Cl_2 (40 mL) at 0 °C. After 1 h at room temperature, a white precipitate had formed. A solution of ester **4-77** (4.80 g, 10.7 mmol) in CH_2Cl_2 (60 mL) was added and the reaction mixture was immediately heated to reflux and held for 45 min. The cooled reaction mixture was treated slowly with aq. Rochelle's salt and stirred for 3 h. The aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL) and the combined organic layers were dried ($MgSO_4$), filtered, concentrated and purified by chromatography on SiO_2 (3:1→2:1 hexanes/EtOAc) to provide the anilide **4-78** (3.82 g, 53%) as a white foam: mp 94.5-102.6 °C (CH_2Cl_2); IR (neat) 3284, 2978, 1686, 1482, 1390, 1256 cm^{-1}; ^{1}H NMR (DMSO-d_6, 353 K) δ 8.98 (br s, 1 H), 8.74 (s, 1 H), 7.87 (dd, 1 H, J = 8.1, 1.5 Hz), 7.66 (dd, 1 H, J = 9.0, 1.2

Hz), 7.01-6.84 (m, 5 H), 4.03-4.00 (m, 1 H), 3.83 (dd, 1 H, *J* = 9.0, 6.0 Hz), 3.76 (dd, 1 H, *J* = 8.7, 1.8 Hz), 2.96 (dd, 1 H, *J* = 13.2, 9.0 Hz), 2.65 (dd, 1 H, *J* = 13.2, 9.0 Hz), 1.66 (d, 3 H, *J* = 6.9 Hz), 1.45 (s, 12 H), 1.41 (s, 3 H); ^{13}C NMR (DMSO-d_6, 353 K) δ 165.3, 153.1, 150.8, 138.6, 137.7, 134.2 (2 C), 132.2, 131.4, 129.5, 129.3, 128.0, 122.5, 121.6, 115.6, 100.8, 92.6, 78.5, 65.5, 58.0, 37.5, 27.7 (3 C), 26.3, 23.5, 14.2; MS (ESI) *m/z* (rel intensity) 695 ([M+Na]$^+$, 20), 693 ([M+Na]+, 20), 572 (95), 571 (100); HRMS (ESI) *m/z* calcd for $C_{27}H_{32}BrIN_2O_5Na$ 693.0437 [M+Na], found 693.0425; $[\alpha]_D^{23}$ -27.3 (*c* 1.0, CH_2Cl_2).



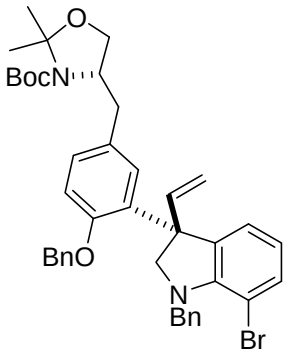
(*S*)-*tert*-Butyl 4-(3-((*E*)-1-(*N*-benzyl-N-(2-bromo-6-iodophenyl)carbamoyl)prop-1-enyl)-4-(benzyloxy)benzyl)-2,2-dimethyloxazolidine-3-carboxylate (4-79). A solution of anilide **4-78** (6.80 g, 10.1 mmol) in THF (100 mL) was treated with NaH (1.22 g of 60% NaH, 30.4 mmol) at 0 °C. After 30 min, the reaction mixture was treated with TBAI (374 mg, 1.01 mmol) and BnBr (6.01 mL, 50.6 mmol) and heated to 65 °C for 30 min. The cooled reaction mixture was quenched by the addition of H_2O and the aqueous layer was extracted with Et_2O (4 x 30 mL) and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered, concentrated and purified by chromatography on SiO_2 (3:1 hexanes/EtOAc) to provide anilide **4-79** (7.24 g, 84%) as a white foam and several atropdiastereomers as indicated by ^{1}H NMR analysis: mp 73.6-78.0 °C (CH_2Cl_2); IR (neat) 2977, 2934, 1696, 1653, 1434, 1388, 1254, 734 cm^{-1}; ^{1}H NMR (DMSO-d_6, 353 K, reported as

seen) δ 7.58 (dd, 1 H, *J* = 9.0, 3.9 Hz), 7.47-7.44 (m, 5 H), 7.43-7.25 (m, 3.5 H), 7.23-7.12 (m, 6 H), 7.08-7.01 (m, 1 H), 7.01-6.93 (m, 1 H), 6.93-6.84 (m, 1 H), 6.76-6.64 (m, 1.5 H), 6.58 (app q, 1 H, *J* = 5.4 Hz), 6.35-6.23 (m, 1 H), 5.18 (s, 0.5 H), 5.00-4.92 (m, 2 H), 4.90-4.68 (m, 3 H), 4.05-3.97 (m, 1 H), 3.90-3.70 (m, 3 H), 3.66-3.58 (m, 1 H), 3.12-2.98 (m, 1 H), 2.89-2.68 (m, 1 H), 2.46-2.33 (m, 1 H), 1.69 (d, 1 H, *J* = 7.5 Hz), 1.47 (s, 9 H), 1.47-1.45 (m, 2.5 H), 1.44 (s, 2 H), 1.41 (s, 1.5 H); ^{13}C NMR (DMSO-d_6, 353 K, reported as seen) δ 168.6, 153.9, 150.7, 141.5, 138.9, 136.8, 136.0, 134.8, 134.7, 133.0, 130.0, 129.8, 129.7, 129.0, 128.9, 128.8, 127.7, 127.5, 127.1, 127.0, 126.7, 126.5, 124.1, 122.7, 112.0, 102.2, 92.7, 78.6, 68.8, 65.3, 57.8, 57.8, 51.5, 37.4, 27.8, 36.4, 23.4, 14.1; HRMS (ESI) *m/z* calcd for $C_{41}H_{45}BrIN_2O_5$ [M+H] 851.1557, found 851.1592; $[\alpha]_D^{23}$ -11.0 (*c* 0.5, CH_2Cl_2).



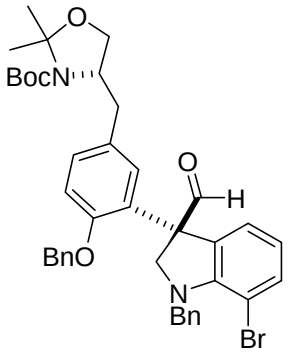
(*S*)-*tert*-Butyl-4-(3-((*S*)-1-benzyl-7-bromo-2-oxo-3-vinylindolin-3-yl)-4-(benzyloxy)benzyl)-2,2-dimethyloxazolidine-3-carboxylate (4-80). A mixture of amide **4-79** (3.00 g, 3.52 mmol), Pd_2dba_3-$CHCl_3$ (365 mg, 0.352 mmol), (*S*)-BINAP (483 mg, 0.775 mmol), and PMP (2.55 mL, 14.1 mmol) in freshly distilled NMP (35 mL) was degassed (F-P-T, 3x). The reaction mixture was heated at 110 °C for 3.5 h, at which time HPLC indicated completion of the reaction. The cooled reaction mixture was poured into Et_2O (50 mL) and H_2O (50 mL). The aqueous layer was extracted with

Et_2O (3 x 50 mL), and the combined organic layers were washed with H_2O (5x), brine, dried ($MgSO_4$), filtered, concentrated and purified by chromatography on SiO_2 (3:1 hexanes/EtOAc) to furnish oxindole **4-80** (2.14 g, 84%) as a white foam which was 77:23 mixture of diastereomers by HPLC: mp 77.5-84.2 °C (CH_2Cl_2); IR (neat) 2978, 2872, 1725, 1697, 1388, 1257, 1017, 738 cm^{-1}; ^1H NMR (DMSO-d_6, 353 K) δ 7.40-7.32 (m, 4 H), 7.30 (d, 1 H, *J* = 1.8 Hz), 7.26-7.12 (m, 4 H), 7.08-6.80 (m, 7 H), 6.30 (dd, 1 H, *J* = 17.4, 10.2 Hz), 5.40 (d, 1 H, *J* = 10.2), 4.93 (d, 1 H, *J* = 17.1 Hz), 4.85-4.71 (m, 3 H), 4.64 (d, 1 H, *J* = 16.8 Hz), 4.10-3.98 (m, 1 H), 3.88 (dd, 1 H, *J* = 9.0, 5.7 Hz), 3.76 (dd, 1 H, *J* = 9.0, 1.5 Hz), 3.05-2.98 (m, 1 H, signal obscured by H_2O contaminating DMSO), 2.78-2.68 (m, 1 H), 1.48 (s, 9 H), 1.47 (s, 3 H), 1.44 (s, 3 H); ^{13}C NMR δ 176.7, 153.8, 150.8, 139.8, 137.8, 137.0, 135.7, 133.8, 132.9, 129.9, 129.8, 129.3, 128.0 (2 C), 127.8 (2 C), 127.6, 127.4, 127.3 (2 C), 126.2, 125.4 (2 C), 123.1, 123.0, 117.1, 112.2, 101.1, 92.8, 78.7, 69.6, 65.4, 58.0, 57.0, 43.0, 37.7, 27.8 (3 C), 26.4, 23.3; HRMS (ESI) *m/z* calcd for $C_{41}H_{43}BrN_2O_5Na$ [M+Na] 745.2253, found 745.2269; $[\alpha]_D^{23}$ +86.9 (*c* 1.0, CH_2Cl_2).



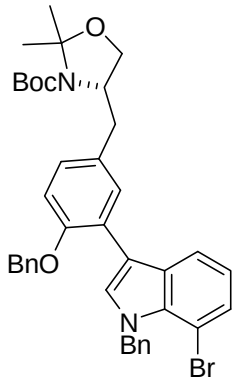
(*S*)-*tert*-Butyl 4-(3-((*S*)-1-benzyl-7-bromo-3-vinylindolin-3-yl)-4-(benzyloxy)benzyl)-2,2-dimethyloxazolidine-3-carboxylate (4-82). A solution of oxindole **4-80** (5.05 g, 6.99 mmol) in THF (10 mL) was treated with DIBAL (28.0 mL of a 1 M solution, 28.0 mmol) at room temperature.

The reaction mixture was heated at reflux for 40 min and cooled to room temperature upon consumption of the starting material. The cooled reaction mixture was treated with aq. Rochelle's salt and stirred for 3 h. The aqueous layer was extracted with Et_2O (3 x 30 mL) and the combined organic layers washed with brine, dried ($MgSO_4$), filtered, concentrated and purified by chromatography on SiO_2 (5:1 hexanes/EtOAc) to provide hydroindole **4-82** (3.78 g, 76%) as a white foam: mp 46.2-54.1 °C (CH_2Cl_2); IR (neat) 2977, 2933, 2873, 1697, 1388, 1095, 735 cm^{-1}; ^1H NMR (DMSO-d_6, 353 K) δ 7.34-7.18 (m, 9 H), 7.15-7.12 (m, 2 H), 7.08 (dd, 1 H, *J* = 8.4, 1.8 Hz), 7.05-7.00 (m, 1 H), 6.92 (d, 1 H, *J* = 1.8 Hz), 6.82 (dd, 1 H, *J* = 7.2, 1.2 Hz), 6.63 (dd, 1 H, *J* = 7.5, 7.5 Hz), 6.21 (dd, 1 H, *J* = 17.1, 10.5 Hz), 5.06 (dd, 1 H, *J* = 10.5, 0.9 Hz), 4.96 (d, 1 H, *J* = 11.7 Hz), 4.85 (d, 1 H, *J* = 12.0 Hz), 4.76 (app t, 2 H, *J* = 15.3 Hz), 4.34 (d, 1 H, *J* = 15.6 Hz), 3.98-3.87 (m, 1 H), 3.83-3.78 (m, 2 H), 3.68-3.60 (m, 2 H), 2.89 (dd, 1 H, *J* = 13.5, 3.6 Hz), 2.60 (dd, 1 H, *J* = 13.2, 9.0 Hz), 1.43 (s, 3 H), 1.42 (s, 9 H), 1.41 (s, 3 H); ^{13}C NMR (DMSO-d_6, 353 K) δ 154.3, 150.7, 147.5, 142.8, 138.3, 137.5, 136.4, 132.3, 131.9, 129.2, 129.0, 128.6, 127.6(4) (2 C), 127.6(0) (2 C), 127.0, 126.9 (2 C), 126.8 (2 C), 126.2, 124.0, 119.0, 112.9, 112.3, 102.2, 92.7, 78.5, 69.4, 65.4, 64.3, 57.8, 53.5, 52.9, 37.7, 27.7 (3 C), 26.3, 23.3; MS (ESI) *m/z* (rel intensity) 711 ($[M+H]^+$, 48), 709 ($[M+H]^+$, 48), 574 (100); HRMS (ESI) *m/z* calcd for $C_{41}H_{46}BrN_2O4$ 709.2641, found 709.2645; $[\alpha]_D^{23}$ -2.5 (*c* 1.0, CH_2Cl_2). Characteristic data for minor diastereomer: ^1H NMR (DMSO-d_6, 353 K) δ 6.81 (dd, 1 H, *J* = 7.2, 1.2 Hz), 6.62 (dd, 1 H, *J* = 7.5, 7.5 Hz), 5.07 (dd, 1 H, *J* = 10.5, 0.9 Hz), 4.33 (d, 1 H, *J* = 15.6 Hz); ^{13}C NMR (DMSO-d_6, 353 K) δ 137.6, 129.0, 128.5, 123.9, 27.7.



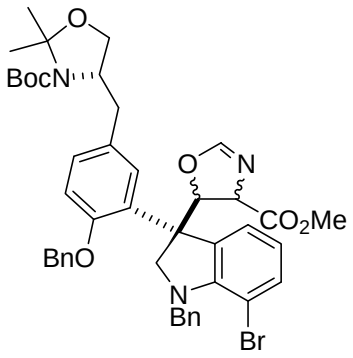
(*S*)-*tert*-Butyl 4-(3-((*R*)-1-benzyl-7-bromo-3-formylindolin-3-yl)-4-(benzyloxy)benzyl)-2,2-dimethyloxazolidine-3-carboxylate (4-83). A solution of hydroindole **4-82** (3.76 g, 5.31 mmol) in THF/Acetone/pH 7 phosphate buffer (6/6/6 mL) was treated with NMO (1.06 g, 7.96 mmol) and OsO_4 (2.41 mL of a 0.33 M solution, 0.796 mmol) at room temperature. After 8 h, aq. $NaHSO_3$ was added and the mixture extracted with EtOAc (3 x 80 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The crude residue was dissolved in THF/pH 7 phosphate buffer (25/5 mL) and treated with $NaIO_4$ (3.41 g, 15.9 mmol). After 40 min, the solution was diluted with brine, extracted with EtOAc (3 x 60 mL) and the combined organic layers washed with brine, dried ($MgSO_4$), filtered, concentrated, and the residue purified by chromatography on SiO_2 (4:1 hexanes/EtOAc) to furnish the aldehyde as a white foam and 3.3:1 mixture of diastereomers as indicated by ^{1}H NMR analysis: mp 56.0-63.2 °C (hexanes/EtOAc); IR (neat) 2977, 2933, 1728, 1696, 1388, 1256, 1094, 735 cm^{-1}; ^{1}H NMR (DMSO-d_6, 353 K) δ 9.64 (s, 1 H), 7.38 (dd, 1 H, *J* = 8.1, 0.9 Hz), 7.35-7.21 (m, 10 H), 7.16-7.07 (m, 3 H), 6.78 (dd, 1 H, *J* = 6.0, 2.1 Hz), 6.71 (dd, 1 H, *J* = 7.7, 7.7 Hz), 5.04 (d, 2 H, *J* = 2.4 Hz), 4.75 (d, 2 H, *J* = 2.4 Hz), 4.40 (d, 1 H, *J* = 0.8 Hz), 3.95-3.88 (m, 1 H), 3.83 (d, 1 H, *J* = 9.0 Hz), 3.65 (dd, 1 H, *J* = 8.7, 1.2 Hz), 3.36 (d, 1 H, *J* = 10.8 Hz), 2.86 (dd, 1 H, *J* = 13.2, 3.3 Hz), 2.63 (dd, 1 H, *J* = 13.5, 9.0 Hz), 1.41 (s, 3 H), 1.40 (s, 3 H), 1.38 (s, 9 H); ^{13}C NMR (DMSO-d_6, 353 K) δ 195.1, 153.5,

150.7, 148.3, 137.9, 135.9, 134.0, 130.3, 129.8, 129.5, 128.9, 127.7(2) (2 C), 127.7(0) (3 C), 127.2, 126.9 (2 C), 126.8 (2 C), 126.4, 125.4, 119.5, 112.6, 102.6, 92.7, 78.5, 69.8, 65.4, 61.5, 60.4, 57.7, 52.7, 37.6, 27.6 (3 C), 26.2, 23.2; MS (ESI) *m/z* (rel intensity) 713($[M+H]^+$, 4), 711 ($[M+H]^+$, 4), 657 (74), 547 (100); HRMS (ESI) *m/z* calcd for $C_{40}H_{43}BrN_2O_5$ 711.2434, found 711.2488; $[\alpha]_D^{23}$: -135.5 (c = 1.0, CH_2Cl_2). Characteristic data for minor diastereomer: ^{1}H NMR (DMSO-d_6, 353 K) δ 9.66 (s, 1 H), 1.45 (s, 3 H), 1.42 (s, 3 H); ^{13}C NMR (DMSO-d_6, 353 K) δ 195.2, 130.4, 130.0, 129.9, 129.3, 125.3, 112.7, 65.3, 61.5, 58.0, 37.8, 27.7, 26.3.



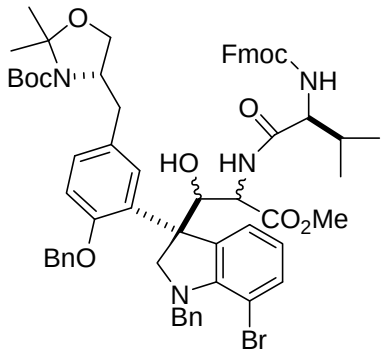
(*S*)-*tert*-Butyl 4-(3-(1-benzyl-7-bromo-1*H*-indol-3-yl)-4-(benzyloxy)benzyl)-2,2-dimethyl oxazolidine-3-carboxylate (4-85). Colorless oil: IR (neat) 2976, 2929, 1696, 1388, 1251, 1174 cm^{-1}; ^{1}H NMR (DMSO-d_6, 353 K) δ 7.66 (dd, 1 H, *J* = 6.9, 0.6 Hz), 7.61 (s, 1 H), 7.37-7.30 (m, 2 H), 7.30-7.17 (m, 8 H), 7.16-7.11 (m, 2 H), 7.08-7.01 (m, 2 H), 6.96 (t, 1 H, *J* = 7.8 Hz), 5.84 (s, 2 H), 5.07 (s, 2 H), 4.11-4.00 (m, 1 H), 3.88 (dd, 1 H, *J* = 8.7, 5.7 Hz), 3.78 (dd, 1 H, *J* = 9.0, 1.8 Hz), ~3.02 (dd, 1 H, signal obscured by H_2O contaminating DMSO), 2.73 (dd, 1 H, *J* = 13.2, 9.0 Hz), 1.46 (s, 3 H), 1.43 (s, 3 H), 1.42 (s, 9 H); ^{13}C NMR (DMSO-d_6, 353 K) δ 153.9, 150.8, 138.6, 136.7,

131.8, 131.5, 130.8, 130.4, 130.0, 127.9 (3 C), 127.6 (2 C), 126.9, 126.7 (2 C), 126.5, 126.2, 125.6 (2 C), 123.0, 120.3, 119.4, 113.5, 112.0, 102.7, 92.7, 78.6, 69.9, 65.6, 58.0, 50.2, 37.6, 27.6 (3 C), 26.3, 23.4; MS (ESI) *m/z* (rel intensity) 705 ($[M+Na]^+$, 100), 703 ($[M+Na]^+$, 100), 627 (95); HRMS (ESI) *m/z* calcd for $C_{39}H_{41}BrN_2O_4Na$ [M+Na] 703.2147, found 703.2162, $[\alpha]_D^{23}$ -23.0 (*c* 0.5, CH_2Cl_2).



Methyl 5-((*R*)-3-(5-(((*S*)-3-(tert-butoxycarbonyl)-2,2-dimethyloxazolidin-4-yl)methyl)-2-(benzyloxy)phenyl)-1-benzyl-7-bromoindolin-3-yl)-4,5-dihydrooxazole-4-carboxylate (4-94). A solution of aldehyde **4-83** (2.75 g, 3.87 mmol) and methyl isocyanoacetate (1.06 mL, 11.6 mmol) in CH_2Cl_2 (40 mL) was treated with DBU (1.74 mL, 11.6 mmol) at room temperature. After 1 h, the volatiles were evaporated and the residue purified by chromatography on SiO_2 (1:1 hexanes/EtOAc) to furnish oxazoline 4-94 (3.10 g, 99%) as a white foam and a mixture of several diastereomers as indicated by ^{1}H NMR analysis: mp 73.1-82.9 °C (CH_2Cl_2); IR (neat) 2977, 1746, 1696, 1388, 1256, 1098, 738 cm^{-1}; ^{1}H NMR (DMSO-d_6, 353 K, reported as seen) δ 7.38-7.21 (m, 10 H), 7.17-7.10 (m, 4 H), 7.09-6.98 (m, 2 H), 6.81-6.75 (m, 0.3 H), 6.65-6.51 (m, 1 H), 5.62 (d, 0.6 H, *J* = 7.8 Hz), 5.49 (d, 0.4 H, *J* = 7.5 Hz), 5.06-4.72 (m, 3 H), 4.37 (dd, 0.3 H), 4.17-4.11 (m, 1 H), 4.30-3.89 (m, 1 H), 3.88-3.77 (m, 1 H), 3.74-3.58 (m, 3 H), 3.53 (s, 2.3 H), 3.80 (d, 0.4 H, *J* = 1.8 Hz), 2.94 (dd, 1 H, *J* =

13.2, 2.7 Hz), 2.71-2.59 (m, 1 H), 1.47-1.41 (m, 15 H) ; ^{13}C NMR (DMSO-d_6, 353 K, reported as seen) δ 170.3, 169.9, 156.1, 155.8, 154.3, 154.2, 150.7, 148.8, 148.7, 138.1, 137.8, 135.9, 135.8, 133.5, 133.2, 133.0, 131.7, 130.4, 129.4, 129.3, 129.2, 128.7, 127.8, 127.7(6), 127.6, 127.3, 127.2(5), 127.2, 127.0, 126.8, 126.7(6), 126.3, 126.2(5), 125.5, 123.5, 119.1, 119.0, 113.0, 112.8, 102.6, 101.9, 95.1, 92.7, 83.7, 82.8, 78.5, 69.8, 69.7, 68.8, 68.6, 65.4, 62.2, 57.9, 57.7, 53.7, 53.4, 53.2, 53.1, 51.5, 51.3, 37.8, 27.6, 26.2, 23.3; MS (ESI) *m/z* (rel intensity) 812 ([M+H]$^+$, 100), 810 ([M+H]$^+$, 100), 637 (100); HRMS (ESI) *m/z* calcd for $C_{44}H_{49}BrN_3O_7$ [M+H] 810.2754, found 810.2734; $[\alpha]_D^{23}$ +14.3 (*c* 1.0, CH_2Cl_2).



(*S*)-*tert*-Butyl 4-(3-((*R*)-3-(2-((*S*)-2-(((9*H*-fluoren-9-yl)methoxy)carbonylamino)-3-methyl butanamido)-1-hydroxy-3-methoxy-3-oxopropyl)-1-benzyl-7-bromoindolin-3-yl)-4-(benzyloxy) benzyl)-2,2-dimethyloxazolidine-3-carboxylate (4-98). A solution of oxazoline **4-94** (870 mg, 1.08 mmol) in CH_2Cl_2 (5 mL) was treated with Fmoc-Val-Cl (577 mg, 1.61 mmol) at room temperature. After 1 h, a solution of Et_3N (300 μL, 2.15 mmol) and H_2O (39 μL, 2.15 mmol) in THF (0.5 mL) was added and the reaction mixture was stirred for 1 h. The volatile components were evaporated and the residue dissolved in MeOH (10 mL) and treated with $KHCO_3$ (215 mg, 2.15 mmol). After 1 h, the mixture was filtered, evaporated and the residue purified on SiO_2 (2:1

hexanes/EtOAc) to provide alcohol **4-98** (797 mg, 66%) as a colorless oil and a mixture of several diastereomers as indicated by ^{1}H NMR analysis: IR (neat) 3345, 2924, 2853, 1696, 1453, 1389, 1247 cm^{-1}; ^{1}H NMR (DMSO-d$_6$, 353 K, reported as seen) δ 7.85 (dd, 1.5 H, *J* = 7.2, 3.9 Hz), 7.73 (d, 1.5 H, *J* = 7.2 Hz), 7.44-7.25 (m, 12 H), 7.18-7.08 (m, 1.5 H), 7.05 (s, 1.5 H), 6.77 (d, 0.5 H), 6.67-6.58 (m, 0.5 H), 6.50 (t, 0.5 H, *J* = 6.9 Hz), 6.32 (d, 0.5 H, *J* = 9.0 Hz), 5.40-5.33 (m, 1 H), 5.12-4.93 (m, 2 H), 4.81-4.61 (m, 1 H), 4.50-4.25 (m, 3 H), 4.00-3.90 (m, 1.5 H), 3.83-3.62 (m, 3 H), 3.55-3.43 (m, 1.5 H), 3.39 (s, 0.5 H), 3.38-2.93 (m, 1 H), 2.58-2.41 (m, 1 H), 2.17-1.83 (m, 1 H), 1.51-1.42 (m, 15 H), 0.97-0.86 (m, 1.5 H), 0.85-0.68 (m, 4.5 H); ^{13}C NMR (DMSO-d$_6$, 353 K, major resonances only, reported as seen) δ 170.9, 154.3, 150.7, 143.6, 143.4, 140.4, 140.3, 138.3, 136.3, 129.4, 129.0, 128.0, 127.7, 127.6, 127.5, 127.4(9), 127.3, 127.2, 127.1(7), 127.1, 127.0, 126.9, 126.6, 126.4, 126.3, 126.2, 124.6, 119.4, 118.1, 112.9, 101.8, 92.6, 78.5, 69.8, 65.5, 65.3, 59.4, 57.9, 55.7, 53.3, 53.0, 51.0, 46.6, 37.7, 30.0, 27.7, 26.3, 18.8, 18.3, 17.3; MS (ESI) *m/z* (rel intensity) 1123 ([M+H]$^+$, 72), 1121 ([M+H]$^+$, 54); HRMS (ESI) *m/z* calcd for $C_{63}H_{70}BrN_4O_{10}$ [M+H] 1121.4275, found 1121.4340; $[\alpha]_D^{23}$ -20.0 (*c* 0.1, CH_2Cl_2).

APPENDIX A

X-RAY DATA FOR COMPOUND 1-38

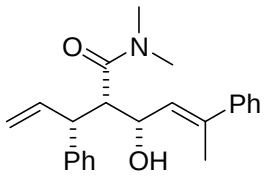


Table 1. Crystal data and structure refinement for dw1030u.

Identification code	dw1030u	
Empirical formula	$C_{23}H_{27}NO_2$	
Formula weight	349.46	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 8.087(2) Å	α= 90°.
	b = 6.2187(16) Å	β= 95.836(5)°.
	c = 19.865(5) Å	γ = 90°.
Volume	993.8(4) $Å^3$	
Z	2	
Density (calculated)	1.168 Mg/m^3	

Absorption coefficient	0.074 mm^{-1}
F(000)	376
Crystal size	0.23 x 0.30 x 0.40 mm^3
Theta range for data collection	2.06 to 32.55°.
Index ranges	-12<=h<=11, -9<=k<=9, -29<=l<=29
Reflections collected	12877
Independent reflections	6679 [R(int) = 0.0927]
Completeness to theta = 32.55°	96.3 %
Absorption correction	Sadabs
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6679 / 1 / 242
Goodness-of-fit on F^2	0.920
Final R indices [I>2sigma(I)]	R1 = 0.0721, wR2 = 0.1343
R indices (all data)	R1 = 0.1736, wR2 = 0.1673
Absolute structure parameter	0.4(18)
Largest diff. peak and hole	0.335 and -0.243 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for dw1030u. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	-1923(2)	4938(4)	2711(1)	34(1)
O(2)	827(2)	6722(3)	2218(1)	33(1)
N(1)	3159(3)	4795(4)	2458(1)	27(1)
C(1)	2795(3)	4746(5)	4651(1)	32(1)
C(2)	3664(4)	5365(5)	5246(2)	38(1)
C(3)	3722(4)	4094(6)	5810(2)	42(1)
C(4)	2934(4)	2110(6)	5766(1)	40(1)
C(5)	2060(4)	1483(5)	5172(1)	33(1)
C(6)	1945(3)	2791(4)	4601(1)	26(1)
C(7)	958(3)	2155(4)	3956(1)	24(1)
C(8)	879(4)	-231(5)	3805(2)	37(1)
C(9)	203(3)	3603(5)	3547(1)	25(1)
C(10)	-764(3)	3235(5)	2872(1)	27(1)
C(11)	414(3)	2966(5)	2314(1)	24(1)
C(12)	1508(3)	4949(5)	2326(1)	24(1)

C(13)	4036(4)	2820(5)	2658(2)	43(1)
C(14)	4139(4)	6743(5)	2444(2)	48(1)
C(15)	-508(3)	2690(5)	1599(1)	27(1)
C(16)	-1715(4)	856(5)	1585(1)	34(1)
C(17)	-3324(4)	1044(7)	1430(1)	46(1)
C(18)	733(3)	2398(5)	1077(1)	28(1)
C(19)	1044(4)	4090(5)	652(1)	36(1)
C(20)	2179(4)	3870(7)	184(2)	47(1)
C(21)	2993(4)	1934(7)	122(2)	47(1)
C(22)	2683(4)	249(6)	544(2)	41(1)
C(23)	1565(3)	482(5)	1015(1)	32(1)

Table 3. Bond lengths [Å] and angles [°] for dw1030u.

O(1)-C(10)	1.428(3)
O(2)-C(12)	1.241(3)
N(1)-C(12)	1.337(3)
N(1)-C(14)	1.450(4)
N(1)-C(13)	1.453(4)
C(1)-C(2)	1.368(4)
C(1)-C(6)	1.395(4)
C(2)-C(3)	1.369(4)
C(3)-C(4)	1.387(5)
C(4)-C(5)	1.369(4)
C(5)-C(6)	1.391(4)
C(6)-C(7)	1.492(4)
C(7)-C(9)	1.320(4)
C(7)-C(8)	1.514(4)
C(9)-C(10)	1.501(4)
C(10)-C(11)	1.542(4)
C(11)-C(12)	1.516(4)
C(11)-C(15)	1.544(3)

C(15)-C(16)	1.500(4)
C(15)-C(18)	1.526(4)
C(16)-C(17)	1.311(4)
C(18)-C(23)	1.380(4)
C(18)-C(19)	1.388(4)
C(19)-C(20)	1.378(4)
C(20)-C(21)	1.383(5)
C(21)-C(22)	1.380(5)
C(22)-C(23)	1.374(4)

C(12)-N(1)-C(14)	118.3(3)
C(12)-N(1)-C(13)	124.3(3)
C(14)-N(1)-C(13)	117.3(2)
C(2)-C(1)-C(6)	120.9(3)
C(1)-C(2)-C(3)	121.1(3)
C(2)-C(3)-C(4)	119.0(3)
C(5)-C(4)-C(3)	120.1(3)
C(4)-C(5)-C(6)	121.5(3)
C(5)-C(6)-C(1)	117.4(2)
C(5)-C(6)-C(7)	122.0(3)
C(1)-C(6)-C(7)	120.6(2)
C(9)-C(7)-C(6)	121.4(3)
C(9)-C(7)-C(8)	122.6(3)
C(6)-C(7)-C(8)	116.0(2)
C(7)-C(9)-C(10)	127.8(3)
O(1)-C(10)-C(9)	111.0(2)
O(1)-C(10)-C(11)	111.0(2)
C(9)-C(10)-C(11)	110.8(2)
C(12)-C(11)-C(10)	107.6(2)
C(12)-C(11)-C(15)	109.4(2)
C(10)-C(11)-C(15)	113.4(2)
O(2)-C(12)-N(1)	120.9(3)
O(2)-C(12)-C(11)	118.1(2)
N(1)-C(12)-C(11)	121.0(3)
C(16)-C(15)-C(18)	111.6(2)
C(16)-C(15)-C(11)	110.7(2)

C(18)-C(15)-C(11)110.4(2)
C(17)-C(16)-C(15)124.4(3)
C(23)-C(18)-C(19)118.7(3)
C(23)-C(18)-C(15)121.6(3)
C(19)-C(18)-C(15)119.7(3)
C(20)-C(19)-C(18)120.6(3)
C(19)-C(20)-C(21)120.1(3)
C(22)-C(21)-C(20)119.3(3)
C(23)-C(22)-C(21)120.4(3)
C(22)-C(23)-C(18)120.8(3)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for dw1030u. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}	
O(1)24(1)	44(1)	35(1)	0(1)	3(1)	10(1)	
O(2)30(1)	22(1)	46(1)	6(1)	1(1)	5(1)	
N(1)23(1)	23(1)	34(1)	0(1)	2(1)	0(1)	
C(1)34(2)	24(2)	36(2)	6(1)	-2(1)	1(1)	
C(2)36(2)	28(2)	49(2)	0(1)	-4(1)	1(1)	
C(3)39(2)	51(2)	33(2)	-5(2)	-4(1)	-3(2)	
C(4)40(2)	50(2)	30(2)	9(2)	3(1)	0(2)	
C(5)36(2)	32(2)	32(2)	3(1)	6(1)	-4(1)	
C(6)23(1)	24(2)	31(1)	-1(1)	4(1)	2(1)	
C(7)25(1)	24(2)	25(1)	0(1)	8(1)	-1(1)	
C(8)48(2)	21(2)	43(2)	-1(1)	4(1)	-2(2)	
C(9)24(1)	25(2)	26(1)	-3(1)	6(1)	0(1)	
C(10)	26(1)	25(2)	30(2)	2(1)	5(1)	1(1)
C(11)	24(1)	24(2)	24(1)	2(1)	2(1)	2(1)
C(12)	25(1)	25(2)	21(1)	-1(1)	3(1)	1(1)
C(13)	29(2)	30(2)	71(2)	6(2)	6(2)	9(2)
C(14)	33(2)	33(2)	74(2)	7(2)	-3(2)	-9(2)

C(15)	24(1)	27(2)	29(1)	2(1)	-1(1)	3(1)
C(16)	32(2)	40(2)	30(2)	-4(1)	2(1)	-6(1)
C(17)	35(2)	62(2)	43(2)	-13(2)	6(1)	-12(2)
C(18)	26(1)	38(2)	19(1)	1(1)	-1(1)	-5(1)
C(19)	43(2)	38(2)	27(2)	4(1)	1(1)	1(2)
C(20)	52(2)	58(2)	32(2)	10(2)	10(2)	-10(2)
C(21)	35(2)	75(3)	33(2)	-7(2)	11(1)	-10(2)
C(22)	32(2)	51(2)	41(2)	-8(2)	7(1)	7(2)
C(23)	29(2)	33(2)	36(2)	0(1)	6(1)	1(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for dw1030u.

	x	y	z	U(eq)
H(1O)	-1290(60)	5700(80)	2540(20)	78(17)
H(1A)	2769	5640	4275	38
H(2)	4226	6672	5267	46
H(3)	4280	4553	6217	50
H(4)	3000	1204	6140	48
H(5)	1531	154	5149	39
H(8A)	278	-462	3369	56
H(8B)	324	-955	4145	56
H(8C)	1987	-788	3805	56
H(9)	281	5021	3695	30
H(10)	-1394	1897	2898	32
H(11)	1118	1704	2419	29
H(13A)	3681	2314	3077	65
H(13B)	5210	3091	2715	65
H(13C)	3795	1750	2314	65
H(14A)	3721	7607	2064	71
H(14B)	5278	6375	2405	71
H(14C)	4067	7538	2855	71
H(15)	-1141	4008	1487	32
H(16)	-1294	-506	1694	41

H(17A)	-3784	2383	1318	56
H(17B)	-4003	-162	1431	56
H(19)	481	5384	683	44
H(20)	2398	5025	-91	56
H(21)	3742	1770	-200	57
H(22)	3234	-1052	508	49
H(23)	1367	-666	1296	39

APPENDIX B

X-RAY DATA FOR COMPOUND 1-77

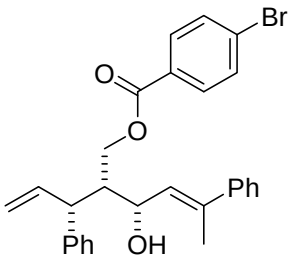


Table 1. Crystal data and structure refinement for dw1010.

Identification code	dw1010	
Empirical formula	$C_{28}H_{27}BrO_3$	
Formula weight	491.41	
Temperature	298(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 27.5495(14) Å	α= 90°.
	b = 7.4365(4) Å	β= 95.9190(10)°.
	c = 11.4908(6) Å	γ = 90°.
Volume	2341.6(2) $Å^3$	
Z	4	
Density (calculated)	1.394 Mg/m^3	

Absorption coefficient	1.783 mm^{-1}
F(000)	1016
Crystal size	0.10 x 0.10 x 0.40 mm^3
Theta range for data collection	2.23 to 32.58°.
Index ranges	-41<=h<=40, -11<=k<=11, -16<=l<=17
Reflections collected	29664
Independent reflections	8292 [R(int) = 0.0781]
Completeness to theta = 32.58°	97.0 %
Absorption correction	Sadabs
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	8292 / 0 / 289
Goodness-of-fit on F^2	0.934
Final R indices [I>2sigma(I)]	R1 = 0.0568, wR2 = 0.1237
R indices (all data)	R1 = 0.1694, wR2 = 0.1610
Largest diff. peak and hole	0.823 and -0.283 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for dw1010. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Br	364(1)	3815(1)	7864(1)	86(1)
O(1)	3060(1)	-2371(3)	8029(2)	56(1)
O(2)	2668(1)	1478(2)	6985(2)	44(1)
O(3)	2861(1)	3752(2)	8220(2)	53(1)
C(1)	1350(1)	-2520(4)	6244(2)	53(1)
C(2)	850(1)	-2459(5)	6037(3)	65(1)
C(3)	612(1)	-3271(5)	5067(3)	68(1)
C(4)	880(1)	-4125(4)	4315(3)	67(1)
C(5)	1381(1)	-4195(4)	4508(3)	54(1)
C(6)	1632(1)	-3357(3)	5474(2)	41(1)
C(7)	2174(1)	-3421(3)	5685(2)	40(1)
C(8)	2421(1)	-2320(3)	6442(2)	43(1)
C(9)	2959(1)	-2307(3)	6781(2)	43(1)
C(10)	3239(1)	-701(3)	6347(2)	39(1)
C(11)	3795(1)	-1142(3)	6422(2)	43(1)
C(12)	4106(1)	256(3)	5888(2)	42(1)

C(13)	3976(1)	956(4)	4786(3)	59(1)
C(14)	4286(1)	2076(5)	4253(3)	69(1)
C(15)	4727(1)	2532(4)	4817(3)	63(1)
C(16)	4863(1)	1875(4)	5894(3)	60(1)
C(17)	4555(1)	741(4)	6436(3)	50(1)
C(18)	2426(1)	-4792(4)	4985(3)	59(1)
C(19)	3884(1)	-2928(4)	5873(3)	58(1)
C(20)	4064(1)	-4330(4)	6449(4)	84(1)
C(21)	3184(1)	1010(3)	7033(3)	46(1)
C(22)	2559(1)	2844(3)	7654(2)	38(1)
C(23)	2024(1)	3108(3)	7655(2)	37(1)
C(24)	1855(1)	4192(3)	8503(2)	48(1)
C(25)	1365(1)	4414(4)	8568(3)	54(1)
C(26)	1039(1)	3548(4)	7760(3)	49(1)
C(27)	1196(1)	2483(4)	6897(2)	50(1)
C(28)	1692(1)	2256(4)	6853(2)	45(1)

Table 3. Bond lengths [Å] and angles [°] for dw1010.

Br-C(26)	1.887(2)
O(1)-C(9)	1.433(3)
O(2)-C(22)	1.326(3)
O(2)-C(21)	1.459(3)
O(3)-C(22)	1.208(3)
C(1)-C(2)	1.376(4)
C(1)-C(6)	1.384(4)
C(2)-C(3)	1.372(4)
C(3)-C(4)	1.352(5)
C(4)-C(5)	1.375(4)
C(5)-C(6)	1.392(4)
C(6)-C(7)	1.489(3)
C(7)-C(8)	1.330(3)
C(7)-C(18)	1.511(4)
C(8)-C(9)	1.495(3)
C(9)-C(10)	1.531(3)
C(10)-C(21)	1.513(3)

C(10)-C(11)	1.561(3)
C(11)-C(19)	1.501(4)
C(11)-C(12)	1.516(3)
C(12)-C(17)	1.378(4)
C(12)-C(13)	1.382(4)
C(13)-C(14)	1.380(4)
C(14)-C(15)	1.361(4)
C(15)-C(16)	1.348(4)
C(16)-C(17)	1.389(4)
C(19)-C(20)	1.305(4)
C(22)-C(23)	1.487(3)
C(23)-C(24)	1.381(4)
C(23)-C(28)	1.385(3)
C(24)-C(25)	1.371(4)
C(25)-C(26)	1.382(4)
C(26)-C(27)	1.374(4)
C(27)-C(28)	1.382(3)

C(22)-O(2)-C(21)	115.96(19)
C(2)-C(1)-C(6)	121.5(3)
C(3)-C(2)-C(1)	120.7(3)
C(4)-C(3)-C(2)	118.7(3)
C(3)-C(4)-C(5)	121.3(3)
C(4)-C(5)-C(6)	121.3(3)
C(1)-C(6)-C(5)	116.5(3)
C(1)-C(6)-C(7)	122.0(2)
C(5)-C(6)-C(7)	121.5(2)
C(8)-C(7)-C(6)	121.6(2)
C(8)-C(7)-C(18)	122.1(2)
C(6)-C(7)-C(18)	116.3(2)
C(7)-C(8)-C(9)	127.0(2)
O(1)-C(9)-C(8)	110.2(2)
O(1)-C(9)-C(10)	107.4(2)
C(8)-C(9)-C(10)	116.0(2)
C(21)-C(10)-C(9)	113.9(2)
C(21)-C(10)-C(11)	107.3(2)

C(9)-C(10)-C(11) 110.0(2)
C(19)-C(11)-C(12)108.2(2)
C(19)-C(11)-C(10)111.4(2)
C(12)-C(11)-C(10)115.2(2)
C(17)-C(12)-C(13)117.1(2)
C(17)-C(12)-C(11)120.8(2)
C(13)-C(12)-C(11)121.7(2)
C(14)-C(13)-C(12)121.4(3)
C(15)-C(14)-C(13)120.2(3)
C(16)-C(15)-C(14)119.8(3)
C(15)-C(16)-C(17)120.5(3)
C(12)-C(17)-C(16)121.0(3)
C(20)-C(19)-C(11)124.4(3)
O(2)-C(21)-C(10) 109.25(19)
O(3)-C(22)-O(2) 123.8(2)
O(3)-C(22)-C(23) 123.6(2)
O(2)-C(22)-C(23) 112.6(2)
C(24)-C(23)-C(28)119.2(2)
C(24)-C(23)-C(22)118.9(2)
C(28)-C(23)-C(22)121.8(2)
C(25)-C(24)-C(23)121.0(3)
C(24)-C(25)-C(26)118.8(3)
C(27)-C(26)-C(25)121.5(2)
C(27)-C(26)-Br 119.5(2)
C(25)-C(26)-Br 119.0(2)
C(26)-C(27)-C(28)118.9(2)
C(27)-C(28)-C(23)120.5(2)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for dw1010. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br37(1)	89(1)	136(1)	8(1)	23(1)	8(1)

O(1)56(1)	55(1)	56(1)	6(1)	2(1)	-8(1)	
O(2)31(1)	38(1)	64(1)	-9(1)	7(1)	3(1)	
O(3)39(1)	45(1)	75(1)	-13(1)	-2(1)	-2(1)	
C(1)44(2)	61(2)	53(2)	-8(1)	6(1)	-11(1)	
C(2)47(2)	80(2)	71(2)	-9(2)	15(2)	-7(2)	
C(3)44(2)	73(2)	86(2)	3(2)	-2(2)	-7(2)	
C(4)58(2)	69(2)	68(2)	-4(2)	-19(2)	-10(2)	
C(5)63(2)	50(2)	49(2)	-2(1)	0(1)	-6(1)	
C(6)46(1)	37(1)	41(1)	2(1)	6(1)	-8(1)	
C(7)45(1)	37(1)	38(1)	3(1)	9(1)	-5(1)	
C(8)41(1)	33(1)	56(2)	-6(1)	10(1)	0(1)	
C(9)40(1)	37(1)	53(2)	-7(1)	6(1)	1(1)	
C(10)	32(1)	37(1)	48(2)	-3(1)	6(1)	3(1)
C(11)	33(1)	45(2)	52(2)	0(1)	6(1)	7(1)
C(12)	33(1)	41(1)	52(2)	-5(1)	7(1)	7(1)
C(13)	41(2)	71(2)	64(2)	6(2)	5(1)	-11(1)
C(14)	64(2)	80(2)	64(2)	12(2)	14(2)	-7(2)
C(15)	49(2)	55(2)	90(3)	-6(2)	27(2)	-2(2)
C(16)	33(1)	52(2)	94(3)	-15(2)	5(2)	-3(1)
C(17)	38(1)	51(2)	62(2)	-8(1)	1(1)	8(1)
C(18)	54(2)	66(2)	59(2)	-19(2)	13(1)	-5(2)
C(19)	49(2)	50(2)	79(2)	-7(2)	24(2)	3(1)
C(20)	71(2)	51(2)	134(3)	0(2)	28(2)	15(2)
C(21)	30(1)	41(2)	68(2)	-3(1)	8(1)	1(1)
C(22)	36(1)	33(1)	45(2)	6(1)	6(1)	0(1)
C(23)	35(1)	32(1)	43(1)	4(1)	5(1)	1(1)
C(24)	45(2)	41(2)	57(2)	-5(1)	6(1)	2(1)
C(25)	49(2)	47(2)	67(2)	-4(1)	18(2)	10(1)
C(26)	33(1)	42(2)	73(2)	10(1)	10(1)	3(1)
C(27)	39(1)	47(2)	62(2)	0(1)	-1(1)	-3(1)
C(28)	43(1)	42(2)	50(2)	-4(1)	6(1)	1(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for dw1010.

	x	y	z	U(eq)

H(1A)	3022	-3401	8257	83
H(1B)	1503	-1986	6917	63
H(2A)	670	-1860	6560	78
H(3A)	274	-3235	4930	82
H(4A)	723	-4677	3654	80
H(5A)	1556	-4813	3984	65
H(8A)	2239	-1466	6799	51
H(9A)	3094	-3400	6464	52
H(10A)	3120	-477	5526	47
H(11A)	3914	-1232	7253	52
H(13A)	3673	667	4395	70
H(14A)	4192	2519	3506	83
H(15A)	4934	3296	4460	76
H(16A)	5166	2183	6278	72
H(17A)	4653	302	7181	60
H(18A)	2772	-4731	5196	89
H(18B)	2356	-4540	4165	89
H(18C)	2311	-5974	5149	89
H(19A)	3807	-3042	5070	69
H(20A)	4146	-4261	7254	101
H(20B)	4111	-5398	6055	101
H(21A)	3317	838	7841	55
H(21B)	3362	1978	6704	55
H(24A)	2078	4779	9037	57
H(25A)	1253	5135	9147	64
H(27A)	973	1925	6351	60
H(28A)	1803	1525	6279	54

APPENDIX C

X-RAY DATA FOR COMPOUND 3-21

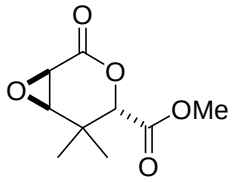


Table 1. Crystal data and structure refinement for grenon1t.

Identification code	compound9	
Empirical formula	C9H12O5	
Formula weight	200.19	
Temperature	295(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C 2/c	
Unit cell dimensions	a = 25.345(17) Å	a= 90°.
	b = 6.038(4) Å	b= 104.129(18)°.
	c = 12.627(10) Å	g = 90°.
Volume	1874(2) $Å^3$	
Z	8	
Density (calculated)	1.419 Mg/m^3	
Absorption coefficient	0.117 mm^{-1}	
F(000)	848	

Crystal size	0.28 x 0.18 x 0.12 mm^3
Theta range for data collection	1.66 to 25.00°.
Index ranges	-30<=h<=25, -6<=k<=7, -15<=l<=15
Reflections collected	4776
Independent reflections	1647 [R(int) = 0.2741]
Completeness to theta = 25.00°	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9861 and 0.9680
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1647 / 0 / 130
Goodness-of-fit on F^2	1.132
Final R indices [I>2sigma(I)]	R1 = 0.1225, wR2 = 0.2742
R indices (all data)	R1 = 0.1859, wR2 = 0.3053
Largest diff. peak and hole	0.406 and -0.398 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for grenon1t. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	1875(2)	-1574(8)	5239(4)	44(1)
C(1)	1822(3)	0(12)	4631(5)	37(2)
O(2)	2379(2)	2448(8)	3728(4)	39(1)
C(2)	2157(3)	322(12)	3833(5)	34(2)
O(3)	1431(2)	1441(8)	4633(3)	36(1)
C(3)	1942(3)	1664(12)	2866(5)	34(2)
C(4)	1397(2)	2796(10)	2755(5)	25(2)
O(4)	437(2)	3109(9)	4097(6)	70(2)
O(5)	779(2)	6390(7)	3879(4)	39(1)
C(5)	1350(2)	3394(10)	3924(5)	27(2)
C(6)	1405(3)	4928(12)	2108(6)	46(2)
C(7)	958(3)	1207(12)	2174(6)	39(2)
C(8)	798(3)	4208(11)	3980(5)	30(2)
C(9)	281(3)	7423(14)	4022(7)	51(2)

Table 3. Bond lengths [Å] and angles [°] for grenon1t.

O(1)-C(1)	1.208(8)
C(1)-O(3)	1.320(8)
C(1)-C(2)	1.480(10)
O(2)-C(2)	1.421(8)
O(2)-C(3)	1.432(8)
C(2)-C(3)	1.456(9)
C(2)-H(2)	0.9800
O(3)-C(5)	1.465(8)
C(3)-C(4)	1.515(9)
C(3)-H(3)	0.9800
C(4)-C(7)	1.517(9)
C(4)-C(6)	1.527(9)
C(4)-C(5)	1.553(8)
O(4)-C(8)	1.169(8)
O(5)-C(8)	1.323(8)
O(5)-C(9)	1.456(8)
C(5)-C(8)	1.499(9)
C(5)-H(5)	0.9800
C(6)-H(6A)	0.9600
C(6)-H(6B)	0.9600
C(6)-H(6C)	0.9600
C(7)-H(7A)	0.9600
C(7)-H(7B)	0.9600
C(7)-H(7C)	0.9600
C(9)-H(9A)	0.9600
C(9)-H(9B)	0.9600
C(9)-H(9C)	0.9600

O(1)-C(1)-O(3)	118.9(6)
O(1)-C(1)-C(2)	122.9(7)
O(3)-C(1)-C(2)	118.1(6)
C(2)-O(2)-C(3)	61.4(4)
O(2)-C(2)-C(3)	59.7(4)

O(2)-C(2)-C(1) 119.2(6)
C(3)-C(2)-C(1) 119.0(6)
O(2)-C(2)-H(2) 115.8
C(3)-C(2)-H(2) 115.8
C(1)-C(2)-H(2) 115.8
C(1)-O(3)-C(5) 121.5(5)
O(2)-C(3)-C(2) 58.9(4)
O(2)-C(3)-C(4) 116.0(5)
C(2)-C(3)-C(4) 118.3(5)
O(2)-C(3)-H(3) 116.9
C(2)-C(3)-H(3) 116.9
C(4)-C(3)-H(3) 116.9
C(3)-C(4)-C(7) 107.7(5)
C(3)-C(4)-C(6) 107.4(5)
C(7)-C(4)-C(6) 112.2(5)
C(3)-C(4)-C(5) 107.3(5)
C(7)-C(4)-C(5) 112.9(5)
C(6)-C(4)-C(5) 109.1(5)
C(8)-O(5)-C(9) 115.3(5)
O(3)-C(5)-C(8) 103.2(5)
O(3)-C(5)-C(4) 111.2(5)
C(8)-C(5)-C(4) 114.3(5)
O(3)-C(5)-H(5) 109.3
C(8)-C(5)-H(5) 109.3
C(4)-C(5)-H(5) 109.3
C(4)-C(6)-H(6A) 109.5
C(4)-C(6)-H(6B) 109.5
H(6A)-C(6)-H(6B)109.5
C(4)-C(6)-H(6C) 109.5
H(6A)-C(6)-H(6C)109.5
H(6B)-C(6)-H(6C)109.5
C(4)-C(7)-H(7A) 109.5
C(4)-C(7)-H(7B) 109.5
H(7A)-C(7)-H(7B)109.5
C(4)-C(7)-H(7C) 109.5
H(7A)-C(7)-H(7C)109.5

H(7B)-C(7)-H(7C)109.5
O(4)-C(8)-O(5) 124.4(6)
O(4)-C(8)-C(5) 126.0(6)
O(5)-C(8)-C(5) 109.6(5)
O(5)-C(9)-H(9A) 109.5
O(5)-C(9)-H(9B) 109.5
H(9A)-C(9)-H(9B)109.5
O(5)-C(9)-H(9C) 109.5
H(9A)-C(9)-H(9C)109.5
H(9B)-C(9)-H(9C)109.5

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for grenon1t. The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

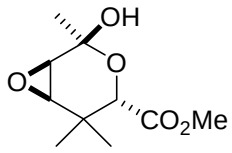
U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)42(3)	41(3)	47(3)	16(2)	9(2)	9(2)
C(1)38(4)	43(4)	27(4)	-3(3)	3(3)	4(4)
O(2)22(2)	53(3)	43(3)	4(2)	10(2)	-6(2)
C(2)31(3)	41(4)	31(4)	2(3)	7(3)	7(3)
O(3)39(3)	38(3)	33(3)	5(2)	12(2)	1(2)
C(3)25(3)	57(5)	23(3)	3(3)	10(3)	5(3)
C(4)24(3)	30(4)	22(3)	-3(3)	8(3)	-4(3)
O(4)37(3)	50(4)	138(6)	-9(3)	46(4)	-10(3)
O(5)27(3)	32(3)	65(3)	1(2)	22(2)	3(2)
C(5)23(3)	26(3)	33(4)	3(3)	8(3)	0(3)
C(6)45(4)	48(5)	52(5)	15(4)	24(4)	18(4)
C(7)41(4)	40(4)	35(4)	-7(3)	5(3)	0(4)
C(8)31(4)	27(4)	34(4)	-6(3)	16(3)	-5(3)
C(9)46(5)	46(4)	69(6)	0(4)	26(4)	20(4)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for grenon1t.

	x	y	z	U(eq)
H(2)	2382	-942	3732	41
H(3)	2034	1202	2189	41
H(5)	1623	4515	4236	33
H(6A)	1687	5885	2505	70
H(6B)	1060	5660	2001	70
H(6C)	1473	4578	1411	70
H(7A)	1048	651	1527	59
H(7B)	615	1969	1975	59
H(7C)	932	-6	2650	59
H(9A)	-17	7021	3424	77
H(9B)	324	9003	4041	77
H(9C)	209	6926	4695	77

APPENDIX D

X-RAY DATA FOR COMPOUND 3-26



Crystal Data

Formula	C10 H16 O5
Formula Weight	216.23
Crystal System	Monoclinic
Space group	P21/c (No. 14)
a, b, c [Angstrom]	8.849(2) 15.512(3) 8.0902(17)
alpha, beta, gamma [deg]	90 101.154(19) 90
V [Ang**3]	1089.5(4)
Z	4
D(calc) [g/cm**3]	1.318
Mu(MoKa) [/mm]	0.106
F(000)	464
Crystal Size [mm]	0.00 x 0.00 x 0.00

Data Collection

Temperature (K)	208
Radiation [Angstrom]	MoKa 0.71073
Theta Min-Max [Deg]	2.3, 26.0
Dataset	-10: 10 ; -19: 17 ; -3: 9
Tot., Uniq. Data, R(int)	2284, 2132, 0.024

Observed data [I > 0.0 sigma(I)] 1408

Refinement

Nref, Npar 2132, 200
R, wR2, S 0.0567,0.1445,1.03
w = 1/[\s^2^(Fo^2^)+(0.0554P)^2^+0.8218P] where P=(Fo^2^+2Fc^2^)/3
Max. and Av. Shift/Error 0.00,0.00
Min. and Max. Resd. Dens. [e/Ang^3] -0.21,0.25

Table S2 - Final Coordinates and Equivalent Isotropic Displacement Parameters of the non-Hydrogen atoms
for: compound15P 21/c R = 0.06

Atom	x	y	z	U(eq) [Ang^2]
O1	0.2256(2)	0.79114(12)	0.1214(2)	0.0345(7)
O2	0.4175(2)	0.96400(11)	0.1784(2)	0.0283(6)
O3	0.3308(3)	1.11782(14)	0.2665(3)	0.0517(9)
O4	0.0822(2)	1.08403(14)	0.1849(3)	0.0468(8)
O5	0.4059(2)	0.88161(14)	-0.0649(3)	0.0346(7)
C1	0.2584(3)	0.97140(18)	0.1849(4)	0.0272(8)
C2	0.2162(3)	0.91172(18)	0.3232(3)	0.0283(8)
C3	0.2732(3)	0.82226(18)	0.2906(4)	0.0302(9)
C4	0.3866(3)	0.80822(18)	0.1848(4)	0.0316(9)
C5	0.4581(3)	0.88404(17)	0.1100(3)	0.0282(9)
C6	0.2323(3)	1.06554(18)	0.2173(3)	0.0305(9)
C7	0.2951(4)	0.9402(2)	0.4992(4)	0.0400(11)
C8	0.0419(4)	0.9064(2)	0.3095(5)	0.0415(11)
C9	0.6326(4)	0.8799(2)	0.1607(5)	0.0383(11)
C10	0.0405(6)	1.1718(3)	0.2188(7)	0.0604(16)

U(eq) = 1/3 of the trace of the orthogonalized U Tensor

Table S3 - Hydrogen Atom Positions and Isotropic Displacement Parameters
for: compound15P 21/c R = 0.06

Atom	x	y	z	U(iso) [Ang^2]
H1	0.201(3)	0.9564(17)	0.078(4)	0.025(7)
H3	0.270(3)	0.7838(16)	0.378(3)	0.012(6)
H4	0.453(3)	0.758(2)	0.202(3)	0.034(8)
H5O	0.462(4)	0.914(2)	-0.111(4)	0.045(10)
H7A	0.273(4)	0.901(2)	0.588(4)	0.054(10)
H7B	0.411(4)	0.942(2)	0.514(4)	0.049(9)
H7C	0.257(4)	1.001(2)	0.529(4)	0.059(10)
H8A	0.017(4)	0.863(2)	0.388(4)	0.047(9)
H8B	-0.004(3)	0.959(2)	0.339(4)	0.035(8)
H8C	-0.008(4)	0.889(2)	0.193(4)	0.044(9)
H9A	0.665(3)	0.8684(17)	0.282(4)	0.026(7)
H9B	0.666(4)	0.831(2)	0.110(4)	0.042(9)
H9C	0.677(4)	0.933(2)	0.127(4)	0.053(10)
H10A	0.074(5)	1.189(3)	0.332(6)	0.080(14)
H10B	-0.061(7)	1.175(3)	0.193(6)	0.111(19)
H10C	0.074(5)	1.207(3)	0.140(6)	0.092(17)

The Temperature Factor has the Form of Exp(-T) Where

T = 8*(Pi**2)*U*(Sin(Theta)/Lambda)**2 for Isotropic Atoms

Table S4 - (An)isotropic Displacement Parameters
for: compound15P 21/c R = 0.06

Atom	U(1,1) or U	U(2,2)	U(3,3)	U(2,3)	U(1,3)	U(1,2)
O1	0.0359(11)	0.0307(11)	0.0385(12)	-0.0066(9)	0.0109(9)	-0.0080(9)
O2	0.0258(10)	0.0242(10)	0.0373(11)	-0.0019(8)	0.0120(8)	-0.0014(8)
O3	0.0413(13)	0.0279(11)	0.0873(19)	-0.0100(12)	0.0159(12)	-0.0019(10)
O4	0.0355(12)	0.0370(12)	0.0656(16)	-0.0050(11)	0.0044(11)	0.0127(10)
O5	0.0370(12)	0.0371(12)	0.0316(12)	-0.0009(9)	0.0116(9)	-0.0063(9)
C1	0.0223(14)	0.0308(15)	0.0290(15)	-0.0022(12)	0.0059(11)	-0.0013(11)
C2	0.0289(15)	0.0273(14)	0.0297(15)	-0.0003(12)	0.0084(11)	-0.0030(11)
C3	0.0354(16)	0.0264(15)	0.0292(15)	0.0023(13)	0.0072(12)	-0.0060(12)
C4	0.0308(16)	0.0233(15)	0.0406(17)	0.0014(12)	0.0067(13)	0.0023(12)
C5	0.0278(15)	0.0260(14)	0.0321(16)	-0.0026(12)	0.0094(12)	0.0014(11)
C6	0.0311(16)	0.0315(15)	0.0305(16)	0.0031(12)	0.0098(12)	0.0015(13)
C7	0.046(2)	0.043(2)	0.0319(17)	-0.0023(15)	0.0097(14)	-0.0078(15)
C8	0.0344(17)	0.042(2)	0.052(2)	-0.0033(17)	0.0181(16)	-0.0060(15)
C9	0.0305(17)	0.0374(18)	0.047(2)	-0.0019(16)	0.0077(15)	0.0042(14)
C10	0.058(3)	0.048(2)	0.074(3)	-0.007(2)	0.010(2)	0.025(2)

The Temperature Factor has the Form of Exp(-T) Where
T = 8*(Pi**2)*U*(Sin(Theta)/Lambda)**2 for Isotropic Atoms
T = 2*(Pi**2)*Sumij(h(i)*h(j)*U(i,j)*Astar(i)*Astar(j)), for
Anisotropic Atoms. Astar(i) are Reciprocal Axial Lengths and
h(i) are the Reflection Indices.

Table S5 - Bond Distances (Angstrom)
for: compound15P 21/c R = 0.06

O1	-C3	1.436(4)	C5	-C9	1.520(5)
O1	-C4	1.442(3)	C1	-H1	0.94(3)
O2	-C1	1.424(3)	C3	-H3	0.93(2)
O2	-C5	1.432(3)	C4	-H4	0.97(3)
O3	-C6	1.201(4)	C7	-H7A	0.99(3)
O4	-C6	1.334(3)	C7	-H7B	1.01(4)
O4	-C10	1.451(5)	C7	-H7C	1.05(3)
O5	-C5	1.402(3)	C8	-H8A	0.98(3)
O5	-H5O	0.84(3)	C8	-H8B	0.96(3)
C1	-C2	1.552(4)	C8	-H8C	1.00(3)
C1	-C6	1.509(4)	C9	-H9A	0.98(3)
C2	-C7	1.525(4)	C9	-H9B	0.94(3)
C2	-C8	1.527(5)	C9	-H9C	0.97(3)
C2	-C3	1.517(4)	C10	-H10A	0.95(5)
C3	-C4	1.456(4)	C10	-H10B	0.88(6)
C4	-C5	1.516(4)	C10	-H10C	0.93(5)

Table S6 - Bond Angles (Degrees)
for: compound15P 21/c R = 0.06

C3	-O1	-C4	60.77(18)	O2	-C1	-H1	107.9(17)
C1	-O2	-C5	114.1(2)	C2	-C1	-H1	110.6(17)
C6	-O4	-C10	116.4(3)	C6	-C1	-H1	108.9(16)

C5	-O5	-H5O	109(2)	O1	-C3	-H3	117.6(15)
O2	-C1	-C2	110.9(2)	C2	-C3	-H3	113.3(16)
O2	-C1	-C6	105.7(2)	C4	-C3	-H3	118.5(16)
C2	-C1	-C6	112.7(2)	O1	-C4	-H4	115.7(17)
C1	-C2	-C7	111.7(2)	C3	-C4	-H4	120.2(15)
C1	-C2	-C8	111.1(2)	C5	-C4	-H4	113.1(17)
C1	-C2	-C3	106.6(2)	C2	-C7	-H7A	112.4(19)
C3	-C2	-C8	107.6(2)	C2	-C7	-H7B	112.9(18)
C7	-C2	-C8	110.9(3)	C2	-C7	-H7C	111.5(18)
C3	-C2	-C7	108.7(2)	H7A	-C7	-H7B	106(3)
O1	-C3	-C4	59.84(18)	H7A	-C7	-H7C	106(3)
C2	-C3	-C4	122.0(2)	H7B	-C7	-H7C	108(3)
O1	-C3	-C2	115.3(2)	C2	-C8	-H8A	110(2)
O1	-C4	-C3	59.39(17)	C2	-C8	-H8B	113.9(17)
O1	-C4	-C5	117.4(2)	C2	-C8	-H8C	110(2)
C3	-C4	-C5	120.5(2)	H8A	-C8	-H8B	105(3)
O2	-C5	-O5	110.8(2)	H8A	-C8	-H8C	108(3)
O2	-C5	-C4	111.3(2)	H8B	-C8	-H8C	109(3)
O5	-C5	-C4	107.5(2)	C5	-C9	-H9A	111.2(16)
O5	-C5	-C9	113.0(2)	C5	-C9	-H9B	108(2)
C4	-C5	-C9	109.9(2)	C5	-C9	-H9C	109(2)
O2	-C5	-C9	104.5(2)	H9A	-C9	-H9B	104(3)
O3	-C6	-C1	125.8(3)	H9A	-C9	-H9C	112(2)

O4	-C6	-C1	110.7(2)	H9B	-C9	-H9C	113(3)
O3	-C6	-O4	123.5(3)	O4	-C10	-H10A	114(3)

Table S6 - Bond Angles (Degrees) (continued)
for: compound15P 21/c R = 0.06

O4	-C10	-H10B	107(3)	H10A	-C10	-H10C	115(4)
O4	-C10	-H10C	107(3)	H10B	-C10	-H10C	104(4)
H10A	-C10	-H10B	109(4)				

Table S7 - Torsion Angles (Degrees)
for: compound15P 21/c R = 0.06

C4	-O1	-C3	-C2	113.7(3)
C3	-O1	-C4	-C5	-110.9(3)
C5	-O2	-C1	-C2	71.6(3)
C5	-O2	-C1	-C6	-166.1(2)
C1	-O2	-C5	-O5	73.6(3)
C1	-O2	-C5	-C4	-45.9(3)
C1	-O2	-C5	-C9	-164.4(2)
C10	-O4	-C6	-O3	-2.5(4)
C10	-O4	-C6	-C1	177.1(3)
O2	-C1	-C2	-C3	-52.4(3)
O2	-C1	-C2	-C7	66.1(3)
O2	-C1	-C2	-C8	-169.4(2)
C6	-C1	-C2	-C3	-170.6(2)
C6	-C1	-C2	-C7	-52.1(3)

C6	-C1	-C2	-C8	72.4(3)
O2	-C1	-C6	-O3	-15.8(4)
O2	-C1	-C6	-O4	164.7(2)
C2	-C1	-C6	-O3	105.4(3)
C2	-C1	-C6	-O4	-74.2(3)
C1	-C2	-C3	-O1	-51.3(3)
C1	-C2	-C3	-C4	17.6(4)
C7	-C2	-C3	-O1	-171.8(2)
C7	-C2	-C3	-C4	-102.9(3)
C8	-C2	-C3	-O1	68.0(3)
C8	-C2	-C3	-C4	136.9(3)
O1	-C3	-C4	-C5	105.8(3)
C2	-C3	-C4	-O1	-102.7(3)
C2	-C3	-C4	-C5	3.1(4)

Table S7 - Torsion Angles (Degrees) (continued)
for: compound15P 21/c R = 0.06

O1	-C4	-C5	-O2	77.8(3)
O1	-C4	-C5	-O5	-43.7(3)
O1	-C4	-C5	-C9	-167.0(2)
C3	-C4	-C5	-O2	8.9(4)
C3	-C4	-C5	-O5	-112.5(3)
C3	-C4	-C5	-C9	124.1(3)

Table S8 - Contact Distances(Angstrom)
for: compound15P 21/c R = 0.06

O1	.O2	3.160(3)	O5	.H1	2.60(3)
O1	.O5	2.778(3)	O5	.H3_c	2.83(3)
O1	.C10_b	3.308(6)	C3	.O1_h	3.297(4)
O1	.C3_c	3.297(4)	C6	.C9_d	3.593(5)
O2	.O3	2.646(3)	C7	.O3	3.386(4)
O2	.O1	3.160(3)	C8	.O4	2.979(4)
O2	.O5_d	3.095(3)	C9	.C6_d	3.593(5)
O3	.O5_d	3.092(3)	C10	.O1_b	3.308(6)
O3	.C7	3.386(4)	C1	.H9C_d	3.07(3)
O3	.O2	2.646(3)	C3	.H10B_a	2.98(5)
O4	.C8	2.979(4)	C4	.H3_c	2.88(2)
O5	.O1	2.778(3)	C4	.H1	2.86(3)
O5	.O3_d	3.092(3)	C6	.H9C_d	3.04(3)
O5	.O2_d	3.095(3)	C6	.H5O_d	3.01(4)
O1	.H8C	2.72(3)	C6	.H7C	2.68(3)
O1	.H1	2.59(3)	C6	.H8B	2.98(3)
O1	.H10B_a	2.91(5)	H1	.O1	2.59(3)
O1	.H10B_b	2.73(5)	H1	.O5	2.60(3)
O1	.H3_c	2.38(2)	H1	.C4	2.86(3)
O2	.H5O_d	2.29(3)	H1	.H8C	2.46(4)

O2	.H7B	2.75(3)	H3	.H7A	2.49(4)
O3	.H4_e	2.88(3)	H3	.H8A	2.57(4)
O3	.H10A	2.67(5)	H3	.H10B_a	2.49(6)
O3	.H10C	2.69(5)	H3	.O1_h	2.38(2)
O3	.H7B_f	2.77(3)	H3	.O5_h	2.83(3)
O3	.H5O_d	2.47(3)	H3	.C4_h	2.88(2)
O4	.H8B	2.50(3)	H4	.H9A	2.53(4)
O5	.H7A_g	2.84(3)	H4	.H9B	2.44(4)

Table S8 - Contact Distances(Angstrom) (continued)
for: compound15P 21/c R = 0.06

H4	.O3_i	2.88(3)	H8B	.C6	2.98(3)
H5O	.H9C	2.45(5)	H8B	.H7C	2.60(5)
H5O	.O2_d	2.29(3)	H8C	.O1	2.72(3)
H5O	.O3_d	2.47(3)	H8C	.H1	2.46(4)
H5O	.C6_d	3.01(4)	H9A	.H4	2.53(4)
H7A	.O5_j	2.84(3)	H9A	.H7C_f	2.55(4)
H7A	.H3	2.49(4)	H9B	.H4	2.44(4)
H7A	.H8A	2.58(5)	H9C	.H5O	2.45(5)
H7B	.O2	2.75(3)	H9C	.C1_d	3.07(3)
H7B	.O3_f	2.77(3)	H9C	.C6_d	3.04(3)
H7B	.H7B_f	2.43(5)	H10A	.O3	2.67(5)
H7C	.C6	2.68(3)	H10B	.O1_k	2.91(5)

H7C .H8B 2.60(5) H10B .C3_k 2.98(5)

H7C .H9A_f 2.55(4) H10B .H3_k 2.49(6)

H8A .H3 2.57(4) H10B .O1_b 2.73(5)

H8A .H7A 2.58(5) H10C .O3 2.69(5)

H8A .H10C_a 2.55(6) H10C .H8A_k 2.55(6)

H8B .O4 2.50(3)

Table S9 - Hydrogen Bonds (Angstrom, Deg)
for: compound15P 21/c R = 0.06

O5	-- H5O	.. O2	0.84(3)	2.29(3)	3.095(3)	160(3) 3_675
O5	-- H5O	.. O3	0.84(3)	2.47(3)	3.092(3)	132(3) 3_675
C3	-- H3	.. O1	0.93(2)	2.38(2)	3.297(4)	167(2) 4_565
C8	-- H8B	.. O4	0.96(3)	2.50(3)	2.979(4)	111(2) .

Translation of Symmetry Code to Equiv.Pos

a =[2545.00] = -x,-1/2+y,1/2-z
b =[3575.00] = -x,2-y,-z
c =[4564.00] = x,3/2-y,-1/2+z
d =[3675.00] = 1-x,2-y,-z
e =[2655.00] = 1-x,1/2+y,1/2-z
f =[3676.00] = 1-x,2-y,1-z
g =[1554.00] = x,y,-1+z
h =[4565.00] = x,3/2-y,1/2+z
i =[2645.00] = 1-x,-1/2+y,1/2-z
j =[1556.00] = x,y,1+z
k =[2555.00] = -x,1/2+y,1/2-z

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