DISSERTATION

PALLADIUM(II)-CATALYZED RING EXPANSION OF 1-VINYL-1-CYCLOBUTANOLS, SYNTHESIS AND COUPLING OF α-HETEROATOM STANNYL- AND SILYL- REAGENTS, AND SYNTHESIS AND REACTIONS OF ALLENYL STANNANES AND ASYMMETRIC SYNTHESIS OF γ-HYDROXY-β-AMINO ACID DERIVATIVES.

Submitted by

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Department of Chemistry

In partial fulfillment of the requirements

For the degree of Doctor of Philosophy

Colorado State University

Fort Collins, CO

Spring 2003

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COLORADO STATE UNIVERSITY

December 16, 2002

WE HEREBY RECOMMEND THAT THE DISSERTATION PREPARED UNDER OUR SUPERVISION BY PETER BENJAMIN DOUGLAS RANSLOW ENTITLED: PALLADIUM(II)-CATALYZED RING EXPANSION OF 1-VINYL-1-CYCLOBUTANOLS, SYNTHESIS AND COUPLING OF α-HETEROATOM STANNYL- AND SILYL- REAGENTS, AND SYNTHESIS AND REACTIONS OF ALLENYL STANNANES AND SYNTHESIS OF γ-HYDROXY-β-AMINO ACID DERIVATIVES BE ACCEPTED AS FULFILLING IN PART REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

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ABSTRACT OF DISSERTATION

PALLADIUM(II)-CATALYZED RING EXPANSION OF 1-VINYL-1-CYCLOBUTANOLS, SYNTHESIS AND COUPLING OF α-HETEROATOM STANNYL- AND SILYL- REAGENTS, AND SYNTHESIS AND REACTIONS OF ALLENYL STANNANES; ASYMMETRIC SYNTHESIS OF γ-HYDROXY-β-AMINO ACID DERIVATIVES.

Conditions for the palladium(II) catalyzed, oxidative ring expansion of α-alkoxy-1-vinyl-1-cyclobutanols were developed. Using conditions found in the literature to effect this transformation led to isomerization of the newly formed double bond into the ring, destroying the α-alkoxy chiral center. It was found that using palladium(II) acetate as the palladium source and DDQ as the hydride receptor led to formation of the desired alkylidenecyclopentanone products in high yield.

The insertion reaction of Fisher carbene complexes into group(IV) metal hydride bonds to form the corresponding of α-heteroatom group(IV) species is a well known process. The inherent non-reactivity of these α-heteroatom group(IV) species, however, has greatly limited the utility of this reaction. Use of stannatrane hydrides as the group(IV) metal hydride species could lead to the

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synthesis of α-heteroatom stannatrane species that would be reactive under Stille coupling conditions.

γ-Hydroxy-β-amino acids are interesting structural moieties found in several natural products. By using a novel allenyl stannane reagent, similar to those studied by Marshall, it was possible to construct a propargyl amino-alcohol system that could be transformed to the desired γ-hydroxy-β-amino acid derivatives in only two subsequent steps. The requisite chiral N-oxazolidinone allenyl stannane reagents were not known, and synthesis of these reagents proved not to be trivial. The condensation reactions of these chiral N-oxazolidinone allenyl stannane reagents with various aldehydes proceeded in very high yield and with good selectivity, marking the first example of nitrogen-substituted allenyl stannanes in this type of reaction. The condensation reaction tolerated many, diverse aldehydes, proving this methodology is viable for the synthesis of a variety of 1,2-amino alcohol products.

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ACKNOWLEDGEMENTS

I would like to thank many people for making all of this possible. First and foremost I would like to thank professor Louis S. Hegedus for allowing me to join his research group and being not just an advisor, but a true mentor. I would also like to thank the members of the Hegedus research group, past and present. In particular I would like to thank Michal Achmatowicz and Angela Bullert for X-ray analyses, and Michal again for being a great lab mate. I would also like to thank my parents and sister and the rest of my family, all of whose undying support has made all of this possible. Lastly, I would like to thank Heather Grieser, who has been there for me to come home to through good times and bad and who listened to me complain and commiserated about my problems.

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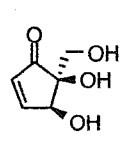
Chapter 1: Palladium(II)-Catalyzed Ring Expansion of 1-Vinyl-1-Cyclobutanols[1]

Introduction

Synthesis of chiral molecules is an area of great importance in chemistry today. Development of new chiral building blocks from which to construct natural products in a non-racemic manner is an area of much study. The cyclopentanoid and cyclopentenoid skeleton is found in many natural products[2]. These include (-)-pentenomycin I (**1**)[3a], methylenomycins A (**2**) andB (**3**)[3b], sarkomycin A (**4**)[3c], and kjellmanianone (**5**)[3d]. The prostaglandins and



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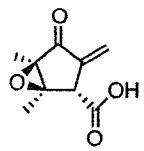

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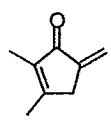

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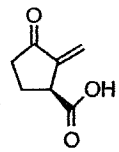

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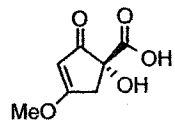
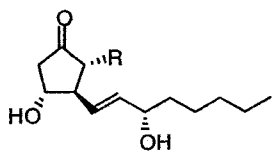


5

prostanoids also constitute an enormous class of cyclopentanoid and cyclopentenoid natural products.[4] The E prostaglandins **5** are shown below as well as one of the more recently isolated prostanoid natural products, clavulone (**6**)[5]. These natural products, while having different biological activities, all



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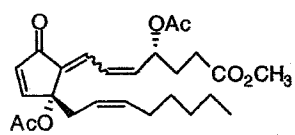

6

contain cyclopentenone functionality.

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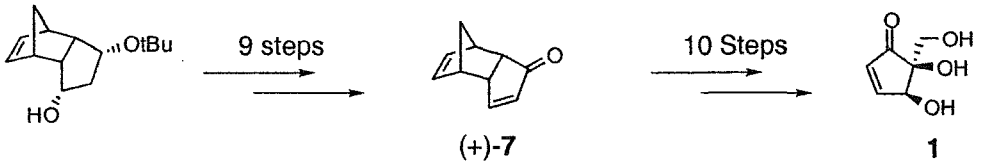
Synthesis of these chiral molecules has typically involved many steps. For instance, a recent synthesis of (-)-pentenomycin I (**1**) was completed in 10 linear steps starting from the chiral species (+)-Ketodicyclopentadiene (**(+)-KDP**) ((+)-**7**) (Scheme 1).[6] This chiral cyclopentadienone equivalent itself

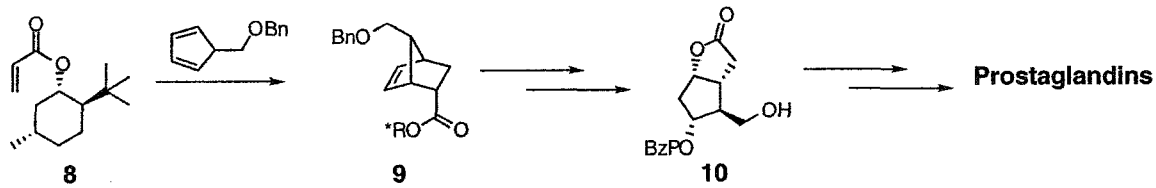
Scheme 1



(+)-**7** **1**

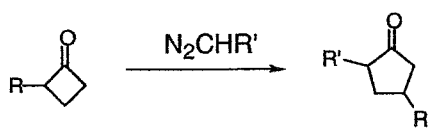
required 9 linear steps to synthesize, including a lipase-mediated kinetic resolution,[7] resulting in a 19 step total synthesis of a molecule containing only six carbons and two chiral centers. A general route to the enantioselective synthesis of the prostaglandins, via the intermediate carbocycle **10**, was developed by Corey.[8] This intermediate was synthesized by the stereoselective Diels-Alder reaction of the chiral acrylate **8**. The Bicyclic [2.2.1] compound **9** was then converted into carbocycle **10** in 7 steps (scheme 2).

Scheme 2



8 **9** **10**

Much attention has been paid to ring expansion of cyclobutanones and derivatives to the corresponding cyclopentanone.[9] Diazomethane is a common reagent used in the ring expansion of cyclobutanones (Equation 1).[10] This



eq. 1

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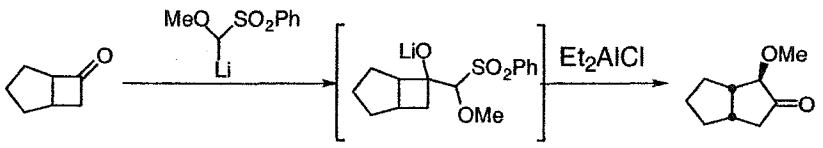
reagent is available in substituted forms as well, allowing the incorporation of the substituent into the product.[10] Generally, with unsymmetrical substrates, this reaction proceeds with migration of the less-substituted carbon, but regioselectivity of this ring expansion is not always high and mixtures of products are formed.[10c] A second method utilized in ring expansion of cyclobutanones to cyclopentanones involves addition of a sulfone-stabilized anion to the cyclobutanone, followed by Lewis-Acid catalyzed ring expansion to the cyclopentanone (Scheme 3).[11] Unlike diazomethane ring

Scheme 3



expansions, this reaction proceeds with migration of the more substituted carbon. Again, use of substituted sulfone anions leads to substituted cyclopentanone products. Variations of this reaction have used selenoxide-stabilized anions[12] or phenyl sulfide in place of the methoxyl group.[11a]

A third method for the ring expansion of cyclobutanone derivatives involves transition metal catalysis. Palladium (II) catalyzes the ring expansion of 1-vinyl-1-cyclobutanols **10** to the corresponding cyclopentenones.[13] Generally, the reaction proceeds with migration of the more-substituted carbon adjacent to the allylic alcohol moiety and the initally-formed product **12** rearranges, if one of the substituents on the migrating carbon is hydrogen, to give products with the double bond within the ring **13** (Scheme 4). This

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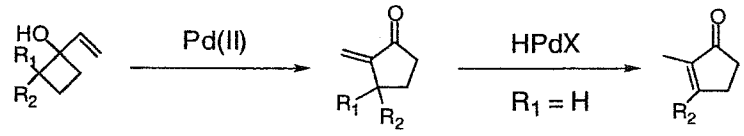
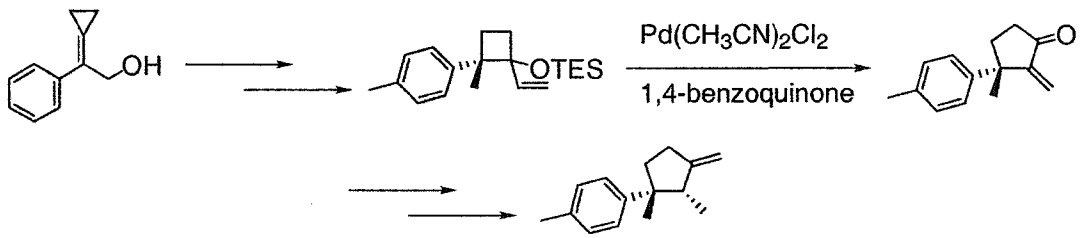
Scheme 4



10 **11** **12**

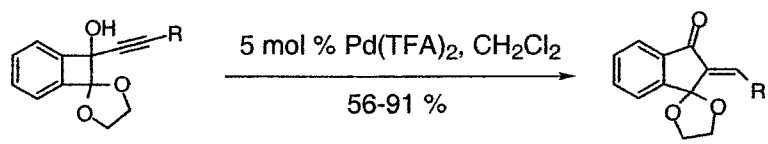
reaction has been utilized on the triethylsilyl ether derivative of the 1-vinyl-1-cyclobutanone in a total synthesis of (+)-laurene (Scheme 5).[13b]

Scheme 5



(+)-Laurene

A variation of this methodology, first pioneered by Liebeskind,[14a] uses palladium(II) trifluoroacetate, to expand 1-alkynyl-1-cyclobutanols **14** (Equation 2).[14] This sequence tolerates substitution on the alkynes, which results in



eq. 2

14 **15**

substituted alkylidenecyclopentanones of the type **15**. This rearrangement has been used in the synthesis of racemic benzoabikovirmycin.[14c] Recently this reaction has been expanded to include the simultaneous substitution/ring expansion of 1-alkynyl-1-cyclobutanols to disubstituted alkylidenecyclopentanone (Equation 3).[15]

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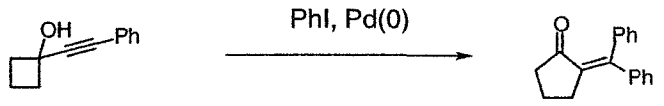
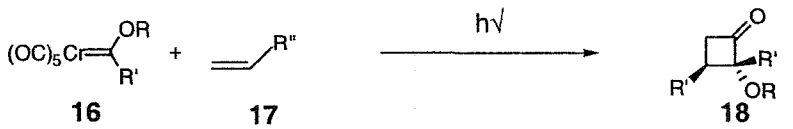


eq. 3

One method of generating cyclobutanones is photolysis of oxygen-stabilized chromium carbene complexes (**16**) with electron-rich olefins (**17**) (Equation 4).[16] This proceeds with a wide variety of olefins to give



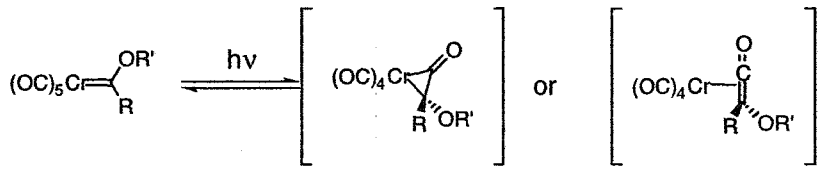
16 **17** **18**

eq. 4

R = alkyl, aryl; R' = alkyl; R" = alkyl, aryl, vinyl, NR_2, OR, SR .....

cyclobutanones (**18**) in moderate to high yield and with high diastereoselectivity. Unforutnately, carbene complexes with aryl or vinyl substituents do not to react in this manner. The exact mechanism of the photolysis of chromium carbene complexes to give cyclobutanones is not known. It is known that photolysis of chromium carbene complexes leads to a transient excited state complex, which is believed to reversibly insert a carbonyl ligand from the chromium to give a metallacyclopropanone or metal-bound ketene.[17] This species has never been directly observed and its existence is inferred from the reactivity of carbene complexes, which give products similar to those obtained in reactions of ketenes (Scheme 6).[16b] When photolyzed with

Scheme 6



optically active ene-carbamates this reaction also gives products in an enantioselective manner.[18] Photolysis of (4S,5R)-4,5-diphenyl-3-vinyl-2-

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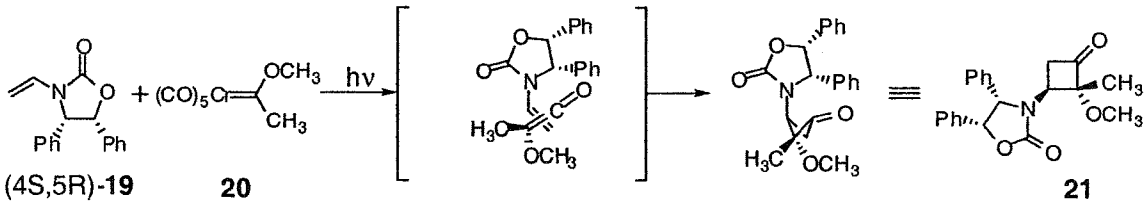
oxazolidinone ((4S,5R)-**19**)[19] with pentacarbonyl[(methoxy)(methyl)carbene]chromium(0) (**20**) gave a single diastereomer and enantiomer of cyclobutanone (**21**), in good 60-75 % yield (Scheme 7). The requisite chromium carbene complexes can be generated via

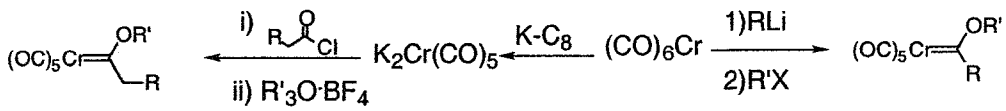
Scheme 7



several different methods.

One route to carbene complexes is the addition of alkyllithium reagents to chromium hexacarbonyl, followed by O-alkylation with a hard alkylating agent (Scheme 8, path a).[20] A second method involves the addition of chromium pentacarbonyl dianion to acid chlorides followed by alkylation of the resulting anionic acyl complex with Meerwein's reagent (Scheme 8, path b).[21] These

Scheme 8



chromium carbene complexes, which are highly reactive compounds, have found numerous uses in organic chemistry.[22]

Previous work in this group has shown that diazomethane ring expansion of cyclobutanone **21** to cyclopentanone **22** proceeds in high yield.[23] However, whereas diazomethane ring expansions are prone to give poor seletivity , this ring expansion proceeded with high selectivty for migration of the

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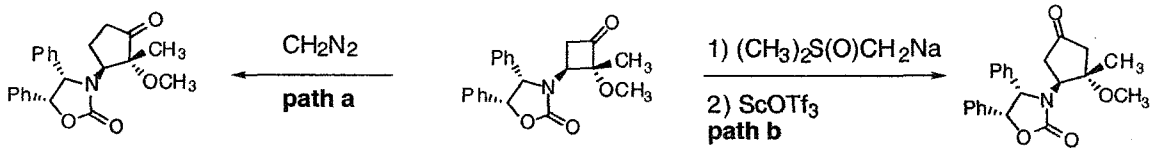
less-substituted carbon with substrates containing electronegative substituents in the β-position. For the case shown below only the product from migration of the less-substituted carbon (**22**) was observed (Scheme 9,path a). Conversely, a sulfoxonium ylide ring expansion, developed in this group by Brian Brown, proceeds with migration of the more-substituted carbon resulting in cyclopentanones such as **23** (Scheme 9, path b).[24] This ring

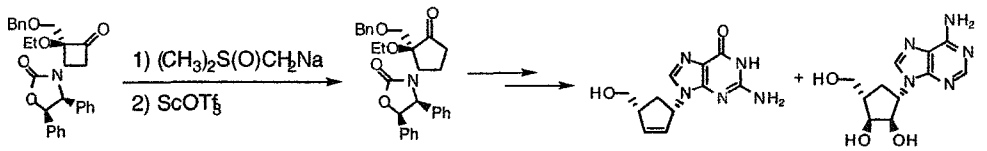
Scheme 9



22 **21** **23**

exanpansion was utitlized in the total synthesis of (+)-carbovir (**26**) and (+)-aristeromicin (**27**) from the chiral non-racemic cyclobutanone **24** (Scheme 10).[24b] Although the utility of this ring expansion has been shown, the protocol

Scheme 10



24 **25** **26** **27**

introduces no new fuctionality into the product, which may limit the uses of this reaction.

Rationale

Application of the ring expansion of 1-vinyl-1-cyclobutanols to photolytically generated cyclobutanones would represent a significant addition to available methodology for the construction of functionalized

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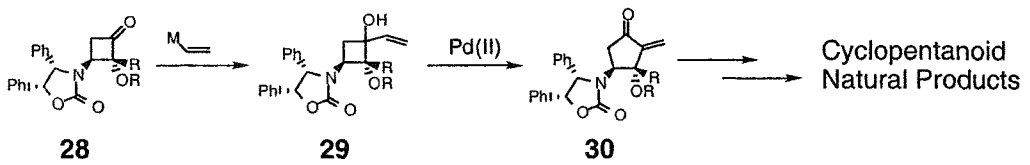
cyclopentanones. The propensity of the more highly-substituted carbon to migrate in this reaction results in the formation alkylidnecyclopentanones similar to structure **30** from 1-vinyl-1-cyclobutanols of structure **29**. These compounds should be readily available from addition of vinylmetal reagents to cyclobutanones **28** (Scheme 11). The starting cyclobutanones are avialable

Scheme 11



28 **29** **30**

as either enantiomer, in relatively few steps and good overall yield, from readily available starting materials, allowing the synthesis of diverse structures. The highly-functionalized alkylidenecyclopentanones produced from this ring expansion could then be further elaborated to cyclopentanoid natural products or other cyclopentanoid compounds of interest. Application of this methodology would have to take into account the existing chiral center adjacent to the carbonyl of cyclobutanone **28**. The alkoxy substituent on this, the migrating carbon, could prove to be more labile than the carbon subsituents seen in previous examples of this reaction.[13] Destruction or racemization of this existing chiral center would be counter-productive.

Results and discussion

Vinyl cyclobutanols can be produced from cyclobutanones via the addition of vinylmagnesium bromide.[25] Treatment of cyclobutanone **21** with vinylmagnesium bromide gave vinyl cyclobutanol **31** in 87 % yield as a single

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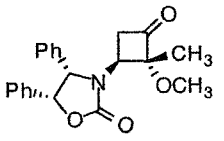
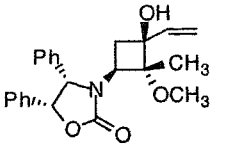
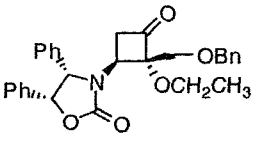
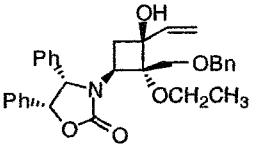
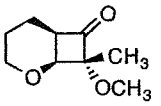
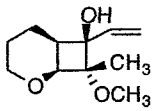
diastereomer. Cyclobutanones **32** and **33** similarly produced vinyl cyclobutanols **34** and **35**, both as single diastereomers, upon treatment with vinylmagnesium bromide (Table 1). Cyclobutanone **32**, which differs from

Table 1[a]

Cyclobutanone	Product	yield[b]
 **24**	 **31**	87 %
 **32**	 **34**	54 %
 **33**	 **35**	84 %

[a]reactions were carried out in THF using 3 eq. vinyl magnesium bromide while the temperature was allowed to slowly warm from -78°C to rt, [b] yield is for pure isolated products.

24 only in the substitution at the adjacent chiral center, gave the product **34** in only modest yield despite attempts to optimize this reaction. The stereochemical outcome of the reaction is thought to result from the large oxazolidinone chiral auxiliary and the methyl group blocking the top face of the molecule, favoring attack from the bottom face of the molecule. Also the methoxy substitutent could deliver the reagent from same face, to produce a transition state similar to that shown below (Scheme 12) and result in the

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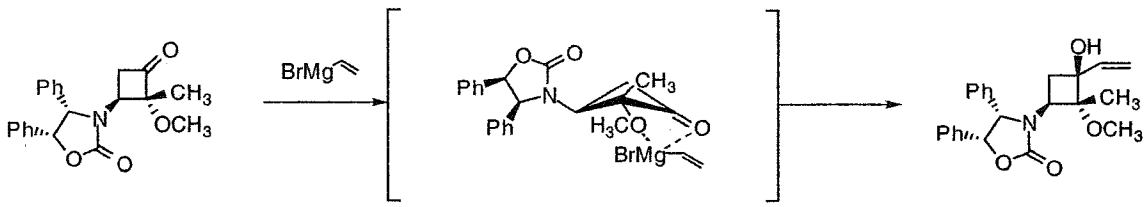
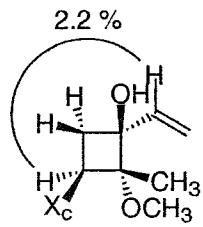
Scheme 12



24 31

stereochemistry shown for the product 1-vinyl-1- cyclobutanol **31**. The stereochemical assignment for **31** was supported by NOE experiments (Figure 1). The observed NOE between the two protons shown could only occur if they

Figure 1
Observed NOE's of compounds **24**



24

were on the same face of the molecule, thus supporting the assigned stereochemistry.

Cyclobutanone **36** was synthesized via samarium (II) iodide reduction of cyclobutanone **24**.[26] Treatment of this cyclobutanone with vinylmagnesium bromide gave a 90 % yield of a 2:1 mixture of diastereomeric 1-vinyl-1-cyclobutanols **37** and **38** (Scheme 13). The stereochemistry of these products

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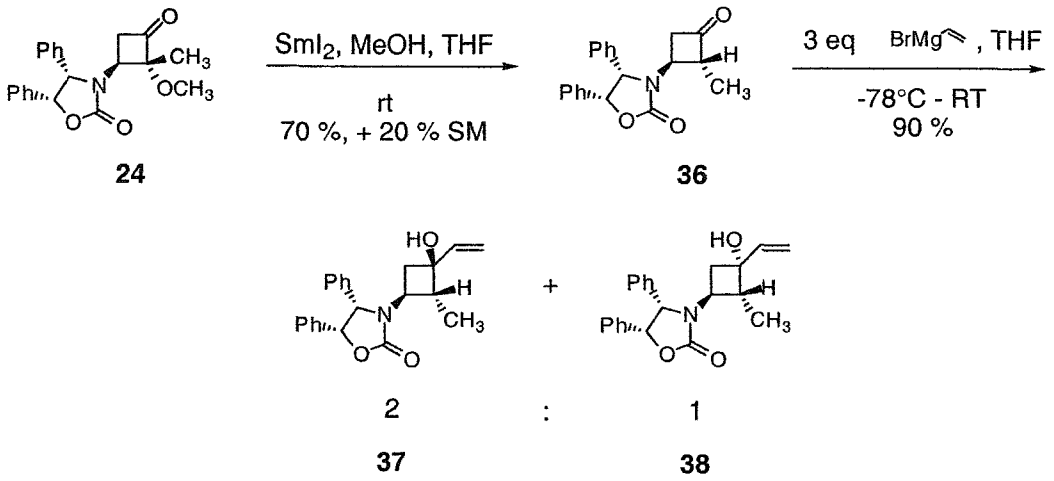
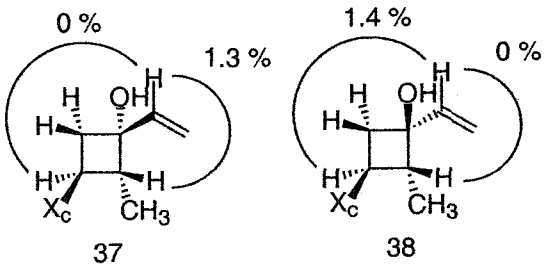
Scheme 13



was controlled primarily by steric interactions between the incoming nucleophile and the oxazolidinone and methyl group of cyclobutanone **36**. The large oxazolidinone group would block the top face of the molecule directing attack from the bottom. The smaller methyl group would block the bottom face of the molecule directing attack from the top, thus causing conflicting steric interactions. The larger oxazolidinone group would cause a larger steric interaction with the incoming nucleophile. The steric interactions of the incoming nucleophile with these two groups explains the poor 2:1 diastereoselectivity observed in the product 1-vinyl-1-cyclobutanols. The stereochemistry of 1-vinyl-1-cyclobutanols **37** and **38** was also established via NOE experiments (figure 2).

Figure 2
Observed NOE's of compounds **30** and **31**



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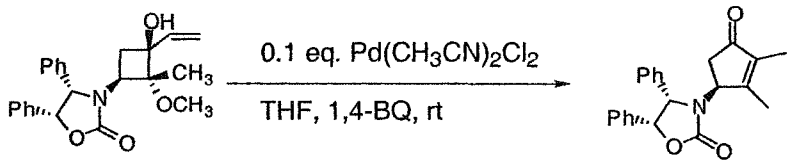
Treatment of 1-vinyl-1-cyclobutanol **31** with 10 mol % bis(acetonitrile) palladium (II) chloride, in THF as solvent, with 1.2 equivalents 1,4-benzoquinone produced a 68 % yield of cyclopentenone **39** (Equation 5). The

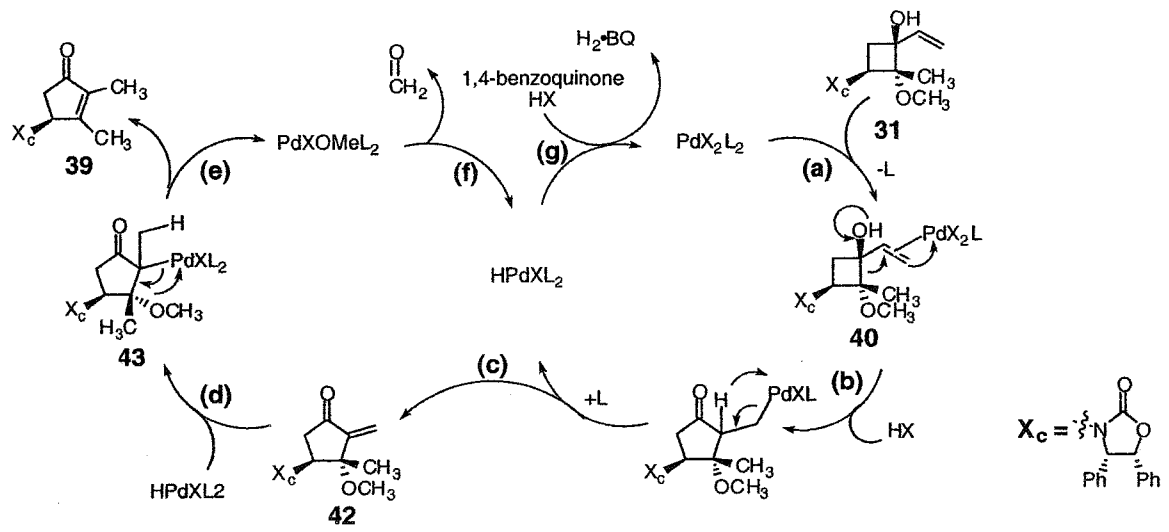


31 **39**, 68 % **eq. 5**

benzoquinone is required in this reaction as a hydride accepter to maintain the palladium (II) catalytic species which, during the reaction, forms a palladium (II) hydride species that can reductively eliminate HX to form palladium (0).

Removal of the methoxide moeity in the transformation of **31** to **39** represents the destruction of one of the stereocenters generated in the photoreaction, an undesired result. A possible catalytic cycle leading to this product is shown in scheme 14. The cycle begins with complexation of

Scheme 14



palladium (II) to the starting 1-vinyl-1-cyclobutanol **31** to give the palladium complex **40** (a). This complex then undergoes bond migration of the more

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substituted bond adjacent to the alcohol giving sigma-alkylpalladium complex **41** and losing a proton from the starting alcohol and a counter-ion from palladium (b). Complex **41** can undergo β-hydride elimination to give the initially-formed product alkylidenecyclopentanone **42**, and a palladium (II) hydride species (c). This palladium (II) hydride species can re-add to alkylidenecyclopentanone **42**, with opposite regioselectivity, to give the new sigma-alkylpalladium (II) species **43** (d). This can undergo β-alkoxide elimination to give the observed product, cyclopentenone **39**, and a palladium (II) methoxide species (e). The palladium (II) methoxide species can then undergo β-hydride elimination to give a palladium (II) hydride species and formaldehyde as a side product (f). Hydride abstraction from the palladium (II) hydride species by the quinone in the presence of the acid (HX) formed earlier, regenerates the palladium (II) catalyst and hydroquinone (g). Conditions to allow ring expansion with subsequent isolation of alkylidenecyclopentanone **42** were desired (essentially elimination of step d from the catalytic cycle), but not immediately forthcoming.

During related studies of the palladium (II)-catalyzed Wacker type chemistry of 1-vinyl-1-cyclobutanol **31**[27], it was observed that reaction of **24** with palladium (II) chloride, in a 10 % water/DMF mixture as solvent, resulted in a 32 % isolated yield of alkylidenecyclopentanone **42** as well as a 65 % yield of cyclopentenone **39**. The hydride abstraction from the initally-formed palladium (II) hydride species may be facilitated in solvents containing water, thus limiting the amount of palladium (II) hydride available to re-add to

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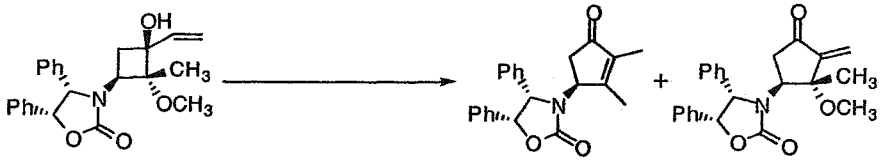
alkylidenecyclopentanone **42**. This unexpected result lead to attempts to control the re-addition of palladium hydride by use of mixtures of water/DMF as solvent. This resulted in up to a 55 % isolated yield of **42**. Next the catalyst was changed from palladium (II) chloride to palladium (II) acetate, to hopefully further limit the amount of re-addition of palladium (II) hydride. It was thought that the intermediate hydridopalladium (II) acetate species would not re-add as well as the hydridopalladium (II) chloride due to the decreased electrophilicity of palladium (II) acetate salts and stabilization of this intermadiate by the bidentate acetate ligand. With this new catalyst cyclopentenone **39** was no longer present in the crude reaction mixture, and in water/DMF solvent systems it was possible to isolate up to 54 % yield of alkylidenecyclopentanone **42**, with no cyclopentenone **39** detected. When a 10 % water/THF system was used as solvent a 72 % yield of **42** was isolated (Table 2). These conditions, however,

Table 2[a]



31 **39** **42**

Catalyst	Mol %	Solvent	39	42	(% yield)[b]
$(MeCN)_2PdCl_2$	10	THF	68	0	
$PdCl_2$	10	10 % H_2O/DMF	65	32	
$PdCl_2$	10	33 % H_2O/DMF	40	55	
$Pd(OAc)_2$	25	12 % H_2O/DMF	0	54	
$Pd(OAc)_2$	25	20 % H_2O/THF	0	43	
$Pd(OAc)_2$	25	10 % H_2O/THF	0	72	

[a] Allreactions were carried out at rt, using 1.2 eq. 1,4-benzoquinone as a reoxidant for pallaidium, [b] yields are for isolated purified products.

required the use of 25 mol % palladium acetate catalyst, representing only 4 turnovers for the catalytic species. Attempts to lower the catalyst loading

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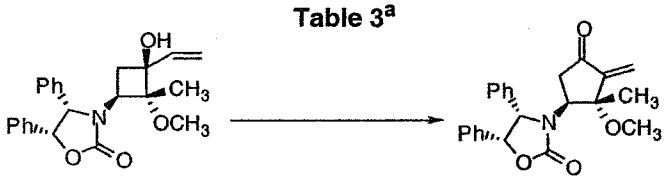
resulted in incomplete reaction. Thus, although re-addition of the palladium (II) species no longer seemed to be the problem, regeneration of the catalyst by hydride abstraction was not taking place at a reasonable rate. In order for the reaction to go to completion water had to be used as co-solvent and 25 mol % had to be employed catalyst. Because of this use of other, stronger, hydride acceptors was investigated.

Substitution of electron-withdrawing groups on 1,4-benzoquinones increases the oxidation potential of those quinones and oxidation potential of quinones has been correlated to rate, and ability, of hydride abstraction.[28] Several electronegatively-substituted, 1,4-benzoquinones were employed as hydride-accepting agents in this reaction (Table 3). 2,3-Dichloro- 5,6-

Table 3[a]



31 **42**

Mol %	Quinone	yield (**42**)[b]
10	1,4-benzoquinone	< 10
10	chloranil	< 10
10	bromanil	< 50
25	DDQ	62
05	DDQ	67

[a] All reactions were carried out at rt using $Pd(OAc)_2$ as catalyst, in THF as solvent, at rt, and with 1.2 eq. quinone, [b] yields are for isolated purified products.

dicyanobenzoquinone (DDQ) was best able to regenerate the catalytic species of any of the quinones tried. Even with 5 mol % catalyst the reaction was complete overnight and the yield of **42** was comparable to any of the other systems employed (*vide supra*).

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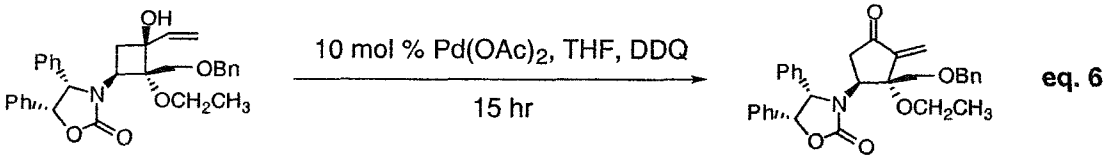
Once conditions for the palladium(II)-catalyzed oxidative ring expansion of vinylcyclobutanol **31** to alkylidenecyclopentanone **42** were developed, application of this reaction to the ring expansion of the other vinyl cyclobutanones was undertaken. Treatment of vinylcyclobutanone **34** under the same conditions as above resulted in an 89 % yield of alkylidenecyclopentanone **43** (Equation 6). The reaction of 1-



34 **43**, 89 % **eq. 6**

vinyl-1-cyclobutanol **35**, with a tertiary carbon on the non-migrating carbon and no oxazolidinone group, was not as facile. Reaction in THF took several days to complete and yields of alkylidenecyclopentanone were < 50 %. The solvent was changed to methylene chloride resulting in a somewhat improved rate of reaction. The reaction however, was still slow to go to completion, taking several days, and resulting in only up to 48 % yield of alkylidenecyclopentanone **44** with small(< 10 %) amounts of starting material also recoveredBy stopping the reaction after only nineteen hours, the yield of alkylidenecyclopentanone **44** was increased to 64 %, with 30 % recovered starting material, suggesting that the product was slowly decomposing under the reaction conditions. This corresponds to 90 % yield of **44** based on consumed starting material (Equation 7). Lastly, reduced vinylcyclobutanol **37**, with a hydrogen replacing

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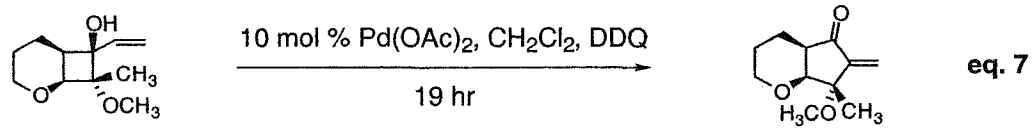
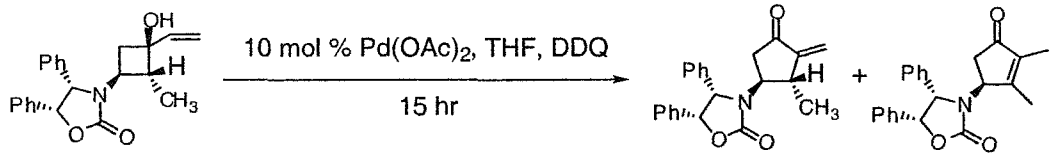


35 **44**, 63 % + 30 % recov'd **35** **eq. 7**

the α-methoxy group, was ring expanded under the developed conditions. This reaction gave 34 % of alkylidenecyclopentanone **45** and 51 % of cyclopentenone **39** (Equation 8). Although the yield of methylene



37 **45**, 34 % **39**, 51 % **eq. 8**

cyclopentanone **45** was low for this reaction, it represents a significant improvement over the maximum yield of alkylidenecyclopentanones obtained in previous studies of this reaction on substrates containing hydrogen on the migrating carbon.

In an attempt to expand this reaction to include generation of six-membered rings from cyclobutanones, 1-allyl-1-cyclobutanol **46** was synthesized using allyl bromide and zinc, in the presence of ammonium chloride.[29] Treatment of 1-allyl-1-cyclobutanol **46** with palladium(II) acetate and palladium(II) chloride salts failed to change the starting material. Using tetrakis(acetonitrile)palladium(II) bis-tetrafluoroborate as catalyst, a highly electrophillic palladium(II) salt, none of the desired two-carbon homologated cyclohexenone product was formed. Instead a 95 % yield of the isomerized 1-propenyl-1-cyclobutanol **47** was isolated (Scheme 15). 1-Propenyl-1-

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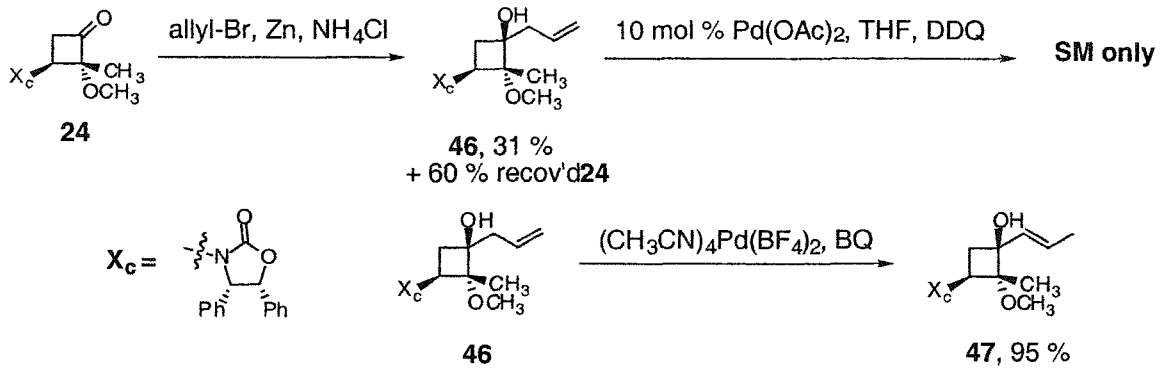
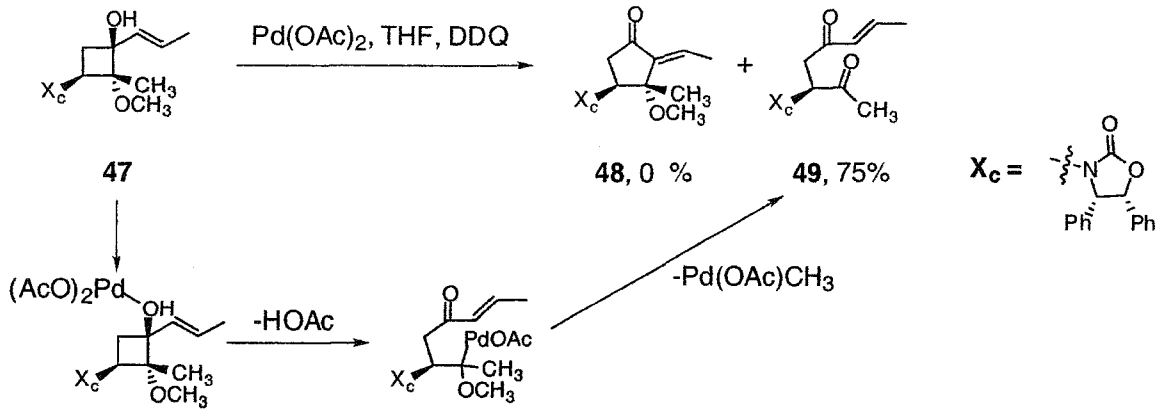
Scheme 15



cyclobutanol **47** was subjected to the oxidative ring expansion conditions described above. None of the homologated product **48** was formed. Only ring-opened diketone **41** was isolated from this reaction (Equation 9). Presumably this ring-opening reaction takes place via a ß-carbon elimination pathway.[30]

Scheme 15



An attempt to adapt Liebeskind's procedure for ring expansion of 1-alkynyl-1-cyclobutanones to the ring expansion of photolytically-generated cyclobutanones was made. 1-Alkynyl-1-cyclobutanone **50** was synthesized from cyclobutanone **24** in 54 % yield over two steps (Equation 10). This was

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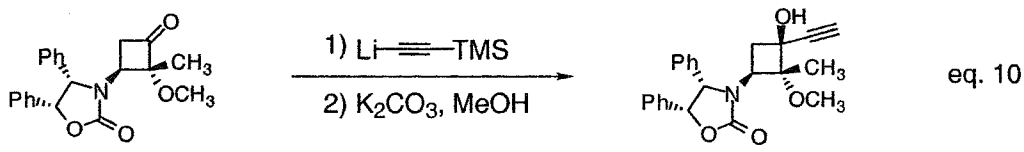
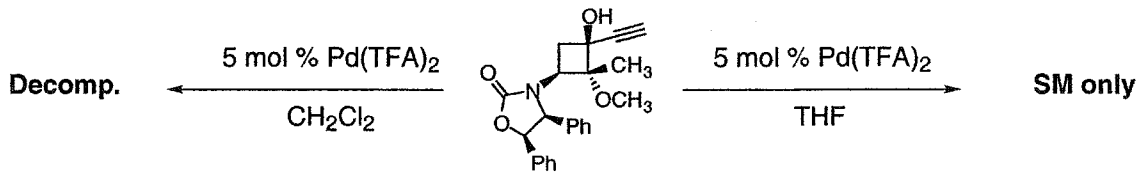


eq. 10

24 **50**, 54%

subjected to the reaction conditions conditions utilized by Liebeskind. Only decomposition of **50** was observed. The solvent was changed from methylene chloride to THF, to try and reduce the electrophilicity of the palladium catalyst by coordination to the solvent. Under these conditions the reaction failed, resulting only in unchanged starting material (Scheme 16).

Scheme 16



50

Conclusion

The primary aim of this project, extension of the palladium(II) catalyzed ring expansion of 1-vinyl-1-cyclobutanols to include ring expansion of α-alkoxy-1-vinyl-1-cyclobutanols **31**, **34**, and **35** to alkylidenecyclpentanones, has been achieved. This process is simple and high yielding, requiring only 2 steps from the corresponding photolytically-generated cyclobutanone, generating the corresponding alkylidenecyclopentanones **42**, **43**, and **44**. Extension of this reaction to include 1-vinyl-1-cyclobutanol **37** with an α-hydrogen, met with limited success, producing mostly the rearranged cyclopentenone **39**.

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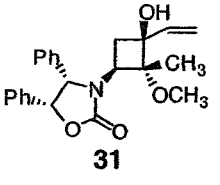
However, a significant amount of the desired alkylidenecyclopentanone product **45** was isolated from this reaction.

Experimental

General: THF was distilled from sodium-benzophenone ketyl, and CH_2Cl_2 was distilled from CaH_2. Commercially available reagents were used as received except as indicated. ^1H NMR (JS-300, 300 MHz), ^{13}C NMR (JS-300, 75 MHz) and (Inova 400,100 MHz), and NOE (Inova 400, 100 MHz) spectra were recorded in $CDCl_3$ unless otherwise noted. Proton chemical shifts are given in ppm relative to $CHCl_3$ (7.27 ppm) and carbon shifts are relative to CD Cl_3 (77.23 ppm). IR spectroscopy was done on a Perkin-Elmer 1600 series FTIR. Column chromatography was performed with ICN 32-66 nm, 60 Å silica gel using flash column techniques unless otherwise noted. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ. All reactions were performed under an atmosphere of argon unless otherwise noted. Cyclobutanones **24**[24a], **33**[24a], **34**[16a], and **36**[24a] were prepared by literature procedures.



31

Addition of vinyl Grignard reagent to cyclobutanone 24, synthesis of 1-vinyl-1-cyclobutanol 31: To a chilled solution of cyclobutanone **24** (500 mg, 1.42 mmol) in THF (0.1 M,14 mL), at -78 °C, was added a 1 M solution of vinylmagnesium bromide (4.2 mL). The solution was allowed to warm to -40 °C over 1.5 and to remain at -40 to -

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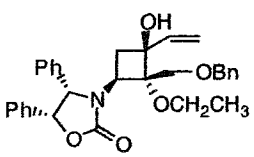
30 °C for 1-2 , until no starting material remained. It was then allowed to warm to rt. After quenching with sat. NH_4Cl (25 mL) the crude mixture was partitioned between ether (50 mL) and water (20 mL). The layers were separated and the aqueous layer was extracted with ether (50 mL). The combined organic layer was washed with water (30 mL) then brine(30 mL) , dried over magnesium sulfate, filtered, and the solvent was removed under reduced pressure. Purification on silica gel (2% methanol in chloroform) gave 1-vinyl-1-cyclobutanol **31** (750 mg, 87%) as a white solid.

IR (nujol): 1747 (CO) cm^{-1}.

^1H NMR δ: 10 (m, 6H), 6.98 (m, 2H), 6.78 (m, 2H), 6.28 (dd, J_1=11.1, J_2=17.1, 1H), 5.87 (d, J=7.2, 1H), 5.27 (dd, J_1=0.9, J_2=17.4, 1H), 5.19 (dd, J_1=0.6, J_2=11.1, 1H), 5.05 (d, J=7.5, 1H), 4.23 (dd, J_1=9.6, J_2=10.8, 1H), 3.33 (S, 3H), 1.80 (s, 1H, -OH), 1.76 (dd, J_1=9.6, J_2=12.3, 1H), 1.58 (dd, J_1=10.8, J_2=12.3, 1H), 1.50 (s, 3H).

^{13}C NMR (75 MHz) δ: 158.2, 139.3, 135.8, 133.8, 128.5, 128.4, 128.3, 128.0, 127.0, 126.3, 112.8, 87.7, 80.5, 75.8, 65.3, 51.7, 51.5, 35.0, 12.8.

Elemental Analysis, for $C_{23}H_{25}NO_4$, (calc.) C 72.80, H 6.64, N 3.69, (found) C 72.94, H 6.56, N 3.78.



34

1-Vinyl-1-cyclobutanol 34: Following the above procedure, treatment of cyclobutanone **32** (200 mg, 0.425 mmol) with vinylmagnesium bromide (1.3 mL, 1.3 mmol). Purification

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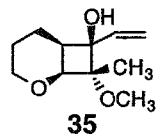
on silica gel (2% EtOAc in CH_2Cl_2) gave 1-vinyl-1-cyclobutanol **34** (115 mg, 54 %) as a white solid.

IR (thin film): 1751 (CO) cm^{-1}

^1H NMR δ: 7.48 (m, 5H), 7.04 (m, 6H), 6.83 (m, 2H), 6.57 (m, 2H), 6.1 (dd, J_1=10.5, J_2=16.8, 1H), 5.59 (d, J=7.5, 1H), 5.33 (dd, J_1=1.5, J_2=17.4, 1H), 5.15 (dd, J_1=1.5, J_2=10.5, 1H), 5.01 (d, J=7.5, 1H), 4.81 (d, J=11.4, 1H), 4.68 (d, J=11.1, 1H), 4.31 (t, J=10.5, 1H), 4.09 (dd, J_1=1.8, J_2=9.9, 2H), 3.75 (m, 1H), 3.55 (m, 1H), 3.43, (s, 1H, -OH), 1.73 (m, 2H), 1.20 (t, J=6.9, 3H).

^{13}C NMR (100 MHz) δ: 158.5, 138.3, 137.0, 136.2, 133.9, 129.2, 128.9, 128.5, 128.3, 128.2, 128.1, 128.0, 126.9, 126.3, 113.1, 88.0, 80.5, 76.1, 74.8, 68.9, 64.9, 60.6, 50.7, 36.9, 16.2.

Elemental analysis, for $C_{31}H_{33}NO_5$, (calc.) C 74.53, H 6.66, N 2.80, (found) C 74.34, H 6.72, N 2.81.



35

1-Vinyl-1-cyclobutanol 35: Following the above procedure, treatment of cyclobutanone **33** (250 mg, 1.47 mmol) with vinylmagnesium bromide (4.4 mL, 4.4 mmol). Purification on silica gel (25% EtOAc in hexanes) gave 1-vinyl-1-cyclobutanol **35** (245 mg, 84 %) as a white solid.

IR (thin film): 2935 (CO) cm^{-1}.

^1H NMR δ: 6.06 (dd, J_1=10.8, J_2=17.4, 1H), 5.3 (dd, J_1=1.2, J_2=17.4, 1H), 5.15 (dd, J_1=1.5, J_2=10.8, 1H), 3.99 (d, J=6.6, 1H), 3.89 (dt, J_1=11.4, J_2=6.0, 1H), 3.42

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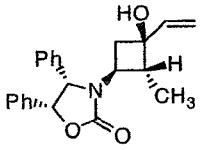
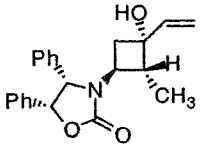
(m, 1H), 3.23 (s, 3H), 2.50 (m, 1H), 2.19 (s, 1H, -OH), 1.86-1.79 (m, 2H), 1.70 (m, 1H), 1.64-1.47 (m, 1H), 1.30 (s, 3H).

^{13}C NMR (75 MHz) δ: 139.4, 112.9, 87.2, 80.6, 73.5, 64.4, 51.2, 38.2, 22.6, 17.2, 11.6.

Elemental analysis, for $C_{11}H_{18}O_3$, (calc.) C 66.64, H 9.15, (found) C 66.62, H 9.17.



37



38

1-Vinyl-1-cyclobutanols 37 & 38: Following the above procedure, treatment of cyclobutanone **36** (150 mg, 0.47 mmol) with vinylmagnesium bromide (1.4 mL, 1.4 mmol). Purification on a Chromatotron, model 7924, 1 mm silica/gypsum plate, (8:1.5:1 Hexanes:CH_2Cl_2:EtOAc) gave 1-vinyl-1-cyclobutanol **37** (90 mg, 55 %) and 1-vinyl-1-cyclobutanol **38** (37 mg, 23 %) both as white solids.

1-Vinyl-1-cyclobutanol 37:

IR (thin film): 1736 (CO) cm^{-1}.

^1H NMR δ: 7.10 (m, 6H), 6.99 (m, 2H), 6.89 (m, 2H), 5.88 (m, 2H), 5.12 (dd, J_1=0.6, J_2=13.8, 1H), 5.02 (dd, J_1=0.9, J_2=8.7, 1H), 4.99 (d, J=6.0, 1H), 3.88 (q, J=6.6, 1H), 2.86 (dq, J_1=6.3, J_2=4.8, 1H), 2.22 (dd, J_1=6.9, J_2=8.7, 1H), 2.03 (dd, J_1=6.0, J_2=9.0, 1H), 0.95 (d, J=5.1, 3H).

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^{13}C NMR (100 MHz) δ: 157.7, 143.1, 135.8, 134.7, 128.9, 128.6, 128.5, 128.1, 127.8, 126.2, 112.7, 79.9, 77.7, 73.1, 65.3, 52.4, 44.8, 38.7, 11.3.

Elemental analysis, for $C_{22}H_{23}NO_3$, (calc.) C 75.62, H 6.63, N 4.01, (found) C 75.45, H 7.00, N 4.06.

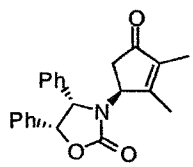
1-Vinyl-1-cyclobutanol 38:

IR (thin film): 1735 (CO) cm^{-1}.

^1H NMR δ: 7.11 (m, 6H), 7.00 (m, 2H), 6.89 (m, 2H), 5.86 (m, 2H), 5.23 (m, 2H), 5.07 (d, J=8.1, 1H), 3.47 (q, J=8.7, 1H), 2.80 (dq, J_1=6.9, J_2=0.9, 1H), 2.30 (dd, J_1=8.7, J_2=12.3, 1H), 2.20 (s, 1H, -OH), 2.04 (dd, J_1=9.0, J_2=11.7, 1H), 0.97 (d, J=7.2, 3H).

^{13}C NMR (100 MHz) δ: 158.1, 138.6, 135.9, 134.4, 128.5, 128.2, 128.1, 127.6, 126.3, 114.3, 80.3, 72.2, 64.6, 49.4, 48.2, 39.6, 38.5, 13.7.

Elemental analysis, for $C_{22}H_{23}NO_3$, (calc.) C 75.62, H 6.63, N 4.01, (found) C 75.81, H 6.78, N 3.96.



39

Methyl cyclopentenone 39: To a stirred solution of 1-vinyl-1-cyclobutanol **31** (40 mg, 0.106 mmol) in THF (5 mL, 0.02 M) was added bis(acetonitrile) palladium(II) chloride (1.93 mg, 0.007 mmol) and BQ (22.9 mg, 0.212 mmol). The resulting yellow solution was stirred 14 h. at rt. Ether (25 mL) was added and the mixture was washed with 10 % sodium thiosulfate solution (2 x 10 mL) and water (2 x 10 mL). The

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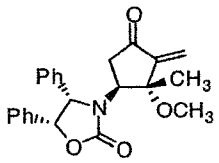
organic layer was dried over magnesium sulfate, filtered, and the solvent was removed under reduced pressure. Purification on silica gel (33 % EtOAc in hexanes) gave methyl cyclopentenone **39** (25.8 mg, 68 %) as a white solid.

IR (thin film): 1753 (CO) cm^{-1}.

^1H NMR δ: 7.15 (m, 6H), 6.99 (m, 2H), 6.85 (m, 2H), 5.86 (d, J=8.1, 1H), 4.93 (m, 1H), 4.73 (d, J=8.1, 1H), 2.47 (dd, J_1=7.2, J_2=18.6, 1H), 2.16 (s, 3H), 2.05 (dd, J_1=3.0, J_2=18.6, 1H), 1.77 (d, J=0.9, 3H)

^{13}C NMR (100 MHz) δ: 204.6, 164.6., 140.3, 135.2, 134.1, 129.0, 128.8, 128.3, 128.2, 126.1, 80.6, 77.4, 77.1, 63.4, 55.9, 38.4, 14.6, 8.5.

Elemental analysis, for $C_{22}H_{21}NO_3$, (calc.) C 76.06, H 6.09, N 4.03, (found) C 75.95, H 6.18, N 4.04.



42

Palladium(II) catalyzed ring expansion of 1-vinyl-1-cyclobutanol 31, synthesis of alkylidenecyclopentanone 42:

To a stirred solution of 1-vinyl-1-cyclobutanol **31** (50 mg, 0.13 mmol) in THF (0.05 M, 2.6 mL) was added palladium acetate (3.0 mg, 0.013 mmol) and DDQ (30 mg, 0.13 mmol). The resulting dark gold solution was stirred overnight (12-25 h.) at rt. The dark brown solution was filtered through a small plug of Celite rinsed with CH_2Cl_2 (30 mL) and the solvent was removed under reduced pressure. Purification on silica gel (5% EtOAc in CH_2Cl_2) gave alkylidenecyclopentanone **43** (33.4 mg, 67 %) as an off white solid.

IR (thin film): 1748 (CO) cm^{-1}.

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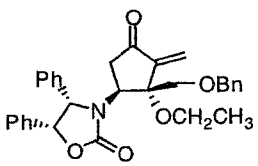
^{1}H NMR δ: 7.10 (m, 6H), 6.98 (m, 2H), 6.81 (m, 2H), 6.37 (s, 1H), 5.80 (d, J=7.2, 1H), 5.58 (s, 1H), 4.79 (dd, J_1=4.2, J_2=8.7, 1H), 4.70 (d, J=7.5, 1H), 3.16 (s, 3H), 2.56 (dd, J_1=8.7, J_2=19.2, 1H), 2.00 (dd, J_1=4.2, J_2=18.9, 1H), 1.58 (s, 3H).

^{13}C NMR (75 MHz) δ: 202.1, 158.5, 145.5, 135.4, 133.5, 128.9, 128.6, 128.2, 128.0. 127.4, 126.1, 126.0, 120.7, 116.3, 83.3, 80.7, 64.1, 56.2, 50.1, 39.5, 18.0.

Elemental analysis, for $C_{23}H_{23}NO_4$, (calc.) C 73.19, H 6.14, N 3.71, (found) C 73.13, H 6.02, N 3.80.



43

Alkylidenecyclopentanone 43: Following the above procedure, treatment of 1-vinyl-1-cyclobutanol **34** (50 mg, 0.10 mmol) in THF (0.05 M) with palladium(II) acetate (2.3 mg, 0.01 mmol) and DDQ (23 mg, 0.1 mmol). Purification on silica gel (2% EtOAc in CH_2Cl_2) gave alkylidenecyclopentanone **43** (44.6 mg, 89 %) as a white solid.

IR (thin film): 1754 (CO) cm^{-1}.

^{1}H NMR δ: 7.36 (m, 5H), 7.04 (m, 7H), 6.82 (m, 3H), 6.41 (s, 1H), 5.61 (d, J=7.2, 1H), 5.80 (s, 1H), 5.03 (t, J=9.9, 1H), 4.95 (d, J=7.5, 1H), 4.62 (d, J=11.7, 1H), 4.53 (d, J=11.7, 1H), 4.15 (d, J=9.0, 1H), 3.82 (dq, J_1=6.9, J_2=8.4, 1H), 3.62 (d, J=8.7, 1H), 3.37 (dq, J_1=6.9, J_2=8.4, 1H), 2.28 (dd, J_1=10.8, J_2=18.3, 1H), 2.12 (dd, J_1=9.0, J_2=18.0, 1H), 1.20 (t, J=6.9, 3H).

^{13}C NMR (100 MHz) δ: 200.4, 158.8, 144.7, 137.1, 136.2, 133.7, 129.0, 128.5, 128.4, 128.3, 128.1, 128.0, 126.3, 121.7, 84.5, 80.8, 75.2, 74.3, 63.8, 58.1, 52.5,

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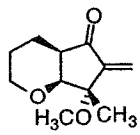
40.8, 15.8.

Elemental analysis, for $C_{31}H_{31}NO_5$, (calc.) C 74.83, H 6.28, N 2.81, (found) C 74.92, H 6.29, N 2.87.



44

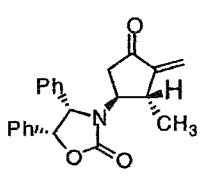
Alkylidenecyclopentanone 44: Following the above procedure, treatment of 1-vinyl-1-cyclobutanol **35** (50 mg, 0.25 mmol) in CH_2Cl_2 (0.05 M) with palladium(II) acetate (5.6 mg, 0.025 mmol) and DDQ (58 mg, 0.25 mmol). Purification on silica (17 % EtOAc in hexanes) gave alkylidenecyclopentanone **44** (31.7 mg, 64 %) as a colorless oil and starting 1-vinyl-1-cyclobutanol **35** (15.0 mg, 30 %: 90 % yield based on consumed starting material) as a white solid.

IR (thin film): 2923 (CO) cm^{-1}.

^1H NMR δ: 6.36 (s, 1H), 5.47 (s, 1H), 3.88 (d, J=4.2, 1H), 3.84 (m, 1H), 3.36 (m, 1H), 3.11 (s, 3H), 2.73 (m, 1H), 2.37 (m, 1H), 1.69 (m, 1H), 1.43 (s, 3H), 1.37 (m, 2H).

^{13}C NMR (75 MHz) δ: 205.4, 145.3, 120.6, 80.9, 80.5, 67.1, 49.9, 45.9, 22.5, 20.2, 14.6.

Elemental analysis, for $C_{11}H_{16}O_3$, (calc.) C 67.32, H 8.22, (found) C 67.18, H 8.39.



45

Alkylidenecyclopentanone 45: Following the above procedure,

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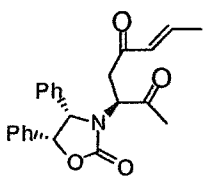
treatment of 1-vinyl-1-cyclobutanol **37** (30 mg, 0.09 mmol) in THF with palladium(II) acetate (1.9 mg, 0.009 mmol) and DDQ (20 mg, 0.09 mmol). Purification on silica gel (33% EtOAc in hexanes) gave alkylidenecyclopentanone **45** (10.1 mg, 34 %) and methyl cyclopentenone **39** (15.2 mg, 51 %) both as white solids.

IR (thin film): 1748 (CO) cm^{-1}.

^1H NMR δ: 7.11 (m, 6H), 7.01 (m, 2H), 6.91 (m, 2H), 6.08 (d, J=3.3, 1H), 5.89 (d, J=7.8, 1H), 5.31 (d, J=2.7, 1H), 5.02 (d, J=8.1, 1H), 4.01 (dt, J_1=7.8, J_2=11.1, 1H), 3.20 (m, 1H), 2.4 (dd, J_1=7.5, J_2=18.0, 1H), 2.10 (dd, J_1=11.1, J_2=18.0, 1H), 1.32 (d, J=6.6, 3H).

^{13}C NMR (100 MHz) δ: 201.8, 148.0, 135.3, 134.1, 129.0, 128.7, 128.6, 128.3, 128.2, 127.9, 126.2, 118.0, 80.6, 63.6, 56.6, 41.4, 40.0, 29.9, 16.2 (some impurities are visible in spectrum).

Elemental analysis, for $C_{22}H_{21}NO_3$, (calc.) C 76.06, H 6.09, N 4.03, (found) C 76.11, H 6.22, N 3.92.



49

Diketone 49: Following the above procedure, treatment of 1-propenyl-1-cyclobutanol **47** (10 mg, 0.026 mmol) in THF with palladium(II) acetate (0.6 mg, 0.0026 mmol) and DDQ (5.9 mg, 0.025 mmol). Purification on silica gel (25 % EtOAc in hexanes) gave diketone **49** (7.4 mg, 75 %) as a white solid.

IR (thin film): 1754 (CO) cm^{-1}.

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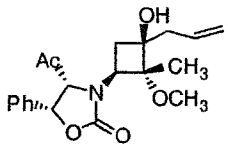
^{1}H NMR δ: 7.15 (m, 6H), 7.00 (m, 4H), 6.60 (dq, J_1=6.9, J_2=15.6, 1H), 5.93 (d, J8.4, 1H), 5.86 (dd, J_1=1.8, J_2=16.2, 1H), 5.13 (d, J=8.4, 1H), 4.60 (t, J=5.4, 1H), 3.11 (dd, J_1=5.4, J_2=18.0, 1H), 2.98 (dd, J_1=6.6, J_2=18.3, 1H), 2.25 (s, 3H), 1.79 (dd, J_1=1.8, J_2=7.2, 3H).

^{13}C NMR (100 MHz) δ: 203.9, 196.8, 158.2, 144.4, 135.1, 134.6, 131.1, 128.7, 128.5, 128.2, 128.1, 126.4, 126.1, 80.7, 64.7, 58.5, 38.9, 27.5, 18.5.



46

1-Allyl-1-cyclobutanol 46: Zinc (78.4 mg, 1.2 mmol), allyl bromide (104 μL, 1.2 mmol), and cyclobutanone **24** (350 mg, 1.0 mmol) were added to a flask containing THF (200 μL). Saturated aqueous ammonium chloride (1 mL) was added and the reaction was stirred for 20 minutes. The reaction mixture was partitioned between saturated aqueous ammonium chloride (10 mL) and CH_2Cl_2 (50 mL). The organic layer was separated and the aqueous layer was further extracted with CH_2Cl_2 (50 mL). The combined organic layer was dried over magnesium sulfate, filtered, and the solvent was removed under reduced pressure. Purification on silica gel (25 % EtOAc in hexanes) gave 1-allyl-1-cyclobutanol **46** (121 mg, 31 %) and recovered cyclobutanone **24** (238 mg, 60 %) both as white solids.

IR (thin film): 1742 (CO) cm^{-1}.

^{1}H NMR δ: 7.10 (m, 6H), 6.97 (m, 2H), 6.76 (m, 2H), 5.85 (d, J=7.2, 1H), 5.84 (m, 1H), 5.14 (m, 2H), 5.02 (d, J=7.2, 1H), 4.16 (t, J=9.9, 1H), 3.40 (s, 3H), 2.51

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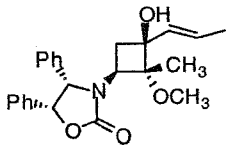
(dd, J_1=7.2, J_2=13.5, 1H), 2.28 (dd, J_1=7.8, J_2=13.8, 1H), 1.93, (s, 1H, -OH), 1.67 (dd, J_1=9.6, J_2=12.3, 1H), 1.45 (s, 3H), 1.39 (dd, J_1=12.0, J_2=10.8, 1H).

^{13}C NMR (100 MHz) δ: 136.0, 133.8, 133.7, 128.6, 128.4, 128.3, 128.2, 128.1, 126.4, 120.4, 87.1, 80.6, 73.9, 65.3, 51.8, 51.4, 40.4, 34.1, 13.0.



47

1-Propenyl-1-cyclobutanol 47: To a stirred solution of 1-allyl-1-cyclobutanol **46** (40 mg, 1.0 mmol) in THF (5.0 mL) was added tetrakis(acetonitrile)palladium(II) bis-tetrafluoroborate (4.8 mg, 0.007 mmol), and BQ (22 mg, 0.20 mmol). The resulting yellow solution was stirred 17 h at rt. Ether (25 mL) was added and the resulting solution was washed with 10 % aqueous sodium thiosulfate (2 x 10 mL) and water (2 x 10 mL). The organic layer was dried with magnesium sulfate, filtered, and the solvent was removed under reduced pressure. Purification on silica gel (50 % EtOAc in hexanes) gave 1-propenyl-1-cyclobutanol **47** (37.9 mg, 95 %) as a white solid.

IR (thin film): 1740 (CO) cm^{-1}.

^{1}H NMR δ: 7.10 (m, 6H), 6.98 (m, 2H), 6.78 (m, 2H), 5.88 (m, 2H), 5.69 (dq, J_1=6.3, J_2=15.9, 1H), 5.04 (d, J=7.2, 1H), 4.17 (dd, J_1=7.2, J_2=10.8, 1H), 3.34 (s, 3H), 1.75 (m, 4H), 1.55 (d, J=10.2, 1H), 1.48 (s, 3H).

^{13}C NMR (100 MHz) δ: 158.3, 136.0, 133.9, 132.0, 128.6, 128.4, 128.3, 128.1, 127.1, 126.4, 124.7, 87.5, 80.5, 75.3, 65.3, 51.7, 51.4, 35.2, 18.1, 12.8.

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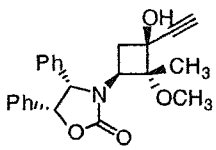

50

1-Alkynyl-1-cyclobutanone 50: To a stirred solution of cyclobutanone **24** (250 mg, 0.71 mmol) in THF (14 mL, 0.05 M) at -78°C was added lithium trimethylsilyl acetylide (1.7 mL of a 0.5 M solution in hexanes, 0.85 mmol). The reaction was then allowed to warm to room temperature. At 3 h Thin layer Chromatography showed no starting material remaining and the reaction was quenched by addition of saturated aqueous ammonium chloride solution (5 mL). Water (5 mL) was added and the reaction was extracted with 25 % methylene chloride in diethyl ether (2 x 50 mL). The combined organic layer was washed with brine, dried over magnesium sulfate, filtered, and the solvent was removed under reduced pressure. The crude product was dissloved in methanol (30 mL, 0.025 M), cooled to 0°C, and potassium carbonate (50 mg, 0.36 mmol) was added. The reaction mixture was allowed to warm to rt and stirred for 15 h, at which time the methanol was removed under reduced pressure. The residue was dissolved in methylene chloride (50 mL) and washed with saturated aqueous sodium bicarbonate solution (30 mL). The organic layer was washed with brine, dried over magnesium sulfate, filtered, and the solvent was removed under reduced pressure. Purification on silica gel (20 % ethyl acetate in mehylene chloride) to gave 1-alkynyl-1-cyclobutanone **50** (145 mg, 54 %) as a white solid.

IR (thin film): (CO) cm^{-1}.

^1H NMR δ: 7.51 (m, 6H), 6.97 (m, 2H), 6.78 (m, 2H), 5.86 (d, J=7.5, 1H), 5.05 (d, J=7.2, 1H), 4.32 (dd, J_1=9.1, J_2=10.5, 1H), 3.46 (s, 3H), 2.63 (s, 1H), 2.20 (s,

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1H), 2.03 (dd, J_1=9, J_2=11.7, 1H), 1.63 (dd, J_1=11.1, J_2=22.8, 1H), 1.47 (s, 3H).

^{13}C NMR (100 MHz) δ: 135.7, 133.8, 128.6, 128.5, 128.3, 128.1, 127.0, 126.3, 87.6, 80.5, 75.5, 69.8, 65.4, 52.1, 51.6, 36.8, 12.3.

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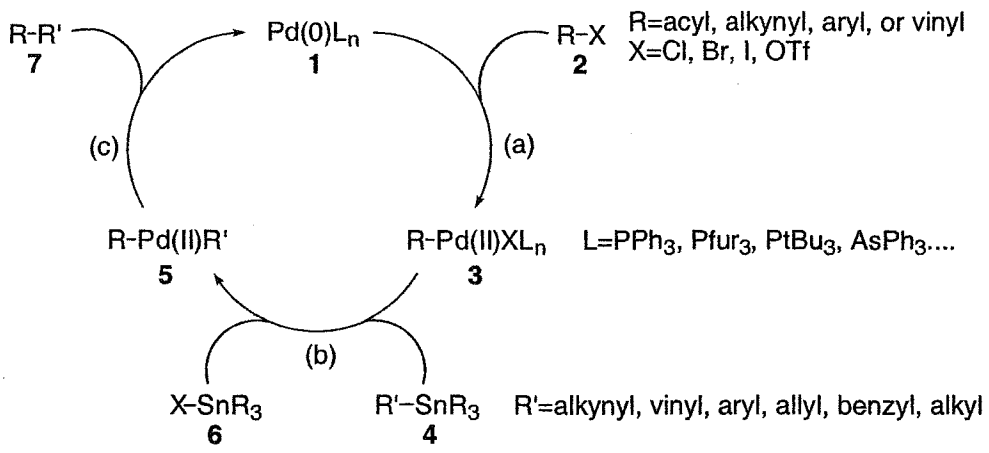
Chapter 2: Synthesis and Coupling of α-Heteroatom Stannyl- and Silyl- Reagents

Introduction

The palladium(0)-catalyzed coupling reactions of organostannanes (Stille Coupling)[31] and organosilanes (Hiyama Coupling)[32] are powerful methodologies in organic synthesis. Stille coupling, in particular, has been used in the total synthesis of many natural products.[31, 33] Stille coupling has been known since the late 1970's.[31] The reaction allows for the palladium catalyzed cross-coupling of organic halide or triflate electrophiles with tin nucleophiles. The catalytic cycle for this reaction is shown below (Scheme 1).

Scheme 1



The reaction proceeds by oxidative addition of the palladium(0) to the organic halide or triflate to give a mono-organopalladium(II) species **3** (a). Fast β-hydride elimination from palladium(II) sigma-alkyl compounds generally

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precludes the use of alkylhalides and triflates with β-hydrogens as electrophiles with the exception of acylhalides, which do not generally undergo β-hydride elimination. Oxidative addition is followed by transmetallation (which is usually the rate determining step of the sequence) from the tin reagent **4** to palladium to give a di-organopalladium (II) species **5** and a tin-halide or triflate by-product **6** (b). Typically organotrimethyl or tributyltin compounds are employed in this reaction and the rate of transmetallation from tin is: alkynyl > vinyl > aryl > allyl / benzyl >> alkyl / substituted alkyl. Alkyl groups have a very slow rate of transfer from tin, which generally precludes them from use in this reaction. Several exceptions to this exist, which will be discussed later. Lastly, the product is formed by reductive elimination of the organic groups from palladium (c) to give the cross-coupled product **7** and regenerate the palladium(0) species **1**. Highly polar solvents such as tetrahydrofuran (THF), dimethylsulfoxide (DMSO), N,N-dimethylformamide (DMF), or N-methylpyrrolidine (NMP) are typically used for this reaction, although many solvents will work.[31] Stille coupling generally proceeds without the need for activation of the organostannane reagent. However in some cases addition of cuprous chloride[34] or lithium chloride,[35] to promote the transmetallation (b) from tin to palladium is needed. The choice of ligand for palladium also influences the rate of transmetallation, with less-powerful sigma-donors leading to more facile transmetallation.[33,& 35]

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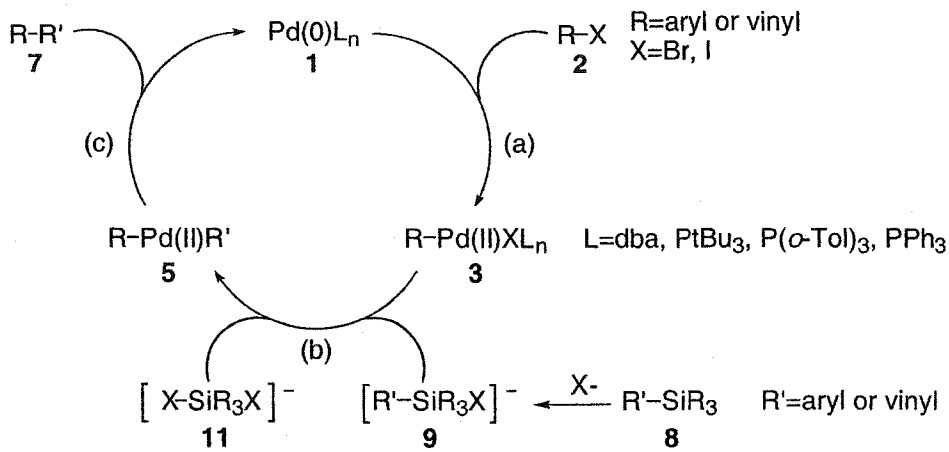
Hiyama coupling is a newer reaction than Stille coupling and the scope of this reaction has not yet been fully investigated. The transmetallation step in Hiyama coupling requires activation of the organosilane (Scheme 2, **8** -> **9**),

Scheme 2



making it less efficient than the Stille reaction. Typically fluoride ion has been used to activate the silane,[32, 36] however several groups have found that formation of a hydroxy-silane (in situ formation works), followed by treatment with base will sufficiently activate the reagent.[37] Hiyama has shown that silver (I) oxide also can be used to activate silanols.[38] Despite the required activation, which may limit the amount of functionality that is tolerated by the reaction conditions, this reaction is still very appealing due to the relative non-toxicity of organosilanes compared to the highly-toxic tin reagents and by-products of the Stille reaction.

One problem with the Stille reaction is poor coupling of alkylstannanes and α-heteroatom-alkylstannanes. One method to effect this cross-coupling involves use of co-catalytic amounts of Cu(I) salts.[39] The copper is believed to facilitate transmetallation of the organic fragment from tin to palladium. This

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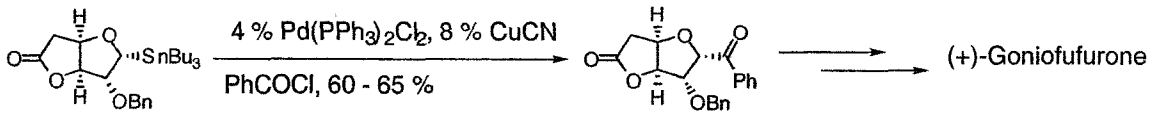
methodology has been studied by Falck and utilized in the total synthesis of (+)-goniofufurone.[40] The key transformation was coupling of the α-heteoatom stannane **12** with benzoyl chloride which led to fufurone **13**. This reaction proceeded with almost complete retention of configuration at the carbon center and the product **13** was taken on to the natural product in 2 steps (Scheme 3).[40b] Further studies into use of co-catalytic copper (I) salts in Stille reactions

Scheme 3



12 **13**

led to the postulate that palladium would not be required to accomplish coupling.[41] These studies have led to cross-coupling of organostannanes and aryl- and alkenyl iodides using only Cu(I) salts as catalyst,[42] Even copper(I) cyanide catalyzed coupling of α-heteroatom alkyl-tributylstannanes with various aryl- and allyl-halides and chlorothioformates, examples of which are shown below (Table 1).[43]

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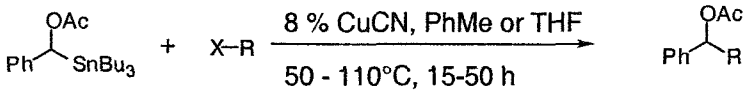
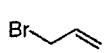
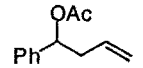
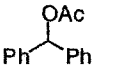
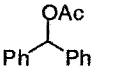
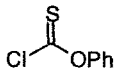
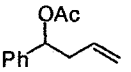
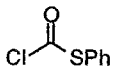
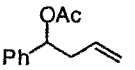
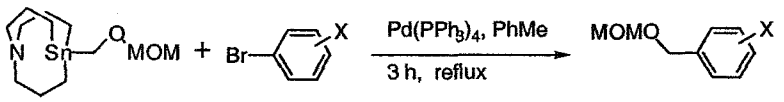
Table 1



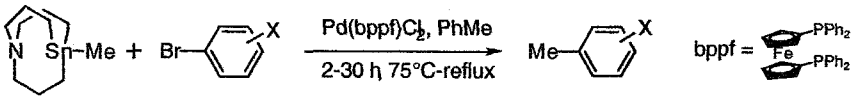
Halide	Sol., Temp, Time, Yield	Product
	THF, 65°C, 27 h, 80 %	
Br–Ph	PhMe, 110°C, 50 h, 20 %	
I–Ph	THF, 60°C, 48 h, 50 %	
	PhMe, 75°C, 15 h, 96 %	
	PhMe, 75°C, 21 h, 98 %	

Intermolecular coordination of nitrogen to tin has also been used to facilitate cross-coupling of alkyl and α-heteroatom substituted stannanes.[44] Vedejs first showed that internal coordination of the nitrogen of 1-aza-5-stannabicyclo[3.3.3]undecanes, also called carba-stannatranes or simply stannatranes, sufficiently activates generally unreactive organotin reagents to allow for transmetallation (Equation 1 and 2).[44a] The requisite organo-



eq. 1

X = *p*-OMe, 61 %; *p*-$N(CH_3)_2$, 63 %; *m*-NO_2, 80 %



eq. 2

X = *p*-OMe, 94 %; *p*-$N(CH_3)_2$, 56 %; *m*-NO_2, 93 %

stannatrane reagents can be synthesized via addition of alkyllithium reagents to chlorostannatrane **15** (Scheme 4). Synthesis of chlorostannatrane **15** can be accomplished via several different methods,[44a, 45] the simplest of which

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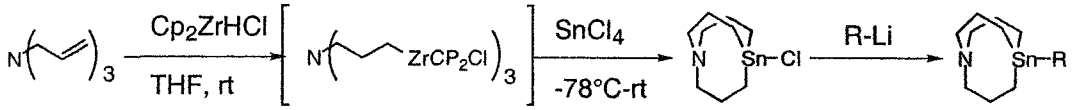
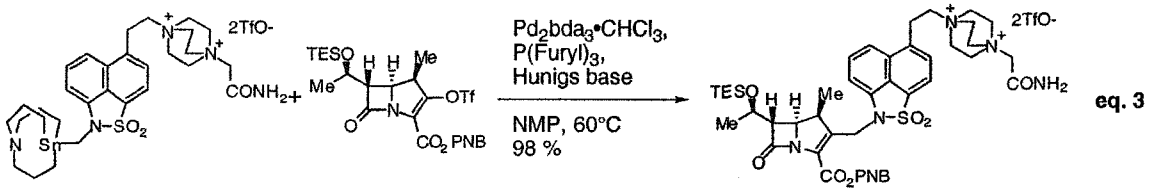
involves hydrozirconation of triallyl amine followed by addition to tin tetrachloride (Scheme 4).[44a] X-ray crystal structural analysis of chlorostannatrane **15** has

Scheme 4



15

shown short intermolecular distances between the nitrogen and tin, indicating some bonding interaction, and a 0.1 Å increase in the tin-chloride bond length.[46] In a recent application of this methodology, stannatrane **16** was coupled with vinyl triflate **17** to give β-lactam **18** in very high yield.[44b] B-lactam**18** was transformed, with one additional step, into a clinical candidate for treatment of drug-resistant bacterial strains, exemplifying the utility of this process (Equation 3). The stannatrane by-products from this reaction were



16 **17** **18** **eq. 3**

converted back to the chloride and recovered by a simple work up procedure.

Synthesis of stannane and silane reagents can be accomplished many ways.[47] The most utilized method involves addition of an active metal reagent to the corresponding stannyl or silyl halide reagent (Equation 4). The reverse of this reaction, addition of a silyl or stannyl metal reagent to an organic halide, also allows for the synthesis of silane and stannane reagents (Equation 5).

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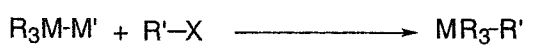
$R_3M\text{-}X + R'\text{–}M' \longrightarrow MR_3\text{-}R'$ **eq. 4**



$R_3M\text{-}M' + R'\text{–}X \longrightarrow MR_3\text{-}R'$ **eq. 5**

M=Si, Sn; R=Me, Bu, Ph ....; M'=Li, MgX....; R'=Aryl, Vinyl, Alkynyl, allyl, benzyl.....

These methods allow for the synthesis of many, diverse stannanes and silanes, dependant only on the availability of the tin or silicon reagents and the organic reagents. A second general way to synthesize organosilanes and stannanes is hydrometallation of carbon-carbon multiple bonds, either alkenes (Equation 6) or alkynes (Equation 7). This method, again, is limited primarily by

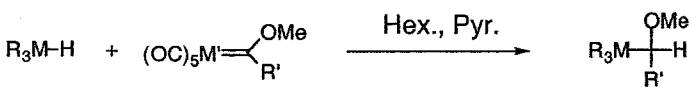
eq. 6

eq. 7

M=Si, Sn; R=Me, Bu, Ph ....

availability of the starting reagents.

An alternate method to synthesize organosilane and stannane reagents involves carbene insertion of heteroatom-stabilized chromium and tungsten carbene complexes into a metal-hydride bond. This reaction, first discovered by E. O. Fischer, involves the reaction of group IV metal (Si, Ge, Sn) hydride reagents **19** with chromium or tungsten carbene complexes **20** to give the α-heteroatom metal species **21** (Equation 8).[48] Many different carbene



19 **20** **21** **eq. 8**

R_3M= Et_3Si, Ph_3Si, Bu_3Sn, Ph_3Sn, Et_3Ge, Ph_3Ge; M'= Cr, W; R'= Aryl, Alkyl

fragments have been utilized in this reaction. Nakamura was first to show asymmetric induction in this reaction.[49] Using chiral alkyl groups on the

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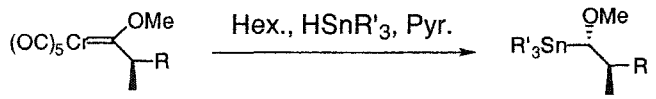
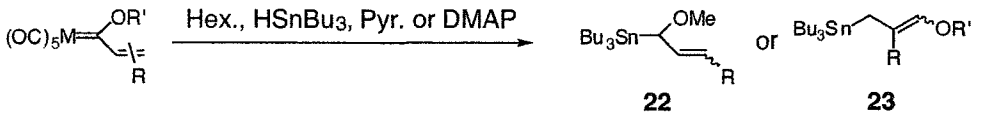
carbene fragment, in reactions with tributyltin- and triphenyltin hydride, from 77:23 to 93:7 diastereoselectivity was observed in the newly-formed chiral center of the stannane (Equation 9). Merlic has shown that both vinyl- and



eq. 9

R= Ph, iPr, CH(Ph)$SnBu_3$, CH(Ph)2-Cyclohexanone; R'= Bu, Ph
43 - 82 %, 77:23 - 93:7 ds

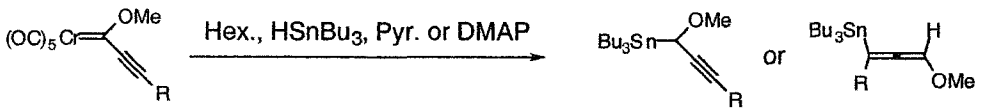
alkynylcarbene complexes react to give allyl and propargyl, and in some cases allenyl, products.[50] Products such as **22** arising from 1,1-addition to vinyl carbene complexes resulted in most cases, however several terminal olefins gave products of structure **23** resulting from 1,3-addition (Equation 10). The formation of propargyl or allenyl products also depends on the nature of the



22 **23**

eq. 10

starting alkynyl carbene complex. Large, bulky trialkylsilyl-substituted alkynes gave propargyl products **24**, whereas aryl- and vinyl-substituted alkynes gave allenyl products **25** (Equation 11). Due to unavailability, unsubstituted alkynyl



24 R= TMS, TIPS

25 R= aryl vinyl

eq. 11

carbene complexes were not used. Previous work in our group by John Masters focussed on development of improved conditions to effect this insertion reaction.[51] Under conditions previously reported certain carbene

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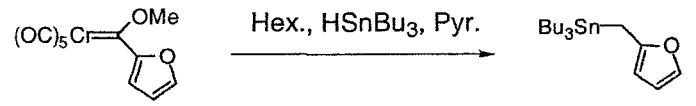
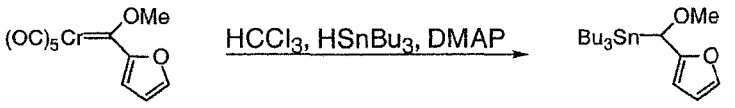
comlexes, such as furanocarbene **26**, would give stannanes such as **27**, without the alkoxy substituent (Equation 12). These products arise from



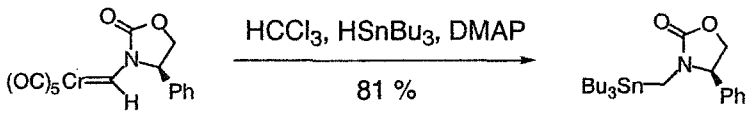
26 **27** **eq. 12**

reduction of the initally-formed α-methoxystannane by tributyltin hydride. It was found that reaction in chloroform with DMAP, to scavenge the chromium by-products, resulted in no observed reduction and a good yield of the desired stannane product **28** (Equation 13).[51] These conditions proved to be applicable

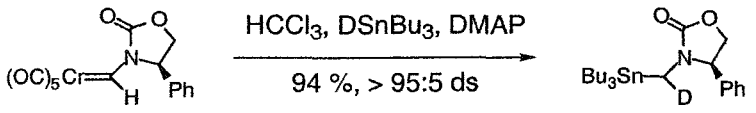


26 **28** **eq. 13**

to many carbene complexes, including hydrido(oxazolidinone) carbene complex **28**. This carbene complex, with a chiral center on the heteroatom substituent, underwent reaction with both tributyltin hydride and tributyltin deuteride to give the corresponding α-oxazolidinone stannanes **29** and **30** in excellent yield and, in the case of tributyltin deuteride, excellent (> 95:5) diastereoselectivity as well, although the absolute configuration was not determined (Equations 14 and 15).[51] Wulff has also worked with chiral



29 **30** **eq. 14**



29 **31** **eq. 15**

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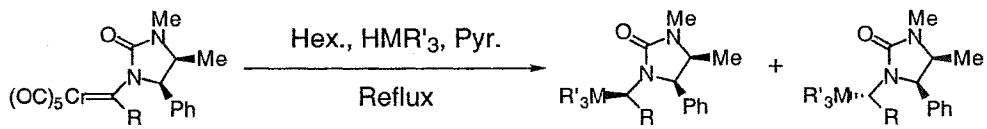
carbene complexes in this reaction.[52] He found that chiral imidazolidinone carbene complexes (**32**) reacted with tributyltin hydride, as well as several different silanes, to give the corresponding diastereomeric insertion products (**33a** and **b**) in good to high yield and with moderate to good diastereoselectivity (Table 2).

Table 2



32 **33a** **33b**

R	MR'_3	Yield	ds (**33a**:**33b**)
Ph	$SnBu_3$	52 %	> 98:2
Ph	$SiPh_3$	55 %	> 98:2
Ph	$SiPhMe_2$	66 %	67:33
Ph	$SiEt_3$	88 %	67:33
Styryl	$SiPh_3$	54 %	85:15
Styryl	$SiPhMe_2$	57 %	64:36
Styryl	$SiEt_3$	42 %	64:36

Use of these carbene-generated stannanes in coupling reactions has been investigated in this group, primarily by Katherine Dubuisson, and has met with limited success.[53] Coupling under standard Stille coupling conditions failed to provide any coupled product. Use of palladium (0) catalysis to cross-couple benzylic stannanes generated from aryl carbene complexes failed. Copper-catalyzed coupling of carbene complexes under the conditions described by Falck and co-workers resulted in only modest amounts of coupled products after extended reaction times at high temperature. Due to these lack-luster results this project was discontinued.

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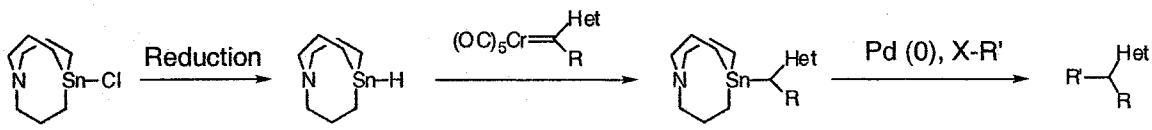
Rationale

Finding a general method for coupling of α-heteroatom stannanes produced via the insertion reaction discussed above would provide a significant addition to current Stille coupling methodology. Combination of the stannatrane coupling reaction of Vedejs (*vide supra*) with the carbene insertion reaction might provide that methodology. Reduction of stannatrane chloride **15** would give stannatrane hydride **34**. Reaction stannatrane hydride **34** with carbene complexes would lead to α-heteroatom stannatranes such as **35**. The internal coordination of the nitrogen of stannatrane hydride **34** may even increase the reactivity of this tin reagent in the insertion reaction. The new stannatranes produced in this manner should be limited only by availability of carbene complexes. As shown previously (*vide supra*), these stannatranes should then react with organic halides and triflates, with palladium catalysis, to give the corresponding cross-coupled products **36** (Scheme 5). Use of chiral

Scheme 5



15 **34** **35** **36**

carbene complexes in the insertion reaction leads to diastereoselective formation of products (*vide supra*). Use of a chiral oxazolidinone-containing carbene complex may lead to increased diastereoselectivity and yield in the insertion reaction. The chiral stannatranes thus formed could then be coupled to give chiral non-racemic products in highly diastereoselective fashion.

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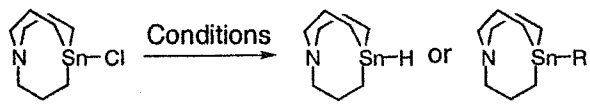
Results and Discussion

In order to use stannatrane hydride **34**, which has not been reported in the liturature, in carbene insertion reactions it must first be synthesized. Stannatrane chloride **15** was allowed to react with several different reducing agents and under a variety of conditions, all of which proved ineffective (Table 3). Use of sodium borohydride and lithium aluminum hydride, at

Table 3



15 **34** **37**, R = tBu; **38**, R = iBu; **39**, R = Et

Conditions	Result
LAH, Et_2O, 0°C - RT	SM
LAH, THF, 0°C - RT	SM
LAH, THF, reflux	SM
1) Li°, THF, RT, 2) H_2O	SM
1) Na°, THF, RT, 2) H_2O	SM
1) Na°, THF, reflux, 2) H_2O	SM
1) tBuLi, THF, -78°C, 2) H_2O	**37**
Dibal-H, THF, RT	**38**
LiHAlEt3, THF, RT	**39**

room temperature or reflux, resulted only in recovered starting material. Use of lithium or sodium metal, followed by protonolysis of the expected anion again resulted only in recovered stannatrane chloride **15**. Next, halogen-metal exchange with tert-butyllithium was attempted. This resulted in recovered starting material, with a small amount of the tert-butyl stannatrane **37**. This result was unexpected due to the hindered nature of both **15** and tert-butyllithium. Lastly, Dibal-H and lithium triethylaluminum hydride (super

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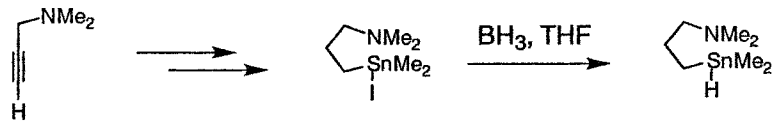
hydride) were tried. Amazingly, both of these reagents transferred an alkyl group to the stannatrane instead of a hydride, giving the isobutyl and ethyl stannatranes **38** and **39**. This inability to produce stannatrane hydride **34** is likely due to the internal coordination of the nitrogen to the tin. This could not only stabilize the stannatrane chloride, making it resistant to reduction, but also destabilize stannatrane hydride **34**, possibly to the point of spontaneous decomposition. This, combined with the lack of any references to this potentially interesting a tin hydride reagent in the literature led us to forego any further efforts to produce stannatrane hydride **34**.

The "mono-tethered" stannatrane hydride **41** is known.[54] This reagent can be prepared from reduction of the iodostannane **40**, which is itself made from 1-dimethylamino-2-propyne in 3 steps (Scheme 6).[54] Iodostannane **40**

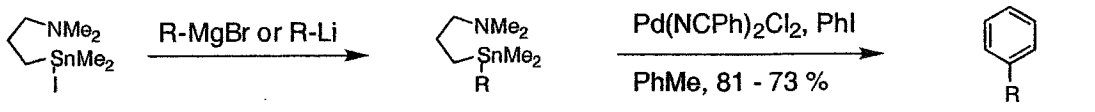
Scheme 6



40 **41**

reacts with aryl and alkynyl metal reagents to give the resulting aryl- or alkynyl-mono-tethered stannatrane compound **42**. These compounds have been shown to be very reactive tin reagents for Stille coupling reactions. The high reactivity of these compounds is postulated to be a result of internal coordination of the nitrogen and tin (Scheme 7).[54] Use of mono-tethered

Scheme 7



40 **42**, R = Ph, CCPh R = Ph, CCPh

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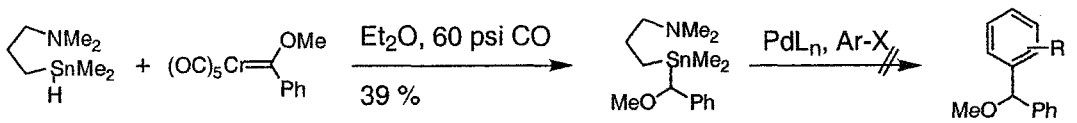
stannatrane hydride **41** for the carbene insertion reaction and Stille coupling reactions of the resulting α-heteroatom mono-tethered stannatranes was investigated. Tin iodide **41** reacted with the phenyl(methoxy) carbene complex to give the mono-tethered stannatrane **43**, albeit in modest 39 % yield. This stannatrane, however was found to be unreactive in coupling reactions run under conditions to promote transmetallation (Scheme 8).[35]

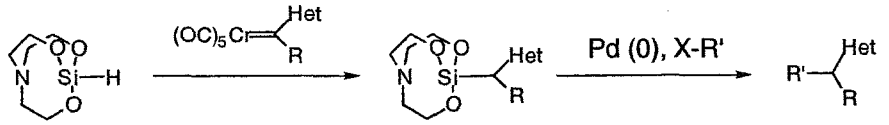
Scheme 8



41 **43**

Since synthesis of stannatrane hydride **34** failed, investigations into the use of known silatrane **44**[55] with similar aims, were undertaken. These silatranes have received some attention due to some interesting biological activity, including treatment of burns, wounds, and ulcers, anti-tumor activity, and intensification of hair growth.[56] Trialkoxysilanes are known to participate in Hiyama coupling reactions once activated by a nucleophile (*vide supra*). It was postulated that the nitrogen of α-heteroatom silatranes such as **45**, from the reaction of silatrane **44** and carbene complexes, might provide the necessary activation, thus allowing the coupling of carbon fragments from the carbene insertion reaction into group (IV) metal hydrides (Scheme 9).

Scheme 9



44 **45** **36**

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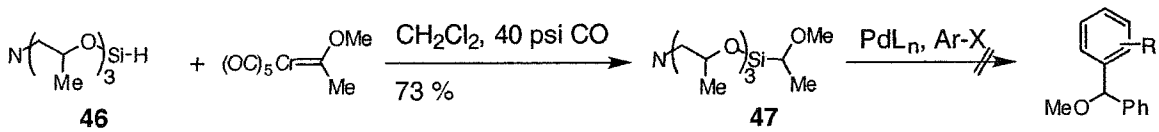
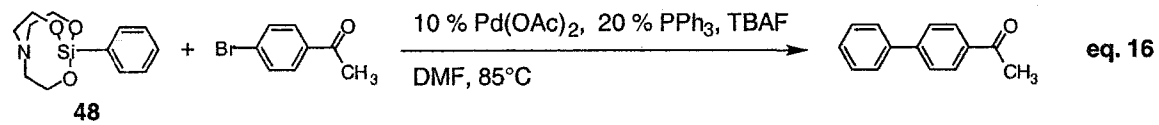
In order to test this, trimethylsilatrane **46**, which was chosen due to its in-house availability from the Maciel group, was allowed to react with the methyl(methoxy)carbene complex in methylene chloride under 40 psi of carbon monoxide, providing 1-methoxyethyl silatrane **47** in 73 % yield. Reaction of silatrane **47** with various aryl bromides and iodides under several different conditions failed to provide any coupled product, resulting only in recovered starting materials, even when fluoride was used to help activiate the silatrane (Scheme 10). Phenyl silatrane **48** was then synthesized,[57] to evaluate if the

Scheme 10



internal coordination of the nitrogen of this aryl silatrane would be sufficient to allow for coupling. Although many different conditons were investigated, this silatrane needed activation with tetrabutylammonium fluoride (TBAF) before coupling would occur (Equation 16). This result indicates internal



eq. 16

coordinationof the nitrogen of silatranes does not sufficiently activate them to obviate the need for additives and this aspect of the project was ended.

The insertion reaction of tin-carbon bonds into carbene complexes has not been reported. Presumably this is due to the relative non-reactivity of tin-carbon bonds compared to tin-hydrogen bonds. The organostannatranes might activate the organo group opposite the nitrogen sufficiently to allow for its

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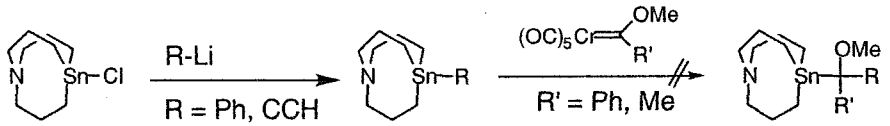
selective insertion into carbene complexes to give the new stannatranes **50**. Phenyl and alkynyl stannatrane **49** were synthesized via the corresponding lithium reagents and chlorostannatrane **15** to test this. These stannatranes however, both failed to react with either of the carbene complexes tried, resulting only in recovered stannatrane and decomposed carbene complex (Scheme 11).

Scheme 11



15 **45** **50**

Conclusion

Synthesis of stannatrane hydride **34** could not be accomplished, although a variety of methods and conditions were utilized, and use of this stannatrane in carbene insertion reactions could not be investigated. Attempts to take advantage of the increased reactivity of stannatrane compounds, via use of propargyl- and aryl-stannatranes **45** in carbene insertion reactions, resulted in no formation of the desired stannatrane products. The "mono-tethered" stannatrane **41**, which is known,[56] did undergo insertion into tin-hydride bonds to give the corresponding stannatrane **43**. Stannatrane **43**, however, did not undergo coupling under all conditions tried. Lastly, while silatrane **46** reacted with carbene complexes to give the corresponding insertion product, these products were also inert in coupling reactions. Due to this lack of positive results this project was ended. However, the carbene insertion reaction into

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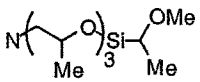
group(IV) metal hydrides was investigated for use in other processes (*vide infra*).

Experimental

General: CH_2Cl_2 was distilled from CaH_2. Commercially available reagents were used as received except as indicated. ^1H NMR (JS-300, 300 MHz), ^{13}C NMR (JS-300, 75 MHz) and (Inova 400,100 MHz), and NOE (Inova 400, 100 MHz) spectra were recorded in $CDCl_3$ unless otherwise noted. Proton chemical shifts are given in ppm relative to $CHCl_3$ (7.27 ppm) and carbon shifts are relative to CD Cl_3 (77.23 ppm). Column chromatography was performed with ICN 32-66 nm, 60 Å silica gel using flash column techniques unless otherwise noted. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ.



47

Methyl-methoxy trimethylsilatrane 47: A solution of methyl-methoxy carbene complex (110 mg, .44 mmol) and trimethylsilatrane 15 (67.6 mg, .4 mmol) in methylene chloride were mixed in an ace glass pressure tube with a stir bar under argon. This solution was then degassed, via vaccuum to argon method, five times. This solution was then flushed with 40 psi CO five times then pressurized to 40 psi. The resulting solution was then heated to 85°C behind a blast shield and stirred at that temperature overnight. After approximately 20 h of stirring the CO is vented

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in a fume hood, the solution was transferred to a rb flask, and the solvent was removed under reduced pressure. The chromium hexacarbonyl was removed by sublimation at 50°C under reduced pressure. The resulting green solid was purified via column chromatography on alumina (25 g) eluting with 1:1 hexanes:ethyl acetate. The fractions that stained with phosphomolybdic acid were collected and the solvent removed under reduced pressure to give methyl-methoxy trimethylsilatrane **47** (66.4 mg, 73 %) as a crystalline solid.

^{1}H NMR δ: 3.92 (m, 3 H), 3.37 (d, j=0.9 Hz, 3 H), 2.80 (dd, J_1=3.9 Hz, J_2=12 Hz, 3 H), 2.25 (t, J=12 Hz, 3 H), 1. (q, J=8.7 Hz, 1 H), 1.25 (d, J=7.5 Hz, 3 H), 1.19 (d, J=5.7 Hz, 9 H).

^{13}C NMR (100 MHz) δ: 72.3, 63.4 (d1), 63.3 (d2), 59.2 (d1), 59.1 (d2), 58.3, 20.7, 16.5 (d1), 16.1 (d2).

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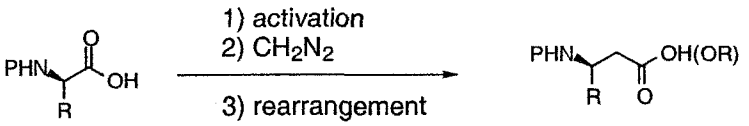
Chapter 3: Synthesis and Reactions of Allenyl Stannanes; Asymmetric Synthesis of γ-Hydroxy-β-Amino Acid Derivatives

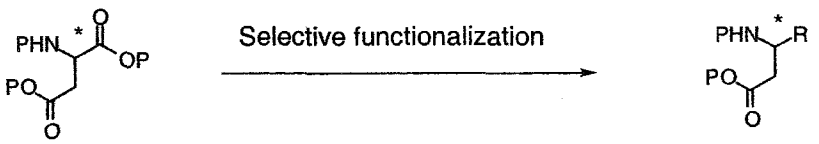
Introduction

β-Amino acids are found in many naturally occurring compounds and are also frequent precursors to β-lactams .[58] There are many general routes to these molecules and the desired product will often dictate which route ismost efficient. Two of the most general routes to β-amino acid derivatives invole the Arndt-Eistert homologation and derivatization of aspartic acid.[58] The Arndt-Eistert homologation reaction is a multistep sequence involving



eq. 1

formation of a diazoketone from a carboxylic acid, followed by rearrangement to give the homologated acid or ester (Equation 1). Derivitazation of aspartic acid allows for generation of β-amino acids since it is essentially an α-amino acid on one side and a β-amino acid on the other. Thus selective functionalization of the α-acid allows for the generation of many β-amino acid derivatives (Equation 2). Since aspartic acid is available as either enantiomer, this



D- or L- Aspartic Acid

eq. 2

method allows for synthesis of either enantiomer of a variety of β-amino acids.

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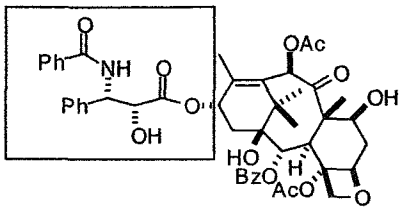
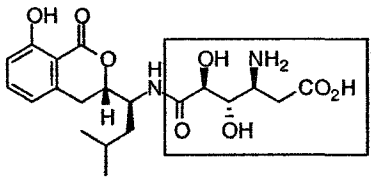
Perhaps the most well known β-amino acid is the α-hydroxy β-amino acid (2R, 3S)-N-Benzoyl-3-phenylisoserine side chain of Paclitaxel (**1**), well



Paclitaxel (1)

known for its anticancer activity. This α-hydroxy β-amino acid side chain (shown in box) has often been modified in studies of the biological activity of Paclitaxel.[58] Another class of β-amino acids are the γ-hydroxy β-amino acids. While not as extensively studies as their α-hydroxy counterparts, these compounds are present in several biologically interesting molecules. One example of a γ-hydroxy β-amino acid containing natural product is AI-77-B (**2**), first isolated in 1982, which shows antiulcerogenic properties.[59] The pseudopeptide side chain (shown in box) contains a γ-δ-hydroxy β-amino acid



AI-77-B (2)

moiety. A second γ-hydroxy β-amino acid containing natural product is theonellamide F .[60] This large, cyclic polypeptide, which has activity against a number of pathogenic fungi and several lines of leukemia cells, contains the γ-hydroxy β-amino octadienoic acid **3** as one of its peptide untis.[60]

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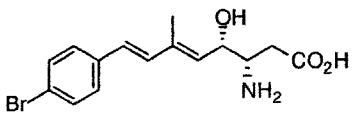
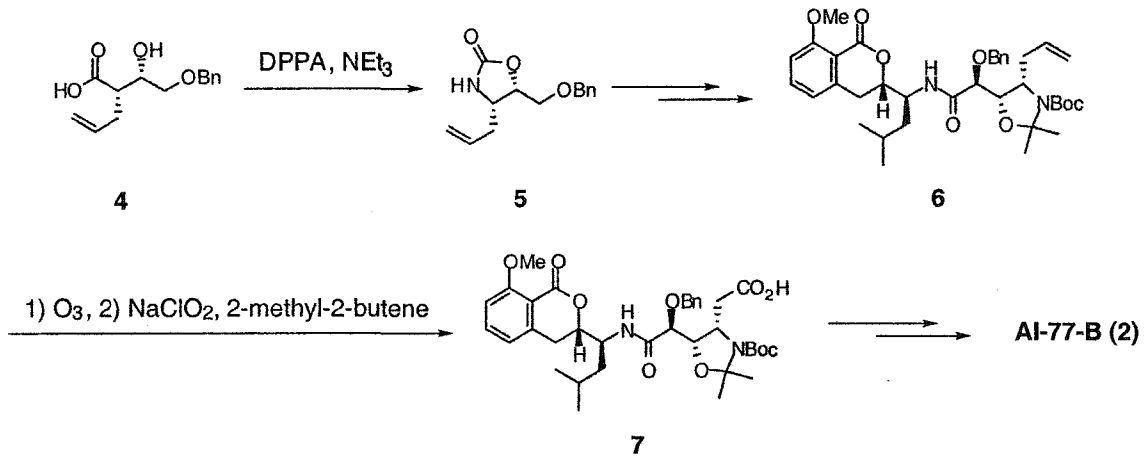


3

Synthesis of these interesting structural untis has been acomplished via several methods. The side chain of AI-77-B (**2**) was synthesized in two steps.[61] First, the amine was installed via Curtius rearrangement of the acid **4**, using diphenylphosphoryl azide (DPPA), to give the oxazolidinone **5** (Scheme 1).

Scheme 1



4 **5** **6**

7

Later, to complete the synthesis, the olefin of the protected amino alcohol **6** was ozonolyzed to give the acid **7**, which was then carried on to the natural product. In a synthetic study of theonellamide F, a protected analog of the γ-hydroxy β-amino acid peptide was synthesized. Addition of the Grignard reagent **8** to the *in situ*-generated aluminum complex from the reduction of protected (S)-homoserine derivative **9**, followed by treatment with biscyclopentadienylzirconium dichloride gave the amino alcohol **10** (Scheme 2). This reaction however, gave only a low 46 % yield of the desired amino

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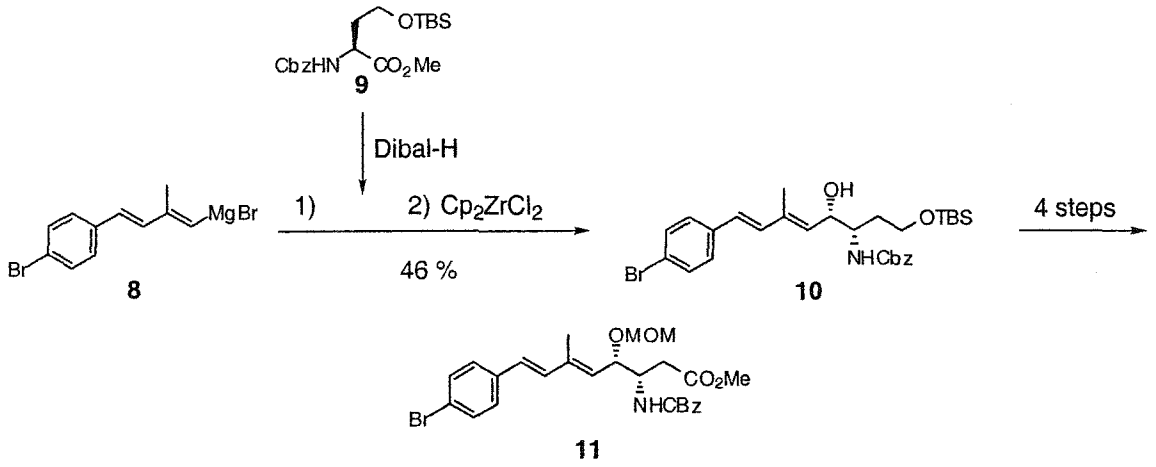
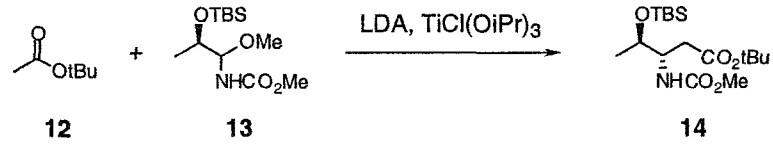
Scheme 2



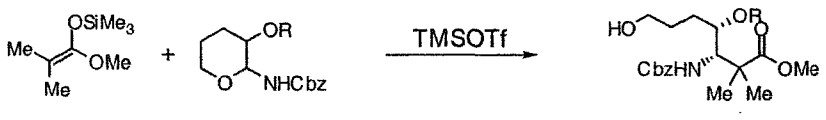
alcohol **10**, which was protected and oxidized to the fully protected side chain **11** in 4 further steps. In addition to the methods utilized in the synthesis of these biologically interesting molecules, several other methods for the production of this structural moiety exists. One such method is the addition of enolates to N,O-acetals. This reaction has been used to selectively produce the anti-amino alcohol **14** from the lithium enolate of tertbutyl acetate **12** and acetal **13**, in the presence of chlorotitanium triisopropoxide (Equation 1).[62] A



64% yield, 80:20 anti:syn **eq. 1**

12 **13** **14**

similar process has been utilized for cyclic N,O-acetals.[63] The silyl enol acetal of methyl isobutyrate (**15**) was allowed to react with cyclic N,O-acetal **16** in the presence of a catalytic amount trimethylsilyl triflate to give the γ-hydroxy β-amino acid derivative **17** (Equation 2). This reaction proceeded in high yield and with



R = Ac; 87 %
R = Bn; 94 % **eq. 2**

15 **16** **17**

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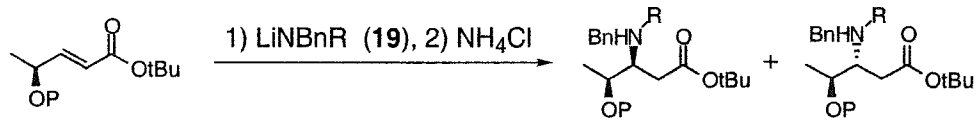
excellent syn:anti diastereoselectivity, favoring the syn product in a 94:6 ratio. Another route to these β-amino acids involves Michael addition of nitrogen nucleophiles to unsaturated ester derivatives. This reaction has been utilized to synthesize chiral γ-hydroxy β-amino ester derivatives.[64] Reaction of protected γ-hydroxy unsaturated ester **18** with lithium amide **19** gave γ-hydroxy β-amino acids **20** (Table 1). The results for this study were generally good, with the

Table 1

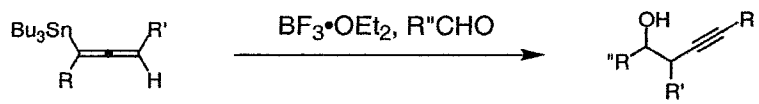


18 **20** syn **20** anti

OP	R	Syn:Anti	yield (%)
$tBuMe_2SiO$	TMS	54:46	91
$tBuPh_2SiO$	TMS	89:11	99
iPr_3SiO	TMS	90:10	95
Ph_3CO	Bn	30:70	79
MeO	TMS	~100:0	77
	Bn	63:37	83

β-γ syn-amino-alcohol favored in all but one case, however some cases of poor selectivity were observed with the relatively smaller oxygen protecting groups.

The Lewis acid promoted condensation reaction of allenyl and alkynyl stannanes with aldehydes has been much studied, primarily by Marshall.[65] Reaction of allenyl stananne **21** with various aldehydes, using boron trifluoride etherate as the Lewis acid proceeds via an *anti* S_E2' pathway, to give the homopropargyl alcohol **22** as the product (equaiton 3). Use of butyltin



21 **22** **eq. 3**

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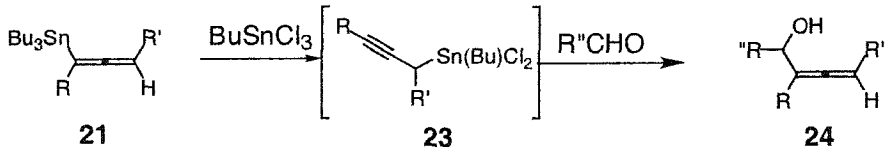
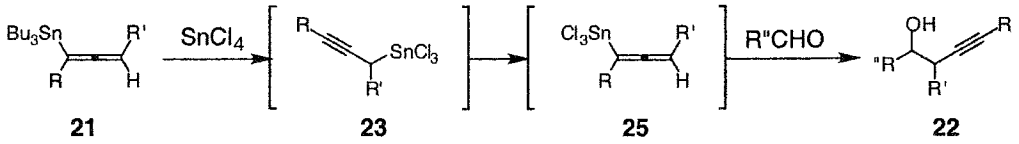
trichloride as the promoter can lead, under certain conditions, to the formation of allenyl carbinol products (Equation 4). This reaction proceeds via



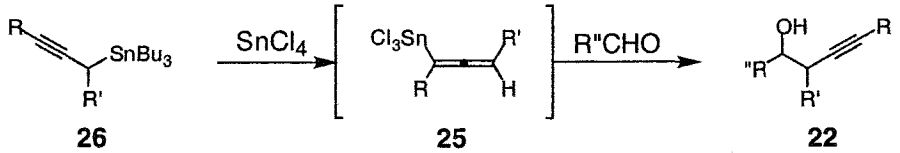
21 23 24 eq. 4

formation of the transmetallated propargyl tin trichloride intermediate **23**, followed by reaction with the aldehyde, via an S_E2' pathway, to give the product allenyl carbinol **24**.[66] If this reaction is allowed to warm to 0° C prior to addition of the aldehyde the intermediate propargyl stannane **23** will isomerize to the more stable allenyl stannane **25**, which, upon reaction with the aldehyde, results in the production of homopropargylic alcohol **22** (Equation 5). Propargyl



21 23 25 22 eq. 5

stannanes have been less extensively studied than their allenyl counterparts. Most examples use either a tetra- or trichlorotin or boron promoter, in the reaction with propargyl stannane **26**, and result in the formation of homopropargylic alcohols **22**, proceeding through an allenyl metal intermediate **25** (Equation 6).[67] However, reaction of propargyl stannane **27**



26 25 22 eq. 6

with various aldehydes, in the presence of a chiral (S)-BINOL-titanium (IV) catalyst and diethylborane isopropylthioate, led to clean formation of allenyl carbinols **28** (Equation 7).[68]

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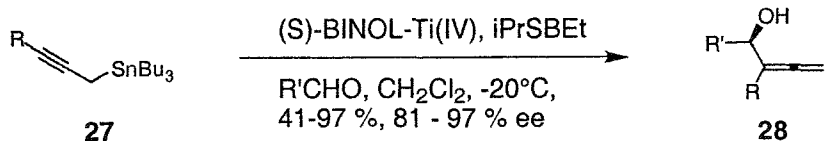
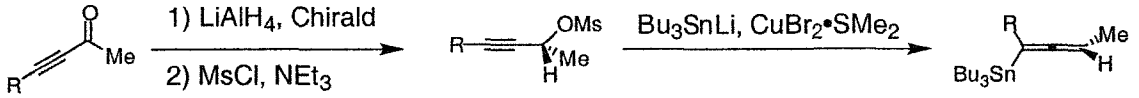


27 28 eq. 7

Several stereochemical considerations exist for this reaction. Absolute stereochemistry is controlled in Marshall's chemistry via use of chiral non-racemic allenyl stannanes.[69] These stannanes are avaiable as either enantiomer from chiral reduction of the corresponding methyl propargyl ketone **29** with the Darvon alcohol, followed by mesylation to give the propargyl mesylate **30**. S_N2' displacement of the mesylate with tributyltin lithium and cupric bromide dimethyl sulfide complex then gives the chiral allenyl stannane **31** (Scheme 3).[69] Enantiomeric excess for this sequence is usually

Scheme 3



29 **30** **31**

approximately 90 %, and use of these enantioenriched allenyl stannanes results in vey high transfer of chirality in all cases.[69] It should be noted that this S_N2' substitution, like other cuprate additions to propargylic mesylates,[70] proceeds via anti addition of the cuprate leading to chiral non-racemic allenyl stannanes as shown. Absolute stereocontrol has been exerted, for achiral propargyl and allenyl stannanes, via a procedure pioneered by Corey.[67e] This method involes transmetallation from tin to boron in the presence of the chiral bissulfonimide derived from (R,R)-1,2-diphenyl-1,2-diaminoethane **32**. Use of this chiral ligand allows for formation of product homopropargylic alcohols **33**

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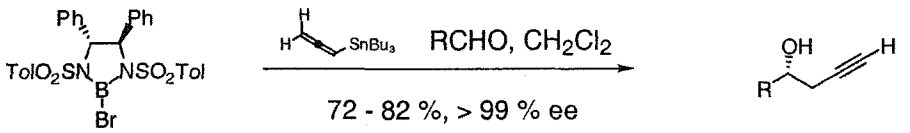
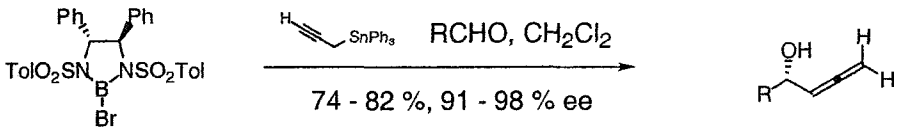
or allenyl carbinols **34**, with high enantiopurity, from the addition of either allenyl or propargyl stannanes to achiral aldehydes (Equation 8 and 9).

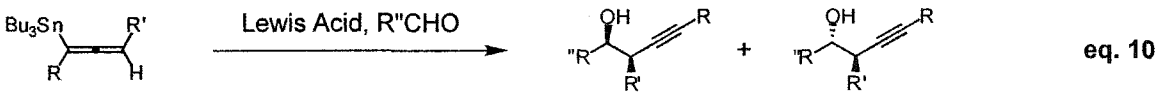


32 **33** **eq. 8**



32 **34** **eq. 9**

In reactions leading to propargyl alcohols, in which there is substitution on the carbon forming the bond to the aldehyde, relative stereochemistry must also be controlled. Products with either a 1,2-syn (**35**) or 1,2-anti (**36**) relationship can be formed (Equation 10). Syn/anti stereocontrol is influenced



35 **36** **eq. 10**

by, among other things, the choice of Lewis acid promotor. The reaction of allenyl stannane **37**, substituted with a methyl group at the 3 position, with iso-butyraldehyde and pivaldehyde, using boron trifluoride diethyl etherate as the Lewis acid, gave the homopropargylic alcohol product **38s**, in high yield and with > 99:1 preference for the 1,2-syn relationship of the two new stereocenters (Table 2, entry 1 and 2).[71] Addition to linear septylaldehyde, again using

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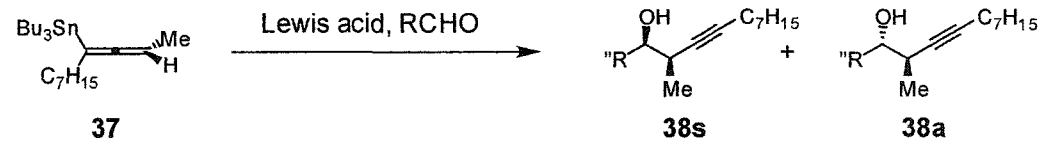
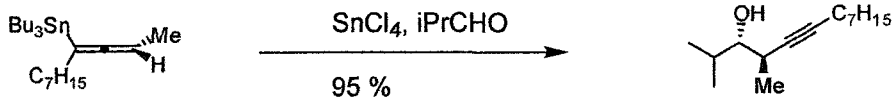
Table 2



37 **38s** **38a**

Entry	Lewis Acid	R	Yield (%)	**38s:38a**
1	$BF_3{\cdot}OEt_2$	i-propyl	80	99:1
2	$BF_3{\cdot}OEt_2$	t-buty	92	99:1
3	$BF_3{\cdot}OEt_2$	n-hexyl	83	37:63
4	$MgBr_2{\cdot}OEt_2$	i-propyl	56	88:12
5	$MgBr_2{\cdot}OEt_2$	n-hexyl	48	69:31

boron trifluoride etherate, resulted in a change of selectivity leading to the 1,2-anti product **38a** being formed in slight, 63:37, preference (Table 1, entry 3). Changing the Lewis acid from boron trifluoride etherate to magnesium bromide etherate, in the reaction with n-octylaldehyde and iso-butyraldehyde, resulted in preference for the 1,2-syn product **38s** in both cases. However selectivity was only moderate and yields were poor (Table 2, entries 4 and 5). Use of tin terachloride, to first transmetallate to allenyl stannane **37**, followed by addition of the adlehyde, led to exclusive formation of the 1,2-anti homopropargylyic alcohol product **38a** in 90 % yield (equaiton 11).[66] The use of



37 **38a** **eq. 11**

tin (IV) salts also allows for the formation of 1,2-anti adducts from the reaction of propargyl stannanes and aldehydes. Roush found that when trimethylsilylpropargyl stannane **39** was allowed to react with aldehydes, using butyltin trichloride to promote the reaction, a good yield of the 1,2-anti diol **40** was produced (Equation 12).[67a] Marshall showed that additions of the (R)- and

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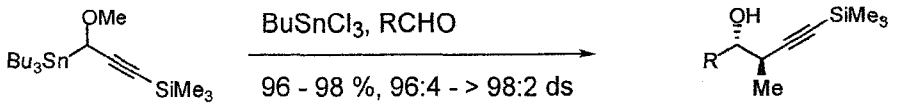


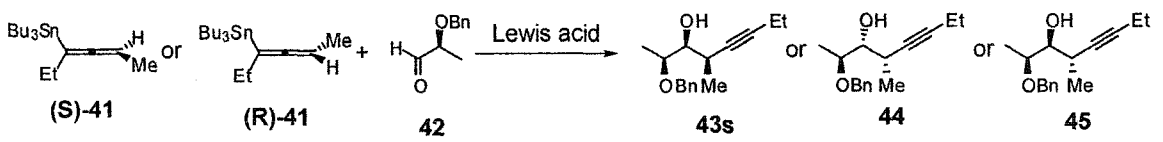
39

40, R = iPr, Ph, propenyl, styryl, tBu

eq. 12

(S)- stannane **41** to (S)-benzyloxy aldehyde **42** was dependant on which Lewis acid was used and the stereochemical interaction of the aldehyde and stannane (Table 3).[69] Addition of (S)-stannane **41** to aldehyde **42**, using boron

Table 3



(S)-41 **(R)-41** **42** **43s** **44** **45**

Entry	Lewis Acid	Stannane	Yield (%)	Prod	Syn:Anti
1	$BF_3 \cdot OEt_2$	**(S)-41**	92	**43**	87:13
2	$MgBr_2 \cdot OEt_2$	**(S)-41**	98	**43**	>99:1
3	$BF_3 \cdot OEt_2$	**(R)-41**	89	**44**	>99:1
4	$MgBr_2 \cdot OEt_2$	**(R)-41**	95	**45**	1:99

trifluoride and magnesium bromide, led to 1,2-syn homopropargylic alcohol **43**, although higher selectivity was achieved with magnesium bromide (Entry 1 and 2). Switching from stannane (S)-**41** to the (R) enantiomer, with boron trifluoride, gave homopropargylic alcohol **44** with increased syn selectivity, indicating a possible matched/mismatched interaction for the (R)- versus (S)-stannane **41** (Entry 3). The same reaction with magnesium bromide led to near exclusive formation of the 1,2-anti homopropargylyic alcohol **45**, with very high selectivity, a complete switch from syn to anti selectivity (Entry 4). Marshall explains these selectivities via transition state models. He uses chelated models to explain the selectivity of the magnesium bromide additons (Figure 1 and 2). The

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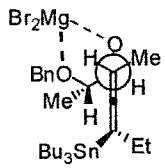

Figure 1:
$MgBr_2$, (S)-41

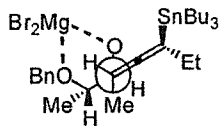

Figure 2:
$MgBr_2$, (R)-41

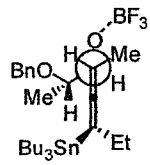

Figure 3:
BF_3, (S)-41

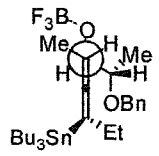

Figure 4:
BF_3, (S)-41

magnesium chelates to both the carbonyl oxygen and the benzyl ether oxygen forming a rigid complex with the aldehyde. The allenyl stannane then approaches from the β-face, as drawn, to minimize interactions with the methyl group on the α face and with the tributyltin group facing out, consistent with an *anti*-S_E2' mechanism. The orientation of the (S)-stannane **41** in figure 1 is such that the hygrogen assumes a position over the most sterically-congested region of the aldehyde complex, with the methyl group gauche to the carbonyl and hydrogen of the aldehyde, leading to propargylic aclohols with the the observed 1,2-syn stereocheistry. The (R)-stannane **41**, in order to minimize steric interactions, approches with the hydrogen again gauche to the carbonyl and the alkyl group of the alhdhyde (Figure 2). This orientation however, forces the allenyl carbon now to bisect the carbonyl and hydrogen of the aldehyde and the methyl to be opposite the carbonyl, which leads to the observed 1,2-anti orientation of the product . Using boron trifluoride etherate as the Lewis acid in the reaction with aldehyde **42**, Marshall explains the stereochemical outcome via a Felkin-Ahn transition state in the case of (S)-stannane **41** and via a Cornforth transition state in the case of (R)-stannane **41** (Figure 3 and 4).[65] The selectivity observed in both of these is due to minimization of steric interactions in the transition state, and in both cases leds to formation of the 1,2-syn

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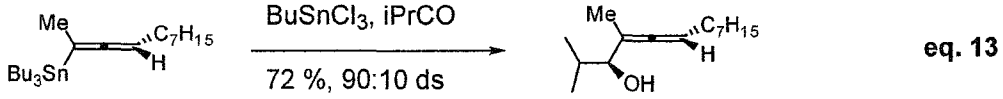
homopropargyl alcohol products. The transmetallation of allenyl stannanes with tin salts to give allenyl carbinol products (Equation 4) also has several possible stereooutcomes. Reaction of the chiral allenyl stannane **(S)-46** with isobutyraldehyde, using butyltin trichloride to first transmetallate, resulted in formation of the *syn* allenyl carbinol product **47** in 72 % yield and with 90:10 syn:anti selectivity (Equation 13). The stereochemical outcome of this reaction



eq. 13

(S)-46 **47**

is rationalized using a Felkin-Ahn transition state model (Figure 5). The stannane intermedate adopts a conformation placing the large butyl group on

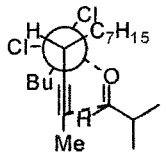


Figure 5

the tin and the septyl group of the propargyl portion as far apart as possible, to minimize any steric interaction. The aldehyde chelates to the electophilic tin center and approachs from the α face of the molecule, with the isopropyl group facing away from butyl group of the tin. Bond formation from this transition state, through a *syn*-S_E2' pathway results in the stereochemistry shown in the product.

Asymmetric additions of allenyl and propargyl stannanes have been utilized many times in total synthesis. In a formal total synthesis of the protein phosphatase inhibitor tautomycin (**48**), the C13, C14, C15 stereotriad was

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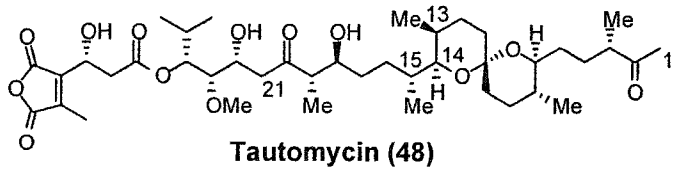
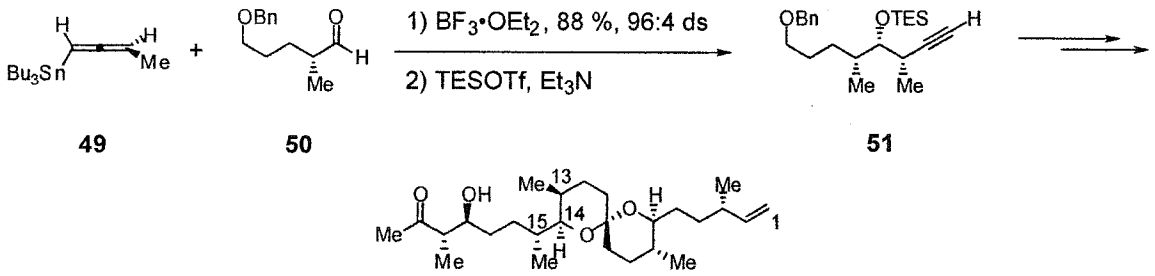


Tautomycin (48)

constructed via addition of chiral allenyl stannane **49** to aldehyde **50**. This reaction gave, after protection, the stereotriad unit **51** (Scheme 4).[72] This

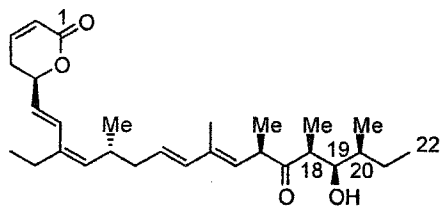
Scheme 4



49 **50** **51**

C1 - C21 subunit

alkyne was then elaborated to the full C1-C21 subunit to intersect Chamberlin's intermediate and complete the formal total synthesis.[73] In his synthesis of a stereopentad precursor to callystatin A (**52**), Marshall again used asymmetric



Calistatin A (52)

allenyl stannane addition to set 3 of the stereocenters.[74] Addition of chiral allenyl stannane **53** to the chiral aldehyde **54** set the C18, C19, C20 stereocenters, to give the homopropargyl alcohol **55** (Scheme 5).

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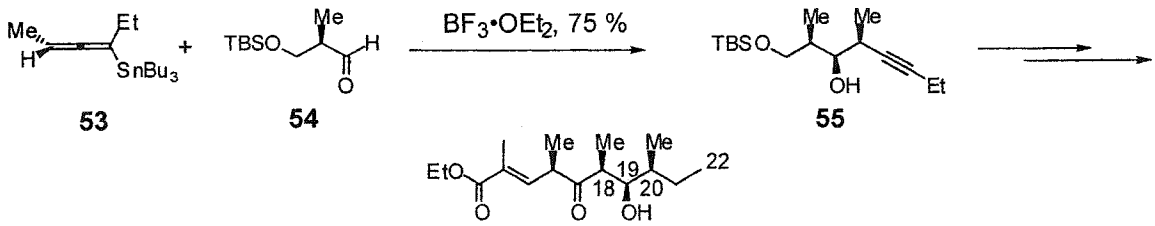
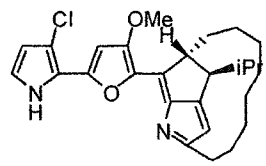
Scheme 5



Calistatin A precursor 56

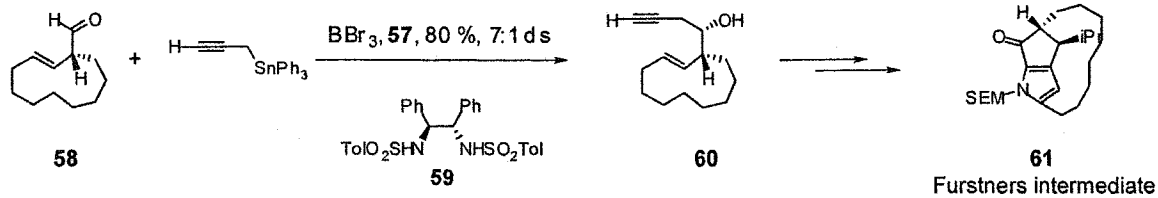
This alcohol was then eleborated to give the callystatin A precursor **56**. Trost has used Corey's procedure for asymmetric addition of allenyl stannanes to aldehydes in his formal total synthesis of roseophillin (**57**).[67c] Boron



Roseophilin (57)

tribromide-promoted addition of (triphenyl)(propargyl)tin to the chiral aldehyde **58**, in the presence of the chiral ligand **59**, gave the homopropargyl alcohol **60** in 80 % yield and with 7:1 diastereoselectivity (Scheme 6). This intermediate

Scheme 6



was then transformed to **61**, an advanced intermediate in Fürstners earlier racemic total synthesis of roseophillin.[75] While this process as shown above (*vide infra*) has been found much use in organic synthesis with carbon- and oxygen-substituted allenyl and propargyl stannanes, no liturature examples of nitrogen-substituted allenyl or propargyl stannanes have been reported.

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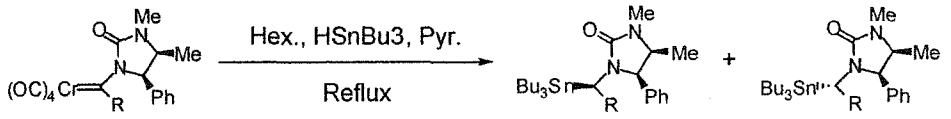
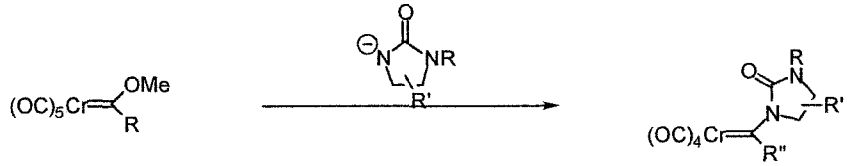
As discussed in chapter 2, Wulff was able to react chiral imidazolidinone-containing carbene complexes with tributyltin hydride to give the corresponding α-(imidazolidinone) stannanes (Equation 14).[52] The

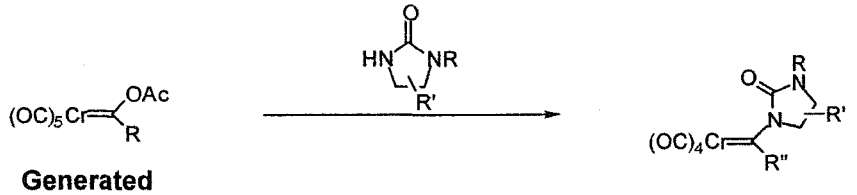


eq. 14

chiral auxilliary-containing carbene complexes for this reaction can be formed via several different methods. [76] Imidazolidinone containing carbene complexes can be formed in good yield either by direct addition of the N-deprotonated imidizolidinone to the corresponding methoxy carbene complex (Equation 15) or by addition N-protonated imidazolidinone complex to the acetoxy-carbene complex (Equation 16). The chromium fragment is formally



eq. 15



eq. 16

Generated *in situ*

chromium tetracarbonyl due to the imidazolidinone oxygen occupying one of the coordination sites on chromium.[76] Synthesis of oxazolidinone-containing carbene complexes proved not to be so straightforward, in part due to their decreased stability compared to their imidazolidinone counterparts. Formation of these complexes is achieved in a two step transformation. First addition of an amino alcohol to the corresponding alkoxy carbene complex to form the

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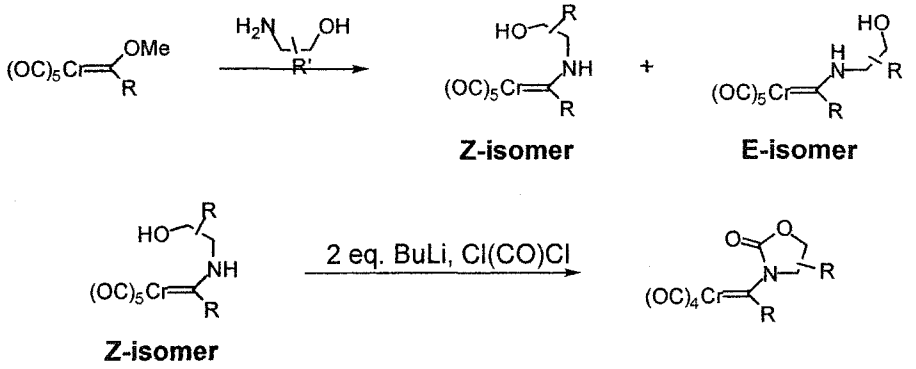
amino carbene complex, followed by deprotonation of both the nitrogen and oxygen protons and treatment with phosgene to form the oxazolidinone complex (Scheme 7). This methodology has several drawbacks. First, if the

Scheme 7



carbene complex has an alkyl side chain with α-hydrogens, this reaction fails, producing instead only ene-carbamates.[77] Also, the amino carbene complexes, due to resonance of the nitrogen lone pair, exist as two distict isomers at the nitrogen, generall forming the E-isomer in preference, and only the Z-isomer will react to give oxazolidinone carbene complexes. Lastly, when olefinic- or propargyl carbene complexes are used the possibilty of Michael addtions to the carbene exist. These Michael adducts cannot form oxazilidinone carbene complexes and are unproductive side products in this reaction.

Rationale

Synthesis of many diverse γ-hydroxy β-amino acids **62** should be possible via oxidation of the alkynyl-amino alcohol **63** and removal of the oxazolidinone chiral auxilliary (Scheme 8). These alkynyl-amino alcohols

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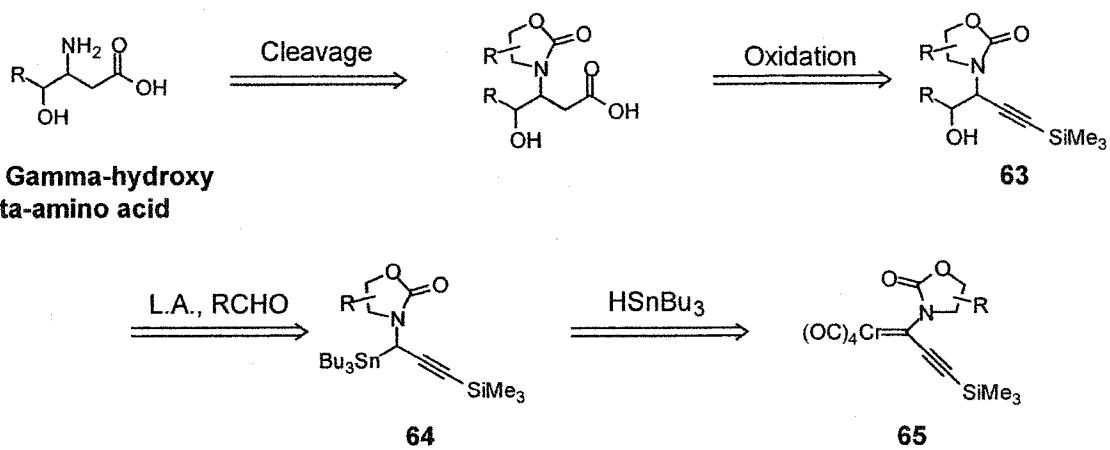
should be available via Lewis acid promoted condensation of chiral-nitrogen containing propargyl stannane **64** with aldehydes, similar to the sequence reported by Roush (*vide supra*),[67a] an unreported reaction. Since the condensation reaction of aldehydes with propargyl stannanes in known to work well with a wide variety of aldehydes substrates (*vide supra*), this process

Scheme 8



62 Gamma-hydroxy beta-amino acid

63

64

65

should provide a general route to propargyl amino alcohols **63**, that may be converted to the corresponding amino acid derivative. In turn, the propargyl stannane **64** should be available by the reaction of tribtyltin hydride with the chiral oxazolidinone carbene complex **65**. If the tin hydride-carbene insertion reaction proves a unusable route to the requisite propargyl stannane **64**, **64** should also be accessable via chemistry similar to that used by Roush to make his α-methoxy propargyl stannane **39**,[67a] starting from the known propargyl oxazolidinone **66** (Equation 16).[78] The oxazolidinone chiral auxilliary

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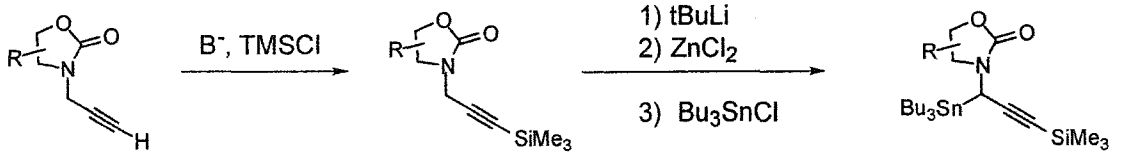
Scheme 9



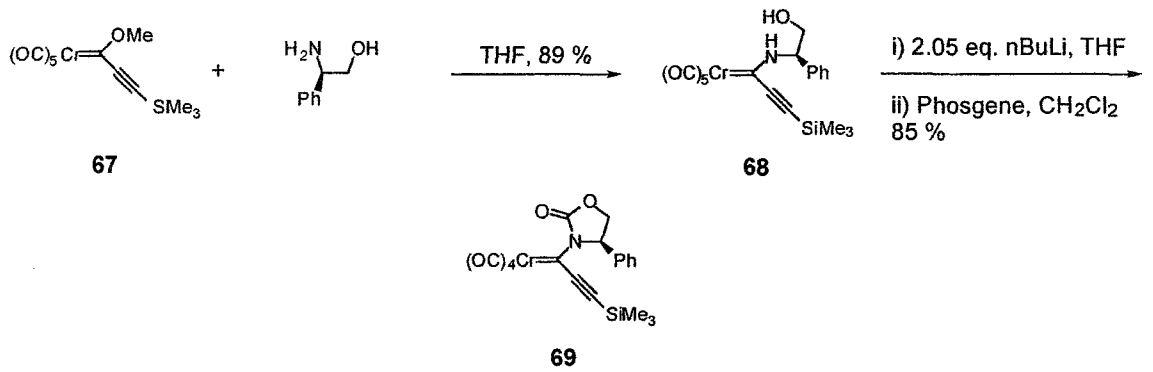
66 **64** W

as chosen for these studies due its ability to be cleaved via hydrolysis or, in some cases, hydrogenation, whereas the imidazolidine chiral auxilliry utilized by Wulff is very difficult to cleave.

Results and Discussion

Synthesis of the oxazolidinone carbene complexes began with aminolysis of the known carbene complex **67**, with (R)-2-amino-2-phenylethanol, to give the aminocarbene complex **68** (Scheme 10). The

Scheme 10



67 **68**

69

product from this reaction was formed as only one isomer around the nitrogen-carbene carbon bond and none of the possible, unproductive Michael adduct was formed. The aminocarbene complex **68** was then deprotonated with n-butyllithium and the dianion treated with phosgene to give the oxazolidinone carbene complex **69**, which decomposed rapidly upon standing and was thus

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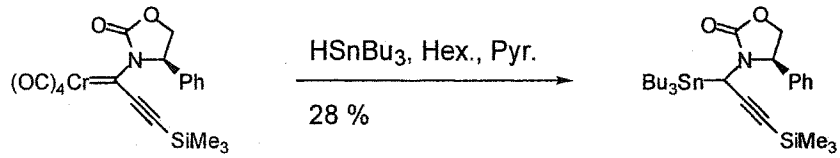
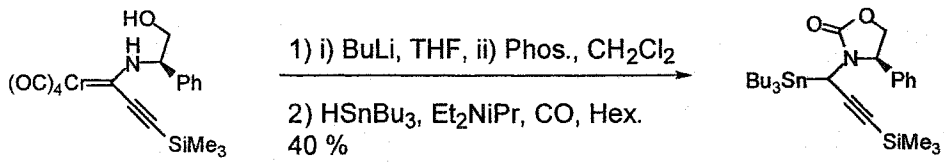
used as soon as possible. The high 85 % yield from this reaction suggests that the reactive Z-isomer of **68** was formed as the product in preference to the non-reactive E-isomer. The carbene complex **69** was then allowed to react with tributyltin hydride in hexane, with pyridine to scavenge the chromium by-products, to give the α-oxazolidinone propargyl stannane **70** in low 28 % yield. This product was isolated as a single diastereomer by NMR spectroscopy of the crude reaction mixture, although the absolute configuration of this molecule is not known (Equation 17). This poor yield is partly attributed to rapid



69 **70** **eq. 17**

decomposition of the oxazolidinone carbene complex **69**. To minimize the amount of decomposition, and maximize the yield from this important reaction, conditions were developed to effect the transformation of the amino carbene complex **68** directly to propargyl stannane **70**. Concentration of the crude reaction mixture from the oxazolidinone-forming reaction followed by treatment with tributyltin hydride and Hunig's base, under an atmosphere of carbon monoxide, produced the propargyl stannane **70** in 40 % yield (Equation 18).



68 **70** **eq. 18**

The reaction of (dimethyl(phenyl)silyl)alkynyl carbene complex **72**, made from complex **71** in the same manner as for **68**, gave comparable results to the

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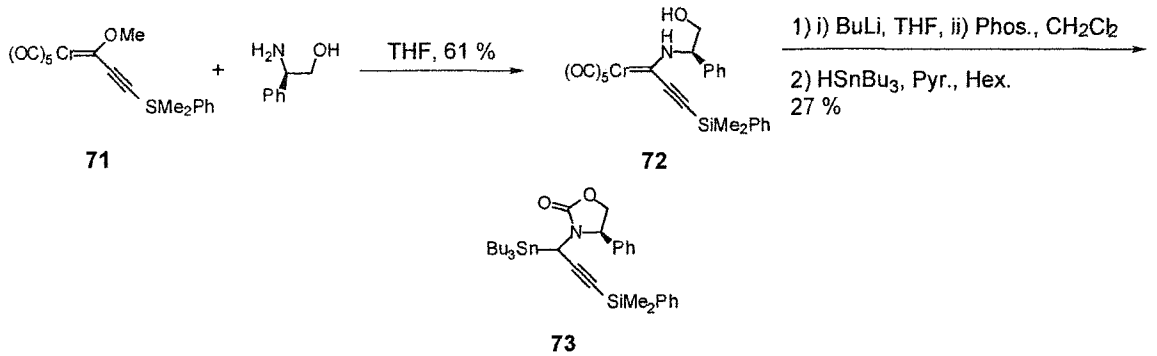
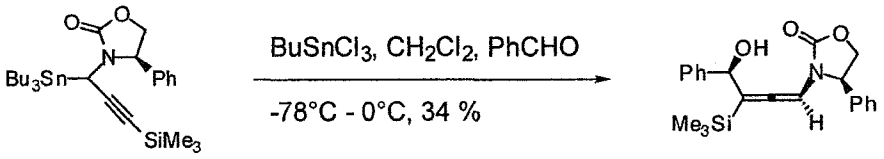
(trimethylsilyl)alkynyl carbene complex **68** upon reaction under similar conditions, giving the corresponding propargyl stannane **73** in 27 % yield as a single diastereomer (Scheme 11).

Scheme 11



71 **72** **73**

With a route, however inefficient, to chiral oxazolidinone propargyl stannanes **70** and **73** in hand, the reactivity of these compounds was explored. Reaction of propargyl stannane **70** with benzaldehyde and butyltin trichloride, under the conditions developed by Roush,[67a] resulted in a 34 % yield of the allenyl carbinol product **74**, not the expected homopropargyl alcohol product, isolated as a single diastereomer (Equation 19). The formation of the allenyl



70 **74** **eq. 19**

carbinol product, as opposed to the expected homopropargylic alcohol product, was evidenced by the proton NMR resonance at 6.79, indicative of an allenyl C-H, and the carbon NMR resonance at 199.3, indicative of an allenyl central carbon. Reaction of propargyl stannanes **70** and **73** with isobutyraldehyde, under the same conditions, give the corresponding allenyl carbinol products **75**

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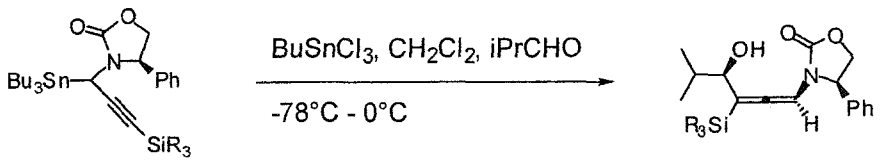
and **76** in 66 and 63 % yield respectively (Equation 20). Proof of the allenyl



eq. 20

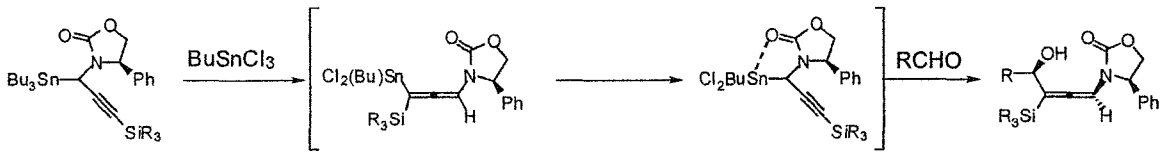
70, R = Me
73, R = Me_2Ph

75, R = Me, 66 %
76, R = Me_2Ph, 63 %

carbinol structure and unambiguous determination of the absolute sterochemistry of this reaction was achieved by X-ray crystallography of allenyl carbinol **75**.

This reaction likely proceeds through transmetallation of the tributyl(propargyl) stannane starting material with the butyltin trichloride Lewis acid to form the allenyl intermediate **77** (Scheme 12). This allenyl stannane

Scheme 12



77 **78**

intermediate can then isomerize, possibly with the aid of a second equivalent of butyltin trichloride, to the propargyl intermediate **78**. Generally the allenyl stannanes intermediate is considered to be the more stable (*vide infra*),[66] however in this case, due to coordination of the electron rich oxazolidinone carbonyl to the electrophilic tin center, the propargyl intermediate **78** is more stable. Reaction of this intermediate with the aldehyde through a *syn*-S_E2' mechanism results in the observed allenyl carbinol.

The stereochemical outcome of this reaction can be rationalized using a Felkin-Ahn model, similar to that utilized by Marshall to explain the observed

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stereochemical outcome in Figure 5. The tin center has 6 groups coordinating to it in an octahedral geometry with the two chlorines cis to each other. The largest groups, the butyl group of the tin and oxazoldinone, which is complexed to the tin center through the cabonyl group, adopt an anti relationship, to minimize steric interactions (Figure 6). The aldehyde coordinates to the

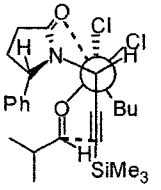

Figure 6

electrophilic tin center cis to the tin propargylic-carbon bond, approaching from the beta face as drawn. Orientation of the aldehyde puts the largest group (isopropyl in this case) on the side opposite the bulky butyl group of the tin. Bond formation from this transition state leads to the observed stereochemistry of allenyl carbinol **75**.

Although the formation of the allenyl carbinols **74**, **75**, and **76** proved very interesting, the route to propargyl stannanes **70** and **73** was not efficient. A simpler and higher yielding route to these compounds was needed for this process to prove synthetically useful. The propargyl oxazolidinone **79** was synthesized using the conditions described by Hsung,[78] followed by silylation, via deprotonation and addition of trimethylsilyl chloride, to give the (trimethylsilyl)propargyl oxazolidinone **80** in 83 % yield (Scheme 13).

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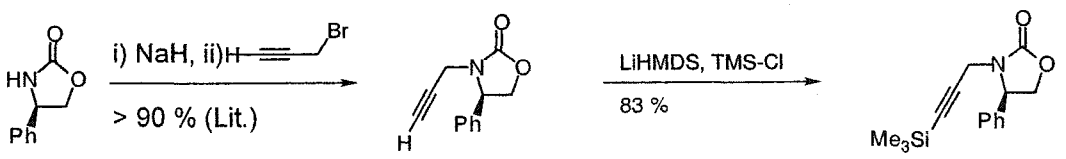
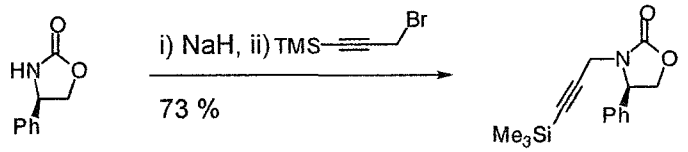
Scheme 13



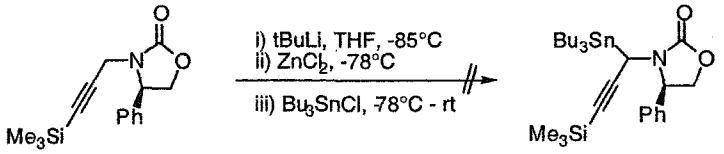
79 **80**

Alternatively, (trimethylsilyl)propargyl oxazolidinone **80** was synthesized directly from the corresponding oxazolidinone using sodium hydride and (trimethylsilyl)propargyl bromide (Equation 21). This method provided **80** in



80 **eq. 21**

one step, but due to the slight decrease in yield and the expense of (trimethylsilyl)propargyl bromide, the two step method described in scheme 13 was typically used to make this reagent. Use of the conditions described by Roush (*vide supra*) to synthesize propargyl stannane **70** gave only a complex mix of products that were not fully identified (Equation 22). Deprotonation with



80 **70** **eq. 22**

tert-butyllithium followed by transmetallation to titanium(IV) and direct addition to benzaldehyde failed to produce any condensation products and again resulted in a complex mixture of products (Equation 23). To examine if

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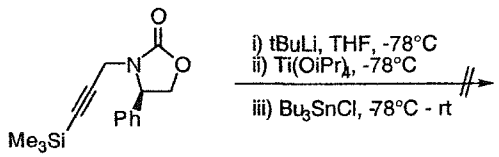
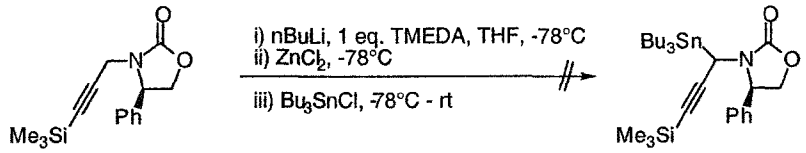


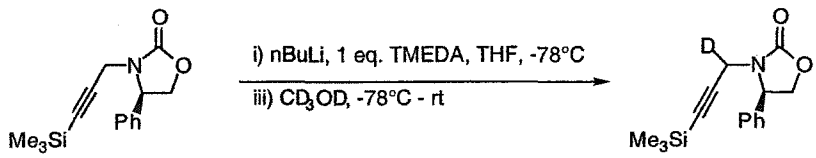
80 **eq. 23**

tert-butyllithium was actually deprotonating α to the oxazolidinone of (trimethysilyl)propargyl oxazolidinone **80**, as opposed to a more kinetically favorable position leading to the observed decomposition of the starting material, other bases and conditions were examined. N-butyllithium, a less kinetically basic reagent, with N,N,N',N'-tetramethylethylenediamine (TMEDA) , which has been used to aid deprotonation of oxazolidinone-substituted substrates,[79] was used to deprotonate **80**. Deprotonation was followed by transmetallation to zinc and addition of tributyltin chloride (Equation 24). These



80 **70** **eq. 24**

conditions produced none of the desired propargyl stannane **70**, resulting primarily in recovered starting material. To test if deprotonation was actually occurring, **80** was treated with n-butyllithium in the presence of TMEDA followed by quenching with deuterated methanol (Equation 25). This reaction resulted



80 **eq. 25**

in near complete deuteration of the starting material with very high diastereoselectivity, indicating that not only was deprotonation taking place but

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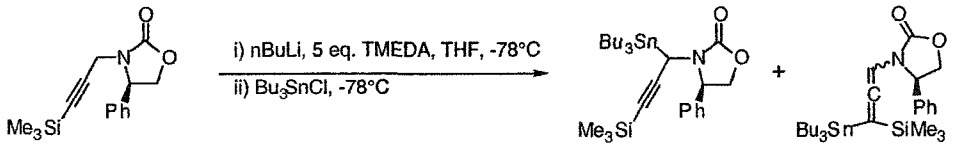
the anion generated was configurationally stable. This reaction also suggested that rather than deprotonation being the problem step, either transmetallation to zinc or quenching of the anion by residual water in the zinc choride was the problem with the reaction. Reaction of the anion generated by deprotonation of **80** with n-butyllithium and 5 equivalents of TMEDA followed directly by addition of tributyltin chloride led to the isolation of propargyl stannane **70** in 47 % yield, as a single diastereomer identical to that produced by reaction of tributyltin hydride with carbene complexes (Equation 26). In



80 **70**, 47 % **81**, 27 % **82**, 17 % **eq. 26**

addition to propargyl stannane **70** a mixture of two diastereomeric allenyl stannanes **81** and **82** were produced in this reaction. The allenyl stannanes were formed in a 1.7:1 diastereomeric ratio, judging by NMR analysis of the crude reaction mixture, and were isolated in 27 % and 17 % respectively.

Adjustment of the amount of TMEDA from 0.25 to 10 equivalents, did not signifacantly increase the yield of propargyl stannane or alter the ratio of propargyl to allenyl stannane products (Table 4, entries 1-4, allenyl stannaes were not isolated from these reactions). However, changing the solvent from

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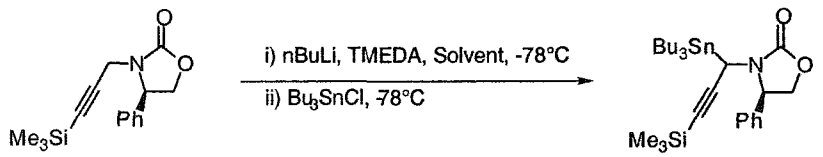
Table 4

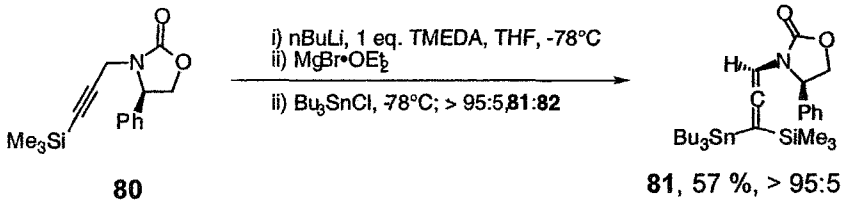


80 **70**

Entry	TMEDA (eq.)	Solvent	yield (**70**)
1	0.25	THF	42 %
2	1	THF	34 %
3	10	THF	37 %
4	5	Et_2O	52 %

THF to diethyl ether, using 5 equivalents of TMEDA, allowed for the isolation of propargyl stannane **70** in 52 % yield, the highest isolated yield of this product (Table 4, Entry 4).

Use of zinc(II) chloride as a transmetallating agent failed to result in any isolable propargyl of allenyl stannane products, possible due to residual moisture in the zinc salt. Use of the magnesium(II) bromide, a much less hygroscopic reagent, led to exclusive formation of the allenyl stannanes **81** and **82** in a > 95:5 diastereomeric ratio (Equation 27). Allenyl stannane **81** could be



80 **81**, 57 %, > 95:5 ds **eq. 27**

isolated from this reaction as a > 95 % diastereomerically pure product in moderate, 57 %, yield, along with a small amount of recovered starting material. Use of freshly-made magnesium bromide in THF, taking caution to exclude moisture at all steps, resulted in a reproducible 80 % yield of allenyl stannane **81** as a >95:5 mixture of diastereomers (Equation 28).

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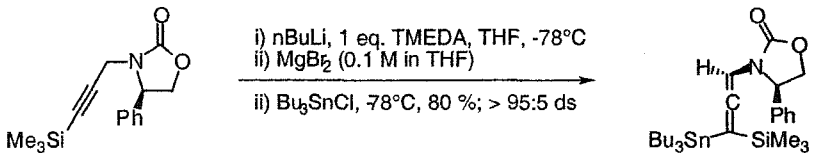
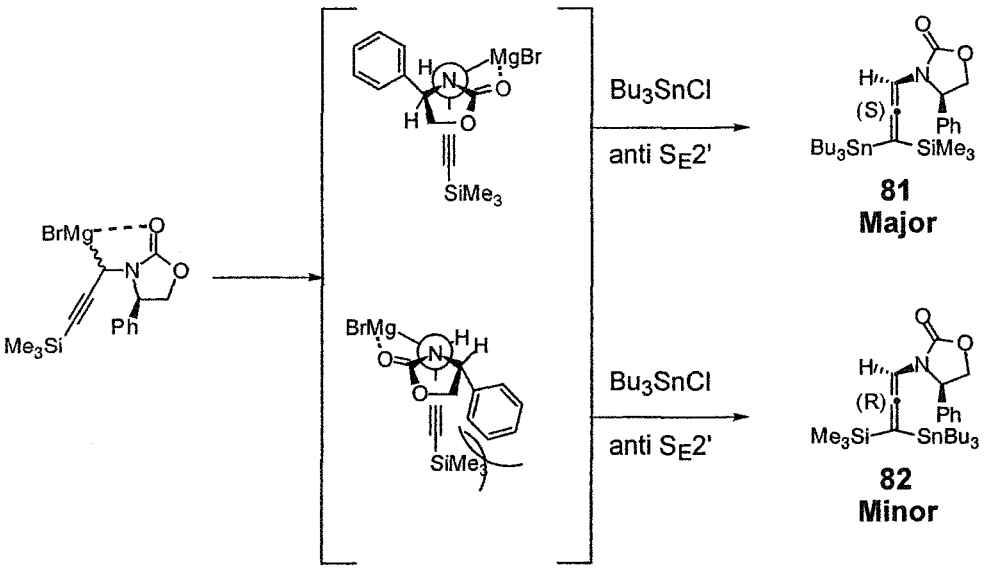


80 **81** **eq. 28**

The allene geometry of the major diastereomer **81** and the minor diastereomer **82** were assigned as (S) and (R) respectively. This assignment was made by examining the possible transitions states from an intermediate magnesium bromide salt (Scheme 14). Coordination of the electron rich

Scheme 14



oxazolidinone carbonyl to the magnesium will force this reaction to proceed from a propargyl magnesium bromide intermediate, which can exist in two diastereomeric configurations. The first configuration, with the magnesium on the right side as drawn (in a Fischer projection looking down the nitrogen/propargylic carbon bond) and with the oxazolidinone coordinated to the magnesium, puts the phenyl group of the oxazolidinone up and away from the rest of the molecule. Bond formation from this configuration, through and *anti-*

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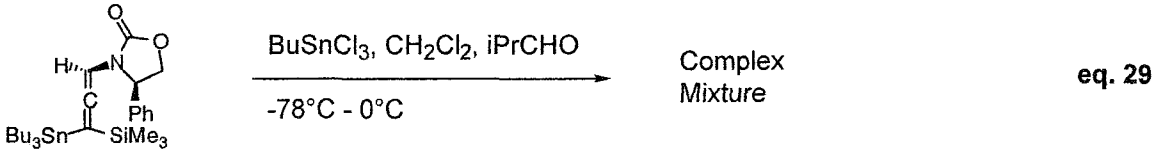
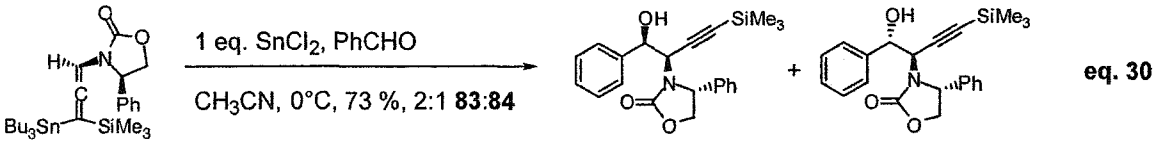
S_E2' pathway, leads to the (S) allene geometry and is assigned as the major diastereomer **81**. The second configuration, with magnesium on the left side of the molecule, puts the oxazolidinone down and in proximity to the large trimethylsilyl group of the propargyl system, resulting in a steric interaction between these two groups and disfavoring this configuration. Bond formation ,as before, from this configuration leads to the (R) allene geometry and is assigned as the minor diastereomer **82**. Since allenyl stannane **81** was more available via synthesis than its propargyl counterpart **70**, this reagent was investigated for use in condensation reactions with aldehydes.

Reaction of allenyl stannane **81** benzaldehyde under the conditions



81

described in equations 19 and 20 led only to decomposition of the starting stannane into a complex mixture of unidentified products (Equation 29). Use of tin(II) dichloride as the Lewis acid promoter led to formation of a 73 % combined yield of a 2:1 mixture of diastereomeric homopropargylic alcohols **83** and **84** respectively (Equation 30).[80] The relative and absolute stereochemistry



81 **83** **84**

of these two products was established by X-ray crystallographic analysis. Repeated attempts to adjust these conditions to favor formation of one

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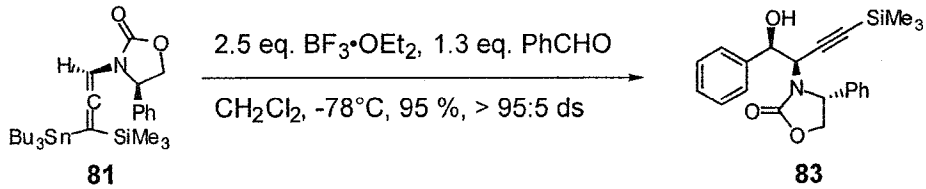
diastereomer met with no success. Conditions found in Marshall's work specifically for condensation of allenyl stannanes with aldehydes were then used.[72] Treatment of allenyl stannane **81** and benzaldehyde with 2.5 molar equivalents of boron trifluoride etherate in methylene chloride at -78°C led to clean formation of homopropargyl alcohol **83** in 95 % yield (Equation 31). This



81 **83** **eq. 31**

product was formed in a > 95:5 diastereomeric ratio, determined by analysis of the crude NMR spectrum, and was isolated as a single diastereomer. A number of other aldehydes were subjected to reaction with allenyl stannane **81** under the conditions described above (Table 5). With the exception of the highly electron-rich formyl-imidazole (Entry 8), which did not react, all aldehydes subjected to these conditions produced the corresponding homopropargyl alcohol products **83** - **90** in high yield and diastereoselectivity. The reaction tolerated branched (Entry 2) and unbranched (Entry 3) alkyl side chains with very high diastereoselectivity. Also, these conditions tolerated unsaturated side chains, with no Michael adducts being detected in the crude product mixture (Entry 4). The presence of chiral centers adjacent to the aldehyde had only a slight effect on diastereoselectivity and yield in this process (Entries 5, 6, and 7), with the largest side chain having the most profound effect, slightly lowering both yield and diastereoselectivity (Entry 5). The possibility of matched/mismatched interactions, which Marshall had found to greatly

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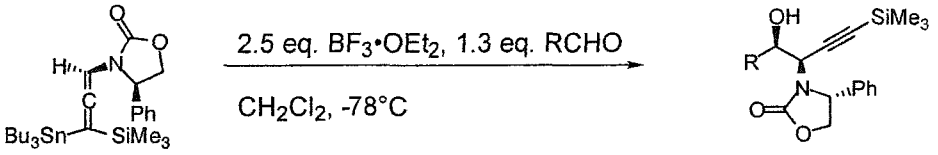
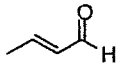
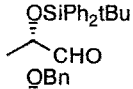
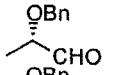
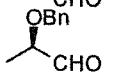
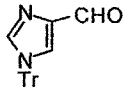
Table 5



81

Entry	Aldehyde	R	prod. #	Yield[a]	ds[b]	x-ray
1	PhCHO	Ph	**83**	95	> 95:5	yes
2	iPrCHO	iPr	**85**	95	> 95:5	no
3	nPrCHO	nPr	**86**	93	> 95:5	no
4			**87**	80	> 90:10	no
5			**88**	68	85:15	no
6			**89**	87	92:8	yes
7			**90**	87	nd	yes
8				NR		

a) all yields are for pure products isolated as single diastereomers, b) diastereoselectivity determined by analysis of the crude reaction product by NMR.

influence selectivity (*vide supra*), was explored via the reaction of both (S)- and (R)-2-benzyloxypropanal (Entries 6 and 7). The yield and 1,2-syn selectivity in both of these cases was identical, and although an absolute diastereoselectivity could not be determined in entry 7, the 87 % yield of homopropargylic alcohol **90** indicates at least an 87:13 diastereomeric ratio and the true diastereoselectivity was probably much greater than this and comparable to that observed in entry 6. To ensure that the adjacent chiral center was not influencing the stereochemical outcome of the reaction, the absolute stereochemistry of homopropargylic alcohols **89** and **90** was proven via X-ray crystallographic analysis.

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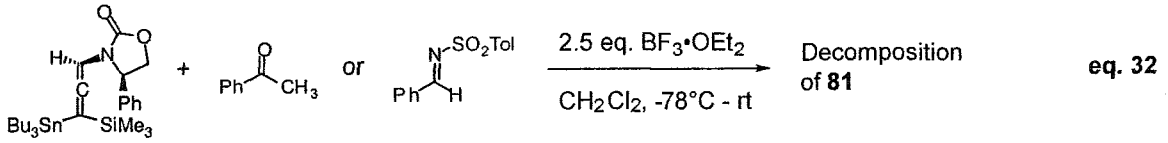
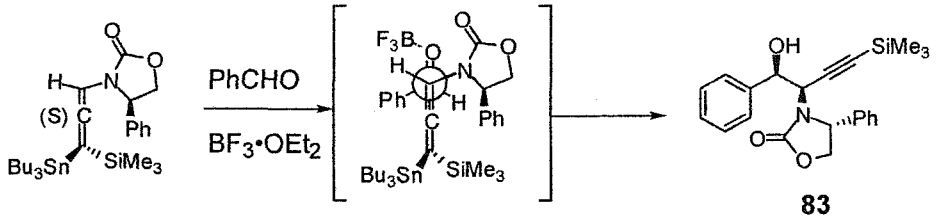
Expansion of this reaction to include additions to imines and ketones met with no success. Use of either acetophenone or the toluenesulfonylimine of benzaldehyde resulted in no formation of condensation products at -78°C. Allowing the temperature slowly rise resulted in only decomposition of allenyl stannane **81** (Equation 32).



81 **eq. 32**

The stereochemical outcome of the condensation reaction of allenyl stannane **81** can be rationalized by use of a Felkin-Ahn transition state model, assuming the reaction proceeds via an anti-S_E2' as proposed by Marshall (Figure 7).[69] This model also leads to the assignment of the allene geometry of



81 **83**

Figure 7 transition state for 81

allenyl stannane **81** as (S). Starting with the (S)-allene geometry and with approach of the aldehyde from the β-face, the large oxazolidinone group is gauche to the two smallest groups of the aldehyde, the carbonyl and the hydrogen, to minimize steric interactions. The largest group of the aldehyde (phenyl in this case) is anti to the oxazoldinone and gauche to the hydrogen and the allenyl group of the stannane. Bond formation from this transition state

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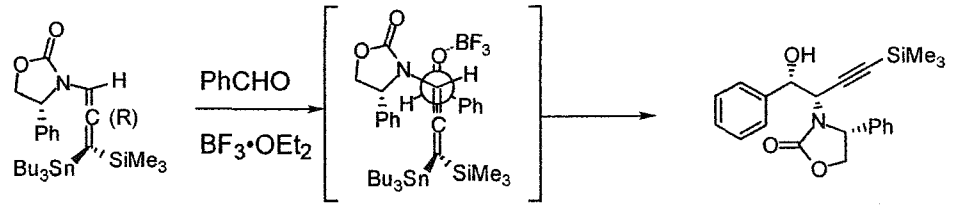
model leads to the observed 1,2-syn stereochemical outcome of homopropargylic alcohol **83** as well as the correct absolute stereochemical outcome of this reaction. Starting from the (R)-allene geometry (assigned as the minor diastereomer, allenyl stannane **82**) leads to the near mirror image of the transition state (Figure 8). The oxazolidinone is again anti to the phenyl and



82 **epi-83**

Figure 8 transition state for 82

gauche to the carbonyl and hydrogen of the aldehyde. The aldehyde phenyl is again gauche to the allene and hydrogen of the stannane. This transition state also leads to 1,2-syn products. However, the absolute stereochemistry is reversed at the newly-formed alcohol and amine stereocenters leading to the opposite absolute stereochemistry of the 1,2-amino hydroxy moiety of homopropargylic alcohol **epi-83**. Transitions states in which the aldehyde phenyl was not anti to the oxazolidinone group, the most favorable steric arrangement, were not considered becaue they would lead to the formation of 1,2-anti amino-alcohol products. Since the (S)-allene geometry of allenyl stannane **81** clearly leas to formation of the observed stereochemistry of the homopropargylic alcohol **83**, this reinforces the assignment of the allene geometry of allenyl stannane **81** discussed previously (*vide supra*).

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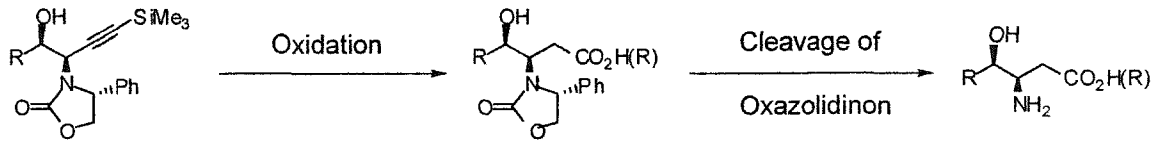
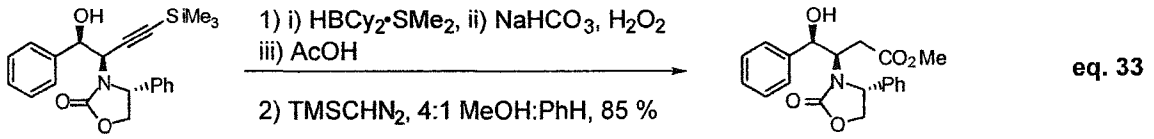
To complete the synthesis of γ-hydroxy-β-amino acid derivatives the homopropargylic alcohols must be oxidized at the terminal carbon of the alkyne and the oxazoldinone cleaved, leaving the nitrogen (Scheme 15).

Scheme 15



Homopropargylic alcohol **83** was converted to the N-oxazoldinone-γ-hydroxy-β-amino ester **91** in good yield over the 2 steps, with a small amount of contamination with dimethyl sulfone formed via oxidation of methyl sulfide (Equation 33).[81] However, examination of this molecule led to the conclusion



83 **91** **eq. 33**

that the strongly basic conditions to remove the oxazolidinone chiral auxilliary, either hydrolysis with refluxing aqueous potassium hydroxide or dissolving metal reduction, would be incompatible with the rest of the molecule. To overcome these problems the diphenyl oxazolidinone chiral auxiliary, which earlier work in this group has shown can be removed via hydrogenation,[77, 82] was used. Starting with propargyl oxazolidinone **92**,[78] the synthesis of the diphenyl oxazolidinone containing allenyl stannane **94** was achieved using the conditions developed for the monophenyl oxazolidinone-containing allenyl stannane **81** (Scheme 16). The yields in this process were comparable to

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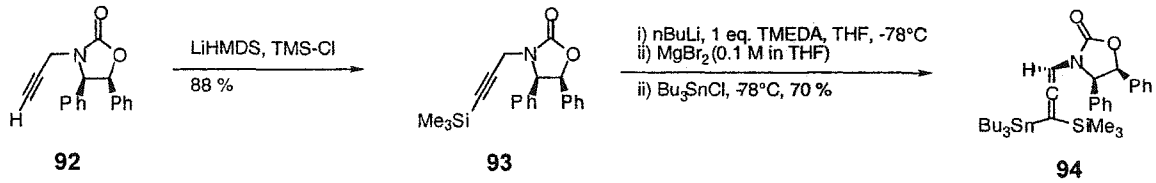
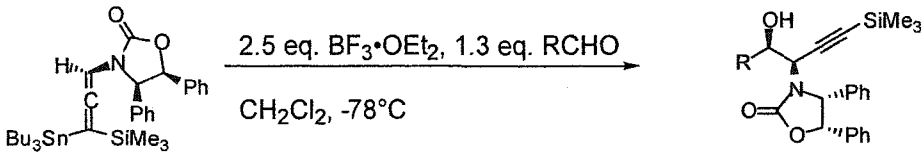
Scheme 16



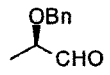
92 93 94

those obtained with the monophenyl compounds. The condensation reaction of stannane **94** with aldehydes, under the same conditions as described in equation 30 resulted in formation of the corresponding homopropargylic alcohols **95** - **97**, also in comparable yields to those achieved with the monophenyl allenyl stannane **81** (Table 6).

Table 6



94

Entry	Aldehyde	R	prod. #	Yield[a]	ds[b]
1	PhCHO	Ph	**95**	85	~ 95:5
2	iPrCHO	iPr	**96**	90	> 95:5
3			**97**	61	> 90:10

a) all yields are for pure products isolated as single diastereomers, b) diastereoselectivity determined by analysis of the crude reaction product by NMR.

Hydroboration/oxidation of these homopropargyl alcohols followed by esterification, as described in equation 33, furnished the N-oxazolidinone-γ-hydroxy β-amino ester derivatives **98** - **100** in good yield (Table 7). In some

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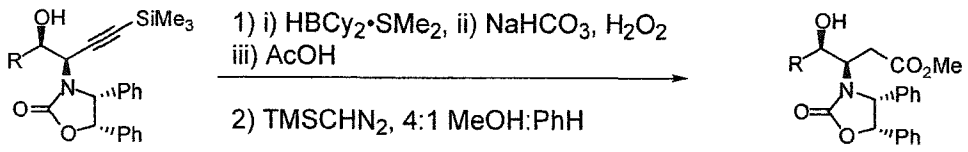
Table 7

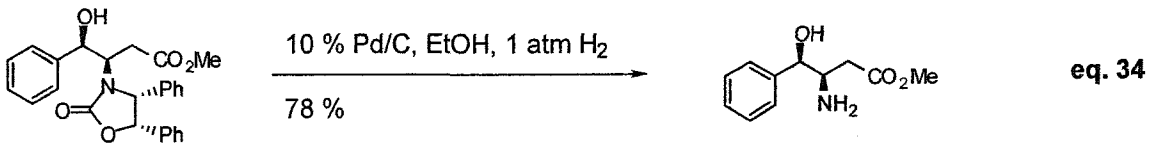


Entry	SM #	R	prod. #	Yield[a]
1	**95**	Ph	**98**	64
2	**96**	iPr	**99**	63
3	**97**		**100**	62

a) yields are calculated for isolated products, in all cases some persistant impurities (> 5 %) that could not be removed remained and compounds were used as obtained

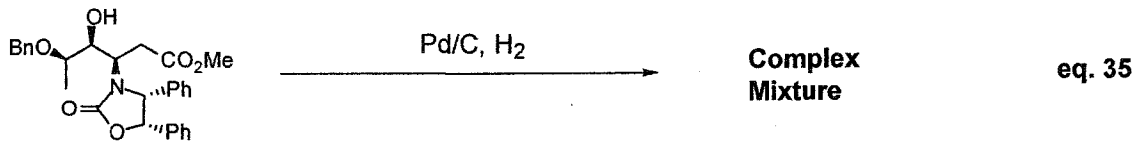
cases the products from this reaction were contaminated with up to 1 equivalent of dimethyl sulfone, which was removed by sublimation.

Hydrogenolysis of the oxazolidinone chiral auxilliary of γ-hydroxy methyl ester **99**, in ethanol for 16 hours, gave γ-hydroxy β-amino ester **101** in 78 % yield (Equation 34). This compound was left as the methyl ester to facilitate



98 **101** **eq. 34**

isolation and purification. Hydrogenation of δ–benzyloxy-γ-hydroxy ester **100**, under a variety of conditions, led to formation of a complex mixture of products that could not be separated (Equation 35). The complex mixture produced from



100 **eq. 35**

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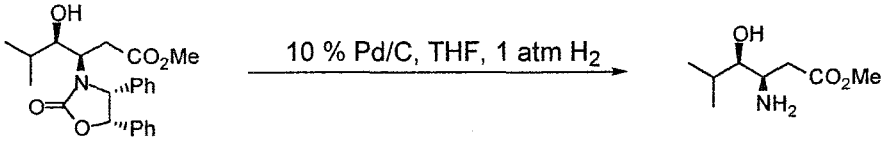
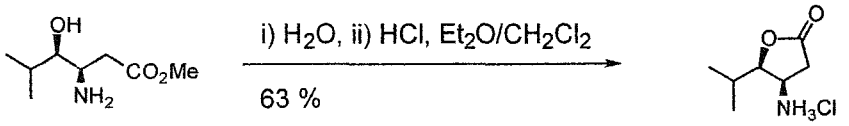
this reaction arises from partial hydrogenation of the benzyloxy group, as well as cyclization to form the 5- and 6-membered lactone products. Hydrogenation of γ-hydroxy ester **98** using either ethanol or methanol as solvent proceeded very slowly, taking several days to complete and resulting in a mixture of cyclized and uncyclized products. Use of THF as the hydrogenation solvent resulted in greatly increased reaction rate with no detectable cyclization, giving the amino ester **102** (Equation 36). Due to the volatility of this product and



99 **102** **eq. 36**

problems with purification, **102** was converted into the lactone and treated with hydrochloric acid to provide, upon recrystallization, a 63 % yield of the β-amino γ-butyrolactone hydrochloride salt **103** (Equation 37).



102 **103** **eq. 37**

Conclusion

In summary the synthesis of chiral propargyl stannanes **70** and **73** from carbene complexes, via group (IV) metal hydride insertion, proved to be an inefficient process, resulting in poor yields of these products. This problem was surmounted by the synthesis of the stannanes by deprotonation of (trimethylsilyl)propargyl oxazolidinone compounds and addition of tributyltin hydride. The propargyl stannanes, upon treatment with butyltin trichloride in the presence of aldehydes, did not give the expected homopropargyl alcohol products, instead forming the allenyl carbinol products **74**, **75**, and **76**. These

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compounds, while interesting targets in and of themselves, were not the desired intermediates in the synthesis of γ-hydroxy-β-amino acid derivatives. The use of magnesium bromide in the stannane-forming reaction resulted in the isolation of allenyl stannane **81** and **94**. Reaction of these chiral allenyl stannanes with various aldehydes gave the corresponding 1,2-syn homopropargylic alcohol products in excellent yield and diastereoselectivity from a number of different classes of aldehydes. This process tolerated aryl, alkyl (straight-chain and branched), alkenyl, and chiral 2-alkoxy-aldehydes, giving the corresponding homopropargylic alcohol in high yield and with excellent diastereoselectivity. This marks the first example of nitrogen-substituted allenyl stannanes in condensation reactions with aldehydes. The synthesis of γ-hydroxy-β-amino ester **101** and γ-butyro-β-amino lactone **103** was achieved in only two further steps from the diphenyl oxazolidinone containing homopropargylic alcohols produced from the condensation reaction of allenyl stannane **94**. Use of the diphenyl oxazolidinone chiral auxiliary in this reaction proved important, allowing removal of the chiral auxilliary under neutral conditions by hygrogenolysis. This process enables the synthesis of γ-hydroxy-β-amino acid derivatives in only 3 linear steps from the diphenyl oxazolidinone containing allenyl stannane **94**.

Experimental

General: THF was distilled from sodium-benzophenone ketyl, and CH_2Cl_2 was distilled from CaH_2. Commercially available reagents were used

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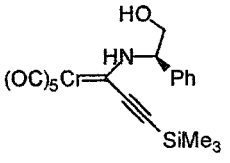
as received except as indicated. ^{1}H NMR (JS-300, 300 MHz; Inova 400, 400 MHz), ^{13}C NMR (JS-300, 75 MHz) and (Inova 400,100 MHz), and NOE (Inova 400, 100 MHz) spectra were recorded in $CDCl_3$ unless otherwise noted. Proton chemical shifts are given in ppm relative to $CHCl_3$ (7.27 ppm) or CD_3OH (4.87 ppm) and carbon shifts are relative to $CDCl_3$ (77.23 ppm) or CD_3OD (49.15 ppm). ^{1}H NMR spectra were recorded on the JS-300 spectrophotometer unless otherwise noted. IR spectra were recorded on a Perkin-Elmer 1600 series FTIR. Column chromatography was performed with ICN 32-66 nm, 60 Å silica gel using flash column techniques unless otherwise noted. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ. All reactions were performed under an atmosphere of argon gas unless otherwise noted. Compounds **80** and **92** were synthesized according to literature procedures.[78] Diasteroselectivity was determined in the condensation reactions, unless otherwise noted, by analysis of the crude ^{1}H NMR spectra.



68

General Method for the Synthesis of (Propargyl)Aminocarbene Complexes; Synthesis of ((Trimethylsilyl)Propargyl)Amino Carbene Complex 68: To a stirred solution of ((trimethylsilyl)propargyl)methoxy carbene complex **67** (1.0 g, 3.0 mmol), in THF (10 mL) at -78°C, was added (R)-2-amino-2-phenylethanol (455 mg, 3.3 mmol) in one portion. The reaction was stirred at -78°C for 1 hour

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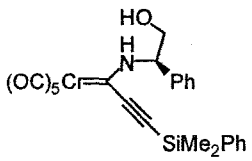
then warmed to room temperature and stirred an additional 2.5 hours. The reaction mixture was then filtered through a plug of 1:1 silica:celite, rinsing through with THF (20 mL), and concentrated under reduced pressure to give the crude reaction product as a deep orange oil. Purification via flash column chromatography with silica gel, eluting with 3:1 hexanes:ethyl acetate, gave ((trimethylsilyl)propargyl)amino carbene complex **68** (1.17 g, 89 %) as a deep orange, viscous oil contaminated with a small amount of ethyl acetate. This compound was used without further purification.

^{1}H NMR δ: 9.50 (m, 1H), 7.38 (m, 3H), 7.29 (m, 2H), 5.36 (p, J=4.2, 1H), 4.13 (m, 1H), 4.05 (m, 1H), 1.72 (t, J=5.7, 1H), 0.20 (s, 9H).



72

((Dimethyl(Phenyl)silyl)Propargyl)Aminocarbene Complex 72: This compound was synthesized according to the general method described above using ((Dimethyl(Phenyl)silyl)Propargyl)methoxy Carbene Complex **71** (1.0 g, 2.54 mmol) and (R)-2-amino-2-phenylethanol (383 mg, 2.79 mmol) in THF (9 mL). Purification gave ((dimethyl(phenyl)silyl)propargyl)amino carbene complex **72** (770 mg, 61 %) as a viscous orange oil with a small amount of ethyl acetate which was used without further purification.

^{1}H NMR δ: 9.56 (m, 1H), 7.49 (m, 2H), 7.41 (m, 6H), 7.24 (m, 2H), 5.35 (p, J=3.6, 1H), 4.12 (m, 1H), 4.02 (m, 1H), 1.71 (m, 1H), 0.46 (s, 3H), 0.44 (s, 3H).

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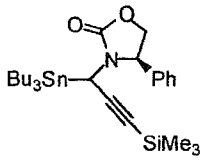

70

Synthesis of Propargyl Stannane 70 from ((Trimethylsilyl)Propargyl)Amino Carbene Complex 68: To a stirred solution of carbene complex **68** (200 mg, 0.46 mmol) in THF (3 mL) at -78°C, was slowly added butyllithium (1.6 M in hexane, 0.94 mmol). The reaction was stirred at -78°C for 45 minutes followed by addition of phosgene solution (1.9 M in toluene, 0.5 mmol). The reaction was stirred for an additional 20 minutes -78°C then warmed to room temperature and stirred a final 15 minutes. The solvent was removed under reduced pressure at 0°C with stirring. To ensure no phosgene remained in the removed solvent, it was trapped through a tube of potassium hydroxide. Once the reaction had been sufficiently concentrated, hexane (3 mL) was added. The reaction was placed under a carbon monoxide atmosphere, cooled to 0°C, and Hunig's base (2 drops) and tributyltin hydride (123 μL, 0.46 mmol) were added. After stirring for 30 minutes the reaction was again concentrated and purified by flash column chromatography on silica gel, eluting with 5 % diethyl ether in hexane, to give propargyl stannane **70** (102 mg, 40 %) as a pale yellow oil.

^1H NMR δ: 7.42 (m, 3H), 7.30 (m, 2H), 5.05 (t, J=8.4, 1H), 4.63 (t, J=8.7, 1H), 4.09 (t, J=8.4, 1H), 3.15 (s, 1H), 1.52 (m, 6H), 1.30 (m, 6H), 1.04 (m, 6H), 0.89 (t, J=7.2, 9H), 0.15 (s, 9H).

^{13}C NMR (75 MHz) δ: 159.1, 137.9, 129.4, 129.2, 127.6, 105.0, 69.6, 60.7, 31.2, 29.2, 27.6, 14.0, 12.9, 0.4.

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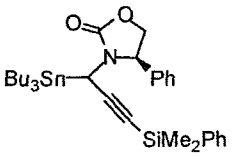
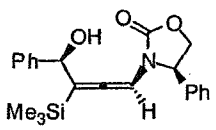


73

Synthesis of Propargyl Stannane 73 from ((Dimethyl(Phenyl)silyl)Propargyl)Amino Carbene Complex 72: To a stirred solution of carbene complex **72** (750 mg, 1.5 mmol) in THF (10 mL) at -78°C, was slowly added butyllithium (1.4 M in hexane, 3.1 mmol). The reaction was stirred at -78°C for 45 minutes followed by addition of phosgene solution (1.9 M in toluene, 1.65 mmol). The reaction was stirred for an additional 20 minutes -78°C then warmed to room temperature and stirred a final 15 minutes. The solvent was removed under reduced pressure at 0°C with stirring. To ensure no phosgene remained in the removed solvent, it was trapped through a tube of potassium hydroxide. Once the reaction had been sufficiently concentrated, hexane (10 mL) was added and the reaction was cooled to 0°C. Pyridine (360 µL, 4.5 mmol) and tributyltin hydride (403 µL, 1.5 mmol) were added. After stirring for 30 minutes the reaction was again concentrated and purified by flash column chromatography on silica gel, eluting with 5 % diethyl ether in hexane, followed by a second purification on silica, eluting with 1:1 hexane:methylene chloride, to give propargyl stannane **73** (251.3 mg, 27 %) as a pale yellow oil.

^{1}H NMR δ: 7.62 (m, 2 H), 7.40 (m, 6H), 7.28 (m, 2H), 5.04 (t, J=9, 1H), 4.62 (t, J=9, 1H), 4.09 (t, J=8.7, 1H), 3.19 (s, 1H), 1.51 (m, 6H), 1.29 (h, J=7.8, 6H), 1.06 (m, 6H), 0.87 (t, J=7.2, 9H), 0.40 (s, 3H), 0.39 (s, 3 H).



74

General Method for the Butyltin Trichloride-Promoted Condensation of Propargyl Stannanes 70 and 73 with

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Aldehydes; Synthesis of Allenyl Carbinol 74: To a stirred solution of (trimethylsilyl)propargyl stannane **70** (50 mg, 0.09 mmol) and benzaldehyde (7.5 µL, 0.074 mmol), cooled to -78°C, was added butyltin trichloride (1 M in methylene chloride, 0.09 mmol) dropwise. The resulting solution was stirred and gradually, over approximately 1 hour, allowed to warm to 0°C and stirred at that temperature for a further 30 minutes. The reaction was quenched by addition of dilute, aqueous hydrochloric acid (0.1 N, 500 µL) and extracted with diethyl ether (4 mL). The resulting solution was stirred with potassium fluoride/celite (100 mg) for 1.5 hours then filtered through a plug of celite and concentrated under reduced pressure to give the crude reaction product. Purification via flash column chromatography with silica, eluting with 5:1 hexane:ethyl acetate gave allenyl carbinol **74** (9.5 mg, 34 %) as a white crystalline solid.

MP: 112 - 146°C

IR (thin film): 3554 cm^{-1} (OH), 1754 cm^{-1} (CO).

^{1}H NMR δ: 7.46 (m, 3H), 7.34 (m, 2H), 7.21 (m, 3H), 6.96 (m, 2H), 6.79 (d, J=2.1, 1H), 4.92 (dd, J_1=6.6, J_2=9.3, 1H), 4.76 (t, J=9.3, 1H), 4.62 (dd, J_1=2.7, J_2=4.5, 1H), 4.11 (dd, J_1=6.6, J_2=8.4, 1H), 1.29 (d, J=4.8, 1H), -0.10 (s, 9H).

^{13}C NMR (75 MHz) δ: 199.3, 155.7, 142.1, 138.3, 129.6, 129.4, 129.3, 128.7, 128.6, 128.3, 127.6, 127.4, 126.6, 126.4, 117.0, 93.9, 75.7, 74.3, 70.6, 70.5, 60.6, 59.9, 0.0, -0.4.

Elemental Analysis, for $C_{22}H_{25}NO_3Si$, (calc.) C 69.62, H 6.64, N 3.69, (found) C 69.57, H 6.68, N 3.58.

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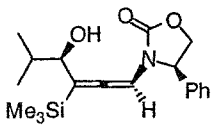


75

Allenyl Carbinol 75: This compound was prepared by the general method described above using (trimethylsilyl)propargyl stannane **70** (80 mg, 0.14 mmol), isobutyraldehyde (11 μL, 0.12 mmol), and butyltin trichloride (1 M in methylene chloride, 0.14 mmol). Purification via flash column chromatography with silica gel, eluting with 5:1 hexane:ethyl acetate, gave allenyl carbinol **75** (27.1 mg, 66 %) as a white crystalline solid.

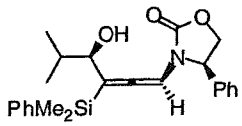
MP: 116 - 117°C

IR (thin film): 3478 cm^{-1} (OH), 1748 cm^{-1} (CO).

^1H NMR δ: 7.41 (m, 3H), 7.25 (m, 2H), 6.65 (d, J=1.8, 1H), 4.83 (dd, J_1=6.6, J_2=9.0, 1H), 4.72 (t, J=8.7, 1H), 4.09 (dd, J_1=6.3, J_2=8.4, 1H), 3.08 (bs, 1H), 1.64 (m, 1H), 0.66 (d, J6.6, 6H), 0.12 (s, 9H).

^{13}C NMR (75 MHz) δ: 199.2, 155.6, 138.4, 129.4, 129.0, 126.6, 116.4, 92.9, 79.6, 70.6, 59.8, 32.8, 28.1, 27.1, 19.8, 17.7, 17.2, 13.8, 0.0.

The absolute configuration of this product was determined by single-crystal X-ray analysis (see appendix 1).



76

Allenyl Carbinol 76: This compound was prepared by the general method described above using ((dimethyl)(phenyl)silyl)propargyl stannane **73** (100 mg, 0.16 mmol), isobutyraldehyde (21.5 μL, 0.24 mmol), and butyltin trichloride (1 M in methylene chloride, 0.176 mmol). Purification via flash column

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chromatography with silica gel, eluting with 5:1 hexane:ethyl acetate, gave allenyl carbinol **76** (41.1 mg, 63 %) as a white crystalline solid.

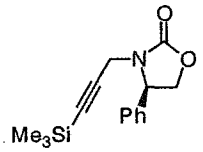
MP: 66 - 68°C

IR (thin film): 3492 cm^{-1} (OH), 1755 cm^{-1} (CO).

^1H NMR δ: 7.52 (m, 2H), 7.40 (m, 3H), 7.34 (m, 3H), 7.01 (dd, J_1=5.1, J_2=6.9, 2H), 6.69 (d, J=2.1, 1H), 4.59 (t, J=8.7, 1H), 4.41 (dd, J_1=6.3, J_2=8.7, 1H), 4.00 (dd, J_1=6.3, J_2=8.4, 1H), 2.98 (dt, J_1=1.8, J_2=6, 1H), 1.29 (m, 1H), 0.70 (d, J=6, 1H), 0.60 (dd, J_1=6.3, J_2=10.8, 6H), 0.44 (s, 3H), 0.42 (s, 3H).

^{13}C NMR (75 MHz) δ: 200.3, 155.5, 138.3, 138.2, 134.1, 129.6, 129.2, 128.9, 128.0, 126.8, 126.5, 115.4, 93.3, 79.5, 70.5, 59.3, 32.7, 19.8, 17.1, -1.8, -1.9.

Elemental Analysis, for $C_{24}H_{29}NO_3Si$, (calc.) C 70.72, H 7.17, N 3.44, (found) C 70.60, H 6.89, N 3.39.



80

General Procedure for the Synthesis of (Trimethylsilyl)propargyl Oxazoldinones 80 and 93; (Trimethylsilyl)propargyl Oxazolidinone 80: To a stirred solution of propargyl oxazolidinone **79** (1.24 g, 6.2 mmol), in THF (30 mL, 0.2 M) cooled to -78°C, was added lithium hexamethyldisilazane (1.0 M in THF, 6.8 mmol). After stirring for 5 minutes at -78°C, trimethylsilyl chloride (875 µL, 6.9 mmol) was added. After stirring a further 10 minutes the reaction was quenched by addition of saturated ammonium chloride solution (15 mL) at -78°C and allowed to warm to room temperature. Once the mixture had warmed to room temperature, water (5 mL) and diethyl ether (60 mL) were

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added and the organic layer was separated. The aqueous layer was again extracted with diethyl ether (60 mL) and the combined organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford the crude reaction product. Purification via flash column chromatography with silica gel, eluting with 5:1 hexane:ethyl acetate gave (trimethylsilyl)propargyl oxazolidinone **80** (1.41 g, 83 %) as a white solid.

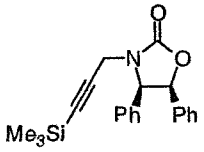
MP: 64 - 66°C

IR (thin film): 1761 cm^{-1} (CO).

^1H NMR δ: 7.42 (m, 3 H), 7.31 (m, 2H), 4.96 (t, J=8.4, 1 H), 4.67 (t, J=8.7, 1H), 4.42 (d, J=17.4, 1H), 4.17 (t, J=7.5, 1H), 3.44 (d, J=17.7, 1H), 0.17 (s, 9H).

^{13}C NMR (75 MHz) δ: 157.9, 137.1, 129.5, 129.4, 127.5, 98.2, 90.7, 70.1, 59.3, 33.3, 0.0.

Elemental Analysis, for $C_{15}H_{19}NO_2Si$, (calc.) C 65.90, H 7.00, N 5.12, (found) C 65.08, H 6.96, N 5.03.



93

(Trimethylsilyl)Propargyl Oxazolidinone 93: Following the above procedure using propargyl oxazolidinone **91** (350 mg, 1.26 mmol), lithium hexamethyldisilazane (1.0 M, 1.39 mmol), and trimethylsilyl chloride (192 µL, 1.51 mmol) in THF (6.3 mL, 0.2 M) led to the isolation of (trimethylsilyl)propargyl oxazolidinone **93** (388.6 mg, 88%) as a white solid.

MP: 122 - 123°C

IR (thin film): 1760 cm^{-1} (CO).

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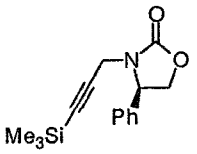
^{1}H NMR δ: 7.18 (m, 6 H), 6.98 (m, 2H), 6.86 (m, 2H), 5.91 (d, J=8.4, 1H), 5.25 (d, J=8.4, 1H), 4.56 (d, J=17.7, 1H), 3.53 (d, J=17.7, 1H), 0.17 (s, 9H).

^{13}C NMR (75 MHz) δ: 157.9, 134.8, 133.6, 128.7, 128.6, 128.2, 128.1, 128.0, 126.2, 98.5, 90.6, 79.8, 64.2, 33.9, 0.0.

Elemental Analysis, for $C_{21}H_{23}NO_2Si$, (calc.) C 72.17, H 6.63, N 4.01, (found) C 71.83, H 6.58, N 3.95.



80

Alternative Method for the Synthesis of (Trimethylsilyl)Propargyl Oxazolidinone 80: To stirred solution of (R)-4-phenyl-2-oxazolidinone (375 mg, 2.3 mmol), in THF (14 mL, 0.167 M), was added sodium hydride (60 %, 110 mg, 2.76 mmol) in small portions to avoid excess bubbling. After completion of the addition of sodium hydride, the reaction was stirred an additional 30 minutes at which point 3-bromo-1-(trimethylsilyl)-1-propyne (650 µL, 4.6 mmol) was added. After stirring overnight the suspension was concentrated under reduced pressure to give a white viscous suspension. Diethyl ether (40 mL) was added and the suspension was filtered trough a pad of celite and again concentrated to give the crude reaction product. Purification via flash column chromatography with silica gel, eluting with 5:1 hexane:ethyl acetate gave (trimethylsilyl)propargyl oxazolidinone **80** (460 mg, 73 %). This compound was identical to that prepared by the alternate procedure.

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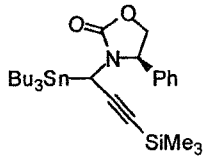
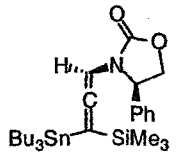


70

Preparation of Propargyl Stannane 70 From (Trimethylsilyl)Propargyl Oxazolidinone 80: To a stirred mixture of (trimethylsilyl)propargyl oxazolidinone **80** (100 mg, 0.37 mmol) and TMEDA (275 µL, 1.83 mmol), in diethyl ether (3.6 mL) at -78°C, was added n-butyllithium (1.54 M, 0.40 mmol). The reaction mixture was stirred for 1 hour at -78°C, during which time an orange color developed. At this time, tributyltin chloride (99 µL, 0.37 mmol) was added and the reaction was stirred a final 30 minutes at -78°C. The reaction was quenched by addition of 10 % aqueous ammonium chloride solution (5 mL) and allowed to warm to room temperature. Diethyl ether (40 mL) is added and the aqueous layer is separated. The organic layer is washed with brine (5 mL), dried with magnesium sulfate, filtered, and concentrated under reduced pressure to give the crude reaction product. Purification via flash column chromatography with silica gel, eluting with 9:1 hexane:diethyl ether, gave the title compound **70** (106.9 mg, 52 %) as a clear oil. Spectroscopic data matched that shown above.



81

Synthesis of Allenyl Stannanes 82 and 94 from (Trimethylsilyl)Propargylic Oxazolidinone 80; Allenyl Stannane 81: To a stirred solution of (trimethylsilyl)propargyl oxazolidinone **80** (1.0 g, 3.66 mmol) and TMEDA (550 µL, 3.66 mmol) in THF (36 mL), cooled to -78°C, was added n-butyllithium (1.48 M in hexane, 4.03 mmol). The mixture was stirred for 45 minutes at -78°C, during which time an orange color

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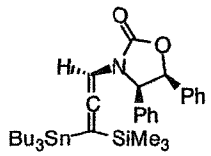
developed, then magnesium(II) bromide (0.12 M in THF, 4.03 mmol) was added and the reaction was stirred an additional 15 minutes. Tributyltin chloride (990 µL, 3.66 mmol) was added and the reaction was stirred a final 30 minutes at -78°C. The reaction was quenched by the addition of saturated aqueous sodium bicarbonate solution (25 mL) at -78°C, allowed to warm to room temperature, and extracted with diethyl ether (200 mL). The organic layer was dried with magnesium sulfate, filtered, and concentrated under pressure to give the crude reaction product. Purification via silica flash chromatography with silica gel, eluting with 4:1 hexane:diethyl ether, gave allenyl stannane **81** (1.60 g, 80 %) as a white wax of >95 % de (determined by comparison of the tin satelites of the major diastereomer to the minor peak of the allenyl proton in the ^{1}H NMR spectrum).

^{1}H NMR (400 MHz) δ : 7.36 (m, 3H), 7.23 (m, 2H), 6.23 (s, 1H), 4.66 (m, 2H), 4.04 (dd, J_1=4.5, J_2=7.8, 1H), 1.28 (m, 12H), 0.89 (t, J=7.2, 9H), 0.66 (m, 6H), 0.09 (s, 9H).

^{13}C NMR (75 MHz) δ: 202.2, 155.8, 140.0, 129.4, 128.8, 126.5, 102.9, 84.9, 70.8, 60.3, 29.1, 28.1, 27.8, 27.5, 13.9, 10.8, 0.0.



94

Allenyl Stannane 94: This compound was made by the procedure described above using (trimethylsilyl)propargyl oxazolidinone **93** (2.0 g, 5.7 mmol), TMEDA (860 µL, 5.7 mmol), n-butyllithium (1.5 M in hexane, 6.3 mmol), magnesium(II) bromide (0.1 M in THF, 5.7 mL), and tributyltin hydride (1.7 mL, 6.3 mmol), in THF (57 mL).

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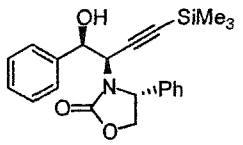
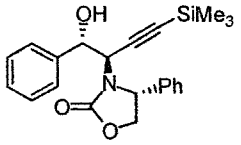
Purification via silica flash chromatography with silica gel, eluting with 4:1 hexane:diethyl ether, gave allenyl stannane **94** (2.55 g, 70 %) as an off-white oil of >95 % de (determined by comparison of the tin satelites of the major diastereomer to the minor peak of the allenyl proton in the ^{1}H NMR spectrum).

^{1}H NMR (400 MHz) δ : 7.05 (m, 6H), 6.94 (m, 2H), 6.79 (m, 2H), 6.32 (s, 1H), 5.86 (d, J=8.1, 1H), 4.87 (d, J=8.1, 1H), 1.20 (m, 12 H), 0.84 (t, J=6.6, 9H), 0.57 (m, 6H), 0.10 (s, 9H).

^{13}C NMR (75 MHz) δ: 202.5, 155.3, 135.1, 134.4, 128.4, 128.2, 128.1, 128.0, 127.4, 126.5, 102.9, 85.0, 80.5, 65.1, 29.1, 27.7, 27.4, 13.9, 10.7, 0.0.



83



84

Tin(II) Chloride Promoted Condensation of Allenyl Stannane 81 with Benzaldehyde; Synthesis of Diastereomeric Homopropargylic Alcohols 83 and 84: To a stirred solution of allenyl stannane **81** (500 mg, 0.89 mmol) and benzaldehyde (91 µL, 0.89 mmol), cooled to 0°C, was added tin(II) chloride (169 mg, 0.89 mmol) in one portion. The reaction was stirred at 0°C for 4 hours then allowed to slowly warm to room temperature overnight. The reaction was quenched by pouring into 10 % aqueous ammonium chloride (25 mL) and diluted with diethyl ether (100 mL). The organic layer was separated, washed with brine, dried with magnesium sulfate, filtered, and concentrated under reduced pressure to give the crude reaction product. NMR spectroscopy of the crude reaction mixture showed an approximate 2:1 mixture of diastereomeric products. Purification

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via flash column chromatography with silica gel, eluting with 3:1 hexane:ethyl acetate gave homopropargylic alcohol **83** (156.7 mg, 46 %) and homopropargylic alcohol **84** (89.9 mg, 27 %) both as white solids.

Homopropargylic Alcohol 83:

MP: 171 - 173°C

IR (thin film): 3438 cm^{-1} (OH), 1731 cm^{-1} (CO).

^1H NMR (400 MHz) δ : 7.32 (m, 8H), 7.14 (m, 2H), 5.11 (t, J=5.6, 1H), 4.88 (t, J=8.4, 1H), 4.54 (t, J=8.4, 1H), 4.39 (d, J=6.8, 1H), 4.05 (dd, J_1=7.6, J_2=8.4, 1H), 3.85 (d, J=5.6, 1H), 0.00 (s, 9H).

^{13}C NMR (75 MHz) δ: 159.2, 140.1, 137.5, 129.2, 128.4, 128.3, 127.6, 126.8, 98.8, 92.9, 74.6, 71.2, 60.4, 53.6, -0.2.

The absolute configuration of this product was determined by single-crystal X-ray analysis (see appendix 2).

Homopropargylic Alcohol 84:

This product was not fully characterized.

^1H NMR (400 MHz) δ : 7.35 (m, 3H), 7.30 (s, 5H), 7.14 (m, 2H), 5.22 (t, J=3.9, 1H), 4.88 (t, J=8.4, 1H), 4.60 (t, J=8.7, 1H), 4.16 (d, J=4.5, 1H), 4.09 (t, J=7.8, 1H), 3.92 (d, J=3.6, 1H), 0.09 (s, 9H). Some minor impurities are visible in this spectrum.

The absolute configuration of this product was determined by single-crystal X-ray analysis (see appendix 3).

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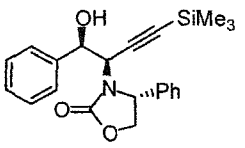
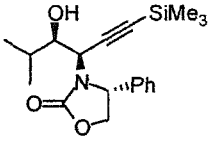


83

General Procedure for the Condensation of Allenyl Stannanes 81 and 93 with Aldehydes; Synthesis of Homopropargylic Alcohol 83: To stirred solution of allenyl stannane **81** (100 mg, 0.18 mmol) and benzaldehyde (24 µL, 0.23 mmol), in methylene chloride (900 µL) at -78°C, was added boron trifluoride diethyl etherate (55 µL, 0.45 mmol). The reaction was stirred at -78°C for 2.5 - 3 hours, until no allenyl stannane remained by TLC, then quenched at -78°C with saturated sodium bicarbonate (5 mL) and stirred an additional 15 - 20 minutes while arming to room temperature. The reaction mixture was diluted with diethyl ether (40 mL) and the organic phase was separated, dried with magnesium sulfate, filtered, and concentrated under reduced pressure to give the crude reaction product The diastereoselectivity of this reaction was determined to be > 95:5. Purification through silica gel, eluting with 3:1 hexane:ethyl acetate, gave homopropargylic alcohol **83** (64.2 mg, 95 %) as a white solid. Spectral data matched that shown above.



85

Homopropargyl Alcohol 85: This compound was made according to the general procedure using allenyl stannane **81** (100 mg, 0.18 mmol), isobutyraldehyde (21 µL, 0.23 mmol), and boron trifluoride diethyl etherate (55 µL, 0.45 mmol) in methylene chloride (900 µL). The diastereoselectivity of this reaction was determined to be > 95:5. Purification via flash column chromatography with silica gel, eluting with 3:1

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hexanes:ethyl acetate, gave homopropargylic alcohol **85** (58.6 mg, 95 %) as a white crystalline solid.

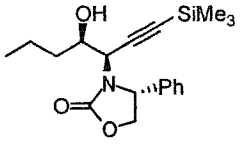
MP: 167 - 168°C

IR (thin film): 3342 cm^{-1} (OH), 1714 cm^{-1} (CO).

^1H NMR δ: 7.38 (m, 5H), 5.04 (dd, J_1=6.9, J_2=8.7, 1H), 4.65 (t, J=8.7, 1H), 4.43 (d, J=7.8, 1H), 4.16 (dd, J_1=6.9, J_2=7.5, 1H), 3.77 (ddd, J_1=5.1, J_2=7.2, J_3=12.0, 1H), 2.36 (d, J=6.9, 1H), 1.96 (m, 1H), 0.94 (dd, J_1=7.2, J_2=12.6, 6H), -0.01 (s, 9H).

^{13}C NMR (75 MHz) δ: 159.1, 138.4, 129.1, 129.0, 127.8, 99.9, 92.0, 76.6, 71.1, 59.6, 50.3, 30.0, 20.1, 15.9, -0.1.

Elemental Analysis, for $C_{19}H_{27}NO_3Si$, (calc.) C 66.05, H 7.88, N 4.05, (found) C 65.94, H 7.85, N 4.05.



86

Homopropargyl Alcohol 86: This compound was made according to the general procedure using allenyl stannane **81** (100 mg, 0.18 mmol), butyraldehyde (21 µL, 0.23 mmol), and boron trifluoride diethyl etherate (55 µL, 0.45 mmol) in methylene chloride (900 µL). The diastereoselectivity of this reaction was determined to be > 95:5. Purification via flash column chromatography with silica gel, eluting with 3:1 hexanes:ethyl acetate, gave homopropargylic alcohol **86** (56.9 mg, 93 %) as a white crystalline solid.

MP: 123 - 126°C

IR (thin film): 3494 cm^{-1} (OH), 1716 cm^{-1} (CO).

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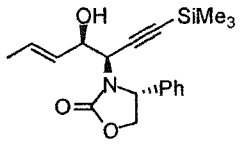
^{1}H NMR δ: 7.38 (s, 5H), 5.04 (dd, J_1=5.1, J_2=6.3, 1H), 4.66 (t, J=6.6, 1H), 4.23 (d, J=5.4, 1H), 4.15 (dd, J_1=5.4, J_2=6.6, 1H), 3.99 (dq, J_1=2.4, J_2=6.6, 1H), 2.69 (d, J=4.8, 1H), 1.62 (m, 2 H), 1.42 (m, 2H), 0.93 (t, J=5.4, 3H), 0.0 (s, 9H).

^{13}C NMR (75 MHz) δ: 159.0, 138.2, 129.2, 127.8, 99.8, 92.2, 72.3, 71.1, 59.9, 52.5, 36.3, 19.0, 14.2, -0.1.

Elemental Analysis, for $C_{19}H_{27}NO_3Si$, (calc.) C 66.05, H 7.88, N 4.05, (found) C 66.26, H 8.05, N 4.20.



87

Homopropargyl Alcohol 87: This compound was made according to the general procedure using allenyl stannane **81** (100 mg, 0.18 mmol), crotonaldehyde (29.5 µL, 0.36 mmol), and boron trifluoride diethyl etherate (55 µL, 0.45 mmol) in methylene chloride (900 µL). The diastereoselectivity of this reaction was determined to be > 90:10. Purification via flash column chromatography with silica gel, eluting with 3:1 hexanes:ethyl acetate, gave homopropargylic alcohol **87** (49.4 mg, 80 %) as a white crystalline solid.

MP: 179 - 183°C

IR (thin film): 3398 cm^{-1} (OH), 1747 cm^{-1} (CO).

^{1}H NMR δ: 7.38 (s, 5H), 5.82 (ddq, J_1=1.2, J_2=6.6, J_3=15.3, 1H), 5.47 (ddd, J_1=1.5, J_2=6.0, J_3=15.0, 1H), 5.02 (dd, J_1=7.2, J_2=8.7, 1H), 4.63 (t, J=8.4, 1H), 4.44 (q, J=6.6, 1H), 4.30 (d, J=6.9, 1H), 4.14 (dd, J_1=6.9, J_2=8.4, 1H), 2.88 (d, J=6.3, 1H), 1.73 (d, J=6.6, 3H), 0.0 (s, 9H).

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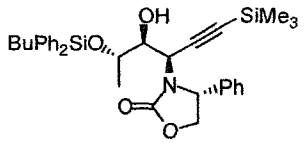
^{13}C NMR (75 MHz) δ: 159.0, 138.2, 129.6, 129.3, 129.2, 129.1, 127.8, 99.2, 92.6, 73.1, 71.1, 59.9, 52.4, 18.0, -0.1.

Elemental Analysis, for $C_{19}H_{25}NO_3Si$, (calc.) C 66.44, H 7.34, N 4.08, (found) C 66.28, H 7.13, N 4.06.



88

Homopropargyl Alcohol 88: This compound was made according to the general procedure using allenyl stannane **81** (100 mg, 0.18 mmol), (S)-2-(tertbutyldiphenylsilyloxy)propanal (72.2 mg, 0.23 mmol), and boron trifluoride diethyl etherate (55 μL, 0.45 mmol) in methylene chloride (900 μL). The diastereoselectivity of this reaction was determined to be 85:15. Purification via flash column chromatography with silica gel, eluting with 3:1 hexanes:ethyl acetate, gave homopropargylic alcohol **88** (70.8 mg, 68 %) as a white crystalline solid.

MP: 197 - 198°C

IR (thin film): 3381 cm^{-1} (OH), 1705 cm^{-1} (CO).

^1H NMR (400 MHz) δ: 7.68 (m, 4H), 7.42 (m, 5H), 7.36 (m, 6H), 4.94 (t, J=8.8, 1H), 4,90 (d, J=10.0, 1H), 4.63 (t, J=8.8, 1H), 4.26 (q, J=10.4, 1H), 4.12 (t, J=10, 1H), 3.65 (t, J= 10.0, 1H), 2.50 (d, J=10.8, 1H), 1.04 (d, J=7.2, 3H), 1.03 (s, 9H), -0.01 (s, 9H).

^{13}C NMR (75 MHz) δ: 159.5, 138.5, 136.1, 136.0, 134.3, 133.0, 130.1, 129.9, 129.6, 129.0, 128.0, 127.7, 127.5, 99.7, 92.1, 75.2, 71.0, 68.7, 59.0, 49.8, 27.1, 26.9, 21.1, 19.7, 0.1, -0.2..

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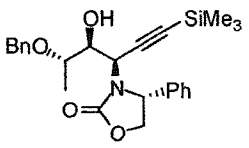
Elemental Analysis, for $C_{34}H_{43}NO_4Si$, (calc.) C 69.70, H 7.40, N 2.47, (found) C 69.80, H 7.47, N 2.47.



89

Homopropargyl Alcohol 89: This compound was made according to the general procedure using allenyl stannane **81** (100 mg, 0.18 mmol), (S)-2-benzyloxypropanal (0.26 M in methylene chloride, 0.23 mmol), and boron trifluoride diethyl etherate (55 µL, 0.45 mmol). The diastereoselectivity of this reaction was determined to be > 92:8. Purification via flash column chromatography with silica gel, eluting with 3:1 hexanes:ethyl acetate, gave homopropargylic alcohol **89** (67.7 mg, 87 %) as a white crystalline solid.

MP: 110 - 112°C

IR (thin film): 3382 cm^{-1} (OH), 1713 cm^{-1} (CO).

^1H NMR (400 MHz) δ: 7.37 (m, 7H), 7.29 (m, 3H), 4.95 (t, J=8.7, 1H), 4.80 (d, J=9.9, 1H), 4.64 (d, J=12.9, 1H), 4.62 (t, J=8.4, 1H), 4.44 (d, J=11.7, 1H), 4.11 (t, J=8.4, 1H), 3.87 (q, J=6.3, 1H), 3.73 (t, J=10.2, 1H), 2.36 (d, J=10.5, 1H), 1.31 (d, J=6.3, 3H), -0.07 (s, 9H).

^{13}C NMR (75 MHz) δ: 159.3, 138.4, 138.0, 129.1, 129.0, 128.6, 128.0, 127.9, 99.8, 92.0, 74.8, 72.7, 71.4, 71.0, 59.0, 49.6, 16.7, -0.2.

The absolute configuration of this product was determined by single-crystal X-ray analysis (see appendix 4).

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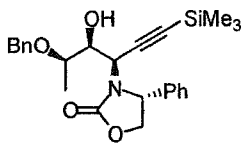


90

Homopropargyl Alcohol 90: This compound was made according to the general procedure using allenyl stannane **81** (100 mg, 0.18 mmol), (R)-2-benzyloxypropanal (0.26 M in methylene chloride, 0.23 mmol), and boron trifluoride diethyl etherate (55 µL, 0.45 mmol). The diastereoselectivity of this reaction was not able to be determined. Purification via flash column chromatography through silica gel, eluting with 3:1 hexanes:ethyl acetate, gave homopropargylic alcohol **90** (67.5 mg, 87 %) as a white crystalline solid.

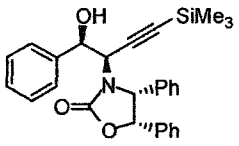
MP: 220 - 221°C

IR (thin film): 1719 cm^{-1} (CO).

^1H NMR (400 MHz) δ: 7.32 (M, 10 H), 5.00 (dd, J_1=6.9, J_2=8.7, 1H), 4.57 (m, 3H), 4.44 (d, J=11.7, 1H), 4.10 (m, 2H), 3.75 (dq, J_1=4.2, J_2=6.3, 1H), 2.85 (d, J=4.5, 1H), 1.24 (d, J=63, 3H), -0.04 (s, 9H).

^{13}C NMR (75 MHz) δ: 159.0, 138.4, 129.1, 129.0, 128.6, 128.0, 127.9, 99.4, 92.1, 74.9, 73.1, 71.0, 70.8, 59.4, 48.5, 13.9, -0.2.

The absolute configuration of this product was determined by single-crystal X-ray analysis (see appendix 5).



95

Homopropargyl Alcohol 95: This compound was made according to the general procedure using allenyl stannane **94** (500 mg, 0.78 mmol), benzaldehyde (104 µL, 1.02 mmol), and boron trifluoride diethyl etherate (240 µL, 1.96 mmol) in methylene chloride (4.0 mL). The extraction solvent was 4:1 diethyl ether:methylene chloride (100

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mL) due to solubility problems. The diastereoselectivity of this reaction was determined to be ~ 95:5. Purification via flash column chromatography through silica gel, eluting with 97:3 methylene chloride:ethyl acetate, gave homopropargylic alcohol **95** (308.5 mg, 85 %) as a white crystalline solid.

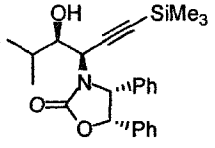
MP: 252 - 254°C

IR (thin film): 3434 cm^{-1} (OH), 1721 cm^{-1} (CO).

^1H NMR (300 MHz) δ: 7.41 (m, 5H), 7.03 (m, 6H), 6.85 (m, 2H), 6.70 (d, J=6.9, 2H), 5.64 (d, J=7.8, 1H), 5.15 (t, J=6.0, 1H), 5.05 (d, J=7.8, 1H), 4.71 (d, J=6.9, 1H), 3.61 (d, J=5.7, 1H), -0.07 (s, 9H).

^{13}C NMR (75 MHz) δ: 158.9, 139.8, 134.4, 134.2, 128.6, 128.5, 128.3, 128.2, 128.1, 128.0, 126.9, 126.4, 98.5, 93.9, 81.2, 75.0, 64.7, 53.5, -0.3.

Elemental Analysis, for $C_{28}H_{29}NO_3Si$, (calc.) C 73.81, H 6.42, N 3.07, (found) C 74.00, H 6.47, N 3.18.



96

Homopropargyl Alcohol 96: This compound was made according to the general procedure using allenyl stannane **94** (500 mg, 0.78 mmol), isobutyraldehyde (93 µL, 1.02 mmol), and boron trifluoride diethyl etherate (240 µL, 1.96 mmol) in methylene chloride (4.0 mL). The extraction solvent was 4:1 diethyl ether:methylene chloride (100 mL) due to solubility problems. The diastereoselectivity of this reaction was determined to be > 95:5. Purification via flash column chromatography through silica gel, eluting with 97:3 methylene chloride:ethyl acetate, gave homopropargylic alcohol **96** (295.9 mg, 90 %) as a white crystalline solid.

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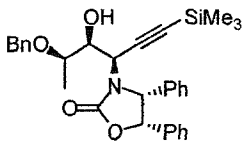
MP: 96 - 106°C

IR (thin film): 3531 cm^{-1} (OH), 1725 cm^{-1} (CO).

^1H NMR (300 MHz) δ: 7.06 (m, 6H), 6.93 (m, 4H), 5.85 (d, J=7.5, 1H), 5.29 (d, J=8.1, 1H), 4.71 (d, J=6.9, 1H), 3.75 (q, J=6.0, 1H), 2.37 (d, J=5.7, 1H), 2.03 (septet, J=6.0, 1H), 1.04 (d, J=6.9, 3H), 0.99 (d, J=6.6, 3H), -0.1 (s, 9H).

^{13}C NMR (75 MHz) δ:158.7, 134.9, 134.3, 128.3, 128.2, 128.1, 128.0, 126.4, 99.7, 92.9, 81.1, 78.1, 64.3, 50.2, 30.1, 20.0, 16.6, -0.3.

Elemental Analysis, for $C_{25}H_{31}NO_3Si$, (calc.) C 71.22, H 7.41, N 3.32, (found) C 71.41, H 7.24, N 3.40.



97

Homopropargyl Alcohol 97: This compound was made according to the general procedure using allenyl stannane **94** (500 mg, 0.78 mmol), (R)-2-benzyloxypropanal (0.26 M in methylene chloride, 1.02 mmol), and boron trifluoride diethyl etherate (240 µL, 1.96 mmol). The extraction solvent was 4:1 diethyl ether:methylene chloride (100 mL) due to solubility problems. Purification via flash column chromatography through silica gel, eluting 97:3 methylene chloride:ethyl acetate, gave homopropargylic alcohol **97** (245.9 mg, 61 %) as a white crystalline solid.

MP: 150 - 152°C

IR (thin film): 3459 cm^{-1} (OH), 1733 cm^{-1} (CO).

^1H NMR (300 MHz) δ: 7.37 (m, 5H), 7.07 (m, 6H), 6.89 (m, 4H), 5.71 (d, J=7.5, 1H), 5.21 (d, J=7.8, 1H), 4.83 (d, J=7.2, 1H), 4.65 (d, J=11.4, 1H), 4.50 (d,

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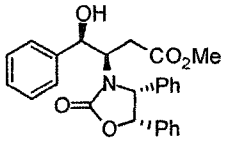
J=11.4, 1H), 4.05 (m, 1H), 3.81 (quintet, J=5.7, 1H), 2.73 (d, J=4.5, 1H), 1.32 (d, J=6.3, 3H), -0.12 (s, 9H).

^{13}C NMR (75 MHz) δ: 158.6, 138.3, 135.0, 134.5, 128.7, 128.3, 128.2, 128.1, 128.0, 127.9, 126.4, 99.2, 92.9, 81.0, 74.9, 74.3, 71.0, 64.0, 48.7, 14.3, -0.3.

Elemental Analysis, for $C_{31}H_{35}NO_4Si$, (calc.) C 72.48, H 6.87, N 2.73, (found) C 72.43, H 6.78, N 2.59.



98

Hydroboration/Oxidation of (Trimethylsilyl)Alkynes to the Corresponding Ester; Synthesis of β-Amino Ester 98: To a stirred solution of cyclohexene (115 µL, 1.1 mmol) in THF (1.1 mL), cooled to 0°C, was added borane methylsulfide complex (55 µL, 0.55 mmol). The reaction was warmed to room temperature and stirred for 1 hour, then re-cooled to 0°C. Homopropargylic alcohol **95** (50 mg, 0.11 mmol) in THF (1.1 mL) was added dropwise and reaction was again allowed to warm to room temperature and stirred for 1.5 hours (until no **95** was visible by TLC). The reaction was then quenched by the addition of saturated ammonium bicarbonate solution (1.1 mL) followed by addition of 30 % aqueous hydrogen peroxide (400 µL). The reaction was stirred a final 3 hours, re-cooled to 0°C, and acetic acid (220 µL) was added. The reaction was stirred overnight then extracted with methylene chloride (4 x 5 mL). The combined organic extracts were dried with magnesium sulfate, filtered, and concentrated under reduced pressure. The white residue thus generated was re-dissolved in 4:1 benzene:methanol (2.2 mL), (trimethylsilyl)diazomethane (2.0 M in hexane, 0.22

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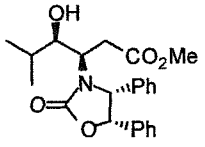
mmol) was added, and the reaction allowed to stir for 30 minutes then concentrated under reduced pressure to give the crude reaction product. Purification by flash column chromatography with silica gel, eluting with 95:5 methylene chloride:ethyl acetate, gave β-amino ester **98** (30.6 mg, 64 %) as a white solid with some (< 1 equivalent) dimethyl sulfone contaminant. The dimethyl sulfone was removed by sublimation under reduced pressure, heating to approximately 40°C and this compound was used without further purification.

IR (thin film): 3467 cm^{-1} (OH), 1735 cm^{-1} (CO).

^1H NMR (300 MHz) δ: 7.30 (m, 5H), 7.05 (m, 4H), 6.91 (m, 2H), 6.80 (m, 2H), 6.41 (bs, 2H), 5.71 (d, J=8.4, 1H), 5.21 (d, J=8.4, 1H), 4.99 (t, J=7.5, 1H), 4.64 (d, J=8.4, 1H), 3.99 (q, J=6.0, 1H), 3.67 (s, 3H), 2.86 (dd, J_1=7.5, J_2=16.8, 1H), 2.77 (dd, J_1=5.7, J_2=16.8, 1H).

^{13}C NMR (75 MHz) δ: 172.0, 159.9, 141.3, 134.6, 133.7, 128.7, 128.6, 128.5, 128.2, 128.1, 128.0, 127.9, 126.6, 126.1, 81.0, 75.2, 66.2, 57.4, 52.2, 34.4.



99

Synthesis of β-Amino Ester 99: This compound was made by the procedure described above using cyclohexene (150 µL, 1.42 mmol) and borane methylsulfide complex (71 µL, 0.71 mmol) in THF (1.4 mL), homopropargylic alcohol **96** (60 mg, 0.142 mmol) in THF (1.4 mL), saturated aqueous sodium bicarbonate (1.4 mL), 30 % hydrogen peroxide (500 µL), and acetic acid (300 µL). The crude product was esterified in 4:1 benzene:methanol (2.8 mL) using (trimethylsilyl)diazomethane (150 µL,

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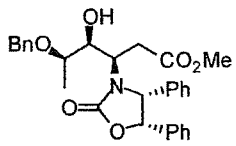
0.284 mmol). Purification by flash column chromatography with silica gel, eluting with 95:5 methylene chloride:ethyl acetate, followed by sublimation, gave β-amino ester **99** (35.5 mg, 63 %) as a white solid.

IR (thin film): 3468 cm^{-1} (OH), 1747 cm^{-1} (CO).

^1H NMR (300 MHz) δ: 7.09 (m, 6H), 7.00 (m, 4H), 5.90 (d, J=8.4, 1H), 5.32 (d, J=8.1, 1H), 4.19 (dt, J_1=4.5, J_2=7.2, 1H), 3.64 (s, 3H), 3.36 (dt, J_1=3.3, J_2=4.5, 1H), 3.17 (d, J=7.2, 1H), 2.68 (dd, J_1=7.8, J_2=16.2, 1H), 2.49 (dd, J_1=6.3, J_2=16.5, 1H), 1.72 (sextet, J=6.6, 1H), 0.97 (d, J=6.6, 3H), 0.69 (d, J=6.6, 3H).

^{13}C NMR (75 MHz) δ: 172.2, 158.9, 135.8, 134.6, 128.7, 128.4, 128.1, 127.9, 126.0, 80.9, 78.4, 65.9, 53.6, 52.1, 35.9, 31.1, 19.6, 18.4.



100

Synthesis of β-Amino Ester 100: This compound was made by the procedure described above using cyclohexene (307 μL, 2.92 mmol) and borane methylsulfide complex (146 μL, 1.46 mmol) in THF (2.9 mL), homopropargylic alcohol **97** (150 mg, 0.292 mmol) in THF (2.9 mL), saturated aqueous sodium bicarbonate (2.9 mL), 30 % hydrogen peroxide (1000 μL), and acetic acid (580 μL). The crude product was esterified in 4:1 benzene:methanol (5.8 mL) using (trimethylsilyl)diazomethane (300 μL, 0.58 mmol). Purification by flash column chromatography with silica gel, eluting with 95:5 methylene chloride:ethyl acetate, followed by sublimation, gave β-amino ester **100** (88.4 mg, 62 %) as a white solid.

IR (thin film): 3416 cm^{-1} (OH), 1740 cm^{-1} (CO).

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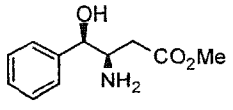
^{1}H NMR (300 MHz) δ: 7.25 (m, 5H), 7.06 (m, 6H), 6.93 (m, 4H), 5.74 (d, J=8.1, 1H), 5.28 (d, J=7.8, 1H), 4.44 (d, J=11.4, 1H), 4.39 (m, 1H), 3.94 (d, J=10.8, 1H), 3.80 (d, J=6.6, 1H), 3.71 (q, J=3.6, 1H), 3.61 (s, 3H), 3.53 (t, J=6.3, 1H), 2.79 (dd, J_1=7.5, J_2=16.8, 1H), 2.51 (dd, J_1=6.0, J_2=17.1, 1H), 1.31 (d, J=5.7, 3H).



101

Synthesis of γ-Hydroxy-β-Amino Ester 101: A stirred solution of β-amino ester **98** (29.8 mg, 0.069 mmol) in ethanol (7.0 mL), under argon, was added 10 % palladium on carbon (15 mg, 0.014 mmol). The reaction mixture was flushed with hydrogen gas for 15 seconds then stirred under a balloon of hydrogen 17 hours. The reaction was filtered through a pad of celite, rinsing with ethanol (5 mL), and concentrated under reduced pressure to give the crude reaction mixture. The crude residue was dissolved in diethyl ether and again filtered through a pad of celite, to remove any insoluble impurities, and again concentrated under reduced pressure. The dibenzyl by-product was removed by trituration with hexane (4 x 1 mL) to give γ-hydroxy-β-amino ester **101** (11.2 mg, 78 %) as a white crystalline solid.

MP: 97 - 98°C

IR (thin film): 3123 cm^{-1} (OH), 1729 cm^{-1} (CO).

^{1}H NMR (300 MHz) δ: 7.36 (s, 5H), 4.44 (d, J=6.0, 1H), 3.68 (s, 3H), 3.35 (m, 1H), 2.50 (dd, J_1=4.2, J_2=15.9, 1H), 2.34 (dd, J_1=9.3, J_2=16.2, 1H), 2.13 (bs, 2H).

^{13}C NMR (75 MHz) δ: 172.8, 141.8, 128.7, 128.1, 126.8, 76.6, 54.6, 51.9, 39.0.

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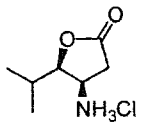
Elemental Analysis, for $C_{11}H_{15}NO_3 \cdot 0.5H_2O$, (calc.) C 60.54, H 7.39, N 6.42, (found) C 60.27, H 6.94, N 6.17.

HRMS for $C_{11}H_{16}NO_3$, (calc.) 210.113019, (found) 210.112010.



103

Synthesis of β-Amino-γ-Butyrolactone Hydrochloride Salt 103: A stirred solution of β-amino ester **99** (50 mg, 0.126 mmol) in THF (6.3 mL), under argon, was added 10 % palladium on carbon (53.2 mg, 0.05 mmol). The reaction mixture was flushed with hydrogen gas for 15 seconds then stirred under a balloon of hydrogen 24 hours. The reaction was filtered through a pad of celite, rinsing with THF (10 mL), and concentrated under reduced pressure to give the crude reaction mixture. The crude residue was dissolved in diethyl ether and again filtered through a pad of celite, to remove any insoluble impurities, into a small round bottomed flask and again concentrated under reduced pressure. Water (2 mL) was then added and suspension was gently heated and swirled for approximately 2 – 3 minutes. The suspension was filtered through a plug of cotton and the filtrate was extracted with methylene chloride (5 x 5 mL) and dried with sodium sulfate. The residue on the cotton filter and in the round bottomed were dissolved in methylene chloride, dried with sodium sulfate, combined with dried methylene chloride layer from the extraction, and concentrated under reduced pressure to approximately 5 mL volume. Excess hydrochloric acid (saturated in diethyl ether, 250 μL) was added, and the solution was allowed to stand for 1-2 minutes, then concentrated to dryness under reduced pressure. The dibenzyl

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byproduct was removed by trituration with hexane (4 x 1 mL) and the remaining solid was recrystallized from ethanol:hexane (3 crops total) to give β-amino-γ-butyrolactone hydrochloride salt **103** (14.2 mg, 63 %) as a white cottony solid.

MP: 228 - 230°C

IR (thin film): 2918 cm^{-1} (NH_3^+), 1770 cm^{-1} (CO).

^1H NMR (300 MHz, D_4-methanol) δ: 4.26 (m, 2H), 3.25 (dd, J_1=6.1, J_2=18.3, 1H), 2.62 (d, J=18.3, 1H), 1.92 (d septets, J_1=6.0, J_2=4.2, 1H), 1.19 (d, J=6.0, 3H), 1.03 (d, J=6.6, 3H).

^{13}C NMR (75 MHz) δ: 174.8, 87.4, 51.4, 36.8, 28.7, 20.4, 18.1.

Elemental Analysis, for $C_7H_{14}ClNO_3$, (calc.) C 46.80, H 7.86, N 7.80, (found) C, 47.03 H 7.65, N 7.73.

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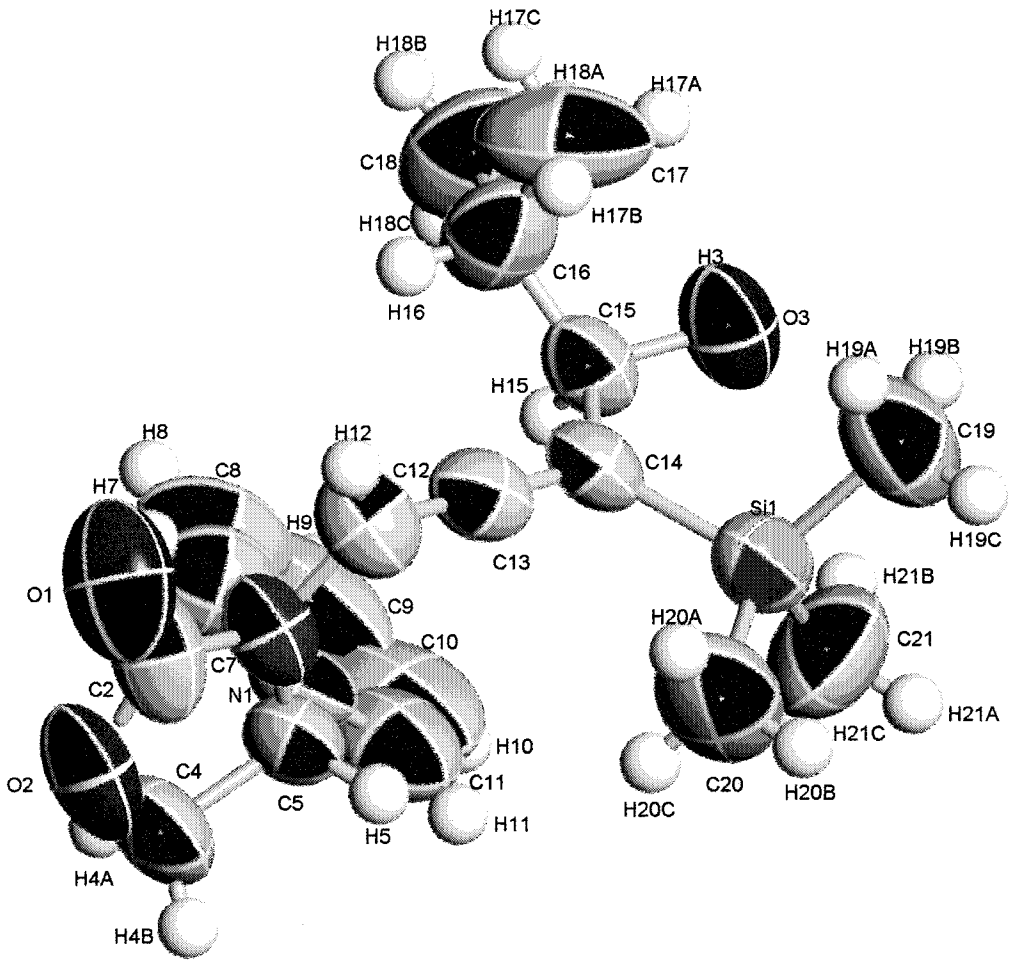
Appendix 1: X-ray structure of compound **75**



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Appendix 1: Crystal data and structure refinement for compound **75**.

Identification code	pbdr – 3466RX	
Empirical formula	C19 H27 N O3 Si	
Formula weight	345.51	
Temperature	298(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhobmic	
Space group	P(2)1(2)1(2)1	
Unit cell dimensions	a = 8.4892(15) Å	α= 90°.
	b = 15.160(3) Å	β= 90°.
	c = 16.637(3) Å	γ = 90°.
Volume	2141.0(7) Å^3	
Z	4	
Density (calculated)	1.072 Mg/m^3	
Absorption coefficient	0.124 mm^{-1}	
F(000)	744	
Crystal size	0.24 x 0.20 x 0.20 mm^3	
Theta range for data collection	3.43 to 23.27°.	
Index ranges	-9<=h<=9, -16<=k<=16, -18<=l<=18	
Reflections collected	13691	
Independent reflections	3080 [R(int) = 0.0793]	
Completeness to theta = 23.27°	99.6 %	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3080 / 0 / 224	
Goodness-of-fit on F^2	0.845	
Final R indices [I>2sigma(I)]	R1 = 0.0466, wR2 = 0.0797	
R indices (all data)	R1 = 0.1394, wR2 = 0.0979	
Absolute structure parameter	0.0(2)	
Extinction coefficient	0.0006(7)	
Largest diff. peak and hole	0.100 and -0.102 e.Å^{-3}	

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Appendix 1: Bond lengths [Å] and angles [°] for compound **75**.

Si(1)-C(19)	1.850(4)	C(2)-O(2)-C(4)	111.0(4)
Si(1)-C(20)	1.856(5)	C(2)-N(1)-C(12)	120.5(5)
Si(1)-C(21)	1.856(5)	C(2)-N(1)-C(5)	114.1(4)
Si(1)-C(14)	1.866(4)	C(12)-N(1)-C(5)	124.2(4)
O(1)-C(2)	1.201(5)	O(1)-C(2)-O(2)	124.8(6)
O(2)-C(2)	1.341(6)	O(1)-C(2)-N(1)	126.9(6)
O(2)-C(4)	1.410(5)	O(2)-C(2)-N(1)	108.3(5)
O(3)-C(15)	1.419(4)	O(2)-C(4)-C(5)	107.1(4)
N(1)-C(2)	1.351(6)	N(1)-C(5)-C(6)	113.3(4)
N(1)-C(12)	1.412(5)	N(1)-C(5)-C(4)	99.0(4)
N(1)-C(5)	1.456(5)	C(6)-C(5)-C(4)	113.2(4)
C(4)-C(5)	1.533(5)	C(11)-C(6)-C(7)	119.0(5)
C(5)-C(6)	1.505(5)	C(11)-C(6)-C(5)	118.8(6)
C(6)-C(11)	1.360(6)	C(7)-C(6)-C(5)	122.1(5)
C(6)-C(7)	1.369(6)	C(6)-C(7)-C(8)	121.7(6)
C(7)-C(8)	1.386(6)	C(9)-C(8)-C(7)	114.8(7)
C(8)-C(9)	1.347(8)	C(10)-C(9)-C(8)	130.1(11)
C(9)-C(10)	1.324(11)	C(9)-C(10)-C(11)	112.2(9)
C(10)-C(11)	1.449(9)	C(6)-C(11)-C(10)	122.0(7)
C(12)-C(13)	1.311(5)	C(13)-C(12)-N(1)	123.8(4)
C(13)-C(14)	1.295(6)	C(14)-C(13)-C(12)	178.2(4)
C(14)-C(15)	1.512(5)	C(13)-C(14)-C(15)	120.4(4)
C(15)-C(16)	1.528(5)	C(13)-C(14)-Si(1)	119.0(3)
C(16)-C(18)	1.524(6)	C(15)-C(14)-Si(1)	120.4(3)
C(16)-C(17)	1.534(6)	O(3)-C(15)-C(14)	108.4(4)
C(19)-Si(1)-C(20)	109.5(2)	O(3)-C(15)-C(16)	109.7(4)
C(19)-Si(1)-C(21)	110.7(2)	C(14)-C(15)-C(16)	114.6(4)
C(20)-Si(1)-C(21)	108.7(3)	C(18)-C(16)-C(15)	111.5(4)
C(19)-Si(1)-C(14)	111.8(2)	C(18)-C(16)-C(17)	111.4(4)
C(20)-Si(1)-C(14)	107.4(2)	C(15)-C(16)-C(17)	111.0(4)
C(21)-Si(1)-C(14)	108.7(2)		

Symmetry transformations used to generate equivalent atoms:

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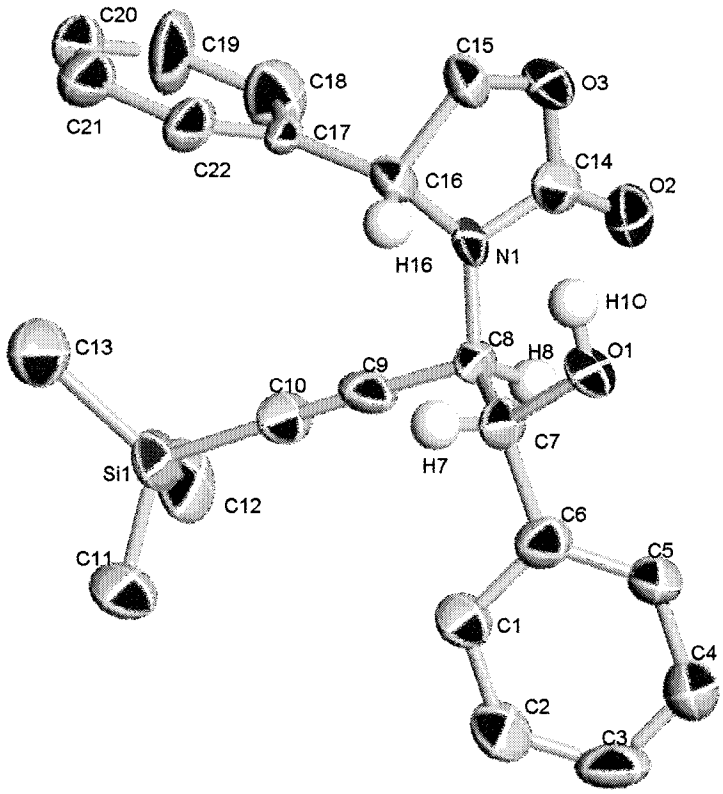
Appendix 2: X-ray structure of compound **83**



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Appendix 2: Crystal data and structure refinement for compound **83**

Identification code	lsh112	
Empirical formula	C22 H25 N O3 Si	
Formula weight	379.52	
Temperature	177(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 11.212(7) Å	α= 90°.
	b = 10.079(6) Å	β= 90.094(12)°.
	c = 18.506(11) Å	γ = 90°.
Volume	2091(2) $Å^3$	
Z	4	
Density (calculated)	1.205 Mg/m^3	
Absorption coefficient	0.133 mm^{-1}	
F(000)	808	
Crystal size	0.10 x 0.10 x 0.60 mm^3	
Theta range for data collection	3.50 to 23.16°.	
Index ranges	-10<=h<=9, -11<=k<=11, -18<=l<=18	
Reflections collected	6268	
Independent reflections	4113 [R(int) = 0.0836]	
Completeness to theta = 23.16°	69.8 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4113 / 1 / 499	
Goodness-of-fit on F^2	0.935	
Final R indices [I>2sigma(I)]	R1 = 0.0568, wR2 = 0.1366	
R indices (all data)	R1 = 0.1042, wR2 = 0.1722	
Absolute structure parameter	-0.5(3)	
Extinction coefficient	0.0102(18)	
Largest diff. peak and hole	0.295 and -0.328 $e.Å^{-3}$	

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Appendix 2: Bond lengths [Å] and angles [°] for compound **83**

Si(1)-C(10)	1.671(10)
Si(1)-C(11)	1.838(12)
Si(1)-C(13)	1.934(10)
Si(1)-C(12)	1.967(13)
O(1)-C(7)	1.294(9)
O(2)-C(14)	1.353(12)
O(3)-C(14)	1.346(11)
O(3)-C(15)	1.605(13)
N(1)-C(14)	1.369(13)
N(1)-C(8)	1.409(10)
N(1)-C(16)	1.604(11)
C(1)-C(6)	1.304(12)
C(1)-C(2)	1.385(12)
C(2)-C(3)	1.387(13)
C(3)-C(4)	1.271(12)
C(4)-C(5)	1.378(12)
C(5)-C(6)	1.382(12)
C(6)-C(7)	1.511(12)
C(7)-C(8)	1.528(15)
C(8)-C(9)	1.382(12)
C(9)-C(10)	1.067(11)
C(15)-C(16)	1.432(11)
C(16)-C(17)	1.462(11)
C(17)-C(18)	1.443(15)
C(17)-C(22)	1.477(14)
C(18)-C(19)	1.358(13)
C(19)-C(20)	1.473(17)
C(20)-C(21)	1.403(17)
C(21)-C(22)	1.366(12)
Si(1X)-C(10X)	1.672(10)
Si(1X)-C(11X)	1.856(10)
Si(1X)-C(13X)	1.944(12)
Si(1X)-C(12X)	2.009(12)
O(1X)-C(7X)	1.277(9)
O(2X)-C(14X)	1.375(11)
O(3X)-C(14X)	1.301(11)
O(3X)-C(15X)	1.595(13)
N(1X)-C(14X)	1.314(11)
N(1X)-C(8X)	1.403(11)
N(1X)-C(16X)	1.584(13)
C(1X)-C(6X)	1.278(12)
C(1X)-C(2X)	1.391(15)
C(2X)-C(3X)	1.406(16)
C(3X)-C(4X)	1.271(12)
C(4X)-C(5X)	1.443(14)
C(5X)-C(6X)	1.394(15)
C(6X)-C(7X)	1.485(14)
C(7X)-C(8X)	1.597(11)
C(8X)-C(9X)	1.370(12)
C(9X)-C(10X)	1.079(11)
C(15X)-C(16X)	1.433(11)
C(16X)-C(17X)	1.469(12)
C(17X)-C(18X)	1.454(13)
C(17X)-C(22X)	1.480(15)
C(18X)-C(19X)	1.396(14)
C(19X)-C(20X)	1.465(15)
C(20X)-C(21X)	1.417(13)
C(21X)-C(22X)	1.385(13)
C(10)-Si(1)-C(11)	105.4(5)
C(10)-Si(1)-C(13)	110.6(5)
C(11)-Si(1)-C(13)	104.5(5)
C(10)-Si(1)-C(12)	101.4(5)
C(11)-Si(1)-C(12)	116.2(5)
C(13)-Si(1)-C(12)	118.1(5)
C(14)-O(3)-C(15)	115.1(8)
C(14)-N(1)-C(8)	113.5(8)

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C(14)-N(1)-C(16)	121.5(7)	C(10X)-Si(1X)-C(12X)	100.4(5)
C(8)-N(1)-C(16)	122.9(8)	C(11X)-Si(1X)-C(12X)	114.3(5)
C(6)-C(1)-C(2)	115.2(9)	C(13X)-Si(1X)-C(12X)	117.9(5)
C(1)-C(2)-C(3)	127.0(9)	C(14X)-O(3X)-C(15X)	113.0(7)
C(4)-C(3)-C(2)	117.6(9)	C(14X)-N(1X)-C(8X)	115.6(9)
C(3)-C(4)-C(5)	115.8(10)	C(14X)-N(1X)-C(16X)	119.1(8)
C(4)-C(5)-C(6)	127.6(8)	C(8X)-N(1X)-C(16X)	123.7(7)
C(1)-C(6)-C(5)	116.6(8)	C(6X)-C(1X)-C(2X)	117.7(11)
C(1)-C(6)-C(7)	114.5(9)	C(1X)-C(2X)-C(3X)	128.1(9)
C(5)-C(6)-C(7)	128.4(8)	C(4X)-C(3X)-C(2X)	115.5(11)
O(1)-C(7)-C(6)	105.5(7)	C(3X)-C(4X)-C(5X)	116.1(11)
O(1)-C(7)-C(8)	106.2(8)	C(6X)-C(5X)-C(4X)	127.7(8)
C(6)-C(7)-C(8)	107.8(8)	C(1X)-C(6X)-C(5X)	114.8(10)
C(9)-C(8)-N(1)	104.0(7)	C(1X)-C(6X)-C(7X)	119.8(11)
C(9)-C(8)-C(7)	110.3(8)	C(5X)-C(6X)-C(7X)	125.3(7)
N(1)-C(8)-C(7)	113.8(8)	O(1X)-C(7X)-C(6X)	107.4(8)
C(10)-C(9)-C(8)	177.6(12)	O(1X)-C(7X)-C(8X)	103.9(7)
C(9)-C(10)-Si(1)	178.2(11)	C(6X)-C(7X)-C(8X)	108.6(7)
O(3)-C(14)-O(2)	126.9(9)	C(9X)-C(8X)-N(1X)	104.9(7)
O(3)-C(14)-N(1)	98.8(9)	C(9X)-C(8X)-C(7X)	108.0(7)
O(2)-C(14)-N(1)	134.2(9)	N(1X)-C(8X)-C(7X)	112.4(7)
C(16)-C(15)-O(3)	105.2(7)	C(10X)-C(9X)-C(8X)	178.8(13)
C(15)-C(16)-C(17)	106.0(7)	C(9X)-C(10X)-Si(1X)	178.1(11)
C(15)-C(16)-N(1)	95.8(7)	O(3X)-C(14X)-N(1X)	103.4(9)
C(17)-C(16)-N(1)	116.5(8)	O(3X)-C(14X)-O(2X)	125.0(9)
C(18)-C(17)-C(16)	117.0(10)	N(1X)-C(14X)-O(2X)	131.6(9)
C(18)-C(17)-C(22)	124.0(8)	C(16X)-C(15X)-O(3X)	104.0(8)
C(16)-C(17)-C(22)	118.9(10)	C(15X)-C(16X)-C(17X)	106.7(8)
C(19)-C(18)-C(17)	114.8(11)	C(15X)-C(16X)-N(1X)	96.4(7)
C(18)-C(19)-C(20)	120.5(12)	C(17X)-C(16X)-N(1X)	118.9(8)
C(21)-C(20)-C(19)	124.9(9)	C(18X)-C(17X)-C(16X)	114.2(10)
C(22)-C(21)-C(20)	115.7(12)	C(18X)-C(17X)-C(22X)	125.9(9)
C(21)-C(22)-C(17)	120.0(11)	C(16X)-C(17X)-C(22X)	119.9(8)
C(10X)-Si(1X)-C(11X)	104.4(5)	C(19X)-C(18X)-C(17X)	111.8(10)
C(10X)-Si(1X)-C(13X)	110.2(5)	C(18X)-C(19X)-C(20X)	121.3(9)
C(11X)-Si(1X)-C(13X)	108.6(6)	C(21X)-C(20X)-C(19X)	126.9(9)

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C(22X)-C(21X)-C(20X)	113.1(10)
C(21X)-C(22X)-C(17X)	120.8(9)

Symmetry transformations used to generate equivalent atoms:

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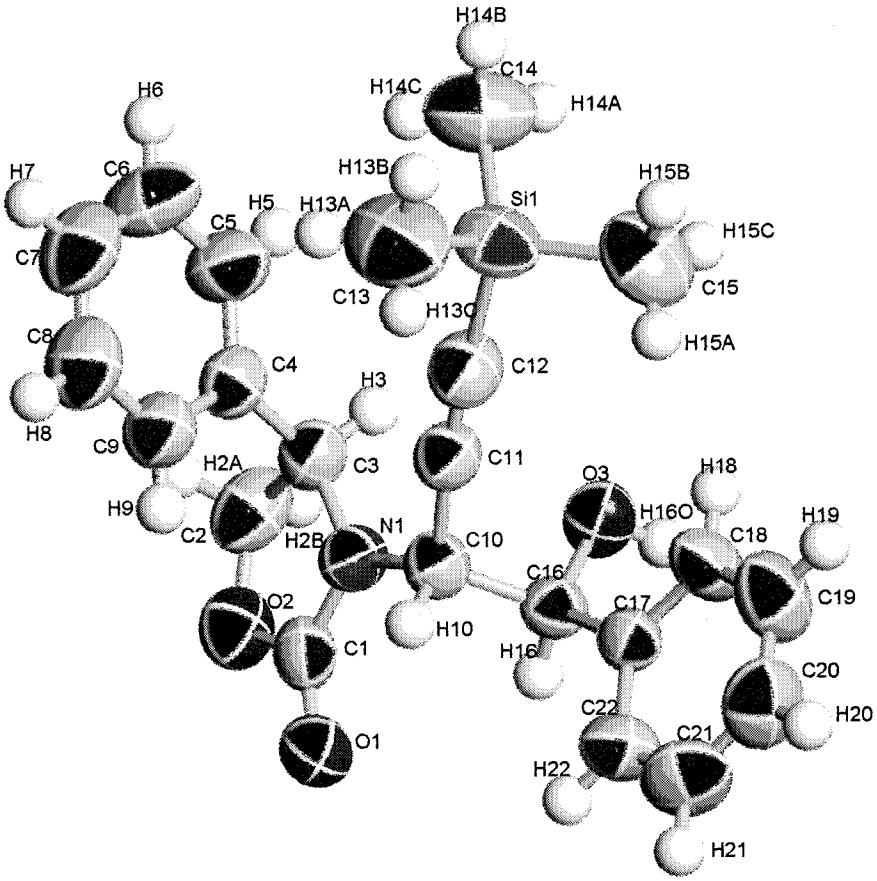
Appendix 3: X-ray structure of compound **84**



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Appendix 3: Crystal data and structure refinement for compound **84**

Identification code	lsh117m	
Empirical formula	C22 H25 N O3 Si	
Formula weight	379.52	
Temperature	298(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 6.7923(10) Å	α= 90°.
	b = 16.041(2) Å	β= 90°.
	c = 19.873(3) Å	γ = 90°.
Volume	2165.2(6) $Å^3$	
Z	4	
Density (calculated)	1.164 Mg/m^3	
Absorption coefficient	0.129 mm^{-1}	
F(000)	808	
Crystal size	0.40 x 0.40 x 0.60 mm^3	
Theta range for data collection	3.26 to 23.27°.	
Index ranges	-7<=h<=7, -17<=k<=17, -22<=l<=22	
Reflections collected	14031	
Independent reflections	3123 [R(int) = 0.0282]	
Completeness to theta = 23.27°	99.6 %	
Absorption correction	SADABS	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3123 / 0 / 264	
Goodness-of-fit on F^2	1.045	
Final R indices [I>2sigma(I)]	R1 = 0.0337, wR2 = 0.0863	
R indices (all data)	R1 = 0.0435, wR2 = 0.0920	
Absolute structure parameter	0.01(14)	
Extinction coefficient	0.0044(11)	
Largest diff. peak and hole	0.108 and -0.108 $e.Å^{-3}$	

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Appendix 3: Bond lengths [Å] and angles [°] for compound **84**.

Si(1)-C(12)	1.841(3)
Si(1)-C(13)	1.849(3)
Si(1)-C(14)	1.851(3)
Si(1)-C(15)	1.855(3)
O(1)-C(1)	1.215(3)
O(2)-C(1)	1.342(3)
O(2)-C(2)	1.428(3)
O(3)-C(16)	1.413(3)
N(1)-C(1)	1.341(3)
N(1)-C(3)	1.455(3)
N(1)-C(10)	1.471(3)
C(2)-C(3)	1.541(3)
C(3)-C(4)	1.516(3)
C(4)-C(5)	1.370(3)
C(4)-C(9)	1.373(3)
C(5)-C(6)	1.386(4)
C(6)-C(7)	1.358(4)
C(7)-C(8)	1.353(5)
C(8)-C(9)	1.384(4)
C(10)-C(11)	1.457(3)
C(10)-C(16)	1.540(3)
C(11)-C(12)	1.195(3)
C(16)-C(17)	1.507(3)
C(17)-C(18)	1.371(3)
C(17)-C(22)	1.381(3)
C(18)-C(19)	1.385(3)
C(19)-C(20)	1.356(4)
C(20)-C(21)	1.348(4)
C(21)-C(22)	1.366(3)
C(12)-Si(1)-C(13)	107.54(14)
C(12)-Si(1)-C(14)	109.05(14)
C(13)-Si(1)-C(14)	111.51(18)
C(12)-Si(1)-C(15)	106.42(13)
C(13)-Si(1)-C(15)	110.00(17)
C(14)-Si(1)-C(15)	112.08(17)
C(1)-O(2)-C(2)	109.14(18)
C(1)-N(1)-C(3)	112.63(19)
C(1)-N(1)-C(10)	120.37(19)
C(3)-N(1)-C(10)	127.00(18)
O(1)-C(1)-N(1)	127.1(2)
O(1)-C(1)-O(2)	122.6(2)
N(1)-C(1)-O(2)	110.3(2)
O(2)-C(2)-C(3)	105.87(19)
N(1)-C(3)-C(4)	114.0(2)
N(1)-C(3)-C(2)	99.24(19)
C(4)-C(3)-C(2)	112.89(19)
C(5)-C(4)-C(9)	118.6(2)
C(5)-C(4)-C(3)	119.5(2)
C(9)-C(4)-C(3)	121.8(2)
C(4)-C(5)-C(6)	119.8(3)
C(7)-C(6)-C(5)	121.0(3)
C(8)-C(7)-C(6)	119.7(3)
C(7)-C(8)-C(9)	119.9(3)
C(4)-C(9)-C(8)	120.9(3)
C(11)-C(10)-N(1)	111.65(17)
C(11)-C(10)-C(16)	111.34(17)
N(1)-C(10)-C(16)	111.12(16)
C(12)-C(11)-C(10)	174.4(2)
C(11)-C(12)-Si(1)	176.1(2)
O(3)-C(16)-C(17)	113.96(17)
O(3)-C(16)-C(10)	106.75(17)
C(17)-C(16)-C(10)	110.12(16)
C(18)-C(17)-C(22)	117.8(2)
C(18)-C(17)-C(16)	122.49(19)
C(22)-C(17)-C(16)	119.73(19)
C(17)-C(18)-C(19)	120.6(2)

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C(20)-C(19)-C(18)	120.6(3)	C(20)-C(21)-C(22)	121.5(2)
C(21)-C(20)-C(19)	119.0(3)	C(21)-C(22)-C(17)	120.5(2)

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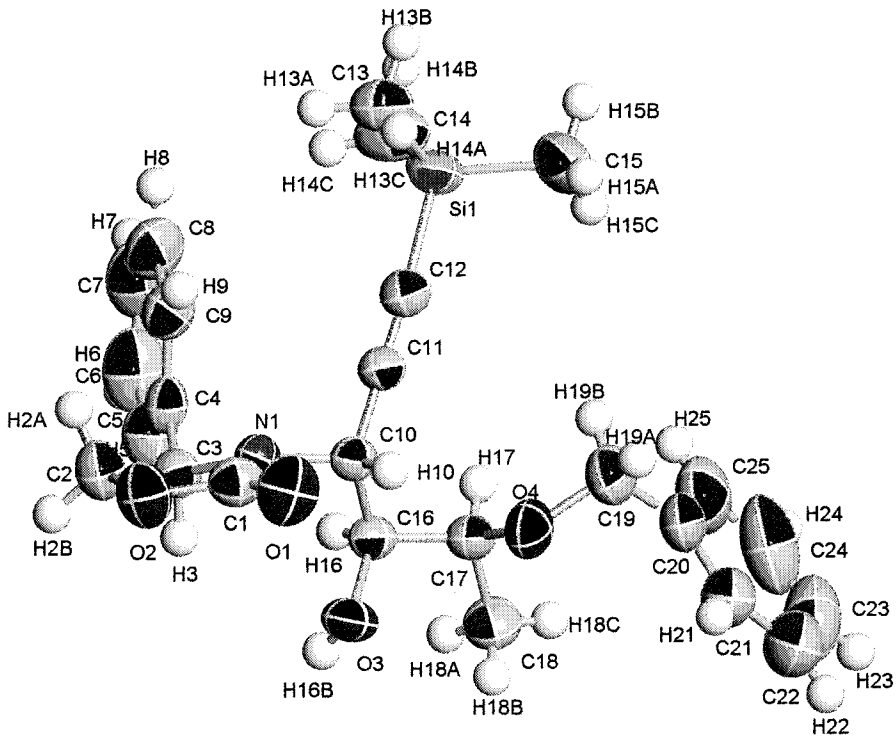
Appendix 4: X-ray structure of compound **89**



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Appendix 4: Crystal data and structure refinement for **89**

Identification code	lsh118m	
Empirical formula	C25 H31 N O4 Si	
Formula weight	437.60	
Temperature	298(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 9.0262(13) Å	α= 90°.
	b = 13.0717(19) Å	β= 90°.
	c = 21.253(3) Å	γ = 90°.
Volume	2507.5(6) $Å^3$	
Z	4	
Density (calculated)	1.159 Mg/m^3	
Absorption coefficient	0.122 mm^{-1}	
F(000)	936	
Crystal size	0.24 x 0.25 x 0.45 mm^3	
Theta range for data collection	3.26 to 23.27°.	
Index ranges	-10<=h<=10, -14<=k<=14, -23<=l<=23	
Reflections collected	16188	
Independent reflections	3596 [R(int) = 0.0363]	
Completeness to theta = 23.27°	99.6 %	
Absorption correction	SADABS	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3596 / 0 / 316	
Goodness-of-fit on F^2	1.031	
Final R indices [I>2sigma(I)]	R1 = 0.0357, wR2 = 0.0711	
R indices (all data)	R1 = 0.0477, wR2 = 0.0753	
Absolute structure parameter	-0.06(14)	
Extinction coefficient	0.0000(8)	
Largest diff. peak and hole	0.119 and -0.123 $e.Å^{-3}$	

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Appendix 4: Bond lengths [Å] and angles [°] for compound **89**

Si(1)-C(12)	1.845(2)
Si(1)-C(13)	1.846(3)
Si(1)-C(15)	1.853(3)
Si(1)-C(14)	1.853(3)
O(1)-C(1)	1.213(3)
O(2)-C(1)	1.347(3)
O(2)-C(2)	1.445(3)
O(3)-C(16)	1.416(3)
O(4)-C(17)	1.422(3)
O(4)-C(19)	1.432(3)
N(1)-C(1)	1.349(3)
N(1)-C(10)	1.469(3)
N(1)-C(3)	1.475(3)
C(2)-C(3)	1.525(3)
C(3)-C(4)	1.501(3)
C(4)-C(5)	1.375(3)
C(4)-C(9)	1.383(3)
C(5)-C(6)	1.399(4)
C(6)-C(7)	1.365(5)
C(7)-C(8)	1.360(5)
C(8)-C(9)	1.374(4)
C(10)-C(11)	1.466(3)
C(10)-C(16)	1.527(3)
C(11)-C(12)	1.198(3)
C(16)-C(17)	1.518(3)
C(17)-C(18)	1.517(4)
C(19)-C(20)	1.490(4)
C(20)-C(25)	1.374(5)
C(20)-C(21)	1.374(4)
C(21)-C(22)	1.371(4)
C(22)-C(23)	1.341(5)
C(23)-C(24)	1.359(6)
C(24)-C(25)	1.422(6)

C(12)-Si(1)-C(13)	105.56(11)
C(12)-Si(1)-C(15)	107.78(12)
C(13)-Si(1)-C(15)	111.69(13)
C(12)-Si(1)-C(14)	111.13(12)
C(13)-Si(1)-C(14)	110.24(13)
C(15)-Si(1)-C(14)	110.32(14)
C(1)-O(2)-C(2)	108.46(18)
C(17)-O(4)-C(19)	115.2(2)
C(1)-N(1)-C(10)	120.19(18)
C(1)-N(1)-C(3)	110.47(18)
C(10)-N(1)-C(3)	124.05(18)
O(1)-C(1)-O(2)	121.8(2)
O(1)-C(1)-N(1)	127.7(3)
O(2)-C(1)-N(1)	110.5(2)
O(2)-C(2)-C(3)	104.94(18)
N(1)-C(3)-C(4)	115.33(18)
N(1)-C(3)-C(2)	99.06(18)
C(4)-C(3)-C(2)	113.45(19)
C(5)-C(4)-C(9)	118.8(2)
C(5)-C(4)-C(3)	119.5(2)
C(9)-C(4)-C(3)	121.7(2)
C(4)-C(5)-C(6)	119.9(3)
C(7)-C(6)-C(5)	119.8(3)
C(8)-C(7)-C(6)	120.7(3)
C(7)-C(8)-C(9)	119.7(3)
C(8)-C(9)-C(4)	121.1(3)
C(11)-C(10)-N(1)	111.17(17)
C(11)-C(10)-C(16)	114.14(19)
N(1)-C(10)-C(16)	111.80(17)
C(12)-C(11)-C(10)	177.3(2)
C(11)-C(12)-Si(1)	172.7(2)
O(3)-C(16)-C(17)	112.35(18)

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O(3)-C(16)-C(10)	106.19(18)	C(22)-C(21)-C(20)	121.3(3)
C(17)-C(16)-C(10)	112.22(18)	C(23)-C(22)-C(21)	119.9(4)
O(4)-C(17)-C(18)	111.9(2)	C(22)-C(23)-C(24)	122.0(4)
O(4)-C(17)-C(16)	107.4(2)	C(23)-C(24)-C(25)	118.1(4)
C(18)-C(17)-C(16)	111.4(2)	C(20)-C(25)-C(24)	120.2(4)
O(4)-C(19)-C(20)	113.7(2)		
C(25)-C(20)-C(21)	118.4(3)		
C(25)-C(20)-C(19)	121.8(3)		
C(21)-C(20)-C(19)	119.8(3)		

Symmetry transformations used to generate equivalent atoms:

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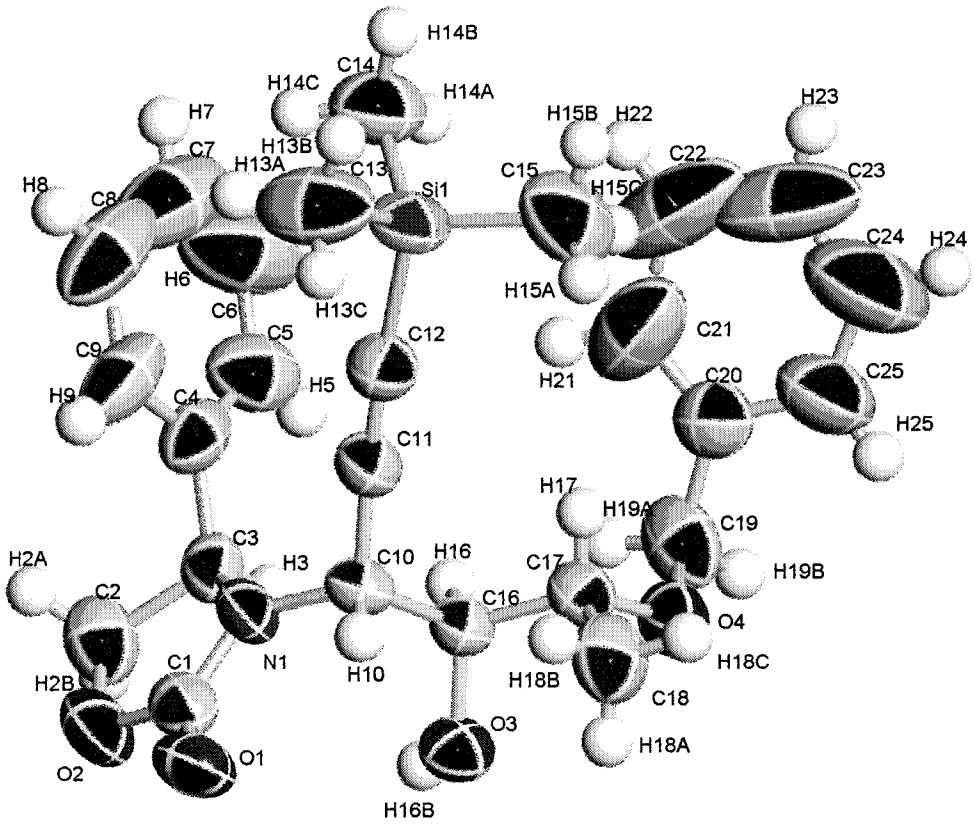
Appendix 5: X-ray structure of compound **90**



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Appendix 5: Crystal data and structure refinement for compound **90**

Identification code	lsh123m	
Empirical formula	C25 H31 N O4 Si	
Formula weight	437.60	
Temperature	298(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 10.1690(14) Å	α= 90°.
	b = 7.4217(10) Å	β= 94.094(3)°.
	c = 17.006(2) Å	γ = 90°.
Volume	1280.2(3) $Å^3$	
Z	2	
Density (calculated)	1.135 Mg/m^3	
Absorption coefficient	0.120 mm^{-1}	
F(000)	468	
Crystal size	0.10 x 0.10 x 0.30 mm^3	
Theta range for data collection	3.40 to 23.28°.	
Index ranges	-11<=h<=11, -8<=k<=8, -18<=l<=18	
Reflections collected	7423	
Independent reflections	3609 [R(int) = 0.0438]	
Completeness to theta = 23.28°	99.1 %	
Absorption correction	SADABS	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3609 / 1 / 302	
Goodness-of-fit on F^2	1.003	
Final R indices [I>2sigma(I)]	R1 = 0.0502, wR2 = 0.1066	
R indices (all data)	R1 = 0.0711, wR2 = 0.1146	
Absolute structure parameter	-0.13(18)	
Extinction coefficient	0.0000(18)	
Largest diff. peak and hole	0.203 and -0.137 $e.Å^{-3}$	

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Appendix 5: Bond lengths [Å] and angles [°] for compound **90**

Si(1)-C(12)	1.837(3)
Si(1)-C(14)	1.850(5)
Si(1)-C(13)	1.854(5)
Si(1)-C(15)	1.855(4)
O(1)-C(1)	1.219(5)
O(2)-C(1)	1.354(4)
O(2)-C(2)	1.437(5)
O(3)-C(16)	1.417(3)
O(4)-C(19)	1.420(5)
O(4)-C(17)	1.437(4)
N(1)-C(1)	1.352(5)
N(1)-C(3)	1.466(5)
N(1)-C(10)	1.471(4)
C(2)-C(3)	1.534(5)
C(3)-C(4)	1.514(5)
C(4)-C(9)	1.363(6)
C(4)-C(5)	1.386(6)
C(5)-C(6)	1.378(7)
C(6)-C(7)	1.307(9)
C(7)-C(8)	1.354(10)
C(8)-C(9)	1.465(8)
C(10)-C(11)	1.474(4)
C(10)-C(16)	1.533(5)
C(11)-C(12)	1.207(4)
C(16)-C(17)	1.528(5)
C(17)-C(18)	1.491(5)
C(19)-C(20)	1.491(6)
C(20)-C(25)	1.353(6)
C(20)-C(21)	1.354(7)
C(21)-C(22)	1.487(11)
C(22)-C(23)	1.302(11)
C(23)-C(24)	1.329(11)
C(24)-C(25)	1.355(7)
C(12)-Si(1)-C(14)	110.2(2)
C(12)-Si(1)-C(13)	107.9(2)
C(14)-Si(1)-C(13)	110.8(2)
C(12)-Si(1)-C(15)	106.52(19)
C(14)-Si(1)-C(15)	109.9(3)
C(13)-Si(1)-C(15)	111.5(3)
C(1)-O(2)-C(2)	109.6(3)
C(19)-O(4)-C(17)	116.3(3)
C(1)-N(1)-C(3)	112.0(3)
C(1)-N(1)-C(10)	120.0(3)
C(3)-N(1)-C(10)	125.0(3)
O(1)-C(1)-N(1)	127.9(4)
O(1)-C(1)-O(2)	121.7(4)
N(1)-C(1)-O(2)	110.4(4)
O(2)-C(2)-C(3)	106.3(3)
N(1)-C(3)-C(4)	114.6(3)
N(1)-C(3)-C(2)	100.6(3)
C(4)-C(3)-C(2)	114.8(3)
C(9)-C(4)-C(5)	118.9(4)
C(9)-C(4)-C(3)	121.8(5)
C(5)-C(4)-C(3)	119.3(4)
C(6)-C(5)-C(4)	121.6(6)
C(7)-C(6)-C(5)	117.8(8)
C(6)-C(7)-C(8)	126.9(8)
C(7)-C(8)-C(9)	114.7(7)
C(4)-C(9)-C(8)	120.0(6)
N(1)-C(10)-C(11)	112.3(3)
N(1)-C(10)-C(16)	110.5(3)
C(11)-C(10)-C(16)	114.1(3)
C(12)-C(11)-C(10)	175.1(4)
C(11)-C(12)-Si(1)	176.9(3)
O(3)-C(16)-C(17)	108.7(3)
O(3)-C(16)-C(10)	108.5(3)

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C(17)-C(16)-C(10)	112.8(3)
O(4)-C(17)-C(18)	106.9(3)
O(4)-C(17)-C(16)	110.6(3)
C(18)-C(17)-C(16)	113.2(3)
O(4)-C(19)-C(20)	114.2(3)
C(25)-C(20)-C(21)	116.9(5)
C(25)-C(20)-C(19)	119.3(4)
C(21)-C(20)-C(19)	123.7(5)
C(20)-C(21)-C(22)	120.9(6)
C(23)-C(22)-C(21)	113.1(7)
C(22)-C(23)-C(24)	129.0(9)
C(23)-C(24)-C(25)	114.9(8)
C(20)-C(25)-C(24)	124.9(6)

Symmetry transformations used to generate equivalent atoms:

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