ABSTRACT

Title of Thesis:	EFFORTS TOWARD (±)-7-DEOXYPANCRATISTATIN FEATURING A PALLADIUM CATALYZED ALLYLIC ARYLATION
	Bridget Rebecca Duvall, Master of Science, 2005
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The synthesis of pancratistatin, 7-deoxypancratistatin, and its analogs have attracted the interest of synthetic chemists due to both their structural complexity as well as interesting biological activity. Although previous syntheses have been reported, a general and efficient route to produce multigram quantities of these compounds has remained elusive. Herein is described a general approach to this class of compounds. The optimized route is reported. All work towards effecting and understanding the key allylic arylation reaction is described.

EFFORTS TOWARD (±)-7-DEOXYPANCRATISTATIN FEATURING A PALLADIUM CATALYZED ALLYLIC ARYLATION

By

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Dedication

To my parents.

Acknowledgement

I would like to thank Phil DeShong for his encouragement and mentorship during the course of this work. I am greatly indebted.

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Introduction

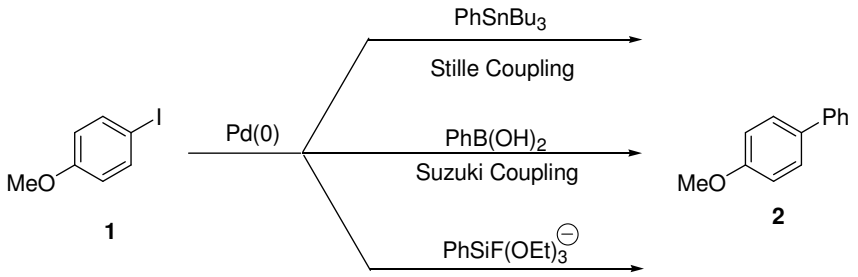
Efficient carbon-carbon bond forming reactions have long been a goal of synthetic organic chemists. Among the most prominent of the carbon-carbon bond forming reactions are the Stille and Suzuki [1-4]. Since their development these cross-coupling reactions have been widely used in the construction of highly functionalized and structurally-complex molecules[5-7].

The Stille coupling is a Pd-mediated reaction in which a carbon-carbon bond is formed between the aryl group of an aryl halide **1** and an aryl group from the corresponding stannane to afford a biaryl product **2** [8-12] (Scheme 1). The wide utility of this reaction has long been hampered by the toxicity of stannanes and the inherent difficulty in removing tin by-products from the reaction mixtures. Closely related to the Stille reaction is the Suzuki coupling. An analogous carbon-carbon bond construction is feasible with this methodology, however, in the Suzuki method a carbon-carbon bond is formed between the aryl group of the aryl halide **1** and the aryl group of the boronic acid (or borate ester)[13]. Again the product is **2.** Drawbacks to the Suzuki coupling surround the use of the boronic acids which are often difficult to purify. Additionally, boronic acids are acid sensitive – negating their introduction early in the synthesis in preparation for a late stage coupling sequence.

The difficulties in aryl-aryl coupling have prompted chemists to persevere in the advancement of innovative methodologies. In the early 1990's the DeShong group began investigating an aryl-aryl coupling methodology complementary to the

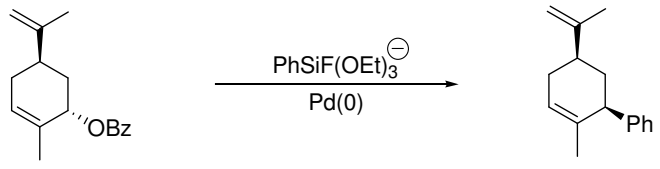
Stille and Suzuki couplings. In this new methodology aryl-aryl carbon bonds are formed between the same aryl halide **1** and an aryl siloxane in the presence of both palladium (0) and a hypercoordinate siloxane moiety (Scheme 1)[14-17]. Product **2** is formed. The advantages to the siloxane mediated cross coupling are many. Silicon based arylating agents are easily prepared (by several methods)[14,16,18,19] and are easily purified (distillation or chromatography) compared with their boronic acid counterparts. Siloxanes are substantially less toxic than their organotin counterparts and maintain a wide functional group tolerance.

Scheme 1



The use of hypercoordinate siloxanes has since been extended to facilitate the transfer an aryl group from a siloxane to an allylic system such as **3** to catalytically prepare compounds such as **4** [20-25]. (Scheme 2) Catalytic allylic alkylations are also well known in the literature[26-34]. Generally, allylic alkylations

Scheme 2

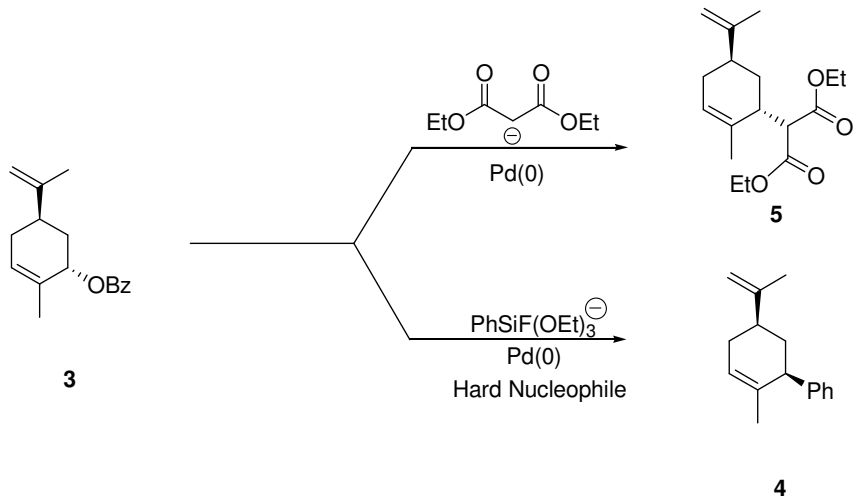


3 **4**

are organized into two varieties: those using “soft nucleophiles”and those using “hard nucleophiles”[4,29,35]. The terms “hard” and “soft” nucleophile are not well defined. Generally, soft nucleophiles are described as those nucleophiles whose conjugate base has a pK_a <25, e.g. diethylmalonate. Comparatively, hard nucleophiles are defined as those nucleophiles whose pk_a is >25. Examples of hard nucleophiles include Grignard reagents and siloxanes.

Soft and hard nucleophiles exhibit different mechanistic reactivity and different reaction stereoselectivity (Scheme 3). Consider the stereoselectivity first. Allylic alkylation involving soft nucleophiles occurs with overall retention of stereochemistry with respect to the original stereochemistry, i.e. in the starting material **3** the benzoate group in the *S* configuration; in the product, alkylation with diethylmalonate occurs on the bottom face of the system to afford **5**. This is an overall retention of stereochemical configuration. The opposite is observed with hard nucleophiles. The stereochemistry of the starting benzoate is *S* (**3**);

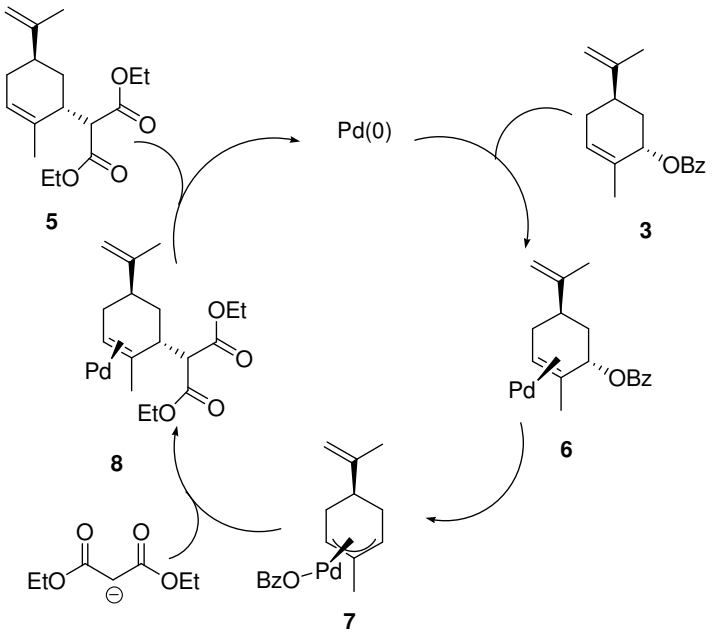
Scheme 3.



arylation, however, occurs on the top face of the allyl system resulting in overall inversion of stereochemistry (**4**).

The origin of the stereochemical differences for soft and hard nucleophiles can be explained by considering their respective mechanisms [4,35]. Consider first, the mechanism of allylic alkylation with soft nucleophiles (Scheme 4). Palladium (0) complexes the sterically less demanding face of olefin **3** forming the palladium complexed intermediate **6**. Palladium oxidatively adds to the π-allyl system

Scheme 4.

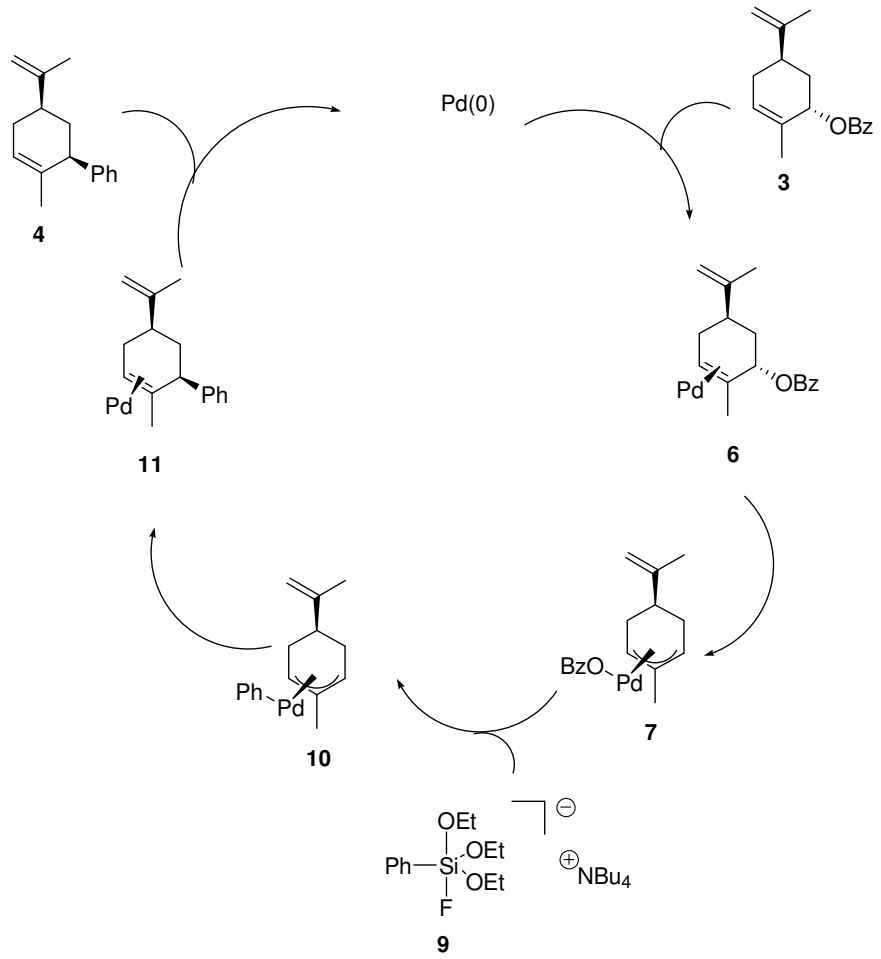


displacing the benzoate (**7**). In the presence the nucleophile, the conjugate base of diethylmalonate (soft nucleophile), the nucleophile adds to the less hindered bottom face of the π-allyl forming intermediate **8**. Decomplexation of the palladium from the olefin affords the allylic alkylation product (**5**) and regenerates palladium (0). *The displacement of the benzoate by palladium from the opposite face of the leaving group (inversion), followed by displacement of the palladium by diethylmalonate*

anion from the opposite face of the metal (inversion) results in overall retention of stereochemistry at the reaction center.

The mechanism of allylic alkylation is different when a hard nucleophile is used. Palladium (0) complexes the sterically less demanding face of olefin **3** forming

Scheme 5.



the palladium complexed intermediate **6**. Palladium oxidatively adds to the π-allyl system displacing the benzoate (**7**). In the presence of a hypercoordinate siloxane **9**, the phenyl ring is transmetallated to the palladium affording the intermediate **10**. Subsequently, the palladium reductively transfers the phenyl ring to the π-allyl system; this occurs from the same face occupied by the palladium, the top face (**11**).

Upon decomplexation of palladium from the olefin, the allylic arylation product **4** is formed and palladium (0) is regenerated. *The displacement of the benzoate by palladium from the opposite face of the leaving group (inversion), followed reductive elimination of the phenyl ring by palladium on the same face of the metal center (retention) results in overall inversion of stereochemistry at the reaction center.*

The goal of all synthetic methodology is practical utility. In an effort to validate the utility of the allylic arylation methodology developed in the DeShong lab, the synthesis of 7-deoxypancratistatin was targeted. In addition to being an appropriate target for the application of the said chemistry, 7-deoxypancratistatin exhibits interesting biological activity.

In the early 1970's, the National Cancer Institutes exploratory plant screening program identified potent anti-cancer activity from extracts of *Amaryllidacea* alkaloids[36]. Extracts from one species in particular, the Hawaiian *Pancratium littorale*, showed remarkable potential in early screening assays. Upon isolation and analysis of the active components, it was found that pancratistatin **16**, was responsible for the observed biological activity.[36,37] Subsequently, 7-deoxypancratistatin **22** was isolated; this analogue was found to possess improved biological activity with reduced toxicity[38].

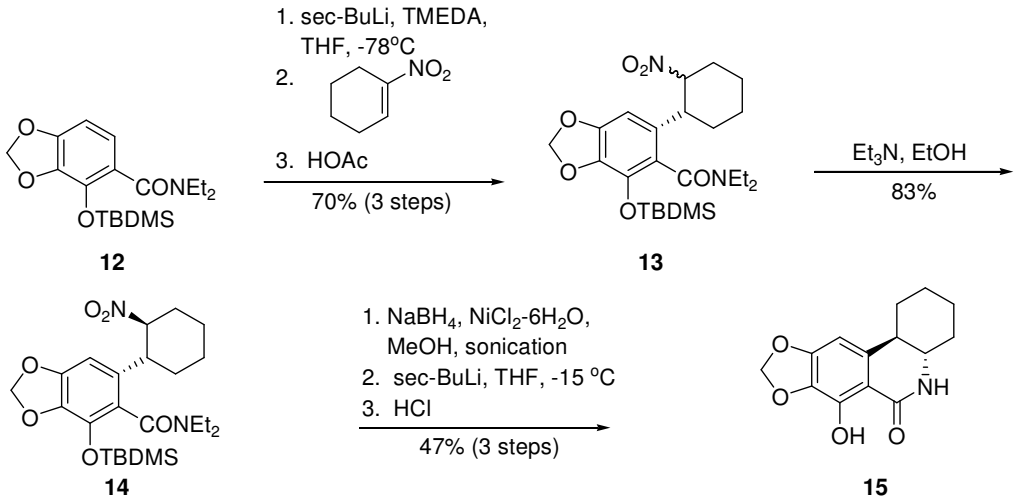
Studies have revealed the cancer fighting mechanism of 7-deoxypancratistatin to be involved with the inhibition of ribosomal peptidyl transferase, i.e. inhibiting protein synthesis at the step of peptide bond formation[39-41]. More detailed investigations into improving the activity of the molecule and decreasing its *in vivo* toxicity are limited by its natural abundance. Therefore, the need for an efficient route to **22** is needed.

The syntheses of pancratistatin, 7-deoxypancratistatin, and its analogues have attracted the interest of synthetic chemists due to both their structural complexity as well as interesting biological activity. Greater than 10 groups are pursuing the synthesis of pancratistatin and its analogues; most seek to discover a general approach to the skeleton of these alkaloids.

In 1992, Heathcock proposed a general methodology to prepare the basic ABC framework of the this class of compounds.[42] His goal was a low cost route to multi-gram quantities of Amaryllidaceae alkaloids for use in clinical trial investigations.

The previously prepared amide **12** was orthometallated in the presence of sec-BuLi, trapped with electrophilic 1-nitrocyclohexene, and after acidic workup afforded a mixture of the *cis* and *trans* aryl nitrocyclohexanes products **13**.

Scheme 6

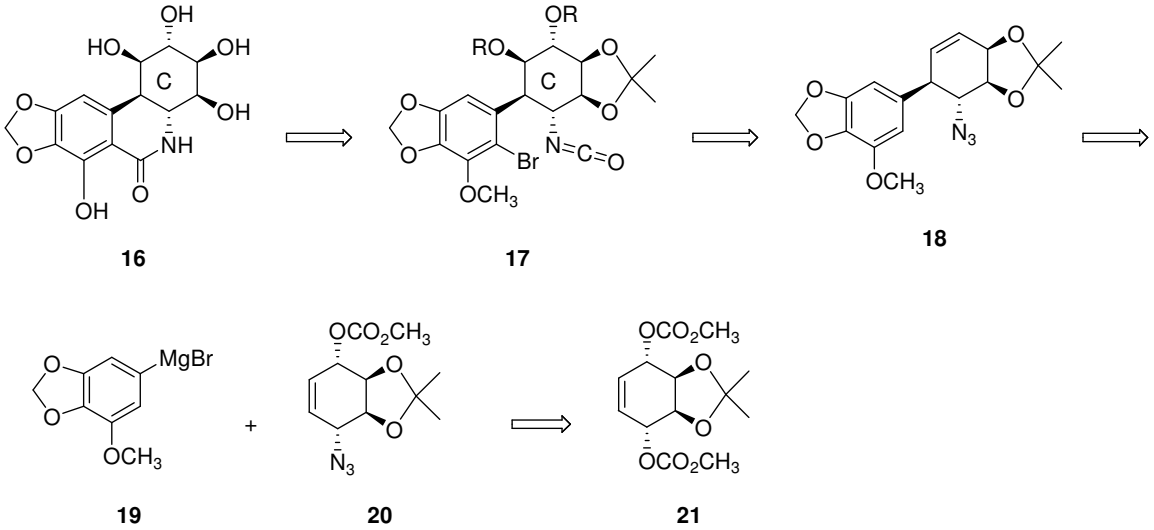


Equilibration of the cis/trans mixture with Et_3N afforded the more stable 1,2-trans substituted system **14**. The nitro group was reduced to amine in the presence of $NiCl_2$ and upon addition of sec-BuLi the amine underwent an intramolecular

cyclization to afford the lactam. Deprotection of the TBDMS ether with acid gave the core ABC ring structure of pancratistatin **15**.

Trost reported the first asymmetric total synthesis of (+)-pancratistatin.[43] The route involved the classic desymmetrization strategy employed by Trost in his own allylic alkylation methodology[1,29,32,34,43-45] (Scheme 7). Retrosynthetically, (+)-pancratistatin (**16**) was prepared from isocyanate **17**. Compound **17** was treated with *tert*-butyl lithium to effect lithium halogen exchange. The aryl lithium species, generated *in situ* underwent an intramolecular addition onto the isocyanate affording the intact A-B-C ring structure. Compound **17** was prepared from **18**. Electrophilic aromatic bromination followed by conversion of the azide to the isocyanate afforded **17**. Compound **18**, in turn, was prepared utilizing organocuprate chemistry to effect the coupling between **19** and **20**. The enantiomerically pure allyl azide **20** was prepared from the dimethylcarbonate **21** upon desymmetrization with a chiral palladium complex and a nitrogen nucleophile (85%, ee >95%).

Scheme 7.



The Mehta group is currently working on the total synthesis of pancratistatin and more specifically, on a general route to approach the phenanthridone alkaloids family.[46] In 1998, Mehta published his preliminary work towards this goal. Below in Scheme 8 is the retrosynthesis.

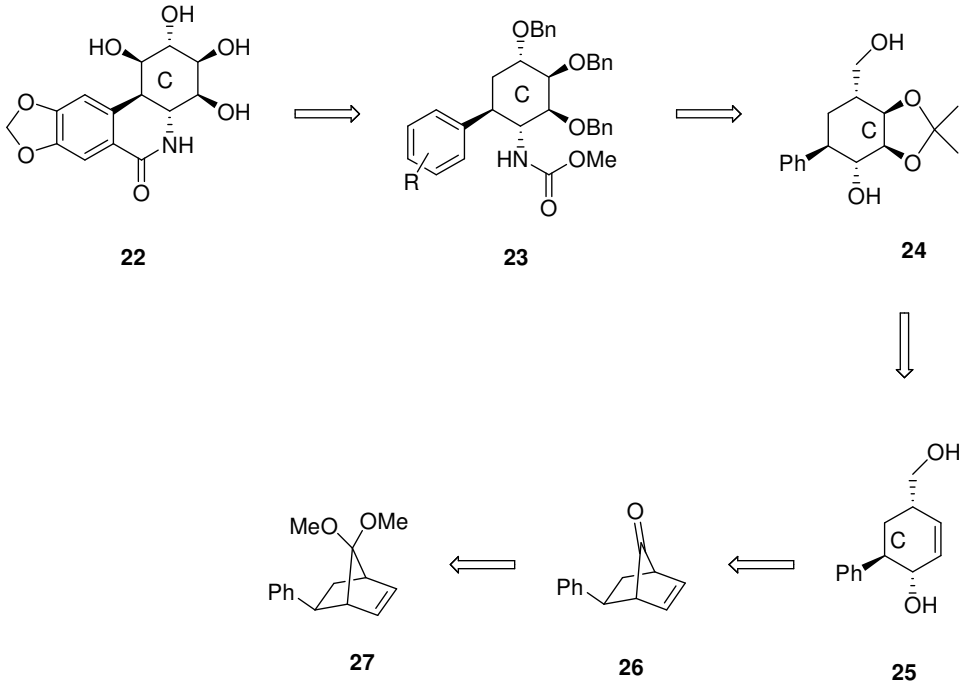
Retrosynthetically, 7-deoxypancratistatin **22**, would be available from the highly functionalized precursor **23**. Mehta envisioned **23** being easily prepared from dihydroxy compound **25**. Compound **24** was prepared in two steps (a. OsO_4, NMO b. Amberlyst-15, MeOH, Ac_2O, Py) from the corresponding olefin **25**. Allylic alcohol **25** was prepared *via* Baeyer-Villiger oxidation of the bicyclic ketone **26**. Compound **26**, in turn, is prepared from the readily available *endo*-phenyl-7-norbornenone-dimethyl acetal **27**.

The last report in the literature from the Mehta group detailing their progress towards the pancratistatin family was in 1998. At the time, the group had completed the highly functionalized core containing the 6 contiguous stereogenic centers of the C ring. However, to date, the elaboration of the system to complete the synthesis has not yet been realized.

Despite not yet having completed the total synthesis of pancratistatin, the approach developed by Mehta has the potential to construct pancratistatin in an asymmetric fashion, but also maintains the inherent ability to easily access other highly functionalized cyclohexanoid systems. The generality of this methodology is easily amenable to the synthesis of closely related analogues for structure activity analysis.

In 1993, Martin reported a formal synthesis of (±)-pancratistatin **16** (via the synthesis of (±)-lycoricidine **28**)(Scheme 9).[47] Analyzing Martin's disconnection approach, (±)-lycoricidine **28** and hence (±)-pancratistatin **16** would be available from

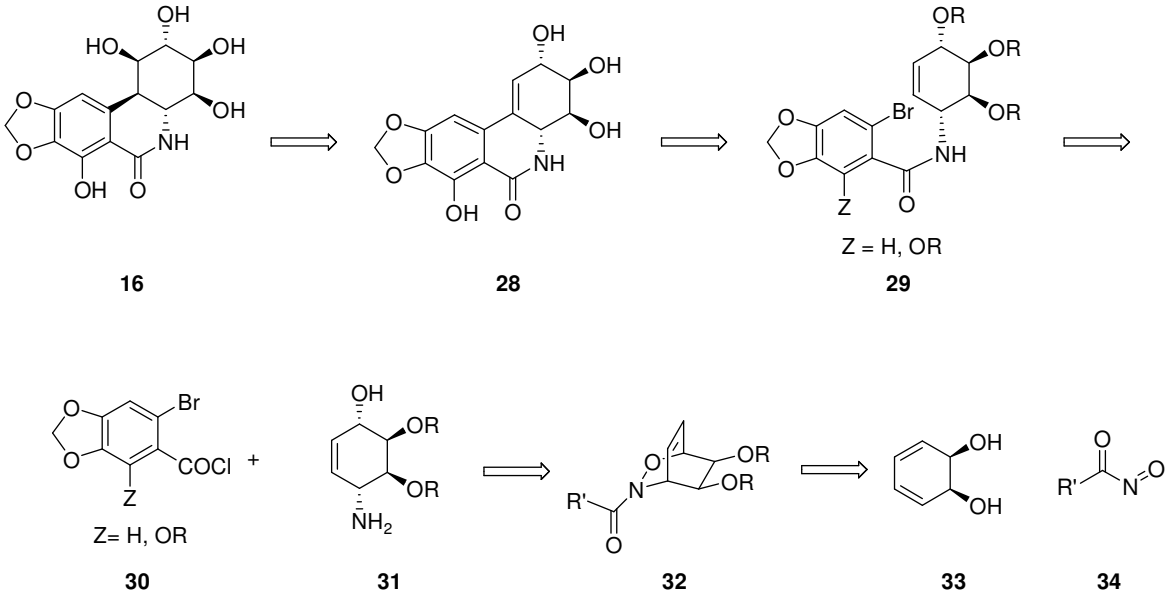
Scheme 8.



the intramolecular Heck coupling of aryl bromide with double bond of the C ring **29**. The aryl amide **29** was easily constructed from the nucleophilic acyl substitution reaction between aryl acid chloride **30** and allylic amine **31**. Compound **32** was prepared from the hetero Diels - Alder reaction of diene **33** and the *in situ* generated acyl nitroso compound **34**.

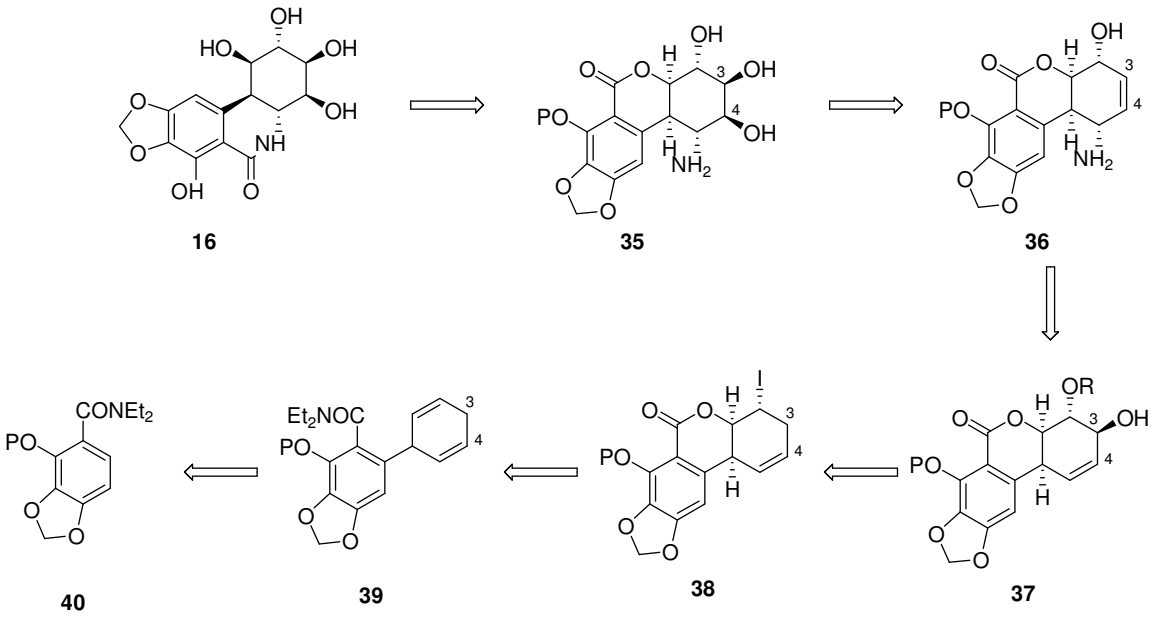
The first total synthesis of (±)-pancratistatin was reported in 1989 by Samuel Danishefsky (Scheme 10).[48] Retrosynthetically, the group envisioned the preparation of (±)-pancratistatin **16** from lactone **35**. Saponification of the lactone **35** with K_2CO_3 presumably through the amino-carboxylic acid intermediate followed by treatment with treatment with DCC afforded the pancratistatin lactam. Oxidation of carbons 3 and 4 of **36** with catalytic osmium tetraoxide / NMO afforded the desired

Scheme 9.



amino triol **35**. The existing 1,4-amino alcohol directed the osmylation at the β-face of the molecule. The installation of the C-3 alcohol of **38** and migration of the double bond was effected by the Overman rearrangement; the C-3 alcohol was converted to the corresponding imidate (NaH, trichloroacetonitrile). The C-3 imidate (neat) rearranged under high vacuum and pyrolysis (100 °C – 105 °C) conditions to afford **37**. Compound **38** was prepared from **37** in 6 steps through a series of "carbohydrate reminiscent" functional group manipulations required for achieving the desired stereochemistry on the highly oxygenated C ring. Halolactonization ($(Bu_2Sn)_2O$, I_2) of compound **39** afforded compound **38**. Compound **39** is prepared from the orthometallation of **40** followed by a DMF quench to afford the corresponding aldehyde. The aldehyde was elaborated to a 1,3 butadiene moiety; this diene underwent a Diels Alder reaction with a known masked alkynyl dienophile to generate the 1,4-cyclohexadiene substrate **39**. Compound **40** is known from the literature.

Scheme 10.

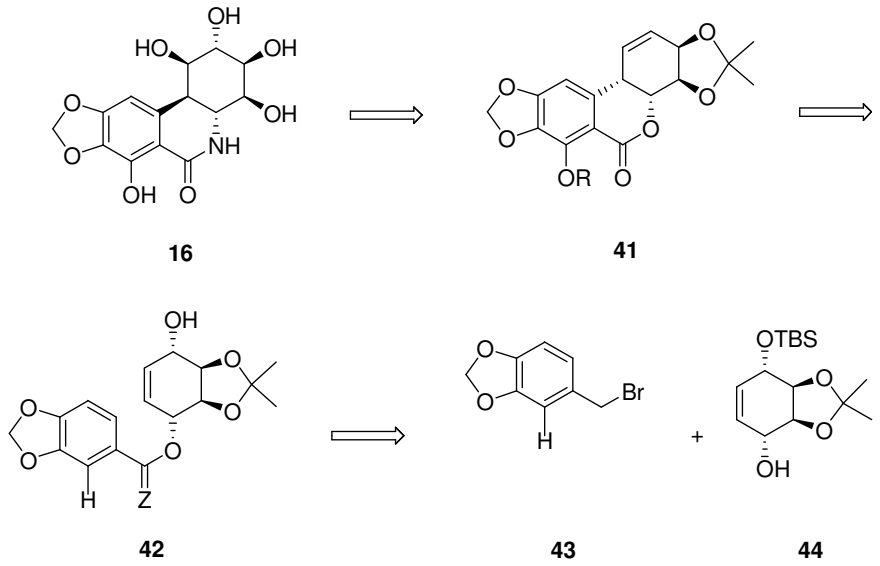


In the late 1990's, John Hasteltine published the completion of a formal total synthesis of (+)-pancratistatin.[49,50] The key step in the route was an electrophilic aromatic substitution reaction to construct the B – ring. Depicted below is the retrosynthesis (Scheme 11).

(±)–Pancratistatin **16** would be available in a formal synthesis from the di-deoxy compound **41** (An intermediate in the Danishefsky synthesis). Elaboration from **41** to **16** required 6 additional steps).[48] Compound **41** was prepared from the intramolecular electrophilic aromatic substitution reaction between the functionalized arene of the A ring with the olefin of **42**. Compound **42** was constructed via the S_N2 displacement by the alcoholate of **44** with benzylbromide **43**.

Several problems make the Haseltine synthesis inappropriate for large-scale (+)-pancratistatin production. First and foremost, the synthesis is long; the longest linear sequence contains 27 steps. Many transformations including those towards

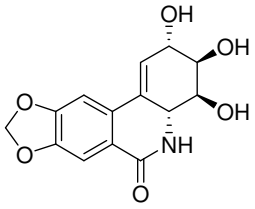
Scheme 11.



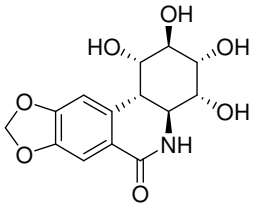
the end of the synthesis suffer from low yields. The key electrophilic aromatic substitution step used to construct the ABC ring system is intolerant of structure diversity; for all variants, save the one employed, an undesired rearrangement was observed. Lastly, as is the case with most attempts towards pancratistatin, researchers were plagued with poor atom economy as excessive protections and deprotections were required to differentiate the C ring hydroxyls and achieve the requisite stereochemistry.

The Hudlicky group has been prolific in the development of a rational synthesis of (+)-pancratistatin and (+)-7-deoxypancratistatin. In addition, the syntheses of several analogues have elucidated interesting structural activity features of this class of molecules[51,52]. Total syntheses of narciclasine **45**, *ent*-7-deoxypancratistatin **46**, 10b-*epi*-deoxypancratistatin **47** have been reported as well as the synthesis of several abridged systems.[51] (Figure 1).

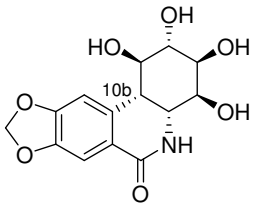
Figure 1. Analogues of 7-Deoxypancratistatin.



narciclasine
45



ent-deoxypancratistatin
46



10b-*epi*-deoxypancratistatin
47

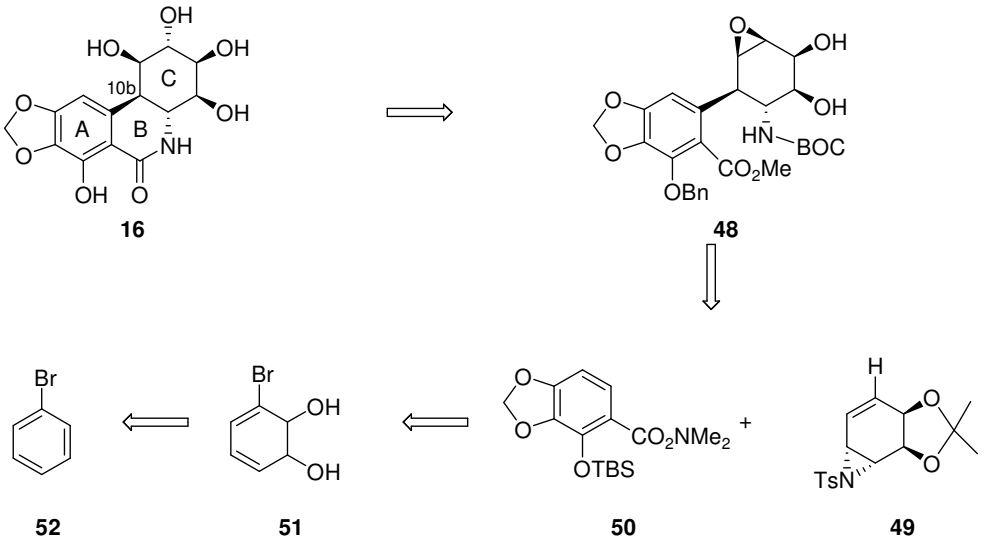
Over a period of 10 years the group has published several syntheses of these biologically relevant compounds, each time addressing and improving upon previous synthetic hurdles.

The Hudlicky group published syntheses of both (+)-pancratistatin and (+)-7-deoxypancratistatin in 1995.[53,54] The retrosynthesis for the pancratistatin synthesis is shown below (Scheme 12). Pancratistatin **16** was prepared in one step from **48**. Under conditions which effect the opening of the epoxide, the BOC group was cleaved; additionally under these reaction conditions, the free amine condensed upon the methyl ester thereby affording the desired lactam of **16**. The carbon-carbon bond fusing ring A with ring B was effected by preparing the organocuprate of **50** (1. *s*-BuLi, TMEDA 2. CuCN) and coupling it with the tosylaziridine **49**. The aziridine **49** was prepared in 3 steps from bromodiol **51**. Compound **51** was prepared as the featured intermediate from **52**, utilizing enzymatic oxidation with *Pseudomonas putida*.

Although the first generation Hudlicky synthesis was fairly concise (requiring only 13 steps) several of the steps would be problematic in the elaboration of this synthesis to large-scale preparation of pancratistatin. The copper mediate coupling of **50** and **49** was prone to epimerization at carbon 10b. Furthermore, the late

installation of the intact ABC ring system made selective β-epoxidation difficult as a result of atropisomerism at the AC ring.

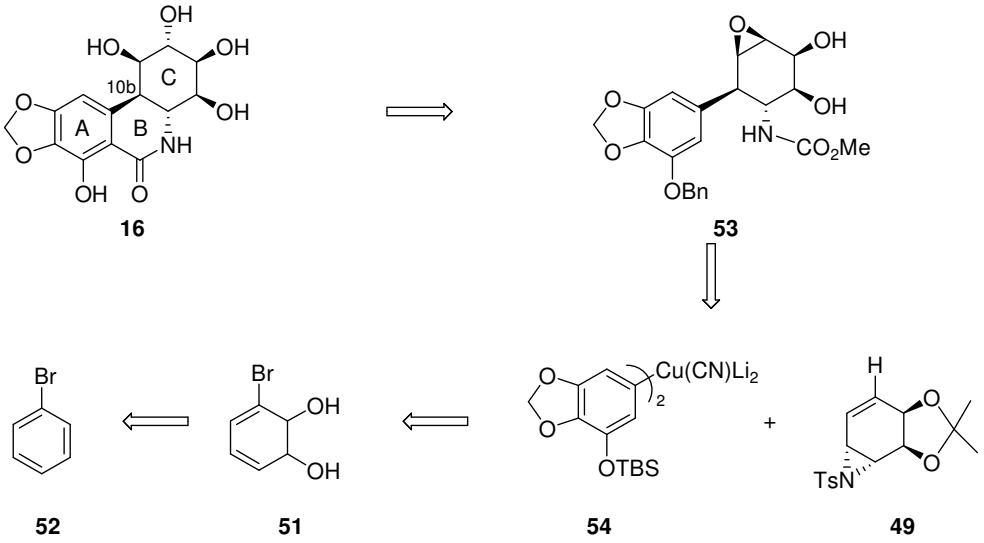
Scheme 12.



In an effort to address some of the synthetic "pitfalls" encountered in their first generation synthesis of (+)-pancratistatin, Hudlicky soon thereafter reported a revised synthesis[54]. The group initially sought to address two key problems in the maiden synthesis: The problems addressed were the detosylation of the aziridine followed by its reprotection as the carbamate and secondly the issues associated with atropisomerism about the AC ring system. In practice, however, this second generation synthesis only addressed the latter problem. (Scheme 13). The second-generation synthesis circumvented problems surrounding the hindered rotation about the AC ring by a few simple changes. Again, retrosynthetically, (+)-pancratistatin **16** was prepared from the Bischler-Napieralski cyclization of **53**. Intermediate **53** was available from the copper-mediated coupling of **49** and **54**; the optimized yield for this key carbon-carbon bond forming reaction was 32%. The low yield was attributed to either the instability of the organolithium species from which **54** was prepared or the

instability of the cuprate, itself. (The cuprate of **50** in the previous synthesis was believed to possess enhanced stability due to the presence of the amide at the *ipso* position.) The tosyl aziridine **49** was prepared as in the first synthesis, featuring the enzymatic oxidation of a substituted benzene **52** affording diol **51**.

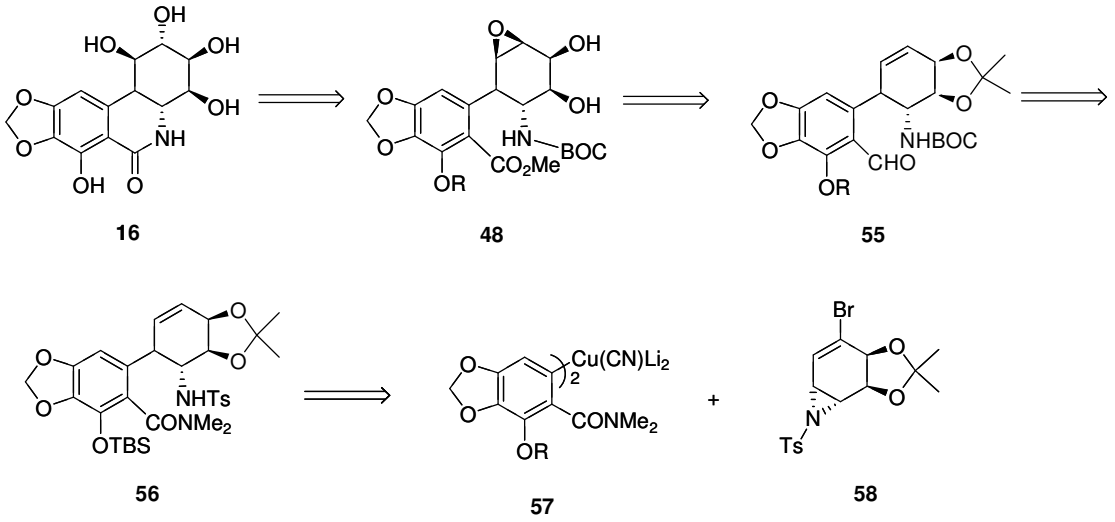
Scheme 13.



One key hurdle was overcome in the Hudlicky synthesis: the problem of atropisomerism was circumvented by avoiding a coupling reaction in connecting the AC ring system in which there were 2 *ortho* substituents as in the previous synthesis (Scheme 12 and Scheme 13, Figure **48** vs. **53**). However, a snag in the synthesis emerged – a drastic reduction in yield was observed in the coupling reaction.

A third generation approach to (+)-pancratistatin and (+)-7-deoxypancratistatin was published in 1996[55]. The retrosynthesis for the former is given below in Scheme 14. The retrosynthesis for (+)-7-deoxypancratistatin can be found in Scheme 15.

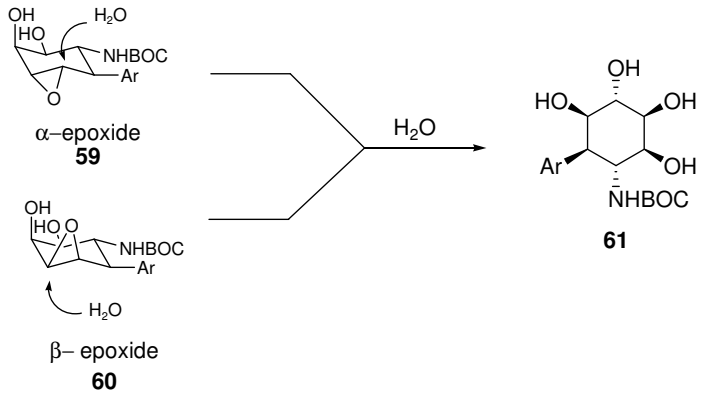
Scheme 14.



Again, retrosynthetically the Hudlicky group prepared the enantiomerically pure pancratistatin **16** from intermediate **48** upon the BOC deprotection of the C ring nitrogen followed by cyclization onto the ester to afford the B ring β-lactam and simultaneous nucleophilic epoxide opening. Ester **48** was prepared from the corresponding aldehyde **55** which was in turn was prepared from the corresponding amide **56**. The AC bond was accomplished via the copper mediated coupling of aryl cuprate **57** with vinyl aziridine **58**.

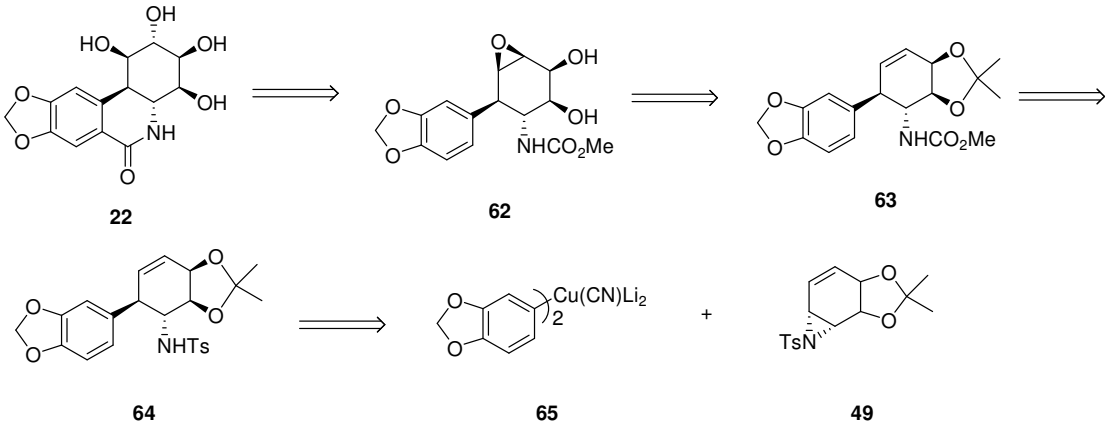
The Hudlicky group made several insights during this synthesis. The first insight gathered, circumvented some of the stereochemical problems which plagued the earlier syntheses. First, although compound **48** exists in two atropisomeric forms, the face of epoxidation is immaterial. Ring opening is degenerate and should give the same product **61** for both the α- (**59**) and the β-epoxide (**60**) (Figure 2).

Figure 2. Degenerate Epoxide Ring Opening.



The (+)-7-deoxypancratistatin retrosynthesis follows (Scheme 15). It applies much of the knowledge attained from the (+)-pancratistatin synthesis.

Scheme 15.



7-Deoxypancratistatin was derived from epoxide **62.** Nucleophilic ring opening of epoxide **62** followed by cyclization under Banwell's Bischler-Napieralski conditions afforded the target molecule **22**. The epoxide **62** was prepared from the corresponding olefin **63**. The methylcarbamate of **63** was prepared from the corresponding tosyl amide **49**. The intact AC ring system was prepared as

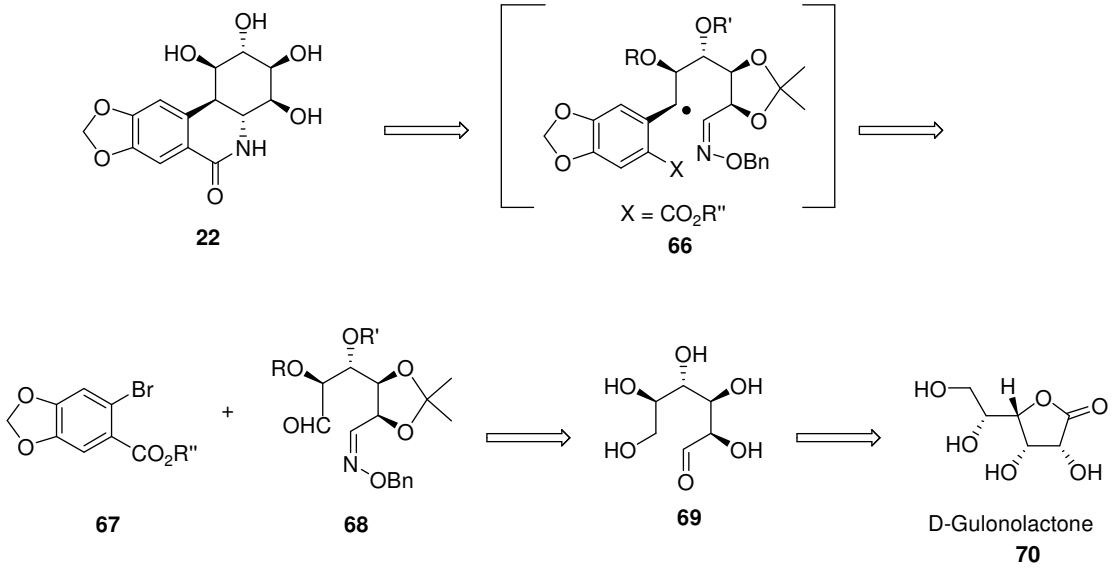
previously described via the copper-mediated coupling of cuprate **65** with tosylaziridine **49**.

Within months of the Hudlicky group publishing their first generation synthesis of (+)–7-deoxypancratistatin, the Keck group published their first total synthesis.[56] Since the initial report, two subsequent improvements have been reported.[57,58] The retrosynthesis below details the Keck approach, which features a stereo-selective radical cyclization to effect the C ring.

Retrosynthetically, (+) -7-deoxypancratistatin **22** was prepared from the 6-*exo* radical cyclization of the benzylic radical onto the oxime ether **66** followed by the Danishefsky "Overman rearrangement approach". Addition of the aryl Grignard of **67** onto oxime **68** allowed the construction of "radical cyclization precursor" **66**. Compound **68** was prepared from **69** upon conversion of the existing aldehyde to the oxime ether, oxidation of the primary alcohol to the aldehyde and the differential protection of the C1-4 hydroxyls. Compound **69** is easily available in enantiomerically pure form from the chiral pool. DIBAL reduction of D-Gulonolactone **70** affords **69** in excellent yield.

The stereoselectivity in the radical cyclization can be explained by considering the relative energy of the radical intermediates (Scheme 17). The two possible reactive conformers are depicted below: intermediate **71** depicts the fusion of the BC ring in a *cis* fashion; intermediate **72** depicts the fusion of the BC ring in a *trans* fashion. It is well known in decalin systems that the *cis* fused system is more stable than the corresponding *trans* fused system as the conformational flexibility

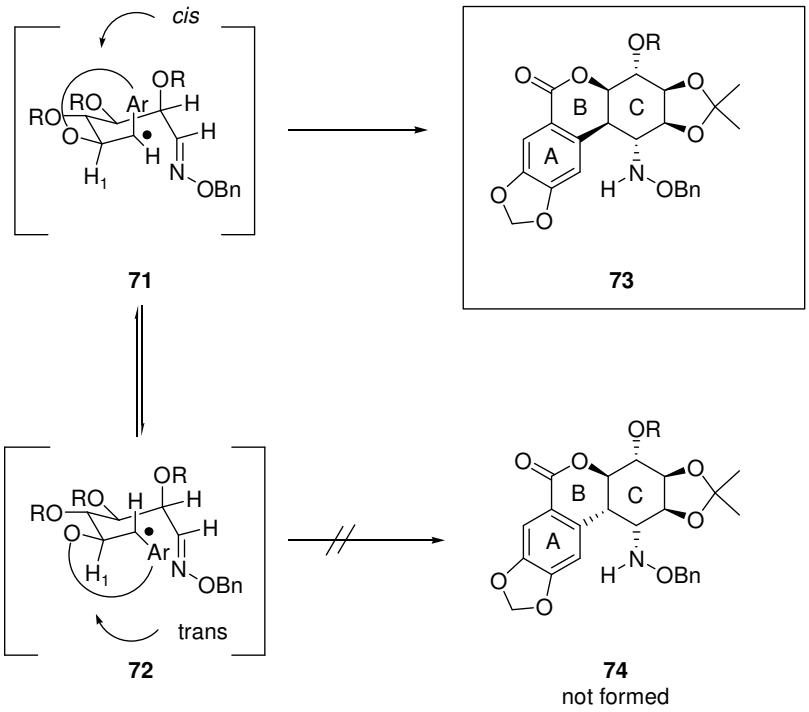
Scheme 16.



contributes to the thermodynamic stability, hence the product observed possesses a *cis* fusion at the BC ring juncture.

The Keck synthesis was successful in proving the viability of the radical cyclization approach towards the construction of highly functionalized molecules. The synthesis was significantly shorter than many of the earlier attempts ((+) – 7-deoxypancratistatin was prepared in 21 steps). Ultimately, the weakness of the synthesis was two-fold. The approach lacked convergence as the aryl portion of the molecular was coupled with the aliphatic moiety very early in the synthesis. Secondly, the key step, the radical cyclization was capricious; control of the stereochemistry at the BC juncture was problematic as was the competitive reduction of the B ring lactone.

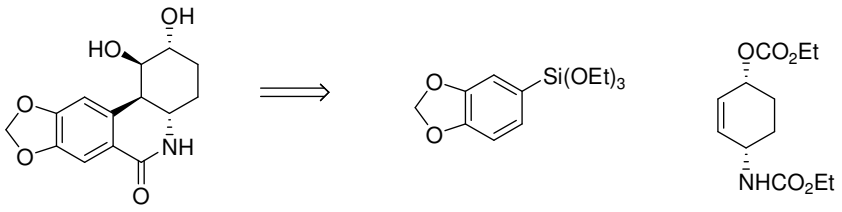
Scheme 17.



The goal of my project was to develop a concise and general approach to the Amaryllidaceae alkaloids using the allylic coupling reaction developed in our lab. To exemplify the feasibility of this approach, 7-deoxpancratistatin was targeted. As previously described, this molecule is a highly sought synthetic target due to both its structural complexity and interesting biological activity. Furthermore, previous syntheses of this compound lacked the necessary efficiency that would allow a full-scale investigation of this compound as a drug candidate.

Prior to the undertaking of this formidable synthetic target, 7-deoxypancratistatin, a simplified model system **75** was completed to assess the feasibility of the key allylic arylation reaction. The retrosynthetic approach mirrors that used in the 7-deoxypancratistatin synthesis. In terms of functionality, the

Scheme 18.

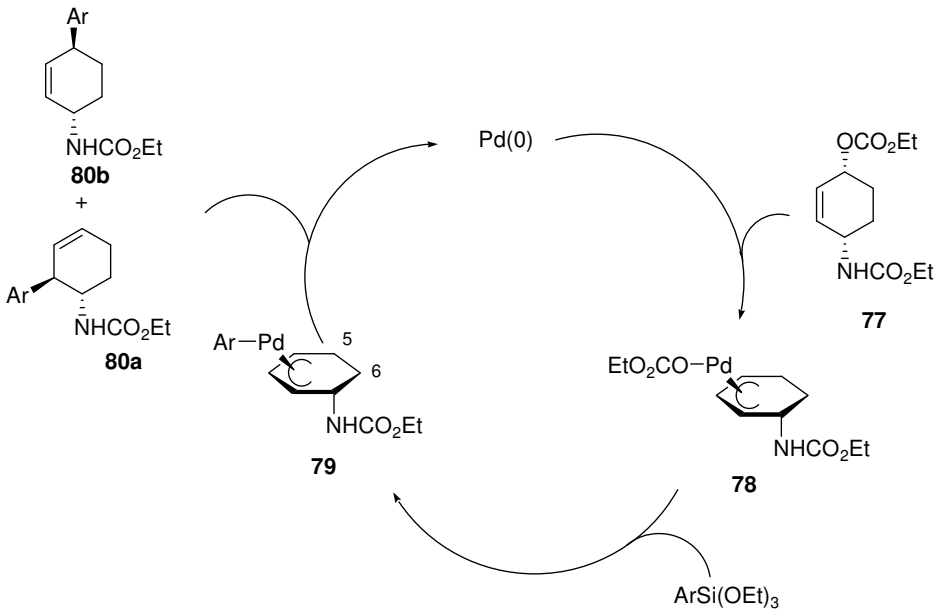


75 **76** **77**

model chosen lacked only the C3, C4 *cis* hydroxyl groups. The model compound was prepared from the allylic arylation reaction of siloxane **76** with allylic carbonate **77** in the presence of palladium (0)[24]. The reaction predictably provided a 1:1 mixture of regioisomers; this lack of selectivity can be explained by analyzing the π-allyl intermediate.

The mechanism of this coupling reaction is analogous to that described previously in Scheme 5. For simplicity, palladium-olefin coordination was omitted for clarity. The arylation group, siloxane **76**, was simplified to $ArSi(OEt)_3$ below in Scheme 19. Upon coordination of Pd(0) to the olefin of **77**, Pd(0) displaces the carbonate group from the less sterically encumbered top face of the molecule. The π-allyl intermediate **78** is formed. In the presence of aryl siloxane (**76**) and a fluoride source, the aryl group is transferred from silicon to palladium to form species **79**. Reductive elimination occurs with equal proclivity to provide the 1,2-allylic arylation isomer **80a** and the 1,4-allylic arylation isomer **80b** in a 1:1 ratio. Selectivity is not observed in this reductive elimination as there are no substituents in the 5 or 6 positions on the top face of the cyclohexyl system to bias the elimination. Correspondingly, the carbamate moiety cannot influence the selectivity of this reductive elimination as the chemistry is occurring on the top face of the molecule and the carbamate resides on the bottom face.

Scheme 19.



The success of this allylic arylation reaction had demonstrated several details about the allylic arylation reaction. The coupling occurred, as predicted, without selectivity. This result validated our confidence in both the application of this methodology to 7-deoxypancratistatin and our understanding of the mechanism.

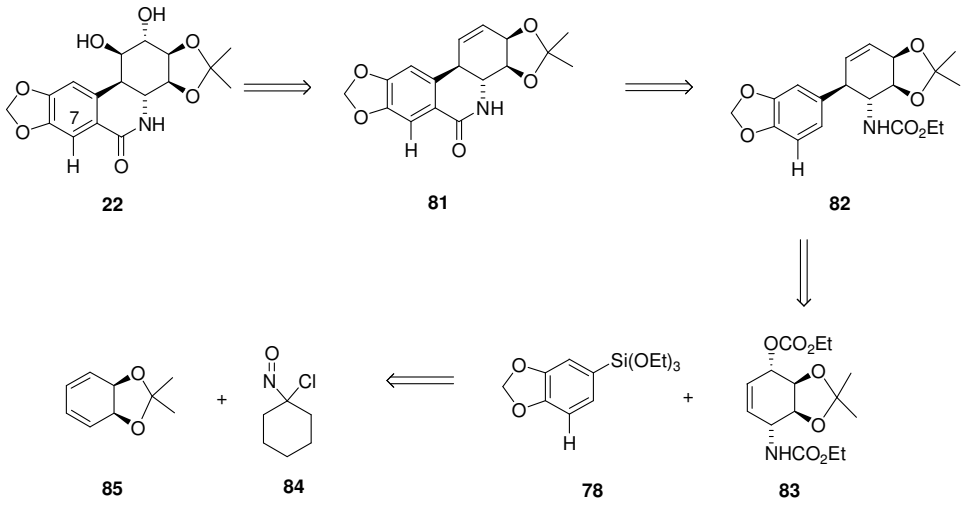
At this point the project was divided into two separate pieces. The first target was the completion of the synthesis for the model system, *i.e.* carrying coupling product through the remainder of the synthesis. Model compound **77** was synthetically much simpler to prepare and its elaboration would facilitate the total synthesis of 7-deoxypancratistatin. The second project was the total synthesis of (±)-7-deoxypancratistatin. The latter was the focus of my thesis research.

Results and Discussion

The approach to (±)-7-deoxypancratistatin is described retrosynthetically in Scheme 20. Preparation of 7-deoxypancratistatin **22** is readily feasible from olefin **81**

upon epoxidation and subsequent ring opening[55,59,60]. Olefin **81** would be prepared from compound **82**, employing Bischler-Napieralski chemistry[61,62]. The key step in the sequence is the coupling of aryl siloxane **78** with allylic carbonate **83**. The allylic carbonate of **83** was prepared from the Diels-Alder reaction of diene **85** with nitroso compound **84**[63-70].

Scheme 20.



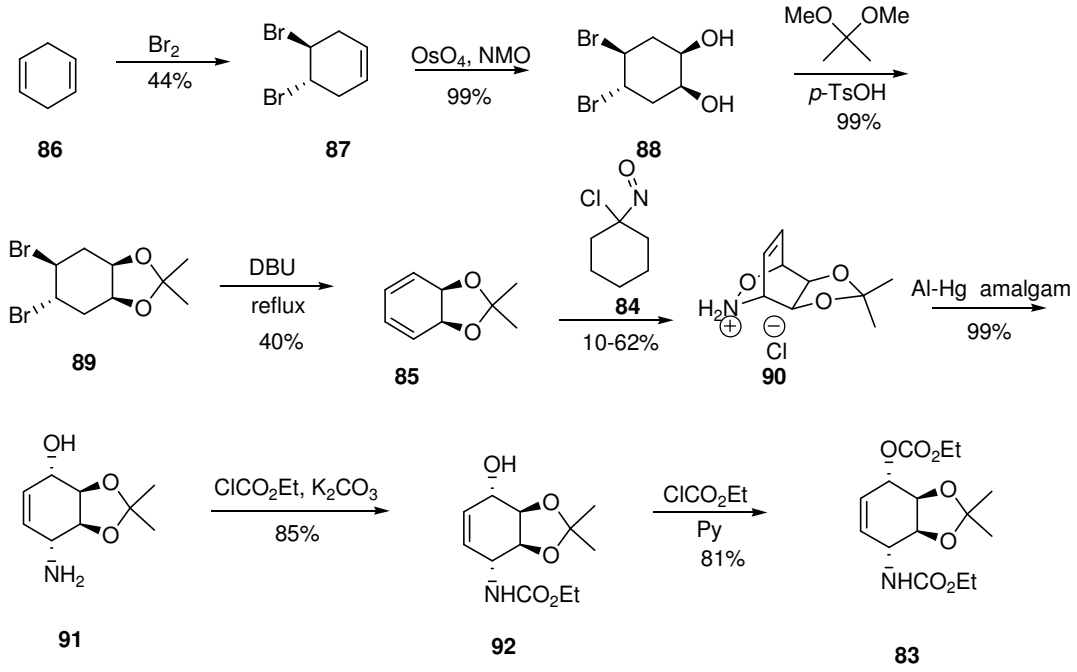
This synthetic approach has many potential advantages over the previously reported methods. First, the route described herein is towards racemic 7-deoxypancratistatin; this route can be easily adapted, using well-known and well-precedented chemistry to the synthesis of the enantiomerically pure target.[71] Secondly, the key synthetic intermediate (diene **85**) was prepared in four steps from commercially available materials. From a process chemistry point-of-view, elimination of these four steps would be facile. This diene (and many related analogues) are available from the enzymatic oxidation of benzene (and its derivatives) to afford, in one step, the desired diene (**85**) in >99% yield[72-75]. Biooxidations of this type are well studied and are now widely used organic synthons. These compounds are routinely prepared on the hundred-kilogram scale.

A third advantage to this synthetic strategy is the high regioselectivity expected from the key coupling reaction. This transformation which accomplishes the key carbon-carbon bond between the A and C rings has been a hurdle in previous syntheses. (Recall the Hudlicky synthesis; Hudlicky uses a higher order cuprate coupling and accomplishes the transformation in a 30 % optimized yield.) Lastly, the product of the allylic arylation coupling reaction will accomplish a formal synthesis of the target in 4 steps from commercially available materials. A total synthesis should be possible in 3 additional steps (Bischler- Napieralski cyclization, epoxidation/ring opening, and global deprotection). The shortest synthesis of (+)-pancratistatin to-date is 15 steps.

Our first generation synthesis of allylic carbonate **83** is given below in Scheme 21. The starting material for this synthesis was commercially available 1,4-cyclohexadiene **86**. Upon bromination at –78 °C dibromoalkene **87** can be prepared in 82% yield[76]. (The formation of the dibrominated product in preference to the tetrabrominated product is attributed to the insolubility of the dibrominated product at the reaction temperature.) Dihydroxylation is accomplished using catalytic osmium tetraoxide and stoichiometric *N*-methylmorpholine *N*-oxide as the sacrificial oxidant (**88**). Protection of the diol as the isopropylidene is easily obtained with 2,2-dimethoxypropane and a catalytic amount of *p*-toluenesulfonic acid (**89**)[77]. The dehydrobromination of **89** affords the requisite diene **85**[76]. Diene **85** underwent a hetero Diels-Alder cyclization with the α-chloronitroso compound **84**[78,79] yielding **90**[71,80] as the hydrochloride salt. Subsequent reduction of the N-O bond using Al-Hg amalgam afforded allylic alcohol **91** without incident[81]. Protection of the amine and alcohol as the ethyl carbamate (**92**) and ethyl carbonate (**83**), respectively, affords the desired allylic coupling partner.

During the course of the synthesis, however, it was found that the route utilizing the α-chloro nitroso Diels-Alder reaction was cumbersome. Most significantly, the reaction set-up for the Diels-Alder reaction was lengthy, requiring several hours of preparation; additionally, the reaction yields were low, irreproducible, and reactions times required greater than 5 days at 0 °C. The separate steps required to protect the alcohol and the amine decreased the elegancy

Scheme 21.



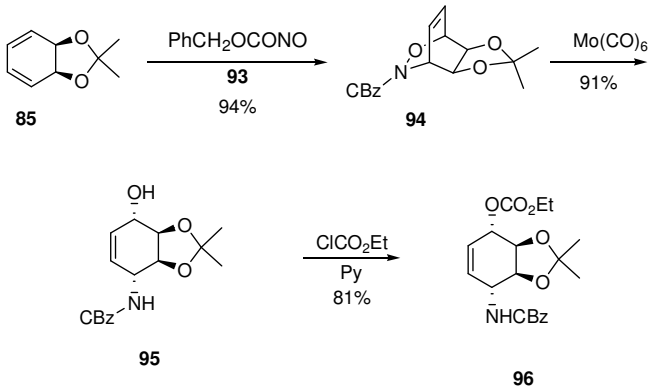
of the synthesis; this was another area that required improvement. Finally, as a matter of compound manipulation, i.e. chromatographic purification and the monitoring of the reaction's progress was difficult due to the lack of UV activity of this series of compounds.

In an attempt to address some of these synthetic hurdles, the synthesis was rerouted. Scheme 22 depicts the modified course. All of the impediments of the maiden synthesis were addressed in this second generation route. First and most importantly, the Diels-Alder sequence was much improved; the α-chloro nitroso

dienophile was replaced with an acyl nitroso dienophile **93**[82]. The acyl nitroso dienophile much easier to handle when compared with the chloronitroso analogue, i.e. the reaction set-up was simplified, the yield was much improved, and the reaction time was decreased. Additionally, utilizing nitroso compound **93**, the number of steps in the overall synthesis was reduced as protection of the amine was accomplished during the cycloaddition. Lastly, the handling and preparation of the acyl nitroso was much simpler than the analogous α-chloronitroso compound.

With Diels-Alder adduct **94** in hand, the N-O reduction sequence was addressed. Previous studies in the DeShong laboratory revealed that reduction of an acylated nitrogen of an N-O bond is more resistant to reduction that a free amine[24]. In this light, a literature search detailed a procedure for effecting this transformation utilizing a catalytic amount of $Mo(CO)_6$ in the presence of a stoichiometric amount of $NaBH_4$.[83]. The reaction proceeded without incident to provide the desired allylic alcohol **95** and the nitrogen protected as a carbamate. Treatment of the allylic alcohol with ethylchloroformate afforded the desired coupling partner **96** in good yield.

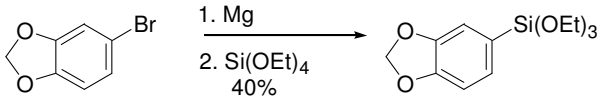
Scheme 22.



85 94 95 96

The siloxane coupling partner was easily prepared from commercially available aryl bromide **97** (Scheme 23). Treatment of bromide with magnesium (0) generated the desired Grignard reagent which was quenched with tetraethylorthosilicate. The desired product **78** was easily obtained via distillation. The modest reaction yield for this transformation is attributed to the instability of the ensuing Grignard species as well as the lack of electrophilicity of the tetraethylorthosilicate.

Scheme 23.



97 **78**

Once completing the syntheses for the obligatory allylic carbonate **96** and aryl siloxane **78**, the two were reacted under standard allylic arylation conditions (Pd_2dba_3, TBAF, THF, 50 °C, Scheme **24**). Analysis of the reaction mixture has shown that all starting material is consumed during the course of the reaction, however, the desired coupling product **98** was not observed. Recall, however, that the coupling of aryl siloxane **78** with the simplified allylic carbonate system **77** resulted in efficient coupling (Scheme 24) as **83** and **77** differ only in the presence of the cis diol moiety at the 3 and 4 positions on the C ring, it can be rationalized that this moiety is responsible for sterically impeding the desired coupling. The modifications to the synthesis were directed at correcting this problem.

Scheme 24.

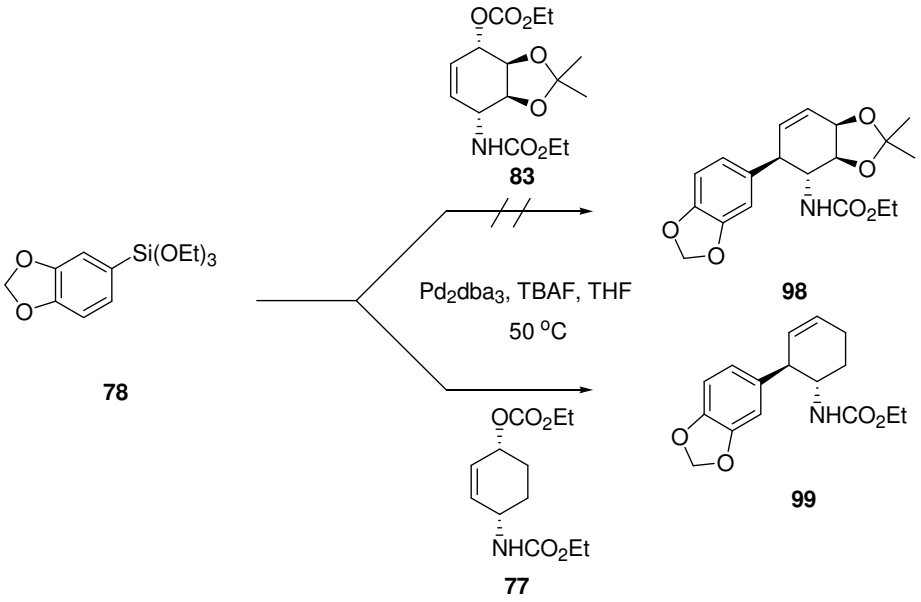
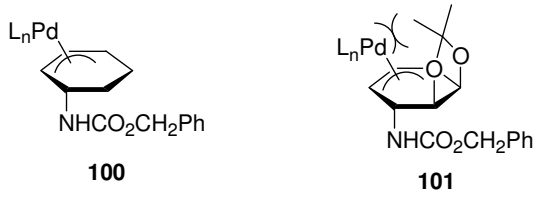


Figure 3. Sterics Involved with π-Allyl Formation.



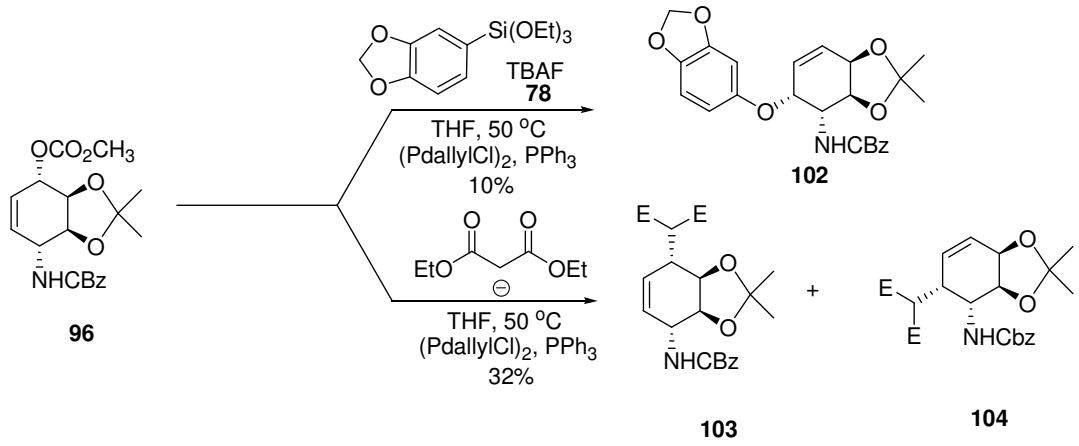
In addition to reworking the key step of the synthesis, the chemical literature was also explored for insight. In a 1998 review article Trost described the application of allylic alkylation methodology to a variety of total syntheses.[29] The catalyst of choice for most of these allylic alkylations was $Pd(dba)_2$, however, the catalyst used for a substrate reminiscent of **83** was allyl palladium chloride dimer[29]. Although no comment was made for use of this catalyst, it can be surmised that the typical catalyst choice ($Pd(dba)_2$) was ineffective and a more "active" catalyst choice should be considered.

Supplied with the knowledge that our typical catalyst choice may have been ineffective in achieving our desired allylic arylation the following two control

experiments were performed (Scheme 25). First, allylic carbonate **96** was reacted under identical reactions conditions save for the use of allyl palladium chloride dimer in place of $Pd(dba)_3$. In the presence of this presumably more activated catalyst system, an unexpected aryl ether **102** was isolated from the reaction mixture[24]. Additionally, as a control experiment, allyl carbonate **96** was subjected to allylic alkylation conditions and the nucleophile was varied. In the presence of the soft nucleophile, the anion of diethylmalonate, coupling was observed and the expected mixture of products **103** and **104** were isolated.

This set of experiments has provided a number of interesting insights. Consider the siloxane mediated allylic arylation. First, merely changing the catalyst

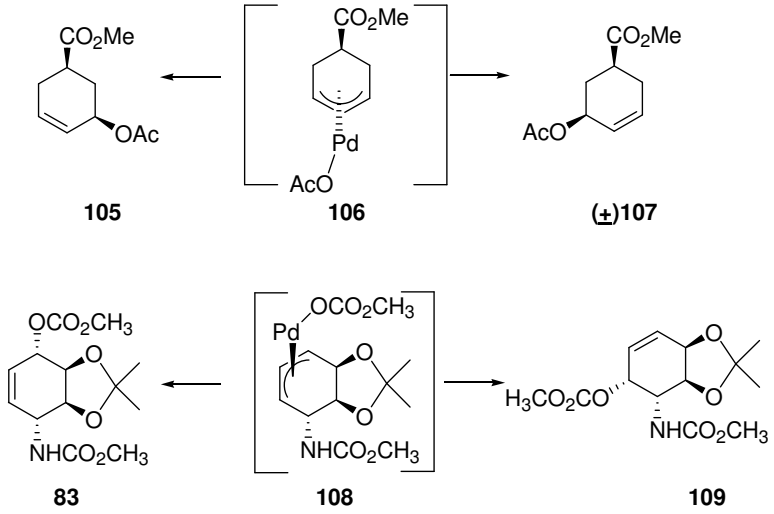
Scheme 25.



from $Pd(dba)_3$ to allyl palladium chloride dimer afforded an arylation product; albeit an undesired aryl ether. The formation of such a product has not been described in the literature. There exists several possibilities for the origin of oxygen incorporation. The oxygen may be derived from the TBAF solution which was used as the fluoride source; all commercially available TBAF solutions such as that used during the course of these experiments contains 5% water. A second possibility is that the ether oxygen is derived from the carbonate following its rearrangement and

subsequent hydrolysis (Scheme 26). This phenomenon is well-precedented in carbohydrate and even allylic allylation chemistry; acetates are known to frequently migrate from hydroxyl to hydroxyl. In the presence of palladium, chiral allylic acetate **105** undergoes desymmetrization upon forming π-allyl **106**[84]. Eventually, the racemic product **107** is observed. The same explanation could explain the migration of the allylic carbonate of **83** through the palladium π-allyl **108** to afford the regioisomeric product **109**. The allylic alcohol formed upon subsequent hydrolysis of carbonate **109** could potentially be responsible for the formation of aryl ether **102**. Despite these hypotheses a clear arrow-pushing mechanism to explain the formation of aryl ether **102** from **83** has remained elusive.

Scheme 26.



Unfortunately, neither of these mechanistic pathways have been validated or eliminated to date. On the other hand, consider the stereochemical implications of each scenario. The ether product has been determined to be *cis* with respect to the carbamate moiety by X-ray crystallographic analysis. It is arguable that incorporation of the ether oxygen via water (TBAF) could occur in either a *cis* or a *trans* fashion,

but only the *cis* product is observed. Should the oxygen incorporation result from carbonate hydrolysis and subsequent rearrangement, the oxygen should inherently be *cis* relative to the carbamate. In either case, a definitive answer has not yet been found.

The success of the allylic alkylation with the soft nucleophile, diethyl malonate, affording **103** and **104** was a result that provided much insight into the problems with the key coupling step. This experiment has shown that all the steps prior to the allylic alkylation occurred without incident, i.e. oxidative addition and allylic alkylation. As described previously in the introduction, hard and soft nucleophiles react in allylic arylation reactions via an unique mechanistic pathways. Mechanistically, hard nucleophiles undergo a transmetallation step while soft nucleophiles do not. Additionally, the reductive elimination pathway is different. Recall, in the presence of a hard nucleophile reductive elimination occurs from the same face as the metal center. In the case of a soft nucleophile, the reductive elimination occurs on the face opposite the metal center. One of two conclusions can be drawn from this experiment. The first, during the course of allylic arylation reaction (Scheme 24), the transmetallation step was not feasible. The second possibility is that reductive elimination is not favorable. In either case, we had hoped to facilitate the transmetallation step and/ or the reductive elimination step by reducing the steric bulk about the metal center and thereby favoring the desired pathway.

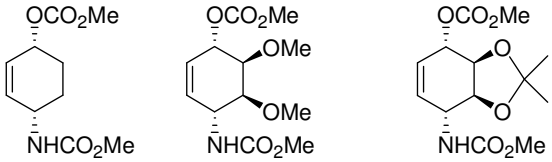
As was discussed previously, in terms of functionality, the compound used in model investigations differed only in that it lacked two hydroxyl groups, which were present in the actual system. The model compound **77** easily yielded to the reaction conditions and gave the desired allylic arylation products; surprisingly, allyl carbonate

83 was unreactive to the same conditions. Therefore, it would lend that either the cis hydroxyls and/or their protecting group are impeding efficient coupling (Figure 2).

In an effort to troubleshoot the coupling reaction we: 1) used molecular modeling to investigate the possible energy barriers impeding our reaction and 2). varied the protecting groups on the *cis* diols to experimentally access these same barriers.

All molecular modeling experiments were performed using a Piroda DFT calculator[85,86] and were completed by Dr. Andrei Vedernikov. The first set of data collected investigated the oxidative addition of palladium (0) into substrates **110**, **111**, and **112**. The calculations have shown that oxidative addition into **112**, is

Figure 4. Substrates Evaluated Using Molecular Modeling.



110 **111** **112**

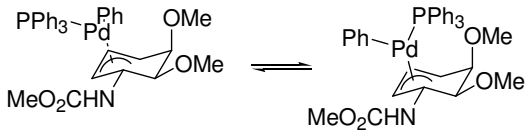
less favored by 4 kcal/mol compared with **110** and **111**. This data supports the hypothesis that the *cis* diols constrained to a ring as in **112** are too sterically constrained to undergo allylic arylation. As a matter of conformation, oxidative addition requires palladium to be planar with the three carbons atoms of the π-allyl system. One would expect that planarity would be easier for monocyclic systems **110** and **111**. For **112**, the planarity that would be required for oxidative addition would severely destabilize the bicycle due to immense torsional and steric strain of such an unfavored conformation.

Calculation data was also collected to provide insight into the reductive elimination sequence. This step in the catalytic cycle was scrutinized based on the

information described previously in Scheme 25, namely that allylic carbonate **83** effectively couples with soft nucleophiles, but not with hard nucleophiles such as **78**. In this light, the relative Gibbs energies for the two transition state extremes (**113** and **114**) were modeled. The data has shown that the Gibbs activation energy for **113** is 20.8 kcal/mol. For **114** the Gibbs activation energy was calculated to be 18.2 kcal/mol. The higher energy calculated for **113** over **114** can be rationalized by the unfavorable steric interaction between the phenyl ring on the palladium and the axial methoxy substituent.

The three conclusions drawn from this calculation data were 1) oxidative addition may be impeded by the presence of a fused ring system 2) sterics

Scheme 27.



113 **114**

also play an important role in the reductive elimination step and 3) if reductive elimination is the rate determining step, the reductive elimination should favor the formation of a 1-4 phenylated product (as predicted) over the possible 1-2 phenylated product.

Given that the molecular modeling calculations have shown that the coupling reaction utilizing isopropylidene protected diol compound **83** is less energetically favorable than its acyclic protective counterpart we sought to investigate protecting group alternatives. A variety of protecting groups were investigated during the course of this synthesis.

Early in the synthesis we had defined a series of requirements for any protecting group employed in the synthesis. First, the group should be relatively small and the *cis* hydroxyl groups should not be confined to a ring as in **83**. The protecting group should also withstand the basic coupling reaction conditions and should be removable at the end of the reaction. Common protecting groups that were immediately eliminated included acetates, which are known to hydrolyze under our coupling conditions. Additionally, silyl protecting groups were eliminated as they are readily cleaved in the presence of fluoride – another necessary component of our coupling reactions.

An obvious first choice was the protection of the diols as their dimethyl ethers. The literature is abundant with protocols for achieving this transformation under either acidic or basic conditions. Despite the fact that methylation of an aliphatic alcohol is essentially an irreversible process, coupling of this analogue would provide valuable insight into the coupling process. The success of this coupling would validate the hypothesis that the isopropylidene protecting group sterically impeded the reaction.

A multitude of methylation procedures and reagents were attempted, but all were unsuccessful in the preparation of dimethylated analogue of allylic carbonate **83**. Methylation was also attempted at a variety of stages in the synthetic sequence. Logically, protection was initially attempted early in the synthesis at to avoid a series of protections and deprotections . Dibromodiol **88** was subjected to numerous methylation conditions. The first attempt at methylation utilized methyl iodide and a general base, triisopropylethylamine. Unfortunately the dibromodiol was resistant to methylation and only starting material was isolated. Variants on this traditional methylation procedure were attempted using a variety of bases. Strong bases such as potassium hydroxide and sodium hydride resulted in decomposition of the

substrate due to competing elimination reactions, even at low temperatures. Stronger methylation agents were also investigated; they included trimethyl oxonium tetrafluoroborate, diazomethane, and dimethylsulfate. Although the dibromodiol was not completely unreactive to these conditions, only mixtures of monoalkylated products were isolated. The reactions could not be driven to completion even upon extended reaction times (> 7 days) at high temperatures (reflux).

Hoping to protect the *cis* diol as its dimethyl ether derivative, the protection was attempted at other points in the synthesis, for example, at bicycle **90** or **94**. One advantage to protecting the diol at this stage was the fact that the bicycles **90** and **94** were far less acid and base sensitive than dibromodiol **88**. One disadvantage to performing the protection at this point was that additional steps would be added to the synthesis, i.e. the isopropylidene would be present early in the synthesis and would later be replaced by the dimethyl ethers. Unfortunately, methylation, even monomethylation could not be accomplished. More vigorous conditions were again employed (refluxing dimethyl sulfate), but methylation was not observed.

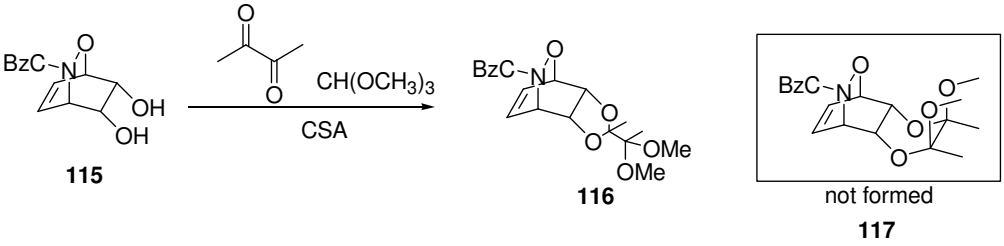
At this point, the synthetic strategy was revised slightly. Initially, attempts were made to protect the *cis* diol with some aliphatic protecting group. Sensing methylation was not feasible, other potential protecting group targets were investigated. Toward this end, diallyl ethers were examined as potential protecting groups for the diol. Allyl protecting groups are well known in carbohydrate chemistry and the ring C of pancratistatin bears some resemblance to a sugar[87-95]. Unfortunately, after several unsuccessful attempts, allylation chemistry was abandoned.

Again the synthetic strategy was revamped. Due to the lack of success at protecting the *cis* diol in an acyclic fashion, a ring size larger than that of the isopropylidene (5 membered) was considered as it might facilitate efficient allylic

arylation. In this regard, attempts were made to prepare 6-membered *bis*-acetal **117**. Again this chemistry is well established in the literature[96,97]. Treatment of bicyclic diol **115** with 2,3-butadione, trimethylorthoformate, and a catalytic amount of camphor sulfonic acid, did not afford the desired product. Surprisingly, the five-membered adduct **116** was preferentially formed and the structure determined by single X-ray crystallographic analysis upon the cleavage of the N-O bond and subsequent protection of the allylic alcohol as the ethyl carbonate (Appendix A).

The final strategy toward the completion of this project was to prepare the six membered analogue of **119** – a less rigid and more conformationally flexible analogue of **83**. Diol **118** was treated with 2,3-butadione, trimethylorthoformate, and a catalytic amount of camphor sulfonic acid. A mixture of products **119** were obtained which was inseparable by flash chromatography.

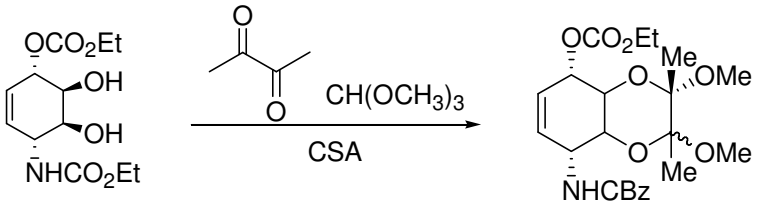
Scheme 28.



115 **116** **117**

The synthetic difficulties described herein are characteristic of the difficulties experienced by all chemists targeting the 7-deoxypancratistatin, specifically achieving the requisite functionality for the C ring. Unfortunately, the work towards validating the siloxane mediated allylic arylation as a viable approach towards the synthesis of this family of compounds is incomplete. However, much knowledge has been gained to aid in this effort. First the synthetic route to allylic carbonate **83** has been optimized. Several key control experiments have also provided invaluable insight into this complex system.

Scheme 29.



118 **119**

Future work for the completion of this project will involve the separation of the diastereomeric bisacetals **119** and its successful coupling with aryl siloxane **78**. Alternatively, the cis diol moiety must be alternatively protected. Experience has shown that this protection must include the incorporation of an acetonide or bisacetal-like group as the molecule is resistant to the incorporation of an acyclic protection group. The appropriate protection the cis diols should hopefully facilitate the completion of the total synthesis.

Experimental

Thin-layer chromatography (TLC) was performed on 0.25 mm Merck silica gel coated plates treated with a UV-active binder with compounds being identified by one or more of the following methods: UV (254 nm), iodine, vanillin/sulfuric acid charring, $KMnO_4$ charring, or *p*-anisaldehyde charring. Flash chromatography was performed using a thick walled columns and medium pressure silica gel (Whatman 200-245 mesh), with column length and diameter being determined by the method of Still.[98]

Melting points were taken in Kimax soft glass capillary tubes using a Thomas-Hoover Uni-Melt capillary melting point apparatus (Model 6406K) equipped with a calibrated thermometer. Melting points are corrected.

Infrared spectra were recorded on a Nicolet 5DXC FT-IR spectrophotometer. Samples were either dissolved in carbon tetrachloride, prepared as a potassium bromide pellet or as a Nujol mull. Band positions are reported in reciprocal centimeters (cm^{-1}) and relative intensities are listed as br (broad), s (strong), m (medium), or w (weak).

Nuclear magnetic resonance (^{1}H, ^{13}C NMR) spectra were recorded on a Bruker DRX-400 spectrometer. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane (TMS). Coupling constants (*J* values) are reported in Hertz (Hz), and spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br s (broad singlet).

Low resolution mass spectrometry (LRMS) and high resolution mass spectrometry (HRMS) were obtained on a VG-7070E magnetic sector instrument.

Gas chromatography was performed on a Hewlett Packard 5890 GC equipped with a flame ionization detector using a 25m methyl silicon column.

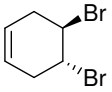
Tetrahydrofuran (THF) and diethyl ether were distilled from sodium/benzophenone ketyl. Methylene chloride, tetraethylorthosilicate, and pyridine were distilled from calcium hydride. Dimethylformamide (DMF) was distilled from calcium sulfate. Benzene was stored over 4 Å molecular sieves prior to use.

Bis(dibenzylideneacetone)palladium ($Pd(dba)_2$), and allylpalladium chloride dimer ($(allylPdCl)_2$) were purchased from Acros and used as received. Triphenyl phosphine (PPh_3) was purchased from Aldrich and recrystallized from hexanes prior to use. All other reagents were bought from commercial sources and used without purification unless otherwise noted.

All glassware used in these reactions was either oven dried at 120°C for 12 hours or flame dried prior to use. All reactions were conducted under an atmosphere

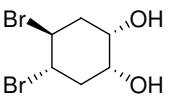
of anhydrous argon.

All compounds were determined to be >95% pure by ^{1}H NMR or GC analysis, unless otherwise noted. Previously reported compounds were characterized by ^{1}H NMR, ^{13}C NMR, and IR and compared to literature values. All new compounds were characterized using ^{1}H NMR, ^{13}C NMR, IR, low resolution, and high resolution mass spectroscopy.



87

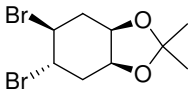
The dibromide **87** was prepared from 1,4-cycohexadiene according to the procedure of Yang.[76] To 21.2 g of 1,4-cyclohexadiene (264 mmol) in 60 ml of $CHCl_3$ at –78 °C was added 13.6 ml of Br_2 (264 mmol) dropwise over 2 h. The reaction mixture was allowed to stir for 45 minutes and the reaction was quenched by the addition of 100 ml of a 10% aqueous sodium thiosulfate. The mixture was extracted with $CHCl_3$ (3 x 100 ml). The combined organic extracts were washed with brine (1 x 100 ml), dried over $MgSO_4$, filtered, and concentrated in vacuo to afford 27.4 g (44%) of dibromide **87** as a white solid, mp 35-36 °C (lit.[76] 34 - 37°C), which was used without further purification. IR (CCl_4) 3040 (w), 2943 (w), 2881 (w), 2819 (w), 2365 (w), 2322 (w), 1421 (m) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.58 (d, *J* = 19Hz, 2H), 3.17 (d, *J* = 19Hz, 2H), 4.50 (s, 2H), 5.65 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 122.4, 48.8, 31.5. LRMS (EI^+) *m/z* 240 (M^+ 25), 161 (23), 159 (25), 79 (100), 77 (38).



88

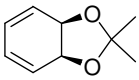
To 27.4 g (115 mmol) of the dibromoalkene **87** in 680 ml of acetone and 74 ml H_2O was added 20.2 g (173 mmol) *N*-methylmorpholine *N*-oxide hydrate followed by 250 mg (0.98 mmol) of OsO_4 at room temperature with stirring. The heterogeneous yellow solution became homogeneous within 2 h. The reaction was allowed to stir at room temperature for 24 h and was quenched by the

addition of 280 mg (1.47 mmol) sodium metabisulfite in 100 ml H_2O. The solution was concentrated in vacuo to 200 ml and extracted with Et_2O (3 x 350 ml). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo to afford a white solid. Recrystallization from chloroform afforded 31.5 g (99 %) of the dibromodiol **88** as a white solid, mp 89-91°C (lit.[76] 103-105 °C). IR (CCl_4) 3491-2953 (br s), 2951 (w), 2889 (w), 1685 (w) cm^{-1}. ^1H NMR (py - d_5) δ 2.15 (ddd, *J* = 15, 12, 2, 1H), 2.71 (dddd, *J* = 12, 4,4, 1, 1H), 2.84 (ddd, *J* = 15, 4, 3, 1H), 2.94 (ddd, *J* = 12, 12, 11 Hz, 1H), 3.98 (ddd, *J* = 12, 4, 3, 1H), 4.26 (m, 1H), 4.40 (ddd, *J* = 12, 11, 4, 1H), 4.86 (ddd, *J* = 12, 11, 4, 1H), 6.11 (br s, 2H). ^{13}C NMR (py-d_5) δ 42.1, 43.7, 55.6, 56.5, 70.9, 71.5. LRMS (EI^+) *m/z* 274 (M^+, 5), 195 (90), 193 (95), 177 (78), 175 (98), 113 (28), 95 (100), 67 (94), 55 (51). The IR, ^1H NMR, and ^{13}C NMR spectra matched that previously reported in the literature.[99]



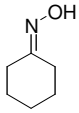
89

To 26.0 g (94.9 mmol) of the dibromodiol **88** in 1L CH_2Cl_2 was added 120 g (141 ml, 1.14 mol) of 2,3-dimethoxypropane dropwise followed by 500 mg of *p*-toluenesulfonic acid monohydrate. The reaction was allowed to stir for 12 hours and was then diluted with saturated $NaHCO_3$ (1 x 500 ml) and extracted with CH_2Cl_2 (3 x 500 ml). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo to give a yellow oil. Purification by column chromatography (25% EtOAc/Hexanes; R_f 0.3) afforded 29.8 g (99%) of the acetonide protected diol **89** as a yellow oil. IR (CCl_4) 2990 (m), 2932 (m), 2877 (m), 2827 (w), 1720 (w), 1456 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.31 (s, 3H), 1.51 (s, 3H), 2.20 (m, 1H), 2.36 (m, 1H), 2.71-2.75 (m, 2H), 4.15-4.20 (m, 2H), 4.26-4.30 (m 1H), 4.39-4.43 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 26.5, 28.7, 35.0, 36.5, 49.4, 51.6, 72.6, 73.0, 109.4. ^1H NMR, and ^{13}C NMR spectral data match that previously reported in the literature.[77]

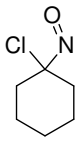


85

The diene **85** was prepared according to the procedure of Yang.[76] To 29.8 g (94.9 mmol) of the isopropylidene **89** in 1500 ml of benzene was added 34.1 ml (52.0 g, 342 mmol) of DBU dropwise using an addition funnel. The yellow heterogeneous mixture was heated at reflux for 11 hours. The HBr was removed by vacuum filtration and the filtrate was diluted with saturated $NaHCO_3$ (1 x 150 ml) and extracted with benzene (3 x 200 ml). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo to give a yellow oil. Column chromatography (33% CH_2Cl_2/Pentane, R_f 0.25) afforded 14.4 g (40%) of diene **85** as a yellow oil. IR (CCl_4) 3049 (m), 2986 (m), 2928 (m), 2862 (m), 2792 (w), 2769 (w), 1961 (w), 1472 (w), 1441 (m), 1383 (m), 1351 (m), 1243 (m), 1216 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.38 (s, 3H), 1.40 (s, 3H), 3.46 (s, 2H), 5.87 (m, 2H), 5.96 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 25.2, 27.8, 70.2, 104.5, 123.7, 126.7. ^1H and ^{13}C spectral data match that previously reported in the literature.[77]

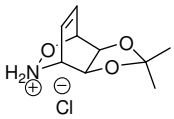


To 18.0 ml (16.6 g, 0.170 mmol) of cyclohexanone in 500 ml H_2O was added 21.9 g $NaHCO_3$ followed by NH_2OH-HCl portion wise. Vigorous bubbling occurred. The reaction was allowed to proceed for 30 minutes at room temperature. The solid product was collected *via* vacuum filtration. Recrystallization from hexanes afforded the product, cyclohexanone oxime, as a white solid, mp 88-90 °C (lit.[100] 91 °C). IR (KBr) 3221 (br s), 1691 (m), 942 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.63 (m, 6H), 2.19 (t, *J*= 6 Hz, 2H), 2.49 (t, *J* = 6 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 24.4, 25.6, 25.8, 26.8, 32.1, 160.7. The spectral data was identical to that reported by Hwu.[101]



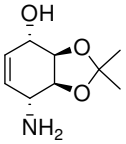
84

To 7.25 g (64.0 mmol) of the cyclohexanone oxime in 56 mL Et_2O was added 189 mL of 0.338 M HOCl dropwise with stirring under an atmosphere of argon. Upon the addition of HOCl, the reaction solution turned blue. The reaction was allowed to stir 30 minutes following the addition of HOCl and then diluted with water (1 x 100 ml) and extracted with Et_2O (3 x 100 ml). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford a blue oil. Purification by column chromatography (100% pentane, R_f 0.35) afforded 4.25 g (46%) of the α-chloronitroso compound as a blue oil. IR (CCl_4) 3600 (m), 3417-3126 (s br), 2936 (m), 2854 (m), 2664 (w), 2357 (w), 2334 (w), 1713 (m), 1573 (m), 1557 (m), 1449 (m), 1425 (m), 1344 (w), 1309 (w), 1250 (w), 1223 (w) cm^{-1}. Further characterization was not attempted due to the instability of the compound. The IR data was identical to that reported by Corey.[78]



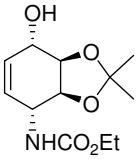
90

To 3.80 g (25.4 mmol) of the diene **85** in 8 ml Et_2O and 2 ml EtOH was added 3.97 g (26.7 mmol) of the α-chloronitroso **84** in 8 ml Et_2O. The homogeneous blue mixture was stirred under argon for 30 minutes and then placed in the freezer at 0 °C for 5 days at which time all the blue color had disappeared. The solid yellow product was collected by gravity filtration, was washed with cold EtOH to afford 3.66 g (62%) of the Diels Alder adduct **90** as a white solid (mp 135°C - 160 °C decomp., lit.[102] 180-182 °C decomp). IR (nujol) 2954 (m), 2923 (m), 2850 (m), 1460 (w), 1370 (w) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.22-1.25 (m, 6 H), 4.56 (m, 1H), 4.75 (m, 1H), 4.92 (m, 1H), 5.25 (m, 1H), 6.50-6.51 (m, 1H), 6.68-6.70 (m, 1H). ^{13}C NMR (*d_6* - DMSO) δ 52.1, 52.3, 76.8, 95.8, 97.4, 98.7, 137.2, 155.0, 160.0. LRMS (FAB) *m/z* 367.1 ($2M^+$ 12), 184.1 (100). HRMS (FAB) calcd for 184.0974, found 184.0974. The IR, ^1H NMR, and ^{13}C NMR spectra matched that previously reported in the literature.[102]



91

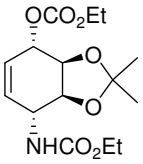
The amino alcohol **91** was prepared according to the procedure of Elango and Yan.[103] To 3.66 g (16.7 mmol) of the Diels Alder adduct **90** in 100 ml THF and 10 ml H_2O was added 3.15 g (117 mmol) of Al(Hg) amalgam. The amalgam was prepared by exposing 3.15 g (117 mmol) of aluminum foil to 50 ml of each of the following for 20 seconds each: 1M KOH, distilled H_2O, 0.5% $HgCl_2$, distilled H_2O, and THF. The amalgam was then added to the reaction mixture containing the Diels Alder adduct. The gray heterogeneous mixture was allowed to stir at 0 °C under argon for 12 hours and was then filtered through Celite and concentrated in vacuo to afford 3.6 g (100%) of the amino alcohol, **91** as a white solid which, was used without further purification. IR (CCl_4) 3700-3300 (br s), 3090 (m), 2990 (m), 2600 (w), 1625 (w), 1470 (w) cm^{-1}. ^1H NMR (d_6- DMSO) δ 1.30 (s, 3H), 1.39 (s, 3H), 3.45 (m, 1H), 3.98-4.03 (m, 3H), 5.58-5.62 (m, 1H), 5.76-5.81 (m, 1H). ^{13}C NMR (CD_3OD) δ 24.3, 26.8, 51.7, 69.7, 78.4, 80.2, 110.0, 128.2, 133.4. LRMS (FAB) *m/z* 186 (100), 110 (33), 45 (43). HRMS (FAB) calcd 186.1130, found 186.1121. ^1H and ^{13}C spectral data match that previously reported in the literature.[103]



92

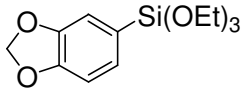
To 2.57 g (10.1 mmol) of the amino alcohol **91** in 12.5 MeOH and 53 ml of acetone was added 4.27 g (40.4 mmol) Na_2CO_3 and 3.28 g (2.89 ml, 30.3 mmol) of ethylchloroformate. The solution was stirred for 45 minutes and then was concentrated in vacuo. The crude oil was diluted with 100 ml of saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 100 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to afford 2.18 g (85%) of the

carbamate **92** as a white solid. The compound was used without further purification. IR (CCl_4) 3617 (w), 3451 (w), 2988 (w), 2902 (w), 1735 (s), 1545 (m), 1210 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.23 (t, *J* = 7 Hz, 3H), 1.33 (s, 3H), 1.43 (s, 3H), 2.47 (br s, 1H), 4.11 (m, 3H), 4.19-4.24 (m, 3H), 5.14 (br s, 1H), 5.81-5.78 (m, 1H), 5.90 - 5.93 (m, 1H) cm^{-1}. ^{13}C NMR (*d_6*-DMSO) δ 14.6, 25.0, 27.2, 51.5, 59.7, 69.2, 75.9, 79.8, 107.9, 129.5, 132.6, 155.9. LRMS (FAB) *m/z* 258 ($M+1^+$, 42), 240 (66), 182 (70), 154 (63), 110 (100); HRMS *m/z* calcd. 258.1342, found 258,1341. IR, ^1H and ^{13}C spectral data match that previously reported in the literature.[104]



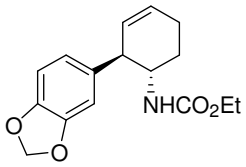
83

To 2.18 g (8.47 mmol) of the carbamate **92** in 78 ml CH_2Cl_2 was added 19.4 ml of anhydrous pyridine and 1.38 g (2 ml, 12.71 mmol) of anhydrous ethylchloroformate which caused the evolution of a yellow gas from the reaction solution upon the addition. The yellow solution was stirred for 48 hours and was then diluted with 150 ml CH_2Cl_2 and washed with saturated NaCl (1 x 150 ml) and extracted with CH_2Cl_2 (3 x 100 ml). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to afford the carbonate **83** as a white solid. Purification by column chromatography (10% to 25% EtOAc/hexanes, gradient elution, R_f 0.1) afforded 2.26 g (81%) of a white solid. IR (CCl_4) 3437 (w), 2988 (w), 2937 (2), 1749 (s), 1728 (s), 1552 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.17 (m, 3H), 1.25 (m, 6H), 1.39 (m, 3H), 4.06 (m, 2H), 4.15 (m, 4H), 4.28 (m, 1H), 5.06 (m, 1H), 5.21 (br s, 1H), 5.81 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 14.1, 14.4, 24.8, 26.8, 50.3, 60.9, 64.3, 74.0, 75.8, 76.0, 109.2, 126.9, 131.3, 154.2, 156.0. LRMS (FAB) m/z 330 ($M+1^+$, 6), 154(38), 136(40), 73(48); HRMS (FAB) calcd $(M + 1)^+$ 330.1553, found 330.1553. IR, ^1H and ^{13}C spectral data match that previously reported in the literature.[104]



78

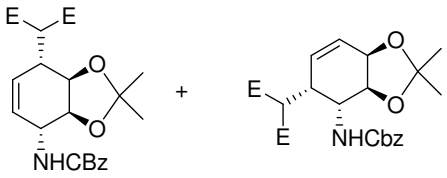
To 1.5 g (62.5 mmol) of magnesium turnings in 10 ml of anhydrous THF was added 8.38 g (41.6 mmol) of the aryl bromide **97** dropwise with stirring. After the reaction became warm, an additional 30 ml of THF was added to the mixture. After 48 hours, the Grignard mixture was cannulated into 13.1 g of $Si(OEt)_4$ in 60 ml anhydrous THF. The solution was allowed to stir for 48 hours. The solution was then diluted with 100 ml H_2O and extracted with Et_2O (3 x 100 ml), dried over $MgSO_4$, filtered, and concentrated in vacuo to a brown oil. After a Kugelrohr distillation (0.3 atm, 100-120°C), the desired aryl siloxane **78** was obtained as a colorless oil, 4.8 g (40%). IR 3056 (w), 2971 (m), 2932 (m), 2885 (m), 2773 (w), 2834 (w), 1876 (w), 1619 (w), 1603 (w), 1507 (m), 1484 (m), 1425 (m), 1390 (m), 1239 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.36 (t, *J* = 7 Hz, 9H), 3.98 (q, *J* = 7 Hz, 6H), 6.05 (s, 2H), 6.97 (d, J = 8 Hz, 1H), 7.24 (s, 1H), 7.31 (d, J = 8 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 16.5, 57.0, 98.9, 106.9, 112.3, 122.1, 127.7, 145.7, 147.8. LRMS (FAB) 284.4 (M^+, 100), 283.4 (42), 239 (80), 161 (65). HRMS (FAB) calcd. 284.1080 (M^+), found 284.1080. The spectral data was identical to that reported by Manoso.[19]



99

To a solution of 0.22 g of siloxane **78** (0.39 mmol) and 100 mg carbonate **77** (0.20 mmol) in 5 ml THF was added 20 mg Pd_2dba_3-$CHCl_3$ (5 mol %) to give a deep purple solution. Lastly, tetrabutylammonium fluoride (0.8 ml, 1M in THF) was added and the amber reaction mixture was subjected to one freeze-pump-thaw cycle. The reaction mixture was heated to 55 °C for 20h, cooled and quenched by the addition of water (10 ml). The black suspension was extracted with ether (3 x 40 ml), dried over $MgSO_4$ and

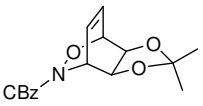
concentrated in vacuo. Flash chromatography on silica gel (25 % EtOAc/hex, R_f = 0.38) gave 75 mg (67%) of **99** and its regioisomer in a 1:1 ratio. A small amount of the mixture was separated on preparative HPLC (25% EtOAc/hex) for spectral analysis. IR (CCl_4) 3447 (w), 3029 (w), 2933 (w), 1729 (s), 1552 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.73-6.67 (m, 3H), 5.91 (s, 2H), 5.87 (d, *J* = 10 Hz, 1H), 5.66 (d, *J* = 10 Hz, 1H), 4.76-4.74 (m, 1H), 4.03 (q, *J* = 7 Hz, 2H), 3.74-3.71 (m, 1H), 3.23-3.21 (m, 1H), 2.20-2.04 (m, 2H), 1.90-1.86 (m, 1H), 1.62-1.53 (m, 1H), 1.18 (t, *J* = 7 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 156.0, 147.6, 146.2, 136.5, 128.0, 127.9, 121.5, 108.7, 108.0, 100.9, 60.6, 52.7, 47.6, 25.5, 22.9, 14.5; LRMS (FAB) *m/z* 290 ((M+H)+, 21), 201 (100), 174 (31), 135 (81), 73 (90); HRMS (FAB) calcd for $C_{16}H_{20}O_4N$ (M+H)+ 290.1392, found 290.1379.



103 **104**

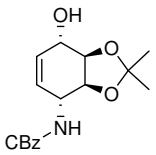
To 158 mg (0.404 mmol) of allyl carbonate **96** in 2 ml THF was added 16 mg (0.061 mmol) of triphenylphosphine and 7.4 mg (0.020 mmol) of allyl palladium chloride dimer. The reaction was allowed to stir under an atmosphere of argon. Immediately, 68 mg (0.424 mmol) of deprtonated diethyl malonate in1 ml of THF was cannulated into the allyl carbonate reaction mixture. The amber reaction mixture was subjected to one freeze-pump-thaw cycle. The reaction mixture was heated to 55 °C for 20h, cooled and quenched by the addition of water (10 ml). The black suspension was extracted with ether (3 x 40 ml), dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromatography (20 % EtOAc/hex, R_f = 0.13) afforded 186 mg (32%) of the desired product **103** as a white solid. IR (CCl_4) 3441 (m), 3029 (w), 2990 (m), 2936 (m), 2897 (w), 2365 (w), 2338 (w), 1755 (s), 1732 (s), 1503 (s), 1375 (m), 1212 (s), 1049

(m) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.20-1.24 (m, 6H), 1.34 (s, 3H), 1.45 (s, 3H), 3.45 (s, 2H), 4.08-4.21 (m, 5 H), 4.30 (s, 2H), 4.52 (s, 1H), 5.06 (s, 2H), 5.73-5.81 (m, 2H), 7.24-7.33 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 13.9, 14.0, 26.2, 27.7, 34.6, 51.2, 52.6, 61.7,61.9, 67.0, 70.6, 74.2, 77.2, 109.7, 127.3, 128.2, 128.3, 128.5 136.0, 155.8, 167.8, 168.4. LRMS (FAB) *m/z* 462 (10), 404 (50), 91 (100); HRMS (FAB) calcd for $C_{24}H_{31}NO_8$ 462.2128, found 462.2131.



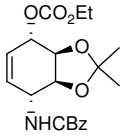
94

To 2.60 g (17.1 mmol) of diene **85** was added 193 ml of $CHCl_3$, 150 ml DMF, and 10.4 g (24 mmol) of tetrabutylammonium periodate. Using a solid addition funnel 3.2 g (24.0 mmol) of hydroxamic acid **93** was added portionwise over 2 hours. The light yellow and heterogeneous solution was stirred under argon for 48 hours at which time the reaction mixture had turned dark yellow in color. The reaction was diluted with CH_2Cl_2 and washed with H_2O (3 x 150 ml). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo to afford a dark brown oil. Purification by column chromatography (20% EtOAc/Hexanes, R_f 0.21) afforded 2.54 g (94%) of the Diels Alder adduct **94** as a light yellow solid. IR (CCl_4) 3607 (m), 3087(w), 3067(m), 3029(m), 2932(m), 2873(m), 2361(w), 2330 (w), 1775 (s), 1708 (s), 1499 (m), 1456 (s), 1382 (m), 1328 (m), 1242 (s), 1207 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.28 (s, 3H), 2.29 (s, 3H), 4.48-4.55 (m, 2H), 4.89 (m, 1H), 5.05-5.06 (m, 1H), 5.10-5.21 (ABX system, J = 12 Hz, 2H), 6.39-6.43 (m, 2H), 7.30-7.36 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 25.4, 25.6, 53.0, 68.2, 71.3, 72.5,73.1,111.0,128.1, 128.4,128.5, 129.5,130.5,135.5,157.8. LRMS (FAB) *m/z* 635 (2M + H, 12), 318 (100), 274 (30), 216 (20), 152 (20), 91 (90), 85 (35); HRMS (FAB) calcd for $C_{17}H_{19}NO_4$ $(M + H)^+$ 318.1336, found 318.1341.



95

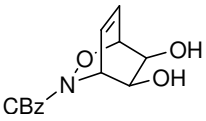
To 3.31 g (15.46 mmol) of the Diels-Alder adduct **94** dissolved in 260 mL of CH_3CN and 12 mL H_2O was added 816 mg (3.09mmol) of $Mo(CO)_6$ and 1.20 g (30.9 mmol) $NaBH_4$ portionwise. The reaction mixture was heated at reflux under an atmosphere of argon for 12 hours. Upon cooling, the mixture was filtered through a plug of SiO_2 and concentrated to a dark brown oil. Purification by column chromatography (20% EtOAc/Hexanes, R_f 0.14) afforded 4.50 g (91%) of the allylic alcohol **95** as a colorless oil. IR (neat) 3463 (br m), 3300 (br, m,) 3043 (w), 2985 (w), 2903 (w), 1678 (s), 1544 (m), 1269 (m) cm^{-1}. ^1H NMR (CH_3OD) δ 1.33 (s, 3H), 1.43 (s, 3H), 2.03 (br s, 1H), 4.12-4.15 (m, 1H), 4.21-4.24 (m, 3H), 5.06-5.14 (m, 2H), 5.24 (br s, 1H), 5.80-5.82 (d, *J* = 9 Hz, 1H), 5.91-5.94 (d, *J* = 9 Hz, 1H), 7.30-7.38 (m, 5H). ^{13}C NMR (CH_3OD) δ 25.6, 28.0, 53.6, 68.0, 71.6, 78.5, 81.6, 110.7, 129.3, 129.5, 129.9, 130.9, 133.4, 138.7, 158.9. LRMS (FAB) *m/z* 320 (M +, 35), 302 (30), 262 (15), 135 (20), 91 (100), 85 (25).



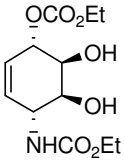
96

To 1.16 g (3.60 mmol) of the allylic alcohol **95** in 10 ml CH_2Cl_2 was added 40.0 ml of anhydrous pyridine and 590 mg (520 µl, 5.45 mmol) of anhydrous ethylchloroformate which caused the evolution of a yellow gas from the reaction solution upon the addition. The yellow solution was stirred for 48 hours and was then diluted with 150 ml CH_2Cl_2 and washed with saturated NaCl (1 x 150 ml) and extracted with CH_2Cl_2 (3 x 100 ml). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to afford the carbonate **96** as a white solid. Purification by column chromatography (20% EtOAc/hexanes, R_f 0.28) afforded 1.14 g (81%) of the product as a white solid. IR (CCl_4) 3370 (br m), 2979 (w), 2932 (w), 2366 (w), 2331 (w), 1748 (s), 1701 (s), 1514 (m), 1456 (w), 1374 (w), 1246 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.28-1.32 (m, 6H), 1.44 (s, 3H), 4.20-4.23 (m, 4H),

4.40 (s, 1H), 5.10-5.11 (m, 4H), 5.89 (m, 2H), 7.34-7.35 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 14.1, 24.8, 26.9, 29.7, 50.3, 64.4, 67.0, 73.8, 75.8, 76.1, 109.3, 127.2, 128.2, 128.5, 131.2, 136.2, 154.3, 155.8. LRMS (FAB) *m/z* 392 (M +, 23), 302 (90), 258 (18), 154 (21), 110 (25), 91 (100). HRMS (FAB) calcd for $C_{20}H_{25}NO_7$ $(M + H)^+$ 392.1729, found 392.1709.

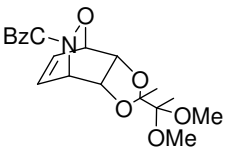


The Diels-Alder adduct **94** 2.54 g (9.16 mmol) was dissolved in 50 ml THF. To the reaction solution was added 50 ml of 1N HCl. The white reaction mixture was then heated at reflux for 12 hours. The THF was removed in vacuo and the remaining solution was diluted with CH_2Cl_2 and extracted with 150 ml CH_2Cl_2 (3x). Purification by column chromatography (50% EtOAc/Hexanes, R_f 0.14) afforded 1.8 g (77%) of the desired diol as a colorless oil. IR (neat) 3500-3000 (br s), 2925 (w), 1810 (w), 1699 (s), 1389 (w), 1246 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.49 (m, 1H), 2.67 (m, 1H), 4.28 (s, 2H), 4.77 (m, 1H), 4.92 (m, 1H), 5.20 – 5.10 (ABX system, *J* = 12 Hz, 2H), 6.54-6.50 (m, 1H), 6.56-6.59 (m, 1H), 7.28-7.36 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 54.4, 65.0, 65.7, 68.3, 72.3, 128.1, 128.4, 128.6, 130.5, 131.7, 135.4, 157.8. LRMS (EI) *m/z* 277 (8), 111 (12), 91 (100), 65 (18).



The acetonide **83** 2.50 g (7.50 mmol) was dissolved in 120 ml THF and 120 ml 1M HCl. The reaction was stirred at room temperature overnight. The THF was removed in vacuo and the remaining solution was diluted with CH_2Cl_2 and extracted with 150 ml CH_2Cl_2 (3x). The organic layers were dried over MgSO4, filtered and concentrated to afford 1.17 g (54%) of a white crystalline solid (mp 113-115 °C) that was used without further purification. IR (CCl_4) 3448 (m),

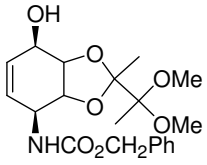
3409 (m), 2978 (w), 2935 (w), 2376 (w), 2330 (w), 1747 (s), 1693 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.24 (t, *J* = 7 Hz, 3H), 1.30 (t, *J* = 7 Hz, 3H), 3.24 (s, 1H), 3.85 (m, 2H), 4.00 (s, 1H), 4.12 (q, *J* = 7 Hz, 2H), 4.20 (q, *J* = 7 Hz, 2H), 4.36 (br s, 1H), 4.83 (m, 1H), 5.18 (m, 1H), 5.73 (m, 1H), 5.83 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 17.5, 17.9, 55.8, 64.8, 68.1, 73.9, 75.4, 79.4, 129.5, 134.5, 159.3, 161.8. LRMS (FAB) *m/z* 290 (27), 200 (100), 152 (15), 111 (15), 90 (12). HRMS (FAB) calcd for $C_{12}H_{19}NO_7$ $(M + H)^+$ 290.1240, found 290.1237.



116

To 300 mg (1.08 mmol) of diol **115** in 4 ml of methanol was added 27.6 mg (0.119 mmol) of camphor sulfonic acid, 233 mg (237 µl, 2.71 mmol) of butanediol, and 916 mg (945 µl, 8.64 mmol) of timethylorthoformate. The yellow reaction solution was refluxed under an atmosphere of argon for 48 hours; during the course of the reaction a color change from light yellow to red was noted. Upon cooling, the reaction was quenched by the addition of 3 ml of Et_3N. The reaction mixture was diluted with water and extracted into EtOAc (3 x 50 ml). The combined organic layers were dried over MgSO4, filtered, and concentrated to afford a brown oil. Purification by column chromatography (35% EtOAc/Hexanes, R_f 0.25) afforded 470 mg (56%) of the desired product as a yellow oil. **^1H** NMR ($CDCl_3$) δ 1.24, (s, 3H), 1.34 (s, 3H), 3.27 (s, 6H), 4.47– 4.56 (m, 2H), 4.94 (m, 1H), 5.10-5.21 (m, 3H), 6.37-6.41 (m, 2H), 7.30-7.34 (m, 5). ^{13}C NMR ($CDCl_3$) δ 1.41, 16.3, 18.6, 51.3, 53.3, 68.7, 71.5, 72.1, 72.6, 77.1, 102.5, 113.5, 128.5, 128.8, 129.0, 129.9, 131.1, 135.9, 158.2. IR (CCl_4) 3064 (w), 3033 (w), 2994 (m), 2944 (m), 2831 (w), 2365 (w), 2342 (w), 1755 (s), 1717 (s), 1456 (m), 1398 (m), 1371 (m), 1243 (s) cm^{-1}. (EI) *m/z* 391 (5), 302 (7), 116 (8), 91

(100) 89 (72), 43 (7). HRMS (EI) calcd for $C_{20}H_{25}NO_7$ $(M + H)^+$ 391.1631, found 391.1631.



To 40 mg (0.102 mmol) of **116** in 4 ml of acetonitrile and 200 µl of deionized water was added 7.70 mg of $NaBH_4$ and 5.50 mg of $Mo(CO)_6$. The reaction was heated at reflux for 24 hours. Upon cooling the crude reaction mixture was diluted with EtOAc (20 ml), filtered through a pad of celite, and the solvent removed in vacuo. Purification by column chromatography (35% EtOAc/Hexanes, R_f 0.5) afforded 25 mg (62%) of a white solid. Recrystallization from EtOAc/Hexanes afforded colorless cubic crystals (m.p. = 117-118 °C) suitable for x-ray crystallographic analysis. ^{1}H NMR ($CDCl_3$) δ 1.34-1.40 (m, 6H),, 3.60 (br s, 1H), 3.29 (s, 6H), 4.24 (s, 2H), 4.29 –4.32 (m, 1H), 4.41 (br s, 1H), 5.10 (s, 2H), 5.20 (s, 1H), 5.72 –5.75 (dt, *J* = 10 Hz, *J*=2 Hz, 1H), 5.87 –5.89 (d, *J* = 10 Hz, 1H), 7.31 – 7.35 (m, 5H). IR (CCl_4) 3619 (m), 3441 (m), 3029 (w), 2990 (m), 2944 (m), 2835 (m), 1736 (s), 1507 (s), 1450 (m), 1371 (m), 1243 (m), 1216 (m), 1130 (m), 1107 (w) cm^{-1}.

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