Synthetic Applications of a Novel Pericyclic Imino Ene Reaction of Allenyl Silanes

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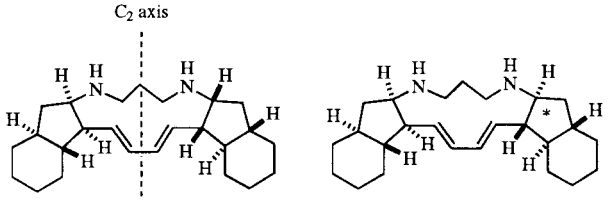
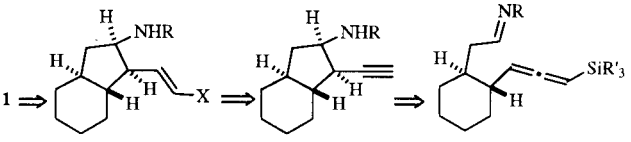
The impetus for the work described here was the appearance in 1988 of two publications reporting a pair of interesting, structurally unique marine natural products. Scheuer and coworkers first isolated (-)-papuamine (**1**) from a red encrusting sponge (*Haliclona sp*) collected in the waters near Papua New Guinea [1]. The structure of this unusual marine alkaloid, which was established by a series of NMR experiments, incorporates two identical *trans*-fused perhydroindane moieties connected by a 13-membered macrocyclic ring containing a conjugated *E,E*-1,3-diene and two basic nitrogens. The molecule exhibits a C_2 axis of symmetry as shown. A closely related alkaloid, haliclonadiamine (**2**), was subsequently found as a metabolite in a similar sponge collected near Palau by Faulkner and coworkers [2]. Haliclonadiamine, whose constitution was determined by X-ray crystallography, is identical to papuamine except for the configuration at one of the eight chiral centers (*) present in these molecules. The original structure work on these alkaloids did not establish their absolute configurations, however. Both of these compounds were found to have significant antimicrobial activity, and papuamine has antifungal properties as well.



1 (papuamine) **2** (haliclonadiamine)

Shortly after the structures of **1** and **2** first appeared, we became interested in developing a synthetic route to these fascinating natural products and decided to initially tackle papuamine (**1**), since its C_2 symmetry simplifies the strategy relative to its congener, haliclonadiamine (**2**). Our originally conceived route to papuamine (Scheme 1) was based upon a homocoupling of an enantiomerically pure vinyl-substituted perhydroindane derivative **3** either by first generating the *E,E*-1,3-diene, or by initial introduction of a three carbon bridge between nitrogens [3]. It should be noted that shortly after we completed our total synthesis of **1**, Barrett *et al.* described a synthesis of the unnatural (+)-enantiomer of the alkaloid using a conceptually similar homocoupling strategy [4]. In our case, it was anticipated that an intermediate **3** could be made from a terminal alkyne **4**. Our hope was that a system such as **4** could be prepared by cyclization of an allenyl silane imine **5**. This proposed transformation was based upon extensive work by Danheiser and coworkers on intermolecular additions of allenyl silanes to various types of electrophiles [5].

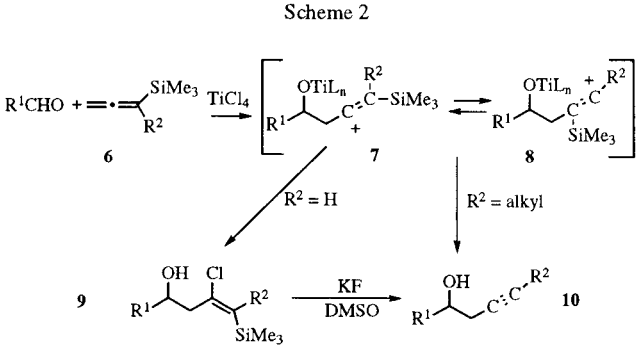
Scheme 1



3 **4** **5**

In particular, Danheiser found that reaction of an allenyl silane **6** with an aldehyde in the presence of titanium tetrachloride leads to a silyl-stabilized vinyl cation **7**, which can rearrange to isomer **8**. If R^2 = H, cation **7** will usually provide a ß-chloro vinyl silane **9**, but if R^2 = alkyl, an internal hydroxy alkyne **10** is produced. Treatment of ß-chloro vinyl silane **9** with fluoride ion induces formation of the homopropargyl alcohol **10** [5b].

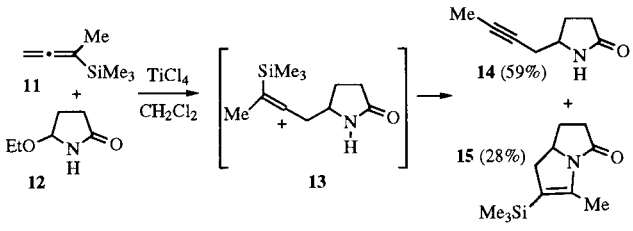
Scheme 2



6 **7** **8** **9** **10**

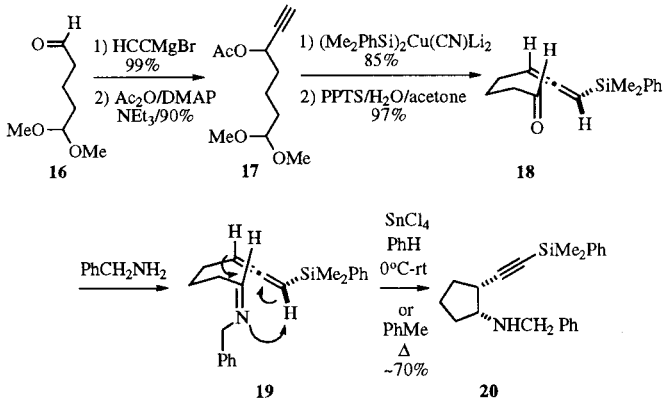
A closely related reaction involving an imino electrophile was also reported [5c]. Thus, allenyl silane **11** reacts with the *N*-acyl iminium species derived from ethoxy lactam **12** to afford an intermediate cation **13** (Scheme 3), which can lose the silyl group to give alkyne **14** as the major reaction product. Rearrangement of cation **13** (*cf.* **7** to **8**) leads to bicyclic pyrrolidinone **15** as a minor product.

Scheme 3



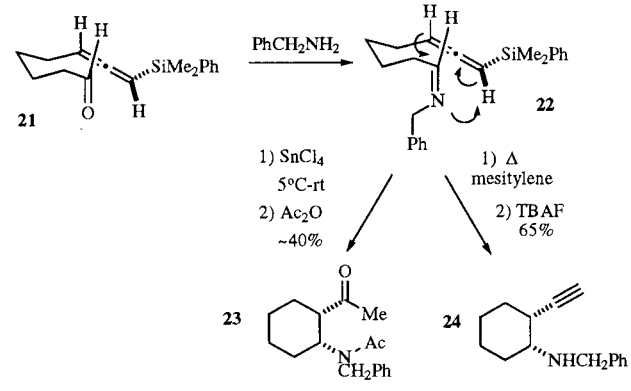
Based upon these precedents, we were optimistic that an allenyl silane imine **5** could be cyclized to a perhydroindane **4**, although curiously there were no examples in the literature of any intramolecular versions of Danheiser reactions. It should also be noted that we could only speculate at this point as to whether this key cyclization would be stereoselective, and if so, whether the requisite papuamine stereoisomer **4** would be produced. These basic questions have been probed in some simple model systems.

Scheme 4



A route to a model substrate commenced with the known aldehyde acetal **16** [7], which was converted to propargyl acetate **17** in high yield (Scheme 4). Using silyl cuprate methodology developed by Fleming and Terrett [8], it was possible to produce an allenyl silane *via* an $S_N^{2'}$ displacement process. Subsequent acetal cleavage afforded allenyl silane aldehyde **18** which could be converted to the corresponding imine **19** with benzylamine. Although exposure of the imine to $TiCl_4$ under Danheiser conditions [5] led to a complex mixture of products, we were pleased to find that use of stannic chloride in benzene at room temperature led to a single stereoisomeric cyclization product characterized as the *cis*-amino silyl acetylene **20** (70% yield). The high degree of stereoselectivity of this process, along with the fact that the product is a silyl acetylene, and not a ß-chloro vinyl silane or a terminal alkyne (*cf.* Schemes 2 and 3), suggested that in fact this transformation proceeds *via* a concerted, pericyclic imino ene reaction rather than by a stepwise, ionic mechanism of the Danheiser type. We believe this cycloaddition occurs *via* the conformation shown in **19**, which is nicely aligned stereoelectronically for a concerted ene reaction. Support for this supposition was provided by the fact that simply refluxing imine **19** in toluene for 16 hours provided cyclization product **20** in about the same yield. It should be mentioned that imino ene reactions are still quite rare [9], and this case is apparently the first example of a thermal process involving a simple unactivated imine.

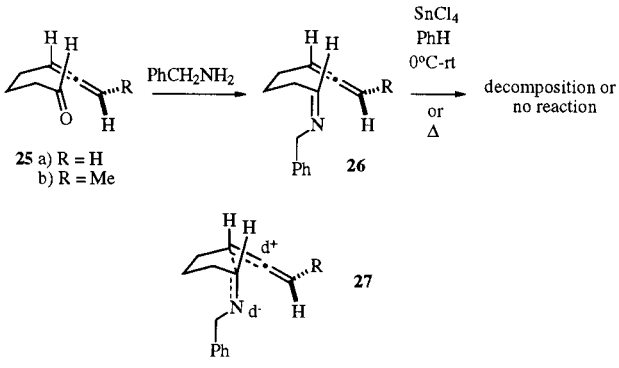
Scheme 5



This imino ene reaction can also be used to construct six-membered rings. Therefore, the homologated allenyl silane aldehyde **21**, prepared by a route similar to the one used to synthesize **18**, was converted to *N*-benzyl imine **22** (Scheme 5). Attempted Lewis acid catalyzed ene reaction of **22** led to the *cis*-amino ketone, isolated as its *N*-acetyl derivative **23**. We believe that the desired silyl acetylene is initially formed, but in this case is prone to hydration on aqueous workup and chromatography. However, simply heating imine **22** in mesitylene, followed by removal of the silyl group, provides *cis*-homopropargyl amine **24**. Once again, we believe this cyclization occurs *via* a chair-like conformation **22** which is well set up for a concerted imino ene reaction.

One fundamental question concerning this intramolecular ene chemistry which arose was whether the silyl group on the allene is, in fact, required. To probe this key point, allenyl aldehydes **25a/b** lacking the silyl functionality were prepared (Scheme 6). The aldehydes could be converted to *N*-benzyl imines **26**, but upon exposure to $SnCl_4$ or upon heating only decomposition products and/or starting materials were observed. A possible rationale for these results is that there is dipolar character in the imino ene transition state (*cf.* **27**) with

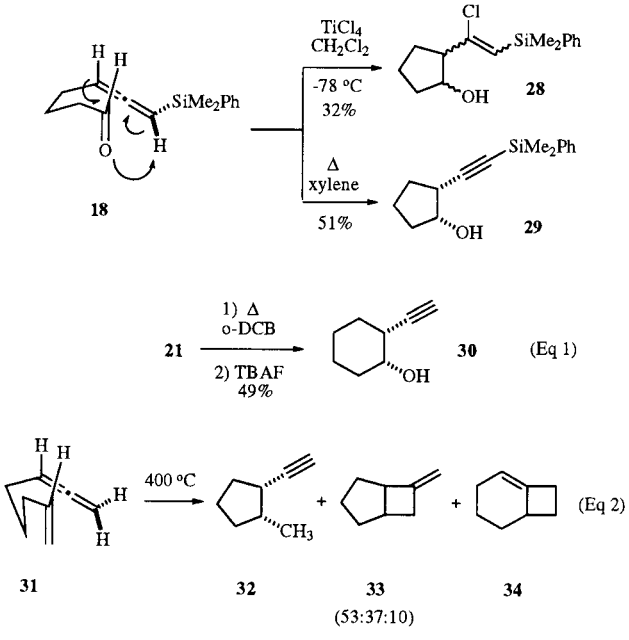
Scheme 6



partial positive charge at the central carbon of the allene. The silyl group stabilizes this charge more effectively than does a hydrogen or a methyl group, thus facilitating the cycloaddition [10].

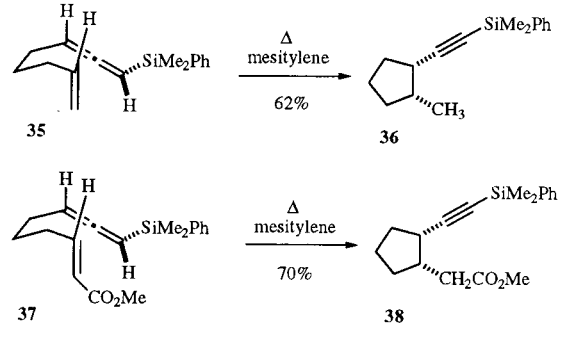
Some further model experiments were conducted to explore the scope and potential utility of allenyl silane ene reactions. It was found that if allenyl silane aldehyde **18** is exposed to $TiCl_4$, a low yield of a Danheiser-type ß-chloro vinyl silane **28** is formed as a mixture of isomers in poor yield (Scheme 7). However, upon refluxing **18** in xylene, a moderate yield of the *cis*-hydroxy silyl acetylene **29** is produced. This latter transformation is believed to occur *via* a pericyclic aldehyde ene reaction [11] through the conformation shown. Similarly, the homologated allenyl silane aldehyde **21** afforded a complex product mixture with $TiCl_4$, but upon heating, followed by desilylation, the *cis*-hydroxy acetylene **30** is formed stereoselectively (Eq. 1).

Scheme 7



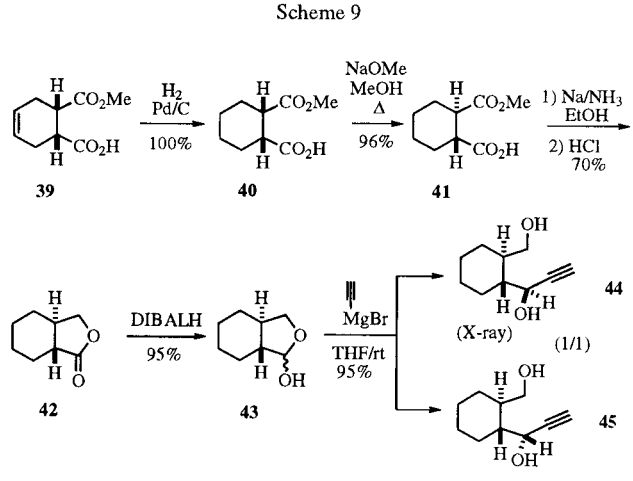
The possibility of using allenyl silanes in "all carbon" intramolecular ene reactions was also briefly explored [12]. It has previously been reported that thermolysis of ene allene **31** in a flow system at 400° C affords a mixture of ene product **32**, along with [2+2]-cycloadducts **33** and **34**, in unspecified yields (Eq. 2) [13]. We have found that simply refluxing the silyl analogue **35** in mesitylene for 15 hours produces the *cis*-disubstituted silyl alkyne **36** (Scheme 8). Similarly, heating the α,ß-unsaturated ester **37** stereoselectively yields *cis*-ene product **38**. Thus, it is clear that the silyl group has a profound affect on the course of these ene reactions.

Scheme 8



The route to the requisite papuamine substrate commenced with the enantiomerically pure acid ester **39**, which is readily prepared by PLE-mediated partial hydrolysis of the corresponding *meso*-dimethyl ester [14] (Scheme 9). Catalytic hydrogenation of the double bond in **39** yielded cyclohexane acid ester **40**, which could be epimerized at the ester group by refluxing in methanolic sodium methoxide for 5 days affording *trans* compound **41**.

Scheme 9

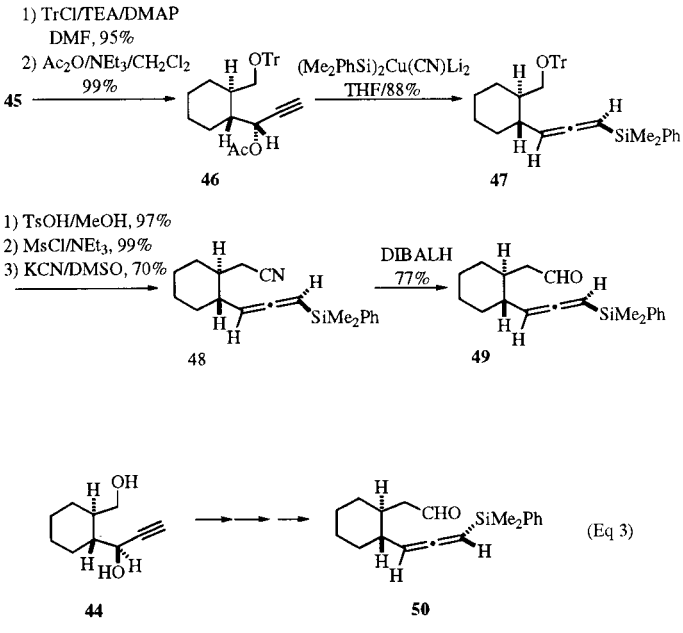


At this point in the synthesis, a decision had to be made as to which enantiomer of papuamine would be synthesized. Since the absolute configuration of the natural product was not known at this time, we arbitrarily decided to prepare the antipode shown in structure **1**. We therefore reduced the ester moiety of **41** under Bouveault-Blanc conditions [15] to produce the lactone **42** [16]. Partial reduction of this lactone yielded lactol **43**, which upon treatment with ethynylmagnesium bromide gave a chromatographically separable 1/1 mixture of propargyl alcohols **44** and **45**. At this stage, we were anticipating that both isomers **44** and **45** would prove equally useful in the projected Danheiser cyclization (*cf.* Scheme 1) since the model studies outlined above had not yet been completed. However, this did not prove to be the case (*vide infra*), and in order to fully understand the eventual results, the stereochemistry of these isomers had to be proven, which was done by X-ray crystallography of diol **44** [17].

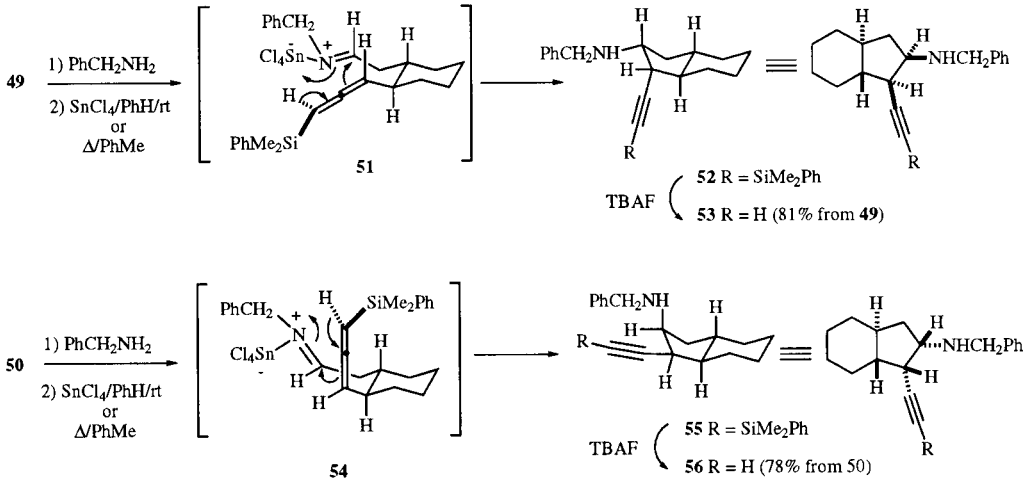
The propargyl alcohol isomers **44** and **45** were individually processed through a series of high yielding steps to generate the key cyclization substrates (Scheme 10). Thus, diol **45** was converted to trityl ether propargyl acetate **46**, which could be stereospecifically converted to allenyl silane **47** again using the silyl cuprate methodology of Fleming and Terrett [8]. This compound was then homologated by one carbon *via* nitrile **48**, and subsequently converted to the desired allenyl silane aldehyde **49**. In a similar manner, epimeric propargyl alcohol **44** was transformed to diastereomeric allenyl silane aldehyde **50** (Eq. 3).

Cyclization substrate **49** was next converted to the *N*-benzyl imine, which upon exposure to stannic chloride afforded a single stereoisomeric amino silyl alkyne **52** in good yield (Scheme 11). The structure and stereochemistry of this compound was confirmed by desilylation to amino acetylene **53** and X-ray analysis of its HCl salt [17]. Similarly, diastereomeric allenyl silane aldehyde **50** was converted to its *N*-benzyl imine, which on treatment with $SnCl_4$ was stereospecifically transformed to bicyclic silyl acetylene **55**. Once again, the configuration of this cyclization product was proven by X-ray analysis [17] of the hydrochloride of the desilylated amino alkyne **56**. As can be seen, perhydroindane **53** has the requisite stereochemistry for papuamine (*cf.* **4**, Scheme 1), whereas **56** is a stereoisomer not useful for synthesis of either alkaloid. It was also found that heating the *N*-benzyl imines derived from **49** and **50** in refluxing

Scheme 10



Scheme 11

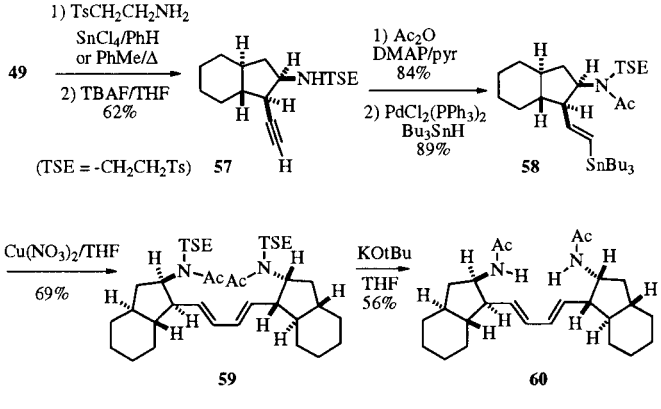


toluene also stereospecifically produced **52** and **55**, respectively, although in somewhat lower yields (~70%).

It seems quite reasonable that these transformations once again involve concerted, pericyclic imino ene cyclizations. In the case of the imine from aldehyde **49**, the imino ene reaction, if concerted, for stereoelectronic reasons must occur *via* the conformation shown in **51**, which leads to product **52**. Likewise, the imine form diastereomeric substrate **50** undergoes ene cyclization through conformation **54**, providing silyl acetylene isomer **55**.

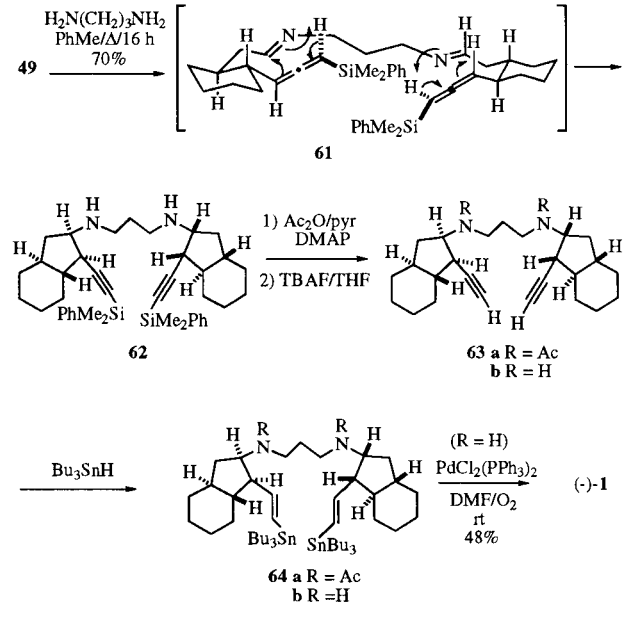
We next turned to developing methodology for the planned homocoupling of a perhydroindane unit such as **53** (*cf.* Scheme 1). However, there were some concerns here that removal of the *N*-benzyl protecting group in the presence of an alkyne or a 1,3-diene could be problematic. We, therefore, decided to investigate use of a benzylamine substitute, ß-tosylethylamine, which we recently developed [18]. Treatment of allenyl silane aldehyde isomer **49** with ß-tosylethylamine gave an imine, which upon either treatment with $SnCl_4$ or heating afforded a single imino ene cyclization product isolated as the desilylated compound **57** (Scheme 12). Yields of product were about the same for both the Lewis acid and thermal reactions. Amine **57** could be *N*-acetylated and the terminal alkyne was converted to the *E*-vinyl stannane **58** [19] in good yields. This intermediate could be successfully homocoupled by the procedure of Kyler and coworkers [20] to afford the *E,E*-1,3-diene **59**. The ß-tosylethyl group was then removed by ß-elimination using potassium *t*-butoxide [18] yielding *bis*-acetamide **60**. Unfortunately, all attempts to introduce a three carbon unit between the nitrogens of **60** failed [21]. It might also be noted that the *bis*-triflamide corresponding to *bis*-amide **60** was prepared by a similar route, but once again all attempts at annulation of this compound were unsuccessful [21].

Scheme 12



While the above experiments were in progress, an alternative convergent strategy was being simultaneously investigated which ultimately proved successful in synthesis of papuamine. It was discovered that if allenyl silane aldehyde **49** is treated with 0.5 equivalents of 1,3-diaminopropane, followed by heating in refluxing toluene, a single tetracyclic *bis*-silyl acetylene **62** is produced in good yield (Scheme 13). The most likely scenario for the formation of **62** involves an intermediate *bis*-imine **61** which undergoes two stereospecific imino ene reactions through the conformation shown. Compound **62** has all eight of the chiral centers of papuamine and all that remained for completion of the synthesis was an intramolecular C-C bond coupling to form the *E,E*-1,3 diene and 13-membered ring of the alkaloid. Since we were initally concerned about the compatibility of the basic nitrogens in **62** with the projected coupling conditions, we chose to protect the amino groups at this stage. These amines appeared to be rather hindered, although it was possible to produce the *bis*-acetamide, which was desilylated to *bis*-alkyne **63a** (87% for the two steps). The terminal alkynes could then be converted to the *bis-E*-vinyl stannane **64a** [19] in 62% yield. However, all attempts to intramolecularly couple this system to the desired 1,3-diene failed [21]. We speculate that one problem here may be that due to unfavorable amide rotamers, the conformation required for cyclization may not be readily attainable.

Scheme 13

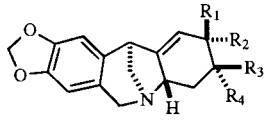


The solution to this problem proved simply to leave the amino groups unprotected. Thus, cycloadduct **62** was desilylated to *bis*-alkyne **63b** (74%), and then transformed to *bis-E*-vinyl stannane **64b** (80%) using free radical methodology [22]. After some experimentation [21], it

was discovered that intramolecular coupling of the *bis*-vinyl stannane could be effected in dilute solution with a catalytic amount of $PdCl_2(PPh_3)_2$ in the presence of oxygen [23].

Some unexpected difficulties arose, however, in purification of the alkaloid. It was found that upon preparative tlc of the crude alkaloid eluting with a mixture of CH_2Cl_2/MeOH/NH_4OH, material was isolated which had the solubility properties of an amine salt, and which had NMR spectra very similar to that of papuamine dihydrochloride [24], despite the fact that the sample was never exposed to strong acid. We believe that this may in fact be a carbonate salt arising from absorption by the amine during chromatography of atmospheric CO_2, although we have not yet been able to prove this supposition due to lack of sufficient material. However, ion exchange chromatography of this salt afforded the free base which was identical to natural (-)-papuamine (**1**) ($[\alpha]_D^{26}$ = -140° (*c* = 0.02, CH_3OH); lit $[\alpha]_D$ = -150° (*c* = 1.5, CH_3OH)) [1,24]. Thus, we have developed a total synthesis of (-)-papuamine (**1**) in 16 steps from readily available scalemic acid ester **39** *via* this novel imino ene chemistry. The synthesis also confirms the absolute configuration of the alkaloid.

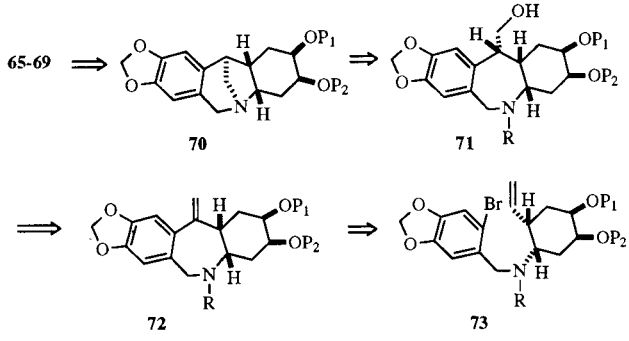
Recently, we have turned to another application of intramolecular allenyl silane imino ene chemistry in the area of alkaloid synthesis. The methanomorphanthridine subgroup of *Amaryllidaceae* alkaloids, represented by **65-69**, has been known for about 40 years [25]. However, until lately these structurally interesting compounds have received little attention from synthetic chemists despite the considerable activity in synthesis of other *Amaryllidaceae* alkaloids. Two nice synthetic approaches to these natural products have appeared. In 1991, Hoshino and coworkers [26] first described total synthesis of racemic montanine (**65**), coccinine (**66**), pancracine (**67**) and brunsvigine (**68**). Shortly thereafter, Overman and Shim reported total synthesis of both racemic and (-)-pancracine (**67**) [27].



65 (montanine)	R_1 = H, R_2 = OMe, R_3 = OH, R_4 = H
66 (coccinine)	R_1 = OMe, R_2 = H, R_3 = OH, R_4 = H
67 (pancracine)	R_1 = H, R_2 = OH, R_3 = OH, R_4 = H
68 (brunsvigine)	R_1 = H, R_2 = OH, R_3 = H, R_4 = OH
69 (manthine)	R_1 = H, R_2 = OMe, R_3 = OMe, R_4 = H

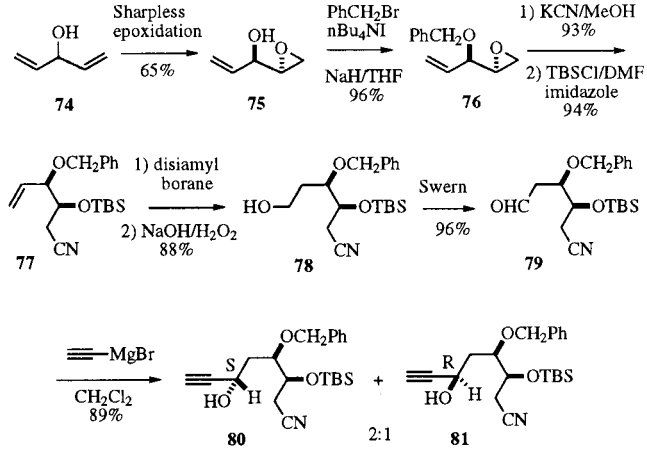
We are currently engaged in an enantioselective approach to these methanomorphanthridine alkaloids using the basic strategy outlined in Scheme 14. A pivotal intermediate is to be pentacycle **70**, which is closely related to a compound which Hoshino *et al.* have converted to several of the alkaloids [26]. We anticipated preparing **70** from hydroxymethyl compound **71** *via* a transannular cyclization, again precedented in the Hoshino work [26]. Intermediate **71** was to be generated by hydroboration from the least hindered face of exocyclic olefin **72**, which in turn was to be synthesized by Heck cyclization of bromo alkene **73**. The intent was to construct **73** utilizing intramolecular allenyl silane imino ene chemistry (*vide infra*).

Scheme 14

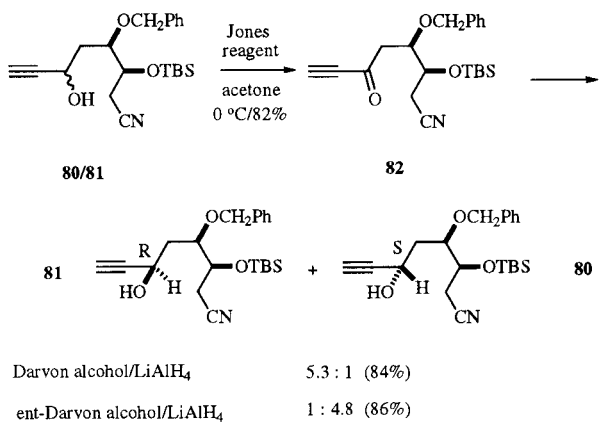


Our synthesis began with the optically pure epoxy alcohol **75**, which is available in large quantity from Sharpless epoxidation of divinyl carbinol (**74**) [28] (Scheme 15). The alcohol functionality of **75** was protected as its benzyl ether **76**. The epoxide could be opened regioselectively with cyanide [29], followed by silylation of the resulting alcohol, to produce intermediate **77**. Hydroboration [30] of **77** led to primary alcohol **78** which could be cleanly oxidized to yield aldehyde **79**. Addition of ethynylmagnesium bromide to **79** was not very selective, affording a chromatographically separable 2/1 mixture of *S*- and *R*-propargyl alcohols **80** and **81**, respectively.

Scheme 15



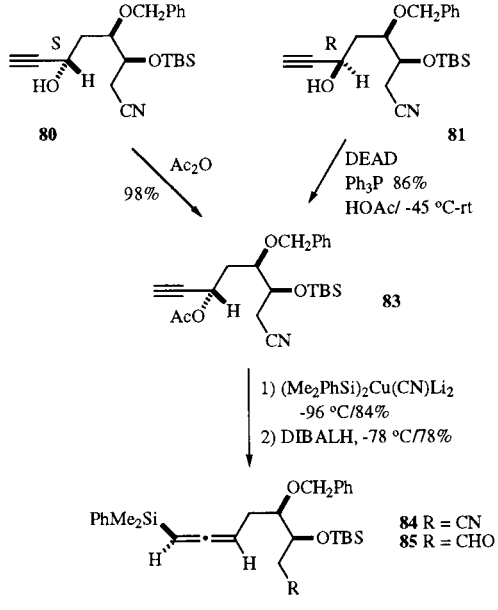
Scheme 16



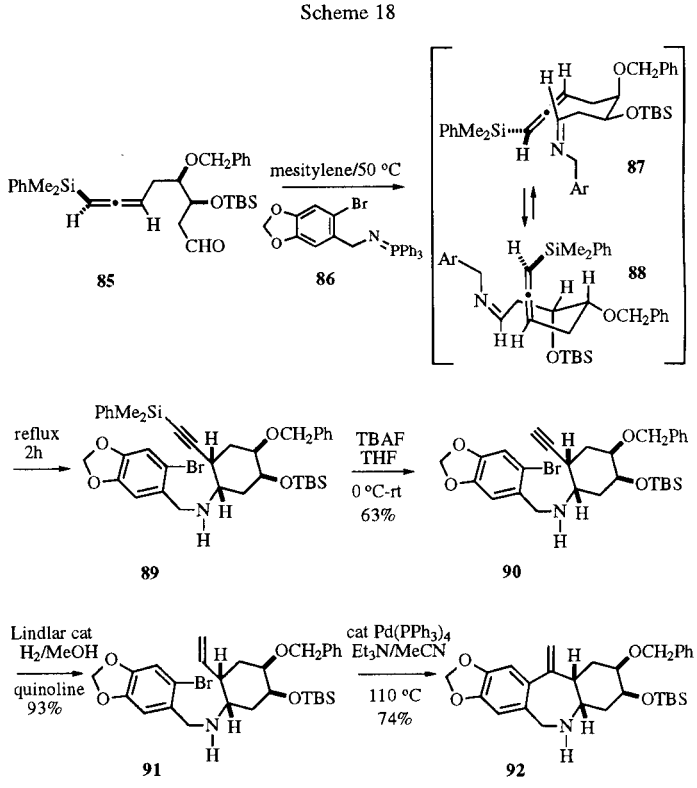
In order to establish the configuration of alcohols **80** and **81**, as well as to try to improve the selectivity in synthesis of these key intermediates, we investigated the reactions shown in Scheme 16. Using Jones reagent, propargyl alcohols **80/81** could be converted to acetylenic ketone **82**. Enantioselective reduction of **82** using $LiAlH_4$/Darvon alcohol complex [31] provided a 5.3/1 mixture of **81** and **80**. The configuration of the major isomer **81** has been tentatively assigned as *R* based upon the known propensity of Darvon alcohol to generate this configuration in $LiAlH_4$ reductions of alkynyl ketones [31]. Similarly, reduction of ketone **82** with $LiAlH_4$/ent-Darvon alcohol provided a 1/4.8 mixture of the alcohols **81/80**. Although the selectivity here is somewhat better than in the direct preparation of these propargyl alcohols from aldehyde **79**, the two extra steps involved do not make this sequence an attractive alternative, particularly since it was found that both **80** and **81** can be used for the synthesis (*vide infra*).

Thus, *S*-propargyl alcohol **80** can be acetylated to ester **83** (Scheme 17). The *R*-alcohol **81** can also be converted to *S*-acetate **83** by a Mitsunobu inversion procedure [32]. *S*-Propargyl acetate **83** is, in fact, the one required to prepare the correct allene diastereomer for the pivotal imino ene reaction (*vide infra*). Application of the silyl cuprate methodology [8] to **83** afforded allenyl silane **84** stereospecifically. Reduction of the cyano group then led to the requisite aldehyde allenyl silane cyclization substrate **85**.

Scheme 17



Scheme 18



Aldehyde **85** could be converted to the corresponding imine on condensation with imino phosphorane **86** [33], which was prepared by reaction of the corresponding benzyl azide with triphenylphosphine [34] (Scheme 18). We were gratified to find that refluxing this imine in mesitylene for 2 hours gave a single cyclization product **89**, which was immediately desilylated to amino acetylene **90** in 63% yield for the three steps. We believe the product **89** is produced by an imino ene process involving imine conformer **87** and/or **88**. Inspection of models indicates that conformation **87** is stereoelectronically more favorably disposed for the ene reaction than is **88**. However, both conformations lead to the desired cycloadduct **89**.

Continuing the synthesis, alkyne **90** was partially hydrogenated using Lindlar catalyst to afford the terminal alkene **91**. It was then possible to effect an intramolecular Heck reaction [35] on bromo alkene **91** to generate the seven-membered ring exocyclic alkene **92** in good yield. We are currently investigating the hydroboration of olefin **92**, or an *N*-protected derivative, to produce a hydroxymethyl compound like **71** (Scheme 14) which we then hope to convert to a bridged Hoshino intermediate **70**.

In summary, we have discovered a new intramolecular imino ene reaction of allenyl silanes which is totally stereospecific in all cases studied to date. The reaction appears to be quite general, and as we have demonstrated, is useful in alkaloid total synthesis. Extensions and additional applications of the methodology are currently under investigation.

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