Total Synthesis of the Unusual Marine Alkaloid (−)-Papuamine Utilizing a Novel Imino Ene Reaction

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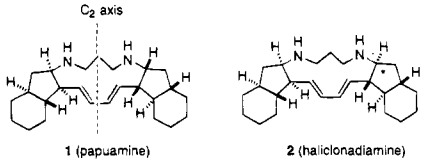
Abstract: A concise enantioselective total synthesis of the recently isolated antibacterial and antifungal marine alkaloid (−)-papuamine (**1**) is described. The key feature of the synthesis includes the development and subsequent implementation of a novel pericyclic imino ene reaction. Starting from readily available enantiomerically pure acid ester **11**, allenyl silane *N*-benzyl imines **24** and **27** were generated *in situ* from aldehydes **23a/b**. These imines undergo concerted stereospecific imino ene reactions to afford silyl acetylenes **25** and **28**, respectively, in high yields. The ene reactions were found to be promoted both thermally in refluxing toluene and at lower temperatures using the Lewis acid stannic chloride as a catalyst. Desilylation of compounds **25** and **28** afforded terminal alkynes **26** and **29**, respectively, whose structures and stereochemistry were unambiguously established by single crystal X-ray structure analysis of the corresponding HCl salts. In a more highly convergent approach to the alkaloid **1**, aldehyde allenyl silane **23a** was treated with 0.5 equiv of 1,3-diaminopropane in refluxing toluene to afford homopropargylic diamine **40** as one stereoisomer via a double imino ene reaction, which effectively established the remaining four of the eight stereogenic centers of papuamine in one simple operation. To complete the route to the natural enantiomer of papuamine, a Pd(II) catalyzed macrocyclization of bis-*E*-vinyl stannane **42b** was effected in moderate yield.

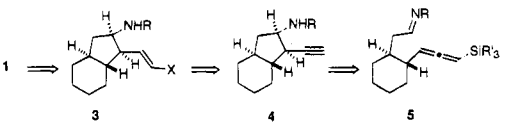
In 1988, Scheuer and co-workers isolated papuamine (**1**) as the major metabolite of a bright red encrusting sponge (*Haliclona sp*) collected near South Lion Head Island, Papua New Guinea.[1] The pentacyclic structure of this unique alkaloid, along with its relative, but not absolute stereochemistry, was established by a variety of 1- and 2-D NMR experiments. Very shortly thereafter, Faulkner, Clardy and co-workers reported the constitution of a related alkaloidal metabolite haliclonadiamine (**2**), which is produced, along with a smaller amount of papuamine, by a similar sponge from Palau.[2] Papuamine and haliclonadiamine are identical in structure except for the stereochemistry at one chiral center (*). Both alkaloids display significant inhibitory activity against the growth of *Candida albicans*, *Bacillus subtilis*, and *Staphylococcus aureus*. Papuamine also shows antifungal activity against *Trichophyton mentagrophytes*.



1 (papuamine) 2 (haliclonadiamine)

The highly unusual structures of these two marine alkaloids, coupled with their interesting biological activity, make them attractive targets for total synthesis. We decided to initially undertake an approach to papuamine since its C_2 symmetry greatly simplifies the synthetic design relative to haliclonadiamine. The strategy to be adopted, as outlined in Scheme 1, would involve a homocoupling of an enantiomerically pure perhydroindane system **3** to first generate the *E,E*-1,3-diene, followed by introduction of a three carbon unit between the nitrogens to generate the 13-membered macrocyclic ring or vice versa. Shortly before preliminary disclosure of our papuamine synthesis,[3] Barrett et al. described implementation of a similar strategy in construction of the unnatural (+)-antipode of the natural product.[4]

Scheme 1



3 4 5

It was our intent to prepare an *E*-vinyl-substituted synthon **3** from the corresponding acetylene **4** by *syn*-addition of HX across the triple bond. In order to prepare the bicyclic homopropargyl amine **4**, we considered the possibility of cyclizing an imino allenyl silane like **5**. This proposed transformation was based upon the extensive work of Danheiser et al. on intermolecular reactions of allenyl silanes with electrophiles.[5] In particular, it had been reported that allenyl silane **6** reacts under Lewis acid catalysis with the electrophilic *N*-acyl imine derived from ethoxy lactam **7** to produce an intermediate β-silyl-stabilized cation **8**, which then collapses to homopropargyl amine derivative **9**, along with cyclization product **10** (Scheme 2). We hoped that a similar process would occur with allenyl silane **5**, although

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[⊗] Abstract published in *Advance ACS Abstracts,* October 15, 1995.

(1) Baker, B. J.; Scheuer, P. J.; Shoolery, J. N. *J. Am. Chem. Soc.* **1988**, *110*, 965.

(2) Fahy, E.; Molinski, T. F.; Harper, M. K.; Sullivan, B. W.; Faulkner, D. J.; Parkany, L.; Clardy, J. *Tetrahedron Lett.* **1988**, *29*, 3427.

(3) For a preliminary account of this work, see: Borzilleri, R. M.; Weinreb, S. M.; Parvez, M. *J. Am. Chem. Soc.* **1994**, *116*, 9789.

(4) Barrett, A. G. M.; Boys, M. L.; Boehm, T. L. *J. Chem. Soc., Chem. Commun.* **1994**, 1881.

(5) (a) Danheiser, R. L.; Carini, D. J. *J. Org. Chem.* **1980**, *45*, 3925. (b) Danheiser, R. L.; Carini, D. J.; Kwasigroch, C. A. *J. Org. Chem.* **1986**, *51*, 3870. (c) Danheiser, R. L.; Kwasigroch, C. A.; Tsai, Y.-M. *J. Am. Chem. Soc.* **1985**, *107*, 7233. (d) Danheiser, R. L.; Stoner, E. J.; Koyama, H.; Yamashita, D. S.; Klade, C. A. *J. Am. Chem. Soc.* **1989**, *111*, 4407. (e) Becker, D. A.; Danheiser, R. L. *J. Am. Chem. Soc.* **1989**, *111*, 389.

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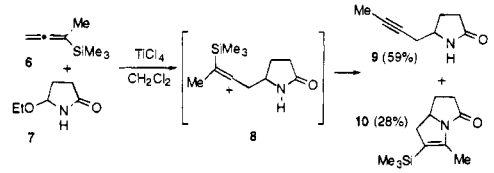
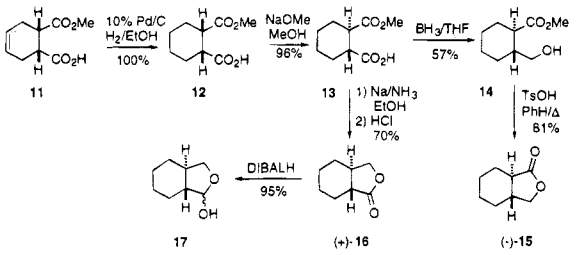
Scheme 2



Scheme 3



critical questions which required exploration were (1) could such a transformation be effected intramolecularly and (2) if so, what degree of stereoselectivity, if any, would result?

The starting material for preparation of cyclization substrate **5** was known chiral acid ester **11**, which is available in high enantiomeric excess by PLE catalyzed partial hydrolysis of the corresponding *meso* dimethyl ester (Scheme 3).[6] Hydrogenation of the double bond in **11** afforded cyclohexane derivative **12** in quantitative yield.[7] It was then found that refluxing acid ester **12** in methanol containing sodium methoxide for 5 days led to the desired *trans* system **13**.[8]

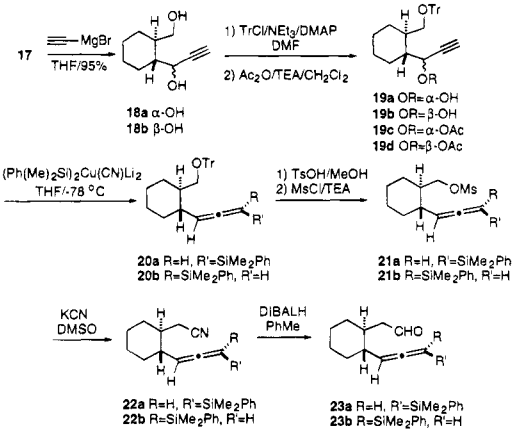
In order to assess the enantiomeric purity of intermediate **13**, the carboxylic acid moiety was reduced with diborane to the corresponding primary alcohol **14**, and the Mosher ester was prepared.[9] ^{19}F NMR analysis of the crude product indicated a 97% ee. Acid catalyzed cyclization of ester alcohol **14** then afforded the *trans*-fused (−)-lactone **15**. Alternatively, the enantiomeric (+)-lactone **16** could be prepared by Bouveault−Blanc reduction[10] of the ester functionality of **13**, followed by acid-promoted cyclization of the intermediate hydroxy acid.

At the time that the work described here was underway, the absolute configuration of natural papuamine was unknown.[1,4] We thus arbitrarily decided to synthesize the enantiomer shown in structure **1**, and for this purpose the (+)-lactone **16** was most conveniently utilized. Reduction of this lactone to lactol **17** could be effected in high yield with DIBALH.

Reaction of the lactol with ethynylmagnesium bromide cleanly afforded a chromatographically separable 1:1 mixture of epimeric propargyl alcohols **18a/18b** (Scheme 4). At this point, we expected that the configuration of these alcohol intermediates would be of no consequence in regard to the proposed Danheiser cyclization (*cf.* Scheme 1). However, as we eventually discovered (*vide infra*) the stereochemistry of these alcohols is in fact of major significance, and we therefore established the configuration of compound **18b** by X-ray crystallography.[11]

To continue the synthesis of the requisite cyclization precursor, propargyl alcohols **18a/b** were processed individually as

Scheme 4



shown in Scheme 4. Thus, **18a** and **18b** were converted to the corresponding trityl ethers **19a/19b**, which were acetylated to give esters **19c** and **19d**, respectively, in high yields. Compounds **19c** and **19d** could then be converted stereospecifically into allenyl silane isomers **20a** and **20b**, respectively, utilizing silyl cuprate chemistry developed by Fleming and Terrett.[12,13] This transformation has been shown to proceed via an *anti* S_N2' process and therefore knowing the configuration of the starting propargyl acetates allows unambiguous assignment of the absolute stereochemistry of the allenyl silane diastereomers.

The allenyl silanes **20a/b** were next detritylated, and the resulting primary alcohols were mesylated to provide **21a/b** in good yields. Homologation of the mesylates via cyanide displacement gave nitriles **22a/b**, which could be cleanly reduced with DIBALH to afford the desired allenyl silane aldehydes **23a/b**.

With these substrates in hand, we next turned to an investigation of the pivotal intramolecular Danheiser-type cyclization. Aldehyde allenyl silane **23a** could be readily converted to an imine with benzylamine in the presence of 4Å molecular sieves. When exposed to $TiCl_4$ under the conditions of Danheiser[5] this imine gave a complex mixture of products. However, if the *N*-benzyl imine was instead treated with stannic chloride in benzene at room temperature, a clean reaction occurred producing silyl acetylene **25** in 87% yield (Scheme 5). The structure and stereochemistry of this material was established by desilylation to alkyne amine **26**, followed by single crystal X-ray analysis of its hydrochloride salt. We were pleased to find that compound **26** possessed the requisite configuration for papuamine. A similar sequence of reactions was performed with allenyl silane aldehyde diastereomer **23b**. Thus, treatment of

(6) (a) Kobayashi, S.; Kamiyama, K.; Ohno, M. *Chem. Pharm. Bull.* **1990**, *38*, 350. (b) Schneider, M.; Engel, N.; Honicke, P.; Heinemann, G.; Gorisch, H. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 67.

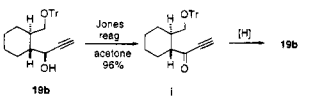
(7) In our hands, PLE mediated partial hydrolysis of *cis*-dimethyl cyclohexanedicarboxylate gave monoacid **12** of only 70−80% ee. *Cf.*: Sabbioni, G.; Jones, J. B. *J. Org. Chem.* **1987**, *52*, 4565.

(8) This transformation was initially performed: Ralbovsky, J. L. Ph.D. Thesis, The Pennsylvania State University, 1993.

(9) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

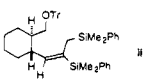
(10) *Cf.*: Paquette, L. A.; Nelson, N. A. *J. Org. Chem.* **1962**, *27*, 2272.

(11) A few attempts were later made to convert the undesired β-propargyl alcohol **19b** to the desired α-compound. Oxidation of **19b** afforded ketone **i**, but all hydride reductions led to >95% of the starting β-alcohol (*e.g.*, $NaBH_4$, L-Selectride, DIBALH, S-Alpine borane, Chirald/$LiAlH_4$). Mitsunobu inversion of **19b** to acetate **19c** was also unsuccessful.

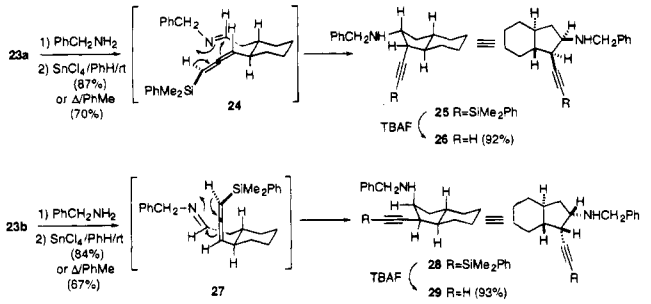


(12) Fleming, I.; Terrett, N. K. *J. Organomet. Chem.* **1984**, *264*, 99.

(13) Care must be taken not to let the reaction mixture rise above −65 °C or the major product isolated is the disilyl compound **ii** resulting from silyl cuprate over addition to the allenyl silane (see: Fleming, I.; Takaki, K.; Thomas, A. P. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2269).



Scheme 5



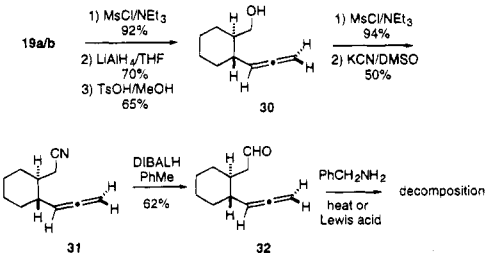
this compound with benzylamine, followed by stannic chloride, cleanly yielded isomeric silyl acetylene **28**, whose structure was again proven by X-ray analysis of the HCl salt of the desilylated product **29**.

We were very surprised by two particular aspects of these allenyl silane imine cyclizations: (1) the reaction products were silyl acetylenes, *not* terminal alkynes or chloro vinylsilanes as would be anticipated from a Danheiser reaction involving an intermediate vinyl cation (*cf.* **8**)[5] and (2) the cyclizations of **23a** and **23b** were each completely stereospecific. We believe that in fact these reactions do not occur via a stepwise, ionic process of the type described by Danheiser and co-workers[5] but are actually concerted, pericyclic imino ene reactions.[14] Support for this supposition comes from the fact that simply heating the *N*-benzyl imines from aldehydes **23a** and **23b** in refluxing toluene in the absence of a Lewis acid stereospecifically affords the cyclization products **25** and **28**, respectively.

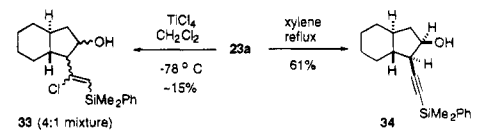
A concerted imino ene reaction of silyl allene diastereomer **23a** must occur via a conformation as shown in **24**, which is nicely aligned stereoelectronically for the process. Such a conformation leads to the stereochemistry observed in the product **25**. Similarly, diastereomeric allenyl silane imine **23b** requires a conformation **27** for such a concerted pericyclic reaction, leading to isomeric silyl alkyne **28**. Interestingly, in no case do we observe transfer of a silyl group to nitrogen, which would have the net effect of eroding the stereospecificity of the reactions. It might also be noted that reports of imino ene reactions are still relatively rare,[14] and the examples described here are the first thermal ones involving a simple unactivated *N*-alkyl imine. This type of allenyl silane-imine intramolecular ene reaction appears to be quite general, and we have executed several additional examples.[15,16]

In order to further explore some of the features of this imino ene chemistry, we decided to determine whether the silyl functionality on the allene is actually required. Therefore, an epimeric mixture of propargyl alcohols **18a/b** was converted in three steps to the simple unsubstituted allene **30** (Scheme 6). The primary alcohol functionality was next homologated via nitrile **31** to allene aldehyde **32**.[17] This aldehyde could be converted to the corresponding *N*-benzyl imine, but attempted thermal or Lewis acid catalyzed cyclizations led only to decomposition products. Thus, it seems that the silyl group is in fact necessary for the imino ene reaction to occur. One possible explanation for this result is that the ene transition state has dipolar character[18] with partial positive charge developing

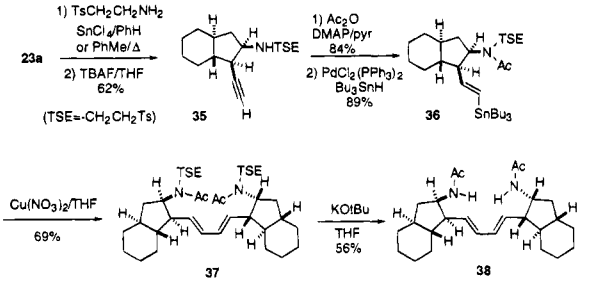
Scheme 6



Scheme 7



Scheme 8



at the central carbon of the allene. The silyl group is therefore required in order to stabilize this charge by the β-effect of silicon.[19]

One additional series of experiments to probe this novel ene reaction was conducted with allenyl silane aldehyde **23a**. Treating this compound with $TiCl_4$ under the conditions of Danheiser[5] produced a complex reaction mixture from which a small amount of a 4:1 isomeric mixture of chloro vinylsilanes **33** could be isolated (Scheme 7). This type of adduct is commonly seen in Lewis acid catalyzed intermolecular reactions of allenyl silanes with aldehydes.[5] However, upon simply heating **23a** in refluxing xylene cyclization occurred stereospecifically to afford a single homopropargyl alcohol derivative whose stereochemistry has been tentatively assigned as shown in **34**. This compound probably arises via a concerted carbonyl ene reaction via a conformation analogous to **24**. Cyclization product **34** may prove useful in construction of the "eastern" segment of haliclonadiamine (**2**).

The next stage of the synthesis entailed developing methodology for homocoupling of the perhydroindane system generated by our imino ene procedure. However, we had some concerns as to whether a *N*-benzyl protecting group, as in cyclization product **25**, would be removable in the presence of an alkyne or 1,3-diene moiety which would be extant in late intermediates. Recently, we introduced β-tosylethylamine as a benzylamine substitute,[20] and we decided to apply this reagent to the papuamine synthesis. Therefore, allenyl silane aldehyde **23a** was converted to the corresponding imine with β-tosylethylamine. This imine could be cyclized equally well with either $SnCl_4$ as catalyst or thermally in the absence of a Lewis acid to stereospecifically yield after desilylation TSE-protected amino alkyne **35** (Scheme 8). The amine could be acetylated, and tributyltin hydride was then added to the terminal alkyne using

(14) For a review of the imino ene reaction, see: Borzilleri, R. M.; Weinreb, S. M. *Synthesis* **1995**, 347.

(15) For further recent studies on various intramolecular ene reactions of allenyl silanes, see: Jin, J.; Smith, D. T.; Weinreb, S. M. *J. Org. Chem.* **1995**, *60*, 5366.

(16) Jin, J.; Weinreb, S. M. Unpublished results.

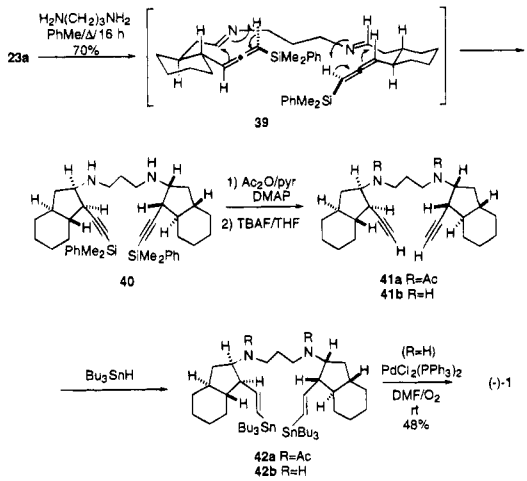
(17) For further details, see: Borzilleri, R. M. Ph.D. Thesis, The Pennsylvania State University, 1994.

(18) For a theoretical treatment of the imino ene reaction, see: Thomas, B. E.; Houk, K. N. *J. Am. Chem. Soc.* **1993**, *115*, 790.

(19) Lambert, J. B. *Tetrahedron Rep.* **1990**, *46*, 2677.

(20) DiPietro, D.; Borzilleri, R. M.; Weinreb, S. M. *J. Org. Chem.* **1994**, *59*, 5856.

Scheme 9



the procedure of Zhang et al.[21] to give the *E*-vinyl stannane **36**. Using methodology of Kyler and co-workers,[22] homocoupling of stannane **36** successfully led to the desired *E,E*-1,3-diene **37**. The TSE groups of **37** were then cleaved by β-elimination induced by potassium *tert*-butoxide affording bisacetamide **38**.[20] A number of attempts were subsequently made to form the macrocyclic 13-membered ring of papuamine by *N*-alkylation of **38** with 1,3-diiodo- and 1,3-dibromopropane.[17] However, in no case was any *N,N*-diacetylpapuamine produced.[23]

In view of these disappointing results, we decided to investigate what ultimately proved to be a more interesting and highly convergent approach to the alkaloid. It was found that if allenyl silane aldehyde **23a** is heated in toluene with 0.5 equiv of 1,3-diaminopropane the tetracyclic bissilyl acetylene **40** is produced in 70% yield as a single stereoisomer (Scheme **9**). We believe this transformation proceeds via a bisimine **39** which undergoes two simultaneous allenyl silane imino ene reactions via the conformation shown in **39** to produce the observed product. This double imino ene reaction can also be catalyzed by stannic chloride but produces **40** in substantially lower yield (45%).

The final phase of the total synthesis now entailed developing a procedure for intramolecular coupling of the alkyne moieties of **40** to produce the requisite *E,E*-1,3-diene. A macrocyclization of this type was unprecedented. Initially, we believed it would be prudent to protect the two secondary amino groups as nonbasic derivatives. Thus, diamine **40** was acetylated, and the silyl groups were removed to yield bisalkyne bisacetamide **41a**. It was then possible to stereoselectively add tributyltin hydride to **41a** using $PdCl_2(PPh_3)_2$ as catalyst leading to *E,E*-bis-vinyl stannane **42a**. Unfortunately, all attempts at intramolecular coupling gave no trace of *N,N*-diacetylpapuamine.[22,24,25] One rationale for this failure of **42a** to undergo ring closure is that the conformation necessary for cyclization may not be attainable due to unfavorable amide rotamers. We thus decided to conduct the sequence without protection of the amino nitrogens.

It was discovered that bisalkyne **41b**, produced by TBAF promoted desilylation of ene product **40** (74%), could best be converted to *E,E*-bisvinyl stannane **42b** under free radical conditions (Bu_3SnH, AIBN, Δ, toluene, 80% yield).[26] After investigating a number of coupling procedures[17,22,28] for stannane **42b**, it was found that using $PdCl_2(PPh_3)_2$ in the presence of oxygen[24] gave positive results, although some unexpected problems arose in the final purification of the alkaloid. Preparative TLC of the crude alkaloid eluting with CH_2Cl_2/MeOH/NH_4OH (8/1.5/0.5) on silica gel afforded a polar, water soluble compound which had ^1H and ^{13}C NMR data very similar to that of papuamine dihydrochloride.[27] This material appeared to be an amine salt, despite the fact that it was never exposed to acid on removal from the silica gel. We believe this compound may in fact be a carbonate salt produced from absorption of atmospheric CO_2 by the alkaloid. We have been unable to fully characterize this product since its mass spectrum is identical to that of the free base, and there is no observable carbonate peak in the ^{13}C NMR spectrum, although such absorption is expected to be quite weak.[28] However, if this "salt" is passed through a Porasil HPLC column (EtOAc/NEt_3, 95/5), or an Amberlite basic ion exchange column eluting with methanol, (−)-papuamine (**1**) can be isolated as the free base (48% based upon recovered bisstannane **42b**). This material has $[\alpha]^{26}_D = -140°$ (*c* 0.02, CH_3OH) [lit.[1] $[\alpha]_D = -150°$ (*c* 1.5, CH_3OH)] and ^1H and ^{13}C NMR spectra identical to the natural product.[27]

In conclusion, we have developed a total synthesis of the natural (−)-enantiomer of papuamine (**1**) in 16 steps starting from scalemic acid ester **11**. The route to the alkaloid uncovered a novel and apparently general type of imino ene reaction of allenyl silanes. We are currently investigating extensions and applications of this new methodology.[15,16]

Experimental Section

All nonaqueous reactions were run under a positive pressure of dry argon at room temperature unless otherwise noted. Melting points are uncorrected. Low-resolution mass spectra (MS) were obtained at 50−70 eV by electron impact (EI). Chemical ionization mass spectra (CIMS) were obtained using isobutane as a carrier gas. Analytical and preparative TLC were performed on E. M. Science silica gel 60 PF_{254}. Flash chromatography was performed using Baker silica gel (25−40 mm). THF, benzene, and ether were dried over and distilled from sodium/benzophenone ketyl. Methylene chloride, toluene, triethylamine, pyridine, *p*-xylene, DMF, and DMSO were distilled from CaH_2, and methanol was distilled from magnesium turnings.

Hydrogenation of Scalemic *cis*-Ester Acid 11. A suspension of *cis*-ester acid **11**[6a] (25 g, 0.14 mol), 10% Pd/C (1.3 g, 10 mol %), and 125 mL of absolute ethanol in a Parr pressure reaction apparatus was agitated for 3 h under 15 psi of H_2. The ethanol was removed *in vacuo*, and the resulting mixture was diluted with ethyl acetate (250 mL) and filtered through a short column of Celite using ethyl acetate as the eluant. The ethyl acetate was removed *in vacuo* to afford saturated *cis*-ester acid **12** (25 g, 99%), which was used without further purification. The spectral data and the optical rotation were identical to that reported by Kobayashi and co-workers[6a] and Schneider et al.[6b]

Epimerization of (+)-*cis*-Ester Acid 12. Sodium metal (19 g, 0.80 g atom) was added in small portions to 450 mL of methanol at 0 °C. Enantiomerically pure *cis*-ester acid **12** (25 g, 0.13 mol) in 40 mL of methanol was added to the sodium methoxide solution, and the resulting solution was heated at reflux for 5 days. The methanol was removed

(21) Zhang, H. X.; Guibe, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857.

(22) Ghosal, S.; Luke, G. P.; Kyler, K. S. *J. Org. Chem.* **1987**, *52*, 4296.

(23) The bistriflamide corresponding to bisacetamide **38** was prepared by a similar route. However, all attempts to couple this intermediate with a three-carbon unit to generate the 13-membered ring also failed.[17]

(24) (a) Kanemoto, S.; Matsubara, S.; Oshima, K.; Utimoto, K.; Nozaki, H. *Chem. Lett.* **1985**, 5. (b) Liebeskind, L. S.; Riesinger, S. W. *Tetrahedron Lett.* **1991**, *32*, 5681.

(25) Tolstikov, G. A.; Miftakhov, M. S.; Danilova, N. A.; Vel'der, Y. L.; Spirikhin, L. V. *Synthesis* **1989**, 633.

(26) Jung, M. E.; Light, L. A. *Tetrahedron Lett.* **1982**, *23*, 3851. Tolstikov, G. A.; Miftakhov, M. S.; Danilova, N. S.; Vel'der, Y. L. *Synthesis* **1986**, 496.

(27) We are very grateful to Professor Paul Scheuer for a small sample and copies of proton and carbon NMR spectra of natural (−)-papuamine, as well as NMR spectra of its HCl salt.

(28) See, for example: McGhee, W.; Riley, D.; Christ, K.; Pan, Y.; Parnas, B. *J. Org. Chem.* **1995**, *60*, 2820.

in vacuo, and the remaining white solid was cooled to 0 °C, dissolved in H_2O (200 mL), and acidified to pH 2 using concentrated HCl. The mixture was extracted with ethyl acetate (3 × 200 mL), washed with brine (300 mL), dried over $MgSO_4$, and concentrated. The crude *trans*-ester acid **13** (24 g, 96%) was isolated as a yellow oil and was sufficiently pure to use in subsequent reactions: $[\alpha]^{26}_D = -25.0°$ (*c* 0.1, CH_3OH); IR (film) 3680−3120, 2920, 2840, 1700, 1435, 1420, 1095 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 3.64 (3 H, s), 2.64−2.50 (2 H, m), 2.10−2.01 (2 H, m), 1.77−1.75 (2H, m), 1.40−1.22 (4 H, m); ^{13}C NMR (90 MHz, $CDCl_3$) δ 181.2, 175.3, 51.7, 44.5, 44.3, 28.7, 25.0; CIMS m/z 187.2 (M^+ + H), 169.2, 155.2, 141.2, 127.2, 109.1, 81.1, 67.1; EIMS *m/z* (rel intensity) 186 (M^+, 2), 155 (14), 140 (20), 126 (18), 108 (17), 81 (100), 67 (24), 55 (22), 41 (27), 31 (28); HREIMS *m/z* 186.0893 ($C_9H_{14}O_4$ requires 186.0892).

Reduction of (−)-*trans*-Ester Acid 13. To a solution of ester acid (−)-**13** (0.61 g, 3.2 mmol) dissolved in 5 mL of THF at 0 °C was added borane−THF complex (1.0 M in THF, 3.9 mL, 3.9 mmol). The resulting solution was stirred for 2 h at room temperature, slowly poured into H_2O (15 mL), and extracted with ether (2 × 20 mL). The combined organic extracts were washed with brine (25 mL), dried over Na_2SO_4, and concentrated *in vacuo* to provide (−)-ester alcohol **14** (0.32 g, 57%) as a colorless liquid: IR (film) 3690−3050, 2940, 2850, 1720, 1445, 1430, 1255, 1165, 1030 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 3.55 (3 H, s), 3.33 (2 H, d, *J* = 5.3 Hz), 2.08−2.03 (1 H, m), 1.81−1.62 (5 H, m), 1.37−1.33 (1 H, m), 1.18−0.95 (3 H, m); ^{13}C NMR (90 MHz, $CDCl_3$) δ 176.7, 66.0, 51.2, 46.0, 41.5, 29.4, 28.1, 25.0, 24.9; CIMS *m/z* 173.0 (M^+ + H), 155.0, 141.0, 123.0, 112.0, 95.1; 81.1; EIMS *m/z* (rel intensity) 172 (M^+, 3), 142 (24), 112 (11), 95 (16), 67 (18), 55 (21), 49 (100), 41 (19); HREIMS *m/z* 172.1105 ($C_9H_{16}O_3$ requires 172.1099).

Mosher Ester of (−)-Alcohol 14. A solution of alcohol (−)-**14** (55 mg, 3.2 mmol) in 1.5 mL of toluene was treated with Mosher's acid chloride[9] (0.12 g, 4.8 mmol) and pyridine (28 mL, 3.5 mmol). The reaction mixture was stirred for 5 h, poured into H_2O (15 mL) and extracted with ether (3 × 10 mL). The organic extracts were washed with 3 M NaOH (3 × 15 mL), brine (15 mL), and dried over Na_2SO_4. The solvent was evaporated *in vacuo* to afford Mosher ester (0.11 g, 95%, 97% de based on ^{19}F NMR) as a colorless oil: IR (film) 2930, 2850, 1780, 1735, 1445, 1250, 1170, 1120, 1080, 1020, 995, 710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.55−7.39 (5 H, m), 4.26−4.11 (2 H, m), 3.66 (3 H, s), 3.55 (3 H, d, *J* = 1.1 Hz), 2.36−2.21 (1 H, m), 2.19−1.95 (2 H, m), 1.82−1.70 (3 H, m), 1.58−1.40 (1 H, m), 1.36−1.08 (3 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.4, 166.5, 130.3, 129.5, 128.3, 127.3, 121.4, 68.9, 55.4, 51.5, 45.2, 38.2, 29.6, 28.4, 25.0, 24.9; ^{19}F NMR (188 MHz, $CDCl_3$) δ 56.5 (residual Mosher's acid), 54.9 (98.5%), 54.8 (1.5%); CIMS *m/z* 389.0 (M^+ + H), 369.0, 358.0, 341.0, 319.0, 275.0, 243.0, 235.0, 229.0, 216.0.

Lactonization of (−)-*trans*-Ester Acid 13. An oven-dried, three-necked, 250 mL flask fitted with a reflux condenser and a syringe cap was cooled to −50 °C, and approximately 75 mL of NH_3 was condensed into the flask. (−)-Ester acid **13** (2.4 g, 12 mmol) dissolved in 8 mL of absolute ethanol was added and the mixture was stirred for 3 min. Sodium metal (1.5 g, 6.5 × 10^{-2} g atom) was added in small portions to produce a deep blue solution, and the resulting mixture was stirred for an additional 15 min. The reaction mixture was warmed to room temperature, and ethanol (10 mL) was slowly added until the blue color dissipated. Once the NH_3 had evaporated, H_2O (100 mL) was added followed by concentrated HCl (~25 mL) until the solution became strongly acidic to pH paper (pH 2). The solution was extracted with ether (3 × 100 mL), washed with brine (200 mL), dried over $MgSO_4$, and concentrated under vacuum. Purification of the yellow residue by Kugelrohr distillation (70 °C, 0.6 mmHg) afforded lactone (+)-**16** (1.3 g, 70%) as a colorless amorphous solid: $[\alpha]^{26}_D = +17.7°$ (*c* 0.35, CH_3OH); IR (film) 2920, 2840, 1770, 1725, 1440, 1365, 1225, 1080 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 4.18−4.08 (1 H, m), 3.72−3.59 (1H, m), 1.94−1.61 (6 H, m), 1.09−0.98 (4 H, m); ^{13}C NMR (90 MHz, $CDCl_3$) δ 176.8, 71.5, 44.3, 42.9, 27.3, 24.8, 24.2, 24.1; CIMS *m/z* 141.2 (M^+ + H), 123.2, 111.2, 95.2, 85.2, 79.1, 67.1, 61.1; EIMS *m/z* (rel intensity) 140 (26), 96 (5.0), 81 (39), 67 (100), 54 (45), 41 (20), 28 (48); HREIMS *m/z* 140.0840 ($C_8H_{12}O_2$ requires 140.0837). Anal. Calcd for $C_8H_{12}O_2$: C, 68.59; H, 8.63. Found: C, 68.28; H, 8.65.

Synthesis of Enantiomeric γ-Lactone (−)-15. To a solution of ester alcohol (−)-**14** (55 mg, 0.32 mmol) in 3 mL of toluene was added *p*-toluenesulfonic acid monohydrate (30 mg, 1.6 × 10^{-4} mol) and the resulting mixture was heated at reflux for 16 h. The mixture was then cooled to 0 °C, neutralized with saturated $NaHCO_3$ solution (5 mL), and extracted with ether (3 × 8 mL). The combined organic extracts were washed with water (10 mL), brine (10 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Flash column chromatography of the concentrate using hexanes−ethyl acetate (1:1) gave γ-lactone (−)-**15** (36 mg, 81%) as a colorless oil: $[\alpha]^{26}_D = -16.8°$ (*c* 0.50, CH_3OH). The spectral data were the same as for compound (+)-**16**.

Reduction of Lactone (+)-16 to Lactol 17. To a solution of lactone (+)-**16** (2.6 g, 19 mmol) in 40 mL of toluene at −78 °C was added DIBALH (1.0 M in hexanes, 20.4 mL, 20.4 mmol) over 2 min. The solution was stirred for 10 min at −78 °C, poured into saturated sodium potassium tartrate solution (Rochelle's salt, 175 mL), and stirred for an additional 1 h. The mixture was extracted with ethyl acetate (3 × 125 mL), and the combined organic layers were washed with brine (250 mL) and dried over Na_2SO_4. The solvents were evaporated *in vacuo* to give lactol **17** (2.5 g, 95%) as a colorless oil, which was used immediately without further purification: IR (film) 3580−3100, 2920, 2850, 1720, 1440, 1135, 1080 cm^{-1}; CIMS *m/z* 143.1 (M^+ + H), 125.1, 107.1, 96.1, 84.0, 81.1, 67.1.

Preparation of Propargylic Alcohols 18a and 18b. To a solution of lactol **17** (5.3 g, 37 mmol) dissolved in 150 mL of THF at 0 °C was added ethynylmagnesium bromide (0.5 M in THF, 0.16 L, 82 mmol) over 40 min. The dark orange mixture was stirred at room temperature for 19 h, cooled to 0 °C, and slowly diluted with saturated NH_4Cl solution (200 mL). The resulting solution was extracted with ether (3 × 200 mL), washed with brine (2 × 250 mL), dried over $MgSO_4$, and concentrated *in vacuo* to give a 1:1 mixture of alcohol epimers. Flash chromatography of the dark red residue using hexanes−ethyl acetate (1:1) afforded colorless propargylic alcohols **18a** and **18b**.

18b: Recrystallized from hexanes−ethyl acetate (1:9): (3.0 g, 46%); mp 102.0−102.5 °C; $[\alpha]^{23}_D = -25.2°$ (*c* 0.1, CH_3OH); IR (film) 3650−3020, 2960, 2840, 1480, 1370, 1210, 1050, 960 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.39 (1 H, dd, *J* = 4.7, 2.2 Hz), 3.79 (1 H, dd, *J* = 11.3, 3.0 Hz), 3.49 (1 H, dd, *J* = 11.3, 7.3 Hz), 2.49 (1 H, d, *J* = 2.2 Hz), 1.78−1.52 (6 H, m), 1.33−1.22 (3 H, m), 1.18−1.04 (1 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 83.4, 74.1, 67.5, 66.4, 47.3, 41.1, 29.7, 29.2, 25.9, 25.8; EIMS *m/z* (rel intensity) 168 (M^+, 2), 150 (9), 135 (11), 121 (16), 107 (14), 95 (100), 91 (12), 81 (28), 67 (21), 55 (11), 28 (14); HREIMS *m/z* 168.1143 ($C_{10}H_{16}O_2$ requires 168.1150);

18a: Recrystallized from hexanes−ethyl acetate (1:1) to give a crystalline solid: (3.0 g, 49%); mp 79.0−80.0 °C; $[\alpha]^{26}_D = -49.5°$ (*c* 0.2, CH_3OH); IR (film) 3620−3520, 2940, 2870, 2130, 1460, 1260, 1050, 980 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 4.51 (1 H, dd, *J* = 5.5, 2.1 Hz), 3.63 (1 H, dd, *J* = 11.2, 3.9 Hz), 3.55 (1 H, dd, *J* = 11.2, 5.1 Hz), 2.48 (1 H, d, *J* = 2.1 Hz), 2.03−1.97 (1 H, m), 1.73−1.66 (3 H, m), 1.58−1.49 (1 H, m), 1.47−1.38 (1 H, m), 1.24−1.12 (4 H, m); ^{13}C NMR (90 MHz, $CDCl_3$) δ 83.7, 74.0, 66.1, 64.8, 45.7, 42.5, 29.8, 27.3, 25.8, 25.5; EIMS *m/z* (rel intensity) 168 (M^+, 2), 107 (11), 95 (100), 81 (32), 67 (47), 55 (17), 41 (62), 28 (42); HREIMS *m/z* 168.1148 ($C_{10}H_{16}O_2$ requires 168.1150). Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.45; H, 9.61. Found: C, 71.61; H, 10.11.

Preparation of Acetoxy Ethers 19c and 19d. Diol **18a** or **18b** (1.1 g, 6.5 mmol) was dissolved in 50 mL of DMF and cooled to 0 °C. Triphenylmethyl chloride (2.4 g, 8.5 mmol), a catalytic amount of DMAP (80 mg, 0.65 mmol), and Et_3N (1.4 mL, 9.8 mmol) were added sequentially, and the solution was heated at 45 °C for 18 h. The reaction mixture was cooled to room temperature, poured into H_2O (100 mL), and extracted with ether (2 × 100 mL). The combined organic extracts were washed with H_2O (2 × 50 mL) and brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography of the residue using hexanes−ethyl acetate (3:1) provided the hydroxy ethers.

Hydroxy trityl ether **19b**: yellow foam (2.5 g, 95%); $[\alpha]^{24}_D = -7.0°$ (*c* 0.1, CH_3OH); IR (film) 3560−3300, 1480, 1440, 1210, 1050 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.63−7.49 (6 H, m), 7.39−7.27 (9 H, m), 4.37 (1 H, dd, *J* = 10.8, 2.3 Hz), 4.07 (1 H, br d OH, *J* = 8.5 Hz), 3.26 (1 H, dd, *J* = 9.7, 2.8 Hz), 3.00 (1 H, dd, *J* = 9.7, 7.0 Hz), 2.56 (1 H, d, *J* = 2.3 Hz, 2.04−1.96 (1 H, m), 1.83−1.68 (4 H, m), 1.52−1.41 (1 H, m), 1.39−1.10 (4 H, m); ^{13}C NMR (90 MHz, $CDCl_3$) δ

143.6, 128.5, 127.8, 127.0, 87.7, 84.1, 73.5, 68.7, 65.3, 47.5, 38.6, 30.3, 27.8, 26.0, 25.9; EIMS *m/z* (rel intensity) 410 (M^+, 1), 260 (6), 243 (100), 228 (3), 183 (30), 165 (31), 154 (4), 105 (27), 91 (4), 77 (13), 55 (9), 41 (5), 28 (5); HREIMS *m/z* 410.2253 ($C_{29}H_{30}O_2$ requires 410.2246).

Hydroxy trityl ether **19a**: white foam (2.6 g, 99%); $[\alpha]^{26}_D = -39.8°$ (*c* 0.13, CH_3OH); IR (film) 3620−3300, 2100, 1580, 1490, 1450, 1220, 1040 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.52−7.46 (6 H, m), 7.36−7.27 (9 H, m), 4.42 (1 H, m), 3.17 (1 H, dd J = 9.4, 3.8 Hz), 3.03 (1 H, dd J = 9.5, 3.8 Hz), 2.41 (1 H, d, J = 2.1 Hz), 2.34 (1 H, br s OH), 2.02−1.95 (1 H, m), 1.83−1.71 (3 H, m), 1.70−1.60 (2 H, m), 1.38−1.20 (4 H, m); ^{13}C NMR (90 MHz, $CDCl_3$) δ 144.1, 128.6, 127.7, 126.9, 86.6, 83.1, 73.9, 66.5, 64.1, 45.5, 40.2, 30.4, 26.0, 25.6, 25.4; HREIMS *m/z* 410.2253 ($C_{29}H_{30}O_2$ requires 410.2246).

The above hydroxyl trityl ethers **19a/19b** (2.6 g, 6.3 mmol) were dissolved in 50 mL of CH_2Cl_2 and cooled to 0 °C. Et_3N (1.3 mL, 9.5 mmol), a catalytic amount of DMAP (77 mg, 0.63 mmol), and acetic anhydride (0.72 mL, 7.6 mmol) were added sequentially, and the solution was stirred at room temperature for 16 h. The reaction mixture was poured into H_2O (50 mL) and extracted with ether (2 × 75 mL). The combined organic extracts were washed with H_2O (2 × 50 mL) and brine(50 mL) and dried over Na_2SO_4. The solvent was removed *in vacuo* to yield the corresponding ether propargylic acetate **19c** or **19d** as viscous yellow oils, which were sufficiently pure to use in the next step:

19d: pale yellow foam (2.8 g, 99%); $[\alpha]^{23}_D = -47.0°$ (*c* 0.1, CH_3OH); IR (film) 3280, 3040, 3010, 2920, 2840, 2220, 1740, 1590, 1480, 1450, 1370, 1220, 1040 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.60−7.48 (6 H, m), 7.40−7.27 (9 H, m), 5.29 (1 H, dd, J = 4.7, 2.2 Hz), 3.41 (1 H, dd, J = 9.2, 3.5 Hz), 2.95 (1 H, dd, J = 9.2, 6.9 Hz), 2.47 (1 H, d, J = 2.2 Hz), 2.24−2.18 (1 H, m), 2.14−2.00 (1 H, m), 1.96 (3 H, s), 1.92−1.81 (3 H, m), 1.78−1.69 (1 H, m), 1.47−1.33 (4 H, m); ^{13}C NMR (90 MHz, $CDCl_3$) δ 169.3, 144.3, 128.6, 127.8, 127.1, 86.2, 80.1, 74.0, 65.4 (2C), 43.0, 39.0, 30.0, 27.0, 25.8, 25.6, 20.7.

19c: white foam (2.8 g, 99%); $[\alpha]^{26}_D = -12.2°$ (*c* 0.1, $CHCl_3$); IR (film) 3280, 3040, 3010, 2910, 2840, 2240, 1750, 1580, 1470, 1450, 1370, 1240, 1040 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.54−7.50 (6 H, m), 7.37−7.27 (9 H, m), 5.61 (1 H, dd, J = 3.4, 2.1 Hz), 3.15 (1 H, dd, J = 9.4, 3.8 Hz), 3.03 (1 H, dd, J = 9.4, 4.3 Hz), 2.44 (1 H, d, J = 2.1 Hz), 2.08 (3 H, s), 1.98−1.74 (6 H, m), 1.46−1.25 (4 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4, 144.2, 128.6, 127.7, 127.0, 86.5, 79.4, 74.5, 66.1, 65.8, 42.9, 39.6, 30.1, 25.8, 25.7, 25.2, 21.0; CIMS *m/z* 452.2 (M^+ + H), 407.2, 392.2, 375.2, 347.1, 333.2, 285.2, 243.1, 165.1, 105.0, 77.0. Anal. Calcd for $C_{31}H_{32}O_3$: C, 82.20; H, 7.13. Found: C, 81.70; H, 7.38.

Formation of Trityl Ether Allenyl Silanes 20a and 20b. Lithium dimethylphenyl silane[12] (1.8 g, 13 mmol) dissolved in 35 mL of THF was added to a suspension of CuCN (0.57 g, 6.4 mmol) in 72 mL of THF at 0 °C. The resulting dark red mixture of this silyl cuprate reagent was stirred for 30 min and cooled to −78 °C, and ether propargylic acetate **19c** or **19d** (2.9 g, 6.4 mmol) dissolved in 7 mL of THF was added slowly over 20 min. (*Note: If the reaction temperature rises above −65 °C, the undesired trityl ether vinyl allyl silane* ***ii*** *is obtained*[13].) After 1 h, the reaction was quenched with H_2O (50 mL) at −78 °C and diluted with ether (75 mL). After washing with H_2O (3 × 60 mL) and brine (60 mL), the organic extract was dried over Na_2SO_4 and concentrated *in vacuo*. Dry column flash chromatography of the residue eluting with hexanes−ethyl acetate (9:1) gave the corresponding ether allenyl silane **20a** or **20b** (3.0 g, 88%) which was used immediately in the next step.

Preparation of Mesylates 21a and 21b. A solution of ether allenyl silane **20a** or **20b** (3.0 g, 5.8 mmol) was dissolved in 75 mL of MeOH, and after the addition of *p*-toluenesulfonic acid monohydrate (0.11 g, 0.57 mmol), the solution was stirred for 3 h at room temperature. The solution was poured into saturated $NaHCO_3$ solution (150 mL) and extracted with ethyl acetate (2 × 150 mL). The combined organic extracts were washed with H_2O (150 mL) and brine (150 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Flash chromatography of the residue using a gradient elution (10%, 25%, 50% ethyl acetate in hexanes) afforded the corresponding alcohol allenyl silane:

Alcohol from **20b**: colorless oil (1.5 g, 97%); $[\alpha]^{23}_D = -133.4°$ (*c* 0.1, CH_3OH); IR (film) 3640−3080, 1930, 1440, 1420, 1240, 1110, 1040 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.67−7.59 (2 H, m), 7.42−7.37 (3 H, m), 5.14 (1 H, dd, J = 6.8, 1.1 Hz), 4.86 (1 H, dd, J = 7.5, 6.8 Hz), 3.65 (1 H, dd, J = 10.8, 3.7 Hz), 3.44 (1 H, dd, J = 10.8, 6.2 Hz), 1.89−1.65 (5 H, m), 1.60−1.48 (1 H, br s, OH), 1.30−1.11 (5 H, m), 0.43 (3 H, s), 0.42 (3 H, s); ^{13}C NMR (90 MHz, $CDCl_3$) δ 210.1, 138.4, 133.6, 129.1, 127.7, 88.1, 81.6, 66.5, 45.1, 39.3, 31.2, 29.3, 26.1, 25.7, −2.1, −2.2; EIMS *m/z* (rel intensity) 286 (M^+, 19), 271 (100), 255 (4), 193 (38), 135 (25), 105 (7), 89 (15), 75 (22), 57 (9), 43 (11); HREIMS *m/z* 286.1733 ($C_{18}H_{26}OSi$ requires 286.1753).

Alcohol from **20a**: colorless oil (1.6 g, 99%); $[\alpha]^{26}_D = +42.7°$ (*c* 0.45, CH_3OH); IR (film) 3620−3080, 1940, 1440, 1430, 1250, 1110, 1040 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.58−7.54 (2 H, m), 7.39−7.36 (3 H, m), 5.10 (1 H,, dd, J = 6.8, 1.5 Hz), 4.78 (1 H, dd, J = 8.6, 6.8 Hz), 3.69 (1 H, dd, J = 10.9, 3.9 Hz), 3.53 (1 H, dd, J = 10.9, 5.5 Hz), 1.84−1.71 (5 H, m), 1.56 (1 H, br s, OH), 1.25−1.09 (5 H, m), 0.39 (3 H, s), 0.38 (3 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.9, 138.5, 133.7, 129.1, 127.7, 88.1, 81.3, 66.9, 45.6, 40.2, 34.0, 29.4, 26.0, 25.7, −2.3 (2C); EIMS *m/z* (rel intensity) 286 (M^+, 2), 271 (4), 247 (5), 232 (4), 208 (4), 193 (7), 135 (100), 105 (25), 91 (23), 67 (17), 55 (14), 41 (20); HREIMS *m/z* 286.1748 ($C_{18}H_{26}OSi$ requires 286.1753).

The above alcohol allenyl silanes (1.3 g, 4.5 mmol) were dissolved in 25 mL of CH_2Cl_2 and cooled to 0 °C. Methanesulfonyl chloride (0.46 mL, 5.9 mmol) and Et_3N (1.0 mL, 6.8 mmol) were added sequentially, and the solution was allowed to warm to room temperature. After 14 h, the solution was poured into H_2O (50 mL) and extracted with ether (2 × 50 mL). The combined organic extracts were washed with brine (2 × 50 mL), dried over Na_2SO_4, and concentrated *in vacuo* to yield mesylate allenyl silane **21a** or **21b** as yellow oils, which were used without further purification.

21b: (1.5 g, 99%); IR (film) 2910, 2840, 1950, 1440, 1420, 1360, 1240, 1105, 1040 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.59−7.56 (2 H, m), 7.40−7.35 (3 H, m), 5.18 (1 H, dd, J = 6.9, 1.7 Hz), 4.86 (1 H, dd, J = 7.3, 6.9 Hz), 4.34 (1 H, dd, J = 9.6, 3.2 Hz), 4.06 (1 H, dd, J = 9.6, 7.3 Hz), 2.93 (3 H, s), 1.95−1.91 (1 H, m), 1.86−1.73 (4 H, m), 1.54−1.51 (1 H, m), 1.28−1.15 (4 H, m), 0.42 (3 H, s), 0.41 (3 H, s); ^{13}C NMR (90 MHz, $CDCl_3$) δ 209.8, 138.1, 133.5, 129.1, 127.7, 87.1, 82.4, 73.4, 42.0, 37.9, 36.8, 33.8, 29.1, 25.7, 25.2, −2.3 (2C); CIMS *m/z* 365.3 (M^+ + H), 343.2, 269.8, 227.4, 209.3, 153.3, 135.4, 95.4.

21a: (1.5 g, 99%); IR (film) 2920, 2840, 1930, 1440, 1420, 1350, 1240, 1040 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.56−7.49 (2 H, m), 7.39−7.27 (3 H, m), 5.07 (1 H, dd, J = 6.8, 1.4 Hz), 4.69 (1 H, dd, J = 8.6, 6.8 Hz), 4.25 (1 H, dd, J = 9.5, 3.1 Hz), 4.10 (1 H, dd, J = 9.5, 6.2 Hz), 2.94 (3 H, s), 1.84−1.68 (5 H, m), 1.42−1.11 (5 H, m), 0.33 (6 H, s); CIMS *m/z* 365.4 (M^+ + H), 343.2, 327.3, 283.0, 269.1, 255.4, 193.0, 153.1, 135.1, 119.1, 95.0.

Preparation of Nitrile Allenyl Silanes 22a and 22b. To a solution of mesylate allenyl silane **21a** or **21b** (1.2 g, 3.2 mmol) dissolved in 15 mL of DMSO was added KCN (0.30 g, 4.3 mmol), and the mixture was stirred at 45 °C for 2 days. The orange solution was cooled to room temperature, poured into H_2O (25 mL), and extracted with ethyl acetate (2 × 50 mL). The combined organic extracts were washed with H_2O (2 × 35 mL) and brine (35 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Flash column chromatography of the residue eluting with hexanes−ethyl acetate (3:1) afforded nitrile allenyl silane **22a** or **22b**.

22b: yellow oil (0.68 g, 70%); $[\alpha]^{23}_D = -142.0°$ (*c* 0.1, $CHCl_3$); IR (film) 3040, 2920, 2840, 2230, 1930, 1440, 1420, 1240, 1110 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.61−7.57 (2 H, m), 7.43−7.38 (3 H, m), 5.18 (1 H, dd, J = 6.8, 1.6 Hz), 4.70 (1 H, dd, J = 8.4, 6.8 Hz), 2.33 (1 H, dd, J = 16.8, 3.6 Hz), 2.08 (1 H, dd, J = 16.8, 7.7 Hz), 1.96−1.71 (5 H, m), 1.38−1.11 (5 H, m), 045 (3 H, s), 0.43 (3 H, s); ^{13}C NMR (90 MHz, $CDCl_3$) δ 209.8, 137.7, 133.7, 129.2, 127.7, 118.8, 86.9, 82.3, 41.7, 39.2, 34.0, 31.5, 25.6, 25.5, 22.4, −2.1, −2.4; EIMS *m/z* (rel intensity) 295 (M^+, 23), 269 (10), 250 (11), 199 (26), 187 (33), 173 (30), 159 (100), 135 (81), 105 (23), 81 (62), 53 (34); HREIMS *m/z* 295.1759 ($C_{19}H_{25}NSi$ requires 295.1756).

22a: colorless oil (0.75 g, 77%); $[\alpha]^{25}_D = +11.8°$ (*c* 0.51, $CHCl_3$); IR (film) 3040, 2920, 2840, 2230, 1940, 1440, 1420, 1250, 1110 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.60−7.56 (2 H, m), 7.42−7.37 (3 H, m), 5.16 (1 H, dd, J = 6.8, 1.2 Hz), 4.67 (1 H, dd, J = 8.4, 6.8 Hz), 2.51 (1 H, dd, J = 16.7, 3.5 Hz), 2.29 (1 H, dd, J = 16.7, 7.5 Hz),

1.97−1.94 (1 H, m), 1.85−1.74 (4 H, m), 1.37−1.11 (5 H, m), 0.41 (6 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.0, 138.0, 133.6, 129.1, 127.7, 118.8, 86.7, 81.8, 42.2, 40.0, 33.6, 31.6, 25.6, 25.5, 22.5, −2.3, −2.4; EIMS *m/z* (rel intensity) *m/z* 295 (M^+, 4), 271 (3), 255 (2), 215 (3), 199 (2), 173 (2), 152 (15), 137 (100), 91 (8), 84 (70), 49 (81), 28 (63); HREIMS *m/z* 295.1754 ($C_{19}H_{25}NSi$ requires 295.1756).

Preparation of Aldehyde Allenyl Silanes 23a and 23b. To a solution of nitrile allenyl silane **22a** or **22b** (0.34 g, 1.2 mmol) dissolved in 5 mL of toluene at −78 °C was added DIBALH (1.0 M in hexanes, 1.5 mL, 1.5 mmol) over 5 min. The solution was warmed to 0 °C over 1 h and stirred for an additional 1.5 h. The reaction mixture was poured into saturated Rochelle's salt (15 mL), stirred for 30 min, and extracted with ethyl acetate (2 × 15 mL). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography of the residue eluting with hexanes−ethyl acetate (9:1) yielded aldehyde allenyl silane **23a** or **23b** as colorless oils:

23b: (0.26 g, 77%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.64 (1 H, dd, J = 2.2, 1.3 Hz), 7.59−7.32 (5 H, m), 5.08 (1 H, dd, J = 7.0, 1.0 Hz), 4.69 (1 H, dd, J = 8.2, 7.0 Hz), 2.55 (1 H, dd, J = 16.6, 3.1 Hz), 2.05−1.91 (1 H, m), 1.79−1.55 (6 H, m), 1.25−0.92 (4 H, m), 0.34 (3 H, s), 0.33 (3 H, s).

23a: (0.25 g, 74%); $[\alpha]^{26}_D$ = +93.7° (*c* 0.3, $CHCl_3$); IR (film) 3080, 3020, 2960, 2880, 2710, 1950, 1730, 1450, 1430, 1260, 1120 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.72 (1 H, dd, J = 2.7, 1.9 Hz), 7.58−7.53 (2 H, m), 7.39−7.33 (3 H, m), 5.07 (1 H, d, J = 6.7 Hz), 4.64 (1 H, dd, J = 8.2, 6.7 Hz), 2.68 (1 H, ddd, J = 16.5, 4.2, 1.9 Hz), 2.17 (1 H, ddd, J = 16.5, 7.7, 2.7 Hz), 1.81−1.64 (6 H, m), 1.29−1.02 (4 H, m), 0.37 (6 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.4, 203.1, 138.4, 133.7, 129.1, 127.7, 87.9, 81.2, 49.4, 43.5, 38.6, 34.0, 32.9, 25.9, 25.8, −2.3 (2C); MS (FAB$^+$, glycerol) *m/z* 297.3 (M^+ − H), 221.3, 209.3, 195.3, 149.0, 135.0.

Conversion of Aldehyde Allenyl Silanes 23a and 23b to Silyl Acetylenes 25 and 28, Respectively. Method A. To a solution of aldehyde allenyl silane **23a** or **23b** (0.10 g, 0.33 mmol) dissolved in 2 mL of benzene was added 4Å molecular sieve powder and benzylamine (38 μL, 0.35 mmol). The mixture wwas stirred a room temperature for 1.5 h, cooled to 5 °C, and treated with $SnCl_4$ (1.0 M in CH_2Cl_2, 0.50 mmol). The resulting orange mixture was warmed to room temperature, stirred for 16 h, diluted with 15% NaOH solution (10 mL), and extracted with ether (2 × 15 mL). The combined organic extracts were washed with saturated $NaHCO_3$ solution (2 × 10 mL), H_2O (10 mL), and brine (10 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Dry column flash chromatography of the concentrate using hexanes−ethyl acetate (1:1) gave the corresponding silyl acetylene **25** or **28**.

28: yellow oil (0.11 g, 84%); $[\alpha]^{23}_D$ = −23.7° (*c* 0.04, $CHCl_3$); IR (film) 3280, 3040, 3010, 2910, 2840, 2140, 1480, 1440, 1420, 1110 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67−7.62 (2 H, m), 7.42−7.22 (8 H, m), 3.91 (1 H, d, J = 12.3 Hz), 3.67 (1 H, d, J = 12.3 Hz), 3.33 (1 H, dt, J = 9.6, 6.2 Hz), 3.21 (1 H, dd, J = 6.2, 5.8 Hz), 2.55−2.36 (1 H, br NH s), 1.90−1.45 (7 H, m), 1.39−1.21 (3 H, m), 1.17−0.85 (2 H, m), 0.43 (3 H, s), 0.42 (3 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.2, 137.6, 133.6, 129.2, 128.4, 128.3, 127.8, 126.8, 106.7, 88.3, 59.9, 52.5, 48.4, 41.0, 40.7, 37.3, 32.0, 28.6, 26.3, 26.0, −0.46, −0.52; CIMS *m/z* 388.5 (M^+ + H), 372.5, 339.5, 310.4, 296.4, 252.3, 214.2, 170.1, 135.1, 121.1, 105.0, 91.0; EIMS *m/z* (rel intensity) 387 (M^+, 7), 296 (6), 252 (55), 214 (8), 170 (6), 135 (45), 120 (8), 105 (5), 91 (100), 59 (7); HREIMS *m/z* 387.2380 ($C_{26}H_{33}NSi$ requires 387.2382).

25: yellow oil (0.11 g, 87%); IR (film) 3290, 3050, 3010, 2910, 2840, 2150, 1440, 1420, 1250, 1110 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65−7.60 (2 H, m), 7.41−7.23 (8 H, m), 3.84−3.82 (2 H, m), 3.24−3.19 (1 H, m), 2.47 (1 H, dd, J = 11.5, 8.2 Hz), 2.19−2.12 (2 H, m), 2.09−1.98 (1 H, m), 1.88−1.78 (3 H, m), 1.49−1.43 (1 H, m), 1.30−0.94 (6 H, m), 0.40 (6 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.5, 137.5, 133.6, 129.2, 128.3, 128.0, 127.8, 126.7, 108.5, 86.4, 56.8, 51.9, 50.9, 44.6, 42.6, 39.9., 31.6, 30.3, 26.3, 26.1, −0.61 (2C); EIMS *m/z* (rel intensity) 387 (M^+, 12), 296 (4), 283 (4), 252 (40), 135 (56), 106 (20), 91 (100), 75 (18), 28 (100); HREIMS 387.2408 ($C_{26}H_{33}NSi$ requires 387.2382).

Method B. A solution of aldehyde allenyl silane **23a** or **23b** (0.10 g, 0.33 mmol) and 4Å molecular sieves in 3 mL of toluene was stirred for 1.5 h at room temperature. The mixture was refluxed for 18 h, cooled to room temperature, and filtered through a fritted glass funnel. The orange crude product was purified as described above in **Method A** to give the corresponding silyl acetylene **28** (80 mg, 67%) or **25** (91 mg, 70%).

Desilylation of Silyl Acetylenes 25 and 28 to Alkynes 26 and 29, Respectively. Silyl acetylene **25** or **28** (0.11 g, 0.29 mmol) was dissolved in 5 mL of THF, cooled to 0 °C, and treated with tetrabutylammonium fluoride (1.0 M in THF, 0.50 mL, 0.50 mmol). The reaction mixture was warmed to room temperature, stirred for 2 h, poured into saturated $NaHCO_3$ solution (15 mL), and extracted with ether (2 × 15 mL). The combined organic extracts were washed with H_2O (2 × 20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude products were purified by flash chromatography using a gradient elution (10%, 50%, 90% ethyl acetate in hexanes) to afford the corresponding alkyne **26** or **29** as white solids.

29: (66 mg, 93%); $[\alpha]^{23}_D$ = −7.7° (*c* 0.02, $CHCl_3$); IR (film) 3280, 3040, 3020, 2900, 2840, 2090, 1480, 1440, 1170 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.42−7.24 (5 H, m), 3.89 (1 H, d, J = 12.6 Hz), 3.69 (1 H, d, J = 12.6 Hz), 3.29 (1 H, ddd, J = 9.9, 5.9, 3.6 Hz), 3.09 (1 H, ddd, J = 6.3, 5.9, 2.5 Hz), 2.23 (1 H, d, J = 2.5 Hz), 2.14−2.01 (1 H, br s NH), 1.90−1.43 (8 H, m), 1.30−1.20 (3 H, m), 1.16−0.92 (1 H, m); ^{13}C NMR (90 MHz, $CDCl_3$) δ 140.2, 128.4, 128.3, 126.9, 82.0, 73.7, 59.5, 52.3, 48.1, 40.8, 39.4, 37.2, 32.0, 28.4, 26.2, 26.0; CIMS *m/z* 254.2 (M^+ + H), 238.1, 210.1, 196.1, 171.1, 162.1, 133.1, 106.1, 91.1, 65.0; EIMS *m/z* (relative intensity) 253 (M^+, 9), 171 (17), 146 (5), 132 (7), 120 (8), 106 (11), 91 (100), 65 (15), 28 (12); HREIMS *m/z* 253.1830 ($C_{18}H_{23}N$ requires 253.1830).

26: (68 mg, 92%); IR (film) 3280, 3040, 3010, 2910, 2840, 2100, 1490, 1450 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.40−7.22 (5 H, m), 3.83 (1 H, d, J = 13.4 Hz), 3.81 (1 H, d, J = 13.4 Hz), 3.20 (1 H, ddd, J = 8.4, 6.8, 1.7 Hz), 2.39 (1 H, ddd, J = 8.4, 5.7, 2.5 Hz), 2.21 (1 H, d, J = 2.5 Hz), 2.18−2.04 (3 H, m), 1.89−1.70 (2 H, m), 1.49−1.38 (1 H, m), 1.30−0.91 (6 H, m); ^{13}C NMR (90 MHz, $CDCl_3$) δ 140.4, 128.3, 128.2, 126.8, 84.1, 72.0, 56.5, 51.9, 51.0, 44.4, 41.0, 39.8, 31.5, 30.3, 26.2, 26.0; EIMS *m/z* (rel intensity) 253 (M^+, 87), 210 (14), 170 (100), 106 (8), 91 (89), 28 (51); HREIMS *m/z* 253.1822 ($C_{18}H_{23}N$ requires 253.1830).

Preparation of the HCl Salt of Alkynes 26 and 29 for X-ray Analysis. A saturated methanolic-HCl solution (~100 μL, prepared from bubbling HCl(g) through 5 mL of methanol at 0 °C for 4 min) was added to the alkyne **26** or **29** (~50 mg, 0.19 mmol) which was dissolved in 0.5 mL of MeOH at 0 °C. The solution was swirled for 2 min, warmed to room temperature, and concentrated *in vacuo* to give a white solid. Recrystallization of the crude solid from ether−methanol (20:1) gave single crystals suitable for X-ray analysis (see supporting information for details).

Thermal Ene Cyclization of Aldehyde Allenyl Silane 23a to Alcohol Silyl Acetylene 34. Aldehyde allenyl silane **23a** (80 mg, 0.27 mmol) was dissolved in 2 mL of *p*-xylene and heated at reflux for 18 h. The solvent was removed *in vacuo*, and the resulting yellow residue was purified by preparative TLC eluting with hexanes−ethyl acetate (9:1) to afford alcohol silyl acetylene **34** (49 mg, 61%) as a colorless oil: IR (film) 3580−3150, 3060, 3030, 2920, 2840, 2160, 1450, 1430, 1250, 1120 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.67−7.62 (2 H, m), 7.41−7.27 (3 H, m), 4.25−4.21 (1 H, m), 2.35−2.28 (2 H, m), 2.27 (1 H, br OH s), 2.10−2.06 (1 H, m), 1.88−1.75 (3 H, m), 1.50−1.41 (1 H, m), 1.33−0.98 (6 H, m), 0.44 (6 H, s); ^{13}C NMR (90 MHz, $CDCl_3$) δ 137.2, 133.5, 129.4, 127.9, 106.6, 87.7, 70.7, 49.1, 45.5, 40.0, 31.6, 30.0, 26.2, 26.0, −0.61; EIMS *m/z* (rel intensity) 298 (M^+, 5), 283 (11), 254 (35), 222 (20), 205 (10), 145 (13), 135 (100), 121 (16), 105 (14), 91 (12), 75 (45), 28 (31); HREIMS *m/z* 298.1754 ($C_{19}H_{26}OSi$ requires 298.1753).

Conversion of Aldehyde Allenyl Silane 23a to TSE-Protected Amino Silyl Alkyne 35. Either the $SnCl_4$ or thermal ene cyclization procedures used for the synthesis of silyl alkynes **25** and **28**, followed by the TBAF desilylation was applied to produce alkyne **35**. **35**: (52 mg from **23a**, 62%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.78 (2 H, d, J = 8.2 Hz), 7.34 (2 H, d, J = 8.2 Hz), 3.30−3.23 (2 H, m), 3.15−2.91 (3 H, m), 2.42 (3 H, s), 2.30 (1 H, ddd, J = 8.4, 5.4, 2.5 Hz), 2.10 (1 H, d, J = 2.5 Hz), 2.09−1.96 (1 H, m), 1.81−1.70 (4 H, m), 1.29−1.17 (3 H, m), 1.16−0.84 (4 H, m).

Preparation of Acetamide Vinyl Stannane 36. To a solution of alkyne **35** (0.13 g, 0.38 mmol) dissolved in 2 mL of pyridine was added a catalytic amount of DMAP (5.0 mg, 3.8×10^{-4} mol) and acetic anhydride (71 mL, 0.75 mmol). The resulting solution was stirred for 4 h at room temperature, poured into H_2O (10 mL), and extracted with ether (2 × 15 mL). The combined organic extracts were washed with H_2O (3 × 15 mL) and brine (15 mL) and dried over Na_2SO_4. The solvent was removed *in vacuo* to afford the acetamide (0.12 g, 84%) as a white solid, which was sufficiently pure to use in subsequent reactions: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.78 (2 H, d, J = 8.3 Hz), 7.34 (2 H, d, J = 8.3 Hz, 4.32−4.19 (1 H, m), 3.97−3.66 (2 H, m), 3.37−2.89 (2 H, m), 2.51−2.40 (1 H, m), 2.37 (3 H, s), 2.01 (1 H, d, J = 2.6 Hz), 1.99 (3 H, s), 1.89−1.58 (4 H, m), 1.34−0.78 (8 H, m).

A solution of the above alkyne (0.11 g, 0.28 mmol) dissolved in 0.5 mL of THF was treated with a catalytic amount of $PdCl_2(PPh_3)_2$ (10 mg, 1.4×10^{-2} mmol) followed by tributyltin hydride (0.10 mL, 0.34 mmol). The resulting black mixture was stirred for 30 min, concentrated *in vacuo*, and purified by flash chromatography eluting with hexanes−ethyl acetate (1:1) to give *E*-vinyl stannane **36** (0.17 g, 89%) as a white solid: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.81 (2 H, d, J = 8.4 Hz), 7.37 (2 H, d, J = 8.4 Hz), 5.92 (1 H, d, J = 18.9 Hz), 5.54 (1 H, dd, J = 18.9, 8.3 Hz), 4.30−4.16 (1 H, m), 3.87−3.70 (2 H, m), 3.21−2.85 (2 H, m), 2.43 (3 H, s), 2.42−2.1 (1 H, m), 2.02 (3 H, s), 1.97−1.62 (3 H, m), 1.49−1.01 (27 H, m), 1.00−0.62 (9 H, m).

Homocoupling of *E*-Vinyl Stannane 36. To a solution of vinyl stannane **36** (0.20 g, 0.29 mmol) dissolved in 0.3 mL of THF was added cupric nitrate trihydrate (0.11 mg, 0.44 mmol). The resulting blue mixture was stirred for 24 h, poured into 7% NH_4OH solution (10 mL) and extracted with ether (2 × 15 mL). The combined organic extracts were washed with H_2O (2 × 8 mL), brine (10 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Dry column chromatography of the concentrate using ethyl acetate−methanol (20:1) gave (*E,E*)-1,3-diene **37** (79 mg, 69%) as a white solid: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.41 (4 H, d, J = 8.5 Hz), 7.38 (4 H, d, J = 8.5 Hz), 6.01−5.82 (2 M, m), 5.31−5.10 (2 H, m), 4.35−4.18 (2 H, m), 3.99−3.65 (4 H, m), 3.11−2.82 (4 H, m), 2.47 (6 H, s), 2.45−2.23 (2 H, m), 2.01 (6 H, s), 1.96−1.48 (8 H, m), 1.45−0.85 (16 H, m).

Deprotection of (*E,E*)-1,3-Diene 37 to *bis*-Acetamide 38. To a solution of (*E,E*)-diene **37** (67 mg, 0.091 mmol) in 0.5 mL of THF at 0 °C was added potassium *tert*-butoxide (58 mg, 0.52 mmol). The mixture was warmed to room temperature, stirred for 1.5 h, poured into H_2O (5 mL), and extracted with ether (3 × 5 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Preparative TLC of the residue using ethyl acetate−methanol (20:1) gave bisacetamide **38** (12 mg, 56%) as a white solid: ^{1}H NMR (360 MHz, $CDCl_3$) δ 6.03 (1 H, dd, J = 14.5, 10.2 Hz), 5.39 (1 H, dd, J = 14.5, 3.1 Hz), 5.31 (1 H, NH br d, J = 8.6 Hz), 4.47−4.38 (1 H, m), 2.67−2.27 (2 H, m), 1.93 (3 H, s), 1.95−0.94 (11 H, m); EIMS *m/z* (rel intensity) 412 (M^+, 6), 369 (8), 353 (14), 294 (100), 266 (5), 172 (25), 121 (22), 105 (16), 91 (27), 81 (26), 67 (25), 57 (38), 43 (74); HREIMS *m/z* 412.3109 ($C_{26}H_{40}N_2O_2$ requires 412.3090).

Conversion of Aldehyde Allenyl Silane 23a to Bissilyl Acetylene 40. Method A. To a solution of aldehyde allenyl silane **23a** (0.16 g, 0.54 mmol) dissolved in 3 mL of benzene was added 4Å molecular sieve powder and 1,3-diaminopropane (22 μL, 0.27 mmol). The reaction mixture was stirred for 1.5 h, cooled to 5 °C, and treated with $SnCl_4$ (1.0 M in CH_2Cl_2, 1.1 mL, 1.1 mmol). The solution was warmed to room temperature, stirred for 18 h, diluted with 15% NaOH (8 mL), and extracted with ether (2 × 15 mL). The combined organic extracts were washed with saturated $NaHCO_3$ solution (2 × 10 mL), H_2O (10 mL), and brine (10 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Dry column flash chromatography using a gradient elution with hexanes−ethyl acetate (1:1) and ethyl acetate−triethylamine (95:5) gave bissilyl acetylene **40** (0.15 g, 45%) as a pale yellow oil: IR (film) 3450−3180, 3050, 3020, 2940, 2140, 1440, 1420, 1250, 1110 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65−7.61 (4 H, m), 7.38−7.27 (6 H, m), 3.15−3.08 (2 H, m), 2.65−2.59 (4 H, m), 2.42 (2 H, dd, J = 11.5, 3.2 Hz), 2.18−2.04 (4 H, m), 1.84−1.61 (8 H, m), 1.45−0.90 (14 H, m), 0.40 (12 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.6, 133.6, 129.2, 127.8, 108.5, 86.1, 57.8, 50.8, 46.6, 44.5, 42.6, 40.0, 31.5, 30.5, 30.3, 26.2, 26.1, −0.50 (2C); CIMS *m/z* 635.4 (M^+ + H), 557.3, 499.3, 365.2, 325.2, 232.1, 190.1, 135.0, 91.0; EIMS *m/z* (rel intensity) 634 (M^+, 19), 499 (60), 365 (12), 325 (41), 310 (28), 296 (11), 190 (46), 135 (100), 121 (18), 28 (48); HREIMS *m/z* 634.4105 ($C_{41}H_{58}N_2Si_2$ requires 634.4138).

Method B. To a solution of aldehyde allenyl silane **23a** (0.40 g, 1.3 mmol) dissolved in 10 mL of toluene was added 4Å molecular sieves and 1,3-diaminopropane (57 μL, 0.67 mmol). The mixture was stirred for 1.5 h at room temperature, heated at reflux for 21 h, cooled to room temperature, and filtered through a fritted glass funnel. The crude product was purified as described above in **Method A** to give bissilyl acetylene **40** (0.30 g, 70%).

Desilylation of Bissilyl Acetylene 40 to Diamine 41b. Bissilylene acetylene **40** (0.30 g, 0.47 mmol) was dissolved in 8 mL of THF, cooled to 0 °C, and treated with tetrabutylammonium fluoride (1.0 M in THF, 1.4 mL, 1.4 mmol). The reaction mixture was warmed to room temperature, stirred for 2 h, poured into saturated $NaHCO_3$ solution (15 mL), and extracted with ether (2 × 15 mL). The combined organic extracts were washed with H_2O (2 × 20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Flash column chromatography of the dark orange concentrate using ethyl acetate−triethylamine (95:5) afforded diamine **41b** (0.13 g, 74%) as a yellow solid: $[\alpha]^{26}_D$ = −61.0° (*c* 0.1, $CHCl_3$); IR (film) 3290, 2920, 2840, 2100, 1450, 1350 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.16 (1 H, d, J = 7.0 Hz), 3.11 (1 H, d, J = 6.7 Hz), 2.73−2.57 (4 H, m), 2.34 (2 H, ddd, J = 11.2, 8.6, 2.4 Hz), 2.14 (2 H, d, J = 2.4 Hz), 2.11−2.00 (4 H, m), 1.82−1.65 (10 H, m), 1.41−0.91 (14 H, m); ^{1}H NMR (300 MHz, C_6D_6) δ 3.03 (1 H, d, J = 6.8 Hz), 2.98 (1 H, d, J = 6.8 Hz), 2.81−2.65 (4 H, m), 2.24−2.09 (6 H, m), 2.01 (2 H, d, J = 2.5 Hz), 1.93 (2 H, dt, J = 12.2, 6.8 Hz), 1.78−1.56 (8 H, m), 1.47 (2 H, dq, J = 11.4, 3.3 Hz), 1.13−0.73 (12 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 84.0, 71.8, 57.7, 50.9, 46.8, 44.3, 41.0, 40.0, 31.5 (2C), 30.3, 26.2, 26.0; ^{13}C NMR (75 MHz, C_6D_6) δ 84.3, 72.3, 58.4, 50.8, 47.2, 44.6, 41.8, 40.4, 32.0, 31.2, 30.6, 26.6, 26.4; EIMS *m/z* (rel intensity) 366 (M^+, 24), 351 (3), 269 (5), 231 (18), 202 (13), 191 (75), 176 (63), 108 (49), 94 (44), 80 (100), 56 (52), 41 (45), 28 (89); HREIMS *m/z* 366.3012 ($C_{25}H_{38}N_2$ requires 366.3035).

Formation of Bis-*E*-vinyl Stannane 42b. A solution of diamine **41b** (58 mg, 0.16 mmol) dissolved in 1.3 mL of toluene was treated with azobisisobutyronitrile (AIBN, 3.0 mg, 1.6×10^{-2} mmol) followed by tributyltin hydride (0.13 mL, 0.48 mmol). The mixture was heated at reflux for 3.5 h, concentrated *in vacuo*, and purified by flash column chromatography using a gradient elution of hexanes−ethyl acetate (1:1), followed by ethyl acetate and ethyl acetate−triethylamine (95:5) to give bis-*E*-vinyl stannane **42b** (0.12 g, 80%) as a colorless oil: $[\alpha]^{26}_D$ = −61.4° (*c* 0.71, C_6H_6); IR (film) 3300, 2920, 2860, 2820, 1580, 1380, 1190, 1070 cm^{-1}; ^{1}H NMR (360 MHz, C_6D_6) δ 6.31 (2 H, dd, J = 19.0, 8.4 Hz), 6.11 (2 H, d, J = 19.0 Hz), 3.27−3.20 (2 H, m), 2.76−2.61 (4 H, m), 2.23−2.11 (4 H, m), 1.99−1.83 (2 H, m), 1.79−1.69 (2 H, m), 1.67−1.53 (17 H, m), 1.51−1.36 (10 H, m), 1.35−1.26 (2 H, m), 1.22−0.88 (45 H, m); ^{13}C NMR (90 MHz, C_6D_6) δ 150.8, 129.2, 60.8, 58.9, 50.0, 47.7, 44.9, 41.4, 32.4, 31.8, 30.6, 29.7, 27.7, 26.9, 14.0, 9.9. Anal. Calcd for $C_{49}H_9N_2Sn_2$: C, 62.04; H, 9.99. Found: C, 62.30; H, 9.97.

Intramolecular Coupling of Bis-*E*-vinyl Stannane 42b to (−)-Papuamine (1). To a solution of bis-*E*-vinyl stannane **42b** (28 mg, 3.0×10^{-2} mmol) in 0.8 mL of DMF was added $PdCl_2(PPh_3)_2$ (4.1 mg, 5.9×10^{-3} mmol). The reaction mixture was stirred for 16 h, treated again with $PdCl_2(PPh_3)_2$ (4.1 mg, 5.9×10^{-3} mmol), and stirred for an additional 5 h. After removal of the solvent *in vacuo*, the crude residue was partitioned between a two phase mixture of hexanes and CH_3CN (1:1, 10 mL). The hexane layer was washed with CH_3CN (2 × 5 mL) and concentrated *in vacuo*, and the residue was purified by preparative TLC eluting with CH_2Cl_2−MeOH−NH_4OH (8:1.5:0.5) to afford a salt of papuamine as a white film: $[\alpha]^{26}_D$ = −108° (*c* 0.025, CH_3OH) (lit[1] HCl salt $[\alpha]_D$ = −140° (*c* = 1.3, CH_3OH); ^{1}H NMR (300 MHz, CD_3OD) δ 6.42 (2 H, dd, J = 15.1, 9.8 Hz), 5.78 (2 H, dd, J = 15.1, 8.7 Hz), 3.50 (2 H, dd, J = 8.2, 8.1 Hz), 3.16−3.05 (2 H, m), 2.99−2.91 (2 H, m), 2.56 (2 H, dd, J = 9.2, 9.1 Hz), 2.37−2.31 (2 H, m), 1.92−1.69 (10 H, m), 1.32−0.88 (14 H, m); ^{13}C NMR (75 MHz, CD_3OD) δ 134.9, 129.2, 61.0, 49.3, 48.1, 46.4, 43.6, 37.9, 31.0, 29.8, 25.9, 25.0.

The free amine was obtained by HPLC using a Waters Porasil column and eluting with EtOAc−Et_3N (95:5)[1] or column chromatography (6 × 1 cm) on pretreated Amberlite, strongly basic anionic exchange resin (Aldrich, IRA-400(OH)) eluting with MeOH to produce (−)-papuamine (**1**) as a white film: (3.0 mg, 48% based on 12 mg of recovered starting vinyl stannane **42b**); $[\alpha]^{26}_D = -140°$ (*c* 0.02, CH_3OH) (lit[1] $[\alpha]_D = -150°$ (*c* 1.5, CH_3OH); ^1H NMR (300 MHz, CD_3OD) δ 6.18 (2 H, dd, J = 15.0, 9.6 Hz), 5.66 (2 H, dd, J = 15.0, 8.5 Hz), 3.05 (2 H, dd, J = 8.5, 8.2 Hz), 2.66−2.58 (2 H, m), 2.36−2.21 (4 H, m), 2.20−2.14 (2 H, m), 1.84−1.62 (8 H, m), 1.61−1.54 (4 H, m), 1.23−0.88 (14 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.1, 129.6, 61.0, 51.0, 48.8, 45.9, 43.8, 41.6, 31.7, 30.5, 26.4; CIMS *m/z* 369.2 ($M^+ + H$), 325.1, 262.0, 231.1, 204.1, 178.1, 121.0, 79.0; EIMS *m/z* (rel intensity) 368 (M^+, 23), 338 (5), 322 (9), 271 (6), 149 (31), 97 (30), 85 (47), 71 (63), 57 (100), 43 (63); HREIMS *m/z* 368.2313 ($C_{25}H_{40}N_2$ requires 368.3191).

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Supporting Information Available: X-ray data for compounds **18b** and the HCl salts of **26** and **29** (61 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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