Total Synthesis of Papuamine via a Stereospecific Intramolecular Imino Ene Reaction of an Allenylsilane

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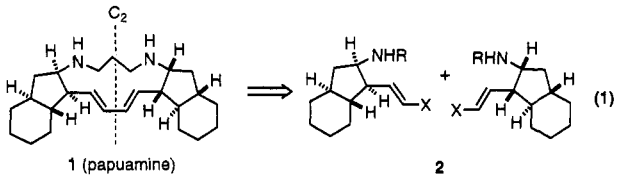
Received July 22, 1994

Papuamine is a marine alkaloid isolated in 1988 from *Haliclona sp.*, a sponge collected in Papua, New Guinea.[1,2] The compound was determined by spectral analysis to have the unprecedented pentacyclic C_2-symmetric structure **1**. Papuamine was found to possess antifungal activity against *Trichophyton mentagrophytes*. A total synthesis of the enantiomer of papuamine has very recently been reported by Barrett and co-workers.[3] In this communication we describe an enantioselective total synthesis of the natural antipode of this unique natural product utilizing a novel imino ene reaction as a key step.

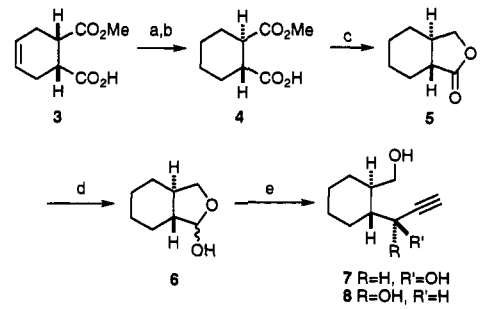


1 (papuamine) 2 (1)

The symmetry elements in papuamine (**1**) suggested to us an approach involving homocoupling of an enantiomerically pure system **2** (eq 1). Our starting material for the synthesis of this fragment was the known acid ester **3**, which can be prepared optically pure by PLE-catalyzed partial hydrolysis of the corresponding meso diester.[4] Hydrogenation of **3** followed by base-catalyzed epimerization of the methyl ester moiety yielded *trans*-acid ester **4** (Scheme 1). Since the absolute stereochemistry of papuamine had not been established,[1,3] we decided to arbitrarily synthesize the enantiomer of the alkaloid shown in structure **1**. Therefore, the ester group of **4** was reduced by a Bouveault–Blanc reduction,[5] leading to γ-lactone **5**.[6] This compound was first reduced to lactol **6**, and addition of ethynylmagnesium bromide subsequently led to a chromatographically separable 1:1 mixture of alcohols **7** and **8**. The stereochemistry of isomer **7** was established by X-ray crystallography.

Propargyl alcohol **8** was then converted to trityl ether acetate **9** (Scheme 2). Using methodology developed by Fleming and Terrett,[7] acetate **9** was stereospecifically transformed to allenyl silane **10** via S_N2' anti addition of a silyl cuprate reagent. Homologation of the primary alcohol group of **10** gave nitrile **11**, which was reduced to allenylsilane aldehyde **12**. Using an identical

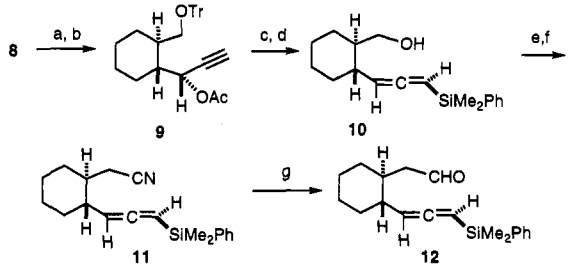
Scheme 1[a]



3 4 5 6 7 R=H, R'=OH 8 R=OH, R'=H

[a] (a) 10% Pd/C, EtOH, 15 psi H_2, 99%; (b) NaOMe, MeOH, reflux, 5 days, 96%; (c) Na/NH_3, EtOH, 70%; (d) DibalH, PhMe, –78 °C, 95%; (e) ethynylmagnesium bromide, THF, 0 °C, 95%.

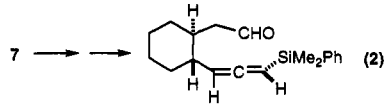
Scheme 2[a]



9 10 11 12

[a] (a) Ph_3CCl, DMAP, NEt_3, DMF, 45 °C, 18 h, 95%; (b) Ac_2O, DMAP, NEt_3, CH_2Cl_2, room temperature, 16 h, 99%; (c) $Me_2PhSiLi$, CuCN, THF, –78 °C 88%; (d) TsOH, MeOH, room temperature 3 h, 97%; (e) MsCl, NEt_3, CH_2Cl_2, room temperature, 14 h, 99%; (f) KCN, DMSO 45 °C, 2 days, 70%; (g) DibalH, PhMe, –78 to 0 °C, 77%.

sequence of reactions, epimeric propargyl alcohol **7** was cleanly converted to diastereomeric allenylsilane aldehyde **13** (eq 2).



(2)

13

It was our intention to utilize the methodology of Danheiser, involving cyclization of an imine/allenylsilane to produce a homopropargylamine as a precursor to **2**.[8] Therefore, allenylsilane aldehyde **12** was converted to the corresponding imine with benzylamine and then treated with stannic chloride to afford cyclized silylacetylene **15** as a single stereoisomer (Scheme 3). The structure and stereochemistry of this product were established by desilylation to acetylene **16**, whose hydrochloride salt was subjected to X-ray crystal structure analysis. Compound **16** possesses the requisite configuration for papuamine (**1**) (cf. **2**).

The high stereospecificity of this cyclization, along with the fact that a silyl group is present in the alkyne product, indicates that this transformation cannot be proceeding via a stepwise, ionic mechanism of the Danheiser type.[8] Rather, we believe that, in fact, the cyclization occurs by a novel imino ene process, a relatively rare type of pericyclic reaction.[9,10] Thus, due to the "twist" in the allene, conformation **14** of the iminium complex is properly aligned for concerted hydrogen transfer and C–C bond formation, leading to the observed product **15**. Further support for this pericyclic mechanism is provided by the fact that simply heating the *N*-benzyl imine derived from **12** in refluxing

† Author to be contacted regarding X-ray determinations.

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

(2) For a closely related alkaloid, haliclonadiamine, see: Fahy, E.; Molinski, T. F.; Harper, M. K.; Sullivan, B. W.; Faulkner, D. J.; Parkany, L.; Clardy, J. *Tetrahedron Lett.* **1988**, *29*, 3427.

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

(4) Kobayashi, S.; Kamiyama, K.; Ohno, M. *Chem. Pharm. Bull.* **1990**, *38*, 350.

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

(6) The enantiomer of lactone **5** has also been synthesized by reduction of the acid moiety of **4** with diborane.

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

(8) Danheiser, R. L.; Carini, D. J.; Kwasigroch, C. A. *J. Org. Chem.* **1986**, *51*, 3870. Danheiser, R. L.; Kwasigroch, C. A.; Tsai, Y.-M. *J. Am. Chem. Soc.* **1985**, *107*, 7233.

(9) For lead references to imino ene reactions, see: Laschat, S.; Grehl, M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 458.

(10) For an example of an intermolecular imino ene reaction of an allene, see: Baumann, H.; Duthaler, R. O. *Helv. Chim. Acta* **1988**, *71*, 1025.

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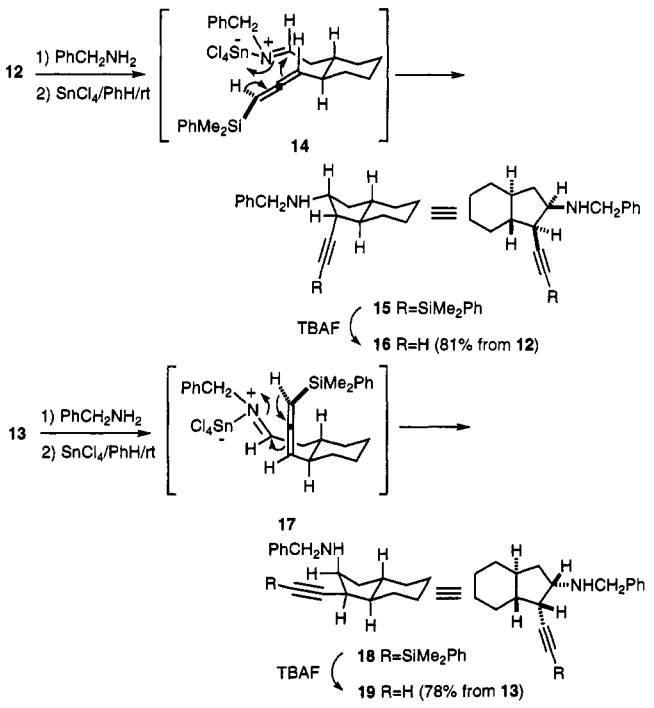
Scheme 3



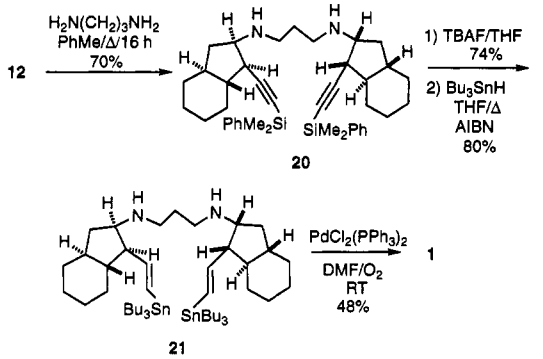
toluene in the absence of a Lewis acid also produces **15** stereospecifically.

Additional confirmation of the imino ene mechanism was provided by conducting the cyclization with diastereomeric allenylsilane aldehyde **13**. Conversion of this compound to its *N*-benzyl imine, followed by exposure to stannic chloride, cleanly led to silylacetylene **18**. The stereochemistry of this compound was confirmed by X-ray analysis of the hydrochloride of the desilylated acetylene **19**. Formation of **18** is best rationalized as proceeding in this case via conformation **17** of the imine Lewis acid complex, again through a concerted ene process. Once again, thermolysis of the *N*-benzyl imine also stereospecifically afforded cyclization product **18**.[11]

Although ene product **15** could, in principle, be used to prepare the desired papuamine intermediate **2**, we decided to explore a shorter, more convergent approach to the alkaloid. Therefore, allenylsilane aldehyde **12** was refluxed in toluene with 0.5 equiv of propylenediamine to stereospecifically yield tetracyclic bis-silylacetylene **20** in good yield via a double imino ene reaction (Scheme 4). Subsequent desilylation of **20** followed by addition of tributyltin hydride to the terminal acetylene units afforded

(11) This type of intramolecular allenylsilane/imine ene reaction appears to be general, and additional examples will be reported in due course.

Scheme 4



bis-(*E*)-vinylstannane **21**.[12] Finally, intramolecular coupling of **21** using Pd^{II} catalysis[13] afforded papuamine (**1**), isolated as a salt by preparative TLC,[14] which can be converted to the free base by passing it through an Amberlite IR-400 (OH) ion exchange column[15] in methanol (48% yield based on recovered bis-stannane **21**). This material had ^1H and ^{13}C NMR spectra and TLC indistinguishable from those of the natural product.[16,17] Comparison of the optical rotation of the free base of synthetic papuamine with that reported for the natural material[1,17] indicated that the alkaloid has the absolute configuration shown in **1**.[18]

Acknowledgment. We are grateful to the National Institutes of Health for financial support with Grant CA-34303. We also thank Professor Raymond Funk for helpful discussions.

Supplementary Material Available: Experimental procedures and spectral data for all new compounds, as well as ORTEP drawings for compounds **7**, **16**·HCl, and **19**·HCl (81 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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

(13) Kanemoto, S.; Matsubara, S.; Oshima, K.; Utimoto, K.; Nozaki, H. *Chem. Lett.* **1987**, 5. Liebeskind, L. S.; Riesinger, S. W. *Tetrahedron Lett.* **1991**, *32*, 5681.

(14) Inexplicably, a salt was produced here despite care not to expose the material to acid. This salt, whose composition is presently unknown, has ^1H and ^{13}C NMR spectral data virtually identical with those of the hydrochloride of papuamine.[1,15]

(15) Prepared also by HPLC of the salt on a Waters Porasil column eluting with $EtOAc/NEt_3$ (95/5).

(16) We are grateful to Professor Paul Scheuer for a TLC sample of **1** and copies of the ^1H and ^{13}C NMR spectra of papuamine and its hydrochloride.

(17) For data, see supplementary material.

(18) Presented at the 207th National Meeting of the American Chemical Society; San Diego, CA, March 15, 1994, paper 211.