Stereocontrolled Synthesis of the Tetracyclic Core of the Bisguanidine Alkaloids Palau'amine and Styloguanidine

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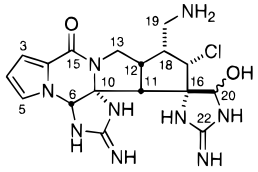
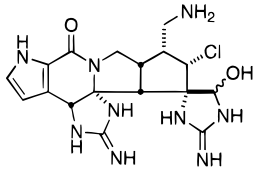
A diversity of structurally novel secondary metabolites is found in sponges.[2] Among the most remarkable is palau'amine (**1**), which was isolated by Kinnel, Gehrken, and Scheuer from a sponge (*Stylotella agminata*) collected in the Western Caroline Islands.[3] The unprecedented hexacyclic bisguanidine structure of palau'amine was proposed following extensive mass spectral and NMR investigations.[4] Two years later, the isomeric alkaloid styloguanidine (**2**), two brominated analogs, and palau'amine were reported from a sponge (*Stylotella aurantinium*) collected in the Yap sea.[5] Palau'amine is reasonably nontoxic, exhibits



palau'amine (**1**)

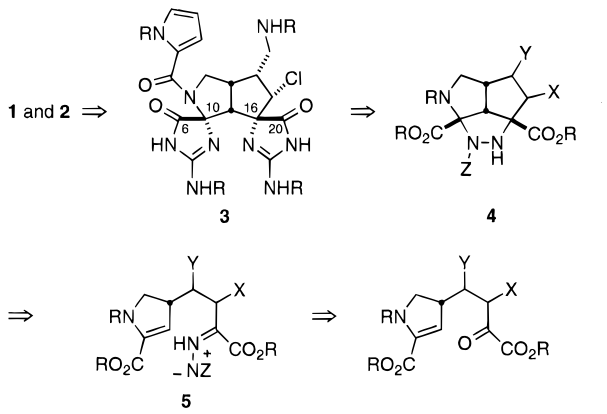


styloguanidine (**2**)

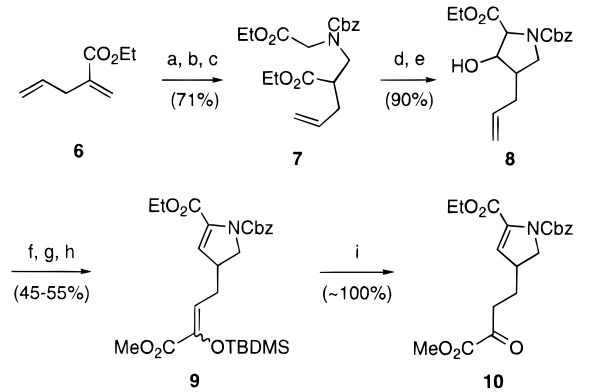
cytotoxic, antibiotic, antifungal activities and shows particularly striking immunomodulatory activity;[3] styloguanidine is a powerful chitinase inhibitor.[5] Palau'amine is stable in acid; however, it decomposes rapidly above pH 6.5.[3] This instability, and the complex hexacyclic constitution of palau'amine and styloguanidine, renders these marine alkaloids daunting total synthesis targets.[6] Much of their structural complexity resides in the central 3-azabicyclo[3.3.0]octane ring system, particularly the cyclopentane ring which is substituted on the α face at each carbon. This density of functionality and the stereochemical relationship of the two spirocyclic guanidine subunits present a formidable challenge to synthesis. In this paper, we report a concise strategy for assembling the central *cis*-3-azabicyclo-[3.3.0]octane core of palau'amine and styloguanidine in which the critical stereochemical relationship between the ring fusion stereocenters C-11 and C-12 and the two spiro guanidine units (C-10 and C-16) is established by an intramolecular azomethine imine cycloaddition.[7,8]

Disconnection of the linkage between C-6 and the 2-acylpyrrole unit of palau'amine (**1**) and styloguanidine (**2**) and adjustment of the oxidation state of carbons 6 and 20 afford **3**, a pentacyclic intermediate that could serve as a common precursor of **1** and **2** (Scheme 1). A formidable challenge in constructing **3** is relating the orientation of the two spiro guanidine units and the *cis*-3-azabicyclo[3.3.0]octane unit. Our approach to palau'amine and styloguanidine is driven by the perception that this stereorelationship could be established through intramolecular cycloaddition of azomethine imine **5** to form triazahexahydrotriquinacene **4**.[9] In order to facilitate initial investigations of this pivotal intramolecular cycloaddition step, we chose to investigate the sequence depicted in Scheme 1 in a model series that lacks functionality (X and/or Y) which would eventually be required for introduction of the aminomethyl and chloride substituents.

Scheme 1



Scheme 2[a]



[a] Key: (a) $H_2NCH_2CO_2Na$, EtOH, reflux; (b) H_2SO_4, EtOH, reflux; (c) CbzCl, Et_3N; (d) ^tBuOK, THF, −78 °C; (e) $NaBH_4$, EtOH; (f) MsCl, Et_3N, DMAP, C_6H_6, 0 °C; (g) O_3, CH_2Cl_2; Ph_3P; (h) LiCl, DBU, MeCN, $(MeO)_2POCH(OTBDMS)CO_2Me$; (i) CsF, AcOH, MeCN.

In our initial survey, α-keto ester cycloaddition substrate **10** was assembled by the sequence summarized in Scheme 2. Conjugate addition of the sodium salt of glycine to ethyl (2-allyl)acrylate (**6**),[10] followed by Fisher esterification and protection of nitrogen with a benzyloxycarbonyl group, delivered **7**. Dieckmann cyclization[11] of **7** and subsequent reduction[12] of the β-keto ester product provided pyrrolidine **8** in good yield. Reaction of **8** with methanesulfonyl chloride, followed by direct

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(2) Faulkner, D. J. *Nat. Prod. Rep.* **1996**, *13*, 75 and earlier reviews in this series.

(3) Kinnel, R. B.; Gehrken, H.-P.; Scheuer, P. J. *J. Am. Chem. Soc.* **1993**, *115*, 3376.

(4) Palau'amine isolated from *S. agminata* is levorotatory; however, the absolute stereochemistry is unknown.

(5) Kato, T.; Shizuri, Y.; Izumida, H.; Yokoyama, A.; Endo, M. *Tetrahedron Lett.* **1995**, *36*, 2133.

(6) The tetracyclic skeleton defined by carbons 1−15 of **1** and **2** is found in the marine alkaloid dibromophakellin. For a pioneering synthesis of this simpler marine metabolite, see: Foley, L. H.; Büchi, G. *J. Am. Chem. Soc.* **1982**, *104*, 1776.

(7) (a) Oppolzer, W. *Tetrahedron Lett.* **1970**, *35*, 3091. (b) For a brief review of intramolecular azomethine ylide cycloadditions, see: Wade, P. A. Intramolecular 1,3-Dipolar Cycloadditions. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: London, 1991; Vol. 4, pp 1144−49.

(8) For the seminal use of intramolecular azomethine imine cycloadditions for the synthesis of guanidine alkaloids, see: (a) Jacobi, P. A.; Martinelli, M. J.; Polanc, S. *J. Am. Chem. Soc.* **1984**, *106*, 5595. (b) Jacobi, P. A.; Brownstein, A.; Martinelli, M.; Grozinger, K. *J. Am. Chem. Soc.* **1981**, *103*, 239. (c) Martinelli, M. J.; Brownstein, A. D.; Jacobi, P. A.; Polanc, S. *Croat. Chem. Acta* **1986**, *59*, 267.

(9) For the construction of diazahexahydrotriquinacenes by intramolecular azomethine ylide cycloadditions, see: Overman, L. E.; Tellew, J. E. *J. Org. Chem.* **1996**, *61*, 8338.

(10) Helquist, P.; Yu, L. C. *J. Org. Chem.* **1981**, *46*, 4536.

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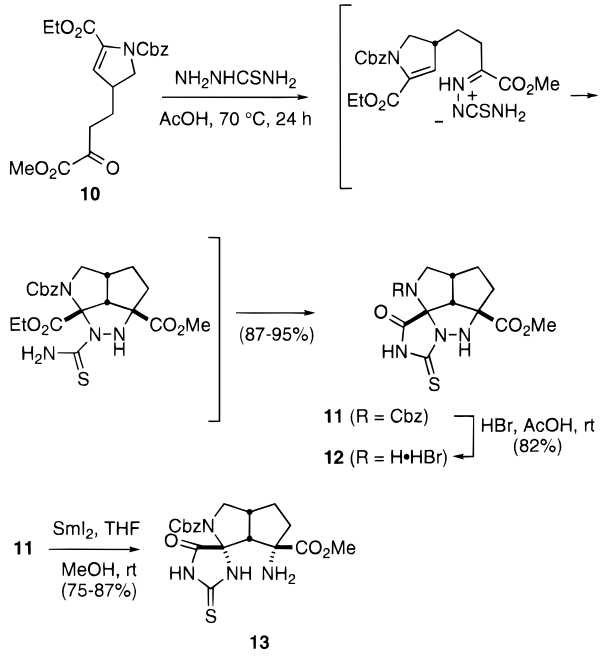
Scheme 3

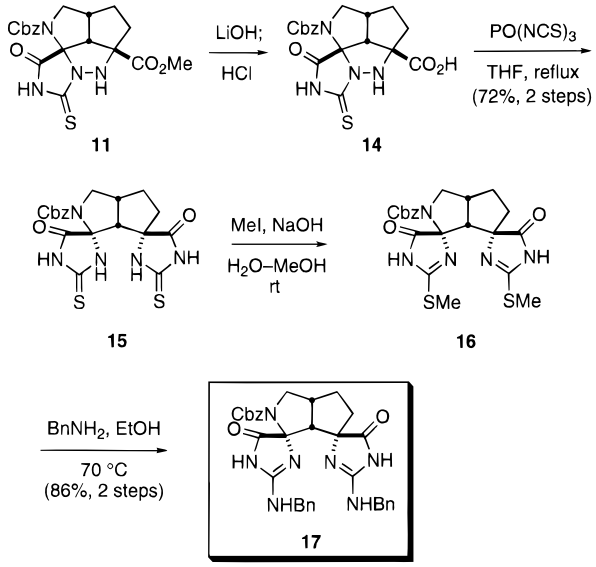


ozonolysis of the somewhat unstable crude mesylate derivative, yielded the corresponding aldehyde, which was directly condensed with methyl 2-(*tert*-butyldimethylsiloxy)-2-(dimethylphosphono)acetate[13] in the presence of excess 1,8-diazobicyclo-[5.4.0]undec-7-ene (DBU) and LiCl.[14] This three-step sequence provided dihydropyrrole **9** in 50% overall yield. Desilylation of **9** with CsF provided racemic α-keto ester **10** in high yield.

When an acetic acid solution of **10** and thiosemicarbazide (3 equiv) was heated at 70 °C, intramolecular cycloaddition and subsequent acylation took place smoothly to deliver tetracycle **11** in excellent yield (Scheme 3). In this pivotal step, the single stereogenic center of **10** directs formation of the three additional stereocenters in **11**. Treatment of **11** at room temperature with HBr in AcOH provided the crystalline hydrobromide salt **12**, whose structure was confirmed by single-crystal X-ray diffraction analysis.[15] Cleavage of the N−N bond of **11** proceeded smoothly in the presence of 2 equiv of SmI_2 in THF−MeOH (9:1) to yield tricyclic α-amino ester **13**, whose constitution was also established by single-crystal X-ray diffraction analysis.[15,16]

Initial attempts to fashion a second spiro thiohydantoin from the α-amino ester functionality of **11** by reaction with an isothiocyanate followed by base-promoted cyclization proved unproductive.[17] However, hydrolysis of ester **11** and subsequent treatment of carboxylic acid **14** with 2.5 equiv of phosphoryl isothiocyanate[18] in refluxing THF provided bis(thiohydantoin) **15** in 72% overall yield from **11** (Scheme 4). Not only had

Scheme 4



reaction of **14** with phosphoryl isothiocyanate fashioned the second thiohydantoin ring but it also accomplished reductive cleavage of the N−N bond.[19,20] Finally, the two spiro thiohydantoins were efficiently converted into the desired bis-(acylguanidine) units of **17** by sequential reaction of **15** with MeI and benzylamine.[21]

In conclusion, a concise approach to the total synthesis of the complex hexacyclic bisguanidine alkaloids palau'amine (**1**) and styloguanidine (**2**) has been defined in a model series. The central step is an intramolecular azomethine imine cycloaddition, **10** → **11**, which fashions the *cis*-3-azabicyclo[3.3.0]octane and two pendant spiro guanidine units with complete stereocontrol. Current efforts focus on elaborating this strategy to realize a comprehensive solution to the total synthesis challenge posed by **1** and **2**.

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Supporting Information Available: Characterization data and preliminary experimental procedures for preparing compounds **7**−**12**, **15**, and **17** (5 pages). See any current masthead page for ordering and Internet access instructions.

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(15) Crystallographic data for this compound has been deposited with the Cambridge Crystallographic Data Centre. The coordinates can be obtained on request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.

(16) Freshly prepared SmI_2 was required to obtain reproducible yields for this reaction.

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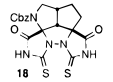
(19) To our knowledge, this is the first use of phosphoryl isothiocyanate to form thiohydantoins from α-amino acids; however, this reagent has previously been used to prepare acyl isothiocyanates from simple carboxylic acids.[18]

(20) At this point only speculation can be advanced regarding the mechanism of this unexpected reduction. We would note that the N−N bond of **14**, or potential pentacyclic intermediate **18**, would be significantly weakened by ring strain. Whether the reductant is thiocyanate or a trivalent phosphorous species is under investigation.



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