CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200900622

Toward Palau′amine: $Hg(OTf)_2$-Catalyzed Synthesis of the Cyclopentane Core

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The pyrrole–imidazole alkaloids, which comprise a large family of natural products, have received a great deal of attention due to their potent biological activities and tremendous structural diversity.[1] Palau′amine (**1**) was originally isolated from a sponge, *Stylotella agminata*, in 1993 by Scheuer as a novel class of the pyrrole–imidazole alkaloid.[2] Since the initial disclosure of its proposed structure (**1a**), palau′amine (**1**; Figure 1) has been an attractive synthetic target because of its intriguing molecular architecture and significant biological properties such as antifungal, antitumor, and immunosuppressive activities. However, according to several groups, the originally proposed structure **1a** was recently revised as **1b**, which instead possesses the indicated the *trans*-D/E ring junction and the β-chlorine substituent.[3,5e,g] The noteworthy structural features of palau′amine include: two guanidine moieties, a fused polycyclic system with a spiro cycle, a fully substituted complex cyclopentane ring, and eight contiguous stereogenic centers including a nitrogen-substituted quaternary carbon center.

Not surprisingly, many attempts to synthesize palau′amine and related natural products have been reported so far,[4,5] and the first total synthesis of the related natural products axinellamines A/B (**2**)[6a,b] and massadine/massadine chloride[6c] was recently accomplished. However, a total synthesis of palau′amine itself has not yet been reported. Efficient construction of the complex cyclopentane core with the correct stereochemistry at each carbon center, including a quaternary carbon center, is definitely one of the most difficult synthetic challenges of the synthesis of palau′amine. Herein, we describe an efficient synthesis of the cyclopentane core of palau′amine by the application of a highly efficient novel $Hg(OTf)_2$-catalyzed cyclization reaction developed in our laboratory.[7] In 2008, the $Hg(OTf)_2$-catalyzed alkyne cyclization method was extended to the alkene cyclization reactions of allylic alcohols and vinyl methyl ethers which, after cyclization, undergo a smooth proto-demercuration to give the cyclized products and the regenerated the $Hg(OTf)_2$ catalyst.[8] For instance, the $Hg(OTf)_2$-catalyzed cyclization of *N*-tosylanilino allylic alcohol **3** provided 2-vinylindolines **4** in high yield (Scheme 1).[8b] Thus, the cyclization of cyclopentylidene alcohol **5** could potentially give **6**, simultaneously constructing a quaternary carbon center that corresponds to the C16 of palau′amine. However, the alternative cyclization mode of amide **5** is also possible, which gives the *O*-cyclized product **7** in preference to the *N*-cyclized product **6**. Indeed, we confirmed that this was the case. Conventionally, *N*-selective cyclization of amide has been achieved by the cumbersome substrate modifications, addition of strong

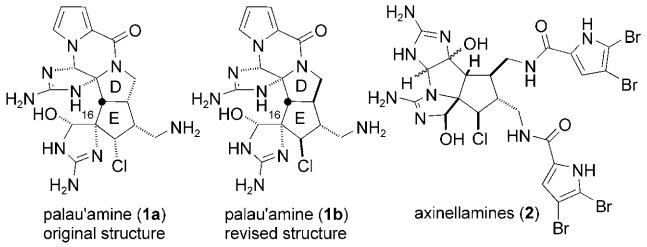

Figure 1. Structure of palau′amine (original and revised structures) and axinellamines (**2**).

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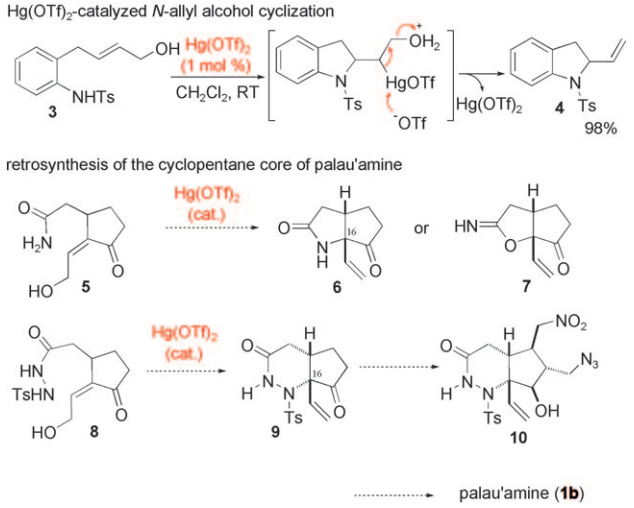
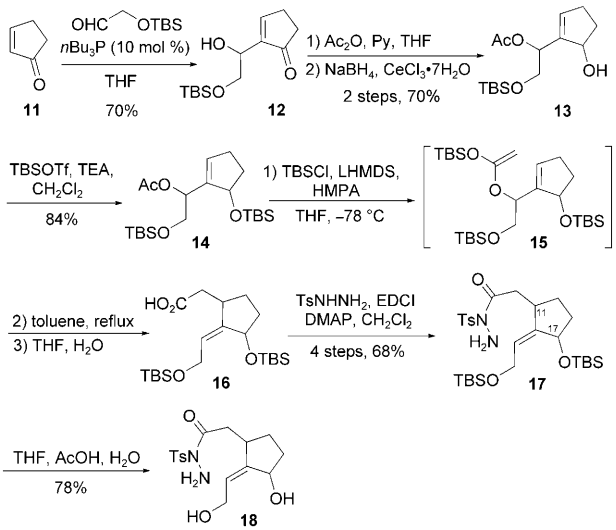
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200900622.

Lewis acids and/or strong base, or the formation of an *N*-radical.[9] Moreover, the catalytic cyclization method, which simultaneously creates a quaternary carbon center, has not yet been established. Therefore, we designed an acyl tosylhydrazide **8** as a simple substitute of the primary amides **5** for the $Hg(OTf)_2$-cataylized cyclization. The vinyl lactam **9**, prepared by the $Hg(OTf)_2$-catalyzed cyclization of **8**, could serve as an excellent precursor for the cyclopentane core **10**. Introduction of the two CH_2-N side chains to lactam **9** finishes the construction of **10** (Scheme 1).



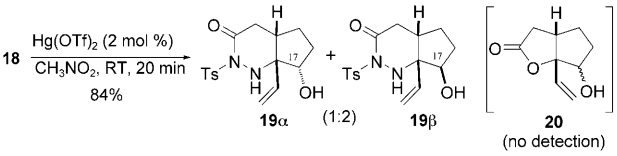
Scheme 1. $Hg(OTf)_2$-catalyzed cyclization of allylic alcohol and synthetic design of palau′amine cyclopentane core **10**.

Our synthesis started with a Morita-Baylis–Hillman reaction of the two commercially available compounds, 2-cyclopentene-1-one (**11**) and (*tert*-butyldimethylsilyloxy)acetaldehyde, to afford **12** in 70% yield (Scheme 2). Compound **12** was subsequently converted to a 1:2 diastereomeric mixture of the acetates **14** by a sequential operation of acetylation, a Luche reduction,[10] and a TBS protection. Without separation, the diastereomeric mixture of the acetates **14** was subjected to an Ireland–Claisen rearrangement.[11,12] After the treatment of **14** with LHMDS/TBSCl/HMPA in THF at −78 °C, refluxing in toluene induced the desired Ireland–Claisen rearrangement to afford the cyclopentylidene carboxylic acid **16** via **15** in good yield. The double bond geometry of **16** was determined to be *Z* by the NOE experiment of its amide derivative. Next, we attempted to prepare an acyl tosylhydrazide by the coupling of **16** with *N*-tosylhydrazide by the combined action of EDCI and DMAP in dichloromethane. Surprisingly, the nitrogen atom masked with a tosyl group participated in the condensation to give a 1:2 diastereomeric mixture of **17** in 68% overall yield after four steps from **14**. Presumably, the nucleophilicity of the more basic primary amine was attenuated due to the protonation by the HCl derived from an EDCI-HCl salt.[13] The TBS groups were then cleaved under mild acidic conditions to give diol **18** (Scheme 2).



Scheme 2. Synthesis of hydrazide **18**.

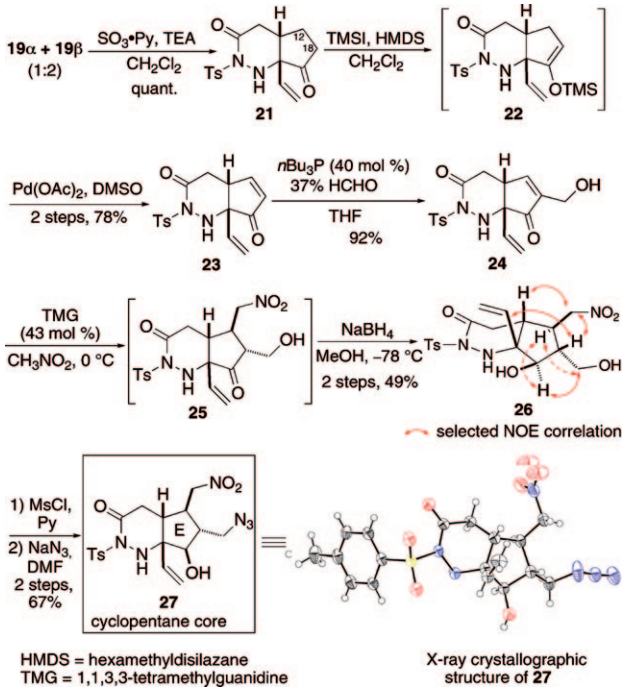
Treatment of **18** with 2 mol% of $Hg(OTf)_2$ in nitromethane at room temperature smoothly afforded **19α** and **19β** in 84% yield as a separable 1:2 diastereomeric mixture (Scheme 3). The lactone **20** was not detected. Stereochemical outcome at the ring junction was completely controlled to be *cis* regardless of the stereochemistry of the secondary alcohol at C17. The structures of **19α** and **19β** were unambiguously confirmed by an X-ray diffraction study and NOE studies (see the Supporting Information).[14] We thus established an efficient $Hg(OTf)_2$-catalyzed protocol of *N*-selective cyclizations of *N*-acyl compounds, which is difficult to achieve using the conventional combinations of substrates and methods.[15]



Scheme 3. $Hg(OTf)_2$-catalyzed allyl alcohol cyclization of acylhydrazide.

Having prepared a sufficient amount of the *N*-cyclized product **19**, we attempted to complete the construction of the cyclopentane core of palau′amine. SO_3·pyridine oxidation of the mixture of **19α** and **19β** gave the ketone **21** in quantitative yield.[16] Direct oxidation of **21** to enone **23** using IBX[17] or selenium dioxide was not successful. Neither was oxidation of **21** via its enolate using selenium halide, sulfinimidoyl chloride,[18] or NBS. Although the preparation of the silyl enol ether was initially difficult, a combination of TMSI and hexamethyldisilazane in dichloromethane was later found to give trimethylsilyl enolether **22** in quantitative yield.[19,20] Saegusa–Ito oxidation of **22** provided enone **23** in good yield.[21] A Morita-Baylis–Hillman reaction of **23** with formaldehyde gave alcohol **24** in excellent yield. Subsequent

1,4-addition of nitromethane in the presence of a catalytic amount of 1,1,3,3-tetramethylguanidine (TMG) afforded the desired 1,4-adduct **25**.[22] We found that **25** was readily underwent dehydration during column chromatography purification to give the exomethylene product. Therefore, the crude **25** was directly subjected to reduction with $NaBH_4$ to give **26**. The stereochemistry of **26** was confirmed to be as we planned for our palau′amine synthesis by an NOE experiment. Finally, the primary alcohol of **26** was converted to azide **27**, which is the targeted cyclopentane core intermediate of palau′amine. The structure of **27** was unequivocally established by an X-ray diffraction study (Scheme 4 and the Supporting Information).[23]



Scheme 4. Synthesis and X-ray crystallographic structure of **27**.

In summary, we have developed a selective $Hg(OTf)_2$-catalyzed *N*-cyclization protocol of acyl tosylhydrazide and established an efficient route to the cyclopentane **27**, our E ring synthetic intermediate of palau′amine, featuring this novel $Hg(OTf)_2$-catalyzed cyclization as a key reaction. Furthermore, our current study clearly demonstrated that this catalytic *N*-cyclization protocol of acyl tosylhydrazide is applicable for the construction of a quaternary carbon center and is a powerful synthetic method for the construction of natural products-like complex carbon frameworks. Total synthesis of palau′amine, one of the most challenging synthetic targets in the last decade, is currently underway in our laboratory.

Experimental Section

Experimental details, full data, ^1H and ^{13}C NMR spectra of each intermediate from **11** to **27**, and data of X-ray analysis are available in the Supporting Information.

Acknowledgements

This work was supported by Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology of Japanese Government, MEXT. HAITEKU, 2003–2007, and the Global COE Program (Project No. B01: Catalysis as the Basis for Innovation in Materials Science). We acknowledge financial support from the National Institutes of Health (NIH Grant GM068011 to R.M.W. and K.N., Colorado State University). K.N. is grateful to Astellas Co., Inc. and JSPS, for a Research Fund for Young Scientists.

Keywords: alkaloids · cyclization · natural products · palau′amine

[1] For recent reviews on this family of natural products, see: a) A. Al Mourabit, P. Potier, *Eur. J. Org. Chem.* **2001**, 237–243; b) Z. Jin, *Nat. Prod. Rep.* **2006**, *23*, 464–496; c) M. Köck, A. Grube, I. B. Seiple, P. S. Baran, *Angew. Chem.* **2007**, *119*, 6706–6714; *Angew. Chem. Int. Ed.* **2007**, *46*, 6586–6594.

[2] a) R. B. Kinnel, H.-P. Gehrken, P. J. Scheuer, *J. Am. Chem. Soc.* **1993**, *115*, 3376–3377; b) R. B. Kinnel, H.-P. Gehrken, R. Swali, G. Skoropowski, P. J. Scheuer, *J. Org. Chem.* **1998**, *63*, 3281–3286.

[3] a) A. Grube, M. Köck, *Angew. Chem.* **2007**, *119*, 2372–2376; *Angew. Chem. Int. Ed.* **2007**, *46*, 2320–2324; b) M. S. Buchanan, A. R. Carroll, R. Addelpalli, V. M. Avery, J. N. Hooper, R. J. Quinn, *J. Org. Chem.* **2007**, *72*, 2309–2317; c) H. Kobayashi, K. Kitamura, K. Nagai, Y. Nakao, N. Fusetani, R. W. M. van Soest, S. Matsunaga, *Tetrahedron Lett.* **2007**, *48*, 2127–2129; d) M. S. Buchanan, A. R. Carroll, R. J. Quinn, *Tetrahedron Lett.* **2007**, *48*, 4573–4574.

[4] For recent reviews of synthetic studies towards palau′amine, see: a) H. Hoffman, T. Lindel, *Synthesis* **2003**, 1753–1783; b) D. E. N. Jacquot, T. Lindel, *Curr. Org. Chem.* **2005**, *9*, 1551–1565; c) H.-D. Arndt, A. M. Riedrich, *Angew. Chem.* **2008**, *120*, 4864–4867; *Angew. Chem. Int. Ed.* **2008**, *47*, 4785–4788.

[5] For recent advances toward Palau' amine not cited in ref. [4], see: a) H. Garrido-Hernandez, M. Nakadai, M. Vimolratana, Q. Y. Li, T. Doundoulakis, P. G. Harran, *Angew. Chem.* **2005**, *117*, 775–779; *Angew. Chem. Int. Ed.* **2005**, *44*, 765–769; b) S. Wang, A. Dilley, K. G. Poullennec, D. Romo, *Tetrahedron* **2006**, *62*, 7155–7161; c) X. Tan, C. Chen, *Angew. Chem.* **2006**, *118*, 4451–4454; *Angew. Chem. Int. Ed.* **2006**, *45*, 4345–4348; d) D. P. O′Malley, K. Li, M. Maue, A. L. Zografos, P. S. Baran, *J. Am. Chem. Soc.* **2007**, *129*, 4762–4775; e) B. A. Lanman, L. E. Overman, R. Pulini, N. S. White, *J. Am. Chem. Soc.* **2007**, *129*, 12896–12900; f) R. Sivappa, N. M. Hernandez, Y. He, C. J. Lovely, *Org. Lett.* **2007**, *9*, 3861–3864; g) M. A. Zancanella, D. Romo, *Org. Lett.* **2008**, *10*, 3685–3688; h) M. S. Bultman, J. Ma, D. Y. Gin, *Angew. Chem.* **2008**, *120*, 6927–6930; *Angew. Chem. Int. Ed.* **2008**, *47*, 6821–6824; i) J. Hudon, T. A. Cernak, J. A. Ashenhurst, J. L. Gleason, *Angew. Chem.* **2008**, *120*, 9017–9020; *Angew. Chem. Int. Ed.* **2008**, *47*, 8885–8888.

[6] a) J. Yamaguchi, I. B. Seiple, I. S. Young, D. P. O′Malley, M. Maue, P. S. Baran, *Angew. Chem.* **2008**, *120*, 3634–3636; *Angew. Chem. Int. Ed.* **2008**, *47*, 3578–3580; b) D. P. O′Malley, J. Yamaguchi, I. S. Young, I. B. Seiple, P. S. Baran, *Angew. Chem.* **2008**, *120*, 3637–3639; *Angew. Chem. Int. Ed.* **2008**, *47*, 3581–3583; c) S. Su, I. B. Seiple, I. S. Young, P. S. Baran, *J. Am. Chem. Soc.* **2008**, *130*, 16490–16491.

[7] a) M. Nishizawa, V. K. Yadav, M. Skwarczynski, H. Takao, H. Imagawa, T. Sugihara, *Org. Lett.* **2003**, *5*, 1609–1611; b) M. Nishizawa, H. Takao, V. K. Yadav, H. Imagawa, T. Sugihara, *Org. Lett.* **2003**, *5*, 4563–4565; c) H. Imagawa, T. Kurisaki, M. Nishizawa, *Org. Lett.* **2004**, *6*, 3679–3681; d) H. Imagawa, T. Iyenaga, M. Nishizawa, *Org. Lett.* **2005**, *7*, 451–453; e) H. Imagawa, T. Iyenaga, M. Nishizawa, *Synlett* **2005**, 703–705; f) H. Yamamoto, M. Nishiyama, H. Imagawa, M. Nishizawa, *Tetrahedron Lett.* **2006**, *47*, 8369–8373; g) H. Yamamoto, I. Sasaki, H. Imagawa, M. Nishizawa, *Org. Lett.* **2007**, *9*, 1399–1402; h) H. Yamamoto, G. Pandey, Y. Asai, M. Nakano, A. Kinoshita, K. Namba, H. Imagawa, M. Nishizawa, *Org. Lett.* **2007**, *9*, 4029–4032.

[8] a) K. Namba, H. Yamamoto, I. Sasaki, K. Mori, H. Imagawa, M. Nishizawa, *Org. Lett.* **2008**, *10*, 1767–1770; b) K. Namba, Y. Nakagawa, H. Yamamoto, H. Imagawa, M. Nishizawa, *Synlett* **2008**, 1719–1723.

[9] a) S. Knapp, K. E. Rodriques, A. T. Levorse, R. M. Ornaf, *Tetrahedron Lett.* **1985**, *26*, 1803–1806; b) O. Kitagawa, M. Fujita, H. Li, T. Taguchi, *Tetrahedron Lett.* **1997**, *38*, 615–618; c) P. Gaudreault, C. Drouin, J. Lessard, *Can. J. Chem.* **2005**, *83*, 543–545; d) R. D. Richardson, J. M. Zayed, S. Altermann, D. Smith, T. Wirth, *Angew. Chem.* **2007**, *119*, 6649–6652; *Angew. Chem. Int. Ed.* **2007**, *46*, 6529–6532; e) E. J. Corey, Y.-Y. Yeung, *Tetrahedron Lett.* **2007**, *48*, 7567–7570.

[10] J. L. Luche, *J. Am. Chem. Soc.* **1978**, *100*, 2226–2227.

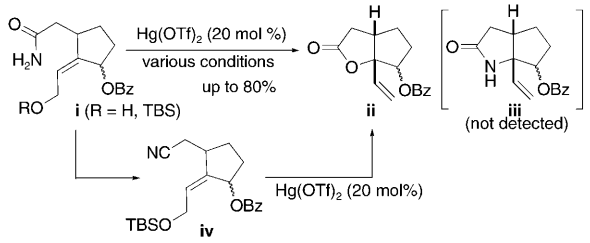
[11] The direct *ortho*-ester Claisen rearrangement of **11** resulted in the formation of a complex mixture formation. For a related successful example, see: C. Chapuis, G. H. Büchi, H. Wüest, *Helv. Chim. Acta* **2005**, *88*, 3069–3088.

[12] R. E. Ireland, R. H. Mueller, A. K. Willard, *J. Am. Chem. Soc.* **1976**, *98*, 2868–2877.

[13] Generalization of this hydrazide formation is currently under investigation.

[14] CCDC 711310 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

[15] The $Hg(OTf)_2$-catalyzed cyclization of the primary amides **i** afforded only lactone **ii**, and lactam **iii** was not detected at all under a variety of reaction conditions examined (solvent effect or addition of Lewis acids). The reaction of nitrile **iv** did not afford lactam **iii**, either.



[16] Oxidation with Dess–Martin periodinane resulted in modest yield.

[17] a) K. C. Nicolaou, T. Montagnon, P. S. Baran, *Angew. Chem.* **2002**, *114*, 1035–1038; *Angew. Chem. Int. Ed.* **2002**, *41*, 993–996; b) K. C. Nicolaou, D. L. F. Gray, T. Montagnon, S. Harrison, *Angew. Chem.* **2002**, *114*, 1038–1042; *Angew. Chem. Int. Ed.* **2002**, *41*, 996–1000.

[18] T. Mukaiyama, J. Matsuo, H. Kitagawa, *Chem. Lett.* **2000**, 1250–1251.

[19] M. E. Kuehne, W. G. Bornmann, W. H. Parsons, T. D. Spitzer, J. F. Blount, J. Zubieta, *J. Org. Chem.* **1988**, *53*, 3439–3450.

[20] Other conditions such as LHMDS/TMSCl/THF, large excess of LHMDS/TMSCl/THF, LDA/TMSCl/THF, TEA/TMSCl/CH_2Cl_2, TEA/TBSOTf/CH_2Cl_2, TEA/TESOTf/CH_2Cl_2, and TEA/TMSOTf/benzene reflux did not give any silyl enol ether.

[21] Y. Ito, T. Hirao, T. Saegusa, *J. Org. Chem.* **1978**, *43*, 1011–1013.

[22] J. Petrignet, I. Prathap, S. Chandrasekhar, J. S. Yadav, R. Greé, *Angew. Chem.* **2007**, *119*, 6413–6416; *Angew. Chem. Int. Ed.* **2007**, *46*, 6297–6300.

[23] CCDC 713396 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

Received: March 9, 2009
Published online: June 2, 2009

