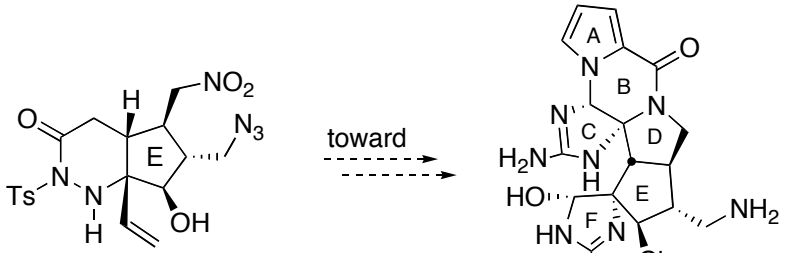
Toward Palau'amine: $Hg(OTf)_2$-Catalyzed Synthesis of the Cyclopentane Core



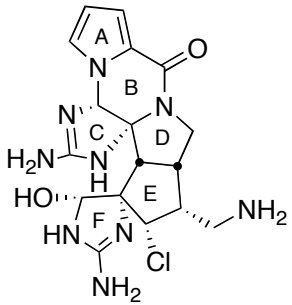
Namba, K.; Kaihara, Y.; Yamamoto, H.; Imagawa, H.; Tanino, K.; Williams, R. M.; Nishizawa, M.
Chem. Eur. J. **2009**, *Early View*

John Maciejewski

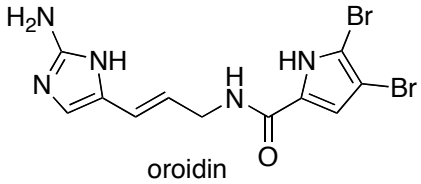
Wipf Group - Current Literature
20 June 2009

Palau'amine

- Isolated in 1993 from marine sponge *Stylotella agminata*[1]
- Exhibits antifungal and antitumor activitiy[2]
- Complex and compact pyrrole-imidazole alkaloid of the oroidin family[3]
- Pentasubstituted E-ring poses synthetic challenge
- Absolute stereochemistry not yet confirmed
- *No total synthesis to date*



palau'amine



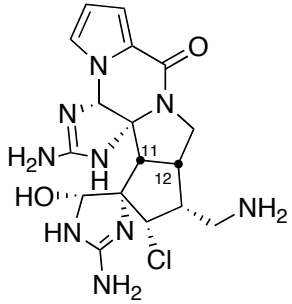
oroidin

1) Scheuer, P. J. *et al. J. Am. Chem. Soc.* **1993**, *115*, 3376
2) Romo, D. *et al. Tetrahedron*, **2006**, *62*, 7155
3) P. Potier *et al. Eur. J. Org. Chem.* **2001**, 237

Revised Structure of Palau'amine

In 2007 the ring junction of the azabicyclo[3,3,0]octane was corrected

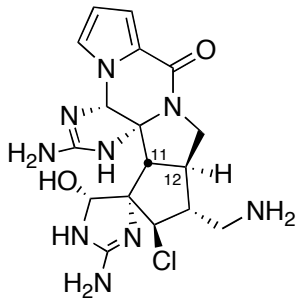
$J_{11\text{-}12}$ = 14.1 Hz
cis-azabicyclo[3,3,0]octane



palau'amine
(original structure)

cis-fused 5,5-bicycle calculated to be 27.3 kJ/mol lower in energy than *trans*

$J_{11\text{-}12}$ = 14.4 Hz
trans-azabicyclo[3,3,0]octane



palau'amine
(revised structure)

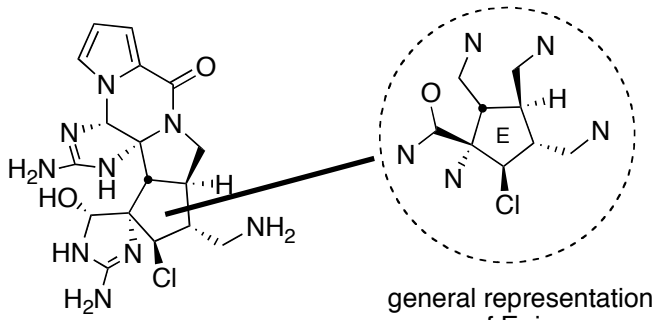
trans-fused 5,5-bicycles uncommon

- Spectroscopic and computational methods
- Coupling constant between $J_{11\text{-}12}$ was investigated

Baran, P. S. *et al. Angew. Chem. Int. Ed.* **2007**, *46*, 6586
Grube, A. *et al. Angew. Chem. Int. Ed*. **2007**, *46*, 2320
Quinn, R. J. *et al. Tetrahedron Lett.* **2007**, *48*, 4573

Current Challenges in Palau'amine Synthesis

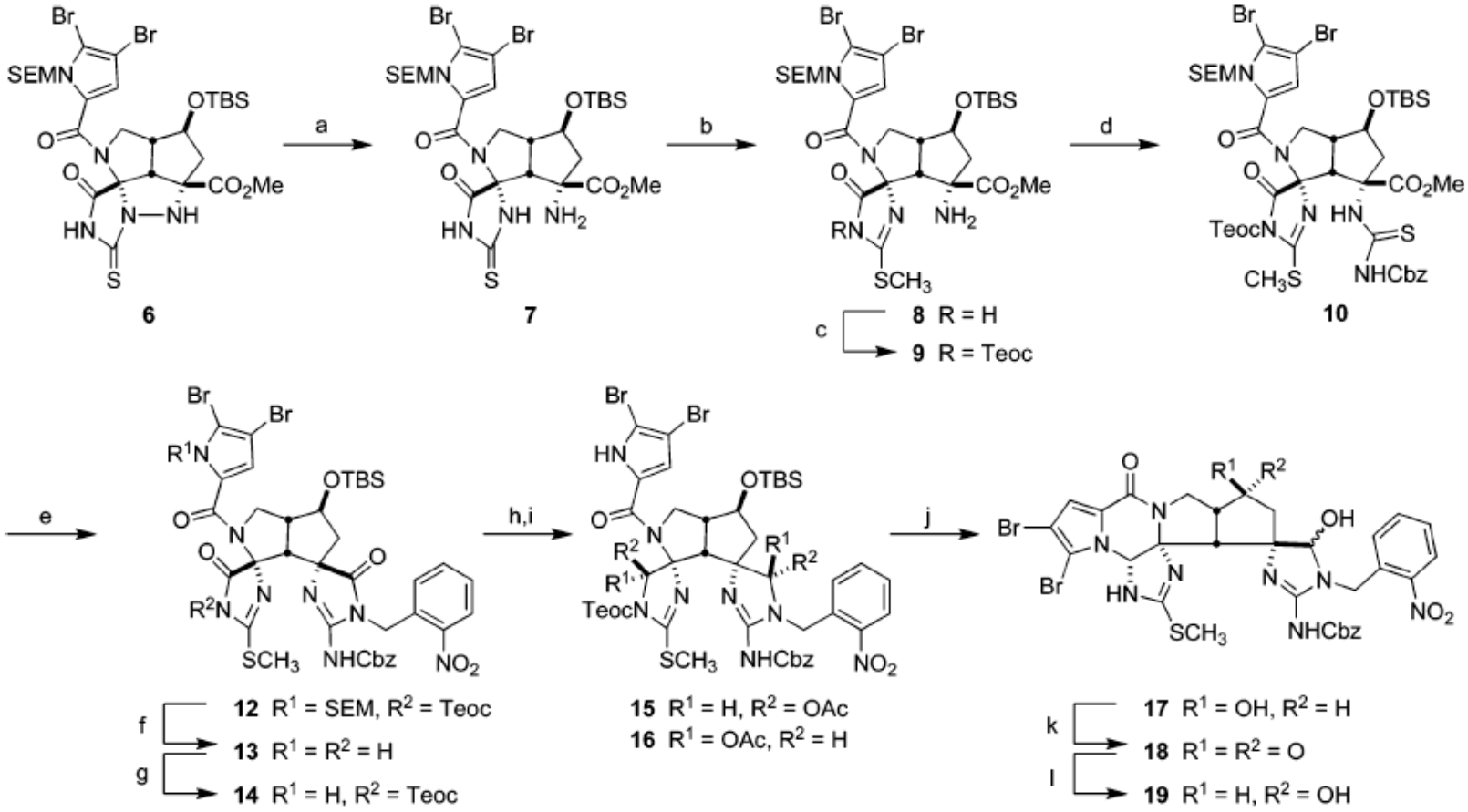
- Some groups may need to reformulate synthetic approach
- Highly functionalized *trans*-azabicyclo[3,3,0]octane
- Construction of the complex cyclopentane core (E ring) is of popular focus



palau'amine
(revised structure)

general representation
of E ring

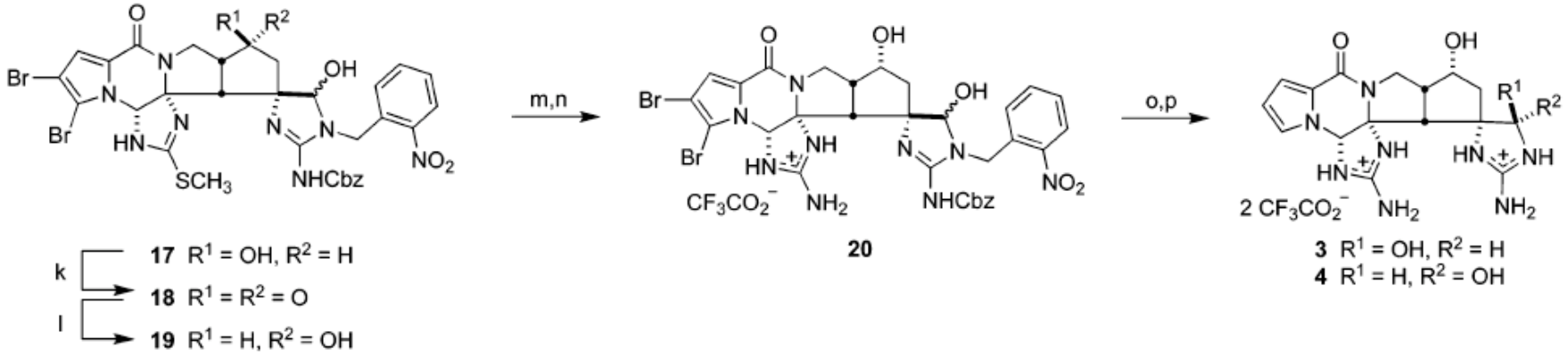
Synthesis of the *cis*-5,5 bicyclic Core of Palau'amine



[a] Conditions: (a) SmI_2, THF/MeOH, 23 °C, 15 min, 79%; (b) MeI, *i*-Pr_2EtN, DMAP, CH_2Cl_2, 23 °C, 2 h, 96%; (c) Teoc-Cl, *i*-Pr_2EtN, CH_2Cl_2, 23 °C, 30 min, quant; (d) benzyloxycarbonyl isothiocyanate (**11**), CH_2Cl_2, 40 °C, 1.5 h, 92%; (e) EDCI, 2-nitrobenzylamine hydrochloride, *i*-Pr_2EtN, CH_2Cl_2, 40 °C, 2.5 h, 93%; (f) TFA, CH_2Cl_2, 23 °C, 1 h, then saturated aq Na_2CO_3, 94%; (g) Teoc-Cl, Pr_2EtN, CH_2Cl_2, 23 °C, 30 min, 90%; (h) $NaBH_4$, MeOH/THF (2:1), 0 °C, 40 min; (i) Ac_2O, pyridine, DMAP, CH_2Cl_2, 23 °C, 4 h, 51% (**15**), 29% (**16**) (two steps); (j) TBAF, THF, 23 °C, 8 min, 95%; (k) IBX, DMSO, 23 °C, 4 h, 96%; (l) $NaBH_4$, MeOH, 0 °C, 30 min, 94%;

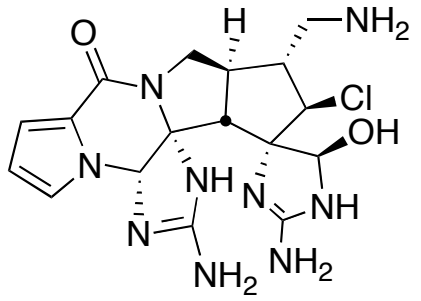
Overman, L. E. *et al. J. Am. Chem. Soc.* **2007**, *129*, 12896

Synthesis of the *cis*-5,5 bicyclic Core of Palau'amine



(l) $NaBH_4$, MeOH, 0 °C, 30 min, 94%; (m) *m*-CPBA, CH_2Cl_2, 0 → 23 °C, 40 min; (n) NH_3, CH_2Cl_2, −78 → 23 °C, 14 h, 79% (two steps); (o) hν, dioxane, 23 °C, 2.5 h; (p) H_2, Pd/C, dioxane/H_2O (0.1% TFA), 43% (**3**), 22% (**4**) (two steps). DMAP = *N*,*N*-dimethylaminopyridine, Teoc-Cl = 2-trimethylsilylethyl chloroformate, EDCI = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, TFA = trifluoroacetic acid, TBAF = tetra(*n*-butyl)ammonium fluoride, IBX = *o*-iodoxybenzoic acid, *m*-CPBA = *m*-chloroperoxybenzoic acid.

- **3** and **4** obtained in a 2:1 ratio (8 mg of **3** and 4.1 mg of **4**)
- NMR data confirm the revised structure of palau'amine

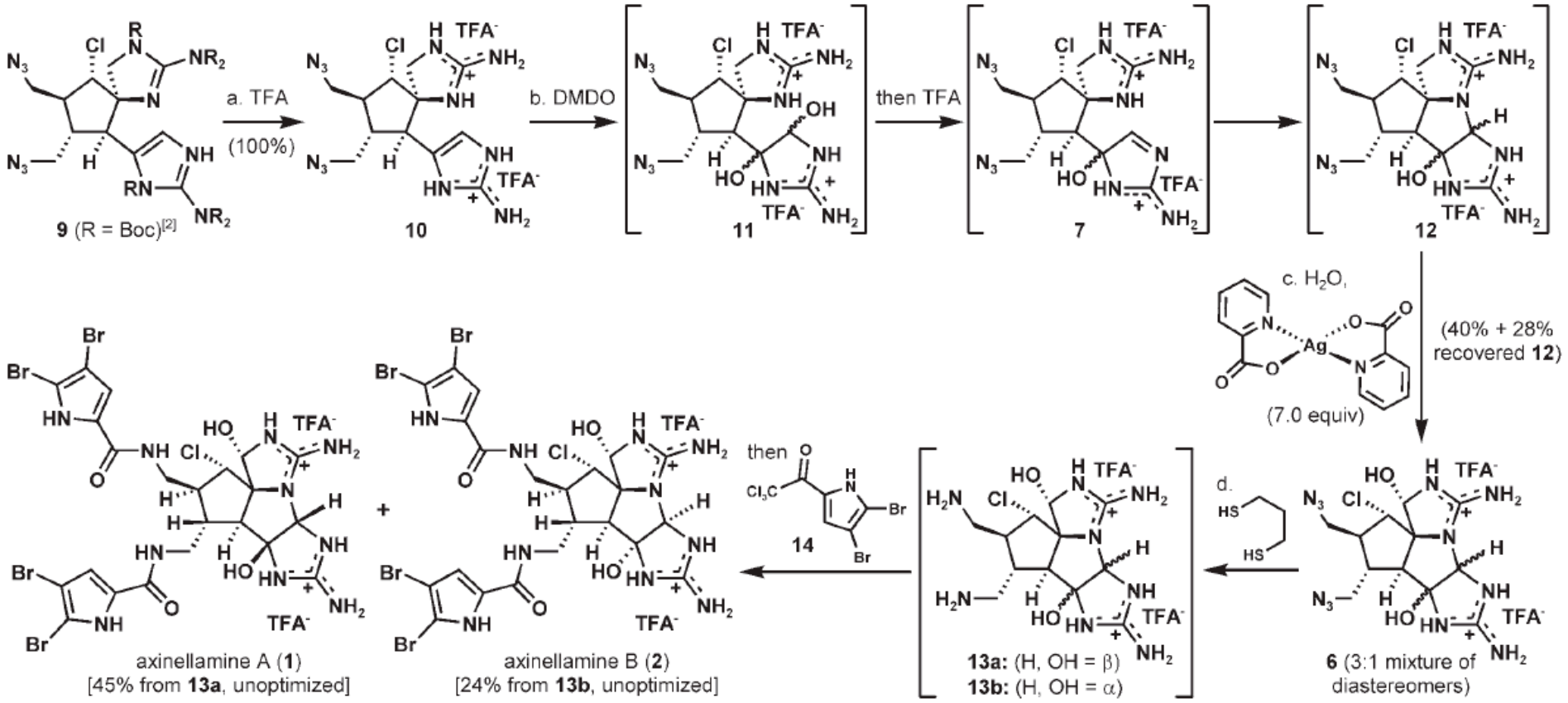


palau'amine

Overman, L. E. *et al. J. Am. Chem. Soc.* **2007**, *129*, 12896

In the Palau'amine Family

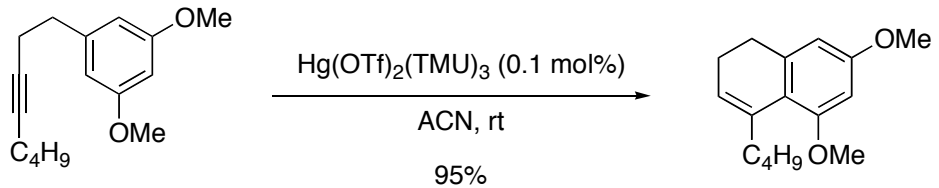
Baran's Synthesis of Axinellamines A and B



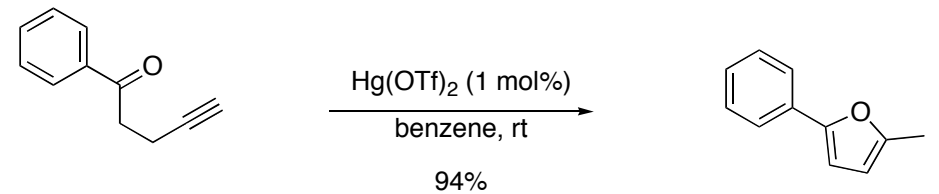
Baran, P. S. *et al. Angew. Chem.* **2008**, *120*, 3634 (for synthesis of **9**)
Baran, P. S. *et al. Angew. Chem. Int. Ed.* **2008**, *47*, 3581

Palau'amine and Mercury

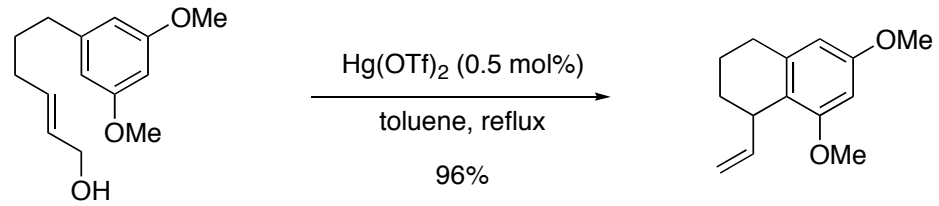
Applications of $Hg(OTf)_2$-Catalyzed Cyclization



Nishizawa, M. *et al. Org. Lett.* **2003**, *5*, 4563



Nishizawa, M. *et al. Org. Lett.* **2004**, *6*, 3679

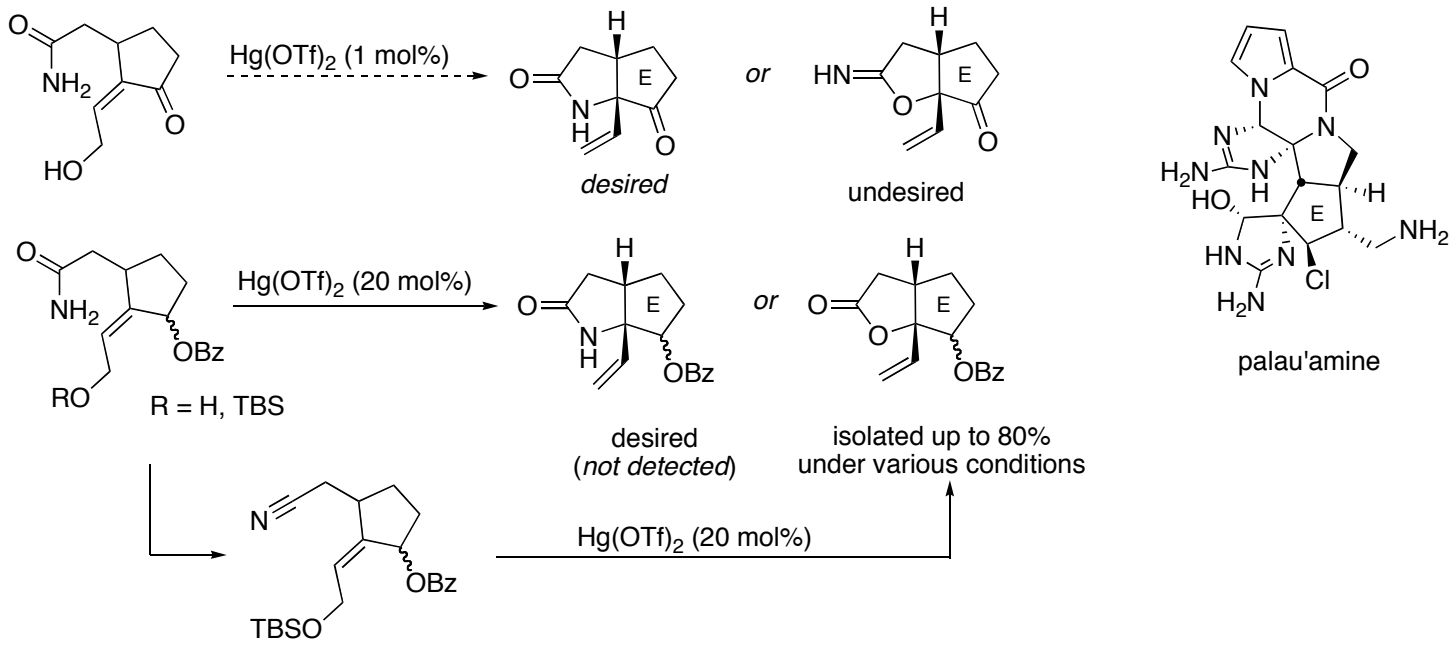


Nishizawa, M. *et al. Org. Lett.* **2008**, *10*, 1767

- Carbo- and oxymercuration of alkynes and alkenes
- General method of annulation

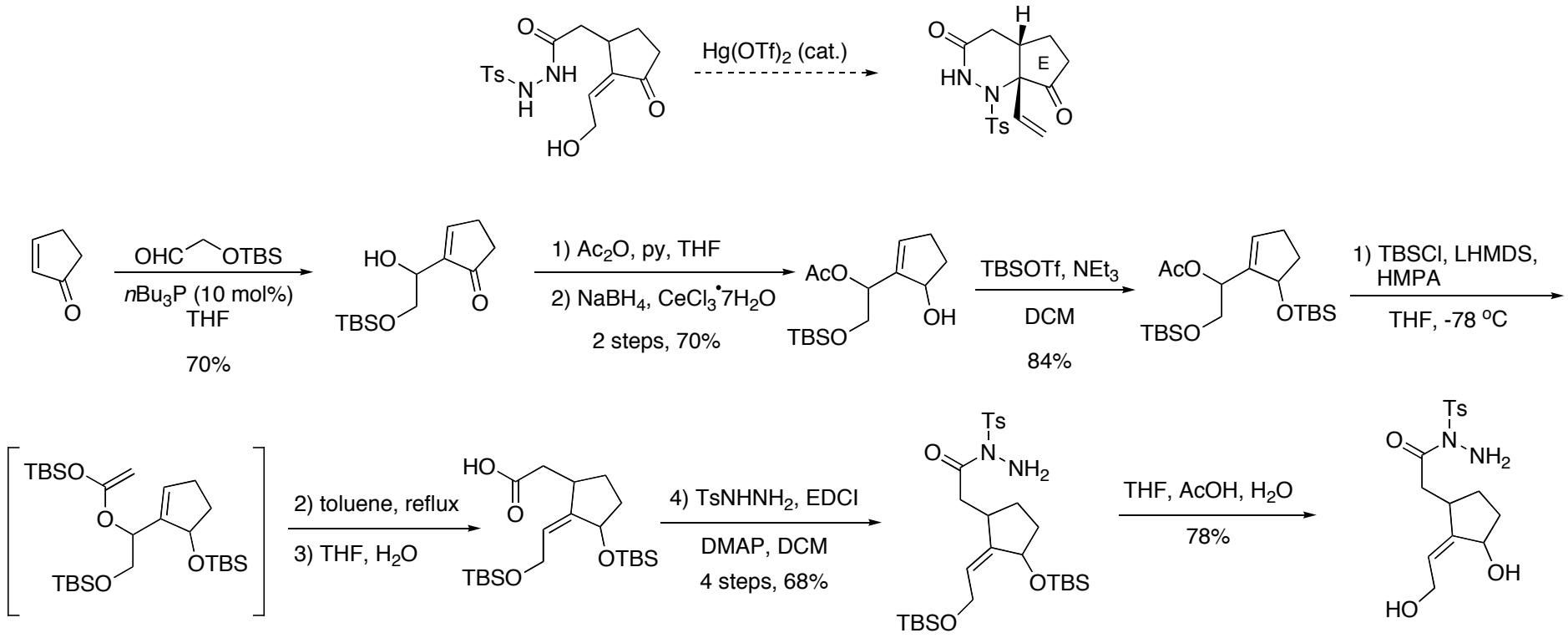
Approach Toward Complex Cyclopentane Core

Apply $Hg(OTf)_2$ catalyzed annulation to form E ring of palau'amine



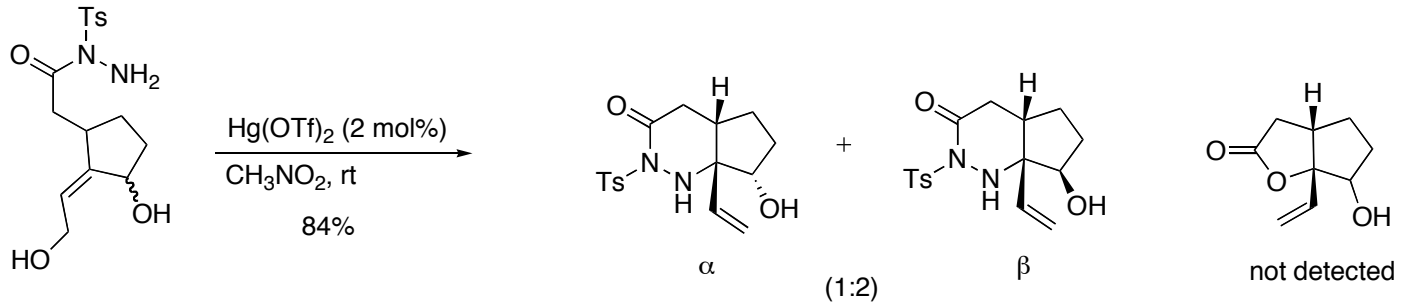
Nishizawa, M. *et al. Chem. Eur. J.* **2009**, *Early View*

Preparation of the Model System



Nishizawa, M. *et al. Chem. Eur. J.* **2009**, *Early View*

Key Step - Aminomercuration/elimination

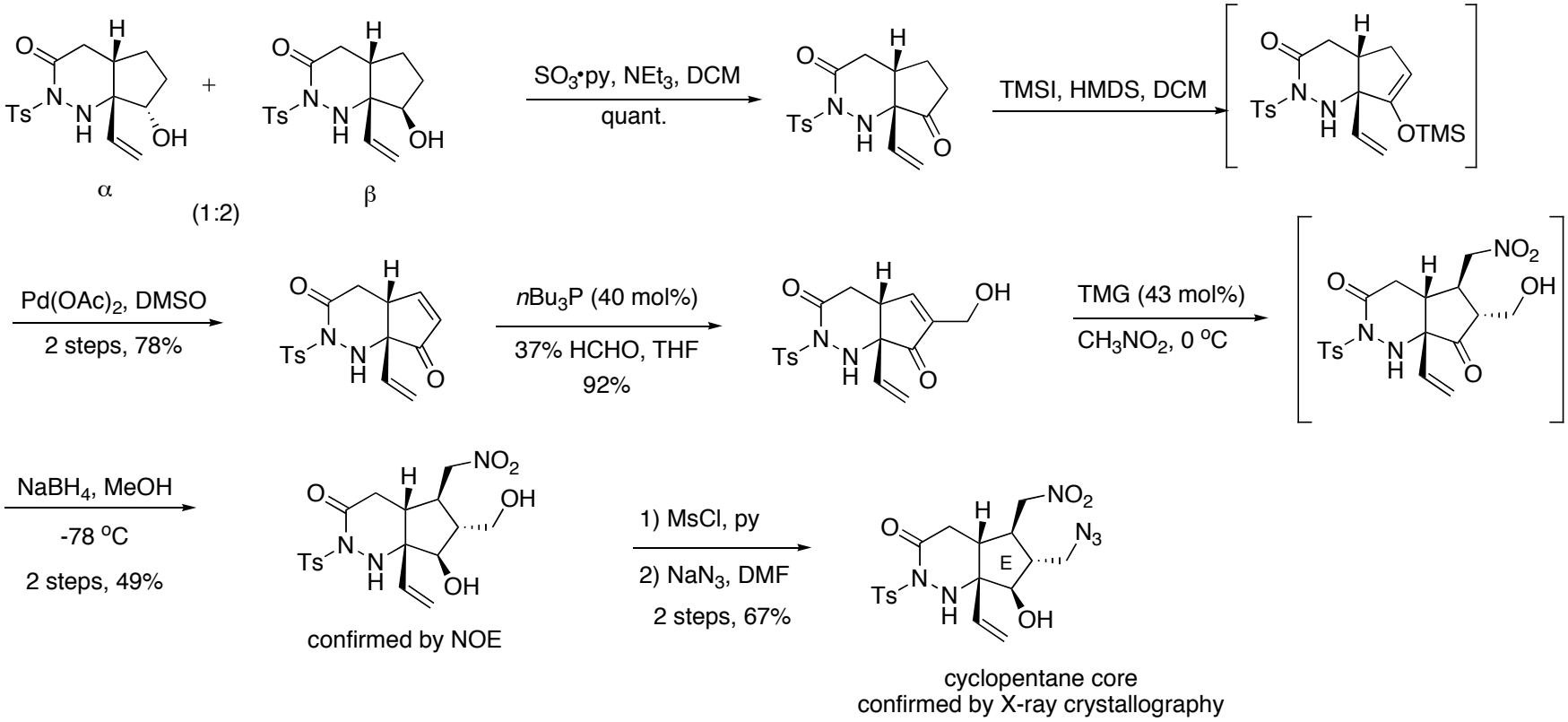


structures confirmed by NOE and X-ray crystallography

- Key step works efficiently, avoiding undesired lactone formation
- *N* selective cyclization of *N*-acyl compounds
- α and β epimers to be oxidized later

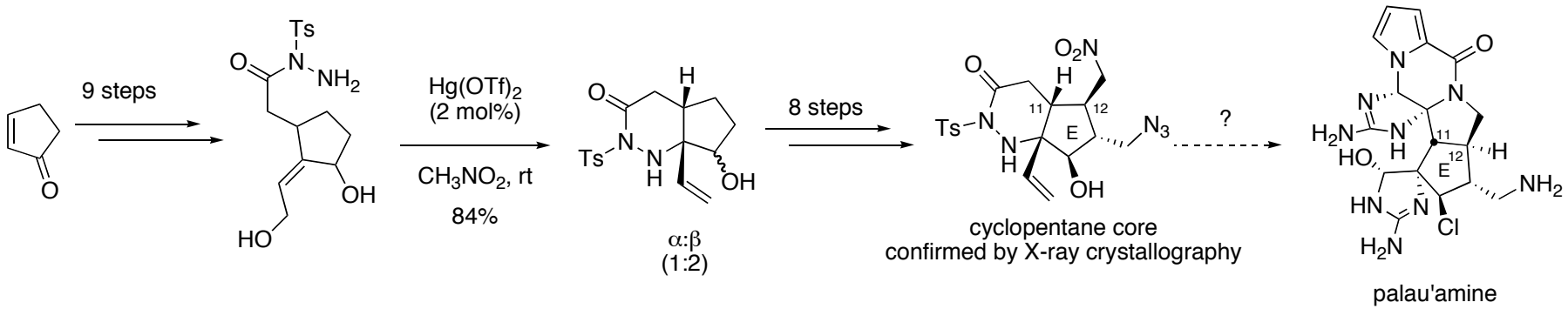
Nishizawa, M. *Chem. Eur. J.* **2009**, *Early View*

Endgame Toward E-ring of Palau'amine



Nishizawa, M. *et al. Chem. Eur. J.* **2009**, *Early View*

Summary



- The race for the first total synthesis of palau'amine continues
- Structural revision in 2007 confirms its truly exotic structure
- $Hg(OTf)_2$ catalyzed cyclization demonstrates a novel approach to E-ring
- Synthetic efforts towards palau'amine continue in Nishizawa laboratory