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.


John Maciejewski

*Wipf Group - Current Literature*

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Palau’amine

- Isolated in 1993 from marine sponge *Stylorella agminata*\(^1\)
- Exhibits antifungal and antitumor activity\(^2\)
- 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*

\[ \text{\textbf{Palau’amine}} \]

\[ \text{\textbf{Oroidin}} \]

Revised Structure of Palau’amine

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

\[ J_{11-12} = 14.1 \text{ Hz} \]

*cis*-azabicyclo[3,3,0]octane

\[ J_{11-12} = 14.4 \text{ Hz} \]

*trans*-azabicyclo[3,3,0]octane

- Spectroscopic and computational methods

- Coupling constant between \( J_{11-12} \) was investigated

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

[Diagram of palau'amine (revised structure) and general representation of E ring]
Synthesis of the cis-5,5 bicyclic Core of Palau’amine

Synthesis of the cis-5,5 bicyclic Core of Palau’amine

- 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

In the Palau’amine Family

Baran’s Synthesis of Axinellamines A and B

Palau’amine and Mercury
Applications of Hg(OTf)$_2$-Catalyzed Cyclization

- Carbo- and oxymercurcation 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

Preparation of the Model System

Key Step - Aminomercuration/elimination

\[
\text{Hg(OTf)$_2$ (2 mol\%)} \rightarrow \text{CH$_3$NO$_2$, rt} \rightarrow 84\%
\]

structures confirmed by NOE and X-ray crystallography

- Key step works efficiently, avoiding undesired lactone formation
- \(N\) selective cyclization of \(N\)-acyl compounds
- \(\alpha\) and \(\beta\) epimers to be oxidized later

Endgame Toward E-ring of Palau’amine

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