Total Synthesis of Palau’amine

Isolation and Biological Activity

Meaning of Hawaiian word palau: *war club*

- Isolated in 1993 from the sea sponge *Stylotella agminata* collected from the Western Caroline Islands in the Republic of Palau
- Low acute toxicity (LD$_{50}$ 13mg/kg, mice)
- Significant immunosuppressive and antitumor activities (IC$_{50}$'s for P-388 and A-549 were 0.1 and 0.2 µg/mL, respectively)
- Displays antifungal and antibacterial activities
- Authors note that the dust from the sponge caused allergic reactions consisting of *severe* shortness of breath lasting for about 4 h and skin rashes.

Synthetic Challenges

A Formidable Opponent.....

Synthetic Publications: 34
PhD. Dissertations: 26
Total Synthesis: 1 (title paper)

- Unusually high nitrogen content (N/C ~ 1 : 2)
- Highly strained core with 8 contiguous stereocenters
- High polarity translates into difficulty in performing manipulations (solubility, purifications, etc.)
- pH stability (decomposes under basic conditions above pH 6.5)
- Absolute stereochemistry is unknown

Structure revision:
Hypothetical Biosynthesis


Histidine

Proline

Palau'amine
Oroidin-Derived Alkaloids

Figure blatantly stolen from:

Disclaimer: Relative stereochemistry unrevised
Highlights of Selected Previous Efforts Towards Palau’amine (Romo)

Highlights of Selected Previous Efforts Towards Palau’amine (Overman)

Synthesis of Functionalized Cyclopentane Core


Addition of TFA accelerates reaction (5 min)
- Completely chemoselective (!)

TM-mediated coupling conditions were unsuccessful

Completion of Racemic Palau’amine

The following was taken from the SI:

• Attempted purification of intermediates (*in the above sequence*) led to a reduced yield of ‘final product’ due to their extreme polarity leading to difficulty in separation

• Purification of ‘final product’ had to be performed twice on two columns (RP HPLC) in 5-8 batches each


……*what was the inspiration for the trans-annular cyclization?*
### Spectroscopic Comparison (\(^{1}\text{H NMR}\))

<table>
<thead>
<tr>
<th>Position</th>
<th>Natural (Quinn)(^a)</th>
<th>Natural (Scheuer)(^b)</th>
<th>Synthetic</th>
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<tr>
<td>3</td>
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<td>6.85 (dd, 3.9, 1.5)</td>
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<td>6.35 (dd, 3.9, 2.8)</td>
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<td>6.99 (dd, 2.8, 1.5)</td>
<td>7.02 (dd, 2.7, 1.6)</td>
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<td>6.37 (s)</td>
<td>6.33 (s)</td>
<td>6.37 (s)</td>
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<td>8-NH(_2)</td>
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Inspiration for “Macro-Palau’amine”?  


“…exemplifies the innovative retrosynthetic analysis and mechanistic thinking that underpins the Baran group’s remarkable string of total synthesis…” - C&EN, 2010, 88(2), 5.

“…the macro-intermediate is just off the charts, and alone places Baran in rarified territory. It is not just non-obvious, it is totally counter intuitive on many levels…” – www.totallysynthetic.com, blogpost, Jan. 2, 2010.
Summary

- First synthesis of Palau’amine completed over 16 years after initial isolation

- Minimal protecting group operations

- Functionalized cyclopentane core prepared using strategic Diels-Alder, intramolecular aldol, and tandem oxidation/spirocyclization reactions

- Late stage chemoselective Ag(II)-picolinate oxidation installs key hemiaminal

- Uncatalyzed coupling of pyrrole surrogate gives access to pyrrole acid intermediate

- Intriguing trans-annular cyclization establishes elusive trans-5,5 ring core and completes the synthesis

- According to Baran, an enantioselective, scalable variant is coming soon…………please stay tuned.