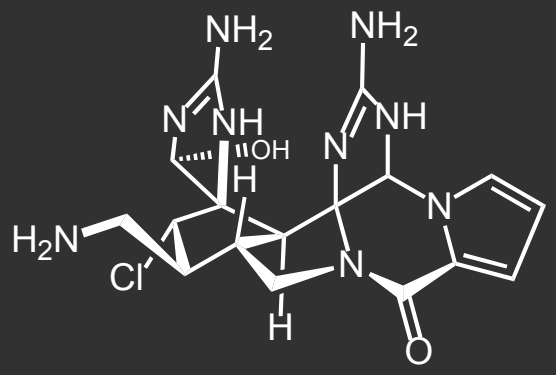
Total Synthesis of Palau'amine

I. B. Seiple, S. Su, I. S. Young, C. A. Lewis, J. Yamaguchi, and P. S. Baran,
Angew. Chem. Int. Ed. **2009**, *49*, 1095-1098.

Hong Ren @ The Wulff Group
03-05-10

What is Palau'amine?



palau'amine

- Synthesized naturally by *Stylotella agminata*
- Cytotoxic and immunosuppressive
- In 1993, first isolated by P. J. Scheur and co-workers
- In 2007, structure revision proposed by M. Kock
- 26 Ph. D theses and 31 publications

Kock, M.; Grube, A.; Seiple, I. B.; Baran, P. S. *Angew. Chem. Int. Ed*. **2007**, *46*, 6586-6594.

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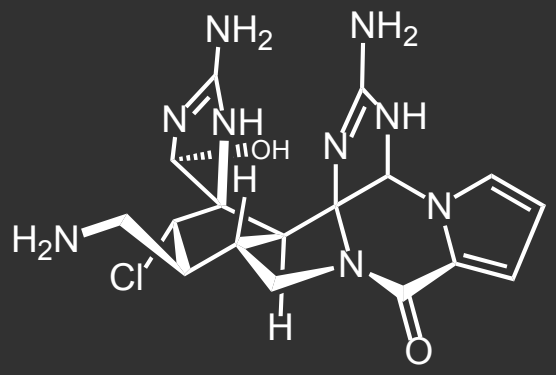

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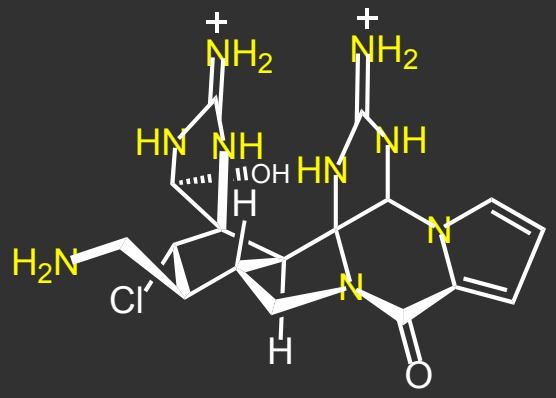
Structural Features



palau'amine

- Nine nitrogens

Kock, M.; Grube, A.; Seiple, I. B.; Baran, P. S. *Angew. Chem. Int. Ed*. **2007**, *46*, 6586-6594.

Structural Features

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- Nine nitrogens
- Eight contiguous stereogenic centers

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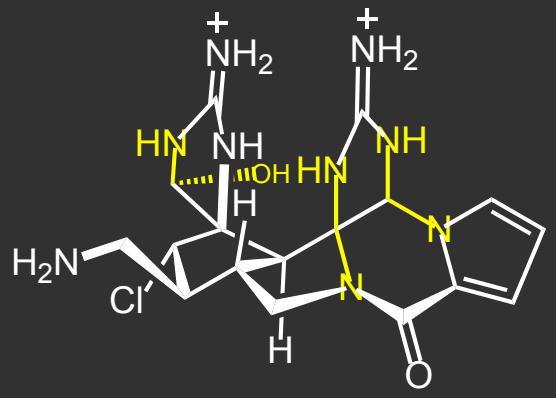

palau'amine

- Nine nitrogens
- Eight contiguous stereogenic centers
- Reactive (hemi)aminal moieties

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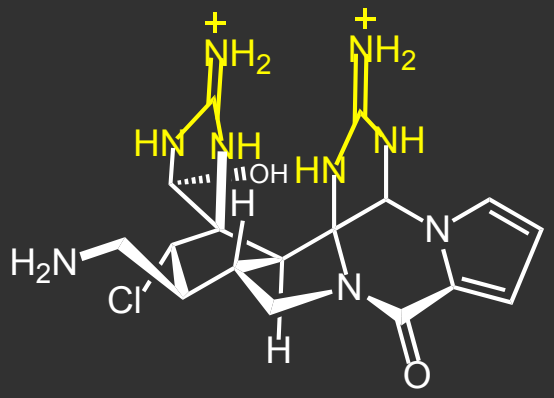

palau'amine

- Nine nitrogens
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- Reactive (hemi)aminal moieties
- Highly polar bis-guanidines

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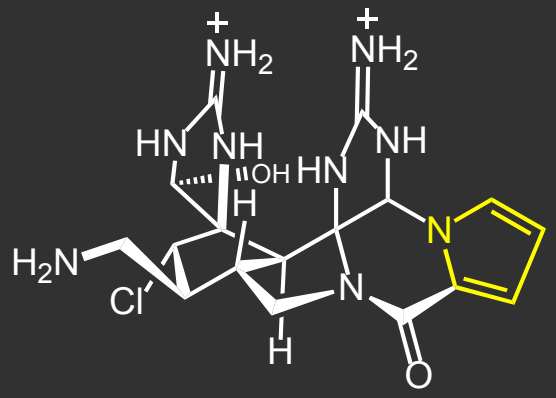

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- Eight contiguous stereogenic centers
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- Oxidation-prone pyrroles

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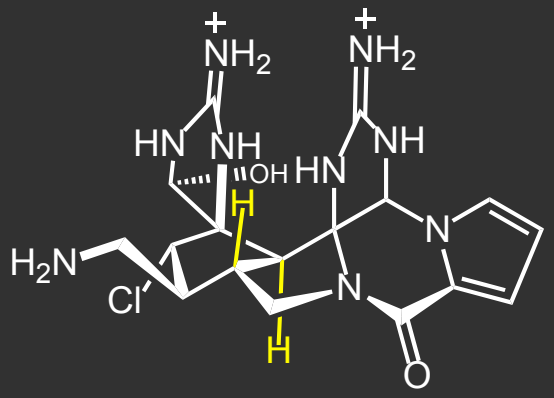

palau'amine

- Nine nitrogens
- Eight contiguous stereogenic centers
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- Highly polar bis-guanidines
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- Strained *trans* – fused 5,5'- azabicyclic ring

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Structural Features

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- Reactive (hemi)aminal moieties
- Highly polar bis-guanidines
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- Strained *trans* – fused 5,5'- azabicyclic ring
- Unprecedented hexacyclic core

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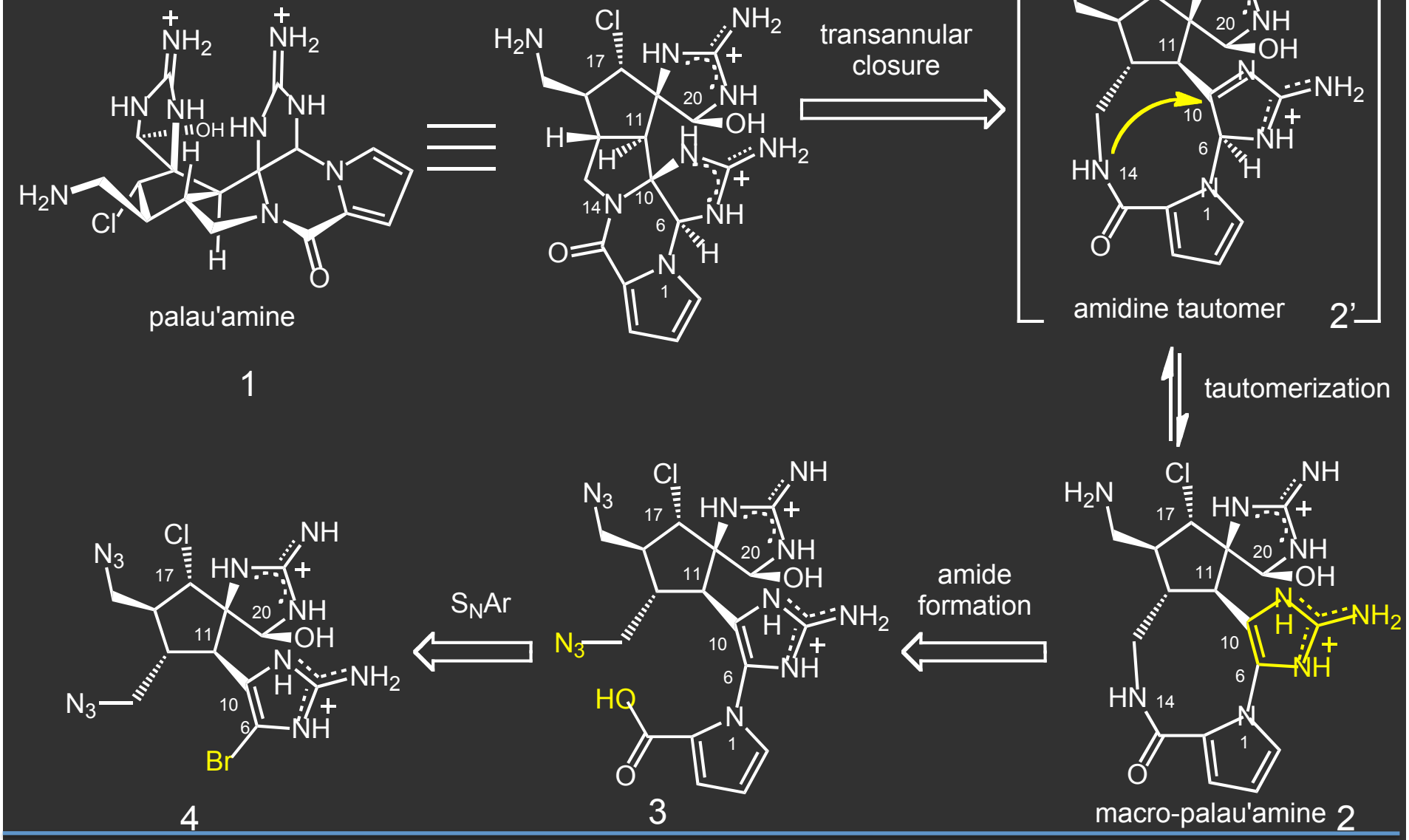
Retrosynthetic Analysis



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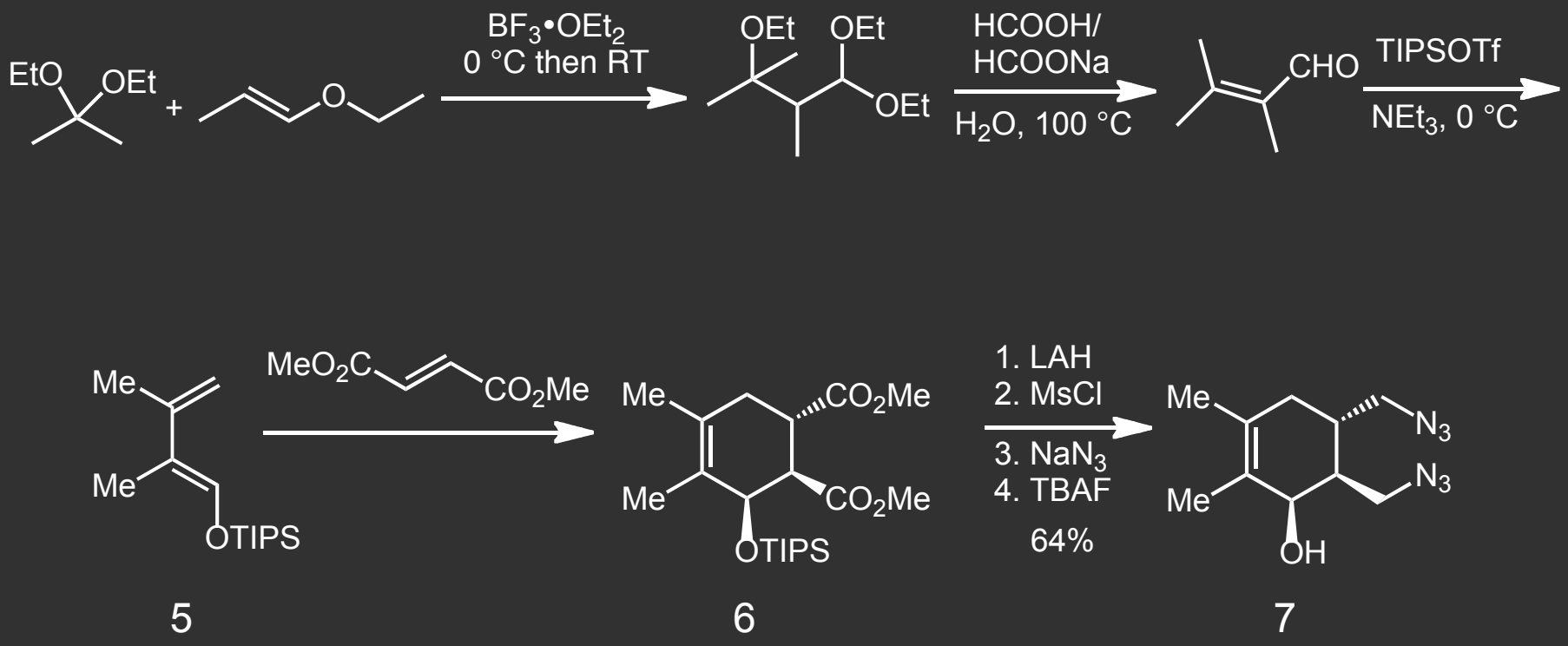
Forward Synthesis



5 6 7

Yamaguchi, J.; Grube, A.; Seiple, I. B.; Young, I. S.; Baran, P. S. *Angew. Chem. Int. Ed*. **2008**, *47*, 3578-3580.
Gosselin, P.; Bourdy, C.; Mille, S.; Perrotin, A. *J. Org .Chem*. **1999**, *64*, 9557-9565.

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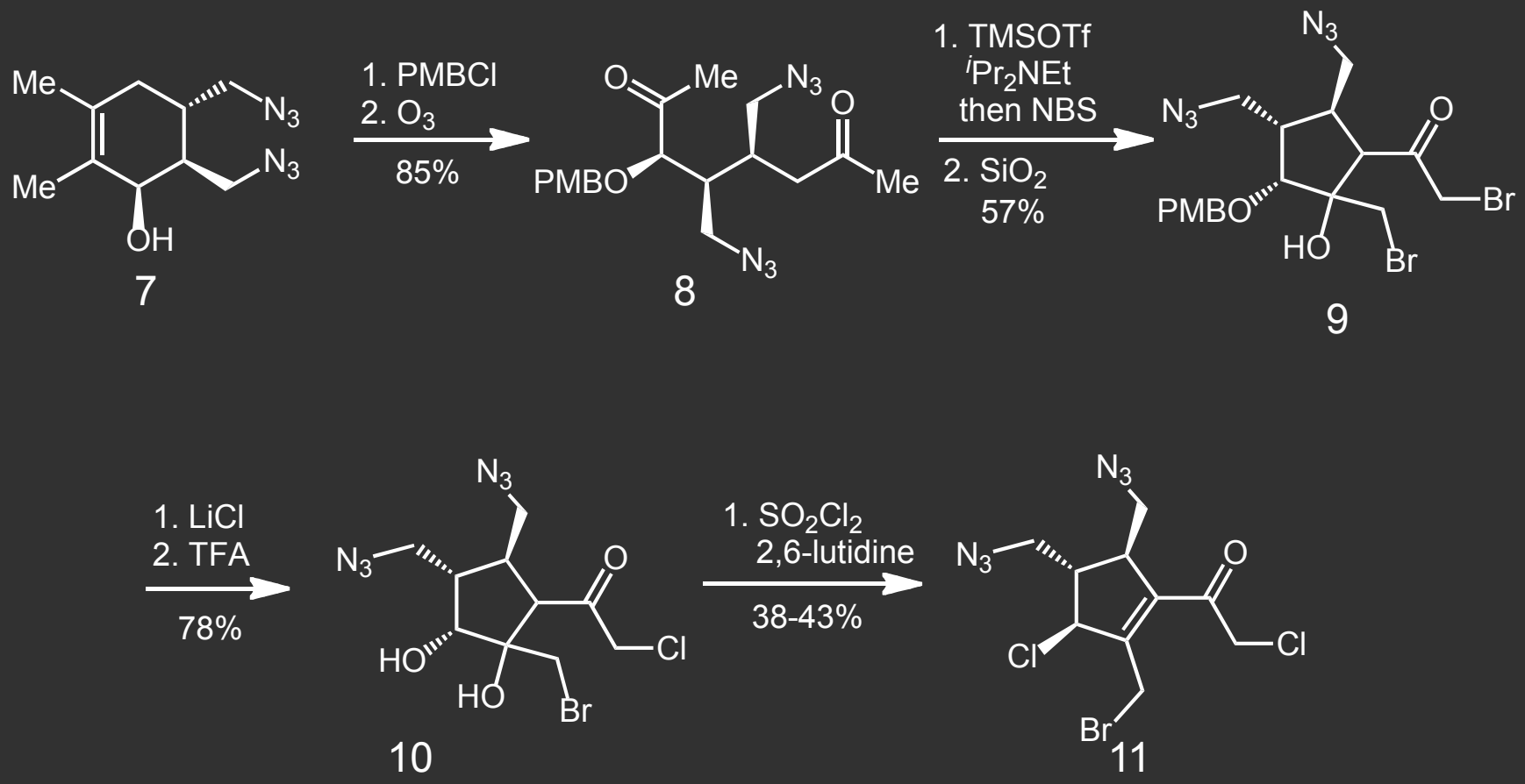

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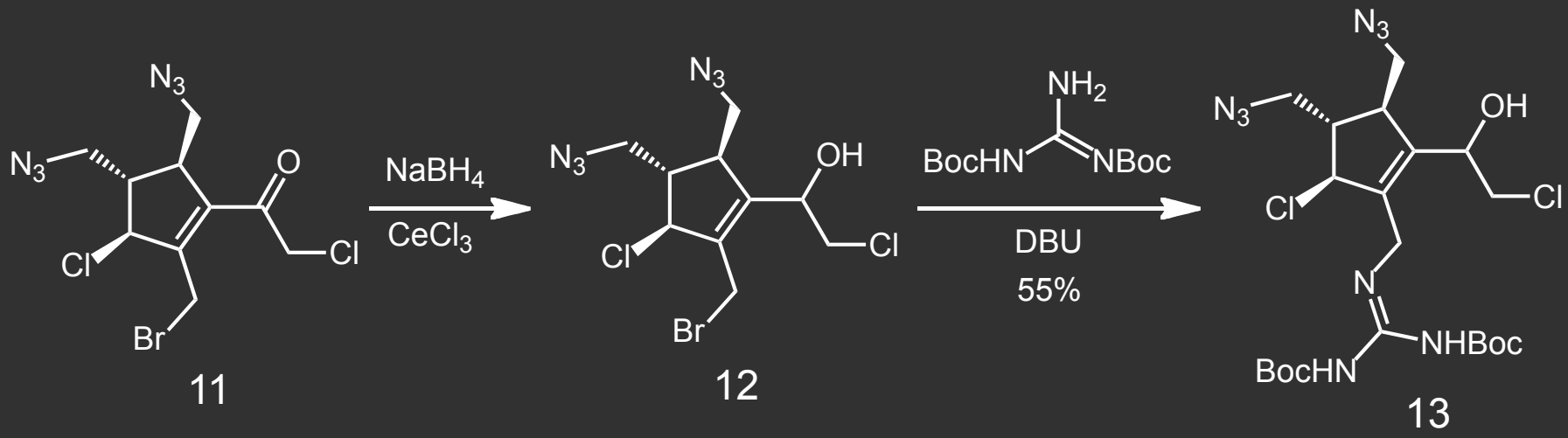

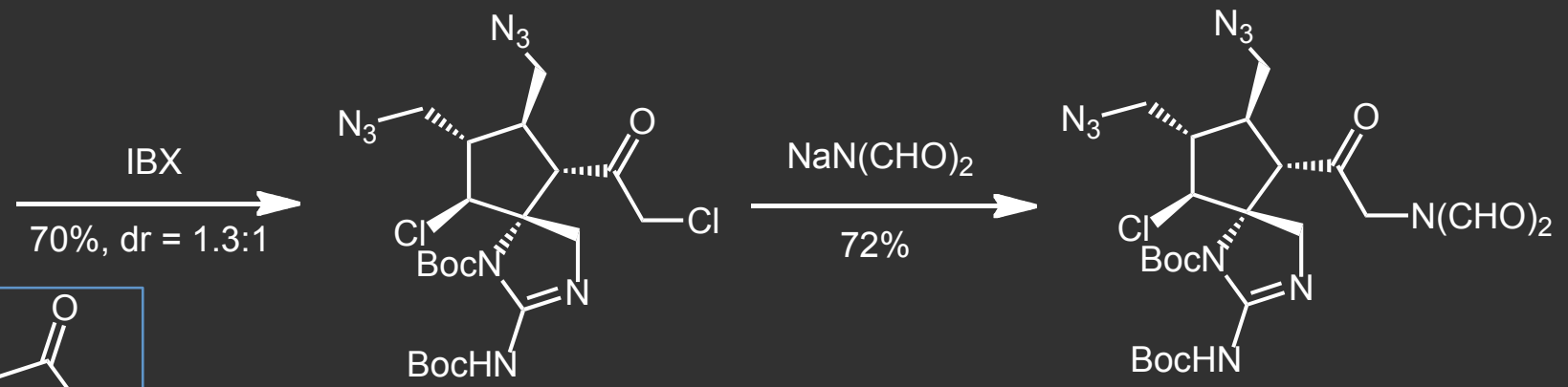

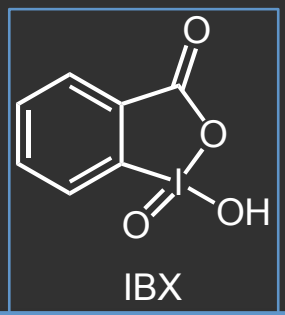

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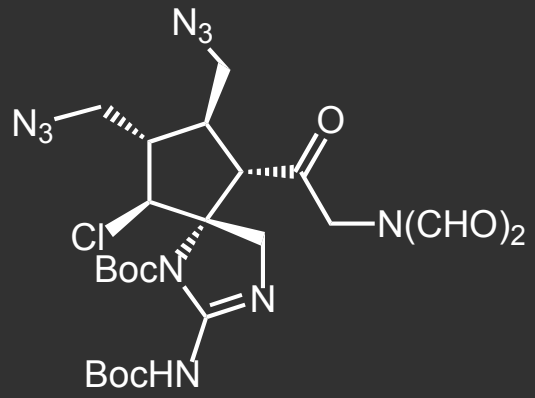
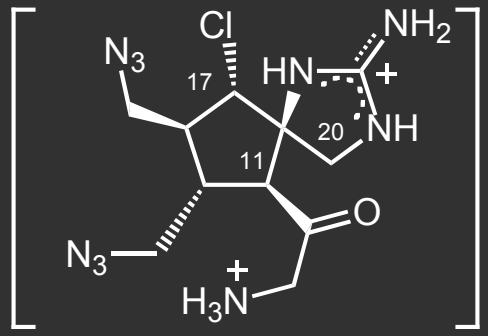


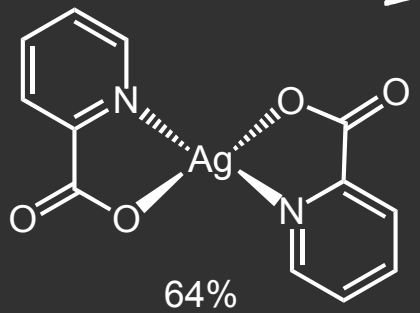
15

50% aq. TFA

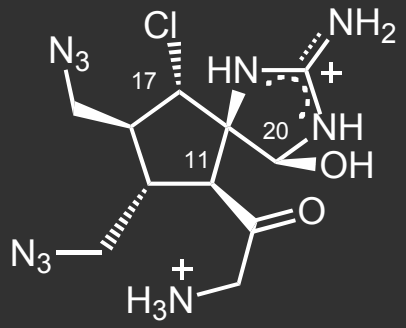


16

then aq 10% TFA

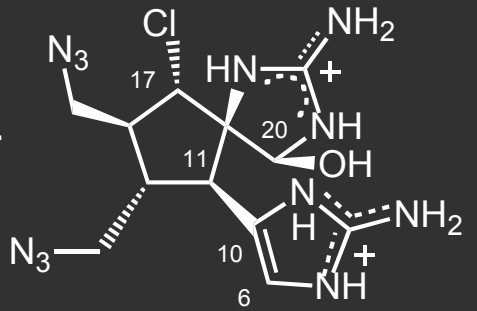


64%



17

H_2NCN
brine
65%



18

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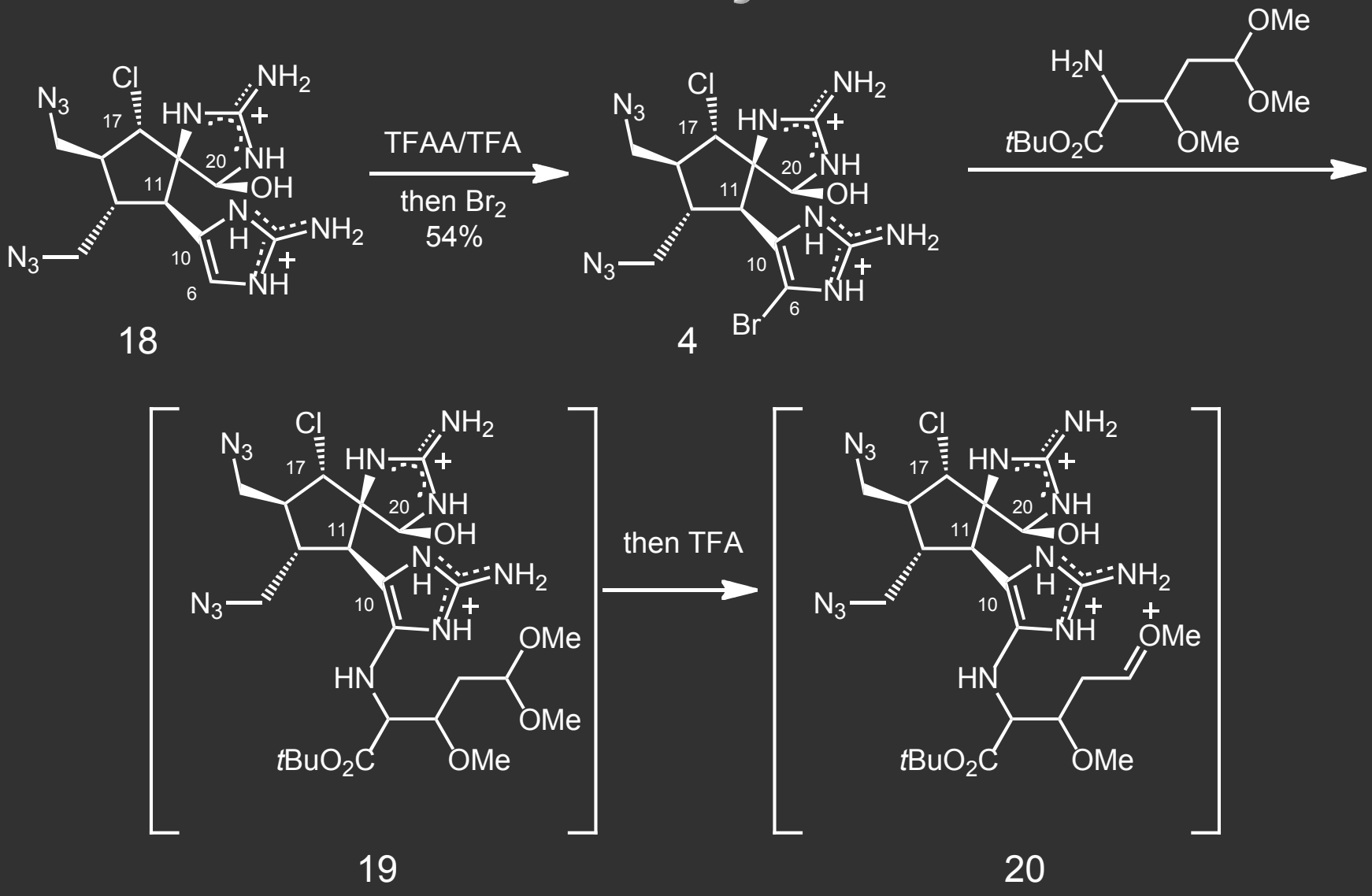

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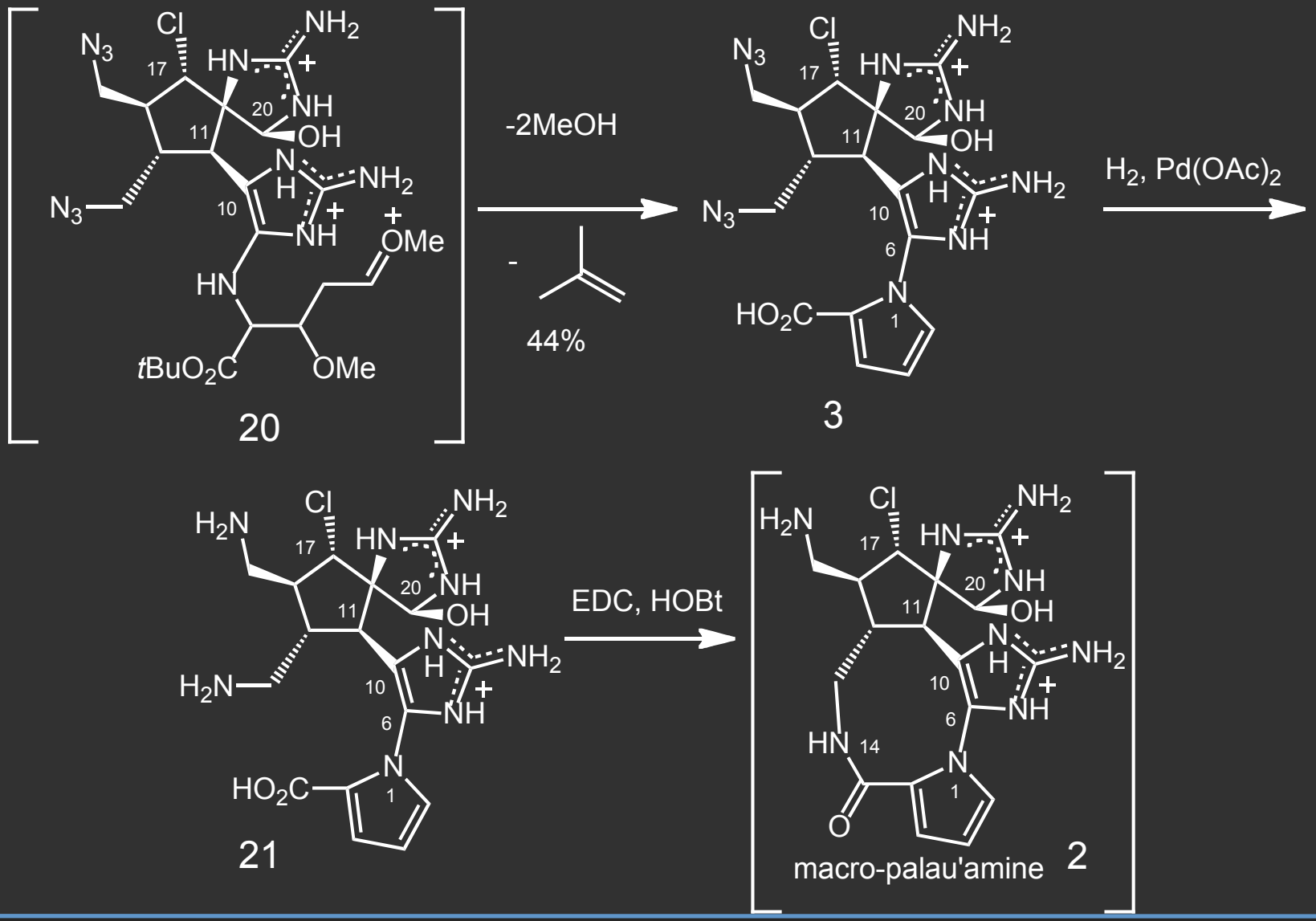

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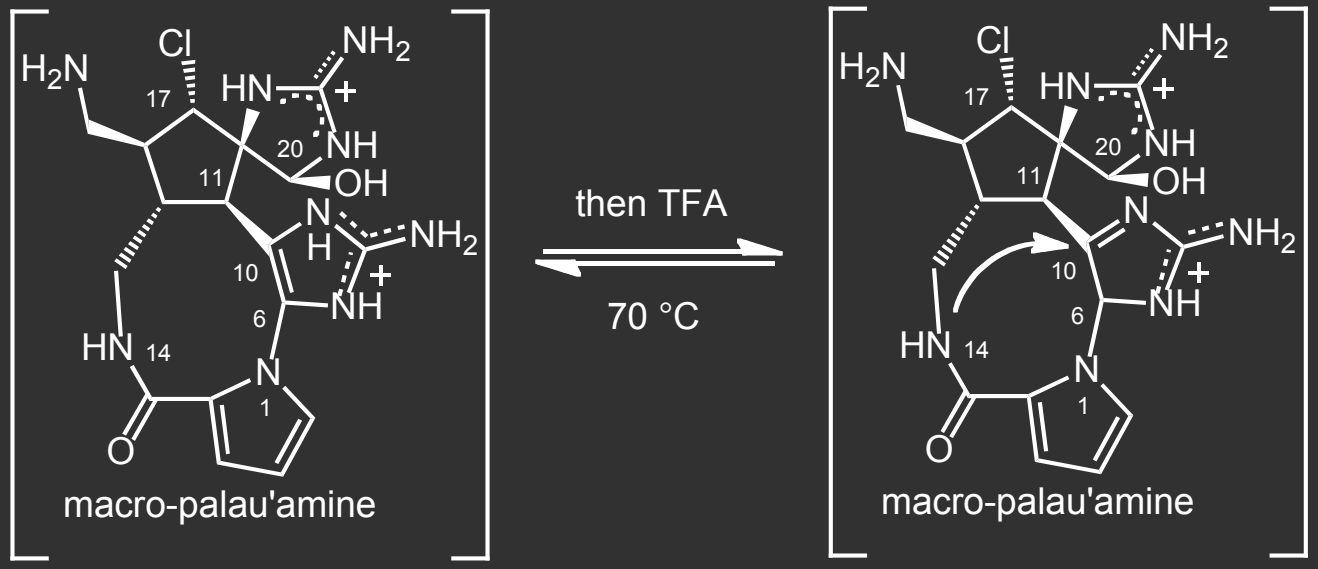
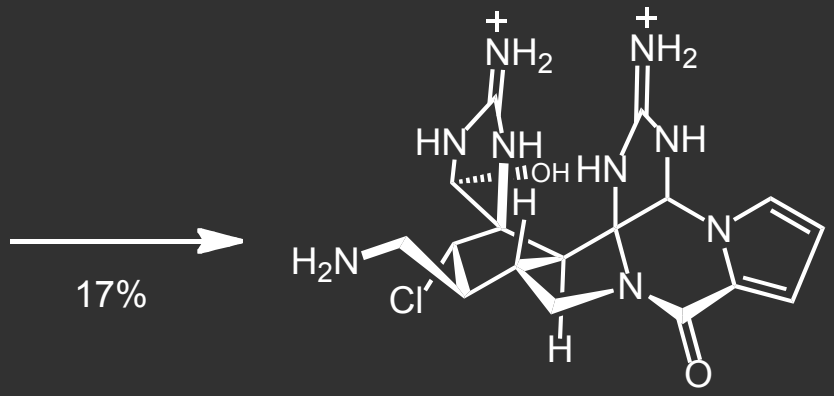
Stitching together Palau'amine





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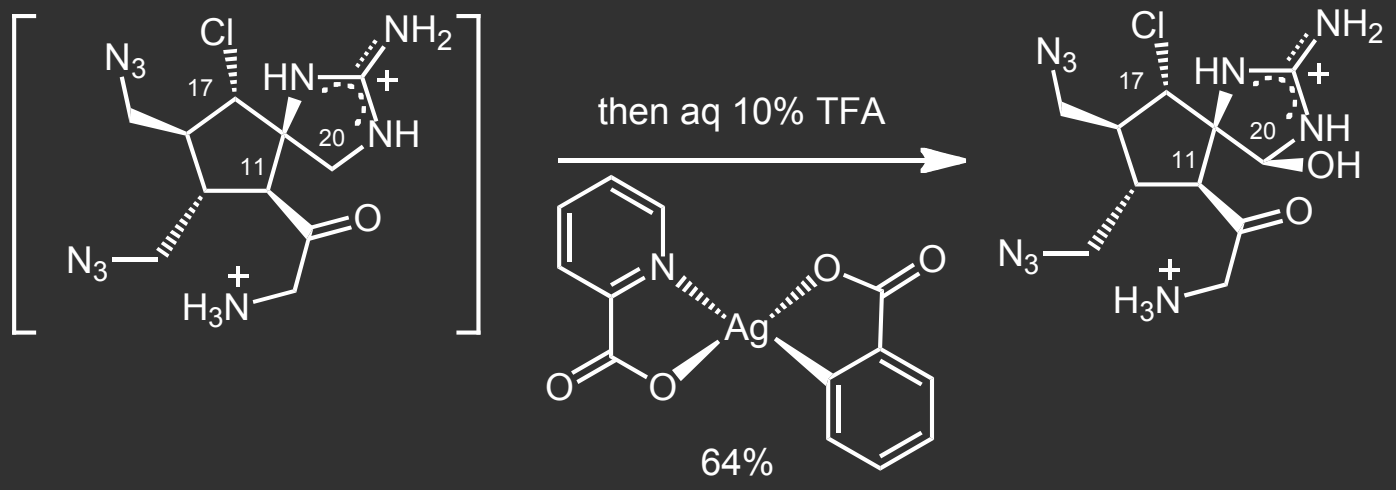
Highlights

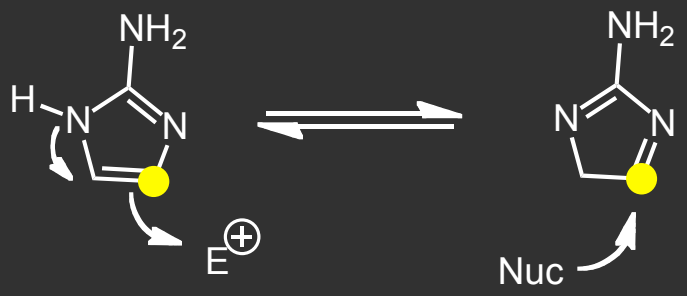
- 25 steps, 0.015% overall yield
- Multiple cascade reactions
- Minimal use of protection groups: PMBCl
- Late-stage, chemoselective, silver-mediated oxidation to the hemiaminal unit

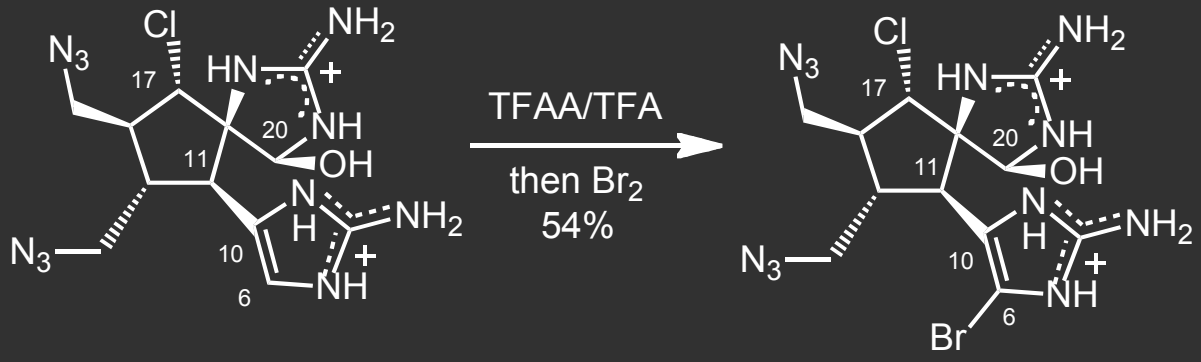


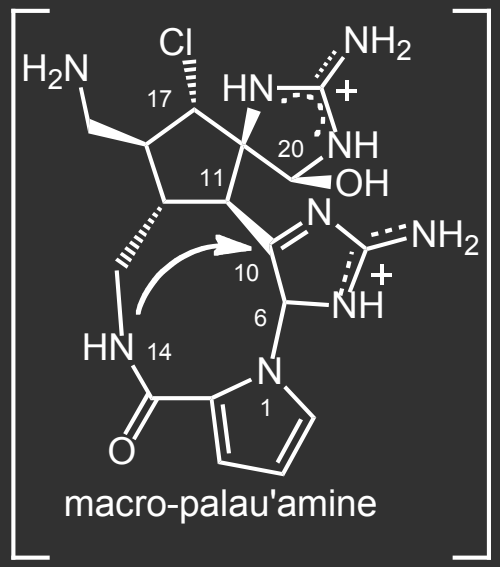
64%

Highlights

- The ambiphilic reactivity of 2-aminoimidazole







- Across ring stitching