Jounal Club 2014.11.06

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Total Synthesis of (+)-Ileabethoxazole via an Iron-Mediated Pauson-Khand [2 + 2 + 1] Carbocyclization

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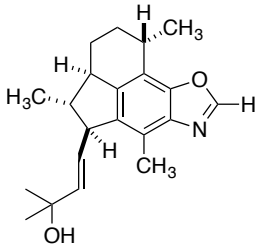
J. Am. Chem. Soc. **2014**, *136*, 8829–8836.

1. Introduction

• Ileabethoxazole was isolated from the Caribbean octacoral *Pseudopterogorgia elisabethae* by Rodriguez et al. in 2006.[1]

• Ileabethoxazole shows strong inhibition (92%) of *Mycobacterium tuberculosis.*

• Total synthesis of ileabethoxazole has not been reported.



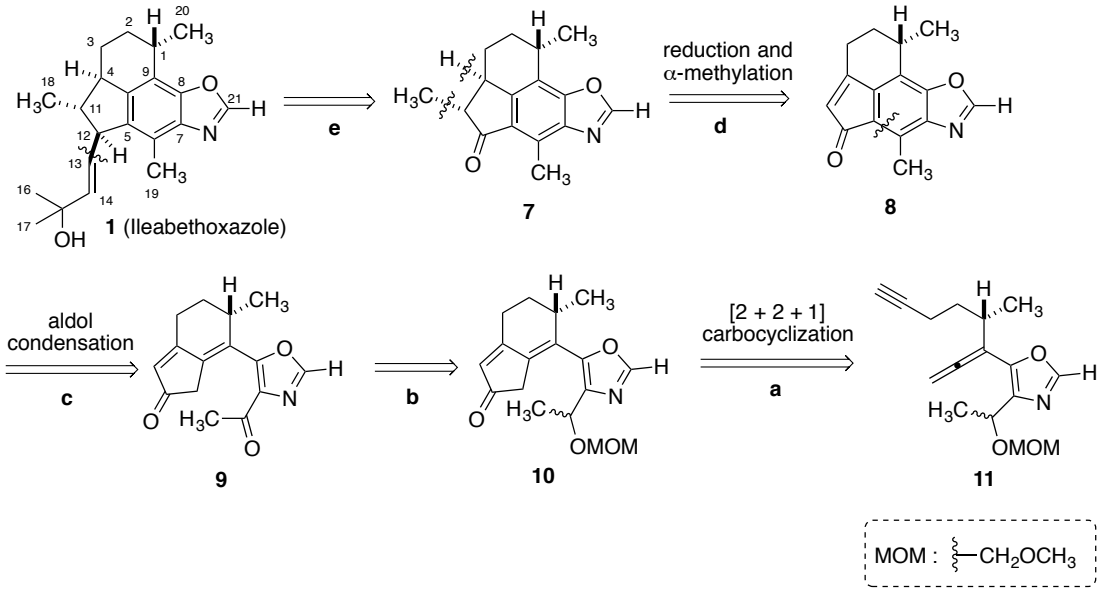
1 (Ileabethoxazole)

• Synthesis of this class of compounds containing benzoxazole unit and fused cyclopentane has not been achieved to date.

2. Results and Discusstion

2-1. Synthesis Strategy

Scheme 1. Retrosynthetic analysis for ileabethoxazole **1**



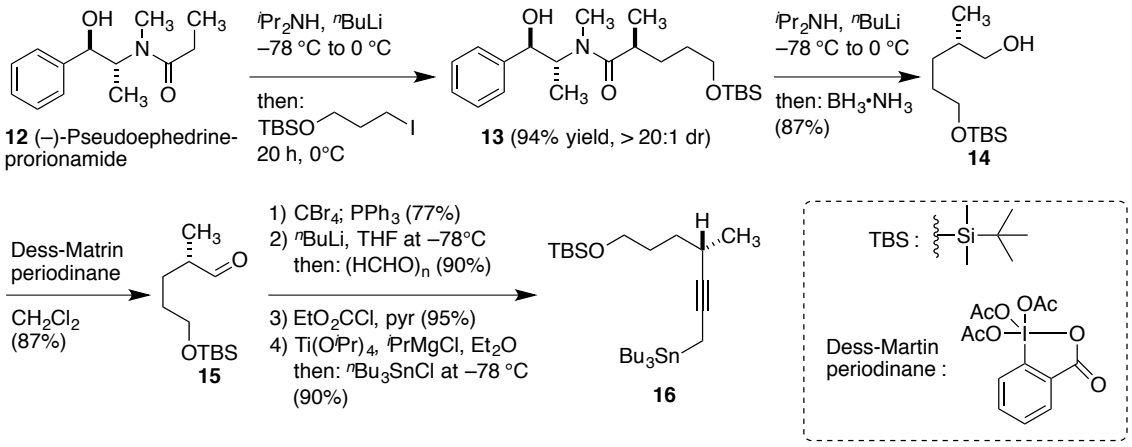
• The authors envisioned that **8** could be synthesized via their previously developed [2 + 2 + 1] carbocyclization of the allene **11** to produce an

unsaturated five-membered cyclopentenone **10**.[2]

2-2. Preparation of Nonracemic Allene 11

2-2-1. Synthesis of Stannane 16 for Preparation of Nonracemic Allene 11

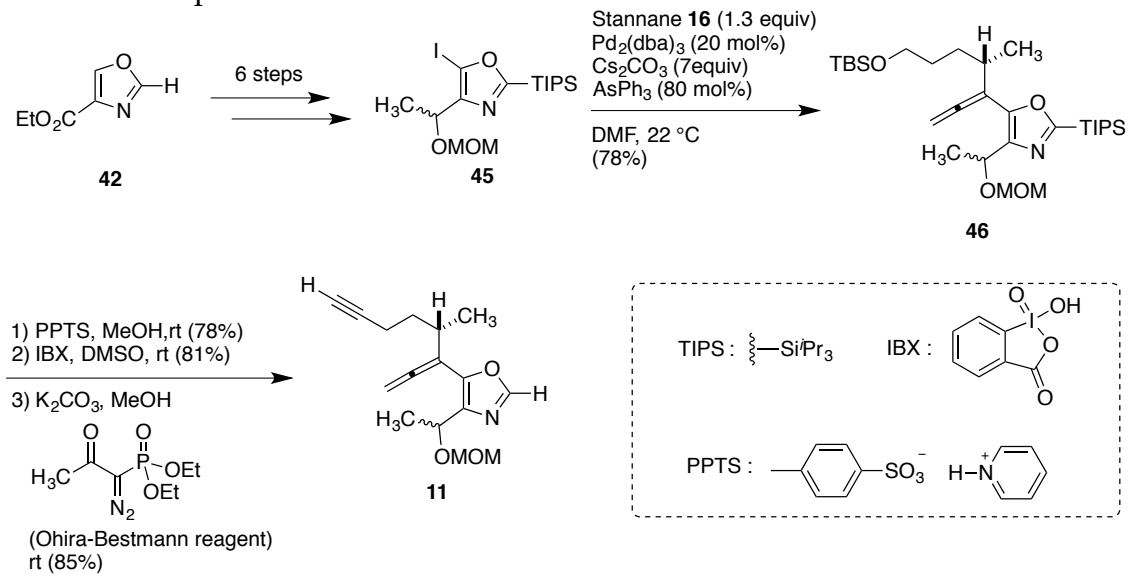
Scheme 2. Synthesis of stannane **16**



• The propargyl stannane **16** was synthesized from commercially available compound **12** in 7 steps.

2-2-2. **Preparation of Nonracemic Allene 11**

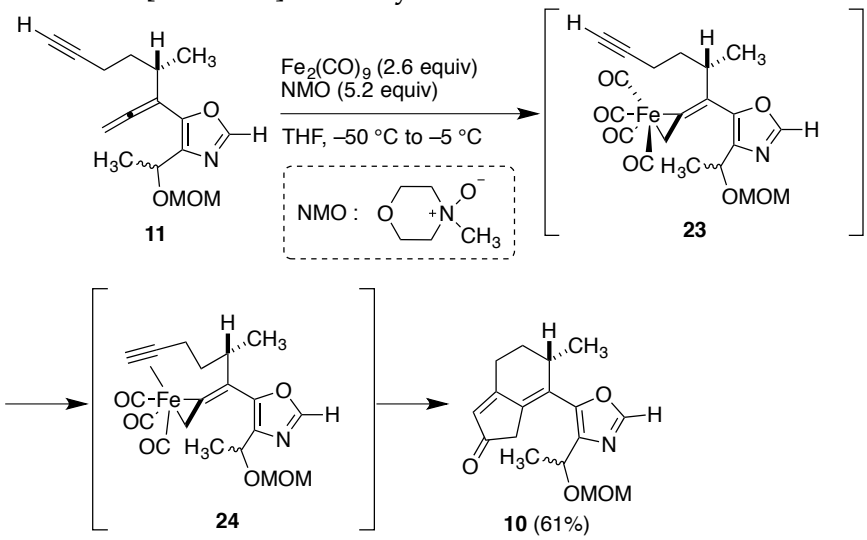
Scheme 3. Preparation of nonracemic allene **11**



• 1,1-disubstituted allene **11** was formed via regioselective Stille cross-coupling reaction of propargylic stannane **16** with 5-iodo-1,3-oxazoles **45**.[3]

2-3. [2 + 2 + 1] Carbocyclization (a)

Scheme 3. [2 + 2 + 1] Carbocyclization



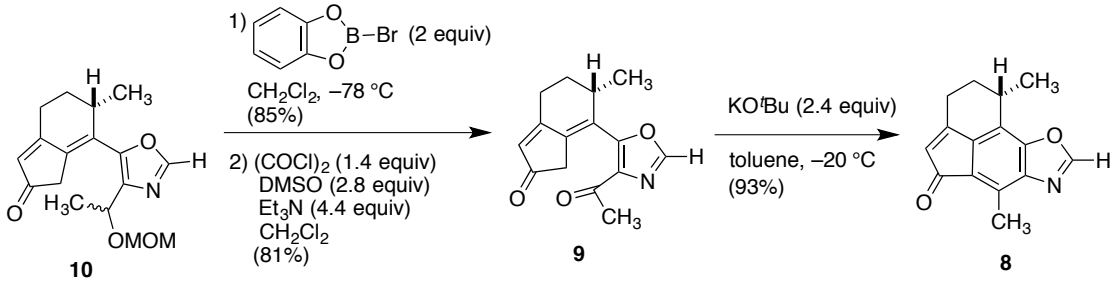
• [2 + 2 + 1] Carbocyclization proceeded under mild conditions when diiron nonacarbonyl was used.[2]

• [2 + 2 + 1] Carbocyclization did not took place under this conditions when $Co_2(CO)_8$ or $Mo(CO)_6$ was used. The use of $W(CO)_6$ led to poor conversions.

• Iron-mediated carbocyclizations was tolerant of wide range of sensitive functionality.

2-4. Benzoxazole Formation (b, c)

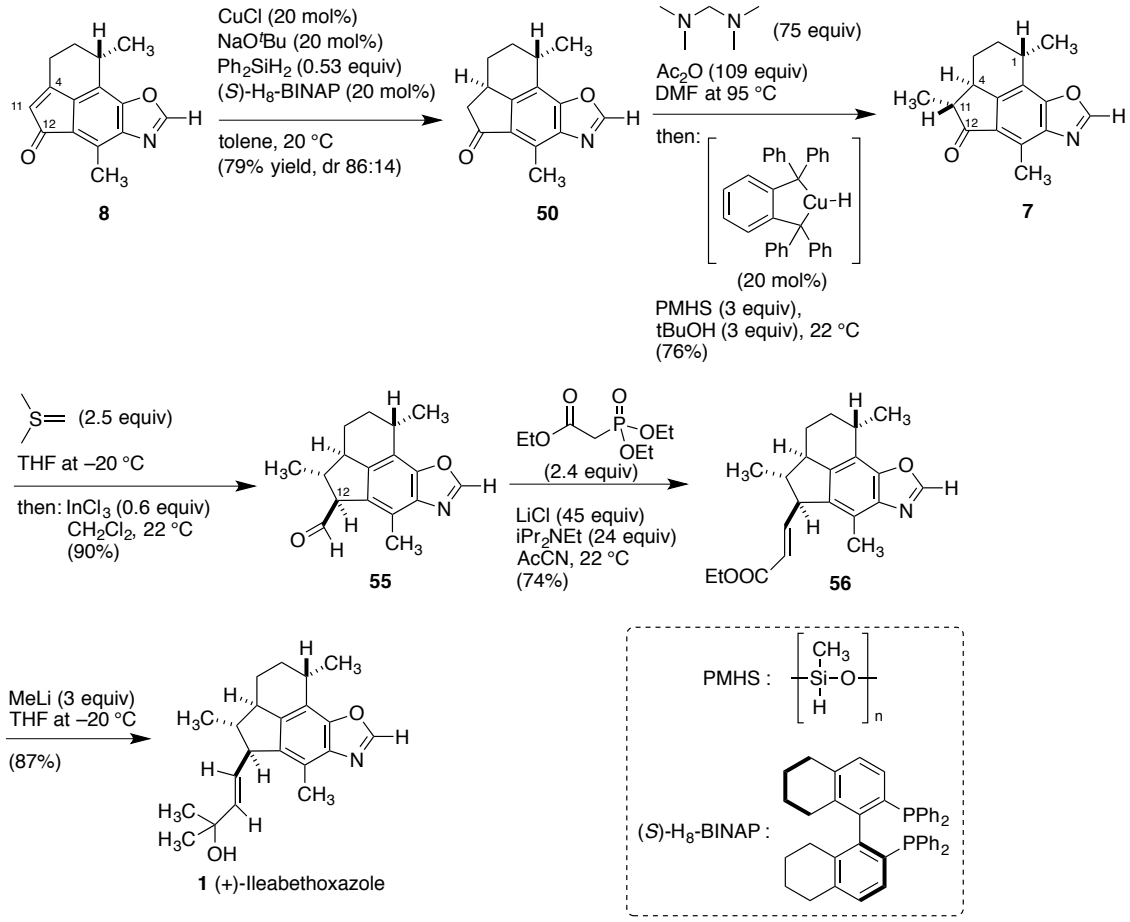
Scheme 4. Formation of the Tetracyclic Benzoxazole **8**



• Cyclization and aromatization was achieved via aldol condensation to give benzoxazole **8**.

2-5. Completion of the Synthesis of (+)-Ileabethoxazole (d, e)

Scheme 5. Completion of the synthesis of (+)-ileabethoxazole **1**



• Finally, the total synthesis of (+)-ileabethoxazole **1** was completed.

3. Conclusion

• The authors achieved the first total synthesis of (+)-ileabethoxazole.

• Key features included the effective preparation of 1,1-disubstituted allenes via a Stille cross coupling of propargylic stannanes, and iron-mediated [2 + 2 + 1] carbocyclization.

4. References

(1) Rodriguez, I. I.; Rodriguez, A. D.; Wang, Y.; Franzblau, S. G. *Tetrahedron Lett.* **2006**, *47*, 3229.

(2) Williams, D. R.; Shah, A. A.; Mazumder, S.; Baik, M.-H. *Chem. Sci.* **2013**, *4*, 238–247.

(3) Williams, D. R.; Shah, A. A. *Chem. Commun.* **2010**, *46*, 4297–4299.