Gold(I)-Catalyzed Bis-Spiroketalization: Synthesis of the Trioxadispiroketal-Containing A-D Rings of Azaspiracid

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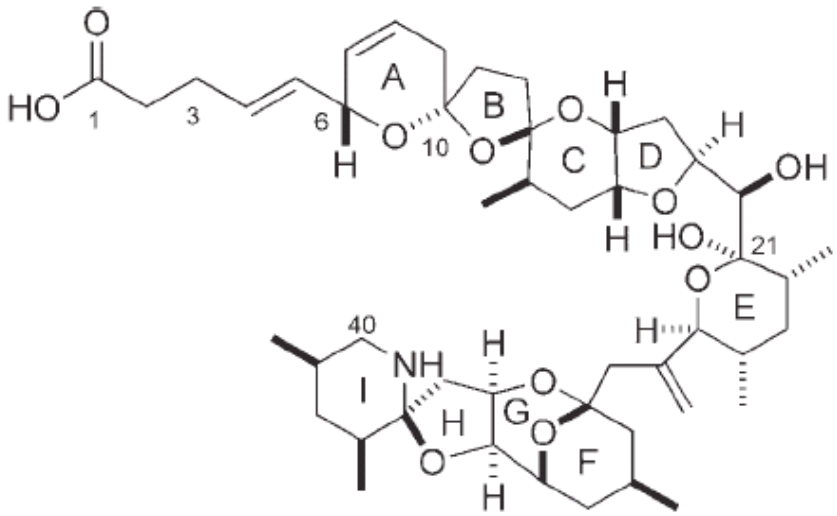
Azaspiracid-1

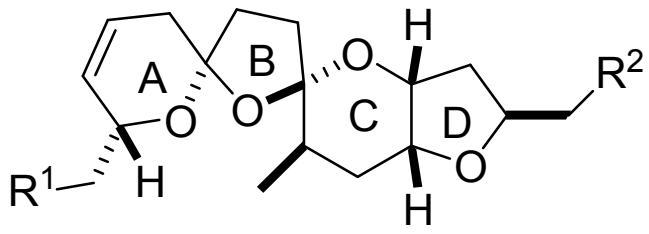
Mytilus edulis



- Isolated from Irish mussel (*Mytilus edulis*) in 1998.
- Marine toxin, responsible for human poisoning in the Netherlands in 1995.
- Shows acute and chronic effects on the liver, pancreas, thymus, and spleen in mice.
- One total synthesis by Nicolaou in 2004.

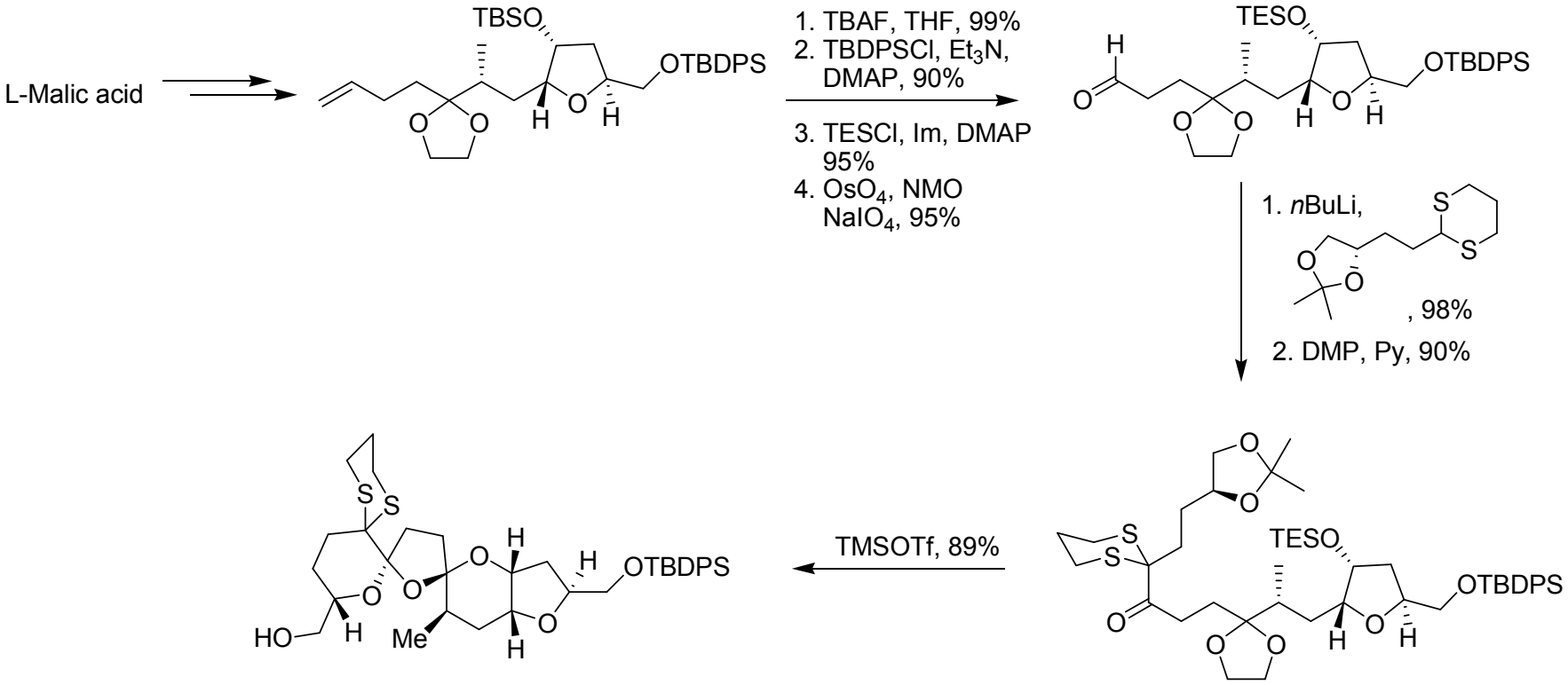
Forsyth, *Angew. Chem. Int. Ed*. **2007**, *46*, 279.

ABCD domain of Azaspiracid



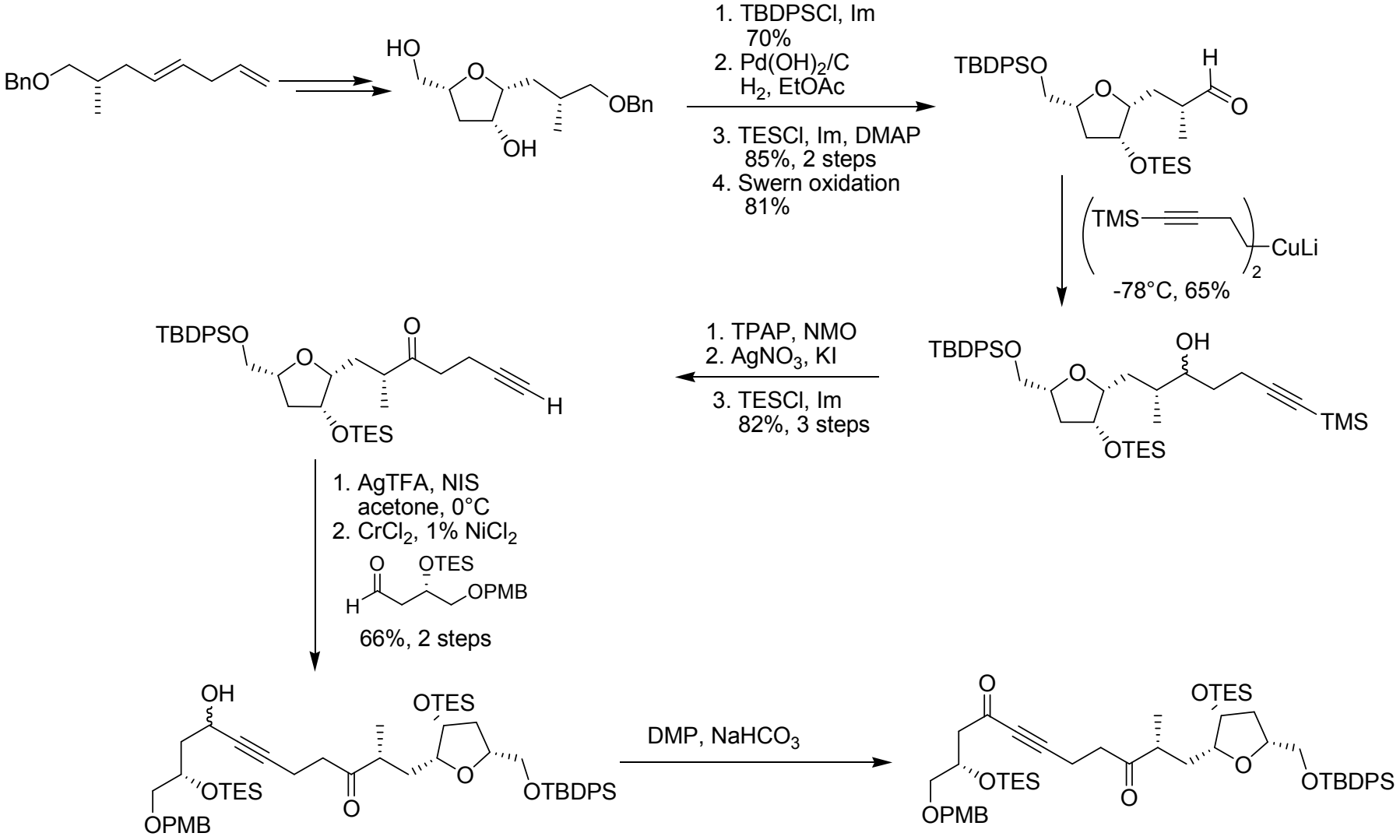
- Spiroketal
- 4 rings, 7 stereocenters
- Several wrong structures proposed before correct structure was elucidated by Nicolaou's total synthesis

Nicolaou's ABCD-ring synthesis



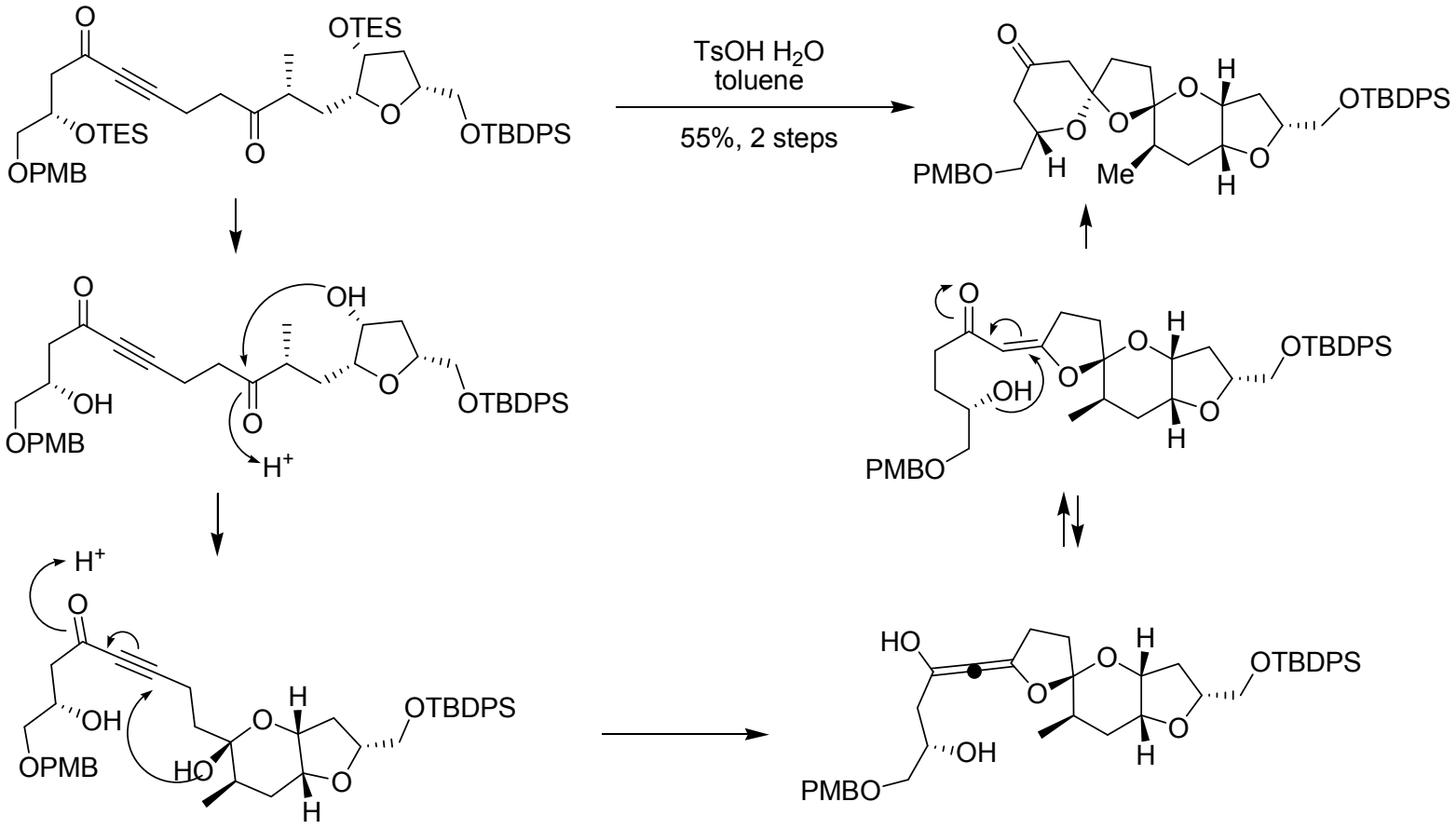
Nicolaou, *Angew. Chem. Int. Ed*. **2004**, *43*, 4318.

Forsyth's previous synthesis



Forsyth, *Org. Lett.* **2004**, *6*, 4159.

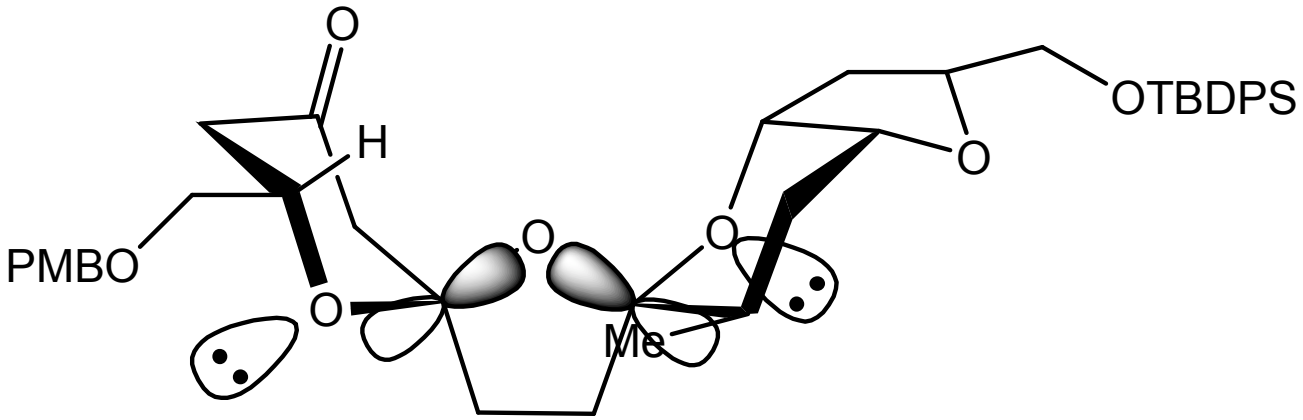
DIHMA spiroketalization



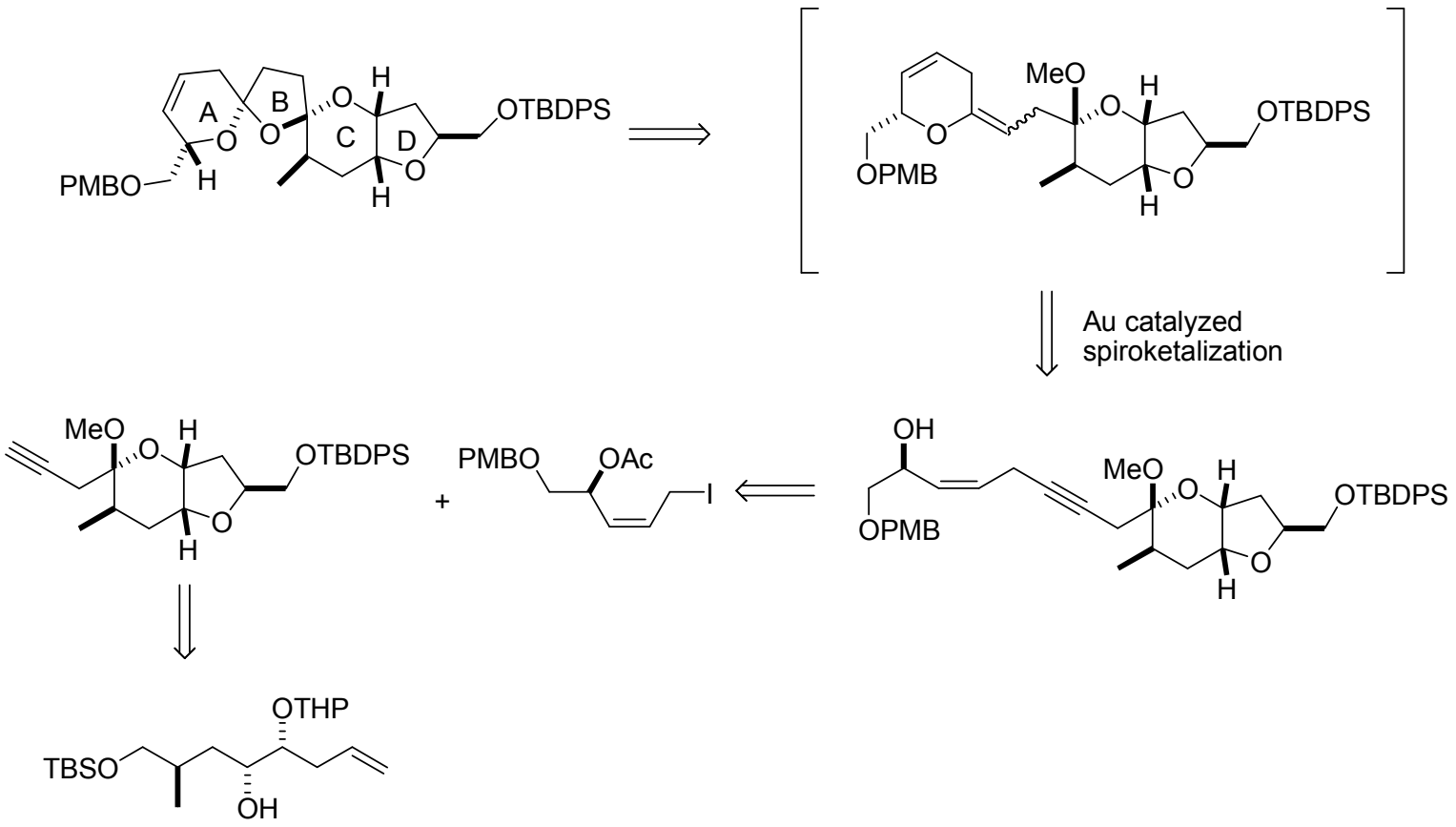
Forsyth, *Org. Lett.* **2004**, *6*, 4159.

Stereochemistry of the cyclization

The most thermodynamically stable product is formed: anomeric effect



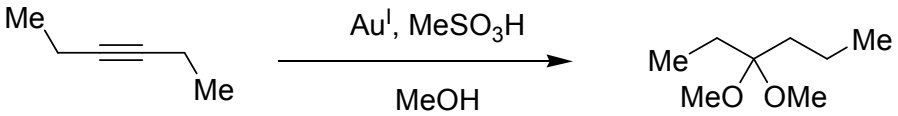
Forsyth's new approach
Retrosynthetic analysis



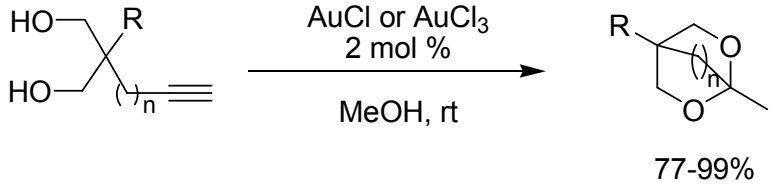
Forsyth, *Angew. Chem. Int. Ed*. **2007**, *46*, 279.

Gold catalyzed additions of alcohols to alkynes: ketal formation

Utimoto, *J. Org. Chem.* **1991**, *56*, 3729.

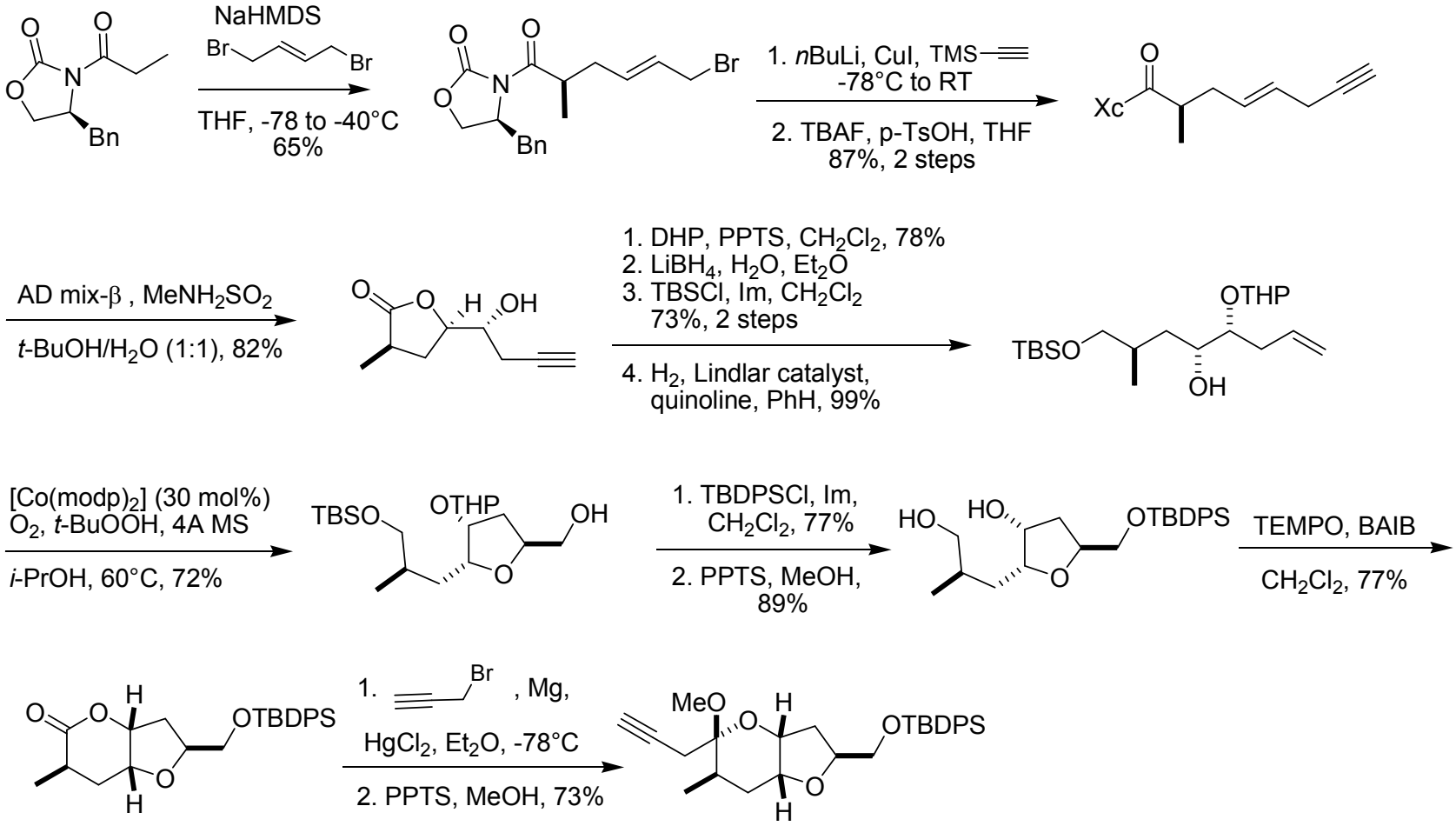


Teles, *Angew. Chem. Int. Ed.* **1998**, *37*, 1415.



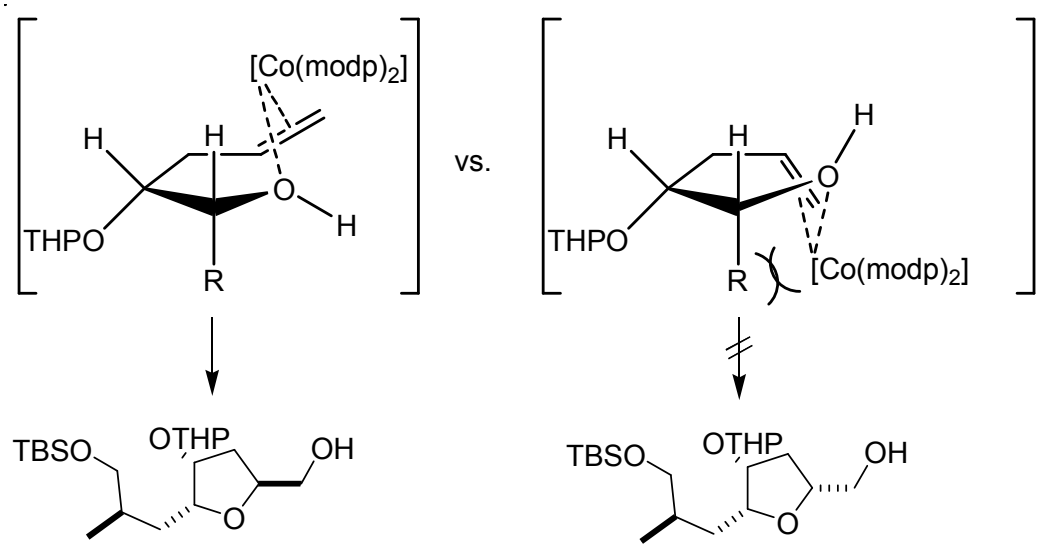
Genet, *J. Am. Chem. Soc.* **2005,** *127*, 9976.

Forsyth's new approach



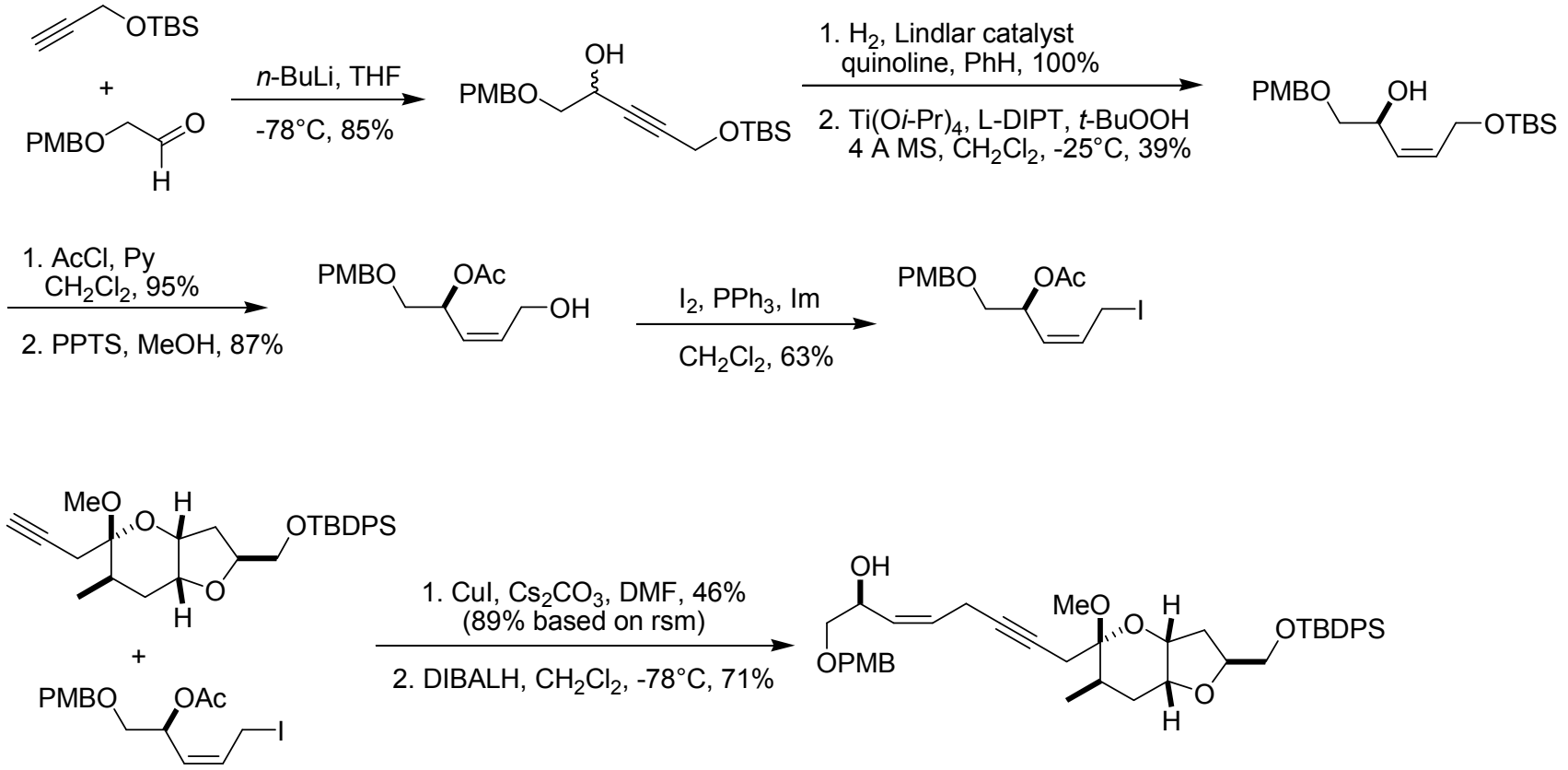
Forsyth, *Angew. Chem. Int. Ed*. **2007**, *46*, 279.

Forsyth's new approach
Co-mediated ring closure



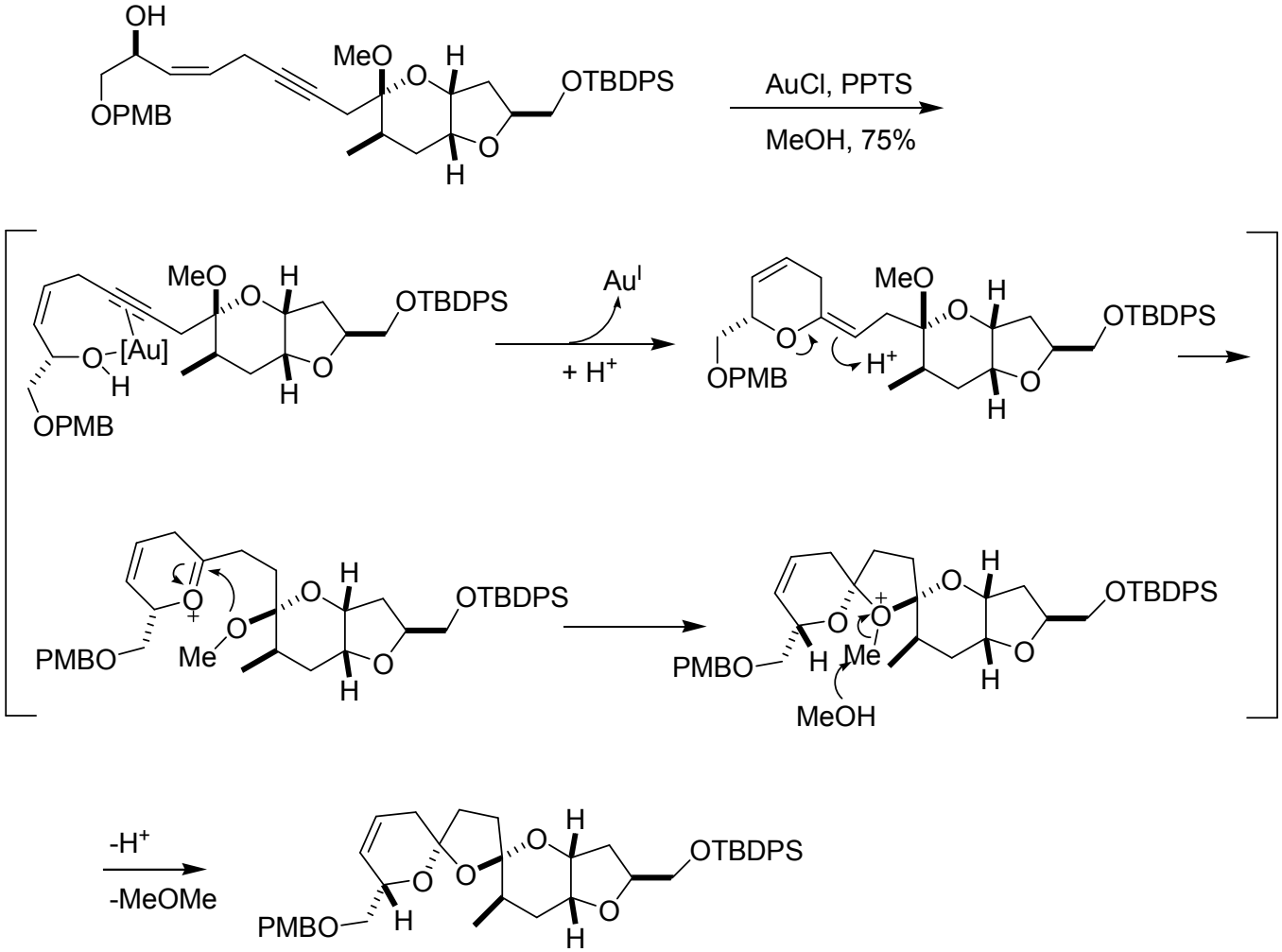
Forsyth, *Angew. Chem. Int. Ed*. **2007**, *46*, 279.
Mukaiyama, *Chem. Lett.* **1990,** 67.

Forsyth's new approach



Forsyth, *Angew. Chem. Int. Ed*. **2007**, *46*, 279.

Gold catalyzed spiroketalization



Forsyth, *Angew. Chem. Int. Ed*. **2007**, *46*, 279.

Conclusion

- Novel synthesis of ABCD domain of Azaspiracid was developed
- A cobalt catalyzed oxaetherification was used to form the 2,5-*trans*-fused trisubstituted tetrahydrofuran D ring
- Gold(I)-catalyzed *bis*-spiroketal formation was accomplished using an alkyne as a surrogate for the ketal
- This method provided the intermediate with the C7-C8 double bond in the correct position, which was the problem with the previous DIHMA approach