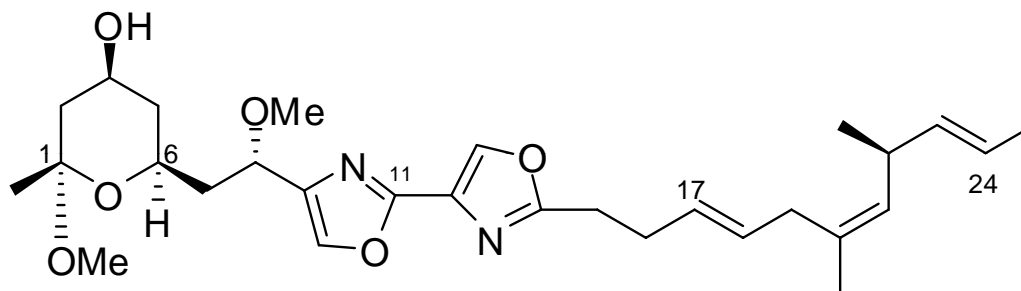


Hennoxazole A



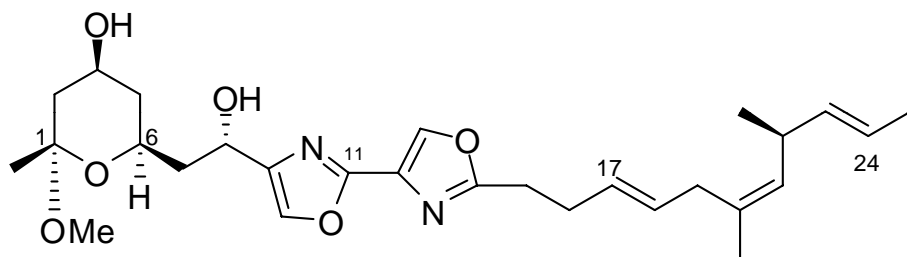
Philip Williams
Group Meeting
December 12, 2007

Discovered

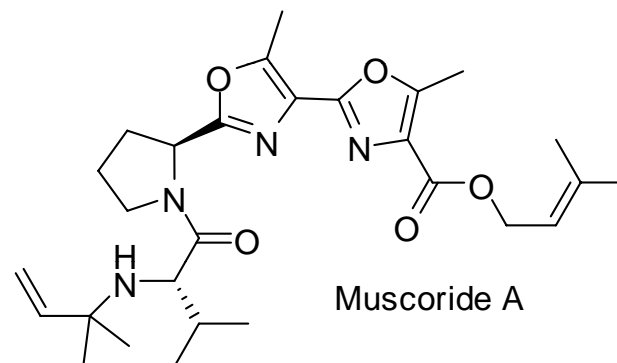
- Discovered by Paul Scheuer at the University of Hawaii in 1991.
- Isolated 480mg Hennoxazole A from 4.5kg from the sponge *Polyfibrospongia* species.
- Also obtained Hennoxazoles B-D, though smaller amounts.
- Initial bio-activity assays displayed that Hennoxazole A is active against herpes simplex virus type 1 (IC_{50} 0.6 $\mu\text{g}/\text{mL}$) and has peripheral analgesic activity similar to indomethacin when tested in mice.
- The absolute stereochemistry was not fully determined.



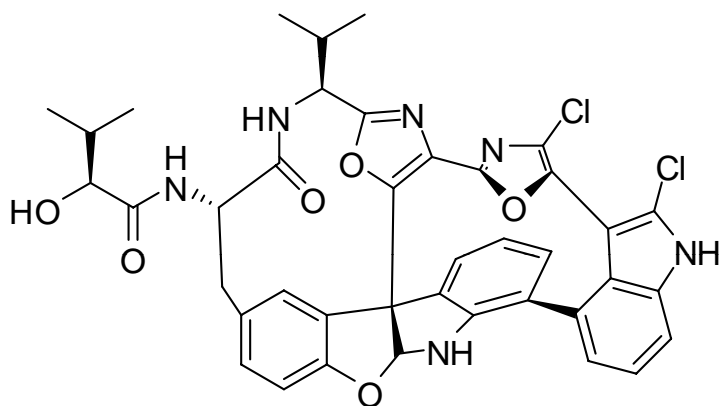
Structure and Design



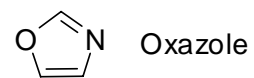
(+) Hennoxazole A



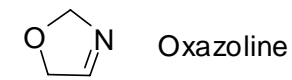
Muscoride A



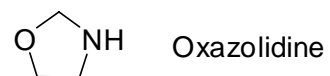
Diazonamide A



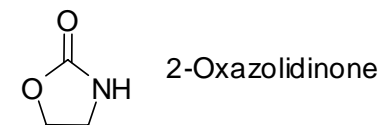
Oxazole



Oxazoline

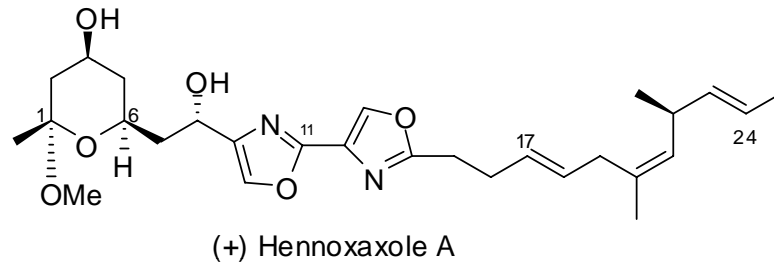


Oxazolidine



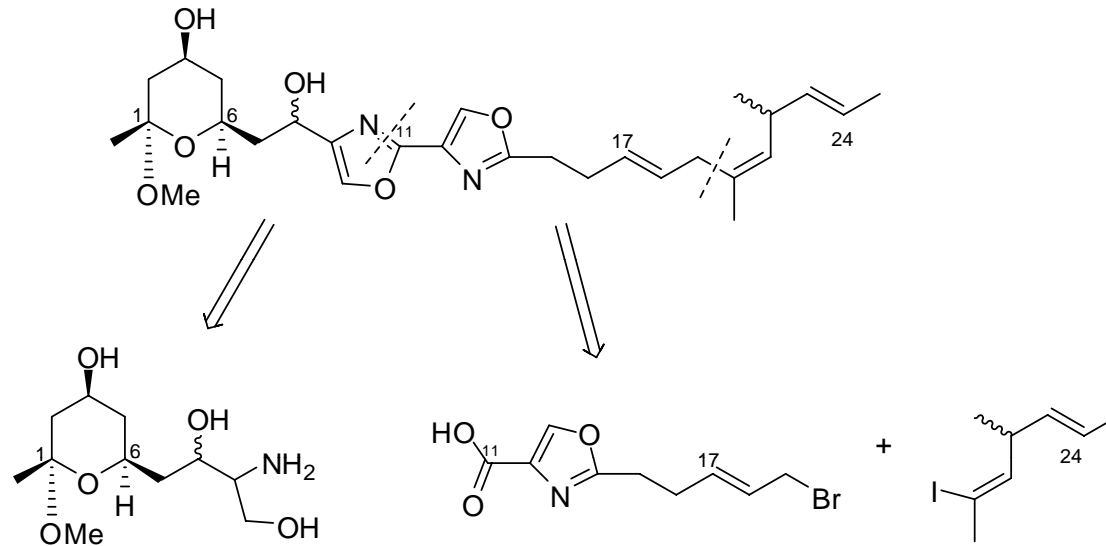
2-Oxazolidinone

Retro?



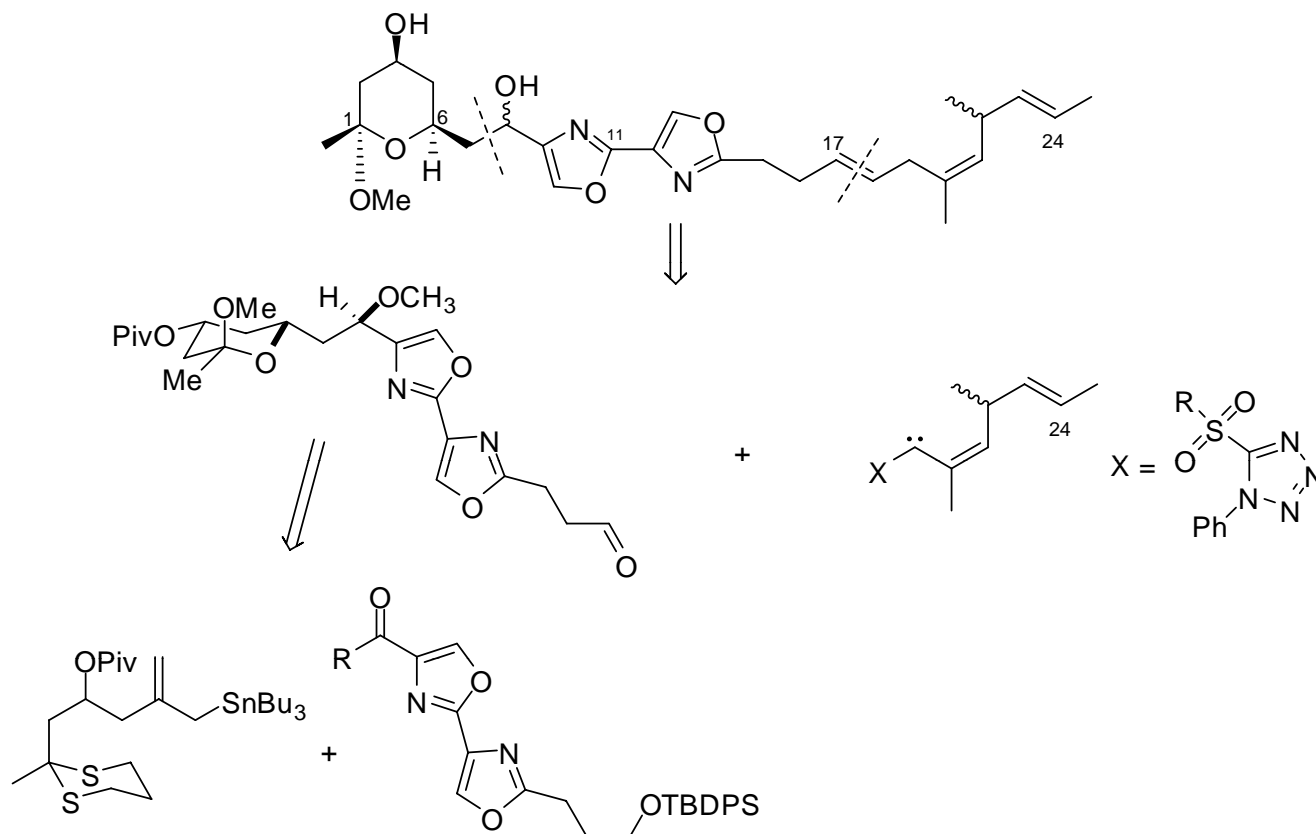
4 Total Syntheses: Wipf, Williams, Shioiri, and Smith.

Retro - 1996 - Wipf



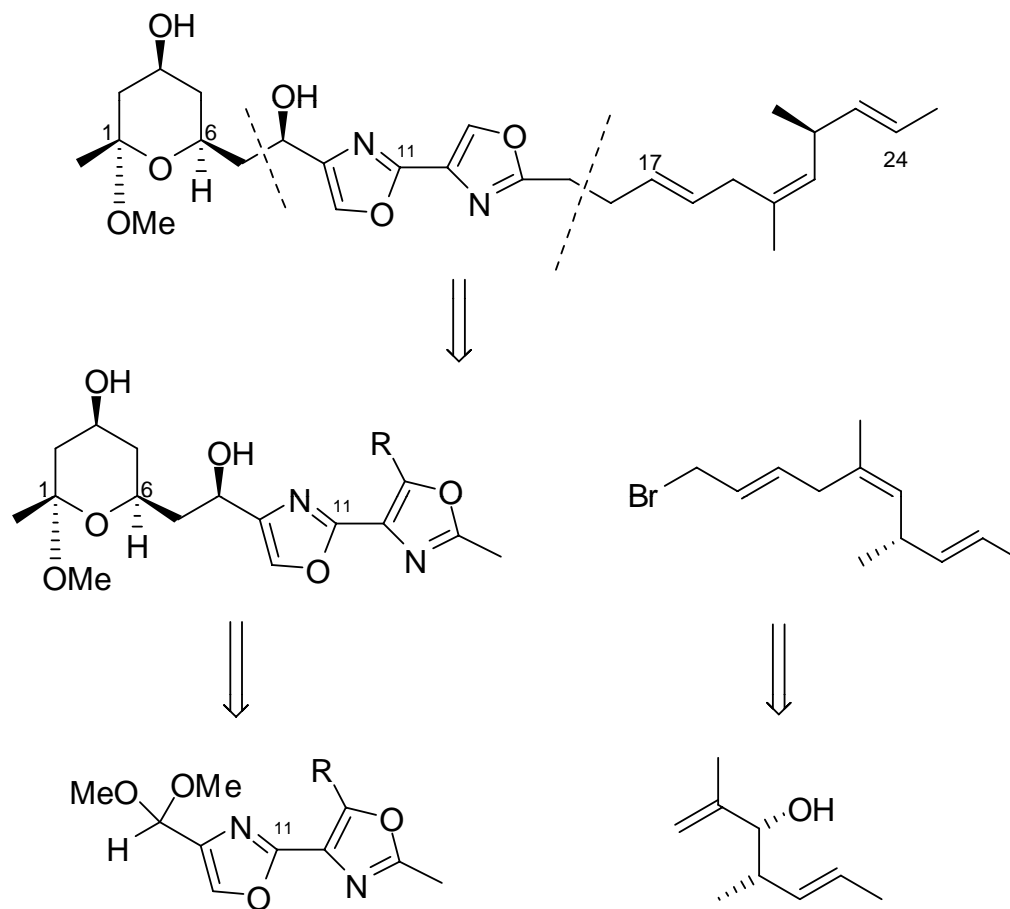
- Wipf was the first to synthesize Hennoxazole A.
- Designed his endgame to couple the bis-oxazole moiety last – the big challenge.
- Remember, he didn't know the stereochemistry at C8 and C22!

Retro – 1999 – Williams, D.



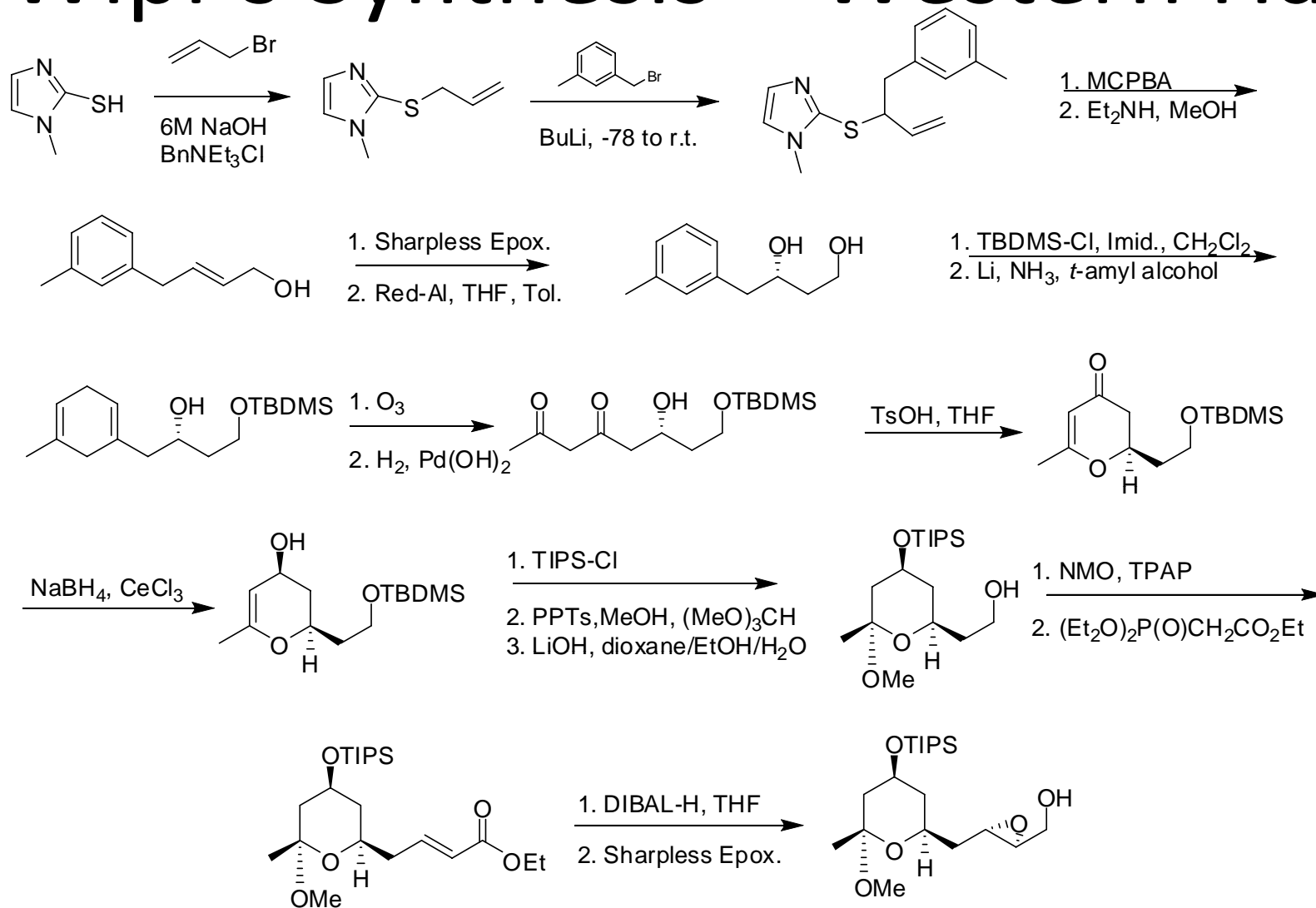
- Concern over the stability of the skipped triene caused Williams to build that in to the molecule last.

Retro – 2007 - Smith



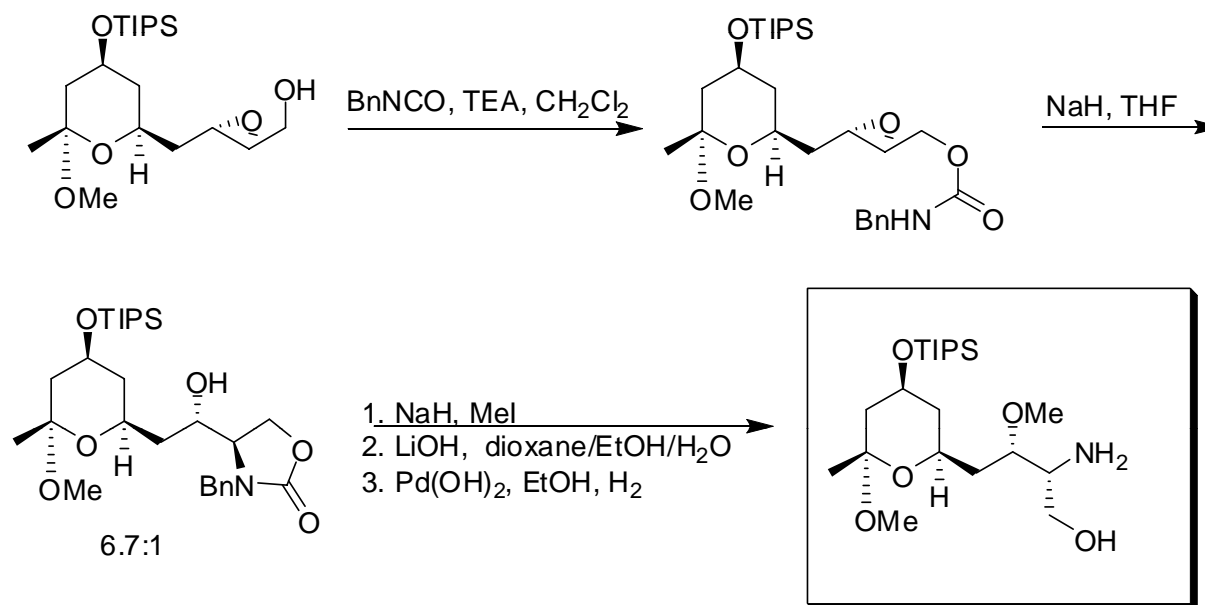
- Smith intended to apply some of the oxazole alkylation work his lab had been working on.

Wipf's Synthesis – Western Half



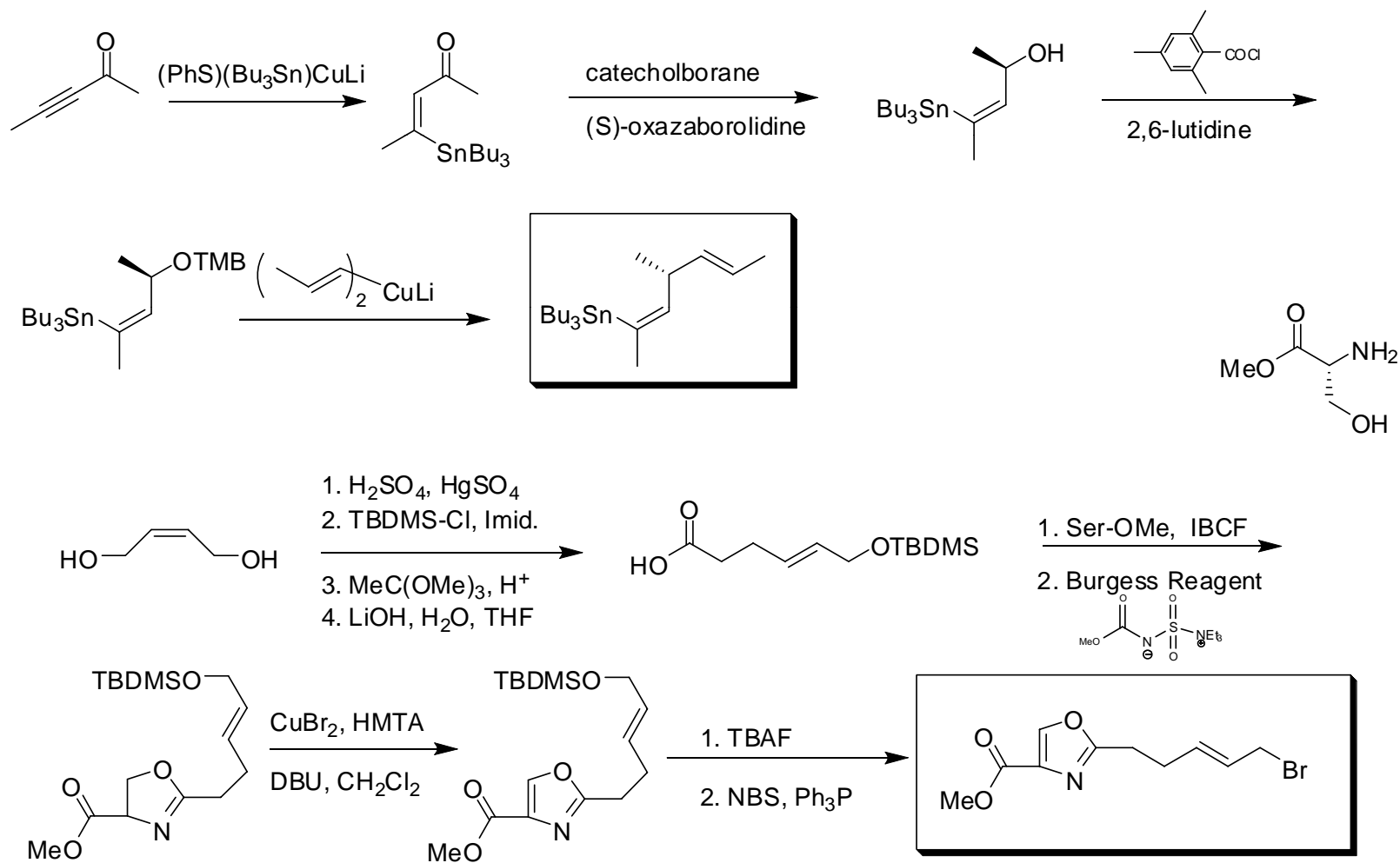
- Absolute configuration of C8 stereocenter was chosen arbitrarily.
- Installing the desired anomer of the mixed acetal was challenging due to the potential elimination of the beta silyl ether.

Wipf's Synthesis – Western Half



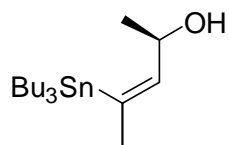
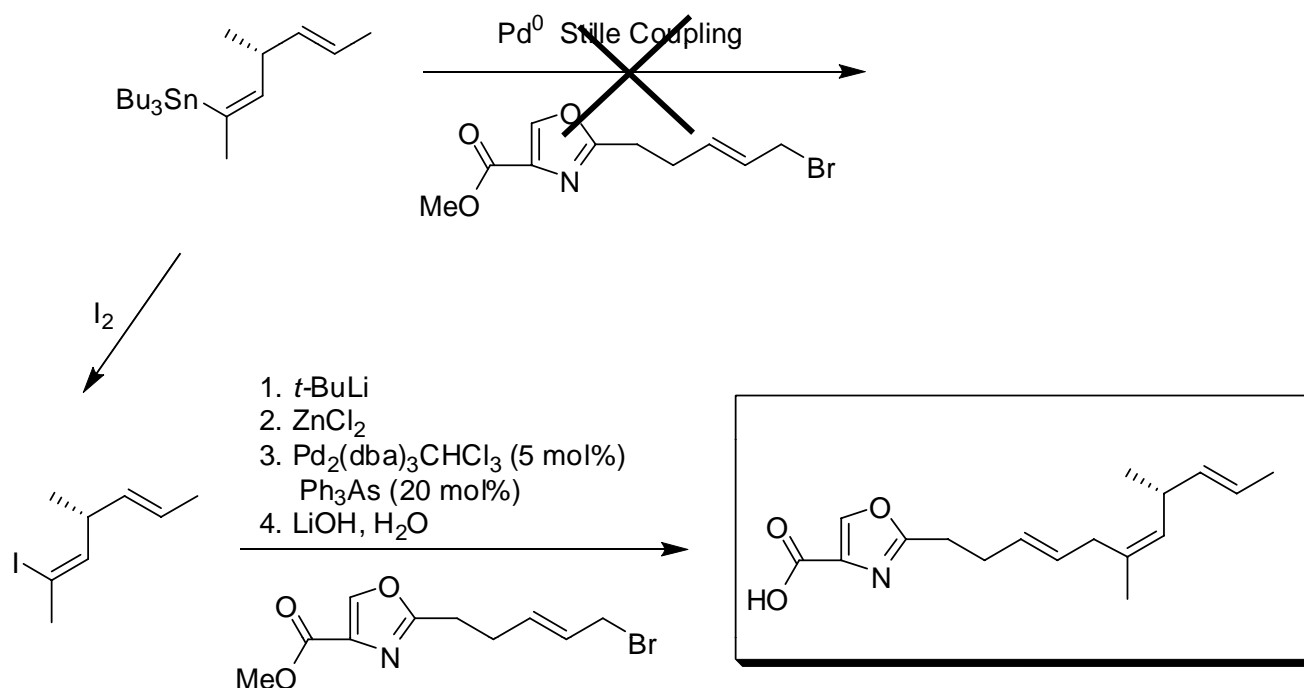
- Urethane cyclization proceeded in a 6.7:1 ratio of isomers.
- 22 steps, 5% yield.

Wipf's Synthesis – Eastern Half



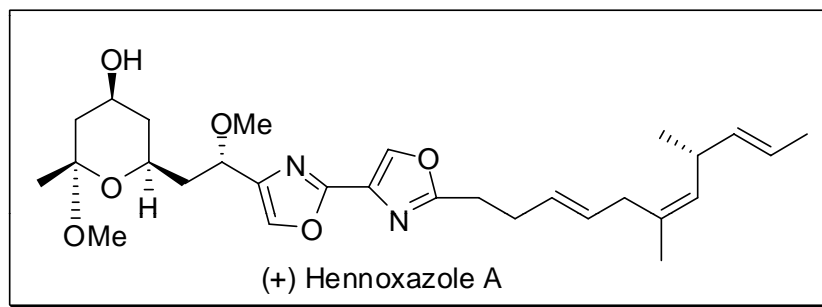
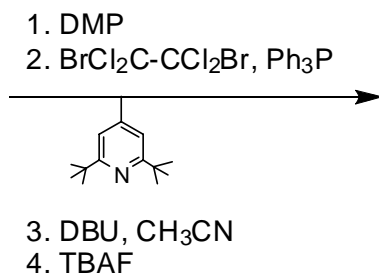
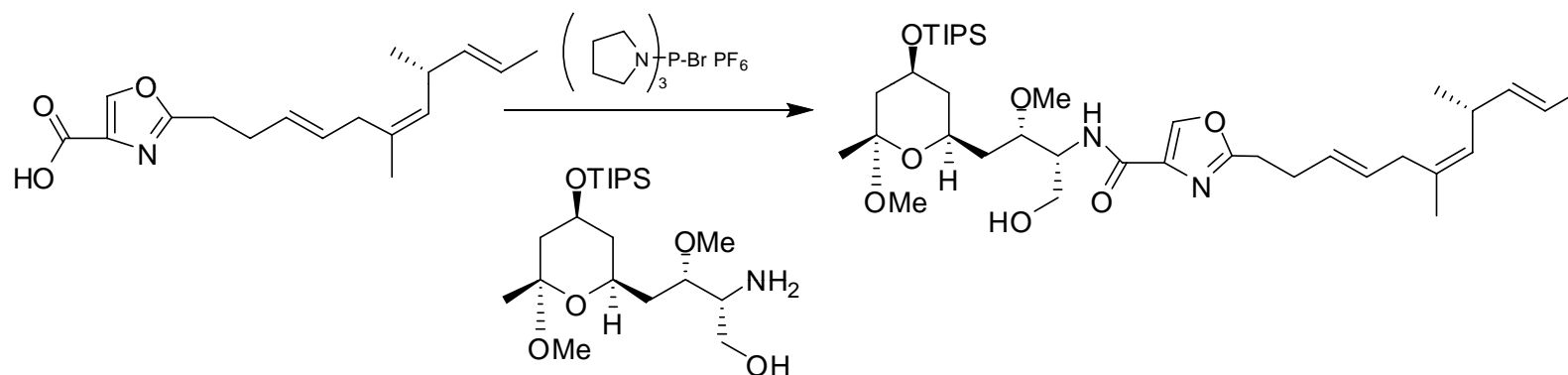
- EWG was critical for first oxazole formation.
- Methyl stereocenter at C22 was also arbitrarily chosen

Wipf's Synthesis - coupling



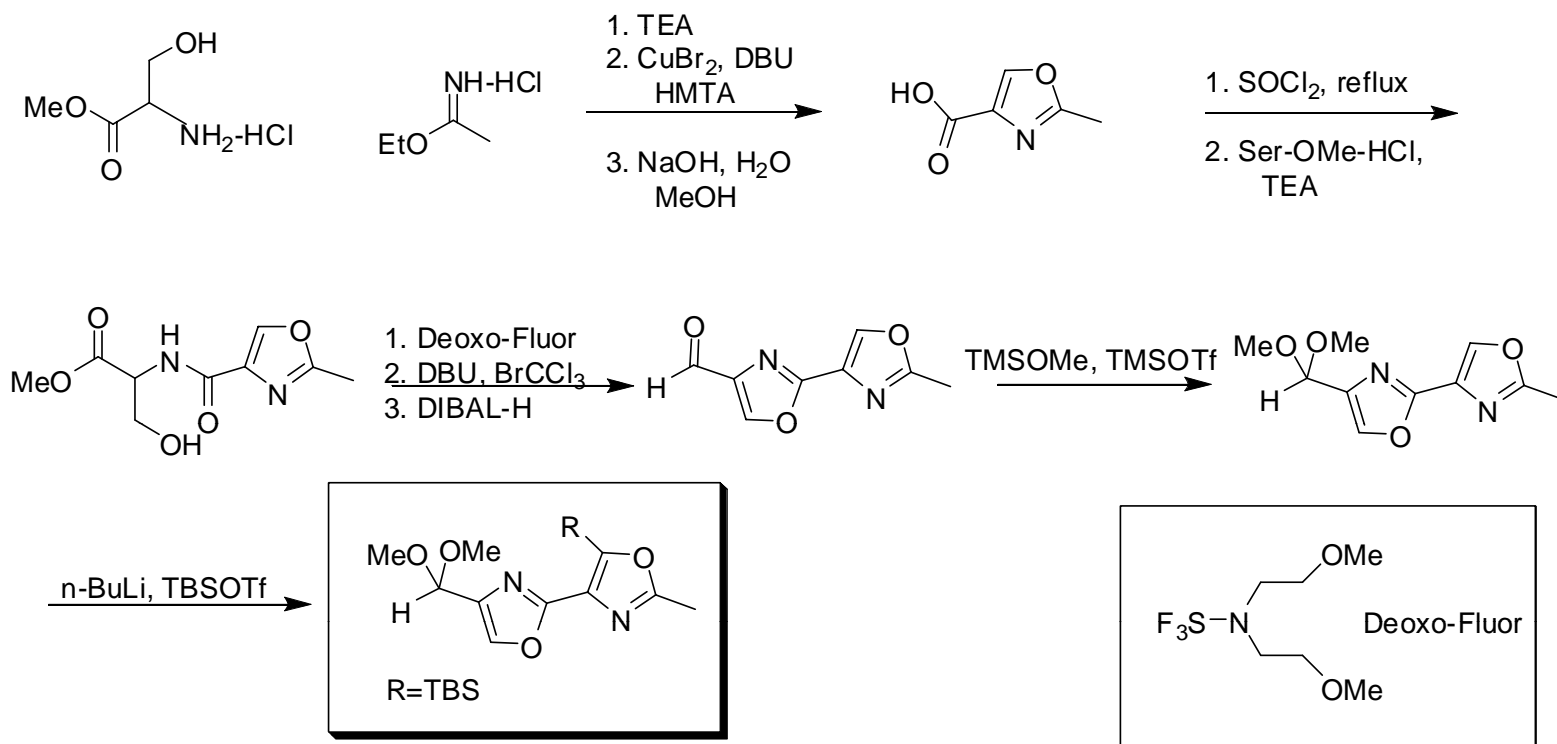
- Stille coupling failed presumably due to the severe A¹⁻³ strain of the stannane.

Wipf's Synthesis – Endgame

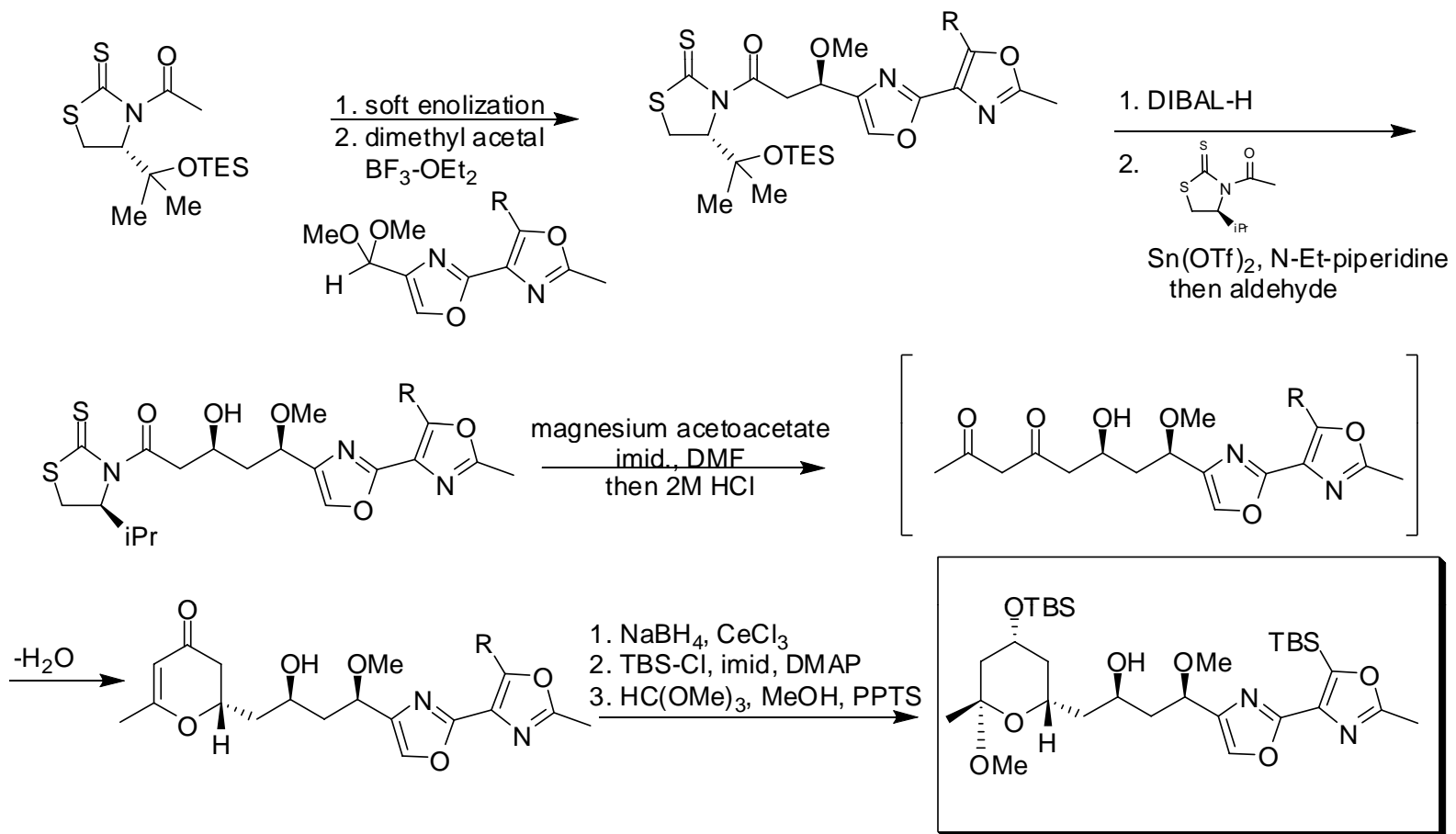


- 28 steps (longest sequence).
- Spectroscopic investigation determined the natural stereoisomer of the natural product. Matches up with *van't Hoff's* principle of optical superposition.

Smith's Synthesis – Western Half

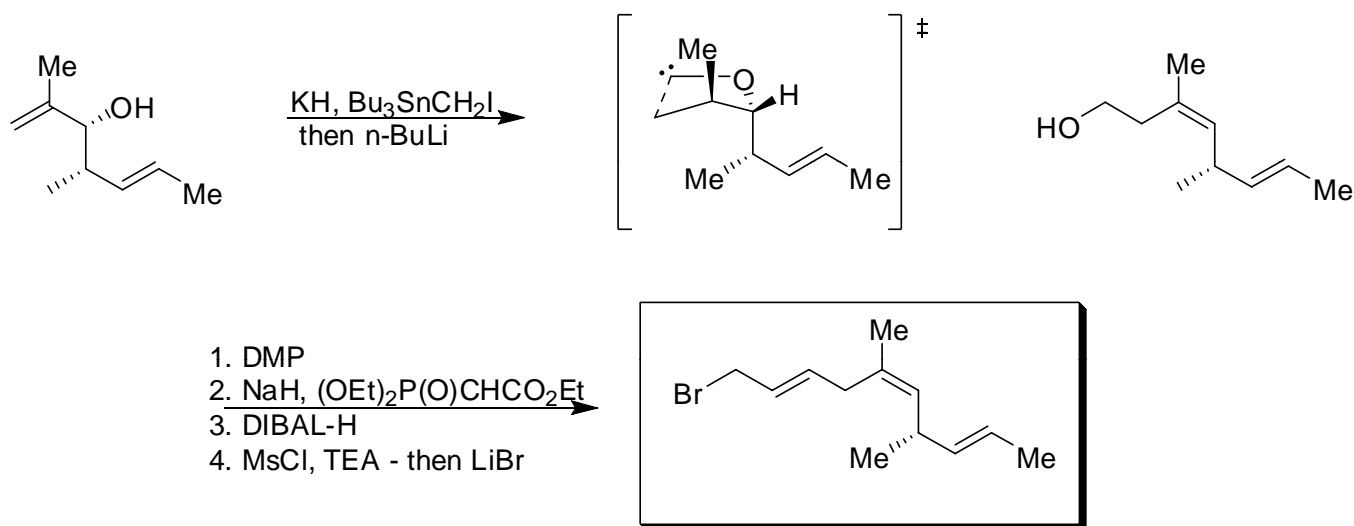


Smith's Synthesis – Western Half



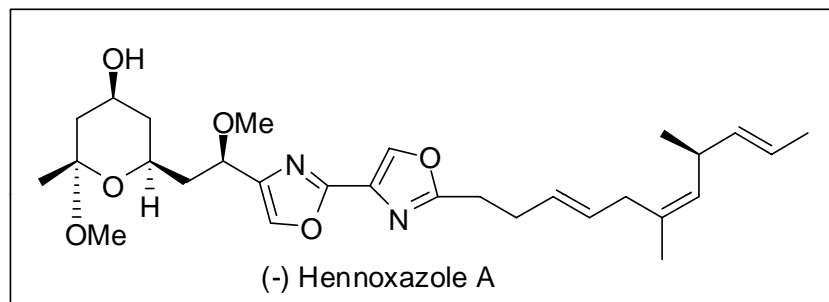
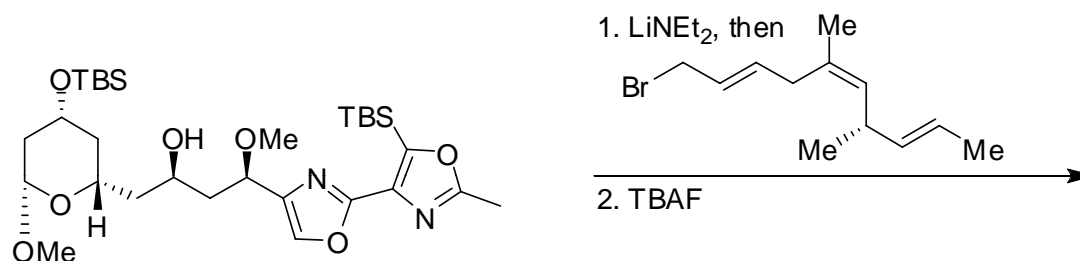
- Many of the current directed acetate aldol auxiliaries were tested.

Smith's Synthesis – Eastern Half



- Smith's design of a [2,3] Wittig-Still rearrangement allowed him to access this fragment in 6 steps fewer than Williams' synthesis.

Smith's Synthesis - Endgame



- 14 steps from commercially available materials. (really 17 steps...)
- Employed a one-pot acylation/decarboxylation/cyclodehydration and determined the alkylation selectivities for bis-oxazoles.

References

- Scheuer, P. J., *et. al*, *J. Am. Chem. Soc.*, **1991** 113, 3173.
- Wipf, P., *et. al*, *Chimia*, **1996** 50(4), 157.
- Wipf, P., Miller, C.P., *J. Org. Chem.*, **1993** 58, 3604.
- Smith, T.E., *et. al.*, *J. Org. Chem.* **2007** ASAP.
- Smith, T.E., *et. al.*, *Org. Lett.*, **2004** 6(14), 2317.
- Smith, T.E., Balskus, E.P., *Heterocycles*, **2002** 57(7), 1219.
- Smith, T.E., *et. al.*, *Org. Lett.*, **2007** 9(6), 1153.
- Shioiri, T., *et. al.*, *Org. Lett.*, **2000** 2(26), 4169.
- Shioiri, T., *et. al.*, *Synlett*, **1997** 1, 109.
- Shioiri, T., *et. al.*, *Heterocycles*, **1998** 47(8), 73.
- Leahy, J. W., *et. al.*, *Synlett*, **2007** 4, 623.
- Williams, D.R., *et. al.*, *Tett. Lett.*, **1997** 38(3), 331.
- Williams, D., *et. al*, *J. Am. Chem. Soc.*, **1999** 121, 4924.