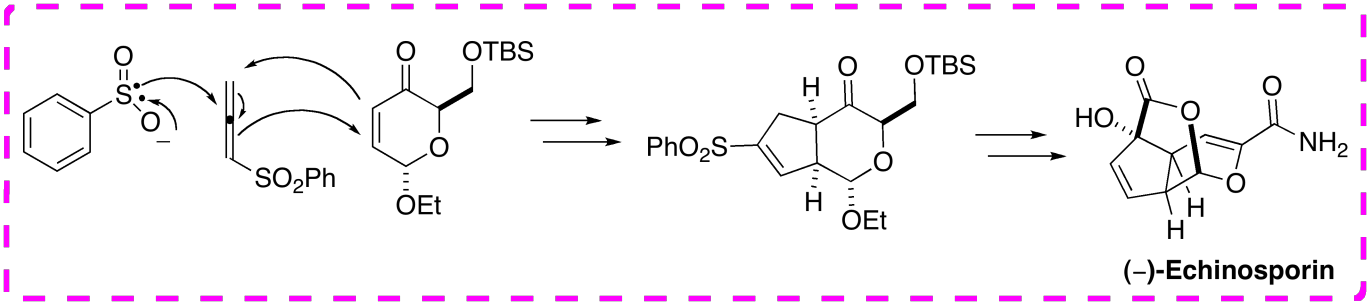
A New Stereocontrolled Synthetic Route to (−)-Echinosporin from D-Glucose via Padwa Allenylsulfone [3+2]-Anionic Cycloadditive Elimination



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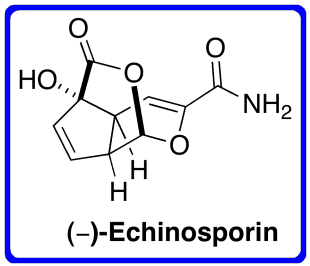
Org. Lett. ASAP

Elisa Farber – Current Literature – 06/09/2012

(–)-Echinosporin

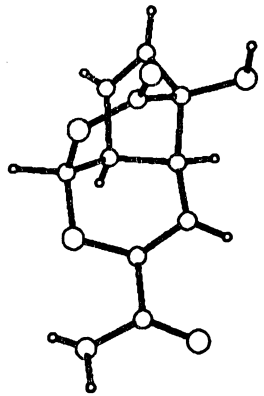
- In 1981 Sato and co-workers isolated (−)-echinosporin, from *Streptomyces echinosporus and* discovered in the microbial screening of a mexican soil sample.



(–)-Echinosporin

- Exhibited weak antibacterial activities MIC 100 µg/mL against with *Proteus vulgaris, Salmonella typhosa*, *Shigella sonnei*, and higher than 200 µg/mL against *Escherichia coli* and *Bacillus subtilis*.

- Exhibited antitumor activity against systems such as leukemia P388, P388/VCR and fibrosarcoma Meth 1. Marginal activity against melanoma B16 and sarcoma 180.


(Ref. 2)

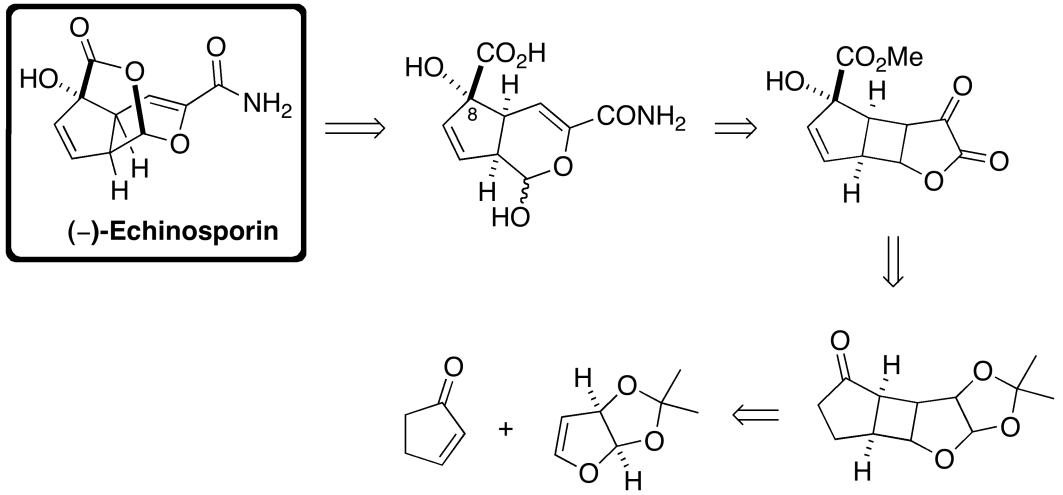
- It is a highly oxygenated tricyclic structure initially deduced by chemical derivatization and by NMR analysis and confirmed by X-ray analysis.[1] The absolute configuration was defined later by Amos B. Smith and co-workers.[2]

[1] Hirayama, N.; Iada, T.; Shirahata, K.; Ohashi, Y.; Sasada, Y. Bull. Chem. Soc. Jpn **1983**, 56, 287.
[2] Smith, A. B., III; Sulikowski, G. A.; Fujimoto, K. *J. Am. Chem. Soc.* **1989**, *111*, 8039.

First Total Synthesis of (–)-Echinosporin

- In 1989, Amos B. Smith and co-workers reported the first total synthesis and absolute configuration of (–)-echinosporin.

- Retrosynthesis:

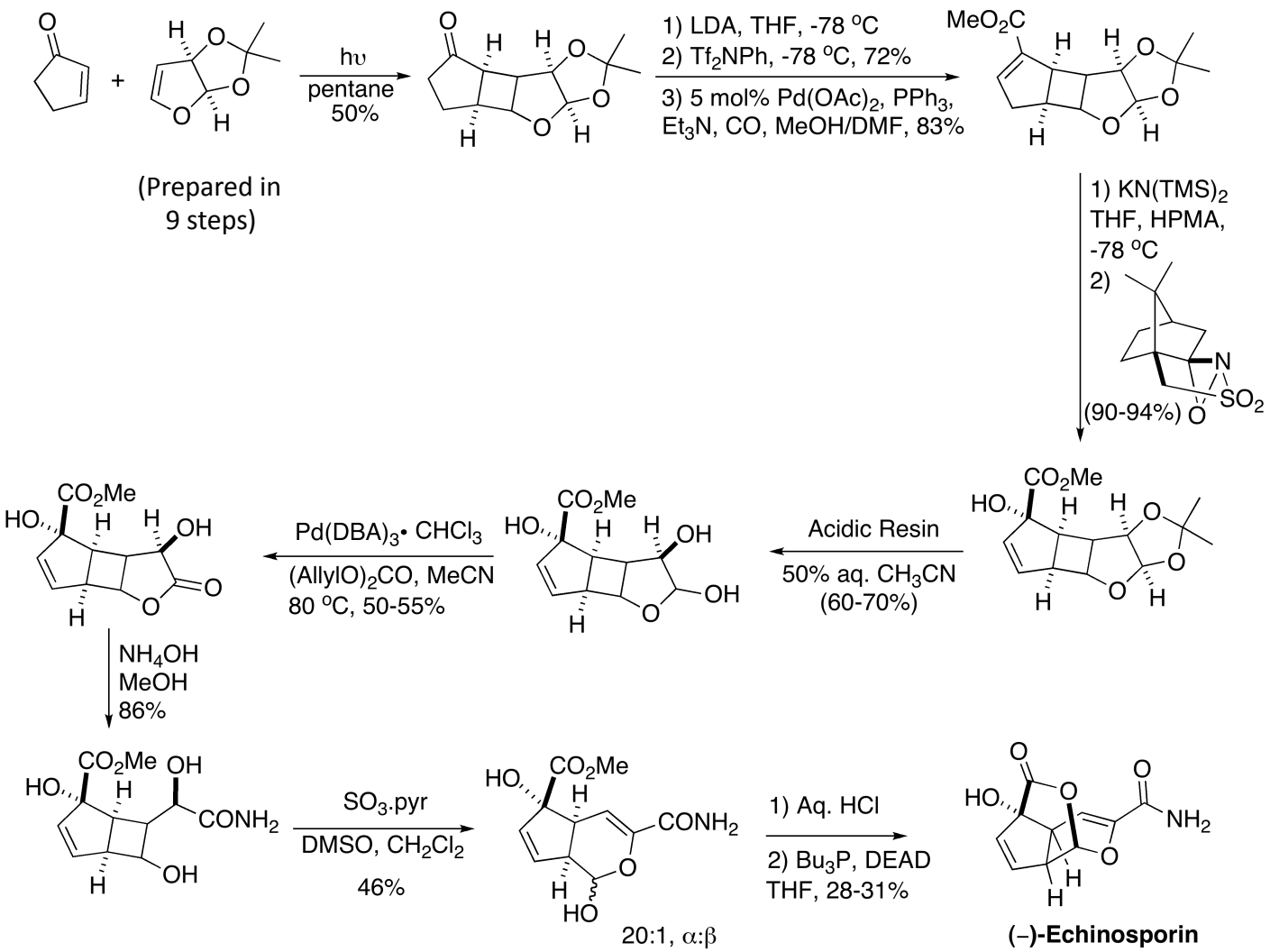


Key Steps:

- [2+2]-Photocycloaddition of cyclopentenone to dihydrofuran
- Functionalization at C-8: Pd-catalyzed carbomethoxylation of the derived enol triflate
- Stereocontrolled deconjugative α-hydroxylation

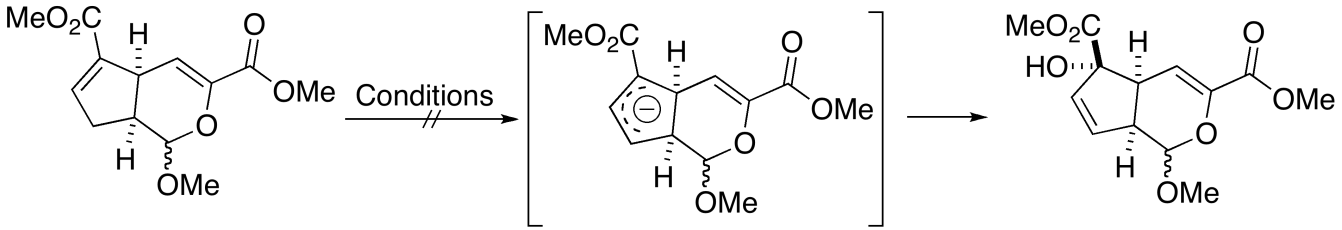
Smith, A. B., III; Sulikowski, G. A.; Fujimoto, K. *J. Am. Chem. Soc.* **1989**, *111*, 8039

First Total Synthesis of (–)-Echinosporin



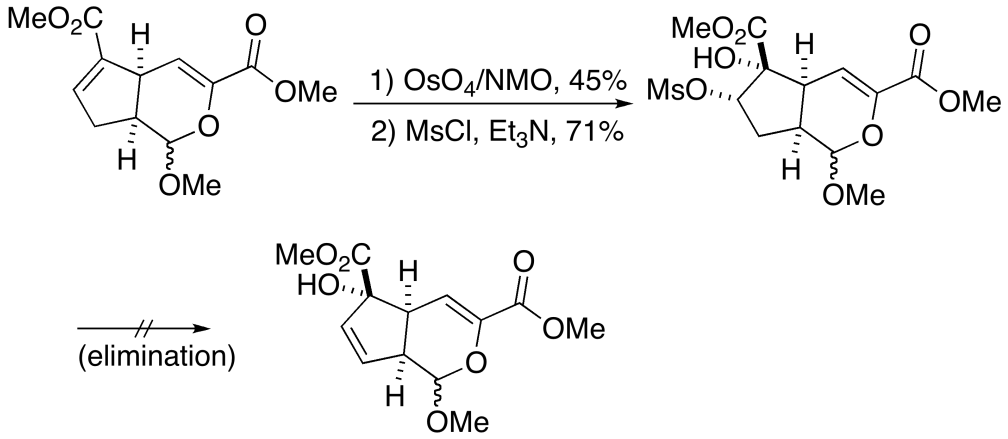
Smith, A. B., III; Sulikowski, G. A.; Fujimoto, K. *J. Am. Chem. Soc.* **1989**, *111*, 8039

Weinreb's Approach to (–)-Echinosporin



Bases: LDA, LiTMP, KH, KO*t*-Bu
Electrophiles: MoOPh, D_2O, MeI, TMSCl

- Alternative Attempt:

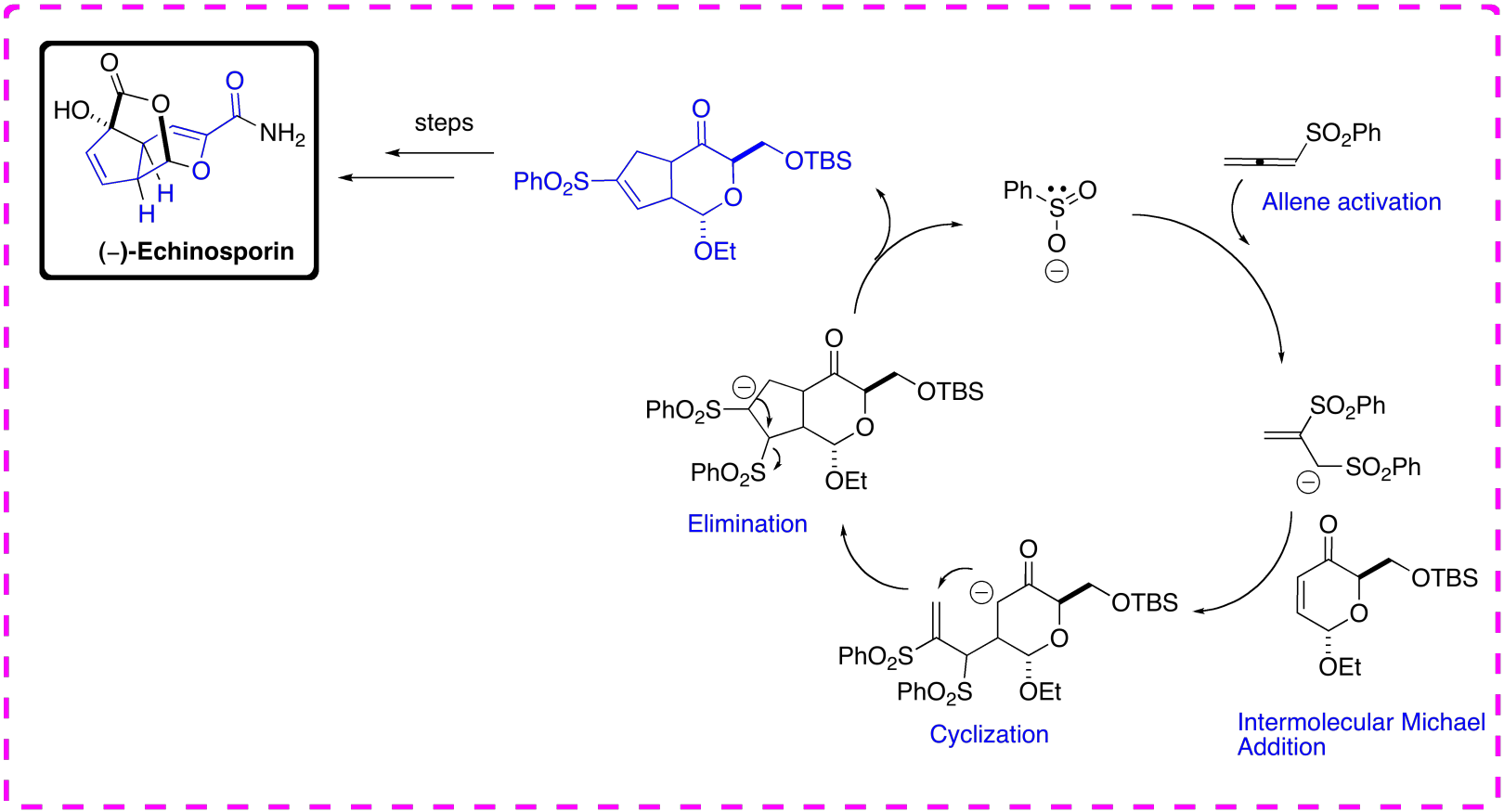


* A number of bases were used to promote elimination

Kinsella, M. A.; Kalish, V. J.; Weinreb, S. M. *J. Org. Chem.* **1990**, 55 , 105.

Title Paper

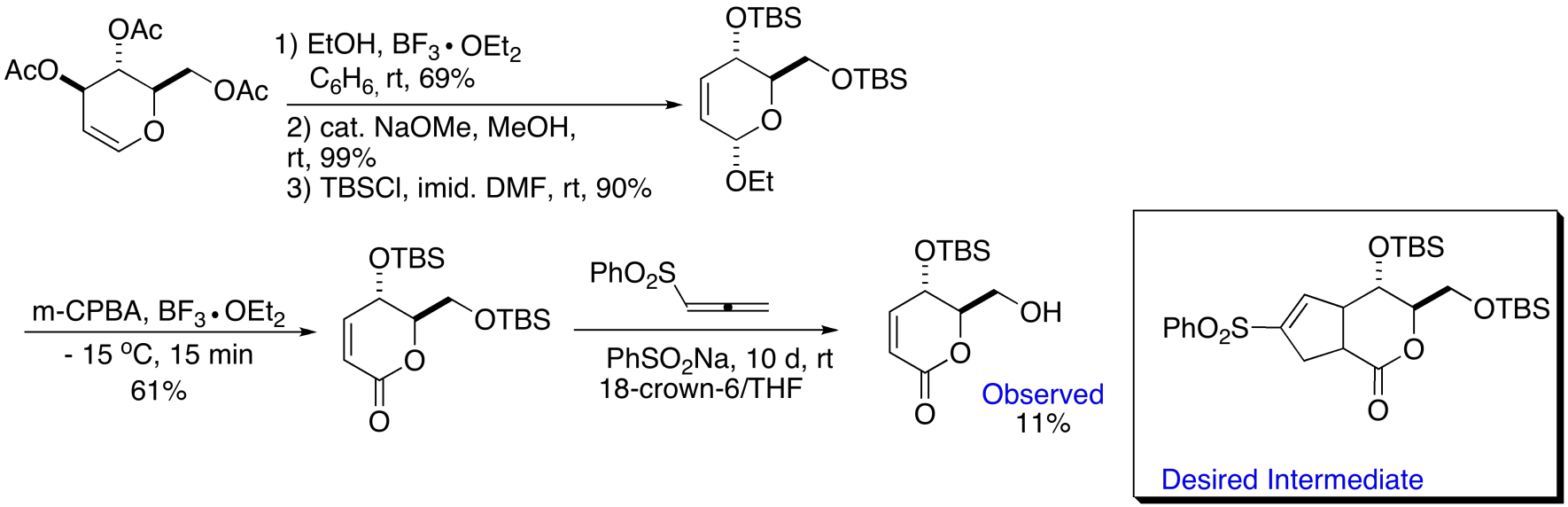
- **Interested in using Padwa Allenylsulfone [3+2]-Anionic Cycloadditive Elimination**



Based on: Chem. Eur. J. 2010, 16, 5443.

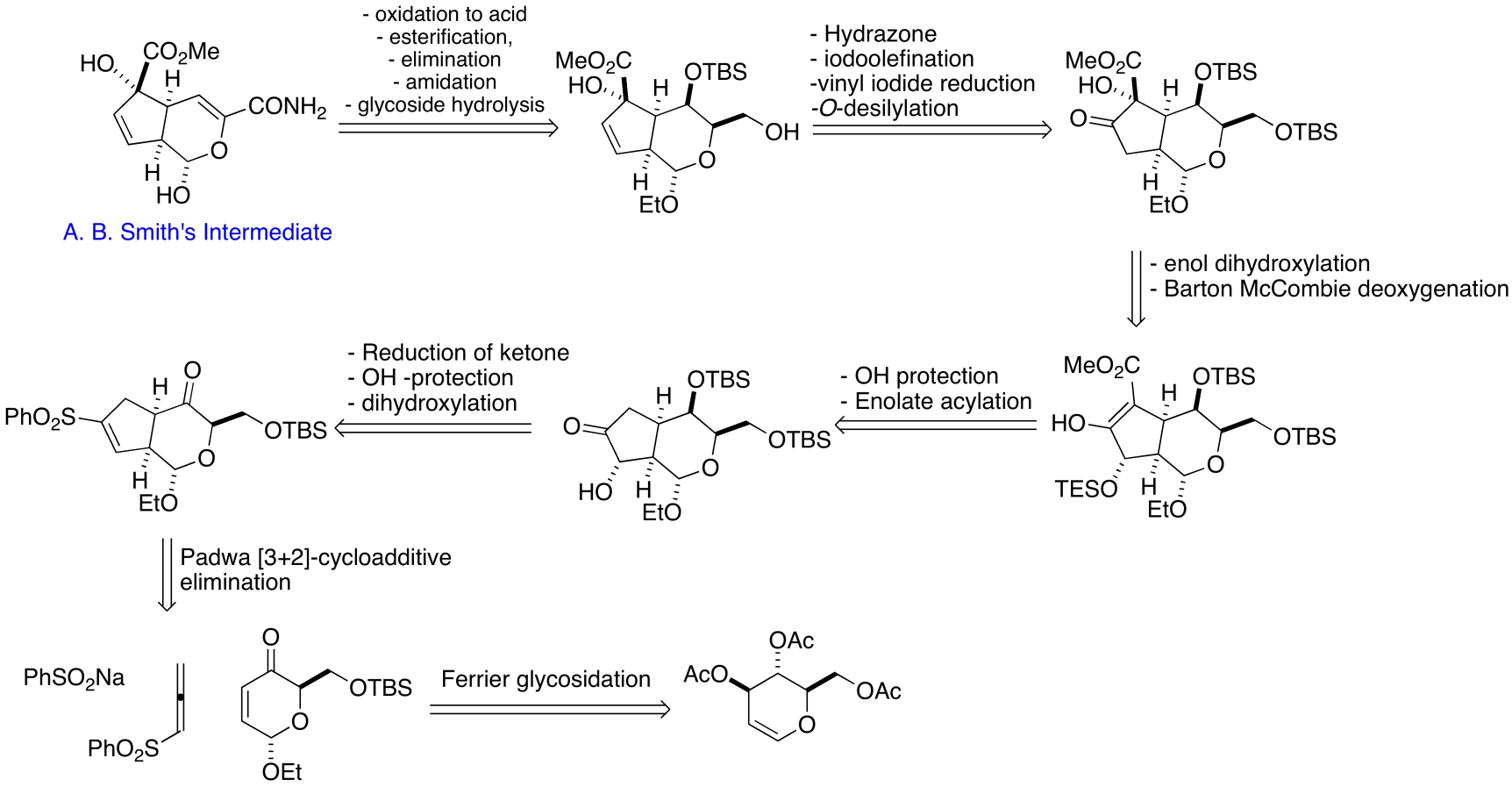
Title Paper

- **First Plan:**

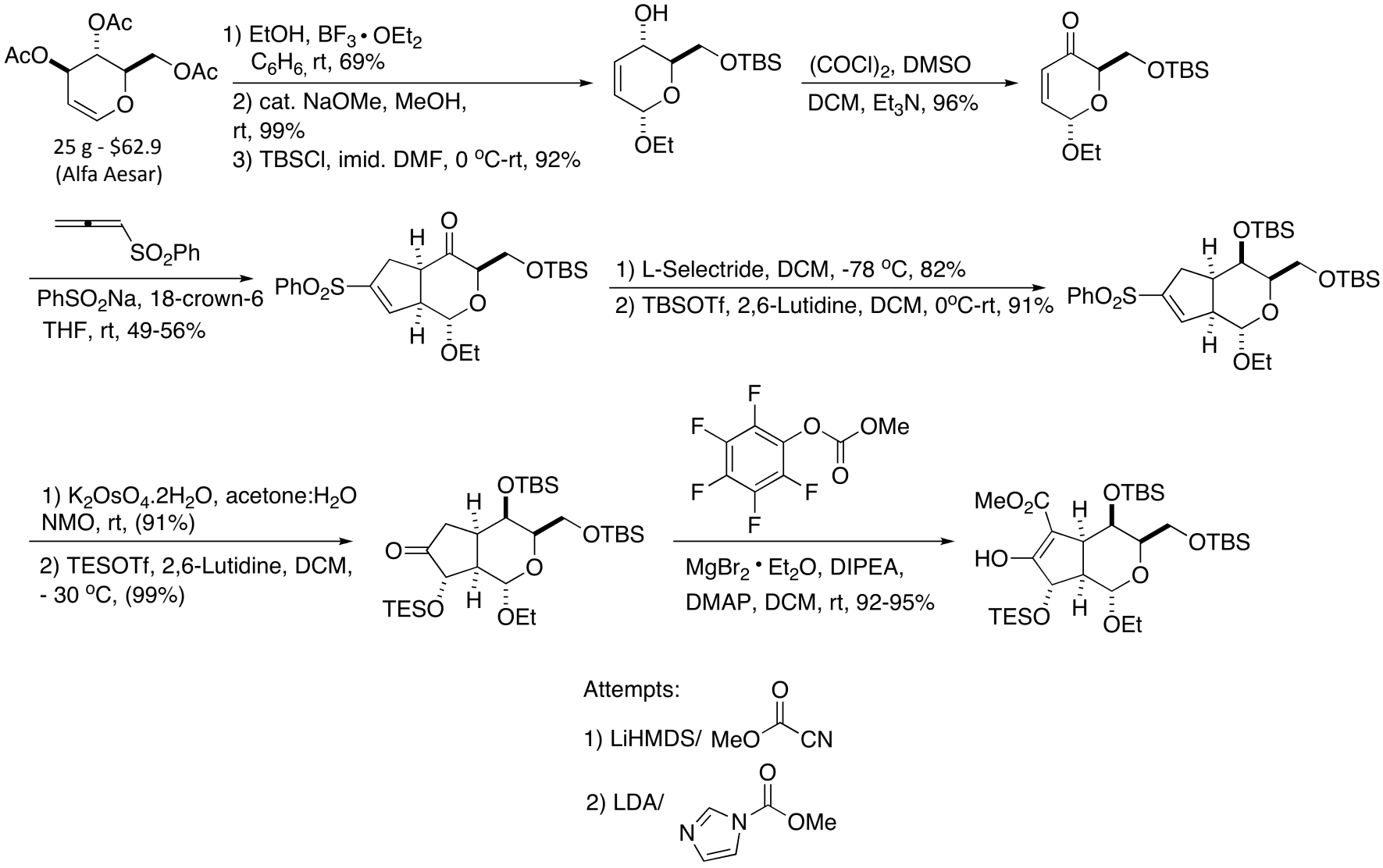


Retrosynthetic Plan

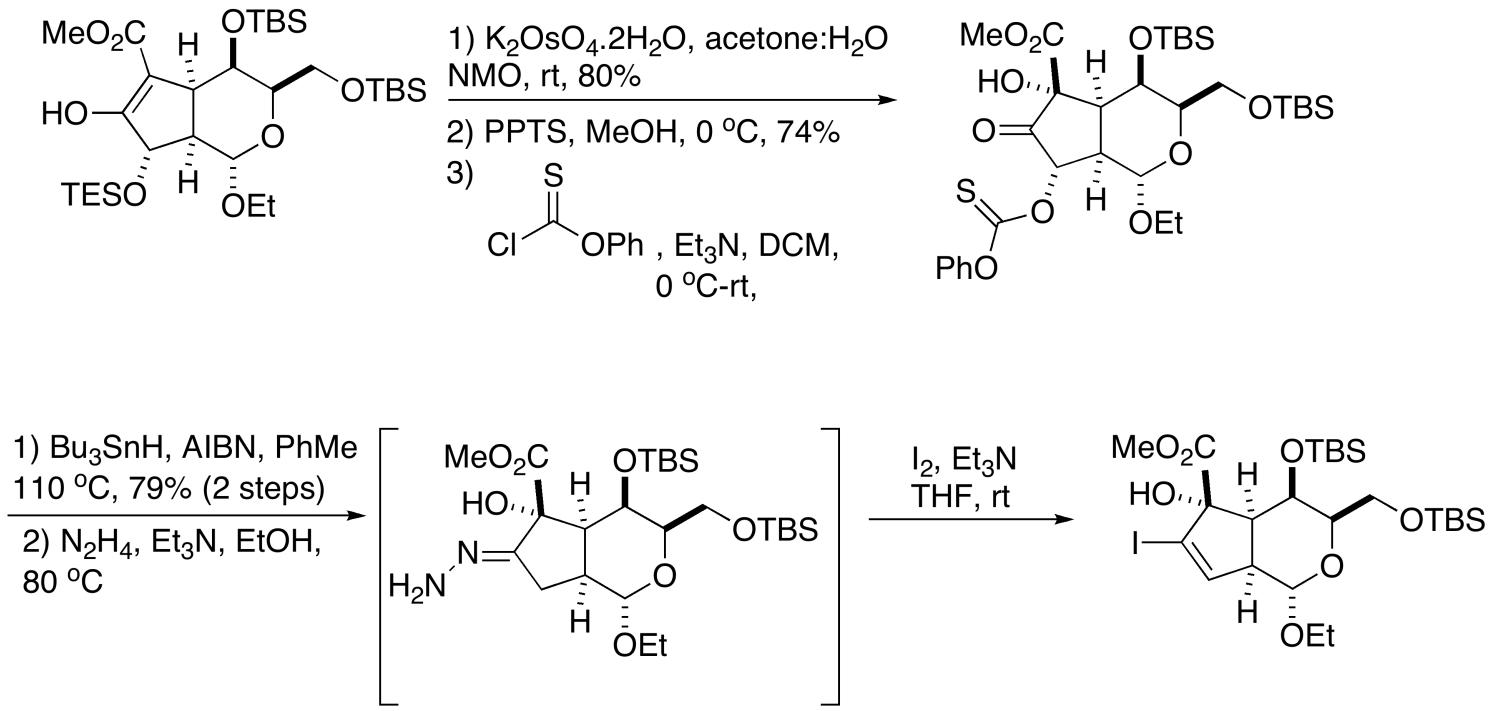
- **Access (–)-Echinosporin through A.B. Smith's Intermediate:**



Synthesis of β-Keto Ester Intermediate



Completion of the Formal Synthesis of (–)-Echinosporin



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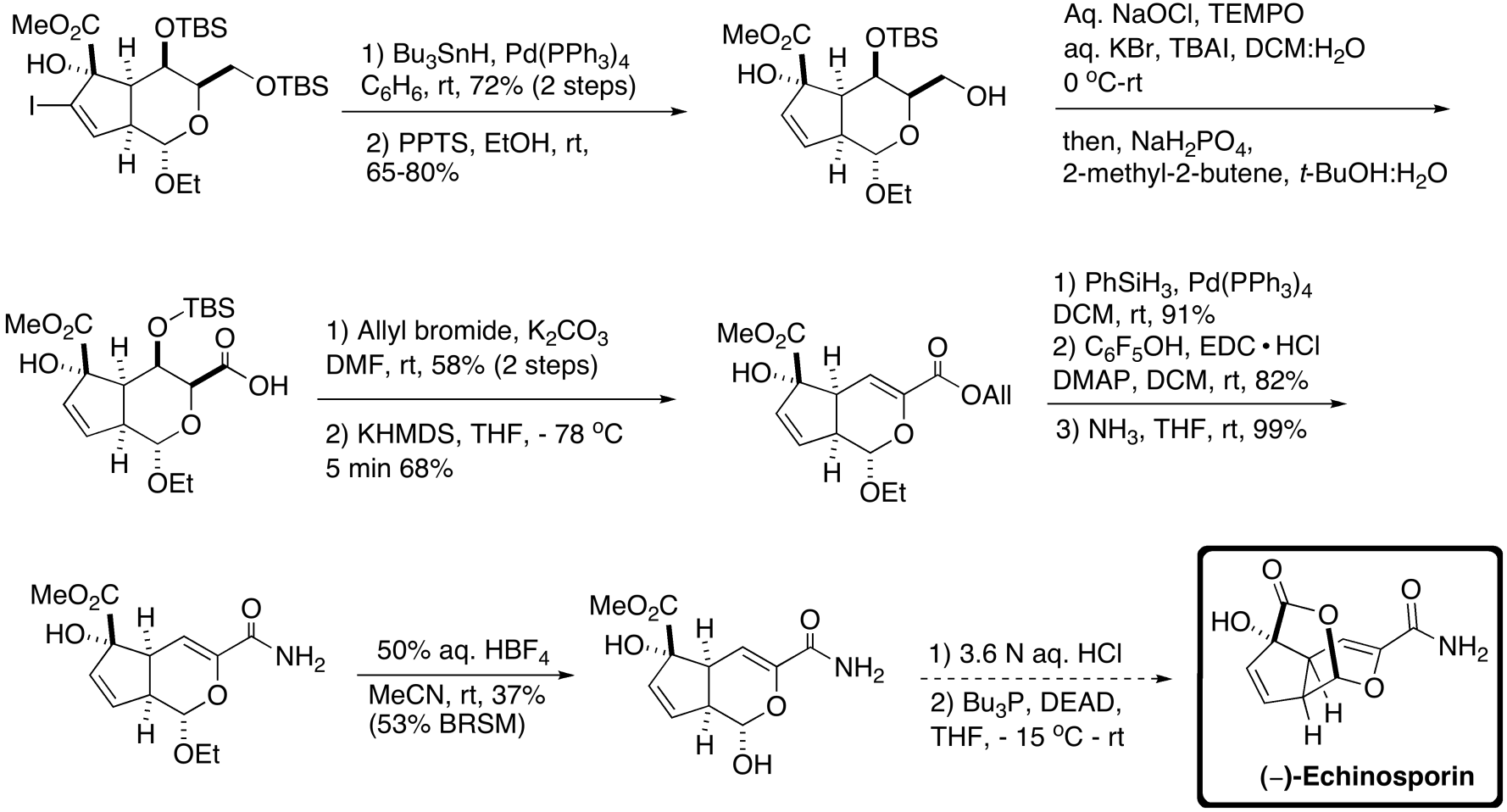

Conclusion

- A new enantioselective route to (−)-echinosporin has been developed
- Accessed in 23 steps from Tri-*O*-acetyl-D-glucal
- The first application of Padwa allenylsulfone [3+2]-cycloadditive elimination reaction in a natural product total synthesis
- Described a new protocol for *C*-acylation to prepare β-keto esters.