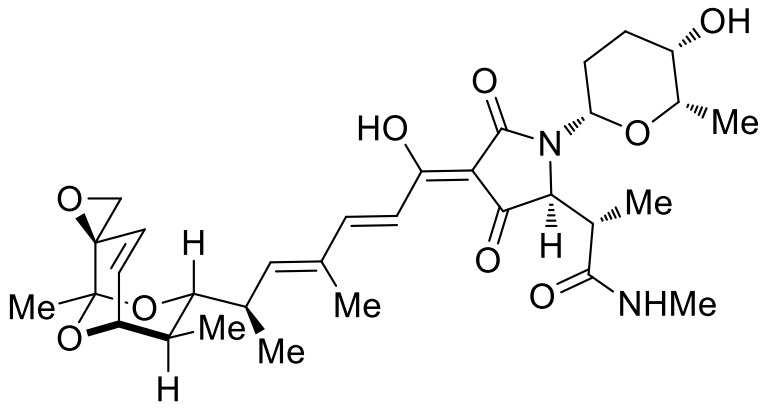
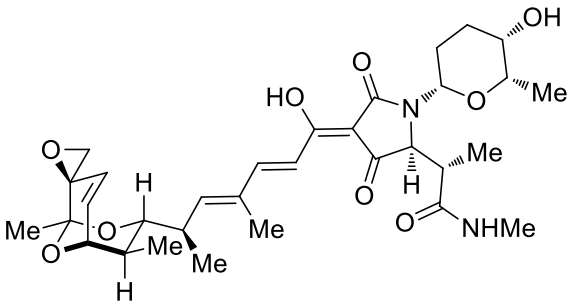
Synthesis of Streptolydigin, a Potent Bacterial RNA Polymerase Inhibitor

Pronin, S. V.; Kozmin, S. A
J. Am. Chem. Soc. 2010, *132,* 14394-14396

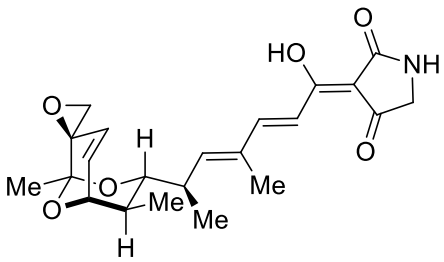


Sarang Kulkarni
Current Literature Presentation
October 23, 2010

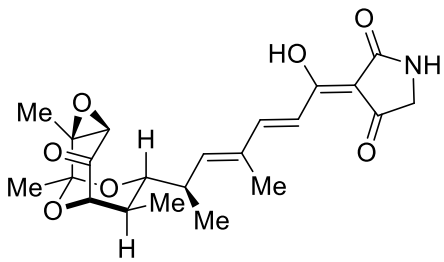
Streptolydigin



Streptolydigin



Tirandalydigin

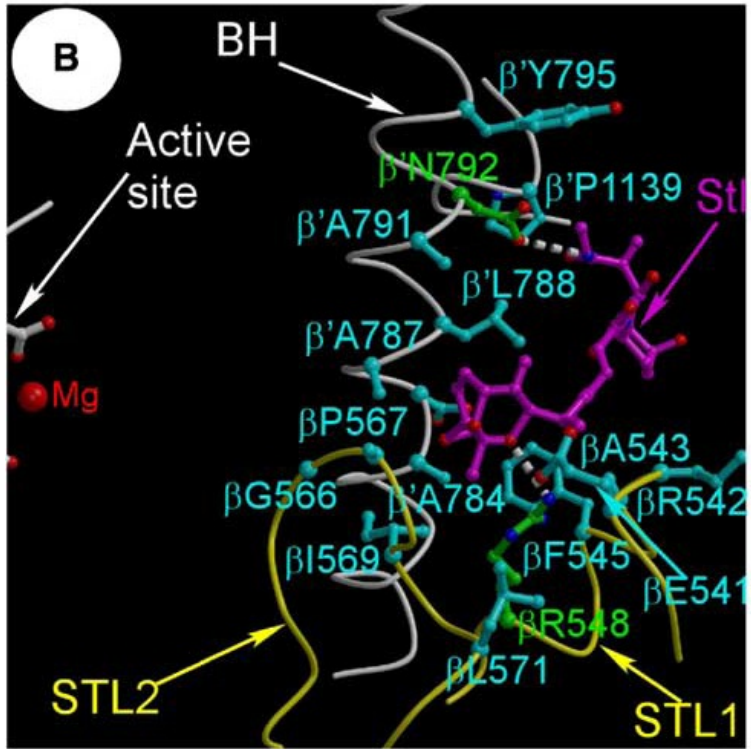


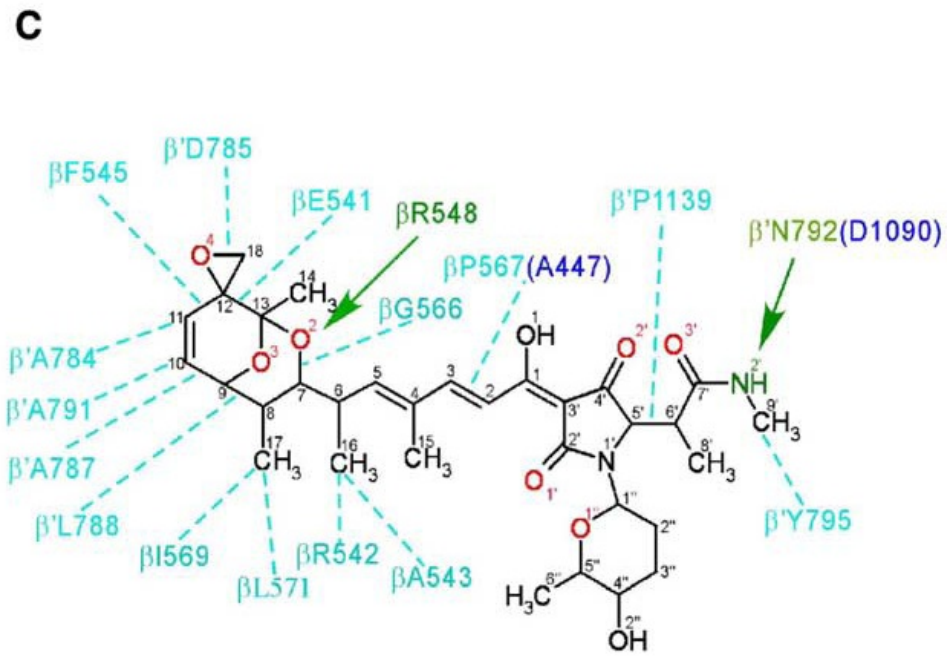
Tirandamycin A

- Highly potent, broad-spectrum antibiotic produced by *Streptomyces lydicus*
- Isolated by DeBoer and co-workers in 1956
- Potent inhibitor of bacterial RNA polymerase
- Structure determined by Rinehart and co-workers

DeBoer, C.; Dietz, A.; Silver, W. S.; Savage, G. M. *Antibiotics Ann.* **1956**, 886-892
Eble, T. E.; Large, C. M.; DeVries, W. H.; Crum, G. F.; Shell, J. W. *Antibiotics Ann.* **1956**, 893-896
Lewis, C.; Wilkins, J. R.; Schwartz, D. F.; Nikitas, C. T. *Antibiotics Ann.*, **1956**, 897-902

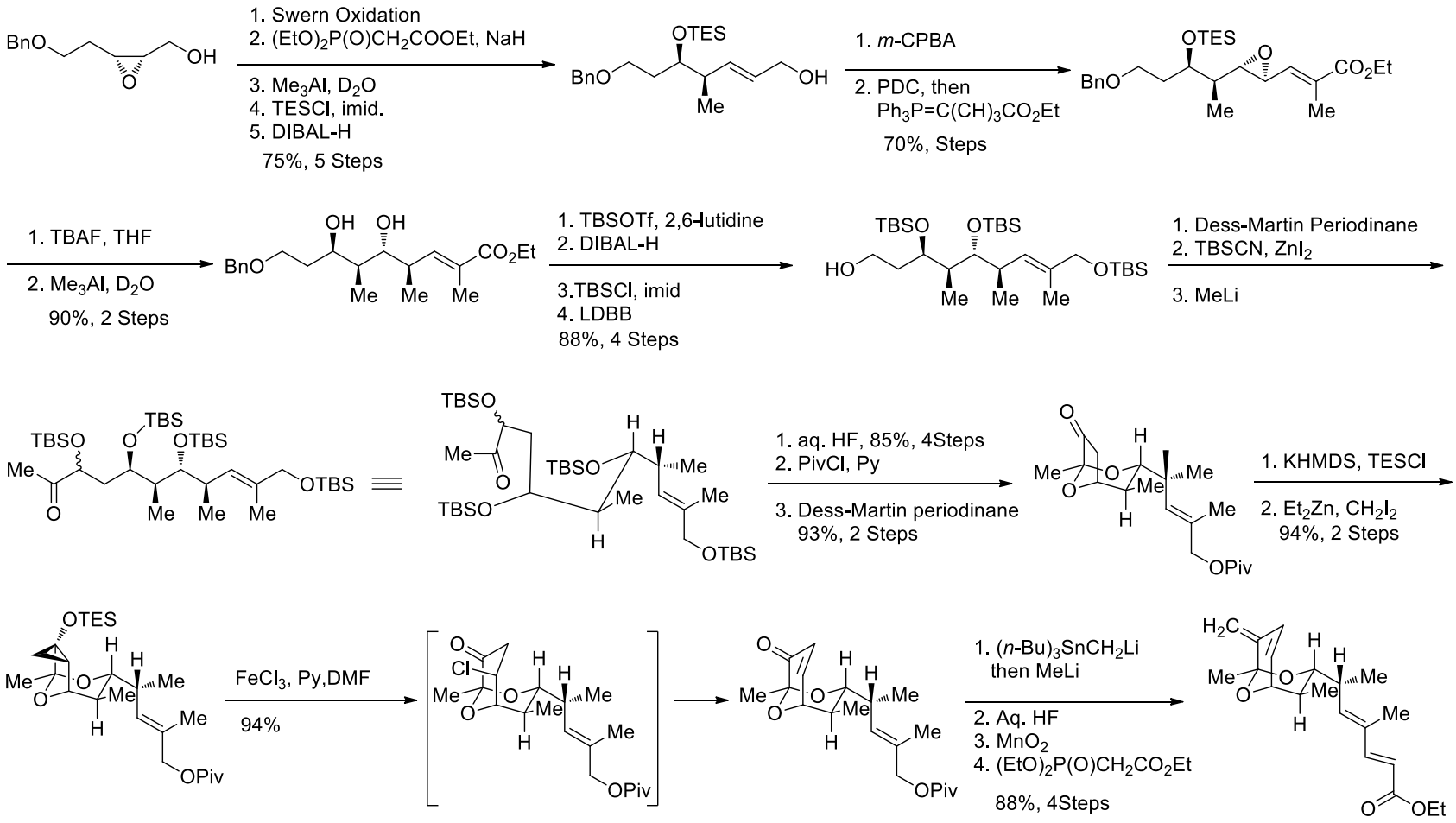
Streptolydigin binding with bacterial RNA polymerase





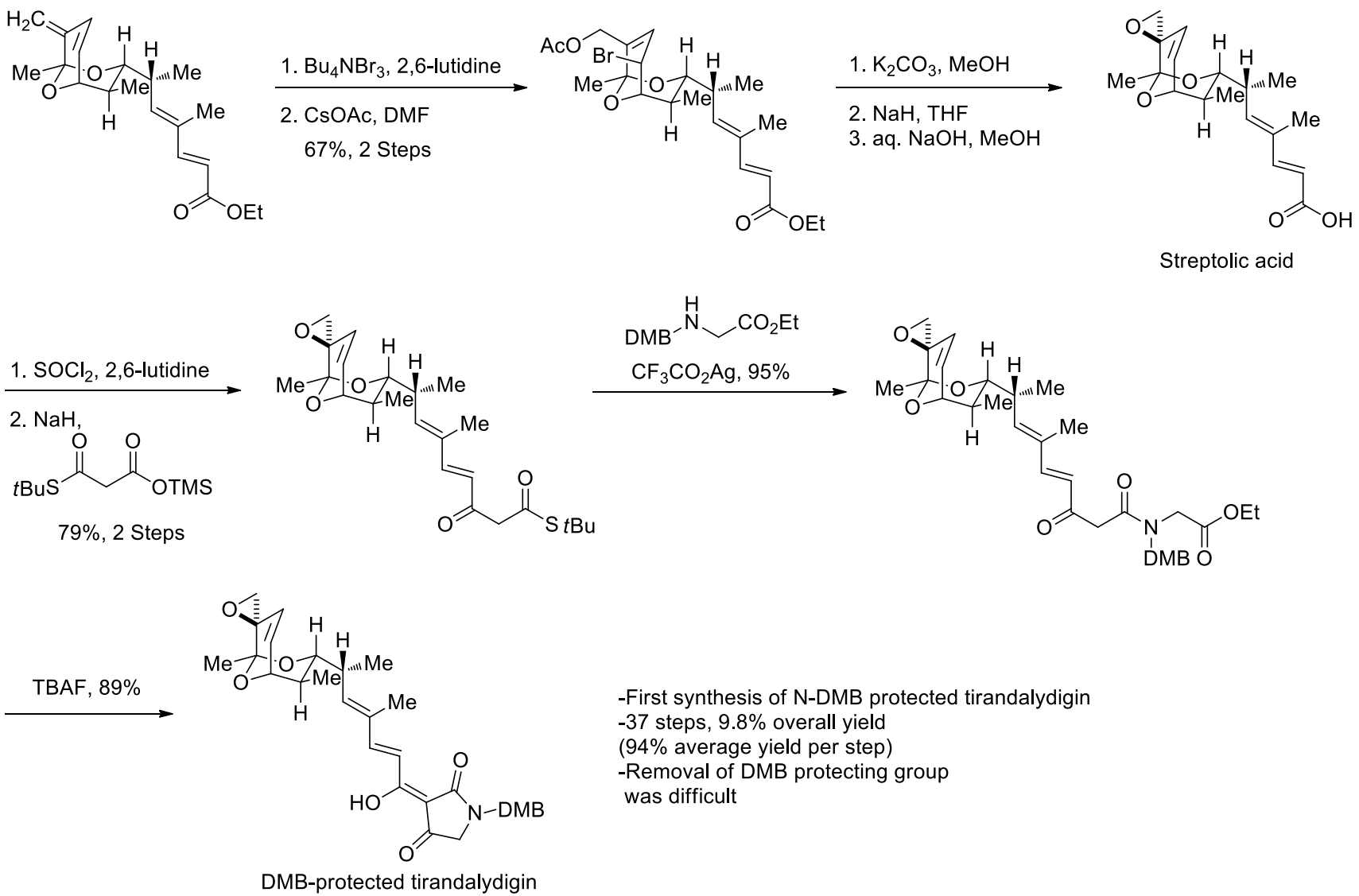
Temiakov, D.; Zenkin, N.; Vassylyeva, M. N.; Perederina, A.; Tahirov, T. H.; Kashkina, E.; Zorov, S.; Nikiforov, V.; Igarashi, N.; Matsugaki, N.; Wataksuki, S.; Severinov, K.; Vassylyev, D. G. *Mol. Cell*. **2005**, *19*, 655-666

Synthesis of Tirandalydigin via Ring Expansion



Iwata, Y.; Maekawara, N.; Tanino, K.; Miyashita, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 1532

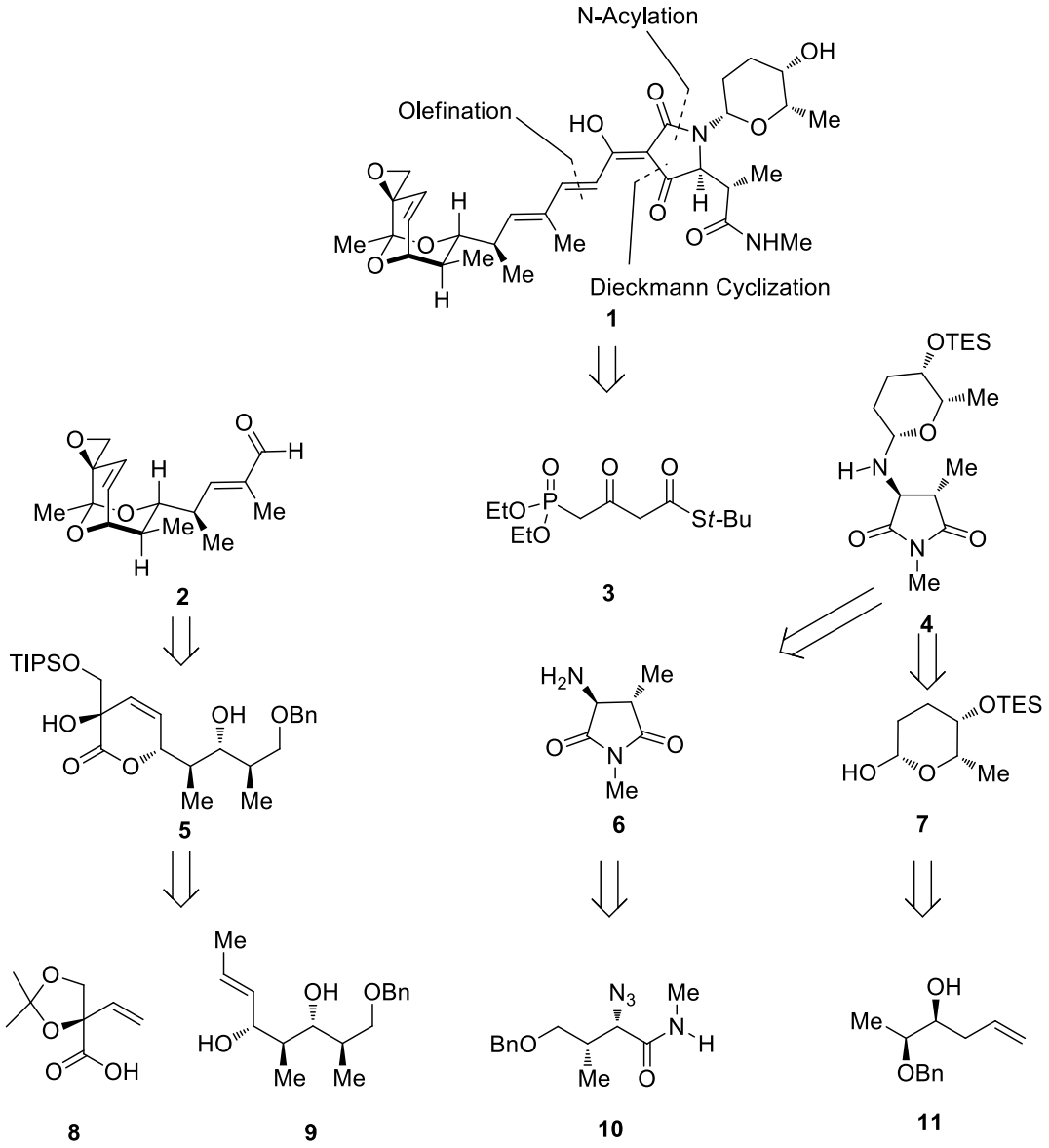
Synthesis of Tirandalydigin via Ring Expansion



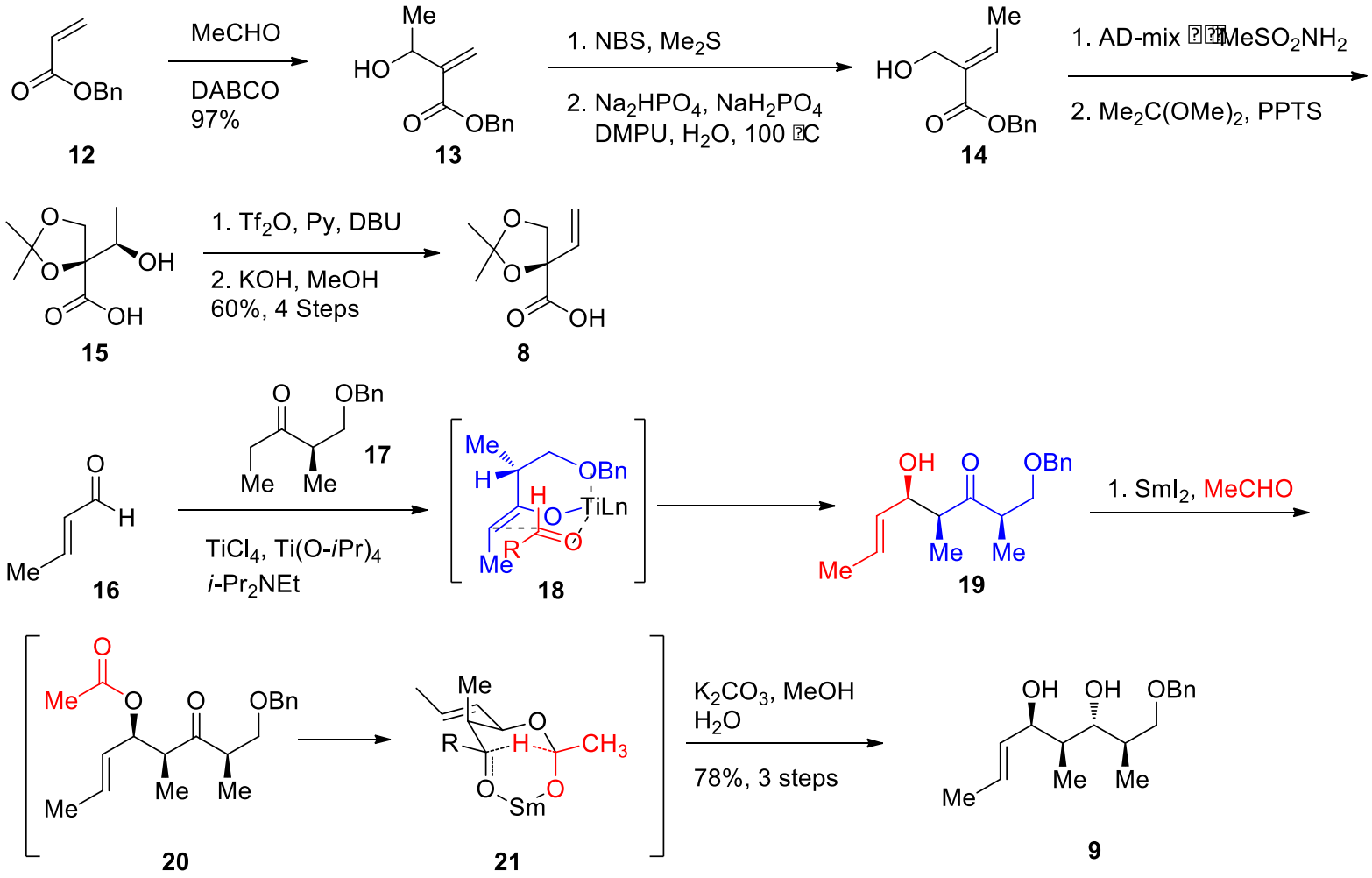
-First synthesis of N-DMB protected tirandalydigin
-37 steps, 9.8% overall yield
(94% average yield per step)
-Removal of DMB protecting group
was difficult

Iwata, Y.; Maekawara, N.; Tanino, K.; Miyashita, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 1532

Retrosynthesis

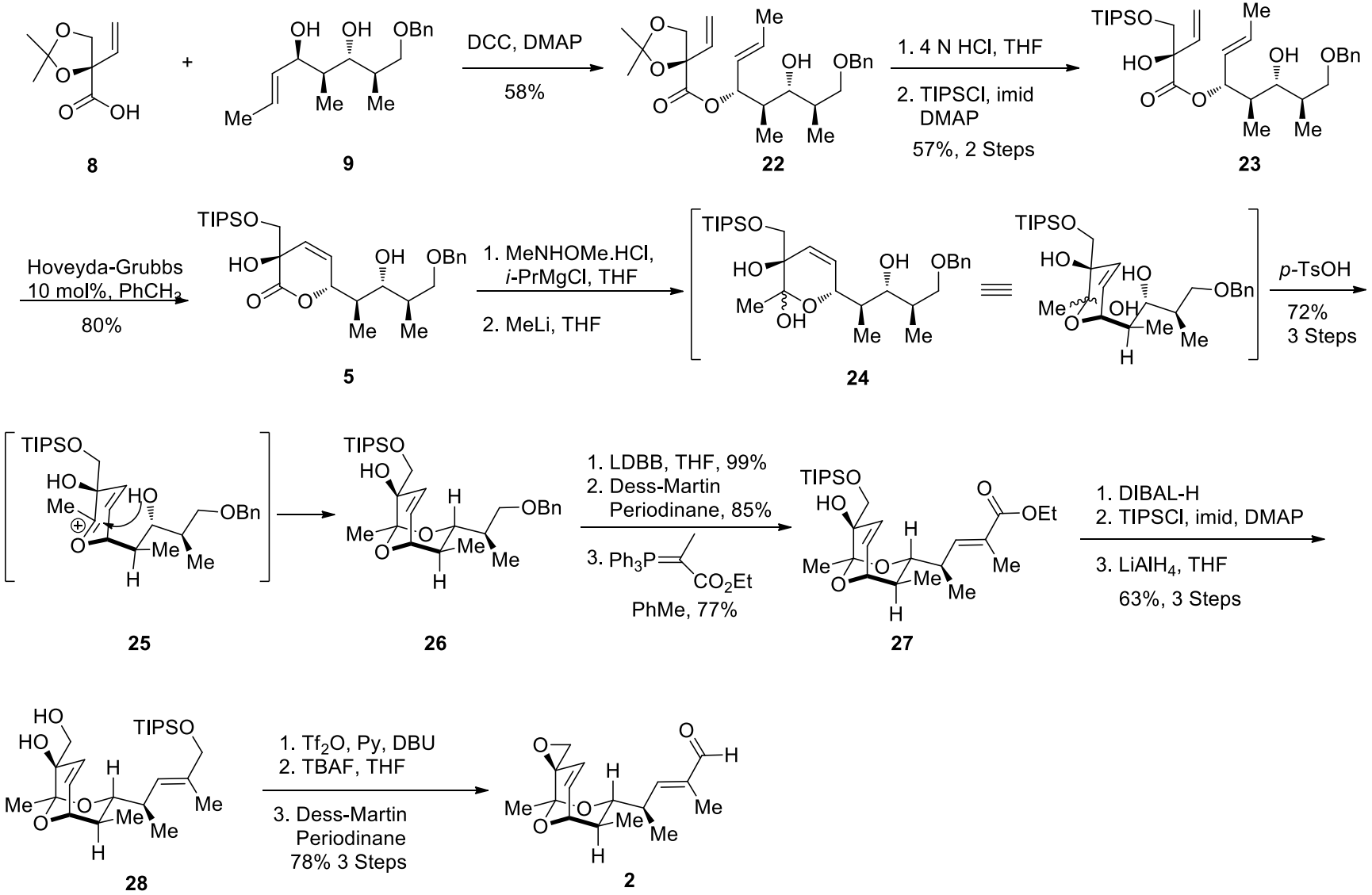


Synthesis of Acid **8** and Alcohol **9**



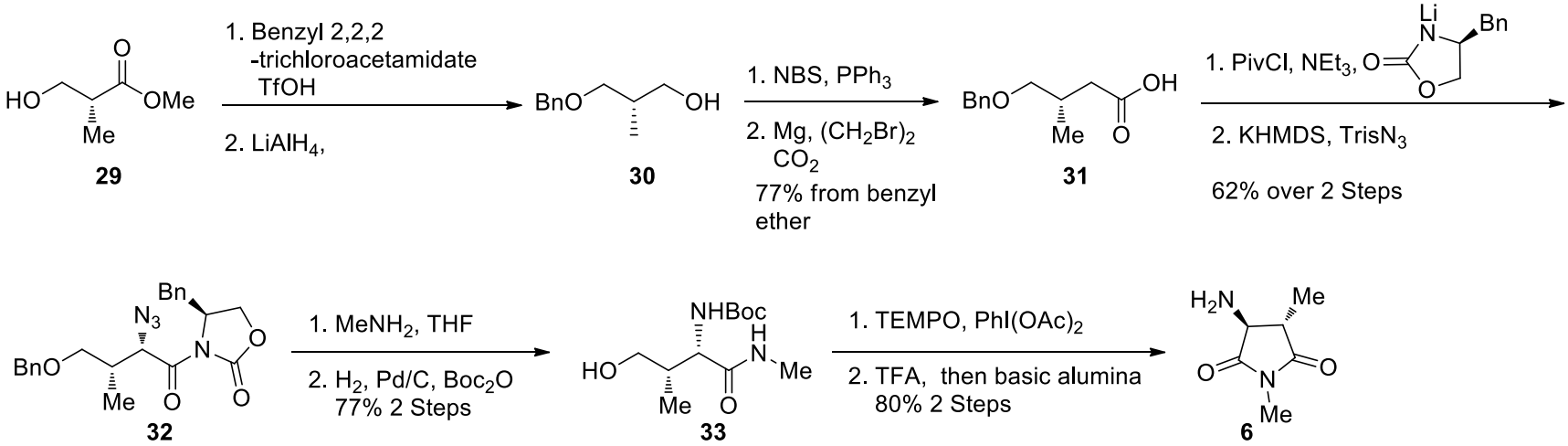
Solsona, J. G.; Nebot, J.; Romea, P.; Urpi, F. *J. Org. Chem.* **2005**, *70*, 6533-6536.
Evans, D. A.; Hoveyda, A. M. *J. Am. Chem. Soc.* **1990**, *112*, 6447-6449

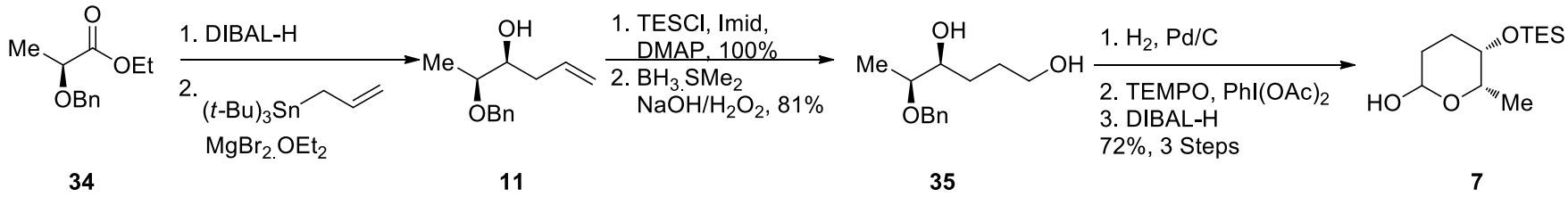
Synthesis of bicyclic acetal

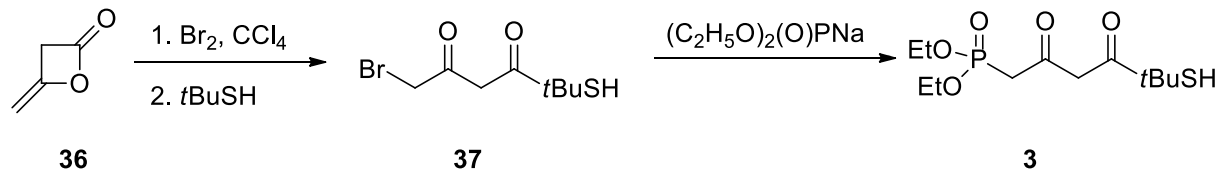


Garber, S. V.; Kingsbury, J. S.; Gary, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168-8179

Synthesis of subunits **6**, **7** and **3**







Evans, D. A.; Britton, T. C. *J. Am. Chem. Soc.* **1987**, *109*, 6881-6883

Schlessinger, R. H.; Graves, D. D. *Tel. Lett.* **1987**, *28*, 4381-4384

Ley, S. V.; Woodward, P. R. *Tet. Lett.* **1987**, *28*, 345-346

Synthesis of Streptolydigin

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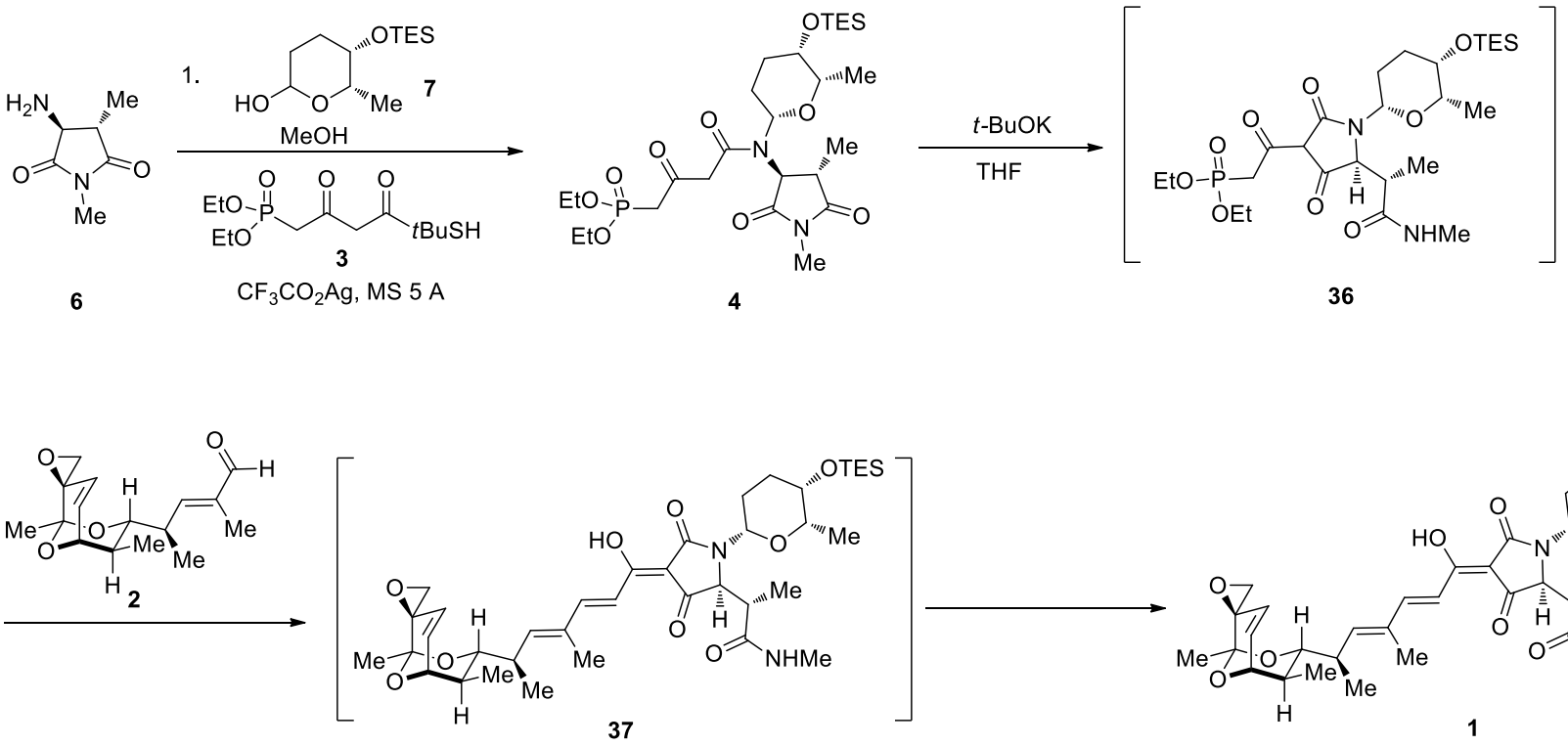

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Boeckman, R. K., Jr.; Potenza, J. C.; Enholm, E. J. *J. Org. Chem.* **1987**, *52*, 469-472

Cartwright, D.; Lee, V. J.; Rinehart, K. L., Jr. *J. Am. Chem. Soc.* **1978**, *100*, 4237-4239

Conclusions

- Total synthesis of Streptolydigin has been achieved in 24 steps (longest linear squence)

- Synthesis features a three step one-pot procedure involving Dieckmann cyclization with imide ring opening, Horner-Wadsworth-Emmons olefination and desilylation

- Further synthesis of simpler synthetic antibiotics can be achieved using this route