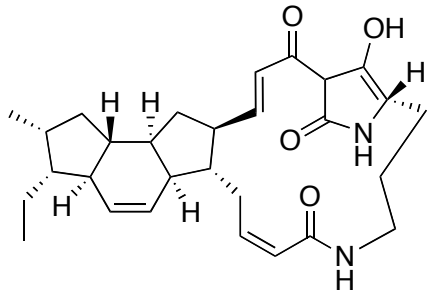
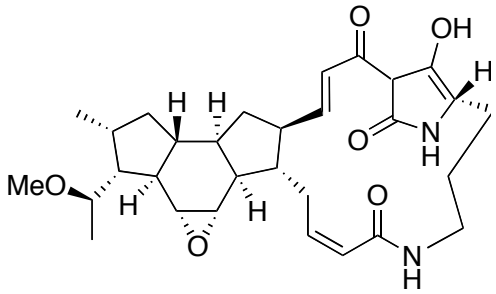
Spinosyn G: Proof of Structure by Semisynthesis

Graupner, P. R.; Martynow, J.; Anzeveno, P. B.
J. Org. Chem. **2005**, *70*, 2154-2160.

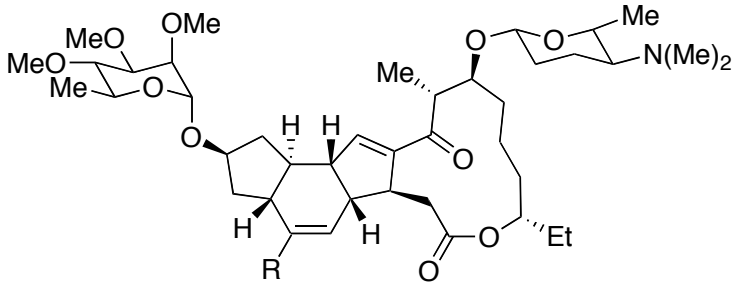
Natural products that contain the tricyclic core



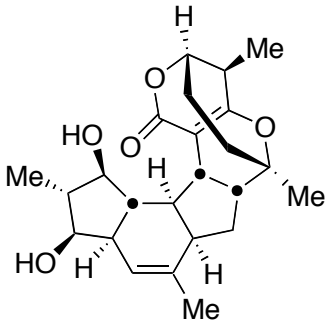
ikarugamycin



capsimycin



(-)-spinosyn A, R = H
a.k.a. (-)-A83543A, (-)-lepicidin A
(-)-spinosyn D, R = Me



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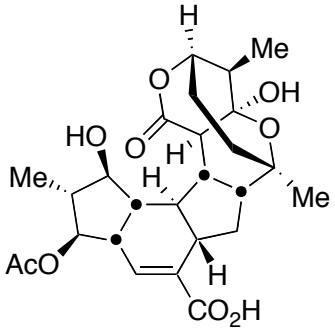
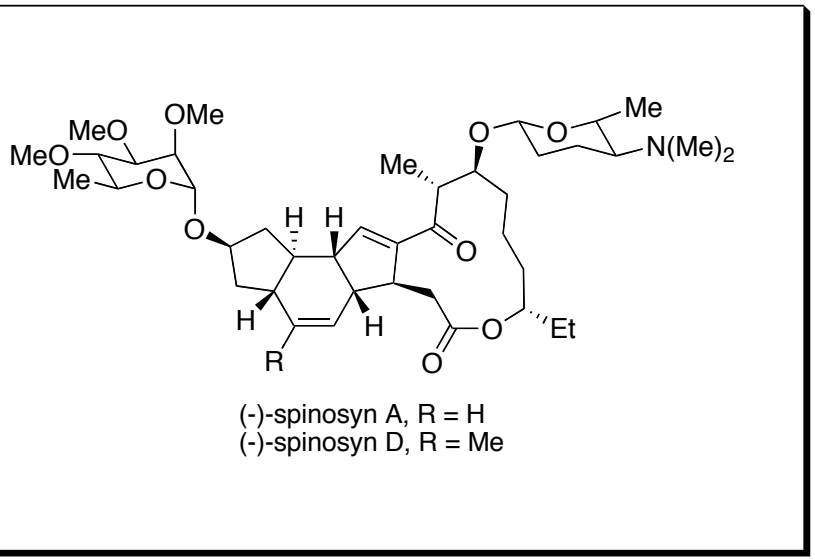


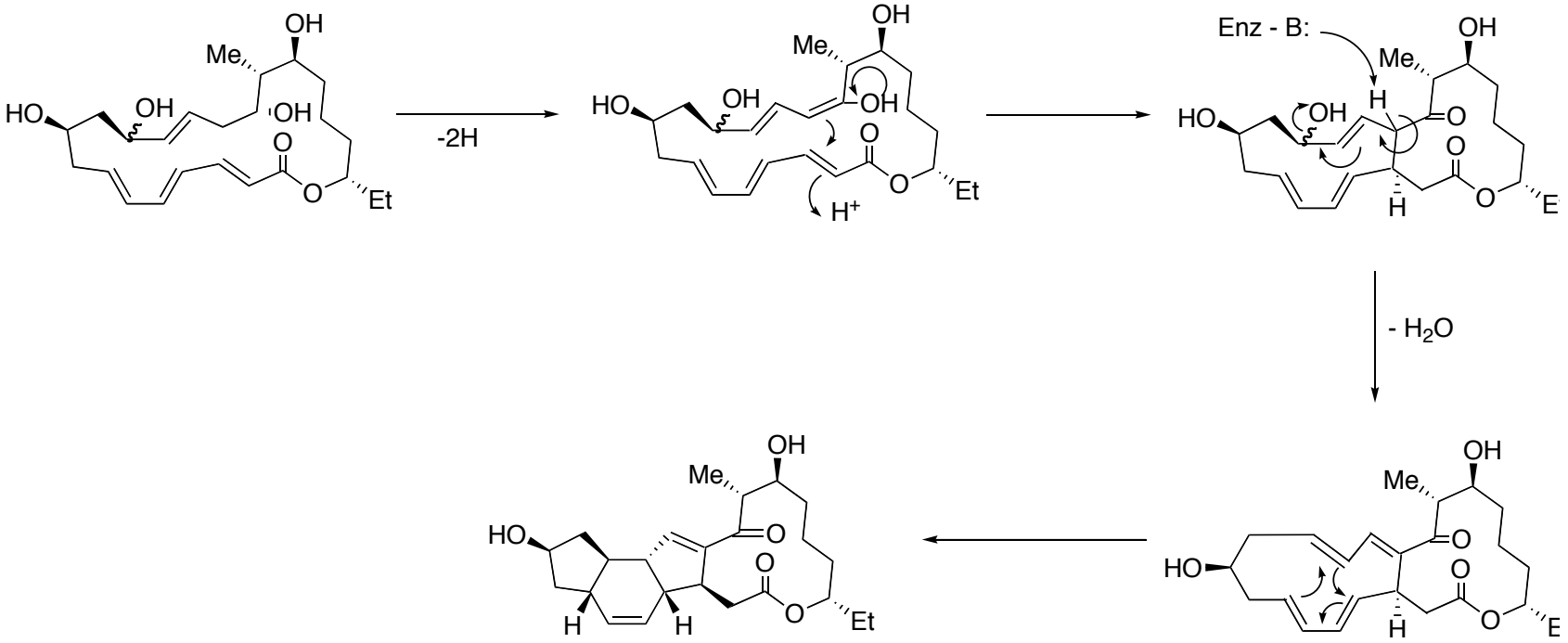
hexacyclinic acid



(-)-spinosyn A, R = H
(-)-spinosyn D, R = Me

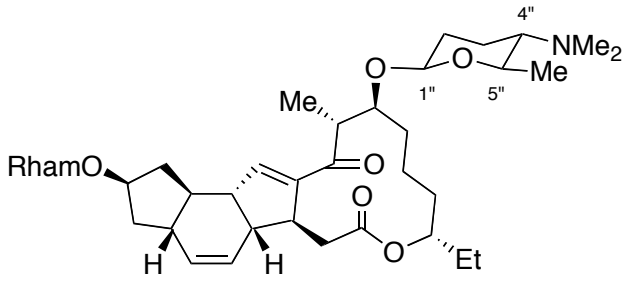
- Spinosyn A isolated in 1990 from the fermentation broth of the soil microbe *Saccharopolyspora spinosa*.
- Spinosad (Tracer® Naturalyte®, SpinTor® and Conserve®) is an environmentally benign insecticide marketed by Dow-Elanco for crop protection. Spinosad is marketed to the retail market for the control of fire ants.
- Manufactured by fermentation and consists of a 90:10 mixture of spinosyn A and spinosyn D.
- 24 spinosyns have been characterized.
- Based on tentative assignments, Spinosyn G is the only compound with a sugar of the L-configuration (L-ossamine).
- Is the assignment of spinosyn G correct?

Proposed Mechanism for the formation of Spinosyn from the PKS Product

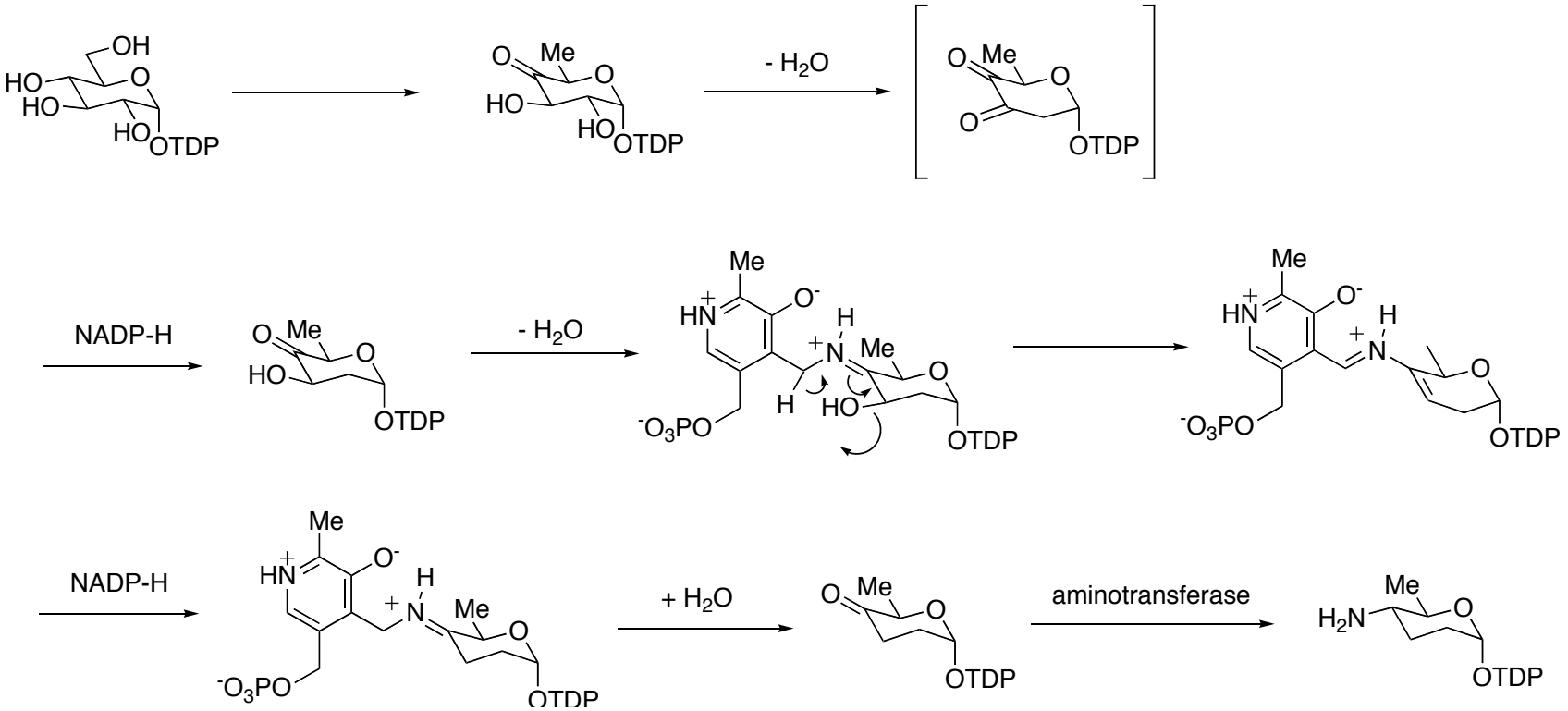


Martin, C. J.; Timoney, M. C.; Sheridan, R. M.; Kendrew, S. G.; Wilkinson, B.; Staunton, J.; Leadley, P. F. *Org. Biomol. Chem.* **2003**, *1*, 4144-4147.

Biosynthesis of Forosamine

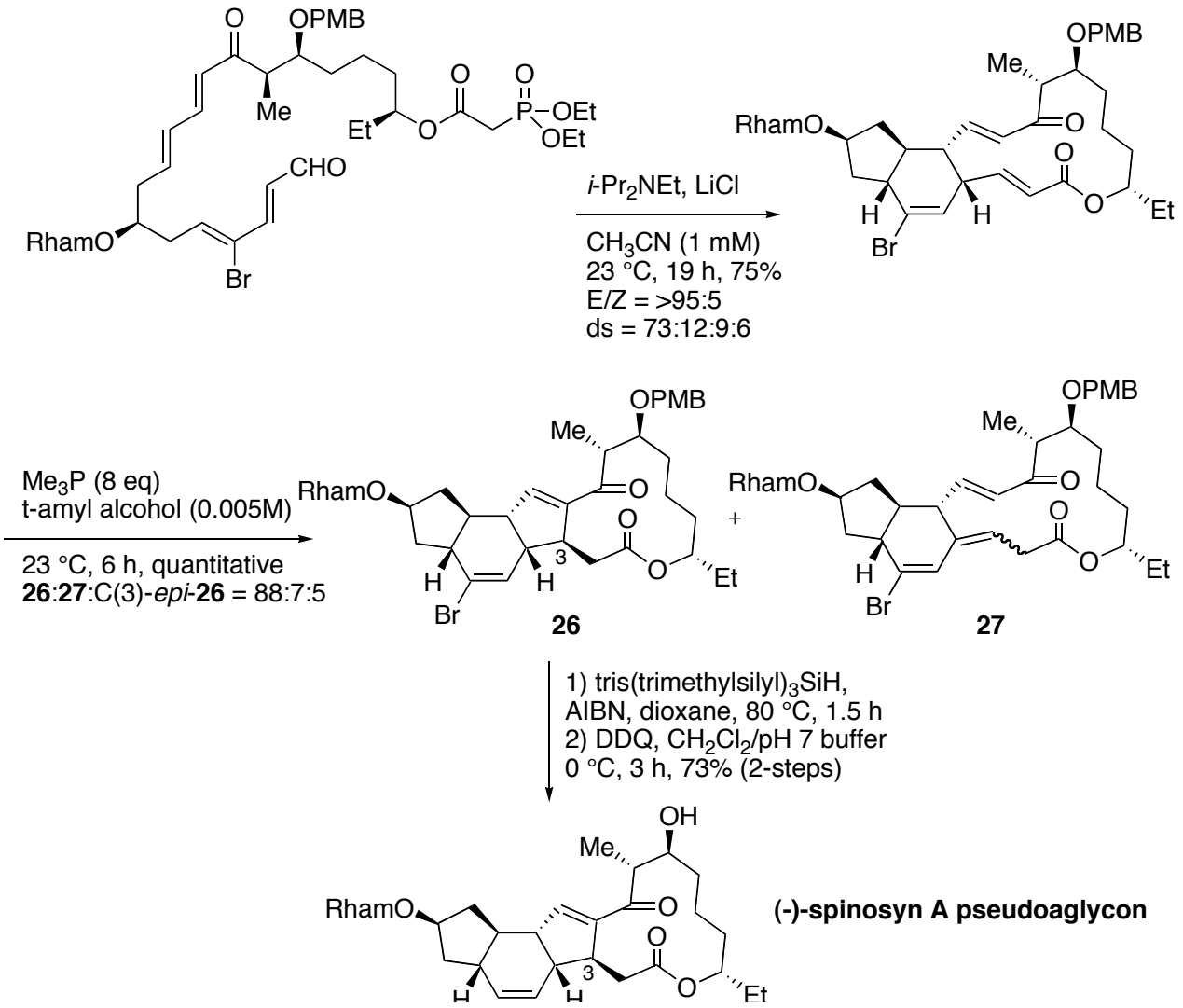


(-)-spinosyn A



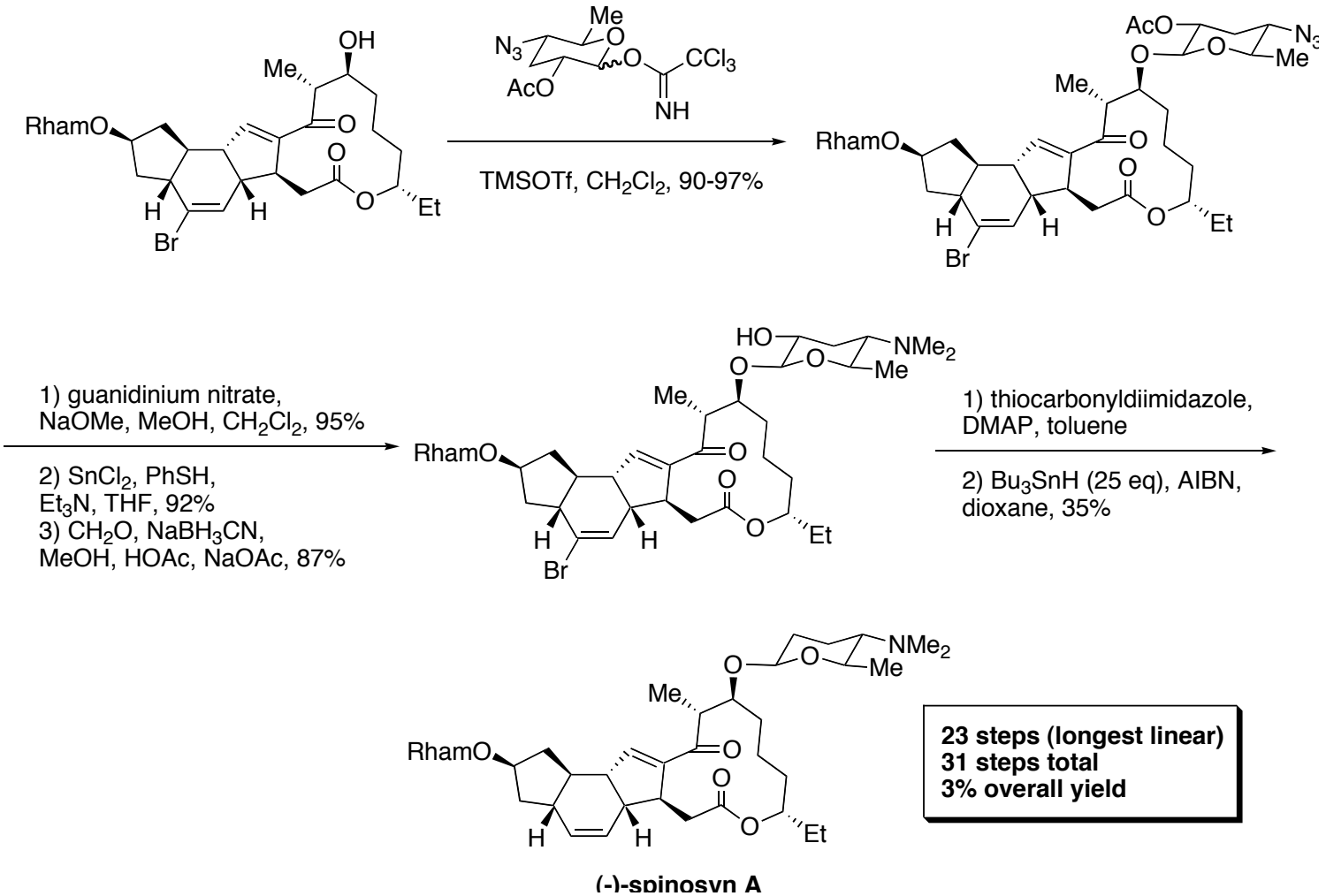
Zhao, Z.; Hong, L.; Liu, H,-w. *J. Am. Chem. Soc.* **2005**, *127*, 7692-7693.

Roush's Synthesis of (-)-Spinosyn A



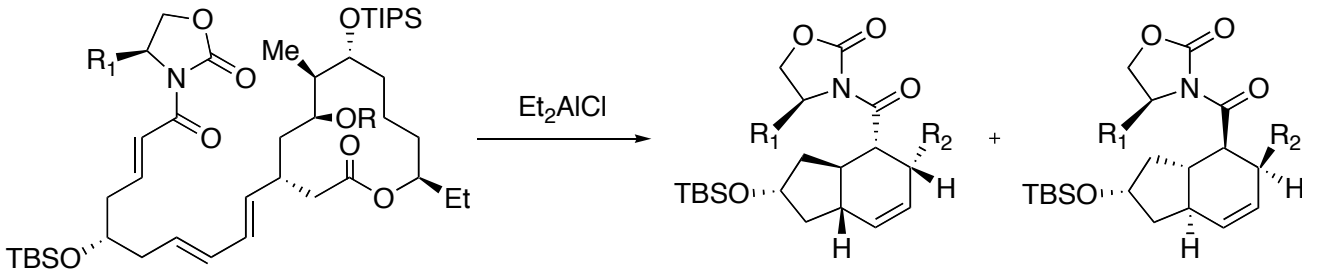
Mergott, D. J.; Frank, S. A.; Roush, W. R. *PNAS*, **101**, 11955-11959.

Completion of the Synthesis



Mergott, D. J.; Frank, S. A.; Roush, W. R. *PNAS*, **101**, 11955-11959.

Evans' Synthesis of (+)-Spinosyn A

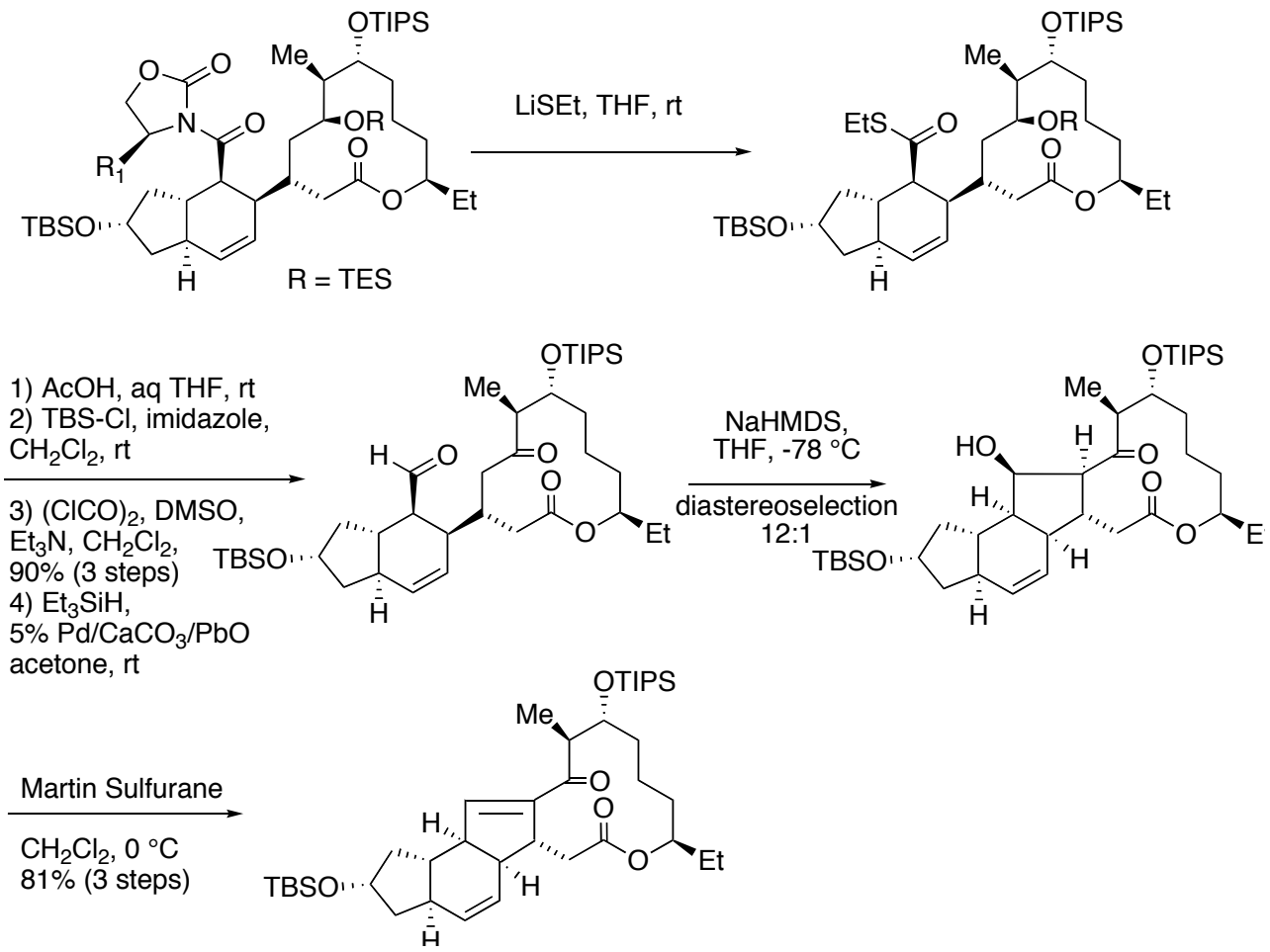


1, R = TES, R_1 = H
2, R = TES, R_1 = Bn

1a	71%, 6:1	**1b**
2a	74%, 1:10	**2b**

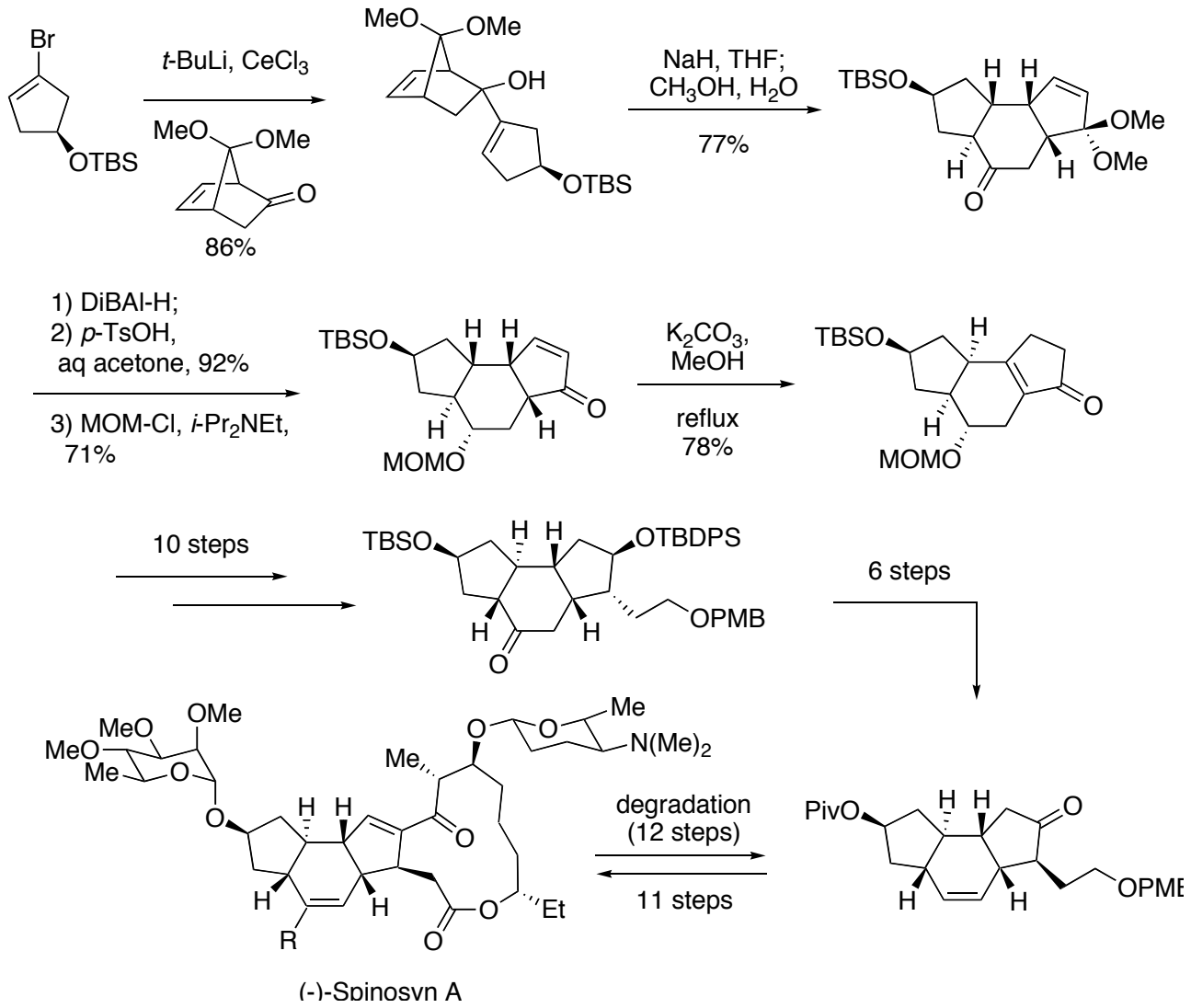
Evans, D. A. and Black, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 4497-4513

Evans' Synthesis of (+)-Spinosyn A



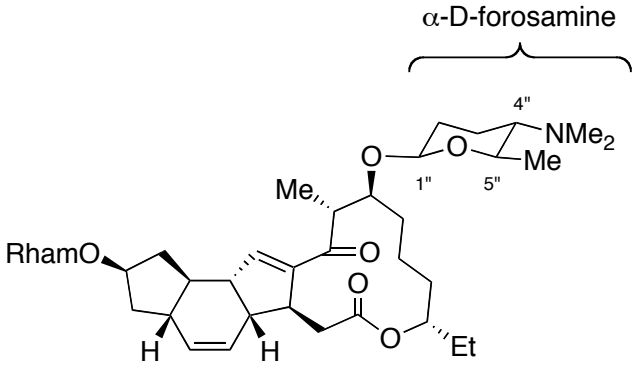
Evans, D. A. and Black, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 4497-4513

Paquette's Synthesis of Spinosyn A

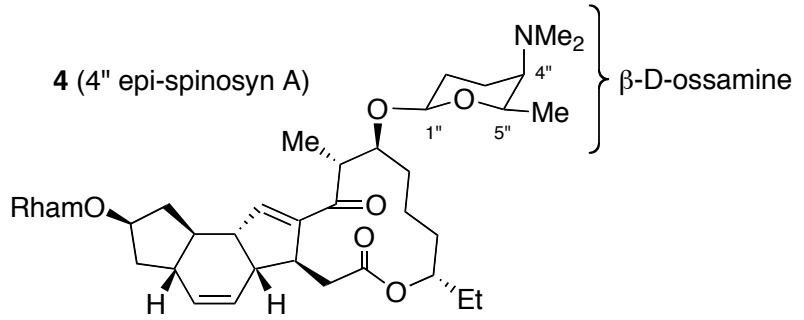


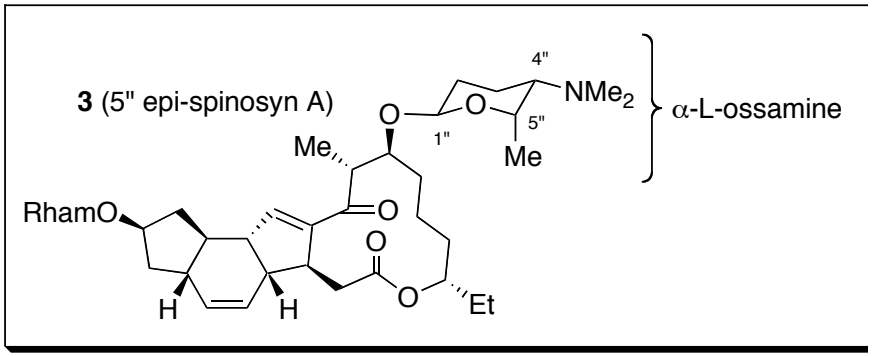
Paquette et. al. *J. Am. Chem. Soc.* **1998**, *120*, 2543-2552
Paquette et. al. *J. Am. Chem. Soc.* **1998**, *120*, 2553-2562

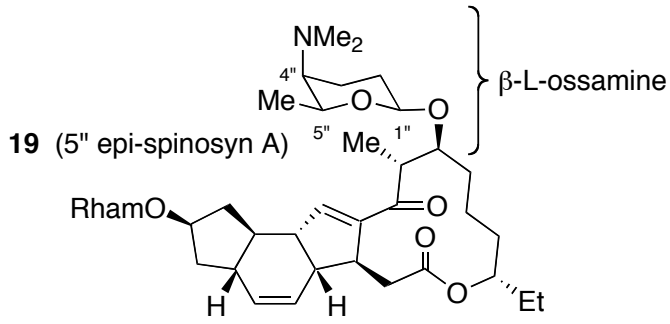
Which of the Structures is Spinosyn G?



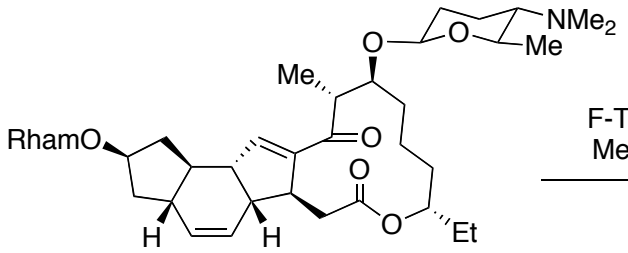
(-)-spinosyn A





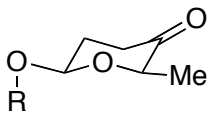


Synthesis of β-D-ossamine Spinosyn



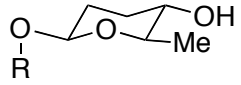
(-)-spinosyn A

F-TEDA, pyridine
$MeCN\text{-}H_2O$, 0°C



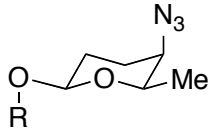
$Li(t\text{-}BuO)_3AlH$

Et_2O, 0° C



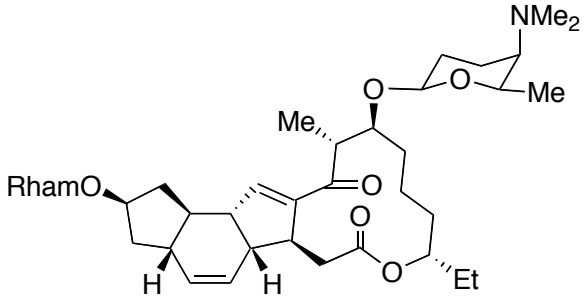
1) $MeSO_2Cl$, $(i\text{-}Pr)_2NEt$,
CH_2Cl_2, 0°C

2) NaN_3, DMF, 120 °C

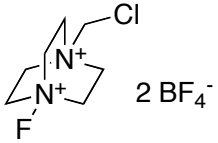


1) $SnCl_2$, MeOH, rt

2) MeI (excess),
MeCN, reflux
3) *m*-xylene, reflux

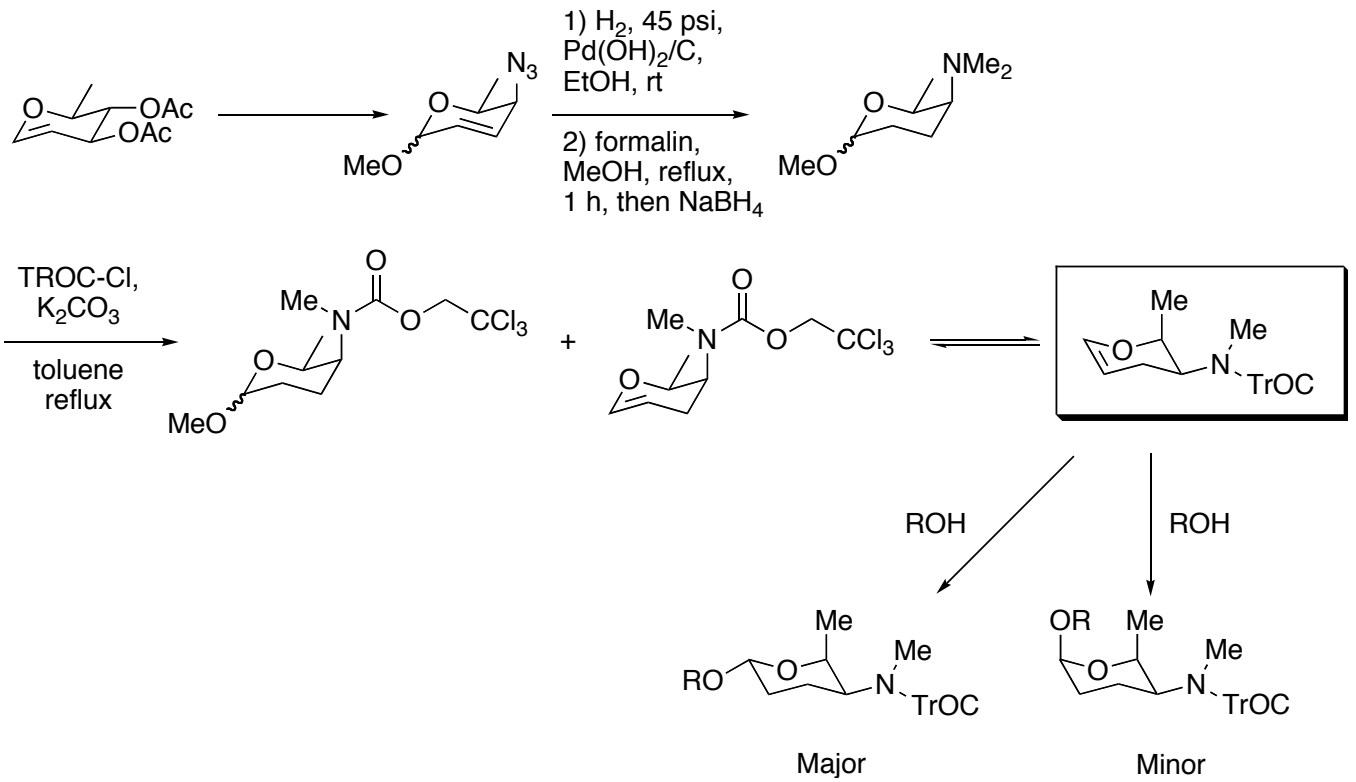


4

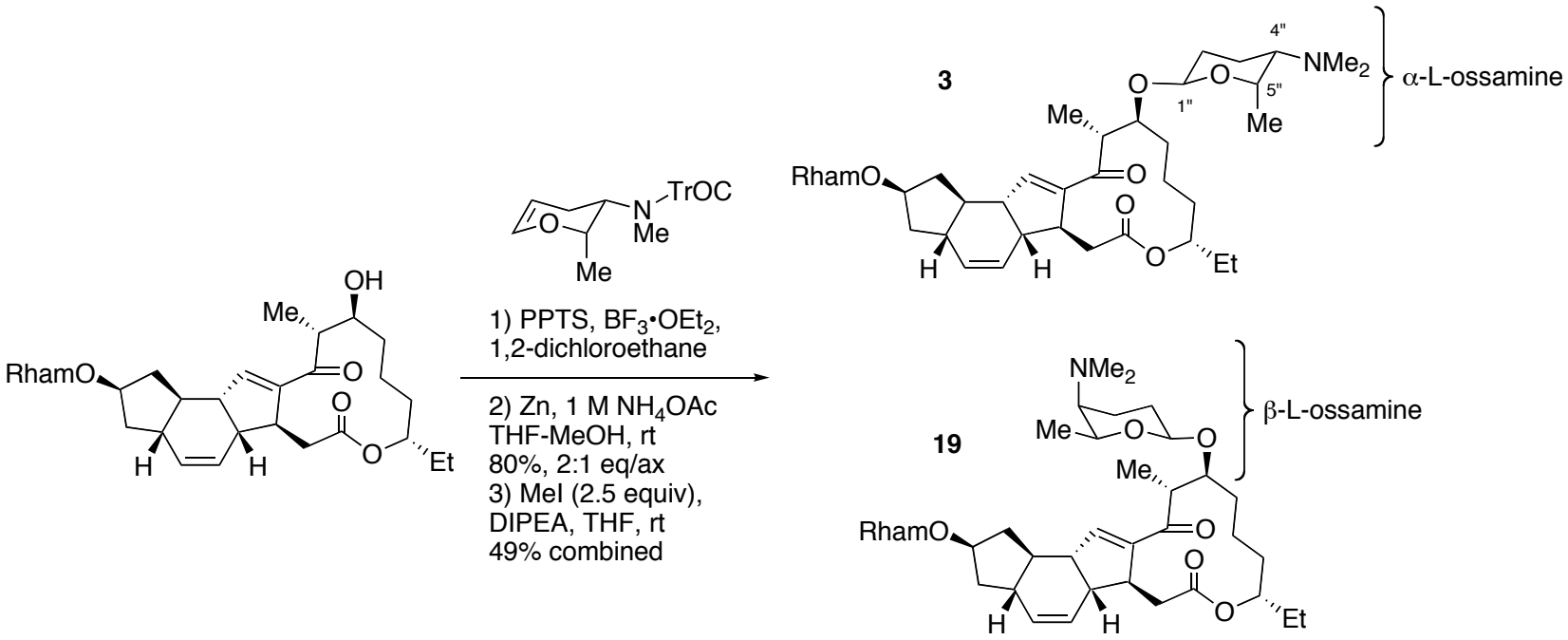


F-TEDA
(Selectfluor™)

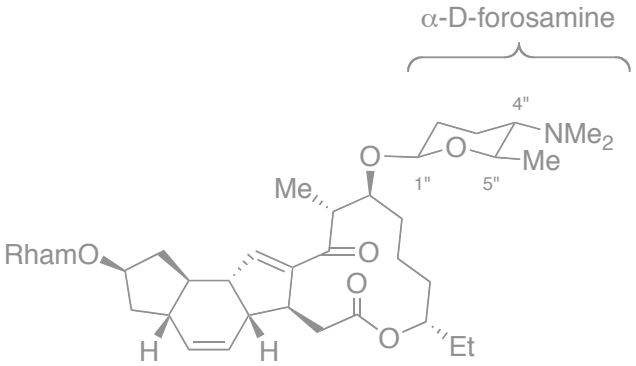
Synthesis of the Ossamines



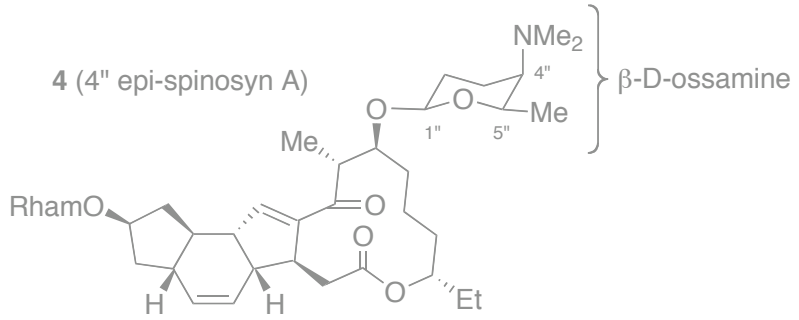
α-L-Ossamine and β-L-Ossamine

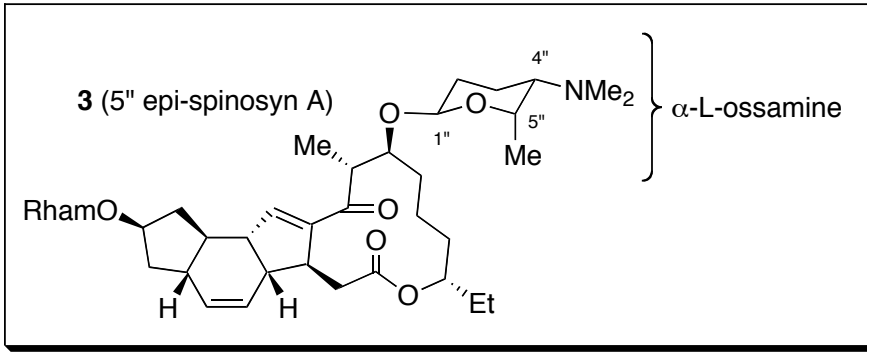


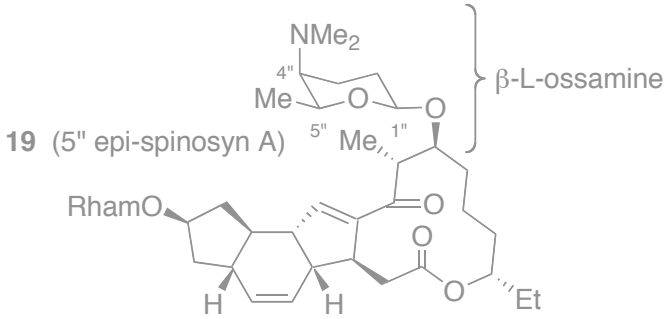
Conclusions:



(-)-spinosyn A







- The structure of Spinosyn G has been unambiguously assigned and contains the L-ossamine residue.
- The result has important implications for understanding the biosynthesis of the spinosyn class of molecules.