Total Synthesis of Rapamycin

Matthew L. Maddess, Miles N. Tackett, Hidenori Watanabe, Paul E. Brennan, Christopher D. Spilling, James S. Scott, David P. Osborn, and Steven V. Ley*

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Presented by: Sami Osman
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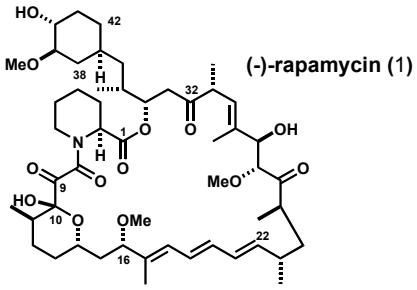
Introduction

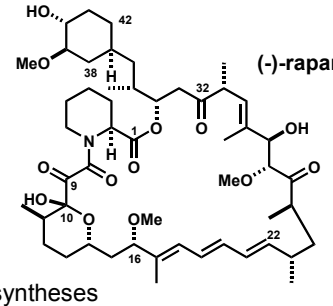


(-)-rapamycin (1)

- First isolated in 1975 from *Streptomyces hygroscopicus* found in Easter Island soil
- Recognized for its potent immunosuppressive action
- Blocks entry of resting immune cells into the cell cycle
  - Blocks progression of cells in the early phase of the cell cycle, causing cell cycle arrest
- Mammalian target for rapamycin is serine/threonine protein kinase
  - Involved in intracellular events such as proliferation, growth, differentiation, migration, and survival.

-Schreiber, S. L. *Cell* **1992**, *70, 365-368*
- Schreiber, S. L. *et. al. Angew. Chem., In. Ed. Eng.* **1992**, *31, 384-400*

Previous Syntheses

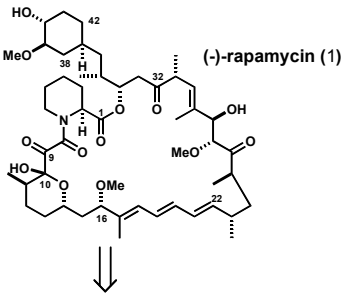


(-)-rapamycin (1)

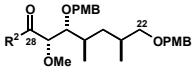
- 4 previous total syntheses
- First synthesis of naturally occurring enantiomer was by the Nicolaou group
- Then came the Schreiber group with their synthesis, using the Evans-Tischenko reaction, and later in the synthesis the Mukaiyama macrocyclization.
- The Danishefsky group completed their synthesis, highlighting at the end of the synthesis the aldol reaction via Ti enolate, to the macrocycle structure.
- Finally the Smith group came with their synthesis
  - longest linear sequence from first point convergence of 14 steps
  - first synthesis of Demethoxy-rapamycin
  - convergent approach permitted straight forward preparation of analogs.

-K.C. Nicolaou *et. al., JACS* ***1993,*** *115, 4419*
-S. L. Schreiber *et. al., JACS* ***1993****, 115, 7906*
-S. J. Danishefsky *et. al., JACS* ***1993,*** *115, 9345*
-A. B. Smith *et. al. JACS* ***1995,*** 117, 5407

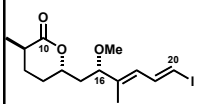
Retrosynthetic Analysis



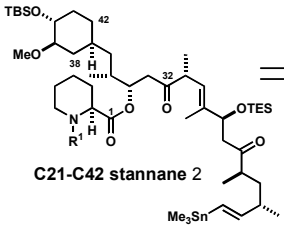
(-)-rapamycin (1)



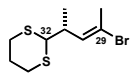
C22-C28 electrophile 5



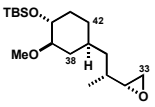
C10-C20 lactone 3



C21-C42 stannane 2

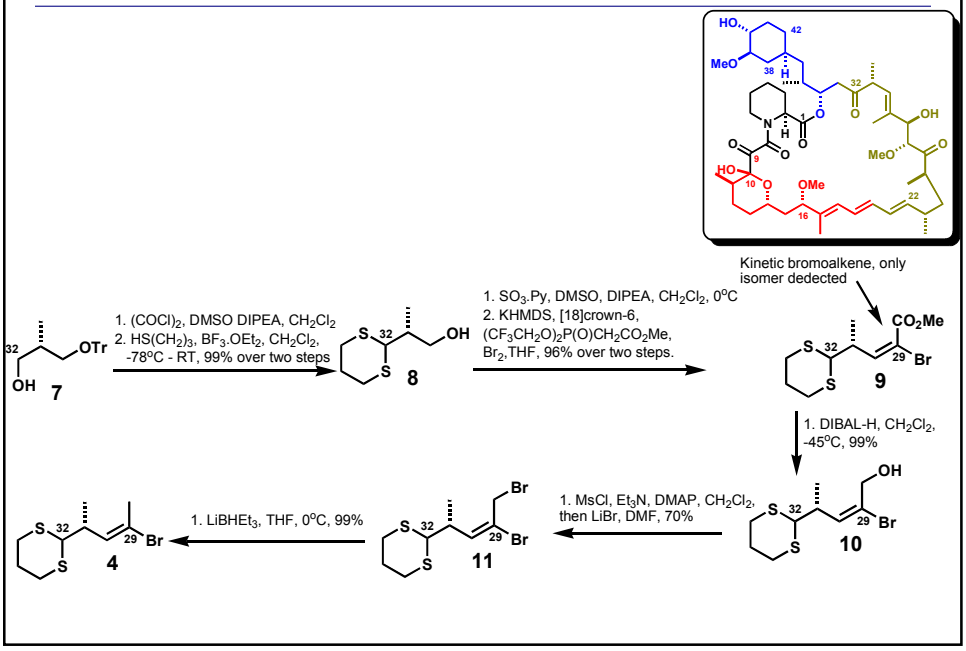


C29-C32 bromide 4

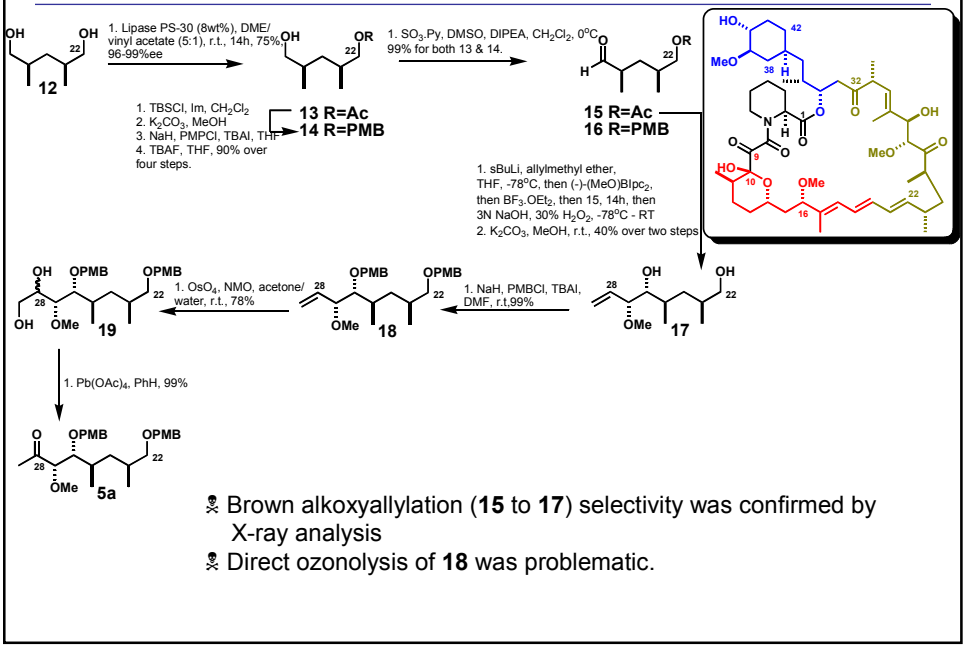


C33-C42 epoxide 6

Synthesis of C29-C32 bromide 4

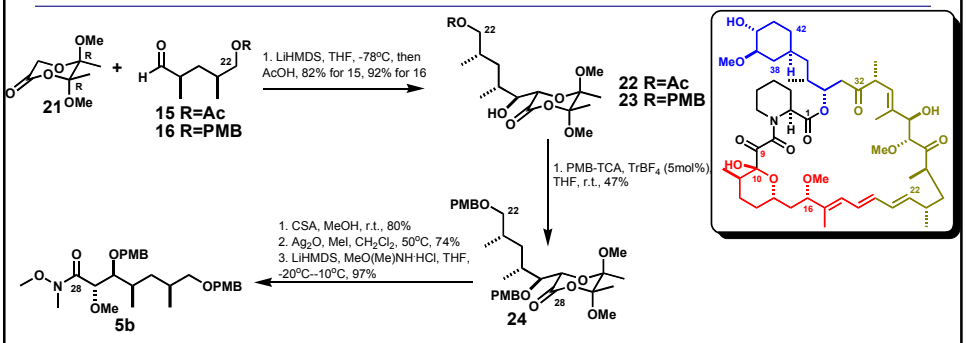


Synthesis of C22-C28 Electrophile 5



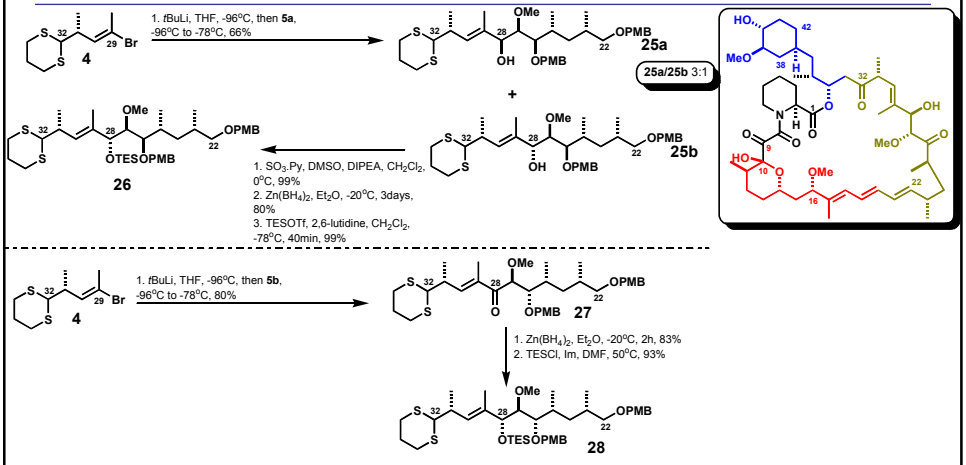
- Brown alkoxyallylation (**15** to **17**) selectivity was confirmed by X-ray analysis
- Direct ozonolysis of **18** was problematic.

Synthesis of C22-C28 Electrophile 5



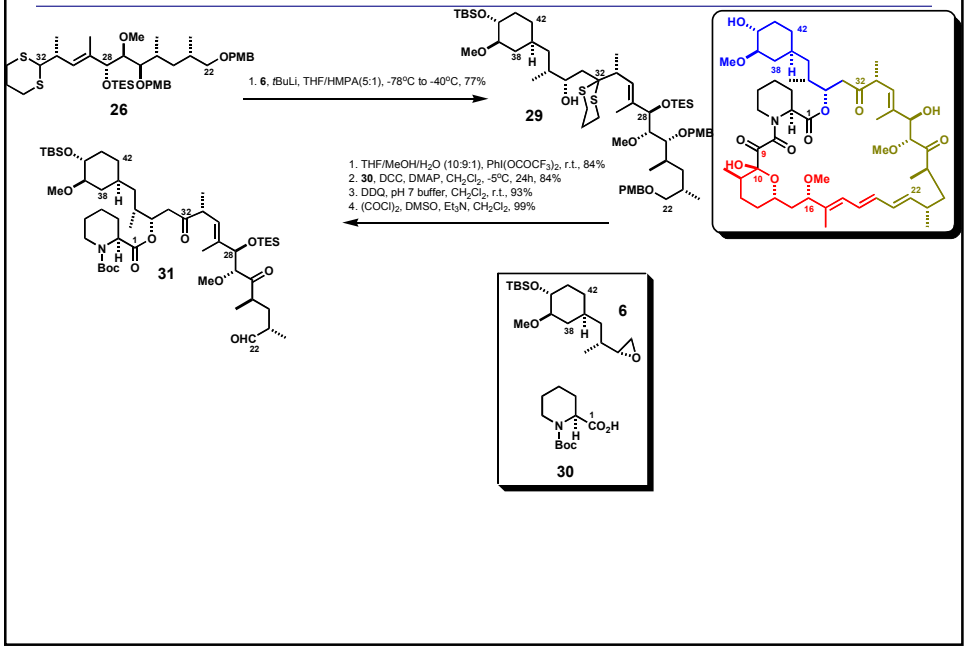
- Second approach for electrophile 5 using the groups recently developed butane-2,3-diacetal (BDA, **21**).
- BDA allowed for a highly selective aldol condensation with **15** or **16**.

Synthesis of C22-C32 Fragment

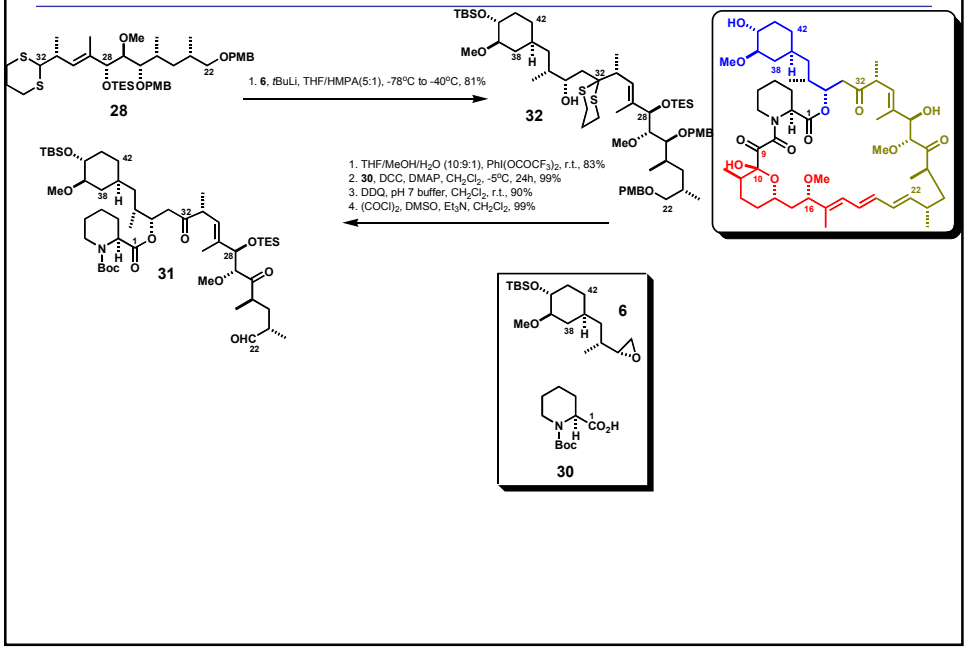


- $Zn(BH_4)_2$ afforded correct stereochemistry
- Addition of **4** and Weinreb amide **5b** offered higher yields to give **27** without any diastereomeric mixtures.
- Control D_2O studies indicated C29-C32 vinyl bromide 4 cleanly transmetalated, without abstraction of H from C32 dithiane.

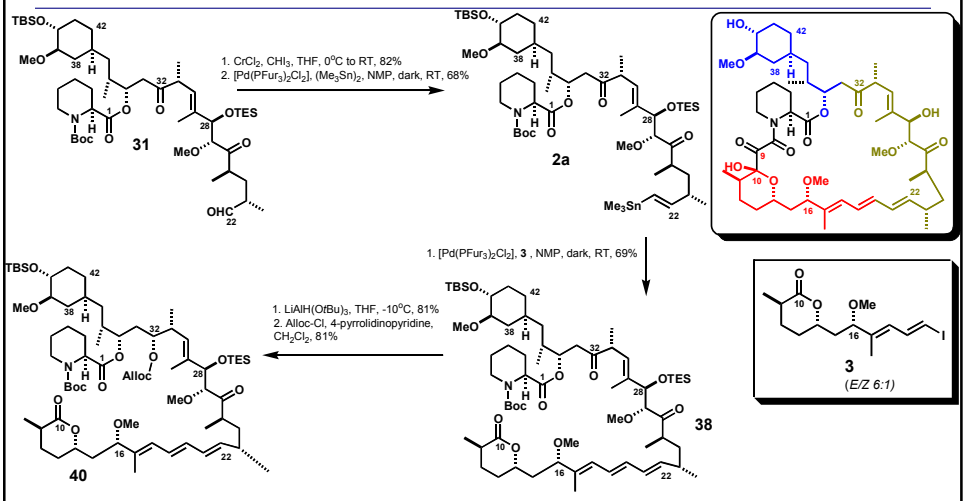
Synthesis of C22-C42 Fragment



Synthesis of C22-C42 Fragment

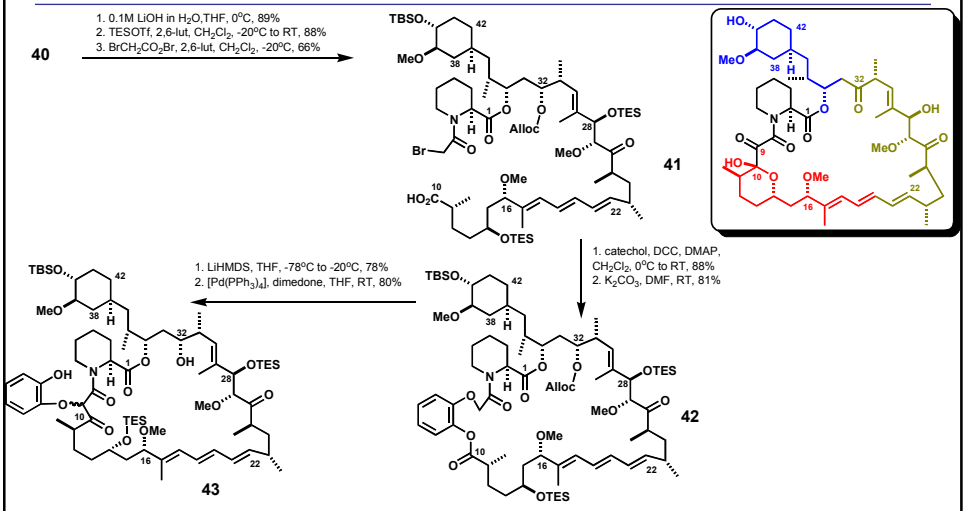


Final Stage of Synthesis



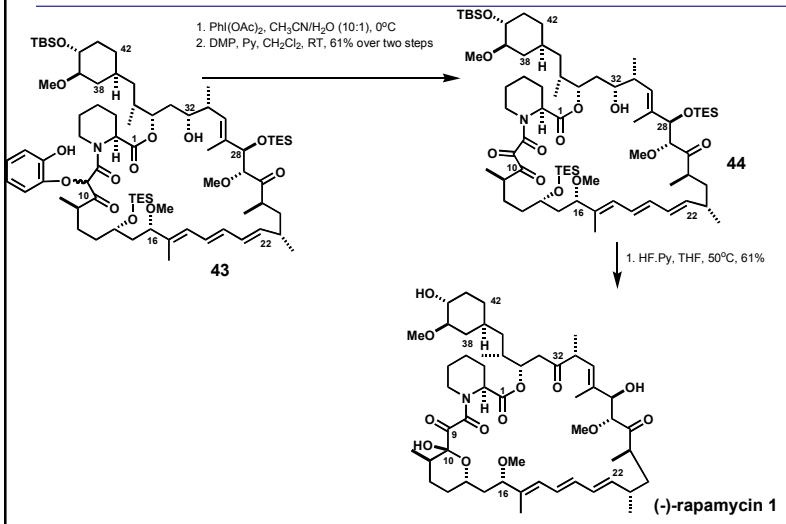
- No minor geometric isomer was detected of the Stille coupling
- Possibly *Z* isomer of 3 equilibrated with the *E*, or *Z* isomer react slower than *E* isomer

Final Stage of Synthesis



- Sequence of events from 40 to 41 is crucial to avoid epimerization of C11 Methy group.

Final Stage of Synthesis



Summary

- New and efficient convergent route to the synthesis of (-)-Rapamycin
- Used their recently developed butane-2,3-diacetal chemistry as protecting and stereodirecting functionality for the aldol reaction
- Efficient macroetherification/catechol strategy for the formation of the macrocyclic core of rapamycin.