Total Synthesis of Rapamycin

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Angew. Chem. Int. Ed. 2007, 46, 591 – 597

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Introduction

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
Previous Syntheses

- 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 macrcyclization.
- 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 reaction from first point convergence of 14 steps
  - first synthesis of Demethoxy-rapamycin
  - convergent approach permitted straight forward preparation of analogs.

\[ (-)-\text{rapamycin (1)} \]

-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

- C21-C42 stannane
- C29-C32 bromide
- C33-C42 epoxide
- C10-C20 lactone
- C22-C28 electrophile
**Synthesis of C29-C32 bromide 4**

1. (COCl)₂, DMSO, DIPEA, CH₂Cl₂, 0°C
2. HS(CH₂)₃BF₃OE₃, CH₂Cl₂, -78°C - RT, 99% over two steps

**Synthesis of C22-C28 Electrophile 5**

1. Lipase PS-30 (8wt%), DME/ vinyl acetate (5:1), r.t., 14h, 75%, 96-99% ee

‡ 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(BH₄)₂ afforded correct stereochemistry
Addition of 4 and Weinreb amide 5b offered higher yields to give 27 without any diastereomeric mixtures.
Control D₂O studies indicated C29-C32 vinyl bromide 4 cleanly transmetalated, without abstraction of H from C32 dithiane.
Synthesis of C22-C42 Fragment

1. t-BuLi, THF/HMPA (5:1), -78°C to -40°C, 77%
2. THF/MeOH/H₂O (10:9:1), PhI(OCOCF₃)₂, r.t., 84%
3. DCC, DMAP, CH₂Cl₂, -5°C, 24h, 99%
4. DDQ, pH 7 buffer, CH₂Cl₂, r.t., 93%
5. (COCl)₂, DMSO, Et₃N, CH₂Cl₂, 99%

Synthesis of C22-C42 Fragment

1. t-BuLi, THF/HMPA (5:1), -78°C to -40°C, 81%
2. THF/MeOH/H₂O (10:9:1), PhI(OCOCF₃)₂, r.t., 83%
3. DDQ, pH 7 buffer, CH₂Cl₂, r.t., 90%
4. (COCl)₂, DMSO, Et₃N, CH₂Cl₂, 99%
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

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.