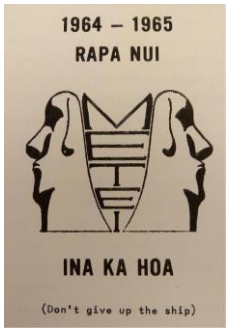
Rapamycin (Schreiber, 1993)

Rapamycin or “sirolimus” (brand name: Rapamune).

- METEI (Medical Expedition to Easter Island), a Canadian-led expedition to **Easter Island** in 1964, led to the discovery of rapamycinthis.
- Discovered as an antibiotic produced by an aerobic Gram-positive soil bacterium, specifically *Streptomyces hydroscopicus* AY B-994 [NRRL 5491].
- Immunosuppressant & antiproliferative effects.
- FDA approved (1999), treat kidney cancer (2007), “fountain of youth” (2009). Now owned by Pfizer.



METEI logo and inscription by Georges Nogrady

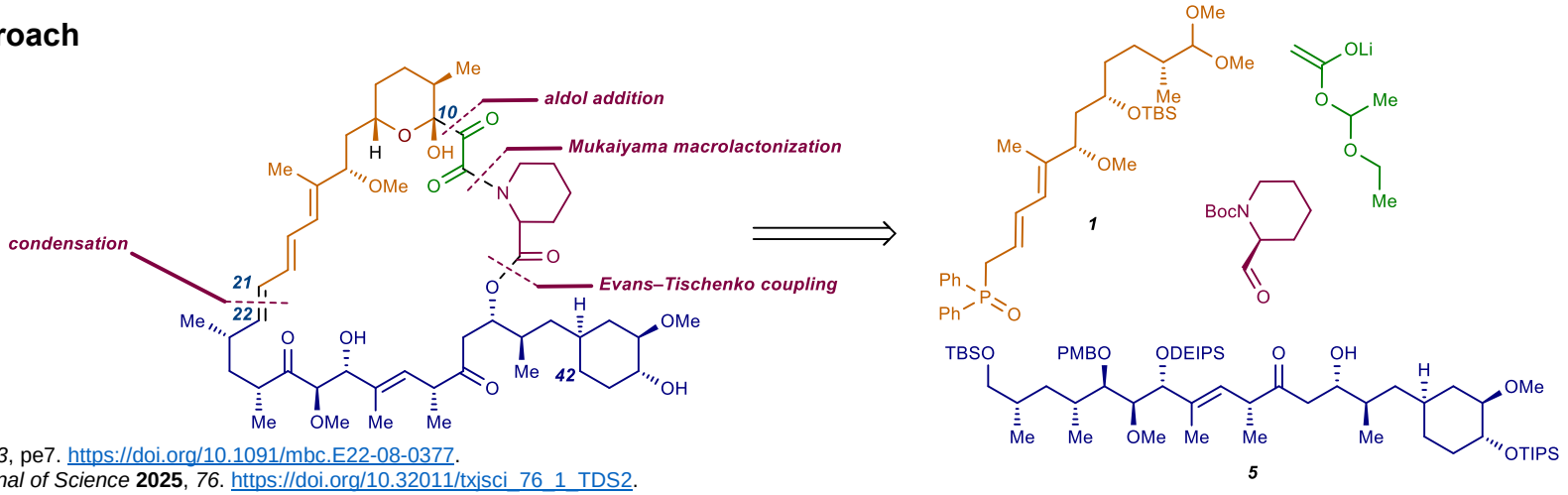
Team Rapamycin Celebration Dinner (1993)

with Stephanie Meyer, Daniel Romo, Laura Romo, Donna Johnson, Stuart Schreiber (left to right; inset: Dr. Tetsuo Miwa who had returned to Japan).

Total Syntheses of Rapamycin

- Nicolaou, K. C.; Chakraborty, T. K.; Piscopio, A. D.; Minowa, N.; Bertinato, P. *J. Am. Chem. Soc.* **1993**, *115*, 4419–4420. https://doi.org/10.1021/ja00063a093.
- Romo, D.; Meyer, S. D.; Johnson, D. D.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 7906–7907. https://doi.org/10.1021/ja00070a058.
- Hayward, C. M.; Yohannes, D.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1993**, *115*, 9345–9346. https://doi.org/10.1021/ja00073a083.
- Smith, A. B.; Condon, S. M.; McCauley, J. A.; Leazer, J. L.; Leahy, J. W.; Maleczka, R. E. *J. Am. Chem. Soc.* **1997**, *119*, 962–973. https://doi.org/10.1021/ja963067o.
- Ley, S. V.; Tackett, M. N.; Maddess, M. L.; Anderson, J. C.; Brennan, P. E.; Cappi, M. W.; Heer, J. P.; Helgen, C.; Kori, M.; Kouklovsky, C.; Marsden, S. P.; Norman, J.; Osborn, D. P.; Palomero, M. Á.; Pavey, J. B. J.; Pinel, C.; Robinson, L. A.; Schnaubelt, J.; Scott, J. S.; Spilling, C. D.; Watanabe, H.; Wesson, K. E.; Willis, M. C. *Chem. - Eur. J.* **2009**, *15*, 2874–2914. https://doi.org/10.1002/chem.200801656.

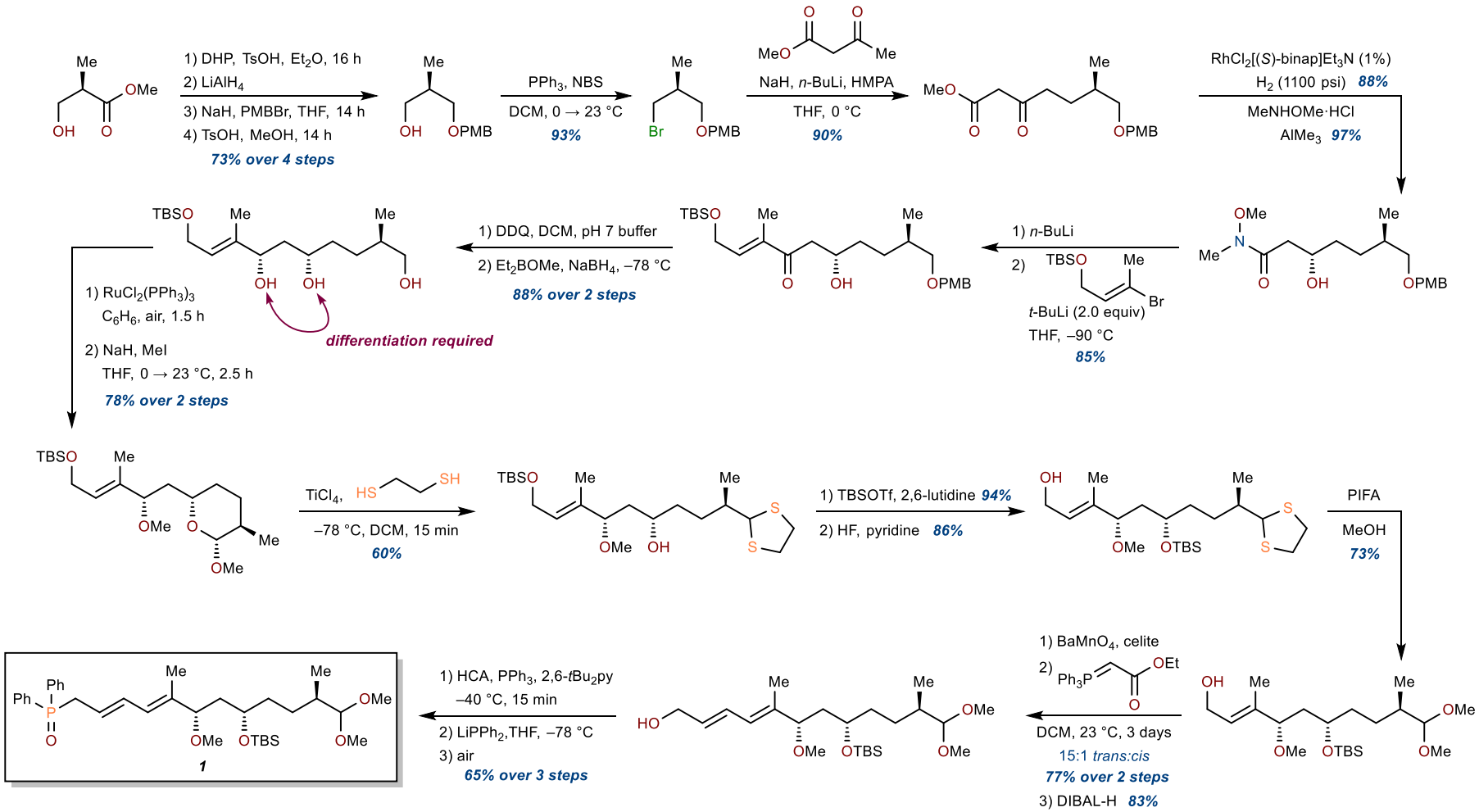
Schreiber’s Approach



Powers, T. *MBoC* **2022**, *33*, pe7. https://doi.org/10.1091/mbc.E22-08-0377.
Romo, D. *The Texas Journal of Science* **2025**, *76*. https://doi.org/10.32011/txjsci_76_1_TDS2.

Rapamycin (Schreiber, 1993)

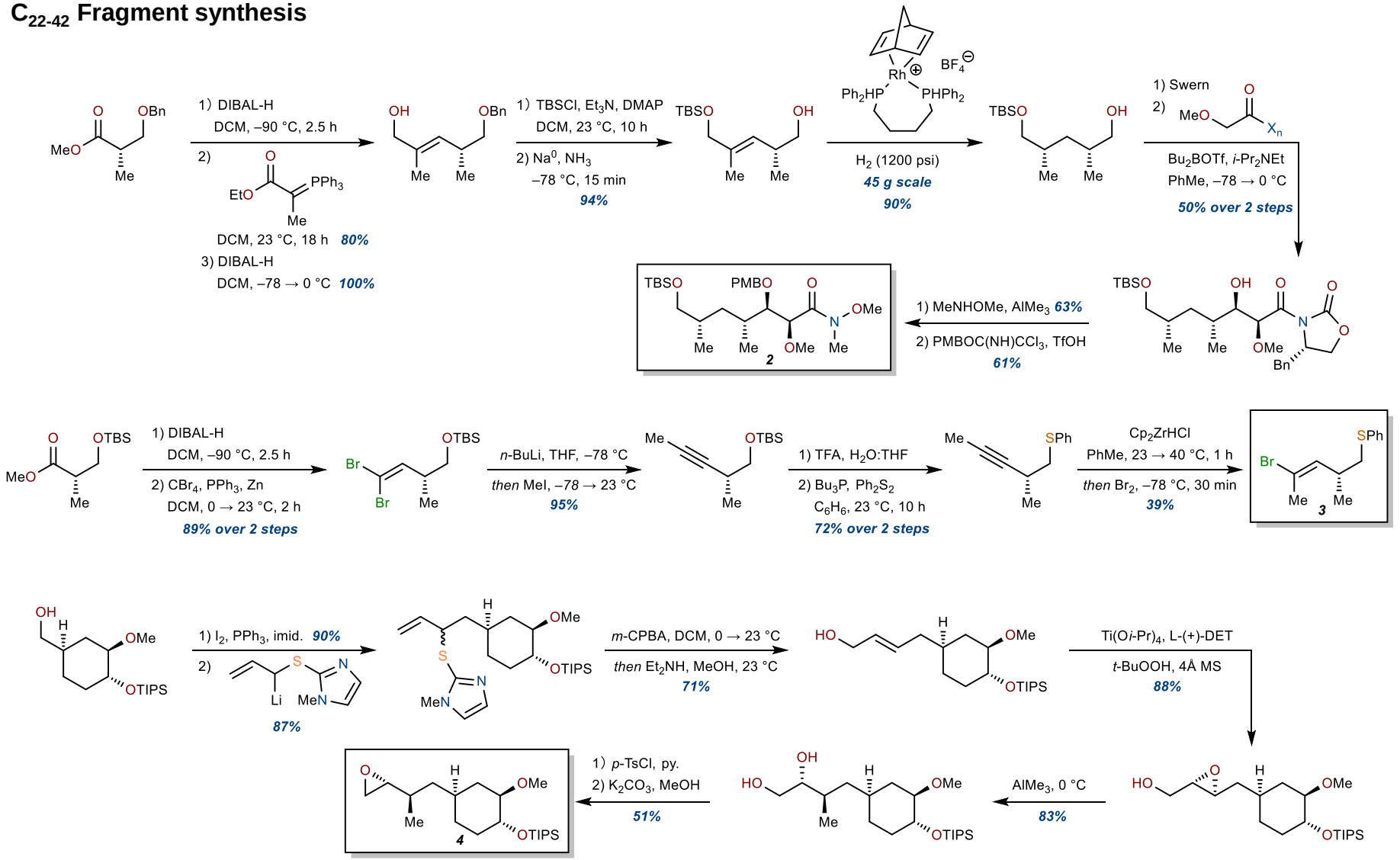
$C_{10\text{-}21}$ Fragment synthesis



Meyer, S. D.; Miwa, T.; Nakatsuka, M.; Schreiber, S. L. *J. Org. Chem.* **1992**, *57*, 5058–5060. https://doi.org/10.1021/jo00045a007.

Rapamycin (Schreiber, 1993)

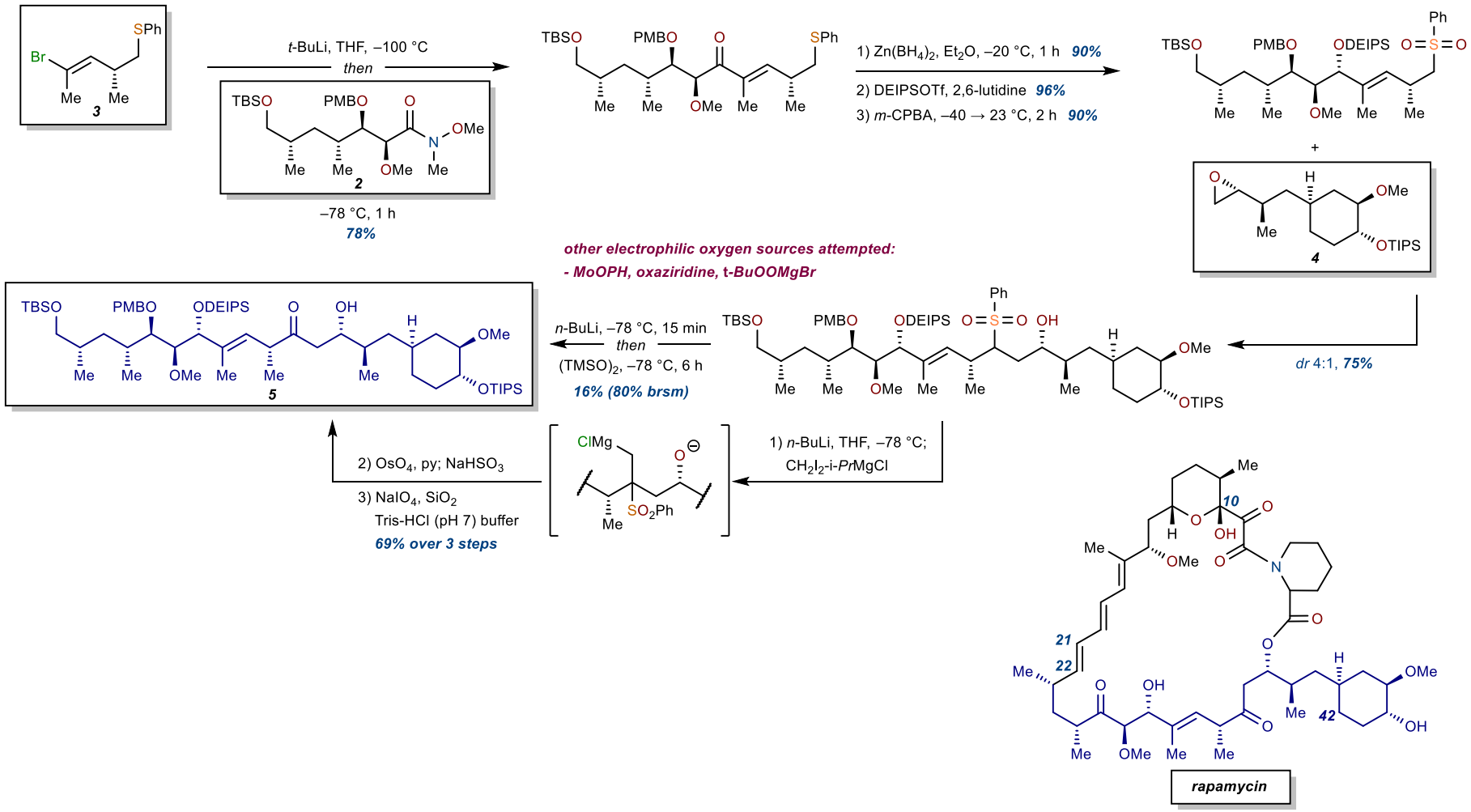
$C_{22\text{-}42}$ Fragment synthesis



Romo, D.; Johnson, D. D.; Plamondon, L.; Miwa, T.; Schreiber, S. L. *J. Org. Chem.* **1992**, *57*, 5060–5063. https://doi.org/10.1021/jo00045a008.

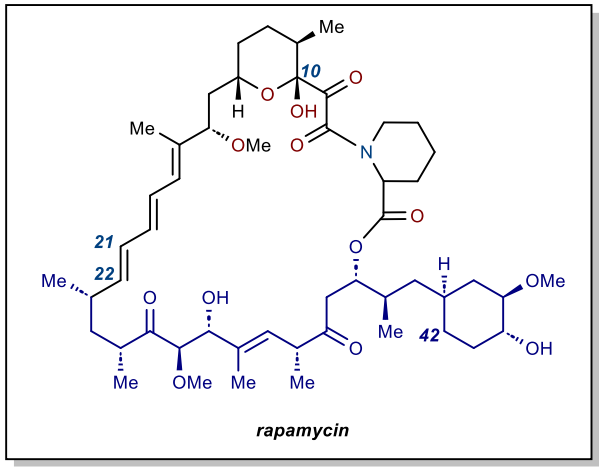
Rapamycin (Schreiber, 1993)

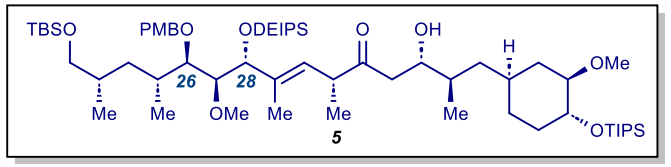
Fragments Assembling – Endgame



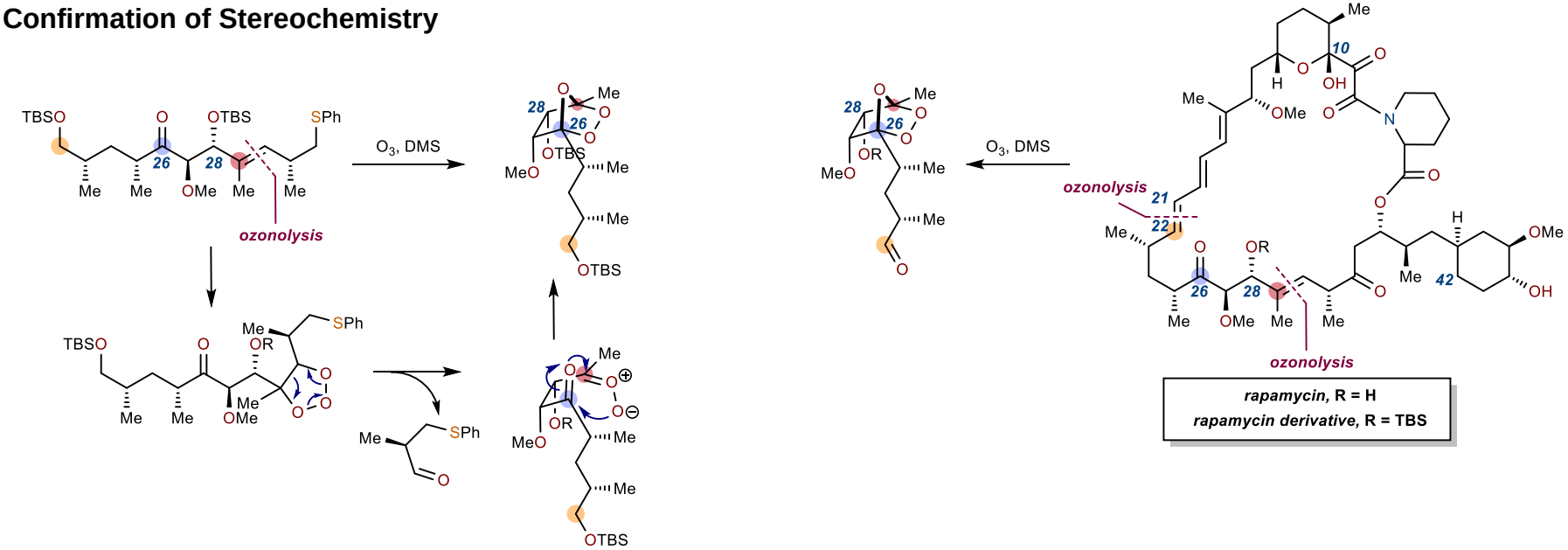
Julia's carbenoid electrophile: Lima, C. D.; Julia, M.; Verpeaux, J.-N. *Synlett* **2002**, *1992*, 133–134. https://doi.org/10.1055/s-1992-21291.

Rapamycin (Schreiber, 1993)





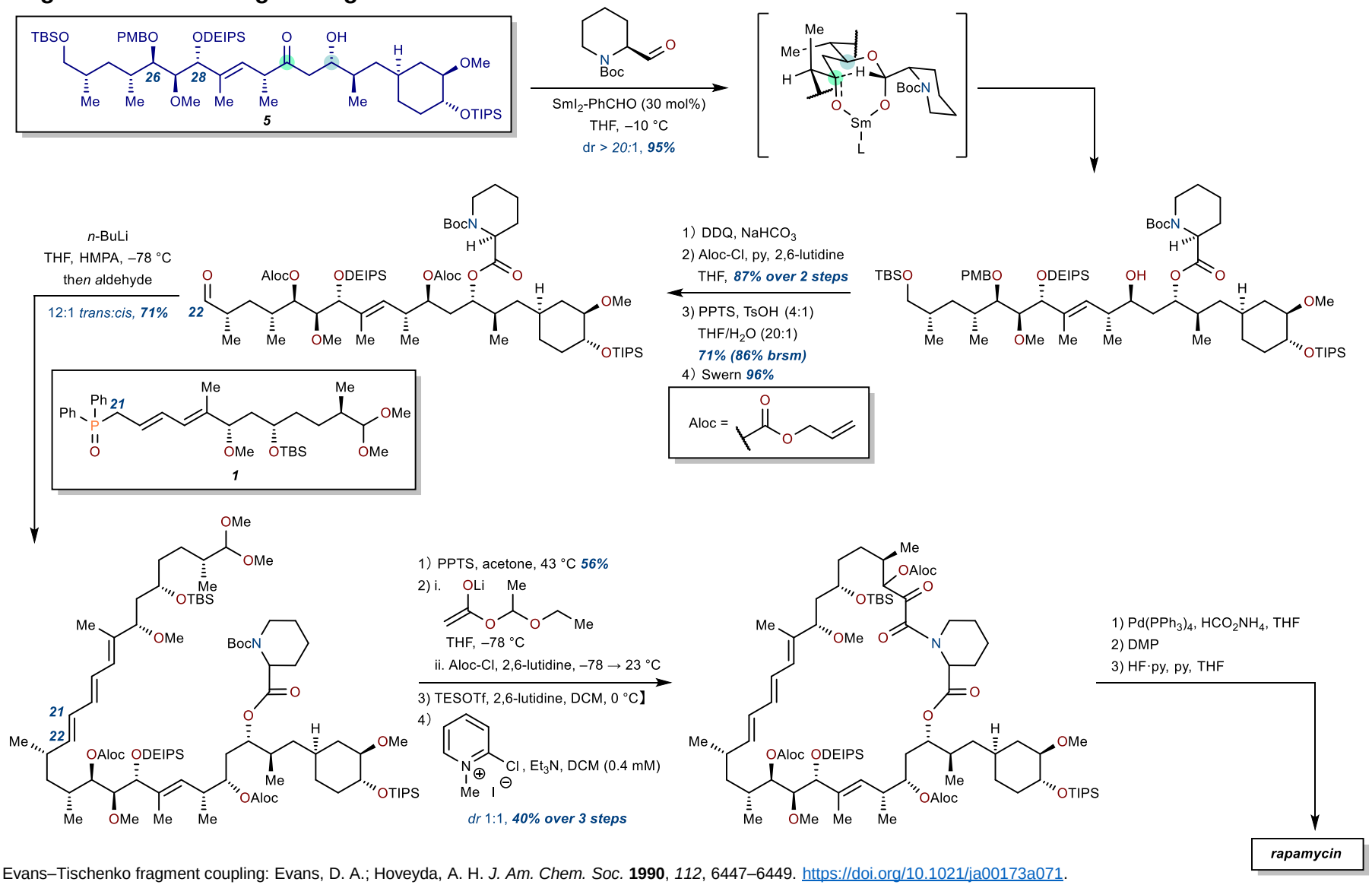
Confirmation of Stereochemistry



T. Goulet, M.; Boger, J. *Tetrahedron Letters* **1990**, *31*, 4845–4848. https://doi.org/10.1016/S0040-4039(00)97748-7.
Romo, D.; Johnson, D. D.; Plamondon, L.; Miwa, T.; Schreiber, S. L. *J. Org. Chem.* **1992**, *57*, 5060–5063. https://doi.org/10.1021/jo00045a008.

Rapamycin (Schreiber, 1993)

Fragments Assembling – Endgame



Evans–Tischenko fragment coupling: Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447–6449. https://doi.org/10.1021/ja00173a071.
Mukaiyama macrolactonization: Bald, E.; Saigo, K.; Mukaiyama, T. *Chemistry Letters* **1975**, *4*, 1163–1166. https://doi.org/10.1246/cl.1975.1163.
Romo, D.; Meyer, S. D.; Johnson, D. D.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 7906–7907. https://doi.org/10.1021/ja00070a058.