Total Synthesis of Thapsigargin
a Potent SERCA Pump Inhibitor


Also:
• S. V. Ley et. al., *PNAS*, 2004, 12073
The Thapsigargins

- Family of 17 Guaianolides.
- Sesquiterpene lactone with a 5-7-5 core
- 8 stereocentres, 4 different esters

- Thapsigargin isolated in 1978 from Mediterranean plant *Thapsia Garganica* L., which is resistant to cultivation.

- Thapsigargin costs 128$CAD per mg from Sigma Aldrich.

- Thapsigargin is a potent inhibitor (≤2.2 pM) of sarco/endoplasmic reticulum Ca\(^{2+}\) ATPase (SERCA).
  - Disrupts cellular Ca\(^{2+}\) levels, eventually causing apoptosis.
  - Promising lead as a treatment for prostate cancer.
  - Routinely used for studying Ca\(^{2+}\)-dependant cell process.

- Thapsigargin is highly toxic: it selectively inhibits SERCA (i.e. does not affect Na/K pumps) but is non-selective between cell types.
Thapsigargin Prodrug and Prostate Cancer

- Prostate Cancer accounts for 25% of new cancer diagnoses in men in the UK (population ca. 61 million).
- **There is currently no cure for androgen-independent prostate cancers.**
- The prodrug is cell impermeant but stable in blood plasma.
- **PSA is found in the vicinity of the cancerous cells and releases a cell permeable and active thapsigargin derivative.**

Thapsigargin prodrug

- Total syntheses of five thapsigargin natural products.
- Ley group have produced SERCA ligands more potent than thapsigargin
- Several unnatural analogues have also been prepared by total synthesis.
Retrosynthesis

- 42 linear steps, **89% average yield**.
- Substrate-control exploited extensively
1. AllylMgBr
MgBr₂, DME

84 % over 2 steps

1. t-BuLi, THF,
ethylvinyl ether
2. TESCl, DMAP,
Imidazole, DMF

65 % over 2 steps

DDQ, DCM
phosphate buffer

dr = >19:1
LHMDS -78 to -15 °C then PhSeCl, -90 °C
\[ \text{dr} = 4:1 \]
O₃, DCM, -78 °C then iPr₂NH, -78 °C to rt

\[ 4:1 \]
1. Zn(BH₄)₂, Et₂O, -30 °C, then TBAF 80% (d.r. 9:1)

2. PhMe, NaHCO₃, 80 °C, 2 days, 98%

1. Octanoic anhydride, DMAP

2. Isopropenyl acetate, TsOH 86% over 2 steps

MeOH, TsOH, 83%

Butyric anhydride DMAP, DCM, 91%

thapsigargin