Total Synthesis of Five Thapsigargins: Guaianolide Natural Products Exhibiting Sub-Nanomolar SERCA Inhibition

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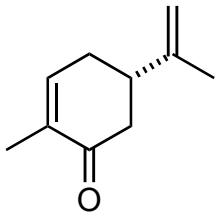

1-6

1) H_2O_2, NaOH
2) TFA, LiCl
3) 2,3-dihydropyran, PPTS
4) NaOMe, MeOH
5) MeOH, PPTS
6) TBDPSCl, imidazole

1) Name of the starting material?

4) Named reaction?

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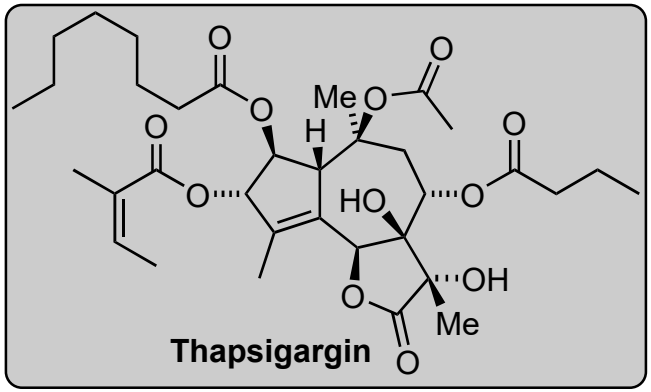
7-17

7) $LiAlH_4$
8) NaH, PMBCl
9) OsO_4, NMO *then* $NaIO_4$
10) $MgBr_2 \cdot Et_2O$, allylmagnesium bromide
11) MOMCl, DIPEA
12) DDQ, pH 7 buffer
13) DMP
14) Ethyl vinyl ether, *t*-BuLi
15) TESCl, imidazole
16) Grubbs II catalyst
17) AD-mix alpha, $NaHCO_3$



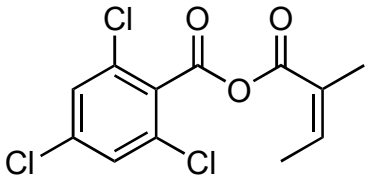
Thapsigargin

18-28

29-40

Thapsigargin

18) EDCI, $HO_2CCH(Me)P(O)(OEt)_2$
19) NaH
20) $LiBH_4$
21) Ac_2O
22) MOMCl, DIPEA
23) OsO_4, quinuclidine, K_2CO_3, $K_3Fe(CN)_6$
24) K_2CO_3
25) 10 mol% TPAP, NMO
26) Amberlyst 15, wet Me_2CO,
2,2-dimethoxypropane *then* mol. sieves
27) TBAF
28) DMP



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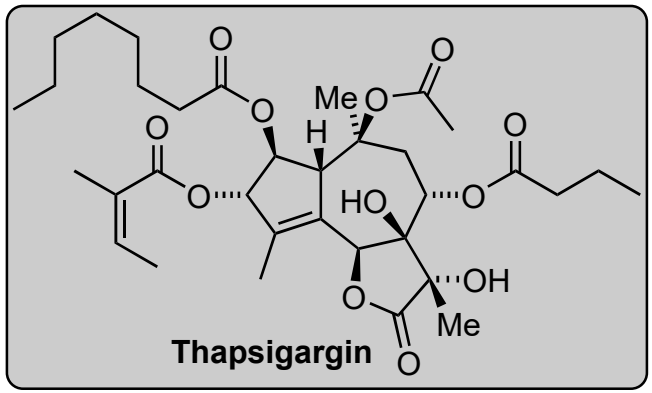
29) TMSCl, NEt_3, 130 °C, 43 h
30) DMDO, Me_2CO, *then* RT
31) SEMCl, DIPEA
32) LiHMDS *then* PhSeCl
33) O_3 *then* DIPA
34) $Zn(BH_4)_2$ *then* TBAF
35) **1**, $NaHCO_3$
36) *n*-BuSH, $MgBr_2 \bullet Et_2O$, K_2CO_3
37) octanoic anhydride, DMAP
38) isopropenyl acetate, *p*-TsOH
39) HCl, MeOH
40) butyric anhydride, DMAP

19) Named reaction?

24) *hint: two transformations happen*

36) *hint: deprotection*



Thapsigargin