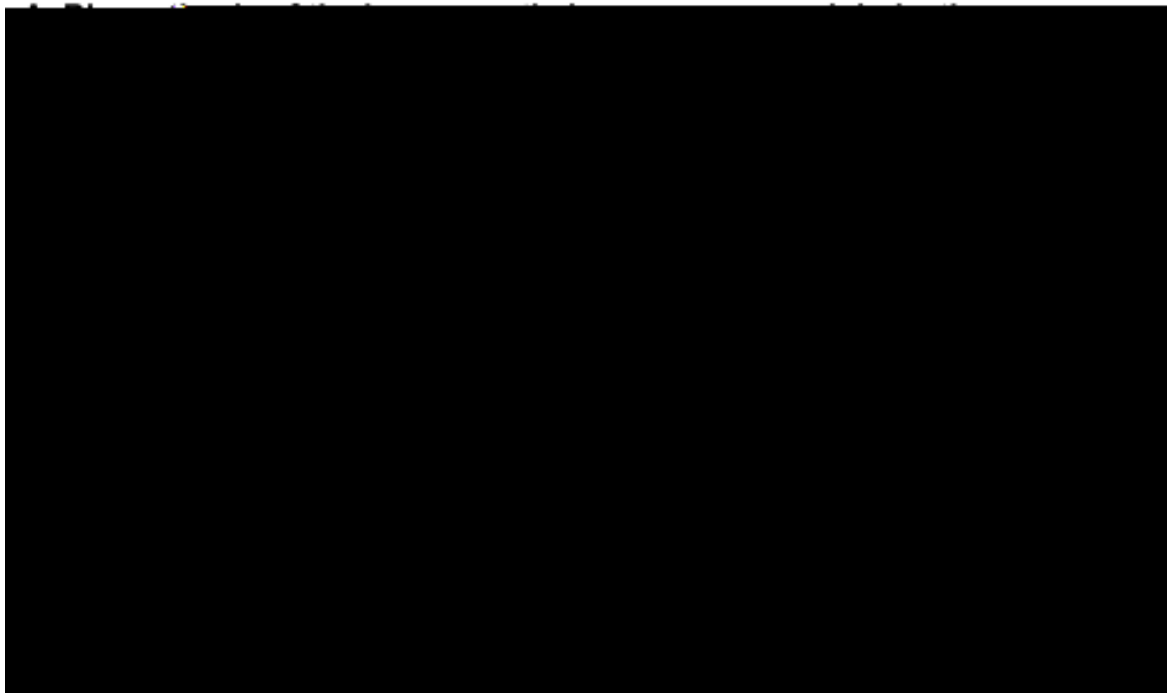
Convergent Total Synthesis of Principinol D, a Rearranged Kaurane Diterpenoid

Turlik, A. ; Chen Y.; Scruse A. C.; Newhouse T.R. Yale University



Grayananes diterpenoids are among a broader class of rearranged kauranes . They are formed by rearrangement of the kaurane 6,6- ring system to a 5,7-ring system.

The kauranes are derived from rearrangement and cyclization of pimaranes via the beyeranes

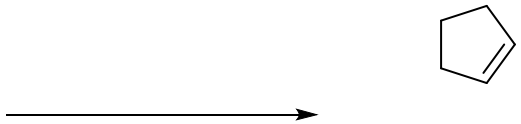
Grayananes diterpenoids have recently been identified as structurally novel allosteric inhibitors of carbonic anhydrases and phosphatase

Potential therapeutic development could span numerous differentdisease areas from neurological dysfunction to cancer.

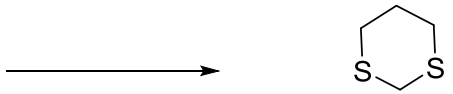
Synthetic efforts toward the grayananes have been especially limited to linear cyclization strategies.

Newhouse group speculated that a convergent retrosynthetic strategy, which isolates the two main constellations of stereocenters, would yield a laboratory route that could enable synthesis of grayanane analogs.

Herein, they report the first total synthesis of the grayanane analog principinol D

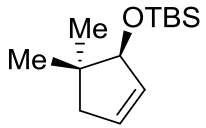


Dithiane addition

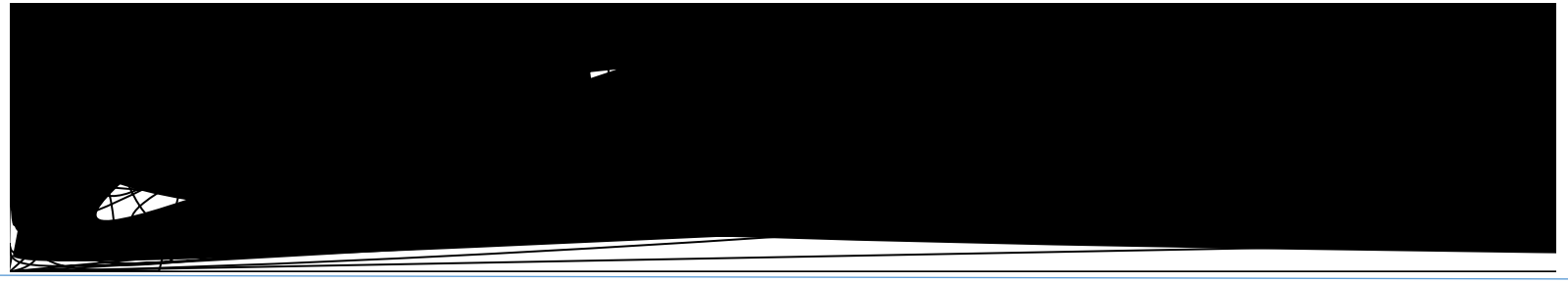


Dithiane deprotection

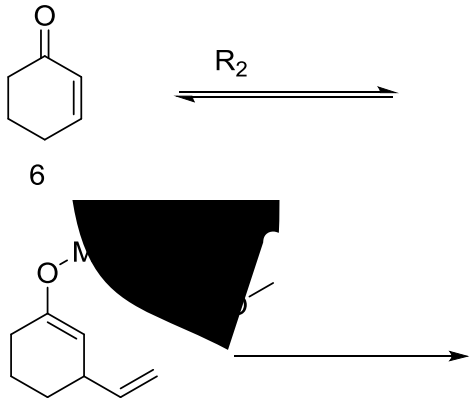
MOM protection



Synthesis of Bicyclo[3.2.1]octane Fragment Coupling Partner 3

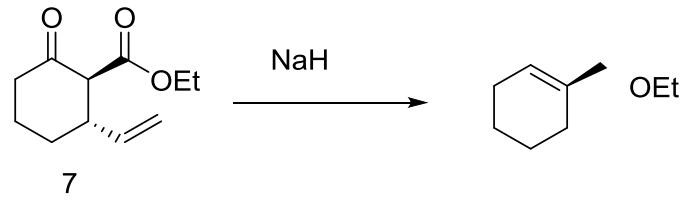


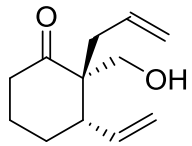
Vicinal difunctionalization



Selective reduction of esters in the presence of ketone

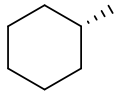
Allylation

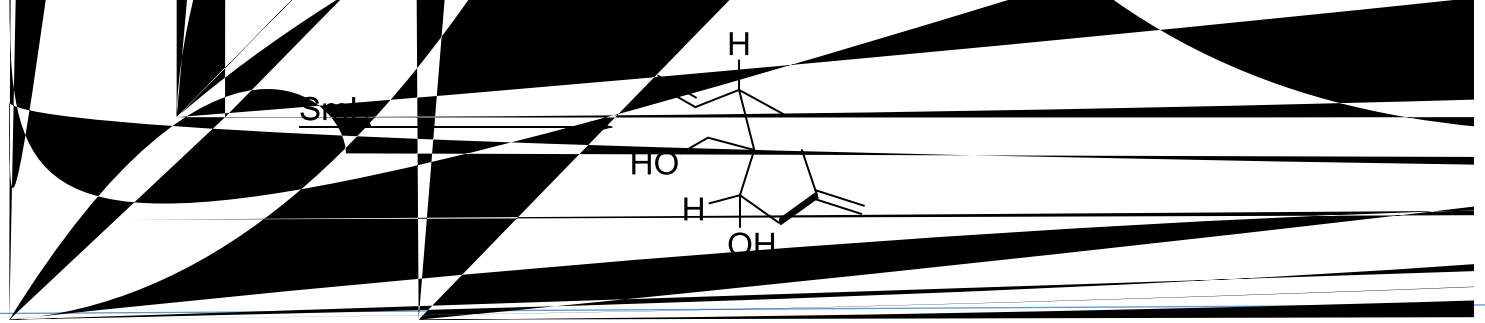




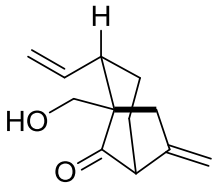
4.

Ni catalyized C-vinylation

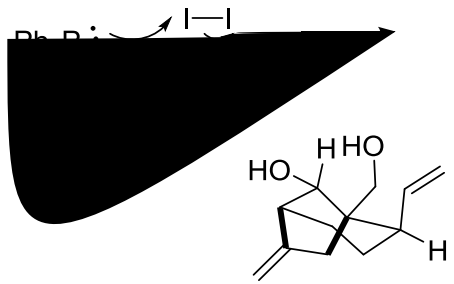




SmI_2-mediated diastereoselective ketone reduction



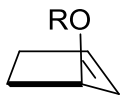
Appel reaction



14. SmI

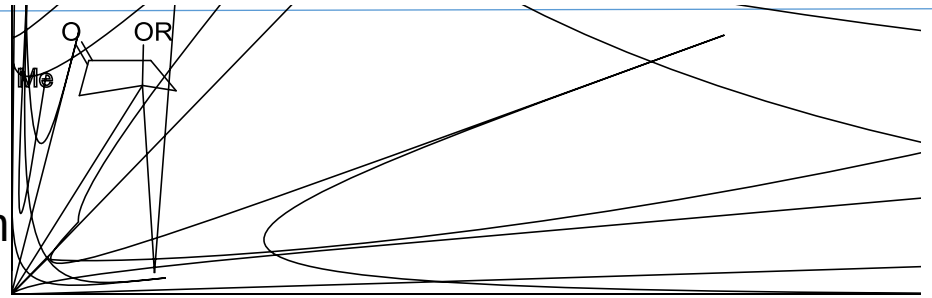
Selective oxidative cleavage of monosubstituted alkene (Lemieux-Johnson Oxidation)

SmI2-mediated ring-closing and DMP



Peterson adduct

Mukaiyama Hydration



Global MOM deprotection