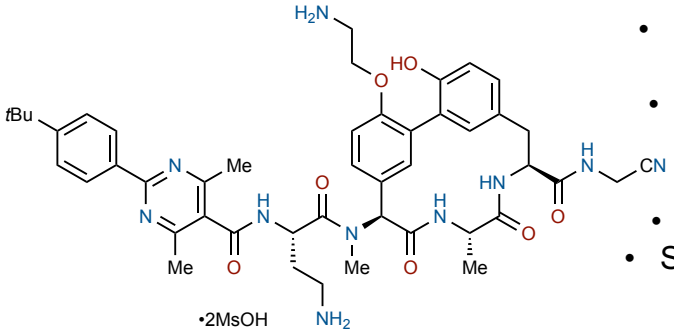
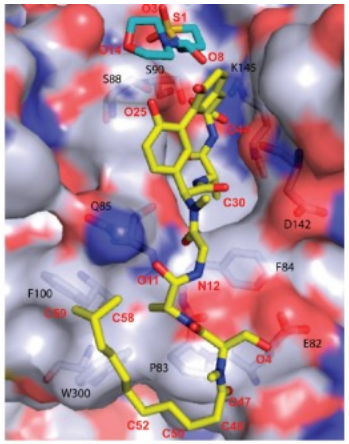
GDC-5338 (Genentech)

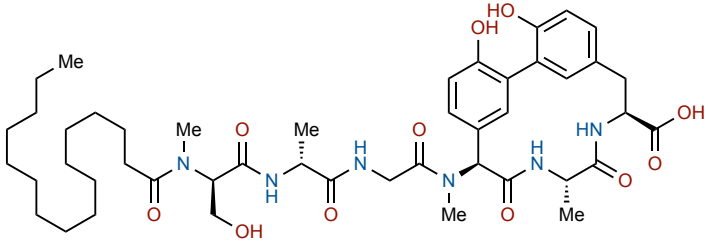


- No new classes of Gram-Negative antibiotics have been FDA-approved in 60 years!
  - Arylomycins A and B were isolated in 2002
- These antibiotics (and their analogues) act against type I signal peptidase (SPase)
  - Despite several total syntheses, arylomycin has not been developed into a G-N antibiotic drug
- Poor penetration of the double cell wall prevents arylomycin from reaching SPase
- Synthetic analogues improve penetration and can serve as broad spectrum antibiotics

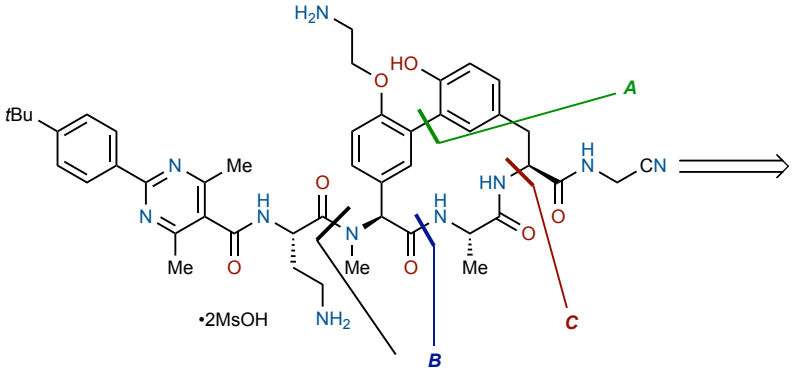
https://doi.org/10.1021/acs.orglett.9b03481

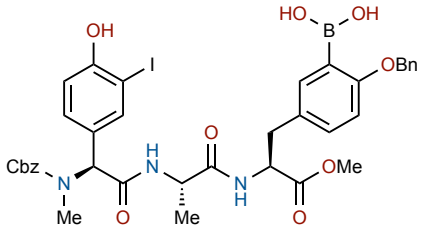


- The arylomycins bind to the target peptidase (on left)
- Lipophilicity and high MW prevent cell penetration
- Arylomycins are not potent against ESKAPE pathogens



Arylomycin A-C$_{16}$

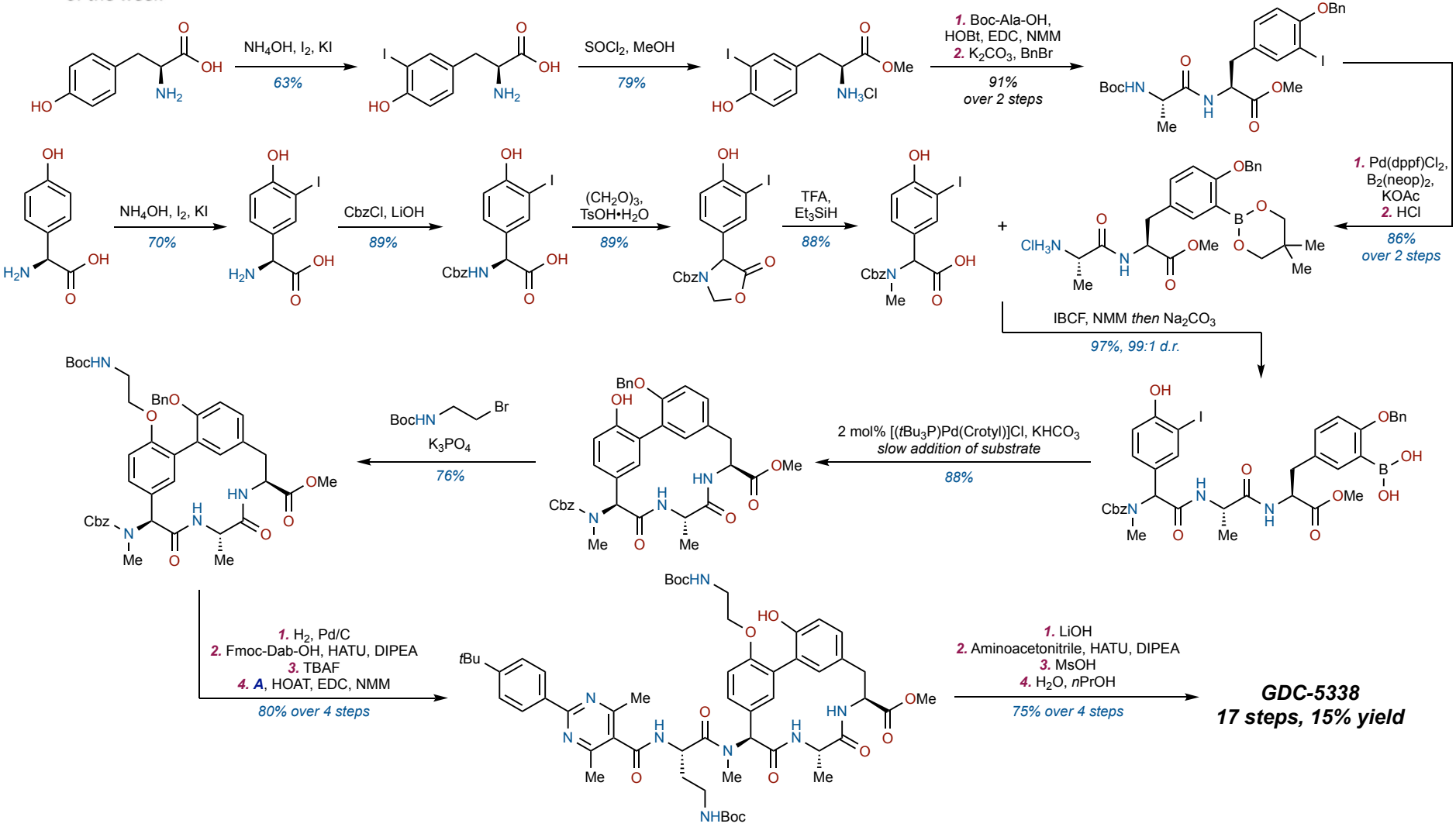




Only reported Suzuki coupling on large scale proceeded in less than 20% isolated yield

For disconnections B and C see:
https://doi.org/10.1021/acs.orglett.8b03603

GDC-5338 (Genentech)



Intramolecular Suzuki is highly air-sensitive!
Inclusion of even 5 ppm O_2 led to deborylation
[Pd] precatalyst is air and moisture stable