

Best of OPRD 2019

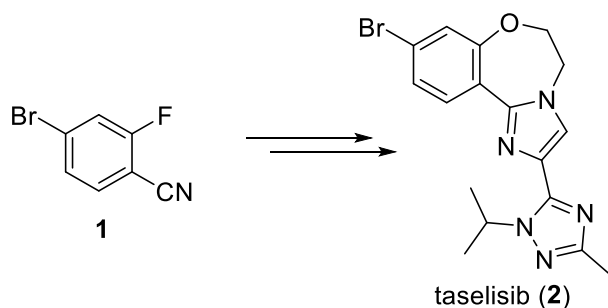
This weeks' problems will focus on the impressive achievements of process chemists as published in the 2019 edition of OPRD. Please refrain from looking up the solutions and come up with your own ideas!

A) Manufacture of PI3K β -Sparing Inhibitor Taselisib

From *OPRD*, **2019**, 23, 783

“As part of a phase I to phase III accelerated drug development program, multikilogram amounts of tselisib active pharmaceutical ingredient [active against PIK3CA mutant breast cancer] were required to support human clinical studies.”

Starting from compound **1**, please propose a route that might be amenable to large scale synthesis (16.2 kg were produced in a single batch).

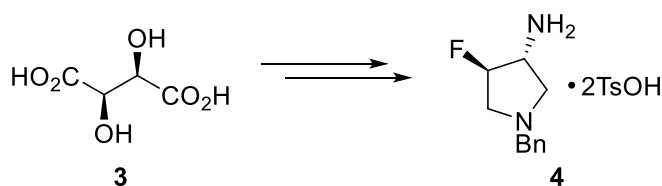


B) Enantioselective Synthesis of (3R,4R)-1-Benzyl-4-fluoropyrrolidin-3-amine utilizing a Burgess-type transformation

From *OPRD*, **2019**, 23, 1970

“In our process development work toward a recent oncology candidate for treatment of epidermal growth factor receptor T790M secondary mutations, we encountered the difficult synthesis of trans-3-fluoro-4aminopyrrolidine [**4**]”

Enantiopure compounds on a process scale are often prepared via resolution or from chiral pool starting materials. The present case is an example for the latter. Starting from L-tartronic acid (**3**) 120 kg of **4** were prepared in a single batch.



Hint: The title gives a key hint on how you might achieve this.

C) Practical Synthesis of a 6-Triazolylazabicyclo[3.1.0]hexane

From *OPRD*, **2018**, 23, 728

“The 1,2,4-triazole nucleus is featured in a variety of biologically and medicinally interesting molecules [...]. To support the production of such promising lead molecules, we developed and executed a fit-for-purpose kilogram-scale synthesis of *exo*-triazolyl azabicyclo [5].”

In the publication a rather niche reaction was employed to great effect. To not force you down a route that relies on one particular disconnection, no starting material will be given. Bear in mind that 18.2 kg were produced in a single batch, so your starting material should be readily available.

