MK-4256

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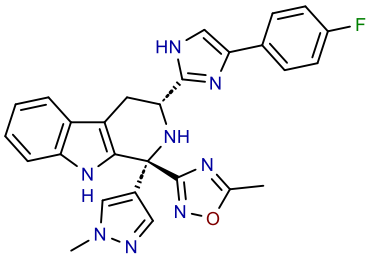
- Developed as a treatment for type two diabetes.
- If left untreated or not managed properly can cause diabetic retinopathy or neuropathy.
- Targets the protein SSTR3, which is one of the proteins that mediate somatostatin.
- Somatostatin is known to suppress production of insulin, making it a potential target. Therefore, antagonism of this protein has potential to promote glucose dependent insulin secretion.



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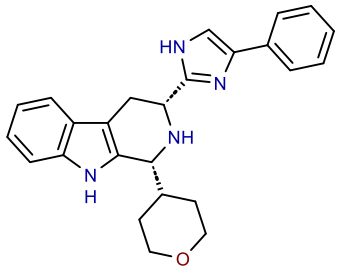
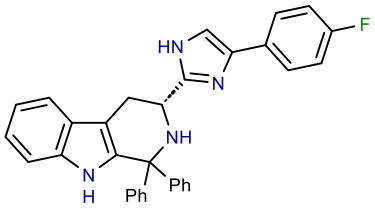
ACS Med. Chem. Lett. **2012**, 3, 484–489 https://doi.org/10.1021/ml300063m

Initial scaffold optimization



Aryl flourine increases SSTR3 binding affinity.

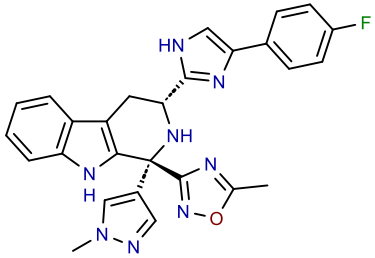
diaryl substitution futher increases binding affinity.



Has strong binding affinity to hERG.

High SSTR3 affinity.

Lowered hERG binding affinity.



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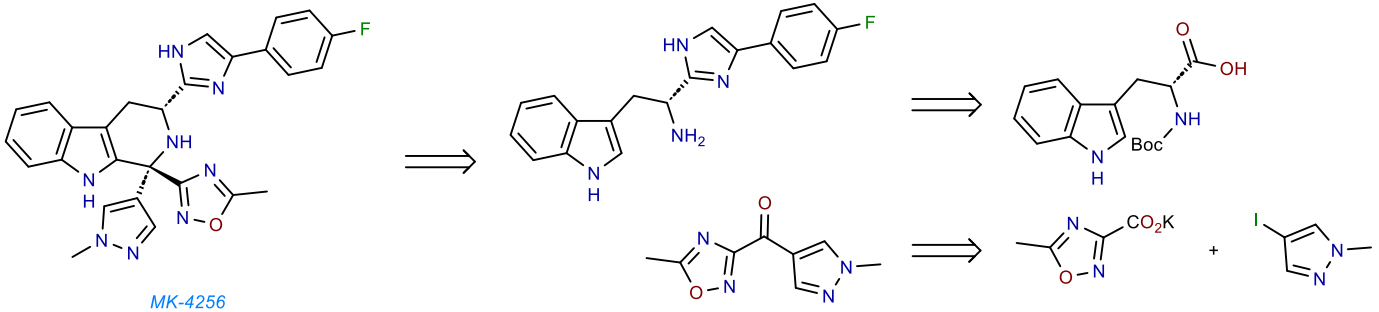
Retrosynthesis



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Org. Process Res. Dev. **2012**, 16, 1329–1337 https://doi.org/10.1021/op300128c

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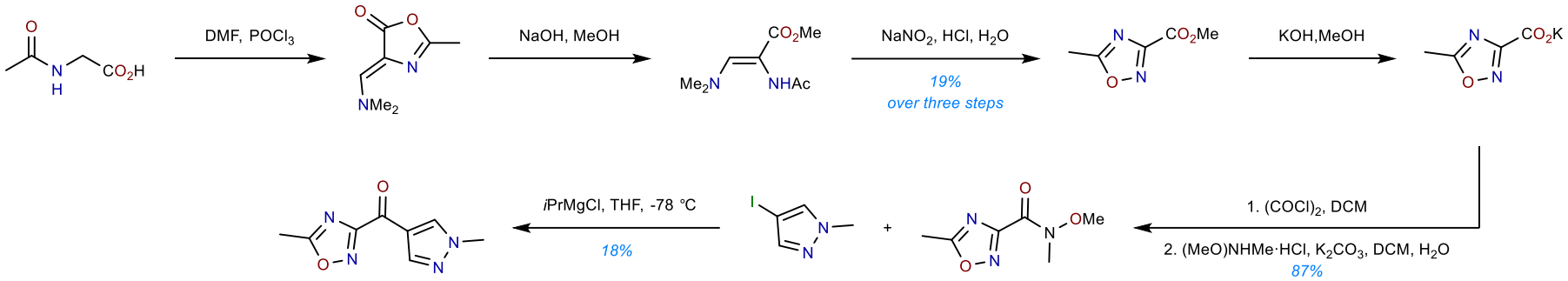
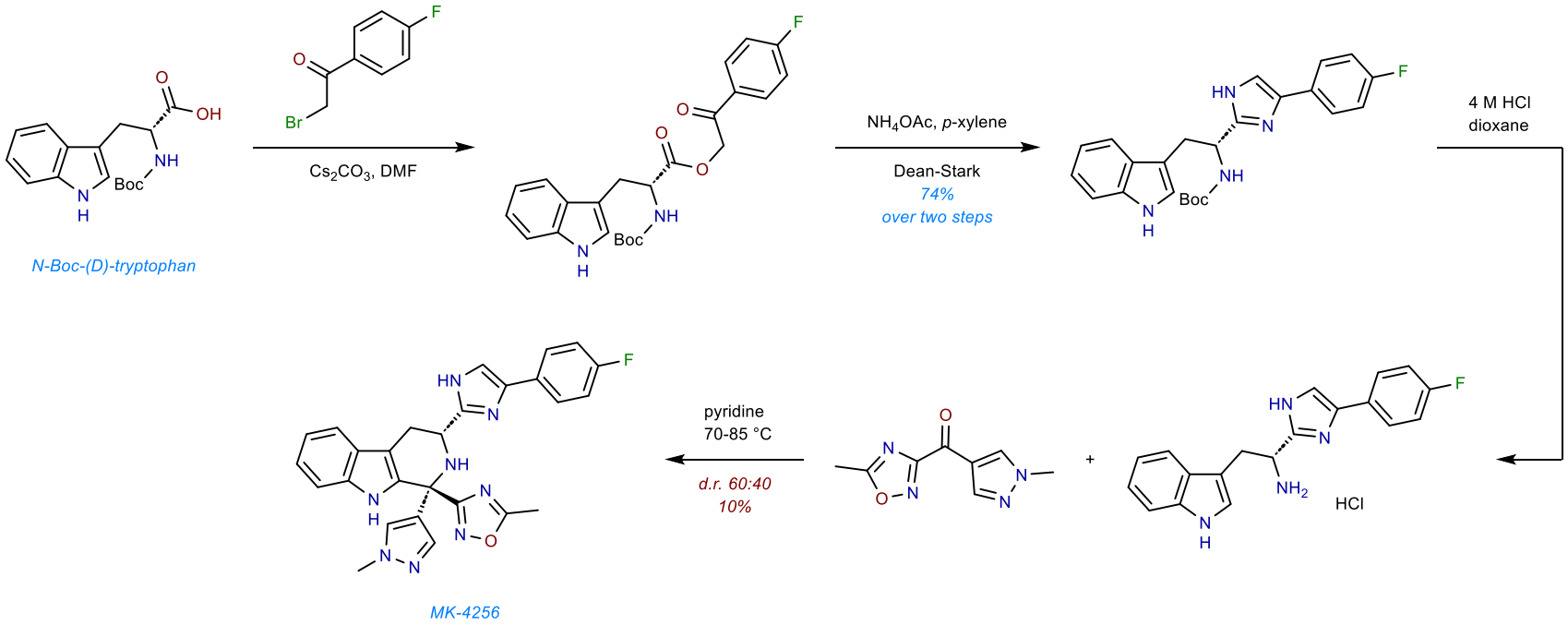
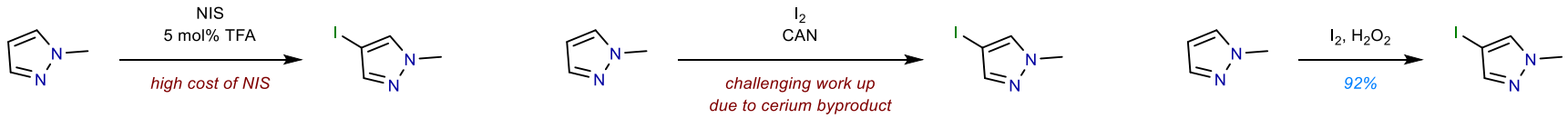
Synthesis of heterocycle



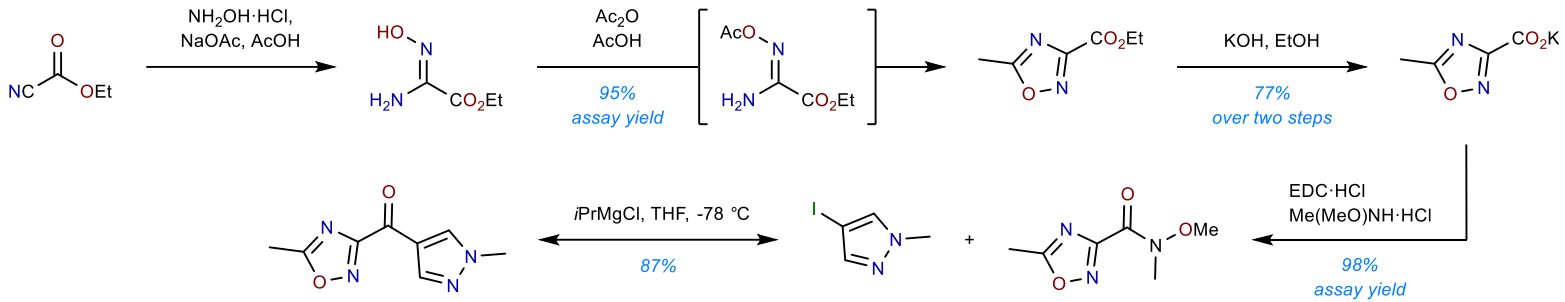
Pictet-Spengler



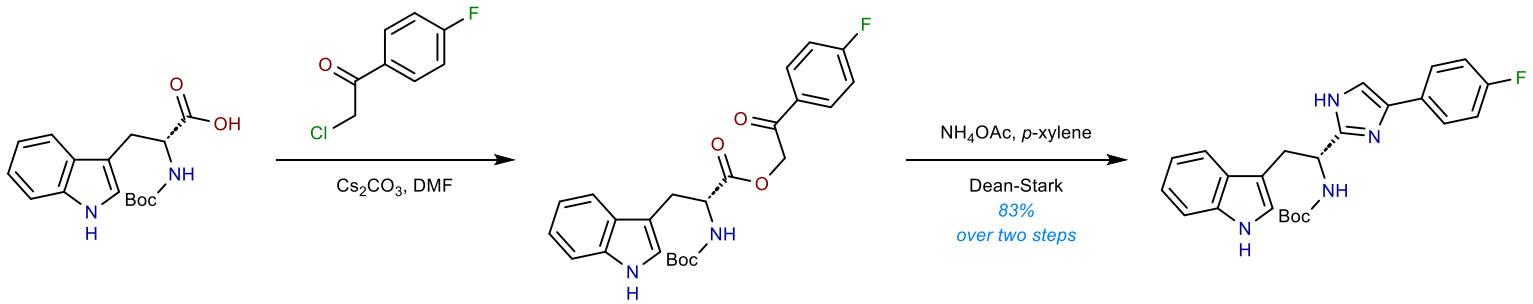
Process Route



- While the iodopyrazole was purchased for the discovery route, it was found to be significantly cheaper to start from N-methylpyrazole ($956 per kg) *vs*. 4-iodo-N-methylpyrazol ($3360 per kg).

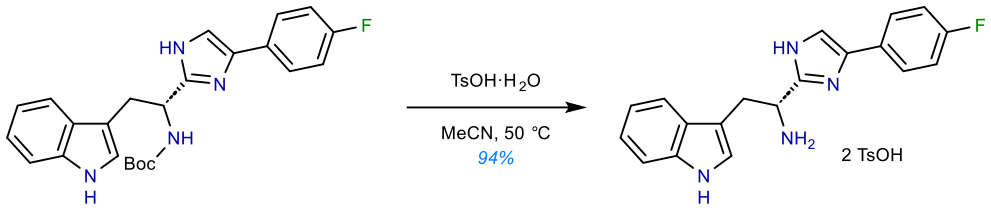


- Switching to ethyl ester was found to allow for an easier isolation of the potassium salt, after hydrolysis.
- While the yield of the 1,2 addition into Weinreb amide was quite low, only a change in the work up procedure (switching from EtOAc to DCM) followed by a recrystallization gave a massive improvement in the yield.

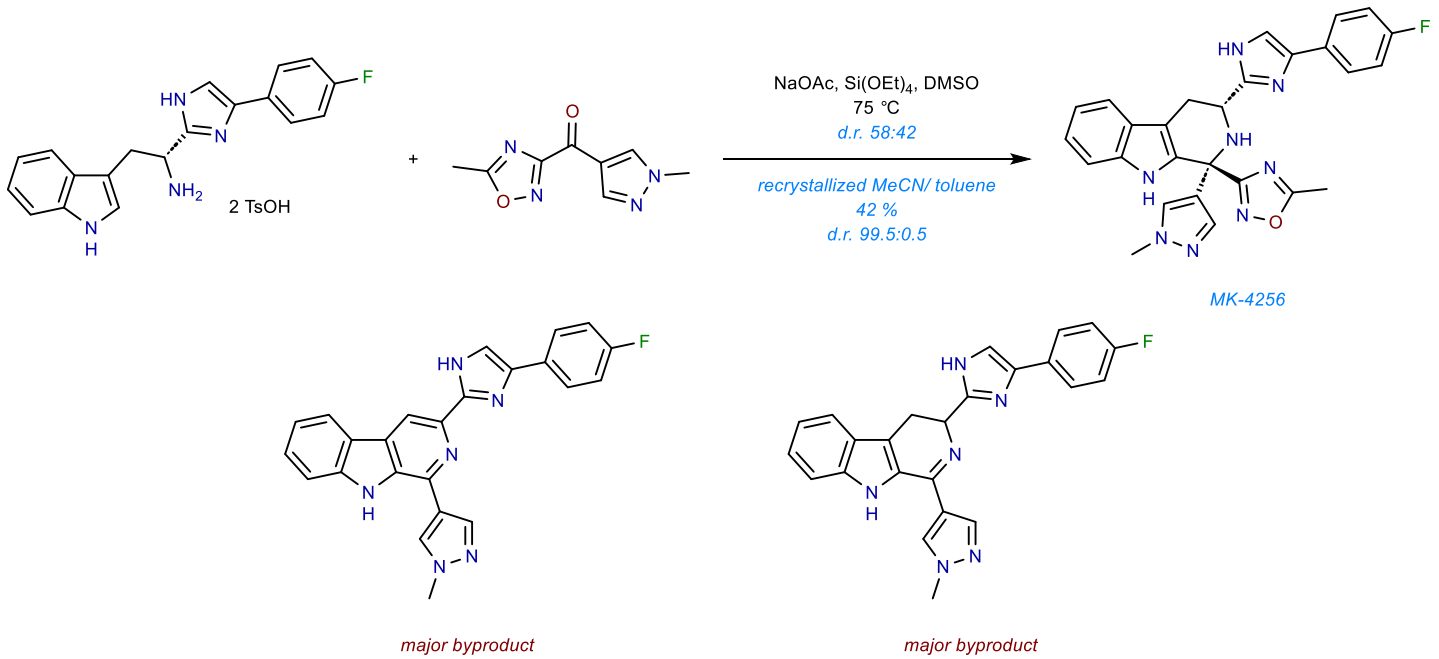


- The α-bromo ketone was not available in large enough quantities to support multi kilogram preparation of MK-4256.

Process Route



- The hydrochloride salt used by the discovery team was challenging to isolate and needed multiple days under vacuum to yield a workable foam, which was ultimately unpractical on multi kilogram scale.
- Solvent choice and crystallization temperature on scale proved critical to obtain a crystal size that could be filtered easily.



- Scaling up the discovery team's conditions the formation of the pyridine was observed, after elimination of the oxadiazole and subsequent oxidation.
- Extensive solvent screening showed DMSO as the optimal solvent for the Pictet-Spengler, but now elimination was observed as a major byproduct (without concomitant oxidation to the pyridine). Therefore, incorporation of one equivalent of NaOAc was used to only allow for a single equivalent of TsOH to be present.