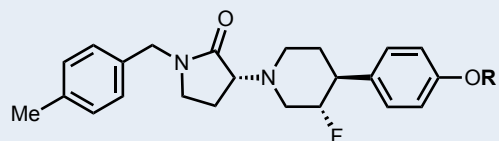
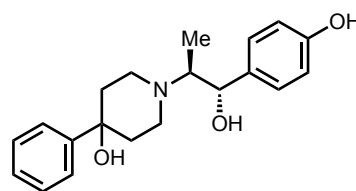


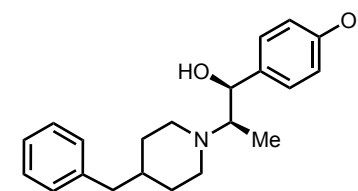
Bristol-Myers Squibb



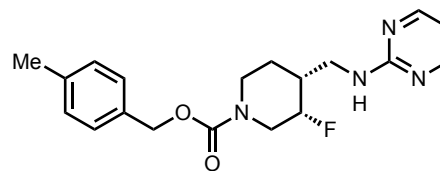
R = H **BMS-986163**
 R = P(O)(OH)₂ **BMS-986169**



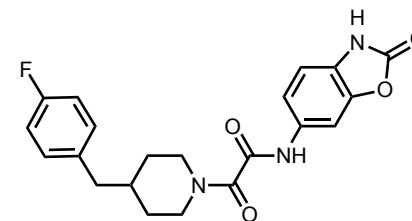
Traxoprodil



CERC-301/MK-0657

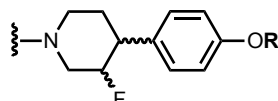


Ifenprodil

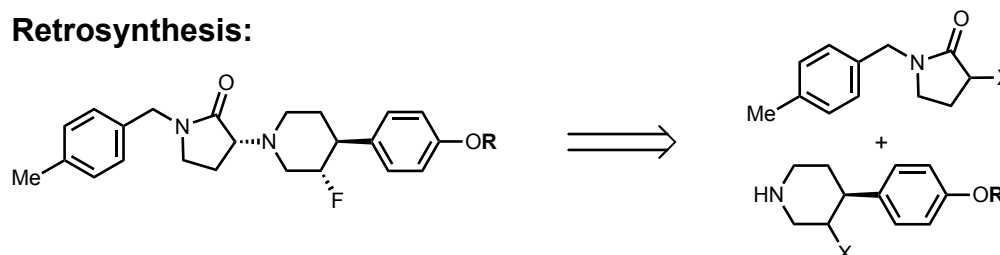


Radiprodil

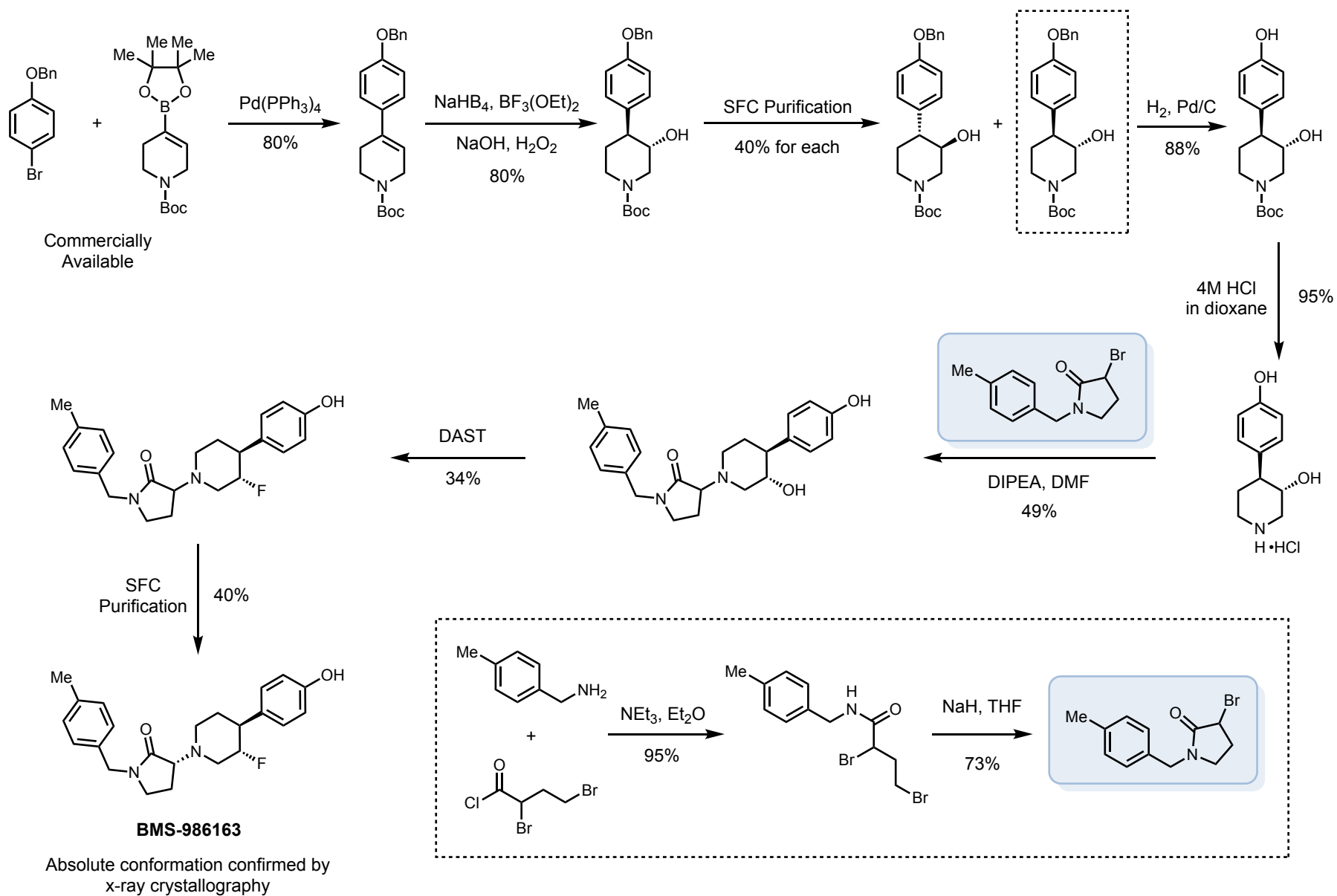
- Investigated to treat major depressive disorder (MDD)
- Condition affects over 350 million people worldwide
- 20-30% of MDD patients may be diagnosed with treatment-resistant depression
- BMS-986163 were determined to be a negative allosteric modulator (NAM) for glutamate N2B NMDA receptors. A number of NAMs have been developed (right) that are characterized by two aromatic rings connected by a tether containing a basic nitrogen
- Prodrug BMS-986169 is water-soluble
- All possible stereoisomers derived from the piperidine substituents have been tested

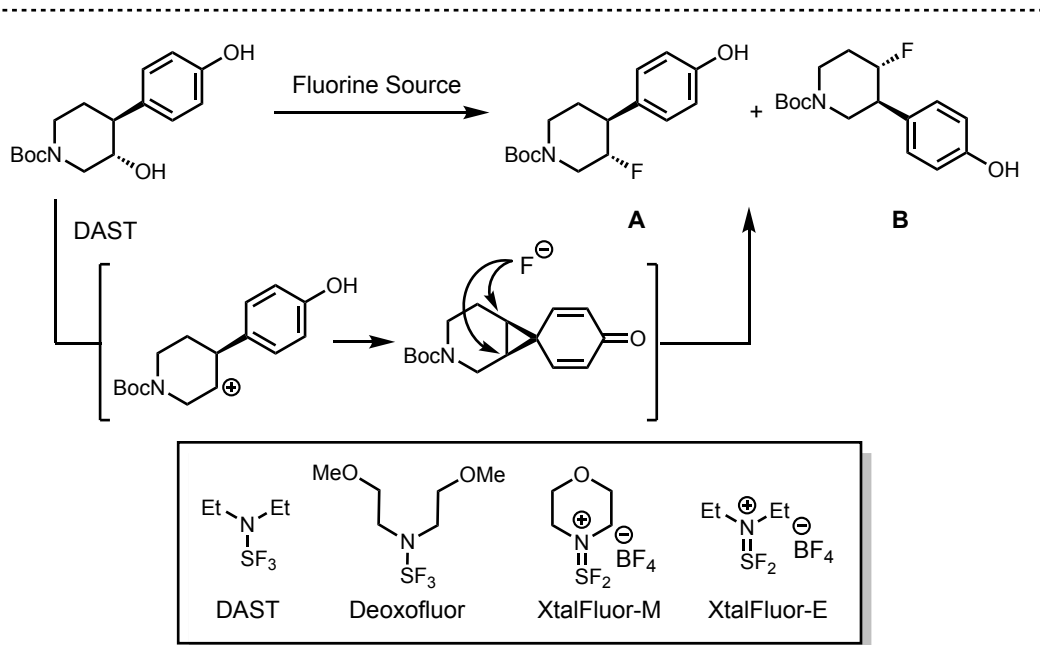
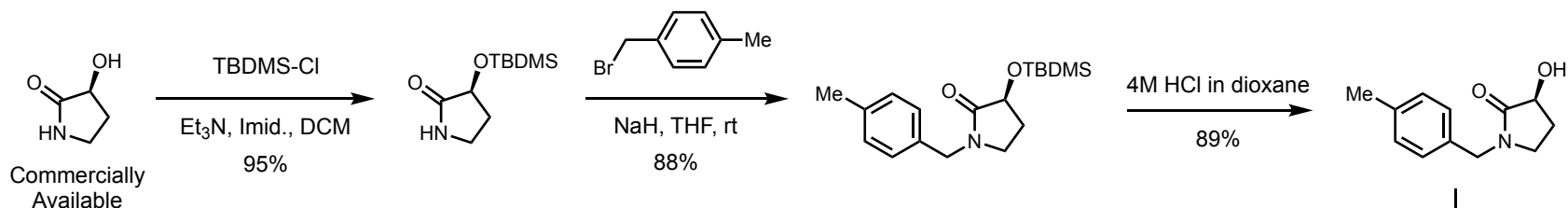


Retrosynthesis:

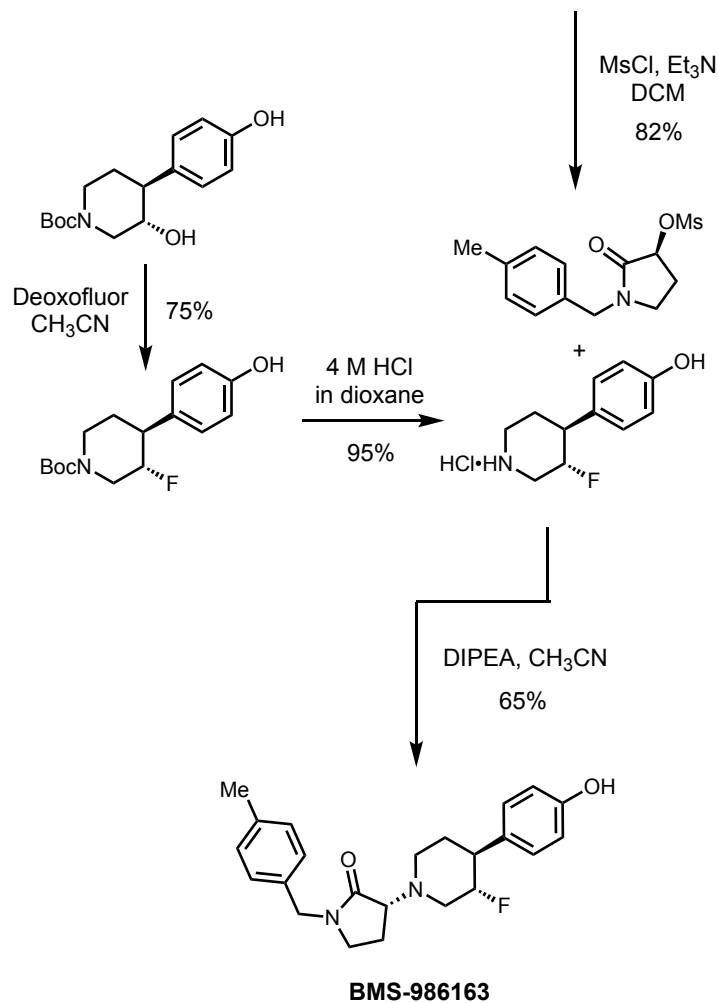


First Generation Synthesis:

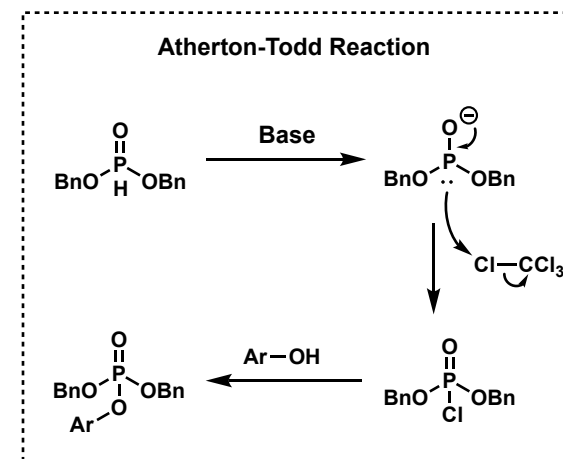
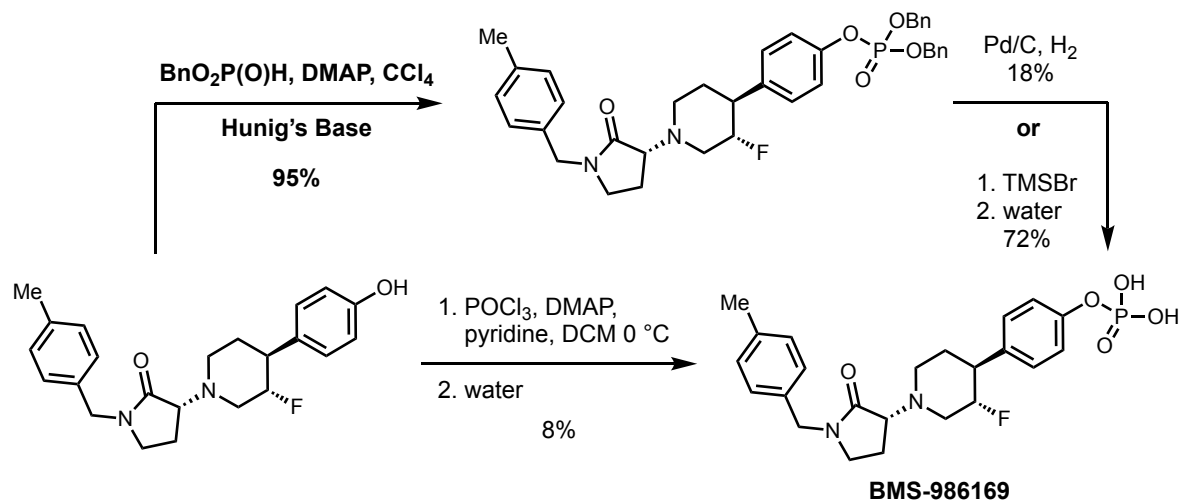




Entry	F ⁻ Source	equiv.	temp. (°C)	A:B	Isolated Yield of A (%)
1	DAST	1.0	0	2:1	34
2	DAST	3.0	0	2.6:1	40
3	DAST	3.0	-78 to 0	13:1	50
4	XtalFluor-M	1.5	-78 to rt	1:2	33
5	XtalFluor-E	3.0	-78 to rt	1.4:1	26
6	Deoxo-Fluor	1.5	0	30:1	75



Original Attempt to Prodrug:



Optimized Synthesis of Prodrug:

