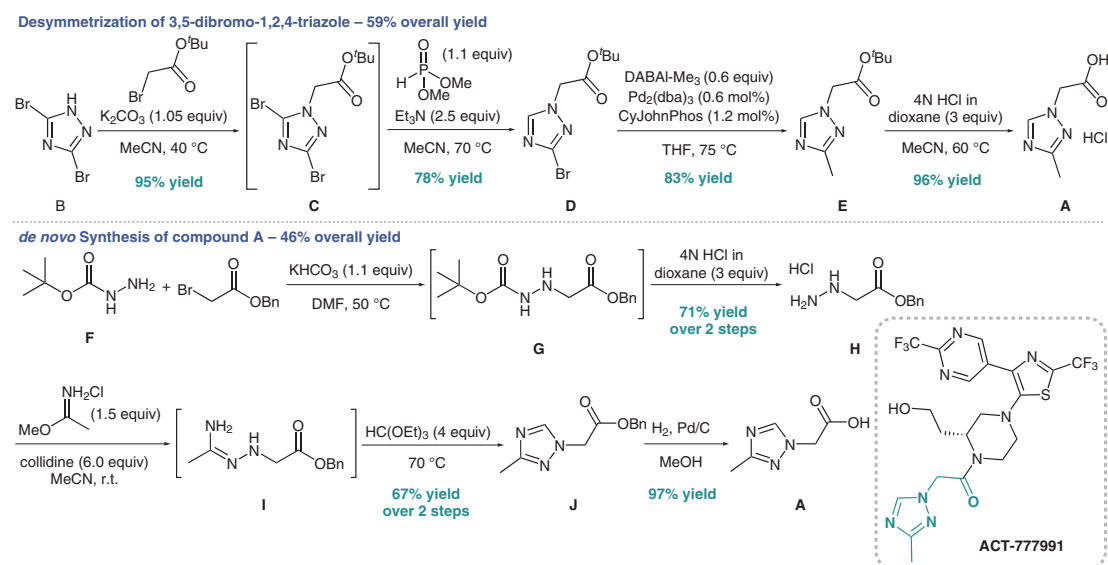


Conquering Regioselectivity Issues: Scalable Synthesis to an Alkylated 1,2,4-Triazole Building Block



Significance: ACT-777991 is a CXCR3 antagonist currently investigated in Phase 1 clinical trials for the treatment of type 1 diabetes which affects about 9 million people worldwide. Davenport et al. developed two scalable synthetic routes to 1,2,4-triazole fragment **A** of ACT-777991 whose initial synthesis via direct triazole alkylation suffered from poor regioselectivity control, thus providing **A** only in about 16% overall yield (not shown).

Comment: The first synthetic route to **A** involved alkylation of symmetrical 3,5-dibromo-1,2,4-triazole (**B**) with *tert*-butyl-2-bromoacetate to yield intermediate **C** which was telescoped into the reduction step to selectively form intermediate **D**. Methylation of **D** was accomplished via a palladium-catalyzed cross-coupling reaction with 1,4-diazabicyclo[2.2.2]octan-bis(trimethylaluminum) (DABAI-Me₃) as the methylating agent. Notably, save removal of DABAI-Me₃ from the end of reaction mixture containing **E** required a reverse quenching procedure into aqueous acidic acid to control methane off-gassing. After isolation of **E**, hydrolysis of the benzyl ester provided **A** as an HCl salt in 59% overall yield. To circumvent the use of DABAI-Me₃, a second synthesis was developed which proceeded via hydrazine HCl salt **H**. Slow addition of **H** to methylacetimidate formed condensation product **I** in high conversion, and a subsequent reaction with triethylorthoformate yielded benzyl ester **J** in 67% yield over two steps. The *de novo* synthesis provided **A** in 46% overall yield and was shown to be in the most cost-effective.