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]octane-bis(trimethylaluminum) (DABAl-Me3) as the methylating agent. Notably, save removal of DABAl-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 DABAl-Me3, a second synthesis was developed which proceeded via hydrazine HCl salt H. Slow addition of H to methylacetimide 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.