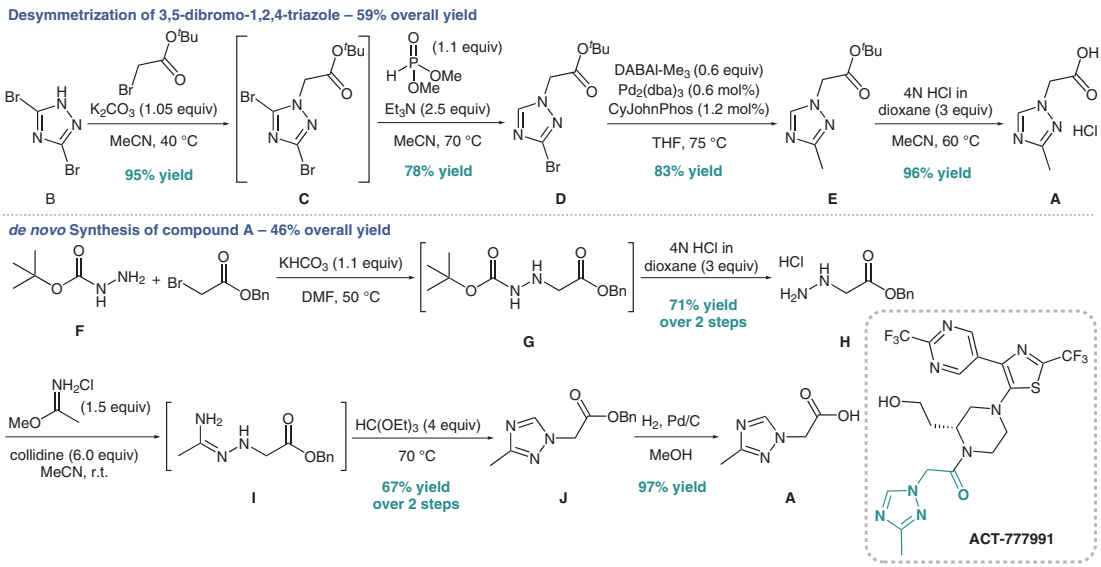
R. DAVENPORT*, A. PRUD'HOMME, F. MASSE, G. SCHÄFER (IDORSIA PHARMACEUTICALS LTD., ALLSCHWIL, SWITZERLAND)

Development of a Scalable Route toward an Alkylated 1,2,4-Triazol, a Key Starting Material for CXCR3 Antagonist ACT-777991
Org. Process Res. Dev. **2023**, *27*, 928–937, DOI: 10.1021/acs.oprd.3c00051.

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) (DABAl-Me_3) as the methylating agent. Notably, save removal of DABAl-Me_3 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-Me_3, 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.

SYNFACTS Contributors: Antonia F. Stepan (Roche), Nadine Kuhl (MSD)
Synfacts 2023, 19(07), 0719 Published online: 16.06.2023
DOI: 10.1055/s-0042-1752712; **Reg-No.:** A02923SF

Category
Innovative Drug Discovery and Development

Key words
CXCR3 inhibitors
1,2,4-triazoles
DABAl-Me_3
process safety

Synfact of the Month