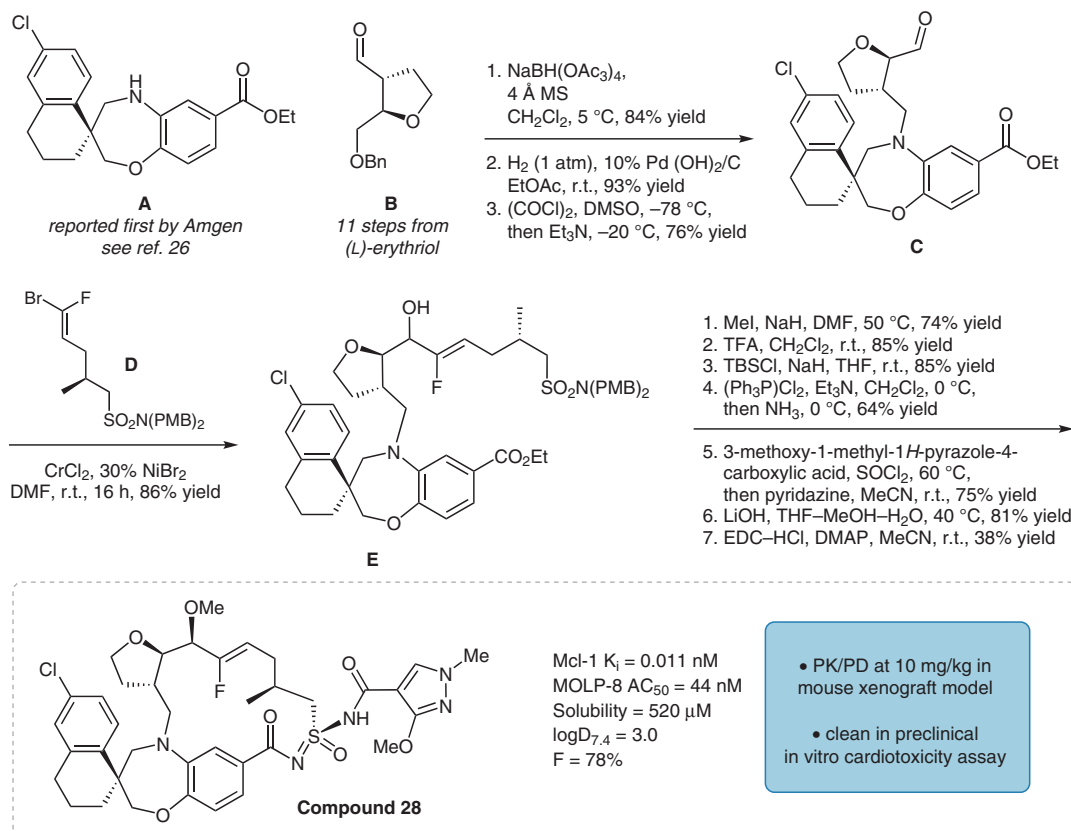


# Toward Improved On-Target Safety: Discovery of Potent, Short Half-Life Macrocyclic Inhibitors of Mcl-1



**Significance:** Overexpression of the pro-survival and anti-apoptotic protein myeloid cell leukemia 1 (Mcl-1) is a hallmark of many human cancers. As Mcl-1 is also expressed in cardiomyocytes, there exists the potential for on-target cardiotoxicity. Jerhaoui and co-workers report the design of Mcl-1 inhibitor **28** that addresses the concern of on-target cardiotoxicity via a C<sub>max</sub>-driven approach, achieving maximal concentration (C<sub>max</sub>) quickly and pairing that with a short half-life to avoid prolonged systemic exposure. Excellent potency and oral bioavailability were achieved, and in vivo efficacy was observed in a mouse xenograft model. Also, the potential for off-target cardiotoxicity was de-risked through in vitro profiling in stem-cell-derived cardiomyocytes.

**Comment:** Compound **28** is constructed through key intermediate **A** (reported by Amgen for the synthesis of AMG176, ref. 26 of original article), tetrahydrofuran aldehyde **B** and (*E*)-bromo fluoroalkene **D**. Reductive amination between core **A** and aldehyde **B** followed by debenylation and oxidation afforded intermediate **C**. A nickel/chromium-mediated Nozaki–Hiyama–Kishi (NHK) coupling of aldehyde **C** with alkene **D** afforded intermediate **E** which was poised to undergo macrocyclization followed by sulfonimidamide formation to afford compound **28**.