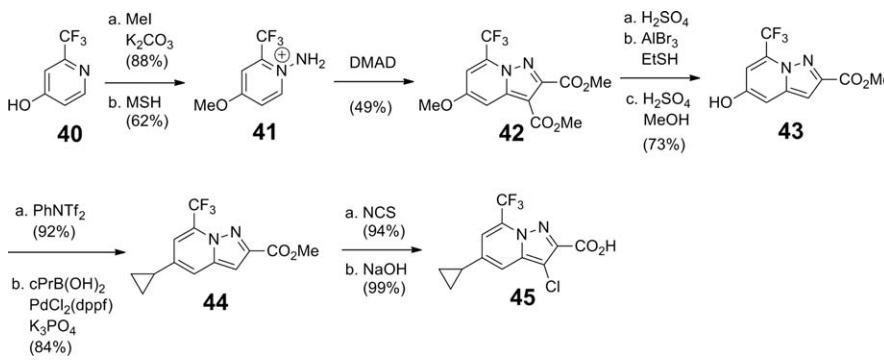
against the wild-type replicons was similar for all of the analogs but was significantly diminished *versus* the H94N variant. With respect to replicon potency, the pyrazolopyridine **37** and benzofuran **39** cores appeared superior to the benzimidazole **38** scaffold, especially against the H94N mutant replicon. The benzofuran derivatives appeared slightly more potent than the corresponding pyrazolopyridine analogs, but this core was also associated with a greater increase in lipophilicity (cLog*P*). For this reason, we opted to explore the pyrazolopyridine series further.

The development of the SARs within the pyrazolopyridine series required access to large quantities of the intermediate acid **45**. The 10-step synthetic route relied on the *de novo* construction of the pyrazolopyridine core from the commercially available pyridine **40** (Scheme 5.1).[37] Unfortunately, the critical step involving *N*-amination of the pyridine was problematic owing to the low reactivity of the nitrogen, a consequence of the electron-withdrawing CF_3 substituent. Traditional reagents for this transformation, such as hydroxylamine-*O*-sulfonic acid (HOSA), failed to deliver the desired product and a more reactive reagent was required. Treating **40** with *O*-(mesitylenesulfonyl)hydroxylamine (MSH) afforded **41**,[39,40] which subsequently underwent a 1,3-dipolar cycloaddition reaction with dimethylacetylene dicarboxylate (DMAD) to give the pyrazolopyridine core **42** in 30% yield.[41,42] Heating the diester **42** in the presence of H_2SO_4 led to hydrolysis followed by selective decarboxylation at C3 of the pyrazolopyridine.[43] The resulting intermediate was then converted to the requisite acid **45** in six additional steps.[37]

The initial route provided gram quantities of acid **45**, which was sufficient for developing SARs within the pyrazolopyridine series. However, the progression of lead molecules into *in vivo* animal studies demanded greater compound quantities and necessitated a more efficient synthesis. The low yield for the formation of the pyrazolopyridine ring system and the required use of MSH, a thermally unstable reagent, were major limitations to the existing route. The simplest solution to both issues was to avoid the *N*-amination reaction and begin with the pyrazolopyridine ring system already intact. Unfortunately, no 7-(trifluoromethyl)pyrazolopyridine analogs were available from commercial



Scheme 5.1 First-generation route to the pyrazolopyridine core acid **45**.