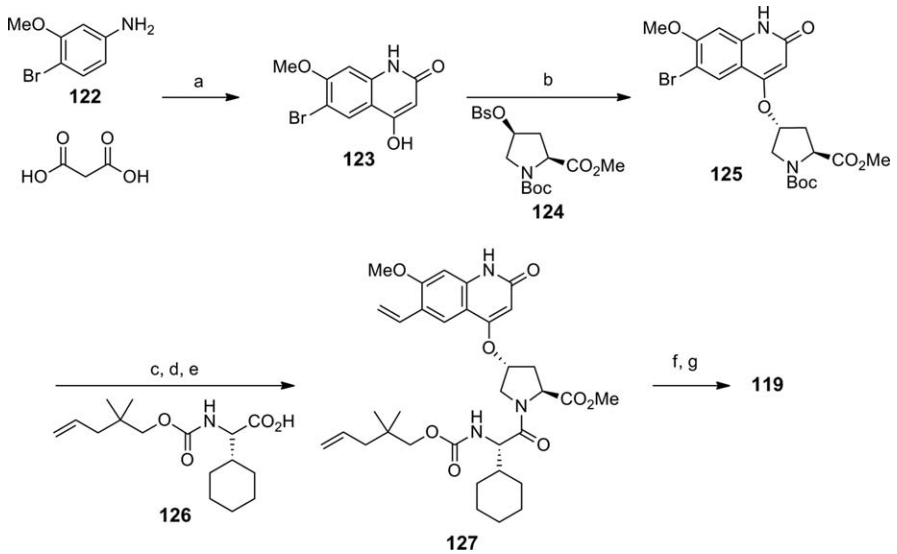

Scheme 7.7 Conditions: (a) 1 equiv. $POCl_3$, 105 °C, 1 h, neat, 74%; (b) **124**,[87] NMP, Cs_2CO_3, 50%; (c) HCl–dioxane; (d) HATU, DMF, DIEA, 80%, two steps; (e) EtOH, Et_3N, 5% Pd(dppf)Cl_2, (CH_2=CH_2BF_3)K, reflux, 94%; (f) 10% Zhan 1b,[88] DCE, 45°C, 93%; (g) 5% Pd/C, H_2, EtOH, 90%.

available through the use of Meerwein-type reagents in the absence of base, which led to nearly exclusive *O*-alkylation.[112] More functionalized ethers were selectively accessed through the Mitsunobu reaction[113] or alkylation of alkyl halides in the presence of silver salts.[114]

As Table 7.21 illustrates, a variety of 2-alkoxyquinolines showed excellent genotype 3a potency. Methoxy- and ethoxyquinolines (**136**, **137**) were particularly potent and generally exhibited excellent cellular potency and rat liver exposure. Increasing the size or complexity of the alkyl group did not generally lead to any further improvement (**138**). However, methylthiazole analog **139** does have slightly improved gt3a potency (3 nM) and also offers an improved gt1 replicon activity with 50% NHS compared with ethyl analog **137**, and also improved rat liver exposure compared with methyl analog **136**.

In an effort to explore further the space occupied by the alkoxy groups,[105] an effort was made to tie back the substituent into another ring, thus forming a tricyclic P2 group. The versatility of the triflate intermediate **128** was again exploited through simple conversion to imidazo tricycle **140** (Scheme 7.8).[105]

P2 tricyclic analog **140** (Table 7.22) possesses excellent gt3a potency (1.8 nM); unfortunately, it has relatively poor gt1 replicon potency and rat liver exposure. Removal of the C7-methoxy group (**141**) reduces the gt3a potency slightly (5.2 nM) and this compound also suffers from poor replicon potency