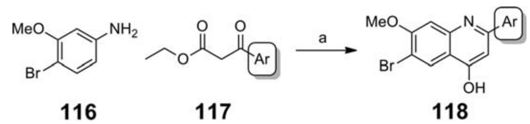
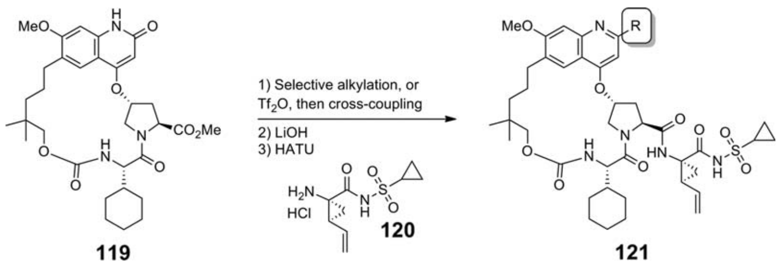


Scheme 7.5 Conditions: (a) polyphosphoric acid, heat.



Scheme 7.6

route, was developed. In this vein, **119** could serve as a common intermediate to introduce a variety of groups in the 2-position (Scheme 7.6). These intermediates could then be transformed into the desired compounds in two straightforward steps.

In practice, a regioselective hydroxyquinolone formation utilizing bromomethoxyaniline **122** and malonic acid[107] was followed by chemoselective alkylation[108] at the 4-position with brosylate **124**[87] (Scheme 7.7). Removal of the Boc group, HATU coupling with **126**[109] and vinylation with Molander's vinyl trifluoroborate reagent[110] led to intermediate **127**. RCM using the Zhan 1B catalyst[88] then produced the desired macrocycle in good yield. Hydrogenation of the styrene double bond yielded key intermediate **119** in seven steps with an overall yield of 23%.

In order to access various aryl and heteroaryl groups, **119** was first converted to the corresponding quinoline-2-triflate (**128**) and then Suzuki reactions[111] were carried out with selected boronic acids (Table 7.20). These intermediates were readily converted into the desired target compounds **129**–**134** using standard conditions. As is readily apparent from Table 7.20, substitution at the *ortho*-, *meta*- and *para*-positions (**129**–**133**) led to either no improvement or a reduction in gt3a potency, although similar rat liver concentrations and replicon potency was generally maintained. Changing the simple aryl ring to a pyridine (**134**) did not lead to improved gt3a potency either and also resulted in the loss of rat liver exposure.

Neither phenols nor simple alcohols participated in triflate-displacement reactions or palladium-catalyzed cross-couplings, hence quinolone **119** was utilized in a series of oxygen-selective alkylations to access a range of 2-alkoxyquinolines. Simple alkyl ethers such as methyl and ethyl were readily