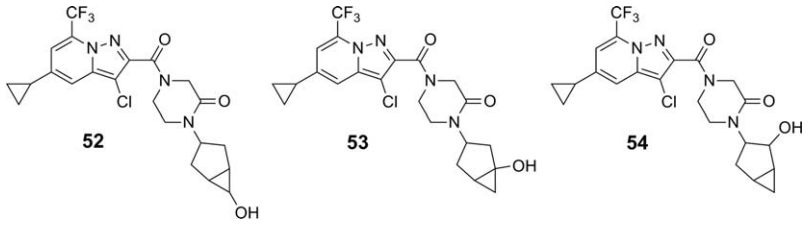
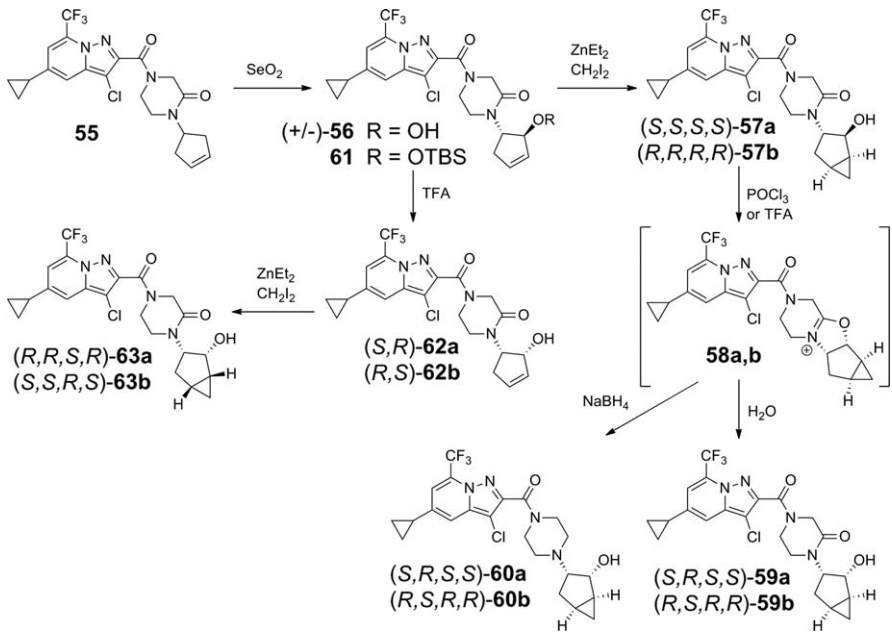



**Figure 5.13** A series of envisioned hydroxylated [3.1.0]bicyclohexane derivatives (**52**–**54**) aimed at reducing metabolic clearance and lipophilicity.




**Scheme 5.3** Syntheses of a series of [3.1.0]bicyclohexan-2-ol derivatives.

centers and structural similarity with the 4-cyclohexanol derivatives known to bind NS4B (*e.g.* **31** and **37**–**39a**). Unfortunately, the desired amine intermediate appeared unstable under acidic conditions and further efforts were abandoned. There were stability concerns and a lack of literature precedent related to analog **53**, so attention shifted to the 2-hydroxybicyclohexane derivative **54**.

The synthesis of **54** began with allylic oxidation of the pendant cyclopentene ring of **55**, which occurred opposite the bulky piperazinone substituent, thereby affording **56** as a racemic mixture (Scheme 5.3).[52] The resulting hydroxyl group directed the cyclopropanation to the *syn* face of the olefin to give (±)-**57**,[53,54] which upon resolution by chiral supercritical fluid chromatography (SFC) yielded enantiomers (+)-**57a** and (–)-**57b**.[37] In the course of exploring the SARs within the bicyclohexan-2-ol series, we found that treatment of **57b** with $POCl_3$