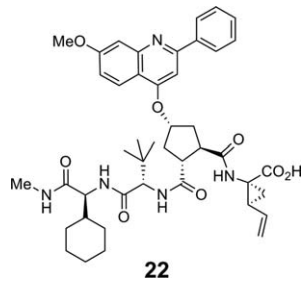
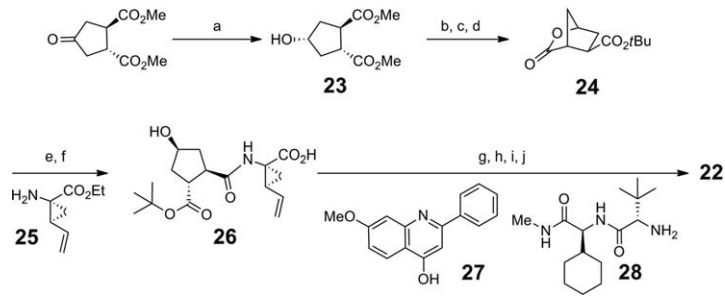


Figure 7.8 Cyclopentyl core-containing compound **22**.



Scheme 7.1 Conditions: (a) $NaBH_4$, MeOH, 0 °C, 76%; (b) NaOH, MeOH; (c) Ac_2O, pyridine, 88%, two steps; (d) Boc_2O, DMAP, DCM, 52%; (e) LiOH, dioxane–water, 0 °C; (f) **25**, HATU, DIEA, DMF, 89%, two steps; (g) **27**, PPh_3, DIAD, THF, 68%; (h) TFA, Et_3SiH, DCM; (i) **28**, HATU, DIEA, DMF, 74%, two steps; (j) LiOH, THF, MeOH, water, 67%.

Mitsunobu reaction with quinolinol **27**,[52,58] deprotection, amide coupling to chiral amine **28** and hydrolysis. Overall, the original sequence is 10 linear steps and provided **22** in 10% overall yield.

A structure–activity relationship (SAR) study was then undertaken within this series of compounds (Table 7.1). Initially, simplified analogs **29**–**31** established the stereochemical requirements for active inhibitors as *S*; inhibitors **30** and **31**, containing (*R*)-amino acids at either stereocenter in the P3/P4 region, were significantly less potent. Replacement of the methyl ester with a methylamide also had little effect (**32**). As can been seen in Table 7.1, incorporation of more highly optimized[59,60] P1 groups (**33**, **34**) leads to a large increase in potency, as was previously seen with proline-based HCV NS3/4a protease inhibitors.[59] The importance of the H-bond donors in P3/P4 is also readily seen in **35**, where methylation of the cyclohexyl glycine amine amide results in complete loss of potency. In contrast, methylation of the terminal amide has no significant effect (compare **33** with **34**). Inhibitors with truncated P3/P4 chains have also been demonstrated to have reduced potency.[55]