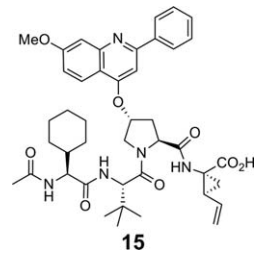
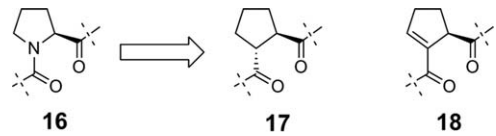


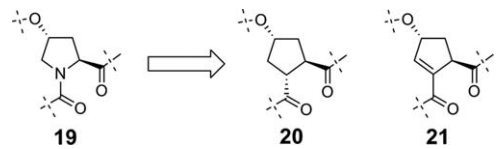
15

Figure 7.5 Example of a potential initial lead for the Medivir/Tibotec NS3 program.



16 **17** **18**

Figure 7.6 Proline replacement strategy in the thrombin program.



19 **20** **21**

Figure 7.7 Medivir/Tibotec's hydroxyproline replacement strategy in the HCV NS3 program.

In the case of HCV NS3/4a protease, the more highly substituted (4*R*)-hydroxyproline could potentially be replaced by the corresponding hydroxy-substituted cyclopentanes or cyclopentenes, **20** and **21** (Figure 7.7).

As an initial proof-of-concept using the linear inhibitor **15** as a starting point, **22** (Figure 7.8) was prepared and demonstrated promising activity of 22 nM in the enzymatic inhibitions assay against gt1a NS3.[55] This is especially interesting, because in order to avoid a ketone linker, the P3/P4 side chain is changed to a reverse amide and thus the location of the sterically bulky *tert*-butyl and cyclohexane groups, and also the H-bond donor, are shifted by one position relative to the starting core ring structure. Additionally, the hybridization of the connecting atom is changed from proline's sp^2-nitrogen to an sp^3-carbon.

The synthesis of **22** is shown in Scheme 7.1 and begins with the known chiral building-block (–)-*trans*-(3*R*,4*R*)-bis(methoxycarbonyl)cyclopentanone.[56] Reduction of the ketone to give **23**, followed by cyclization and protection of the resultant carboxylic acid as the *tert*-butyl ester, led to bicyclic lactone **24**. Mild opening of the lactam followed by amide coupling to the known vinylcyclopropylamine **25**[57] gave intermediate **26**. Conversion to desired product **22** was accomplished by inverting the hydroxyl chiral center using a