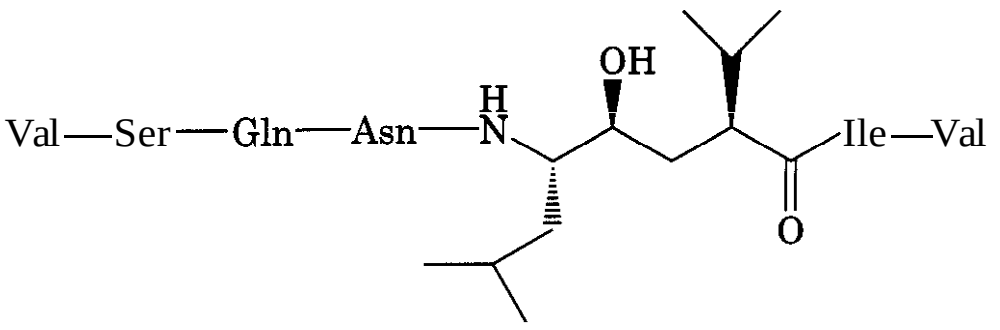


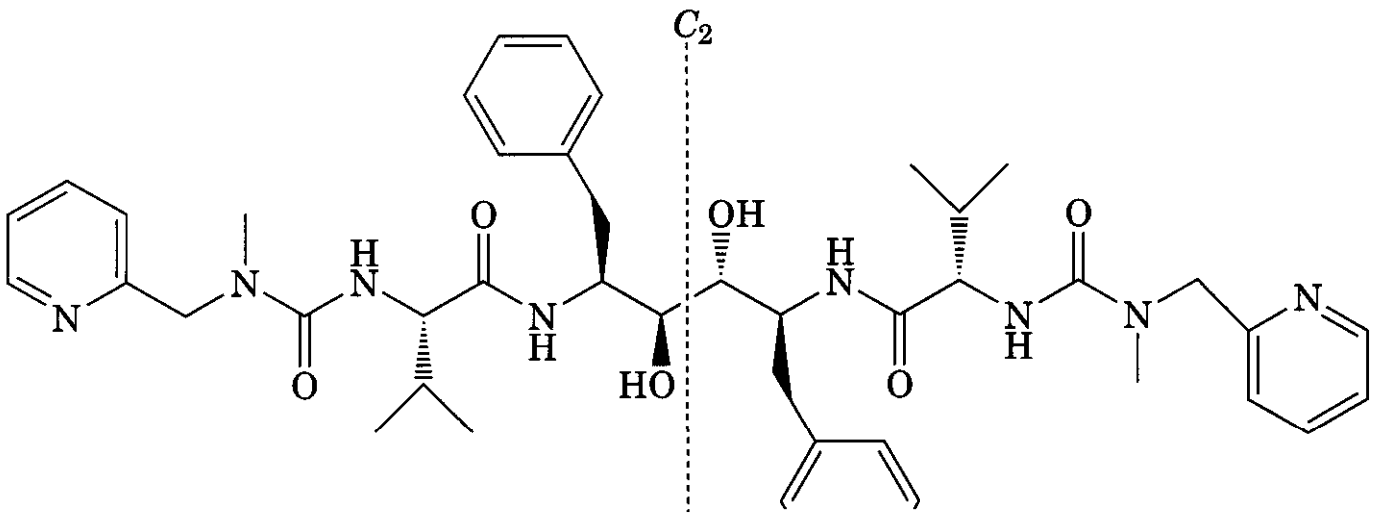
(32)

inhibitor was the modified octapeptide (32, U-85548) developed at Upjohn (96).

This subnanomolar inhibitor was used to define the extensive hydrophobic and hydrogen bonding interactions available in the HIV-P active site (97). A common feature in the binding of (31)and (32) to HIV-P is the interaction of the central hydroxyl group of the inhibitors with the carboxylates of both Asp25 and Asp25′. This hydroxyl group replaces a water molecule that likely binds between these aspartyl side chains during peptide hydrolysis by HIV-P. The inhibitors can therefore be seen as mimics of a "collected substrate." The liberation of this water to bulk solvent probably contributes about 5 kcal mol^{-1} to the free energy of inhibitor binding, based on the studies by Rich and his colleagues on similar inhibitors of pepsin (98, 99). An interesting difference between (31)and (32) is that (31) has R stereochemistry at the hydroxymethyl center, whereas in (32) this is an S center. Part of the reason for this is that when (31) binds to HIV-P, the decahydroquinoline ring system induces a conformational change in the protein, affecting primarily site S,'. The optimal stereochemistry at the hydroxymethyl center appears to be whichever one will allow the interaction of the hydroxyl with both catalytic aspartates while accommodating the placement of inhibitor moieties in the S„ S„ S,', and S,' sites with minimal conformational strain on the inhibitor (9).

Both (31)(Fig. 10.9b) and (32) (Fig. 10.11) bind to the HIV-P active site asymmetrically. However, after the X-ray studies of crystalline HIV-P apoenzyme revealed it to be a symmetrical dimer, C2 symmetric inhibitors were designed to take advantage of this structural feature (Fig. 10.12). Both alcohol diarnines and diol diamines were examined. For example, the C2 symmetric compound (33) (A-77003) was synthesized at Abbott and entered clinical trials as an antiviral agent for intravenous treatment of AIDS (100).

The X-ray structures of complexes between HIV-P and diol diamine derivatives like (33) showed (101) that, although one of the hydroxyl groups bound between the catalytic aspartyl carboxylates and made contacts with both, the second hydroxyl made only one such



(33) A-77003