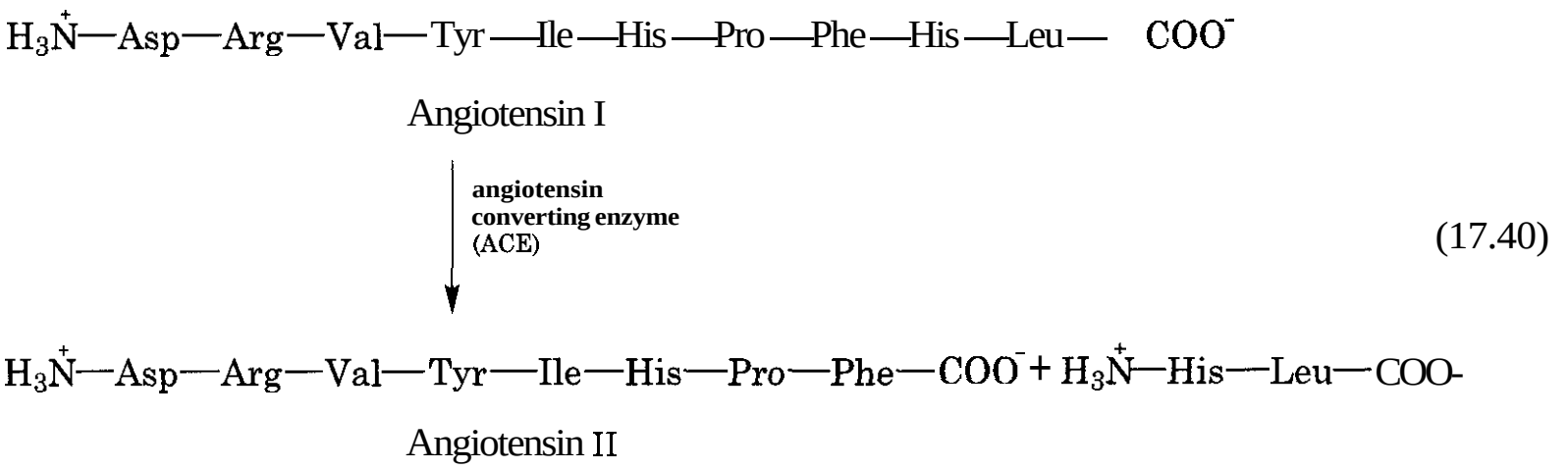

(17.40)

ray structures of HMG-CoA reductase complexed with both substrates and products were obtained (114, 115). These structures showed that, if the statins bound so the HMG-like groups bound the HMG-binding pocket of the active site, the bulky hydrophobic groups of the statins would clash with the residues lining the narrow pocket into which part of the coenzyme A bound (115). However, recently, Istvan and Deisenhofer have obtained X-ray structures of HMG-CoA reductase bound to six individual statins, including (**9**), (**31**), (**34**), and (35) (116). This study showed the substrate-binding pocket rearranges to accommodate the statins, that the statins do bind to the *HMG-binding* region, that a shallow hydrophobic groove now accommodates the hydrophobic groups, and that none of the NADP(H)-binding pocket is occupied (116). In *toto*, the structural studies supported all interpretations made some 15 years earlier based on kinetic studies, and provided definitive evidence for a hydrophobic anchor enhancing the binding of the mevalonate portion of the statins.

The evolution of the angiotensin converting enzyme (ACE) inhibitors is an illuminating story in the development of enzyme inhibitors as therapeutic agents. As shown in Equation 17.40, ACE catalyzes the conversion of angiotensin I to angiotensin II.

Angiotensin II, itself a potent hypertensive agent, also stimulates the release of a second hypertensive agent, aldosterone. In addition, ACE catalyzes the cleavage of the nonapeptide vasodilating agent, bradykinin (not shown). Therefore an ACE inhibitor was seen to have the potential to limit three hypertensive actions. This premise was validated by in *vivo* results with teprotide, a peptide inhibitor of ACE, which had been isolated from a South American pit viper (117).

At that time the structure of ACE was unknown, although it had been identified as a zinc metalloprotease. It was surmised that its mechanism and active site may resemble that of another metalloprotease, carboxypeptidase A, whose X-ray structure was known. (*R*)-2-Benzylsuccinic acid (36) (Fig. 17.21) had been identified as a potent inhibitor of carboxypeptidase A, and it was suggested that (36) resembled the collected products of the hydrolysis reaction (Fig. 17.21). In other words, (36) was a biproduct analog and, not unexpectedly, it was found to bind with an affinity resembling the combined affinities of the two products (118). Carboxypeptidase A appeared to have three main interactions with (36). Two substrate-binding sites bound the phenyl group and one carboxylate, and the Zn^{2+} ion, usually coordinated to the carbonyl of the amide bond being cleaved, was now bound to the second carboxylate. Combining those suggestions with studies with viper venom peptides, indicating that a C-terminal proline was effective in inhibiting ACE, a number of carboxyalkanoylproline derivatives were tested as ACE inhibitors (119). Of these, the succinyl-L-proline derivative (37) was found to be the most effective, with an IC_{50} value of **330** μM. Given that one carboxylate bound to the Zn^{2+} ion, a better zinc ligand, a thiol group, was substituted for this carboxylate, resulting in (38) with the IC_{50} value now reduced to 0.2 μM. Finally, after taking into account the differences between the active sites of ACE and carboxypeptidase A, captopril (**39**) was prepared. Captopril was found to be a competitive inhibitor of ACE, with a K_i value of 1.7 nM, and was