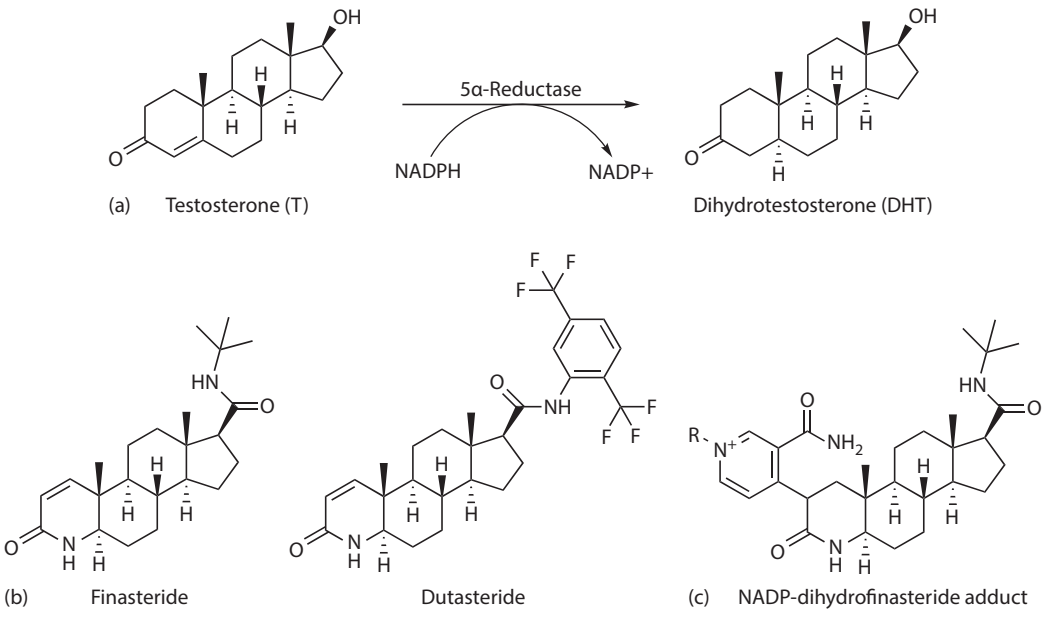

FIGURE 11.4 (a) 5α-Reductase catalyzed conversion of testosterone (T) to dihydrotestosterone (DHT); (b) chemical structures for finasteride and dutasteride; and (c) the proposed structure of the NADP-dihydrofinasteride adduct. R = phosphoadenosine diphosphoribose.

buildup of potentially toxic precursors occurs upon inhibition. In 1976, Japanese microbiologist Akira Endo isolated a series of compounds from *Penicillium citrinum*, including ML236B (compactin), with powerful inhibitory effect on HMG-CoA reductase. Since then, several HMG-CoA reductase inhibitors have become marketed drugs for lowering cholesterol levels (Figure 11.5).

These HMG-CoA reductase inhibitors, commonly referred to as statins, have accounted for the majority of prescriptions for cholesterol-lowering drugs worldwide. All the statins in clinical use are analogs of the substrate HMG-CoA with an HMG-like moiety which may be present in an inactive lactone form in the prodrugs (Figure 11.5). Statins are classified into two groups according to their molecular structures. Type I statins, including lovastatin and simvastatin, are lactone prodrugs originally isolated from fungi. They are enzymatically hydrolyzed in vivo to produce the active drug. Type II statins are all synthetic products with larger groups attached to the HMG-like moiety. All the statins are competitive with respect to HMG-CoA and noncompetitive with respect to NADPH, a cosubstrate of the reaction. Crystal structures of HMG-CoA reductase complexed with six different statins showed that the statins occupy the HMG-binding region, but do not extend into the NADPH site. The orientation and bonding interactions of the HMG-like moiety of the statins resemble those of the substrate complex. However, from a combination of crystal structures, binding thermodynamics, and SAR studies it is clear that the 5′-hydroxyl group of the acidic side chain acts as a mimetic of the tetrahedral intermediate of the reduction reaction. The multiple hydrogen bonds between the C5–OH of the statins and the HMG-CoA reductase active site contribute significantly to the tight binding of the statin inhibitors. Strictly speaking, the HMG-CoA reductase inhibitors are not products of rational design; rather they were identified through natural product screening and analoguing of the natural product hits. Nevertheless, it is quite clear that all statins share a common strategy for inhibiting their target: tetrahedral intermediate state mimicry.

11.4.2.2 Inhibitors of Purine Nucleoside Phosphorylase

Purine nucleoside phosphorylase (PNP) catalyzes the phosphorolysis of 6-oxypurine nucleosides and deoxynucleosides. In humans, the PNP pathway is the only route for deoxyguanosine degradation,