HBV DNA polymerase and consequently causes DNA chain termination after incorporation into viral DNA.[23] The clinical use of adefovir is limited by its poor intestinal permeability, presumably due to its charged phosphonate group ($F = 7.8–11\%$ in rat, 4% in monkey).[24] To circumvent this problem, a bis(pivaloyloxymethyl) ester prodrug [bis(POM)], adefovir dipivoxil (**11**, Figure 12.7), was developed.[25,26] Adefovir dipivoxil demonstrated improved antiviral activity relative to adefovir in cell culture and an improved oral bioavailability ($F = 42\%$ in rat, 27% in cynomolgus monkey).[26] Adefovir dipivoxil was successful in reducing HBV DNA and alanine aminotransaminase (ALT) levels in HBV-infected patients at doses of 10 and 30 mg, where 21% of patients at the 10 mg dose and 39% of patients at the 30 mg dose achieved undetectable serum HBV DNA levels. Unfortunately, adefovir dipivoxil was shown to be associated with dose-limiting renal toxicity even at the suboptimal 10 mg dose and was licensed as Hepsera for human use only at the lower dose.[23] In addition, the generation of pivalic acid from decomposition of the pivaloyloxyalkyl ester promoiety has the potential to decrease serum carnitine levels, which is a concern.

In an effort to overcome the toxicity associated with adefovir dipivoxil, a prodrug strategy that attempted to deliver adefovir directly to the target organ, the liver, was developed.[27] The liver targeted prodrug technology, HepDirect, employed a cyclic 1-aryl-1,3-propanyl ester of the phosphonate moiety (Figure 12.6).[28] This prodrug is sensitive to cytochrome P450 (CYP450)-mediated oxidative cleavage. Since CYP450 enzymes are predominantly expressed in the liver, HepDirect technology offered liver targeting potential. By targeting the liver, it was hypothesized that reduced circulating levels of adefovir would result in a lower risk of renal toxicity. Application of HepDirect technology to adefovir led to the identification of the clinical candidate pradefovir (**12**, Figure 12.8).[27,29] Cleavage of pradefovir was shown to occur *via*

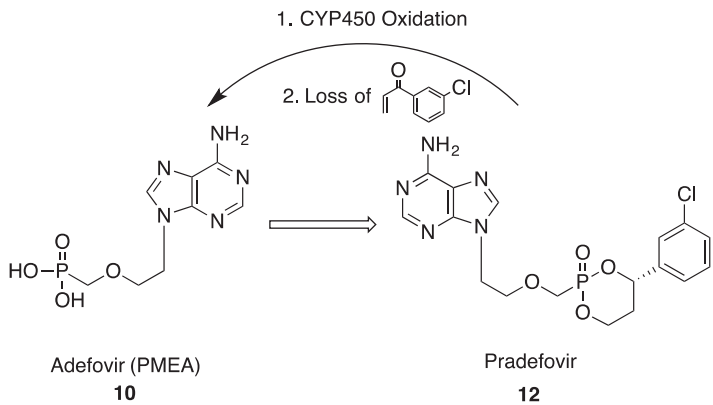

Figure 12.8 Pradefovir (**12**) is a prodrug of adefovir (**10**) using the HepDirect prodrug strategy to enable liver targeting for the treatment of HBV infection.