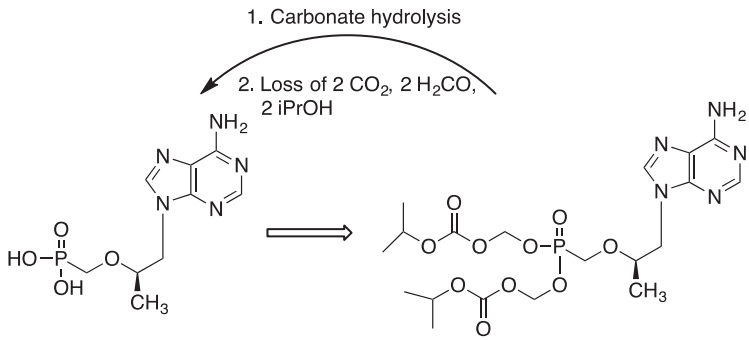
a CYP3A4-mediated oxidation followed by a β-elimination to produce adefovir and an aryl vinyl ketone. Removal of the aryl vinyl ketone is believed to occur by glutathione trapping *in vivo*. Relative to adefovir, pradefovir showed approximately a ninefold increase in adefovir-diphosphate levels in rat hepatocytes *in vitro* and, when given orally to mice and rats, pradefovir demonstrated a 4.5- and 7.5-fold greater exposure of adefovir mono- and diphosphate in the liver relative to kidney and intestine with an oral absorption of 29% and 65% in the rat and monkey, respectively.[30,31] In human clinical studies, pradefovir was rapidly absorbed and converted to adefovir and demonstrated efficacy in reducing serum HBV DNA levels at doses of 10, 20 and 30 mg.[31] Although pradefovir metabolism releases a molecule of aryl vinyl ketone, a nucleophile acceptor, no toxicity concerns were reported in preclinical studies; however, reports of increased cancer risk at high doses in rat and mouse long-term toxicity studies have raised concerns about this drug.[32] Irrespective of these concerns, pradefovir is still in clinical development for the treatment of HBV infection.

Another acyclic nucleotide phosphonate, tenofovir ([9-*R*-(2-phosphonomethoxypropyl)adenine] (PMPA) (**13**, Figure 12.9), was shown to be a potent inhibitor of HIV-1 by inhibiting the viral polymerase.[33] However, despite confirmed limited efficacy both in animal models of HIV-1 and in human clinical trials, PMPA was hampered by poor oral bioavailability ($F<2\%$ in mice), presumably because of the presence of a charged phosphonate moiety.[33,34] To overcome this problem, a prodrug effort was initiated which led to the development of bis(isopropyloxymethylcarbonyl)PMPA (tenofovir disoproxil fumarate, TDF (**14**, Figure 12.9).[26,33,34] The isopropyloxymethylcarbonyl (POC) promoiety was chosen instead of the bis(pivaloyloxymethyl) promoiety found in adefovir dipivoxyl (**11**). Release of the POC



Tenofovir (PMPA)
13

Tenofovir disoproxil
14

Figure 12.9 Tenofovir disoproxil (**14**) is the phosphonate prodrug of acyclic phosphonate nucleotide tenofovir (PMPA) (**12**). It utilizes the isopropyloxymethylcarbonyl (POC) phosphonate prodrug construct to enable more effective oral absorption. Tenofovir disoproxil is currently used for the treatment of HIV and HBV infection.