promoiety produces PMPA and the promoiety byproducts isopropanol, CO_2 and formaldehyde. One factor that contributed to the choice of the POC promoiety was the desire to circumvent the potential issue related to suppression of carnitine levels associated with the release of pivalic acid from the bis(pivaloyloxymethyl) promoiety. In addition, the bis(POC)PMPA derivative demonstrated ~100-fold improvement in potency against HIV-infected cells and at least threefold improvement relative to the bis(POM)PMPA derivative with less cytotoxicity.[33,34] This increased activity could be attributed to the fact that bis(POC)PMPA is rapidly taken up into cells and provides very high intracellular levels of PMPA and its active phosphorylated metabolite.[34] TDF was shown to have an oral bioavailability of 20–36% in mice and dogs and ~20% in monkeys and was shown to be rapidly converted to PMPA.[35,36] In human clinical studies, TDF demonstrated an oral bioavailability of 41% and was highly efficacious in the treatment of HIV-1 infection in humans.[37] Tenofovir disoproxil fumarate was approved for the treatment of HIV-1 infection in humans and is sold under the trade-name Viread. In addition, tenofovir disoproxil fumarate has been approved for the treatment of HBV infection. TDF has also been coformulated with several other antiretroviral drugs. These fixed dose combinations are sold as Truvada, Complera and Atripla.

With the success of highly active antiretroviral therapy (HAART) that combines several drugs, including the prodrug tenofovir disoproxil fumarate (TDF), in fixed-dose combinations for the treatment of HIV-1 infection, HIV-1 has become a long-term manageable disease. However, there is still the risk for the emergence of drug resistance, side effects from long-term use and drug–drug interactions as the patient population ages. The search for new more effective and convenient therapies has continued in the fight against HIV/AIDS. One area of continued effort is in the search for nucleos(t)ide reverse transcriptase inhibitors (N(t)RTIs) that have improved dosing schedules, resistance profiles and reduced long-term toxicity concerns and can be combined with other antiretrovirals in a HAART-type regimen. To this end, the novel nucleotide **16** (Figure 12.10) was identified.[38] This phosphonate nucleotide had an improved resistance profile relative to tenofovir and other N(t)RTIs.[38] However, a prodrug of this novel phosphonate nucleotide analog was desired to deliver the parent ideally to lymphoid cells after successfully traversing the gut and surviving hepatic and plasma enzymes. Early studies showed that the phosphonamidate prodrug of tenofovir GS-7340 (**15**, Figure 12.10) could survive hepatic and plasma enzymes and be preferentially cleaved within lymphoid cells.[39] GS-7340 was shown to be 400-fold more potent than tenofovir in PBMCs and 200-fold more stable in plasma than TDF, resulting in circulating levels of prodrug. Cleavage of the phosphonamidate prodrug was found to be mediated by lysosomal cathepsin A, which is highly expressed in PBMCs.[39–42] Following cathepsin A cleavage of the terminal amino acid ester, cyclization to expel the phenol followed by a series of enzymatic or chemical hydrolyses in the cytosol, the parent drug is released. Studies with tenofovir in dogs and humans confirmed that relative to the POC prodrug TDF, a phosphonamidate