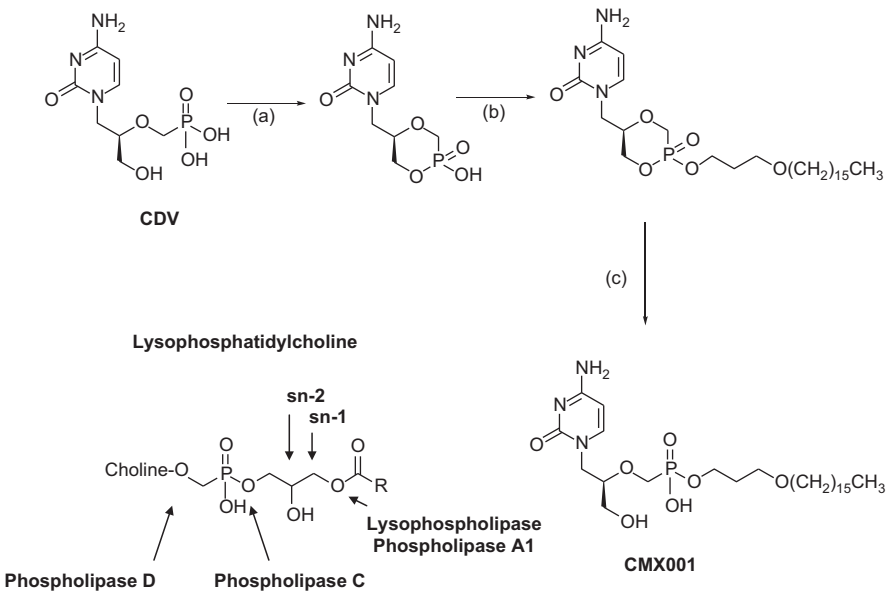
been extensively evaluated in multiple animal models of OPV infection (reviewed by Smee[37]). Intravenous administration of CDV protected mice from lethal infection with vaccinia, cowpox and extromelia virus. Administration of CDV as an inhaled powder or by intravenous injection protected rabbits from lethal infection of aerosolized rabbitpox virus.[72] CDV has also been shown to be effective at reducing mortality and lesional disease in non-human primates infected with monkeypox or variola virus.[46,73] While the cCDV is more potent than CDV *in vitro* against poxvirus infections, it is less active than CDV in mice infected with vaccinia virus.[74,75] Despite extensive evaluation of the efficacy of CDV in animals, efficacy studies in humans have been limited to compassionate use cases due to the nephrotoxicity associated with systemic compound delivery. Therefore, for now, the clinical utility of CDV is limited to topical applications.

4.4.2 CMX001

CMX001 is a prodrug of CDV that was designed to improve the compound's pharmacokinetic properties and safety profile (Figure 4.3) (reviewed by Hostetler[76]). Although CDV exhibits broad-spectrum activity and has established clinical effectiveness, it is not readily absorbed and exhibits poor oral



(a) *N*,*N*-dicyclohexylmorpholinocarboxamide, *N*,*N*-cyclohexylcarbodiimide, pyridine, 100 °C
(b) 1-bromo-3-hexadecyloxypropane (HDP), *N*,*N*-dimethylformamide, 80 °C
(c) 0.5 M NaOH

Figure 4.3 Synthesis of CMX001 and similarity to lysophosphatidylcholine. Chemical synthesis of CMX001 and structure of lysophosphatidylcholine adapted from Kern, Hostetler and co-workers.[75,76]