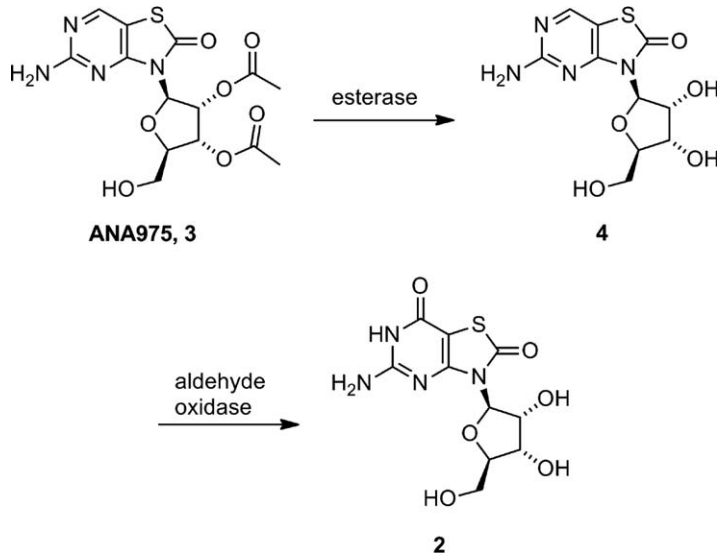

Figure 10.2 Conversion of ANA975, a prodrug of isatoribine, to the active species.

prodrug inactive as a TLR-7 agonist. This resulted in ANA975, **3**, which was further investigated clinically.[30]

In vitro experiments suggested that ANA975 would be metabolized to isatoribine *in vivo*. The mechanism by which this occurred involved removal of the acetate esters by an esterase to produce compound **4** and oxidation of C4 of the guanine-like base by aldehyde oxidase to ultimately yield isatoribine (**2**). This metabolic pathway was supported by the pharmacokinetics of ANA975 in HCV patients. Following oral administration, deacetylation and hepatic oxidative metabolism produced isatoribine, which is the predominant species detected in plasma, thus delivering the active TLR-7 agonist. Oral doses of 975 mg of ANA975 as a solution or powder-in-capsule produced plasma levels of isatoribine that were comparable to those from intravenous administration of isatoribine at 245 mg. Furthermore, the fact that ANA975 and its deacetylated analog **4** are both significantly less active as TLR-7 agonists than isatoribine results in minimization of any gastrointestinal side effects that may result from stimulating TLR-7 in the gut before absorption into systemic circulation and conversion to the active agonist.

ANA975 was evaluated clinically with once-per-day dosing, but the clinical trial was suspended owing to toxicology findings in animal species upon chronic daily dosing. A prodrug of an analog of isatoribine, ANA773, which is reported to have a similar structure to ANA975 and that utilized the same prodrug strategy, was subsequently taken into clinical development with an every-other-day oral dosing frequency.[31] In HCV patients, at the highest dose of 2000 mg, a mean reduction in serum HCV RNA of $1.26\log_{10}$ units was achieved, with a maximum reduction of $3.1\log_{10}$. The decrease in HCV RNA