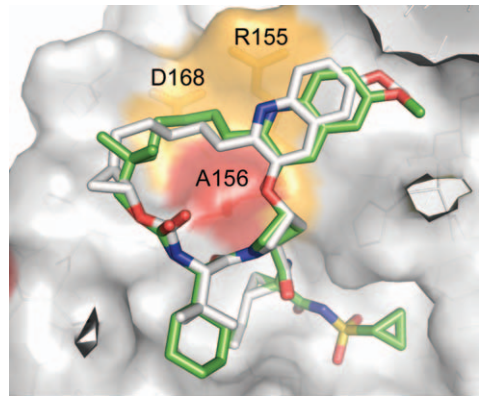

Figure 7.16 Comparison of the energy-minimized conformations of **167** (magenta) and **169** (green) docked in the gt1b NS3/4a active site.

Ring contraction to a fused cyclopropyl further improved the activity and gave a compound (**169**) with excellent liver exposure. Modeling results with **167** and **169** give some insight into the reasons for the 4–10-fold improvement against A156 mutant enzymes (Figure 7.16). The cyclopropyl constraint of **169** seems to shift the macrocycle away from the A156 residue compared with **167**. Since the A156 residue is positioned close to the middle of the macrocyclic ring, this slight shift may allow more space for the macrocycle of **169** to accommodate the A156T or A156V mutation. Compound **169** met second-generation HCV protease potency and PK criteria and was evaluated in a battery of studies as a prelude to its selection as a development candidate.

During this candidate work-up, an important pharmacokinetics-related issue regarding the behavior of pharmaceutical salts of **169** emerged, which represented a major development hurdle. Although the crystalline potassium salt of **169** has good aqueous solubility (9.7 mg mL^{-1}), it readily disproportionates to a crystalline zwitterionic form that has a greatly reduced aqueous solubility of <0.009 mg mL^{-1}. This behavior is driven by the moderate basicity of the quinoline P2 group of **169** (calculated $pK_a = 4.47$),[120] along with moderate acidity of the acylsulfonamide (calculated $pK_a = 3.67$). *In vivo*, this process is promoted in the stomach where the native pH of the dosing solution is attenuated, giving rise to non-reproducible pharmacokinetics.[121] Poor absorption of the crystalline zwitterionic form of **169** that is formed *in vivo* significantly capped the achievable plasma and liver exposures of **169** in preclinical species. Given the excellent overall profile of **169**, Merck examined alternative P2 heterocycles with less basic functionality that potentially would maintain a similar potency and PK profile. From this work, P2 quinoxalines emerged as the most promising subclass, with lower pK_a reducing the risk of zwitterion formation (calculated $pK_a \sim 1.2$). Incorporating a quinoxaline into the optimized framework gave **14** (Table 7.28). Overall, **14** maintained the excellent potency against the gt3a enzyme and also a broad panel of mutant enzymes and showed excellent rat liver exposure. The potassium salt of **14**