almost always impossible, as there are many procedures and methods that are impractical to replicate on an industrial scale. Consider, for example, a synthetic sequence that requires a temperature of −78 °C. In a laboratory focused on preparing small amounts of material (>20 g), one can simply cool a reaction vessel with a dry ice/acetone bath. Cooling an industrial scale reactor designed to make 200 kg of the same material (a 10,000-fold increase in scale, Figure 9.4) would be challenging and expensive. Purification of

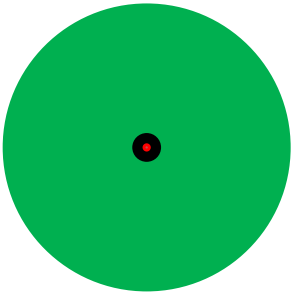

FIGURE 9.4 The center red circle represents 20 g. The black circle represents a 100-fold increase in size, while the green circle represents a 10,000-fold increase in size.

intermediates and the final product can also be an issue. Chromatography methods suitable for laboratory scale synthesis, for example, are generally not feasible for industrial scale production and must be replaced with recrystallizations, precipitations, or distillations as appropriate.

The concept of polymorphism can also create unexpected issues in moving from laboratory scale to GMP production. Polymorphism refers to the ability of a solid material, such as a candidate compound, to exist in more than one crystalline form.[14] If multiple crystal forms are possible, they may have different physical properties, which may have an impact on pharmacokinetic properties. If, for example, one crystal form of a compound (a polymorph) dissolves more slowly than a second crystal form (a different polymorph) of the same compound, the bioavailability of the compound may be significantly lower if the second crystal form is employed. Norvir® (Ritonavir, Figure 9.5), an HIV protease inhibitor, for example, was

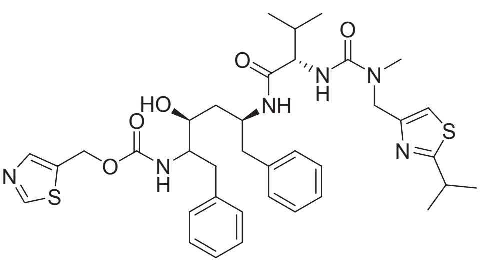

FIGURE 9.5 Norvir® (Ritonavir).