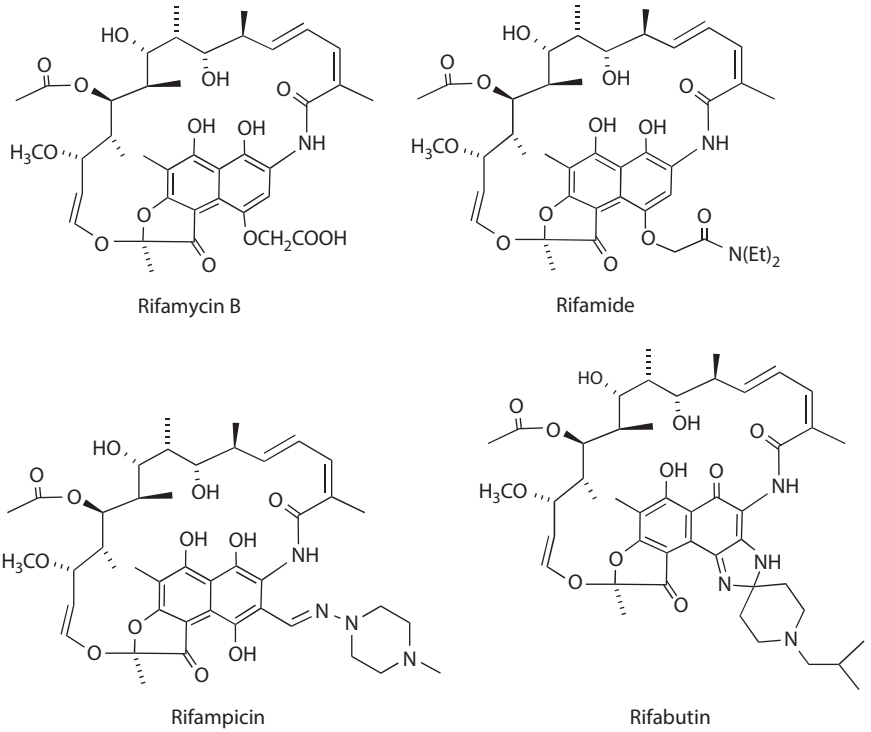

FIGURE 7.9 Rifamycin B and semisynthetic analogs.

of the successful application of semisynthesis is in the case of the rifamycin antibiotics, shown in Figure 7.9. Rifamycin B is the originally isolated natural product derived from *Nocardia mediterranei*. Rifamycins have potent activity against gram-positive bacteria and are of greatest importance to inhibit the growth of the tuberculosis causing organism *Mycobacterium tuberculosis*. Rifamycin B was only modestly effective when administered to infected animals and this led to investigation of derivatives in search of improved potency. Greater potency was achieved through substitutions on the aromatic portion as exemplified by rifamide, rifampicin, and rifabutin. The latter two compounds continue to be important drugs for the treatment of re-emerging epidemics of tuberculosis.

7.5.2 Improvements in Natural Products through Total Synthesis

Although the total synthesis of natural products has been the forte of many prominent academic laboratories, only a few totally synthetic analogs of natural products have been introduced into commerce. The continued development of efficient and selective synthetic methods could provide alternative supply routes for simpler natural products of the future. Regardless of the issue of practical scalability, total synthesis enables the production and testing of analogs that often illuminate key features of the structure that are critical for biological activity. Paul Wender's research on the bryostatins, potent cytotoxic principles isolated from marine invertebrates, illustrates some of the key insights that can be revealed through total synthesis.

7.5.3 Biosynthetic Modifications

Genetic engineering of biosynthetic pathways to create specific modifications in the chemical structure of secondary metabolites is now a practical reality in bacterial systems. In the simplest cases, a single enzymatic function is eliminated by inactivating the respective gene, resulting in an