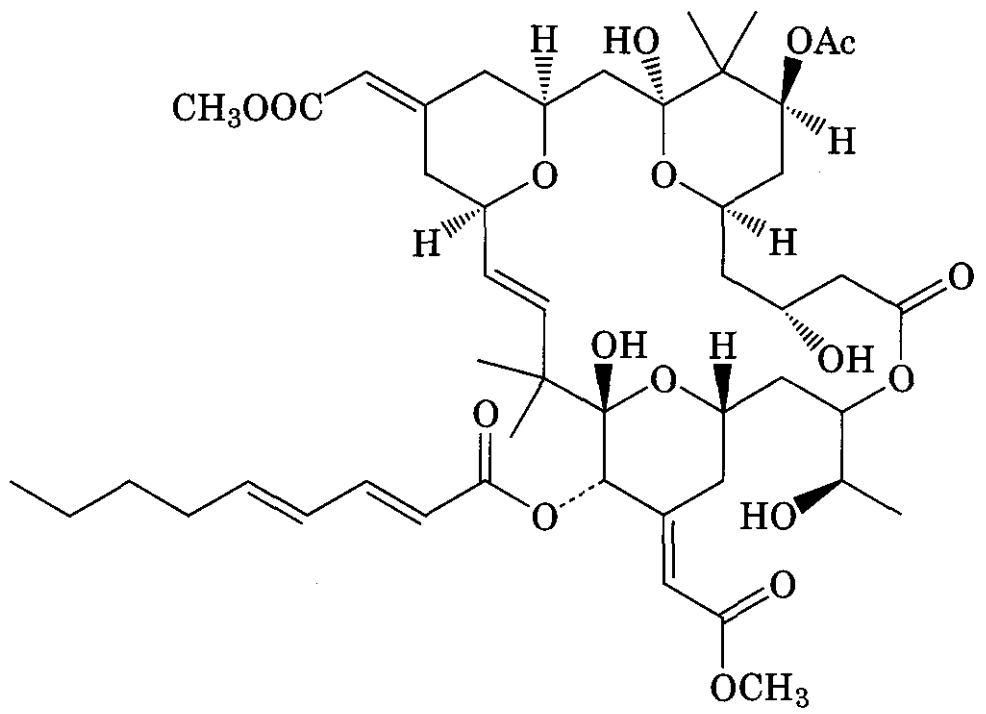
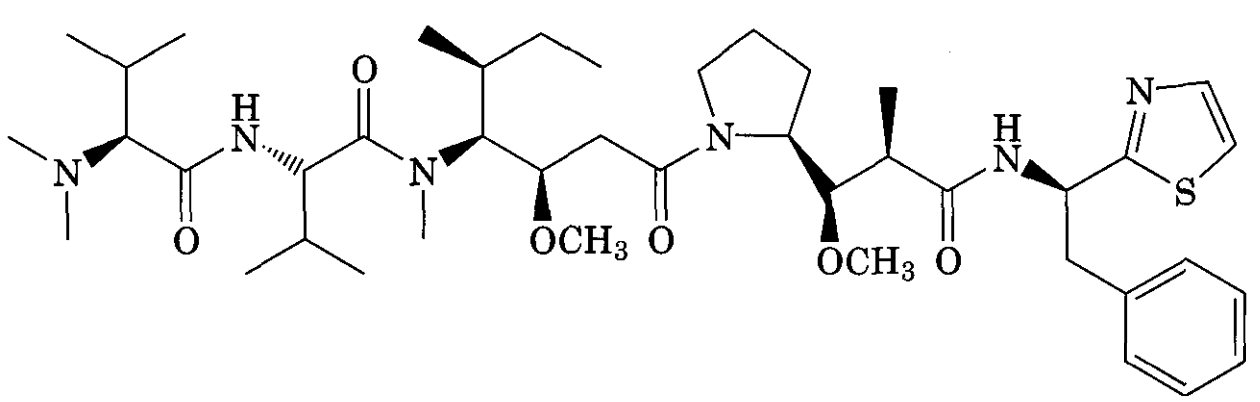


(73) Bryostatin 1



(74) Dolastatin 10

The discovery that the fused β-lactam nucleus, 6-aminopenicillanic acid (6-APA) (**76**), could be obtained from cultures of Penicillium chrysogenum led to the preparation of new, semisynthetic derivatives with improved stability to gastric acid and p-lactamases, and with activity against a wider range of pathogenic organisms (121). Sheehan (122) showed that compound (76) would react readily with acid chlorides to form new penicillin derivatives with novel substituents at the 6-position. Methicillin (**77**), with a sterically demanding 2,6-dimethoxybenzamide side-chain, was the first semisynthetic penicillin to show resistance to staphylococcal p-lactamases, although the compound was still acid labile. Ampicillin (**78**) has an a-aminophenylatamido side-chain and displays good activity against Gram-negative organisms, it is stable to acid and thus can be administered orally, although it is susceptible to degradation by p-lactamases. Amoxycillin (79) differs from ampicillin by the addition of a single hydroxy group, but the compound is better absorbed by the gastrointestinal tract.

Clavulanic acid (**80**), isolated from *Streptomyces clavuligerus*, is similar in structure to the penicillins, except oxygen replaces sulfur in the five-membered ring (123). Clavulanic acid has weak antibacterial activity, but is a potent inhibitor of p-lactamases (124). A mixture of clavulanic acid and the β-lactamase–sensitive amoxycillin was introduced in 1981 as Augmentin and has proved to be an effective combination to combat β-lactamase–producing bacteria (125). In 2001, 20 years after its launch, Augmentin is the best-selling antibacterial worldwide.

The clinical introduction of the penicillin group of antibiotics prompted an intensive search for novel antibiotic-producing organisms and Selman Waksman demonstrated the value of actinomycetes in this role, discovering the aminoglycoside streptomycin (**81**) from Streptomyces griseus in 1943 (126). Pharma-