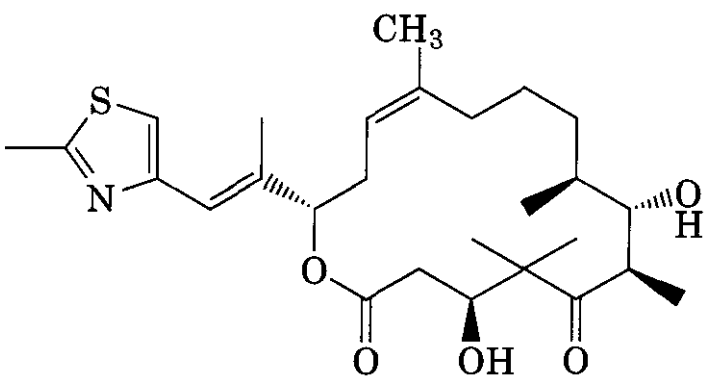
analogs for biological evaluation, including the use of solid-phase combinatorial approaches.

The academic groups focused on modifications around the core macrocyclic lactone, establishing important structure–activity relationships, but not improving on the in vitro biological activity of the most active natural product, epothilone B (**57**). In vivo biological data were comparatively scarce and, although one group reported that epothilones B (57) and D (58) showed activity in murine tumor models, researchers at Bristol-Myers Squibb have shown that (58) lacks in vivo activity as a result of rapid metabolic inactivation (90). It was postulated that esterase-mediated hydrolysis of the macrocyclic lactone formed an inactive ring-opened species and, therefore, efforts were focused on replacing the lactone with a more stable macrocyclic lactam moiety. Several macrocyclic lactam derivatives were synthesized from (**57**) and (**58**). Of note was the preparation of BMS-247550 (**59**) in a three-step synthesis from epothilone B (**57**), utilizing a novel Pd(0)-catalyzed ring-opening reaction followed by reduction and macrolactamization. BMS-247550 (**59**), which is in phase I clinical trials, retains its activity against human cancer cells that are naturally insensitive to paclitaxel or that have developed resistance to paclitaxel, both in vitro and in vivo (91).



(58) epothilone D

4.5 Podophyllotoxin, Etoposide, and Teniposide

The development of the natural constituents of Podophyllum Resin into effective semisynthetic and, ultimately, totally synthetic compounds for the treatment of various kinds of cancer provides one of the most sustained and intriguing stories of drug discovery (92, 93). The story has all the classic ingredients, starting with observation and reasoning, extending through chance into new areas, and characterized throughout by persistence and determination, particularly when biological activity had to be traced to very minor constituents in the crude plant extract.

Podophyllum *peltatum* (may apple, or American mandrake) and P. *emodi* are. respectively, American and Himalayan plants, widely separated geographically but used in both places as cathartics in folk medicine (94). An alcoholic extract of the rhizome known as podophyllin was included in many pharmacopoeias for its gastrointestinal effects; it was included in the U.S.P., for example, from 1820 to 1942. At about this time the beneficial effect of podophyllin, applied topically to benign tumors known as condylomata acuminata, was demonstrated clinically (95). This usage was not inspirational, given that there are records of topical application in the treatment of cancer by the Penobscot Indians of Maine and, subsequently, by various medical practitioners in the United States from the 19th century (96). The crude resinous podophyllin is an irritant and unpleasant mixture unsuited to systemic administration.

The first chemical constituent was isolated from podophyllin in 1880 and named podophyllotoxin (97). A structure was proposed in 1932 and after some fine-tuning (98) was shown to be the lignan (60). As might be expected, the crude resin contains a variety of chemical types, including the flavonols quercetin and kaempferol (99). Although these other constituents undoubtedly have biological activity, it is the lignans that have received most attention and to which we shall devote the remainder of this section.

Chemists at Sandoz in the early 1950s reasoned that crude podophyllin might contain lignan glycosides with anticancer activity, which might be more water soluble and less toxic than podophyllotoxin (92). The reasoning for the latter is not entirely clear, but in the event they proved to be correct in both respects. Careful isolation gave podophyllotoxin β-D-glucopyranoside (61) its 4'-desmethyl analog (62) and some less important lignans lacking the B-ring hydroxy group (100–102). Unfortunately, the sugar deriva-