Plants are phenomenally adept at biosyntheses of complex and potentially useful terpenoids. A considerable number of species from plant families rich in terpenoids, such as the Compositae, have been used in primitive cancer treatment from a pre-Christian period of unknown length. The possibilities for isolation of anticancer agents from the Compositae—and, for example, the Euphorbiaceae—were anticipated at least 20 years ago by Hartwell at the U.S. National Cancer Institute (NCI), as noted in Chapter 2. Subsequent investigations of Compositae, particularly by Hertz and Kupchan, have led to a number of new sesquiterpenes capable of substantially inhibiting (ED$_{50}$ < 10 μg/ml) the KB cell line. The application of this in vitro screening technique for bioassay markedly enhanced the facility with which such cytotoxic substances can be isolated. Unfortunately, in a significant number of cases, the cytotoxicity has not been translated into in vivo activity against the NCI's lymphocytic leukemia P388 (the PS system, significant activity $\geq$ 125 T/C), Walker carcinosarcoma 256 (the WA system, significant activity $\leq$ 42 T/C), or lymphoid leukemia L1210 (the LE system, significant activity $\geq$ 125 T/C). Because the main emphasis of this volume is on the potential of biosynthetic products for cancer chemotherapy, the discussion here will be limited to those terpenoids with in vivo antineoplastic activity. However, all of those available in the literature

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with cytotoxic activity have been listed in the tabular survey of Volume 2. The same format has been followed in each subsequent chapter.

The C15 sesquiterpenoid alcohol farnesol is believed to be a biological precursor of the sesquiterpenes. Almost every reasonable cyclization and rearrangement conceivable for farnesol is reflected in the sesquiterpenes, and a number of these possibilities, as highly oxygenated derivatives, have been found to be cytotoxic and/or antineoplastic agents. The eudesmane skeleton appears in the unusual seco-eudesmanolides eriolangin (41) and eriolanin (42) from *Eriophyllum lanatum* Forbes (Compositae).203 Vernolepin (43) is an unusual emanolide from *Vernolia hymenolepis* A. Rich. (Compositae).214,219 The somewhat related iridoid lactone, allamandin (44) from the Apocynaceae species *Allamanda cathartica* Linn., provides an example from a plant family better known for its alkaloid constituents.212

The sesquiterpene hydrocarbon germacrane appears in the germacranolide lactones represented by structures 45 through 52. Each was isolated by the Kupchan group211 from a Compositae, and liatrin (49) was found to possess an interesting level of PS activity. Three other cytotoxic germacranolides have been found by Doskotch and co-workers in the Magnoliaceae plant *Liriodendron tulipifera* L.85,86

Three sesquiterpene lactones with the guaiane carbon framework have been located that possess solid tumor activity. The tumor inhibitory activity reported by the Cole group401 for ambrosin (53, Asteraceae) is surprisingly high. Of eight cytotoxic lactones isolated from *Eupatorium rotundifolium* L. (Compositae), the two given by structures 54 and 55 were found active in the WA system. The pseudoguaiane carbon network corresponds to a one carbon shift of the cyclopentane methyl group into the guaiane ring juncture. A number of such pseudoguaianolides are known.156,346

Our group has found the common sneeze-weed170 of Oregon, *Helenium autumnale* L. Var. *Montanum* (Nutt.) Fern. (Compositae), to give extracts with a good level of PS activity,