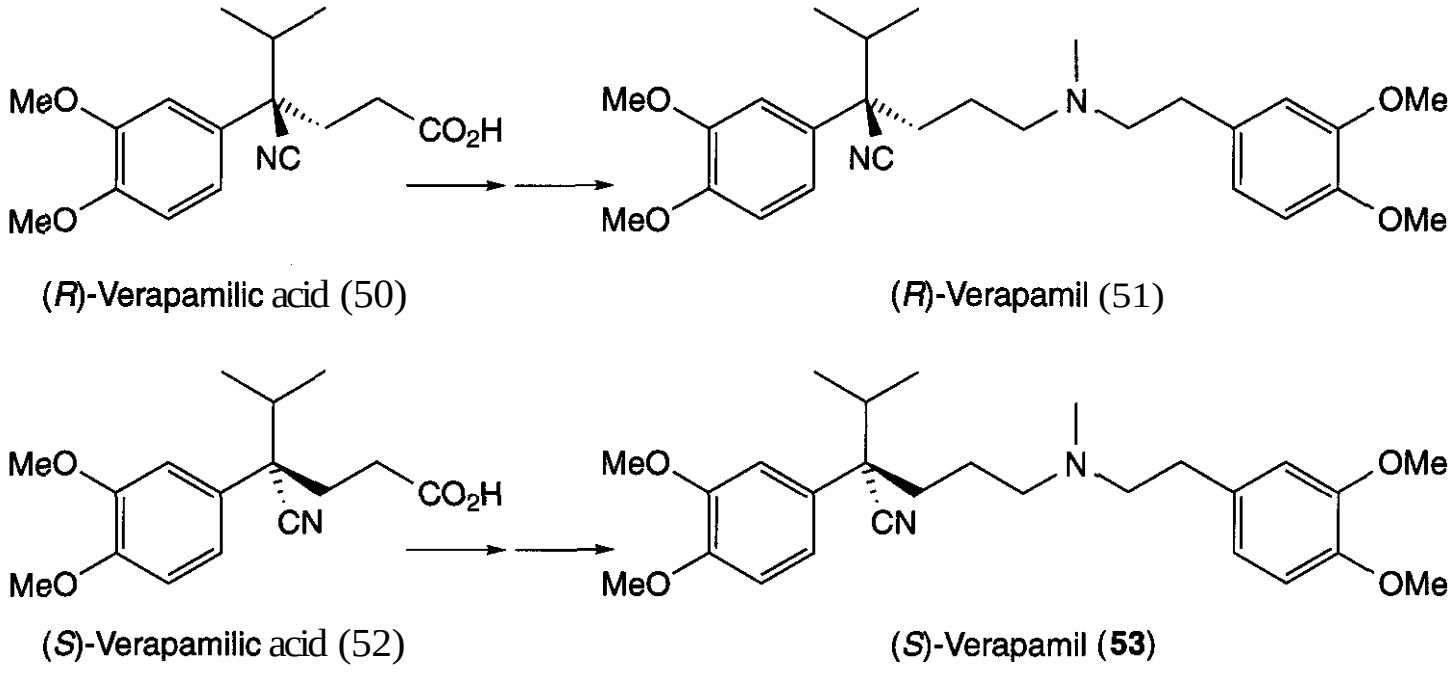

Figure 18.19.

does offer several advantages from the point of view of time and quality aspects, there are also a number of drawbacks. If, for example, a racemization of the unwanted isomer cannot be found, there would be a waste of 50% of material. Therefore, it can often be advantageous to conduct the separation at an earlier stage in the synthesis of the drug. This leads to better atom efficiency compared with resolution of the final product, resulting in a reduction of the overall amount of waste and cost.

One such example is Verapamil, which is a well-established treatment of cardiovascular ailments (77). *S*-(−)-Verapamil (51) has specific transmembrane calcium channel antagonist activity, whereas its antipode (53) influences a wider range of cell pump actions, including those for sodium ions (78). Verapamil has been separated into its single enantiomers by resolution with expensive resolving agents, which required multiple recrystallizations to effect complete separation (79). Looking into the synthetic sequence of Verapamil, several intermediates seemed to be attractive alternatives to Verapamil (80). The intermediate verapamilic acid (Fig. 18.19) was efficiently separated using a-methylbenzylamine (a-MBA), which is an extremely cheap resolving agent (81). Subsequent transformation of the easily obtained R- or S-verapamilic acid (50 or 52), required a further three to four synthetic steps to yield the active pharmaceutical ingredient.

The racemate aminoglutethimide (27) has been shown to be effective in the treatment of hormone-dependent breast cancer (Fig. 18.20). Further studies have shown that the *R*-enantiomer is more potent than its antipode as an aromatase inhibitor (82). The resolution of aminoglutethimide itself has been reported in the literature, using tartaric acid. This resolution suffers from the formation of solid solutions (83), which require endless crystallizations to deliver the single enantiomer (84). Use of a suitable precursor (54) enabled separation of the intermediate (55), by treatment with the alkaloid resolving agent (−)-cinchonidine. This chiral acid was then cyclized to nitroglutethimide, which on reduction, gave the desired R-aminoglutethimide (56) (85). It is noteworthy that in the case of aminoglutethimide, the amine functionality is an aniline moiety. Because of the low pK_a associated with this amine (2.5–4.6), the number of acidic resolving agents that can be employed are reduced, because they need to be of relatively high acidity to form a salt.

3.3 Crystallization-Induced Asymmetric Transformation

A number of amino acids have been separated by resolution, in certain cases the yield of the required diastereoisomer has been greater than 50% (86). *p*-Chlorophenylalanine is of considerable pharmacological interest, because of its ability to inhibit serotonin forma-