



Figure 18.20.

tion in laboratory animals (87). Both the R- and S-enantiomers have also been used as building blocks in the synthesis of other drugs. An ingenious approach to *R-p*-chlorophenylalanine methyl ester, which is based on a one-pot resolution-racemization sequence, is highlighted in Fig. 18.21. Here, treatment of racemic *p*-chlorophenylalanine methyl ester (57) with 0.5 eq of D-tartaric acid and 0.1 eq of salicylaldehyde in methanol gave a 68% yield of 98% enantiomeric purity of the 2:1 *R-p*-chlorophenylalanine D-tartaric acid salt (58). The reason that the absolute yield is greater than 50% is caused by the S-enantiomer being racemized *in situ*. The 2:1 tartrate salt is crystalline and is therefore removed from the system by virtue of its insolubility. This drives the equilibrium further in favor of the 2:1 *R-p*-chlorophenylalanine D-tartrate salt (88).

While the common goal remains to be the rational design of resolving agents (89), it is clear that we are still away from this actually happening. An alternative "family" approach to classical resolution has been demonstrated by Vries et al. (90). A group of similar resolving agents are mixed simultaneously with the racemate. This was done to shorten the time required to complete the resolving agent screen. Note should be made that the families of resolving agents are very similar and that the crystalline species obtained by this method contained more than one of the resolv-

ing agents. As with all screens, analysis of the data is often time consuming and laborious. Bruggink et al. have shown that differential scanning calorimetry (DSC) of the isolated salts can help to quickly determine whether the isolated salt will provide a through resolution (91). However, with a methodical and precise screening protocol, it is nearly always possible to find a suitable resolving agent that effects separation of the enantiomers (92).

## 4 NONCLASSICAL RESOLUTION

### 4.1 Preferential Crystallization

A brief description of the type of "racemic" compounds is necessary for the reader to better understand the principles behind the application of crystallization methods to the separation of enantiomers. Three fundamental types of crystalline racemates exist. In the first, the crystalline **racemate** is a conglomerate, which exists as a mechanical mixture of crystals of two pure enantiomers. The second, which is the most common, consists of the two enantiomers in equal proportions in a well-defined arrangement within the crystal lattice; this is termed racemic compound. The third possibility occurs with the formation of a solid solution between the two enantiomers that coexist in an unordered manner in the crystal. This kind of **racemate** is called a pseu-