enantiopure product. Below this, the enantiopurity is reduced. In this case, it is advantageous to recrystallize the diastereomeric salt precursor to optical purity before proceeding to final product.

4.3 Resolution by Direct Crystallization

It is important to show how conglomerates are identified. We have already seen that they have specific phase diagrams as shown in Fig. 18.23. Other such data that support identification of a conglomerate are IR, X-ray data, and observation of a spontaneous resolution or resolution by entrainment. Note should be made that in 1848, Louis Pasteur separated the dextrorotatory and levorotatory crystals of sodium ammonium tartrate. This manual sorting of crystals is also known as triage, and by its very nature is time consuming and laborious. The readers are again directed towards the Jaques et al. monograph, which lists over 250 known examples of conglomerates (57). There are two possibilities for separation of enantiomers by direct crystallization. The first uses spontaneous resolution, which occurs when a conglomerate crystallizes. This crystallization may be followed by the mechanical separation of the crystals of the two enantiomers. Various techniques have been developed that aid this separation.

The second type of resolution by direct crystallization is known as entrainment. Here, the differences in the rate of crystallization of the enantiomers in a supersaturated solution give rise to a separation. Strict control of the conditions for the crystallization are required, with the system of crystals and solution not being allowed to come to equilibrium and time playing an important role. The occurrence of conglomerates has been estimated to be approximately 10% of all racemic compounds. We will now illustrate this phenomenon with some pertinent examples.

An example of use of the conglomerate Narwedine (59) in the synthesis of a natural product Galanthamine (61) which is an *Amarylli-daceae* alkaloid and has been used clinically for 30 years for neurological illnesses (98). More recently it has been approved for the use in the treatment of Alzheimer's disease (AD) (99). Galanthamine acts to inhibit acetylcholinesterase (AChE), thus increasing the levels of acetylcholine. An increase in the level of acetylcholine in patients with AD has been shown to improve their cognitive performance. Galanthamine has been extracted from botanical sources; however, several tons of daffodil bulbs are needed to produce 1 kg of product. A synthetic route has been developed that uses a crystallization-induced chiral transformation (Fig. 18.25). This crystallization was first reported by Barton and Kirby (100) and further developed by Shieh and Carlson (101). The success of this transformation is based on two phenomena: narwedine (59), which crystallizes as a conglomerate, and (−)-narwedine (60), which equilibrates with (+)-narwedine through a retro-Michael intermediate. This process has now been developed so that (−)-narwedine (60) is routinely obtained in 80% yield from the racemate input, as shown in Fig. 18.25 (102).

Recently a number of potent 5-HT, receptor antagonists such as Ondansetron have been reported to be clinically effective for the blockade of chemotherapy-induced nausea and emesis (103). The structurally novel compound (62) has also been shown to be a highly potent 5-HT, antagonist (104); specifically, the R-(−)-(62) enantiomer was shown to be the most active. Comparison of the physical data of the racemate and single enantiomer indicated that this structure (62) exists as a conglomerate (104). By careful experimentation, the best concentration, temperature, and time for crystallization were discovered. Table 18.1 highlights the results obtained for the entrainment.

The initial concentration of the solution was 10.0 g of (±)-(62) in 50 g of acetone. In all runs, 10 mg of seed crystals were used. From the 10 runs highlighted in the 18.1, 21.0 g of *R*-(−)-(62) of >92.0% ee and 21.4 g of (*S*)-(+)-(62) of >90% ee are obtained from an input of 50.4 g of racemate. The table also nicely illustrates the continuous nature of the process, which coupled with the fact that no resolving agent, chiral auxiliary, enzyme, or catalyst is needed, underlines the economic advantages of this type of process.

The importance of amino acids as building blocks for asymmetric synthesis is well documented (105). A number of amino acids have been shown to exist as conglomerates. Shi-