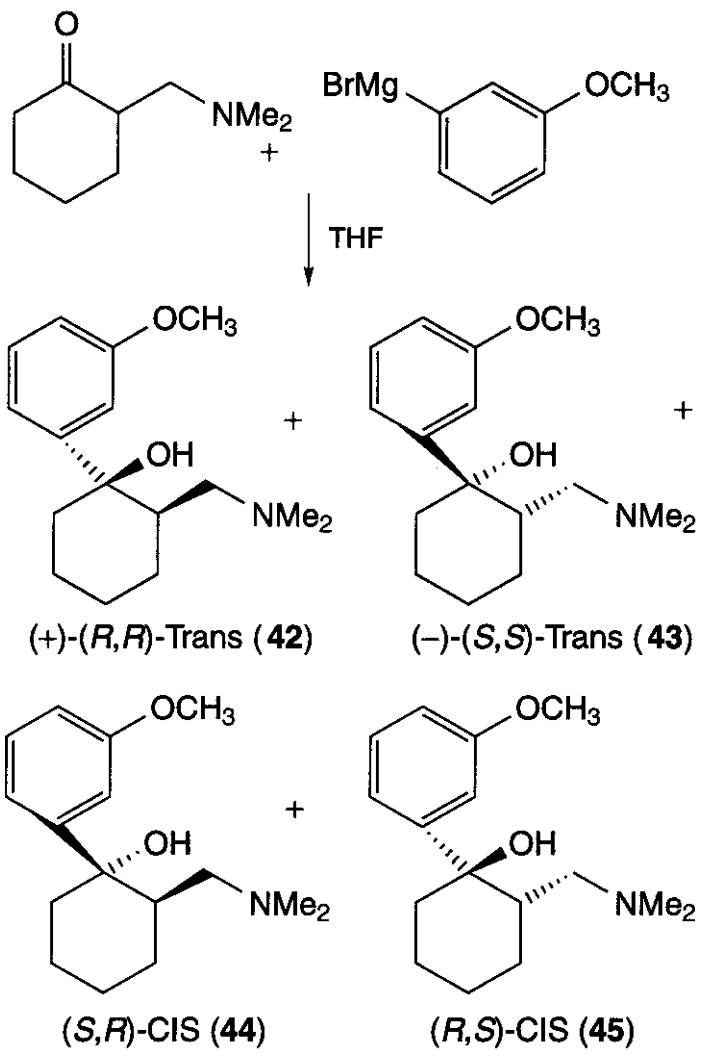


Figure 18.16.

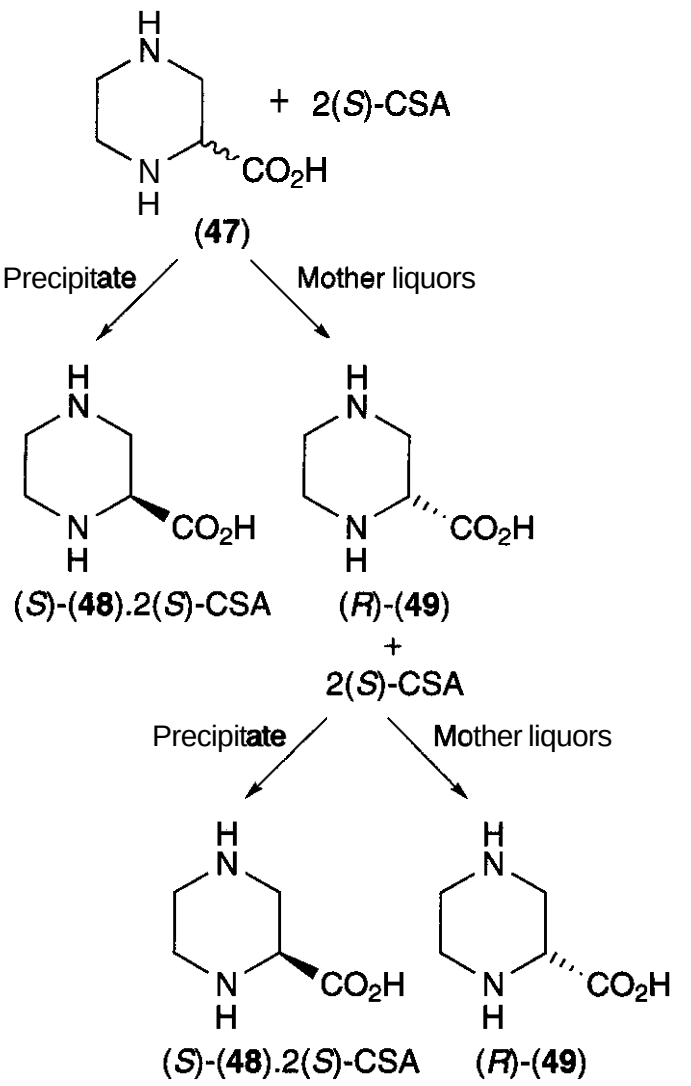
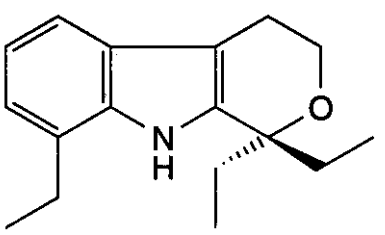


Figure 18.18.

the enantiomers, but it can also be used as the pharmaceutical salt form of choice.

In addition to the racemic drugs discussed in this section, resolutions are also used in the isolation of key building blocks for the pharmaceutical industry. An important class of these intermediates are amino acids, many of which are available as the single isomer from natural sources (see INTRODUCTION). The use of unnatural amino acids and D configured ones are expected to have a greater influence at the biological level. In the drive for molecular diversity and metabolic stability, a number of unnatural amino acids such as the non-proteinogenic piperazine carboxylic acid (47) (Fig. 18.18) have been developed. Specifically,



Etodolac (46)

Figure 18.17.

this amino acid has found use as an intermediate compound of the HIV proteinase inhibitor L-735,525 (75). The racemic cyclic amino acid (47) has been resolved with *S*-camphorsulfonic acid (CSA), which yields the *S*-isomer as the double CSA salt (48) as the precipitate (76). Retained in the mother liquors is the R-isomer (**49**). This can neatly be racemized to the S-isomer by mixing with S-CSA in a suitable solvent. On seeding with pure (*S*,*S*)-diastereomeric salt, a further quantity of the desired (*S*,*S*) product (**48**) is obtained, leaving the R-isomer (49) once more in the liquors. The whole cycle can be repeated and has been demonstrated with four complete cycles. To complete the whole process, the resolving agent is also readily recovered and recycled.

3.2 Separation of Intermediates to Single Enantiomer Active Pharmaceutical Ingredient

The previous examples given for diastereomeric salt resolution have all involved separation of the active pharmaceutical ingredient (API) or late stage intermediate. Whereas this