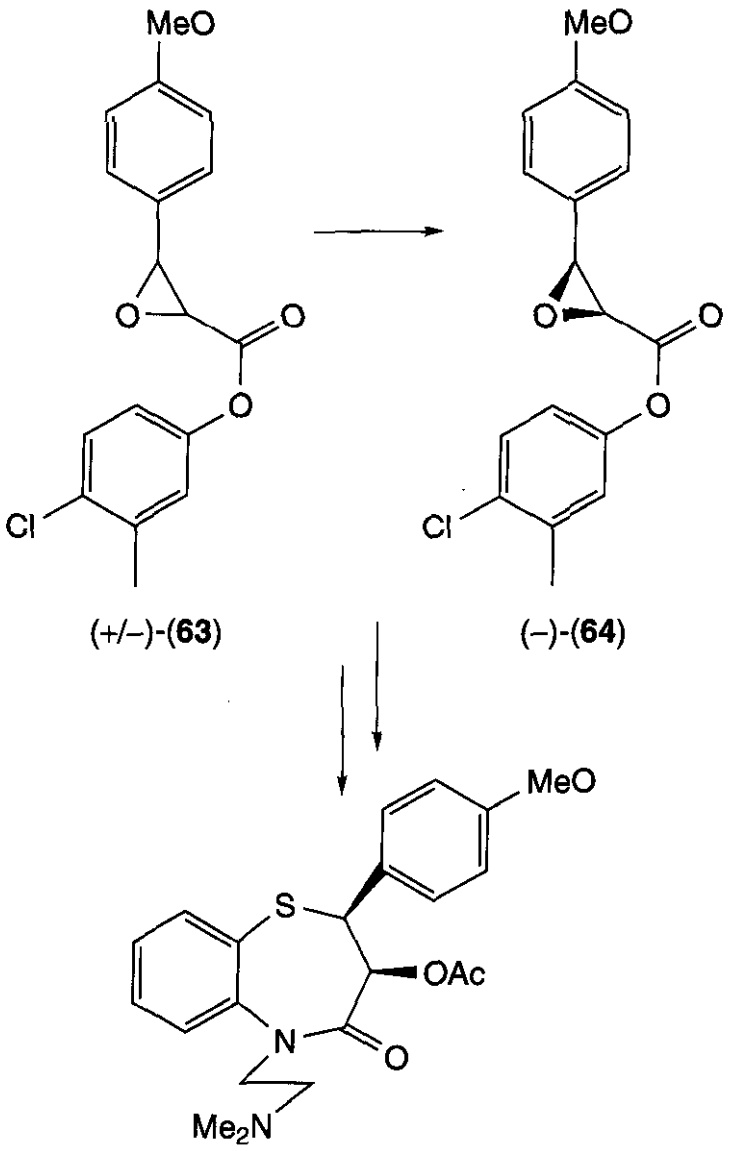


**Figure 18.27.**

anticipated that medicinal chemists will more commonly use these enzymes in the future.

The coupling of dipeptide (69) to the protected a-thio carboxylic acid (70) was conducted in organic solvent at high concentration with the desired product produced in a few hours with high enantiospecificity.

## 5.2 Transesterification and Hydrolysis

A widely used technique for separating racemic mixture is the use of enzyme mediated transesterification or hydrolysis. One important example is the separation of Naproxen (**33**), which is a member of the 2-arylpropionic acid class of profens that are broadly used as NSAIDs (see Section 2 for the separation of enantiomers using a crystallization approach). The important association between chirality and biological activity of this class of drugs has been extensively researched, where the role of cyclooxygenase-independent properties of the R-enantiomers in the gastrointestinal toxicity of the racemates and the likelihood that the use of racemates increases the propensity of profens to alter the pharmacokinetics of other drugs has been described (118).

Whereas not all profens are sold as single isomers, Naproxen is sold as the single S-enantiomer (**36**) where various strategies including crystallization, chromatographic separation, asymmetric hydrogenation and enzymatic hydrolysis, and esterification have been used to prepare the single isomer (65). Specific examples include the use of Candida *cylindracea* lipase to enantioselectively prepare single isomer naproxen ester with trimethyl silyl methanol (119) and the use of Candida rugosa lipase in an enantioselective continuous hydrolysis of Naproxen methyl ester (120).

Pipecolic acid is a component of a number of active drugs, including bupivacaine (38) and thioridazine (72) (Fig. 18.30), which has been efficiently resolved as the racemic n-octyl pipecolate with Aspergillus niger. The *S*-isomer is obtained as the free acid in a 40% yield based on the available enantiomer with a 97% ee (121).

Propanolol (**14**) is a broadly used β-adrenergic receptor blocking agent that is sold as the racemate. However, the majority of the activity is associated with the S-enantiomer (**74**) (see Section 2) (122). The asymmetric

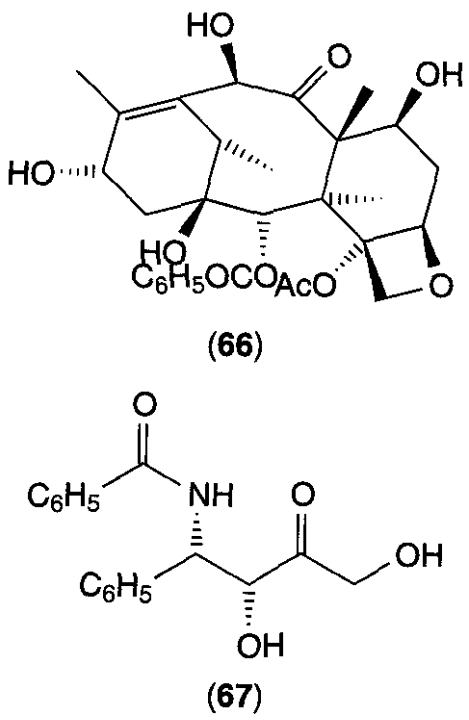


**Figure 18.28.**