

Figure 18.31.

6 ASYMMETRIC SYNTHESIS

Synthetic organic chemists have a vast array of tools at their disposal when faced with the challenge of preparing a chiral compound as a single enantiomer. The purpose of this section is to introduce the reader to some asymmetric approaches toward chiral drugs and medicinal compounds, highlighting examples where the stereoisomers behave differently in biological systems. There are many excellent books and reviews covering methods for asymmetric synthesis and their application to the preparation of pharmaceutical agents and complex natural products (127).

6.1 Chiral Pool

The use of enantiopure starting materials from nature in the synthesis of chiral drugs is not only of great historical significance but remains of critical importance to the pharmaceutical industry. Consideration of the current biggest-selling single enantiomer drugs shows how important this approach is (8 of the top 10 in 1996 were obtained from chiral pool

starting materials or by synthetic manipulation of fermentation products) (127). The optically pure starting materials that have been used in drug synthesis include amino acids, **hydroxy** acids, terpenes, alkaloids, carbohydrates, and many more structurally diverse compounds. There are many syntheses involving clever manipulation of chiral pool starting materials and use of these chiral centers to induce further asymmetry (i.e., by **diastereoselective** reactions). We will **briefly** consider some examples in which all or most of the chiral centers in the target molecule originate directly from nature.

Angiotensin-converting enzymes (ACE) inhibitors are used mainly for the treatment of cardiovascular disorders and are among the biggest selling drugs worldwide (128). **Enalapril** (80) is synthesized from the natural amino acids L-alanine and L-proline (129). **Lisinopril** (81) incorporates a lysine derivative (130). One of the chiral centers in Captopril (82) is derived from **proline**, but the other is generated by chemical or enzymatic resolution (131). **Cilazapril** (83) is a **conformationally** restricted second generation ACE inhibitor developed by **Roche**, and the core is synthesized from a glutamic acid derivative and an amino acid-derived pyridazine (128, 132).

There are many other examples of drugs based on an amino acid backbone. Stoner et al. recently reported a synthesis of the HIV protease inhibitor ABT-378 (**Lopinavir**) (84) (133). In a similar synthesis to that of the related compound, Ritonavir, key intermediate (85) is prepared by **stepwise** diastereoselective reduction of enaminone (86). This means that the existing chiral center, derived from natural L-phenylalanine (protected to **87**), controls the formation of the two new stereocenters as

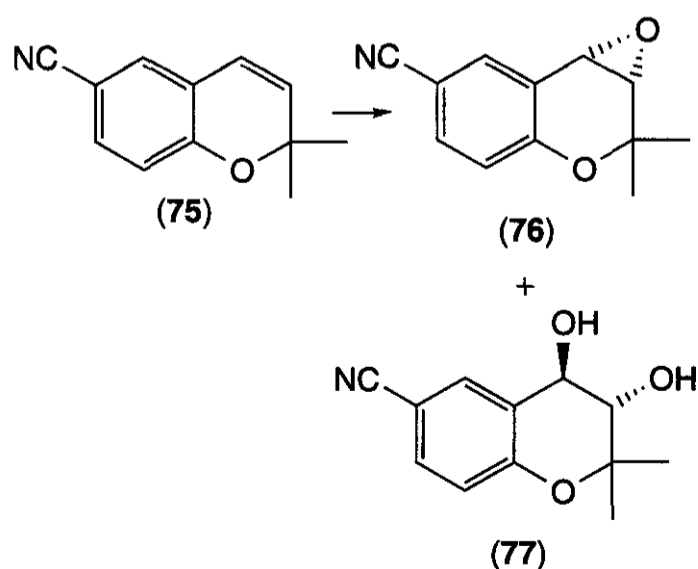


Figure 18.32.