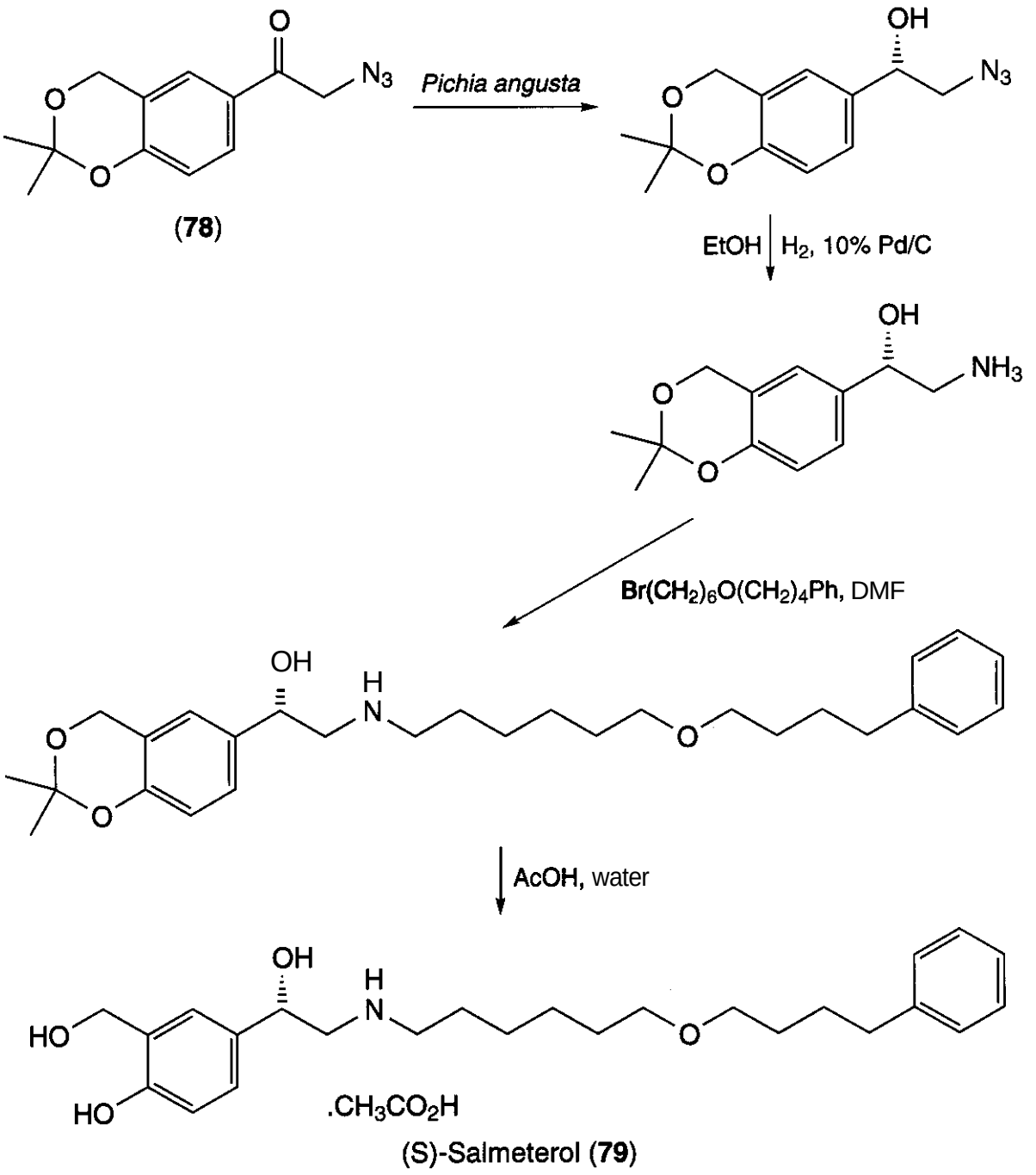

Figure 18.33.

discussed for chiral auxiliaries below. Two acylations then complete the synthesis, with the final chiral center clearly derived from L-valine.

The stereospecificity of binding at the histamine H_3-receptor was investigated by preparing a series of ligands from D- or L-histidine (88)(134). It was found that compounds such as (*S*)-(**89**) had greater affinity for the receptor than their R-enantiomers. In addition, replacing the aromatic moiety with a cyclohexyl group (e.g., 90) switched the activity to agonism for compounds with an amino group in the chain.

Hydroxy acids are important chiral starting materials in the synthesis of many biologically active compounds (135). (*S*)-3-Hydroxy-y-butyrolactone **(91)** is a very useful synthetic unit available from D-pyranoses (136). Workers at Schering-Plough used this as the key starting material in a concise synthesis of Sch 57939 (**92**), a β-lactam–based cholesterol absorption inhibitor (137). The condensation between the dianion of (*S*)-3-hydroxy-γ-butyrolactone and an appropriate diaryl imine proceeded with very high diastereo- and enantioselectivity, generating azetidinone (93) with a *trans*:*cis* ratio of >95:5.

Researchers at Abbott have been investigating the use of pyrrolidinylisoxazoles as nicotinic cholinergic channel activators (138). Until recently, ABT-418 (97) was undergoing clinical trials as a potential treatment for cognitive impairment and decline and for Alzheimer's disease. A short synthesis of ABT-418 was devised starting from commercially avail-