

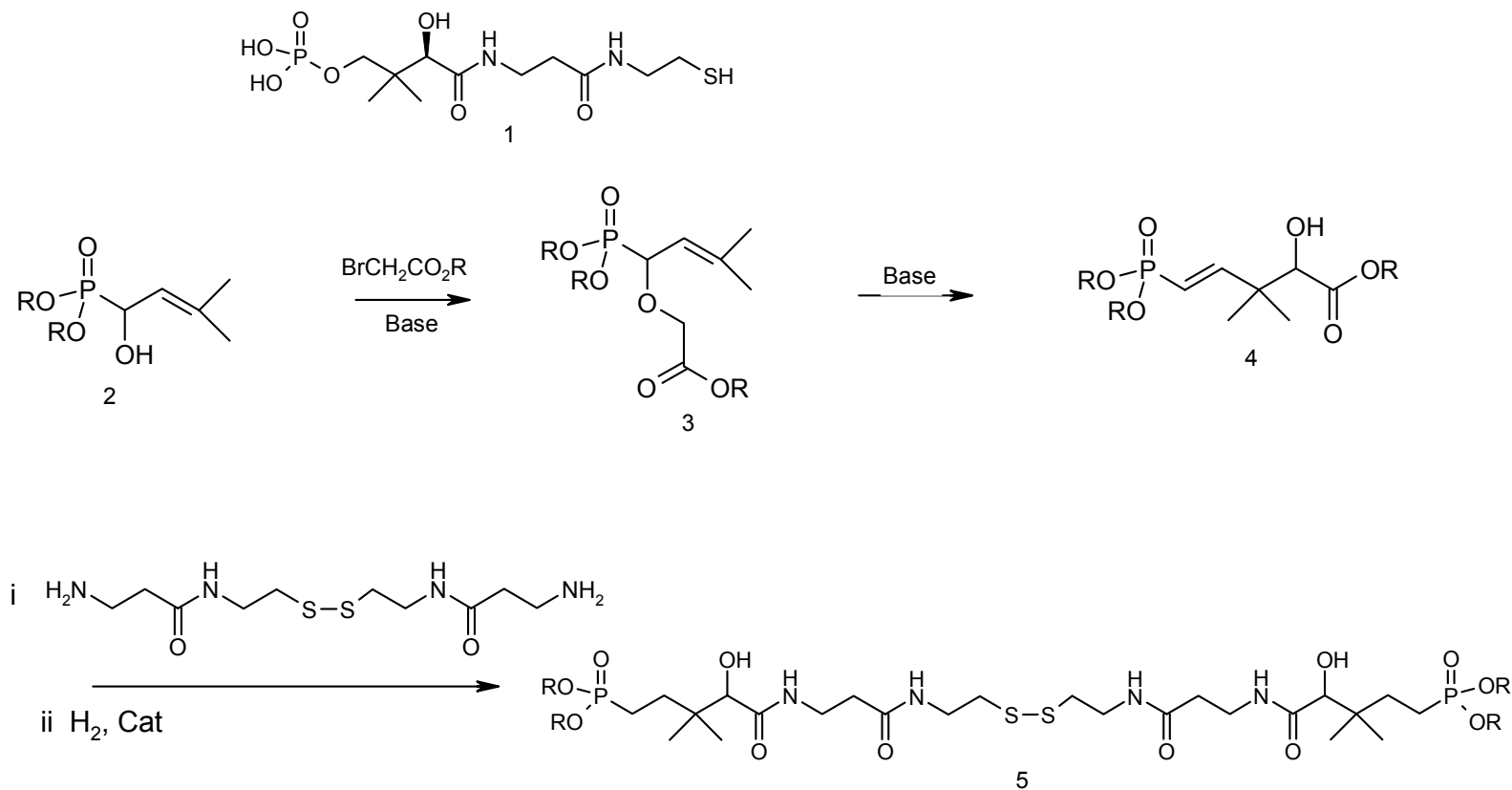
Case histories in the synthesis of organophosphorus compounds at Almac Sciences

In addition to phosphate salts and esters, compounds containing at least one P-C bond are marketed or in development as drugs for a wide range of indications. Activities include NMDA antagonists, metalloproteinase inhibitors, lipoprotein lipase activators, immunosuppressants, anti-viral and anti-bacterial agents. In many cases the rationale for these activities is the generation of a phosphate isostere. However, the synthesis of such compounds is frequently much more challenging than that of the parent phosphates.

Over the past 15 years Almac Sciences has built up extensive experience in this synthetic area and the following case histories illustrate a small part of this experience.

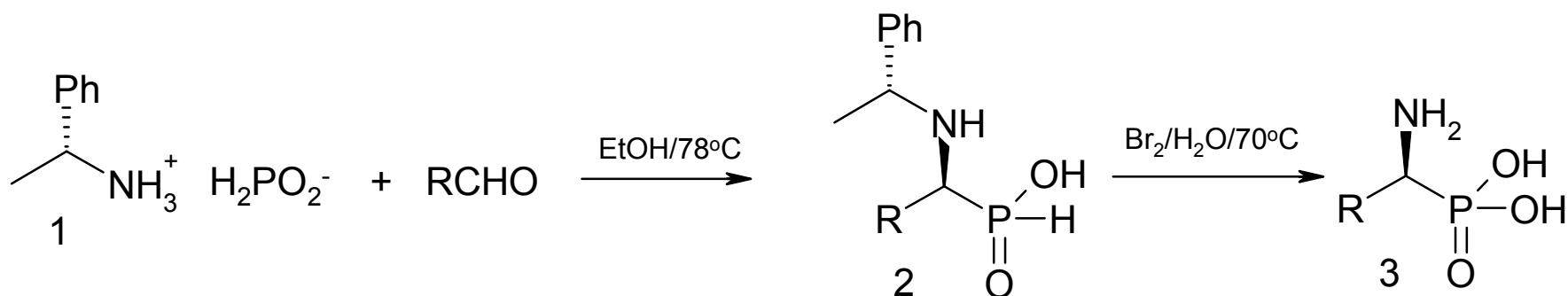
CASE HISTORY 1

Pantetheine phosphate (1) is an intermediate in a number of biological processes and, bound to adenosine via its biphosphate, constitutes the Coenzyme A structure. In view of the interest in phosphate isosteres, a synthesis of the phosphonate analogue of (1), or the corresponding disulfide (5), was required. Various synthetic approaches were unsuccessful, presumably due to the *neopentyl* function in (1), and racemic (5) was finally prepared by a novel Wittig Rearrangement of (3), followed by peptide coupling and hydrogenation.



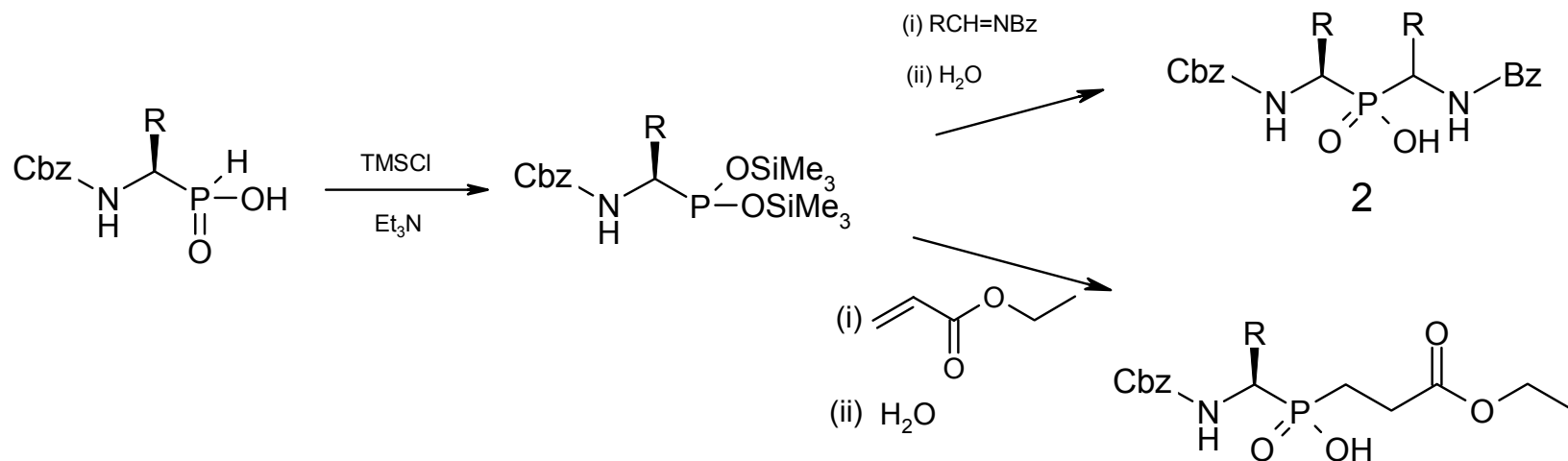
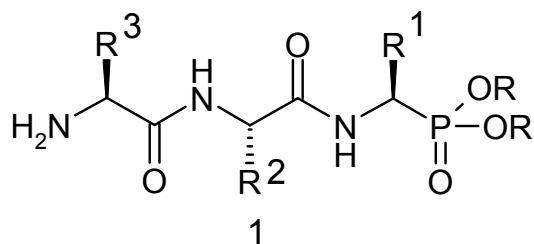
CASE HISTORY 2

α -Aminophosphonic acids (3), the phosphonic acid analogues of α -amino carboxylic acids, and derived compounds, have a wide range of biological activity. Almac Sciences has developed a highly convenient route to either single enantiomer of a wide range of compounds (3). The chiral hypophosphorous acid salt (1) reacts with a wide variety of aldehydes to give on cooling a precipitate of a single diastereomer (2), which in most cases requires minimal purification. Treatment of (2) with bromine water provides a simultaneous oxidation/deprotection sequence to give (3). E.e. values for (3) are 95-99% and overall yields from (1) are 25-45%.



CASE HISTORY 3

The selectivity and potency of enzyme- or receptor-binding of α -aminophosphonic acids and esters can be increased by coupling to the appropriate peptide sequence, e.g. (1). Such extension into the P₁ region has been extensively used. However, extension by peptide formation on the opposite side of the P-atom (into the P₂ region) has been less investigated. Two different synthetic approaches are shown in figure 1. Due to their C₂ symmetry, peptides derived from compound (2, R=PhCH₂) have been investigated as HIV proteinase inhibitors.²



CASE HISTORY 4

A client company interested in racemic switches awarded Almac Sciences a contract to design a synthesis of single enantiomer ifosfamide, an anti-cancer drug previously administered to patients in racemic form. Almac devised an asymmetric synthesis utilising camphorsulfonic acid as a chiral auxiliary in a highly diastereoselective reaction leading to a key intermediate.

