Synthesis of chiral phosphonic acid analogues to proteinogenic and non proteinogenic amino acids

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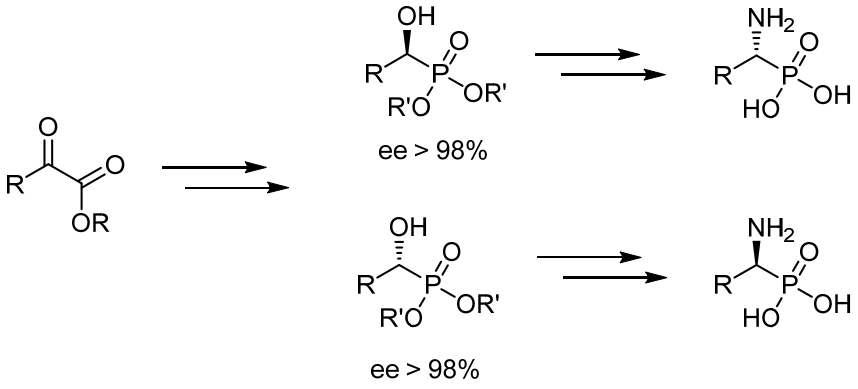
Replacing the planar carboxyl group in α-amino acids with a sterically more demanding tetrahedral phosphonic acid group, leads to the formation of highly potent inhibitors of different enzymatic transformations with properties ranging from anti-viral to anti-fungal agents.[1] Owing to the tetrahedral configuration at the phosphorous atom, α-aminophosphonic acids act as stable transition-state analogues of amide hydrolysis and formation.[2]



Scheme 1. Synthetic strategy to obtain α-aminophosphonic acids

Here we want to present a new access to a variety of phosphonic acid analogues to proteinogenic amino acids and some analogues thereof in excellent ee (> 98%). Starting from commercial available carboxylic acids, synthesis can be achieved in five steps (Scheme 1) involving acid activation, a ruthenium-catalyzed transfer hydrogenation,[3] a Mitsunobu reaction, followed by a reduction of the azido functionality and ultimately global deprotection.

[1] M. Sienczyk, J. Oleksyszyn, Curr. Med. Chem. 16, 1673 (2009).

[2] R. Rozenfeld, X. Iturrioz, M. Okada, B. Maigret, Biochemistry, 42, 14785 (2003).

[3] M.T. Corbett, J. S. Johnson, J. Am. Chem. Soc. 135, 594 (2013).