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An overview of stereoselective synthesis of α-aminophosphonic acids and derivatives

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Abbreviations: ABSA, 4-acetamidobenzenesulfonyl azide; Ac, acetyl; acac, acetylacetone; BINAP, 2,20-bis(diphenylphosphanyl)-1,10-binaphthyl; BINOL, 1,10-bi-2-naphthol; Bn, benzyl; Boc, *tert*-butoxycarbonyl; BtH, benzotriazole; BuLi, butyl lithium; CALB, *Candida antarctica* lipase B; CAN, ceric ammonium nitrate; Cbz, benzyloxycarbonyl; DAM, di-*p*-anisylmethyl; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DEAD, diethyl azodicarboxylate; DMAP, 4-dimethylaminopyridine; DME, 1,2-dimethoxyethane; DMF, *N*,*N*-dimethylformamide; DMSO, dimethylsulfoxide; DMTP, dimethyl thiophosphite; dr, diastereoisomeric ratio; ee, enantiomeric excess; HFIP, hexafluoroisopropyl alcohol; HIV, human immunodeficiency virus; LDA, lithium diisopropylamide; LHMDS, lithium bis(trimethylsilyl)amide; LPDE, lithium perchlorate diethyl eter; KHMDS, potasium bis(trimethylsilyl)amide; MBA, methylbenzylamine; MMPs, matrix metalloproteinases; MS, molecular sieves; Ms, methanesulfonyl (mesyl); NaHMDS, sodium bis(trimethylsilyl)amide; PEAphos, phosphineaminophosphine; PKAP, porcine kidney alkaline phosphatase; PMB, *p*-methoxybenzyl; PMP, *p*-methoxyphenyl; PTPases, protein tyrosine phosphatases; QN, quinidine; rt, room temperature; TADDOL, α,α,α′,α′-tetraphenyl-2,2-dimethyl-1,3-dioxolane-4,5-dimethanol; TBAF, tetra-*n*-butylammonium fluoride; TBDMSOTf, *tert*-butyldimethylsilyl triflate; TBS, *tert*-butyldimethylsilyl; Tf, trifluoromethanesulfonyl; TFA, trifluoroacetic acid; THF, tetrahydrofuran; TIPS, triisopropylsilyl; TMSBr, trimethylsilyl; Tol, tolyl; Troc, 2,2,2-trichloroethoxycarbonyl; Ts, *p*-toluenesulfonyl (tosyl).

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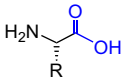
1. Introduction

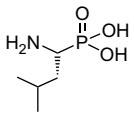
α-Aminoalkylphosphonic acids **1** are structurally analogous to α-amino acids **2**, obtained by isosteric substitution of the planar and less bulky carboxylic acid (CO_2H) by a tetrahedral phosphonic acid functionality (PO_3H_2). Several aminophosphonic, aminophosphinic, and aminophosphonous acids have been isolated from various natural sources, either as free amino acids or as constituents of more complex molecules.[1] Many natural and synthetic aminophosphonic acids, their phosphonate esters and short peptides incorporating this unit exhibit a variety of biological properties.[2] Their diverse applications include enzyme inhibitors[3] such as synthase,[4] HIV protease,[5] renin,[6] phosphatase activity,[7] PTPases,[8] and potent antibiotics,[9] as antibacterial agents,[10] antiviral,[11] antifungal,[12] herbicides,[13] and antitumor agents.[14] Their role for antibody generation is also well documented.[15] In addition, the incorporation of cyclic amino acids of medium ring size into key positions in peptide chains plays an important synthetic role, and constitutes the most prominent pathway to conformationally constrained peptidomimetics, a tool in modern drug discovery.[16]

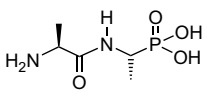

α-aminophosphonic acid, **1**


α-amino acid, **2**

In addition, α-aminophosphonic acids and their monoalkyl esters are also of interest in hydrometallurgy in order to extract metals[17] and in diagnostic medicine as screening agents, once complexed with lanthanides and actinides.[18,19]

It is well known that the biological activity of α-aminophosphonic acids and derivatives depends on the absolute configuration of the stereogenic α-carbon to phosphorous.[20] For example, (*R*)-phospholeucine **3** is a more potent inhibitor of leucine aminopeptidase than the *S* enantiomer,[21] and (*S*,*R*)-alafosfalin **4** shows higher antibacterial activity against both Gram-positive and Gram-negative microorganisms than the other three diastereoisomers.[22]


(*R*)-phospholeucine, **3**

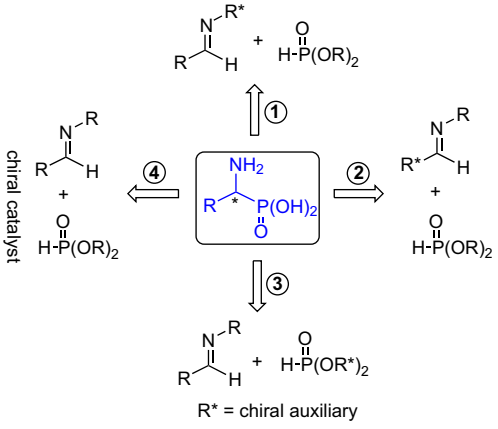

(*S*,*R*)-alafosfalin, **4**

In view of the different biological and chemical applications of the α-aminophosphonic acids and derivatives, in the last 35 years the development of suitable synthetic methodologies for their preparation in optically pure form has been a topic of great interest in several research groups. In this context, several protocols for efficient asymmetric synthesis of α-aminophosphonic acids and derivatives have emerged in recent years and several reviews have been published.[23] Now we would like to report herein an update of the stereoselective synthesis of α-aminophosphonic acids and their derivatives from 1998 to 2007. The principal synthetic strategies for α-aminophosphonic acids and their derivatives in an optically pure form can be classified into C–P bond formation using the Strecker-type process, C–C bond formation derived from diastereoselective alkylation of phosphonoglycine equivalents, C–N bond formation derived from diastereoselective electrophilic amination, catalytic hydrogenation of dehydroaminophosphonates, resolution, and chiral pool processes.

2. Stereoselective synthesis of α-aminophosphonic acids and derivatives

2.1. Stereoselective C–P bond formation

The nucleophilic addition of a dialkyl or diaryl phosphite to imines or oxoiminium derivatives, the Pudovik reaction,[24] is one of the most convenient methods for the preparation of α-aminophosphonates, key intermediates in the synthesis of α-aminophosphonic acids. In this context, the stereoselective synthesis of α-aminophosphonates can be carried out by four routes: (1) addition of alkyl phosphites to chiral imines readily obtained by condensation of aldehydes with chiral amines, (2) addition of alkyl phosphites to chiral imines readily obtained by condensation of chiral aldehydes with non-chiral amines, (3) addition of chiral alkyl phosphites to non-chiral imines, and (4) addition of non-chiral alkyl phosphites to non-chiral imines in the presence of a chiral catalyst (Scheme 1).



Scheme 1.

2.1.1. Addition of alkyl phosphites to imines derived from chiral amines

The first synthesis of enantiomerically pure α-aminophosphonic acids was described by Gilmore and McBride in 1972.[25] They reported that the addition of diethyl phosphite to the imine (*S*)-**5a**, readily obtained by condensation of benzaldehyde and (*S*)-α-methylbenzylamine [(*S*)-α-MBA], afforded the α-aminophosphonates (*R*,*S*)-**6a** and (*S*,*S*)-**7a** (X=O) with a 66:34