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Diastereoselective addition of diethyl difluoromethylphosphonate to enantiopure sulfinimines: synthesis of α,α-difluoro-β-aminophosphonates, phosphonic acids, and phosphonamidic acids

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Abstract—Addition of diethyl lithiodifluoromethylphosphonate to enantiomerically pure aromatic, heteroaromatic, and aliphatic aldehyde-derived sulfinimines afforded *N*-sulfinyl α,α-difluoro-β-aminophosphonates with generally good enantioselectivity and in high yield. The reaction with acetophenone-derived sulfinimine resulted in the formation of the addition product with high diastereoselectivity and in only moderate yield. A two-step deprotection involving treatment of diastereomerically pure *N*-sulfinyl α,α-difluoro-β-aminophosphonates with trifluoroacetic acid in EtOH followed by refluxing with 10 N HCl provided enantiopure α,α-difluoro-β-aminophosphonates and α,α-difluoro-β-aminophosphonic acids. The *N*-Cbz derivative of (*R*)-2-amino-1,1-difluoro-2-phenylethylphosphonate was a convenient starting point for the preparation of corresponding difluorophosphonate monoester, difluorophosphonic acid, and difluorophosphonamidic acid. At 21 °C difluorophosphonamidic acid was stable in aqueous solution at pH above 5.

1. Introduction

The importance of the aminophosphonic acids as structural analogs of amino carboxylic acids is well recognized.[1] Replacement of hydrogen atoms by fluorine atoms in amino carboxylic acids has been found to provide increased lipophilicity, resistance to oxidative and proteolytic degradation, changes in basicity or acidity of neighboring groups, conformational restrictions on the peptide chain, and modification of enzyme/substrate interaction,[2] therefore fluorinated aminophosphonic acids are of interest as biologically active compounds as well as building blocks for the preparation of peptidic materials with unique structural properties. Particular attention is devoted to aminophosphonic acids that contain a difluoromethylene group connected to a phosphorus atom in their role as hydrolytically stable phosphoamino acid mimetics in terms of both steric factors and pK_a value (Fig. 1).[3] Such mimetics have found application in the design of protein phosphatases, glycosyltransferases, and L-aspartate-β-semialdehyde dehydrogenase inhibitors.[4]

Current approaches to nonracemic difluoromethylene containing aminophosphonic acids have been largely based on the coupling of phosphonodifluoromethyl organometallic reagents with electrophilic substrates for the preparation of chain-extended adducts. The difluoromethylene analog of phosphoserine **1** was obtained in a multistep pathway using the reaction of dialkyl lithiodifluoromethylphosphonate with a primary triflate derived from (*R*)-isopropylideneglycerol as source of chirality.[5a] Owing to the inertness of dialkyl lithiodifluoromethylphosphonate toward secondary triflates, the condensation of dialkyl lithiodifluoromethylphosphonates with an ester, methyl Grignard addition, and radical deoxygenation of an intermediate tertiary alcohol sequence has been applied for the synthesis of difluoromethylene analogs of phosphothreonine **2** and *allo*-phosphothreonine **3** from L-glycerate and D-serine, respectively.[5b] Stereoselective synthesis of phosphothreonine **2** and *allo*-phosphothreonine **3** mimetics as well as their enantiomers was also achieved by applying a Cu(I)-mediated coupling reaction of [(diethoxyphosphinyl)difluoromethyl]zinc bromide and β-iodo-α,β-unsaturated ester followed by diastereoselective hydrogenation and amination using bornane-10,2-sultam as a chiral auxiliary.[5c] Nucleophilic opening of furanosylamines with diethyl lithiodifluoromethylphosphonate led to the formation of diastereomeric mixture of acyclic aminophosphonates with moderate diastereoselectivity. Separation of

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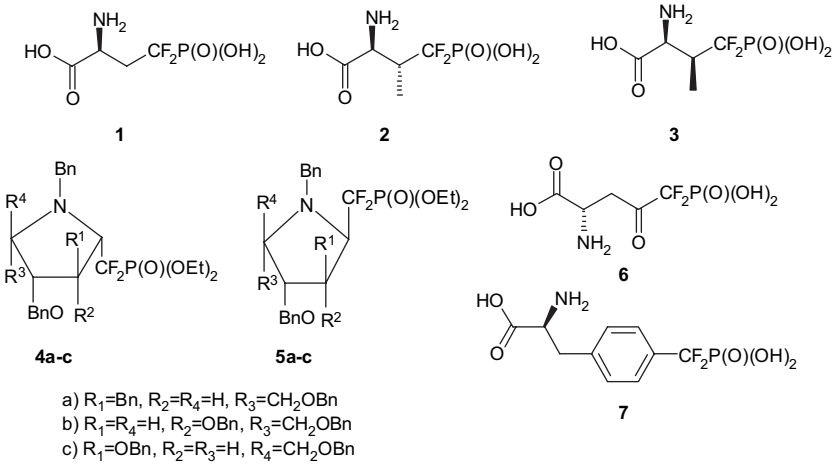


Figure 1.

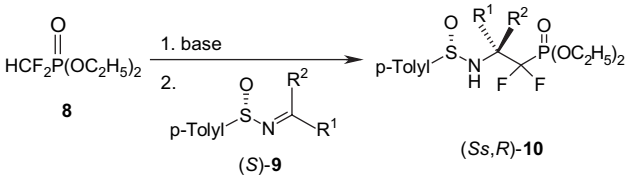
aminophosphonates followed by cyclization afforded azasugars **4** and **5** bearing difluoromethylenephosphonate group in good yields.[6]

Preparation of the difluoromethylene analog of β-aspartyl phosphate **6** was reported through addition of trimethylsilyl-difluoromethylphosphonate in the presence of a catalytic amount of TBAF to protected L-aspartate semialdehyde,[7a,b] or directly by Cu(I)-mediated coupling reaction of [(diethoxyphosphinyl)difluoromethyl]zinc bromide and protected aspartic acid chloride.[7c] Another methodology involving the use of benzylic α,α-difluorophosphonates in transition metal-catalyzed cross-coupling and alkylation reactions with L-alanine[8a] and glycine[8b] derivatives has been applied for the preparation of the difluoromethylene analog of phosphotyrosine **7**.

The nucleophilic addition of methyl- and chloromethylphosphonate carbanions to the C=N bond of enantiopure sulfinimines was found to be effective in the asymmetric syntheses of β-aminophosphonates and β-aminophosphonic acids due to exceptional characteristics of the chiral sulfinyl group.[9] The *N*-*p*-toluenesulfinyl substituent in imines provides high diastereofacial selectivity and activates the C=N bond for addition of different classes of nucleophiles.[10] Moreover a wide range of *N*-*p*-toluenesulfinylimines can be easily prepared by condensation of *p*-toluenesulfinamide, which is readily available in either configuration, with appropriate aldehydes and ketones according to the procedures reported by Davis et al.[11] Addition of a methylphosphonate carbanion to aldehyde-derived (*S*)-sulfinimines afforded *N*-sulfinyl β-aminophosphonates with the (*R*)-absolute configuration at the newly generated stereocenter of the major diastereomers. Stereoselectivity ranged between 66 and 82% de depending on the nature of the imine and the reaction conditions.[9a,b] The highest de was observed in the addition of dimethyl lithiomethylphosphonate to a benzaldehyde-derived sulfinimine in THF. In the analogous reactions of aldehyde-derived (*S*)-sulfinimines with chloromethylphosphonate carbanions, the corresponding α-chloro-β-amino adducts were isolated with the exclusive (*R*)-absolute configuration at the β-carbon atom.[9c] The induced configuration at the β-carbon atom in both cases was the opposite to that obtained in reaction of sulfinimines with organometallic reagents including enolates, Grignard reagents, metallo phosphite, and ethylaluminum cyanoisopropoxide.[10] Recently, in our preliminary communication, we reported that sulfinimines are also effective substrates for the addition of a difluoromethylphosphonate carbanion.[12] In this paper, we wish to report in full our studies concerning the addition reactions of difluoromethylphosphonate carbanion to sulfinimines with diverse steric and electronic properties. The effect of different methods for the preparation of the difluoromethylphosphonate carbanion on stereoselectivity is also discussed.

2. Results and discussion

Initially, we have found that addition of the phosphonodifluoromethyl carbanion, prepared by deprotonation of diethyl difluoromethylphosphonate **8** with LDA in THF at −78 °C, to enantiomerically pure sulfinimine (*S*)-**9a** proceeded smoothly within 1 h to afford, after mild acidic work-up, the corresponding *N*-sulfinyl α,α-difluoro-β-aminophosphonate **10a** with 90% de (Scheme 1, Table 1, entry 1). In spite of the relatively weak nucleophilicity and thermal instability of diethyl lithiodifluoromethylphosphonate,[13] *N*-sulfinyl α,α-difluoro-β-aminophosphonate **10a** was obtained in high combined yield. Direct crystallization of the crude reaction mixture from ether afforded the pure major diastereoisomer. Variation of the base (Table 1, entry 2) and the solvent (Table 1, entries 3 and 4) did not improve the selectivity of addition and resulted in incomplete conversion of the starting sulfinimine (*S*)-**9a**, as indicated by ^{1}H NMR and TLC analysis of crude products.



Scheme 1.