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Synthesis of the (α,α-Difluoroalkyl)phosphonate Analogue of Phosphoserine

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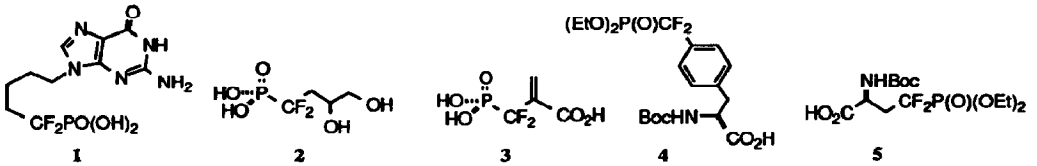
Abstract: The synthesis of the (α,α-difluoroalkyl)phosphonate analogue of L-phosphoserine, **5**, in a form appropriate for solid phase peptide synthesis, is reported. Two independent routes are described, starting from L-serine or (R)-isopropylideneglycerol. In each case, PCF_2-C bond formation is achieved by triflate displacement with diethyl lithiodifluoromethylphosphonate.

There is currently considerable interest in (α,α-difluoroalkyl)phosphonates as analogues of naturally occurring phosphates.[1] Data in the literature support the notion that phosphate mimics of this class do indeed bind to enzymatic phosphate binding sites. For example, **1** is a potent bisubstrate analogue inhibitor of purine nucleoside phosphorylase.[2] **2** is a substrate for glycerol 3-phosphate dehydrogenase,[3] and **3** is an irreversible inhibitor of EPSP synthase.[4] More recently, the (α,α-difluoroalkyl)phosphonate analogue of phosphotyrosine **4**, was synthesized by two groups[5,6] and has been incorporated into peptides.[5a]

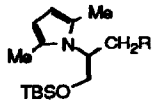


1 **2** **3** **4** **5**

The members of the protein phosphoserine/threonine phosphatase class of enzymes, PP1, PP2A, PP2B and PP2C, are important mediators of signal transduction events.[7] For example, PP2B (calcineurin) is the common target of the immunosuppressants cyclosporin and FK-506.[8] Enzymes in this family are known to dephosphorylate peptides, in addition to their usual protein substrates.[9] Therefore, peptides containing an effective, but hydrolytically stable, phosphoserine mimic, are potential inhibitors of this class of enzymes. We report herein the synthesis of **5**, a phosphoserine mimic bearing protecting groups amenable to automated solid phase peptide synthesis.[5a]

Recently, we discovered that (α,α-difluoroalkyl)phosphonates may be conveniently synthesized via the direct displacement of primary alkyl triflates by diethyl lithiodifluoromethylphosphonate (**6**).[10a] We sought to apply this methodology to the synthesis of **5**. Initially, our approach was to construct a D- or L-serinol derived triflate and to examine its triflate displacement chemistry. We were pleased to find that triflates **7a-9a** could all be synthesized from the corresponding alcohols and were stable to silica gel chromatography. Furthermore, **7a-9a** do undergo displacement with **6** in 35-70% yields to provide the corresponding (α,α-

difluoroalkyl)phosphonates, **7b**-**9b**. Unfortunately, in all three cases, attempts to remove the nitrogen protecting group [2,5-dimethylpyrrole (**7b**),[11] N-tosyl (**8b**),[12] and N-benzyl (**9b**)[13]] were unsuccessful.



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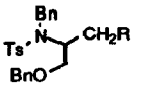

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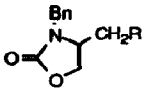
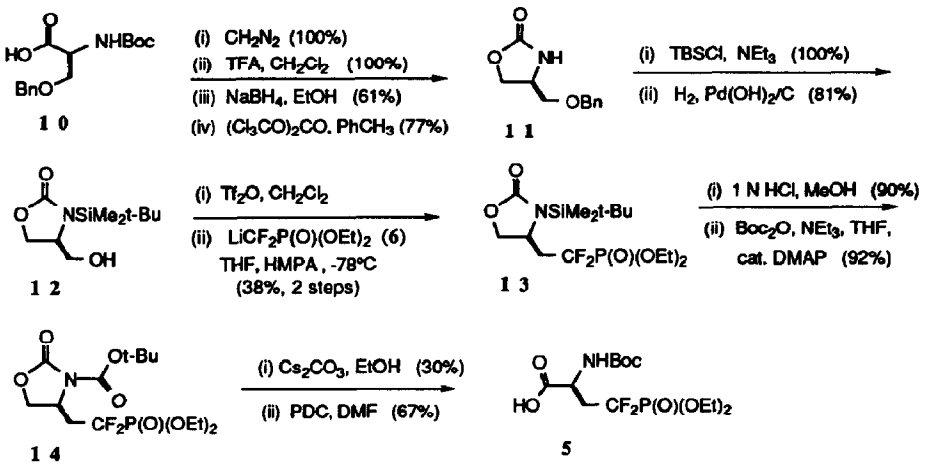


9

a R = OTf
b R = $CF_2P(O)(OEt)_2$

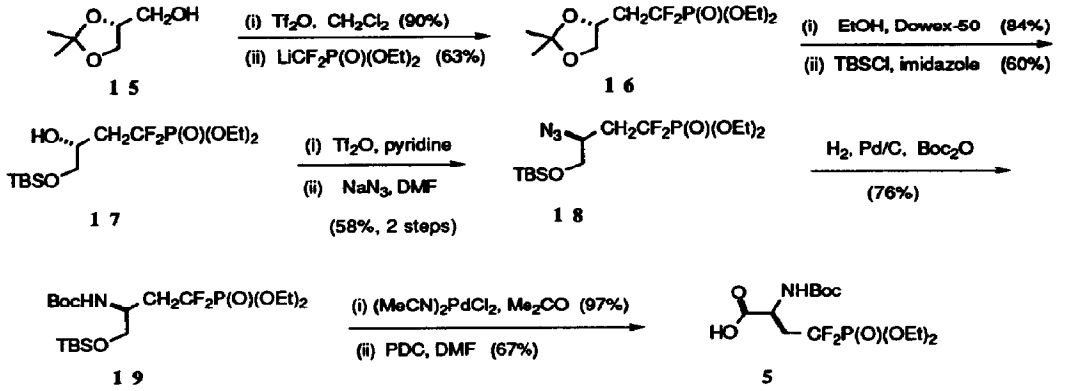
This problem was solved by using a readily removable *tert*-butyldimethylsilyl protecting group[14] for the carbamate nitrogen (see Scheme 1). Thus, starting from the known L-serine derivative **10**,[15] esterification, Boc removal and ester reduction ($NaBH_4$) proceed smoothly. The resulting (R)-*O*-benzylserinol is transformed into the corresponding oxazolidinone **11** using triphosgene as a convenient phosgene source.[16] N-Silylation[17] and benzyl ether hydrogenolysis yield alcohol **12**. The corresponding triflate, being quite labile, is generated, and then immediately subjected to our usual displacement conditions[10] to provide (α,α-difluoroalkyl)phosphonate **13**. In this case, N-deprotection is facile (13:1 MeOH/1N HCl rt, 12 h).[14] Installation of the requisite N-Boc protecting group and oxazolidinone ring-opening are accomplished by a modification (EtOH as solvent) of the procedure reported by Ishizuka and Kunieda, in quite modest yield.[18] Finally, four-electron oxidation under the Corey-Schmidt conditions (6 equivalents of PDC)[19] yields the desired, protected phosphoserine analog **5**.[20]



Scheme 1

Parallel to these studies, we explored a complementary route to **5** which begins from the readily available chiral building block **15**.[21] Strategically, this approach differs from the previous route, in that here the α-amino group is installed late in the synthesis, and in this way the N-protecting group issue in circumvented. Triflate synthesis and displacement[10] proceed cleanly to give phosphonate **16**.[22] Acetonide cleavage is achieved with ethanol, containing Dowex-50 (rt, 2 days). Selective silylation of the primary hydroxyl then gives **17**. Formation of the secondary triflate is followed by displacement with sodium azide (5 equiv. NaN_3, rt, 2 h).

Azide hydrogenolysis in the presence of Boc_2O[23] yields the necessary Boc-protected aminophosphonate **19**, directly. Chemoselective cleavage of the TBS ether, in the presence of the N-Boc and diethyl difluoromethylphosphonate functional groups, is best achieved using the mildly Lewis acidic conditions described by Lipshutz.[24] Oxidation, as before, yields the title compound.



15 16 17 18 19 5

Scheme 2

In summary, we have described the synthesis of L-phosphoserine analog **5**, by two independent routes. Both emanate from readily available building blocks out of the chiral pool. In each case, the critical PCF_2-C bond is fashioned by the direct displacement of a primary triflate with **6**.[10] The synthesis of **5** from (R)-isopropylideneglycerol is clearly the more efficient procedure, at this time. Studies on the effectiveness of **5** as a hydrolytically stable phosphoserine mimic will be reported in due course.

Acknowledgment.

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20. For **5**: ^{1}H NMR (360 MHz, $CDCl_3$): δ 1.34-1.38 (t, J = 7 Hz, 6 H), 1.42 (s, 9 H), 2.56-2.75 (m, 2 H), 4.22-4.30 (app quintet, J = 7 Hz, 4 H), 4.55-4.59 (m, 1 H), 5.37-5.40 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 16.27, 16.30 (2 X $OCH_2\underline{C}H_3$); 28.3 ($OC\underline{Me}_3$); 35.3-35.4 (br, $\underline{C}H_2CF_2$); 48.4 (C_α); 65.0-65.1 (br, 2 X $O\underline{C}H_2CH_3$); 80.5 ($O\underline{C}Me_3$); 155.5 ($Me_3CO\underline{C}$=O); 173.0 ($\underline{C}O_2H$); HRMS (FAB, 3-NOBA/Na_2CO_3) calcd for $C_{13}H_{24}F_2NO_7PNa$ $(M+Na)^+$ 398.1156, obsd 398.1155; $[\alpha]^{25}_D$ -10.8° (*c* 2.20, MeOH). **5** obtained from (R)-isopropylideneglycerol is ≥ 96% ee as judged by ^{1}H NMR [A single Mosher ester is seen (500 MHz, $CDCl_3$) following the sequence: (a) CH_2N_2; (b) HCl, EtOAc; (c) (S)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride].
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