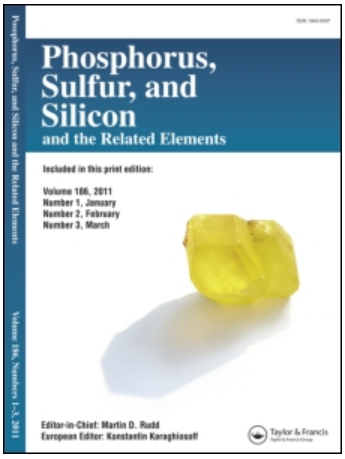

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ISOSTERES OF NATURAL PHOSPHATES. METHYLENE AND HYDROXYMETHYLENE ANALOGUES OF TYROSINE *O*-PHOSPHATE

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The ability of phosphonic acid analogues isosteric with natural phosphate esters to serve as inhibitors of enzymatic phosphate hydrolysis has been documented in a wide variety of systems.[1] The use of such an analogue in place of the natural phosphate ester provides a functionality which the enzyme may not be able to distinguish from the natural ester, but which is incapable of being hydrolyzed. In some instances the use of hydroxymethylene analogues has resulted in a greater degree of recognition, and resultant inhibition of hydrolytic activity, than the simple methylene analogues.[2] On this basis, the methylene and hydroxymethylene analogues of tyrosine *O*-phosphate appear to be reasonable candidates to serve as inhibitors for phosphoprotein phosphatases and alkaline phosphatase, and as probes for biological mechanisms.

The isosteric methylene analogue of tyrosine *O*-phosphate has been synthesized beginning with an Arbuzov reaction performed on *p*-bis(bromomethyl)benzene using triethyl phosphite. The isolated yield of the desired monosubstitution product was optimized at 48.5% by the use of a two-fold amount of the dibromide and controlling the heating at 120 for 3 hours. (Under these conditions the yield of the disubstitution diphosphonate by-product was limited to 11.8%.) The remaining bromide was then displaced using diethyl acetamidomalonate anion by a standard procedure,[3] and the target isosteric analogue of tyrosine *O*-phosphate was isolated by acidic hydrolysis and the accompanying decarboxylation.

Initial attempts to generate the hydroxymethylene analogue *via* a standard Abramov reaction of diethyl phosphite with *p*-(bromomethyl)benzaldehyde failed under all conditions attempted.[4] An alternative approach involved the direct introduction of a hydroxyl group at the site adjacent to the phosphonic ester function of the material previously described, the phosphonic ester upon which displacement of the remaining bromide using diethyl acetamidomalonate anion had been performed. This was accomplished using a modification of a procedure commonly used for allylic oxidation,[5] the benzylic site adjacent to the phosphonic ester functionality exhibiting behavior analogous to that of an allylic site. Treatment of this phosphonic ester with a catalytic portion of selenium dioxide and an excess of the regenerating agent, *t*-butylhydroperoxide, standard conditions for allylic oxidation, introduced with reasonable efficiency the hydroxyl group on carbon adjacent to phosphorus. Unmasking and subsequent decarboxylation of this material to generate the desired hydroxymethylenephosphonate analogue of tyrosine *O*-phosphate was again accomplished under acidic conditions.

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