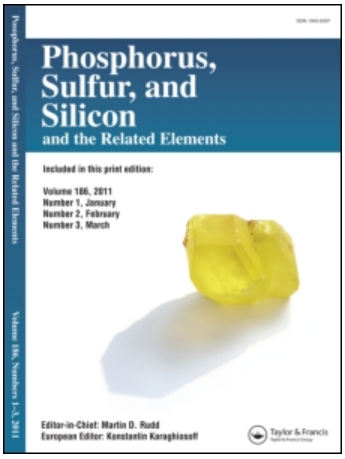

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Synthesis of Phosphonic Acids Related to the Antibiotic Fosmidomycin from Allylic α- and γ-Hydroxyphosphonates

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SYNTHESIS OF PHOSPHONIC ACIDS RELATED TO THE ANTIBIOTIC FOSMIDOMYCIN FROM ALLYLIC α- AND γ-HYDROXYPHOSPHONATES

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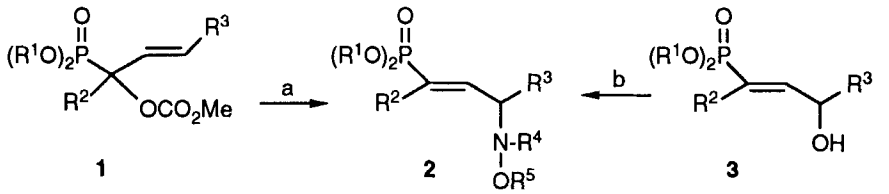
Fosmidomycin is the most active compound of a group of natural phosphonic acid antibiotics bearing a unique hydroxamic acid functionality in the γ-position [1]. We present here two efficient and novel routes to precursors and analogues of these compounds.

Pd(0) catalyzed amination of dialkyl (1-methoxycarbonyloxy-2-alkenyl)phosphonates **1** (R^2 = H) with the hydroxylamine derivatives BocNHOBoc, MocNHOMoc, BocNHOBn, and AcNHOAc proceeds regiospecifically and with high (*E*)-stereoselectivity to give the protected (3-hydroxyamino-1-alkenyl)phosphonates **2** in good to excellent yields.[2] Alternatively compounds **2** (R^2 = H or alkyl) can be prepared with yields of 84-96% by N-alkylation of BocNHOBoc and MocNHOMoc with allylic γ-hydroxyphosphonates **3** under Mitsunobu conditions. Poor results have been obtained using BocNHOBzl or AcNHOAc as nucleophiles.



a: $Pd(PPh_3)_4$ / R^4NHOR^5 / THF; b: PPh_3 / DEAD / R^4NHOR^5 / toluene

Compounds **2** are easily transformed to precursors and analogues of the natural phosphonic acid antibiotics.

1. K. HEMMI, H. TAKENO, M. HASHIMOTO and T. KAMIYA, *Chem. Pharm. Bull.* **30**, 111 (1983), and references therein.
2. For preliminary results with propenylphosphonates (**1**: R^2, R^3=H) and for leading references see E. ÖHLER and S. KANZLER, *Synthesis* **1995**, 539.