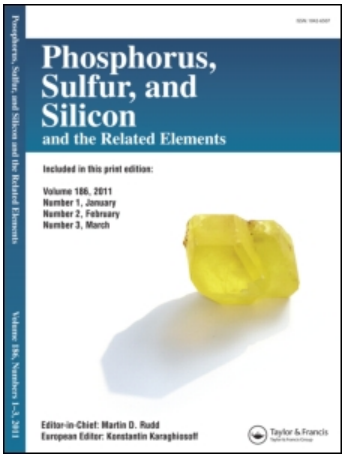

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Synthesis of Acyclic γ-Amino Mono-or Bisphosphonates Via Pentacovalent Oxaphosphorane Chemistry

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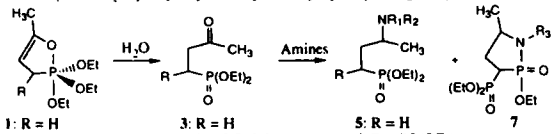
Geminal bisphosphonic acids and their salts have long been known to be effective inhibitors of bone resorption and mineralization, which are common symptoms of diseases such as osteoporosis and Paget's disease [1]. Utilizing pentacovalent oxaphosphorane chemistry, a variety of acyclic γ-amino mono- and bisphosphonates can be efficiently synthesized. Hydrolysis of the P(V) oxaphospholenes, **1** and **2**, followed by reductive amination [2] of the resulting ketones, leads directly to the γ-amino mono- and bisphosphonates, **5** and **6**. The reaction of secondary amines with ketones **3** and **4** are slow and low yielding. In reactions with ketones containing a bisphosphonate, the primary product is the cyclic bisphosphonates, **7**. Reactions of primary amines with ketones containing a mono-phosphonate are generally better, giving higher yields of the desired product in a shorter reaction time. Syntheses of compounds, **9-11** were also performed (R_1 = H, R_2 = pentyl, cyclohexyl, benzyl, phenyl) in good yields.

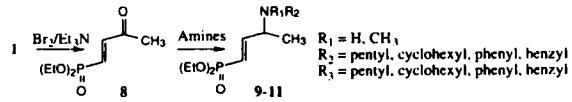


1: R = H
2: R = PO(OEt)$_2$

3: R = H
4: R = PO(OEt)$_2$

5: R = H
6: R = PO(OEt)$_2$

7



8

9-11

R_1 = H, CH_3
R_2 = pentyl, cyclohexyl, phenyl, henzyl
R_3 = pentyl, cyclohexyl, phenyl, henzyl

Conversion of the resulting secondary amine to the tertiary amine, followed by introduction of the second phosphonate using a base and diethyl chlorophosphate, has led to the synthesis of new γ-amino bisphosphonates. Research is underway to develop optimal conditions in the synthesis of these desired γ-amino mono- and bisphosphonates. Biological activity of the synthetic γ-amino bisphosphonate will be investigated and reported in the future.

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