

## The Preparation of New Phosphorus-Centered Functional Groups for Modified Oligonucleotides and Other Natural Phosphates

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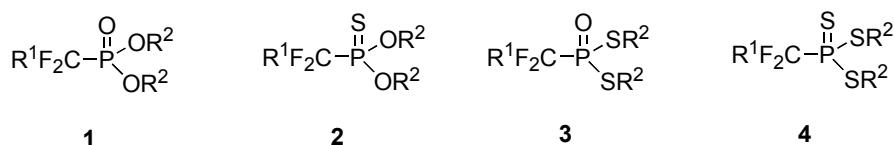
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$\alpha,\alpha$ -Difluorophosphonates have gone a long way since their introduction slightly more than two decades ago. Indeed, physicochemical studies have since then provided some rationale for the isosteric behavior of the above function to the phosphate group, and numerous applications have flourished. Two methodologies have been developed and used to either introduce or construct the requisite functional group in more complex structures. We will first report on the stabilities and reactivities of the sulfur analogues of **1** ( $R^1 = Li$ ), i. e. the corresponding phosphonothioates **2** ( $R^1 = Li$ ), -dithioates **3** ( $R^1 = Li$ ) and -trithioates **4** ( $R^1 = Li$ ). Interconversion methods have been carried out, thus allowing the efficient preparation of  $\alpha,\alpha$ -difluorophosphonates **1** ( $R^1 = alkyl$ ) from  $\alpha,\alpha$ -difluorophosphonothioates **2** ( $R^1 = alkyl$ ), and *vice-versa*.



The usefulness of reagent **2** ( $R^1 = Li$ ) will be demonstrated through the preparation of analogues of nucleoside-3'-phosphates **5**. Alternatively, a second, successful approach relying on the addition of phosphorus-centered radicals onto *gem*-difluoroalkenes was studied and will be presented. Thus both methodologies allow for the first time the stereoselective preparation of modified nucleotides featuring phosphonodifluoromethyl and phosphonothiodifluoromethyl units in position 3' of the ribose. Additionally, the radical approach also provides an entry into the difluorophosphinyl functional group. Implications of these methodologies in the field of both antisense oligonucleotides and cyclitol phosphates (e. g. **6**) will be discussed.

