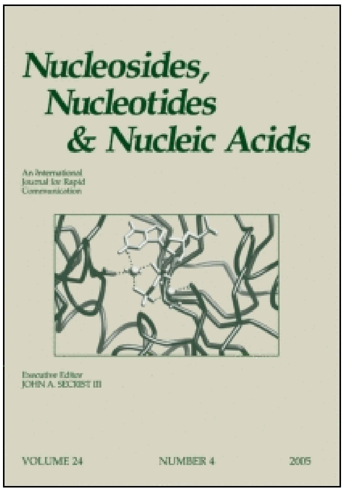

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SYNTHESIS AND PHOTOCHEMICAL BEHAVIOUR OF A T-T DIMER CONTAINING AN AMIDE LINKAGE

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ABSTRACT

A T-T dimer characterized by an amide linkage to replace the phosphodiester backbone has been synthesized using a modified radical strategy. The new synthetic approach makes use of a thymidin-3′-yl phosphorodithioate derivative as a precursor of 3′-allyl-3′-deoxythymidine. Standard chemical transformations of this derivative led to the desired T-T dimer incorporating an amide bond. The latter was irradiated with 254 nm wavelength light to yield mainly cyclobutane and [6–4] photoadducts.

During the last few years "amide-3" linkages have been sucessfully proposed as surrogates of phosphodiester bonds (1). Such neutral and nuclease resistant amide motifs have found applications in the antisense (2) and ribozyme fields (3). Indeed, the introduction of such bonds in oligonucleotides might help to increase their relevant biological properties and be useful for the design of various biological experiments.

Herein, we proposed to expand the scope of "amide-3" linkage applications to the domain of UV induced DNA lesion studies (Fig. 1). For this purpose, a modified radical based synthesis of an amide containing T-T dimer analogue was established starting from the thymidin-3′-yl phosphorodithioate derivative

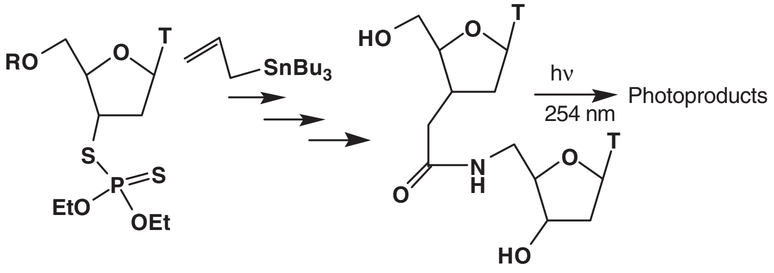
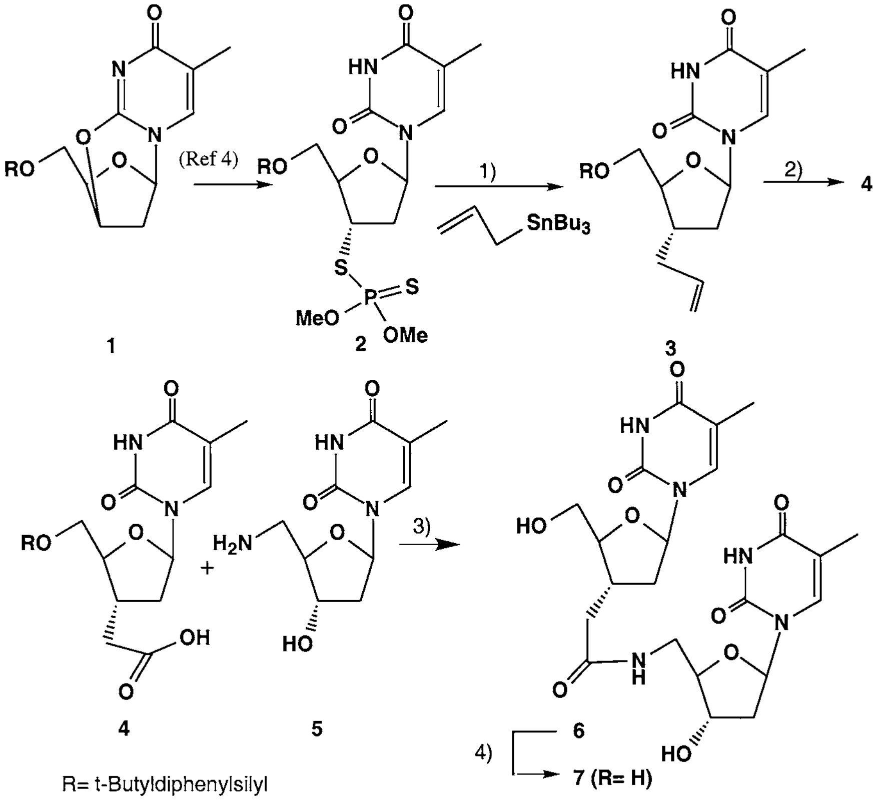
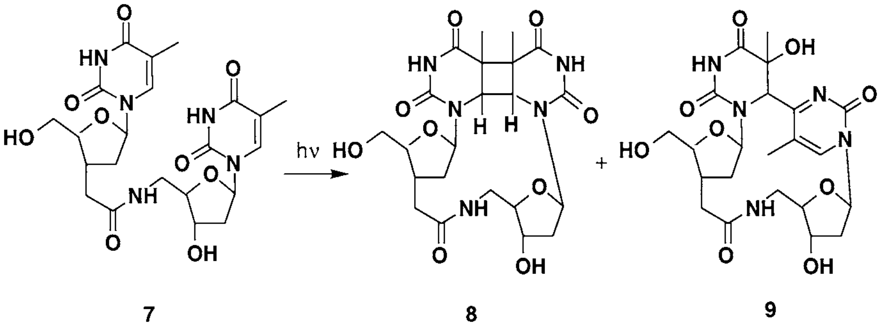


Figure 1.

2 which is readily obtained by ring opening of the cyclic thymidine derivative **1** (4). Treatment of compound **2** with allyltributylstannane in refluxing benzene in the presence of AIBN provided the 3′-allylthymidine derivative **3** in good yield together with a minor amount of the corresponding 3′-deoxythymidine derivative. Using known chemical transformations (1) compound **3** served to prepare the acetic



Scheme 1. Reaction conditions: 1) AIBN, benzene, reflux, 12 h, 72%; 2) i) OsO_4, $NaIO_4$, dioxane:H_2O (3:1), 18 h; ii) $NaOCL_2$, tBuOH:THF:H_2O, 5 h, 45% (2 steps); 3) HBTU, HOBT, THF:MeCN, rt, 2 h, 75%; 4) TBAF, AcOH, THF, 64%.



7 8 9

Scheme 2.

acid derivative **4** which was combined with 5′-amino-5′-deoxythymidine **5** upon *O*-benzotriazol-1-yl-tetramethyluronium hexafluorophosphate (HBTU) activation to give the 5′-protected T-T dimer **6** in good yield. Final deprotection of this compound to provide **7** was efficiently accomplished by a treatment of **6** with tetrabutylammonium fluoride (TBAF) in the presence of one equivalent of acetic acid.

When compound **7** was irradiated in water solution using 254 nm light, it exhibited a behaviour closely reminiscent of that of its phosphate analogue TpT (5). Indeed reverse phase HPLC purification (water/acetonitrile, 250 × 10 cm 5 μm Hypersil HS C18 column, Waters system) of the crude irradiation mixture provided a cyclobutane cycloadduct **8** together with the [6–4] photoproduct **9**, the latter in preparative yield (Scheme 2). The proposed structures of the photoproducts were in complete agreement with their NMR data.

In conclusion we have designed a new route to phosphate dimer analogues featuring an amide bond instead of a phosphodiester linkage. Irradiation of the corresponding T-T derivative **7** led to the neutral analogues of the photoproducts which are formed at TpT sites of DNA. Hopefully, these new derivatives will find useful applications in a biological context.

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