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Incorporation of the bioactive moiety of leinamycin into thymidine

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Dedicated to Professor Ferenc Sztaricskai, on the occasion of his 70th birthday

Abstract—A simple synthesis of 1,2-dithiolan-3-ones from α,β-unsaturated thiophenyl esters has been elaborated. With the aim of introducing the biologically active 1,2-dithiolan-3-one-1-oxide moiety of leinamycin into a nucleoside, the method was successfully applied to thymidine-5′-aldehyde.

Leinamycin was isolated[1] from the fermentation broth of a *Streptomyces* species, and besides antibacterial activity, possesses anticancer activity on experimental tumors in mice. It was shown that leinamycin inhibits the synthesis of bacterial DNA and in vitro causes single-strand cleavage of supercoiled double-helical plasmid DNA.[2] The compound is built up[3] from a thiazole-containing 18-membered lactam to which a spiro-linked 1,2-dithiolan-3-one-1-oxide moiety is attached. This sulfur-containing heterocycle, hitherto unknown in natural compounds, was recognized as the 'warhead' responsible[4] for the DNA-cleaving effect of the antibiotic. In addition to the total synthesis[5] of leinamycin, the preparation of various dithiolanone type compounds has also been studied[6–10] in order to develop simple analogues of the parent antibiotic (Fig. 1).

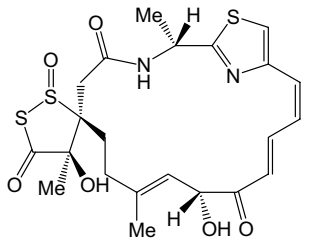

Figure 1. Structure of leinamycin.

As Hara et al.[2] have suggested that 'a combination of the 1,3-dioxo-1,2-dithiolane DNA-cleaving moiety with a DNA recognition element might provide a novel approach for the design of new cancer chemotherapeutic agents' we thought that this principle might be realized by the incorporation of the foregoing, small heterocycle into a nucleoside molecule. Although synthesis of the 1,2-dithiolan-3-one ring has been accomplished, we intended to develop an alternative, new, simple methodology allowing incorporation of this moiety into nucleosides.

Firstly, in a model reaction, 3-phenylpropionaldehyde (**1**) was transformed by a Wittig reaction into the α,β-unsaturated active ester **2**, which was then treated with hydrogen sulfide in dioxane in the presence of triethylamine. Conjugate addition and nucleophilic substitution by the SH^- ion resulted in the formation of a mercaptothio acid **3**, which was oxidized, without isolation, with iodine into the disulfide, that is, the dithiolanone **4** (Scheme 1).

By applying this strategy to *aldehydo*-D-arabinose[11] (**5**), compound **7** was obtained as a diastereoisomeric mixture (Scheme 2).

Our goal was to incorporate the dithiolanone moiety into uridine. Thus, a Wittig reaction of the aldehyde **9**, prepared[12] from isopropylidene uridine (**8**), with phenylthiocarbonylmethylenetriphenylphosphorane gave the thioester **10**, (Scheme 3) but subsequent thiolysis and oxidation led to a complex reaction mixture.

Keywords: Leinamycin; DNA cleaving; Wittig reaction; Conjugate addition; Ring closure.

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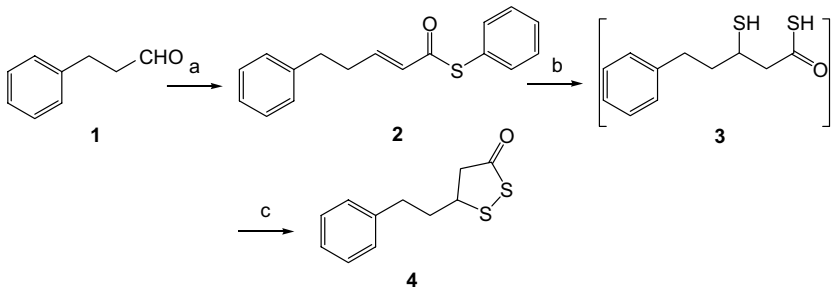
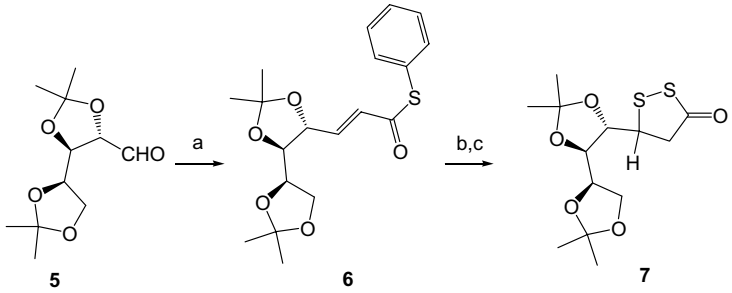
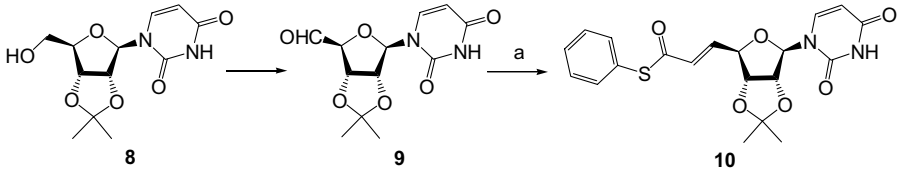


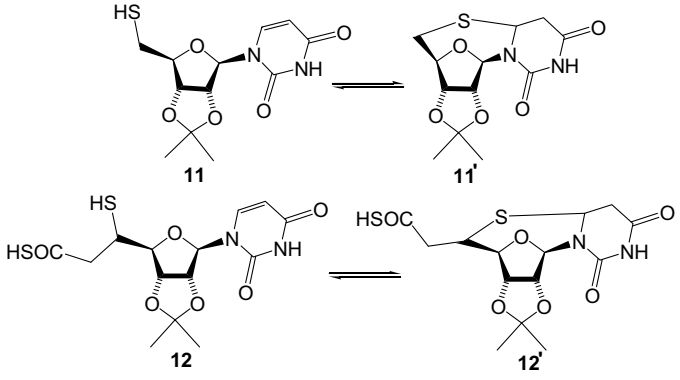
Scheme 1. Reagents and conditions: (a) $(C_6H_5)_3PCHCOSC_6H_5$, toluene, rt, 48 h, 80%; (b) Et_3N, H_2S, 1,4-dioxane, rt, 2 h; (c) Et_3N, I_2, 1,4-dioxane, rt, 1 h, 60% (b + c).



Scheme 2. Reagents and conditions: (a) $(C_6H_5)_3PCHCOSC_6H_5$, toluene, rt, 48 h, 78%; (b) Et_3N, H_2S, 1,4-dioxane, rt, 2 h; (c) Et_3N, I_2, 1,4-dioxane, rt, 1 h, 63% (b + c).



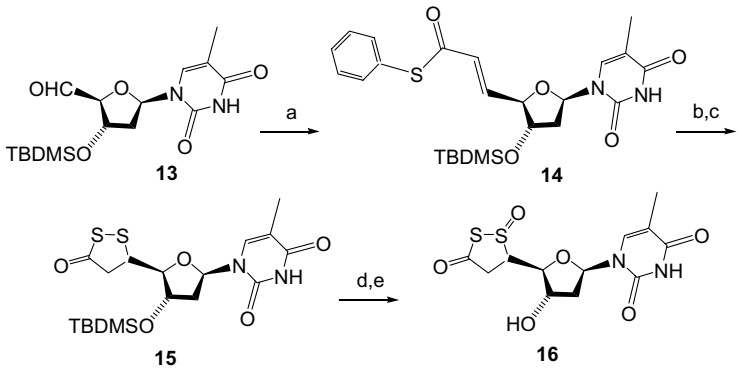
Scheme 3. Reagents and conditions: (a) $(C_6H_5)_3PCHCOSC_6H_5$, toluene, rt, 48 h, 71%.



Scheme 4.

When oxidizing the 5′-thio derivative **11** of uridine, Goodman and co-workers[13] observed the formation of compound **11′** (Scheme 4). In our case the presumed intermediate **12** might also be in equilibrium with the adduct **12′**. Goodman explained the transformation **11**→**11′** in terms of the strained conformation of the sugar carrying the dioxolane ring, which places the SH group at an appropriate distance to the double bond to permit addition.

We supposed that in the absence of the dioxolane ring the intramolecular addition would be inhibited. There-



Scheme 5. Reagents and conditions: (a) $(C_6H_5)_3PCHCOSC_6H_5$, toluene, rt, 48 h, 74%; (b) Et_3N, H_2S, 1,4-dioxane, rt, 2 h; (c) $K_3[Fe(CN)_6]$, 1,4-dioxane, rt, 16 h, 42% (b + c); (d) *p*-TsOH, 1,4-dioxane–H_2O = 9:1, rt, 18 h, 47%; (e) dimethyl dioxirane, acetone, rt, 2 h, 96%.

fore, the thymidine derivative[14] **13** was converted into compound **14** by means of a conventional Wittig reaction with phenylthiocarbonylmethylenetriphenylphosphorane. After treatment with hydrogen sulfide, oxidation of the intermediate with iodine gave a complex mixture of products. In contrast, when the oxidation was accomplished with potassium hexacyanoferrate(III) the expected dithiolanone **15** could be isolated (Scheme 5). Desilylation under acidic conditions, followed by oxidation[8] with dimethyl dioxirane then furnished the desired substance **16**,[15] biological investigation of which are in progress.

Acknowledgements

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