Synthesis and Cytotoxicity of Leinamycin Antibiotic Analogues

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A simple synthesis of 1,2-dithiolan-3-ones from α,β-unsaturated thiophenyl esters is reported. Introduction of the biologically active 1,2-dithiolan-3-one-1-oxide moiety of leinamycin into *aldehydo*-D-arabinose **11**, the uridine derivative **16**, and the deoxythymidine **21** was established. An extended bioactive part of leinamycin carrying a carbon−carbon triple bond was also synthesized. All of these analogues of leinamycin showed cytotoxic activity against HeLa3 tumor cells. Interestingly, the lipophilic, silyl group-containing derivatives proved to be more active than the hydrophilic counterparts.

Introduction

Leinamycin[1] is a macrolactam-type antibiotic isolated[1,2] from the fermentation broth of *Streptomyces atroolivaceus* in 1989. Early biological studies have shown that leinamycin is an antibacterial antibiotic which cleaves single-strand plasmid DNA,[3] and for this effect the presence of a thiol (i.e. 2-mercaptoethanol, dithiothreitol, glutathione, and propanethiol) is essential. Following structural elucidation,[2,4] the synthesis of the antibiotic was also accomplished.[5,6]

To the 18-membered lactam ring of leinamycin is attached a 1,2-dithiolan-3-one-*S*-oxide ring (Figure 1), which is responsible for DNA-splitting, and till now, such a ring-system has not been found as a constituent of a natural product. The biological effect is manifested in a cytotoxic antitumor activity;[3] therefore, this topic is an intensively studied field.

By chemical transformations, Japanese authors[7−9] succeeded in preparing semisynthetic derivatives of leinamycin possessing stronger cytotoxic effect than that of the parent antibiotic.

A mechanism for DNA cleavage given[10] by the researchers of the Kyowa Hakko Kogyo (Scheme 1) assumes an episulfonium intermediate formed from the dithiolanone-*S*-oxide by the action of the trigger thiol that splits a guanyl radical from the guanosine portion of the DNA to result in chain cleavage. Besides this mode of action, on the basis of DNA alkylation, Gates et al.[9,11,12,13] also suggested a thiol-triggered, but oxidative, DNA splitting, with a major role of oxygen radicals derived from intermediate **C** (Scheme 1). The Gates group also observed the DNA-splitting properties of simple dithiolanone-*S*-oxide model compounds. However, the problem appears to be more complicated since Gates et al. have discovered[14] an additional way for the alkylative DNA cleavage of leinamycin that is independent of thiols, and water serves as the trigger. Although the DNA splitting of several simple 1,2-dithiolan-3-one-*S*-oxides have been demonstrated, only one report[15] deals with their biological activity, and the investigated compounds were found to be slightly cytostatic or were inactive.

The aim of the present work was to incorporate the 1,2-dithiolanon-*S*-oxide molecular fragment of leinamycin into various simple compounds and to examine the cytotoxic effect[1] of the products.

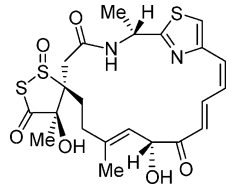
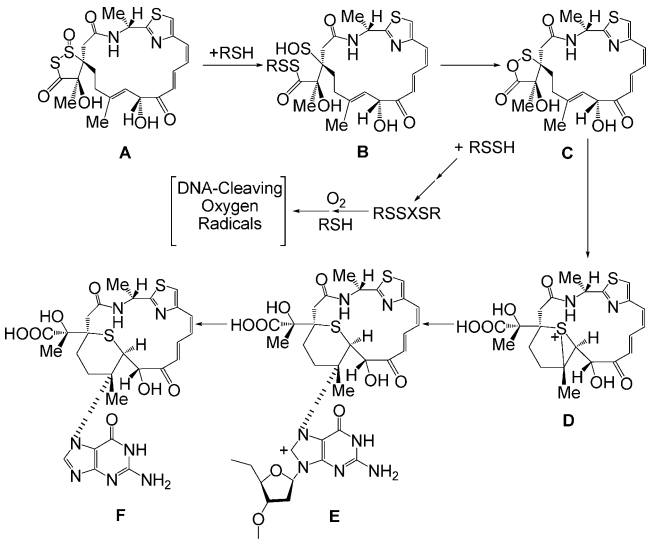


Figure 1. Structure of leinamycin.

Scheme 1. DNA Cleavage Mechanism of Leinamycin



Chemistry. As reported in a preliminary paper,[16] our primary goal was to elaborate a new method for the synthesis of the bioactive heterocyclic ring of leinamycin. According to a general methodology, the reaction of the starting aldehyde (**1**) with a phosphorane affords the α,β-unsaturated *E*-thiophenyl active esters (**2**), whose treatment with SH^- anion yields the 3-mercaptothiolic acid **4**. Oxidation of this latter compound leads to the disulfide-type 1,2-dithiolan-3-one (**5**), and subsequent oxidation of **5** with dimethyldioxirane then gives rise[17] to the *S*-oxide **6** (Scheme 2).

The demonstration of our method (Scheme 3) starts with the model compound 3-phenylpropionaldehyde (**7**) and then continues with 2,3:4,5-di-*O*-isopropylidene-*aldehydo*-D-arabinose (**11**, Scheme 4).

Applying the above general protocol, the reaction of **7** and **11** with phenylthiocarbonylmethylenetriphenylphosphorane,[18]

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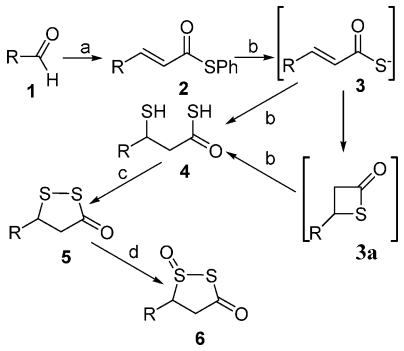
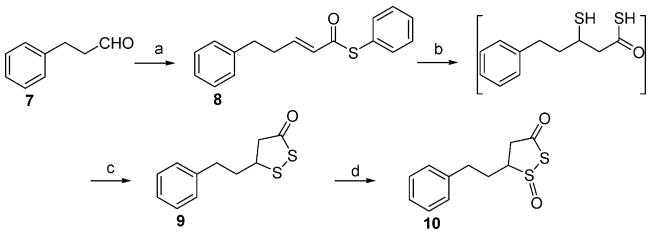
Scheme 2. A New Synthesis of Dithiolanone-*S*-oxide[a]



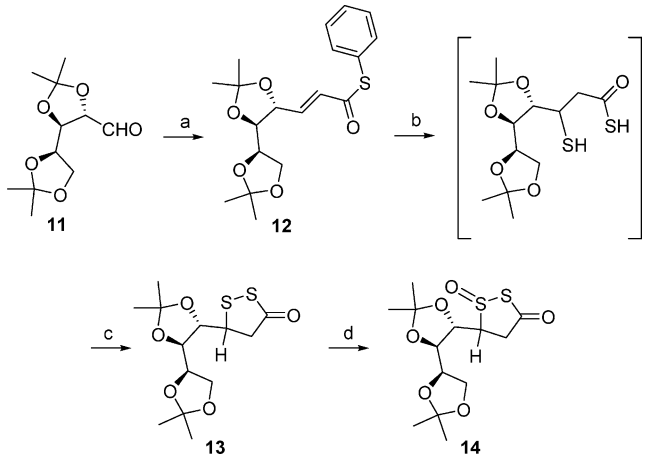
[a] Reagents: (a) $Ph_3PCHCOSPh$ (1.2−1.4 equiv), room temperature, 16−48 h; (b) Et_3N (triethylamine, 2.1 equiv), H_2S, 1,4-dioxan, room temperature, 2 h; (c) $K_3[Fe(CN)_6]$ (1.5 equiv), 1,4-dioxane/water, room temperature, 12−16 h; (d) dimethyldioxirane (1.0 equiv), acetone, room temperature, 2 h.

Scheme 3. Reactions with 3-Phenylpropionaldehyde[a]



[a] Reagents: (a) $Ph_3PCHCOSPh$ (1.3 equiv), toluene, room temperature, 48 h, 80%; (b) Et_3N (2.1 equiv), H_2S, 1,4-dioxane, room temperature, 2 h; (c) $K_3[Fe(CN)_6]$ (1.5 equiv), 1,4-dioxane/water, room temperature, 12 h, 60% (b+c); (d) dimethyldioxirane (1.0 equiv), acetone, room temperature, 2 h, 97%.

Scheme 4. Reactions with Arabinose[a]



[a] Reagents: (a) $Ph_3PCHCOSPh$ (1.3 equiv), toluene, room temperature, 48 h, 81%; (b) Et_3N (2.1 equiv), H_2S, 1,4-dioxane, room temperature, 2 h; (c) $K_3[Fe(CN)_6]$ (1.5 equiv), 1,4-dioxane/water, room temperature, 14 h, 73% (b+c); (d) dimethyldioxirane (1.0 equiv), acetone, room temperature, 2 h, 95%.

carrying an active ester, gave the α,β-unsaturated thioesters with *E*-configuration (**8** and **12**, respectively) in a stereoselective manner (Schemes 3 and 4). Thiolysis of **8** and **12** with the SH^- ion generated from hydrogen sulfide with triethylamine proceeded with conjugate addition and subsequent ester hydrolysis, and the resulting β-mercaptothiolic acid intermediates were oxidized, without isolation, with potassium hexacyanoferrate-(III) into the dithiolanones **9** and **13**, respectively. Th end products (**10** and **14**) of these syntheses were obtained by dimethyldioxirane oxidation.

In 1990, Hara et al.[3] suggested that 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. On the basis of this, we thought that incorporation of the "warhead" of leinamycin into nucleosides might manage delivery to the target point of action by the formation of a base pair. Therefore, we applied our procedure to the 5′-aldehyde **16**, derived from 2′,3′-di-*O*-silyluridine[19] (**15**), and through the intermediates **17**, **18a**, and **19a**, the dithiolane-*S*-oxides **18b** and **19b** were obtained (Scheme 5).

By the oxidation[19] of the silyl ether of 2′-deoxythimidine (**20**) followed by Wittig reaction, the same sequence shown above (involving the intermediates **21** and **22)** furnished the leinamycin analogues **23b** and **24b** (Scheme 6).

An intermediate of the DNA cleavage mechanism of leinamycin is the episulfonium salt **D** (Scheme 1), which is produced from the 1,2-dithiolan-3-one-*S*-oxide by incorporation of the carbon−carbon double bond at γ-position. Recently Lee et al.[20] and the Gates group[21] have also synthesized simple substances carrying the above-mentioned structural elements that might be able to alkylate DNA.

We also decided to investigate the cytotoxic activity of simple dithiolanone-*S*-oxides in which a triple bond is present at γ-position to the heteroring. Consequently, by the Michael addition of the lithio-cuprate derived from the allyl tetrahydropyranyl ether **25** the derivative **26** was prepared. Subsequent transformations following our general protocol (Scheme 7) gave rise to the dithiolanone derivatives **28a** and **28b**.

Results and Discussion

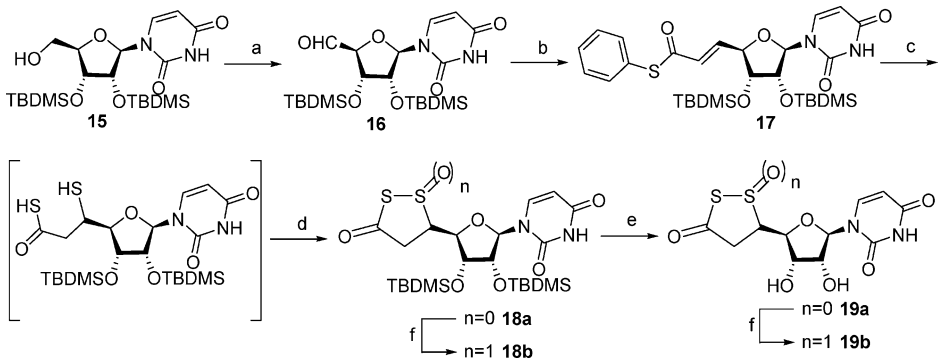
Investigation of the potential antitumor activity of the leinamycin analogues was carried out by determining the IC_{50} values on HeLa-3-tumor cells using daunomycin, useful in tumor chemotherapy, as the reference material. The IC_{50} values were measured in the absence of a thiol and also in the presence of ethanethiol, assuming that the cytotoxic effect is manifested due to DNA cleavage and for such an action of leinamycin the presence of a thiol serving as trigger is necessary.

Since Padrón et al.[22] reported recently that the presence of lipophilic silyl groups enhances the cytotoxicity of certain substances toward human tumor cells, the synthetic intermediates of the nucleoside derivatives carrying one or more TBDMS (*tert*-butyldimethylsilyl) group(s) were also investigated. As the data presented in Table 1 demonstrate, all of the derivatives show a cytotoxic effect in micromolar concentrations. However, only a few of our compounds possessed an activity comparable to that of daunomycin.

It is also clear that ethanethiol significantly enhanced the cytotoxic effect in each case, so the assumption that for the activity of the dithiolanone-*S*-oxides the presence of a thiol is necessary is correct. At the same time, it is very interesting that the cyclic disulfide-type intermediates (**9**, **13**, **18a**, **19a**, **23a**, **24a**, and **28a**) are also active, although to a less extent than the corresponding *S*-oxide analogues (indicated with the sign **b**), which are chemically more reactive. In compounds **9**, **10**, **13**, and **14** the "warhead" was coupled to molecules that are not as important as considered on the basis of the mechanism of action, but a slight activity was still observed also in these cases.

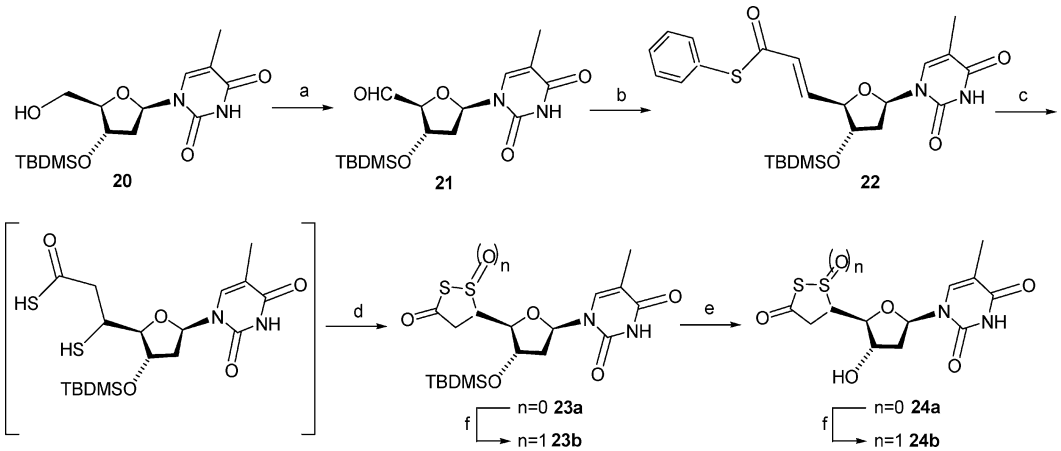
The nucleoside derivatives **18a**, **18b**, **23a**, and **23b** possessed strong cytotoxicity, and the activity of the silyl ether **18a** was comparable to that of daunomycin. In agreement with our working hypothesis, it is assumed that the comparatively good efficacy of these nucleoside−leinamycin analogues is attributed to the formation of base pairs with DNA.

Scheme 5. Reactions with Uridine[a]



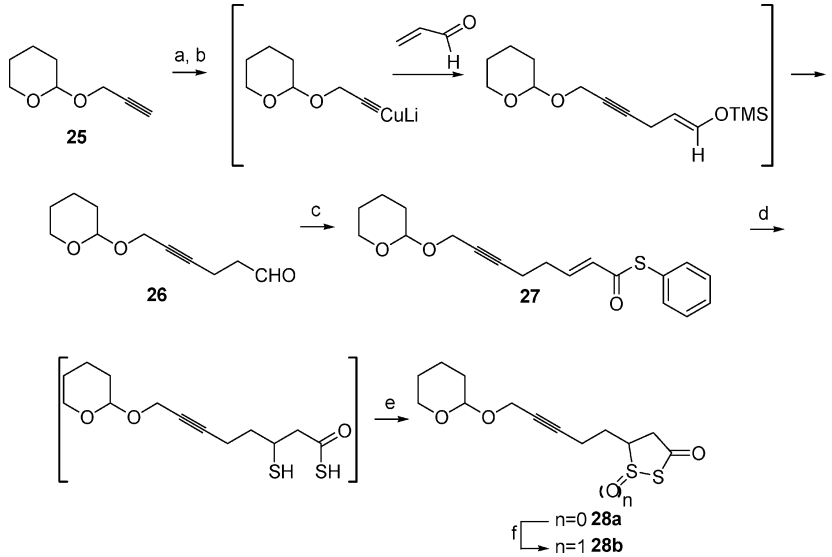
[a] Reagents: (a) Dess−Martin periodinane (1.5 equiv), CH_2Cl_2, 0 °C/room temperature, 1.5 h; (b) $Ph_3PCHCOSPh$ (1.4 equiv), 1,4-dioxan, room temperature, 22 h, 79% (a+b); (c) Et_3N (2.1 equiv), H_2S, 1,4-dioxane, room temperature, 2 h; (d) $K_3[Fe(CN)_6]$ (1.5 equiv), 1,4-dioxane/water, room temperature, 16 h, 63% (c+d); (e) trifluoroacetic acid:H_2O:THF 1:1:4, 0 °C, 6 h, 94%; (f) dimethyldioxirane, acetone, room temperature, 2 h, 96%, 95%.

Scheme 6. Reactions with Thymidine[a]



[a] Reagents: (a) Dess−Martin periodinane (1.5 equiv), CH_2Cl_2, 0 °C/room temperature, 1.5 h; (b) $Ph_3PCHCOSPh$ (1.4 equiv), 1,4-dioxane, room temperature, 22 h, 74% (a+b); (c) Et_3N (2.1 equiv), H_2S, 1,4-dioxane, room temperature, 2 h; (d) $K_3[Fe(CN)_6]$ (1.5 equiv), 1,4-dioxane/water, room temperature, 15 h, 65% (c+d); (e) trifluoroacetic acid:H_2O:THF 1:1:4, 0 °C, 6 h, 95%; (f) dimethyldioxirane, acetone, room temperature, 2 h, 94%, 95%.

Scheme 7. Synthesis of an Improved Open Chain Analogue[a]



[a] Reagents: (a) *n*-buthyllithium (1.0 equiv), THF, −10 °C, 15 min, Cu(I)I·0.75Me_2S (1.1 equiv), THF, −10 °C, 45 min; (b) Me_3SiI (1.0 equiv), THF, −78 °C, 10 min, acrolein (1.0 equiv), THF, −78 °C, −30 °C, 2.5 h, 42% (a+b); (c) $Ph_3PCHCOSPh$ (1.25 equiv), 1,4-dioxan, room temperature, 16 h, 75%; (d) Et_3N (2.1 equiv), H_2S, 1,4-dioxane, room temperature, 2 h; (e) $K_3[Fe(CN)_6]$ (1.5 equiv), 1,4-dioxane/water, room temperature, 17 h, 62% (d+e); (f) dimethyldioxirane, acetone, room temperature, 2 h, 98%.

The cytotoxicity data of our compounds was also investigated in relation with their liphophilic character. The logarithmic form of the octanol/water distribution coefficient (CLogP) can be approached theoretically, and this is extensively used for the characterization of water solubility and membrane transport. Data that came out of our studies are collected in Table 1, which

Table 1. Mean Cytotoxicities of Leinamycin Antibiotic Analogues toward Human Cancer Cells[a]

compound	cytotoxicity IC$_{50}$[a]	cytotoxicity IC$_{50}$[a] (+EtSH[b])	CLogP
daunomycin	2.96	−	−1.621
9	257.7	65.54	3.607
10	68.43	24.75	1.875
13	35.93	16.87	2.338
14	18.15	12.60	0.634
18a	10.04	7.84	5.397
18b	3.68	2.67	3.694
19a	62.23	20.72	−1.449
19b	50.71	7.01	−3.152
23a	n.d.	16.69	2.766
23b	43.12	6.61	1.063
24a	298.8	54.62	−0.615
24b	118.7	29.69	−2.318
28a	123.7	20.11	2.831
28b	62.88	8.33	1.009

[a] Cytoxicity values are micromolar concentrations (μM) corresponding to 50% growth inhibition. [b] Ethanethiol.

indicate that in the case of the pair of compounds **23a**/**24a**, **23b**/**24b**, **18a**/**19a**, and **18b**/**19b** carrying the silyl-protecting group and the free hydroxyl, respectively, the cytotoxicity of the lipophilic silyl compounds is higher than that of the respective pair with a negative CLogP value. Compound **28b**, which carries a triple bond analogue of the molecular fragment of leinamycin responsible for the DNA cleaving effect, is also a comparatively active member of the series.

The cytotoxicity of simple leinamycin analogues has not been extensively investigated. The results presented here demonstrate that some derivatives of leinamycin with very simplified structures, such as the dithiolanone-*S*-oxides, possess comparative efficacy. Therefore further investigations of related compounds may be worthwile. For this purpose, noncomplicated, convenient synthetic procedures such as that described in this paper can be extended to additional aldehydes. It is believed that we have also succeeded in proving the cytotoxicity-enhancing properties of silyl ethers, first reported by Padron et al.,[22] by using completely different structures, and this encourages further systematic studies on the topic.

Experimental Section

^{1}H and ^{13}C NMR spectra were recorded at 400.13 and 100.61 MHz, respectively, with a Bruker WP-400 SY spectrometer, or at 360.13 and 90.55 MHz, respectively, with a Bruker WP-360 SY spectrometer. Mass spectra were recorded with Bruker Biflex-III MALDI TOF MS (matrix-assisted laser desorption time-of-flight mass spectrometry) and Bruker BioTOF II ESI TOF (electrospray ionization time-of-flight) mass spectrometers. For column chromatography, Merck silica gel (Kieselgel 60), 0.063−0.200 mm (70−230 mesh), was used. Thin-layer chromatography (TLC) was performed on Kieselgel 60 F_{254} (Merck). The synthesis of key final compounds **18b**, **23b**, and **28b** are indicated below. For more information, see Supporting Information.

1-((2′*R*,3′*R*,4′*R*,5′*S*)-3′,4′-Bis(*tert*-butyldimethylsilyloxy)-5′-((S)-[5″-(2″,5″-dioxo-1″,2″-dithiolan-3″-yl)]-terahydrofuran-2′-yl)pyrimidin-2,4(1*H*,3*H*)-dione (18b). To a pale yellow solution of **18a** (55 mg, 0.099 mmol) in dry acetone (5 mL) was added a dimethyldioxirane solution (1.60 mL, C = 0.062 mol/L, 1.0 equivalent), and the mixture was stirred at room temperature for 2 h. Evaporation furnished a colorless solid **18b** (54.7 mg, 96% yield). TLC: R_f 0.33 (F: 7:3 hexane−acetone). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.09−0.14 (12H, s, Si(CH_3)$_2$), 0.91−0.95 (18H, s, C(CH_3)$_3$), 3.12 (2H, m, H-4″), 4.11 (1H, t, H-5′), 4.21 (1H, m, H-3″), 4.42 (1H, t, H-4′), 4.89 (1H, s, H-3′), 5.59−5.61 (1H, d, H-2′), 5.70−5.75 (1H, q, H-5), 7.10−7.13 and 7.53−7.56 (1H, dd, H-6), 9.16 (NH). MS: calcd for $C_{23}H_{40}O_7N_2S_2Si_2Na$ $[M + Na]^+$ 599.84, found 599.80. Mp 51−53 °C. Anal. ($C_{23}H_{40}O_7N_2S_2Si_2$) C, H, N.

1-((2′*R*,4′*S*,5′*S*)-4′-(*tert*-Butyldimethylsilyloxy)-5′-((S)-[5″-(2″,5″-dioxo-1″,2″-dithiolan-3″-yl)]-tetrahydrofuran-2′-yl]-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (23b). To a solution of **23a** (222 mg, 0.50 mmol) in dry acetone (25 mL) was added a dimethyldioxirane solution (6.25 mL, *C* = 0.080 mol/L, 1.0 equiv), and the mixture was stirred at room temperature for 2 h. Evaporation gave **23b** (216 mg, 94% yield), as a pale yellow solid, TLC: R_f 0.33 (D: 8:2 hexanes−EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.17 (6H, s, Si(CH_3)$_2$), 0.89 (9H, s, C(CH_3)$_3$), 1.89 (3H, s, C(CH_3)), 2.32 (2H, m, H-3′), 3.14 (2H, d, J = 8 Hz, H-4″), 3.25 (1H, m, H-3″), 4.10 (1H, m, H-4′), 4.59 (1H, m, H-5′), 6.13 (1H, dt (restricted rotation), H-2′), 7.39 (1H, d, J = 4 Hz, H-6), 8.44 (NH). MS: calcd for $C_{18}H_{29}S_2O_6N_2Si$ $[M + H]^+$ 461.73, found 461.76. Mp 54−56 °C. Anal. ($C_{18}H_{28}S_2O_6N_2Si$) C, H, N.

5-(5′-(Tetrahydro-2*H*-pyran-2′-yloxy)pent-3′-ynyl)-1,2-dithiolan-3-one-1-oxide (28b). To a solution of **28a** (70 mg, 0.245 mmol) in acetone (5 mL) was added a dimethyldioxirane solution (3.65 mL, C = 0.067 mol/L, 1.0 equiv), and the mixture was stirred at room temperature for 2 h. Following concentration, the product **28b** (73 mg, 98% yield) was isolated as a yellow syrup, TLC: R_f 0.15 (C: 9:1 hexanes−EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54−1.75 (6H, m, THP), 2.00−2.12 (2H, m, H-1′), 2.45−2.51 (2H, s, H-2′), 2.68−2.76 and 3.04−3.12 (2H, dd, H-4), 3.51−3.55 (2H, m, THP), 3.70−3.87 (2H, m, H-5′), 4.16−4.33 (1H, q, H-5), 4.74 (1H, t, THP). MS: calcd for $C_{13}H_{18}O_4S_2Na$ $[M + Na]^+$ 325.04, found. 325.01. Anal. Calcd for ($C_{13}H_{18}O_4S_2$ C) C, H, N.

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Supporting Information Available: Experimental procedures and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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