## Synthetic Studies on Leinamycin. A Synthesis of the 1-Oxo-1,2-dithiolan-3-one Moiety

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**Abstract:** A synthesis of the 1-oxo-1,2-dithiolan-3-one moiety of antitumor antibiotic leinamycin (1) is described. An intramolecular delivery of a sulfur atom (7 to 8) and a facile Beckmann fragmentation (10 to 12) constitute the backbone of our synthesis.

Leinamycin (1) has recently been isolated from a fermentation broth of *Streptomyces sp.* by chemists at Kyowa Hakko and has been shown to exhibit potent antitumor activities.<sup>1</sup> Leinamycin preferentially inhibits DNA synthesis in *Bacillus subtilis* and causes single strand scission of plasmid DNA *in vitro* in the presence of thiol cofactors.<sup>2</sup> The relative configuration of leinamycin was determined by an X-ray crystallographic analysis<sup>3</sup> as well as extensive NMR studies.<sup>4</sup> The absolute configuration was deduced as shown based on the isolation of partially racemized D-alanine by acid hydrolysis of leinamycin. The unique structural features of leinamycin include the 1-oxo-1,2-dithiolan-3-one moiety fused in a spiro fashion to an 18-membered lactam with an extensively conjugated thiazole ring. No other natural products with such an unusual dithiolanone moiety have been isolated to date. These challenging structural features as well as the interesting antitumor activities have prompted us and the others<sup>5</sup> to undertake the total synthesis of leinamycin. In this communication we report a facile synthesis of the 1-oxo-1,2-dithiolan-3-one moiety of leinamycin 2.



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In view of the generally high reactivities of organosulfur compounds, it would be advantageous to introduce sulfur atoms toward the end of a multi-step total synthesis. During the course of our preliminary studies, however, we have experienced enormous difficulties in intermolecularly delivering a sulfur atom to the C-3 position (leinamycin numbering) of our synthetic intermediates 3. These difficulties could mainly be attributed to the steric congestion at C-3. In order to circumvent the steric problem, an intramolecular version has been developed as shown below (Scheme 1).



Readily available 4-oxo-3-methyl-2-pentenoic acid  $4^6$  was converted to cyclohexyl amide  $5^7$  via a mixed anhydride in 54% yield8 ((1) i-BuOCOCI, Et3N, CH2Cl2, 0 °C, 10 min. (2) cyclohexylamine, 0 °C, 15 min). Addition of  $\alpha$ -ethoxyvinyllithium to 5 furnished the adduct 6, which was subsequently treated with Nbromosuccinimide to give  $\alpha$ -bromoketone 7 in 58% yield ((1) EtOCH=CH<sub>2</sub>, t-BuLi, THF, -78 to 0 °C, then 5, -78 °C. (2) NBS, CH<sub>3</sub>CN/H<sub>2</sub>O, 0 °C, 10 min). Intramolecular delivery of a sulfur atom to the C-3 position of 7 was achieved by treatment with hydrogen sulfide in the presence of triethylamine (THF, 23 °C, 8 h), giving a 4:1 diastereomeric mixture of 8 in 77% yield. The major isomer 8a proved to be our desired compound based on the NOE studies. The ketone 8a was converted to the novel oxime 9 in 74% yield using a conventional procedure (i-AmONO, NaOMe, MeOH, 23 °C, 1.5 h). The critical Beckmann fragmentation was performed by activation of oxime 9 as 2,6-dimethylbenzoate 10 (2,6-Me<sub>2</sub>C<sub>6</sub>H<sub>3</sub>COCl, Py, CHCl<sub>3</sub>, 23 °C, 10 min), followed by treatment with a large excess of sodium ethanethiolate (THF, 23 °C, 20 min) to give the desired thiolester 12 in 57% yield. The intermediate 11 could not be detected under the reaction conditions. Conversion of 12 to dithiolanone 13 was effected in 75% yield by treatment with sodium bisulfide (THF, 23 °C, 1 h) followed by oxidation with iodine in THF. Upon treatment of 13 with m-chloroperoxybenzoic acid (CHCl<sub>3</sub>, 0 °C, 10 min), a 4:3 diastereomeric mixture of 1-oxo-1,2-dithiolan-3-one 14 with undetermined relative stereochemistry was obtained in 95% yield. Application of this methodology to the total synthesis of leinamycin is currently under way in our laboratories.







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## **References and Notes**

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- Satisfactory spectroscopic data were obtained for all new compounds. <sup>1</sup>H NMR spectra (100 MHz, CDCl<sub>3</sub> unless otherwise noted) of the key intermediates are as follows: 5: δ 6.56 (q, J=1.2 Hz, 1H), 5.55 (brs, 1H), 3.80 (m, 1H), 2.34 (s, 3H), 2.15 (d, J=1.2 Hz, 3H), 2.05-1.0 (m, 10H); 7: δ 6.08 (q, J=1.2 Hz, 1H), 5.50 (brs, 1H), 4.34 (d, J=14 Hz, 1H), 4.16 (d, J=14 Hz, 1H), 3.78 (m, 1H), 2.01 (d, J=1.2 Hz, 1H), 1.56 (s, 3H), 2.0-1.0 (m, 10H); 8a: δ 5.0 (brs, 1H), 3.7 (m, 1H), 3.46 (d, J=17 Hz, 1H), 3.30 (d, J=17 Hz, 1H), 2.88 (d, J=15 Hz, 1H), 2.38 (d, J=15 Hz, 1H), 1.95-1.0 (m, 10H), 1.55 (s, 3H), 1.37 (s, 3H); 9 (CDCl<sub>3</sub>-CD<sub>3</sub>OD): δ 3.6 (m, 1H), 2.84 (d, J=15 Hz, 1H), 2.52 (d, J=15 Hz, 1H), 1.93-0.90 (m, 10H), 1.47 (s, 3H), 1.40 (s, 3H); 12: 7.25 (brs, 1H), 5.60 (brs, 1H), 3.80 (m, 1H), 2.92 (d, J=15 Hz, 1H), 2.05-1.05 (m, 10H); 13 (400 MHz): δ 5.64 (brs, 1H), 3.80 (m, 1H), 2.73 (d, J=14.3 Hz, 1H), 2.57 (d, J=14.3 Hz, 1H), 1.95-1.10 (m, 10H), 1.57 (s, 3H), 1.49 (s, 3H), 1.33 (s, 3H), 2.05-1.0 (m, 10H); 14 (minor isomer): δ 5.9-5.6 (m, 1H), 3.7 (m, 1H), 3.09 (d, J=15.6 Hz, 1H), 2.79 (d, J=15.6 Hz, 1H), 1.66 (s, 3H), 1.33 (s, 3H), 2.05-1.0 (m, 10H); 14 (minor isomer): δ 5.9-5.6 (m, 1H), 3.7 (m, 1H), 2.61 (d, J=14.9 Hz, 1H), 2.25 (d, J=14.9 Hz, 1H), 1.81 (s, 3H), 1.40 (s, 3H), 2.05-1.0 (m, 10H).
- 8. Yields are not optimized.

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