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# TOTAL SYNTHESIS OF (±)-THIOLACTOMYCIN[1]

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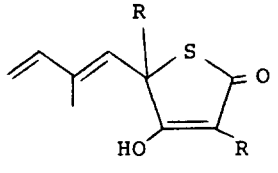
**ABSTRACT:** We have completed the first total synthesis of (±)-thiolactomycin by a five-step procedure in 10% overall yield starting from ketoester **6**. The key step involves addition of dianion **3** to 3-ethoxy-2-methyl-2-propenal. The resulting aldehyde **11** was then converted into (±)-thiolactomycin.

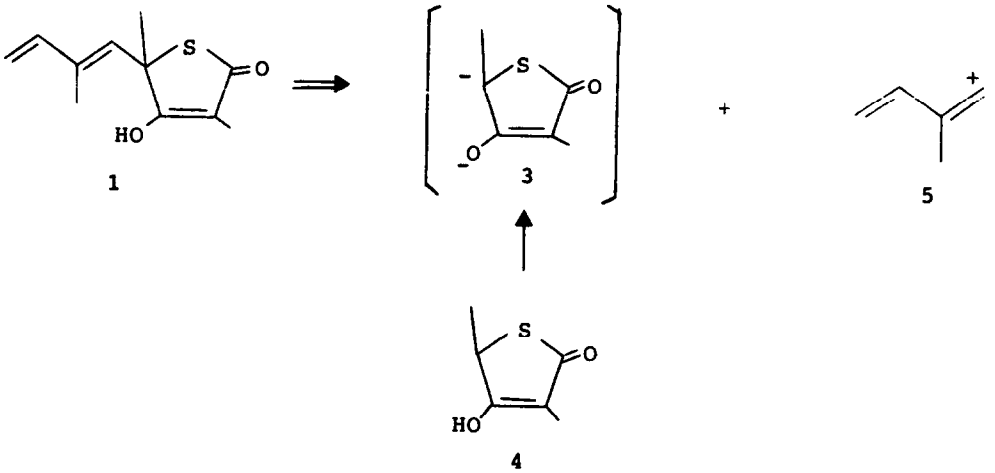
Thiolactomycin (**1**), a new antibiotic produced by a soil isolate, Nocardia sp. No. 2-200, contains a unique thiolactonic structure and shows activity against many species of pathogens including Gram-positive cocci, enteric bacteria, acid-fast bacteria and anaerobic bacteria.[2] Furthermore, the combination of thiolactomycin and β-lactam antibiotics produced a synergistic effect against several inducible β-lactamase-producing microorganisms.[2C] A structurally similar antibiotic, thiotetromycin (**2**), showed selective activity against Bacteroides fragilis as well as inhibited the proliferation of T-cells stimulated with concanavalin A.[3] Herein we report the first total synthesis of (±)-thiolactomycin.



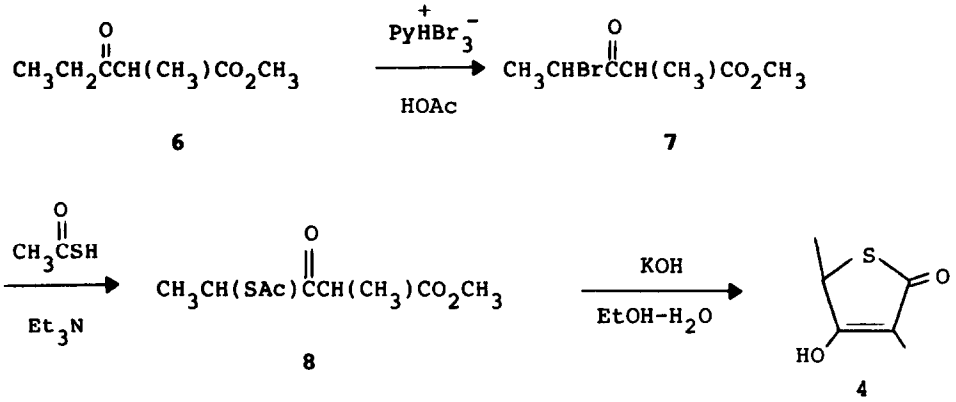

**1**, R = $CH_3$, thiolactomycin

**2**, R = $C_2H_5$, thiotetromycin

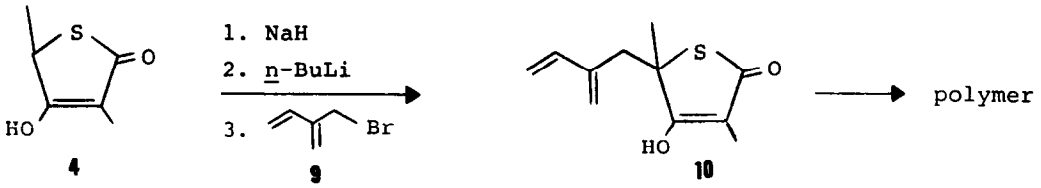
The key step in our synthetic strategy is the coupling of dianion **3** generated from thiolactone **4** with an isoprene cation equivalent **5**. Compound **4** was readily prepared from methyl α-propionylpropionate (**6**)[4] by a three-step procedure. Thus, bromination of **6** with pyridinium bromide perbromide in acetic acid at room temperature gave bromoketoester **7** in 88% yield after distillation [bp 69° (0.5 mm); IR($CH_2Cl_2$) 1755, 1730 $cm^{-1}$; NMR ($CDCl_3$) δ 6.70 (q, J=7Hz, 1H), 4.06 (q, J=7Hz, 1H), 3.67 (2S, 3H), 1.70 (2d, J=7Hz, 3H), 1.37 (2d, J=7Hz, 3H); HRMS m/z 221.9899 ($M^+$)]. The bromide **7** was treated with thioacetic acid in the presence of triethylamine at 0° to afford thioacetate **8** in 60% yield after flash column



chromatography [IR(neat) 1750, 1710 $cm^{-1}$; NMR ($CDCl_3$) δ 4.50 (2q, J=7Hz, 1H), 3.80 (q, J=7Hz, 1H), 3.67 (s, 3H), 2.30 (S, 3H), 1.30 (2d, J=7Hz, 6H); HRMS m/z 219.0693 ($M^+$+1)]. Finally, treatment of **8** with potassium hydroxide in water and ethanol at room temperature overnight gave thiolactone **4** as a white solid [mp 128-130°; IR($CH_2Cl_2$) 3200, 1650, 1610 $cm^{-1}$; NMR ($d_6$-acetone) δ 4.20 (q, 1H), 1.60-1.50 (m, 6H); HRMS m/z 144.0215 ($M^+$)] in 83% yield.

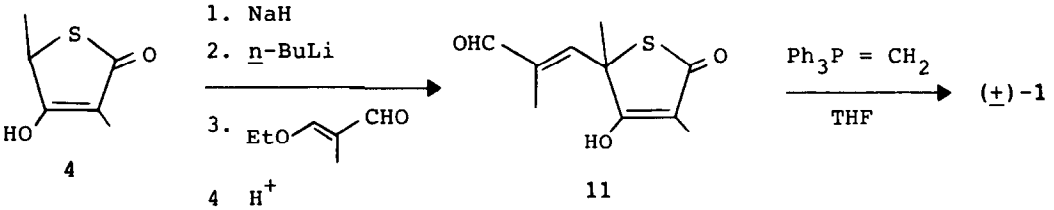


For an isoprene cation equivalent, we chose 2-bromomethyl-1,3-butadiene (**9**)[5] as our first candidate in the hope that we could isomerize the vinylidene double bond of the expected allylation product **10**. Dianion **3**, prepared by treatment of **4** first with one equivalent of sodium hydride at 0° in 1:1 tetrahydrofuran and hexamethylphosphoramide and then with one equivalent of n-butyllithium[6] at -20°, indeed reacted with **9** to give **10**. However, compound **10** was easily polymerized and all the efforts to isomerize the double bond failed.[7]




4 9 10

After several other attempts,[8] our best efforts had produced only a nonstereospecific synthesis of (±)-thiolactomycin in low yield.[9] Being unable to find an acceptable five carbon isoprene equivalent, we had to change the synthetic strategy. We were gratified to find that dianion 3 reacted with 3-ethoxy-2-methyl-2-propenal[10] after acid hydrolysis to give aldehyde 11 which was exclusively the E-isomer [mp 130-131°; IR($CH_2Cl_2$) 1605 $cm^{-1}$ (br); NMR ($CDCl_3$) δ 9.36 (s, 1H), 6.61 (q, 1H), 1.97 (s, 3H), 1.79 (m, 6H)] in 40% yield. Subsequent treatment of 11 with methylene-triphenylphosphorane afforded (±)-thiolactomycin in 60% yield. The spectroscopic (NMR and IR, and MS) data and TLC behavior of synthetic 1




4 11

were in agreement with those reported in the literature.[2b,12] Thus, an efficient synthesis of (±)-thiolactomycin by utilizing the dianion chemistry has been completed.

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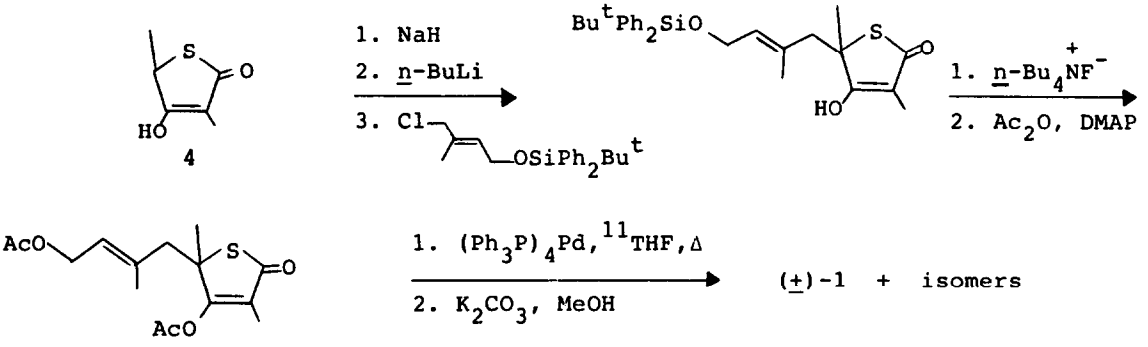
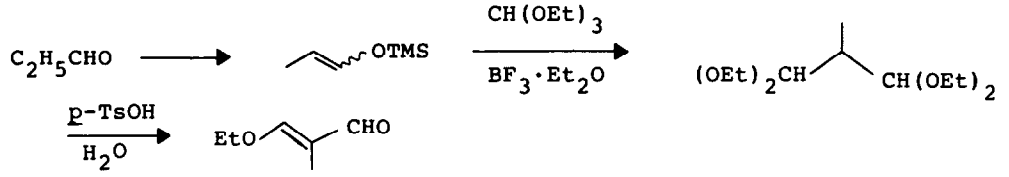
7. For example, treatment of **10** with $RhCl_3 \cdot xH_2O$ or $(Ph_3P)_3RhCl$ in refluxing ethanol afforded polymeric product.

8. For example, we tried to use tigaldehyde and its γ-phenylthio substituted derivatives as isoprene cation equivalents.

9. The synthetic sequence is as follows:




10. E. Breitmaier and S. Gassenmann, Chem. Ber., **104**, 665 (1971). We used a slightly modified procedure:




11. For palladium-catalyzed 1,4-elimination of allylic acetates, see a) H. Matsushita and E.-i. Negishi, J. Org. Chem., **47**, 4161 (1982); b) B. M. Trost, T. R. Verhoeven and J. M. Fortunak, Tetrahedron Lett., 2301 (1979).

12. We were unable to obtain an authentic sample of thiolactomycin from Chugai Pharmaceutical Co., Japan.

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