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Efficient synthesis of enantiomeric pairs of thiolactomycin and its 3-demethyl derivative

Kohei Ohata[a,*] and Shiro Terashima[b]

[a]*Kyorin Pharmaceutical Co. Ltd, Discovery Research Laboratories, 2399-1 Nogi, Nogi-Machi, Shimotsuga, Tochigi 329-0114, Japan*
[b]*Sagami Chemical Research Center, 2743-1 Hayakawa, Ayase, Kanagawa 252-1193, Japan*

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Abstract—Starting with commercially available tiglic aldehyde, the title synthesis was achieved by employing deconjugative asymmetric α-sulfenylation of the chiral 3-(α,β,γ,δ-unsaturated acyl)-2-oxazolidinone with a methanethiosulfonate as a key step.

(*R*)-(+)-Thiolactomycin (**1**) is a thiolactone antibiotic isolated from a soil bacterium, *Nocardia* sp.[1] and exhibits moderate in vitro activity against a number of pathogens including Gram-positive and Gram-negative bacteria,[2] *Mycobacterium tuberculosis*[3] and malaria parasites.[4] It was also reported that **1** shows inhibitory activity against fatty acid synthase (FAS).[5] In addition, it appeared that **1** inhibits bacterial and plant type-II FAS but not mammalian type-I FAS.[6] On the other hand, Townsend et al. quite recently reported that **1** and its derivatives exhibit inhibitory activity against type-I FAS.[7] Taking into account these reported results which seem to be somewhat confusing,[2–7] **1** and its analogues are anticipated to constitute intriguing drug targets not only for infective diseases but also for cancer and obesity treatments.

Reflecting the interesting situation delineated above, three total syntheses of **1** have hitherto been reported.[8–10] Thus, Wang et al. reported the first total synthesis of racemic **1** in which alkylation of the thiotetronic acid dianion is employed as a key step.[8] Starting with (*S*)-ethyl lactate, the first asymmetric synthesis of unnatural (*S*)-(−)-thiolactomycin (*ent*-**1**) was accomplished in 20 steps by Thomas et al.[9] In this total synthesis, stereoselective [3,3]-rearrangement of the allyl xanthate to dithiocarbonate was featured as a key step, leading to determination of the absolute stereochemistry of **1**.[9] In 2002, Townsend et al. developed a nine-step asymmetric synthesis of naturally occurring **1** by employing (*R*)-alanine as the origin of chirality.[10] Considering the potential of **1** and its derivatives as promising drug targets, we also embarked on exploration of a novel synthetic route to **1**, which is more efficient and amenable to the synthesis of various structural types of derivatives of **1** than those reported.[8–10]

Our novel synthetic strategy to **1** is outlined in Scheme 1 in which deconjugative asymmetric α-sulfenylation of the chiral 3-(α,β,γ,δ-unsaturated acyl)-2-oxazolidinone **8** with thiosulfonate **6** (vide infra) is employed as a key step. Thus, deprotonation of **8** will afford trienolate **7**, which on treatment with **6** undergoes deconjugative asymmetric α-sulfenylation under the influence of the chiral auxiliary, producing the α-sulfenylated product **5**. It is expected that, in addition to the absolute stereochemistry, the geometry at the C-3′ position may be controlled to have (*E*)-configuration probably due to steric and/or electronic effect. To our knowledge, this sort of deconjugative asymmetric α-sulfenylation which can directly construct a quaternary asymmetric center bearing a sulfur atom has not hitherto been reported.[11] Subsequent imide–ester exchange,[12] deacetalization, retro-Michael reaction and acylation readily afford α-acylthio ester **3**. Dieckmann cyclization of **3** following the reported protocol[10] gives rise to **1**. The chiral 2-oxazolidinone **8** is readily obtainable from tiglic aldehyde **9**. Preparation of **6** may be accomplished starting with 3-bromopropionaldehyde dimethylacetal with some modification of the reported procedure.[13] According to this designed synthetic scheme, the 3-demethyl derivative **2**

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* Corresponding author. Tel.: +81 (0)280 56 2201; fax: +81 (0)280 57 1293; e-mail: kouhei.oohata@mb.kyorin-pharm.co.jp

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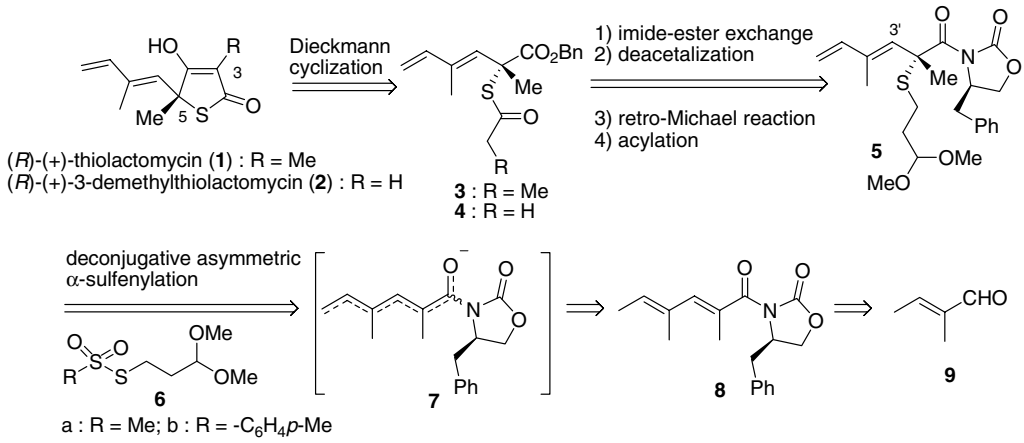


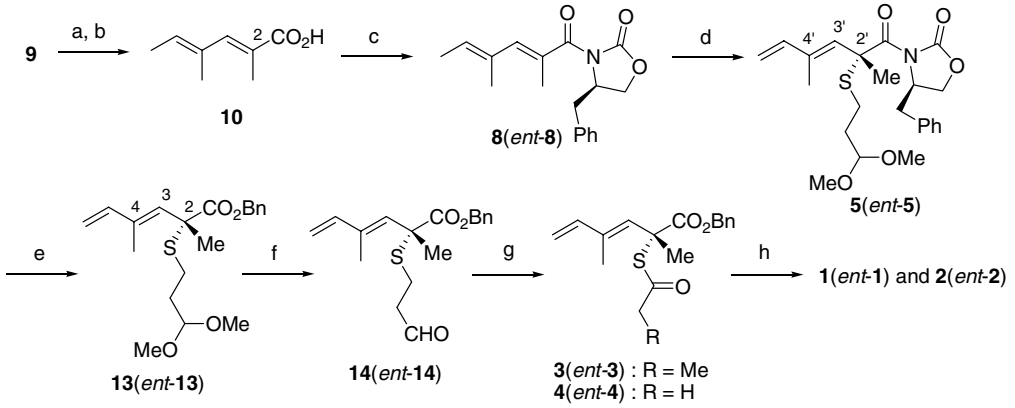
Scheme 1. Synthetic strategy of natural (*R*)-(+)-thiolactomycin (**1**) and its 3-demethyl derivative (**2**).

of **1** will be obtained similarly to **1** when acylation is performed using acetyl chloride instead of propionyl chloride. It is also obvious that use of the optically active 2-oxazolidinone derivative enantiomeric to that utilized for preparing **8** can furnish *ent*-**1** and *ent*-**2** in the same manner as for the preparation of **1** and **2**.

Following the novel synthetic scheme designed above, we embarked on the synthesis of **1** and **2**. As shown in Scheme 2, Horner–Wadsworth–Emmons reaction of **9**.[14] followed by alkaline hydrolysis afforded the hexadienoic acid **10** in 87% yield. This was converted to **8** in 91% yield by sequential reaction with pivaloyl chloride and (*R*)-4-benzyl-2-oxazolidinone.[15]

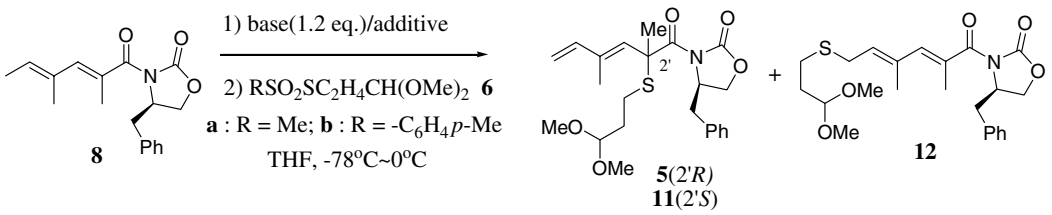
With **8** in hand, deconjugative asymmetric α-sulfenylation, which constitutes the key synthetic step, was next examined. Representative results collected by changing the metal disilazide (LiHMDS, NaHMDS and KHMDS), the amount of HMPA as an additive, and the sulfenylating agent (**6a**,**b**)[16] are shown in Table 1. Taking into account the stereoselectivity as well as the chemical yield, NaHMDS was found to be the metal disilazide of choice (entries 1–3). The sulfenylation with or without HMPA clearly disclosed that HMPA is indispensable for this deconjugative asymmetric reaction (entries 2 and 4). Increasing the amount of HMPA turned out to give better reactivity and stereoselectivity (entries 2 and 5). Use of **6b** in place of **6a** as a sulfenylating agent resulted in decreased regioselectivity (entries 2 and 6). Based on these experiments, the best condition described below was established (entry 5).

Thus, on treatment with NaHMDS (1.2 equiv) in the presence of HMPA (4.0 equiv) in THF at −78 °C, **8** smoothly underwent deprotonation, producing trienolate **7**. Subsequent addition of a THF solution of **6a** (1.5 equiv) followed by gradual warming up to 0 °C over 2 h afforded a mixture of **5** and its C-2′ diastereomer **11** (8:1 by ^{1}H NMR and HPLC analysis) in 92% yield along with the ω-sulfenylated by-product **12** (7% yield) after aqueous workup and separation by column chromatography (SiO_2). The C4′- and/or the *O*-sulfenylated compounds which may constitute other by-products were



Scheme 2. Synthesis of enantiomeric pairs of (*R*)-(+)-thiolactomycin (**1** and *ent*-**1**) and its 3-demethyl derivative (**2** and *ent*-**2**). Reagents and conditions: (a) *t*-BuOLi, $(EtO)_2P(O)CHMeCO_2Et$, hexane, rt; (b) 10%NaOH aq, EtOH, 50 °C, 87% from **9**; (c) *t*-BuCOCl, Et_3N, THF, −15 °C, then LiCl, (*R*) or (*S*)-4-benzyl-2-oxazolidinone, rt 91% for **8**; 89% for *ent*-**8**; (d) NaHMDS, HMPA, −78 °C, then **6a**, −78 °C–0 °C, 74% for **5**; 67% for *ent*-**5**; (e) $Ti(OiPr)_4$, BnOH, 70 °C, 83% for **13**; 81% for *ent*-**13**; (f) 6% HCl aq, THF, rt, 97% for **14**; 99% for *ent*-**14**; (g) Cs_2CO_3, EtOH, 0 °C, then CH_3CH_2COCl or CH_3COCl, Et_3N, CH_2Cl_2, 0 °C, 75% for **3**; 77% for *ent*-**3**; 68% for **4**; 82% for *ent*-**4**; (h) LiHMDS, THF, −78 °C–0 °C, 63% for **1**; 43% for *ent*-**1**; 59% for **2**; 55% for *ent*-**2**.

Table 1. Deconjugative asymmetric α-sulfenylation of the chiral 3-(α,β,γ,δ-unsaturated acyl)-2-oxazolidinone **8**



Run	Base	Additive	6	Yields (%)		
				5 + **11** (**5**:**11**)[a,b]	**12**	Recovery of **8**
1	LiHMDS	HMPA (3 equiv)	**6a**	62 (4:1)	9	—
2	NaHMDS	HMPA (3 equiv)	**6a**	57 (5:1)	7	—
3	KHMDS	HMPA (3 equiv)	**6a**	31 (1:1)	6	—
4	NaHMDS	None	**6a**	3 (1:1.8)	nd[c]	92[d]
5	NaHMDS	HMPA (4 equiv)	**6a**	90 (10:1)	8	—
6	NaHMDS	HMPA (3 equiv)	**6b**	64 (6:1)	25	—

[a] Diastereomer ratio of **5** to **11** was determined by ^{1}H NMR spectrum of the mixture.
[b] This sample contained the corresponding (*Z*)-isomer, which is inseparable from the (*E*)-isomer by column chromatography (SiO_2) (see the text).
[c] Not detected.
[d] This sample was contaminated with a small amount of unknown impurities, which are presumably derived from the sulfenylating agent. Separation of pure **8** was impossible by column chromatography (SiO_2).

not detected at all. Separation of **5** and **11** could not be accomplished by usual column chromatography (SiO_2). The ^{1}H NMR spectrum of the mixture of **5** and **11** clearly showed that **5** consists of the desired (3′*E*) and the undesired (3′*Z*)-isomer in a ratio of ca. 12:1. Further separation of the mixture of **5** and **11** by preparative HPLC[17] gave pure samples of **5**, the (3′*Z*)-isomer of **5**, and **11** in 74%, 6%, and 9% yield, respectively.[18] While the (3′*Z*)-isomer of **5** could be separated by preparative HPLC, the presence of the (3′*Z*)-isomer of **11** was not detected probably due to its extremely minute amount. Structures of **5**, its (3′*Z*)-isomer, and **11** were rigorously determined by their ^{1}H NMR spectra[18,19] and successful synthesis of natural (*R*)-(+)-thiolactomycin **1** from **5** (vide infra).

Taking into account the structure of **5** and the use of HMPA as an additive, the deconjugative asymmetric α-sulfenylation might proceed through the non-chelated (*E*)-trienolate **I** rather than the non-chelated (*Z*)-trienolate **II** with the sterically less hindered α-attack of **6** (Fig. 1).[20]

Since the designed asymmetric reaction could be realized, transformation of **5** to the target molecule **1** was next attempted. Thus, treatment of **5** with Ti(O*i*Pr)$_4$ in benzyl alcohol effected imide-ester exchange,[12] affording benzyl ester **13** in 83% yield. Acidic hydrolysis of the acetal moiety in **13** gave rise to α-(2-formylethylthio) ester **14** in 97% yield. With **14** in hand, retro-Michael reaction of **12** followed by acylation of the produced thiol functionality was next studied. After some unsuccessful experimentation, it was finally found that when **12** was treated with Cs_2CO_3 and the formed cesium thiolate was reacted with propionyl chloride in the presence of Et_3N, the desired α-propionylthio ester **3** was produced in 75% yield. When acetyl chloride was used in place of

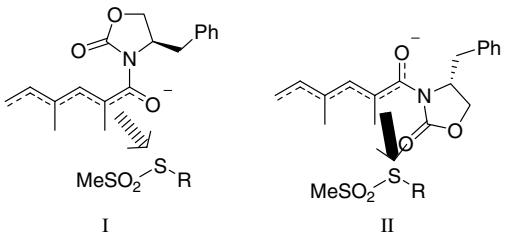


Figure 1. Plausible mechanism for deconjugative asymmetric α-sulfenylation.

propionyl chloride, the α-acetylthio ester **4** was similarly obtained. According to the reported protocol,[10] **3** underwent Dieckmann cyclization on treatment with LiHMDS, giving rise to natural (*R*)-(+)-thiolactomycin **1**[21,22] in 63% yield. In a similar manner, (*R*)-(+)-3-demethylthiolactomycin **2**[21,22] was obtained from **4** in 59% yield. Spectral properties of **1** and **2** were identical to those reported.[10,23] When the same synthetic scheme as described above was traced by utilizing (*S*)-4-benzyl-2-oxazolidinone as a chiral auxiliary, unnatural (*S*)-(−)-thiolactomycin (*ent*-**1**) and its 3-demethyl derivative (*ent*-**2**) were similarly produced.[24]

As described above, we have succeeded in exploring a novel synthetic route to enantiomeric pairs of optically pure thiolactomycin (**1** and *ent*-**1**) and its 3-demethyl derivative (**2** and *ent*-**2**) by employing deconjugative asymmetric α-sulfenylation of the chiral 3-(α,β,γ,δ-unsaturated acyl)-2-oxazolidinone (**8** and *ent*-**8**) as a key step. The successful synthesis of enantiomeric pairs of optically pure **1** and **2** obviously shows the efficiency and flexibility of the developed synthetic scheme. Taking into account these aspects, various structural types of novel congeners of **1**, which are of interest from the viewpoint of pharmacological activity, can be prepared

by employing this synthetic scheme. Research along this line is in progress.

Acknowledgements

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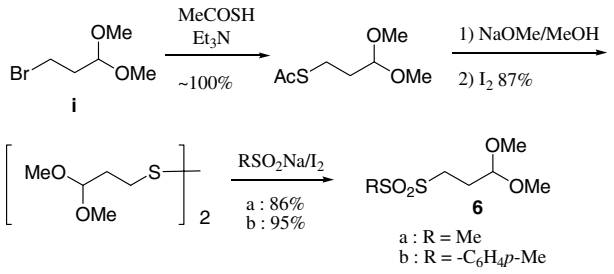
13. According to the procedure reported by Fujiki et al., **6** was prepared from 3-bromopropionaldehyde dimethylacetal (**i**) as shown below. Fujiki, K.; Tanifuji, N.; Sakaki, Y.; Yokoyama, T. *Synthesis* **2002**, 343–348.



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16. Prior to selecting **6** as a sulfenylating agent, various *S*-electrophiles were examined in the preliminary experiments. Thus, acetylsulfenyl chloride which was initially considered to be one of the most attractive *S*-electrophiles turned out not to react with **7** at all. While methyl methanethiosulfonate ($MeSSO_2Me$) and (2-trimethylsilyl)ethyl *p*-toluenethiosulfonate ($TMSCH_2CH_2SSO_2C_6H_4p$-Me) underwent deconjugative asymmetric α-sulfenylation similar to **1**, the methylsulfenyl and the (2-trimethylsilyl)ethylsulfenyl group introduced into the reaction products could not be elaborated to a thiol or an acylsulfenyl group.
17. Separation of **5**, the (3′*Z*)-isomer of **5** and **11** was performed by HPLC with a chiral column [Daicel Chiralpak AD-H, ∅2.0 cm × 25 cm, hexane/EtOH/*i*PrOH = 91:6:3, flow rate 10 mL/min]. HPLC analysis [Daicel Chiralpak AD-H, ∅0.46 cm × 25 cm, hexane/*i*PrOH = 95:5, flow rate 1.0 mL/min; t_R 14.7 min (**5**), 10.4 min [the (3′*Z*)-isomer of **5**], 25.1 min (**11**)].
18. Representative physical and spectral data of **5**, the (3′*Z*)-isomer of **5**, and **11** are as follows. Compound **5**, oil, $[\alpha]_D^{23}$ −253 (*c* 0.50, MeOH), ^{1}H NMR ($CDCl_3$) δ (ppm): 1.72 (3H, d, *J* = 1.2 Hz), 1.82–1.89 (2H, m), 1.95 (3H, s), 2.62 (2H, t, *J* = 7.3 Hz), 2.72 (1H, dd, *J* = 13, 10 Hz), 3.318 (3H, s), 3.324 (3H, s), 3.27–3.38 (1H, m), 4.09–4.14 (2H, m), 4.48 (1H, t, *J* = 5.5 Hz), 4.65–4.71 (1H, m), 5.01 (1H, d, *J* = 11 Hz), 5.14 (1H, d, *J* = 17 Hz), 5.72 (1H, s), 6.36 (1H, dd, *J* = 17, 11 Hz), 7.22–7.36 (5H, m). MS (EI^+) (*m*/*z*): 433 (M^+), HRMS (EI^+) (*m*/*z*): Calcd for $C_{23}H_{31}NO_5S$ (M^+): 433.1923. Found 433.1941.
(3′*Z*)-Isomer of **5**, oil, ^{1}H NMR ($CDCl_3$) δ (ppm): 1.83 (3H, d, *J* = 1.2 Hz), 1.83–1.90 (2H, m), 1.96 (3H, s), 2.65–2.74 (3H, m), 3.318 (3H, s), 3.324 (3H, s), 3.29–3.37 (1H, m), 4.04 (1H, q, *J* = 7.9 Hz), 4.09 (1H, dd, *J* = 8.6, 2.4 Hz), 4.48 (1H, t, *J* = 6.1 Hz), 4.59–4.63 (1H, m), 5.11 (1H, d, *J* = 11 Hz), 5.22 (1H, d, *J* = 17 Hz), 5.60 (1H, s), 6.62 (1H, dd, *J* = 17, 11 Hz), 7.22–7.36 (5H, m). MS (EI^+) (*m*/*z*): 433 (M^+), HRMS (EI^+) (*m*/*z*): Calcd for $C_{23}H_{31}NO_5S$ (M^+): 433.1923. Found 433.1901.
Compound **11**, oil, ^{1}H NMR ($CDCl_3$) δ (ppm): 1.71 (3H, d, *J* = 1.2 Hz), 1.84 (3H, s), 1.84–1.91 (2H, m), 2.59–2.70 (3H, m), 3.313 (3H, s), 3.318 (3H, s), 3.34 (1H, dd, *J* = 13, 3.1 Hz), 4.06–4.14 (2H, m), 4.47 (1H, t, *J* = 5.5 Hz), 4.65–4.70 (1H, m), 5.01 (1H, d, *J* = 11 Hz), 5.13 (1H, d, *J* = 18 Hz), 5.77 (1H, s), 6.36 (1H, dd, *J* = 18, 11 Hz), 7.24–7.37 (5H, m). MS (CI^+) (*m*/*z*): 434 (M^+H), HRMS (CI^+) (*m*/*z*): Calcd for $C_{23}H_{32}NO_5S$ (M^+H): 434.2001. Found 434.1967.
19. The structure of the (3′*Z*)-isomer of **5** was determined by NOESY spectrum which was observed between C-3′ H and C-4′ Me.
20. Taking into account its electronic and steric effects, it is anticipated that **I** can participate in the reaction more preferentially than **II**. See: Hosokawa, S.; Sekiguchi, K.; Enemoto, M.; Kobayashi, S. *Tetrahedron Lett.* **2000**, *41*, 6429–6433.

21. The optical purity of **1**, *ent*-**1**, **2** and *ent*-**2** was determined by HPLC analysis with a chiral column (Daicel Chiralcel OJ ∅0.46 cm × 25 cm, hexane/*i*PrOH/TFA = 95:5:0.2, flow rate 1.0 mL/min, t_R 11.0 min (**1**), 14.9 min (*ent*-**1**). Daicel Chiralcel OJ ∅0.46 cm × 25 cm, hexane/EtOH/TFA = 99:1:0.1, flow rate 1.0 mL/min, 17.9 min (**2**) and 22.5 min (*ent*-**2**) detection at 238 nm).
22. Physical data of **1**, *ent*-**1**, **2** and *ent*-**2** are as follows. **1**: mp 118.5–120 °C [lit.[10], mp 119.5–121 °C; lit.[22], mp 120 °C], and $[\alpha]_D^{29}$ +197 (*c* 1.00, MeOH) (>99% ee[20]) [lit.[10], $[\alpha]_D^{20}$ +174 (*c* 0.6, MeOH); lit.[22], $[\alpha]_D^{20}$ +176 (*c* 1.0, MeOH)]. *ent*-**1**: mp 118.5–120 °C, $[\alpha]_D^{29}$ −192 (*c* 1.03, MeOH) (>99% ee[20]) [lit.[9c], $[\alpha]_D$ −172 (*c* 0.2, MeOH)]. Compound **2**: mp 119.5–121.0 °C, $[\alpha]_D^{29}$ +186 (*c* 1.01, MeOH) (99% ee[20]). *ent*-**2**: mp 119–120.5 °C, $[\alpha]_D^{29}$ −184 (*c* 1.01, MeOH) (99% ee[20]).
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