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Lipase-catalyzed kinetic resolution of thiotetronic acid derivatives bearing a chiral quaternary carbon: total synthesis of (*R*)-thiolactomycin and its O-analogue

Ken-ichi Toyama, Tetsuo Tauchi, Nobuyuki Mase, Hidemi Yoda and Kunihiko Takabe*

Department of Molecular Science, Faculty of Engineering, Shizuoka University, 3-5-1 Johoku, Hamamatsu 432-8561, Japan

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Abstract—We have developed a chemoenzymatic synthesis of (*R*)-thiolactomycin (**1**) having a chiral quaternary carbon atom at C5. In the kinetic resolution of the thiotetronic acid precursor **4**, both enantiomers were obtained with high enantiomeric excess by use of Chirazyme® L-2. Chemical transformations of the (*R*)-alcohol **4** provided the chiral (*R*)-thiolactomycin (**1**) in 36% yield in five steps.

Malaria is a serious and sometimes fatal disease caused by malaria parasites such as *Plasmodium falciparum*, *P. vivax*, *P. ovale* and *P. malariae*. Although an eradication campaign was started in the 1950s, it globally failed because of problems including the resistance of mosquitoes to insecticides and the drug-resistant malaria parasites. Furthermore, the eradication campaign was not undertaken in most of Africa, where an estimated 0.7–2.7 million persons die of malaria each year, 75% of them African children. Prevention and treatment by the use of mosquito net, insecticides, malaria vaccine and antimalarial drugs is required for saving the world. Especially, an antimalarial drug based on a different inhibition mechanism from that of available drugs must be developed. Recently, inhibition of the fatty acid biosynthesis pathway of *P. falciparum* is focused on as a target to solve the problem of drug-resistant malaria parasite.[1] Fatty acid synthesis is a fundamental function of biological cells. The main steps in this process on animals are carried out by a single, multifunctional polypeptide fatty acid synthase (type I FAS), whereas plants and bacteria utilize a dissociable multienzyme system (type II FAS). Therefore, the selective inhibitor of the type II FAS enzymes has possibilities to be a new antimalarial agent.

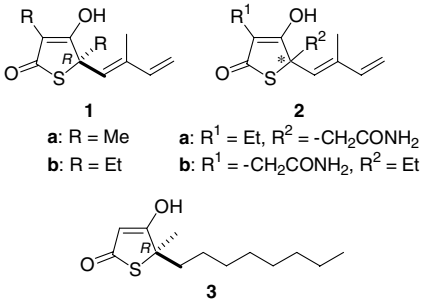

Figure 1. (*R*)-Thiolactomycin and related compounds.

Naturally occurring thiolactomycin (**1**), which was isolated from a soil sample collected in Japan in 1982,[2] is well known as an inhibitor of the dissociable type II FAS enzymes.[3] Thiolactomycin (**1**) has a unique structure of a chiral quaternary carbon atom at C5. Members of this group include thiotetromycin (**1b**),[4] Tu 3010 (**2a**),[5] U 68204 (**2b**),[6] and C 247 (**3**)[7] (see Fig. 1). The important biological properties and negligible toxicity to mammals have aroused great interest in the total synthesis[8–10] of **1** and its derivatives.[11,12] Previously, two successful syntheses of chiral thiolactomycin (**1**) were reported.[9] Chambers and Thomas developed the first synthesis of (*S*)-**1**, in which stereoselective [3,3]-rearrangement of an allyl xanthate derived from (*S*)-ethyl lactate was a key step.[9a,b] Recently, Townsend and co-workers used D-alanine as the source of chirality to prepare (*R*)-**1**.[9c,d] Here we report the chemoenzymatic

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* Corresponding author. Tel./fax: +81 53 478 1148; e-mail: tcktaka@ipc.shizuoka.ac.jp

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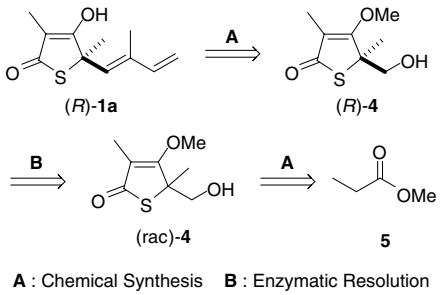


Scheme 1. Chemoenzymatic synthesis of (*R*)-thiolactomycin (**1**).

total synthesis of (*R*)-(−)-thiolactomycin (**1**), that is, efficient lipase-catalyzed kinetic resolution of thiotetronic acid precursor **4** and chemical transformation of (*R*)-**4** into (*R*)-**1a** as shown in Scheme 1.

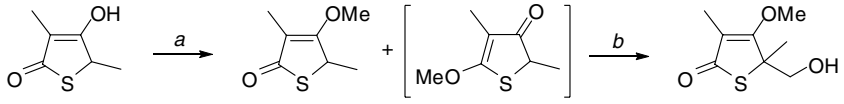
The racemic thiotetronic acid precursor (*rac*)-**4** was prepared. Chemoselective methylation of the thiotetronic acid **6**, which is readily prepared from methyl propionate **5**,[8,11,12f] was examined. The results are shown in Table 1. Chemoselectivities are dependent upon the reagents used. Diazomethane yielded 2-methoxy isomer **8** as a major product in **7**/**8** ratio of 27/73 (entry 2), while the tetrabutylammonium salt of **6** was methylated with dimethyl sulfate to furnish 4-methoxy isomer **7** in **7**/**8** ratio of 82/18 (entry 5).[13] The 4-methoxy isomer **7** was converted to the racemic thiotetronic acid precursor (*rac*)-**4** in good yields.

The racemic thiotetronic acid (*rac*)-**4** was then submitted to enzyme screening to select the optimal enzyme for enantioselective acetylation. Only the lipase Chirazyme® L-2 (*Candida antarctica* (lipase B), Roche Molecular Biochemicals) succeeded in kinetic resolution of (*rac*)-**4**. The (*S*)-acetate **9** and the recovered alcohol (*R*)-**4** with high enantiomeric excess was obtained by controlling the reaction time (entries 4–5). Lipase AY (*Candida rugosa*, Amano Enzyme Co., Ltd.), Lipase PS-D (*Burkholderia cepacia*, Amano Enzyme Co., Ltd.), and Lipase AK (*Pseudomonas fluorescens*, Amano Enzyme Co., Ltd.) showed low reactivity and ee, even after prolonged reaction times (entries 1–3) (see Table 2).

The synthesis of thiolactomycin (*R*)-**1** was examined; however, our initial approach failed. Wittig reaction of the aldehyde **10** did not proceed (Scheme 2). After several unsuccessful attempts using Horner–Wadsworth–Emmons reaction, Peterson olefination, and aldol condensation, we found that deformylation occurred as shown in Scheme 3 because of strong stabilization of anion intermediate **13** by the sulfur atom and tautomerization.[13]

Finally, we succeeded in the construction of the C-4 unit by Lewis acid-catalyzed allylation of the aldehyde **10**

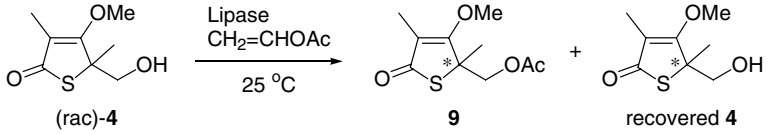
Table 1. Methylation of the tetronic acid **6** and hydroxymethylation of **7**



Entry	Conditions[a]	Time (h)	Temp (°C)	Ratio **7**:**8**	**7** Yield[c] (%)	**8** Yield[c] (%)
1	CH_3OH/concd H_2SO_4	57	65	—	0	0
2	CH_2N_2	2	0	27:73	26	70
3	CH_3I/NaH	144	rt	100:0	9	0
4	CH_3OH/PPh_3/DEAD	21	rt	70:30	46	20
5	$Bu_4N^+OH^-$/$(CH_3)_2SO_4$	0.2	rt	82:18	78	17

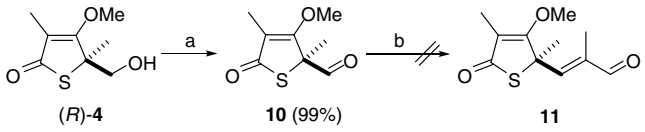
[a] See Table 1.
[b] LDA, $(CH_2O)_n$, THF, −78 °C to rt, 19 h.
[c] Isolated yield.

Table 2. Lipase-catalyzed kinetic resolution of the alcohol **4**

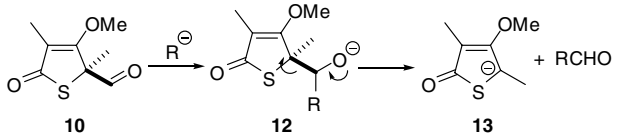


Entry	Lipase	Time (h)	Acetate **9**[a]		Recovered **4**[a]	
			Yield (ee)	Configuration	Yield (ee)	Configuration
1	AY	12	8 (30)	*R*	24 (11)	*S*
2	PS-D	22	36 (3)	*S*	28 (17)	*R*
3	AK	36	31 (25)	*S*	56 (0.4)	*R*
4	Chirazyme®-L2	0.2	30 (91)	*S*	52 (38)	*R*
5	Chirazyme®-L2	5	57 (63)	*S*	38 (>99)	*R*

[a] Determined by chiral-phase HPLC analysis (CHIRALPAK AD, Hexane:EtOH = 95:5, 0.4 mL/min, $\lambda = 254$ nm).



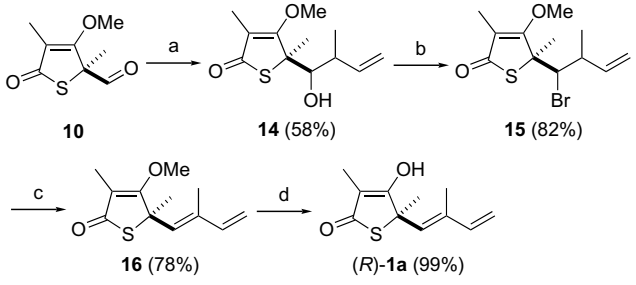
Scheme 2. Reagents and conditions: (a) $(COCl)_2$, DMSO, Et_3N, THF, −78 °C to rt, 2 h; (b) $Ph_3P{=}C(CH_3)CHO$, THF, reflux, 48 h.



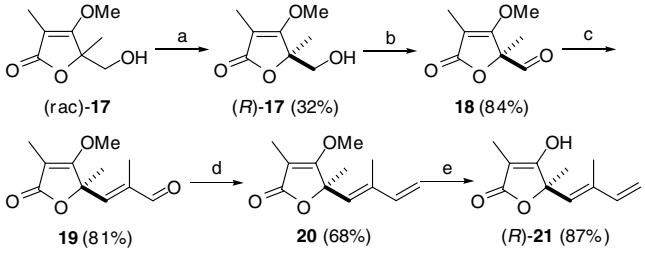
Scheme 3. Deformylation of **10**.

with crotyl tributylstannane. Bromination under neutral condition, followed by elimination afforded an inseparable mixture of 4-methoxy thiolactomycin **16** in good yields in an *E*/*Z* ratio of 9/1. Standard condition for the deprotection of the methoxy group using lithium thiolate led to thiolactomycin (*R*)-**1a** in 36% yield in five steps from chiral thiotetronic acid (*R*)-**4** (see Scheme 4).

Asymmetric synthesis of tetronic acid analogue **21** of thiolactomycin (**1**) was examined as shown in Scheme 5, because Still and Drewery reported the synthesis of racemate **21** from the precursor (*rac*)-**17**.[14] Lipase PS-D-catalyzed kinetic resolution of the tetronic acid **17** gave the corresponding (*S*)-acetate in 58% yield with 50% ee along with the recovered (*R*)-alcohol **17** in 32% yield with 99% ee.[15] The Swern oxidation of (*R*)-**17** followed by construction of the C-4 side chain using α-formylethylidenephosphorane and Wittig reagents provided 4-methoxy tetronic acid analogue **20**. The conversion of **20** to the desired tetronic acid (*R*)-**21** was achieved by use of lithium 1-propanethiolate in 87% yield. We succeeded in the first total synthesis of chiral tetronic acid (*R*)-**21** from the (*R*)-alcohol **17** in 40% yield in four steps.



Scheme 4. Reagents and conditions: (a) $CH_3CH{=}CHCH_2SnBu_3$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C, 3 h; (b) PPh_3, CBr_4, CH_2Cl_2, reflux, 2 h; (c) DBU, toluene, rt, 24 h; (d) *n*-C_3H_7SLi, HMPA, rt, 0.5 h.



Scheme 5. Reagents and conditions: (a) Lipase PS-D, vinyl acetate, 25 °C, 24 h, 99% ee; (b) $(COCl)_2$, DMSO, Et_3N, THF, −65 °C to rt, 1 h; (c) $Ph_3P{=}C(CH_3)CHO$, THF, reflux, 48 h; (d) *n*-BuLi, Ph_3PCH_3I, THF, rt, 16 h; (e) *n*-C_3H_7SLi, HMPA, rt, 14 h.

In summary, we have developed a chemoenzymatic synthesis of (*R*)-thiolactomycin and its O-analogue having a chiral quaternary carbon atom at C5. The lipase-catalyzed kinetic resolution of the thiotetronic acid derivatives demonstrated good enantioselectivity; both enantiomers were obtained with high enantiomeric excess by use of Chirazyme® L-2. Chemical transformation of (*R*)-alcohol **4** provided chiral (*R*)-thiolactomycin (**1**) in 36% yield in five steps. We hope that this simple synthesis of (*R*)-**1** will be helpful for the syntheses of chiral analogues and for solving unidentified bioactive properties in the future.

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