## Natural Product Synthesis

## Variable Synthesis of the Optically Active Thiotetronic Acid Antibiotics Thiolactomycin, Thiotetromycin, and 834-B1\*\*

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Bacterial infections continue to threaten human life, in particular because of the increasing number of organisms resistant to present-day antibiotics.<sup>[1]</sup> In the development of new antibacterial agents, one approach is to trace back antibiotic natural products to "lead structures" and improve their activity by variation of the substituents. With this background, the thiotetronic acid (+)-thiolactomycin (1; Scheme 1), which is produced by the actinomycete Nocardia sp.<sup>[2]</sup> and is active against a number of pathogens<sup>[2]</sup> including Mycobacterium tuberculosis<sup>[3]</sup> and the malaria parasite Plasmodium falciparum,<sup>[4]</sup> became a source of inspiration recently. The interest in 1 is spurred by its rapid absorption in tissues, its effectiveness in mouse infection models,<sup>[2,5,6]</sup> and its low toxicity in animals.<sup>[2]</sup> On a molecular level, 1 is an inhibitor<sup>[5]</sup> of the bacterial,<sup>[7]</sup> but not human, enzymes that convert malonyl acyl carrier protein ("malonyl-ACP") and the acyl-ACP intermediates of growing chain lengths through β-ketoacyl-ACPs into lipids.<sup>[5,8]</sup> X-ray analysis of enzymebound thiolactomycin indicates that the latter functions as a malonyl-ACP surrogate.<sup>[9,10]</sup>

Since its isolation,<sup>[2]</sup> racemic thiolactomycin has been synthesized once,<sup>[13]</sup> its dextrorotatory isomer three times,<sup>[14–16]</sup> and the levorotatory isomer twice.<sup>[17,15]</sup> The synthesis of (-)-**1** by Thomas and Chambers started from ethyl L-lactate, comprised 19 linear steps, gave 0.3% overall yield



Scheme 1. Retrosynthetic analysis of (+)-thiolactomycin (1).

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of product, and elucidated its configuration.<sup>[17]</sup> Townsend and co-workers needed nine steps to transform D-alanine into the first synthetic specimen of (+)-1 (6% overall yield).<sup>[14]</sup> Ohata and Terashima synthesized (+)-1 via a D-phenylalanine-based enolate and (-)-1 via its L isomer in eight steps with one separation by HPLC (22% overall yield).<sup>[15]</sup> Very recently, Takabe and co-workers completed a 12-step synthesis of (+)-1 (3% overall yield) from methyl propionate that included an enzymatic resolution.<sup>[16]</sup> Modifications of the above-mentioned routes,<sup>[13,14]</sup> spin-off products thereof,<sup>[15,17]</sup> or semisyntheses<sup>[18]</sup> from natural (+)-1 have provided dozens of racemic<sup>[19]</sup> or enantiomerically pure<sup>[20]</sup> thiolactomycin analogues with non-natural substituents at centers C-3, O-4, and/or C-5. Nevertheless, in early 2006 medicinal chemists emphasized that "one of the problems in making progress in this area is the difficult chemical synthetic route to thiolactomycin analogues".<sup>[6]</sup> In this regard, the approach to such compounds disclosed herein provides new opportunities. One of its assets is that thiotetronic acids like thiolactomycin are obtained for the first time through catalytic asymmetric synthesis. Moreover, our strategy highlights an innovative and completely diastereoselective way of establishing a stereogenic C–S bond.

Retrosynthetically, (+)-thiolactomycin (1) was traced back to the polyfunctional diester 2 with syn-oriented C-S and C-OH bonds (Scheme 1) or the diastereomeric diester with the identical orientation of the C-S bond but the opposite orientation of the C-OH bond (not shown). This plan relied on the feasibility of a vic-didesoxygenation/ Dieckmann condensation sequence for the conversion of either of these compounds into (+)-1. Specifically, diester isomer 2 would be the precursor of 1 if vinyl epoxide 4 and thiocarboxylate **3** underwent a syn-selective  $S_N'$  ring-opening reaction. Conversely, the epimeric diester would become the precursor of 1 if vinyl epoxide ent-4 and thiocarboxylate 3 combined by an *anti*-selective S<sub>N</sub>' attack. The stereochemistry of such vinyl epoxide openings has been investigated almost<sup>[22]</sup> only with non-sulfur nucleophiles<sup>[23a,b]</sup> and only<sup>[24]</sup> with simpler vinyl epoxides than our sterically hindered and alkoxycarbonyl-substituted substrates 4 or ent-4; both syn<sup>[23]</sup> and anti<sup>[23a,b]</sup> selectivity as well as no stereoselectivities were observed. Making up for the incertitude that these findings implied for our endeavors, either of the vinyl epoxides 4 and ent-4 would be accessible by the silvlation of an appropriately configured vinyl glycidol. The latter would be obtained from a Sharpless asymmetric epoxidation<sup>[25]</sup> (SAE) of the underlying allyl alcohol in the presence of L- and D-diisopropyl tartrate (DIPT), for 4 and ent-4, respectively.

The required allyl alcohol was the ethoxycarbonyl-substituted pentadienol **7** (Scheme 2), which was synthesized<sup>[26]</sup>



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**Scheme 2.** Synthesis of vinyl epoxide **4**. a) Addition of **5** to a solution of **6** (1.1 equiv) in  $CH_2Cl_2$ , 50°C, 5 h (Ref. [21]; 85%); b) NaOH (5 mol%), EtOH, 25°C, 12 h; 84% over two steps (Ref. [21]; 91%; 77% over both steps); c) tBuOOH (2.0 equiv), L-(+)-DIPT (12 mol%), Ti(OiPr)<sub>4</sub> (10 mol%), CH<sub>2</sub>Cl<sub>2</sub>, 4-Å M.S., -30°C, 12 h; PPh<sub>3</sub> (2.0 equiv); tBuPh<sub>2</sub>SiCl (1.0 equiv), imidazole (2.2 equiv), CH<sub>2</sub>Cl<sub>2</sub>, 25°C, 1 h; 83%. DIPT = diisopropyl tartrate.

by a Wittig reaction between aldehyde  $5^{[27]}$  and phosphorane **6** and a subsequent ethanolysis, as reported previously.<sup>[21]</sup> Pentadienol **7** was then subjected to a catalytic<sup>[25b]</sup> SAE.<sup>[28]</sup> The resulting epoxy-alcohol **8** could be protected with *tert*butyldiphenylsilyl chloride without the need for workup in between. This one-pot procedure afforded the siloxy- and ethoxycarbonyl-substituted vinyl epoxide **4** in 83 % yield and with 93 % *ee*.<sup>[29]</sup> Likewise, SAE of pentadienol **7** in the presence of D-(-)-DIPT followed by in situ silylation provided the enantiomeric epoxide *ent*-**4** with 92 % *ee*.<sup>[29]</sup>

Thiolyses of vinyl epoxide 4 were first studied employing thioacetic acid (Scheme 3 and Table 1), which is commercially available and was hence a good substitute for the thiopropionic acid to be prepared later from propionyl chloride and H<sub>2</sub>S. We expected difficulties in directing the nucleophile towards position C-2 of our substrate 4 ( $S_N$ ' reaction) rather than positions C-3 (conjugate addition) or C-4 or C-5 ( $S_N$ reactions). However, site-selectivity was not an issue whereas the lack of reactivity and/or chemoselectivity was. Thioacetic acid alone or combined with Na<sub>2</sub>CO<sub>3</sub> led to only incomplete conversion of 4, while Cs<sub>2</sub>CO<sub>3</sub>, triethylamine, Hünig's base, or pyridine as additives led to its decomposition. Thioacetic acid in the presence of Ti(OiPr)4[30] led to ring opening of 2,3-epoxy-1-hexanol but not of epoxide 4. However, mixtures of epoxide 4 and thioacetic acid could be activated by other Lewis acids (see Table 1). This approach furnished the desired  $S_{N}$  product 9 with the expected E configuration of the C=C bond as well as a seemingly single, although unassigned, configuration at C-2. Moreover, we obtained some lactone 12, apparently from an intramolecular transesterification of the isomeric  $S_{N'}$  product *iso*-9 with the Z-configured C=C bond. In addition, products without incorporation of thioacetic acid were isolated, namely aldehyde 10 and the conjugated diene 11. Aldehyde 10 appears to result from a semipinacol rearrangement of the substrate 4, a well-established transformation of silylated epoxy-alcohols.<sup>[31]</sup> Diene 11 could originate from substrate 4 by a 1,4-elimination or from initially formed 9 by a 1,2-elimination. The highest yield of  $S_{N'}$ product 9 (48%) and the best chemoselectivity (almost no byproducts 10-12) were obtained when exactly 5.0 equivalents each of Me<sub>3</sub>Al and thioacetic acid were combined in



**Scheme 3.** Optimization of a model thiolysis. a) Reagents (see Table 1),  $CH_2Cl_2$ ,  $-78^{\circ}C$ , 3 h; b) reagents,  $CH_2Cl_2$ ,  $-78 \rightarrow 25^{\circ}C$ , 60 min;  $-78^{\circ}C$ , addition of 4;  $-78 \rightarrow 25^{\circ}C$ , 2 h; c) reagents,  $CH_2Cl_2$ ,  $-78 \rightarrow 25^{\circ}C$ , 60 min; addition of epoxide 4 at 25°C, 1 h.

Table 1: Reaction conditions and product yields (see Scheme 3).

Conditions	Reagents (equiv)	Isolated products
а	BF <sub>3</sub> ·OEt <sub>2</sub> (1.0), AcSH (0.0–1.0)	up to 50% <b>10</b> (51% ee)
Ь	AlMe <sub>3</sub> (4.0), AcSH	19% <b>9 +</b> up to 10% <b>11</b> ,
	(4.0–5.0)	+ up to 10% <b>12</b>
с	AlMe3 (5.0), AcSH (5.0)	48% <b>9</b>

dichloromethane at -78 °C and the solution was warmed to room temperature before adding vinyl epoxide **4**.<sup>[21,32]</sup>

The thiolysis conditions from Scheme 3 were readily applicable to the opening of vinyl epoxide 4 by thiopropionic acid (Scheme 4, step a). Thus,  $S_N'$  13 was isolated in 60% yield<sup>[33]</sup> as a single diastereomer and with 93% *ee* according to HPLC analysis. This result proved that there was 100% transfer of chirality from the C<sup>4</sup>–O bond (broken) to the C<sup>2</sup>–S bond (newly established). That the stereostructure of compound 13 was indeed 2, that is, that the C–OH and the C–S bond are *syn*- rather than *anti*-oriented, followed from the fact that our synthesis gave dextrorotatory thiolactomycin. As the latter is *R*-configured,<sup>[17]</sup> the corresponding stereocenter of compound 13 must also have this configuration. This finding is tantamount to assigning 100% *syn* selectivity to the epoxide-opening step,  $4\rightarrow$ 13.

Proceeding towards thiolactomycin (Scheme 4, steps b–e), desilylation of compound 13 with the HF/pyridine complex provided glycol 14 in 85 % yield. Initially, glycol 14 was cleaved oxidatively by NaIO<sub>4</sub> to afford aldehyde 16 in 90 % yield. Surprisingly, olefination of 16 with methylene-triphenylphosphorane gave the required diene 15 with



Scheme 4. Total synthesis of (+)-thiolactomycin (1). a) Thiopropionic acid (5.0 equiv), AlMe<sub>3</sub> (5.0 equiv),  $CH_2CI_2$ ,  $-78 \rightarrow 25$  °C, 60 min; -78 °C; addition of 4,  $CH_2CI_2$ ,  $-78 \rightarrow 25$  °C, 2 h; 60%; b) HF/pyridine, THF, 25 °C, 1.5 h; 85%; c) I<sub>2</sub> (4.0 equiv), PPh<sub>3</sub> (4.0 equiv), imidazole (5.0 equiv), toluene,  $0 \rightarrow 25$  °C, 40 min; 69%; d) NaIO<sub>4</sub> (1.0 equiv), dioxane/H<sub>2</sub>O, 25 °C, 20 min; 90%; e) LiHMDS (2.5 equiv), THF, -78 °C, 2.5 h; 65% (Ref. [14]: 70%); f) MePPh<sub>3</sub>Br (1.3 equiv), nBuLi (1.1 equiv), THF (degassed),  $0 \rightarrow 25$  °C, 30 min; addition of 16, exclusion of light, 25 °C, 10 min; 55%. LiHMDS = lithium hexamethyldisilazide.

variable (2–55%) but mostly low yields (30%). Neither the exclusion of light, the addition of a radical scavenger, nor the use of degassed solvents and eluents during and after the reaction led to an improvement. Fortunately, Garegg and Samuelsson's reductive *vic*-didesoxygenation with PPh<sub>3</sub>, imidazole, and  $I_2^{[34]}$  applied to glycol **14** avoided this bottleneck. This transformation afforded diene **15** reproducibly in 69% yield. Moreover, it shortened our synthesis by one step. The last step towards (+)-**1** (94% *ee*<sup>[29]</sup>) involved a Dieckmann condensation of diester **15** (Scheme 4, step e) as reported by Townsend and co-workers,<sup>[14]</sup> It completed the hitherto shortest synthesis of (+)-thiolactomycin in seven steps from aldehyde **5** and ylide **6**.

The flexibility of our approach was used to synthesize the analogous thiotetronic acids (+)-17 (92 %  $ee^{[29]}$ ), (+)-18 (95 %  $ee^{[29]}$ ), and (+)-19 (90 %  $ee^{[29]}$ ) in the same straightforward fashion (Scheme 5).<sup>[35]</sup> Thiotetronic acid (+)-17 is a non-natural homologue of thiolactomycin (1), whereas (+)-18 and (+)-19 are antibiotics known as 834-B1<sup>[36]</sup> and thiotetromycin, respectively.<sup>[37]</sup> Their syntheses have not been reported before.

In summary, short asymmetric syntheses of thiotetronic acid antibiotics were accomplished. Starting with the aldehyde intermediate **5** of the technical synthesis of vitamin A, the natural products thiolactomycin (1), 834-B1 (18), and thiotetromycin (19) were each synthesized in seven steps and with overall yields reaching 16%. Key transformations were



**Scheme 5.** More thiotetronic acids prepared by the strategy shown in Schemes 2 and 4.

SAEs of alkoxycarbonyl-substituted pentadienols, *anti*-selective  $S_{N}'$  thiolyses of vinyl epoxides, and olefin-forming *vic*-didesoxygenations.

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- [33] **13**: Thiopropionic acid (1.03 g, 11.4 mmol, 5.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (40 mL) was added to AlMe<sub>3</sub> (2.0 m in heptane, 5.7 mL, 11 mmol, 5.0 equiv) in  $CH_2Cl_2$  (40 mL) at  $-78\,^{\circ}C$  over 25 min. The reaction mixture was allowed to warm to room temperature during 60 min and then recooled to -78°C. A solution of vinyl epoxide 4 (93% ee in this experiment; 1.0 g, 2.3 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (40 mL) was then added over 40 min. The resulting mixture was slowly warmed to room temperature and stirred for 30 min. After the addition of NaOH (1M, 40 mL) and phase separation, the aqueous layer was extracted with  $CH_2Cl_2$  (3×60 mL). The combined organic phases were washed with H<sub>2</sub>O (80 mL) and saturated Na/K tartrate solution (80 mL), dried over MgSO<sub>4</sub>, and concentrated under vacuum. The residue was chromatographed on silica gel (eluent cyclohexane/ethyl acetate 7:1) to give the title compound, namely ethyl (2R,5R)-6-(tert-butyldiphenylsiloxy)-5-hydroxy-2,4-dimethyl-2-(propionylsulfanyl)-3hexenoate (13; 730 mg, 60%) as a colorless oil.  $[\alpha]_{D}^{25} = +13.3$  $(c = 1.03 \text{ in CHCl}_3)$ ; 93% ee determined by HPLC on a chiral stationary phase (L 7100, Merck Hitachi LaChrom; Chiralpak AD column, n-heptane/EtOH 19:1, 1.0 mLmin<sup>-1</sup>, 25°C, UV detection at 230 nm);  $t_{\rm r}(R \text{ enantiomer}) = 10.59 \text{ min},$  $t_r(S \text{ enantiomer}) = 12.55 \text{ min}; {}^{1}\text{H NMR}$  (300.1 MHz, TMS internal standard in CDCl<sub>3</sub>):  $\delta = 1.06 \ (m_c, C(CH_3)_3), 1.11 \ (t, J_{3',2'} =$ 7.5 Hz, 3'-H<sub>3</sub>), 1.22 (t,  $J_{2'',1''} = 7.1$  Hz, 2''-H<sub>3</sub>), 1.66 (d,  ${}^{4}J_{4-Me,3} =$ 1.0 Hz, 4-CH<sub>3</sub>), 1.84 (s, 2-CH<sub>3</sub>), 2.48 (q, J<sub>2',3'</sub> = 7.6 Hz, 2'-H<sub>2</sub>), 2.60 (d,  $J_{5-OH,5} = 3.1$  Hz, 5-OH), AB signal ( $\delta_A = 3.53$ ,  $\delta_B = 3.65$ ,  $J_{AB} =$ 10.2 Hz, in addition split by  $J_{A,5} = 7.5$  Hz,  $J_{B,5} = 4.0$  Hz, 6-H<sub>2</sub>), 4.05 (m<sub>c</sub>, 5-H), 4.17 (q,  $J_{1'',2''} = 7.1$  Hz, 1"-H<sub>2</sub>), 5.72 (br s, 3-H), 7.36-7.47 (m, 4×meta-H, 2×para-H), 7.64-7.67 ppm (m, 4× ortho-H]); <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub> internal standard in CDCl<sub>3</sub>):  $\delta = 9.55$  (C-3'), 14.05 (4-Me, C-2"), 19.31 (C(CH<sub>3</sub>)<sub>3</sub>), 25.94 (2-Me), 26.92 (C(CH<sub>3</sub>)<sub>3</sub>), 36.90 (C-2'), 54.72 (C-2), 61.97 (C-1"), 66.72 (C-6), 76.96 (C-5), 126.09 (C-3), 127.91 (C<sub>meta</sub>), 129.96 and 129.99 ( $C_{para}$ ), 133.06 and 133.10 ( $C_{ipso}$ ), 135.62 (Cortho), 139.58 (C-4), 172.19 (C-1), 199.30 ppm (C-1'); IR (film):  $\tilde{v} = 3510, 2975, 2930, 2860, 1735, 1695, 1460, 1445, 1380, 1115,$ 1075 cm<sup>-1</sup>; elemental analysis (%) calcd for  $C_{29}H_{40}O_5SSi$  (528.8): C 65.87, H 7.62, S 6.06; found: C 65.70, H 7.59, S 6.09.
- [34] Method: P. J. Garegg, B. Samuelsson, Synthesis 1979, 469-470.
- [35] The *ee* values of (+)-1, (+)-17, (+)-18, and (+)-19 varied somewhat (90–95%) because their precursors were derived from different samples of vinyl epoxide 4 and its  $\alpha$ -ethyl analogue. The enantiopurity of these epoxides depended critically on the epoxidizing temperature and was not always the same.
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