Natural Product Synthesis

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

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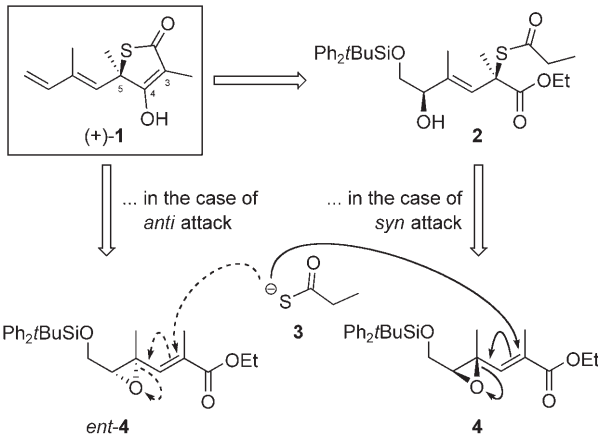
Bacterial infections continue to threaten human life, in particular because of the increasing number of organisms resistant to present-day antibiotics.[1] In the development of new antibacterial agents, one approach is to trace back antibiotic natural products to "lead structures" and improve their activity by variation of the substituents. With this background, the thiotetronic acid (+)-thiolactomycin (**1**; Scheme 1), which is produced by the actinomycete *Nocardia* sp.[2] and is active against a number of pathogens[2] including *Mycobacterium tuberculosis*[3] and the malaria parasite *Plasmodium falciparum*,[4] became a source of inspiration recently. The interest in **1** is spurred by its rapid absorption in tissues, its effectiveness in mouse infection models,[2,5,6] and its low toxicity in animals.[2] On a molecular level, **1** is an inhibitor[5] of the bacterial,[7] 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.[5,8] X-ray analysis of enzyme-bound thiolactomycin indicates that the latter functions as a malonyl-ACP surrogate.[9,10]

Since its isolation,[2] racemic thiolactomycin has been synthesized once,[13] its dextrorotatory isomer three times,[14–16] and the levorotatory isomer twice.[17,15] The synthesis of (−)-**1** by Thomas and Chambers started from ethyl L-lactate, comprised 19 linear steps, gave 0.3% overall yield of product, and elucidated its configuration.[17] Townsend and co-workers needed nine steps to transform D-alanine into the first synthetic specimen of (+)-**1** (6% overall yield).[14] 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).[15] Very recently, Takabe and co-workers completed a 12-step synthesis of (+)-**1** (3% overall yield) from methyl propionate that included an enzymatic resolution.[16] Modifications of the above-mentioned routes,[13,14] spin-off products thereof,[15,17] or semisyntheses[18] from natural (+)-**1** have provided dozens of racemic[19] or enantiomerically pure[20] 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".[6] 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.



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

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_N' attack. The stereochemistry of such vinyl epoxide openings has been investigated almost[22] only with non-sulfur nucleophiles[23a,b] and only[24] with simpler vinyl epoxides than our sterically hindered and alkoxycarbonyl-substituted substrates **4** or *ent*-**4**; both *syn*[23] and *anti*[23a,b] 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 silylation of an appropriately configured vinyl glycidol. The latter would be obtained from a Sharpless asymmetric epoxidation[25] (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[26]

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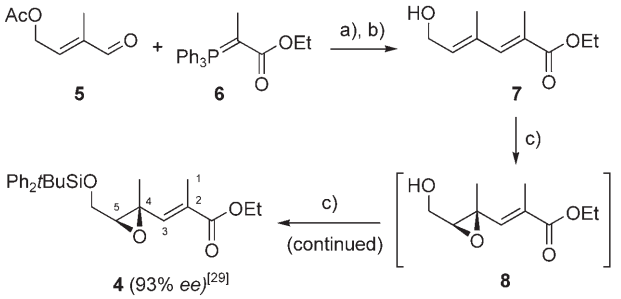
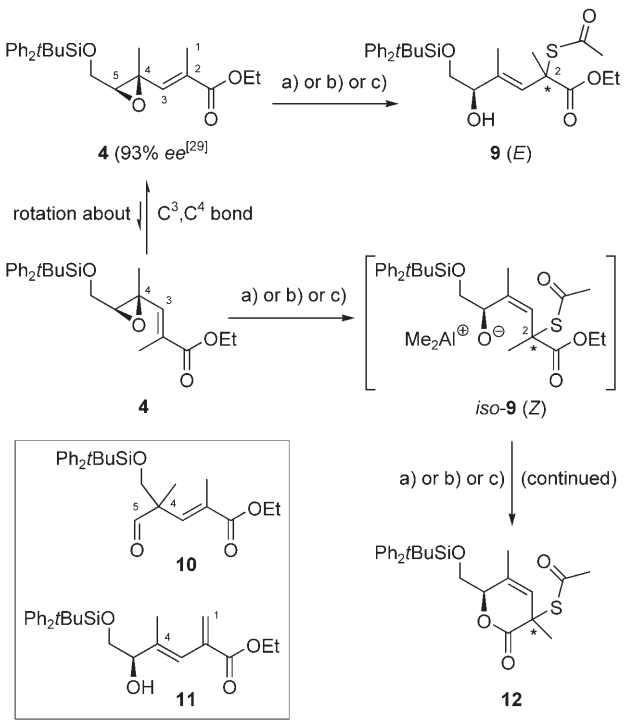


Scheme 2. Synthesis of vinyl epoxide **4**. a) Addition of **5** to a solution of **6** (1.1 equiv) in CH_2Cl_2, 50 °C, 5 h (Ref. [21]: 85 %); b) NaOH (5 mol %), EtOH, 25 °C, 12 h; 84 % over two steps (Ref. [21]: 91 %; 77 % over both steps); c) *t*BuOOH (2.0 equiv), L-(+)-DIPT (12 mol %), $Ti(OiPr)_4$ (10 mol %), CH_2Cl_2, 4-Å M.S., −30 °C, 12 h; PPh_3 (2.0 equiv); $tBuPh_2SiCl$ (1.0 equiv), imidazole (2.2 equiv), CH_2Cl_2, 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.[21] Pentadienol **7** was then subjected to a catalytic[25b] SAE.[28] 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*.[29] 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*.[29]

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_2S. 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_2CO_3 led to only incomplete conversion of **4**, while Cs_2CO_3, 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.[31] 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 by-products **10**–**12**) were obtained when exactly 5.0 equivalents each of Me_3Al and thioacetic acid were combined in



Scheme 3. Optimization of a model thiolysis. a) Reagents (see Table 1), CH_2Cl_2, −78 °C, 3 h; b) reagents, CH_2Cl_2, −78→25 °C, 60 min; −78 °C, addition of **4**; −78→25 °C, 2 h; c) reagents, CH_2Cl_2, −78→25 °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
a	$BF_3{\cdot}OEt_2$ (1.0), AcSH (0.0–1.0)	up to 50 % **10** (51 % *ee*)
b	$AlMe_3$ (4.0), AcSH (4.0–5.0)	19 % **9** + up to 10 % **11**, + up to 10 % **12**
c	$AlMe_3$ (5.0), AcSH (5.0)	48 % **9**

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

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[33] 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^4–O bond (broken) to the C^2–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,[17] 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**→**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 $NaIO_4$ to afford aldehyde **16** in 90 % yield. Surprisingly, olefination of **16** with methylenetriphenylphosphorane gave the required diene **15** with

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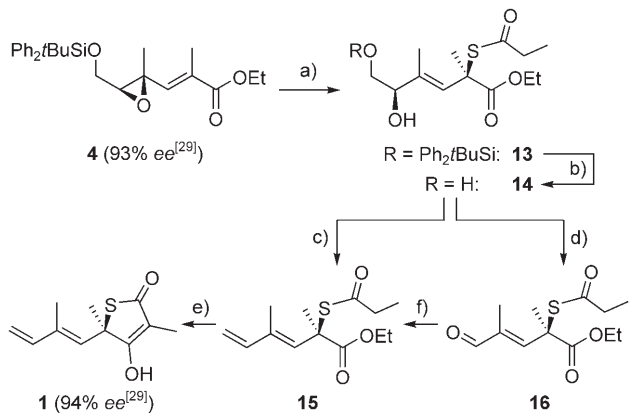
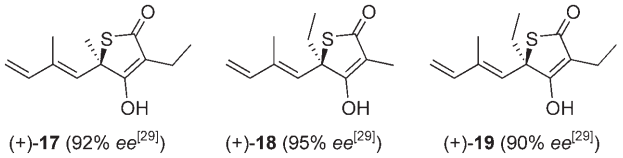


Scheme 4. Total synthesis of (+)-thiolactomycin (**1**). a) Thiopropionic acid (5.0 equiv), $AlMe_3$ (5.0 equiv), CH_2Cl_2, −78→25 °C, 60 min; −78 °C; addition of **4**, CH_2Cl_2, −78→25 °C, 2 h; 60%; b) HF/pyridine, THF, 25 °C, 1.5 h; 85%; c) I_2 (4.0 equiv), PPh_3 (4.0 equiv), imidazole (5.0 equiv), toluene, 0→25 °C, 40 min; 69%; d) $NaIO_4$ (1.0 equiv), dioxane/H_2O, 25 °C, 20 min; 90%; e) LiHMDS (2.5 equiv), THF, −78 °C, 2.5 h; 65% (Ref. [14]: 70%); f) $MePPh_3Br$ (1.3 equiv), *n*BuLi (1.1 equiv), THF (degassed), 0→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_3, 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*[29]) involved a Dieckmann condensation of diester **15** (Scheme 4, step e) as reported by Townsend and co-workers.[14] 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).[35] Thiotetronic acid (+)-**17** is a non-natural homologue of thiolactomycin (**1**), whereas (+)-**18** and (+)-**19** are antibiotics known as 834-B1[36] and thiotetromycin, respectively.[37] 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 SAEs of alkoxycarbonyl-substituted pentadienols, *anti*-selective S_N' thiolyses of vinyl epoxides, and olefin-forming *vic*-didesoxygenations.



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

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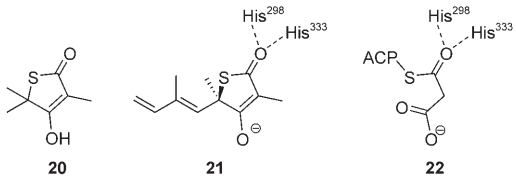
[1] a) J. Wang, S. M. Soisson, K. Young, W. Shoop, S. Kodali, A. Galgoci, R. Painter, G. Parthasarathy, Y. S. Tang, R. Cummings, S. Ha, K. Dorso, M. Motyl, H. Jayasuriya, J. Ondeyka, K. Herath, C. Zhang, L. Hernandez, J. Allocco, A. Basilio, J. R. Tormo, O. Genilloud, F. Vicente, F. Pelaez, L. Colwell, S. H. Lee, B. Michael, T. Felcetto, C. Gill, L. L. Silver, J. D. Hermes, K. Bartizal, J. Barrett, D. Schmatz, J. W. Becker, D. Cully, S. B. Singh, *Nature* **2006**, *441*, 358–361; b) F. von Nussbaum, M. Brands, B. Hinzen, S. Weigand, D. Häbich, *Angew. Chem.* **2006**, *118*, 5194–5254; *Angew. Chem. Int. Ed.* **2006**, *45*, 5072–5129.
[2] H. Oishi, T. Noto, H. Sasaki, K. Suzuki, T. Hayashi, H. Okazaki, K. Ando, M. Sawada, *J. Antibiot.* **1982**, *35*, 391–419.
[3] R. A. Slayden, R. E. Lee, J. W. Armour, A. M. Cooper, I. M. Orme, P. J. Brennan, G. S. Besra, *Antimicrob. Agents Chemother.* **1996**, *40*, 2813–2819.
[4] a) R. F. Waller, P. J. Keeling, R. G. Donald, B. Streipen, E. Handman, E. Lang-Umnasch, A. F. Cowman, G. S. Besra, D. S. Roos, G. I. McFadden, *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 12352–12357; b) S. M. Jones, J. E. Urch, R. Brun, J. L. Harwood, C. Berry, I. H. Gilbert, *Biorg. Med. Chem.* **2004**, *12*, 683–692.
[5] Review: R. J. Heath, S. W. White, C. O. Rock, *Appl. Microbiol. Biotechnol.* **2002**, *58*, 695–703.
[6] Y.-M. Zhang, S. W. White, C. O. Rock, *J. Biol. Chem.* **2006**, *281*, 17541–17544.
[7] R. J. Heath, S. Jackowski, C. O. Rock in *Biochemistry of Lipids, Lipoproteins and Membranes* (Eds.: D. E. Vance, J. E. Vance), 4th ed., Elsevier, **2002**, pp. 56–63 and 88–89.
[8] J. T. Tsay, C. O. Rock, S. Jackowski, *J. Bacteriology* **1992**, *174*, 508–513.
[9] A. C. Price, K.-H. Choi, R. J. Heath, Z. Li, S. W. White, C. O. Rock, *J. Biol. Chem.* **2001**, *276*, 6551–6559.
[10] If the acidities of thiolactomycin and malonyl-ACP in the enzyme pocket resemble those of model compounds **20**[11] ($pK_a = 4.1$)[12] and monoethyl malonate ($pK_a = 3.7$)[12] in water, the enzyme is likely to bind the deprotonated rather than neutral forms of thiolactomycin (**21**) and malonyl-ACP (**22**).



[11] K. L. Dormann, Dissertation in preparation, Universität Freiburg.
[12] From titrations of 5–10 μM aqueous solutions with 0.1M NaOH from a Schellbach burette using a membrane pH meter HI 8314 (HANNA instruments) and with graphical interpretation of data.
[13] C.-L. J. Wang, J. M. Salvino, *Tetrahedron Lett.* **1984**, *25*, 5243–5246 (11% yield over the five steps from methyl α-propionate).
[14] J. M. McFadden, G. L. Frehywot, C. A. Townsend, *Org. Lett.* **2002**, *4*, 3859–3862.

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[15] K. Ohata, S. Terashima, *Tetrahedron Lett.* **2006**, *47*, 2787 – 2791.

[16] K.-i. Toyama, T. Tauchi, N. Mase, H. Yoda, K. Takabe, *Tetrahedron Lett.* **2006**, *47*, 7163 – 7166. The authors reported the synthesis of "*R*-(−)"-thiolactomycin but meant *R*-(+)-thiolactomycin (personal communication between N.M. and R.B.).

[17] M. S. Chambers, E. J. Thomas, *J. Chem. Soc. Chem. Commun.* **1989**, 23 – 24.

[18] a) S. M. Sakya, M. Suarez-Contreras, J. P. Dirlam, T. N. O'Connell, S. F. Hayashi, S. L. Santoro, B. J. Kamicker, D. M. George, C. B. Ziegler, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2751 – 2754; b) P. Kim, Y.-M. Zhang, G. Shenoy, Q.-A. Nguyen, H. I. Boshoff, U. H. Manjunatha, M. B. Goodwin, J. Lonsdale, A. C. Proce, D. J. Miller, K. Duncan, S. W. White, C. O. Rock, C. E. Barry III, C. S. Dowd, *J. Med. Chem.* **2006**, *49*, 159 – 171.

[19] Racemic analogues of (+)-**1** synthesized since 2003: a) S. J. Senior, P. A. Illarionov, S. S. Gurcha, I. B. Campbell, M. L. Schaeffer, D. E. Minnikin, G. S. Besra, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3685 – 3688; b) Ref. [4b]; c) J. M. McFadden, S. M. Medghalchi, J. N. Thupari, M. L. Pinn, A. Vadlamudi, K. I. Miller, F. P. Kuhajda, C. A. Townsend, *J. Med. Chem.* **2005**, *48*, 946 – 961; d) A. Kamal, A. A. Shaik, R. Sinha, J. S. Yadav, S. K. Arora, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1927 – 1929; e) P. Kim, C. E. Barry III, C. S. Dowd, *Tetrahedron Lett.* **2006**, *47*, 3447 – 3451.

[20] Enantiomerically pure analogues of (+)-**1**: a) M. S. Chambers, E. J. Thomas, D. J. Williams, *J. Chem. Soc. Chem. Commun.* **1987**, 1228 – 1230; b) Ref. [17]; c) M. S. Chambers, E. J. Thomas, *J. Chem. Soc. Perkin Trans. 1* **1997**, 417 – 431; d) Ref. [18]; e) Ref. [15]; f) Ref. [19e].

[21] O. Böhnke, Dissertation, Universität Freiburg, **2002**.

[22] S nucleophiles such as PhSH (with CuI, $AlEt_3$, or Et_3B), Me_3SiSPh (with ZnI_2 or a Pd catalyst), and $Bi(SPh)_3$ effect S_N' openings of vinyl epoxides devoid of a possibility of *syn*- or *anti*-selectivity. To the best of our knowledge, the only precedents of the latter bias stem from S_N' (versus S_N) ring openings of vinyl epoxides with RSH/NEt_3; they proceeded with a 1:1 ratio of *syn*/*anti* attack: E. J. Corey, W.-G. Su, *Tetrahedron Lett.* **1990**, *31*, 2113 – 2116.

[23] Reviews on non-catalyzed S_N' openings of vinyl epoxides: a) R. M. Magid, *Tetrahedron* **1980**, *36*, 1901 – 1930; b) J. A. Marshall, *Chem. Rev.* **1989**, *89*, 1503 – 1511. Reviews on *syn*-selective Pd-catalyzed S_N' openings of vinyl epoxides: c) B. M. Trost, D. L. Van Vranken, *Chem. Rev.* **1996**, *96*, 395 – 422; d) J. Tsuji, T. Mandai, *Synthesis* **1996**, 1 – 24; e) A. Heumann in *Transition Metals in Organic Synthesis* (Eds.: M. Beller, C. Bolm), Wiley-VCH, Weinheim, **2004**, pp. 307 – 320.

[24] With Pd catalysis, alkoxycarbonyl-substituted vinyl epoxides related to **4** underwent stereoselective ring openings by O nucleophiles, albeit in the S_N rather than S_N' mode: B. M. Trost, J. K. Lynch, S. R. Angle, *Tetrahedron Lett.* **1987**, *28*, 375 – 378.

[25] Method: a) Using stoichiometric or near-stoichiometric amounts of Ti^{IV} tartrate: T. Katsuki, K. B. Sharpless, *J. Am. Chem. Soc.* **1980**, *102*, 5974 – 5976; b) using molecular sieves and less than 10 mol% of Ti^{IV} tartrate: R. M. Hanson, K. B. Sharpless, *J. Org. Chem.* **1986**, *51*, 1922 – 1925; Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko, H. Masamune, K. B. Sharpless, *J. Am. Chem. Soc.* **1987**, *109*, 5765 – 5780.

[26] All new compounds gave satisfactory ^1H NMR, ^{13}C NMR, and IR spectra (except **11, 12**) and correct combustion analyses (except **11**; low-resolution MS for **10**; high-resolution MS for **12**, **17**–**19**).

[27] Aldehyde **5** is an intermediate of the industrial synthesis of vitamin A by BASF.

[28] First SAE of an alkoxycarbonyl-substituted pentadienol: T. Takahashi, H. Watanabe, T. Kitahara, *Tetrahedron Lett.* **2003**, *44*, 9219 – 9222.

[29] The *ee* values of **4** and *ent*-**4** were determined by HPLC on a chiral stationary phase (L 7100, Merck Hitachi LaChrom; Chiralpak OD-H column, *n*-heptane/*i*PrOH 200:1, 0.8 mL min^{-1}, 25 °C, UV detection at 230 nm); t_r(*S* enantiomer) = 8.68 min, t_r(*R* enantiomer) = 10.25 min. The *ee* values of (+)-**1**, (+)-**17**, (+)-**18**, and (+)-**19** were measured by the same method but using different absorbents/eluents; in each case, we found t_r(minor enantiomer) < t_r(major enantiomer).

[30] Footnote [25] in: M. Caron, K. B. Sharpless, *J. Org. Chem.* **1985**, *50*, 1557 – 1560.

[31] a) T. Ooi, H. Yamamoto, *J. Am. Chem. Soc.* **1989**, *111*, 6431 – 6432; b) K. Maruoka, S. Nagahara, T. Ooi, H. Yamamoto, *Tetrahedron Lett.* **1989**, *30*, 5607 – 5610; c) M. E. Jung, R. Marquez, *Tetrahedron Lett.* **1999**, *40*, 3129 – 3132.

[32] Epoxide opening with Me_2AlSAc (prepared as described by E. J. Corey, D. J. Beames, *J. Am. Chem. Soc.* **1973**, *95*, 5829 – 5831): R. C. Newbold, T. L. Shih, H. Mrozik, M. H. Fisher, *Tetrahedron Lett.* **1993**, *34*, 3825 – 3828.

[33] **13**: Thiopropionic acid (1.03 g, 11.4 mmol, 5.0 equiv) in CH_2Cl_2 (40 mL) was added to $AlMe_3$ (2.0 M in heptane, 5.7 mL, 11 mmol, 5.0 equiv) in CH_2Cl_2 (40 mL) at −78 °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_2Cl_2 (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 (1 M, 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_2O (80 mL) and saturated Na/K tartrate solution (80 mL), dried over $MgSO_4$, and concentrated under vacuum. The residue was chromatographed on silica gel (eluent cyclohexane/ethyl acetate 7:1) to give the title compound, namely ethyl (2*R*,5*R*)-6-(*tert*-butyldiphenylsiloxy)-5-hydroxy-2,4-dimethyl-2-(propionylsulfanyl)-3-hexenoate (**13**; 730 mg, 60%) as a colorless oil. $[\alpha]_D^{25} = +13.3$ ($c = 1.03$ 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 mL min^{-1}, 25 °C, UV detection at 230 nm); t_r(*R* enantiomer) = 10.59 min, t_r(*S* enantiomer) = 12.55 min; ^1H NMR (300.1 MHz, TMS internal standard in $CDCl_3$): $\delta = 1.06$ (m_c, $C(CH_3)_3$), 1.11 (t, $J_{3',2'} = 7.5$ Hz, 3′-H_3), 1.22 (t, $J_{2'',1''} = 7.1$ Hz, 2″-H_3), 1.66 (d, $^4J_{4\text{-Me},3} = 1.0$ Hz, 4-CH_3), 1.84 (s, 2-CH_3), 2.48 (q, $J_{2',3'} = 7.6$ Hz, 2′-H_2), 2.60 (d, $J_{5\text{-OH},5} = 3.1$ 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_2), 4.05 (m_c, 5-H), 4.17 (q, $J_{1'',2''} = 7.1$ Hz, 1″-H_2), 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]); ^{13}C NMR (100.6 MHz, $CDCl_3$ internal standard in $CDCl_3$): $\delta = 9.55$ (C-3′), 14.05 (4-Me, C-2″), 19.31 ($C(CH_3)_3$), 25.94 (2-Me), 26.92 ($C(CH_3)_3$), 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_{meta}), 129.96 and 129.99 (C_{para}), 133.06 and 133.10 (C_{ipso}), 135.62 (C_{ortho}), 139.58 (C-4), 172.19 (C-1), 199.30 ppm (C-1′); IR (film): $\tilde{\nu} = 3510$, 2975, 2930, 2860, 1735, 1695, 1460, 1445, 1380, 1115, 1075 cm^{-1}; 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 α-ethyl analogue. The enantiopurity of these epoxides depended critically on the epoxidizing temperature and was not always the same.

[36] T. Sato, K. Suzuki, S. Kadota, K. Abe, S. Takamura, M. Iwanami, *J. Antibiot.* **1989**, *42*, 890 – 896.

[37] S. Omura, Y. Iwai, A. Nakagawa, R. Iwata, Y. Takahashi, H. Shimizu, H. Tanaka, *J. Antibiot.* **1983**, *36*, 109 – 114.

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