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The first total synthesis of trichostatin D

Seijiro Hosokawa,* Takashi Ogura, Hidetaka Togashi and Kuniaki Tatsuta*

Department of Applied Chemistry, School of Science and Engineering, Waseda University, 3-4-1 Ohkubo, Shinjuku-ku, Tokyo 169-8555, Japan

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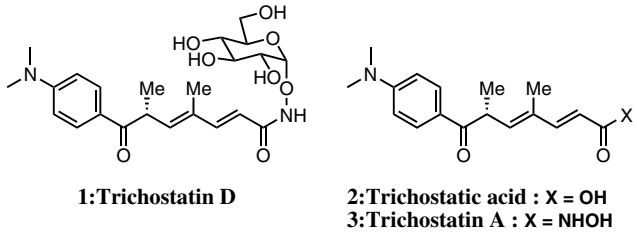
Abstract—Trichostatin D and 6-*epi*-trichostatin D have been stereoselectively synthesized through a remote stereoinduction with a chiral vinylketene silyl *N*,*O*-acetal and glycosylation of hydroxyimide under Mitsunobu conditions.

Trichostatin D[1] (**1**) was isolated as an inducer of phenotypic reversion in oncogene-transformed cells from the broth of an actinomycete *Streptomyces violaceusniger*. Because various oncogenes correlate with tumor phenotypes, the inducers of phenotypic reversion in oncogene-transformed cells are expected to be selective antitumor agents. On the other hand, trichostatin A[2] (**3**) has been used widely as a histone deacetylase inhibitor to a variety of biological researches.[3] Therefore, trichostatin families are interested in biological activities.

Trichostatic acid[4] (**2**), the common ketodiene unit of trichostatin families, and trichostatin A were synthesized to determine their absolute structures.[5]

Recently, we have established a novel stereoselective synthesis of the ketodiene skeleton by remote stereoinduction with vinylketene silyl *N*,*O*-acetals.[6] Such transformation is ideally suited for the syntheses of trichostatin families. Herein, we report a novel stereoselective synthesis of trichostatic acid (**2**) as well as the first synthesis of trichostatin D (**1**) and 6-*epi*-trichostatin D (**21**) (Fig. 1).

Our synthetic plan is shown in Scheme 1. Trichostatin D (**1**) would be synthesized by coupling of trichostatic acid (**2**) and *O*-glucosylhydroxyamine **4**. *O*-Glucosylhydroxyamine **4** might be derived directly from the protected glucose **5** by our methodology.[7] Trichostatic acid (**2**) should be synthesized from the C-7 hydroxy precursor



1:Trichostatin D

2:Trichostatic acid : X = OH
3:Trichostatin A : X = NHOH

Figure 1. Structure of trichostatin D and its congeners.

6 without epimerization at C-6 position. Stereoselective construction of **6** would be achieved by our remote stereocontrol methodology with the chiral vinylketene silyl *N*,*O*-acetal **8**.

At first, we examined stereoselective vinylogous Mukaiyama aldol reaction with the chiral vinylketene silyl *N*,*O*-acetal **8** and *p*-dimethylaminobenzaldehyde **7a** (Table 1). Only the conditions described as entry 1 gave the coupling products in high yield with fairly good selectivity. The major product was determined to be the (6*R*,7*R*)-isomer by X-ray crystallographic analysis.[8] Although the major product possessed the desired stereochemistry at C-6 position, the reaction took a long time with difficult separation from other isomers bearing unknown stereochemistries. Therefore, we further examined such remote stereoinduction with *p*-bromobenzaldehyde, which could be transformed to the *N*,*N*-dimethylaniline derivative (entries 2–4). With *p*-bromobenzaldehyde **7b**, the reaction proceeded smoothly and the coupling products were obtained in excellent yield with high stereoselectivity. The detectable isomers were only two in which the one isomer was produced predominantly.

Keywords: Total synthesis; Trichostatin D; Vinylketene silyl *N*,*O*-acetal; Glycosylation.
* Corresponding author. Tel./fax: +81 33 2003 203; e-mail: tatsuta@waseda.jp

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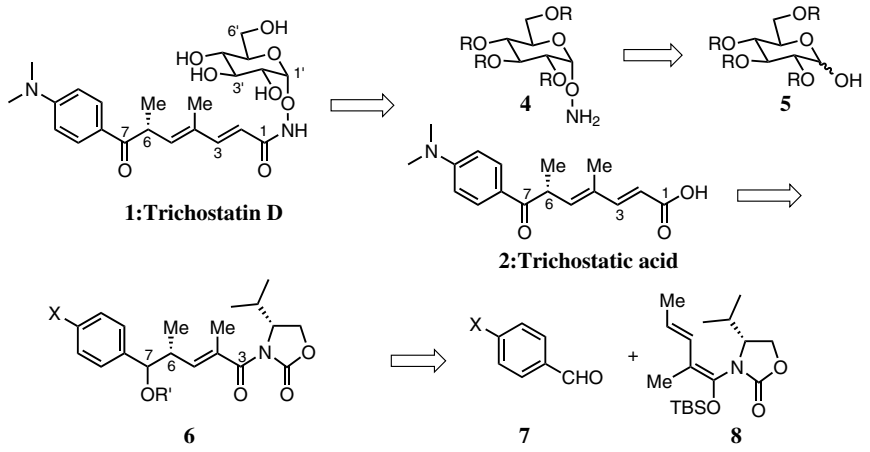
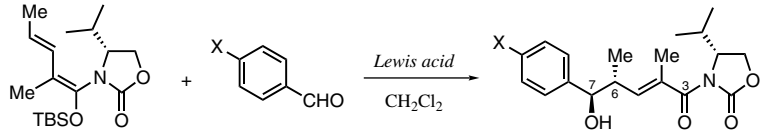


Scheme 1. Synthetic planning of trichostatic acid and trichostatin D.

Table 1. Asymmetric remote stereoinduction with 4-substituted benzaldehyde



Entry	Aldehyde	Lewis acid	Temperature (°C)	Time	Product	Yield (%)	Diastereo ratio[a,b]
1	**7a**	$BF_3{\cdot}OEt_2$	−30	5 days	**9a**	88	89:8:1.5:1.5
2	**7b**	$BF_3{\cdot}OEt_2$	−50	2.5 days	**9b**	85	94:6:<1:<1
3	**7b**	$SnCl_4$	−50	1.5 days	**9b**	98	96:4:<1:<1
4	**7b**	$TiCl_4$	−50	4 h	**9b**	97	96:4:<1:<1

[a] The diastereo ratio was determined by ^1H NMR spectroscopy.
[b] The stereochemistries of the minor isomers derived from **7a** were not determined and the minor product derived from **7b** was determined to be the (6*R*,7*S*)-isomer.

The stereochemistry of the major product was determined to be the (6*R*,7*R*)-isomer and the minor product to be the (6*R*,7*S*)-isomer by X-ray analysis. Both isomers were found to have the desired 6*R* stereochemistry. In the studies of the vinylogous Mukaiyama aldol reaction with the vinylketene silyl *N*,*O*-acetals, we proposed the transition state with the conformation of **8** shown in Figure 2.[6] Here we have disclosed the X-ray crystallographic studies of the starting vinylketene silyl *N*,*O*-acetal **8** (Fig. 2). Obviously, the isopropyl group covers the β face of the dienolate and the rotation of oxazolidone is restricted by the TBS group and the dienolate chain. As expected with this figure, we obtained only (6*R*)-isomers by coupling of **8** and **7b**. This finding suggested that the dienolate **8** would take a similar conformation in the solution at low temperature and be submitted to attack of an electrophile from the α face to afford the 6*R* configuration.

The major product of the remote stereoinduction with *p*-bromobenzaldehyde was isolated, after *O*-TBS protecting, by silica gel column chromatography (Scheme 2).

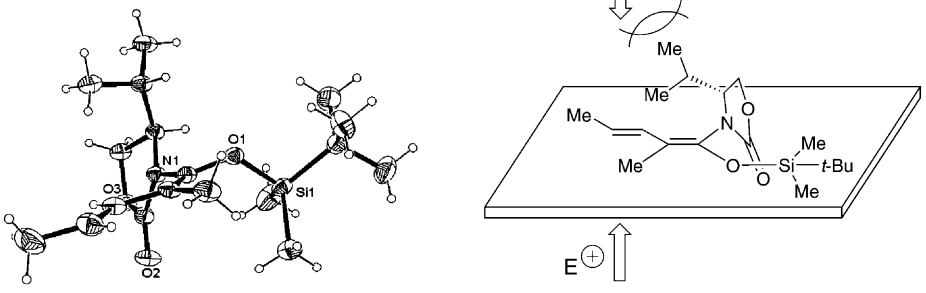
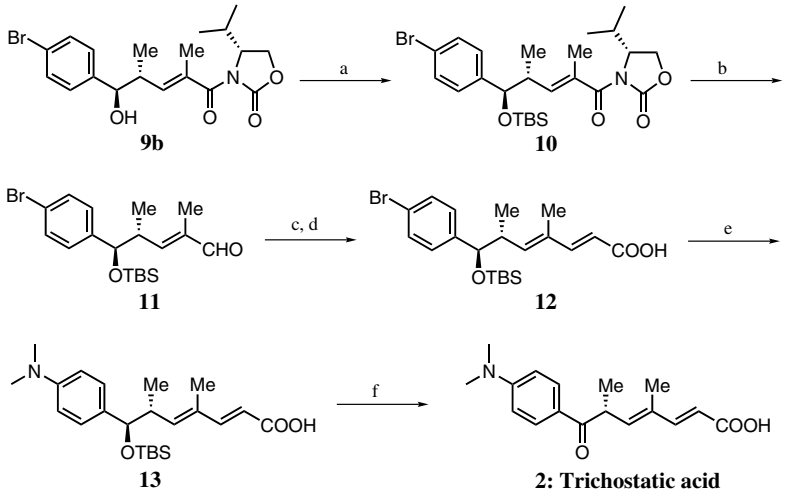


Figure 2. ORTEP drawing of the vinylketene silyl *N*,*O*-acetal **8**.



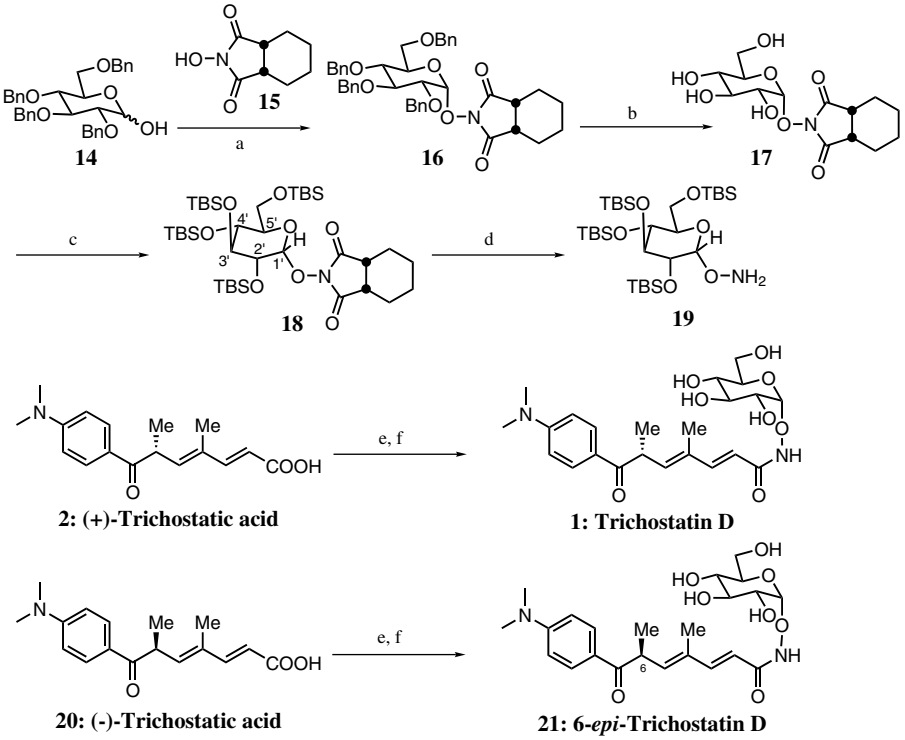
Scheme 2. Reagents and conditions: (a) TBSCl, imidazole, DMF, 50 °C, 36 h, quant; (b) DIBAL, CH_2Cl_2, −78 °C, 20 min, 91%; (c) $Ph_3P{=}CHCO_2Et$, PhMe, 70 °C, 13 h, 97%; (d) 0.5 M LiOH aq, MeOH, 50 °C, 2d, quant; (e) $Pd_2(dba)_3{\cdot}CHCl_3$, *t*-Bu_2P(*o*-biphenyl), Me_2NH, PhMe, 70 °C, 15 h, 71%; (f) DDQ, CH_2Cl_2–H_2O (20:1), 0 °C, 5 min, 72%.

Thus, we chose the product **9b** as an intermediate for the enantioselective synthesis of trichostatins.

Synthesis of (+)-trichostatic acid (**2**) is shown in Scheme 2. The imide **10** was directly converted to the α,β-unsaturated aldehyde **11** in high yield by treatment with DIBAL at −78 °C. Wittig reaction followed by hydrolysis gave the carboxylic acid **12**, which was submitted to the next palladium catalyzed amination.[9] Oxidation at the benzyl position of **13** gave (+)-trichostatic acid (**2**), which was identical with the natural product in NMR, IR, mass spectral analysis, and optical rotation.[2,5b]

Synthesis of *O*-glucosylhydroxyamine and achievement of total synthesis of trichostatin D (**1**) are described in Scheme 3.

Hydroxyimide **15**[10] was introduced at the anomeric position of the suitably protected D-glucose **14** with diisopropylazodicarbonate and triphenylphosphine at



Scheme 3. Reagents and conditions: (a) DIAD, PPh_3, PhMe, 100 °C, 20 min, 83% (α:β = 5:1); (b) H_2, $Pd(OH)_2$–C, EtOH, rt, 2 h, quant; (c) TBSOTf, 2,6-lutidine, DMF, rt, 2 h, 60%; (d) $MeNH{-}NH_2$, MeOH, rt, 10 h, quant; (e) **19**, WSCI·HCl, THF, 50 °C, 5.5 h, 48% for **1**; 14.5 h, 52% for **21**; (f) 70% aq TFA, rt, 1 h, quant. for **1**; 10 min, 91% for **21**. WSCI = 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide.

100 °C in toluene in 83% yield with α:β = 5:1 selectivity. After separation of anomers by silica gel column chromatography, de-*O*-benzylation followed by silylation gave the glucoside **18** ($J_{1',2'} = 4$ Hz, $J_{2',3'} = 4$ Hz, $J_{2',4'} = 1$ Hz, $J_{3',4'} = 0$ Hz, $J_{4',5'} = 9$ Hz). De-*N*-protection of **18** with methylhydrazine gave the *O*-glucosylhydroxyamine **19**. Finally, condensation of **2** with **19** followed by de-*O*-protection afforded trichostatin D (**1**), which was identical in all respects with the natural product.[11–13] Additionally, we synthesized 6-*epi*-trichostatin D **21** by coupling of (−)-trichostatic acid **20**[14] with the *O*-glucosylhydroxyamine **19**. It was found that the optical rotations of these isomers (**1** and **21**) were much different (trichostatin D (**1**): $[\alpha]_D^{25} + 225$ (*c* 0.53, MeOH), 6-*epi*-trichostatin D (**21**): $[\alpha]_D^{26} + 46$ (*c* 0.43, MeOH), although NMR spectra of these isomers were superimposed.[13]

In conclusion, we have achieved the stereoselective synthesis of (+)-trichostatic acid, trichostatin D and 6-*epi*-trichostatin D by our original methodologies including remote stereoinduction with vinylketene silyl *N*,*O*-acetal, direct reduction of α,β-unsaturated imide to α,β-unsaturated aldehyde, and direct glycosylation of D-glucose with *N*-hydroxyimide using Mitsunobu conditions.

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8. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 249741 for **8**, CCDC 249740 for **9a**, CCDC 249742 for **9b**, and CCDC 249438 for (6*R*,6*S*)-isomer of **9b**. Copies of the data can be obtained, free charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: http://deposit@ccdc.cam.ac.uk].
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11. The spectra including ^{1}H NMR, ^{13}C NMR, IR of synthetic trichostatin D were identical with those of the natural product kindly supplied by Prof. Yoichi Hayakawa (Tokyo University of Science).
12. We also examined this transformation with the 2′,3′,4′-tris(trimethylsiloxy) analogue of **19** to avoid epimerization at C-6 position during de-protection. Removal of silyl groups proceeded under milder conditions (HF–pyridine: pyridine = 1:6 in CH_2Cl_2, rt, 30 min), but the product was isolated in lower yield (21% in 2 steps) with lower $[\alpha]_D$ value ($[\alpha]_D^{25} = +210$, *c* 0.19, MeOH).
13. Selected data; **9b**: $[\alpha]_D^{27} + 100$ (*c* 1.02, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.79 (3H, d, *J* = 7.0 Hz), 0.94 (3H, d, *J* = 7.0 Hz), 0.95 (3H, d, *J* = 7.0 Hz), 2.00 (3H, d, *J* = 1.5 Hz), 2.35 (1H, qqd, *J* = 7.0, 7.0, and 4.5 Hz), 2.77 (1H, ddq, *J* = 10.0, 9.0, and 7.0 Hz), 3.81 (1H, d, *J* = 2.0 Hz), 4.21 (1H, dd, *J* = 9.0 and 6.0 Hz), 4.28 (1H, dd, *J* = 9.0 and 2.0 Hz), 4.36 (1H, dd, *J* = 9.0 and 9.0 Hz), 4.60 (1H, ddd, 9.0, 6.0, and 4.5 Hz), 5.84 (1H, dq, *J* = 10.0 and 1.5 Hz), 7.26 (2H, d, *J* = 8.5 Hz), 7.47 (2H, d, *J* = 8.5 Hz). **19**: $[\alpha]_D^{27} + 56$ (*c* 0.49, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.06 (6H, s, –SiMe × 2), 0.07 (6H, s, –SiMe × 2), 0.08 (3H, s, –SiMe), 0.09 (3H, s, –SiMe), 0.10 (3H, s, –SiMe), 0.88 (18H, s, *t*-Bu × 2), 0.90 (18H, s, *t*-Bu × 2), 3.65 (1H, ddd, *J* = 8.5, 2.0, and 1.0 Hz, H-4), 3.68 (1H, dd, *J* = 11.0 and 6.0 Hz, H-6), 3.77 (1H, dd, *J* = 4.5 and 2.0 Hz, H-3), 3.84 (1H, dd, *J* = 11.0 and 2.5 Hz, H-6), 3.89 (1H, ddd, *J* = 4.5, 3.5, and 1.0 Hz, H-2), 3.95 (1H, ddd, *J* = 8.5, 6.0, and 2.5 Hz, H-5), 4.87 (1H, d, *J* = 3.5 Hz, H-1), 5.39–5.51 (2H, br s, $–NH_2$). (+)-Trichostatic acid (**2**): $[\alpha]_D^{26} + 154$ (*c* 0.32, MeOH). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.32 (3H, d, *J* = 7.0 Hz), 1.93 (3H, d, *J* = 1.0 Hz), 3.06 (6H, s), 4.40 (1H, dq, *J* = 9.5 and 7.0 Hz), 5.83 (1H, d, *J* = 16.0 Hz), 6.09 (1H, br d, *J* = 9.5 Hz), 6.65 (2H, d, *J* = 9.0 Hz), 7.38 (1H, d, *J* = 16.0 Hz), 7.85 (2H, d, *J* = 9.0 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ 12.5, 17.7, 30.9, 40.0, 40.8, 110.7, 115.8, 123.8, 130.6, 132.6, 142.9, 151.3, 153.5, 171.8, 198.3, 207.0. Trichostatin D (**1**): $[\alpha]_D^{25} + 225$ (*c* 0.53, MeOH). ^{1}H NMR (600 MHz, DMSO-d_6, 75 °C): δ 1.20 (3H, d, *J* = 6.0 Hz, 6-Me), 1.86 (3H, s, 4-Me), 3.00 (6H, s, $–NMe_2$), 3.20 (1H, ddd, *J* = 9.0, 9.0, and 4.0 Hz, H-4′), 3.31 (1H, dd, *J* = 9.0 and 3.0 Hz, H-2′), 3.46 (1H, br dd, *J* = 9.0 and 9.0 Hz, H-3′), 3.54 (1H, ddd, *J* = 12.0, 5.0, and 5.0 Hz, H-6′), 3.61 (1H, br d, *J* = 12.0 Hz, H-6′), 3.71 (1H, m, H-5′), 4.04 (1H, br, –OH), 4.44 (1H, dq, *J* = 9.0 and 6.0 Hz, H-6), 4.58 (1H, br, –OH), 4.65 (1H, d, *J* = 4.0 Hz, –OH), 4.80 (1H, br, –OH), 4.91 (1H, d, *J* = 3.0 Hz, H-1′), 5.84 (1H, d, *J* = 16.0 Hz,

H-2, 25 °C), 5.90 (1H, d, J = 9.0 Hz, H-5), 6.71 (2H, d, J = 9.0 Hz, H-10 and H-12), 7.07 (1H, d, J = 15.0 Hz, H-3), 7.79 (2H, d, J = 9.0 Hz, H-9 and H-13). ^{13}C NMR (150 MHz, DMSO-d_6): δ 12.6, 17.8, 60.4, 69.6, 71.7, 73.3, 73.8, 104.2, 111.0, 116.9, 123.3, 130.5, 140.2, 144.2, 153.5, 197.9. 6-*epi*-Trichostatin D (**22**): $[\alpha]_D^{26}$ + 46 (*c* 0.43, MeOH). ^{1}H NMR (600 MHz, DMSO-d_6, 75 °C): δ 1.20 (3H, d, J = 7.0 Hz, 6-Me), 1.86 (3H, d, J = 1.0 Hz, 4-Me), 3.00 (6H, s, –NMe_2), 3.20 (1H, ddd, J = 10.0, 10.0, and 4.0 Hz, H-4′), 3.30 (1H, dd, J = 10.0 and 3.0 Hz, H-2′), 3.45 (1H, ddd, J = 10.0, 10.0, and 4.0 Hz, H-3′), 3.55 (1H, dd, J = 12.0 and 5.0 Hz, H-6′), 3.61 (1H, dd, J = 12.0 and 2.0 Hz, H-6′), 3.72 (1H, ddd, J = 10.0, 5.0, and 2.0 Hz, H-5′), 4.05 (1H, br, –OH), 4.44 (1H, dq, J = 9.0 and 7.0 Hz, H-6), 4.58 (1H, d, J = 5.0 Hz –OH), 4.65 (1H, d, J = 4.0 Hz, –OH), 4.91 (1H, d, J = 3.0 Hz, H-1′), 5.83 (1H, d, J = 16.0 Hz, H-2, 25 °C), 5.90 (1H, d, J = 9.0 Hz, H-5), 6.71 (2H, d, J = 9.0 Hz, H-10 and H-12), 7.07 (1H, d, J = 15.0 Hz, H-3), 7.79 (2H, d, J = 9.0 Hz, H-9 and H-13). ^{13}C NMR (150 MHz, DMSO-d_6): δ 12.6, 17.8, 60.4, 69.6, 71.7, 73.3, 73.8, 104.2, 111.0, 117.0, 123.3, 130.5, 140.2, 144.2, 153.5, 197.9.

14. (−)-Trichostatic acid (**20**) ($[\alpha]_D^{26}$ − 150, *c* 0.32, MeOH) was synthesized from the *ent*-**8** in the same manner.