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Efficient, Enantioselective Organocatalytic Synthesis of Trichostatin A

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Abstract: An efficient, highly stereocontrolled total synthesis of trichostatin A (**1**) has been achieved in 9 steps with 17.4% overall yield and >99% optical purity from readily available achiral starting materials. The key features of this synthesis include the L-proline-promoted, highly enantioselective cross-aldol reaction as a crucial step for the construction of the C-6 chiral center and the minimization of racemization by final step oxidation of the OH group to a ketone at position 7.

Keywords: aldol reaction; asymmetric organocatalysis; HDAC inhibitors; proline; trichostatin A

Introduction

The intriguing biological activity of trichostatin A (**1**) on histone deacetylases (HDACs) has elicited a considerable amount of attention from both the synthetic and the biological communities (Figure 1).[1] As a potent and specific HDAC inhibitor,[2] trichostatin A (**1**) has been extensively used as a valuable biological tool for studying the functions of the enzyme and as a lead compound for developing new anti-cancer agents.[1–3] To date, surprisingly, only two methods for its total synthesis have been described, reported by the research groups of Fleming[4] and Mori,[5] respectively. In Mori's asymmetric synthesis of trichostatin A (**1**), the approach starting from chiral (*R*)-methyl 3-hydroxy-2-methylpropionate suffers from a long synthetic sequence (18 steps) and a low overall yield (6.1%).[5] In this paper, we disclose a practical, enantioselective organocatalytic route to the preparation of the title compound in 9 steps with a significantly improved yield (17.4% overall) from readily available, achiral starting materials.

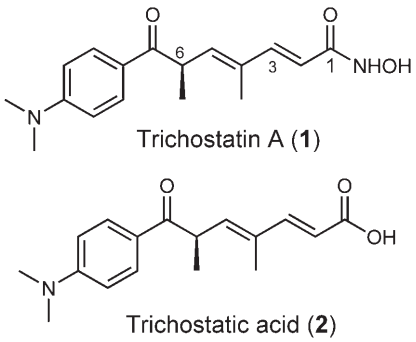

Figure 1. (+)-Trichostatin A (**1**) and trichostatic acid (**2**).

Results and Discussion

Our synthesis strategy is described in Scheme 1. To develop an efficient, enantioselective approach to the synthesis of (+)-trichostatin A (**1**), two critical issues need to be addressed: building the chiral center at C-6 and minimizing its racemization during the course of the synthesis because of the adjacent carbonyl chiral center C-6 easily undergoes racemization. We postulate that one stone can kill two birds at the same time by using a catalytic, enantioselective aldol reaction as a key step to form a chiral β-hydroxy aldehyde **4**, which can be accessed by an L-proline-catalyzed cross-aldol reaction between aldehydes **5** and **6**.[6–10] The aldol adduct **4** serves as a precursor for the synthesis of the key intermediate **3** *via* the Wittig reac-

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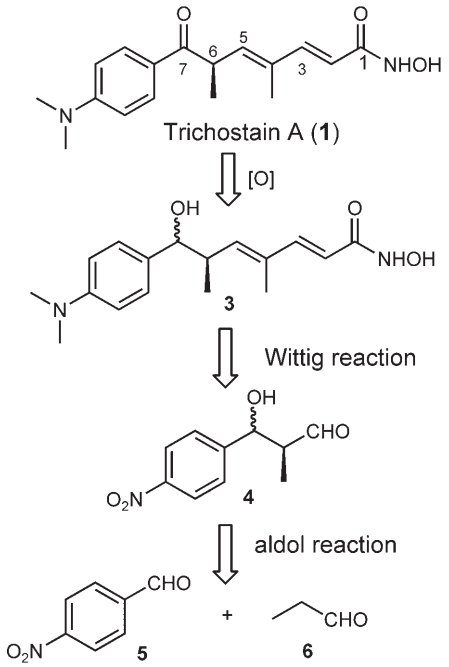


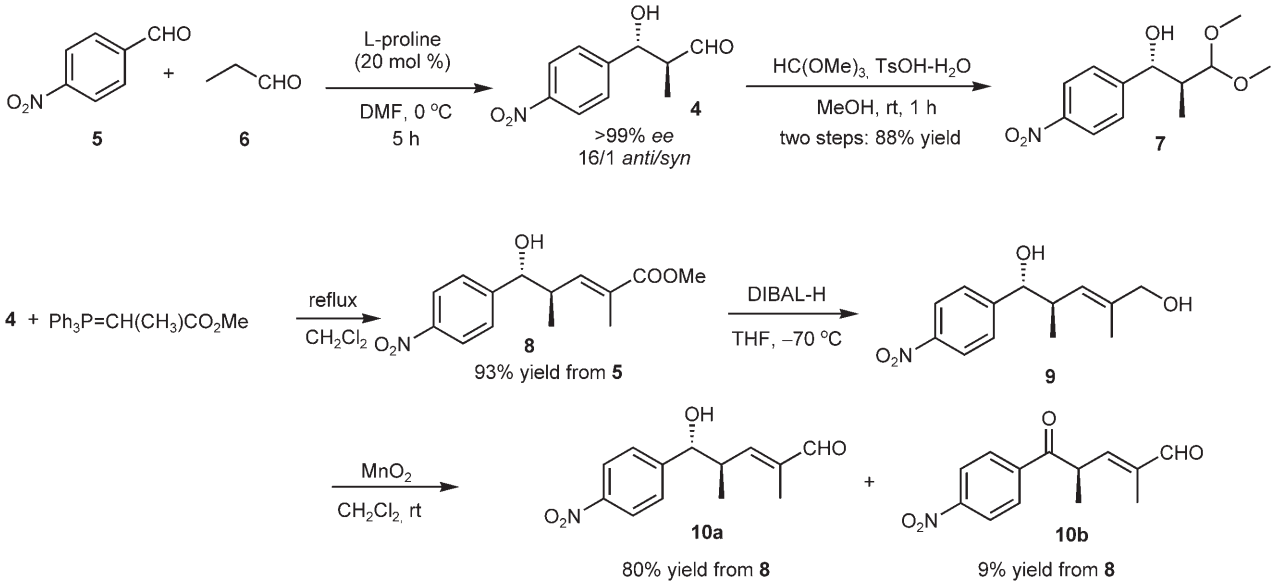
Scheme 1. Retrosynthetic analysis of trichostatin A (**1**).

tion. Oxidation of the hydroxy group in **3** in the last step can lead to the target molecule **1** so that racemization can be significantly minimized during the synthesis. As demonstrated, the synthetic route we explore here can allow us to obtain **1** with an *ee* value of >99%.

After surveying several sets of reaction conditions, we found that by using MacMillan's protocol,[7d] the L-proline-catalyzed cross-aldol reaction between *p*-nitrobenzaldehyde (**5**) and propionaldehyde (**6**) afforded the desired aldol adduct **4** with the best results (> 99% *ee*, 16/1 *anti/syn* ratio) (Scheme 2). It should be noted that we found that, in this case, it was not necessary to add **6** dropwise to a solution of **5** for the cross-aldol reaction, as was required in MacMillan's procedure since the more reactive *p*-nitrobenzaldehyde (**5**) was used.[7d] Because of its quick decomposition on silica gel,[11] compound **4** was directly converted into acetal **7**. The more stable **7** enabled us to determine the stereoselectivities by its conversion into the respective Mosher esters (see Supporting Information).[12] Without purification, crude **4** was transformed into α, β-unsaturated ester **8** by a Wittig reaction with $Ph_3P{=}CH(CH_3)CO_2Me$ in 93% yield in two steps. The DIBAL-H mediated reduction was followed by MnO_2 oxidation[13] to give aldehyde **10a** as a major product in 80% yield in a two-step conversion and the overoxidized dicarbonyl species **10b** was identified as a minor product (9% yield).

Alternatively, compound **10a** could been obtained by reaction of **4** with 2-(triphenylphosphoranylidene)-propionaldehyde (**11**) in one step,[14] however, the low yield and poor *Z/E* selectivity were observed (Scheme 3).

The resulting aldehyde **10a** underwent a Horner–Emmons reaction with triethyl phosphonoacetate **(13)** to produce conjugated ester **14** in an excellent yield (Scheme 4).[15] It is realized that the C-6 chiral center in trichostatin A (**1**) is prone to racemization under both acid and basic conditions, and in Mori's approach, it took four more steps to prepare **1** from trichostatic acid (**2**) (Figure 1) in only 27% yield.[5] Therefore, as discussed earlier, our strategy was to perform the oxidation of the alcohol in the last step in order to avoid this problem. The nitro group in **14**



Scheme 2. Synthesis of intermediate **10a**.

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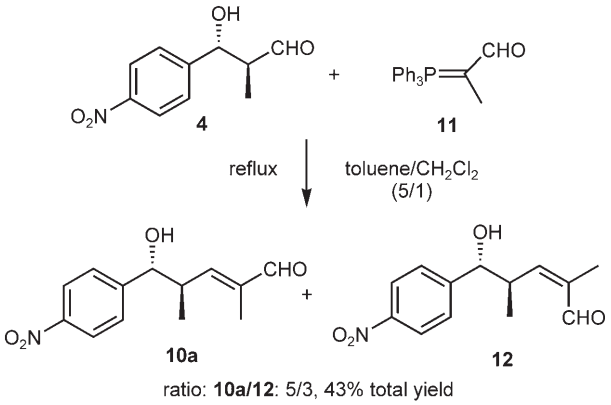


Scheme 3. An alternative approach to synthesis of **10a**.

was selectively reduced to the amine in **15** by Lindlar's catalyst-promoted hydrogenation without touching the unsaturated conjugated system.[16] Pure product **15** was obtained by recrystallization from a mixture of ethyl acetate and petroleum ether in 62% yield. Reductive amination[17] by the treatment with HCHO and $NaBH(OAc)_3$ in THF furnished the dimethylamine **16**, which was subsequently exposed to NH_2OH/MeOH solution to provide the hydroxamic acid **3.** Finally, benefiting from the strong electron-donating effect of the *p*-dimethylamine group, the benzylic hydroxy group of **3** was selectively oxidized by DDQ in dioxane without affecting the hydroxamic acid group to give the target trichostatin A (**1**).[5] The spectral data for the synthesized trichostatin A (**1**) matched those of the naturally occurring compound[18] and its optical purity was determined by chiral HPLC analysis with > 99% *ee*.[19]

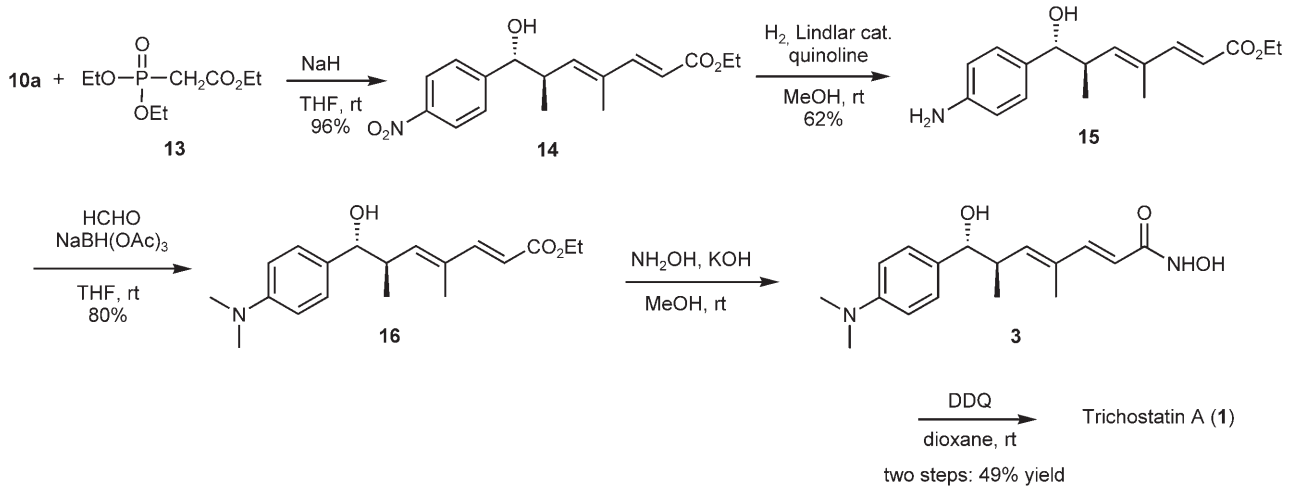
Conclusions

In conclusion, we have achieved a short, enantioselective synthesis of trichostatin A (**1**) in 9 steps with 17.4% overall yield. The key step in the synthesis is the utilization of L-proline-promoted aldol reactions to establish the chiral center in a completely stereocontrolled manner. Optically pure target molecule (> 99% *ee*) has been obtained by the developed synthetic route. To our knowledge, this synthesis is the shortest reported so far using readily available, cheap achiral materials. Our current efforts are directed toward applying this strategy for the large-scale synthesis of trichostatin A (**1**) and the preparation of its analogues to explore their biological activities.

Experimental Section

General Remarks

All non-aqueous reactions were performed in flame-dried glassware under an atmosphere of dry Ar, unless otherwise specified. THF was freshly distilled from sodium/benzophenone under Ar; CH_2Cl_2 was freshly distilled from CaH_2 under Ar. All other solvents were reagent grade. Petroleum ether refers to a mixture of alkanes with the boiling range 60–90 °C. ^1H and ^{13}C NMR spectra were recorded on Varian Mercury-300 and Varian Mercury-400 spectrometers. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, m = multiplet, br = broad. Infrared spectra were recorded on a Nicolet 750 FT-IR. Optical rotations were measured on a Perkin–Elmer model 341 polarimeter. Mass spectrometry was performed on Finnigan MAT 95 and Finnigan LCQ Deca spectrometers. High resolution mass spectra were measured on Finnigan MAT 95 and MicroMass Q-Tof ultima^{TM} mass spectrometers.



Scheme 4. Synthesis of trichostatin A (**1**).

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(*2S,3R*)-3-Hydroxy-2-methyl-3-(4-nitrophenyl)propanal (4)

To a solution of *p*-nitrobenzaldehyde (**5**; 3.02 g, 20 mmol) and L-proline (460 mg, 4 mmol, 0.2 equivs.) in 70 mL of DMF was added propionaldehyde (**6**; 2.88 mL, 40 mmol, 2.0 equivs.) in one portion at 0 °C. The resulting mixture was then stirred at same temperature for 5 h to reach completion. The reaction was quenched by addition of water and extracted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The resulting oil was used without further purification for next step; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.80$ (1 H, d, $J = 1.2$ Hz), 8.22 (2 H, d, $J = 8.8$ Hz), 7.55 (2 H, d, $J = 8.4$ Hz), 4.97 (1 H, d, $J = 8.0$ Hz), 3.41 (1 H, br), 2.77 (1 H, m), 1.00 (3 H, d, $J = 7.6$ Hz).

(*1R,2S*)-3, 3-Dimethoxy-2-methyl-1-(4-nitrophenyl)-propan-1-ol (7)

To a solution of **4** (2 mmol) in 4 mL of MeOH was added trimethyl orthoformate (0.32 g, 3 mmol, 1.5 equivs.) and *p*-toluenesulfonic acid monohydrate (38 mg, 0.2 mmol, 0.1 equiv.). The resulting pale yellow solution was stirred at room temperature for 1 h, then quenched by addition of saturated aqueous $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified on silica gel (petroleum ether/EtOAc, 6:1) to afford a colorless oil; yield: 0.45 g (88 %, two steps from **5**); $[\alpha]_D^{23}$: −6.94° (*c* 3.10, $CHCl_3$); IR (KBr): $\nu = 3444$, 2939, 2834, 1666, 1606, 1520, 1456, 1348, 1196, 1107, 1068, 947, 852, 756, 708 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.20$ (2 H, d, $J = 8.7$ Hz), 7.51 (2 H, d, $J = 8.7$ Hz), 4.72 (1 H, d, $J = 8.4$ Hz), 4.31 (1 H, d, $J = 5.7$ Hz), 3.50 (3 H, s), 3.42 (3 H, s), 2.11 (1 H, m), 0.69 (3 H, d, $J = 7.2$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 150.7$, 147.7, 128.2, 123.8, 108.9, 75.8, 56.5, 54.1, 42.8, 12.6; MS (EI): *m/z* (%) = 256 [M^++H], 223 (2.0), 152 (10), 75 (100), 72 (67); HR-MS (EI): *m/z* = 256.1199, calcd. for $C_{12}H_{18}NO_5$ (M^++H): 256.1185.

(*4R,5R,E*)-Methyl 5-Hydroxy-2, 4-dimethyl-5-(4-nitrophenyl)pent-2-enoate (8)

To a solution of **4** (20 mmol) in 40 mL of CH_2Cl_2 was added (1-methoxycarbonylethylidene)triphenylphosphorane (8.35 g, 24 mmol, 1.2 equivs.). The resulting yellow mixture was refluxed for 5 h. The reaction mixture was concentrated under reduced pressure and purified by silica gel column chromatography (petroleum ether/AcOEt, 5/1) to give a colorless oil; yield: 5.19 g (93 % in two steps); $[\alpha]_D^{24}$: +102.2° (*c* 1.024, $CHCl_3$); IR (KBr): $\nu = 3537$, 2960, 1714, 1649, 1603, 1514, 1437, 1342, 1265, 1240, 1221, 1065, 856, 748, 704 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.17$ (2 H, d, $J = 8.7$ Hz), 7.49 (2 H, d, $J = 8.7$ Hz), 6.69 (1 H, dd, $J = 9.9$, 1.5 Hz), 4.66 (1 H, d, $J = 6.6$ Hz), 3.71 (3 H, s), 2.82 (1 H, m), 2.61 (1 H, s), 1.73 (3 H, d, $J = 1.5$ Hz), 0.95 (3 H, d, $J = 6.9$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 168.3$, 149.8, 147.4, 142.3, 129.4, 127.4, 123.5, 77.2, 51.9, 41.3, 16.4, 12.6; MS (ESI): *m/z* = 302.08 (M^++Na); HR-MS (ESI): *m/z* = 302.0995, calcd. for $C_{14}H_{17}NO_5Na$ (M^++Na): 302.1004.

(*4R,5R,E*)-2, 4-Dimethyl-5-(4-nitrophenyl)pent-2-ene-1,5-diol (9)

To a solution of compound **8** (0.927 g, 3.33 mmol) in THF (10 mL) was added dropwise DIBAL-H (11.5 mL, 1.0 M in toluene, 11.5 mmol, 3.45 equivs.) at −70 °C under an argon atmosphere over a period of 30 min. After being stirred at the same temperature for another 30 min, the reaction mixture was quenched with saturated Rochelle salt solution (20 mL) and the temperature of the mixture was raised to room temperature. After being stirred at room temperature for 1 h vigorously, the mixture was extracted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was used for the next reaction without further purification; $[\alpha]_D^{24}$: +100.6° (*c* 0.638, $CHCl_3$); IR (KBr): $\nu =$ 3373, 2966, 2928, 2872, 1606, 1518, 1456, 1348, 1109, 1013, 851, 754, 704 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.18$ (2 H, d, $J = 8.7$ Hz), 7.50 (2 H, d, $J = 8.7$ Hz), 5.34 (1 H, dd, $J = 9.9$, 1.5 Hz), 4.46 (1 H, d, $J = 7.8$ Hz), 4.01 (2 H, s), 2.69 (1 H, m), 2.6–1.8 (2 H, br), 1.61 (3 H, d, $J = 1.2$ Hz), 0.84 (3 H, d, $J = 6.9$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 150.3$, 147.2, 137.9, 127.6, 126.3, 123.3, 78.0, 68.0, 40.5, 17.2, 14.1; MS (EI): *m/z* (%) = 233 [M^+-H_2O], 216, 203, 185 (6.0), 153 (100), 142 (70), 136 (46), 106 (20), 100 (23), 82 (84), 77 (12), 67 (28), 60 (8).

(*4R,5R,E*)-5-Hydroxy-2,4-dimethyl-5-(4-nitrophenyl)-pent-2-enal (10a)

To a solution of compound **9** in CH_2Cl_2 (40 mL) was added γ-MnO_2 (3.2 g). The resulting mixture was then stirred at room temperature for 1 h to reach completion. The mixture was filtered and washed with a large amount of EtOAc. The organic layer was concentrated under reduced pressure and purified by silica gel column chromatography (petroleum ether/AcOEt, 3/1) to give **10a** as a crystalline product; yield: 663 mg (80 % in two steps). Compound **10b** was obtained as a by-product; yield: 73 mg (8.9 % in two steps).

Compound **10a**: mp 92–94 °C; $[\alpha]_D^{21}$: +76.5° (*c* 0.702, $CHCl_3$); IR (KBr): $\nu = 3518$, 2968, 2928, 1670, 1641, 1606, 1518, 1350, 1184, 1086, 1013, 845, 746 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 9.40$ (1 H, s), 8.20 (2 H, d, $J = 8.7$ Hz), 7.51 (2 H, d, $J = 8.7$ Hz), 6.46 (1 H, d, $J = 9.6$ Hz), 4.80 (1 H, dd, $J = 5.7$, 2.7 Hz), 3.05 (1 H, m), 2.36 (1 H, d, $J = 3.3$ Hz), 1.60 (3 H, d, $J = 0.6$ Hz), 1.08 (3 H, d, $J = 7.2$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 195.2$, 154.4, 149.9, 147.3, 140.2, 127.1, 123.5, 76.9, 41.3, 16.6, 9.3; MS (EI): *m/z* (%) = 249 [M^+], 233 (11), 218 (7), 205 (3), 152 (27), 122 (4), 106 (8), 98 (100), 83 (17), 77 (10), 69 (13), 55 (4); HR-MS (EI): *m/z* = 249.1005, calcd. for $C_{13}H_{15}NO_4$ (M^+): 249.1001.

Compound **10b**: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 9.45$ (1 H, s), 8.34 (2 H, d, $J = 9.0$ Hz), 8.10 (2 H, d, $J = 9.0$ Hz), 6.70 (1 H, dd, $J = 9.6$, 1.5 Hz), 4.59 (1 H, m), 1.89 (3 H, d, $J =$ 1.5 Hz), 1.45 (3 H, d, $J = 6.9$ Hz).

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(*4R,5R E*)-5-Hydroxy-2,4-dimethyl-5-(4-nitrophenyl)pent-2-enal (10a) and (*4R, 5R, Z*)-5-Hydroxy-2,4-dimethyl-5-(4-nitrophenyl)pent-2-enal (12)

To a solution of **4a** (0.5 mmol) in 1 mL of CH_2Cl_2 and 5 mL of toluene was added 2-(triphenylphosphoranylidene)-propionaldehyde (**11**; 318 mg, 1 mmol, 2 equivs.). The resulting yellow mixture was refluxed for 3 h. The reaction was concentrated under reduced pressure and purified by silica gel column chromatography (petroleum ether/AcOEt, 2/1) to give the compound **10a** and **12** (yield: 54 mg, 43% in two steps). The ratio of **10a**:**12** was 5:3 determined by ^{1}H NMR analysis.

(*2E,4E,6R,7R*)-Ethyl 7-Hydroxy-4, 6-dimethyl-7-(4-nitrophenyl)hepta-2, 4-dienoate (14)

To a suspension of sodium hydride (120 mg, 60% in oil, 3.0 mmol, 3.0 equivs.) in THF (5.0 mL) was added dropwise a solution of triethyl phosphonoacetate (**13**; 720 μL, 4.0 mmol, 4.0 equivs.) in THF (5.0 mL) at room temperature under argon over a period of 10 min. After being stirred at room temperature for another 20 min, a solution of **10a** (249 mg, 1.0 mmol) in THF (5.0 mL) was added dropwise. The resulting mixture was then stirred for 30 min to reach completion. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ and the mixture extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/AcOEt, 5/1) to give a colorless oil; yield: 306 mg (96%); $[\alpha]_D^{23}$: +128° (*c* 0.140, $CHCl_3$); IR (KBr): ν = 3466, 3078, 2978, 1693, 1622, 1516, 1456, 1348, 1180, 1026, 847, 750, 704 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.19 (2H, d, *J* = 8.7 Hz), 7.50 (2H, d, *J* = 8.4 Hz), 7.30 (1H, dd, *J* = 0.6, 15.9 Hz), 5.80 (1H, d, *J* = 15.3 Hz), 5.80 (1H, d, *J* = 10.5 Hz), 4.65 (1H, d, *J* = 6.6 Hz), 4.20 (2H, q, *J* = 7.2 Hz), 2.87 (1H, m), 2.27 (1H, d, *J* = 3.0 Hz), 1.67 (3H, d, *J* = 0.9 Hz), 1.29 (3H, t, *J* = 7.2 Hz), 0.97 (3H, d, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.5, 150.3, 148.9, 147.1, 141.7, 134.3, 127.3, 123.3, 116.6, 77.2, 60.3, 41.1, 16.9, 14.2, 12.3; MS (EI): *m/z* (%) = 320 [M^++H], 274 (7), 168 (100), 152 (23), 139 (34), 122 (24), 111 (13), 95 (81), 79 (18), 67 (6), 55 (5); HR-MS (EI): *m/z* = 320.1481, calcd. for $C_{17}H_{22}NO_5$ (M^++H): 320.1498.

(*2E,4E,6R,7R*)-Ethyl 7-(4-Aminophenyl)-7-hydroxy-4,6-dimethylhepta-2, 4-dienoate (15)

To a solution of compound **14** (306 mg, 0.96 mmol) in 10 mL of MeOH was added 210 mg of Lindlar's catalyst and 90 μL of quinoline. The resulting mixture was then stirred under an H_2 atmosphere for 10 h. The reaction mixture was filtered and washed with EtOAc. The organic layer was concentrated under reduced pressure and purified by silica gel column chromatography (petroleum ether/AcOEt, 2/1) to give 244 mg of crude product and, after recrystallization from petroleum ether and AcOEt, the crystalline material; yield: 172 mg (62%); mp 126–128 °C; $[\alpha]_D^{23}$: +177° (*c* 0.850, $CHCl_3$); IR (KBr): ν = 3458, 3346, 2976, 1695, 1618, 1518, 1392, 1311, 1292, 1246, 1186, 1028, 986, 829, 582 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36 (1H, dd, *J* = 15.6, 0.6 Hz), 7.11 (2H, d, *J* = 8.4 Hz), 6.66 (2H, d, *J* = 8.4 Hz), 5.84 (1H, d, *J* = 10.2 Hz), 5.81 (1H, d, *J* = 15.6 Hz), 4.36 (1H, d, *J* = 7.5 Hz), 4.21 (2H, q, *J* = 7.2 Hz), 3.67 (2H, br), 2.84 (1H, m), 1.77 (3H, d, *J* = 1.2 Hz), 1.30 (3H, t, *J* = 7.2 Hz), 0.86 (3H, d, *J* = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.4, 149.4, 145.9, 144.1, 133.7, 132.5, 127.7, 116.0, 114.8, 78.3, 60.1, 41.2, 16.8, 14.2, 12.4; MS (EI): *m/z* = 289 [M^+], 271 (2), 198 (5), 168 (14), 149 (5), 139 (5), 122 (100), 94 (16), 77 (11); HRMS (EI): *m/z* = 289.1687, calcd. for $C_{17}H_{23}NO_3$ (M^+): 289.1678.

(*2E,4E,6R,7R*)-Ethyl 7-[4-(Dimethylamino)phenyl]-7-hydroxy-4,6-dimethylhepta-2,4-dienoate (16)

To a solution of compound **15** (600 mg, 2.08 mmol) in THF (35 mL) was added formaldehyde (505 mg, 37% aqueous, 6.23 mmol, 3.0 equivs.). The mixture was stirred at room temperature for 10 min. Then sodium triacetoxyborohydride (1.32 g, 6.23 mmol, 3.0 equivs.) was added and the resulting mixture was stirred at room temperature for 10 h. The reaction mixture was filtered and washed with EtOAc. The organic layer was concentrated under reduced pressure and purified by silica gel column chromatography (petroleum ether/AcOEt, 5/1 → 3/1) to give the compound **16**; yield: 527 mg (80%); $[\alpha]_D^{23}$: +180° (*c* 0.441, $CHCl_3$); IR (KBr): ν = 3466, 2978, 1705, 1616, 1522, 1446, 1348, 1308, 1165, 1026, 984, 945, 820 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36 (1H, dd, *J* = 15.9, 0.6 Hz), 7.18 (2H, d, *J* = 8.7 Hz), 6.70 (2H, d, *J* = 8.7 Hz), 5.86 (1H, d, *J* = 9.9 Hz), 5.81 (1H, d, *J* = 15.9 Hz), 4.37 (1H, d, *J* = 7.5 Hz), 4.20 (2H, q, *J* = 7.2 Hz), 2.94 (6H, s), 2.87 (1H, m), 1.97 (1H, br), 1.79 (3H, d, *J* = 1.2 Hz), 1.30 (3H, t, *J* = 7.2 Hz), 0.85 (3H, d, *J* = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.5, 150.3, 149.4, 144.2, 133.7, 130.3, 127.5, 116.1, 112.3, 78.4, 60.1, 41.2, 40.6, 16.9, 14.3, 12.5; MS (EI): *m/z* (%) = 317 [M^+], 299 (55), 226 (100), 211 (38), 150 (73); HR-MS (EI): *m/z* = 317.1973, calcd. for $C_{19}H_{27}NO_3$ (M^+): 317.1991.

(*2E,4E,6R,7R*)-7-[4-(Dimethylamino)phenyl]-*N*,7-dihydroxy-4, 6-dimethylhepta-2, 4-dienamide (3)

To a solution of compound **16** (140 mg, 0.44 mmol) in 4 mL of MeOH was added NH_2OH (10 mL, 1.5 M in MeOH). The resulting mixture was then stirred at room temperature for 2 h to reach completion. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ and the mixture extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The resulting oil was used without further purification for the next step; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.24 (1H, d, *J* = 15.6 Hz), 7.16 (2H, d, *J* = 8.4 Hz), 6.71 (2H, d, *J* = 8.7 Hz), 5.80–5.73 (2H, m), 4.30

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(1H, d, $J=7.5$ Hz), 2.91 (6H, s), 2.81 (1H, m), 1.72 (3H, s), 0.76 (3H, d, $J=6.3$ Hz).

Trichostatin A (1)

To a solution of compound **3** in dioxane (5 mL) was added dropwise DDQ (0.10 M in dioxane). The reaction process was monitored by TLC to avoid addition of excess DDQ. When compound **3** has disappeared, about 2.6 mL of DDQ (0.26 mmol, 0.59 equivs.) had been consumed. The resulting pale mixture was filtered and washed with dioxane. The organic layer was concentrated under reduced pressure and purified by silica gel column chromatography (CH_2Cl_2/MeOH, 20/1) to give a yellow solid; yield: 65 mg (49% in two steps); mp 140–143 °C; $[\alpha]_D^{21}$: +106° (*c* 0.095, EtOH); IR (KBr): $\nu=3423$, 3232, 2924, 1655, 1595, 1547, 1375, 1244, 1188, 1171, 1059, 974, 824 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta=7.85$ (2H, d, $J=9.0$ Hz), 7.20 (1H, d, $J=15.6$ Hz), 6.66 (2H, d, $J=9.0$ Hz), 5.96 (1H, d, $J=9.9$ Hz), 5.78 (1H, d, $J=15.9$ Hz), 4.41 (1H, m), 3.08 (6H, s), 1.90 (3H, s), 1.30 (3H, d, $J=6.6$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$:$CD_3OD=7.5$:1): $\delta=199.5$, 165.0, 153.5, 144.8, 139.9, 132.5, 130.5, 123.2, 115.2, 110.5, 40.4, 39.6, 17.5, 12.2; MS (EI): $m/z=302$ [M^+], 287 (0.6), 274 (3.5), 148 (100); HRMS (EI): $m/z=302.1621$, calcd. for $C_{17}H_{22}N_2O_3$ (M^+): 302.1630; Daicel CHIRALPAK AS-H, hexane/EtOH, 50:50 with 0.1% TFA, flow rate 0.5 mL min^{-1}, $\lambda=254$ nm, $t_R=14.78$ min (major), minor one is not observed, >99% *ee*.

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References

[1] For recent reviews related to biological functions and applications of HDACs, see: a) A. Yarnell, *Chem. Eng. News* **2006**, *84*, 43; b) P. A. Marks, V. M. Richon, R. Breslow, R. A. Rifkind, *Curr. Opin. Oncol.* **2001**, *13*, 477; c) P. A. Marks, R. A. Rifkind, V. M. Richon, R. Breslow, T. Miller, W. K. Kelly, *Nat. Rev. Cancer* **2001**, *1*, 194; d) M. Yoshida, A. Matsuyama, Y. Komatsu, N. Nishino, *Curr. Med. Chem.* **2003**, *10*, 2351; e) M. Jung, *Curr. Med. Chem.* **2001**, *8*, 1505; f) G. Bouchain, D. Delorme, *Curr. Med. Chem.* **2003**, *10*, 2359; g) V. Tamara, P. Peggy, E. Greetje, R. Vera, *Curr. Med. Chem.* **2004**, *11*, 1629.

[2] M. Yoshida, M. Kijama, M. Akita, T. Beppu, *J. Biol. Chem.* **1990**, *265*, 17174.

[3] For selected examples using trichostatin A as a tool for studying biological functions of HDACs and drug discovery, see: a) M. S. Finnin, J. R. Donigian, A. Cohen, V. M. Richon, R. A. Rifkind, P. A. Marks, R. Breslow, N. P. Pavletich, *Nature* **1999**, *401*, 188; b) V. M. Richon, S. Emiliani, E. Verdin, Y. Webb, R. Breslow, R. A. Rifkind, P. A. Marks, *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 3003; c) R. Furumai, Y. Komatsu, N. Nishino, S. Khochbin, M. Yoshida, *Proc. Natl. Acad. Sci. USA* **2001**, *98*, 87; d) A. Saito, T. Yamashita, Y. Mariko, Y. Nosaka, K. Tsuchiya, T. Ando, T. Suzuki, T. Tsuruo, O. Nakanishi, *Proc. Natl. Acad. Sci. USA* **1999**, *96*, 4592; e) K. M. Koeller, S. J. Haggarty, B. D. Perkins, I. Leykin, J. C. Wong, M.-C. J. Kao, S. L. Schreiber, *Chem. Biol.* **2003**, *10*, 397; f) S. J. Haggarty, K. M.; Koeller, J. C. Wong, C. M. Grozinger, S. L. Schreiber, *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 4389; g) J. C. Wong, R. Hong, S. L. Schreiber, *J. Am. Chem. Soc.* **2003**, *125*, 5586.

[4] I. Fleming, J. Iqbal, E. P. Krebs, *Tetrahedron* **1983**, *39*, 841.

[5] K. Mori, K. Koseki, *Tetrahedron* **1988**, *44*, 6013.

[6] For selected recent reviews of organocatalysis, see: a) A. Berkessel, H. Groger, *Asymmetric Organocatalysis – From Biomimetic Concepts to Applications in Asymmetric Synthesis* Wiley-VCH, Weinheim, Germany, **2005**; b) P. I. Dalko, L. Moisan, *Angew. Chem.* **2001**, *113*, 3840; *Angew. Chem. Int. Ed.* **2001**, *40*, 3726; c) P. I. Dalko, L. Moisan, *Angew. Chem.* **2004**, *116*, 5248; *Angew. Chem. Int. Ed.* **2004**, *43*, 5138.

[7] For L-proline-promoted aldol reactions, see: a) B. List, R. A. Lerner, C. F. Barbas, III, *J. Am. Chem. Soc.* **2000**, *122*, 2395; b) K. Sakthivel, W. Notz, T. Bui, C. F. Barbas, III, *J. Am. Chem. Soc.* **2001**, *123*, 5260; c) R. Thayumanavan, F. Tanaka, C. F. Barbas, III, *Org. Lett.* **2004**, *6*, 3541; d) A. B. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 6798; e) D. Enders, C. Grondal, *Angew. Chem.* **2005**, *117*, 1235; *Angew. Chem. Int. Ed.* **2005**, *44*, 1210; f) J. Casas, M. Engqvist, I. Ibrahem, B. Kaynak, A. Córdova, *Angew. Chem.* **2005**, *117*, 1367; *Angew. Chem. Int. Ed.* **2005**, *44*, 1343; g) Q. Pan, B. Zou, Y. Wang, D. Ma, *Org. Lett.* **2004**, *6*, 1009; h) S. Chandrasekhar, C. Narsihmulu, R. Reddy, S. S. Sultana, *Chem. Commun.* **2004**, 2450; i) A. B. Northrup, D. W. C. MacMillan, *Science* **2004**, *305*, 1752; j) J. T. Suri, D. B. Ramachary, C. F. Barbas, III, *Org. Lett.* **2005**, *7*, 1383.

[8] For proline derivatives-catalyzed aldol reactions, see: a) N. Mase, F. Tanaka, C. F. Barbas III, *Angew. Chem.* **2004**, *116*, 2474; *Angew. Chem. Int. Ed.* **2004**, *43*, 2420; b) M. Nakadai, S. Saito, H. Yamamoto, *Tetrahedron* **2002**, *58*, 8167; c) Z. Tang, F. Jiang, L.-T. Yu, X. Cui, L.-Z. Gong, A.-Q. Mi, Y.-Z. Jiang, Y.-D. Wu, *J. Am. Chem. Soc.* **2003**, *125*, 5262; d) P. Krattiger, R. Kovasy, J. D. Revell, S. Ivan, H. Wennemers, *Org. Lett.* **2005**, *7*, 1101; e) H. Torii, M. Nakadai, K. Ishihara, S. Saito, H. Yamamoto, *Angew. Chem.* **2004**, *116*, 2017; *Angew. Chem. Int. Ed.* **2004**, *43*, 1983; f) A. J. A. Cobb, D. M. Shaw, D. A. Longbottom, S. V. Ley, *Org. Biomol. Chem.* **2005**, *3*, 84; g) Y. Hayashi, T. Sumiya, J. Takahashi, H. Gotoh, T. Urushima, M. Shoji, *Angew. Chem.* **2006**, *117*, 972; *Angew. Chem. Int. Ed.* **2006**, *45*, 958; h) S. Samanta, J. Liu, R. Dodda, C.-G. Zhao, *Org. Lett.* **2005**, *7*, 5221; i) Z. Tang, Z.-H. Yang, X.-H. Chen, L.-F. Cun, A.-Q. Mi, Y.-Z. Jiang, L.-Z. Gong, *J. Am. Chem. Soc.* **2005**, *127*, 9285; j) S. S. Chimni, D. Mahajan, V. V. S. Babu, *Tetrahedron Lett.* **2005**, *46*, 5617; k) E. Bellis, K. Vasilatou, G. Kokotos, *Synthesis* **2005**, 2407; l) J.-R. Chen, H.-H. Lu, X.-Y. Li, L. Cheng, J. Wan, W.-

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J. Xiao, *Org. Lett.* **2005**, *7*, 4543; m) H. Ikishima, Y. Sekiguchi, Y. Ichikawa, H. Kotsuki, *Tetrahedron* **2006**, *62*, 311.

[9] Recently we have uncovered the pyrrolidine sulfonamide/amide system as effective organocatalysts for asymmetric organic transformations, see: a) aldol reaction: W. Wang, H. Li, J. Wang, *Tetrahedron Lett.* **2005**, *46*, 5077; b) Michael addition: W. Wang, J. Wang, H. Li, *Angew. Chem.* **2005**, *117*, 1393; *Angew. Chem. Int. Ed.* **2005**, *44*, 1369; J. Wang, H. Li, L Zu, W. Wang, *Adv. Synth. Catal.* **2006**, *348*, 413; c) α-selenenylation: W. Wang, J. Wang, H. Li, *Org. Lett.* **2004**, *6*, 2817; J. Wang, H. Li, Y.-J. Mei, B. Lou, D.-G. Xu, D.-Q. Xie, H. Guo, W. Wang, *J. Org. Chem.* **2005**, *70*, 5678; d) Mannich elimination reaction: W. Wang, Y.-J. Mei, H. Li, J. Wang, *Org. Lett.* **2005**, *7*, 601; e) α-aminoxylation: W. Wang, J. Wang, H. Li, L.-X. Liao, *Tetrahedron Lett.* **2004**, *45*, 7235; f) Mannich-type reaction: W. Wang, J. Wang, H. Li, *Tetrahedron Lett.* **2004**, *45*, 7243; g) α-sulfenylation: W. Wang, H. Li, J. Wang, L.-X. Liao, *Tetrahedron Lett.* **2004**, *45*, 8229.

[10] For selected examples using L-proline-catalyzed aldol reactions in natural product synthesis, see: a) I. K. Mangion, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 3696; b) P. M. Pihko, A. Erkkila, *Tetrahedron Lett.* **2003**, *44*, 7607.

[11] S. R. Chemler, W. R. Roush, *J. Org. Chem.* **2003**, *68*, 1319.

[12] W. Wang, C. Xiong, J. Yang, V. J. Hruby, *Synthesis* **2002**, 94.

[13] a) E. J. Corey, J. W. Suggs, *Tetrahedron Lett.* **1975**, *16*, 2647; b) M. A. Brimble, M. R. Nairn, J. Park, *Org. Lett.* **1999**, *1*, 1459.

[14] A. N. Cuzzupe, C. A. Hutton, M. J. Lilly, R. K. Mann, M. A. Rizzacasa, S. C. Zammit, *Org. Lett.* **2000**, *2*, 191.

[15] H. Toshima, H. Oikawa, T. Toyomasu, T. Sassa, *Tetrahedron* **2000**, *56*, 8443.

[16] D. A. Evans, S. J. Miller, M. D. Ennis, *J. Org. Chem.* **1993**, *58*, 471.

[17] A. F. Abdel-Magid, K. G. Carson, B. D. Harris, C. A. Maryanoff, R. D. Shah, *J. Org. Chem.* **1996**, *61*, 3849.

[18] N. Tsuji, M. Kobayashi, K. Nagashima, Y. Wakisaka, K. Koizumi, *J. Antibiot.* **1976**, *29*, 1.

[19] The optical rotation values, reported in the literature, are not consistent: naturally occurring trichostatin A: [α]: 2.8° (EtOH) (ref.[18]); synthesized trichostatin A by Mori (ref.[5]) with 93% *ee*: [α]: +77° (EtOH); our result with > 99% *ee*: $[\alpha]_D^{21}$: +106° (*c* 0.095, EtOH).

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