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A total synthesis of spiruchostatin A

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Abstract—We achieved the total synthesis of the histone deacetylase inhibitor spiruchostatin A, as the prelude to the preparation of a combinatorial library of its analogues. Two key reactions were an asymmetric acetate aldol reaction using a Zr-enolate and macrolactonization using the Shiina method.

Spiruchostatin A (**1a**) and B (**1b**), isolated from *Pseudomonas* sp., exhibit potent inhibitory activity against histone deacetylases (HDACs).[1] Spiruchostatin A is a cyclic depsipeptide consisting of (3*S*,4*R*)-statine, D-cysteine, D-alanine, and (*E*)-3-hydroxy-7-thio-4-heptenoic acid. The two thiol-groups were connected as a disulfide forming a bicyclic depsipeptide. This structure is similar to FR-901228 (FK-228),[2] a HDAC inhibitor currently in advanced clinical trials as an anticancer agent. One total synthesis of FK-228 has been reported,[3] while the total synthesis of **1a** was recently achieved.[4] Potent activity was observed for **1a** in models for anticancer activity and cardiac hypertrophy. In order to discover analogues of **1**, which are more potent and selective HDAC inhibitors, we planned a total synthesis of **1a** in order to validate the route before proceeding with combinatorial library synthesis.

An outline of the synthetic strategy is illustrated in Scheme 1. Spiruchostatin A (**1a**) can be synthesized through macrolactonization of *seco*-acid derivative **2** and disulfide formation. Compound **2** would be prepared by the sequential coupling of D-valine-derived (3*S*,4*R*)-statine allyl ester **3b** (R = allyl), D-cysteine **4**, D-alanine **5**, and β-hydroxy acid **6** by sequential coupling. We selected allyl ester in **3** because it endures under the selective deprotection of *N*-Boc and *N*-Fmoc groups at the N-terminus for the homologation of the peptide. At the same time, the allyl ester can be selectively removed by palladium-catalyzed reaction under mild conditions in the presence of *S*-trityl groups to afford *seco*-acid **2**. Successful model studies can then be applied to solid-phase synthesis using a similar allyl linker.

In the synthesis of β-hydroxy acid **6** (Scheme 2), the acetate aldol reaction of enal **8**[5] is a key step. Since acetate aldols proceed with poor diastereoselectivity with the classical Evans' oxazolidin-2-one auxiliary, previous syntheses have employed alternative approaches: an aldol with a chiral Ti-catalyst,[3] an oxazolidinethione auxiliary,[5] an oxazolidinone derivative from chloroacetic acid,[5] and a thiazolidinethione auxiliary.[4] We were interested in investigating the potential of Seebach's *N*-acetyl-oxazolidin-2-one **7**[6] for this reaction, although only a few examples of its acetate aldol reactions were reported.[6a,7] Addition of the Li-enolate of **7** to enal **8** afforded a 77:23 mixture of aldols **9** and **10** in 89% combined yield (entry 1). The Zr-enolate,[8] generated by transmetalation of the Li-enolate with Cp_2ZrCl_2, effectively increased the stereoselectivity of **9** up to 93% in 55% yield (entry 3), while the Ti-enolate[9] generated in situ with $TiCl(O\textit{i}\text{-}Pr)_3$ did not affect the selectivity (entry 2). The samarium-Reformatsky reaction of **7b** (X = Br) gave **9** with 87% diastereoselectivity in 57%

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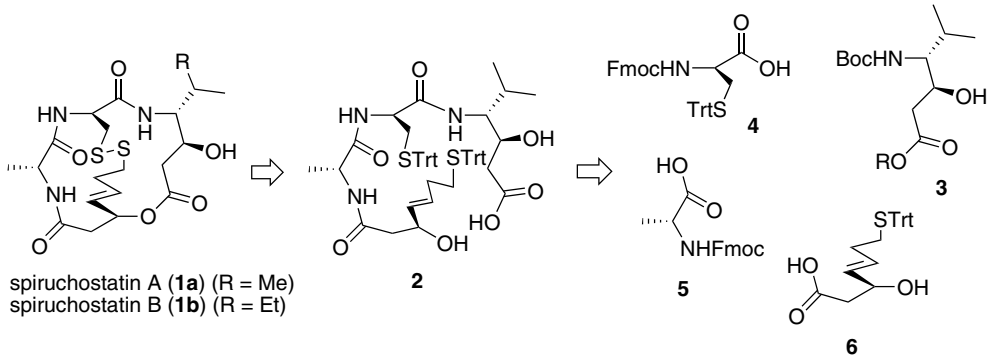
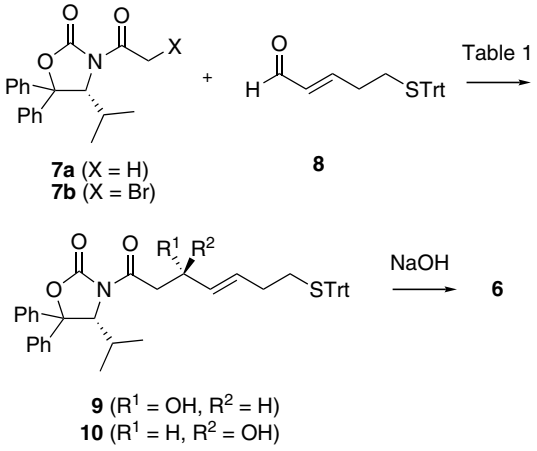


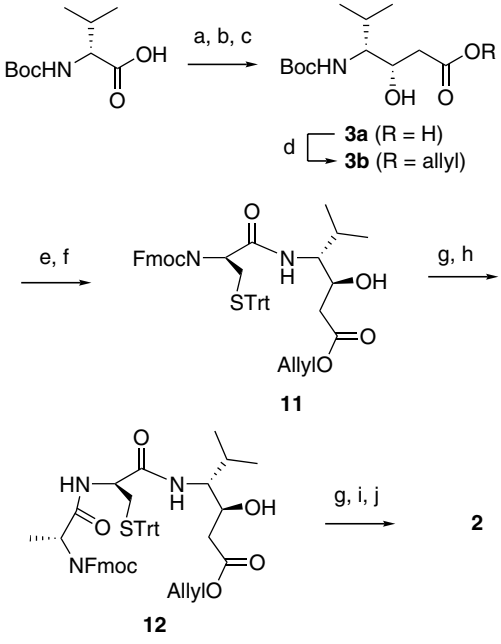
Scheme 1. Retro-synthesis of spiruchostatin A (**1a**).



Scheme 2. Asymmetric aldol reactions of acetate derivatives **7** with **8**.

yield (entry 4).[7] After simple purification by silica gel column chromatography, hydrolysis of **9** afforded **6** in 76% yield.[10] The absolute configuration was determined as *S* by the modified Mosher method[11] after converting into its methyl ester (Table 1).

The D-valine-derived (3*R*,4*S*)-statine **3a** (R = H) was prepared from *N*-Boc-D-Val-OH by condensation with ethyl magnesium malonate,[12] followed by stereoselective reduction with $NaBH_4$[13] and hydrolysis of ethyl ester in 34% overall yield (Scheme 3). After formation of allyl ester **3b** (R = allyl) and removal of the Boc group, coupling with **4** (EDCI–HOBt) provided **11** in 76% yield. Removal of the Fmoc group with Et_2NH, followed by coupling with **5** afforded **12** in 79% yield. After removal of the Fmoc group, condensation of **6** was achieved using PyBOP. The allyl ester was removed by

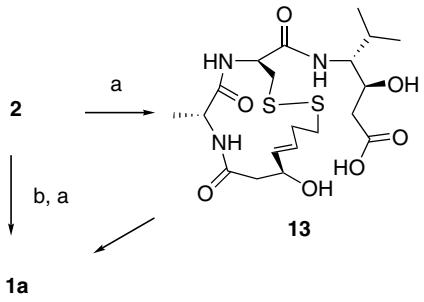


Scheme 3. Synthesis of cyclization precursor **2**. Reagents and conditions: (a) carbonyldiimidazole, $(EtO_2CCH_2CO_2)_2Mg$, THF; (b) $NaBH_4$, THF–MeOH (84:16), (c) LiOH, THF–H_2O; recrystallization (34% in three steps); (d) K_2CO_3, allyl bromide, (e) 4 M HCl–EtOAc; (f) *N*-Fmoc-D-Cys(*S*-Trt)-OH (**4**), EDCI–HOBt, DIEA (76% in three steps); (g) Et_2NH; (h) *N*-Fmoc-D-Ala-OH (**5**), EDCI–HOBt, DIEA (79% in two steps); (i) **6**, PyBOP, DIEA (65%); (j) $Pd(PPh_3)_4$, morpholine, MeOH (87%). EDCI = 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide, HOBt = 1-hydroxybenzotriazole, DIEA = *N*,*N*-diisopropylethylamine, PyBOP = benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate.

Table 1. Asymmetric aldol reaction of **7** with **8**

Entry	Substrate	Additive	Temp/°C	Yield/%	Ratio (**9**:**10**)[d]
1[a]	**7a**	None	−78	89	77:23
2[a]	**7a**	$TiCl(O\textit{i}\text{-}Pr)_3$[c]	−78 to −40	94	76:24
3[a]	**7a**	Cp_2ZrCl_2[c]	−78 to rt	55	93:7
4[b]	**7b**	None	−78	57	87:13

[a] Compound **7a** was treated with BuLi in THF forming enolate.
[b] Compound **7b** was treated with SmI_2 in THF forming the samarium enolate.
[c] 1.2 equiv.
[d] The ratio was determined by ^1H NMR (400 MHz).



Scheme 4. Synthesis of **1a**. Reagents and conditions: (a) I_2, CH_2Cl_2–MeOH (quant.); (b) MNBA (1.2 equiv), DMAP (2.4 equiv), CH_2Cl_2, rt, 67%.

palladium-catalyzed reaction with morpholine to provide cyclization precursor **2**.

Removal of trityl groups of **2** followed by disulfide formation[3,14] provided **13** in quantitative yield (Scheme 4). The macrolactonization of **13** failed under various attempts although molecular mechanics calculation (MMFF) suggested that there would be an appropriate conformation for the cyclization within 3 kcal/mol from the global minimum.[15] On the other hand, the macrolactonization of **2** by the Shiina method using 2-methyl-6-nitrobenzoic anhydride (MNBA)[16,17] efficiently proceeded at room temperature (67%) without protection of the hydroxy group in the statine unit, whereas the reported Yamaguchi method[18] required 80 °C and proceeded in 40% yield.[4] Finally disulfide formation between the di-*S*-trityl moieties furnished spiruchostatin (**1a**) in quantitative yield.[4] The synthetic **1a** exhibited ^1H and ^{13}C NMR spectral data as well as optical rotation identical to those published for the natural product.[1,19]

In summary, we have completed a total synthesis of spiruchostatin A. Compared to the first synthesis,[4] the present route illustrates several new features. We have demonstrated an asymmetric aldol reaction using the Zr-enolate of acetyl *N*-oxazolidin-2-one derivative that proceeds with high diastereoselectivity. The synthesis of the statine involves a malonate condensation under mild conditions, and the use of an allyl ester protecting group was found to be compatible with highly functionalized intermediates. Finally, the macrolactonization was efficiently achieved with the Shiina reagent, and provides another example of the utility of this methodology for such reactions. Interestingly, the macrolactonization failed if performed after disulfide bond formation, and this suggests that subtle conformational differences exist between **2** and **13**. A solid-phase synthesis based on these results and its application toward a combinatorial library of spiruchostatin analogues is underway in our laboratory.

Acknowledgments

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References and notes

1. Masuoka, Y.; Nagai, A.; Shin-ya, K.; Furihata, K.; Nagai, K.; Suzuki, K.; Hayakawa, Y.; Seto, H. *Tetrahedron Lett.* **2001**, *42*, 41–44.
2. (a) Ueda, H.; Nakajima, H.; Hori, Y.; Fujita, T.; Nishimura, M.; Goto, T.; Okuhara, M. *J. Antibiot.* **1994**, *47*, 301–310; (b) Furumai, R.; Matsuyama, A.; Kobashi, N.; Lee, K.-Y.; Nishiyama, M.; Nakajima, H.; Tanaka, A.; Komatsu, Y.; Nishino, N.; Yoshida, M.; Horinouchi, S. *Cancer Res.* **2002**, *62*, 4916–4921.
3. Li, K. W.; Wu, J.; Xing, W.; Simon, J. A. *J. Am. Chem. Soc.* **1996**, *118*, 7237–7238.
4. (a) Yurek-George, A.; Habens, F.; Brimmell, M.; Packham, G.; Ganesan, A. *J. Am. Chem. Soc.* **2004**, *126*, 1030–1031; (b) Davidson, S. M.; Townsend, P. A.; Carroll, C.; Yurek-George, A.; Balasubramanyam, K.; Kundu, T. K.; Stephanou, A.; Packham, G.; Ganesan, A.; Latchman, D. S. *Chem. BioChem.* **2005**, *6*, 162–170.
5. Chen, Y.; Gambs, C.; Abe, Y.; Wentworth, P., Jr.; Janda, K. D. *J. Org. Chem.* **2003**, *68*, 8902–8905.
6. (a) Hintermann, T.; Seebach, D. *Helv. Chim. Acta* **1998**, *81*, 2093–2126; (b) Gibson, C. L.; Gillon, K.; Cook, S. *Tetrahedron Lett.* **1998**, *39*, 6733–6736; (c) Isobe, T.; Fukuda, K. JP09143173, 1995; *Chem. Abstr.* **1997**, *127*, 50635.
7. Fukuzawa, S.; Matsuzawa, H.; Yoshimitsu, S. *J. Org. Chem.* **2000**, *65*, 1702–1706.
8. (a) Evans, D. A.; McGee, L. R. *Tetrahedron Lett.* **1980**, *21*, 3975–3978; (b) Evans, D. A.; McGee, L. R. *J. Am. Chem. Soc.* **1981**, *103*, 2876–2878; (c) Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1985**, *26*, 5807–5810.
9. (a) Nerz-Stormes, M.; Thornton, E. R. *J. Org. Chem.* **1991**, *56*, 2489–2498; (b) Yan, T.-H.; Hung, A.-W.; Lee, H.-C.; Chang, C.-S.; Liu, W.-H. *J. Org. Chem.* **1995**, *60*, 3301–3306.
10. Spectral data of **6**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.41–7.19 (m, 15H), 5.59 (ddd, $J = 15.5$, 6.8, 6.3 Hz, 1H), 5.42 (dd, $J = 15.5$, 6.3 Hz, 1H), 4.45 (m, 1H), 2.55 (m, 2H), 2.21 (m, 2H), 2.09 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 144.9, 131.6, 130.7, 129.6, 127.9, 126.6, 68.5, 66.6, 41.1, 31.4, 31.3; IR (neat) 3417, 3056, 3030, 2925, 1713, 1595, 1489, 1444, 1280, 1183, 1101, 1083, 1034, 1002, 972, 743, 700, 676, 621, 506 cm^{-1}; $[\alpha]_D^{25}$ −4.99 (*c* 1.55, CH_2Cl_2) [lit.[3] $[\alpha]_D^{20}$ −5.0 (*c* 2.0, CH_2Cl_2)], HRMS (ESI-TOF) calcd for $[C_{26}H_{26}O_3+Na]^+$ 441.1500, found 441.1495.
11. Ohtani, I.; Kusumi, T.; Kashman, T.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096.
12. Brooks, D. W.; Lu, L. D.-L.; Masamune, S. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 72–74.
13. (a) Jouin, P.; Poucet, J.; Dufour, M.-N.; Pantaloni, A.; Castro, B. *J. Org. Chem.* **1989**, *54*, 617–627; (b) Harris, B. D.; Joullié, M. M. *Tetrahedron* **1988**, *44*, 3489–3500.
14. Kamber, B.; Hartmann, A.; Eisler, K.; Riniker, B.; RInk, H.; Siber, P.; Rittel, W. *Helv. Chim. Acta* **1980**, *63*, 899–915.
15. Macromodel (version 6.0) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440–467.
16. (a) Shiina, I.; Ibuka, R.; Kubota, M. *Chem. Lett.* **2002**, 286–287; (b) Shiina, I.; Kubota, M.; Ibuka, R. *Tetrahedron Lett.* **2002**, *43*, 7535–7539; (c) Shiina, I.; Oshiumi, H.; Hashizume, M.; Yamai, Y. S.; Ibuka, R. *Tetrahedron Lett.* **2004**, *45*, 543–547; (d) Shiina, I.; Kubota, M.; Oshiumi, H.; Hashizume, M. *J. Org. Chem.* **2004**, *60*, 1822–1830.
17. Inoue, M.; Sasaki, T.; Hatano, S.; Hirama, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 6500–6505.

18. Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.
19. Spectral data of synthetic **1a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, $J = 7.3$ Hz, 1H), 6.72 (d, $J = 9.2$ Hz, 1H), 6.39 (m, 1H), 5.93 (br s, 1H), 5.66 (d, $J = 15.5$ Hz, 1H), 5.50 (br s, 1H), 4.92 (dt, $J = 9.2$, 3.8 Hz, 1H), 4.57 (m, 1H), 4.27 (dq, $J = 7.3$, 3.9 Hz, 1H), 3.37 (m, 2H), 3.23 (m, 1H), 3.15 (d, $J = 5.9$ Hz, 1H), 2.77–2.69 (m, 5H), 2.57 (d, $J = 13.1$ Hz, 1H), 2.50–2.35 (m, 2H), 1.51 (d, $J = 7.3$ Hz, 3H), 1.03 (d, $J = 6.8$ Hz, 3H), 0.93 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 171.2, 171.1, 169.3, 132.7, 129.6, 71.1, 68.7, 62.5, 56.1, 52.3, 40.9×2, 39.7, 39.3, 32.6, 29.9, 20.5, 19.8, 16.3; IR (neat) 3328, 2964, 2933, 1730, 1661, 1543, 1432, 1370, 1274, 1162, 1043, 985, 754, 666, 565 cm^{-1}; $[\alpha]_D^{26}$ −61.1 (*c* 0.965, MeOH) [lit.[1] $[\alpha]_D^{26}$ −63.6 (*c* 0.14, MeOH), lit.[4] $[\alpha]_D^{26}$ −61.1 (*c* 0.14, MeOH)], HRMS (ESI-TOF) calcd for $[C_{20}H_{31}N_3O_6S_2 + Na]^+$ 496.1552, found 496.1547.