ORGANIC LETTERS

2010
Vol. 12, No. 4
832−834

An Efficient Synthesis of (±)-Trichostatic Acid and Analogues: A New Route to (±)-Trichostatin A

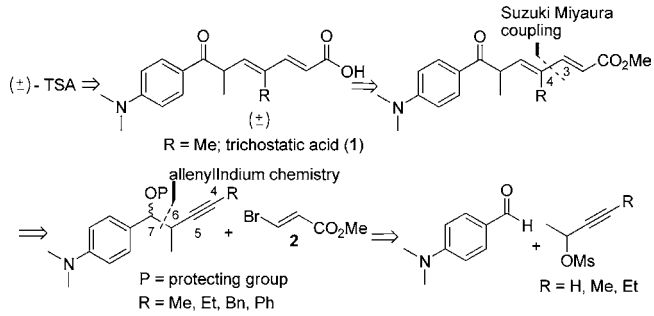
Anamitra Chatterjee, Joshua Richer, Tyler Hulett, Vijaya Bhaskara Reddy Iska, Olaf Wiest, and Paul Helquist*

Department of Chemistry and Biochemistry, 251 Nieuwland Science Hall, University of Notre Dame, Indiana 46556

phelquis@nd.edu

Received December 17, 2009

ABSTRACT



An efficient synthesis of *rac*-trichostatic acid (1) and its analogues is reported starting from a commercially available aldehyde. Further manipulations of *rac*-1 led to *rac*-trichostatin A (TSA). Construction of the desired molecular architecture entails a two-component union, achieved through an in situ hydroboration followed by a Suzuki−Miyaura coupling with 2. The requisite homopropargyl alcohol was synthesized by exploiting allenylindium chemistry. This new protocol paved the way for the synthesis of analogues of trichostatic acid and hence TSA.

(*R*)-(+)-Trichostatic acid (**1**) was first isolated from the culture fluid of *Streptomyces sioyaensis* and showed differentiation inducing activity in Friend leukemia cells.[1] Apart from its biological activity, the greater importance of trichostatic acid is that it is both a hydrolysis product of (*R*)-(+)-trichostatin A (TSA)[2] and an advanced precursor for its synthesis.[3] (*R*)-(+)-TSA is one member of a potent class of histone deacetylase inhibitors (HDACi's). These compounds have recently emerged as promising therapeutic agents for treating several diseases, including many forms of cancer.[4] (*R*)-(+)-TSA has shown activity in studies of several cancer cell lines, rare genetic diseases, and malaria.[5] It also has promise for ex vivo expansion of stem cells.[6] The lack of efficient synthetic procedures for the preparation of the trichostatic acid system prompted us to develop a general route to prepare trichostatic acid and its

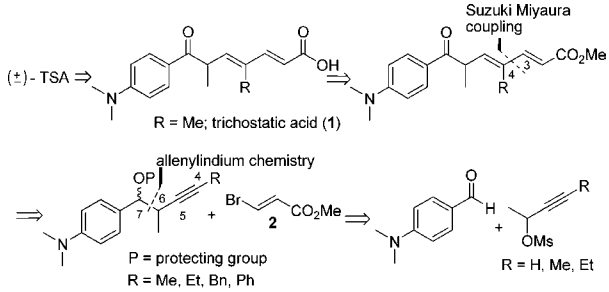
(1) (a) Morioka, H.; Ishihara, M.; Takezawa, M.; Hirayama, K.; Suzuki, E.; Komoda, Y.; Shibai, H. *Agric. Biol. Chem.* **1985**, *49*, 1365.
(2) Tsuji, N.; Kobayashi, M. *J. Antibiot.* **1978**, *31*, 939.
(3) (a) Fleming, I.; Iqbal, J.; Krebs, E.-P. *Tetrahedron* **1983**, *39*, 841. (b) Mori, K.; Koseki, K. *Tetrahedron* **1988**, *44*, 6013. (c) Zhang, S.; Duan, W.; Wang, W. *Adv. Synth. Catal.* **2006**, *348*, 1228. (d) HelquistP.; Lofstedt, J. Process for Preparing Histone Deacetylase Inhibitors and Intermediates thereof. U.S. Patent 7,235688, June 26, 2007.
(4) (a) Meinke, P. T.; Liberator, P. *Curr. Med. Chem.* **2001**, *8*, 211. (b) Carew, J. S.; Giles, F. J.; Nawrocki, S. T. *Cancer Lett.* **2008**, *269*, 7. (c) Wiech, N. L.; Fisher, J. F.; Helquist, P.; Wiest, O. *Curr. Top. Med. Chem.* **2009**, *9*, 257. (d) Newkirk, T. L.; Bowers, A. A.; Williams, R. M. *Nat. Prod. Rep.* **2009**, *26*, 1293.
(5) (a) Minucci, S.; Pelicci, P. G. *Nat. Rev. Cancer* **2006**, *6*, 38. (b) Bolden, J. E.; Peart, M. J.; Johnstone, R. W. *Nat. Rev. Drug Disc.* **2006**, *5*, 769. (c) Garber, K. *Nat. Biotechnol.* **2007**, *25*, 17. (d) Paris, M.; Porcelloni, M.; Binaschi, M.; Fattori, D. *J. Med. Chem.* **2008**, *51*, 1505. (e) Andrews, K. T.; Tran, T. N.; Lucke, A. J.; Kahnberg, P.; Le, G. T.; Boyle, G. M.; Gardiner, D. L.; Skinner-Adams, T. S.; Fairlie, D. P. *Antimicrob. Agents Chemother.* **2008**, *52*, 1454. (f) Codd, R.; Braich, N.; Liu, J.; Soe, C. Z.; Pakchung, A. A. H. *Int. J. Biochem. Cell Biol.* **2009**, *41*, 736.
(6) (a) Miller, T. A.; Witter, D. J.; Belvedere, S. *J. Med. Chem.* **2003**, *46*, 5097. (b) Vanhaecke, T.; Papeleu, P.; Elaut, G.; Rogiers, V. *Curr. Med. Chem.* **2004**, *11*, 1629. (c) Araki, H.; Yoshinaga, K.; Boccuni, P.; Zhao, Y.; Hoffman, R.; Mahmud, N. *Blood* **2007**, *109*, 3570.

10.1021/ol9029116
Published on Web 01/27/2010

analogues.[7] These compounds could then serve as direct precursors of new HDACi's.The synthesis of the (±)-trichostatic acid system presented here provides a shorter, more efficient route to this series of compounds than the previous reports.

In our retrosynthetic analysis, the formation of the trichostatic acid (**1**) backbone was envisaged to arise from the corresponding ester, which can be assembled via Suzuki−Miyaura cross-coupling between a vinyl bromide **2** and a vinylborane, derived from a homopropargyl alcohol (Scheme 1). Further analysis of

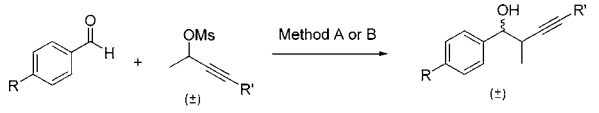
Scheme 1. Retrosynthetic Analysis of (±)-TSA



this advanced intermediate revealed a convergent approach, whereby the corresponding aldehyde can be coupled with a propargyl mesylate, using allenylmetal chemistry as described by Marshall et al.[8]

Aromatic aldehydes have rarely been documented as substrates in the Marshall allenylmetal chemistry.[8b] We expected electron-rich aromatic aldehydes, as would be implemented in a trichostatic acid system, to be especially challenging substrates. In initial model studies (Table 1), using an allenylzinc reagent,

Table 1. Preparation of Homopropargylic Alcohols[a]



entry	product	R	R′	method	isolated yield (%)	anti/syn[b]
1	**3**	H	Me	**A**	40	56/44
2	**4**	NO_2	Me	**A**	48	54/46
3	**5**	Me_2N	Me	**B**	94	48/52
4	**6**	Me_2N	Et	**B**	86	44/56
5	**7**	Me_2N	H	**B**	80	52/48

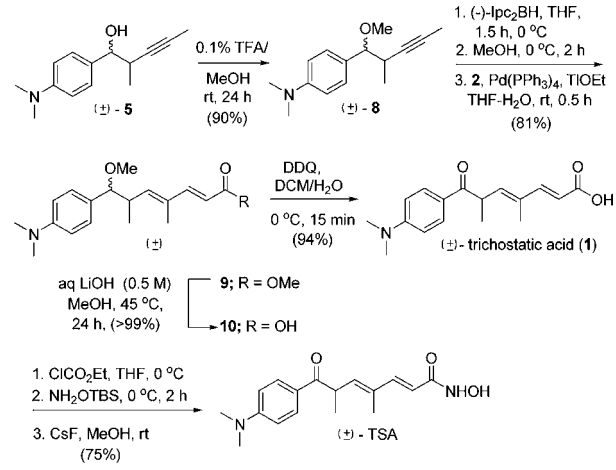
[a] Method A: $Pd(OAc)_2$, PPh_3, Et_2Zn, THF, −78 °C to rt, 1 h. Method B: $PdCl_2$(dppf) (5 mol %), InI, THF−HMPA, rt, 10 min. [b] Determined by ^1H NMR.

benzaldehyde and *p*-nitrobenzaldehyde functioned well as substrates (entries 1 and 2), whereas 4-(dimethylamino)benzaldehyde failed to provide any product. Undeterred, we adopted a modified protocol employing an allenylindium reagent.[8a]

Gratifyingly, a stoichiometric amount of InI and catalytic $PdCl_2$(dppf) furnished the desired compound **5** in excellent yield (94%, entry 3). The poor anti/syn selectivity observed was of no consequence in our synthesis as we planned to remove the newly generated benzylic stereocenter in due course. Most importantly from a general perspective, the success of this reaction demonstrates the usefulness of this propargylation procedure even with an electron-rich aromatic aldehyde. Interestingly, exposure of other homologues of the mesylate, containing an ethyl or a hydrogen moiety at the terminal acetylene, yielded the corresponding homopropargyl alcohols (**6** and **7**) as precursors of trichostatic acid analogues in comparable yields and diastereoselectivities (Table 1, entries 4 and 5).

Having prepared the *rac*-homopropargylic alcohol **5** in good yield, the free alcohol was protected as a methyl ether under solvolytic condition to provide **8** in excellent yield (90%) (Scheme 2). Following a similar protocol as described

Scheme 2. Synthesis of *rac*-Trichostatic Acid and TSA



by Roush et al.,[9] in a one-pot procedure, hydroboration was performed using diisopinocampheylborane. After completion, the reaction was quenched with MeOH followed by a sequential addition of the coupling partner **2**, Pd catalyst, and TlOEt at room temperature to furnish the desired coupled product **9** (81%) as a single isomer (*E*,*E*). Hydrolysis of the ester was effected using a 0.5 M aqueous solution of LiOH to provide the free acid **10** in quantitative yield. The crude acid **10** was subjected to oxidation without further purification using DDQ to provide *rac*-trichostatic acid (**1**) (94%).

Next, we turned our attention toward the preparation of a variety of analogues[7] of trichostatic acid (**1**) using the modified propargylation product **6** and **7**. The choice of analogues was based upon the consideration of the multiple hydrophobic regions present in the 11 Å channel of histone deacetylase-like protein (HDLP) complex of TSA as revealed by X-ray crystallographic analysis (Figure 1).[10] Among several amino

(7) Charrier, C.; Roche, J.; Gesson, J.-P.; Bertrand, P. *J. Chem Sci.* **2009**, *121*, 471.

(8) (a) Marshall, J. A.; Grant, C. M. *J. Org. Chem.* **1999**, *64*, 696. For a review, see: (b) Marshall, J. A. *Chem. Rev.* **2000**, *100*, 3163.

(9) Handa, M.; Scheidt, K. A.; Bossart, M.; Zheng, N.; Roush, W. R. *J. Org. Chem.* **2008**, *73*, 1031.

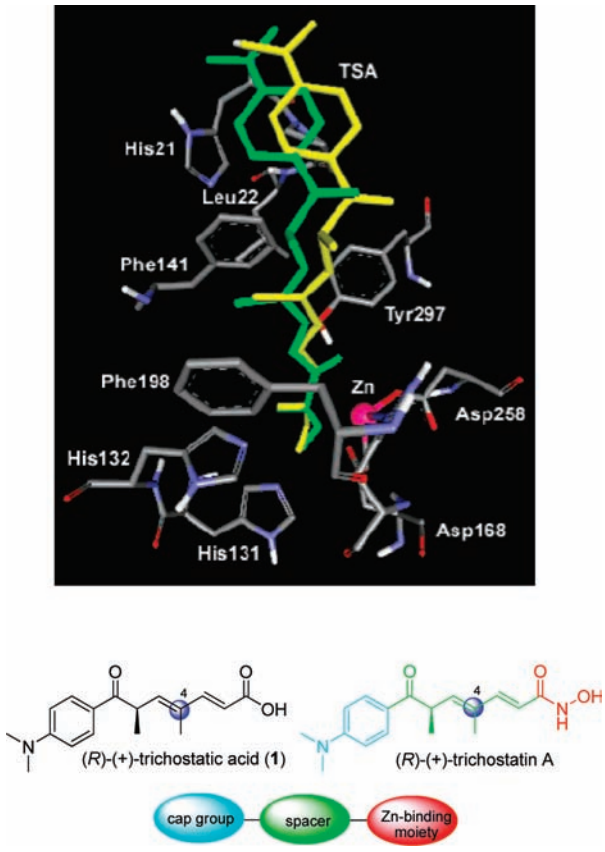


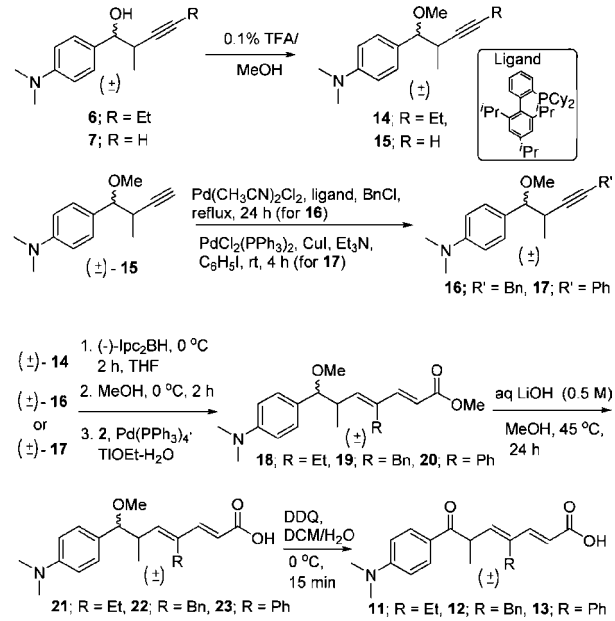
Figure 1. (Top) X-ray structure (yellow) and the best docked structures (green) of the HDLP−TSA complex.[11]

acid residues, we were particularly interested in the two parallel phenyl groups of residues Phe141 and Phe198 near the middle of the channel that leads to the active site.[11] In order to take advantage of these aromatic groups to increase favorable interactions with analogues, we planned to replace the C-4 methyl group present in trichostatic acid with an ethyl, benzyl, or phenyl group. The stronger binding of these analogues to the active site may be expected to reduce the need for incorporating the hydroxamic acid group of TSA. Short physiological lifetime and undesired side effects may be attributed to this reactive functional group and therefore use of alternative binding groups may be desirable.

The synthesis of the racemic C-4 ethyl analogue **11** commenced from compound **6** (Scheme 3). Following a protocol similar to the previous scheme, **11** was obtained in excellent yield (53% overall) and selectivity. For the preparation of the racemic C-4 benzyl (**12**) and phenyl (**13**) analogues, installation of the benzyl[12] and phenyl[13] groups at the terminal alkyne group of **7** was achieved using literature procedures.Gratifyingly, the in situ hydroboration of the protected homopropargyl alcohols

(10) Finnin, M. S.; Donigian, J. R.; Cohen, A.; Richon, V. M.; Rifkind, R. A.; Marks, P. A.; Breslow, R.; Pavletich, N. P. *Nature* **1999**, *401*, 188.
(11) Wang, D.-F.; Wiest, O.; Helquist, P.; Lan-Hargest, H.-Y.; Wiech, N. L. *J. Med. Chem.* **2004**, *47*, 3409.
(12) Larsen, C. H.; Anderson, K. W.; Tundel, R. E.; Buchwald, S. L. *Synlett* **2006**, 2941.
(13) Yue, D.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 1905.

Scheme 3. Synthesis of Various Analogues of Trichostatic Acid



16 and **17** with Ipc_2BH was again regioselective, and Suzuki coupling with **2** furnished the unsaturated esters **19** and **20** as single *E*,*E* isomers in moderate yields. Hydrolysis of the esters followed by DDQ oxidation of **22** and **23** provided the corresponding *rac*-trichostatic acid derivatives **12** and **13** in 30% and 26% overall yields, respectively. All the compounds in this series can potentially be converted into hydroxamic acid derivatives (which we have already confirmed in the conversion of (±)-trichostatic acid itself to provide *rac*-TSA; see the Supporting Information) or to alternative Zn-binding analogues.

In conclusion, we have developed a cost-effective and scalable route for the preparation of *rac*-trichostatic acid and analogues starting from a commercially available aromatic aldehyde by a shorter route and in higher yields (overall 61% for **1**) than the previous reports.[3] Minor modifications of our route led for the first time to the ethyl (**11**), benzyl (**12**) and phenyl (**13**) analogues of *rac*-trichostatic acid. An enantioselective version of this route is currently being studied in our laboratory. The modified route and the HDACi activities of the analogues will be reported in due course.

Acknowledgment. Financial support by Ara Parseghian Medical Research Foundation, The Edison Foundation, and Circagen are gratefully acknowledged. We would also like to thank Dr. Norbert L. Wiech (Chromatin Therapeutics), Dr. Jed Fisher (University of Notre Dame), Leslie Patterson (University of Notre Dame), and John Markiewicz (University of Notre Dame) for assistance and valuable discussions.

Supporting Information Available: Detailed experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL9029116