ORGANIC LETTERS

2011
Vol. 13, No. 14
3564–3567

Concise, Convergent Syntheses of (±)-Trichostatin A Utilizing a Pd-Catalyzed Ketone Enolate α-Alkenylation Reaction

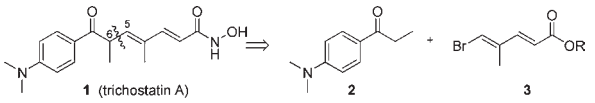
Casey C. Cosner and Paul Helquist*

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

phelquis@nd.edu

Received April 12, 2011

ABSTRACT



Two concise, convergent syntheses of (±)-trichostatin A (1), a potent histone deacetylase inhibitor, have been accomplished. The key step in both is a Pd-catalyzed α-alkenylation reaction between ketone 2 and either dienyl bromide 3 or alkenyl bromide 9 using a modification of cross-coupling conditions described by Negishi and Hartwig. A brief investigation has shown the potential utility of a Ni-catalyzed version of this reaction. The overall synthetic routes are short and amenable to scaleup, providing access to trichostatin A via trichostatic acid as a direct precursor.

Within the past decade, members of several protein classes known as histone deacetylases (HDAC) have become popular cellular targets for epigenetic regulation of gene expression. Arising from these studies have been a number of histone deacetylase inhibitors (HDACi) as small molecule drugs. Many of these compounds have most commonly been recognized for their remarkable anticancer activity.[1] HDACi also have potential for the treatment of other ailments,[2] including inflammatory diseases,[3] malaria,[4] motor neuron diseases,[5] and Niemann–Pick type C disease (NPC), a rare lipid storage disorder.[6] The potential for these compounds to be useful drugs was recently substantiated by the FDA approval of Vorinostat (suberoylanilide hydroxamic acid, SAHA) for the treatment of cutaneous T-cell lymphoma.[7]

Besides SAHA, several additional HDACi have been identified, one of the most potent being (*R*)-(+)-trichostatin A (TSA, **1**).[8] Originally isolated from *Streptomyces hygroscopicus*, (*R*)-(+)-TSA has been reported to have a K_i of 3.4 nM as an HDACi[9] and to be active in studies of cancer, lupus, malaria, and several other diseases.[2,10] Most recently, we have found that treating NPC cells with TSA significantly lowered the levels of accumulated cholesterol within the cells as a means of correcting the phenotype of this disease.[11] As our laboratory has a vested interest in the

(1) (a) Johnstone, R. W. *Nat. Rev. Drug Discovery* **2002**, *1*, 287. (b) Marks, P. A.; Rifkind, R. A.; Richon, V. M.; Breslow, R.; Miller, T.; Kelly, W. K. *Nat. Rev. Cancer* **2001**, *1*, 194.

(2) Wiech, N. L.; Fisher, J. F.; Helquist, P.; Wiest, O. *Curr. Top. Med. Chem.* **2009**, *9*, 257.

(3) (a) Shuttleworth, S. J.; Bailey, S. G.; Townsend, P. A. *Curr. Drug Targets* **2010**, *11*, 1449. (b) Halili, M. A.; Andrews, M. R.; Sweet, M. J.; Fairlie, D. P *Curr. Top. Med. Chem.* **2009**, *9*, 309.

(4) Andrews, K. T.; Tran, T. N.; Wheatley, N. C.; Fairlie, D. P. *Curr. Top. Med. Chem.* **2009**, *9*, 292.

(5) Echaniz-Laguna, A.; Bousiges, O.; Loeffler, J.-P.; Boutillier, A.-L. *Curr. Med. Chem.* **2008**, *15*, 1263.

(6) Kim, S.-J.; Lee, B.-H.; Lee, Y.-S.; Kang, K.-S. *Biochem. Biophys. Res. Commun.* **2007**, *360*, 593.

(7) Grant, S.; Easley, C.; Kirkpatrick, P. *Nat. Rev. Drug Discovery* **2007**, *6*, 21.

(8) Tsuji, N.; Kobayashi, M.; Nagashima, K.; Wakisaka, Y.; Koizumi, K. *J. Antiobiot.* **1976**, *29*, 1.

(9) Yoshida, M.; Kijima, M.; Akita, M.; Beppu, T. *J. Biol. Chem.* **1990**, *265*, 17174.

(10) (a) Mishra, N.; Brown, D. R.; Olorenshaw, I. M.; Kammer, G. M. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 2628. (b) Andrews, K. T.; Walduck, A.; Kelso, M. J.; Fairlie, D. P.; Saul, A.; Parsons, P. G. *Int. J. Parasitol.* **2000**, *30*, 761.

(11) Pipalia, N. H.; Cosner, C. C.; Huang, A.; Chatterjee, A.; Bourbon, P.; Farley, N.; Helquist, P.; Wiest, O.; Maxfield, F. R. *Proc. Natl. Acad. Sci. U.S.A.* **2011**, *108*, 5620.

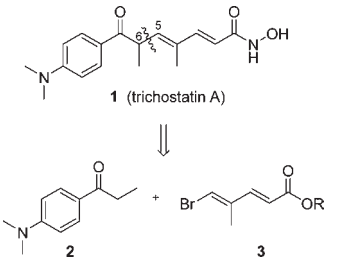
(12) (a) Cosner, C. C.; Markiewicz, J. T.; Bourbon, P.; Mariani, C. J.; Wiest, O.; Rujoi, M.; Rosenbaum, A. I.; Huang, A. Y.; Maxfield, F. R.; Helquist, P. *J. Med. Chem.* **2009**, *52*, 6494. (b) Rosenbaum, A. I.; Cosner, C. C.; Mariani, C. J.; Maxfield, F. R.; Wiest, O.; Helquist, P. *J. Med. Chem.* **2010**, *53*, 5281.

10.1021/ol200964m
Published on Web 06/21/2011

development of NPC therapeutics,[12] we became interested in the synthesis of TSA for further study as a potential NPC treatment.

TSA has been prepared a number of times,[13] but some of the previous syntheses are long or low-yielding. In an effort to combat this issue, our group recently reported two distinct routes,[14] including the shortest synthesis of TSA to date.[14b] This latter route provided access to substantial quantities of material for biological evaluation; however, the starting materials are costly, and many of the reagents are difficult to handle, making scaleup difficult. To overcome these problems, we sought to devise a more effective route to (±)-TSA. We now wish to report our third and significantly improved strategy for the synthesis of this compound.

Scheme 1. Retrosynthetic Analysis of (±)-TSA (**1**)

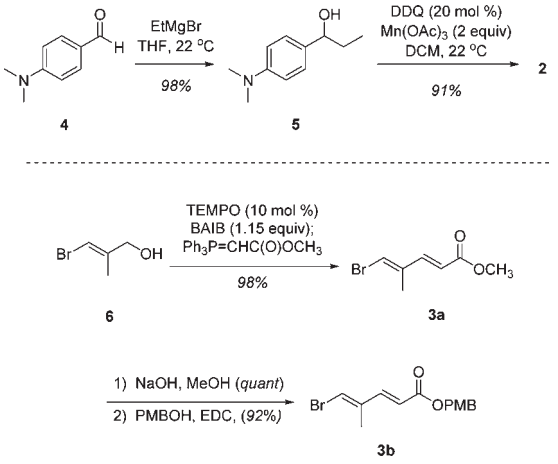


In designing our synthesis of trichostatin A, we envisaged a key bond connection between C(5) and C(6) and sought to accomplish this bond formation via a transition-metal-catalyzed α-alkenylation reaction between ketone **2** and dienyl halide **3** (Scheme 1). While many α-alkenylation examples have been reported in the literature,[15] few have been conducted intermolecularly.[16] Furthermore, because isomerization of the resulting β,γ-unsaturated product is a potential problem, the use of mild conditions to conduct this reaction is necessary for this approach to be viable. Recently, zinc enolates have been shown to be effective in related α-arylation reactions.[17] Given the mild nature and high functional group tolerance of organozinc reagents, we decided to utilize zinc enolates in our studies.

The synthesis of the coupling components **2** and **3** on multigram scales commenced with the addition of EtMgBr to commercially available 4-(dimethylamino)benzaldehyde (**4**) to furnish alcohol **5** in 98% yield (Scheme 2). The subsequent oxidation was conducted using a new $Mn(OAc)_3$/catalytic DDQ oxidation protocol to furnish ketone **2** in 91% yield.[18] Dienyl bromide **3a** containing a methyl ester was synthesized in a single operation from the known alkenyl bromide **6**[19] using a one-pot oxidation/Wittig protocol in 98% yield.[20] Hydrolysis of the methyl ester (NaOH) and re-esterification (*p*-methoxybenzyl alcohol, EDC) also provided facile access to the PMB ester **3b** to allow for greater flexibility in removal of the ester group in later stages of the synthesis.

We quickly found efficient cross-coupling conditions employing LiTMP and $ZnCl_2$ to generate the zinc enolate of ketone **2** followed by reaction with bromide **3a** or **3b**, $Pd(dba)_2$, and 1,1′-bis(di-*tert*-butylphosphino)ferrocene

Scheme 2. Synthesis of Ketone **2** and Alkenyl Bromides **3a** and **3b**



(dtbpf) to give the desired **7a** or **7b** in 73% or 82% yield, respectively, with complete retention of diene configuration and regiochemistry (eqs 1 and 2). The coupling is very ligand-dependent and gave the best results with electron-rich, sterically demanding alkyl phosphines. Q-phos (employed by Hartwig in related reactions[17a]) and *t*-Bu_3P also promote the coupling but in lower yield than dtbpf, whereas several phenylphosphines give greatly inferior results. As a control, the reaction fails in the absence of Pd. Furthermore, isomerization of the resulting

(13) (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.

(14) (a) Markiewicz, J. T.; Schauer, D. J.; Löfstedt, J.; Corden, S. J.; Wiest, O.; Helquist, P. *J. Org. Chem.* **2010**, *75*, 2061. (b) Chatterjee, A.; Richer, J.; Hulett, T.; Iska, V. B. R.; Wiest, O.; Helquist, P. *Org. Lett.* **2010**, *12*, 832.

(15) (a) Piers, E.; Marais, P. *J. Org. Chem.* **1990**, *55*, 3454. (b) Solè, D.; Peidro, E.; Bonjoch, J. *Org. Lett.* **2000**, *2*, 2225. (c) Wang, T.; Cook, J. M. *Org. Lett.* **2000**, *2*, 2057.

(16) For examples of transition-metal-catalyzed intermolecular α-alkenylations, see: (a) Fauvarque, J.; Jutand, A. *J. Organomet. Chem.* **1981**, *209*, 109. (b) Chieffi, A.; Kamikawa, K.; Åhman, J.; Fox, J. M.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 1897. (c) Huang, J.; Bunel, E.; Faul, M. M. *Org. Lett.* **2007**, *9*, 4343. (d) Taylor, A. M.; Altman, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 9900.

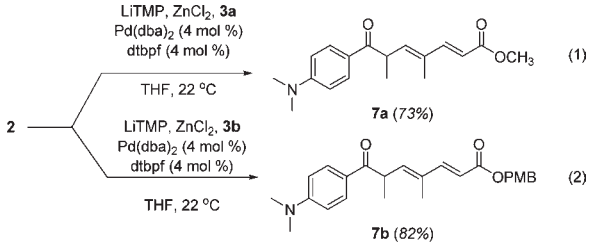
(17) (a) Hama, T.; Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 4976. (b) Hama, T.; Liu, X.; Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 11176. (c) Hlavinka, M. L.; Hagadorn, J. R. *Organometallics* **2007**, *26*, 4105. (d) Hlavinka, M. L.; Hagadorn, J. R. *Tetrahedron Lett.* **2006**, *47*, 5049. (e) Duez, S.; Bernhardt, S.; Heppekausen, J.; Fleming, F. F.; Knochel, P. *Org. Lett.* **2011**, *13*, 1690.

(18) Cosner, C. C.; Cabrera, P. J.; Byrd, K. M.; Thomas, A. M. A.; Helquist, P. *Org. Lett.* **2011**, *13*, 2071.

(19) (a) Handa, M.; Scheidt, K. A.; Bossart, M.; Zheng, N.; Roush, W. R. *J. Org. Chem.* **2008**, *73*, 1031. (b) Nicolaou, K. C.; Fylaktakidou, K. C.; Monenschein, H.; Li, Y.; Weyershausen, B.; Mitchell, H. J.; Wei, H.-X.; Guntupalli, P.; Hepworth, D.; Sugita, K. *J. Am. Chem. Soc.* **2003**, *125*, 15433.

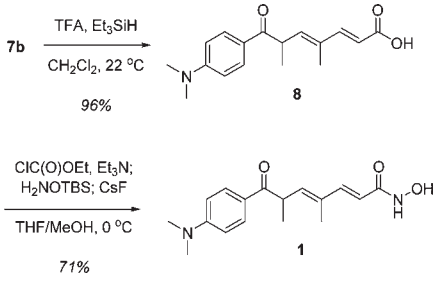
(20) Vatèle, J.-M. *Tetrahedron Lett.* **2006**, *47*, 715.

cross-coupled products was never observed under these conditions.



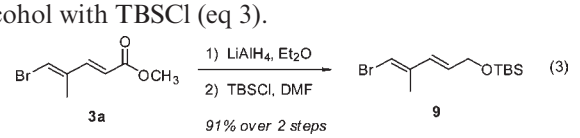
For the next step of the synthesis of TSA, conventional hydrolysis of the methyl ester **7a** with metal hydroxides to form trichostatic acid (**8**) was not possible, due to the sensitivity of this system to basic conditions. Alternative methods (LiI, NaCN, KOTMS) led to the recovery of starting material or degradation of material. On the other hand, the TSA core is stable toward many acidic conditions, which permitted us to cleave the PMB ester **7b** with TFA and Et_3SiH, furnishing (±)-**8** in 96% yield (Scheme 3). Conversion into (±)-TSA (**1**) was accomplished in 72% yield by treatment with ethyl chloroformate and *O*-TBS hydroxylamine followed by immediate deprotection with

Scheme 3. Synthesis of (±)-TSA from Ester **7b**



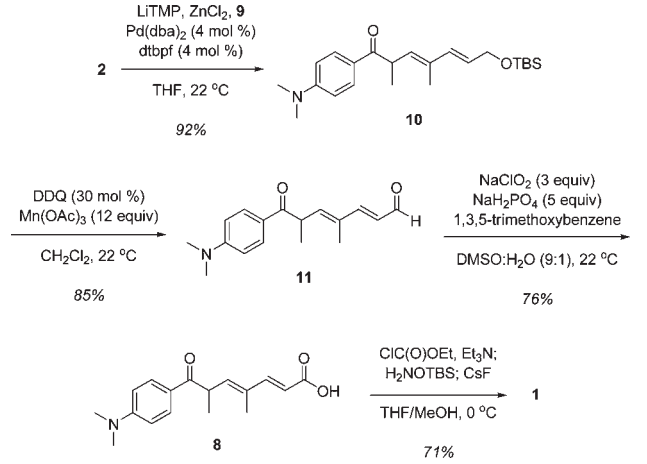
CsF.[14b] We find H_2NOTBS to be particularly useful as an easily prepared and readily handled, storable solid reagent.[21]

Having accomplished a very efficient synthesis of TSA, we briefly examined the range of alkenyl halides that would be useful in this same manifold, including the possibility of extending the α-alkenylation to alkenyl bromides related to **3** that do not possess an activating carbonyl group. To assess this idea and to apply it toward the synthesis of TSA, we prepared alkenyl bromide **9** in 91% yield over two steps by $LiAlH_4$ reduction of ester **3a** and protection of the crude alcohol with TBSCl (eq 3).



To our delight, subjection of this material to the conditions of the α-alkenylation provided the desired cross-coupled product **10** in 92% yield after purification with complete retention of the double bond configurations (Scheme 4). Inspired by a report from Paterson's group,[22] we sought to conduct a one-pot deprotection−oxidation sequence to convert **10** into the corresponding aldehyde using DDQ as the oxidant. While the protocol did furnish the desired aldehyde, it was contaminated with an *N*-dealkylated byproduct that was difficult to remove from the desired product. This problem was overcome by again employing the new catalytic DDQ/$Mn(OAc)_3$ protocol.[18] Under these conditions, the desired aldehyde **11** was isolated in 85% yield and was completely free of the *N*-dealkylated byproduct. The oxidation to the carboxylic acid was troublesome.[23] Although Pinnick oxidations are typically very clean with little to no byproducts, very

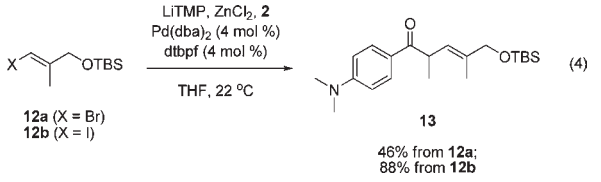
Scheme 4. Synthesis of (±)-TSA Using Alkenyl Bromide **9**



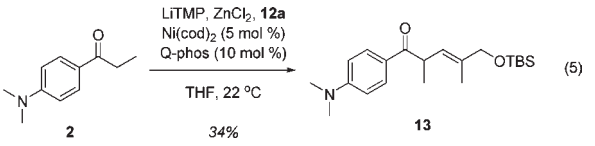
electron-rich aromatic rings are often chlorinated, even in the presence of a large excess of chlorine scavengers such as 2-methyl-2-butene. Indeed, this side reaction was a problem for us, as we routinely obtained 30% −45% of chlorinated material. Even employing DMSO as the solvent did not completely prevent chlorination of the substrate.[24] However, addition of 1,3,5-trimethoxybenzene as an additional scavenger prevented chlorination of our substrate[25] and allowed us to obtain **8** cleanly in 72% yield after purification. The final step was the installation of the hydroxmate, which we accomplished in the same manner as that shown in Scheme 3.

(21) Apfel, C; Banner, D. W.; Bur, D.; Dietz, M.; Hirata, T.; Hubschwerlen, C.; Locher, H.; Page, M. G. P.; Pirson, W.; Rossé, G.; Specklin, J.-L. *J. Med. Chem.* **2000**, *43*, 2324.
(22) Paterson, I.; Woodrow, M. D.; Cowden, C. J. *Tetrahedron Lett.* **1998**, *39*, 6041.
(23) Bal, B. S.; Childers, W. E.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091.
(24) Dalcanale, E.; Montanari, F. *J. Org. Chem.* **1986**, *51*, 567.
(25) Lindren, B. O.; Nilsson, T. *Acta Chem. Scand.* **1973**, *27*, 888.
(26) Werle, S.; Fey, T.; Neudörfl, J. M.; Schmalz, H.-G. *Org. Lett.* **2007**, *9*, 3555.
(27) Lipshutz, B. H.; Lee, C.-T.; Servesko, J. M. *Org. Lett.* **2007**, *9*, 4713.

We next examined the use of the known nonconjugated alkenyl bromide **12a**[26] or iodide **12b**.[27] Applying our standard conditions (LiTMP, $ZnCl_2$, $Pd(dba)_2$, and dtbpf) to the cross-coupling with ketone **2**, we found that bromide **12a** suffered from low conversion, even with the extended reaction times. In contrast, iodide **12b** underwent smooth reaction to give the desired product **13** in 88% yield (eq 4).



We have also attempted to conduct the α-alkenylation reaction using $Ni(cod)_2$ as a less expensive catalyst. For both the α-alkenylation and α-arylation reactions, there are significantly fewer precedents for employing Ni rather than Pd.[16a,28] Most of our attempts with $Ni(cod)_2$ were disappointing; conversions of starting material and isolated yields were often extremely low. The most promising result was obtained when we employed $Ni(cod)_2$ with ketone **2** and alkenyl bromide **12a** whereby the desired product **13** was obtained in 34% yield (eq 5). In this case, Q-phos outperformed dtbpf. This result indicates that if further optimization is possible, Ni has the potential to be an effective catalyst for the α-alkenylation reaction. At this point, we are unable to rule out the possibility of the reaction being promoted by trace quantities of another metal as a contaminant in the Ni catalyst. Further work in these regards is currently underway.



In conclusion, we have developed two new concise, scaleable routes for the production of (±)-trichostatin A. The key step in each is a Pd-catalyzed cross-coupling between a zinc enolate and an alkenyl or dienyl halide, resulting in the desired β,γ-unsaturated ketone. Other notable features of the synthesis include use of a new catalytic oxidation procedure at two points in the route and the preliminary indication of Ni as a potentially useful and far less expensive catalyst for the critical coupling reaction. We are currently applying these routes to the synthesis of a variety of TSA analogues. Further exploration of the cross-coupling reaction is underway, particularly with the use of chiral ligands for enantioselective applications such as the natural (+)-TSA and improvements in the use of Ni catalysts. The results of these additional studies will be reported in due course.

Acknowledgment. Acknowledgment is made to the Ara Parseghian Medical Research Foundation (APMRF), the National Science Foundation, and the donors of the American Chemical Society Petroleum Research Fund for support of this research. C.C.C. is the recipient of the J. Peter Grace Fellowship from the University of Notre Dame. We gratefully acknowledge Dr. Douglas Schauer (Ivy Tech Community College) and Dr. Anamitra Chatterjee (Notre Dame) for valuable discussions.

Supporting Information Available. Detailed experimental procedures, copies of ^1H and ^{13}C NMR spectra, and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(28) (a) Helquist, P. Applications of Zerovalent Nickel Complexes to Synthetic Organic Chemistry. Ph.D. Thesis, Cornell University, Ithaca, NY, January 1973. (b) Semmelhack, M. F.; Stauffer, R D.; Rogerson, T. D. *Tetrahedron Lett*. **1973**, *14*, 4519. (c) Semmelhack, M. F.; Chong, B. P.; Stauffer, R D.; Rogerson, T. D.; Chong, A.; Jones, L. D. *J. Am. Chem. Soc*. **1975**, *97*, 2507. (d) Millard, A. A.; Rathke, M. W. *J. Am. Chem. Soc*. **1977**, *99*, 4833. (e) Spielvogel, D. J.; Buchwald, S. L. *J. Am. Chem. Soc*. **2002**, *124*, 3500. (f) Matsubara, K.; Ueno, K.; Koga, Y.; Hara, K. *J. Org. Chem*. **2007**, *72*, 5069. (g) Liao, X.; Weng, Z.; Hartwig, J. F. *J. Am. Chem. Soc*. **2008**, *130*, 195. (h) Johansson, C. C. C.; Colacot, T. J. *Angew. Chem., Int. Ed*. **2010**, *49*, 676. (i) Bellina, F.; Rossi, R. *Chem. Rev*. **2010**, *110*, 1082.