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Evolution of Concise and Flexible Synthetic Strategies for Trichostatic Acid and the Potent Histone Deacetylase Inhibitor Trichostatin A

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(*R*)-(+)-Trichostatic acid and (*R*)-(+)-trichostatin A (TSA) are natural products that have attracted considerable attention in the field of epigenetic therapies. TSA in particular is a naturally occurring hydroxamic acid having potent activity as a histone deacetylase inhibitor (HDACi) and having significant potential for treatment of a myriad of genetically based diseases. Development of TSA and other trichostatic acid derivatives into useful small-molecule therapies has been hindered by the low natural abundance and high cost associated with these compounds. We report herein our collective efforts towards the development of concise and scalable routes for the synthesis of trichostatic acid and TSA in both racemic and enantioenriched forms. Three independent synthetic pathways were developed with varying degrees of efficiency and convergency. In the first synthesis, the key step was a vinylogous Horner–Wadsworth–Emmons condensation. A Marshall propargylation reaction was used as the key step in the second synthesis, and Pd-catalyzed α-alkenylation of a ketone zinc enolate by using various functionalized alkenyl or dienyl halides was developed for the third synthesis. The second pathway proved to be readily amenable to an enantioselective modification, and both the second and third pathways were straightforwardly adapted for the facile preparation of new analogues of trichostatic acid and TSA.

Introduction

Within the last decade, members of several protein classes known as histone deacetylases have become popular cellular targets for epigenetic regulation of gene expression. Arising from these studies have been a number of histone deacetylase inhibitors (HDACi) that are small-molecule drugs. These compounds have most commonly been recognized for their 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). NPC is a rare fatal lysosomal lipid storage disorder characterized by abnormal accumulation of cholesterol and other lipids in organelles within cells.[6] The potential for HDACi as drugs has been substantiated by the Federal Drug Administration approval of vorinostat (suberoylanilide hydroxamic acid, SAHA, Zolinza™) and romidepsin (Istodax™) for the treatment of cutaneous T-cell lymphoma.[7,8]

Besides vorinostat and romidepsin, a large number of additional HDACi have been identified, one of the most potent being trichostatin A (TSA, **1**, Scheme 1). TSA is the hydroxamic acid derivative of trichostatic acid (**2**).[9] The latter acid is itself a naturally occurring compound, which was first isolated from *Streptomyces sioyaensis* and which was reported to induce differentiation of leukemia cells.[10] TSA was originally isolated from *Streptomyces hygroscopicus* and was first reported to have antibacterial activity. It was later found to have an inhibition constant, K_i, of 3.4 nM as an HDACi[11] and to be active in studies of cancer, lupus, malaria, and several other diseases.[2,12]

Most recently, we have found that treating human NPC cells with TSA significantly lowered the levels of accumulated cholesterol within storage organelles as a means of correcting the phenotype of this disease.[13] As our laboratory has a vested interest in the development of therapeutic agents for lysosomal storage disorders,[13,14] we became interested in the synthesis of trichostatic acid, TSA, and analogues for further study as potential treatments for NPC and other members of this class of diseases.

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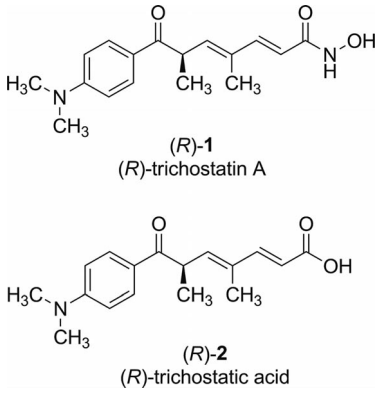


Scheme 1. Structures of target compounds.

Results and Discussion

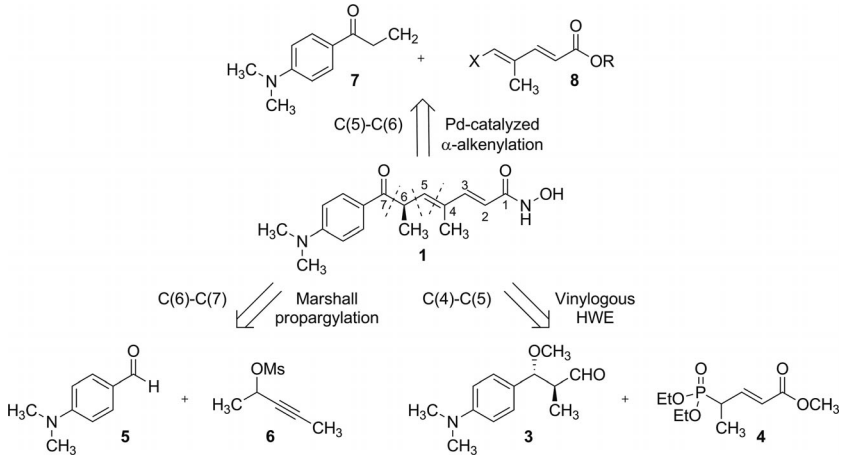
Evaluation of the chemical literature reveals that several syntheses of trichostatic acid and TSA have been reported,[15] but some of these syntheses have been long and low yielding. To improve upon these earlier efforts, we kept the following criteria in mind to guide our planning: (1) minimization of length and maximization of efficiency of any new routes, (2) flexibility for preparation of new analogues for subsequent drug development efforts, and (3) amenability to enantioselective synthesis. In working towards achieving these goals, we have developed and published initial accounts of three quite diverse approaches to trichostatic acid and TSA, each with various advantages (Scheme 2). The first approach utilized a vinylogous Horner–Wadsworth–Emmons (HWE) reaction to install the diene moiety as the key C(4)–C(5) bond-forming step.[16] The second relied on a Marshall propargylation reaction to form the C(6)–C(7) bond,[17] and the third strategy was based on a Pd-catalyzed α-alkenylation of an enolate to form C(5)–C(6) of the β,γ-unsaturated ketone moiety.[18] We now wish to report our collective findings on all three of our approaches to trichostatic acid and TSA, including the evolution of our synthetic strategies, a newly developed enantioselective adaptation of one of the routes, and a summary of analogues that we have been able to obtain by using two of these routes. To set the stage for presentation of these more recent results, we begin with brief overviews and critical evaluations of our previously published syntheses.

Previously Published Syntheses

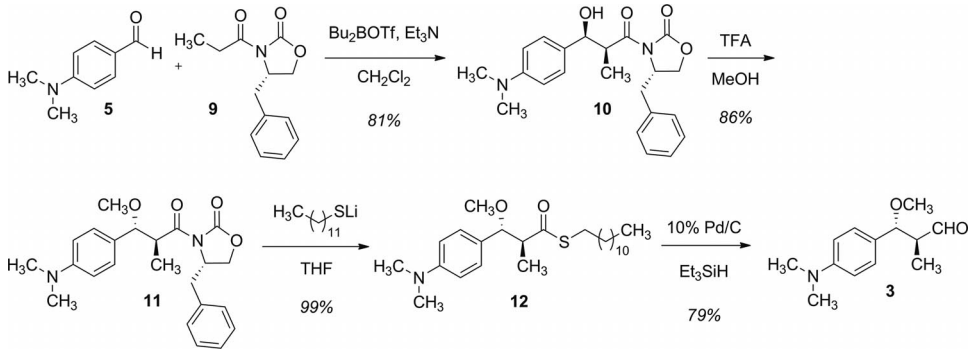
First-Generation Synthesis

Although each of the earlier reported syntheses of trichostatic acid and TSA by other investigators relied on different strategies, many of them retained identical or at least similar steps. The most noticeable of these steps are those employed for the formation of the conjugated diene moiety. This construction typically focused on a stepwise sequence involving (1) olefination of an aldehyde by using an ester-containing organophosphorus reagent, (2) reduction and oxidation to generate an α,β-unsaturated aldehyde, and (3) a second olefination. Although this sequence is commonly employed for diene synthesis in general, its repetitive nature adds a significant number of steps to a synthesis. We therefore initially sought to design a synthesis of trichostatic acid in which this sequential construction is replaced with a more direct approach. Our first synthesis of trichostatic acid achieved this goal by employing a condensation between aldehyde **3** and vinylogous HWE reagent **4** [see C(4)–C(5) in Scheme 2].[16]

Aldehyde **3** was prepared by a sequence beginning with an Evans aldol condensation[19] of commercially available 4-(dimethylamino)benzaldehyde (**5**) followed by straightforward functional group manipulations[20,21] of aldol product **10** (Scheme 3). The *syn*/*anti* conversion that occurred was of no consequence because the configuration of the C(7) ether (trichostatic acid numbering scheme) was lost owing to a later oxidation. Reaction with phosphonate **4**[22] as a mixture of alkene positional isomers furnished an 80% yield of **13** as a 2:1 mixture of *E*,*E*/*E*,*Z* dienes (Scheme 4). Preparative-scale separation of the isomers was unsuccessful, and attempts to affect double-bond isomerization by using standard methods failed to alter the ratio. Only after

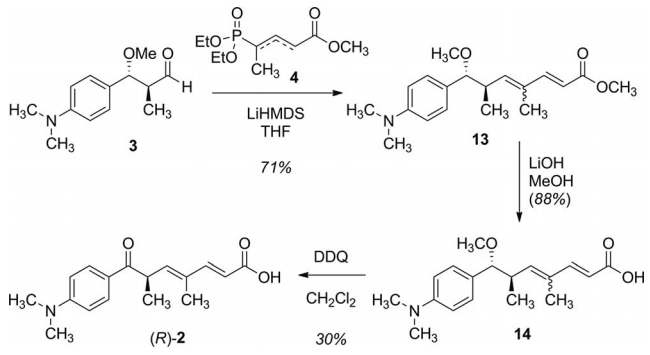


Scheme 2. Key bond-forming strategies for three syntheses of TSA.



Scheme 3. Synthesis of aldehyde **3**.

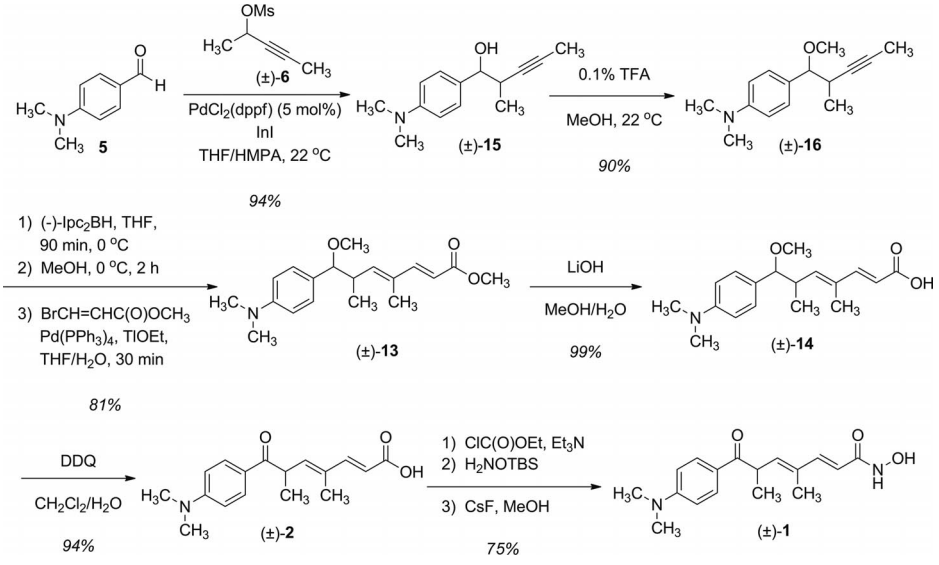
further conversion to trichostatic acid could the diene isomers be separated chromatographically. This difficult separation on a small scale resulted in a low yield of 30% of the isolated (+)-trichostatic acid (*R*)-**2** as the correct *E*,*E* isomer and with an *ee* of 87%. Although this route demonstrated a concise approach for installation of the diene moiety of TSA, and even though this route was directly amenable to an enantioselective implementation, the low *E*,*E*/*E*:*Z* ratio of the HWE product and the difficulty in separating the diene isomers detracted from its efficiency and practicality.



Scheme 4. Completion of the first-generation of (*R*)-trichostatic acid.

Second-Generation Synthesis

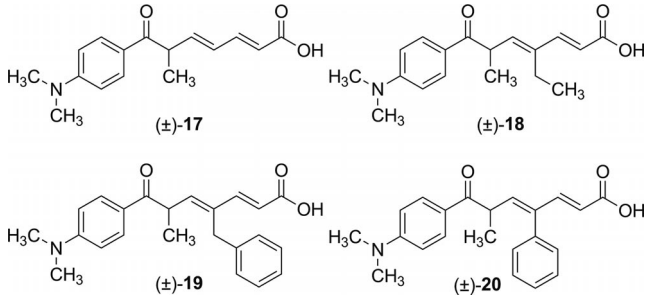
A quite different strategy was based upon a key bond formation using a propargylation reaction described by Marshall[23] [see C(6)–C(7) in Scheme 2] followed by a Suzuki–Miyaura coupling to construct the desired diene.[17] Beginning again with aldehyde **5**, reaction with an allenylindium intermediate generated from racemic propargyl mesylate **6** provided racemic homopropargylic alcohol **15** in 94% yield as an approximately 1:1 mixture of *syn*/*anti* diastereomers (Scheme 5),[23] which again was inconsequential. In a one-pot procedure, hydroboration of the alkyne in homopropargyl ether **16** and Pd-catalyzed coupling of the resulting alkenylborane with methyl (*E*)-3-bromomethacrylate provided exclusively *E*,*E*-**13** in 81% isolated yield, which marks a significant improvement over the first-generation synthesis. Subsequent steps provided racemic trichostatic acid (±)-**2** in 94% yield. Installation of the hydroxamic acid group was accomplished by reaction of a mixed anhy-



Scheme 5. Second-generation synthesis of (±)-TSA.

dride with *O*-*tert*-butyldimethylsilyl (TBS) hydroxylamine followed by deprotection to furnish (±)-TSA (**1**) in 75% yield.

The second synthesis proved to be amenable to the production of trichostatic acid analogues whereby a range of C(4) substituents could be introduced in place of the dienyl methyl group in TSA (Scheme 6). The choice of analogues was based upon analysis of the X-ray crystal structure of the histone deacetylase-like protein complex of TSA.[24] We chose to replace the C(4) methyl group with hydrogen (**17**) as a point of comparison and most importantly with ethyl (**18**), benzyl (**19**), and phenyl (**20**) groups to take advantage of their interactions within the 11 Å binding channel. As starting points for the synthesis of the desired analogues, alcohols **21** and **22**, were obtained by Marshall propargylation reactions by using the corresponding propargylic mesylates (Scheme 7). Upon conversion of the desired homopropargyl alcohols into ethers, **24** served as the precursor



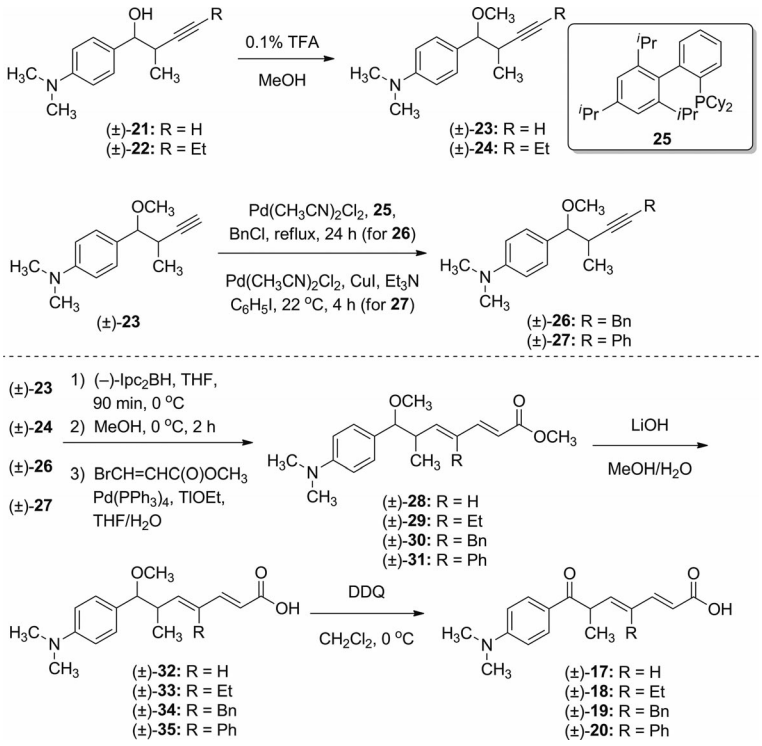
Scheme 6. (±)-Hydrogen (**17**), (±)-ethyl (**18**), (±)-benzyl (**19**), and (±)-phenyl (**20**) analogues of trichostatic acid.

for ethyl-TSA analogue **18**, and **23** served as the precursor of hydrogen, benzyl, and phenyl analogues, **17**, **19**, and **20**, respectively.

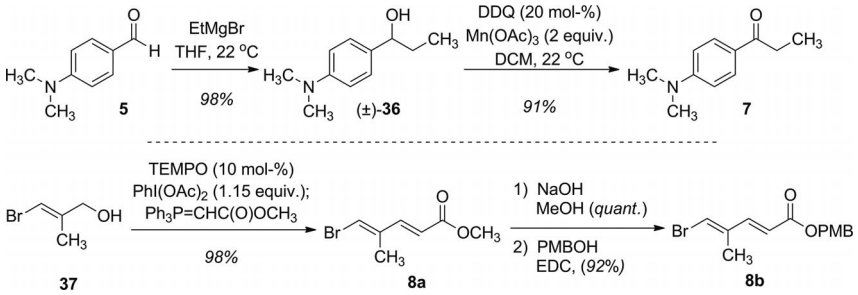
Third-Generation Synthesis

Although our second-generation synthesis proved to be efficient, the sequence is entirely linear similar to many previously published syntheses of TSA.[15] Bearing in mind that a more convergent route may have greater overall efficiency, we devised a third-generation synthesis.[18] We saw an opportunity to employ a transition metal-catalyzed cross-coupling reaction between an alkenyl halide and an enolate to form the C(5)–C(6) bond in a convergent manner (see Scheme 2). α-Alkenylation of enolates has not been employed as commonly in an intermolecular sense[25] relative to intramolecular applications of this coupling reaction.[26]

The synthesis started with aldehyde **5**, which was subjected to a Grignard reaction to provide alcohol **36** in 98% yield (Scheme 8). The subsequent oxidation with some common protocols (Swern, Moffatt, IBX, etc.) either failed completely or gave low yields of ketone **7**, but a recently reported catalytic 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)/$Mn(OAc)_3$ oxidation method[27] provided **7** in 91% yield. The preparation of dienyl bromides **8a** and **8b** employed readily available (*E*)-3-bromo-2-methyl-2-propenol (**37**) in a one-pot oxidation/Wittig protocol to furnish **8a** in 98% yield as a single *E*,*E*-isomer.[28] The methyl ester was converted into *p*-methoxybenzyl ether (PMB) ester **8b** to permit a choice of ester deprotection strategies during the later stages of the synthesis. Corresponding iodide **8c** was also prepared in parallel with the bromide.



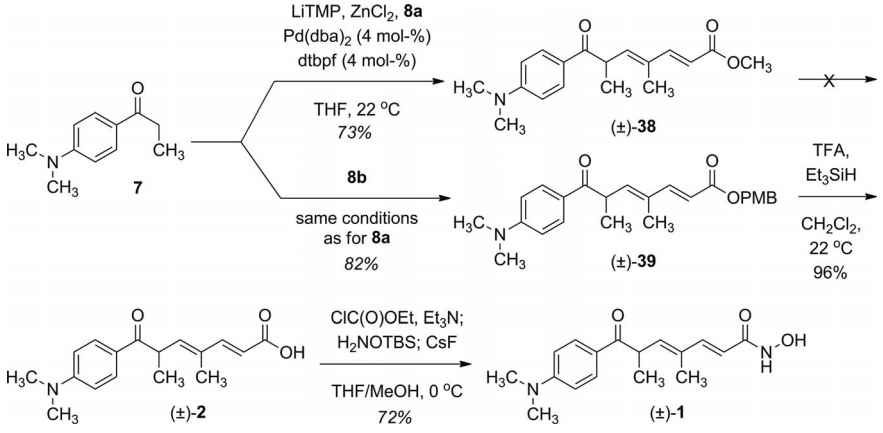
Scheme 7. Synthesis of (±)-trichostatic analogues **17**–**20**.



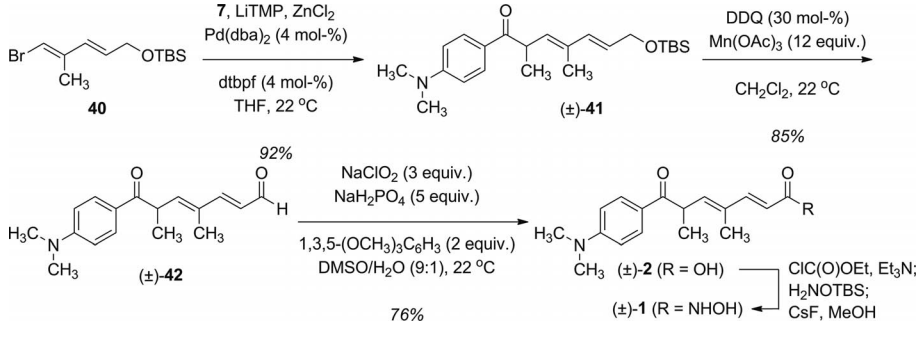
Scheme 8. Synthesis of ketone **7** and alkenyl bromides **8a** and **8b**.

We chose to employ a Zn enolate in the key coupling step owing to decreased basicity and precedents provided in related α-arylation reactions.[29] Treatment of ketone **7** with lithium tetramethylpiperidide (LiTMP) and $ZnCl_2$ followed by reaction with **8a** or **8b**, $Pd(dba)_2$, and 1,1′-bis(di-*tert*-butylphosphanyl)ferrocene (dtbpf) furnished cross-coupling products **38** and **39** in 73% and 82% isolated yields, respectively, with retention of diene configuration (Scheme 9). Other electron-rich sterically-demanding phosphanes such as Q-Phos (used by Hartwig for similar reactions),[29a] tBu_3P, and 1-(di-*tert*-butylphosphanyl)biphenyl also promoted the reaction but in lower yields than dtbpf, whereas the use of several arylphosphanes [Ph_3P, $(o\text{-tolyl})_3P$, dppe, and dppf] failed completely. Dienyl iodide **8c** was also a useful substrate as demonstrated below in later analogue syntheses. Methyl ester **38** failed to undergo deprotection under commonly used conditions (LiOH, NaOH, LiI, KOTMS, NaCN), but PMB ester **39** was cleanly converted with TFA and Et_3SiH into trichostatic acid **2** in 96% yield. (±)-TSA [(±)-**1**] was obtained through use of the same procedure as in the preceding synthesis.[17]

In a slight modification of this synthesis, the coupling reaction was performed with dienyl bromide **40** (prepared in two steps from **8a** by using iBu_2AlH and TBSOTf) containing a protected allylic alcohol rather than an ester to give cross-coupled product **41** in 92% yield (Scheme 10). This result demonstrates that activation of the dienyl bromide moiety by a conjugated electron-withdrawing group is not necessary for successful implementation of this coupling reaction. Oxidation of silyl ether **41** by using the catalytic $DDQ/Mn(OAc)_3$ system provided aldehyde **42** in a single step,[27,30] whereas the use of stoichiometric quantities of



Scheme 9. Pd-catalyzed enolate coupling with dienyl bromides and subsequent formation of racemic TSA [(±)-**1**].



Scheme 10. Alternative synthesis of (±)-TSA by using a Pd-catalyzed α-alkenylation.

DDQ furnished an *N*-demethylated side-product that was inseparable from the desired product. Subsequent Pinnick oxidation[31] by using DMSO[32] as the solvent and 1,3,5-trimethoxybenzene[33] as a chlorine scavenger followed by further conversion as above again provided (±)-TSA.[17]

Assessment of the Three Pathways and Use in New Studies

The first synthesis was too inefficient and troublesome to employ in further investigations owing to the poor stereoselectivity of the key phosphonate condensation reaction and the difficulty separating the resulting diene isomers. The second and third syntheses are far superior and permit good throughput of material. They are also flexible in terms of permitting facile synthesis of a number of types of analogues of the trichostatic acid core. For example, the modified third synthesis (Scheme 10) provides ready access to aldehyde **42**, a potentially versatile intermediate for the production of TSA analogues. The aldehyde functionality serves as a direct precursor of several Zn-binding groups other than the hydroxamic acid that are found in other HDACi, including methyl ketones, epoxy ketones, *o*-aminobenzamides, and thiols among others.[1–5] Introduction of these Zn-binding elements into the TSA core could serve to produce analogues that retain HDACi activity while minimizing possible deleterious properties associated with hydroxamic acids.

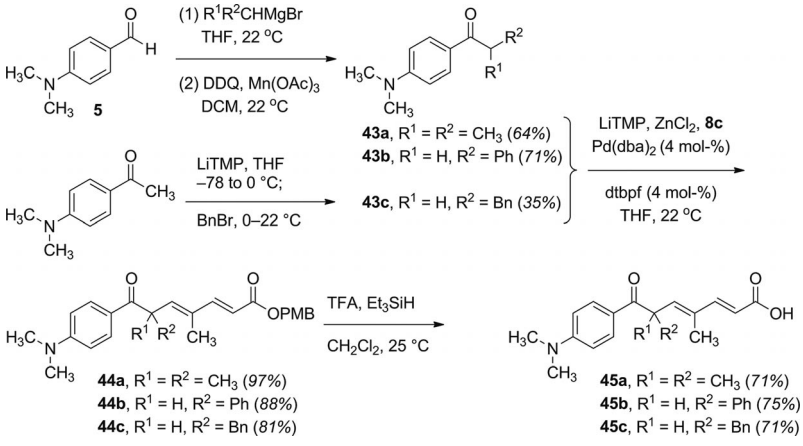
Synthesis of Additional Analogues

Another aspect of analogue development is the aforementioned variation of the substitution pattern of the diene-containing chain lying between the hydroxamic acid and aromatic group. Whereas the second-generation synthesis proved to be readily amenable to variation of the substituent at C(4), the third-generation synthesis is especially conducive to modifications at C(6) α to the ketone carbonyl group based on the selection of other ketone substrates in place of 4-(dimethylamino)propiophenone (**7**) for use in the enolate alkenylation reaction. As a demonstration of this variation, we have employed the readily prepared isobutyrophenone **43a**, α-phenylacetophenone **43b**, and α-benzylacetophenone **43c** derivatives as precursors of the trichostatic acid analogues **45a**–**c** (Scheme 11).

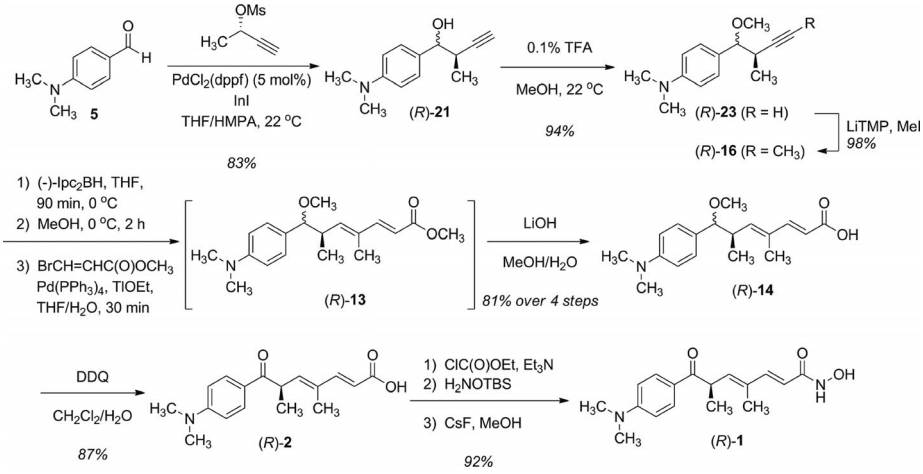
For these syntheses, dienyl iodide **8c** was interchanged with previously employed bromide **8b** to demonstrate its utility. We found that the coupling reaction works equally well by using this alternative substrate and our usual coupling conditions. The PMB-protected analogues thus obtained were submitted to the same deprotection conditions used above to yield corresponding carboxylic acids **45** in good yields. The first of the analogues, **45a**, has a *gem*-dimethyl substitution pattern and has been reported previously,[34] but the second and third analogues appear to be new. Clearly, the second- and third-generation syntheses are conveniently complementary for analogue studies. On the other hand, both of these routes would allow for facile variation of substitution patterns on the aromatic ring as another element of structural diversity.

Enantioselective Synthesis of TSA and Analogues

Although we have successfully prepared (±)-TSA and analogues by using our second- and third-generation syntheses, it is important to note that whereas (*R*)-**1** is biologically active, its enantiomer, (*S*)-**1**, is inactive.[35] For this reason, enantioselective syntheses of **1** are of great importance.[15b,15c] Although our first route clearly provided an enantioselective entry to TSA, we ruled out its further use owing to the other problems already discussed. Upon further evaluation of our other routes, we judged our second-generation synthesis to be more readily amenable to the production of single enantiomers at this time owing to previously well-developed enantioselective versions of the Marshall propargylation reaction used in a key step of this route.[23] Our third-generation synthesis, although attractively short and efficient, is based upon a metal-catalyzed enolate alkenylation reaction for which the development of appropriate enantioselective versions[25f,25g,25i,25k] is less mature than for the Marshall reaction. We therefore decided to make appropriate adaptations in our second-generation synthesis as a means for enantioselective production of the desired final products.



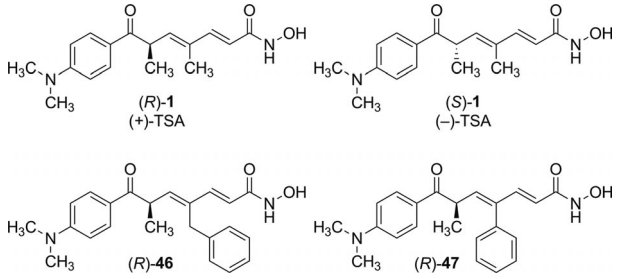
Scheme 11. Synthesis of C(6)-analogues of TSA by using Pd-catalyzed α-alkenylation.



Scheme 12. Enantioselective synthesis of (*R*)-trichostatin A.

Our synthesis of (*R*)-(+)-**1** is shown in Scheme 12. Rather than by using a racemic propargyl mesylate as in Scheme 5, we employed an enantiomerically enriched (*S*)-mesylate (94% *ee*) in the Marshall reaction. The anticipated alcohol (*R*)-**21** was produced in 83% yield as a 1:1 mixture of *syn*- and *anti*-diastereomers with the methyl-bearing C(6) having the desired configuration in both isomers based upon subsequent successful conversion of the mixture to (*R*)-(+)-TSA. No assignment of *ee* values was made for this mixture. After protection of the benzylic hydroxy group as methyl ether (*R*)-**23**, the terminal alkyne was alkylated by using LiTMP and MeI to furnish (*R*)-**16** (92% over two steps). The same cross-coupling conditions employed above in our second-generation synthesis furnished intermediate (*R*)-**13**. This material was subjected directly to hydrolysis to produce free acid (*R*)-**14**, which was isolated in 81% over four steps. Treatment of this material with DDQ furnished (*R*)-trichostatic acid [(*R*)-**2**] in 87% yield after purification, and subsequent conversion to (*R*)-trichostatin A [(*R*)-**1**; 81% *ee*] was accomplished as in the racemic synthesis.[17] This route supplied enantioenriched (*R*)-TSA on a gram scale.

Because of the literature report of the difference in activity between the (*R*)- and (*S*)-enantiomers,[35] we used our second-generation route to synthesize (+)-TSA (*S*-**1**, 91% *ee*) (Scheme 13). The route and the reagents employed for this compound were identical to those in Scheme 12, with the exception of beginning with the (*S*)-enantiomer of the starting propargyl mesylate. Likewise, we have synthesized trichostatic acid analogues **19** and **20** in enantioenriched form having the (*R*)-configuration at C(6) by replacing (±)-**23** with (*R*)-**23** as a key intermediate in Scheme 7. However, unlike the racemic analogues, we have further converted the enantioenriched acids into corresponding hydroxamic acids (*R*)-**46** (80% *ee*) and (*R*)-**47** (>95% *ee*). In all of these syntheses of enantioenriched TSA and analogues, the overall enantioselectivities varied from 80 to >95% *ee*, which may be attributed in part to the expected lability of the stereogenic center in these compounds being α to a ketone and adjacent to a conjugated dienoic acid system.



Scheme 13. Enantioenriched TSA and analogues prepared by using modifications of the second-generation synthesis.

Conclusions

We have described the evolution of our synthetic strategies towards the production of trichostatic acid and TSA, a potent histone deacetylase inhibitor. Each generation of our syntheses permitted us either to design and implement new chemistry or to modify existing methods to incorporate a broader substrate scope into our pathways. Each synthesis posed its own unique challenges that were addressed in subsequent syntheses. The ultimate result is the availability of two efficient and flexible syntheses of the desired compounds from readily available materials. In new studies, the two top performing syntheses exhibit complementary flexibility for production of different series of TSA analogues. One of the syntheses has been conducted enantioselectively on a gram scale. The enantioselective route also proved amenable for the synthesis of trichostatic acid analogues. In addition to providing the compounds targeted in this work, the chemistry presented here, especially the enolate alkenylation coupling reaction, is also expected to find use in a variety of other synthetic applications. The biological activity of the final products resulting from our routes is the subject of ongoing studies.

Experimental Section

General Methods: All reactions were performed under an atmosphere of argon unless otherwise stated. Tetrahydrofuran (THF)

and diethyl ether were purified by using an Innovative Technologies™ solvent purification system. Anhydrous dichloromethane and methanol were purchased from Aldrich in containers equipped with Sure Seal septa. All reagents were used as received unless otherwise noted. Flash chromatography was performed with 60 Å silica gel (230–400 mesh). ^{1}H NMR (300 and 500 MHz) and ^{13}C NMR (75 and 125 MHz) spectra were recorded with a Varian Inova-300 & 500 spectrometers, respectively, and ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded with a Bruker DPX-400 spectrometer. All ^{1}H NMR spectra were recorded in $CDCl_3$ or MeOD, and chemical shifts are given relative to $CDCl_3$ (δ =7.27 ppm) or CD_3OD (3.34 and 4.87 ppm). ^{13}C NMR spectra are referenced to $CDCl_3$ (δ =77.23 ppm) or CD_3OD (δ =49.86 ppm). IR spectra were obtained with a Perkin–Elmer Paragon 1000 FT-IR spectrophotometer by using neat thin films or $CHCl_3$ solutions between NaCl plates. Mass spectra were recorded with a JEOL JMS-AX505 HA double sector mass spectrometer. Enantiomeric excess (*ee*) values were determined by using isocratic 1:99 2-propanol/hexanes with a CHIRALPAK OD column on a Waters 600 HPLC.

The experimental procedures, characterization data, and Supporting Information for compounds described in Schemes 2, 3, 4, 5, 6, 7, and 8 have been published previously and are not repeated here.[16b,17,18]

(*R*)-1-[4-(Dimethylamino)phenyl]-2-methylbut-3-yn-1-ol [(*R*)-21]: Based on a previously published procedure,[17,23] to a solution of (*S*)-but-3-yn-2-yl methanesulfonate (1.61 g, 10.9 mmol) and 4-(dimethylamino)benzaldehyde (**5**, 1.25 g, 8.39 mmol) in dry THF (30 mL) and HMPA (6 mL) stirred at 0 °C, $PdCl_2$(dppf) (31 mg, 0.42 mmol, 5 mol-%) and InI (4.06 g, 16.8 mmol) were added successively. The resulting dark-green colored mixture was stirred for 1 h, during which time the color turned brick red. The reaction mixture was quenched after 1 h by the addition of water (50 mL) and was diluted with diethyl ether (50 mL). The organic layer was separated, and the aqueous layer was further washed with diethyl ether (3 × 50 mL). The combined organic layers were washed with brine, dried with anhydrous $MgSO_4$ and concentrated under vacuum. The resulting crude mixture was purified by using flash chromatography (hexane/EtOAc, 9:1) to give (*R*)-**21** as a 1:1 mixture of *syn* and *anti* diastereomers (1.41 g, 83%). The ^{1}H NMR spectrum was identical with the previous report for the racemic compound.[17] ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.31–7.20 (m, 4 H), 6.78–6.69 (m, 4 H), 4.62 (d, *J* = 2.5 Hz, 1 H), 4.43 (d, *J* = 2.5 Hz, 1 H), 2.96 (s, 12 H), 2.90–2.82 (m, 1 H), 2.82–2.75 (m, 1 H), 2.50–2.48 (b, 1 H), 2.22–2.20 (m, 1 H), 2.11–2.09 (m, 1 H), 1.17 (d, *J* = 2.54 Hz, 3 H), 1.11–1.06 (d, *J* = 2.54 Hz, 3 H) ppm.

4-[(2*R*)-1-Methoxy-2-methylbut-3-yn-1-yl]-*N*,*N*-dimethylaniline [(*R*)-23]: Based upon a published procedure,[17] to a solution of (*R*)-**21** (1.31 g, 6.45 mmol) in MeOH (45 mL) was added a solution of 0.1% TFA in MeOH (75 mL, v/v), and the mixture was stirred at 25 °C for 48 h. The resulting dark-brown solution was neutralized by careful addition of Et_3N, and all volatile materials were removed under vacuum. The resulting crude mixture was purified by using flash chromatography (hexane/EtOAc, 9:1) to give (*R*)-**23** as a 1:1 mixture of *syn* and *anti* diastereomers (1.32 g, 94%). The ^{1}H NMR spectrum was identical to the previous report for the racemic compound.[17] ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.26–7.14 (m, 4 H), 6.74 (d, *J* = 8.7 Hz, 4 H), 3.98 (d, *J* = 2.5 Hz, 2 H), 3.22 (s, 3 H), 3.21 (s, 3 H), 2.94 (s, 12 H), 2.90–2.83 (m, 1 H), 2.81–2.73 (m, 1 H), 2.16 (d, *J* = 2.4 Hz, 1 H), 2.03 (d, *J* = 2.4 Hz, 1 H), 1.21 (d, *J* = 6.9 Hz, 3 H), 1.03 (d, *J* = 6.9 Hz, 3 H) ppm.

4-[(2*R*)-1-Methoxy-2-methylpent-3-yn-1-yl]-*N*,*N*-dimethylaniline [(*R*)-16]: To a solution of (*R*)-**23** (1.27 g, 5.86 mmol) in dry THF (20 mL) was added LiTMP (1.55 g in 20 mL of THF, 10.6 mmol) at –78 °C through cannula. After the mixture was stirred for 30 min at –78 °C, MeI (0.44 mL, 7.0 mmol) was added. The resulting mixture was stirred for another 30 min at –78 °C before it was warmed to 0 °C and stirred for 6 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (20 mL). The organic layer was separated, and the aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. The crude mixture was purified by column chromatography (EtOAc/hexanes, 1:4) to obtain (*R*)-**16** (1.33 g, 98%) as a 1:1 mixture of diastereomers. The ^{1}H NMR spectrum was identical with the previous report for the racemic compound.[17] ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.23–7.15 (m, 4 H), 6.77–6.69 (m, 4 H), 3.94 (d, *J* = 2.4 Hz, 2 H), 3.92 (d, *J* = 2.4 Hz, 2 H), 3.23 (s, 6 H), 2.97 (s, 12 H), 2.83–2.63 (m, 2 H), 1.83 (d, *J* = 2.4 Hz, 3 H), 1.74 (d, *J* = 2.4 Hz, 3 H), 1.14 (d, *J* = 7.1 Hz, 3 H), 1.00 (d, *J* = 7.2 Hz, 3 H) ppm.

(2*E*,4*E*,6*R*)-7-[4-(Dimethylamino)phenyl]-7-methoxy-6-methylhepta-2,4-dienoic Acid [(*R*)-14]: According to the previously published procedure,[17] (–)-Ipc_2BH (1.94 g, 6.77 mmol) was weighed in a glove box into a round-bottom flask. The flask was placed in an ice bath, and a solution of (*R*)-**16** (1.30 g, 5.64 mmol) in THF (20 mL) was added. The mixture was stirred for 2 h at 0 °C, and then MeOH (0.53 mL, 13 mmol) was added. After 2 h, to the resulting solution at 0 °C was added a solution of (*E*)-methyl 3-bromoacrylate (1.39 g, 8.46 mmol) in THF (20 mL), and the flask was warmed to 25 °C. To the solution were added $Pd(PPh_3)_4$ (65 mg, 0.56 mmol, 10 mol-%) and TlOEt (1.2 mL, 17 mmol) in H_2O (12 mL). The resulting off-white mixture was stirred for 1 h at 25 °C, and the mixture was diluted with 1 M aqueous $NaHSO_4$ (20 mL). The mixture was filtered and extracted with Et_2O (3 × 50 mL). The organic extracts were washed with brine, dried with $MgSO_4$, and concentrated. The crude product was purified by flash chromatography (hexanes/EtOAc, 95:5 to 90:10) to give methyl (2*E*,4*E*,6*R*)-7-[4-(dimethylamino)phenyl]-7-methoxy-6-methylhepta-2,4-dienoate [(*R*)-**13**] with some inseparable impurities. This material was used directly without any further purification. According to the published method,[17] this material (1.61 g, 5.08 mmol) was dissolved in MeOH (40 mL), and treated with 0.5 M aqueous LiOH (13 mL, 6.1 mmol). The resulting mixture was stirred at 45 °C for 24 h and then neutralized with pH 7 buffer. The volatile part was removed under vacuum, and the remaining yellow residue was washed with EtOAc (2 × 20 mL). The aqueous layer was acidified to approximately pH 4 by using 1 N HCl and was extracted with $CHCl_3$ (3 × 50 mL). The combined organic extracts were dried and concentrated under vacuum to give the crude product as a yellowish syrup. The compound was purified by flash chromatography (hexanes/EtOAc, 4:1 to 1:1) to obtain (*R*)-**14** (1.38 g, 81%) as a 1:1 mixture of diastereomers. The ^{1}H NMR spectrum was identical with the previous report for the racemic compound.[17] ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.45 (d, *J* = 15.6 Hz, 1 H), 7.31 (d, *J* = 15.6 Hz, 1 H), 7.19–7.08 (m, 4 H), 6.76–6.65 (m, 4 H), 5.94 (d, *J* = 9.8 Hz, 1 H), 5.82–5.70 (m, 3 H), 3.95–3.89 (m, 2 H), 3.20 (s, 3 H), 3.18 (s, 3 H), 2.98 (s, 6 H), 2.96 (s, 6 H), 2.94–2.83 (m, 2 H), 1.74 (s, 3 H), 1.63 (s, 3 H), 1.09 (d, *J* = 6.9 Hz, 3 H), 0.86 (d, *J* = 6.9 Hz, 3 H) ppm.

(*R*,2*E*,4*E*)-7-[4-(Dimethylamino)phenyl]-6-methyl-7-oxohepta-2,4-dienoic Acid [(*R*)-2]: According to a previously published method,[17] (*R*)-**14** (1.29 g, 4.27 mmol) was dissolved in CH_2Cl_2/H_2O (50 mL, 2:1) and treated with DDQ (920 mg, 4.06 mmol) in 3 portions over a period of 5 min at 0 °C. The resulting mixture was stirred vigorously for another 5 min at 0 °C and was diluted with CH_2Cl_2 (20 mL). The mixture was filtered through Celite, and the filter pad

was washed with CH_2Cl_2 (50 mL). The combined filtrates were dried with $MgSO_4$ and concentrated under vacuum to obtain reddish brown (*R*)-**2** (1.07 g, 87%). The ^1H NMR spectrum was identical with the previous report for the racemic compound.[17] $[a]_D^{25}$ = +138 (*c* = 0.095, Ethos); [ref.[15b] $[a]_D^{22}$ = +138 (*c* = 0.35, MeOH)] ^1H NMR (300 MHz, $CDCl_3$): δ_H = 7.85 (d, *J* = 9.0 Hz, 2 H), 7.39 (d, *J* = 15.6 Hz, 1 H), 6.65 (d, *J* = 9.0 Hz, 2 H), 6.10 (d, *J* = 9.6 Hz, 1 H), 5.83 (d, *J* = 15.6 Hz, 1 H), 4.41 (dq, *J* = 9.6, 6.6 Hz, 1 H), 3.07 (s, 6 H), 1.95 (s, 3 H), 1.34 (d, *J* = 6.6 Hz, 3 H) ppm.

(*R*)-(+)-Trichostatin A [(*R*)-1]: According to a previously published method,[17] (*R*)-**2** (1.02 g, 3.54 mmol) and Et_3N (1.1 mL, 7.78 mmol) were dissolved in CH_2Cl_2 (20 mL) and cooled to 0 °C. Chloroethyl formate (0.4 mL, 4 mmol) was added, and the solution was stirred at 0 °C for 2 h followed by the addition of NH_2OTBS (780 mg, 5.3 mmol). After the mixture was stirred for 30 min, the cooling bath was removed, and the mixture was warmed to 25 °C and stirred for 2 h. The reaction mixture was diluted with CH_2Cl_2 (30 mL), and the organic layer was washed with water (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine, dried with anhydrous $MgSO_4$, and concentrated under vacuum to obtain crude *O*-TBS protected hydroxamic acid which was used directly in the next step without further purification. The crude compound was dissolved in anhydrous MeOH (30 mL), and dry CsF (645 mg, 4.24 mmol) was added. The mixture was stirred at 25 °C for 3 h and diluted with EtOAc (50 mL). The organic layer was washed with water (20 mL), and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were combined, dried with $MgSO_4$, and concentrated under vacuum. The resulting solid mass was triturated with hexanes/Et_2O (4:1) to obtain pure (*R*)-**1** (0.98 g, 92% overall). The ^1H NMR spectrum was identical with the previous report for the racemic compound.[17] $[a]_D^{25}$ = +96 (*c* = 0.13, EtOH); [ref.[15b] $[a]_D^{22}$ = +96 (*c* = 0.31 , MeOH)]; *ee* 81%. ^1H NMR (300 MHz, CD_3OD): δ_H = 7.83 (d, *J* = 9.0 Hz, 2 H), 7.15 (d, *J* = 15.6 Hz, 1 H), 6.70 (d, *J* = 9.0 Hz, 2 H), 5.89 (d, *J* = 9.6 Hz, 1 H), 5.83 (d, *J* = 15.6 Hz, 1 H), 4.54 (dq, *J* = 9.6, 6.6 Hz, 1 H), 3.03 (s, 6 H), 1.91 (d, *J* = 1.2 Hz, 3 H), 1.23 (d, *J* = 6.6 Hz, 3 H) ppm. IR ($CHCl_3$): $\tilde{\nu}\tilde{\nu}$ = 3427, 3236, 2928, 1659, 1599, 1551, 1379, 1248, 1192, 1058, 972, 818 cm^{-1}. HRMS (ESI): calcd for $C_{17}H_{23}N_2O_3$ $[M + H]^+$ 303.1703; found 303.1722.

(*S*)-(–)-Trichostatin A [(*S*)-1]: The preceding sequence of reactions was followed except (*S*)-but-3-yn-2-yl methanesulfonate (807 mg, 5.5 mmol) was used in place of the (*R*)-enantiomer as the starting material to provide (*S*)-**21** (732 mg, 86%), (*S*)-**23** (721 mg, 93%), (*S*)-**16** (728 mg, 95%), (*S*)-**12** (872 mg as a crude product), (*S*)-**13** (778 mg, 84%), (*S*)-**14** (575 mg, 85%), and (*S*)-**1** (498 mg, 89%): $[a]_D^{25}$ = –84 (*c* = 0.11, EtOH); [ref.[15b] $[a]_D^{22}$ = –82 (*c* = 0.24, MeOH)]; *ee* 91%. The ^1H NMR spectra of all of these products matched those of the (*R*)-enantiomers in the previous sequence of reactions.

4-(Dimethylamino)isobutyrophenone (43a): Through use of the previously reported reaction sequence for the preparation of **7**,[18] 4-(dimethylamino)benzaldehyde and *i*PrMgBr provided **43a** (64%) as an off-white solid having an NMR spectra in agreement with literature data. ^1H NMR (400 MHz, $CDCl_3$): δ_H = 7.90 (d, *J* = 9.1 Hz, 2 H), 6.66 (d, *J* = 9.1 Hz, 2 H), 3.50 (m, 1 H), 3.05 (s, 6 H), 1.19 (d, *J* = 6.8 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_c = 202.7, 153.2, 130.5, 124.0, 110.7, 40.0, 34.4, 19.5 ppm. (ref.[36] ^1H NMR. ^{13}C NMR).

1-[4-(Dimethylamino)phenyl]-2-phenylethanone (43b): The preceding procedure was employed with benzylmagnesium chloride to give **43b** (71%) as a slightly yellow solid after flash chromatography (CH_2Cl_2). The NMR spectra were in agreement with literature data. ^1H NMR (400 MHz, $CDCl_3$): δ_H = 7.93 (d, *J* = 9.1 Hz, 2 H), 7.30–7.15 (m, 5 H), 6.64 (d, *J* = 9.1 Hz, 2 H), 4.18 (s, 2 H), 3.05 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_c = 195.7, 153.5, 135.8, 130.9, 129.3, 128.5, 126.5, 124.6, 110.7, 44.9, 40.0 ppm. (ref.[37] ^1H NMR. ^{13}C NMR).

1-[4-(Dimethylamino)phenyl]-3-phenyl-1-propanone (43c): To a solution of tetramethylpiperidine (1 mmol, 168 μL) in THF (5 mL) at –78 °C was added *n*-butyllithium (1 mmol, 400 μL, 2.5 M in hexane) over a 5-min period. After the solution was stirred for 30 min at –78 °C, 4-(dimethylamino)acetophenone was added in THF (5 mL), and the reaction mixture was warmed to 0 °C. After 30 min, benzyl bromide (2 mmol, 240 μL) was added dropwise. The mixture was stirred at 22 °C for 12 h. The reaction was quenched with saturated aqueous NH_4Cl. The aqueous phase was extracted twice with Et_2O. The combined organic extracts were dried with $MgSO_4$ and the solvents evaporated. Flash chromatography of the crude material gave **43c** as pale yellow crystals (90 mg, 35%) having NMR spectra in agreement with literature data. ^1H NMR (400 MHz, $CDCl_3$): δ_H = 7.90 (d, *J* = 9.1 Hz, 2 H), 7.34–7.15 (m, 5 H), 6.65 (d, *J* = 9.1 Hz, 2 H), 3.20–3.24 (m, 2 H), 3.01–3.09 [m, overlapping with (δ = 3.05 ppm), 2 H], 3.05 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_c = 195.4, 153.4, 141.8, 130.3, 128.46, 128.45, 126.0, 124.9, 110.7, 40.0, 39.7, 30.7 ppm. (ref.[38] ^1H NMR. ^{13}C NMR).

General Procedure for 44a–c: The previously published procedure for the preparation of **39**, was followed.[18] Tetramethylpiperidine (0.38 mmol, 63 μL) was dissolved in THF (1 mL). The solution was cooled to 0 °C, and *n*BuLi (0.38 mmol, 2.5 M in hexane, 150 μL) was added dropwise. After 10 min, a solution of ketone **43** (0.34 mmol) in THF (1 mL) was added. After 20 min, the mixture was warmed to 22 °C, and $ZnCl_2$ (0.45 mmol, 62 mg) was added. The resulting solution was stirred for 30 min during which all of the solid $ZnCl_2$ disappeared. The resulting zinc enolate solution was added to a THF solution of alkenyl iodide **8c** (0.29 mmol), dtbpf (0.012 mmol), $Pd(dba)_2$ (0.012 mmol). After TLC indicated that the starting iodide was consumed (approximately 1 h), the reaction mixture was poured into saturated aqueous sodium potassium tartrate solution and extracted with two portions of Et_2O. The combined organic extracts were dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by using flash chromatography (hexanes/EtOAc, 7:3) to give products **44**.

44a: Obtained as an off white solid in 97% yield. ^1H NMR (400 MHz, $CDCl_3$): δ_H = 7.86 (d, *J* = 8.8 Hz, 2 H), 7.32 (d, *J* = 9.0 Hz, 2 H), 7.31 (d, *J* = 43 Hz, 2 H), 6.89 (d, *J* = 8.4 Hz, 2 H), 6.65 (d, *J* = 8.8 Hz, 2 H), 6.36 (s, 2 H), 5.73 (d, *J* = 15.7 Hz, 1 H), 5.12 (s, 2 H), 3.81 (s, 3 H), 3.02 (s, 6 H), 1.45 (s, 3 H), 1.43 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_c = 201.3, 167.3, 161.2, 159.6, 152.8, 150.0, 148.3, 133.9, 131.8, 130.1, 128.3, 122.0, 116.2, 113.9, 110.2, 65.9, 55.3, 47.9, 39.9, 28.0, 12.6 ppm. HRMS (ESI): calcd. for $C_{26}H_{32}NO_4$ $[M + H]^+$ 422.2331; found 422.2323.

44b: Obtained as a gray solid in 88% yield. ^1H NMR (400 MHz, $CDCl_3$): δ_H = 7.82 (d, *J* = 9.2 Hz, 2 H), 7.33 (d, *J* = 15.6 Hz, 1 H), 7.27–7.13 (m, 5 H), 6.79 (d, *J* = 8.8 Hz, 2 H), 6.50 (d, *J* = 9.2 Hz, 2 H), 5.76 (d, *J* = 15.7 Hz, 1 H), 5.48 (d, *J* = 9.5 Hz, 1 H), 5.02 (s, 2 H), 3.70 (s, 3 H), 2.91 (s, 6 H), 1.78 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_c = 195.3, 167.0, 159.6, 153.4, 149.4, 140.0, 139.4, 133.1, 131.1, 130.0, 129.0, 128.3, 128.1, 127.0, 123.8, 116.8, 113.9, 110.7, 65.9, 55.3, 52.2, 39.9, 12.8 ppm. HRMS (ESI): calcd. for $C_{30}H_{32}NO_4$ $[M + H]^+$ 470.2331; found 470.2316.

44c: Obtained as a gray solid in 81% yield. ^1H NMR (400 MHz, $CDCl_3$): δ_H = 7.71 (d, *J* = 8.8 Hz, 2 H), 7.24–7.00 (m, 8 H), 6.78

(d, J = 8.4 Hz, 2 H), 6.51 (d, J = 8.9 Hz, 2 H), 5.88 (d, J = 10.3 Hz, 1 H), 5.66 (d, J = 15.7 Hz 1 H), 5.01 (m, 2 H), 4.44 (m, 2 H), 3.70 (s, 3 H), 3.17 (m, 1 H), 2.75 (m, 1 H), 2.93 (s, 6 H), 1.41 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_c = 197.2, 167.0, 159.6, 153.5, 149.1, 139.6, 139.3, 134.3, 130.6, 130.1, 129.2, 128.3, 126.2, 124.2, 116.7, 113.9, 110.7, 65.9, 55.3, 49.1, 40.0, 38.7, 12.3 ppm. HRMS (ESI): calcd. for $C_{31}H_{34}NO_4$ $[M + H]^+$ 484.2487; found 484.2487.

General Procedure for 45a–c: The previously published procedure for the conversion of **39** into **2** was followed.[18] PMB-protected material **44** (0.5 mmol) was dissolved in CH_2Cl_2 (4 mL) at 22 °C. Trifluoroacetic acid (0.75 mL) was added followed by triethylsilane (0.75 mL, 10 equiv.). The reaction mixture was stirred until TLC indicated complete consumption of starting material (approximately 10 min). Saturated aqueous $NaHCO_3$ (10 mL) was added, and the pH was adjusted to 3 by adding 2N HCl. The mixture was extracted three times with CH_2Cl_2. The combined organic extracts were dried with $MgSO_4$ and concentrated in vacuo. Flash chromatography (gradient elution with 0 to 7% MeOH in CH_2Cl_2) of the residue yielded products **45** as white solids.

45a: Obtained as a white solid in 71% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.86 (d, J = 9.0 Hz, 2 H), 7.41 (d, J = 15.6 Hz, 1 H), 6.57 (d, J = 9.7 Hz, 2 H), 6.41 (s, 1 H), 5.70 (d, J = 15.6 Hz, 1 H), 3.03 (s, 6 H), 1.48 (s, 3 H), 1.44 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_c = 201.2, 172.4, 152.8, 151.9, 149.3, 133.9, 131.8, 121.9, 115.6, 110.2, 48.0, 39.9, 28.0, 12.6 ppm. HRMS (ESI): calcd. for $C_{18}H_{24}NO_3$ $[M + H]^+$ 302.1756; found 302.1740.

45b: Obtained as a white solid in 75% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.91 (d, J = 9.2 Hz, 2 H), 7.48 (d, J = 15.8 Hz, 1 H), 7.34–7.20 (m, 5 H), 6.61 (m, 3 H), 5.82 (d, J = 16.3 Hz, 1 H), 5.58 (d, J = 9.7 Hz, 1 H), 3.04 (s, 6 H), 1.93 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_c = 192.6, 169.2, 150.9, 148.8, 138.5, 136.7, 130.5, 128.5, 126.4, 125.5, 124.5, 121.2, 113.4, 108.1, 49.7, 37.4, 10.2 ppm. HRMS (ESI): calcd. for $C_{22}H_{24}NO_3$ $[M + H]^+$ 350.1756; found 350.1742.

45c: Obtained as a white solid in 71% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.81 (d, J = 8.8 Hz, 2 H), 7.34 (d, J = 15.6 Hz, 1 H), 7.26–7.14 (m, 5 H), 6.62 (d, J = 8.8 Hz, 2 H), 6.02 (d, J = 10.0 Hz, 1 H), 5.72 (d, J = 15.7 Hz, 1 H), 4.54 (m, 1 H), 3.27 (dd, J = 5.6, 5.4 Hz, 1 H), 3.05 (s, 6 H), 2.85 (dd, J = 8.6, 8.3 Hz, 1 H), 1.53 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_c = 197.2, 172.1, 153.3, 150.9, 140.5, 139.2, 134.4, 130.6, 129.2, 128.3, 126.2, 124.2, 116.1, 110.7, 49.1, 40.0, 38.7, 12.3 ppm. HRMS (ESI): calcd. for $C_{23}H_{26}NO_3$ $[M + H]^+$ 364.1913; found 364.1895.

(*R*,2*E*,4*E*)-4-Benzyl-7-[4-(dimethylamino)phenyl]-*N*-hydroxy-6-methyl-7-oxohepta-2,4-dienamide [(*R*)-46]: A previously published procedure[17] for the synthesis of (±)-**19** was followed except (*R*)-**23** (455 mg, 2.10 mmol) was used in place of the racemic material to give (*R*)-**26** (606 mg, 92%), (*R*)-**30** (338 mg, 48%), (*R*)-**34** (241 mg, 74% yield), and (*R*)-**19** (134 mg, 82%). The spectroscopic data were identical to the previous report for the racemic compound.[17] Based on the procedure for synthesis of (*R*)-**1**, carboxylic acid (*R*)-**19** (116 mg, 0.32 mmol) was used in a reaction with $ClCO_2Et$ (0.04 mL, 0.4 mmol), Et_3N (0.1 mL, 0.7 mmol), and NH_2OTBS (71 mg, 0.48 mmol) followed by CsF (58 mg, 0.38 mmol) to give (*R*)-**46** (37 mg, 31%). $[a]_D^{25}$ = +129 (c = 0.16, EtOH); *ee* 80%. ^{1}H NMR (400 MHz, CD_3OD): δ_H = 7.68 (d, J = 8.7 Hz, 2 H), 7.27 (d, J = 15.6 Hz, 1 H), 7.19–7.12 (m, 2 H), 7.12–7.05 (m, 3 H), 6.59 (d, J = 8.7 Hz, 2 H), 6.18 (d, J = 9.0 Hz, 1 H), 5.68 (d, J = 15.6 Hz, 1 H), 4.52 (dq, J = 9.9, 6.9 Hz, 1 H), 3.78 (dd, J = 16.5, 6.6 Hz 2 H), 3.0 (s, 6 H), 1.24 (d, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_c = 201.1, 170.5, 155.4, 149.8, 144.6, 139.7, 137.0, 131.9, 129.4, 127.3, 124.6, 119.4, 111.9, 41.5, 40.1, 33.7, 19.0 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3415, 3228, 2920, 1651, 1589, 1546, 1377, 1241, 1187, 964 cm^{-1}. HRMS (ESI): calcd. for $C_{23}H_{27}N_2O_3$ $[M + H]^+$ 379.2012; found 379.2016.

(*R*,2E,4Z)-7-[4-(Dimethylamino)phenyl]-*N*-hydroxy-6-methyl-7-oxo-4-phenylhepta-2,4-dienamide [(*R*)-47]: A previously published procedure[17] for the synthesis of (±)-**20** was followed except (*R*)-**23** (407 mg, 1.88 mmol) was used in place of the racemic material to give (*R*)-**27** (543 mg, 97%), (*R*)-**31** (317 mg, 47%), (*R*)-**35** (261 mg, 87%), and (*R*)-**20** (191 mg, 81%). The spectroscopic data were identical to the previous report for the racemic compound.[17] Based on the procedure for synthesis of (*R*)-**1**, carboxylic acid (*R*)-**20** (173 mg, 0.49 mmol) was used in a reaction with $ClCO_2Et$ (0.06 mL, 0.6 mmol), Et_3N (0.15 mL, 1.1 mmol), NH_2OTBS (108 mg, 0.73 mmol) followed by treatment with CsF (89 mg, 0.59 mmol) to give (*R*)-**47** (61 mg, 34%). $[a]_D^{25}$ = +161 (c = 0.14, EtOH); *ee* >95%. ^{1}H NMR (400 MHz, CD_3OD): δ_H = 7.48–7.37 (m, 6 H), 7.20 (d, J = 9.0 Hz, 2 H), 6.57 (d, J = 8.9 Hz, 2 H), 6.27 (d, J = 10.2 Hz, 1 H), 5.33 (d, J = 15.6 Hz, 1 H), 4.08 (dq, J = 10.2, 6.6 Hz, 1 H), 2.99 (s, 6 H), 1.21 (d, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_c = 201.8, 170.9, 155.4, 149.1, 143.3, 142.3, 137.4, 132.0, 130.1, 129.9, 128.7, 124.1, 121.3, 112.1, 103.8, 42.8, 39.7, 18.2 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3421, 3230, 2922, 1653, 1591, 1545, 1379, 1241, 1188, 1051, 965 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{24}N_2O_3$ $[M + H]^+$ 365.1812; found 365.1860.

Supporting Information (see footnote on the first page of this article): Supporting Information includes ^{1}H NMR and ^{13}C NMR spectra and chiral HPLC traces of newly reported compounds.

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[1] a) R. W. Johnstone, *Nat. Rev. Drug Discovery* **2002**, *1*, 287–299; b) P. A. Marks, R. A. Rifkind, V. M. Richon, R. Breslow, T. Miller, W. K. Kelly, *Nat. Rev. Cancer* **2001**, *1*, 194–202–202.
[2] N. L. Wiech, J. F. Fisher, P. Helquist, O. Wiest, *Curr. Top. Med. Chem.* **2009**, *9*, 257–271.
[3] a) S. J. Shuttleworth, S. G. Bailey, P. A. Townsend, *Curr. Drug Targets* **2010**, *11*, 1430–1438; b) M. A. Halili, M. R. Andrews, M. J. Sweet, D. P. Fairlie, *Curr. Top. Med. Chem.* **2009**, *9*, 309–319.
[4] K. T. Andrews, T. N. Tran, N. C. Wheatley, D. P. Fairlie, *Curr. Top. Med. Chem.* **2009**, *9*, 292–308.
[5] A. Echaniz-Laguna, O. Bousiges, J.-P. Loeffler, A.-L. Boutillier, *Curr. Med. Chem.* **2008**, *15*, 1263–1273.
[6] S.-J. Kim, B.-H. Lee, Y.-S. Lee, K.-S. Kang, *Biochem. Biophys. Res. Commun.* **2007**, *360*, 593–609.
[7] S. Grant, C. Easley, P. Kirkpatrick, *Nat. Rev. Drug Discovery* **2007**, *6*, 21–22.

[8] C. Tiffon, J. Adams, L. van der Fits, S. Wen, P. Townsend, A. Ganesan, E. Hodges, M. Vermeer, G. Packham, *Br. J. Pharmacol.* **2011**, *162*, 1590–1602.
[9] N. Tsuji, M. Kobayashi, K. Nagashima, Y. Wakisaka, K. Koizumi, *J. Antiobiot.* **1976**, *29*, 1–6.
[10] H. Morioka, M. Ishihara, M. Takezawa, K. Hirayama, E. Suzuki, Y. Komoda, H. Shibai, *Agric. Biol. Chem.* **1985**, *49*, 1365–1370.
[11] M. Yoshida, M. Kijima, M. Akita, T. Beppu, *J. Biol. Chem.* **1990**, *265*, 17174–17179.
[12] a) N. Mishra, D. R. Brown, I. M. Olorenshaw, G. M. Kammer, *Proc. Natl. Acad. Sci. USA* **2001**, *98*, 2628–2633; b) K. T. Andrews, A. Walduck, M. J. Kelso, D. P. Fairlie, A. Saul, P. G. Parsons, *Int. J. Parasitol.* **2000**, *30*, 761–768.
[13] N. H. Pipalia, C. C. Cosner, A. Huang, A. Chatterjee, P. Bourbon, N. Farley, P. Helquist, O. Wiest, F. R. Maxfield, *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 5620–5625.
[14] a) C. C. Cosner, J. T. Markiewicz, P. Bourbon, C. J. Mariani, O. Wiest, M. Rujoi, A. I. Rosenbaum, A. Y. Huang, F. R. Maxfield, P. Helquist, *J. Med. Chem.* **2009**, *52*, 6494–6498; b) A. I. Rosenbaum, C. C. Cosner, C. J. Mariani, F. R. Maxfield, O. Wiest, P. Helquist, *J. Med. Chem.* **2010**, *53*, 5281–5289.
[15] a) I. Fleming, J. Iqbal, E.-P. Krebs, *Tetrahedron* **1983**, *39*, 841–846; b) K. Mori, K. Koseki, *Tetrahedron* **1988**, *44*, 6013–6020; c) S. Zhang, W. Duan, W. Wang, *Adv. Synth. Catal.* **2006**, *348*, 1228–1234.
[16] a) P. Helquist, J. Löfstedt, U. S. Patent 7,235,688, June 26, **2007**; b) J. T. Markiewicz, D. J. Schauer, J. Löfstedt, S. J. Corden, O. Wiest, P. Helquist, *J. Org. Chem.* **2010**, *75*, 2061–2064.
[17] A. Chatterjee, J. Richer, T. Hulett, V. B. R. Iska, O. Wiest, P. Helquist, *Org. Lett.* **2010**, *12*, 832–834.
[18] C. C. Cosner, P. Helquist, *Org. Lett.* **2011**, *13*, 3564–3567.
[19] J. R. Gage, D. A. Evans, *Org. Synth.* **1990**, *68*, 83–88.
[20] R. E. Damon, G. M. Coppola, *Tetrahedron Lett.* **1990**, *31*, 2849–2852.
[21] T. Fukuyama, S. C. Lin, L. P. Li, *J. Am. Chem. Soc.* **1990**, *112*, 7050–7051.
[22] R. Verhe, V. G. van Heeke, N. Schamp, *Med. Fac. Landbouww. Rijksuniv. Gent.* **1988**, *53*, 77–83.
[23] a) J. A. Marshall, C. M. Grant, *J. Org. Chem.* **1999**, *64*, 696–697; b) J. M. Marshall, *Chem. Rev.* **2000**, *100*, 3163–3186.
[24] 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*, 188–193.
[25] a) A. A. Millard, M. W. Rathke, *J. Am. Chem. Soc.* **1977**, *99*, 4833–4835; b) J. Fauvarque, A. Jutand, *J. Organomet. Chem.* **1981**, *209*, 109–114; c) M. Kosugi, I. Hagiwara, T. Sumiya, T. Migita, *Bull. Chem. Soc. Jpn.* **1984**, *57*, 242–246; d) C. D. Roberts, R. Schütz, C. J. Leumann, *Synlett* **1999**, 819–821; e) P. Almendros, A. Rae, E. J. Thomas, *Tetrahedron Lett.* **2000**, *41*, 9565–9568; f) A. Chieffi, K. Kamikawa, J. Åhman, J. M. Fox, S. L. Buchwald, *Org. Lett.* **2001**, *3*, 1897–1900; g) T. Hamada, S. L. Buchwald, *Org. Lett.* **2002**, *4*, 999–1001; h) S. Torssell, E. Wanngren, P. Somfai, *J. Org. Chem.* **2007**, *72*, 4246–4249; i) J. Huang, E. Bunel, M. M. Faul, *Org. Lett.* **2007**, *9*, 4343–4346; j) M. Riou, L. Barriault, *J. Org. Chem.* **2008**, *73*, 7436–7439; k) A. M. Taylor, R. A. Altman, S. L. Buchwald, *J. Am. Chem. Soc.* **2009**, *131*, 9900–9901; l) L. Jiang, S. Weist, S. Jansat, *Org. Lett.* **2009**, *11*, 1543–1546; m) D. S. Huang, J. F. Hartwig, *Angew. Chem.* **2010**, *122*, 5893–5897; *Angew. Chem. Int. Ed.* **2010**, *49*, 5757–5761; n) Q. Xiao, W.-W. Ren, Z.-X. Chen, T.-W. Sun, Y. Li, Q.-D. Ye, J.-X. Gong, F.-K. Meng, L. You, Y.-F. Liu, M.-Z. Zhao, L.-M. Xu, Z.-H. Shan, Y. Shi, Y.-F. Tang, J.-H. Chen, Z. Yang, *Angew. Chem.* **2011**, *123*, 7511–7515; *Angew. Chem. Int. Ed.* **2011**, *50*, 7373–7377.
[26] a) E. Piers, P. C. Marais, *J. Org. Chem.* **1990**, *55*, 3454–3455; b) T. Wang, J. M. Cook, *Org. Lett.* **2000**, *2*, 2057–2059; c) D. Solè, E. Peidró, J. Bonjoch, *Org. Lett.* **2000**, *2*, 2225–2228; d) D. Solè, F. Diaba, J. Bonjoch, *J. Org. Chem.* **2003**, *68*, 5746–5749; e) D. Solè, X. Urbaneja, J. Bonjoch, *Org. Lett.* **2005**, *7*, 5461–5464; f) H. Zhang, J. Boonsombat, A. Padwa, *Org. Lett.* **2007**, *9*, 279–282; g) A. B. Dounay, P. G. Humphreys, L. E. Overman, A. D. Wrobleski, *J. Am. Chem. Soc.* **2008**, *130*, 5368–5377; h) C. R. Edwankar, R. V. Edwankar, S. Rallapalli, J. Cook, *Nat. Prod. Commun.* **2008**, *3*, 1839–1870; i) H. Shigehisa, T. Jikihara, O. Takizawa, H. Nagase, T. Honda, *Tetrahedron Lett.* **2008**, *49*, 3983–3986; j) M. Utsugi, Y. Kamada, M. Nakada, *Tetrahedron Lett.* **2008**, *49*, 4754–4757; k) M. J. Wanner, R. N. A. Boots, B. Eradus, R. de Gelder, J. H. van Maarseveen, H. Hiemstra, *Org. Lett.* **2009**, *11*, 2579–2581; l) W. Yin, M. S. Kabir, Z. Wang, S. K. Rallapalli, J. Ma, J. M. Cook, *J. Org. Chem.* **2010**, *75*, 3339–3349; m) G. Li, A. Padwa, *Org. Lett.* **2011**, *13*, 3767–3769; n) R. V. Edwankar, C. R. Edwankar, J. Deschamps, J. M. Cook, *Org. Lett.* **2011**, *13*, 5216–5219; o) P. Liu, J. Wang, J. Zhang, F. G. Qiu, *Org. Lett.* **2011**, *13*, 6426–6428.
[27] C. C. Cosner, P. J. Cabrera, K. M. Byrd, A. M. A. Thomas, P. Helquist, *Org. Lett.* **2011**, *13*, 2071–2073.
[28] J.-M. Vatèle, *Tetrahedron Lett.* **2006**, *47*, 715–718.
[29] a) T. Hama, D. A. Culkin, J. F. Hartwig, *J. Am. Chem. Soc.* **2006**, *128*, 4976–4985; b) T. Hama, X. Liu, D. A. Culkin, J. F. Hartwig, *J. Am. Chem. Soc.* **2003**, *125*, 11176–11177; c) M. L. Hlavinka, J. R. Hagadorn, *Organometallics* **2007**, *26*, 4105–4108; d) M. L. Hlavinka, J. R. Hagadorn, *Tetrahedron Lett.* **2006**, *47*, 5049–5055; e) S. Duez, S. Bernhardt, J. Heppekausen, F. F. Fleming, P. Knochel, *Org. Lett.* **2011**, *13*, 1690–1693.
[30] a) I. Paterson, M. D. Woodrow, C. J. Cowden, *Tetrahedron Lett.* **1998**, *39*, 6041–6044; b) I. Paterson, C. J. Cowden, V. S. Rahn, M. D. Woodrow, *Synlett* **1998**, 915–917.
[31] B. S. Bal, W. E. Childers, H. W. Pinnick, *Tetrahedron* **1981**, *37*, 2091–2096.
[32] E. Dalcanale, F. Montanari, *J. Org. Chem.* **1986**, *51*, 567–569.
[33] B. O. Lindren, T. Bilsson, *Acta Chem. Scand.* **1973**, *27*, 888–890.
[34] a) W. Duan, X. Zhao, S. Zhang, J. Ding, M. Gui, *Faming Zhuanli Shenqing* **2008**, CN 101239929 A 20080813; b) C. Charrier, J. Roche, J.-P. Gesson, P. Bertrand, *J. Chem. Sci.* **2009**, *121*, 471–479.
[35] M. Yoshida, Y. Hoshikawa, K. Koseki, K. Mori, T. Beppu, *J. Antibiot.* **1990**, *43*, 1101–1106.
[36] M. Jean, J. Renault, P. van de Weghe, *Tetrahedron Lett.* **2009**, *50*, 6546–6548.
[37] E. Dolhem, R. Barhdadi, J. C. Folest, J. Y. Nédelec, M. Troupel, *Tetrahedron* **2001**, *57*, 525–529.
[38] H. Tatamidani, K. Yokota, F. Kakiuchi, N. Chatani, *J. Org. Chem.* **2004**, *69*, 5615–5621.

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