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Total synthesis of the HDAC inhibitor (+)-(R)-trichostatin A via O-directed dialkylacetylene free radical hydrostannation with Ph₃SnH/Et₃B. The unusual inhibitory effect of a proximal α -OPv group on the course of a vinyl iodide Stille cross-coupling†‡

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In this paper, a new asymmetric total synthesis of optically pure (+)-trichostatin A (1a) is described via a route that utilises a Marshall chiral allenylzinc addition between 9 and 4-dimethylaminobenzaldehyde (10) and an O-depivaloylation at its early stages. O-Directed free radical hydrostannation of the resulting propargylic alcohol 15 with Ph_3SnH/cat . Et_3B/O_2 in PhMe at rt thereafter provided the (Z)- α -triphenylstannylvinyltin **16** in 80–89% yield, with complete stereocontrol and very high α : β regioselectivity (25:1). A stereoretentive I-Sn exchange reaction between 16 and I₂ (1.4 equiv.) in CH₂Cl₂ (-78 °C to rt, 1 h) subsequently secured the vinyl iodide 18 in 84-96% yield. The latter was transformed into the enal 4 by successive TPAP/NMO (Ley-Griffith) oxidation and a high yielding (80%) Stille reaction between the α-iodo enal 20 and Me₄Sn, catalysed by Pd(PPh₃)₄ in DMF at 60 °C, under the Baldwin-Lee conditions, which use CsF and Cul as promoters. A Wittig reaction between 4 and Ph₃P=CHCO₂Et (5), saponification, and DDQ oxidation next afforded (+)-trichostatic acid (22). Helquist's ethyl chloroformate mixed-anhydride/TBSONH2 coupling procedure (ref. 17e) thereafter secured (+)-trichostatin A (1a) in good yield. This new total synthesis of 1a is the first-ever successful application of the O-directed dialkylacetylene free radical hydrostannation with Ph₃SnH/cat. Et₃B/O₂ in a dialkylaniline N-containing disubstituted alkynol system, and it now provides a convenient means of accessing many novel trichostatin analogues for future biological screening.

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† Dedicated with admiration and respect to the memory of the great Professor Amos B. Smith III (2014 William H. Nichols Gold Medallist, 2015 RSC Perkin Prize Winner, 2009 RSC Simonsen Medallist, and 2002 RSC Centenary Prize Medallist) in recognition of his numerous magnificent achievements in complex natural product total synthesis, new synthetic methodology development, materials science, and his rational design of a totally new class of HIV-1-neutralising drugs. Sadly, Professor Smith passed away on the morning of Monday February 3rd, 2025, aged 80 years. His landmark contributions to the fields of organic synthesis and medicinal chemistry will continue to serve as a source of much future inspiration to us all. He will forever be missed by his many friends, former students, postdoctoral fellows, Associate Editors, and admirers within the world of organic chemistry. Professor Smith was a recipient of the Order of the Rising Sun of Japan.

‡Electronic supplementary information (ESI) available: experimental procedures for the synthesis of 15, copies of the NMR, IR, and HR mass spectra of all compounds, TLC photos, and additional experimental discussions. See DOI: https://doi.org/10.1039/d4ob01848f

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Introduction

For some time now, we have been studying the scope, ^{1,2a} mechanism, ^{3,4} and utility ¹ of the *O*-directed free radical hydrostannation reaction of various propargylically-oxygenated dialkylacetylenes with stannanes, ¹⁻⁴ and the protocol that has consistently emerged best for most acyclic synthetic applications is the room temperature Ph₃SnH/cat. Et₃B variant of this reaction performed in PhMe (Scheme 1). ^{2a}

But that is not to say that the thermally-mediated Bu₃SnH/AIBN counterpart⁴ of this reaction does not have an equally important role to play in synthesis, particularly where tandem radical cyclisation is a cardinal requirement, as in Alabugin's traceless polyaromatic ring construction reactions,⁵ where his team's powerful contributions have been particularly elegant, innovative and synthetically impactful. Those same studies⁵ have also provided profound computational and experimental insights into the detailed mechanistic workings of the free radical hydrostannation reaction of propargylically-oxygenated

Scheme 1 The rt O-directed free radical hydrostannylative synthesis of (Z)-trisubstituted alkenes with Ph₃SnH/cat. Et₃B.

disubstituted acetylenes, and affirmed the entirely free radical O-directed mechanism proposed for this process. $^{3,4a-c}$

The O-directed Ph₃SnH/cat. Et₃B variant^{1,2} of this reaction has now shown its versatility in a wide range of complex settings that have included total syntheses of the natural products (+)-pumiliotoxin B^6 and (-)-(3R)-inthomycin C^7 . A noteworthy double O-directed free radical hydrostannation has also been introduced for the simultaneous installation of two structurally distinct trisubstituted alkenes within target structures. Its synthetic utility was powerfully demonstrated by the fully stereocontrolled route that was developed to the C(7)-C(22)-sector of (+)-acutiphycin.⁸ The Furstner team has likewise elegantly employed an O-directed free radical hydrostannation with Ph₃SnH, cat. AIBN and PhMe in their total synthesis of (+)-isomigrastatin.9 In each of these synthetic applications, I-SnPh3 exchange has played a central role in final trisubstituted alkene elaboration¹⁰ and, for the synthesis of all-carbon branched alkene structures, the CuI/CsF Baldwin-Lee¹¹ and Farina Ph₃As variants¹² of the Stille reaction have both proven themselves immensely valuable. 6-8,10 Other Pd(0)-mediated cross-coupling methods (e.g. Suzuki, Negishi, and Cuprate) and carbonylations have shown themselves to be equally applicable in this sphere.¹⁰

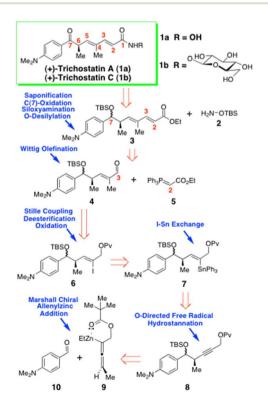
While there have now been many impressive displays of the utility of the rt Ph₃SnH/cat. Et₃B *O*-directed hydrostannation in synthesis, ^{6–8,10} there remain some classes of alkynes on which this reaction has yet to be successfully applied. Prominent amongst these substrates are propargyloxy dialkylacetylenes with an *unprotected* amine functionality. These generally form a complex with the Et₃B initiator, to prevent the O₂-mediated S_H2 radical initiation event from ever taking place. Although a stoichiometric excess of Et₃B can sometimes allow radical initiation to occur, frequently the outcomes of these processes are disappointing.

Despite all of the past difficulties, we recently decided to investigate whether weakly basic amines, such as anilines, might prove compatible with the Ph_3SnH/cat . Et_3B *O*-directed hydrostannation method. In this paper, we now report that the 4-dimethylanilino functionality is indeed well tolerated in this process, as demonstrated by our new asymmetric total synthesis of (+)-trichostatin A, where this reaction protocol was very effectively deployed alongside a Marshall chiral allenylzinc addition process. 13

We also document here, for the first time ever, the profound inhibitory effect that an allylic OPv group can have on the course of a Pd-catalysed cross-coupling of a vinyl iodide. The latter observation was made quite by chance, whilst we were attempting to apply such a coupling to a trisubstituted vinyl iodide with such a functionality. Given this synthetic impasse, we thought it important to record this difficulty here, to prevent others from becoming similarly ensuared in the future.

(+)-Trichostatin A (1a) is a highly potent, naturally-occurring, histone deacetylase (HDAC) inhibitor that has elicited considerable medicinal interest as a possible antifungal, 14a anticancer, 14b,c immunosuppressive, 14d and anti-Duchenne muscular dystrophy drug, 15 but its clinical use has so far been precluded by its remarkably short plasma half-life (<6.3 min at 80 mg kg⁻¹)^{14c} and its pronounced genotoxicity. It is widely thought that if these undesirable properties could somehow be ablated by careful structural modification, as was recently found for glycosylated (+)-trichostatin C (1b),16 and HDAC specificity could also be improved, such trichostatin analogues might potentially become useful new treatments for a host of diseases. It was with such pharmaceutical and synthetic objectives in mind that we first embarked on the development of a new improved total synthesis¹⁷ of (+)-trichostatin A (1a) (R = OH), for the purpose of providing novel C(4)-analogues^{17e} for drug screening and X-ray crystallographic/NMR studies. It was hoped that such studies might provide useful new insights into how individual HDAC isozymes work, as well as new therapeutic drugs.

Accordingly, we duly formulated the retrosynthetic plan of Scheme 2 for the synthetic acquisition 17 of (+)-(R)-trichostatin



Scheme 2 Retrosynthetic planning for (+)-(6R)-trichostatin A (1a).

A (1a). Underpinning our approach would be the O-directed free radical hydrostannation of alkyne 8 with Ph₃SnH/Et₃B, which would be allied with an I-Sn exchange and a Stille cross-coupling with Me₄Sn. An O-depivaloylation and an alcohol oxidation would thereafter procure 4. The latter would then be chain extended with the vlide 5, the C(1)-carboxyl subsequently unmasked, and the C(7)-ketone thereafter elaborated, prior to C(1)-oxyamidation with TBSONH2. An O-desilylation would then complete the synthesis of 1a. 17 Alkyne 8 would itself be created through a new Marshall chiral allenylzing addition between the known chiral allenylzing 9 13 and 4-dimethylaminobenzaldehyde (10) under Pd(0)-catalysis.

Results and discussion

Our first objective was the preparation of the chiral allenylzing 9 from the known propargyl O-mesylate 11 (Scheme 3)¹³ by the method of Marshall and Xie.13 Specifically, 11 was added dropwise to a solution of Pd(OAc)2 (0.05 equiv.) and Ph3P (0.05 equiv.) that had been pre-aged for 20 min in dry THF at -20 °C, under N₂. The reactants were then stirred for a further 5 min post-addition, before 4-dimethylaminobenzaldehyde (10) was added dropwise, followed by Et₂Zn (3 equiv.). Stirring was then continued at -20 °C for 48 h to give an essentially inseparable 1:1 mixture of two alcohol diastereomers at C(5). This was inconsequential for further synthetic progression, since the C(5)-alcohols of 12 would ultimately be oxidized to the C(7) ketone in 1a, at the penultimate step, and this same reaction had fully controlled the stereochemistry of the key C(4)-Me group in 12 (this would be C(6) in 1a). After O-silylation with TBSCl, the alkynyl O-pivaloate 8 was subjected

> To Pd(OAc)₂ (0.05 equiv) dry THF, -20 °C, Ph₃P (0.05 equi stir 5 min, ar -20 °C, (1.5 equiv) mid (6 equiv) n add 10 in THF drop ed by Et₂Zn in hex (3 equiv DMF. 50°C stir -20 °C 48 h (58-81%) CH₂Cl₂, 0 °C 2 h, then NIS DMF then add Ph₃P)₄Pd (0.05 equiv) sealed tube. 18 h

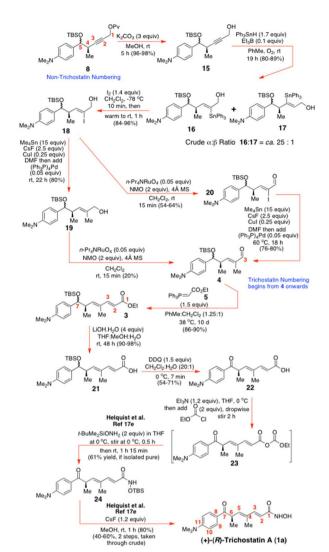
Initially investigated route to 7 and 14.

to an O-directed free radical hydrostannation with Ph₃SnH (1.5 equiv.) and Et3B (0.1 equiv.) in PhMe under our standard rt conditions. This reaction proceeded efficiently, affording 7 as two C(5)-diastereomeric products in 78% yield after 18 h. With 7 in hand, the key I-Sn exchange was investigated to obtain 6. It was found that when this reaction was performed with just 1.5 equiv. of NIS at 0 °C, it did not proceed to completion, even after 2 h. However, when an additional 4 equiv. of NIS was added at rt,7 and the reactants were stirred for a further 2 h, the reaction did deliver the slightly impure vinyl iodide 6, as a much slower-moving product spot on TLC analysis. The necessity for such a large excess of the NIS was indicative of strong internal O-Sn coordination occurring within 7, between the pivaloyloxy-carbonyl-O and the SnPh3 substituent, which preferentially enhanced the reactivity of the Ph groups. As a result, a highly polar vinyltin triiodide initially needed to form, which was then eventually replaced by the desired vinyl iodide after prolonged stirring at rt. Iodide 6 was next subjected to a Stille cross-coupling with Me₄Sn under the normally successful Baldwin-Lee conditions. 11 Surprisingly, this reaction performed very poorly; an outcome that we have attributed to an analogous strong internal coordinative effect from the nearby OPv group, which we believe displaces the iodide from the initially formed vinyl-palladium(II) iodide to give 13,18 whose high stability then halts iodide return, to prevent the key transmetallation step from ever occurring with the Me₄Sn or hypervalent [Me₄SnF]⁻.

In light of this setback, we decided to cleave the OPv group from 8 with i-Bu₂AlH (2 equiv.) in CH₂Cl₂ at -78 °C. The reaction took 2 h to reach completion, affording the desired alkynol 15 in 83% yield after extractive work up and SiO2 flash chromatography. It was later found more convenient and higher yielding (96-98% yield) to use K2CO3 in MeOH to accomplish this transformation over 5 h at rt (Scheme 4). The resulting alkynol 15 was then subjected to O-directed hydrostannation with Ph₃SnH (1.7 equiv.) and Et₃B (0.1 equiv.) and O2 in PhMe (1 M in 15) for 19 h at rt. This afforded a 25:1 mixture of α : β vinyltriphenylstannanes **16** and **17**, from which the two α -stannylated C(5)-diastereomers 16 could typically be purified with 80-89% yield after SiO₂ flash chromatography.

Now that the Pv protecting group had been detached, the requisite I-Sn exchange reaction proceeded successfully with 16 to give 18 in >90% yield using only 1.4 equiv. of I2. This result provided good confirmatory evidence that the OPv group had been adversely involved in strong internal O-coordination to the metal centre in both 7 and 13, and our combined findings now pointed to a new strategic way forward.

The iodo-allylic alcohol 18 was next subjected to a Baldwin-Lee Stille cross-coupling with Me₄Sn.¹¹ It provided 19 efficiently in 80% yield after 22 h at rt. Importantly, this reaction had to be performed in complete darkness, inside a sealed vessel under N₂, to prevent light-induced vinyl iodide decomposition. Notwithstanding this success, difficulties soon arose when attempts were made to oxidise alcohol 19 under Swern, PCC, or MnO₂ oxidation conditions, due to the presence of the di-



Scheme 4 The O-directed hydrostannylative route to (+)-(R)-trichostatin A (1).

methylamino group. Only cat. TPAP/NMO¹⁹ afforded the desired enal 4, but in a disappointing 20% yield.

Even so, this positive outcome did prompt us to evaluate the Ley-Griffith TPAP (0.05 equiv.)/NMO (2 equiv.) oxidising system¹⁹ on the iodoallylic alcohol 18 in CH₂Cl₂ in the presence of 4 Å sieves. This reaction worked reasonably well at rt, providing the desired α-iodo-enal 20 in 54-64% yield after just 15 min. To our surprise, a much slower-moving by-product was also formed alongside 20; this is suspected to be the N-oxide based upon ¹H and ¹³C NMR analysis. Fortunately, it could be separated from 20 by SiO2 flash chromatography. The unstable iodo-enal 20 was thereafter used quickly for a Baldwin-Lee Stille cross-coupling with Me₄Sn (15 equiv.), CsF (2.5 equiv.) and CuI (0.25 equiv.) in DMF at 60 °C; a reaction that needed to be conducted in darkness. The success of this coupling (76–80% yield) was confirmed by the presence of two new allylic methyl doublets at δ 1.62 ppm (J = 1.2 Hz) and 1.61 ppm (J = 1.6 Hz) in CDCl₃. Due to 20 and 4 both having

near identical TLC plate mobilities after a single elution, it was necessary to follow the progress of this reaction by multielution TLC with 3:1 petrol/CH₂Cl₂ as the eluent. The product enal 4 moved as a slightly slower single spot, when compared with the iodo-enal 20; 4 also stained dark blue when the TLC plate was heated with the anisaldehyde/H₂SO₄ stain. The iodoenal 20 stained brown. It is worth noting that performing this coupling at a temperature significantly below 60 °C led to a marked diminution in the yield of 4; so 60 °C is essential and optimal.

Surprisingly the Wittig condensation of aldehyde 4 with stabilised P-vlide 5 took 6-10 d to reach completion at 38-40 °C in PhMe/CH₂Cl₂ (1.25:1), and again, 4 and 3 had near identical TLC mobilities. When complete, the reaction furnished the dienoate 3 in 86-90% yield with total geometric control.

Unfortunately, the subsequent O-desilylation of 3 with n-Bu₄NF in THF, or CsF in DMF, or HF/pyridine did not lead to the expected alcohol but, instead, a multitude of products. With $n\text{-Bu}_4\text{NF}$, 4-dimethylaminobenzaldehyde (10) was observed amongst the products, confirming that a retro-vinylogous aldol cleavage occurred at C(6)/C(7). This unexpected result led to an immediate change in our synthetic planning.

Without separation, the two C(7)-diastereoisomers of ester 3 were saponified with 90-98% yield with LiOH (4 equiv.) in 1:1:1 THF/MeOH/H₂O. The known acid 21^{17} was then oxidatively converted into (+)-trichostatic acid (22) by brief exposure to 1.5 equiv. of DDQ in 20:1 CH₂Cl₂/H₂O at 0 °C for just 7 min. Such precise timing was essential to avoid extensive decomposition of the (+)-trichostatic acid 22 so formed. Although, in principle, the viability of this reaction had already been demonstrated by Hosokawa and Tatsuta in 2005, 17f these workers never supplied an experimental procedure for this reaction, which meant that considerable experimentation was needed on our part to obtain a successful outcome. Nonetheless, with the new procedure reported here, the above reaction can now deliver 22 in 54-71% yield, with only a small amount of the starting material ever remaining at the reaction end.

With acid 22 in hand, it could be converted into the mixed anhydride 23 by treatment with 2 equiv. of ethyl chloroformate at 0 °C in THF. 17b,e Exposure to 2 equiv. of TBSO-NH2 according to Helquist's procedure 17e thereafter afforded 24, which was deprotected with CsF in MeOH to obtain (+)-(R)-trichostatin A (1) in 40-60% yield over 2 steps, without loss of chirality.¹⁷ The latter was proven by our synthetic conversion of 22 ²⁰ into its naturally-occurring β-glucoside, (+)-trichostatin C (1b) (NMR data in the ESI‡), which also, simultaneously, unambiguously confirmed the assigned structure of that natural product. 16,20

Conclusions

With this new enantioselective total synthesis of (+)-trichostatin A that has been developed,²¹ we have provided yet another powerful demonstration of the utility of the room temperature O-directed free radical hydrostannation of propargylically-oxygenated dialkylacetylenes with Ph_3SnH and Et_3B/O_2 in complex molecule total synthesis, $^{1-3,6-8,22}$ and we have exemplified how it can be successfully deployed in an alkyne system that bears the dialkylaniline N-functionality. We have also shown how vinyl iodides with a proximal $-CH_2OPv$ group can internally O-coordinate to a vinyl palladium(II) intermediate in a manner that prevents it from successfully engaging in transmetallation 18 and reductive elimination.

Experimental

Procedures for the total synthesis of (+)-(R)-trichostatin A (1)

For the synthesis of propargyl alcohol 15 see the accompanying ESI.‡

O-Directed hydrostannation of 15: synthesis of vinyl triphenyltin 16

Inside a sealed glove bag filled with an N2 atmosphere, Ph₃SnH (5.11 g, 14.56 mmol, 1.7 equiv.) was quickly weighed into a pear-shaped flask fitted with a rubber septum. When the weighing process was complete, the septum-sealed flask was removed from the glove bag and fitted with an N2-filled balloon connected to a Luer-locked needle. Dry PhMe (8.5 mL) was added to the neat Ph₃SnH and that solution was cannulated into alkynol 15 (2.98 g, 8.57 mmol) under N2 at rt. A solution of Et₃B (1.0 M in hex, 1.30 mL, 1.30 mmol, 0.15 equiv.) was then added dropwise to the two reactants. Air (20 mL) was thereafter injected into the reaction mixture twice at 5 min and then at 1 h. The reaction mixture was stirred at rt for 19 h with the N₂ atmosphere being maintained throughout. The reaction mixture was then diluted with EtOAc (20 mL) and quenched with H₂O (20 mL). The aqueous layer was extracted with EtOAc (20 mL × 5). The combined organic extracts were then dried using MgSO₄, filtered and concentrated under reduced pressure. The crude residue, which consisted essentially of a 25:1 α : β mixture of 16:17, was purified by gradient elution SiO₂ flash chromatography initially using petrol: CH_2Cl_2 (3:1 \rightarrow 2:1 \rightarrow 1:1) to remove the tin residues and other impurities. Gradient elution with petrol: EtOAc $(18:1 \rightarrow 15:1)$ thereafter gave the entire product 16 (4.76 g, 80%) as a mixture of C5-epimers and as a colourless oil. A small amount of the β-vinyltin adduct 17 was subsequently eluted with petrol: EtOAc (12:1 \rightarrow 8:1) as the eluent. It was characterised and identified by ¹H NMR spectroscopy (see the ESI[‡] for a copy of the 600 MHz ¹H NMR spectrum of 17). Data for 16: IR of 16 (neat film): 3423 (m), 3063 (m), 3050 (m), 2959 (s), 2926 (s), 2856 (s), 1730 (w), 1615 (s), 1524 (s), 1431 (s), 1385 (m), 1254 (m), 1073 (s), 864 (m), 837 (m), 779 (m), 731 (s), $698 (s) cm^{-1}$.

¹H NMR of pure **16** (pure α-diastereoisomer 1) (399.9 MHz, CDCl₃): δ 7.60 (m, 6H, ${}^{3}J^{119/117}Sn^{-1}H = ca. 48.0 Hz, o-CH,$ $-SnPh_3$), 7.35 (m, 9H, p- and m-CH, $-SnPh_3$), 6.78 (d, J =8.4 Hz, 2H, H7), 6.35 (d, J = 8.7 Hz, 2H, H8), 6.43 (d, J =10.0 Hz, ${}^{3}J^{119}Sn^{-1}H = 173.6$ Hz, ${}^{3}J^{117}Sn^{-1}H = 153.6$ Hz, 1H, H3), 4.32 (s, 2H, CH₂, ${}^{3}J^{119/117}$ Sn- ${}^{1}H$ = 54.0 Hz, H1a,b), 4.22 (d, 1H, J = 6.8 Hz, H5), 2.92 (s, 6H, N(CH₃)₂), 2.47 (m, 1H, J =6.8 Hz, H4), 1.32 (br, 1H, OH), 0.83 (s, 9H, t-Bu of OTBS), 0.56 $(d, J = 6.8 \text{ Hz}, C4\text{-Me}), -0.09 \text{ (s, 3H, CH}_3\text{Si)}, -0.27 \text{ (s, 3H, CH}_3\text{Si})}$ CH₃Si) ppm. ¹³C NMR of **16** (pure α-diastereoisomer 1) (100.57 MHz, CDCl₃): δ 149.6 (C9), 149.2 (C3, 2J $^{119/117}$ Sn $^{-13}$ C = 32.2 Hz), 139.7 (C2), 139.4 (quaternary C, -SnPh₃), 137.2 (o-C, $-SnPh_3$, 3J ${}^{119/117}Sn-{}^{13}C = 38.2$ Hz), 131.4 (C6), 128.7 (*p*-C, $-SnPh_3$, 4J ${}^{119/117}Sn$ $-{}^{13}C$ = 12.1 Hz), 128.5 (*m*-C, $-SnPh_3$, $^{3}J^{119}Sn^{-13}C = 52.3 Hz$, 127.9 (C7), 111.8 (C8), 79.3 (C5), 70.4 (C1, ${}^{2}J^{119/117}Sn^{-13}C = 46.3 Hz$), 47.4 (C4, ${}^{3}J^{119/117}Sn^{-13}C =$ 38.2 Hz), 40.6 (N(CH₃)₂), 25.9 ((CH₃)₃CSi), 18.3 ((CH₃)₃CSi), 17.6 (C4-Me), -4.4 (CH₃Si), -5.1 (CH₃Si) ppm.

¹H NMR of the other diastereoisomer (α-diastereoisomer 2) (399.9 MHz, CDCl₃). Resonances and multiplicities have been reported, where determinable, from the purified but diastereomerically enriched 3:1 mixture of C5 epimers: δ 7.61 (m, 6H, o-CH, -SnPh₃, ${}^{3}J^{-119/117}$ Sn- ${}^{1}H$ = 48.4 Hz), 7.38 (m, 9H, $-\text{SnPh}_3$), 6.44 (d, J = 8.8 Hz, 2H, H7) superimposed upon 6.42 (m, 1H, H3), 6.40 (d, J = 8.8 Hz, 2H, H8), 4.43 (d, J = 3.6 Hz, 1H, H5), 4.32 (s, 2H, H1), 2.88 (s, 6H, N(CH₃)₂), 2.27 (m, 1H, H4), 1.32 (br, 1H, OH), 0.91 (s, 9H, t-Bu of OTBS), 0.74 (d, J = 6.8 Hz, 3H, C4-Me), -0.00 (s, 3H, CH_3Si), -0.23 (s, 3H, CH₃Si) ppm. ¹³C NMR (100.57 MHz, CDCl₃) of the other diastereoisomer of 16 (α -diastereoisomer 2). Resonances and J values have been reported, where determinable, from the purified but diastereomerically enriched 3:1 mixture: δ 150.1 (C9), 149.2 (C3), 139.2 (Sn-C-CH, $-SnPh_3$), 138.8 (C2), 137.1 (o- \underline{C} , $-SnPh_3$, 3J $^{119/117}Sn^{-13}C$ = 38.2 Hz), 131.6 (C6), 128.9 (p-C, -SnPh₃, ${}^{4}J^{119/117}$ Sn- ${}^{13}C$ = 12.1 Hz), 128.6 (*m*- \underline{C} , -SnPh₃, ${}^{4}J^{\overline{119/117}}$ Sn- ${}^{13}C$ = 52.3 Hz), 126.8 (C7), 111.7 (C8), 77.1 (C5), 70.3 (C1, ${}^2J^{119/117}\text{Sn}^{-13}\text{C} = 46.3 \text{ Hz}$), 47.12 (CH-Me), 40.7 (N(CH₃)₂), 25.9 ((CH₃)₃CSi), 18.3 $((CH_3)_3CSi)$, 13.8 $(CH-CH_3)$, -4.5 (CH_3Si) , -5.0 (CH_3Si) ppm.

TOF ES⁺ HRMS of **16**: calcd for $C_{38}H_{50}NO_2SiSn [M + H]^+$: 700.2640. Found: 700.2611.

I-Sn exchange of 16: preparation of vinyl iodide 18

Before commencing this experiment, the reaction flask was covered with Al-foil to protect it from the adverse effects of light. Thereafter, to a stirred -78 °C solution of the vinyl triphenyltin 16 (4.76 g, 6.81 mmol) in dry CH₂Cl₂ (68 mL) under N₂ was added I₂ (2.42 g, 9.52 mmol, 1.4 equiv.) in one portion. Stirring was continued at -78 °C for 10 min, after which the cooling bath was removed, and the reactants were allowed to stir at rt for a further 1 h. The reaction mixture was then

diluted with CH₂Cl₂ (50 mL) and quenched with H₂O (50 mL). The aqueous layer was extracted with EtOAc (50 mL × 3) and the combined organic extracts were successively washed with saturated aq. $Na_2S_2O_3$ (100 mL) and H_2O (50 mL × 2). The organic extract was then dried over MgSO4, filtered and concentrated in vacuo. The crude residue was purified by gradient elution SiO₂ flash chromatography using petrol: CH₂Cl₂ $(3:1 \rightarrow 2:1 \rightarrow 1:1)$ as the eluent to remove tin residues, and thereafter petrol: EtOAc (15:1 \rightarrow 10:1) to elute iodide 18 (3.0 g, 93%) as a C5-mixture of epimers; it was obtained as an amber oil. IR for the 18 mixture (neat film): 3383 (m), 3101 (w), 3075 (w), 2959 (s), 2927 (s), 2856 (s), 2800 (m), 1738 (w), 1617 (s), 1521 (s), 1471 (m), 1357 (m), 1254 (m), 1074 (s), 941 (m), 876 (s), 835 (s), 775 (s) cm^{-1} .

Data for pure 18: ¹H NMR of 18 (pure isomer 1) (399.9 MHz, CDCl₃): δ 7.16 (d, J = 8.6 Hz, 2H, H7), 6.68 (d, J = 8.6 Hz, 2H, H8), 5.81 (d, J = 8.9 Hz, 1H, H3), 4.64 (d, 1H, J = 4.2Hz, H5), 4.19 (s, 2H, H1a,b), 2.94 (s, 6H, N(CH₃)₂), 2.65 (m, 1H, H4), 1.79 (br, 1H, OH), 0.94 (d, J = 7.0 Hz, 3H, C4-Me), 0.90 (s, 9H, t-Bu of OTBS), 0.02 (s, 3H, CH₃Si), -0.20 (s, 3H, CH₃Si) ppm. ¹³C NMR of **18** (pure isomer 1) (100.57 MHz, $CDCl_3$): δ 149.8 (C9), 139.4 (C3), 130.9 (C6), 127.6 (C7), 111.9 (C8), 107.8 (C2), 76.8 (CH-OTBS), 71.9 (C1), 49.3 (C4), 40.7 $(N(CH_3)_2)$, 25.8 $((CH_3)_3CSi)$, 18.2 $((CH_3)_3CSi)$, 15.3 (C4-Me), -4.5 (CH₃Si), -5.0 (CH₃Si) ppm.

¹H NMR of **18** (isomer 2) (399.9 MHz, CDCl₃). Resonances and I values have been reported, where determinable, from the purified but diastereomerically enriched 3:1 mixture: δ 7.10 (d, J = 8.8 Hz, 2H, H7), 6.66 (d, J = 8.0 Hz, 2H, H8), 5.72 (d, J = 8.0 Hz, 2H, H8)8.8 Hz, 1H, H3), 4.49 (d, 1H, J = 6.0 Hz, H5), 4.19 (s, 2H, H1), 2.94 (s, 6H, N(CH₃)₂), 2.74 (m, 1H, H4), 1.58 (br, 1H, OH), 0.89 (d, J = 6.8 Hz, 3H, C4-Me), 0.87 (s, 9H, t-Bu of OTBS), -0.02 (s, 9H, t-Bu of OTBS)3H, CH₃Si), -0.20 (s, 3H, CH₃Si) ppm. ¹³C NMR of **18** (isomer 2) (100.57 MHz, CDCl₃): δ 149.8 (C9), 139.4 (C3), 130.9 (C6), 127.6 (C7), 111.9 (C8), 107.7 (C2), 77.5 (C5), 71.9 (C1), 49.3 (C4), 40.7 (N(CH₃)₂), 25.9 ((CH₃)₃CSi), 18.2 ((CH₃)₃CSi), 15.3 (C4-Me), -4.5 (CH_3Si) , -5.0 (CH_3Si) ppm.

TOF ES⁺ HRMS for 18: calcd for $C_{20}H_{35}NO_2ISi$ [M + H]⁺: 476.1482. Found: 476.1500.

Preparation of allylic alcohol 19

To the iodovinylic alcohol 18 (0.3065 g, 0.645 mmol) inside a small pear-shaped flask capped with a rubber septum and an N₂-filled balloon was added dry DMF (1.28 mL) via a syringe. The outside of the flask was wrapped in Al-foil to protect it from daylight. While maintaining the N₂ atmosphere inside the flask, Me₄Sn (1.34 mL, 9.67 mmol, 15 equiv.) was added in one portion via a syringe. CsF (0.2448 g, 1.6 mmol, 2.5 equiv.), CuI (30.7 mg, 0.16 mmol, 0.25 equiv.), and (Ph₃P)₄Pd (37.2 mg, 0.032 mmol, 0.05 equiv.) were then sequentially and successively added to the reaction flask in that order, maintaining the N₂ atmosphere throughout the various additions. The reaction mixture was then left to stir at rt for 22 h, whereafter TLC analysis revealed that two C5-diastereomeric products 19 had formed that had exactly the same TLC mobility (in 5:1 hexane: EtOAc) as the starting iodovinylic alcohol 18. Staining and heating of this TLC plate with the anisaldehyde/ H₂SO₄ stain did, however, show that the two newly formed products of structure 19 both stained with a purple/blue colour, which allowed them to be readily distinguished from their precursor 18; this revealed that the reaction was complete, and that no starting 18 remained. The reaction mixture was thereupon diluted with EtOAc (10 mL), transferred to a separatory funnel and H2O (15 mL) was added. After extraction and separation, the aqueous later was extracted with additional EtOAc (6 × 20 mL), and the combined organic extracts were washed with H_2O (2 × 50 mL). The organic layer was then dried over MgSO₄, filtered, and concentrated in vacuo. The resulting oil was then purified by gradient elution SiO2 flash chromatography with petrol: EtOAc 20:1 \rightarrow 15:1 initially, to remove reagent-related impurities, followed by petrol: EtOAc 12:1 → 10:1 to secure the entire allylic alcohol 19 (0.189 g, 80%) product as an oil, and as a C5-mixture of epimers.

Data for pure 19: ¹H NMR of 19 (pure isomer 1) (600.13 MHz, CDCl₃): δ 7.09 (d, J = 8.4 Hz, 2H, H7), 6.66 (d, J = 7.8 Hz, 2H, H8), 5.26 (ddd, J = 9.6 Hz, 1H, H3), 4.35 (d, J =6.0 Hz, 1H, H5), 3.98 (s, 2H, H1a,b), 2.93 (s, 6H, N(CH₃)₂), 2.616 (m, 1H, H4), 1.557 (d, J = 1.2 Hz, C2-Me), 1.25 (br s, 1H, OH), 0.85 (s, 9H, t-Bu of OTBS), 0.82 (d, J = 6.6 Hz, 3H C4-Me), -0.02 (s, 3H, CH₃Si), -0.22 (s, 3H, CH₃Si) ppm. ¹³C NMR of **19** (pure isomer 1) (150.92 MHz, CDCl₃): δ C9 not detected, 134.5 (C3), 129.9 (C6), 127.6 (C7 and C2), 111.9 (C8), 78.9 (C5), 69.4 (C1), 41.1 (N(CH₃)₂), 40.7 (C4), 25.8 ((CH₃)₃CSi), 18.2 $((CH_3)_3CSi)$, 17.0 (C2-Me), 13.9 (C4-Me), -4.5 (CH_3Si) , -5.0 (CH_3Si) ppm.

¹H NMR of **19** (pure isomer 2) (600.13 MHz, CDCl₃): δ 7.09 (m, 2H, H7), 6.64 (m, 2H, H8), 5.23 (ddd, J = 10.2, 3.0, 1.2 Hz,1H, H3), 4.35 (d, J = 6.0 Hz, 1H, H5), 3.89 (s, 2H, H1a,b), 2.92(s, 6H, N(CH₃)₂), 2.59 (m, J = 9.6, 6.0 Hz, 1H, H4), 1.464 (d, J =1.2 Hz, C2-Me), 1.25 (br s, 1H, OH), 0.96 (d, J = 7.2 Hz, C4-Me), 0.85 (s, 9H, t-Bu of OTBS), -0.013 (s, 3H, CH₃Si), -0.21 (s, 3H, CH₃Si) ppm. ¹³C NMR of **19** (pure isomer 2) (150.92 MHz, CDCl₃): δ 149.4 (C9), 134.2 (C3), 130.0 (C6), 127.5 (C7 and C2), 111.7 (C8), 78.7 (C5), 69.3 (C1), 41.2 (N(CH₃)₂), 40.7 (C4), 25.9 $((CH_3)_3CSi)$, 18.3 $((CH_3)_3CSi)$, 16.0 (C2-Me), 13.8 (C4-Me), -4.5 (CH_3Si) , -5.1 (CH_3Si) ppm.

TPAP/NMO oxidation¹⁹ of iodo-allylic alcohol 18 to iodoenal 20

Before commencing this experiment, the reaction flask was covered with Al-foil to protect it from the adverse effects of visible light. Thereafter, to a stirred rt solution of the iodovinylic alcohol 18 (3.55 g, 7.47 mmol) in dry CH₂Cl₂ (74.7 mL) under N₂ was successively added powdered 4 Å molecular sieves (flame dried,

3.60 g), *N*-methylmorpholine-*N*-oxide (NMO, 1.75 g, 14.93 mmol, 2 equiv.) and tetrapropylammonium perruthenate¹⁹ (TPAP, n-Pr₄NRuO₄, 0.13 g, 0.37 mmol, 0.05 equiv.), each in one portion. Stirring was continued at rt for 15 min. The reaction mixture was then filtered to remove the sieves, the filtrate was concentrated *in vacuo*, and the resulting crude residue was purified by SiO₂ flash chromatography with 40:1 petrol: EtOAc as the eluent. Following purification, aldehyde **20** (2.10 g, 59%) was obtained as a C5-epimeric mixture (ca. 3:1) as an amber oil.

Data for **20** (*ca.* 3:1 mixture of isomers of tentatively assigned stereochemistry at C5): IR of the **20** mixture (neat film): 3393 (w), 2959 (s), 2929 (s), 2856 (s), 2806 (w), 1701 (s), 1615 (s), 1524 (s), 1461 (m), 1388 (s), 1355 (m), 1251 (m), 1186 (w), 1168 (m), 1080 (s), 1027 (m), 1007 (m), 944 (w), 858 (m), 838 (m), 780 (m) cm⁻¹.

¹H NMR of **20** (minor isomer 1 – *anti*) (399.9 MHz, CDCl₃): δ 8.64 (s, 1H, H1), 7.10 (d, J = 8.4 Hz, 2H, H7), 7.09 (d, J = 9.2 Hz, 1H, H3), 6.66 (d, J = 8.4 Hz, 2H, H8), 4.61 (d, 1H, J = 6.0 Hz, H5), 3.18 (m, 1H, H4), 2.94 (s, 6H, N(CH₃)₂), 1.02 (d, J = 6.8 Hz, 3H, C4-Me), 0.86 (s, 9H, t-Bu of OTBS), 0.028 (s, 3H, CH₃Si), -0.20 (s, 3H, CH₃Si) ppm. ¹³C NMR of **20** (minor isomer 1 – *anti*) (100.57 MHz, CDCl₃): δ 188.1 (C1), 165.3 (C3), 150.0 (C9), 130.1 (C6), 127.33 (C7), 112.0 (C8), 111.3 (C2), 77.6 (C5), 50.2 (C4), 40.5 (N(CH₃)₂), 25.79 ((CH₃)₃CSi), 18.1 ((CH₃)₃CSi), 15.2 (C4-Me), -4.5 (CH₃Si), -5.1 (CH₃Si) ppm.

¹H NMR of **20** (major isomer 2 – *syn*) (399.9 MHz, CDCl₃): δ 8.59 (s, 1H, H1), 7.16 (d, J = 8.4 Hz, 2H, H7), 7.05 (d, J = 9.6 Hz, 1H, H1), 6.68 (d, J = 8.4 Hz, 2H, H8), 4.73 (d, 1H, J = 4.4 Hz, H5), 3.12 (m, 1H, H4), 2.95 (s, 6H, N(CH₃)₂), 1.07 (d, J = 6.8 Hz, 3H, C4-Me), 0.90 (s, 9H, t-Bu of OTBS), -0.012 (s, 3H, CH₃Si), -0.17 (s, 3H, CH₃Si) ppm. ¹³C NMR of **20** (major isomer 2) (100.57 MHz, CDCl₃): δ 188.09 (C1), 165.3 (C3), 149.9 (C9), 129.8 (C6), 127.29 (C7), 111.9 (C8), 110.4 (C2), 76.4 (C5), 49.7 (C4), 40.5 (N(CH₃)₂), 25.84 ((CH₃)₃CSi), 18.2 ((CH₃)₃CSi), 13.3 (C4-Me), -4.5 (CH₃Si), -5.1 (CH₃Si) ppm.

TOF ES⁺ HRMS of **20**: calcd for $C_{20}H_{33}NO_2ISi [M + H]^+$: 474.1325. Found: 474.1317.

Baldwin–Lee Stille cross-coupling of iodo enal 20 to obtain trisubstituted enal 4

A solution of the iodoenal **20** (0.98 g, 2.06 mmol) in dry DMF (4.12 mL) was transferred via a cannula into a Teflon-screw-capped sealed tube temporarily fitted with a rubber septum under N_2 . Me₄Sn (4.29 mL, 30.90 mmol, 15 equiv.), CsF (0.78 g, 5.15 mmol, 2.5 equiv.), CuI (0.10 g, 0.52 mmol, 0.25 equiv.), and (Ph₃P)₄Pd (0.12 g, 0.10 mmol, 0.05 equiv.) were then successively added in that order, and the septum was replaced with the Teflon-screw cap, maintaining the N_2 atmosphere throughout the addition and sealing process. The sealed tube was then covered with Al-foil, placed inside an oil

bath, and heated at 60 °C overnight (18 h) with vigorous magnetic stirring. The reaction mixture was then cooled to rt, carefully opened, and diluted with EtOAc (5 mL) before being fully quenched with H2O (10 mL). The sealed tube was rinsed multiple times with EtOAc (20 mL × 5) and H₂O (20 mL × 3) and the combined reaction washings were filtered through Celite, before being fractionated in a separatory funnel. The aqueous layer was further extracted with EtOAc (50 mL × 3), and the combined organic extracts were washed with H_2O (100 mL × 2), dried over MgSO4, filtered and concentrated under reduced pressure. The crude residue was purified by SiO2 flash chromatography using 45:1 petrol: EtOAc as an eluent to afford 4 (0.59 g, 79%) as a mixture of C5-epimers and as a colourless oil. IR of the 4 mixture (neat film): 3353 (w), 2959 (s), 2932 (s), 2858 (s), 2808 (m), 2707 (w), 1690 (s), 1617 (s), 1524 (s), 1466 (m), 1385 (m), 1355 (m), 1257 (m), 1186 (w), 1072 (m), 1022 (m), 949 (w), 863 (m), 835 (m), 777 (m), 671 (w), 565 (w) cm⁻¹.

Data for 4: ¹H NMR of 4 (*ca.* 3 : 1 mixture of isomers at C5) (isomer 1 – major) (399.9 MHz, CDCl₃): δ 9.40 (s, 1H, H1), 7.09 (d, J = 8.8 Hz, 2H, H7), 6.65 (d, J = 8.8 Hz, 2H, H8), 6.43 (dd, J = 10.0 Hz, 1.2 Hz, 1H, H3), 4.47 (d, 1H, J = 6.0 Hz, H5), 2.93 (br m, 1H, H4) superimposed upon 2.93 (s, 6H, N(CH₃)₂), 1.62 (d, J = 1.2 Hz, 3H, C2-Me), 0.95 (d, J = 6.8 Hz, 3H, C4-Me), 0.84 (s, 9H, t-Bu of OTBS), -0.011 (s, 3H, CH₃Si), -0.23 (s, 3H, CH₃Si) ppm. ¹³C NMR of 4 (isomer 1 – major) (100.57 MHz, CDCl₃): δ 195.6 (C1), 158.0 (C3), 149.9 (C9), 139.1 (C2), 130.9 (C6), 127.3 (C7), 112.0 (C8), 78.6 (C5), 42.9 (C4), 40.55 (N(CH₃)₂), 25.75 ((CH₃)₃CSi), 18.1 ((CH₃)₃CSi), 16.5 (C4-Me), 9.31 (C2-Me), -4.5 (CH₃Si), -5.1 (CH₃Si) ppm.

¹H NMR of 4 (isomer 2 – minor) (399.9 MHz, CDCl₃): δ 9.31 (s, 1H, H1), 7.08 (d, J = 8.8 Hz, 2H, H7), 6.63 (d, J = 8.7 Hz, 2H, H8), 6.30 (dd, J = 10.0 Hz, 1.2 Hz, 1H, H3), 4.50 (d, 1H, J = 5.6 Hz, H5), 2.93 (br m, 1H, H4) superimposed upon 2.93 (s, 6H, N(CH₃)₂), 1.61 (d, J = 1.6 Hz, 3H, C2-Me), 1.07 (d, J = 6.4 Hz, 3H, C4-Me), 0.89 (s, 9H, t-Bu of OTBS), -0.04 (s, 3H, CH₃Si), -0.20 (s, 3H, CH₃Si) ppm. ¹³C NMR of 4 (isomer 2 – minor) (100.57 MHz, CDCl₃): δ 195.6 (C1), 157.4 (C3), 149.8 (C9), 138.5 (C2), 130.6 (C6), 127.3 (C7), 111.8 (C8), 77.8 (C5), 42.6 (C4), 40.53 (N(CH₃)₂), 25.83 ((CH₃)₃CSi), 18.2 ((CH₃)₃CSi), 15.3 (C4-Me), 9.3 (C2-Me), -4.5 (CH₃Si), -5.1 (CH₃Si) ppm.

TOF ES⁺ HRMS of 4: calcd for $C_{21}H_{36}NO_2Si [M + H]^+$: 362.2515. Found: 362.2517.

Wittig olefination of enal 4 to obtain dienoate 3

To a stirred rt solution of the enal 4 (0.5777 g, 1.60 mmol) in dry CH_2Cl_2 (1.6 mL) and PhMe (2 mL) under N_2 was added carbethoxymethylenetriphenylphosphorane (0.835 g, 2.40 mmol, 1.5 equiv.) and the reactants were stirred at 38 °C for 10 d. The reaction mixture was thereafter evaporated to dryness before petrol (5 mL) was added and the resulting mixture was stirred for 2 h. The reaction mixture was filtered

to remove Ph₃P=O and concentrated under reduced pressure. The crude residue was purified by SiO₂ flash chromatography using petrol: EtOAc (50:1) as the eluent to give 3 (0.62 g, 90%) as a colorless oil and mixture of C7-epimers (N.B.: (+)-(R)-trichostatin A numbering is now being used here onwards). IR of the 3 mixture (neat film): 2959 (m), 2934 (m), 2856 (m), 1721 (m), 1620 (s), 1521 (m), 1458 (m), 1388 (s), 1310 (w), 1259 (w), 1168 (m), 1097 (w), 1070 (w), 1029 (w), 871 (w), 780 (w) cm⁻¹.

¹H NMR of 3 (isomer 1 – minor) (399.9 MHz, CDCl₃): δ 7.32 (dd, J = 15.6, 0.4 Hz, 1H, H2), 7.07 (d, J = 8.8 Hz, 2H, H9), 6.64(d, J = 8.8 Hz, 2H, H10), 5.79 (d, 1H, J = 10.0 Hz, H5), 5.75 (d, 1H, J = 10J = 15.2 Hz, 1H, H3), 4.39 (d, J = 6.0 Hz, 1H, H7), 4.20 (m, J = 6.0 Hz)7.2 Hz, 2H, CH₂ of OEt), 2.93 (s, 6H, N(CH₃)₂), 2.76 (m, 1H, H6), 1.64 (d, J = 1.2 Hz, 3H, C4-Me), 1.30 (t, J = 7.2 Hz, 3H, Me of OEt), 0.87 (d, C6-Me) 0.83 (s, 9H, t-Bu of OTBS), -0.03 (s, 3H, CH₃Si), -0.23 (s, 3H, CH₃Si) ppm. ¹³C NMR of 3 (isomer 1 – minor) (100.57 MHz, CDCl₃): δ 167.8 (C1), 150.0 (C2), 149.8 (C11), 145.4 (C5), 132.6 (C4), 131.6 (C8), 127.5 (C9), 115.4 (C3), 111.94 (C10), 78.8 (C7), 60.1 (CH₂ of OEt), 42.4 (C6), 40.6 $(N(CH_3)_2)$, 25.8 $((CH_3)_3CSi)$, 18.1 $((CH_3)_3CSi)$, 16.9 (C6-Me), 14.3 (Me of OEt), 12.4 (C4-Me), -4.6 (CH₃Si), -5.1 (CH₃Si) ppm.

¹H NMR of 3 (isomer 2 – major) (399.9 MHz, CDCl₃): δ 7.23 (d, J = 15.6, 0.4 Hz, 1H, H2), 7.06 (d, J = 8.8 Hz, 2H, H9), 6.63 $(d, J = 8.4 \text{ Hz}, 2H, H10), 5.71 (d, J = 15.6 \text{ Hz}, 1H, H3), 5.70 (d, J = 15.6 \text$ 1H, J = 10.0 Hz, H5), 4.41 (d, J = 6.0 Hz, 1H, H7), 4.20 (m, J =7.2 Hz, 2H, CH₂ of OEt), 2.92 (s, 6H, N(CH₃)₂), 2.76 (m, 1H, H6), 1.60 (d, J = 1.2 Hz, 3H, C4-Me), 1.29 (t, J = 7.2 Hz, 3H, Me of OEt), 1.00 (d, J = 6.8 Hz, 3H, C6-Me), 0.88 (s, 9H, t-Bu of OTBS), -0.015 (s, 3H, CH₃Si), -0.22 (s, 3H, CH₃Si) ppm. ¹³C NMR of 3 (isomer 2 - major) (100.57 MHz, CDCl₃): δ 167.7 (C1), 149.9 (C2), 149.7 (C11), 145.0 (C5), 132.1 (C4), 131.4 (C8), 127.4 (C9), 115.5 (C3), 111.9 (C10), 78.3 (C7), 60.1 (CH₂ of OEt), 42.4 (C6), 40.6 (N(CH₃)₂), 25.9 ((CH₃)₃CSi), 18.2 $((CH_3)_3CSi)$, 15.9 (C6-Me), 14.3 (Me of OEt), 12.3 (C4-Me), -4.5 (CH_3Si) , -5.1 (CH_3Si) ppm.

TOF ES⁺ HRMS of 3: calcd for $C_{25}H_{42}NO_3Si$ [M + H]⁺: 432.2934. Found: 432.2942.

Preparation of 7-OTBS trichostatic acid 21

To a stirred rt solution of ester 3 (1.06 g, 2.46 mmol) in THF/ H₂O/MeOH (2 mL: 2 mL) was added LiOH monohydrate (0.41 g, 9.82 mmol, 4 equiv.) and the mixture was thereafter allowed to stir vigorously for 48 h. The reaction mixture was then diluted with EtOAc (10 mL) and acidified with 10% aq. HCl until pH 5 was attained. The aqueous layer was extracted with EtOAc (20 mL \times 3). The combined organic layer was washed with H₂O (50 mL × 2), dried over MgSO₄, filtered and concentrated under reduced pressure. The crude mixture was purified by gradient elution SiO₂ flash chromatography with $6:1 \rightarrow 4:1$ petrol: EtOAc as an eluent to obtain 21 (0.97 g, 98%) as a colourless oil.

Data for 21 (for a 3:1 mixture of C7-epimers): IR of the 21 mixture (neat film): 3376 (extremely br), 2959 (s), 2932 (s), 2858 (m), 2806 (w), 1688 (s), 1617 (s), 1524 (s), 1468 (m), 1383 (m), 1282 (m), 1254 (m), 1209 (w), 1072 (s), 1029 (m), 987 (w), 871 (s), 777 (m) cm⁻¹.

¹H NMR of **21** (isomer 1 – minor) (399.9 MHz, CDCl₃): δ 10.58 (very br, 1H, -CO₂H), 7.41 (d, J = 15.6 Hz, 1H, H2), 7.08 (d, 2H, H9), 6.65 (d, 2H, H10), 5.86 (d, 1H, J = 9.6 Hz, H5), 5.72 (d, J = 15.6 Hz, 1H, H3), 4.40 (d, J = 6.0 Hz, 1H, H7), 2.93 (s, H)6H, N(CH₃)₂), 2.78 (m, 1H, H6), 1.66 (s, 3H, C4-Me), 0.89 (d, 3H, C6-Me obscured by a large singlet for t-Bu for the major isomer of 21), 0.84 (s, 9H, t-Bu of OTBS), -0.02 (s, 3H, CH₃Si), -0.23 (s, 3H, CH₃Si) ppm. ¹³C NMR of 21 (isomer 1 - minor) (100.57 MHz, CDCl₃): δ 172.9 (C1), 152.3 (C2), 149.8 (C11), 146.8 (C5), 132.7 (C4), 131.6 (C8), 127.5 (C9), 114.5 (C3), 112.0 (C10), 78.8 (C7), 42.6 (C6), 40.7 (N(CH₃)₂), 25.8 ((CH₃)₃CSi), 18.1 ((CH₃)₃CSi), 16.9 (C6-Me), 12.4 (C4-Me), -4.6 (CH₃Si), -5.1 (CH₃Si) ppm.

¹H NMR of **21** (isomer 2 - major) (399.9 MHz, CDCl₃): δ 10.58 (very br, 1H, -CO₂H), 7.32 (d, J = 15.6 Hz, 1H, H2), 7.07 $(d, J = 8.4 \text{ Hz}, 2H, H9), 6.65 (d, J = 8.4 \text{ Hz}, 2H, H10), 5.76 (d, J = 8.4 \text{$ 1H, J = 10.4 Hz, H5), 5.71 (d, J = 15.6 Hz, 1H, H3), 4.43 (d, J = 15.6 Hz, 1H2), 4.43 (d, J = 15.6 Hz, 1H2), 4.43 (d, J =6.0 Hz, 1H, H7), 2.93 (s, 6H, N(CH₃)₂), 2.78 (m, 1H, H6), 1.62 (s, 3H, C4-Me), 1.01 (d, J = 6.8 Hz, 3H, C6-Me), 0.89 (s, 9H, SiC $(CH_3)_3$, -0.01 (s, 3H, CH_3 Si), -0.21 (s, 3H, CH_3 Si) ppm. ¹³C NMR of 21 (isomer 2 – major) (100.57 MHz, CDCl₃): δ 172.8 (C=O), 152.2 (C2), 149.7 (C11), 146.4 (C5), 132.2 (C4), 131.4 (C8), 127.4 (C9), 114.7 (C3), 112.0 (C10), 78.2 (C7), 42.5 (C6), 40.7 (N(CH₃)₂), 25.9 ((CH₃)₃CSi), 18.2 ((CH₃)₃CSi), 15.8 (C6-Me), 12.3 (C4-Me), -4.5 (CH₃Si), -5.1 (CH₃Si) ppm.

TOF ES⁺ HRMS of 21: calcd for C₂₃H₃₈NO₃Si [M + H]⁺: 404.2621. Found: 404.2613.

Conversion of 7-OTBS trichostatic acid 21 into (+)-(R)trichostatic acid (22)

To a stirred 0 °C solution of 7-OTBS trichostatic acid 21 (0.61 g, 1.51 mmol) in CH_2Cl_2/H_2O (20:1) (9.88 mL; made up)from 9.41 mL CH₂Cl₂: 0.47 mL H₂O) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 0.51 g, 2.26 mmol, 1.5 equiv.) in one portion and the cold reaction mixture was vigorously stirred for just 7 min (important note: stirring for longer than this time caused significant decomposition). The reaction mixture was then diluted with CH2Cl2 (10 mL) and quenched with H2O (10 mL). The aqueous layer was extracted with CH₂Cl₂ (50 mL × 3). The combined organic extracts were washed with H₂O multiple times (50 mL × 8), dried over MgSO₄, filtered and concentrated under reduced pressure. The crude mixture was purified by gradient elution SiO2 flash chromatography with petrol: EtOAc $(1:1 \rightarrow 1:2)$ as an eluent with 21 (0.31 g, 71%) being obtained as an amber oil.

Data for 22: $[\alpha]_D$ = +150.7° (c 0.416, CH₂Cl₂), mp 89–90 °C [literature mp¹⁷ 88-89 °C].

IR of 22 (neat film): 3600-2300 (extremely br), 2980 (m), 2932 (m), 2874 (m), 2669 (w), 2596 (w), 1685 (s), 1597 (s), 1552 (m), 1438 (m), 1380 (s), 1272 (m), 1244 (m), 1191 (m), 1171 (m), 1004 (w), 979 (w), 858 (w), 828 (w), 737 (m) cm⁻¹.

¹H NMR of pure 22 (400.11 MHz, CDCl₃): δ 7.84 (d, J = 9.2 Hz, 2H, H9), 7.36 (d, J = 15.6 Hz, 1H, H2), 6.64 (d, J =9.2 Hz, 2H, H10), 6.06 (d, J = 9.6 Hz, 1H, H5), 5.85 (d, 1H, J =15.6 Hz, H3), 4.38 (m, 1H, H6), 3.05 (s, 6H, N(CH₃)₂), 1.92 (d, J = 1.2 Hz, 3H, C4-Me), 1.31 (d, J = 6.8 Hz, 3H, C6-Me) ppm. ¹³C NMR of 22 (100.57 MHz, CDCl₃): δ 198.3 (C7), 171.7 (C1), 153.5 (C11), 151.4 (C2), 143.0 (C5), 132.6 (C4), 130.6 (C9), 123.9 (C8), 115.7 (C3), 110.8 (C10), 40.9 (C6), 40.0 (N(CH₃)₂), 17.7 (C6-Me), 12.5 (C4-Me) ppm.

TOF ES⁺ HRMS of 22: calcd for $C_{17}H_{22}NO_3$ [M + H]⁺: 288.1600. Found: 288.1584.

Conversion of (+)-(6R)-trichostatic acid (22) into (+)-(6R)trichostatin A (1a)

Following Helquist's procedure, 17e a stirred 0 °C solution of (+)-(6R)-trichostatic acid 22 (56.2 mg, 0.195 mmol) in dry THF (1 mL) under N2 was treated with freshly distilled dry Et3N (0.03 mL, 0.23 mmol, 1.2 equiv.) followed by dropwise addition of ethyl chloroformate (0.04 mL, 0.40 mmol, 2 equiv.). The reactants were allowed to stir at 0 °C for 2 h, whereafter a solution of TBSONH₂ (57.6 mg, 0.39 mmol, 1.95 equiv.) in dry THF (0.5 mL) was added via a microcannula. The reaction mixture was stirred at 0 °C for 0.5 h and then warmed to rt for 1.5 h. It was then diluted with EtOAc (1 mL) and quenched with H2O (1 mL). The aqueous layer was extracted with EtOAc (10 mL × 3). The organic layer was washed with H_2O (10 mL \times 2), dried over MgSO₄, filtered and concentrated under reduced pressure and the crude residue of 24 was used directly without further purification.

To a stirred rt solution of the aforementioned TBS-protected crude trichostatin A 24 in dry MeOH (2 mL) under N2 was added solid CsF (35.6 mg, 0.23 mmol, 1.2 equiv.) (pre-dried at 120 °C under high vacuum for 2 h), and the reactants were allowed to stir for 1 h. The reaction mixture was then diluted with CH₂Cl₂ (5 mL) and washed with H₂O (2 mL). The aqueous layer was then further extracted with CH_2Cl_2 (10 mL × 5). The combined organic extracts were washed with H_2O (20 mL × 1), dried over MgSO₄, filtered and concentrated under reduced pressure. The crude mixture was purified by gradient elution SiO_2 flash chromatography with $CH_2Cl_2/MeOH$ (25:1 \rightarrow 20:1) to obtain (+)-(R)-trichostatin A (1a) (35 mg, 59% over 2 steps) as a white solid.

Data for (R)-(+)-trichostatin A (1a): $[\alpha]_D = +88.8^\circ$ (c 0.26, MeOH), mp 140-143 °C [lit.¹⁷ 140-143 °C]. IR of (+)-TSA (1a) (neat film): 3234 (br, s), 2927 (s), 2853 (s), 1650 (m), 1595 (s), 1547 (m), 1383 (s), 1249 (m), 1189 (s), 1059 (m), 976 (m) cm⁻¹.

¹H NMR of (+)-TSA (1a) (600.13 MHz, CD₃OD): δ 7.87 (d, J = 9.0 Hz, 2H, H9), 7.18 (d, I = 15.0 Hz, 1H, H2), 6.72 (d, I = 19.6 Hz, 2H, H10), 5.91 (d, J = 9.6 Hz, 1H, H5), 5.87 (d, 1H, J = 15.6 Hz, H3), 4.53 (dq, J = 9.0, 6.6 Hz, 1H, H6), 3.06 (s, 6H, $N(CH_3)_2$), 1.92 (s, 3H, C4-Me), 1.27 (d, J = 6.6 Hz, 3H, C6-Me) ppm.

¹³C NMR of (+)-TSA (1a) (150.92 MHz, CD₃OD): δ 201.4 (C7), 166.8 (C1), 155.5 (C11), 145.9 (C2), 141.3 (C5), 134.3 (C8), 131.9 (C9), 124.7 (C4), 117.1 (C3), 111.9 (C10), 41.7 (C6), 40.1 (N(CH₃)₂), 18.3 (C6-Me), 12.7 (C4-Me) ppm.

TOF ES⁺ HRMS of (+)-TSA (1a): [M + H]⁺ calcd for C₁₇H₂₃N₂O₃: 303.171. Found: 303.177.

Data availability

All data supporting this article are included in the ESI.‡

Conflicts of interest

There are no conflicts to declare.

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- 21 A reviewer of our paper has requested that we briefly compare our new synthetic route with the other total syntheses of trichostatin A that are listed in ref. 17. We will duly do this here. (a) The first total synthesis of (\pm) -trichostatin A to be achieved was that of Fleming and coworkers in 1983. It provided the natural product in racemic form in 5 steps (ref. 17a), but according to Mori and Koseki (ref. 17b), its final KOH/NH2OH-mediated ester N-hydroxyammonolysis step cannot be used to secure biologicallyactive (+)-trichostatin A; (b) Although Mori and Koseki's later synthesis of (+)-trichostatin A (1a) (ref. 17b) did deliver the natural product in \geq 98% ee from (R)-(-)-3-hydroxy-2methyl-propionate, it did require 18 steps to be implemented overall, and it had a longest linear sequence of 16 steps. While Mori's synthesis was perfectly stereocontrolled, with respect to installation of the (6R)-stereocentre and the C(2)-C(5)-dienoate array, it did encounter low yields during its final stages; its penultimate steps 14 and 15 proceeded with a combined yield of 11%; (c) Helquist later published three synthetic routes to (±)-trichostatin A (ref. 17d, e and g), one of which (ref. 17e) was subsequently rendered enantioselective. The latter route required 17 steps to be implemented overall, when the more reliable and higher yielding 7-step (S)-ethyl lactate pathway was used to access its key (S)-3-butyn-2-yl O-mesylate starting material. Importantly, Helquist's asymmetric route to 1a had a longest linear sequence of 10 steps, and its yields were largely good throughout. It was also fully stereocontrolled with regard to installation of the C(6)-Me group and

the C(2)-C(5)-dienyl array. It did, however, produce (+)-(R)trichostatin A (1a) in only 81% ee; (d) Contrastingly, our new O-directed hydrostannylative route to (+)-trichostatin A proceeds in 18 steps overall (which is one step more than Helquist's), and it has a longest linear sequence of 12 steps. It also proceeds with a maximal overall yield of 8%. However, most critically, it does provide (+)-(R)-trichostatin A in >98% ee, as evidenced by our conversion of 1a to (+)-trichostatin C, without the accompanying formation of the C(6)-(S)- β -glycoside diastereoisomer. Importantly, our prior derivatisation of 15 to obtain 25 (see ESI) also confirmed that 15 was of \geq 98% ee; (e) Although Wang's 2006 report (ref. 17c) did describe a 10 step L-proline-catalysed aldol route to (+)-(R)-trichostatin A, which delivered a material of ≥99% ee in an apparently good overall yield (17.4%), its final benzylic alcohol oxidation step had to be conducted with just 0.59 equiv. of DDQ in dioxane. Presumably this was done to minimise or prevent competing N-oxidation of the hydroxamic acid unit to give a highly reactive N-acyl-nitroso intermediate, which would almost certainly self-condense, if generated. We note here that the ref. 17c team were unable to recover any of their unreacted starting hydroxamic acid amide precursor from this DDQ

- oxidation, which proceeded with 49% yield for these last two steps. Contrastingly, each of the other enantioselective routes to (+)-trichostatin A have utilised an O-alkoxy/siloxyamine coupling strategy with a mixed anhydride derived from (+)-trichostatic acid to install the hydroxamic acid motif of the natural product.
- (a) For a recent outstanding review on alkyne hydrometallation with Group IV metal hydrides, see the following book chapter by: T. Wiesner and M. Haas, Reference Module in Chemistry, Molecular Sciences and Chemical Engineering, Elsevier, 2024, DOI: 10.1016/B978-0-323-96025-0.00125-3 (b) For McLaughlin and Roberts' 2023 report on the highly regiocontrolled PtCl2/XPhos-catalysed hydrostannation of terminal aryl acetylenes and propargylic alcohols, see: D. D. Roberts and M. G. McLaughlin, Adv. Synth. Catal., 2023, 365, 1602. This paper lists much valuable new metalcatalysed hydrostannation literature that has recently appeared; (c) For McLaughlin's landmark application of the PtCl₂/XPhos/Et₃SiH-catalyst system to mediate an analogous highly regiocontrolled hydroboration of terminal alkyl, aryl and heteroaryl acetylenes with HBPin, see: K. L. E. Hale, D. D. Roberts and M. G. McLaughlin, Eur. J. Org. Chem., 2025, e202401355.