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Total Synthesis of the Proposed Structure of Trichodermatide A

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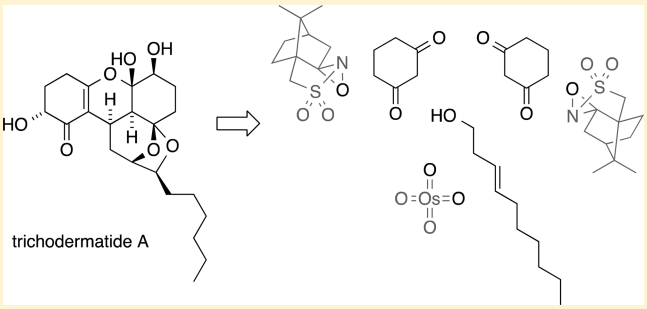
Supporting Information

ABSTRACT: A short total synthesis of the published structure of racemic trichodermatide A is reported. Our synthesis involves a Knoevenagel condensation/Michael addition sequence, followed by the formation of tricyclic hexahydroxanthene-dione and a diastereoselective bis-hydroxylation. The final product, the structure of which was confirmed by X-ray crystallography, has NMR spectra that are very similar, but not identical, to those of the isolated natural product. Quantum chemically computed ^{13}C shifts agree well with the present NMR measurements.



The trichodermatides are a family of natural products with unusual features that have attracted considerable attention in the chemical community (Figure 1). Isolated

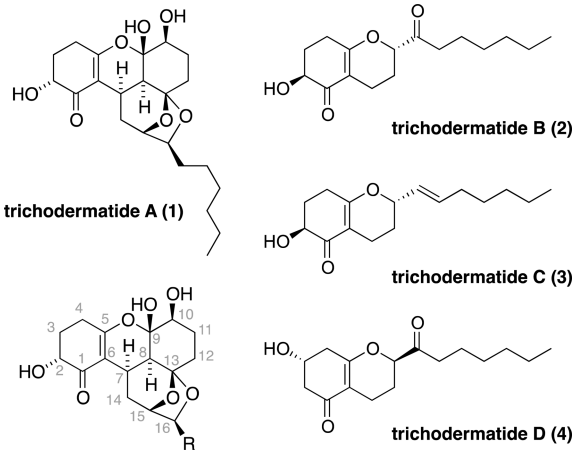
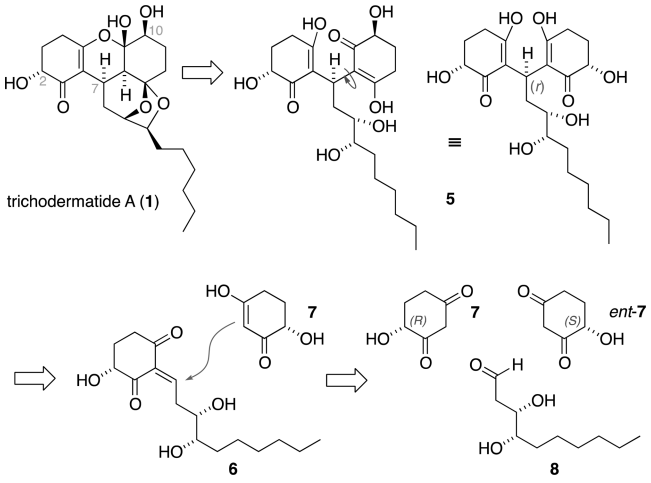


Figure 1. Proposed structures of the trichodermatides.

from the marine-derived fungus *Trichoderma reesei* by Pei and co-workers, these compounds have shown a variety of interesting bioactivities.[1] Trichodermatide A, whose relative and absolute configuration was elucidated using a combination of NMR spectroscopy and CD measurements, has a particularly interesting structure featuring a pentacyclic ring system with eight stereocenters. Hiroya and co-workers have recently reported its first total synthesis.[2]

The highly unusual carbon skeleton and the intricate stereochemical features of trichodermatide A are best revealed through a retrosynthetic analysis (Scheme 1). Hydrolysis of

Scheme 1. Retrosynthetic Analysis of Trichodermatide A



the acetal and cleavage of the hemiacetal affords alkylidene-bis-1,3-cyclohexanedione derivative **5**, shown here in its enolized form and as two conformers. The conformer on the right side emphasizes that C7 (trichodermatide numbering) is a pseudo-asymmetric center. Dissection of **5** via a retro-Michael reaction (→6), and then a retro-Knoevenagel condensation, affords two 6-hydroxy-cyclohexane-1,3-diones of opposite absolute configurations, **7** and *ent*-**7**, and chiral dihydroxy aldehyde **8**.

In the forward direction, the formation of alkylidene-bis-1,3-diones from aldehydes and 1,3-diones via Knoevenagel

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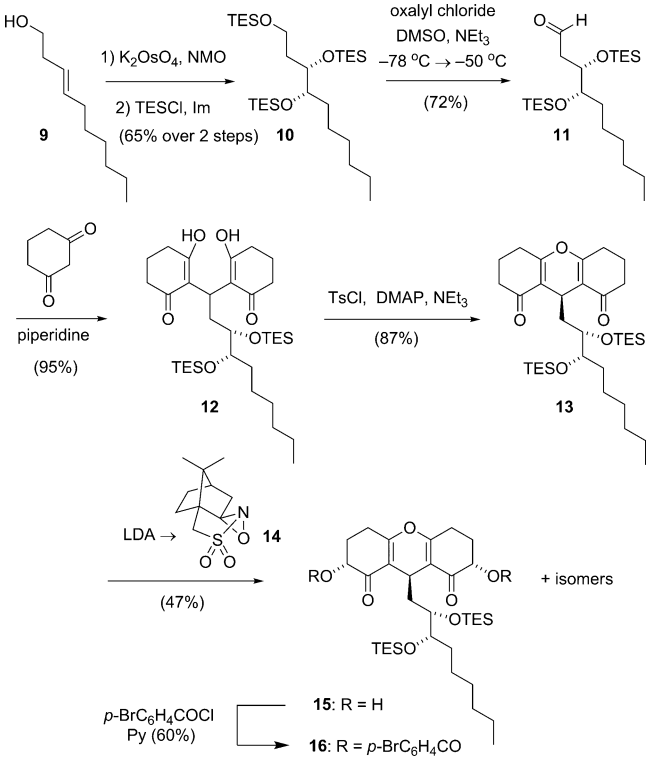
condensation and Michael addition is a well-documented process.[3] However, we deemed it unlikely that such a reaction would proceed cleanly with a racemate of 4-hydroxycyclohexane-1,3-dione **7** or a protected derivative thereof. We, therefore, decided to simplify the synthetic plan by introducing the two hydroxy groups at C2 and C10 (trichodermatide A numbering) at a later stage. It was hoped that, by trapping the two cyclohexane-1,3-dione moieties in a stiff polycyclic form, we would be able to carry out a 2-fold hydroxylation with a high degree of diastereoselectivity.

Our synthesis of racemic trichodermatide A started with the dihydroxylation[4] of known (*E*)-3-decen-1-ol **9** (Scheme 2).[5]

Scheme 2. Synthesis of Hexahydroxanthene-dione 15



Triple silylation of the resultant racemic triol using triethyl chlorosilane gave **10**, which could be selectively deprotected and oxidized under Swern conditions.[6] This gave aldehyde **11** contaminated with 10−15% of the silyl ether **10**, from which it could not be separated. However, this impurity did not interfere in the subsequent Knoevenagel condensation/Michael addition sequence using 1,3-cyclohexadione, which afforded alkylidene-bis-cyclohexane-1,3-dione **12** in excellent yield. Optimized conditions for this transformation included the use of piperidine as a catalyst and the presence of an excess amount of 1,3-cyclohexadione.

With **12** in hand, dehydrative cyclization to the vinylogous anhydride **13** was investigated. This cyclization was effected cleanly when a slight excess of tosyl chloride in methylene chloride was added dropwise to a solution of **12**, in the presence of a base (NEt_3) and a catalytic amount of DMAP. Generation of the bis-lithium enolate and subsequent addition of Davis' (+)-(camphorsulfonyl)oxaziridine[7] **14** resulted in 2-fold hydroxylation, yielding the desired compound **15** as the major diastereomer. This result indicated that hexahydroxanthene-dione **13** with its bulky side chain exerts a considerable degree of substrate control, overwhelming the reagent control of enantiomerically pure oxaziridine **14**. The structure of **15** was unequivocally confirmed by conversion into its bis-bromobenzoate **16** and single-crystal X-ray analysis.[8] The attractive "scorpion-like" structure of **16** in the solid state is shown in Figure 2.

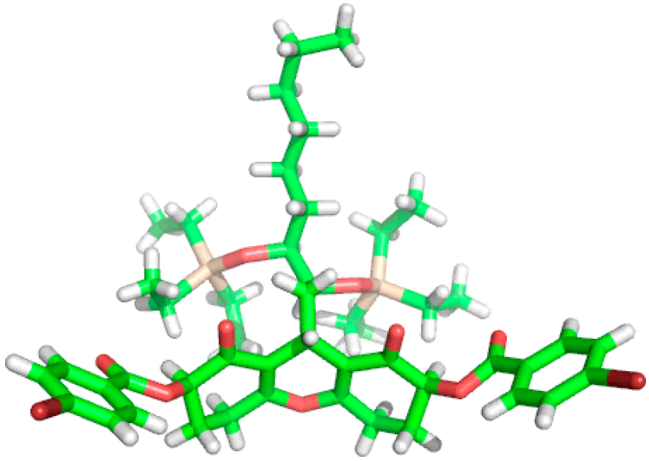
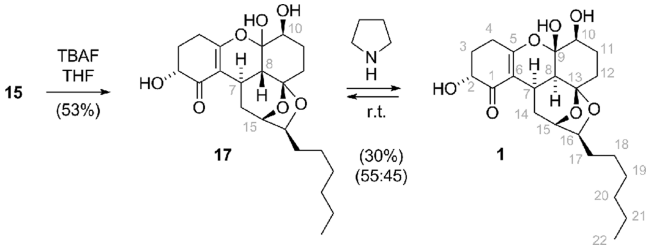


Figure 2. X-ray structure of **16**.

With ample amounts of **15** in hand, we studied its desilylation and isomerization to trichodermatide A. The latter seemingly only requires hydrolysis, followed by diastereotopos-selective acetal formation and diastereoselective hemiacetal formation. We anticipated that both of these operations could be carried out under thermodynamic control.

When a solution of **15** in THF was treated with an excess amount of TBAF (10 equiv) and the mixture was allowed to stir overnight at room temperature, conversion to a more polar compound was observed. To our surprise, this compound, which was isolated as an oil, turned out to be 8-*epi*-trichodermatide **17** (Scheme 3). The *trans* relationship between protons at C7 and C8 was evident from the large coupling constant found in the ^{1}H NMR spectrum.

Scheme 3. Synthesis of 1, the Proposed Structure of Trichodermatide A



Convinced that trichodermatide A represents a thermodynamic minimum, we next investigated the isomerization of **17** to the desired target compound. Several ways in which this could be achieved can be imagined, including retro-Michael/Michael addition and cycloreversion/cycloaddition. In the event, we found that stirring a solution of **17** in CH_2Cl_2 in the presence of excess pyrrolidine at room temperature overnight gave a 55:45 mixture of the starting material **17** and a new isomer (Scheme 3).[9] This isomer was isolated as a

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white solid, facilitating its purification and structure elucidation.

Intriguingly, the NMR spectra of this new isomer closely, but not fully, matched the spectra of enantiomerically pure **1** reported by Pei and co-workers.[1] The most remarkable difference was found for the signals at C8, the ^{13}C signal of which was found to resonate at 42.2 ppm instead of the reported value of 38.1 ppm (150 MHz, d_6-DMSO). The proton at C8 is also shifted from 1.60 to 1.94 ppm (600 MHz, d_6-DMSO). The analysis of 2D-NMR spectra measured in d_6-DMSO was confounded by extensive signal overlap, but 2D-NMR in CD_3Cl showed the same key NOESY correlations between H7 and H8, H16 and H7, H8 and H10, and OH9 and H11, as reported by Pei and co-workers.[1] HMBC correlations between OH9 and C8, OH9 and C9, and H2 and C1 were also found. The identity of our compound with the reported structure of trichodermatide A (**1**) was firmly established using single-crystal X-ray analysis.[10] The structure of racemic **1** in the solid state is shown in Figure 3.

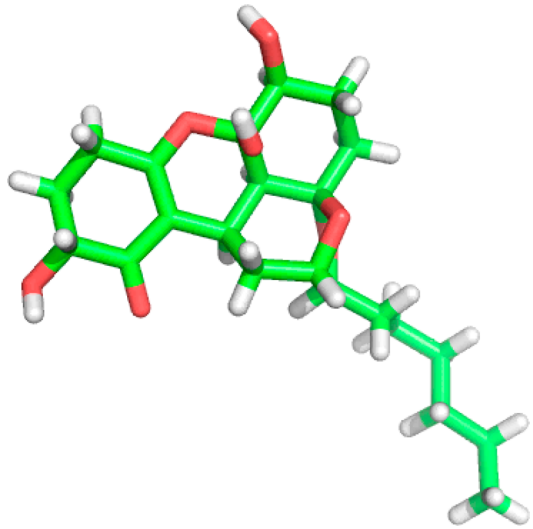

Figure 3. X-ray structure of **1**.

The batch of crystals with similar morphology from which the single crystal for analysis was picked was redissolved and subjected to NMR spectroscopy. The spectra thus obtained were identical to those previously recorded.

Since the NMR spectra of our racemic material do not fully match the spectra reported for trichodermatide A, the question arises whether the real natural product could be a closely related isomer of **1**. Indeed, several stereoisomers of **1** and constitutional isomers involving different acetals can be imagined. This number is even larger, when one takes the possibility into account that the α-hydroxy ketone moieties epimerize. In principle, all stereocenters in trichodermatide A, with the exception of C15 and C16, could epimerize under relatively mild conditions.

To explore this possibility, we calculated the relative stability and NMR spectra of 13 possible stereoisomers with their alkyl side chain at C17 truncated to a methyl group (see the Supporting Information).[11] According to our quantum-chemical calculations, the published structure of trichodermatide A indeed represents the lowest energy isomer of the series by about 0.7 kcal/mol (results from the B3LYP/6-31G(d) and RI-MP2/SVP calculations; see the Supporting Information for details). The ^{13}C NMR chemical shifts of the different isomers were calculated at the MP2/SVP level of theory, with the structures reoptimized using the RI-MP2/SVP level of theory. In addition, calculations of ^{13}C NMR shifts were carried out at the MP2/TZVP (frag) + HF/TZVP(full)-HF/TZVP(frag) level of theory starting from the measured X-ray structure.[12−15] Here, the intermediate reference method[16] was utilized in the calculation of the NMR shieldings. All NMR computations employ gauge-including atomic orbitals (GIAO).[17] Basis sets as large as def2-TZVP need to be used for the NMR calculations. Furthermore, ^{13}C shifts were computed for optimized structures in the absence of solvent and including three explicit DMSO solvent molecules.

Computed shifts for the reported structure of trichodermatide A were compared both to our experimental NMR data (obtained from **1**) and to the one reported by Pei and co-workers.[1] The agreement of theoretical vs experimental shifts was better for our data set. The standard deviation (STD) was found to be 1.6 ppm, in contrast to a STD of 2.8 ppm for isolated trichodermatide. The inclusion of three DMSO molecules lowers the standard deviation of the computed carbon shifts with respect to present NMR measurements by roughly 0.4 ppm, within the intermediate reference method, with both the SVP and def2-TZVP basis set. With respect to C8, where the mismatch between reported and synthesized results was more evident, the computed shift was found to be in good agreement with our experimental value (41.8 ppm vs 42.2 ppm). Unfortunately, comparison of the calculated spectra of the other 12 isomers with the reported spectra of the natural product was inconclusive and did not allow for structural reassignment. Direct comparison of our synthetic material with the natural product was also impossible due to the unavailability of a sample from the isolation group.

In summary, we have synthesized the proposed structure of trichodermatide A (**1**) as a racemate and confirmed its identity by X-ray crystallography. While our NMR spectra came close, they did not fully match the published spectra. A sample of the natural product for direct comparison was not available. The recently reported total synthesis of trichodermatide A by Hiroya et al.[2] does not represent structural proof, since epimerizations similar to the one in Scheme 3 could have happened under their conditions as well. Interestingly, the proposed structures of the simpler congeners trichodermatides B (**2**) and C (**3**) have been recently synthesized by Hsung and co-workers,[18] and the spectra of the synthetic, racemic compounds were found to be in disagreement with the published ones as well. According to our work, it is possible that natural trichodermatide A is also an isomer of compound **1**, but we cannot confidently say which one it is.

■ EXPERIMENTAL SECTION

All reactions were carried out under an inert N_2 atmosphere in oven-dried glassware. Flash column chromatography was performed using the analytical grade solvents indicated and silica gel (40−63 μm, 60 Å) as the stationary phase. Reactions and chromatography fractions were monitored with Merck silica gel 60 F254 glass plates and visualized using a 254 nm UV lamp and/or by treatment with a suitable dip, followed by heating: potassium permanganate and ceric ammonium molybdate. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. Diisopropylamine was distilled from and stored over CaH_2. *n*-Butyllithium (*n*BuLi) was titrated with diphenylacetic acid prior to use. All other solvents, as well as starting

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materials and reagents, were used without further purification from commercial sources.

Unless otherwise specified, proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded at 18 °C in base-filtered $CDCl_3$ or CD_2Cl_2 on spectrometers operating at 300 Hz, 400 and 600 MHz for proton nuclei (75 MHz, 100 and 150 MHz for carbon nuclei). For ^{1}H NMR spectra, signals arising from residual proton forms of the solvent were used as the internal standards. ^{1}H NMR data are recorded as follows: chemicals shift (δ) [multiplicity, coupling constant(s) J (Hz), relative integral], where multiplicity is defined as s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; br = broad, or combinations of the above. The residual peaks of $CHCl_3$ (δ 7.24 ppm) or CH_2Cl_2 peak (δ 5.32 ppm) were used as reference for ^{1}H NMR spectra (for $CDCl_3$ or CD_2Cl_2, respectively). The central peak (δ 77.16 ppm) of the $CDCl_3$ "triplet" was used as reference for proton-decoupled ^{13}C NMR spectra. Mass spectroscopy (MS) experiments were performed either on an electron ionization (EI) or on an electrospray ionization (ESI) instrument using a time-of-flight analyzer. Infrared (IR) spectra were recorded on an FTIR system equipped with an attenuated total reflection (ATR) measuring unit. Suitable crystals for single-crystal diffractometry were selected by means of a polarization microscope and placed on the tip of a glass fiber. The data collections were performed on four-circle diffractometers at 293 K (**16**) and 173 K (**1**) using MoKα radiation (λ = 0.71073 Å). The structures were solved by direct methods with SIR97[19] and refined by least-squares methods against F^2 with SHELXL-97.[20] In **16**, the disorder of ethyl groups has been described by split models. All nondisordered non-hydrogen atoms were refined anisotropically; all disordered atoms have been refined isotropically. The hydrogen atoms were placed in ideal geometry riding on their parent atoms.

Alcohol 9. Under a nitrogen atmosphere, a solution of commercially available 3-decyn-1-ol (5.17 g, 33.52 mmol) in THF (9 mL) was added to a solution of $LiAlH_4$ (3.78 g, 100.55 mmol) in diglyme (50 mL) and THF (15 mL) at 0 °C. The mixture was heated at reflux for 72 h, then cooled to room temperature, and slowly quenched with water and 10% NaOH. This mixture was then poured into 10% aq. HCl and extracted into hexane. The combined organic layers were washed with water, then brine, dried over $MgSO_4$, and concentrated *in vacuo*. Vacuum distillation (bp 70 °C, 6.5×10^{-1} mbar) provided alkene **9** as a colorless oil (4.12 g, 79%). R_f = 0.57 (hexanes/EtOAc 7:3). The analytical data for **9** matched those provided in the literature.[21]

3,4-*syn*-Decane-1,3,4-triol. NMO (0.56 g, 4.82 mmol) and $K_2OsO_4{\cdot}2H_2O$ (12 mg, 0.032 mmol) were added to a solution of alkene **9** (0.50 g, 3.2 mmol) in acetone/H_2O (1:1, 10 mL). The resulting solution was stirred at room temperature for 12 h. A saturated solution of sodium sulfite (20 mL) was added, and the mixture was allowed to stir for 15 min. CH_2Cl_2 (50 mL) was added, and the layers were separated. The aqueous layer was further extracted with CH_2Cl_2 (50 mL). The combined organic layers were washed with saturated ammonium chloride (50 mL) and brine (50 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude residue was purified by column chromatography (CH_2Cl_2/MeOH 19:1 as eluent) to give the corresponding triol as a clear oil (0.43 g, 71% yield). R_f = 0.38 ($CHCl_3$/MeOH 17:3). The analytical data for 3,4-*syn*-decane-1,3,4-triol matched those given in the literature.[19]

Silyl Ether 10. Imidazole (34.9 g, 512.8 mmol) was added to a 500 mL flask containing a solution of 3,4-*syn*-decane-1,3,4-triol (12.18 g, 64.1 mmol) in 250 mL of DMF. The solution was cooled to 0 °C, and TESCl (64.4 mL, 384.6 mmol) was added dropwise over a period of 10 min. The resulting solution was allowed to warm to room temperature and was stirred for 12 h. The reaction mixture was poured into water (2500 mL), and the resulting aqueous mixture was extracted into diethyl ether (3 × 1000 mL). The combined organic layers were washed with brine (1000 mL), dried over $MgSO_4$, and concentrated under reduced vacuum. The crude residue was purified using silica gel column chromatography (hexanes as eluent) to give the protected triol **10** as a clear oil (31.4 g, 92% yield). The analytical data for **10** are as follows: R_f = 0.33 (hexanes/EtOAc 99:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.77−3.59 (m, 3H), 3.54 (m, 1H), 1.87 (dtd, J(H,H) = 13.5, 8.3, 2.6 Hz, 1H), 1.60 (m, 1H), 1.51−1.38 (m, 2H), 1.34−1.10 (m, 8H), 0.98−0.89 (m, 27H), 0.86 (t, J(H,H) = 7.0 Hz, 3H), 0.62−0.45 ppm (m, 18H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 75.2, 71.6, 60.0, 33.6, 31.8, 30.2, 29.5, 26.6, 22.6, 14.1, 6.92 (3C), 6.86 (3C), 6.7 (3C), 5.15 (3C), 5.07 (3C), 4.4 ppm (3C); HRMS (ESI): m/z calcd for $C_{28}H_{64}O_3Si_3$ + Na^+: 555.4061 [M + Na^+]; found: 555.4055.

Aldehyde 11. Oxalyl chloride (2.61 mL, 30.47 mmol) was added to a 500 mL flask containing 175 mL of dry CH_2Cl_2 under N_2. The solution was cooled to −78 °C, and DMSO (2.76 mL, 39.00 mmol) was added dropwise. The resulting solution was stirred for 15 min at −78 °C. TES-protected triol **10** (12.98 g, 24.37 mmol) was added to the solution dropwise over 30 min. The resulting solution was then allowed to warm slowly to −55 °C and was then stirred at that temperature for approximately 90 min. The solution was then cooled to −78 °C, NEt_3 (16.95 mL, 121.85 mmol) was added slowly over a 5 min period, and the solution was allowed to warm to 0 °C over 1 h. The reaction mixture was poured into sat. aq. $NaHCO_3$ (300 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (150 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced vacuum. The crude residue was purified using silica gel column chromatography (hexanes, then 3% EtOAc in hexanes as eluent) to give 8.14 g of a pale yellow liquid. The ^{1}H NMR spectrum of the material showed that it contained the aldehyde **11** and the TES-protected triol **10** in a molar ratio of 9:1. The material was used directly in the next step. The analytical data for pure sample of **11** are as follows: R_f = 0.30 (hexanes/EtOAc 19:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.76 (dd, J(H,H) = 2.9, 1.9 Hz, 1H), 4.18 (dt, J(H,H) = 8.4, 4.2 Hz, 1H), 3.59 (ddd, J(H,H) = 8.8, 4.5, 2.7 Hz, 1H), 2.65 (ddd, J(H,H) = 15.8, 4.0, 1.9 Hz, 1H), 2.44 (ddd, J(H,H) = 15.8, 8.3, 2.9 Hz, 1H), 1.64 (m, 1H), 1.45 (m, 1H), 1.34−1.13 (m, 8H), 0.96−0.89 (m, 18H), 0.86 (t, J(H,H) = 7.0 Hz, 3H), 0.60−0.52 ppm (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.9, 74.8, 70.5, 45.7, 31.8, 30.3, 29.4, 26.4, 22.6, 14.1, 6.8 (3C), 6.7 (3C), 5.0 (3C), 4.9 (3C); IR (thin film): ν = 2953, 2935, 2913, 2876, 1730, 1458, 1238, 1091, 1003, 720 cm^{-1}; HRMS (ESI): m/z calcd for $C_{22}H_{48}O_3Si_2$ + Na^+: 439.3040 [M + Na^+]; found: 439.3033.

Alkylidene-bis-cyclohexane-1,3-dione 12. Crude aldehyde **11** (17.62 mmol as determined using ^{1}H NMR spectroscopy; contaminated with TES-protected triol **10**) was dissolved in CH_2Cl_2 (250 mL). 1,3-Cyclohexadione (8.77 g, 78.27 mmol) and piperidine (200 mL, 1.96 mmol) were added, and the resulting solution was stirred at room temperature for 48 h. The reaction mixture was concentrated under reduced pressure, and the crude residue was purified directly by silica gel column chromatography (1−5% EtOAc in hexanes, gradient) to give the title compound as a white solid (10.4 g, 95% yield). Analytic data for **12** are as follows: R_f = 0.36 (hexanes/EtOAc 17:3); ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 12.96 (s, 1H), 12.31 (s, 1H), 4.12 (dd, J(H,H) = 10.9, 3.3 Hz, 1H), 3.56 (ddd, J(H,H) = 9.2, 4.3, 2.2 Hz, 1H), 3.42 (ddd, J(H,H) = 10.4, 4.3, 2.2 Hz, 1H), 2.81 (ddd, J(H,H) = 13.6, 11.0, 2.3 Hz, 1H), 2.50−2.38 (m, 4H), 2.34−2.23 (m, 4H), 1.95−1.71 (m, 4H), 1.56 (m, 1H), 1.47 (m, 1H), 1.37 (ddd, J(H,H) = 13.9, 10.4, 3.4 Hz, 1H), 1.32−1.07 (m, 8H), 1.00−0.91 (m, 18H), 0.88 (t, J(H,H) = 7.0 Hz, 3H), 0.62−0.54 ppm (m, 12H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 193.1, 192.5, 191.0, 190.6, 120.0, 117.2, 75.7, 74.2, 34.2, 33.9, 33.6, 33.0, 32.4, 31.4, 30.9, 30.2, 27.3, 25.9, 23.2, 20.5, 20.3, 14.4, 7.4 (3C), 7.3 (3C), 5.8 (3C), 5.7 ppm (3C); IR (thin film): ν = 2951, 2933, 2875, 1578, 1424, 1378, 1194, 1005, 980, 932, 908, 894, 738, 724 cm^{-1}; HRMS (ESI): m/z calcd for $C_{34}H_{62}O_6Si_2$ + Na^+: 645.3983 [M + Na^+]; found: 645.3969.

Vinylogous Anhydride 13. NEt_3 (31.55 mmol, 4.4 mL) and DMAP (0.63 mmol, 77 mg) were added to a solution of bis(1,3-cyclohexadione) compound **12** (6.31 mmol, 3.93 g) in CH_2Cl_2 (150 mL) at room temperature. A solution of TsCl (6.94 mmol, 1.32 g) in CH_2Cl_2 (10 mL) was then added dropwise, and the solution was stirred for 2 h. The reaction mixture was poured into saturated

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aqueous $NaHCO_3$ (100 mL). The organic layer was separated, and the aqueous layer was extracted with another portion of CH_2Cl_2 (150 mL). The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The resulting oil was purified using silica gel column chromatography using 10% EtOAc/Hexanes containing 1% NEt_3 to give the title compound **13** as an oil (3.3 g, 87% yield). The compound was not stable, even when stored at −20 °C and so needs to be consumed within a few days. Analytic data for 13 are as follows: R_f = 0.19 (hexanes/EtOAc 17:3); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.84 (br dd, J(H,H) = 9.0, 2.7 Hz, 1H), 3.58 (ddd, J(H,H) = 9.5, 4.2, 2.0 Hz, 1H), 3.46 (ddd, J(H,H) = 8.8, 4.1, 2.4 Hz, 1H), 2.58−2.20 (m, 8H), 2.05−1.90 (m, 4H), 1.62−1.48 (m, 2H), 1.40−1.10 (m, 10H), 1.02−0.84 (m, 18H), 0.84 (t, J(H,H) = 7.0 Hz, 3H), 0.80−0.47 ppm (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.1, 196.4, 165.3, 165.0, 118.6, 117.9, 75.6, 72.7, 39.1, 37.1, 37.1, 31.4, 30.3, 29.6, 27.4, 27.2, 26.8, 22.6, 21.9, 20.3, 19.9, 14.1, 7.10 (3C), 7.07 (3C), 5.33 (3C), 5.32 ppm (3C); IR (thin film): ν = 2952, 2874, 1672, 1378, 1173, 1130, 1093, 742 cm^{-1}; HRMS (ESI): m/z calcd for $C_{34}H_{60}O_5Si_2$ + Na^+: 627.3877 [M + Na^+]; found: 627.3863.

Diol 15. THF (5 mL) and diisopropylamine (1.19 mmol, 0.167 mL) were added to a 50 mL Schlenk flask under an N_2 atmosphere, and the resulting solution was cooled to 0 °C. 2.5 M *n*BuLi in hexanes (1.19 mmol, 0.47 mL) was added, and the resulting mixture was allowed to stir at 0 °C for approximately 20 min. The solution was then cooled to −78 °C (dry ice/acetone), and the diketone **13** (0.496 mmol, 300 mg) was added dropwise as a solution in THF (1 mL). The mixture was stirred at that temperature for 20 min. A solution of Davis oxaziridine **14** (1.49 mmol, 341 mg) in THF (2 mL) was added dropwise, and once all of it had been added, the flask was removed from the −78 °C cooling bath and placed in an ice bath. After 5 min, the reaction mixture was poured into a flask containing 10 mL of phosphate-buffered H_2O (300 mM, pH 7). CH_2Cl_2 (100 mL), and 100 mL of phosphate-buffered H_2O (300 mM, pH 7) was then added. The organic layer was separated, and the aqueous layer was extracted with another portion of CH_2Cl_2 (100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was then triturated using 10% EtOAc in hexanes (2 × 5 mL), the insoluble oxaziridine byproduct being discarded. The resulting oil was purified by silica gel column chromatography to give the title compound **15** (150 mg, 47% yield). Other fractions contained a mixture of other diastereomers (∼30 mg, ∼10% yield, slightly more polar than title compound) and a mixture of monohydroxylated compounds (∼30 mg, ∼10% yield, which were slightly less polar than the title compound). Analytic data for **15** are as follows: R_f = 0.39 (hexanes/EtOAc 3:2); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 4.07−4.13 ppm (m, 2H), 4.01 (br d, J(H,H) = 8.0 Hz, 1H), 3.82 (d, J(H,H) = 1.8 Hz, 1H), 3.78 (d, J(H,H) = 1.7 Hz, 1H), 3.43−3.47 (m, 2H), 2.68−2.77 (m, 2H), 2.41−2.49 (m, 4H), 1.83−1.93 (m, 2H), 1.76 (ddd, J(H,H) = 14.4, 8.1, 1.6 Hz, 1H), 1.31−1.43 (m, 2H), 1.46 (m, 1H), 1.18−1.28 (m, 6H), 1.04−1.09 (m, 2H), 0.97 (app t, J(H.H) = 8.0 Hz, 6H), 0.90 (app t, J(H,H) = 8.0 Hz, 6H), 0.85 (t, J(H,H) = 7.0 Hz, 3H), 0.43−0.68 (m, 18H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 198.2, 197.4, 164.4, 164.1, 115.3, 114.3, 75.4, 73.0, 71.6, 71.5, 35.4, 31.8, 30.3, 30.2, 29.9, 29.6, 26.8, 26.2, 26.0, 23.6, 22.6, 14.0, 7.04 (3C), 7.00 (3C), 5.4 (3C), 5.3 ppm (3C); IR (thin film): ν = 3480, 2951, 2874, 1671, 1374, 1361, 1170, 1089, 1075, 1003, 723 cm^{-1}; HRMS (ESI): m/z calcd for $C_{34}H_{60}O_7Si_2$ + Na^+: 659.3775 [M + Na^+]; found: 659.3760.

Bis-bromobenzoate 16. NEt_3 (55 mL, 0.392 mmol) and DMAP (2.0 mg, 0.016 mmol) were added to a solution of **15** (50 mg, 0.079 mmol) in CH_2Cl_2 (2 mL). The solution was cooled to 0 °C, and *p*-bromobenzoyl chloride (51 mg, 0.235 mmol) was added in one portion. The resulting solution was allowed to stir at that temperature for 5 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and was poured into sat. aq. $NaHCO_3$ (10 mL), and the layers were separated. The aqueous layer was further extracted with two portions of CH_2Cl_2 (10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified using silica gel column chromatography (hexanes/ethyl acetate 4:1 as eluent) to give the title compound as an oil (47 mg, 60% yield). Analytic data for **16** are as follows: R_f = 0.35 (hexanes/EtOAc 4:1); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.91−7.94 ppm (m, 4H), 7.55−7.59 (m, 4H), 5.56 (dd, J(H,H) = 11.7, 5.1 Hz, 1H), 5.52 (dd, J(H,H) = 11.3, 5.0 Hz, 1H), 4.02 (dd, J(H,H) = 8.0, 3.0 Hz, 1H), 3.41−3.48 (m, 2H), 2.79−2.87 (m, 2H), 2.55−2.63 (m, 2H), 2.39−2.45 (m, 2H), 2.26−2.34 (m, 2H), 1.67 (ddd, J(H,H) = 13.9, 8.8, 1.8 Hz, 1H), 1.50 (m, 1H), 1.42 (ddd, J(H,H) = 13.9, 9.8, 3.0 Hz, 1H), 1.36 (m, 1H), 1.18−1.28 (m, 6H), 1.02−1.10 (m, 2H), 0.90−0.96 (m, 18H), 0.84 (t, J(H,H) = 8.0 Hz, 3H), 0.50−0.68 ppm (m, 12H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 191.1, 190.3, 164.9, 164.8, 164.0, 163.4, 131.7 (4C), 131.4 (2C), 131.4 (2C), 128.7, 128.5, 128.4, 128.3, 117.0, 116.5, 75.5, 72.85, 72.82, 72.4, 36.4, 31.8, 30.2, 29.6, 27.1 (2C), 26.9, 25.8, 25.5, 23.3, 22.6, 14.0, 7.1 (6C), 5.4 (3C), 5.3 ppm (3C); IR (thin film): ν = 2954, 1728, 1690, 1267, 1167, 1116, 1101, 1012, 749 cm^{-1}; HRMS (ESI): m/z calcd for $C_{48}H_{66}Br_2O_9Si_2$ + Na^+: 1023.2510 [M + Na^+]; found: 1023.2511. Single crystals suitable for X-ray crystallography were obtained by recrystallization from hexanes.

Compound 17. Under an atmosphere of N_2, TBAF as a 1 M solution in THF (20 mmol, 20 mL) was added using a syringe to a dry flask containing triethylsilyl-protected tetraol **15** (1 mmol, 0.65 g). The resulting light-brown solution was stirred overnight at room temperature. The reaction mixture was poured into a flask containing 300 mL of phosphate-buffered H_2O (300 mM, pH 7), and resulting mixture was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (CH_2Cl_2/acetone 3:1 as eluent) to give the title compound **17** as a foamy solid, together with a minor isomer that could not be fully characterized (222 mg, 53% yield). Analytic data for **17** are as follows: R_f = 0.20 (CH_2Cl_2/acetone 3:1); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 4.21 ppm (t, J(H,H) = 2.6 Hz, 1H; H15), 4.17 (t, J(H,H) = 6.6 Hz, 1H; H16), 4.05 (dd, J(H,H) = 12.9, 5.6 Hz, 1H; H2), 3.97 (br. s, 1H; OH), 3.95 (t, J(H,H) = 3.0 Hz, 1H; H10), 3.85 (br. s, 1H; OH), 2.93 (br. app. t, J(H,H) = 12.5 Hz, 1H; H7), 2.74 (ddd, J(H,H) = 14.0, 5.0, 2.5 Hz, 1H; H14), 2.64 (dddd, J(H,H) = 17.5, 12.6, 5.2, 3.0 Hz, 1H; H4), 2.44 (dddd, J(H,H) = 17.5, 5.2, 2.0, 2.0 Hz, 1H; H4′), 2.35 (dddd, J(H,H) = 12.7, 5.4, 5.4, 2.2 Hz, 1H; H3), 2.18 (ddd, J(H,H) = 13.8, 13.8, 5.4 Hz, 1H; H12), 2.05 (d, J(H,H) = 12.5 Hz, 1H; H8), 1.98 (dddd, J(H,H) = 14.7, 14.7, 4.5, 2.5 Hz, 1H; H11), 1.91 (m, 1H; H11′), 1.80 (dddd, J(H,H) = 12.7, 12.7, 12.7, 5.5 Hz, 1H; H3′), 1.60−1.66 (m, 2H; H12′, H14′), 1.43−1.56 (m, 2H; H17, H17′), 1.21−1.35 (m, 9H; OH, H18−H21, H18′−H21′), 0.87 ppm (t, J(H,H) = 6.8 Hz, 3H; H22, H22′, H22″); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 198.2 (C1), 169.1(C5), 111.5 (C6), 106.3 (C13), 98.8 (C9), 80.8 (C16), 77.7 (C15), 71.3 (C2), 69.7 (C10), 42.7 (C8), 35.5 (C17), 31.7 (alkyl chain), 31.0 (C14), 29.8 (C3), 29.1 (alkyl chain), 27.4 (C4), 26.7 (C12), 25.3 (alkyl chain), 24.9 (C11), 22.6 (alkyl chain), 22.2 (C7), 14.0 ppm (C22); IR (thin film): ν = 3410 (brd), 1627, 1592 cm^{-1}; HRMS (ESI): m/z calcd for $C_{22}H_{32}O_7$: 408.2148 [M]; found: 408.2108.

Compound 1, Proposed as Trichodermatide A. Pyrrolidine (6 mL, 0.0735 mmol) was added to a solution of **17** (10 mg, 0.0245 mmol) in CH_2Cl_2 (0.5 mL). The resulting solution was stirred overnight at room temperature. The reaction mixture was poured into a flask containing 10 mL of phosphate-buffered H_2O (300 mM, pH 7), and the resulting biphasic mixture was stirred vigorously for 15 min. CH_2Cl_2 (10 mL) was added, and the layers were separated. The aqueous layer was extracted with another portion of CH_2Cl_2 (10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The ^{1}H NMR spectrum of the crude material showed that it consisted of a 55:45 mixture of starting material **17** and the required isomer **1** (R_f = 0.19, CH_2Cl_2/acetone 3:1). Compound **1** was purified using silica gel flash chromatography (CH_2Cl_2/acetone 3:1 as eluent), followed by trituration in CH_3CN. Trichodermatide A **1** was obtained as a white solid (3 mg, 30% yield). ^{1}H and ^{13}C NMR spectral data for **1** are provided in the

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Supporting Information. In $CDCl_3$, **1** exists predominantly as one isomer; in d_6-DMSO, **1** exists as a mixture of isomers. IR (thin film): ν = 3339 (brd), 1647, 1596 cm^{-1}; HRMS (ESI): m/z calcd for $C_{22}H_{31}O_7$: 407.2070 [M − H^+]; found: 407.2075. X-ray quality crystals were obtained by recrystallization from acetonitrile.

■ ASSOCIATED CONTENT

Supporting Information

NMR spectra, X-ray data of **1** and **16**, Cartesian coordinates of optimized isomers, figures, and computed ^{13}C NMR shifts. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(9) A minor isomer that could not be identified was observed in the NMR solution of **17** and **1**. Signals for a minor isomer were also detected by Pei and co-workers (ref 1).

(10) X-Ray crystal structure of **1**: CCDC 985619. Copies of the data can be obtained free of charge upon application to CCDC, 12, Union Road, Cambridge CB2 1EZ, U.K.; E-mail: deposit@ccdc.cam.ac.uk.

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