The Total Synthesis of (−)-Callystatin A

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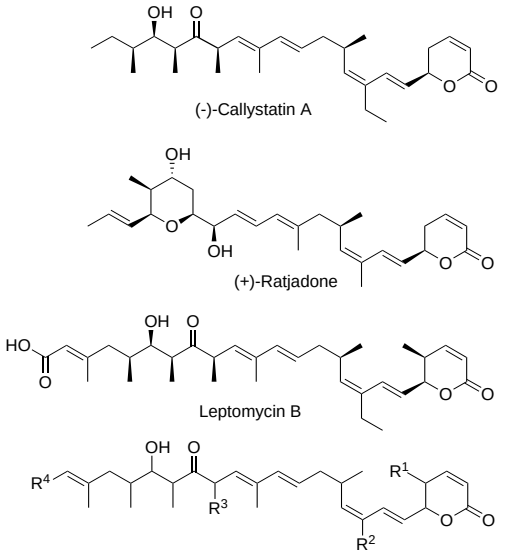
Abstract: Callystatin A is a prominent member of a class of natural products which display promising growth inhibition of cancer cells in their biological profile. The challenging structure and the interesting biological activity of (−)-callystatin A fueled our interest in the synthesis of this marine natural product. We achieved the total synthesis using a highly convergent approach joining four subunits together with a Wittig olefination, a selective Heck reaction and an aldol reaction as the pivotal steps. The aldol reaction as one of the final transformations during the synthesis opens fast access to a variety of structural analogues and circumvents tedious protecting group manipulations. Here we report an improved synthesis utilizing a modified vinyl iodide which shortens the synthesis by two steps. Additionally, first biological results will be reported.

Keywords: aldol reaction · antibiotics · callystatin · Heck reaction · polyketides

Introduction

(−)-Callystatin A was isolated in 1997 by Kobayashi and coworkers from the marine sponge *Callyspongia truncata* collected from Goto Islands, Nagasaki Prefecture (Japan).[1] It exhibits remarkable cytotoxicity with a IC_{50} value of 10 pg mL^{-1} against KB cell lines and 20 pg mL^{-1} against L1210 cells. The relative and absolute stereochemistry of (−)-callystatin A was confirmed by partial and total synthesis coupled with incisive analyses of NMR spectroscopical data.[2] Recently, Kobayashi et al. reported the synthesis of various structural analogues and their structure – activity relationship (SAR).[3] (−)-Callystatin A belongs to a class of natural products which are characterized by an unsaturated lactone moiety and two conjugated diene systems bridged by two saturated carbon units. Leptomycin B, a structurally related antitumor agent was shown to exhibit a similar cytotoxic profile.[4] Other structurally similar natural products are (+)-ratjadone,[5] kazusamycin,[6] anguinomycin,[7] leptofuranin[8] and leptolstatin[9] (Scheme 1). Owing to its challenging structural features and promising biological activity, (−)-



Scheme 1. Callystatin and related compounds.

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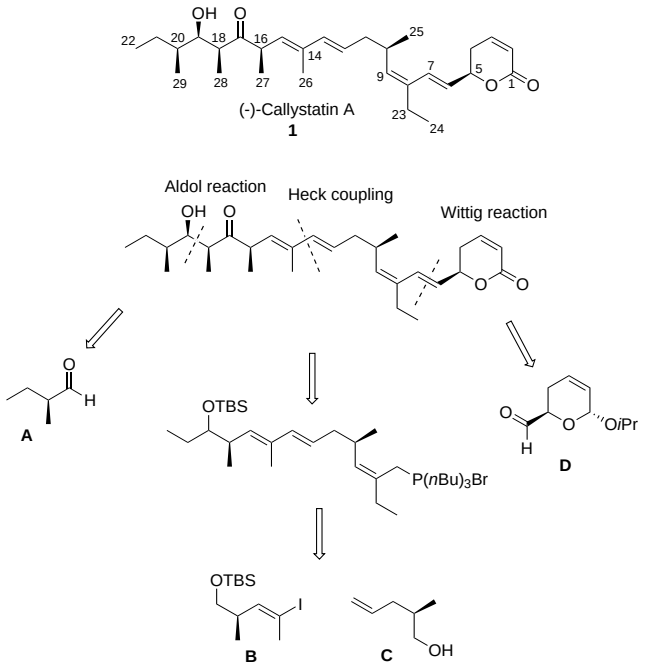
callystatin A has witnessed elegant total syntheses[10] from the groups of Kobayashi,[2] Crimmins,[11] Smith,[12] Marshall[13] and Enders.[14]

Our interest in this group of natural products resulted in the first total synthesis of (+)-ratjadone and the evaluation of the structure–activity relationship (SAR).[15] A detailed study helped us to show that the lactone as well as the diene moieties are crucial for the observed bioactivity, whereas the hydroxy part can be changed without significantly losing the tumor growth inhibitory effect. It is predicted that (−)-callystatin A, which has a similar structural motif, may also display enhanced anti-cancer properties by the variation of the side chain of the β-hydroxy unit, while keeping the crucial conjugated diene, the C10 methyl group and the α,β-unsaturated lactone moiety intact. To realize these predictions, we needed a flexible and stereoselective route for the synthesis of (−)-callystatin A. This prompted us towards the total synthesis of (−)-callystatin A. The key elements in our synthesis are a catalytic asymmetric hetero Diels–Alder reaction to generate the precursor for the unsaturated lactone[16] and exploiting the propensity of allylic strain within the ethyl ketone precursor to stereoselectively direct the final aldol reaction.[17]

Scheme 2 delineates the retrosynthetic disconnection of (−)-callystatin A between C6–C7, C13–C14 and C18–C19 affording four key fragments, namely 2-methyl propional **A**, vinyl iodide **B**, unsaturated alcohol **C** and the aldehyde **D**. In

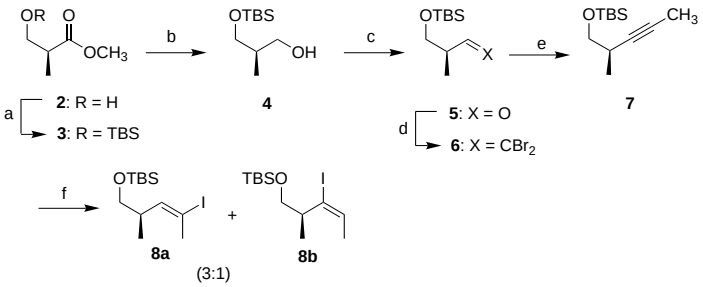


Scheme 2. Retrosynthetic analysis of (−)-callystatin A.

the synthetic direction fragments **B** and **C** are joined by a Heck coupling using the conditions reported by Jeffery[24] followed by sequential oxidation and Still–Gennari reaction affording the *Z*-configured α,β-unsaturated ester **11** (*E*:*Z* 1:8). The use of fragment **B** and introducing the ethyl group at a later stage has the advantage of shortening the linear sequence by two steps and avoids to carry diastereomers through the major part of the synthesis. The Wittig reaction of the aldehyde **D** with the phosphonium salt derived from the Still–Gennari product **14** in three steps yields the majority of the Eastern portion of (−)-callystatin A. The **BCD** moiety is transformed to the ethyl ketone precursor in four steps. The aldol reaction of the **BCD** moiety with the aldehyde **A** furnishes the all-*syn*-configured product which is finally transformed to (−)-callystatin A (**1**) in two succeeding steps.

Results and Discussion

Synthesis of fragment B: The synthesis of the fragment **B** started from the commercially available (*S*)-methyl 3-hydroxyisobutyrate (**2**) according to the procedure described by Schreiber et al.[18] TBS protection under standard conditions followed by DIBAl-H reduction afforded the alcohol **4** in 94% yield over two steps (Scheme 3). Dess–Martin[19] oxidation of **4** in CH_2Cl_2 furnished the corresponding aldehyde **5**, which was subsequently transformed to the dibromide **6** in 96% yield following the Corey–Fuchs[20] protocol.



Scheme 3. a) Imidazole, TBSCl, cat. 4-DMAP, THF, RT, 3 h, 99%; b) DIBAl-H (1M in hexane), CH_2Cl_2, −78 °C, 30 min, 89%; c) Dess–Martin periodinane, CH_2Cl_2, 0 °C → RT, 45 min, 89%; d) PPh_3, CBr_4, CH_2Cl_2, −78 °C, Et_3N, 1.1 h, 96%; e) i) *n*BuLi (1.6M in hexane), THF, −78 → −20 °C, ii) MeI, −20 → 0 °C, 76%; f) Schwartz reagent, THF/benzene 1:1, 8 h, I_2, 59% (compound **8a**).

The reaction of dibromide **6** with two equivalents of *n*-BuLi in THF at −78 °C resulted in the rapid formation of the corresponding acetylide, which was subsequently quenched with MeI to generate the methyl acetylene derivative **7** in 79% yield. In the next step compound **7** was treated with bis(cyclopentadienyl)zirconium chloride hydride (Schwartz reagent)[21] in THF/benzene (1:1) to provide the desired terminal iodide **8a** in 59% yield with 20% of its regioisomer **8b**. Initially we had expected higher regioselectivity since similar systems were reported to provide essentially one regioisomer in good yields.[22] Nevertheless, a detailed analysis of product distributions under various conditions such as elevated temperatures and different solvents to favor equilibrating conditions did not improve the selectivity. Even more surprisingly these conditions reported in the literature (benzene, 45 °C, 4 h) gave only a 1:1 mixture of regioisomers. It turned out the initially employed mixture of benzene and THF gave highest yield and selectivity in our system.

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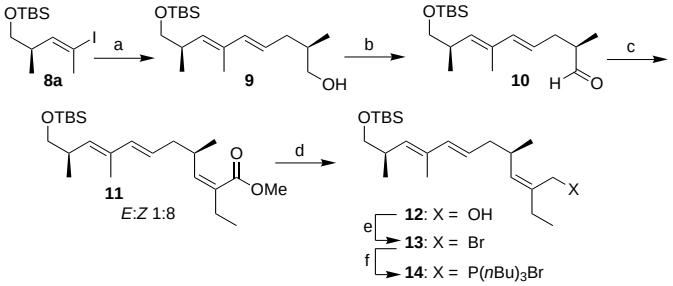
Coupling of the fragments B and C: Alcohol **C** was synthesized following literature method[23] in three steps. Our synthesis plan involved in the connection of the fragments **B** and **C** by Heck coupling under the conditions reported by Jeffery (Scheme 4).[24] Thus, the reaction of the fragment **B** with **C** at room temperature using a catalytic amount of palladium(II) acetate in the presence of silver acetate in DMF led to a highly regioselective formation of the alcohol (*E*)-**9** in 70% yield.

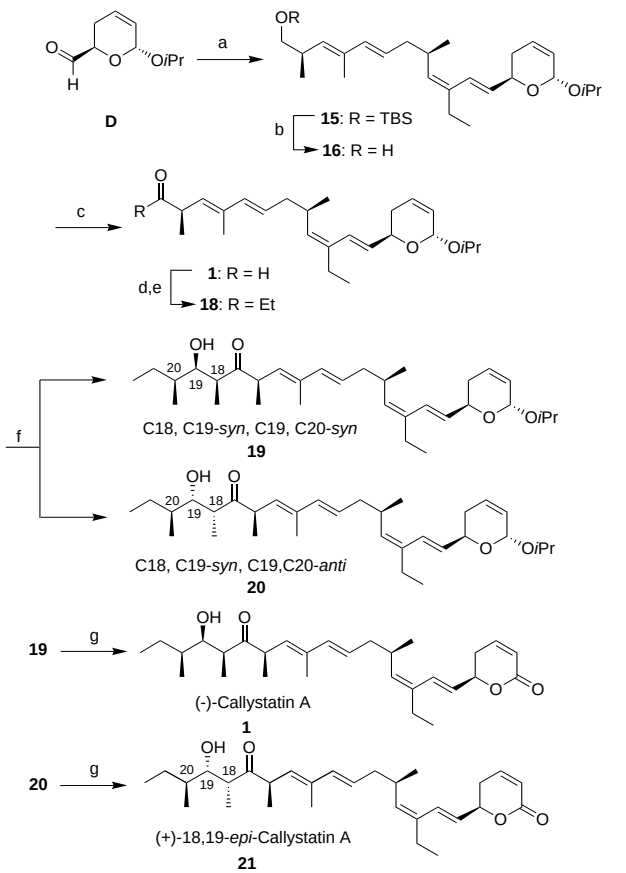


Scheme 4. a) Alcohol **C**, DMF, cat. $Pd(OAc)_2$, AgOAc, RT, 30 min, 70%; b) Dess–Martin periodinane, CH_2Cl_2, 0 °C → RT, 1 h, 99%; c) Still–Gennari reagent $[(CF_3CH_2O)_2P(O)CH(C_2H_5)COOCH_3]$, KHMDS (1M in toluene), THF, 0 → −78 °C then aldehyde **10**, 2 h, 70%; d) DIBAl-H (1M in hexane), CH_2Cl_2, −78 °C, 2 h, 85%; e) PPh_3, CBr_4, acetonitrile, RT, 15 min, 70%; f) $P(nBu)_3$, acetonitrile, RT, 30 min.

Wittig salt formation: In the next step Dess–Martin oxidation of alcohol **9** afforded the corresponding aldehyde **10** in 99% yield (Scheme 4). Reaction of **10** with the Still–Gennari[25] reagent in THF at 0 °C in the presence of KHMDS resulted in the formation of the conjugated α,β-unsaturated methyl ester **11** (*E*:*Z* 1:8). The desired major *Z* isomer was easily separated from the *E* isomer by flash chromatography. DIBAl-H reduction of ester **11** furnished the corresponding allylic alcohol **12** in 85% yield. The next steps of the synthesis involved the transformation of alcohol **12** to the Wittig salt **14** via the corresponding bromide **13**. Thus, the reaction of the alcohol **12** with two equivalents of PPh_3 and CBr_4 in acetonitrile at room temperature resulted in the formation of the corresponding bromide **13** within five minutes. The bromide was purified by flash chromatography and was immediately treated with five equivalents of tributylphosphine in acetonitrile to furnish the Wittig salt **14**.

Synthesis of the BCD fragment: Wittig reaction of the salt **14** with aldehyde **D** in THF at 0 °C in the presence of KO*t*Bu furnished the Wittig product **15** in 72% yield (Scheme 5). The reaction of Wittig product **15** with TBAF (1M in THF) in THF at room temperature provided alcohol **16** in 95% yield. Swern oxidation of alcohol **16** then gave the corresponding aldehyde **17** in 70% yield. The addition of EtMgBr to **17** generated the corresponding secondary alcohol which on Swern oxidation furnished the ethyl ketone **18** in 73% yield over two steps.

Aldol reaction: Given the preponderance of allylic strain in the ethyl ketone[17] **18**, we anticipated the preferential formation of one major isomer in the aldol reaction of **18** with the aldehyde **A** (Scheme 5).[26] Gratifyingly, the aldol



Scheme 5. a) Wittig salt **14**, KO*t*Bu (1M in THF), toluene, 0 °C, 2 h, 72%; b) TBAF (1M in THF), THF, RT, 3 h, 95%; c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 2 h, 70%; d) EtMgBr (1M in THF), THF, −78 °C, 30 min, 75%; e) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 30 min, 73%; f) LiHMDS (1M in hexane), THF, −78 °C, then aldehyde **A**, 20 min, 63% (all *syn* product **19**); g) i) PPTS, acetone/water 3:1, RT, 2 h; ii) MnO_2, pyridine, CH_2Cl_2, RT, 30 min, 81% over two steps.

reaction generated two *syn* isomers in 2:1 ratio in favor of the all-*syn* isomer **19** (C18, C19-*syn*, C19, C20-*syn*), and isomer **20** (C18, C19-*syn*, C19, C20-*anti*) which were separated by flash chromatography. We rationalize the observed selectivity for the major isomer **19** in the aldol step with a chair-like transition state in which the pseudo 1,3-diaxial interactions between the ketone side chain and the aldehyde hydrogen are minimized (Scheme 6). Face selectivity is derived through the allylic strain situation adjacent to the keto group. Furthermore, the conformation of the enolate is directed by the minimization of pseudo 1,3-diaxial interactions in the transition state.

Synthesis of (−)-callystatin A: The next step of the synthesis involves a two step transformation of the aldol products to the callystatin A (Scheme 5). Both of the isomers **19** and **20** were independently treated with pyridinium *para*-toluenesulfonic acid (PPTS) in acetone/water (3:1) at room temperature resulting in a quantitative formation of the corresponding lactols. Reaction of the lactols with MnO_2 buffered by the addition of additional pyridine furnished (−)-callystatin A (**1**) and (+)-18,19-*epi*-callystatin (**21**) in 81% yield. Synthetic (−)-callystatin A (**1**) has shown identical spectroscopic data (^1H,

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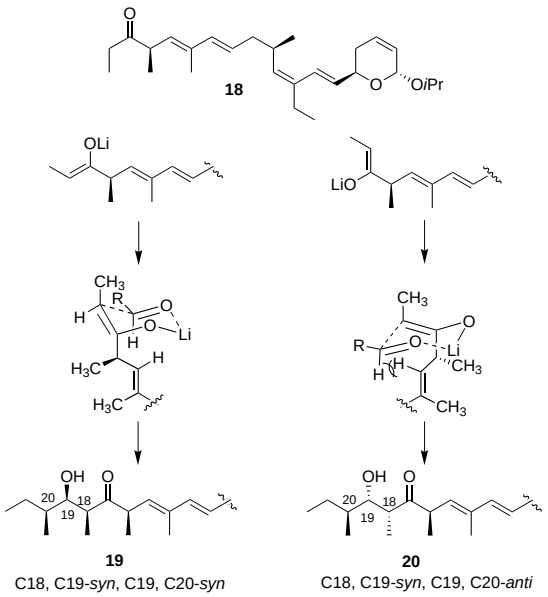

Scheme 6. Allylic strain favors the linear chain conformation as depicted. The sterically congested α center dictates facial selectivity in the aldol reaction with the aldehyde approaching from the opposite side of the methyl group.

^{13}C NMR), and the optical rotation with that of the natural (−)-callystatin A.

Biological testings: In order to analyze the ability to inhibit the proliferation of tumor cells both callystatins **1** and **21** were analyzed. With the aid of flow-cytometry we were able to analyze the number of living jurkat cells at different concentrations. The results indicated in Figure 1 show that both compounds inhibit tumor growth to the same extent at different concentrations. Surprisingly, we observed that cells which were treated with low concentrations of callystatin resumed cell division after an initial inhibition. This phenomena was never observed for ratjadone or its analogues and diastereomers. Experiments that could help to unravel whether this is due to resistance or reversibility of the callystatin binding to its receptor are currently in progress.

Despite these differences to ratjadone, treatment of jurkat cell with callystatin also resulted in apoptosis of cells. Figure 2 shows jurkat cells (T-Lymphocytes) at 400-fold magnification in the phase contrast. The cells were cultivated in RPMI-1640 media with 5% NCS at 5% CO_2. The pictures were taken in 4 h intervals after the addition of callystatin (10 nM). The first picture shows an untreated jurkat cell (normal cell shape). After 4 h a change in cell morphology can be observed and the membrane forms bulges, which is typical for apoptotic cells. After 8 h the change in morphology is even more pronounced. At higher concentrations and after longer exposure to callystatin a significant number of necrotic cells can be observed.

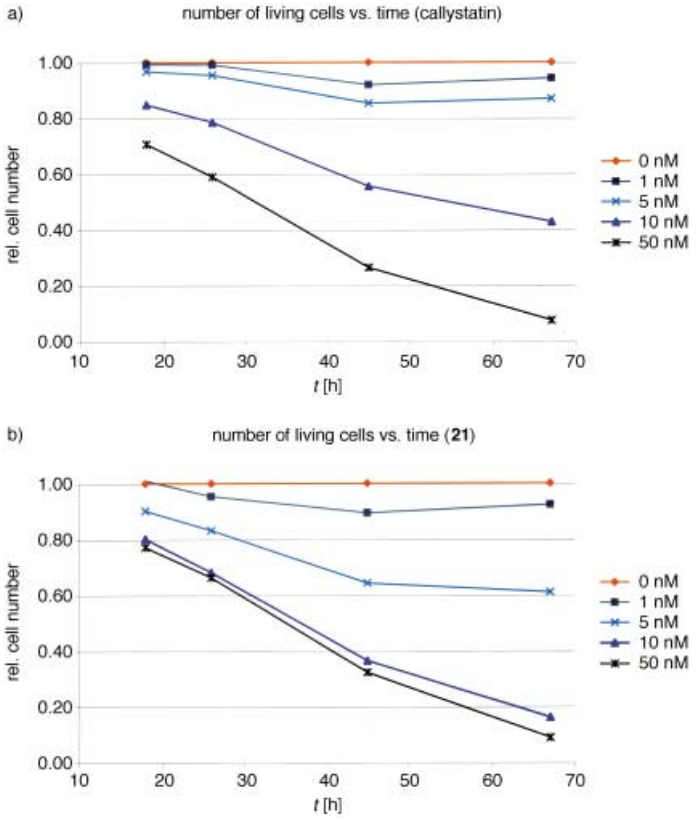

Figure 1. Jurkat cells were cultivated in 6-well microtiter plates. The cells were incubated for the given time period (see diagram) at the different callystatin concentrations (see diagram) in RPMI-1640 medium supplemented with 5% newborn calf serum at 37 °C and 5% CO_2 for a) callystatin A (**1**) and b) compound **21**.

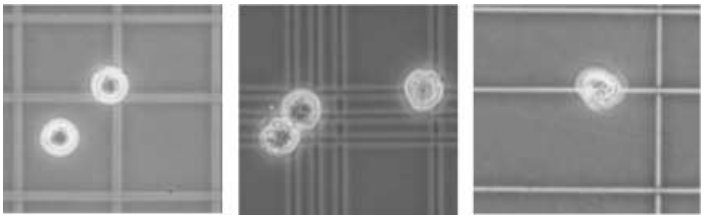

Figure 2. Cells were treated with callystatin and pictures were taken in 4 h intervals. Treatment of jurkat cells induces apoptosis which is evident by the typical change in cell morphology.

Conclusion

We have demonstrated a highly convergent and stereoselective strategy towards the synthesis of the promising spongean cytotoxic polyketide (−)-callystatin A emanating from easily available starting materials. Our approach can be readily adapted to the synthesis of various structural analogues of (−)-callystatin A by the variation of the side chain next to the β-hydroxy ketone moiety through a tactical selection of structurally important and divergent class of aldehydes in the final aldol reaction with the ethyl ketone precursor **18**. The present strategy opens access to novel and unique structural analogues of callystatin A and provides ample opportunity for the evaluation of extensive SAR studies. Efforts along these lines are underway and will be reported in due course.

Experimental Section

General methods: All commercial materials were used without purification unless otherwise noted. Tetrahydrofuran (THF) and diethyl ether were

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distilled over sodium/benzophenone and CH_2Cl_2 was distilled over CaH_2 immediately prior to use. DMF, acetonitrile, triethylamine and benzene were distilled and stored over 4 Å molecular sieves. ^1H NMR and ^{13}C NMR were recorded at 500, 400 and 125, 100 MHz, respectively; optical rotations were taken from Perkin Elmer 341 digital polarimeter; IR spectra were recorded with Bruker FTIR spectrometer IFS 25; Mass spectra (HRMS) were recorded with VG spectrometer. Thin-layer Chromatography was performed using E. Merck silica gel 60 F254 and flash chromatography was performed using silica gel 230–400 mesh. Spots on the TLC plates were detected by either vanillin ($MeOH/H_2SO_4$), or cerium reagents ($Ce(SO_4)_2/H_2SO_4$ molybdenum phosphate).

Ester 3: Imidazole (4.32 g, 63.13 mmol), TBSCl (8.94 g, 59.31 mmol) and a catalytic amount of 4-DMAP (0.42 g, 3.38 mmol) were added under argon atmosphere to a solution of (*S*)-methyl-3-hydroxyisobutyrate (**2**; 5.00 g, 42.37 mmol) in THF (150 mL). The mixture was stirred at room temperature for 3 h and quenched with saturated aqueous $NaHCO_3$ solution (50 mL) and extracted with MTBE (3 × 100 mL). The combined organic portions were dried over Na_2SO_4, filtered and concentrated in vacuo. Flash chromatography using hexane/ethyl acetate (10:1) afforded TBS protected methyl ester **3** (9.80 g, 99%) as a colorless liquid. $R_f = 0.3$ (hexane/ethyl acetate 10:1); $[\alpha]_D^{20} = +18.8^\circ$ ($c = 1.0$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.02$ (s, 6H), 0.85 (s, 9H), 1.11 (d, $J = 7.0$ Hz, 3H), 2.64 (sextet-like, $J = 7.0$ Hz, 1H), 3.62 (dd, $J = 6.0$, 9.6 Hz, 1H), 3.66 (s, 3H), 3.76 (dd, $J = 6.9$, 9.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -5.17$, 13.78, 18.54, 26.11, 42.88, 51.78, 65.59, 175.75; IR: $\tilde{\nu} = 1025$, 1059, 1091, 1715, 1775, 1197, 1253, 1362, 1462, 1741, 2857, 2963 cm^{-1}; HRMS: calcd for $C_7H_{15}O_3Si$: 175.0790; found: 175.0782 [$M^+ - t$Bu].

Alcohol 4: DIBAl-H (1M in hexane, 98 mL, 98.00 mmol) was added to a solution of ester **3** (8.00 g, 34.35 mmol) in CH_2Cl_2 (180 mL) at −78 °C under argon atmosphere. After 30 min the reaction mixture was quenched with water (7 mL) and diluted with MTBE (50 mL). The resulting solution was warmed to room temperature and stirred until a white gel was formed (10 min), then 4N NaOH (7 mL) and water (7 mL) were added. Stirring was continued until the generation of white precipitate (5 min). Subsequently Na_2SO_4 was added, the mixture was filtered and concentrated in vacuo. Flash chromatography using hexane/ethyl acetate (4:1) furnished alcohol **4** (6.18 g, 89%) as a colorless liquid. $R_f = 0.4$ (hexane/ethyl acetate 4:1); $[\alpha]_D^{20} = +14.28^\circ$ ($c = 0.7$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.06$ (s, 6H), 0.81 (d, $J = 7.0$ Hz, 3H), 0.88 (s, 9H), 1.88–1.98 (m, 1H), 2.96–3.02 (m, 1H), 3.53 (dd, $J = 8.1$, 9.9 Hz, 1H), 3.57–3.66 (m, 2H), 3.72 (ddq, $J = 0.7$, 4.4, 9.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -5.28$, 13.40, 18.49, 26.18, 37.36, 68.59, 69.04; IR: $\tilde{\nu} =$ 1034, 1088, 1252, 2955 cm^{-1}; HRMS: calcd for $C_6H_{15}O_2Si$: 147.0841; found: 147.0833 [$M^+ - t$Bu].

Aldehyde 5: Dess–Martin periodinane (13.69 g, 32.36 mmol) was added at 0 °C under argon atmosphere to a solution of alcohol **4** (6.00 g, 29.40 mmol) in CH_2Cl_2 (295 mL) and the reaction was stirred for 10 min and then warmed to room temperature. After 45 min, the reaction was quenched by the addition of $Na_2S_2O_3$ (7.5 g) dissolved in saturated aqueous $NaHCO_3$ solution (75 mL). The mixture was stirred vigorously until a clear solution resulted. The organic portion was collected and the aqueous layer was extracted using CH_2Cl_2 (3 × 50 mL). The combined organic portions were dried over Na_2SO_4, filtered and concentrated in vacuo. Precipitation of Dess–Martin salts using hexane at 0 °C afforded the aldehyde **5** (5.23 g, 89%). The aldehyde was immediately used in the next reaction.

Dibromide 6: CBr_4 (15.55 g, 46.88 mmol) was added under argon atmosphere to a solution of PPh_3 (24.59 g, 93.76 mmol) in CH_2Cl_2 (295 mL), and the reaction mixture was cooled to −78 °C resulting a reddish-brown solution. To this solution a mixture of TBS aldehyde **5** (4.73 g, 23.44 mmol) and Et_3N (3.39 mL, 23.44 mmol) taken in CH_2Cl_2 (20 mL) were added dropwise and the reaction stirred for 30 min at −78 °C, then warmed to room temperature. After 40 min of stirring the reaction was diluted with hexane (150 mL) and filtered through a short pad of silica gel and washed with hexane/ethyl acetate (3:1, 100 mL). The combined organic portions were concentrated in vacuo. Flash chromatography using hexane afforded the dibromide **6** (7.76 g, 96%) as a colorless liquid. $R_f = 0.4$ (hexane/ethyl acetate 20:1); $[\alpha]_D^{20} = -18.3^\circ$ ($c = 1.0$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.04$ (s, 6H), 0.89 (s, 9H), 1.02 (d, $J = 6.7$ Hz, 3H), 2.57–2.68 (m, 1H), 3.49 (d, $J = 1.4$ Hz, 2H), 6.26 (d, $J = 9.3$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -5.02$, 15.82, 18.63, 26.21, 41.40, 66.33, 88.80, 141.77; IR: $\tilde{\nu} =$ 773, 832, 1100, 1253, 1361, 1471, 1617 cm^{-1}; HRMS: calcd for $C_7H_{13}Br_2OSi$: 298.9102; found: 298.9089 [$M^+ - t$Bu].

Acetylene 7: A solution of dibromide **6** (7.36 g, 20.56 mmol) in THF (190 mL) under argon atmosphere was cooled to −78 °C. *n*BuLi (1.6M in hexane, 25.69 mL, 41.18 mmol) was added dropwise over a period of 30 min and the reaction was warmed to −20 °C and then stirred for 90 min at the same temperature. To the in situ generated lithium derivative, methyl iodide (6.40 mL, 102.79 mmol) was added dropwise and the solution was stirred for 10 min and then warmed to 0 °C. The reaction was continued to stir at the same temperature for 1 h and then brought to room temperature and quenched with saturated aqueous NH_4Cl solution (20 mL). The organic portion was collected and the aqueous layer was extracted using MTBE (3 × 50 mL). The combined organic portions were dried over Na_2SO_4 filtered and concentrated in vacuo. Flash chromatography using hexane afforded methyl acetylene **7** (3.10 g, 76%) as a colorless liquid. $R_f = 0.3$ (hexane); $[\alpha]_D^{20} = +2.3^\circ$ ($c = 1.0$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.05$ (s, 6H), 0.89 (s, 9H), 1.12 (d, $J = 6.9$ Hz, 3H), 1.77 (d, $J = 2.3$ Hz, 3H), 2.45–2.56 (m, 1H), 3.39 (dd, $J = 8.3$, 9.6 Hz, 1H), 3.66 (dd, $J = 5.6$, 9.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -4.99$, −4.94, 3.81, 17.99, 18.70, 26.24, 29.50, 67.97, 76.79, 81.73; IR: $\tilde{\nu} =$ 774, 834, 1006, 1087, 1254, 1362, 1386, 1463, 1472, 3305 cm^{-1}; HRMS: calcd for $C_8H_{15}OSi$: 155.0892; found: 155.0889 [$M^+ - t$Bu].

Iodide 8a: A solution of methyl acetylene **7** (0.48 g, 2.28 mmol) dissolved in THF/benzene (18 mL) was added under argon atmosphere at room temperature to a solution of Schwartz reagent (1.20 g, 4.65 mmol) in THF/benzene (1:1) (18 mL). After 8 h stirring iodine (0.59 g, 2.28 mmol) was added to the reaction, the pale yellow solution turned to reddish-brown. The reaction mixture was diluted with MTBE and washed successively with water, 10% aq. $Na_2S_2O_3$ solution and brine. The combined organic portions were dried over Na_2SO_4 filtered and concentrated in vacuo. Flash chromatography using hexane afforded the desired iodide **8a** (0.46 g, 59%) as a colorless liquid. $R_f = 0.3$ (hexane); $[\alpha]_D^{20} = +18.5^\circ$ ($c = 0.8$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.06$ (s, 6H), 0.80 (s, 9H), 0.84 (d, $J = 6.8$ Hz, 3H), 2.29 (d, $J = 1.5$ Hz, 3H), 2.42–2.52 (m, 1H), 3.31 (d, $J = 6.5$ Hz, 2H), 5.84 (dd, $J = 1.5$, 9.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -5.06$, −4.94, 16.80, 18.63, 26.24, 28.35, 38.82, 67.41, 94.66, 144.45; IR: $\tilde{\nu} =$ 774, 833, 1047, 1102, 1251, 1361, 1385, 1471 cm^{-1}; HRMS: calcd for $C_8H_{16}IOSi$: 283.0015; found: 283.0017 [$M^+ - t$Bu].

Alcohol 9: A catalytic amount of palladium(II) acetate (35 mg, 0.15 mmol) was added to a solution of iodide **8a** (0.80 g, 2.56 mmol) and alcohol **C** (0.36 g, 3.59 mmol) in DMF (8 mL) and the reaction was stirred at room temperature for 5 min. Silver acetate (0.52 g, 3.09 mmol) was added to the reaction and stirred for 2 h. The reaction mixture was diluted with MTBE and filtered through a short pad of celite. The organic portion was washed with water. The combined organic portions were dried over Na_2SO_4, filtered and concentrated in vacuo. Flash chromatography using hexane/ethyl acetate (4:1) afforded the alcohol **9** (0.52 g, 70%) as a colorless liquid. $R_f = 0.3$ (hexane/ethyl acetate 4:1); $[\alpha]_D^{20} = -4.1^\circ$ ($c = 1.0$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.03$ (s, 6H), 0.88 (s, 9H), 0.93 (d, $J = 6.8$ Hz, 3H), 0.97 (d, $J = 6.7$ Hz, 3H), 1.36 (br, 1H), 1.70–1.74 (m, 1H), 1.74 (d, $J = 1.0$ Hz, 3H), 1.99 (ddt, $J = 1.5$, 7.3, 15.3 Hz, 1H), 2.15–2.24 (m, 1H), 2.59–2.71 (m, 1H), 3.36 (dd, $J = 7.4$, 9.8 Hz, 1H), 3.43–3.55 (m, 3H), 5.13 (d, $J = 9.4$ Hz, 1H), 5.57 (dt, $J = 7.3$, 15.1 Hz, 1H), 6.04 (d, $J = 15.6$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -4.99$, −4.94, 13.23, 16.85, 17.64, 18.71, 26.28, 35.95, 36.63, 37.17, 68.21, 68.36, 125.91, 133.93, 134.00, 136.89; IR: $\tilde{\nu} =$ 1039, 1084, 1251, 1388, 1462, 3334 cm^{-1}; HRMS: calcd for $C_{18}H_{36}O_2Si$: 312.2484; found: 312.2475 [M^+].

Aldehyde 10: Dess–Martin periodinane (0.72 g, 1.70 mmol) was added under argon atmosphere at 0 °C to a solution of alcohol **9** (0.48 g, 1.54 mmol) in CH_2Cl_2 (16 mL). After 5 min the reaction was warmed to room temperature and stirred for an additional hour. The reaction was quenched by the addition of $Na_2S_2O_3$ (2.40 g) dissolved in saturated aqueous $NaHCO_3$ (5 mL) and stirred vigorously to result a clear solution (10 min). The organic layer was separated and the aqueous layer was extracted using CH_2Cl_2 (3 × 50 mL). The combined organic portions were dried over Na_2SO_4 filtered and concentrated in vacuo. The Dess–Martin salts were precipitated with hexane at 0 °C. The combined hexane portions were concentrated to afford the aldehyde **10** as a colorless liquid which was used immediately in the next step.

Ester 11: KHMDS (0.5M in toluene, 3.09 mL, 1.55 mmol) was added dropwise at 0 °C under argon atmosphere to a solution of 18-crown-6 (2.04 g, 7.75 mmol) and Still–Gennari reagent (0.54 g, 1.55 mmol) in THF (31 mL). The reaction was stirred for 15 min and then cooled to −78 °C.

Aldehyde **10** (0.48 g, 1.55 mmol) dissolved in THF (3 mL) was added dropwise and the reaction was stirred for 2 h at −78 °C. The solution was then brought to room temperature and stirred for an additional 1 h. The reaction was quenched with brine (200 mL) and diluted with MTBE. The organic portion was separated and the aqueous layer was extracted using MTBE (3 × 50 mL). The combined organic portions were dried over Na_2SO_4, filtered and concentrated in vacuo. Flash chromatography using hexane/ethyl acetate (40:1) afforded ester **11** (0.43 g, 70 %). $R_f = 0.3$ (hexane/ethyl acetate 20:1); $[\alpha]_D^{20} = +32.4°$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.02$ (s, 6H), 0.88 (s, 9H), 0.96 (d, $J = 6.8$ Hz, 3H), 0.98 (d, $J = 7.6$ Hz, 3H), 1.02 (t, $J = 7.4$ Hz, 3H), 1.72 (d, $J = 1.0$ Hz, 3H), 2.01 – 2.16 (m, 2H), 2.23 (q, $J = 7.3$ Hz, 2H), 2.59 – 2.70 (m, 1H), 3.01 – 3.13 (m, 1H), 3.35 (dd, $J = 7.4$, 9.8 Hz, 1H), 3.46, (dd, $J = 5.9$, 9.8 Hz, 1H), 3.72 (s, 3H), 5.11 (d, $J = 9.4$ Hz, 1H), 5.51 (dt, $J = 7.2$, 15.1 Hz, 1H), 5.62 (d, $J = 9.9$ Hz, 1H), 5.99 (d, $J = 15.6$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -5.0$, −4.93, 13.18, 14.15, 17.65, 18.70, 20.44, 26.28, 27.94, 34.17, 35.94, 40.81, 51.47, 68.23, 125.76, 132.63, 133.76, 134.07, 136.75, 146.06, 169.10; IR: $\tilde{\nu} =$ 1082, 1121, 1195, 1231, 1381, 1434, 1460, 1645, 1718 cm^{-1}; HRMS: calcd for $C_{19}H_{33}O_3Si$: 337.2198; found: 337.2201 [$M^+ - t$Bu].

Alcohol 12: DIBAl-H (1M in hexane, 2.17 mL, 2.17 mmol) was added dropwise at −78 °C under argon atmosphere to a solution of ester **11** (0.30 g, 0.761 mmol) in CH_2Cl_2 (4 mL), and the reaction was stirred for 2 h. After complete consumption of the starting material the reaction was quenched by the addition of water (0.2 mL) and diluted with MTBE (10 mL). The resulting solution was stirred at room temperature until a white gel was formed (5 min), then 4N NaOH (0.2 mL), water (0.2 mL) were added. The reaction was stirred until a white precipitate was formed (5 min). To this Na_2SO_4 was added and the resulting clear suspension was filtered and concentrated in vacuo. Flash chromatography using hexane/ethyl acetate (4:1) afforded alcohol **12** (0.23 g, 85 %) as a colorless liquid. $R_f = 0.4$ (hexane/ethyl acetate 4:1); $[\alpha]_D^{20} = +2.9°$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.02$ (s, 6H), 0.88 (s, 9H), 0.96 (d, $J = 6.6$ Hz, 3H), 0.97 (d, $J = 6.4$ Hz, 3H), 1.03 (t, $J = 7.4$ Hz, 3H), 1.72 (d, $J = 0.9$ Hz, 3H), 1.95 – 2.09 (m, 2H), 2.13 (q, $J = 7.5$ Hz, 2H), 2.46 – 2.57 (m, 1H), 2.59 – 2.68 (m, 1H), 3.36 (dd, $J = 7.4$, 9.7 Hz, 1H), 3.45 (dd, $J = 5.9$, 9.7 Hz, 1H), 4.07 (d, $J = 11.7$, Hz, 1H), 4.12 (d, $J = 11.6$, 1H), 5.06 (d, $J = 9.8$ Hz, 1H), 5.14 (d, $J = 9.3$ Hz, 1H), 5.50 (dt, $J = 7.4$, 15.2 Hz, 1H), 5.99 (d, $J = 15.6$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -5.0$, −4.93, 13.17, 13.45, 17.63, 18.70, 21.73, 26.28, 28.22, 33.20, 35.95, 41.33, 60.99, 68.18, 126.21, 133.63, 133.84, 134.14, 136.84, 139.36; IR: $\tilde{\nu} =$ 1008, 1084, 1120, 1251, 1361, 1389, 1461, 1624, 3308 cm^{-1}; HRMS: calcd for $C_{22}H_{42}O_2Si$: 366.2954; found: 366.2952 [M^+].

Wittig product 15: PPh_3 (0.17 g, 0.65 mmol) was added in one portion under argon atmosphere to a solution of alcohol **12** (0.12 g, 0.33 mmol) in acetonitrile (4 mL) and the reaction was stirred at room temperature to result a homogeneous solution (4 min). To this CBr_4 (0.22 g, 0.65 mmol) was added in one portion and the reaction was stirred at room temperature for 15 min then quenched by the addition of saturated aqueous $NaHCO_3$ (1 mL) and diluted with MTBE (20 mL). The organic portion was collected and the aqueous phase was extracted using MTBE (3 × 25 mL). The combined organic portions were dried over Na_2SO_4 filtered and concentrated in vacuo. Flash chromatography using hexane/ethyl acetate (10:1) afforded the bromide **13** as a colorless liquid. The bromide was immediately used in the next reaction. To a solution of bromide **13** (38 mg, 0.09 mmol) in acetonitrile (0.6 mL) under argon atmosphere at room temperature P(nBu)$_3$ (0.11 mL, 0.45 mmol) was added and the reaction was stirred for 30 min. The solvent was evaporated from the reaction and to the resulting Wittig salt **14** in toluene (1 mL) under argon atmosphere aldehyde **D** (18 mg, 0.11 mmol) was added and the reaction was cooled to 0 °C. Then KOtBu (1M in THF, 130 μL, 0.13 mmol) was added dropwise and the reaction was stirred for 2 h. The reaction was quenched with water (2 mL), diluted with MTBE (20 mL) and warmed to room temperature. The organic portion was collected and the aqueous phase was extracted using MTBE (3 × 30 mL). The combined organic portions were dried over Na_2SO_4, filtered and concentrated in vacuo. Flash chromatography using hexane/ethyl acetate (20:1) furnished the Wittig product **15** (32 mg, 72 %) as a colorless liquid. $R_f = 0.4$ (hexane/ethyl acetate 20:1); $[\alpha]_D^{20} = +39.71°$ ($c = 0.7$, CH_3OH); ^{1}H NMR (400 MHz, CD_3OD): $\delta = 0.07$ (s, 6H), 0.9 (s, 9H), 0.97 (d, $J = 6.8$, Hz, 6H), 1.05 (t, $J = 7.5$ Hz, 3H), 1.16 (d, $J = 6.2$ Hz, 6H), 1.72 (d, $J = 1.1$ Hz, 3H), 2.01 – 2.14 (m, 4H), 2.16 – 2.25 (m, 2H), 2.60 – 2.74 (m, 2H), 3.34 (m, 2H), 3.92 (heptet, $J = 6.2$ Hz, 1H), 4.37 (dd, $J = 6.4$, 6.9 Hz, 1H), 4.90 (s, 1H), 5.15 (d, $J = 9.4$, 1H), 5.18 (d, $J = 9.7$ Hz, 1H), 5.51 (dt, $J = 7.3$, 15.4 Hz, 1H), 5.71 – 5.80 (m, 2H), 6.02 (m, 2H), 5.94 – 6.07 (d, $J = 15.9$ Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD): $\delta = -5.73$, 13.00, 14.21, 17.62, 19.18, 21.36, 25.25, 26.34, 27.69, 31.97, 33.52, 36.66, 42.10, 64.75, 68.09, 68.73, 97.26, 126.53, 127.05, 128.33, 129.77, 129.84, 134.20, 135.31, 136.57, 137.36, 137.58; IR: $\tilde{\nu} =$ 1003, 1030, 1057, 1099, 1124, 1131, 1253, 1316, 1381, 1400, 1457, 1508, 1541, 1558, 1578, 1653 cm^{-1}; HRMS: calcd for $C_{31}H_{54}O_3Si$: 502.3842; found: 502.3841 [M^+].

Alcohol 16: TBAF (1M in THF, 0.16 mL, 0.16 mmol) was added under argon atmosphere to a solution of compound **15** (39 mg, 0.08 mmol) in THF (0.4 mL) and the reaction was stirred at room temperature for 3 h. The reaction was quenched with water (1 mL) and diluted with MTBE. The organic portion was collected and the aqueous phase was extracted using MTBE (3 × 30 mL). The combined organic portions were dried over Na_2SO_4 filtered and concentrated in vacuo. Flash chromatography using hexane/ethyl acetate (9:1 → 4:1) furnished alcohol **16** (28 mg, 95 %) as a colorless liquid. $R_f = 0.2$ (hexane/ethyl acetate 4:1); $[\alpha]_D^{20} = +96.60°$ ($c = 1.0$, CH_3OH); ^{1}H NMR (400 MHz, CD_3OD): $\delta = 0.96$ (d, $J = 6.6$ Hz, 3H), 0.98 (d, $J = 6.5$ Hz, 3H), 1.05 (t, $J = 7.4$ Hz, 3H), 1.16 (d, $J = 6.2$ Hz, 3H), 1.22 (d, $J = 6.2$ Hz, 3H), 1.71 (d, $J = 1.1$ Hz, 3H), 1.98 – 2.14 (m, 4H), 2.16 – 2.27 (m, 2H), 2.59 – 2.74 (m, 2H), 3.31 – 2.43 (m, 2H), 3.39 (dd, $J = 6.3$, 10.7 Hz, 1H), 4.0 (heptet, $J = 6.3$ Hz, 1H), 4.44 (dd, $J = 6.9$, 13.7 Hz, 1H), 5.12 (s-like, 1H), 5.16 (dd, $J = 9.9$, 14.8 Hz, 1H), 5.51 (dt, $J = 7.2$, 14.9 Hz, 1H), 5.67 – 5.78 (m, 2H), 5.98 – 6.05 (m, 2H), 6.60 (d, $J = 15.9$ Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD): $\delta = 13.01$, 14.19, 17.63, 21.28, 22.50, 24.23, 27.69, 32.00, 33.53, 36.65, 42.10, 68.08, 68.58, 71.24, 94.90, 126.98, 127.20, 128.40, 129.45, 129.85, 134.19, 135.28, 136.54, 137.36, 137.59; IR: $\tilde{\nu} =$ 1000, 1100, 1126, 1181, 1316, 1381, 1400, 1455, 1655, 1731, 3026, 3423 cm^{-1}; HRMS: calcd for $C_{25}H_{40}O_3$: 388.2967; found: 388.2972 [M^+].

Aldehyde 17: DMSO (7 μL, 0.10 mmol) in CH_2Cl_2 (30 μL) was added at −78 °C under argon atmosphere over 2 min to a solution of oxalyl chloride (5 μL, 0.05 mmol) in CH_2Cl_2 (120 μL), and the reaction mixture was stirred for 10 min. A solution of the alcohol **16** (18 mg, 0.05 mmol) in CH_2Cl_2 (50 μL) was added over 5 min, and the reaction was stirred for 2 h. The reaction was quenched with water (1 mL) diluted with CH_2Cl_2 (5 mL) and warmed to room temperature. The organic portion was collected and the aqueous phase was extracted using CH_2Cl_2 (3 × 10 mL). The combined organic portions were dried over Na_2SO_4 filtered and concentrated in vacuo. Flash chromatography using hexane/ethyl acetate (4:1) furnished the aldehyde **17** (12 mg, 70 %) as a colorless liquid. $R_f = 0.5$ (hexane/ethyl acetate 4:1); $[\alpha]_D^{20} = +57°$ ($c = 0.2$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.96$ (d, $J = 6.6$ Hz, 3H), 1.04 (t, $J = 7.4$ Hz, 3H), 1.17 (d, $J = 5.9$ Hz, 3H), 1.24 (d, $J = 6.5$ Hz, 6H), 1.77 (d, $J = 0.9$ Hz, 3H), 2.05 – 2.13 (m, 4H), 2.15 – 2.24 (m, 2H), 2.66 (m, 1H), 3.36 (m, 1H), 4.01 (heptet, $J = 6.2$ Hz, 1H), 4.49 (m, 1H), 5.10 – 5.19 (m 3H), 5.62 (dt, $J = 7.3$, 15.1 Hz, 1H), 5.69 – 5.78 (m, 2H), 5.98 – 6.05 (m, 1H), 6.07 (d, $J = 15.56$, 1H), 6.57 (d, $J = 15.9$ Hz, 1H), 9.49 (d, $J = 1.88$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.50$, 13.87, 14.53, 21.16, 22.52, 24.21, 26.74, 30.05, 31.23, 32.41, 41.26, 46.84, 67.50, 70.06, 93.71, 125.47, 126.53, 127.66, 128.52, 128.86, 129.00, 135.36, 135.50, 136.44, 138.24, 201.19; IR: $\tilde{\nu} =$ 1001, 1028, 1055, 1099, 1126, 1180, 1286, 1316, 1380, 1400, 1454, 1510, 1657, 1679, 1725 cm^{-1}; HRMS: calcd for $C_{25}H_{38}O_3$: 386.2820; found: 386.2808 [M^+].

Ethyl ketone 18: Ethyl magnesium bromide (1M in THF, 0.16 mL, 0.16 mmol) was added under argon atmosphere at −78 °C to a solution of aldehyde **17** (61 mg, 0.16 mmol) in THF (2 mL). The reaction was stirred for 30 min and quenched with saturated aqueous NH_4Cl solution and diluted with MTBE. The organic portion was collected and the aqueous phase was extracted using MTBE (3 × 25 mL). The combined organic portions were dried over Na_2SO_4 filtered and concentrated in vacuo. Flash chromatography using hexane/ethyl acetate (4:1) afforded the alcohol (50 mg, 75 %) as a colorless liquid.

To a solution of the oxalyl chloride (12 μL, 0.14 mmol) in CH_2Cl_2 (2 mL) at −78 °C under argon atmosphere, DMSO (19 μL, 0.27 mmol) in CH_2Cl_2 (2 mL) was added and the reaction was stirred for 5 min. A solution of the alcohol (50 mg, 0.12 mmol) prepared above dissolved in CH_2Cl_2 (2 mL) was added to the reaction. After 10 min Et_3N (84 μL, 0.61 mmol) was added. The reaction was stirred for 5 min, then quenched with water (1 mL) and diluted with CH_2Cl_2 and warmed to room temperature. The organic portion was collected and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic portions were dried over Na_2SO_4 filtered and concentrated in vacuo. Flash chromatography using hexane/ethyl-

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acetate (10:1, $R_f = 0.3$) furnished ethyl ketone **18** as a colorless liquid (37 mg, 73 %). ^{1}H NMR (500 MHz, CD_3OD): $\delta = 1.02$ (t, $J = 7.3$ Hz, 3H), 1.03 (d, $J = 6.5$ Hz, 3H), 1.09 (t, $J = 7.5$ Hz, 3H), 1.15 (d, $J = 6.8$ Hz, 3H), 1.21 (d, $J = 6.3$ Hz, 3H), 1.25 (d, $J = 6.3$ Hz, 3H), 1.83 (d, $J = 1.4$ Hz, 3H), 2.07–2.29 (m, 6H), 2.54–2.59 (m, 2H), 2.69–2.79 (m, 1H), 3.62 (dq, $J =$ 6.8, 9.8 Hz, 1H), 4.03 (heptet, $J = 6.2$ Hz, 1H), 4.46–4.53 (m, 1H), 5.14–5.17 (m, 1H), 5.18–5.27 (m, 2H), 5.65 (dt-like, $J = 7.0$, 15.6 Hz, 1H), 5.70–5.76 (m, 1H), 5.78 (ddd, $J = 0.7$, 6.0, 15.9 Hz, 1H), 6.02–6.10 (m, 2H), 6.64 (dt-like, $J = 1.0$, 15.9 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD): $\delta = 8.45$, 13.39, 14.51, 17.25, 21.65, 22.82, 24.55, 27.99, 32.31, 33.72, 35.11, 42.33, 47.48, 68.83, 71.54, 95.22, 127.53, 128.59, 128.97, 129.73, 130.24, 130.48, 136.68, 136.86, 137.34, 137.98, 214.96; HRMS: calcd for $C_{27}H_{42}O_3$: 414.3133; found: 414.3138 [M^+].

Compound 19: LiHMDS (80 μL, 0.08 mmol, 1M in THF) was dissolved in THF (0.3 mL) and cooled to −78 °C. The ethyl ketone **18** (22 mg, 0.05 mmol) dissolved in THF (0.2 mL) was added over 5 min and then stirred for 15 min. Aldehyde **A** (9 mg, 0.11 mmol) was added and the reaction was quenched after 15 min with saturated aqueous NH_4Cl solution at −78 °C and the aqueous layer was extracted with MTBE (50 mL). The organic layer was dried over Na_2SO_4 filtered and concentrated in vacuo. Flash chromatography using hexane/ethyl acetate (5:1, $R_f = 0.3$) afforded C18, 19-*syn*, C19, C20-*syn* **19** (17 mg, 63 %). ^{1}H NMR (500 MHz, CD_3OD): $\delta = 0.78$ (d, $J = 6.4$ Hz, 3H), 0.91 (t, $J = 7.1$ Hz, 3H), 1.02 (d, $J = 6.7$ Hz, 3H), 0.95–1.06 (m, 2H), 1.09 (t, $J = 7.4$ Hz, 3H), 1.13 (d, $J = 6.6$ Hz, 3H), 1.17 (d, $J = 7.0$ Hz, 3H), 1.21 (d, $J = 6.2$ Hz, 3H), 1.26 (d, $J = 6.2$ Hz, 3H), 1.89 (d, 1.2 Hz, 3H), 2.06–2.19 (m, 5H), 2.20–2.28 (m, 2H), 2.71–2.79 (m, 1H), 2.90 (dd, $J = 7.0$, 8.6 Hz, 1H), 3.69 (dd, $J = 2.6$, 7.65 Hz, 1H), 3.79 (dd, $J = 6.7$, 10.3 Hz, 1H), 4.05 (heptet, $J = 6.2$ Hz, 1H), 4.50 (q, $J = 6.7$ Hz, 1H), 5.09–5.25 (m, 3H), 5.62–5.82 (m, 3H), 6.00–6.10 (m, 2H), 6.65 (d, $J =$ 5.9 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD): $\delta = 12.33$, 13.60, 13.72, 14.50, 14.94, 16.99, 21.47, 22.83, 24.57, 25.75, 27.97, 28.56, 32.32, 33.53, 39.43, 42.32, 47.23, 68.83, 71.59, 75.56, 95.23, 127.50, 128.40, 129.19, 129.79, 129.99, 130.26, 136.72, 136.94, 137.75, 137.88, 216.68; HRMS: calcd for $C_{32}H_{52}O_4$: 500.3864; found: 500.3867 [M^+].

(−)-Callystatin A (1): Acetal **19** (12 mg, 0.02 mmol) was dissolved in a 3:1 mixture of acetone and water (0.5 mL), pyridinium *p*-toluenesulfonate (PPTS) (5 mg) was added and the reaction mixture was stirred for 2 h at room temperature. The reaction was then quenched with saturated aqueous $NaHCO_3$ solution and the aqueous layer was extracted with MTBE (3 × 20 mL). The organic layer was dried over Na_2SO_4 filtered and concentrated in vacuo. Activated MnO_2 (100 mg) was suspended in CH_2Cl_2 (0.5 mL) containing pyridine (10 μL). The crude lactol dissolved in CH_2Cl_2 (0.5 mL) was added at room temperature. After the reaction was allowed to stir for 30 min MnO_2 was removed by filtration through a short plug of celite. After concentration the product was purified by flash chromatography using hexane/ethyl acetate (3:1, $R_f = 0.2$) to yield synthetic (−)-callystatin A (**1**; 7 mg, 81 %, over two steps). $[\alpha]_D^{20} = -105°$ ($c = 0.1$, MeOH); ref.: −107° ($c = 0.1$, MeOH)[1a]; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.85$ (t, $J = 7.4$ Hz, 3H), 0.89 (d, $J = 6.6$ Hz, 3H), 0.97 (d, $J = 6.7$ Hz, 3H), 1.05 (t, $J = 7.4$ Hz, 3H), 1.12 (d, $J = 7.13$ Hz, 3H), 1.14 (d, $J = 6.6$ Hz, 3H), 1.31–1.44 (m, 3H), 1.82 (d, $J = 1.2$ Hz, 3H), 2.09 (t-like, $J = 6.8$ Hz, 2H), 2.14–2.23 (m, 2H), 2.45–2.48 (m, 2H), 2.62 (d, $J = 3.43$ Hz, 1H), 2.64–2.70 (m, 1H), 2.86 (dq, $J = 4.4$, 7.3 Hz, 1H), 3.58 (ddd, $J = 3.4$, 4.3, 6.6 Hz, 1H), 3.66 (dq, $J = 6.6$, 10.0 Hz, 1H), 4.98 (q-like, $J = 7.1$ Hz, 1H), 5.13 (d, $J = 10.0$ Hz, 1H), 5.25 (d, $J = 9.7$ Hz, 1H), 5.58 (dt, $J = 7.6$, 15.5 Hz, 1H), 5.76 (dd, $J = 6.8$, 15.8 Hz, 1H), 6.01 (d, $J = 15.5$ Hz, 1H), 6.06 (dt, $J =$ 1.8, 9.9 Hz, 1H), 6.64 (d, $J = 15.8$ Hz, 1H), 6.90 (dt, $J = 4.3$, 9.7 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD): $\delta = 10.95$, 11.94, 13.54, 14.43, 16.52, 16.93, 21.61, 25.74, 27.87, 31.25, 33.67, 39.66, 41.75, 42.26, 46.49, 76.99, 80.75, 121.85, 126.93, 129.02, 130.63, 130.98, 137.04, 137.31, 137.43, 138.43, 148.27, 165.79, 215.26; HRMS: calcd for $C_{29}H_{44}O_4$: 456.3238; found: 456.3240 [M^+].

(+)-18,19-*epi*-Callystatin A (21): Following the same procedure as for compound **1**, (+)-18,19-*epi*-callystatin A (**21**) was prepared from compound **20** in 81 % yield over two steps. $[\alpha]_D^{20} = +410°$ ($c = 0.1$, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.82$ (d, $J = 6.8$ Hz, 3H), 0.90 (t, $J = 7.6$ Hz, 3H), 0.97 (d, $J = 6.7$ Hz, 3H), 1.04 (d, $J = 7.0$ Hz, 3H), 1.05 (t, $J = 7.4$ Hz, 3H), 1.16 (d, $J = 6.9$ Hz, 3H), 1.31–1.44 (m, 3H), 1.79 (d, $J = 1.4$ Hz, 3H), 2.08 (t-like, $J = 6.8$ Hz, 2H), 2.14–2.24 (m, 2H), 2.45–2.48 (m, 2H), 2.64–2.70 (m, 1H), 2.71 (d, $J = 3.2$ Hz, 1H), 2.88 (dq, $J = 2.9$, 7.1 Hz, 1H), 3.48–3.52 (m, 1H), 3.65 (dq, $J = 6.8$, 9.7 Hz, 1H), 4.98 (q-like, $J = 7.1$ Hz, 1H), 5.22–5.26 (m, 2H), 5.58 (dt, $J = 8.3$, 15.6 Hz, 1H), 5.76 (ddd, $J = 0.7$, 7.0, 15.9 Hz, 1H), 6.02 (d, $J = 15.6$ Hz, 1H), 6.06 (dt, $J = 1.8$, 9.9 Hz, 1H), 6.64 (d, $J = 15.8$ Hz, 1H), 6.89 (dt, $J = 4.4$, 9.9 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD): 10.95, 11.94, 13.54, 14.43, 16.52, 16.93, 21.61, 25.74, 27.87, 31.25, 33.67, 39.66, 41.75, 42.26, 46.49, 76.99, 80.75, 121.85, 126.93, 129.02, 130.63, 130.98, 137.04, 137.31, 137.43, 138.43, 148.27, 165.79, 215.26; HRMS: calcd for $C_{29}H_{44}O_4$: 456.3238; found: 456.3240 [M^+].

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